A61K 31/121 (2006.01)  A61P 31/16 (2006.01)
A61K 31/232 (2006.01)  A61P 25/28 (2006.01)
A61K 31/23 (2006.01)  A61P 25/00 (2006.01)
A61K 31/223 (2006.01)

Title: SUBLINGUAL FORMULATIONS INCLUDING GERANYLGERANYLACETONE AND GERANYLGERANYLACETONE DERIVATIVES

Abstract: Provided herein are sublingual formulations of geranylgeranylacetone, geranylgeranylacetone derivatives, and drug conjugates of each thereof, and methods of using them. Also provided are methods for treating osteopenia with geranylgeranyl acetone (GGA) and derivatives thereof and compositions useful for the same. Also provided are polyisoprenyl phosphonate derivatives, pharmaceutical compositions comprising the polyisoprenyl phosphonate derivatives, and uses thereof.
WO 2014/151719 A1


Published:
— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

Declarations under Rule 4.17:
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(3))
SUBLINGUAL FORMULATIONS INCLUDING GERANYLGERANYLACETONE AND
GERANYLGERANYLACETONE DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a PCT application that claims the benefit of US Patent Application Nos. 13/815,831 and 13/815,792, both filed on March 15, 2013, and U.S. Provisional Application Nos.: 61/845,303 filed July 11, 2013; 61/856,391 filed July 19, 2013; 61/878,489 filed September 16, 2013; and 61/920,441 filed December 23, 2013, the entire content of each of which is incorporated herein by reference.

Field of the Invention

Provided herein are methods for treating osteopenia including osteoporosis with geranylgeranyl acetone (GGA) and derivatives thereof and compositions useful for the same. 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. Further provided herein are sublingual formulations comprising geranylgeranylacetone and geranylgeranylacetone derivatives and uses thereof. Dstill further provided here are polyisoprenyl phosphonate derivatives pharmaceutical compositions comprising polyisoprenyl phosphonate derivatives, and uses thereof.

State of the Art

Geranylgeranyl acetone (GGA) has the formula:

and is reported to have neuroprotective and related effects. See, for example, PCT Pat. App. Pub. Nos. WO 2012/031028, WO 2013/052148, and WO 2013/130654, each of which is incorporated herein by reference in its entirety.

Neurodegeneration is often the result of increased age, sporadic mutations, disease, and/or protein aggregation in neural cells. Neurodegenerative diseases are often characterized by a progressive neurodegeneration of tissues of the nervous system and a loss of functionality of the neurons themselves. One commonality seen among most neurodegenerative
diseases is the accumulation of protein aggregates intracellular or in the extracellular space between neurons.

There is a need for more effective therapies for neural and neurodegenerative diseases. There is also a need for more effective therapies for the treatment of osteopenia, including osteoporosis.

There is also a need for more effective sublingual therapies. Sublingual administration of a drug involves applying the drug beneath the tongue of a subject. When the drug comes in contact with the mucous membrane beneath the tongue, it diffuses through it. Because the connective tissue beneath the epithelium contains a profusion of capillaries, the substance then diffuses into them and enters the venous circulation. In contrast, substances absorbed in the intestines are subject to "first pass metabolism" in the liver before entering the general circulation.

Sublingual administration has certain advantages over oral administration. Being more direct, it is often faster, and it ensures that the substance will risk degradation only by salivary enzymes before entering the bloodstream, whereas orally administered drugs must survive passage through the hostile environment of the gastrointestinal tract, which risks degrading them, either by stomach acid or bile, or by the many enzymes therein, such as monoamine oxidase (MAO). Furthermore, after absorption from the gastrointestinal tract, such drugs must pass to the liver, where they may be extensively altered; this is known as the "first pass effect" of drug metabolism. Due to the digestive activity of the stomach and intestines and the solubility of the G| tract, the oral route is not ideal for certain substances.

However, sublingual administration requires that the drug must partition into the mucosa more favorably than water (saliva); the drug must be able to be absorbed quickly before enzymes in the saliva degrade the drug or a portion of the drug in saliva is swallowed; the drug must then be able to pass through the capillaries and into the blood. Thus, for a sublingual administration of a drug to be effective, the drug must be sufficiently hydrophobic to partition favorably into the mucosa relative to saliva of a subject and yet be sufficiently hydrophilic to subsequently pass from the mucosa into the subject's bloodstream to exert a therapeutic effect. Ideally, sublingual administration of a drug will provide a bioavailability of the drug that is comparable to an i.v. administration of the drug. In practice, very few compounds are amenable to sublingual administration.
Furthermore, one needs to recognize that at least a portion of the drug will be swallowed. So the total therapeutic affect is actually the aggregate of sublingual plus gastrointestinal absorption. Therefore it is unpredictable as to whether a given drug is amenable to sublingual delivery. There is a need to sublingual deliver a variety of drugs for faster action, lower first pass metabolism, and the like.

GGA is a known anti-ulcer drug used commercially and in clinical situations. There is a need for sublingual formulations of GGA derivatives, e.g., for the treatment or prevention of disorders and diseases which can be treated with GGA or a GGA derivative.

**SUMMARY OF THE INVENTION**

In some aspects, provided herein are methods for inhibiting neural death, increasing neural activity and for treating osteopenia, including osteoporosis, or reducing the negative effects of osteopenia with the derivatives and pharmaceutical compositions provided herein. It is contemplated that these derivatives may possess one or more properties such as increased blood brain barrier penetration, enhanced activity, improved serum half-life, and/or lower toxicity.

Also provided herein are methods for treating osteopenia including osteoporosis with compounds provided herein and/or utilized herein, including geranylgeranyl acetone (GGA) and derivatives thereof and compositions useful for the same. In one aspect, provided herein are methods for treating osteopenia or reducing the negative effects of bone loss comprising administering to a subject in need thereof a therapeutically effective amount of GGA or a GGA derivative. As used herein, subject or patient refers to a mammal, preferably humans.

In some embodiments, treating osteopenia includes without limitation, modulating osteoclast and/or osteoblast function, and preferably, decreasing osteoclast function in diseases such as osteoporosis, hypercalcemia of malignancy, cancer metastasis to the bone, arthritis, Rheumatoid arthritis, bone loss due to immobilization, Paget's disease of the bone, bone loss due to hyperparathyroidism and other metabolic diseases, bone loss due to treatment with corticosteroids, bone loss due to treatment with aromatase inhibitors, periodontal disease, prosthetic loosening and the like. In some embodiments, treating osteopenia includes treating osteoporosis,
In another aspect, provided herein are methods for decreasing osteoclast activity and decreasing bone resorption comprising contacting an osteoclast with an effective amount of GGA or a GGA derivative. In another aspect, provided herein are methods for shifting the balance between osteoclast and osteoblast activity comprising contacting an osteoclast and/or osteoblast with an effective amount of GGA or GGA derivative. In one embodiment, the method further comprises decreasing osteoclast activity and/or increasing osteoblast activity, and/or decreasing bone resorption. In another aspect, provided herein are methods of blocking osteoclast differentiation and/or osteoclast activation of bone resorption, the method comprising contacting an osteoclast with an effective amount of GGA or a GGA derivative.

In another aspect, provided herein are methods for inhibiting loss of bone density in a patient in need thereof comprising administering to the patient an effective amount of GGA or a GGA derivative. In another aspect, provided herein are methods for inhibiting bone fracture in a patient at risk thereof which bone fracture arises at least in part from pathological bone loss comprising administering to the patient an effective amount of GGA or a GGA derivative. In one embodiment, the bone fracture is fracture of the hip. In one embodiment, the bone fracture is fracture of the vertebrae.

In another aspect, provided herein are methods for inhibiting bone loss and/or facilitating bone growth in a patient at a risk of loss of bone density, comprising administering to the patient an effective amount of GGA or a GGA derivative. Without being bound by theory, it is contemplated that the methods and compositions provided herein can increase bone formation and/or reduce bone resorption.

In another aspect, provided herein are methods for treating a subject who undergoes or has undergone a bone grafting procedure, where the bone grafting procedure is autologous (with bone harvested from the patient's own body) includes an allograft (with cadaveric bone usually obtained from a bone bank), or a synthetic graft. The methods described herein can be used to treat a subject prior to, during and/or after a bone grafting procedure.

In another aspect, provided herein is a method of a decreasing osteoclast activity or modulating osteoclast resorption by administering sublingual^ a parathyroid hormone (PTH) or a PTH like receptor (PTHrP) in combination with or conjugated to a bisphosphonate provided herein. Without being bound by theory, it is contemplated that the
bisphosphonates provided and/or utilized herein will reduce side effects related to elevated calcium levels, while delivering PTH or the PTHrP sublingually, and suppressing the side effects of PTH and PTHrP. In one embodiment, the osteoclast activity is decreases. In another embodiment, the osteoclast resorption is modulated.

5 Preferably, the GGA or the GGA derivative includes the all-trans (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 embodiments, at least 90%, more preferably, at least 95%, yet more preferably at least 99%, and most preferably, at least 99.5% of the GGA or the GGA derivative is present as a trans isomer.

In another aspect, provided herein are sublingual formulations of GGA or a GGA derivative.

10 Surprisingly, it has been discovered that GGA is efficiently provided to a subject via sublingual delivery. The bioavailability of GGA obtained via sublingual administrations is surprisingly high, and almost parallels those obtained from IV injections.

In one aspect, provided herein is a method of maintaining exposure of an effective amount of GGA or a GGA derivative for a period of up to 1 hour, up to 2 hours, or up to 3 hours, in a patient comprising administering the GGA or the GGA derivative sublingually to the patient in need thereof. In some embodiments, the effective amount of GGA or the GGA derivative varies by less that 50%, preferably by less than 25%, and more preferably by less than 10% during the period when the exposure is maintained.

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 sublingually. 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 sublingual 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.
Provided herein are compounds, compositions, and methods for sublingual 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.

In another aspect, provided herein are drug conjugates of GGA or drug conjugates of GGA derivatives, that are therapeutically useful for sublingual formulation and delivery to a subject. In some embodiments, provided herein are compounds of formula [G-L-]_v-D, wherein v is 1-10, preferably 1-5, more preferably 1-3, still more preferably 1, 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: \( =N-Li-CO-, =N-Li-O-, =N-U-OCO-, =CO-Li-CO-, =CO-Li-O-, =CO-Li-OCO-, =CO-LO-Li-CO-, and the likes. The drug can be any drug, preferably one that contains one or more \(-CO_2H, -OH, -NH_2, and/or -SH, and such other groups that can be covalently conjugated as provided herein. L_1 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, \( L_1 \) comprises a \( C_1-C_{20} \) alkylene or \( C_1-C_{20} \) heteroalkylene, \( C_3-C_{10} \) cycloalkyl, \( C_1-C_{20} \) heteroaryl, \( C_2-C_{10} \) heterocycl moiety, which is opinally substituted. Certain preferred substituents include \( C_1-Ce \) alkyl, \(-OH, \) amino, \( C_{1-6} \) alkylamino, \( C_{1-6} \) alkylamino, \( C_3-CB \) cycloalkyl, \( C_1-C_{20} \) heteroaryl, or \( C_2-C_{10} \) heterocycl. In some embodiments, \( L_i \) comprises an amino acid moiety. In some embodiments, \( L_i \) 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 provided 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 (Beta type naturietic protein) - congestive heart failure; Calcitonin for hypercalcemia; 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 one aspect, provided herein is a method of maintaining exposure of an effective amount of a drug for a period of up to 1 hour, up to 2 hours, or up to 3 hours, in a patient comprising administering a GGA or a GGA derivative conjugate of the drug sublingually to the patient in need thereof. In some embodiments, the effective amount of the drug varies by less that 50%, preferably by less than 25%, and more preferably by less than 10% during the period when the drug exposure is maintained.

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 N-H hydrogen.

Certain non-limiting GGA derivatives utilized herein 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\(^\circ\) or Zofran\(^\circ\) (GlaxoSmithKline, London, U.K.) or vancomycin. In some embodiments, the drug that is conjugated to GGA or a GGA derivative is a peptide or a protein drug. Non-limiting examples of such peptide drugs include the thyrotropin-releasing hormone, (pyro)Glu-His-Pro-N\(_2\), having a MW=362, octretide, and the likes. 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.

In some embodiments, the drug that is conjugated is a nucleic acid, a nucleotide, or a nucleoside.

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.

It is contemplated that the administration of an effective amount of these sublingual 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-sublingual formulation comprising the comparable amount of GGA or a GGA derivative. It is further contemplated that such
sublingual 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 sublingual formulations of GGA or a GGA derivative avoid stomach acid induced conversion of the all trans form to a mixed cis- and trans- form. In some embodiments, at least one of the double bonds in GGA or the GGA derivative of the sublingual 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 sublingual formulation is in the cis configuration.

These sublingual formulations of GGA or a GGA derivative exhibit bioavailability and/or pharmacokinetic profiles that do not require the subject to fast before administration. In other words, food intake by the subject is less apt to alter the bioavailability and/or pharmacokinetic profiles of these sublingual formulations of GGA or a GGA derivative, than corresponding oral formulations. In another embodiment, the sublingual formulation contains an effective amount of GGA or the GGA derivative. In some embodiments, these sublingual formulations of GGA or a GGA derivative exhibit bioavailability and/or pharmacokinetic profiles that are comparable to those obtained from an i.v. administration of GGA or a GGA derivative.

It is further contemplated that these sublingual formulations of GGA or a GGA derivative partition more favorably into the oral mucosa than into saliva. As such, little or none of the sublingual formulations of GGA or a GGA derivative is swallowed by the subject before it can be absorbed sublingually. It is further contemplated that these sublingual formulations of GGA or a GGA derivative are compatible with the enzymes in the oral cavity.

In one aspect, provided herein are sublingual formulation of GGA or GGA derivatives, such as those utilized herein, and sublingual delivery thereof to a subject. Preferably, GGA or the GGA derivative is the sole active agent in these formulations and methods. In certain embodiments, such sublingual formulations provided herein are useful for treating or alleviating the negative effects of various neurological diseases and disorders described herein.

In another aspect, provided herein are methods for sublingual delivery of therapeutically active GGA or GGA derivatives, where the GGA or the GGA derivative is the sole
therapeutically effective agent. Such delivery will exclude a drug either as a mixture or a conjugate as described herein.

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 or provided 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 transportation of GGA or the GGA derivative, or the drug conjugate of GGA or a GGA derivative from an aqueous phase into the sublingual 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 salivary aqueous environment into blood.

In one aspect, provided herein are sublingual pharmaceutical compositions (or sublingual formulations) comprising an effective amount of 5E, 9E, 13E geranylgeranyl acetone or a GGA derivative, and optionally at least one pharmaceutical excipient, wherein the effective amount is from about 1 mg/kg/day to about 12 mg/kg/day. In another embodiment the effective amount is from about 1 mg/kg/day to about 5 mg/kg/day or from about 6 mg/kg/day to about 12 mg/kg/day. Preferably, the effective amount is about 3 mg/kg/day, about 6 mg/kg/day, or about 12 mg/kg/day.

In certain aspects, provided herein are pharmaceutical uses of geranylgeranyl acetone (GGA) and GGA derivatives, sublingual 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, utilized herein is a 5-trans isomer compound of formula VI:
wherein VI is at least 80% in the 5E, 9E, 13E configuration. In one embodiment, the compound utilized herein 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.

Another aspect utilizes a 5-cis isomer compound of formula VII:

\[
\text{VII}
\]

wherein VII is at least 80% in the 5Z, 9E, 13E configuration, or a ketal thereof of formula XII:

\[
\text{XII}
\]

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, \(C_1-C_6\) 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:

\[
\text{XII}
\]

In another aspect, GGA derivatives provided and/or utilized herein are of formulas (XVIII), (XIX) or (XX), and subformulas thereof:

\[
\text{XVIII}
\]

\[
\text{XIX}
\]
or a pharmaceutically acceptable salt thereof, pharmaceutical compositions comprising the
compounds and uses thereof, wherein the substituents are defined herein.

In another aspect, provided herein are sublingual pharmaceutical compositions of for
increasing the expression and/or release of one or more neurotransmitters from a neuron at
risk of developing pathogenic protein aggregates associated with AD or ALS, said
composition comprising a protein aggregate inhibiting amount of GGA, a GGA derivative, or
an isomer or a mixture of isomers thereof.

In another aspect, provided herein are sublingual pharmaceutical compositions for
increasing the expression and/or release of one or more neurotransmitters from a neuron at
risk of developing extracellular pathogenic protein aggregates, said composition comprising
an extracellular protein aggregate inhibiting amount of GGA, a GGA derivative, or an isomer
or a mixture of isomers thereof.

Examples of sublingual compositions include without limitation lozenges, tablets, including
fast dissolving and lipid matrix formulations, sprays, films, gels, granule, neat, capsules,
powders, and liquid.

In one embodiment, the GGA utilized herein is 5-trans GGA or substantially pure 5-trans
GGA which is optionally free of cis GGA or is essentially free of cis GGA. In other
embodiments, the GGA is a mixture of cis and trans isomer, or pure or substantially pure cis
isomer.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 graphically demonstrates a liquid chromatography and mass spectroscopy
(LC/MS/MS) based method used to measure the appearance in rat plasma of CNS following
a single 30 mg/kg sublingual dose and a representative PK profile is shown below in the
graph.

FIG. 2 graphically shows the sublingual delivery of a highly fluorescent dansyl hydrazone
derivative of CNS administered in a single sublingual dose of 48 mg/kg or a single IV dose of
16 mg/kg; the concentration averages of the data from two animals per time point per treatment group are shown below along with standard deviation error bars.

FIG. 3 graphically shows the transportation of a dansylated peptide of approximate molecular weight of 1.3 kDa by showing the average plasma levels for each of two animals per time point per treatment group given in a single dose of 48 mg/kg by either sublingual or iv administration.

Fig. 4 graphically shows plasma levels minus pre-dose values for each time point per animal per treatment group (N=4 for the dansyl peptide control; N = 8 for the cNs peptide.

DETAILED DESCRIPTION

It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

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 "an excipient" includes a plurality of excipients.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention provided herein belongs. As used herein the following terms have the following meanings.

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 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 the invention provided herein.
The term "drug conjugate of GGA or a GGA derivative" refers to the covalent attachment of the drug to the GGA or GGA derivative. Non-limiting covalent linkages that can be used to attach the drug to the GGA or GGA derivative include, esters, amides, cabamates, carbonates, ureas, Seiff's bases and selenylated amides.

The term "drug" refers to approved agents for treating diseases or disorders, or agents that are undergoing development for treating such diseases or disorders. Preferably, the drug contains a moiety capable of forming a conjugate in the manner contemplated and provided herein.

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.

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 within 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 within the brain such as glia.

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 herein are granular protein aggregates.

As used herein, the term "protein aggregate inhibiting amount" refers to an amount of GGA 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.

As used herein, the term "intranuclear" or "intranuclearly" refers to the space inside the nuclear compartment of an animal cell.

The term "cytoplasm" refers to the space outside of the nucleus but within the outer cell wall of an animal cell.

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.

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.

As used herein, the term "ALS" refers to amyotrophic lateral sclerosis disease.

As used herein, the term "AD" refers to Alzheimer's disease.

The term "neurotransmitter" refers to chemicals that 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, γ-aminobutyric acid, and glycine; monoamines such as dopamine, norepinephrine, epinephrine, histamine, serotonin, and melatonin; and other molecules such as acetylcholine, adenosine, anadamide, and nitric oxide.

The term "synapse" refers to junctions between neurons. These junctions allow for the passage of chemical signals from one cell to another.

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. RHOA, 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.

As used herein, the term "treatment" or "treating" means any treatment of a disease or condition in a patient, including one or more of:

- preventing or protecting against the disease or condition, that is, causing the clinical symptoms not to develop, for example, in a subject at risk of suffering from such a disease or condition, thereby substantially averting onset of the disease or condition;
- inhibiting the disease or condition, that is, arresting or suppressing the development of clinical symptoms; and/or
- relieving the disease or condition that is, causing the regression of clinical symptoms.

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.

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 β-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 Sodl protein has similar pathology to humans with ALS. Similarly, a transgenic mouse that overexpresses APP has similar pathology to humans with AD.
An effective amount of a compound disclosed or utilized herein, including e.g., a polyisoprenyl phosphonate derivative or GGA or a GGA derivative is the amount of the compound required to produce a protective effect in vitro or in vivo. In some embodiments the effective amount in vitro is about from 0.1 nM to about 1 mM. In some embodiments the effective amount in vitro is from about 0.1 nM to about 0.5 nM or from about 0.5 nM to about 1.0 nM or from about 1.0 nM to about 5.0 nM or from about 5.0 nM to about 10 nM or from about 10 nM to about 50 nM or from about 50 nM to about 100 nM or from about 100 nM to about 500 nM or from about 500 nM to about 1 mM. In some embodiments, the effective amount for an effect in vivo is about 0.1 mg to about 100 mg, or preferably, from about 1 mg to about 50 mg, or more preferably, from about 1 mg to about 25 mg per kg/day. In some other embodiments, the effective amount in vivo is from about 10 mg/kg/day to about 100 mg/kg/day, about 20 mg/kg/day to about 90 mg/kg/day, about 30 mg/kg/day to about 80 mg/kg/day, about 40 mg/kg/day to about 70 mg/kg/day, or about 50 mg/kg/day to about 60 mg/kg/day. In some embodiments, the effective amount in vivo is from about 1 mg/kg/day to about 5 mg/kg/day, in some embodiments, the effective amount in vivo is from about 6 mg/kg/day to about 12 mg/kg/day, in one embodiment, the effective amount in vivo is about 3 mg/kg/day. In another embodiment, the effective amount in vivo is about 6 mg/kg/day. In another embodiment, the effective amount in vivo is about 12 mg/kg/day. In still some other embodiments, the effective amount in vivo is from about 100 mg/kg/day to about 1000 mg/kg/day.

Routes of administration refers to the method for administering a compound disclosed or utilized herein, including e.g., a polyisoprenyl phosphonate derivative or GGA or a GGA derivative to a mammal. Administration can be achieved by a variety of methods. These include but are not limited to subcutaneous, intravenous, transdermal, sublingual, or intraperitoneal injection or oral administration.

The term "about" when used before a numerical designation, e.g., temperature, time, amount, and concentration, including range, indicates approximations which may vary by (+) or (-) 10 %, 5 %, or 1 %.

The term "halogenating" is defined as converting a hydroxy group to a halo group. The term "halo" or "halo group" refers to fluoro, chloro, bromo and iodo.
The term "stereoselective" is defined as providing over 90% of the E isomer for the newly formed double bond.

"Geometrical isomer" or "geometrical isomers" refer to compounds that differ in the geometry of one or more olefinic centers. "E" or "(E)" refers to the trans orientation and "Z" or "(Z)" refers to the cis orientation.

Geranylgeranyl acetone (GGA) refers to a compound of the formula:

wherein compositions comprising the compound are mixtures of geometrical isomers of the compound.

The 5-trans isomer of geranylgeranyl acetone refers to a compound of the formula VI:

wherein the number 5 carbon atom is in the 5-trans (5E) configuration.

The 5-cis isomer of geranylgeranyl acetone refers to a compound of the formula VII:

wherein the number 5 carbon atom is in the 5-cis (5Z) configuration.

As used herein, the term "polyisoprenyl phosphonate" or "polyisoprenyl phosphonate derivative" refers to any of the compounds of Formula (XVIII), (XIX) or (XX) described herein and such other compounds known in the art.

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.
As used herein, $C_m^m$-$C_n^n$ such as $C_1$-$C_{10}$, $C_1$-$C_6$, or $C_1$-$C_4$ 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 $(+\frac{1}{-\frac{1}{2}}) \times 10\%$, $5\%$ or $1\%$.

The term "alkoxy" refers to $-O$-alkyl.

The term "alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms (i.e., $C_1$-$C_{10}$ alkyl) or 1 to 6 carbon atoms (i.e., $C_1$-$C_6$ alkyl), or 1 to 4 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH$_3$), ethyl (CH$_3$CH$_2$), n-propyl (CH$_3$CH$_2$CH$_2$), isopropyl ((CH$_3$)$_2$CH), n-butyl (CH$_3$CH$_2$CH$_2$CH$_2$), isobutyl ((CH$_3$)$_2$CHCH$_2$), sec-butyl ((CH$_3$)(CH$_3$CH$_2$)CH), tert-butyl ((CH$_3$)$_3$C), rt-pentyl (CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$), and neopentyl ((CH$_3$)$_3$CH$_2$). In some embodiments, the term "alkyl" refers to substituted or unsubstituted, straight chain or branched alkyl groups with $C_1$-$C_{12}$, $C_2$-$C_6$ and preferably $C_1$-$C_4$ carbon atoms.

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.

The term "alkynyl" 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 triple bond.

The term "acyl" refers to $-C(\equiv)$-alkyl, where alkyl is as defined above.

The term "alkoxy" refers to $-O$-alkyl.

The term "nitro" refers to $-NO_2$.

The term "cyano" refers to $-CN$.

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:
In some embodiments, the term "aryl" refers to a 6 to 10 membered, preferably 6 membered aryl group. An aryl group may be substituted with 1-5, preferably 1-3, halo, alkyl, and/or —O-alkyl groups.

The term "-CO2H ester" refers to an ester formed between the -CO2H group and an alcohol, preferably an aliphatic alcohol. A preferred example included -CO2R, wherein R is alkyl or aryl group optionally substituted with an amino group.

"Co-crystal," or as sometimes referred to herein "co-precipitate" refers to a solid, preferably a crystalline solid, comprising GGA or a GGA derivative, and urea or thiourea, more preferably, where, the GGA or the GGA derivative reside within the urea or thiourea lattice, such as in channels formed by urea or thiourea.

"Complexed" refers to GGA or a GGA derivative bound by certain quantifiable intermolecular forces, non-limiting examples of which include hydrogen bonding and Van-der Waals' interactions, and also by entropic effects.

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. Non limiting 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.

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:
The term "halo" refers to F, Cl, Br, and/or I.

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:

The term "heterocydyl" 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 heterocydyl preferably refers to saturated ring systems, it also includes ring systems containing 1-3 double bonds, provided that they ring is non-aromatic. Nonlimiting examples of heterocydyl include, azalactones, oxazoline, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, and tetrahydropyranyl. The condensed rings may or may not contain a non-aromatic heteroatom containing ring provided that the point of attachment is a heterocydyl group. For example, and without limitation, the following is a heterocydyl group:

The term "hydrolyzing" refers to breaking an $R^1$-0-CO-, $R^1$-0-CS-, or an $R^1$-0-S0$_2$- moiety to an $R^1$-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.
The term "oxo" refers to a C=0 group, and to a substitution of 2 geminal hydrogen atoms with a C=0 group.

The term "pharmacologically acceptable" refers to safe and non-toxic for in vivo, preferably, human administration.

The term "pharmacologically acceptable salt" refers to a salt that is pharmacologically acceptable.

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, NH₄, Ca, Ba, imidazolium, and ammonium cations based on naturally occurring amino acids. When the compounds provided and/or utilized herein contain basic functionaly, such salts include, without limitation, salts of organic acids, such as carboxylic acids and sulfonic 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 tribasic phosphate, mesylate, tosylate, and the likes.

The term "substantially pure" in terms of cis or trans isomer refers to a cis or trans isomer that is by molar amount 70%, 80%, or 95%, preferably 96%, more preferably 99%, and still more preferably 99.5% or more a cis or trans isomer with the rest being the corresponding trans or cis isomer.

"Trans" in the context of GGA and GGA derivatives refer to the GGA scaffold as illustrated below:

\[
\begin{align*}
    &\text{wherein } F^-R^5 \text{ is defined herein and } q \text{ is 0-2. As shown, each double bond is in a trans or E configuration. In contrast, a cis form of GGA or a GGA derivative will contain one or more of}
\end{align*}
\]
these bonds in a cis or Z configuration. Cis refers to a form where one or more bonds in the GGA or the GGA derivative are of cis geometry, as understood by the skilled artisan. Such cis isomers may be prepared following various known methods and from the mother-liquor of clathrate crystallization as disclosed in US patent application no. 61/708,570, which is incorporated herein in its entirety by reference.

The term "osteopenia" refers to a disease where osteoclasts dissolve more bone than produced by the bone forming cells, osteoblasts. As used herein, treating osteopenia includes without limitation, modulating osteoclast and/or osteoblast function, and preferably, decreasing osteoclast function in diseases such as osteoporosis, hypercalcemia of malignancy, cancer metastasis to the bone, arthritis, Rheumatoid arthritis, bone loss due to immobilization, Paget's disease of the bone, bone loss due to hyperparathyroidism and other metabolic diseases, bone loss due to treatment with corticosteroids, bone loss due to treatment with aromatase inhibitors, periodontal disease, prosthetic loosening and the like. Methods for modulating and or inhibiting osteoclast function are well known to the skilled artisan, and described, for example, in Boyle et al., EP1717315.

In certain embodiments, the composition is suitable for the treatment of a neural disease selected from the group consisting of Alzheimer's disease, Parkinson's disease, multiple sclerosis, a prion disease, amyotrophic lateral sclerosis, damage to the spinal cord, and neural death during an epileptic seizure.

Compounds

GGA

Utilized herein are compounds and pharmaceutical compositions of isomers of geranylgeranyl acetone. In certain aspects, utilized herein is a synthetic 5-trans isomer compound of formula VI:

![Chemical Structure](image)

wherein VI is at least 80% in the 5E, 9E, 13E configuration. In some embodiments, the invention utilizes a compound of formula VI wherein VI is 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 the compound of formula VI does not contain any of the cis-isomer of GGA.

Another aspect utilizes a synthetic 5-cis isomer compound of formula VII:

![Chemical Structure](image)

wherein VII is at least 75% in the 5Z, 9E, 13E configuration. In certain embodiments, the compound utilized is 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, the compound of formula VII does not contain any of the trans-isomer of GGA.

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.

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:

![Chemical Structure](image)

or a tautomer or pharmaceutically acceptable salt thereof, wherein

- n² is 1 or 2;
- each R¹ and R² are independently C₁-C₆ alkyl, or R¹ and R² together with the carbon atom they are attached to form a C₂-C₇ cycloalkyl ring optionally substituted with 1-3 C₁-C₆ alkyl groups;
- each of R³, R², and R⁵ independently are hydrogen or C₁-C₆ alkyl;
Q$^1$ is $-(C=O)$, $-(C=S)$, or $-S(O)_{2}$;
Q$^2$ is hydrogen, R$^6$, -O-R$^6$, -NR$^7$R$^8$, or is a chiral moiety;
R$^8$ is:

- C$_i$-C$_6$ alkyl, optionally substituted with -CO$_2$H or an ester thereof, C$_i$-C$_6$ alkoxy, oxo,
- OH, -CR=CR$_2$, -C≡CR, c$_3$-c$_{10}$ cycloalkyl, c$_3$-c$_8$ heterocyclyl, c$_6$-c$_{10}$ aryl, C$_2$-C$_{10}$ heteroaryl,

wherein each R independently is hydrogen or C$_2$-C$_6$ alkyl;

- CO- C$_i$-Cs alkyl;
- c$_3$-c$_{10}$ cycloalkyl;
- C$_3$-C$_6$ heterocyclyl;
- c$_5$-C$_{10}$ aryl; or
- C$_2$-C$_{10}$ heteroaryl;

wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl groups; -CF$_3$, 1-3 halo, preferably, chloro or fluoro, groups; 1-3 nitro groups; 1-3 C$_i$-C$_6$ alkoxy groups; -CO-phenyl; or -NR$_{18}$R$_{19}$, each R$_{18}$ and R$_{19}$ independently is hydrogen; C$_2$-C$_6$
alkyl, optionally substituted with -CO$_2$H or an ester thereof, C$_2$-C$_6$ alkoxy, oxo, -CR=CR$_2$, -CCR,
c$_3$-c$_{10}$ preferably C$_3$-C$_8$ cycloalkyl, C$_3$-C$_8$ heterocyclyl, C$_6$-C$_{10}$ aryl, or C$_2$-C$_{10}$ heteroaryl, wherein each R independently is hydrogen or C$_i$-C$_6$ alkyl; C$_3$-C$_{10}$ cycloalkyl; C$_3$-C$_8$ heterocyclyl; C$_6$-C$_{10}$ aryl; or C$_2$-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 R$_{18}$ and 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 R$^8$; and

refers to a mixture of cis and trans isomers at the corresponding position.

In some embodiments, at least 80% and, preferably, no more than 95% of the compound of

Formula (I) is present as a trans isomer.

In one embodiment, the GGA derivative utilized is of Formula (I-A):
as a substantially pure 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.

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

In another embodiment, the GGA derivative provided and/or utilized is of Formula (I-B):

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

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

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.

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

\[
\begin{align*}
\text{(I-D)} & \\
\text{(I-E)} & \\
\text{(I-F)} & \\
\end{align*}
\]

wherein \( R^6 - R^8 \) are defined as in Formula (I) above.

In another embodiment, the GGA derivative utilized is of Formula (I-G), (I-H), or (I-I):

\[
\begin{align*}
\text{(I-G)} & \\
\end{align*}
\]
as a substantially pure trans isomer around the 2,3 double bond wherein R6-R8 are defined as in Formula (I) above.

In a preferred embodiment, R6 is C6-C10 aryl, such as naphthyl. In another preferred embodiment, R5 is a heteroaryl, such as quinolinyl.

In another aspect, the GGA derivative utilized herein is of Formula (II):

\[
\begin{align*}
\text{(II)}
\end{align*}
\]

or a pharmaceutically acceptable salt thereof, wherein

m is 0 or 1;

n is 0, 1, or 2;

each R1 and R2 are independently C1-C6 alkyl, or R1 and R2 together with the carbon atom they are attached to form a C5-C7 cycloalkyl ring optionally substituted with 1-3 C1-C6 alkyl groups;

each of R3, R4, and R5 independently are hydrogen or C1-C6 alkyl;

\( \frac{3}{4} \) is -OH, -NR22-R3, -X-CO-NR25, -X-CS-NR25, or -X-S02-NR25;

X is -O-, -S-, -NR25, or -CR27-R28;

each R21 and R23 independently is hydrogen; C1-C6 alkyl, optionally substituted with C1-C6 alkoxy; and C3-C10 cycloalkyl;

each R24 and R25 independently is hydrogen, C1-C6 alkyl, optionally substituted with -CO2H or an ester thereof, C1-C6 alkoxy, oxo, -OH, -CR=CR2, -C=C, C3-C10 cycloalkyl, C3-C8 heterocyclyl, C6-C10 aryl, C2-C10 heteroaryl, wherein each R independently is hydrogen or C1-C6 alkyl;

c3-C10 cycloalkyl;

C3-C8 heterocyclyl;

C6-C10 aryl; or

C2-C10 heteroaryl;
wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl groups; -CF₃, 1-3 halo, preferably, chloro or fluoro, groups; 1-3 nitro groups; 1-3 C1-C6 alkoxy groups; -CO-phenyl; or -NR³R⁴;
each R¹⁸ and R¹⁹ independently is hydrogen; C₁-C₆ alkyl, optionally substituted with -C0₂H or an ester thereof, C₁-C₆ alkoxy, oxo, -CR=CR₂, -CCR, C₃-C₁₀ preferably C₅-C₈ cycloalkyl, C₃-C₈ heterocyclyl, C₆Cl₂aryl, or C₂-C₆ heteroaryl, wherein each R independently is hydrogen or Cl-C₆ alkyl; C₃-C₁₀ cycloalkyl; C₃-C₈ heterocyclyl; C₆Cl₂aryl; or C₂-C₈ 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 R¹⁸ and R¹⁹ together with the nitrogen atom they are attached to form a 5-7 membered heterocycle;
R²⁶ is hydrogen or together with R²⁴ or R²₅ and the intervening atoms form a 5-7 membered heterocyclic ring optionally substituted with 1-3 C₁-C₆ alkyl groups; and each R²⁷ and R²⁸ independently are hydrogen, Cl-C₆ alkyl, -COR²¹ or -C₀₂R²¹, or R²⁷ together with R²⁴ or R²⁵ and the intervening atoms form a 5-7 membered heterocyclyl ring optionally substituted with 1-3 C₁-C₆ alkyl groups.
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 C₁-C₆ alkyl ester, which phenyl or alkyl group is optionally substituted with a amino group.
In one embodiment, Q₃ is -NR²²R²³.X-CO-NR²⁴R²⁵, -X-CS-NR²⁴R²⁵, or -X-SO₂-NR²⁴R²⁵. In another embodiment, Q₃ is -X-CO-NR²⁴R²⁵, -X-CS-NR²⁴R²⁵, or -X-SO₂ NR²⁴R²⁵. In another embodiment, Q₃ is -NR²²R²³. In another embodiment, Q₃ is -OH.
In one embodiment, the compound of Formula (II) is of formula:

![Formula Image]

wherein R¹, R², R³, R⁴, and Q₃ are defined as in any aspect or embodiment herein. In another embodiment, the GGA derivative utilized is of formula:

![Formula Image]

wherein R¹, R², R⁴, R⁵, and ¾ are defined as in any aspect and embodiment here. In one embodiment, the compound of Formula (II) is of formula:
wherein $R^1$, $R^2$, $R^5$, and $\frac{3}{4}$ are defined as in any aspect or embodiment herein.

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

$$
\begin{align*}
\text{wherein } R^1, R^2, R^3, R^4, R^5, m, n, x, R^{24} \text{ and } R^{25} \text{ are defined as in any aspect and embodiment here.}
\end{align*}
$$

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

$$
\begin{align*}
\text{wherein } R^1, R^2, R^3, R^4, R^5, m, n, R^{24} \text{ are defined as in any aspect and embodiment here.}
\end{align*}
$$

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

$$
\begin{align*}
\text{wherein } R^{24} \text{ is defined as in any aspect and embodiment here.}
\end{align*}
$$

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

$$
\begin{align*}
\text{wherein } R^{24} \text{ is defined as in any aspect and embodiment here.}
\end{align*}
$$

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

$$
\begin{align*}
\text{wherein } R^{24} \text{ is defined as in any aspect and embodiment here.}
\end{align*}
$$

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

$$
\begin{align*}
\text{wherein } R^{24} \text{ is defined as in any aspect and embodiment here.}
\end{align*}
$$
In another embodiment, the GGA derivative utilized is of formula:

\[
\text{formula image}
\]

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

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

\[
\text{formula image}
\]

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

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

\[
\text{formula image}
\]

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

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

In another embodiment, \( R^1 \) and \( R^2 \) are independently \( \text{C}_1-\text{C}_6 \) alkyl. In another embodiment, \( R^1 \) and \( R^2 \) independently are methyl, ethyl, or isopropyl.

In another embodiment, \( R^1 \) and \( R^2 \) together with the carbon atom they are attached to form a \( \text{C}_5-\text{C}_7 \) cycloalkyl ring optionally substituted with 1-3 \( \text{C}_1-\text{C}_6 \) alkyl groups. In another embodiment, \( R^1 \) and \( R^2 \) together with the carbon atom they are attached to form a ring that is:

\[
\text{ring image}
\]

In another embodiment, \( R^3, R^4, \) and \( R^5 \) are independently \( \text{C}_1-\text{C}_6 \) 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, $R^1$, $R^2$, and $R^S$ are hydrogen. In another embodiment, $R^1$, $R^2$, and $R^S$ are methyl.


In another embodiment, $X$ is -O-. In another embodiment, $X$ is -NR$R^2$. In another embodiment, $X$ is or -CR$_2$R$R^2$.

In another embodiment, one of $R^24$ and $R^25$ is hydrogen. In another embodiment, one or both of $R^24$ and $R^25$ are C$_1$-C$_6$ alkyl. In another embodiment, one or both of $R^24$ and $R^25$ are C$_1$-C$_6$ alkyl, optionally substituted with an $R^{20}$ group, wherein $R^{20}$ is -C0$_2$H or an ester thereof, C$_1$-C$_6$ alkyl, C$_3$-C$_5$ cycloalkyl, C$_3$-C$_8$ heterocyclyl, C$_8$-C$_{10}$ aryl, or C$_2$-C$_{10}$ heteroaryl. In another embodiment, one or both of $R^24$ and $R^25$ are C$_3$-C$_{10}$ cycloalkyl. In another embodiment, one or both of $R^24$ and $R^25$ are C$_3$-C$_{10}$ cycloalkyl substituted with 1-3 alkyl groups. In another embodiment, one or both of $R^24$ and $R^25$ are C$_3$-C$_8$ heterocyclyl. In another embodiment, one or both of $R^24$ and $R^25$ are C$_5$-C$_{10}$ aryl. In another embodiment, one or both of $R^24$ and $R^25$ are C$_2$-C$_{10}$ heteroaryl. In another embodiment, $R^4$ and $R^S$ together with the nitrogen atom they are attached to form a 5-7 membered heterocycle.

In another embodiment, $R^{20}$ is -C0$_2$H or an ester thereof. In another embodiment, $R^{20}$ is C$_1$-C$_6$ alkyl. In another embodiment, $R^{20}$ is C$_3$-C$_{10}$ cycloalkyl. In another embodiment, $R^{20}$ is C$_3$-C$_9$ heterocyclyl. In another embodiment, $R^{20}$ is C$_6$-C$_{10}$ aryl. In another embodiment, $R^{20}$ is or C$_2$-C$_{10}$ heteroaryl.

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

![Diagram](image)

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 $\text{Ci-C}_6$ alkyl, or $R^1$ and $R^2$ together with the carbon atom they are attached to form a $\text{C}_5$-$\text{C}_7$ cycloalkyi ring optionally substituted with 1-3 $\text{Ci-C}_6$ alkyl groups;

each of $R^3$, $R^4$, and $R^5$ independently are hydrogen or $\text{C}_1$-$\text{C}_6$ alkyl;

$Q_3$ is $-\text{X-CO-NR}^5\text{R}^2$ or $-\text{X-SO}_2\text{N-R}^2\text{R}^5$;

$X$ is $-\text{O}$, $-\text{NR}^6$, or $-\text{CR}^8$;

$R^2$ is hydrogen or together with $R^2$ and $R^5$ and the intervening atoms form a 5-7 membered ring optionally substituted with 1-3 $\text{Ci-C}_6$ alkyl groups;

each $R^2$ and $R^5$ independently is hydrogen,

$\text{Ci-C}_e$ alkyl, optionally substituted with $-\text{CO}_2\text{H}$ or an ester thereof, C$3$-$\text{C}_{10}$ preferably $\text{C}_2$-$\text{C}_8$ cycloalkyi, $\text{C}_3$-$\text{C}_8$ heterocyclyl, $\text{C}_9$-$\text{Cl}_{10}$ aryl, or $\text{C}_2$-$\text{C}_{10}$ heteroaryl,

$\text{C}_3$-$\text{C}_8$ cycloalkyi,

$\text{C}_3$-$\text{C}_8$ heterocyclyl,

$\text{C}_6$-$\text{C}_{10}$ aryl, or

$\text{C}_2$-$\text{C}_{10}$ heteroaryl,

wherein each cycloalkyi, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 $\text{Ci-C}_6$ alkyl groups, or $R^2$ and $R^5$ together with the nitrogen atom they are attached to form a 5-7 membered heterocycle.

In another embodiment, provided herein are compounds of formula:

$$\begin{align*}
\text{N} & \text{O} \\
\text{R}^{25} & \text{R}^{24} \\
\text{m} & = 0, n = 1, R^{24} = \text{cyclohexyl, and } R^{25} = \text{methyl} \\
\text{m} & = 1, n = 1, R^{24} = \text{cyclohexyl, and } R^{25} = \text{methyl} \\
\text{m} & = 1, n = 2, R^{24} = \text{cyclohexyl, and } R^{25} = \text{methyl} \\
\text{m} & = 0, n = 1, R^{24} = \text{n-pentyl, and } R^{25} = \text{methyl} \\
\text{m} & = 1, n = 1, R^{24} = \text{n-pentyl, and } R^{25} = \text{methyl} \\
\text{m} & = 1, n = 2, R^{24} = \text{n-pentyl, and } R^{25} = \text{methyl}
\end{align*}$$

In another aspect, the GGA derivative utilized herein is of Formula III:
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 cycloalkyi 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;

R^30 is selected from the group consisting of:

when X^1 is bonded via a single bond, X^1 is -0-, -NR^31-, or -CR^32R^31-, and when X^1 is bonded via a double bond, X^1 is -CR^32-;

Y^1 is hydrogen, -OH or -O-R^30, Y^2 is -OH, -OR^11 or -NHR^12, or Y^1 and Y^2 are joined to form an oxo group (=0), an imine group (=NR^13), a oxime group (=N-OR^14), or a substituted or unsubstituted vinylidene (=CR^15R^17);

R^30 is Ci-C_6 alkyl optionally substituted with 1-3 alkoxy or 1-5 halo group, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_10 cycloalkyi, C_6-Ci_0 aryl, C_3-C_8 heterocyclyl, or C_2-Ci_0 heteroaryl, wherein each cycloalkyi 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 Ci-C_6 alkyl or nitro groups, or R^30 is -NR^34R^35;

R^31 is hydrogen or together with R^30 and the intervening atoms form a 5-7 membered ring optionally substituted with 1-3 Ci-C_6 alkyl groups;

each R^32 and R^33 independently are hydrogen, C_4-C_6 alkyl, -COR^31 or -CO_2R^31, or R^32 together with R^30 and the intervening atoms form a 5-7 membered cycloalkyi or heterocyclyl ring optionally substituted with oxo or 1-3 Ci-C_6 alkyl groups;

R^30 is C_4-C_6 alkyl;


R\textsuperscript{11} and R\textsuperscript{12} are independently C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{2}-Cl\textsubscript{10} cycloalkyl, -C0\textsubscript{2}R\textsuperscript{15}, or -CON(R\textsuperscript{15})\textsubscript{2}, or R\textsuperscript{10} and R\textsuperscript{11} together with the intervening carbon atom and oxygen atoms form a heterocycle optionally substituted with 1-3 C\textsubscript{2}-C\textsubscript{6} alkyl groups;

R\textsuperscript{13} is C\textsubscript{1}-C\textsubscript{6} alkyl or C\textsubscript{2}-Cl\textsubscript{10} cycloalkyl optionally substituted with 1-3 C\textsubscript{2}-C\textsubscript{6} alkyl groups;

R\textsuperscript{14} is hydrogen, C\textsubscript{2}-C\textsubscript{8} heterocyclyl, or C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted with a -C0\textsubscript{2}H or an ester thereof or a C\textsubscript{6}-C\textsubscript{10} aryl, C\textsubscript{2}-C\textsubscript{6} alkenyl, C\textsubscript{2}-Cl\textsubscript{10} cycloalkyl, or a C\textsubscript{2}-C\textsubscript{6} heterocyclyl, wherein each cycloalkyl, heterocyclyl, or aryl, is optionally substituted with 1-3 alkyl groups;

each R\textsuperscript{15} independently are hydrogen, C\textsubscript{3}-C\textsubscript{10} cycloalkyl, C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted with 1-3 substituents selected from the group consisting of -C0\textsubscript{2}H or an ester thereof, aryl, or C\textsubscript{3}-C\textsubscript{8} heterocyclyl, or two R\textsuperscript{15} groups together with the nitrogen atom they are bonded to form a 5-7 membered heterocycle;

R\textsuperscript{16} is hydrogen or C\textsubscript{1}-C\textsubscript{6} alkyl;

R\textsuperscript{17} is hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl substituted with 1-3 hydroxy groups, -CHO, or is C0\textsubscript{2}H or an ester thereof;

each R\textsuperscript{14} and R\textsuperscript{15} independently is hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl, optionally substituted with -C0\textsubscript{2}H or an ester thereof, C\textsubscript{2}-C\textsubscript{10} cycloalkyl, C\textsubscript{3}-C\textsubscript{8} heterocyclyl, C\textsubscript{6}-C\textsubscript{10} aryl, or C\textsubscript{2}-C\textsubscript{10} heteroaryl, or is C\textsubscript{3}-C\textsubscript{10} cycloalkyl, C\textsubscript{2}-C\textsubscript{8} heterocyclyl, C\textsubscript{6}-Cl\textsubscript{6} aryl, or C\textsubscript{2}-Cl\textsubscript{10} heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl groups, or R\textsuperscript{14} and R\textsuperscript{15} together with the nitrogen atom they are attached to form a 5-7 membered heterocycle; and

each R\textsuperscript{11} independently is C\textsubscript{1}-C\textsubscript{6} 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 (III) is of formula:

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{Q} \\
\end{array}
\]

wherein 0, R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, R\textsuperscript{4}, R\textsuperscript{5}, X\textsuperscript{1}, Y\textsuperscript{1}, and Y\textsuperscript{2} are defined as in any aspect or embodiment herein.

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

$$\begin{align*}
\text{R}_1 & \rightarrow \text{R}_2 \\
\text{R}_2 & \rightarrow \text{R}_3 \\
\text{R}_3 & \rightarrow \text{R}_4 \\
\text{R}_4 & \rightarrow \text{R}_5 \\
\text{R}_5 & \rightarrow \text{R}_3 \text{O}_4
\end{align*}$$

wherein $R_1, R_2, R_3, R_4, R_5$, and $O_4$ are defined as in any aspect and embodiment herein.

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

$$\begin{align*}
\text{R}_1 & \rightarrow \text{R}_2 \\
\text{R}_2 & \rightarrow \text{R}_3 \\
\text{R}_3 & \rightarrow \text{R}_4 \\
\text{R}_4 & \rightarrow \text{R}_5 \\
\text{R}_5 & \rightarrow \text{R}_3 \text{SO}_2
\end{align*}$$

wherein $R_1, R_2, R_3, R_4, m, n, X_1, \text{ and } R_5$ are defined as in any aspect and embodiment here.

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

$$\begin{align*}
\text{R}_1 & \rightarrow \text{R}_2 \\
\text{R}_2 & \rightarrow \text{R}_3 \\
\text{R}_3 & \rightarrow \text{R}_4 \\
\text{R}_4 & \rightarrow \text{R}_5 \\
\text{R}_5 & \rightarrow \text{R}_3 \text{NHR}_4
\end{align*}$$

wherein $R_1, R_2, R_3, R_4, m, n,$ and $R_4$ are defined as in any aspect and embodiment here.

In another embodiment, the GGA derivative utilized is of formula:
wherein \( R^1, R^2, R^3, R^4, R^5, m, n, \) and \( R^6 \) are defined as in any aspect and embodiment here.

In another embodiment, each \( R^1 \) and \( R^2 \) are \( \text{Cl-C}_6 \) alkyl. In another embodiment, each \( R^1 \) and \( R^2 \) are methyl, ethyl, or isopropyl. In another embodiment, \( R^3 \) and \( R^4 \) together with the carbon atom they are attached to form a 5-6 membered ring optionally substituted with 1-3 \( \text{Cl-C}_6 \) alkyl groups. In another embodiment, \( R^3 \) and \( R^4 \) together with the carbon atom they are attached to form a ring that is:

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

In another embodiment, \( R^3 \) and \( R^4 \) are \( \text{Cl-C}_6 \) alkyl. In another embodiment, one of \( R^3 \), \( R^5 \), and \( R^6 \) 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 \( R^6 \) are methyl.

In another embodiment, \( X^1 \) is 0. In another embodiment, \( X^1 \) is \(-\text{NR}^3 \). In another embodiment, \( R^1 \) is hydrogen. In another embodiment, \( R^1 \) together with \( R^0 \) and the intervening atoms form a 5-7 membered ring optionally substituted with 1-3 \( \text{Cl-C}_6 \) alkyl groups. In another embodiment, \( X^1 \) is \(-\text{CR}^3 \). In another embodiment, \( X^1 \) is \(-\text{CR}^3 \). In another embodiment, each \( R^3 \) and \( R^4 \) independently are hydrogen, \( \text{Cl-C}_6 \) alkyl, \(-\text{COR}^3 \), or \(-\text{CO}_2 \). In another embodiment, \( R^3 \) is hydrogen, and \( R^4 \) is hydrogen, \( \text{C}_2 \-\text{C}_6 \) alkyl, \(-\text{COR}^3 \), or \(-\text{CO}_2 \). In another embodiment, \( R^3 \) is hydrogen. In another embodiment, \( R^3 \) \( \text{C}_2 \-\text{C}_6 \) alkyl. In another embodiment, \( R^3 \) is methyl. In another embodiment, \( R^3 \) is \(-\text{CO}_2 \). In another embodiment, \( R^3 \) is \(-\text{COR}^3 \).

In another embodiment, \( R^3 \) together with \( R^0 \) and the intervening atoms form a 5-7 membered ring. In another embodiment, the moiety:

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

which is "QA" has the structure:
wherein R3 is hydrogen, C1-C6 alkyl, or -C0 \(_3\) \(_2\) and n is 1, 2, or 3. Within these embodiments, in certain embodiments, R3 is hydrogen or C1-C6 alkyl. In one embodiment, R3 is hydrogen. In another embodiment, R3 is C1-C6 alkyl.

In another embodiment, R30 is d-C6 alkyl. In another embodiment, R30 is methyl, ethyl, butyl, isopropyl, or tertiary butyl. In another embodiment, R30 is C1-C6 alkyl substituted with 1-3 alkoxy or 1-5 halo group. In another embodiment, R30 is alkyl substituted with an alkoxy group. In another embodiment, R30 is alkyl substituted with 1-5, preferably, 1-3, halo, preferably fluoro, groups.

In another embodiment, R30 is NR34R36. In a preferred embodiment, R36 is H. In a preferred embodiment, R34 is C1-C6 alkyl, optionally substituted with a group selected from the group consisting of -C0 \(_2\) \(_2\)H or an ester thereof, C3-C10 cycloalkyl, C3-C8 heterocyclyl, C6-C10 aryl, or C2-C8 heteroaryl. In another preferred embodiment, R34 is C3-C10 cycloalkyl, C2-C8 heterocyclyl, C6-C10 aryl, or C2-C8 heteroaryl. In a more preferred embodiment, R34 is C3-C8 cycloalkyl.

In another embodiment, R30 is C2-C6 alkenyl or C2-C6 alkynyl. In another embodiment, R30 is C2-C8 alkenyl. In another embodiment, R30 is C3-C10 cycloalkyl. In another embodiment, R30 is C3-C10 cycloalkyl substituted with 1-3 C1-C6 alkyl groups. In another embodiment, R30 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or adamantyl. In another embodiment, R30 is C6-C10 aryl or C2-C8 heteroaryl. In another embodiment, R30 is a 5-7 membered heteroaryl containing at least 1 oxygen atom. In another embodiment, R30 is C6-C10 aryl, C2-C8 heterocyclyl, or C2-C8 heteroaryl, wherein each aryl, heterocyclyl, or heteroaryl is optionally substituted with 1-3 C1-C6 alkyl groups.

In another embodiment, Y2 is -O-R. In another embodiment, Y1 and Y2 are joined to form =NR. In another embodiment, Y1 and Y2 are joined to form =NOR. In another embodiment, Y1 and Y2 are joined to form =CR. In another embodiment, Q4 is -CR33COR30. In another embodiment, R30 is C1-C6 alkyl optionally substituted with an alkoxy group. In another embodiment, R30 is C1-C6 cycloalkyl.
In another embodiment, R is hydrogen. In another embodiment, R is Cl-C₆ alkyl. In another embodiment, R is CO₂R. In another embodiment, R is COR. In another embodiment, R is C₇ cycloalkyl. In another embodiment, R is C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of -C₀₂H or an ester thereof, aryl, or C₃-C₈ heterocyclyl. In a preferred embodiment within these embodiments, R is Cl-C₆ alkyl.

In another embodiment, Q₄ is -O-CO-NHR. Within these embodiment, in another embodiment, R is Cl-C₆ alkyl, optionally substituted with -C₀₂H or an ester thereof, C₃-C₈ cycloalkyl, C₄-C₈ heterocyclyl, C₂-C₆ aryl, or C₂-C₆ heteroaryl. In yet another embodiment, R is C₇-C₈ cycloalkyl, C₃-C₈ heterocyclyl, C₂-C₁₀ aryl, or C₂-C₆ heteroaryl.

In another embodiment, R is Cl-C₆ alkyl optionally substituted with a -C₀₂H or an ester thereof or C₃-C₆ aryl optionally substituted with 1-3 alkyl groups. In another embodiment, R is C₂-C₆ alkynyl. In another embodiment, R is C₂-C₆ alkynyl. In another embodiment, R is C₇-C₈ cycloalkyl optionally substituted with 1-3 alkyl groups. In another embodiment, R is C₃-C₈ heterocyclyl optionally substituted with 1-3 alkyl groups.

In another embodiment, preferably, R is hydrogen. In another embodiment, R is Cl-C₆ alkyl optionally substituted with a -C₀₂H or an ester thereof. In another embodiment, R is Cl-C₆ alkyl substituted with 1-3 hydroxy groups. In another embodiment, R is Cl-C₆ alkyl substituted with 1 hydroxy group. In another embodiment, R is -CH₂OH.

In another embodiment, R and R together with the intervening carbon atom and oxygen atoms form a heterocycle of formula:

```
q
\[\text{O} \quad \text{R}_{36} \quad \text{O} \quad \text{p}\]
```

wherein q is 0 or 1, p is 0, 1, 2, or 3, and R is Cl-C₆ 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.

38
In one aspect, the GGA derivative utilized herein is of Formula (IV):

![Formula (IV)](image)

or a tautomer thereof, 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 \( \text{Ci-C}_6 \) 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 \( \text{Ci-C}_6 \) alkyl groups;
- each of \( R^3 \), \( R^4 \), and \( R^5 \) independently are hydrogen or \( \text{C}_1-\text{C}_6 \) alkyl, or \( R^5 \) and \( Q_5 \) together with the intervening carbon atoms form a 6 membered aryl ring, or a 5-8 membered cycloalkenyl ring, or a 5-14 membered heteroaryl or heterocycle, wherein each aryl, cycloalkenyl, heteroaryl, or heterocycle, ring is optionally substituted with 1-2 substituents selected from the group consisting of halo, hydroxy, oxo, \(-\text{N}(\text{R}^{40})_2\), and \( \text{C}_2-\text{C}_6 \) alkyl group;
- \( Q_5 \) is \(-\text{C}(=\text{O})\text{H}, \ -\text{C}_0\text{H}_2\text{H} \) or \(-\text{CH}=\text{CHC}_0\text{H}_2\text{H}, \) or a \( \text{C}_2-\text{C}_6 \) alkyl ester or acyl halide thereof, wherein the ester is optionally substituted with \(-\text{CO}-\text{phenyl}; \) a 6-10 membered aryl or a 5-14 membered heteroaryl or heterocycle containing up to 6 ring heteroatoms, wherein the heteroatom is selected from the group consisting of \( \text{O, N, S, and oxidized forms of N and S,} \) and further wherein the aryl, heteroaryl, or heterocyclic ring is optionally substituted with 1-3 substituents selected from the group consisting of:
  - hydroxy, oxo, \(-\text{N}(\text{R}^{40})_2\), \( \text{C}_1-\text{C}_6 \) alkoxy group, and \( \text{C}_1-\text{C}_6 \) alkyl group,
  - wherein the alkyl group is optionally substituted with 1-3 substituents selected from hydroxy, \( \text{NH}_2\), \( \text{C}_6-\text{C}_6 \) aryl, \(-\text{C}_0\text{H}_2\text{H} \) or an ester or an amide thereof,
  - a 5-9 membered heteroaryl containing up to 3 ring heteroatoms, wherein the heteroaryl is optionally substituted with 1-3 hydroxy, \(-\text{N}(\text{R}^{40})_2\), and \( \text{C}_1-\text{C}_6 \) alkyl group,
  - benzyl, and phenyl optionally substituted with 1-3 substituents selected from the group consisting of \( \text{C}_1-\text{C}_6 \) alkyl, \( \text{C}_1-\text{C}_6 \) alkoxy, hydroxy, and halo groups; and
  - wherein each \( \text{R}^{40} \) independently is hydrogen or \( \text{C}_1-\text{C}_6 \) 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 C₁-C₆ alkyl ester, which phenyl or alkyl group is optionally substituted with a
amino group. As used herein, an amide refers preferably to a moiety of formula -CON(R⁰)₂,
wherein R⁰ is defined as above.

In some embodiments, Q₄ 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.

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

\[
\begin{align*}
&\text{IV-A} \\
&\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
Q_5
\end{array}
\end{align*}
\]

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

\[
\begin{align*}
&\text{IV-B} \\
&\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
Q_5
\end{array}
\end{align*}
\]

wherein R¹, R², R³, R⁴, and Q₄ are defined as in any aspect and embodiment here.

In another embodiment, Q₅ is selected from the group consisting of:

\[
\begin{align*}
&\text{IV-A} \\
&\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
Q_5
\end{array}
\end{align*}
\]

wherein R¹ is Cl-C₆ alkyl, C₆-Cl₀ aryl, C₃-C₆ heteroaryl, C₂-C₆ heteroaryl, C₂-Cl₀ cycloalkyl, and
the alkyl group is optionally substituted with 1-3 Cl₀ aryl, C₃-C₆ heteroaryl, C₂-C₆ heteroaryl,
C₃-C₁₀ cycloalkyl groups, and the aryl, heteroaryl, heteroaryl, cycloalkyl groups are optionally substituted with 1-3 Cl-C₆ alkyl, C₂-C₆ alkoxy, halo, preferably chloro or
fluoro, C₆-C₁₀ aryl, C₃-C₆ heteroaryl, C₂-C₆ heteroaryl, C₃-C₁₀ cycloalkyl group.

In another embodiment, Q₅ is phenyl, optionally substituted as described herein. In another
embodiment, Q₅ is benzimidazole, benzindazole, and such other 5-6 fused 9-membered
bicyclic heteroaryl or heterocycle. In another embodiment, Q₅ is quinoline, isoquinoline,
and such other 6-6 fused 10 membered heteroaryl or heterocycle. In another embodiment,
is benzodiazepine or a derivative thereof, such as, a benzodiazepinone. Various benzodiazepine and derivatives thereof are well known to the skilled artisan.

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

In another embodiment, \( R_1^1 \) and \( R_2^2 \) are independently \( C_2^2-C_6^6 \) alkyl. In another embodiment, \( R_1 \) and \( R_2 \) independently are methyl, ethyl, or isopropyl.

In another embodiment, \( R_1^1 \) and \( R_2^2 \) together with the carbon atom they are attached to form a \( C_5^5-C_7^7 \) cycloalkyl ring optionally substituted with 1-3 \( C_1^1-C_6^6 \) alkyl groups. In another embodiment, \( R_1^1 \) and \( R_2^2 \) together with the carbon atom they are attached to form a ring that is:

\[
\begin{array}{c}
\text{(or)} \\
\text{(or)}
\end{array}
\]

In another embodiment, \( R_3^3, R_4^4, \) and \( R_5^5 \) are independently \( C_1^1-C_6^6 \) alkyl. In another embodiment, one of \( R_3^3, R_4^4, \) and \( R_5^5 \) are alkyl, and the rest are hydrogen. In another embodiment, two of \( R_3^3, R_4^4, \) and \( R_5^5 \) are alkyl, and the rest are hydrogen. In another embodiment, \( R_3^3, R_4^4, \) and \( R_5^5 \) are hydrogen. In another embodiment, \( R_3^3, R_4^4, \) and \( R_5^5 \) are methyl.

In another embodiment, utilized herein is a compound selected from the group consisting of:
wherein $R_1$ is defined as above.

In another aspect, GGA derivatives utilized herein are of formula (V):

\[
\begin{align*}
\text{or a pharmaceutically acceptable salt thereof, wherein} \\
m &\text{is O or 1;} \\
n &\text{is 0, 1, or 2;} \\
\text{each } R^1 \text{ and } R^2 \text{ independently are } C_2-C_6 \text{ alkyl, or } R^1 \text{ and } R^2 \text{ together with the carbon atom they are attached to form a } C_5-C_7 \text{ cycloalkyi ring optionally substituted with 1-3 } C_1-C_6 \text{ alkyl groups;} \\
\text{each of } R^3, R^4, \text{ and } R^5 \text{ independently is hydrogen or } C_2-C_6 \text{ alkyl;} \\
Q_6 &\text{is selected from the group consisting of:} \\
\text{when } X^2 \text{ is bonded via a single bond, } X^2 \text{ is } -0-, \text{ -NR}_2^2, \text{ or } -CR^2_2; \\
\text{and when } X^2 \text{ is bonded via a double bond, } X^2 \text{ is } -CR^3_3; \\
Y^1 &\text{is hydrogen, -OH or -OR};
\end{align*}
\]
Y^{22} is -OH, -OR^{56}, -NHR^{57}, or -O-CO-NR^{58}R^{59}, or Y^{1}_1 and Y^{22} are joined to form an oxo group (=O), an imine group (=NR^{50}), a oxime group (=N-OR^{51}), or a substituted or unsubstituted vinylidene (=CR^{63}R^{64});

R^{3}_1 is C_{1}-C_{6} alkyl, C_{2}-C_{6} alkynyl, C_{3}-C_{10} cycloalkyl, C_{5}-C_{6} heterocyclyl, C_{6}-C_{10} aryl, C_{2}-C_{10} heteroaryl, or -NR^{55}R^{56}, wherein each cycloalkyl or heterocyclyl is optionally substituted with 1-3 C_{2}-C_{6} alkyl groups, and wherein each aryl or heteroaryl is optionally substituted independently with 1-3 nitro and C_{1}-C_{6} alkyl groups;

R^{3}_2 is hydrogen or together with R^{6}_1 and the intervening atoms form a 5-7 membered ring optionally substituted with 1-3 C_{2}-C_{6} alkyl groups;

each R^{3}_3 and R^{4}_4 independently are hydrogen, C_{1}-C_{6} alkyl, -COR^{51}, -CO_{2}R^{51}, or -CONH R^{52}, or R^{53} together with R^{51} and the intervening atoms form a 5-7 membered cycloalkyl or heterocyclyl ring optionally substituted with 1-3 C_{1}-C_{6} alkyl groups;

R^{5}_5 is C_{1}-C_{6} alkyl;

each R^{6}_6 and R^{7}_7 independently are C_{1}-C_{6} alkyl, C_{3}-C_{10} cycloalkyl, -CO_{2}R^{52}, or -CON(R^{63})_{2}; or R^{55} and R^{56} together with the intervening carbon atom and oxygen atoms form a heterocycle optionally substituted with 1-3 C_{1}-C_{6} alkyl groups;

R^{8}_8 is: C_{3}-C_{10} cycloalkyl, C_{2}-C_{6} alkyl optionally substituted with -OH, CO_{2}H or an ester thereof, or C_{3}-C_{10} cycloalkyl;

R^{59}_9 is hydrogen or C_{2}-C_{6} alkyl;

R^{60}_0 is: C_{1}-C_{6} alkyl or C_{3}-C_{10} cycloalkyl optionally substituted with 1-3 C_{1}-C_{6} alkyl groups, or is:

R^{51}_1 is hydrogen, C_{2}-C_{6} heterocyclyl, or C_{1}-C_{6} alkyl optionally substituted with a -CO_{2}H or an ester thereof or a C_{5}-C_{10} aryl, C_{2}-C_{6} alkenyl, C_{2}-C_{6} alkynyl, C_{3}-C_{10} cycloalkyl, or a
C₃-C₈ heterocyclyl, wherein each cycloalkyi, heterocyclyl, or aryl, is optionally substituted with 1-3 alkyl groups;

each R₃₂ independently are hydrogen, C₃-C₆ cycloalkyi, C₅-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of -C₀₂H or an ester thereof, aryl, C₃-C₈ heterocyclyl, or two R₃₂ groups together with the nitrogen atom they are bonded to form a 5-7 membered heterocycle;

R₆₅ is hydrogen or C₁-C₆ alkyl;

R₆₄ is hydrogen, C₁-C₆ alkyl substituted with 1-3 hydroxy groups, -CHO, or is C₀₂H or an ester thereof;

one or both of R₆⁵ and R₆⁶ independently are hydrogen, C₁-C₆ alkyl, optionally substituted with -C₀₂H or an ester thereof, C₃-C₆ cycloalkyi, C₅-C₈ heterocyclyl, C₂-C₆ alkyl, or C₃-C₆ heteroaryl, or is C₃-C₁₀ cycloalkyi, C₅-C₈ heterocyclyl, C₆-C₁₀aryl, or CrC₁₀ heteroaryl, wherein each cycloalkyi, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl groups, or R₆⁵ and R₆⁶ together with the nitrogen atom they are bonded to form a 5-7 membered heterocycle, and if only one of R₆⁵ and R₆⁶ are defined as above, then the other one is

provided that, when X² is bonded via a single bond, and R₅³ or R₆⁴ is not -CON HRF₃², Y¹¹ and Y²² are joined to form an imine group (=NR₆⁰), and R⁰ is:

or Y²² is -O-CO-NR₅₈ R₅₉;

or provided that, when Q₆ is:
and \( R^{53} \) is not \(-\text{CONH}R^{82}, \) \( \gamma^{22} \) is \(-\text{O-CO-NR}^{58}R^{55}\); 
or provided that, when \( Q_6 \) is \(-\text{O-CO-NA}^{65}R^{66}\), then at least one of \( R^{65} \) and \( R^{66} \) is:

In one embodiment, the GGA derivative utilized are of formula:
In another aspect, the GGA derivatives useful herein are selected from:

\[
\begin{align*}
V & : \quad \frac{n}{2} = \text{-OH} \\
XIV & : \quad R = \text{-CH}_2\text{OH} \\
XI & : \quad R_7\text{CH}_2 = \text{C}_6\text{H}_5\text{COCH}_3 \\
V & : \quad -\text{CH}_2\text{CH}_2\text{OH} \\
\end{align*}
\]

In one embodiment, the compounds provided herein utilizes the compound of formula:

\[
\begin{align*}
\text{wherein } L \text{ is 0, 1, 2, or 3, and } R^{17} \text{ is } \text{CO}_2\text{H} \text{ or an ester thereof, or is } \text{-CH}_2\text{OH} \text{, or is a C}_{1-}C_{6} \text{ alkyl ester of } \text{-CH}_2\text{OH}.}
\end{align*}
\]

In another embodiment, examples of compounds utilized herein include certain compounds tabulated below. Compound ID numbers in Table 1 refer to synthetic schemes in Example 7.

<table>
<thead>
<tr>
<th>Compound ID (see Example 7)</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Structure 1]</td>
</tr>
<tr>
<td>2a</td>
<td>![Structure 2a]</td>
</tr>
<tr>
<td>2b</td>
<td>![Structure 2b]</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2l</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>4a</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>4b</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>4c</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>6a</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>6b</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7a</td>
<td><img src="image7" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7b</td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7c</td>
<td><img src="image9" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7d</td>
<td><img src="image10" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7e</td>
<td><img src="image11" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7f</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>7g</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7h</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7i</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7j</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7k</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7l</td>
<td><img src="image7" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7m</td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7n</td>
<td><img src="image9" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7o</td>
<td><img src="image10" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7p</td>
<td><img src="image11" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7q</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>---</td>
<td>----------------------------</td>
</tr>
<tr>
<td>7r</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7s</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7t</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7u</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7v</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7w</td>
<td><img src="image7" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7x</td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>7y</td>
<td><img src="image9" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>8j</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>----</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>8k</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>8l</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>8m</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>8n</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>8o</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9a</td>
<td><img src="image7" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9b</td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9c</td>
<td><img src="image9" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9d</td>
<td><img src="image10" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9e</td>
<td><img src="image11" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9f</td>
<td><img src="9f.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9g</td>
<td><img src="9g.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9h</td>
<td><img src="9h.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9i</td>
<td><img src="9i.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9j</td>
<td><img src="9j.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9k</td>
<td><img src="9k.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>10a</td>
<td><img src="10a.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>10b</td>
<td><img src="10b.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>10c</td>
<td><img src="10c.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>10d</td>
<td><img src="10d.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>10e</td>
<td><img src="10e.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10f</td>
<td><img src="image1" alt="Structure 10f" /></td>
</tr>
<tr>
<td>10g</td>
<td><img src="image2" alt="Structure 10g" /></td>
</tr>
<tr>
<td>10h</td>
<td><img src="image3" alt="Structure 10h" /></td>
</tr>
<tr>
<td>10i</td>
<td><img src="image4" alt="Structure 10i" /></td>
</tr>
<tr>
<td>10j</td>
<td><img src="image5" alt="Structure 10j" /></td>
</tr>
<tr>
<td>10k</td>
<td><img src="image6" alt="Structure 10k" /></td>
</tr>
<tr>
<td>10l</td>
<td><img src="image7" alt="Structure 10l" /></td>
</tr>
<tr>
<td>10m</td>
<td><img src="image8" alt="Structure 10m" /></td>
</tr>
<tr>
<td>12</td>
<td><img src="image9" alt="Structure 12" /></td>
</tr>
<tr>
<td>14</td>
<td><img src="image10" alt="Structure 14" /></td>
</tr>
<tr>
<td>15</td>
<td><img src="image11" alt="Structure 15" /></td>
</tr>
<tr>
<td>16</td>
<td><img src="image12" alt="Structure 16" /></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>17a</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>17b</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>17c</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>17d</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>17e</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>19</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>20a</td>
<td><img src="image7" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>20b</td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>20c</td>
<td><img src="image9" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>20d</td>
<td><img src="image10" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>20e</td>
<td><img src="image11" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>20f</td>
<td><img src="image12" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>20g</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td></td>
</tr>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>20h</td>
<td></td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>20i</td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>20j</td>
<td></td>
</tr>
<tr>
<td><img src="image4" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>23a</td>
<td></td>
</tr>
<tr>
<td><img src="image6" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>23b</td>
<td></td>
</tr>
<tr>
<td><img src="image7" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>23c</td>
<td></td>
</tr>
<tr>
<td><img src="image8" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>23d</td>
<td></td>
</tr>
<tr>
<td><img src="image9" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>23e</td>
<td></td>
</tr>
<tr>
<td><img src="image10" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>23f</td>
<td></td>
</tr>
<tr>
<td><img src="image11" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>23g</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>24</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>25</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>27a</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>27b</td>
<td><img src="image7" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>27c</td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>27d</td>
<td><img src="image9" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>27e</td>
<td><img src="image10" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>27f</td>
<td><img src="image11" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>27g</td>
<td><img src="image12" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>
In another embodiment, examples of compounds utilized herein include certain compounds
tabulated below.

| 37d | ![Image 37d] |
| 38a | ![Image 38a] |
| 38b | ![Image 38b] |
| 39  | ![Image 39]  |
| 40a | ![Image 40a] |
| 40b | ![Image 40b] |
| 41  | ![Image 41]  |
| 42  | ![Image 42]  |
| 43  | ![Image 43]  |
Table 2

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>![Structure 1]</td>
</tr>
<tr>
<td>52</td>
<td>![Structure 2]</td>
</tr>
<tr>
<td>54</td>
<td>![Structure 3]</td>
</tr>
<tr>
<td>55</td>
<td>![Structure 4]</td>
</tr>
<tr>
<td>56</td>
<td>![Structure 5]</td>
</tr>
<tr>
<td>57</td>
<td>![Structure 6]</td>
</tr>
<tr>
<td>58</td>
<td>![Structure 7]</td>
</tr>
<tr>
<td>59</td>
<td>![Structure 8]</td>
</tr>
<tr>
<td>60</td>
<td>![Structure 9]</td>
</tr>
<tr>
<td>61</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>62</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>63</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>64</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>65</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>66</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>67</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>68</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>69</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>70</td>
<td><img src="image" alt="Molecule 70" /></td>
</tr>
<tr>
<td>----</td>
<td>---------------------</td>
</tr>
<tr>
<td>71</td>
<td><img src="image" alt="Molecule 71" /></td>
</tr>
<tr>
<td>72</td>
<td><img src="image" alt="Molecule 72" /></td>
</tr>
<tr>
<td>73</td>
<td><img src="image" alt="Molecule 73" /></td>
</tr>
<tr>
<td>74</td>
<td><img src="image" alt="Molecule 74" /></td>
</tr>
<tr>
<td>75</td>
<td><img src="image" alt="Molecule 75" /></td>
</tr>
<tr>
<td>76</td>
<td><img src="image" alt="Molecule 76" /></td>
</tr>
<tr>
<td>77</td>
<td><img src="image" alt="Molecule 77" /></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>78</td>
<td>![Chemical Structure 1]</td>
</tr>
<tr>
<td>6979</td>
<td>![Chemical Structure 2]</td>
</tr>
<tr>
<td>80</td>
<td>![Chemical Structure 3]</td>
</tr>
<tr>
<td>81</td>
<td>![Chemical Structure 4]</td>
</tr>
<tr>
<td>82</td>
<td>![Chemical Structure 5]</td>
</tr>
<tr>
<td>83</td>
<td>![Chemical Structure 6]</td>
</tr>
<tr>
<td>84</td>
<td>![Chemical Structure 7]</td>
</tr>
<tr>
<td>85</td>
<td>![Chemical Structure 8]</td>
</tr>
<tr>
<td>86</td>
<td>![Chemical Structure 9]</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
</tr>
<tr>
<td>87</td>
<td><img src="image" alt="Structure 87" /></td>
</tr>
<tr>
<td>88</td>
<td><img src="image" alt="Structure 88" /></td>
</tr>
<tr>
<td>89</td>
<td><img src="image" alt="Structure 89" /></td>
</tr>
<tr>
<td>90</td>
<td><img src="image" alt="Structure 90" /></td>
</tr>
<tr>
<td>91</td>
<td><img src="image" alt="Structure 91" /></td>
</tr>
<tr>
<td>92</td>
<td><img src="image" alt="Structure 92" /></td>
</tr>
<tr>
<td>93</td>
<td><img src="image" alt="Structure 93" /></td>
</tr>
<tr>
<td>94</td>
<td><img src="image" alt="Structure 94" /></td>
</tr>
<tr>
<td>95</td>
<td><img src="image" alt="Structure 95" /></td>
</tr>
<tr>
<td>96</td>
<td><img src="image" alt="Structure 96" /></td>
</tr>
<tr>
<td>97</td>
<td><img src="image" alt="Structure 97" /></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>98</td>
<td><img src="image1" alt="Diagram" /></td>
</tr>
<tr>
<td>99</td>
<td><img src="image2" alt="Diagram" /></td>
</tr>
<tr>
<td>100</td>
<td><img src="image3" alt="Diagram" /></td>
</tr>
<tr>
<td>101</td>
<td><img src="image4" alt="Diagram" /></td>
</tr>
<tr>
<td>102</td>
<td><img src="image5" alt="Diagram" /></td>
</tr>
<tr>
<td>103</td>
<td><img src="image6" alt="Diagram" /></td>
</tr>
<tr>
<td>104</td>
<td><img src="image7" alt="Diagram" /></td>
</tr>
<tr>
<td>105</td>
<td><img src="image8" alt="Diagram" /></td>
</tr>
<tr>
<td>106</td>
<td><img src="image9" alt="Diagram" /></td>
</tr>
<tr>
<td>107</td>
<td><img src="image10" alt="Diagram" /></td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
</tr>
<tr>
<td>------</td>
<td>-------------------</td>
</tr>
<tr>
<td>108</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>109</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>110</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>111</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>112</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>113</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>114</td>
<td><img src="image7" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>115</td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>116</td>
<td><img src="image9" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>117</td>
<td><img src="image10" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>118</td>
<td>![Structure 118]</td>
</tr>
<tr>
<td>119</td>
<td>![Structure 119]</td>
</tr>
<tr>
<td>120</td>
<td>![Structure 120]</td>
</tr>
<tr>
<td>121</td>
<td>![Structure 121]</td>
</tr>
<tr>
<td>122</td>
<td>![Structure 122]</td>
</tr>
<tr>
<td>123</td>
<td>![Structure 123]</td>
</tr>
<tr>
<td>124</td>
<td>![Structure 124]</td>
</tr>
<tr>
<td>125</td>
<td>![Structure 125]</td>
</tr>
<tr>
<td>126</td>
<td>![Structure 126]</td>
</tr>
<tr>
<td>127</td>
<td>![Structure 127]</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
</tr>
<tr>
<td>---</td>
<td>--------------</td>
</tr>
<tr>
<td>128</td>
<td><img src="https://example.com/structure128.png" alt="Structure 128" /></td>
</tr>
<tr>
<td>129</td>
<td><img src="https://example.com/structure129.png" alt="Structure 129" /></td>
</tr>
<tr>
<td>130</td>
<td><img src="https://example.com/structure130.png" alt="Structure 130" /></td>
</tr>
<tr>
<td>131</td>
<td><img src="https://example.com/structure131.png" alt="Structure 131" /></td>
</tr>
<tr>
<td>132</td>
<td><img src="https://example.com/structure132.png" alt="Structure 132" /></td>
</tr>
<tr>
<td>133</td>
<td><img src="https://example.com/structure133.png" alt="Structure 133" /></td>
</tr>
<tr>
<td>134</td>
<td><img src="https://example.com/structure134.png" alt="Structure 134" /></td>
</tr>
<tr>
<td>135</td>
<td><img src="https://example.com/structure135.png" alt="Structure 135" /></td>
</tr>
<tr>
<td>136</td>
<td><img src="https://example.com/structure136.png" alt="Structure 136" /></td>
</tr>
<tr>
<td>137</td>
<td><img src="https://example.com/structure137.png" alt="Structure 137" /></td>
</tr>
</tbody>
</table>
Exemplary compounds include:
In certain aspects, the compound provided or utilized herein is of Formula (XVIII), (XIX) or (XX):

wherein

\( R^{95} \) is C5-C20 alkyl or C5-C20 alkenyl optionally substituted with 1-3 C6-C23 arylene groups in the chain and that is optionally substituted with 1-3 halo, trifluoromethyl, -OR\(^97\), -P(=0)(OR\(^8\))(OR\(^9\)) or -NR\(^0\)R\(^1\) groups;
R^{92} is (C_5-C_{30})alkyl or C_5-C_{30} alkenyl optionally substituted with 1-3 C_6-C_{20} aryl groups, which aryl group(s) are optionally substituted with 1-3 halo, trifluoromethyl, -OR, -P(=O)(OR^3_8) or -NR^3_9 groups; each R^93, R^94, R^95, and R^{96} is independently OH or C_i-C_6 alkoxy; each R^{97}, R^{98} and R^{99} is independently hydrogen, C_1-C_6 alkyi or C_6-C_{20} aryl; and each R^{100} and R^{101} is independently hydrogen, C_1-C_6 alkyi or C_6-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^{97}, R^{98}, R^{99}, R^{100} and R^{101} is optionally substituted with 1-3 C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_i-C_6 alkanoyloxy, C_1-C_6 alkoxy carbonyl, halo, cyano, nitro, carboxyl, trifluoromethyl, trifluoromethoxy, NR^{102}_1R^{103}_2, or S(O)^2R^{102}_1R^{103}_2 groups, wherein each R^{102}_1 and R^{103}_2 is independently hydrogen or C_i-C_6 alkyi; R^{104} and R^{105} are independently selected from the group consisting of hydrogen, C_i-C_6 alkyi, C_3-C_7 cycloalkyl, C_2-C_6 alkenyl, C_1-C_6 alkynyl, optionally substituted C_6-C_{20} aryi, optionally substituted C_{6-7} aryi, C_{1-6} alkoxy, optionally substituted heteroaryl and optionally substituted heteroaryl-C_i-C_6 alkyi, 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_i-C_6 alkyi, C_i-C_6 alkoxy, -NO_2, and -NR^1_9R^{101}_1 groups; or R^{104} and R^{105} together with the carbon atom they are attached to form a C_3-C_7 cycloalkyl ring optionally substituted with 1-3 C_1-C_6 alkyi groups; R^{106} and R^{107} independently are hydrogen or C_1-C_6 alkyi; each R^{108} and R^{109} are independently selected from the group consisting of a hydrogen, C_i-C_6 alkyi, and a group of Formula (XXI): 

![Formula (XXI)](image)

wherein R^{104}-R^{107} and n are as defined herein;
Y is -P(=0)(OR\(^{108}\))(OR\(^{109}\))\(-CO\(_2\)R\(^{110}\)) or -SO\(_2\)OR\(^{110}\), wherein R\(^{110}\) is selected from the group consisting of a hydrogen and C\(_2\)-C\(_6\) alkyl;

\[ Z_{\text{i}} = \frac{1}{2} \cdot A - N - (CH\(_2\))\(_r\) - \frac{1}{2} \]

wherein R\(^{111}\) is hydrogen or C\(_1\)-C\(_6\) alkyl; A is C\(_1\)-C\(_5\) alkylene which may have a substituent selected from -OH, halo, C\(_3\)-C\(_6\) alkyl, and C\(_2\)-C\(_6\) 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:

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

wherein R\(_{121}\) is a lower (e.g. C\(_i\)-C\(_6\)) alkyl group, optionally substituted with 1 to 4 substituents selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkoxy, halogenated lower alkyl, halogenated lower alkoxy, cyano; a 5- or 6-membered (hetero) aromatic ring which may be substituted by hydroxyl, lower alkyl, lower alkoxy, halogen, amino, lower alkylamino; 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\(_4\) alkyl groups

R\(_{126}\) is CH(O) or C\(_m\)H\(_{2m}\)-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\(_{27}\) - wherein R\(_{27}\) is hydrogen or a C\(_1\)-C\(_4\) alkyl group.

In one aspect, the GGA derivative utilized herein is of formula (XVIII):
In some embodiments, \( R_{0}^{10} \) and \( R_{101}^{10} \) 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.

In another aspect, the compound is of formula (XIX):

\[
\begin{align*}
\text{(XIX)}
\end{align*}
\]

wherein \( R_{104}^{10} \) and \( R_{105}^{10} \) each represent a hydrogen atom, a lower alkyl, cycloalkyl, alkenyl or alkynyl group, an aryl group which may be substituted, an arylalkyl group in which the aryl group may be substituted, or a heteroaryl or heteroarylalkyl group: \( R_{108}^{10} \) and \( R_{109}^{10} \) each represent a hydrogen atom, a lower alkyl group or an alkali metal; \( Y \) represents a group represented by the formula:

\[
\begin{align*}
\text{(XIXa)}
\end{align*}
\]

wherein \( R_{130}^{10} \) and \( R_{131}^{10} \) each represent a hydrogen atom, a lower alkyl group or an alkali metal or a group represented by the formula: \(-\text{C}^2\text{O}_{\alpha}R_{132}^{10}\) (wherein \( R_{132}^{10} \) represents a hydrogen atom, a lower alkyl group or an alkali metal); \( Z \) represents a group represented by the Formula: \(-\text{CH}_{2m}^n\) (wherein \( m \) is an integer of 0 to 3), a group represented by the formula: \(-\text{CH}_{2p}^q-\text{CH}=\text{CH}-\text{CH}_{2}^n\) (wherein \( p \) is 0 or 1 and \( q \) is 1 or 2) or a group represented by the Formula:

\[
\begin{align*}
\text{(XIXb)}
\end{align*}
\]

wherein \( R_{111}^{10} \) represents a hydrogen atom or a lower alkyl group; \( A \) represents an alkylene 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.

In further, provided herein is a compound is provided of Formula (XIX):

\[
\begin{align*}
\text{(XIX)}
\end{align*}
\]
or a pharmaceutically acceptable salt thereof,

wherein

R\textsuperscript{104} and R\textsuperscript{105} are independently selected from the group consisting of

- hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{7} cycloalkyl, C\textsubscript{2}-C\textsubscript{5} alkenyl, C\textsubscript{2}-C\textsubscript{5} alkynyl,
- optionally substituted C\textsubscript{6}-C\textsubscript{10} aryl, optionally substituted C\textsubscript{6}-C\textsubscript{10} aryl-C\textsubscript{6} alkyl, optionally substituted heteroaryl and optionally substituted heteroaryl C\textsubscript{1}-C\textsubscript{5} 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\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{2}-C\textsubscript{6} alkoxy, -NO\textsubscript{2}, and -NR\textsuperscript{100}R\textsuperscript{101} groups; or

R\textsuperscript{104} and R\textsuperscript{105} with the carbon atom they are attached to form a C\textsubscript{3}-C\textsubscript{7} cycloalkyl ring optionally substituted with 1-3 C\textsubscript{1}-C\textsubscript{5} alkyl groups;

R\textsuperscript{106} and R\textsuperscript{107} independently are hydrogen, methyl or C\textsubscript{2}-C\textsubscript{6} alkyl, provided that, when one of R\textsuperscript{108} and R\textsuperscript{109} is not:

and each of R\textsuperscript{106} and R\textsuperscript{107} is methyl, then R\textsuperscript{104} and R\textsuperscript{105} are defined as follows: R\textsuperscript{104} and R\textsuperscript{105} together with the carbon atom they are attached to form a C\textsubscript{5}-C\textsubscript{7} cycloalkyl optionally substituted with 1-3 C\textsubscript{1}-C\textsubscript{6} alkyl groups;

R\textsuperscript{108} and R\textsuperscript{109} are independently selected from the group consisting of a hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl and a group of Formula (XXI):
Y is -P(=0)(0R^{108})(0R^{109}) or
-CO2R^{110}, wherein R^{110} is selected from the group consisting of hydrogen and C1-C6 alkyl;

Z is
\[
\begin{array}{c}
\frac{1}{2} \cdot \text{A} \\
\text{N} \\
(\text{CH}_2)_r
\end{array}
\]

wherein R^{111} is hydrogen or C1-C6 alkyl; A is C1-C5 alkyne which may have a substituent selected from -OH, halo, C1-C6 alkyl, and C1-C6 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 further aspects, a composition is provided comprising the compound of Formula (II), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, provided that, when one of R^{108} and R^{109} is not:

and each of R^{106} and R^{107} is methyl, then R^{104} and R^{105} together with the carbon atom they are attached to form a C5-C7 cycloalkyl optionally substituted with 1-3 C1-C6 alkyl groups, and the other variables are defined as above.

In still further aspects, a method of: inhibiting neural death, increasing neural activity, and/or of reducing one or more negative effects of neurodegeneration, or treating osteopenia and/or reducing one or more negative effects of osteopenia is provided comprising administering the compound of Formula (XIX), a pharmaceutically acceptable salt thereof, or a composition comprising the compound of Formula (XIX) to a patient in need thereof, provided that, when one of R^{108} and R^{109} is not:
and each of R^1, R^4 and R^7 is methyl, then R^104 and R^105 together with the carbon atom they are attached to form a C₅-C₇ cycloalkyl optionally substituted with 1-3 C₄-C₆ alkyl groups,

In some embodiments the compound of formula (XVI) or (XIX) is selected from the group consisting of:
and the corresponding ethyl and other C1-C6 alkyl esters.


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 disclosure provided herein. As will also be understood, various mixtures of cis and trans forms of GGA and GGA derivatives are also useful in accordance with the disclosure provided herein. 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.

In another aspect provided herein are polyisoprenyl conjugates of bisphosphonate drugs useful for treating osteopenia including osteoporosis. Non-limiting examples of such drugs include those shown below.

Risedronic acid

Zoledronic acid

Alendronic acid

Nitrogenous Bisphosphonates

Etidronic Acid

Chlodronic Acid

Tiludronic Acid

Pharmaceutical Compositions

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

Sublingual Compositions

In one aspect, provided herein are GGA or GGA derivatives, such as those of Formulas (I) - (V) and sub-formulas thereof, that are therapeutically useful for sublingual delivery to a subject.

In another aspect, provided herein are GGA derivatives that are drug conjugates of GGA or drug conjugates of a GGA derivative, that are therapeutically useful for sublingual delivery to a subject.

In one embodiment of the present invention the sublingual dosage form comprises one or more fillers (e.g., soluble saccharides), binder, disintegrant and/or lubricant.
Exemplary and nonlimiting fillers include mannitol, lactose, xylitol and mixtures thereof which are preferred on account of their water solubility.

A binder may be employed, in a minimum quantity to prevent unnecessary reduction in the rate of dissolution. A preferred binder is gelatin although polyvinyl pyrrolidone or hydroxymethyl polyvinyl pyrrolidone may also be used. Preferred binders are soluble in water. Gelatin has been found to bind tablets of good quality which disintegrate within two minutes.

Suitable disintegrants include starches such as maize starch and rice starch, cross-linked N-vinyl-2-pyrrolidone (CLPVP), sodium starch glycolate, croscarmelose sodium and formaldehyde casein or combinations thereof. A preferred disintegrant is sodium starch glycolate.

Suitable lubricants include magnesium or calcium stearates or other long chain fatty acid salts. Magnesium stearate is especially preferred.

The pharmaceutical compositions herein can be formulated for sublingual administration.

Sublingual dosage forms include drops, gels, tablets, pills, powders, and oral liquids, including suspensions, solutions and emulsions. All sublingual 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). Rapid dissolution of the dosage form which is necessary to facilitate sublingual absorption may be achieved by selection of an appropriate method of dosage form (e.g., tablet) manufacture.

Tablets for sublingual delivery may also include conventional excipients. These may include flavouring agents, for example flavourings such as menthol, peppermint, vanilla or fruit flavourings. Sweeteners e.g., aspartame or sodium saccharinate may be used. Further excipients may also include colouring agents, preservatives and fillers.

The sublingual compositions are comprised of in general, GGA or a trans-isomer compound of GGA or a mixture thereof in combination with at least one pharmaceutically acceptable excipient for sublingual administration. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compounds provided and/or utilized herein. Such excipients may be any solid, liquid, or semi-solid excipient that is generally available to one of skill in the art. Sublingual pharmaceutical
compositions in accordance with the invention are prepared by conventional means using methods known 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 the sublingual preparations. Solutions can be prepared using water or physiologically compatible organic solvents such as ethanol, 1,2-propylene glycol, polyglycols, dimethylsulfoxide, 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.

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%.

Compounds and pharmaceutical compositions provided herein 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 provided and/or utilized herein 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. Such administration most advantageously proceeds by delivering both active ingredients simultaneously in a novel pharmaceutical composition in accordance with the present invention.
In some embodiments, a compound utilized herein can be used as an adjunct to conventional drug therapy.

In certain preferred embodiments, there is provided a pharmaceutical composition comprising the compound of Formula (XVIII), (XIX) or (XX) and α-tocopherol. A related embodiment provides for a pharmaceutical composition comprising the compound of Formula (XVIII), (XIX) or (XX), α-tocopherol, and hydroxypropyl cellulose. In another embodiment, there is provided a pharmaceutical composition comprising the compound of Formula (XVIII), (XIX) or (XX), α-tocopherol, and gum arabic. In a further embodiment, there is a pharmaceutical composition comprising the compound of Formula (XVIII), (XIX) or (XX), and gum arabic. In a related embodiment, there is provided the compound of Formula (XVIII), (XIX) or (XX), gum arabic and hydroxypropyl cellulose.

When α-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 α-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.

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.

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.

The concentration of the polyisoprenyl phosphonate derivative can be from about 1 to about 99% by weight in the pharmaceutical compositions provided herein. In certain embodiments, the concentration of the polyisoprenyl phosphonate 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%, or about 22%, or about 25%, or about 26%, or about 28%, or about 30%, or about 32%, or about 34%, or about 36%, or about 38%, or about 40%, or about 42%, or about 44%, or about 46%, or about 48%, or about 50%, or about 52%, or about 54%, or about 56%, or about 58%, or about 60%, or about 64%, or about 68%, or about 72%, or about 76%, or about 80% by weight.

In one embodiment, provided herein are sustained release formulations such as drug depots or patches comprising an effective amount of the polyisoprenyl phosphonate derivative. In another embodiment, the patch further comprises gum Arabic or hydroxypropyl cellulose separately or in combination, in the presence of alpha-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. The patch contains, in various embodiments, an amount of the polyisoprenyl phosphonate derivative, which is sufficient to maintain a therapeutically effective amount the polyisoprenyl phosphonate derivative in the plasma for about 12 hours.

Neural and Neurodegenerative Diseases

In certain embodiments, the methods described herein are suitable for the treatment of a neural disease selected from the group consisting of Alzheimer's disease, Parkinson's disease, multiple sclerosis, a prion disease amyotrophic lateral sclerosis, damage to the spinal cord, and neural death during an epileptic seizure.
Neurodegeneration is often the result of increased age, sporadic mutations, disease, and/or protein aggregation in neural cells. Neurodegenerative diseases are often characterized by a progressive neurodegeneration of tissues of the nervous system and a loss of functionality of the neurons themselves. One commonality seen in most neurodegenerative diseases is the accumulation of protein aggregates intracellular or in the extracellular space between neurons.

Protein aggregation is facilitated by partial unfolding or denaturation of cellular proteins. This may be due to mutations in the sequence of the DNA, transcriptional misincorporation, modifications to the RNA, and modifications or oxidative stress to the protein. There is an increasing amount of evidence to suggest that protein aggregates contribute to disease progression. In one study, aggregates of two non-disease proteins were formed in vitro and added to the medium of cultured cells. Addition of granular-structured, protein aggregates significantly reduced the cell viability of both the fibroblastic cell line (NIH-3T3) and neural cell line (PC12). However, addition of more organized fibrillar protein aggregates did not compromise the cell viability. (Bucciantini et al. (2002) Nature 14:507-510.)

Protein aggregates can be extracellular (i.e. in the space between neural cells), intracellular such as intranuclear (i.e. in the nucleus of the cell), or in the cytoplasm. Extracellular and/or cytoplasm protein aggregates are a pathological characteristic of Alzheimer’s disease (AD) and amyotrophic lateral sclerosis (ALS). AD is a progressive brain disease that destroys memory and cognitive function. AD has been linked to the aggregation of the β-amylloid peptide. The β-amylloid peptide is derived from the amyloid precursor protein (APP) that has been processed by two aspartyl proteases called β and γ secretases. Similar to AD, ALS is also a progressive neurodegenerative disease and is characterized by loss of functionality of motor neurons. The progressive degeneration of motor neurons results in loss of ability of the brain to initiate and control muscle movement. ALS is a devastating disease, in which the last stage is complete paralysis. The complete molecular mechanism of disease progression in ALS is not yet clear, but mutations in the Cu/Zn superoxide dismutase (Sod) gene, Sodl, have been linked to the degeneration of motor neurons. The disease symptoms of ALS and AD may differ, but the presence of cytotoxic aggregate proteins in both diseases suggests a common mechanism in pathogenicity. (Ross & Poirier. (2004) Nat Med. ppS10-S17; Irvine et al. (2008) Mol Med. 14(7-8):45 1-464; Wang et al. (2008) PLoS One Vol. 6, Issue
Recently, it was also found that depletion of the TDP-43 protein (TAR DNA binding protein or TARDBP) in Neuro-2a cells causes protein aggregation similar to what is observed in ALS. In fact, point mutations in TARDBP have been linked to familial and sporadic ALS. TDP-43 depletion by TARDBP siRNA in Neuro-2a cells also causes inhibition of the biological activity of the Rho family of small G proteins. Therefore, TDP-43 and Rho family proteins negatively affect protein aggregate formation in neural cells. The Rho family proteins are responsible for regulating cell movement, cell survival, cell growth, transcription, and motility of cells (Iguchi et al. 2009 J. Bio Chem. Vol. 284 no. 33 pp. 22059-22066). Therapies that prevent reduction in the amount and/or activity of TDP-43 or Rho family proteins may have a neuroprotective effect on cells.

Provided herein are methods for using the polyisoprenyl phosphonate derivative, or an isomer thereof for inhibiting neural death and increasing neural activity. For example, and without limitation, the invention provides methods for impeding the progression of neurodegenerative diseases or injury using the polyisoprenyl phosphonate derivative. The pharmaceutical compositions and/or compounds described above are useful in the methods described herein.

In one aspect, there are methods for increasing the axon growth of neurons by contacting said neurons with an effective amount of the polyisoprenyl phosphonate derivative. Neural diseases can result in an impairment of signaling between neurons. This can in part be due to a reduction in the growth of axonal projections. Contacting neurons with the polyisoprenyl phosphonate derivative enhances axonal growth. It is contemplated that the polyisoprenyl phosphonate derivative will restore 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.

Methods include the use of the polyisoprenyl phosphonate derivative. One embodiment is directed to a method for inhibiting the cell death of neurons susceptible to neuronal cell death, which method comprises contacting said neurons with an effective amount of the polyisoprenyl phosphonate derivative. Neurons susceptible to neuronal cell death include those that have the characteristics of a neurodegenerative 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 the polyisoprenyl phosphonate derivative 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 an effective amount of the polyisoprenyl phosphonate derivative. The term "neurite" refers to both axons and dendrites. Neural diseases can result in an impairment of signaling between neurons. This can in part be due to a reduction in the growth of axonal and/or dendritic projections. It is contemplated that contacting neurons with the polyisoprenyl phosphonate derivative will enhance neurite growth, it is further contemplated that the polyisoprenyl phosphonate derivative will restore neurite grown 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 is directed to a method for increasing the expression and/or release of one or more neurotransmitters from a neuron by contacting said neurons with an effective amount of the polyisoprenyl phosphonate derivative. It is contemplated that contacting neurons with an effective amount of the polyisoprenyl phosphonate derivative will increase the expression level of one or more neurotransmitters. It is also contemplated that contacting neurons with the polyisoprenyl phosphonate derivative 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 is directed to a method for inducing synapse formation of a neuron by contacting said neurons with an effective amount of the polyisoprenyl phosphonate
derivative. 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 of the
polyisoprenyl phosphonate derivative will increase synapse formation in neurons that
otherwise experience reduced synapse formation as a result of neural disease.

Another embodiment is directed to a method for increasing electrical excitability of a
neuron by contacting said neurons with an effective amount of the polyisoprenyl
phosphonate derivative. Electrical excitation is one mode of communication among two or
more neurons. It is contemplated that contacting neurons with an effective amount of the
polyisoprenyl phosphonate derivative 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 administration of the polyisoprenyl
phosphonate derivative 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 an effective amount of the polyisoprenyl phosphonate derivative
to said patient.

Another embodiment 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 an amount of the polyisoprenyl
phosphonate derivative inhibitory to protein aggregate formation, provided that said
pathogenic protein aggregates are not related to SBMA. In one embodiment, the
pathogenic protein aggregates form between or outside of the neurons. In another
embodiment, the pathogenic protein aggregates form inside said neurons. In one
embodiment, 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 the polyisoprenyl phosphonate derivative will inhibit their death as measured by a MTT assay or other techniques commonly known to one skilled in the art.

Another embodiment 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 an amount of the polyisoprenyl phosphonate derivative that inhibits further pathogenic protein aggregation. In one embodiment, contacting said neurons and/or said pathogenic protein aggregates with an effective amount of the polyisoprenyl phosphonate derivative alters the pathogenic protein aggregates into a non-pathogenic form. Without being limited to any theory, it is contemplated that contacting the neurons and/or the pathogenic protein aggregates with the polyisoprenyl phosphonate derivative 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 the polyisoprenyl phosphonate derivative 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.

In yet another embodiment is directed to a method for protecting neurons from pathogenic intracellular protein aggregates which method comprises contacting said neurons with an amount of the polyisoprenyl phosphonate derivative which will inhibit further pathogenic protein aggregation 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 polyglutamines 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 with an effective amount of the polyisoprenyl phosphonate derivative will alter the pathogenic protein aggregate into a non-pathogenic form.

One embodiment is directed to a method of modulating the activity of G proteins in neurons which method comprises contacting said neurons with an effective amount of the polyisoprenyl phosphonate derivative. It is contemplated that contacting neurons with the polyisoprenyl phosphonate derivative will alter the sub-cellular localization, thus changing the activities of the G protein in the cell. In one embodiment, contacting neurons with the polyisoprenyl phosphonate derivative will enhance the activity of G proteins in neurons. It is contemplated that contacting the polyisoprenyl phosphonate derivative with neurons will increase the expression level of G proteins. It is also contemplated that contacting the polyisoprenyl phosphonate derivative with neurons 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.

One embodiment 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 an effective amount of the polyisoprenyl phosphonate derivative. 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 with the polyisoprenyl phosphonate derivative. It is further contemplated that the polyisoprenyl phosphonate derivative 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.

Another embodiment is directed to a method for inhibiting the neurotoxicity of β-amyloid peptide by contacting the β-amyloid peptide with an effective amount of the polyisoprenyl phosphonate derivative. In one embodiment the β-amyloid peptide is between or outside of neurons. In yet another embodiment, the β-amyloid peptide is part of the β-amyloid plaque. It is contemplated that contacting neurons with the polyisoprenyl phosphonate
derivative will result in solubilizing at least a portion of the β-amyloid peptide, thus
decreasing its neurotoxicity. It is further contemplated that the polyisoprenyl phosphonate
derivative 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 the polyisoprenyl phosphonate
derivative 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.

One embodiment 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 an amount of the polyisoprenyl
phosphonate derivative which will inhibit further pathogenic protein aggregation. 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.

Neural diseases such as AD and ALS disease have the common characteristic of protein
aggregates either inside neural cells in cytoplasm or in the extracellular space between two
or more neural cells. Provided herein are methods for using the polyisoprenyl phosphonate
derivative 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,

In one embodiment the mammal is a human afflicted with a neural disease. In one
embodiment, 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 the polyisoprenyl
phosphonate derivative 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 the polyisoprenyl phosphonate derivative 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 US 5851783 and US 7356521 both of which are incorporated herein by reference in their entirety.

In one embodiment 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 polyisoprenyl phosphonate derivative will prevent or inhibit the formation of extracellular or intracellular protein aggregates. It is also contemplated that the polyisoprenyl phosphonate derivative 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 US 6130048 and US 6391553 both of which are incorporated herein by reference in their entirety.

In another embodiment, the mammal is a laboratory research mammal such as a mouse. In one embodiment, the neural disease is ALS. One such mouse model for ALS is a transgenic mouse with a Sodl mutant gene. It is contemplated that the polyisoprenyl phosphonate derivative will enhance the motor skills and body weights when administered to a mouse with a mutant Sodl gene. It is further contemplated that administering a polyisoprenyl phosphonate derivative to this mouse will increase the survival rate of Sodl mutant mice. Motor skills can be measured by standard techniques known to one skilled in the art. Sodl mutant mice provide an accepted mouse model for modeling ALS in humans. Accordingly, method aspects of this disclosure relate to a method for prolonging the survival or reducing mortality of a subject with ALS, comprising administering a therapeutically effective amount of the polyisoprenyl phosphonate derivative.

In yet another embodiment, 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 administering the polyisoprenyl phosphonate derivative to a transgenic AD mouse will improve the learning and memory skills of said mouse. It is further
contemplated that the polyisoprenyl phosphonate derivative 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.

In one embodiment administering the polyisoprenyl phosphonate derivative to a mammal alters the pathogenic protein aggregate present into a non-pathogenic form. In another embodiment, administering the polyisoprenyl phosphonate derivative to a mammal will prevent pathogenic protein aggregates from forming.

Another aspect relates to a method for reducing seizures in a mammal in need thereof, which method comprises administering a therapeutically effective amount of the polyisoprenyl phosphonate derivative, 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 provided herein prevent neural death during epileptic seizures. The severity of the seizure can be measured by one skilled in the art.

In certain aspects, the methods described herein relate to administering the polyisoprenyl phosphonate derivative or the compositions of the polyisoprenyl phosphonate derivative in vitro. In other aspects the administration is in vivo. In yet other aspects, the in vivo administration is to a mammal. Mammals include but are not limited to humans and common laboratory research animals such as, for example, mice, rats, dogs, pigs, cats, and rabbits.

In certain aspects, a composition is provided for inhibiting neural death, increasing neural activity, and/or for reducing one or more negative effects of neurodegeneration. In one embodiment, the composition includes a compound of Formula (XVIII), (XIX) or (XX), or subformulas thereof, as defined herein. Preferred neural or a neurodegenerative diseases, and one or more negative effects of neurodegeneration treated or improved herein are described herein.
Assaying Compounds

There are multiple osteoclast culture systems or methods and bone formation assays that can be used successfully to screen potential anti-resorptive compounds provided or utilized herein. See, e.g., U.S. Pat. No. 6,080,779.

One osteoclast culture for use in screening is a neonatal mouse calvaria assay. Briefly, four days after birth, the front and parietal bones of neonatal mouse pups (e.g., ICR Swiss white mice) are removed by microdissection and split along the sagittal suture. The bones are then incubated in a specified medium, wherein the medium contains either test or control compounds. Following the incubation, the bones are removed from the media, and fixed in 10% buffered formalin, decalcified in EDTA, processed through graded alcohols, and embedded in paraffin wax. Sections of the calvaria are prepared and assessed using histomorphometric analysis of bone formation and bone resorption. Bone changes are measured on sections. Osteoblasts and osteoclasts are identified by their distinctive morphology.

In addition to this assay, the effect of compounds on murine calvarial bone growth can also be tested in vivo. In one such example of this screening assay, young male mice (e.g., ICR Swiss white mice), aged 4-6 weeks are employed, using 4-5 mice per group. Briefly, the test compound or the appropriate control is injected into subcutaneous tissue over the right calvaria of normal mice. The mice are sacrificed (after allowing for bone growth or loss to occur, e.g. on day 14), and net bone growth is measured by histomorphometric means. Bone samples are cleaned from adjacent tissues and fixed in 10% buffered formalin, decalcified, processed through graded alcohols, and embedded in paraffin wax. Sections of the calvaria are prepared, and representative sections are selected for histomorphometric assessment of the effects of bone formation and bone resorption. In one embodiment, sections are measured by using a camera lucida attachment to trace directly the microscopic image onto a digitizing plate. Bone changes are measured on sections over adjacent 1x1 mm fields on both the injected and noninjected sides of calvaria. New bone may be identified by those skilled in the art by its characteristic tinctorial features, and osteoclasts and osteoblasts may be identified by their distinctive morphology or other suitable marker recognized by the skilled artisan. Histomorphometry software (OsteoMeasure, Osteometrix,
Inc., Atlanta) can be used to process digitized input to determine cell counts and measure areas or perimeters.

Additional exemplary in vivo assays include dosing assays in intact animals, including dosing assays in acute ovariectomized (OVX) animals and assays in chronic OVX animals.

Prototypical dosing in intact animals may be accomplished by subcutaneous, intraperitoneal or oral administration, and may be performed by injection, sustained release or other delivery techniques. The time period for administration of test compound may vary (for instance, 14 days, 28 days, as well as 35 days or longer may be appropriate). As an example, in vivo oral or subcutaneous dosing assay may be performed as described: In a typical study, 70 three-month-old female Sprague-Dawley rats are weight-matched and divided into treatment groups, with at least several animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; a control group administered vehicle only; a PBS or saline-treated control group; and a positive group administered a compound known to enhance net bone formation. Three dosage levels of the test compound are administered to the remaining groups. Test compound, saline, and vehicle are administered (e.g. once per day) for a number of days (for instance at least 14 days, 28 days, or 35 days - wherein an effect is expected in the positive group). All animals are injected with calcein nine days and two days before sacrifice (to ensure proper labeling of newly formed bone). Weekly body weights are determined. At the end of the period of compound administration, the animals are weighed and bled by orbital or cardiac puncture. Serum calcium, phosphate, osteocalcin, and CBCs are determined. Both leg bones (femur and tibia) and lumbar vertebrae are removed, cleaned of adhering soft tissue, and stored in 70% ethanol or 10% formalin for evaluation, for instance as performed by peripheral quantitative computed tomography (pQCT; Ferretti, J. Bone, 17: 353S-364S, 1995), dual energy X-ray absorptiometry (DEXA; Laval-Jeantet A. et al., Calcif Tissue Intl, 56:14-18, 1995, and Casez J. et al., Bone and Mineral, 26:61-68, 1994) and/or histomorphometry. The effect of test compounds on bone remodeling or net bone formation, including bone loss and osteoclast function can thus be evaluated.

Test compounds can also be assayed in acute ovariectomized animals. Such assays may also include an estrogen-treated group as a control. An example of the test in these animals is briefly described: In a typical study, 80 three-month-old female Sprague-Dawley rats are
weight-matched and divided into treatment groups, with at least several animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; three control groups (sham OVX and vehicle only, OVX and vehicle only, and OVX and PBS only); and a control OVX group that is administered a compound known to block or reduce bone resorption or enhance bone formation (including an anti-resorptive or anabolic compound). Different dosage levels of the test compound are administered to remaining groups of OVX animals.

Since ovariectomy induces hyperphagia, all OVX animals are pair-fed with sham OVX animals throughout the study. Test compound, positive control compound, PBS or saline or vehicle alone is administered orally or subcutaneously (e.g., once per day) for the treatment period. As an alternative, test compounds can be formulated in implantable pellets that are implanted, or may be administered orally, such as by gastric gavage. All animals are injected with calcein nine days and two days before sacrifice. Weekly body weights are determined. At the end of the treatment cycle, the animals blood and tissues are processed as described above.

Test compounds may also be assayed in chronic OVX animals. Briefly, six month old female Sprague-Dawley rats are subjected to sham surgery (sham OVX), or ovariectomy (OVX) at the beginning of the experiment, and animals are sacrificed at the same time to serve as baseline controls. Body weights are monitored weekly. After approximately six weeks or more of bone depletion, sham OVX and OVX rats are randomly selected for sacrifice as depletion period controls. Of the remaining animals, 10 sham OVX and 10 OVX rats are used as placebo-treated controls. The remaining animals are treated with 3 to 5 doses of test compound for a period of 35 days. As a positive control, a group of OVX rats can be treated with a known anabolic or anti-resorptive agent in this model, such as bisphosphonate, a calcitonin, a calcitriol, an estrogen, selective estrogen receptor modulators (SERM's) and a calcium source, a supplemental bone formation agent parathyroid hormone (PTH) or its derivative (Kimmel et al., Endocrinology, 132: 1577-1584, 1993), PTHRP, a bone morphogenetic protein, osteogenin, NaF, PGE2 agonists, a statin, and a RANK ligand (RANKL), including an osteogenic form of RANKL such as GST-RANKL or other oligomerized form of RANKL. At the end of the experiment, the animals are sacrificed and femurs, tibiae, and lumbar vertebral to 4 are excised and collected. The proximal left and right tibiae are
used for pQCT measurements, cancellous bone mineral density (BMD), and histology, while the midshaft of each tibia is subjected to cortical BMD or histology. The femurs are prepared for pQCT scanning of the midshaft prior to biomechanical testing. With respect to lumbar vertebrae (LV), LV2 are processed for BMD (pQCT may also be performed), LV3 are prepared for undecalcified bone histology, and LV4 are processed for mechanical testing.

In addition, osteoclast cultures, containing macrophages, osteoclast precursors and osteoclasts, can be generated from bone marrow precursors, particularly from bone marrow macrophages and utilized in assessment of compounds for osteoclast modulating activity. Bone marrow macrophages are cultured in 48- or 96-well cell culture dishes in the presence of M-CSF (IOng/ml), RANKL (IOng/ml), with or without addition of compound(s) or control(s), and medium changed (e.g. on day 3). Osteoclast-like cells are characterized by staining for tartrate-resistant acid phosphatase (TRAP) activity. In assessing bone resorption, for instance using a pit assay, osteoclasts are generated on whale dentin slices from bone marrow macrophages. After three days of culture to generate osteoclasts, compound(s) or control(s) are added to the culture for two days. At the end of the experiment, cells are TRAP stained and photographed to document cell number. Cells are then removed from the dentin slices with 0.5M ammonium hydroxide and mechanical agitation. Maximum resorption lacunae depth is measured using a confocal microscope (Microradiance, Bio-Rad Laboratories, Hercules, CA). For evaluation of pit number and resorbed area, dentin slices are stained with Coumassie brilliant blue and analyzed with light microscopy using Osteomeasure software (Osteometries, Decatur, Georgia) for quantitation.

In a further method, osteoclast modulating ability of GGA and derivatives can be tested in an in vitro assay utilizing osteoclasts, osteoclast precursor cells or osteoclast-like cells. General protocols for treatment of osteoclasts with a compound are well established and known in the art. For instance, bone marrow macrophages may be utilized to generate osteoclasts in vitro as described herein. It is to be noted that the conditions used will vary according to the cell lines and compound used, their respective amounts, and additional factors such as plating conditions and media composition. Such adjustments are readily determined by one skilled in this art.

Synthetic Methods
The compounds utilized herein can be prepared following synthetic methods comprising one or more of the following steps:

(i) reacting a compound of formula III under halogenation conditions to provide a compound of formula IX:

(ii) reacting the compound of formula IX with alkyl acetoacetate under alkylation conditions to provide a compound of formula X, where the stereochemistry at sterogenic center can be a racemic, R or S configuration:

(iii) reacting the compound of formula V under hydrolysis and decarboxylation conditions to provide a compound of formula XI:

(iv) reacting the compound of formula XI with a compound of formula XII:

wherein \( R_{74}, R_{75}, R_{85} \) and each \( R_{86} \) independently are alkyl or substituted or unsubstituted aryl, under olefination conditions to selectively provide a compound of formula XIII:
(v) reacting the compound of formula XIII under reduction conditions to provide a compound of formula XIV

\[
\text{XIV}
\]

Compound VIII is combined with at least an equimolar amount of a halogenating agent typically in an inert solvent. As used in this application, an "inert solvent" is a solvent that does not react under the reaction conditions in which it is employed as a solvent. The reaction is typically run at a temperature of about 0°C to 20°C for a period of time sufficient to effect substantial completion of the reaction. Suitable solvents include, by way of example only, diethyl ether, acetonitrile, and the like. Suitable halogenating agents include PBr₃ or PPH₃/CBr₄. After reaction completion, the resulting product, compound IX, can be recovered under conventional conditions such as extraction, precipitation, filtration, chromatography, and the like or, alternatively, used in the next step of the reaction without purification and/or isolation.

Compound IX is combined with at least an equimolar amount of an alkyl acetoacetate, in the presence of a base and an inert solvent. The reaction is typically run initially at 0°C, and then warmed up to room temperature for a period of time sufficient to effect substantial completion of the reaction. Suitable solvents include, by way of example only, various alcohols, such as ethanol, dioxane, and mixtures thereof. Suitable bases include, by way of example only, alkali metal alkoxides, such as sodium ethoxide.

Compound X is reacted with at least an equimolar amount, preferably, an excess of aqueous alkali. The reaction is typically run at about 40 to 80°C and preferably about 80°C for a period of time sufficient to effect substantial completion of the reaction. Suitable solvents include, by way of examples only, alcohols, such as methanol, ethanol, and the like.

Compound XI is combined with at least an equimolar amount, preferably, an excess of a compound of formula XII, and at least an equimolar amount, preferably, an excess of base, in an inert solvent. The reaction is typically run, initially at about -30°C for about 1-2 hours, and at room temperature for a period of time sufficient to effect substantial completion of the reaction. Suitable solvents include, by way of examples only tetrahydrofuran, dioxane, and the like. Suitable bases include, by way of example only, alkali metal hydrides, such as
sodium hydride, or potassium hexamethyldisilazide (KHMDS), or potassium tertiary butoxide CBuOK).

Compound XIII is combined with a reducing agent in an inert solvent. The reaction is typically run at about 0°C for about 15 minutes, and at room temperature for a period of time sufficient to effect substantial completion of the reaction. Suitable reducing agents include, without limitation, LiAlH₄. Suitable solvents include, by way of examples only diethyl ether, tetrahydrofuran, dioxane, and the like.

As will be apparent to the skilled artisan, after reaction completion, the resulting product, can be recovered under conventional conditions such as precipitation, filtration, chromatography, and the like, or alternatively, used in the next step of the reaction without purification and/or isolation.

In some embodiments, the method further comprises repeating steps (i), (ii), and (iii) sequentially with compound of formula XIII to provide the compound of formula VI-B, wherein m is 2.

\[
\text{VI-B}
\]

In another embodiment, the method or procedure further comprises repeating steps (i), (ii), (iii), (iv), and (v), sequentially, 1-3 times.

In another of its synthetic method aspects, there is provided a method comprising one or more of the following steps:

(i) reacting a compound of formula VIII-B:

\[
\text{VIII-B}
\]

wherein m is 1-3, under halogenation conditions to provide a compound of formula IX-B:

\[
\text{IX-B}
\]
(ii) reacting the compound of formula IX-B with alkyl acetoacetates, under alkylating conditions to provide a compound of formula X-B, where the stereochemistry at sterogenic center can be a racemic, R or S configuration:

\[ \text{X-B} \]

wherein \( R^1 \) alkyl is substituted or unsubstituted alkyl.

(iii) reacting a compound of formula X-B under hydrolysis and decarboxylation conditions to provide a compound of formula XI-B:

\[ \text{XIB} \]

The method can comprise step (i) or step (ii) or steps (i) + (ii):  

(i) reacting a compound of formula XV-C:

\[ \text{XV-C} \]

with alkyl acetoacetate under alkylating conditions to provide a compound of formula XVI-C, where the stereochemistry at sterogenic center can be a racemic, R or S configuration:

\[ \text{XVI-C} \]

wherein \( R_{31} \) is as defined herein, and

(ii) reacting the compound XVI-C obtained under hydrolysis and decarboxylation conditions to provide a compound of formula VII:

\[ \text{VII} \]
As will be apparent to the skilled artisan, the various reaction steps leading to compound XI-B or to the 5Z isomer are performed in the manner described hereinabove. In another of its synthetic method aspects, the method comprises reacting a ketal compound of formula XVII:

wherein each $R_{70}$ independently is C1-C6 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, C1-C6 alkyl groups, under hydrolysis conditions to provide a compound of formula II,

The ketal is combined with at least a catalytic amount, such as, 1-20 mole% of an aqueous acid, preferably, an aqueous mineral acid in an inert solvent. The reaction is typically run about 25°C to about 80°C, for a period of time sufficient to effect substantial completion of the reaction. Suitable acids include, without limitation, HCl, H2SO4, and the like. Suitable solvents include alcohols, such as methanol, ethanol, tetrahydrofuran, and the like.

In another embodiment, the method comprises reacting a compound of formula XVI:

under hydrolysis and subsequently decarboxylation conditions to form a compound of formula I:

Alternatively, reacting compound of formula XII with XV followed by in situ hydrolysis and decarboxylation of compound with formula XVI can afford the compound of formula VI.
In another embodiment, the method comprises reacting a compound of formula XVI-C:

\[ \text{XVI-C} \]

under hydrolysis and subsequent decarboxylation conditions to form the compound of formula VII:

\[ \text{VII} \]

Hydrolysis and decarboxylation conditions useful in these methods will be apparent to the skilled artisan upon reading this disclosure.

It will also be apparent to the skilled artisan that the methods further employ routine steps of separation or purification to isolate the compounds, following methods such as chromatography, distillation, or crystallization.

**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 is 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, \(^1\)H-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 herein are synthesized, e.g., from a compound of formula (III-A):
wherein \( n \), \( R - R^5 \) and \( L \) 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. No. WO 2012/031028, WO 2013/052148, 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 (viii) is reduced, for example with LiAlH\(_4\), to provide alcohol (ix).
As will be apparent to the skilled artisan, a compound of Formula (III), where \( n = 2 \), is synthesized by repeating the reaction sequence of alkylation with a beta-keto ester, hydrolysis, decarboxylation, Wittig-Horner olefination, and UAIH₄ reduction.

Certain illustrative and non-limiting synthesis of compounds utilized herein are schematically shown below. Compounds where \( Q^1 \) is -(C=S)- or \(-S0₂^-\) are synthesized by substituting the carbonyl group of the reactants employed, as will be apparent to the skilled artisan.

\( R^6 \) in the schemes below may also correspond to \( R^{10} \) and \( R^{14} \) as defined herein. \( R^7 \) in the schemes below may also correspond to \( R^{16} \), \( R^{11} \) and \( R^{15} \) as defined herein. \( R^8 \) in the schemes below may also correspond to \( R^{17} \), \( R^{12} \) and \( R^{16} \) as defined herein. \( R^9 \) in the schemes below may also correspond to \( R^{18} \), \( R^{13} \) and \( R^{17} \) as defined herein. \( R^{10} \) in the schemes below may also correspond to \( R^{16} \) as defined herein. \( R^{11} \) in the schemes below may also correspond to \( R^{20} \) as defined herein. \( R^{12} \) in the schemes below may also correspond to \( R^{21} \), \( R^{17} \) and \( R^{20} \) as defined herein.

\( R^{13} \) in the schemes below may also correspond to \( R^{22} \), \( R^{18} \) and \( R^{21} \) as defined herein. \( R^{14} \) in the schemes below may also correspond to \( R^{23} \), \( R^{19} \) and \( R^{22} \) as defined herein. \( R^{15} \) in the schemes below may also correspond to \( R^{24} \), \( R^{20} \) and \( R^{23} \) as defined herein. \( R^{16} \) in the schemes below may also correspond to \( R^{25} \), \( R^{21} \) and \( R^{24} \) as defined herein. \( R^{17} \) in the schemes below may also correspond to \( R^{26} \), \( R^{22} \) and \( R^{25} \) as defined herein. \( R^{18} \) in the schemes below may also correspond to \( R^{27} \), \( R^{23} \) and \( R^{26} \) as defined herein. \( R^{19} \) in the schemes below may also correspond to \( R^{28} \), \( R^{24} \) and \( R^{27} \) as defined herein. \( R^{20} \) in the schemes below may also correspond to \( R^{29} \), \( R^{25} \) and \( R^{28} \) as defined herein. \( R^{21} \) in the schemes below may also correspond to \( R^{30} \), \( R^{26} \) and \( R^{29} \) as defined herein. \( R^{22} \) in the schemes below may also correspond to \( R^{31} \), \( R^{27} \) and \( R^{30} \) as defined herein. \( R^{23} \) in the schemes below may also correspond to \( R^{32} \), \( R^{28} \) and \( R^{31} \) as defined herein. \( R^{24} \) in the schemes below may also correspond to \( R^{33} \), \( R^{29} \) and \( R^{32} \) as defined herein. \( R^{25} \) in the schemes below may also correspond to \( R^{34} \), \( R^{30} \) and \( R^{33} \) as defined herein. \( R^{26} \) in the schemes below may also correspond to \( R^{35} \), \( R^{31} \) and \( R^{34} \) as defined herein. \( R^{27} \) in the schemes below may also correspond to \( R^{36} \), \( R^{32} \) and \( R^{35} \) as defined herein. \( R^{28} \) in the schemes below may also correspond to \( R^{37} \), \( R^{33} \) and \( R^{36} \) as defined herein. \( R^{29} \) in the schemes below may also correspond to \( R^{38} \), \( R^{34} \) and \( R^{37} \) as defined herein. \( R^{30} \) in the schemes below may also correspond to \( R^{39} \), \( R^{35} \) and \( R^{38} \) as defined herein. \( R^{31} \) in the schemes below may also correspond to \( R^{40} \), \( R^{36} \) and \( R^{39} \) as defined herein. \( R^{32} \) in the schemes below may also correspond to \( R^{41} \), \( R^{37} \) and \( R^{40} \) as defined herein. \( R^{33} \) in the schemes below may also correspond to \( R^{42} \), \( R^{38} \) and \( R^{41} \) as defined herein. \( R^{34} \) in the schemes below may also correspond to \( R^{43} \), \( R^{39} \) and \( R^{42} \) as defined herein. \( R^{35} \) in the schemes below may also correspond to \( R^{44} \), \( R^{40} \) and \( R^{43} \) as defined herein. \( R^{36} \) in the schemes below may also correspond to \( R^{45} \), \( R^{41} \) and \( R^{44} \) as defined herein. \( R^{37} \) in the schemes below may also correspond to \( R^{46} \), \( R^{42} \) and \( R^{45} \) as defined herein. \( R^{38} \) in the schemes below may also correspond to \( R^{47} \), \( R^{43} \) and \( R^{46} \) as defined herein. \( R^{39} \) in the schemes below may also correspond to \( R^{48} \), \( R^{44} \) and \( R^{47} \) as defined herein. \( R^{40} \) in the schemes below may also correspond to \( R^{49} \), \( R^{45} \) and \( R^{48} \) as defined herein. \( R^{41} \) in the schemes below may also correspond to \( R^{50} \), \( R^{46} \) and \( R^{49} \) as defined herein. \( R^{42} \) in the schemes below may also correspond to \( R^{51} \), \( R^{47} \) and \( R^{50} \) as defined herein. \( R^{43} \) in the schemes below may also correspond to \( R^{52} \), \( R^{48} \) and \( R^{51} \) as defined herein. \( R^{44} \) in the schemes below may also correspond to \( R^{53} \), \( R^{49} \) and \( R^{52} \) as defined herein. \( R^{45} \) in the schemes below may also correspond to \( R^{54} \), \( R^{50} \) and \( R^{53} \) as defined herein. \( R^{46} \) in the schemes below may also correspond to \( R^{55} \), \( R^{51} \) and \( R^{54} \) as defined herein. \( R^{47} \) in the schemes below may also correspond to \( R^{56} \), \( R^{52} \) and \( R^{55} \) as defined herein. \( R^{48} \) in the schemes below may also correspond to \( R^{57} \), \( R^{53} \) and \( R^{56} \) as defined herein. \( R^{49} \) in the schemes below may also correspond to \( R^{58} \), \( R^{54} \) and \( R^{57} \) as defined herein. \( R^{50} \) in the schemes below may also correspond to \( R^{59} \), \( R^{55} \) and \( R^{58} \) as defined herein. \( R^{51} \) in the schemes below may also correspond to \( R^{60} \), \( R^{56} \) and \( R^{59} \) as defined herein. \( R^{52} \) in the schemes below may also correspond to \( R^{61} \), \( R^{57} \) and \( R^{60} \) as defined herein. \( R^{53} \) in the schemes below may also correspond to \( R^{62} \), \( R^{58} \) and \( R^{61} \) as defined herein. \( R^{54} \) in the schemes below may also correspond to \( R^{63} \), \( R^{59} \) and \( R^{62} \) as defined herein. \( R^{55} \) in the schemes below may also correspond to \( R^{64} \), \( R^{60} \) and \( R^{63} \) as defined herein. \( R^{56} \) in the schemes below may also correspond to \( R^{65} \), \( R^{61} \) and \( R^{64} \) as defined herein. \( R^{57} \) in the schemes below may also correspond to \( R^{66} \), \( R^{62} \) and \( R^{65} \) as defined herein. \( R^{58} \) in the schemes below may also correspond to \( R^{67} \), \( R^{63} \) and \( R^{66} \) as defined herein. \( R^{59} \) in the schemes below may also correspond to \( R^{68} \), \( R^{64} \) and \( R^{67} \) as defined herein. L is a leaving group as known to one of ordinary skill in the art.
As shown above, R^E is alkyl.

Compound (ix) with alcohol functionality is an intermediate useful for preparing the compounds utilized in herein. Compound (x), where L is an R^8SO_2 group, is made by reacting compound (ix) with R^8SO_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 R^A*R^B 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).

The intermediates prepared above are converted to the compounds utilized in herein as schematically illustrated below:

As used herein, for example, and without limitation, m is 0 or 1 and R³-R⁵ 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 herein by reacting with suitable isocyanates or carbamoyl chlorides, which are prepared by art known methods. The thiocarbamates and thioureas utilized herein are prepared according to the methods described above and replacing the isocyanates or the carbamoyl chlorides with isothiocyanates (R¹⁸-N=C=S) or thiocarbamoyl chlorides (R¹⁸-NH-C(=S)Cl or R¹⁸R¹⁹N-C(=S)Cl). These and other compounds utilized herein 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

[Diagram of chemical structures]
utilized herein containing various $R^1R^3$ substituents are illustrated in the examples section and/or are well known to the skilled artisan.

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

Certain compounds utilized herein are obtained by reacting compound (x) with the anion $Q,(-)$, which can be generated by reacting the compound $QH$ with a base. Suitable nonlimiting examples of bases include hydroxide, hydride, amides, alkoxides, and the like. Various compounds utilized herein, 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.

Other methods for making the compounds utilized herein are schematically illustrated below:

The metallation is performed, by reacting the ketone with a base such as dimethyl anion, a hindered amide base such as diisopropylamide, or hexamethyldisilazide, along with the corresponding metal cation, $M$. The amino carbonyl chloride or the isocyanate is prepared,
for example, by reacting the amine \((R^4)_2\text{NH}\) with phosgene or an equivalent reagent well known to the skilled artisan.

\[
\begin{align*}
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{R}^5\text{R}^6 \quad & \quad \text{hydrolysis} \\
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{R}^5\text{R}^6 \quad & \quad \text{activation of } -\text{CO}_2\text{H} \text{ group;} \\
\text{R}^8\text{NH}_2 \quad & \\
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{R}^5\text{R}^6\text{CONHR}^8 \quad & 
\end{align*}
\]

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 0-Benzotriazole-N,N,N'-tetramethyl-uronium-hexafluoro-phosphate (HBTU) and reacted with the amine.

\[
\begin{align*}
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{R}^5\text{R}^6 \quad & \quad \text{R}^{13}\text{NH}_2/\text{dehydrating agent} \\
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{R}^5\text{R}^6 \quad & \quad \text{such as molecular sieves} \\
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{R}^5\text{R}^6 \quad & \quad \text{R}^{13} 
\end{align*}
\]

Various other compounds utilized herein are prepared from the compounds made in the scheme above based on art known methods,

\[
\begin{align*}
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{R}^5\text{R}^6 \quad & \quad \text{Hydrolysis} \\
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{R}^5\text{R}^6 \quad & \quad \text{R}^{13}\text{NH}_2 \quad \text{viii} \\
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{R}^5\text{R}^6 \quad & \quad \text{CO}_2\text{R}^8 \quad \text{x}
\end{align*}
\]

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

The intermediates prepared above are converted to the compounds utilized herein as schematically illustrated below:
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 hydroxylamine, an amino alcohol, or an amino acid, and the intermediate dehydrated to provide a compound of Formula (IV). Alternatively, the allylic alcohol (ix) is oxidized to the aldehyde (xi), which is then reacted with a cyanohydrin or cyanotosylmethane to provide further compounds utilized herein.

GGA derivatives utilized herein can also be synthesized employing art known methods and those disclosed here by alkene-aryl, alkene-heteroaryl, or alkene-alkene 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 herein.

\[
\begin{align*}
\text{Wittig olefination} & \\
\text{Heck/Stille/Suzuki coupling} & \\
\end{align*}
\]

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 herein.

Compounds utilized herein are also prepared as shown below

\[
\begin{align*}
\alpha^5\text{CH}_2\text{-L} & \xrightarrow{\text{PAR}_3} \quad \alpha^5\text{CH}_2\text{-PAR}_3(+)\text{L}(-) & \xrightarrow{\text{base}} & \quad \alpha^5\text{CH}^=\text{PAR}_3 \\
\end{align*}
\]

L is a leaving group and Qs are as defined herein, Ar is a preferably an aryl group such as phenyl, the base employed is an alkoxide such as tert-butoxide, 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 herein are schematically illustrated below:
The metallation is performed, by reacting the ketone with a base such as dimethyl anion, a hindered amide base such as diisopropylamide, or hexamethyldisilazide, along with the corresponding metal cation, M. The amino carboxyl chloride or the isocyanate is prepared, for example, by reacting the amine $R^1 R^4 NH$ 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 diimidazole, or 0-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.

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

**Synthesis of the Polyisoprenyl Phosphonate Derivatives**

The compounds can be synthesized following methods and/or modifications thereof well known in the art. See, for example, Fieser, Mary ed. *Fieser and Fieser's Reagents for Organic Synthesis*. Wiley, NY; Smith and March, *March's Advanced Organic Chemistry*, 6th Edition, John Wiley & Sons, Inc., New York, 2011; Larock, *Comprehensive Organic Transformations*, 2nd edition, VCH Publishers, Inc., New York, 1999; T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, 4th edition, John Wiley & Sons, 2006 and the likes. The starting materials are commercially available from Sigma Aldrich Company (St. Louis, MO) and such other commercial suppliers. It will also be apparent to the skilled artisan that the methods further employ routine steps of separation or purification to isolate the compounds, following methods such as chromatography, distillation, or crystallization.

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, $^1$H 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.
Specific non-limiting examples of bisphosphonate conjugates provided herein and their methods of synthesis are described below. Other such conjugates can be synthesized following adaptation of art known methods and those described herein.

Risedronic Acid
Z = protecting group
MOM ether of GG-alcohol

GG-alcohol - 1 conjugate
I
Alendronic Acid
Z = protecting group
1. carbonyl diimidazole
2. deprotect

GG-alcohol

GG-alcohol I conjugate

GG-acetone

GG-acetone-1 conjugate

Other such compounds having the:
moiety, instead of the polyprenyl moiety shown above, wherein the variables are defined as herein are also provided herein.

Examples of the Invention

The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses which are encompassed within the spirit of the invention as defined by the scope of the claims will occur to those skilled in the art.

In the examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

\[\begin{align*}
\circ^{\circ}\text{C} & = \text{degrees Celsius} \\
PBr_3 & = \text{phosphorus tribromide} \\
EE & = \text{ethyl ether} \\
EtOH & = \text{Ethanol} \\
NaOEt & = \text{sodium ethoxide} \\
oet & = \text{Ethoxide} \\
N & = \text{Normal} \\
KOH & = \text{potassium hydroxide} \\
aq & = \text{aqueous} \\
h & = \text{hour(s)} \\
RT & = \text{Room temperature} \\
LAH & = \text{lithium aluminum hydride} \\
THF & = \text{Tetrahydrofuran} \\
min & = \text{minute(s)} \\
Et & = \text{Ethyl} \\
MeOH & = \text{Methanol}
\end{align*}\]
NaH = sodium hydride
ON = Overnight
E or (E) = Trans
Z or (Z) = Cis
TLC = thin layer chromatography
GGA = geranylgeranyl acetone
µL = Microliter
mL = Milliliter
PK = negative logarithm of the dissociation constant K
HPC = hydroxypropyl cellulose
DI = Deionized
Mn = number average molar mass
Av = Average
p-TsOH = p-toluenesulfonic acid
Ph₃P = Triphenylphosphine
Br⁻ = bromide ion
CBr₄ = Tetrabromomethane
LC-MS = Liquid chromatography-mass spectrometry
Rf = retardation factor
PEG-200 = polyethylene glycol
KHMDA = potassium hexamethylenediamine
ACN = Acetonitrile
TBDMs = tert-butyldimethyl silyl
Kp = Ratio of AUCtissue to AUCplasma
AUC = Area Under the curve

**LC-MS Parameters for Analysis**

System: Agilent 1100 LC-MSD

Parameters:

*Sample Concentration:* 7.2 mg in 1.44 mL DMSO (5mg/mL). Dilute 10µL to 0.5
mL acetonitrile (100ug/mL)

**HPLC Column:** Xterra MS, C18, 50 x 2.1, 3.5 micron

**Column Temperature:** 40 oC

**Mobile Phase A:** 0.1% formic acid in water

**Mobile Phase B:** 0.1% formic acid in acetonitrile

**Flow Rate:** 0.3 mL/min

**Injection Volume:** 5 uL

**Gradient LC-MS:**

<table>
<thead>
<tr>
<th>time (min)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>25.1</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
</tr>
</tbody>
</table>

**MS Parameters:**

**Ion Source:** Electrospray

**Polarity:** Positive

**Mass Range:** 100 - 1000 amu

**Fragmentor:** 80

**Dry Gas:** 10 l/min

**Dry Gas temp:** 350 oC

**Vcap:** 4000

**Nebulizer Pressure:**

**Gain:** 5

The starting materials for the reactions described below are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis., USA), Bachem (Torrance, Calif., USA), Emka-Chemce or Sigma (St. Louis, Mo., USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-15 and Supplemental (Elsevier Science

Example 1: 5E,9E,13E-Geranylgeranyl Acetone Synthesis

Synthesis of S-rrcms-isomer: 5E,9E,13E-Geranylgeranyl acetone 1: The synthesis of S-trans isomer: 5E,9E,13E-geranylgeranyl acetone 1 can be achieved as per outlined in the scheme-1.

Scheme 1

The 2E,6E-farnesyl alcohol 3 (where the geometry at C2 and C6 positions is already fixed as trans- or E) was designed and used as a commercially available starting material for the synthesis of 5E,9E,13E-geranylgeranyl acetone 1. The alcohol function of 2E,6E-farnesyl alcohol 3 was converted to the corresponding bromide 4 by the treatment of phosphorus tribromide (PBr₃) in ethyl ether (EE) or with Ph₃P and CBr₄ in acetonitrile (ACN) at 0°C. The resulting bromide was then reacted with carbanion (derived from the reaction of ethyl
acetoacetate 5 and sodium ethoxide) to yield the desired 5E,9E-farnesyl ketoester 6. The homologated ketoester 6 after hydrolysis and decarboxylation using aqueous 5N KOH yielded the expected 5E,9E-farnesyl acetone 7. A one pot conversion of bromide 4 to the corresponding farnesyl acetone 7 can be possible without isolating intermediate ketoester 6.

In order to generate the trans-orientation of olefin at C2 of conjugated olefin 8 in a key step, the reaction of 5E,9E-farnesyl acetone 7 with carbanion [derived from the reaction of (EtO)2PO-CH2-COOEt and sodium hydride (NaH)] at -30°C was conducted to obtain the desired 2E,6E,10E-conjugated ester 8. The formation of the product 8 with the exclusive trans (E) geometry was observed when the reaction was conducted at -30°C or temperature below -30°C, where all the three olefins are set in a trans (E) orientation (Ref.: Kato et al., J. Org. Chem. 1980, 45, 1126-1130 and Wiemer et al., Organic Letters, 2005, 7(22), 4803-4806). The minor cis- (Z)-isomer was eliminated/separated from the trans- (E)-isomer 8 by a careful silica gel column chromatographic purification. However, it was also noted that the formation the corresponding c/s-isomer (Z) was increased when the reaction was conducted at 0°C or at higher temperature. It was also noted that the mixture of cis (2Z)- and trans (2E)- isomer of 8 can be separated by a very careful column chromatographic separation.

The resulting 2E-conjugated ester 8 was reduced to the corresponding 2E-alcohol 9 by means of a lithium aluminum hydride (LAH) treatment, which was then converted into the corresponding 2E,6E,10E-geranylgeranyl bromide 10 by means of phosphorus tribromide (PBr3) treatment in ethyl ether (EE) or with Ph3P and CBr4 in acetonitrile (ACN) at 0°C. Furthermore, the interaction of carbanion (derived from ethyl acetoacetate 5 and sodium ethoxide) with the bromide 10 at 0°C afforded the desired 2E,6E,10E-geranylgeranyl ketoester 11, a precursor needed for 5E,9E,13E-geranylgeranyl acetone 1. The subsequent ester hydrolysis and decarboxylation of ketoester 11 using aq. 5N KOH at 80°C yielded the requisite 5E,9E,13E-geranylgeranyl acetone 1. TLC Rf: 0.28 (5% Ethyl Acetate in Hexanes); LC Retention time: 16.68 min; MS (m/e): 313 [M - 18 + H]+, 331 [MH]+, 353 [M + K].
Example 2: 5-Z,9E,13E-Geranylgeranyl Acetone Synthesis

Scheme 2

The 2E,6E-farnesyl alcohol 3 (where the geometry at C2 and C6 positions is already fixed as trans- or E) was used as a commercially available starting material for the synthesis of 5Z,9E,13E-geranylgeranyl acetone 2. The reaction of farnesyl alcohol 3 with phosphorus tribromide (PBr$_3$) in ethyl ether (EE) or with Ph$_3$P and CBr$_4$ in acetonitrile (ACN) at 0°C afforded the requisite bromide 4, which was then reacted with carbanion (derived from the reaction of ethyl acetoacetate 5 and sodium ethoxide) to yield the desired 5E,9E-farnesyl ketoester 6. The homologated ketoester 6 after hydrolysis and decarboxylation using aqueous 5N KOH yielded the expected 5E,9E-farnesyl acetone 7, one of the key intermediate for the synthesis of 5E,9E,13E-geranylgeranyl acetone 1 and 5Z,9E,13E-geranylgeranyl acetone 2.

With a view to obtain product with c/s-geometry at C2 with the conjugated olefin 12, the reaction of 5E,9E-farnesyl acetone 7 with carbanion (derived from the reaction of (EtO)$_2$PO-
CH₂-CO₂Et and sodium hydride (NaH) at 0°C was conducted. This reaction afforded a mixture of 2E,6E,10E-conjugated ester 8 and 2Z,6E,10E-conjugated ester 12, from which the C2-cis (Z)-isomer 12 was separated by a repeated and careful silica gel column chromatography (Ref. Kato et al., J. Org. Chem., 1980, 45, 1126-1130).

The resulting 2Z-conjugated ester 12 was converted into the corresponding 2Z-alcohol 13 by means of a lithium aluminum hydride (LAH) treatment. The 2Z-alcohol 13 was transformed into the corresponding 2Z,6E,10E-geranylgeranyl bromide 14 by using phosphorus tribromide (PBr₃) treatment in ethyl ether (EE) or with Ph₃P and CBr₄ acetonitrile (ACN) at 0°C, and then reacted with carbanion (derived from ethyl acetoacetate 5 and sodium ethoxide) at 0°C afforded the desired 2Z,6E,10E-geranylgeranyl ketoester 15, a precursor needed for 5Z,9E,13E-geranylgeranyl acetone 2. The subsequent ester hydrolysis and decarboxylation of ketoester 15 using aq. 5N KOH at 80°C yielded the requisite 5Z,9E,13E-geranylgeranyl acetone 2.

**Example 3: 5Z,9E,13E-Geranylgeranyl Acetone Synthesis**

Alternative synthesis of 5-c/s Isomer: 5Z,9E,13E-Geranylgeranyl acetone 2: The alternative synthesis of 5Z,9E,13E-geranylgeranyl acetone 2 can be achieved as shown in the scheme-3.
The use of 5E,9E-farnesyl acetone 7, as a key intermediate, can be used to generate additional double bond with cis-(Z)-orientation. In one approach, the reaction of 5E,9E-farnesyl acetone 7 with the witting reagent 16 can afford the conjugated ester 12 with cis-(Z)-geometry at C2 position. The subsequent reduction of ester 12 with lithium aluminum hydride (LAH) can generate the corresponding alcohol 13, which then can be converted into the corresponding bromide 14. The conversion of bromide 14 to the ketoester 15 followed by hydrolysis and decarboxylation can afford the desired 5-cis (Z) isomer; 5Z,9E,13E-geranygeranyl acetone (2).

In an alternative approach, the reaction of 5E,9E-farnesyl acetone 7 with triphenyl methylphosphorane bromide 17 under a basic conditions followed by treatment with formaldehyde (monomeric) can afford the 2Z,6E,10E-geranylgeranyl alcohol 13 with cis (Z)-orientation at C2 (Ref.: Wiemer et al., Organic Letters, 2005, 7(22), 4803-4806). The
conversion of bromide 14 to the ketoester 15 followed by hydrolysis and decarboxylation can afford the desired 5-cis (Z)-isomer; 5Z,9E,13E-geranylgeranyl acetone (2). TLC Rf: 0.32 (5% Ethyl Acetate in Hexanes); LC: Retention time: 17.18 min; MS (m/e): 313 [M - 18 + H]+, 331 [MH, very weak ionization^], 339 [M - CH₂ + Na], 353 [M + K].

All the intermediate products were purified by silica gel column chromatography and then used in the next step, except the bromides 4, 10 and 14. Due to the unstable nature of bromides 4, 10 and 14 towards silica gel column chromatography, these bromides were used in the next step without purification. Alternatively, all the intermediate products shown in the schemes 1, 2 and 3 are liquids and therefore can be separated and purified by a distillation process under appropriate levels of vacuum. All the intermediates and final products were characterized by LC-MS for mass along with the Thin Layer Chromatography (TLC) for Rf values.

Example 4: 5-Z,9E,13E-Geranylgeranyl Acetone Synthesis

Alternative synthesis of 5-cis Isomer: 5Z,9E,13E-Geranylgeranyl acetone 2: The alternative synthesis of 5Z,9E,13E-geranylgeranyl acetone 2 can be achieved as shown in the scheme-4
The convergent synthesis of 5Z,9E,13E-GGA 2 has been shown in the above scheme and is outlined as follows.

The 2E,6E-farnesyl alcohol 3 (where the geometry at C2 and C6 positions is already fixed as trans- or E) was used as a commercially available starting material for the synthesis of 5Z,9E,13E-geranylgeranyl acetone 2. The reaction of farnesyl alcohol 3 with phosphorus tribromide (PBr₃) in ethyl ether (EE) or with Ph₃P and CBr₄ in acetonitrile (ACN) at 0 °C afforded the requisite bromide 4, which was then reacted with carbanion (derived from the reaction of ethyl acetoacetate 5 and sodium ethoxide) to yield the desired 5E,9E-farnesyl ketoester 6. The homologated ketoester 6 after hydrolysis and decarboxylation using aqueous 5 N KOH yielded the expected 5E,9E-farnesyl acetone 7, one of the key intermediate for the synthesis of 5E,9E,13E-geranylgeranyl acetone 1 and 5Z,9E,13E-geranylgeranyl acetone 2,
The other synthon, namely the ylide \( \text{21} \) can be synthesized from a commercially available starting material, ethyl levulinate \( \text{16} \), a sugar industry by-product. The ketalization of ethyl levulinate \( \text{16} \) using conventional conditions (ethylene glycol, p-TsOH, azeotropic reflux) can yield the desired 2-oxo-ketal \( \text{17} \), which then can be reduced using LAH in THF at 0 °C to the corresponding alcohol \( \text{18} \). Furthermore, the alcohol \( \text{18} \) then can be treated with Ph\(_3\)Br in diethyl ether at 0 °C to obtain the bromide \( \text{19} \), which then after treatment with Ph\(_3\)P can yield the phosphonium bromide salt \( \text{20} \). The bromide salt \( \text{20} \) upon treatment with mild alkali (IN NaOH) can furnish the desired ylide \( \text{21} \), required to complete the synthesis of 5Z-GGA \( \text{2} \).

With a view to obtain product with c/s-geometry, the reaction of 5E,9E-farnesyl acetone \( \text{7} \) with the ylide \( \text{21} \) in DCM at RT can afford the desired 5Z-oxoketal \( \text{22} \) (Ref.: Ernest et al, Tetrahedron Lett. 1982, 23(2), 167-170). The protected oxo-function from \( \text{22} \) can be removed by means of a mild acid treatment to yield the expected 5Z,9E,13E-GGA \( \text{2} \).

**Example 5:** 5E,9E,13E-Geranylgeranyl Acetone Synthesis

Alternative synthesis of 5-trans Isomer: 5E,9E,13E-Geranylgeranyl acetone \( \text{1} \): The alternative synthesis of 5E,9E,13E-geranylgeranyl acetone \( \text{1} \) can be achieved as shown in the scheme-5.

**Scheme 5:**

![Scheme 5 Diagram](image)

The 5E, 9E, 13E-geranyl geranyl acetone \( \text{1} \) can be prepared by reacting 6E-10E-geranyl linalool \( \text{23} \) with diketene \( \text{24} \) catalyzed by DMAP in ethyl ether to give the ester \( \text{25} \). The ester \( \text{25} \) in the Carroll rearrangement using Al(OiPr)\(_3\) at elevated temperature can afford the desired 5E, 9E, 13E-geranyl geranyl acetone \( \text{1} \). In another approach, the GGA \( \text{1} \) can be prepared by treating geranyl linalool \( \text{23} \) with the Meldrum's acid \( \text{26} \) in the Carroll rearrangement.
rearrangement using Al(OiPr)$_3$ at 160 °C. Similarly, the use of fert-butyl acetoacetate (27) with geranyl linalool (23) in the Carroll rearrangement can also give the desired 5E, 9E, 13E-geranyl geranyl acetone (1).

**Example 6: 5-Z,9E,13E-Geranylgeranyl Acetone Synthesis**

The alternative synthesis of 5Z,9E,13E-geranylgeranyl acetone 2 can be achieved as shown in the scheme-6.

**Scheme 6:**

Alternative synthesis of 5-cis isomer: 5Z,9E,13E-Geranylgeranyl acetone 2: The 2E,6E-farnesyl alcohol 3 (where the geometry at C2 and C6 positions is already fixed as trans- or E) was used as a commercially available starting material for the synthesis of 5Z,9E,13E-geranylgeranyl acetone 2. The reaction of farnesyl alcohol 3 with phosphorus tribromide (PBr$_3$) in ethyl ether (EE) or with Ph$_3$P and CBr$_4$ in acetonitrile (ACN) at 0 °C afforded the requisite bromide 4, which was then reacted with carbanion (derived from the reaction of ethyl acetoacetate 5 and sodium ethoxide) to yield the desired 5E,9E-farnesyl ketoester 6. The homologated ketoester 6 after hydrolysis and decarboxylation using aqueous 5N KOH...
yielded the expected 5E,9E-farnesyl acetone 7, one of the key intermediate for the synthesis of 5E,9E,13E-geranylgeranyl acetone 1 and 5Z,9E,13E-geranylgeranyl acetone 2.

The ylide 31 synthesized from a commercially available mono-TBDMS protected ethylene glycol 28. The conversion of alcohol function of 28 by using Ph3P and CBr4 in acetonitrile can afford the corresponding bromide 29, which then can be used to make a phosphonium bromide salt 30 by treatment with Ph3P at elevated temperature. The bromide salt 30 upon treatment with KHMDS in THF can afford the ylide 31, which then can be reacted in-situ with ketone 7 in a key step to establish cis geometry with the newly created double bond at C2 position and obtain the 2Z-TBDMS ether 32 (ref: Still et al, J. Org. Chem., 1980, 45, 4260-4262 and Donetti et al, Tetrahedron Lett. 1982, 23(21), 2219-2222). The deprotection of TBDMS with aqueous HCl to afford the corresponding alcohol 13 followed by conversion of alcohol to bromide using Ph3P and CBr4 can afford the desired bromide 14. The bromide 14 upon reaction with ethyl acetoacetate can give ketoester 15, which then upon hydrolysis followed by decarboxylation can yield the desired 5-Z-GGA (5-cis) 2.

Example 7: The Synthesis of Additional Compounds

Scheme 7:

2E, 6E, 10E-Geranylgeranyl Alcohol 1

2E, 6E, IOE-Geranylgeranyl acetate (2a) (R= Methyl): A dry reaction flask equipped with a stir bar and N2 inlet was charged with Geranylgeranyl alcohol 1 (0.087 g, 0.3 mmol), triethyl amine (0.062 mL, 0.45 mmol) and dichloromethane, DCM (1 mL) and cooled to 0 °C. To it was added acetyl chloride (1M solution in DCM, 0.42 mL, 0.042 mmol) drop-wise and the resulting reaction was stirred at room temperature for overnight, ~24h. The reaction was quenched with aqueous NaHCO3 solution, extracted with DCM (3 x 20 mL), the DCM extract was washed with water (20 mL), dried over anhydrous Na2SO4 and solvent was evaporated under a reduced pressure. The resulting oily residue was purified by a silica gel column chromatography using n-hexanesto 1-2% EtOAC in n-hexanesto afford a colorless liquid of ester 2a. Yield: 0.059 mg (60%); TLC Rf: 0.58 (10% EtOAc/n-Hexanes); LCMS: M+ (m/z): 333.4 (M+H); Ret. Time: 14.13 minutes.
2E, 6E, 10E- Geranylgeranyl propionate (2b) (R= Ethyl): Similar to the preparation of ester 2a, the reaction of alcohol 1 with n-propionyl chloride afforded the desired compound 2b in 63% yield (0.065 g) as colorless oil. TLC Rf: 0.57 (10% EtOAc/n-hexanes); LCMS: MS (m/z): 347 (M+H), ret. time: 14.60 min.

5 2E, 6E, 10E- Geranylgeranyl iso-butyrate (2c) (R= iso-Propyl): Similar to the preparation of ester 2a, the reaction of alcohol 1 with iso-butryl chloride afforded the desired compound 2c in 57% yield (0.061 g) as colorless oil. TLC Rf: 0.55 (10% EtOAc/n-hexanes); LCMS: MS (m/z): 361 (M+H), ret. time: 14.14 min.

2E, 6E, 10E- Geranylgeranyl cyclopropionate (2d) (R= Cyclopropyl): Similar to the preparation of ester 2a, the reaction of alcohol 1 with cyclopropanecarbonyl chloride gave the desired compound 2d in 54% yield (0.057 g) as colorless oil. TLC Rf: 0.54 (10% EtOAc/n-hexanes); LCMS: MS (m/z): 290 (M- Cyclopropyl), ret. time: 14.83 min.

2E, 6E, 10E- Geranylgeranyl cyclopentanooate (2e) (R= Cyclopentyl): Similar to the preparation of ester 2a, the reaction of alcohol 1 with cyclopentanecarbonyl chloride gave the compound 2e in 61% yield (0.065 g) as colorless oil. TLC Rf: 0.53 (10% EtOAc/n-hexanes); LCMS: MS (m/z): 290 (M- Cyclopentancarbonyl), ret. time: 14.60 min.

2E, 6E, 10E- Geranylgeranyl cyclohexanoate (2f) (R= Cyclohexyl): Similar to the preparation of ester 2a, the reaction of alcohol 1 with cyclohexanecarbonyl chloride gave the compound 2f in 65% yield (0.078 g) as colorless oil. TLC Rf: 0.53 (10% EtOAc/n-hexanes); LCMS: MS (m/z): 401 (M+H), ret. time: 15.98 min.

The following Esters (2g-k) were prepared as a mixture of trans and cis isomers.

2E, 6E, 10E- Geranylgeranyl-3',5'-dinitrobenzoate (2g) (R= 3',5'-Dinitrophenyl): Similar to the preparation of ester 2a, the reaction of alcohol 9 with 3,5-dinitrobenzoyl chloride gave the desired compound 2g in 60% yield (0.145 g) as colorless oil. TLC Rf: 0.46 (7% EtOAc/n-hexanes); LCMS: MS (m/z): 484.30 (M+).

2E, 6E, 10E- Geranylgeranyl-3',4',5'-trimethoxybenzoate (2h) (R= 3',4',5'-trimethoxyphenyl): Similar to the preparation of ester 2a, the reaction of alcohol 1 (1.00g, 3.44 mmol) with 3,4,5-trimethoxybenzoyl chloride (0.871g, 5.16 mmol) gave the desired compound 2h in 77% yield (1.28 g) as colorless oil.; LCMS: MS (m/z) 471.0 (MH-CH3).
2E, 6E, 10E-Geranylgeranyl-3',5'-diethoxybenzoate (2i) (R = 3',5'-diethoxyphenyl): Similar to the preparation of ester 2a, the reaction of alcohol 1 (1.00g, 3.44 mmol) with 3,5-diethoxybenzoyl chloride (0.861g, 5.16 mmol) gave the desired compound 2i in 73% yield (1.28 g) as colorless oil.; LCMS: M+S (m/z) 483.15 (M+H).

2E, 6E, 10E-Geranylgeranyl-2'ethoxybenzoate (2j) (R = 2'-Ethoxyphenyl): Similar to the preparation of ester 2a, the reaction of alcohol 1 (0.580g, 2 mmol) with 2-ethoxybenzoyl chloride (0.340mL, 3 mmol) gave the desired compound 2j in 78% yield (0.684 g) as colorless oil.; LCMS: M+S (m/z) 477.25 (M+Na).

2E, 6E, 10E-Geranylgeranyl-2',4'-dimethoxybenzoate (2k) (R = 2',4'-Dimethoxyphenyl): Similar to the preparation of ester 2a, the reaction of alcohol 1 (0.580g, 2 mmol) with 2,4-dimethoxybenzoyl chloride (0.576g, 3 mmol) gave the desired compound 2k in 76% yield (0.664 g) as colorless oil.; LCMS: M+S (m/z) 477.90 (M+acetonitrile).

Scheme 8:

2E, 6E, 10E-Geranylgeranyl methanesulfonate (4a) (R = Methyl): A dry reaction flask equipped with a stir bar and N₂ inlet was charged with geranylgeranyl alcohol 1 (0.087 g, 0.3 mmol), pyridine (0.048 mL, 0.6 mmol) in DCM (2 mL). To it was added, methanesulfonyl chloride 3a (0.035 mL, 0.45 mmol) and stirred for 48h at room temperature. The reaction was followed by TLC. After the completion of the reaction, it was quenched with water (10 mL), extracted with DCM (3 x 20 mL) and the combined DCM solution was washed with 2N NaOH solution (20 mL) followed by water (20 mL). The DCM layer upon drying over anhydrous Na₂SO₄ was evaporated and the residue was purified by silica gel column chromatography using n-hexane:ether 1:2% EtOAc in n-hexanesthe afford the desired sulfonate 4a. Yield: 0.066 g (66%); TLC Rf: 0.54 (10% EtOAc/n-Hexanes); LCMS: M+S (m/z): 367.10 (M-H).
The following sulfonates 4b and 4c were prepared according to the procedure used to prepare sulfonate 4a.

2E, 6E, 10E-Geranylgeranyl benzenesulfonate (4b) (R= Phenyl): The reaction of alcohol 1 with benzenesulfonyl chloride afforded the requisite sulfonate 4b. Yield: 0.087 g (68%); TLC Rf: 0.45 (10% EtOAc/n-Hexanes); LCMS: MS (m/z): 471.30 (M + Acetonitrile).

2E, 6E, 10E-Geranylgeranyl p-toluenesulfonate (4c) (R= p-Toluene): The reaction of alcohol 1 with p-toluenesulfonyl chloride afforded the requisite sulfonate 4c. Yield: 0.072 g (54%); TLC Rf: 0.42 (10% EtOAc/n-Hexanes); LCMS: MS (m/z): 443.50 (M-H).

Scheme 9:

Scheme 10:

2E, 6E-Farnesyl benzenesulfonate (6a) (R= Phenyl): A dry reaction flask equipped with a stir bar and N₂ inlet was charged with 2E,6E-Farnesy alcohol 5 (0.165 g, 0.75 mmol), pyridine (0.120 mL, 1.5 mmol) in DCM (2 mL). To it was added, benzenesulfonyl chloride 3a (0.087 mL, 1.12 mmol) and stirred for 12h at room temperature. The reaction was followed by TLC. After the completion of the reaction, it was quenched with water (10 mL), extracted with DCM (3 x 20 mL) and the combined DCM solution was washed with 2N NaOH solution (20 mL) followed by water (20 mL). The DCM layer upon drying over anhydrous Na₂SO₄ was evaporated and the residue was purified by silica gel column chromatography using n-hexanes the 1-2% EtOAc in n-hexanes to afford the desired sulfonate 6a. Yield: 0.119 g (44%).

2E, 6E-Farnesyl p-toluenesulfonate (6b) (R= p-Toluene): Sulfonate 6b was prepared according to the procedure used to prepare sulfonate 6a. The reaction of alcohol 5 with p-toluenesulfonyl chloride afforded the requisite sulfonate 6b. Yield: 0.107 g (38%); LCMS: MS (m/z): 377.2 (M+H).
Ethyl 2E,6E,10E-geranylgeranyl carbamate (7a) (R= Ethyl-): A dry reaction flask equipped with a stir bar, N₂ inlet was charged with alcohol 1 (0.060 g, 0.2 mmol), pyridine (0.032 ml), 0.4 mmol) and DCM (2 mL). After cooling it to 0 °C, ethyl isocyanate was added dropwise and the resulting reaction mixture was allowed to stir for 24 h. The reaction was monitored by TLC. After completion of the reaction, it was quenched with H₂O (5 mL), acidified, extracted with n-hexanes (3 x 15 mL) and the combined n-hexanes were washed with H₂O (10 mL). After drying the organic solution over anhydrous Na₂SO₄ the solvent was evaporated and the resulting residue was purified by silica gel column chromatography using 1-2% EtOAc in n-hexanes to afford the desired carbamate 7a. Yield: 0.039g (54%); TLC Rf: 0.30 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 412 (M + Na); ret. time: 14.39 min.

The following carbamates 7b to 7z were prepared according to the procedure that was used to prepare carbamate 7a.

sec-Butyryl 2E,6E,10E-geranylgeranyl carbamate (7b) (R= sec-Butyryl-): The reaction of alcohol 1 with sec-butyryl isocyanate afforded carbamate 7b. Yield: 0.039g (54%); TLC Rf: 0.40 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 412 (M + Na); ret. time: 15.79 min.

iso-Propyl 2E,6E,10E-geranylgeranyl carbamate (7c) (R= iso-Propyl-): The reaction of alcohol 1 with iso-propyl isocyanate gave the desired carbamate 7c. Yield: 0.039g (52%); TLC Rf: 0.32 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 376.40 (M+H); ret. time: 14.34 min.

n-Pentyl 2E,6E,10E-geranylgeranyl carbamate (7d) (R= n-Pentyl): The reaction of alcohol 1 with n-pentyl isocyanate gave the expected carbamate 7d. Yield: 0.054g (67%); TLC Rf: 0.35 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 426 (M+H); ret. time: 16.40 min.

n-Hexyl 2E,6E,10E-geranylgeranyl carbamate (7e) (R= n-Hexyl-): The reaction of alcohol 1 with n-hexyl isocyanate gave the carbamate 7e. Yield: 0.026g (31%); TLC Rf: 0.29 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 418 (M+H); ret. time: 15.28 min.

Cyclopentyl 2E, 6E, 10E-geranylgeranyl carbamate (7f) (R= Cyclopentyl-): The reaction of alcohol 1 with cyclopentyl isocyanate gave the desired carbamate 7f. Yield: 0.034g (42%); TLC Rf: 0.32 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 402 (M+H).

Cyclohexyl 2E, 6E, 10E-geranylgeranyl carbamate (7g) (R= Cyclohexyl-): The reaction of alcohol 1 with cyclohexyl isocyanate gave the desired carbamate 7g. Yield: 0.043g (51%); TLC Rf: 0.29 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 416.30 (M+H).
Cyclohexylmethyl 2E, 6E, IOE-geranylgeranyl carbamate (7h) (R= Cyclohexylmethyl-): The reaction of alcohol 1 with cyclohexylmethyl isocyanate afforded the expected carbamate 7h. Yield: 0.039g (45%); TLC Rf: 0.23 (10% EtOAc/ n-Hexanes); LCMS: M S (m/z): 430.40.

Cyclohexylmethyl 2E, 6E, IOE-geranylgeranyl carbamate (7i) (R= Cyclohexylmethyl-): The interaction of alcohol 1 with cyclohexyl isocyanate afforded the carbamate 7i. Yield: 0.034g (39%); TLC Rf: 0.61 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 430.40 (M+H).

Methyl 2-(S)-(−)-3-methylbutyrate 2E,6E,10E-geranylgeranyl Carbamate (7j) (R= 2-methyl-(S)-(−)-3-methyl butyrate): The reaction of alcohol 1 with methyl-(S)-(−)-3-methyl isobutyryl isocyanate gave the carbamate 7j. Yield: 0.032g (42%); TLC Rf: 0.19 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 450.30 (M+2H).

Allyl 2E, 6E, IOE-geranylgeranyl carbamate (7k) (R= Allyl-): The interaction of alcohol 1 (0.145g, 0.5 mmol) with allyl isocyanate (0.131 mL, 0.75 mmol) afforded the carbamate 7k. Yield: 0.091g (41%); TLC Rf: 0.61 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 374.3 (M+H).

Benzyl 2E, 6E, IOE-geranylgeranyl carbamate (7l) (R= Benzyl-): The interaction of alcohol 1 (0.145g, 0.5 mmol) with benzyl isocyanate (0.185 mL, 0.75 mmol) afforded the carbamate 7l. Yield: 0.082g (39%); LCMS: M S (m/z): 424.3 (M+H).

Ethoxycarbonyl ethyl 2E, 6E, IOE-geranylgeranyl carbamate (7m) (R= Ethoxycarbonyl ethyl-): The interaction of alcohol 1 (0.145g, 0.5 mmol) with ethoxycarbonyl ethyl isocyanate (0.197 mL, 0.75 mmol) afforded the carbamate 7m. Yield: 0.093g (43%); LCMS: M S (m/z): 434.3 (M+H).

Phenyl 2E, 6E, IOE-geranylgeranyl carbamate (7n) (R= Phenyl-): The interaction of alcohol 1 with phenyl isocyanate afforded the carbamate 7n. Yield: 0.087 g (56%); TLC Rf: 0.69 (10% EtOAc/hexanes); 1H NMR (300 MHz, CDCl3): δ 7.40-7.25 (m, 5H), 6.60 (brs, 1H), 5.40 (t, 1H), 5.10 (m, 3H), 4.68 (d, 2H), 2.14-1.92 (m, 12H), 1.75 (s, 3H), 1.68 (s, 3H), 1.60 (s, 9H). LCMS: MS (m/z): 432.5 (M+Na).

P-Tolyl 2E, 6E, IOE-geranylgeranyl carbamate (7o) (R= p-Tolyl-): The interaction of alcohol 1 (0.145g, 0.5 mmol) with p-tolyl isocyanate (0.188 mL, 0.75 mmol) afforded the carbamate 7o. Yield: 0.095g (45%); LCMS: MS (m/z): 424.3 (M+H).
Ethoxycarbonyl methyl 2E, 6E, IOE-geranylgeranyl carbamate (7p) (R = ethoxycarbonyl methyl-): The interaction of alcohol 1 (0.145g, 0.5 mmol) with ethoxycarbonyl methyl isocyanate (0.193g, 0.75 mmol) afforded the carbamate 7p. Yield: 0.077g (37%); LCMS: 436.3 (M+H)

5 p-Trifluoromethylphenyl 2E, 6E, IOE-geranylgeranyl carbamate (7q) (R = p-Trifluoromethylphenyl-): The interaction of alcohol 1 with p-trifluoromethylphenyl isocyanate afforded the carbamate 7q. Yield: 0.076g (42%); TLC Rf: 0.69 (10% EtOAc/hexanes); 1H NMR (300 MHz, CDCl3): δ 7.55 (d, 2H), 7.48 (d, 2H), 6.75 (br s, 1H), 5.39 (t, 1H), 5.10 (m, 3H), 4.70 (d, 2H), 2.14-1.98 (m, 12H), 1.75 (s, 3H), 1.68 (s, 3H), 1.60 (s, 9H).

10 The following carbamates (7s-y) were prepared as a mixture of 90:10 (trans/xcis) isomers.

1'-Naphthyl 2E, 6E, IOE-geranylgeranyl carbamate (7r) (R = 1'-Naphthyl-): The interaction of alcohol 1 (0.725g, 2.5 mmol) with 1-naphthyl isocyanate (0.430 mL, 3.00 mmol) afforded the carbamate 7r. Yield: 0.906g (79%); LCMS: MS (m/z): 482.20 (M+Na).

2'-Naphthyl 2E, 6E, IOE-geranylgeranyl carbamate (7s) (R = 2'-Naphthyl-): The interaction of alcohol 1 (0.725g, 2.5 mmol) with 2-naphthyl isocyanate (0.430 mL, 3.00 mmol) afforded the carbamate 7s. Yield: 0.946g (93%); LCMS: MS (m/z): 482.30 (M+Na).

3',4'-Dimethoxyphenyl 2E, 6E, IOE-geranylgeranyl carbamate (7t) (R = 3',4'-Dimethoxyphenyl-): The interaction of alcohol 1 (0.725g, 2.5 mmol) with 3,4-dimethoxyphenyl isocyanate (0.446 mL, 3.00 mmol) afforded the carbamate 7t. Yield: 0.914g (78%); LCMS: MS (m/z): 492.30 (M+Na).

p-Benzoyl phenyl 2E, 6E, IOE-geranylgeranyl carbamate (7u) (R = p-Benzoyl phenyl-): The interaction of alcohol 1 (0.725g, 2.5 mmol) with p-benzoylphenyl isocyanate (0.669 g, 3.00 mmol) afforded the carbamate 7u. Yield: 0.872g (68%); LCMS: MS (m/z): 514.3 (M+H).

3',4',5'-Trimethoxyphenyl 2E, 6E, IOE-geranylgeranyl carbamate (7v) (R = 3',4',5'-Trimethoxyphenyl-): The interaction of alcohol 1 (0.725g, 2.5 mmol) with 3,4,5-trimethoxyphenyl isocyanate (0.537 mL, 3.00 mmol) afforded the carbamate 7v. Yield: 1.08g (87%); MS (m/z): LCMS: MS (m/z): 522.40 (M+Na).

2',4'-Dimethoxyphenyl 2E, 6E, IOE-geranylgeranyl carbamate (7w) (R = 2',4'-Dimethoxyphenyl-): The interaction of alcohol 1 (0.725g, 2.5 mmol) with 2,4-
dimethoxyphenyl isocyanate (0.537g, 3.00 mmol) afforded the carbamate 7w. Yield: 0.996g (85%); LCMS: M S (m/z): 492.30 (M+Na).

9'H-Fluoren-2'-yl isocyanate 2E, 6E, 10E-geranylgeranyl carbamate (7x) (R= 9'H-Fluoren-2'-yl isocyanate): The interaction of alcohol 1 (0.725g, 2.5 mmol) with 9H-fluoren-2-yl isocyanate (0.621 mL, 3.00 mmol) afforded the carbamate 7x. Yield: 0.968g (78%); LCMS: M S (m/z): 520.30 (M+Na).

3',4',5'-Trichlorophenyl 2E, 6E, 10E-geranylgeranyl carbamate (7y) (R= 3',4',5'-Trichlorophenyl): The interaction of alcohol 1 (0.725g, 2.5 mmol) with 3,4,5-trichlorophenyl isocyanate (0.666g, 3.00 mmol) afforded the carbamate 7y. Yield: 0.932g (73%); LCMS: M S (m/z): 534.10 (M+Na).

3'-Pyridyl 2E, 6E,10E-geranylgeranyl carbamate (7z): The reaction of alcohol 1 with 3-pyridyl isocyanate afforded carbamate 7z. Yield: 0.112 g (48%); TLC Rf: 0.6 (5% MeOH/CH₂Cl₂); LCMS: M S (m/z): 411 (M+H).

2'-Furanyl methyl 2E, 6E,10E-geranylgeranyl carbamate (7aa): The reaction of alcohol 1 with 2-furanylmethyl isocyanate afforded carbamate 7aa. Yield: 0.111 g (45%). LCMS: M S (m/z): 436.2 (M+Na).

2E,6E,10E-Geranylgeranyl Memantinyl Carbamate 41 (R= Memantinyl): The reaction of alcohol 9 with memantine N-carbamoyl chloride gave the carbamate 41. Yield: 0.038 g (38%); TLC Rf: 0.47(10% EtOAc/n-hexanes).

Scheme 11:
iso-Propyl 2E,6E-farnesyl carbamate (8a) (R= isoPropyl): A dry reaction flask equipped with a stir bar, N₂ inlet was charged with alcohol 5 (0.165 g, 0.75 mmol), TEA (0.2 mL, 1.4 mmol) and DCM (2 mL). After cooling it to 0 °C, isopropyl isocyanate (0.137 mL, 1.4 mmol) was added dropwise and the resulting reaction mixture was allowed to stir for 24 h. The reaction was monitored by TLC. After completion of the reaction, it was quenched with H₂O (5 mL), acidified, extracted with n-hexanes (3 x 15 mL) and the combined n-hexanes were washed with H₂O (10 mL). After drying the organic solution over anhydrous Na₂SO₄, the solvent was...
evaporated and the resulting residue was purified by silica gel column chromatography using 1-2% EtOAc in n-hexanes to afford the desired carbamate 8a. Yield: 0.103g (45%); LCMS: MS (m/z): 330.25 (M+Na).

The following carbamates 8b to 8o were prepared according to the procedure that was used to prepare carbamate 8a.

n-Pentyl 2E, 6E-farnesyl carbamate (8b) (R= n-Pentyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with n-pentyl isocyanate (0.180g, 1.4 mmol) afforded the carbamate 8b. Yield: 0.080 g (32%); LCMS: MS (m/z): 358.25 (M+Na).

Cyclopentyl 2E, 6E-farnesyl carbamate (8c) (R= Cyclopentyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with cyclopentyl isocyanate (0.158 mL, 1.4 mmol) afforded the carbamate 8c. Yield: 0.094 g (38%); LCMS: MS (m/z): 356.25 (M+Na).

Cycloheptyl 2E, 6E-farnesyl carbamate (8d) (R= Cycloheptyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with cycloheptyl isocyanate (0.185 mL, 1.4 mmol) afforded the carbamate 8d. Yield: 0.105 g (39%); LCMS: MS (m/z): 384.3 (M+Na).

Adamantyl 2E, 6E-farnesyl carbamate (8e) (R= Adamentyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with adamantyl isocyanate (0.248g, 1.4 mmol) afforded the carbamate 8e. Yield: 0.094 g (38%); LCMS: MS (m/z): 400.65 (M+H).

Cyclohexyl 2E, 6E-farnesyl carbamate (8f) (R= Cyclohexyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with cyclohexyl isocyanate (0.179 mL, 1.4 mmol) afforded the carbamate 8f. Yield: 0.109 g (42%); LCMS: MS (m/z): 370.20 (M+Na).

Sec-Butyl 2E, 6E-farnesyl carbamate (8g) (R= sec-Butyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with sec-butyl isocyanate (0.160 mL, 1.4 mmol) afforded the carbamate 8g. Yield: 0.052 g (29%); LCMS: MS (m/z): 344.30 (M+Na).

Ethyl 2E, 6E-farnesyl carbamate (8h) (R= Ethyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with ethyl isocyanate (0.111 mL, 1.4 mmol) afforded the carbamate 8h. Yield: 0.094 g (44%); LCMS: MS (m/z): 316.25 (M+Na).

Hexyl 2E, 6E-farnesyl carbamate (8i) (R= Hexyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with hexyl isocyanate (0.203 mL, 1.4 mmol) afforded the carbamate 8i. Yield: 0.063 g (34%); LCMS: MS (m/z): 372.3 (M+Na).
Allyl 2E, 6E-farnesyl carbamate (8j) (R= Allyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with allyl isocyanate (0.124 mL, 1.4 mmol) afforded the carbamate 8j. Yield: 0.071 g (31%); LCMS: M S (m/z): 328.2 (M+Na).

Carboethoxymethyl 2E, 6E-farnesyl carbamate (8k) (R= Carboethoxymethyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with carboethoxymethyl isocyanate (0.157 mL, 1.4 mmol) afforded the carbamate 8k. Yield: 0.105 g (40%); LCMS: M S (m/z): 374.2 (M+Na).

p-Tolyl 2E, 6E-farnesyl carbamate (8l) (R= p-Tolyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with p-tolyl isocyanate (0.158 mL, 1.4 mmol) afforded the carbamate 8l. Yield: 0.119 g (33%); LCMS: M S (m/z): 378.20 (M+Na).

Carboethoxy-2’-ethyl 2E, 6E-farnesyl carbamate (8m) (R= Carboethoxy-2’-ethyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with carboethoxy-2-ethyl isocyanate (0.180 mL, 1.4 mmol) afforded the carbamate 8m. Yield: 0.112 g (35%); LCMS: M S (m/z): 388.20 (M+Na).

p-Trifluoromethylphenyl 2E, 6E-farnesyl carbamate (8n) (R= p-trifluoromethylphenyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with p-trifluoromethylphenyl isocyanate (0.158 mL, 1.4 mmol) afforded the carbamate 8n. Yield: 0.128 g (31%); LCMS: M S (m/z): 432.2 (M+Na).

Phenyl 2E, 6E-farnesyl carbamate (8o) (R= Phenyl-): The reaction of alcohol 5 (0.165g, 0.75 mmol) with phenyl isocyanate (0.150 mL, 1.4 mmol) afforded the carbamate 8o. Yield: 0.066 g (26%); LCMS: M S (m/z): 364.20 (M+Na).

Scheme 12:

Ethyl 2E, 6E-farnesyl thiocarbamate (9a) (R= Ethyl-): A dry reaction flask equipped with a stir bar, N\textsubscript{2} inlet was charged with alcohol 5 (0.111 g, 0.5 mmol), pyridine (0.08 mL, 1.0 mmol) and DCM (1 mL). After cooling it to 0 °C, ethyl thioisocyanate (0.065 g, 1.0 mmol) was added dropwise and the resulting reaction mixture was allowed to stir for 24 h. The reaction was monitored by TLC. After completion of the reaction, it was quenched with H\textsubscript{2}O (5 mL), acidified, extracted with n-hexanes (3 x 15 mL) and the combined n-hexanes were
washed with H₂O (10 mL). After drying the organic solution over anhydrous Na₂SO₄, the solvent was evaporated and the resulting residue was purified by silica gel column chromatography using 1-2% EtOAc in n-hexanes to afford the desired thiocarbamate 9a. **Yield:** 0.044 g (29%); LCMS: M⁺ (m/z): 310.2 (M+H).

The following carbamates 9b to 9k were prepared according to the procedure that was used to prepare carbamate 9a.

**sec-Butyl 2E, 6E-farnesyl thiocarbamate (9b) (R= sec-butyryl-):** The reaction of alcohol 5 (0.117 g, 0.5 mmol) with sec-butyl thioisocyanate (0.086 g, 1.0 mmol) afforded the thiocarbamate 9b. **Yield:** 0.045 g (27%); LCMS: M⁺ (m/z): 338.2 (M+H).

**n-Butyl 2E, 6E-farnesyl thiocarbamate (9c) (R= n-Butyl-):** The reaction of alcohol 5 (0.117 g, 0.5 mmol) with n-butyl thioisocyanate (0.090 g, 1.0 mmol) afforded the thiocarbamate 9c. **Yield:** 0.053 g (32%); LCMS: M⁺ (m/z): 338.20 (M+H).

**Cyclopropyl 2E, 6E-farnesyl thiocarbamate (9d) (R= Cyclopropyl-):** The reaction of alcohol 5 (0.117 g, 0.5 mmol) with cyclopropyl thioisocyanate (0.070 g, 1.0 mmol) afforded the thiocarbamate 9d. **Yield:** 0.062 g (39%); LCMS: M⁺ (m/z): 322.25 (M+H).

**n-Hexyl 2E, 6E-farnesyl thiocarbamate (9e) (R= n-Hexyl-):** The reaction of alcohol 5 (0.117 g, 0.5 mmol) with n-hexyl thioisocyanate (0.115 g, 1.0 mmol) afforded the thiocarbamate 9e. **Yield:** 0.069 g (38%); LCMS: M⁺ (m/z): 366.20 (M+H).

**Methoxy-2-ethyl 2E, 6E-farnesyl thiocarbamate (9f) (R= Methoxy-2'-ethyl-):** The reaction of alcohol 5 (0.117 g, 0.5 mmol) with methoxy-2-ethyl thioisocyanate (0.087 g, 1.0 mmol) afforded the thiocarbamate 9f. **Yield:** 0.030 g (18%); LCMS: M⁺ (m/z): 340.2 (M+H).

**exo-Norbornyl 2E, 6E-farnesyl thiocarbamate (9g) (R= exo-Norbornyl-):** The reaction of alcohol 5 (0.117 g, 0.5 mmol) with exo-norbornyl thioisocyanate (0.114 g, 1.0 mmol) afforded the thiocarbamate 9g. **Yield:** 0.065 g (35%); LCMS: M⁺ (m/z): 375.30 (M+H).

**Phenyl 2E, 6E-farnesyl thiocarbamate (9h) (R= Phenyl-):** The reaction of alcohol 5 (0.117 g, 0.5 mmol) with Phenyl thioisocyanate (0.065 g, 1.0 mmol) afforded the thiocarbamate 9h. **Yield:** 0.073 g (41%); LCMS: M⁺ (m/z): 358.20 (M+H).
Piperidinyl-2'ethyl 2E, 6E-farnesyl thiocarbamate (i) (R= Piperidinyl-2'ethyl-): The reaction of alcohol 5 (0.117g, 0.5 mmol) with piperidinyl-2-ethyl thioisocyanate (0.123g, 1.0 mmol) afforded the thiocarbamate 9i. Yield: 0.054 g (28%); LCMS: M S (m/z): 393.30 (M+H).

Morpholinyl-N-2'-ethyl 2E, 6E-farnesyl thiocarbamate (9j) (R= Morpholinyl-N-2-ethyl-):
The reaction of alcohol 5 (0.117g, 0.5 mmol) with morpholinyl-2-ethyl thioisocyanate (0.065g, 1.0 mmol) afforded the thiocarbamate 9j. Yield: 0.061 g (31%); LCMS: M S (m/z): 395.25 (M+H).

Morphol1nyl-N-3'-propyl 2E, 6E-farnesyl thiocarbamate (9k) (R= Morpholinyl-N-3'-propyl-):
The reaction of alcohol 5 (0.117g, 0.5 mmol) with morpholinyl-N-3-propyl thioisocyanate (0.065g, 1.0 mmol) afforded the thiocarbamate 9k. Yield: 0.055 g (27%); LCMS: M S (m/z): 395.3 (M+H).

Scheme 13:

Methyl 2E,6E,10E-geranylgeranyl thiocarbamate (10a) (R= Methyl-): A dry reaction flask equipped with a stir bar, N₂ inlet was charged with alcohol 1 (0.087 g, 0.3 mmol), pyridine (0.48 mL, 0.6 mmol) and DCM (1 mL). After cooling it to 0 °C, methyl thioisocyanate (0.051 mL, 1.0 mmol) was added dropwise and the resulting reaction mixture was allowed to stir for 24 h. The reaction was monitored by TLC. After completion of the reaction, it was quenched with H₂O (5 mL), acidified, extracted with n-hexanes (3 x 15 mL) and the combined n-hexanes were washed with H₂O (10 mL). After drying the organic solution over anhydrous Na₂SO₄, the solvent was evaporated and the resulting residue was purified by silica gel column chromatography using 1-2% EtOAc in n-hexanes to afford the desired thiocarbamate 10a. Yield: 0.030g (28%); LCMS: M S (m/z): 386.4 (M+Na).

The following carbamates 10b to 10m were prepared according to the procedure that was used to prepare carbamate 10a.

Ethyl 2E,6E,10E-geranylgeranyl thiocarbamate (10b) (R= Ethyl-): The reaction of alcohol 1 (0.117g, 0.5 mmol) with ethyl thioisocyanate (0.040g, 0.6 mmol) afforded the thiocarbamate 10b. Yield: 0.034 g (30%); LCMS: M S (m/z): 378.35 (M+H).
sec-Butyryl 2E,6E,10E-geranylgeranyl thiocarbamate (10c) (R= sec-Butyryl-): The reaction of alcohol 1 (O.llg, 0.5 mmol) with sec-butyryl thioisocyanate (0.052g, 0.6 mmol) afforded the thiocarbamate 10c. Yield: 0.038 g (32%); LCMS: M S (m/z): 408.4 (M+H).

Ethoxycarbonylmethyl 2E,6E,10E-geranylgeranyl thiocarbamate (10d) (R= Ethoxycarbonylmethyl-): The reaction of alcohol 1 (O.llg, 0.5 mmol) with ethoxycarbonylmethyl thioisocyanate (0.039g, 0.6 mmol) afforded the thiocarbamate 10d. Yield: 0.027 g (21%); 1H NMR (300 MHz, CDCl₃): δ 6.71 (s, 1H), 5.44-5.39 (m, 1H), 5.13-5.08 (m, 3H), 4.98 (s, 1H), 4.95 (m, 1H), 4.33-4.21 (m, 3.6H), 4.04 (d, 0.4H), 2.09-1.97 (m, 12H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60-1.57 (m, 9H), 2.12-1.97 (m, 12H), 2.12-1.97 (m, 12H). LCMS: M S (m/z): 436.3 (M+H).

n-Butyl 2E,6E,10E-geranylgeranyl thiocarbamate (10e) (R= n-Butyl-): The reaction of alcohol 1 (O.llg, 0.5 mmol) with butyl thioisocyanate (0.054 mL, 0.6 mmol) afforded the thiocarbamate 10e. Yield: 0.043 g (27%); TLC Rf: 0.7 (10% EtOAc/hexanes); 1H NMR (300 MHz, CDCl₃): δ 6.46 (br s, 0.4H), 6.20 (br s, 0.6H), 5.40 (t, 1H), 5.08 (m, 3H), 5.00 (d, 0.8H), 4.93 (s, 1.2H), 3.25 (d, 1.2H), 3.24 (m, 0.8H), 2.12-1.97 (m, 12H), 1.66 (s, 3H), 1.62 (s, 3H), 1.60 (s, 9H), 1.50-1.33 (m, 4H), 0.93 (m, 3H). LCMS: M S (m/z): 406 (M+H).

Cyclopropyl 2E,6E,10E-geranylgeranyl thiocarbamate (10f) (R= Cyclopropyl-): The reaction of alcohol 1 (O.llg, 0.5 mmol) with cyclopropyl thioisocyanate (0.042 mL, 0.6 mmol) afforded the thiocarbamate 10f. Yield: 0.036 g (31%); LCMS: M S (m/z): 390.3 (M+H).

Acetyl 2E,6E,10E-geranylgeranyl thiocarbamate (10g) (R= Acetyl-): The reaction of alcohol 1 (O.llg, 0.5 mmol) with acetyl thioisocyanate (0.039 mL, 0.6 mmol) afforded the thiocarbamate 10g. Yield: 0.019 g (16%); LCMS: M S (m/z): 414.30 (M+Na).

n-Hexyl 2E,6E,10E-geranylgeranyl thiocarbamate (10h) (R= n-Hexyl-): The reaction of alcohol 1 (O.llg, 0.5 mmol) with n-hexyl thioisocyanate (0.069 mL, 0.6 mmol) afforded the thiocarbamate 10h. Yield: 0.053 g (41%); LCMS: M S (m/z): 434.3 (M+H).

Methoxy-2'-ethyl 2E,6E,10E-geranylgeranyl thiocarbamate (10i) (R= Methoxy-2'ethyl-): The reaction of alcohol 1 (O.llg, 0.5 mmol) with methoxy-2-ethyl thioisocyanate (0.048 mL, 0.6 mmol) afforded the thiocarbamate 10i. Yield: 0.023 g (19%); 1H NMR (300 MHz, CDCl₃): δ 6.84 and 6.59 (m, 1H total), 5.43-5.38 (m 1H), 5.13-5.10 (m, 3H), 5.03-4.94 (m, 2H), 3.77-3.73 (m, 1H), 3.56-3.52 (m, 1H), 3.45 (s, 1H), 3.36 (s, 3H), 2.11-1.98 (m, 12H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60-1.58 (m, 10H). LCMS: M S (m/z): 408.4 (M+H).
Exo-Norbornyl 2E,6E,10E-geranylgeranyl thiocarbamate (IOj) (R=exo-Norbornyl-): The reaction of alcohol 1 (0.11g, 0.5 mmol) with exo-norbornyl thioisocyanate (0.061 mL, 0.6 mmol) afforded the thiocarbamate IOj. Yield: 0.038 g (29%); H NMR (300 MHz, CDCl₃): δ 6.46 and 6.11 (m, 1H total), 5.45-5.36 (m, 1H), 5.11-5.08 (m, 3H), 5.03-5.00 (m, 2H), 4.03-3.95 (m, 0.6H), 3.65-3.58 (m, 0.4H), 2.35-2.21 (m, 2H), 2.09-1.93 (m, 12H), 1.74-1.60 (m, 6H), 1.57-1.52 (m, 12H), 1.34-1.12 (m, 5H). LCMS: M S (m/z): 444.4 (M+H).

Phenyl 2E,6E,10E-geranylgeranyl thiocarbamate (IOk) (R=Phenyl-): The reaction of alcohol 1 (0.11g, 0.5 mmol) with phenyl thioisocyanate (0.053 mL, 0.6 mmol) afforded the thiocarbamate IOk. Yield: 0.047 g (37%); LCMS: M S (m/z): 426.30 (M+H).

Piperidinyl-2'-ethyl 2E,6E,10E-geranylgeranyl thiocarbamate (IOl) (R=Piperidinyl-2'-ethyl-): The reaction of alcohol 1 (0.11g, 0.5 mmol) with piperidinyl-2'-ethyl thioisocyanate (0.069 mL, 0.6 mmol) afforded the thiocarbamate IOl. Yield: 0.026 g (35%); H NMR (300 MHz, CDCl₃): δ 5.45-5.40 (m, 1H), 5.13-5.08 (m, 3H), 5.02-4.95 (m, 2H), 3.72-3.66 (m, 1.4H), 3.39-3.32 (m, 0.6H), 2.66-2.52 (m, 3H), 2.44-2.34 (m, 3H), 1.74-1.43 (m, 21H), 1.26 (m, 3H). LCMS: M S (m/z): 461.5 (M+H).

Morpholinyl-2'-ethyl 2E,6E,10E-geranylgeranyl thiocarbamate (IOM) (R=Morpholinyl-2'-ethyl-): The reaction of alcohol 1 (0.11g, 0.5 mmol) with morpholinyl-2-ethyl thioisocyanate (0.063 mL, 0.6 mmol) afforded the thiocarbamate IOM. Yield: 0.040 g (29%); H NMR (300 MHz, CDCl₃): δ 7.26 and 6.83 (m, 1H total), 5.46-5.40 (m, 1H), 5.11-5.08 (m, 3H), 5.03-4.95 (m, 2H), 3.72-3.66 (m, 4H), 3.68-3.59 (m, 1H), 3.41-3.34 (m, 0.6H), 2.58-2.53 (m, 1H), 2.49-2.41 (m, 4.4H), 2.12-1.98 (m, 13H), 1.74 (s, 3H), 1.68 (s, 3H), 1.60 (s, 9H). LCMS: M S (m/z): 463.6 (M+H).

Scheme 14:

5-((1E,5E)-2,6,10-trimethylundeca-1,5,9-trien-1-yl)oxazole

2E,6E-Farnesyl aldehyde 11 + TosMIC NaOEt, MeOH

2E,6E-Farnesyl 1',4'-oxazole 12

(12): A dry reaction flask equipped with a stirring bar and N₂ inlet was charged with aldehyde 11 (0.110 g, 0.5 mmol) in 1 mL EtOH followed by NaOEt (21% solution in EtOH, 0.404 mL, 1.25 mmol). To this at 0 °C was added TosMIC (0.102g, 0.525 mmol) and the
resulting reaction was stirred at Room temperature for 24 h. The reaction mixture was quenched with 1 N HCl (1 mL), H2O (5 mL), and extracted with DCM (2 x 5 mL). After drying over anhydrous sodium sulfate, the solvent was removed under a reduced pressure and the residue was chromatographed over silica gel using n-hexane then 2% EtOAc in n-hexane to yield the desired oxazole 12. Yield: 0.040 g (30%). LCMS: MS (m/z): 260.2 (M+H).

Scheme-15:

2E,6E,10E-Geranylgeranyl-r,4'-oxazole: 5-((lE,(5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-l-yl)oxazole (14): A dry reaction flask equipped with a stirring bar and N2 inlet was charged with aldehyde 13 (0.057 g, 0.2 mmol) in 0.5 mL EtOH followed by NaOEt (21% solution in EtOH, 0.161 mL, 0.5 mmol). To this at 0 °C was added TosMIC (0.041 g, 0.21 mmol) and the resulting reaction was stirred at Room temperature for 24 h. The reaction mixture was quenched with 1 N HCl (0.5 mL), extracted with DCM (2 x 3 mL). After drying over anhydrous sodium sulfate, the solvent was removed under a reduced pressure and the residue was chromatographed over silica gel using n-hexane then 2% EtOAc in n-hexane to yield the desired oxazole 14. Yield: 19 mg (28%). 1H NMR (300 MHz, CDCl3): δ 7.78 (s, 1H), 6.92 (s, 1H), 6.09 (s, 1H), 5.13-5.07 (m, 3H), 2.22-2.20 (m, 9H), 2.08-1.96 (m, 9H), 1.96 (s, 3H), 1.68-1.60 (m, 11H). LCMS: MS (m/z): 328.2 (M+H).

Scheme-16:

2E,6E-Farnesyl-5'-methyl-l',3'-oxazole: 5-methyl-2-((lE,5E)-2,6,10-trimethylundeca-1,5,9-trien-l-yl)oxazole (15): A dry reaction flask equipped with a stirring bar and N2 inlet at 0 °C was charged with aldehyde 11 (0.110 g, 0.5 mmol) diethyl ether (EE, 1 mL), lactonitrile (0.072 mL, 1 mmol) followed by cone. HCl (0.1 mL). The resulting reaction was stirred at room temperature for overnight (~16 h). The reaction mixture was quenched with H2O (5 mL), and extracted with EE (2 x 5 mL). After drying over anhydrous sodium sulfate, the solvent was removed under a reduced pressure and the residue was chromatographed over silica gel.
using n-hexane then 2% EtOAc in n-hexane to yield the desired oxazole 15. Yield: 0.064g (47%).

Scheme 17:

\[
\begin{align*}
\text{2E, 6E, 10E-Geranylgeranyl aldehyde 13} & \quad \text{Lactonitrile} \\
\text{2E, 6E, 10E-Geranylgeranyl-5'-methyl-5',3'-oxazole 16}
\end{align*}
\]

5 \text{2E,6E,10E-Geranylgeranyl-5'-methyl-1',3'-oxazole:} 5-methyl-2-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-l,5,9,13-tetraen-l-yl)oxazole (16): A dry reaction flask equipped with a stirring bar and \( \text{N}_2 \) inlet at 0 °C was charged with aldehyde 13 (0.144 g, 0.5 mmol) diethyl ether (EE, 1 mL), lactonitrile (0.072 mL, 1 mmol) followed by cone. HCl (0.1 mL). The resulting reaction was stirred at room temperature for overnight (~16h). The reaction mixture was quenched with H\( _2 \)O (5 mL), and extracted with EE (2 x 5 mL). After drying over anhydrous sodium sulfate, the solvent was removed under a reduced pressure and the residue was chromatographed over silica gel using n-hexane then 2% EtOAc in n-hexane to yield the desired oxazole 16. Yield: 0.075g (44%). LCMS: M\( \text{S} \) (m/z): 364.30 (M+Na).

Scheme 18:

\[
\begin{align*}
\text{2E, 6E,10-Geranylgeranyl alcohol 1} & \quad \text{Amines} \\
\text{2E, 6E,10-Geranylgeranyl Amines 17a-e}
\end{align*}
\]

15 \text{N-Cyclohexyl N-Methyl-2E,6E,10E-Geranylgeranyl amine (17a):} To a dry reaction flask equipped with stir bar, \( \text{N}_2 \) inlet was placed alcohol 1 (0.145g, 0.5 mmol), triphenylphosphine (0.196g, 0.75 mmol) and N-methylcyclohexylamine (0.065 mL, 0.5 mmol) in anhydrous THF (1 mL). The reaction was cooled to 0 °C and to it was added DIAD (0.151 g, 0.75 mmol) drop wise and the resulting reaction was stirred at room temperature for overnight (~16h). After quenching it with H\( _2 \)O (5 mL), it was extracted with DCM (2 x 10 mL), dried over anhydrous sodium sulfate and the solvent was removed under a reduced pressure. The resulting residue was chromatographed over silica gel using n-hexane and then 2-5% EtOAc in n-hexane to afford the desired amine 17a, yield: 0.072g (38%). LCMS: M\( \text{S} \) (m/z): 408.4 (M+Na).

By employing the procedure that was used to prepare amine 17a, the following amines 17b-e have been prepared.
N-Methyl-N-n-pentyl-2E,6E,10E-Geranylgeranyl amine (17b): The reaction of alcohol 1 with N-methyl-N-n-pentylamine (R₁=Me; R₂=n-pentyl) afforded the amine 17b. Yield: 0.076g (41%); LCMS: MS (m/z): 374.50 (M+H).

N-Heptyl-N-Methyl-2E,6E,10E-Geranylgeranyl amine (17c): The reaction of alcohol 1 with N-n-heptyl-N-methylamine (R₁=Me; R₂=n-heptyl) afforded the amine 17c. Yield: 0.072g (36%); LCMS: MS (m/z): 402.4 (M+H).

N-(3'-iso-Propoxypropyl)-2E,6E,10E-Geranylgeranyl amine (17d): The reaction of alcohol 1 with 3-isopropoxypropylamine (R₁=H; R₂=3-isopropoxypropyl-) afforded the amine 17d. Yield: 0.056g (29%); LCMS: MS (m/z): 390.0 (M+H).

N-Adamantyl-2E,6E,10E-Geranylgeranyl amine (17e): The reaction of alcohol 1 with adamantylamine (R₁=H; R₂=adamantyl) afforded the amine 17e. Yield: 0.071g (31%); LCMS: MS (m/z): 424.4 (M+H).

Scheme 19: Alternative synthesis of 17d:

To a solution of aldehyde 13 (150 mg, 0.523 mmol) in benzene (5 mL) was added 3-isopropoxypropylamine (61 mg, 0.523 mmol) and the reaction mixture was stirred at rt for 12 h. Solvent was removed and the residue was taken in MeOH (5 mL) and cooled to 0 °C. Then NaBH₄ (40 mg, 1.05 mmol) was added and the reaction mixture was stirred at rt for 15 h. Saturated NaHCO₃ was added and the reaction mixture was extracted with EtOAc. Dried and solvent was evaporated to give a residue, which was purified by column chromatography (DCM/MeOH) to afford amine 17d in 65% (132 mg) yield. TLC Rf: 0.46 (10% MeOH/DCM); ¹H NMR (300 MHz, CDCl₃): δ 5.26 (m, 1H), 5.10 (m, 3H), 3.50 (m, 2H), 3.30 (t, 2H), 2.79 (m, 2H), 2.10-1.90 (m, 12H), 1.80 (m, 2H), 1.66 (s, 1H), 1.64 (s, 1H), 1.59 (s, 9H), 1.14 (d, 6H); LCMS: MS (m/z): 390 (M+H).
5E, 9E-Farnesyl 2-acetol (19): A reaction flask with a stir bar and N₂ inlet was charged with ketone 18 (1.2 g, 5 mmol) and MeOH (10 mL). After cooling the reaction flask to 0 °C, the addition of NaBH₄ (0.190 g, 5 mmol) was performed in portions over several minutes and the reaction was stirred for additional hour. The reaction was monitored by TLC. The reaction was quenched with H₂O (40 mL) and the product was extracted with EtOAc (3 x 50 mL), dried over anhydrous Na₂SO₄ and solvent was removed under a reduced pressure to obtain the desired alcohol 19. Yield: 1.25 g (95%); TLC Rf: 0.24 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 265 (M+H).

Ethyl 5E,9E-farnesyl prop-2-yl carbamate (20a) (R= Ethyl): A dry reaction flask equipped with a stir bar, N₂ inlet was charged with alcohol 19 (0.052 g, 0.2 mmol), pyridine (0.032 mL, 0.4 mmol) and DCM (2 mL). After cooling it to 0 °C, ethyl isocyanate was added dropwise and the resulting reaction mixture was allowed to stir for 24 h. The reaction was monitored by TLC. After completion of the reaction, it was quenched with H₂O (5 mL), acidified, extracted with n-hexanes (3 x 15 mL) and the combined n-hexanes were washed with H₂O (10 mL). After drying the organic solution over anhydrous Na₂SO₄, the solvent was evaporated and the resulting residue was purified by silica gel column chromatography using 1-2% EtOAc in n-hexanes to afford the desired carbamate 20a. Yield: 0.037 g (52%); TLC Rf: 0.23 (5% EtOAc/n-Hexanes); LCMS: M S (m/z): 336.40 (M+H).

The following carbamates 20b to 20j were prepared according to the procedure that was used to prepare carbamate 20a.

sec-Butyryl 5E, 9E-farnesyl prop-2-yl carbamate (20b) (R= iso-Butyryl): The reaction of alcohol 19 with sec-butyryl isocyanate afforded the expected carbamate 20b. Yield: 0.038 g (50%); TLC Rf: 0.43 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 364 (M+H).
iso-Propyl 5E, 9E-farnesyl prop-2-yl carbamate (20c) (R= iso-Propyl): The reaction of alcohol 19 with iso-propyl isocyanate afforded the expected carbamate 20c. Yield: 0.036g (48%); TLC Rf: 0.41 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 350.40 (M+H).

n-Pentyl 5E, 9E-farnesyl prop-2-yl carbamate (20d) (R= n-Pentyl): The reaction of alcohol 19 with n-pentyl isocyanate afforded the expected carbamate 20d. Yield: 0.043g (54%); TLC Rf: 0.40 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 378 (M+H).

n-Hexyl 5E, 9E-farnesyl prop-2-yl carbamate (20e) (R= n-Hexyl): The reaction of alcohol 19 with n-hexyl isocyanate afforded the expected carbamate 20e. Yield: 0.040g (49%); TLC Rf: 0.41 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 392 (M+H).

Cyclopentyl 5E, 9E-farnesyl prop-2-yl carbamate (20f) (R= Cyclopentyl): The reaction of alcohol 19 with cyclopentyl isocyanate afforded the expected carbamate 20f. Yield: 0.035g (45%); TLC Rf: 0.36 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 376.40 (M+H).

Cyclohexyl 5E, 9E-farnesyl prop-2-yl carbamate (20g) (R= Cyclohexyl): The reaction of alcohol 19 with cyclohexyl isocyanate afforded the expected carbamate 20g. Yield: 0.040g (54%); TLC Rf: 0.40 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 390.60 (M+H).

Cyclohexylmethyl 5E, 9E-farnesyl prop-2-yl carbamate (20h) (R= Cyclohexylmethyl): The reaction of alcohol 19 with cyclohexylmethyl isocyanate afforded the expected carbamate 20h. Yield: 0.037g (47%); TLC Rf: 0.40 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 404.60 (M+H).

Cycloheptyl 5E, 9E-farnesyl prop-2-yl carbamate (ZOi) (R= Cycloheptyl): The reaction of alcohol 19 with cycloheptyl isocyanate afforded the expected carbamate 20i. Yield: 0.043g (54%); TLC Rf: 0.54 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 404.60 (M+H).

5E,9E-farnesyl prop-2-yl Methyl 2-((S)-(3-methylbutyrate Carbamate Carbamate (20j) (R= Methyl-2-(S)-(3-methylbutyrate): The reaction of alcohol 19 with methyl 2-((S)-(3-methylbutyrl isocyanate afforded the expected carbamate 20j. Yield: 0.41g (49%); TLC Rf: 0.28 (10% EtOAc/n-Hexanes); LCMS: M S (m/z): 422.60 (M+H).
Scheme 21:

\[
\begin{align*}
\text{5E, 9E, 13E-Geranylgerany Acetone (21)} & \xrightarrow{\text{NaBH}_4, \text{MeOH}} \text{5E, 9E, 13E-Geranylgeranyl rac-Acetone-2-ol (22)} \\
\end{align*}
\]

5E, 9E, 13E-Geranylgeranyl-roc-prop-2-yl iso-propyl carbamate (23a) (\(R=\text{iso-Propyl}\)):

A dry reaction flask equipped with a stir bar, \(N_2\) inlet was charged with alcohol 22 (0.052 g, 0.2 mmol), pyridine (0.032 mL, 0.4 mmol) and DCM (2 mL). After cooling it to 0 °C, isopropyl isocyanate (0.49 mL, 0.5 mmol) was added dropwise and the resulting reaction mixture was allowed to stir for 24 h. The reaction was monitored by TLC. After completion of the reaction, it was quenched with \(H_2O\) (5 mL), acidified, extracted with n-hexanes (3 x 15 mL) and the combined n-hexanes were washed with \(H_2O\) (10 mL). After drying the organic solution over anhydrous \(\text{Na}_2\text{SO}_4\), the solvent was evaporated and the resulting residue was purified by silica gel column chromatography using 1-2% EtOAc in n-hexanes to afford the desired carbamate 23a. Yield: 0.037 g (52%); TLC Rf: 0.23 (5% EtOAc/n-Hexanes); LCMS: M+ (m/z): 418.40 (M+H), ret time 16.28 min.

The following carbamates 23b to 23g were prepared according to the procedure that was used to prepare carbamate 23a.
5E, 9E, 13E-Geranylgeranyl-rac-prop-2-yl n-pentyl carbamate (23b) (R= n-Pentyl): The reaction of alcohol 22 with n-pentyl isocyanate afforded the desired carbamate 23b. Yield: 0.040g (46%); TLC Rf: 0.33 (10% EtOAc/n-Hexanes); LCMS: M.S (m/z): 446.60 (M+H).

Cyclopentyl 5E, 9E, 13E-geranylgeranyl-rac-prop-2-yl carbamate (23c) (R= cyclopentyl): The reaction of alcohol 22 with cyclopentyl isocyanate afforded the desired carbamate 23c. Yield: 0.041g (47%); TLC Rf: 0.39 (10% EtOAc/n-Hexanes); LCMS: MS (m/z): 444.60 (M+H).

Cyclohexylmethyl 5E, 9E, 13E-geranylgeranyl-rac-prop-2-yl carbamate (23d) (R= cyclohexylmethyl): The reaction of alcohol 22 with n-cyclohexylmethyl isocyanate afforded the desired carbamate 23d. Yield: 0.045g (48%); TLC Rf: 0.25 (10% EtOAc/n-Hexanes); LCMS: MS (m/z): 472.60 (M+H).

Cycloheptyl 5E, 9E, 13E-geranylgeranyl-rac-prop-2-yl carbamate (23e) (R= cycloheptyl): The reaction of alcohol 22 with cycloheptyl isocyanate afforded the desired carbamate 23e. Yield: 0.048g (51%); TLC Rf: 0.57 (10% EtOAc/n-Hexanes); LCMS: MS (m/z): 472.40 (M+H).

5E, 9E, 13E-Geranylgeranyl-rac-prop-2-yl n-hexyl carbamate (23f) (R= n-Hexyl): The reaction of alcohol 22 with n-hexyl isocyanate afforded the desired carbamate 23f. Yield: 0.039g (44%); TLC Rf: 0.36 (10% EtOAc/n-Hexanes); LCMS: MS (m/z): 460.50 (M+H).

5E, 9E, 13E-Geranylgeranyl-rac-prop-2-yl methyl 2-(S)-(−)-3-methylbutyryl carbamate (23g) (R= Methyl 2-(S)-(−)-3-methylbutyrate): The reaction of alcohol 22 with methyl 2-(S)-(−)-3-methylbutyryl isocyanate afforded the desired carbamate 23g. Yield: 0.049g (51%); TLC Rf: 0.37 (10% EtOAc/n-Hexanes); LCMS: MS (m/z): 490.60 (M+H).
2E,6E,10E-geranylgeranyl aldehyde (13): Alcohol 1 (5.0 g, 17.2 mmol) was stirred in hexane (85 mL) and MnO₂ (12.3 g, 13.6 mmol) was added, and the mixture was stirred at rt for 15 h. The mixture was filtered, concentrated and purified by a silica gel chromatography (Ethyl acetate: Petroleum ether = 1:60) to afford the product 13 (3.5 g, 67%); TLC Rf: 0.58 (3.3% Ethyl acetate/ Petroleum ether).

2E,6E,10E-geranylgeranyl carboxylic acid (24): To a solution of compound 13 (4.0 g, 13.9 mmol), KH₂PO₄ (18.9 g, 139 mmol) and 2-methyl-2-butene (9.73 g, 139 mmol) in THF-H₂O-t-butanol (50mL-25mL-25mL) was added NaClO₂ (4.87 g, 69.5 mmol) at 0°C portionwise. The mixture was stirred at 0°C for 30 min and rt for 4 h. Saturated NaHSO₃ solution was added at 0°C. The mixture was extracted with DCM (100 mL). The organic layer was dried, concentrated and purified by a silica gel chromatography (Petroleum ether / Ethyl acetate = 30:1) to get the product 24 (2.0 g, 47%).

2E,6E,10E)-geranylgeranyl carbonyl chloride (25): To a solution of compound 24 (100 mg, 0.309 mmol) in DCM (3 mL) was added oxalyl chloride (43.3 mg, 0.340 mmol) at rt dropwise.
DMF (1 drop) was added. The mixture was stirred at rt for 1 h. The mixture was concentrated to give 25, which was used directly for the next step.

(S)-4-isopropyl-2-(((E,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)-4,5-dihydrooxazole (27a): To a solution of compound 26a (27.8 mg, 0.37 mmol) and triethylamine (91.8 mg, 0.91 mmol) in DCM (2 mL) was added acyl chloride 25 (0.309 mmol in 1 mL of DCM) dropwise. The mixture was stirred for 3 h. The mixture was quenched by water and washed with HCl (IN in water), MsCl (35 mg, 0.309 mmol) was added to the residue and TEA (94 mg, 0.930 mmol) in DCM (2 mL). After stirring for 12 h, the result mixture was washed by water and extracted by DCM. The organic layer was dried and concentrated to give a residue, which was purified by prep-HPLC to afford the product 27a (20.0 mg, 17%);

TLC Rf: 0.32 (20% EtOAc/petroleum ether);
1H NMR (400 MHz, CDCl3): δ 6.11 (s, 1H), 5.02-4.99 (m, 3H), 4.86 (m, 1H), 4.60-4.58 (m, 1H), 4.22-4.20 (m, 1H), 2.29-2.25 (m, 2H), 2.12 (m, 5H), 1.98-1.66 (m, 8H), 1.59 (m, 5H), 1.51 (s, 9H), 0.95-0.88 (dd, 6H). LCMS: M S (m/z): 372.45 (M+H); ret. time: 6.77 min.

(S)-4-methyl-2-(((E,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)-4,5-dihydrooxazole (27b): Similar to the preparation of 27a, the reaction of 25 with 26b afforded the desired compound 27b (12 mg, 11%) as oil. TLC Rf: 0.35 (20% EtOAc/petroleum ether);
1H NMR (400 MHz, CDCl3): δ 5.11-5.08 (m, 2H), 4.33-4.31 (m, 1H), 3.76-3.77 (m, 1H), 2.14-1.94 (m, 12H), 1.72-1.41 (m, 16H), 1.28-1.19 (m, 5H). LCMS: M S (m/z): 344.30 (M+H); ret. time: 5.23 min.

(S)-4-isobutyl-2-(((E,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)-4,5-dihydrooxazole (27c): Similar to the preparation of 27a, the reaction of 25 with 26c afforded the desired compound 27c (7.1 mg, 6%) as oil. TLC Rf: 0.30 (20% EtOAc/petroleum ether);
1H NMR (400 MHz, CDCl3): δ 5.72 (m, 1H), 5.13-5.10 (m, 3H), 4.34-4.30 (m, 2H), 4.20-4.10 (m, 1H), 3.80 (m, 1H), 2.20-1.98 (m, 11H), 1.86 (s, 2H), 1.80-1.56 (m, 13H), 1.31-1.20 (m, 3H), 0.96-0.92 (m, 6H). LCMS: M S (m/z): 386.3 (M+H); ret. time: 9.07 min.

(R)-4-methyl-2-(((E,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)-4,5-dihydrooxazole (27d): Similar to the preparation of 27a, the reaction of 25 with 26d afforded the desired compound 27d (5.0 mg, 4.7%) as oil. TLC Rf: 0.31 (20% EtOAc/petroleum ether);
1H NMR (400 MHz, CDCl3): δ 5.09 (m, 2H), 4.34-4.32 (m, 1H), 3.79-3.75 (m, 1H), 2.14-1.93
(m, 12H), 1.72-1.41 (m, 16H), 1.28-1.19 (m, 5H). LCMS: MS (m/z): 344.35 (M+H); ret. time: 5.42 min.

(R)-4-isopropyl-2-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)-4,5-dihydrooxazole (27e): Similar to the preparation of 27a, the reaction of 25 with 26e afforded the desired compound 27e (8.0 mg, 7%) as oil. TLC Rf: 0.35 (20% EtOAc/petroleum ether); 1H NMR (400 MHz, CDCl3): δ 5.14-5.09 (m, 3H), 4.25-4.20 (m, 1H), 3.95-3.90 (m, 3H), 2.20-1.60 (m, 28H), 0.99-0.97 (m, 3H), 0.89-0.87 (m, 3H). LCMS: MS (m/z): 372.30 (M+H); ret. time: 6.31 min.

(R)-4-isobutyl-2-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)-4,5-dihydrooxazole (27f): Similar to the preparation of 27a, the reaction of 25 with 26f afforded the desired compound 27f (7 mg, 5.9%) as oil. TLC Rf: 0.30 (20% EtOAc/petroleum ether); 1H NMR (400 MHz, CDCl3): δ 5.14-5.09 (m, 3H), 4.35-4.30 (m, 2H), 4.17-4.15 (m, 1H), 3.82-3.78 (m, 1H), 2.15-1.60 (m, 28H), 1.31-1.26 (m, 2H), 0.96-0.92 (m, 6H). LCMS: MS (m/z): 386.3 (M+H); ret. time: 7.32 min.

(S)-4-benzyl-2-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)-4,5-dihydrooxazole (27g): Similar to the preparation of 27b, the reaction of 25 with 26a afforded the desired compound 27g (15 mg, 11%) as oil. TLC Rf: 0.34 (20% EtOAc/petroleum ether); 1H NMR (400 MHz, CDCl3): δ 7.35-7.20 (m, 5H), 6.23 (s, 1H), 5.30-5.02 (m, 3H), 5.09-5.04 (m, 2H), 3.28-3.24 (m, 1H), 2.97-2.94 (m, 1H), 2.34-2.30 (m, 2H), 2.22-2.16 (m, 2H), 2.13-1.94 (m, 12H), 1.70 (s, 3H), 1.59 (m, 9H). LCMS: MS (m/z): 420.50 (M+H); ret. time: 6.30 min.
Scheme 23:

2-phenyl-5-((1E,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)-1,3,4-oxadiazole (29a): To a solution of compound 28a (56 mg, 0.37 mmol) and triethylamine (91.8 mg, 0.91 mmol) in DCM (2 mL) was added acyl chloride 25 (0.309 mmol, in 1 mL of DCM) dropwise. The mixture was stirred for 3 h. The mixture was quenched with water and washed by HCl (IN in water), TsCl (71 mg, 0.370 mmol) was added to the residue and TEA (113 mg, 1.11 mmol) in DCM (2 mL). After stirring for 12 h, the result mixture was washed with water and extracted by DCM. The combined organic layers were dried and concentrated to get a residue, which was purified by prep-HPLC to give the product 29a (10.8 mg, 9%); TLC Rf: 0.42 (20% EtOAc/n-Hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.03 (d, 2H), 7.51-7.49 (m, 3H), 5.11-5.09 (m, 3H), 4.98 (d, 2H), 3.67 (s, 2H), 2.19-2.17 (m, 4H), 2.07-2.04 (m, 4H), 1.99-1.96 (m, 4H), 1.67 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H). LCMS: MS (m/z): 405.40 (M+H); ret. time: 9.06 min.

2-((1E,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)-5-(p-tolyl)-1,3,4-oxadiazole (29b): Similar to the preparation of 29a, the reaction of 25 with 28b afforded the desired compound 29b (20.8 mg, 16%) as oil. TLC Rf: 0.42 (20% EtOAc/ petroleum ether); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.92 (d, 2H), 7.29 (d, 2H) 5.11-5.09 (m, 3H), 4.98 (d, 2H), 3.65 (s, 2H), 2.42 (s, 3H), 2.18-2.16 (m, 4H), 2.07-2.04 (m, 4H), 1.99-1.96 (m, 4H), 1.67 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H). LCMS: MS (m/z): 419.40 (M+H); ret. time: 8.32 min.
2-(4-methoxyphenyl)-5-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-l,5,9,13-tetraen-l-yl)-1,3,4-oxadiazole (29c): Similar to the preparation of 29a, the reaction of 25 with 28c afforded the desired compound 29c (12.1 mg, 9 %) as oil. TLC RF: 0.42 (20% EtOAc/petroleum ether); 1H NMR (400 MHz, CDCl3): δ 7.93 (d, 2H), 7.08 (d, 2H), 5.11-5.06 (m, 4H), 5.02 (s, 1H), 4.98 (s, 1H), 3.87 (s, 3H), 3.70 (s, 2H), 2.20-2.15 (m, 4H), 2.06-1.97 (m, 4H), 1.96-1.90 (m, 4H), 1.63 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.55 (s, 3H). LCMS: MS (m/z): 406.45 (M+H); ret. time: 9.09 min.

2-(3,4-dimethoxyphenyl)-5-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-l,5,9,13-tetraen-l-yl)-1,3,4-oxadiazole (29d): Similar to the preparation of 29a, the reaction of 25 with 28d afforded the desired compound 29d (12.8 mg, 8.9%) as oil. TLC RF: 0.45 (20% EtOAc/petroleum ether); 1H NMR (400 MHz, CDCl3): δ 7.59-7.58 (m, 2H), 6.94 (d, 1H), 5.11-5.09 (m, 3H), 5.00 (s, 1H), 4.96 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.65 (s, 2H), 2.18-2.17 (m, 4H), 2.07-2.04 (m, 4H), 1.99-1.89 (m, 4H), 1.67 (s, 3H), 1.61-1.59 (s, 9H). LCMS: MS (m/z): 465.55 (M+H); ret. time: 6.44 min.

2-(pyridin-3-yl)-5-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-l,5,9,13-tetraen-l-yl)-1,3,4-oxadiazole (29e): Similar to the preparation of 29a, the reaction of 25 with 28e afforded the desired compound 29e (14 mg, 11%) as oil. TLC RF: 0.36 (20% EtOAc/petroleum ether); 1H NMR (400 MHz, CDCl3): δ 9.27 (s, 1H), 8.81 (s, 1H), 8.50 (d, 1H), 7.62-7.59 (m, 1H), 5.11-5.09 (m, 3H), 5.03 (s, 1H), 4.98 (s, 1H), 3.70 (s, 2H), 2.21-2.14 (m, 4H), 2.09-2.02 (m, 4H), 2.00-1.94 (m, 4H), 1.67 (s, 3H), 1.64 (s, 3H), 1.59-1.58 (m, 3H), 1.56 (m, 3H). LCMS: MS (m/z): 406.45 (M+H); ret. time: 8.59 min.

2-(pyridin-4-yl)-5-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-l,5,9,13-tetraen-l-yl)-1,3,4-oxadiazole (29f): Similar to the preparation of 29a, the reaction of 25 with 28f afforded the desired compound 29f (17 mg, 14%) as oil. TLC RF: 0.36 (20% EtOAc/petroleum ether); 1H NMR (400 MHz, CDCl3): δ 8.85 (m, 2H), 8.04-8.03 (m, 2H), 5.10-5.09 (m, 3H), 5.04 (m, 1H), 4.99 (s, 1H), 3.71 (s, 2H), 2.23-2.18 (m, 4H), 2.06-2.02 (m, 4H), 2.00-1.96 (m, 4H), 1.67 (s, 3H), 1.61-1.59 (m, 9H). LCMS: MS (m/z): 406.45 (M+H); ret. time: 9.09 min.
Scheme 24:

(E)-2-oxo-2-phenylethyl 3,7-dimethylocta-2,6-dienoate (31): To a solution of compound 30 (500 mg, 2.98 mmol) and Cs2CO3 (1.8 g, 4.46 mmol) in DMF (5 mL) at rt was added 2-bromo-1-phenyl-ethanone (593 mg, 2.98 mmol) dropwise. After stirring for 7 h, the mixture was quenched with water and extracted with ether (100 mL). The organic layer was dried and concentrated to give a residue (350 mg, 41%). The residue was used directly for the next step. TLC Rf: 0.60 (20% EtOAc in petroleum ether).

(E)-2-(2,6-dimethylhepta-1,5-dien-1-yl)-4-phenyloxazole (32): A solution of compound 31 (200 mg, 0.699 mmol) and NH4OAc (538 mg, 6.99 mmol) in xylenes (5 mL) in a sealed tube was stirred at 140 °C for 2.5 h. The mixture was diluted with water and extracted by ether (100 mL). The organic layer was dried and concentrated to give a residue, which was purified by prep-TLC to afford the desired product 32 (8 rug, 4%) as a mixture of isomers; TLC Rf: 0.60 (20% EtOAc/petroleum ether); H NMR (400 MHz, CDCl3): δ 7.83-7.82 (m, 1H), 7.77-7.75 (m, 2H), 7.42-7.38 (m, 2H), 7.32-7.26 (m, 1H), 6.18-6.15 (m, 1H), 5.22 (m, 0.23H), 5.14 (m, 0.78 H), 2.76-2.72 (m), 2.28-2.19 (m, 7H), 1.70-1.58 (m, 6H). LCMS: MS (m/z): 267.4 (M+H); ret. time: 9.48 min.

Scheme 25:

(E)-5-(2,6-dimethylhepta-1,5-dien-1-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole (35a): A dry reaction flask equipped with a stir bar was charged with compound 30 (150 mg, 0.9 mmol),
DCM (5 mL). To the solution was added oxalyl chloride (112 mg, 0.9 mmol) dropwise and the reaction was stirred at rt for 3 h. The mixture was concentrated to get crude compound 33, which was re-dissolved in dioxane (10 mL).

To above mixture were added compound 34a (123 mg, 0.9 mmol) and magnesium oxide (0.36 g, 9.0 mmol). The mixture was stirred at 80 °C overnight. The reaction was filtered and concentrated under reduced pressure, and the resulting oily residue was purified by silica gel column chromatography using (PE/EtOAc, 5/1) to afford a colorless liquid of compound 35a (50 mg, 21%) as a mixture of isomers; TLC Rf: 0.38 (20% EtOAc/n-Hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 9.31 (m, 1H), 8.71-8.70 (m, 1H), 8.36-8.33 (m, 1H), 7.40-7.37 (m, 1H), 6.29 (s, 1H), 5.08 (m, 1H), 2.32-2.04 (m, 7H), 1.67-1.58 (m, 6H). LCMS: M (m/z): 270.3 (M+H); ret. time: 3.98 min.

(E)-5-(2,6-dimethylhepta-1,5-dien-1-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (35b): Similar to the preparation of 35a, the reaction of 33 with 34b afforded the desired compound 35b (80 mg, 31%) as colorless oil. TLC Rf: 0.30 (20% EtOAc/PE); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.12-8.08 (m, 2H), 7.18-7.13 (m, 2H), 6.29 (m, 1H), 5.11 (m, 1H), 2.34-2.24 (m, 7H), 1.70-1.61 (m, 6H). LCMS: M (m/z): 287.40 (M+H); ret. time: 8.19 min.

(E)-5-(2,6-dimethylhepta-1,5-dien-1-yl)-3-phenyl-1,2,4-oxadiazole (35c): Similar to the preparation of 35a, the reaction of 33 with 34c afforded the desired compound 35c (50 mg, 21%) as colorless oil. TLC Rf: 0.32 (20% EtOAc/PE); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.13-8.10 (m, 2H), 7.49-7.46 (m, 3H), 6.30 (br s, 1H), 5.12 (m, 1H), 2.35-2.25 (m, 7H), 1.70-1.63 (m, 6H). LCMS: M (m/z): 269.20 (M+H); ret. time: 8.04 min.

(E)-5-(2,6-dimethylhepta-1,5-dien-1-yl)-3-(pyridin-4-Yl)-1,2,4-oxadiazole (35d): Similar to the preparation of 35a, the reaction of 33 with 34d afforded the desired compound 35c (40 mg, 17%) as colorless oil. TLC Rf: 0.24 (20% EtOAc/PE); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.77-8.75 (m, 2H), 7.97-7.95 (m, 2H), 6.31 (s, 1H), 5.10 (m, 1H), 2.35-2.06 (m, 7H), 1.69-1.62 (m, 6H). LCMS: M (m/z): 270.05 (M+H); ret. time: 3.42 min.
Scheme 26:

(R)-4-isopropyl-2-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)oxazol-5(4H)-one (37a): A dry reaction flask equipped with a stir bar was charged with compound 24 (100 mg, 0.3 mmol), DCM (5 mL). Oxalyl chloride (37 mg, 0.3 mmol) was added dropwise and the resulting reaction was stirred at rt for 3 h. The mixture was concentrated to get compound 25, which was used directly for the next step. To the compound 25 in DCM (10 mL) at -30 °C were added compound 36a (44 mg, 0.3 mmol) and DCC (68 mg, 0.3 mmol) in DCM (2 mL) drop-wise. The mixture was stirred at -30 °C for 4 h and quenched with aqueous NaHCO₃ solution, extracted with DCM (3 x 10 mL). The DCM extract was washed with water (20 mL), dried over anhydrous Na₂SO₄ and solvent was evaporated under reduced pressure. The resulting oily residue was purified by a silica gel column chromatography using (petroleum ether/EtOAc = 5/1) to afford a colorless liquid of compound 37a (20 mg, 16%); TLC Rt: 0.68 (20% EtOAc/petroleum ether); ¹H NMR (400 MHz, CDCl₃): 6 5.12-5.08 (m, 3H), 3.85-3.80 (m, 1H), 3.70-3.65 (m, 1H), 2.17-1.87 (m, 12 H), 1.69-1.62 (m, 6 H), 1.34-1.16 (m, 12 H). LCMS: MS (m/z): 386.6 (M+H); ret. time: 8.11 min.

(S)-4-isopropyl-2-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)oxazol-5(4H)-one (37b): Similar to the preparation of 37a, the reaction of 25 with 36b afforded the desired compound 37b (15 mg, 12%) as colorless oil. TLC Rt: 0.34 (20% EtOAc/n-Hexanes); ¹H NMR (400 MHz, CDCl₃): 6 5.12-5.08 (m, 3H), 3.85-3.80 (m, 1H), 3.70-3.65 (m, 1H), 2.17-1.87 (m, 12 H), 1.69-1.62 (m, 6 H), 1.34-1.16 (m, 12 H). LCMS: MS (m/z): 386.35 (M+H); ret. time: 7.70 min.

(R)-4-isobutyl-2-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)oxazol-5(4H)-one (37c): Similar to the preparation of 37a, the reaction of 25 with 36c afforded the
desired compound 37c in 11% yield (0.015 g) as colorless oil. TLC Rf: 0.32 (20% EtOAc/n-Hexanes); \textsuperscript{1}H NMR (400 MHz, CDCl3): \(\delta\) 5.10-5.08 (m, 3H), 3.85-3.80 (m, 1H), 3.70-3.65 (m, 1H), 2.15-1.60 (m, 28 H), 1.25-1.21 (m, 2H), 0.94-0.90 (m, 6 H). LCMS: MS (m/z): 400.40 (M+H); ret. time: 4.22 min.

5 (S)-4-isobutyl-2-((lE,5E,9E)-2,6,10,14-tetramethylpentadeca-1,5,9,13-tetraen-1-yl)oxazol-5(4H)-one (37d): Similar to the preparation of 37a, the reaction of 25 with 36d afforded the desired compound 37d (12 mg, 10%) as colorless oil. TLC Rf: 0.32 (20% EtOAc/n-Hexanes); \textsuperscript{1}H NMR (400 MHz, CDCl3): \(\delta\) 5.75-5.65 (m, 3H), 5.09-5.07 (m, 1H), 4.00-3.80 (m, 1H), 2.15-1.80 (m, 14 H), 1.65-1.50 (m, 6 H), 1.30-1.10 (m, 6 H), 0.95-0.80 (m, 6H). LCMS: MS (m/z): 400.40 (M+H); ret. time: 4.98 min.

Scheme 27:

O-((2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl)pyridin-3-ylcarbamothioate (38a): To a solution of NaH (60% dispersed in oil, 32 mg, 0.81 mmol) in THF (4 mL) at 0 °C was added alcohol 1 (180 mg, 0.62 mmol) in THF (1 mL) and the reaction mixture was stirred for 30 min at this temperature. Then 3-pyridyl isothiocyanate (169 mg, 124 mmol) in THF (1 mL) was added and stirred at rt. After stirring for 12 h, the reaction mixture was quenched with water and extracted with EtOAc (3x). The organic layer was dried and concentrated to yield thiocarbamate 38a as a viscous liquid (179 mg, 70%). TLC Rf: 0.23 (20% EtOAc/hexanes); \textsuperscript{1}H NMR (300 MHz, CDCl3): \(\delta\) 8.55 (d, 1H), 8.40 (d, 1H), 7.95 (m, 1H), 7.30 (m, 2H), 5.49 (t, 1H), 5.11 (m, 3H), 4.70 (d, 2H), 2.16-1.19 (m, 12H), 1.76 (s, 3H), 1.68 (s, 3H), 1.60 (s, 9H); LCMS: MS (m/z): 427 (M+H).

O-((2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl)pyrimidin-3-ylcarbamothioate (38b): Similar to the preparation of 38a, the reaction of alcohol 1
with 2-furanylmethyl isothiocyanate afforded the desired compound 38b in 23% yield (55 mg) as a viscous oil. Column (EtOAc/Hexane); TLC Rf: 0.65 (20% EtOAc/hexanes); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.35 (s 1H), 6.35 (m, 1H), 5.15 (m, 3H), 5.04 (d, 0.4H), 4.95 (d, 0.6H), 4.75 (d, 0.6H), 4.42 (d, 0.4H), 2.14-1.94 (m, 12H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60 (s, 9H); LCMS: MS (m/z): 430.2 (M+H).

Alternative synthesis of IOe

O-((2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-l-yl) butylcarbamothioate (IOe): Similar to the preparation of 38a, the reaction of alcohol 1 with pentyl isothiocyanate afforded the desired compound IOe in 60% yield (135 mg) as a viscous oil. Column (EtOAc/Hexane); TLC Rf: 0.70 (10% EtOAc/hexanes); LCMS: MS (m/z): 406.1 (M+H).

Scheme 28:

$$\begin{align*}
\text{1} & \text{ + R-N=C=O + NaH} & \text{THF} \\
\text{39} & \\
\text{(2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-l-yl) pyridin-4-ylcarbamate}
\end{align*}$$

(39): Similar to the preparation of 38a, the reaction of alcohol 1 with 4-pyridyl isocyanate afforded the desired compound 39 in 3% yield (10 mg) as a viscous oil. Column (DCM/MeOH); TLC Rf: 0.34 (10% MeOH/DCM); LCMS: MS (m/z): 411 (M+H).

Scheme 29:

$$\begin{align*}
\text{1} & \text{ + H-NR}_1R_2 + \text{CDI} & \text{DCM, DMAP} \\
\text{40a-b} & \\
\text{R}_1 & \text{R}_2
\end{align*}$$
E E O E - S -tetramethYlhexadeca-Z^^O^^tetraen - l -yl-methylpiperazine - l -

carboxylate (40a): To a solution of alcohol 1 (160 mg, 55 mmol) in DCM (3 mL) at 0 °C was
added carbonyldimidazole (CDI) (107 mg, 0.66 mmol) and the reaction was stirred for 1 h.
Then N-methylpiperazine (80 mg, 0.72 mmol) and DMAP (68 mg, 0.55 mmol) were added
and stirred for 12 h. Solvent was removed and the residue was purified by column
chromatography (DCM/MeOH) to give the carbamate 40a as a viscous oil in 88 % yield (191
mg). TLC Rf: 0.54 (10% MeOH/DCM); 1H NMR (300 MHz, CDCl3): δ 5.34 (t, 3H), 5.08 (m, 3H),
4.59 (d, 2H), 3.49 (m, 4H), 2.35 (m, 4H), 2.29 (s, 3H), 2.10-1.97 (m, 12H), 1.70 (s, 3H), 1.67 (s,
3H), 1.59 (s, 9H); LCMS: M S (m/z): 417 (M+H).

(2E,6E,10E)-3,7,11,15-tetramethYlhexadeca-2,6,10,14-tetraen - l -yl pyridin-2-ylcarbamate
(40b): Similar to the preparation of 40a, the reaction of alcohol 1 with 2-aminopyridine and
CDI afforded the desired compound 40b in 40% yield (30 mg) as a viscous solid. Column
(DCM/MeOH); TLC Rf: 0.34 (10% MeOH/DCM); 1H NMR (300 MHz, CDCl3): δ 8.48 (s, 1H),
8.30 (d, 1H), 7.95 (m, 1H), 6.65 (s, 1H), 5.40 (t, 1H), 5.11 (m, 3H), 4.70 (d, 2H), 2.16-1.94 (m,
12H), 1.76 (s, 3H), 1.69 (s, 3H), 1.61 (s, 9H); LCMS: M S (m/z): 411 (M+H).

(2E,6E,10E)-3,7,11,15-tetramethYlhexadeca-2,6,10,14-tetraen - l -yl (3,5-
dimethyladamantan - l -yl)carbamate (41): Similar to the preparation of 40a, the reaction of
alcohol 1 with memantine and CDI afforded the desired compound 41 as a viscous oil.
Column (DCM/MeOH); TLC Rf: 0.70 (10% EtOAc/Hexanes).

O-((2E,6E)-3,7,11-trimethYldodeca-2,6,10-trien - l -yl) methylcarbamothioate (43): Similar to
the preparation of 38a, the reaction of a licohol 5 with methyl thioisocyanate afforded the
desired compound 43 in 47% yield (316 mg) as a viscous oil as a mixture of isomers; TLC Rf:
38 (10% EtOAc/hexanes); 1H NMR (300 M Hz, CDCl3): δ 6.5 (br s, 0.3H), 6.2 (br s, 0.7H), 5.40-
5.39 (m, 1H), 5.09-5.08 (m, 2H), 5.03-5.01 (d, 0.7H), 4.97-4.94 (d, 1.3H), 3.09-3.08 (d, 2H),
2.88-2.86 (d, 1H), 2.12-1.96 (m, 8H), 1.73-1.72 (m, 3H), 1.68 (m, 3H), 1.60 (m, 6H). 13CNM R
(75 MHz, CDCl3): δ 143.1, 135.7, 131.6, 124.5, 123.8, 118.9, 118.2, 69.2, 67.6, 39.9, 39.8,
21.1, 30.0, 26.9, 26.4, 26.0, 18.0, 17.0, 16.9, 16.3.

Example 8

Argatroban conjugates of GGA or a GGA derivative: Provided 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 9

Zofran conjugates of GGA or a GGA derivative: Provided 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.

Example 10

Representative linkages for drug conjugates of GGA or a GGA derivative: Provided 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:

\[
\begin{align*}
&\text{R}_1\text{R}_2\text{R}_3\text{R}_4\text{R}_5\text{OH} \quad \text{H}_2\text{O} \quad \text{Z-Drug} \\
&\text{R}_1\text{R}_2\text{R}_3\text{R}_4\text{R}_5\text{NH}_2 \quad \text{H}_2\text{O} \quad \text{Z-Drug} \\
&\text{R}_1\text{R}_2\text{R}_3\text{R}_4\text{R}_5\text{NH} \quad \text{H}_2\text{O} \quad \text{Z-Drug}
\end{align*}
\]

\[Z = \text{bond, O, NH, N(C}_1\text{-C}_6\text{alkyl)}\]

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

\[
\begin{align*}
&\text{R}_1\text{R}_2\text{R}_3\text{R}_4\text{R}_5\text{OH} \quad \text{H}_2\text{O} \quad \text{HX-Drug} \\
&\text{R}_1\text{R}_2\text{R}_3\text{R}_4\text{R}_5\text{X} \quad \text{HX-Drug}
\end{align*}
\]

\[X = 0, S \text{ or } \text{NH}\]
**Schiff's bases**

\[ R^1 = \text{H or CH_3} \]

\[ \text{Hydrolytic conditions} \]

\[ \text{In vivo} \]

\[ \text{Revert to Starting Materials} \]

**Sulfenylated amides**

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

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

**Example 1: Synthetic Examples**

**Preparation of Compound 2**

To a solution of 1 (300 mg, 1.03 mmol) and pyridine (40 mg, 0.51 mmol) in n-hexane (20 mL) at -20 °C was added dropwise PBr₃ (150 mg, 0.55 mmol). The reaction mixture was warmed
to rt and stirred for 16 h, then water (10 mL) was added. The aqueous phase was extracted with ethyl ether (20 mL x 2) and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated, the residue 2 (380 mg, 99%) was used for next step without further purification. TLC $R_f$ = 0.7 (petroleum ether (PE), visualized with KMnO$_4$); $^1$H NMR (400 MHz, CDCl$_3$) 55.54 (t, $J$ = 8.4 Hz, 1H), 5.11-5.10 (m, 3H), 4.03 (d, $J$ = 8.4 Hz, 2H), 2.06-2.13 (m, 12H), 1.76 (s, 3H), 1.70 (s, 3H), 1.61 (s, 9H).

**Preparation of Compound 4**

To a suspension of NaH (60%, 43 mg, 1.07 mmol) in anhydrous DMF (5 mL) at 0 °C was added 3 (310 mg, 1.07 mmol). The reaction mixture was stirred for 30 minutes, then 2 (380 mg, 1.07 mmol) was added. The reaction mixture was warmed to rt and stirred for 1 h, then water (5 mL) was added. The aqueous phase was extracted with ethyl ether (20 mL x 2) and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated, the residue was purified by flash column on silica (dichloromethane (DCM):MeOH = 100:0-50:1) to give 4 (230 mg, 44%). LC-MS: 561.5 (M+H)$^+$; TLC $R_f$ = 0.3 (DCM:MeOH = 20:1, KMnO$_4$); $^1$H NMR (400 MHz, CDCl$_3$) 55.32 (t, $J$ = 6.8 Hz, 1H), 5.11-5.10 (m, 3H), 4.21-4.14 (m, 8H), 2.70-2.60 (m, 2H), 2.39-2.26 (m, 1H), 2.07-1.96 (m, 12H), 1.68 (s, 3H), 1.65 (s, 3H), 1.60 (s, 9H), 1.33 (t, $J$ = 7.0 Hz, 12H).

**Preparation of Compound 5**

To a solution of 4 (200 mg, 0.36 mmol) in DCM (20 mL) was added 2,4,6-collidine (0.15 mL) and TMSBr (0.45 mL) at room temperature. The reaction mixture was stirred for 16 h. The solvent was removed. The residue was dissolved in methanol, followed by the addition of NaOH (200 mg, 5 mmol). The obtained mixture was stirred for 30 minutes and concentrated. The residue was dissolved in water and extracted with DCM. The aqueous phase was adjusted to pH = 1 with concentrated HCl and extracted with ethyl acetate (EA),
washed with brine, dried over Na₂SO₄, concentrated to give 5 (80 mg, 50%). LC-MS: 447.4
(M-H); ¹H NMR (400 MHz, CD₃OD) δ 5.42 (t, J = 7.2 Hz, 1H), 5.13-5.08 (m, 3H), 2.67-2.61 (m, 2H), 2.16-1.96 (m, 13H), 1.69-1.59 (m, 15H).

**Preparation of Compound 6**

To a suspension of NaH (60%, 20 mg, 0.48 mmol) in anhydrous THF at 0°C was added 15-crown-5 (60 mg, 0.27 mmol) followed by 3 (130 mg, 0.45 mmol). The reaction mixture was stirred for 30 minutes and 2 (420 mg, 1.18 mmol) was added. The reaction mixture was warmed to rt and stirred for 1 h, then water (5 mL) was added. The aqueous phase was extracted with ethyl ether (20 mL x 2) and the combined organic layers were dried over Na₂SO₄ and concentrated, the residue was purified by flash column on silica (DCM:MeOH = 100:0-50:1) to give 6 (230 mg, 75%). TLC R₅ = 0.4 (DCM:MeOH = 20:1, KMnO₄). ¹H NMR (400 MHz, CDCl₃) δ 55.43 (t, J = 6.8 Hz, 2H), 5.14-5.10 (m, 6H), 4.21-4.13 (m, 8H), 2.63 (dt, J = 16.0, 6.8 Hz, 4H), 2.07-1.96 (m, 24H), 1.68 (s, 6H), 1.62 (s, 6H), 1.60 (s, 18H), 1.33 (t, J = 6.8 Hz, 12H).

**Preparation of Compound 7**

To a solution of compound 6 (230 mg, 0.46 mmol) in DCM (3 mL) at 0°C was added 2,4,6-collidine (0.12 mL, 0.92 mmol, 4.0 equ), and TMSBr (0.37 mL, 2.8 mmol, 12 equ). The mixture was stirred at 0°C for 1 h, and at rt for 12 h. The reaction mixture was concentrated. To the residue was added methanol (5 mL), followed by the addition of NaOH (300 mg, 7.5 mmol). The obtained mixture was stirred for 30 minutes and concentrated. The residue was dissolved in water and extracted with DCM. The aqueous phase was adjusted to
pH 1 with concentrated HCl and extracted with EA, washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by CI-18 column to provide 7 (34 mg, 13%) as an oil. LC-MS: 719.4 (M-1); TLC Rₗ = 0.2 (DCM : MeOH = 20:1, KMnO₄); ¹H NMR (CDCl₃, 300 MHz) 5.34 (s, 2H), 5.09 (s, 6H), 2.66 (m, 2H), 2.03-1.97 (m, 24H), 1.58 (m, 24H).

**Preparation of Compound 8**

To a suspension of NaH (60%, 177 mg, 4.43 mmol) in anhydrous THF (20 mL) at 0 °C was added 15-crown-5 (160 mg, 0.73 mmol) followed by 3 (500 mg, 1.74 mmol). The reaction mixture was stirred for 30 minutes and geranyl bromide (942 mg, 4.34 mmol) was added. The reaction mixture was warmed to rt and stirred for 1 h, and then water (5 mL) was added. The aqueous phase was extracted with ethyl ether (30 mL x 2) and the combined organic layers were dried over Na₂SO₄ and concentrated, the residue was purified by flash column on silica (DCM:MeOH = 100:0-50:1) to give 8 (700 mg, 72%). LC-MS: 561.6 (M+1); TLC Rₗ = 0.4 (DCM : MeOH = 20:1, KMnO₄); ¹H NMR (400 MHz, CDCl₃) 55.40 (t, J = 6.8 Hz, 2H), 5.10 (t, J = 6.8 Hz, 2H), 4.19-4.12 (m, 8H), 2.62 (dt, J = 16.0, 7.2 Hz, 4H), 2.08-1.98 (m, 8H), 1.66 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H).

**Preparation of Compound 9**

To a solution of 8 (600 mg, 1.07 mmol) in 20 mL of DCM was added 2,4,6-collidine (0.4 mL) and TMSBr (1.2 mL). The reaction mixture was stirred for 16 h. The solvent was removed. The residue was dissolved in methanol, followed by the addition of NaOH (300 mg, 7.5 mmol). The obtained mixture was stirred for 30 minutes and concentrated. The residue was dissolved in water and extracted with DCM. The aqueous phase was adjusted to pH 1 with concentrated HCl and extracted with EA, washed with brine, dried over Na₂SO₄.
concentrated to give 9 (200 mg, 42%). LC-MS: 447 (M+); $^1$H NMR (400 MHz, CDC$_3$I) δ 8.89 (br s, 4H), 5.34 (br s, 2H), 5.06 (br s, 2H), 2.66-2.65 (m, 2H), 2.07-1.99 (m, 8H), 1.64 (s, 3H), 1.58 (s, 3H), 1.56 (s, 3H).

**Preparation of Compound 10**

To a suspension of NaH (60%, 40 mg, 1 mmol) in anhydrous DMF at 0 °C was added 3 (288 mg, 1 mmol). The reaction mixture was stirred for 30 minutes and farnesyl bromide (285 mg, 1 mmol) was added. The reaction mixture was warmed to it and stirred for 4 h, then water (5 mL) was added. The aqueous phase was extracted with ethyl ether (20 mL x 2) and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated, the residue was purified by flash column on silica (DCM:MeOH = 100:0-50:1) to give 10 (310 mg, 63%). LC-MS: 493.4 (M+); TLC $R_f = 0.3$ (DCM:MeOH = 20:1, KMnO$_4$); $^1$H NMR (400 MHz, CDC$_3$I) δ 5.30 (t, $J = 7$ Hz, 1H), 5.11-5.06 (m, 2H), 4.20-4.12 (m, 8H), 2.68-2.56 (m, 2H), 2.36-2.24 (m, 1H), 2.10-1.91 (m, 8H), 1.66 (s, 3H), 1.63 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.32 (dt, $J = 7.2$, 1.6 Hz, 12H).

**Preparation of Compound 11**

To a solution of 10 (270 mg, 0.63 mmol) in 20 mL of DCM was added of 2,4,6-collidine (0.2 mL) and TMSBr (0.6 mL) and the reaction mixture was stirred for 16 h. The solvent was removed. The residue was dissolved in methanol, followed by the addition of NaOH (200 mg, 5 mmol). The obtained mixture was stirred 30 minutes and concentrated. The residue was dissolved in water and extracted with DCM. The aqueous was adjusted to pH 1 with concentrated HCl and extracted with EA, washed with brine, dried over Na$_2$SO$_4$, concentrated to give 11 (30 mg, 12%). LC-MS: 379.3 (M+); $^1$H NMR (400 MHz, CD$_3$OD) δ 5.42 (t, $J = 7.2$ Hz, 1H), 5.14-5.08 (m, 2H), 2.70-2.57 (m, 2H), 2.22-1.94 (m, 9H), 1.66 (s, 6H), 1.59 (s, 6H).
Preparation of Compound 13 and 14

To a suspension of NaH (60%, 80 mg, 2 mmol) in anhydrous DMF at 0 °C was added 12 (450 mg, 2 mmol). The reaction mixture was stirred for 30 minutes and farnesyl bromide (570 mg, 2 mmol) was added. The reaction mixture was warmed to rt and stirred for 1 h, then water (5 mL) was added. The aqueous phase was extracted with ethyl ether (20 mL x 2) and the combined organic layers were dried over Na2SO4 and concentrated, the residue was purified by flash column on silica (DCM:MeOH = 100:0-50:1) to give 13 (400 mg, 48 %) and 14 (160 mg, 13 %).

Compound 13: LC-MS: 429.3 (M+I)⁺; TLC Rf = 0.3 (PE: EA = 3:1, KMnO4); ¹H NMR (400 MHz, CDCl3) 55.07-5.04 (m, 3H), 4.21-4.11 (m, 6H), 2.98-2.89 (m, 1H), 2.72-2.64 (m, 1H), 2.52-2.47 (m, 1H), 2.05-1.94 (m, 8H), 1.74 (s, 3H), 1.70 (s, 3H), 1.66 (s, 3H), 1.64 (s, 3H), 1.40 (dt, J = 7.2, 2.4 Hz, 6H), 1.33 (t, J = 7 Hz, 3H).

Compound 14: LC-MS: 655.5 (M+Na)⁺; TLC Rf = 0.4 (PE: EA = 3:1, KMnO4); ¹H NMR (400 MHz, CDCl3) 55.16 (t, J = 6.8 Hz, 2H), 5.05-5.02 (m, 4H), 4.17-4.05 (m, 6H), 2.61-2.54 (m, 4H), 2.02-1.89 (m, 16H), 1.62 (s, 6H), 1.53-1.56 (m, 18H), 1.28-1.20 (m, 9H).

Preparation of Compound 15

To a solution of 13 (300 mg, 0.73 mmol) in 20 mL of DCM was added of 2,4,6-collidine (0.2 mL) and TMSBr (0.6 mL) and the reaction mixture was stirred for 16 h. The solvent was removed. The residue was dissolved in methanol, followed by the addition of NaOH (200 mg, 5 mmol). The obtained mixture was stirred for 30 minutes and concentrated. The residue was dissolved in water and extracted with DCM. The aqueous was adjusted to pH 1 with concentrated HCl and extracted with EA, washed with brine, dried over Na2SO4.
To a suspension of NaH (60%, 40 mg, 1 mmol) in anhydrous DMF (5 mL) at 0 °C was added 12 (250 mg, 1.02 mmol). The reaction mixture was stirred for 30 minutes and 2 (300 mg, 0.85 mmol) was added. The reaction mixture was warmed to rt and stirred for 1 h, and then water (5 mL) was added. The aqueous phase was extracted with ethyl ether (20 mLx 2) and the combined organic layers were dried over Na₂SO₄ and concentrated, the residue was purified by flash column on silica (PE:EA = 100:1-5:1) to give 16 (230 mg, 76%) and 17 (100 mg, 16%).

**Compound 16:** LC-MS: 497.6 (M+1)⁺; TLC R₅ = 0.3 (PE: EA = 3: 1, KMnO₄); ¹H NMR (400 MHz, CDCl₃) δ 5.17-5.05 (m, 3H), 5.10 (br s, 6H), 4.22-4.12 (m, 6H), 2.99-2.90 (m, 1 H), 2.75-2.65 (m, 1H), 2.56-2.48 (m, 1H), 2.08-1.96 (m, 12H), 1.69 (s, 3H), 1.65 (s, 3H), 1.60 (s, 12H), 1.34 (dt, J = 6.8, 2 Hz, 6H), 1.20 (t, J = 7.2 Hz, 3H).

**Compound 17:** LC-MS: 791.9 (M+Na)⁺; TLC R₅ = 0.4 (PE: EA = 3: 1, KMnO₄); ¹H NMR (400 MHz, CDCl₃) δ 5.22 (t, J = 7 Hz, 2H), 5.10 (br s, 6H), 4.25-4.10 (m, 6H), 2.67-2.60 (m, 4H), 2.07-1.95 (m, 24H), 1.68 (s, 6H), 1.62 (m, 6H), 1.60 (s, 18 H), 1.33-1.26 (m, 9H).

**Preparation of Compound 18**
To a solution of 16 (230 mg, 0.73 mmol) in DCM (3 mL) was added 2,4,6-collidine (0.12 mL, 0.92 mmol) and TMSBr (0.37 mL, 2.8 mmol), and the reaction mixture was stirred for 16 h. The solvent was removed. The residue was dissolved in methanol. The obtained mixture was stirred for 30 minutes and concentrated. The residue was dissolved in aqueous NaHCO₃, and extracted with DCM. The aqueous was adjusted to pH 1 with concentrated HCl and extracted with EA, washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by C-18 column to give 18 (43 mg, 14%). LC-MS: 439.2 (M-1).

**General Procedure for Preparation of Compound 19**

To a suspension of NaH (60%, 40 mg, 1 mmol) in anhydrous DMF (5 mL) at 0 °C was added 12 (220 mg, 1 mmol). The reaction mixture was stirred for 30 minutes and geranyl bromide (220 mg, 1 mmol) was added. The reaction mixture was warmed to rt and stirred for 1 h, then water (5 mL) was added. The aqueous phase was extracted with ethyl ether (20 mL x 2) and the combined organic layers were dried over Na₂SO₄ and concentrated, the residue was purified by flash column on silica (DCM:MeOH = 100:0-50:1) to give 19 (120 mg, 33%). LC-MS: 361.5 (M+1); TLC Rf = 0.3 (PE: EA = 3:1, KMnO₄): ¹H NMR (400 MHz, CDCl₃) (55.13-5.05 (m, 2H), 4.23-4.11 (m, 6H), 2.96-2.87 (m, 1 H), 2.69-2.63 (m, 1H), 2.57-2.51 (m, 1H), 2.13-1.99 (m, 5H), 1.74 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 1.36-1.26 (m, 9H).

**Example 11**

**Preparation of sublingual tablet dosage form:** An exemplary and nonlimiting sublingual tablet formulation (about 70 mg each) includes:

- GGA or a GGA derivative: 10 mg
- Mannitol: 19 mg
- Sodium starch glycolate (Primojel™): 1.2 mg
- Lactose (Pharmatose™): 100 M 38.3 mg
- Magnesium stearate: 0.6 mg
- Gelatin: 0.92 mg
A binding solution is prepared by addition of gelatin to cold purified water followed by heating on a water bath to a temperature of about 75 °C until a clear solution is obtained. GGA or a GGA derivative, mannitol and half of the sodium starch glycolate are mixed. The homogeneous mixture is wet granulated with the binder solution. The granulates are wet sieved, dried and ground using a screen of mesh size 0.63 nm. The resultant dry granules are mixed with lactose monohydrate and the second half of the sodium starch glycolate. The lubricant is added and the final mixture is compressed to form tablets having a weight of about 70 mg.

Example 12

Efficient Sublingual delivery of GGA to rats

Sublingual Formulations

30 mg/kg sublingual formulation (s.l.) formulation, dose: 0.16 ml/kg, 21% CNS-102, 79%
Excipients (10% hydrogenated castor oil, 1% potassium sorbate, 0.8% NaCl, 0.05% Disodium Edate in H₂O)

100 mg/kg s.l. formulation, dose: 0.16 ml/kg, 70% CNS-102 (trans or all trans GGA), 30%
Excipients (10% hydrogenated castor oil, 1% potassium sorbate, 0.8% NaCl, 0.05% Disodium Edate in H₂O)

30 mg/kg s.l. neat, dose: 33.66 ul/kg, 100% CNS-102,

100 mg/kg s.l. neat, dose: 112.2 ul/kg, 100% CNS-102

Subcutaneous Formulations

30 mg/kg s.c. formulation, dose: 5 ml/kg, 0.6% CNS-102, 99.4 % Excipients (2.5 % hydrogenated castor oil, 1% potassium sorbate, 0.8% NaCl, 0.05% Disodium Edate in H₂O)

100 mg/kg s.c. formulation, dose: 5 ml/kg, 2% CNS-102, 98% Excipients (2.5 % hydrogenated castor oil, 1% potassium sorbate, 0.8% NaCl, 0.05% Disodium Edate in H₂O)

Procedure

- Male Sprague Dawley rats were administered a single dose of CNS-102
- 200 ul of blood were sampled at 0.5, 1, 2, 4, 6, 8, 12, 24h after dosing, or at 0.25, 0.5, 1, 2, 4, 8h after dosing.
Concentration of CNS-102 was measured in plasma by LC-MS.

Comparison of average plasma concentrations [ng/ml] after oral gavage, sublingual, and subcutaneous dosing

<table>
<thead>
<tr>
<th>Time [h]</th>
<th>Oral gavage</th>
<th>s.l. formulation</th>
<th>s.l. neat</th>
<th>s.c formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1339</td>
<td>5855</td>
<td>5661</td>
<td>35</td>
</tr>
<tr>
<td>1</td>
<td>800</td>
<td>4959</td>
<td>4625</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>417</td>
<td>5744</td>
<td>6050</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>317</td>
<td>1157</td>
<td>1115</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>215</td>
<td>not determined</td>
<td>not determined</td>
<td>not determined</td>
</tr>
<tr>
<td>8</td>
<td>90</td>
<td>526</td>
<td>599</td>
<td>103</td>
</tr>
<tr>
<td>12</td>
<td>not determined</td>
<td>57</td>
<td>103</td>
<td>107</td>
</tr>
<tr>
<td>24</td>
<td>not determined</td>
<td>0</td>
<td>0</td>
<td>67</td>
</tr>
</tbody>
</table>

Comparison of pharmacokinetic parameters after oral gavage, sublingual, and subcutaneous dosing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>30 mg/kg CNS-102</th>
<th>100 mg/kg CNS-102</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC [ng x h/ml]</td>
<td>2715</td>
<td>18503</td>
</tr>
<tr>
<td>Cmax [ng/ml]</td>
<td>1341</td>
<td>7231</td>
</tr>
<tr>
<td>tmax [h]</td>
<td>0.625</td>
<td>1</td>
</tr>
</tbody>
</table>

171
Example 13 Sublingual Delivery in Rats - Further Data

This example demonstrates the surprisingly effective sublingual delivery of GGA.

Provided is a summary of sublingual data with CNS-101, CNS-102, CNS-103, and CNS-106. All compounds are dosed neat at 30 mg/kg (33.66μL/kg) as described in Example 12.

<table>
<thead>
<tr>
<th></th>
<th>CNS-101</th>
<th>CNS-102</th>
<th>CNS-103</th>
<th>CNS-106</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC [ng x h/ml]</td>
<td>11358</td>
<td>14226</td>
<td>7606</td>
<td>443</td>
</tr>
<tr>
<td>Cmax [ng/ml]</td>
<td>4584</td>
<td>5128</td>
<td>1610</td>
<td>155</td>
</tr>
<tr>
<td>tmax [h]</td>
<td>1.25</td>
<td>1.44</td>
<td>0.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Averages of plasma concentrations is measured at each time point [ng/ml]

Averages were calculated from 4 rats (CNS-101, CNS-103, CNS-106) or 8 rats (CNS-102)

<table>
<thead>
<tr>
<th>time [h]</th>
<th>CNS-101</th>
<th>CNS-102</th>
<th>CNS-103</th>
<th>CNS-106</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>118</td>
<td>51</td>
<td>321</td>
<td>34</td>
</tr>
<tr>
<td>0.5</td>
<td>2053</td>
<td>3981</td>
<td>3221</td>
<td>175</td>
</tr>
<tr>
<td>1</td>
<td>4073</td>
<td>3669</td>
<td>2793</td>
<td>248</td>
</tr>
<tr>
<td>2</td>
<td>2936</td>
<td>3908</td>
<td>1088</td>
<td>125</td>
</tr>
<tr>
<td>4</td>
<td>647</td>
<td>1069</td>
<td>751</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>587</td>
<td>450</td>
<td>190</td>
<td>0</td>
</tr>
</tbody>
</table>

High bioavailability and fast absorption of sublingual *cis* GGA is tabulated below
Example 14:

This rat pharmacokinetics study demonstrates the bioavailability of Hydrazone-dansyl-CNS-102 conjugate after sublingual dosing. To test the absorption of hydrazone-dansyl-CNS-102 conjugate (Molecular weight 600) in the blood after sublingual dosing, 4 male Sprague-Dawley rats were dosed sublingually with 48 mg/kg hydrazone-dansyl-CNS-102 conjugate in ethanol. The dosing volume was 115 ul/kg. Trunk blood was harvested from 2 rats 1 hour after dosing and from another 2 rats, 2 hours after dosing.

In a parallel experiment, 4 male Sprague-Dawley rats were dosed intravenously (i.v.) with 16 mg/kg hydrazone-dansyl-CNS-102 conjugate in ethanol. The dosing volume was 35 ul/kg. Trunk blood from i.v. dosed rats was harvested from 2 rats 20 minutes after dosing and from another 2 rats, 1 hour after dosing.

Plasma was obtained after 20min, 1hr, and 2hr after administrations of the conjugate to the rats. The conjugate that was contained in the collected plasma was extracted by organic solvent, and fluorescent signals of the conjugated extracted were quantified by a fluorometer.

The results are tabulated below, and demonstrate the surprising efficacy of trans GGA to transport an agent conjugated to GGA by sublingual route following sublingual delivery of the conjugate.

<table>
<thead>
<tr>
<th>Animals</th>
<th>s.l. 1hr</th>
<th>s.l. 2hr</th>
<th>iv 20 min</th>
<th>iv 1hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.71</td>
<td>2.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.51</td>
<td>4.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7.08*</td>
<td>3.6*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 15

This rat pharmacokinetics study demonstrates the bioavailability of an octreotide dansyl-CNS-102 conjugate after sublingual dosing. Octreotide is an octapeptide that mimics natural somatostatin pharmacologically, and potent inhibitor of growth hormone, glucagon, and insulin.

To test absorption of octreotide-dansyl-CNS-102 conjugate (Molecular weight 1619-2219) in the blood after sublingual dosing, 6 male Sprague-Dawley rats were dose sublingual with 48 mg/kg of the octreotide-dansyl-CNS-102 conjugate in ethanol. The dosing volume was 117 ul/kg. Trunk blood was harvested from 3 rats 1 hour after dosing and from another 3 rats, 2 hours after dosing.

In a parallel experiment, 3 male Sprague-Dawley rats were dosed intravenously (i.v.) with 48 mg/kg octreotide-dansyl-CNS-102 conjugate in ethanol. The dosing volume was 117 ul/kg. Trunk blood from i.v. dosed rats was harvested 20 minutes after dosing.

Plasma that was obtained in 20min, 1hr, and 2hr after administrations of the conjugate to the rats. Fluorescent signals from the plasma collected from the animals were quantified by a fluorometer.

The results are tabulated below, and demonstrate the surprising efficacy of trans GGA to transport a drug conjugated to GGA by sublingual route following sublingual delivery of the conjugate. Because peptides and proteins can be susceptible to breakdown by digestive enzymes in stomach upon oral delivery, a therapeutically active peptide or protein, when conjugated in accordance with the present invention, can be efficiently delivered to blood by avoiding decomposition by stomach enzymes.

<table>
<thead>
<tr>
<th>animals</th>
<th>sl 1hr</th>
<th>sl 2hr</th>
<th>iv 20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Unit: Mg/ml extracted plasma

*Values of fluorescent signals shown in the table were adjusted by amounts dosed to animals.
Example 16

Sublingual delivery of non-limiting representative drugs such as Ceredist, Sandostatin, and Forteo, using GGA as a passive carrier, is tested. Furthermore, Ceredist can be replaced with Byetta when testing three examples of the Schiff's base modified delivery system.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

The experimental data provided herein demonstrate that GGA and the described and disclosed GGA derivatives are useful according to the methods disclosed herein.

In particular, the data provided herein demonstrate that GGA and the described and disclosed GGA derivatives are suitable for sublingual administration to a subject. In some cases, this sublingual route of administration provides a bioavailability of GGA or a GGA derivative that is comparable to an i.v. administration of GGA or GGA derivative.

The GGA and GGA derivatives described and disclosed herein are sufficiently hydrophobic to partition favorably into the mucosa relative to the saliva of a subject and yet the GGA and GGA derivatives are also sufficiently hydrophilic to subsequently pass from the mucosa into the subject's blood stream to exert a therapeutic effect.
Example 17: Inhibition of osteoclast differentiation and activation in vitro and in vivo

Osteoclasts are large multinucleated cells derived from the myelomonocytic lineage that adhere to and resorb bone through the local production of the lytic enzymes cathepsin K and tartrate-resistant acid phosphatase (TRAP), which degrade bone protein and mineral content. Osteoclasts can be isolated from animal bones or can be generated from myeloid precursors via differentiation in vitro. Myeloid cells treated in vitro with the cytokines Colony-Stimulating Factor-1 (CSF-1) and receptor activator of nuclear factor kappa-B ligand (RANKL) (Boyle, W.J. et al., Nature 423(6937):337-42, 2003) differentiate into mature osteoclasts that express Cathepsin K and TRAP and are capable of resorbing cortical bone slices. Compounds that are used to treat bone diseases characterized by pathologic bone loss either block osteoclast differentiation and/or osteoclast activation of bone resorption.

Example 18: Effect of GGA on osteoclastogenesis

To determine the effect of geranylgeranylacetone (GGA) on osteoclastogenesis, osteoclast precursors are derived by taking the nonadherent bone marrow cells after an overnight incubation in CSF-1/M-CSF (macrophage colony stimulating factor), and culturing the cells for an additional 4 days with 1,000 - 2,000 U/ml CSF-1. (Lacey et al., Cell 93, 165-176, 1998). Following 4 days of culture, the adherent cells, which are bone marrow macrophages, can then be exposed to 100 ng/ml RANKL and cultured for 3-5 days. The generation of mature osteoclast can be measured by counting multinucleated TRAP positive cells or by measuring TRAP enzyme activity using histoperoxidase assays as described. Test agents such as GGA and derivatives can be added during this terminal period as well to determine their effects on osteoclast differentiation.

Example 19: Effects of GGA and GGA derivatives on bone resorption in vitro

To assess the effects of GGA and derivatives on bone resorption in vitro one can use the bone pit assay as described by Burgess et al. (J. Cell Biol. 145(3): 527-538, 1999). Osteoclasts can be differentiated on the surface or cortical or dentin bone slices in the presence of CSF-1 and RANKL, then treated with test compounds to look at the impact on bone resorption pit formation as described.
Example 20: Inhibition of osteoclast function in vivo by monitoring bone resorption

GGA and derivaties can be tested for their ability to modulate osteoclast function by administering to animals and monitoring bone resorption. One model is to determine the effects on bone resorption of young growing mice as previously described (Schenk et al., Calci.Tissues Int 38:342-349, 1986; Simonet et al., Cell 89, 308-319, 1997). Young growing mice aged 3-4 weeks, weight range 9.2-15.7 g are divided into groups of ten mice per group. These mice are injected subcutaneously with saline or test compounds bid for 14 days (5mg/kg/day). The mice are then radiographed before treatment, at day 7 and on day 14. The mice were sacrificed 24 hours after the final injection. The right femur is then removed, fixed in zinc formalin, decalcified in formic acid and embedded in paraffin. Sections are cut through the mid region of the distal femoral metaphysis and the femoral shaft. Bone density, by histomorphometry, is determined in six adjacent regions extending from the metaphyseal limit of the growth plate, through the primary and secondary spongiosa and into the femoral diaphysis (shaft). Radiographic changes are observed after seven days of treatment to detect evidence of a zone of increased bone density in the spongiosa associated with the growth plates in the GGA treated mice relative to that seen in the controls. Histological changes are observed in the distal femoral metaphysis as shown by increased bone density in a region 1.1 to 2.65 mm in distance from the growth plate. This is a region where bone is rapidly removed by osteoclast-mediated bone resorption in mice.

In these rapidly growing young mice, the increase in bone in this region observed with treatment is consistent with an inhibition of bone resorption.

Example 21: Effects of GGA and GGA derivatives on bone loss in ovariectomized rats

Effects of GGA and derivatives on bone loss can also be assessed in ovariectomized rats, an animal model for postmenopausal osteoporosis. In this model, typically twelve week old female Fisher rats are ovariectomized (OVX) or sham operated and dual x-ray absorptiometry (DEXA) measurements are made of the bone density in the distal femoral metaphysis. After 3 days recovery period, the animals receive daily injections for 14 days as follows: Ten sham operated animals receive vehicle (phosphate buffered saline); Ten OVX animals receive vehicle (phosphate buffered saline); Six OVX animals receive test compounds; Six OVX animals receive pamidronate (PAM) 5mg/kg SC as a positive control bisphosphonate; Six OVX animals receive estrogen (ESTR) 40ug/kg SC. After 7 and 14 days
post treatment the animals have bone density measured by DEXA. Two days after the last injection the animals are sacrificed and the right tibia and femur removed for histological evaluation.

The DEXA measurements of bone density will allow detection of a trend to reduce bone density following ovariectomy that is modulated by test compounds and positive controls. The histomorphometric analysis of these animals will confirm bone density increases due to the preservation of cortical bone due to inhibition of osteoclast mediated bone resorption.

Example 22

Demonstrating Sublingual Drug Delivery

Feasibility studies described herein demonstrate the delivery of a 1.3 kD conjugated drug that was measurable in plasma within 2 hours after sublingual administration. CNS102 (trans) and CNS103 (cis) are geometric isomers, that cross the sublingual barrier efficiently and rapidly. A natural transport mechanism is contemplated.

Feasibility studies of sublingual delivery

1. Smaller molecular weight (MW~ 300) compound conjugated to CNS
   - Detected in plasma in 1 hour

2. Larger molecular weight compound (~1.3 kD) conjugated to CNS
   - Detected in plasma in 1 hour
   - Peak detection at 2 hour
   - Return to background levels at 4 and 8 hours

Sublingual Drug Delivery Studies

Liquid chromatography and mass spectroscopy (LC/MS/MS) was used to measure the appearance in rat plasma of CNS following a single 30 mg/kg sublingual dose and a representative PK profile is shown below in the graph.

\[
\begin{align*}
\text{AUC} &= 13705 \\
\text{Cmax} &= 5110 \\
\text{tmax} &= 0.75 \text{ (h)}
\end{align*}
\]
Passive Mixtures as a Sublingual Delivery System

Exploratory sublingual studies using CNS compounds as passive delivery carriers (i.e., not covalently bound to the drug) for various test drugs gave no evidence of sublingual transport of these drugs up to ~6 kDa molecular weight under the conditions tested.

5 Fluorescence Label Detection in Plasma

A study of the efficacy of drug transport by covalent conjugation was conducted using the dansylhydrazone derivative of CNS. The highly fluorescent hydrazone was administered in a single sublingual dose of 48 mg/kg or a single IV dose of 16 mg/kg. All the conjugates were part of mixtures. The concentration averages of the data from two animals per time point per treatment group are shown below along with standard deviation error bars.

Transport of this conjugate into the blood following a single sublingual dose was measured by comparison of fluorescence in plasma compared to a standard curve. The conjugate was extracted from plasma and identified as the administered dansylhydrazone conjugate using thin-layer chromatography. Thus, covalent conjugation and sublingual administration provides a viable way to deliver drugs to the bloodstream.

Dansyl Peptide CNS Conjugate

Studies were expanded to examine the transport of larger molecules, beginning with a CNS conjugate of a dansylated peptide (dansyl ocreotide) of approximate molecular weight of 1.3 kDa. The peptide was fluorescently labeled with dansyl chloride, conjugated with CNS and given in a single dose of 48 mg/kg by either sublingual or IV administration. Average plasma levels for each of two animals per time point per treatment group are shown below.

<table>
<thead>
<tr>
<th></th>
<th>SL 60</th>
<th>SL 120</th>
<th>IV 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average ug/ml</td>
<td>1.10</td>
<td>1.17</td>
<td>6.22</td>
</tr>
<tr>
<td>t-value</td>
<td>4.58</td>
<td>5.78</td>
<td>2.01</td>
</tr>
<tr>
<td>p-value</td>
<td>0.02</td>
<td>0.01</td>
<td>0.09</td>
</tr>
</tbody>
</table>

SL: sublingual; IV: intravenous

These data showed that the conjugate crossed the sublingual mucosa.
A Time Study of Dansyl-Peptide-CNS Conjugate (DPC) Compared to Dansyl-Peptide Control (DP).

For confirmation, an expanded experiment was conducted that included additional time points and the unconjugated dansyl-labeled peptide as a control. Each compound was administered in two repeated sublingual doses of 58.5 mg/kg, 5 minutes apart. Plasma levels minus pre-dose values for each time point per animal per treatment group are shown in the graph below (N=4 for the dansyl peptide control; N = 8 for the CNS peptide conjugate). All averages for the dansyl peptide control, and the data at 4 and 8 hours for its CNS conjugate were indistinguishable from the background fluorescence found in pre-dose bleeds for each animal as shown in the table.

<table>
<thead>
<tr>
<th>Treat</th>
<th>Time</th>
<th>N</th>
<th>Average</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>30</td>
<td>4</td>
<td>0.018</td>
<td>0.8550</td>
</tr>
<tr>
<td>DP</td>
<td>60</td>
<td>4</td>
<td>-0.020</td>
<td>0.8340</td>
</tr>
<tr>
<td>DP</td>
<td>120</td>
<td>4</td>
<td>0.045</td>
<td>0.6380</td>
</tr>
<tr>
<td>DPC</td>
<td>30</td>
<td>8</td>
<td>0.124</td>
<td>0.0740</td>
</tr>
<tr>
<td>DPC</td>
<td>60</td>
<td>8</td>
<td>0.108</td>
<td>0.1190</td>
</tr>
<tr>
<td>DPC</td>
<td>120</td>
<td>8</td>
<td>0.279</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

DP: dansyl peptide control  DPC: CNS peptide conjugate

The appearance in plasma of fluorescence from the conjugated peptide compared to the unconjugated control within the first two hours after administration is interpreted as confirmation of the active role of CNS in crossing the sublingual barrier. The return of this fluorescence to background levels at 4 and 8 hours is consistent with metabolic processing of the conjugate.

IgG Conjugate

An experiment was conducted to provide evidence for the proof of concept that CNS102 conjugation facilitates uptake of goat IgG into the blood stream after sublingual administration. Polyclonal goat IgG was used in this experiment. It has approximately 80 binding sites for covalent binding of CNS102. The conjugate prepared from IgG reacted with 10 equivalents of CNS102: IgG-CNS102\(_10\).
Analysis was performed with a commercially available goat specific ELISA kit with no significant cross reactivity to rat IgG. A separate standard curve was prepared for the IgG-CNS102 conjugate and for the non-conjugated IgG that was used as the negative control. Serum concentrations of IgG-CNS102(1o) and of IgG were determined at 5 min, 20 min, 1 hour, 3 hours, 8 hours and 24 hours. 3 rats were examined at each time point and in each dosing group. IgG-CNS102(1o) was dosed at 35 mg/kg (both i.v. and s.l.), IgG was dosed at 32 mg/kg.

The table of results shows the average serum concentrations of three samples ± standard deviation.

<table>
<thead>
<tr>
<th>time after dosing [h]</th>
<th>IgG-CNS102 conc. after s.l. dosing [ug/ml]</th>
<th>IgG conc. after s.l. dosing [ug/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.08</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>0.3</td>
<td>0.091 ± 0.051.8</td>
<td>0.057 ± 0.019</td>
</tr>
<tr>
<td>1</td>
<td>0.069 ± 0.037</td>
<td>0.040 ± 0.027</td>
</tr>
<tr>
<td>3</td>
<td>0.021 ± 0.012</td>
<td>0.028 ± 0.018</td>
</tr>
<tr>
<td>8</td>
<td>0.030 ± 0.023</td>
<td>0.017 ± 0.023</td>
</tr>
<tr>
<td>24</td>
<td>0.045 ± 0.008</td>
<td>0.023 ± 0.012</td>
</tr>
</tbody>
</table>

Throughout the description provided herein, reference is made to various patent applications and publications, each of which is herein incorporated by reference in their entirety.
What is claimed is:

1. A compound comprising GGA or a GGA derivative conjugated with a drug optionally via a linker that is labile in vivo.

2. A pharmaceutical sublingual composition comprising the compound of claim 1.

3. A method of sublingually delivering the compound of claim 1, comprising sublingually administering GGA or the GGA derivative conjugated with a drug optionally via a linker to a patient in need thereof.

4. A method of sublingually delivering GGA or a GGA derivative, comprising sublingually administering GGA or the GGA derivative to a patient in need thereof.

5. A pharmaceutical composition comprising GGA or a GGA derivative admixed with a drug.

6. The composition of claim 5, which is for sublingual delivery.

7. A method of maintaining exposure of an effective amount of GGA or a GGA derivative for a period of up to 1 hour, up to 2 hours, or up to 3 hours, in a patient comprising administering the GGA or the GGA derivative sublingually to the patient in need thereof.

8. A method of maintaining exposure of an effective amount of a drug for a period of up to 1 hour, up to 2 hours, or up to 3 hours, in a patient comprising administering a GGA or a GGA derivative conjugate of the drug sublingually to the patient in need thereof.

9. A composition for treating osteopenia and/or reducing one or more negative effects of bone loss, the composition comprising an effective amount of geranylgeranyl acetone (GGA) or a GGA derivative, and a pharmaceutically acceptable excipient.

10. The composition of claim 9, 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.

11. A method for treating osteopenia and/or reducing one or more negative effects of bone loss comprising administering an effective amount of GGA or a GGA derivative, or a composition of claim 9 to a patient in need thereof.

12. A method for inhibiting loss of bone density in a patient in need thereof comprising administering to the patient an effective amount of GGA or a GGA derivative, or a composition of claim 9.
13. A method for inhibiting bone fracture in a patient at risk thereof which bone fracture arises at least in part from pathological bone loss comprising administering to the patient an effective amount of GGA or a GGA derivative, or a composition of claim 9.

14. The method of claim 13, wherein the bone fracture is fracture of the hip.

15. The method of claim 13, wherein the bone fracture is fracture of the vertebrae.

16. A method for inhibiting bone loss and/or facilitating bone growth in a patient at a risk of loss of bone density, comprising administering to the patient an effective amount of GGA or a GGA derivative, or a composition of claim 9.

17. The method of any one of claims 11-16, 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.

18. A composition for inhibiting neural death, increasing neural activity and/or for reducing one or more negative effects of neurodegeneration comprising a compound of Formula (XVIII) or (XIX):

\[
\begin{align*}
&\text{(XVIII)} \\
&\text{(XIX)} \\
\end{align*}
\]

or a pharmaceutically acceptable salt thereof

wherein

- \( R^{91} \) is C5-C20 alkyl or C5-C20 alkenyl optionally substituted with 1-3 C6-C20 arylene groups in the chain and that is optionally substituted with 1-3 halo, trifluoromethyl, -OR, -P(=0)(OR)(OR) or -NR100R101 groups;
- \( R^{92} \) is (C5-C20)alkyl or C5-C20 alkenyl optionally substituted with 1-3 C6-C20 aryl groups, which aryl group(s) are optionally substituted with 1-3 halo, trifluoromethyl, -OR, -P(=0)(OR)(OR) or -NR100R101 groups;
- each \( R^{93}, R^{94}, R^{95}, \) and \( R^{96} \) is independently OH or C6-C10 alkoxy;
- each \( R^{97}, R^{98} \) and \( R^{99} \) is independently hydrogen, C1-C6 alkyl or C6-C20 aryl; and each \( R^{100} \) and \( R^{101} \) is independently hydrogen, C1-C6 alkyl or C6-C20 aryl; or \( R^{101} \) and \( R^{102} \) together with the nitrogen to which they are attached form a C3-C7 heterocycle;
wherein each aryl group of $R_9^7$, $R_9^8$, $R_9^{10}$ and $R_9^{01}$ is optionally substituted with 1-3 C$_2$-C$_6$ alkyl, Cl-Ce alkoxy, C$_1$-C$_6$ alkanoyl, C$_1$-C$_6$ alkanoyloxy, C$_1$-C$_6$ alkoxy carbonyl, halo, cyano, nitro, carboxy, trifluoromethyl, trifluoromethoxy, $NR_9^{102}R_9^{03}$, or $S(O)$$_2$NR$_9^{102}R_9^{03}$ groups, wherein each $R_9^{102}$ and $R_9^{03}$ is independently hydrogen or C$_x$-C$_6$ alkyl;

$R_9^{104}$ and $R_9^{105}$ are independently selected from the group consisting of hydrogen, C$_2$-C$_6$ alkyl, C$_3$-C$_7$ cycloalkyl, C$_2$-C$_6$ alkenyl, C$_1$-C$_5$ alkynyl, optionally substituted C$_6$-$C_{20}$ aryl, optionally substituted C$_6$-$C_{20}$ aryl-Ci-Ce alkyl, optionally substituted heteroaryl and optionally substituted heteroaryl-Ci-Ce 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, Cl-C$_6$ alkyl, C$_2$-C$_6$ alkoxy, -NO$_2$, and -NR$_9^{106}$R$_9^{110}$ and $R_9^{105}$ together with the carbon atom they are attached to form a C$_3$-C$_7$ cycloalkyl ring optionally substituted with 1-3 Ci-C$_6$ alkyl groups;

$R_9^{106}$ and $R_9^{107}$ are independently hydrogen or C$_6$-alkyl;

each $R_9^{106}$ and $R_9^{109}$ are independently selected from the group consisting of a hydrogen, Cl-C$_6$ alkyl, and a group of Formula (XXI):

$$\begin{align*}
R_9^{104} & - R_9^{105} - R_9^{106} - R_9^{107} - n - \frac{2}{2} \\
\end{align*}$$

(XXI)

wherein $R_9^{104}$- $R_9^{107}$ and $n$ are as defined herein;

$Y$ is -P(=O)(OR$_9^{108}$)(OR$_9^{109}$), -CO$_2$R$_9^{110}$ or -SO$_2$OR$_9^{110}$, wherein $R_9^{110}$ is selected from the group consisting of a hydrogen and C$_2$-C$_6$ alkyl;

$Z$ is $\frac{1}{2}$-$A$-$\frac{1}{2}$-N-$\frac{1}{2}$-(CH$_2$)$_2$-$\frac{1}{2}$-

wherein $R_9^{111}$ is hydrogen or C$_2$-C$_6$ alkyl; A is C$_1$-C$_5$ alkyne which may have a substituent selected from -OH, halo, Cl-C$_6$ alkyl, and Cl-C$_6$ alkoxy groups on each carbon;

$r$ is 0, 1, 2, 3, 4 or 5; and

$n$ is 0, 1, 2, 3, 4 or 5.
19. The composition of claim 18, wherein the compound is of Formula (XIXa)

\[
\begin{align*}
R^{104} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \Quad
21. The composition of claim 18, wherein the compound is selected from the group consisting of:

\[
\begin{align*}
&\text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{PO} \left( \text{OCH}_2 \right)_2 - \\
&\text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{PO} \left( \text{OCH}_3 \right)_2 - \\
&\text{CH}_3 - \text{CH}_3 - \text{PO} \left( \text{OH} \right)_2 - \\
&\text{CH}_3 - \text{CH}_3 - \text{PO} \left( \text{OH} \right)_2
\end{align*}
\]

; and

22. A compound of Formula (XIX):

\[
\begin{align*}
R^{104} & - \text{R}^{105} - \text{R}^{106} - \text{R}^{107} - \text{R}^{108} - \text{R}^{109} \quad \text{(XIX)}
\end{align*}
\]

or a pharmaceutically acceptable salt thereof,

wherein

\[R^{104}\] and \[R^{105}\] are independently selected from the group consisting of hydrogen, \(\text{C}_2-\text{C}_6\) alkyl, \(\text{C}_3-\text{C}_7\) cycloalkyl, \(\text{C}_2-\text{C}_5\) alkenyl, \(\text{C}_1-\text{C}_5\) alkynyl, optionally substituted \(\text{C}_6-\text{C}_{20}\) aryl, optionally substituted \(\text{C}_6-\text{C}_{20}\) aryl-\(\text{C}_1-\text{C}_5\) alkyl, optionally substituted heteroaryl and optionally substituted heteroaryl \(\text{C}_2-\text{C}_5\) 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, Ci-Ce alkyl, C1-C6 alkoxy, -N02, and -IM groups; or

\[ R^{104} \text{ and } R^{105} \text{ with the carbon atom they are attached to form a } C_3-C_7 \]

cycloalkyl ring optionally substituted with 1-3 Ci-C6 alkyl groups;

\[ R^{106} \text{ and } R^{107} \text{ independently are hydrogen, methyl or } C_2-C_6 \text{ alkyl, provided that, when one of } R^{106} \text{ and } R^{109} \text{ is not:} \]

and each of \( R^{106} \) and \( R^{107} \) is methyl, then \( R^{104} \) and \( R^{105} \) are defined as follows: \( R^{104} \) and \( R^{105} \) together with the carbon atom they are attached to form a \( C_5-C_7 \) cycloalkyl optionally substituted with 1-3 Ci-C6 alkyl groups;

\( R^{108} \) and \( R^{109} \) are independently selected from the group consisting of a hydrogen, Ci-C6 alkyl and a group of Formula (XXI):

\[ Y \text{ is } -P(=0)(OR^{108})(OR^{109}) \text{ or } -CO_2R^{110}, \text{ wherein } R^{110} \text{ is selected from the group consisting of hydrogen and } C_1-C_6 \text{ alkyl;} \]

\[ Z \text{ is } ^\frac{1}{2}A \rightarrow \mathrm{N}-(\mathrm{CH}_2)_n^\frac{1}{2} \]

wherein \( R^{111} \) is hydrogen or Ci-C6 alkyl; \( A \) is \( C_2-C_6 \) alkylen which may have a substituent selected from -OH, halo, Ci-C6 alkyl, and Ci-C6 alkoxy groups on each carbon;

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

\( n \) is 0, 1, 2, 3, 4 or 5.
23. A composition comprising the compound of claim 22 and at least one pharmaceutically acceptable excipient.

24. A method for inhibiting neural death, increasing neural activity, and/or of reducing one or more negative effects of neurodegeneration comprising administering a compound of claim 22 or a composition of claim 23 to a patient in need thereof.

25. A method for treating osteopenia and/or reducing one or more negative effects of osteopenia comprising administering an effective amount of a compound of claim 22 or a composition of claim 23 to a patient in need thereof.

26. A method for inhibiting neural death, increasing neural activity, and/or of reducing one or more negative effects of neurodegeneration comprising administering to a patient in need thereof an effective amount of a compound selected from the group consisting of:
27. A method for treating osteopenia and/or reducing one or more negative effects of osteopenia comprising administering to a patient in need thereof an effective amount of a compound selected from the group consisting of:
FIG. 1

CNS102 Sublingual Delivery

AUC = 13705  Cmax = 5110  tmax = 0.75 (h)
FIG. 2

Feasibility Study
Dansyl CNS from Plasma

ug/ml

SL 60
SL 120
IV 20
IV 60

Route and Time (min)

sl dose: 48 mg/kg

iv dose: 16 mg/kg
FIG. 3

Feasibility Study
Dansylated Peptide CNS Conjugate

dose administered: 48 mg/kg

Route and Time (min)

<table>
<thead>
<tr>
<th>Route</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SL 60</td>
<td></td>
</tr>
<tr>
<td>SL 120</td>
<td></td>
</tr>
<tr>
<td>IV 20</td>
<td></td>
</tr>
</tbody>
</table>

 ug/ml
FIG. 4

Time Course of Appearance in Plasma

Comparison of Averages to Zero

DP: dansyl peptide control (squares)  DPC: CNS peptide conjugate (circles)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/121(2006.01)i, A61K 31/232(2006.01)i, A61K 31/23(2006.01)i, A61K 31/223(2006.01)i, A61P 31/16(2006.01)i, A61P 25/28(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 31/24; A61K 31/675; C07F 9/02; C07K 2/00; A61K 3/045; C07C 29/147; A61K 38/06; A61K 31/232; A61K 3/223; A61P 31/16; A61P 25/28; 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 practicable, search terms used)
eKOMPASS(KXPO internal) & Keywords: geranylgeranyl acetone, polyisoprenyl phosphonate, carrier, vehicle

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>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 2009-0054623 Al (DEFREES, SHAWN) 26 February 2009</td>
<td>1-2, 5-6</td>
</tr>
<tr>
<td>A</td>
<td>US 2002-0082244 Al (RESZKA, A. et al.) 27 June 2002</td>
<td>1-2, 5-6</td>
</tr>
<tr>
<td>A</td>
<td>US 2012-0172453 Al (BARRES, B. A. et al.) 05 July 2012</td>
<td>1-2, 5-6</td>
</tr>
<tr>
<td>A</td>
<td>US 5453524 A (TAGAMI, K. et al.) 26 Sept ember 1995</td>
<td>1-2, 5-6</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search
28 August 2014 (28.08.2014)

Date of mailing of the international search report
28 August 2014 (28.08.2014)

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongna-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
CHOI, Sung Hee
Telephone No. +82-42-481-8740

Form PCT/ISA/210 (second sheet) (July 2009)
<table>
<thead>
<tr>
<th>Box No. II</th>
<th>Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:</td>
</tr>
<tr>
<td></td>
<td>1. ☒ Claims Nos.: 3-4,7-8,11-17,24-27 because they relate to subject matter not required to be searched by this Authority, namely:</td>
</tr>
<tr>
<td></td>
<td>Claims 3-4,7-8,11-17,24-27 pertain to methods for treatment of the human body 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.</td>
</tr>
<tr>
<td></td>
<td>2. ☐ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:</td>
</tr>
<tr>
<td></td>
<td>3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Box No. III</th>
<th>Observations where unity of invention is lacking (Continuation of item 3 of first sheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>This International Searching Authority found multiple inventions in this international application, as follows:</td>
</tr>
<tr>
<td></td>
<td>Group 1, claims 1, 2, 5 and 6, related to a composition comprising GGA or a GGA derivative as a passive carrier.</td>
</tr>
<tr>
<td></td>
<td>Group 2, claims 9-10, related to a composition for treating osteopenia and/or reducing one or more negative effects of bone loss comprising an effective amount of GGA or a GGA derivative.</td>
</tr>
<tr>
<td></td>
<td>Group 3, claims 18-21, related to a composition for inhibiting neural death, increasing neural activity and/or for reducing one or more negative effects of neurodegeneration comprising a GGA derivative of Formula (XVIII) or (XIX).</td>
</tr>
<tr>
<td></td>
<td>Group 4, claims 22-23, related to a compound of a GGA derivative of Formula (XIX).</td>
</tr>
</tbody>
</table>

|            | 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 fee. |
|            | 3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: |
|            | 4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-2,5-6 |

<p>| 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. |</p>
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>wo 2006-066258 A3</td>
<td>10/08/2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 757104 B2</td>
<td>30/01/2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2336201 Al</td>
<td>29/12/1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1088333 Al</td>
<td>04/04/2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2002-519305 A</td>
<td>02/07/2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6432931 Bl</td>
<td>13/08/2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6699850 B2</td>
<td>02/03/2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 99-67809 Al</td>
<td>29/12/1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 99-67809 A9</td>
<td>22/03/2001</td>
</tr>
<tr>
<td>US 2008-0113919 Al</td>
<td>15/05/2008</td>
<td>US 2005-0026812 Al</td>
<td>03/02/2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 2005-016864 Al</td>
<td>24/02/2005</td>
</tr>
<tr>
<td>US 2012-0172453 Al</td>
<td>05/07/2012</td>
<td>AU 2011-295920 Al</td>
<td>24/01/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2806238 Al</td>
<td>08/03/2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 103052619 A</td>
<td>17/04/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2611765 A2</td>
<td>10/07/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2611765 A4</td>
<td>11/06/2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 10-2013-0109103 A</td>
<td>07/10/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX 2013001236 A</td>
<td>01/05/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 2012-031028 A2</td>
<td>08/03/2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 2012-031028 A3</td>
<td>05/07/2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0609440 Bl</td>
<td>28/04/1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 05-239075 A</td>
<td>17/09/1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 93-04073 Al</td>
<td>04/03/1993</td>
</tr>
</tbody>
</table>