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(54) Title: COMPOSITIONS AND METHODS FOR TREATING MYOCARDIAL INFARCTION

(57) Abstract: Methods of treating inflammation conditions in a subject is provided, including administering to the subject an effective amount of one or more caffeic acid derivatives to effectively alter the polarization of macrophages from M1 to M2, i.e., from a pro-inflammatory phenotype to a reparative phenotype activation of macrophages. In some embodiments, the caffeic acid derivative is administered to treat myocardial infarction, attenuate the chemotaxis and phagocytosis of macrophages, increase the viability of cardiomyocytes in an ischemia-mimicking environment, and/or increase the activities of antioxidant enzymes in the tissues. In some embodiments, the caffeic acid derivatives have an improved half-life in plasma or pathophysiological conditions. A facile and cost-effective method of making these caffeic acid derivatives is also provided.



COMPOSITIONS AND METHODS FOR TREATING MYOCARDIAL INFARCTION

FIELD OF THE INVENTION

The disclosed invention is generally in the field of treatment of myocardial
5 infarction and specifically in the area of modulating macrophages for resolution of
inflammation.

BACKGROUND OF THE INVENTION

Myocardial infarction is a leading cause of morbidity and mortality worldwide
(Bonow RO, et al., *Circulation*, 106(13):1602-1605 (2002); Yellon DM, et al., *The New*
10 *England Journal of Medicine*, 357(11):1121-1135 (2007)). Myocardial infarction
triggers a sequence of inflammatory reactions involving the infiltration, activation,
apoptosis and clearance of polymorphonuclear leukocytes such as neutrophils and
macrophages (Jordan JE, et al., *Cardiovascular Research*, 43(4):860-878 (1999)).
Neutrophils and macrophages play important roles in tissue damage, wound healing,
15 cardiac remodeling and scar formation (Jordan JE, et al., *Cardiovascular Research*,
43(4):860-878 (1999); Nahrendorf M, et al., *Circulation*, 121(22):2437-2445 (2010)).
Upon activation, neutrophils release reactive oxygen species, reactive nitrogen species,
proteases, and possibly chemoattractant mediators for recruiting new inflammatory cells.
On the other hand, macrophages undergo dynamic phenotypic and functional
20 transformation from pro-inflammatory M1 and anti-inflammatory M2 (Mosser DM, et al.,
Nature Reviews Immunology, 8(12):958-969 (2008)). Importantly, timely phenotypic and
functional switch of macrophages is critical for macrophages to clear neutrophils within
infarcted myocardium.

Current anti-inflammatory drugs for myocardial infarction are neither designed to
25 target macrophages nor neutrophils. The available therapeutic drugs used for the
treatment of inflammatory diseases is composed primarily of non-steroidal anti-
inflammatory drugs (NSAIDS) and glucocorticoids. However, these drugs possess severe
side effects and provide unsatisfactory results in some pathologies (Sautebin L, et al.,
Fitoterapia, 71, S48-S57 (2000)).

30 Therefore, it is an object of the invention to provide a method of treating
myocardial infarction by targeting the transformation of macrophages.

It is another object of the invention to provide compositions with desirable pharmacological profiles in the method to treat myocardial infarction.

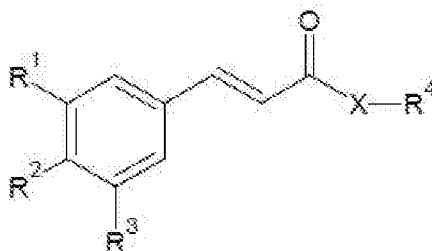
SUMMARY OF THE INVENTION

The present invention provides a method for treating a subject having a condition
 5 having greater M1 macrophage polarization than M2 macrophage polarization, by administering at least a caffeic acid derivative having the structure of Formula 3, where the caffeic acid derivative is effective to alter the polarization of macrophages from M1 macrophages to M2 macrophages and thereby reduce the effects of M1 macrophages.

In one aspect, the condition having greater M1 macrophage polarization than M2
 10 macrophage polarization is or results in reduced or absent blood flow to one or more tissues of the subject. The caffeic acid derivative is administered during or following reduced or absent blood flow, and/or following diagnosis of current or prior reduced or absent blood flow to one or more tissues of the subject.

In another aspect, the condition having greater M1 macrophage polarization than
 15 M2 macrophage polarization is or results in myocardial infarction, where the tissue is myocardial tissue and administering at least the caffeic acid derivative having the structure of Formula 3 leads to reduced infarct inflammation. Administering at least the caffeic acid derivative takes place within four hours of the appearance of symptoms or the diagnosis.

20 An important feature of this method by administering at least the caffeic acid derivatives is altering the polarization from M1 macrophages to M2 macrophages, reducing the infarct size compared to that of an untreated control, enhancing the survival of cardiomyocytes against oxygen glucose deprivation, attenuating the infiltration of polymorphonuclear leukocytes and damage of the tissues, decreasing lipid peroxidation,
 25 increasing the activities of antioxidant enzymes in the tissues including, but not limited to, catalase (CAT), superoxide dismutase (SOD), myeloperoxidase (MPO), malonaldehyde (MDA), or a combination thereof.



Formula 3

In Formula 3, R^1 , R^2 , and R^3 are, independently, hydroxyl, hydrogen, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl; X is O, S, or NR^a wherein R^a is H or substituted or unsubstituted C_1 - C_{10} , alkyl, alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl; and R^4 is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C_3 - C_{20} cyclic, heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C_3 - C_{20} cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, hydrogen, or, if R^a forms two bonds with the N, absent; wherein at least one of R^1 , R^2 , and R^3 is hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl; wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl.

The present invention also provides a method for attenuating the chemotaxis and phagocytosis of macrophages in a subject reacting to an inflammatory insult, by administering at least a caffeic acid derivative having the structure of Formula 3, where the caffeic acid derivative is effective to attenuate the chemotaxis and phagocytosis of macrophages in the subject.

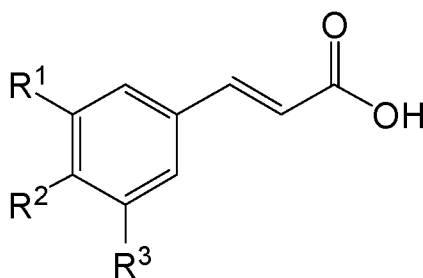
In a further aspect, the method is provided where the caffeic acid derivatives of Formula 3 have at least two of R^1 , R^2 , and R^3 being hydroxyl or other substitute group as defined above. In some embodiments, two adjacent R^1 , R^2 , or R^3 , are hydroxyl or other

substitute groups. In some embodiments, the method is provided where the caffeic acid derivatives of Formula 3 have R^1 , R^2 , and R^3 being independently hydrogen or hydroxyl.

In a preferred form of any one of the foregoing embodiments, the caffeic acid derivative is (2E)-3-(3,4-dihydroxyphenyl)-N-propyl-acrylamide (DHPPA),
5 corresponding to Formula 3 wherein R^1 is hydroxyl, R^2 is hydroxyl, R^3 is hydrogen, R^4 is a propyl group, and X is NH, in all its stereoisomeric and tautomeric forms.

In one aspect, the caffeic acid derivative of any one of the foregoing embodiments is formulated for intraperitoneal administration. In another aspect, it is formulated for intravenous administration.

10 The present invention also provides a method of synthesizing the caffeic acid derivative of Formula 3 by direct amidation of gallic acid, or a salt thereof, with an amine-functionalized compound. In some embodiments, a compound of Formula 5 or a salt thereof is mixed with H-X- R^4 in dichloromethane and triethylamine (Et_3N). The reaction is carried on with the addition of benzotriazol-1-yloxy tris
15 (dimethylamino)phosphonium hexafluorophosphate while stirring on ice. The product can be purified by evaporating the solvent of the reaction.



Formula 5

20 Additional advantages of the disclosed method and compositions will be set forth in part in the description which follows, and in part will be understood from the description, or may be learned by practice of the disclosed method and compositions. The advantages of the disclosed method and compositions will be realized and attained by means of the elements and combinations particularly pointed out in the appended
25 claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the disclosed method and compositions and together with the description, serve to explain the principles of the disclosed method and compositions.

Figures 1A and 1B are bar graphs showing the cell viabilities (%) of cardiomyocytes after oxygen glucose deprivation (OGD) condition with subsequent treatments with or without different caffeic acid derivatives at 10 μ M, and with DHPPA at different concentrations, respectively. Cardiomyocytes without treatment of caffeic acid derivatives or OGD are considered 100% viable. Different caffeic acid derivatives include DHPPA, caffeic acid phenethyl ester (CAPE), and propyl caffeate (PCE). (Mean $\pm$ SD of three independent experiments. *, $p < 0.05$ and **, $p < 0.01$).

Figures 2A-2G are bar graphs showing the levels of biomarkers relating to cardiac and oxidative stress in the blood samples and heart tissues from mice having undergone ischemia and reperfusion (I/R) with and without the treatment of DHPPA in between. Specifically, figures 2A-2C show the serum levels of lactate dehydrogenase (LDH), creatine kinase (CK), and myocardial muscle creatine kinase (CK-MB); and figures 2D-2G show the levels of catalase (CAT), superoxide dismutase (SOD), myeloperoxidase (MPO), and malonaldehyde (MDA) in cardiac tissues. (**, $P < 0.01$ and ***, $p < 0.001$ for sample vs sham group; #, $P < 0.05$, ##, $P < 0.01$, and ###, $P < 0.01$ for sample vs I/R group.)

Figure 3A is a bar graph showing the relative chemotaxis (folds of change) of macrophages stimulated by lipopolysaccharide (LPS) after treatments with caffeic acid (CA) or different caffeic acid derivatives compared to the migration of macrophages without LPS stimulation or caffeic acid derivative treatment. Figure 3B is a bar graph showing the phagocytosis of latex beads, represented by bead-to-cell ratios, by macrophages with and without LPS stimulation and in the presence or absence of CA or different caffeic acid derivatives. Figure 3C is a bar graph showing the phagocytosis of apoptotic cardiomyoblasts H9C2 by macrophages RAW264.7, represented by the ratio of H9C2 to RAW264.7. (*, $p < 0.05$ and **, $p < 0.01$.) The caffeic acid derivatives include DHPPA, PCE, N-propargyl caffeamide (PACA), and CAPE.

Figures 4A and 4B are bar graphs showing the folds of change of the gene expression levels of M1 biomarkers and M2 biomarkers of macrophages, respectively,

after real-time reverse transcription-polymerase chain reactions (RT-PCR) of isolated total mRNAs from RAW 264.7 macrophages that are treated with different caffeic acid derivatives and LPS sequentially. M1 biomarkers tested include tumor necrosis factor alpha (TNF- α), C-X-C motif chemokine 10 (CXCL10), and inducible nitric oxide synthase (iNOS); and tested M2 biomarkers include Ym-1 (also called T-lymphocyte-derived eosinophil chemotactic factor) and arginase-1. House-keeping gene, β -actin, is shown as a loading control.

Figure 5A is a line graph showing the percentage of remaining DHPPA (in natural log scale; Ln %) in rat serum over time (minutes) *in vitro* at three temperatures: 60 °C (solid triangles, $R^2=0.983$), 37 °C (solid squares, $R^2=0.995$), and 25 °C (solid circles, $R^2=0.963$). Figure 5B is a line graph showing the plasma concentration of DHPPA (in natural log scale; Ln %, $\times 10^3$) over time after administration to male Sprague-Dawley rats (mean $\pm$ standard deviation, $n=3$).

DETAILED DESCRIPTION OF THE INVENTION

The disclosed method and compositions may be understood more readily by reference to the following detailed description of particular embodiments and the Example included therein and to the Figures and their previous and following description.

It is to be understood that the disclosed method and compositions are not limited to specific synthetic methods, specific analytical techniques, or to particular reagents unless otherwise specified, and, as such, may vary. 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.

I. Definitions

The term “macrophage polarization” refers to a process when macrophage expresses different functional programs in response to microenvironmental signals. These functional programs, or polarization of macrophages, occur at the level of gene expression, protein, metabolite, microbicidal activity, or a combination thereof.

The term “infarction” refers to tissue death (necrosis) caused by a local lack of oxygen, due to an obstruction of the tissue's blood supply. The resulting lesion is referred to as an infarct. Myocardial infarction is the partial death of heart tissue commonly known as heart attack.

The term “ischemia” refers to a restriction in blood supply to tissues, causing a shortage of oxygen and glucose needed for cellular metabolism .

The term “activity” refers to a biological activity.

The terms “high,” “higher,” “increases,” “elevates,” or “elevation” refer to increases above basal levels, e.g., as compared to a control. The terms “low,” “lower,” “reduces,” or “reduction” refer to decreases below basal levels, e.g., as compared to a control.

The term “inhibit” means to reduce or decrease in activity or expression. This can be a complete inhibition or activity or expression, or a partial inhibition. Inhibition can be compared to a control or to a standard level. Inhibition can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%.

The term “in need of treatment” as used herein refers to a judgment made by a caregiver (e.g. physician, nurse, nurse practitioner, or individual in the case of humans; veterinarian in the case of animals, including non-human mammals) that a subject requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a care giver's expertise, but that include the knowledge that the subject is ill, or will be ill, as the result of a condition that is treatable by the compounds of the invention.

As used herein, “subject” includes, but is not limited to, humans and non-human animals. The subject can be a vertebrate, more specifically a mammal (e.g., a human, horse, pig, rabbit, dog, sheep, goat, non-human primate, cow, cat, guinea pig or rodent), a fish, a bird or a reptile or an amphibian. The subject can be an invertebrate, more specifically an arthropod (e.g., insects and crustaceans). The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. A patient refers to a subject afflicted with a disease or disorder. The term “patient” includes human and veterinary subjects.

By “treatment” and “treating” is meant the medical management of a subject with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes

palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. It is understood that treatment, while intended to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder, need not actually result in the cure, ameliorization, stabilization or prevention. The effects of treatment can be measured or assessed as described herein and as known in the art as is suitable for the disease, pathological condition, or disorder involved. Such measurements and assessments can be made in qualitative and/or quantitative terms. Thus, for example, characteristics or features of a disease, pathological condition, or disorder and/or symptoms of a disease, pathological condition, or disorder can be reduced to any effect or to any amount.

By “reacting to an inflammatory insult,” “inflammatory reaction,” and “inflammatory response” is meant a subject’s response to an inflammatory insult such as injury, trauma, heat, toxin, infection or exposure to a bacteria, virus, or other foreign cell, where cells are damaged and the damaged cells release mediators or stimulators of inflammation. An inflammatory insult is a condition, composition, or object that causes or stimulates an inflammatory response.

By “pharmaceutically acceptable” is meant a material that is not biologically or otherwise undesirable, i.e., the material can be administered to a subject along with the selected compound without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

“Substituted,” as used herein, refers to all permissible substituents of the compounds or functional groups described herein. In the broadest sense, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, but are not limited to, halogens, hydroxyl groups, or any other organic groupings containing any number of carbon atoms, preferably 1-14 carbon atoms, and optionally include one or more heteroatoms such as oxygen, sulfur, or nitrogen grouping in linear, branched, or cyclic structural formats. Representative substituents

include alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxyl, arylalkyl, substituted arylalkyl, alkoxy, substituted alkoxy, phenoxy, substituted phenoxy, aroxy, substituted aroxy, alkylthio, substituted alkylthio, phenylthio, substituted phenylthio, arylthio, substituted arylthio, cyano, isocyano, substituted isocyano, carbonyl, substituted carbonyl, carboxyl, substituted carboxyl, amino, substituted amino, amido, substituted amido, sulfonyl, substituted sulfonyl, sulfonic acid, phosphoryl, substituted phosphoryl, phosphonyl, substituted phosphonyl, polyaryl, substituted polyaryl, C₃-C₂₀ cyclic, substituted C₃-C₂₀ cyclic, heterocyclic, substituted heterocyclic, amino acid, poly(lactic-co-glycolic acid), peptide, and polypeptide groups. Such alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxyl, arylalkyl, substituted arylalkyl, alkoxy, substituted alkoxy, phenoxy, substituted phenoxy, aroxy, substituted aroxy, alkylthio, substituted alkylthio, phenylthio, substituted phenylthio, arylthio, substituted arylthio, cyano, isocyano, substituted isocyano, carbonyl, substituted carbonyl, carboxyl, substituted carboxyl, amino, substituted amino, amido, substituted amido, sulfonyl, substituted sulfonyl, sulfonic acid, phosphoryl, substituted phosphoryl, phosphonyl, substituted phosphonyl, polyaryl, substituted polyaryl, C₃-C₂₀ cyclic, substituted C₃-C₂₀ cyclic, heterocyclic, substituted heterocyclic, amino acid, poly(lactic-co-glycolic acid), peptide, and polypeptide groups can be further substituted.

Heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. It is understood that “substitution” or “substituted” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, i.e. a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

“Aryl,” as used herein, refers to C₅-C₂₆-membered aromatic, fused aromatic, fused heterocyclic, or biaromatic ring systems. Broadly defined, “aryl,” as used herein, includes 5-, 6-, 7-, 8-, 9-, 10-, 14-, 18-, and 24-membered single-ring aromatic groups, for example, benzene, naphthalene, anthracene, phenanthrene, chrysene, pyrene, corannulene, coronene, etc.

“Aryl” further encompasses polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (i.e., “fused rings”) wherein at least one of the rings is aromatic, e.g., the other cyclic ring or rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocycles.

5 The term “substituted aryl” refers to an aryl group, wherein one or more hydrogen atoms on one or more aromatic rings are substituted with one or more substituents including, but not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, carbonyl (such as a ketone, aldehyde, carboxyl, alkoxy carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or
10 quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, imino, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl (such as CF₃, -CH₂-CF₃, -CCl₃), -CN, aryl, heteroaryl, and combinations thereof.

15 “Heterocycle,” “heterocyclic” and “heterocyclyl” are used interchangeably, and refer to a cyclic radical attached via a ring carbon or nitrogen atom of a monocyclic or bicyclic ring containing 3-10 ring atoms, and preferably from 5-6 ring atoms, consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, C₁-C₁₀ alkyl, phenyl
20 or benzyl, and optionally containing 1-3 double bonds and optionally substituted with one or more substituents. Heterocyclyl are distinguished from heteroaryl by definition. Examples of heterocycles include, but are not limited to piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, dihydrofuro[2,3-*b*]tetrahydrofuran, morpholinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pyranyl, 2H-pyrrolyl, 4*H*-quinoliziny, quinuclidinyl, tetrahydrofuranyl, 6*H*-1,2,5-thiadiazinyl. Heterocyclic groups can
25 optionally be substituted with one or more substituents as defined above for alkyl and aryl.

 The term “heteroaryl” refers to C₅-C₂₆-membered aromatic, fused aromatic, biaromatic ring systems, or combinations thereof, in which one or more carbon atoms on
30 one or more aromatic ring structures have been substituted with an heteroatom. Suitable heteroatoms include, but are not limited to, oxygen, sulfur, and nitrogen. Broadly defined, “heteroaryl,” as used herein, includes 5-, 6-, 7-, 8-, 9-, 10-, 14-, 18-, and 24-membered single-ring aromatic groups that may include from one to four heteroatoms, for example,

pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. The heteroaryl group may also be referred to as “aryl heterocycles” or “heteroaromatics”. “Heteroaryl” further encompasses polycyclic ring systems having two or more rings in which two or more carbons are common to two adjoining rings (*i.e.*, “fused rings”) wherein at least one of the rings is heteroaromatic, *e.g.*, the other cyclic ring or rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heterocycles, or combinations thereof. Examples of heteroaryl rings include, but are not limited to, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, 4*aH*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizyl, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, naphthyridinyl, octahydroisoquinolinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl and xanthenyl. One or more of the rings can be substituted as defined below for “substituted heteroaryl”.

The term “substituted heteroaryl” refers to a heteroaryl group in which one or more hydrogen atoms on one or more heteroaromatic rings are substituted with one or more substituents including, but not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, carbonyl (such as a ketone, aldehyde, carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, imino, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl,

heterocyclyl, alkylaryl, haloalkyl (such as CF₃, -CH₂-CF₃, -CCl₃), -CN, aryl, heteroaryl, and combinations thereof.

“Alkyl,” as used herein, refers to the radical of saturated aliphatic groups, including straight-chain alkyl, alkenyl, or alkynyl groups, branched-chain alkyl, cycloalkyl (alicyclic), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chains, C₃-C₃₀ for branched chains), preferably 20 or fewer, more preferably 15 or fewer, most preferably 10 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure. The term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having one or more substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents include, but are not limited to, halogen, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, a phosphinate, amino, amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, aralkyl, or an aromatic or heteroaromatic moiety.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Throughout the application, preferred alkyl groups are lower alkyls. In preferred embodiments, a substituent designated herein as alkyl is a lower alkyl.

“Alkyl” includes one or more substitutions at one or more carbon atoms of the hydrocarbon radical as well as heteroalkyls. Suitable substituents include, but are not limited to, halogens, such as fluorine, chlorine, bromine, or iodine; hydroxyl; -NRR', wherein R and R' are independently hydrogen, alkyl, or aryl, and wherein the nitrogen atom is optionally quaternized; -SR, wherein R is hydrogen, alkyl, or aryl; -CN; -NO₂; -COOH; carboxylate; -COR, -COOR, or -CON(R)₂, wherein R is hydrogen, alkyl, or aryl; azide, aralkyl, alkoxyl, imino, phosphonate, phosphinate, silyl, ether, sulfonyl, sulfonamido, heterocyclyl, aromatic or heteroaromatic moieties, haloalkyl (such as -

CF₃, -CH₂-CF₃, -CCl₃); -CN; -NCOCOCH₂CH₂; -NCOCOCHCH; -NCS; and combinations thereof.

It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include halogen, hydroxy, nitro, thiols, amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl, sulfoxide, and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), haloalkyls, -CN and the like. Cycloalkyls can be substituted in the same manner.

The terms “alkenyl” and “alkynyl” refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

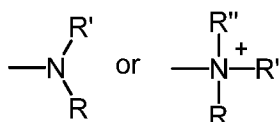
The term “substituted alkenyl” refers to alkenyl moieties having one or more substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

The term “substituted alkynyl” refers to alkynyl moieties having one or more substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

The term “phenyl” is art recognized, and refers to the aromatic moiety -C₆H₅, *i.e.*, a benzene ring without one hydrogen atom.

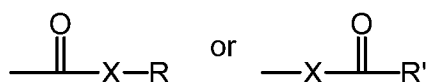
The term “substituted phenyl” refers to a phenyl group, as defined above, having one or more substituents replacing one or more hydrogen atoms on one or more carbons of the phenyl ring. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocycl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

“Amino” and “Amine,” as used herein, are art-recognized and refer to both substituted and unsubstituted amines, e.g., a moiety that can be represented by the general formula:



wherein, R, R', and R'' each independently represent a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbonyl, or $-(\text{CH}_2)_m\text{---R}'''$, or R and R' taken together with the N atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; wherein R''' represents a hydroxy group, substituted or unsubstituted carbonyl group, an aryl, a cycloalkyl ring, a cycloalkenyl ring, a heterocycle, or a polycycle; and m is zero or an integer ranging from 1 to 8. In preferred embodiments, only one of R and R' can be a carbonyl, e.g., R and R' together with the nitrogen do not form an imide. In preferred embodiments, R and R' (and optionally R'') each independently represent a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or $-(\text{CH}_2)_m\text{---R}'''$. Thus, the term ‘alkylamine’ as used herein refers to an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto (i.e., at least one of R, R', or R'' is an alkyl group).

“Carbonyl,” as used herein, is art-recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond, or represents an oxygen or a sulfur, and R represents a hydrogen, a substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or

unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-(CH_2)_m-R'$, or a pharmaceutical acceptable salt thereof; wherein R'

5 represents a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or $-(CH_2)_m-R''$; wherein R'' represents a hydroxy group, substituted or unsubstituted carbonyl group, an aryl, a cycloalkyl ring, a cycloalkenyl ring, a heterocycle, or a polycycle; and m is zero or an integer ranging from 1 to 8.

Where X is oxygen and R is defines as above, the moiety is also referred to as a carboxyl group. When X is oxygen and R is hydrogen, the formula represents a 'carboxylic acid'.

Where X is oxygen and R' is hydrogen, the formula represents a 'formate.' Where X is

15 oxygen and R or R' is not hydrogen, the formula represents an "ester." In general, where the oxygen atom of the above formula is replaced by a sulfur atom, the formula represents a 'thiocarbonyl' group. Where X is sulfur and R or R' is not hydrogen, the formula represents a 'thioester.' Where X is sulfur and R is hydrogen, the formula represents a 'thiocarboxylic acid.' Where X is sulfur and R' is hydrogen, the formula represents a 'thioformate.' Where X is a bond and R is not hydrogen, the above formula represents a 'ketone.' Where X is a bond and R is hydrogen, the above formula represents an 'aldehyde.'

The term "substituted carbonyl" refers to a carbonyl, as defined above, wherein one or more hydrogen atoms in R , R' or a group to which the moiety

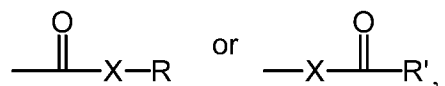


is attached, are independently substituted. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate,

30 phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido,

sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

The term “carboxyl” is as defined above for the formula



- 5 and is defined more specifically by the formula $\text{—R}^{\text{iv}}\text{COOH}$, wherein R^{iv} is an alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylaryl, arylalkyl, aryl, or heteroaryl. In preferred embodiments, a straight chain or branched chain alkyl, alkenyl, and alkynyl have 30 or fewer carbon atoms in its backbone (e.g., $\text{C}_1\text{—C}_{30}$ for straight chain alkyl, $\text{C}_3\text{—C}_{30}$ for branched chain alkyl, $\text{C}_2\text{—C}_{30}$ for straight chain alkenyl and alkynyl, $\text{C}_3\text{—C}_{30}$ for
- 10 branched chain alkenyl and alkynyl), preferably 20 or fewer, more preferably 15 or fewer, most preferably 10 or fewer. Likewise, preferred cycloalkyls, heterocyclyls, aryls and heteroaryls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

- The term “substituted carboxyl” refers to a carboxyl, as defined above, wherein
- 15 one or more hydrogen atoms in R^{iv} are substituted. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano,
- 20 nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

- “Heteroalkyl,” as used herein, refers to straight or branched chain, or cyclic carbon-containing radicals, or combinations thereof, containing at least one heteroatom.
- 25 Suitable heteroatoms include, but are not limited to, O, N, Si, P and S, wherein the nitrogen, phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized.

- Examples of saturated hydrocarbon radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl,
- 30 (cyclohexyl)methyl, cyclopropylmethyl, and homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl. Examples of unsaturated alkyl groups include, but are

not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, and 3-butenyl.

The terms "alkoxyl" or "alkoxy," "aroxy" or "aryloxy," generally describe compounds represented by the formula -OR^v, wherein R^v includes, but is not limited to, substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, arylalkyl, heteroalkyls, alkylaryl, alkylheteroaryl.

The terms "alkoxyl" or "alkoxy" as used herein refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, and -O-alkynyl. The term alkoxy also includes cycloalkyl, heterocyclyl, cycloalkenyl, heterocycloalkenyl, and arylalkyl having an oxygen radical attached to at least one of the carbon atoms, as valency permits.

The term "substituted alkoxy" refers to an alkoxy group having one or more substituents replacing one or more hydrogen atoms on one or more carbons of the alkoxy backbone. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

The term "phenoxy" is art recognized, and refers to a compound of the formula -OR^v wherein R^v is (*i.e.*, -O-C₆H₅). One of skill in the art recognizes that a phenoxy is a species of the aroxy genus.

The term "substituted phenoxy" refers to a phenoxy group, as defined above, having one or more substituents replacing one or more hydrogen atoms on one or more carbons of the phenyl ring. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, phosphinate,

amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

5 The terms "aroxy" and "aryloxy," as used interchangeably herein, are represented by -O-aryl or -O-heteroaryl, wherein aryl and heteroaryl are as defined herein.

The terms "substituted aroxy" and "substituted aryloxy," as used interchangeably herein, represent -O-aryl or -O-heteroaryl, having one or more substituents replacing one or more hydrogen atoms on one or more ring atoms of the aryl and heteroaryl, as defined herein. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, 10 alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, 15 haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. The "alkylthio" moiety is represented by -S-alkyl.

Representative alkylthio groups include methylthio, ethylthio, and the like. The term "alkylthio" also encompasses cycloalkyl groups having a sulfur radical attached thereto.

20 The term "substituted alkylthio" refers to an alkylthio group having one or more substituents replacing one or more hydrogen atoms on one or more carbon atoms of the alkylthio backbone. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a 25 thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

30 The term "phenylthio" is art recognized, and refers to -S-C₆H₅, *i.e.*, a phenyl group attached to a sulfur atom.

The term "substituted phenylthio" refers to a phenylthio group, as defined above, having one or more substituents replacing a hydrogen on one or more carbons of the phenyl ring. Such substituents include, but are not limited to, halogen, azide, alkyl,

aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

“Arylthio” refers to -S-aryl or -S-heteroaryl groups, wherein aryl and heteroaryl as as defined herein.

The term “substituted arylthio” represents -S-aryl or -S-heteroaryl, having one or more substituents replacing a hydrogen atom on one or more ring atoms of the aryl and heteroaryl rings as defined herein. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

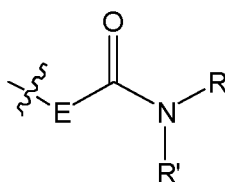
“Arylalkyl,” as used herein, refers to an alkyl group that is substituted with a substituted or unsubstituted aryl or heteroaryl group.

“Alkylaryl,” as used herein, refers to an aryl group (e.g., an aromatic or hetero aromatic group), substituted with a substituted or unsubstituted alkyl group.

“Phenylalkyl,” as used herein, refers to an alkyl group that is substituted with a substituted or unsubstituted phenyl or heterophenyl group.

“Alkylphenyl,” as used herein, refers to an phenyl group, substituted with a substituted or unsubstituted alkyl group.

The terms “amide” or “amido” are used interchangeably, refer to both “unsubstituted amido” and “substituted amido” and are represented by the general formula:



wherein, E is absent, or E is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, wherein

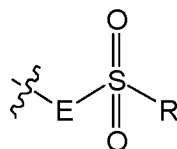
5 independently of E, R and R' each independently represent a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbonyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or

10 unsubstituted heteroaryl, or $-(CH_2)_m-R'''$, or R and R' taken together with the N atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; wherein R''' represents a hydroxy group, substituted or unsubstituted carbonyl group, an aryl, a cycloalkyl ring, a cycloalkenyl ring, a heterocycle, or a polycycle; and m is zero or an integer ranging from 1 to 8. In preferred embodiments, only one of R and

15 R' can be a carbonyl, e.g., R and R' together with the nitrogen do not form an imide. In preferred embodiments, R and R' each independently represent a hydrogen atom, substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, or $-(CH_2)_m-R'''$. When E is oxygen, a carbamate is formed. The carbamate cannot be attached to another chemical species, such as to form an oxygen-oxygen bond, or other unstable bonds, as

20 understood by one of ordinary skill in the art.

The term "sulfonyl" is represented by the formula



wherein E is absent, or E is alkyl, alkenyl, alkynyl, aralkyl, alkylaryl, cycloalkyl, aryl, heteroaryl, heterocyclyl, wherein independently of E, R represents a hydrogen,

25 substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amine, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or $-(CH_2)_m-R'''$, or E and R taken together with

30 the S atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; R''' represents a hydroxy group, substituted or unsubstituted

carbonyl group, an aryl, a cycloalkyl ring, a cycloalkenyl ring, a heterocycle, or a polycycle; and m is zero or an integer ranging from 1 to 8. In preferred embodiments, only one of E and R can be substituted or unsubstituted amine, to form a “sulfonamide” or “sulfonamido.” The substituted or unsubstituted amine is as defined above.

5 The term “substituted sulfonyl” represents a sulfonyl in which E, R, or both, are independently substituted. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quaternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, 10 alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

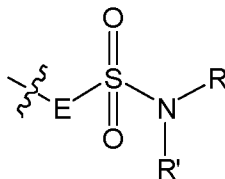
 The term “sulfonic acid” refers to a sulfonyl, as defined above, wherein R is hydroxyl, and E is absent, or E is substituted or unsubstituted cycloalkyl, substituted or 15 unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

 The term “sulfate” refers to a sulfonyl, as defined above, wherein E is absent, oxygen, alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above, and R 20 is independently hydroxyl, alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above. When E is oxygen, the sulfate cannot be attached to another chemical species, such as to form an oxygen-oxygen bond, or other unstable bonds, as understood by one of ordinary skill in the art.

 The term “sulfonate” refers to a sulfonyl, as defined above, wherein E is oxygen, 25 alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above, and R is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amine, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted 30 or unsubstituted aryl, substituted or unsubstituted heteroaryl, or $-(CH_2)_m-R'''$; wherein R''' represents a hydroxy group, substituted or unsubstituted carbonyl group, an aryl, a cycloalkyl ring, a cycloalkenyl ring, a heterocycle, or a polycycle; and m is zero or an integer ranging from 1 to 8. When E is oxygen, sulfonate cannot be attached to another

chemical species, such as to form an oxygen-oxygen bond, or other unstable bonds, as understood by one of ordinary skill in the art.

The term “sulfamoyl” refers to a sulfonamide or sulfonamide represented by the formula

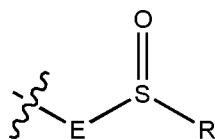


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wherein E is absent, or E is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, wherein independently of E, R and R' each independently represent a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbonyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or $-(CH_2)_m-R'''$, or R and R' taken together with the N atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; wherein R''' represents a hydroxy group, substituted or unsubstituted carbonyl group, an aryl, a cycloalkyl ring, a cycloalkenyl ring, a heterocycle, or a polycycle; and m is zero or an integer ranging from 1 to 8. In preferred embodiments, only one of R and R' can be a carbonyl, e.g., R and R' together with the nitrogen do not form an imide.

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The term “sulfoxide” is represented by the formula

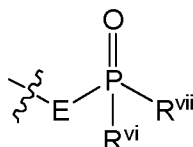


wherein E is absent, or E is alkyl, alkenyl, alkynyl, aralkyl, alkylaryl, cycloalkyl, aryl, heteroaryl, heterocyclyl, wherein independently of E, R represents a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amine, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted

25

alkylaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl,
 substituted or unsubstituted heteroaryl, or $-(CH_2)_m-R'''$, or E and R taken together with
 the S atom to which they are attached complete a heterocycle having from 3 to 14 atoms
 in the ring structure; wherein R''' represents a hydroxy group, substituted or
 5 unsubstituted carbonyl group, an aryl, a cycloalkyl ring, a cycloalkenyl ring, a
 heterocycle, or a polycycle; and m is zero or an integer ranging from 1 to 8.

The term “phosphonyl” is represented by the formula



wherein E is absent, or E is substituted or unsubstituted alkyl, substituted or
 10 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted
 aralkyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted cycloalkyl,
 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or
 unsubstituted heterocyclyl, wherein, independently of E, R^{vi} and R^{vii} are independently
 hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,
 15 substituted or unsubstituted alkynyl, substituted or unsubstituted carbonyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or
 unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted or
 unsubstituted aryl, substituted or unsubstituted heteroaryl, or $-(CH_2)_m-R'''$, or R^{vi} and
 R^{vii} taken together with the P atom to which they are attached complete a heterocycle
 20 having from 3 to 14 atoms in the ring structure; wherein R''' represents a hydroxy group,
 substituted or unsubstituted carbonyl group, an aryl, a cycloalkyl ring, a cycloalkenyl
 ring, a heterocycle, or a polycycle; and m is zero or an integer ranging from 1 to 8.

The term “substituted phosphonyl” represents a phosphonyl in which E, R^{vi} and
 R^{vii} are independently substituted. Such substituents include, but are not limited to,
 25 halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a
 carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a
 thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate,
 phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido,
 sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl,
 30 heterocyclyl, alkylaryl, haloalkyl, $-CN$, aryl, heteroaryl, and combinations thereof.

The term “phosphoryl” defines a phosphonyl in which E is absent, oxygen, alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above, and independently of E, R^{vi} and R^{vii} are independently hydroxyl, alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above. When E is oxygen, the phosphoryl cannot be attached to another chemical species, such as to form an oxygen-oxygen bond, or other unstable bonds, as understood by one of ordinary skill in the art. When E, R^{vi} and R^{vii} are substituted, the substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

The term “polyaryl” refers to a chemical moiety that includes two or more aryls, heteroaryls, and combinations thereof. The aryls, heteroaryls, and combinations thereof, are fused, or linked via a single bond, ether, ester, carbonyl, amide, sulfonyl, sulfonamide, alkyl, azo, and combinations thereof.

The term “substituted polyaryl” refers to a polyaryl in which one or more of the aryls, heteroaryls are substituted, with one or more substituents including, but not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

The term “C₃-C₂₀ cyclic” refers to a substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl that have from three to 20 carbon atoms, as geometric constraints permit. The cyclic structures are formed from single or fused ring systems. The substituted cycloalkyls, cycloalkenyls, cycloalkynyls and heterocyclyls are substituted as defined above for the alkyls, alkenyls, alkynyls and heterocyclyls, respectively.

The terms “hydroxyl” and “hydroxy” are used interchangeably and are represented by -OH.

The terms “thiol” and “sulfhydryl” are used interchangeably and are represented by -SH.

5 The term “oxo” refers to =O bonded to a carbon atom.

The terms “cyano” and “nitrile” are used interchangeably to refer to -CN.

The term “nitro” refers to -NO₂.

The term “phosphate” refers to -O-PO₃.

The term “azide” or “azido” are used interchangeably to refer to -N₃.

10 The term “substituted C_x-C_y alkyl” (where x and y are integers where x < y) refers to alkyl groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y alkyl” (where x and y are integers where x < y) refers to alkyl groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y alkylene” (where x and y are integers where x < y) refers to alkylene groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C₁-C₁₀ alkylene” (where x and y are integers where x < y) refers to alkylene groups having from x to y carbon atoms that are not substituted. The term “alkylene” as used herein, refers to a moiety with the formula - (CH₂)_a-, wherein “a” is an integer from x to y.

20 The term “substituted C_x-C_y alkenyl” (where x and y are integers where x < y) refers to alkenyl groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y alkenyl” (where x and y are integers where x < y) refers to alkenyl groups having from x to y carbon atoms that are not substituted.

25 The term “substituted C_x-C_y alkynyl” (where x and y are integers where x < y) refers to alkynyl groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y alkynyl” (where x and y are integers where x < y) refers to alkynyl groups having from x to y carbon atoms that are not substituted.

30 The term “substituted C_x-C_y alkoxy” (where x and y are integers where x < y) refers to alkoxy groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y alkoxy” (where x and y are integers

where $x < y$) refers to alkoxy groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y alkylamino” (where x and y are integers where $x < y$) refers to alkylamino groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y alkylamino” (where x and y are integers where $x < y$) refers to alkyl groups having from x to y carbon atoms that are not substituted. The terms “alkylamine” and “alkylamino” are used interchangeably. In any alkylamino, where the nitrogen atom is substituted with one, two, or three substituents, the nitrogen atom can be referred to as a secondary, tertiary, or quaternary nitrogen atom, respectively.

The term “substituted C_x-C_y alkylthio” (where x and y are integers where $x < y$) refers to alkylthio groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y alkylthio” (where x and y are integers where $x < y$) refers to alkylthio groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y carbonyl” (where x and y are integers where $x < y$) refers to carbonyl groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y carbonyl” (where x and y are integers where $x < y$) refers to carbonyl groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y carboxyl” (where x and y are integers where $x < y$) refers to carboxyl groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y carboxyl” (where x and y are integers where $x < y$) refers to carboxyl groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y amido” (where x and y are integers where $x < y$) refers to amido groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y amido” (where x and y are integers where $x < y$) refers to amido groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y sulfonyl” (where x and y are integers where $x < y$) refers to sulfonyl groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y sulfonyl” (where x and y are integers

where $x < y$) refers to sulfonyl groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y sulfonic acid” (where x and y are integers where $x < y$) refers to sulfonic acid groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y sulfonic acid” (where x and y are integers where $x < y$) refers to sulfonic acid groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y sulfamoyl” (where x and y are integers where $x < y$) refers to sulfamoyl groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y sulfamoyl” (where x and y are integers where $x < y$) refers to sulfamoyl groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y sulfoxide” (where x and y are integers where $x < y$) refers to sulfoxide groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y sulfoxide” (where x and y are integers where $x < y$) refers to sulfoxide groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y phosphoryl” (where x and y are integers where $x < y$) refers to phosphoryl groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y phosphoryl” (where x and y are integers where $x < y$) refers to phosphoryl groups having from x to y carbon atoms that are not substituted.

The term “substituted C_x-C_y phosphonyl” (where x and y are integers where $x < y$) refers to phosphonyl groups having from x to y carbon atoms, wherein at least one carbon atom is substituted. The term “unsubstituted C_x-C_y phosphonyl” (where x and y are integers where $x < y$) refers to phosphonyl groups having from x to y carbon atoms that are not substituted.

The terms substituted “ C_x alkyl,” “ C_x alkylene,” “ C_x alkenyl,” “ C_x alkynyl,” “ C_x alkoxy,” “ C_x alkylamino,” “ C_x alkylthio,” “ C_x carbonyl,” “ C_x carboxyl,” “ C_x amido,” “ C_x sulfonyl,” “ C_x sulfonic acid,” “ C_x sulfamoyl,” “ C_x phosphoryl,” and “ C_x phosphonyl” (where x is an integer) refer to alkyl, alkylene, alkenyl, alkynyl, alkoxy, alkylamino, alkylthio, carbonyl, carboxyl, amido, sulfonyl, sulfonic acid, sulfamoyl, sulfoxide, phosphoryl, and phosphonyl groups, respectively, having x carbon atoms,

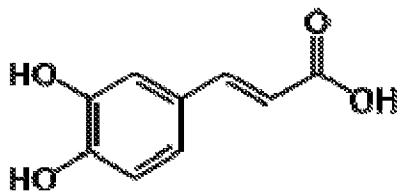
wherein at least one carbon atom is substituted. The terms unsubstituted “C_x alkyl,” “C_x alkylene,” “C_x alkenyl,” “C_x alkynyl,” “C_x alkoxy,” “C_x alkylamino,” “C_x alkylthio,” “C_x carbonyl,” “C_x carboxyl,” “C_x amido,” “C_x sulfonyl,” “C_x sulfonic acid,” “C_x sulfamoyl,” “C_x phosphoryl,” and “C_x phosphonyl” (where x is an integer) refer to alkyl, alkylene, alkenyl, alkynyl, alkoxy, alkylamino, alkylthio, carbonyl, carboxyl, amido, sulfonyl, sulfonic acid, sulfamoyl, sulfoxide, phosphoryl, and phosphonyl groups, respectively, having x carbon atoms where none of the carbons are substituted.

II. Compounds and Compositions

It has been discovered that caffeic acid and some of its derivatives exert anti-oxidant, chemopreventive, anticancer and antibacterial properties in a structure-dependent and cell-type-specific manner (da Cunha FM, et al., *Free Radical Research*, 38(11):1241-1253 (2004); Fiuza SM, et al., *Bioorganic & Medicinal Chemistry*, 12(13):3581-3589 (2004); Rajan P, et al., *Bioorganic & Medicinal Chemistry*, 11(2):215-217 (2001)). For example, caffeic acid phenethyl ester (CAPE) attenuates ischemic injury in several *in vitro* and *in vivo* studies (Kart A, et al., *Food Chem Toxicol.*, 47(8):1980-1984 (2009); Koltuksuz U, et al., *J. Pediatr Surg.*, 34(10):1458-1462 (1999); Wei X, et al., *Brain*, 127:2629-2635 (2004)). However, CAPE is not stable enough and has short life-time in male Sprague–Dawley rats (Wang XY, et al., *Biomed Chromatogr*, 21(4):343-350 (2007)). Alternatively, several different caffeic acid amide derivatives including N-methyl, N-propargyl, N-anilide, N-phenethyl and pyrrolidinyl caffeamide have been developed (Rajan P, *Bioorganic & Medicinal Chemistry Letters*, 11(2):215-217 (2001); Ho YJ, *Cardiovascular Diabetology*, 13:98 (2014); Lee SY, *J Biomed Sci.*, 22:18 (2015)). Nevertheless, pharmaceutical compositions for treating myocardial infarction and other macrophage-mediated inflammatory disorders are provided, to reduce, decrease, limit or prevent the symptoms of myocardial infarction by targeting the transformation of macrophages in a subject relative to an untreated control subject.

A. Caffeic acid derivatives

Caffeic acid is a natural dietary phenolic compound found in plants. It is a key intermediate in the biosynthesis of lignin, one of the principal components of plant biomass and its residues.



Formula 1: Structure of caffeic acid (3,4-dihydroxycinnamic acid).

Caffeic acid exhibits an antioxidant property, as discovered in several *in vitro* and *in vivo* assays (Sato Y, et al., *Int J Pharm*, 403(1-2): 136-8 (2011)). It was also found to possess an antihyperglycemic property in model diabetic animals (Jung UJ, *The Journal of Pharmacology and Experimental Therapeutics*, 318(2):476-483 (2006)).

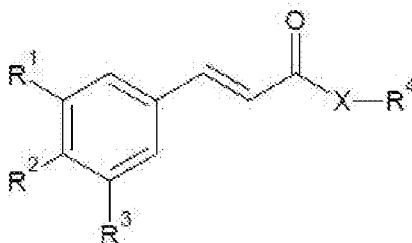
Derivatives of caffeic acid or modified cinnamic acid are shown by Formula 2.



Formula 2: Modification or substitution of caffeic acid.

In Formula 2, $(R')_n$ is n number of R' , which is a functional group substituted for n number of hydrogens of the aryl group, wherein $n = 0, 1, 2$, or 3 . R' is independently selected from hydroxy, substituted or unsubstituted alkoxy, or substituted or unsubstituted aryloxy; linker is a substituted or unsubstituted alkyl, alkene, or alkyne; Y is O, S, or NR wherein R is substituted or unsubstituted hydrocarbons; X is O, S, or NR wherein R is substituted or unsubstituted hydrocarbons; R'' is substituted or unsubstituted hydrocarbons; and substitution refers to substitution with one or more heteroatoms.

In a preferred embodiment, one or more caffeic acid derivatives have a structure shown by Formula 3.



Formula 3: Preferred structures of caffeic acid derivatives.

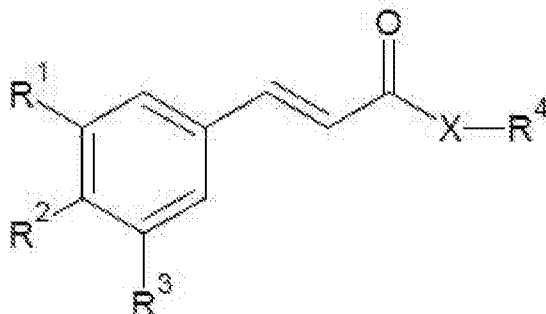
In Formula 3, R^1 , R^2 , R^3 , and R^4 are independently hydrogen, hydroxyl, methyl, a halogen atom, or one or more linear, branched, or cyclic alkyl, substituted alkyl, propargyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbonyl, substituted carbonyl, carboxyl, substituted carboxyl, amino, substituted amino, amido, substituted

amido, sulfonyl, or substituted sulfonyl groups having from 1 to 30 carbon atoms that can be substituted with one or more heteroatoms.

In some embodiments, R^1 , R^2 , and R^3 are, independently, hydroxyl, hydrogen, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl; R^4 is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C_3 - C_{20} cyclic, heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C_3 - C_{20} cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, hydrogen, or, if the R in X forms two bonds with the N, absent; and wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl.

In some embodiments, the caffeic acid derivative can be in any of its stereoisomeric and tautomeric forms, and mixtures thereof in all ratios, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable solvate thereof, a pharmaceutically acceptable polymorph thereof, or a prodrug thereof.

In some embodiments, the caffeic acid derivative has the structure of Formula 3



Formula 3

In some embodiments, R^1 , R^2 , and R^3 are, independently, hydroxyl, hydrogen,
 5 amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10}
 alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10}
 alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10}
 sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10}
 phosphonyl;

10 X is O, S, or NR^a , wherein R^a is H or substituted or unsubstituted C_1 - C_{10} , alkyl,
 alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl;
 and

R^4 is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy,
 arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C_3 - C_{20} cyclic,
 15 heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted
 phenyl, substituted aryl, substituted heteroaryl, substituted alkoxy, substituted phenoxy,
 substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted
 arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido,
 substituted polyaryl, substituted C_3 - C_{20} cyclic, substituted heterocyclic, amino acid,
 20 poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group,
 hydrogen, or, if R^a forms two bonds with the N, absent.

In some embodiments, at least one of R^1 , R^2 , and R^3 is hydroxyl, amino, thiol,
 oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10}
 alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10}
 25 carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10}
 sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl.

In some embodiments, the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

In some embodiments, at least two of R¹, R², and R³ are, independently, hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

In some embodiments, at least two adjacent R¹, R², and R³ are, independently, hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

In some embodiments, R¹, R², and R³ are, independently, hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

In some embodiments, R² is hydrogen and R¹ and R³ are, independently, hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

In some embodiments, two of R¹, R², and R³ are hydrogen and one of R¹, R², and R³ is hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀

sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

In some embodiments, R¹ and R² are hydroxyl, R³ is hydrogen, X is O, and R⁴ is:
 alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio,
 5 alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C₃-C₂₀ cyclic, heterocyclic, C₅-C₇
 or C₉-C₃₀ alkyl; or

phenyl substituted with hydroxyl, amino, thiol, oxo, phosphate, C₃-C₁₀ alkyl,
 substituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl,
 C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-
 10 C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-
 C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl; or

substituted naphthyl, substituted thienyl, substituted indolyl, substituted biphenyl,
 substituted azulenyl, substituted anthracenyl, substituted phenanthrenyl, substituted alkyl,
 substituted alkenyl, substituted alkynyl, substituted heteroaryl, substituted alkoxy,
 15 substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted
 phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted
 amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted
 heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, or
 polypeptide group.

In some embodiments, R¹ and R² are hydroxyl, R³ is hydrogen, X is NH, and R⁴ is:
 alkyl, alkenyl, ethynyl, 1-propynyl, C₄-C₃₀ alkynyl, phenyl, aryl, heteroaryl,
 alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl,
 C₃-C₂₀ cyclic, or heterocyclic; or

alkynyl substituted with hydroxyl, amino, thiol, oxo, phosphate, C₂-C₁₀ alkyl,
 25 substituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl,
 C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-
 C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-
 C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl; or

phenyl substituted with hydroxyl, amino, thiol, oxo, phosphate, methyl, C₃-C₁₀
 30 alkyl, substituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₁-C₁₀ alkylene, C₂-C₁₀
 alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀
 carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀
 sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl; or

substituted naphthyl, substituted thienyl, substituted indolyl, substituted biphenyl, substituted azulenyl, substituted anthracenyl, substituted phenanthrenyl, substituted alkyl, substituted alkenyl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, or hydrogen.

In some embodiments, R¹ and R² are hydroxyl, R³ is hydrogen, X is S or NR^a, where R^a is substituted or unsubstituted C₁-C₁₀ alkyl, alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl, wherein R^a, if present, has only one bond with the N, and R⁴ is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C₃-C₂₀ cyclic, heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, or hydrogen.

In some embodiments, R¹ and R² are hydroxyl, R³ is hydrogen, X is S or NR^a, where R^a is substituted C₁-C₁₀ alkyl, unsubstituted C₃, C₄, or C₆-C₁₀ alkyl, or substituted or unsubstituted C₁-C₁₀ alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl, wherein R^a, if present, has two bonds bond with the N, and R⁴ is absent.

In some embodiments, R¹ and R² are hydroxyl, R³ is hydrogen, X is S or NR^a, where R^a is substituted or unsubstituted C₁-C₁₀ alkyl, alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl, with the proviso that NR^a, if present, is not 1-pyrrolidinyl, and R⁴ is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C₃-C₂₀ cyclic, heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio,

substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, hydrogen, or, if R^a forms two bonds with the N, absent.

5 In some embodiments, R¹ and R² are methoxy, R³ is hydrogen, X is O, S, or NR^a, where R^a is H or substituted or unsubstituted C₁-C₁₀, alkyl, alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl, and R⁴ is:

alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C₃-C₂₀ cyclic, or heterocyclic; or

10 phenyl substituted with hydroxyl, amino, thiol, oxo, phosphate, methyl, C₃-C₁₀ alkyl, substituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl; or

15 substituted naphthyl, substituted thienyl, substituted indolyl, substituted biphenyl, substituted azulenyl, substituted anthracenyl, substituted phenanthrenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, or hydrogen.

In some embodiments, R¹, R², and R³ are, independently, hydroxyl, hydrogen, amino, thiol, oxo, or substituted or unsubstituted C₁-C₃ alkyl, C₁-C₃ alkylene, C₂-C₃ alkenyl, C₂-C₃ alkynyl, C₁-C₃ alkoxy, C₁-C₃ alkylamino, C₁-C₃ alkylthio, C₁-C₃ carbonyl, C₁-C₃ carboxyl, C₁-C₃ amino, or C₁-C₃ amido; X is NH or O; and R⁴ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, phenyl, aryl, heteroaryl, C₁-C₂₀ alkoxy, phenoxy, aroxy, arylthio, C₁-C₂₀ alkylthio, C₁-C₂₀ carbonyl, C₁-C₂₀ carboxyl, amino, C₁-C₂₀ amido, polyaryl, C₃-C₂₀ cyclic, heterocyclic, substituted C₁-C₂₀ alkyl, substituted C₂-C₂₀ alkenyl, substituted C₂-C₂₀ alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted C₁-C₂₀ alkoxy, substituted phenoxy, substituted aroxy, substituted C₁-C₂₀ alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted C₁-C₂₀

carbonyl, substituted C₁-C₂₀ carboxyl, substituted amino, substituted C₁-C₂₀ amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, or substituted heterocyclic.

In some embodiments, R¹, R², and R³ are, independently, hydroxyl, hydrogen, amino, thiol, or unsubstituted C₁-C₃ alkyl, C₁-C₃ alkylene, C₂-C₃ alkenyl, C₂-C₃ alkynyl, C₁-C₃ alkoxy, C₁-C₃ alkylamino, C₁-C₃ alkylthio, C₁-C₃ carbonyl, C₁-C₃ amino, or C₁-C₃ amido; X is NH or O; and R⁴ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ carbonyl, C₁-C₂₀ carboxyl, amino, C₁-C₂₀ amido, substituted C₁-C₂₀ alkyl, substituted C₂-C₂₀ alkenyl, substituted C₂-C₂₀ alkynyl, substituted C₁-C₂₀ alkoxy, substituted C₁-C₂₀ alkylthio, substituted C₁-C₂₀ carbonyl, substituted C₁-C₂₀ carboxyl, substituted amino, or substituted C₁-C₂₀ amido.

In some embodiments, R¹, R², and R³ are, independently, hydroxyl, hydrogen, amino, thiol, or unsubstituted C₁-C₃ alkyl, C₁-C₃ alkylene, C₂-C₃ alkenyl, C₂-C₃ alkynyl, C₁-C₃ alkoxy, C₁-C₃ alkylamino, C₁-C₃ alkylthio, or C₁-C₃ amino; X is NH or O; and R⁴ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ carbonyl, C₁-C₂₀ carboxyl, amino, C₁-C₂₀ amido, substituted C₁-C₂₀ alkyl, substituted C₂-C₂₀ alkenyl, substituted C₂-C₂₀ alkynyl, substituted C₁-C₂₀ alkoxy, substituted C₁-C₂₀ alkylthio, substituted C₁-C₂₀ carbonyl, substituted C₁-C₂₀ carboxyl, substituted amino, or substituted C₁-C₂₀ amido.

In some embodiments, R¹, R², and R³ are, independently, hydroxyl, hydrogen, or unsubstituted C₁-C₂ alkyl, C₁-C₂ alkylene, C₂ alkenyl, C₂ alkynyl, C₁-C₂ alkoxy, C₁-C₂ alkylamino, C₁-C₂ alkylthio, or C₁-C₂ amino; X is NH or O; and R⁴ is C₃-C₂₀ alkyl, C₃-C₂₀ alkenyl, C₃-C₂₀ alkynyl, C₃-C₂₀ alkoxy, C₃-C₂₀ alkylthio, C₃-C₂₀ carbonyl, C₃-C₂₀ carboxyl, amino, C₃-C₂₀ amido, substituted C₃-C₂₀ alkyl, substituted C₃-C₂₀ alkenyl, substituted C₃-C₂₀ alkynyl, substituted C₃-C₂₀ alkoxy, substituted C₃-C₂₀ alkylthio, substituted C₃-C₂₀ carbonyl, substituted C₃-C₂₀ carboxyl, substituted amino, or substituted C₃-C₂₀ amido.

In some embodiments, R¹, R², and R³ are independently hydrogen or hydroxyl. In some embodiments, R¹ is hydroxyl, R² is hydroxyl, R³ is hydrogen, R⁴ is a propyl group, and X is NH. In some embodiments, R⁴ is not a substituted phenyl. In some embodiments, R⁴ is substituted aryl but excluding substituted phenyl.

In some embodiments, when R¹-, R²-, R³- are any one of the combination resulting from each independently being any one of the mentioned groups, with the

proviso that R^1 -, R^2 -, R^3 - are not two adjacent hydroxyl or two adjacent methoxy groups, $-X-R^4$ is any one of the mentioned groups.

In some embodiments, when R^1 -, R^2 -, R^3 - are two adjacent hydroxyl groups, $-X-R^4$ is any one of the mentioned groups with the proviso that $-X-R^4$ is not $-NH-CH_2-$

5 $C\equiv CH$, $-O-CH_2Ph$, $-O-(CH_2)_2Ph$, $-NH-(CH_2)_2Ph$, methoxy, ethoxy, propyloxy, butyloxy, octyloxy, or pyrrolidinyl group.

In some embodiments, when R^1 -, R^2 -, R^3 - are two adjacent methoxy groups, $-X-R^4$ is any one of the mentioned groups with the proviso that $-X-R^4$ is not $-NH-(CH_2)_2Ph$.

In some embodiments, R^4 , R^a , and substituents are, independently, C_1-C_7 or C_9-
 10 C_{30} alkyl, C_1-C_7 or $C_{10}-C_{30}$ alkyl, C_1-C_7 or $C_{11}-C_{30}$ alkyl, C_1-C_7 or $C_{12}-C_{30}$ alkyl, C_1-C_7 or $C_{13}-C_{30}$ alkyl, C_1-C_7 or $C_{14}-C_{30}$ alkyl, C_1-C_7 or $C_{15}-C_{30}$ alkyl, C_1-C_7 or $C_{16}-C_{30}$ alkyl, C_1-
 C_7 or $C_{17}-C_{30}$ alkyl, C_1-C_7 or $C_{18}-C_{30}$ alkyl, C_1-C_7 or C_9-C_{20} alkyl, C_1-C_7 or $C_{10}-C_{20}$ alkyl, C_1-C_7 or $C_{11}-C_{20}$ alkyl, C_1-C_7 or $C_{12}-C_{20}$ alkyl, C_1-C_7 or $C_{13}-C_{20}$ alkyl, C_1-C_7 or $C_{14}-C_{20}$
 alkyl, C_1-C_7 or $C_{15}-C_{20}$ alkyl, C_1-C_7 or $C_{16}-C_{20}$ alkyl, C_1-C_7 or $C_{17}-C_{20}$ alkyl, C_1-C_7 or
 15 $C_{18}-C_{20}$ alkyl, C_1-C_7 or C_9-C_{15} alkyl, C_1-C_7 or $C_{10}-C_{15}$ alkyl, C_1-C_7 or $C_{11}-C_{15}$ alkyl, C_1-
 C_7 or $C_{12}-C_{15}$ alkyl, C_1-C_7 or $C_{13}-C_{15}$ alkyl, or C_1-C_7 or $C_{14}-C_{15}$ alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C_1-C_6 or C_9-
 C_{30} alkyl, C_1-C_6 or $C_{10}-C_{30}$ alkyl, C_1-C_6 or $C_{11}-C_{30}$ alkyl, C_1-C_6 or $C_{12}-C_{30}$ alkyl, C_1-C_6 or
 $C_{13}-C_{30}$ alkyl, C_1-C_6 or $C_{14}-C_{30}$ alkyl, C_1-C_6 or $C_{15}-C_{30}$ alkyl, C_1-C_6 or $C_{16}-C_{30}$ alkyl, C_1-
 20 C_6 or $C_{17}-C_{30}$ alkyl, C_1-C_6 or $C_{18}-C_{30}$ alkyl, C_1-C_6 or C_9-C_{20} alkyl, C_1-C_6 or $C_{10}-C_{20}$ alkyl,
 C_1-C_6 or $C_{11}-C_{20}$ alkyl, C_1-C_6 or $C_{12}-C_{20}$ alkyl, C_1-C_6 or $C_{13}-C_{20}$ alkyl, C_1-C_6 or $C_{14}-C_{20}$
 alkyl, C_1-C_6 or $C_{15}-C_{20}$ alkyl, C_1-C_6 or $C_{16}-C_{20}$ alkyl, C_1-C_6 or $C_{17}-C_{20}$ alkyl, C_1-C_6 or
 $C_{18}-C_{20}$ alkyl, C_1-C_6 or C_9-C_{15} alkyl, C_1-C_6 or $C_{10}-C_{15}$ alkyl, C_1-C_6 or $C_{11}-C_{15}$ alkyl, C_1-
 C_6 or $C_{12}-C_{15}$ alkyl, C_1-C_6 or $C_{13}-C_{15}$ alkyl, or C_1-C_6 or $C_{14}-C_{15}$ alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C_1-C_5 or C_9-
 C_{30} alkyl, C_1-C_5 or $C_{10}-C_{30}$ alkyl, C_1-C_5 or $C_{11}-C_{30}$ alkyl, C_1-C_5 or $C_{12}-C_{30}$ alkyl, C_1-C_5 or
 $C_{13}-C_{30}$ alkyl, C_1-C_5 or $C_{14}-C_{30}$ alkyl, C_1-C_5 or $C_{15}-C_{30}$ alkyl, C_1-C_5 or $C_{16}-C_{30}$ alkyl, C_1-
 C_5 or $C_{17}-C_{30}$ alkyl, C_1-C_5 or $C_{18}-C_{30}$ alkyl, C_1-C_5 or C_9-C_{20} alkyl, C_1-C_5 or $C_{10}-C_{20}$ alkyl,
 C_1-C_5 or $C_{11}-C_{20}$ alkyl, C_1-C_5 or $C_{12}-C_{20}$ alkyl, C_1-C_5 or $C_{13}-C_{20}$ alkyl, C_1-C_5 or $C_{14}-C_{20}$
 30 alkyl, C_1-C_5 or $C_{15}-C_{20}$ alkyl, C_1-C_5 or $C_{16}-C_{20}$ alkyl, C_1-C_5 or $C_{17}-C_{20}$ alkyl, C_1-C_5 or
 $C_{18}-C_{20}$ alkyl, C_1-C_5 or C_9-C_{15} alkyl, C_1-C_5 or $C_{10}-C_{15}$ alkyl, C_1-C_5 or $C_{11}-C_{15}$ alkyl, C_1-
 C_5 or $C_{12}-C_{15}$ alkyl, C_1-C_5 or $C_{13}-C_{15}$ alkyl, or C_1-C_5 or $C_{14}-C_{15}$ alkyl.

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C₃₀ alkyl, C₂-C₇ or C₁₀-C₃₀ alkyl, C₂-C₇ or C₁₁-C₃₀ alkyl, C₂-C₇ or C₁₂-C₃₀ alkyl, C₂-C₇ or

C₁₃-C₃₀ alkyl, C₂-C₇ or C₁₄-C₃₀ alkyl, C₂-C₇ or C₁₅-C₃₀ alkyl, C₂-C₇ or C₁₆-C₃₀ alkyl, C₂-C₇ or C₁₇-C₃₀ alkyl, C₂-C₇ or C₁₈-C₃₀ alkyl, C₂-C₇ or C₉-C₂₀ alkyl, C₂-C₇ or C₁₀-C₂₀ alkyl, C₂-C₇ or C₁₁-C₂₀ alkyl, C₂-C₇ or C₁₂-C₂₀ alkyl, C₂-C₇ or C₁₃-C₂₀ alkyl, C₂-C₇ or C₁₄-C₂₀ alkyl, C₂-C₇ or C₁₅-C₂₀ alkyl, C₂-C₇ or C₁₆-C₂₀ alkyl, C₂-C₇ or C₁₇-C₂₀ alkyl, C₂-C₇ or C₁₈-C₂₀ alkyl, C₂-C₇ or C₉-C₁₅ alkyl, C₂-C₇ or C₁₀-C₁₅ alkyl, C₂-C₇ or C₁₁-C₁₅ alkyl, C₂-C₇ or C₁₂-C₁₅ alkyl, C₂-C₇ or C₁₃-C₁₅ alkyl, or C₂-C₇ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₂-C₆ or C₉-C₃₀ alkyl, C₂-C₆ or C₁₀-C₃₀ alkyl, C₂-C₆ or C₁₁-C₃₀ alkyl, C₂-C₆ or C₁₂-C₃₀ alkyl, C₂-C₆ or C₁₃-C₃₀ alkyl, C₂-C₆ or C₁₄-C₃₀ alkyl, C₂-C₆ or C₁₅-C₃₀ alkyl, C₂-C₆ or C₁₆-C₃₀ alkyl, C₂-C₆ or C₁₇-C₃₀ alkyl, C₂-C₆ or C₁₈-C₃₀ alkyl, C₂-C₆ or C₉-C₂₀ alkyl, C₂-C₆ or C₁₀-C₂₀ alkyl, C₂-C₆ or C₁₁-C₂₀ alkyl, C₂-C₆ or C₁₂-C₂₀ alkyl, C₂-C₆ or C₁₃-C₂₀ alkyl, C₂-C₆ or C₁₄-C₂₀ alkyl, C₂-C₆ or C₁₅-C₂₀ alkyl, C₂-C₆ or C₁₆-C₂₀ alkyl, C₂-C₆ or C₁₇-C₂₀ alkyl, C₂-C₆ or C₁₈-C₂₀ alkyl, C₂-C₆ or C₉-C₁₅ alkyl, C₂-C₆ or C₁₀-C₁₅ alkyl, C₂-C₆ or C₁₁-C₁₅ alkyl, C₂-C₆ or C₁₂-C₁₅ alkyl, C₂-C₆ or C₁₃-C₁₅ alkyl, or C₂-C₆ or C₁₄-C₁₅ alkyl.

15 In some embodiments, R⁴, R^a, and substituents are, independently, C₂-C₅ or C₉-C₃₀ alkyl, C₂-C₅ or C₁₀-C₃₀ alkyl, C₂-C₅ or C₁₁-C₃₀ alkyl, C₂-C₅ or C₁₂-C₃₀ alkyl, C₂-C₅ or C₁₃-C₃₀ alkyl, C₂-C₅ or C₁₄-C₃₀ alkyl, C₂-C₅ or C₁₅-C₃₀ alkyl, C₂-C₅ or C₁₆-C₃₀ alkyl, C₂-C₅ or C₁₇-C₃₀ alkyl, C₂-C₅ or C₁₈-C₃₀ alkyl, C₂-C₅ or C₉-C₂₀ alkyl, C₂-C₅ or C₁₀-C₂₀ alkyl, C₂-C₅ or C₁₁-C₂₀ alkyl, C₂-C₅ or C₁₂-C₂₀ alkyl, C₂-C₅ or C₁₃-C₂₀ alkyl, C₂-C₅ or C₁₄-C₂₀ alkyl, C₂-C₅ or C₁₅-C₂₀ alkyl, C₂-C₅ or C₁₆-C₂₀ alkyl, C₂-C₅ or C₁₇-C₂₀ alkyl, C₂-C₅ or C₁₈-C₂₀ alkyl, C₂-C₅ or C₉-C₁₅ alkyl, C₂-C₅ or C₁₀-C₁₅ alkyl, C₂-C₅ or C₁₁-C₁₅ alkyl, C₂-C₅ or C₁₂-C₁₅ alkyl, C₂-C₅ or C₁₃-C₁₅ alkyl, or C₂-C₅ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₂-C₄ or C₉-C₃₀ alkyl, C₂-C₄ or C₁₀-C₃₀ alkyl, C₂-C₄ or C₁₁-C₃₀ alkyl, C₂-C₄ or C₁₂-C₃₀ alkyl, C₂-C₄ or C₁₃-C₃₀ alkyl, C₂-C₄ or C₁₄-C₃₀ alkyl, C₂-C₄ or C₁₅-C₃₀ alkyl, C₂-C₄ or C₁₆-C₃₀ alkyl, C₂-C₄ or C₁₇-C₃₀ alkyl, C₂-C₄ or C₁₈-C₃₀ alkyl, C₂-C₄ or C₉-C₂₀ alkyl, C₂-C₄ or C₁₀-C₂₀ alkyl, C₂-C₄ or C₁₁-C₂₀ alkyl, C₂-C₄ or C₁₂-C₂₀ alkyl, C₂-C₄ or C₁₃-C₂₀ alkyl, C₂-C₄ or C₁₄-C₂₀ alkyl, C₂-C₄ or C₁₅-C₂₀ alkyl, C₂-C₄ or C₁₆-C₂₀ alkyl, C₂-C₄ or C₁₇-C₂₀ alkyl, C₂-C₄ or C₁₈-C₂₀ alkyl, C₂-C₄ or C₉-C₁₅ alkyl, C₂-C₄ or C₁₀-C₁₅ alkyl, C₂-C₄ or C₁₁-C₁₅ alkyl, C₂-C₄ or C₁₂-C₁₅ alkyl, C₂-C₄ or C₁₃-C₁₅ alkyl, or C₂-C₄ or C₁₄-C₁₅ alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C_2 - C_3 or C_9 - C_{30} alkyl, C_2 - C_3 or C_{10} - C_{30} alkyl, C_2 - C_3 or C_{11} - C_{30} alkyl, C_2 - C_3 or C_{12} - C_{30} alkyl, C_2 - C_3 or C_{13} - C_{30} alkyl, C_2 - C_3 or C_{14} - C_{30} alkyl, C_2 - C_3 or C_{15} - C_{30} alkyl, C_2 - C_3 or C_{16} - C_{30} alkyl, C_2 -

C₃ or C₁₇-C₃₀ alkyl, C₂-C₃ or C₁₈-C₃₀ alkyl, C₂-C₃ or C₉-C₂₀ alkyl, C₂-C₃ or C₁₀-C₂₀ alkyl, C₂-C₃ or C₁₁-C₂₀ alkyl, C₂-C₃ or C₁₂-C₂₀ alkyl, C₂-C₃ or C₁₃-C₂₀ alkyl, C₂-C₃ or C₁₄-C₂₀ alkyl, C₂-C₃ or C₁₅-C₂₀ alkyl, C₂-C₃ or C₁₆-C₂₀ alkyl, C₂-C₃ or C₁₇-C₂₀ alkyl, C₂-C₃ or C₁₈-C₂₀ alkyl, C₂-C₃ or C₉-C₁₅ alkyl, C₂-C₃ or C₁₀-C₁₅ alkyl, C₂-C₃ or C₁₁-C₁₅ alkyl, C₂-C₃ or C₁₂-C₁₅ alkyl, C₂-C₃ or C₁₃-C₁₅ alkyl, or C₂-C₃ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₂ or C₉-C₃₀ alkyl, C₂ or C₁₀-C₃₀ alkyl, C₂ or C₁₁-C₃₀ alkyl, C₂ or C₁₂-C₃₀ alkyl, C₂ or C₁₃-C₃₀ alkyl, C₂ or C₁₄-C₃₀ alkyl, C₂ or C₁₅-C₃₀ alkyl, C₂ or C₁₆-C₃₀ alkyl, C₂ or C₁₇-C₃₀ alkyl, C₂ or C₁₈-C₃₀ alkyl, C₂ or C₉-C₂₀ alkyl, C₂ or C₁₀-C₂₀ alkyl, C₂ or C₁₁-C₂₀ alkyl, C₂ or C₁₂-C₂₀ alkyl, C₂ or C₁₃-C₂₀ alkyl, C₂ or C₁₄-C₂₀ alkyl, C₂ or C₁₅-C₂₀ alkyl, C₂ or C₁₆-C₂₀ alkyl, C₂ or C₁₇-C₂₀ alkyl, C₂ or C₁₈-C₂₀ alkyl, C₂ or C₉-C₁₅ alkyl, C₂ or C₁₀-C₁₅ alkyl, C₂ or C₁₁-C₁₅ alkyl, C₂ or C₁₂-C₁₅ alkyl, C₂ or C₁₃-C₁₅ alkyl, or C₂ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₃-C₇ or C₉-C₃₀ alkyl, C₃-C₇ or C₁₀-C₃₀ alkyl, C₃-C₇ or C₁₁-C₃₀ alkyl, C₃-C₇ or C₁₂-C₃₀ alkyl, C₃-C₇ or C₁₃-C₃₀ alkyl, C₃-C₇ or C₁₄-C₃₀ alkyl, C₃-C₇ or C₁₅-C₃₀ alkyl, C₃-C₇ or C₁₆-C₃₀ alkyl, C₃-C₇ or C₁₇-C₃₀ alkyl, C₃-C₇ or C₁₈-C₃₀ alkyl, C₃-C₇ or C₉-C₂₀ alkyl, C₃-C₇ or C₁₀-C₂₀ alkyl, C₃-C₇ or C₁₁-C₂₀ alkyl, C₃-C₇ or C₁₂-C₂₀ alkyl, C₃-C₇ or C₁₃-C₂₀ alkyl, C₃-C₇ or C₁₄-C₂₀ alkyl, C₃-C₇ or C₁₅-C₂₀ alkyl, C₃-C₇ or C₁₆-C₂₀ alkyl, C₃-C₇ or C₁₇-C₂₀ alkyl, C₃-C₇ or C₁₈-C₂₀ alkyl, C₃-C₇ or C₉-C₁₅ alkyl, C₃-C₇ or C₁₀-C₁₅ alkyl, C₃-C₇ or C₁₁-C₁₅ alkyl, C₃-C₇ or C₁₂-C₁₅ alkyl, C₃-C₇ or C₁₃-C₁₅ alkyl, or C₃-C₇ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₃-C₆ or C₉-C₃₀ alkyl, C₃-C₆ or C₁₀-C₃₀ alkyl, C₃-C₆ or C₁₁-C₃₀ alkyl, C₃-C₆ or C₁₂-C₃₀ alkyl, C₃-C₆ or C₁₃-C₃₀ alkyl, C₃-C₆ or C₁₄-C₃₀ alkyl, C₃-C₆ or C₁₅-C₃₀ alkyl, C₃-C₆ or C₁₆-C₃₀ alkyl, C₃-C₆ or C₁₇-C₃₀ alkyl, C₃-C₆ or C₁₈-C₃₀ alkyl, C₃-C₆ or C₉-C₂₀ alkyl, C₃-C₆ or C₁₀-C₂₀ alkyl, C₃-C₆ or C₁₁-C₂₀ alkyl, C₃-C₆ or C₁₂-C₂₀ alkyl, C₃-C₆ or C₁₃-C₂₀ alkyl, C₃-C₆ or C₁₄-C₂₀ alkyl, C₃-C₆ or C₁₅-C₂₀ alkyl, C₃-C₆ or C₁₆-C₂₀ alkyl, C₃-C₆ or C₁₇-C₂₀ alkyl, C₃-C₆ or C₁₈-C₂₀ alkyl, C₃-C₆ or C₉-C₁₅ alkyl, C₃-C₆ or C₁₀-C₁₅ alkyl, C₃-C₆ or C₁₁-C₁₅ alkyl, C₃-C₆ or C₁₂-C₁₅ alkyl, C₃-C₆ or C₁₃-C₁₅ alkyl, or C₃-C₆ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₃-C₅ or C₉-C₃₀ alkyl, C₃-C₅ or C₁₀-C₃₀ alkyl, C₃-C₅ or C₁₁-C₃₀ alkyl, C₃-C₅ or C₁₂-C₃₀ alkyl, C₃-C₅ or C₁₃-C₃₀ alkyl, C₃-C₅ or C₁₄-C₃₀ alkyl, C₃-C₅ or C₁₅-C₃₀ alkyl, C₃-C₅ or C₁₆-C₃₀ alkyl, C₃-C₅ or C₁₇-C₃₀ alkyl, C₃-C₅ or C₁₈-C₃₀ alkyl, C₃-C₅ or C₉-C₂₀ alkyl, C₃-C₅ or C₁₀-C₂₀ alkyl, C₃-C₅ or C₁₁-C₂₀ alkyl, C₃-C₅ or C₁₂-C₂₀ alkyl, C₃-C₅ or C₁₃-C₂₀ alkyl, C₃-C₅ or C₁₄-C₂₀

alkyl, C₃-C₅ or C₁₅-C₂₀ alkyl, C₃-C₅ or C₁₆-C₂₀ alkyl, C₃-C₅ or C₁₇-C₂₀ alkyl, C₃-C₅ or C₁₈-C₂₀ alkyl, C₃-C₅ or C₉-C₁₅ alkyl, C₃-C₅ or C₁₀-C₁₅ alkyl, C₃-C₅ or C₁₁-C₁₅ alkyl, C₃-C₅ or C₁₂-C₁₅ alkyl, C₃-C₅ or C₁₃-C₁₅ alkyl, or C₃-C₅ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₃-C₄ or C₉-C₃₀ alkyl, C₃-C₄ or C₁₀-C₃₀ alkyl, C₃-C₄ or C₁₁-C₃₀ alkyl, C₃-C₄ or C₁₂-C₃₀ alkyl, C₃-C₄ or C₁₃-C₃₀ alkyl, C₃-C₄ or C₁₄-C₃₀ alkyl, C₃-C₄ or C₁₅-C₃₀ alkyl, C₃-C₄ or C₁₆-C₃₀ alkyl, C₃-C₄ or C₁₇-C₃₀ alkyl, C₃-C₄ or C₁₈-C₃₀ alkyl, C₃-C₄ or C₉-C₂₀ alkyl, C₃-C₄ or C₁₀-C₂₀ alkyl, C₃-C₄ or C₁₁-C₂₀ alkyl, C₃-C₄ or C₁₂-C₂₀ alkyl, C₃-C₄ or C₁₃-C₂₀ alkyl, C₃-C₄ or C₁₄-C₂₀ alkyl, C₃-C₄ or C₁₅-C₂₀ alkyl, C₃-C₄ or C₁₆-C₂₀ alkyl, C₃-C₄ or C₁₇-C₂₀ alkyl, C₃-C₄ or C₁₈-C₂₀ alkyl, C₃-C₄ or C₉-C₁₅ alkyl, C₃-C₄ or C₁₀-C₁₅ alkyl, C₃-C₄ or C₁₁-C₁₅ alkyl, C₃-C₄ or C₁₂-C₁₅ alkyl, C₃-C₄ or C₁₃-C₁₅ alkyl, or C₃-C₄ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₃ or C₉-C₃₀ alkyl, C₃ or C₁₀-C₃₀ alkyl, C₃ or C₁₁-C₃₀ alkyl, C₃ or C₁₂-C₃₀ alkyl, C₃ or C₁₃-C₃₀ alkyl, C₃ or C₁₄-C₃₀ alkyl, C₃ or C₁₅-C₃₀ alkyl, C₃ or C₁₆-C₃₀ alkyl, C₃ or C₁₇-C₃₀ alkyl, C₃ or C₁₈-C₃₀ alkyl, C₃ or C₉-C₂₀ alkyl, C₃ or C₁₀-C₂₀ alkyl, C₃ or C₁₁-C₂₀ alkyl, C₃ or C₁₂-C₂₀ alkyl, C₃ or C₁₃-C₂₀ alkyl, C₃ or C₁₄-C₂₀ alkyl, C₃ or C₁₅-C₂₀ alkyl, C₃ or C₁₆-C₂₀ alkyl, C₃ or C₁₇-C₂₀ alkyl, C₃ or C₁₈-C₂₀ alkyl, C₃ or C₉-C₁₅ alkyl, C₃ or C₁₀-C₁₅ alkyl, C₃ or C₁₁-C₁₅ alkyl, C₃ or C₁₂-C₁₅ alkyl, C₃ or C₁₃-C₁₅ alkyl, or C₃ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₄-C₇ or C₉-C₃₀ alkyl, C₄-C₇ or C₁₀-C₃₀ alkyl, C₄-C₇ or C₁₁-C₃₀ alkyl, C₄-C₇ or C₁₂-C₃₀ alkyl, C₄-C₇ or C₁₃-C₃₀ alkyl, C₄-C₇ or C₁₄-C₃₀ alkyl, C₄-C₇ or C₁₅-C₃₀ alkyl, C₄-C₇ or C₁₆-C₃₀ alkyl, C₄-C₇ or C₁₇-C₃₀ alkyl, C₄-C₇ or C₁₈-C₃₀ alkyl, C₄-C₇ or C₉-C₂₀ alkyl, C₄-C₇ or C₁₀-C₂₀ alkyl, C₄-C₇ or C₁₁-C₂₀ alkyl, C₄-C₇ or C₁₂-C₂₀ alkyl, C₄-C₇ or C₁₃-C₂₀ alkyl, C₄-C₇ or C₁₄-C₂₀ alkyl, C₄-C₇ or C₁₅-C₂₀ alkyl, C₄-C₇ or C₁₆-C₂₀ alkyl, C₄-C₇ or C₁₇-C₂₀ alkyl, C₄-C₇ or C₁₈-C₂₀ alkyl, C₄-C₇ or C₉-C₁₅ alkyl, C₄-C₇ or C₁₀-C₁₅ alkyl, C₄-C₇ or C₁₁-C₁₅ alkyl, C₄-C₇ or C₁₂-C₁₅ alkyl, C₄-C₇ or C₁₃-C₁₅ alkyl, or C₄-C₇ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₄-C₆ or C₉-C₃₀ alkyl, C₄-C₆ or C₁₀-C₃₀ alkyl, C₄-C₆ or C₁₁-C₃₀ alkyl, C₄-C₆ or C₁₂-C₃₀ alkyl, C₄-C₆ or C₁₃-C₃₀ alkyl, C₄-C₆ or C₁₄-C₃₀ alkyl, C₄-C₆ or C₁₅-C₃₀ alkyl, C₄-C₆ or C₁₆-C₃₀ alkyl, C₄-C₆ or C₁₇-C₃₀ alkyl, C₄-C₆ or C₁₈-C₃₀ alkyl, C₄-C₆ or C₉-C₂₀ alkyl, C₄-C₆ or C₁₀-C₂₀ alkyl, C₄-C₆ or C₁₁-C₂₀ alkyl, C₄-C₆ or C₁₂-C₂₀ alkyl, C₄-C₆ or C₁₃-C₂₀ alkyl, C₄-C₆ or C₁₄-C₂₀ alkyl, C₄-C₆ or C₁₅-C₂₀ alkyl, C₄-C₆ or C₁₆-C₂₀ alkyl, C₄-C₆ or C₁₇-C₂₀ alkyl, C₄-C₆ or

C₁₈-C₂₀ alkyl, C₄-C₆ or C₉-C₁₅ alkyl, C₄-C₆ or C₁₀-C₁₅ alkyl, C₄-C₆ or C₁₁-C₁₅ alkyl, C₄-C₆ or C₁₂-C₁₅ alkyl, C₄-C₆ or C₁₃-C₁₅ alkyl, or C₄-C₆ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₄-C₅ or C₉-C₃₀ alkyl, C₄-C₅ or C₁₀-C₃₀ alkyl, C₄-C₅ or C₁₁-C₃₀ alkyl, C₄-C₅ or C₁₂-C₃₀ alkyl, C₄-C₅ or C₁₃-C₃₀ alkyl, C₄-C₅ or C₁₄-C₃₀ alkyl, C₄-C₅ or C₁₅-C₃₀ alkyl, C₄-C₅ or C₁₆-C₃₀ alkyl, C₄-C₅ or C₁₇-C₃₀ alkyl, C₄-C₅ or C₁₈-C₃₀ alkyl, C₄-C₅ or C₉-C₂₀ alkyl, C₄-C₅ or C₁₀-C₂₀ alkyl, C₄-C₅ or C₁₁-C₂₀ alkyl, C₄-C₅ or C₁₂-C₂₀ alkyl, C₄-C₅ or C₁₃-C₂₀ alkyl, C₄-C₅ or C₁₄-C₂₀ alkyl, C₄-C₅ or C₁₅-C₂₀ alkyl, C₄-C₅ or C₁₆-C₂₀ alkyl, C₄-C₅ or C₁₇-C₂₀ alkyl, C₄-C₅ or C₁₈-C₂₀ alkyl, C₄-C₅ or C₉-C₁₅ alkyl, C₄-C₅ or C₁₀-C₁₅ alkyl, C₄-C₅ or C₁₁-C₁₅ alkyl, C₄-C₅ or C₁₂-C₁₅ alkyl, C₄-C₅ or C₁₃-C₁₅ alkyl, or C₄-C₅ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₄ or C₉-C₃₀ alkyl, C₄ or C₁₀-C₃₀ alkyl, C₄ or C₁₁-C₃₀ alkyl, C₄ or C₁₂-C₃₀ alkyl, C₄ or C₁₃-C₃₀ alkyl, C₄ or C₁₄-C₃₀ alkyl, C₄ or C₁₅-C₃₀ alkyl, C₄ or C₁₆-C₃₀ alkyl, C₄ or C₁₇-C₃₀ alkyl, C₄ or C₁₈-C₃₀ alkyl, C₄ or C₉-C₂₀ alkyl, C₄ or C₁₀-C₂₀ alkyl, C₄ or C₁₁-C₂₀ alkyl, C₄ or C₁₂-C₂₀ alkyl, C₄ or C₁₃-C₂₀ alkyl, C₄ or C₁₄-C₂₀ alkyl, C₄ or C₁₅-C₂₀ alkyl, C₄ or C₁₆-C₂₀ alkyl, C₄ or C₁₇-C₂₀ alkyl, C₄ or C₁₈-C₂₀ alkyl, C₄ or C₉-C₁₅ alkyl, C₄ or C₁₀-C₁₅ alkyl, C₄ or C₁₁-C₁₅ alkyl, C₄ or C₁₂-C₁₅ alkyl, C₄ or C₁₃-C₁₅ alkyl, or C₄ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₅-C₇ or C₉-C₃₀ alkyl, C₅-C₇ or C₁₀-C₃₀ alkyl, C₅-C₇ or C₁₁-C₃₀ alkyl, C₅-C₇ or C₁₂-C₃₀ alkyl, C₅-C₇ or C₁₃-C₃₀ alkyl, C₅-C₇ or C₁₄-C₃₀ alkyl, C₅-C₇ or C₁₅-C₃₀ alkyl, C₅-C₇ or C₁₆-C₃₀ alkyl, C₅-C₇ or C₁₇-C₃₀ alkyl, C₅-C₇ or C₁₈-C₃₀ alkyl, C₅-C₇ or C₉-C₂₀ alkyl, C₅-C₇ or C₁₀-C₂₀ alkyl, C₅-C₇ or C₁₁-C₂₀ alkyl, C₅-C₇ or C₁₂-C₂₀ alkyl, C₅-C₇ or C₁₃-C₂₀ alkyl, C₅-C₇ or C₁₄-C₂₀ alkyl, C₅-C₇ or C₁₅-C₂₀ alkyl, C₅-C₇ or C₁₆-C₂₀ alkyl, C₅-C₇ or C₁₇-C₂₀ alkyl, C₅-C₇ or C₁₈-C₂₀ alkyl, C₅-C₇ or C₉-C₁₅ alkyl, C₅-C₇ or C₁₀-C₁₅ alkyl, C₅-C₇ or C₁₁-C₁₅ alkyl, C₅-C₇ or C₁₂-C₁₅ alkyl, C₅-C₇ or C₁₃-C₁₅ alkyl, or C₅-C₇ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₅-C₆ or C₉-C₃₀ alkyl, C₅-C₆ or C₁₀-C₃₀ alkyl, C₅-C₆ or C₁₁-C₃₀ alkyl, C₅-C₆ or C₁₂-C₃₀ alkyl, C₅-C₆ or C₁₃-C₃₀ alkyl, C₅-C₆ or C₁₄-C₃₀ alkyl, C₅-C₆ or C₁₅-C₃₀ alkyl, C₅-C₆ or C₁₆-C₃₀ alkyl, C₅-C₆ or C₁₇-C₃₀ alkyl, C₅-C₆ or C₁₈-C₃₀ alkyl, C₅-C₆ or C₉-C₂₀ alkyl, C₅-C₆ or C₁₀-C₂₀ alkyl, C₅-C₆ or C₁₁-C₂₀ alkyl, C₅-C₆ or C₁₂-C₂₀ alkyl, C₅-C₆ or C₁₃-C₂₀ alkyl, C₅-C₆ or C₁₄-C₂₀ alkyl, C₅-C₆ or C₁₅-C₂₀ alkyl, C₅-C₆ or C₁₆-C₂₀ alkyl, C₅-C₆ or C₁₇-C₂₀ alkyl, C₅-C₆ or C₁₈-C₂₀ alkyl, C₅-C₆ or C₉-C₁₅ alkyl, C₅-C₆ or C₁₀-C₁₅ alkyl, C₅-C₆ or C₁₁-C₁₅ alkyl, C₅-C₆ or C₁₂-C₁₅ alkyl, C₅-C₆ or C₁₃-C₁₅ alkyl, or C₅-C₆ or C₁₄-C₁₅ alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C_5 or C_9 - C_{30} alkyl, C_5 or C_{10} - C_{30} alkyl, C_5 or C_{11} - C_{30} alkyl, C_5 or C_{12} - C_{30} alkyl, C_5 or C_{13} - C_{30} alkyl, C_5 or C_{14} - C_{30} alkyl, C_5 or C_{15} - C_{30} alkyl, C_5 or C_{16} - C_{30} alkyl, C_5 or C_{17} - C_{30} alkyl, C_5 or C_{18} - C_{30} alkyl, C_5 or C_9 - C_{20} alkyl, C_5 or C_{10} - C_{20} alkyl, C_5 or C_{11} - C_{20} alkyl, C_5 or C_{12} - C_{20} alkyl, C_5 or C_{13} - C_{20} alkyl, C_5 or C_{14} - C_{20} alkyl, C_5 or C_{15} - C_{20} alkyl, C_5 or C_{16} - C_{20} alkyl, C_5 or C_{17} - C_{20} alkyl, C_5 or C_{18} - C_{20} alkyl, C_5 or C_9 - C_{15} alkyl, C_5 or C_{10} - C_{15} alkyl, C_5 or C_{11} - C_{15} alkyl, C_5 or C_{12} - C_{15} alkyl, C_5 or C_{13} - C_{15} alkyl, or C_5 or C_{14} - C_{15} alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C_9 - C_{30} alkyl, C_{10} - C_{30} alkyl, C_{11} - C_{30} alkyl, C_{12} - C_{30} alkyl, C_{13} - C_{30} alkyl, C_{14} - C_{30} alkyl, C_{15} - C_{30} alkyl, C_{16} - C_{30} alkyl, C_{17} - C_{30} alkyl, C_{18} - C_{30} alkyl, C_9 - C_{20} alkyl, C_{10} - C_{20} alkyl, C_{11} - C_{20} alkyl, C_{12} - C_{20} alkyl, C_{13} - C_{20} alkyl, C_{14} - C_{20} alkyl, C_{15} - C_{20} alkyl, C_{16} - C_{20} alkyl, C_{17} - C_{20} alkyl, C_{18} - C_{20} alkyl, C_9 - C_{15} alkyl, C_{10} - C_{15} alkyl, C_{11} - C_{15} alkyl, C_{12} - C_{15} alkyl, C_{13} - C_{15} alkyl, or C_{14} - C_{15} alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C_1 - C_9 alkyl, C_1 - C_7 alkyl, C_1 - C_6 alkyl, C_1 - C_5 alkyl, C_1 - C_4 alkyl, C_1 - C_3 alkyl, C_1 - C_2 alkyl, C_1 or C_{10} alkyl, C_2 - C_9 alkyl, C_2 - C_7 alkyl, C_2 - C_6 alkyl, C_2 - C_5 alkyl, C_2 - C_4 alkyl, C_2 - C_3 alkyl, C_2 alkyl, C_3 - C_9 alkyl, C_3 - C_7 alkyl, C_3 - C_6 alkyl, C_3 - C_5 alkyl, C_3 - C_4 alkyl, C_3 alkyl, C_4 - C_9 alkyl, C_4 - C_7 alkyl, C_4 - C_6 alkyl, C_4 - C_5 alkyl, C_4 alkyl, C_5 - C_9 alkyl, C_5 - C_7 alkyl, C_5 - C_6 alkyl, C_5 alkyl, C_6 - C_9 alkyl, C_6 - C_7 alkyl, C_6 alkyl, C_7 - C_9 alkyl, C_7 alkyl, C_9 alkyl, or C_{10} alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C_1 - C_8 or C_{10} alkyl, C_1 - C_7 or C_{10} alkyl, C_1 - C_6 or C_{10} alkyl, C_1 - C_5 or C_{10} alkyl, C_1 - C_4 or C_{10} alkyl, C_1 - C_3 or C_{10} alkyl, C_1 - C_2 or C_{10} alkyl, C_1 or C_{10} alkyl, C_2 - C_8 or C_{10} alkyl, C_2 - C_7 or C_{10} alkyl, C_2 - C_6 or C_{10} alkyl, C_2 - C_5 or C_{10} alkyl, C_2 - C_4 or C_{10} alkyl, C_2 - C_3 or C_{10} alkyl, C_2 or C_{10} alkyl, C_3 - C_8 or C_{10} alkyl, C_3 - C_7 or C_{10} alkyl, C_3 - C_6 or C_{10} alkyl, C_3 - C_5 or C_{10} alkyl, C_3 - C_4 or C_{10} alkyl, C_3 or C_{10} alkyl, C_4 - C_8 or C_{10} alkyl, C_4 - C_7 or C_{10} alkyl, C_4 - C_6 or C_{10} alkyl, C_4 - C_5 or C_{10} alkyl, C_4 or C_{10} alkyl, C_5 - C_8 or C_{10} alkyl, C_5 - C_7 or C_{10} alkyl, C_5 - C_6 or C_{10} alkyl, C_5 or C_{10} alkyl, C_6 - C_8 or C_{10} alkyl, C_6 - C_7 or C_{10} alkyl, C_6 or C_{10} alkyl, C_7 - C_8 or C_{10} alkyl, C_7 or C_{10} alkyl, or C_8 or C_{10} alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C_1 - C_7 or C_9 - C_{10} alkyl, C_1 - C_6 or C_9 - C_{10} alkyl, C_1 - C_5 or C_9 - C_{10} alkyl, C_1 - C_4 or C_9 - C_{10} alkyl, C_1 - C_3 or C_9 - C_{10} alkyl, C_1 - C_2 or C_9 - C_{10} alkyl, C_1 or C_9 - C_{10} alkyl, C_2 - C_7 or C_9 - C_{10} alkyl, C_2 - C_6 or C_9 - C_{10} alkyl, C_2 - C_5 or C_9 - C_{10} alkyl, C_2 - C_4 or C_9 - C_{10} alkyl, C_2 - C_3

or C₉-C₁₀ alkyl, C₂ or C₉-C₁₀ alkyl, C₃-C₇ or C₉-C₁₀ alkyl, C₃-C₆ or C₉-C₁₀ alkyl, C₃-C₅ or C₉-C₁₀ alkyl, C₃-C₄ or C₉-C₁₀ alkyl, C₃ or C₉-C₁₀ alkyl, C₄-C₇ or C₉-C₁₀ alkyl, C₄-C₆ or C₉-C₁₀ alkyl, C₄-C₅ or C₉-C₁₀ alkyl, C₄ or C₉-C₁₀ alkyl, C₅-C₇ or C₉-C₁₀ alkyl, C₅-C₆ or C₉-C₁₀ alkyl, C₅ or C₉-C₁₀ alkyl, C₆-C₇ or C₉-C₁₀ alkyl, C₆ or C₉-C₁₀ alkyl, C₇ or C₉-C₁₀ alkyl, or C₉-C₁₀ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₁-C₆ or C₈-C₁₀ alkyl, C₁-C₅ or C₈-C₁₀ alkyl, C₁-C₄ or C₈-C₁₀ alkyl, C₁-C₃ or C₈-C₁₀ alkyl, C₁-C₂ or C₈-C₁₀ alkyl, C₁ or C₈-C₁₀ alkyl, C₂-C₆ or C₈-C₁₀ alkyl, C₂-C₅ or C₈-C₁₀ alkyl, C₂-C₄ or C₈-C₁₀ alkyl, C₂-C₃ or C₈-C₁₀ alkyl, C₂ or C₈-C₁₀ alkyl, C₃-C₆ or C₈-C₁₀ alkyl, C₃-C₅ or C₈-C₁₀ alkyl, C₃-C₄ or C₈-C₁₀ alkyl, C₃ or C₈-C₁₀ alkyl, C₄-C₆ or C₈-C₁₀ alkyl, C₄-C₅ or C₈-C₁₀ alkyl, C₄ or C₈-C₁₀ alkyl, C₅-C₆ or C₈-C₁₀ alkyl, C₅ or C₈-C₁₀ alkyl, C₆ or C₈-C₁₀ alkyl, or C₈-C₁₀ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₁-C₅ or C₇-C₁₀ alkyl, C₁-C₄ or C₇-C₁₀ alkyl, C₁-C₃ or C₇-C₁₀ alkyl, C₁-C₂ or C₇-C₁₀ alkyl, C₁ or C₇-C₁₀ alkyl, C₂-C₅ or C₇-C₁₀ alkyl, C₂-C₄ or C₇-C₁₀ alkyl, C₂-C₃ or C₇-C₁₀ alkyl, C₂ or C₇-C₁₀ alkyl, C₃-C₅ or C₇-C₁₀ alkyl, C₃-C₄ or C₇-C₁₀ alkyl, C₃ or C₇-C₁₀ alkyl, C₄-C₅ or C₇-C₁₀ alkyl, C₄ or C₇-C₁₀ alkyl, C₅ or C₇-C₁₀ alkyl, or C₇-C₁₀ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₁-C₄ or C₆-C₁₀ alkyl, C₁-C₃ or C₆-C₁₀ alkyl, C₁-C₂ or C₆-C₁₀ alkyl, C₁ or C₆-C₁₀ alkyl, C₂-C₄ or C₆-C₁₀ alkyl, C₂-C₃ or C₆-C₁₀ alkyl, C₂ or C₆-C₁₀ alkyl, C₃-C₄ or C₆-C₁₀ alkyl, C₃ or C₆-C₁₀ alkyl, C₄ or C₆-C₁₀ alkyl, C₆-C₁₀ alkyl, C₁-C₃ or C₅-C₁₀ alkyl, C₁-C₂ or C₅-C₁₀ alkyl, C₁ or C₅-C₁₀ alkyl, C₂-C₃ or C₅-C₁₀ alkyl, C₂ or C₅-C₁₀ alkyl, C₃ or C₅-C₁₀ alkyl, C₅-C₁₀ alkyl, C₁-C₂ or C₄-C₁₀ alkyl, C₁ or C₄-C₁₀ alkyl, C₂ or C₄-C₁₀ alkyl, C₄-C₁₀ alkyl, C₁ or C₃-C₁₀ alkyl, C₁ or C₃-C₁₀ alkyl, C₃-C₁₀ alkyl, C₂-C₁₀ alkyl, or C₁-C₁₀ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₁-C₇ or C₉-C₁₀ alkyl, C₁-C₇ or C₁₀-C₃₀ alkyl, C₁-C₇ or C₁₁-C₃₀ alkyl, C₁-C₇ or C₁₂-C₃₀ alkyl, C₁-C₇ or C₁₃-C₃₀ alkyl, C₁-C₇ or C₁₄-C₃₀ alkyl, C₁-C₇ or C₁₅-C₃₀ alkyl, C₁-C₇ or C₁₆-C₃₀ alkyl, C₁-C₇ or C₁₇-C₃₀ alkyl, C₁-C₇ or C₁₈-C₃₀ alkyl, C₁-C₇ or C₉-C₂₀ alkyl, C₁-C₇ or C₁₀-C₂₀ alkyl, C₁-C₇ or C₁₁-C₂₀ alkyl, C₁-C₇ or C₁₂-C₂₀ alkyl, C₁-C₇ or C₁₃-C₂₀ alkyl, C₁-C₇ or C₁₄-C₂₀ alkyl, C₁-C₇ or C₁₅-C₂₀ alkyl, C₁-C₇ or C₁₆-C₂₀ alkyl, C₁-C₇ or C₁₇-C₂₀ alkyl, C₁-C₇ or C₁₈-C₂₀ alkyl, C₁-C₇ or C₉-C₁₅ alkyl, C₁-C₇ or C₁₀-C₁₅ alkyl, C₁-C₇ or C₁₁-C₁₅ alkyl, C₁-C₇ or C₁₂-C₁₅ alkyl, C₁-C₇ or C₁₃-C₁₅ alkyl, or C₁-C₇ or C₁₄-C₁₅ alkyl.

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In some embodiments, R^4 , R^a , and substituents are, independently, C_1 - C_2 or C_9 - C_{10} alkyl, C_1 - C_2 or C_{10} - C_{30} alkyl, C_1 - C_2 or C_{11} - C_{30} alkyl, C_1 - C_2 or C_{12} - C_{30} alkyl, C_1 - C_2 or C_{13} - C_{30} alkyl, C_1 - C_2 or C_{14} - C_{30} alkyl, C_1 - C_2 or C_{15} - C_{30} alkyl, C_1 - C_2 or C_{16} - C_{30} alkyl, C_1 - C_2 or C_{17} - C_{30} alkyl, C_1 - C_2 or C_{18} - C_{30} alkyl, C_1 - C_2 or C_9 - C_{20} alkyl, C_1 - C_2 or C_{10} - C_{20} alkyl, C_1 - C_2 or C_{11} - C_{20} alkyl, C_1 - C_2 or C_{12} - C_{20} alkyl, C_1 - C_2 or C_{13} - C_{20} alkyl, C_1 - C_2 or C_{14} - C_{20} alkyl, C_1 - C_2 or C_{15} - C_{20} alkyl, C_1 - C_2 or C_{16} - C_{20} alkyl, C_1 - C_2 or C_{17} - C_{20} alkyl, C_1 - C_2 or C_{18} - C_{20} alkyl, C_1 - C_2 or C_9 - C_{15} alkyl, C_1 - C_2 or C_{10} - C_{15} alkyl, C_1 - C_2 or C_{11} - C_{15} alkyl, C_1 - C_2 or C_{12} - C_{15} alkyl, C_1 - C_2 or C_{13} - C_{15} alkyl, or C_1 - C_2 or C_{14} - C_{15} alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₁ or C₉-C₁₀ alkyl, C₁ or C₁₀-C₃₀ alkyl, C₁ or C₁₁-C₃₀ alkyl, C₁ or C₁₂-C₃₀ alkyl, C₁ or C₁₃-C₃₀ alkyl, C₁ or C₁₄-C₃₀ alkyl, C₁ or C₁₅-C₃₀ alkyl, C₁ or C₁₆-C₃₀ alkyl, C₁ or C₁₇-C₃₀ alkyl, C₁ or C₁₈-C₃₀ alkyl, C₁ or C₉-C₂₀ alkyl, C₁ or C₁₀-C₂₀ alkyl, C₁ or C₁₁-C₂₀ alkyl, C₁ or C₁₂-C₂₀ alkyl, C₁ or C₁₃-C₂₀ alkyl, C₁ or C₁₄-C₂₀ alkyl, C₁ or C₁₅-C₂₀ alkyl, C₁ or C₁₆-C₂₀ alkyl, C₁ or C₁₇-C₂₀ alkyl, C₁ or C₁₈-C₂₀ alkyl, C₁ or C₉-C₁₅ alkyl, C₁ or C₁₀-C₁₅ alkyl, C₁ or C₁₁-C₁₅ alkyl, C₁ or C₁₂-C₁₅ alkyl, C₁ or C₁₃-C₁₅ alkyl, or C₁ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₂-C₇ or C₉-C₁₀ alkyl, C₂-C₇ or C₁₀-C₃₀ alkyl, C₂-C₇ or C₁₁-C₃₀ alkyl, C₂-C₇ or C₁₂-C₃₀ alkyl, C₂-C₇ or C₁₃-C₃₀ alkyl, C₂-C₇ or C₁₄-C₃₀ alkyl, C₂-C₇ or C₁₅-C₃₀ alkyl, C₂-C₇ or C₁₆-C₃₀ alkyl, C₂-C₇ or C₁₇-C₃₀ alkyl, C₂-C₇ or C₁₈-C₃₀ alkyl, C₂-C₇ or C₉-C₂₀ alkyl, C₂-C₇ or C₁₀-C₂₀ alkyl, C₂-C₇ or C₁₁-C₂₀ alkyl, C₂-C₇ or C₁₂-C₂₀ alkyl, C₂-C₇ or C₁₃-C₂₀ alkyl, C₂-C₇ or C₁₄-C₂₀ alkyl, C₂-C₇ or C₁₅-C₂₀ alkyl, C₂-C₇ or C₁₆-C₂₀ alkyl, C₂-C₇ or C₁₇-C₂₀ alkyl, C₂-C₇ or C₁₈-C₂₀ alkyl, C₂-C₇ or C₉-C₁₅ alkyl, C₂-C₇ or C₁₀-C₁₅ alkyl, C₂-C₇ or C₁₁-C₁₅ alkyl, C₂-C₇ or C₁₂-C₁₅ alkyl, C₂-C₇ or C₁₃-C₁₅ alkyl, or C₂-C₇ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₂-C₆ or C₉-C₁₀ alkyl, C₂-C₆ or C₁₀-C₃₀ alkyl, C₂-C₆ or C₁₁-C₃₀ alkyl, C₂-C₆ or C₁₂-C₃₀ alkyl, C₂-C₆ or C₁₃-C₃₀ alkyl, C₂-C₆ or C₁₄-C₃₀ alkyl, C₂-C₆ or C₁₅-C₃₀ alkyl, C₂-C₆ or C₁₆-C₃₀ alkyl, C₂-C₆ or C₁₇-C₃₀ alkyl, C₂-C₆ or C₁₈-C₃₀ alkyl, C₂-C₆ or C₉-C₂₀ alkyl, C₂-C₆ or C₁₀-C₂₀ alkyl, C₂-C₆ or C₁₁-C₂₀ alkyl, C₂-C₆ or C₁₂-C₂₀ alkyl, C₂-C₆ or C₁₃-C₂₀ alkyl, C₂-C₆ or C₁₄-C₂₀ alkyl, C₂-C₆ or C₁₅-C₂₀ alkyl, C₂-C₆ or C₁₆-C₂₀ alkyl, C₂-C₆ or C₁₇-C₂₀ alkyl, C₂-C₆ or C₁₈-C₂₀ alkyl, C₂-C₆ or C₉-C₁₅ alkyl, C₂-C₆ or C₁₀-C₁₅ alkyl, C₂-C₆ or C₁₁-C₁₅ alkyl, C₂-C₆ or C₁₂-C₁₅ alkyl, C₂-C₆ or C₁₃-C₁₅ alkyl, or C₂-C₆ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₂-C₅ or C₉-C₁₀ alkyl, C₂-C₅ or C₁₀-C₃₀ alkyl, C₂-C₅ or C₁₁-C₃₀ alkyl, C₂-C₅ or C₁₂-C₃₀ alkyl, C₂-C₅ or

C₁₃-C₃₀ alkyl, C₂-C₅ or C₁₄-C₃₀ alkyl, C₂-C₅ or C₁₅-C₃₀ alkyl, C₂-C₅ or C₁₆-C₃₀ alkyl, C₂-C₅ or C₁₇-C₃₀ alkyl, C₂-C₅ or C₁₈-C₃₀ alkyl, C₂-C₅ or C₉-C₂₀ alkyl, C₂-C₅ or C₁₀-C₂₀ alkyl, C₂-C₅ or C₁₁-C₂₀ alkyl, C₂-C₅ or C₁₂-C₂₀ alkyl, C₂-C₅ or C₁₃-C₂₀ alkyl, C₂-C₅ or C₁₄-C₂₀ alkyl, C₂-C₅ or C₁₅-C₂₀ alkyl, C₂-C₅ or C₁₆-C₂₀ alkyl, C₂-C₅ or C₁₇-C₂₀ alkyl, C₂-C₅ or C₁₈-C₂₀ alkyl, C₂-C₅ or C₉-C₁₅ alkyl, C₂-C₅ or C₁₀-C₁₅ alkyl, C₂-C₅ or C₁₁-C₁₅ alkyl, C₂-C₅ or C₁₂-C₁₅ alkyl, C₂-C₅ or C₁₃-C₁₅ alkyl, or C₂-C₅ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₂-C₄ or C₉-C₁₀ alkyl, C₂-C₄ or C₁₀-C₃₀ alkyl, C₂-C₄ or C₁₁-C₃₀ alkyl, C₂-C₄ or C₁₂-C₃₀ alkyl, C₂-C₄ or C₁₃-C₃₀ alkyl, C₂-C₄ or C₁₄-C₃₀ alkyl, C₂-C₄ or C₁₅-C₃₀ alkyl, C₂-C₄ or C₁₆-C₃₀ alkyl, C₂-C₄ or C₁₇-C₃₀ alkyl, C₂-C₄ or C₁₈-C₃₀ alkyl, C₂-C₄ or C₉-C₂₀ alkyl, C₂-C₄ or C₁₀-C₂₀ alkyl, C₂-C₄ or C₁₁-C₂₀ alkyl, C₂-C₄ or C₁₂-C₂₀ alkyl, C₂-C₄ or C₁₃-C₂₀ alkyl, C₂-C₄ or C₁₄-C₂₀ alkyl, C₂-C₄ or C₁₅-C₂₀ alkyl, C₂-C₄ or C₁₆-C₂₀ alkyl, C₂-C₄ or C₁₇-C₂₀ alkyl, C₂-C₄ or C₁₈-C₂₀ alkyl, C₂-C₄ or C₉-C₁₅ alkyl, C₂-C₄ or C₁₀-C₁₅ alkyl, C₂-C₄ or C₁₁-C₁₅ alkyl, C₂-C₄ or C₁₂-C₁₅ alkyl, C₂-C₄ or C₁₃-C₁₅ alkyl, or C₂-C₄ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₂-C₃ or C₉-C₁₀ alkyl, C₂-C₃ or C₁₀-C₃₀ alkyl, C₂-C₃ or C₁₁-C₃₀ alkyl, C₂-C₃ or C₁₂-C₃₀ alkyl, C₂-C₃ or C₁₃-C₃₀ alkyl, C₂-C₃ or C₁₄-C₃₀ alkyl, C₂-C₃ or C₁₅-C₃₀ alkyl, C₂-C₃ or C₁₆-C₃₀ alkyl, C₂-C₃ or C₁₇-C₃₀ alkyl, C₂-C₃ or C₁₈-C₃₀ alkyl, C₂-C₃ or C₉-C₂₀ alkyl, C₂-C₃ or C₁₀-C₂₀ alkyl, C₂-C₃ or C₁₁-C₂₀ alkyl, C₂-C₃ or C₁₂-C₂₀ alkyl, C₂-C₃ or C₁₃-C₂₀ alkyl, C₂-C₃ or C₁₄-C₂₀ alkyl, C₂-C₃ or C₁₅-C₂₀ alkyl, C₂-C₃ or C₁₆-C₂₀ alkyl, C₂-C₃ or C₁₇-C₂₀ alkyl, C₂-C₃ or C₁₈-C₂₀ alkyl, C₂-C₃ or C₉-C₁₅ alkyl, C₂-C₃ or C₁₀-C₁₅ alkyl, C₂-C₃ or C₁₁-C₁₅ alkyl, C₂-C₃ or C₁₂-C₁₅ alkyl, C₂-C₃ or C₁₃-C₁₅ alkyl, or C₂-C₃ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₂ or C₉-C₁₀ alkyl, C₂ or C₁₀-C₃₀ alkyl, C₂ or C₁₁-C₃₀ alkyl, C₂ or C₁₂-C₃₀ alkyl, C₂ or C₁₃-C₃₀ alkyl, C₂ or C₁₄-C₃₀ alkyl, C₂ or C₁₅-C₃₀ alkyl, C₂ or C₁₆-C₃₀ alkyl, C₂ or C₁₇-C₃₀ alkyl, C₂ or C₁₈-C₃₀ alkyl, C₂ or C₉-C₂₀ alkyl, C₂ or C₁₀-C₂₀ alkyl, C₂ or C₁₁-C₂₀ alkyl, C₂ or C₁₂-C₂₀ alkyl, C₂ or C₁₃-C₂₀ alkyl, C₂ or C₁₄-C₂₀ alkyl, C₂ or C₁₅-C₂₀ alkyl, C₂ or C₁₆-C₂₀ alkyl, C₂ or C₁₇-C₂₀ alkyl, C₂ or C₁₈-C₂₀ alkyl, C₂ or C₉-C₁₅ alkyl, C₂ or C₁₀-C₁₅ alkyl, C₂ or C₁₁-C₁₅ alkyl, C₂ or C₁₂-C₁₅ alkyl, C₂ or C₁₃-C₁₅ alkyl, or C₂ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₃-C₇ or C₉-C₁₀ alkyl, C₃-C₇ or C₁₀-C₃₀ alkyl, C₃-C₇ or C₁₁-C₃₀ alkyl, C₃-C₇ or C₁₂-C₃₀ alkyl, C₃-C₇ or C₁₃-C₃₀ alkyl, C₃-C₇ or C₁₄-C₃₀ alkyl, C₃-C₇ or C₁₅-C₃₀ alkyl, C₃-C₇ or C₁₆-C₃₀ alkyl, C₃-C₇ or C₁₇-C₃₀ alkyl, C₃-C₇ or C₁₈-C₃₀ alkyl, C₃-C₇ or C₉-C₂₀ alkyl, C₃-C₇ or C₁₀-C₂₀ alkyl,

C₃-C₇ or C₁₁-C₂₀ alkyl, C₃-C₇ or C₁₂-C₂₀ alkyl, C₃-C₇ or C₁₃-C₂₀ alkyl, C₃-C₇ or C₁₄-C₂₀ alkyl, C₃-C₇ or C₁₅-C₂₀ alkyl, C₃-C₇ or C₁₆-C₂₀ alkyl, C₃-C₇ or C₁₇-C₂₀ alkyl, C₃-C₇ or C₁₈-C₂₀ alkyl, C₃-C₇ or C₉-C₁₅ alkyl, C₃-C₇ or C₁₀-C₁₅ alkyl, C₃-C₇ or C₁₁-C₁₅ alkyl, C₃-C₇ or C₁₂-C₁₅ alkyl, C₃-C₇ or C₁₃-C₁₅ alkyl, or C₃-C₇ or C₁₄-C₁₅ alkyl.

5 In some embodiments, R⁴, R^a, and substituents are, independently, C₃-C₆ or C₉-C₁₀ alkyl, C₃-C₆ or C₁₀-C₃₀ alkyl, C₃-C₆ or C₁₁-C₃₀ alkyl, C₃-C₆ or C₁₂-C₃₀ alkyl, C₃-C₆ or C₁₃-C₃₀ alkyl, C₃-C₆ or C₁₄-C₃₀ alkyl, C₃-C₆ or C₁₅-C₃₀ alkyl, C₃-C₆ or C₁₆-C₃₀ alkyl, C₃-C₆ or C₁₇-C₃₀ alkyl, C₃-C₆ or C₁₈-C₃₀ alkyl, C₃-C₆ or C₉-C₂₀ alkyl, C₃-C₆ or C₁₀-C₂₀ alkyl, C₃-C₆ or C₁₁-C₂₀ alkyl, C₃-C₆ or C₁₂-C₂₀ alkyl, C₃-C₆ or C₁₃-C₂₀ alkyl, C₃-C₆ or C₁₄-C₂₀ alkyl, C₃-C₆ or C₁₅-C₂₀ alkyl, C₃-C₆ or C₁₆-C₂₀ alkyl, C₃-C₆ or C₁₇-C₂₀ alkyl, C₃-C₆ or C₁₈-C₂₀ alkyl, C₃-C₆ or C₉-C₁₅ alkyl, C₃-C₆ or C₁₀-C₁₅ alkyl, C₃-C₆ or C₁₁-C₁₅ alkyl, C₃-C₆ or C₁₂-C₁₅ alkyl, C₃-C₆ or C₁₃-C₁₅ alkyl, or C₃-C₆ or C₁₄-C₁₅ alkyl.

10 In some embodiments, R⁴, R^a, and substituents are, independently, C₃-C₅ or C₉-C₁₀ alkyl, C₃-C₅ or C₁₀-C₃₀ alkyl, C₃-C₅ or C₁₁-C₃₀ alkyl, C₃-C₅ or C₁₂-C₃₀ alkyl, C₃-C₅ or C₁₃-C₃₀ alkyl, C₃-C₅ or C₁₄-C₃₀ alkyl, C₃-C₅ or C₁₅-C₃₀ alkyl, C₃-C₅ or C₁₆-C₃₀ alkyl, C₃-C₅ or C₁₇-C₃₀ alkyl, C₃-C₅ or C₁₈-C₃₀ alkyl, C₃-C₅ or C₉-C₂₀ alkyl, C₃-C₅ or C₁₀-C₂₀ alkyl, C₃-C₅ or C₁₁-C₂₀ alkyl, C₃-C₅ or C₁₂-C₂₀ alkyl, C₃-C₅ or C₁₃-C₂₀ alkyl, C₃-C₅ or C₁₄-C₂₀ alkyl, C₃-C₅ or C₁₅-C₂₀ alkyl, C₃-C₅ or C₁₆-C₂₀ alkyl, C₃-C₅ or C₁₇-C₂₀ alkyl, C₃-C₅ or C₁₈-C₂₀ alkyl, C₃-C₅ or C₉-C₁₅ alkyl, C₃-C₅ or C₁₀-C₁₅ alkyl, C₃-C₅ or C₁₁-C₁₅ alkyl, C₃-C₅ or C₁₂-C₁₅ alkyl, C₃-C₅ or C₁₃-C₁₅ alkyl, or C₃-C₅ or C₁₄-C₁₅ alkyl.

20 In some embodiments, R⁴, R^a, and substituents are, independently, C₃-C₄ or C₉-C₁₀ alkyl, C₃-C₄ or C₁₀-C₃₀ alkyl, C₃-C₄ or C₁₁-C₃₀ alkyl, C₃-C₄ or C₁₂-C₃₀ alkyl, C₃-C₄ or C₁₃-C₃₀ alkyl, C₃-C₄ or C₁₄-C₃₀ alkyl, C₃-C₄ or C₁₅-C₃₀ alkyl, C₃-C₄ or C₁₆-C₃₀ alkyl, C₃-C₄ or C₁₇-C₃₀ alkyl, C₃-C₄ or C₁₈-C₃₀ alkyl, C₃-C₄ or C₉-C₂₀ alkyl, C₃-C₄ or C₁₀-C₂₀ alkyl, C₃-C₄ or C₁₁-C₂₀ alkyl, C₃-C₄ or C₁₂-C₂₀ alkyl, C₃-C₄ or C₁₃-C₂₀ alkyl, C₃-C₄ or C₁₄-C₂₀ alkyl, C₃-C₄ or C₁₅-C₂₀ alkyl, C₃-C₄ or C₁₆-C₂₀ alkyl, C₃-C₄ or C₁₇-C₂₀ alkyl, C₃-C₄ or C₁₈-C₂₀ alkyl, C₃-C₄ or C₉-C₁₅ alkyl, C₃-C₄ or C₁₀-C₁₅ alkyl, C₃-C₄ or C₁₁-C₁₅ alkyl, C₃-C₄ or C₁₂-C₁₅ alkyl, C₃-C₄ or C₁₃-C₁₅ alkyl, or C₃-C₄ or C₁₄-C₁₅ alkyl.

25 In some embodiments, R⁴, R^a, and substituents are, independently, C₃ or C₉-C₁₀ alkyl, C₃ or C₁₀-C₃₀ alkyl, C₃ or C₁₁-C₃₀ alkyl, C₃ or C₁₂-C₃₀ alkyl, C₃ or C₁₃-C₃₀ alkyl, C₃ or C₁₄-C₃₀ alkyl, C₃ or C₁₅-C₃₀ alkyl, C₃ or C₁₆-C₃₀ alkyl, C₃ or C₁₇-C₃₀ alkyl, C₃ or C₁₈-C₃₀ alkyl, C₃ or C₉-C₂₀ alkyl, C₃ or C₁₀-C₂₀ alkyl, C₃ or C₁₁-C₂₀ alkyl, C₃ or C₁₂-C₂₀ alkyl, C₃ or C₁₃-C₂₀ alkyl, C₃ or C₁₄-C₂₀ alkyl, C₃ or C₁₅-C₂₀ alkyl, C₃ or C₁₆-C₂₀ alkyl,

C₃ or C₁₇-C₂₀ alkyl, C₃ or C₁₈-C₂₀ alkyl, C₃ or C₉-C₁₅ alkyl, C₃ or C₁₀-C₁₅ alkyl, C₃ or C₁₁-C₁₅ alkyl, C₃ or C₁₂-C₁₅ alkyl, C₃ or C₁₃-C₁₅ alkyl, or C₃ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₄-C₇ or C₉-C₁₀ alkyl, C₄-C₇ or C₁₀-C₃₀ alkyl, C₄-C₇ or C₁₁-C₃₀ alkyl, C₄-C₇ or C₁₂-C₃₀ alkyl, C₄-C₇ or C₁₃-C₃₀ alkyl, C₄-C₇ or C₁₄-C₃₀ alkyl, C₄-C₇ or C₁₅-C₃₀ alkyl, C₄-C₇ or C₁₆-C₃₀ alkyl, C₄-C₇ or C₁₇-C₃₀ alkyl, C₄-C₇ or C₁₈-C₃₀ alkyl, C₄-C₇ or C₉-C₂₀ alkyl, C₄-C₇ or C₁₀-C₂₀ alkyl, C₄-C₇ or C₁₁-C₂₀ alkyl, C₄-C₇ or C₁₂-C₂₀ alkyl, C₄-C₇ or C₁₃-C₂₀ alkyl, C₄-C₇ or C₁₄-C₂₀ alkyl, C₄-C₇ or C₁₅-C₂₀ alkyl, C₄-C₇ or C₁₆-C₂₀ alkyl, C₄-C₇ or C₁₇-C₂₀ alkyl, C₄-C₇ or C₁₈-C₂₀ alkyl, C₄-C₇ or C₉-C₁₅ alkyl, C₄-C₇ or C₁₀-C₁₅ alkyl, C₄-C₇ or C₁₁-C₁₅ alkyl, C₄-C₇ or C₁₂-C₁₅ alkyl, C₄-C₇ or C₁₃-C₁₅ alkyl, or C₄-C₇ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₄-C₆ or C₉-C₁₀ alkyl, C₄-C₆ or C₁₀-C₃₀ alkyl, C₄-C₆ or C₁₁-C₃₀ alkyl, C₄-C₆ or C₁₂-C₃₀ alkyl, C₄-C₆ or C₁₃-C₃₀ alkyl, C₄-C₆ or C₁₄-C₃₀ alkyl, C₄-C₆ or C₁₅-C₃₀ alkyl, C₄-C₆ or C₁₆-C₃₀ alkyl, C₄-C₆ or C₁₇-C₃₀ alkyl, C₄-C₆ or C₁₈-C₃₀ alkyl, C₄-C₆ or C₉-C₂₀ alkyl, C₄-C₆ or C₁₀-C₂₀ alkyl, C₄-C₆ or C₁₁-C₂₀ alkyl, C₄-C₆ or C₁₂-C₂₀ alkyl, C₄-C₆ or C₁₃-C₂₀ alkyl, C₄-C₆ or C₁₄-C₂₀ alkyl, C₄-C₆ or C₁₅-C₂₀ alkyl, C₄-C₆ or C₁₆-C₂₀ alkyl, C₄-C₆ or C₁₇-C₂₀ alkyl, C₄-C₆ or C₁₈-C₂₀ alkyl, C₄-C₆ or C₉-C₁₅ alkyl, C₄-C₆ or C₁₀-C₁₅ alkyl, C₄-C₆ or C₁₁-C₁₅ alkyl, C₄-C₆ or C₁₂-C₁₅ alkyl, C₄-C₆ or C₁₃-C₁₅ alkyl, or C₄-C₆ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₄-C₅ or C₉-C₁₀ alkyl, C₄-C₅ or C₁₀-C₃₀ alkyl, C₄-C₅ or C₁₁-C₃₀ alkyl, C₄-C₅ or C₁₂-C₃₀ alkyl, C₄-C₅ or C₁₃-C₃₀ alkyl, C₄-C₅ or C₁₄-C₃₀ alkyl, C₄-C₅ or C₁₅-C₃₀ alkyl, C₄-C₅ or C₁₆-C₃₀ alkyl, C₄-C₅ or C₁₇-C₃₀ alkyl, C₄-C₅ or C₁₈-C₃₀ alkyl, C₄-C₅ or C₉-C₂₀ alkyl, C₄-C₅ or C₁₀-C₂₀ alkyl, C₄-C₅ or C₁₁-C₂₀ alkyl, C₄-C₅ or C₁₂-C₂₀ alkyl, C₄-C₅ or C₁₃-C₂₀ alkyl, C₄-C₅ or C₁₄-C₂₀ alkyl, C₄-C₅ or C₁₅-C₂₀ alkyl, C₄-C₅ or C₁₆-C₂₀ alkyl, C₄-C₅ or C₁₇-C₂₀ alkyl, C₄-C₅ or C₁₈-C₂₀ alkyl, C₄-C₅ or C₉-C₁₅ alkyl, C₄-C₅ or C₁₀-C₁₅ alkyl, C₄-C₅ or C₁₁-C₁₅ alkyl, C₄-C₅ or C₁₂-C₁₅ alkyl, C₄-C₅ or C₁₃-C₁₅ alkyl, or C₄-C₅ or C₁₄-C₁₅ alkyl.

In some embodiments, R⁴, R^a, and substituents are, independently, C₄ or C₉-C₁₀ alkyl, C₄ or C₁₀-C₃₀ alkyl, C₄ or C₁₁-C₃₀ alkyl, C₄ or C₁₂-C₃₀ alkyl, C₄ or C₁₃-C₃₀ alkyl, C₄ or C₁₄-C₃₀ alkyl, C₄ or C₁₅-C₃₀ alkyl, C₄ or C₁₆-C₃₀ alkyl, C₄ or C₁₇-C₃₀ alkyl, C₄ or C₁₈-C₃₀ alkyl, C₄ or C₉-C₂₀ alkyl, C₄ or C₁₀-C₂₀ alkyl, C₄ or C₁₁-C₂₀ alkyl, C₄ or C₁₂-C₂₀ alkyl, C₄ or C₁₃-C₂₀ alkyl, C₄ or C₁₄-C₂₀ alkyl, C₄ or C₁₅-C₂₀ alkyl, C₄ or C₁₆-C₂₀ alkyl, C₄ or C₁₇-C₂₀ alkyl, C₄ or C₁₈-C₂₀ alkyl, C₄ or C₉-C₁₅ alkyl, C₄ or C₁₀-C₁₅ alkyl, C₄ or C₁₁-C₁₅ alkyl, C₄ or C₁₂-C₁₅ alkyl, C₄ or C₁₃-C₁₅ alkyl, or C₄ or C₁₄-C₁₅ alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C₅-C₇ or C₉-C₁₀ alkyl, C₅-C₇ or C₁₀-C₃₀ alkyl, C₅-C₇ or C₁₁-C₃₀ alkyl, C₅-C₇ or C₁₂-C₃₀ alkyl, C₅-C₇ or C₁₃-C₃₀ alkyl, C₅-C₇ or C₁₄-C₃₀ alkyl, C₅-C₇ or C₁₅-C₃₀ alkyl, C₅-C₇ or C₁₆-C₃₀ alkyl, C₅-C₇ or C₁₇-C₃₀ alkyl, C₅-C₇ or C₁₈-C₃₀ alkyl, C₅-C₇ or C₉-C₂₀ alkyl, C₅-C₇ or C₁₀-C₂₀ alkyl, C₅-C₇ or C₁₁-C₂₀ alkyl, C₅-C₇ or C₁₂-C₂₀ alkyl, C₅-C₇ or C₁₃-C₂₀ alkyl, C₅-C₇ or C₁₄-C₂₀ alkyl, C₅-C₇ or C₁₅-C₂₀ alkyl, C₅-C₇ or C₁₆-C₂₀ alkyl, C₅-C₇ or C₁₇-C₂₀ alkyl, C₅-C₇ or C₁₈-C₂₀ alkyl, C₅-C₇ or C₉-C₁₅ alkyl, C₅-C₇ or C₁₀-C₁₅ alkyl, C₅-C₇ or C₁₁-C₁₅ alkyl, C₅-C₇ or C₁₂-C₁₅ alkyl, C₅-C₇ or C₁₃-C₁₅ alkyl, or C₅-C₇ or C₁₄-C₁₅ alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C₅-C₆ or C₉-C₁₀ alkyl, C₅-C₆ or C₁₀-C₃₀ alkyl, C₅-C₆ or C₁₁-C₃₀ alkyl, C₅-C₆ or C₁₂-C₃₀ alkyl, C₅-C₆ or C₁₃-C₃₀ alkyl, C₅-C₆ or C₁₄-C₃₀ alkyl, C₅-C₆ or C₁₅-C₃₀ alkyl, C₅-C₆ or C₁₆-C₃₀ alkyl, C₅-C₆ or C₁₇-C₃₀ alkyl, C₅-C₆ or C₁₈-C₃₀ alkyl, C₅-C₆ or C₉-C₂₀ alkyl, C₅-C₆ or C₁₀-C₂₀ alkyl, C₅-C₆ or C₁₁-C₂₀ alkyl, C₅-C₆ or C₁₂-C₂₀ alkyl, C₅-C₆ or C₁₃-C₂₀ alkyl, C₅-C₆ or C₁₄-C₂₀ alkyl, C₅-C₆ or C₁₅-C₂₀ alkyl, C₅-C₆ or C₁₆-C₂₀ alkyl, C₅-C₆ or C₁₇-C₂₀ alkyl, C₅-C₆ or C₁₈-C₂₀ alkyl, C₅-C₆ or C₉-C₁₅ alkyl, C₅-C₆ or C₁₀-C₁₅ alkyl, C₅-C₆ or C₁₁-C₁₅ alkyl, C₅-C₆ or C₁₂-C₁₅ alkyl, C₅-C₆ or C₁₃-C₁₅ alkyl, or C₅-C₆ or C₁₄-C₁₅ alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C₅ or C₉-C₁₀ alkyl, C₅ or C₁₀-C₃₀ alkyl, C₅ or C₁₁-C₃₀ alkyl, C₅ or C₁₂-C₃₀ alkyl, C₅ or C₁₃-C₃₀ alkyl, C₅ or C₁₄-C₃₀ alkyl, C₅ or C₁₅-C₃₀ alkyl, C₅ or C₁₆-C₃₀ alkyl, C₅ or C₁₇-C₃₀ alkyl, C₅ or C₁₈-C₃₀ alkyl, C₅ or C₉-C₂₀ alkyl, C₅ or C₁₀-C₂₀ alkyl, C₅ or C₁₁-C₂₀ alkyl, C₅ or C₁₂-C₂₀ alkyl, C₅ or C₁₃-C₂₀ alkyl, C₅ or C₁₄-C₂₀ alkyl, C₅ or C₁₅-C₂₀ alkyl, C₅ or C₁₆-C₂₀ alkyl, C₅ or C₁₇-C₂₀ alkyl, C₅ or C₁₈-C₂₀ alkyl, C₅ or C₉-C₁₅ alkyl, C₅ or C₁₀-C₁₅ alkyl, C₅ or C₁₁-C₁₅ alkyl, C₅ or C₁₂-C₁₅ alkyl, C₅ or C₁₃-C₁₅ alkyl, or C₅ or C₁₄-C₁₅ alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C₉-C₁₀ alkyl, C₁₀-C₃₀ alkyl, C₁₁-C₃₀ alkyl, C₁₂-C₃₀ alkyl, C₁₃-C₃₀ alkyl, C₁₄-C₃₀ alkyl, C₁₅-C₃₀ alkyl, C₁₆-C₃₀ alkyl, C₁₇-C₃₀ alkyl, C₁₈-C₃₀ alkyl, C₉-C₂₀ alkyl, C₁₀-C₂₀ alkyl, C₁₁-C₂₀ alkyl, C₁₂-C₂₀ alkyl, C₁₃-C₂₀ alkyl, C₁₄-C₂₀ alkyl, C₁₅-C₂₀ alkyl, C₁₆-C₂₀ alkyl, C₁₇-C₂₀ alkyl, C₁₈-C₂₀ alkyl, C₉-C₁₅ alkyl, C₁₀-C₁₅ alkyl, C₁₁-C₁₅ alkyl, C₁₂-C₁₅ alkyl, C₁₃-C₁₅ alkyl, or C₁₄-C₁₅ alkyl.

In some embodiments, R^4 , R^a , and substituents are, independently, C₁ alkyl, C₂ alkyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, C₆ alkyl, C₇ alkyl, C₈ alkyl, C₉ alkyl, C₁₀ alkyl, C₁₁ alkyl, C₁₂ alkyl, C₁₃ alkyl, C₁₄ alkyl, C₁₅ alkyl, C₁₆ alkyl, C₁₇ alkyl, C₁₈ alkyl, C₁₉ alkyl,

C₂₀ alkyl, C₂₁ alkyl, C₂₂ alkyl, C₂₃ alkyl, C₂₄ alkyl, C₂₅ alkyl, C₂₆ alkyl, C₂₇ alkyl, C₂₈ alkyl, C₂₉ alkyl, or C₃₀ alkyl.

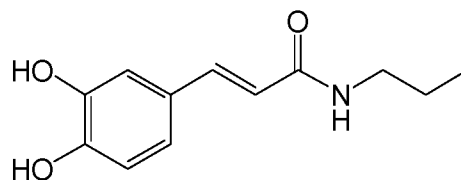
In some embodiments, the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

In some embodiments, the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, or C₁-C₁₀ amido.

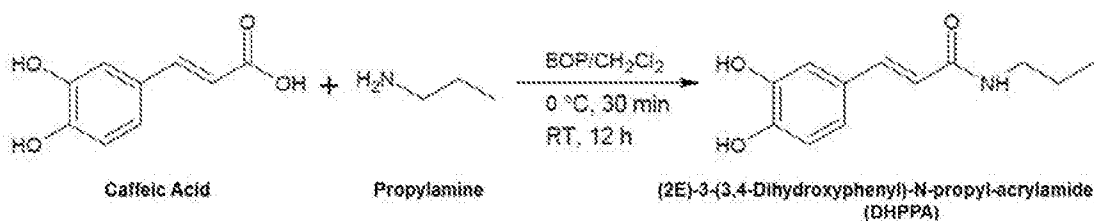
In some embodiments, the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, or C₁-C₁₀ amido.

In some embodiments, the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or unsubstituted C₁-C₃ alkyl, C₁-C₃ alkylene, C₂-C₃ alkenyl, C₂-C₃ alkynyl, C₁-C₃ alkoxy, C₁-C₃ alkylamino, C₁-C₃ alkylthio, C₁-C₃ carbonyl, C₁-C₃ carboxyl, or C₁-C₃ amido.

In some embodiments, the caffeic acid derivative is (2E)-3-(3,4-dihydroxyphenyl)-N-propyl-acrylamide (DHPPA) (shown in Formula 4, and prepared as shown in Scheme 1), or its analogs, in all its stereoisomeric and tautomeric forms.



Formula 4. Chemical structure of DHPPA.



Scheme 1. Preparation of DHPPA via direct amidation in a one-pot synthesis. (BOP is benzotriazol-1-yloxytris (dimethylamino)phosphonium hexafluorophosphate.)

The caffeic acid derivatives can be in any of its stereoisomeric and tautomeric forms, and mixtures thereof in all ratios, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable solvate thereof, a pharmaceutically acceptable polymorph thereof, or a prodrug thereof.

B. Formulations

The disclosed compositions containing a caffeic acid derivative, analog or prodrug, or a pharmacologically active salt thereof can be formulated as pharmaceutical compositions, with one or more additional active agents and/or one or more pharmaceutically acceptable excipients.

a. Additional Active Agents

Pharmaceutical compositions can contain one or more additional active agents which are not present in the caffeic acid derivatives. In some cases, one or more additional active agents may be mixed with, dispersed with, or co-dissolved with caffeic acid derivatives. In certain embodiments, one or more additional active agents may be dissolved or suspended in the pharmaceutically acceptable carrier.

In certain embodiments, the pharmaceutical composition further contains one or more agents to dissolve the thrombus to restore coronary blood flow and/or agents to decrease myocardial oxygen consumption.

Active agents to dissolve the thrombus include fibrinolytic agents (e.g. streptokinase, tissue plasminogen activator), antiplatelet agents (e.g. aspirin) and antithrombins (e.g. heparin).

Active agents to decrease myocardial oxygen consumption include beta blockers, glyceryl trinitrate, and possibly angiotensin-converting enzyme (ACE) inhibitors. Decreased oxygen consumption is achieved by lowering heart rate, blood pressure and cardiac filling pressures.

b. Excipients

Representative excipients include solvents, diluents, pH modifying agents, preservatives, antioxidants, suspending agents, wetting agents, viscosity modifiers, tonicity agents, stabilizing agents, and combinations thereof. Suitable pharmaceutically acceptable excipients are preferably selected from materials which are generally recognized as safe (GRAS), and may be administered to an individual without causing undesirable biological side effects or unwanted interactions.

Pharmaceutical compositions may be for administration by parenteral (intramuscular, intraperitoneal, intravenous (IV) or subcutaneous injection), oral, transdermal (either passively or using iontophoresis or electroporation), transmucosal (nasal, vaginal, rectal, or sublingual) routes of administration or using bioerodible inserts and can be formulated in unit dosage forms appropriate for each route of administration.

c. Parenteral Administration Formulation

In some embodiments, the compositions of caffeic acid derivatives are administered in an aqueous solution, by parenteral injection. The formulation may also be in the form of a suspension or emulsion. In general, pharmaceutical compositions are provided including effective amounts of caffeic acid derivatives, or an analog or a prodrug, or a pharmacologically active salt thereof and optionally include pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents sterile water, buffered saline of various buffer content (*e.g.*, Tris-HCl, acetate, phosphate), pH and ionic strength; and optionally, additives such as detergents and solubilizing agents (*e.g.*, TWEEN®20, TWEEN®80, Polysorbate 80), anti-oxidants (*e.g.*, ascorbic acid, sodium metabisulfite), and preservatives (*e.g.*, Thimersol, benzyl alcohol) and bulking substances (*e.g.*, lactose, mannitol). Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. The formulations may be lyophilized and redissolved/resuspended immediately before use. The formulation may be sterilized by, for example, filtration through a bacteria retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions.

d. Oral Administration Formulation

In some embodiments, the caffeic acid derivatives are formulated for oral administration. Oral solid dosage forms are described generally in Remington's Pharmaceutical Sciences, 18th Ed. 1990 (Mack Publishing Co. Easton Pa. 18042) at Chapter 89. Solid dosage forms include tablets, capsules, pills, troches or lozenges, cachets, pellets, powders, or granules or incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Such compositions may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the present proteins and derivatives. See, *e.g.*, Remington's Pharmaceutical Sciences, 18th Ed. (1990), Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712 which are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder (*e.g.*, lyophilized) form. Liposomal or proteinoid encapsulation may be used to formulate the compositions (as, for example, proteinoid microspheres reported in U.S. Pat. No. 4,925,673). Liposomal encapsulation may be used and the liposomes may be derivatized with various polymers (*e.g.*, U.S. Pat. No. 5,013,556). See also Marshall, K. In: Modern Pharmaceutics Edited by G. S. Banker and C. T. Rhodes, Chapter 10, 1979.

Another embodiment provides liquid dosage forms for oral administration, including pharmaceutically acceptable emulsions, solutions, suspensions, and syrups, which may contain other components including inert diluents; adjuvants such as wetting agents, emulsifying and suspending agents; and sweetening, flavoring, and perfuming agents.

Controlled release oral formulations may be desirable. Caffeic acid derivatives, analogs or prodrugs, or a pharmacologically active salt thereof can be incorporated into an inert matrix which permits release by either diffusion or leaching mechanisms, *e.g.*, gums. Slowly degrading matrices may also be incorporated into the formulation. Another form of a controlled release is based on the Oros therapeutic system (Alza Corp.), i.e., the drug is enclosed in a semipermeable membrane which allows water to enter and push drug out through a single small opening due to osmotic effects. For oral formulations, the location of release may be the stomach, the small intestine (the duodenum, the jejunum, or the ileum), or the large intestine. Preferably, the release will avoid the deleterious effects of the stomach environment, either by protection of the caffeic acid derivatives or by release of the caffeic acid derivatives beyond the stomach

environment, such as in the intestine. To ensure full gastric resistance a coating impermeable to at least pH 5.0 is essential. Examples of the more common inert ingredients that are used as enteric coatings are cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), HPMCP 50, HPMCP 55, polyvinyl acetate phthalate (PVAP), Eudragit L30D, Aquateric, cellulose acetate phthalate (CAP), Eudragit L, Eudragit S, and Shellac. These coatings may be used as mixed films.

Caffeic acid derivatives may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the component molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the component or components and increase in circulation time in the body. PEGylation is a preferred chemical modification for pharmaceutical usage. Other moieties that may be used include: propylene glycol, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, polyproline, poly-1,3-dioxolane and poly-1,3,6-tioxocane (see, *e.g.*, Abuchowski and Davis (1981) "Soluble Polymer-Enzyme Adducts," in *Enzymes as Drugs*. Hoenberg and Roberts, eds. (Wiley-Interscience: New York, N.Y.) pp. 367-383; and Newmark, et al., *J. Appl. Biochem.* 4:185-189 (1982)).

e. Controlled Delivery Formulations

Controlled release polymeric devices can be used for long term release following implantation or administration of a polymeric device (rod, cylinder, film, disk) or injection (microparticles). The device can be in the form of microparticles (or nanoparticles) such as microspheres (nanosphere), where one or more caffeic acid derivatives are dispersed within a solid polymeric matrix or capsules, where the core is of a different material than the polymeric shell, and the caffeic acid derivative is dispersed or suspended in the core, which may be liquid or solid in nature. Unless specifically defined herein, microparticles, microspheres, and microcapsules are used interchangeably. Alternatively, the polymer may be cast as a thin slab or film, ranging from nanometers to four centimeters, a powder produced by grinding or other standard techniques, or even a gel such as a hydrogel.

Either non-biodegradable or biodegradable matrices can be used for delivery of caffeic acid derivatives, although biodegradable matrices are preferred. These may be

natural or synthetic polymers, although synthetic polymers are preferred due to the better characterization of degradation and release profiles. The polymer is selected based on the period over which release is desired. In some cases linear release may be useful, although in others a pulse release or “bulk release” may provide more effective results.

- 5 The polymer may be in the form of a hydrogel (typically in absorbing up to about 90% by weight of water), and can optionally be complexed with multivalent ions or polymers.

The matrices can be formed by solvent evaporation, spray drying, solvent extraction and other methods known to those skilled in the art. Bioerodible microspheres can be prepared using any of the methods developed for making microspheres for drug
10 delivery, for example, as described by Mathiowitz and Langer, *J. Controlled Release*, 5,13-22 (1987); Mathiowitz, et al., *Reactive Polymers*, 6, 275-283 (1987); and Mathiowitz, et al., *J. Appl. Polymer Sci.*, 35, 755-774 (1988).

The devices can be formulated for local release to treat the area that is subject to a disease, which will typically deliver a dosage that is much less than the dosage for
15 treatment of an entire body or systemic delivery. These can be implanted or injected subcutaneously, into the muscle, fat, or swallowed.

III. Methods for Treating Myocardial Infarction

A. Transforming macrophages

It has been discovered that the macrophage subpopulation, i.e., M2 macrophages,
20 is highly correlated with infarct repair (Ben-Mordechai T., et al., *Pre-Clinical Research*, 62(20):1890-901 (2013)). Yet current anti-inflammatory drugs for myocardial infarction are not designed to target macrophages.

Macrophages are a heterogeneous population of innate myeloid cells. They are functionally diverse (plastic), and their main function is to respond to pathogens and to
25 modulate the adaptive immune response through antigen processing and presentation. Macrophages derived from monocyte precursors undergo specific differentiation depending on the local tissue environment (Steinman and Idoyaga, *Immunol Rev.*, 234:5-17 (2010)). The various macrophage functions are linked to the type of receptor interaction on the macrophage and the presence of cytokines (Taylor PR, et al., *Annu Rev Immunol.*, 23:901-944 (2005)). Two distinct states of polarized activation for
30 macrophages have been defined: the classically activated (M1) macrophage phenotype and the alternatively activated (M2) macrophage phenotype. Classically activated (M1) macrophages have the role of effector cells in T helper type 1 (TH1) cellular immune

responses. The alternatively activated (M2) macrophages appear to be involved in immunosuppression and tissue repair. Lipopolysaccharide (LPS) and the TH1 cytokine IFN-gamma polarize macrophages towards the M1 phenotype which induces the macrophage to produce large amounts of cytokines, such as TNF, IL-12, and IL-23. This helps to drive antigen specific TH1 and TH17 cell inflammatory responses forward. The clearance of invading microorganisms can trigger tissue damage (toxic activity or reactive oxygen), resulting in an uncontrolled macrophage inflammatory response which could become pathogenic. In contrast, exposure of macrophages to the TH2 cytokine IL-4 produces a M2 phenotype which induces the production of high levels of IL-10 and IL-1RA and low expression of IL-12. These cells help with parasite clearance, reduce inflammation, are immunoregulators, promote tissue remodeling and tumor progression. M2 macrophages can be further divided into subsets (see table 2): M2a, M2b, and M2c based on gene expression profiles (Mantovani A, *et al.*, *Blood*, 108(2):408 (2004)). M2 macrophages also express high levels of scavenger mannose and galactose receptors. M1 and M2 macrophages have distinct chemokine and chemokine receptor profiles, with M1 secreting the TH1 cell-attracting chemokines CXCL9 and CXCL10 with M2 macrophages expressing chemokines CCL17, CCL22 and CCL24. Chemokines CCL2 and CXCL10 polarize macrophages to an M2 like phenotype (Mantovani, *Blood*, 108(2):408 (2006)). It has recently been demonstrated that macrophages in vitro are capable of complete repolarization from M2 to M1, and change again in response to fluctuations in the cytokine environment (Davis MJ, *et al.*, *mBio.*, 4:1-10 (2013)). The change in polarization is rapid and occurs at the level of gene expression, protein, metabolite, and microbicidal activity.

Hence, in a preferred embodiment, an effective amount of caffeic acid derivatives is administered to a subject suffering from myocardial infarction to increase the population of M2 macrophages, increase the relative population of M2 macrophages compared to M1 macrophages, and/or decrease the population of M1 macrophages.

In some embodiments, an effective amount of caffeic acid derivatives is administered to increase the gene expression of M2 macrophages (e.g., CD163, MHC II, SR, CD206, MR, TGM2, DecoyR, IL-1R II, TLR1, TLR8, and for mouse only, Ym1, Fizz1, and Arginase-1), increase the relative gene expression of M2 macrophages

compared to that of M1 macrophages (e.g., CD80, IL-1R I, TLR2, TLR4, and iNOS), and/or decrease the gene expression of M1 macrophages.

In some embodiments, an effective amount of caffeic acid derivatives is administered to increase the cytokines produced by M2 macrophages (e.g., IL-10, TGF-beta, IL-1ra, and IL-10), increase the relative cytokines produced by M2 macrophages compared to that by M1 macrophages (e.g., TNF-alpha, IL-1beta, IL-12, and IL-23), and/or decrease the cytokines produced by M1 macrophages.

B. Diseases and conditions to be treated

a. Myocardial Infarction

Myocardial infarction (i.e., heart attack) is the necrosis of heart muscle secondary to prolonged ischemia. In acute myocardial infarction, the infarct is diffusely hemorrhagic. The mechanism of death was hemopericardium. The damage in the myocardium includes apoptosis (cell death) and inflammatory changes. In addition to the direct effects of ischemia and tissue hypoxia, decreased removal of noxious metabolites, including potassium, calcium, amphophilic lipids, and oxygen-centered free radicals, also impair ventricular performance. These abnormalities promote potentially lethal arrhythmias. Epicardial inflammation may initiate pericarditis, i.e., a swelling and irritation of the thin sac-like membrane surrounding the heart (pericardium). Commonly, expansion of infarcted myocardium and resultant ventricular dilatation (i.e., ventricular remodeling) ensues within a few hours after the onset of a myocardial infarction.

Hence, in some embodiments, an effective amount of caffeic acid derivatives is administered to reduce, decrease, limit or inhibit one or more of the above-mentioned symptoms or complications of myocardial infarction.

In some embodiments, an effective amount of caffeic acid derivatives is administered to reduce the size of infarct.

Another embodiment provides administering an effective amount of caffeic acid derivatives to a subject to improve the viability of cardiomyocytes and/or reduce the apoptosis of cardiomyocytes.

Yet another embodiment provides administering an effective amount of caffeic acid derivatives to a subject to attenuate the infiltration of polymorphonuclear leukocytes and the damage of cardiac tissues after ischemia reperfusion injury.

Yet another embodiment provides administering an effective amount of caffeic acid derivatives to a subject to decrease lipid peroxidation and/or to increase the activities of antioxidant enzymes (e.g., CAT and SOD) in myocardial infarction.

Yet another embodiment provides administering an effective amount of caffeic acid derivatives to a subject to attenuate the chemotaxis and phagocytosis of macrophages in response to LPS treatment.

b. Other diseases and conditions

Macrophage-mediated inflammatory disorders include sepsis-related multiple organ dysfunction/failure, microbial infection, acute brain/lung/hepatic/renal injuries, neurodegenerative disorders, tumorigenesis, osteoporosis/osteonecrosis, cardiovascular and metabolic diseases, and autoimmune diseases.

Hence, in some embodiments, an effective amount of caffeic acid derivatives is administered to reduce, decrease, limit or inhibit one or more symptoms or complications of one or more of the above-mentioned disorders.

C. Further methods of using caffeic acid derivatives

a. Effective Amounts

As used herein the term “effective amount” or “therapeutically effective amount” means a dosage sufficient to treat, inhibit, or alleviate one or more symptoms of the disorder being treated or to otherwise provide a desired pharmacologic and/or physiologic effect. The amount of one or more caffeic acid derivatives administered to a subject is typically enough to prevent, reduce, decrease, or inhibit the symptoms of myocardial infarction or other macrophage-mediated inflammatory disorders.

b. Controls

The effect of one or more caffeic acid derivatives can be compared to a control. For example, in some embodiments, one or more of the pharmacological or physiological markers or pathways affected by treatment with one or more caffeic acid derivatives is compared to the same pharmacological or physiological marker or pathway in untreated control subjects or in subjects before treatment. In preferred embodiments the subject suffers the same disease or conditions as the treated subject.

Alternatively, subjects treated with one or more caffeic acid derivatives, or an analog or prodrug thereof, can be compared to subjects treated with pharmaceutical agents known to prevent, reduce or decrease the symptoms of myocardial infarction or other macrophage-mediated inflammatory disorders. The cells or subjects treated with

caffeic acid derivatives can have a greater increase in the viability of cardiomyocytes, a greater reduction in the infarct size, a greater attenuation of the infiltration of polymorphonuclear leukocytes, a greater reduction in lipid peroxidation, a greater increase in the activities of antioxidant enzymes, a greater attenuation of the chemotaxis and phagocytosis of macrophages, or a combination thereof.

One or more caffeic acid derivatives, or an analog or prodrug, or a pharmacologically active salt thereof can be administered enterally or parenterally. One or more LTPs, or a derivative, analog or prodrug, or a pharmacologically active salt thereof can be part of a pharmaceutical composition that includes a pharmaceutically acceptable carrier.

c. Therapeutic Administration

Pharmaceutical compositions including one or more caffeic acid derivatives, analog or prodrug, or a pharmacologically active salt thereof, may be administered in a number of ways depending on whether local or systemic treatment is desired, and depending on the area to be treated. For all of the disclosed compounds, as further studies are conducted, information will emerge regarding appropriate dosage levels for treatment of various conditions in various patients, and the ordinary skilled worker, considering the therapeutic context, age, and general health of the recipient, will be able to ascertain proper dosing. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment desired. Generally dosage levels of 0.01 to 100 mg/kg of body weight are administered to mammals in the treatment of myocardial infarction (e.g. within minutes to hours of the occurrence of ischemia, preferably within an hour, more preferably within 10 minutes) or daily in the prevention of myocardial infarction.

In some embodiments the disclosed methods and compositions are administered to a subject for prophylactic treatment of a condition, disease or disorder. Methods for the treatment of a disease, disorder or condition in a subject wherein the subject has not been diagnosed with a disease or who does not have symptoms of a disease are provided. In some embodiments the subject has one or more risk factors associated with the development of myocardial infarction, e.g., high blood pressure, obesity, smoking, high blood cholesterol levels, diabetes, or a combination thereof.

The caffeic acid derivatives and pharmaceutical compositions described herein can be administered to the subject in a number of ways depending on whether local or

systemic treatment is desired, and on the area to be treated. Thus, for example, a compound or pharmaceutical composition can be administered to a subject vaginally, rectally, intranasally, orally, by inhalation, or parenterally, for example, by intradermal, subcutaneous, intramuscular, intraperitoneal, intrarectal, intraarterial, intralymphatic, intravenous, intrathecal and intratracheal routes. Parenteral administration, if used, is generally characterized by injection.

Examples

10 Example 1. Synthesis and chemical characterization of DHPPA.

Materials and Methods

Synthesis and purification of DHPPA

Mixtures of caffeic acid (100 mg), propylamine (1.2 equiv) and triethylamine (Et₃N, 0.08 mL) were dissolved in 1 mL dichloromethane (DCM). While stirring on ice, a solution of benzotriazol-1-yloxytris (dimethylamino)phosphonium hexafluorophosphate (BOP) (1.2 equiv) in 5 mL DCM was subsequently added into caffeic acid solution. The reaction mixture was stirred at 0 °C for 30 min and at room temperature overnight. At the end of reaction, the solvent was removed by rotary evaporator under vacuum. The residues were extracted five times with ethyl acetate (EtOAc). The organic phase was sequentially washed with 3 M HCl aqueous solution, and 10% NaHCO₃ in water. The product DHPPA was purified by column chromatography on silica gel with chloroform and methanol (PE : EtOAc = 1 : 1.5).

Characterization of DHPPA

DHPPA was further characterized by mass spectroscopy (MS) and nuclear magnetic resonance (NMR) spectroscopy. MS analysis was performed on an ABI/ Sciex triple quadrupole 3200 QTRAP mass spectrometer (Framingham, MA, USA) equipped with an TurboV Source operating in positive ionization mode under the control of Analyst v1.4.2 data system (Applied Biosystems/MDS Sciex, Concord, ON, Canada). ESI-MS (m/z): 222.1 [M+H]⁺. HRMS for C₁₂H₁₅NO₃: calculated, 222.1125 [M + H]⁺; experimental, 222.1127 [M + H]⁺. NMR spectra were recorded in DMSO-d₆ on a Varian Unity plus NMR 600 MHz spectrometer (Varian Inc., Palo Alto, CA, USA). ¹H NMR (DMSO-d₆, 600 MHz): 9.22 (s, 2-OH), 7.95 (t, J=5.6 Hz, 1-NH), 7.22 (d, J=15.7 Hz, 1H), 6.94 (d, J=1.9 Hz, 1H), 6.83 (dd, J=8.2, 1.9 Hz, 1H), 6.74 (d, J=8.2 Hz, 1H), 6.33

(d, $J=15.7$ Hz, 1H), 3.11(m, 2H), 1.46 (m, 2H), 0.87 (t, $J=7.4$, 3H); and ^{13}C NMR (DMSO- d_6 , 150 MHz): 165.8, 147.7, 146.0, 139.3, 126.9, 120.7, 119.2, 116.2, 114.3, 40.9, 22.9, 11.9.

Results

5 The reaction starting with 100 mg caffeic acid yielded a yellow powder of 86 mg (70% yield) after purification by column chromatography.

MS and NMR further confirmed the identity and purity of DHPPA.

Example 2. DHPPA rescued cardiomyocytes by enhancing their survival after oxygen glucose deprivation.

Materials and Methods

Induction of oxygen glucose deprivation (OGD) and treatment with drugs

Rat cardiomyocyte H9c2 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 2 mM glutamine, antibiotics (100 U/ml of penicillin A and 100 U/ml of streptomycin), and 10% heat-inactivated fetal bovine serum (Gibco/BRL, Gaithersburg, MD, USA) and maintained in a 37°C humidified incubator containing 5% CO_2 . For drug treatment, H9c2 cells were seeded at the density of 1.0×10^5 in 96-well plate overnight and exposed to oxygen glucose deprivation (OGD) condition for 10 hours. The cells were subsequently treated with DHPPA, caffeic acid phenethyl ester (CAPE) and CPE at 10 μM under normoxia condition for another 14 hours. Alternatively, the cells were treated with DHPPA at various concentrations including 10, 20, 50, and 100 μM .

Cell viability assay

The cell viability was evaluated by a colorimetric tetrazolium (MTT) assay. Briefly, MTT (final concentration of 0.5 mg/mL) was added to cell culture in a 96-well plate. After 4 h incubation at 37 °C, the supernatant was removed. The formazan products in viable cells were solubilized in 150 μL of DMSO and quantified by measuring the absorbance at 570 nm on a Bio-Rad microplate reader (Hercules, CA, USA).

Results

30 Figure 1A shows treating cardiomyocytes with DHPPA and other caffeic acid derivatives significantly enhanced the survival of the cardiomyocytes after OGD condition compared to that without drug treatment.

Figure 1B shows that DHPPA at concentrations ranging from 10 μ M to 100 μ M significantly increased the viability of cardiomyocytes after OGD condition compared to that of the ones without drug treatment after OGD.

5 **Example 3. DHPPA reduced infarct size in mice after myocardial infarction.**

Materials and Methods

Myocardial infarction was induced by ligating the left anterior descending coronary artery (LAD) in male C57BL/6J mice as previously described (Xu ZB, et al., *Jove-J Vis Exp.*, 86 (2014)). In brief, following thoracotomy between the 3rd and 4th intercostal space, a surgery was performed to expose the heart. A 6-0 silk suture was used to ligate the left main coronary artery to induce ischemia and the sutured ligation remained for 30 min. At 10 min after the beginning of ligation, DHPPA was administered via i.p. injection, whereas equal volume of vehicle was injected to the animals in Sham and Model groups. After 30 min ischemia, the suture was removed to allow reperfusion for 24 h. At the end of ischemia reperfusion, the hearts were recovered. Mice were randomly divided into the following four groups: (1) Sham, receiving sham surgery and vehicle (i.p.); (2) Model, ischemia induction, receiving vehicle (50% propanediol + 50% saline) at 10 min after ischemia induction, and reperfusion (i.p.); (3) DHPPA (5 mg/kg); ischemia reperfusion and receiving 5 mg DHPPA /kg of mice at 10 min after ischemia induction; (4) DHPPA (20 mg/kg); ischemia reperfusion and receiving 20 mg DHPPA /kg of mice at 10 min after ischemia induction. At the end of ischemia reperfusion, mice were first anesthetized by i.p. injection of a mixture of midazolam (5 mg/kg), fentanyl (0.5 mg/kg) and medetomidine (0.05 mg/kg) and subsequently ventilated under a mouse volume-control ventilator. Five slices of the myocardium were staining in 0.5% triphenyltetrazolium chloride (TTC) for 15 min, the TTC-free areas indicated infarct size. On the other hand, the heart tissues from each experimental group were fixed in 4% formalin and embedded in paraffin. The embedded tissues were cut into 4 μ m sections and stained with hematoxylin and eosin stain (H&E).

Results

30 Acute myocardial infarction was induced following the procedures described above. The myocardia of mice in different groups were analyzed for their macroscopic infarct size, and treatment with DHPPA effectively reduced infarct size compared to treatment with vehicle after ischemia induction. Microscopic histology of myocardia of

mice in different groups showed the acute ischemia model led to un-smooth myocardium with “cracks” and unstained “holes” in mice, indicating infarction, whereas mice having undergone sham surgery had smooth and tight myocardium. Treatment with 5 or 20 mg DHPPA/kg of mice reduced the “cracks” and “holes” in myocardium .

5

Example 4. *In vivo* effect of DHPPA on the cardiac biomarkers and oxidative stress enzymes following acute myocardial infarction.

Materials and Methods

Following the myocardial infarction procedure, the blood samples were collected
10 in heparinized tubes at the end of reperfusion to assay the activities of lactate dehydrogenase (LDH), creatine kinase (CK) and myocardial muscle creatine kinase (CK-MB). After 10 min centrifugation at 5700 rpm, plasma was used to measure the levels of LDH and CK using commercial LDH and CK detection Kits (Nanjing Jiancheng Bioengineering Institute, China). The plasma level of CK-MB was determined with a
15 commercial ELISA kit from USCN Life Science Inc (Wuhan, China).

The heart tissues from each experimental group were homogenized in 0.9% NaCl saline buffer to measure superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA) and myeloperoxidase (MPO). After centrifugation, the supernatants were
20 collected for the measurement of the SOD, CAT, MDA and MPO activities with commercial assay kits (Nanjing Jiancheng Bioengineering Institute) according to the manufacturer’s instructions. The activities of SOD and CAT were expressed as U/mg proteins. The MDA level was represented in nmol/mg proteins. MPO activity was expressed as U/mg wet tissues.

Results

25]

Figure 2A shows while the acute myocardium infarction led to significantly increased LDH activity in mouse blood compared to sham surgical procedure, DHPPA administered at 5 or 10 mg/kg in between ischemia and reperfusion (I/R) significantly reduced the activity of LDH compared to that resulting from the infarction. Similarly
30 while the acute myocardium infarction led to significantly increased CK activity in blood compared to sham surgical procedure, DHPPA administered at 10 mg/kg significantly reduced its activity compared to that resulting from the infarction (Figure 2B). Figure 2C shows similar trend in the assay of CK-MB as that of LDH.

Figures 2D and 2E show while the acute myocardium infarction led to significantly reduced CAT and SOD activities, respectively, in the heart tissues compared to sham surgical procedure, DHPPA administered at 5 or 10 mg/kg in I/R significantly increased their activities compared to that resulting from the infarction.

5 Figures 2F and 2G show while the acute myocardium infarction led to significantly increased MPO and MDA activities, respectively, in the heart tissues compared to sham surgical procedure, DHPPA administered at 5 or 10 mg/kg in I/R significantly reduced their activities compared to that resulting from the infarction.

10 **Example 5. *In vitro* effect of DHPPA on the chemotaxis and phagocytosis capability of macrophages.**

Materials and Methods

Preparation of conditioned media and Transwell migration assay

15 Mouse macrophage RAW264.7 cells were treated with 1 µg/ml lipopolysaccharide (LPS) and 10 µM DHPPA or related caffeic acid derivatives added to the medium, alone or in combination. After 24 h of the treatment, the cell culture media were recovered as conditioned media.

In the Transwell migration assay, the conditioned medium was placed in the lower chamber of Transwell plate, whereas fresh and untreated macrophages were placed
20 in the upper chamber of Transwell plate containing regular cell culture medium. RAW264.7 cells were allowed to migrate through the membrane over 4 h. At the end of migration, RAW264.7 cells inside the upper chamber were removed. The cells which migrated through the membrane were fixed with methanol for 20 min, and subsequently stained with 0.1% crystal violet for 15 min. After the removal of excessive dye, the
25 membranes were carefully placed onto the glass slide, and imaged under a microscopy (Carl-Zeiss, Jena, Germany). After imaging, the membranes were washed with 30% glacial acetic acid for the quantification of macrophage migration on a Bio-Rad microplate reader (Hercules, CA, USA) at the wavelength of 570 nm.

Phagocytosis of latex beads by macrophages

30 FluoSpheres[®] fluorescent carboxylated beads (1.0 µm) (Invitrogen, Carlsbad, CA, USA) were used for the phagocytosis by macrophages. RAW 264.7 cells (0.1×10^6 /ml) were seeded in 6-well plate and treated with control, LPS (1 µg/ml), compounds only (10 µM), or the combination of LPS and compounds (10 µM) for 24 h. Cells were incubated with 9×10^6

FluoSpheres[®] fluorescent carboxylated beads for additional 90 min at 37°C. The cells were washed 5 times with cold phosphate buffered saline (PBS) and finally suspended in PBS containing 5% FBS. Macrophages were detached from the wells using 4 mM EDTA in PBS. The phagocytic activity was determined by fluorescent imaging under a fluorescence microscope.

Phagocytosis of apoptotic cardiomyoblasts by macrophages

Macrophage RAW 264.7 cells were treated with control, LPS (1 µg/ml), or the combination of LPS and different compounds (10 µM) for 24h. Macrophages were labeled with Cell Tracker Orange dye for 30 min.

Cardiomyocyte H9C2 cells were challenged with OGD to induce apoptosis, and subsequently labeled with Cell Tracker Green CMFDA dye for 30 min. After washed for 5 times with PBS, apoptotic H9C2 cells were centrifuged and re-suspended in cell culture medium.

To allow phagocytosis, RAW264.7 cells were incubated with apoptotic H9C2 cells at the ratios of 5:1 or 10:1 for 90 min. After washing for 5 times with PBS, the cells were centrifuged, re-suspended in PBS, and imaged under a fluorescence microscope.

Results

Figure 3A shows the chemotaxis of macrophages towards conditioned media prepared with the combination of LPS and any one of the caffeic acid derivatives including DHPPA was significantly decreased compared to that towards conditioned media prepared with LPS and no caffeic acid derivative.

Without the stimulation of LPS, macrophages treated with DHPPA and those treated with PACA had a significant increase in the phagocytosed bead-to-cell ratios compared to those treated with vehicle only (Figure 3B, bars in the lighter color, on the left-hand side of every group). With the stimulation of LPS, macrophages treated with either DHPPA, PACA, PCE, or CA significantly increased the phagocytosis of beads compared to those treated with vehicle only (Figure 3B, bars in the denser color, on the right-hand side of every group).

Figure 3C shows that in the presence of LPS stimulation, macrophages treated with either DHPPA, PACA, or PCE had a significant increase in the phagocytosis of beads compared to those treated with vehicle only, whereas in the absence of LPS stimulation macrophages treated with DHPPA, PACA and PCE had a significant increase in the phagocytosis of beads compared to those treated with vehicle only.

Example 6. Effects of DHPPA on turning M1 macrophages into M2 macrophages.**Materials and Methods**

Macrophage RAW264.7 cells were treated with caffeic acid derivatives for 2 h prior to the stimulation of 1 µg/mL LPS for another 24 h. The total RNAs were isolated with Trizol reagent following the manufacture's instruction (Invitrogen, CA, USA) and converted into corresponding cDNAs using SuperScript III reverse transcriptase and oligo primers (Thermo, Waltham, MA, USA) as described in Cheng YY, et al., *Oxidative Medicine and Cellular Longevity* (2015). The primers for macrophage biomarkers were listed as follows:

iNOS, forward, 5'- AAAGTGACCTGAAAGAGGAAAAGGA (SEQ ID NO:1), and reverse, 5'- TTGGTGACTCTTAGGGTCATCTTGTA (SEQ ID NO:2);

Arginase I, forward, 5'- CTCCAAGCCAAAGTCCTTAGAG (SEQ ID NO:3), and reverse, 5'- AGGAGCTGTCATTAGGGACATC (SEQ ID NO:4);

Ym-1, forward, 5'- CATGAGCAAGACTTGCGTGAC (SEQ ID NO:5), and reverse, 5'- GGTCCAAACTTCCATCCTCCA (SEQ ID NO:6);

TNF-α, forward, 5'- ATGAGCACAGAAAGCATG (SEQ ID NO:7), and reverse, 5'- AGACAGAAGAGCGTGGTGGC (SEQ ID NO:8);

CXCL10, forward, 5'- TCTGAGTGGGACTCAAGGGAT (SEQ ID NO:9), and reverse, 5'- TCGTGGCAATGATCTCAACACG (SEQ ID NO:10);

β-actin, forward, 5'- ATGGATGACGATATCGCTGC (SEQ ID NO:11), and reverse, 5'- TTCTGACCCATTCCCACCATC (SEQ ID NO:12).

PCR amplifications were performed as follows: after an initial denaturation at 94°C for 3 min, 30 cycles of 94°C for 30 sec, 60°C for 30 sec, and 72°C for 1 min, extension at 72°C for 10 min. PCR products were analyzed by gel electrophoresis in 2% agarose containing GelRed Nucleic acid (Biotium, Hayward, CA, USA) and visualized under UV light.

Results

Figure 6 shows DHPPA and related caffeic acid derivatives suppressed the expression of M1 biomarkers and increased the expression of M2 biomarkers.

Specifically, LPS stimulation was used to induce M1 activation of macrophages. With DHPPA pre-treatment prior to LPS stimulation, macrophages had a 0.60-fold reduction in the intensity of the TNF-α band, normalized to that of the β-actin band,

compared to macrophages directly subjected to LPS stimulation without any pre-treatment with caffeic acid derivatives. Similarly, PCE, PACA, CAPE, and CA pre-treatments to the macrophages prior to LPS stimulation led to 0.47-, 0.78-, 0.58-, and 0.52-fold reduction, respectively, in expression of TNF- α , compared to direct LPS stimulation of macrophages. With DHPPA pre-treatment prior to LPS stimulation, macrophages had a 0.12-fold reduction in the intensity of the CXCL10 band, normalized to that of the β -actin band, compared to macrophages directly subjected to LPS stimulation without any pre-treatment with caffeic acid derivatives. Similarly, PCE, PACA, CAPE, and CA pre-treatments to the macrophages prior to LPS stimulation led to 0.25-, 0.47-, 0, and 0-fold reduction, respectively, in expression of CXCL10, compared to direct LPS stimulation of macrophages. With DHPPA pre-treatment prior to LPS stimulation, macrophages had a 0.2-fold reduction in the intensity of the iNOS band, normalized to that of the β -actin band, compared to macrophages directly subjected to LPS stimulation without any pre-treatment with caffeic acid derivatives. Similarly, PCE, PACA, CAPE, and CA pre-treatments to the macrophages prior to LPS stimulation led to 0.03-, 0.21-, 0.55, and 0-fold reduction, respectively, in expression of iNOS compared to direct LPS stimulation of macrophages.

In contrast, pretreating macrophages with these caffeic acid derivatives (DHPPA, PCE, PACA, CAPE and CA) prior to LPS stimulation led to a 2.12-, 1.74-, 2.37-, 2.11-, and 1.53-fold increase in the expression of Ym-1 (M2 marker) and 1.61-, 2.04-, 1.70-, 1.14- and 0-fold increase in Arginase-1 (M2 marker).

Example 7. *In vitro* stability and *in vivo* pharmacokinetics of DHPPA.

Materials and Methods

***In vitro* stability assay**

The method of collecting plasma as described in Yang J, et al., *Biomed Chromatogr.*, 26(5):594-598 (2012) was followed and plasma of male *Sprague Dawley* (SD) rats (body weight 250 ± 20 g) were collected. 10 μ L of DHPPA (2 mg/mL) was incubated with rat plasma (180 μ L) at 25, 37 and 60°C for different times. After adding 10 μ L of resveratrol solution (400 μ g/mL), samples were immediately extracted with 600 μ L of ethyl acetate. The solvent was removed by passing a stream of nitrogen at 25 °C. The sample was reconstituted in 200 μ L of MeOH. The methanolic solution (5 μ L) was analyzed through a C₁₈ reverse phase UPLC column (5 μ , 4.6 $\times$ 150 mm). The separation and detection were operated on a Thermo (Thermo Scientific, USA) DIONEX series LC

system equipped with a ultimate 3000 RS pump, 3000 RS auto-sampler, 3000 RS column compartment along with an 3000 RS diode array DAD detector. The flow rate was set at 0.4 mL/min. Detection wavelength was set to UV 320 nm. The concentration of intact DHPPA was determined at minimal five time points for each temperature.

- 5 Three replicates were analyzed at each time point. The stability of DHPPA was correlated with the half-life of DHPPA at each respective temperature and the energy of activation (E_a) was also calculated.

In vivo pharmacokinetic assay

- Male SD rats (body weight 250 ± 20 g) were obtained from Laboratory Animal Unit, University of Hong Kong. Animals were housed in a well-controlled environmental conditions (*relative humidity*, 40%–60%; *temperature*, 23°–26°C), and with access to food and water. All animals were acclimated in the laboratory for seven days prior to the experiment and fasted but allowed the access to water for 12 h before experiments.

- A solution of DHPPA (15 mg/kg) in 80% sterile saline and 20% ethanol was administrated intravenously (0.8 mL) over a period of 20 seconds via femoral vein. Blood samples (0.3 mL) were collected in 1.5 mL tube before injection as well as at 5, 15, and 30 min, and 1, 2, 4, 6 and 8 h for analysis of DHPPA. After immediate centrifugation at 5700 rpm for 10 min, the plasma was recovered and stored at -80°C until analysis. To prepare samples for analysis, plasma sample (100 μL) was mixed with 200 ng of resveratrol as internal standard (IS) in 200 μL acetonitrile. The samples were vortexed for 5 min and then centrifuged at 13000 rpm for 10 min. The supernatants were evaporated and reconstitution with 100 μL of MeOH.

- The methanolic solution (20 μL) was analyzed on a Synergi hydro-RP C18 column (150 mm $\times$ 4.6 mm, 4 μm) at the flow rate of 0.8 mL/min. The separation was operated under the control of an Agilent HPLC system equipped with a 1525 Separations Module and a 2998 DAD Unit. Mobile phase compositions were (A) water with 0.4% (v/v) formic acid and (B) acetonitrile. Gradient was set as follows: 0-2 min, 80% A; 2-5 min, 80-50% A; 5-7 min, 50-80% A; 7-8 min, 80% A. The elution was analyzed on an ABI/Sciex triple quadrupole mass spectrometer 3200 QTRAP system (Framingham, MA, USA) equipped with an ESI-Turbo V source operating in positive ionization mode under the control of Analyst v1.4.2 data system (Applied Biosystems/MDS Sciex, Concord, ON, Canada). Mass spectrometry was operated under the conditions as follows: drying gas N_2 , 10 L/min; capillary voltage, 20 V; pressure of nebulizer, 30 psi; ion spray voltage,

5.5 kV; and capillary temperature, 325 °C. Multiple reaction monitoring (MRM) parameters were optimized for analysis of DHPPA and IS, respectively. Analyst 1.5.1 software (AB Sciex, Foster, CA, USA) was used for the control of equipment, data acquisition and analysis.

5 **Results**

Figures 5A and 5B show the stability and relatively long half-time of DHPPA in plasma.

10 It is understood that the disclosed method and compositions are not limited to the particular methodology, protocols, and reagents described as these may vary. 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 limit the scope of the present invention which will be limited only by the appended claims.

15 It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a caffeic acid derivative" includes a plurality of molecules of such caffeic acid derivative, reference to "the caffeic acid derivative" is a reference to one or more caffeic acid derivatives and equivalents thereof known to those skilled in the art, and so forth.

20 Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

25 "Optional" or "optionally" means that the subsequently described event, circumstance, or material may or may not occur or be present, and that the description includes instances where the event, circumstance, or material occurs or is present and instances where it does not occur or is not present.

30 Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, also specifically contemplated and considered disclosed is the range from the one particular value and/or to the other particular value unless the context specifically indicates otherwise. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another, specifically contemplated

embodiment that should be considered disclosed unless the context specifically indicates otherwise. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint unless the context specifically indicates otherwise. Finally, it should be understood that all of the individual values and sub-ranges of values contained within an explicitly disclosed range are also specifically contemplated and should be considered disclosed unless the context specifically indicates otherwise. The foregoing applies regardless of whether in particular cases some or all of these embodiments are explicitly disclosed.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed method and compositions belong. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present method and compositions, the particularly useful methods, devices, and materials are as described. Publications cited herein and the material for which they are cited are hereby specifically incorporated by reference. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such disclosure by virtue of prior invention. No admission is made that any reference constitutes prior art. The discussion of references states what their authors assert, and applicants reserve the right to challenge the accuracy and pertinency of the cited documents. It will be clearly understood that, although a number of publications are referred to herein, such reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

Although the description of materials, compositions, components, steps, techniques, etc. may include numerous options and alternatives, this should not be construed as, and is not an admission that, such options and alternatives are equivalent to each other or, in particular, are obvious alternatives. Thus, for example, a list of different caffeic acid derivatives does not indicate that the listed caffeic acid derivatives are obvious one to the other, nor is it an admission of equivalence or obviousness.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the method and compositions described herein. Such equivalents are intended to be encompassed by the following claims.

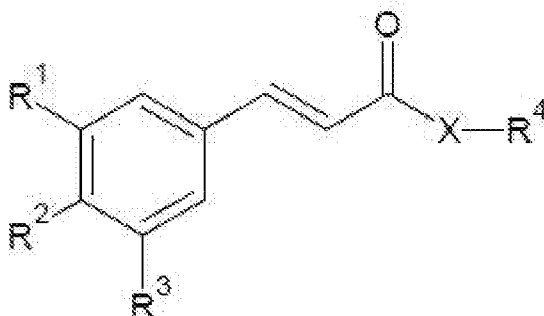
CLAIMS

We claim:

1. A method for treating a subject having a condition having greater M1 macrophage polarization than M2 macrophage polarization, comprising administering to the subject in need thereof a composition comprising

an effective amount of a caffeic acid derivative in any of its stereoisomeric and tautomeric forms, and mixtures thereof in all ratios, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable solvate thereof, a pharmaceutically acceptable polymorph thereof, or a prodrug thereof,

wherein the caffeic acid derivative has the structure of Formula 3



Formula 3

and a pharmaceutically acceptable excipient;

wherein

the caffeic acid derivative is effective to alter the polarization of macrophages from M1 macrophages to M2 macrophages and thereby reduce the effects of M1 macrophages;

R^1 , R^2 , and R^3 are, independently, hydroxyl, hydrogen, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl;

X is O, S, or NR^a , wherein R^a is H or substituted or unsubstituted C_1 - C_{10} , alkyl, alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl; and

R^4 is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C_3 - C_{20} cyclic, heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted phenyl, substituted aryl, substituted

heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, hydrogen, or, if R^a forms two bonds with the N, absent;

wherein at least one of R¹, R², and R³ is hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

2. The method of claim 1, wherein the condition is or results in reduced or absent blood flow to one or more tissues of the subject.

3. The method of claim 2, wherein the composition is administered during or following reduced or absent blood flow to one or more tissues of the subject.

4. The method of claim 3, wherein the composition is administered following diagnosis of current or prior reduced or absent blood flow to one or more tissues of the subject.

5. The method of any one of claims 1-4, wherein the condition is myocardial infarction, wherein the tissue is myocardial tissue, and wherein the reduced effects of M1 macrophages is reduced infarct inflammation.

6. The method of claim 5, wherein the composition is administered within four hours of symptoms of myocardial infarction appearing or being diagnosed in the subject.

7. The method of claim 3, wherein the reduced or absent blood flow to one or more tissues results in infarction, wherein the infarction in the subject has a reduced size relative to an untreated control infarction.

8. The method of claim 6 or 7, wherein the caffeic acid derivative is effective to enhance the survival of cardiomyocytes against oxygen glucose deprivation and reduce the infarct size against ischemia reperfusion injury.

9. The method of any one of claims 1-8, wherein the caffeic acid derivative is effective to attenuate the infiltration of polymorphonuclear leukocytes and damage of the tissues after ischemia reperfusion injury.

10. The method of any one of claims 1-9, wherein the caffeic acid derivative is effective to decrease lipid peroxidation and increases the activities of antioxidant enzymes in the tissues.

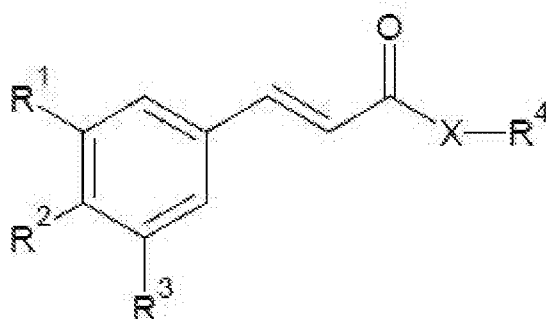
11. The method of claim 10, wherein the antioxidant enzymes are selected from catalase (CAT), superoxide dismutase (SOD), myeloperoxidase (MPO), malonaldehyde (MDA), or a combination thereof.

12. The method of any one of claims 1-11, wherein the caffeic acid derivative is effective to enhance the survival of cells of the tissues against oxygen glucose deprivation and reduce the infarct size against ischemia reperfusion injury.

13. A method for attenuating the chemotaxis and phagocytosis of macrophages in a subject reacting to an inflammatory insult, comprising administering to the subject in need thereof a composition comprising

an effective amount of a caffeic acid derivative in any of its stereoisomeric and tautomeric forms, and mixtures thereof in all ratios, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable solvate thereof, a pharmaceutically acceptable polymorph thereof, or a prodrug thereof,

wherein the caffeic acid derivative has the structure of Formula 3



Formula 3

and a pharmaceutically acceptable excipient;
wherein

the caffeic acid derivative is effective to attenuate the chemotaxis and phagocytosis of macrophages in the subject;

R^1 , R^2 , and R^3 are, independently, hydroxyl, hydrogen, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl;

X is O, S, or NR^a , wherein R^a is H or substituted or unsubstituted C_1 - C_{10} , alkyl, alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl; and

R^4 is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C_3 - C_{20} cyclic, heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C_3 - C_{20} cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, hydrogen, or, if R^a forms two bonds with the N, absent;

wherein at least one of R^1 , R^2 , and R^3 is hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl.

14. The method of any one of claims 1-13, wherein at least two of R^1 , R^2 , and R^3 are, independently, hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino, C_1 - C_{10} alkylthio, C_1 - C_{10} carbonyl, C_1 - C_{10} carboxyl, C_1 - C_{10} amido, C_1 - C_{10} sulfonyl, C_1 - C_{10} sulfonic acid, C_1 - C_{10} sulfamoyl, C_1 - C_{10} sulfoxide, C_1 - C_{10} phosphoryl, or C_1 - C_{10} phosphonyl.

15. The method of any one of claims 1-14, wherein at least two adjacent R^1 , R^2 , and R^3 are, independently, hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkylamino,

C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

16. The method of any one of claims 1-15, wherein R¹, R², and R³ are, independently, hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

17. The method of any one of claims 1-15, wherein R² is hydrogen and R¹ and R³ are, independently, hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

18. The method of any one of claims 1-13, wherein two of R¹, R², and R³ are hydrogen and one of R¹, R², and R³ is hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

19. The method of any one of 1-17, wherein R¹ and R² are hydroxyl; wherein R³ is hydrogen; wherein X is O; and

wherein R⁴ is:

alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C₃-C₂₀ cyclic, heterocyclic, or C₅-C₇ or C₉-C₃₀ alkyl; or

phenyl substituted with hydroxyl, amino, thiol, oxo, phosphate, C₃-C₁₀ alkyl, substituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl; or

substituted naphthyl, substituted thienyl, substituted indolyl, substituted biphenyl, substituted azulenyl, substituted anthracenyl, substituted phenanthrenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio,

substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, or polypeptide group;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

20. The method of any one of claims 1-17, wherein R¹ and R² are hydroxyl; wherein R³ is hydrogen; wherein X is NH; and

wherein R⁴ is:

alkyl, alkenyl, ethynyl, 1-propynyl, C₄-C₃₀ alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C₃-C₂₀ cyclic, or heterocyclic; or

alkynyl substituted with hydroxyl, amino, thiol, oxo, phosphate, C₂-C₁₀ alkyl, substituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl; or

phenyl substituted with hydroxyl, amino, thiol, oxo, phosphate, methyl, C₃-C₁₀ alkyl, substituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl; or

substituted naphthyl, substituted thienyl, substituted indolyl, substituted biphenyl, substituted azulenyl, substituted anthracenyl, substituted phenathrenyl, substituted alkyl, substituted alkenyl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, or hydrogen;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-

C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

21. The method of any one of claims 1-17, wherein R¹ and R² are hydroxyl; wherein R³ is hydrogen; wherein X is S or NR^a, wherein R^a is substituted or unsubstituted C₁-C₁₀ alkyl, alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl, wherein R^a, if present, has only one bond with the N; and

wherein R⁴ is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C₃-C₂₀ cyclic, heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, or hydrogen;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

22. The method of any one of claims 1-17, wherein R¹ and R² are hydroxyl; wherein R³ is hydrogen; wherein X is S or NR^a, wherein R^a is substituted C₁-C₁₀ alkyl, unsubstituted C₃, C₄, or C₆-C₁₀ alkyl, or substituted or unsubstituted C₁-C₁₀ alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl, wherein R^a, if present, has two bonds with the N; and

wherein R⁴ is absent;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

23. The method of any one of claims 1-17, wherein R¹ and R² are hydroxyl; wherein R³ is hydrogen; wherein X is S or NR^a, wherein R^a is substituted or unsubstituted C₁-C₁₀ alkyl,

alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl, with the proviso that NR^a , if present, is not 1-pyrrolidinyl; and

wherein R^4 is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, $\text{C}_3\text{-C}_{20}$ cyclic, heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted $\text{C}_3\text{-C}_{20}$ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, hydrogen, or, if R^a forms two bonds with the N, absent;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkylene, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{10}$ alkynyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_1\text{-C}_{10}$ alkylamino, $\text{C}_1\text{-C}_{10}$ alkylthio, $\text{C}_1\text{-C}_{10}$ carbonyl, $\text{C}_1\text{-C}_{10}$ carboxyl, $\text{C}_1\text{-C}_{10}$ amido, $\text{C}_1\text{-C}_{10}$ sulfonyl, $\text{C}_1\text{-C}_{10}$ sulfonic acid, $\text{C}_1\text{-C}_{10}$ sulfamoyl, $\text{C}_1\text{-C}_{10}$ sulfoxide, $\text{C}_1\text{-C}_{10}$ phosphoryl, or $\text{C}_1\text{-C}_{10}$ phosphonyl.

24. The method of any one of claims 1-17, wherein R^1 and R^2 are methoxy; wherein R^3 is hydrogen; wherein X is O, S, or NR^a , wherein R^a is H or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl; and

R^4 is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, $\text{C}_3\text{-C}_{20}$ cyclic, or heterocyclic; or

phenyl substituted with hydroxyl, amino, thiol, oxo, phosphate, methyl, $\text{C}_3\text{-C}_{10}$ alkyl, substituted $\text{C}_1\text{-C}_{10}$ alkyl, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkylene, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{10}$ alkynyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_1\text{-C}_{10}$ alkylamino, $\text{C}_1\text{-C}_{10}$ alkylthio, $\text{C}_1\text{-C}_{10}$ carbonyl, $\text{C}_1\text{-C}_{10}$ carboxyl, $\text{C}_1\text{-C}_{10}$ amido, $\text{C}_1\text{-C}_{10}$ sulfonyl, $\text{C}_1\text{-C}_{10}$ sulfonic acid, $\text{C}_1\text{-C}_{10}$ sulfamoyl, $\text{C}_1\text{-C}_{10}$ sulfoxide, $\text{C}_1\text{-C}_{10}$ phosphoryl, or $\text{C}_1\text{-C}_{10}$ phosphonyl; or

substituted naphthyl, substituted thienyl, substituted indolyl, substituted biphenyl, substituted azulenyl, substituted anthracenyl, substituted phenanthrenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted $\text{C}_3\text{-C}_{20}$ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, or hydrogen;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

25. The method of any one of claims 1-13, wherein

R¹, R², and R³ are, independently, hydroxyl, hydrogen, amino, thiol, oxo, or substituted or unsubstituted C₁-C₃ alkyl, C₁-C₃ alkylene, C₂-C₃ alkenyl, C₂-C₃ alkynyl, C₁-C₃ alkoxy, C₁-C₃ alkylamino, C₁-C₃ alkylthio, C₁-C₃ carbonyl, C₁-C₃ carboxyl, C₁-C₃ amino, or C₁-C₃ amido;

X is NH or O;

R⁴ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, phenyl, aryl, heteroaryl, C₁-C₂₀ alkoxy, phenoxy, aroxy, arylthio, C₁-C₂₀ alkylthio, C₁-C₂₀ carbonyl, C₁-C₂₀ carboxyl, amino, C₁-C₂₀ amido, polyaryl, C₃-C₂₀ cyclic, heterocyclic, substituted C₁-C₂₀ alkyl, substituted C₂-C₂₀ alkenyl, substituted C₂-C₂₀ alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted C₁-C₂₀ alkoxy, substituted phenoxy, substituted aroxy, substituted C₁-C₂₀ alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted C₁-C₂₀ carbonyl, substituted C₁-C₂₀ carboxyl, substituted amino, substituted C₁-C₂₀ amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, or substituted heterocyclic;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

26. The method of any one of claims 1-13 and 25, wherein

R¹, R², and R³ are, independently, hydroxyl, hydrogen, amino, thiol, or unsubstituted C₁-C₃ alkyl, C₁-C₃ alkylene, C₂-C₃ alkenyl, C₂-C₃ alkynyl, C₁-C₃ alkoxy, C₁-C₃ alkylamino, C₁-C₃ alkylthio, C₁-C₃ carbonyl, C₁-C₃ amino, or C₁-C₃ amido;

X is NH or O;

R⁴ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ carbonyl, C₁-C₂₀ carboxyl, amino, C₁-C₂₀ amido, substituted C₁-C₂₀ alkyl, substituted C₂-C₂₀ alkenyl, substituted C₂-C₂₀ alkynyl, substituted C₁-C₂₀ alkoxy, substituted C₁-C₂₀ alkylthio, substituted C₁-C₂₀ carbonyl, substituted C₁-C₂₀ carboxyl, substituted amino, or substituted C₁-C₂₀ amido;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, or C₁-C₁₀ amido.

27. The method of any one of claims 1-13, 25, and 26, wherein

R¹, R², and R³ are, independently, hydroxyl, hydrogen, amino, thiol, or unsubstituted C₁-C₃ alkyl, C₁-C₃ alkylene, C₂-C₃ alkenyl, C₂-C₃ alkynyl, C₁-C₃ alkoxy, C₁-C₃ alkylamino, C₁-C₃ alkylthio, or C₁-C₃ amino;

X is NH or O;

R⁴ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ carbonyl, C₁-C₂₀ carboxyl, amino, C₁-C₂₀ amido, substituted C₁-C₂₀ alkyl, substituted C₂-C₂₀ alkenyl, substituted C₂-C₂₀ alkynyl, substituted C₁-C₂₀ alkoxy, substituted C₁-C₂₀ alkylthio, substituted C₁-C₂₀ carbonyl, substituted C₁-C₂₀ carboxyl, substituted amino, or substituted C₁-C₂₀ amido;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, or C₁-C₁₀ amido.

28. The method of any one of claims 1-13 and 25-27, wherein

R¹, R², and R³ are, independently, hydroxyl, hydrogen, or unsubstituted C₁-C₂ alkyl, C₁-C₂ alkylene, C₂ alkenyl, C₂ alkynyl, C₁-C₂ alkoxy, C₁-C₂ alkylamino, C₁-C₂ alkylthio, or C₁-C₂ amino;

X is NH or O;

R⁴ is C₃-C₂₀ alkyl, C₃-C₂₀ alkenyl, C₃-C₂₀ alkynyl, C₃-C₂₀ alkoxy, C₃-C₂₀ alkylthio, C₃-C₂₀ carbonyl, C₃-C₂₀ carboxyl, amino, C₃-C₂₀ amido, substituted C₃-C₂₀ alkyl, substituted C₃-C₂₀ alkenyl, substituted C₃-C₂₀ alkynyl, substituted C₃-C₂₀ alkoxy, substituted C₃-C₂₀ alkylthio, substituted C₃-C₂₀ carbonyl, substituted C₃-C₂₀ carboxyl, substituted amino, or substituted C₃-C₂₀ amido;

wherein the substituents are independently hydroxyl, amino, thiol, oxo, phosphate, or unsubstituted C₁-C₃ alkyl, C₁-C₃ alkylene, C₂-C₃ alkenyl, C₂-C₃ alkynyl, C₁-C₃ alkoxy, C₁-C₃ alkylamino, C₁-C₃ alkylthio, C₁-C₃ carbonyl, C₁-C₃ carboxyl, or C₁-C₃ amido.

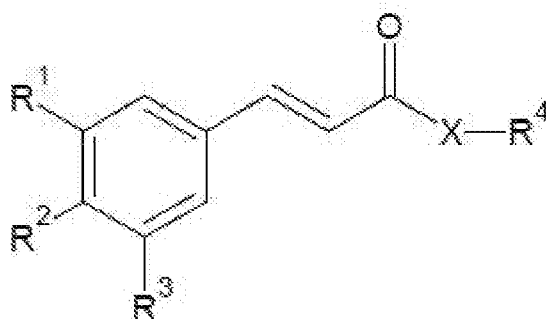
29. The method of any one of claims 1-13 and 25-28, wherein R¹, R², and R³ are independently hydrogen or hydroxyl.

30. The method of any one of claims 1-13, 19-23, and 25-29, wherein R^1 is hydroxyl, R^2 is hydroxyl, R^3 is hydrogen, R^4 is a propyl group, and X is NH.

31. The method of any one of claims 1-30, wherein the composition is formulated for intraperitoneal administration.

32. The method of any one of claims 1-30, wherein the composition is formulated for intravenous administration.

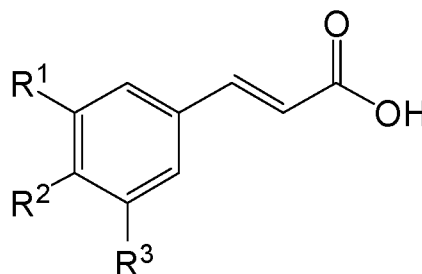
33. A method of synthesizing a caffeic acid derivative having the structure of Formula 3



Formula 3

the method comprising

(a) mixing a compound of Formula 5 or a salt thereof



Formula 5

with H-X- R^4 in dichloromethane and triethylamine (Et_3N);

(b) adding benzotriazol-1-yloxy tris (dimethylamino)phosphonium hexafluorophosphate (BOP) in dichloromethane to the mixture of (a) while stirring on ice; and

(c) removing solvent by evaporation;

wherein

R^1 , R^2 , and R^3 are, independently, hydroxyl, hydrogen, amino, thiol, oxo, phosphate, or substituted or unsubstituted C_1 - C_{10} alkyl, C_1 - C_{10} alkylene, C_2 - C_{10} alkenyl,

C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl;

X is NR^a, wherein R^a is hydrogen or substituted or unsubstituted C₁-C₁₀, alkyl, alkylene, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, arylalkyl, or acyl; and

R⁴ is alkyl, alkenyl, alkynyl, phenyl, aryl, heteroaryl, alkoxy, phenoxy, aroxy, arylthio, alkylthio, carbonyl, carboxyl, amino, amido, polyaryl, C₃-C₂₀ cyclic, heterocyclic, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted phenyl, substituted aryl, substituted heteroaryl, substituted alkoxy, substituted phenoxy, substituted aroxy, substituted alkylthio, phenylthio, substituted phenylthio, substituted arylthio, substituted carbonyl, substituted carboxyl, substituted amino, substituted amido, substituted polyaryl, substituted C₃-C₂₀ cyclic, substituted heterocyclic, amino acid, poly(ethylene glycol), poly(lactic-co-glycolic acid), peptide, polypeptide group, hydrogen, or, if R^a forms two bonds with the N, absent;

wherein at least one of R¹, R², and R³ is hydroxyl, amino, thiol, oxo, phosphate, or substituted or unsubstituted C₁-C₁₀ alkyl, C₁-C₁₀ alkylene, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylamino, C₁-C₁₀ alkylthio, C₁-C₁₀ carbonyl, C₁-C₁₀ carboxyl, C₁-C₁₀ amido, C₁-C₁₀ sulfonyl, C₁-C₁₀ sulfonic acid, C₁-C₁₀ sulfamoyl, C₁-C₁₀ sulfoxide, C₁-C₁₀ phosphoryl, or C₁-C₁₀ phosphonyl.

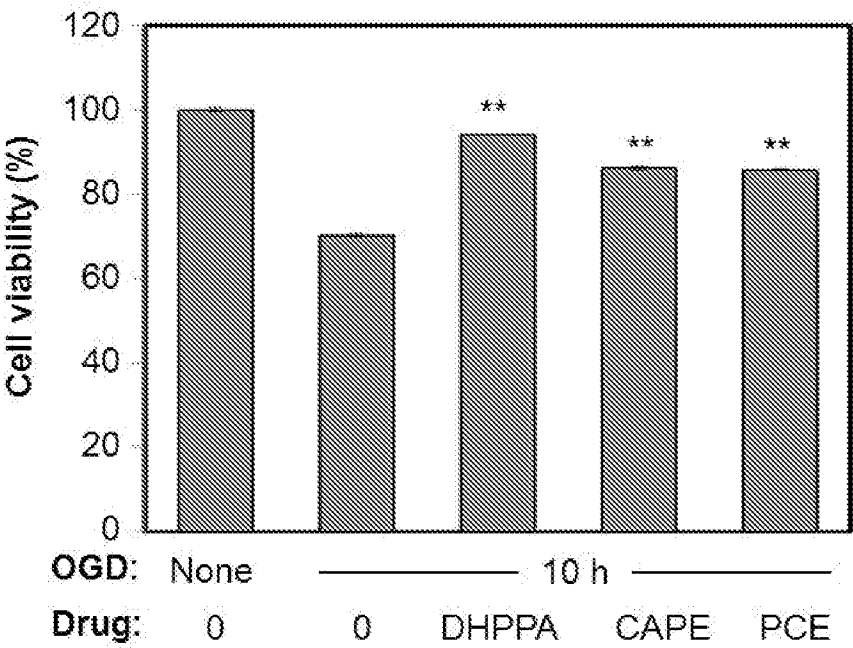


FIG. 1A

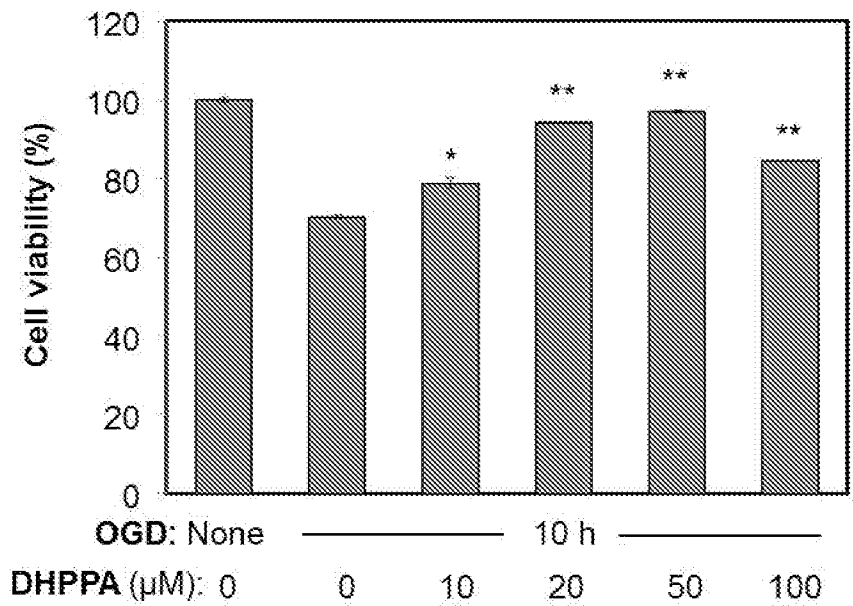


FIG. 1B

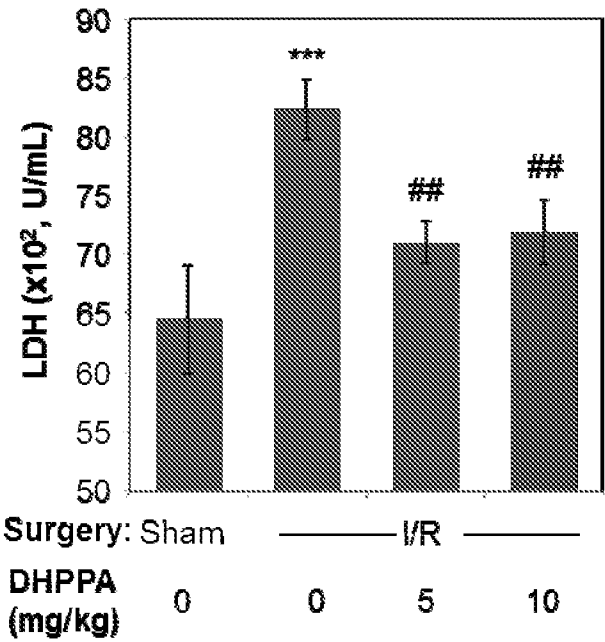


FIG. 2A

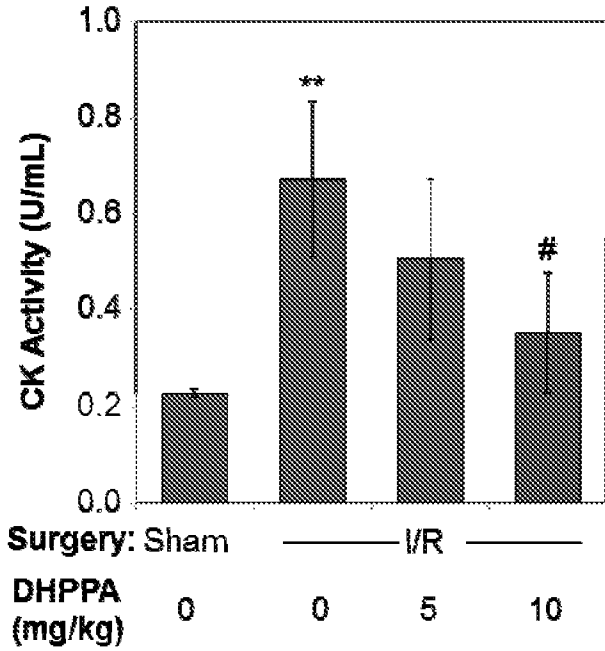


FIG. 2B

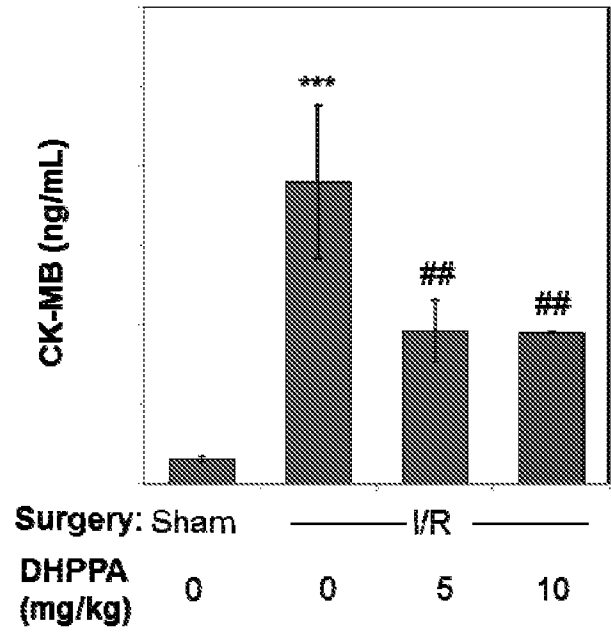
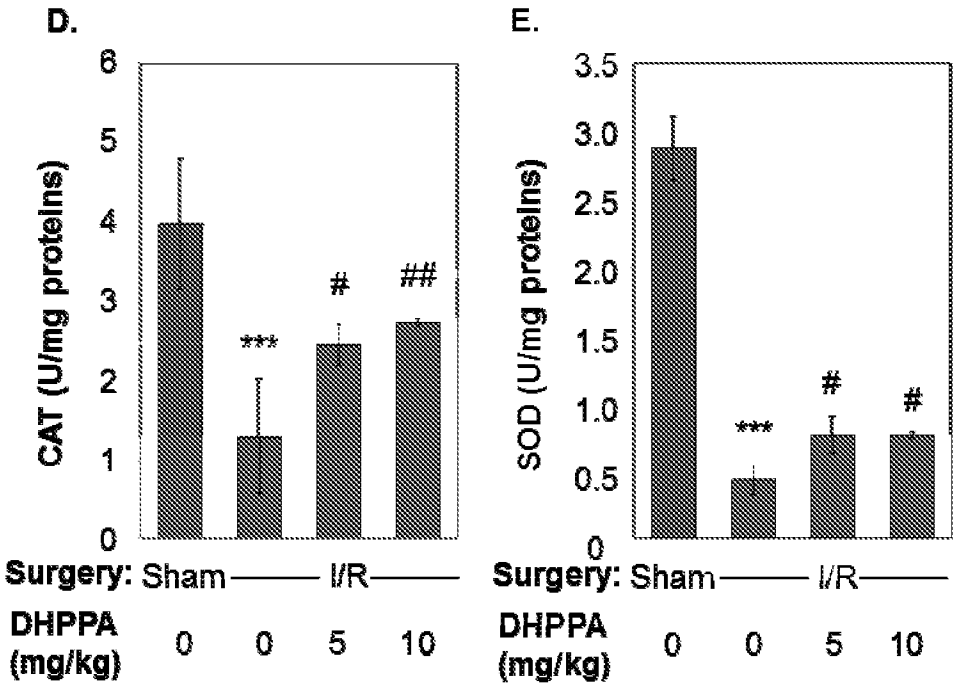
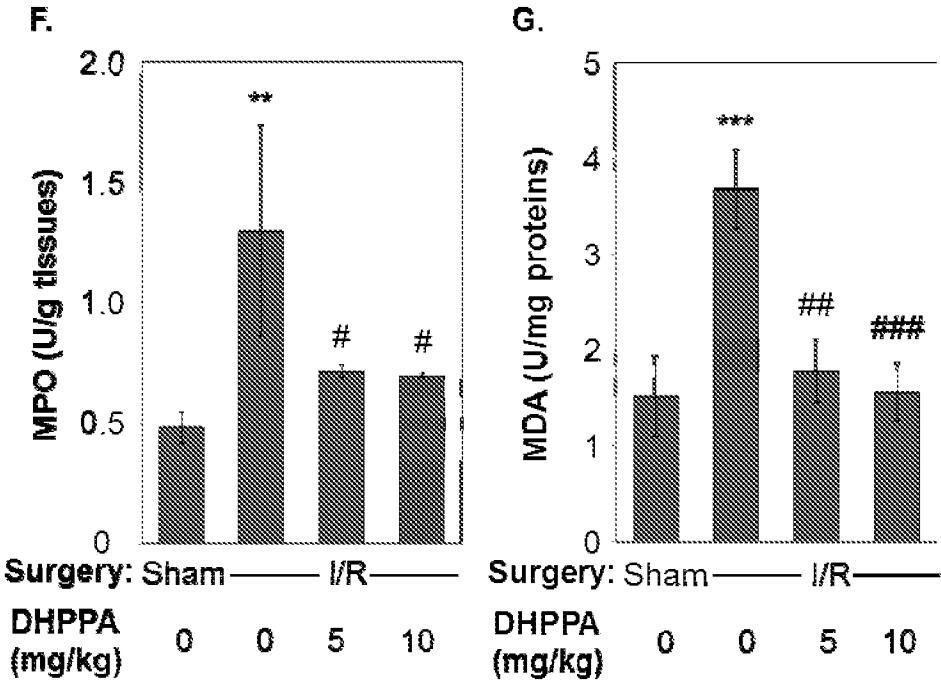


FIG. 2C



FIGS. 2D-2E



FIGS. 2F-2G

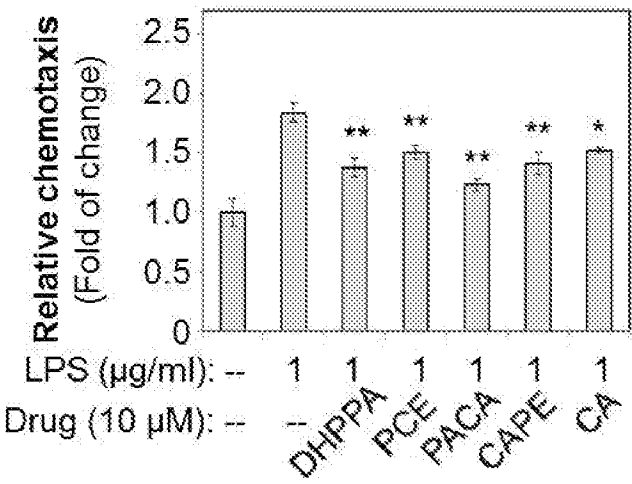


FIG. 3A

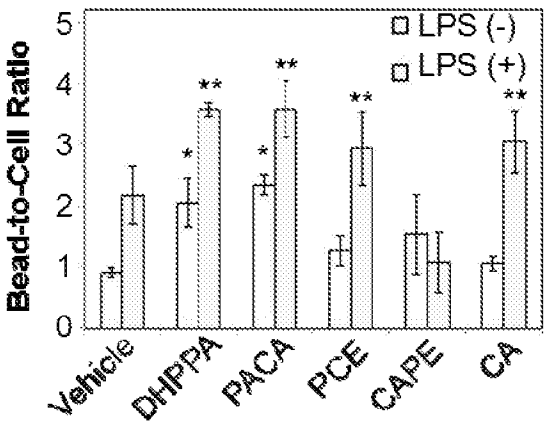


FIG. 3B

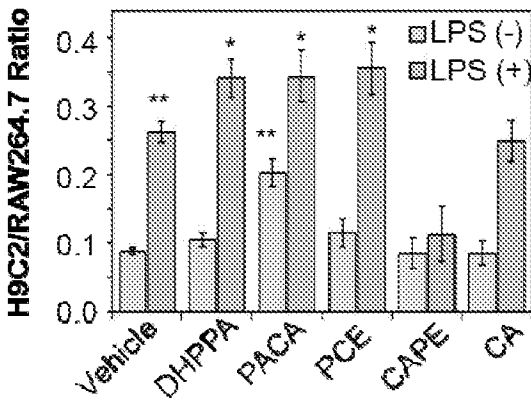


FIG. 3C

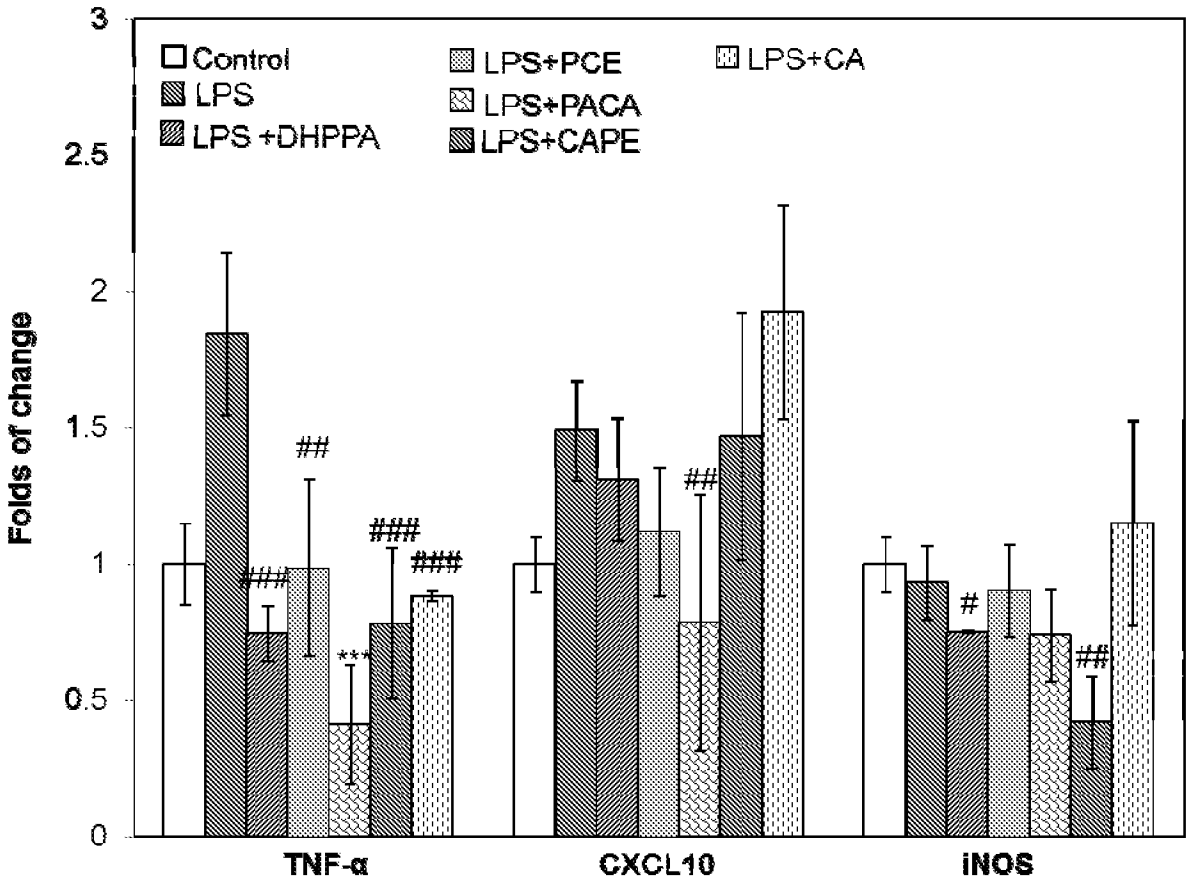


FIG. 4A

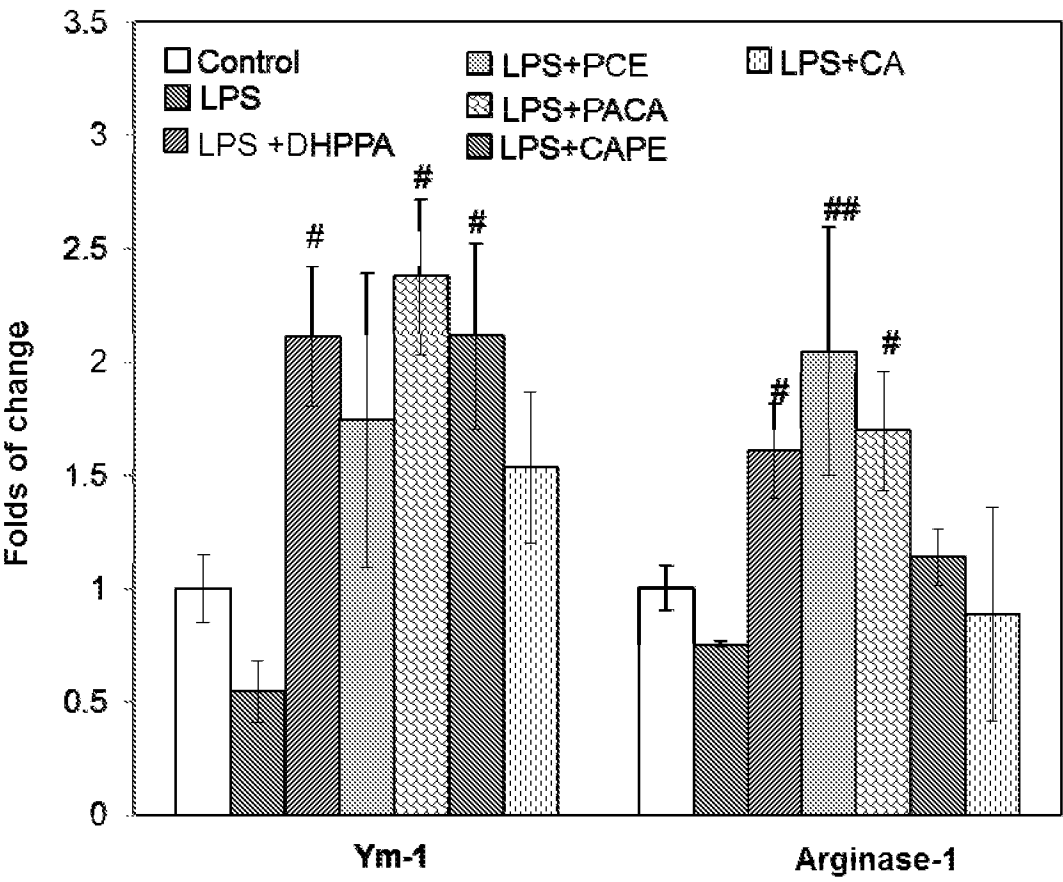


FIG. 4B

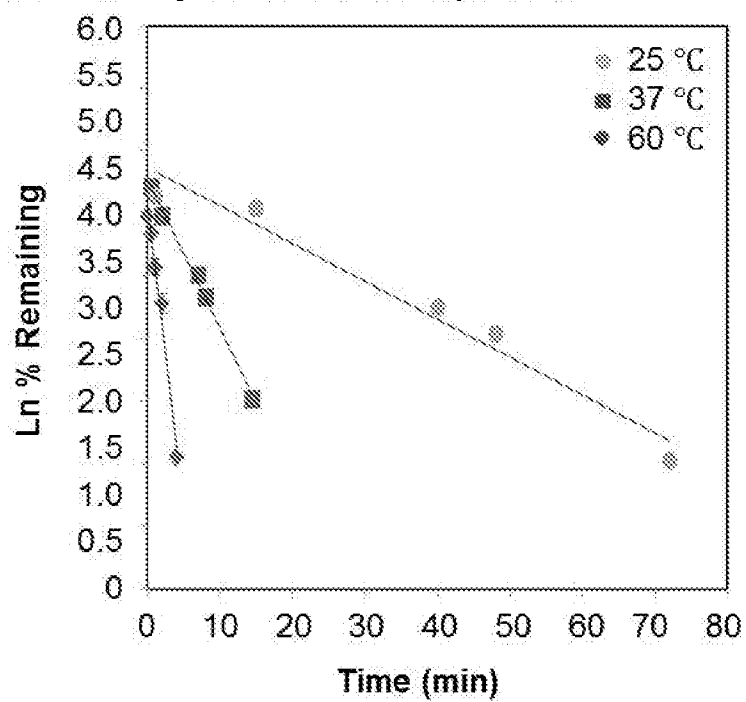
A. Stability of DHPPA in rat plasma

FIG. 5A

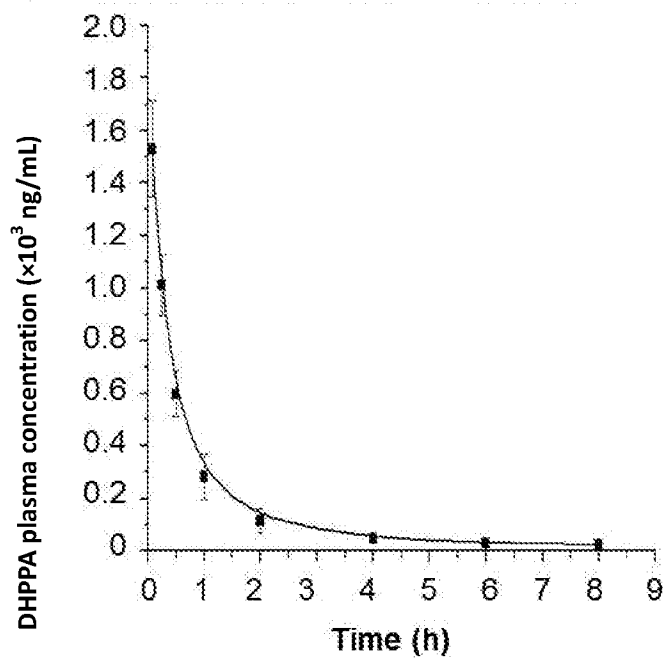
B. Pharmacokinetics of DHPPA in rats

FIG. 5B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/082794**A. CLASSIFICATION OF SUBJECT MATTER**

C07C 39/23(2006.01)i; C07C 233/01(2006.01)i; A61K 31/216(2006.01)i; A61K 31/16(2006.01)i; A61P 9/10(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)

C07C; A61K; A61P

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

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

CNPAT(Cprs), CTCMPD, CNKI Full-Text database, Chinese Medicine Abstract, WPI, EPODOC, STN; search based on the structure of compounds of the present application, macrophage, inflammation, inflammatory, myocardial infarction, neutrophil, polarization

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Kanno, Yoshinori et al. "Chlorogenic acid attenuates ventricular remodeling after myocardial infarction in mice" <i>International Heart Journal</i> , pages 176-180, Vol. 3, No. 54, 31 May 2013 (2013-05-31), see abstract, page 179 right column lines 15-17	1-33

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

15 February 2017

Date of mailing of the international search report

24 February 2017

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/082794

Box No. I **Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

a. (means)

☐

on paper

☒

in electronic form

b. (time)

☒

in the international application as filed

☐

together with the international application in electronic form

☐

subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/082794

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

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

1. ☒ Claims Nos.: **1-32**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 1-32 are directed to a method of treatment of the human/animal body(PCT Article 17 (2) (a) (i) and Rule 39. 1(iv)), however, the search has been carried out and based on the use of compound in manufacturing medicament for treating corresponding diseases in claims 1-32.
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:
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).