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(54) **Title:** BIOCATALYTIC SYNTHESIS OF UNNATURAL MYCOSPORINE-LIKE AMINO ACIDS

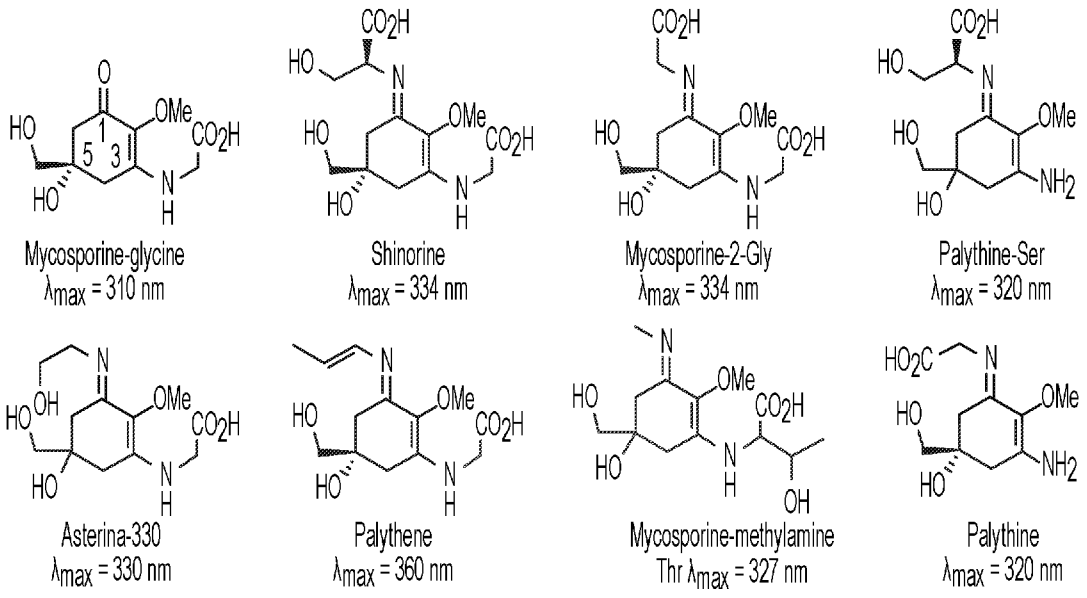

FIG. 1A

(57) **Abstract:** The present invention relates to methods of producing compounds of interest in a recombinant microorganism. In particular, the present invention relates to using a recombinant microorganism comprising a heterologous nucleic acid encoding one or more mycosporine-like amino acid (MAA) biosynthetic enzymes (e.g., MysD) to produce compounds of interest using unnatural amino acids or amine containing substrates. Compositions comprising compounds produced using such methods are also provided herein. The present disclosure also provides methods of preventing sunburn, cancer, and chronic inflammatory diseases by administering such compositions to subjects in need thereof.

[Continued on next page]

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BIOCATALYTIC SYNTHESIS OF UNNATURAL MYCOSPORINE-LIKE AMINO ACIDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/346,791, filed May 27, 2022, and U.S. Provisional Application No. 63/392,462, filed July 26, 2022, all of which are incorporated herein by reference in their entireties.

GOVERNMENT SUPPORT

[0002] This invention was made with government support under Grant No. 2108383 awarded by the National Science Foundation. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Skin cancers are among the most common cancer types in the United States with about 1.2 million Americans living with melanoma and 3 million more affected by nonmelanoma skin cancers.[1,2] Solar radiation, especially ultraviolet (UV) radiation, is an established risk factor of skin cancers,[3] as more than 90% of melanoma in some populations are linked to sunlight exposure.[4] UV rays, mainly UVA (315-400 nm) and UVB (280-315 nm), induce a variety of damages on biomolecules (*e.g.*, DNA and proteins) of living organisms on earth.[5] In addition to behavioral changes, proper skin protection from excessive sun exposure has proven to be effective in reducing skin cancers.[6] In this regard, many organic and inorganic compounds have been developed to dissipate the energy of UV rays and/or directly block their reach on the skin, and some have been used as active ingredients of commercial sunscreens.[7] However, there are increasing concerns regarding the potential negative health impact of synthetic sunscreens (*e.g.*, endocrine disruption, neurotoxicity, and systemic absorption),[8-10] while multiple organic UV filters are accumulated in almost all water sources globally and may be potential contributors to coral reef bleaching, raising a severe environmental concern over their use.[11] Accordingly, there is a need for safer, biodegradable, and environmentally friendly new compounds with UV-modulating, anti-inflammatory, and/or anti-oxidative properties.

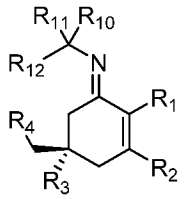
SUMMARY OF THE INVENTION

[0004] Natural organisms have developed multiple effective UV mitigation strategies when utilizing solar energy, including the biosynthesis of diverse natural products as

photoprotectants.[12,13] These natural products (*e.g.*, flavonoids, phenols, terpenoids, and polyketides) absorb UV radiation and release energy through thermal de-excitation, similar to synthetic chemical UV filters, while providing additional protection from UV-induced damages with other biological functions, *e.g.*, antioxidants, anti-inflammation, and immunomodulation.[14] These compounds provide important inspiration for the development of new generation sunscreens.[15] One such example, mycosporine-like amino acids (MAAs), are a family of natural, thermally and photochemically stable UV protectants (**FIG. 1A**).[16] The superior UV protection properties of MAAs has potential to impact the development of next-generation sunscreens for broad cosmetic applications if the low quantity available from natural resources or the lack of efficient synthetic preparation were properly addressed.[25-26]

[0005] Accordingly, in one aspect, the present disclosure provides methods for producing a compound (*e.g.*, an MAA, or a derivative thereof, and any of the compounds delineated herein). The methods of the present invention comprise culturing a recombinant microorganism under conditions suitable for production of the compound and isolating the compound from the recombinant microorganism, wherein the recombinant microorganism comprises a heterologous nucleic acid encoding one or more mycosporine-like amino acid (MAA) biosynthetic enzymes (*e.g.*, a D-alanine-D-alanine ligase (MysD), or a homolog thereof). In some embodiments, the one or more MAA biosynthetic enzymes include MysA, MysB, MysC, MysE, and/or MysH.

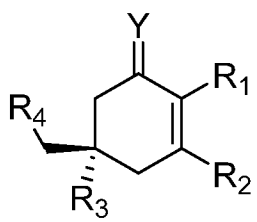
[0006] In certain embodiments, the compound is of Formula (I), or a salt thereof:



Formula (I)

wherein R_1, R_2, R_3, R_4, R_{10}, R_{11}, and R_{12} are as defined herein.

[0007] In some embodiments, the methods described herein further comprise providing a substrate of the one or more MAA biosynthetic enzymes to the recombinant microorganism. In certain embodiments, the substrate is a compound of Formula (II), or a salt thereof:



Formula (II)

wherein R_1, R_2, R_3, R_4, and Y are as defined herein.

[0008] In another aspect, the present disclosure provides a recombinant microorganism comprising a heterologous nucleic acid encoding one or more MAA biosynthetic enzymes. In some embodiments, the one or more MAA biosynthetic enzymes comprise a D-alanine-D-alanine ligase (MysD), or a homolog thereof.

[0009] In another aspect, the present disclosure provides compositions comprising a compound produced by the methods disclosed herein. In some embodiments, the composition comprises an excipient. The composition may be formulated for topical administration (*e.g.*, for use as a sunscreen or a cosmetic). In certain embodiments, the present disclosure provides methods of making the compositions disclosed herein. Such methods may comprise producing a compound using the methods disclosed herein and adding the compound to one or more excipients to produce the composition.

[0010] In another aspect, the present disclosure provides methods of administering a composition (*e.g.*, any of the compositions described herein), comprising applying to composition to a subject. In some embodiments, the composition is applied to the skin of a subject. In certain embodiments, the method is a method of preventing sunburn. In certain embodiments, the method is a method of preventing cancer. In certain embodiments, the method is a method of preventing or treating a chronic inflammatory disease.

[0011] In another aspect, the present disclosure provides compounds produced using the methods disclosed herein. In some embodiments, the compounds are of Formula (I), or a salt thereof, as provided herein.

[0012] It should be appreciated that the foregoing concepts, and the additional concepts discussed below, may be arranged in any suitable combination, as the present disclosure is not limited in this respect. Further, other advantages and novel features of the present disclosure will become apparent from the following detailed description of various non-limiting embodiments when considered in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure, which can be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

[0014] FIGS. 1A-1B show the structures and biosynthesis of mycosporine-like amino acids. **FIG. 1A** provides the chemical structures and maximal absorbance of representative mycosporine-like amino acid analogs. **FIG. 1B** shows the biosynthetic pathway of shinorine, porphyra-334, palythine-Ser, and palythine-Thr.

[0015] FIGS. 2A-2B show structures of the native and unnatural substrates. **FIG. 2A** provides the chemical structures of the substrates tested in the MysD reaction. **FIG. 2B** shows the chemical structures of the corresponding predicted MAA analogs.

[0016] FIG. 3 shows extracted ion chromatogram (EIC) traces of the in-vitro MysD reaction using different amino acid substrates. Five MAA analogs were detected.

[0017] FIG. 4 shows HRMS traces of produced unnatural MAA analogs in the MysD reaction. **FIG. 4A** shows an HRMS trace of the unnatural MAA analog produced from L-ornithine in the MysD reaction. **FIG. 4B** shows an HRMS trace of the unnatural MAA analog produced from 4-aminobutanoic acid in the MysD reaction. **FIG. 4C** shows an HRMS trace of the unnatural MAA analog produced from (*S*)-2-aminobut-3-enoic acid in the MysD reaction, along with its UV absorption spectrum. **FIG. 4D** shows an HRMS trace of the unnatural MAA analog produced from (*S*)-2,3-diaminopropanoic acid in the MysD reaction, along with its UV absorption spectrum.

[0018] FIG. 5 shows SSN analysis of 249 cyanobacterial MysD homologs with a filter value at 172.

[0019] FIG. 6 shows the predicted structure of MysD from Nostoc linckia NIES-25.

[0020] FIG. 7 shows unnatural substrates tested in the MysD reaction.

[0021] FIG. 8 shows biocatalytic synthesis of unnatural palythines.

[0022] FIG. 9 shows the relative activity of MysD mutants compared to WT (L-Thr as the substrate).

[0023] FIG. 10 shows the relative activity of MysD mutants compared to WT (α-aminobutyric acid (AABA) as the substrate).

DEFINITIONS

[0024] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., *Dictionary of Microbiology and Molecular Biology* (2nd ed. 1994); *The Cambridge Dictionary of Science and Technology* (Walker ed., 1988); *The Glossary of Genetics*, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale &

Marham, *The Harper Collins Dictionary of Biology* (1991). As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0025] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Michael B. Smith, *March's Advanced Organic Chemistry*, 7th Edition, John Wiley & Sons, Inc., New York, 2013; Richard C. Larock, *Comprehensive Organic Transformations*, John Wiley & Sons, Inc., New York, 2018; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0026] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, Tetrahedron 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, S.H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0027] The compounds herein may also contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, e.g., restriction resulting from the presence of a ring or double bond. Accordingly, all cis/trans and E/Z isomers are expressly included in the present disclosure. The compounds herein may also be represented in multiple tautomeric forms; in such instances, the present disclosure expressly includes all tautomeric forms of the compounds and oligonucleotides described herein, even though only a single tautomeric form may be represented. All such isomeric forms of such compounds herein are expressly included in the present disclosure. The term "isomers" is intended to include

diastereoisomers, enantiomers, regioisomers, structural isomers, rotational isomers, tautomers, and the like. For compounds that contain one or more stereogenic centers, e.g., chiral compounds, the methods of the present disclosure may be carried out with an enantiomerically enriched compound, a racemate, or a mixture of diastereomers. All isomers of compounds delineated herein are expressly included in the present disclosure

[0028] When a range of values ("range") is listed, it encompasses each value and sub-range within the range. A range is inclusive of the values at the two ends of the range unless otherwise provided. For example "C_{1-6} alkyl" encompasses, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0029] The term "aliphatic" refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term "heteroaliphatic" refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

[0030] The term "alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group has 1 to 12 carbon atoms ("C_{1-12} alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), propyl (C_3) (*e.g.*, *n*-propyl, isopropyl), butyl (C_4) (*e.g.*, *n*-butyl, *tert*-butyl, *sec*-butyl, isobutyl), pentyl (C_5) (*e.g.*, *n*-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, *tert*-amyl), and hexyl (C_6) (*e.g.*, *n*-hexyl). Additional examples of alkyl groups include *n*-heptyl (C_7), *n*-octyl (C_8), *n*-dodecyl (C_{12}), and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents (*e.g.*, halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted C_{1-12} alkyl (such as unsubstituted C_{1-6} alkyl, *e.g.*, $-CH_3$ (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.*, unsubstituted n-propyl (n-Pr), unsubstituted isopropyl (*i*-Pr)), unsubstituted butyl (Bu, *e.g.*, unsubstituted *n*-butyl (*n*-Bu), unsubstituted

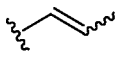
tert-butyl (*tert*-Bu or *t*-Bu), unsubstituted *sec*-butyl (*sec*-Bu or *s*-Bu), unsubstituted isobutyl (*i*-Bu)). In certain embodiments, the alkyl group is a substituted C_{1-12} alkyl (such as substituted C_{1-6} alkyl, *e.g.*, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, or benzyl (Bn)).

[0031] The term "haloalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. "Perhaloalkyl" is a subset of haloalkyl and refers to an alkyl group wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 20 carbon atoms ("C_{1-20} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 10 carbon atoms ("C_{1-10} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 9 carbon atoms ("C_{1-9} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 7 carbon atoms ("C_{1-7} haloalkyl").In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 5 carbon atoms ("C_{1-5} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). In some embodiments, all of the haloalkyl hydrogen atoms are independently replaced with fluoro to provide a "perfluoroalkyl" group. In some embodiments, all of the haloalkyl hydrogen atoms are independently replaced with chloro to provide a "perchloroalkyl" group. Examples of haloalkyl groups include $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

[0032] The term "heteroalkyl" refers to an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 20 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-20} alkyl"). In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 12 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-12} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 11 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-11} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkyl").

In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-9} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-7} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-5} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-12} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-12} alkyl.

[0033] The term "alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds) ("C_{2-20} alkenyl"). In some embodiments, the group $=CH_2$ along with the sp^2-hybridized carbon to which it is attached form an alkenyl group. In some embodiments, an alkenyl group has 2 to 20 carbon atoms ("C_{2-20} alkenyl"). In some embodiments, an alkenyl group has 2 to 12 carbon atoms ("C_{2-12} alkenyl"). In some embodiments, an alkenyl group has 2 to 11 carbon atoms ("C_{2-11} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_{2-10} alkenyl"). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some

embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C_{2-20} alkenyl. In certain embodiments, the alkenyl group is a substituted C_{2-20} alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, $-CH=CHCH_3$ or ) may be in the (*E*)- or (*Z*)-configuration.

[0034] The term "heteroalkenyl" refers to an alkenyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 20 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-20} alkenyl"). In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 12 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-12} alkenyl"). In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 11 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-11} alkenyl"). In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond,

and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkenyl"). In some embodiments, a heteroalkenyl group has 2 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_2 alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{2-20} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-20} alkenyl.

[0035] The term "alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) ("C_{1-20} alkynyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted

(an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C_{2-20} alkynyl. In certain embodiments, the alkynyl group is a substituted C_{2-20} alkynyl.

[0036] The term "heteroalkynyl" refers to an alkynyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 20 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-20} alkynyl"). In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkynyl"). In some embodiments, a heteroalkynyl group has 2 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_2 alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC_{2-20} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-20} alkynyl.

[0037] The term "carbocyclyl" or "carbocyclic" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero

heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 13 ring carbon atoms ("C_{3-13} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 12 ring carbon atoms ("C_{3-12} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 11 ring carbon atoms ("C_{3-11} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. Exemplary C_{3-8} carbocyclyl groups include the aforementioned C_{3-10} carbocyclyl groups as well as cycloundecyl (C_{11}), spiro[5.5]undecanyl (C_{11}), cyclododecyl (C_{12}), cyclododecenyl (C_{12}), cyclotridecane (C_{13}), cyclotetradecane (C_{14}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon-carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is

an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl.

[0038] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C_{4-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl. In certain embodiments, the carbocyclyl includes 0, 1, or 2 C=C double bonds in the carbocyclic ring system, as valency permits.

[0039] The term "heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–14 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon-carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number

of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl is substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl, wherein 1, 2, or 3 atoms in the heterocyclic ring system are independently oxygen, nitrogen, or sulfur, as valency permits.

[0040] In some embodiments, a heterocyclyl group is a 5–10 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0041] Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include triazinyl.

Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[0042] The term "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is a substituted C_{6-14} aryl.

[0043] "Aralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety.

[0044] The term "heteroaryl" refers to a radical of a 5-14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms

provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *e.g.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl). In certain embodiments, the heteroaryl is substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur. In certain embodiments, the heteroaryl is substituted or unsubstituted, 9- or 10-membered, bicyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur.

[0045] In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each

instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5-14 membered heteroaryl.

[0046] Exemplary 5-membered heteroaryl groups containing 1 heteroatom include pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing 4 heteroatoms include tetrazolyl. Exemplary 6-membered heteroaryl groups containing 1 heteroatom include pyridinyl. Exemplary 6-membered heteroaryl groups containing 2 heteroatoms include pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing 3 or 4 heteroatoms include triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 heteroatom include azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

[0047] "Heteroaralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[0048] The term "unsaturated bond" refers to a double or triple bond.

[0049] The term "unsaturated" or "partially unsaturated" refers to a moiety that includes at least one double or triple bond.

[0050] The term "saturated" or "fully saturated" refers to a moiety that does not contain a double or triple bond, *e.g.*, the moiety only contains single bonds.

[0051] Affixing the suffix "-ene" to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl,

heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0052] A group is optionally substituted unless expressly provided otherwise. The term "optionally substituted" refers to being substituted or unsubstituted. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. "Optionally substituted" refers to a group which is substituted or unsubstituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds and includes any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety. The invention is not limited in any manner by the exemplary substituents described herein.

[0053] Exemplary carbon atom substituents include halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$,

$-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)(N(R^{bb})_2)_2$, $-OP(=O)(N(R^{bb})_2)_2$, $-NR^{bb}P(=O)(R^{aa})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, $-P(R^{cc})_2$, $-P(OR^{cc})_2$, $-P(R^{cc})_3^+X^-$, $-P(OR^{cc})_3^+X^-$, $-P(R^{cc})_4$, $-P(OR^{cc})_4$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3^+X^-$, $-OP(R^{cc})_4$, $-OP(OR^{cc})_4$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, heteroC_{1-20} alkyl, heteroC_{1-20} alkenyl, heteroC_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

wherein:

each instance of R^{aa} is, independently, selected from C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, heteroC_{1-20} alkyl, heteroC_{1-20}alkenyl, heteroC_{1-20}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-CN$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)(N(R^{cc})_2)_2$, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, heteroC_{1-20}alkyl, heteroC_{1-20}alkenyl, heteroC_{1-20}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, heteroC_{1-20} alkyl, heteroC_{1-20} alkenyl, heteroC_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups are joined to form a 3-14 membered heterocyclyl or 5-14

membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, heteroC_{1-10}alkyl, heteroC_{1-10}alkenyl, heteroC_{1-10}alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents are joined to form =O or =S; wherein X^- is a counterion;

each instance of R^{ee} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{1-10} alkenyl, heteroC_{1-10} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{1-10} alkenyl, heteroC_{1-10} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-10 membered heterocyclyl or 5-10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{gg} is, independently, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_3^+X^-$, $-NH(C_{1-6}$ alkyl$)_2^+X^-$, $-NH_2(C_{1-6}$ alkyl$)^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl$)$, $-N(OH)(C_{1-6}$ alkyl$)$, $-NH(OH)$, $-SH$, $-SC_{1-6}$ alkyl, $-SS(C_{1-6}$ alkyl$)$, $-C(=O)(C_{1-6}$ alkyl$)$, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl$)$, $-OC(=O)(C_{1-6}$ alkyl$)$, $-OCO_2(C_{1-6}$ alkyl$)$, $-C(=O)NH_2$, $-C(=O)N(C_{1-6}$ alkyl$)_2$,

$-OC(=O)NH(C_{1-6}$ alkyl), $-NHC(=O)(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$C(=O)(C_{1-6}$ alkyl), $-NHCO_2(C_{1-6}$ alkyl), $-NHC(=O)N(C_{1-6}$ alkyl)$_2$, $-NHC(=O)NH(C_{1-6}$ alkyl), $-NHC(=O)NH_2$, $-C(=NH)O(C_{1-6}$ alkyl), $-OC(=NH)(C_{1-6}$ alkyl), $-OC(=NH)OC_{1-6}$ alkyl, $-C(=NH)N(C_{1-6}$ alkyl)$_2$, $-C(=NH)NH(C_{1-6}$ alkyl), $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6}$ alkyl)$_2$, $-OC(NH)NH(C_{1-6}$ alkyl), $-OC(NH)NH_2$, $-NHC(NH)N(C_{1-6}$ alkyl)$_2$, $-NHC(=NH)NH_2$, $-NHSO_2(C_{1-6}$ alkyl), $-SO_2N(C_{1-6}$ alkyl)$_2$, $-SO_2NH(C_{1-6}$ alkyl), $-SO_2NH_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2OC_{1-6}$ alkyl, $-OSO_2C_{1-6}$ alkyl, $-SOC_{1-6}$ alkyl, $-Si(C_{1-6}$ alkyl)$_3$, $-OSi(C_{1-6}$ alkyl)$_3$ $-C(=S)N(C_{1-6}$ alkyl)$_2$, $C(=S)NH(C_{1-6}$ alkyl), $C(=S)NH_2$, $-C(=O)S(C_{1-6}$ alkyl), $-C(=S)SC_{1-6}$ alkyl, $-SC(=S)SC_{1-6}$ alkyl, $-P(=O)(OC_{1-6}$ alkyl)$_2$, $-P(=O)(C_{1-6}$ alkyl)$_2$, $-OP(=O)(C_{1-6}$ alkyl)$_2$, $-OP(=O)(OC_{1-6}$ alkyl)$_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{1-10} alkenyl, heteroC_{1-10} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, or 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; and

each X^- is a counterion.

[0054] In certain embodiments, each carbon atom substituent is independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, $–NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$. In certain embodiments, each carbon atom substituent is independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, $–NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, an oxygen protecting group (*e.g.*, silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, t-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (*e.g.*, acetamidomethyl, t-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, each carbon atom substituent is independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, or $–NO_2$. In certain embodiments, each carbon atom substituent is independently halogen, substituted (*e.g.*, substituted with one or more halogen moieties) or unsubstituted C_{1-10} alkyl, $-OR^{aa}$, $-SR^{aa}$,

$-N(R^{bb})_2$, –CN, –SCN, or $-NO_2$, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, an oxygen protecting group (*e.g.*, silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, t-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (*e.g.*, acetamidomethyl, t-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[0055] In certain embodiments, the molecular weight of a carbon atom substituent is lower than 250, lower than 200, lower than 150, lower than 100, or lower than 50 g/mol. In certain embodiments, a carbon atom substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, nitrogen, and/or silicon atoms. In certain embodiments, a carbon atom substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, and/or nitrogen atoms. In certain embodiments, a carbon atom substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, and/or iodine atoms. In certain embodiments, a carbon atom substituent consists of carbon, hydrogen, fluorine, and/or chlorine atoms.

[0056] The term "halo" or "halogen" refers to fluorine (fluoro, −F), chlorine (chloro, −Cl), bromine (bromo, −Br), or iodine (iodo, −I).

[0057] The term "hydroxyl" or "hydroxy" refers to the group −OH. The term "substituted hydroxyl" or "substituted hydroxyl," by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-OR^{aa}$, $-ON(R^{bb})_2$, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OSi(R^{aa})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3{}^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3{}^+X^-$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, and $-OP(=O)(N(R^{bb}))_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein.

[0058] The term "thiol" or "thio" refers to the group –SH. The term "substituted thiol" or "substituted thio," by extension, refers to a thiol group wherein the sulfur atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-SR^{aa}$, $-S{=}SR^{cc}$, $-SC(=S)SR^{aa}$, $-SC(=S)OR^{aa}$, $-SC(=S)\ N(R^{bb})_2$, $-SC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)N(R^{bb})_2$, and $-SC(=O)R^{aa}$, wherein R^{aa} and R^{cc} are as defined herein.

[0059] The term "amino" refers to the group $-NH_2$. The term "substituted amino," by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino. In certain embodiments, the "substituted amino" is a monosubstituted amino or a disubstituted amino group.

[0060] The term "monosubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen, and includes groups selected from $-NH(R^{bb})$, $-NHC(=O)R^{aa}$, $-NHCO_2R^{aa}$, $-NHC(=O)N(R^{bb})_2$, $-NHC(=NR^{bb})N(R^{bb})_2$, $-NHSO_2R^{aa}$, $-NHP(=O)(OR^{cc})_2$, and $-NHP(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $-NH(R^{bb})$ is not hydrogen.

[0061] The term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from $-N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}SO_2R^{aa}$, $-NR^{bb}P(=O)(OR^{cc})_2$, and $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[0062] The term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from $-N(R^{bb})_3$ and $-N(R^{bb})_3{}^+X^-$, wherein R^{bb} and X^- are as defined herein.

[0063] The term "sulfonyl" refers to a group selected from $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, and $-SO_2OR^{aa}$, wherein R^{aa} and R^{bb} are as defined herein.

[0064] The term "sulfinyl" refers to the group $-S(=O)R^{aa}$, wherein R^{aa} is as defined herein.

[0065] The term "acyl" refers to a group having the general formula $-C(=O)R^{X1}$, $-C(=O)OR^{X1}$, $-C(=O)-O-C(=O)R^{X1}$, $-C(=O)SR^{X1}$, $-C(=O)N(R^{X1})_2$, $-C(=S)R^{X1}$, $-C(=S)N(R^{X1})_2$, and $-C(=S)S(R^{X1})$, $-C(=NR^{X1})R^{X1}$, $-C(=NR^{X1})OR^{X1}$, $-C(=NR^{X1})SR^{X1}$, and $-C(=NR^{X1})N(R^{X1})_2$, wherein R^{X1} is hydrogen; halogen; substituted or unsubstituted hydroxyl; substituted or unsubstituted thiol; substituted or unsubstituted amino; substituted or unsubstituted acyl, cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkyl; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy,

arylthioxy, heteroarylthioxy, mono- or di- aliphaticamino, mono- or di- heteroaliphaticamino, mono- or di- alkylamino, mono- or di- heteroalkylamino, mono- or di-arylamino, or mono- or di-heteroarylamino; or two R^{X1} groups taken together form a 5- to 6-membered heterocyclic ring. Exemplary acyl groups include aldehydes (−CHO), carboxylic acids (−CO_2H), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas. Acyl substituents include, but are not limited to, any of the substituents described herein, that result in the formation of a stable moiety (*e.g.*, aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

[0066] The term "carbonyl" refers to a group wherein the carbon directly attached to the parent molecule is sp^2 hybridized, and is substituted with an oxygen, nitrogen or sulfur atom, *e.g.*, a group selected from ketones (–$C(=O)R^{aa}$), carboxylic acids (–CO_2H), aldehydes (–CHO), esters (–CO_2R^{aa}, –$C(=O)SR^{aa}$, –$C(=S)SR^{aa}$), amides (–$C(=O)N(R^{bb})_2$, –$C(=O)NR^{bb}SO_2R^{aa}$, –$C(=S)N(R^{bb})_2$), and imines (–$C(=NR^{bb})R^{aa}$, –$C(=NR^{bb})OR^{aa}$), –$C(=NR^{bb})N(R^{bb})_2$), wherein R^{aa} and R^{bb} are as defined herein.

[0067] The term "silyl" refers to the group –$Si(R^{aa})_3$, wherein R^{aa} is as defined herein.

[0068] The term "phosphino" refers to the group –$P(R^{cc})_2$, wherein R^{cc} is as defined herein.

[0069] The term "phosphono" refers to the group – $(P=O)(OR^{cc})_2$, wherein R^{aa} and R^{cc} are as defined herein.

[0070] The term "phosphoramido" refers to the group –$O(P=O)(N(R^{bb})_2)_2$, wherein each R^{bb} is as defined herein.

[0071] The term "oxo" refers to the group =O, and the term "thiooxo" refers to the group =S.

[0072] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include hydrogen, −OH, −OR^{aa}, −$N(R^{cc})_2$, −CN, −$C(=O)R^{aa}$, −$C(=O)N(R^{cc})_2$, −CO_2R^{aa}, −SO_2R^{aa}, −$C(=NR^{bb})R^{aa}$, −$C(=NR^{cc})OR^{aa}$, −$C(=NR^{cc})N(R^{cc})_2$, −$SO_2N(R^{cc})_2$, −SO_2R^{cc}, −SO_2OR^{cc}, −SOR^{aa}, −$C(=S)N(R^{cc})_2$, −$C(=O)SR^{cc}$, −$C(=S)SR^{cc}$, −$P(=O)(OR^{cc})_2$, −$P(=O)(R^{aa})_2$, −$P(=O)(N(R^{cc})_2)_2$, $C_{1–20}$ alkyl, $C_{1–20}$ perhaloalkyl, $C_{1–20}$ alkenyl, $C_{1–20}$ alkynyl, hetero $C_{1–20}$ alkyl, hetero $C_{1–20}$ alkenyl, hetero $C_{1–20}$ alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached

to an N atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0073] In certain embodiments, each nitrogen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a nitrogen protecting group. In certain embodiments, each nitrogen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a nitrogen protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group. In certain embodiments, each nitrogen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl or a nitrogen protecting group.

[0074] In certain embodiments, the substituent present on the nitrogen atom is a nitrogen protecting group (also referred to herein as an "amino protecting group"). Nitrogen protecting groups include $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{1-20} alkenyl, C_{1-20} alkynyl, hetero C_{1-20} alkyl, hetero C_{1-20} alkenyl, hetero C_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0075] For example, in certain embodiments, at least one nitrogen protecting group is an amide group (*e.g.*, a moiety that include the nitrogen atom to which the nitrogen protecting groups (*e.g.*, $-C(=O)R^{aa}$) is directly attached). In certain such embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-

phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivatives, benzamide, *p*-phenylbenzamide, *o*-nitophenylacetamide, *o*-nitrophenoxyacetamide, acetoacetamide, (*N*'-dithiobenzyloxyacylamino)acetamide, 3-(*p*-hydroxyphenyl)propanamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *N*-acetylmethionine derivatives, *o*-nitrobenzamide, and *o*-(benzoyloxymethyl)benzamide.

[0076] In certain embodiments, at least one nitrogen protecting group is a carbamate group (*e.g.*, a moiety that includes the nitrogen atom to which the nitrogen protecting groups (*e.g.*, $-C(=O)OR^{aa}$) is directly attached). In certain such embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluoroenylmethyl carbamate, 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1–(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-t-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenylyl)ethyl carbamate (Bpoc), 1-(3,5-di-t-butylphenyl)-1-methylethyl carbamate (t-Bumeoc), 2-(2′- and 4′-pyridyl)ethyl carbamate (Pyoc), 2-(N,N-dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC or Boc), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, N-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-

6-chromonylmethyl carbamate (Tcroc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxyacylvinyl carbamate, *o*-(*N*,*N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N*,*N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p*'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0077] In certain embodiments, at least one nitrogen protecting group is a sulfonamide group (*e.g.*, a moiety that include the nitrogen atom to which the nitrogen protecting groups (*e.g.*, $-S(=O)_2R^{aa}$) is directly attached). In certain such embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4′,8′-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0078] In certain embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of phenothiazinyl-(10)-acyl derivatives, *N*'-*p*-toluenesulfonylaminoacyl derivatives, *N*'-phenylaminothioacyl derivatives, *N*-benzoylphenylalanyl derivatives, *N*-acetylmethionine derivatives, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-

dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypropylamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethyleneamine, *N*-ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N'*-oxide, *N*-1,1-dimethylthiomethyleneamine, *N*-benzylideneamine, *N*-p-methoxybenzylideneamine, *N*-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*-(*N',N'*-dimethylaminomethylene)amine, *N*-p-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentaacylchromium- or tungsten)acyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys). In some embodiments, two instances of a nitrogen protecting group together with the nitrogen atoms to which the nitrogen protecting groups are attached are *N,N'*-isopropylidenediamine.

[0079] In certain embodiments, at least one nitrogen protecting group is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[0080] In certain embodiments, each oxygen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or an oxygen protecting group. In certain embodiments, each oxygen atom substituents is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or an oxygen protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one

or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group. In certain embodiments, each oxygen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl or an oxygen protecting group.

[0081] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an "hydroxyl protecting group"). Oxygen protecting groups include $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0082] In certain embodiments, each oxygen protecting group, together with the oxygen atom to which the oxygen protecting group is attached, is selected from the group consisting of methyl, methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (p-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl *S*,*S*-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p*,*p*'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''-tris(4,5-

dichlorophthalimidophenyl)methyl, 4,4′,4″-tris(levulinoyloxyphenyl)methyl, 4,4′,4″-tris(benzoyloxyphenyl)methyl, 4,4'-Dimethoxy-3"'-[N-(imidazolylmethyl)]trityl Ether (IDTr-OR), 4,4'-Dimethoxy-3"'-[N-(imidazolylethyl)carbamoyl]trityl Ether (IETr-OR), 1,1-bis(4-methoxyphenyl)-1′-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl *S*,*S*-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, p-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, *t*-butyl carbonate (BOC or Boc), *p*-nitrophenyl carbonate, benzyl carbonate, *p*-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, *o*-nitrobenzyl carbonate, *p*-nitrobenzyl carbonate, *S*-benzyl thiocarbonate, 4-ethoxy-1-napththyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl carbonate (MTMEC-OR), 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenoate, *o*-(methoxyacyl)benzoate, α-naphthoate, nitrate, alkyl *N*,*N*,*N*',*N*'-tetramethylphosphorodiamidate, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0083] In certain embodiments, at least one oxygen protecting group is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl.

[0084] In certain embodiments, each sulfur atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a sulfur protecting group. In certain embodiments, each sulfur

atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a sulfur protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group. In certain embodiments, each sulfur atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl or a sulfur protecting group.

[0085] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a "thiol protecting group"). In some embodiments, each sulfur protecting group is selected from the group consisting of $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0086] In certain embodiments, the molecular weight of a substituent is lower than 250, lower than 200, lower than 150, lower than 100, or lower than 50 g/mol. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, nitrogen, and/or silicon atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, and/or nitrogen atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, and/or iodine atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, and/or chlorine atoms. In certain embodiments, a substituent comprises 0, 1, 2, or 3 hydrogen bond donors. In certain embodiments, a substituent comprises 0, 1, 2, or 3 hydrogen bond acceptors.

[0087] A "counterion" or "anionic counterion" is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (*e.g.*, including one formal negative charge). An anionic counterion may also be multivalent (*e.g.*, including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HCO_3^-, HSO_4^-, sulfonate ions (*e.g.*, methansulfonate, trifluoromethanesulfonate, *p*–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate,

naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), carboxylate ions (*e.g.*, acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF_4^-, PF_4^-, PF_6^-, AsF_6^-, SbF_6^-, $B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$, $B(C_6F_5)_4^-$, BPh_4^-, $Al(OC(CF_3)_3)_4^-$, and carborane anions (*e.g.*, $CB_{11}H_{12}^-$ or $(HCB_{11}Me_5Br_6)^-$). Exemplary counterions which may be multivalent include CO_3^{2-}, HPO_4^{2-}, PO_4^{3-}, $B_4O_7^{2-}$, SO_4^{2-}, $S_2O_3^{2-}$, carboxylate anions (*e.g.*, tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

[0088] A "leaving group" (LG) is an art-understood term referring to an atomic or molecular fragment that departs with a pair of electrons in heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. As used herein, a leaving group can be an atom or a group capable of being displaced by a nucleophile. *See e.g.*, Smith, March Advanced Organic Chemistry 6th ed. (501–502). Exemplary leaving groups include, but are not limited to, halo (*e.g.*, fluoro, chloro, bromo, iodo) and activated substituted hydroxyl groups (*e.g.*, $–OC(=O)SR^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–OC(=O)N(R^{bb})_2$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})N(R^{bb})_2$, $–OS(=O)R^{aa}$, $–OSO_2R^{aa}$, $–OP(R^{cc})_2$, $–OP(R^{cc})_3$, $–OP(=O)_2R^{aa}$, $–OP(=O)(R^{aa})_2$, $–OP(=O)(OR^{cc})_2$, $–OP(=O)_2N(R^{bb})_2$, and $–OP(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein). Additional examples of suitable leaving groups include, but are not limited to, halogen alkoxycarbonyloxy, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, aryloxy, methoxy, *N*,*O*-dimethylhydroxylamino, pixyl, and haloformates. In some embodiments, the leaving group is a sulfonic acid ester, such as toluenesulfonate (tosylate, –OTs), methanesulfonate (mesylate, –OMs), *p*-bromobenzenesulfonyloxy (brosylate, –OBs), $–OS(=O)_2(CF_2)_3CF_3$ (nonaflate, –ONf), or trifluoromethanesulfonate (triflate, –OTf). In some embodiments, the leaving group is a brosylate, such as *p*-bromobenzenesulfonyloxy. In some embodiments, the leaving group is a nosylate, such as 2-nitrobenzenesulfonyloxy. In some embodiments, the leaving group is a sulfonate-containing group. In some embodiments, the leaving group is a tosylate group. In some embodiments, the leaving group is a phosphineoxide (*e.g.*, formed during a Mitsunobu reaction) or an internal leaving group such as an epoxide or cyclic sulfate. Other non-limiting examples of leaving groups are water, ammonia, alcohols, ether moieties, thioether moieties, zinc halides, magnesium moieties, diazonium salts, and copper moieties.

[0089] Use of the phrase "at least one instance" refers to 1, 2, 3, 4, or more instances, but also encompasses a range, *e.g.*, for example, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 4, from 2 to 3, or from 3 to 4 instances, inclusive.

[0090] A "non-hydrogen group" refers to any group that is defined for a particular variable that is not hydrogen.

[0091] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and Claims. The invention is not limited in any manner by the above exemplary listing of substituents.

[0092] As used herein, the term "salt" refers to any and all salts and encompasses pharmaceutically acceptable salts. Salts include ionic compounds that result from the neutralization reaction of an acid and a base. A salt is composed of one or more cations (positively charged ions) and one or more anions (negative ions) so that the salt is electrically neutral (without a net charge). Salts of the compounds of this invention include those derived from inorganic and organic acids and bases. Examples of acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid, or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate, hippurate, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further salts include ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0093] A "subject" to which administration is contemplated refers to a human (*i.e.*, male or female of any age group, *e.g.*, pediatric subject (*e.g.*, infant, child, or adolescent) or adult

subject (*e.g.*, young adult, middle-aged adult, or senior adult)) or non-human animal. In certain embodiments, the non-human animal is a mammal (*e.g.*, primate (*e.g.*, cynomolgus monkey or rhesus monkey), commercially relevant mammal (*e.g.*, cattle, pig, horse, sheep, goat, cat, or dog), or bird (*e.g.*, commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a transgenic animal or genetically engineered animal. The term "patient" refers to a human subject in need of treatment of a disease.

[0094] The term "administer," "administering," or "administration" refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound described herein, or a composition thereof, in or on a subject.

[0095] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0096] The term "prevent," "preventing," or "prevention" refers to a prophylactic treatment of a subject who is not and was not with a disease but is at risk of developing the disease or who was with a disease, is not with the disease, but is at risk of regression of the disease. In certain embodiments, the subject is at a higher risk of developing the disease or at a higher risk of regression of the disease than an average healthy member of a population. In some embodiments, the subject is at risk of developing a disease or condition due to environmental factors (*e.g.*, exposure to the sun).

[0097] An "effective amount" of a compound described herein refers to an amount sufficient to elicit the desired biological response. An effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, severity of side effects, disease, or disorder, the identity, pharmacokinetics, and pharmacodynamics of the particular compound, the condition being treated, the mode, route, and desired or required frequency of administration, the species, age and health or general condition of the subject. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a prophylactic treatment. In certain embodiments, an

effective amount is the amount of a compound described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound described herein in multiple doses. In certain embodiments, the desired dosage is delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage is delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[0098] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human comprises about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[0099] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[0100] A "therapeutically effective amount" of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, a therapeutically effective amount is an amount sufficient to provide anti-oxidative or anti-inflammatory effects. In some embodiments, a therapeutically effective amount is an amount sufficient to provide UV-modulating effects (*e.g.*, absorption of UV wavelengths between 280 and 400 nm). In certain embodiments, a therapeutically effective amount is an amount sufficient for preventing sunburn. In certain embodiments, a therapeutically effective amount is an amount sufficient for preventing cancer. In certain embodiments, a therapeutically effective amount is an amount sufficient for preventing or treating a chronic inflammatory disease.

[0101] The term "cancer" refers to a class of diseases characterized by the development of abnormal cells that proliferate uncontrollably and have the ability to infiltrate and destroy normal body tissues. *See e.g.*, *Stedman's Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990. Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett's adenocarcinoma); Ewing's sarcoma; ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic

lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*,bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.*, prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.*, Paget's disease of the vulva). In some embodiments, cancer is skin cancer (*e.g.*, basal-cell skin cancer, squamous-cell skin cancer, or melanoma).

[0102] The terms "inflammatory disease" and "inflammatory condition" are used interchangeably herein, and refer to a disease or condition caused by, resulting from, or resulting in inflammation. A "chronic inflammatory disease" is an inflammatory disease that causes symptoms over a prolonged period of time. Inflammatory diseases and conditions include those diseases, disorders or conditions that are characterized by signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and/or loss of function (functio laesa, which can be partial or complete, temporary or permanent). Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation. The term "inflammatory disease" may also refer to a dysregulated inflammatory reaction that causes an exaggerated response by macrophages, granulocytes, and/or T-lymphocytes leading to abnormal tissue damage and/or cell death. An inflammatory disease can be either an acute or chronic inflammatory condition and can result from infections or non-infectious causes. Inflammatory diseases include, without limitation, atherosclerosis, arteriosclerosis, autoimmune disorders, multiple sclerosis, systemic lupus erythematosus, polymyalgia rheumatica (PMR), gouty arthritis, degenerative arthritis, tendonitis, bursitis, psoriasis, cystic fibrosis, arthrosteitis, rheumatoid arthritis, inflammatory arthritis, Sjogren's syndrome, giant cell arteritis, progressive systemic sclerosis (scleroderma), ankylosing spondylitis, polymyositis, dermatomyositis, pemphigus, pemphigoid, diabetes (*e.g.*, Type I), myasthenia gravis, Hashimoto's thyroiditis, Graves' disease, Goodpasture's disease, mixed connective tissue disease, sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pernicious anemia, inflammatory dermatoses, usual interstitial pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis, pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic allergic alveolitis, Wegener's granulomatosis and related forms of angiitis (temporal arteritis and polyarteritis nodosa), inflammatory dermatoses, hepatitis, delayed-type hypersensitivity reactions (*e.g.*, poison ivy dermatitis), pneumonia, respiratory tract inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate hypersensitivity reactions, asthma, hayfever, allergies,

acute anaphylaxis, rheumatic fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis, ischemia (ischemic injury), reperfusion injury, allograft rejection, host-versus-graft rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, ileitis, iritis, laryngitis, myelitis, myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis, urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing fasciitis, and necrotizing enterocolitis. An ocular inflammatory disease includes, but is not limited to, post-surgical inflammation.

[0103] Additional exemplary inflammatory conditions include, but are not limited to, inflammation associated with acne, anemia (*e.g.*, aplastic anemia, haemolytic autoimmune anaemia), asthma, arteritis (*e.g.*, polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (*e.g.*, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, cermatomyositis, diverticulitis, diabetes (*e.g.*, type I diabetes mellitus, Type II diabetes mellitus), a skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with

brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, schleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis. In certain embodiments, the inflammatory disorder is selected from arthritis (*e.g.*, rheumatoid arthritis), inflammatory bowel disease, inflammatory bowel syndrome, asthma, psoriasis, endometriosis, interstitial cystitis and prostatistis. In certain embodiments, the inflammatory condition is an acute inflammatory condition (*e.g.*, for example, inflammation resulting from infection). In certain embodiments, the inflammatory condition is a chronic inflammatory condition (*e.g.*, conditions resulting from asthma, arthritis and inflammatory bowel disease). The compounds may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The compounds disclosed herein may also be useful in treating inflammation associated with cancer.

[0104] A "microorganism" refers to a single-celled organism, or a colony of such cells. In some embodiments, the microorganism is a eukaryote. In certain embodiments, the eukaryote is a species of yeast. In some embodiments, the microorganism is a prokaryote. In certain embodiments, the prokaryote is a species of cyanobacteria or a species of bacteria from the human microbiome. In certain embodiments, the prokaryote is *E. coli*. A "recombinant microorganism" refers to a microorganism that has been genetically altered to express one or more heterologous genes. The genome of the microorganism may be altered, for example, by genetic engineering techniques. In some embodiments, the microorganism is transformed with a vector comprising one or more heterologous genes (*e.g.*, heterologous nucleic acid encoding one or more MAA biosynthetic enzymes, as described herein).

[0105] The term "cyanobacteria" refers to members from the group of photoautotrophic prokaryotic microorganisms which can utilize solar energy and fix carbon dioxide. Cyanobacteria are also referred to as blue-green algae. The cyanobacteria species of the present invention can be selected from the group consisting of *Synechocystis*, *Synechococcus*, *Anabaena*, *Chroococcidiopsis*, *Cyanothece*, *Lyngbya*, *Phormidium*, *Nostoc*, *Spirulina*, *Arthrospira*, *Trichodesmium*, *Leptolyngbya*, *Plectonema*, *Myxosarcina*, *Pleurocapsa*, *Oscillatoria*, *Pseudanabaena*, *Cyanobacterium*, *Geitlerinema*, *Euhalothece*, *Calothrix*, and *Scytonema*.

[0106] The term "human microbiome" refers to the aggregate of all the microorganisms that reside on or within human tissues. In some cases, the human microbiome refers specifically to all of the species of bacteria that reside on or within human tissues. Species of human microbiome bacteria for use in the present invention can be selected from the group consisting of, but not limited to, *Achromobacter, Acidaminococcus, Acinetobacter, Actinomyces, Aeromonas, Aggregatibacter, Acidaminococcus, Anaerobiospirillum, Alcaligenes, Arachnia, Bacillus, Bacteroides, Bacterionema, Burkholderia, Bifidobacterium, Buchnera, Butyriviberio, Campylobacter, Capnocytophaga, Candida, Clostridium, Chlamydia, Chlamydophila, Citrobacter, Cornybacterium, Cutibacterium, Demodex, Eikenella, Epidermophyton, Enterobacter, Enterococcus, Escherichia, Eubacterium, Faecalibacterium, Flavobacterium, Fusobacterium, , Gingiva, Gordonia, Haemophilus, Lactobacillus, Leptotrichia, Malassezia, Methanobrevibacter, Morganella, Mycoplasma, Microbacterium, Micrococcus, Moraxella, Mycobacterium, Mycoplasma, Neisseria, Peptococcus, Peptostreptococcus, Plesiomonas, Porphyromonas, Propionibacterium, Providencia, Pseudomonas, Ruminococcus, Rothia, Ruminococcus, Sarcina, Staphylococcus, Streptococcus, Torulopsis, Treponema, Trichophyton, Veillonella, Vibrio, Wolinella,* and *Yersinia*.

[0107] The term "unnatural amino acid" refers to amino acids that are non-proteinogenic amino acids, *i.e.*, amino acids that are not L-alanine, L-arginine, L-asparagine, L-aspartic acid, L-cysteine, L-glutamic acid, L-glutamine, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, and L-valine. In some embodiments, the unnatural amino acid is an unnatural α-amino acid. In some embodiments, the unnatural amino acid is an unnatural β-amino acid. In some embodiments, the unnatural amino acid is an unnatural γ-amino acid.

[0108] Another object of the present disclosure is the use of a compound as described herein in the manufacture of a medicament for use in the treatment of a disorder or disease described herein. Another object of the present disclosure is the use of a compound as described herein for use in the treatment of a disorder or disease described herein. Another object of the present disclosure is the use of a compound as described herein in the manufacture of a sunscreen for use in skin protection described herein. Another object of the present disclosure is the use of a compound as described herein for use in skin protection described herein. Another object of the present disclosure is the use of a compound as described herein in the manufacture of a sunscreen for use as a cosmetic as described herein. Another object of the

present disclosure is the use of a compound as described herein for use as a cosmetic as described herein.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0109] The aspects described herein are not limited to specific embodiments, systems, compositions, methods, or configurations, and as such can, of course, vary. The terminology used herein is for the purpose of describing particular aspects only and, unless specifically defined herein, is not intended to be limiting.

Methods for Producing a Compound

[0110] In one aspect, provided herein are methods for producing a compound comprising a) culturing a recombinant microorganism under conditions suitable for production of the compound; and b) isolating the compound from the recombinant microorganism. In some embodiments, the recombinant microorganism comprises a heterologous nucleic acid encoding (*e.g.*, that encodes) one or more mycosporine-like amino acid (MAA) biosynthetic enzymes, wherein the one or more MAA biosynthetic enzymes comprise a D-alanine-D-alanine ligase (MysD), or a homolog thereof.

[0111] Exemplary MysD enzymes for use in the present invention include, but are not limited to, the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 1:

[0112] A0A1Z4LFR3 (SEQ ID NO: 1)

MPVLRILHLVGSAQDDFYCDLSRLYAQDCLAAMAELPYDSAIAYITPDGQWRFPRSL
SREDIAQAKPMPVSEAIEFIAAQNIDIVLPQMFCIPGMTYYRALFDLLEIPYIGNTPDL
MAITAHKARTKAIVEAAGVKVPRGEVLRRGDVPTITPPVVIKPVSSDNSLGVTLVKD
AAEYEAALEKAFEHGDEAIVETFIEGREVRCGIIVKDGELIGLPLEEYLIDSQEKPIRTY
ADKLKKTDDGSLGFAAKGNNKSWILDPNDPITQKVQEVAKKCHQALGCRHYSLFDF
RIDSQGQPWFLEAGLYCSFAPKSVISSMAKAVGIPLNELLTIAIAETLGSNKYSDRISV
VEINEPSKTPRKERELSQMI

[0113] Biosynthetic enzymes other than MysD may also be encoded by the recombinant microorganism used in the methods disclosed herein. In some embodiments, the one or more MAA biosynthetic enzymes further comprise a phytanoyl-CoA dioxygenase (MysH), or a homolog thereof. Exemplary MysH enzymes for use in the present invention include, but are not limited to, those of SEQ ID NOs: 2-12, or an amino acid sequence at least 70%, at least

75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of any one of SEQ ID NOs: 2-12:

[0114] A0A1Z4LFF0 (SEQ ID NO: 2)

MASLENQIILITGASSGIGTACAKIFAGAGAKLILAARRLERLQQLADILTQDFNTEVH
LLELDVRDRSAVESAISNLPASWSDIDILINNAGLSRGLDKLHEGSFTDWEEMIDTNIK
GLLYLSRYVVPGMVSRGRGHVVNLGSIAGHQTYPGGNVYCATKAAVRAISEGLKQ
DLLGTPVRVTSVDPGMVETEFSQVRFHGNAQRANQVYQGVTPLTPDDVADVIFFCV
TRSPHVNINEVVLMPVDQASATLVNRRT

[0115] A0A367QPY5 (SEQ ID NO: 3):

MLKVDTLKISSQQVEAFERDGVICVKNALDDIWVERLRTAVDRNISIPGPLEEKNAPR
PEGSVEHASSLWLVDADFRALAFESPLPTLAAQVLKSEKLNFLADGFFVKKPKTNGH
IGWHNDLPYWPVQGWQCCKIWLPLDTVKQENGRLEYIKGSHQWGKELRERSNPSW
FVEPEPHEILSWDMEAGDCLIHHFLTIHHSVTNISSTQRRAIVTNWTGDDVTYYQRPK
AWPFKPLEEIDLPEFNSFKTKKVGEPIDCDIFPRVEVFR

[0116] A0A2Z6D3B5 (SEQ ID NO: 4):

MLKLELPKITLQEIEAFEQDGVICVKNVLDNIWVERMRKAVDKNISIAGPLEVKGISK
PEGNVEHTNSLWLVDADFRALVFESPLATLAAQILKSTKLNFLADGFFVKQPKATSR
VGWHNDLPYWPIQGWQCCKIWLALDKVNQQNGRLEYIKGSHRWGKELREDSNPA
WFSQPESHELLSWDMEPGDCLVHHLLTIHHSVTNISSTQRRAVVTNWTGDDVTYYP
RPKAWPFRPLDEIDIPEFDSLKAKKPGEPIDCDMFPKIKWHR

[0117] A0A2T1LWM2 (SEQ ID NO: 5):

MLIANSSKISRQEVENFKRDGVICLKNVVDDYWVERMRKAVDRNLLNSNGVRGRK
LKTGDVVHDYGLWLKDNDFRDLVFKSPLARVAAQIMESETINFLCDGFFVKKAKAD
SHVGWHNDLPYWPVKGWKCCKIWLALDPVNQENGRLEYIKGSHLWNKDLRENSN
VSWFSEPSYSDILYWDMEPGDALVHHFQTIHHSIGNTTYKSRRAIVTNWTGDDVVY
DPSPQTWPFQPIEEIGISEFNSLDTLRSGESIDCEIFPKIDLTPSPSPTSRGEQNPNFLKFP
HRL

[0118] A0A2L2NS52 (SEQ ID NO: 6):

MLKVDTSKITTQQVEAFERDGVICVKNVLDDIWVERMRRAVDKNVLIPGPLEVKGIP
RAEGHVEHTSSLWLTDADFRALAFESPLATLTAQVLKSKKLNFLGDGFFVKKPKGET
GVGWHNDKSYWPIQGWQCCKIWLALDSVNQENGKLEYIKASHLWGKELREASDPS
WFVEPEPHEIISWDMEPGDCLVHHFMTIHHSVRNTSSTRRRAVVINWTGDDVTYERR
PNAWPFRPLEEIDIPEFESLKAKKSGEPIDCDIFPRVELHR

[0119] A0A2C6TQQ8 (SEQ ID NO: 7):

MLKVDTPKISPQQVEAFERDGVICVKNALDDIWIERMRKAVDKNISIPGPLEGKNTPK
KEASAEHTSSLWLVDADFRALAFESPLPKLAVGVLKSEKLNFLADGFFVKRPEANGR
IGWHNDLPYWPVQGWQCCKIWLALDTVKQENGRLEYIKGSHQWGRELRERSNPSW
FVEPEPHEILSWDMEAGDCLIHHFLTIHHSVTNKSSTQRRAIVTNWTGDDVTYYQRP
KAWPFKPLEEIDLPQFNSLKTKKFGEPIDCDIFPRVEVHRHRTHI

[0120] A0A252E419 (SEQ ID NO: 8):

MLKIDTLKISLQQIEAFERDGVICLRNVLDESWVERMRTAVDKNVSIPGPLEVKGISR
PEASVEHTSSLWLVDPDFRALVFESPLSTIAAQLLRSEKLNFLADGFFVKKPKATSRV
GWHNDLPYWPIQGWQFCKIWLALDNVNEENGRLEYIKGSHQWGKELREDSNPSWF
VEPEPHELLSWDMEPGDCLVHHLLTIHHSVTNISSRQRRAVVTNWTGDDVTYYPRL
KAWPFRPLEEIDLPEFNSLKTKKTGEQIDCYMFPPIQLHR

[0121] A0A1Z4LFC6 (SEQ ID NO: 9):

MLKVDTQKISPQQVEAFERDGVICVKNAVDDIWVERMRTAVDKNISIPGPLEDKNVP
KPQGSAEHASSIWLIDADFRALAFESPLPTLAAQVLKSKKLNFLADGFFVKKPESNGR
IGWHNDLPYWPVQGWQCCKIWLALDTVKQENGRLEYIKGSHQWGKELRERSNPSW
FIEPEPHEILSWDMEAGDCLIHHFLTIHHSVTNISSTQRRAIVTNWTGDDVTYYQRPK
AWPFKPLEEIDLPEFNSLKTKKSGEPIDCDIFPRVQVHR

[0122] A0A1Z4IIA4 (SEQ ID NO: 10):

MLKLDLPKITLQEIEAFEQDGVICVKNVLDNIWVERMRKAVDKNLSIAGPLEVKGIT
KPEGNVEHSNSLWLVDTDFRALVFESPLANLAAQFLKSTKLNFLADGFFVKQPKASS
RVGWHNDLPYWPIQGWQCCKIWLALDKVNQQNGRLEYIKGSHRWGKELREDSNPS
WFSEPEPHELLSWDMEPGDCLVHHLLTIHHSVTNISSTKRRAVVTNWTGDDVTHYP
RPKAWPFRPLDEIDIPEFDSLKAKKPGEPIDCDMFPKIKWHR

[0123] A0A1Z4HWL1 (SEQ ID NO: 11):

MLKIDTSKISFQQIGAFERDGVICLRNVLDENWVERMRTAVDKNVSINGPLEAKGISR
AEASVEHTSSLWLVDPDFRALVFESPLSTIAAQLLQSEKLNFLADGFFVKKPKATSRV
GWHNDLPYWPIQGWQCCKIWLALDHVNEKNGRLEYIKGSHKWGKELREDSNPLWF
VEPEPHELLSWNMEPGDCLVHHLLTIHHSVTNISSTQRRAVVTNWTGDDVTYYPRPK
AWPFRSVEEIDLPEFNSLKTKKTGEPIDCDMFPQVQLH

[0124] A0A1U7I924 (SEQ ID NO: 12):

MLKVDTRKISHQQVEAFERDGVICVKNAVDDIWVQRMRTAVDKNVLIPGPLEEKNA
PKPEASAEHTSNLWLVDADFRALAFESPLPTLAVQVLKSKKLNFLADGFFVKKPKSN
SRIGWHNDLPYWPIQGWQCCKIWLALDTVNQENGRLEYIKGSHRWGKELRERSNPS

WFVEPKPHEILSWDMEAGDCLIHHFLTIHHSVTNISSRQRRAVVTNWTGDDVTYYQR
PKAWPFKSIEEIDLPQFNSFKTKKSGEPLDCDIFPRIEVHR

[0125] In some embodiments, the one or more biosynthetic enzymes comprise an ATP-grasp enzyme (MysC), or a homolog thereof. Exemplary MysC enzymes for use in the present invention include, but are not limited to, the amino acid sequence of any one of SEQ ID NOs: 13-105, or an amino acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of any one of SEQ ID NOs: 13-104:

[0126] A0A0Q2QHP0 (SEQ ID NO: 13)

MSGVRVHRIWDAGPGRTVAALAALCATLPVDLAVVLVALLVGRQPPRGRLPAEAR
RTVLLNGGKMTKALQLARSFHLAGHRVILVESAKYRWTGHRFSRAVDAFYCVPEPG
TPGYAPALLNIVRYENVDVYVPVSSPAGSVPDAVARELLDGACDVVHSDAKTVQLL
DDKAEFASTAASLSLQVPDSHRITDARQVADFPFPPGRSYILKRIAYNPVGRMNLTRL
SAATPDRNAAYARSLSISEDDPWILQEFIEGREYCTHGTARSGRLQVYGCCESSAAQ
VNYRSVDKPEIRRWVETFVKNLNLSGQVSFDFIEAHDGQVYAIECNPRTHSAITMFH
DHPDLAAAYLNDGHPLITPKHNSRPTYWIYHELWRLLRHPGRLGRLATILRGTDAIFT
GWDPVPYLMVHHLQIPALLWANLRVGKGWSRIDFNIGKLVENGGD

[0127] A0A3S0TU06 (SEQ ID NO: 14)

MGRTLATLVVLFGTLPFDLALVLVALLAGRRPSRGRLPAQARRTILLNGGKMTKAL
QLARSFHLAGHRVILVESEKYRWTGHRFSRAVDAFYCVPEPTEPGYALALLDIVRYE
NVDVYVPVSSPAGSVPDAVARELLDGACDVVHSDAKTVQLLDDKAEFASTAASLSL
RVPDSHRITDARQVVDFAFPAGRSYILKRIAYDPVGRMNLTRLSGATPDHNAAYARS
LPISEDDPWILQEFIEGREYCTHGTARSGRLQVYGCCESSSAQVNYRNVDKPEIRRWV
ETFVKNLNLSGQVSFDFIEARDGQVYAIECNPRTHSAITMFHDHPDLAAAYLDDNHP
LITPNDGARPTYWIYHELWRLLRHRGRISRLVTMLRGKDAIFAGWDPMPYLMVHHL
QIPALLWANLRAGKGWSRIDFNIGKLVENGGD

[0128] A0A5A7SAT3 (SEQ ID NO: 15)

MREVFQAKTIGTLALLQVVLPLNLALTTFALLRGVFVAPPPVAVAAQRKTILVSGGK
MTKALQLARSFHAAGHRVVLVESSKYRFNGHRFSRAVDRFYTVPAPDSDNYAVALL
AVVRAEEVDVYVPVCSPVASYYDALAKDQLSPHCEVLHCDADMVARLDDKYEFFA
LVASLGLSTPETHRVTAPGQVEEFDFTGTDYILKSIPYDPVHRRDMTTVPRPTATETT
TYARSKPITEATPWIMQEFVRGQEYCTHSLVRDGAVQVFCCCESSAFQINYRMVDKP
EIEEWVGEFAQRLNLTGQVSFDFIQGDDGRLHAIECNPRTHSAITMFYDHPDLARAY

LERGVPVVKPLPHSKPTYWIYHELWRLVTQRGGRAHRLAVIAQGKDAIFDWDDPLP
FLLVHHLQIPSLLLSNLLRRKGWTGIDFNIGKLIEAAGD

[0129] A0A0G4HZ53 (SEQ ID NO: 16)

MCRVETRPQVGEHAGMESVPLKAAEGGLVEERKAFLPQSYSLWKDSIEGRLWSLLT
LFGLFISSPFLFAFVALSVLSAVVRKLLRLPAARKLPEGSNKGRGRTALVTGGKMTKS
LDVCRHLKNEGFRVILTETPRYWMSASRFSSAVDKFVVLPVAPETHPEGYVEALRNL
FEKENVSLFAPVCSPFSSLYDAKAAESLPEGAISWSLPAEMVQQLDDKVEFARMAKE
VGLPVPDTLRVESKEEVRRFNSELAEKWRRDSSSAIASGAEKKKTDCRRYILKTLDY
DPMRRLDLFTLPCGPKELEKYLDETTISPDRPWLVQEFLEGREYSSCALSWKGKLLA
FTDNEAVISCYNFKYAGRDKIQEWVRVFCEKYQLSGVICVDFFERADGTQLAIECNP
RFSSNMTAFYNNPRLGAAMADPDLALRSGVTETPLPSSKESNWTLVDLYFHSYTQM
MKNPLAAFTAAAGLLLVSEETKEKQDAYWAPEDPLPSLALHCFHMPALLVRNVWD
GRKWAKIDFCIGKMTEENGD

[0130] R1G4T9 (SEQ ID NO: 17)

EVKPNGKVAIVSGGKMTKAYVIARQLKAQGCRVVLLETSKYWMVASRASNCVDRF
AMVPLPEKDLAGYLDAVRALAIEEKADLFIPVTSPAASEYEAQVAPVLPAGCVSWSL
DLETVRDLDDKTAFCSSAERLGLPAPRSHRVASDEEAHAFNEKLLAEAATATAGAET
RYILKSLAYDSMHRLDLFTLPCAPDNPWIIQTFVVGDEYSTCALVKEGRLLAFTDNR
ACLSCFNYTPARSEALRSWVRDFCAARRLSGVVCIDFIVDAQSGTPYAIECNPRFSSN
VLNLFWNPPFGGALFRPHKGGGVEAFFWPPPPPPPLQIWALLSKRPFSLRSAGALLST
VATKKDAYFDVADPLPFIAHLFVHIPALLARNLSTGNKWAKIDPCIGKLTEENGD

[0131] A0A433W0B3 (SEQ ID NO: 18)

MLLPQSITPTMQIFAVFQNLGTLLLLAIAFPFNCIVVLTALLWNLVSKPFRDRGILPVH
PKNIMLTGGKMTKALQLARSFHMVGHRVVLVETHKYWLTGHRFSNAVDRFYTVPA
PEKDPEAYSQALLAIAKQENIDVYVPVCSPVASYYDSVAKSVLSGCCEVFHFDAEVT
QMLDDKYEFAEKARSLGLSVPKSFKITNPEQVINFDFSDAERPYILKSIPYDSVRRLNL
TKLPCATPAETAAFVNSLPISPEKPWIMQEFIPGQEYCTHSTVRNGELRMHCCCESSA
FQVNYENVDKPEILAWVRHFVKELGITGQASFDFIQAEDGNVYAIECNPRTHSAITMF
YNHPGVADAFCRDVTCNTSTSRAGLLNSSFINNISGEPAPTIYPLQPLSTSKPTYWTY
HELWRLTGIRSFPQLQTWCKNILRGKDAIFAIDDPLPFLMVHHWQIPLLLLDNLRRLK
GWIRIDFNIGKIVELGGD

[0132] A0A139WZN8 (SEQ ID NO: 19)

MTQSISFSSPVPATPPISVKARFIALFQNLGTLTLLLLALPVNAVIVVISLVWNSLTRLF

STQQTTVARSKNILISGGKMTKALQLARSFGAAGHRVVLIETHKYWLSGHRFSNAVS
RFYTTPTPQYDPEAYIQTLIDIVKRENIDVYVPVTSPVASYYDSLAKPALSPYCEVLHF
DADVTKMLDDKFAFSEKARDLGLSVPKSFKITNPEQVLNFDFSQETRKYILKSIPYDS
VRRLDLTKLPCDTLEETAAFVKSLPISPEKPWIMQEFIPGKEFCTHSTVRNGELRLHCC
SESSAFQVNYENVENPEIQAWVKHFVNGLGFTGQVSFDFIQTDDGKVYAIECNPRTH
SAITMFYNHPQVSDAYLGTEPLTEPLQPLPNSKPTYWLYHEVWRLTGIRSFSQLQNW
VRNIFRGTDAIYKLHDPLPFLTVHHWQIPLLLLNNLWQLRGWTKIDFNIGKLVEFGG
D

[0133] A0A2Z5X784 (SEQ ID NO: 20)

MLCPYERLVFCLKEKLMTQSIPLSFSQPTTPLTVVKTKIVALFKTLGTLALLLLALPLN
GFVVLISLLWVIVRNPFTKPTAVAAHPQNILVSGAKMTKALQLARSFHAAGNRVILIE
GHKYWLSGHRFSNAVSRFYTVPAPQDDPESYTQALLEIVKKEKIDVYIPVCSPVASY
YDSLAKPVLSEYCEVFHFDADITAMLDDKFAFTDQARSLGLSVPKSFKITDPEQIINFD
FSQETRKYIIKSISYDSVRRLNLTKLPCDTPEETAAFVRSLPISPEKPWIMQEFIPGKEL
CTHSTVRDGELRLHCCSNSSAFQINYENVENPQIREWVQHFVKSLRLTGQVSFDFIQA
EDGTVYAIECNPRTHSAITMFYNHPGVAQAYLGKTPQAAPLEPLADSKPTYWLYHEI
WRLTSIRSWKHLQTWFKNLVRGTDAIYSMDDPIPFLTLHHWQITLLLLQNLQQLKG
WVKIDFN

[0134] A0A1Z4GTP3 (SEQ ID NO: 21)

MAQSISLSLPSSTTPSTGVRVKIVALFKTLGTLTLLLIALPFNALIVLIALLWGIARSPF
TKKAVVAANPQTILVSGAKMTKALQLARSFHAAGHRVILIEGHKYWLSGHRFSQAV
SRFYTVPAPQSDPEAYIQALVEIVKKEKVDIYVPVCSPVASYYDSLAKPTLSEYCEVF
HFDADITKMLDDKFAFTDKARSLGLSVPKSFKITDPQQVINFDFSQETRKYILKSIAYD
SVRRLDLTKLPCDSPEETAAFVNSLPISPENPWIMQEFIPGKEFCTHSTVRDGELRLHC
CCHSSAFQINYENVENPQIREWVQQFVKSLRLTGQVSFDFIQAEDGTVYAIECNPRTH
SAITMFYNHPGVAEAYFGKTPLAAPLEPLASSKPTYWIYHEIWRLTNIRSWKQLQTRL
NILFRGTDAIFRLNDPVPFLTLHHWQIPLLLLQNLQKLKGWVKIDFNIGKLVELGGD

[0135] A0A1Q4RU46 (SEQ ID NO: 22)

MAQSISLSSPAKTHAPGISASSLKTLGTLTLLLLALPLNASLVLVALLLKSLRPQNVTT
EEPKNILISGGKMTKALQLARSFHEQGHRVILLEAHKYWLTGHRFSFAVNKFYTVEA
PEKDPEGYIQSLVNIVEKENIDVYVPVCSPVASYYDSLAKKALPQCEVIHCDAEMTQ
MLDDKYAFAQTAQSFGLSVPKSFKITEPEQVINFDFSQEKRKYILKSIPYDSVRRLDLT
KLPCDTPEATAAFVRSLPISPEKPWIMQEFIPGKEYCTHSTVRNGVITLHCCCESSAFQ
VNYENVDNPKIFEWVSRFVKELGITGQVSFDFIEAEDGNIYAIECNPRTHSAITMFYN

HPGVADAYLGTGSNLAEPIQPKSTSKPTYWTYHEVWRLITTRSWSDFVYRFKIITHG
KDAIFSWQDPLPFLMNPHWQIFLLLIQNLQKNRGWVRIDFNIGKLVELGGD

[0136] A0A0C2R3C6 (SEQ ID NO: 23)

MAQSLPLTSAGGATSPTAFVAQVKALFQNIATLTILLLVLPINAAIVLTSLFWSRVSRF
VRPQTVVAANRKNILISGGKMTKALQIARSFHAAGHRVVLIETHKYWLSGHRFSDAI
SRFYTTPTPQYDPEAYIQALLDIVKKENIDVYVPVTSPVASYYDSLAKPALSPYCEVF
HFDADVTQMLDDKFAFSEKARSFGLSVPKSFKITNPEQVLNFDFSGETRKYILKSIPY
DSVRRLDLTKLPCDTPEETAAFVRSLPISPEKPWIMQEFIPGKEFCTHSTVKNGELRLH
CCAESSAFQVNYENVENPKIQEWVRHFVKELGITGQVSFDFIQAEDGTVYAIECNPRT
HSAITMFYNHPDVADAYLSEEPFTEPLVPLPNSKPTYWTYHEVWRLTGIHSFAQLQT
WIRNFLQGTDAIYQLDDPLPFLMVHHWQIPLLLLNNLRQLKGWTKIDFNIGKLVEIG
GD

[0137] A0A2R5FKA4 (SEQ ID NO: 24)

MRKYIFVVFQNLGTLVLLAIAFPLNCIVVLTSLLWNFLKQPFNKSIVVNPNSKNILIAG
ARMTKTLQLARSFHAAGHRVIIIDIEKFWSSGNKYSNSVAGFYTVPDPSKDLEGYVES
LHAIAKTEKIDFFIPVAIFSVIHYDQGQPPLPDFVEFFHFDADVTKILDDKFAFAETARS
FGLSVPKSFKITHPEQVINFDFSHEKRKYILKSIPYDQIRRLNLTKLPCATSAETAAFVN
SLPISEENPWIMQEFIPGKEYCTHTTARDGESRMYCCCESSAFQVNYENVDQQEIMQ
WATHFTKELGKTGQLSFDFIQAEDGTVYAIECNPRTHSAITMFYNHPGVADAYLGKE
PLAESLQPLADSKPTYWLYHEVWRLNEIRNFEQLQTWVRNIRRGKEAIFEVSDPLPFL
MVHHWQIPLLILDNLRRLKGWIRIDFNMGELIE

[0138] A0A0M0SH70 (SEQ ID NO: 25)

MTQSISVASPAPKTQSVPLGLRISALWKNVGTLALLLLVLPINAVIVLVSLLLGHQSQ
AIATEPKNILISGAKMTKALQLARSFHAAGHRVVLVETHKYWLTGHRFSKAVSRFYT
VPTPQSDPEAYTQALLDIVKTENIDVYVPVCSPIASYYDSLAKPVLSKFCEVFHCDAD
VTQMLDDKYAFAEKARSLGLSVPKSFKITDPEQILNFDFSQEKRQYILKSIPYDSVRR
LDLTKLPCETPEATADFVNSLPISPQKPWIMQEFIPGKEYCTHSTVRNGELRMHCCCE
SSAFQVNYENVDHPQILEWVRHFVKALGITGQVSFDFIQAEDGTIYAIECNPRTHSAIT
MFYNHPHVADAYLSEIPQLEPIQPLTNSKPTYWTYHEIWRLTGIRSFSQLQTWLKTFF
GGKDAIYCFSDPLPFLTVHHWQIPLLLLQNLQQLKGWIRIDFNIGKLVEFGGD

[0139] A0A2T1F866 (SEQ ID NO: 26)

MLLPQSITPTMQIFAVFQNLGTLLLLAIAFPFNCIVVLTALLGNLVSKPFRDRGILPVS
HPKNIMLTGGKMTKALQLARSFHMVGHRVVLVETHKYWLTGHRFSNAVDRFYTVP
APEKDPEGYSQALLAIAKQENIDVYVPVCSPVASYYDSVAKSVLSGCCEVFHFDAEV

TQMLDDKYEFAEKARSLGLSVPKSFKITNPEQVINFDFSDAERPYILKSIPYDSVRRLN
LTKLPCATPAETAAFVNSLPISPEKPWIMQEFIPGQEYCTHSTVRNGELRMHCCCESS
AFQVNYENVDKPEILAWVRHFVKELGITGQASFDFIQAEDGNVYAIECNPRTHSAIT
MFYNHPGVADAFCRDVTCNTSTSRAGLLNSSFINNISGEPAPTIYPLQPLSTSKPTYW
TYHELWRLTGIRSFPQLQTWCKNILRGKDAIFAIDDPLPFLMVHHWQIPLLLLDNLRR
LKGWIRIDFNIGKIVELGGD

[0140] A0A367QNV7 (SEQ ID NO: 27)

MAQSISVSSSPAIPSFPSETKIAVIIQNLLTLALLLLALPINATIVLVTLLWHTISRPFQQP
ATKAANPKNILISGGKMTKALQLARSCNAAGHRVVLIETHKYWLSGHRFSQAVDKF
YTVPAPQENPERYTQALIDIIKQENIDVYIPVTSPLGSYYDSLAKPLLSKYCEVFHFDA
DITERLDDKFAFAETARSLGLSVPKSFKITKAEQVLNFDFSQESRKYILKSIPYDSVRR
LDLTKLPCATPEETAAFVRSLPISPEKPWIMQEFIPGKEFCTHSTVRDGELRLHCCCES
SAFQVNYENVENSQIREWVRHFVKELKLTGQVSFDFIQAEDGKVYAIECNPRTHSAIT
TFYDHPQVAQAYLDNEPMAQTLQPLPSSKPTYWTYHEVWRLTGIRSLTQFKKWIANI
WRGTDAIYKSDDPLPFLMVHHWQIPLLLIKNLRQLKGWTRIDFNIGKLVELGGD

[0141] A0A2N6JWS5 (SEQ ID NO: 28)

MAQLQSIQASIFAVLQNLGTLALLMIAFPFNCIVVLLSLLLNFLSRPFHKPVILTKNPR
NIMIAGARMTKTLQLARSFHAAGHRVILVDTEKFWLSGNQFSHAVAGFYTVPDPHK
DLEGYTQALRAIAKKENIDFFIPVAIFAVIYYDSMSQHQLFDCCEVFHFNADVTKMLD
DKFAFAEKARSLSLSVPKSFKITAPEQILNFDFSNEKRKYILKSIPYDAVRRLNMTLLP
CDTPEQTAAFVKSLPISEEKPWIMQEFIPGKEYCTHSTVRDGKQTIYCCCESSAFQVN
YENVDKPEILQWVNHFVKELGLTGQISFDFIQAVDGTVYVIECNPRTHSAITMFYNHP
GVADAYLSKQPLAEPLQPLSDSKPTYWLYHEVWRLNEIRSLKQLQTWIKNILRGKDA
IFTVNDPLPFLMVHHWQIPLLLLDNLRRLKGWIRIDFNPLLSL

[0142] B4VP63 (SEQ ID NO: 29)

MTNSLILAVLQNLGTLTLLAIAFPFNLTVVVVALVWDSLTRPFQNPKVANPNPKTIM
LTGGKMTKSLQLARSFYADGHRVILVESHKYWLVGHRFSRAVDRFYTVPAPNKDPD
GYMEGLLAIAKQENVDVYVPVCSPVASYYDSLAKPVLSGCCEVFHFDPDVTQLLDD
KFAFAQKAREFGLSVPKSFKITDPQQVIDFDFRGEKRKYILKSIPYDSVRRLNLTKLPC
KTPSETAAFVKSLPISEDKPWIMQEFIPGKEYCTHSTVRNGELRLHCCCESSAFQVNY
ENVDQPDILQWVSRFVQGLNLTGQASFDFIKTEDGIVYAIECNPRTHSAITMFYNHPG
VAEAYLSDTPLPEPLQPLPESKPTYWLYHEVWRLNEIRSFGDIRRWFKTVFGGKDAIF
QVNDPLPFLMVHHWQIPLLLLDNLRRMQGWIRIDFNIGKLVELGGD

[0143] K9QUQ5 (SEQ ID NO: 30)

MAQSISFDSSPATPSLGLETKIAAIIQNILTLALLLLALPINAIIVCIALVLGTIFRPQTTK
TSNPKNILISGGKMTKALQLARSFHADGHRVVLLETHKYWLTGHRFSQAVDKFYTT
PAPQKKPEDYIKALVDIVKRENIDVYIPVTSPVGSYYDSLAKPELSHHCEVFHFDAEIT
QMLDDKFAMAEKARSLGLSVPKSFKITSGEQVINFDFSRETRKYILKSIAYDSVRRLD
LTKLPCATPEETAAFVRKLPISPEKPWIMQEFIPGKEFCTHSTVRDGEIRLHCCCESSA
FQVNYENIENPQILEWVRHFVKELKLTGQISFDFIQTEDGQVYAIECNPRTHSAITTFY
NHPQVAEAYIGKQPMAETLQPLATSKPTYWTYHEIWRLTGIRSFTQLKTWLKNIWR
GTDAILQLHDPLPFLMVHHWQIPLLLLNNLRQLKGWTRIDFNIGKLVEFGGD

[0144] A0A0S3U2V2 (SEQ ID NO: 31)

MLNKLIAALQNLLTLTALLITLPINLAIVLIASLIGLFQRETIPQSNSPKRILITGGKMTK
ALQLARSFHAAGHFVVLVETQKYWLTGHQFSNAVDRFYTVPAPKQDSEAFIQALVD
IVQRENIDFFVPVTSPIESYYCSLAKPELSKYCEVLHFDVGITQLLDDKFELSEKARSL
NLTAPKTYRITDPQQVLDFEFDSSQYILKSIAYNSVHRLDMTKYPLESKAAMKAHLA
TLPISEDNPWILQEFISGQEYCTHSTVRDGKVRLHCCAKSSAFQVNYEQVENSEIQAW
VTTFVKALNLSGQISFDFIESSSGEVYAIECNPRTHSAITMFYNHPDVAKAYLGEPLTV
EPIQPLPTSKPTYWTYHEVWRLITGDRPLYRLQTILHGKDAILQTSDPIPFLMVHHWQI
PLLLLNNLRHLKGWVRIDFNIGKLVELGGD

[0145] K9TVZ3 (SEQ ID NO: 32)

MLLPQSITPTMQIFAVFQNLGTLLLLAIAFPFNCIVVLTALLWNLVSKPFRDRGILPVS
HPKNIMLTGGKMTKALQLARSFHMVGHRVVLVETHKYWLTGHRFSNAVDRFYTVP
APEKDPEAYSQALLAIAKQENIDVYVPVCSPVASYYDSVAKSVLSGCCEVFHFDAEV
TQMLDDKYEFAEKARSLGLSVPKSFKITNPEQVINFDFSDAERPYILKSIPYDSVRRLN
LTKLPCATPAETAAFVNSLPISPEKPWIMQEFIPGQEYCTHSTVRNGELRMHCCCESS
AFQVNYENVDKPEIIAWVRHFVKELGITGQASFDFIQAEDGNVYAIECNPRTHSAITM
FYNHPGVADAFCRDVTCNTSTSRAGLLNSSFINNISGEPAPTIYPLQPLSTSKPTYWTY
HELWRLTGIRSFPQLQTWCKNILRGKDAIFAIDDPLPFLMVHHWQIPLLLLDNLRRLK
GWIRIDFNIGKIVELGGD

[0146] A0A2N6MZD6 (SEQ ID NO: 33)

MAQLQSIQASIFAVLQNLGTLALLMIAFPFNCIVVLLSLLLNFLSRPFHKPVILTKNPR
NIMIAGARMTKTLQLARSFHAAGHRVILVDTEKFWLSGNQFSHAVAGFYTVPDPHK
DLEGYTQALRAIAKKENIDFFIPVAIFAVIYYDLMSQHPLFDCCEVFHFNADVTKMLD
DKFAFAEKARLLSLSVPKSFKITAPEQILDFDFSNEKRKYILKSIPYDAVRRLNMTLLP
CDTPEQTAAFVKSLPISEEKPWIMQEFIPGKEYCTHSTVRDGKQTIYCCCESSAFQVN

YENVDKPEILQWVNHFVKELGLTGQISFDFIQAVDGTVYAIECNPRTHSAITMFYNHP
GVADAYLSKQPLAEPLQPLSDSKPTYWLYHEVWRLNEIRSLKQLQTWVKNILRGKD
AIFTVNDPLPFLMVHHWQIPLLLLDNLRRLKGWIRIDFNIGELIE

[0147] A0A218PXL8 (SEQ ID NO: 34)

MAQSISLSLAKSPGSSTGVWVKLVALFKTLGTLTLLLIALPFNALIVLISLLWGFVRSP
FRQKAVVADHPQTILVSGAKMTKALQLARCFHAAGHRVILIEGHKYWLSGHRFSKA
VSGFYTVPAPELDPLGYIQALVEIVKKEKVDVYVPVCSPVASYYDSLAKPALSEYCE
VFHFDADVTKMLDDKFAFTDQARSLGLSVPKSFKITDHQQVINFDFSQETHKYILKNI
AYDSVRRLNLTKLPCDTPEETAAFVNSLPISEENPWIMQEFIPGKELCTHSTVRDGEL
RLHCCSDSSAFQINYENVENPQIREWVQHFVKSLALTGQVSFDFIQAESGTVYAIECN
PRTHSAITMFYNHPGVAEAYLGKTPLTDLTEPLANSKPTYWIYHEIWRLTGIRSWKQ
LQTSINTLAQGTDAVYQLDDPIPFLTLHHWQIPLLLLKNLQQLKGWVKIDFNIGKLVE
LGGD

[0148] A0A1Z4HW63 (SEQ ID NO: 35)

MAQSISLSLPESTTPATSVGVKIAALFKTLGTLTLLLIALPFNALIVLIALLWGIVRSPF
TKKAVVAAHSQTILVSGAKMTKALQLARSFHAAGHRVILIEGHKYWLSGHRFSQAV
SRFYTVPAPQSDSEGYIQALVEIVKQEKVDIYVPVCSPIASYYDSLAKPALSEYCEVFH
FDADITKMLDDKFAFTDKARSLGLSVPKSFKITDPQQVINFDFSQETRKYILKSIAYDS
VRRLDLTKLPCNTSEETAAFVNSLPISPENPWIMQEFIPGKEFCTHSTVRDGELRLHCC
CHSSAFQINYENVENPQICEWVQQFVKSLQLTGQVSFDFIQAEDGSVYAIECNPRTHS
AITMFYNHHGVADAYFGKTPLAAPLEPLASSKPTYWIYHEIWRLTGIRSWKQLQTSV
NTLLRGTDAIYNLNDPVPFLTLHHWQIPLLLLKNLQQLKGWVKIDFNIGKLVELGGD

[0149] A0A1Z4LYV8 (SEQ ID NO: 36)

MAQSSVSVSASQPIAPPTSIGMRFFALFQNLATLTLLLLALPINATIVLTTLLLNILTSP
FQKKQTTVVATEKKNILISGGKMTKALQLARFFHSAGHRVILTETHKYWLSGHRFSQ
SVDKFYTTPVPQKDSQAYTQALIDIINKEGIDIYIPVTSPIASYYDSLAKPALSEYCEVF
HIDAATCEMLDDKFAFSEKARSFGLSIPKCFKITNPEQVINFDFSGETRKYILKSIPYDS
VRRLDLTKLPCDTPEETEAFVRSLPISPQKPWIMQEFIPGKEYCTHSTVRDGVMRLHC
CCESSAFQVNYENVENPKIREWVTHFVKELGVTGQLSFDFIEAEDGNVYAIECNPRT
HSAITIFHDQLQQAANAYLSKEPIAAPLQALPNSKPTYWTYHEFWRLNEIRSLSQLGN
WIKNMLRGTDAIYTFDDCLPFLMVHHWQIPVLLLKNLSKLKGWTRIDFNIGKLVELG
GD

[0150] A0A654SJH1 (SEQ ID NO: 37)

MAKSVSLSLAKSTTPSTDVRLKLVALFKTLGTLTLLLIALPFNGLIVLIALLWGIVQWP
LRKKALVAADPRTVLVSGGKMTKALQLARCFHGAGHRVILIETHKYWLSGHKFSRA
VSAFYTVPSPQSDPEGYIQSLVAIVKKEKVDFYVPVCSPVASYYDSLAKPALSAYCEV
FHFDADITKMLDDKFAFTEQGRSLGLSVPKSFQITDPQQVINFDFSQETRKYILKNIAY
DSVRRLNLTKLPCNTPEETAAFVNSLPISAQNPWIMQEFIPGKELCTHSTVRDGELRL
HCCSNSSAFQINYQNVENPQIRQWVQQFVKSLGLTGQVSFDFIQAEDGTVYAIECNP
RTHSAITMFYNHPGVADAYLGKTPQAAPVEPLANSKPTYWLYHEIWRLTGIRSWKQ
LQTSVNTLVGGTDAIFCFDDPVPFLTLYHWQIPLLLLKNLQDLKGWVKIDFNIGKLVE
LDGD

[0151] A0A2C6VZE1 (SEQ ID NO: 38)

MAQSISVSSSPAIPSFPSETKIAVIIQNLLTLALLLLALPFNATIVLVTLLWHTISRPFQ
QATTKTANPKNVLISGAKMTKALQLARSFNAAGHRVVLIETHKYWLSGHRFSQAVD
KFYTVPAPQENPERYTQALIDIIKQENIDVYVPVTSPLGSYYDSLAKPMLSNYCEVFH
FDADITQKLDDKFAFAETARSLGLSVPKSFKITSAEQVLNFDFSQESRKYILKSIPYDS
VRRLDLTKLPCATPEETAAFVKSLPISPEKPWIMQEFIPGKEFCTHSTVRNGELRLHCC
CESSAFQVNYENVENSQIREWVRHFVKEQKLTGQVSFDFIQAEDGRVYAIECNPRTH
SAITTFYDHPQVAQAYLDKEPMAETLQPLPTSKPTYWTYHEVWRLTGIRSFTQLKK
WIANIWRGTDAIYKPDDPLPFLMVHHWQIPLLLLKNLRQLKGWTRIDFNIGKLVELG
GD

[0152] A0A2T1EQS1 (SEQ ID NO: 39)

MLALFQNLGTLLLLALAFPFNCIVVLVALLTKPKLPQATVAKAQNILISGGKMTKAL
QLARSFYAAGHRVVLIETDKYWLTGHRFSRAVDAFYTVPAPQKDPEAYIQALVNIA
KKENIDVYIPVCSPISSYYDSLAKPALAGCCEVFHFDADITKMLDDKFAFAQTAQSFG
LSVPKSYKITHPQQVLDFDFSTEQNKYILKSIPYDSVRRLNLTKLPCNTRAETAAFVN
SLPISEEKPWIMQEFITGKEYCTHSTVRDGELRLHCCCESSAFQVNYENVDQPEILQW
VSHFVKQLGVTGQASFDFIRAENGNIYAIECNPRTHSAITMFYNHPGVASAYLSSQPL
KPLQPLTDSKPTYWLYHEVWRLNEIRSLQQLQTWFKNIRRGKESIFAFNDPLPFLMV
HHWQIPLLLLDNLRRLAGWIRIDFNIGKLVEFGGD

[0153] A0A1E5QWM1 (SEQ ID NO: 40)

MFSTTFKSLGTLALLKLALPFNLTLVLIASIINIFSTPFKIKKKPNINSKTVLLTGGKMT
KALQLARSFYSAGHRVILVETHKYWLSGHRFSVAVDKFFTIPDPVKDKEGYIDGLLDI
VKRENVDIFIPVSSPVASYYDSVAKMVLSPYCKVLHFDVEMTLVLDDKASLCQKASS
LGLTSPASYLITDVQEILDFDFSKNNHKYILKSIKYDSVYRLNMTQFPFEGMEEYVRS

LPISEENPWVMQQFITGQEYCTHSTVLNGKIRLHCCSMSSHFQVNYEHVDNQKIYEW
VEEFVGKLNLTGQISFDFIQTDDGTVYPIECNPRTHSAISMFYNHPLVADAYLNDGDD
APITPLESSKPTFWTYHELWRLTEVRSPQDLSQWWQKVTKGQDGIFSWQDPLPFLM
VHHWQIPLLLFGNLIKLKPWVKIDFNIGKLVESAGD

[0154] A0A2I8ACV8 (SEQ ID NO: 41)

MAQSISFDSSPATPSLGLETKIAAIIQNILTLTLLLLALPINTAIVFIYLVVGAIFRPQTSK
TSNPKNILISGGKMTKSLQLARSFHAPGHRVVLVETHKYWLTGHRFSQAVDKFYTTP
APQKDPEAYIQALEEIVKRENIDVYIPVTSPVGSYYDSLAKPKLSPHCEVLHFDAEITQ
MLDDKFAMAEKARSLGLSVPKSFKITSSEQVINFDFSGETRKYILKSIPYDSVRRLDLT
KLPCATPEETAAFVRNLPISPEKPWIMQEFIPGKEFCTHSTVRDGEIKLHCCCESSAFQ
VNYENVENPQILEWVKHFVKELKLTGQISFDFIQTEDGQVYAIECNPRTHSAITAFYN
HPLVAEAYIGSVTETLQPLSTSKPTYWTYHEVWRLTGIRSFTQLKTWLHNIWRGTDA
ILKLDDPLPFLMVHHWQIPLLLLNNLRQLKGWTRIDFNIGKLVELGGD

[0155] A0A2D3HK59 (SEQ ID NO: 42)

MRKHIFVVFQNLGTLVLLAIAFPLNCIVVLTSLLWSFIKQPFNKSIVVNPNSKNILIAG
ARMTKTLQLARSFHAAGHRVIIIDIEKYWLSGNKYSNSVAGFYTVPDPSKDLEGYVE
TLHAIANTEKIDFFIPVAIFSVIHYDQGKPPLPDCVEFFHFDADVTKILDDKFAFAETA
RSFGLSVPKSFKITDPEQVLNFDFSQEKRKYILKSIPYDQVRRLNLTKLPCDTKSETAA
FVKSLPISEENPWIMQEFIPGKEYCTHTTARDGESRMYCCCESSAFQVNYENVDQREI
MQWASHFTKELGKTGQLSFDFIQAEDGTVYAIECNPRTHSAITMFYNHPGVADAYL
GKEPLAESLQPLPDSKPTYWLYHEVWRLNEIRSFKQLQTWVRNIRRGKEAIFEVSDPL
PFLMVHHWQIPLLILDNLRRLKGWIRIDFNMGELIE

[0156] A0A2S6VI18 (SEQ ID NO: 43)

MKSRQTPRERTFALLKSLGTLSLLLLAFPFSLSAVVGALLWSSLASLFQKRRVQAEPK
RILLTGAKMTKCLTLARSFHAAGHQVVMVETHKYWLSGNRFSNCVEAFYTVPAPQ
HDAEGYIQGLLNIVKQEKIDMFIPVSSPVASYYDSLAKPALSPYCEVFAFDAETTKLL
DNKFTFNQKAHSVGLSAPKTFLITNPEQVLNFDFAADGSQYILKSIAYDSINRLALLK
LPCAPQKMAEYVRSLPISEENPWIMQEFLKGQEYCTHAVVRDGKLLLYACSKSCDFL
VNYEHDYNPAILDWVTRFVKELNLTGQICLDFIQAEDGTVYPIECNPRTSTCITMFHD
QPKVVADAYLSSGAQASKEPVQPLPDSKPTYWTFHELWRLLTKVKSWKDLQYRLGI
IFNGVDPVFHPRDPLPFLGVNHWQIPLLILNNVRQLKGWERIDFNIGKLVQLGGD

[0157] K9X913 (SEQ ID NO: 44)

MQSGQTTSERTFALLKSLGTLTLLLLAFPFSLSVVVGALLWSSLTSLFQKRRVQVEPK
RILLTGAKMTKCLTLARSFHAAGHQVFMVETKKYWLSGNQFSNCVEALYTVPAPQH

DAEGYIQGLLNIVKQEKIDMFIPVSSPVASYYDSLAKPALSPYCEVFAFDAETTKLLD
NKFTFNQKAHSVGLSAPKTFLITNPEQVLNFDFAADGSQYILKSIAYDSINRLALLKLP
CAPEKMAEYVHSLPISAENPWIMQEFLKGQEYCTHAVVRDGKLLLYACSKSCDFLV
NYEHDYNPAILDWVTRFVKELNLTGQICLDFIQAEDGTVYPIECNPRTSTCITMFHDQ
PKVVADAYLSSSAQAPKEPVQPLPESKPTYWTFHELWRLLTKVKSWKDLQYRLGIIF
NGVDPVFHPRDPLPFLGVNHWQIPLLILNNVRQLKGWERIDFNIGKLVQLGGD

[0158] A0A1Y0RL91 (SEQ ID NO: 45)

MAHSISLSSRPATPAISIKALLVALFQNLGTLTILLLVLPINAAIVLISLLWSRLSSPWRS
QKAVVATHRKNILISGGKMTKALQLARSFHAAGHRVVLIETHKYWLSGHRFSNAVS
RFYTTPTPQHNPEAYIQALLDIVKREKIDVYVPVTSPVASYYDSLAKPALSPYCEVFH
FDADVTQMLDDKFAFSEKARALGLSVPKSFKITNPEQVINFDFSQETRKYILKSIPYDS
VRRLDLTKLPCDTPEETAAFVRSLPISPEKPWIMQEFIPGKEFCTHSTVKNGELRLHCC
SESSAFQVNYENIENPKIQKWVTHFVKELGITGQISFDFIQAEDGTVYAIECNPRTHSA
ITMFYNHPQVADAYLSQEAFTEPQEPLPNSKPTYWTYHEVWRLTGIRSFAQLQTWIR
NFLRGKDAIYQVDDPLPFLMVHHWQIFLLLLDNLRQFRGWTRIDFNIGKLVELGGD

[0159] A0A2P8QMI8 (SEQ ID NO: 46)

MQIFAVFQNLGTLLLLAIAFPFNCIVVLTALFWNLVSKPFRDRGILPVSHPKNIMLTG
GKMTKALQLARSFHMVGHRVVLVETHKYWLTGHRFSNAVDRFYTVPAPEKDPEGY
SQALLAIAKQENIDVYVPVCSPVASYYDSVAKSVLSGCCEVFHFDAEVTQMLDDKY
EFAEKARSLGLSVPKSFKITNPEQVINFDFSDAERPYILKSIPYDSVRRLNLTKLPCATQ
AETAAFVNSLPISPEKPWIMQEFIPGQEYCTHSTVRNGELRMHCCCESSAFQVNYEN
VDKPEILAWVRHFVKELGITGQASFDFIQAEDGNVYAIECNPRTHSAITMFYNHPGV
ADAFCRDVTCNVSTLYPLQPLSTSKPTYWTYHELWRLTGIRSFPQLQTWFKNILRGK
DAIFAIDDPLPFLMVHHWQIPLLLLDNLRRLKGWIRIDFNIGKIVELGGD

[0160] A0A6B3P645 (SEQ ID NO: 47)

MALILFVQGRAYALFQNLGTLILLLIVLPFNFLKVIPSLLWNFISQPFQKKVVAENPKN
ILITGAKMTKCLQLARSFHAAGHKVFLLEANKYWLSGNRFSNAVTGFYTLPFPQKD
WEGYSQGLLEIIKKEKIDVFIPVSSPAGSYYESLAKPLISEHCEVLHFDAEITQLLDNKF
TFIEKAKSFGLSVPKSFLITNPEQVLNFDFATDGSKYILKSIPYDSVRRLDMTKLPMNS
KAEMEEFVNSLPISEQRPWIMQEFVKGKEYCTHSTVRKGKVRLYCCCESSEFQVNYH
HVDRPQIYQWVEKFVRELNITGQISFDFIQTEDGRVYPIECNPRTHSAITTFYDHPGVA
DAYLKDSKDENEASLIPLPNSKPTYWTYHELWRLTGIRSLGQLKTWINRIFQGTDGIF
QINDPLPFLMVHHWQIPLLLLGNLQKLKGWVRIDFNIGKLVELGGD

[0161] A0A6B3MZW3 (SEQ ID NO: 48)

MGLISGSQKPIYTVLQNLGTLTLLLSVLPFNLLKVLPALLWNFLSKPFQKKLVVENSK
NIILTGAKMTKCLQLARSFQAAGHKVFMLETDKYWLSGNRFSNSVTGFYTVPNPKK
DWNGYCQKLLDIVKKENIDVFIPVSSAVLNYYESLVKPILSEYCEVLHFDVEITKLLD
NKFTFIEKAKSFGLTVPKSFLITKPEQIINFDFATDGSQYILKSIPYDSVRRLNMTKLPM
KSVQEMSNFVKSLPINQEKPWIMQEFVKGKEYCTHSTVRKGQIRLHCCCESSEFQVN
YEHVDHPQIYEWIEKFVKELNLTGQISFDFIQTEDNRVYPIECNPRTHSAITTFYNHPE
VADAYLNDSQNDNESPITPLSNSKPTYWTYHELWRLTAIRSWEQLKAWSKKITAGT
DSIFQFNDPLPFLMVHHWQIPLLLLENLKKLKGWVMIDFNIGKLVELEED

[0162] A0A2K8WS68 (SEQ ID NO: 49)

MFLTTFKSLGTLALLKLALPFNLTLVLIASIINIFSNPFKIKKKPNINSKTVLLTGGKMT
KALQLARSFHSAGHRVILVETHKYWLSGHRFSVAVDKFFTMPNPVKDKEGYIDGLL
DIVKRESVDIFIPVSSPVASYYDSVAKMVLSPYCEVLHFDVEMTLVLDDKANLCKKA
SSLGLTSPASYLITNVQEILDFDFSKNNHKYILKSIKYDSVYRLNMTQFPFEGMEEYV
RSLPISEENPWVMQQFITGQEYCTHSTVRNGKIRLHCCSESSHFQVNYKHIDNQKIYE
WVEEFVGKLNLTGQISFDFIQTDDGTVYPIECNPRTHSAISMFYNHPLVADAYLNDG
DDAPITPLESSKPTFWTYHELWRLTEVRSPQDLSQWWQKVTKGQDGIFSWQDPLPFL
MVHHWQIPLLLFGNLMKLKPWVKIDFNIGKLVESAGD

[0163] A0A4Q9JE38 (SEQ ID NO: 50)

MTQSISVASVGQTTQSVTLGLRISALFKNLATLALLLLVLPINAAIVLVSLLLGSQSQA
IATEPKNILISGGKMTKALQLARSFHAAGHRVVLVETHKYWLTGHRFSKAVSRFYTL
PTPQSDPEAYTQALLDIVQKENIDVYVPVCSPVASYYDSLAKPVLSKYCEVFHCDAD
VTQMLDDKYAFVEKARSLGLSVPKSFKITDPEQVSNFDFSQEKRKYILKSIPYDSVRR
LDLTKLPCETPEATADFVNSLPISSQKPWIMQEFIPGKEFCTHSTVRNGELRMHCCCE
SSAFQVNYENVDHPQILEWVRHFVKALGITGQVSFDFIEAQDGTIYAIECNPRTHSAIT
MFYNHPDVANAYLSEIPQVEPIQPLINSKPTYWTYHEIWRLTGIRSFSQLQTWLKNFF
GGKDAIYSLSDPLPFLTVHHWQIPLLLLQNLQQLKGWIRIDFNIGKLVEFGGD

[0164] Q3M6C5 (SEQ ID NO: 51)

MAQSLPLSSAPATPSLPSQTKIAAIIQNICTLALLLLALPINATIVFISLLVFRPQKVKA
ANPQTILISGGKMTKALQLARSFHAAGHRVVLVETHKYWLTGHRFSQAVDKFYTVP
APQDNPQAYIQALVDIVKQENIDVYIPVTSPVGSYYDSLAKPELSHYCEVFHFDADIT
QMLDDKFALTQKARSLGLSVPKSFKITSPEQVINFDFSGETRKYILKSIPYDSVRRLDL
TKLPCATPEETAAFVRSLPITPEKPWIMQEFIPGKEFCTHSTVRNGELRLHCCCESSAF
QVNYENVNNPQITEWVQHFVKELKLTGQISFDFIQAEDGTVYAIECNPRTHSAITTFY

DHPQVAEAYLSQAPTTETIQPLTTSKPTYWTYHEVWRLTGIRSFTQLQRWLGNIWRG
TDAIYQPDDPLPFLMVHHWQIPLLLLNNLRRLKGWTRIDFNIGKLVELGGD

[0165] A0A252E4S5 (SEQ ID NO: 52)

MAQSISLSLPESTTPSTSAGVKIVALFKTLGTLTLLLIALPFNALIVLIALLWGIVRRPF
TKKAAVAAHPQTILVSGAKMTKALQLARSFHAAGHRVILIEGHKYWLSGHRFSKAV
SRFYTVPAPQKDPEGYIQALVEIVKKEKVDVYVPVCSPVASYYDSLAKPALSEYCEV
FHFDADITKMLDDKFAFTDKARSLGLSVPKSFKITDPQQVINFDFSQETRKYILKSIAY
DSVRRLDLTKLPCDTPEETAAFVNSLPISSENPWIMQEFIPGKEFCTHSTVRDGELRLH
CCCNSSAFQINYENVENPQIREWVQQFVKSLRLTGQVSFDFIQAEDGTVYAIECNPRT
HSAITMFYNHPGVADAYLGKTPLAAPLEPLASSKPTYWIYHEIWRLTGIRSWKQLQT
SINTLLRGTDAICCLDDPVPFLTLHHWQIPLLLLKNLQQLKGWVKIDFNIGKLVELGG
D

[0166] A0A367RKS4 (SEQ ID NO: 53)

MAQSISLSLPQSTTPSTGVKVKIVALFKTLGTLTLLLIALPFNALIVLISLLWGIGRSPF
TKKAVVATHPQTILVSGAKMTKALQLARSFHAAGHRVILIEGHKYWLSGHRFSKAV
SRFYTVPAPQEDPEGYIQALVEIVKQEKVDVYVPVCSPVASYYDSLAKPALSEYCEV
FHFDADITKMLDDKFAFTDRARSLGLSVPKSFKITDPQQVINFDFSQEIRKYILKSISY
DSVRRLDLTKLPCDTPEQTAAFVNSLPISPEKPWIMQEFIPGKELCTHSTVRNGELRL
HCCSNSSAFQINYENVENPRIREWVQHFVKSLGLTGQVSFDFIQAEDGTTYAIECNPR
THSAITMFYNHSGVANAYFGKTLLDAPLEPLASSKPTYWIYHEIWRLTGIRSWKQLQ
TSVNTIVRGTDAIYCLDDPVPFLTLYHWQIPLLLLKNLQQLKGWVKIDFNIGKLVELG
GD

[0167] A0A1E2WNZ8 (SEQ ID NO: 54)

MAQSISLSLPESTTPSTGIRIKIVALFKTLGTLTLLLIALPINALIVLLSLLWSILFTKKPA
VAAHPQTILVSGGKMTKALQLARSFHAAGHRVILVEGHKYWLSGHRFSNAVSRFYT
VPAPQDDPEGYIQALLEIVKKEKVDIYVPVCSPVASYYDSLAKPSLSAYCEVFHFDAE
ITKMLDDKFAFTDQARSLGLSVPKSFKITDAEQVINFDFSKETRKYIIKSISYDSVRRL
NLTKLPCDTPEETAAFVKSLPISPEKPWIMQEFIPGKELCTHSTVRDGELRLHCCSDSS
AFQINYENVENPQIRQWVQHFVKSLGLTGQVSFDFIQAEDGTAYAIECNPRTHSAITM
FYNHPGVAEAYFGKTLLAAPLEPLADSKPTYWIYHEIWRLTGIRSAKQLQTWFQRLV
RGTDAIYQINDPIPFLTLHHWQITLLLLQNLQKLKGWVKIDFNIGKLVELGGD

[0168] A0A1B2CWG9 (SEQ ID NO: 55)

MAQSIPFDSASPTPQVSWGVRISALWKTVGTLLLLFLALPVNASIVLISLLWGIFSKPF
EKRVVAAAPKNILISGGKMTKALQLARSFHAAGHRVVLVESHKYWLTGHQFSNAVS

VFYTVSPPEKDPEGYTQQLLDIVKKERIDVYVPVCSPVASYYDSLVKPALSQHCEVF
HCDAEITQMLDDKYAFSEKARSFGLSVPKSFKITNPEQVINFDFSQEKRKYILKSIPYD
SVRRLNLTKLPCDTPEETAAFVRSLPISPEKPWIMQEFIPGKEFCTHSTVRNGELRLHC
CCESSAFQVNYENVNNPQILEWVKHFIKEMGITGQVSFDFIQTEDGTVYAIECNPRTH
SAITMFYNHPGVADAYLGKIPLPEPLQPLADSKPTYWLYHEIWRLTGIRSLSQFWTW
LKNLMRGKDAIYQLNDPLPFLTVPHWQITLLLLQNLRQLRGWVKIDFNIGKLVELGG
D

[0169] A0A1U7HY56 (SEQ ID NO: 56)

MQSGQTIRERTFASLKSLGTLTLLLLAFPFSLSVVVGALLWSSLTSLFQKHRVQVKPK
RILLTGAKMTKCLTLARSFHAAGHQVFMVETKKYWLSGNQFSNCVEALYTVPAPQH
DAEGYIQGLLNIVKQEKIDMFIPVSSPVASYYDSLAKPALSPYCEVFAFDAETTKLLD
NKFTFNQKAHSVGLSAPKTFLITNPEQVLNFDFATDGSQYILKSIAYDSINRLALLKLP
CAPATMAKYVHSLPISEENPWIMQEFLKGQEYCTHAVVREGKLMLYACSKSCDFLV
NYEHDYNPAILDWVTRFVKALNLTGQICLDFIQAEDGTVYPIECNPRTSTCITMFHDQ
PKVVADAYLSSSASILKEPVQPLPDSKPTYWTFHELWRLITKVKSWQDLQYRLGIIFN
GVDPVFHPRDPLPFLGVNHWQIPLLILNNVRQLKGWERIDFNIGKLVQLGGD

[0170] A0A1L9QXK4 (SEQ ID NO: 57)

MLIILFIQNHAYALFQNLSTFLLLTLLLPFNLLKILPVVLWNILTPIRAKPPGYEKPKNI
LITGAKMSKSLQLARSFNGSGHRVFLLEIHKYWLSGNRFSNAIKGFYTVPNPQKDWD
GYQQAVLEIVQKENINLFIPVSSPAGSYDESRLKPILSPYCEVFHFNLDITELLDNKFTF
IEKAKSLGLSVPQSFLITDSKQILDFDFAQDGSRYILKSIPYDSVRRLDMTKLPMKSEQ
EMEEFVKKLPITEDKPWIMQEFVQGKEYCTHSTVRKGKIRLHCCCESSEFQVNYDHV
EEPEIYQWVETFVRALNLTGQISFDFIKTEDGQVYPIECNPRTHSAITTFHDHPGVADA
YLKDAEDETESPIFPLPDSKPTYWTYHELWRVTEIRSFGQFQAWIKRITEGTDGIFQLN
DPLPFLMVHHWQIPLLLLQNLKKMKGWVRIDFNIGKLVELDGD

[0171] A0A2L2NR98 (SEQ ID NO: 58)

MGQSISLSLPQSPTSSTSVRVKIIALFKTLGTLTLLLIALPFNALIVLISLLWGIVRWTLP
RRRRSLFTKNVVAAHPQTILVSGAKMTKALQLARSFHAAGHRVILIEGHKYWLSGH
RFSKAVSRFYTVLAPQSDLEGYIQALVEIVKKEKVDVYVPVSSPVSSYYESLAKAALS
EYCEVFHFDPDITKMLDDKFALTDRARSLGLSVPKSFKITDPQQVINFDFSQETRKYIL
KSIDYDSVRRLNLTKLPCDTPEETAAFVNSLPISPEKPWIMQEFIPGKELCTHSTVRDG
ELRLHCCSDSSAFQINYENVENPQIREWVQHFVKSLALTGQVSFDFIQAQDGTVYAIE
CNPRTHSAITMFYNHPGVADAYLGKTPLAAPLEPLASSKPTYFIYHEIWRLTGIRSWK

QLQTSVNTLVRGTDAIYSLDDPIPFLTLHHWQIPLLLLKNLQQLKGWVKIDFNIGKLV
ELGGD

[0172] A0A2H2XFD9 (SEQ ID NO: 59)

MPQSISLTSSPTINQVNNKSVDISSSLKTLGTLTLLLLALPVNATLVLVALLLNSLRPR
NITTAANPKNILISGGKMTKALQLARSFHNAGHRVVLLEAHKYWLTGHRFSFAVNK
FYTVEAPEKDPEGYVQSLVDIVNKENIDVYVPVCSPVASYYDSLAKKALSSQCEVIH
CDALTTQMLDDKYAFTETARGFGLSVPKSFKITDPEQVINFDFSQEKRKYILKSIPYDS
VRRLDLTKLPCDTPEATAAFVRSLPISPEKPWIMQEFIPGKEYCTHSTVRNGEITLHCC
CESSAFQVNYAQVDNPQIFEWVRHFLKQLGITGQVSFDFIEAEDGTVYAIECNPRTHS
AITMFYNHPGVADAYLGTLNNLEEPIQPLPTSKPTYWIYHEMWRLINAGSWSKFVER
LQIITRGTDAIFSWQDPLPFLMNPHWQIFLLLIQNLQKNRGWIRIDFNIGKLVELGGD

[0173] A0A533NZW2 (SEQ ID NO: 60)

MFLQAKIWAFFQNIGTLTLLLLALPFNAIVVLPCLLWSWIAKLFQKKVVAANPKNILI
TGGKMTKALQLARCFHAAGHTVFLVETHKYWLSGHRFSRAVKGFFTVPAPEKHAN
GYCQGLLDIVKQEKIDVFIPVSSPVASYYDSIAKSLLSPHCEALTFDAEITEMLDNKFT
FCQKARELGLTAPKAFLITDPEQVLNFDFAADGSRYILKSIAYNSVYRLDLTKLPMSS
KEQMASFVKGLPISESQPWIMQEFISGQEYCTHSTVRNGIVRLHCCSQSSPFQVNYEQ
VDNQNIFQWVQQFVKALNLTGQISLDVIQTKDGKVYPVECNPRTHTAIAMFYNHPG
VADAYILDSKDAREPPIQPLPESKPTYWTYHELWRLTGIRSWGQLKGWFNKIIKGTD
GIFQVNDPLPFLMVHHWQIPLLLLNNMRKFKGWVKIDFNIGKLVELGGD

[0174] A0A367RVN3 (SEQ ID NO: 61)

MAQSISLSLPQSPTSSTGIKVKLVALFNTLGTLTLLLIALPFNALIVLISLLWGIVSSPF
TKKAVVAAHPQTILVSGAKMTKALQLARSFHAAGHRVILIEGNKYWLSGHRFSKAV
SRFYTVPAPQEDPEGYIQALVEIVKREKVDVYVPVCSPVASYYDSLAKPLLSEYCEVF
HFDPDITKMLDDKFAFTDRARSLGLSVPKSFKITDPQQVINFDFSQETRKYILKSIDYD
SVRRLNLTKLPCDTPEETAAFVNSLPISAEKPWIMQEFIPGKELCTHSTVRNGELRLH
CCSNSSAFQINYENVENPQIREWVQHFVKSLALTGQVSFDFIQAEDGTAYAIECNPRT
HSAITMFYNHPGVADAYLGKTPLAAPLEPLASSKPTYFLYHEIWRLTGIRSWKQLQT
SVNTLVRGTDAIYSLDDPIPFLTLHHWQIPLLLLKNLQQLKGWVKIDFNIGKLVELGG
D

[0175] A0A1Z4TPY4 (SEQ ID NO: 62)

MLMGFFEGEFMTQSISVASPAPKTQSVPLGFRISALWKNVGTLALLLLVLPINAVIVL
VSLLLGHQSQAIATEPKNILISGGKMTKALQLARSFHAAGHRVVLVETHKYWLTGH
RFSKAVSRFYTLPTPQSDPKAYTQALLDIVKKENIDVYVPVCSPVASYYDSLAKPVLS

KYCEVFHCDADVTQMLDDKYAFAEKARSLGLSVPKSFKITDPEQVINFDFSQEKRQY
ILKSIPYDSVRRLDLTKLPCETPEVTADFVNSLPISPQKPWIMQEFIPGKEFCTHSTVRN
GELRMHCCCESSAFQVNYENVDHPQILEWVRHFVKELGITGQVSFDFIQAEDGTIYAI
ECNPRTHSAITMFYNHPSVADAYLSEIPQLEPIQPLFNSKPTYWIYHEIWRLTGIRHWS
QLQTWLKNFFGGKDAIYSFSDPLPFLTVHHWQIPLLLLQNLQQLKGWLRIDFNIGKL
VEFGGD

[0176] A0A6B3MAD2 (SEQ ID NO: 63)

MGLISRSQKPVYIALQNLGILTLLLSVLPFNLLKVLPAVLWNFISKPFQKKVVAENSK
NIILTGAKMTKCLQLARSFQVAGHKVFMLETDKYWLSGNRFSNTVTGFYTVPNPKK
NWNGYCQELLDIVKREDIDVFIPVSGAALNYYESLIKPILSEHCEVLHFDIEITKLLDN
KFTFIEKAKSFGLAVPKSFLITNPEQILNFDFPADGGQYILKSIPYDSVRRLDMRKLPM
KSAQEMKDFVNSLPISEEKPWIMQEFVKGKEYCTHSTVRKGQIRLHCCCESSEFQVN
YEHVNHPQIYEWVETFVKELNLTGQISFDFIQTEDNRVYPIECNPRTHSAITTFYNHPE
VADAYLNDSQDDNESPLIPLPNSKPTYWIYHELWRLTAIRSWEQLKDWIKKITAGTD
SIFQFNDPLPFLMVHHWQIPLLLLDNLKKLKGWVMIDFNIGKLVELEED

[0177] A0A1Z4IH51 (SEQ ID NO: 64)

MTQSISLSLPESTTPSVGIKVKILALFKTLGTLSLLLVALPFNVLIVLISLLWGIVRVPF
TKNVVATHSQTILVSGAKMTKALQLARSFHADGHRVILIESHKYWLSGHRFSKAVSR
FYTVPSPQKDPESYIQALIEIVKKEKVDVYVPVCSPVASYYDSLAKPALSEYCEVFHF
NADITKMLDDKFAFTQKARALGLSVPKSFKITDPQQVINFDFSQETRKYILKSINYDS
VRRLNLTKLLCDTPEETAAFVKSLPISPETPWIMQEFIPGKEFCTHSTVRDGELRLHCC
CHSSAFQINYENVENPQIREWVQHFVKSLGLTGQVSFDFIQAEDGTVYAIECNPRTHS
AITMFYNHPGVAEAYFGKIPLPAPVEPLATSKPTYWTYHEIWRLTGIRSWKQLQTAIK
TIFQGTDAIYCLDDPLPFLTLHHWQIPLLLLQNLQQLKGWVKIDFNIGKLVELGGD

[0178] A0A1Z4IB36 (SEQ ID NO: 65)

MAQSLSLSSSHATPSIPWQTRVAAILQNIGTLTLLLLALPINASIVFISWLIFRPQKVKA
ANPQNILISGGKMTKALQLARSFHAAGHRVVLLETHKYWLTGHRFSVAVDKFYTVP
APQENPQAYIQALVDIVKQENIDVYVPVTSPAGSYYDSLAKPELSRYCEVFHFDADIT
QMLDDKFALVEKARSLGLSVPKSFKITSPEQVINFDFSGESRKYILKSIPYDSVRRLDL
TKLPCATPEETAAFVRTLPISQEKPWIMQEFIPGKEFCTHSTVRDGELRLHCCCESSAF
QVNYENVDNPQIREWVRRFVKELKLTGQISFDFIQAEDGTVYAIECNPRTHSAITTFY
DHPQVAQAYLSKETTAETLQPLATSKPTYWTYHEVWRLTGIRSLTQLGRWLGNIWR
GTDAIYQPGDPLPFLMVHHWQIPLLLLNNLRRLKGWTRIDFNIGKLVELGGD

[0179] K9VKW1 (SEQ ID NO: 66)

MLETVSVAAMPSERETNTGNRRFPTAFKTIATLILLLLVMPLNLALTAIALLRSIIIKPF
QSRSTTATPQTILISGGKMTKALQLARSFHQAGHRVILVETEKYWLTGHRYSRAVDR
FYTVPNPQTEEYPQALLKIVRQEGVNVYVPVCSPVASYYDAEVKRVLSGHCTVMHV
DVETLQRLDDKYEFATAAQALGLPVPKSYRITNPQQVIDFDFSDAQRKYIIKSIPYDS
VRRLDLTKLPCETPAETAAFVNSLPISESKPWIMQEYIPGQEFCTHSTVRNGHLQLHC
CCKSSAFQVNYENVDRPDIENWIRQFAKSLNLTGQVSFDFIQAADDGEIYAIECNPRT
HSAITMFYNHPDVAKAYLEPDPLPQTVQPLASSRPTYWIYHEIWRLVTHLSSPKLVSE
RLKIIAQGKDAIFDWDDPLPFLMVHHWQIPLLLWGNLQNPKEWIRIDFNIGKLVEIGG
D

[0180] A0A2T1F5R3 (SEQ ID NO: 67)

SRSVDRFYTVPKPQEKDYIDALLEIVQREGVDVYIPVCSPVASYYDALAKQVLSKYC
EVMHFDPELVQKLDDKSEFSAIATSLGLAVPDSYRITDTQQILDFDFAKQAHTYILKSI
PYDSLRRLNLTQLPCETPQQTAAFVEQLPICESNPWIMQAFITGQEYCTHSTVRNGEL
QLHCCCESSAFQINYEMVDKPEIEAWVRKFVSSLKLTGQVSFDFIQTRDGGVYAIEC
NPRTHSAITMFYNHPDVARAYLESDFPLIKPLESSRPTYWIYHEIWRLVTQPTQIGQRL
KIIASGKDAIFDWADPLPFLMVHHAQIPWLLLENLRQLKGWMRIDFNIGKLVEPAGD

[0181] K9W0D3 (SEQ ID NO: 68)

MAQVQPIKARIFAVFQNLGTLALLAIAFPINCIVVLASLLWNFCSRPFSKQGVSTLNPK
NILIGGGKMTKTLQLARLFHAAGHRVILFDSEKFRFSGYRFSNAVDRFYTVPDPQTDL
EGYTQALRAIAKQENIDIFIPVGIFAGGYFDSQRQPVLSGCCELFHFDADTMKMLDNK
FTFGEIARSFGLSVPKTFLITDPEQVLQFDFANEKNKYILKSIVYDSVYRLDMTKLPME
SQEKMAAHVNSLPIRKDNPWILQEFISGKEYCTHSTVRNGELTVHCCCESSAFQVNY
ENVDHPEIMQWVSRFVKELKLSGQISFDFMQAEDGTLYAIECNPRTHSAITMYYNHP
DLADAYLSAERRNYALPLQPLPDSKPTYWLYHEVWRLNEIRSLKQLQTWFKNIWRG
KDAIFEVNDPLPFLMVHHCYIPLLLLDSLRKLKGWVRIDFNIGKLVQLEGD

[0182] A0A1Z4SWP6 (SEQ ID NO: 69)

MPQSISLTSSPTINQVNNKSVDISSSLKTLGTLTLLLLALPVNATLVLVALLLNSLRPR
NITTAANPKNILISGGKMTKALQLARSFHNAGHRVVLLEAHKYWLTGHRFSFAVNK
FYTVEAPEKDPEGYVQSLVDIVNKENIDVYVPVCSPVASYYDSLAKKALSSQCEVIH
CDALTTQMLDDKYAFTETARGFGLSVPKSFKITDPEQVINFDFSQEKRKYILKSIPYDS
VRRLDLTKLPCDTPEATAAFVRSLPISPEKPWIMQEFIPGKEYCTHSTVRNGEITLHCC
CESSAFQVNYAQVDNPQIFEWVRHFLKQLGITGQVSFDFIEAEDGTVYAIECNPRTHS

AITMFYNHPGVADAYLGTLNNLEEPIQPLPTSKPTYWIYHEMWRLINAGSWSKFVER
LQIITRGTDAIFSWQDPLPFLMNPHWQIFLLLIQNLQKNRGWIRIDFNIGKLVELGGD

[0183] A0A1U7I932 (SEQ ID NO: 70)

MAQSISVSSSPAMPSLAVETKIAVIIQNILTLALLLLALPINATIVVVTLLWCNISRPFQ
HSATKAANPKNILISGGKMTKALQLARSFNAAGHRVVLIETHKYWLSGHRFSQAVD
KFYTVPAPQENPECYTQALIDIIKQENIDVYIPVTSPLGSYYDSLAKPLLSEYCEVFHF
DADITQKLDDKFAFAETARSLGLSAPKSFKITSAEQVLNFDFSQESRKYILKSIPYDSV
RRLDLTKLPCATPEETAAFVRSLPISPEKPWIMQEFIPGKEFCTHSTVRDGELRLHCCC
ESSAFQVNYENVENSQIREWVRHFVKELKLTGQISFDFIQAEDGRVYAIECNPRTHSA
ITTFYDHPKVAQAYLDKEPMAETLQPLPTSQPTYWTYHEVWRLTGIRSFTQLKKWIA
NIWRGTDAIYKSDDPLPFLMVHHWQIPLLLIDNLRRLKGWTRIDFNIGKLVELGGD

[0184] A0A1W5CLX0 (SEQ ID NO: 71)

MAQSLPLSSAPATPSLPSQTKIAAIIQNICTLALLLLALPINATIVFISLLVFRPQKVKAA
NPQTILISGGKMTKALQLARSFHAAGHRVVLVETHKYWLTGHRFSQAVDKFYTVPA
PQDNPQAYIQALVDIVKQENIDVYIPVTSPVGSYYDSLAKPELSHYCEVFHFDADITQ
MLDDKFALTQKARSLGLSVPKSFKITSPEQVINFDFSGETRKYILKSIPYDSVRRLDLT
KLPCATPEETAAFVRSLPITPEKPWIMQEFIPGKEFCTHSTVRNGELRLHCCCESSAFQ
VNYENVNNPQITEWVQHFVKELKLTGQISFDFIQAEDGTVYAIECNPRTHSAITTFYD
HPQVAEAYLSQAPTTETIQPLTTSKPTYWTYHEVWRLTGIRSFTQLQRWLGNIWRGT
DAIYQPDDPLPFLMVHHWQIPLLLLNNLRRLKGWTRIDFNIGKLVELGGD

[0185] A0A328IAQ4 (SEQ ID NO: 72)

MTQSISVASVGQTTQSVTLGLRISALFKNLATLALLLLVLPINAVIVLVSVLLGSQSQA
IATEPKNILISGGKMTKALQLARSFHAAGHRVVLVETHKYWLTGHRFSKAVSRFYTL
PTPQSDPQAYTQALLDIVKKESIDVYVPVCSPVASYYDSLAKPVLSKYCEVFHCDAD
VTQMLDDKYAFAEKARSLGLSVPKSFKITDPEQVINFDFSQEKRQYILKSIPYDSVRR
LDLTKLPCETPQATADFVNSLPISPQKPWIMQEFIPGKEYCTHSTVRNGELRMHCCCE
SSAFQVNYENVDHPQILEWVRHFVKALGITGQVSFDFIEAEDGTIYAIECNPRTHSAIT
MFYNHPDVANAYLSEIPQVEPIQPLTNSKPTYWTYHEIWRLTGIRSFSQLQTWVKNFF
GGKDAIYSLSDPLPFLAVHHWQIPLLLLQNLQQLKGWIRIDFNIGKLVEFGGD

[0186] A0A533NF66 (SEQ ID NO: 73)

MFLQAKIWAFFQNIGTLTLLLLALPFNAIVVLPCLLWSWIAKLFQKKVVAANPKNILI
TGGKMTKALQLARCFHAAGHTVFLVETHKYWLSGHRFSRAVKGFFTVPAPEKHAN
GYCQGLLDIVKQEKIDVFIPVSSPVASYYDSIAKSLLSPHCEALTFDAEITEMLDNKFT
FCQKARELGLTAPKAFLITDPEQVLNFDFAADGSRYILKSIAYNSVYRLDLTKLPMSS

KEQMASFVKGLPISESQPWIVQEFISGQEYCTHSTVRNGIVRLHCCSQSSPFQVNYEQ
VDNQKIFQWVQQFVKALNLTGQISLDVIQTKDGKVYPVECNPRTHTAIAMFYNHPG
VADAYLLDSKDAREPPIQPLPESKPTYWTYHELWRLTGIRSWGQLKGWFNKIIKGTD
GIFQVNDPLPFLMVHHWQIPLLLLNNMRKFKGWVKIDFNIGKLVELGGD

[0187] A0A479ZZ55 (SEQ ID NO: 74)

MFPINLTLVITAFLTNLITLPFPKKITYENSKNILLTGGKMTKSLQLARSFHRAGHKVF
MVETHKYWLSGHQYSKAVKKFLTVPAPEKDPEGYCQSLLDIVKREKIDVFIPVSSPV
ASYYDSLAKPILSPYCEVFHFDTEMTKTLDDKFSLCEQARVLGLTAPKVFLITSPGEII
NFDFSQEQNPYIIKSIQYDSVTRLDMTKFPFEGMKEYVKKLPISKERPWVMQEFIKGQ
EYCTHSTVRDGEIRLHCCSKSSPFQVNYEQVDNPEIFQWVQKFVKELNLTGQISFDF
MQTEDGKVYPIECNPRTHTAITMFYDHPGLADAYLEPGKNQPHIEPLPTSKPTYWLY
HELWRITGIRSFNDLTNWLNKVIKGKDAMLDKDDPLPFLMVHHWQIVLLLLQNMV
KLKGWVRIDFNIGKLVEIGGD

[0188] A0A357A498 (SEQ ID NO: 75)

MLIILFIQNRAYALFQNLSTFLLLTLLLPFNLLKILPALLWNILTSIRAKLPGDEKPKNI
LITGAKMSKSLQLARSFNGAGHRVFLLETHKYWLSGNRFSNAIKDFYTVPNSEKNW
DGYQQAVLEIVQKENINLFIPVSSAAGSYDESRLKAILSPYCEVFHFDLDITELLDNKF
TFIEKAKNLGLSVPKSFLMTDSKQILDFDFVQDGSRYILKSIPYDSVRRLDMTKLPMK
SEQEMEEFVKELPITEDKPWIMQEFVQGKEYCTHSTVRKGKIRLYCCCESSEFQVNY
NHVEEPEIYQWVKTFVRALNLTGQISFDFIKTEDGQVYPIECNPRTHSAITTFHDHPGV
ADAYLKDVEDETKSPIFPLPDSKPTYWTYHELWRLTQIRSFGQFKAWIKRMIEGTDGI
FQPHDPLPFLMVHHWQIPLLILQNLKTMKGWVRIDFNIGKLVELDGD

[0189] A0A1Z4QDW0 (SEQ ID NO: 76)

MAQSISVDSSPAIPSLASETKIAVIIQNILTLALLLLALPINATIVLVTLFWGTILRPFQHS
ATKTANPKNILISGGKMTKALQLARSFHAAGHKVVLLETHKYWLTGHRFSQAVDKF
YTVPAPQENPESYTQALIDIIKQENIDVYIPVTSPLGSYYDSLAKPLLSRHCEVFHFDV
DITQNLDDKFEFAQKARSLNLSAPKSFKITSAEQVLNFDFSQESRKYILKSIPYDSVRR
LDLTKLPCATPEETAAFVRSLPISPEKPWIMQEFIPGKEFCTHSTVRDGELRLHCCCES
SAFQVNYENVENSQIREWVRHFVKELKLTGQISFDFIQAEDGAVYAIECNPRTHSAIT
TFYDHPKVAQAYLDQEPMAETLQPLPTSKPTYWTYHEVWRLTGIRSFTQLQKWLAN
IGRGTDAIYKLDDPLPFLMVHHWQIPLLLLNNLLRLKGWTRIDFNIGKLVELGGD

[0190] K9R4C7 (SEQ ID NO: 77)

MAQSSIPVLSSQTATHTISLGRRFVALVQNLATLTALLLALPINATIVFISLVLKILISP

FQKEQTTVTTAERKNILISGGKMTKALQLARFFHAAGHRVVLTETHKYWLSGHRFS
QAVDKFYTTPVPQKDSQIYTQALIDIVNKENIDIYIPVTSPIASYYDALAKQTLSEYCE
VFHIDAATCEMLDDKFAFSEKARSFGLSVPKSFKITNPEQVLNFDFSGETRKYILKSIP
YDSVRRLDLTKLPCDTPEETEAFVRSLPISPQKPWIMQEFIPGKEYCTHSTIRDGVVRL
HCCCESSAFQVNYENVENAKIREWVTHFVKELGVTGQLSFDFIEAEDGNVYAIECNP
RTHSAITIFHDQLQPAANAYLSKEPIKEPLQALINSKPTYWTYHEFWRLNEIRSFSQLG
NWIKNMLQGTDAIYTFDDSLPFLMVHHWQIPLLLLKNLFKLKGWTRIDFNIGKLVES
GGD

[0191] A0A3S0ZZ73 (SEQ ID NO: 78)

MAQSISLTESQTTVKPLAVWGKINALLKNLGTLVLLLVALPINATIVLVSLLWNLLAK
PFQKEQTVAGDRKNILISGAKMTKALQLARSFHAAGHRVVLLETHKYWLSGHRFSK
AVDNFYTTPVPQRDPQAYTQALIDIIEKENIDVYIPVTSPIASYYDSLAKPVLSQYCEV
FHFDAAVTQMLDDKFAFSEKARSLGLSVPKSFKITSPEQVLNFDFSQETRKYILKSIPY
DSVRRLDLTKLPCDTPEQTEAFVRSLPISAQKPWIMQEFIPGKEFCTHSTVRDGEIRLH
CCCESSAFQVNYEHVEHPQISEWIARFVKGLGITGQISFDFIQAEDGSVYAIECNPRTH
SAITTFHDRPEVAQAYLGKEAMTEPLQPLPSSKPTYWLYHEVWRLTSIRSLAQLRTWI
RNIWRGTDAIYKLDDPLPFLMLHHWQIPLLLLNNLWRLKGWTRIDFNIGKLVELGGD

[0192] A0A3C0NJT8 (SEQ ID NO: 79)

MAQLLFVRTPSFTMLKSLGTLTLLLIAFPINSIVVLTSLLWGLLSRPFQKQPLPADNQK
TAMFTGGKMTKALQLARSFHAAGHRVILVETHKYWLTGHRFSNAVDRFYTIPAPQK
DPEGYTQALLNIAKQENVDIYIPVCSPVSSYYDSLAKPALSGCCEVFHFDADITKMLD
DKFAFSEKARALGLSVPKSFKITNPEQVLNFDFSNETRKYILKSIPYDSVRRLNLTKLP
CDTPEETAAFVKSLPISEEKPWIMQEFIPGQEYCTHSTVRDGELRLHCCCESSAFQVN
YENVDQPEIMKWVSHFVKELKLTGQASFDFIQAEDGAIYAIECNPRTHSAITMFYNHP
GVADAYLGKEPLAEPLQPLPDSKPTYWLYHEIWRLNEIRSWSQLQTWMNNLLRGTD
AIFDVNDPLPFLTVHHWQIPVLLLDNLRKLRGWVRIDFNIGKLVESGGD

[0193] B2J6X7 (SEQ ID NO: 80)

MAQSISLSLPQSTTPSKGVRLKIAALLKTIGTLILLLIALPLNALIVLISLMCRPFTKKPA
VATHPQNILVSGGKMTKALQLARSFHAAGHRVILIEGHKYWLSGHRFSNSVSRFYTV
PAPQDDPEGYTQALLEIVKREKIDVYVPVCSPVASYYDSLAKSALSEYCEVFHFDADI
TKMLDDKFAFTDRARSLGLSAPKSFKITDPEQVINFDFSKETRKYILKSISYDSVRRLN
LTKLPCDTPEETAAFVKSLPISPEKPWIMQEFIPGKELCTHSTVRDGELRLHCCSNSSA
FQINYENVENPQIQEWVQHFVKSLRLTGQISLDFIQAEDGTAYAIECNPRTHSAITMF

YNHPGVAEAYLGKTPLAAPLEPLADSKPTYWIYHEIWRLTGIRSGQQLQTWFGRLVR
GTDAIYRLDDPIPFLTLHHWQITLLLLQNLQRLKGWVKIDFNIGKLVELGGD

[0194] A0A0C1NCV3 (SEQ ID NO: 81)

MTKLQPIKARIIAVFQNLGTLLLLAIAFPINCSVVLVSLLWNFFSRPSHKQVVLTENPK
NILIGGGRMTKTLQLARSFHAAGHRVILVDIDKYWLSGHRFSRAVAGYYTVPAPQK
DLEGYTQALRAIAKKENIDFFIPVAIFAVSYFDSKGEPVLSGCCEIFHFDADITKMLDD
KFAFAEKARSLGLSVPKSFKITDPEQVLNFDFSQEKRKYILKSIPYDCLRRLNMTKLP
CDTFDMTAEFVKSLPISEEKPWIMQEFIPGKEYCTHSTVRDGELRLYCCCESSAFQVN
YENVDRPEIRQWVQQFVQEVGLTGEISFDIIQADDGTVYPIECNPRTHSAITMFYNHP
GVANAYLNKEPLVEPLQPLADSKPTYWLYHEVWRLTGIRSLKQLQTWIRNILRGKE
AIFSVSDPLPFMMVHHWQIPLLLLDNLRRLKGWVRIDFNLGELIESEEY

[0195] A0A1Z4S904 (SEQ ID NO: 82)

MAQSISFSSAPATPSVPSTSKIAAIFPNIGTLTLLLLALPINASIVLITLLLRAILRPFQPSA
VKAANPKNILISGGKMTKALQLARSFHAAGHRVVLLETHKYWLTGHQYSQAVDKF
YTVSAPQENPERYTQALVDIIKQENIDVYIPVTSPLGSYYDSLAKPELSRYCEVFHFDA
DITQMLDDKYELAQTARSLGLSVPKSFKITSAEQVLNFDFSGETRKYILKSIPYDSVRR
LDLTKLPCATPEETAAFVRSLPISPEKPWIMQEFIPGKEFCTHSTVRNGELRLHCCCES
SAFQVNYENVENPQILEWVKHFVKELKLTGQISFDFIQAEDGKVYAIECNPRTHSAIT
TFYDHPKVAEAYLSQEATTETLQPLPTSKPTYWTYHEVWRLTGIRSFKQLKTWIVNI
WRGTDAIYKFDDPLPFLMVHHWQIPLLLLKNLRQLKGWTRIDFNIGKLVELGGD

[0196] A0A2K8SZ63 (SEQ ID NO: 83)

MFQNLGTLVLLAIAFPLNCIVVLTSLLWSFIKQPFNKSIVVNPNSKNILIAGARMTKTL
QLARSFHAAGHRVIIIDIEKYWLSGNKYSNSVAGFYTVPDPSKDLEGYVETLHAIANT
EKIDFFIPVAIFSVIHYDQGKPPLPDCVEFFHFDADVTKILDDKFAFAETARSFGLSVPK
SFKITDPEQVLNFDFSQEKRKYILKSIPYDQVRRLNLTKLPCDTKSETAAFVKSLPISEE
NPWIMQEFIPGKEYCTHTTARDGESRMYCCCESSAFQVNYENVDQREIMQWASHFT
KELGKTGQLSFDFIQAEDGTVYAIECNPRTHSAITMFYNHPGVADAYLGKEPLAESL
QPLPDSKPTYWLYHEVWRLNEIRSFKQLQTWVRNIRRGKEAIFEVSDPLPFLMVHHW
QIPLLILDNLRRLKGWIRIDFNMGELIE

[0197] A0A3N6PGG7 (SEQ ID NO: 84)

MALILFVQGRAYALFQNLGTLILLLIVLPFNFLKVIPSLLWNFISQPFQKKVVAENPKN
ILITGAKMTKCLQLARSFHAAGHKVFLLEANKYWLSGNRFSNAVTGFYTLPFPQKD
WEGYSQGLLEIIKKEKIDVFIPVSSPAGSYYESLAKPLISEHCEVLHFDAEITQLLDNKF
TFIEKAKSFGLSVPKSFLITNPEQVLNFDFATDGSKYILKSIPYDSVRRLDMTKLPMNS

KAEMEEFVNSLPISEQRPWIMQEFVKGKEYCTHSTVRKGKVRLYCCCESSEFQVNYH
HVDRPQIYQWVEKFVRELNITGQISFDFIQTEDGRVYPIECNPRTHSAITTFYDHPGVA
DAYLKDSKDENEASLIPLPNSKPTYWTYHELWRLTGIRSLGQLKTWINRIFQGTDGIF
QINDPLPFLMVHHWQIPLLLLGNLQKLKGWVRIDFNIGKLVELGGD

[0198] A0A0C2QMV0 (SEQ ID NO: 85)

MKEQIFIVFQNLGTLVLLAIAFPFNCIVVLTSLVWNFIKQPFSQSIVVNPNSKNILIAGA
RMTKTLQLARSFHAAGHRVIIIDIEKFWSSGNKYSNSVAGFYTVPDPSKDLEGYVESL
HAIAKKEKIDFFIPVAIFSVIHYDSQGKPPLPDDVEFFHFDADVTKILDDKFAFAETAR
SFGLSVPKSFKITDPEQVLNFDFSQEKRKYILKSIPYDQVRRLNLTKLPCDTPSQTAAF
VKTLPISEEKPWIMQEFIPGKEYCTHTTARDGESRMYCCCESSAFQVNYENVDQPEI
MQWASHFTKELGKTGQLSFDFIQAEDGTVYAIECNPRTHSAITMFYNHPGVADAYL
GKEPLAESLQPLSDSKPTYWLYHEVWRLNEIRSFKQLQTWVRNIRRGKEAIFEVSDPL
PFLMVHHWQIPLLILDNLRRLKGWIRIDFNMGELID

[0199] Q3M6C5 (SEQ ID NO: 86)

MAQSLPLSSAPATPSLPSQTKIAAIIQNICTLALLLLALPINATIVFISLLVFRPQKVKA
ANPQTILISGGKMTKALQLARSFHAAGHRVVLVETHKYWLTGHRFSQAVDKFYTVP
APQDNPQAYIQALVDIVKQENIDVYIPVTSPVGSYYDSLAKPELSHYCEVFHFDADIT
QMLDDKFALTQKARSLGLSVPKSFKITSPEQVINFDFSGETRKYILKSIPYDSVRRLDL
TKLPCATPEETAAFVRSLPITPEKPWIMQEFIPGKEFCTHSTVRNGELRLHCCCESSAF
QVNYENVNNPQITEWVQHFVKELKLTGQISFDFIQAEDGTVYAIECNPRTHSAITTFY
DHPQVAEAYLSQAPTTETIQPLTTSKPTYWTYHEVWRLTGIRSFTQLQRWLGNIWRG
TDAIYQPDDPLPFLMVHHWQIPLLLLNNLRRLKGWTRIDFNIGKLVELGGD

[0200] A0A1Z4ND62 (SEQ ID NO: 87)

MIDTVSLNKSLAEKGFGRREIGVIGRNLATLGLLLLVLPINLLLTGVGLISRVSLRNPIS
QKTILISGGKMTKALLIARRFHAAGHRVILIESHKYWLTGHRFSNAVNKFYTVPAPEK
NPSAYIQALLDIIKREKVDLYVPVCSPVASYYDALVKSEMGFLTQVFHCDPEMVKML
DDKFTFAETARKLGLSVPKSFLITHPHQVINFDFQKETRPYILKSIRYDSVRRLDLTKL
PCETPEATERFVRSLPISPENPWIMQEFIPGQEYCTHSTVKNGELRMHCTSKSSAFQV
NYENIDHPRIQSWVSKFVKELGITGQVSFDFIETEDGEVYAIECNPRTHSAITMFYNHP
RVADAYLDEGVWEQPIQPLPDSKPTYWLYHEIWRLTGIRSWKDLQYRWKVLSTGV
DAIYSLDDPLPFLMVHHWQIPLLLWQNLLQLRGWVRIDFNIGKLVELGGD

[0201] A0A0D8ZR72 (SEQ ID NO: 88)

MQKMFAIFQNLGTLTLLAIAFPFNCIVVLSALVWNLISQPFQKQVVFNPDAKNILIGG
GRMTKTLQLARSFHAAGHRVILFDIDKNWFSGYRFSNAVAGFYTVPDPIKDLEGYTI

ALRAIAKQENIDFFVPVGIFANDYFDSKRQPVLSGCCETFHFDADTMKMLDNKFTFT
QKARSLSLSVPKAYLITDPEQVLKFDFSNEKNKYILKSIVYDPVFRLDLTKLPMESLE
KMAIHVRNLPISKDNPWILQEFITGQEYCTHSTVRNGELTVHCCCESSAFQVNYENV
DKPEILQWVSHFVKELQLTGQISFDFIQAEDGTIYAIECNPRTHSAITMYYNHPGLAD
AYLGQKPLAELLQPLPDSKPTYWLYHEVWRLNEIRSLKQLQTWFKNILRGKDAIFDV
NDPLPFLMVHHWHIPLLLLDNLQKLKGWVRIDFNIGKIVQVSD

[0202] A0A2T1LWM6 (SEQ ID NO: 89)

MDNLFNSSADSSSLSKGWLRSIQGSSLKTLGTLLLLLLMLPFNLALTLTALVWSWVW
PFRKRVIASNPKTVMISGGKMTKALQLARSFYMAGHRVILVETHKYWLVGHRYSW
AVDRFYTIPDPKQDTEGYLQGLLDIAQKEQVDLYVPVCSPVASYYDALAKELLAQQ
CDVFHEDAKTVQQLDDKYQFAQAATNLGLTVPKSFKITHPQQVLDFDFSKETHPYII
KSIPYDSVNRLNLTKLPCASRQDTEMFVNSLPISETKPWVMQEFITGQEYCVHSTVK
NGELRVYCCCESSAFQVNYEAVDIPEIKQWVTQFVQGMKLTGQMSFDFIRTPTGEVY
AIECNPRTHSAITLFYNHPDLAKAYLDPEPFSEPLEPLASARPTYWTYHEFWRLVTHL
SSLQEVAYRLGILFKGKDAIFSWNDPLPFLMVHGWQIPLLLLKSLRQGKDWIRIDFNI
GKLVQMGGD

[0203] K9XU47 (SEQ ID NO: 90)

MTQIFFVSGRGSAVLQNLGTLVLLLFLLPFNLIAVAFSAVINIFSGSKQRLTKTDVPKR
ILITGAKMTKALQLARSFHQRGHEVYLVETHKYWLSGHRFSRAVKGFFTVPTPEKEP
DAYCQRLLEIVQQKNIDVFIPVSSPIASYYDSLAKKILEPDCEAIHFDPEITAMLDDKY
AFCTKAKELGLSAPKVFCFTSPQQVIDFDFESDGSQYIVKSIPYDSVRRLDLTKLPFEG
MESYLRSLPISSEKPWVMQEFIRGQEYCFHATVRKGKIRLHCCSQSSPFQVNYEQVD
NPAIYQWVEKFVRELNLTGQICFDMIQTPDGTVYPIECNPRLHSAITMFHDHPGVAD
AYLLDGEQAITPLPDSKPTYWTYHELWRLLQVRSLSELQAWWHKVSRGTDAILQGD
DPLPFLMLHNWQIPLLLLDNLRRLKGWIRIDFNIGKLVELEGD

[0204] A0A2Z6D2K3 (SEQ ID NO: 91)

MTQSISLSLPESTTPSTGIKVKIVALFKTLGTLTLLLIALPFNVLIVLISLLWGIVRVPF
TKNVVATHPQTILVSGAKMTKALQLARSFHADGHRVILIEGHKYWLSGHRFSKAVS
RFYTVPAPQSDPEGYIQALIEIVKKEKVDVYVPVCSPVASYYDSLAKPALSEYCEVFH
FDADITKMLDDKFAFTEKARSLGLSVPKSFKITDPQQVINFDFSQETRKYILKSINYDS
VRRLNLTKLPCDTPEQTAAFVKSLPISPETPWIMQEFIPGKEFCTHSTVRDGELRLHCC
CHSSAFQINYENVENPQIQAWIQHFVKSLRLTGQVSFDFIQAEDGQVYAIECNPRTHS
AITMFYNHPGVAEAYFGKTPLAAPLEPLPSSKPTYWTYHEIWRLTGVRSWKQLQTRL
NILLRGTDAIYCLDDPIPFLTLHHWQIPLLLLQNLQQLKAWVKIDFNIGKLVELGGD

[0205] A0A5P8W9G9 (SEQ ID NO: 92)

MAQSISLSVPKSTTPSTGVSIKIVALFKTLGTLTLLLIALPINAFIVLLSLLWGILFTKK
PAVAAHPQNILVSGGKMTKALQLARSFHAAGHRVILIEGHKYWLSGHRFSNAVSRF
YTVPAPQDDPQGYTQALLEIVKQEKIDIYVPVCSPVASYYDSLAKPALSEYCEVFHFD
ADITKMLDDKFAFTDQARSLGLSVPKSFKITDPEQVINFDFSKETRKYILKSISYDSVR
RLNLTKLPCDTPEETAAFVNSLPISPEKPWIMQEFIPGKELCTHSTVRDGELRLHCCSD
SSAFQINYENVENPQIREWVQHFVKSLGLTGQVSFDFIQAEDGTAYAIECNPRTHSAI
TMFYNHPGVAEAYFGKTPLAAPLEPLADSKPTYWVYHEIWRLTGIRSGKQLQTWFA
RLVRGTDAIYKIDDPLPFLTLHHWQIALLLLQNLQQLKGWVKIDFNIGKLVELGGD

[0206] A0A1S6LXZ0 (SEQ ID NO: 93)

MRKHIFVVFQNLGTLVLLAIAFPLNCIVVLTSLLWSFIKQPFNKSIVVNPNSKNILIAG
ARMTKTLQLARSFHAAGHRVIIIDIEKYWLSGNKYSNSVAGFYTVPDPSKDLEGYVE
TLHAIANTEKIDFFIPVAIFSVIHYDQGKPPLPDCVEFFHFDADVTKILDDKFAFAETA
RSFGLSVPKSFKITDPEQVLNFDFSQEKRKYILKSIPYDQVRRLNLTKLPCDTKSETAA
FVKSLPISEENPWIMQEFIPGKEYCTHTTARDGESRMYCCCESSAFQVNYENVDQREI
MQWASHFTKELGKTGQLSFDFIQAEDGTVYAIECNPRTHSAITMFYNHPGVADAYL
GKEPLAESLQPLPDSKPTYWLYHEVWRLNEIRSFKQLQTWVRNIRRGKEAIFEVSDPL
PFLMVHHWQIPLLILDNLRRLKGWIRIDFNMGELIE

[0207] A0A1Z4LFB5 (SEQ ID NO: 94)

MAQSISVSSSPAIPSFPSETKIAVIIQNLLTLALLLLALPINAAIVLVTLLWHTISRPFQQP
ATKAANPKNILISGGKMTKALQLARSCAAAGHRVILIETHKYWLSGHRFSQAVDKFY
TVPAPQENPERYTQALIDIIKQENIDVYIPVTSPLGSYYDSLAKPLLSEYCEVFHFDIDI
TEKLDDKFAFAETARSLGLSVPKSFKITSAEQVLNFDFSQESRKYILKSIPYDSVRRLD
LTKLPCATPEETAAFVRSLPISPDKPWIMQEFIPGKEFCTHSTVRDGELRLHCCCESSA
FQVNYENVENSQIREWVRHFVKELKLTGQVSFDFIQAEDGRVYAIECNPRTHSAITTF
YDHPQVAQAYLDNEPMAETLQPLPSSKPTYWTYHEVWRLTGIRSFTQLKKWIANIW
RGTDAIYKPDDPLPFLMVHHWQIPLLLLKNLRQIKGWTRIDFNIGKLVELGGD

[0208] A0A4D9CF37 (SEQ ID NO: 95)

MTQSISVASVGQTTQSVTLGLRISALFKNLATLALLLLVLPINAAIVLVSLLLGSQSQA
IATEPKNILISGGKMTKALQLARSFHAAGHRVVLVETHKYWLTGHRFSKAVSRFYTL
PTPQSDPEAYTQALLDIVQKESINVYVPVCSPVSSYYDSLAKPVLSKYCEVFHCDAD
VTQMLDDKYAFAEKARSLGLSVPKSFKITDPKQVINFDFSQEKRKYILKSIPYDSVRR
LDLTKLPCESPEATADFVNSLPISSQKPWIMQEFIPGKEFCTHSTVRNGELRMHCCCE
SSAFQVNYENVDHPQILEWVRHFVKALGITGQVSFDFIEAQDGTIYAIECNPRTHSAIT

MFYNHPDVANAYLSEIPQVEPIQPLINSKPTYWTYHEIWRLTGIRSFSQLQTWVKNFF
GGKDAIYSLSDPLPFLTVHHWQIPLLLLQNLQQLKGWIRIDFNIGKLVEFGGD

[0209] A0A1B2CWF7 (SEQ ID NO: 96)

MAQSIPFDSASPTPQVSWGVRISALWKTVGTLLLLFLALPVNASIVLISLLWGIFSKPF
EKRVVAAAPKNILISGGKMTKALQLARSFHAAGHRVVLVESHKYWLTGHQFSNAVS
VFYTVSPPEKDPEGYTQQLLDIVKKERIDVYVPVCSPVASYYDSLVKPALSQHCEVF
HCDAEITQMLDDKYAFSEKARSFGLSVPKSFKITNPEQVINFDFSQEKRKYILKSIPYD
SVRRLNLTKLPCDTPEETAAFVRSLPISPEKPWIMQEFIPGKEFCTHSTVRNGELRLHC
CCESSAFQVNYENVNNPQILEWVKHFIKEMGITGQVSFDFIQTEDGTVYAIECNPRTH
SAITMFYNHPGVADAYLGKIPLPEPLQPLADSKPTYWLYHEIWRLTGIRSLSQFWTW
LKNLMRGKDAIYQLNDPLPFLTVPHWQITLLLLQNLRQLRGWVKIDFNIGKLVELGG
D

[0210] A0A0C1N3Z4 (SEQ ID NO: 97)

MTQSISFSSPVPATPPFCVKTRFIALFQNLGALTLLLLALPINVAIVLISLIWSFLSRLFS
TQETTVAGAKNILISGGKMTKALQLARFFSAAGHRVVLIETHKYWLSGHRFSNAVSR
FYTTPTPQDEPEEYIQTLVDIVKRENIDVYVPVTSPVASYYDSLAKPALSPYCEVLHF
DADVTKMLDDKFAFSEKARALGLSVPKSFKITNPEQVLNFDFSQETRKYILKSLPYDS
VRRLDLTKLPCNTPEETAAFVKSLPISLEKPWIMQEFIPGKEFCTHSTVRNGDLKLHC
CSESSAFQVNYENVKNPKIQEWVRHFVKGLGLTGQVSFDFIQADDGKVYAIECNPRT
HSAITMFYNHPQVADAYLGTEPLAEPLAPVPNSKPTYWLYHEVWRLTGIRSFAQLQS
WIRNILRGTDAIYELHDPLPFLMVHHWQIALLLLNNLRQLKGWTKIDFNIGKLVELG
GD

[0211] A0A2L2N6B5 (SEQ ID NO: 98)

MRKHIFVVFQNLGTLVLLALAFPLNSIVVLTSLLWNFLKQPFSKSIVVNPNSKNILIAG
ARMTKTLQLARSFHAAGHRVIIIDIEKFWSSGNKYSNSVAGFYTVPDPSKDLEGYVE
TLHAIAKTEKIDFFIPVAIFSVIHYDRGKPPLPDFCEFFHFDADVTKSLDDKFAFAETA
RSFGLSVPKSFKITNPEQVLNFDFSQEKRKYILKSIPYDQIRRLNLTKLPCDTQSETAAF
VKSLPISEENPWIMQEFIPGKEYCTHTTARDGESRMYCCCESSAFQVNYENVDRLEIM
EWASHFTKQLGKTGQLSFDFIQAEDGTVYAIECNPRTHSAITMFYNHPGVADAYLGK
NPLAESLQPLGDSKPTYWLYHEVWRLNEIRSFKQLQTWLRNIRRGKEAMFEVSDPLP
FLMVHHWQIPLLILDNLRRLKGWIRIDFNMGELIE

[0212] A0A1Z4Q915 (SEQ ID NO: 99)

MVELQFIKARIFAVFRNLGTLALLAIAFPFNCIVVLAALLWNFFTRPFQKQVVLSENP
KNILIGGGRMTKTLQLARSFHAAGHRVILVDIHKYWLSGHRFSKAVAGYYTVPEPQK

DLEGYTQALRAIAKKENIDFFIPVAIFAVSYFDPQNKPVLAGCCEIFHFDGEVTKMLD
DKFAFAEKARSFGLSVPKSFKITAPEQVLNFDFSQEKNKYILKSIPYDSVRRLNMTKL
PCDTTEQTAAFVKSLPISEENPWIMQEFIPGQEYCTHSSLRNGELRLHCCCESSAFQV
NYENVDKPEIMQWVSHFVKELGLTGEASFDIIQAVDGTVYPIECNPRTHSAITMFYN
HPGVADAYLGKEPLAEPLQPLPDSKPTHWLYHEVWRLTGIRSLKQLQTWVRNILRG
KDAIFEVHDPLPFLMVHHWQIPLLLLDNLRRLKGWIRIDFNLGELIE

[0213] A0A2Z5VN68 (SEQ ID NO: 100)

MHFNCGAEKLMAQSISLSLPKSTTPSTGVRIKIVALFKTLGTLTLLLIALPINAFIVLLS
LLWSIPFTKKPAVAAHPQNILVSGGKMTKALQLARSFHAAGHRVILVEGHKYWLSG
HRFSKAVSRFYTVPAPQDDPEGYTQALLEIVKQEKIDIYVPVCSPIASYYDSLAKPALS
EYCEVFHFDADITKMLDDKFAFTDQARSLGLSVPKSFKITDPEQVINFDFSKETRKYIL
KSISYDSVRRLNLTKLPCDTPEETAAFVNSLPISPEKPWIMQEFIPGKELCTHSTVRDG
ELRLHCCSDSSAFQINYENVENPQIREWVQHFVKSLGLTGQVSFDFIQAEDGTAYAIE
CNPRTHSAITMFYNHPSVAEAYFGKTPLAAPLEPLADSKPTYWVYHEIWRLTGIRSG
KQLQTWFTRLVRGTDAIYKIDDPLPFLTLHHWQIALLLLQNLQQLKGWVKIDFNIGK
LVELGGD

[0214] A0A1Z4UKN2 (SEQ ID NO: 101)

MFPINLTLVITAFLTNLITLPFQKKITYENPKNILLTGGKMTKSLQLARSFHRAGHKVF
MVETHKYWLSGHQYSKAVKKFLTVPAPEKDPEGYCQSLLDIVKREKIDVFIPVSSPV
ASYYDSLAKPILSPYCEVFHFDTEMTKTLDDKFSLCEQARVLGLTAPKVFLITSPGEII
NFDFSQEQNPYIIKSIQYDSVTRLDMTKFPFEGMKEYVKKLPISKERPWVMQEFIKGQ
EYCTHSTVRDGEIRLHCCSKSSPFQVNYEQVDNPEIFQWVQKFVKELNLTGQISFDF
MQTEDGKVYPIECNPRTHTAITMFYDHPGLADAYLEPGKNQPHIEPLPTSKPTYWLY
HELWRITGIRSFNDLTNWLNKVIKGKDAMLDKDDPLPFLMVHHWQIVLLLLQNMV
KLKGWVRIDFNIGKLVEIGGD

[0215] A0A5Q0GJK5 (SEQ ID NO: 102)

MAQSLPLSSAPATPSLPSQTKIAAIIQNICTLALLLLALPINATIVFISLLVFRPQKVKA
ANPQTILISGGKMTKALQLARSFHAAGHRVVLVETHKYWLTGHRFSQAVDKFYTVP
APQDNPQAYIQALVDIVKQENIDVYIPVTSPVGSYYDSLAKPELSHYCEVFHFDADIT
QMLDDKFALTQKARSLGLSVPKSFKITSPEQVINFDFSGETRKYILKSIPYDSVRRLDL
TKLPCATPEETAAFVRSLPITPEKPWIMQEFIPGKEFCTHSTVRNGELRLHCCCESSAF
QVNYENVNNPQITEWVQHFVKELKLTGQISFDFIQAEDGTVYAIECNPRTHSAITTFY
DHPQVAEAYLSQAPTTETIQPLTTSKPTYWTYHEVWRLTGIRSFTQLQRWLGNIWRG
TDAIYQPDDPLPFLMVHHWQIPLLLLNNLRRLKGWTRIDFNIGKLVELGGD

[0216] A0ZIV3 (SEQ ID NO: 103)

MAQSISLSLGNSPTSSTGVWVKLVALFKTLGTLTLLLIALPFNALIVLISLLWGFVRSP
FRQKAVVAEHPQTILVSGAKMTKALQLARCFHAAGHRVILIEGHKYWLSGHRFSKA
VSGFYTVPAPQLDPEAYIQALVDIVEKEQVDVYVPVCSPVASYYDSLAKPALSEYCE
VFHFDADVTKMLDDKFAFTAQARSLGLSVPKSFKITDTQQVINFDFSQETHKYILKNI
AYDSVRRLNLTKLPCDTPEETAAFVNSLPISEENPWIMQEFIPGKELCTHSTVRDGEL
RLHCCSDSSAFQINYENVENTQIREWVQHFVKSLALTGQISFDFIQAESGTVYAIECNP
RTHSAITMFYNHPGVAEAYLGKTTLDAPLEPLTNSKPTYWIYHEIWRLTGIRSWKQL
QTAVNTLLRGTDAIFQLNDPVPFLTLHHWQIPLLLLKNLQQLKGWVKIDFNIGKLVE
LDGD

[0217] A0A3S1ANM2 (SEQ ID NO: 104)

MIIHMAQSISLSSPAKTHAPGISASSLKTLGTLTLLLLALPLNASLVLVALLLKSLRPQ
NFTTEKPKNILISGGKMTKALQLARSFHNAGHRVILLEAHKYWLTGHRFSSAVNKFY
TVEAPEKDPEGYIQSLVDIVEKENIDVYVPVCSPVASYYDSLAKKALPQCEVIHCDAE
MTQMLDDKHAFAQTAQSFGLSVPKSFKITDPEQVINFDFSQEKRKYILKSIPYDSVRR
LDLTRLPCDTPEATAAFVRSLPISSEKPWIMQEFIPGKEYCTHSTVRNGVITLHCCCES
SAFQVNYENVDNPKIFEWVSRFVKELGITGQVSFDFIEAEDGNIYAIECNPRTHSAITM
FYNHPGVADAYLGTGNNLAEPIQPKFTSKPTYWTYHEIWRLFNTRSWSDFVYRFKII
KHGKDAIFSWQDPLPFLMNPHWQIFLLLIQNLQKNRGWIRIDFNIGKLVELGGD

[0218] In some embodiments, the one or more biosynthetic enzymes comprise a demethyl-4-deoxygadusol synthase (MysA), or a homolog thereof. Exemplary MysA enzymes for use in the present invention include, but are not limited to, the amino acid sequence of any one of SEQ ID NOs: 105-111, or an amino acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of any one of SEQ ID NOs: 105-111:

[0219] A0A2K8WSM2 (SEQ ID NO: 105)

MGNGALAENLKEDDKTVIWRPHEEKYRTSEWYTGSGQITTADEGLSFEVTAVYQLK
SEVKVVKDIFAISNHTLANIYRPRSRCIAVVDQTVAELYGEKIEGYFQAQEIPLELMVI
RAWESDKTPETVHRILAFLGKDGCDVSRNEPVLVIGGGVLSDVAGLACALQHRRTP
YIMIGTTIIAAIDAGPSPRTCTNGTQFKNSIGVYHPPVLTLVDRQFFSTLDMGHIRNGM
AEIIKMAVTDDKELFELLEQYGQELIKTRFATIDASEELEKIADLIIYKALYAYMKHEG
TNMFETYQDRPHAYGHTWSPRFEPAVKLMHGHAVTIGMAFGATLAQELGWLSQEE
CQRIINLSSKLGLSVFHPILEDVQIMVDGQKNMRRKRGDGGLWAPLPTTIGACDYVQ
EVEPELLNQAVVAHKKYCSQLPHEGAGEQMYLSDLGLE

[0220] A0A0D5ACA9 (SEQ ID NO: 106)

MSNLQAQVVAGDRSFRVEGYERIEYDLIYVDGVFAIENTELADSYRPYGRALMVVD
EAVHDIYGDRISAYFDHHEIALTVVPVHIAETAKSLETFERIVGEFDAFGLVRTEPVLV
VGGGLTTDVAGFACASYRRNTPYIRIPTTLIGLIDASVSIKVAVNYGKHKNRLGAYH
ASQKVLLDFSFLGTLPEDQVRNGMAELIKISVVGNLEIFEMLEQYGPELLRTRFGHLD
GTAELRSVADKLTYSAIATMLELEAPNLHEIDLDRVIAFGHTWSPTLELTPPAPFFHG
HAINIDMALSTTVAEQRGHLSTADRDRVLGVMSSIGLALDSPYLTPELLSEATASILK
TRDGILRAAVPDPIGTCRFLNDLDAAELADVLTLHKKICLDFPRAGEGLDMFTAPTP

[0221] A0A0K1S781 (SEQ ID NO: 107)

MAGIKATFTSTDCAFHIQGYEKIDFSLLYVNGAFKIGNPEIAESYAPFRRCLMVIDQT
VYGLYRQQIDQYFAHYQIDLTVFQVSIKEPEKTLRTFEKIVDAFADFGLVRKEPVLVV
GGGLTTDVAGFACSAYRRKTNYIRVPTSLIGLIDASVAIKVAVNHGKLKNRLGAYHA
SQKVILDFSFLGTLPIDQIRNGMAELIKIAVVGNQEIFELLEEHGAALLHSRFGYLNGT
PELQAVGHRLTYKAIQAMLELEVPNLHELDLDRVIAYGHTWSPTLELTPEPPMLHGH
SVNIDMAFTATIAQLRGYISVEDRNRILGLMSRLGLAIDSPYLTPELLWKATEAITRTR
DGLQRAAAPRPIGQCVFMNDLTRSELDKALAVHRAIAQNYPRQGNGEDMYVRLEP
ALEGAGV

[0222] A0A0P4UW20 (SEQ ID NO: 108)

MSSVQAKVEVTDQSFHLEGYEKIEFNLDLIEGLFEVGNSGLADNYRTLGRCLAVVDH
NVDRLYGDQLRSYFEYYEIDLTVFAIEITEPTKTIDTFLKITDAFCDFNLKRKEPVLVIG
GGLVLDVAGFACSAYRRSTNYIRVPSTLIGLIDAGVAIKVAVNHGKLKNRLGAYHPP
KQVILDFSFLKTLPVDQIRNGMAELVKIAVVSNEEVFNLLEQHGEELLYNHFGFVGN
DAELKQIGHRVNYESIKTMLELEAPNLHELMLDRVIAYGHTWSPTLELAPQIPLLHG
HAVNIDMAISATIAEKRGYISALDRDRILGLMSRLGLALDHPLMEIDLMWKATQSIM
LTRDGFLRAAMPRPIGTCYFVNDLTREELESAIADHKRLCADYPRAGAGIDAYVGSS
ELIGSAN

[0223] A0A1Q8JXW2 (SEQ ID NO: 109)

MSNPQAVLSATDTEFRVESWERIEFTLSYVDGVFAPHNTELADLYRPWGRCLMVIDE
TVHEHYGDPIRSYFDHHDIAVTLVPLTIAETAKSLRTLERIVDAYADFGLLRTEPVLV
VGGGLTTDVTGFACASYKRGTPYVRIPTTLIGLIDASVAMKVAVNHGRHKNRLGAF
HASQQVLLDFSFLATLPEAQVRNGVAEMIKIATVANAGLFDLLEKYGDDLLATRFGH
REGTPELRQIAHRCTYDAIHTMLELEHRNLHELDLDRVIAFGHTWSPTLELAPPTPML
HGHAIAIDMAFSATLAARRGDITTGERDRIHRLFSGLGLSVDSTYLTEQLLIDATASIM

QTRAGKLRAALPRPIGTCHFANDIEHTELIETLAAHKAVVAGLPTSVEGVEMWSSAK
TELTTAPNTEART

[0224] A0A347Q3N8 (SEQ ID NO: 110)

MTTNLTATVTATENDFRVRAVEERDYLLTYVDGAFSPESSRIADHHRAHGRCLMIV
DANVHRLHGDRIRAYFEHHGIALTALPLAIDETQKSLRTVERIVDAFGEFGLIRKEPV
LVVGGGLLTDVAGFACAVFRRSTDYVRVPTSLIGLIDASVAIKVAVNHGRTKNRLGA
FHASKEVVLDFSFLGTLPTEQVRNGMAELVKIAVVANAEVFRLLEKYGEDLLHTAFG
TVDGTPQLRETARKVTHEAIGTMLALEAPNLRELDLDRAIAFGHTWSPALELAPETP
YLHGHAISVDMALSCTIAERRGYLATSERDRIFWLLSKVGLSLDSPHLTPELLRAATE
SIVQTRDGLQRAAMPRPIGTCCFVNDLTESELLDGLAAHRELVARYPRGGAGEDVRV
TRSGAA

[0225] A0A6J4VHE9 (SEQ ID NO: 111)

MSTVQAKFEATETAFHVEGYEKIDFSLVFVNGAFDTKNRELADSYRNFGRCLAVVD
ANVNRLYGSQICEYFKYYNIDLNLFPVTISEPTKNLDTFQSIVDAFADFGLVRKEPVLI
VGGGLVTDVAGFACAAYRRSTNYIRIPTTLISLVDAGIAIKVAVNHGKLKNRLGAYH
APKKVMLDFSFLRTLPTPEVRNGMAELVKIAVVSNVEVFELLCEYGADLLTTHFGFD
GGTPLLKEVAHRINYESIKTMLALETPNLHELDLDRVIAYGHTWSPTLELAPSVPLLH
GHAVNIDMALSATIAEKRGYITVEERDRILGLMSQLGLALDHPLLDIDLLWSATQSIT
LTRDGLQRAAMPRPIGKCFFVNDLTREELDAALAEHKHACAQYPRAGAGVDAYVG
SYQQQNLIEGIANV

[0226] In some embodiments, the one or more biosynthetic enzymes comprise an O-methyltransferase (MysB), or a homolog thereof. Exemplary MysB enzymes for use in the present invention include, but are not limited to, the amino acid sequence of SEQ ID NO: 112, or an amino acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 112:

[0227] A0A1Z4LFB8 (SEQ ID NO: 112)

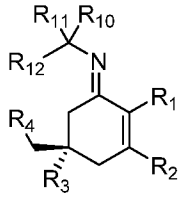
MSTTIAKPTARPVTPVGILAKKLEAIVQKINQRTDLPADLVDNITQAWQLAAGLDPY
LEEYTTSESSALTALAEKTSTEAWQEHFSEGTTVRPLEQEMLSGHVEGQTLKMFVH
MTKAKRVLEIGMFTGYSALAMAEALPPDGVLVACEVDPFAAEVGQAAFDKSPDGK
KIRVELGPALETLNKLVEAGESFDMVFIDADKKEYITYFQTLLDTNLLAPSGFICVDN
TLLQGEVYLPTQQRTANGEAIAQFNRAVALDPRVEQVILPLRDGLTIIRRTA

[0228] In some embodiments, the one or more biosynthetic enzymes comprise a non-ribosomal peptide synthetase (NRPS)-like enzyme (MysE), or a homolog thereof. In certain embodiments, the one or more biosynthetic enzymes comprises an enzyme with an amino

acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of a MysE enzyme, or a homolog thereof.

[0229] In some embodiments, the one or more biosynthetic enzymes comprise a mutated D-alanine-D-alanine ligase (MysD), or a homolog thereof. In some embodiments, the mutated MysD is a Y45A mutant. In some embodiments, the mutated MysD is a R223A mutant. In some embodiments, the mutated MysD is a E239A mutant. In some embodiments, the mutated MysD is a Y241A mutant. In some embodiments, the mutated MysD is a Y325A mutant. In some embodiments, the mutated MysD is a K331A mutant. In some embodiments, the mutated MysD is a S332A mutant. In some embodiments, the mutated MysD has improved activity compared to wild type (WT) MysD. In some embodiments, the mutated MysD has improved activity compared to WT MysD when L-Thr is the amino acid substrate. In some embodiments, the mutated MysD has improved activity compared to WT MysD when α-aminobutyric acid (AABA) is the amino acid substrate. In some embodiments, the mutated MysD has at least 1.1-fold, at least 1.2-fold, at least 1.3-fold, at least 1.4-fold, at least 1.5-fold, at least 1.6-fold, at least 1.7-fold, at least 1.8-fold, at least 1.9-fold, at least 2.0-fold, at least 2.1-fold, at least 2.2-fold, at least 2.3-fold, at least 2.4-fold, at least 2.5-fold, at least 2.6-fold, at least 2.7-fold, at least 2.8-fold, at least 2.9-fold, at least 3.0-fold, at least 3.1-fold, at least 3.2-fold, at least 3.3-fold, at least 3.4-fold, at least 3.5-fold, at least 3.6-fold, at least 3.7-fold, at least 3.8-fold, at least 3.9-fold, at least 4.0-fold, at least 4.1-fold, at least 4.2-fold, at least 4.3-fold, at least 4.4-fold, at least 4.5-fold, at least 4.6-fold, at least 4.7-fold, at least 4.8-fold, at least 4.9-fold, or at least 5.0-fold improved activity compared to WT MysD.

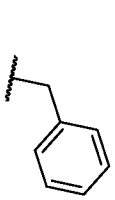
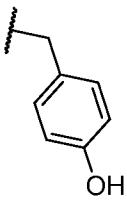
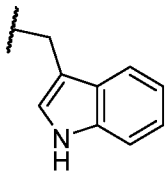
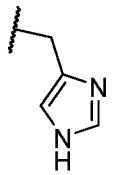
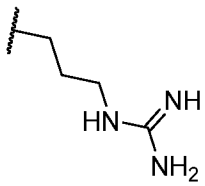
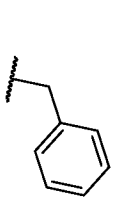
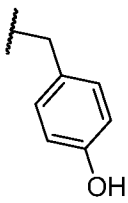
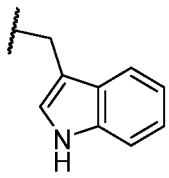
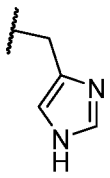
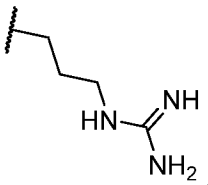
[0230] Compounds of varying structures can be produced using the methods of the present invention. In some embodiments, the compound is a palythine analog. In certain embodiments, the compound has UV-modulating activity. For example, the compounds of the present invention may absorb UV wavelengths between 280 nm and 400 nm. In certain embodiments, the compound is a compound of Formula (I), or a salt thereof:



Formula (I).

[0231] In the compounds of Formula (I) described herein, each of R_1, R_2, R_3, and R_4 may independently be selected from the group consisting of $-OR^a$, $-(NH)R^b$, and $-N(R^b)_2$, wherein

each instance of R^a is independently hydrogen or optionally substituted C_{1-6} alkyl and each instance of R^b is independently hydrogen or optionally substituted C_{1-6} alkyl. In some embodiments, R_1 is $-OR^a$, wherein R^a is optionally substituted C_{1-6} alkyl. In certain embodiments, R_1 is $-OCH_3$. In some embodiments, R_2 is $-NH_2$. In certain embodiments, R_3 is -OH. In some embodiments, R_4 is -OH. In some embodiments, R_1 is $-OCH_3$, R_2 is $-NH_2$, R_3 is -OH, and R_4 is -OH.

[0232] The compounds of Formula (I) described herein also include moieties R_{10}, R_{11}, and R_{12}. R_{10} may be selected from the group consisting of hydrogen and $-CO_2R_{13}$, wherein R_{13} may be selected from the group consisting of hydrogen and optionally substituted alkyl; and each of R_{11} and R_{12} may be independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, or R_{11} and R_{12} are taken together to form an optionally substituted alkenyl group; provided that if R_{10} is $-CO_2R_{13}$ and R_{11} is hydrogen, R_{12} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  ; and provided that if R_{10} is $-CO_2R_{13}$ and R_{12} is hydrogen, R_{11} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  .

[0233] In certain embodiments, R_{10} is hydrogen. In certain embodiments, R_{10} is $-CO_2H$. In certain embodiments, R_{11} is hydrogen. In certain embodiments, R_{11} is optionally substituted alkyl. In certain embodiments, R_{11} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain embodiments, R_{11} is

alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$. In certain enbodiments, R_{12} is hydrogen. In certain embodiments, R_{12} is optionally substituted alkyl. In certain embodiments, R_{12} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain embodiments, R_{12} is alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$.

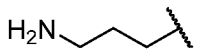
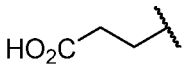
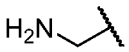
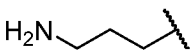
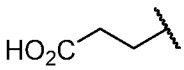
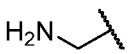
[0234] In certain embodiments, R_{10} is hydrogen and R_{11} is optionally substituted alkyl. In certain embodiments, R_{10} is hydrogen and R_{11} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain embodiments, R_{10} is hydrogen and R_{11} is alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$. In certain embodiments, R_{10} is hydrogen, R_{12} is hydrogen, and R_{11} is optionally substituted alkyl. In certain embodiments, R_{10} is hydrogen, R_{12} is hydrogen, and R_{11} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain embodiments, R_{10} is hydrogen, R_{12} is hydrogen, and R_{11} is alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$.

[0235] In certain embodiments, R_{10} is $-CO_2H$ and R_{11} is optionally substituted alkyl. In certain embodiments, R_{10} is $-CO_2H$ and R_{11} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain embodiments, R_{10} is $-CO_2H$ and R_{11} is alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$.In certain embodiments, R_{10} is $-CO_2H$, R_{12} is hydrogen, and R_{11} is optionally substituted alkyl. In certain embodiments, R_{10} is $-CO_2H$, R_{12} is hydrogen, and R_{11} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain embodiments, R_{10} is $-CO_2H$, R_{12} is hydrogen, and R_{11} is alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$.

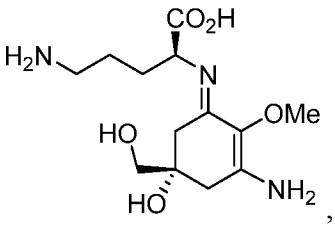
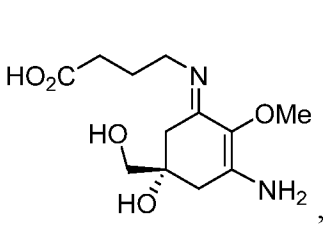
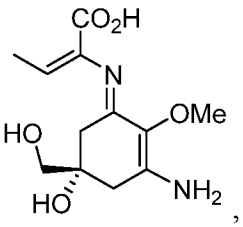
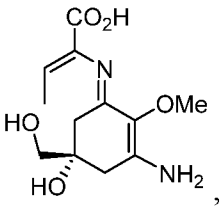
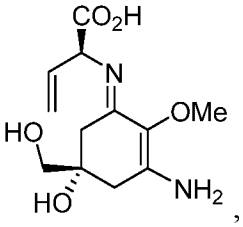
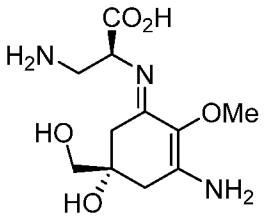
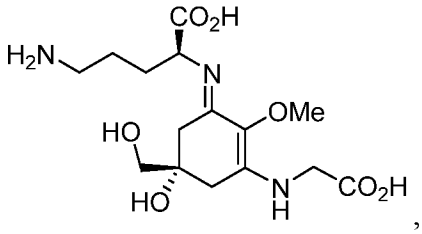
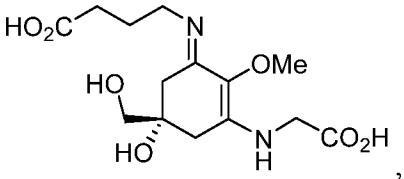
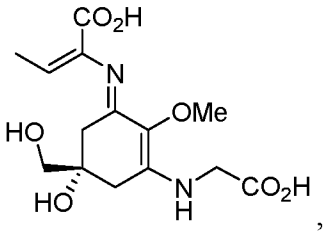
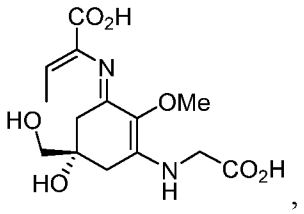
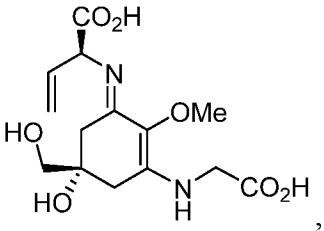
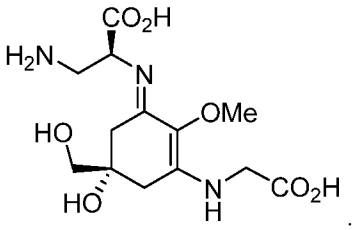
[0236] In certain embodiments, R_{10} is hydrogen and R_{12} is optionally substituted alkyl. In certain embodiments, R_{10} is hydrogen and R_{12} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain embodiments, R_{10} is hydrogen and R_{12} is alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$. In certain embodiments, R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is optionally substituted alkyl. In certain embodiments, R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain

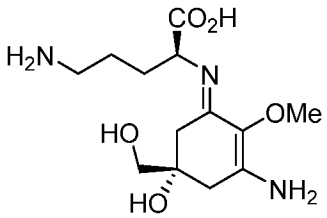
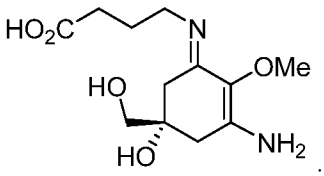
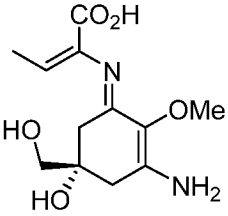
embodiments, R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$.

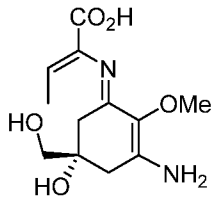
[0237] In certain embodiments, R_{10} is $-CO_2H$ and R_{12} is optionally substituted alkyl. In certain embodiments, R_{10} is $-CO_2H$ and R_{12} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain embodiments, R_{10} is $-CO_2H$ and R_{12} is alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$.In certain embodiments, R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is optionally substituted alkyl. In certain embodiments, R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is alkyl optionally substituted with halogen, optionally substituted hydroxyl, optionally substituted amino, or acyl. In certain embodiments, R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is alkyl optionally substituted with hydroxyl, substituted hydroxyl, amino, substituted amino, or $-CO_2H$.

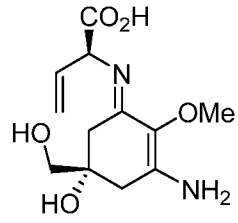
[0238] In certain embodiments, R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  In certain embodiments, R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is  . In some embodments, R_{10} is $-CO_2H$, and R_{11} and R_{12} are taken together to form  . In some embodments, R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  . In some embodiments, R_1 is $-OCH_3$, R_2 is $-NH_2$, R_3 is -OH, R_4 is -OH, R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  . In some embodiments, R_1 is $-OCH_3$, R_2 is $-NH_2$, R_3 is -OH, R_4 is -OH, R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is  . In some embodiments, R_1 is $-OCH_3$, R_2 is $-NH_2$, R_3 is -OH, R_4 is -OH, R_{10} is $-CO_2H$, and R_{11} and R_{12} are taken together to form  . In some embodiments, R_1 is $-OCH_3$, R_2 is $-NH_2$, R_3 is -OH, R_4 is -OH, R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  .

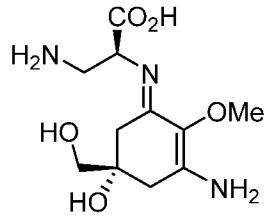
[0239] In some embodiments, the compound of Formula (I) is of the formula:

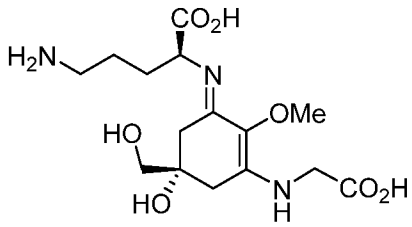













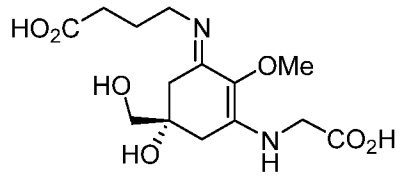
In certain embodiments, the compound of Formula (I) is not  . In certain embodiments, the compound of Formula (I) is not  . In certain embodiments, the compound of Formula (I) is not  . In certain

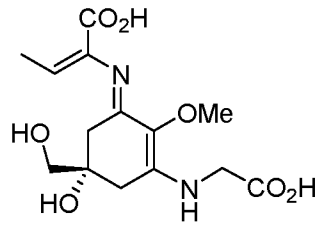
embodiments, the compound of Formula (I) is not  . In certain embodiments,

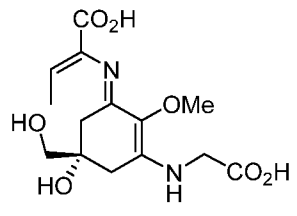
the compound of Formula (I) is not  . In certain embodiments, the

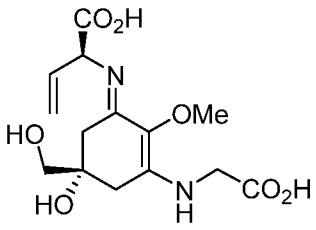
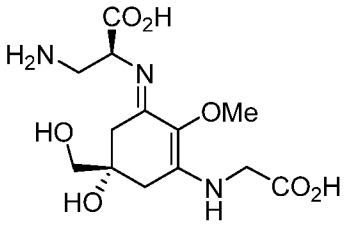
compound of Formula (I) is not  . In certain embodiments, the compound

of Formula (I) is not  . In certain embodiments, the

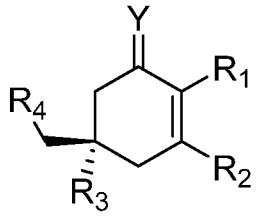
compound of Formula (I) is not  . In certain embodiments, the

compound of Formula (I) is not  . In certain embodiments, the

compound of Formula (I) is not  . In certain embodiments, the

compound of Formula (I) is not  . In certain embodiments, the compound of Formula (I) is not  .

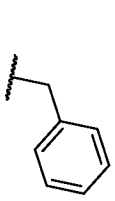
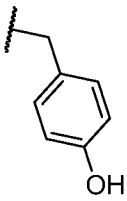
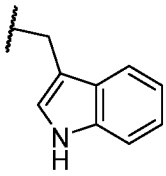
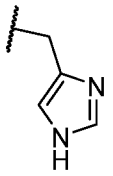
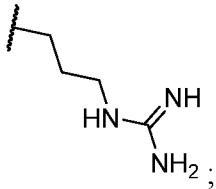
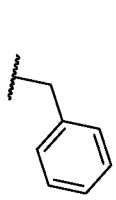
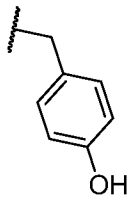
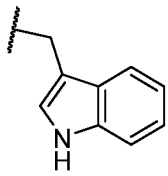
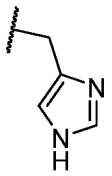
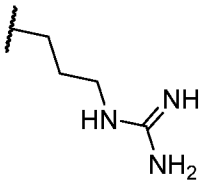
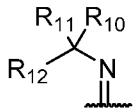
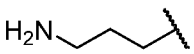
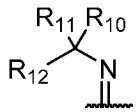
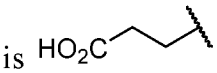
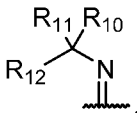
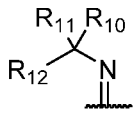
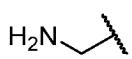
[0240] The methods disclosed herein may further comprise providing a substrate of one of the MAA biosynthetic enzymes to the recombinant microorganism. In some embodiments, the substrate is a compound of Formula (II), or a salt thereof:



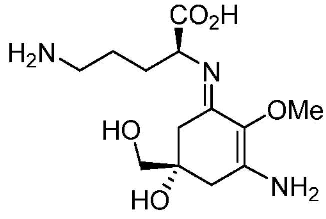
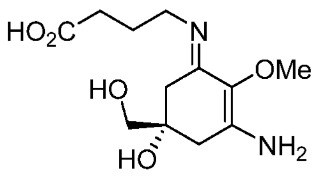
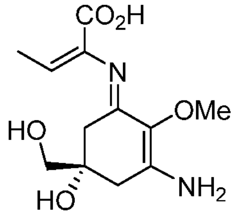
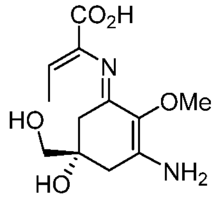
Formula (II).

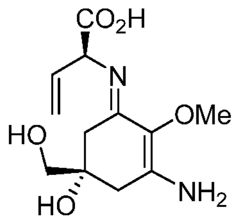
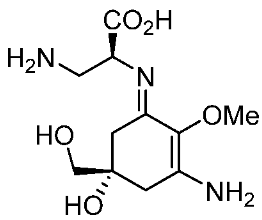
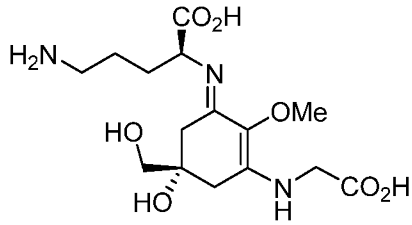
[0241] In the compounds of Formula (II) described herein, each of R_1, R_2, R_3, and R_4 may independently be selected from the group consisting of $-OR^a$, $-(NH)R^b$, and $-N(R^b)_2$, wherein each instance of R^a is independently hydrogen or optionally substituted C_{1-6} alkyl and each instance of R^b is independently hydrogen or optionally substituted C_{1-6} alkyl. In certain embodiments, R_1 is -OH. In certain embodiments, R_1 is $-OCH_3$. In some embodiments, R_2 is -OH. In certain embodiments, R^2 is $-NH_2$. In some embodiments, R_2 is $-(NH)R^b$, wherein R^b is optionally substituted alkyl. In certain embodiments, R_2 is $-NHCH_2CO_2H$. In some embodiments, R_3 is -OH. In some embodiments, R_4 is -OH. In some embodiments, R_1 is $-OCH_3$, R_2 is $-(NH)R^b$, R_3 is -OH, and R_4 is -OH. In some embodiments, R_1 is $-OCH_3$, R_2 is $-NH_2$, R_3 is -OH, and R_4 is -OH. In some embodiments, R_1 is -OH, R_2 is -OH, R_3 is -OH, and R_4 is -OH. In some embodiments, R_1 is $-OCH_3$, R_2 is -OH, R_3 is -OH, and R_4 is -OH.

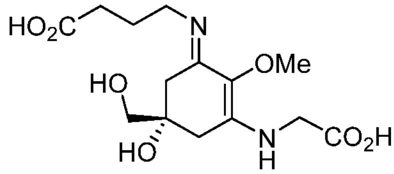
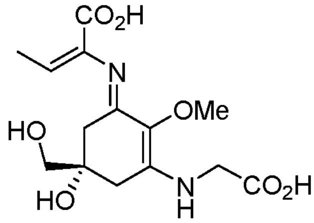
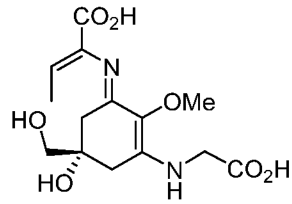
[0242] The compounds of Formula (II) described herein also include a moiety Y. Y may be O or  , wherein R_{10} may be selected from the group consisting of hydrogen and $-CO_2R_{13}$, wherein R_{13} may be selected from the group consisting of hydrogen and optionally

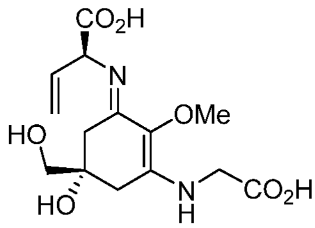
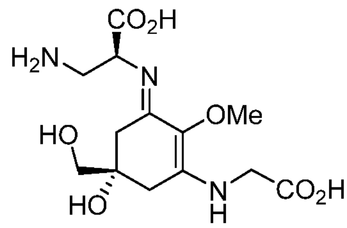
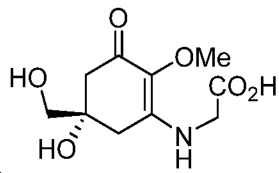
substituted alkyl; and each of R_{11} and R_{12} may be independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, or R_{11} and R_{12} are taken together to form an optionally substituted alkenyl group; provided that if R_{10} is $-CO_2R_{13}$ and R_{11} is hydrogen, R_{12} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  ; and provided that if R_{10} is $-CO_2R_{13}$ and R_{12} is hydrogen, R_{11} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  . In certain embodiments, Y is O. In some embodiments, Y is  . In certain embodiments, Y is  , R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  . In certain embodiments, Y is  , R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is  . In certain embodiments, Y is  , R_{10} is $-CO_2H$, and R_{11} and R_{12} are taken together to form  . In certain embodiments, Y is  , R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  .

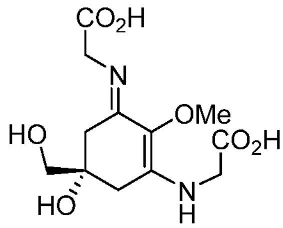
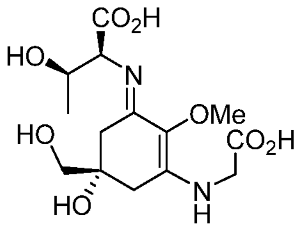
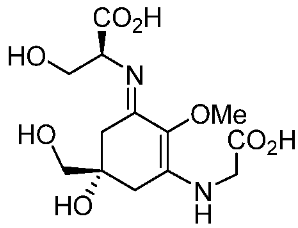
[0243] In some embodiments, the substrate is a compound of the formula:

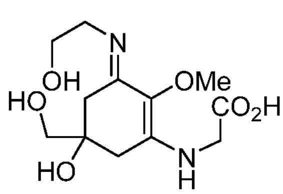
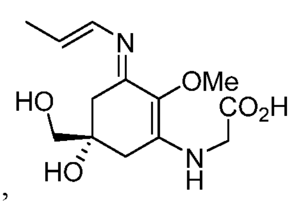
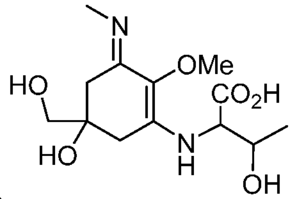
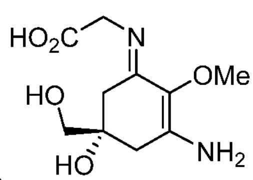
 ,  ,  ,  ,

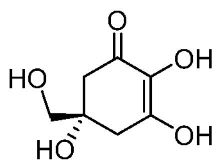
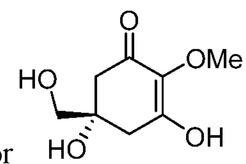
 ,  ,  ,

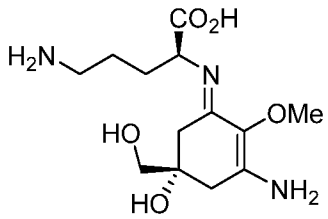
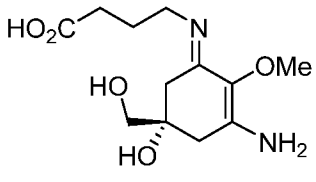
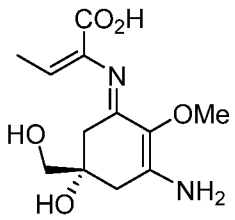
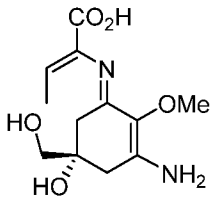
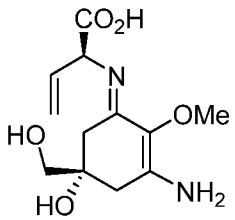
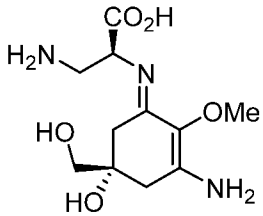
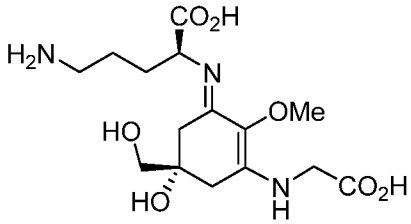
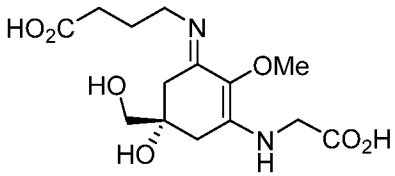
 ,  ,  ,

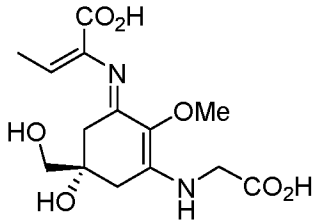
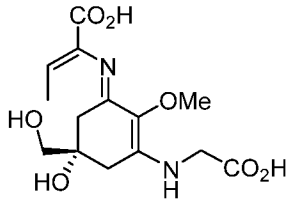
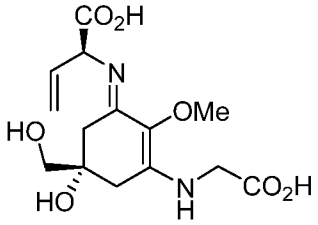
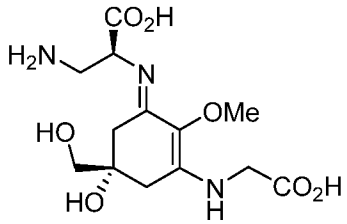
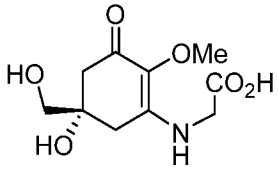
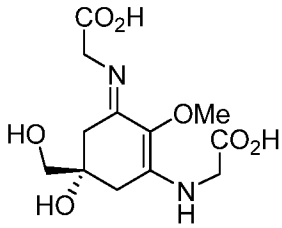
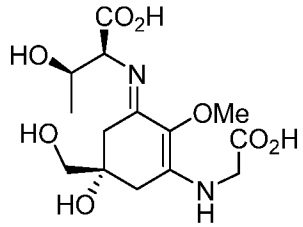
 ,  ,  ,

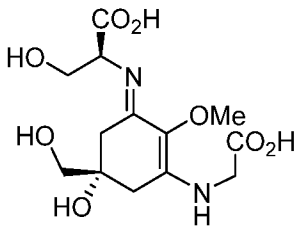
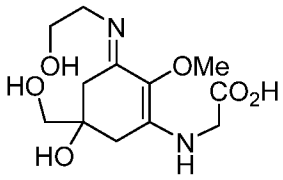
  ,  ,

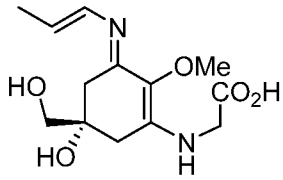
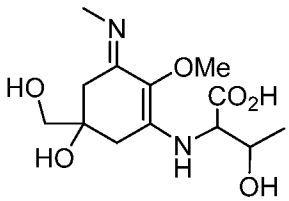
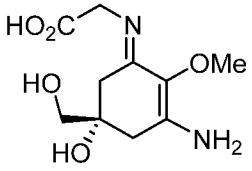
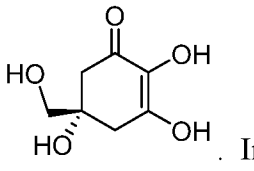
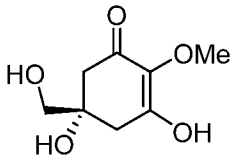
 ,  ,  ,  ,

 , or  . In certain embodiments, the substrate is not a

compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  .

In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  .

embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  .

In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  . In certain embodiments, the substrate is not a compound of the formula  .

[0244] Any suitable microorganism that can be genetically manipulated (*e.g.*, genomically engineered, or transformed with a suitable vector to express a heterologous gene) may be used in the methods of the present invention. For example, the recombinant microorganism may be a species of bacteria or yeast. In some embodiments, the recombinant microorganism is a species of cyanobacteria. In some embodiments, the recombinant microorganism is a

species of bacteria from the human microbiome (*e.g.*, including, but not limited to, any of the species listed herein). In certain embodiments, the recombinant microorganism is *E. coli*.

[0245] The present disclosure also encompasses recombinant microorganisms for use in performing the methods of the present invention. For instance, in one aspect the present disclosure includes recombinant microorganisms comprising a heterologous nucleic acid encoding one or more MAA biosynthetic enzymes, wherein the one or more MAA biosynthetic enzymes comprise a D-alanine-D-alanine ligase (MysD), or a homolog thereof. In another aspect, the present disclosure provides methods of producing a compound, comprising culturing such a recombinant microorganism under conditions suitable for production of the compound and isolating the compound from the recombinant microorganism.

Compositions

[0246] In one aspect, the present disclosure provides compositions comprising a compound produced by the methods of the present invention (*e.g.*, a compound of Formula (I), or a salt thereof). In some embodiments, the composition optionally comprises one or more suitable excipients. In certain embodiments, the compositions described herein comprise a compound of Formula (I), or a salt thereof, and an excipient.

[0247] In certain embodiments, the compound described herein is provided in an effective amount in the composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the compound is provided in an amount effective for preventing sunburn in a subject. In certain embodiments, the compound is provided in an amount effective for preventing cancer (*e.g.*, skin cancer) in the subject. In certain embodiments, the compound is provided in an amount effective for treating or preventing a chronic inflammatory disease or condition in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for reducing symptoms (*e.g.*, symptoms of sunburn) by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 98%.

[0248] Compositions described herein can be prepared by any method known in the art. In general, such preparatory methods include bringing the compound described herein (*i.e.*, the "active ingredient") into association with a carrier or excipient, and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping, and/or packaging the

product into a desired single- or multi-dose unit, or into a formulation for topical administration.

[0249] Relative amounts of the active ingredient, the excipient, and/or any additional ingredients in a composition described herein will vary. The composition may comprise between 0.1% and 100% (w/w) active ingredient.

[0250] Excipients used in the manufacture of the provided compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[0251] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[0252] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[0253] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.*, acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.*, bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.*, stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.*, carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.*, carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.*, polyoxyethylene sorbitan monolaurate (Tween® 20),

polyoxyethylene sorbitan (Tween® 60), polyoxyethylene sorbitan monooleate (Tween® 80), sorbitan monopalmitate (Span® 40), sorbitan monostearate (Span® 60), sorbitan tristearate (Span® 65), glyceryl monooleate, sorbitan monooleate (Span® 80), polyoxyethylene esters (*e.g.*, polyoxyethylene monostearate (Myrj® 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.*, Cremophor®), polyoxyethylene ethers, (*e.g.*, polyoxyethylene lauryl ether (Brij® 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic® F-68, poloxamer P-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[0254] Exemplary binding agents include starch (*e.g.*, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum®), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[0255] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[0256] Exemplary antioxidants include alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[0257] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium

chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[0258] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[0259] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[0260] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[0261] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant® Plus, Phenonip®, methylparaben, Germall® 115, Germaben® II, Neolone®, Kathon®, and Euxyl®.

[0262] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[0263] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[0264] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening

primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[0265] Dosage forms for topical and/or transdermal administration of a compound produced by the methods described herein may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and/or patches. Generally, the active ingredient is admixed under sterile conditions with an acceptable carrier or excipient and/or any needed preservatives and/or buffers as can be required. In some embodiments, the composition for topical administration is formulated as a sunscreen. In certain embodiments, the composition for topical administration is formulated as a cosmetic.

[0266] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi-liquid preparations such as liniments, lotions, oil-in-water and/or water-in-oil emulsions such as creams, ointments, and/or pastes, and/or solutions and/or suspensions. Topically administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[0267] The compositions described herein may also comprise one or more additional active ingredients (*e.g.*, additional compounds with UV-modulating, anti-inflammatory, and/or anti-oxidative activity). In certain embodiments, a composition described herein including a compound described herein and an additional active ingredient shows a synergistic effect (*e.g.*, improved prevention of sunburn in a subject) that is absent in a composition including either the compound or the additional active ingredient, but not both.

[0268] Thus, in one aspect, the present disclosure contemplates compositions comprising a compound produced by any of the methods of the present invention and optionally an excipient. In some embodiments, the composition is for topical administration. In certain embodiments, the composition is formulated as a sunscreen. In certain embodiments, the

composition is formulated as a cosmetic (*e.g.*, make-up, concealer, a moisturizer, etc.). In another aspect, the present disclosure provides methods of making a composition as described herein, comprising culturing a recombinant microorganism under conditions suitable for production of a compound, as described herein, and isolating the compound from the recombinant microorganism, wherein the recombinant microorganism comprises a heterologous nucleic acid encoding one or more MAA biosynthetic enzymes, wherein the one or more MAA biosynthetic enzymes comprise a D-alanine-D-alanine ligase (MysD), or a homolog thereof, and adding the compound to one or more excipients to produce the composition.

Methods of Prevention and Treatment

[0269] In another aspect, the present disclosure includes methods of administering a compound (*e.g.*, any of the compounds disclosed herein). In some embodiments, a method of administering a compound comprises applying any of the compositions disclosed herein to a subject. In certain embodiments, the composition is applied on the skin of a subject in need thereof. In some embodiments, the method is a method preventing sunburn in a subject in need thereof.

[0270] In certain embodiments, the method is a method of preventing cancer in a subject in need thereof (*e.g.*, skin cancers such as melanoma, basal cell carcinoma, or squamous cell carcinoma as described herein). MAAs and related compounds have utility as anti-cancer agents through their antioxidant and anti-proliferative activities (*Mar. Drugs* **2017**, *15*(10), 326). For example, the compounds of the present disclosure have UV-modulating activity and may prevent DNA damage in skin cells caused by UV radiation from the sun when applied to the skin in any of the compositions disclosed herein.

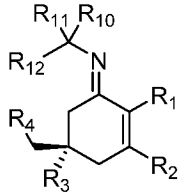
[0271] In certain embodiments, the method is a method of preventing or treating a chronic inflammatory disease in a subject in need thereof. For example, compounds of the present disclosure have anti-oxidative and anti-inflammatory activities and may prevent or alleviate symptoms of an inflammatory disease when applied to the skin in any of the compositions disclosed herein.

Compounds

[0272] In another aspect, the present disclosure provides compounds produced by the methods of the present invention. In some embodiments, the present disclosure provides compounds produced by culturing a recombinant microorganism under conditions suitable

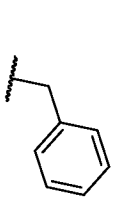
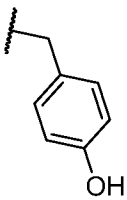
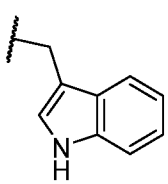
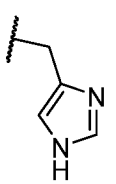
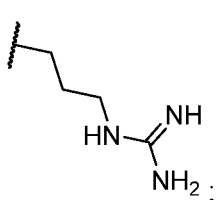
for production of the compound and isolating the compound from the recombinant microorganism. In certain embodiments, the recombinant microorganism comprises a heterologous nucleic acid encoding one or more MAA biosynthetic enzymes, wherein the one or more MAA biosynthetic enzymes comprise a D-alanine-D-alanine ligase (MysD), or a homolog thereof. In some embodiments, the heterologous nucleic acid encodes additional MAA biosynthetic enzymes (*e.g.*, MysA, MysB, MysC, MysE, and/or MysH, or homologs or variants thereof).

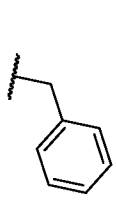
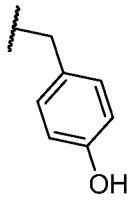
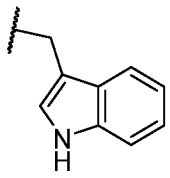
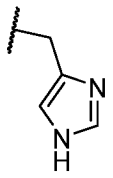
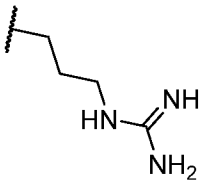
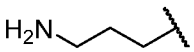
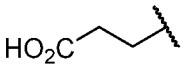
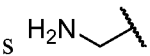
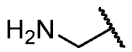
[0273] In some embodiments, the compound is a compound of Formula (I), or a salt thereof:



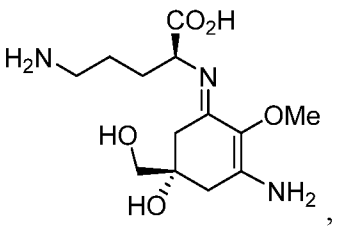
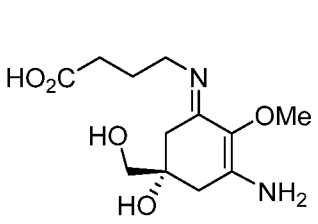
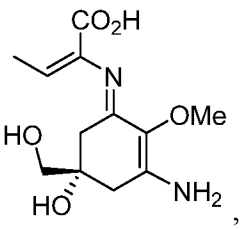
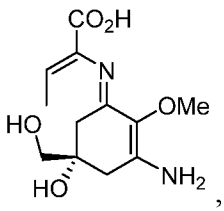
Formula (I).

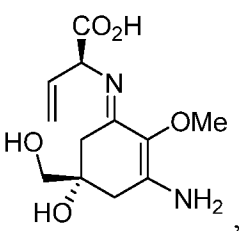
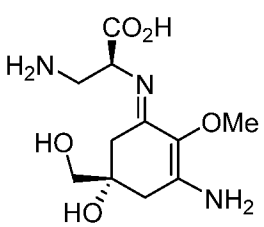
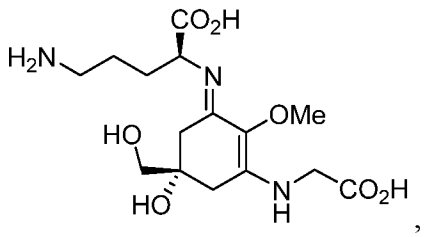
[0274] In the compounds of Formula (I) described herein, each of R_1, R_2, R_3, and R_4 may independently be selected from the group consisting of $-OR^a$, $-(NH)R^b$, and $-N(R^b)_2$, wherein each instance of R^a is independently hydrogen or optionally substituted C_{1-6} alkyl and each instance of R^b is independently hydrogen or optionally substituted C_{1-6} alkyl. In some embodiments, R_1 is $-OR^a$, wherein R^a is optionally substituted C_{1-6} alkyl. In certain embodiments, R_1 is $-OCH_3$. In some embodiments, R_2 is $-NH_2$. In certain embodiments, R_3 is -OH. In some embodiments, R_4 is -OH.

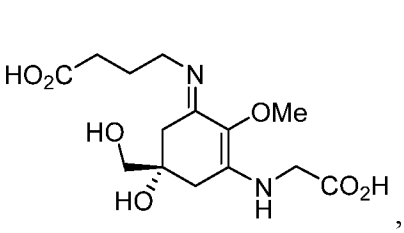
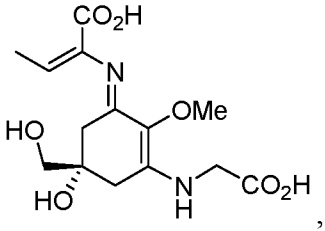
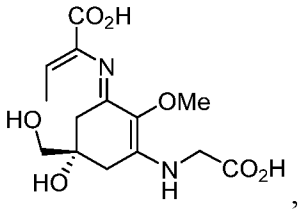
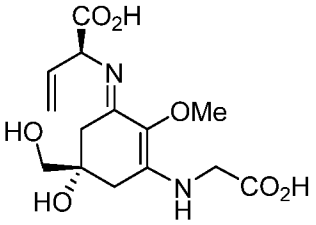
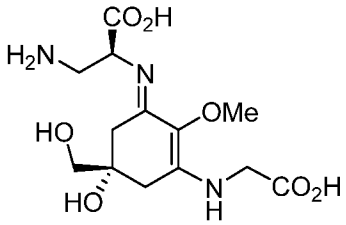
[0275] The compounds of Formula (I) described herein also include moieties R_{10}, R_{11}, and R_{12}. R_{10} may be selected from the group consisting of hydrogen and $-CO_2R_{13}$, wherein R_{13} may be selected from the group consisting of hydrogen and optionally substituted alkyl; and each of R_{11} and R_{12} may be independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, or R_{11} and R_{12} are taken together to form an optionally substituted alkenyl group; provided that if R_{10} is $-CO_2R_{13}$ and R_{11} is hydrogen, R_{12} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  ; and provided that if R_{10} is $-CO_2R_{13}$ and R_{12} is hydrogen, R_{11} is not selected from the group

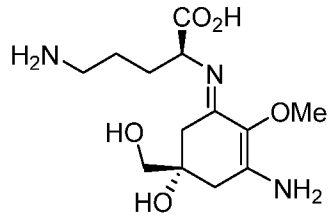
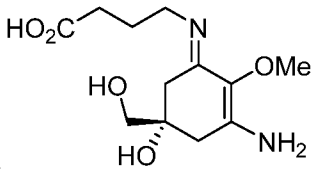
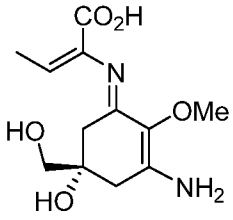
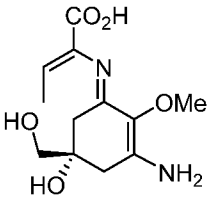
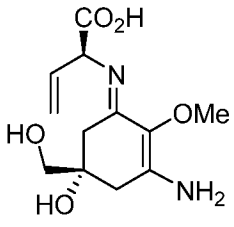
consisting of hydrogen, -CH_3, -$CH(CH_3)_2$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)CH_2CH_3$, -CH_2OH, -$CH(OH)CH_3$, -$CH_2C(O)NH_2$, -$CH_2CH_2C(O)NH_2$, -CH_2SH, -$CH_2CH_2SCH_3$, -CH_2CO_2H, -$CH_2CH_2CO_2H$, -$CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  . In certain embodiments, R_{10} is -CO_2H, R_{11} is hydrogen, and R_{12} is  In certain embodiments, R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is  . In some embodments, R_{10} is -CO_2H, and R_{11} and R_{12} are taken together to form  . In some embodments, R_{10} is -CO_2H, R_{11} is hydrogen, and R_{12} is  . In some embodiments, R_1 is -OCH_3, R_2 is -NH_2, R_3 is -OH, R_4 is -OH, R_{10} is -CO_2H, R_{11} is hydrogen, and R_{12} is  . In some embodiments, R_1 is -OCH_3, R_2 is -NH_2, R_3 is -OH, R_4 is -OH, R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is  . In some embodiments, R_1 is -OCH_3, R_2 is -NH_2, R_3 is -OH, R_4 is -OH, R_{10} is -CO_2H, and R_{11} and R_{12} are taken together to form  . In some embodiments, R_1 is -OCH_3, R_2 is -NH_2, R_3 is -OH, R_4 is -OH, R_{10} is -CO_2H, R_{11} is hydrogen, and R_{12} is  .

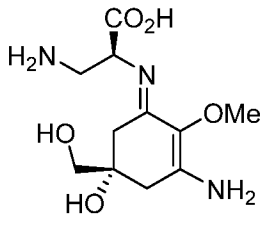
[0276] In some embodiments, the compound of Formula (I) is of the formula:

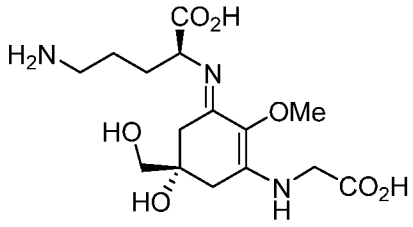
 ,  ,  ,  ,

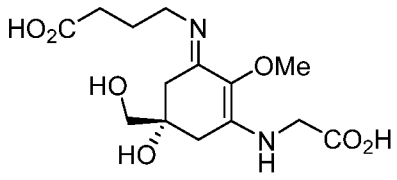
 ,  ,  ,

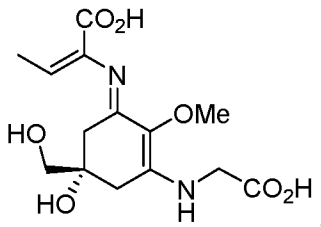






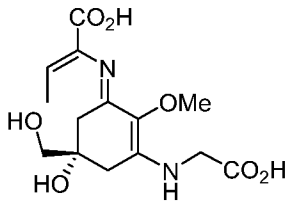
compound of Formula (I) is not  . In certain embodiments, the compound of Formula (I) is not  . In certain embodiments, the compound of Formula (I) is not  . In certain embodiments, the compound of Formula (I) is not  . In certain embodiments, the compound of Formula (I) is not  . In certain embodiments, the compound of Formula (I) is not

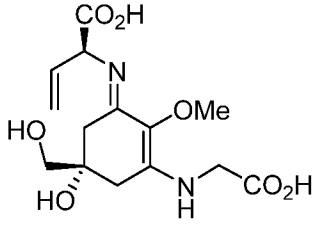

. In certain embodiments, the compound of Formula (I) is not

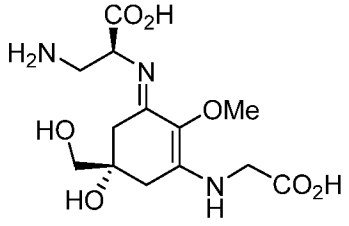

. In certain embodiments, the compound of Formula (I) is not


. In certain embodiments, the compound of Formula (I) is not


. In certain embodiments, the compound of Formula (I) is not


. In certain embodiments, the compound of Formula (I) is not


. In certain embodiments, the compound of Formula (I) is not


.

[0277] In some embodiments, a compound of the present invention, or a salt thereof, is provided in a composition (*e.g.*, in any of the forms disclosed herein). In some embodiments, the composition is for topical administration. In certain embodiments, the composition is

formulated as a sunscreen. In certain embodiments, the composition is formulated as a cosmetic.

[0278] In one aspect, the present disclosure provides methods of administering the compounds of the present invention comprising applying any of the compositions disclosed herein to a subject. In some embodiments, the composition is applied on the skin of a subject. In certain embodiments, the composition is applied on the skin of a subject in need thereof as a method of preventing sunburn (*e.g.*, when the composition is formulated as a sunscreen). In certain embodiments, the composition is applied on the skin of a subject in need thereof as a method of preventing cancer. In certain embodiments, the composition is applied on the skin of a subject in need thereof as a method of treating or preventing a chronic inflammatory disease.

EXAMPLES

[0279] Mycosporine-like amino acids (MAAs) are a family of natural, thermally and photochemically stable UV protectants (**FIG. 1A**).[16] Originally isolated from terrestrial fungal species, over 30 MAA analogs have been identified from taxonomically diverse marine and terrestrial organisms (*e.g.*, cyanobacteria, eukaryotic algae, corals, plants, and vertebrates) and possess various functional groups at the C1 and, to a lesser extent, the C3 of the characteristic cyclohexenimine core (**FIG. 1A**).[16-18] Indeed, the majority of MAAs carry a C3-L-Gly moiety, though L-Ala, L-Glu, and other amine-containing components also appear. Common amino acid building blocks at the C1 include L-Ser (shinorine), L-Thr (porphyra-334), L-Gly (mycosporine-2-Gly) and L-Ala.[16-18] These moieties at the C1 and C3 can likely be converted into other functional groups, including amino alcohol (*e.g.*, asterina-330), enaminone (*e.g.*, palythene), methyl amine (*e.g.*, mycosporine-methylamine-Thr), or an amine group (*e.g.*, palythine and palythine-Ser),[17,19] while glycosylated MAAs have been produced in a variety of organisms.[20,21] Of note, except a few analogs (*e.g.*, mycosporine-glycine, porphyra-334, palythene and palythine),[22-25] the absolute configuration of the majority of MAAs, particularly the C5, has not been fully elucidated. Despite notable structural diversity, these MAA analogs display absorption maxima between 280 and 400 nm and possess extinction coefficients of up to 50,000 $M^{-1} \cdot cm^{-1}$.[16-17] They are among the strongest UV absorbing compounds, and the cyclohexenimine core is critical for the dissemination of UV energy. Furthermore, accumulated evidence demonstrates the

antioxidative, anti-inflammatory and antiaging properties of MAAs, providing another mechanism of photoprotection.[14]

[0280] This study uses unnatural amino acids as the substrates of the MysD reaction.

Example 1: MysD accepts unnatural amino acid substrates.

[0281] Seven amino acids along with L-threonine as the positive control were tested (**Figure 2A**). The chemical structures of corresponding di-substituted MAA analogs were listed in **Figure 2B**. The reaction solution contained 50 mM HEPES, pH 8.0, 10 mM $MgCl_2$, 50 uM mycosporine-glycine (MG), 5 mM amino acid substrates, and 5 mM ATP. The reactions were initiated by adding 0.5 uM MysD and then carried out at room temperature for 4 hours. The reactions were then terminated and centrifuged. The supernatants were analyzed by LC-HRMS, and the extracted ion chromatogram (EIC) traces indicated that, in addition to L-threonine, four unnatural amino acid substrates could be used by MysD to produce unnatural MAA products (**Figure 3**), including L-ornithine, γ-aminobutyric acid, (S)-2-aminobut-3-enoic acid, and (S)-2,3-diaminopropionic acid. The structures of the new MAA analogs were validated by HRMS analysis (**Figure 4**: Compound 2, observed $[M+H]^+$ m/z 360.1792, calculated $[M+H]^+$ 360.1765; Compound 3, observed $[M+H]^+$ m/z 331.1492, calculated $[M+H]^+$ 331.1500; Compound 5, observed $[M+H]^+$ m/z 329.1336, calculated $[M+H]^+$ 329.1343; Compound 7, observed $[M+H]^+$ m/z 332.1439, calculated $[M+H]^+$ 332.1452). Of note, the maximal absorption wavelengths of compounds 5 and 7 were shifted to 337 nm and 327 nm, respectively, instead of the 334 nm for the natural MAA porphyra-334 (**Figure 4C-D**). These results indicate that the incorporation of unnatural amino acid moiety on the C1 could lead to the generation of MAA analogs with a broader UV coverage, aiding their applications in UV protection. MysD was not able to take (*R*)-2,3-diaminopropionic acid as substrate, suggesting its selection toward *S*-amine at the substrate C2.

Example 2: Bioinformatic analysis of MysD.

[0282] MysD from *Nostoc linckia* NIES-25 demonstrates substantial substrate flexibility in synthesizing MAA analogs, and its homologs can possess different substrate scopes. To examine the functional distribution of its homologs, sequence similarity network (SSN) analysis of 249 MysD homologs only from cyanobacterial genomes was performed. When cut-off threshold was set at 172 (corresponding to E-value <1e−160), the MysD homologs were separated into different clusters and singletons (**Figure 5**). MysD from *Nostoc linckia*

NIES-25 sits in the same cluster as the first reported MysD Npf5597 but in a distinct clade. This result aligns well with the results of their biochemical studies as these two MysD homologs have different substrate scopes. MysD of *Nostoc linckia* NIES-25 is a highly flexible enzyme with L-threonine as the best substrate, while Npf5597 favors L-serine over L-glycine and L-threonine (doi: 10.1128/JB.05730-11). Importantly, this result indicates that MysD homologs in different clusters can possess a wide range of substrate flexibility and they can be used to synthesize new unnatural MAA analogs.

Example 3: Structure guided mutagenesis of MysD improves catalytic efficiency.

[0283] Based on the crystal structure of MysD docked with ATP, MG and Thr, several residues potentially important for substrate binding were selected for mutagenesis studies. Generated mutants included Y45A, R223A, E239A, Y241A, Y325A, K331A, and S332A. The relative activity of these MysD mutants was tested using L-Thr or α-aminobutyric acid (AABA) as the amino acid substrate. The results showed that most of these mutants lost the majority of the catalytic ability to both substrates (FIGs. 9 & 10), supporting their importance in substrate binding and/or proper enzyme folding. Surprisingly, the MysD K331A mutant showed significantly improved activity compared to the WT enzyme (3.0-fold activity on Thr and 2.2-fold activity on AABA). These results suggested the engineering of MysD could enable a more effective synthesis of MAA analogs and potentially more analogs.

Example 4: Experimental Procedures.

[0284] *General Experimental Procedures*. Molecular biology reagents and chemicals were purchased from Thermo Scientific, NEB, Fisher Scientific or Sigma-Aldrich. GeneJET Plasmid Miniprep Kit and GeneJETGel Extraction Kit (Thermo Scientific) were used for plasmid preparation and DNA purification, respectively. *E. coli* DH5α (Agilent) was used for routine cloning studies and *E. coli* BL21-gold(DE3) (Agilent) was used for protein expression and heterologous production. The cyanobacterial strain *Nostoc linkia* NIES-25 was obtained from National Institute for Environmental Studies, Japan. DNA sequencing was performed with GENEWIZ or Eurofins. A Shimadzu Prominence UHPLC system (Kyoto, Japan) coupled with a PDA detector was used for HPLC analysis. NMR spectra were recorded in D_2O on a Bruker 600 MHz spectrometer located in the AMRIS facility at the University of Florida, Gainesville, FL, USA. Spectroscopy data were collected using Topspin 3.5 software. HRMS data were generated on a Thermo Fisher Q Exactive Focus mass spectrometer equipped with an electrospray probe on Universal Ion Max API source.

[0285] *MysD Expression and Purification*. The *mysD* gene was amplified from the isolated genomic DNA of *Nostoc linkia* NIES-25 and inserted into the *Nde*I/*Xho*I sites of pET28b, and the resultant construct pET28b-mysD was transformed into *E. coli* BL21-gold(DE3) for the expression of recombinant N-His_6-tagged MysD. Protein expression was carried out in 500 mL Luria-Bertani broth supplemented with 50 μg/mL kanamycin (37 °C, 225 rpm).

[0286] When the cell culture OD_{600} reached 0.5, IPTG (final concentration 0.1 mM) was added to the culture to induce gene expression (18°C, 180 rpm, 20 h). The cells were harvested by centrifugation (6000 rpm, 20 min), and collected cell pellets were resuspended in the lysis buffer (25 mM Tris-Cl, pH 8.0, 100 mM NaCl, 1 mM β-mercaptoethanol and 10 mM imidazole) and lysed by sonication on ice (10 s pulse and 20 s rest, 1 min in total).

[0287] Following centrifugation (15000 rpm, 4 °C, 30 min), recombinant MysD was purified by the HisTrap Ni-NTA affinity column (GE Healthcare). N-His_6-tagged MysD was eluted using a 0-100%B gradient in 15 min at the flow rate of 2 mL/min, using A buffer (25 mM Tris-Cl, pH 8.0, 250 mM NaCl, 1 mM β-mercaptoethanol and 30 mM imidazole) and B buffer (25 mM Tris-Cl, pH 8.0, 250 mM NaCl, 1 mM β-mercaptoethanol and 300 mM imidazole). Fractions with recombinant MysD were collected, concentrated, and buffer-exchanged into storage buffer (50 mM Tris-Cl, pH 8.0, 10% glycerol). The purity of the recombinant protein was analyzed on SDS-PAGE and the concentration was determined by NanoDrop.

[0288] *In Vitro MysD Reactions*. MG was purified from extracts of *E. coli* expressing MysAB2C by HPLC and used as the substrate for the MysD reactions. The quality of MG was calculated based on its extinction coefficient (28,100 $M^{-1}cm^{-1}$). The MysD reactions included MG (50 μM), Mg^{2+} (10 mM), unnatural amino acid substrates (5 mM), and ATP (5 mM) in 50 mM HEPES, pH 8.0. The reactions were initiated by adding MysD (0.5 μM) and then incubated at room temperature for 4 hours. All reactions were quenched by heat inactivation at 95 °C for 10 min. After centrifugation at 20,000 x g for 15 min, the clear supernatants were collected for LC-HRMS analysis.

[0289] To explore the substrate scope of MysD, the natural amino acid L-threonine and the unnatural amino acids L-ornithine, 4-aminobutanoic acid, 2-aminomalonic acid, (*S*)-2-aminobut-3-enoic acid, (*S*)-3-aminobutanoic acid, (*S*)-2,3-diaminopropanoic acid, and (*R*)-2,3-diaminopropanoic acid (each at 5 mM) were each screened in the above reaction mixtures under the optimal conditions. The reactions were terminated and then analyzed in the HPLC and/or LC-MS analysis.

[0290] *HPLC and LC-MS Analysis.* Samples were analyzed on a Shimadzu Prominence UHPLC system (Kyoto, Japan) coupled with a PDA detector. Unless stated elsewhere, the following HPLC procedure was performed. The compounds were separated on a Phenomenex Luna C8 column (4.6 x 250 mm, 5 μm) using the following HPLC program: 2% B for 15 min, 2-90% B gradient in 2 min, 90% B in 2 min, 90-2% in 2 min, and re-equilibration in 2% B for 6 min. The A phase was water with 0.1% formic acid and the B phase was methanol. The flow rate was set at 0.5 mL/min. LC-HRMS and HRMS/MS experiments were conducted on a Thermo Scientific Q Exactive Focus mass spectrometer with a Dionex Ultimate RSLC 3000 uHPLC system, equipped with the H-ESI II probe on an Ion Max API Source. Methanol (B)/water (A) containing 0.1% formic acid were used as mobile phases. The eluents from the first 3 min were diverted to waste by a diverting valve. MS1 signals were acquired under the Full MS positive ion mode, covering a mass range of m/z 150–2000, with resolution at 35 000 and AGC target at 1×10^6.

[0291] *Bioinformatic Analysis of MysD.* Protein sequences from 595 cyanobacteria genomes were obtained by protein BLAST search against the NCBI non-redundant protein database (E-value <1e−5) using query sequences for *Nostoc linckia* NIES-25 MysD (accession: WP_096541781.1). After filtering sequence length to obtain proteins with 300-400 amino acids, 249 MysD homologs were retrieved. The SSN of the MysD homologs was generated by the EFI-Enzyme Similarity Tool (https://efi.igb.illinois.edu/efi-est/) with a filter-value at 172.

[0292] Protein engineering has become a widely used approach to tailor enzyme substrate scopes for chemical synthesis. The protein structure can assist rational engineering of proteins. Since MysD 3-D structure is not available, the structure of MysD of *Nostoc linckia* NIES-25 was predicted using RoseTTAFold (**FIG. 6**) (doi: 10.1126/science.abj8754).

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INCORPORATION BY REFERENCE

[0319] The present application refers to various issued patent, published patent applications, scientific journal articles, and other publications, all of which are incorporated herein by reference. The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

EQUIVALENTS AND SCOPE

[0320] In the articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Embodiments or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[0321] Furthermore, the disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claims that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the disclosure or aspects of the disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0322] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the embodiments. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any embodiment, for any reason, whether or not related to the existence of prior art.

[0323] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended embodiments. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

1. A method for producing a compound, comprising:

a) culturing a recombinant microorganism under conditions suitable for production of the compound; and

b) isolating the compound from the recombinant microorganism,

wherein the recombinant microorganism comprises a heterologous nucleic acid encoding one or more mycosporine-like amino acid (MAA) biosynthetic enzymes, wherein the one or more MAA biosynthetic enzymes comprise a D-alanine-D-alanine ligase (MysD), or a homolog thereof.

2. The method of claim 1, wherein the D-alanine-D-alanine ligase comprises an amino acid sequence of SEQ ID NO: 1, or an amino acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 1.

3. The method of claim 1 or 2, wherein the one or more MAA biosynthetic enzymes further comprise a phytanoyl-CoA dioxygenase (MysH), or a homolog thereof.

4. The method of claim 3, wherein the phytanoyl-CoA dioxygenase comprises an amino acid sequence of any one of SEQ ID NOs: 2-12, or an amino acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of any one of SEQ ID NOs: 2-12.

5. The method of any one of claims 1-4, wherein the one or more MAA biosynthetic enzymes further comprise an ATP-grasp enzyme (MysC), or a homolog thereof.

6. The method of claim 5, wherein the ATP-grasp enzyme comprises an amino acid sequence of any one of SEQ ID NOs: 13-105, or an amino acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of any one of SEQ ID NOs: 13-105.

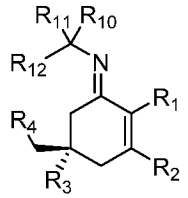
7. The method of any one of claims 1-6, wherein the one or more biosynthetic enzymes further comprise one or more enzymes selected from the group consisting of a demethyl-4-deoxygadusol synthase (MysA), an O-methyltransferase (MysB), and a non-ribosomal peptide synthetase (NRPS)-like enzyme (MysE).

8. The method of any one of claims 1-7, wherein the compound is a mycosporine-like amino acid.

9. The method of any one of claims 1-8, wherein the compound has UV-modulating activity.

10. The method of claim 9, wherein the UV-modulating activity comprises absorption of UV wavelengths between 280 and 400 nm.

11. The method of any one of claims 1-10, wherein the compound is of Formula (I), or a salt thereof:



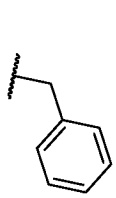
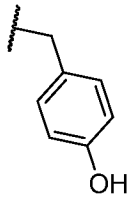
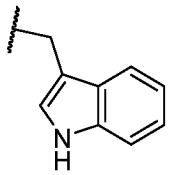
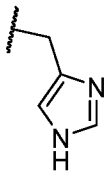
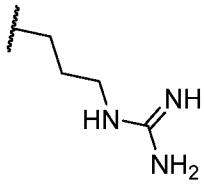
Formula (I)

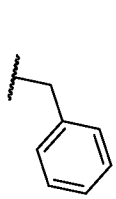
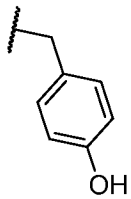
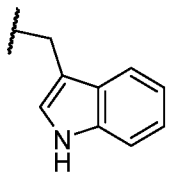
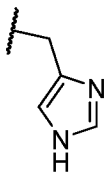
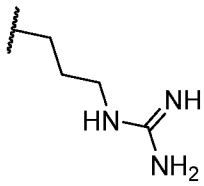
wherein:

each of R_1, R_2, R_3, and R_4 is independently selected from the group consisting of $-OR^a$, $-(NH)R^b$, and $-N(R^b)_2$, wherein each instance of R^a is independently hydrogen or optionally substituted C_{1-6} alkyl and each instance of R^b is independently hydrogen or optionally substituted C_{1-6} alkyl; R_{10} is selected from the group consisting of hydrogen and $-CO_2R_{13}$, wherein R_{13} may be selected from the group consisting of hydrogen and optionally substituted alkyl; and

each of R_{11} and R_{12} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, or R_{11} and R_{12} are taken together to form an optionally substituted alkenyl group;

provided that if R_{10} is $-CO_2R_{13}$ and R_{11} is hydrogen, R_{12} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, -

$CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  ; and

provided that if R_{10} is $-CO_2R_{13}$ and R_{12} is hydrogen, R_{11} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  .

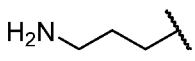
12. The method of claim 11, wherein R_1 is $-OR^a$, wherein R^a is optionally substituted C_{1-6} alkyl.

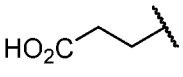
13. The method of claim 12, wherein R_1 is $-OCH_3$.

14. The method of any one of claims 11-13, wherein R_2 is $-NH_2$.

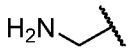
15. The method of any one of claims 11-14, wherein R_3 is -OH.

16. The method of any one of claims 11-15, wherein R_4 is -OH.

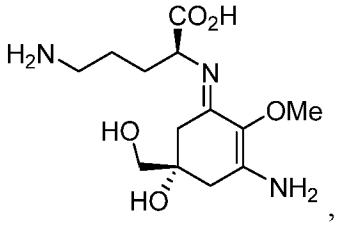
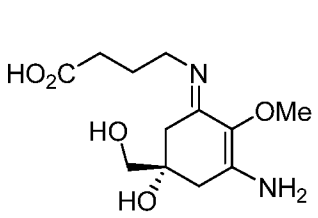
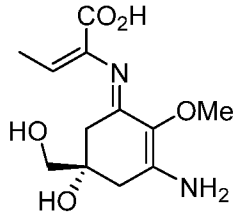
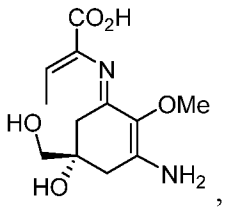
17. The method of any one of claims 11-16, wherein R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  .

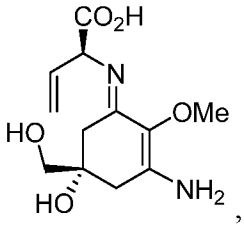
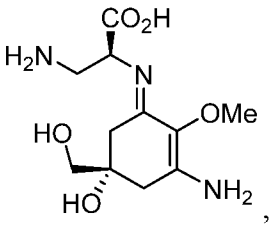
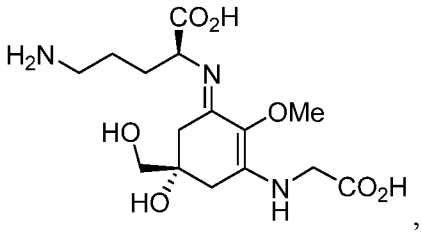
18. The method of any one of claims 11-16, wherein R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is  .

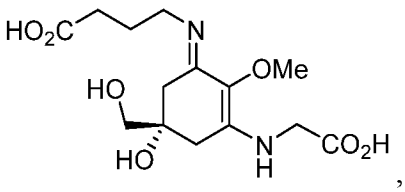
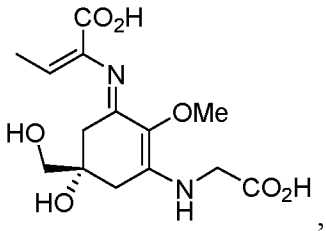
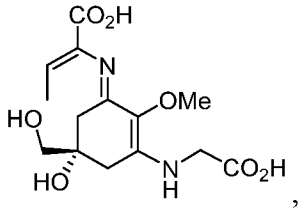
19. The method of any one of claims 11-16, wherein R_{10} is -CO_2H, and R_{11} and R_{12} are taken together to form  .

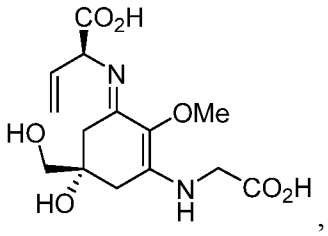
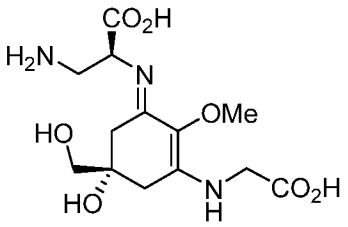
20. The method of any one of claims 11-16, wherein R_{10} is -CO_2H, R_{11} is hydrogen, and R_{12} is  .

21. The method of claim 11, wherein the compound is of the formula:

 ,  ,  ,  ,

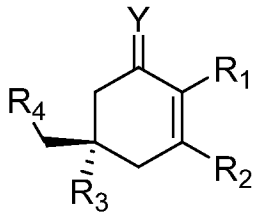
 ,  ,  ,

 ,  ,  ,

 , or  .

22. The method of any one of claims 1-21, further comprising providing a substrate of the one or more mycosporine-like amino acid (MAA) biosynthetic enzymes to the recombinant microorganism.

23. The method of claim 22, wherein the substrate is a compound of Formula (II), or a salt thereof:



Formula (II)

wherein:

each of R_1, R_2, R_3, and R_4 is independently selected from the group consisting of $-OR^a$, $-(NH)R^b$, and $-N(R^b)_2$, wherein each instance of R^a is independently hydrogen or optionally substituted C_{1-6} alkyl and each instance of R^b is independently hydrogen or optionally substituted C_{1-6} alkyl; and

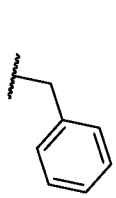
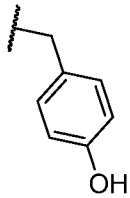
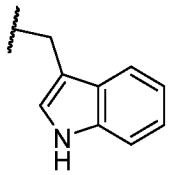
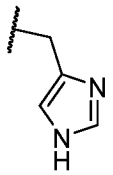
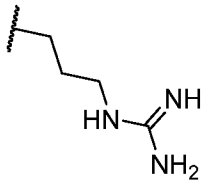
Y is =O or 

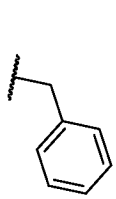
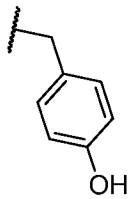
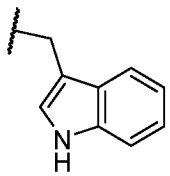
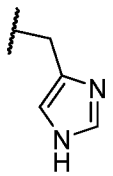
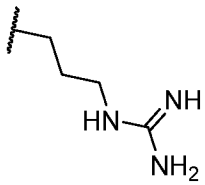
, wherein:

R_{10} is selected from the group consisting of hydrogen and $-CO_2R_{13}$, wherein R_{13} may be selected from the group consisting of hydrogen and optionally substituted alkyl; and

each of R_{11} and R_{12} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, or R_{11} and R_{12} are taken together to form an optionally substituted alkenyl group;

provided that if R_{10} is $-CO_2R_{13}$ and R_{11} is hydrogen, R_{12} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, -

$CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  ; and

provided that if R_{10} is $-CO_2R_{13}$ and R_{12} is hydrogen, R_{11} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  .

24. The method of claim 23, wherein R_1 is -OH.

25. The method of claim 23, wherein R_1 is $-OCH_3$.

26. The method of any one of claims 23-25, wherein R_2 is -OH.

27. The method of any one of claims 23-25, wherein R^2 is $-NH_2$.

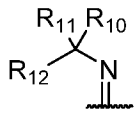
28. The method of any one of claims 23-25, wherein R_2 is $-(NH)R^b$, wherein R^b is optionally substituted alkyl.

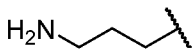
29. The method of claim 28, wherein R_2 is $-NHCH_2CO_2H$.

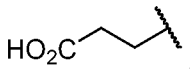
30. The method of any one of claims 23-29, wherein R_3 is -OH.

31. The method of any one of claims 23-30, wherein R_4 is -OH.

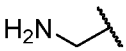
32. The method of any one of claims 23-31, wherein Y is O.

33. The method of any one of claims 23-31, wherein Y is  .

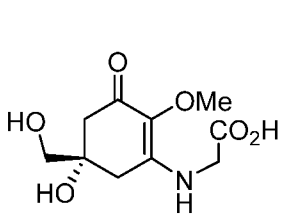
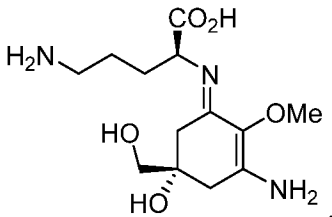
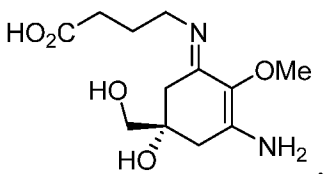
34. The method of claim 33, wherein R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  .

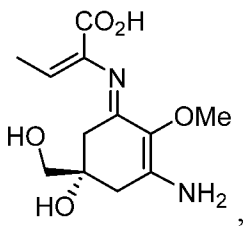
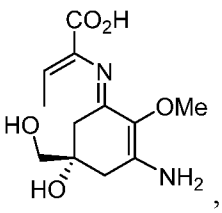
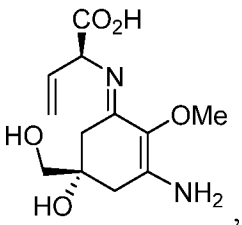
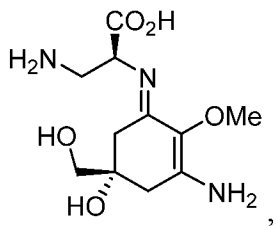
35. The method of claim 33, wherein R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is  .

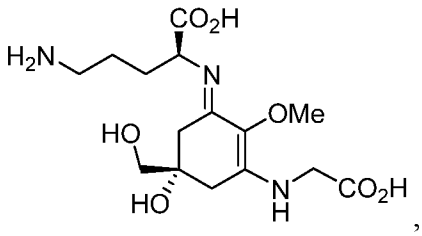
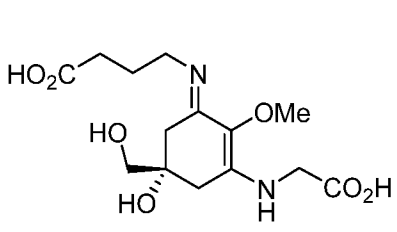
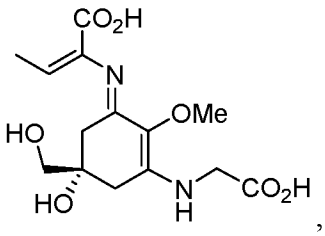
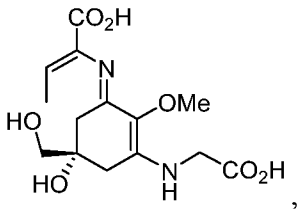
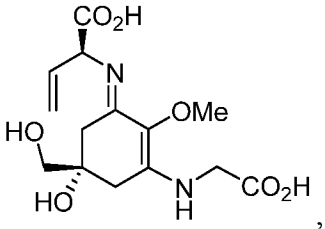
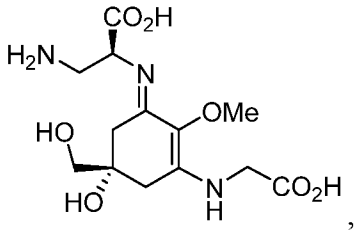
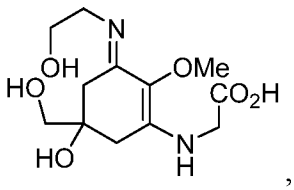
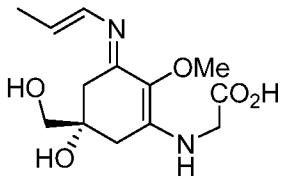
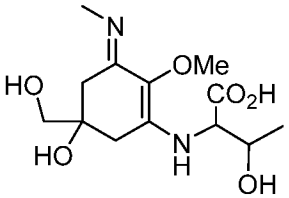
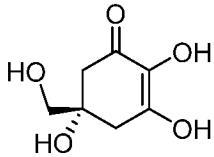
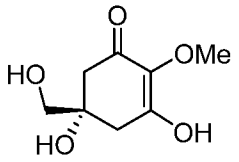
36. The method of claim 33, wherein R_{10} is $-CO_2H$, and R_{11} and R_{12} are taken together to form  .

37. The method of claim 33, wherein R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  .

38. The method of claim 23, wherein the substrate is of the formula:

 ,  ,  ,

 ,  ,  ,  ,











, or


39. The method of any one of claims 1-38, wherein the recombinant microorganism is a species of bacteria or yeast.

40. The method of claim 39, wherein the bacteria is a species of cyanobacteria.

41. The method of claim 39, wherein the bacteria is a species from the human microbiome.

42. The method of claim 39, wherein the bacteria is *E. coli*.

43. A recombinant microorganism comprising a heterologous nucleic acid encoding one or more mycosporine-like amino acid (MAA) biosynthetic enzymes, wherein the one or more MAA biosynthetic enzymes comprise a D-alanine-D-alanine ligase (MysD), or a homolog thereof.

44. A method of producing a compound, comprising:

a) culturing the recombinant microorganism of claim 43 under conditions suitable for production of the compound; and

b) isolating the compound from the recombinant microorganism.

45. A composition comprising a compound produced by the method of any one of claims 1-42 or 44 and optionally an excipient.

46. The composition of claim 45, wherein the composition is for topical administration.

47. The composition of claim 45 or 46, wherein the composition is formulated as a sunscreen.

48. The composition of claim 45 or 46, wherein the composition is formulated as a cosmetic.

49. A method of making the composition of any one of claims 45-48, comprising:

a) culturing a recombinant microorganism under conditions suitable for production of the compound;

b) isolating the compound from the recombinant microorganism,

wherein the recombinant microorganism comprises a heterologous nucleic acid encoding one or more mycosporine-like amino acid (MAA) biosynthetic enzymes, wherein the one or more MAA biosynthetic enzymes comprise a D-alanine-D-alanine ligase (MysD), or a homolog thereof; and

c) adding the compound to one or more excipients to produce the composition.

50. A method of administering a compound, comprising applying the composition of any one of claims 45-48 to a subject.

51. A method of preventing sunburn, comprising applying the composition of any one of claims 45-48 on the skin of a subject in need thereof.

52. A method of preventing cancer, comprising applying the composition of any one of claims 45-48 on the skin of a subject in need thereof.

53. A method of preventing or treating a chronic inflammatory disease, comprising administering the composition of any one of claims 45-48 to a subject in need thereof.

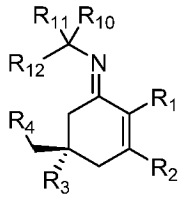
54. A compound produced by:

a) culturing a recombinant microorganism under conditions suitable for production of the compound; and

b) isolating the compound from the recombinant microorganism,

wherein the recombinant microorganism comprises a heterologous nucleic acid encoding one or more mycosporine-like amino acid (MAA) biosynthetic enzymes, wherein the one or more MAA biosynthetic enzymes comprise a D-alanine-D-alanine ligase (MysD), or a homolog thereof.

55. The compound of claim 54, wherein the compound is of Formula (I), or a salt thereof:



Formula (I)

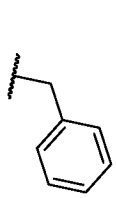
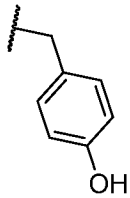
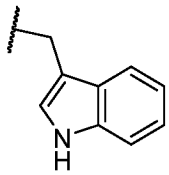
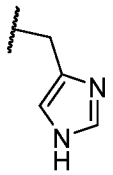
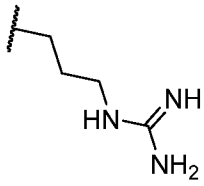
wherein:

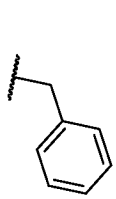
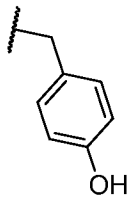
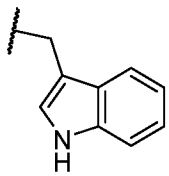
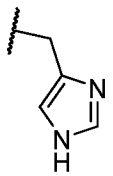
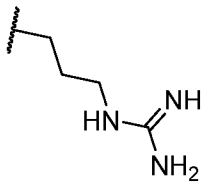
each of R_1, R_2, R_3, and R_4 is independently selected from the group consisting of $-OR^a$, $-(NH)R^b$, and $-N(R^b)_2$, wherein each instance of R^a is independently hydrogen or optionally substituted C_{1-6} alkyl and each instance of R^b is independently hydrogen or optionally substituted C_{1-6} alkyl;

R_{10} is selected from the group consisting of hydrogen and $-CO_2R_{13}$, wherein R_{13} may be selected from the group consisting of hydrogen and optionally substituted alkyl;

each of R_{11} and R_{12} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, or R_{11} and R_{12} are taken together to form an optionally substituted alkenyl group;

provided that if R_{10} is $-CO_2R_{13}$ and R_{11} is hydrogen, R_{12} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, -

$CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  ; and

provided that if R_{10} is $-CO_2R_{13}$ and R_{12} is hydrogen, R_{11} is not selected from the group consisting of hydrogen, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CH_2NH_2$,  ,  ,  ,  , and  .

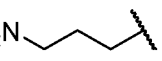
56. The compound of claim 55, wherein R_1 is $-OR^a$, wherein R^a is optionally substituted C_{1-6} alkyl.

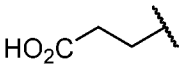
57. The compound of claim 56, wherein R_1 is $-OCH_3$.

58. The compound of any one of claims 55-57, wherein R_2 is $-NH_2$.

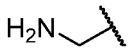
59. The compound of any one of claims 55-58, wherein R_3 is -OH.

60. The compound of any one of claims 55-59, wherein R_4 is -OH.

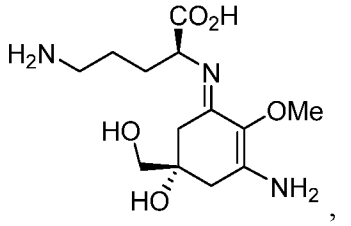
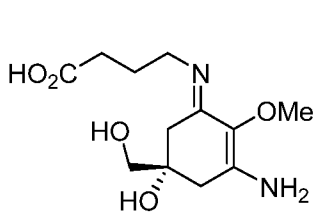
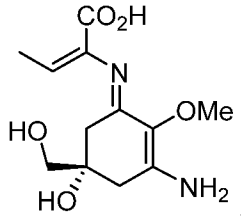
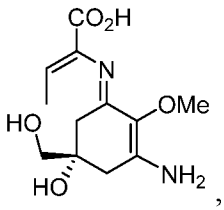
61. The compound of any one of claims 55-60, wherein R_{10} is $-CO_2H$, R_{11} is hydrogen, and R_{12} is  .

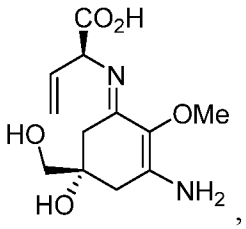
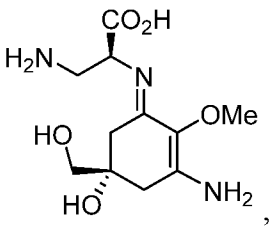
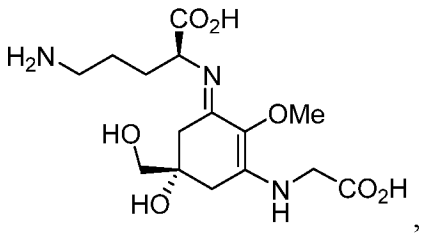
62. The compound of any one of claims 55-60, wherein R_{10} is hydrogen, R_{11} is hydrogen, and R_{12} is  .

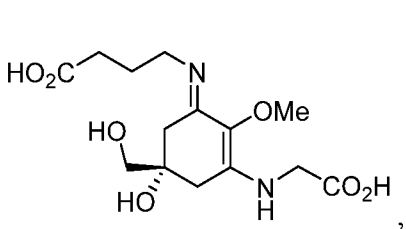
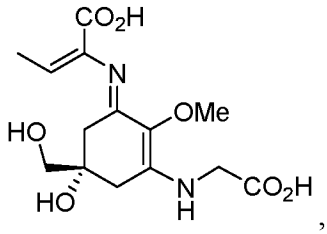
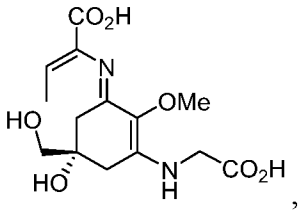
63. The compound of any one of claims 55-60, wherein R_{10} is -CO_2H, and R_{11} and R_{12} are taken together to form  .

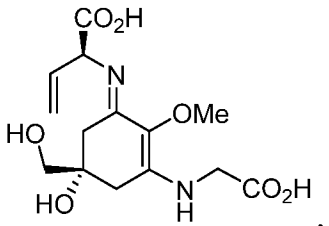
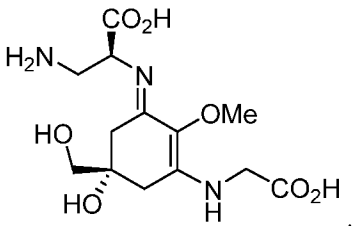
64. The compound of any one of claims 55-60, wherein R_{10} is -CO_2H, R_{11} is hydrogen, and R_{12} is  .

65. The compound of any one of claims 55-64, wherein the compound is of the formula:

 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 , or  .

66. A composition comprising the compound of any one of claims 55-65, or a salt thereof.

67. The composition of claim 66, wherein the composition is for topical administration.

68. The composition of claim 66 or 67, wherein the composition is formulated as a sunscreen.

69. The composition of claim 66 or 67, wherein the composition is formulated as a cosmetic.

70. A method of administering a compound, comprising applying the composition of any one of claims 66-69 to a subject.

71. A method of preventing sunburn, comprising applying the composition of any one of claims 66-69 on the skin of a subject in need thereof.

72. A method of preventing cancer, comprising applying the composition of any one of claims 66-69 on the skin of a subject in need thereof.

73. A method of treating or preventing a chronic inflammatory disease, comprising applying the composition of any one of claims 66-69 on the skin of a subject in need thereof.

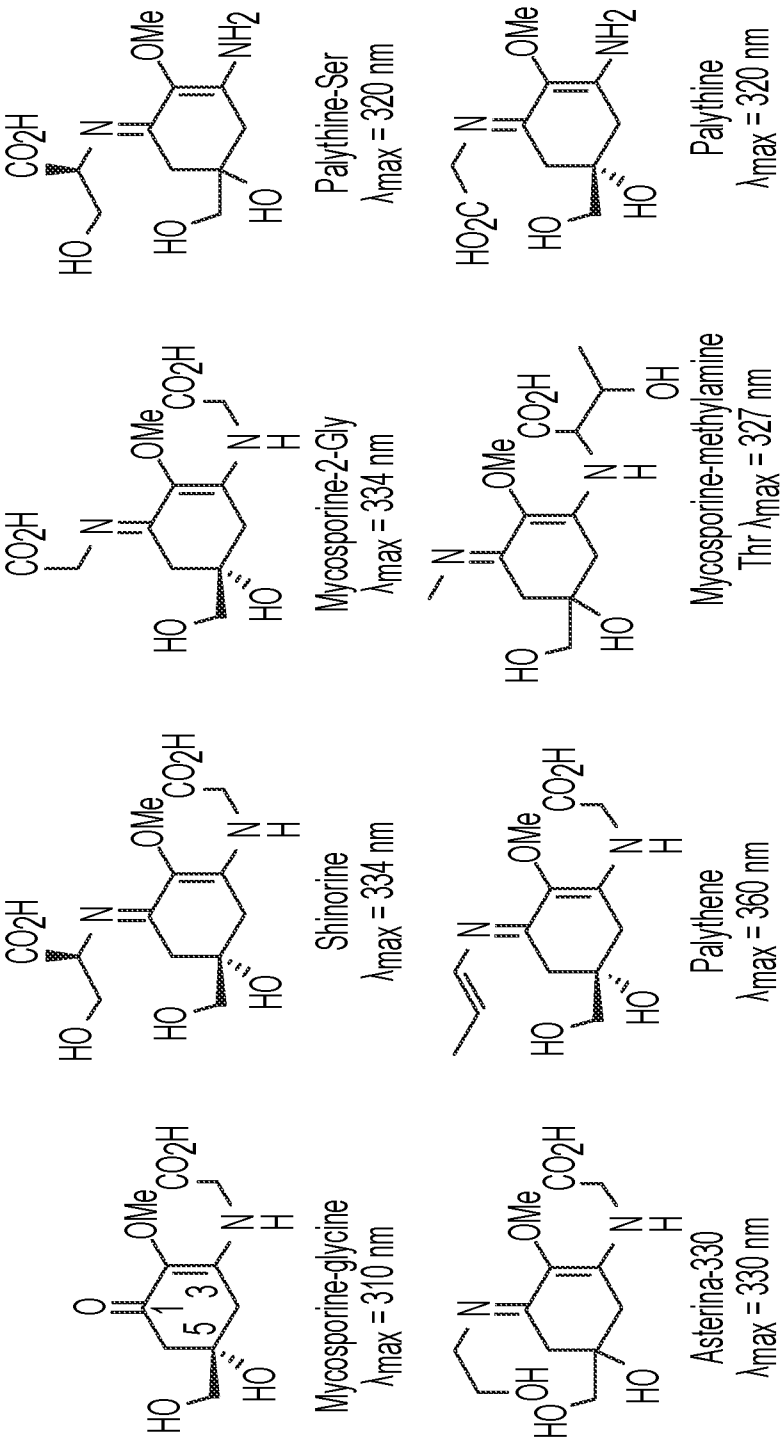

Mycosporine-glycine
λmax = 310 nm
Shinorine
λmax = 334 nm
Palythene
λmax = 360 nm
Asterina-330
λmax = 330 nm
Mycosporine-2-Gly
λmax = 334 nm
Mycosporine-methylamine
Thr λmax = 327 nm
Palythine-Ser
λmax = 320 nm
Palythine
λmax = 320 nm

FIG. 1A

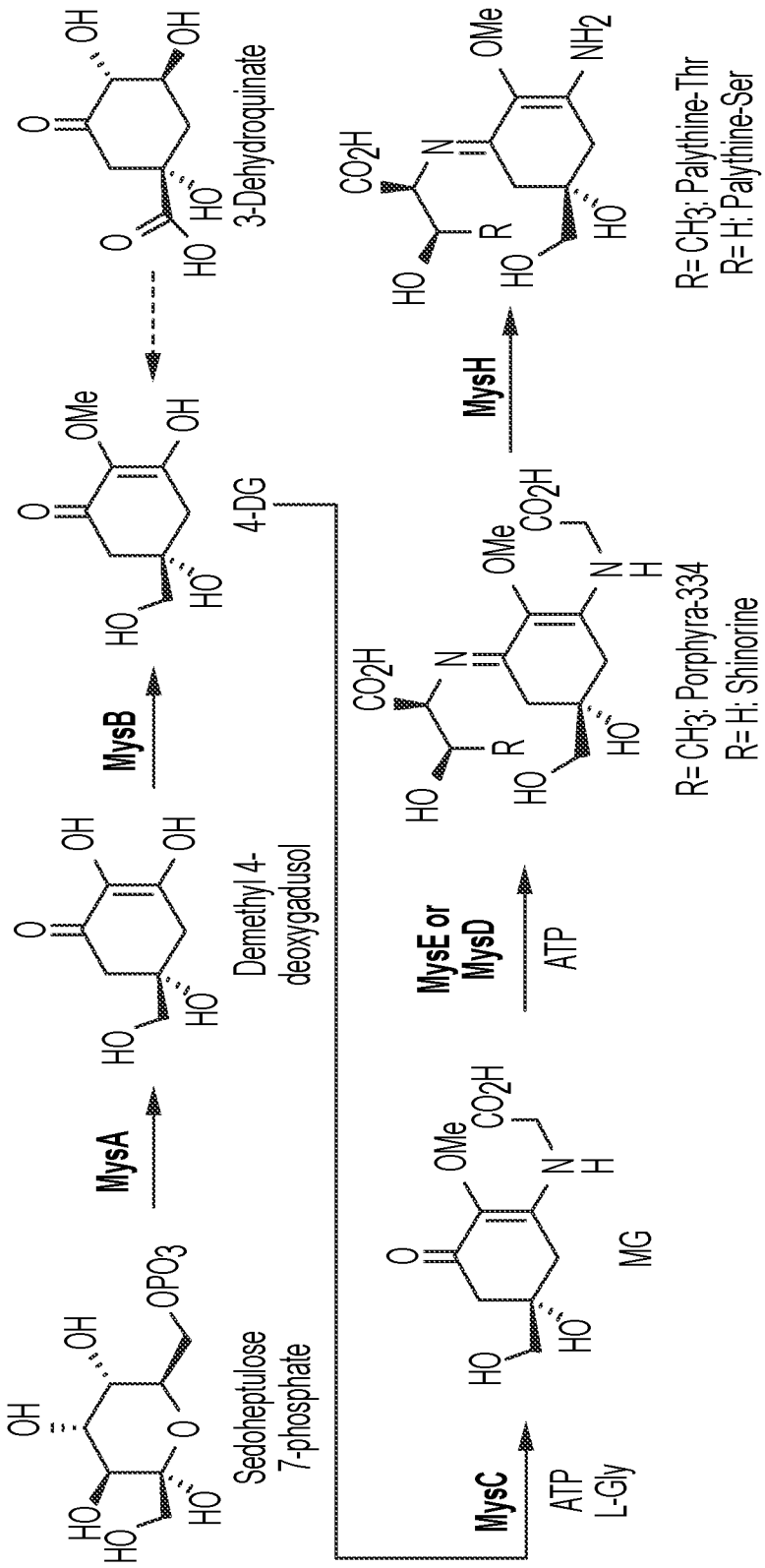

Sedoheptulose 7-phosphate
MysA
Demethyl 4-deoxygadusol
MysB
3-Dehydroquinate
4-DG
MysC
ATP
L-Gly
MG
MysE or MysD
ATP
MysH
R= CH3: Porphyra-334
R= H: Shinorine
R= CH3: Palythine-Thr
R= H: Palythine-Ser

FIG. 1B

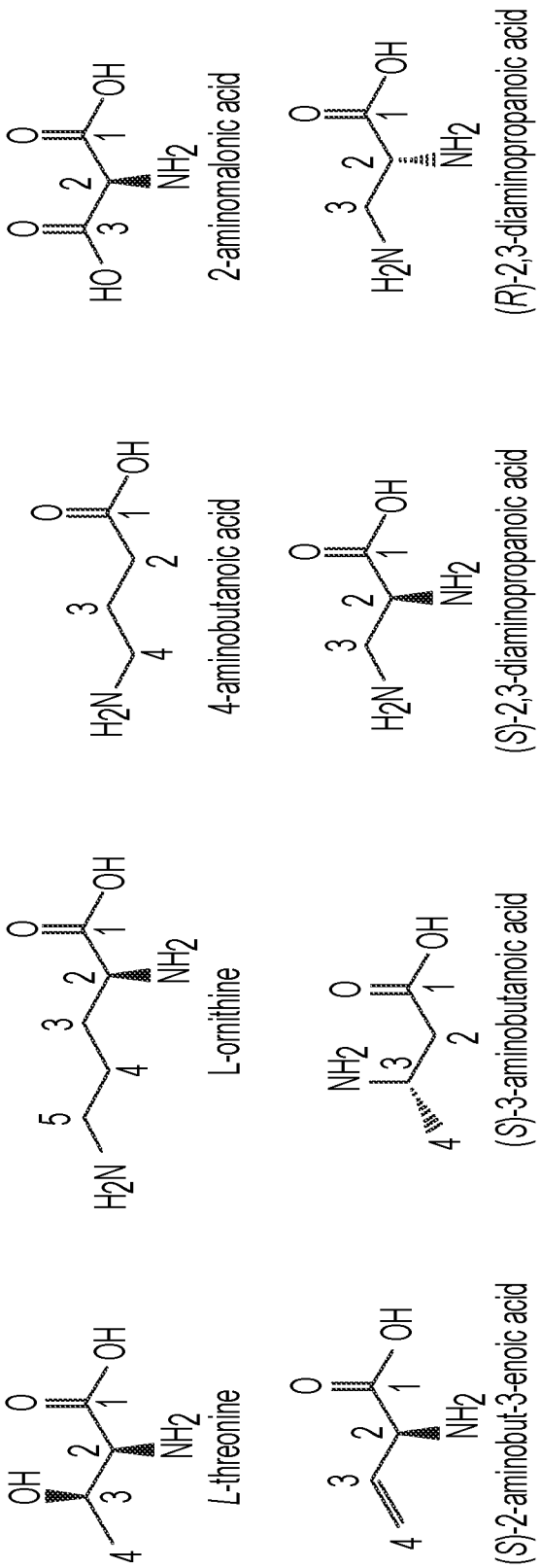

L-threonine
(S)-2-aminobut-3-enoic acid
L-ornithine
(S)-3-aminobutanoic acid
4-aminobutanoic acid
(S)-2,3-diaminopropanoic acid
2-aminomalonic acid
(R)-2,3-diaminopropanoic acid

FIG. 2A

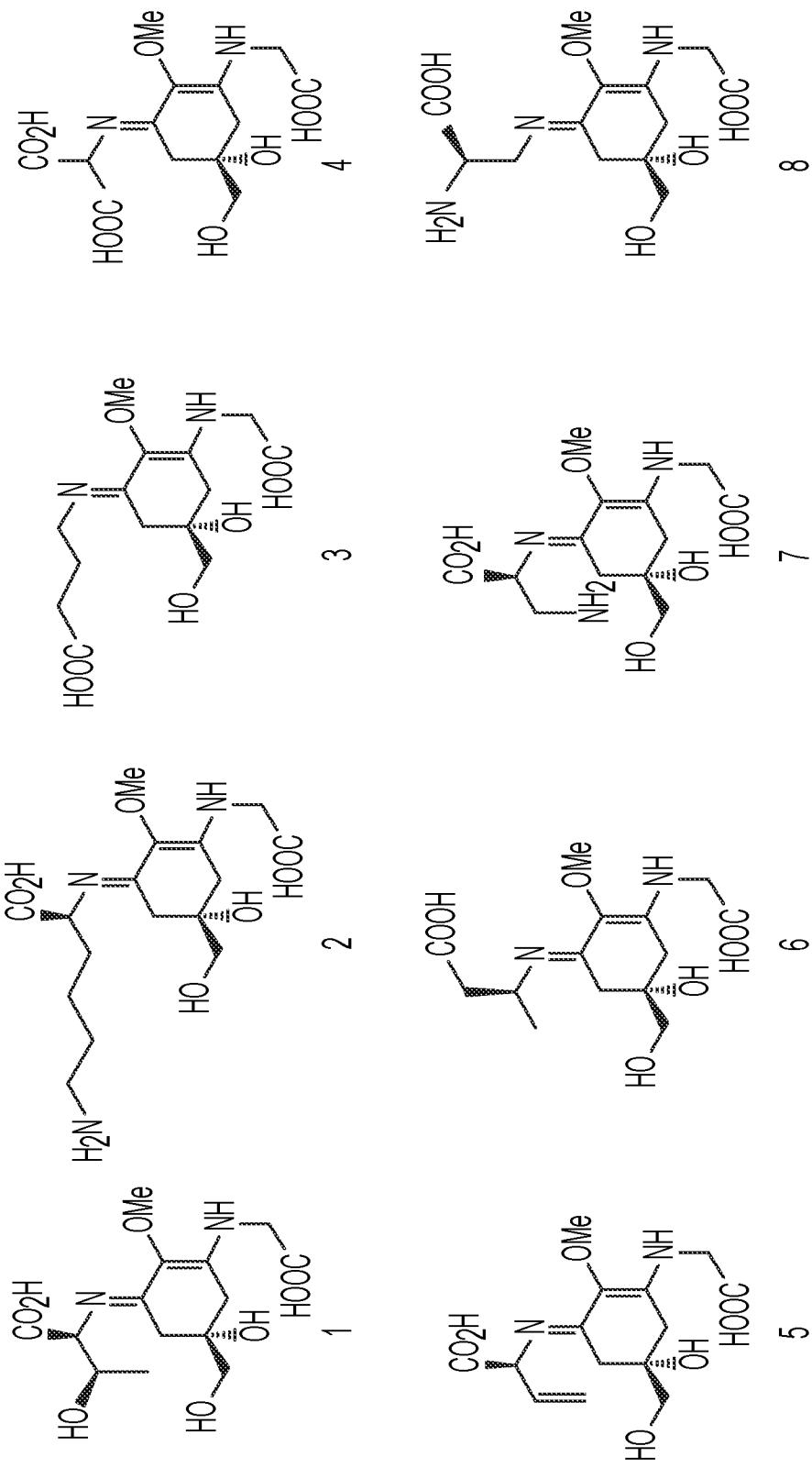


FIG. 2B

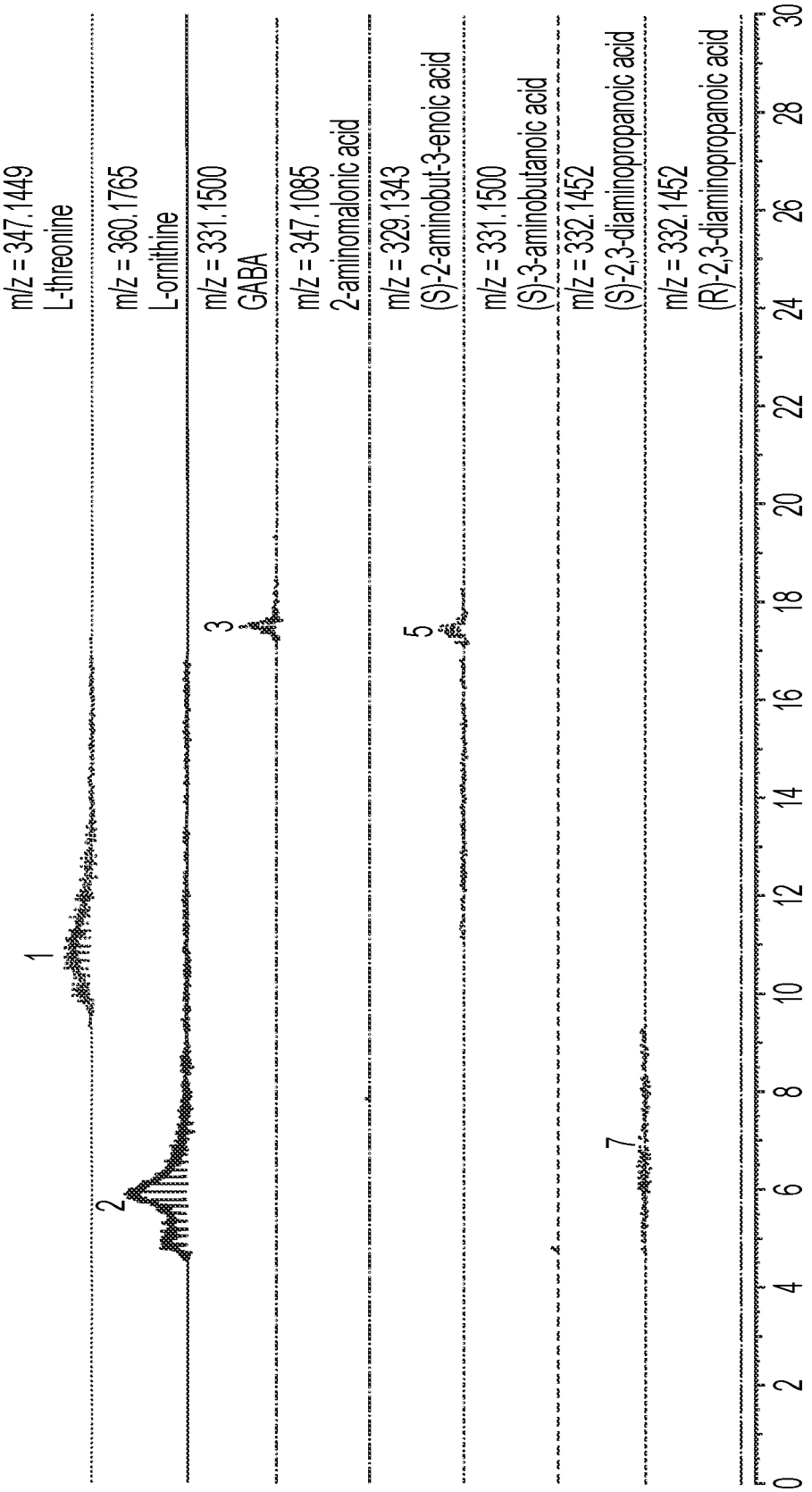

m/z = 347.1449
L-threonine
m/z = 360.1765
L-ornithine
m/z = 331.1500
GABA
m/z = 347.1085
2-aminomalonic acid
m/z = 329.1343
(S)-2-aminobut-3-enoic acid
m/z = 331.1500
(S)-3-aminobutanoic acid
m/z = 332.1452
(S)-2,3-diaminopropanoic acid
m/z = 332.1452
(R)-2,3-diaminopropanoic acid
1
2
3
5
7
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
Time (min)

FIG. 3

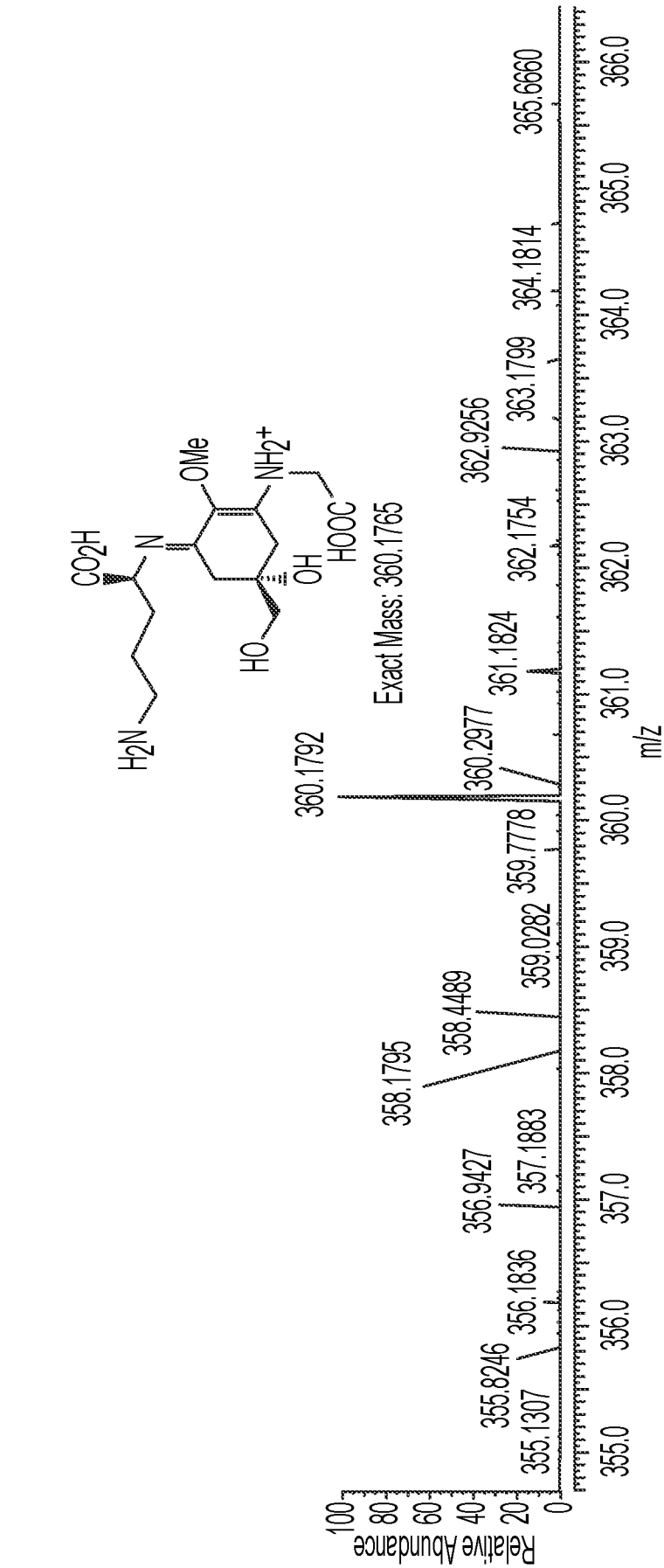

CO2H
N
OMe
NH2+
H2N
HO
OH
HOOC
Exact Mass: 360.1765
Relative Abundance
m/z
100
80
60
40
20
0
355.0
356.0
357.0
358.0
359.0
360.0
361.0
362.0
363.0
364.0
365.0
366.0
355.1307
355.8246
356.1836
356.9427
357.1883
358.1795
358.4489
359.0282
359.7778
360.1792
360.2977
361.1824
362.1754
362.9256
363.1799
364.1814
365.6660

FIG. 4A

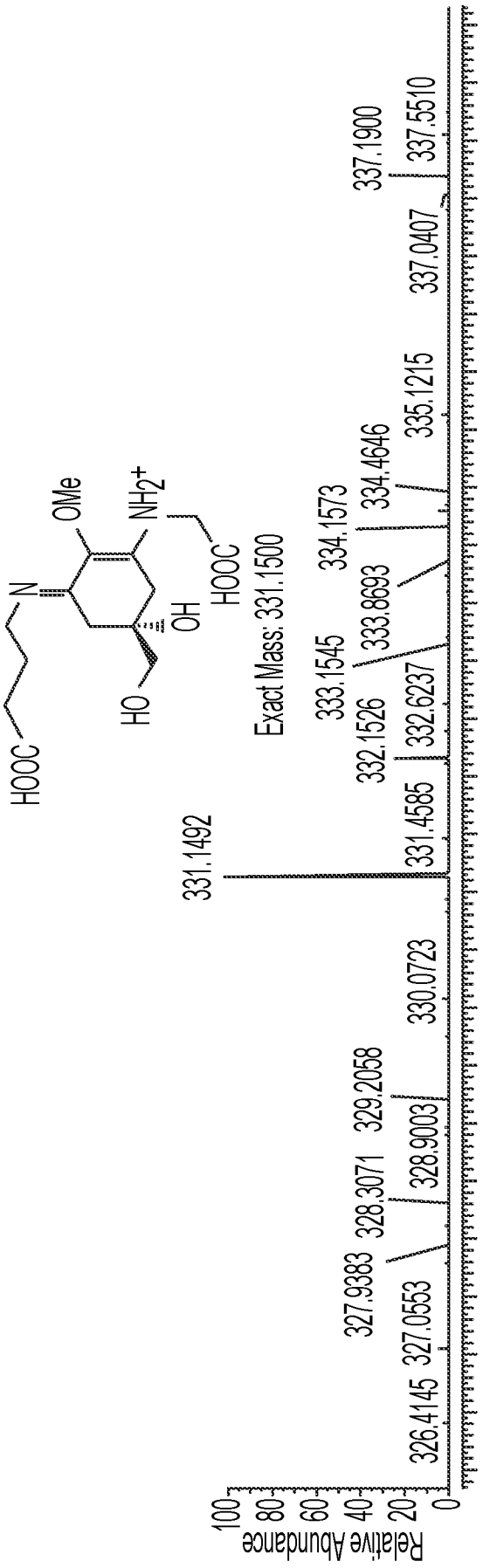

HOOC
N
OMe
NH2+
HO
OH
HOOC
Exact Mass: 331.1500
Relative Abundance
m/z
331.1492
331.4585
332.1526
332.6237
333.1545
333.8693
334.1573
334.4646
335.1215
337.0407
337.1900
337.5510
326.4145
327.0553
327.9383
328.3071
328.9003
329.2058
330.0723

FIG. 4B

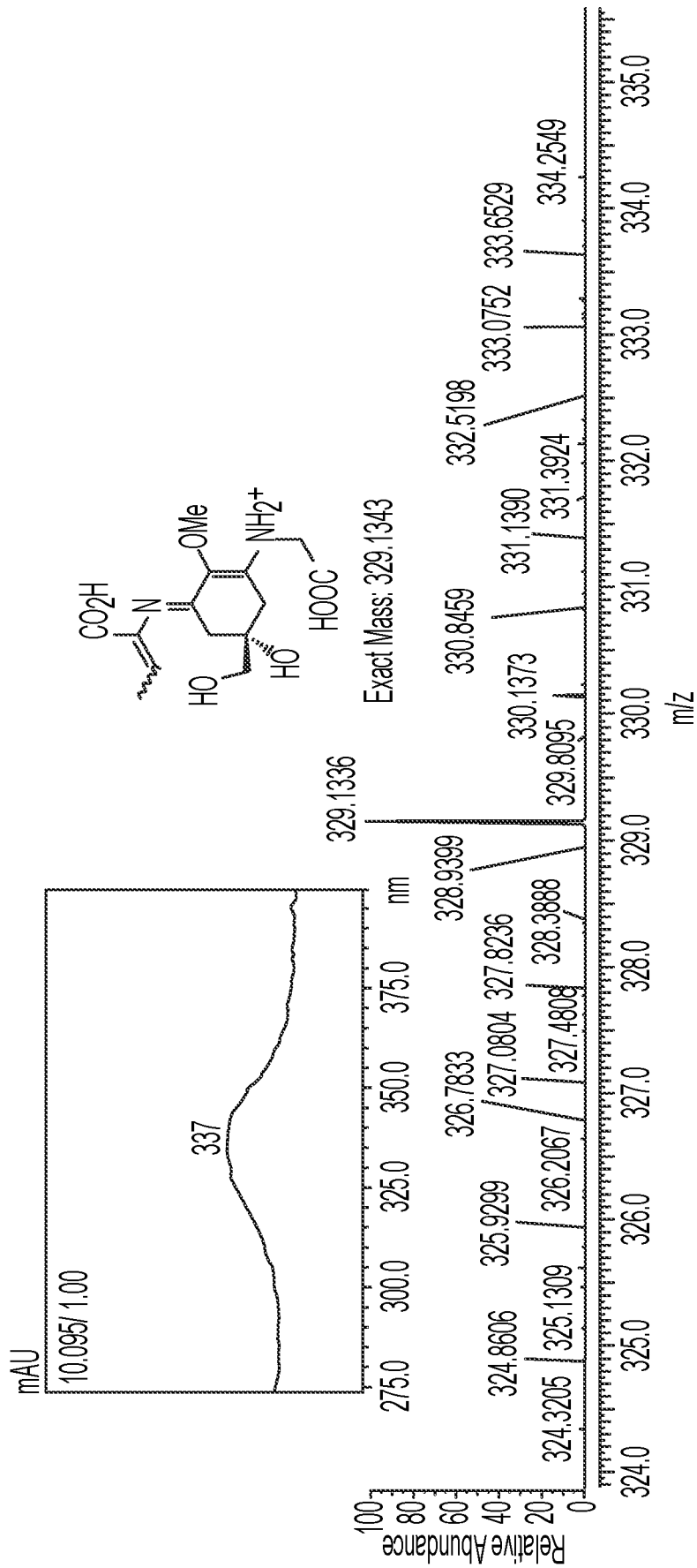

mAU
10.095/1.00
337
275.0
300.0
325.0
350.0
375.0
nm
CO2H
N
OMe
NH2+
HO
HO
HOOC
Exact Mass: 329.1343
Relative Abundance
m/z
329.1336
328.9399
326.7833
327.0804
327.8236
327.4808
328.3888
325.9299
326.2067
324.8606
325.1309
324.3205
330.8459
330.1373
329.8095
331.1390
331.3924
332.5198
333.0752
333.6529
334.2549

FIG. 4C

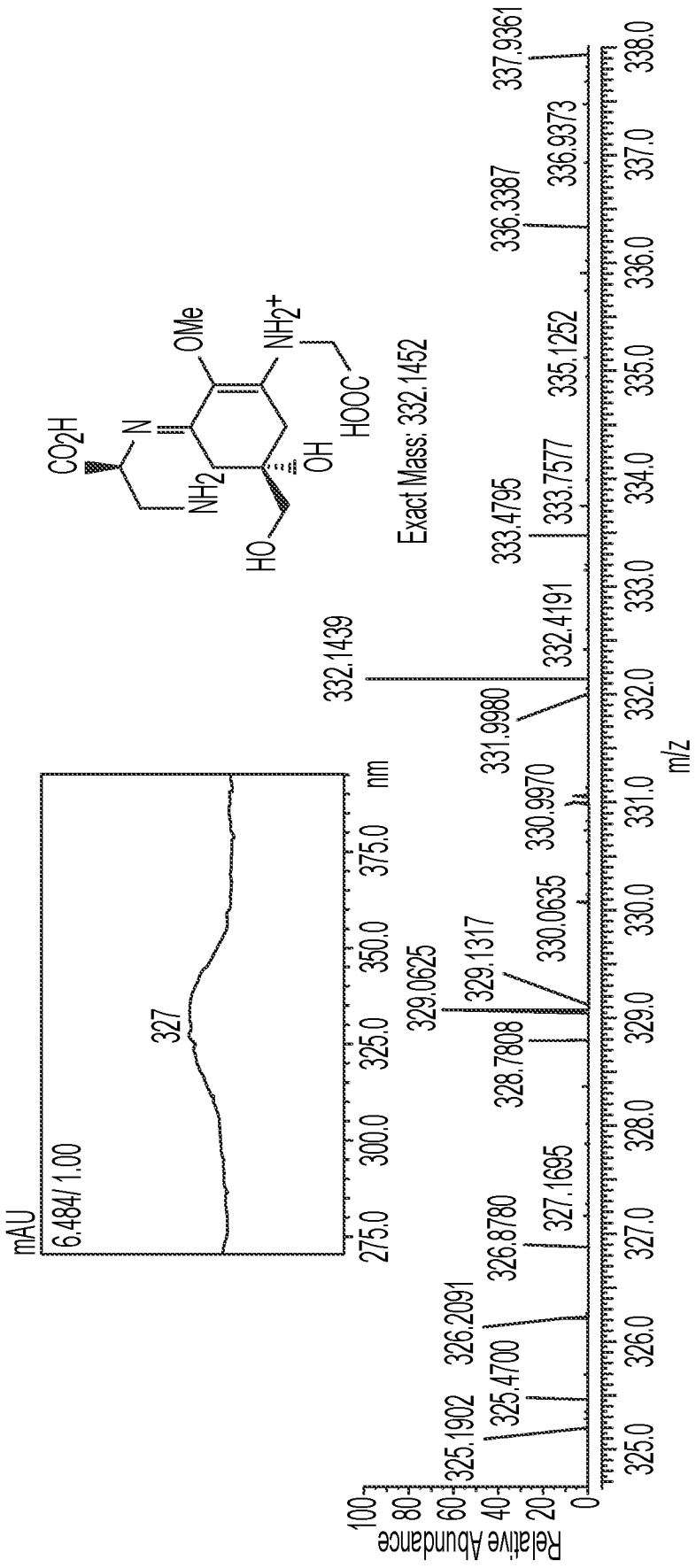

mAU
6.484/1.00
327
275.0
300.0
325.0
350.0
375.0
nm
CO2H
N
NH2
OMe
NH2+
HOOC
OH
HO
Exact Mass: 332.1452
Relative Abundance
m/z
325.1902
325.4700
326.2091
326.8780
327.1695
328.7808
329.0625
329.1317
330.0635
330.9970
331.9980
332.1439
332.4191
333.4795
333.7577
335.1252
336.3387
336.9373
337.9361

FIG. 4D

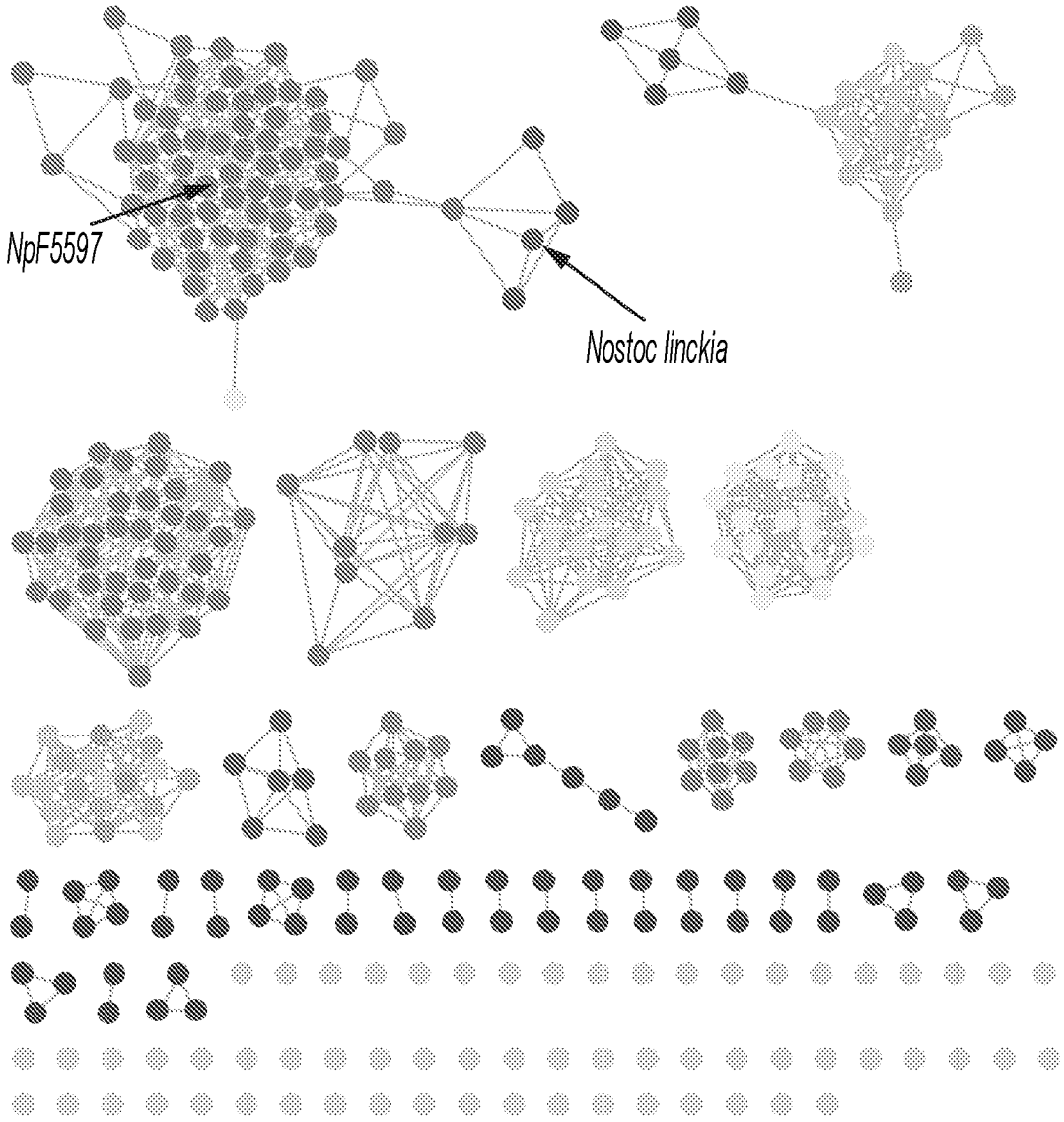


FIG. 5

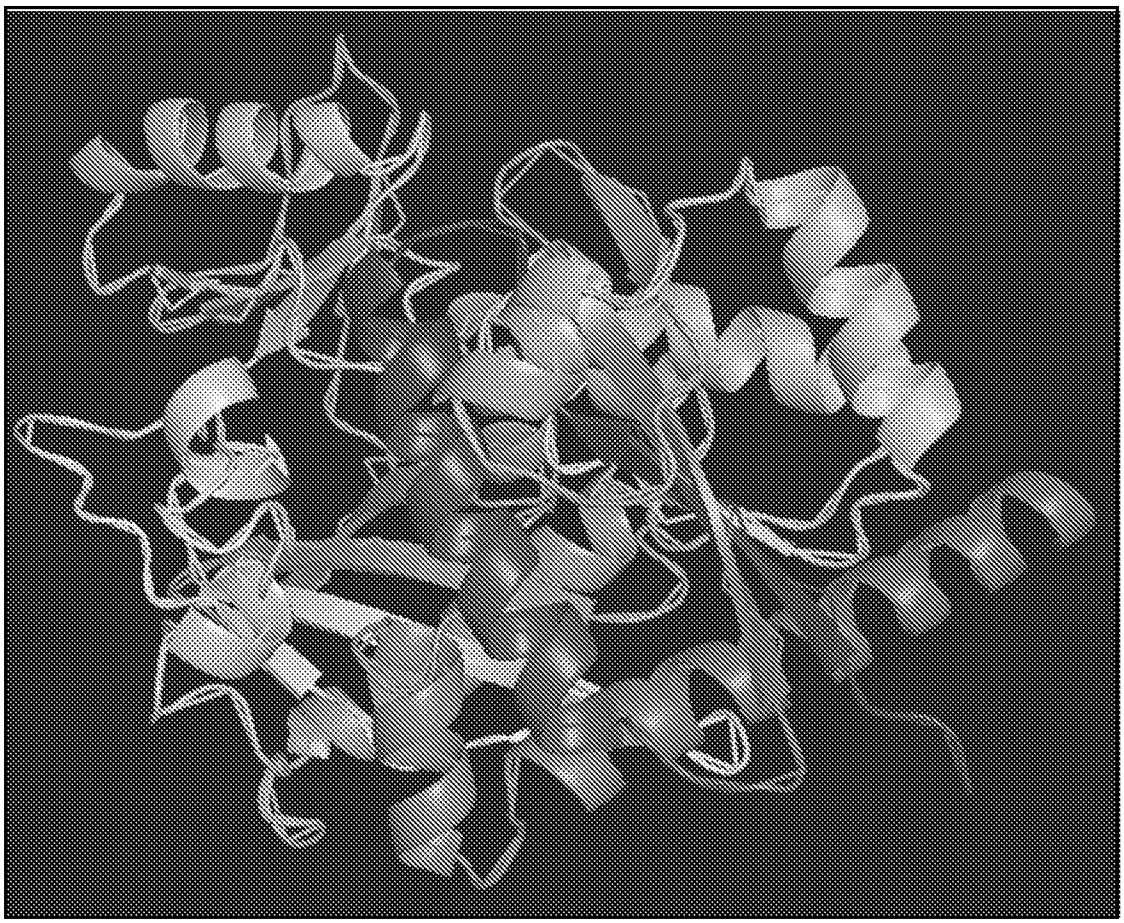
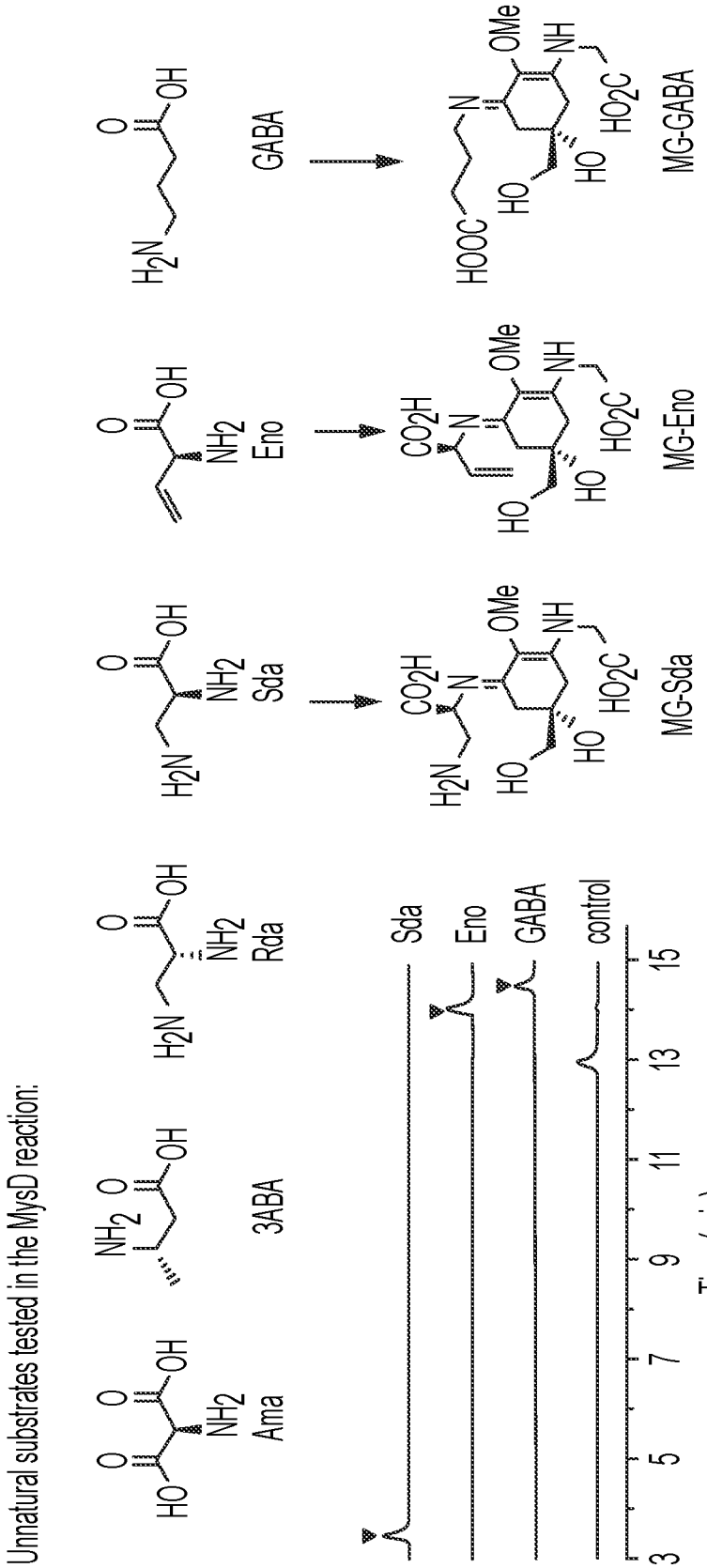
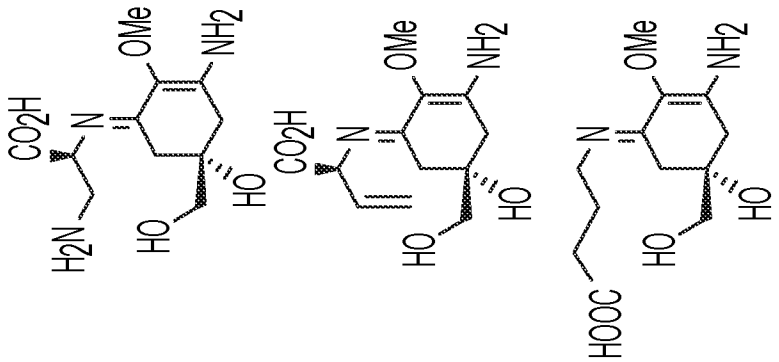


FIG. 6



Ama: 2-Aminomalonic acid; 3ABA: (3S)-Aminobutanic acid; Rda: (R)-2,3-diaminopropanate; Sda: (S)-2,3-diaminopropanate; Eno: (S)-2-aminobut-3-enoic acid; GABA: 4-aminobutanoic acid

FIG. 7


CO2H
N
OMe
NH2
H2N
HO
HO
CO2H
N
OMe
NH2
HO
HO
N
OMe
NH2
HOOC
HO
HO

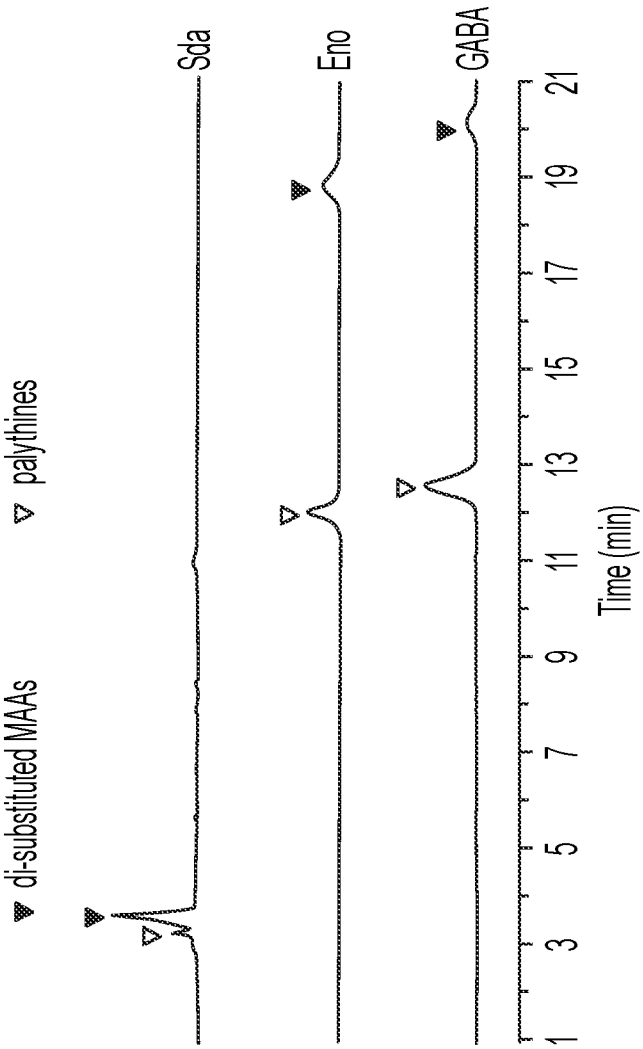

di-substituted MAAs
palythines
Sda
Eno
GABA
1
3
5
7
9
11
13
15
17
19
21
Time (min)

FIG. 8

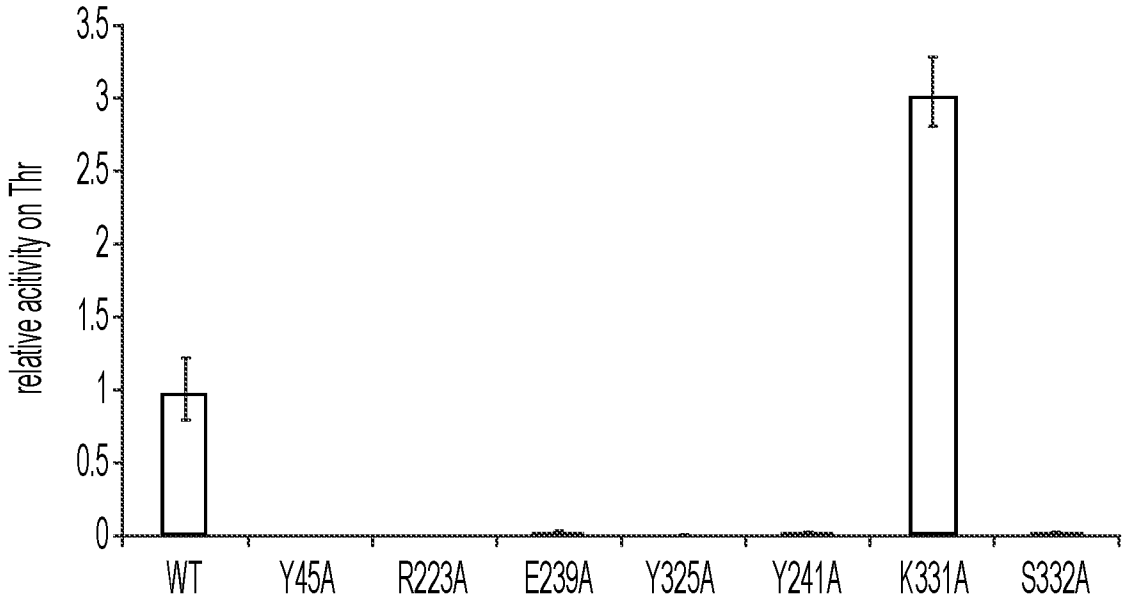

relative acitivity on Thr
3.5
3
2.5
2
1.5
1
0.5
0
WT
Y45A
R223A
E239A
Y325A
Y241A
K331A
S332A

FIG. 9

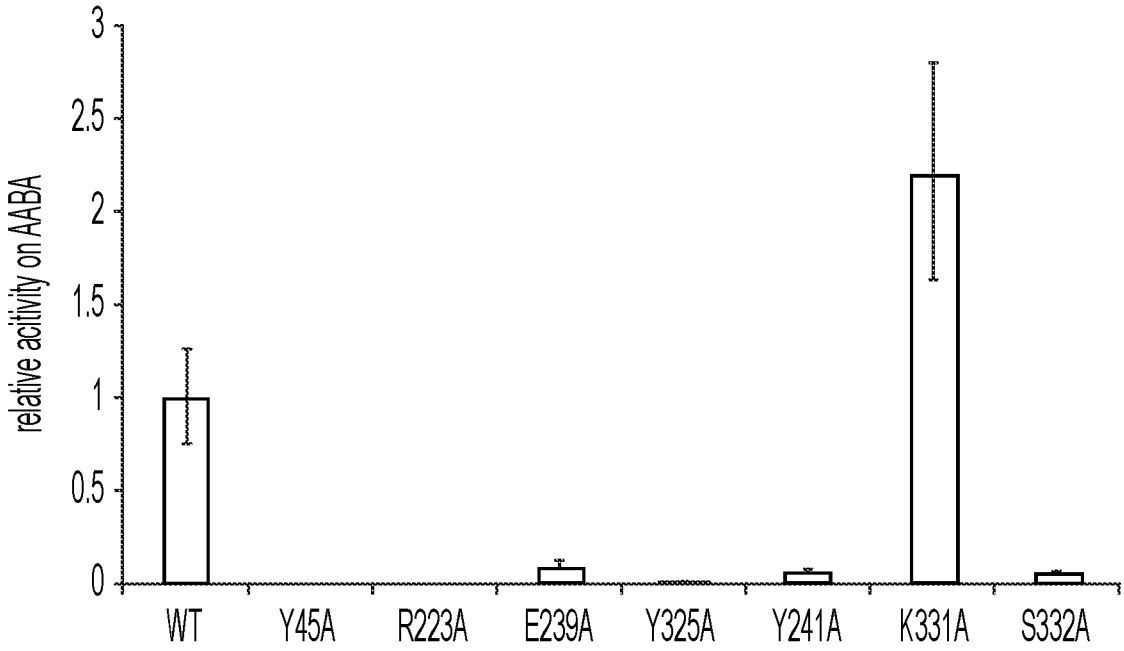

relative acitivity on AABA
3
2.5
2
1.5
1
0.5
0
WT
Y45A
R223A
E239A
Y325A
Y241A
K331A
S332A

FIG. 10