



(51) International Patent Classification:

A23L 1/236 (2006.01) C12P 13/06 (2006.01)
C07C 229/00 (2006.01) C12P 13/20 (2006.01)

(21) International Application Number:

PCT/US2014/056646

(22) International Filing Date:

19 September 2014 (19.09.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/917,425 18 December 2013 (18.12.2013) US
61/985,076 28 April 2014 (28.04.2014) US

(71) Applicant: BOARD OF SUPERVISORS OF LOUISIANA STATE UNIVERSITY AND AGRICULTURAL AND MECHANICAL COLLEGE [US/US]; LSU Agricultural Experiment Station, LSU AG.Center, P.O. Box 25055, Baton Rouge, LA 70894-5055 (US).

(72) Inventors: LIU, Zhijun; 11142 South Lakeside Oaks Avenue, Baton Rouge, LA 70810 (US). SHU, Jicheng; 227 Renewable Natural Resources Building, Louisiana State University, Baton Rouge, LA 70803 (US).

(74) Agents: SHORTELL, D., Brian et al.; Ballard Spahr LLP, 999 Peachtree Street, Suite 1000, Atlanta, GA 30309 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: SUGAR-FREE SWEETENER

(57) Abstract: The compounds and compositions of the invention are useful to sweeten foods, beverages, medicines, and other consumable products (e.g., chewing gum, toothpaste, mouthwash, etc.). The disclosed compounds provide a high intensity sweetness, with no traceable bitter aftertaste. This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.

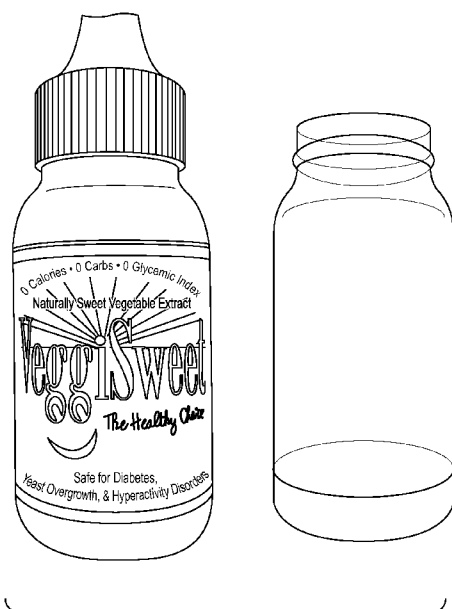


FIG. 1



Declarations under Rule 4.17:

Published:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))* — *with international search report (Art. 21(3))*

SUGAR-FREE SWEETENER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This Application claims the benefit of U.S. Provisional Application No. 61/917,425, filed on December 18, 2013, and U.S. Provisional Application No. 61/985,076, filed on April 28, 2014, which are incorporated herein by reference in their entirety.

BACKGROUND

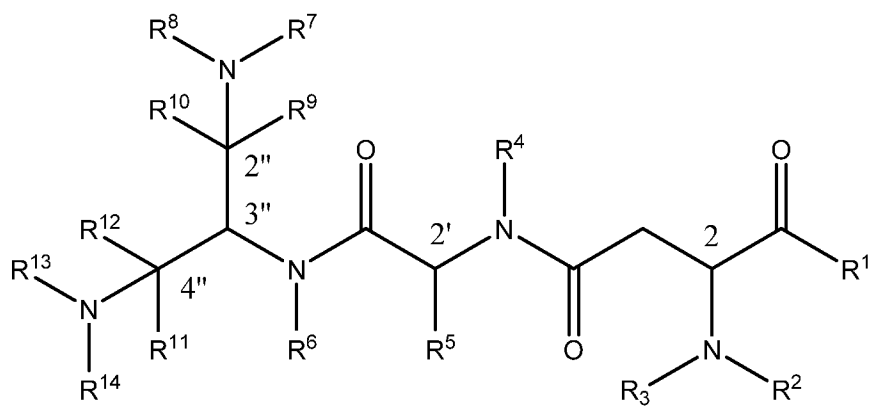
[0002] Sweeteners are an important ingredient in a wide variety of consumable products including food products and beverage products, as well as oral hygiene products such as mouth wash and toothpaste. The development of convenience oriented products has led to increased consumption of sweeteners, while the demand for dietary products has led to attempts to reduce the sweetener contribution of calories and carbohydrates. These attempts involve the use of both natural and artificial sweeteners.

[0003] Many of these sweeteners offer an intense sweetness, but have the disadvantage of having an undesirable, bitter aftertaste, particularly when used at higher concentrations. Additionally, the flavor quality of the sweetness imparted by these sweeteners often differs from sucrose, which serves as a standard for the evaluation of the sweetness, simply because consumers have been accustomed to it for such a long time.

[0004] Accordingly, there remains a need for a sweetener that can provide a high intensity sweetness while not contributing to a strong aftertaste. Additionally, sweeteners that impart a taste that closely mimics the taste of sucrose are desired.

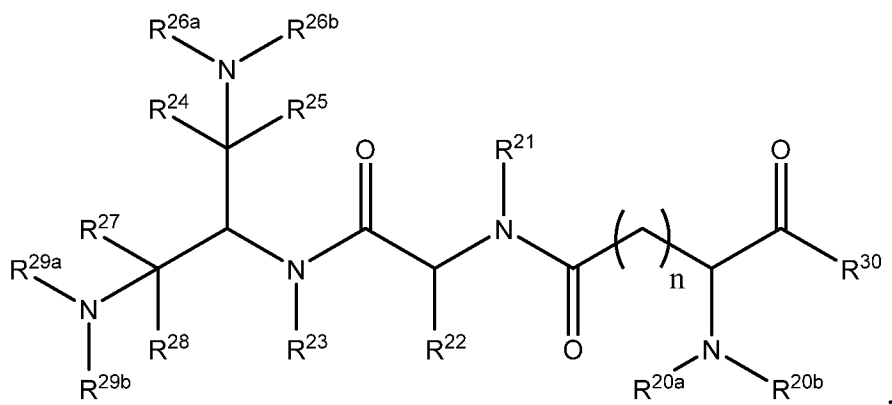
SUMMARY

[0005] In one aspect, the invention relates to compounds having a structure represented by a formula:



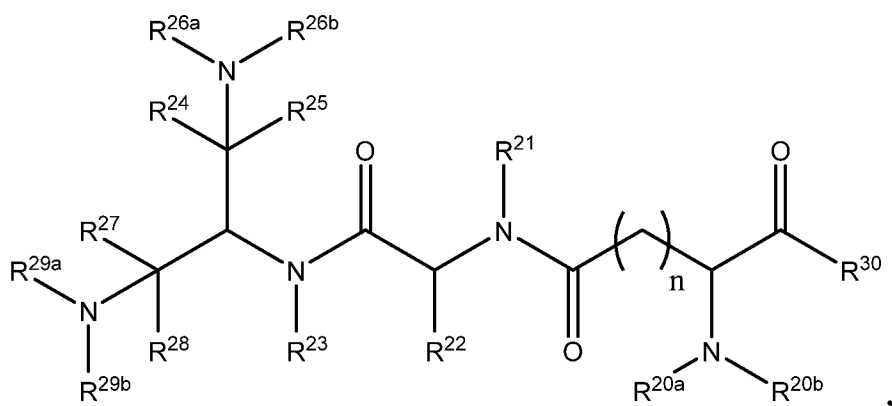
wherein R¹ is selected from halogen, -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, -NH₂, and C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkoxy, thioalkyl, and amino; wherein each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, halogen, -COOH, -CHO, -CH₂OH, -NH₂, and C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino; wherein each of R⁵, R⁹, R¹⁰, R¹¹, and R¹² is independently selected from hydrogen, methyl, -CH₂OH, -CH₂X, -CHX₂, -CHO, -COOH, -CH₂SH, and -CONH₂; wherein each X, when present, is independently selected from fluoro, chloro, bromo, and iodo; wherein each of the 2 and 2' carbon atoms are chiral centers, and wherein each chiral center is independently selected from the *R*- and *S*-stereoisomer, or a racemic mixture thereof; wherein each of the 2'', 3'', and 4'' carbon atoms are optionally a chiral center, and wherein each chiral center, when present, is independently selected from the *R*- and *S*-stereoisomer, or a racemic mixture thereof; and wherein either R¹ is not -OH; or wherein at least one of R², R³, R⁷, R⁸, R¹³, and R¹⁴ is not hydrogen; or wherein at least one of R⁵, R⁹, R¹⁰, R¹¹, and R¹² is not methyl.

[0006] Also disclosed are compounds having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$; wherein Ar^1 is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, $-\text{OH}$, and C1-C4 alkoxy; wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and wherein R^{30} is selected from $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and $-\text{NH}_2$.

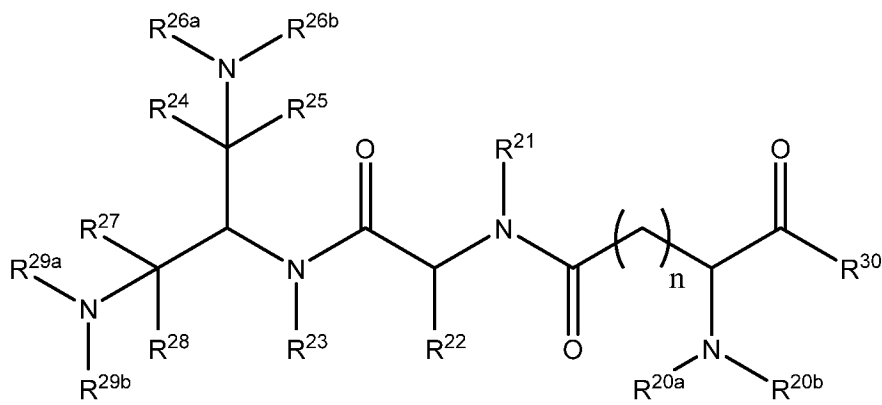
[0007] Also disclosed are compositions comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$; wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4

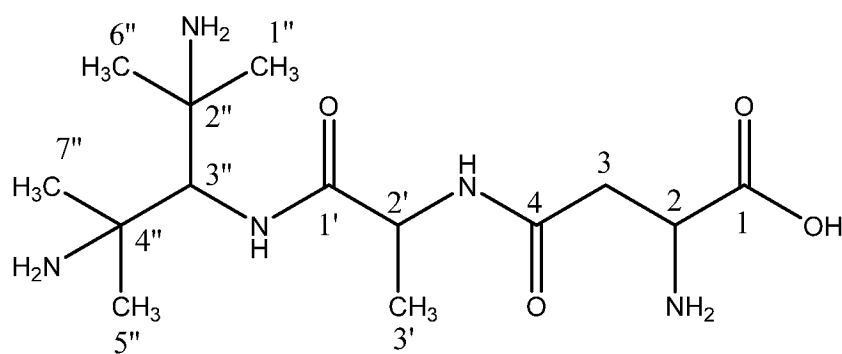
alkyl, and C1-C4 alkoxy; wherein R^{30} is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂; and wherein Ar¹ is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy.

[0008] Also disclosed are compositions comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a}, R^{20b}, R²¹, R²³, R^{26a}, R^{26b}, R^{29a}, and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R²² is selected from hydrogen, C1-C4 alkyl, -CH₂SeH, -CH₂SH, -CH₂CH₂SH, -CH₂CH₂SCH₃, and -CH₂Ar¹; wherein each of R²⁴, R²⁵, R²⁷, and R²⁸ is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; wherein R³⁰ is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂; and wherein Ar¹ is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy; and wherein the composition further optionally comprises a bulking agent; and wherein the composition further comprises at least one of: a) a carrier; b) a flavoring agent; c) a low intensity sweetener; d) a high intensity sweetener; e) a decolorizing agent; f) a taste modifier; g) a plasticizer; h) a film-forming polymer; i) a salt; and j) an internal film release agent.

[0009] Also disclosed are compositions comprising a compound having a structure represented by a formula:



[0010] Also disclosed are compositions comprising a compound selected from 2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, (2*R*)-4-(2*R*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, (2*R*)-4-(2*S*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, (2*S*)-4-(2*R*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, and (2*S*)-4-(2*S*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, or a mixture thereof.

[0011] Also disclosed are compositions comprising a sweetener, wherein the sweetener contains no sugar moieties and wherein the composition is obtained via solvent extraction of a material comprising at least one member of the group consisting of spinach, spinach protein, micronized spinach protein, algae, algae extract, alfalfa, alfalfa extract, Jerusalem artichoke, and Jerusalem artichoke extract.

[0012] Also disclosed are methods of making the disclosed compounds and/or compositions.

[0013] Also disclosed are consumable products admixed with an effective amount of the disclosed compounds and/or compositions.

[0014] Also disclosed are orally ingestible products sweetened with the disclosed compounds and/or compositions.

[0015] Also disclosed are oral products sweetened with the disclosed compounds and/or compositions.

[0016] Also disclosed are medicaments sweetened with the disclosed compounds and/or compositions.

[0017] Also disclosed are methods of sweetening orally ingestible products, the methods comprising incorporating therein the disclosed compounds and/or compositions.

[0018] Also disclosed are methods of sweetening oral products, the methods comprising incorporating therein the disclosed compounds and/or compositions.

[0019] Also disclosed are methods of sweetening medicaments, the methods comprising incorporating therein the disclosed compounds and compositions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects and together with the description serve to explain the principles of the invention.

[0021] **FIG. 1** shows a representative image of the concentration of VeggiSweet from 30 mL (left) to 2 mL (right).

[0022] **FIG. 2** shows representative chromatograms of the raw sample or liquid product, the Methanol-insoluble part and the Methanol-soluble part, generated at 210 nm via HPLC. The sugar-free sweetener had a retention time of 13.5 min and was the dominant peak in the liquid product.

[0023] **FIG. 3** shows a representative diagram of the isolation procedure.

[0024] **FIG. 4** shows representative chromatograms of the fractions from the Methanol-soluble part, generated at 210 nm via HPLC. The sugar-free sweetener had a retention time of 9.3 min and was fractionated nearly completely into Fraction 2.

[0025] **FIG. 5** shows a representative image of the Water-1, Water-2, and Methanol-1 fractions (from left to right).

[0026] FIG. 6 shows representative HPLC-UV chromatograms of Water-1, Water-2, and Methanol-1 fractions at 210 nm. The majority of the sugar-free sweetener was isolated into the Water-2 sample, whereas only a trace amount was seen in Water-1 and none in Methanol-1.

[0027] FIG. 7 shows a representative image of the target compound isolated from VeggiSweet as a yellowish powder.

[0028] FIG. 8 shows a representative ^1H NMR spectrum.

[0029] FIG. 9 shows a representative ^{13}C NMR spectrum.

[0030] FIG. 10 shows a representative DEPT-135 spectrum.

[0031] FIG. 11 shows a representative HSQC spectrum.

[0032] FIG. 12 shows a representative HMBC spectrum.

[0033] FIG. 13 shows a representative H-H COSY spectrum.

[0034] FIG. 14 shows a representative LC-MS spectrum in negative mode.

[0035] FIG. 15 shows a representative LC-MS spectrum in positive mode.

[0036] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION

[0037] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

[0038] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific

synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

[0039] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

[0040] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the passage in which the reference is relied upon. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein may be different from the actual publication dates, which can require independent confirmation.

A. DEFINITIONS

[0041] As used herein, nomenclature for compounds, including organic compounds, can be given using common names, IUPAC, IUBMB, or CAS recommendations for nomenclature. When one or more stereochemical features are present, Cahn-Ingold-Prelog rules for

stereochemistry can be employed to designate stereochemical priority, *E/Z* specification, and the like. One of skill in the art can readily ascertain the structure of a compound if given a name, either by systemic reduction of the compound structure using naming conventions, or by commercially available software, such as CHEMDRAWTM (Cambridgesoft Corporation, U.S.A.).

[0042] As used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a functional group,” “an alkyl,” or “a residue” includes mixtures of two or more such functional groups, alkyls, or residues, and the like. Further, a “functional group” or a “group” may consist of just one atom, or it may contain several atoms.

[0043] Ranges can be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0044] References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight (or mass) relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

[0045] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight (or mass) of the formulation or composition in which the component is included.

[0046] As used herein, the terms “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0047] As used herein, the term “subject” can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses and embryos, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term “patient” includes human and veterinary subjects. In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment of one or more disorders prior to the administering step.

[0048] As used herein, the term “treatment” refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (e.g., a human), and includes: (i) preventing the disease from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease,

i.e., arresting its development; or (iii) relieving the disease, i.e., causing regression of the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human. The term “subject” also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.).

[0049] As used herein, the term “prevent” or “preventing” refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0050] As used herein, the terms “administering” and “administration” refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0051] The term “contacting” as used herein refers to bringing a disclosed compound and a cell, target histamine receptor, or other biological entity together in such a manner that the compound can affect the activity of the target (e.g., receptor, cell, etc.), either directly; i.e., by interacting with the target itself, or indirectly; i.e., by interacting with another molecule, co-factor, factor, or protein on which the activity of the target is dependent.

[0052] As used herein, the terms “effective amount” and “amount effective” refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a “therapeutically effective amount” refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms,

but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a “prophylactically effective amount”; that is, an amount effective for prevention of a disease or condition.

[0053] As used herein, “EC₅₀,” is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% agonism of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an EC₅₀ can refer to the concentration of a substance that is required for 50% agonism *in vivo*, as further defined elsewhere herein. In a further aspect, EC₅₀ refers to the concentration of agonist that provokes a response halfway between the baseline and maximum response.

[0054] As used herein, “IC₅₀,” is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an IC₅₀ can refer to the concentration of a substance that is required for 50% inhibition *in vivo*, as further defined elsewhere herein. In a further aspect, IC₅₀ refers to the half maximal (50%) inhibitory concentration (IC) of a substance.

[0055] The term “pharmaceutically acceptable” describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

[0056] As used herein, the term “derivative” refers to a compound having a structure derived from the structure of a parent compound (e.g., a compound disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity, would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

[0057] The term “leaving group” refers to an atom (or a group of atoms) with electron withdrawing ability that can be displaced as a stable species, taking with it the bonding electrons. Examples of suitable leaving groups include sulfonate esters, including triflate, mesylate, tosylate, brosylate, and halides.

[0058] A residue of a chemical species, as used in the specification and claims, refers to the moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more $\text{-OCH}_2\text{CH}_2\text{O-}$ units in the polyester, regardless of whether ethylene glycol was used to prepare the polyester. Similarly, a sebacic acid residue in a polyester refers to one or more $\text{-CO(CH}_2)_8\text{CO-}$ moieties in the polyester, regardless of whether the residue is obtained by reacting sebacic acid or an ester thereof to obtain the polyester.

[0059] As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more, and they can be the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible

substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms “substitution” or “substituted with” include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (*i.e.*, further substituted or unsubstituted).

[0060] In defining various terms, “A¹,” “A²,” “A³,” and “A⁴” are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

[0061] The term “alkyl” as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl, *s*-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can also be substituted or unsubstituted. The alkyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A “lower alkyl” group is an alkyl group containing from one to six (*e.g.*, from one to four) carbon atoms.

[0062] Throughout the specification “alkyl” is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term “halogenated alkyl” specifically refers to an alkyl group that is substituted with one or more halide, *e.g.*, fluorine, chlorine, bromine, or iodine. The term “alkoxyalkyl” specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term “alkylamino” specifically refers to an alkyl group that is substituted with one or more amino groups, as described below, and the like. When “alkyl” is used in one instance and a specific

term such as “alkylalcohol” is used in another, it is not meant to imply that the term “alkyl” does not also refer to specific terms such as “alkylalcohol” and the like.

[0063] This practice is also used for other groups described herein. That is, while a term such as “cycloalkyl” refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, *e.g.*, an “alkylcycloalkyl.” Similarly, a substituted alkoxy can be specifically referred to as, *e.g.*, a “halogenated alkoxy,” a particular substituted alkenyl can be, *e.g.*, an “alkenylalcohol,” and the like. Again, the practice of using a general term, such as “cycloalkyl,” and a specific term, such as “alkylcycloalkyl,” is not meant to imply that the general term does not also include the specific term.

[0064] The term “cycloalkyl” as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term “heterocycloalkyl” is a type of cycloalkyl group as defined above, and is included within the meaning of the term “cycloalkyl,” where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0065] The term “polyalkylene group” as used herein is a group having two or more CH₂ groups linked to one another. The polyalkylene group can be represented by the formula —(CH₂)_a—, where “a” is an integer of from 2 to 500.

[0066] The terms “alkoxy” and “alkoxyl” as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an “alkoxy” group can be defined as —OA¹ where A¹ is alkyl or cycloalkyl as defined above. “Alkoxy” also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as —OA¹—OA² or —OA¹—(OA²)_a—OA³, where “a” is an integer of from 1 to 200 and A¹, A², and A³ are alkyl and/or cycloalkyl groups.

[0067] The term “alkenyl” as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as $(A^1A^2)C=C(A^3A^4)$ are intended to include both the *E* and *Z* isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0068] The term “cycloalkenyl” as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double bond, *i.e.*, C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The term “heterocycloalkenyl” is a type of cycloalkenyl group as defined above, and is included within the meaning of the term “cycloalkenyl,” where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0069] The term “alkynyl” as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0070] The term “cycloalkynyl” as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bond. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl,

cyclononyl, and the like. The term “heterocycloalkynyl” is a type of cycloalkenyl group as defined above, and is included within the meaning of the term “cycloalkynyl,” where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkynyl group and heterocycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group and heterocycloalkynyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0071] The term “aryl” as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, phenoxybenzene, and the like. The term “aryl” also includes “heteroaryl,” which is defined as a group that contains an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Likewise, the term “non-heteroaryl,” which is also included in the term “aryl,” defines a group that contains an aromatic group that does not contain a heteroatom. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term “biaryl” is a specific type of aryl group and is included in the definition of “aryl.” Biaryl refers to two aryl groups that are bound together *via* a fused ring structure, as in naphthalene, or are attached *via* one or more carbon-carbon bonds, as in biphenyl.

[0072] The term “aldehyde” as used herein is represented by the formula —C(O)H . Throughout this specification “C(O)” is a short hand notation for a carbonyl group, *i.e.*, C=O .

[0073] The terms “amine” or “amino” as used herein are represented by the formula $\text{—NA}^1\text{A}^2$, where A^1 and A^2 can be, independently, hydrogen or alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0074] The term “alkylamino” as used herein is represented by the formula —NH(alkyl) where alkyl is as described herein. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl)amino group, pentylamino group, isopentylamino group, (tert-pentyl)amino group, hexylamino group, and the like.

[0075] The term “dialkylamino” as used herein is represented by the formula —N(alkyl)_2 where alkyl is as described herein. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group and the like.

[0076] The term “carboxylic acid” as used herein is represented by the formula —C(O)OH .

[0077] The term “ester” as used herein is represented by the formula —OC(O)A^1 or —C(O)OA^1 , where A^1 can be an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term “polyester” as used herein is represented by the formula $\text{—(A}^1\text{O(O)C—A}^2\text{—C(O)O)}_a\text{—}$ or $\text{—(A}^1\text{O(O)C—A}^2\text{—OC(O))}_a\text{—}$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and “a” is an integer from 1 to 500. “Polyester” is a term used to describe a group that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

[0078] The term “ether” as used herein is represented by the formula A^1OA^2 , where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term “polyether” as used herein is represented by the formula $\text{—(A}^1\text{O—A}^2\text{O)}_a\text{—}$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and “a” is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

[0079] The term “halide” as used herein refers to the halogens fluorine, chlorine, bromine, and iodine.

[0080] The term “heterocycle,” as used herein refers to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Heterocycles include pyridine, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole, thiadiazole, including, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, triazole, including, 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydropyran, tetrahydrofuran, dioxane, and the like.

[0081] The term “hydroxyl” as used herein is represented by the formula —OH.

[0082] The term “ketone” as used herein is represented by the formula $A^1C(O)A^2$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0083] The term “azide” as used herein is represented by the formula —N₃.

[0084] The term “nitro” as used herein is represented by the formula —NO₂.

[0085] The term “nitrile” as used herein is represented by the formula —CN.

[0086] The term “silyl” as used herein is represented by the formula —SiA¹A²A³, where A¹, A², and A³ can be, independently, hydrogen or an optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0087] The term “sulfo-oxo” as used herein is represented by the formulas —S(O)A¹, —S(O)₂A¹, —OS(O)₂A¹, or —OS(O)₂OA¹, where A¹ can be hydrogen or an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. Throughout this specification “S(O)” is a short hand notation for S=O. The term “sulfonyl” is used herein to refer to the sulfo-oxo group represented by the formula —

$S(O)_2A^1$, where A^1 can be hydrogen or an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term “sulfone” as used herein is represented by the formula $A^1S(O)_2A^2$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term “sulfoxide” as used herein is represented by the formula $A^1S(O)A^2$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0088] The term “thiol” as used herein is represented by the formula $-SH$.

[0089] “ R^1 ,” “ R^2 ,” “ R^3 ,” “ R^n ,” where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (*i.e.*, attached) to the second group. For example, with the phrase “an alkyl group comprising an amino group,” the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

[0090] As described herein, compounds of the invention may contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. It is also contemplated that, in certain

aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[0091] The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain aspects, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0092] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}$ -pyridyl which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3 ; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$ -(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0093] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene) $C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=O$ and $=S$.

[0094] Suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group include the following: $=O$, $=S$, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

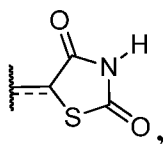
[0095] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, $-(haloR^\bullet)$, $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0096] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0097] Suitable substituents on the aliphatic group of $R^{\bullet}$ are independently halogen, $-R^{\bullet}$, $-(haloR^{\bullet})$, $-OH$, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0098] The term “organic residue” defines a carbon-containing residue, i.e., a residue comprising at least one carbon atom, and includes but is not limited to the carbon-containing groups, residues, or radicals defined hereinabove. Organic residues can contain various heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited to alkyl or substituted alkyl, alkoxy or substituted alkoxy, mono or di-substituted amino, amide groups, etc. Organic residues can preferably comprise 1 to 18 carbon atoms, 1 to 15, carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an organic residue can comprise 2 to 18 carbon atoms, 2 to 15, carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2 to 4 carbon atoms, or 2 to 4 carbon atoms.

[0099] A term closely related to “residue” is “radical,” which as used in the specification and concluding claims refers to a fragment, group, or substructure of a molecule described herein, regardless of how the molecule is prepared. For example, a 2,4-thiazolidinedione radical in a particular compound has the structure:



regardless of whether thiazolidinedione is used to prepare the compound. In some embodiments the radical (for example an alkyl) can be further modified (i.e., substituted alkyl) by having bonded thereto one or more “substituent radicals.” The number of atoms in a given radical is not critical to the present invention unless it is indicated to the contrary elsewhere herein.

[00100] “Organic radicals,” as the term is defined and used herein, contain one or more carbon atoms. An organic radical can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. In a further aspect, an organic radical can have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon atoms. Organic radicals often have hydrogen atoms bound to at least some of the carbon atoms of the organic radical. One example of an organic radical that comprises no heteroatoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some embodiments, an organic radical can contain 1-10 heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of organic radicals include but are not limited to an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals and the like.

[00101] “Inorganic radicals,” as the term is defined and used herein, contain no carbon atoms. Inorganic radicals comprise bonded combinations of atoms selected from, for example, hydrogen, nitrogen, oxygen, silicon, phosphorus, sulfur, selenium, and halogens such as fluorine, chlorine, bromine, and iodine, which can be present individually or bonded together in chemically stable combinations. Inorganic radicals have 10 or fewer, or preferably one to six or

one to four inorganic atoms as listed above bonded together. Examples of inorganic radicals include, but are not limited to, amino, hydroxy, halogens, nitro, thiol, sulfate, phosphate, and the like. Unless otherwise specifically indicated elsewhere herein, the inorganic radicals do not have covalently bonded therein the metallic elements of the periodic table (such as the alkali metals, alkaline earth metals, transition metals, lanthanide metals, or actinide metals), although such metal ions can sometimes serve as a pharmaceutically acceptable cation for anionic inorganic radicals such as a sulfate, phosphate, or like anionic inorganic radical. Inorganic radicals do not comprise metal or metalloid elements such as boron, aluminum, gallium, germanium, arsenic, tin, lead, or tellurium, unless otherwise specifically indicated elsewhere herein.

[00102] Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

[00103] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each enantiomer and diastereomer, and each mixture of isomers, such as a racemic or scalemic mixture.

Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[00104] Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory.

A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that (at each chiral center) they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the disclosed formulas, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines (bonds to atoms below the plane). The Cahn-Ingold-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

[00105] When the disclosed compounds contain one chiral center, the compounds exist in two enantiomeric forms. Unless specifically stated to the contrary, a disclosed compound includes both enantiomers and mixtures of enantiomers, such as the specific 50:50 mixture referred to as a racemic mixture. The enantiomers can be resolved by methods known to those skilled in the art, such as formation of diastereoisomeric salts which may be separated, for example, by crystallization (see, CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation by David Kozma (CRC Press, 2001)); formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step can liberate the desired enantiomeric form. Alternatively, specific enantiomers can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

[00106] Designation of a specific absolute configuration at a chiral carbon in a disclosed compound is understood to mean that the designated enantiomeric form of the compounds can be provided in enantiomeric excess (*e.e.*). Enantiomeric excess, as used herein, is the presence of a particular enantiomer at greater than 50%, for example, greater than 60%, greater than 70%, greater than 75%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 98%, or greater than 99%. In one aspect, the designated enantiomer is substantially free from the other enantiomer. For example, the “R” forms of the compounds can be substantially free from the “S” forms of the compounds and are, thus, in enantiomeric excess of the “S” forms. Conversely, “S” forms of the compounds can be substantially free of “R” forms of the compounds and are, thus, in enantiomeric excess of the “R” forms.

[00107] When a disclosed compound has two or more chiral carbons, it can have more than two optical isomers and can exist in diastereoisomeric forms. For example, when there are two chiral carbons, the compound can have up to four optical isomers and two pairs of enantiomers ((S,S)/(R,R) and (R,S)/(S,R)). The pairs of enantiomers (e.g., (S,S)/(R,R)) are mirror image stereoisomers of one another. The stereoisomers that are not mirror-images (e.g., (S,R) and (R,S)) are diastereomers. The diastereoisomeric pairs can be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Unless otherwise specifically excluded, a disclosed compound includes each diastereoisomer of such compounds and mixtures thereof.

[00108] Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically-labeled or isotopically-substituted compounds identical to those described, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature on the Earth. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds that comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain

isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[00109] The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvate or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

[00110] The term “co-crystal” means a physical association of two or more molecules which owe their stability through non-covalent interaction. One or more components of this molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest molecules are incorporated in the crystalline lattice as anhydrides or solvates, see e.g. “Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?” Almarasson, O., et. al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-toluenesulfonic acid and benzenesulfonic acid.

[00111] It is known that chemical substances form solids which are present in different states of order which are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ, sometimes greatly, in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it

being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

[00112] Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Acros Organics (Morris Plains, N.J.), Fisher Scientific (Pittsburgh, Pa.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[00113] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification. Those of skill in the art will recognize that, in some instances, it is implicit that at least some of the steps of an organic synthesis or of a separation should be carried out in a particular order to produce the desired result.

[00114] Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each

various individual and collective combinations and permutation of these compounds cannot be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

[00115] It is understood that the compositions disclosed herein have certain functions. Disclosed herein are certain structural features for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

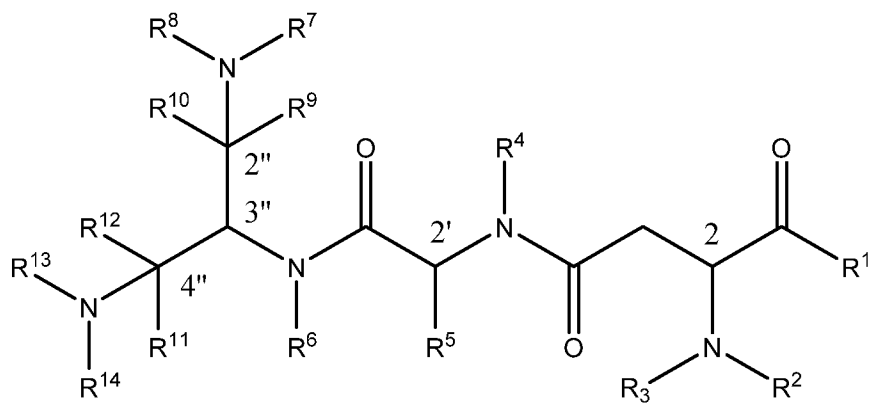
B. COMPOUNDS

[00116] In one aspect, the invention relates to compounds useful to sweeten foods, beverages, medicines, and other consumable products (*e.g.*, chewing gum, toothpaste, mouthwash, etc.). The compound may be supplied in solid form, or dissolved in water or alcohol (preferably ethanol).

[00117] It is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivatives can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

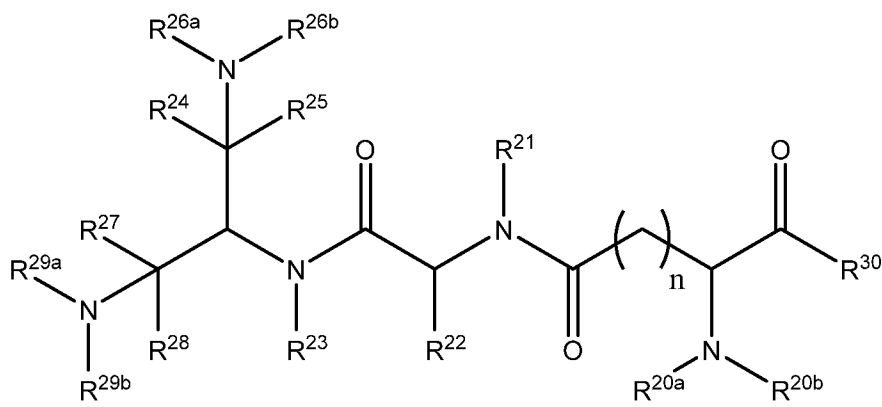
1. STRUCTURE

[00118] The structure of the newly-discovered sweetener may be modified to maintain or enhance sweetness, or to maintain or enhance desirable physical properties such as heat stability during food preparation, stability at different pH, and the like. Thus, in one aspect, the invention relates to compounds having a structure represented by a formula:



wherein R^1 is selected from halogen, -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, -NH₂, and C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkoxy, thioalkyl, and amino; wherein each of R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , R^{13} , and R^{14} is independently selected from hydrogen, halogen, -COOH, -CHO, -CH₂OH, -NH₂, and C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino; wherein each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is independently selected from hydrogen, methyl, -CH₂OH, -CH₂X, -CHX₂, -CHO, -COOH, -CH₂SH, and -CONH₂; wherein each X, when present, is independently selected from fluoro, chloro, bromo, and iodo; wherein each of the 2 and 2' carbon atoms are chiral centers, and wherein each chiral center is independently selected from the *R*- and *S*-stereoisomer, or a racemic mixture thereof; wherein each of the 2'', 3'', and 4'' carbon atoms are optionally a chiral center, and wherein each chiral center, when present, is independently selected from the *R*- and *S*-stereoisomer, or a racemic mixture thereof; and wherein either R^1 is not -OH; or wherein at least one of R^2 , R^3 , R^7 , R^8 , R^{13} , and R^{14} is not hydrogen; or wherein at least one of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is not methyl.

[00119] In one aspect, the invention relates to compounds having a structure represented by a formula:



wherein *n* is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a}, R^{20b}, R²¹, R²³, R^{26a}, R^{26b}, R^{29a}, and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R²² is selected from hydrogen, C1-C4 alkyl, -CH₂SeH, -CH₂SH, -CH₂CH₂SH, -CH₂CH₂SCH₃, and -CH₂Ar¹; wherein Ar¹ is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy; wherein each of R²⁴, R²⁵, R²⁷, and R²⁸ is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and wherein R³⁰ is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂.

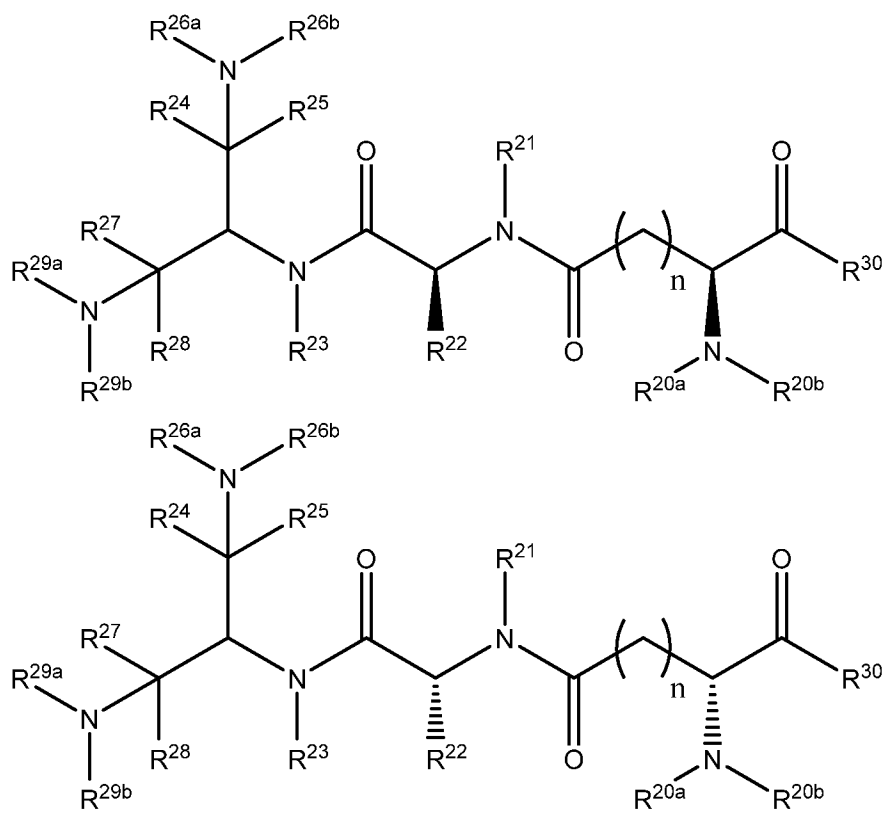
[00120] The 2 carbon atom and the 2' carbon atom are both chiral centers, and each may independently be selected to be the *R*- or *S*-stereoisomer, or a mixture of the two. Additionally, each of the 2'', 3'', and 4'' carbon atoms is a prochiral center, and each has the potential to become a new chiral center following substitution. When a prochiral center becomes a new chiral center, it can create new *R*- and *S*-stereoisomers. All stereoisomers of the structure, or mixtures of stereoisomers, are within the scope of the invention. If the 2'', 3'', or 4'' carbon atom becomes chiral as a result of such a substitution, then in each case the configuration at the resulting chiral center(s) may independently be selected to be the *R*- or *S*-stereoisomer, or a mixture of the two.

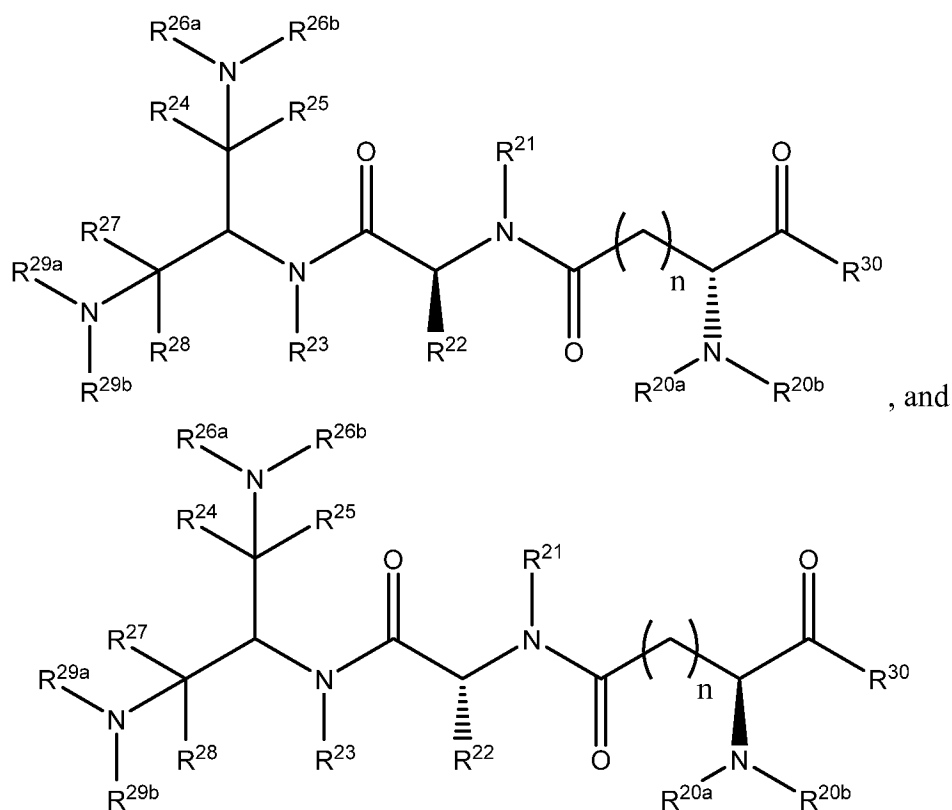
[00121] The compound may be isolated from natural sources as described above, for example by solvent extraction from one or more of spinach, algae, alfalfa, or Jerusalem artichoke, or other plant sources. Alternatively, the compound may be synthesized or semi-synthesized by methods otherwise known in the art. The naturally-occurring stereoisomer is preferred. Alternatively, other stereoisomers, or mixtures of stereoisomers may be used.

[00122] The compound may be isolated or prepared in substantially pure form; where, for this purpose, “substantially pure” means that the compound is present in a composition in a concentration (by mass) greater than or equal to: 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.7%, or 99.9%.

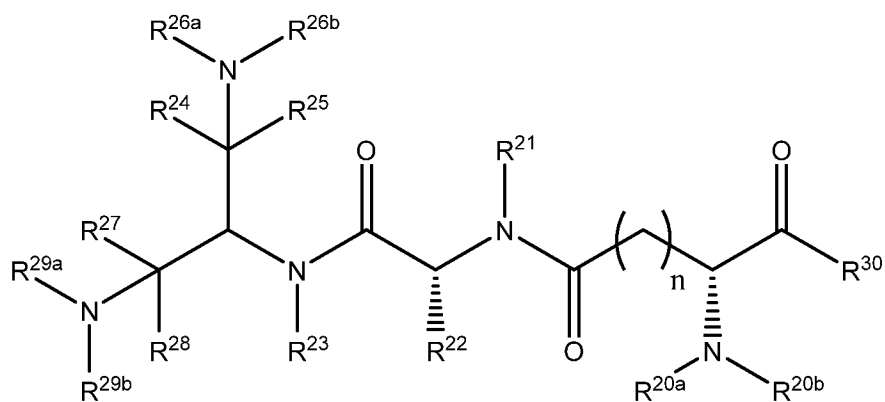
[00123] A “substantially pure” mixture of two or more stereoisomers refers to a composition in which the stereoisomers are present in any proportion(s) relative to one another, and in which the combined total amount of all stereoisomers (by mass) in the composition is greater than or equal to: 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.7%, or 99.9%.

[00124] In a further aspect, the compound has a structure represented by a formula selected from:

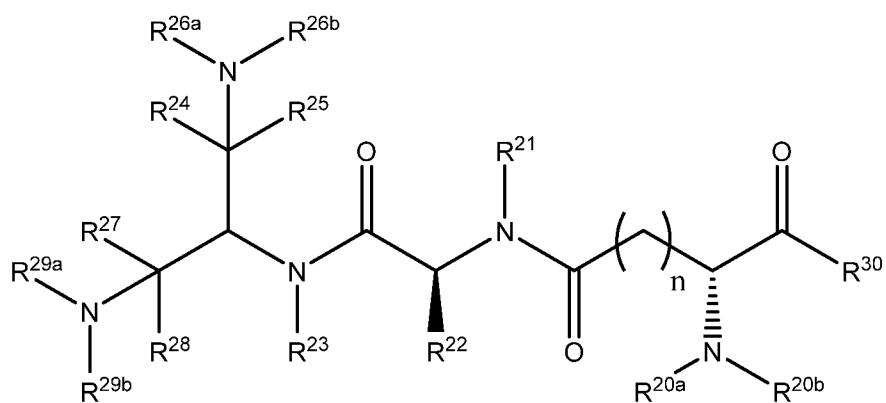




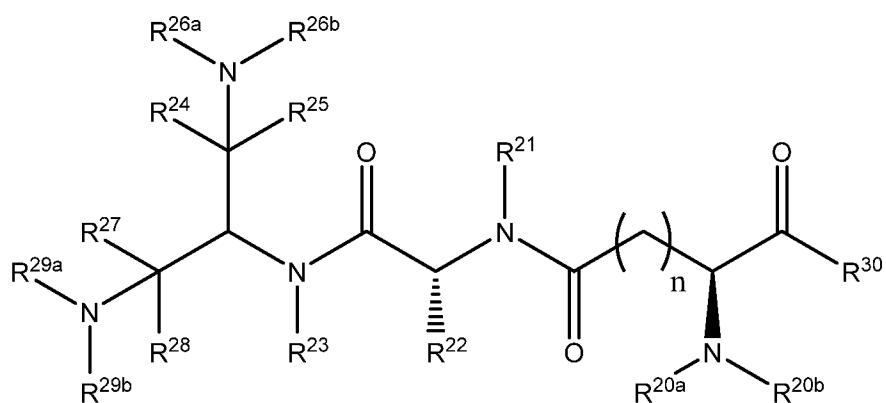
[00125] In a further aspect, the compound has a structure represented by a formula:



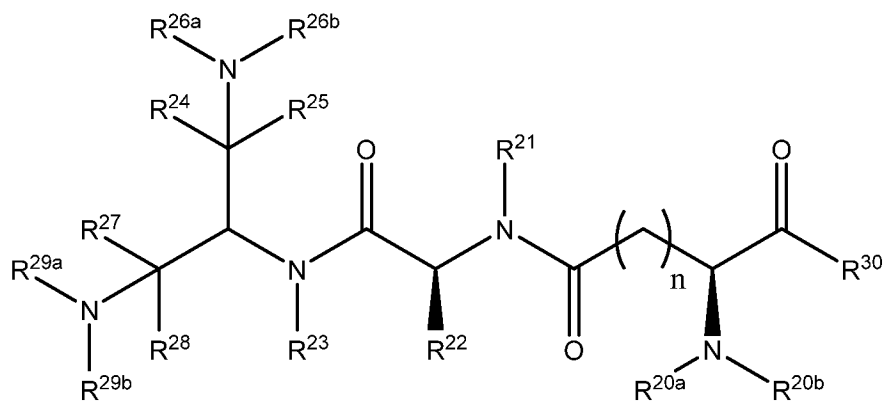
[00126] In a further aspect, the compound has a structure represented by a formula:



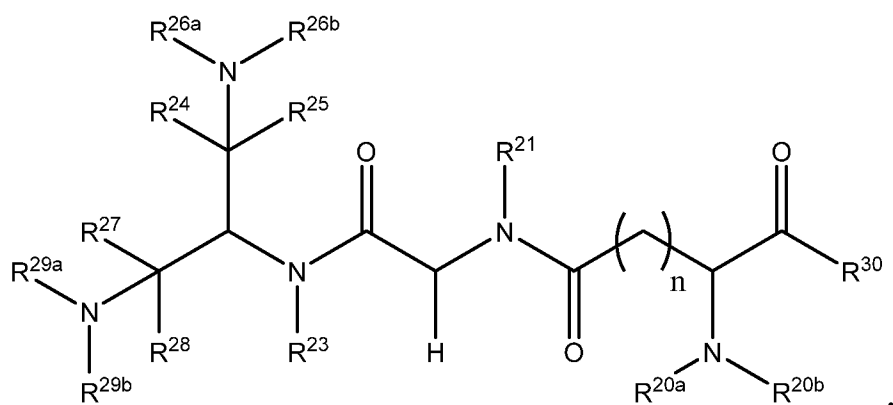
[00127] In a further aspect, the compound has a structure represented by a formula:



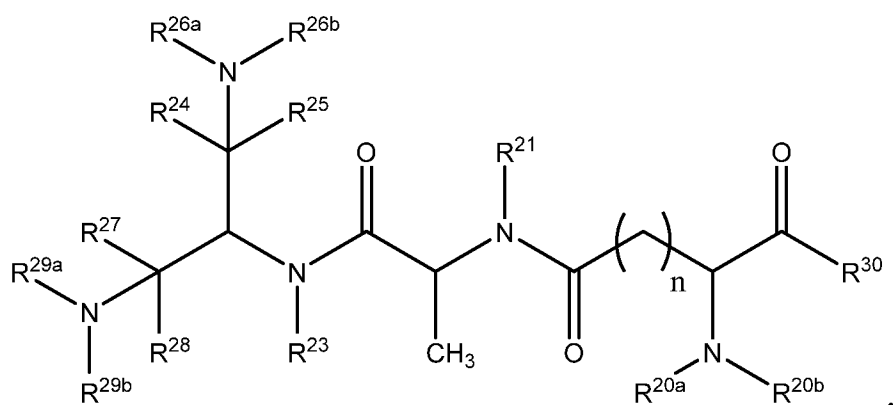
[00128] In a further aspect, the compound has a structure represented by a formula:



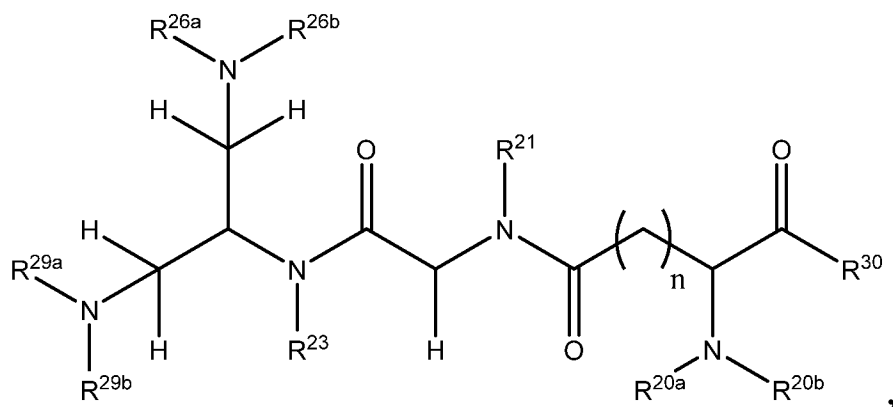
[00129] In a further aspect, the compound has a structure represented by a formula:



[00130] In a further aspect, the compound has a structure represented by a formula:

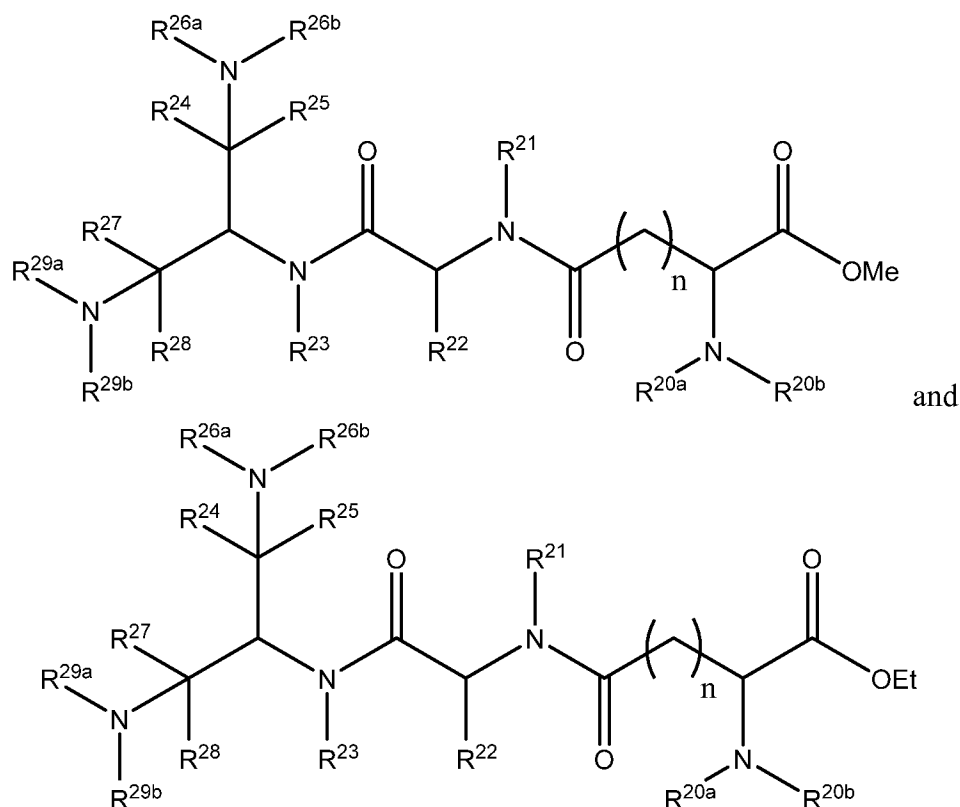


[00131] In a further aspect, the compound has a structure represented by a formula:

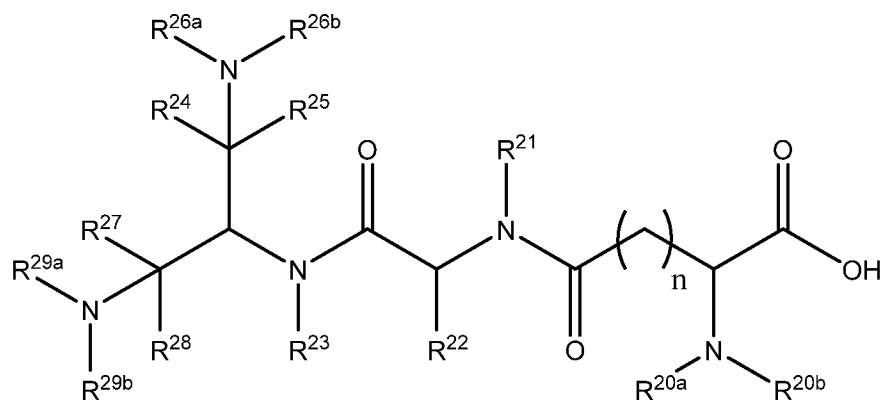


wherein n is an integer selected from 1 and 2.

[00132] In a further aspect, the compound has a structure represented by a formula selected from:

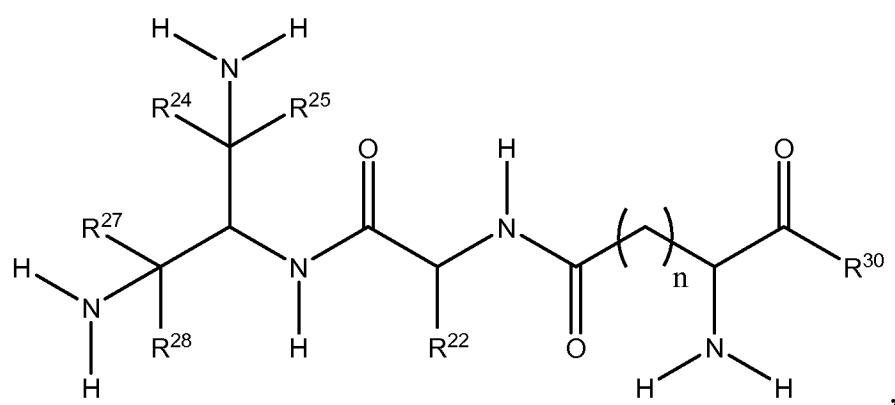


[00133] In a further aspect, the compound has a structure represented by a formula:



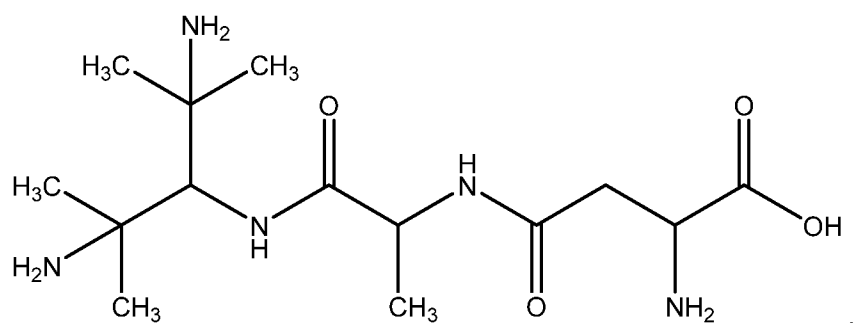
wherein n is an integer selected from 1 and 2.

[00134] In a further aspect, the compound has a structure represented by a formula:

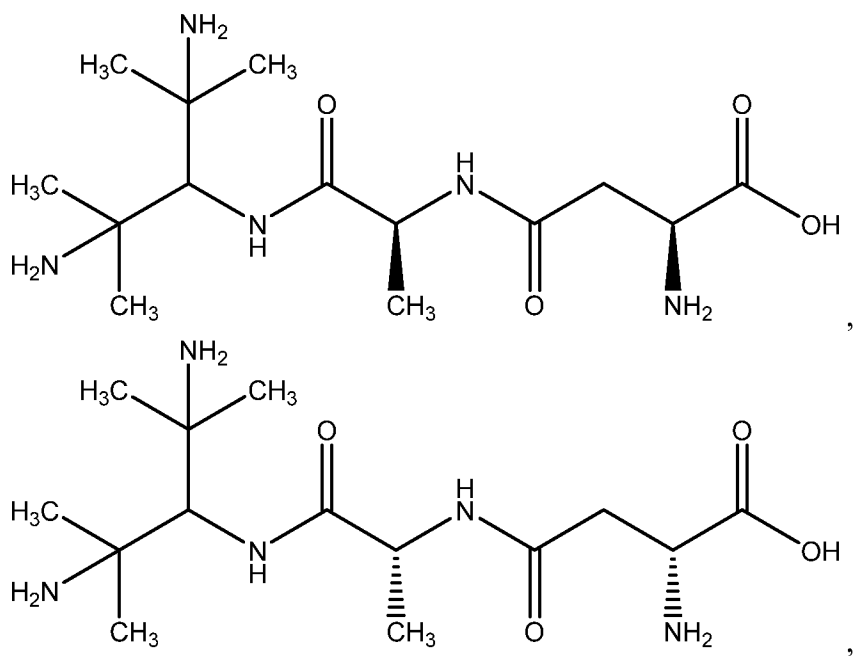


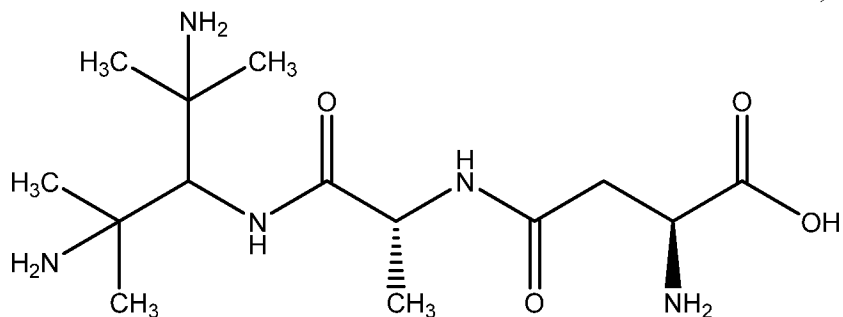
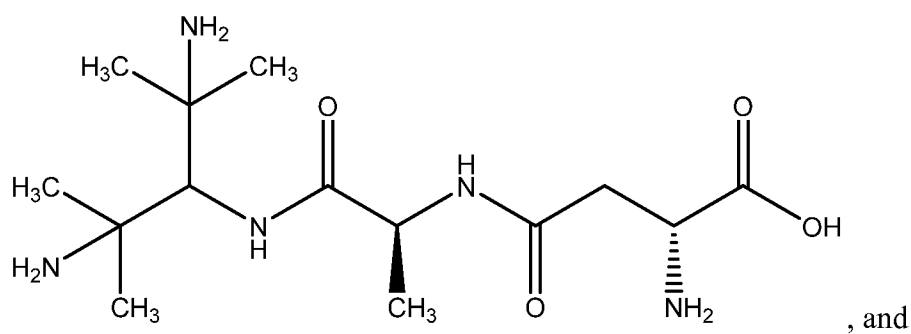
wherein n is an integer selected from 1 and 2.

[00135] In a further aspect, the compound is:

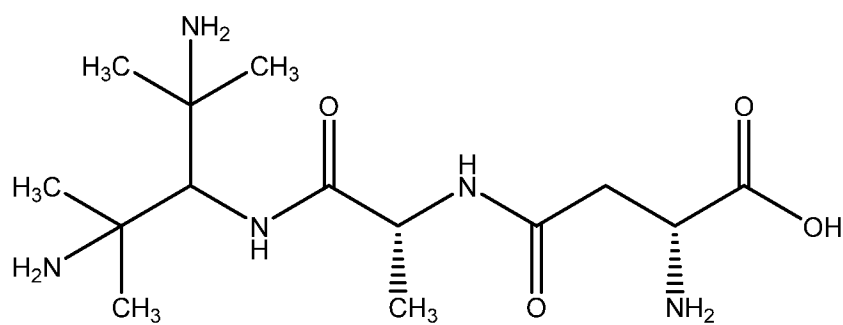


[00136] In a further aspect, the compound is selected from:

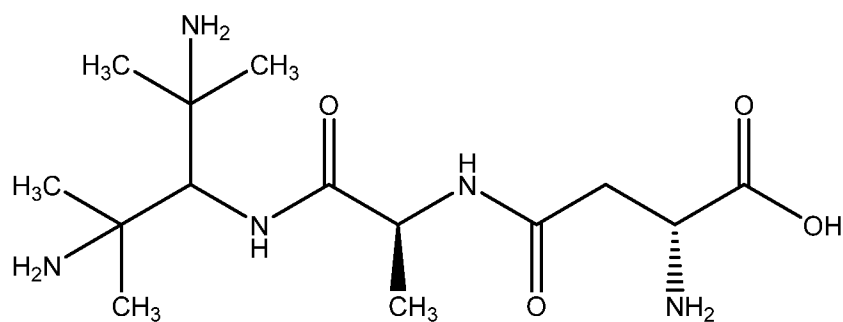




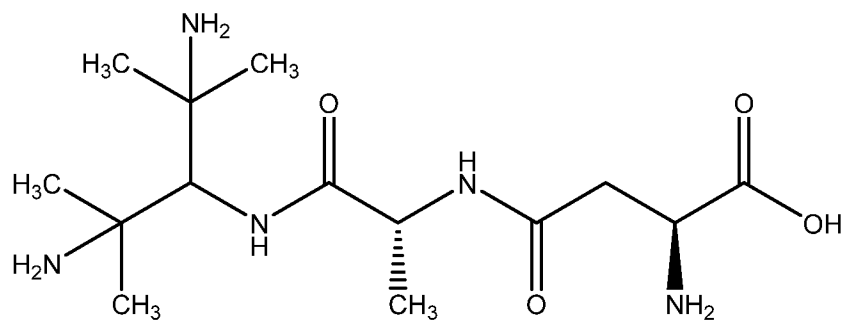
[00137] In a further aspect, the compound is:



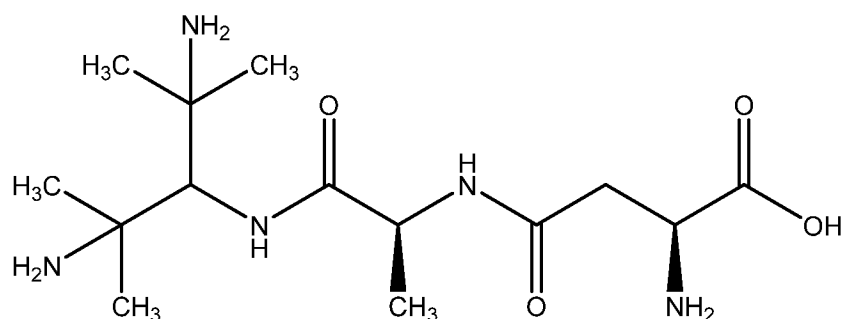
[00138] In a further aspect, the compound is:



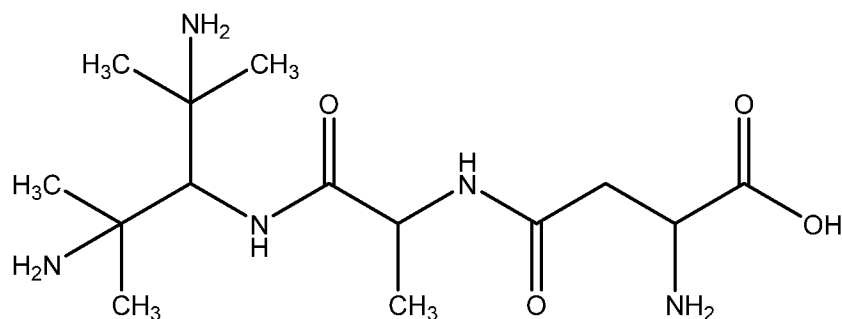
[00139] In a further aspect, the compound is:



[00140] In a further aspect, the compound is:



[00141] In a further aspect, the compound is not:



[00142] In one aspect, n is an integer selected from 1, 2, 3, and 4. In a further aspect, n is an integer selected from 1, 2, and 3. In a still further aspect, n is an integer selected from 1 and 2. In yet a further aspect, n is 4. In an even further aspect, n is 3. In a still further aspect, n is 2. In yet a further aspect, n is 1.

[00143] The substituents and variables shown in the various structural formulas in the specification and claims may, where applicable, be such as are described in the following paragraphs:

a. R¹ GROUPS

[00144] In one aspect, R¹ is selected from halogen, -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, -NH₂, and C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkoxy, thioalkyl, and amino. In a further aspect, R¹ is selected from halogen, -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, -NH₂, and C1-C2 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkoxy, thioalkyl, and amino.

[00145] In a further aspect, R¹ is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂. In a still further aspect, R¹ is selected from -OH, -OCH₃, -SH, -SCH₃, and -NH₂. In yet a further aspect, R¹ is selected from -OH, -SH, and -NH₂. In an even further aspect, R¹ is -NH₂. In a still further aspect, R¹ is -SH. In yet a further aspect, R¹ is -OH.

[00146] In a further aspect, R¹ is halogen. In a still further aspect, R¹ is selected from chloro, bromo, and fluoro. In yet a further aspect, R¹ is selected from chloro and fluoro. In an even further aspect, R¹ is chloro. In a still further aspect, R¹ is fluoro.

[00147] In a further aspect, R¹ is C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkoxy, thioalkyl, and amino. In a still further aspect, R¹ is C1-C4 alkyl optionally substituted with 0, 1, or 2 groups selected from alkoxy, thioalkyl, and amino. In yet a further aspect, R¹ is C1-C4 alkyl optionally substituted with 0 or 1 group selected from alkoxy, thioalkyl, and amino. In an even further aspect, R¹ is unsubstituted C1-C4 alkyl.

[00148] In a further aspect, R¹ is selected from methyl, ethyl, *i*-propyl, *n*-propyl optionally substituted with 0, 1, 2, or 3 groups selected from alkoxy, thioalkyl, and amino. In a still further aspect, R¹ is selected from methyl and ethyl optionally substituted with 0, 1, 2, or 3 groups selected from alkoxy, thioalkyl, and amino. In yet a further aspect, R¹ is methyl optionally substituted with 0, 1, 2, or 3 groups selected from alkoxy, thioalkyl, and amino.

b. R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, AND R¹⁴ GROUPS

[00149] In one aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, halogen, -COOH, -CHO, -CH₂OH, -NH₂, and C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino. In a further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected

from hydrogen, halogen, methyl, ethyl, -COOH, -CHO, -CH₂OH, -NH₂, and C1-C2 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino. In a still further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is hydrogen.

[00150] In a further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, halogen, -COOH, -CHO, -CH₂OH, and -NH₂. In a still further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, -COOH, -CHO, -CH₂OH, and -NH₂. In yet a further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, -COOH, -CH₂OH, and -NH₂. In an even further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, -CH₂OH, and -NH₂.

[00151] In a further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen and halogen. In a still further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, chloro, bromo, and fluoro. In a still further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, chloro, and fluoro. In yet a further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen and fluoro.

[00152] In a further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen and C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino. In a still further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen and C1-C4 alkyl optionally substituted with 0, 1, or 2 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino. In yet a further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen and C1-C4 alkyl optionally substituted with 0 or 1 group selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino. In an even further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen and unsubstituted C1-C4 alkyl.

[00153] In a further aspect, each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, methyl, ethyl, *i*-propyl, and *n*-propyl optionally substituted with 0, 1, 2,

or 3 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino. In a still further aspect, each of R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , R^{13} , and R^{14} is independently selected from hydrogen, methyl, and ethyl optionally substituted with 0, 1, 2, or 3 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino. In yet a further aspect, each of R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , R^{13} , and R^{14} is independently selected from hydrogen and methyl optionally substituted with 0, 1, 2, or 3 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino.

c. R^5 , R^9 , R^{10} , R^{11} , AND R^{12} GROUPS

[00154] In one aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is independently selected from hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{X}$, $-\text{CHX}_2$, $-\text{CHO}$, $-\text{COOH}$, $-\text{CH}_2\text{SH}$, and $-\text{CONH}_2$. In a further aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is hydrogen.

[00155] In a further aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is independently selected from hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CHO}$, $-\text{COOH}$, $-\text{CH}_2\text{SH}$, and $-\text{CONH}_2$. In a still further aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is independently selected from hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CHO}$, $-\text{CH}_2\text{SH}$, and $-\text{CONH}_2$. In yet a further aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is independently selected from hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{SH}$, and $-\text{CONH}_2$. In an even further aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is independently selected from hydrogen and methyl. In a still further aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is methyl.

[00156] In a further aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is independently selected from hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{X}$, $-\text{CHX}_2$, $-\text{CH}_2\text{SH}$, and $-\text{CONH}_2$. In a still further aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is independently selected from hydrogen, methyl, $-\text{CH}_2\text{X}$, and $-\text{CHX}_2$. In yet a further aspect, each of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is independently selected from hydrogen, $-\text{CH}_2\text{X}$, and $-\text{CHX}_2$.

[00157] In a further aspect, R^5 is methyl.

[00158] In a further aspect, at least one of R^5 , R^9 , R^{10} , R^{11} , and R^{12} is not methyl.

d. R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , AND R^{29b} GROUPS

[00159] In one aspect, each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl. In a further aspect, each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is hydrogen.

[00160] In a further aspect, each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In a still further aspect, each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen, methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen, methyl, and ethyl. In an even further aspect, each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and methyl. In a still further aspect, each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is methyl.

e. R^{22} , R^{24} , R^{25} , R^{27} , AND R^{28} GROUPS

[00161] In one aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy. In a further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is hydrogen.

[00162] In a further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen and C1-C4 alkoxy. In a still further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, methoxy, ethoxy, *i*-propoxy, and *n*-propoxy. In yet a further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, methoxy, and ethoxy. In an even further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen and methoxy.

[00163] In a further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, methyl and ethyl. In an even further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen and methyl.

[00164] In a further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is C1-C4 alkyl. In a still further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from methyl and ethyl. In an even further aspect, each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is methyl.

f. R^{30} GROUPS

[00165] In one aspect, R^{30} is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂. In a further aspect, R^{30} is selected from -OH, -OCH₃, -SH, -SCH₃, and -NH₂. In a still further aspect, R^{30} is selected from -OH, -SH, and -NH₂. In yet a further aspect, R^{30} is -OH.

g. Ar^1 GROUPS

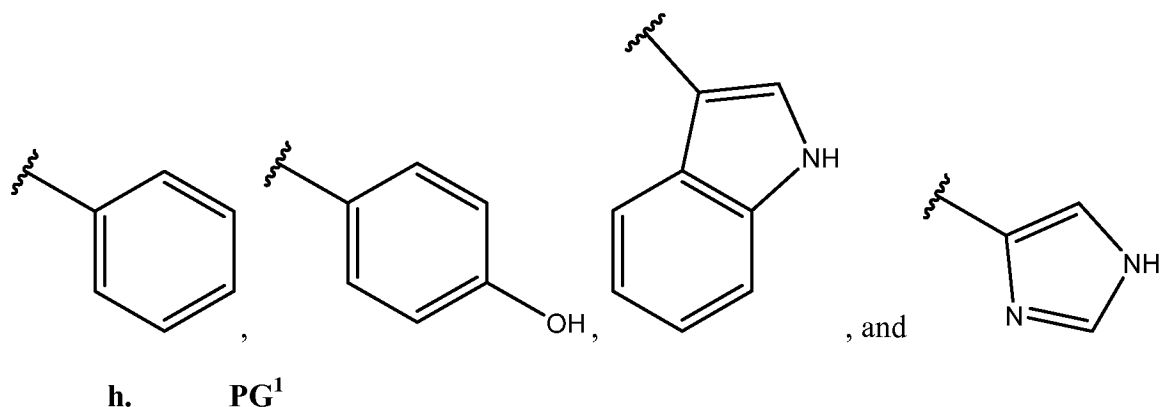
[00166] In one aspect, Ar^1 is selected from phenyl, indole, and imidazole and optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy.

[00167] In a further aspect, Ar^1 is phenyl optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy. In a still further aspect, Ar^1 is unsubstituted phenyl.

[00168] In a further aspect, Ar^1 is indole optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy. In a still further aspect, Ar^1 is unsubstituted indole.

[00169] In a further aspect, Ar^1 is imidazole optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy. In a still further aspect, Ar^1 is unsubstituted imidazole.

[00170] In a further aspect, Ar^1 is selected from:



[00171] In various aspects, PG¹, when present, is an amino protecting group that is stable under basic conditions. In a further aspect, PG¹, when present, is selected from phthalimide, fluorenylmethyloxycarbonyl chloride, *t*-butyloxycarbonyl, and carboxybenzyl. In a still further aspect, PG¹, when present, is selected from fluorenylmethyloxycarbonyl chloride and *t*-butyloxycarbonyl. In yet a further aspect, PG¹, when present, is selected from fluorenylmethyloxycarbonyl chloride and *t*-butyloxycarbonyl.

i. PG²

[00172] In various aspects, PG², when present, is an amino protecting group that is stable under acidic conditions. In a further aspect, PG², when present, is selected from acetyl, trifluoroacetyl, and tosyl. In a still further aspect, PG², when present, is selected from acetyl and trifluoroacetyl. In yet a further aspect, PG², when present, is trifluoroacetyl.

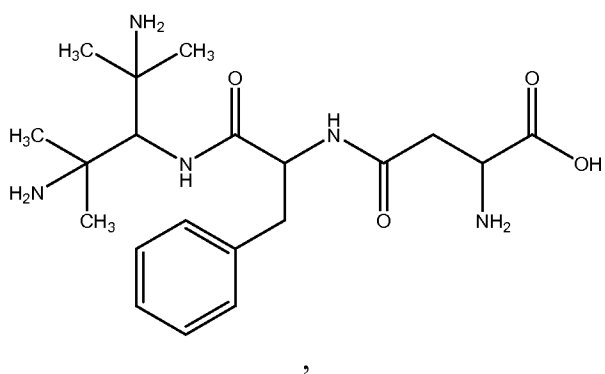
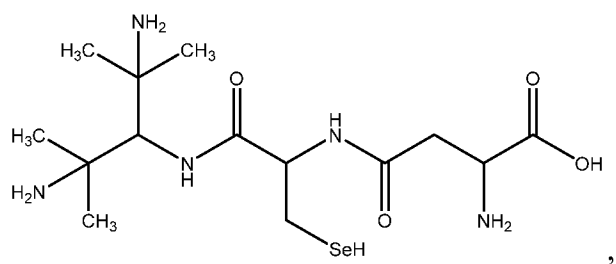
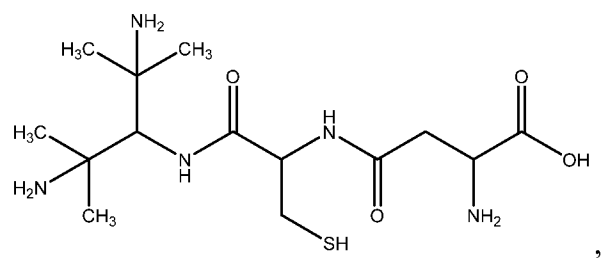
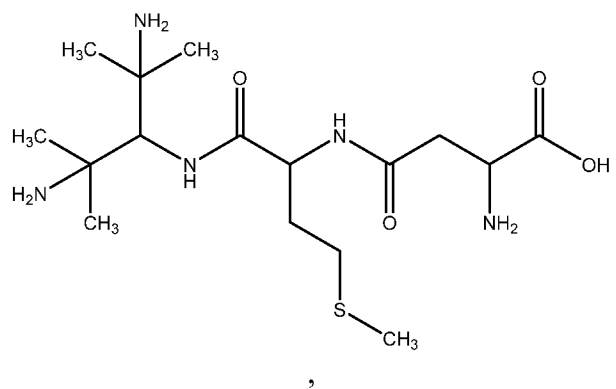
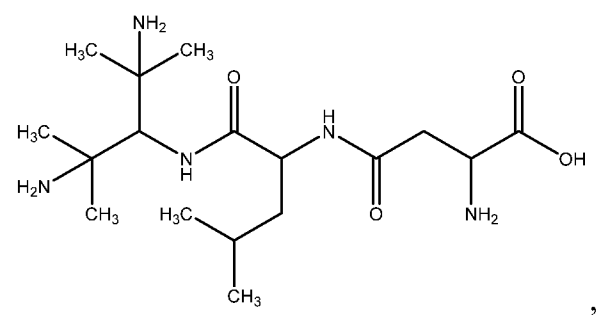
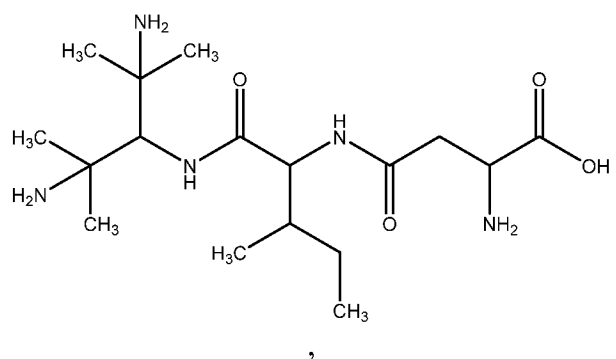
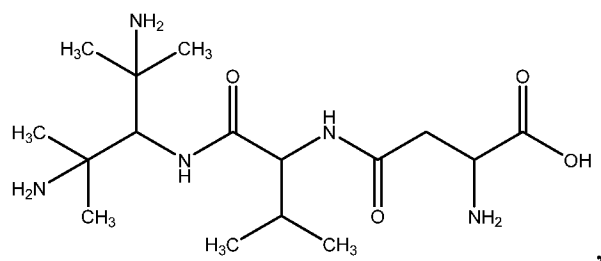
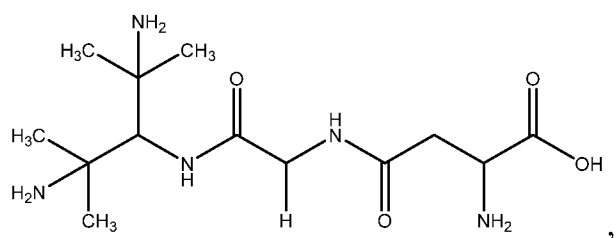
2. PROPERTIES

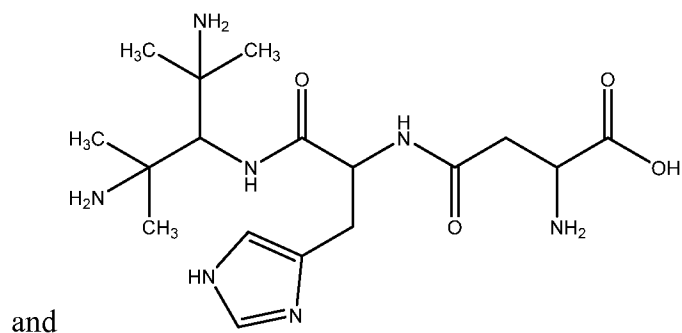
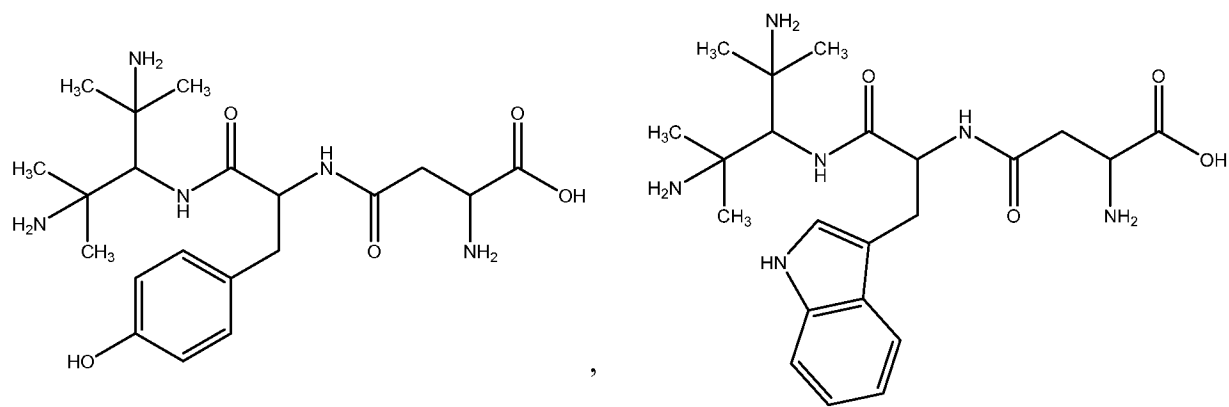
[00173] In various aspects, the disclosed compounds may have a heat stability of at least up to 60 °C. In a further aspect, the disclosed compounds may have a heat stability at higher temperatures under conditions for normal use. For example, the disclosed compounds may have a heat stability at temperatures up to 65 °C, 70 °C, 75 °C, 80 °C, 85 °C, 90 °C, 95 °C, 100 °C, 105 °C, 110 °C, 115 °C, 120 °C, 125 °C, or higher.

3. PROPHETIC COMPOUND EXAMPLES

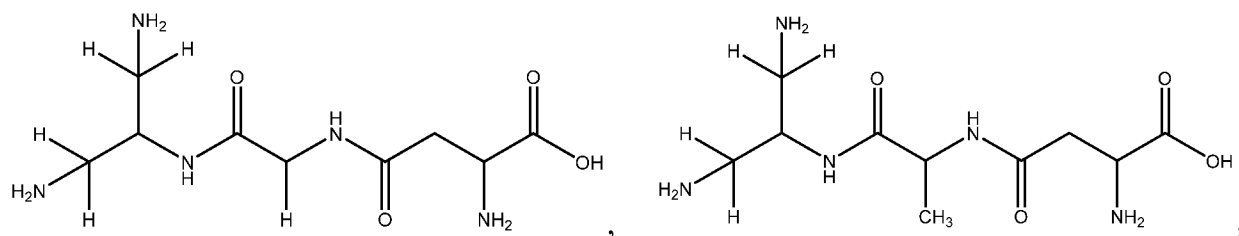
[00174] The following compound examples are prophetic, and can be prepared using the synthesis methods described herein and other general methods as needed as would be known to one skilled in the art. It is expected that the prophetic compounds would be useful to sweeten foods, beverages, medicines, and other consumable products (*e.g.*, chewing gum, toothpaste, mouthwash, etc.), and such utility can be determined using the assay methods described herein.

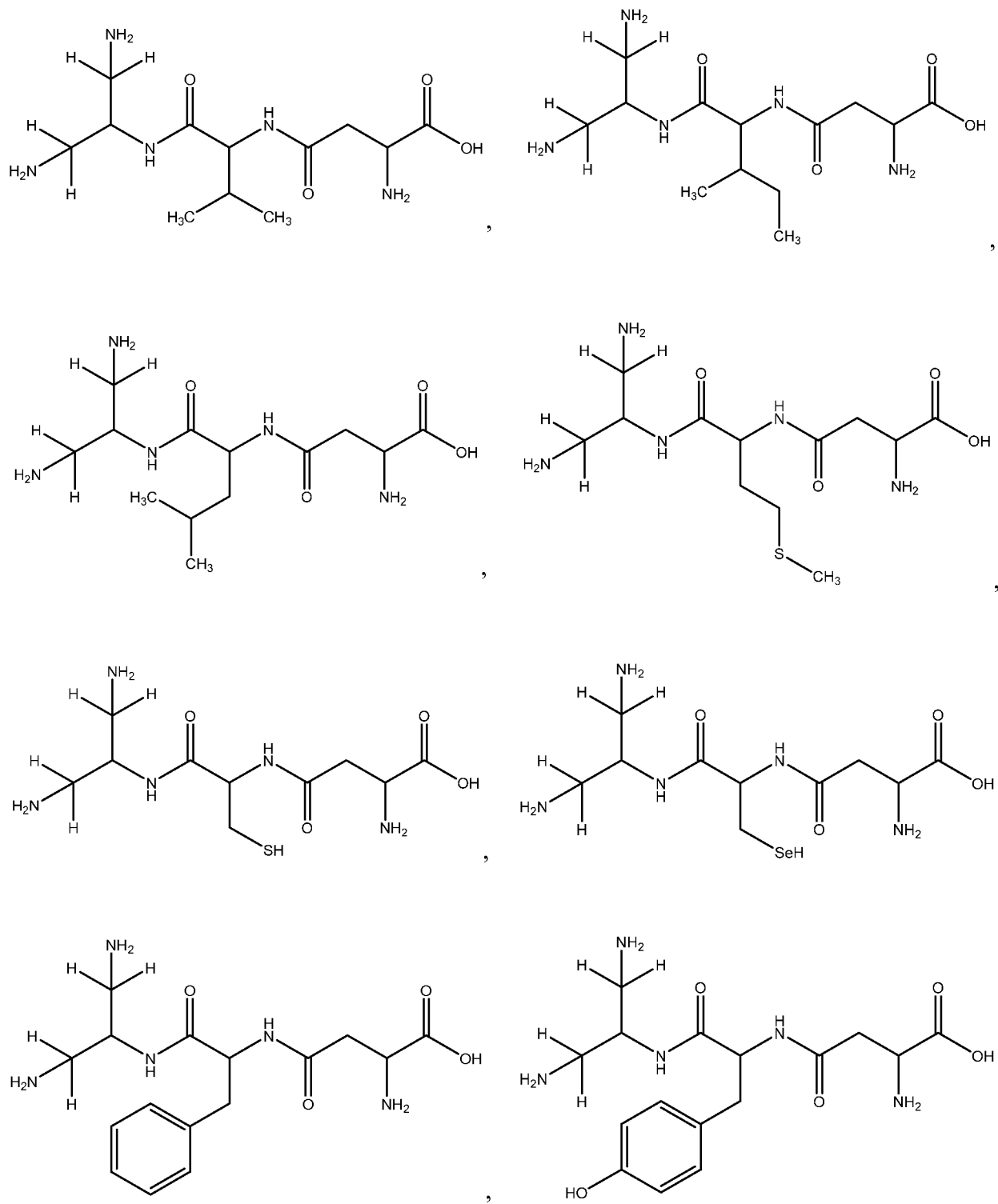
[00175] In one aspect, a compound can be selected from:

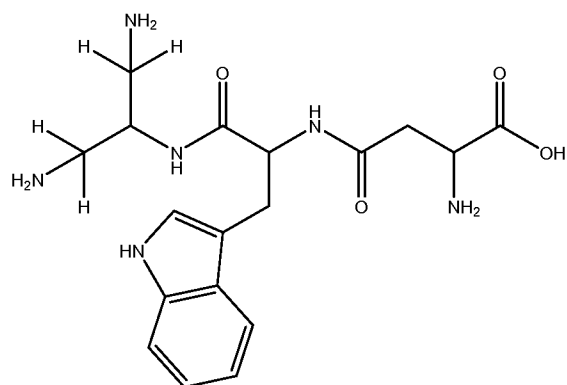




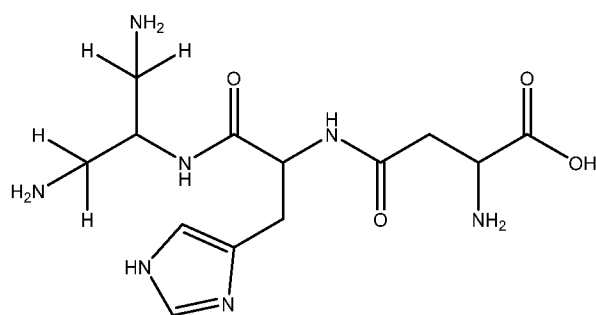
[00176] In one aspect, a compound can be selected from:







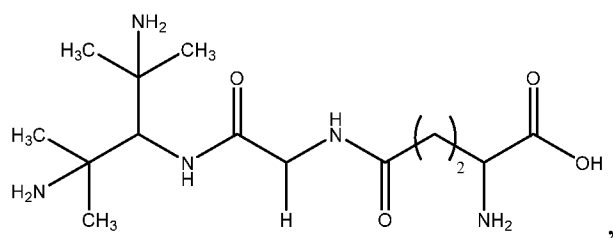
,



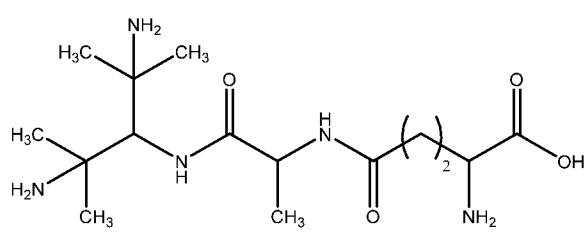
and

.

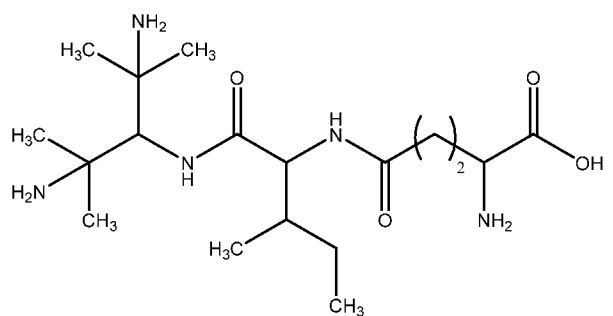
[00177] In one aspect, a compound can be selected from:



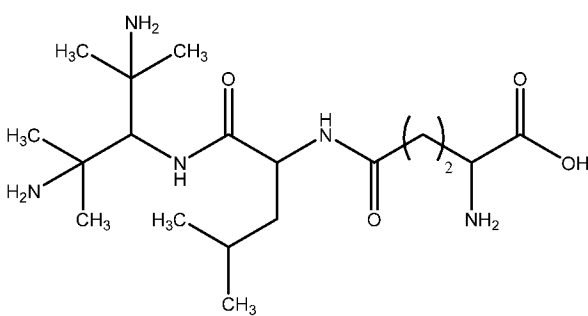
,



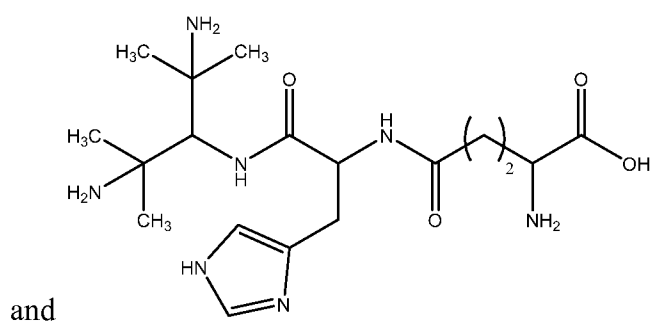
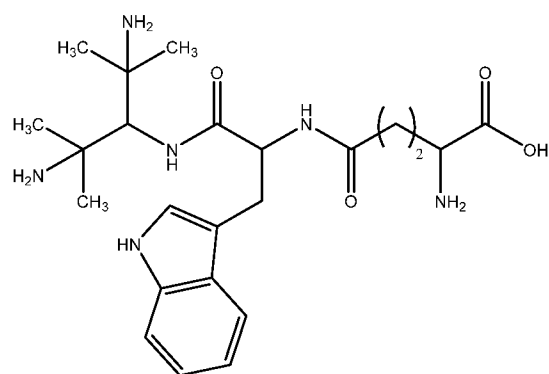
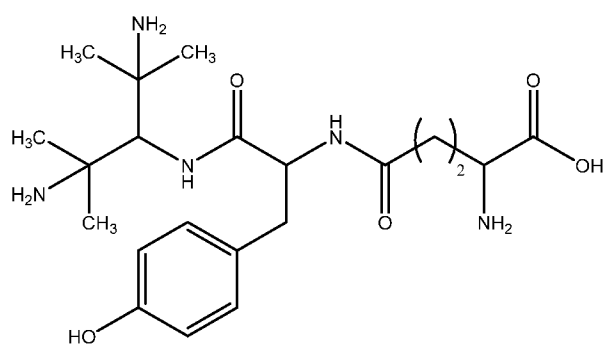
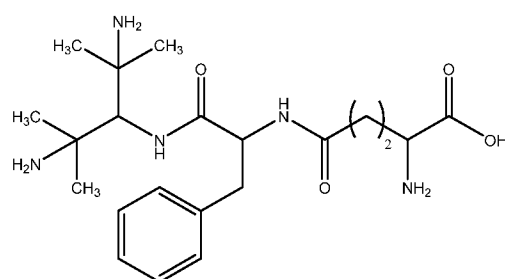
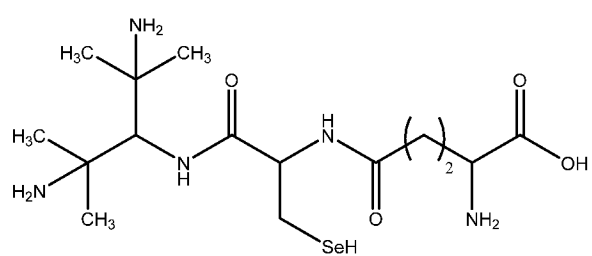
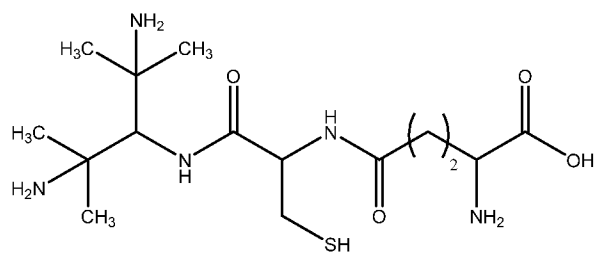
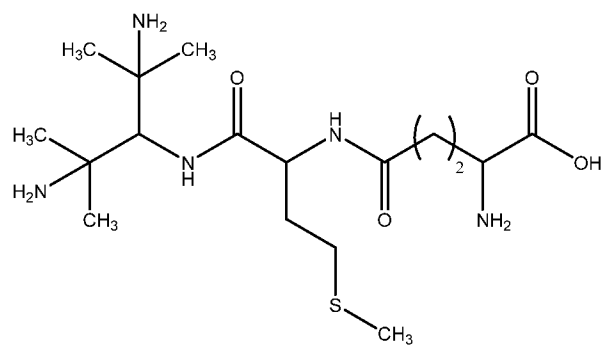
,



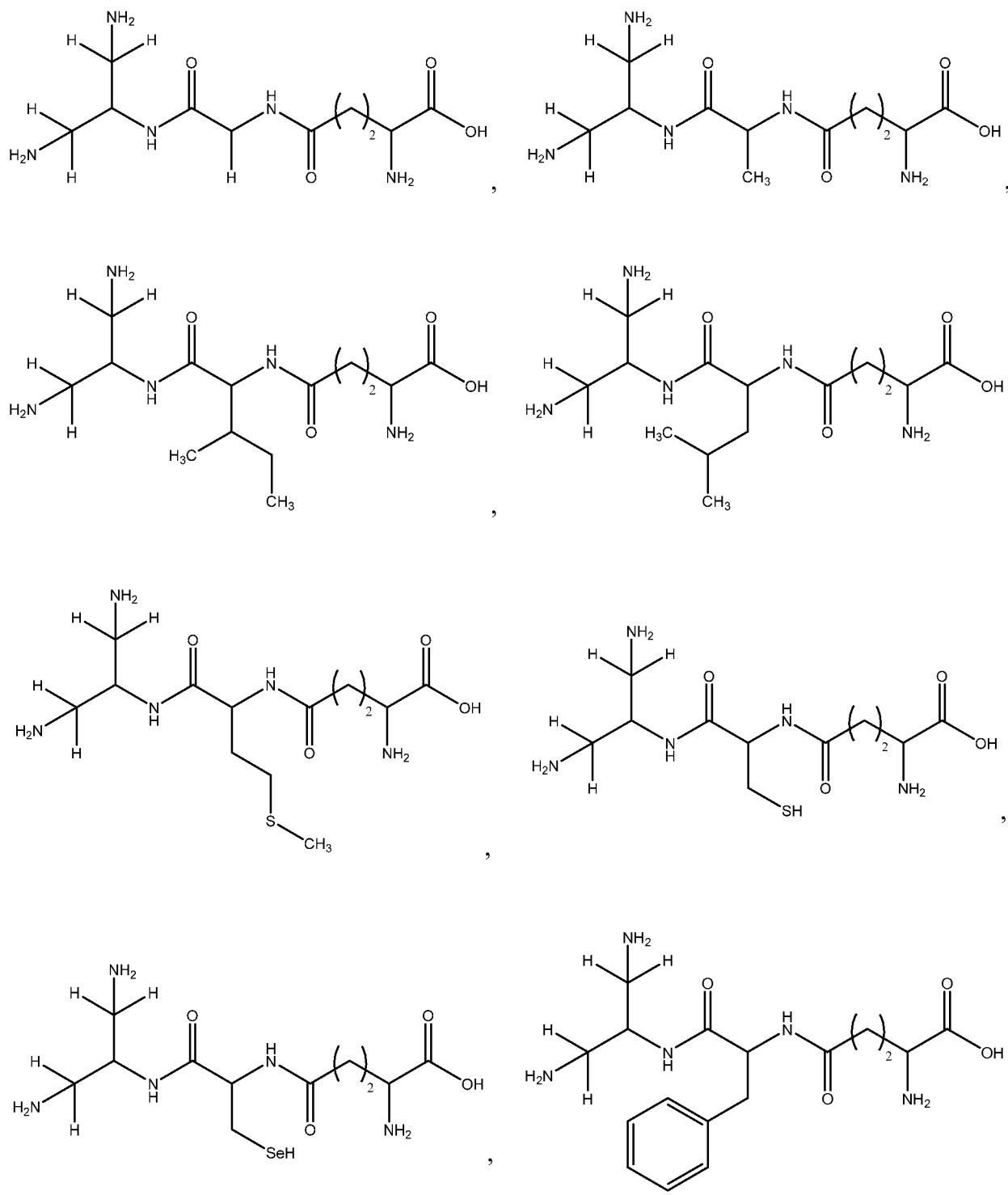
,

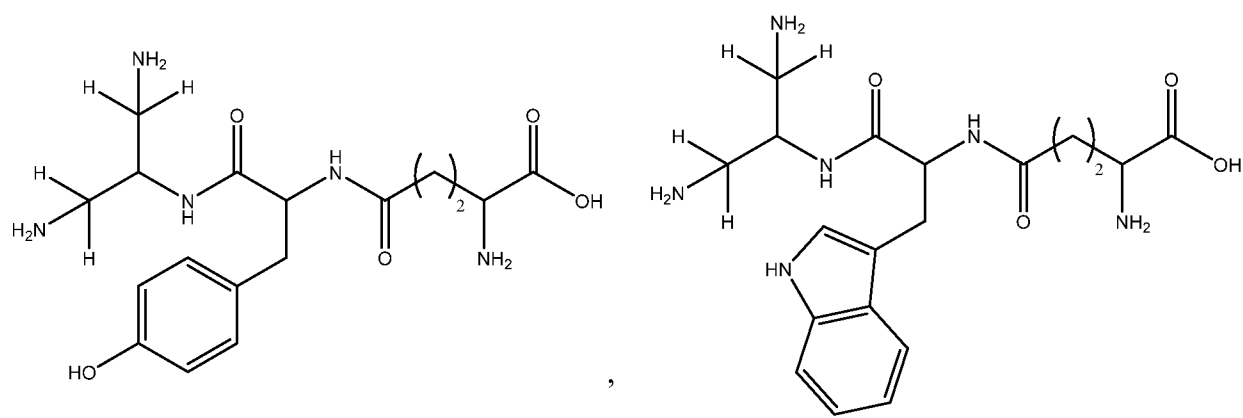


,

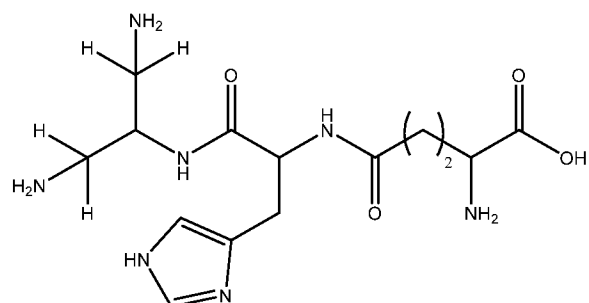


[00178] In one aspect, a compound can be selected from:

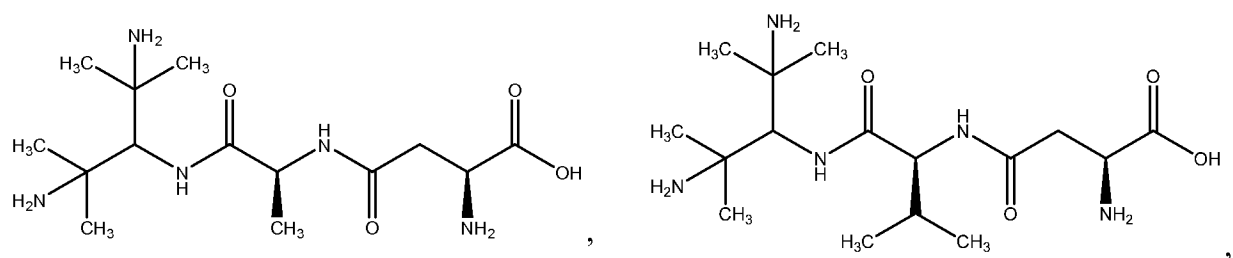


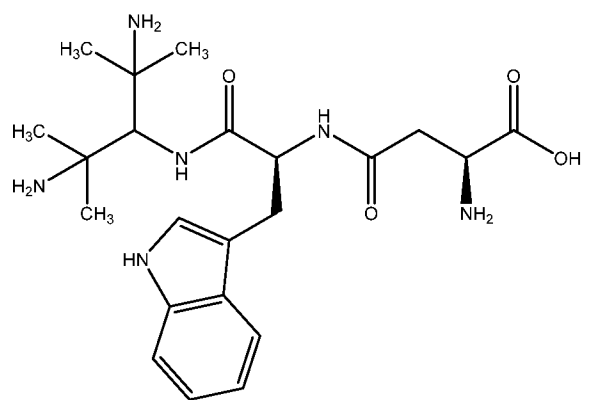
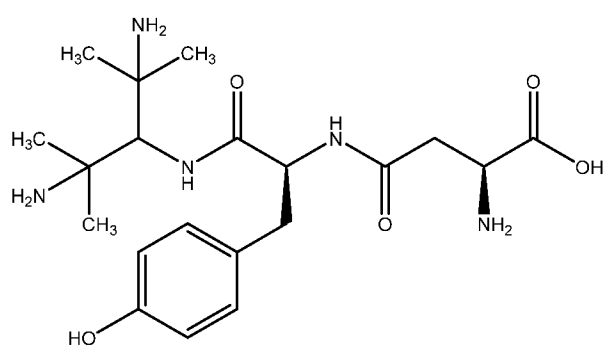
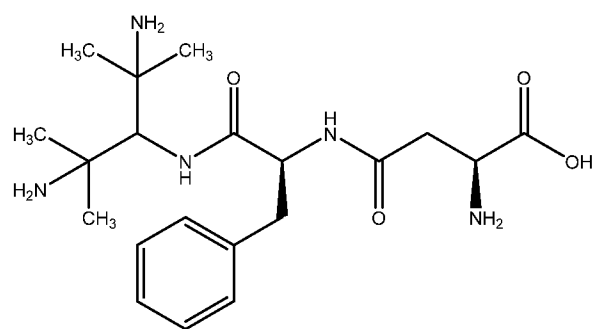
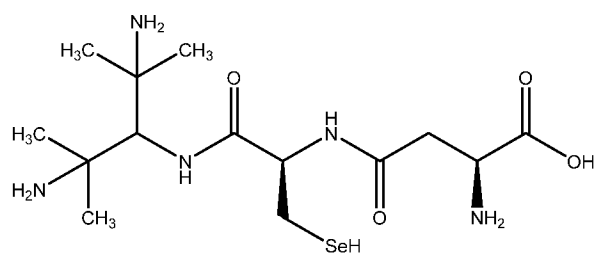
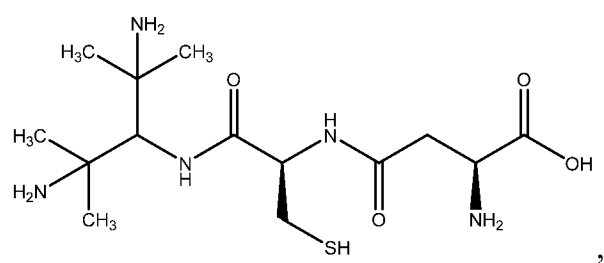
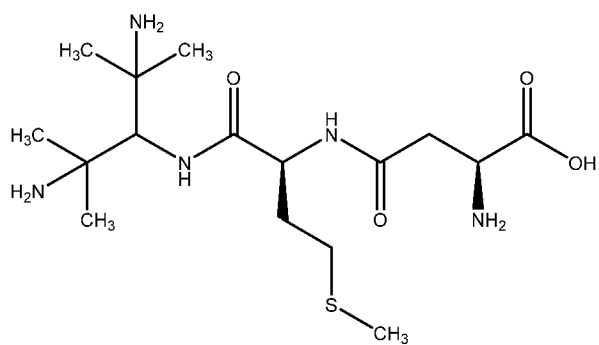
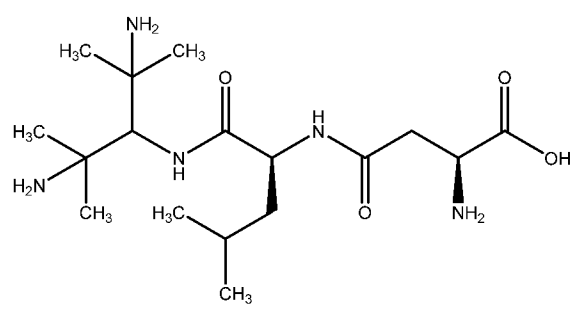
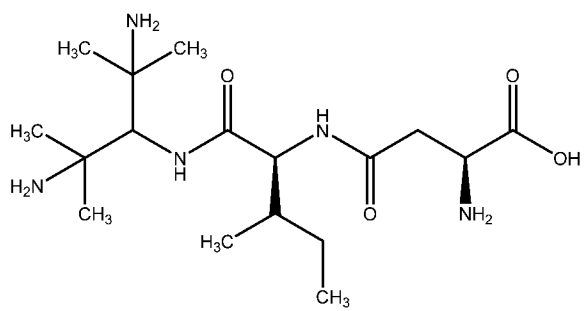


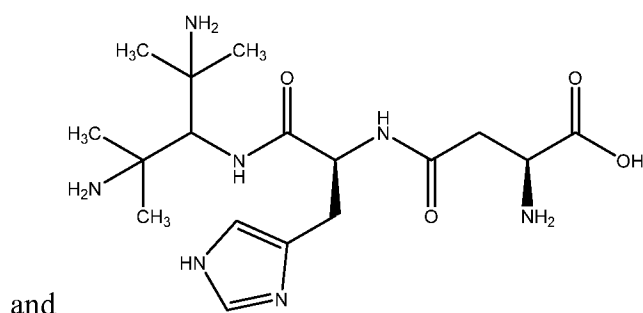
and



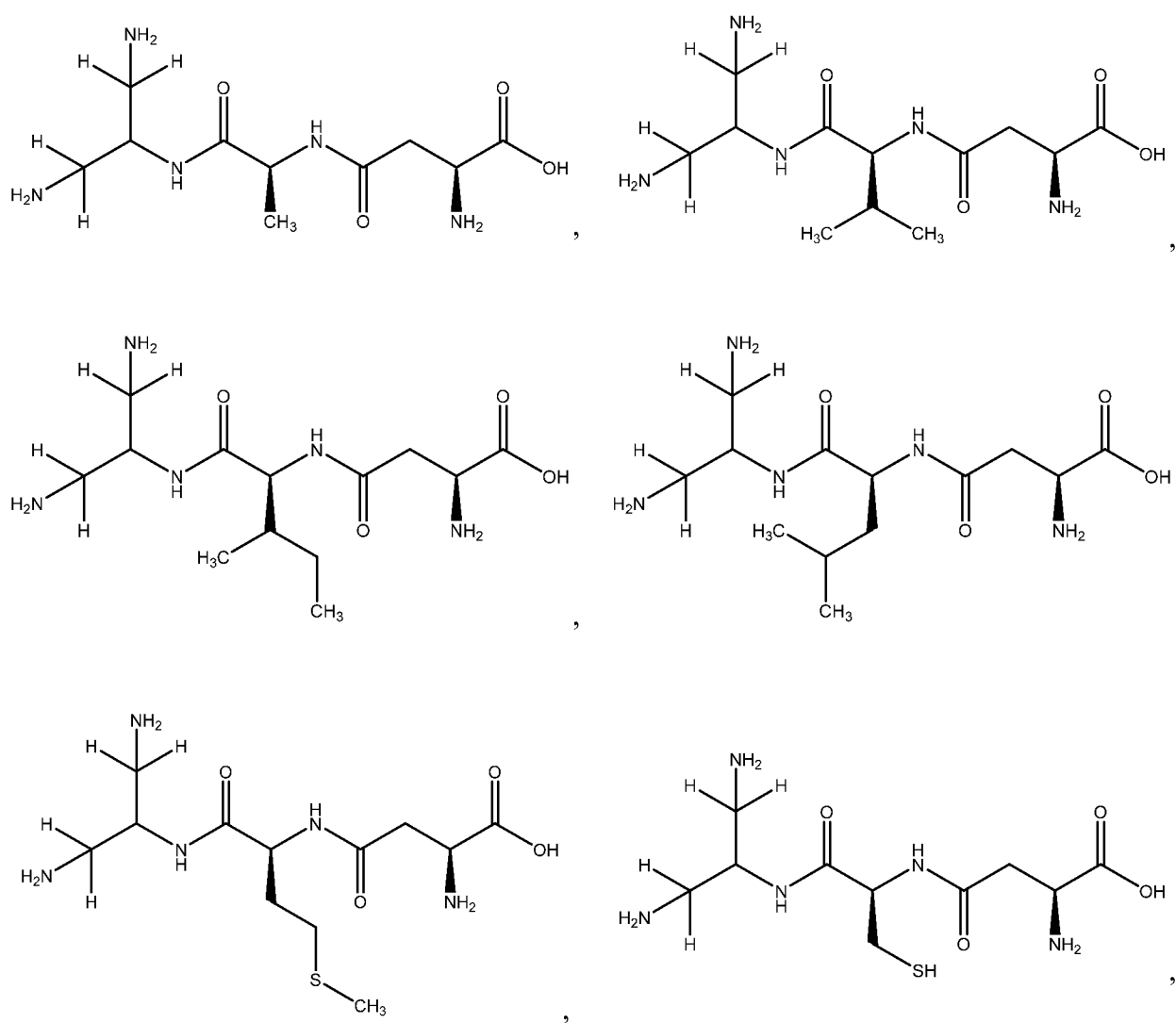
[00179] In one aspect, a compound can be selected from:

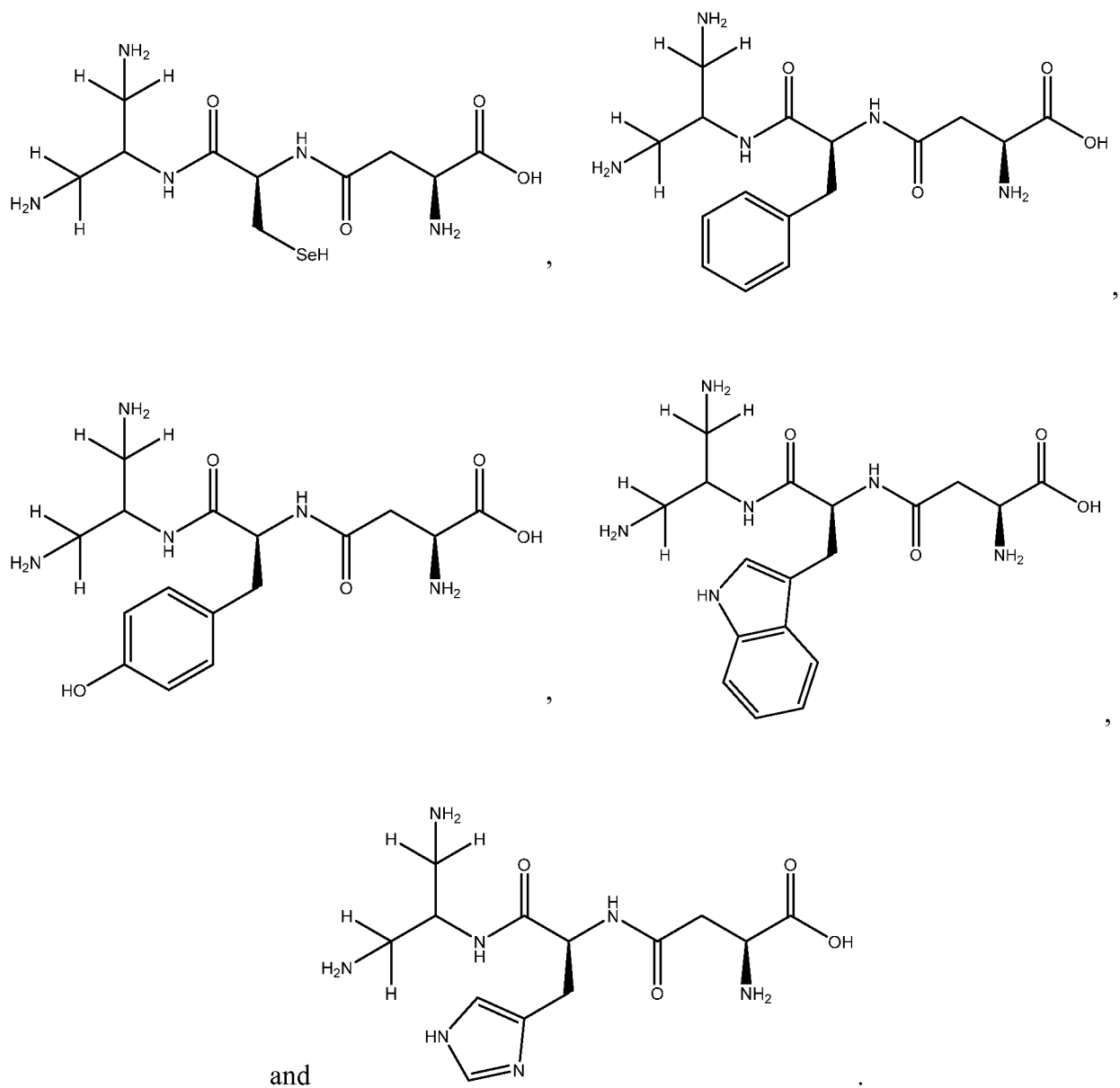




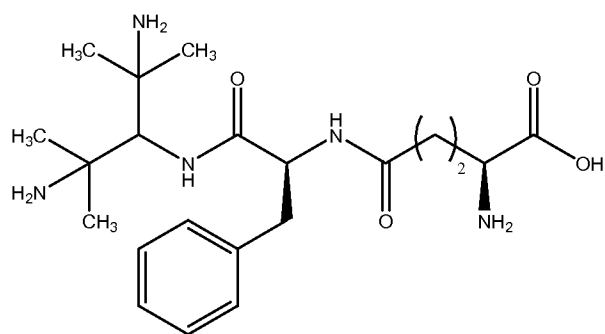
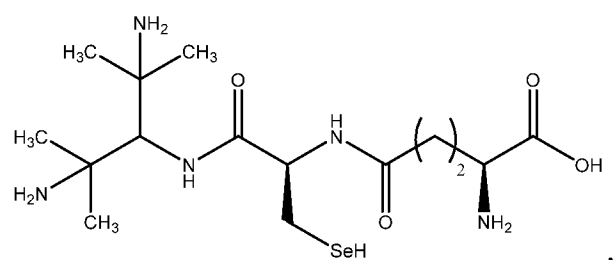
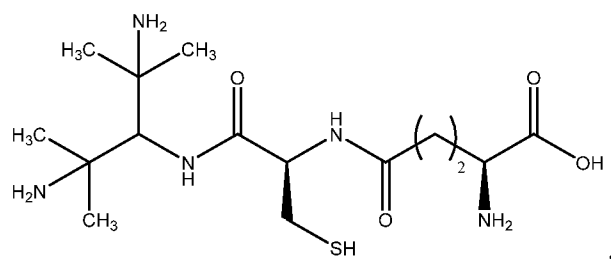
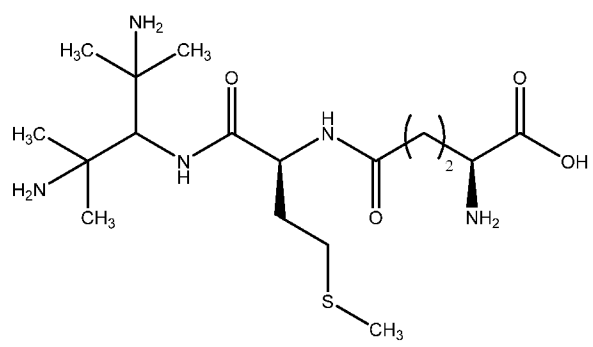
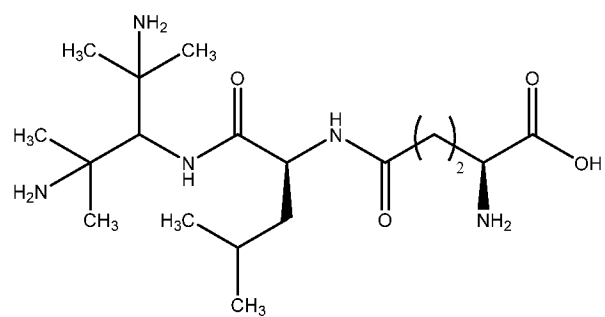
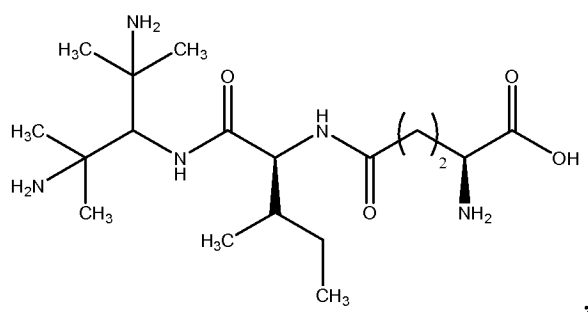
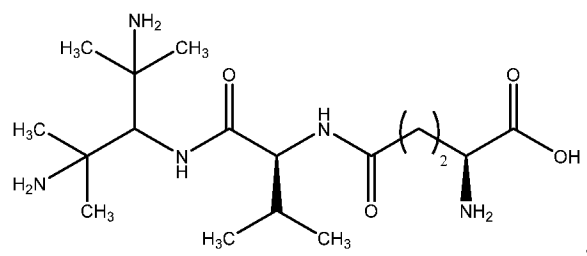
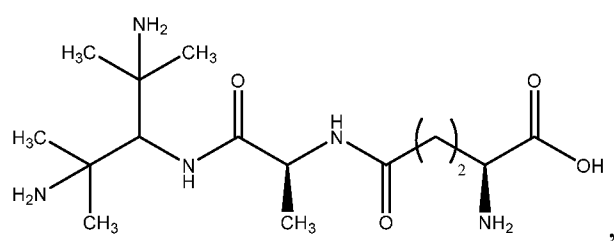


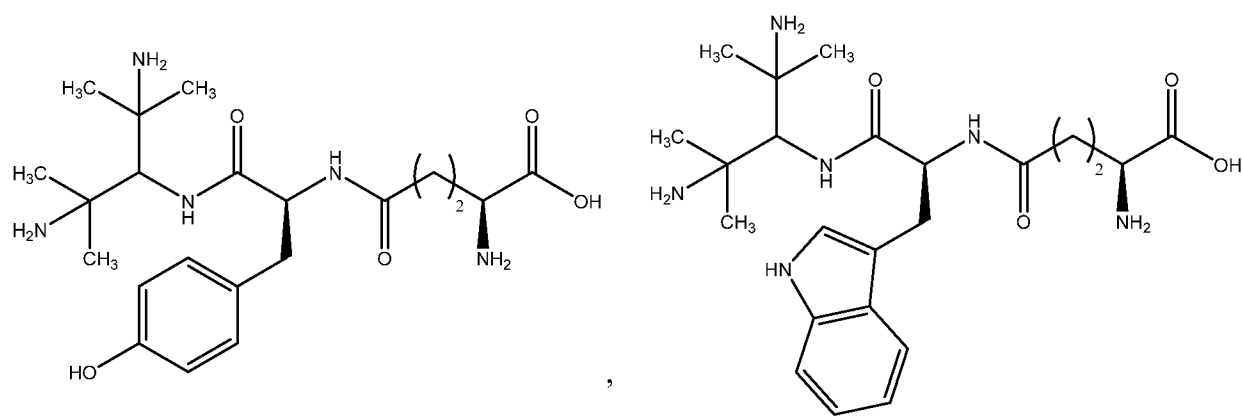
[00180] In one aspect, a compound can be selected from:



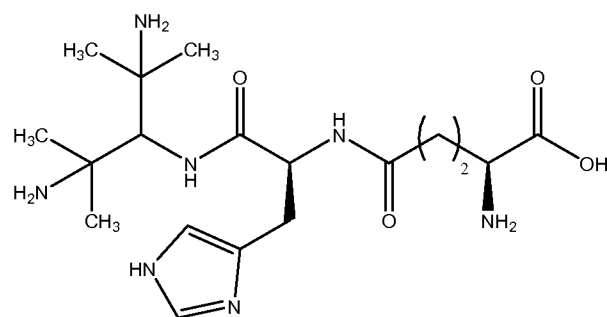


[00181] In one aspect, a compound can be selected as:

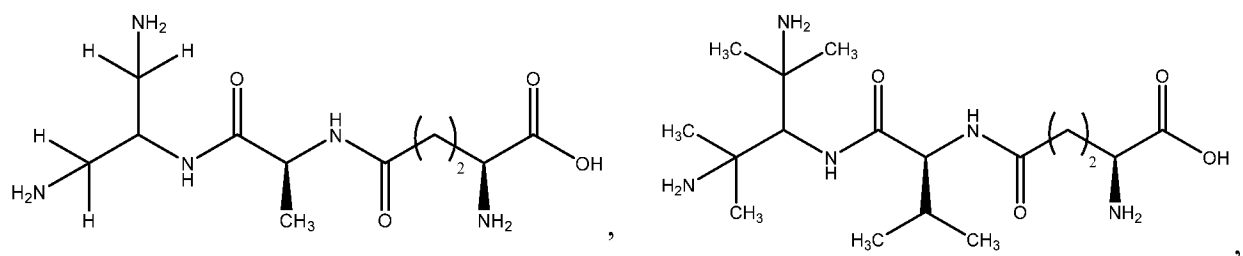


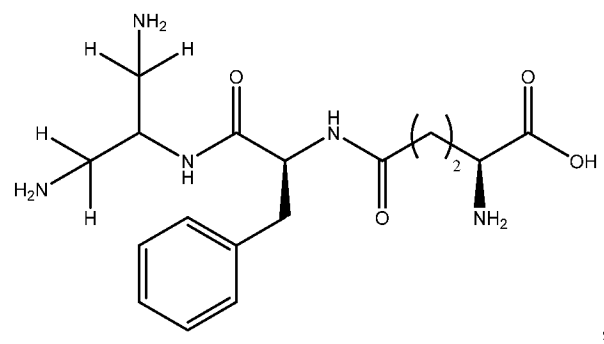
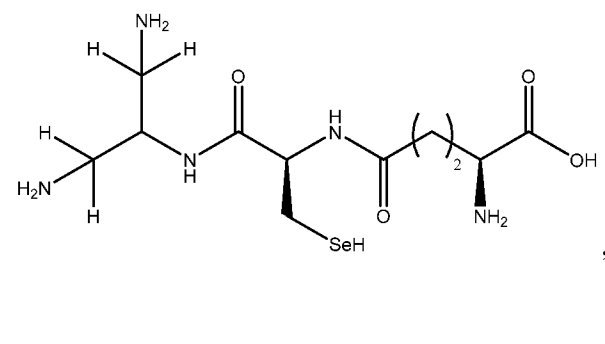
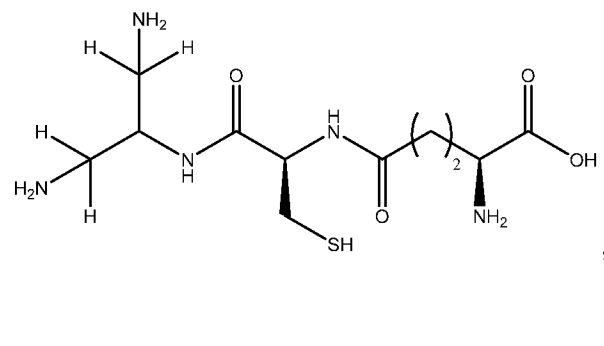
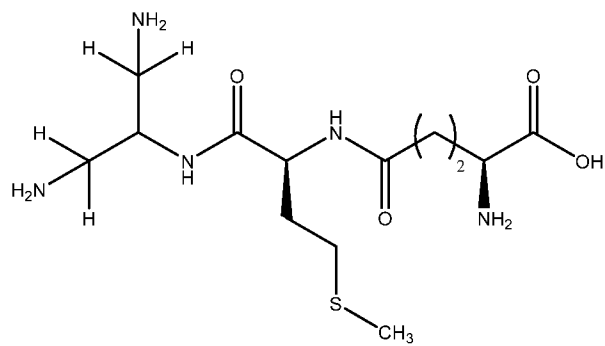
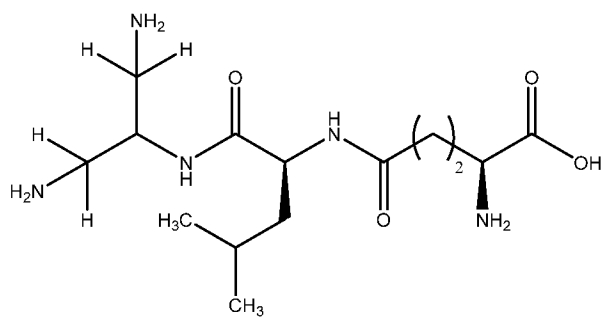
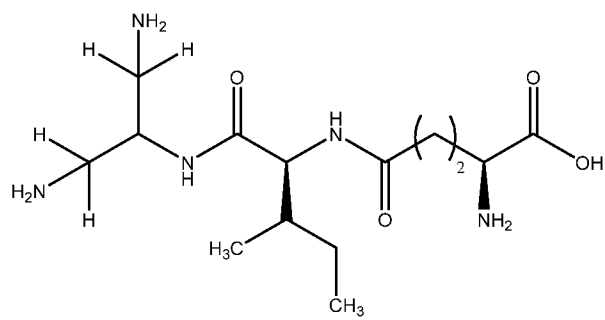


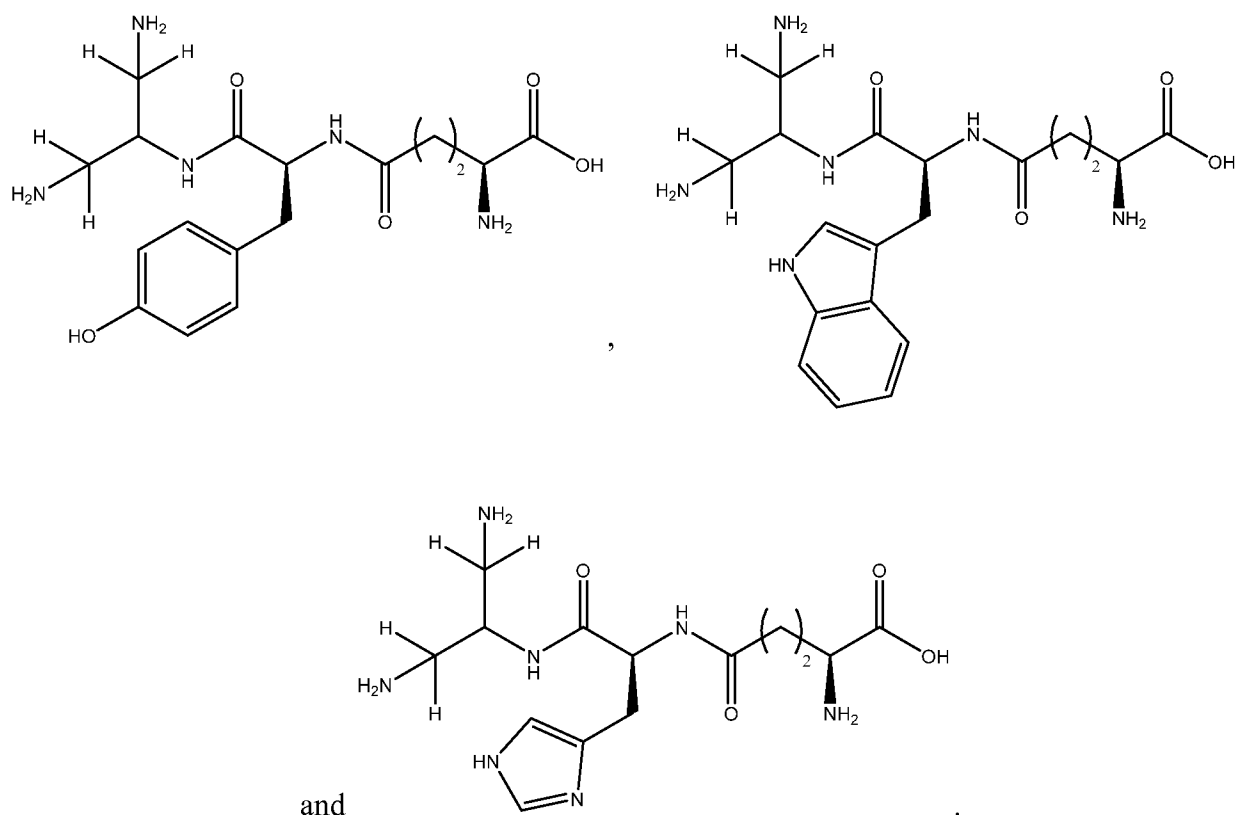
and



[00182] In one aspect, a compound can be selected as:



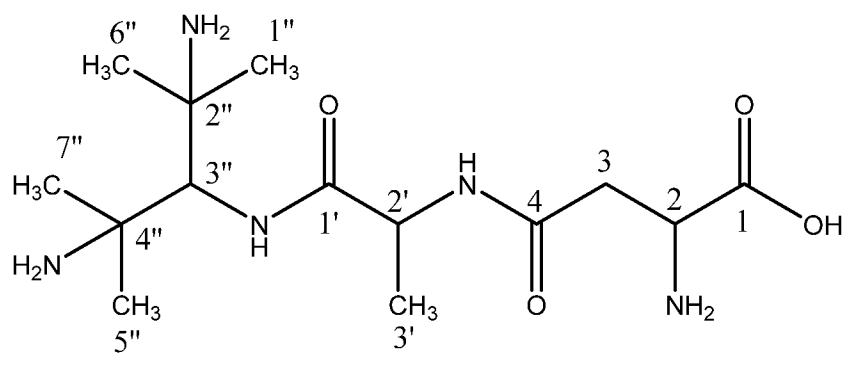




[00183] It is understood that compounds in which one or more amino groups are protected and compounds in which the carboxylate is protected (i.e., esters) are also contemplated.

C. COMPOSITIONS

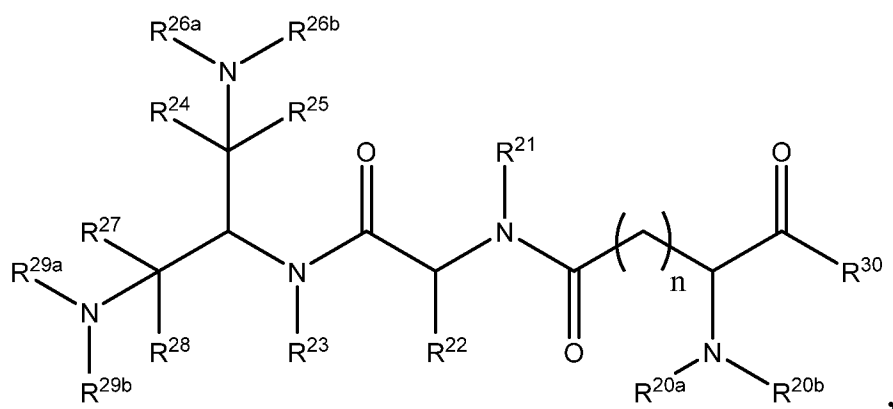
[00184] In one aspect, the invention relates to compositions comprising a compound having a structure represented by a formula:



[00185] In one aspect, the invention relates to compositions comprising a compound selected from 2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, (2*R*)-4-(2*R*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, (2*R*)-4-(2*S*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, (2*S*)-4-(2*R*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, and (2*S*)-4-(2*S*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, or a mixture thereof. In a further aspect, the compound is 2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid. In a still further aspect, the compound is (2*R*)-4-(2*R*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid. In yet a further aspect, the compound is (2*R*)-4-(2*S*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid. In an even further aspect, the compound is (2*S*)-4-(2*R*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid. In a still further aspect, the compound is (2*S*)-4-(2*S*)-2-amino-4-(1-(2,4-diamino-2,4- dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid. In yet a further aspect, the composition comprises at least two of the compounds.

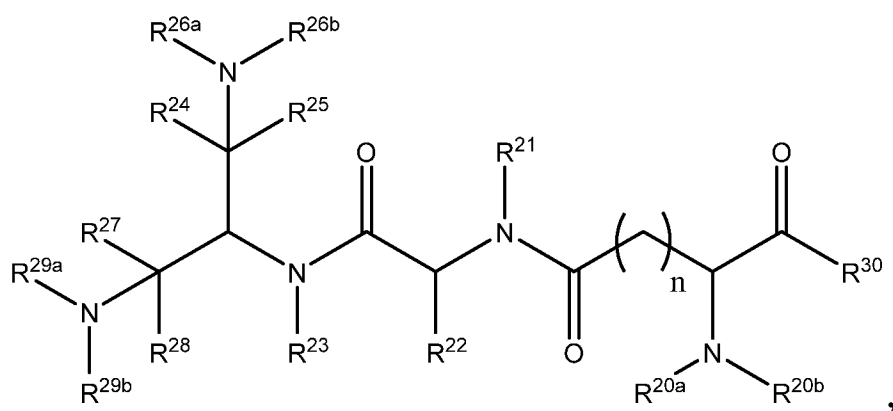
[00186] In one aspect, the invention relates to compositions comprising a sweetener, wherein the sweetener contains no sugar moieties and wherein the composition is obtained via solvent extraction of a material comprising at least one member of the group consisting of spinach, spinach protein, micronized spinach protein, algae, algae extract, alfalfa, alfalfa extract, Jerusalem artichoke, and Jerusalem artichoke extract. In a further aspect, the solvent extraction comprises the steps of: a) concentrating the material to dryness; b) dissolving the material in an appropriate solvent; and c) removing a precipitate, if present.

[00187] In one aspect, the invention relates to compositions comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a}, R^{20b}, R²¹, R²³, R^{26a}, R^{26b}, R^{29a}, and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R²² is selected from hydrogen, C1-C4 alkyl, -CH₂SeH, -CH₂SH, -CH₂CH₂SH, -CH₂CH₂SCH₃, and -CH₂Ar¹; wherein Ar¹ is selected from phenyl, indole, and imidazole and optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy; wherein each of R²⁴, R²⁵, R²⁷, and R²⁸ is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and wherein R³⁰ is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂.

[00188] In one aspect, the invention relates to compositions comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a}, R^{20b}, R²¹, R²³, R^{26a}, R^{26b}, R^{29a}, and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R²² is selected from hydrogen, C1-C4 alkyl, -CH₂SeH, -CH₂SH, -CH₂CH₂SH, -CH₂CH₂SCH₃, and -CH₂Ar¹; wherein Ar¹ is selected from phenyl, indole, and imidazole and is optionally substituted

with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy; wherein each of R²⁴, R²⁵, R²⁷, and R²⁸ is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; wherein R³⁰ is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂; and a bulking agent; and wherein the composition further comprises at least one of: a) a carrier; b) a flavoring agent; c) a low intensity sweetener; d) a high intensity sweetener; e) a decolorizing agent; f) a taste modifier; g) a plasticizer; h) a film-forming polymer; i) a salt; and j) an internal film release agent. In a further aspect, the composition further comprises at least one agent selected from carbohydrates, cellulose, gums, food acids, nutritive sweeteners, gelatin, food grade wax emulsions, colorants, fillers, surfactants, stabilizers, organic acids, and mixtures thereof.

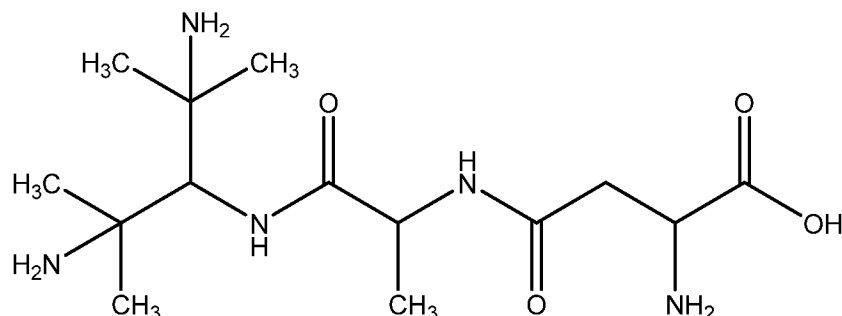
[00189] In a further aspect, the compound is substantially pure.

[00190] In a further aspect, the composition is packaged in one or more of envelopes, canisters, or bulk containers. In a still further aspect, the composition is packaged in envelopes. In yet a further aspect, the envelopes are one-gram envelopes. In an even further aspect, the composition is packaged in canisters. In a still further aspect, the composition is packaged in bulk containers.

[00191] In a further aspect, the composition comprises fractions having water solubility of at least about 5 grams per 100 mL of water at temperatures of from about 10 °C to about 25 °C. In a still further aspect, the composition comprises fractions having water solubility of at least about 10 grams per 100 mL of water at temperatures of from about 10 °C to about 25 °C. In yet a further aspect, the composition comprises fractions having water solubility of at least about 15 grams per 100 mL of water at temperatures of from about 10 °C to about 25 °C. In an even further aspect, the composition comprises fractions having water solubility of at least about 20 grams per 100 mL of water at temperatures of from about 10 °C to about 25 °C.

[00192] In a further aspect, the composition contains less than about 3 Calories/gram. In a still further aspect, the composition contains less than about 2 Calories/gram. In yet a further aspect, the composition contains less than about 1 Calorie/gram. (“Calorie” is used in the sense in which it ordinarily is for nutritional purposes, viz., 1 nutritional Calorie = 1000 chemical calories = 4,187 joules.)

[00193] In various aspects, the composition comprises a compound, wherein the compound is not:



1. ADDITIVES

[00194] In various aspects, the composition can further comprise one or more additives. Thus, additives include, but are not limited to, carriers, bulking agents, flavoring agents, low intensity sweeteners, high intensity sweeteners, decolorizing agents, taste modifiers, plasticizers, film-forming polymers, salts, internal film release agents, carbohydrates, cellulose, gums, food acids, nutritive sweeteners, gelatin, food grade wax emulsions, colorants, fillers, surfactants, stabilizers, organic acids, and mixtures thereof.

a. CARRIERS

[00195] In various aspects, the composition further comprises a carrier. Exemplary carriers include, but are not limited to, dextrose, polydextrose, maltodextrin, gum Arabic, and mixtures thereof. A carrier can be a liquid or a solid. Thus, in various further aspects, a carrier is selected from water, starch, sorbitol, salt, citric acid and other non-toxic substances compatible with the material to be sweetened.

[00196] In a further aspect, the carrier is a bulking agent.

[00197] In a further aspect, the carrier is present in an amount of from about 0.01 wt% to about 99.9 wt%. In a still further aspect, the carrier is present in an amount of from about 0.05 wt% to about 99.9 wt%. In yet a further aspect, the carrier is present in an amount of from about 0.1 wt% to about 99.9 wt%. In an even further aspect, the carrier is present in an amount of from about 0.5 wt% to about 99.9 wt%. In a still further aspect, the carrier is present in an amount of

from about 1 wt% to about 99.9 wt%. In yet a further aspect, the carrier is present in an amount of from about 5 wt% to about 99.9 wt%. In an even further aspect, the carrier is present in an amount of from about 10 wt% to about 99.9 wt%. In a still further aspect, the carrier is present in an amount of from about 25 wt% to about 99.9 wt%. In yet a further aspect, the carrier is present in an amount of from about 50 wt% to about 99.9 wt%. In an even further aspect, the carrier is present in an amount of from about 75 wt% to about 99.9 wt%. In a still further aspect, the carrier is present in an amount of from about 0.01 wt% to about 90 wt%. In yet a further aspect, the carrier is present in an amount of from about 0.01 wt% to about 75 wt%. In an even further aspect, the carrier is present in an amount of from about 0.01 wt% to about 50 wt%. In a still further aspect, the carrier is present in an amount of from about 0.01 wt% to about 25 wt%. In yet a further aspect, the carrier is present in an amount of from about 0.01 wt% to about 10 wt%. In an even further aspect, the carrier is present in an amount of from about 0.01 wt% to about 5 wt%. In a still further aspect, the carrier is present in an amount of from about 0.01 wt% to about 1 wt%. In yet a further aspect, the carrier is present in an amount of from about 0.01 wt% to about 0.5 wt%. In an even further aspect, the carrier is present in an amount of from about 0.01 wt% to about 0.1 wt%. In a still further aspect, the carrier is present in an amount of from about 0.01 wt% to about 0.05 wt%.

b. BULKING AGENTS

[00198] In various aspects, the composition further comprises a bulking agent. Exemplary bulking agents include, but are not limited to, maltodextrin, magnesium carbonate, calcium stearate, colloidal silicon dioxide, starch, dextrose, polydextrose, gum Arabic, and mixtures thereof. Polydextrose may be used in the composition to serve as a humectant, provide solids, decrease water activity, and to control crystallization. Additionally, polydextrose may provide an economical source of prebiotic fiber which may promote digestive system health. Maltodextrin may be used for its easy digestibility and cold water solubility. Maltodextrin may be derived by hydrolysis of corn, potato, or rice starch. In various further aspects, the composition may be adjusted to include a maltodextrin derived from a particular source to render the composition safe for use by individuals suffering from food allergies to corn, wheat, potatoes, or rice, and/or suffering from celiac disease.

[00199] In a further aspect, the bulking agent is present in an amount of from about 10 wt% to about 50 wt%. In a still further aspect, the bulking agent is present in an amount of from about 15 wt% to about 50 wt%. In yet a further aspect, the bulking agent is present in an amount of from about 20 wt% to about 50 wt%. In an even further aspect, the bulking agent is present in an amount of from about 30 wt% to about 50 wt%. In a still further aspect, the bulking agent is present in an amount of from about 40 wt% to about 50 wt%. In yet a further aspect, the bulking agent is present in an amount of from about 10 wt% to about 40 wt%. In an even further aspect, the bulking agent is present in an amount of from about 10 wt% to about 30 wt%. In a still further aspect, the bulking agent is present in an amount of from about 10 wt% to about 20 wt%. In yet a further aspect, the bulking agent is present in an amount of from about 10 wt% to about 15 wt%.

c. FLAVORING AGENTS

[00200] In various aspects, the composition further comprises a flavoring agent. Exemplary flavoring agents include, but are not limited to, cinnamon, raspberry, peach, lemon, French vanilla, hazelnut, and mocha, or a combination thereof.

[00201] A flavoring agent may be used to mask flavors in the composition or to add flavor to the composition. The flavoring agent can be a sweet flavoring agent (i.e., a sweetener), which can be combined with a sour flavoring agent, a bitter flavoring agent, or mixtures thereof. Additionally, the flavoring agent can be selected from the group consisting of natural flavors, natural fruit flavors, artificial flavors, artificial fruit flavors, flavor enhancers, and mixtures thereof.

[00202] Flavoring agents may be a single compound or a blend of compounds whose primary purpose is to provide all or part of the particular flavor or effect to any composition or product. The flavoring agent can be in the forms of oils or extracts. The flavoring agent may be acidic, basic, neutral, or a salt.

[00203] In a further aspect, the flavoring agent is present in an amount of from about 0.01 wt% to about 30 wt%. In a still further aspect, the flavoring agent is present in an amount of from about 0.1 wt% to about 30 wt%. In yet a further aspect, the flavoring agent is present in an amount of from about 1 wt% to about 30 wt%. In an even further aspect, the flavoring agent is

present in an amount of from about 5 wt% to about 30 wt%. In a still further aspect, the flavoring agent is present in an amount of from about 10 wt% to about 30 wt%. In yet a further aspect, the flavoring agent is present in an amount of from about 15 wt% to about 30 wt%. In an even further aspect, the flavoring agent is present in an amount of from about 20 wt% to about 30 wt%. In a still further aspect, the flavoring agent is present in an amount of from about 0.01 wt% to about 20 wt%. In yet a further aspect, the flavoring agent is present in an amount of from about 0.01 wt% to about 15 wt%. In an even further aspect, the flavoring agent is present in an amount of from about 0.01 wt% to about 10 wt%. In a still further aspect, the flavoring agent is present in an amount of from about 0.01 wt% to about 5 wt%. In yet a further aspect, the flavoring agent is present in an amount of from about 0.01 wt% to about 1 wt%. In an even further aspect, the flavoring agent is present in an amount of from about 0.01 wt% to about 0.1 wt%.

d. LOW INTENSITY SWEETENERS

[00204] In various aspects, the composition further comprises a low intensity sweetener. As used herein, the term “low intensity sweetener” refers to a sweetener that delivers between 0.5 to 2 grams of sucrose-equivalent sweetness (SES) per gram of solids. Exemplary low intensity sweeteners include, but are not limited to, erythritol, xylitol, maltitol, maltooligosaccharide, mannitol, sorbitol, tagatose, glucose, fructose, sucrose, sucrose solution, invert sugar, corn syrup, high fructose corn syrup, maltose syrup, sugar alcohol syrups, and mixtures thereof.

[00205] A low intensity sweetener can be, for example, a plant-derived or natural sweetener. As used herein, the term “plant-derived sweetener” refers to a compound or combination of compounds naturally providing the principle sweetness in a plant or plant product. Further, it is understood to include sweeteners modified by enzymatic or microbial means resulting in a compound or combination of compounds naturally providing the principle sweetness in a plant or plant product.

[00206] In various aspects, a low intensity sweetener can be an artificial sweetener.

[00207] In a further aspect, the relative quantities of the compound and the low intensity sweetener are such as to provide a relative sweetness contribution of from about 5:1 to about 1:5. In a still further aspect, the relative quantities of the compound and the low intensity sweetener

are such as to provide a relative sweetness contribution of from about 3:1 to about 1:3. In yet a further aspect, the relative quantities of the compound and the low intensity sweetener are such as to provide a relative sweetness contribution of about 1:1.

[00208] In a further aspect, the low intensity sweetener is present in an amount of from about 0.001 wt% to about 5 wt%. In a still further aspect, the low intensity sweetener is present in an amount of from about 0.01 wt% to about 5 wt%. In yet a further aspect, the low intensity sweetener is present in an amount of from about 0.1 wt% to about 5 wt%. In an even further aspect, the low intensity sweetener is present in an amount of from about 1 wt% to about 5 wt%. In a still further aspect, the low intensity sweetener is present in an amount of from about 0.001 wt% to about 1 wt%. In yet a further aspect, the low intensity sweetener is present in an amount of from about 0.001 wt% to about 0.1 wt%. In an even further aspect, the low intensity sweetener is present in an amount of from about 0.001 wt% to about 0.01 wt%.

e. HIGH INTENSITY SWEETENERS

[00209] In various aspects, the composition further comprises a high intensity sweetener (that is, a compound or mixture of compounds that provides sweetening in addition to the sweetening provided by one or more of the compounds disclosed herein, many of which are themselves high intensity sweeteners). As used herein, the term “high intensity sweetener” refers to a sweetener that delivers at least about 50 grams of SES per gram of solids. Exemplary high intensity sweeteners include, but are not limited to, steviol glycosides including a purified sweet steviol glycoside mixture, stevioside, rebaudioside A, rebaudioside B, rebaudioside C, rebaudioside D, rebaudioside E, rebaudioside F, dulcoside A, dulcoside B, rubusoside, stevia, siamenside, mogroside IV, mogroside V, Luo Han Guo sweetener, monatin and its salts (i.e., monatin SS, RR, RS, SR), glycyrrhizic acid and its salts, curculin, thaumatin, monellin, mabinlin, brazzein, hemandulcin, phyllodulcin, glycyphyllin, phloridzin, trilobatin, baiyunoside, osladin, polypodoside A, pterocaryoside A, pterocaryoside B, mukurozioside, phlomisioside I, periandrin I, abrusoside A, cyclocarioside I, sucralose, saccharin, a dipeptide sweetener, acesulfame-K, cyclamate, and mixtures thereof. A high intensity sweetener can be, for example, a plant-derived sweetener or an artificial sweetener.

[00210] In a further aspect, the relative quantities of the compound and the high intensity sweetener are such as to provide a relative sweetness contribution of from about 5:1 to about 1:5. In a still further aspect, the relative quantities of the compound and the high intensity sweetener are such as to provide a relative sweetness contribution of from about 3:1 to about 1:3. In yet a further aspect, the relative quantities of the compound and the high intensity sweetener are such as to provide a relative sweetness contribution of about 1:1.

[00211] In a further aspect, the high intensity sweetener is present in an amount of from about 0.001 wt% to about 5 wt%. In a still further aspect, the high intensity sweetener is present in an amount of from about 0.01 wt% to about 5 wt%. In yet a further aspect, the high intensity sweetener is present in an amount of from about 0.1 wt% to about 5 wt%. In an even further aspect, the high intensity sweetener is present in an amount of from about 1 wt% to about 5 wt%. In a still further aspect, the high intensity sweetener is present in an amount of from about 0.001 wt% to about 1 wt%. In yet a further aspect, the high intensity sweetener is present in an amount of from about 0.001 wt% to about 0.1 wt%. In an even further aspect, the high intensity sweetener is present in an amount of from about 0.001 wt% to about 0.01 wt%.

f. DECOLORIZING AGENTS

[00212] In various aspects, the composition further comprises a decolorizing agent. A decolorizing agent can include, for example, activated carbon, but other decolorizing agents can also be used. The carbon can be in a powder form or packed in a column. The carbon or other decolorizing agent is preferably removed following decolorization. The amount of carbon may depend on, for example, the type of carbon. Those skilled in the art can readily determine the minimum appropriate amount of carbon to add to decolorize the mixture. The carbon can be removed by conventional means (i.e., via filtration) if added in a loose form.

[00213] In a further aspect, the decolorizing agent is present in an amount of from about 0.001 wt% to about 5 wt%. In a still further aspect, the decolorizing agent is present in an amount of from about 0.01 wt% to about 5 wt%. In yet a further aspect, the decolorizing agent is present in an amount of from about 0.1 wt% to about 5 wt%. In an even further aspect, the decolorizing agent is present in an amount of from about 1 wt% to about 5 wt%. In a still further aspect, the decolorizing agent is present in an amount of from about 0.001 wt% to about 1 wt%. In yet a

further aspect, the decolorizing agent is present in an amount of from about 0.001 wt% to about 0.1 wt%. In an even further aspect, the decolorizing agent is present in an amount of from about 0.001 wt% to about 0.01 wt%.

g. TASTE MODIFIERS

[00214] In various aspects, the composition further comprises a taste modifier. Exemplary taste modifiers include, but are not limited to, aluminum potassium sulfate, Naringin, sodium chloride, monosodium glutamate, ammonium glycyrrhizinate, and mixtures thereof. Taste modifying effects can include, for example, enhancement, synergy, suppression, and masking.

[00215] Taste is often referred to as a taste quality, which is selected from bitter, sweet, sour, salt, and umami. It is possible to have one or more of these taste qualities within the same item. Taste modification often involves either an enhancement or synergy, or a suppression or masking of a particular taste quality. Taste modification may also involve a change in the duration (or time) and intensity of the taste quality. Thus, in a visual sense, a curve of a taste profile can be shifted forward or backward in time, be lengthened or shortened (duration) and certain peaks can be decreased or increased in height (intensity).

[00216] Furthermore, the senses of taste and smell (or odor) are anatomically two separate entities. Taste is stimulated through physical interactions of non-volatile molecules with receptors on the tongue and mouth surfaces, while volatile compounds reaching the receptors in the olfactory epithelium determine smell. At a perceptual level, however, the sensations of taste and smell interact. Interactions may also occur with appearance, sound, and texture.

[00217] In a further aspect, the taste modifier is present in an amount of from about 0.001 wt% to about 5 wt%. In a still further aspect, the taste modifier is present in an amount of from about 0.01 wt% to about 5 wt%. In yet a further aspect, the taste modifier is present in an amount of from about 0.1 wt% to about 5 wt%. In an even further aspect, the taste modifier is present in an amount of from about 1 wt% to about 5 wt%. In a still further aspect, the taste modifier is present in an amount of from about 0.001 wt% to about 1 wt%. In yet a further aspect, the taste modifier is present in an amount of from about 0.001 wt% to about 0.1 wt%. In an even further aspect, the taste modifier is present in an amount of from about 0.001 wt% to about 0.01 wt%.

h. PLASTICIZERS

[00218] In various aspects, the composition further comprises a plasticizer. Exemplary plasticizers include, for example, glycerol, sorbitol, propylene glycol, polyethylene glycol, corn syrup, high fructose corn syrup, fruit juice, sucrose, maltodextrin, corn syrup solids, polydextrose, soluble fiber, and mixtures thereof.

[00219] In a further aspect, the plasticizer is present in an amount of from about 0.001 wt% to about 5 wt%. In a still further aspect, the plasticizer is present in an amount of from about 0.01 wt% to about 5 wt%. In yet a further aspect, the plasticizer is present in an amount of from about 0.1 wt% to about 5 wt%. In an even further aspect, the plasticizer is present in an amount of from about 1 wt% to about 5 wt%. In a still further aspect, the plasticizer is present in an amount of from about 0.001 wt% to about 1 wt%. In yet a further aspect, the plasticizer is present in an amount of from about 0.001 wt% to about 0.1 wt%. In an even further aspect, the plasticizer is present in an amount of from about 0.001 wt% to about 0.01 wt%.

i. FILM-FORMING POLYMERS

[00220] In various aspects, the composition further comprises a film-forming polymer. Exemplary film-forming polymers include, for example, pullulan, pectin, alginates, carrageenans, xanthan gum, modified cellulose, polydextrose, starch, dextrin, maltodextrin, and mixtures thereof.

[00221] The film-forming polymer can be, for example, a water soluble or dispersible film-forming polymer. Water soluble polymers include, but are not limited to, polyvinyl pyrrolidone, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, hydroxyalkyl celluloses such as hydroxypropyl cellulose, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, guar gum, xanthan gum as well as water dispersible polymers such as polyacrylates, carboxyvinyl copolymers, methyl methacrylate copolymers and polyacrylic acid. In a further aspect, the film-forming polymer can be water-insoluble. Additional examples include cellulose derivatives such as ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, methylcellulose, sodium carboxymethylcellulose, and mixtures thereof; acrylic resin dispersions such as polyacrylamide, polyacryldextran, polyalkyl cyanoacrylate, polymethyl methacrylate,

and mixtures thereof; and acacia (gum arabic), modified starches, alginates, and mixtures thereof.

[00222] In a further aspect, the film-forming polymer is present in an amount of from about 0.01 wt% to about 30 wt%. In a still further aspect, the film-forming polymer is present in an amount of from about 0.1 wt% to about 30 wt%. In yet a further aspect, the film-forming polymer is present in an amount of from about 1 wt% to about 30 wt%. In an even further aspect, the film-forming polymer is present in an amount of from about 5 wt% to about 30 wt%. In a still further aspect, the film-forming polymer is present in an amount of from about 10 wt% to about 30 wt%. In yet a further aspect, the film-forming polymer is present in an amount of from about 15 wt% to about 30 wt%. In an even further aspect, the film-forming polymer is present in an amount of from about 20 wt% to about 30 wt%. In a still further aspect, the film-forming polymer is present in an amount of from about 0.01 wt% to about 20 wt%. In yet a further aspect, the film-forming polymer is present in an amount of from about 0.01 wt% to about 15 wt%. In an even further aspect, the film-forming polymer is present in an amount of from about 0.01 wt% to about 10 wt%. In a still further aspect, the film-forming polymer is present in an amount of from about 0.01 wt% to about 5 wt%. In yet a further aspect, the film-forming polymer is present in an amount of from about 0.01 wt% to about 1 wt%. In an even further aspect, the film-forming polymer is present in an amount of from about 0.01 wt% to about 0.1 wt%.

j. SALTS

[00223] In various aspects, the composition further comprises a salt. Exemplary salts include, but are not limited to, sodium chloride, potassium chloride, magnesium chloride, and mixtures thereof.

[00224] In various aspects, the salt can have a cation selected from group I and group II metals and ammonium. For example, the cation can include sodium, potassium, calcium, and magnesium. In a further aspect, the salt can have an anion selected from, for example, chloride and carbonate.

[00225] In a further aspect, the salt is present in an amount of from about 0.001 wt% to about 5 wt%. In a still further aspect, the salt is present in an amount of from about 0.01 wt% to about

5 wt%. In yet a further aspect, the salt is present in an amount of from about 0.1 wt% to about 5 wt%. In an even further aspect, the salt is present in an amount of from about 1 wt% to about 5 wt%. In a still further aspect, the salt is present in an amount of from about 0.001 wt% to about 1 wt%. In yet a further aspect, the salt is present in an amount of from about 0.001 wt% to about 0.1 wt%. In an even further aspect, the salt is present in an amount of from about 0.001 wt% to about 0.01 wt%.

k. INTERNAL FILM RELEASE AGENTS

[00226] In various aspects, the composition further comprises an internal film release agent. Exemplary internal film release agents include, but are not limited to, polyoxyethylene sorbitan monooleate, sodium lauryl sulfate, and mixtures thereof.

[00227] In a further aspect, the internal film release agent is present in an amount of from about 0.001 wt% to about 5 wt%. In a still further aspect, the internal film release agent is present in an amount of from about 0.01 wt% to about 5 wt%. In yet a further aspect, the internal film release agent is present in an amount of from about 0.1 wt% to about 5 wt%. In an even further aspect, the internal film release agent is present in an amount of from about 1 wt% to about 5 wt%. In a still further aspect, the internal film release agent is present in an amount of from about 0.001 wt% to about 1 wt%. In yet a further aspect, the internal film release agent is present in an amount of from about 0.001 wt% to about 0.1 wt%. In an even further aspect, the internal film release agent is present in an amount of from about 0.001 wt% to about 0.01 wt%.

l. OTHER ADDITIVES

[00228] In various aspects, the composition further comprises at least one agent selected from carbohydrates, cellulose, gums, food acids, nutritive sweeteners, gelatin, food grade wax emulsions, colorants, fillers, surfactants, stabilizers, organic acids, and mixtures thereof.

[00229] In a further aspect, the at least one agent is present in an amount of from about 0.001 wt% to about 5 wt%. In a still further aspect, the at least one agent is present in an amount of from about 0.01 wt% to about 5 wt%. In yet a further aspect, the at least one agent is present in an amount of from about 0.1 wt% to about 5 wt%. In an even further aspect, the at least one agent is present in an amount of from about 1 wt% to about 5 wt%. In a still further aspect, the

at least one agent is present in an amount of from about 0.001 wt% to about 1 wt%. In yet a further aspect, at least one agent is present in an amount of from about 0.001 wt% to about 0.1 wt%. In an even further aspect, the at least one agent is present in an amount of from about 0.001 wt% to about 0.01 wt%.

2. PARTICLES

[00230] In various aspects, the composition is in particulate form.

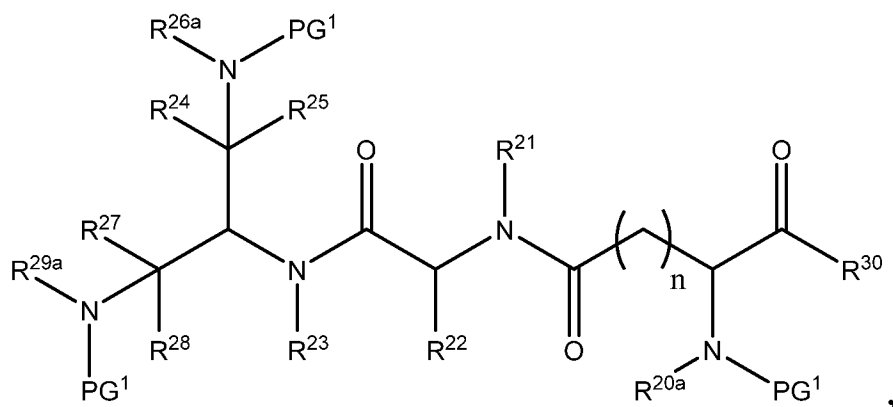
[00231] In a further aspect, the particles have a moisture content of from about 0.5 wt% to about 1.5 wt%. In a still further aspect, the particles have a moisture content of from about 0.75 wt% to about 1.5 wt%. In yet a further aspect, the particles have a moisture content of from about 1 wt% to about 1.5 wt%. In an even further aspect, the particles have a moisture content of from about 1.25 wt% to about 1.5 wt%. In a still further aspect, the particles have a moisture content of from about 0.5 wt% to about 1.25 wt%. In yet a further aspect, the particles have a moisture content of from about 0.5 wt% to about 1 wt%. In an even further aspect, the particles have a moisture content of from about 0.5 wt% to about 0.75 wt%.

[00232] In a further aspect, the particles are granular. In a still further aspect, the particles are in the form of crystalline shards.

[00233] In a further aspect, the particles have an average particle size of about 20 microns. In a still further aspect, the particles have an average particle size of about 15 microns. In yet a further aspect, the particles have an average particle size of about 10 microns. In an even further aspect, the particles have an average particle size of about 5 microns. In a still further aspect, the particles have an average particle size of about 1 micron. In yet a further aspect, the particles have an average particle size of less than 1 micron.

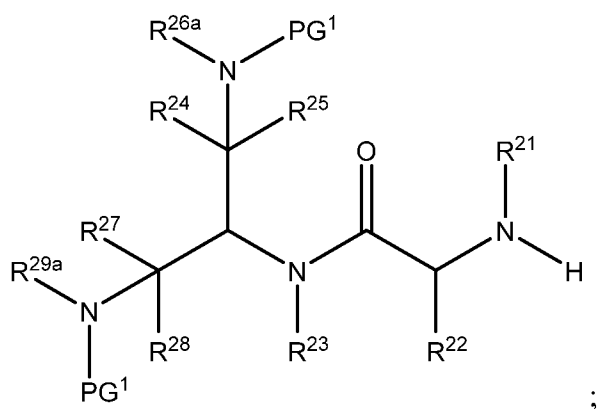
D. METHODS OF MAKING THE COMPOUNDS

[00234] In various aspects, the invention relates to methods of making compounds useful to sweeten foods, beverages, medicines, and other consumable products (*e.g.*, chewing gum, toothpaste, mouthwash, etc.). Thus, in one aspect, the invention relates to methods of making a compound having a structure represented by a formula:

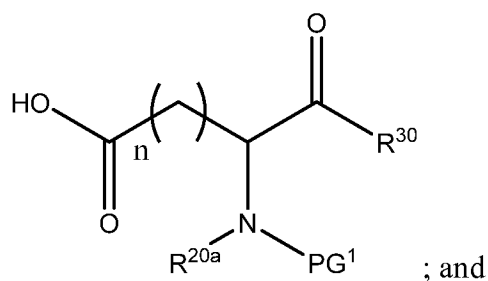


wherein n is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a}, R²¹, R²³, R^{26a}, and R^{29a} is independently selected from hydrogen and C1-C4 alkyl; wherein R²² is selected from hydrogen, C1-C4 alkyl, -CH₂SeH, -CH₂SH, -CH₂CH₂SH, -CH₂CH₂SCH₃, and -CH₂Ar¹; wherein Ar¹ is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy; wherein each of R²⁴, R²⁵, R²⁷, and R²⁸ is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; wherein R³⁰ is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂; and wherein PG¹ is an amino protecting group that is stable under basic conditions, the method comprising the steps of:

(a) providing a first compound having a structure represented by a formula:

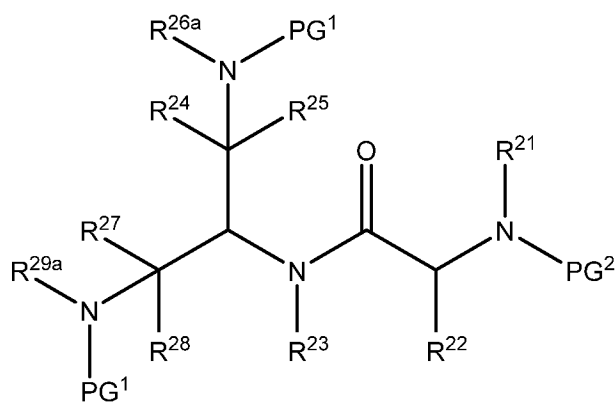


(b) providing a second compound having a structure represented by a formula:



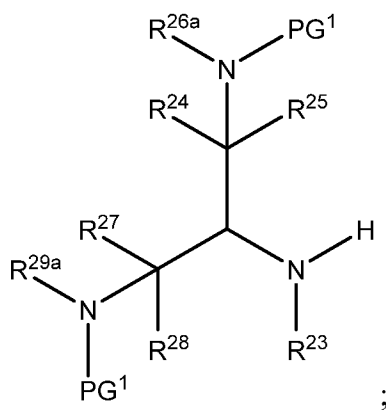
(c) reacting with a coupling agent.

[00235] In one aspect, the invention relates to a method of making a compound having a structure represented by a formula:

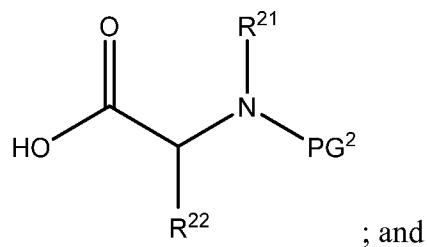


wherein each of R^{21} , R^{23} , R^{26a} , and R^{29a} is independently selected from hydrogen and C1-C4 alkyl; wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-CH_2SeH$, $-CH_2SH$, $-CH_2CH_2SH$, $-CH_2CH_2SCH_3$, and $-CH_2Ar^1$; wherein Ar^1 is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, $-OH$, and C1-C4 alkoxy; wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; wherein PG^1 is an amino protecting group that is stable under basic conditions; and wherein PG^2 is an amino protecting group that is stable under acidic conditions, the method comprising the steps of:

(a) providing a first compound having a structure represented by a formula:



(b) providing a second compound having a structure represented by a formula:



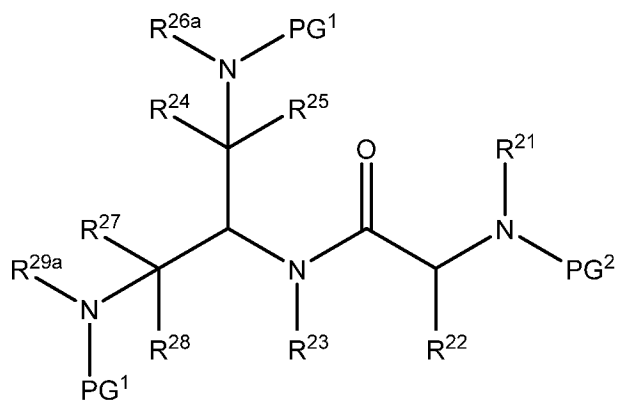
(c) reacting with a coupling agent.

[00236] In a further aspect, PG¹ is *t*-butyloxycarbonyl.

[00237] In a further aspect, PG² is trifluoroacetyl.

[00238] In a further aspect, providing the first compound comprises the steps of:

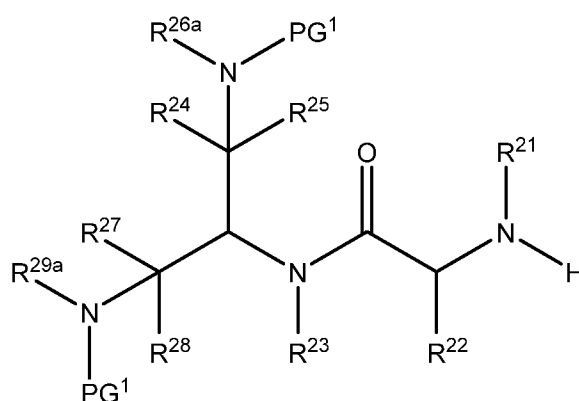
(a) providing a compound having a structure represented by a formula:



wherein PG² is an amino protecting group that is stable under acidic conditions; and

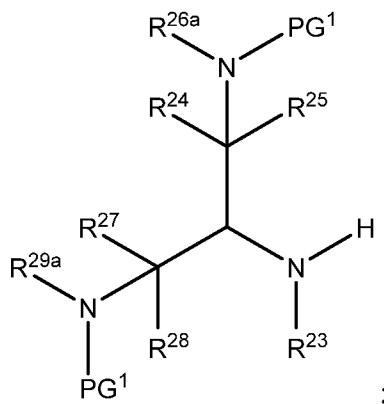
(b) reacting with a base,

thereby affording a compound having a structure represented by a formula:

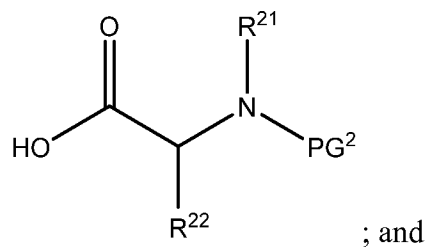


[00239] In a further aspect, providing the compound comprises the steps of:

(a) providing a first compound having a structure represented by a formula:

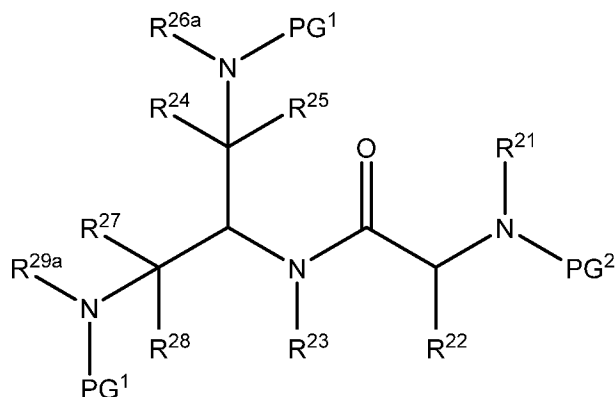


(b) providing a second compound having a structure represented by a formula:



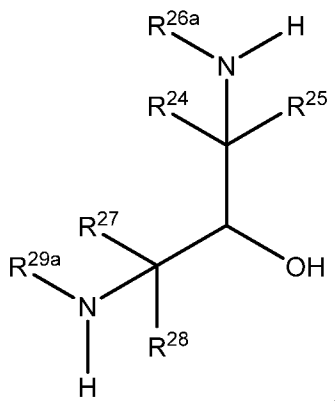
(c) reacting with a coupling agent,

thereby affording a compound having a structure represented by a formula:



[00240] In a further aspect, providing the first compound comprises the steps of:

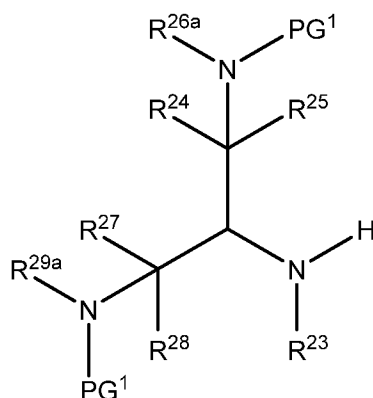
(a) providing a compound having a structure represented by a formula:



(b) reacting with a compound selected from (PG¹)₂O, PG¹OH, and PG¹Cl; and

(c) reacting with a nucleophile,

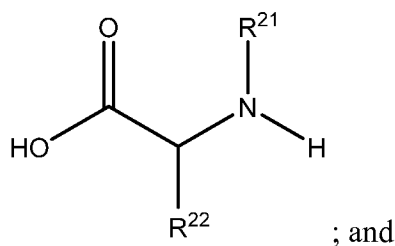
thereby affording a compound having a structure represented by a formula:



[00241] In a further aspect, the nucleophile is sodium azide.

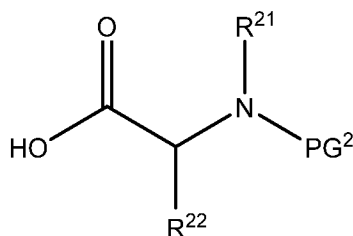
[00242] In a further aspect, providing the second compound comprises the steps of:

(a) providing a compound having a structure represented by a formula:



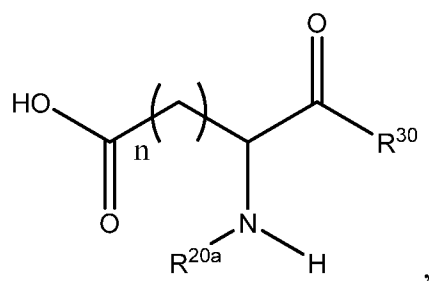
(b) reacting with a compound selected from $(PG^2)_2O$, PG^2OH , and PG^2Cl ,

thereby affording a compound having a structure represented by a formula:

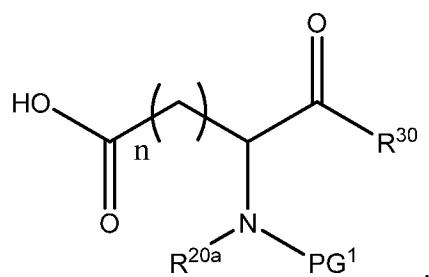


[00243] In a further aspect, providing the second compound comprises the steps of:

(a) providing a compound having a structure represented by a formula:

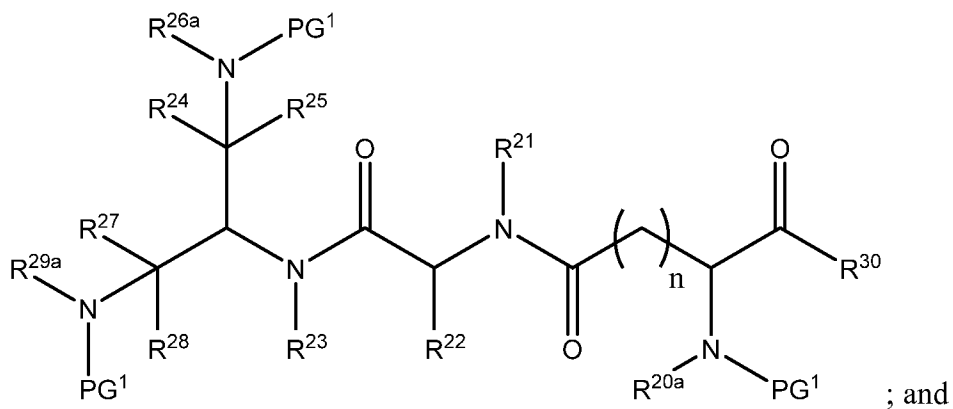


(b) reacting with a compound selected from $(\text{PG}^1)_2\text{O}$, PG^1OH , and PG^1Cl , thereby affording a compound having a structure represented by a formula:



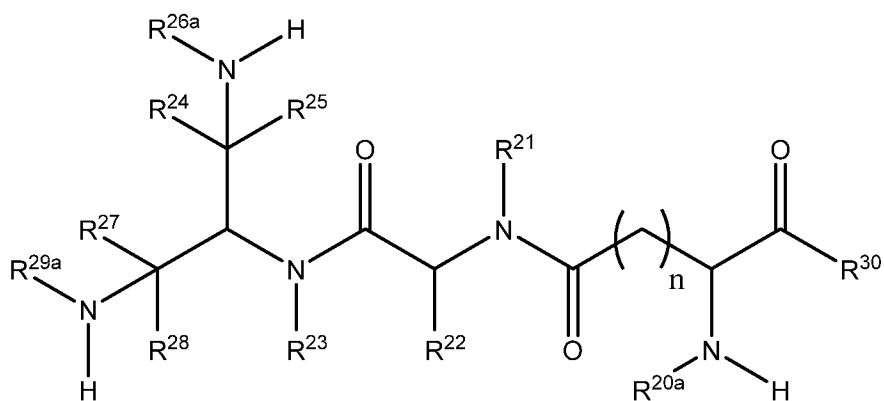
[00244] In a further aspect, the method further comprises the steps of:

(a) providing a compound having a structure represented by a formula:



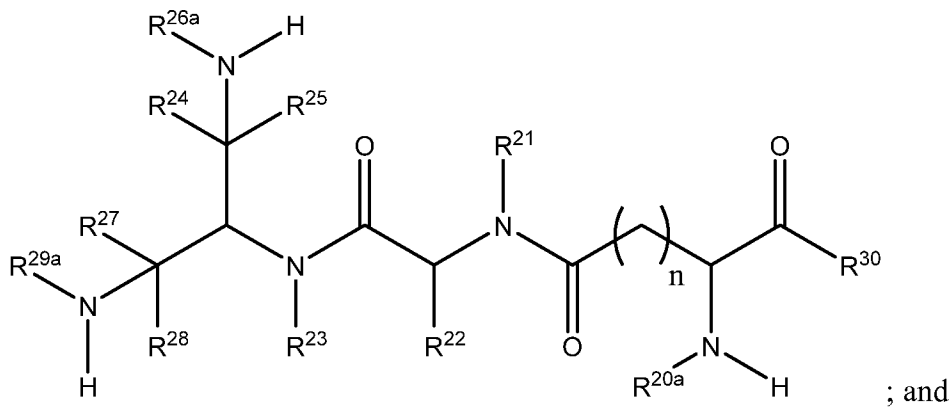
(b) reacting with an acid,

thereby affording a compound having a structure represented by a formula:



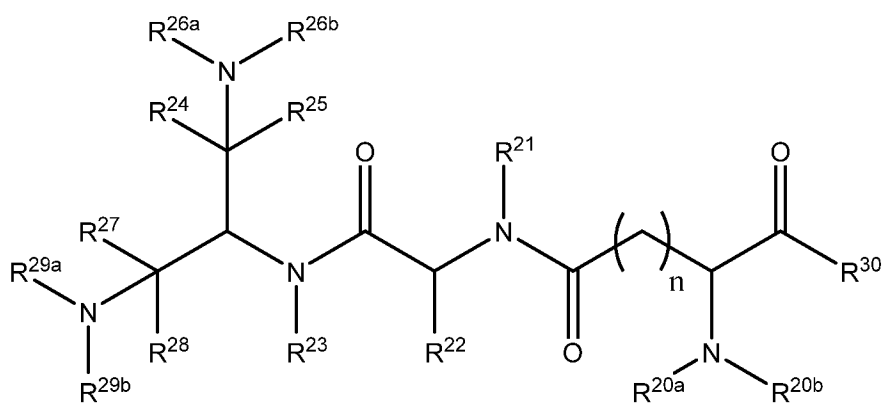
[00245] In a further aspect, the method further comprises the steps of:

(a) providing a compound having a structure represented by a formula:



(b) reacting with an alkyl halide,

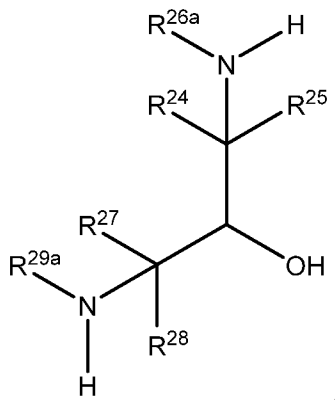
thereby affording a compound having a structure represented by a formula:



wherein each of R^{20b} , R^{26b} , and R^{29a} are independently selected from C1-C4 alkyl.

[00246] In a further aspect, providing the first compound comprises the steps of:

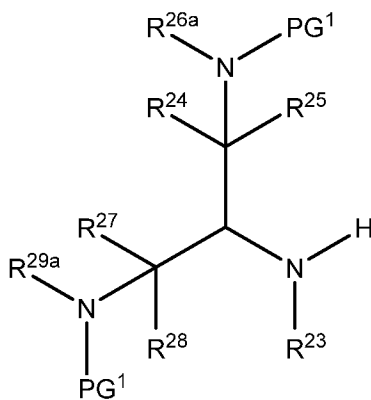
(a) providing a compound having a structure represented by a formula:



(b) reacting with a compound selected from $(PG^1)_2O$, PG^1OH , and PG^1Cl ; and

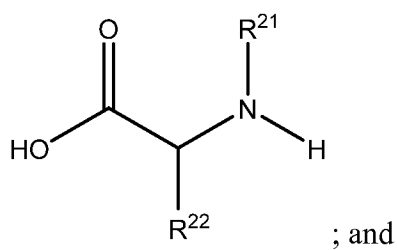
(c) reacting with a nucleophile,

thereby affording a compound having a structure represented by a formula:

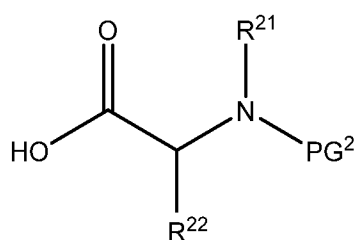


[00247] In a further aspect, providing the second compound comprises the steps of:

(a) providing a compound having a structure represented by a formula:

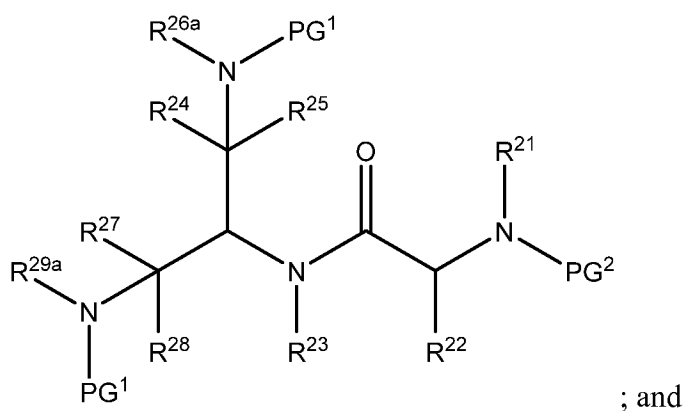


(b) reacting with a compound selected from $(PG^2)_2O$, PG^2OH , and PG^2Cl , thereby affording a compound having a structure represented by a formula:

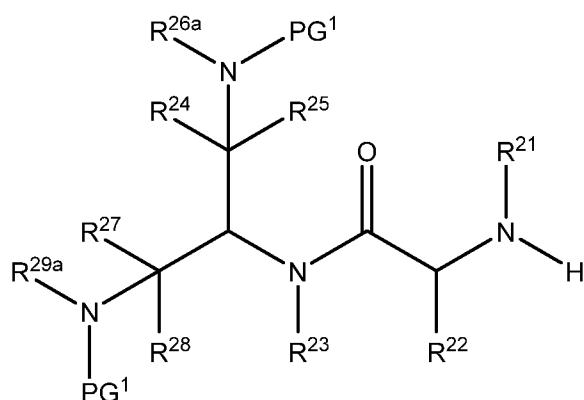


[00248] In a further aspect, the method further comprises the steps of:

(a) providing a compound having a structure represented by a formula:

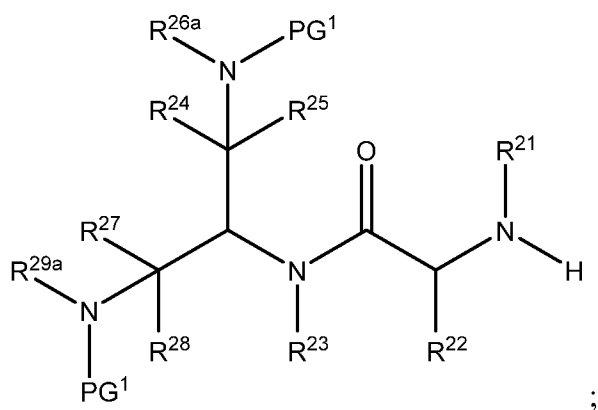


(b) reacting with a base, thereby affording a compound having a structure represented by a formula:

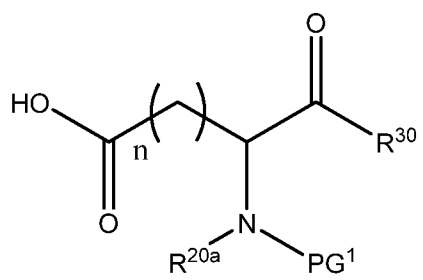


[00249] In a further aspect, the method further comprises the steps of:

(a) providing a first compound having a structure represented by a formula:



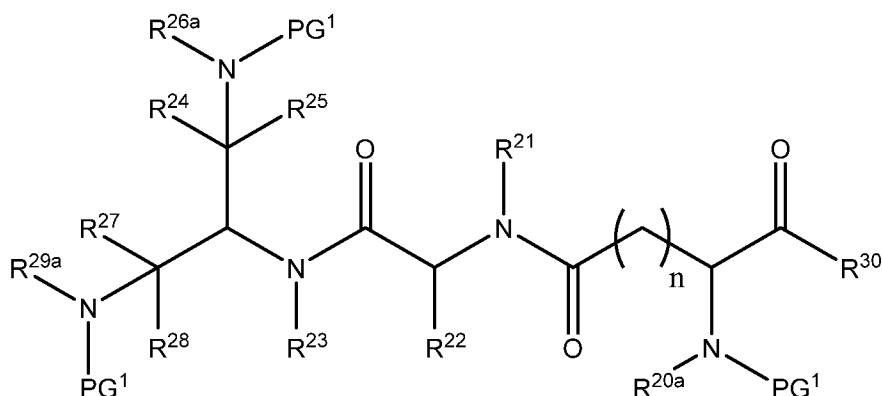
(b) providing a second compound having a structure represented by a formula:



wherein R^{20a} is selected from hydrogen and C1-C4 alkyl; and wherein R³⁰ is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂; and

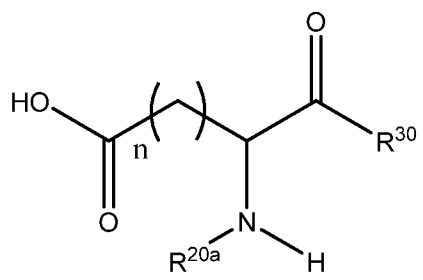
(c) reacting with a coupling agent,

thereby affording a compound having a structure represented by a formula:



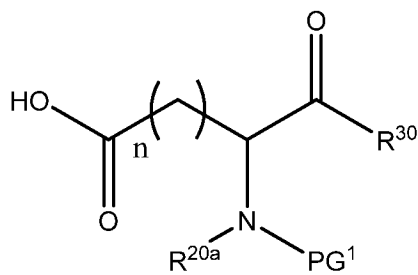
[00250] In a further aspect, providing the second compound comprises the steps of:

(a) providing a compound having a structure represented by a formula:



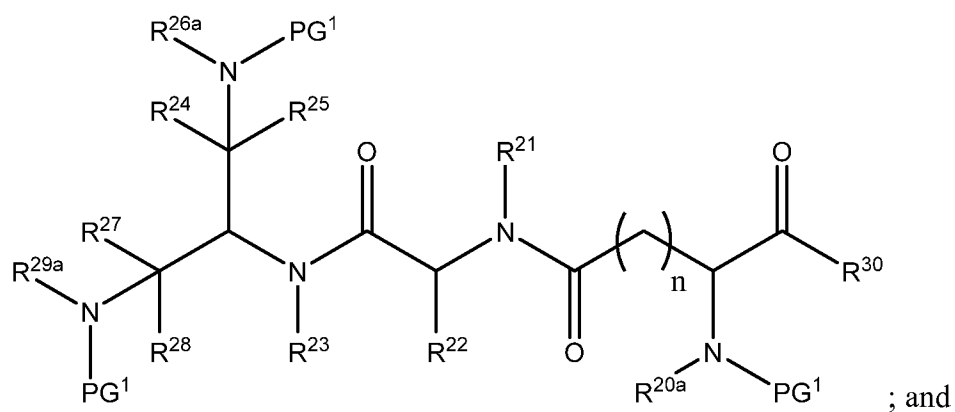
(b) reacting with a compound selected from $(PG^1)_2O$, PG^1OH , and PG^1Cl ,

thereby affording a compound having a structure represented by a formula:



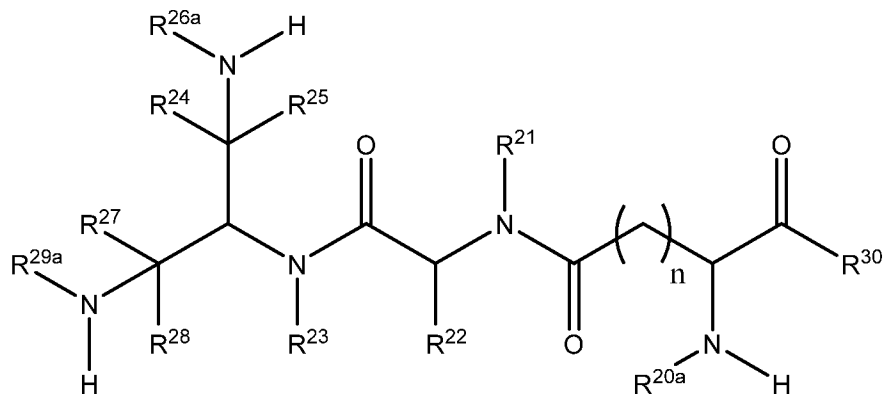
[00251] In a further aspect, the method further comprises the steps of:

(a) providing a compound having a structure represented by a formula:



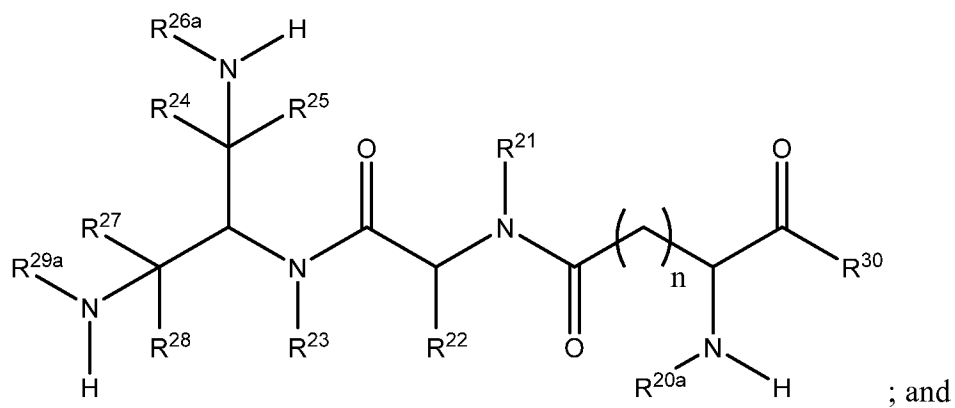
(b) reacting with an acid,

thereby affording a compound having a structure represented by a formula:



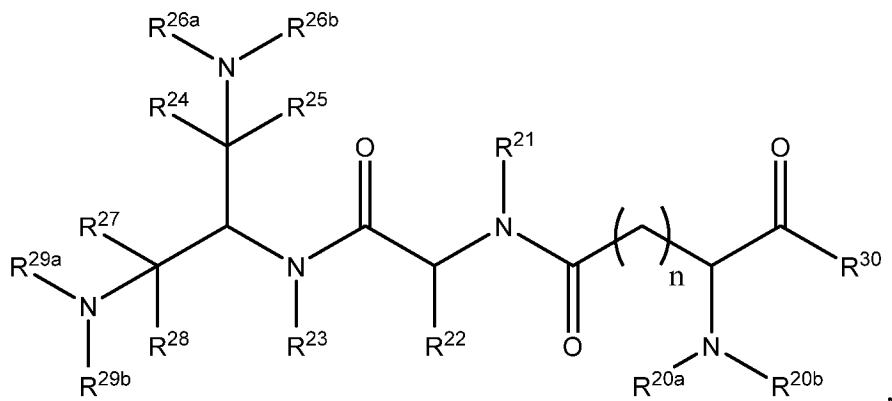
[00252] In a further aspect, the method further comprises the steps of:

(a) providing a compound having a structure represented by a formula:



(b) reacting with an alkyl halide,

thereby affording a compound having a structure represented by a formula:



wherein each of R^{20b} , R^{26b} , and R^{29a} are independently selected from C1-C4 alkyl.

[00253] The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental sections or clear to one skilled in the art. For clarity, examples having a single substituent are shown where multiple substituents are allowed under the definitions disclosed herein.

[00254] Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the following Reaction Schemes, as described and exemplified below. In certain specific examples, the disclosed compounds can be prepared by Route I and Route II, as described and exemplified below. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

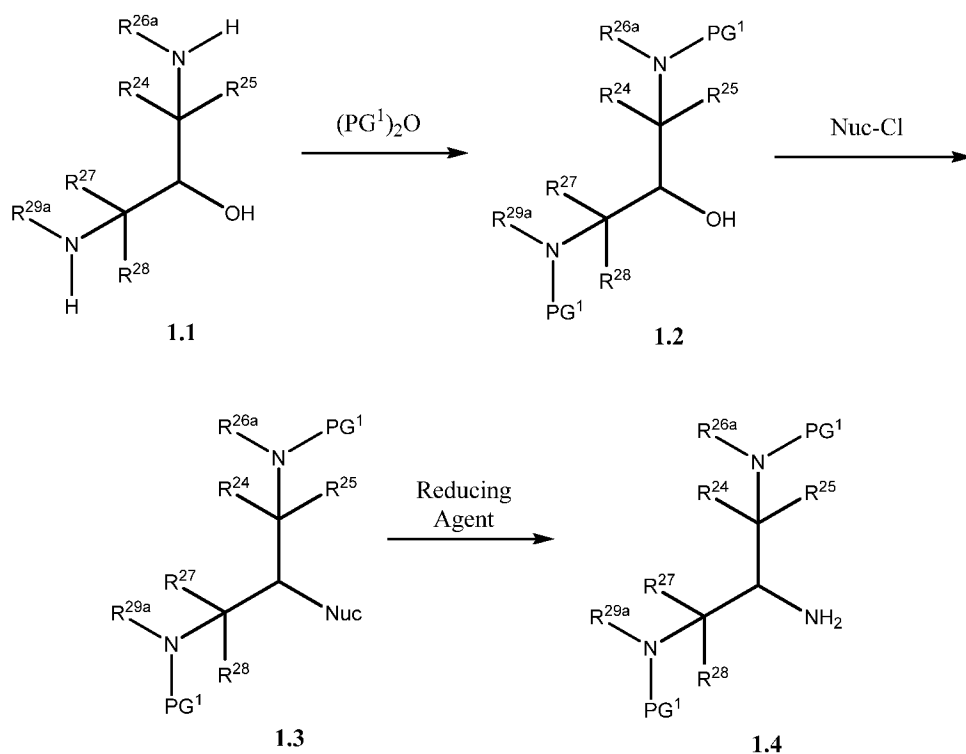
[00255] In one aspect, the disclosed compounds comprise the products of the synthetic methods described herein. In a further aspect, the disclosed compounds comprise a compound produced by a synthetic method described herein. In a still further aspect, the invention comprises a pharmaceutical composition comprising a therapeutically effective amount of the product of the disclosed methods and a pharmaceutically acceptable carrier. In a still further aspect, the invention comprises a method for manufacturing a medicament comprising

combining at least one compound of any of disclosed compounds or at least one product of the disclosed methods with a pharmaceutically acceptable carrier or diluent.

1. ROUTE I

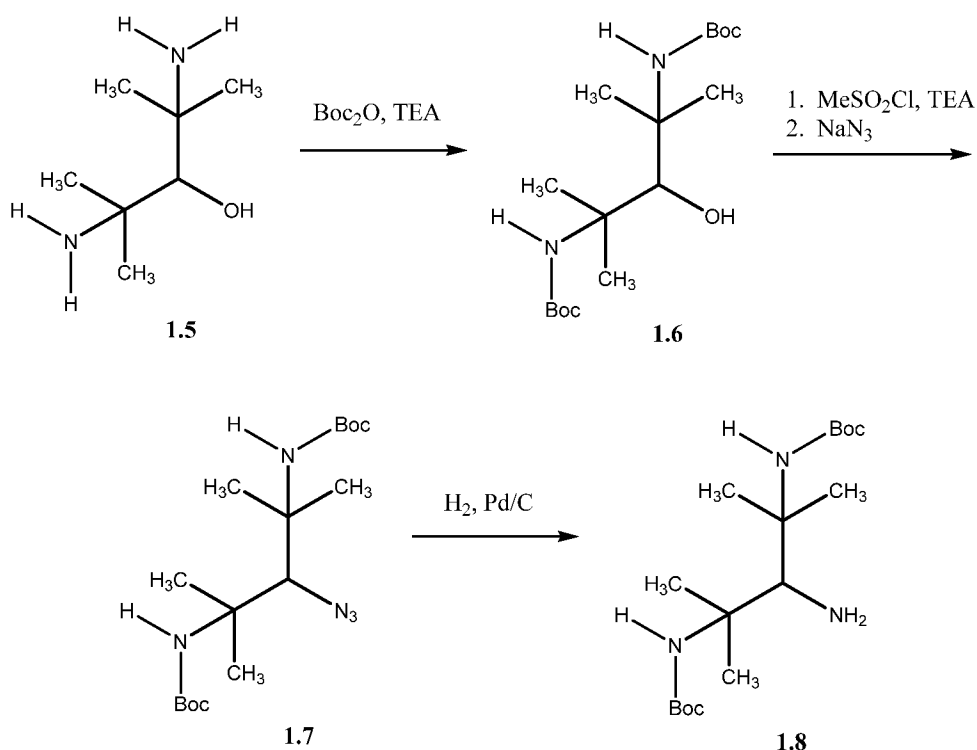
[00256] In one aspect, substituted amines of the present invention can be prepared as shown below.

SCHEME 1A.



[00257] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 1B.



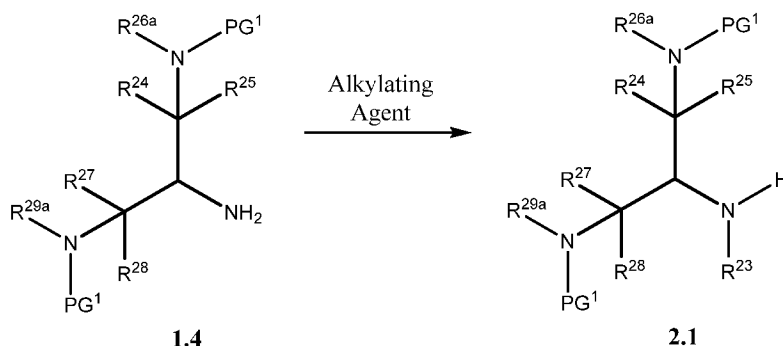
[00258] In one aspect, compounds of type **1.4**, and similar compounds, can be prepared according to reaction **Scheme 1B** above. Thus, compounds of type **1.6** can be prepared by protection of an appropriate diamine, e.g., **1.5** as shown above. Appropriate diamines are commercially available or prepared by methods known to one skilled in the art. The protection is carried out in the presence of an appropriate protecting agent, e.g., di-*tert*-butyl dicarbonate, with an appropriate base, e.g. triethylamine (TEA). Compounds of type **1.7** can be prepared by nucleophilic substitution of an appropriate alcohol, e.g., **1.6** as shown above. The nucleophilic substitution is carried out in the presence of an appropriate activating agent, e.g., methane sulfonyl chloride, with an appropriate base e.g., TEA, followed by displacement with an appropriate nucleophile, e.g., sodium azide. Compounds of type **1.8** can be prepared by reduction of an appropriate reductant, e.g., **1.7** as shown above. The reduction is carried out in the presence of an appropriate reducing agent, e.g., hydrogen gas, in the presence of an appropriate catalyst, e.g., palladium on carbon. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **1.1**, **1.2**, and

1.3), can be substituted in the reaction to provide substituted amine intermediates similar to Formula 1.8.

2. ROUTE II

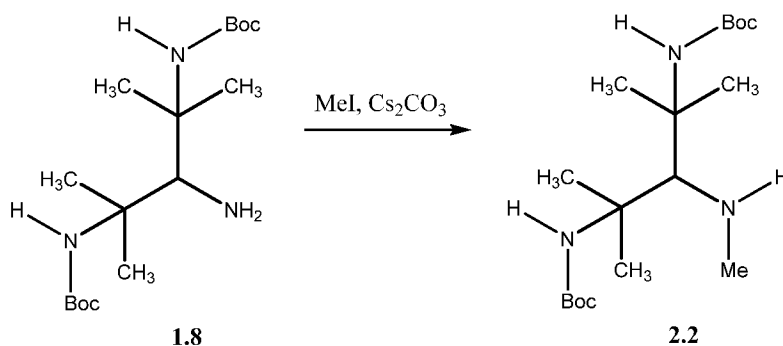
[00259] In one aspect, substituted amines of the present invention can be prepared as shown below.

SCHEME 2A.



[00260] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 2B.



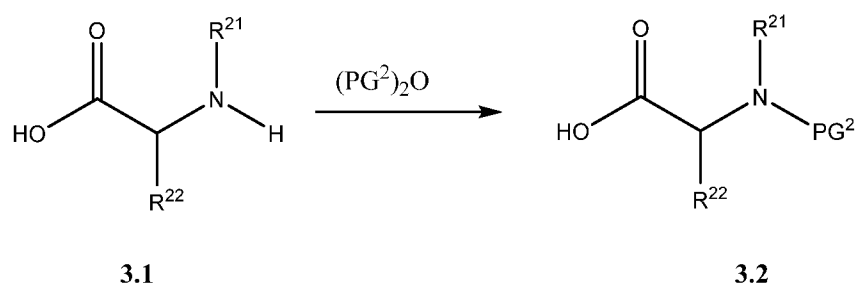
[00261] In one aspect, compounds of type 2.1, and similar compounds, can be prepared according to reaction **Scheme 2B** above. Thus, compounds of type 2.2 can be prepared by alkylation of an appropriate amine, e.g., 1.8 as shown above. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein

compounds similar in structure to the specific reactants above (compounds similar to compounds of type **1.4**), can be substituted in the reaction to provide substituted amine intermediates similar to Formula **2.2**.

3. ROUTE III

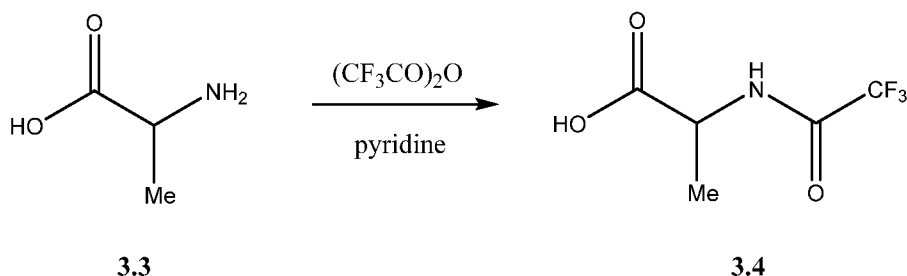
[00262] In one aspect, substituted carboxylic acids of the present invention can be prepared as shown below.

SCHEME 3A.



[00263] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 3B.



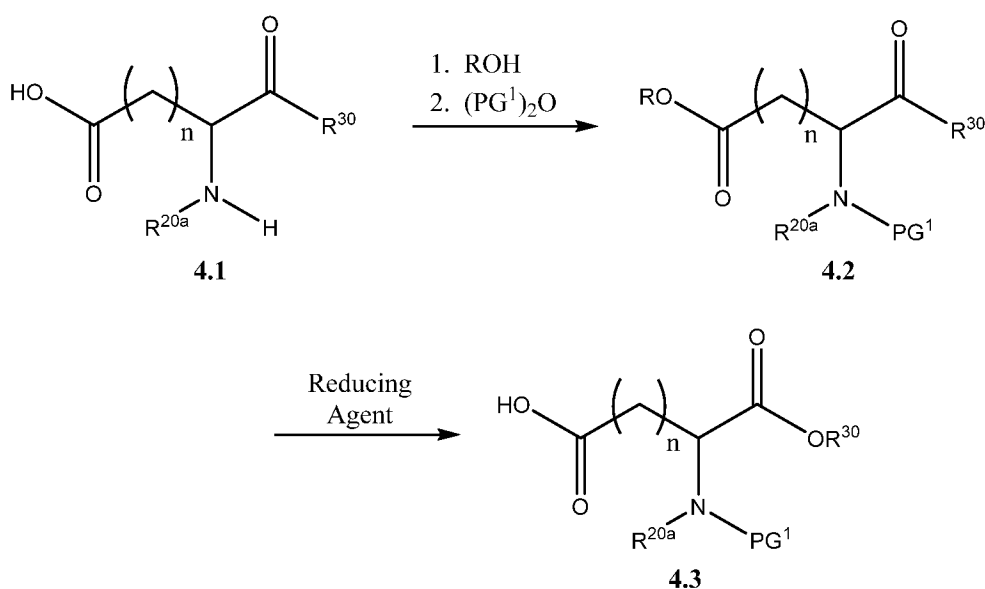
[00264] In one aspect, compounds of type **3.2**, and similar compounds, can be prepared according to reaction **Scheme 3B** above. Thus, compounds of type **3.4** can be prepared by protection of an appropriate amine, e.g., **3.3** as shown above. Appropriate amines are commercially available or prepared by methods known to one skilled in the art. The protection is carried out in the presence of an appropriate protecting agent, e.g., trifluoroacetic anhydride, with an appropriate base, e.g. pyridine. As can be appreciated by one skilled in the art, the above

reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **3.2**), can be substituted in the reaction to provide substituted amine intermediates similar to Formula **3.4**.

4. ROUTE IV

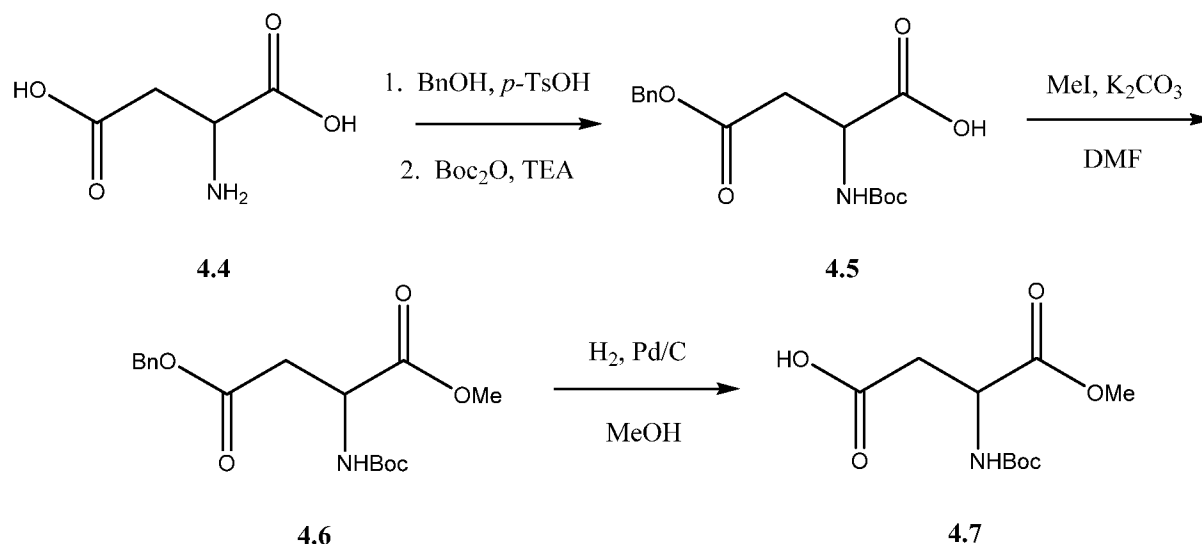
[00265] In one aspect, substituted esters of the present invention can be prepared as shown below.

SCHEME 4A.



[00266] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 4B.

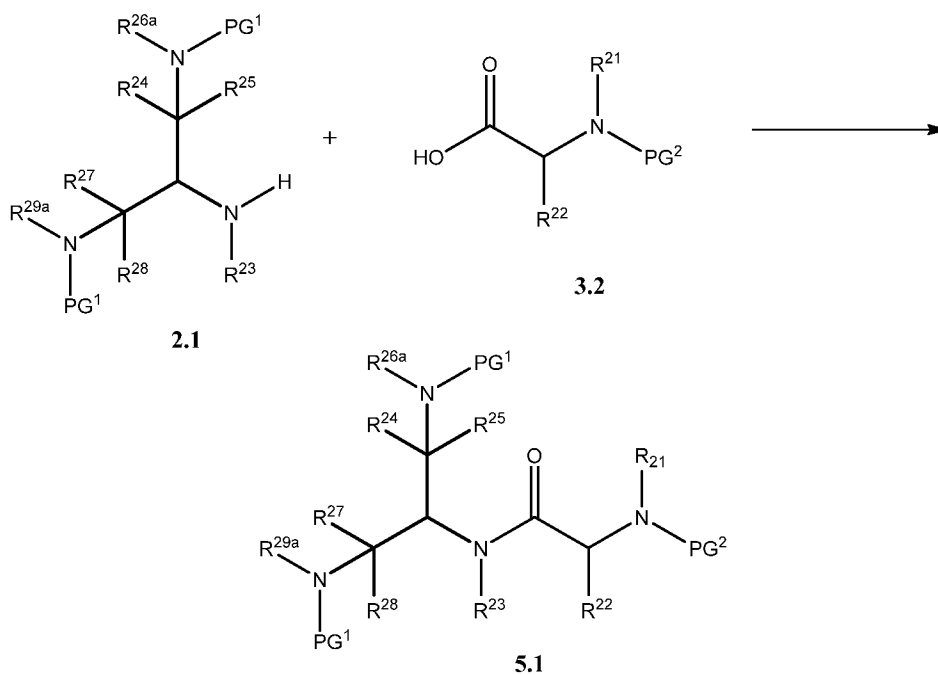


[00267] In one aspect, compounds of type 4.3, and similar compounds, can be prepared according to reaction **Scheme 4B** above. Thus, compounds of type 4.5 can be prepared by protection of an appropriate dicarboxylic acid, e.g., 4.4 as shown above. Appropriate dicarboxylic acids are commercially available or prepared by methods known to one skilled in the art. The protection is carried out in the presence of an appropriate acid protecting agent, e.g., benzyl alcohol (BnOH), with an appropriate acid, e.g., *p*-toluene sulfonic acid, followed by reaction with an appropriate amine protecting agent, e.g., di-*tert*-butyl dicarbonate, with an appropriate base, e.g. TEA. Compounds of type 4.6 can be prepared by esterification of an appropriate carboxylic acid, e.g., 4.5 as shown above. The esterification is carried out in the presence of an appropriate alkylating agent, e.g., methyl iodide, with an appropriate base e.g., potassium carbonate, in an appropriate solvent, e.g., dimethylformamide (DMF). Compounds of type 4.7 can be prepared by reduction of an appropriate reductant, e.g., 4.8 as shown above. The reduction is carried out in the presence of an appropriate reducing agent, e.g., hydrogen gas, in the presence of an appropriate catalyst, e.g., palladium on carbon. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 4.1, and 4.2), can be substituted in the reaction to provide substituted amine intermediates similar to Formula 4.7.

5. ROUTE V

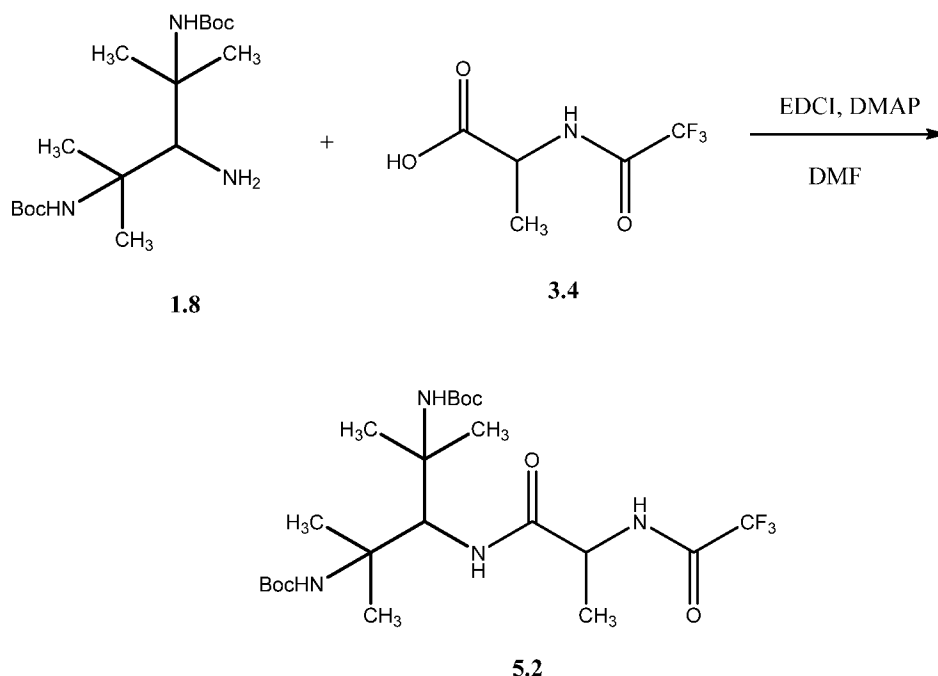
[00268] In one aspect, substituted amides of the present invention can be prepared as shown below.

SCHEME 5A.



[00269] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 5B.

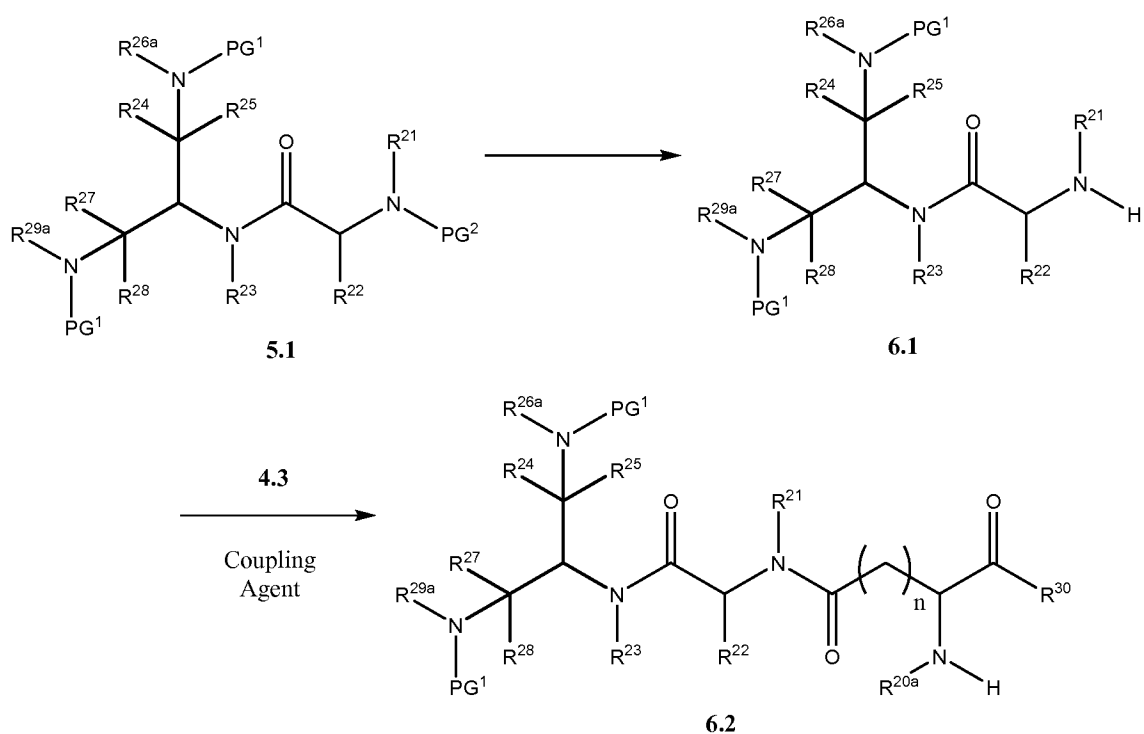


[00270] In one aspect, compounds of type 5.1, and similar compounds, can be prepared according to reaction **Scheme 5B** above. Thus, compounds of type 3.4 can be prepared by coupling of an appropriate amine, e.g., 1.8 as shown above, with an appropriate carboxylic acid, e.g., 3.4 as shown above. The protection is carried out in the presence of an appropriate coupling agent, e.g., 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), with an appropriate activating agent, e.g., 4-dimethylaminopyridine (DMAP), in an appropriate solvent, e.g. DMF. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 2.1 and 3.2), can be substituted in the reaction to provide substituted amine intermediates similar to Formula 5.2.

6. ROUTE VI

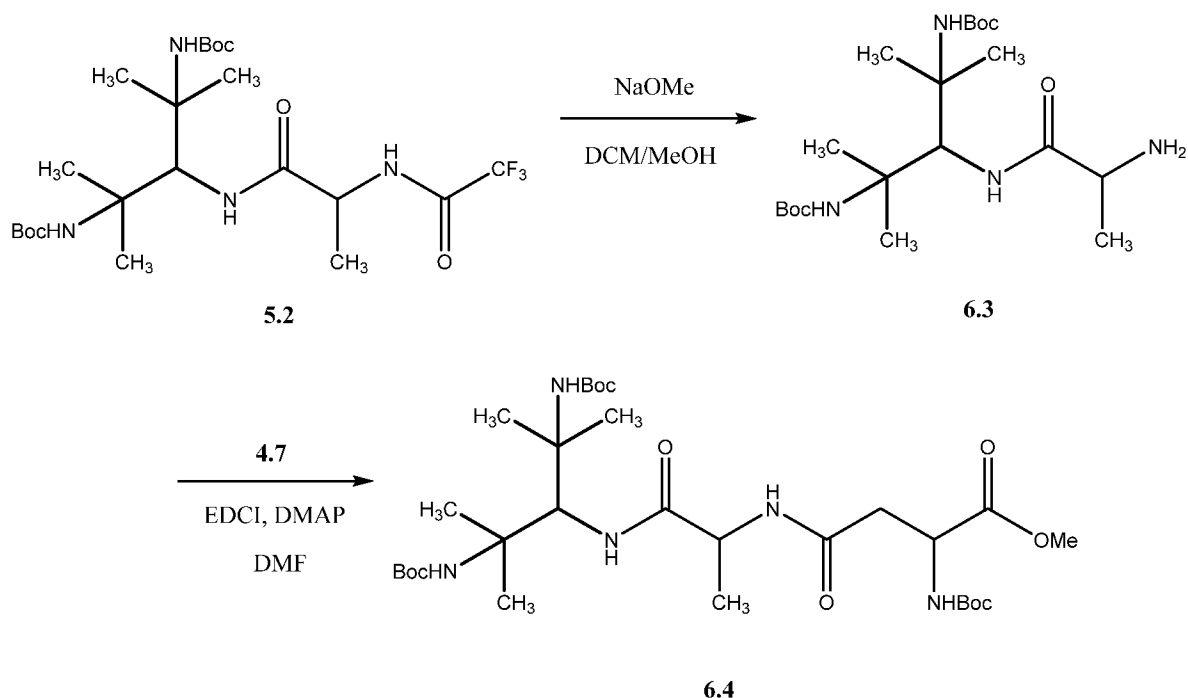
[00271] In one aspect, substituted amides of the present invention can be prepared as shown below.

SCHEME 6A.



[00272] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 6B.

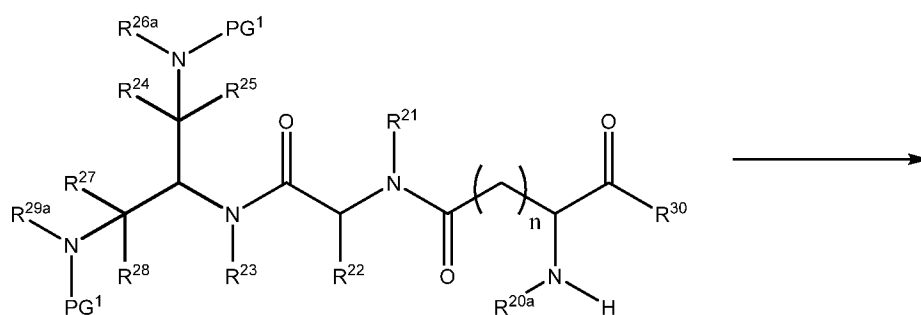


[00273] In one aspect, compounds of type 6.2, and similar compounds, can be prepared according to reaction Scheme 6B above. Thus, compounds of type 6.3 can be prepared by deprotection of an appropriate amide, e.g., 5.2 as shown above. The deprotection is carried out in the presence of an appropriate base, e.g., sodium methoxide, in an appropriate solvent, e.g., dichloromethane/methanol (DCM/MeOH). Compounds of type 6.4 can be prepared by coupling of an appropriate amine, e.g., 6.3 as shown above, with an appropriate carboxylic acid, e.g., 4.7 as shown above. The protection is carried out in the presence of an appropriate coupling agent, e.g., EDCI, with an appropriate activating agent, e.g., DMAP, in an appropriate solvent, e.g. DMF. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 5.1, 6.1 and 4.3), can be substituted in the reaction to provide substituted amine intermediates similar to Formula 6.4.

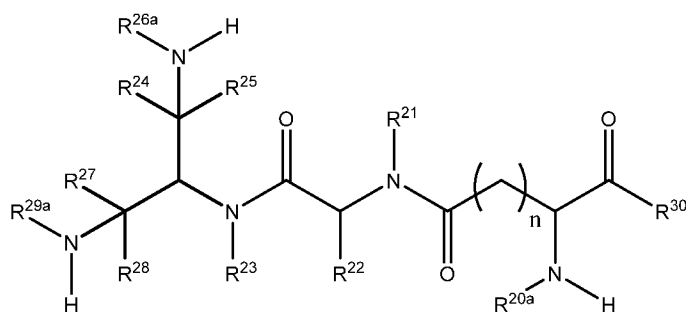
7. ROUTE VII

[00274] In one aspect, substituted amides of the present invention can be prepared as shown below.

SCHEME 7A.



6.2

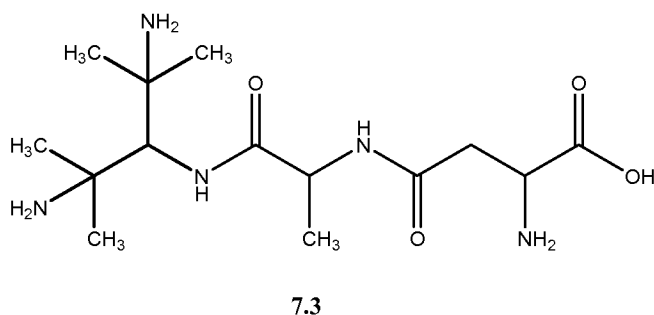
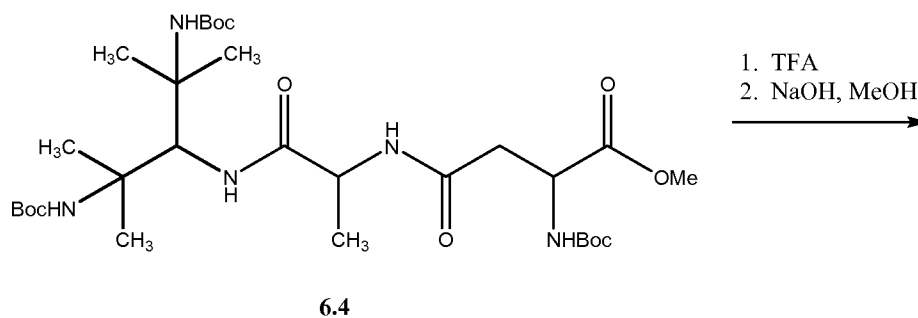
where R³⁰ = OCH₃, OCH₂CH₃, SCH₃, SCH₂CH₃

7.1

where R³⁰ = OH or SH

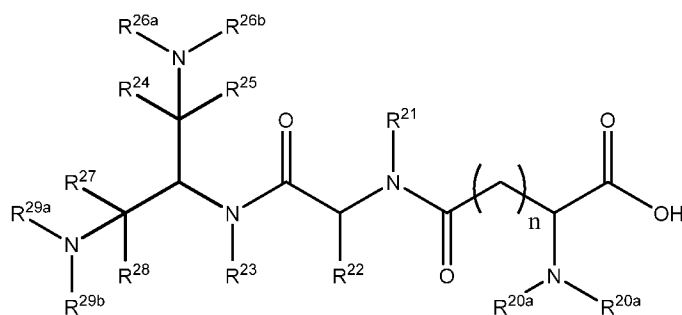
[00275] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 7B.



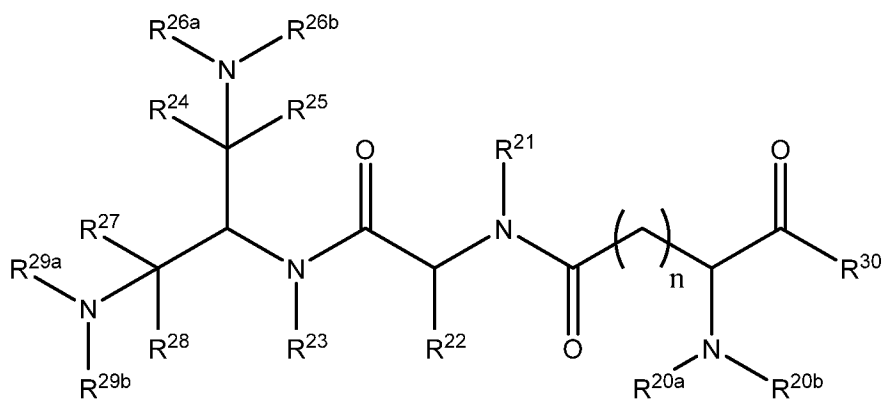
[00276] In one aspect, compounds of type 7.1, and similar compounds, can be prepared according to reaction **Scheme 7B** above. Thus, compounds of type 7.3 can be prepared by deprotection of an appropriate amide, e.g., 6.4 as shown above. The deprotection is carried out in the presence of an appropriate acid, e.g., trifluoroacetic acid, followed by addition of an appropriate base, e.g., sodium hydroxide, in an appropriate solvent, e.g., methanol. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 6.2), can be substituted in the reaction to provide substituted amine intermediates similar to Formula 7.3.

[00277] In various aspects, compounds of type 7.1, and similar compounds, can be further alkylated to afford compounds having a structure represented by a formula:



E. METHODS OF MAKING THE COMPOSITIONS

[00278] In one aspect, the invention relates to methods of making sweetener compositions, the method comprising the step of preparing a blend of a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$; wherein Ar^1 is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, $-\text{OH}$, and C1-C4 alkoxy; wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; wherein R^{30} is selected from $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and $-\text{NH}_2$; and a bulking agent.

[00279] In a further aspect, the method further comprises adjusting the sweetness of the sweetener composition by adding a low intensity sweetener.

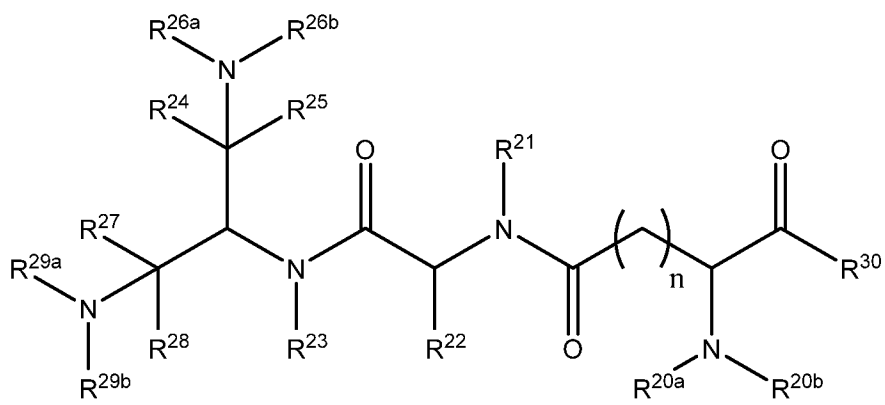
[00280] In a further aspect, the low intensity sweetener is added in an amount of from about 0.1 wt% to about 3 wt%. In a still further aspect, the low intensity sweetener is added in an amount of from about 0.5 wt% to about 3 wt%. In yet a further aspect, the low intensity sweetener is added in an amount of from about 1 wt% to about 3 wt%. In an even further aspect, the low intensity sweetener is added in an amount of from about 0.1 wt% to about 1 wt%. In a still further aspect, the low intensity sweetener is added in an amount of from about 0.1 wt% to about 0.5 wt%.

[00281] In a further aspect, the method further comprises adjusting the sweetness of the sweetener composition by adding a high intensity sweetener.

[00282] In a further aspect, the high intensity sweetener is added in an amount of from about 0.1 wt% to about 3 wt%. In a still further aspect, the high intensity sweetener is added in an amount of from about 0.5 wt% to about 3 wt%. In yet a further aspect, the high intensity sweetener is added in an amount of from about 1 wt% to about 3 wt%. In an even further aspect, the high intensity sweetener is added in an amount of from about 0.1 wt% to about 1 wt%. In a still further aspect, the high intensity sweetener is added in an amount of from about 0.1 wt% to about 0.5 wt%.

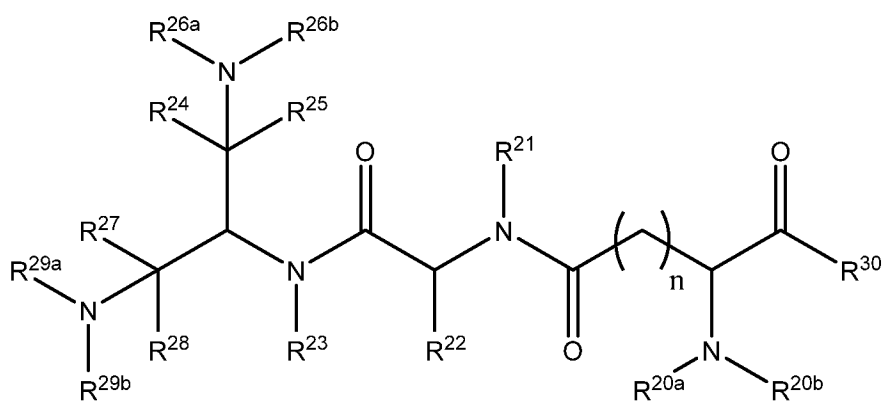
F. METHODS OF SWEETENING PRODUCTS AND MEDICAMENTS

[00283] In one aspect, the invention relates to methods of sweetening an orally ingestible products, the method comprising incorporating therein a composition comprising a compound having a structure represented by a formula:



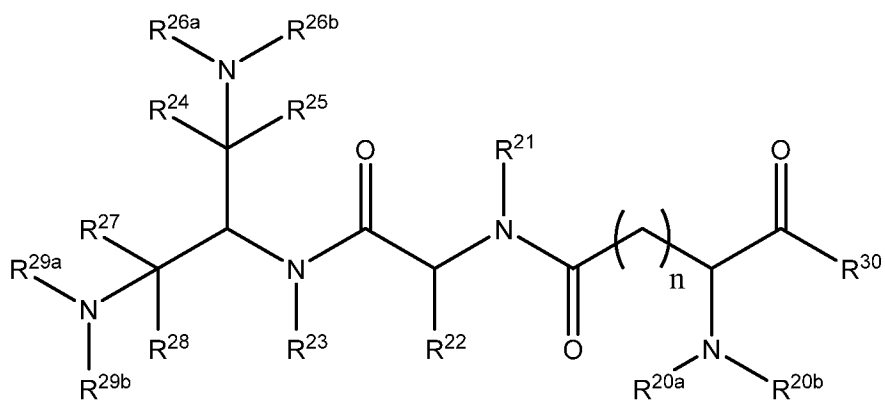
wherein n is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$; wherein Ar^1 is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, $-\text{OH}$, and C1-C4 alkoxy; wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and wherein R^{30} is selected from $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and $-\text{NH}_2$. In a further aspect, the orally ingestible product is selected from food products, beverages, chewing gum compositions, breath fresheners, confectionary products, chocolates, and biscuits.

[00284] In one aspect, the invention relates to methods of sweetening oral products, the method comprising incorporating therein a composition comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$; wherein Ar^1 is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, $-\text{OH}$, and C1-C4 alkoxy; wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and wherein R^{30} is selected from $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and $-\text{NH}_2$. In a further aspect, the oral product is selected from mouthwash and toothpaste.

[00285] In one aspect, the invention relates to methods of sweetening medicaments, the method comprising incorporating therein a composition comprising a compound having a structure represented by a formula:



wherein *n* is an integer selected from 1, 2, 3, and 4; wherein each of R^{20a}, R^{20b}, R²¹, R²³, R^{26a}, R^{26b}, R^{29a}, and R^{29b} is independently selected from hydrogen and C1-C4 alkyl; wherein R²² is selected from hydrogen, C1-C4 alkyl, -CH₂SeH, -CH₂SH, -CH₂CH₂SH, -CH₂CH₂SCH₃, and -CH₂Ar¹; wherein Ar¹ is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy; wherein each of R²⁴, R²⁵, R²⁷, and R²⁸ is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and wherein R³⁰ is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂.

[00286] The disclosed compounds may be used as a sweetener for food and beverage products. For example, approximately 50 g of sugar is typically used to sweeten a 12 ounce can of soda. The same sweetness can be achieved with the present sweetener using only about 0.1 g. Indeed, this sweetener is about 500 times sweeter than sucrose.

[00287] A suitable sweetenable composition can be any material suitable for sweetening with a sweetener, preferably an orally ingestible composition. By the term “orally ingestible composition,” as used herein, is meant substances which are contacted with the mouth of human or animal, including substances which are taken into and subsequently ejected from the mouth and substances which are drunk, eaten, swallowed or otherwise ingested, and are safe for human or animal consumption when used in a generally acceptable range.

[00288] There are no restrictions on the type of orally ingestible compositions encompassed by embodiments of this invention as long as they are safe for human or animal consumption when used in a generally acceptable range. Compositions that may be sweetened with compounds of the present invention include foods, beverages, pharmaceuticals, nutraceuticals, oral hygienic or cosmetic products, and the like. Non-limiting examples of such products include non-carbonated and carbonated beverages such as colas, ginger ales, root beers, ciders, fruit-flavored soft drinks (*i.e.*, citrus-flavored soft drinks such as lemon-lime or orange), powdered soft drinks (*i.e.*, cola, juice, tea, water, coffee), and the like; fruit juices originating in fruits or vegetables, fruit juices including squeezed juices or the like, fruit juices containing fruit particles, fruit beverages, fruit juice beverages, beverages containing fruit juices, beverages with fruit flavorings, vegetable juices, juices containing vegetables, and mixed juices containing fruits and vegetables; sport drinks, energy drinks, near water and the like drinks (*i.e.*, water with natural or artificial flavorings); tea type or favorite type beverages such as coffee, cocoa, black tea, green tea, white tea, yellow tea, oolong tea and the like; beverages containing milk components such as milk beverages, coffee containing milk components, café au lait, milk tea, fruit milk beverages, drinkable yogurt, lactic acid bacteria beverages or the like; dairy products; bakery products; desserts such as yogurt, jellies, drinkable jellies, puddings, Bavarian cream, blancmange, cakes, brownies, mousse and the like, sweetened food products eaten at tea time or following meals; frozen foods; cold confections, *i.e.* types of ice cream such as ice cream, ice milk, lacto-ice and the like (food products in which sweeteners and various other types of raw materials are added to milk products, and the resulting mixture is agitated and frozen), and ice confections such as sherbets, dessert ices and the like (food products in which various other types of raw materials are added to a sugary liquid, and the resulting mixture is agitated and frozen); ice cream; general confections, *i.e.*, baked confections or steamed confections such as cakes, crackers, biscuits, buns with bean-jam filling and the like; rice cakes and snacks; table top products; general sugar confections such as chewing gum (*i.e.* including compositions which comprise a substantially water-insoluble, chewable gum base, such as chicle or substitutes thereof, including jetulong, guttakay rubber or certain comestible natural synthetic resins or waxes), hard candy, soft candy, mints, nougat candy, jelly beans and the like; sauces including fruit flavored sauces, chocolate sauces and the like; edible gels; crèmes including butter crèmes, flour pastes, whipped cream and the like; jams including strawberry jam, marmalade and the

like; breads including sweet breads and the like or other starch products; spices; general condiments including seasoned soy sauce used on roasted meats, roast fowl, barbecued meat and the like, as well as tomato catsup, sauces, noodle broth and the like; processed agricultural products, livestock products or seafood; processed meat products such as sausage and the like; retort food products, pickles, preserves boiled in soy sauce, delicacies, side dishes; snacks such as potato chips, cookies, or the like; cereal products; drugs or quasi-drugs that are administered orally or used in the oral cavity (*i.e.*, vitamins, cough syrups, cough drops, chewable medicine tablets, amino acids, bitter-tasting agents, acidulants or the like), wherein the drug may be in solid, liquid, gel, or spray form such as a pill, tablet, spray, capsule, syrup, drop, troche agent, powder, and the like; personal care products such as other oral compositions used in the oral cavity such as mouth freshening agents, gargling agents, mouth rinsing agents, toothpaste, tooth polish, dentrifices, mouth sprays, teeth whitening agents and the like; dietary supplements; tobacco substitutes formulated from non-tobacco materials; animal feed; nutraceutical products, which includes any food or part of a food that may provide medicinal or health benefits, including the prevention and treatment of disease *i.e.*, cardiovascular disease and high cholesterol, diabetes, osteoporosis, inflammation, or autoimmune disorders), non-limiting examples of nutraceuticals include naturally nutrient-rich or medicinally active food, such as garlic, soybeans, antioxidants, phytosterols and phytostanols and their esters, fibers, glucosamine, chondroitin sulfate, ginseng, ginko, Echinacea, or the like; other nutrients that provide health benefits, such as amino acids, vitamins, minerals, carotenoids, dietary fiber, fatty acids such as omega-3 or omega-6 fatty acids, DHA, EPA, or ALA which can be derived from plant or animal sources (*i.e.*, salmon and other cold-water fish or algae), flavonoids, phenols, polyphenols (*i.e.*, catechins, proanthocyanidins, procyanidins, anthocyanins, quercetin, resveratrol, isoflavones, curcumin, punicalagin, ellagitannin, citrus flavonoids such as hesperidin and naringin, and chlorogenic acid), polyols, prebiotics/probiotics, phytoestrogens, sulfides/thiols, policosanol, saponin, rubisco peptide, appetite suppressants, hydration agents, autoimmune agents, C-reactive protein reducing agents, or anti-inflammatory agents; or any other functional ingredient that is beneficial to the treatment of specific diseases or conditions, such as diabetes, osteoporosis, inflammation, or high cholesterol levels in the blood.

G. METHODS OF USING THE COMPOUNDS AND COMPOSITIONS

[00289] The compounds and pharmaceutical compositions of the invention are useful to sweeten foods, beverages, medicines, and other consumable products. Examples of consumable products include, but are not limited to, chewing gum, toothpaste, mouthwash, carbonated beverages, acid-pH soft drinks, tea, coffee, extruded food products (*i.e.*, breakfast cereals and snack foods), microwave food products, glazed food products (*i.e.*, honey baked hams), hard and soft candies (*i.e.*, caramels and cough drops), deep fried food products (*i.e.*, doughnuts), confectionary foods and tablets, baked goods, dietetic foods, and medicaments.

1. CONSUMABLE PRODUCTS

[00290] In various aspects, this invention relates to foods, beverages, other beverage products such as beverage concentrates and the like, and other consumables such as toothpaste, mouthwash, and chewing gum. Thus, in one aspect the invention relates to consumable products admixed with an effective amount of the disclosed compounds and/or compositions.

[00291] In one aspect, the invention relates to orally ingestible products sweetened with the disclosed compounds and/or compositions. Exemplary orally ingestible products include, but are not limited to, food products, beverages, chewing gum compositions, breath fresheners, confectionary products, chocolates, and biscuits. In a further aspect, the food product is selected from extruded food products, microwave food products, glazed food products, deep fried food products, dietetic food products, and baked goods. In a still further aspect, the beverage is selected from a carbonated beverage, a soft drink, a tea, a coffee, a calorie-reduced beverage, and a dietary beverage. In yet a further aspect, the carbonated beverage is cola. In an even further aspect, the confectionary product is selected from a hard candy and a soft candy.

[00292] In one aspect, the invention relates to oral products sweetened with the disclosed compounds and/or compositions. Exemplary oral products include, but are not limited to, mouthwash and toothpaste.

[00293] In a further aspect, the invention relates to beverages and other beverage products having formulations incorporating a non-nutritive sweetener in accordance with the present invention to meet market demand for nutritional characteristics or flavor profiles in beverages.

[00294] It has long been known to produce beverages of various formulations. Improved and new formulations are desirable to meet changing market demands. In particular, there is market demand for beverages having alternative nutritional characteristics, including, for example, lower calorie content. Also, there is market demand for beverages having alternative flavor profiles, including good taste, mouth feel, etc. In addition, there is consumer interest in beverages and other beverage products, such as beverage concentrates, etc. whose formulations make greater use of natural ingredients, that is, ingredients obtained from plants and other naturally occurring sources.

[00295] Development of new beverage formulations has faced obstacles. For example, U.S. patent No. 4,956,191 suggests that carbonated beverages that contain blends of saccharin or Stevia extract with aspartame tend to be less organoleptically pleasing than those containing sugar.

[00296] It is therefore an object of the present invention to provide foods, beverages, other beverage products, and other consumable products that incorporate a non-nutritive sweetener. It is an object of certain embodiments of the invention (that is, not necessarily all embodiments of the invention) to provide beverages and other beverage products having desirable taste properties and improved formulations.

[00297] In a further aspect, a beverage is provided. The beverage is sweetened with a non-nutritive sweetener in accordance with the invention. The beverage may be a reduced calorie beverage. As used herein, "reduced calorie beverage" means a beverage having at least a 25% reduction in calories per serving as compared to the full calorie version, typically a previously commercialized full-calorie version. The correlative meaning applies to beverage concentrates and other beverage products disclosed here. The beverage may also be a diet beverage. As used herein, "diet" means having fewer than 5 calories per serving, e.g., per 8 oz. for beverages. The reduced calorie beverage may be sweetened entirely with a non-nutritive sweetener in accordance with the present invention, alone or in combination with other nutritive or non-nutritive sweeteners known in the art, such as, for example, sucrose, fructose, glucose, aspartame, stevia, sucralose, etc.

[00298] In a further aspect, a beverage concentrate is provided. In a still further aspect, the beverage concentrate is a syrup. In yet a further aspect, the beverage concentrate is a dry powder mix. The beverage concentrate is sweetened with a non-nutritive sweetener in accordance with the present invention, alone or in combination with other nutritive or non-nutritive sweeteners known in the art, such as, for example, sucrose, fructose, glucose, aspartame, stevia, sucralose, etc.

[00299] It will be appreciated by those skilled in the art, given the benefit of the following description of certain exemplary embodiments of the products disclosed herein, that at least certain aspects of the invention have improved or alternative formulations suitable to provide desirable taste profiles, nutritional characteristics, etc. These and other aspects, features and advantages of the invention or of certain embodiments of the invention will be further understood by those skilled in the art from the following description of exemplary embodiments.

[00300] It should be understood that foods, beverages, other beverage products, and other consumables in accordance with this invention may have any of numerous different specific formulations or constitutions. The formulation of a product in accordance with this invention can vary to a certain extent, depending upon such factors as the product's intended market segment, its desired nutritional characteristics, flavor profile and the like. For example, it will generally be an option to add further ingredients to the formulation of a particular beverage embodiment, including any of the beverage formulations described below. Additional (i.e., more and/or other) sweeteners may be added, flavorings, electrolytes, vitamins, fruit juices or other fruit products, masking agents and the like, flavor enhancers, or carbonation can, for example, be added to any such formulation to vary the taste, mouth-feel, nutritional characteristics, etc. In general, a beverage in accordance with this disclosure typically comprises at least water, sweetener, acidulant, and flavoring. Exemplary flavorings which may be suitable for at least certain formulations in accordance with this disclosure include cola flavoring, citrus flavoring, spice flavorings, and others. Carbonation (i.e., carbon dioxide gas) may be added for effervescence. Preservatives can be added if desired, depending upon the other ingredients, production technique, desired shelf life, etc. Optionally, caffeine can be added. Certain exemplary embodiments of the beverages disclosed herein are cola-flavored carbonated beverages, characteristically containing carbonated water, sweetener, kola nut extract, other

flavorings, caramel coloring, phosphoric acid, and optionally other ingredients. Additional and alternative suitable ingredients will be recognized by those skilled in the art given the benefit of this disclosure.

[00301] The beverage products disclosed herein include beverages, i.e., ready to drink liquid formulations, beverage concentrates and the like. Beverages include, i.e., carbonated and non-carbonated soft drinks, fountain beverages, frozen ready-to-drink beverages, coffee beverages, tea beverages, dairy beverages, powdered soft drinks, as well as liquid, slurry, or solid concentrates, flavored waters, enhanced waters, fruit juice, and fruit juice-flavored drinks, sport drinks, and alcoholic products. In various aspects, the beverage concentrates contemplated are prepared with an initial volume of water to which the additional ingredients are added. Full strength beverage compositions can be formed from the beverage concentrate by adding further volumes of water to the concentrate. Typically, for example, full strength beverages can be prepared from the concentrates by combining approximately 1 part concentrate with between approximately 3 to approximately 7 parts water. In a further aspect, the full strength beverage is prepared by combining 1 part concentrate with 5 parts water. In a still further aspect, the additional water used to form the full strength beverages is carbonated water. In yet a further aspect, a full strength beverage is directly prepared without the formation of a concentrate and subsequent dilution.

[00302] Water is a basic ingredient in the beverages disclosed herein, typically being the vehicle or primary liquid portion in which the remaining ingredients are dissolved, emulsified, suspended, or dispersed. Purified water can be used in the manufacture of various aspects of the beverages disclosed herein, and water of a standard beverage quality can be employed in order not to adversely affect beverage taste, odor, or appearance. The water typically will be clear, colorless, free from objectionable minerals, tastes and odors, free from organic matter, low in alkalinity, and of acceptable microbiological quality based on industry and government standards applicable at the time of producing the beverage. In various aspects, water is present at a level of from about 80 wt% to about 99.9 wt% of the beverage. In a further aspect, the water used in beverages and concentrates disclosed herein is “treated water,” which refers to water that has been treated to reduce the total dissolved solids of the water prior to optional supplementation, e.g., with calcium as disclosed in U.S. Patent No. 7,052,725. Methods of producing treated

water are known to those of ordinary skill in the art and include deionization, distillation, filtration and reverse osmosis (“r-o”), among others. The terms “treated water,” “purified water,” “demineralized water,” “distilled water,” and “r-o water” are understood to be generally synonymous in this discussion, referring to water from which substantially all mineral content has been removed, typically containing no more than about 500 ppm total dissolved solids, i.e. 250 ppm total dissolved solids.

[00303] Optionally, one or more additional sweeteners can be combined with the non-nutritive sweetener of the present invention. Those suitable for use in various embodiments of the beverages disclosed herein include non-nutritive natural and artificial or synthetic sweeteners. Suitable non-nutritive sweeteners and combinations of such sweeteners are selected for the desired nutritional characteristics, taste profile for the beverage, mouth-feel, and other organoleptic factors. Optional additional non-nutritive sweeteners suitable for at least certain exemplary embodiments include, for example, peptide-based sweeteners, i.e., aspartame, neotame, and alitame, and non-peptide based sweeteners, for example, sodium saccharin, calcium saccharin, acesulfame potassium, sodium cyclamate, calcium cyclamate, neohesperidin dihydrochalcone, and sucralose. Alitame may be less desirable for caramel-containing beverages where it has been known to form a precipitate. Other non-nutritive sweeteners suitable for at least certain exemplary embodiments include, for example, sorbitol, mannitol, xylitol, glycyrrhizin, D-tagatose, erythritol, meso-erythritol, malitol, maltose, lactose, fructo-oligosaccharides, Lo Han Guo juice concentrate, Lo Han Guo powder of mogroside V content from 2 to 99%, rebaudioside A, stevioside, other steviol glycosides, stevia rebaudiana extracts, acesulfame, aspartame, other dipeptides, cyclamate, sucralose, saccharin, xylose, arabinose, isomaltose, lactitol, maltitol, trehalose, and ribose; and protein sweeteners such as monatin, thaumatin, monellin, brazzein, L-alanine and glycine; related compounds; and mixtures of any of these sweeteners. It will be within the ability of those skilled in the art, given the benefit of this disclosure, to select suitable compositions for a particular embodiment of the beverage products disclosed herein.

[00304] As used herein, “taste” refers to a combination of sweetness perception, temporal effects of sweetness perception, i.e., onset and duration, off-tastes, i.e. bitterness and metallic taste, residual perception (aftertaste) and tactile perception, i.e. body and thickness. As used

herein, a “full-calorie” beverage formulation is one fully sweetened with a nutritive sweetener such as sucrose, glucose, or fructose. As further discussed below, certain exemplary embodiments of the beverage products disclosed herein comprise nutritive sweeteners in addition to the non-nutritive sweetener of the present invention. The term “nutritive sweetener” refers generally to sweeteners that provide significant caloric content in typical usage amounts, e.g., more than about 5 calories per 8 oz. serving of beverage. As used herein, a “potent sweetener” means a sweetener that is at least twice as sweet as sucrose, that is, a sweetener which on a weight basis requires no more than half the weight of sucrose to achieve an equivalent sweetness. For example, a potent sweetener may require less than one-half the weight of sucrose to achieve an equivalent sweetness in a beverage sweetened to a level of 10 degrees Brix with sucrose. Potent sweeteners include both nutritive and non-nutritive sweeteners. In addition, potent sweeteners include both natural potent sweeteners (i.e., steviol glycosides, Lo Han Guo, etc.) and artificial potent sweeteners (i.e., neotame, etc.). However, for certain market segments, a “natural” beverage product should include only natural potent sweeteners - including those of the present invention. The potency of the sweetener of the present invention has not been fully characterized, but is around 500 times that of sucrose. Commonly accepted potency figures for other potent sweeteners include, for example:

TABLE 1.

Sweetener	Potency Compared to Sucrose
Disclosed sweetener	500 times
Cyclamate	30 times
Stevioside	100-250 times
Mogroside V	100-300 times

Sweetener	Potency Compared to Sucrose
Rebaudioside A	150-300 times
Acesulfame-K	200 times
Aspartame	200 times
Saccharin	300 times
Neohesperidin dihydrochalcone	300 times
Sucralose	600 times
Neotame	8,000 times

[00305] As used herein, a “non-nutritive sweetener” is one that does not provide significant caloric content in typical usage amounts, i.e., one that imparts fewer than 5 calories per 8 oz. serving of beverage to achieve the sweetness equivalent of 10 Brix of sucrose. As used herein, “reduced calorie beverage” means a beverage having at least a 25% reduction in calories as compared to the full calorie version, typically a previously commercialized full-calorie version. As used herein, a “low-calorie beverage” has fewer than 40 calories per 8 oz. serving of beverage. As used herein, “zero-calorie” or “diet” means having fewer than 5 calories per serving, e.g., per 8 oz. for beverages.

[00306] In at least certain exemplary aspects of the beverages disclosed here, an optional sweetener component used in combination with a sweetener of the present invention can include nutritive, natural crystalline, or liquid sweeteners such as sucrose, liquid sucrose, fructose, liquid fructose, glucose, liquid glucose, glucose-fructose syrup from natural sources such as apple,

chicory, honey, etc., i.e., high fructose corn syrup, invert sugar, maple syrup, maple sugar, brown sugar, molasses, i.e., cane molasses, such as first molasses, second molasses, blackstrap molasses, and sugar beet molasses, sorghum syrup, or others. To achieve desired beverage uniformity, texture and taste, in certain exemplary aspects of the natural beverage products disclosed here, standardized liquid sugars as are commonly employed in the beverage industry can be used. Typically such standardized sweeteners are free of traces of non-sugar solids that could adversely affect the flavor, color or consistency of the beverage.

[00307] The sweeteners of the present invention are edible consumables suitable for consumption and for use in food, beverages, and other consumables. By “edible consumable” is meant a food or beverage or other consumable, or an ingredient of a food or beverage or other consumable for human or animal consumption. The sweetener can be a nutritive or non-nutritive, natural or synthetic beverage ingredient or additive (or mixtures of them) that provides sweetness to the beverage, i.e., that is perceived as sweet by the sense of taste. The perception of flavoring agents and sweetening agents may depend to some extent on the interrelation of elements. Flavor and sweetness may also be perceived separately, i.e., flavor and sweetness perception may be either dependent upon one another, or independent of one another, or partially dependent on one another. For example, when a large amount of a flavoring agent is used, a small amount of a sweetening agent may be readily perceptible, or vice versa. Thus, the oral and olfactory interaction between a flavoring agent and a sweetening agent may involve the interrelationship of elements.

[00308] Non-nutritive, high potency sweeteners such as those of the present invention are typically employed at a level of milligrams per fluid ounce of beverage, according to their sweetening power, any applicable regulatory provisions of the country where the beverage is to be marketed, the desired level of sweetness of the beverage, etc. It will be within the ability of those skilled in the art, given the benefit of this disclosure, to select suitable additional or alternative sweeteners for use in various embodiments of the beverage products disclosed herein.

[00309] As mentioned above, at least certain exemplary aspects of the beverages disclosed herein employ as additional sweeteners steviol glycosides, i.e., steviosides, rebaudiosides or related compounds, or mixtures. These compounds can be obtained by extraction or the like

from the stevia plant. Stevia (*e.g.*, *Stevia rebaudiana bectoni*) is a sweet-tasting plant. The leaves contain a complex mixture of natural sweet diterpene glycosides. Steviol glycosides, *e.g.*, steviosides and rebaudiosides, are components of Stevia that contribute to sweetness. Typically, these compounds include stevioside (4-13% dry weight), steviolbioside (trace amounts), the rebaudiosides, including rebaudioside A (2-4%), rebaudioside B (trace amounts), rebaudioside C (1-2%), rebaudioside D (trace amounts), rebaudioside E (trace amounts), and dulcoside A (0.4-0.7%).

[00310] Another additional sweetener that may be used is Lo Han Guo, which has various spellings and pronunciations and is sometimes abbreviated LHG. LHG can be obtained from fruits of the plant family Cucurbitaceae, tribe Jollifiae, subtribe Thladianthinae, genus *Siraitia*. LHG is often obtained from *S. grosvenorii*, *S. siamensis*, *S. silomaradjae*, *S. sikkimensis*, *S. africana*, *S. borneensis*, or *S. taiwaniana*. Suitable fruits include those from *S. grosvenorii*, which is often called Lo Han Guo fruit. LHG contains triterpene glycosides or mogrosides, which constituents may be used as sweeteners. Lo Han Guo is a potent sweetener that can be provided as a natural nutritive or natural non-nutritive sweetener in combination with the non-nutritive sweetener of the present invention. For example, Lo Han Guo juice concentrate may be a nutritive sweetener, while Lo Han Guo powder may be a non-nutritive sweetener. Lo Han Guo can be used as the juice or juice concentrate, powder, etc. Preferably LHG juice concentrate contains about 3 wt% to about 12 wt% mogrosides, *i.e.*, about 6 wt%, preferably of mogroside V, mogroside IV, 11-oxo-mogroside V, siamenoside and mixtures thereof. LHG juice concentrate can be produced, for example, as described in U.S. Patent No. 5,411,755. Sweeteners from other fruits, vegetables or plants also may be used as natural or processed sweeteners or sweetness enhancers in at least certain exemplary aspects of the beverages disclosed herein.

[00311] Acid used in beverages can serve one or more of several functions including, for example, lending tartness to the taste of the beverage, enhancing palatability, increasing thirst quenching effect, modifying sweetness, and acting as a mild preservative. Suitable acids are known and will be apparent to those skilled in the art given the benefit of this disclosure. Exemplary acids suitable for use in the beverage products disclosed herein include one or more of phosphoric, citric, malic, tartaric, lactic, formic, ascorbic, fumaric, gluconic, succinic, maleic

and adipic acids, and mixtures of any of them. The acid can be used in solution or solid form, for example, and in an amount sufficient to provide the desired pH for the beverage. Typically, for example, one or more acids of the acidulant are used in an amount, collectively, of from about 0.01 wt% to about 1.0 wt% of the beverage, i.e., from about 0.05 wt% to about 0.5 wt% of the beverage, such as 0.1 wt% to 0.25 wt% of the beverage, depending upon the acidulant used, desired pH, other ingredients used, etc. The pH of at least certain exemplary embodiments of the beverages disclosed herein can have a value within the range of from about 2.0 to about 5.0. The acid in certain exemplary embodiments enhances beverage flavor. Too much acid can impair the beverage flavor and result in sourness or other off-taste, while too little acid can make the beverage taste flat.

[00312] The particular acid or acids chosen and the amount used will depend, in part, on the other ingredients, the desired shelf life of the beverage product, as well as effects on the beverage pH, titratable acidity, and taste. Those skilled in the art, given the benefit of this disclosure, will recognize that when preparing beverage products that include peptide-based artificial sweeteners such as aspartame, the resulting beverage composition is best maintained below a certain pH to retain the sweetening effect of the artificial sweetener. In calcium-supplemented beverages, additional acid may be needed to maintain the solubility of the calcium. The presence of additional acid in the beverage composition, which increases the titratable acidity of the composition, can impart a more tart or sour taste to the resulting beverage. It will be within the ability of those skilled in the art, given the benefit of this disclosure, to select a suitable acid or combination of acids and the amounts of such acids for the acidulant component of any particular embodiment of the beverage products disclosed herein.

[00313] Certain exemplary embodiments of the beverage products disclosed herein also may contain small amounts of alkaline agents to adjust pH. Such agents include, i.e., potassium hydroxide, sodium hydroxide and potassium carbonate. For example, the alkaline agent potassium hydroxide may be used in an amount of from about 0.02 wt% to about 0.04 wt%, with an amount of about 0.03 wt% being typical for certain beverages. The amount will depend, of course, on the type of alkaline agents and on the degree to which the pH is to be adjusted.

[00314] The beverage products disclosed herein optionally contain a flavor composition, for example, natural and synthetic fruit flavors, botanical flavors, other flavors, and mixtures thereof. As used herein, the term “fruit flavor” refers generally to those flavors derived from the edible reproductive part of a seed plant. Included are both those wherein a sweet pulp is associated with the seed, i.e., banana, tomato, cranberry and the like, and those having a small, fleshy berry. The term berry also is used herein to include aggregate fruits, i.e., not “true” berries, but those that are commonly accepted as a berry. Also included within the term “fruit flavor” are synthetically prepared flavors made to simulate fruit flavors derived from natural sources. Examples of suitable fruit or berry sources include whole berries or portions thereof, berry juice, berry juice concentrates, berry purees and blends thereof, dried berry powders, dried berry juice powders, and the like.

[00315] Exemplary fruit flavors include the citrus flavors, i.e., orange, lemon, lime and grapefruit, and such flavors as apple, grape, cherry, and pineapple flavors and the like, and mixtures thereof. In various aspects the beverage concentrates and beverages comprise a fruit flavor component, i.e., a juice concentrate or juice. As used herein, the term “botanical flavor” refers to flavors derived from parts of a plant other than the fruit. As such, botanical flavors can include those flavors derived from essential oils and extracts of nuts, bark, roots and leaves. Also included within the term “botanical flavor” are synthetically prepared flavors made to simulate botanical flavors derived from natural sources. Examples of such flavors include cola flavors, tea flavors, and the like, and mixtures thereof. The flavor component can further comprise a blend of various flavors. In a further aspect, a cola flavor component is used or a tea flavor component. The particular amount of the flavor component useful for imparting flavor characteristics to the beverages of the present invention will depend upon the flavor(s) selected, the flavor impression desired, and the form of the flavor component. Those skilled in the art, given the benefit of this disclosure, will be readily able to determine the amount of any particular flavor component(s) used to achieve the desired flavor impression.

[00316] Juices suitable for use in at least certain exemplary embodiments of the beverage products disclosed here include, i.e., fruit, vegetable and berry juices. Juices can be employed in the present invention in the form of a concentrate, puree, single-strength juice, or other suitable forms. The term “juice” as used herein includes single-strength fruit, berry, or vegetable juice,

as well as concentrates, purees, milks, and other forms. Multiple different fruit, vegetable or berry juices can be combined, optionally along with other flavorings, to generate a beverage having the desired flavor. Examples of suitable juice sources include plum, prune, date, currant, fig, grape, raisin, cranberry, pineapple, peach, banana, apple, pear, guava, apricot, Saskatoon berry, blueberry, plains berry, prairie berry, mulberry, elderberry, Barbados cherry (acerola cherry), choke cherry, date, coconut, olive, raspberry, strawberry, huckleberry, loganberry, currant, dewberry, boysenberry, kiwi, cherry, blackberry, quince, buckthorn, passion fruit, sloe, rowan, gooseberry, pomegranate, persimmon, mango, papaya, litchi, lemon, orange, lime, tangerine, mandarin orange, tangelo, pomelo, grapefruit, etc. Numerous additional and alternative juices suitable for use in at least certain exemplary embodiments will be apparent to those skilled in the art given the benefit of this disclosure. In the beverages of the present invention employing juice, juice may be used, for example, at a level of at least about 0.2 wt% of the beverage. In various aspects, juice is employed at a level of from about 0.2 wt% to about 40 wt% of the beverage. Typically, juice is used, if at all, in an amount of from about 1 wt% to about 20 wt%.

[00317] Certain juices that are lighter in color can be included in the formulation of certain exemplary embodiments to adjust the flavor or increase the juice content of the beverage without darkening the beverage color. Examples of such juices include apple, pear, pineapple, peach, lemon, lime, orange, apricot, grapefruit, tangerine, rhubarb, cassis, quince, passion fruit, papaya, mango, guava, litchi, kiwi, mandarin, coconut, and banana. De-flavored and de-colored juices can be employed if desired.

[00318] Other flavorings suitable for use in at least certain exemplary embodiments of the beverage products disclosed here include, i.e., spice and other flavorings, such as cassia, clove, cinnamon, pepper, ginger, vanilla, cardamom, rhubarb, coriander, root beer, sassafras, ginseng, and others. Numerous additional and alternative flavorings suitable for use in at least certain exemplary embodiments will be apparent to those skilled in the art given the benefit of this disclosure. Flavorings can be in the form of an extract, oleoresin, juice concentrate, bottler's base, or other forms known in the art. In a further aspect, such spice or other flavors complement that of a juice or juice combination.

[00319] The one or more flavorings can be used in the form of an emulsion. A flavoring emulsion can be prepared by mixing some or all of the flavorings together, optionally together with other ingredients of the beverage, and an emulsifying agent. The emulsifying agent may be added with, before, or after the other flavorings. In various aspects, the emulsifying agent is water-soluble. Exemplary suitable emulsifying agents include gum acacia, modified starch, carboxymethylcellulose, gum tragacanth, gum ghatti and other suitable gums. Additional suitable emulsifying agents will be apparent to those skilled in the art of beverage formulations, given the benefit of this disclosure. The emulsifier in exemplary embodiments comprises greater than about 3% of the mixture of flavorings and emulsifier. In certain exemplary embodiments the emulsifier is from about 5% to about 30% of the mixture. (Unless otherwise clearly stated, or otherwise clearly implied by context, these percentages - and all other percentages (or fractions) mentioned in this disclosure - should be understood to refer to the stated percentage (or fraction) by mass.

[00320] Carbon dioxide is used to provide effervescence to certain exemplary embodiments of the beverages disclosed herein. Any of the techniques and carbonating equipment known in the art for carbonating beverages can be employed. Carbon dioxide can enhance the beverage taste and appearance and can aid in safeguarding the beverage purity by inhibiting and destroying objectionable bacteria. In various aspects, the beverage has a CO₂ level up to about 7.0 volumes carbon dioxide. Typical embodiments may have, for example, from about 0.5 to 5.0 volumes of carbon dioxide. As used here, one “volume” of carbon dioxide is defined as the amount of carbon dioxide absorbed by any given quantity of water at 60 °F (16 °C) and 1.0 atmosphere pressure. A “volume” of gas occupies the same space as does the water (or liquid) by which it is absorbed at the stated temperature and pressure. The carbon dioxide content can be selected by those skilled in the art based on the desired level of effervescence and the impact of the carbon dioxide on the taste or mouth feel of the beverage. The carbonation can be natural or synthetic.

[00321] Optionally, caffeine can be added to various embodiments of the beverages disclosed herein. The amount of caffeine added is determined by the desired beverage properties, any applicable regulatory provisions, etc. In various aspects, caffeine is included at a level of 0.02 wt% or less of the beverage. The caffeine must be of a purity acceptable for use in foods and beverages. The caffeine can be natural or synthetic in origin.

[00322] The beverage concentrates and beverages disclosed herein may contain additional ingredients, including, generally, any of those typically found in beverage formulations. These additional ingredients, for example, can typically be added to a stabilized beverage concentrate. Examples of such additional ingredients include, but are not limited to, caffeine, caramel and other coloring agents or dyes, antifoaming agents, gums, emulsifiers, tea solids, cloud components, and mineral and non-mineral nutritional supplements. Examples of non-mineral nutritional supplement ingredients are known to those of ordinary skill in the art and include, for example, antioxidants and vitamins, including Vitamins A, D, E (tocopherol), C (ascorbic acid), B (thiamine), B2 (riboflavin), B6, B12, and K, niacin, folic acid, biotin, and combinations thereof. The optional non-mineral nutritional supplements are typically present in amounts generally accepted under good manufacturing practices. Exemplary amounts are between about 1% and about 100% recommended daily value (RDV), where an RDV is established. In various aspects, the non-mineral nutritional supplement ingredient(s) are present in an amount of from about 5% to about 20% RDV, where established.

[00323] Preservatives may be used in at least certain embodiments of the beverages disclosed herein. That is, at least certain exemplary embodiments contain an optional dissolved preservative or preservation system. Solutions with a pH below 4 and especially those below 3 typically are “microstable,” *i.e.*, they resist growth of microorganisms, and so are suitable for longer term storage prior to consumption without the need for further preservatives. However, an additional preservative system can be used if desired. If a preservative system is used, it can be added to the beverage product at any suitable time during production, *i.e.*, in some cases prior to the addition of the sweetener and in other cases after. As used herein, the terms “preservation system” or “preservatives” include all suitable preservatives approved for use in food and beverage compositions, including, without limitation, such known chemical preservatives as benzoates, *i.e.*, sodium, calcium, and potassium benzoate, sorbates, *i.e.*, sodium, calcium, and potassium sorbate, citrates, *i.e.*, sodium citrate and potassium citrate, polyphosphates, *i.e.*, sodium hexametaphosphate (SHMP), and mixtures thereof, and antioxidants such as ascorbic acid, EDTA, BHA, BHT, TBHQ, dehydroacetic acid, dimethyldicarbonate, ethoxyquin, heptylparaben, and combinations thereof. Preservatives can be used in amounts not exceeding mandated maximum levels under applicable laws and regulations. The level of preservative used typically is adjusted according to the planned final product pH, as well as an evaluation of the

microbiological spoilage potential of the particular beverage formulation. The maximum level employed typically is about 0.05 wt% of the beverage. It will be within the ability of those skilled in the art, given the benefit of this disclosure, to select a suitable preservative or combination of preservatives for beverages according to this disclosure.

[00324] Other methods of beverage preservation suitable for at least certain exemplary embodiments of the beverage products disclosed herein include, i.e., heat treatment or thermal processing steps, such as hot filling and tunnel pasteurization. Such steps can be used to reduce yeast, mold and microbial growth in the beverage products. For example, U.S. patent No. 4,830,862 to Braun et al. discloses the use of pasteurization in the production of fruit juice beverages as well as the use of suitable preservatives in carbonated beverages. U.S. patent No. 4,925,686 to Kastin discloses a heat-pasteurized freezable fruit juice composition which contains sodium benzoate and potassium sorbate.

[00325] Other methods of beverage preservation suitable for at least certain exemplary embodiments of the beverage products disclosed herein include, i.e., aseptic packaging, heat treatment, or thermal processing steps, such as hot filling and tunnel pasteurization. Such steps can be used to reduce yeast, mold and microbial growth in the beverage products. For example, U.S. Patent No. 4,830,862 to Braun et al. discloses the use of pasteurization in the production of fruit juice beverages as well as the use of suitable preservatives in carbonated beverages. U.S. Patent No. 4,925,686 to Kastin discloses a heat-pasteurized freezable fruit juice composition that contains sodium benzoate and potassium sorbate. In general, heat treatment includes hot fill methods typically using high temperatures for a short time, i.e., about 190 °F for 10 seconds, tunnel pasteurization methods typically using lower temperatures for a longer time, i.e., about 160 °F for 10-15 minutes, and retort methods typically using, i.e., about 250 °F for 3-5 minutes at elevated pressure, i.e., at pressure above 1 atmosphere.

[00326] Those of ordinary skill in the art will understand that, for convenience, some ingredients are described here in certain cases by reference to the original form of the ingredient in which it is used in formulating or producing the beverage product. Such original form of the ingredient may differ from the form in which the ingredient is found in the finished beverage product. Thus, for example, in certain exemplary embodiments of the beverage products

according to this disclosure, sucrose and liquid sucrose would typically be substantially homogenously dissolved and dispersed in the beverage. Likewise, other ingredients identified as a solid, concentrate (i.e., juice concentrate), etc. would typically be homogenously dispersed throughout the beverage or throughout the beverage concentrate, rather than remaining in their original form. Thus, reference to the form of an ingredient of a beverage product formulation should not be taken as a limitation on the form of the ingredient in the beverage product, but rather as a convenient means of describing the ingredient as an isolated component of the product formulation.

[00327] In a further aspect, the consumable product is selected from a food, a beverage, and a medicine.

[00328] In a further aspect, the effective amount is sufficient to give the product a sweeter taste than an otherwise identical consumable product that lacks the composition.

[00329] In a further aspect, the food product is selected from extruded food products, microwave food products, glazed food products, deep fried food products, dietetic food products, and baked goods.

[00330] In a further aspect, the confectionary product is selected from a hard candy and a soft candy.

[00331] In a further aspect, the beverage is selected from carbonated beverages, acid-pH soft drinks, teas, coffees, calorie-reduced beverages, and dietary beverages. In a still further aspect, the carbonated beverage is a cola.

2. MEDICAMENTS

[00332] In various aspects, the invention relates to medicaments sweetened with the disclosed compounds and/or compositions.

H. EXAMPLES

[00333] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely

exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (*e.g.*, amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

1. HPLC ANALYSIS OF THE VEGGISWEET LIQUID PRODUCT

[00334] VeggiSweet is a commercially available liquid product. It is a concentrated sweetener. However, the active sweetening agent has thus far remained elusive. Herein, the active sweetener was isolated and its structure characterized. It is a potent sweetener, with essentially no aftertaste. The active sweetener is a compound that has not previously been described.

a. PREPARATION OF SAMPLE SOLUTIONS

[00335] VeggiSweet was purchased commercially. Its “Nutrition Facts” label identifies its ingredients as “deionized water, micronized spinach protein, algae extract, alfalfa extract, and Jerusalem artichoke extract in a colloidal matrix solution.” One bottle of VeggiSweet, about 30 mL, was concentrated to 2 mL by evaporation. The color of the concentrate was yellow (see FIG. 1). After passing through a 0.22 µm filter, the filtrate was injected into an HPLC instrument.

b. HPLC ANALYSIS OF THE VEGGISWEET LIQUID PRODUCT

[00336] HPLC analysis was performed on a Waters 600E system with an auto sampler and a photodiode array detector. The analysis was conducted on a Phenomenex Luna C18 column (250 mm x 4.6 mm, 5 µm). Mobile phase A was HPLC-grade acetonitrile. Mobile phase B was HPLC-grade water. The gradient eluting mobile phase was from A/B (15:85, v/v) to A/B (35:65, v/v), linearly from 0 to 10 min; the ratio was maintained from 10 to 20 min (A/B (35:65, v/v)); from A/B (35:65, v/v) to A/B (95:5, v/v), linearly from 20 to 30 min; the ratio was maintained from 30 to 40 min (A/B (95:5, v/v)); and from A/B (95:5, v/v) to A/B (15:85, v/v), linearly from 40 to 50 min. The flow rate was set at 1.0 mL/min, the column temperature was maintained at 30 °C, and the injection volume was 20.0 µL. The wavelengths of PDA detection ranged from 200 to 600 nm, and a chromatogram was generated at 210 nm.

c. CHROMATOGRAM

[00337] HPLC analysis at 210 nm showed the retention time of the main compound in VeggiSweet at 13.5 min (FIG. 2).

2. ISOLATION OF SWEETENER FROM THE VEGGISWEET LIQUID PRODUCT

a. EXTRACTION

[00338] A bottle of VeggiSweet (~30 mL) was added to 100 mL ethanol to facilitate evaporation. This water and ethanol mixture was concentrated in a rotary evaporator to dryness. Then 15 mL of methanol was added to the dried product, and extracted at room temperature. The methanol extraction resulted in two parts: the methanol-soluble part, and the methanol-insoluble (precipitate) part. The two parts were separated through centrifugation (5000 rpm, 10 min). The filtrate was injected into the HPLC instrument directly. The precipitate was re-dissolved in water, and injected into the HPLC instrument. Only the methanol-soluble part contained the target compound (sweetener). See FIG. 2.

b. ISOLATION AND PURIFICATION

[00339] A diagram of the isolation procedure is shown in FIG. 3. Briefly, ten (10) bottles of VeggiSweet liquid product were combined and concentrated in a rotary evaporator to dryness (the residue was brown). Then 50 mL methanol was added to dissolve. The methanol-soluble part was separated from the insoluble part by centrifugation (5000 rpm, 10 min). The methanol-soluble part (~50 mL) was concentrated to about 3 mL, which was then loaded into a Sephadex LH-20 chromatographic column containing about 150 g Sephadex LH-20 gel material. The sample was then eluted with methanol. Three eluent fractions were collected based on the color of eluents: designated Fraction 1, Fraction 2, and Fraction 3. Each of the three fractions was analyzed via HPLC under the following conditions: mobile phase A was HPLC-grade acetonitrile; mobile phase B was HPLC-grade water. The iso-line eluting mobile phase was from 0 to 20 min with A/B (20:80, v/v). The results showed that Fraction 2 contained nearly all of the target compound. See FIG. 4. Fraction 2 was dried on a rotary evaporator. The dried Fraction 2 was then dissolved in 1 mL water, which was then loaded onto a 4 g, C18 pre-packed chromatographic column. To obtain the purified target compound, one column volume (CV;

approximately 10 mL) of water was used to elute the column into a water sub-fraction labeled Water-1. Next, 5 CVs of water were used to elute the sample into a second water sub-fraction labeled Water-2. Finally, 3 CVs of methanol were used to elute the sample into a methanol sub-fraction labeled Methanol-1 (FIG. 5). The three parts were then separately analyzed by HPLC. HPLC analysis indicated that the target compound was almost entirely in the Water-2 fraction (FIG. 6).

c. DRYING THE SUGAR-FREE SWEETENER

[00340] The Water-2 fraction, about 50 mL, was freeze-dried for two days, affording 95 mg of a light yellow powder (FIG. 7). HPLC-UV analysis revealed that the isolated compound was about 95% pure.

3. STRUCTURAL ELUCIDATION

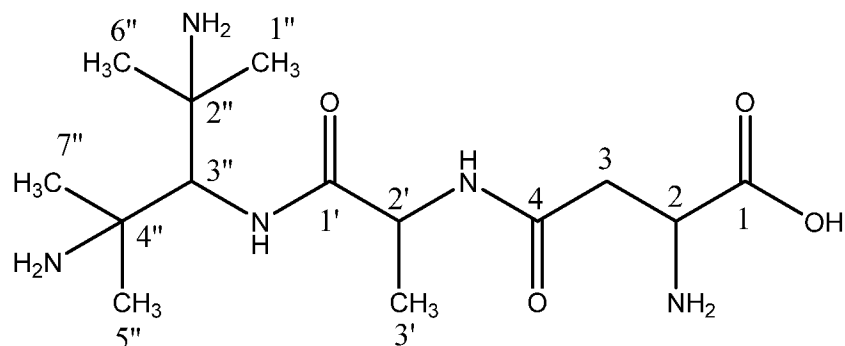
[00341] Data for ^1H -NMR (FIG. 8), ^{13}C -NMR (FIG. 9), DEPT-135 (FIG. 10), HSQC (FIG. 11), HMBC (FIG. 12), and H-H COSY (FIG. 13) were obtained on NMR instruments at the LSU Chemistry Core Facility, Louisiana State University, Baton Rouge, Louisiana.

[00342] The compound was determined to have the IUPAC name 2-amino-4-(1-(2,4-diamino-2,4-dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid. The compound has two chiral centers; the precise stereochemistry has not yet been elucidated. X-ray crystallography, for example, or other techniques known in the art could be used to determine the stereochemistry of the isolated compound.

[00343] Each of the four possible stereoisomers is within the scope of this invention, as are mixtures of the stereoisomers (whether racemic or non-racemic). Thus, in various aspects, the compound is selected from (2*R*)-4-(2*R*)-2-amino-4-(1-(2,4-diamino-2,4-dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, (2*R*)-4-(2*S*)-2-amino-4-(1-(2,4-diamino-2,4-dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, (2*S*)-4-(2*R*)-2-amino-4-(1-(2,4-diamino-2,4-dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid, and (2*S*)-4-(2*S*)-2-amino-4-(1-(2,4-diamino-2,4-dimethylpentan-3-ylamino)-1-oxopropan-2-ylamino)-4-oxobutanoic acid.

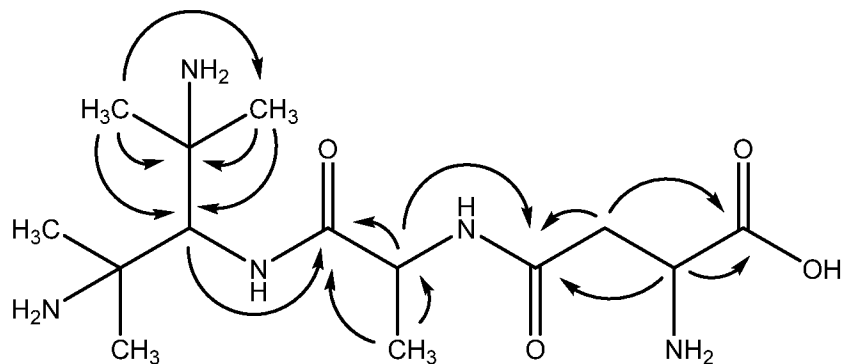
[00344] The sweetener has a molecular weight of 331 g/mol and a chemical formula of $C_{14}H_{29}N_5O_4$. The maximum UV absorption was present at 190 to 210 nm. The compound has two peptide bonds, several amino acid moieties, but contains no sugar moieties. The structure of the sweetener is shown in Scheme 8 below.

SCHEME 8.



[00345] The key correlative signals of HMBC ($H \rightarrow C$) and H-H COSY ($C \rightarrow C$) are shown in Scheme 9 below.

SCHEME 9.



[00346] Data for ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) of the novel sweetener compound (in Methanol- d_4) is illustrated in Table 2.

TABLE 2.

Position	C (ppm)	H (ppm)
1	175.2	-
2	52.4	4.08 (dd, J = 4.7, 9.0 Hz)
3	38.2	2.70 (dd, J = 4.7, 17.0 Hz) 2.60 (dd, J = 9.0, 17.0 Hz)
4	170.1	-
1'	175.2	-
2'	50.6	4.45 (q, J = 7.1 Hz)
3'	18.7	1.37 (d, J = 7.1 Hz)
1''	34.6	1.46 (s)
2''	48.1	-
3''	65.0	4.80 (s)
4''	48.1	-
5''	27.8	1.54 (s)
6''	27.8	1.54 (s)
7''	34.6	1.46 (s)

[00347] X-Ray crystallography could be conducted to determine the 3-dimensional structure.

4. MOLECULAR WEIGHT DETERMINATION

[00348] The target compound was analyzed via LC/MS (negative mode: $M^- = 330$, FIG. 14; positive mode: $M^+ = 332$; $M + Na^+ = 354$, FIG. 15).

5. TASTE OF THE ISOLATED TARGET COMPOUND

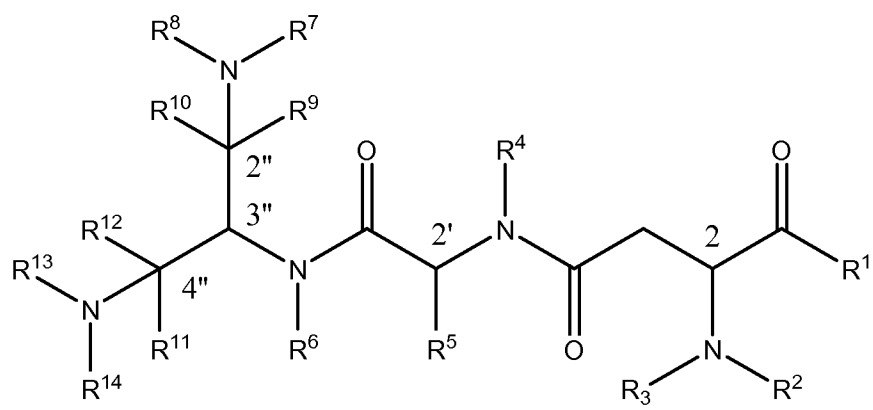
[00349] About 2.3 mg of the isolated target compound was dissolved in 3.8 mL water to make a solution with a concentration of 0.6 mg/mL. A 1:1 dilution produced an aqueous solution containing a concentration of 0.3 mg/mL sweetener. In a separate container, 718 mg of sucrose was dissolved in 4.85 mL water (sucrose control, to approximate the same concentration as would be found in a commercial soda having 50 g sucrose in a 12 ounce or 336 mL serving). The sucrose concentration in the control was 148 mg/mL. A sweetness taste test was performed. The 0.6 mg/mL sweetener solution was much sweeter than the sucrose control. The 0.3 mg/mL sweetener water solution was slightly sweeter than the sucrose control. The sweetener was therefore found to be about 500 times sweeter than sucrose. Neither the 0.6 mg/mL solution nor the 0.3 mg/mL solution imparted a perceptible aftertaste.

[00350] The complete disclosures of all references cited in this specification are hereby incorporated by reference. Also incorporated by reference is the complete disclosure of the inventors' earlier United States provisional application, serial number 61/917,425, filed December 18, 2013, a copy of which is included below as Appendix A. In the event of an otherwise irreconcilable conflict, however, the present specification shall control.

CLAIMS

What is claimed is:

1. A compound having a structure represented by a formula:



wherein R¹ is selected from halogen, -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, -NH₂, and C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkoxy, thioalkyl, and amino;

wherein each of R², R³, R⁴, R⁶, R⁷, R⁸, R¹³, and R¹⁴ is independently selected from hydrogen, halogen, -COOH, -CHO, -CH₂OH, -NH₂, and C1-C4 alkyl optionally substituted with 0, 1, 2, or 3 groups selected from alkyl, carboxylic acid, alcohol, ketone, aldehyde, and amino;

wherein each of R⁵, R⁹, R¹⁰, R¹¹, and R¹² is independently selected from hydrogen, methyl, -CH₂OH, -CH₂X, -CHX₂, -CHO, -COOH, -CH₂SH, and -CONH₂;

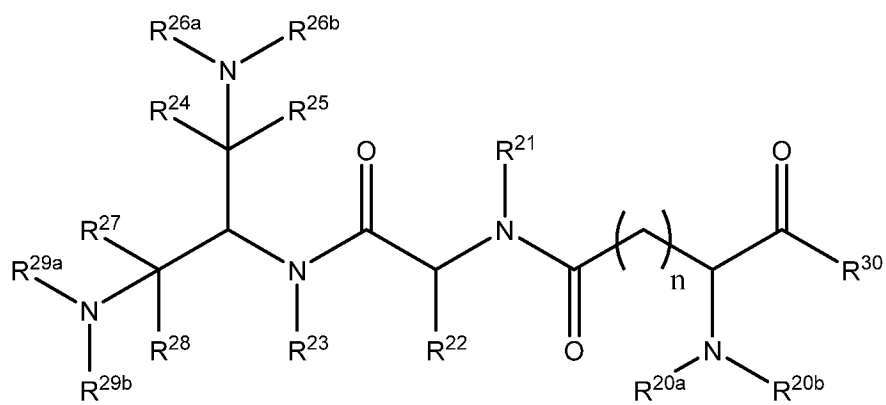
wherein each X, when present, is independently selected from fluoro, chloro, bromo, and iodo;

wherein each of the 2 and 2' carbon atoms are chiral centers, and wherein each chiral center is independently selected from the *R*- and *S*-stereoisomer, or a racemic mixture thereof;

wherein each of the 2'', 3'', and 4'' carbon atoms are optionally a chiral center, and wherein each chiral center, when present, is independently selected from the *R*- and *S*-stereoisomer, or a racemic mixture thereof; and

wherein either R¹ is not -OH; or wherein at least one of R², R³, R⁷, R⁸, R¹³, and R¹⁴ is not hydrogen; or wherein at least one of R⁵, R⁹, R¹⁰, R¹¹, and R¹² is not methyl.

2. A compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4;

wherein each of R^{20a}, R^{20b}, R²¹, R²³, R^{26a}, R^{26b}, R^{29a}, and R^{29b} is independently selected from hydrogen and C1-C4 alkyl;

wherein R²² is selected from hydrogen, C1-C4 alkyl, -CH₂SeH, -CH₂SH, -CH₂CH₂SH, -CH₂CH₂SCH₃, and -CH₂Ar¹;

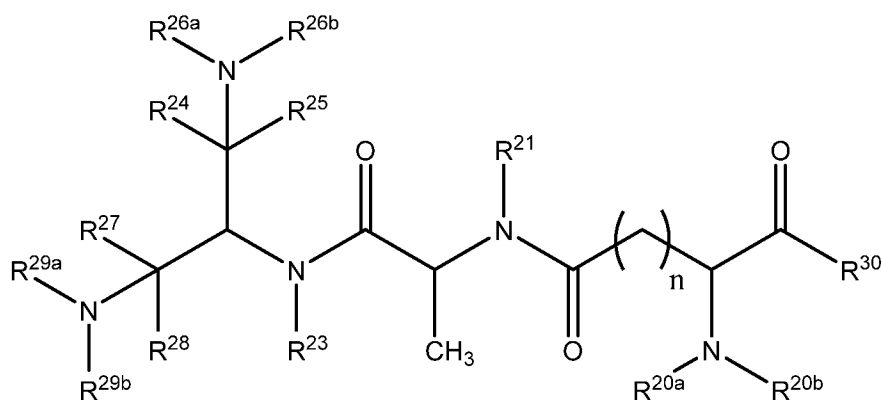
wherein Ar¹ is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, -OH, and C1-C4 alkoxy;

wherein each of R²⁴, R²⁵, R²⁷, and R²⁸ is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and

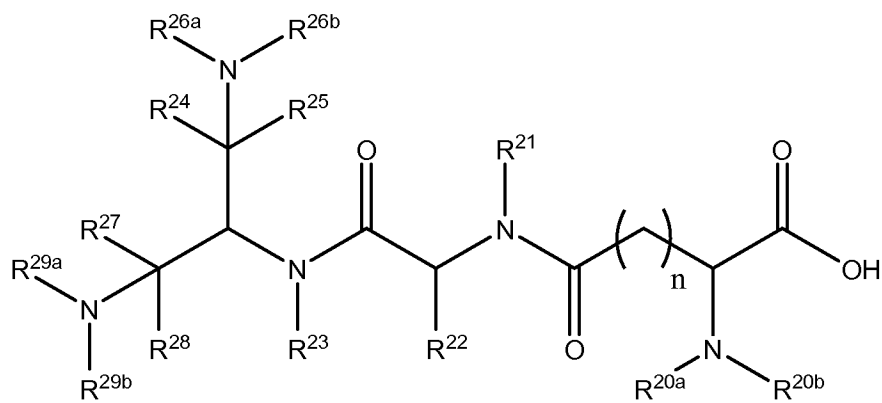
wherein R³⁰ is selected from -OH, -OCH₃, -OCH₂CH₃, -SH, -SCH₃, -SCH₂CH₃, and -NH₂.

3. The compound of claim 2, wherein n is 1.

4. The compound of claim 2, wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is hydrogen.
5. The compound of claim 2, wherein each of R^{22} , R^{24} , R^{25} , R^{27} , and R^{28} is methyl.
6. The compound of claim 2, wherein R^{30} is $-OH$.
7. The compound of claim 2, wherein the compound has a structure represented by a formula:

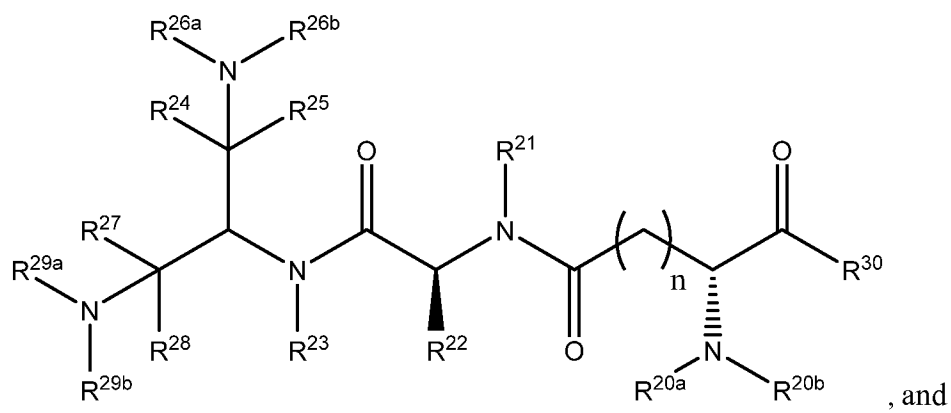
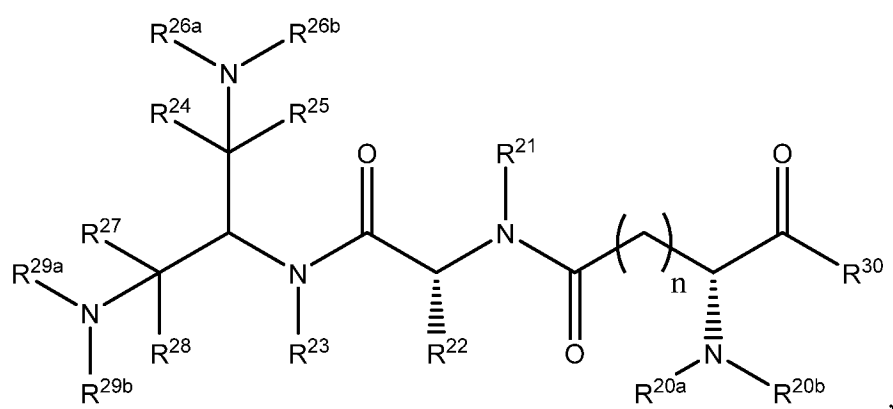
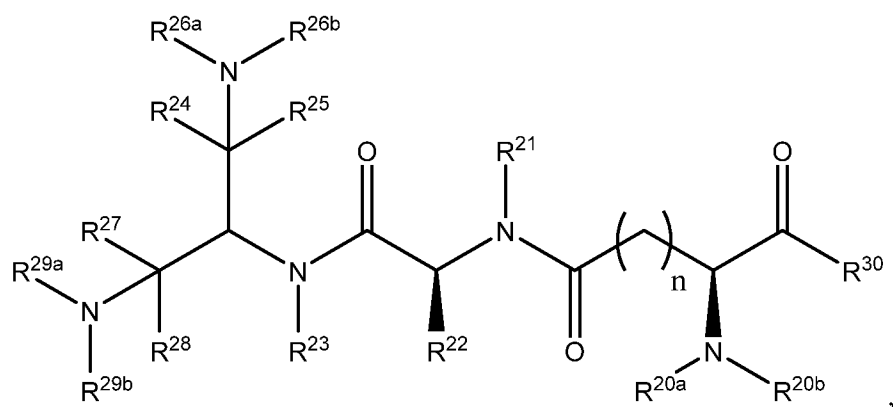


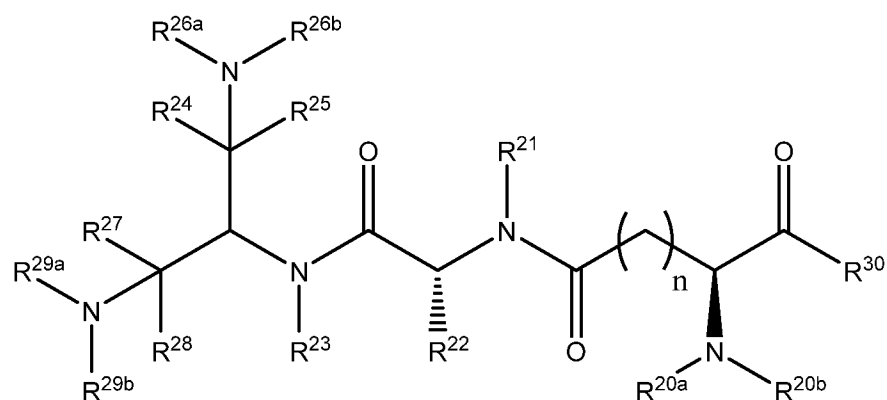
8. The compound of claim 2, wherein the compound has a structure represented by a formula:



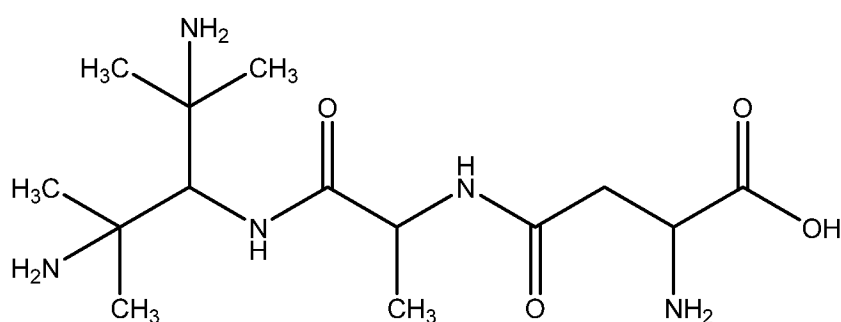
wherein n is an integer selected from 1 and 2.

9. The compound of claim 2, wherein the compound has a structure represented by a formula selected from:

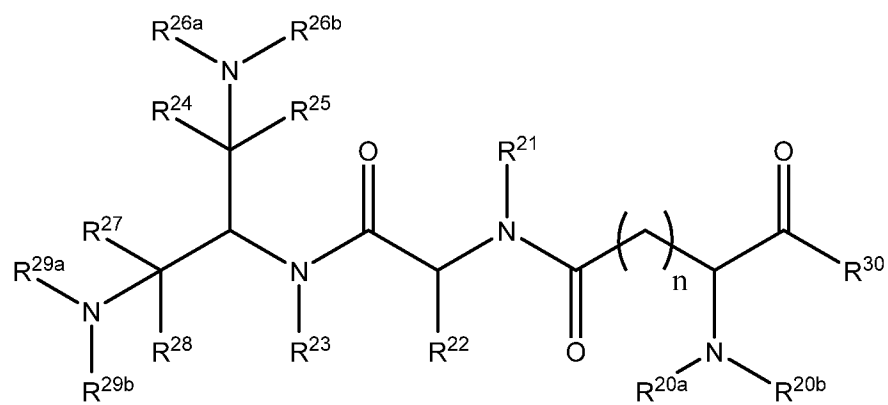




10. The compound of claim 2, wherein the compound is:



11. A composition comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4;

wherein each of R^{20a}, R^{20b}, R²¹, R²³, R^{26a}, R^{26b}, R^{29a}, and R^{29b} is independently selected from hydrogen and C1-C4 alkyl;

wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$;

wherein Ar^1 is selected from phenyl, indole, and imidazole and optionally substituted with 0 or 1 group selected from halogen, $-\text{OH}$, and C1-C4 alkoxy;

wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and

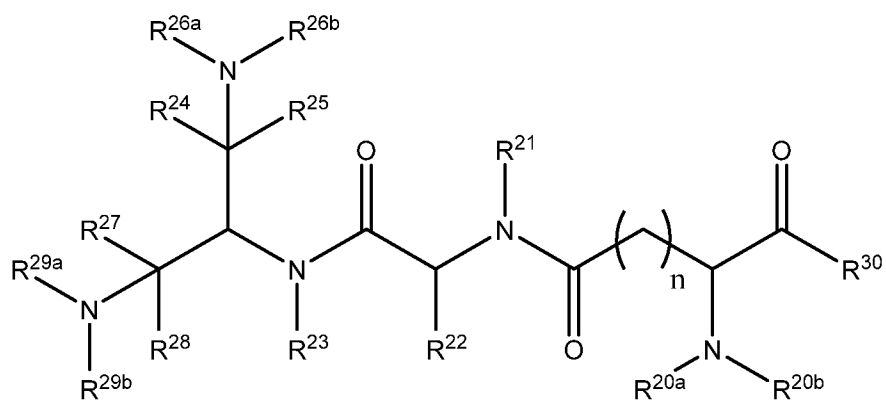
wherein R^{30} is selected from $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and $-\text{NH}_2$.

12. The composition of claim 15, wherein the composition is in particulate form.

13. The composition of claim 15, further comprising at least one agent selected from a carrier, a bulking agent, a flavoring agent, a low intensity sweetener, a high intensity sweetener, a decolorizing agent, a taste modifier, a plasticizer, a film-forming polymer, a salt, an internal film release agent, a carbohydrate, a cellulose, a gum, a food acid, a nutritive sweetener, a gelatin, a food grade wax emulsion, a colorant, a filler, a surfactant, a stabilizer, and an organic acid, or a mixture thereof.

14. The composition of claim 13, wherein the at least one agent is present in an amount of from about 0.001 wt% to about 5 wt%.

15. A composition comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4;

wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl;

wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$;

wherein Ar^1 is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, $-\text{OH}$, and C1-C4 alkoxy;

wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy;

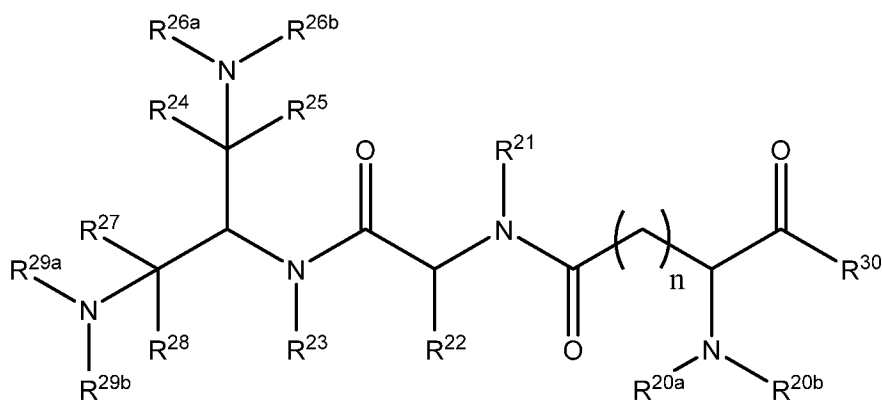
wherein R^{30} is selected from $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and $-\text{NH}_2$; and

a bulking agent; and

wherein the composition further comprises at least one of:

- (a) a carrier;
- (b) a flavoring agent;
- (c) a low intensity sweetener;
- (d) a high intensity sweetener;
- (e) a decolorizing agent;
- (f) a taste modifier;
- (g) a plasticizer;
- (h) a film-forming polymer;
- (i) a salt; and
- (j) an internal film release agent.

16. A method of sweetening an orally ingestible product, the method comprising incorporating therein a composition comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4;

wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl;

wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$;

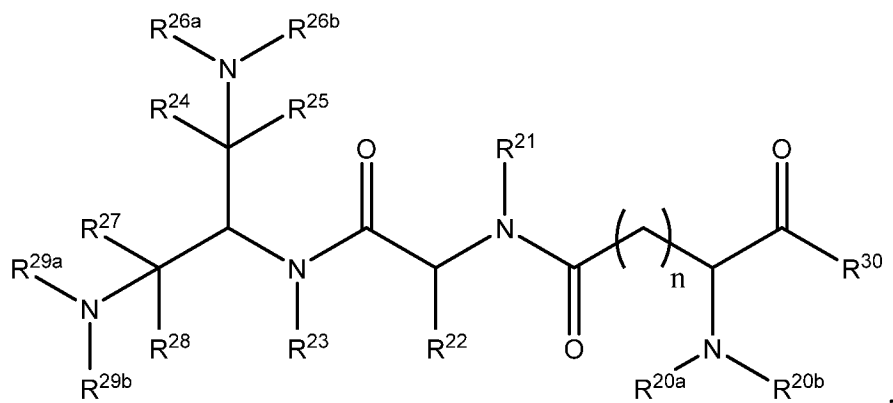
wherein Ar^1 is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, $-\text{OH}$, and C1-C4 alkoxy;

wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and

wherein R^{30} is selected from $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and $-\text{NH}_2$.

17. The method of claim 16, wherein the orally ingestible product is selected from a food product, a beverage, a chewing gum composition, a breath freshener, a confectionary product, a chocolate, and a biscuit.

18. A method of sweetening an oral product, the method comprising incorporating therein a composition comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4;

wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl;

wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$;

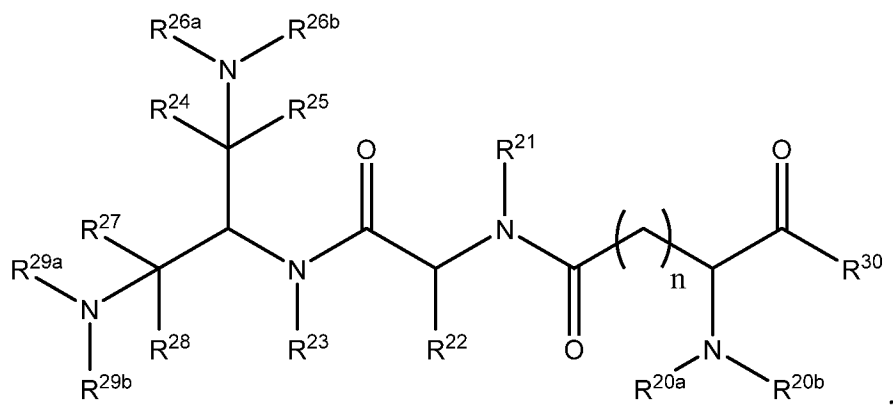
wherein Ar^1 is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, $-\text{OH}$, and C1-C4 alkoxy;

wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and

wherein R^{30} is selected from $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and $-\text{NH}_2$.

19. The method of claim 18, wherein the oral product is selected from mouthwash and toothpaste.

20. A method of sweetening a medicament, the method comprising incorporating therein a composition comprising a compound having a structure represented by a formula:



wherein n is an integer selected from 1, 2, 3, and 4;

wherein each of R^{20a} , R^{20b} , R^{21} , R^{23} , R^{26a} , R^{26b} , R^{29a} , and R^{29b} is independently selected from hydrogen and C1-C4 alkyl;

wherein R^{22} is selected from hydrogen, C1-C4 alkyl, $-\text{CH}_2\text{SeH}$, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SH}$, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, and $-\text{CH}_2\text{Ar}^1$;

wherein Ar^1 is selected from phenyl, indole, and imidazole and is optionally substituted with 0 or 1 group selected from halogen, $-\text{OH}$, and C1-C4 alkoxy;

wherein each of R^{24} , R^{25} , R^{27} , and R^{28} is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 alkoxy; and

wherein R^{30} is selected from $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and $-\text{NH}_2$.

1/15



FIG. 1

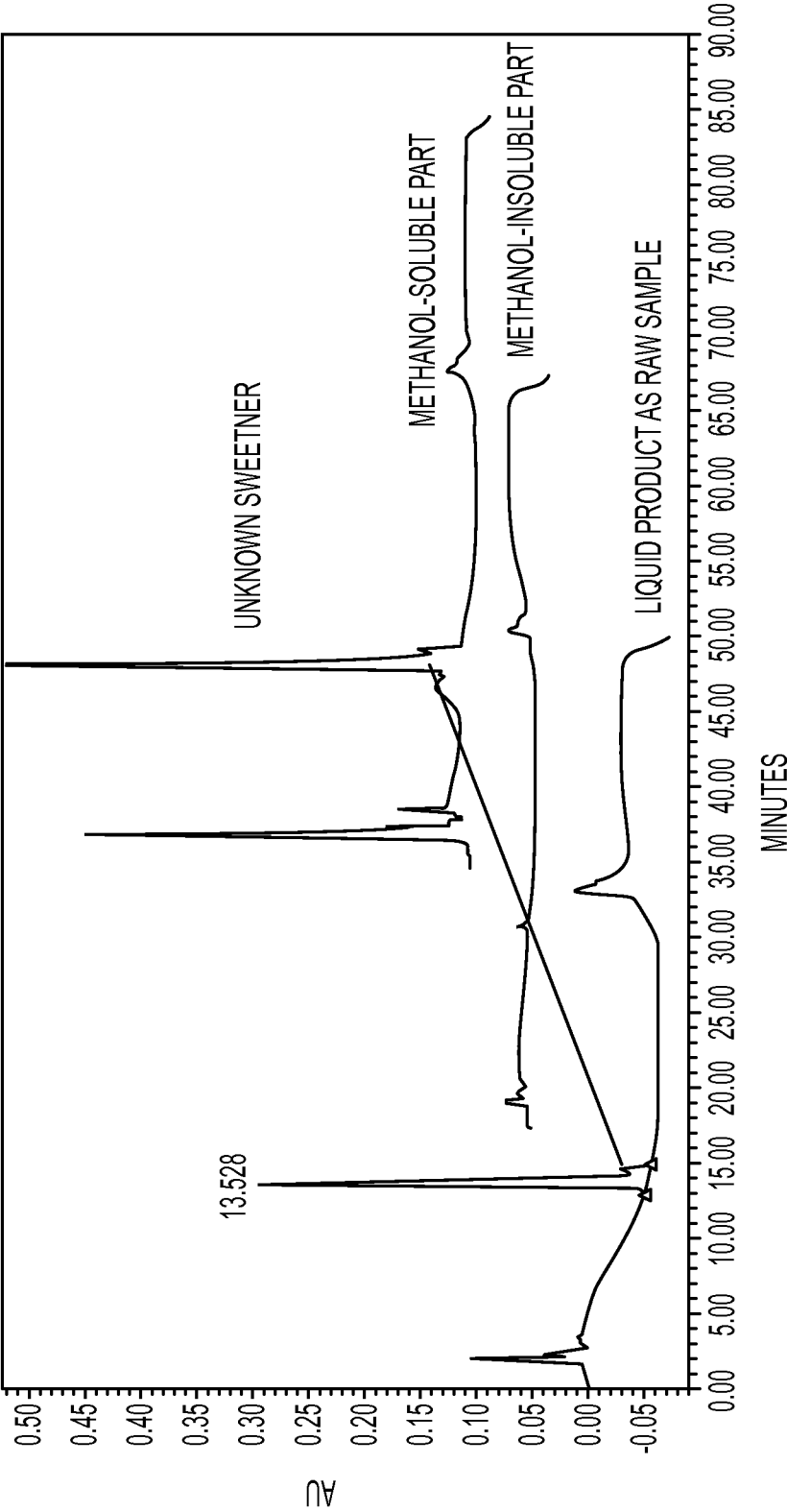


FIG. 2

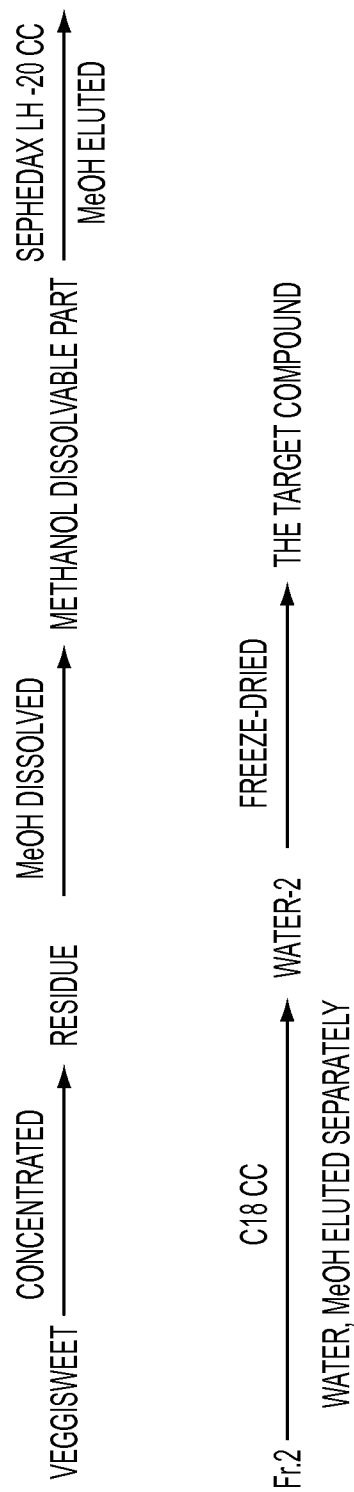


FIG. 3

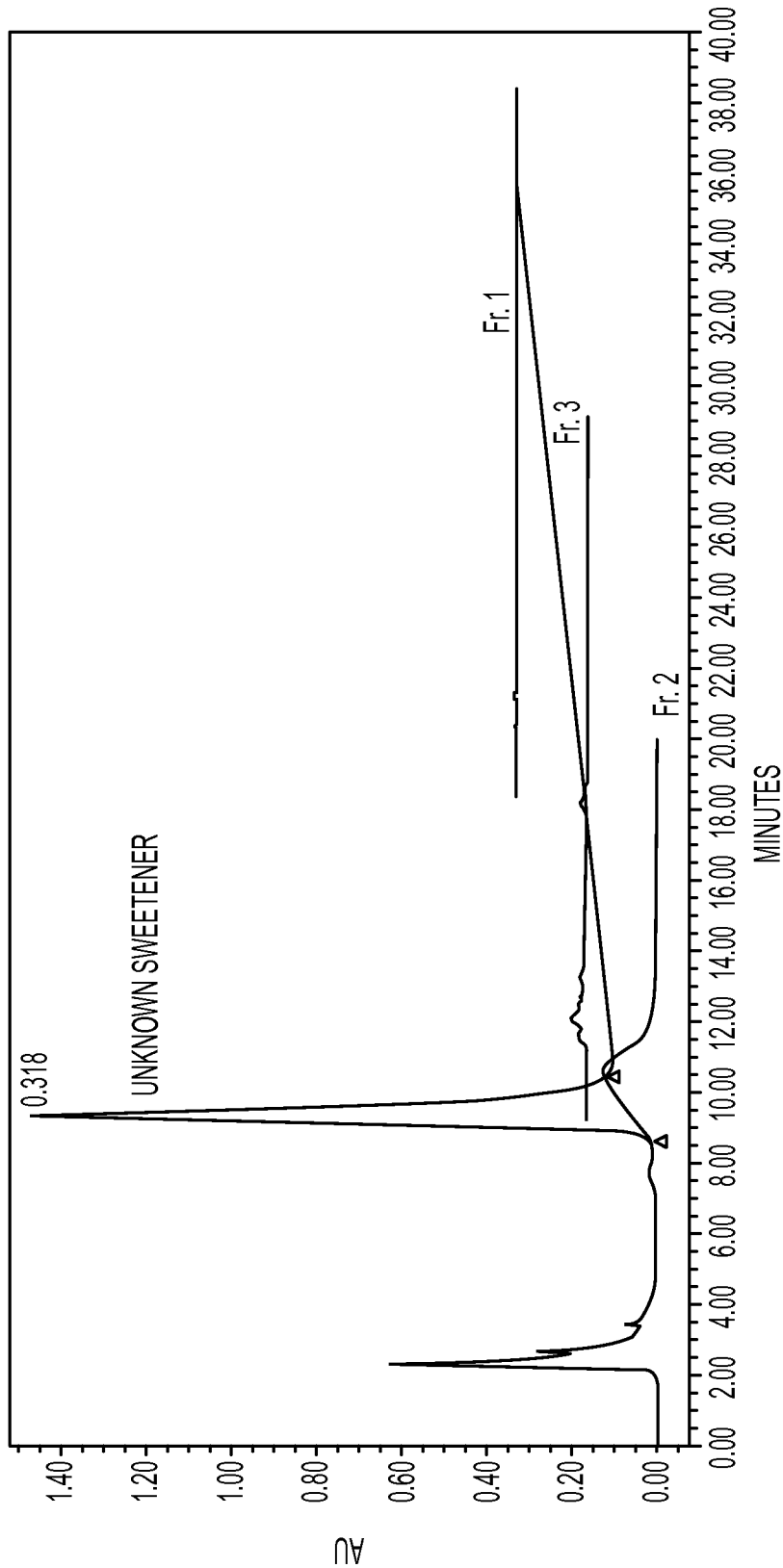


FIG. 4

5/15

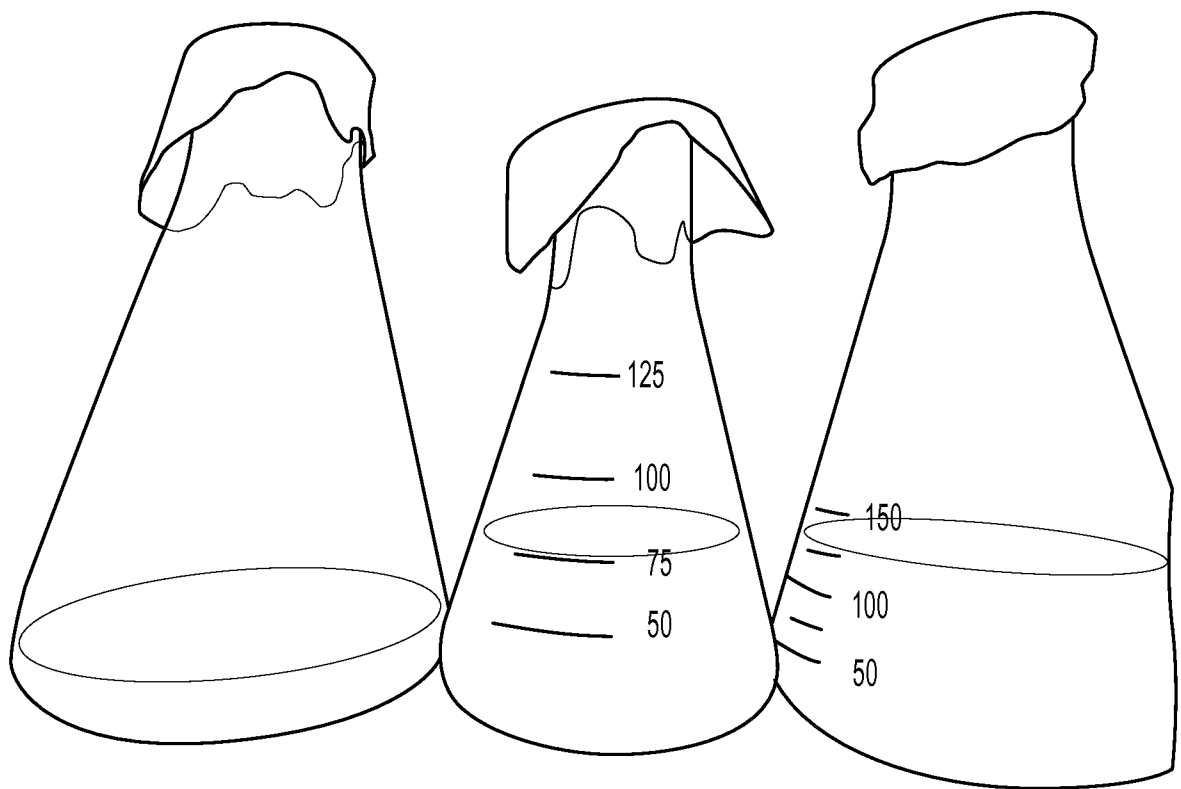


FIG. 5

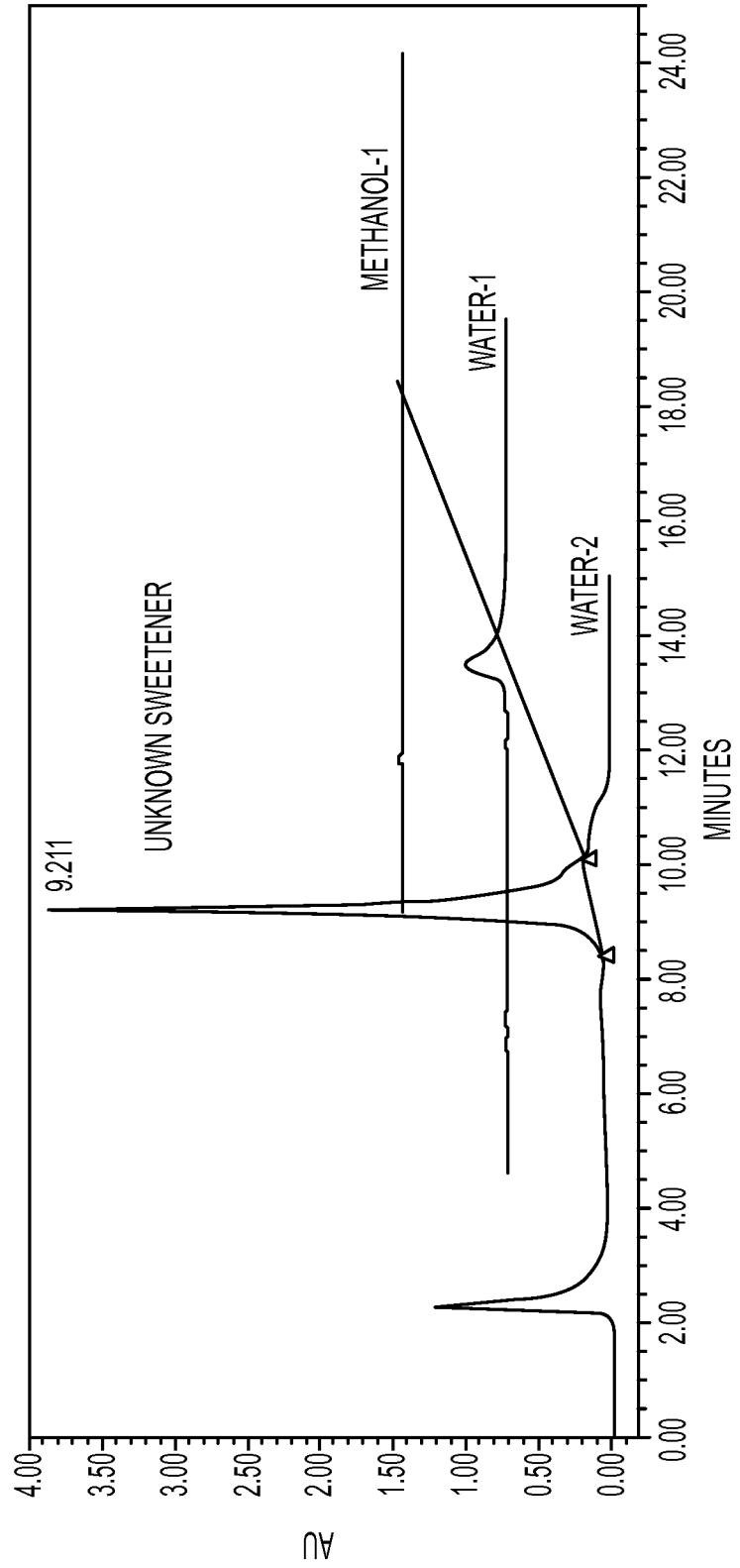


FIG. 6

7/15

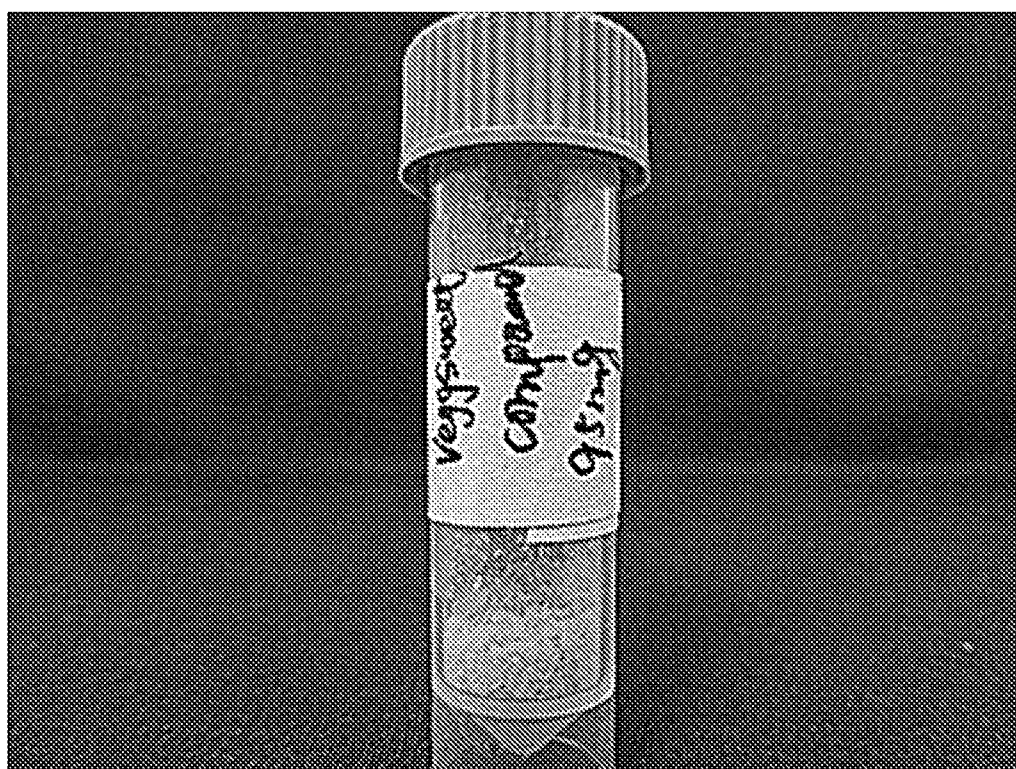


FIG. 7

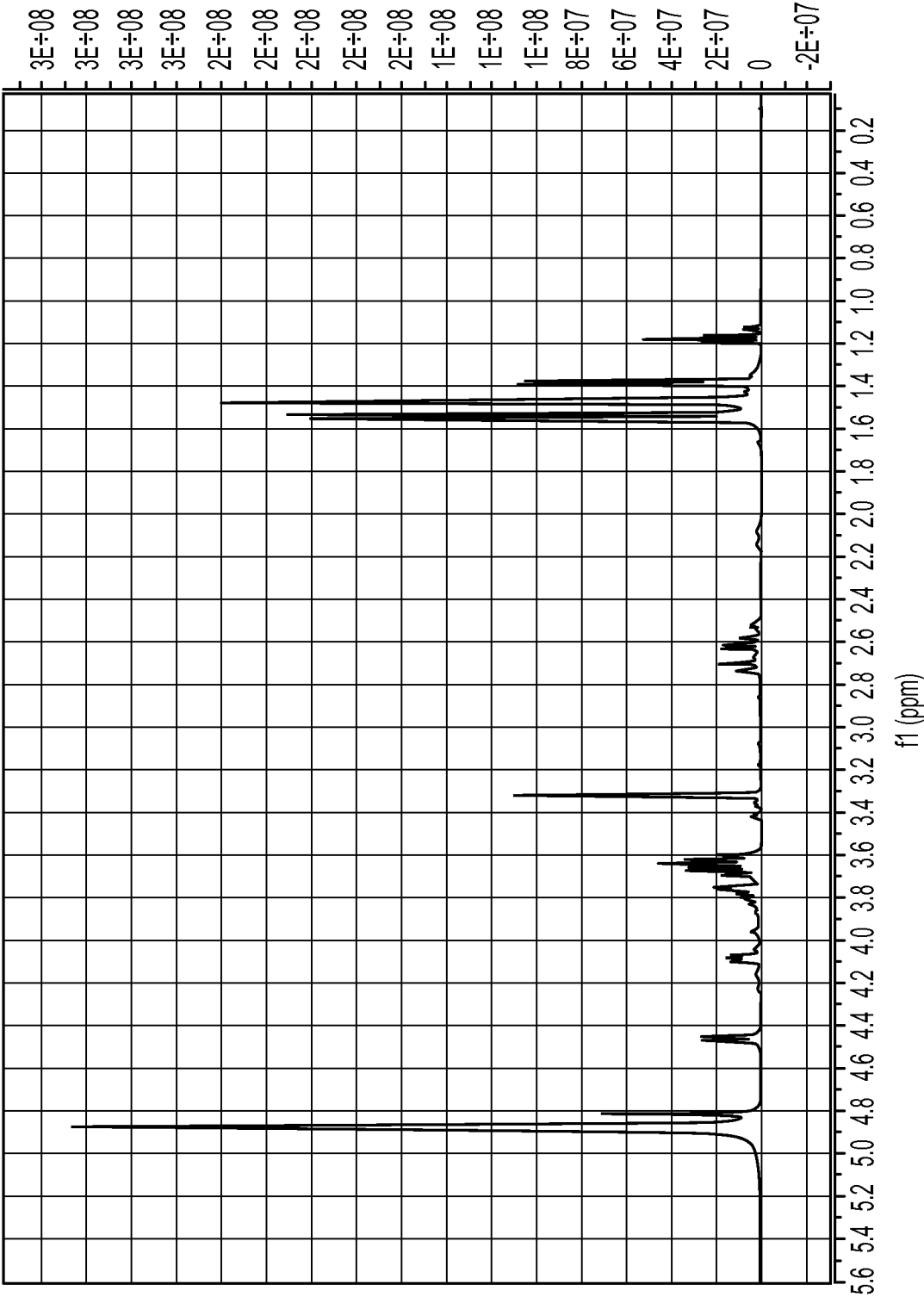
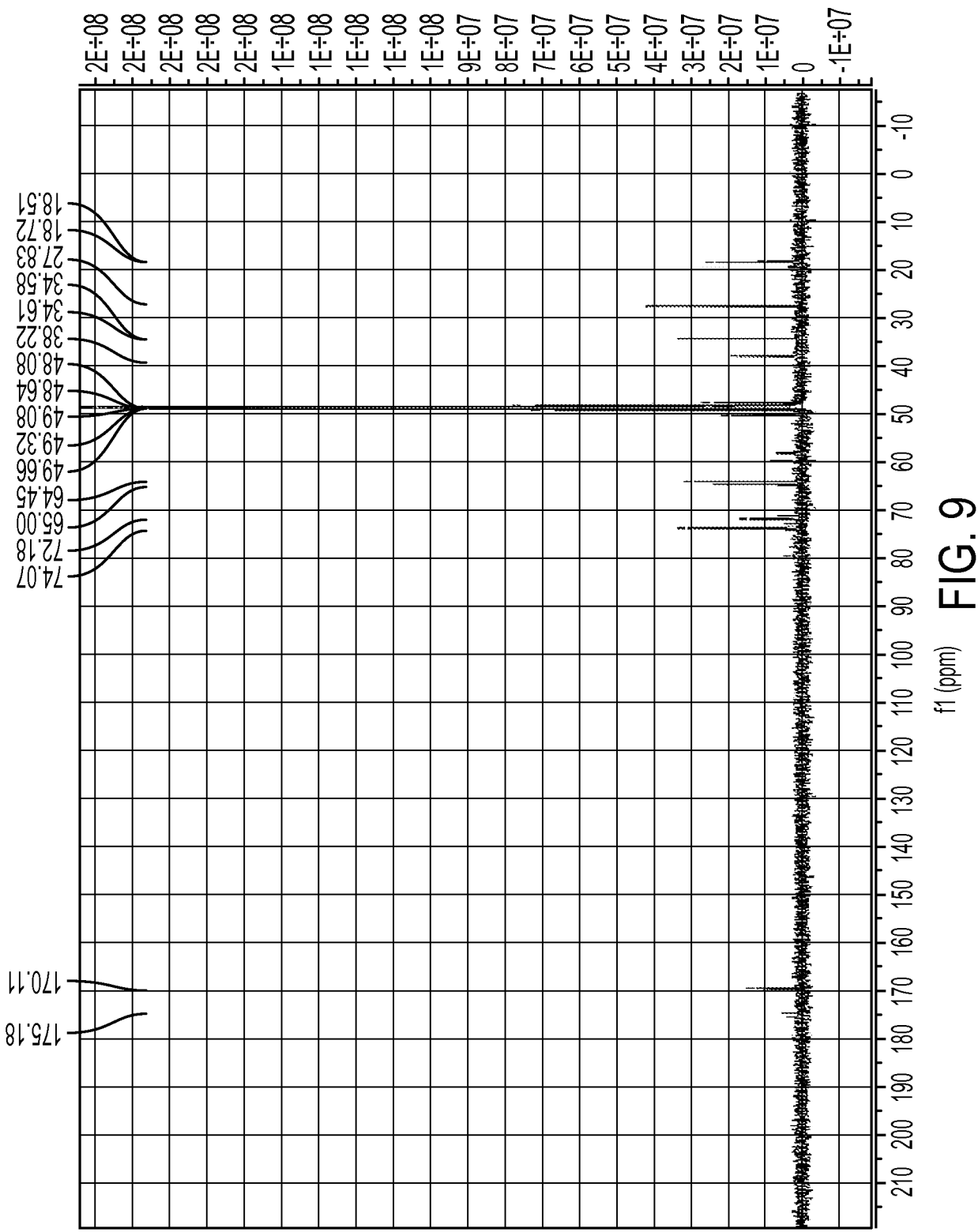


FIG. 8



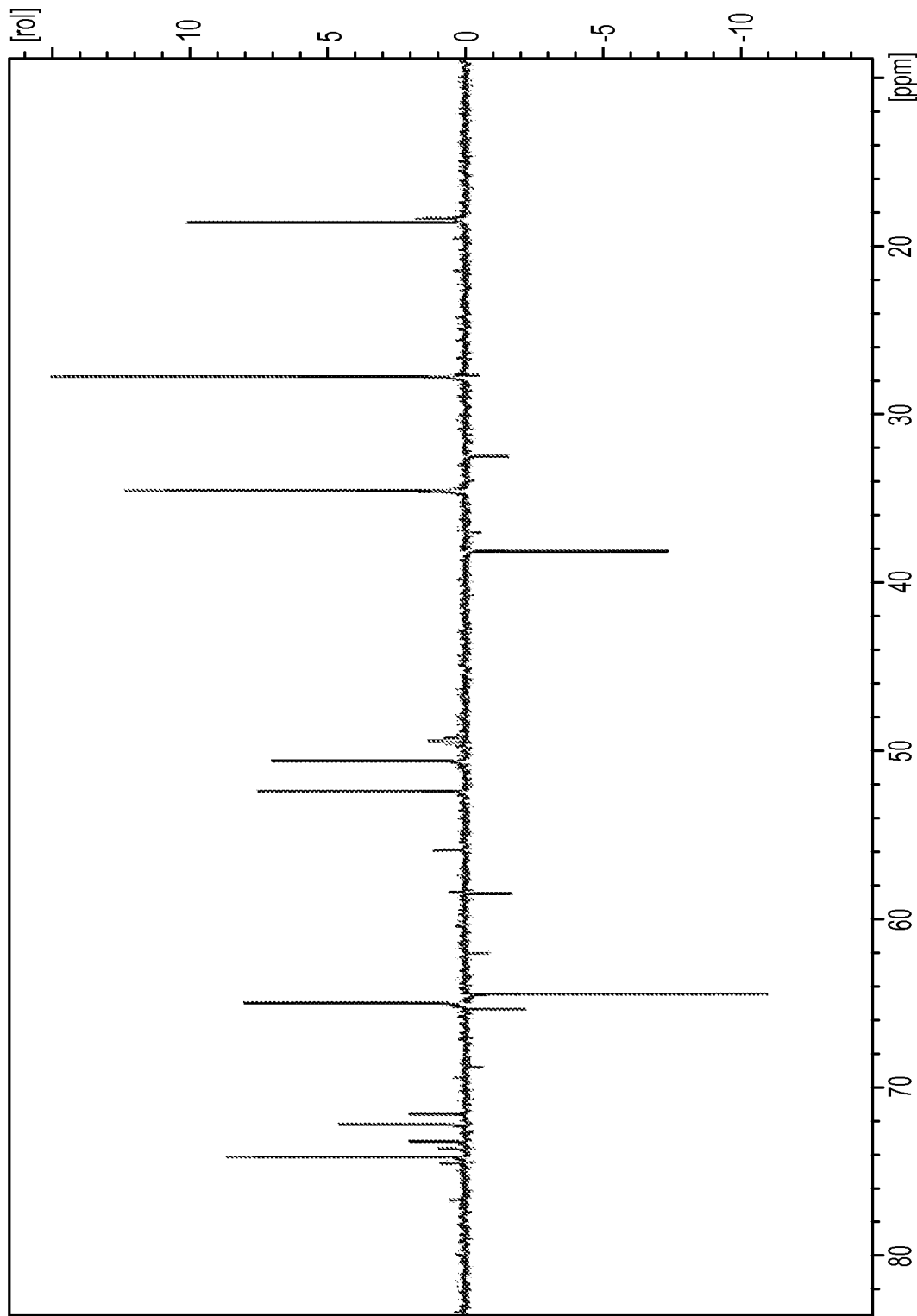


FIG. 10

11/15

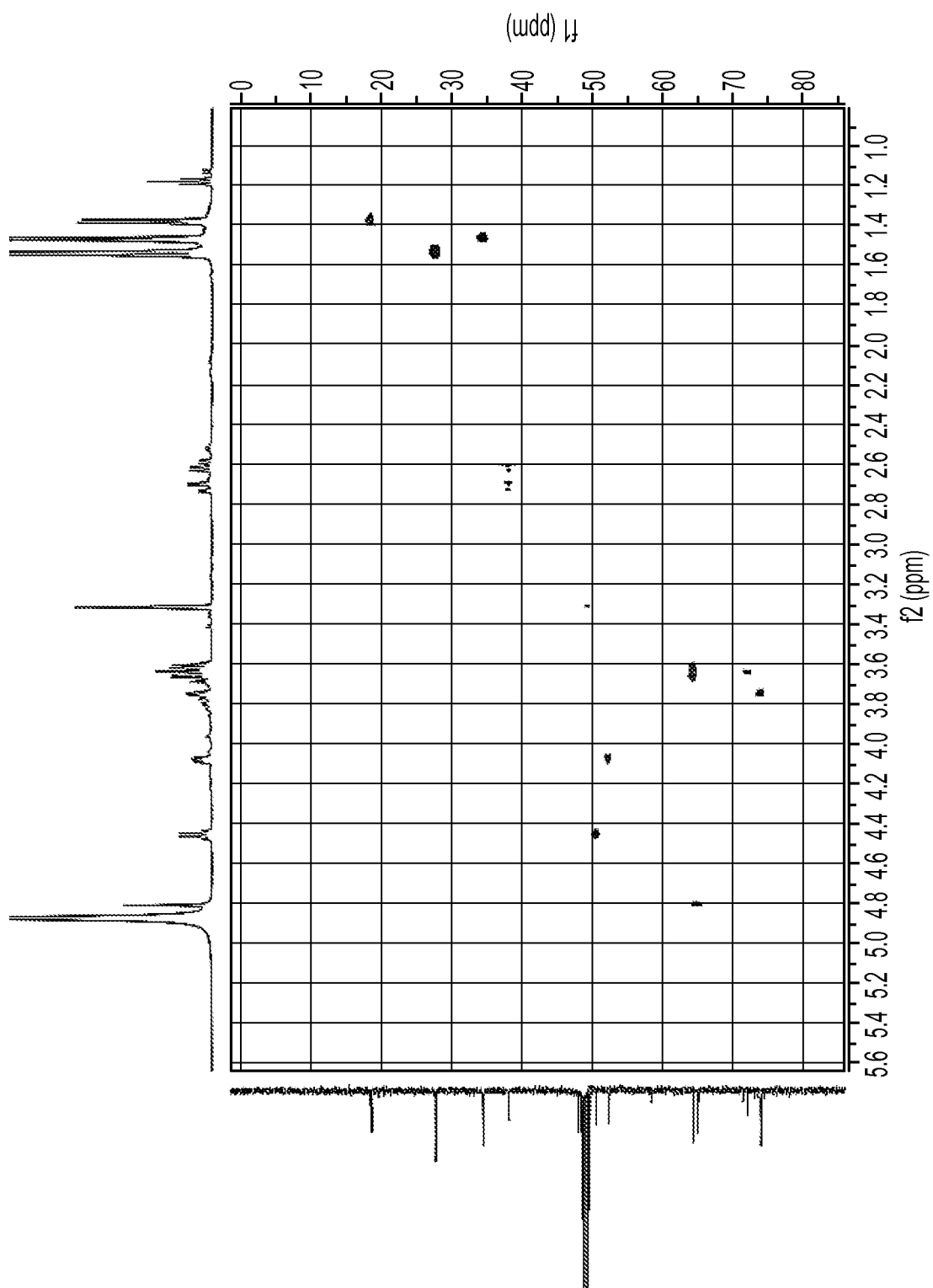


FIG. 11

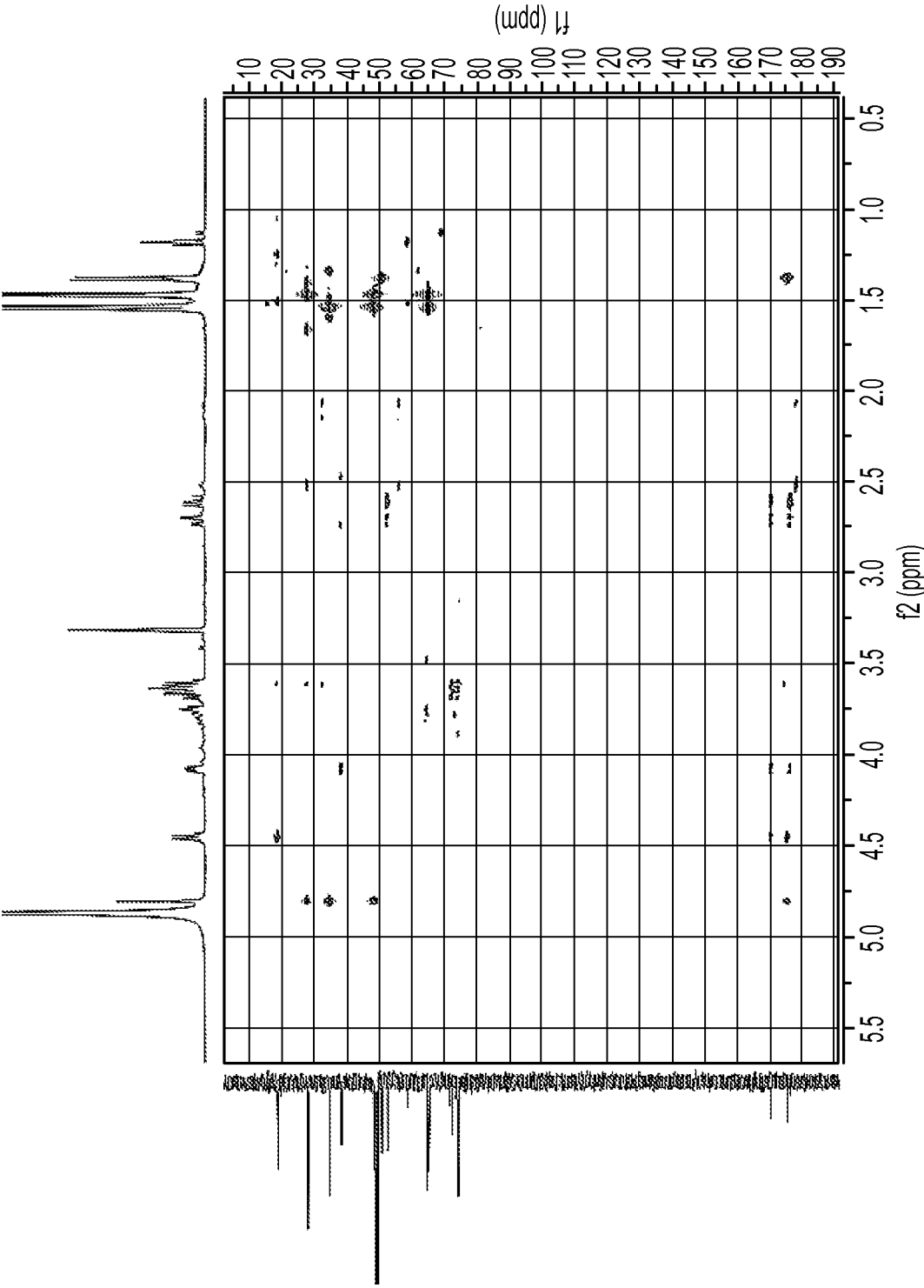


FIG. 12

13/15

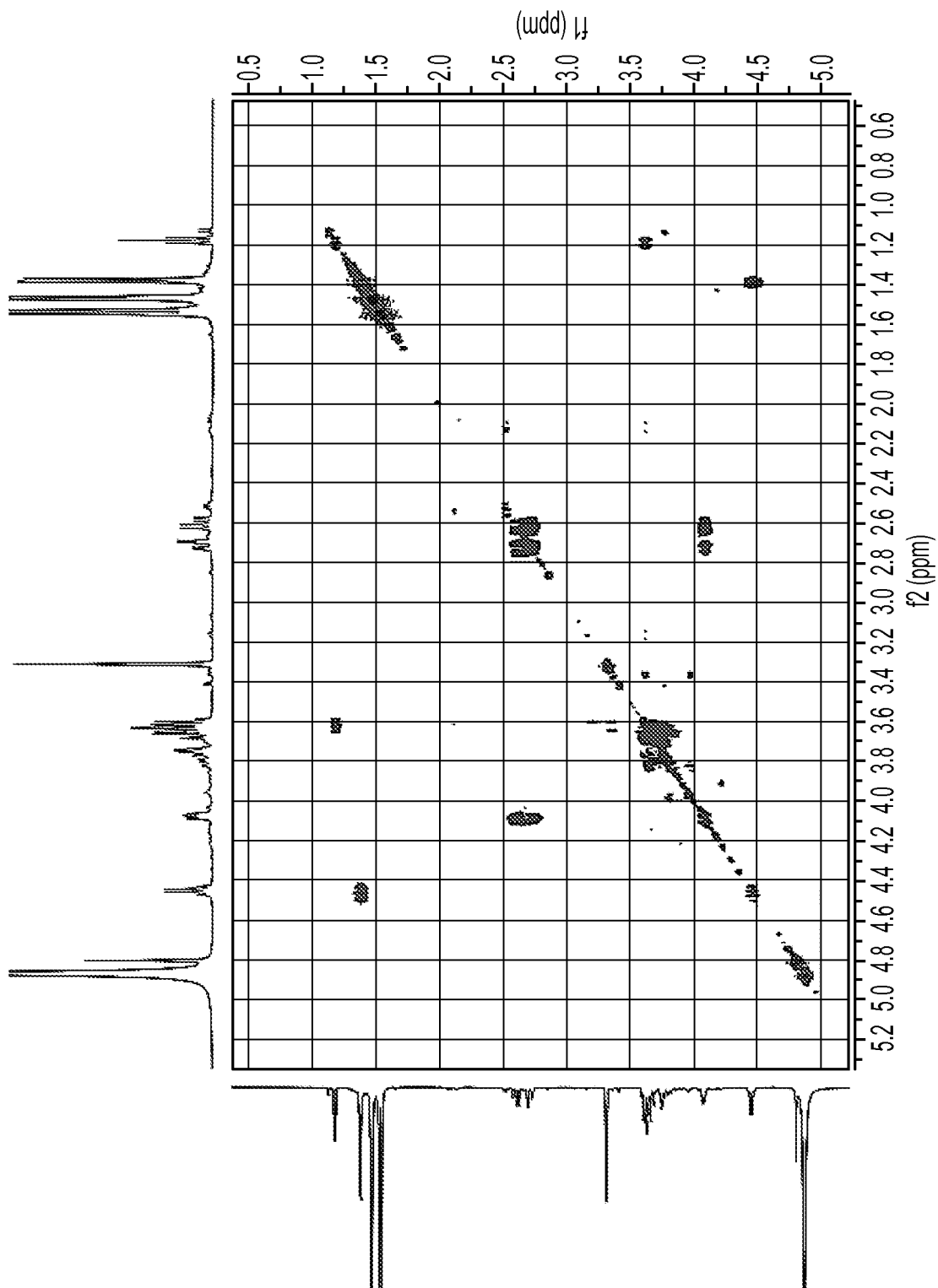


FIG. 13

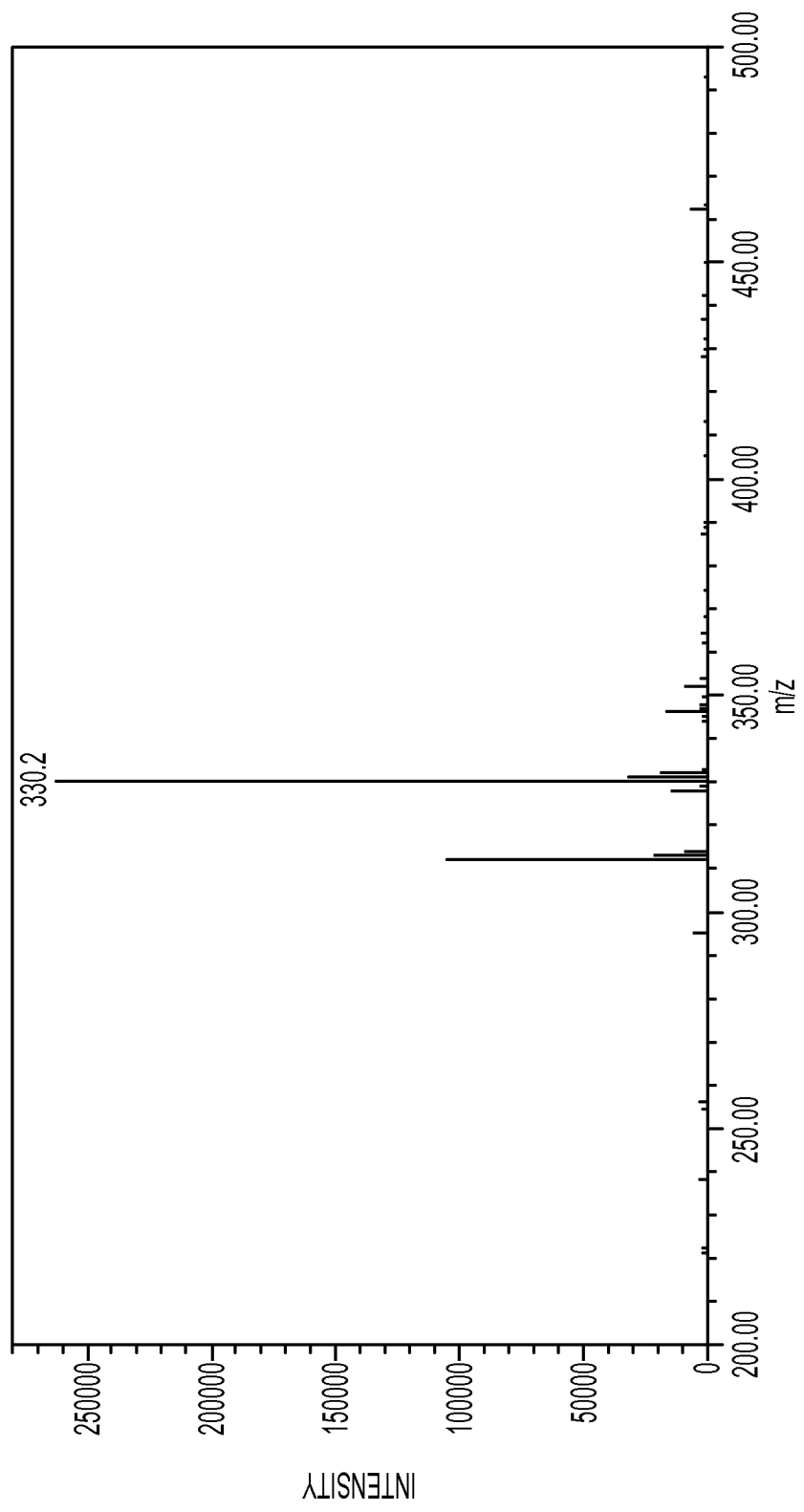


FIG. 14

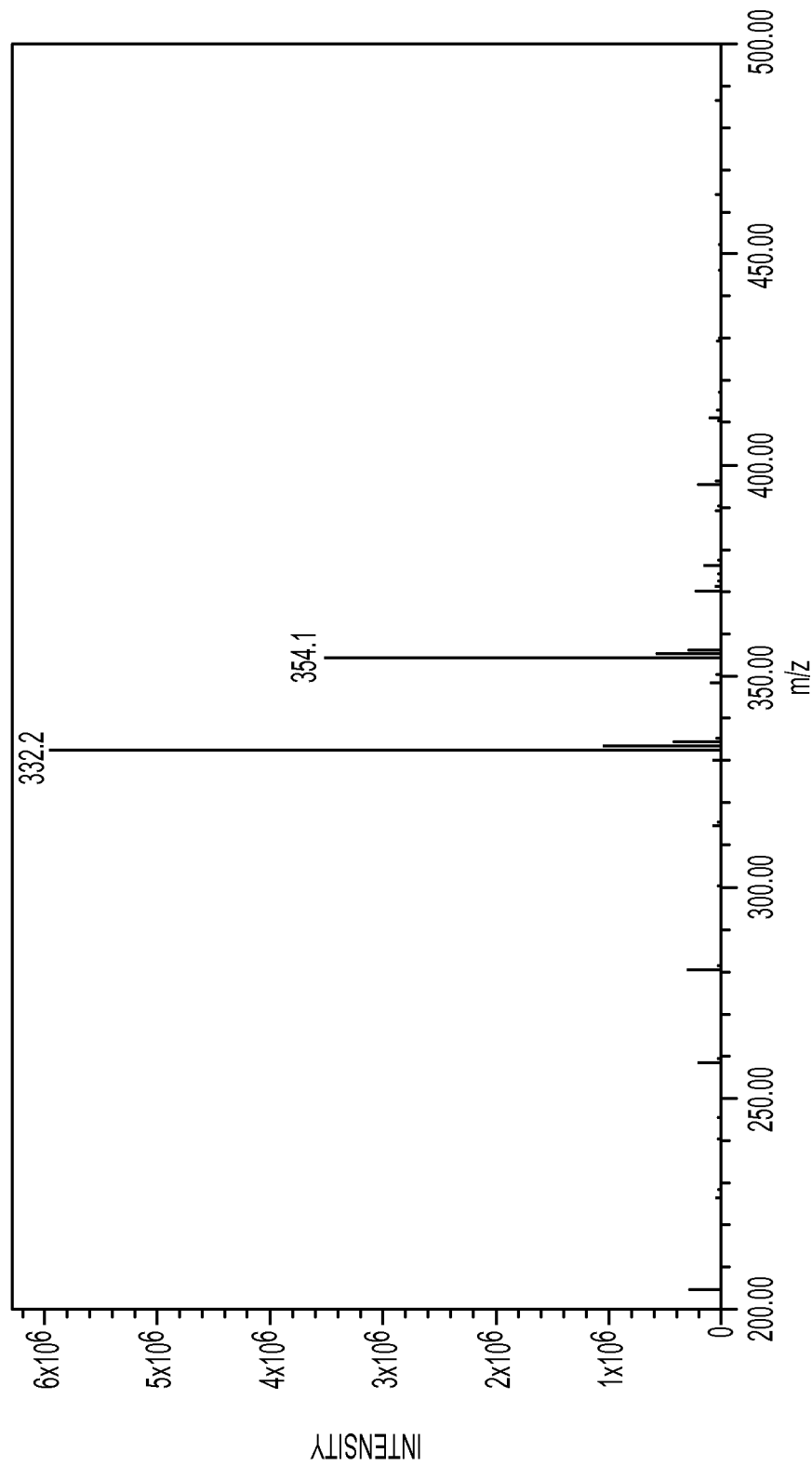


FIG. 15

INTERNATIONAL SEARCH REPORT

PCT/US14/56646 11.12.2014

PCT/US14/56646

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A23L 1/236; C07C 229/00; C12P 13/06,13/20 (2014.01)

CPC - A23L 1/0029, 1/236, 1/293

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (8) - A23L 1/236; C07C 229/00; C12P 13/06,13/20 (2014.01); CPC - A23L 1/0029, 1/236, 1/293, 1/2361, 1/2362
USPC - 426/548; 435/106, 109, 116; 525/54.1; 530/801; 562/433

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

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

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google Scholar; IP.com; ProQuest, Surechem; Sugar-free sweetener, 4-oxobutanoic acid, dipeptide, oxopropan-2-ylamino, 2-amino, food product, chewing gum, breath freshener, extract, aspartic acid, aspartyl, alanine, mouthwash, toothpaste, high intensity sweetener, film forming polymer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0294719 A1 (LERCHEN, HG et al.) December 1, 2011; paragraphs [0009], [0115]	1-20
A	US 2010/0183792 A1 (NAGASAKI, H et al.) July 22, 2010; paragraphs [0003], [0049], [0095]-[0097], [0102]	1-20
A	US 4,894,464 A (BRENNAN, TM et al.) January 16, 1990; column 2, lines 18-22; column 6, lines 1-20; column 20, lines 22-55	1-20
A	US 5,958,496 A (AMINO, Y et al.) September 28, 1999; column 1, lines 47-51; column 2, lines 9-10; lines 30-34; column 6, lines 35-45	1-20

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

17 November 2014 (17.11.2014)

Date of mailing of the international search report

11 DEC 2014

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Shane Thomas

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774