Production of steviol glycosides in recombinant hosts

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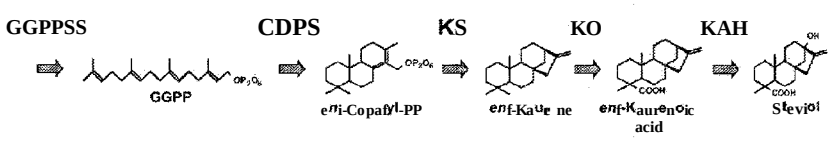
(54) **Title:** PRODUCTION OF STEVIOL GLYCOSIDES IN RECOMBINANT HOSTS

Figure 1



(57) **Abstract:** The invention relates to recombinant microorganisms and methods for producing steviol glycosides and steviol glycoside precursors.

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PRODUCTION OF STEVIOL GLYCOSIDES IN RECOMBINANT HOSTS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This disclosure relates to recombinant production of steviol glycosides and stevioi glycoside precursors in recombinant hosts. In particular, this disclosure relates to production of steviol glycosides comprising steviol-1 3-O-glucoside (13-SMG), steviol-1,2-bioside, steviol-1, 3-bioside, steviol-1 9-O-glucoside (19-SMG), stevioside, 1,3-stevioside, rubusoside, Rebaudioside A (RebA), Rebaudioside B (RebB), Rebaudioside C (RebC), Rebaudioside D (RebD), Rebaudioside E (RebE), Rebaudioside F (RebF), Rebaudioside M (RebM), Rebaudioside Q (RebQ), Rebaudioside I (Rebl), dulcoside A, or isomers thereof in recombinant hosts.

Description of Related Art

[0001] Sweeteners are well known as ingredients used most commonly in the food, beverage, or confectionary industries. The sweetener can either be incorporated into a final food product during production or for stand-alone use, when appropriately diluted, as a tabletop sweetener or an at-home replacement for sugars in baking. Sweeteners include natural sweeteners such as sucrose, high fructose com syrup, molasses, maple syrup, and honey and artificial sweeteners such as aspartame, saccharine, and sucralose. Stevia extract is a natural sweetener that can be isolated and extracted from a perennial shrub, *Stevia rebaudiana.* Stevia is commonly grown in South America and Asia for commercial production of stevia extract. Stevia extract, purified to various degrees, is used commercially as a high intensity sweetener in foods and in blends or alone as a tabletop sweetener.

[0002] Chemical structures for several steviol glycosides are shown in Figure 1, including the diterpene steviol and various steviol glycosides. Extracts of the Stevia plant generally comprise steviol glycosides that contribute to the sweet flavor, although the amount of each steviol glycoside often varies, *inter alia,* among different production batches.

[0002] As recovery and purification of steviol glycosides from the Stevia plant have proven to be labor intensive and inefficient, there remains a need for a recombinant production system that can accumulate high yields of desired steviol glycosides, such as RebD and RebM. There

also remains a need for improved production of steviol glycosides in recombinant hosts for commercial uses.

SUMMARY OF THE INVENTION

[0003] it is against the above background that the present invention provides certain advantages and advancements over the prior art.

[0004] Although this invention disclosed herein is not limited to specific advantages or functionalities, the invention provides a recombinant host comprising one or more of:

(a) a gene encoding an ent-kaurene oxidase (KO) polypeptide;

(b) a gene encoding a cytochrome P450 reductase (CPR) polypeptide; and/or

(c) a gene encoding an ent-kaurenoic acid hydroxylase (KAH) polypeptide;

wherein at least one of the genes is a recombinant gene; and

wherein the recombinant host is capable of producing a steviol glycoside precursor.

[0005] The invention also provides a recombinant host comprising:

(a) a gene encoding a geranylgeranyl diphosphate synthase (GGPPS) polypeptide;

(b) a gene encoding an ent-copalyl diphosphate synthase (CDPS) polypeptide;

(c) a gene encoding an ent-kaurene synthase (KS) polypeptide

(d) a gene encoding an ent-kaurene oxidase (KO) polypeptide;

(e) a gene encoding a cytochrome P450 reductase (CPR) polypeptide; and

(f) a gene encoding an ent-kaurenoic acid hydroxylase (KAH) polypeptide;

wherein at least one of the genes is a recombinant gene; and

wherein the recombinant host is capable **of** producing stevioi.

[0006] In one aspect of the recombinant hosts disclosed herein,

(a) the KO polypeptide comprises a KO polypeptide having at least 60% identity to an amino acid sequence set forth in SEQ ID NO:72 or SEQ ID NO:75; 65% identity to an amino acid sequence set forth in SEQ ID NO:54; at least 70% identity to an amino acid sequence set forth in SED ID NO: 70, SEQ ID NO:71 , or SEQ ID NO:79; at least 40% identity to an amino acid sequence set forth in SEQ

ID NO:77; or at least 50% identity to an amino acid sequence set forth in SEQ ID NO:78;

(b) the CPR polypeptide comprises a CPR polypeptide having at least 70% identity to an amino acid sequences set forth in SEQ ID NO:69, SEQ ID NO:74, SEQ ID N0.76, or SEQ ID NO:87; at least 80% identity to an amino acid sequence set forth in SEQ ID NO;73; at least 85% identity to an amino acid sequence set forth in SEQ ID NO:22; at least 65% identity to an amino acid sequence set forth in SEQ ID NO:28; or at least 50% identity to an amino acid sequence set forth in SEQ ID NO:98; and/or

(c) the KAH polypeptide comprises a KAH polypeptide having at least 40% identity to an amino acid sequence set forth in SEQ ID NO:82; at least 50% identity to an amino acid sequence set forth in SEQ ID NO:91; or at least 60% identity to an amino acid sequence set forth in SEQ ID NO:68.

[0007] The invention further provides a recombinant host comprising one or more of:

(a) a gene encoding a KO polypeptide having at least 60% identity to an amino acid sequence set forth in SEQ ID NO:75;

(b) a gene encoding a KAH polypeptide having at least 40% identity to an amino acid sequence set forth in SEQ ID NO:82; and/or

(c) a gene encoding a CPR polypeptide having at least 50% identity to an amino acid sequence set forth in SEQ ID NO:98;

wherein at least one of the genes is a recombinant gene; and

wherein the recombinant host is capable of producing a steviol glycoside precursor.

[0008] The invention further provides a recombinant host comprising one or more of:

(a) a gene encoding a KO polypeptide having at least 70% identity to an amino acid sequence set forth in SEQ ID NO:70;

(b) a gene encoding a KAH polypeptide having at least 40% identity to an amino acid sequence set forth in SEQ ID NO:82; and/or

(c) a gene encoding a CPR polypeptide having at least 50% identity to an amino acid sequence set forth in SEQ ID NO:98;

wherein at least one of the genes is a recombinant gene; and

wherein the recombinant host is capable of producing a steviol glycoside precursor.

[0009] In one aspect of the recombinant hosts disclosed herein, the host further comprises a gene encoding a KO polypeptide having at least 65% identity to an amino acid sequence set forth in SEQ ID NO:54.

[001 0] In another aspect of the recombinant hosts disclosed herein, the recombinant host further comprises a gene encoding a KAH polypeptide having at least 60% identity to an amino acid sequence set forth in SEQ ID NO:68.

[0011] In another aspect of the recombinant hosts disclosed herein, the recombinant host further comprises a gene encoding a KO polypeptide having at least 70% identity to an amino acid sequence set forth in SEQ ID NO:79,

[0012] In one aspect of the recombinant hosts disclosed herein, the host further comprises one or more of:

(a) a gene encoding a geranylgeranyl diphosphate synthase (GGPPS) polypeptide;

(b) a gene encoding an ent-copalyl diphosphate synthase (CDPS) polypeptide; and/or

(c) a gene encoding an ent-kaurene synthase (KS) polypeptide;

wherein at least one of the genes is a recombinant gene; and

wherein the recombinant host is capable of producing a steviol glycoside precursor.

[0013] In some aspects of the recombinant hosts disclosed herein,

(a) the GGPPS polypeptide comprises a polypeptide having at least 70% identity to an amino acid sequence set forth in SEQ ID NO:49;

(b) the CDPS polypeptide comprises a polypeptide having at least 70% identity to an amino acid sequence set forth in SEQ ID NO:37; and/or

(c) the KS polypeptide comprises a polypeptide having at least 40% identity to an amino acid sequence set forth in SEQ ID NO:6.

[0014] In one aspect of the recombinant hosts disclosed herein, the recombinant host further comprises a gene encoding an endoplasmic reticulum membrane polypeptide.

[001 5] In another aspect of the recombinant hosts disclosed herein, the endoplasmic reticulum membrane polypeptide comprises an Inheritance of cortical ER protein 2 (ICE2)

polypeptide having at least 50% identity to the amino acid sequence set forth in SEQ ID NO:1 14.

[0016] In one aspect of the recombinant host disclosed herein, the KO polypeptide is a fusion construct.

[0017] In another aspect, the fusion construct comprises a polypeptide having at least 60% identity to an amino acid sequence set forth in SEQ ID NO:118 or SEQ ID NO:120.

[0018] In another aspect, the fusion construct has at least 50% identity to an amino acid sequence set forth in SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:1 10, or SEQ ID NO:1 12.

[0019] in one aspect of the recombinant hosts disclosed herein, the host further comprises one or more of:

(a) a gene encoding a UGT85C polypeptide;

(b) a gene encoding a UGT76G polypeptide;

(c) a gene encoding a UGT74G1 polypeptide;

(d) a gene encoding a UGT91 D2 functional homolog polypeptide; and/or

(e) a gene encoding an EUGT11 polypeptide;

wherein at least one of the genes is a recombinant gene; and

wherein the host is capable of producing a stevio! glycoside.

[0020] In some aspects of the recombinant hosts disclosed herein,

(a) the UGT85C2 polypeptide comprises a polypeptide having at least 55% identity to an amino acid sequence set forth in SEQ ID NO:30;

(b) the UGT76G1 polypeptide comprises a polypeptide having at least 50% identity to an amino acid sequence set forth in SEQ ID NO:83;

(c) the UGT74G1 polypeptide comprises a polypeptide having at least 55% identity to an amino acid sequence set forth in SEQ ID NO:29;

(d) the UGT91D2 functional homolog polypeptide comprises a UGT91D2 polypeptide having 90% or greater identity to the amino acid sequence set forth in SEQ ID NO:84 or a UGT91D2e-b polypeptide having 90% or greater identity to the amino acid sequence set forth in SEQ ID NO:88; and/or

(e) the EUGT1 1 polypeptide comprises a polypeptide having at least 65% identity to an amino acid sequence set forth in SEQ ID NO:86.

[0021] In some aspects, the recombinant hosts disclosed herein comprise a plant cell, a mammalian cell, an insect cell, a fungal cell, or a bacterial cell.

[0022] In one aspect, the bacterial cell comprises *Escherichia* bacteria cells, for example, *Escherichia coli* cells; *Lactobacillus* bacteria cells; *Lactococcus* bacteria cells; *Cornebacterium* bacteria cells; *Acetobacter* bacteria cells; *Acinetobacter* bacteria cells; or *Pseudomonas* bacterial cells.

[0023] In one aspect, the fungal cell comprises a yeast cell.

[0024] In one aspect, the yeast cell is a cell from *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Yarrowia lipolytica, Candida glabrata, Ashbya gossypii, Cyberlindnera jadinii, Pichia pastoris, Kluyveromyces lactis, Hansenula polymorpha, Candida boidinii, Arxula adeninivorans, Xanthophyllomyces dendrorhous,* or *Candida albicans* species.

[0025] In one aspect, the yeast ceil is a *Saccharomycete.*

[0026] In one aspect, the yeast cell is a cell from the *Saccharomyces cerevisiae* species.

[0027] The invention further provides a method of producing a steviol glycoside or a steviol glycoside precursor, comprising:

(a) growing a recombinant host disclosed herein in a culture medium, under conditions in which any of the genes disclosed herein are expressed;

wherein the steviol glycoside or the steviol glycoside precursor is synthesized by said host; and/or

(b) optionally quantifying the steviol glycoside or the steviol glycoside precursor; and/or

(c) optionally isolating the steviol glycoside or the steviol glycoside precursor.

[0028] In some aspects, the steviol glycoside comprises steviol-1 3-O-glucoside (13-SMG), steviol-1 ,2-bioside, steviol-1 ,3-bioside, steviol-1 9-Oglucoside (19-SMG), stevioside, 1,3-stevioside, rubusoside, Rebaudioside A (RebA), Rebaudioside B (RebB), Rebaudioside C (RebC), Rebaudioside D (RebD), Rebaudioside E (RebE), Rebaudioside F (RebF), Rebaudioside M (RebM), Rebaudioside Q (RebQ), Rebaudioside I (Rebi), dulcoside A, di-

glycosylated steviol, tri-glycosylated steviol, tetra-glycosylated steviol, penta-glycosylated steviol, hexa-glycosyiated steviol, hepta-glycosylated steviol, or isomers thereof.

[0029] In some aspects, the steviol glycoside or steviol glycoside precursor produced by the recombinant hosts or methods disclosed herein accumulates to a detectable concentration when cultured under said conditions.

[0030] In some aspects, the steviol glycoside or steviol glycoside precursor produced by the recombinant hosts or methods disclosed herein has an undetectable concentration of stevia plant-derived contaminants.

[0031] In some aspects, the steviol glycoside or steviol glycoside precursor produced by the recombinant hosts or methods disclosed herein has a steviol glycoside composition enriched for RebD or RebM relative to the steviol glycoside composition of a wild-type Stevia plant.

[0032] These and other features and advantages of the present invention will be more fully understood from the following detailed description taken together with the accompanying claims. It is noted that the scope of the claims is defined by the recitations therein and not by the specific discussion of features and advantages set forth in the present description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] The following detailed description of the embodiments of the present invention can be best understood when read in conjunction with the following drawings, where like structure is indicated with like reference numerals and in which:

[0034] Figure 1 shows a schematic of the engineered biosynthetic pathway for producing steviol in yeast from geranylgeranyl diphosphate using geranylgeranyl diphosphate synthase (GGPPS), ent-copalyl diphosphate synthase (CDPS), ent-kaurene synthase (KS), ent-kaurene oxidase (KO), and ent-kaurenoic acid hydroxylase (KAH) polypeptides.

[0035] Figure 2 shows representative steviol glycoside glycosylation reactions catalyzed by suitable uridine S'-diphospho (UDP) glycosyi transferases (UGT) enzymes and chemical structures for several steviol glycoside compounds.

[0036] Figure 3 shows Rebaudioside B (RebB) production in a steviol glycoside-producing *S. cerevisiae* strain individually expressing *S. rebaudiana* K01 (SrKOI) encoded by the nucleotide sequence set forth in SEQ ID NO:59, the KO encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:55, or the KO encoded by the nucleotide sequence

set forth in SEQ ID NO:56. RebB production was measured by liquid chromatography-mass spectrometry (LC-MS) analysis as $\mu M/OD_{600}$ of individual cultures. See Example 3.

[0037] Figure 4 shows production of ent-kaurenoic acid in steviol glycoside-producing S. *cerevisiae* strains individually expressing SrKOI encoded by the nucleotide sequence set forth in SEQ ID NO:59, the KO encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:55, or the KO encoded by the nucleotide sequence set forth in SEQ ID NO:56, as measured by LC-MS analysis of culture samples. Ent-kaurenoic acid levels were calculated as the Area under Curve (AUC) of LC-MS peaks corresponding to ent-kaurenoic acid. *See* Example 3.

[0038] Figure 5 shows production of total (extracellular plus intracellular) steviol glycosides in a steviol glycoside-producing S. *cerevisiae* strain overexpressing S. *rebaudiana* KAHel (SrKAHel; encoded by the nucleotide sequence set forth in SEQ ID NO; 18) or in a steviol glycoside-producing S. *cerevisiae* stain co-expressing SrKAHel (encoded by the nucleotide sequence set forth in SEQ ID NO: 18) and a KO encoded by the nucleotide sequences set forth in any one of SEQ ID NOs: 55-60, compared to a control strain that does not overexpress SrKAHel or express a KO encoded by the nucleotide sequence set forth in any one of SEQ ID NOs: 55-60. Production of total steviol glycosides was quantified by comparision to a standard curve. Values plotted on the y-axis in μM are an average of three biological replicates. *See* Example 4.

[0039] Figure 6 shows production of Rebaudioside A (RebA), Rebaudioside D (RebD), and Rebaudioside M (RebM) in a steviol glycoside-producing *S. cerevisiae* strain overexpressing SrKAHel (encoded by the nucleotide sequence set forth in SEQ ID NO:18) and further expressing either the KO encoded by the nucleotide sequence set forth in SEQ ID NO:56 or the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65. Production of RebA + RebD + RebM was measured in μM. *See* Example 4.

[0040] Figure 7 shows production of glycosylated ent-kaurenoic acid in a steviol glycoside-producing S. *cerevisiae* strain overexpressing SrKAHel (encoded by the nucleotide sequence set forth in SEQ ID NO: 18) or in a steviol glycoside-producing strain coexpressing SrKAHel (encoded by the nucleotide sequence set forth in SEQ ID NO: 18) and a KO encoded by the nucleotide sequences set forth in any one of SEQ ID NOs: 55-60). Values were calculated as the AUC of LC-MS peaks corresponding to glycosylated ent-kaurenoic acid and as an average of three biological replicates. *See* Example 4.

[0041] Figure 8 shows production of glycosylated ent-kaurenol in a steviol glycoside-producing *S. cerevisiae* strain overexpressing SrKAHel (encoded by the nucleotide sequence set forth in SEQ ID NO:18) or in a steviol glycoside-producing *S. cerevisiae* strain co-expressing SrKAHel (encoded by the nucleotide sequence set forth in SEQ ID NO:18) and a KO encoded by the nucleotide sequence set forth in SEQ ID NOs: 55-60). Values plotted on the y-axis were calculated as the AUC of LC-MS peaks corresponding to glycosylated ent-kaurenol. See Example 4.

[0042] Figure 9 shows Rebaudioside IVf (RebM) production in a steviol glycoside-producing S. *cerevisiae* strain expressing CPR1 (encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:61) or CPR7 (encoded by the nucleotide sequence set forth in SEQ ID NO:23). Values plotted on the y-axis were measured in μM. *See* Example 5.

[0043] Figure 10 shows Rebaudioside M (RebM) production in a steviol glycoside-producing S. *cerevisiae* strain overexpressing SrKAHel (encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:18) and further expressing CPR4497 encoded by the nucleotide sequence set forth in SEQ ID NO;62. Values plotted on the y-axis indicate μM concentration of RebM. *See* Example 5.

[0044] Figure 11A shows an LC-MS chromatogram of a steviol-1 3-O-glucoside (13-SMG) standard. Figure 11B shows production of 13-SMG by a steviol glycoside-producing S. *cerevisiae* strain expressing the KAH encoded by the nucleotide sequence set forth in SEQ ID NO:80 (amino acid sequence set forth in SEQ ID NO:82). *See* Example 7.

[0045] Figure 12 shows steviol-1 3-O-glucoside (13-SMG) and Rebaudioside B (RebB) production in a steviol glycoside-producing *S. cerevisiae* strain co-expressing a KO and a CPR. The KO was selected from SrKOI (encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:59), the KO encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:63, or the KO encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:64. The cytochrome P450 reductase (CPR) polypeptide was selected from the CPR encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:66 or the CPR encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:67. Values displayed on the y-axis are μM concentrations of the indicated steviol glycosides. *See* Example 6.

[0046] Figure 13 shows production of steviol-1 3-O-glucoside (13-SMG) and rubusoside in a steviol glycoside-producing S. *cerevisiae* strain expressing SrKAHel (encoded by the

nucleotide sequence set forth in SEQ ID NO: 18), the KAH encoded by the nucleotide sequence set forth in SEQ ID NO:80, or the KAH encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:81. Values displayed in the y-axis are μM concentrations of 13-SMG and rubusoside, averaged over eight biological replicates and normalized to OD_{600} measured using a plate reader. Error bars are ± the respective standard deviation. *See* Example 7.

[0047] Figure 14 shows cytochrome P450 reductase (CPR) polypeptide activity on cytochrome c upon incubation with microsomal protein prepared from *S. cerevisiae* strains expressing SrKAHel (encoded by the nucleotide sequence set forth in SEQ ID NO:18) alone or in combination with CPR1 (encoded by the nucleotide sequence set forth in SEQ ID NO:61) or CPR12 (encoded by the nucleotide sequence set forth in SEQ ID NO:97). Results are shown in U/mg as an average of two biological replicates. *See* Example 9.

[0048] Figure 15A shows steviol accumulation upon 30 min incubation of ent-kaurenoic acid with microsomal protein prepared from S. *cerevisiae* strains expressing SrKAHel (encoded by the nucleotide sequence set forth in SEQ ID NO: 18) alone or in combination with CPR1 (encoded by the nucleotide sequence set forth in SEQ ID NO:61) or CPR12 (encoded by the nucleotide sequence set forth in SEQ ID NO:97). Results are shown in AUC as an average of three biological replicates. Control reactions comprised the microsomal protein described above, but these were not incubated for 30 min prior to measurement of steviol accumulation. Figure 15B shows levels of ent-kaurenoic acid following 30 min incubation of ent-kaurenoic acid with microsomal protein prepared from S. *cerevisiae* strains expressing SrKAHel (encoded by the nucleotide sequence set forth in SEQ ID NO:18) alone or in combination with CPR1 (encoded by the nucleotide sequence set forth in SEQ ID NO:61) or CPR12 (encoded by the nucleotide sequence set forth in SEQ ID NO:97). Results are shown in μM as an average of three biological replicates. Control reactions comprised the microsomal protein described above but were not incubated for 30 min prior to measurement of ent-kaurenoic acid levels. *See* Example 9.

[0049] Figure 16 shows steviol-13-O-glucoside (13-SMG), 1,2-bioside, Rebaudioside B (RebB), ent-kaurenoic acid, and ent-kaurene levels accumulated by a steviol glycoside-producing S. *cerevisiae* strain expressing SrKOi (SEQ ID NO:59, SEQ ID NO:79), a KO encoded by the nucleotide sequence set forth in SEQ ID NO:65, or a fusion construct between either SrKOi or the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and the NADPH-dependent P450 oxidoreductase domain of CYP102A1 (referred to herein as the "BMR domain"). Figure 16A shows levels of 13-SMG, 1,2-bioside, and RebB measured by LC-MS for

a steviol glycoside-producing S. *cerevisiae* strain expressing SrKOI (SEQ ID NO:59, SEQ ID NO:79), a fusion construct of SrKOI and BMR (SEQ ID NO:99, SEQ ID NO:100), a fusion construct of SrKOI and BMR W1046A (SEQ ID NO:101, SEQ ID NO:102), a fusion construct of truncated SrKOI and BMR (SEQ ID NO:103, SEQ ID NO:104), a fusion construct of truncated SrKOI and BMR W1046A (SEQ ID NO:105, SEQ ID NO:106), or a control plasmid. Figure 16B shows levels of ent-kaurenoic acid and ent-kaurene measured by LC-UV for a steviol glycoside-producing S. *cerevisiae* strain expressing SrKOI (SEQ ID NO:59, SEQ ID NO:79), a fusion construct of SrKOI and BMR (SEQ ID NO:99, SEQ ID NO:100), a fusion construct of SrKOI and BMR W1046A (SEQ ID NO:101, SEQ ID NO:102), a fusion construct of truncated SrKOI and BMR (SEQ ID NO:103, SEQ ID NO:104), a fusion construct of truncated SrKOI and BMR W1046A (SEQ ID NO:105, SEQ ID NO:106), or a control plasmid. Figure 16C shows levels of 13-SMG, 1,2-bioside, and RebB measured by LC-MS for a steviol glycoside-producing *S. cerevisiae* strain expressing the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65, a fusion construct of the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and BMR (SEQ ID NO:107, SEQ ID NO:108), a fusion construct of the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and BMR W1046A (SEQ ID NO:109, SEQ ID NO:110), a fusion construct of a truncated KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and BMR W1046A (SEQ ID NO:111, SEQ ID NO:112), or a plasmid control. Figure 16D shows levels of ent-kaurenoic acid or ent-kaurene accumulated by a steviol glycoside-producing *S. cerevisiae* strain expressing the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65, a fusion construct of the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and BMR (SEQ ID NO:107, SEQ ID NO:108), a fusion construct of the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and BMR W1046A (SEQ ID NO:109, SEQ ID NO:110), a fusion construct of a truncated KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and BMR W1046A (SEQ ID NO:111, SEQ ID NO:112), or a plasmid control. *See* Example 10.

DETAILED DESCRIPTION OF THE INVENTION

[0050] Before describing the present invention in detail, a number of terms will be defined. As used herein, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. For example, reference to a "nucleic acid" means one or more nucleic acids.

[0051] It is noted that terms like "preferably," "commonly," and "typically" are not utilized herein to limit the scope of the claimed invention or to imply that certain features are critical, essential, or even important to the structure or function of the claimed invention. Rather, these terms are merely intended to highlight alternative or additional features that can or cannot be utilized in a particular embodiment of the present invention.

[0052] For the purposes of describing and defining the present invention it is noted that the term "substantially" is utilized herein to represent the inherent degree of uncertainty that can be attributed to any quantitative comparison, value, measurement, or other representation. The term "substantially" is also utilized herein to represent the degree by which a quantitative representation can vary from a stated reference without resulting in a change in the basic function of the subject matter at issue.

[0053] Methods well known to those skilled in the art can be used to construct genetic expression constructs and recombinant cells according to this invention. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, *in vivo* recombination techniques, and polymerase chain reaction (PGR) techniques. *See,* for example, techniques as described in Green & Sambrook, 2012, MOLECULAR CLONING: A LABORATORY MANUAL, Fourth Edition, Cold Spring Harbor Laboratory, New York; Ausubei *et ai*., 1989, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Greene Publishing Associates and Wiley Interscience, New York, and PGR Protocols: A Guide to Methods and Applications (Innis *et* a*l*., 1990, Academic Press, San Diego, CA).

[0054] As used herein, the terms "polynucleotide", "nucleotide", "oligonucleotide", and "nucleic acid" can be used interchangeably to refer to nucleic acid comprising DNA, RNA, derivatives thereof, or combinations thereof.

[0055] As used herein, the terms "microorganism," "microorganism host," "microorganism host cell," "recombinant host," and "recombinant host cell" can be used interchangeably. As used herein, the term "recombinant host" is intended to refer to a host, the genome of which has been augmented by at ieast one DNA sequence. Such DNA sequences include but are not limited to genes that are not naturally present, DNA sequences that are not normally transcribed into RNA or translated into a protein ("expressed"), and other genes or DNA sequences which one desires to introduce into a host. It will be appreciated that typically the genome of a recombinant host described herein is augmented through stable introduction of one or more recombinant genes. Generally, introduced DNA is not originally resident in the host that is the recipient of the DNA, but it is within the scope of this disclosure to isolate a DNA segment from

a given host, and to subsequently introduce one or more additional copies of that DNA into the same host, e.g., to enhance production of the product of a gene or alter the expression pattern of a gene. In some instances, the introduced DNA will modify or even replace an endogenous gene or DNA sequence by, *e.g.,* homologous recombination or site-directed mutagenesis. Suitable recombinant hosts include microorganisms.

[0056] As used herein, the term "recombinant gene" refers to a gene or DNA sequence that is introduced into a recipient host, regardless of whether the same or a similar gene or DNA sequence may already be present in such a host. "Introduced," or "augmented" in this context, is known in the art to mean introduced or augmented by the hand of man. Thus, a recombinant gene can be a DNA sequence from another species or can be a DNA sequence that originated from or is present in the same species but has been incorporated into a host by recombinant methods to form a recombinant host. It will be appreciated that a recombinant gene that is introduced into a host can be identical to a DNA sequence that is normally present in the host being transformed, and is introduced to provide one or more additional copies of the DNA to thereby permit overexpression or modified expression of the gene product of that DNA. In some aspects, said recombinant genes are encoded by cDNA. In other embodiments, recombinant genes are synthetic and/or codon-optimized for expression in *S. cerevisiae.*

[0057] As used herein, the term "engineered biosynthetic pathway" refers to a biosynthetic pathway that occurs in a recombinant host, as described herein. In some aspects, one or more steps of the biosynthetic pathway do not naturally occur in an unmodified host. In some embodiments, a heterologous version of a gene is introduced into a host that comprises an endogenous version of the gene.

[0058] As used herein, the term "endogenous" gene refers to a gene that originates from and is produced or synthesized within a particular organism, tissue, or cell. In some embodiments, the endogenous gene is a yeast gene. In some embodiments, the gene is endogenous to *S. cerevisiae,* including, but not limited to *S. cerevisiae* strain S288C. In some embodiments, an endogenous yeast gene is overexpressed. As used herein, the term "overexpress" is used to refer to the expression of a gene in an organism at levels higher than the level of gene expression in a wild type organism. *See, e.g.,* Prelich, 2012, *Genetics* 190:841-54. In some embodiments, an endogenous yeast gene is deleted. *See, e.g.,* Giaever & Nislow, 2014, *Genetics* 197(2):451-65. As used herein, the terms "deletion," "deleted," "knockout," and "knocked out" can be used interchangabley to refer to an endogenous gene that

has been manipulated to no longer be expressed in an organism, including, but not limited to, *S. cerevisiae.*

[0059] As used herein, the terms "heterologous sequence" and "heterologous coding sequence" are used to describe a sequence derived from a species other than the recombinant host, in some embodiments, the recombinant host is an S. *cerevisiae* cell, and a heterologous sequence is derived from an organism other than *S. cerevisiae.* A heterologous coding sequence, for example, can be from a prokaryotic microorganism, a eukaryotic microorganism, a plant, an animal, an insect, or a fungus different than the recombinant host expressing the heterologous sequence. In some embodiments, a coding sequence is a sequence that is native to the host.

[0060] A "selectable marker" can be one of any number of genes that complement host cell auxotrophy, provide antibiotic resistance, or result in a color change. Linearized DNA fragments of the gene replacement vector then are introduced into the cells using methods well known in the art *(see* below). Integration of the linear fragments into the genome and the disruption of the gene can be determined based on the selection marker and can be verified by, for example, PGR or Southern blot analysis. Subsequent to its use in selection, a selectable marker can be removed from the genome of the host cell by, *e.g.,* Cre-LoxP systems *(see, e.g.,* Gossen *et* a/., 2002, *Ann. Rev. Genetics* 36:153-173 and U.S. 2006/0014264). Alternatively, a gene replacement vector can be constructed in such a way as to include a portion of the gene to be disrupted, where the portion is devoid of any endogenous gene promoter sequence and encodes none, or an inactive fragment of, the coding sequence of the gene.

[0061] As used herein, the terms "variant" and "mutant" are used to describe a protein sequence that has been modified at one or more amino acids, compared to the wild-type sequence of a particular protein.

[0062] As used herein, the term "inactive fragment" is a fragment of the gene that encodes a protein having, *e.g.,* less than about 10% (e.g., less than about 9%, less than about 8%, less than about 7%, less than about 6%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, less than about 1%, or 0%) of the activity of the protein produced from the full-length coding sequence of the gene. Such a portion of a gene is inserted in a vector in such a way that no known promoter sequence is operably linked to the gene sequence, but that a stop codon and a transcription termination sequence are operably linked to the portion of the gene sequence. This vector can be subsequently linearized in the portion of the gene sequence

and transformed into a cell. By way of single homologous recombination, this linearized vector is then integrated in the endogenous counterpart of the gene with inactivation thereof.

[0063] As used herein, the term "stevio! glycoside" refers to Rebaudioside A (RebA) (CAS # 58543-16-1), Rebaudioside B (RebB) (CAS # 58543-17-2), Rebaudioside C (RebC) (CAS # 63550-99-2), Rebaudioside D (RebD) (CAS # 63279-13-0), Rebaudioside E (RebE) (CAS # 63279-14-1), Rebaudioside F (RebF) (CAS # 438045-89-7), Rebaudioside M (RebM) (CAS # 1220616-44-3), Rubusoside (CAS # 63849-39-4), Dulcoside A (CAS # 64432-06-0), Rebaudioside I (Rebl) (MassBank Record: FU000332), Rebaudioside Q (RebQ), 1,2-Stevioside (CAS # 57817-89-7), 1,3-Stevioside (RebG), 1,2-bioside (MassBank Record: FU000299), 1,3-bioside, Stevioi-13-O-glucoside (13-SMG), Steviol-19-O-glucoside (19-SMG), a tri-glucosylated steviol glycoside, a tetra-glycosylated steviol glycoside, a penta-glucosylated steviol glycoside, a hexa-glucosylated steviol glycoside, a hepta-glucosyiated steviol glycoside, and isomers thereof. *See* Figure 2; *see also,* Steviol Glycosides Chemical and Technical Assessment 69th JECFA, 2007, prepared by Harriet Wallin, Food Agric. Org.

[0064] As used herein, the terms "steviol glycoside precursor" and "steviol glycoside precursor compound" are used to refer to intermediate compounds in the steviol glycoside biosynthetic pathway. Steviol glycoside precursors include, but are not limited to, geranylgeranyl diphosphate (GGPP), ent-copalyl-diphosphate, ent-kaurene, ent-kaurenol, ent-kaurenai, ent-kaurenoic acid, and steviol. *See* Figure 1. In some embodiments, steviol glycoside precursors are themselves steviol glycoside compounds. For example, 19-SMG, rubusoside, stevioside, and RebE are steviol glycoside precursors of RebM. *See* Figure 2. Steviol glycosides and/or steviol glycoside precursors can be produced *in vivo (i.e.,* in a recombinant host), *in vitro (i.e.,* enzymatically), or by whole cell byconversion. As used herein, the terms "produce" and "accumulate" can be used interchangeably to describe synthesis of steviol glycosides and steviol glycoside precursors *in vivo, in vitro,* or by whole cell bioconversion.

[0065] As used herein, the term "di-glycosylated steviol" can be used to refer to a steviol molecule comprising two sugar moieties, such as glucose or N-acetylglucosamine (GicNAc). Non-limiting examples of di-glycosylated steviol molecules include steviol-1,3-bioside, steviol-1,2-bioside, rubusoside, a steviol molecule comprising two glucose moieties, a steviol molecule comprising one glucose moiety and one GicNAc moiety, and isomers thereof.

[0066] As used herein, the term "tri-glycosylated steviol" can be used to refer to a steviol molecule comprising three sugar moieties, such as glucose or GicNAc. Non-limiting examples

of tri-glycosylated steviol molecules include RebB, RebG, stevioside, a steviol molecule comprising two glucose moieties and one GlcNAc moiety, and isomers thereof.

[0067] As used herein, the term "tetra-glycosylated steviol" can be used to refer to a steviol molecuie comprising four sugar moieties, such as glucose or GlcNAc. Non-limiting examples of tetra-glycosylated steviol molecules include RebA, RebE, RebQ, a steviol molecule comprising four glucose moieties, a steviol molecule comprising three glucose moieties and one GlcNAc moiety, and isomers thereof.

[0068] As used herein, the term "penta-glycosylated steviol" can be used to refer to a steviol molecule comprising five sugar moieties, such as glucose or GlcNAc. Non-limiting examples of penta-glycosylated steviol molecules include RebD, a steviol molecule comprising five glucose moieties, a steviol molecule comprising four glucose moieties and one GlcNAc moiety, and isomers thereof.

[0069] As used herein, the term "hexa-glycosyiated steviol" can be used to refer to a steviol molecule comprising six sugar moieties, such as glucose or GlcNAc. Non-limiting examples of hexa-glycosylated steviol molecules include RebM, a steviol molecule comprising six glucose moieties, a steviol molecule comprising five glucose moieties and one GlcNAc moiety, and isomers thereof.

[0070] As used herein, the term "hepta-glycosylated steviol" can be used to refer to a steviol molecule comprising seven sugar moieties, such as glucose or GlcNAc. Non-limiting examples of hepta-glycosylated steviol molecules include a steviol molecule comprising seven glucose moieties and isomers thereof.

[0071] As used herein, the term "glycosylated ent-kaurenoic acid" can be used to refer to an ent-kaurenoic acid molecule comprising sugar moieties, such as glucose or GlcNAc. Non-limiting examples of glycosylated ent-kaurenoic acid molecules include ent-kaurenoic acid molecule comprising two glucose moieties and one GlcNAc moiety, an ent-kaurenoic acid molecule comprising three glucose moieties, an ent-kaurenoic acid molecule comprising one glucose moiety and one GlcNAc moiety, an ent-kaurenoic acid molecule comprising two glucose moieties, and isomers thereof.

[0072] As used herein, the term "glycosylated ent-kaurenol" can be used to refer to an ent-kaurenol molecule comprising sugar moieties, such as glucose or GlcNAc. Non-limiting examples of glycosylated ent-kaurenol molecules include an ent-kaurenol molecule comprising three glucose moieties, an ent-kaurenol molecule comprising one glucose moiety and one

GlcNAc moiety, an ent-kaureno! molecule comprising two glucose moieties, and isomers thereof.

[0073] Recombinant steviol glycoside-producing *Saccharomyces cerevisiae (S. cerevisiae)* strains are described in WO 201 1/153378, WO 2013/022989, WO 2014/122227, and WO 2014/122328. Methods of producing steviol glycosides in recombinant hosts, by whole cell bio-conversion, and *in vitro* are also described in WO 201 1/153378, WO 2013/022989, WO 2014/122227, and WO 2014/122328.

[0074] In some embodiments, steviol glycosides and/or steviol glycoside precursors are produced *in vivo* through expression of one or more enzymes involved in the steviol glycoside biosynthetic pathway in a recombinant host. For example, a steviol-producing recombinant host expressing one or more of a gene encoding a GGPPS polypeptide, a gene encoding a CDPS polypeptide, a gene encoding a KS polypeptide, a gene encoding a KO polypeptide, a gene encoding a KAH polypeptide, a gene encoding a CPR polypeptide, and a gene encoding a UGT polypeptide can produce a steviol glycoside and/or steviol glycoside precursors *in vivo. See, e.g.,* Figures 1 and 2. The skilled worker will appreciate that one or more of these genes can be endogenous to the host provided that at least one (and in some embodiments, all) of these genes is a recombinant gene introduced into the recombinant host.

[0075] in another example, a recombinant host expressing a gene encoding a GGPPS polypeptide, a gene encoding a CDPS polypeptide, a gene encoding a KS polypeptide, a gene encoding a KO polypeptide, a gene encoding a KAH polypeptide, and a gene encoding a CPR polypeptide can produce steviol *in vivo. See, e.g.,* Figures 1. The skilled worker will appreciate that one or more of these genes can be endogenous to the host provided that at least one (and in some embodiments, all) of these genes is a recombinant gene introduced into the recombinant host.

[0076] In another example, a steviol-producing recombinant host expressing a gene encoding a GGPPS polypeptide, a gene encoding a CDPS polypeptide, a gene encoding a KS polypeptide, a gene encoding a KO polypeptide, a gene encoding a KAH polypeptide, a gene encoding a CPR polypeptide, and one or more of a gene encoding a UGT polypeptide can produce a steviol glycoside *in vivo. See, e.g.,* Figures 1 and 2. The skilled worker will appreciate that one or more of these genes can be endogenous to the host provided that at least one (and in some embodiments, all) of these genes is a recombinant gene introduced into the recombinant host.

[0077] Non-limiting examples of KS polypeptides are set forth in SEQ ID NOs:1-4 and SEQ ID NO:6. Non-limiting examples of KO polypeptides are set forth in SEQ ID NOs:7-10, 54, 70-72, 75, and 77-79. Non-limiting examples of KAH polypeptides are set forth in SEQ ID NOs:13-17, 68, 82, and 91. Non-limiting examples of CPR polypeptides are set forth in SEQ ID NOs:20-22, 28, 69, 73, 74, 76, 87, and 98. Non-limiting examples of CDPS polypeptides are set forth in SEQ ID NOs:33-39. Non-limiting examples of CDPS-KS polypeptides are set forth in SEQ ID NOs:40-42. Non-limiting examples of GGPPS polypeptides are set forth in SEQ ID NOs:43-50.

[0078] In some embodiments, a recombinant host comprises a nucleic acid encoding a UGT85C2 polypeptide (SEQ ID NO:32), a nucleic acid encoding a UGT76G1 polypeptide (SEQ ID NO:83), a nucleic acid encoding a UGT74G1 polypeptide (SEQ ID NO:29), a nucleic acid encoding a UGT91D2 polypeptide, and/or a nucleic acid encoding a EUGT11 polypeptide (SEQ ID NO:86). In some aspects, the UGT91D2 polypeptide can be a UGT91D2e polypeptide (SEQ ID NO:84) or a UGT91D2e-b polypeptide (SEQ ID NO:88). The skilled worker will appreciate that expression of these genes may be necessary to produce a particular steviol glycoside but that one or more of these genes can be endogenous to the host provided that at least one (and in some embodiments, all) of these genes is a recombinant gene introduced into the recombinant host. In a particular embodiment, a steviol-producing recombinant microorganism comprises exogenous nucleic acids encoding UGT85C2, UGT76G1, or UGT91D2 polypeptides. In another particular embodiment, a steviol-producing recombinant microorganism comprises exogenous nucleic acids encoding UGT85C2, UGT76G1, UGT74G1, and UGT91D2 polypeptides. In yet another particular embodiment, a steviol-producing recombinant microorganism comprises exogenous nucleic acids encoding UGT85C2, UGT76G1, UGT74G1, and EUGT11 polypeptides. In yet another particular embodiment, a steviol-producing recombinant microorganism comprises the exogenous nucleic acids encoding UGT85C2, UGT76G1, UGT74G1, UGT91D2 (including *inter alia* 91D2e, 91D2m, 91D2e-b, and functional homologs thereof), and EUGT11 polypeptides.

[0079] In certain embodiments, the steviol glycoside is RebA, RebB, RebD, and/or RebM. RebA can be synthesized in a steviol-producing recombinant microorganism expressing UGT85C2, UGT76G1, UGT74G1, and UGT91D2. RebB can be synthesized in a steviol-producing recombinant microorganism expressing UGT85C2, UGT76G1, and UGT91D2. RebD can be synthesized in a steviol-producing recombinant microorganism expressing UGT85C2, UGT76G1 UGT74G1, and UGT91D2 and/or EUGT11. RebM can be synthesized in a steviol-

producing recombinant microorganism expressing UGT85C2, UGT76G1 , UGT74G1, and UGT91 D2 and/or EUGT1 1 (see Figure 2).

[0080] In some embodiments, steviol glycosides and/or steviol glycoside precursors are produced through contact of a steviol glycoside precursor with one or more enzymes involved in the steviol glycoside pathway *in vitro.* For example, contacting steviol with a UGT polypeptide can result in production of a steviol glycoside *in vitro.* In some embodiments, a steviol glycoside precursor is produced through contact of an upstream steviol glycoside precursor with one or more enzymes involved in the steviol glycoside pathway *in vitro.* For example, contacting ent-kaurenoic acid with a KAH enzyme can result in production of steviol *in vitro.*

[0081] In some embodiments, a steviol glycoside or steviol glycoside precursor is produced by whole cell bioconversion. For whole cell bioconversion to occur, a host cell expressing one or more enzymes involved in the steviol glycoside pathway takes up and modifies a stevioi glycoside precursor in the cell; following modification *in vivo,* a steviol glycoside remains in the cell and/or is excreted into the culture medium. For example, a host cell expressing a gene encoding a UGT polypeptide can take up steviol and glycosylate steviol in the cell; following glycosylation *in vivo,* a steviol glycoside can be excreted into the culture medium. In some embodiments, the cell is permeabilized to take up a substrate to be modified or to excrete a modified product.

[0082] In some embodiments, stevioi, one or more steviol glycoside precursors, and/or one or more steviol glycosides are produced by co-culturing of two or more hosts. In some embodiments, one or more hosts, each expressing one or more enzymes involved in the stevioi glycoside pathway, produce stevioi, one or more steviol glycoside precursors, and/or one or more steviol glycosides. For example, a host comprising a GGPPS, a CDPS, a KO, a KS, a KAH, and/or a CPR and a host comprising one or more UGTs produce one or more stevioi glycosides.

[0083] In some embodiments, a steviol glycoside or steviol glycoside precursor composition produced *in vivo, in vitro,* or by whole cell bioconversion comprises less contaminants than a stevia extract from, *inter alia,* a stevia plant. Contaminants include plant-derived compounds that contribute to off-flavors. Potential contaminants include pigments, lipids, proteins, phenolics, saccharides, spathulenol and other sesquiterpenes, labdane diterpenes, monoterpenes, decanoic acid, 8,1 1,14-eicosatrienoic acid, 2-methy!octadecane, pentacosane, octacosane, tetracosane, octadecanol, stigmasterol, β-sitosterol, a-amyrin, β-amyrin, lupeol, β-

amryin acetate, pentacyclic triterpenes, centauredin, quercitin, epi-alpha-cadinoi, carophyllenes and derivatives, beta-pinene, beta-sitosterol, and gibberellin.

[0084] As used herein, the terms "detectable amount," "detectable concentration," "measurable amount," and "measurable concentration" refer to a level of steviol glycosides measured in AUC, $\mu M/OD_{600}$, mg/L, μM, or mM. Steviol glycoside production *(i.e.,* total, supernatant, and/or intracellular steviol glycoside levels) can be detected and/or analyzed by techniques generally available to one skilled in the art, for example, but not limited to, liquid chromatography-mass spectrometry (LC-MS), thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), ultraviolet-visible spectroscopy/ spectrophotometry (UV-Vis), mass spectrometry (MS), and nuclear magnetic resonance spectroscopy (NMR).

[0085] As used herein, the term "undetectable concentration" refers to a level of a compound that is too low to be measured and/or analyzed by techniques such as TLC, HPLC, UV-Vis, MS, or NMR. In some embodiments, a compound of an "undetectable concentration" is not present in a steviol glycoside or steviol glycoside precursor composition.

[0086] As used herein, the terms "or" and "and/or" is utilized to describe multiple components in combination or exclusive of one another. For example, "x, y, and/or z" can refer to "x" alone, "y" alone, "z" alone, "x, y, and z," "(x and y) or z," "x or (y and z)," or "x or y or z." In some embodiments, "and/or" is used to refer to the exogenous nucleic acids that a recombinant cell comprises, wherein a recombinant cell comprises one or more exogenous nucleic acids selected from a group. In some embodiments, "and/or" is used to refer to production of steviol glycosides and/or steviol glycoside precursors. In some embodiments, "and/or" is used to refer to production of steviol glycosides, wherein one or more steviol glycosides are produced. In some embodiments, "and/or" is used to refer to production of steviol glycosides, wherein one or more steviol glycosides are produced through one or more of the following steps: culturing a recombinant microorganism, synthesizing one or more steviol glycosides in a recombinant microorganism, and/or isolating one or more steviol glycosides.

[0087] In some embodiments, the nucleotide sequence of a nucleic acid encoding a KO polypeptide is set forth in SEQ ID NO: 55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60, SEQ ID NO:63, SEQ ID NO:64, or SEQ ID NO:65. In some aspects, the nucleic acid encoding the KO polypeptide has at least 70% identity to the nucleotide sequence set forth in SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59 or SEQ ID NO:60, at least 80% identity to the nucleotide sequence set forth in SEQ ID NO:56 or SEQ ID NO:58, at least 95% identity to the nucleotide sequence set forth in SEQ ID NO:63, or at least

75% identity to the nucleotide sequence set forth in SEQ ID NO:64 or SEQ ID NO:65. In some embodiments, the amino acid sequence of a KO enzyme is set forth in SEQ ID NO:54, SEQ ID NO.70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78, OR SEQ ID NO:79. In some embodiments, a host ceil comprises one or more copies of one or more nucleic acids encoding a KO polypeptide.

[0088] In some embodiments, expression of a KO gene set forth in SEQ ID NO:55 or SEQ ID NO:56 in a RebB-producing S. *cerevisiae* strain results in higher production of RebB compared to expression of SrKOI (SEQ ID NO:59, SEQ ID NO:79) in a RebB-producing S. *cerevisiae* strain. *See* Example 3.

[0089] In some embodiments, expression of a KO gene set forth in SEQ ID NO:55, SEQ ID NO:56, or SEQ ID NO:57 in an *S. cerevisiae* strain capable of producing RebB with a functional KO results in production of ent-kaurenoic acid. *See* Example 3.

[0090] As used herein, the terms "ent-kaurenoic acid hydroxylase" and "steviol synthase" can be used interchangeably and be abbreviated "KAH." In some embodiments, the nucleotide sequence of a nucleic acid encoding a KAH enzyme is set forth in SEQ ID NO:18, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:90, or SEQ ID NO:96. In some aspects, the nucleic acid encoding the KAH polypeptide has at least 75% identity to a nucleotide sequence set forth in SEQ ID NO:80; or at least 70% identity to a nucleotide sequence set forth in SEQ ID NO:18, SEQ ID NO:81, SEQ ID NO:90, or SEQ ID NO:96. In some embodiments, the amino acid sequence of a KAH enzyme is set forth in SEQ ID NO:68, SEQ ID NO:82, or SEQ ID NO:91. In some embodiments, a host cell comprises one or more copies of one or more nucleic acids encoding a KAH enzyme.

[0091] In some embodiments, one or more copies of SrKAHel (SEQ ID NO:18, SEQ ID NO:68) are expressed in an *S. cerevisiae* strain. For example, in some embodiments, two copies of SrKAHel (SEQ ID NO: 18, SEQ ID NO:68) are expressed in an *S. cerevisiae* strain.

[0092] In some embodiments, the nucleotide sequence of a nucleic acid encoding a KAH enzyme is set forth in SEQ ID NO:80. The nucleic acid of SEQ ID NO:80 encodes a KAH with an amino acid sequence set forth in SEQ ID NO:82. A version of SEQ ID NO:80 codon-optimized for expression in *S, cerevisiae* is set forth in SEQ ID NO:81. In some embodiments, a host cell comprises one or more copies of one or more nucleic acids encoding a KAH enzyme. *See* Example 7.

[0093] In some embodiments, SrKAHel (SEQ ID NO:18, SEQ ID NO:68) and either the KAH encoded by the nucleotide sequence set forth in SEQ ID NO:80 or the KAH encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:81 are co-expressed in a steviol glycoside-producing S. *cerevisiae* strain. In some embodiments, co-expression of SrKAHel (SEQ ID NO:18, SEQ ID NO:68) and either the KAH encoded by the nucleotide sequence set forth in SEQ ID NO:80 or the KAH encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:81 in a steviol glycoside-producing strain results in higher production of steviol glycosides compared to a control steviol glycoside-producing strain or a steviol glycoside producing strain overexpressing SrKAHel. *See* Example 7 and Table 6. In some aspects, overexpressing SrKAHel results in production of 85.5 μM 13-SMG, expression of SrKAHel and the KAH encoded by the nucleotide set forth in SEQ ID NO:80 results in production of 153.8 μM 13-SMG, and expression of SrKAHel and the KAH encoded by the nucleotide set forth in SEQ ID NO:81 results in production of 130.5 μM 13-SMG.

[0094] In some embodiments, a KO gene is expressed in a steviol glycoside-producing S. *cerevisiae* strain that further overexpresses SrKAHel (SEQ ID NO:18, SEQ ID NO:68). In some embodiments, expression of a KO gene of SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60, SEQ ID NO:65 in a steviol glycoside-producing S. *cerevisiae* strain overexpressing SrKAHel results in higher expression of steviol glycosides compared to a control steviol-glycoside producing strain or a steviol glycoside-producing strain overexpressing SrKAHel (SEQ ID NO:18, SEQ ID NO:68). *See* Example 4.

[0095] In some embodiments, expression of a KO gene of SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, or SEQ ID NO:60 in a steviol glycoside-producing S. *cerevisiae* strain overexpressing SrKAHel (SEQ ID NO:18, SEQ ID NO:68) results in higher levels of glycosylated ent-kaurenoic acid compared to a control S. *cerevisiae* strain. *See* Example 4.

[0096] In some embodiments, expression of a KO gene of SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, or SEQ ID NO:60 in a steviol glycoside-producing S. *cerevisiae* strain overexpressing SrKAHel (SEQ ID NO:18, SEQ ID NO;68) results in improved metabolic conversion of a glycosylated ent-kaurenol intermediate compound relative to a control S. *cerevisiae* strain or a steviol glycoside-producing S. *cerevisiae* strain overexpressing SrKAHel (SEQ ID NO:18, SEQ ID NO:68). *See* Example 4.

[0097] In some embodiments, a KAH is a *Prunus* KAH, such as a *Prunus avium, Prunus mume,* or *Prunus persica* KAH. In some embodiments, a KAH is a KAH of the CYP72A219 or CYP71A219-like family. In some embodiments, the nucleotide sequence of a nucleic acid

encoding a KAH enzyme is set forth in SEQ ID NO:90 or SEQ ID NO:96. The nucleic acids of SEQ ID NO:90 and SEQ ID NO:96 encode a KAH from *Prunus avium* with an amino acid sequence set forth in SEQ ID NO:91. In some embodiments, a KAH polypeptide is a polypeptide with an amino acid sequence set forth in SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, or SEQ ID NO:95. In some embodiments, a KAH polypeptide is a KAH polypeptide with at least 50% sequence identity to an amino acid sequence set forth in SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, or SEQ ID NO:95. In some embodiments, expression of a gene encoding a polypeptide having at least 50% sequence identity to an amino acid sequence set forth in SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, or SEQ ID NO:95 in a recombinant host results in production of a steviol glycoside or steviol glycoside precursor, such as 13-SMG and/or rubusoside. *See* Example 8.

[0098] In some embodiments, the nucleotide sequence of the nucleic acid encoding a CPR enzyme is set forth in SEQ ID NO:23, SEQ ID NO:51, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:66, SEQ ID NO:67, or SEQ ID NO:97. In some aspects, the nucleic acid encoding the CPR polypeptide has at least 75% identity to the nucleotide sequence set forth in SEQ ID NO:23, SEQ ID NO:61, or SEQ ID NO:62, or at least 70% identity to the nucleotide sequence set forth in SEQ ID NO:24, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:51, or SEQ ID NO:97. In some embodiments, the amino acid sequence of the CPR enzyme is set forth in SEQ ID NO:22, SEQ ID NO:28, SEQ ID NO:69, SEQ ID NO:73, SEQ ID NO:74, or SEQ ID NO:76, SEQ ID NO:87, or SEQ ID NO:98. In some embodiments, a host cell comprises one or more copies of one or more nucleic acids encoding a CPR enzyme.

[0099] In a non-limiting example, SrKAHel is activated by the *S. cerevisiae* CPR encoded by gene NCP1 (YHR042W). Enhanced activation of the KAH encoded by SrKAHel is observed when the *Arabidopsis thaliana* CPR encoded by the gene ATR2 (SEQ ID NO:51) or the *S. rebaudiana* CPR encoded by the genes CPR7 (SEQ ID NO:23) or CPR8 (SEQ ID NO:24, SEQ ID NO:28) are co-expressed in a recombinant cell. Amino acid sequences of the *A. thaliana* polypeptides ATR1 and ATR2 are set forth in SEQ ID NO:25 and SEQ ID NO:26, respectively. The *S. rebaudiana* polypeptides CPR7 and CPR8 are set forth in SEQ ID NO:27 and SEQ ID NO:28, respectively.

[00100] In some embodiments, expression of CPR1 (SEQ ID NO:61, SEQ ID NO:76) or of CPR7 in the steviol glycoside-producing *S. cerevisiae* strain co-expressing *S. rebaudiana* CPR8 (SEQ ID NO:24, SEQ ID NO:28) and *A. thaliana* ATR2 (SEQ ID NO:51) results in higher levels of RebM compared to a control steviol glycoside-producing *S. cerevisiae* strain expressing *S.*

rebaudiana CPR8 (SEQ ID NO:24, SEQ ID NO:28) and *A. thaliana* ATR2 (SEQ ID N0:51). In some embodiments, expression of the CPR set forth in SEQ ID NO:62 in a steviol glycoside-producing *S. cerevisiae* strain overexpressing SrKAHel (SEQ ID NO: 18, SEQ ID NO:68) results in higher levels of RebM compared to a steviol glycoside-producing S. *cerevisiae* strain that does not express the nucleic acid set forth in SEQ ID NO:62 or overexpress SrKAHel. *See* Example 5.

[00101] In some embodiments, co-expression of SrKOI (SEQ ID NO:59, SEQ ID NO:79) and a CPR gene of SEQ ID NO:66 or SEQ ID NO:77 in a RebB-producing strain results in higher production of 13-SMG and RebB than co-expression of a KO gene of SEQ ID NO:63 or SEQ ID NO:64 and a CPR gene of SEQ ID NO:66 or SEQ ID NO:77. *See* Example 6.

[00102] In some embodiments, CPR1 (SEQ ID NO:61, SEQ ID NO:76) or CPR12 (SEQ ID NO:97, SEQ ID NO:98) activates cytochrome c. In some embodiments, CPR1 (SEQ ID NO:61, SEQ ID NO:76) or CPR12 (SEQ ID NO:97, SEQ ID NO:98) in the presence of SrKAHel (SEQ ID NO:18, SEQ ID NO:68) activate cytochrome c. In some embodiments, CPR1 (SEQ ID NO:61, SEQ ID NO:76) or CPR12 (SEQ ID NO:97, SEQ ID NO:98) regulate conversion of ent-kaurenoic acid to steviol. In some embodiments, CPR1 (SEQ ID NO:61, SEQ ID NO:76) or CPR12 (SEQ ID NO:97, SEQ ID NO:98) in combination with SrKAHel (SEQ ID NO: 18, SEQ ID NO:68) convert ent-kaurenoic acid to steviol. In some embodiments, steviol production is detected upon incubation of ent-kaurenoic acid with microsomal protein prepared from S. *cerevisiae* strains expressing CPR1 (SEQ ID NO:61, SEQ ID NO:76) or CPR12 (SEQ ID NO:97, SEQ ID NO:98) in combination with SrKAHel (SEQ ID NO:18, SEQ ID NO:68). In some embodiments, expression of CPR1 (SEQ ID NO:61 , SEQ ID NO:76) or CPR12 (SEQ ID NO:97, SEQ ID NO:98) in a recombinant host results in production of a steviol glycoside or steviol glycoside precursor. *See* Example 9.

[00103] In some embodiments, a steviol glycoside-producing strain expresses a fusion construct comprising a KO and the NADPH-dependent P450 oxidoreductase domain of CYP102A1, referred to herein as "BMR." The codon-optimized nucleotide sequence encoding the BMR polypeptide is set forth in SEQ ID NO:1 17; the BMR amino acid sequence is set forth in SEQ ID NO: 118. In some embodiments, BMR is a mutant BMR, including, but not limited to a BMR W1046A mutant (SEQ ID NO:119, SEQ ID NO:120). The BMR mutant can be specific for NADH. In some embodiments, the KO-BMR fusion construct comprises a linker (SEQ ID NO:121, SEQ ID NO:122). In some embodiments, the KO of the fusion construct is SrKOI (SEQ ID NO:59, SEQ ID NO:79) or the KO encoded by the nucleotide sequence set forth in

SEQ ID NO:65 (corresponding to the amino acid sequence set forth in SEQ ID N0.75). In some embodiments, the KO of the fusion construct is a truncated KO. Exemplary KO-BMR fusion constructs are set forth in SEQ ID NOs:99-1 12. *See* Example 10.

[00104] In some embodiments, expression of SrK01-BMR fusion constructs (SEQ ID NOs:99-106) in a steviol glycoside-producing strain results in an increase in ent-kaurenoic acid, 13-SMG, and RebB levels, compared to expression of SrKOI (SEQ ID NO:59, SEQ ID NO:79) in a steviol glycoside-producing strain. In some embodiments, expression of a fusion construct (SEQ ID NO:107, SEQ ID NO:108) in a steviol glycoside-producing strain results in greater conversion of ent-kaurene to ent-kaurenoic acid and greater conversion of ent-kaurenoic acid to 13-SMG, compared to expression of the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 in a steviol glycoside-producing strain. In some embodiments, expression of a fusion construct comprising the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and the W1046A mutant BMR (SEQ ID NO:109, SEQ ID NO:1 10) results in incrased ent-kaurenoic acid levels. *See* Figure 16 (B and D) and Example 10.

[00105] In some embodiments, a steviol glycoside-producing strain comprises inheritance of cortical ER protein 2 (ICE2; SEQ ID NO:1 13, SEQ ID NO:1 14). ICE2 is also referred to as YIL090W. In some aspects, ICE2 is overexpressed. ICE2 can be expressed in a strain comprising CPR1 (SEQ ID NO:61, SEQ ID NO:76) and/or CPR12 (SEQ ID NO:97, SEQ ID NO:98). In some embodiments, a steviol glycoside-producing strain comprises two copies of ICE2. In some embodiments, expression of ICE2 increases ent-kaurene metabolism (resulting in decreased accumulation of ent-kaurene, ent-kaurenol, ent-kaurenal, and ent-kaurenol glycosides), resulting in increased accumulation of steviol glycosides, compared to a control strain. *See* Table 10 and Example 11.

[00106] In some embodiments, expression of the KO encoded by nucleotide sequence set forth in SEQ ID NO:56 in a steviol glycoside-producing strain cultivated by fermentation results in a lower accumulation of ent-kaurene compounds, compared to a control steviol glycoside-producing strain. In some aspects, higher levels of ent-kaurenoic acid and steviol glycosides result, as compared to a control strain. In some embodiments, expression of the KAH encoded by nucleotide sequence set forth in SEQ ID NO:80, the KO encoded by nucleotide sequence set forth in SEQ ID NO:56, and the KO encoded by nucleotide sequence set forth in SEQ ID NO:65 in a steviol glycoside-producing strain cultivated by fermentation results in decreased accumulation of ent-kaurene, ent-kaurenol, ent-kaurenal, ent-kaurenol glycosides, ent-kaurenoic acid, and ent-kaurenoic acid glycosides and increased production of steviol glycosides, as

compared to a control strain. In some embodiments, expression of CPR12 (SEQ ID NO:97, SEQ ID NO:98), the KAH encoded by nucleotide sequence set forth in SEQ ID NO:80, and the KO encoded by nucleotide sequence set forth in SEQ ID NO;56 cultivated by fermentation results in decreased ent-kaurene, ent-kaurenol, ent-kaurenal, ent-kaurenol glycosides, ent-kaurenoic acid, and ent-kaurenoic acid glycosides accumulation and higher levels of steviol glycosides, as compared to a control strain. *See* Table 12 and Example 12.

Functional Homologs

[00107] Functional homologs of the polypeptides described above are also suitable for use in producing steviol glycosides in a recombinant host. A functional homolog is a polypeptide that has sequence similarity to a reference polypeptide, and that carries out one or more of the biochemical or physiological function(s) of the reference polypeptide. A functional homolog and the reference polypeptide can be a natural occurring polypeptide, and the sequence similarity can be due to convergent or divergent evolutionary events. As such, functional homologs are sometimes designated in the literature as homologs, or orthologs, or paralogs. Variants of a naturally occurring functional homolog, such as polypeptides encoded by mutants of a wild type coding sequence, can themselves be functional homologs. Functional homologs can also be created via site-directed mutagenesis of the coding sequence for a polypeptide, or by combining domains from the coding sequences for different naturally-occurring polypeptides ("domain swapping"). Techniques for modifying genes encoding functional polypeptides described herein are known and include, *inter alia,* directed evolution techniques, site-directed mutagenesis techniques and random mutagenesis techniques, and can be useful to increase specific activity of a polypeptide, alter substrate specificity, alter expression levels, alter subcellular location, or modify polypeptide-polypeptide interactions in a desired manner. Such modified polypeptides are considered functional homologs. The term "functional homolog" is sometimes applied to the nucleic acid that encodes a functionally homologous polypeptide.

[00108] Functional homologs can be identified by analysis of nucleotide and polypeptide sequence alignments. For example, performing a query on a database of nucleotide or polypeptide sequences can identify homologs of steviol glycoside biosynthesis polypeptides. Sequence analysis can involve BLAST, Reciprocal BLAST, or PSI-BLAST analysis of non-redundant databases using a KO, KAH, or CPR amino acid sequence as the reference sequence. Amino acid sequence is, in some instances, deduced from the nucleotide sequence. Those polypeptides in the database that have greater than 40% sequence identity are candidates for further evaluation for suitability as a steviol glycoside biosynthesis polypeptide.

Amino acid sequence similarity allows for conservative amino acid substitutions, such as substitution of one hydrophobic residue for another or substitution of one polar residue for another. If desired, manual inspection of such candidates can be carried out in order to narrow the number of candidates to be further evaluated. Manual inspection can be performed by selecting those candidates that appear to have domains present in steviol glycoside biosynthesis polypeptides, e.g., conserved functional domains. In some embodiments, nucleic acids and polypeptides are identified from transcriptome data based on expression levels rather than by using BLAST analysis.

[00109] Conserved regions can be identified by locating a region within the primary amino acid sequence of a steviol glycoside biosynthesis polypeptide that is a repeated sequence, forms some secondary structure *(e.g.,* helices and beta sheets), establishes positively or negatively charged domains, or represents a protein motif or domain. *See, e.g.,* the Pfam web site describing consensus sequences for a variety of protein motifs and domains on the World Wide Web at sanger.ac.uk/Software/Pfam/ and pfam.janelia.org/. The information included at the Pfam database is described in Sonnhammer *et al., Nucl. Acids Res.,* 26:320-322 (1998); Sonnhammer *et al.,* Proteins, 28:405-420 (1997); and Bateman *et al., Nucl. Acids Res.,* 27:260-262 (1999). Conserved regions also can be determined by aligning sequences of the same or related polypeptides from closely related species. Closely related species preferably are from the same family. In some embodiments, alignment of sequences from two different species is adequate to identify such homologs.

[00110] Typically, polypeptides that exhibit at least about 40% amino acid sequence identity are useful to identify conserved regions. Conserved regions of related polypeptides exhibit at least 45% amino acid sequence identity (e.g., at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% amino acid sequence identity). In some embodiments, a conserved region exhibits at least 92%, 94%, 96%, 98%, or 99% amino acid sequence identity.

[00111] For example, polypeptides suitable for producing steviol in a recombinant host include functional homologs of KO, KAH, and CPR.

[00112] Methods to modify the substrate specificity of, for example, KO, KAH, or CPR, are known to those skilled in the art, and include without limitation site-directed/rational mutagenesis approaches, random directed evolution approaches and combinations in which random mutagenesis/saturation techniques are performed near the active site of the enzyme. For example see Osmani *et al.,* 2009, *Phytochemistry* 70: 325-347.

[00113] A candidate sequence typically has a length that is from 80% to 200% of the length of the reference sequence, *e.g.,* 82, 85, 87, 89, 90, 93, 95, 97, 99, 100, 105, 110, 115, 120, 130, 140, 150, 160, 170, 180, 190, or 200% of the length of the reference sequence. A functional homolog polypeptide typically has a length that is from 95% to 105% of the length of the reference sequence, e.g., 90, 93, 95, 97, 99, 100, 105, 110, 115, or 120% of the length of the reference sequence, or any range between. A% identity for any candidate nucleic acid or polypeptide relative to a reference nucleic acid or polypeptide can be determined as follows. A reference sequence *(e.g.,* a nucleic acid sequence or an amino acid sequence described herein) is aligned to one or more candidate sequences using the computer program Clusta!W {version 1.83, default parameters), which allows alignments of nucleic acid or polypeptide sequences to be carried out across their entire length (global alignment). Chenna *et* a/., 2003, *Nucleic Acids Res.* 31(13):3497-500.

[00114] CiustalW calculates the best match between a reference and one or more candidate sequences, and aligns them so that identities, similarities and differences can be determined. Gaps of one or more residues can be inserted into a reference sequence, a candidate sequence, or both, to maximize sequence alignments. For fast pairwise alignment of nucleic acid sequences, the following default parameters are used: word size: 2; window size: 4; scoring method: % age; number of top diagonals: 4; and gap penalty: 5. For multiple alignment of nucleic acid sequences, the following parameters are used: gap opening penalty: 10.0; gap extension penalty: 5.0; and weight transitions: yes. For fast pairwise alignment of protein sequences, the following parameters are used: word size: 1; window size: 5; scoring method :% age; number of top diagonals: 5; gap penalty: 3. For multiple alignment of protein sequences, the following parameters are used: weight matrix: blosum; gap opening penalty: 10.0; gap extension penalty: 0.05; hydrophilic gaps: on; hydrophilic residues: Gly, Pro, Ser, Asn, Asp, Gin, Glu, Arg, and Lys; residue-specific gap penalties: on. The CiustalW output is a sequence alignment that reflects the relationship between sequences. CiustalW can be run, for example, at the Baylor College of Medicine Search Launcher site on the World Wide Web (searchlauncher.bcm.tmc.edu/multi-align/multi-align.html) and at the European Bioinformatics Institute site on the World Wide Web (ebi.ac.uk/clustalw).

[00115] To determine % identity of a candidate nucleic acid or amino acid sequence to a reference sequence, the sequences are aligned using CiustalW, the number of identical matches in the alignment is divided by the length of the reference sequence, and the result is multiplied by 100. It is noted that the % identity value can be rounded to the nearest tenth. For

example, 78.11, 78.12, 78.13, and 78.14 are rounded down to 78.1, while 78.15, 78.16, 78.17, 78.18, and 78.19 are rounded up to 78.2.

[00116] It will be appreciated that functional KO, KAH, or CPR proteins can include additional amino acids that are not involved in the enzymatic activities carried out by the enzymes. In some embodiments, KO, KAH, or CPR proteins are fusion proteins. The terms "chimera," "fusion polypeptide," "fusion protein," "fusion enzyme," "fusion construct," "chimeric protein," "chimeric polypeptide," "chimeric construct," and "chimeric enzyme" can be used interchangeably herein to refer to proteins engineered through the joining of two or more genes that code for different proteins. In some embodiments, a nucleic acid sequence encoding a KO, KAH, or CPR polypeptide can include a tag sequence that encodes a "tag" designed to facilitate subsequent manipulation *(e.g.*, to facilitate purification or detection), secretion, or localization of the encoded polypeptide. Tag sequences can be inserted in the nucleic acid sequence encoding the polypeptide such that the encoded tag is located at either the carboxyl or amino terminus of the polypeptide. Non-limiting examples of encoded tags include green fluorescent protein (GFP), human influenza hemagglutinin (HA), glutathione S transferase (GST), polyhistidine-tag (HIS tag), and Flag™ tag (Kodak, New Haven, CT). Other examples of tags include a chloroplast transit peptide, a mitochondrial transit peptide, an amyloplast peptide, signal peptide, or a secretion tag.

[00117] In some embodiments, a fusion protein is a protein altered by domain swapping. As used herein, the term "domain swapping" is used to describe the process of replacing a domain of a first protein with a domain of a second protein. In some embodiments, the domain of the first protein and the domain of the second protein are functionally identical or functionally similar. In some embodiments, the structure and/or sequence of the domain of the second protein differs from the structure and/or sequence of the domain of the first protein. In some embodiments, a KO polypeptide is altered by domain swapping. *See* Example 10.

Steviol and Steviol Glycoside Biosynthesis Nucleic Acids

[00118] A recombinant gene encoding a polypeptide described herein comprises the coding sequence for that polypeptide, operably linked in sense orientation to one or more regulatory regions suitable for expressing the polypeptide. Because many microorganisms are capable of expressing multiple gene products from a polycistronic mRNA, multiple polypeptides can be expressed under the control of a single regulatory region for those microorganisms, if desired. A coding sequence and a regulatory region are considered to be operably linked when the regulatory region and coding sequence are positioned so that the regulatory region is effective

for regulating transcription or translation of the sequence. Typically, the translation initiation site of the translational reading frame of the coding sequence is positioned between one and about fifty nucleotides downstream of the regulatory region for a monocistronic gene.

[00119] In many cases, the coding sequence for a polypeptide described herein is identified in a species other than the recombinant host, *i.e.,* is a heterologous nucleic acid. Thus, if the recombinant host is a microorganism, the coding sequence can be from other prokaryotic or eukaryotic microorganisms, from plants or from animals. In some case, however, the coding sequence is a sequence that is native to the host and is being reintroduced into that organism. A native sequence can often be distinguished from the naturally occurring sequence by the presence of non-natural sequences linked to the exogenous nucleic acid, *e.g.,* non-native regulatory sequences flanking a native sequence in a recombinant nucleic acid construct. In addition, stably transformed exogenous nucleic acids typically are integrated at positions other than the position where the native sequence is found. "Regulatory region" refers to a nucleic acid having nucleotide sequences that influence transcription or translation initiation and rate, and stability and/or mobility of a transcription or translation product. Regulatory regions include, without limitation, promoter sequences, enhancer sequences, response elements, protein recognition sites, inducible elements, protein binding sequences, 5' and 3' untranslated regions (UTRs), transcriptional start sites, termination sequences, polyadenylation sequences, introns, and combinations thereof. A regulatory region typically comprises at least a core (basal) promoter. A regulatory region also may include at least one control element, such as an enhancer sequence, an upstream element or an upstream activation region (UAR). A regulatory region is operably linked to a coding sequence by positioning the regulatory region and the coding sequence so that the regulatory region is effective for regulating transcription or translation of the sequence. For example, to operably link a coding sequence and a promoter sequence, the translation initiation site of the translational reading frame of the coding sequence is typically positioned between one and about fifty nucleotides downstream of the promoter. A regulatory region can, however, be positioned as much as about 5,000 nucleotides upstream of the translation initiation site, or about 2,000 nucleotides upstream of the transcription start site.

[00120] The choice of regulatory regions to be included depends upon several factors, including, but not limited to, efficiency, selectability, inducibility, desired expression level, and preferential expression during certain culture stages. It is a routine matter for one of skill in the art to modulate the expression of a coding sequence by appropriately selecting and positioning regulatory regions relative to the coding sequence. It will be understood that more than one

regulatory region may be present, *e.g.,* introns, enhancers, upstream activation regions, transcription terminators, and inducible elements.

[00121] One or more genes can be combined in a recombinant nucleic acid construct in "modules" useful for a discrete aspect of steviol and/or steviol glycoside production. Combining a plurality of genes in a module, particularly a polycistronic module, facilitates the use of the module in a variety of species. For example, a steviol biosynthesis gene cluster, or a UGT gene cluster, can be combined in a polycistronic module such that, after insertion of a suitable regulatory region, the module can be introduced into a wide variety of species. As another example, a UGT gene cluster can be combined such that each UGT coding sequence is operably linked to a separate regulatory region, to form a UGT module. Such a module can be used in those species for which monocistronic expression is necessary or desirable. In addition to genes useful for steviol or steviol glycoside production, a recombinant construct typically also contains an origin of replication, and one or more selectable markers for maintenance of the construct in appropriate species.

[00122] It will be appreciated that because of the degeneracy of the genetic code, a number of nucleic acids can encode a particular polypeptide; *i.e.,* for many amino acids, there is more than one nucleotide triplet that serves as the codon for the amino add. Thus, codons in the coding sequence for a given polypeptide can be modified such that optimal expression in a particular host is obtained, using appropriate codon bias tables for that host (e.g., microorganism). As isolated nucleic acids, these modified sequences can exist as purified molecules and can be incorporated into a vector or a virus for use in constructing modules for recombinant nucleic acid constructs.

[0003] In some cases, it is desirable to inhibit one or more functions of an endogenous polypeptide in order to divert metabolic intermediates towards steviol or steviol glycoside biosynthesis. For example, it may be desirable to downregulate synthesis of sterols in a yeast strain in order to further increase steviol or steviol glycoside production, e.g., by downregulating squalene epoxidase. As another example, it may be desirable to inhibit degradative functions of certain endogenous gene products, e.g., glycohydrolases that remove glucose moieties from secondary metabolites or phosphatases as discussed herein. In such cases, a nucleic acid that overexpresses the polypeptide or gene product may be included in a recombinant construct that is transformed into the strain. Alternatively, mutagenesis can be used to generate mutants in genes for which it is desired to increase or enhance function.

Host Microorganisms

[00123] Recombinant hosts can be used to express polypeptides for the producing steviol glycosides, including mammalian, insect, plant, and algal cells. A number of prokaryotes and eukaryotes are also suitable for use in constructing the recombinant microorganisms described herein, *e.g.,* gram-negative bacteria, yeast, and fungi. A species and strain selected for use as a steviol glycoside production strain is first analyzed to determine which production genes are endogenous to the strain and which genes are not present. Genes for which an endogenous counterpart is not present in the strain are advantageously assembled in one or more recombinant constructs, which are then transformed into the strain in order to supply the missing function(s).

[00124] Typically, the recombinant microorganism is grown in a fermenter at a defined temperature(s) for a desired period of time. The constructed and genetically engineered microorganisms provided by the invention can be cultivated using conventional fermentation processes, including, *inter alia,* chemostat, batch, fed-batch cultivations, semi-continuous fermentations such as draw and fill, continuous perfusion fermentation, and continuous perfusion cell culture. Depending on the particular microorganism used in the method, other recombinant genes such as isopentenyl biosynthesis genes and terpene synthase and cyclase genes may also be present and expressed. Levels of substrates and intermediates, *e.g.,* isopentenyl diphosphate, dimethylailyl diphosphate, GGPP, ent-kaurene and ent-kaurenoic acid, can be determined by extracting samples from culture media for analysis according to published methods.

[00125] Carbon sources of use in the instant method include any molecule that can be metabolized by the recombinant host cell to facilitate growth and/or production of the steviol glycosides. Examples of suitable carbon sources include, but are not limited to, sucrose (e.g., as found in molasses), fructose, xylose, ethanol, glycerol, glucose, cellulose, starch, cellobiose or other glucose-comprising polymer. In embodiments employing yeast as a host, for example, carbons sources such as sucrose, fructose, xylose, ethanol, glycerol, and glucose are suitable. The carbon source can be provided to the host organism throughout the cultivation period or alternatively, the organism can be grown for a period of time in the presence of another energy source, *e.g.,* protein, and then provided with a source of carbon only during the fed-batch phase.

[00126] After the recombinant microorganism has been grown in culture for the desired period of time, steviol and/or one or more steviol glycosides can then be recovered from the culture using various techniques known in the art. In some embodiments, a permeabilizing

agent can be added to aid the feedstock entering into the host and product getting out. For example, a crude iysate of the cultured microorganism can be centrifuged to obtain a supernatant. The resulting supernatant can then be applied to a chromatography column, *e.g.,* a C-18 column, and washed with water to remove hydrophilic compounds, followed by elution of the compound(s) of interest with a solvent such as methanol. The compound(s) can then be further purified by preparative HPLC. *See also,* WO 2009/140394.

[00127] It will be appreciated that the various genes and modules discussed herein can be present in two or more recombinant hosts rather than a single host. When a plurality of recombinant hosts is used, they can be grown in a mixed culture to accumulate steviol and/or steviol glycosides.

[00128] Alternatively, the two or more hosts each can be grown in a separate culture medium and the product of the first culture medium, e.g., steviol, can be introduced into second culture medium to be converted into a subsequent intermediate, or into an end product such as, for example, RebA. The product produced by the second, or final host is then recovered. It will also be appreciated that in some embodiments, a recombinant host is grown using nutrient sources other than a culture medium and utilizing a system other than a fermenter.

[00129] Exemplary prokaryotic and eukaryotic species are described in more detail below. However, it will be appreciated that other species can be suitable. For example, suitable species can be in a genus such as *Agaricus, Aspergillus, Bacillus, Candida, Corynebacteriurn, Eremothecium, Escherichia, Fusarium/Cibberella, Kluyveromyces, Laetiporus, Lentinus, Phaffia, Phanerochaete, Pichia, Physcomitrella, Rhodoturu!a, Saccharomyces, Schizosaccharomyces, Sphaceloma, Xanthophyllomyces* or *Yarrowia.* Exemplary species from such genera include *Lentinus tigrinus, Laetiporus sulphureus, Phanerochaete chrysosporium, Pichia pastoris, Cyberlindnera jadinii, Physcomitrella patens, Rhodoturula glutinis, Rhodoturula mucilaginosa, Phaffia rhodozyma, Xanthophyllomyces dendrorhous, Fusarium fujikuroi/Gibberella fujikuroi, Candida utilis, Candida glabrata, Candida albicans,* and *Yarrowia lipolytica.*

[00130] In some embodiments, a microorganism can be a prokaryote such as *Escherichia* bacteria cells, for example, *Escherichia coli* cells; *Lactobacillus* bacteria cells; *Lactococcus* bacteria cells; *Cornebacterium* bacteria cells; *Acetobacter* bacteria cells; *Acinetobacter* bacteria cells; or *Pseudomonas* bacterial cells.

[00131] In some embodiments, a microorganism can be an Ascomycete such as *Gibberella fujikuroi, Kluyveromyces lactis, Schizosaccharomyces pombe, Aspergillus niger, Yarrowia lipolytica, Ashbya gossypii,* or *S. cerevisiae.*

[00132] in some embodiments, a microorganism can be an algal cell such as *Blakeslea trispora, Dunaliella salina, Haematococcus pluvialis, Chlorella sp., Undaria pinnatifida, Sargassum, Laminaria japonica, Scenedesmus almeriensis* species.

[00133] In some embodiments, a microorganism can be a cyanobacterial cell such as *Blakeslea trispora, Dunaliella salina, Haematococcus pluvialis, Chlorella sp., Undaria pinnatifida, Sargassum, Laminaria japonica, Scenedesmus almeriensis.*

Saccharomyces spp.

[00134] *Saccharomyces* is a widely used chassis organism in synthetic biology, and can be used as the recombinant microorganism platform. For example, there are libraries of mutants, plasmids, detailed computer models of metabolism and other information available for S. *cerevisiae,* allowing for rational design of various modules to enhance product yield. Methods are known for making recombinant microorganisms.

Aspergillus spp.

[001 35] *Aspergillus* **species** such as *A. oryzae, A. niger* and *A. sojae* are widely used microorganisms in food production and can also be used as the recombinant microorganism platform. Nucleotide sequences are available for genomes of *A. nidulans, A. fumigatus, A. oryzae, A. clavatus, A. flavus, A. niger,* and *A. terreus,* allowing rational design and modification of endogenous pathways to enhance flux and increase product yield. Metabolic models have been developed for *Aspergillus,* as well as transcriptomtc studies and proteomics studies. *A. niger* is cultured for the industrial production of a number of food ingredients such as citric acid and gluconic acid, and thus species such as *A. niger* are generally suitable for producing steviol glycosides.

E. ∞ li

[00136] *E. coli,* another widely used platform organism in synthetic biology, can also be used as the recombinant microorganism platform. Similar to *Saccharomyces,* there are libraries of mutants, plasmids, detailed computer models of metabolism and other information available for *E. coli,* allowing for rational design of various modules to enhance product yield. Methods

similar to those described above for *Saccharomyces* can be used to make recombinant *E. coli* microorganisms.

Agaricus. Gibberella, and Phanerochaete spp.

[00137] *Agaricus, Gibberella,* and *Phanerochaete* spp. can be useful because they are known to produce large amounts of isoprenoids in culture. Thus, the terpene precursors for producing large amounts of steviol glycosides are already produced by endogenous genes. Thus, modules comprising recombinant genes for steviol glycoside biosynthesis polypeptides can be introduced into species from such genera without the necessity of introducing mevalonate or MEP pathway genes.

Arxuia adeninivorans (Blastobotrys adeninivorans)

[00138] *Arxuia adeninivorans* is dimorphic yeast (it grows as budding yeast like the baker's yeast up to a temperature of 42°C, above this threshold it grows in a filamentous form) with unusual biochemical characteristics. It can grow on a wide range of substrates and can assimilate nitrate. It has successfully been applied to the generation of strains that can produce natural plastics or the development of a biosensor for estrogens in environmental samples.

Yarrowia lipolytica

[00139] *Yarrowia lipolytica* is dimorphic yeast *(see Arxuia adeninivorans)* and belongs to the family Hemiascomycetes. The entire genome of *Yarrowia lipolytica* is known. *Yarrowia* species is aerobic and considered to be non-pathogenic. *Yarrowia* is efficient in using hydrophobic substrates *(e.g.* aikanes, fatty acids, oils) and can grow on sugars. It has a high potential for industrial applications and is an oleaginous microorgamism. *Yarrowia lipolyptica* can accumulate lipid content to approximately 40% of its dry cell weight and is a model organism for lipid accumulation and remobilization. *See e.g.,* Nicaud, 2012, *Yeast* 29(1 0):409-1 8; Beopoulos *et al.,* 2009, *Biochimie* 91(6):692-6; Bankar *et* a/., 2009, *Appl Microbiol Biotechnol.* 84(5):847-65.

Rhodotorula so.

[00140] *Rhodotorula* is unicellular, pigmented yeast. The oleaginous red yeast, *Rhodotorula glutinis,* has been shown to produce lipids and carotenoids from crude glycerol (Saenge *et al.,* 201 1, *Process Biochemistry* 46(1):21 0-8). *Rhodotorula toruloides* strains have been shown to be an efficient fed-batch fermentation system for improved biomass and lipid productivity (Li *et al.,* 2007, *Enzyme and Microbial Technology* 41:31 2-7).

Rhodosporidium toruioides

[00141] *Rhodosporidium toruioides* is oleaginous yeast and useful for engineering iipid-production pathways (See *e.g.* Zhu *et al.,* 2013, *Nature Commun.* 3:1 112; Ageitos *et al.,* 201 1, *Applied Microbiology and Biotechnology* 90(4): 12 19-27).

Candida boidinii

[00142] *Candida boidinii* is methylotrophic yeast (it can grow on methanol). Like other methylotrophic species such as *Hansenula polymorpha* and *Pichia pastoris,* it provides an excellent platform for producing heterologous proteins. Yields in a multigram range of a secreted foreign protein have been reported. A computational method, IPRO, recently predicted mutations that experimentally switched the cofactor specificity of *Candida boidinii* xylose reductase from NADPH to NADH. *See, e.g.,* Mattanovich *et al.,* 2012, *Methods Mol Biol.* 824:329-58; Khoury *et al.,* 2009, *Protein Sci.* 18(1 0):21 25-38.

Hansenula polymorpha (Pichia anousta)

[00143] *Hansenula polymorpha* is methylotrophic yeast *(see Candida boidinii).* It can furthermore grow on a wide range of other substrates; it is therm o-tolerant and can assimilate nitrate (see also *Kluyveromyces lactis).* It has been applied to producing hepatitis B vaccines, insulin and interferon alpha-2a for the treatment of hepatitis C, furthermore to a range of technical enzymes. *See, e.g.,* Xu *et al.,* 2014, *Virol Sin.* 29(6):403-9.

Kluyveromyces lactis

[00144] *Kluyveromyces lactis* is yeast regularly applied to the production of kefir. It can grow on several sugars, most importantly on lactose which is present in milk and whey. It has successfully been applied among others for producing chymosin (an enzyme that is usually present in the stomach of calves) for producing cheese. Production takes place in fermenters on a 40,000 L scale. *See, e.g.,* van Ooyen *et al.,* 2006, *FEMS Yeast Res.* 6(3):381-92.

Pichia pastoris

[00145] *Pichia pastoris* is methylotrophic yeast (see *Candida boidinii* and *Hansenula polymorpha).* It provides an efficient platform for producing foreign proteins. Platform elements are available as a kit and it is worldwide used in academia for producing proteins. Strains have been engineered that can produce complex human N-glycan (yeast glycans are similar but not identical to those found in humans). *See, e.g.,* Piirainen *et al.,* 2014, *N Biotechnol.* 31(6):532-7.

Physcomitrella spp.

[00146] *Physcomitrella mosses,* when grown in suspension culture, have characteristics similar to yeast or other fungal cultures. This genera can be used for producing plant secondary metabolites, which can be difficult to produce in other types of cells.

Steviol Glycoside Compositions

[00147] Steviol glycosides do not necessarily have equivalent performance in different food systems. It is therefore desirable to have the ability to direct the synthesis to steviol glycoside compositions of choice. Recombinant hosts described herein can produce compositions that are selectively enriched for specific steviol glycosides (e.g., RebD or RebM) and have a consistent taste profile. As used herein, the term "enriched" is used to describe a steviol glycoside composition with an increased proportion of a particular steviol glycoside, compared to a steviol glycoside composition (extract) from a stevia plant. Thus, the recombinant hosts described herein can facilitate the production of compositions that are tailored to meet the sweetening profile desired for a given food product and that have a proportion of each steviol glycoside that is consistent from batch to batch. In some embodiments, hosts described herein do not produce or produce a reduced amount of undesired plant by-products found in Stevia extracts. Thus, steviol glycoside compositions produced by the recombinant hosts described herein are distinguishable from compositions derived from *Stevia* plants.

[00148] The amount of an individual steviol glycoside *(e.g.,* RebA, RebB, RebD, or RebM) accumulated can be from about 1 to about 7,000 mg/L, *e.g.,* about 1 to about 10 mg/L, about 3 to about 10 mg/L, about 5 to about 20 mg/L, about 10 to about 50 mg/L, about 10 to about 100 mg/L, about 25 to about 500 mg/L, about 100 to about 1,500 mg/L, or about 200 to about 1,000 mg/L, at least about 1,000 mg/L, at least about 1,200 mg/L, at least about at least 1,400 mg/L, at least about 1,600 mg/L, at least about 1,800 mg/L, at least about 2,800 mg/L, or at least about 7,000 mg/L. In some aspects, the amount of an individual steviol glycoside can exceed 7,000 mg/L. The amount of a combination of steviol glycosides (e.g., RebA, RebB, RebD, or RebM) accumulated can be from about 1 mg/L to about 7,000 mg/L, *e.g.,* about 200 to about 1,500, at least about 2,000 mg/L, at least about 3,000 mg/L, at least about 4,000 mg/L, at least about 5,000 mg/L, at least about 6,000 mg/L, or at least about 7,000 mg/L. In some aspects, the amount of a combination of steviol glycosides can exceed 7,000 mg/L. In general, longer culture times will lead to greater amounts of product. Thus, the recombinant microorganism can be cultured for from 1 day to 7 days, from 1 day to 5 days, from 3 days to 5 days, about 3 days, about 4 days, or about 5 days.

[00149] It will be appreciated that the various genes and modules discussed herein can be present in two or more recombinant microorganisms rather than a single microorganism. When a plurality of recombinant microorganisms is used, they can be grown in a mixed culture to produce steviol and/or steviol glycosides. For example, a first microorganism can comprise one or more biosynthesis genes for producing a steviol glycoside precursor, while a second microorganism comprises steviol glycoside biosynthesis genes. The product produced by the second, or final microorganism is then recovered. It will also be appreciated that in some embodiments, a recombinant microorganism is grown using nutrient sources other than a culture medium and utilizing a system other than a fermenter.

[00150] Alternatively, the two or more microorganisms each can be grown in a separate culture medium and the product of the first culture medium, *e.g.,* steviol, can be introduced into second culture medium to be converted into a subsequent intermediate, or into an end product such as RebA. The product produced by the second, or final microorganism is then recovered. It will also be appreciated that in some embodiments, a recombinant microorganism is grown using nutrient sources other than a culture medium and utilizing a system other than a fermenter.

[00151] Steviol glycosides and compositions obtained by the methods disclosed herein can be used to make food products, dietary supplements and sweetener compositions. *See, e.g.,* WO 201 1/153378, WO 2013/022989, WO 2014/122227, and WO 2014/122328.

[00152] For example, substantially pure steviol or steviol glycoside such as RebM or RebD can be included in food products such as ice cream, carbonated beverages, fruit juices, yogurts, baked goods, chewing gums, hard and soft candies, and sauces. Substantially pure steviol or steviol glycoside can also be included in non-food products such as pharmaceutical products, medicinal products, dietary supplements and nutritional supplements. Substantially pure steviol or steviol glycosides may also be included in animal feed products for both the agriculture industry and the companion animal industry. Alternatively, a mixture of steviol and/or steviol glycosides can be made by culturing recombinant microorganisms separately, each producing a specific steviol or steviol glycoside, recovering the steviol or steviol glycoside in substantially pure form from each microorganism and then combining the compounds to obtain a mixture comprising each compound in the desired proportion. The recombinant microorganisms described herein permit more precise and consistent mixtures to be obtained compared to current Stevia products.

[00153] In another alternative, a substantially pure steviol or steviol glycoside can be incorporated into a food product along with other sweeteners, e.g. saccharin, dextrose, sucrose, fructose, erythritol, aspartame, sucralose, monatin, or acesulfame potassium. The weight ratio of steviol or steviol glycoside relative to other sweeteners can be varied as desired to achieve a satisfactory taste in the final food product. See, *e.g.,* U.S. 2007/0128311. In some embodiments, the steviol or steviol glycoside may be provided with a flavor (e.g., citrus) as a flavor modulator.

[00154] Compositions produced by a recombinant microorganism described herein can be incorporated into food products. For example, a steviol glycoside composition produced by a recombinant microorganism can be incorporated into a food product in an amount ranging from about 20 mg steviol glycoside/kg food product to about 1800 mg steviol glycoside/kg food product on a dry weight basis, depending on the type of steviol glycoside and food product. For example, a steviol glycoside composition produced by a recombinant microorganism can be incorporated into a dessert, cold confectionary *(e.g.,* ice cream), dairy product (e.g., yogurt), or beverage (e.g., a carbonated beverage) such that the food product has a maximum of 500 mg steviol glycoside/kg food on a dry weight basis. A steviol glycoside composition produced by a recombinant microorganism can be incorporated into a baked good (e.g., a biscuit) such that the food product has a maximum of 300 mg steviol glycoside/kg food on a dry weight basis. A steviol glycoside composition produced by a recombinant microorganism can be incorporated into a sauce *(e.g.,* chocolate syrup) or vegetable product (e.g., pickles) such that the food product has a maximum of 1000 mg steviol glycoside/kg food on a dry weight basis. A steviol glycoside composition produced by a recombinant microorganism can be incorporated into a bread such that the food product has a maximum of 160 mg steviol glycoside/kg food on a dry weight basis. A steviol glycoside composition produced by a recombinant microorganism, plant, or plant cell can be incorporated into a hard or soft candy such that the food product has a maximum of 1600 mg steviol glycoside/kg food on a dry weight basis. A steviol glycoside composition produced by a recombinant microorganism, plant, or plant cell can be incorporated into a processed fruit product (e.g., fruit juices, fruit filling, jams, and jellies) such that the food product has a maximum of 1000 mg steviol glycoside/kg food on a dry weight basis. In some embodiments, a steviol glycoside composition produced herein is a component of a pharmaceutical composition. *See, e.g.,* Steviol Glycosides Chemical and Technical Assessment 69th JECFA, 2007, prepared by Harriet Wailin, Food Agric. Org.; EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), "Scientific Opinion on the safety of steviol glycosides for the proposed uses as a food additive," 2010, *EFSA Journal* 8(4): 1537;

U.S. Food and Drug Administration GRAS Notice 323; U.S Food and Drug Administration GRAS Notice Notice 329; WO 201 1/037959; WO 2010/146463; WO 201 1/046423; and WO 2011/056834.

[001 55] For example, such a steviol glycoside composition can have from 90-99 weight % RebA and an undetectable amount of stevia plant-derived contaminants, and be incorporated into a food product at from 25-1600 mg/kg, *e.g.,* 100-500 mg/kg, 25-100 mg/kg, 250-1000 mg/kg, 50-500 mg/kg or 500-1 000 mg/kg on a dry weight basis.

[00156] Such a steviol glycoside composition can be a RebB-enriched composition having greater than 3 weight % RebB and be incorporated into the food product such that the amount of RebB in the product is from 25-1600 mg/kg, *e.g.,* 100-500 mg/kg, 25-100 mg/kg, 250-1000 mg/kg, 50-500 mg/kg or 500-1 000 mg/kg on a dry weight basis. Typically, the RebB-enriched composition has an undetectable amount of stevia plant-derived contaminants.

[001 57] Such a steviol glycoside composition can be a RebD-enriched composition having greater than 3 weight % RebD and be incorporated into the food product such that the amount of RebD in the product is from 25-1600 mg/kg, *e.g.,* 100-500 mg/kg, 25-100 mg/kg, 250-1000 mg/kg, 50-500 mg/kg or 500-1000 mg/kg on a dry weight basis. Typically, the RebD-enriched composition has an undetectable amount of stevia plant-derived contaminants.

[00158] Such a steviol glycoside composition can be a RebE-enriched composition having greater than 3 weight % RebE and be incorporated into the food product such that the amount of RebE in the product is from 25-1600 mg/kg, *e.g.,* 100-500 mg/kg, 25-100 mg/kg, 250-1000 mg/kg, 50-500 mg/kg or 500-1000 mg/kg on a dry weight basis. Typically, the RebE-enriched composition has an undetectable amount of stevia plant-derived contaminants.

[00159] Such a steviol glycoside composition can be a RebM-enriched composition having greater than 3 weight % RebM and be incorporated into the food product such that the amount of RebM in the product is from 25-1600 mg/kg, e.g., 100-500 mg/kg, 25-100 mg/kg, 250-1000 mg/kg, 50-500 mg/kg or 500-1000 mg/kg on a dry weight basis. Typically, the RebM-enriched composition has an undetectable amount of stevia plant-derived contaminants.

[00160] In some embodiments, a substantially pure steviol or steviol glycoside is incorporated into a tabletop sweetener or "cup-for-cup" product. Such products typically are diluted to the appropriate sweetness level with one or more bulking agents, *e.g.,* maltodextrins, known to those skilled in the art. Steviol glycoside compositions enriched for RebA, RebB, RebD, RebE, or RebM, can be package in a sachet, for example, at from 10,000 to 30,000 mg

steviol glycoside/kg product on a dry weight basis, for tabletop use. In some embodiments, a stevio! glycoside produced *in vitro, in vivo,* or by whole cell byconversion

[00161] The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

[00162] The Examples that follow are illustrative of specific embodiments of the invention, and various uses thereof. They are set forth for explanatory purposes only, and are not to be taken as limiting the invention.

Example 1. LC-MS Analytical Procedures

[00163] Three LC-MS procedures were used herein. In the first method used for Examples 2-6, LC-MS analyses were performed using an Ultimate 3000 UPLC system (Dionex) fitted with a Waters Acquity UPLC ®BEH shield RP18 column (**2.1** x 50 mm, 1.7 µm particles, 130 A pore size) connected to a TSQ Quantum Access (ThermoFisher Scientific) triple quadropole mass spectrometer with a heated electrospray ion (HESI) source. Elution was carried out using a mobile phase of eluent B (MeCN with 0.1% formic acid) and eluent A (water with 0.1% formic acid) by increasing the gradient from 25% to 47% B from min 0.0 to 4.0, increasing 47% to 100% B from min 4.0 to 5.0, and holding 100% B from min 5.0 to 6.5. The flow rate was 0.4 mL/min and the column temperature 35°C. Steviol glycosides were detected using SIM (Single Ion Monitoring) with the following m/z-traces.

Table 1A: LC-MS analytical information for Steviol Glycosides.

Description	Exact Mass	m/z trace (Da)	compound (typical t_R in min)
Steviol + 1 Glucose	$[M+H]^+$ 481.2796 $[M+Na]^+$ 503.2615	481.2± 0.5 503.1± 0.5	19-SMG (2.29), 13-SMG (3.5)
Steviol + 2 Glucose	$[M+Na]^+$ 665.3149	665± 0.5	Rubusoside (2.52) Steviol-1,2-bioside (2.92) Steviol-1,3-bioside (2.28)
Steviol + 3 Glucose	$[M+Na]^+$ 827.3677	827.4 ± 0.5	1,2-Stevioside (2.01) 1,3-Stevioside (2.39) Rebaudioside B (2.88)
Steviol + 4 Glucose	$[M+Na]^+$ 989.4200	989.4 ± 0.5	Rebaudioside A (2.0)
Steviol + 5 Glucose	$[M+Na]^+$ 1151.4728	1151.4 ± 0.5	Rebaudioside D (1.1)
Steviol +	$[M+Na]^+$ 1313.5257	1313.5 ± 0.5	Rebaudioside M (1.3)

Description	Exact Mass	m/z trace (Da)	compound (typical t_R in min)
6 Glucose			

[00164] in the second method used for Examples 7, 8, and 10, LC-MS analyses were performed on Waters ACQUITY UPLC (Waters Corporation, Milford, MA) with coupled to a Waters ACQUITY ESI (electrospray ionization)-TQD triple quadropole mass spectrometer. Compound separation was achieved on Waters ACQUITY UPLC® BEH C18 column (2.1 x 50 mm, 1.7 pm particles, 130 A pore size) equipped with ACQUITY UPLC BEH C18 VanGuard pre-column (130 A, 1.7 pm, 2.1 mm X 5 mm) by using a gradient of the two mobile phases: A (Water with 0.1% formic acid) and B (Acetonitrile with 0.1% formic acid)increasing B from 20% to 50% between 0.3 to 2.0 min up to 100% at 2.01 min, holding to 100% for 0.6 min, and re-equilibrating for 0.6 min. The flow rate was 0.6 mL/ min, and the column temperature was 55°C. The MS acquisition was in negative ion-mode using SIM mode (Single Ion Monitoring). Stevioi glycoside quantification was done by comparison with authentic standards.

Table **1B: MS analytical information for Steviol Glycosides.**

Compound	m/z trace (Da)	Retention time (min)
RebE	965.42	1.06
RebD	1127.48	1.09
RebM	1289.53	1.15
RebA	965.42	1.43
1,3-Stevioside	803.37	1.60
Rubusoside	641.32	1.67
RebB	803.37	1.76
1,2-bioside	641.32	1.77
13-SMG	479.26	2.04

[00165] in the third method used for Example 9, LC-MS analyses were performed on Waters ACQUITY UPLC (Waters Corporation, Milford, MA) using a Waters Acquity UPLC® BEH C18 column (2.1 x 50 mm, 1.7 pm particles, 130 A) coupled to a Waters single quadropole mass spectrometer (SQD), equipped with an ESI and operated in negative mode. Compound separation was achieved by a gradient of the two mobile phases: A (water with 0.1% formic acid) and B (acetonitrile with 0.1% formic acid) by increasing from 60% to 100% B between 0.3 to 2.5 min, holding 100% B for 0.1 min, and re-equilibrating for 0.2 min. The flow rate was 0.6 mL/ min, and the column temperature was set at 55°C. Steviol or ent-kaurenoic acid was

monitored using SIM (Single Ion Monitoring) and quantified by comparing with authentic standards.

Table 1C: MS analytical information for steviol and ent-kaurenoic acid.

Compound	m/z trace (Da)	Retention time (min)
Steviol	317.21	0.61
Ent-kaurenoic acid	301.001	1.46

Example 2. Construction of Steviol Glycoside-Producing and RebB-Producing Yeast Strains

[00166] Steviol glycoside-producing *S. cerevisiae* strains were constructed as described in WO 201 1/153378, WO 2013/022989, WO 2014/122227, and WO 2014/122328. For example, a yeast strain comprising a recombinant gene encoding a *Synechococcus sp.* GGPPS (SEQ ID NO:49) polypeptide, a recombinant gene encoding a truncated *Zea mays* CDPS (SEQ ID NO:37) polypeptide, a recombinant gene encoding an *A. thaliana* KS (SEQ ID NO:6) polypeptide, a recombinant gene encoding an S. *rebaudiana* KO (SEQ ID NO:59, SEQ ID NO:79) polypeptide, a recombinant gene encoding an *A. thaliana* ATR2 (SEQ ID NO:51, SEQ ID NO:87) polypeptide, a recombinant gene encoding an O. *sativa* EUGT1 1 (SEQ ID NO:86) polypeptide, a recombinant gene encoding an SrKAHel (SEQ ID NO:18, SEQ ID NO:68) polypeptide, a recombinant gene encoding an S. *rebaudiana* CPR8 (SEQ ID NO:24, SEQ ID NO:28) polypeptide, a recombinant gene encoding an *S. rebaudiana* UGT85C2 (SEQ ID NO:30) polypeptide, a recombinant gene encoding an *S. rebaudiana* UGT74G1 (SEQ ID NO:29) polypeptide, a recombinant gene encoding an *S, rebaudiana* UGT76G1 (SEQ ID NO:2) polypeptide, and a recombinant gene encoding an S. *rebaudiana* UGT91D2 variant, UGT91D2e-b (SEQ ID NO:88), polypeptide accumulated steviol glycosides.

[00167] The UGT91D2e-b variant of UGT91D2 (SEQ ID NO:5 from PCT/US201 2/050021) includes a substitution of a methionine for leucine at position 2 1 1 and a substitution of an alanine for valine at position 286. Additional variants can include variants (except T144S, M152L, L213F, S364P, and G384C variants) described in Table 14 and Example 11 of the PCT/US201 2/050021 . GeneArt codon-optimized sequence encoding a S. *rebaudiana* UGT91D2e-b with the amino acid modifications L21 1M and V286A (SEQ ID NO:88 for amino acid sequence; codon optimized nucleotide sequence is set forth in SEQ ID NO:89) and

expressed from the native yeast TDH3 promoter and foiiowed by the native yeast CYC1 terminator.

[00168] Cells were grown in Synthetic Complete (SC) medium at 30°C for 5 days with shaking (400 rpm for deep wells and 200 rpm for 15 ml_ Falcon growth tubes) prior to harvest. Culture samples (without cell removal) were heated in the presence of DMSO for detection of total glycoside levels with LC-MS. The strain accumulated total amounts of RebD of over 2500 mg/L, total amounts of RebM of over 2500 mg/L, and total amounts of RebA of over 700 mg/L. *See* WO 2014/122227.

[00169] A separate *S. cerevisiae* strain was constructed to accumulate RebB. This strain comprised a recombinant gene encoding a *Synechococcus sp.* GGPPS (SEQ ID NO:49) polypeptide, a recombinant gene encoding a truncated *Z. mays* CDPS (SEQ ID NO:37) polypeptide, a recombinant gene encoding an *A. thaliana* KS (SEQ ID NO:6) polypeptide, a recombinant gene encoding an *S. rebaudiana* KO (SEQ ID NO:59, SEQ ID NO:79) polypeptide, a recombinant gene encoding an *A. thaliana* ATR2 (SEQ ID NO:51, SEQ ID NO:87) polypeptide, a recombinant gene encoding an O. *sativa* EUGT1 1 (SEQ ID NO:86) polypeptide, a recombinant gene encoding an SrKAHei (SEQ ID NO: 18, SEQ ID NO:68) polypeptide, a recombinant gene encoding an S. *rebaudiana* CPR8 (SEQ ID NO:24, SEQ ID NO:28) polypeptide, a recombinant gene encoding an *S. rebaudiana* UGT85C2 (SEQ ID NO:30) polypeptide, a recombinant gene encoding an S. *rebaudiana* UGT76G1 (SEQ ID NO:2) polypeptide, and a recombinant gene encoding an S. *rebaudiana* UGT91D2 variant, UGT91D2e-b (SEQ ID NO:88), polypeptide accumulated steviol glycosides.

Example 3. Steviol Glycoside Production in Yeast Strains Expressing KO Genes

[00170] To determine whether increased levels of ent-kaurenoic acid improve steviol glycoside production, the activity of KO genes from various species were analyzed. Putative KO genes were identified using the NCBi Basic Local Alignment Sequence Search Tool (BLAST). Genes encoding KO polypeptides were cloned and expressed the RebB-producing *S. cerevisiae* strain described in Example 2, which was modified to lack KO genes. Thus, RebB was only accumulated upon expression of a functional KO.

[00171] Two KO polypeptides identified by the amino acid sequences set forth in SEQ ID NO:54 (nucleotide sequence set forth in SEQ ID NO:55) and SEQ ID NO:75 (nucleotide sequences set forth in SEQ ID NO:56) were found to accumulate higher levels of RebB than

SrKOI (nucleotide sequence set forth in SEQ ID NO:59, amino acid sequences set forth in SEQ ID NO:79) in the RebB-producing strain. RebB levels ($\mu M/00_{60}0$) are shown in Figure 3.

[00172] Expression of genes (SEQ ID NO:55 or SEQ ID NO:56) encoding KO polypeptides in an S. *cerevisiae* steviol glycoside-producing strain also resulted in accumulation of ent-kaurenoic acid (Figure 4). Expression of a gene encoding a codon-optimized KO polypeptide (SEQ ID NO:57) and a gene encoding the KO polypeptide set forth in SEQ ID NO:70 also resulted in accumulation of ent-kaurenoic acid. However, expression of SrKOI (SEQ ID NO:59, SEQ ID NO:79) did not result in measurable levels of ent-kaurenoic acid. Thus, the KO polypeptides encoded by nucleotide sequences set forth in SEQ ID NOs: 55-57 more efficiently converted ent-kaurene, ent-kaurenol, and/or ent-kaurenal to ent-kaurenoic acid in S. *cerevisiae,* as compared to the SrKOI polypeptide encoded by nucleotide sequence set forth in SEQ ID NO:59.

Example 4. Steviol Glycoside Production in Yeast Strains Expressing KO Genes and Further Overexpressing SrKAHel

[00173] Cloned KO genes were individually expressed in a steviol glycoside-producing *S. cerevisiae* strain. The S. *cerevisiae* strain described in Example 2, which expresses SrKOI (SEQ ID NO:59, SEQ ID NO:79), was modified to comprise overexpress SrKAHel (SEQ ID NO:18, SEQ ID NO:68). The coding sequences of the KO genes tested, as well as their corresponding amino acid sequences, are set forth in Table 2. The sequences set forth in SEQ ID NOs: 55, 57, 58, 59, and 60 were codon-optimized for expression in S. *cerevisiae.*

Table 2: KO Genes Expressed in Steviol Glycoside-Producing S. *cerevisiae* strain that Further Overexpresses SrKAHel.

KO Nucleotide Sequence	Corresponding KO Amino Acid Sequence
SEQ ID NO:55	SEQ ID NO:54
SEQ ID NO:56	SEQ ID NO:75
SEQ ID NO:57	SEQ ID NO:70
SEQ ID NO:58	SEQ ID NO:71
SEQ ID NO:59	SEQ ID NO:79
SEQ ID NO:60	SEQ ID NO:72

[00174] *S. cerevisiae* strains co-expressing any of the heterologous nucleic acids encoding a KO enzyme of Table 2 and further overexprssing SrKAHel (SEQ ID NO:18, SEQ ID NO:68)

accumulated higher levels of steviol glycosides than the control S. *cerevisiae* strain (not expressing a KO of Table 2) or a steviol glycoside-producing S. *cerevisiae* strain only overexpressing SrKAHel , as shown in Figure 5. A steviol glycoside-producing *S. cerevisiae* strain expressing a codon-optimized version of SEQ ID NO:56, identified herein as SEQ ID NO:65, and overexpressing SrKAHel accumulated higher levels of steviol glycosides (RebA, RebD, and RebM) than the steviol glycoside-producing *S. cerevisiae* strain co-expressing the nucleic acid set forth in SEQ ID NO:56 and SrKAHel (Figure 6).

[001 75] Additionally, *S, cerevisiae* strains co-expressing a nucleic acid set forth in SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, or SEQ ID NO:60 and further overexpressing SrKAHel accumulated higher levels of glycosylated ent-kaurenoic acid than the control *S. cerevisiae* strain not expressing a KO of Table 2 (Figure 7).

[00176] As well, S. *cerevisiae* strains co-expressing a nucleic acid set forth in SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, or SEQ ID NO:60 and further overexpressing SrKAHel demonstrated improved metabolic conversion of intermediate compound, ent-kaurenol, which, in turn, resulted in reduced accumulation of glycosylated ent-kaurenol, relative to the control *S. cerevisiae* strain not expressing a KO of Table 2 or the steviol glycoside-producing *S. cerevisiae* strain only overexpressing SrKAHel, as shown in Figure 8. The control *S. cerevisiae* strain and the steviol glycoside-producing *S. cerevisiae* strain only overexpressing SrKAHel each accumulated higher leveis of glycosylated ent-kaurenol than did S. *cerevisiae* strains expressing a nucleic acid set forth in SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:59, or SEQ ID NO:60 and further overexpressing SrKAHel.

Example 5. Steviol Glycoside Production in Yeast Strains Expressing CPR Genes

[00177] Cloned CPR genes were individually expressed in a steviol glycoside-producing S. *cerevisiae* strain. The steviol glycoside-producing *S. cerevisiae* strain described in Example 2, which expresses S. *rebaudiana* CPR8 (SEQ ID NO:24, SEQ ID NO:28) and *A. thaliana* ATR2 (SEQ ID NO:51), was modified to co-express a nucleic acid encoding a CPR of Table 3. The coding sequences of the CPR genes tested, as well as their corresponding amino acid sequences, are set forth in Table 3.

Table 3: CPR Genes Tested in Combination with CPR8 and ATR2.

Gene	Nucleotide Sequence	Amino Acid Sequence

S. rebaudiana CPR1	SEQ ID NO:61	SEQ ID NO:76
S. rebaudiana CPR7	SEQ ID NO:23	SEQ ID NO:69
CPR4497	SEQ ID NO:62	SEQ ID NO:74

[00178] As shown in Figure 9, expression of CPR1 (SEQ ID NO:61, SEQ ID NO:76) or of CPR7 (SEQ ID NO:23, SEQ ID NO:69) in the steviol glycoside-producing *S. cerevisiae* strain already expressing *S. rebaudiana* CPR8 (SEQ ID NO:24, SEQ ID NO:28) and *A. thaliana* ATR2 (SEQ ID NO:51) resulted in higher levels of RebM than those accumulated by the control steviol glycoside-producing *S. cerevisiae* strain not expressing CPR1 or CPR7. As well, a steviol glycoside-producing *S. cerevisiae* strain expressing the nucleic acid set forth in SEQ ID NO:62 and overexpressing SrKAHel (SEQ ID NO:18, SEQ ID NO:68) accumulated higher levels of RebM than those accumulated by the control steviol glycoside-producing *S. cerevisiae* strain that only overexpressed SrKAHel (Figure 10).

Example 6. Steviol Glycoside Production in Yeast Strains Co-Expressing KO and CPR Genes

[00179] Steviol glycoside production was tested in the RebB-producing *S. cerevisiae* strain described in Example 2, which was modified to co-express a KO gene of Table 4 and a CPR of Table 5.

Table 4: **KO Genes Tested in Combination with CPR** Genes.

Gene	Nucleotide Sequence	Amino Acid Sequence
SrKO1	SEQ ID NO:59	SEQ ID NO:79
Codon-optimized KO	SEQ ID NO:63	SEQ ID NO:77
Codon-optimized KO	SEQ ID NO:64	SEQ ID NO:78

Table 5: **CPR Genes Tested in Combination with KO Genes.**

Nucleotide Sequence	Amino Acid Sequence
SEQ ID NO:66	SEQ ID NO:73
SEQ ID NO:67	SEQ ID NO:22

[00180] As shown in Figure 12, co-expression of SrKOI (SEQ ID NO:59, SEQ ID NO:79) and either of the CPR genes of Table 5 in the RebB-producing strain resulted in higher production of 13-SMG and RebB than co-expression of a nucleic acid set forth in SEQ ID NO:63 or SEQ ID NO:64 and either of the cytochrome P450 genes of Table 5.

Example 7. Steviol Glycoside Production in Yeast Strains Expressing KAH Genes

[00181] Candidate KAH enzymes were cloned and expressed in an S. *cerevisiae* strain engineered to accumulate 13-SMG. The 13-SMG-producing *S. cerevisiae* strain comprised a recombinant gene encoding a *Synechococcus sp.* GGPPS7 polypeptide (SEQ **ID** NO:49), a recombinant gene encoding a truncated *Z. mays* CDPS polypeptide (SEQ ID NO:37), a recombinant gene encoding an *A. thaliana* KS polypeptide (SEQ ID NO:6), SrKOI (SEQ ID NO:59, SEQ **ID** NO:79), CPR8 (SEQ ID NO:24, SEQ ID NO:28), the KO encoded by the nucleotide sequence set forth in SEQ ID NO:56 (amino acid sequence set forth in SEQ ID NO:75), and UGT85C2 (SEQ ID NO:30) chromosomally integrated in separate expression cassettes (Figure 11B). The strain lacked SrKAHel (SEQ ID NO:18, SEQ ID NO:68); thus, 13-SMG was only accumulated upon transformation of the **S.** *cerevisiae* strain with a functional KAH (Figure 11B).

[001 82] Transformants **were** grown in SC-URA medium for 4 days and extracted with 1:1 with DMSO at 80°C for 10 min. The extracts were analyzed by LC-MS (method 2 of Example 1). **S.** *cerevisiae* transformed with the nucleic acid set forth in SEQ ID NO:80 accumulated 13-SMG (Figure 11B). Thus, the protein encoded by SEQ ID NO:80, set forth in SEQ ID NO:82, is a KAH.

[00183] The KAH encoded by the nucleotide sequence set forth in SEQ ID NO:80 was codon-optimized for expression in yeast (SEQ ID NO:81) and expressed in the above-described 13-SMG-producing *S. cerevisiae* strain. Similar to expression of SrKAHel (SEQ ID NO:18) or the KAH encoded by the nucleotide sequence set forth in SEQ ID NO:80, expression of the codon-optimized nucleotide sequence set forth in SEQ ID NO:81 resulted in production of 13-SMG plus rubusoside (Figure 13).

[00184] The KAHs encoded by the nucleotide sequence set forth in SEQ ID NO:80 and the codon-optimized nucleotide sequence set forth in SEQ ID NO:81 were also individually expressed in a steviol glycoside-producing strain, as described in Example 2, which expresses SrKAHel. Production of 13-SMG was increased upon overexpression of SrKAHel (SEQ ID **NO: 18),** of **the** KAH encoded by the nucleotide sequence set forth in SEQ ID NO:80, or of the KAH encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:81, as compared to a control strain not expressing the KAH encoded by the nucleotide sequence set forth in SEQ ID NO:80, the KAH encoded by the codon-optimized nucleotide sequence set forth

in SEQ ID NO:81, or overexpressing SrKAHel. *See* Table 6. Expression of either the KAH encoded by the nucleotide sequence set forth in SEQ ID NO:80 or the KAH encoded by the codon-optimized nucleotide sequence set forth in SEQ ID NO:81 resulted in higher steviol glycoside production (13-SMG + 1,2-bioside + rubusoside + RebB + RebA + RebD + RebM) than either the controi strain or the S. *cerevisiae* strain overexpressing SrKAHel (SEQ ID NO: 18). *See* Table 6.

Table 6: Quantification of Steviol Glycosides Accumulated| by Yeast Expressing KAH Genes.

	Control (µM)	Overexpression of SrKAHe1 (encoded by the nucleotide set forth in SEQ ID NO:18) (µM)	SrKAHe1 + KAH (encoded by the nucleotide set forth in SEQ ID NO:80) (µM)	SrKAHe1 + KAH (encoded by the nucleotide sequence set forth in SEQ ID NO:81) (µM)
13-SMG	67.6	85.5	153.8	130.5
Steviol-1,2-bioside	0.4	0.3	0.4	0.4
Rubusoside	1.2	1.0	1.4	1.1
RebB	8.6	7.6	9.6	9.6
RebA	30.7	26.0	26.8	28.7
RebD	36.2	27.6	32.9	36.5
RebM	138.3	118.9	100.0	90.3
Sum	282.7	266.2	324.0	296.7

Example 8. Steviol Glycoside Production in Yeast Strain Expressing KAH Gene of the CYP72A219 family

[001 85] **A** nucleic acid of SEQ ID NO:90, which was codon-optimized for expression in *S. cerevisiae* and encodes the polypeptide of SEQ ID NO:91, was cloned and expressed in an *S. cerevisiae* strain described in Example 7, which was engineered to accumulate 13-SMG. The 13-SMG-producing S. *cerevisiae* strain comprised a recombinant gene encoding a *Synechococcus sp.* GGPPS7 polypeptide (SEQ ID NO:49), a recombinant gene encoding a truncated Z. *mays* CDPS polypeptide (SEQ ID NO:37), a recombinant gene encoding an *A. thaliana* KS polypeptide (SEQ ID NO:6), SrKOI (SEQ ID NO:59, SEQ ID NO:79), CPR8 (SEQ ID NO:24, SEQ ID NO:28), the KO encoded by the nucleotide sequence set forth in SEQ ID NO:56 (amino acid sequence set forth in SEQ ID NO:75), and UGT85C2 (SEQ ID NO:30) chromosoma!ly integrated in separate expression cassettes.

[00186] Transformants were grown in SC-URA medium for 4 days and extracted 1:1 with DMSO at 80°C for 10 min. The extracts were analyzed by LC-MS (method 2 of Example 1). S. *cerevisiae* transformed with the nucleic acid set forth in SEQ ID NO:90 accumulated 13-SMG as well as rubusoside (Table 7). Thus, the protein encoded by the nucleic acid sequence of SEQ ID NO:90, set forth in SEQ ID NO:91 , is a KAH.

Table 7: Quantification of Steviol Glycosides Accumulated by Yeast Expressing the KAH encoded by the Nucleotide Sequence Set Forth in SEQ ID NO:90 (Amino Acid Sequence Set Forth in SEQ ID NO:91).

	13-SMG (µM)	Rubusoside (µM)
KAH (encoded by the nucleotide sequence set forth in SEQ ID NO:90)	4.3 ± 0.1	0.2 ± 0.0

Example 9. Determination of CPR1 and CPR12 Activity

[00187] Activity of CPR1 and CPR12 were measured using an *in vitro* microsomal assay. Microsomes were prepared by a modified version of the method taught by Pompon *et al.*, "Yeast expression of animal and plant P450s in optimized redox environments," Methods Enzymol. 272:51-64 (1996). S. *cerevisiae* cells were sedimented for 10 min at 4°C. The pellets were washed with 10 mL TEK buffer (50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 100 mM KCl.) The cells were sedimented again for 10 min at 4°C, and the pellets were resuspended in 1-3 mL of TES2 buffer (50 mM Tri-HCl (pH 7.5) 1 mM EDTA, 600 mM sorbitol). Glass beads (425-600 microns) were added to the samples, and the cells were broken vigorously by shaking and vortexing for 5 min at 4°C. The supernatant was collected, and the beads were washed several times with TES2 buffer. The washes were combined with the supernatant, and the samples were centrifuged for 15 min at 4°C to remove unbroken cells and glass beads. Samples were then ultracentrifuged for 1 h at 4°C. The pellets were washed twice with TES buffer (50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 600 mM sorbitol, 1% (w/V) BSA, 5 mM DTT), and once with TEG buffer (50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 30% (V/V) glycerol). The samples were resuspended in 1-3 mL TEG, and the pellets were homogenized.

[001 88] Wild-type control microsomal protein was prepared as described above from wild-type *S. cerevisiae* cells that did not comprise a heterologous KAH or CPR. Microsomal protein

was also prepared from *S. cerevisiae* cells expressing i) SrKAHel (SEQ ID NO:18, SEQ ID NO:68), ii) SrKAHel (SEQ ID NO:18, SEQ ID NO:68) and CPR1 (SEQ ID NO:61, SEQ ID NO:76), or iii) SrKAHel (SEQ ID NO:18, SEQ ID NO:68) and CPR12 (SEQ ID NO:97, SEQ ID NO:98) from a genetic construct integrated at the chromosome level. Microsomal protein from a steviol glycoside-producing strain was prepared from *S. cerevisiae* cells expressing the genes described in Example 2 and additionally comprising codon-optimized CPR1 from *S. rebaudiana* (SEQ ID NO:61 corresponding to amino acid sequence SEQ ID NO:76) as well as the KO encoded by SEQ ID NO:75).

[00189] CPR1 and CPR12 activities were first determined using a cytochrome C reductase assay kit (Sigma-Aldrich; CY0100-1KT) to measure the ability of CPR1 or CPR12 to reduce cytochrome C in the presence of NADPH *in vitro.* Reduction of cytochrome C resulted in an increase in absorbance at 550 nm, which could quantified spectrophotometrically. Working solution was prepared by adding 9 mg cytochrome C to 20 mt_ assay buffer, and solution was stored at 25°C until use. NADPH was diluted in H_20 to a concentration of 0.85 mg/mL. Final reaction volumes were 1.1 mL (950µLL working solution (0.43 mg cytochrome C), 28 µL enzyme dilution buffer, 100 µL NADPH solution (0.085 mg NADPH), 20µLIL cytochrome C oxidase inhibitor, 2µLL microsomal protein.) Blank samples did not comprise microsomal protein and were prepared with 950µLL working solution (0.43 mg cytochrome C), 30µLL enzyme dilution buffer, 100 µL. NADPH solution (0.085 mg NADPH), and 20 µL cytochrome C oxidase inhibitor. The spectrophotometer was blanked with all components added to the reactions except for NADPH. The enzymatic reactions were initiated by addition of NADPH, the samples were thoroughly mixed by pipetting, and absorbance was measured at 550 nm for 70 s with 10 s intervals between reads. Two independent rate measurements were taken for each microsomal preparation, and rates were averaged for calculation of specific activity. After the reactions were completed, results were normalized to protein concentration, which was measured using a standard BCA assay (Thermo Scientific).

[00190] Units/mL was calculated using the following equation, where ΔA_{550}/min represents the change in absorbance at 550 nm during the absorbance reading period, 1.1 represents the reaction volume in mL, and 21.1 represents the extinction coefficient for reduced cytochrome c:

$$\text{Units/mL} = (\Delta A_{550}/\text{min} \times \text{dilution factor} \times 1.1) / (21.1 \times \text{enzyme volume})$$

[00191] The units/mL value of each sample was divided by its respective microsomal protein concentrations to calculate CPR activity in units/mg. Figure 14 shows the activity measurements of the i) SrKAHel (SEQ ID NO:18, SEQ ID NO:68), ii) SrKAHel (SEQ ID NO:18,

SEQ ID NO:68) and CPR1 (SEQ ID NO:61, SEQ ID NO:76), and iii) SrKAHel (SEQ ID NO: 18, SEQ ID NO:68) and CPR12 (SEQ ID NO:97, SEQ ID NO:98) microsomal samples.

[001 92] The microsomal preparation from the wild-type control showed only minimal CPR activity, reflecting the low activity of native NCP1 (YHR042W). Likewise, the microsomal preparation from a yeast strain overexpressing KAHel did not demonstrate an increase in CPR activity. In contrast, microsomal preparation from strains expressing SrKAHel (SEQ ID NO:18, SEQ ID NO:68) and CPR1 (SEQ ID NO:61, SEQ ID NO:76) or SrKAHel (SEQ ID NO:18, SEQ ID NO:68) and CPR12 (SEQ ID NO:97, SEQ ID NO:98) demonstrated high CPR activity, with 7- and 14-fold higher activity, respectively, compared to the negative control (Figure 14).

[00193] In a separate experiment, formation of steviol and consumption of ent-kaurenoic acid in microsomes, as prepared above, were measured. 33 μM ent-kaurenoic acid, 10 mM NADPH, and 10 μL of microsomal protein in 50 mM phosphate buffer (pH 7.5) were incubated for 30 min at 30°C in a total reaction volume of 100 μL. Control reactions were extracted immediately after addition of all the reaction components, which were mixed on ice and aliquoted prior to incubation. Steviol and ent-kaurenoic acid ievels were quantified using the second LC-MS procedure described in Example 1. For steviol quantification, the microsomal reactions were extracted with DMSO (1:1) at 80°C for 10 min and submitted for LC-MS analysis after centrifugation. For ent-kaurenoic acid quantification the microsomes reactions were extracted with acetonitrile 1:4 (20% microsomal reaction and 80% acetonitrile) at 80°C for 10 min and after centrifugation submitted for LC-MS analysis. The AUC values obtained for the ent-kaurenoic acid measurements were converted to concentrations using a standard curve.

[00194] As shown in Figure 15A, microsomal protein prepared from an *S. cerevisiae* strain expressing SrKAHel (SEQ ID NO: 18, SEQ ID NO:68) and either CPR1 (SEQ ID NO:61, SEQ ID NO:76) or CPR12 (SEQ ID NO:97, SEQ ID NO:98) converted ent-kaurenoic acid to steviol during the 30 minute incubation period. The steviol level shown in Figure 15A for the steviol-glycoside-producing strain control (extracted immediately with no 30 min incubation period) corresponds to steviol that was accumulated by the strain prior to microsomal preparation and that had co-purified with the microsomes. As shown in Figure 15B, ent-kaurenoic acid Ievels decreased upon incubation with microsomal protein prepared from *S. cerevisiae* strains expressing SrKAHel (SEQ ID NO:18, SEQ ID NO:68) alone or in combination with CPR1 (SEQ ID NO:61, SEQ ID NO:76) or CPR12 (SEQ ID NO:97, SEQ ID NO:98). The increased ent-kaurenoic acid Ievels shown in Figure 15B for the steviol glycoside-producing strain microsomal sample incubated for 30 min corresponds to ent-kaurenoic acid that was accumulated by the

strain prior to microsomal preparation and to ent-kaurenoic acid accumulated from ent-kaurene that had co-purified with the microsomes. The levels of ent-kaurenoic acid shown in Figure 15B were corrected for the dilution factor used.

Example 10. Steviol Glycoside Production in *S. cerevisiae* strains comprising Fusion Constructs between a KO and a P450 Reductase Domain

[00195] CYP102A1 (also referred to as $P450_{BM3}$; SEQ ID NO:115, SEQ ID NO:116) is a catalytically self-sufficient soluble enzyme from *Bacillus megatarium. See, e.g.,* Whitehouse *et al,* 2012, Chem Soc Rev. 41(3):1218-60. Two domains are present in the CYP102A1 polypeptide chain: a P450 heme domain (BMP) and an NADPH-dependent P450 oxidoreductase domain (BMR). CYP102A1 utilizes nearly 100% of the reducing power of NADPH to produce a monooxygenated product. *See, e.g.,* Yuan *et al,* 2009, *Biochemistry* 48(38):9140-6.

[00196] The BMR domain of CYP102A1 ("BMR"; codon-optimized nucleotide sequence set forth in SEQ ID NO:117, SEQ ID NO:118) was fused to SrKOi (SEQ ID NO:59, SEQ ID NO:79) or a KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 (amino acid sequence set forth in SEQ ID NO:75) with a linker (SEQ ID NO:121, SEQ ID NO:122), as described in Dodhia *et al,* 2006, J Biol Inorg Chem. 11(7):903-16. A wild-type version of the BMR domain of CYP102A1, as well as a W1046A mutant of the BMR domain (SEQ ID NO:119, SEQ ID NO:120), which has been found to switch the cofactor specificity of CYP102A1 from NADPH to NADH, were used. *See,* Girvan *et al.,* 2011, Arch Biochem Biophys. 507(1):75-85. SrKOi (SEQ ID NO:59, SEQ ID NO:79) and the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 were also truncated prior to fusion with the BMR domain of CYP102A1; these truncations were predicted by bioinformatics to result in loss of membrane anchors of the KO genes and in cytosolic versions of the KO-BMR fusion constructs. The KO-BMR fusion constructs analyzed are shown in Table 8.

Table 8: KO-BMR fusion constructs and sequences.

Fusion Construct	Codon-Optimized Nucleotide Sequence	Amino Acid Sequence
SrKO1-BMR	SEQ ID NO:99	SEQ ID NO:100
SrKO1-BMR W1046A mutant	SEQ ID NO:101	SEQ ID NO:102
Truncated SrKO1-BMR	SEQ ID NO:103	SEQ ID NO:104

Truncated SrKO1-BMR W1046A mutant	SEQ ID NO:105	SEQ ID NO:106
KO (*encoded by nucleotide sequence set forth in SEQ ID NO:65*)-BMR	SEQ ID NO:107	SEQ ID NO:108
KO (*encoded by nucleotide sequence set forth in SEQ ID NO:65*)-BMR W1046A mutant	SEQ ID NO:109	SEQ ID NO:110
Truncated KO (*encoded by nucleotide sequence set forth in SEQ ID NO:65*)-BMR W1046A mutant	SEQ ID NO:111	SEQ ID NO:112

[00197] The KO-BMR fusion constructs were cloned and transformed in the RebB-producing strain described in Example 2, which was modified to not comprise any additional KO genes. Thus, steviol glycosides, including 13-SMG, 1,2-bioside, and RebB, were only accumulated upon expression of a functional KO. Three scrapes (1 µL loop of cells) from each transformation plate were resuspended in 200 µl nanopure H_2O. 70 µL were then transferred to 1 mL SC-URA in a 96 deep well plate and incubated at 30°C for 5 days at 400 rpm. Biological triplicates were analyzed by LC-MS (method 2 of Example 1) to measure 13-SMG, 1,2-bioside, and RebB levels, and single samples were analyzed by LC-UV to measure ent-kaurene and ent-kaurenoic acid levels.

[00198] For LC-MS, 50 µL samples were mixed with 50 µL 100% DMSO and heated to 80°C for 10 min. Subsequently, the samples were spun down at 4000 RCF for 10 min, and 85 µL of the resulting supernatant was transferred to an LC-MS plate. The LC-MS results were normalized by OD_{600} of individual cultures, which was measured by a Wallac, 2104 EnVision (Perkin Elmer) plate reader.

[00199] LC-UV was conducted with an Agilent 1290 instrument comprising a variable wavelength detector (VWD), a thermostatted column compartment (TCC), an autosampler, an autosampler cooling unit, and a binary pump and using SB-C18 rapid resolution high definition (RRHD) 2.1 mm x 300 mm, 1.8 pm analytical columns (two 150 mm columns in series; column temperature of 65°C). Steviol glycosides and steviol glycoside precursors were separated by a reversed phase C18 column followed by detection by UV absorbance at 210 mm. Quantification of steviol glycosides was done by comparing the peak area of each analyte to standards of RebA and applying a correction factor for species with differing molar

absorptivities. Quantification of steviol glycoside precursors (such as kaurenoic acid, kaurenal, kaurenol, ent-kaurene, and geranylgeraniol) was done by comparing the peak area of each analyte to standards of kaurenoic acid and applying a correction factor for species with differing molar absorptivities. For LC-UV, 0.5 rriL cultures were spun down, the supernatant was removed, and the wet weight of the pellets was calculated. The LC-UV results were normalized by pellet wet weight.

[00200] As shown in Figures 16B and 16D, the ***S. cerevisiae*** strain transformed with empty plasmid accumulated ent-kaurene. Transformation with a plasmid comprising SrKOI (SEQ ID NO:59, SEQ ID NO:79) or with a plasmid comprising the KO gene having the nucleotide sequence set forth in SEQ ID NO:65 resulted in accumulation of 13-SMG, 1,2-bioside, and RebB (Figures 16A and 186C).

[00201] Expression of full-length SrKOI -BMR fusion constructs (wild type or W1046A mutant BMR; SEQ ID NOs:99-102), resulted in an increase in ent-kaurenoic acid, 13-SMG, and RebB, compared to expression of SrKOI (SEQ ID NO:59, SEQ ID NO:79). *See* Figures 16A and 16B. Expression of truncated SrKOI -BMR fusion constructs (wild type or W1046A mutant BMR; SEQ ID NOs: 103-1 06) resulted in an increase in ent-kaurenoic acid, compared to expression of SrKOI (SEQ ID NO:59, SEQ ID NO:79) (Figure 16B). Although the truncated SrKOI -BMR fusion constructs also increased steviol glycoside production, glycosyiation activity was higher for the full-length SrKOI-BMR fusion constructs than for the truncated SrKOI -BMR fusion constructs (Figure 16A).

[00202] Expression of a fusion construct comprising the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and the wild type BMR (SEQ ID NO:107, SEQ ID NO: 108) resulted in greater conversion of ent-kaurenoic acid to 13-SMG, compared to the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 (Figure 16C). Expression of a fusion construct comprising the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 and the W1046A mutant BMR (SEQ ID NO: 109, SEQ ID NO:1 10) resulted in decreases in ent-kaurenoic acid levels but glycosyiation activity similar to that of the KO encoded by the nucleotide sequence set forth in SEQ ID NO:65 (Figure 16C).

Example 11. Evaluation of Steviol Glycoside Pathway in *S, cerevisiae* Strain Comprising ICE2

[00203] ICE2 is an endoplasmic reticulum (ER) membrane protein involved in mechanisms such as ER zinc homeostasis and cytochrome P450 stability and/or activity. *See, e.g.,* Estrada de Martin *et al.,* 2005, J Cell Sci. 118(Pt 1):65-77 and Emmerstorfer *et al.,* 2015, Biotechnol J. 10(4):623-35. ICE2 (SEQ ID NO:113, SEQ ID NO:114) was cloned and overexpressed in a steviol glycoside-producing S. *cerevisiae* strain comprising a recombinant gene encoding a *Synechococcus sp.* GGPPS polypeptide (SEQ ID NO:49), a recombinant gene encoding a truncated Z. *mays* CDPS polypeptide (SEQ ID NO:37), a recombinant gene encoding an *A. thaliana* KS polypeptide (SEQ ID NO:6), a recombinant gene encoding a recombinant *S. rebaudiana* KO polypeptide (SEQ ID NO:59, SEQ ID NO:79), a recombinant gene encoding an *A. thaliana* ATR2 polypeptide (SEQ ID NO:51 , SEQ ID NO:87), a recombinant gene encoding an SrKAHel (SEQ ID NO:18, SEQ ID NO:68) polypeptide, a recombinant gene encoding an S. *rebaudiana* CPR8 polypeptide (SEQ ID NO:24, SEQ ID NO:28), a recombinant KAH gene encoded by the nucleotide sequence set forth in SEQ ID NO:81 (corresponding to the amino acid sequence set forth in SEQ ID NO:82), a recombinant KO gene encoded by the nucleotide sequence set forth in SEQ ID NO:56 (corresponding to the amino acid sequence set forth in SEQ ID NO:75), a recombinant KO gene encoded by the nucleotide sequence set forth in SEQ ID NO:65 (corresponding to the amino acid sequence set forth in SEQ ID NO:75), a recombinant gene encoding a UGT76G1 (SEQ ID NO:83) polypeptide, a recombinant gene encoding an *S, rebaudiana* UGT85C2 polypeptide (SEQ ID NO:30), a recombinant gene encoding an S. *rebaudiana* UGT74G1 polypeptide (SEQ ID NO:29), a recombinant gene encoding an EUGT11 (SEQ ID NO:86) polypeptide, a recombinant gene encoding a UGT91 D2e (SEQ ID NO;84) polypeptide, and a recombinant gene encoding a CPR1 (SEQ ID NO:61, SEQ ID NO:76) polypeptide. Overexpression was performed by integration using the USER cloning system; *see, e.g.,* Nour-Eldin *et al.,* 2010, *Methods Mol Biol.* 643:185-200. Table 9 shows additional recombinant genes (ICE2 and/or CPR12) expressed in the above-described strain. The control strain did not comprise recombinant genes encoding ICE2 (SEQ ID NO:113, SEQ ID NO: 114) or CPR12 (SEQ ID NO:97, SEQ ID NO:98) polypeptides.

Table 9: ICE2 **steviol glycoside-producing strains.**

Strain	Sequences
ICE2 "strain A"	ICE2 (SEQ ID NO:113, SEQ ID NO:114) Overexpressed CPR1 (SEQ ID NO:61, SEQ ID NO:76)
ICE2 "strain B"	ICE2 (SEQ ID NO:113, SEQ ID NO:114) (2 copies)

ICE2 "strain C"	ICE2 (SEQ ID NO:113, SEQ ID NO:114) CPR12 (SEQ ID NO:97, SEQ ID NO:98)

[00204] Fed-batch fermentation was carried out aerobically in 2 L fermenters at 30°C with an approximate 16 h growth phase in minimal medium comprising glucose, ammonium sulfate, trace metals, vitamins, salts, and buffer followed by an approximate 110 h feeding phase with a glucose-comprising defined feed medium. A pH near 6.0 and glucose-limiting conditions were maintained. Whole culture samples (without cell removal) were analysed by the LC-UV method of Example 10 to determine levels of steviol glycosides and steviol pathway intermediates.

[00205] The following values were calculated based upon the measured levels of steviol glycosides and steviol glycoside precursors. "Total Flux" was calculated as a sum (in g/L RebD equivalents) of measured RebA, RebB, RebD, RebE, RebM, 13-SMG, rubusoside, steviol-1,2-bioside, di-glycosylated steviol, tri-glycosylated steviol, tetra-glycosylated steviol, penta-glycosytated steviol, hexa-glycosylated steviol, hepta-glycosylated steviol, copalol, ent-kaurenoic acid, glycosylated ent-kaurenoic acid, glycosylated ent-kaurenol, ent-kaurena!, geranylgeraniol, ent-kaurenal, and ent-kaurene levels. "Pre-steviol glycoside/flux" was calculated as (("total flux" - (geranylgeraniol + copalol + ent-kaurene + glycosylated ent-kaurenol + ent-kaurenol + ent-kaurenal + ent-kaurenoic acid + glycosylated ent-kaurenoic acid) / "total flux"). "KAH step/flux" was calculated as ((ent-kaurenoic acid + glycosylated ent-kaurenoic acid) / "total flux"). "KO step/flux" was calculated as ((ent-kaurene + glycosylated ent-kaurenol + ent-kaurenol + ent-kaurenal) / "total flux").

[00206] The pre-steviol glycoside/flux, KO step/flux, and KAH step/flux values are shown in Table 10 below. Decreased amounts of ent-kaurene, ent-kaurenol, ent-kaurenal, glycosylated ent-kaurenol and increased amounts of ent-kaurenoic acid and glycosylated ent-kaurenoic acid were observed in the strains comprising ICE2, as compared to the control steviol glycoside-producing strain. These effects were stronger in the presence of CPR1 and/or CPR12 (Table 10). Overexpression of two copies of ICE2 (ICE2 strain B) resulted decreased ent-kaurene, ent-kaurenol, ent-kaurenal, and ent-kaurenol glycoside levels and increased steviol glycoside levels, compared to the control strain, ICE2 strain A, or ICE2 strain C (Table 10). Steviol glycoside levels increased most in the steviol glycoside-producing strain comprising two copies of ICE2. Thus, ICE2 was found to improve cytochrome P450 function.

Table 10: Pre-steviol glycoside/flux, KO step/flux, and KAH step/flux values for steviol glycoside-producing strains comprising ICE2.

Strain	Pre-Steviol Glycoside/Flux	KO step/Flux	KAH step/Flux
ICE2 "strain A"	0.38	0.36	0.22
ICE2 "strain B"	0.43	0.42	0.10
ICE2 "strain C"	0.39	0.38	0.19
Control	0.41	0.48	0.08

Example 12. Steviol Glycoside Production by Fermentation of *S. cerevisiae* strain comprising CPR1 and CPR12

[00207] Steviol glycoside-producing *S, cerevisiae* strains comprising a recombinant gene encoding a *Synechococcus sp.* GGPPS polypeptide (SEQ ID NO:49), a recombinant gene encoding a truncated *Z. mays* CDPS polypeptide (SEQ ID NO:37), a recombinant gene encoding an *A. thaliana* KS polypeptide (SEQ ID NO:6), a recombinant gene encoding a recombinant S. *rebaudiana* KO polypeptide (SEQ ID NO:59, SEQ ID NO:79), a recombinant gene encoding an *A. thaliana* ATR2 polypeptide (SEQ ID NO:51, SEQ ID NO:87), a recombinant gene encoding an SrKAHei (SEQ ID NO:18, SEQ ID NO:68) polypeptide, a recombinant gene encoding an S. *rebaudiana* CPR8 polypeptide (SEQ ID NO:24, SEQ ID NO:28), a recombinant gene encoding a CPR1 (SEQ ID NO:61, SEQ ID NO:76) polypeptide, a recombinant gene encoding an SrKAHei (SEQ ID NO:18, SEQ ID NO:68) polypeptide, a recombinant KO gene encoded by the nucleotide sequence set forth in SEQ ID NO:56 (corresponding to the amino acid sequence set forth in SEQ ID NO:75), a recombinant gene encoding a UGT76G1 (SEQ ID NO:83) polypeptide, a recombinant gene encoding an S. *rebaudiana* UGT85C2 (SEQ ID NO:30) polypeptide, a recombinant gene encoding an *S. rebaudiana* UGT74G1 (SEQ ID NO:29) polypeptide, a recombinant gene encoding a UGT91D2e-b polypeptide (SEQ ID NO:88), and a recombinant gene encoding an EUGT1 1 (SEQ ID NO:86) polypeptide, as well as the recombinant genes shown in Table 11, which were genomica!ly integrated into the strains, were cultivated by fermentation. Levels of steviol glycosides and steviol glycoside precursors were measured by LC-UV as described in Example 11. The pre-KO/flux, pre-KAH/flux, pre-steviol giycoside/flux values were calculated as described in Example 11.

Table 11: Recombinant genes also expressed in steviol glycoside-producing *S. cerevisiae* strain in Example 12.

Strain	Genes

Example 12, Strain A	KO encoded by nucleotide sequence set forth in SEQ ID NO:56 (corresponding to amino acid sequence set forth in SEQ ID NO:75)
Example 12, Strain B	KAH encoded by nucleotide sequence set forth in SEQ ID NO:80 (corresponding to amino acid sequence set forth in SEQ ID NO:82) KO encoded by nucleotide sequence set forth in SEQ ID NO:56 (corresponding to amino acid sequence set forth in SEQ ID NO:75) KO encoded by nucleotide sequence set forth in SEQ ID NO:65 (corresponding to amino acid sequence set forth in SEQ ID NO:75)
Example 12, Strain C	CPR12 (SEQ ID NO:97, SEQ ID NO:98) KAH encoded by nucleotide sequence set forth in SEQ ID NO:80 (corresponding to amino acid sequence set forth in SEQ ID NO:82) KO encoded by nucleotide sequence set forth in SEQ ID NO:56 (corresponding to amino acid sequence set forth in SEQ ID NO:75)

[00208] The pre-steviol glycoside/flux, KO step/flux, and KAH step/flux values are shown in Table 12 below. In the strain comprising the KO encoded by nucleotide sequence set forth in SEQ ID NO:56 (strain A), lower accumulation of ent-kaurene, ent-kaurenol, ent-kaurnal, and ent-kaurenol glycosides resulted. Higher levels of ent-kaurenoic acid and steviol glycosides were also measured, as compared to the control strain. In the strain comprising the KAH encoded by nucleotide sequence set forth in SEQ ID NO:80, the KO encoded by nucleotide sequence set forth in SEQ ID NO:56 (corresponding to amino acid sequence set forth in SEQ ID NO:75), and the KO encoded by nucleotide sequence set forth in SEQ ID NO:65 (strain B), ent-kaurene, ent-kaurenol, ent-kaurenal, ent-kaurenol glycosides, and ent-kaurenoic acid accumulation decreased and accumulation of steviol glycosides increased, as compared to the control strain. In the strain comprising CPR12 (SEQ ID NO:97, SEQ ID NO:98), the KAH encoded by nucleotide sequence set forth in SEQ ID NO:80, and the KO encoded by nucleotide sequence set forth in SEQ ID NO:56 (strain C), ent-kaurenol, ent-kaurenal, ent-kaurenol glycosides, and ent-kaurenoic acid accumulation decreased and accumulation of steviol glycosides increased, as compared to the control. *See* Table 12. Thus, CPR12 was found to be a reductase protein that improves KAH and/or KO activity.

Table 12. Pre-steviol glycoside/flux, KO step/flux, and KAH step/flux values for steviol glycoside-producing strains of Example 12.

Strain	Pre-Steviol Glycoside/Flux	KO step/Flux	KAH step/Flux
Example 12, Strain A	0.48	0.28	0.22
Example 12, Strain B	0.64	0.18	0.12
Example 12, Strain C	0.55	0.24	0.12
Control	0.40	0.43	0.17

[00209] Having described **the** invention in detail and by reference to specific embodiments thereof, it will be apparent that modifications and variations are possible without departing from **the** scope of the invention defined in the appended claims. More specifically, although some aspects of the present invention are identified herein as particularly advantageous, it is contemplated that the present invention is not necessarily limited to these particular aspects of the invention.

Table 13. Sequences disclosed herein.

SEQ ID NO:1

```
MNLSLCIASP LLTKSNRPAA LSAIHTASTS HGGQTNPTNL IIDTTKERIQ KQFKNVEISV        60
SSYDTAWVAM VPSPNSPKSP CFPECLNWLI NNQLNDGSWG LVNHTHNHNH PLLKDSLSST       120
LACIVALKRW NVGEDQINKG LSFIESNLAS ATEKSQPSPI GFDIIFPGLL EYAKNLDINL       180
LSKQTDFSLM LHKRELEQKR CHSNEMDGYL AYISEGLGNL YDWNMVKKYQ MKNGSVFNSP       240
SATAAAFINH QNPGCLNYLN SLLDKFGNAV PTVYPHDLFI RLSMVDTIER LGISHHFRVE       300
IKNVLDETYR CWVERDEQIF MDVVTCALAF RLLRINGYEV SPDPLAEITN ELALKDEYAA       360
LETYHASHIL YQEDLSSGKQ ILKSADFLKE IISTDSNRLS KLIHKEVENA LKFPINTGLE       420
RINTRRNIQL YNVDNTRILK TTYHSSNISN TDYLRLAVED FYTCQSIYRE ELKGLERWVV       480
ENKLDQLKFA RQKTAYCYFS VAATLSSPEL SDARISWAKN GILTTVVDDF FDIGGTIDEL       540
TNLIQCVEKW NVDVDKDCCS EHVRILFLAL KDAICWIGDE AFKWQARDVT SHVIQTWLEL       600
MNSMLREAIW TRDAYVPTLN EYMENAYVSF ALGPIVKPAI YFVGPKLSEE IVESSEYHNL       660
FKLMSTQGRL LNDIHSFKRE FKEGKLNAVA LHLSNGESGK VEEEVVEEMM MMIKNKRKEL       720
MKLIFEENGS IVPRACKDAF WNMCHVLNFF YANDDGFTGN TILDTVKDII YNPLVLVNEN       780
EEQR                                                                    784
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SEQ ID NO:2

```
MNLSLCIASP LLTKSSRPTA LSAIHTASTS HGGQTNPTNL IIDTTKERIQ KLFKNVEISV        60
SSYDTAWVAM VPSPNSPKSP CFPECLNWLI NNQLNDGSWG LVNHTHNHNH PLLKDSLSST       120
LACIVALKRW NVGEDQINKG LSFIESNLAS ATDKSQPSPI GFDIIFPGLL EYAKNLDINL       180
LSKQTDFSLM LHKRELEQKR CHSNEIDGYL AYISEGLGNL YDWNMVKKYQ MKNGSVFNSP       240
SATAAAFINH QNPGCLNYLN SLLDKFGNAV PTVYPLDLYI RLSMVDTIER LGISHHFRVE       300
IKNVLDETYR CWVERDEQIF MDVVTCALAF RLLRIHGYKV SPDQLAEITN ELAFKDEYAA       360
LETYHASQIL YQEDLSSGKQ ILKSADFLKG ILSTDSNRLS KLIHKEVENA LKFPINTGLE       420
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RINTRRNIQL YNVDNTRILK TTYHSSNISN TYYLRLAVED FYTCQSIYRE ELKGLERWVV      480
QNKLDQLKFA RQKTAYCYFS VAATLSSPEL SDARISWAKN GILTTVVDDF FDIGGTIDEL      540
TNLIQCVEKW NVDVDKDCCS EHVRILFLAL KDAICWIGDE AFKWQARDVT SHVIQTWLEL      600
MNSMLREAIW TRDAYVPTLN EYMENAYVSF ALGPIVKPAI YFVGPKLSEE IVESSEYHNL      660
FKLMSTQGRL LNDIHSFKRE FKEGKLNAVA LHLSNGESGK VEEEVVEEMM MMIKNKRKEL      720
MKLIFEENGS IVPRACKDAF WNMCHVLNFF YANDDGFTGN TILDTVKDII YNPLVLVNEN      780
EEQR                                                                   784
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SEQ ID NO:3

```
MAMPVKLTPA SLSLKAVCCR FSSGGHALRF GSSLPCWRRT PTQRSTSSST TRPAAEVSSG       60
KSKQHDQEAS EATIRQQLQL VDVLENMGIS RHFAAEIKCI LDRTYRSWLQ RHEEIMLDTM      120
TCAMAFRILR LNGYNVSSDE LYHVVEASGL HNSLGGYLND TRTLLELHKA STVSISEDES      180
ILDSIGSRSR TLLREQLESG GALRKPSLFK EVEHALDGPF YTTLDRLHHR WNIENFNIIE      240
QHMLETPYLS NQHTSRDILA LSIRDFSSSQ FTYQQELQHL ESWVKECRLD QLQFARQKLA      300
YFYLSAAGTM FSPELSDART LWAKNGVLTT IVDDFFDVAG SKEELENLVM LVEMWDEHHK      360
VEFYSEQVEI IFSSIYDSVN QLGEKASLVQ DRSITKHLVE IWLDLLKSMM TEVEWRLSKY      420
VPTEKEYMIN ASLIFGLGPI VLPALYFVGP KISESIVKDP EYDELFKLMS TCGRLLNDVQ      480
TFEREYNEGK LNSVSLLVLH GGPMSISDAK RKLQKPIDTC RRDLLSLVLR EESVVPRPCK      540
ELFWKMCKVC YFFYSTTDGF SSQVERAKEV DAVINEPLKL QGSHTLVSDV                  590
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SEQ ID NO:4

```
MSCIRPWFCP SSISATLTDP ASKLVTGEFK TTSLNFHGTK ERIKKMFDKI ELSVSSYDTA       60
WVAMVPSPDC PETPCFPECT KWILENQLGD GSWSLPHGNP LLVKDALSST LACILALKRW      120
GIGEEQINKG LRFIELNSAS VTDNEQHKPI GFDIIFPGMI EYAKDLDLNL PLKPTDINSM      180
LHRRALELTS GGGKNLEGRR AYLAYVSEGI GKLQDWEMAM KYQRKNGSLF NSPSTTAAAF      240
IHIQDAECLH YIRSLLQKFG NAVPTIYPLD IYARLSMVDA LERLGIDRHF RKERKFVLDE      300
TYRFWLQGEE EIFSDNATCA LAFRILRLNG YDVSLEDHFS NSLGGYLKDS GAALELYRAL      360
QLSYPDESLL EKQNSRTSYF LKQGLSNVSL CGDRLRKNII GEVHDALNFP DHANLQRLAI      420
RRRIKHYATD DTRILKTSYR CSTIGNQDFL KLAVEDFNIC QSIQREEFKH IERWVVERRL      480
DKLKFARQKE AYCYFSAAAT LFAPELSDAR MSWAKNGVLT TVVDDFFDVG GSEEELVNLI      540
ELIERWDVNG SADFCSEEVE IIYSAIHSTI SEIGDKSFGW QGRDVKSHVI KIWLDLLKSM      600
LTEAQWSSNK SVPTLDEYMT TAHVSFALGP IVLPALYFVG PKLSEEVAGH PELLNLYKVM      660
STCGRLLNDW RSFKRESEEG KLNAISLYMI HSGGASTEEE TIEHFKGLID SQRRQLLQLV      720
LQEKDSIIPR PCKDLFWNMI KLLHTFYMKD DGFTSNEMRN VVKAIINEPI SLDEL           775
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SEQ ID NO:5

```
cgtcagtcat caaggctaat tcgtcgcgag ttgctacgac gccgtttcgg ttgcttctgg       60
tttctttatg tctatcaacc ttcgctcctc cggttgttcg tctccgatct cagctacttt      120
ggaacgagga ttggactcag aagtacagac aagagctaac aatgtgagct ttgagcaaac      180
aaaggagaag attaggaaga tgttggagaa agtggagctt tctgtttcgg cctacgatac      240
tagttgggta gcaatggttc catcaccgag ctcccaaaat gctccacttt tcccacagtg      300
tgtgaaatgg ttattggata atcaacatga agatggatct tggggacttg ataaccatga      360
ccatcaatct cttaagaagg atgtgttatc atctacactg gctagtatcc tcgcgttaaa      420
gaagtgggga attggtgaaa gacaaataaa caagggtctc cagtttattg agctgaattc      480
tgcattagtc actgatgaaa ccatacagaa accaacaggg tttgatatta tatttcctgg      540
gatgattaaa tatgctagag atttgaatct gacgattcca ttgggctcag aagtggtgga      600
tgacatgata cgaaaaagag atctggatct taaatgtgat agtgaaaagt tttcaaaggg      660
aagagaagca tatctggcct atgttttaga ggggacaaga aacctaaaag attgggattt      720
gatagtcaaa tatcaaagga aaaatgggtc actgtttgat tctccagcca caacagcagc      780
tgcttttact cagtttggga atgatggttg tctccgttat ctctgttctc tccttcagaa      840
attcgaggct gcagttcctt cagtttatcc atttgatcaa tatgcacgcc ttagtataat      900
tgtcactctt gaaagcttag gaattgatag agatttcaaa accgaaatca aaagcatatt      960
ggatgaaacc tatagatatt ggcttcgtgg ggatgaagaa atatgtttgg acttggccac     1020
ttgtgctttg gctttccgat tattgcttgc tcatggctat gatgtgtctt acgatccgct     1080
aaaaccattt gcagaagaat ctggtttctc tgatactttg gaaggatatg ttaagaatac     1140
gttttctgtg ttagaattat ttaaggctgc tcaaagttat ccacatgaat cagctttgaa     1200
gaagcagtgt tgttggacta aacaatatct ggagatggaa ttgtccagct gggttaagac     1260
ctctgttcga gataaatacc tcaagaaaga ggtcgaggat gctcttgctt ttccctccta     1320
tgcaagccta gaaagatcag atcacaggag aaaaatactc aatggttctg ctgtggaaaa     1380
caccagagtt acaaaaacct catatcgttt gcacaatatt tgcacctctg atatcctgaa     1440
gttagctgtg gatgacttca atttctgcca gtccatacac cgtgaagaaa tggaacgtct     1500
tgataggtgg attgtggaga atagattgca ggaactgaaa tttgccagac agaagctggc     1560
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ttactgttat ttctctgggg ctgcaacttt attttctcca gaactatctg atgctcgtat      1620
atcgtgggcc aaaggtggag tacttacaac ggttgtagac gacttctttg atgttggagg      1680
gtccaaagaa gaactggaaa acctcataca cttggtcgaa aagtgggatt tgaacggtgt      1740
tcctgagtac agctcagaac atgttgagat catattctca gttctaaggg acaccattct      1800
cgaaacagga gacaaagcat tcacctatca aggacgcaat gtgacacacc acattgtgaa      1860
aatttggttg gatctgctca agtctatgtt gagagaagcc gagtggtcca gtgacaagtc      1920
aacaccaagc ttggaggatt acatggaaaa tgcgtacata tcatttgcat taggaccaat      1980
tgtcctccca gctacctatc tgatcggacc tccacttcca gagaagacag tcgatagcca      2040
ccaatataat cagctctaca agctcgtgag cactatgggt cgtcttctaa atgacataca      2100
aggttttaag agagaaagcg cggaagggaa gctgaatgcg gtttcattgc acatgaaaca      2160
cgagagagac aatcgcagca aagaagtgat catagaatcg atgaaaggtt tagcagagag      2220
aaagagggaa gaattgcata agctagtttt ggaggagaaa ggaagtgtgg ttccaaggga      2280
atgcaaagaa gcgttcttga aaatgagcaa agtgttgaac ttattttaca ggaaggacga      2340
tggattcaca tcaaatgatc tgatgagtct tgttaaatca gtgatctacg agcctgttag      2400
cttacagaaa gaatctttaa cttgatccaa gttgatctgg caggtaaact cagtaaatga      2460
aaataagact ttggtcttct tctttgttgc ttcagaacaa gaagag                    2506
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SEQ ID NO:6

```
MSINLRSSGC SSPISATLER GLDSEVQTRA NNVSFEQTKE KIRKMLEKVE LSVSAYDTSW        60
VAMVPSPSSQ NAPLFPQCVK WLLDNQHEDG SWGLDNHDHQ SLKKDVLSST LASILALKKW       120
GIGERQINKG LQFIELNSAL VTDETIQKPT GFDIIFPGMI KYARDLNLTI PLGSEVVDDM       180
IRKRDLDLKC DSEKFSKGRE AYLAYVLEGT RNLKDWDLIV KYQRKNGSLF DSPATTAAAF       240
TQFGNDGCLR YLCSLLQKFE AAVPSVYPFD QYARLSIIVT LESLGIDRDF KTEIKSILDE       300
TYRYWLRGDE EICLDLATCA LAFRLLLAHG YDVSYDPLKP FAEESGFSDT LEGYVKNTFS       360
VLELFKAAQS YPHESALKKQ CCWTKQYLEM ELSSWVKTSV RDKYLKKEVE DALAFPSYAS       420
LERSDHRRKI LNGSAVENTR VTKTSYRLHN ICTSDILKLA VDDFNFCQSI HREEMERLDR       480
WIVENRLQEL KFARQKLAYC YFSGAATLFS PELSDARISW AKGGVLTTVV DDFFDVGGSK       540
EELENLIHLV EKWDLNGVPE YSSEHVEIIF SVLRDTILET GDKAFTYQGR NVTHHIVKIW       600
LDLLKSMLRE AEWSSDKSTP SLEDYMENAY ISFALGPIVL PATYLIGPPL PEKTVDSHQY       660
NQLYKLVSTM GRLLNDIQGF KRESAEGKLN AVSLHMKHER DNRSKEVIIE SMKGLAERKR       720
EELHKLVLEE KGSVVPRECK EAFLKMSKVL NLFYRKDDGF TSNDLMSLVK SVIYEPVSLQ       780
KESLT                                                                   785
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SEQ ID NO:7

```
MDAVTGLLTV PATAITIGGT AVALAVALIF WYLKSYTSAR RSQSNHLPRV PEVPGVPLLG        60
NLLQLKEKKP YMTFTRWAAT YGPIYSIKTG ATSMVVVSSN EIAKEALVTR FQSISTRNLS       120
KALKVLTADK TMVAMSDYDD YHKTVKRHIL TAVLGPNAQK KHRIHRDIMM DNISTQLHEF       180
VKNNPEQEEV DLRKIFQSEL FGLAMRQALG KDVESLYVED LKITMNRDEI FQVLVVDPMM       240
GAIDVDWRDF FPYLKWVPNK KFENTIQQMY IRREAVMKSL IKEHKKRIAS GEKLNSYIDY       300
LLSEAQTLTD QQLLMSLWEP IIESSDTTMV TTEWAMYELA KNPKLQDRLY RDIKSVCGSE       360
KITEEHLSQL PYITAIFHET LRRHSPVPII PLRHVHEDTV LGGYHVPAGT ELAVNIYGCN       420
MDKNVWENPE EWNPERFMKE NETIDFQKTM AFGGGKRVCA GSLQALLTAS IGIGRMVQEF       480
EWKLKDMTQE EVNTIGLTTQ MLRPLRAIIK PRI                                    513
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SEQ ID NO:8

```
MAFFSMISIL LGFVISSFIF IFFFKKLLSF SRKNMSEVST LPSVPVVPGF PVIGNLLQLK        60
EKKPHKTFTR WSEIYGPIYS IKMGSSSLIV LNSTETAKEA MVTRFSSIST RKLSNALTVL       120
TCDKSMVATS DYDDFHKLVK RCLLNGLLGA NAQKRKRHYR DALIENVSSK LHAHARDHPQ       180
EPVNFRAIFE HELFGVALKQ AFGKDVESIY VKELGVTLSK DEIFKVLVHD MMEGAIDVDW       240
RDFFPYLKWI PNKSFEARIQ QKHKRRLAVM NALIQDRLKQ NGSESDDDCY LNFLMSEAKT       300
LTKEQIAILV WETIIETADT TLVTTEWAIY ELAKHPSVQD RLCKEIQNVC GGEKFKEEQL       360
SQVPYLNGVF HETLRKYSPA PLVPIRYAHE DTQIGGYHVP AGSEIAINIY GCNMDKKRWE       420
RPEDWWPERF LDDGKYETSD LHKTMAFGAG KRVCAGALQA SLMAGIAIGR LVQEFEWKLR       480
DGEEENVDTY GLTSQKLYPL MAIINPRRS                                         509
```

SEQ ID NO:9

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MSKSNSMNST SHETLFQQLV LGLDRMPLMD VHWLIYVAFG AWLCSYVIHV LSSSSTVKVP        60
VVGYRSVFEP TWLLRLRFVW EGGSIIGQGY NKFKDSIFQV RKLGTDIVII PPNYIDEVRK       120
LSQDKTRSVE PFINDFAGQY TRGMVFLQSD LQNRVIQQRL TPKLVSLTKV MKEELDYALT       180
KEMPDMKNDE WVEVDISSIM VRLISRISAR VFLGPEHCRN QEWLTTTAEY SESLFITGFI       240
```

```
LRVVPHILRP FIAPLLPSYR TLLRNVSSGR RVIGDIIRSQ QGDGNEDILS WMRDAATGEE   300
KQIDNIAQRM LILSLASIHT TAMTMTHAMY DLCACPEYIE PLRDEVKSVV GASGWDKTAL   360
NRFHKLDSFL KESQRFNPVF LLTFNRIYHQ SMTLSDGTNI PSGTRIAVPS HAMLQDSAHV   420
PGPTPPTEFD GFRYSKIRSD SNYAQKYLFS MTDSSNMAFG YGKYACPGRF YASNEMKLTL   480
AILLLQFEFK LPDGKGRPRN ITIDSDMIPD PRARLCVRKR SLRDE                   525
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SEQ ID NO:10

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MEDPTVLYAC LAIAVATFVV RWYRDPLRSI PTVGGSDLPI LSYIGALRWT RRGREILQEG    60
YDGYRGSTFK IAMLDRWIVI ANGPKLADEV RRRPDEELNF MDGLGAFVQT KYTLGEAIHN   120
DPYHVDIIRE KLTRGLPAVL PDVIEELTLA VRQYIPTEGD EWVSVNCSKA ARDIVARASN   180
RVFVGLPACR NQGYLDLAID FTLSVVKDRA IINMFPELLK PIVGRVVGNA TRNVRRAVPF   240
VAPLVEERRR LMEEYGEDWS EKPNDMLQWI MDEAASRDSS VKAIAERLLM VNFAAIHTSS   300
NTITHALYHL AEMPETLQPL REEIEPLVKE EGWTKAAMGK MWWLDSFLRE SQRYNGINIV   360
SLTRMADKDI TLSDGTFLPK GTLVAVPAYS THRDDAVYAD ALVFDPFRFS RMRAREGEGT   420
KHQFVNTSVE YVPFGHGKHA CPGRFFAANE LKAMLAYIVL NYDVKLPGDG KRPLNMYWGP   480
TVLPAPAGQV LFRKRQVSL                                                499
```

SEQ ID NO:11

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aaacaaagaa tgattcaagt tctaacaccg atccttctct tcctcatttt cttcgttttc    60
tggaaggttt acaagcacca gaaaaccaaa atcaatcttc caccgggaag cttcggatgg   120
ccatttctgg gcgaaactct ggcactccta cgtgcaggtt gggactcaga gccggagaga   180
tttgttcgtg aacggatcaa gaaacacgga agtcctctag tgtttaagac gtcgttgttt   240
ggcgaccgtt ttgcggtgtt gtgtggacct gccggaaaca agttcctgtt ctgcaacgag   300
aacaagctgg tggcgtcgtg gtggccggtt ccggtgagga agcttttcgg caagtctctg   360
ctcacgattc gtggtgatga agctaagtgg atgaggaaga tgttgttatc gtatctcggt   420
cctgatgctt tcgcaactca ttatgccgtc accatggacg tcgtcacccg tcggcatatc   480
gacgttcatt ggcgagggaa ggaagaggtg aacgtattcc aaaccgttaa gttatatgcc   540
tttgagcttg catgtcgttt attcatgaac ctagacgacc caaaccacat tgcaaaactc   600
ggttccttgt tcaacatttt cttgaaaggc atcattgagc ttccaatcga cgtcccaggg   660
acacgatttt atagctccaa aaaagcagca gcagctatca ggattgaact aaaaaaattg   720
attaaagcaa gaaaactgga actgaaagaa gggaaggcat catcttcaca agacctctta   780
tcacatttgc ttacatctcc agatgaaaat ggtatgtttc taaccgaaga agagattgta   840
gacaacatct tgttactact ctttgcgggt catgatacct cggctctttc aatcactttg   900
ctcatgaaga ctcttggcga acattctgat gtttatgaca aggtgttaaa agagcaacta   960
gagatatcga agacgaaaga agcatgggag tccctgaaat gggaggacat acaaaagatg  1020
aaatactcct ggagtgttat atgtgaagtc atgagactaa atccacctgt tataggaacc  1080
tatagagagg cccttgtgga tattgattat gcgggttata ccatccccaa aggatggaag  1140
ctgcactgga gtgctgtatc gacacaaagg gacgaggcta actttgaaga cgtaacacgt  1200
tttgacccat cacggtttga aggcgcagga ccgactccat tcacctttgt tccgtttgga  1260
gggggccta gaatgtgttt agggaaagaa tttgctcgat tggaagtact tgcgtttctt  1320
cacaatattg tcaccaattt caaatgggac ctgttgatac ctgatgagaa aatagaatat  1380
gatcccatgg ctaccccagc aaaggggctt ccaattcgtc ttcatcccca tcaagtttga  1440
ttacttcaag catgaatcag tgatgtgaag gtaaaccata atggatctta ttggtagtta  1500
cagattatgt gtttttatgg catgaagaag ttatgataaa taaaattgtg ttattctaca  1560
acttatgtaa tttgtgcctg taagtaactg aatctattaa tgttttatgt gacatgaaac  1620
ataaatgtat aattagtaaa ttttctgctc aaaaaaaaaa aaaaaaaaaa aaaaaaaa    1678
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SEQ ID NO:12

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MIQVLTPILL FLIFFVFWKV YKHQKTKINL PPGSFGWPFL GETLALLRAG WDSEPERFVR    60
ERIKKHGSPL VFKTSLFGDR FAVLCGPAGN KFLFCNENKL VASWWPVPVR KLFGKSLLTI   120
RGDEAKWMRK MLLSYLGPDA FATHYAVTMD VVTRRHIDVH WRGKEEVNVF QTVKLYAFEL   180
ACRLFMNLDD PNHIAKLGSL FNIFLKGIIE LPIDVPGTRF YSSKKAAAAI RIELKKLIKA   240
RKLELKEGKA SSSQDLLSHL LTSPDENGMF LTEEEIVDNI LLLLFAGHDT SALSITLLMK   300
TLGEHSDVYD KVLKEQLEIS KTKEAWESLK WEDIQKMKYS WSVICEVMRL NPPVIGTYRE   360
ALVDIDYAGY TIPKGWKLHW SAVSTQRDEA NFEDVTRFDP SRFEGAGPTP FTFVPFGGGP   420
RMCLGKEFAR LEVLAFLHNI VTNFKWDLLI PDEKIEYDPM ATPAKGLPIR LHPHQV       476
```

SEQ ID NO:13

```
MGLFPLEDSY ALVFEGLAIT LALYYLLSFI YKTSKKTCTP PKASGEHPIT GHLNLLSGSS        60
GLPHLALASL ADRCGPIFTI RLGIRRVLVV SNWEIAKEIF TTHDLIVSNR PKYLAAKILG       120
FNYVSFSFAP YGPYWVGIRK IIATKLMSSS RLQKLQFVRV FELENSMKSI RESWKEKKDE       180
EGKVLVEMKK WFWELNMNIV LRTVAGKQYT GTVDDADAKR ISELFREWFH YTGRFVVGDA       240
FPFLGWLDLG GYKKTMELVA SRLDSMVSKW LDEHRKKQAN DDKKEDMDFM DIMISMTEAN       300
SPLEGYGTDT IIKTTCMTLI VSGVDTTSIV LTWALSLLLN NRDTLKKAQE ELDMCVGKGR       360
QVNESDLVNL IYLEAVLKEA LRLYPAAFLG GPRAFLEDCT VAGYRIPKGT CLLINMWKLH       420
RDPNIWSDPC EFKPERFLTP NQKDVDVIGM DFELIPFGAG RRYCPGTRLA LQMLHIVLAT       480
LLQNFEMSTP NDAPVDMTAS VGMTNAKASP LEVLLSPRVK WS                          522
```

SEQ ID NO:14

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MIQVLTPILL FLIFFVFWKV YKHQKTKINL PPGSFGWPFL GETLALLRAG WDSEPERFVR        60
ERIKKHGSPL VFKTSLFGDR FAVLCGPAGN KFLFCNENKL VASWWPVPVR KLFGKSLLTI       120
RGDEAKWMRK MLLSYLGPDA FATHYAVTMD VVTRRHIDVH WRGKEEVNVF QTVKLYAFEL       180
ACRLFMNLDD PNHIAKLGSL FNIFLKGIIE LPIDVPGTRF YSSKKAAAAI RIELKKLIKA       240
RKLELKEGKA SSSQDLLSHL LTSPDENGMF LTEEEIVDNI LLLLFAGHDT SALSITLLMK       300
TLGEHSDVYD KVLKEQLEIS KTKEAWESLK WEDIQKMKYS WSVICEVMRL NPPVIGTYRE       360
ALVDIDYAGY TIPKGWKLHW SAVSTQRDEA NFEDVTRFDP SRFEGAGPTP FTFVPFGGGP       420
RMCLGKEFAR LEVLAFLHNI VTNFKWDLLI PDEKIEYDPM ATPAKGLPIR LHPHQV           476
```

SEQ ID NO:15

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MESLVVHTVN AIWCIVIVGI FSVGYHVYGR AVVEQWRMRR SLKLQGVKGP PPSIFNGNVS        60
EMQRIQSEAK HCSGDNIISH DYSSSLFPHF DHWRKQYGRI YTYSTGLKQH LYINHPEMVK       120
ELSQTNTLNL GRITHITKRL NPILGNGIIT SNGPHWAHQR RIIAYEFTHD KIKGMVGLMV       180
ESAMPMLNKW EEMVKRGGEM GCDIRVDEDL KDVSADVIAK ACFGSSFSKG KAIFSMIRDL       240
LTAITKRSVL FRFNGFTDMV FGSKKHGDVD IDALEMELES SIWETVKERE IECKDTHKKD       300
LMQLILEGAM RSCDGNLWDK SAYRRFVVDN CKSIYFAGHD STAVSVSWCL MLLALNPSWQ       360
VKIRDEILSS CKNGIPDAES IPNLKTVTMV IQETMRLYPP APIVGREASK DIRLGDLVVP       420
KGVCIWTLIP ALHRDPEIWG PDANDFKPER FSEGISKACK YPQSYIPFGL GPRTCVGKNF       480
GMMEVKVLVS LIVSKFSFTL SPTYQHSPSH KLLVEPQHGV VIRVV                       525
```

SEQ ID NO:16

```
MYFLLQYLNI TTVGVFATLF LSYCLLLWRS RAGNKKIAPE AAAAWPIIGH LHLLAGGSHQ        60
LPHITLGNMA DKYGPVFTIR IGLHRAVVVS SWEMAKECST ANDQVSSSRP ELLASKLLGY       120
NYAMFGFSPY GSYWREMRKI ISLELLSNSR LELLKDVRAS EVVTSIKELY KLWAEKKNES       180
GLVSVEMKQW FGDLTLNVIL RMVAGKRYFS ASDASENKQA QRCRRVFREF FHLSGLFVVA       240
DAIPFLGWLD WGRHEKTLKK TAIEMDSIAQ EWLEEHRRRK DSGDDNSTQD FMDVMQSVLD       300
GKNLGGYDAD TINKATCLTL ISGGSDTTVV SLTWALSLVL NNRDTLKKAQ EELDIQVGKE       360
RLVNEQDISK LVYLQAIVKE TLRLYPPGPL GGLRQFTEDC TLGGYHVSKG TRLIMNLSKI       420
QKDPRIWSDP TEFQPERFLT THKDVDPRGK HFEFIPFGAG RRACPGITFG LQVLHLTLAS       480
FLHAFEFSTP SNEQVNMRES LGLTNMKSTP LEVLISPRLS SCSLYN                      526
```

SEQ ID NO:17

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MEPNFYLSLL LLFVTFISLS LFFIFYKQKS PLNLPPGKMG YPIIGESLEF LSTGWKGHPE        60
KFIFDRMRKY SSELFKTSIV GESTVVCCGA ASNKFLFSNE NKLVTAWWPD SVNKIFPTTS       120
LDSNLKEESI KMRKLLPQFF KPEALQRYVG VMDVIAQRHF VTHWDNKNEI TVYPLAKRYT       180
FLLACRLFMS VEDENHVAKF SDPFQLIAAG IISLPIDLPG TPFNKAIKAS NFIRKELIKI       240
IKQRRVDLAE GTASPTQDIL SHMLLTSDEN GKSMNELNIA DKILGLLIGG HDTASVACTF       300
LVKYLGELPH IYDKVYQEQM EIAKSKPAGE LLNWDDLKKM KYSWNVACEV MRLSPPLQGG       360
FREAITDFMF NGFSIPKGWK LYWSANSTHK NAECFPMPEK FDPTRFEGNG PAPYTFVPFG       420
GGPRMCPGKE YARLEILVFM HNLVKRFKWE KVIPDEKIIV DPFPIPAKDL PIRLYPHKA        479
```

SEQ ID NO:18

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atggaagcct cttacctata catttctatt ttgcttttac tggcatcata cctgttcacc        60
actcaactta gaaggaagag cgctaatcta ccaccaaccg tgtttccatc aataccaatc       120
attggacact tatacttact caaaaagcct ctttatagaa ctttagcaaa aattgccgct       180
aagtacggac caatactgca attacaactc ggctacagac gtgttctggt gatttcctca       240
ccatcagcag cagaagagtg ctttaccaat aacgatgtaa tcttcgcaaa tagacctaag       300
```

```
acattgtttg gcaaaatagt gggtggaaca tcccttggca gtttatccta cggcgatcaa      360
tggcgtaatc taaggagagt agcttctatc gaaatcctat cagttcatag gttgaacgaa      420
tttcatgata tcagagtgga tgagaacaga ttgttaatta gaaaacttag aagttcatct      480
tctcctgtta ctcttataac agtcttttat gctctaacat tgaacgtcat tatgagaatg      540
atctctggca aaagatattt cgacagtggg gatagagaat tggaggagga aggtaagaga      600
tttcgagaaa tcttagacga aacgttgctt ctagccggtg cttctaatgt tggcgactac      660
ttaccaatat tgaactggtt gggagttaag tctcttgaaa agaaattgat cgctttgcag      720
aaaaagagag atgacttttt ccagggtttg attgaacagg ttagaaaatc tcgtggtgct      780
aaagtaggca aaggtagaaa aacgatgatc gaactcttat tatctttgca agagtcagaa      840
cctgagtact atacagatgc tatgataaga tcttttgtcc taggtctgct ggctgcaggt      900
agtgatactt cagcgggcac tatggaatgg gccatgagct tactggtcaa tcacccacat      960
gtattgaaga aagctcaagc tgaaatcgat agagttatcg gtaataacag attgattgac     1020
gagtcagaca ttggaaatat cccttacatc gggtgtatta tcaatgaaac tctaagactc     1080
tatccagcag ggccattgtt gttcccacat gaaagttctg ccgactgcgt tatttccggt     1140
tacaatatac ctagaggtac aatgttaatc gtaaaccaat gggcgattca tcacgatcct     1200
aaagtctggg atgatcctga aacctttaaa cctgaaagat ttcaaggatt agaaggaact     1260
agagatggtt tcaaacttat gccattcggt tctgggagaa gaggatgtcc aggtgaaggt     1320
ttggcaataa ggctgttagg gatgacacta ggctcagtga tccaatgttt tgattgggag     1380
agagtaggag atgagatggt tgacatgaca gaaggtttgg gtgtcacact tcctaaggcc     1440
gttccattag ttgccaaatg taagccacgt tccgaaatga ctaatctcct atccgaactt     1500
taa                                                                  1503
```

SEQ ID NO:19

```
MEASYLYISI LLLLASYLFT TQLRRKSANL PPTVFPSIPI IGHLYLLKKP LYRTLAKIAA       60
KYGPILQLQL GYRRVLVISS PSAAEECFTN NDVIFANRPK TLFGKIVGGT SLGSLSYGDQ      120
WRNLRRVASI EILSVHRLNE FHDIRVDENR LLIRKLRSSS SPVTLITVFY ALTLNVIMRM      180
ISGKRYFDSG DRELEEEGKR FREILDETLL LAGASNVGDY LPILNWLGVK SLEKKLIALQ      240
KKRDDFFQGL IEQVRKSRGA KVGKGRKTMI ELLLSLQESE PEYYTDAMIR SFVLGLLAAG      300
SDTSAGTMEW AMSLLVNHPH VLKKAQAEID RVIGNNRLID ESDIGNIPYI GCIINETLRL      360
YPAGPLLFPH ESSADCVISG YNIPRGTMLI VNQWAIHHDP KVWDDPETFK PERFQGLEGT      420
RDGFKLMPFG SGRRGCPGEG LAIRLLGMTL GSVIQCFDWE RVGDEMVDMT EGLGVTLPKA      480
VPLVAKCKPR SEMTNLLSEL                                                  500
```

SEQ ID NO:20

```
MQSDSVKVSP FDLVSAAMNG KAMEKLNASE SEDPTTLPAL KMLVENRELL TLFTTSFAVL       60
IGCLVFLMWR RSSSKKLVQD PVPQVIVVKK KEKESEVDDG KKKVSIFYGT QTGTAEGFAK      120
ALVEEAKVRY EKTSFKVIDL DDYAADDDEY EEKLKKESLA FFFLATYGDG EPTDNAANFY      180
KWFTEGDDKG EWLKKLQYGV FGLGNRQYEH FNKIAIVVDD KLTEMGAKRL VPVGLGDDDQ      240
CIEDDFTAWK ELVWPELDQL LRDEDDTSVT TPYTAAVLEY RVVYHDKPAD SYAEDQTHTN      300
GHVVHDAQHP SRSNVAFKKE LHTSQSDRSC THLEFDISHT GLSYETGDHV GVYSENLSEV      360
VDEALKLLGL SPDTYFSVHA DKEDGTPIGG ASLPPPFPPC TLRDALTRYA DVLSSPKKVA      420
LLALAAHASD PSEADRLKFL ASPAGKDEYA QWIVANQRSL LEVMQSFPSA KPPLGVFFAA      480
VAPRLQPRYY SISSSPKMSP NRIHVTCALV YETTPAGRIH RGLCSTWMKN AVPLTESPDC      540
SQASIFVRTS NFRLPVDPKV PVIMIGPGTG LAPFRGFLQE RLALKESGTE LGSSIFFFGC      600
RNRKVDFIYE DELNNFVETG ALSELIVAFS REGTAKEYVQ HKMSQKASDI WKLLSEGAYL      660
YVCGDAKGMA KDVHRTLHTI VQEQGSLDSS KAELYVKNLQ MSGRYLRDVW                 710
```

SEQ ID NO:21

```
MTSALYASDL FKQLKSIMGT DSLSDDVVLV IATTSLALVA GFVVLLWKKT TADRSGELKP       60
LMIPKSLMAK DEDDDLDLGS GKTRVSIFFG TQTGTAEGFA KALSEEIKAR YEKAAVKVID      120
LDDYAADDDQ YEEKLKKETL AFFCVATYGD GEPTDNAARF YKWFTEENER DIKLQQLAYG      180
VFALGNRQYE HFNKIGIVLD EELCKKGAKR LIEVGLGDDD QSIEDDFNAW KESLWSELDK      240
LLKDEDDKSV ATPYTAVIPE YRVVTHDPRF TTQKSMESNV ANGNTTIDIH HPCRVDVAVQ      300
KELHTHESDR SCIHLEFDIS RTGITYETGD HVGVYAENHV EIVEEAGKLL GHSLDLVFSI      360
HADKEDGSPL ESAVPPPFPG PCTLGTGLAR YADLLNPPRK SALVALAAYA TEPSEAEKLK      420
HLTSPDGKDE YSQWIVASQR SLLEVMAAFP SAKPPLGVFF AAIAPRLQPR YYSISSSPRL      480
APSRVHVTSA LVYGPTPTGR IHKGVCSTWM KNAVPAEKSH ECSGAPIFIR ASNFKLPSNP      540
STPIVMVGPG TGLAPFRGFL QERMALKEDG EELGSSLLFF GCRNRQMDFI YEDELNNFVD      600
QGVISELIMA FSREGAQKEY VQHKMMEKAA QVWDLIKEEG YLYVCGDAKG MARDVHRTLH      660
TIVQEQEGVS SSEAEAIVKK LQTEGRYLRD VW                                    692
```

SEQ ID NO:22

```
MAELDTLDIV VLGVIFLGTV AYFTKGKLWG VTKDPYANGF AAGGASKPGR TRNIVEAMEE      60
SGKNCVVFYG SQTGTAEDYA SRLAKEGKSR FGLNTMIADL EDYDFDNLDT VPSDNIVMFV     120
LATYGEGEPT DNAVDFYEFI TGEDASFNEG NDPPLGNLNY VAFGLGNNTY EHYNSMVRNV     180
NKALEKLGAH RIGEAGEGDD GAGTMEEDFL AWKDPMWEAL AKKMGLEERE AVYEPIFAIN     240
ERDDLTPEAN EVYLGEPNKL HLEGTAKGPF NSHNPYIAPI AESYELFSAK DRNCLHMEID     300
ISGSNLKYET GDHIAIWPTN PGEEVNKFLD ILDLSGKQHS VVTVKALEPT AKVPFPNPTT     360
YDAILRYHLE ICAPVSRQFV STLAAFAPND DIKAEMNRLG SDKDYFHEKT GPHYYNIARF     420
LASVSKGEKW TKIPFSAFIE GLTKLQPRYY SISSSSLVQP KKISITAVVE SQQIPGRDDP     480
FRGVATNYLF ALKQKQNGDP NPAPFGQSYE LTGPRNKYDG IHVPVHVRHS NFKLPSDPGK     540
PIIMIGPGTG VAPFRGFVQE RAKQARDGVE VGKTLLFFGC RKSTEDFMYQ KEWQEYKEAL     600
GDKFEMITAF SREGSKKVYV QHRLKERSKE VSDLLSQKAY FYVCGDAAHM AREVNTVLAQ     660
IIAEGRGVSE AKGEEIVKNM RSANQYQVCS DFVTLHCKET TYANSELQED VWS             713
```

SEQ ID NO:23

```
atgcaatcgg aatccgttga agcatcgacg attgatttga tgactgctgt tttgaaggac      60
acagtgatcg atacagcgaa cgcatctgat aacggagact caaagatgcc gccggcgttg     120
gcgatgatgt tcgaaattcg tgatctgttg ctgattttga ctacgtcagt tgctgttttg     180
gtcggatgtt tcgttgtttt ggtgtggaag agatcgtccg ggaagaagtc cggcaaggaa     240
ttggagccgc cgaagatcgt tgtgccgaag aggcggctgg agcaggaggt tgatgatggt     300
aagaagaagg ttacgatttt cttcggaaca caaactggaa cggctgaagg tttcgctaag     360
gcacttttcg aagaagcgaa agcgcgatat gaaaaggcag cgtttaaagt gattgatttg     420
gatgattatg ctgctgattt ggatgagtat gcagagaagc tgaagaagga aacatatgct     480
ttcttcttct tggctacata tggagatggt gagccaactg ataatgctgc caaattttat     540
aaatggttta ctgagggaga cgagaaaggc gtttggcttc aaaaacttca atatggagta     600
tttggtcttg gcaacagaca atatgaacat ttcaacaaga ttggaatagt ggttgatgat     660
ggtctcaccg agcagggtgc aaaacgcatt gttcccgttg gtcttggaga cgacgatcaa     720
tcaattgaag acgatttttc ggcatggaaa gagttagtgt ggcccgaatt ggatctattg     780
cttcgcgatg aagatgacaa agctgctgca actccttaca cagctgcaat ccctgaatac     840
cgcgtcgtat ttcatgacaa acccgatgcg ttttctgatg atcatactca aaccaatggt     900
catgctgttc atgatgctca acatccatgc agatccaatg tggctgttaa aaaagagctt     960
catactcctg aatccgatcg ttcatgcaca catcttgaat ttgacatttc tcacactgga    1020
ttatcttatg aaactgggga tcatgttggt gtatactgtg aaaacctaat tgaagtagtg    1080
gaagaagctg ggaaattgtt aggattatca acagatactt atttctcgtt acatattgat    1140
aacgaagatg gttcaccact tggtggacct tcattacaac ctccttttcc tccttgtact    1200
ttaagaaaag cattgactaa ttatgcagat ctgttaagct ctcccaaaaa gtcaactttg    1260
cttgctctag ctgctcatgc ttccgatccc actgaagctg atcgtttaag atttcttgca    1320
tctcgcgagg gcaaggatga atatgctgaa tgggttgttg caaaccaaag aagtcttctt    1380
gaagtcatgg aagctttccc gtcagctaga ccgccacttg gtgttttctt tgcagcggtt    1440
gcaccgcgtt tacagcctcg ttactactct atttcttcct ccccaaagat ggaaccaaac    1500
aggattcatg ttacttgcgc gttggtttat gaaaaaactc ccgcaggtcg tatccacaaa    1560
ggaatctgct caacctggat gaagaacgct gtacctttga ccgaaagtca agattgcagt    1620
tgggcaccga tttttgttag aacatcaaac ttcagacttc caattgaccc gaaagtcccg    1680
gttatcatga ttggtcctgg aaccgggttg gctccattta ggggttttct tcaagaaaga    1740
ttggctctta aagaatccgg aaccgaactc gggtcatcta ttttattctt cggttgtaga    1800
aaccgcaaag tggattacat atatgagaat gaactcaaca actttgttga aaatggtgcg    1860
ctttctgagc ttgatgttgc tttctcccgc gatggcccga cgaaagaata cgtgcaacat    1920
aaaatgaccc aaaaggcttc tgaaatatgg aatatgcttt ctgagggagc atatttatat    1980
gtatgtggtg atgctaaagg catggctaaa gatgtacacc gtacacttca caccattgtg    2040
caagaacagg gaagtttgga ctcgtctaaa gcggagttgt atgtgaagaa tctacaaatg    2100
tcaggaagat acctccgtga tgtttggtaa                                     2130
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SEQ ID NO:24

```
atgcaatcta actccgtgaa gatttcgccg cttgatctgg taactgcgct gtttagcggc      60
aaggttttgg acacatcgaa cgcatcggaa tcgggagaat ctgctatgct gccgactata     120
gcgatgatta tggagaatcg tgagctgttg atgatactca caacgtcggt tgctgtattg     180
atcggatgcg ttgtcgtttt ggtgtggcgg agatcgtcta cgaagaagtc ggcgttggag     240
ccaccggtga ttgtggttcc gaagagagtg caagaggagg aagttgatga tggtaagaag     300
aaagttacgg ttttcttcgg cacccaaact ggaacagctg aaggcttcgc taaggcactt     360
gttgaggaag ctaaagctcg atatgaaaag gctgtcttta aagtaattga tttggatgat     420
tatgctgctg atgacgatga gtatgaggag aaactaaaga aagaatcttt ggccttttcc     480
tttttggcta cgtatggaga tggtgagcca acagataatg ctgccagatt ttataaatgg     540
```

```
tttactgagg gagatgcgaa aggagaatgg cttaataagc ttcaatatgg agtatttggt      600
ttgggtaaca gacaatatga acattttaac aagatcgcaa aagtggttga tgatggtctt      660
gtagaacagg gtgcaaagcg tcttgttcct gttggacttg gagatgatga tcaatgtatt      720
gaagatgact tcaccgcatg gaaagagtta gtatggccgg agttggatca attacttcgt      780
gatgaggatg acacaactgt tgctactcca tacacagctg ctgttgcaga atatcgcgtt      840
gtttttcatg aaaaaccaga cgcgctttct gaagattata gttatacaaa tggccatgct      900
gttcatgatg ctcaacatcc atgcagatcc aacgtggctg tcaaaaagga acttcatagt      960
cctgaatctg accggtcttg cactcatctt gaatttgaca tctcgaacac cggactatca     1020
tatgaaactg gggaccatgt tggagtttac tgtgaaaact tgagtgaagt tgtgaatgat     1080
gctgaaagat tagtaggatt accaccagac acttactcct ccatccacac tgatagtgaa     1140
gacgggtcgc cacttggcgg agcctcattg ccgcctcctt tcccgccatg cactttaagg     1200
aaagcattga cgtgttatgc tgatgttttg agttctccca agaagtcggc tttgcttgca     1260
ctagctgctc atgccaccga tcccagtgaa gctgatagat tgaaatttct tgcatccccc     1320
gccggaaagg atgaatattc tcaatggata gttgcaagcc aaagaagtct ccttgaagtc     1380
atggaagcat tcccgtcagc taagccttca cttggtgttt tctttgcatc tgttgccccg     1440
cgcttacaac caagatacta ctctatttct tcctcaccca agatggcacc ggataggatt     1500
catgttacat gtgcattagt ctatgagaaa acacctgcag gccgcatcca caaaggagtt     1560
tgttcaactt ggatgaagaa cgcagtgcct atgaccgaga gtcaagattg cagttgggcc     1620
ccaatatacg tccgaacatc caatttcaga ctaccatctg accctaaggt cccggttatc     1680
atgattggac ctggcactgg tttggctcct tttagaggtt tccttcaaga gcggttagct     1740
ttaaaggaag ccggaactga cctcggttta tccattttat tcttcggatg taggaatcgc     1800
aaagtggatt tcatatatga aaacgagctt aacaactttg tggagactgg tgctctttct     1860
gagcttattg ttgctttctc ccgtgaaggc ccgactaagg aatatgtgca acacaagatg     1920
agtgagaagg cttcggatat ctggaacttg ctttctgaag gagcatattt atacgtatgt     1980
ggtgatgcca aaggcatggc caaagatgta catcgaaccc tccacacaat tgtgcaagaa     2040
cagggatctc ttgactcgtc aaaggcagaa ctctacgtga agaatctaca aatgtcagga     2100
agatacctcc gtgacgtttg gtaa                                           2124
```

SEQ ID NO:25

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MTSALYASDL FKQLKSIMGT DSLSDDVVLV IATTSLALVA GFVVLLWKKT TADRSGELKP       60
LMIPKSLMAK DEDDDLDLGS GKTRVSIFFG TQTGTAEGFA KALSEEIKAR YEKAAVKVID      120
LDDYAADDDQ YEEKLKKETL AFFCVATYGD GEPTDNAARF YKWFTEENER DIKLQQLAYG      180
VFALGNRQYE HFNKIGIVLD EELCKKGAKR LIEVGLGDDD QSIEDDFNAW KESLWSELDK      240
LLKDEDDKSV ATPYTAVIPE YRVVTHDPRF TTQKSMESNV ANGNTTIDIH HPCRVDVAVQ      300
KELHTHESDR SCIHLEFDIS RTGITYETGD HVGVYAENHV EIVEEAGKLL GHSLDLVFSI      360
HADKEDGSPL ESAVPPPFPG PCTLGTGLAR YADLLNPPRK SALVALAAYA TEPSEAEKLK      420
HLTSPDGKDE YSQWIVASQR SLLEVMAAFP SAKPPLGVFF AAIAPRLQPR YYSISSSPRL      480
APSRVHVTSA LVYGPTPTGR IHKGVCSTWM KNAVPAEKSH ECSGAPIFIR ASNFKLPSNP      540
STPIVMVGPG TGLAPFRGFL QERMALKEDG EELGSSLLFF GCRNRQMDFI YEDELNNFVD      600
QGVISELIMA FSREGAQKEY VQHKMMEKAA QVWDLIKEEG YLYVCGDAKG MARDVHRTLH      660
TIVQEQEGVS SSEAEAIVKK LQTEGRYLRD VW                                    692
```

SEQ ID NO:26

```
MSSSSSSSTS MIDLMAAIIK GEPVIVSDPA NASAYESVAA ELSSMLIENR QFAMIVTTSI       60
AVLIGCIVML VWRRSGSGNS KRVEPLKPLV IKPREEEIDD GRKKVTIFFG TQTGTAEGFA      120
KALGEEAKAR YEKTRFKIVD LDDYAADDDE YEEKLKKEDV AFFFLATYGD GEPTDNAARF      180
YKWFTEGNDR GEWLKNLKYG VFGLGNRQYE HFNKVAKVVD DILVEQGAQR LVQVGLGDDD      240
QCIEDDFTAW REALWPELDT ILREEGDTAV ATPYTAAVLE YRVSIHDSED AKFNDITLAN      300
GNGYTVFDAQ HPYKANVAVK RELHTPESDR SCIHLEFDIA GSGLTMKLGD HVGVLCDNLS      360
ETVDEALRLL DMSPDTYFSL HAEKEDGTPI SSSLPPPFPP CNLRTALTRY ACLLSSPKKS      420
ALVALAAHAS DPTEAERLKH LASPAGKDEY SKWVVESQRS LLEVMAEFPS AKPPLGVFFA      480
GVAPRLQPRF YSISSSPKIA ETRIHVTCAL VYEKMPTGRI HKGVCSTWMK NAVPYEKSEK      540
LFLGRPIFVR QSNFKLPSDS KVPIIMIGPG TGLAPFRGFL QERLALVESG VELGPSVLFF      600
GCRNRRMDFI YEEELQRFVE SGALAELSVA FSREGPTKEY VQHKMMDKAS DIWNMISQGA      660
YLYVCGDAKG MARDVHRSLH TIAQEQGSMD STKAEGFVKN LQTSGRYLRD VW              712
```

SEQ ID NO:27

```
MQSESVEAST IDLMTAVLKD TVIDTANASD NGDSKMPPAL AMMFEIRDLL LILTTSVAVL       60
VGCFVVLVWK RSSGKKSGKE LEPPKIVVPK RRLEQEVDDG KKKVTIFFGT QTGTAEGFAK      120
ALFEEAKARY EKAAFKVIDL DDYAADLDEY AEKLKKETYA FFFLATYGDG EPTDNAAKFY      180
KWFTEGDEKG VWLQKLQYGV FGLGNRQYEH FNKIGIVVDD GLTEQGAKRI VPVGLGDDDQ      240
SIEDDFSAWK ELVWPELDLL LRDEDDKAAA TPYTAAIPEY RVVFHDKPDA FSDDHTQTNG      300
```

```
HAVHDAQHPC RSNVAVKKEL HTPESDRSCT HLEFDISHTG LSYETGDHVG VYCENLIEVV       360
EEAGKLLGLS TDTYFSLHID NEDGSPLGGP SLQPPFPPCT LRKALTNYAD LLSSPKKSTL       420
LALAAHASDP TEADRLRFLA SREGKDEYAE WVVANQRSLL EVMEAFPSAR PPLGVFFAAV       480
APRLQPRYYS ISSSPKMEPN RIHVTCALVY EKTPAGRIHK GICSTWMKNA VPLTESQDCS       540
WAPIFVRTSN FRLPIDPKVP VIMIGPGTGL APFRGFLQER LALKESGTEL GSSILFFGCR       600
NRKVDYIYEN ELNNFVENGA LSELDVAFSR DGPTKEYVQH KMTQKASEIW NMLSEGAYLY       660
VCGDAKGMAK DVHRTLHTIV QEQGSLDSSK AELYVKNLQM SGRYLRDVW                   709
```

SEQ ID NO:28

```
MQSNSVKISP LDLVTALFSG KVLDTSNASE SGESAMLPTI AMIMENRELL MILTTSVAVL        60
IGCVVVLVWR RSSTKKSALE PPVIVVPKRV QEEEVDDGKK KVTVFFGTQT GTAEGFAKAL       120
VEEAKARYEK AVFKVIDLDD YAADDDEYEE KLKKESLAFF FLATYGDGEP TDNAARFYKW       180
FTEGDAKGEW LNKLQYGVFG LGNRQYEHFN KIAKVVDDGL VEQGAKRLVP VGLGDDDQCI       240
EDDFTAWKEL VWPELDQLLR DEDDTTVATP YTAAVAEYRV VFHEKPDALS EDYSYTNGHA       300
VHDAQHPCRS NVAVKKELHS PESDRSCTHL EFDISNTGLS YETGDHVGVY CENLSEVVND       360
AERLVGLPPD TYSSIHTDSE DGSPLGGASL PPPFPPCTLR KALTCYADVL SSPKKSALLA       420
LAAHATDPSE ADRLKFLASP AGKDEYSQWI VASQRSLLEV MEAFPSAKPS LGVFFASVAP       480
RLQPRYYSIS SSPKMAPDRI HVTCALVYEK TPAGRIHKGV CSTWMKNAVP MTESQDCSWA       540
PIYVRTSNFR LPSDPKVPVI MIGPGTGLAP FRGFLQERLA LKEAGTDLGL SILFFGCRNR       600
KVDFIYENEL NNFVETGALS ELIVAFSREG PTKEYVQHKM SEKASDIWNL LSEGAYLYVC       660
GDAKGMAKDV HRTLHTIVQE QGSLDSSKAE LYVKNLQMSG RYLRDVW                     707
```

SEQ ID NO:29

```
MAEQQKIKKS PHVLLIPFPL QGHINPFIQF GKRLISKGVK TTLVTTIHTL NSTLNHSNTT        60
TTSIEIQAIS DGCDEGGFMS AGESYLETFK QVGSKSLADL IKKLQSEGTT IDAIIYDSMT       120
EWVLDVAIEF GIDGGSFFTQ ACVVNSLYYH VHKGLISLPL GETVSVPGFP VLQRWETPLI       180
LQNHEQIQSP WSQMLFGQFA NIDQARWVFT NSFYKLEEEV IEWTRKIWNL KVIGPTLPSM       240
YLDKRLDDDK DNGFNLYKAN HHECMNWLDD KPKESVVYVA FGSLVKHGPE QVEEITRALI       300
DSDVNFLWVI KHKEEGKLPE NLSEVIKTGK GLIVAWCKQL DVLAHESVGC FVTHCGFNST       360
LEAISLGVPV VAMPQFSDQT TNAKLLDEIL GVGVRVKADE NGIVRRGNLA SCIKMIMEEE       420
RGVIIRKNAV KWKDLAKVAV HEGGSSDNDI VEFVSELIKA                             460
```

SEQ ID NO:30

```
MDAMATTEKK PHVIFIPFPA QSHIKAMLKL AQLLHHKGLQ ITFVNTDFIH NQFLESSGPH        60
CLDGAPGFRF ETIPDGVSHS PEASIPIRES LLRSIETNFL DRFIDLVTKL PDPPTCIISD       120
GFLSVFTIDA AKKLGIPVMM YWTLAACGFM GFYHIHSLIE KGFAPLKDAS YLTNGYLDTV       180
IDWVPGMEGI RLKDFPLDWS TDLNDKVLMF TTEAPQRSHK VSHHIFHTFD ELEPSIIKTL       240
SLRYNHIYTI GPLQLLLDQI PEEKKQTGIT SLHGYSLVKE EPECFQWLQS KEPNSVVYVN       300
FGSTTVMSLE DMTEFGWGLA NSNHYFLWII RSNLVIGENA VLPPELEEHI KKRGFIASWC       360
SQEKVLKHPS VGGFLTHCGW GSTIESLSAG VPMICWPYSW DQLTNCRYIC KEWEVGLEMG       420
TKVKRDEVKR LVQELMGEGG HKMRNKAKDW KEKARIAIAP NGSSSLNIDK MVKEITVLAR       480
N                                                                       481
```

SEQ ID NO:31

```
atggatgcaa tggctacaac tgagaagaaa ccacacgtca tcttcatacc atttccagca        60
caaagccaca ttaaagccat gctcaaacta gcacaacttc tccaccacaa aggactccag       120
ataaccttcg tcaacaccga cttcatccac aaccagtttc ttgaatcatc gggcccacat       180
tgtctagacg gtgcaccggg tttccggttc gaaaccattc cggatggtgt ttctcacagt       240
ccggaagcga gcatcccaat cagagaatca ctcttgagat ccattgaaac caacttcttg       300
gatcgtttca ttgatcttgt aaccaaactt ccggatcctc cgacttgtat tatctcagat       360
gggttcttgt cggttttcac aattgacgct gcaaaaaagc ttggaattcc ggtcatgatg       420
tattggacac ttgctgcctg tgggttcatg ggtttttacc atattcattc tctcattgag       480
aaaggatttg caccacttaa agatgcaagt tacttgacaa atgggtattt ggacaccgtc       540
attgattggg ttccgggaat ggaaggcatc cgtctcaagg atttcccgct ggactggagc       600
actgacctca atgacaaagt tttgatgttc actacggaag ctcctcaaag gtcacacaag       660
gtttcacatc atattttcca cacgttcgat gagttggagc ctagtattat aaaaactttg       720
tcattgaggt ataatcacat ttacaccatc ggcccactgc aattacttct tgatcaaata       780
cccgaagaga aaaagcaaac tggaattacg agtctccatg gatacagttt agtaaaagaa       840
gaaccagagt gtttccagtg gcttcagtct aaagaaccaa attccgtcgt ttatgtaaat       900
tttggaagta ctacagtaat gtctttagaa gacatgacgg aatttggttg gggacttgct       960
```

```
aatagcaacc attatttcct ttggatcatc cgatcaaact tggtgatagg ggaaaatgca      1020
gttttgcccc ctgaacttga ggaacatata aagaaaagag gctttattgc tagctggtgt      1080
tcacaagaaa aggtcttgaa gcacccttcg gttggagggt tcttgactca ttgtgggtgg      1140
ggatcgacca tcgagagctt gtctgctggg gtgccaatga tatgctggcc ttattcgtgg      1200
gaccagctga ccaactgtag gtatatatgc aaagaatggg aggttgggct cgagatggga      1260
accaaagtga aacgagatga agtcaagagg cttgtacaag agttgatggg agaaggaggt      1320
cacaaaatga ggaacaaggc taaagattgg aaagaaaagg ctcgcattgc aatagctcct      1380
aacggttcat cttctttgaa catagacaaa atggtcaagg aaatcaccgt gctagcaaga      1440
aactagttac aaagttgttt cacattgtgc tttctattta agatgtaact ttgttctaat      1500
ttaatattgt ctagatgtat tgaaccataa gtttagttgg tctcaggaat tgatttttaa      1560
tgaaataatg gtcattaggg gtgagt                                           1586
```

SEQ ID NO:32

```
atggatgcaa tggcaactac tgagaaaaag cctcatgtga tcttcattcc atttcctgca        60
caatctcaca taaaggcaat gctaaagtta gcacaactat tacaccataa gggattacag       120
ataactttcg tgaataccga cttcatccat aatcaatttc tggaatctag tggccctcat       180
tgtttggacg gagccccagg gtttagattc gaaacaattc ctgacggtgt ttcacattcc       240
ccagaggcct ccatcccaat aagagagagt ttactgaggt caatagaaac caacttttg        300
gatcgtttca ttgacttggt cacaaaactt ccagacccac caacttgcat aatctctgat       360
ggctttctgt cagtgtttac tatcgacgct gccaaaaagt tgggtatccc agttatgatg       420
tactggactc ttgctgcatg cggtttcatg ggtttctatc acatccattc tcttatcgaa       480
aagggttttg ctccactgaa agatgcatca tacttaacca acggctacct ggatactgtt       540
attgactggg taccaggtat ggaaggtata agacttaaag attttccttt ggattggtct       600
acagacctta atgataaagt attgatgttt actacagaag ctccacaaag atctcataag       660
gtttcacatc atatctttca cacctttgat gaattggaac catcaatcat caaaaccttg       720
tctctaagat acaatcatat ctacactatt ggtccattac aattacttct agatcaaatt       780
cctgaagaga aaaagcaaac tggtattaca tccttacacg gctactcttt agtgaaagag       840
gaaccagaat gttttcaatg gctacaaagt aaagagccta attctgtggt ctacgtcaac       900
ttcggaagta caacagtcat gtccttggaa gatatgactg aatttggttg gggccttgct       960
aattcaaatc attactttct atggattatc aggtccaatt tggtaatagg ggaaaacgcc      1020
gtattacctc cagaattgga ggaacacatc aaaaagagag gtttcattgc ttcctggtgt      1080
tctcaggaaa aggtattgaa acatccttct gttggtggtt tccttactca ttgcggttgg      1140
ggctctacaa tcgaatcact aagtgcagga gttccaatga tttgttggcc atattcatgg      1200
gaccaactta caaattgtag gtatatctgt aaagagtggg aagttggatt agaaatggga      1260
acaaaggtta aacgtgatga agtgaaaaga ttggttcagg agttgatggg ggaaggtggc      1320
cacaagatga gaaacaaggc caaagattgg aaggaaaaag ccagaattgc tattgctcct      1380
aacgggtcat cctctctaaa cattgataag atggtcaaag agattacagt cttagccaga      1440
aactaa                                                                 1446
```

SEQ ID NO:33

```
MKTGFISPAT VFHHRISPAT TFRHHLSPAT TNSTGIVALR DINFRCKAVS KEYSDLLQKD        60
EASFTKWDDD KVKDHLDTNK NLYPNDEIKE FVESVKAMFG SMNDGEINVS AYDTAWVALV       120
QDVDGSGSPQ FPSSLEWIAN NQLSDGSWGD HLLFSAHDRI INTLACVIAL TSWNVHPSKC       180
EKGLNFLREN ICKLEDENAE HMPIGFEVTF PSLIDIAKKL NIEVPEDTPA LKEIYARRDI       240
KLTKIPMEVL HKVPTTLLHS LEGMPDLEWE KLLKLQCKDG SFLFSPSSTA FALMQTKDEK       300
CLQYLTNIVT KFNGGVPNVY PVDLFEHIWV VDRLQRLGIA RYFKSEIKDC VEYINKYWTK       360
NGICWARNTH VQDIDDTAMG FRVLRAHGYD VTPDVFRQFE KDGKFVCFAG QSTQAVTGMF       420
NVYRASQMLF PGERILEDAK KFSYNYLKEK QSTNELLDKW IIAKDLPGEV GYALDIPWYA       480
SLPRLETRYY LEQYGGEDDV WIGKTLYRMG YVSNNTYLEM AKLDYNNYVA VLQLEWYTIQ       540
QWYVDIGIEK FESDNIKSVL VSYYLAAASI FEPERSKERI AWAKTTILVD KITSIFDSSQ       600
SSKEDITAFI DKFRNKSSSK KHSINGEPWH EVMVALKKTL HGFALDALMT HSQDIHPQLH       660
QAWEMWLTKL QDGVDVTAEL MVQMINMTAG RWVSKELLTH PQYQRLSTVT NSVCHDITKL       720
HNFKENSTTV DSKVQELVQL VFSDTPDDLD QDMKQTFLTV MKTFYYKAWC DPNTINDHIS       780
KVFEIVI                                                                 787
```

SEQ ID NO:34

```
MPDAHDAPPP QIRQRTLVDE ATQLLTESAE DAWGEVSVSE YETARLVAHA TWLGGHATRV        60
AFLLERQHED GSWGPPGGYR LVPTLSAVHA LLTCLASPAQ DHGVPHDRLL RAVDAGLTAL       120
RRLGTSDSPP DTIAVELVIP SLLEGIQHLL DPAHPHSRPA FSQHRGSLVC PGGLDGRTLG       180
ALRSHAAAGT PVPGKVWHAS ETLGLSTEAA SHLQPAQGII GGSAAATATW LTRVAPSQQS       240
DSARRYLEEL QHRYSGPVPS ITPITYFERA WLLNNFAAAG VPCEAPAALL DSLEAALTPQ       300
GAPAGAGLPP DADDTAAVLL ALATHGRGRR PEVLMDYRTD GYFQCFIGER TPSISTNAHV       360
```

```
LETLGHHVAQ HPQDRARYGS AMDTASAWLL AAQKQDGSWL DKWHASPYYA TVCCTQALAA       420
HASPATAPAR QRAVRWVLAT QRSDGGWGLW HSTVEETAYA LQILAPPSGG GNIPVQQALT       480
RGRARLCGAL PLTPLWHDKD LYTPVRVVRA ARAAALYTTR DLLLPPL                    527
```

SEQ ID NO:35

```
MNALSEHILS ELRRLLSEMS DGGSVGPSVY DTAQALRFHG NVTGRQDAYA WLIAQQQADG        60
GWGSADFPLF RHAPTWAALL ALQRADPLPG AADAVQTATR FLQRQPDPYA HAVPEDAPIG       120
AELILPQFCG EAAWLLGGVA FPRHPALLPL RQACLVKLGA VAMLPSGHPL LHSWEAWGTS       180
PTTACPDDDG SIGISPAATA AWRAQAVTRG STPQVGRADA YLQMASRATR SGIEGVFPNV       240
WPINVFEPCW SLYTLHLAGL FAHPALAEAV RVIVAQLEAR LGVHGLGPAL HFAADADDTA       300
VALCVLHLAG RDPAVDALRH FEIGELFVTF PGERNASVST NIHALHALRL LGKPAAGASA       360
YVEANRNPHG LWDNEKWHVS WLYPTAHAVA ALAQGKPQWR DERALAALLQ AQRDDGGWGA       420
GRGSTFEETA YALFALHVMD GSEEATGRRR IAQVVARALE WMLARHAAHG LPQTPLWIGK       480
ELYCPTRVVR VAELAGLWLA LRWGRRVLAE GAGAAP                                 516
```

SEQ ID NO:36

```
gacctgacca ccaccccccg gccggccctt tcattctttc cttacttttct tcctcctgct        60
gctcttgccg tttcagtgat tattagctgc tgtacgtgcg tgcgtacatt gttctctctg       120
ctgacaccca tacacgctgt agcttctaca cataccagtt cgatcgcaag ctatagcatg       180
gggcttcaat catcgcccat gctgctgcca gcgccgacgg caacggcggc cggcagcggg       240
tcacagtggc gcacggctgt ggcgggtaat ggtaactcgt ttatcttctt ctacacgtaa       300
tctctattat atacctagat tttctccaca ggcagatcag attctttaca cagctgtatt       360
ctcaaaaaaa actcatagaa aaaaaagaaa aaactaaacc aaaggagcga cctcaacctg       420
taccagtgcc cctgctagca gtagcttcgt tctgtccctt ttttttcatt tggatcctct       480
acataaatgc tgggtggtgg tgtcctttca cgcacacatc cgcagatagc gccccagcag       540
catttatgtg gggacgacgg ctctgaaatg aattactagt cagtttcatg cgtttcagtg       600
cgagtattat agtagtagat ctcttctccg atatatccgg ccaaaggaag aagagaagag       660
aaaccacaca tctcattctc aactagtagt agaaaagtaa aaacgtacta caagcgcaag       720
cgcaaagatg gttctttcat cgtcttgcac aacagttcct caccttttct cccttgcggt       780
cgttcaacta ggcccatgga gttcccgcat caagaagaag acggatacag tcgccgtccc       840
cgcggccgcc ggccggtgga ggagggcact ggcgcgggcc cagcacacca gcgaatccgc       900
cgccgtcgcc aaaggtacgg gtgatcgcta gctttgatag ctccaaatct gagcagcaaa       960
ttaaatagct aggtttgtaa cgcacgcacg catgcaggtt cgtccctaac gcccatcgtg      1020
agaaccgatg ccgaaagccg ccgcacgaga tggcctacgg acgacgacga cgctgagccg      1080
ctggtcgacg agatcagggc aatgctgacg tcgatgagcg acggggacat cagcgtgtcg      1140
gcgtacgaca ccgcctgggt gggtcttgtg cccaggctgg acggcggcga gggcccgcag      1200
ttcccggccg ccgtgcggtg gatccggaac aaccagctcc ccgacggctc gtggggcgac      1260
gcggccctgt tctccgcgta cgaccgcctg atcaacacgc tggcgtgcgt cgtcacgctc      1320
accaggtggt cgctggagcc cgagatgcgc ggcagaggta cgtaattact gtgtgctggc      1380
cgatcgagag aacacacgac ggcagtgtac ctcgacagaa aacgggcgtt gctgaagact      1440
caagtgtgtg tgtgtgtgtg ttcacagggc tctctttcct cggccggaac atgtggaagc      1500
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tcgaactagc caagagtctg ggcgtccacg acttcccgta cgaccaccag gctctgcagg      1620
gaatatactc gagcagggag atcaagatga agaggattcc taaggaagtg atgcacacgg      1680
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tcatgaacac cggcgacgac aggtgcttca gctacatcga caggacagtc aagaaattca      1860
acggaggagg tacgcaagca gtagcgtaga tacatgggca tagcatgcat gcatgcaatg      1920
cagcgttgcc cactgcatgc gccttccttc cttccttctc gtctcttcaa cggttcgtct      1980
tctctcgccg tttctcgcag tgcccaacgt ctaccccgtg gacctttttcg agcacatatg      2040
ggctgtcgat cgcctggagc gtctcgggat ctcccgctac ttccagaaag agattgagca      2100
gtgcatggac tacgtgaaca ggcactggac tgaggacggg atctgctggg cgaggaactc      2160
cgacgtgaag gaggtggacg acacggccat ggctttccgc ctgctacggc tgcacggata      2220
cagcgtctcg ccaggtacgt aacaaacaca aaaaaaaaaa acgcgcagac aacagagatc      2280
gtcacgtcat acacacgcgt gtcctgaaca tttttcattt ggtctcccac ccatcgtacg      2340
taataataat aaaaaaaaac gtgcttctgc cctgcctgtg tacgtgtaga tgtgttcaag      2400
aacttcgaga aggacgggga gttcttcgcc ttcgtggggc agtcgaacca ggcggtgacg      2460
gggatgtaca acctcaacag ggcctcccag ataagcttcc cgggggagga cgtcctgcac      2520
cgtgcagggg ctttctcgta cgagtttctc aggcggaaag aggccgaggg agcgctccgt      2580
gacaaatgga tcatatctaa ggacctgcct ggggaggtag tgtacaccct ggacttccct      2640
tggtatggga acctgccgcg cgtggaggcg agagactatc tggaacagta cggcggcggc      2700
gacgatgtct ggatcgggaa gacgctctac aggtagatag atctttttag ctattaattg      2760
gtttcagatc gaccagataa aatttgcatt attggttctt ttgatgcatg taattgaaag      2820
```

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ccaataaata acctcagtat gcgtgatggc tgacttttgc attggcagga tgcctcttgt      2880
gaataacgat gtgtatcttg agctggctag gatggacttc aaccattgcc aagccctaca      2940
tcagcttgag tggcaaggcc tgaaaaggta tgtatgttac tatatatata cagcccggtt      3000
gttgagtttt ttttttattt tatttttttc gcgattacca tttcttctcg atgcaaaata      3060
aatctgcaca gatcatcata tatatccttg atgatatata agggcttctc gtatatatat      3120
cttatcacct atatatacat aggtggtaca ctgagaaccg gctcatggat ttcggagtgg      3180
cgcaagagga tgctctgcga gcgtatttcc tggccgccgc ttccgtctac gagccgtgcc      3240
gagccgcgga gcggcttgcg tgggccagag cggcgatact tgccaacgcc gtctctaccc      3300
atctccgtaa cagcccctca ttcagagaac gcttggaaca ctccttgcgt tgccgcccca      3360
gtgaagaaac ggatggatca tggtaataag ctgatcgatg ggaaattaaa aatttaagtt      3420
tttttttct tttttgttgc cattatctga gaccaatgca atgtggtgca tatatatcca      3480
ggttcaactc atcaagtgga agtgacgctg ttcttgtgaa ggcagttctg cggcttaccg      3540
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agctactgag atcagctgta agttaaacgt aacgttcaga agaagatttt ttttttttt       3660
tgcagttaac aagtactacg acatctatcg tttttgttca gcatgcacag tcatcctagc      3720
tactaatacc attattcttc tgtgaacttg tgtagtgggc tgaatgggtc agggagaagg      3780
cagatgcagc agacagcgtg tgtaatggat ccagtgctgt ggaacaagaa gggtcgcgca      3840
tggttcatga caagcaaacg tgtctgcttt tagctcgaat gatcgagatc agcgctgggc      3900
gagctgcagg tgaggctgcg agcgaagatg gtgaccgtcg gattatccag ctcactgggt      3960
ctatatgtga cagtctcaag cagaagatgc tagtatctca ggtatagcac atatatacta      4020
cagaaagttt gtgcgtagtt attatttccc ttttttcatg tgacgaacat gatgacctga      4080
tgatgcatgt atatggcttc atataggacc ccgagaagaa cgaagagatg atgagccatg      4140
tcgatgacga attgaagctg cgtatacgag agttcgttca gtatcttctg agactcggtg      4200
agaagaaaac cggcagcagc gagacaaggc agacctttct gagcatcgtg aaaagctgtt      4260
actacgctgc tcactgcccg ccgcatgtgg tagacaggca tatttccaga gttatttttg      4320
aacctgtttc cgccgcaaaa taatggtaat ggtagatgtg aatgtgatat ggagataaga      4380
gagagagaaa atgttgatag tggaaattgg cgttgatgtc gcctccacat tctttacgca      4440
aaagtagcgt ctgttttgga taaaaaaaat ccagtttctg taaattatag aataaatcaa      4500
tcgctgtgtc ccaaactcta aaatgttatt ctgtgaagta tggaataaat cggtcactat      4560
acctatcttg tggatgc                                                    4577
```

SEQ ID NO:37

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MVLSSSCTTV PHLSSLAVVQ LGPWSSRIKK KTDTVAVPAA AGRWRRALAR AQHTSESAAV        60
AKGSSLTPIV RTDAESRRTR WPTDDDDAEP LVDEIRAMLT SMSDGDISVS AYDTAWVGLV       120
PRLDGGEGPQ FPAAVRWIRN NQLPDGSWGD AALFSAYDRL INTLACVVTL TRWSLEPEMR       180
GRGLSFLGRN MWKLATEDEE SMPIGFELAF PSLIELAKSL GVHDFPYDHQ ALQGIYSSRE       240
IKMKRIPKEV MHTVPTSILH SLEGMPGLDW AKLLKLQSSD GSFLFSPAAT AYALMNTGDD       300
RCFSYIDRTV KKFNGGVPNV YPVDLFEHIW AVDRLERLGI SRYFQKEIEQ CMDYVNRHWT       360
EDGICWARNS DVKEVDDTAM AFRLLRLHGY SVSPDVFKNF EKDGEFFAFV GQSNQAVTGM       420
YNLNRASQIS FPGEDVLHRA GAFSYEFLRR KEAEGALRDK WIISKDLPGE VVYTLDFPWY       480
GNLPRVEARD YLEQYGGGDD VWIGKTLYRM PLVNNDVYLE LARMDFNHCQ ALHQLEWQGL       540
KRWYTENRLM DFGVAQEDAL RAYFLAAASV YEPCRAAERL AWARAAILAN AVSTHLRNSP       600
SFRERLEHSL RCRPSEETDG SWFNSSSGSD AVLVKAVLRL TDSLAREAQP IHGGDPEDII       660
HKLLRSAWAE WVREKADAAD SVCNGSSAVE QEGSRMVHDK QTCLLLARMI EISAGRAAGE       720
AASEDGDRRI IQLTGSICDS LKQKMLVSQD PEKNEEMMSH VDDELKLRIR EFVQYLLRLG       780
EKKTGSSETR QTFLSIVKSC YYAAHCPPHV VDRHISRVIF EPVSAAK                     827
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SEQ ID NO:38

```
cttcttcact aaatacttag acagagaaaa cagagctttt taaagccatg tctcttcagt        60
atcatgttct aaactccatt ccaagtacaa cctttctcag ttctactaaa acaacaatat       120
cttcttcttt ccttaccatc tcaggatctc ctctcaatgt cgctagagac aaatccagaa       180
gcggttccat acattgttca aagcttcgaa ctcaagaata cattaattct caagaggttc       240
aacatgattt gcctctaata catgagtggc aacagcttca aggagaagat gctcctcaga       300
ttagtgttgg aagtaatagt aatgcattca aagaagcagt gaagagtgtg aaaacgatct       360
tgagaaacct aacggacggg gaaattacga tatcggctta cgatacagct tgggttgcat       420
tgatcgatgc cggagataaa actccggcgt ttccctccgc cgtgaaatgg atcgccgaga       480
accaactttc cgatggttct tggggagatg cgtatctctt ctcttatcat gatcgtctca       540
tcaataccct tgcatgcgtc gttgctctaa gatcatggaa tctctttcct catcaatgca       600
acaaaggaat cacgtttttc cgggaaaata ttgggaagct agaagacgaa aatgatgagc       660
atatgccaat cggattcgaa gtagcattcc catcgttgct tgagatagct cgaggaataa       720
acattgatgt accgtacgat tctccggtct taaaagatat atacgccaag aaagagctaa       780
agcttacaag gataccaaaa gagataatgc acaagatacc aacaacattg ttgcatagtt       840
tggaggggat gcgtgattta gattgggaaa agctcttgaa acttcaatct caagacggat       900
```

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ctttcctctt ctctccttcc tctaccgctt ttgcattcat gcagacccga gacagtaact      960
gcctcgagta tttgcgaaat gccgtcaaac gtttcaatgg aggagttccc aatgtctttc     1020
ccgtggatct tttcgagcac atatggatag tggatcggtt acaacgttta gggatatcga     1080
gatactttga agaagagatt aaagagtgtc ttgactatgt ccacagatat tggaccgaca     1140
atggcatatg ttgggctaga tgttcccatg tccaagacat cgatgataca gccatggcat     1200
ttaggctctt aagacaacat ggataccaag tgtccgcaga tgtattcaag aactttgaga     1260
aagagggaga gtttttctgc tttgtggggc aatcaaacca agcagtaacc ggtatgttca     1320
acctataccg ggcatcacaa ttggcgtttc caagggaaga gatattgaaa aacgccaaag     1380
agttttctta taattatctg ctagaaaaac gggagagaga ggagttgatt gataagtgga     1440
ttataatgaa agacttacct ggcgagattg ggtttgcgtt agagattcca tggtacgcaa     1500
gcttgcctcg agtagagacg agattctata ttgatcaata tggtggagaa aacgacgttt     1560
ggattggcaa gactctttat aggatgccat acgtgaacaa taatggatat ctggaattag     1620
caaaacaaga ttacaacaat tgccaagctc agcatcagct cgaatgggac atattccaaa     1680
agtggtatga agaaaatagg ttaagtgagt ggggtgtgcg cagaagtgag cttctcgagt     1740
gttactactt agcggctgca actatatttg aatcagaaag gtcacatgag agaatggttt     1800
gggctaagtc aagtgtattg gttaaagcca tttcttcttc ttttggggaa tcctctgact     1860
ccagaagaag cttctccgat cagtttcatg aatacattgc caatgctcga cgaagtgatc     1920
atcactttaa tgacaggaac atgagattgg accgaccagg atcggttcag gccagtcggc     1980
ttgccggagt gttaatcggg actttgaatc aaatgtcttt tgacctttc atgtctcatg      2040
gccgtgacgt taacaatctc ctctatctat cgtggggaga ttggatggaa aaatggaaac     2100
tatatggaga tgaaggagaa ggagagctca tggtgaagat gataattcta atgaagaaca     2160
atgacctaac taacttcttc acccacactc acttcgttcg tctcgcggaa atcatcaatc     2220
gaatctgtct tcctcgccaa tacttaaagg caaggagaaa cgatgagaag gagaagacaa     2280
taaagagtat ggagaaggag atggggaaaa tggttgagtt agcattgtcg gagagtgaca     2340
catttcgtga cgtcagcatc acgtttcttg atgtagcaaa agcattttac tactttgctt     2400
tatgtggcga tcatctccaa actcacatct ccaaagtctt gtttcaaaaa gtctagtaac     2460
ctcatcatca tcatcgatcc attaacaatc agtggatcga tgtatccata gatgcgtgaa     2520
taatatttca tgtagagaag gagaacaaat tagatcatgt agggttatca                2570
```

SEQ ID NO:39

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MSLQYHVLNS IPSTTFLSST KTTISSSFLT ISGSPLNVAR DKSRSGSIHC SKLRTQEYIN       60
SQEVQHDLPL IHEWQQLQGE DAPQISVGSN SNAFKEAVKS VKTILRNLTD GEITISAYDT      120
AWVALIDAGD KTPAFPSAVK WIAENQLSDG SWGDAYLFSY HDRLINTLAC VVALRSWNLF      180
PHQCNKGITF FRENIGKLED ENDEHMPIGF EVAFPSLLEI ARGINIDVPY DSPVLKDIYA      240
KKELKLTRIP KEIMHKIPTT LLHSLEGMRD LDWEKLLKLQ SQDGSFLFSP SSTAFAFMQT      300
RDSNCLEYLR NAVKRFNGGV PNVFPVDLFE HIWIVDRLQR LGISRYFEEE IKECLDYVHR      360
YWTDNGICWA RCSHVQDIDD TAMAFRLLRQ HGYQVSADVF KNFEKEGEFF CFVGQSNQAV      420
TGMFNLYRAS QLAFPREEIL KNAKEFSYNY LLEKREREEL IDKWIIMKDL PGEIGFALEI      480
PWYASLPRVE TRFYIDQYGG ENDVWIGKTL YRMPYVNNNG YLELAKQDYN NCQAQHQLEW      540
DIFQKWYEEN RLSEWGVRRS ELLECYYLAA ATIFESERSH ERMVWAKSSV LVKAISSSFG      600
ESSDSRRSFS DQFHEYIANA RRSDHHFNDR NMRLDRPGSV QASRLAGVLI GTLNQMSFDL      660
FMSHGRDVNN LLYLSWGDWM EKWKLYGDEG EGELMVKMII LMKNNDLTNF FTHTHFVRLA      720
EIINRICLPR QYLKARRNDE KEKTIKSMEK EMGKMVELAL SESDTFRDVS ITFLDVAKAF      780
YYFALCGDHL QTHISKVLFQ KV                                               802
```

SEQ ID NO:40

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MEFDEPLVDE ARSLVQRTLQ DYDDRYGFGT MSCAAYDTAW VSLVTKTVDG RKQWLFPECF       60
EFLLETQSDA GGWEIGNSAP IDGILNTAAS LLALKRHVQT EQIIQPQHDH KDLAGRAERA      120
AASLRAQLAA LDVSTTEHVG FEIIVPAMLD PLEAEDPSLV FDFPARKPLM KIHDAKMSRF      180
RPEYLYGKQP MTALHSLEAF IGKIDFDKVR HHRTHGSMMG SPSSTAAYLM HASQWDGDSE      240
AYLRHVIKHA AGQGTGAVPS AFPSTHFESS WILTTLFRAG FSASHLACDE LNKLVEILEG      300
SFEKEGGAIG YAPGFQADVD DTAKTISTLA VLGRDATPRQ MIKVFEANTH FRTYPGERDP      360
SLTANCNALS ALLHQPDAAM YGSQIQKITK FVCDYWWKSD GKIKDKWNTC YLYPSVLLVE      420
VLVDLVSLLE QGKLPDVLDQ ELQYRVAITL FQACLRPLLD QDAEGSWNKS IEATAYGILI      480
LTEARRVCFF DRLSEPLNEA IRRGIAFADS MSGTEAQLNY IWIEKVSYAP ALLTKSYLLA      540
ARWAAKSPLG ASVGSSLWTP PREGLDKHVR LFHQAELFRS LPEWELRASM IEAALFTPLL      600
RAHRLDVFPR QDVGEDKYLD VVPFFWTAAN NRDRTYASTL FLYDMCFIAM LNFQLDEFME      660
ATAGILFRDH MDDLRQLIHD LLAEKTSPKS SGRSSQGTKD ADSGIEEDVS MSDSASDSQD      720
RSPEYDLVFS ALSTFTKHVL QHPSIQSASV WDRKLLAREM KAYLLAHIQQ AEDSTPLSEL      780
KDVPQKTDVT RVSTSTTTFF NWVRTTSADH ISCPYSFHFV ACHLGAALSP KGSNGDCYPS      840
AGEKFLAAAV CRHLATMCRM YNDLGSAERD SDEGNLNSLD FPEFADSAGN GGIEIQKAAL      900
```

```
LRLAEFERDS YLEAFRRLQD ESNRVHGPAG GDEARLSRRR MAILEFFAQQ VDLYGQVYVI        960
RDISARIPKN EVEKKRKLDD AFN                                               983
```

SEQ ID NO:41

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MASSTLIQNR SCGVTSSMSS FQIFRGQPLR FPGTRTPAAV QCLKKRRCLR PTESVLESSP         60
GSGSYRIVTG PSGINPSSNG HLQEGSLTHR LPIPMEKSID NFQSTLYVSD IWSETLQRTE        120
CLLQVTENVQ MNEWIEEIRM YFRNMTLGEI SMSPYDTAWV ARVPALDGSH GPQFHRSLQW        180
IIDNQLPDGD WGEPSLFLGY DRVCNTLACV IALKTWGVGA QNVERGIQFL QSNIYKMEED        240
DANHMPIGFE IVFPAMMEDA KALGLDLPYD ATILQQISAE REKKMKKIPM AMVYKYPTTL        300
LHSLEGLHRE VDWNKLLQLQ SENGSFLYSP ASTACALMYT KDVKCFDYLN QLLIKFDHAC        360
PNVYPVDLFE RLWMVDRLQR LGISRYFERE IRDCLQYVYR YWKDCGIGWA SNSSVQDVDD        420
TAMAFRLLRT HGFDVKEDCF RQFFKDGEFF CFAGQSSQAV TGMFNLSRAS QTLFPGESLL        480
KKARTFSRNF LRTKHENNEC FDKWIITKDL AGEVEYNLTF PWYASLPRLE HRTYLDQYGI        540
DDIWIGKSLY KMPAVTNEVF LKLAKADFNM CQALHKKELE QVIKWNASCQ FRDLEFARQK        600
SVECYFAGAA TMFEPEMVQA RLVWARCCVL TTVLDDYFDH GTPVEELRVF VQAVRTWNPE        660
LINGLPEQAK ILFMGLYKTV NTIAEEAFMA QKRDVHHHLK HYWDKLITSA LKEAEWAESG        720
YVPTFDEYME VAEISVALEP IVCSTLFFAG HRLDEDVLDS YDYHLVMHLV NRVGRILNDI        780
QGMKREASQG KISSVQIYME EHPSVPSEAM AIAHLQELVD NSMQQLTYEV LRFTAVPKSC        840
KRIHLNMAKI MHAFYKDTDG FSSLTAMTGF VKKVLFEPVP E                            881
```

SEQ ID NO:42

```
MPGKIENGTP KDLKTGNDFV SAAKSLLDRA FKSHHSYYGL CSTSCQVYDT AWVAMIPKTR         60
DNVKQWLFPE CFHYLLKTQA ADGSWGSLPT TQTAGILDTA SAVLALLCHA QEPLQILDVS        120
PDEMGLRIEH GVTSLKRQLA VWNDVEDTNH IGVEFIIPAL LSMLEKELDV PSFEFPCRSI        180
LERMHGEKLG HFDLEQVYGK PSSLLHSLEA FLGKLDFDRL SHHLYHGSMM ASPSSTAAYL        240
IGATKWDDEA EDYLRHVMRN GAGHGNGGIS GTFPTTHFEC SWIIATLLKV GFTLKQIDGD        300
GLRGLSTILL EALRDENGVI GFAPRTADVD DTAKALLALS LVNQPVSPDI MIKVFEGKDH        360
FTTFGSERDP SLTSNLHVLL SLLKQSNLSQ YHPQILKTTL FTCRWWWGSD HCVKDKWNLS        420
HLYPTMLLVE AFTEVLHLID GGELSSLFDE SFKCKIGLSI FQAVLRIILT QDNDGSWRGY        480
REQTCYAILA LVQARHVCFF THMVDRLQSC VDRGFSWLKS CSFHSQDLTW TSKTAYEVGF        540
VAEAYKLAAL QSASLEVPAA TIGHSVTSAV PSSDLEKYMR LVRKTALFSP LDEWGLMASI        600
IESSFFVPLL QAQRVEIYPR DNIKVDEDKY LSIIPFTWVG CNNRSRTFAS NRWLYDMMYL        660
SLLGYQTDEY MEAVAGPVFG DVSLLHQTID KVIDNTMGNL ARANGTVHSG NGHQHESPNI        720
GQVEDTLTRF TNSVLNHKDV LNSSSSDQDT LRREFRTFMH AHITQIEDNS RFSKQASSDA        780
FSSPEQSYFQ WVNSTGGSHV ACAYSFAFSN CLMSANLLQG KDAFPSGTQK YLISSVMRHA        840
TNMCRMYNDF GSIARDNAER NVNSIHFPEF TLCNGTSQNL DERKERLLKI ATYEQGYLDR        900
ALEALERQSR DDAGDRAGSK DMRKLKIVKL FCDVTDLYDQ LYVIKDLSSS MK                952
```

SEQ ID NO:43

```
MALVNPTALF YGTSIRTRPT NLLNPTQKLR PVSSSSLPSF SSVSAILTEK HQSNPSENNN         60
LQTHLETPFN FDSYMLEKVN MVNEALDASV PLKDPIKIHE SMRYSLLAGG KRIRPMMCIA        120
ACEIVGGNIL NAMPAACAVE MIHTMSLVHD DLPCMDNDDF RRGKPISHKV YGEEMAVLTG        180
DALLSLSFEH IATATKGVSK DRIVRAIGEL ARSVGSEGLV AGQVVDILSE GADVGLDHLE        240
YIHIHKTAML LESSVVIGAI MGGGSDQQIE KLRKFARSIG LLFQVVDDIL DVTKSTEELG        300
KTAGKDLLTD KTTYPKLLGI EKSREFAEKL NKEAQEQLSG FDRRKAAPLI ALANYNAYRQ        360
N                                                                       361
```

SEQ ID NO:44

```
MAEQQISNLL SMFDASHASQ KLEITVQMMD TYHYRETPPD SSSSEGGSLS RYDERRVSLP         60
LSHNAASPDI VSQLCFSTAM SSELNHRWKS QRLKVADSPY NYILTLPSKG IRGAFIDSLN        120
VWLEVPEDET SVIKEVIGML HNSSLIIDDF QDNSPLRRGK PSTHTVFGPA QAINTATYVI        180
VKAIEKIQDI VGHDALADVT GTITTIFQGQ AMDLWWTANA IVPSIQEYLL MVNDKTGALF        240
RLSLELLALN SEASISDSAL ESLSSAVSLL GQYFQIRDDY MNLIDNKYTD QKGFCEDLDE        300
GKYSLTLIHA LQTDSSDLLT NILSMRRVQG KLTAQKRCWF WK                           342
```

SEQ ID NO:45

```
MEKTKEKAER ILLEPYRYLL QLPGKQVRSK LSQAFNHWLK VPEDKLQIII EVTEMLHNAS
LLIDDIEDSS KLRRGFPVAH SIYGVPSVIN SANYVYFLGL EKVLTLDHPD AVKLFTRQLL
```

```
ELHQGQGLDI YWRDTYTCPT EEEYKAMVLQ KTGGLFGLAV GLMQLFSDYK EDLKPLLDTL       180
GLFFQIRDDY ANLHSKEYSE NKSFCEDLTE GKFSFPTIHA IWSRPESTQV QNILRQRTEN       240
IDIKKYCVQY LEDVGSFAYT RHTLRELEAK AYKQIEACGG NPSLVALVKH LSKMFTEENK       300
```

SEQ ID NO:46

```
MARFYFLNAL LMVISLQSTT AFTPAKLAYP TTTTALNVAS AETSFSLDEY LASKIGPIES        60
ALEASVKSRI PQTDKICESM AYSLMAGGKR IRPVLCIAAC EMFGGSQDVA MPTAVALEMI       120
HTMSLIHDDL PSMDNDDLRR GKPTNHVVFG EDVAILAGDS LLSTSFEHVA RETKGVSAEK       180
IVDVIARLGK SVGAEGLAGG QVMDLECEAK PGTTLDDLKW IHIHKTATLL QVAVASGAVL       240
GGATPEEVAA CELFAMNIGL AFQVADDILD VTASSEDLGK TAGKDEATDK TTYPKLLGLE       300
ESKAYARQLI DEAKESLAPF GDRAAPLLAI ADFIIDRKN                              339
```

SEQ ID NO:47

```
MHLAPRRVPR GRRSPPDRVP ERQGALGRRR GAGSTGCARA AAGVHRRRGG GEADPSAAVH        60
RGWQAGGGTG LPDEVVSTAA ALEMFHAFAL IHDDIMDDSA TRRGSPTVHR ALADRLGAAL       120
DPDQAGQLGV STAILVGDLA LTWSDELLYA PLTPHRLAAV LPLVTAMRAE TVHGQYLDIT       180
SARRPGTDTS LALRIARYKT AAYTMERPLH IGAALAGARP ELLAGLSAYA LPAGEAFQLA       240
DDLLGVFGDP RRTGKPDLDD LRGGKHTVLV ALAREHATPE QRHTLDTLLG TPGLDRQGAS       300
RLRCVLVATG ARAEAERLIT ERRDQALTAL NALTLPPPLA EALARLTLGS TAHPA             355
```

SEQ ID NO:48

```
MSYFDNYFNE IVNSVNDIIK SYISGDVPKL YEASYHLFTS GGKRLRPLIL TISSDLFGGQ        60
RERAYYAGAA IEVLHTFTLV HDDIMDQDNI RRGLPTVHVK YGLPLAILAG DLLHAKAFQL       120
LTQALRGLPS ETIIKAFDIF TRSIIIISEG QAVDMEFEDR IDIKEQEYLD MISRKTAALF       180
SASSSIGALI AGANDNDVRL MSDFGTNLGI AFQIVDDILG LTADEKELGK PVFSDIREGK       240
KTILVIKTLE LCKEDEKKIV LKALGNKSAS KEELMSSADI IKKYSLDYAY NLAEKYYKNA       300
IDSLNQVSSK SDIPGKALKY LAEFTIRRRK                                        330
```

SEQ ID NO:49

```
MVAQTFNLDT YLSQRQQQVE EALSAALVPA YPERIYEAMR YSLLAGGKRL RPILCLAACE        60
LAGGSVEQAM PTACALEMIH TMSLIHDDLP AMDNDDFRRG KPTNHKVFGE DIAILAGDAL       120
LAYAFEHIAS QTRGVPPQLV LQVIARIGHA VAATGLVGGQ VVDLESEGKA ISLETLEYIH       180
SHKTGALLEA SVVSGGILAG ADEELLARLS HYARDIGLAF QIVDDILDVT ATSEQLGKTA       240
GKDQAAAKAT YPSLLGLEAS RQKAEELIQS AKEALRPYGS QAEPLLALAD FITRRQH          297
```

SEQ ID NO:50

```
MASVTLGSWI VVHHHNHHHP SSILTKSRSR SCPITLTKPI SFRSKRTVSS SSSIVSSSVV        60
TKEDNLRQSE PSSFDFMSYI ITKAELVNKA LDSAVPLREP LKIHEAMRYS LLAGGKRVRP       120
VLCIAACELV GGEESTAMPA ACAVEMIHTM SLIHDDLPCM DNDDLRRGKP TNHKVFGEDV       180
AVLAGDALLS FAFEHLASAT SSDVVSPVRV VRAVGELAKA IGTEGLVAGQ VVDISSEGLD       240
LNDVGLEHLE FIHLHKTAAL LEASAVLGAI VGGGSDDEIE RLRKFARCIG LLFQVVDDIL       300
DVTKSSKELG KTAGKDLIAD KLTYPKIMGL EKSREFAEKL NREARDQLLG FDSDKVAPLL       360
ALANYIAYRQ N                                                            371
```

SEQ ID NO:51

```
atgtcttcct cttcctcttc cagtacctct atgattgatt tgatggctgc tattattaaa        60
ggtgaaccag ttatcgtctc cgacccagca aatgcctctg cttatgaatc agttgctgca       120
gaattgtctt caatgttgat cgaaaacaga caattcgcca tgatcgtaac tacatcaatc       180
gctgttttga tcggttgtat tgtcatgttg gtatggagaa gatccggtag tggtaattct       240
aaaagagtcg aacctttgaa accattagta attaagccaa gagaagaaga aatagatgac       300
ggtagaaaga aagttacaat atttttcggt acccaaactg gtacagctga aggttttgca       360
aaagccttag gtgaagaagc taaggcaaga tacgaaaaga ctagattcaa gatagtcgat       420
ttggatgact atgccgctga tgacgatgaa tacgaagaaa agttgaagaa agaagatgtt       480
```

```
gcatttttct ttttggcaac ctatggtgac ggtgaaccaa ctgacaatgc agccagattc      540
tacaaatggt ttacagaggg taatgatcgt ggtgaatggt tgaaaaactt aaagtacggt      600
gttttcggtt tgggtaacag acaatacgaa catttcaaca aagttgcaaa ggttgtcgac      660
gatattttgg tcgaacaagg tgctcaaaga ttagtccaag taggtttggg tgacgatgac      720
caatgtatag aagatgactt tactgcctgg agagaagctt tgtggcctga attagacaca      780
atcttgagag aagaaggtga caccgccgtt gctaccccat atactgctgc agtattagaa      840
tacagagttt ccatccatga tagtgaagac gcaaagttta atgatatcac tttggccaat      900
ggtaacggtt atacagtttt cgatgcacaa cacccttaca aagctaacgt tgcagtcaag      960
agagaattac atacaccaga atccgacaga agttgtatac acttggaatt tgatatcgct     1020
ggttccggtt taaccatgaa gttgggtgac catgtaggtg ttttatgcga caatttgtct     1080
gaaactgttg atgaagcatt gagattgttg gatatgtccc ctgacactta ttttagtttg     1140
cacgctgaaa aagaagatgg tacaccaatt tccagttctt taccacctcc attccctcca     1200
tgtaacttaa gaacagcctt gaccagatac gcttgcttgt tatcatcccc taaaaagtcc     1260
gccttggttg ctttagccgc tcatgctagt gatcctactg aagcagaaag attgaaacac     1320
ttagcatctc cagccggtaa agatgaatat tcaaagtggg tagttgaatc tcaaagatca     1380
ttgttagaag ttatggcaga atttccatct gccaagcctc cattaggtgt cttctttgct     1440
ggtgtagcac ctagattgca accaagattc tactcaatca gttcttcacc taagatcgct     1500
gaaactagaa ttcatgttac atgtgcatta gtctacgaaa agatgccaac cggtagaatt     1560
cacaagggtg tatgctctac ttggatgaaa aatgctgttc cttacgaaaa atcagaaaag     1620
ttgttcttag gtagaccaat cttcgtaaga caatcaaact tcaagttgcc ttctgattca     1680
aaggttccaa taatcatgat aggtcctggt acaggtttag ccccattcag aggtttcttg     1740
caagaaagat tggctttagt tgaatctggt gtcgaattag gtccttcagt tttgttcttt     1800
ggttgtagaa acagaagaat ggatttcatc tatgaagaag aattgcaaag attcgtcgaa     1860
tctggtgcat tggccgaatt atctgtagct ttttcaagag aaggtccaac taaggaatac     1920
gttcaacata agatgatgga taaggcatcc gacatatgga acatgatcag tcaaggtgct     1980
tatttgtacg tttgcggtga cgcaaagggt atggccagag atgtccatag atctttgcac     2040
acaattgctc aagaacaagg ttccatggat agtaccaaag ctgaaggttt cgtaaagaac     2100
ttacaaactt ccggtagata cttgagagat gtctggtga                            2139
```

SEQ ID NO:52

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atggcggaac aacaaaagat caagaaatca ccacacgttc tactcatccc attcccttta       60
caaggccata taaacccttt catccagttt ggcaaacgat taatctccaa aggtgtcaaa      120
acaacacttg ttaccaccat ccacacctta aactcaaccc taaaccacag taacaccacc      180
accacctcca tcgaaatcca agcaatttcc gatggttgtg atgaaggcgg ttttatgagt      240
gcaggagaat catatttgga aacattcaaa caagttgggt ctaaatcact agctgactta      300
atcaagaagc ttcaaagtga aggaaccaca attgatgcaa tcatttatga ttctatgact      360
gaatgggttt tagatgttgc aattgagttt ggaatcgatg gtggttcgtt tttcactcaa      420
gcttgtgttg taaacagctt atattatcat gttcataagg gtttgatttc tttgccattg      480
ggtgaaactg tttcggttcc tggatttcca gtgcttcaac ggtgggagac accgttaatt      540
ttgcagaatc atgagcaaat acagagccct tggtctcaga tgttgtttgg tcagtttgct      600
aatattgatc aagcacgttg ggtcttcaca aatagttttt acaagctcga ggaagaggta      660
atagagtgga cgagaaagat atggaacttg aaggtaatcg ggccaacact tccatccatg      720
taccttgaca aacgacttga tgatgataaa gataacggat ttaatctcta caaagcaaac      780
catcatgagt gcatgaactg gttagacgat aagccaaagg aatcagttgt ttacgtagca      840
tttggtagcc tggtgaaaca tggacccgaa caagtggaag aaatcacacg ggctttaata      900
gatagtgatg tcaacttctt gtgggttatc aaacataaag aagagggaaa gctcccagaa      960
aatctttcgg aagtaataaa aaccggaaag ggtttgattg tagcatggtg caaacaattg     1020
gatgtgttag cacacgaatc agtaggatgc tttgttacac attgtgggtt caactcaact     1080
cttgaagcaa taagtcttgg agtccccgtt gttgcaatgc ctcaattttc ggatcaaact     1140
acaaatgcca agcttctaga tgaaattttg ggtgttggag ttagagttaa ggctgatgag     1200
aatgggatag tgagaagagg aaatcttgcg tcatgtatta agatgattat ggaggaggaa     1260
agaggagtaa taatccgaaa gaatgcggta aaatggaagg atttggctaa agtagccgtt     1320
catgaaggtg gtagctcaga caatgatatt gtcgaatttg taagtgagct aattaaggct     1380
taaatttttg ttgctttgta ttttatgtgt tatggttttt tgatttagat gtattcaatt     1440
aatattgaat cataactaaa ttcaagatta ttgtttgtaa tattctttgt cctaaaattt     1500
tgcgacttaa aacctttagt ttataaaaag aaattagaaa atactattgc acgga           1555
```

SEQ ID NO:53

```
atggaaaaca agaccgaaac aacagttaga cgtaggcgta gaatcattct gtttccagta       60
ccttttcaag ggcacatcaa tccaatacta caactagcca acgttttgta ctctaaaggt      120
ttttctatta caatctttca caccaatttc aacaaaccaa aaacatccaa ttacccacat      180
ttcacattca gattcatact tgataatgat ccacaagatg aacgtatttc aaacttacct      240
acccacggtc ctttagctgg aatgagaatt ccaatcatca atgaacatgg tgccgatgag      300
```

```
cttagaagag aattagagtt acttatgttg gcatccgaag aggacgagga agtctcttgt      360
ctgattactg acgctctatg gtactttgcc caatctgtgg ctgatagttt gaatttgagg      420
agattggtac taatgacatc cagtctgttt aactttcacg ctcatgttag tttaccacaa      480
tttgacgaat tgggatactt ggaccctgat gacaagacta ggttagagga acaggcctct      540
ggttttccta tgttgaaagt caaagatatc aagtctgcct attctaattg gcaaatcttg      600
aaagagatct taggaaagat gatcaaacag acaaaggctt catctggagt gatttggaac      660
agtttcaaag agttagaaga gtctgaattg gagactgtaa tcagagaaat tccagcacct      720
tcattcctga taccattacc aaaacatttg actgcttcct cttcctcttt gttggatcat      780
gacagaacag tttttcaatg gttggaccaa caaccaccta gttctgtttt gtacgtgtca      840
tttggtagta cttctgaagt cgatgaaaag gacttccttg aaatcgcaag aggcttagtc      900
gatagtaagc agtcattcct ttgggtcgtg cgtccaggtt tcgtgaaagg ctcaacatgg      960
gtcgaaccac ttccagatgg ttttctaggc gaaagaggta gaatagtcaa atgggttcct     1020
caacaggaag ttttagctca tggcgctatt ggggcattct ggactcattc cggatggaat     1080
tcaactttag aatcagtatg cgaaggggta cctatgatct tttcagattt tggtcttgat     1140
caaccactga acgcaagata catgtctgat gttttgaaag tgggtgtata tctagaaaat     1200
ggctgggaaa ggggtgaaat agctaatgca ataagacgtg ttatggttga tgaagagggg     1260
gagtatatca gacaaaacgc aagagtgctg aagcaaaagg ccgacgtttc tctaatgaag     1320
ggaggctctt catacgaatc cttagaatct cttgtttcct acatttcatc actgtaa        1377
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SEQ ID NO:54

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MDGVIDMQTI PLRTAIAIGG TAVALVVALY FWFLRSYASP SHHSNHLPPV PEVPGVPVLG        60
NLLQLKEKKP YMTFTKWAEM YGPIYSIRTG ATSMVVVSSN EIAKEVVVTR FPSISTRKLS       120
YALKVLTEDK SMVAMSDYHD YHKTVKRHIL TAVLGPNAQK KFRAHRDTMM ENVSNELHAF       180
FEKNPNQEVN LRKIFQSQLF GLAMKQALGK DVESIYVKDL ETTMKREEIF EVLVVDPMMG       240
AIEVDWRDFF PYLKWVPNKS FENIIHRMYT RREAVMKALI QEHKKRIASG ENLNSYIDYL       300
LSEAQTLTDK QLLMSLWEPI IESSDTTMVT TEWAMYELAK NPNMQDRLYE EIQSVCGSEK       360
ITEENLSQLP YLYAVFQETL RKHCPVPIMP LRYVHENTVL GGYHVPAGTE VAINIYGCNM       420
DKKVWENPEE WNPERFLSEK ESMDLYKTMA FGGGKRVCAG SLQAMVISCI GIGRLVQDFE       480
WKLKDDAEED VNTLGLTTQK LHPLLALINP RK                                     512
```

SEQ ID NO:55

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aagcttacta gtaaaatgga cggtgtcatc gatatgcaaa ccattccatt gagaaccgct        60
attgctattg gtggtactgc tgttgctttg gttgttgcat tatacttttg gttcttgaga       120
tcctacgctt ccccatctca tcattctaat catttgccac cagtacctga agttccaggt       180
gttccagttt tgggtaattt gttgcaattg aaagaaaaaa agccttacat gaccttcacc       240
aagtgggctg aaatgtatgg tccaatctac tctattagaa ctggtgctac ttccatggtt       300
gttgtctctt ctaacgaaat cgccaaagaa gttgttgtta ccagattccc atctatctct       360
accagaaaat tgtcttacgc cttgaaggtt ttgaccgaag ataagtctat ggttgccatg       420
tctgattatc acgattacca taagaccgtc aagagacata ttttgactgc tgttttgggt       480
ccaaacgccc aaaaaaagtt tagagcacat agagacacca tgatggaaaa cgtttccaat       540
gaattgcatg ccttcttcga aaagaaccca aatcaagaag tcaacttgag aaagatcttc       600
caatcccaat tattcggttt ggctatgaag caagccttgg gtaaagatgt tgaatccatc       660
tacgttaagg atttggaaac caccatgaag agagaagaaa tcttcgaagt tttggttgtc       720
gatccaatga tgggtgctat tgaagttgat tggagagact ttttcccata cttgaaatgg       780
gttccaaaca agtccttcga aaacatcatc catagaatgt acactagaag agaagctgtt       840
atgaaggcct tgatccaaga acacaagaaa agaattgcct ccggtgaaaa cttgaactcc       900
tacattgatt acttgttgtc tgaagcccaa accttgaccg ataagcaatt attgatgtct       960
ttgtgggaac ctattatcga atcttctgat accactatgg ttactactga atgggctatg      1020
tacgaattgg ctaagaatcc aaacatgcaa gacagattat acgaagaaat ccaatccgtt      1080
tgcggttccg aaaagattac tgaagaaaac ttgtcccaat tgccatactt gtacgctgtt      1140
ttccaagaaa ctttgagaaa gcactgtcca gttcctatta tgccattgag atatgttcac      1200
gaaaacaccg ttttgggtgg ttatcatgtt ccagctggta ctgaagttgc tattaacatc      1260
tacggttgca acatggataa gaaggtctgg gaaaatccag aagaatggaa tccagaaaga      1320
ttcttgtccg aaaaagaatc catggacttg tacaaaacta tggcttttgg tggtggtaaa      1380
agagtttgcg ctggttcttt acaagccatg gttatttctt gcattggtat cggtagattg      1440
gtccaagatt ttgaatggaa gttgaaggat gatgccgaag aagatgttaa cactttgggt      1500
ttgactaccc aaaagttgca tccattattg gccttgatta acccaagaaa gtaactcgag      1560
ccgcgg                                                                1566
```

SEQ ID NO:56

```
atggccaccc tccttgagca tttccaagct atgcccttg ccatccctat tgcactggct        60
gctctgtctt ggctgttcct cttttacatc aaagtttcat tcttttccaa caagagtgct       120
```

```
caggctaagc tccctcctgt gccagtggtt cctgggctgc cggtgattgg gaatttactg       180
caactcaagg agaagaaacc ctaccagact tttacaaggt gggctgagga gtatggacca       240
atctattcta tcaggactgg tgcttccacc atggtcgttc tcaataccac ccaagttgca       300
aaagaggcca tggtgaccag atatttatcc atctcaacca gaaagctatc aaacgcacta       360
aagattctta ctgctgataa atgtatggtt gcaataagtg actacaacga ttttcacaag       420
atgataaagc gatacatact ctcaaatgtt cttggaccta gtgctcagaa gcgtcaccgg       480
agcaacagag ataccttgag agctaatgtc tgcagccgat tgcattctca agtaaagaac       540
tctcctcgag aagctgtgaa tttcagaaga gtttttgagt gggaactctt tggaattgca       600
ttgaagcaag cctttggaaa ggacatagaa aagcccattt atgtggagga acttggcact       660
acactgtcaa gagatgagat ctttaaggtt ctagtgcttg acataatgga gggtgcaatt       720
gaggttgatt ggagagattt cttcccttac ctgagatgga ttccgaatac gcgcatggaa       780
acaaaaattc agcgactcta tttccgcagg aaagcagtga tgactgccct gatcaacgag       840
cagaagaagc gaattgcttc aggagaggaa atcaactgtt atatcgactt cttgcttaag       900
gaagggaaga cactgacaat ggaccaaata agtatgttgc tttgggagac ggttattgaa       960
acagcagata ctacaatggt aacgacagaa tgggctatgt atgaagttgc taaagactca      1020
aagcgtcagg atcgtctcta tcaggaaatc caaaaggttt gtggatcgga gatggttaca      1080
gaggaatact tgtcccaact gccgtacctg aatgcagttt tccatgaaac gctaaggaag      1140
cacagtccgg ctgcgttagt tcctttaaga tatgcacatg aagataccca actaggaggt      1200
tactacattc cagctggaac tgagattgct ataaacatat acgggtgtaa catggacaag      1260
catcaatggg aaagccctga ggaatggaaa ccggagagat ttttggaccc gaaatttgat      1320
cctatggatt tgtacaagac catggctttt ggggctggaa agagggtatg tgctggttct      1380
cttcaggcaa tgttaatagc gtgcccgacg attggtaggc tggtgcagga gtttgagtgg      1440
aagctgagag atggagaaga agaaaatgta gatactgttg ggctcaccac tcacaaacgc      1500
tatccaatgc atgcaatcct gaagccaaga agtta                                 1535
```

SEQ ID NO:57

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aagcttacta gtaaaatggc ctccatcacc catttcttac aagattttca agctactcca        60
ttcgctactg cttttgctgt tggtggtgtt tctttgttga tattcttctt cttcatccgt       120
ggtttccact ctactaagaa aaacgaatat tacaagttgc caccagttcc agttgttcca       180
ggtttgccag ttgttggtaa tttgttgcaa ttgaaagaaa agaagccata caagactttc       240
ttgagatggg ctgaaattca tggtccaatc tactctatta gaactggtgc ttctaccatg       300
gttgttgtta actctactca tgttgccaaa gaagctatgg ttaccagatt ctcttcaatc       360
tctaccagaa agttgtccaa ggctttggaa ttattgacct ccaacaaatc tatggttgcc       420
acctctgatt acaacgaatt tcacaagatg gtcaagaagt acatcttggc cgaattattg       480
ggtgctaatg ctcaaaagag acacagaatt catagagaca ccttgatcga aaacgtcttg       540
aacaaattgc atgcccatac caagaattct ccattgcaag ctgttaactt cagaaagatc       600
ttcgaatctg aattattcgg tttggctatg aagcaagcct tgggttatga tgttgattcc       660
ttgttcgttg aagaattggg tactaccttg tccagagaag aaatctacaa cgttttggtc       720
agtgacatgt tgaagggtgc tattgaagtt gattggagag acttttccc atacttgaaa       780
tggatcccaa acaagtcctt cgaaatgaag attcaaagat tggcctctag aagacaagcc       840
gttatgaact ctattgtcaa agaacaaaag aagtccattg cctctggtaa gggtgaaaac       900
tgttacttga attacttgtt gtccgaagct aagactttga ccgaaaagca aatttccatt       960
ttggcctggg aaaccattat tgaaactgct gatacaactg ttgttaccac tgaatgggct      1020
atgtacgaat tggctaaaaa cccaaagcaa caagacagat tatacaacga aatccaaaac      1080
gtctgcggta ctgataagat taccgaagaa catttgtcca agttgcctta cttgtctgct      1140
gtttttcacg aaaccttgag aaagtattct ccatctccat tggttccatt gagatacgct      1200
catgaagata ctcaattggg tggttattat gttccagccg gtactgaaat tgctgttaat      1260
atctacggtt gcaacatgga caagaatcaa tgggaaactc cagaagaatg gaagccagaa      1320
agatttttgg acgaaaagta cgatccaatg gacatgtaca agactatgtc ttttggttcc      1380
ggtaaaagag tttgcgctgg ttctttacaa gctagtttga ttgcttgtac ctccatcggt      1440
agattggttc aagaatttga atggagattg aaagacggtg aagttgaaaa cgttgatacc      1500
ttgggtttga ctacccataa gttgtatcca atgcaagcta tcttgcaacc tagaaactga      1560
ctcgagccgc gg                                                          1572
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SEQ ID NO:58

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atgatttcct tgttgttggg ttttgttgtc tcctccttct tgtttatctt cttcttgaaa        60
aaattgttgt tcttcttcag tcgtcacaaa atgtccgaag tttctagatt gccatctgtt       120
ccagttccag gttttccatt gattggtaac ttgttgcaat tgaaagaaaa gaagccacac       180
aagactttca ccaagtggtc tgaattatat ggtccaatct actctatcaa gatgggttcc       240
tcttctttga tcgtcttgaa ctctattgaa accgccaaag aagctatggt cagtagattc       300
tcttcaatct ctaccagaaa gttgtctaac gctttgactg ttttgacctg caacaaatct       360
atggttgcta cctctgatta cgatgacttt cataagttcg tcaagagatg cttgttgaac       420
ggtttgttgg gtgctaatgc tcaagaaaga aaaagacatt acagagatgc cttgatcgaa       480
```

```
aacgttacct ctaaattgca tgcccatacc agaaatcatc cacaagaacc agttaacttc       540
agagccattt tcgaacacga attattcggt gttgctttga aacaagcctt cggtaaagat       600
gtcgaatcca tctatgtaaa agaattgggt gtcaccttgt ccagagatga aattttcaag       660
gttttggtcc acgacatgat ggaaggtgct attgatgttg attggagaga tttcttccca       720
tacttgaaat ggatcccaaa caactctttc gaagccagaa ttcaacaaaa gcacaagaga       780
agattggctg ttatgaacgc cttgatccaa gacagattga atcaaaacga ttccgaatcc       840
gatgatgact gctacttgaa tttcttgatg tctgaagcta agaccttgac catggaacaa       900
attgctattt tggtttggga aaccattatc gaaactgctg ataccacttt ggttactact       960
gaatgggcta tgtacgaatt ggccaaacat caatctgttc aagatagatt attcaaagaa      1020
atccaatccg tctgcggtgg tgaaaagatc aaagaagaac aattgccaag attgccttac      1080
gtcaatggtg tttttcacga aaccttgaga aagtattctc cagctccatt ggttccaatt      1140
agatacgctc atgaagatac ccaaattggt ggttatcata ttccagccgg ttctgaaatt      1200
gccattaaca tctacggttg caacatggat aagaagagat gggaaagacc tgaagaatgg      1260
tggccagaaa gatttttgga agatagatac gaatcctccg acttgcataa gactatggct      1320
tttggtgctg gtaaaagagt ttgtgctggt gctttacaag ctagtttgat ggctggtatt      1380
gctatcggta gattggttca agaattcgaa tggaagttga gagatggtga agaagaaaac      1440
gttgatactt acggtttgac ctcccaaaag ttgtatccat tgatggccat tatcaaccca      1500
agaagatctt aa                                                          1512
```

SEQ ID NO:59

```
atggatgctg tgacgggttt gttaactgtc ccagcaaccg ctataactat tggtggaact        60
gctgtagcat tggcggtagc gctaatcttt tggtacctga aatcctacac atcagctaga       120
agatcccaat caaatcatct tccaagagtg cctgaagtcc caggtgttcc attgttagga       180
aatctgttac aattgaagga gaaaaagcca tacatgactt ttacgagatg ggcagcgaca       240
tatggaccta tctatagtat caaaactggg gctacaagta tggttgtggt atcatctaat       300
gagatagcca aggaggcatt ggtgaccaga ttccaatcca tatctacaag gaacttatct       360
aaagccctga aagtacttac agcagataag acaatggtcg caatgtcaga ttatgatgat       420
tatcataaaa cagttaagag acacatactg accgccgtct tgggtcctaa tgcacagaaa       480
aagcatagaa ttcacagaga tatcatgatg gataacatat ctactcaact tcatgaattc       540
gtgaaaaaca acccagaaca ggaagaggta gaccttagaa aaatctttca atctgagtta       600
ttcggcttag ctatgagaca agccttagga aaggatgttg aaagtttgta cgttgaagac       660
ctgaaaatca ctatgaatag agacgaaatc tttcaagtcc ttgttgttga tccaatgatg       720
ggagcaatcg atgttgattg gagagacttc tttccatacc taaagtgggt cccaaacaaa       780
aagttcgaaa atactattca acaaatgtac atcagaagag aagctgttat gaaatcttta       840
atcaaagagc acaaaaagag aatagcgtca ggcgaaaagc taaatagtta tatcgattac       900
cttttatctg aagctcaaac tttaaccgat cagcaactat tgatgtcctt gtgggaacca       960
atcattgaat cttcagatac aacaatggtc acaacagaat gggcaatgta cgaattagct      1020
aaaaacccta aattgcaaga taggttgtac agagacatta agtccgtctg tggatctgaa      1080
aagataaccg aagagcatct atcacagctg ccttacatta cagctatttt ccacgaaaca      1140
ctgagaagac actcaccagt tcctatcatt cctctaagac atgtacatga agataccgtt      1200
ctaggcggct accatgttcc tgctggcaca gaacttgccg ttaacatcta cggttgcaac      1260
atggacaaaa acgtttggga aaatccagag gaatggaacc cagaaagatt catgaaagag      1320
aatgagacaa ttgattttca aaagacgatg gccttcggtg gtggtaagag agtttgtgct      1380
ggttccttgc aagccctttt aactgcatct attgggattg ggagaatggt tcaagagttc      1440
gaatggaaac tgaaggatat gactcaagag gaagtgaaca cgataggcct aactacacaa      1500
atgttaagac cattgagagc tattatcaaa cctaggatct aa                         1542
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SEQ ID NO:60

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gttttgggtg gtatttcctt ggttgttttg atcttcatca gaagattcgt ttccaacaga       120
aagagatccg ttgaaggttt gccaccagtt ccagatattc caggtttacc attgattggt       180
aacttgttgc aattgaaaga aaagaagcca cataagacct ttgctagatg ggctgaaact       240
tacggtccaa ttttctctat tagaactggt gcttctacca tgatcgtctt gaattcttct       300
gaagttgcca aagaagctat ggtcactaga ttctcttcaa tctctaccag aaagttgtcc       360
aacgccttga agattttgac cttcgataag tgtatggttg ccacctctga ttacaacgat       420
tttcacaaaa tggtcaaggg tttcatcttg agaaacgttt taggtgctcc agcccaaaaa       480
agacatagat gtcatagaga taccttgatc gaaaacatct ctaagtactt gcatgcccat       540
gttaagactt ctccattgga accagttgtc ttgaagaaga ttttcgaatc cgaaattttc       600
ggtttggctt tgaaacaagc cttgggtaag gatatcgaat ccatctatgt tgaagaattg       660
ggtactacct tgtccagaga agaaatttttt gccgttttgg ttgttgatcc aatggctggt       720
gctattgaag ttgattggag agatttttttc ccatacttgt cctggattcc aaacaagtct       780
```

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atggaaatga agatccaaag aatggatttt agaagaggtg ctttgatgaa ggccttgatt      840
ggtgaacaaa agaaaagaat cggttccggt gaagaaaaga actcctacat tgatttcttg      900
ttgtctgaag ctaccacttt gaccgaaaag caaattgcta tgttgatctg ggaaaccatc      960
atcgaaattt ccgatacaac tttggttacc tctgaatggg ctatgtacga attggctaaa     1020
gacccaaata gacaagaaat cttgtacaga gaaatccaca aggtttgcgg ttctaacaag     1080
ttgactgaag aaaacttgtc caagttgcca tacttgaact ctgttttcca cgaaaccttg     1140
agaaagtatt ctccagctcc aatggttcca gttagatatg ctcatgaaga tactcaattg     1200
ggtggttacc atattccagc tggttctcaa attgccatta acatctacgg ttgcaacatg     1260
aacaaaaagc aatgggaaaa tcctgaagaa tggaagccag aaagattctt ggacgaaaag     1320
tatgacttga tggacttgca taagactatg gcttttggtg gtggtaaaag agtttgtgct     1380
ggtgctttac aagcaatgtt gattgcttgc acttccatcg gtagattcgt tcaagaattt     1440
gaatggaagt tgatgggtgg tgaagaagaa aacgttgata ctgttgcttt gacctcccaa     1500
aaattgcatc caatgcaagc cattattaag gccagagaat gactcgagcc gcgg            1554
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SEQ ID NO:61

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aaggcaatgg aaaagttgaa cgctagtgaa tctgaagatc caacaacatt gcctgcacta      120
aagatgctag ttgaaaatag agaattgttg acactgttca caacttcctt cgcagttctt      180
attgggtgtc ttgtatttct aatgtggaga cgttcatcct ctaaaaagct ggtacaagat      240
ccagttccac aagttatcgt tgtaaagaag aaagagaagg agtcagaggt tgatgacggg      300
aaaaagaaag tttctatttt ctacggcaca caaacaggaa ctgccgaagg ttttgctaaa      360
gcattagtcg aggaagcaaa agtgagatat gaaaagacct ctttcaaggt tatcgatcta      420
gatgactacg ctgcagatga tgatgaatat gaggaaaaac tgaaaaagga atccttagcc      480
ttcttcttct tggccacata cggtgatggt gaacctactg ataatgctgc taacttctac      540
aagtggttca cagaaggcga cgataaaggt gaatggctga aaaagttaca atacggagta      600
tttggtttag gtaacagaca atatgaacat ttcaacaaga tcgctattgt agttgatgat      660
aaacttactg aaatgggagc caaaagatta gtaccagtag gattagggga tgatgatcag      720
tgtatagaag atgacttcac cgcctggaag gaattggtat ggccagaatt ggatcaactt      780
ttaagggacg aagatgatac ttctgtgact accccataca ctgcagccgt attggagtac      840
agagtggttt accatgataa accagcagac tcatatgctg aagatcaaac ccatacaaac      900
ggtcatgttg ttcatgatgc acagcatcct tcaagatcta atgtggcttt caaaaaggaa      960
ctacacacct ctcaatcaga taggtcttgt actcacttag aattcgatat ttctcacaca     1020
ggactgtctt acgaaactgg cgatcacgtt ggcgtttatt ccgagaactt gtccgaagtt     1080
gtcgatgaag cactaaaact gttagggtta tcaccagaca catacttctc agtccatgct     1140
gataaggagg atgggacacc tatcggtggt gcttcactac caccaccttt tcctccttgc     1200
acattgagag acgctctaac cagatacgca gatgtcttat cctcacctaa aaaggtagct     1260
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gcttcaccag ccggaaaaga tgaatatgca caatggatcg tcgccaacca acgttctttg     1380
ctagaagtga tgcaaagttt tccatctgcc aagcctccat taggtgtgtt cttcgcagca     1440
gtagctccac gtttacaacc aagatactac tctatcagtt catctcctaa gatgtctcct     1500
aacagaatac atgttacatg tgctttggtg tacgagacta ctccagcagg cagaattcac     1560
agaggattgt gttcaacctg gatgaaaaat gctgtccctt taacagagtc acctgattgc     1620
tctcaagcat ccatttcgt tagaacatca aatttcagac ttccagtgga tccaaaagtt     1680
ccagtcatta tgataggacc aggcactggt cttgccccat tcaggggctt tcttcaagag     1740
agattggcct tgaaggaatc tggtacagaa ttgggttctt ctatcttttt ctttggttgc     1800
cgtaatagaa aagttgactt tatctacgag gacgagctta acaattttgt tgagacagga     1860
gcattgtcag aattgatcgt cgcattttca agagaaggga ctgccaaaga gtacgttcag     1920
cacaagatga gtcaaaaagc ctccgatata tggaaacttc taagtgaagg tgcctatctt     1980
tatgtctgtg gcgatgcaaa gggcatggcc aaggatgtcc atagaactct gcatacaatt     2040
gttcaggaac aagggagtct ggattcttcc aaggctgaat tgtacgtcaa aaacttacag     2100
atgtctggaa gatacttaag agatgtttgg taa                                 2133
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SEQ ID NO:62

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gttgccatct tgaccacttc tattgctgtt atgattggtt gcttcgttgt cttgatgtgg      180
agaagagctg gttctagaaa ggttaagaat gtcgaattgc caaagccatt gattgtccat      240
gaaccagaac ctgaagttga agatggtaag aagaaggttt ccatcttctt cggtactcaa      300
actggtactg ctgaaggttt tgctaaggct ttggctgatg aagctaaagc tagatacgaa      360
aaggctacct tcagagttgt tgatttggat gattatgctg ccgatgatga ccaatacgaa      420
gaaaaattga agaacgaatc cttcgccgtt ttcttgttgg ctacttatgg tgatggtgaa      480
cctactgata atgctgctag attttacaag tggttcgccg aaggtaaaga aagaggtgaa      540
tggttgcaaa acttgcacta tgctgttttt ggttttgggta acagacaata cgaacacttc      600
```

```
aacaagattg ctaaggttgc cgacgaatta ttggaagctc aaggtggtaa tagattggtt      660
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tctttgtggc cagaattgga tatgttgttg agagatgaag atgatgctac tactgttact      780
actccatata ctgctgctgt cttggaatac agagttgtct ttcatgattc tgctgatgtt      840
gctgctgaag ataagtcttg gattaacgct aatggtcatg ctgttcatga tgctcaacat      900
ccattcagat ctaacgttgt cgtcagaaaa gaattgcata cttctgcctc tgatagatcc      960
tgttctcatt tggaattcaa catttccggt tccgctttga attacgaaac tggtgatcat     1020
gttggtgtct actgtgaaaa cttgactgaa actgttgatg aagccttgaa cttgttgggt     1080
ttgtctccag aaacttactt ctctatctac accgataacg aagatggtac tccattgggt     1140
ggttcttcat tgccaccacc atttccatca tgtactttga gaactgcttt gaccagatac     1200
gctgatttgt tgaactctcc aaaaaagtct gctttgttgg ctttagctgc tcatgcttct     1260
aatccagttg aagctgatag attgagatac ttggcttctc cagctggtaa agatgaatat     1320
gcccaatctg ttatcggttc ccaaaagtct ttgttggaag ttatggctga attcccatct     1380
gctaaaccac cattaggtgt ttttttgct gctgttgctc caagattgca acctagattc     1440
tactccattt catcctctcc aagaatggct ccatctagaa tccatgttac ttgtgctttg     1500
gtttacgata agatgccaac tggtagaatt cataagggtg tttgttctac ctggatgaag     1560
aattctgttc caatggaaaa gtcccatgaa tgttcttggg ctccaatttt cgttagacaa     1620
tccaatttta agttgccagc cgaatccaag gttccaatta tcatggttgg tccaggtact     1680
ggtttggctc cttttagagg ttttttacaa gaaagattgg ccttgaaaga atccggtgtt     1740
gaattgggtc catccatttt gtttttcggt tgcagaaaca gaagaatgga ttacatctac     1800
gaagatgaat tgaacaactt cgttgaaacc ggtgctttgt ccgaattggt tattgctttt     1860
tctagagaag gtcctaccaa agaatacgtc caacataaga tggctgaaaa ggcttctgat     1920
atctggaact tgatttctga aggtgcttac ttgtacgttt gtggtgatgc taaaggtatg     1980
gctaaggatg ttcatagaac cttgcatacc atcatgcaag aacaaggttc tttggattct     2040
tccaaagctg aatccatggt caagaacttg caaatgaatg gtagatactt aagagatgtt     2100
tggtaa                                                               2106
```

SEQ ID NO:63

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gctttcggcg catggttatg ttcttatgtg atacatgttt tatcatcttc ctctacagta      180
aaagtgccag ttgttggata caggtctgta ttcgaaccta catggttgct tagacttaga      240
ttcgtctggg aaggtggctc tatcataggt caagggtaca ataagtttaa agactctatt      300
ttccaagtta ggaaattggg aactgatatt gtcattatac cacctaacta tattgatgaa      360
gtgagaaaat tgtcacagga caagactaga tcagttgaac ctttcattaa tgattttgca      420
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caaagactaa ctccaaaatt ggtttccttg accaaggtca tgaaggaaga gttggattat      540
gctttaacaa aagagatgcc tgatatgaaa aatgacgaat gggtagaagt agatatcagt      600
agtataatgg tgagattgat ttccaggatc tccgccagag tctttctagg gcctgaacac      660
tgtcgtaacc aggaatggtt gactactaca gcagaatatt cagaatcact tttcattaca      720
gggtttatct taagagttgt acctcatatc ttaagaccat tcatcgcccc tctattacct      780
tcatacagga ctctacttag aaacgtttca agtggtagaa gagtcatcgg tgacatcata      840
agatctcagc aaggggatgg taacgaagat atactttcct ggatgagaga tgctgccaca      900
ggagaggaaa agcaaatcga taacattgct cagagaatgt taattctttc tttagcatca      960
atccacacta ctgcgatgac catgacacat gccatgtacg atctatgtgc ttgccctgag     1020
tacattgaac cattaagaga tgaagttaaa tctgttgttg gggcttctgg ctgggacaag     1080
acagcgttaa acagatttca taagttggac tccttcctaa aagagtcaca aagattcaac     1140
ccagtattct tattgacatt caatagaatc taccatcaat ctatgacctt atcagatggc     1200
actaacattc catctggaac acgtattgct gttccatcac acgcaatgtt gcaagattct     1260
gcacatgtcc caggtccaac cccacctact gaatttgatg gattcagata tagtaagata     1320
cgttctgata gtaactacgc acaaaagtac ctattctcca tgaccgattc ttcaaacatg     1380
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cctagaaata tcactatcga ttctgatatg attccagacc caagagctag actttgcgtc     1560
agaaaaagat cacttagaga tgaatgaccg cgg                                  1593
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SEQ ID NO:64

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aagcttaaaa tggaagatcc tactgtctta tatgcttgtc ttgccattgc agttgcaact      60
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atcgtgatcg caaatggtcc taaactagct gatgaagtca gacgtagacc agatgaagag      300
ttaaacttta tggacggatt aggagcattc gtccaaacta agtacacctt aggtgaagct      360
```

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attcataacg atccatacca tgtcgatatc ataagagaaa aactaacaag aggccttcca       420
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gaaggtgatg aatgggtgtc cgtaaactgt tcaaaggccg caagagatat tgttgctaga       540
gcttctaata gagtctttgt aggtttgcct gcttgcagaa accaaggtta cttagatttg       600
gcaatagact ttacattgtc tgttgtcaag gatagagcca tcatcaatat gtttccagaa       660
ttgttgaagc caatagttgg cagagttgta ggtaacgcca ccagaaatgt tcgtagagct       720
gttccttttg ttgctccatt ggtggaggaa agacgtagac ttatggaaga gtacggtgaa       780
gactggtctg aaaaacctaa tgatatgtta cagtggataa tggatgaagc tgcatccaga       840
gatagttcag tgaaggcaat cgcagagaga ttgttaatgg tgaacttcgc ggctattcat       900
acctcatcaa acactatcac tcatgctttg taccaccttg ccgaaatgcc tgaaactttg       960
caaccactta gagaagagat cgaaccatta gtcaaagagg agggctggac caaggctgct      1020
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aacatcgtat ctttaactag aatggctgac aaagatatta cattgagtga tggcacattt      1140
ttgccaaaag gtactctagt ggccgttcca gcgtattcta ctcatagaga tgatgctgtc      1200
tacgctgatg ccttagtatt cgatcctttc agattctcac gtatgagagc gagagaaggt      1260
gaaggtacaa agcaccagtt cgttaatact tcagtcgagt acgttccatt tggtcacgga      1320
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attgttctaa actatgatgt aaagttgcct ggtgacggta aacgtccatt gaacatgtat      1440
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agtctataac cgcgg                                                      1515
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SEQ ID NO:65

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gctttgtctt ggttgttttt gttctacatc aaggtttctt tcttctccaa caaatccgct       120
caagctaaat tgccaccagt tccagttgtt ccaggtttgc cagttattgg taatttgttg       180
caattgaaag aaaagaagcc ataccaaacc ttcactagat gggctgaaga atatggtcca       240
atctactcta ttagaactgg tgcttctact atggttgtct tgaacactac tcaagttgcc       300
aaagaagcta tggttaccag atacttgtct atctctacca gaaagttgtc caacgccttg       360
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atgatcaaga gatatatctt gtctaacgtt ttgggtccat ctgcccaaaa aagacataga       480
tctaacagag ataccttgag agccaacgtt tgttctagat tgcattccca agttaagaac       540
tctccaagag aagctgtcaa ctttagaaga gttttcgaat gggaattatt cggtatcgct       600
ttgaaacaag ccttcggtaa ggatattgaa aagccaatct acgtcgaaga attgggtact       660
actttgtcca gagatgaaat cttcaaggtt ttggtcttgg acattatgga aggtgccatt       720
gaagttgatt ggagagattt tttcccatac ttgcgttgga ttccaaacac cagaatggaa       780
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caaaagaaaa gaattgcctc cggtgaagaa atcaactgct acatcgattt cttgttgaaa       900
gaaggtaaga ccttgaccat ggaccaaatc tctatgttgt tgtgggaaac cgttattgaa       960
actgctgata ccacaatggt tactactgaa tgggctatgt acgaagttgc taaggattct      1020
aaaagacaag acagattata ccaagaaatc caaaaggtct gcggttctga aatggttaca      1080
gaagaatact tgtcccaatt gccatacttg aatgctgttt tccacgaaac tttgagaaaa      1140
cattctccag ctgctttggt tccattgaga tatgctcatg aagatactca attgggtggt      1200
tattacattc cagccggtac tgaaattgcc attaacatct acggttgcaa catggacaaa      1260
caccaatggg aatctccaga agaatggaag ccagaaagat ttttggatcc taagtttgac      1320
ccaatggact tgtacaaaac tatggctttt ggtgctggta aaagagtttg cgctggttct      1380
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aagttgagag atggtgaaga agaaaacgtt gatactgttg gtttgaccac ccataagaga      1500
tatccaatgc atgctatttt gaagccaaga tcttaa                                1536
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SEQ ID NO:66

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gcatacttta ctaagggtaa attgtggggt gttaccaagg atccatacgc taacggattc       120
gctgcaggtg gtgcttccaa gcctggcaga actagaaaca tcgtcgaagc tatggaggaa       180
tcaggtaaaa actgtgttgt tttctacggc agtcaaacag gtacagcgga ggattacgca       240
tcaagacttg caaaggaagg aaagtccaga ttcggtttga acactatgat cgccgatcta       300
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ttggctactt acggtgaagg cgaaccaaca gataacgccg tggatttcta tgagttcatt       420
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gttgcgttcg gtctgggcaa caatacctac gaacactaca actcaatggt caggaacgtt       540
aacaaggctc tagaaaagtt aggagctcat agaattggag aagcaggtga gggtgacgac       600
ggagctggaa ctatggaaga ggacttttta gcttggaaag atccaatgtg ggaagccttg       660
gctaaaaaga tgggcttgga ggaaagagaa gctgtatatg aacctatttt cgctatcaat       720
gagagagatg atttgacccc tgaagcgaat gaggtatact tgggagaacc taataagcta       780
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cacttggaag gtacagcgaa aggtccattc aactcccaca acccatatat cgcaccaatt      840
gcagaatcat acgaactttt ctcagctaag gatagaaatt gtctgcatat ggaaattgat      900
atttctggta gtaatctaaa gtatgaaaca ggcgaccata tcgcgatctg gcctaccaac      960
ccaggtgaag aggtcaacaa atttcttgac attctagatc tgtctggtaa gcaacattcc     1020
gtcgtaacag tgaaagcctt agaacctaca gccaaagttc cttttccaaa tccaactacc     1080
tacgatgcta tattgagata ccatctggaa atatgcgctc cagtttctag acagtttgtc     1140
tcaactttag cagcattcgc ccctaatgat gatatcaaag ctgagatgaa ccgtttggga     1200
tcagacaaag attacttcca cgaaaagaca ggaccacatt actacaatat cgctagattt     1260
ttggcctcag tctctaaagg tgaaaaatgg acaaagatac cattttctgc tttcatagaa     1320
ggccttacaa aactacaacc aagatactat tctatctctt cctctagttt agttcagcct     1380
aaaaagatta gtattactgc tgttgtcgaa tctcagcaaa ttccaggtag agatgaccca     1440
ttcagaggtg tagcgactaa ctacttgttc gctttgaagc agaaacaaaa cggtgatcca     1500
aatccagctc cttttggcca atcatacgag ttgacaggac caaggaataa gtatgatggt     1560
atacatgttc cagtccatgt aagacattct aactttaagc taccatctga tccaggcaaa     1620
cctattatca tgatcggtcc aggtaccggt gttgcccctt ttagaggctt cgtccaagag     1680
agggcaaaac aagccagaga tggtgtagaa gttggtaaaa cactgctgtt ctttggatgt     1740
agaaagagta cagaagattt catgtatcaa aaagagtggc aagagtacaa ggaagctctt     1800
ggcgacaaat tcgaaatgat tacagctttt tcaagagaag gatctaaaaa ggtttatgtt     1860
caacacagac tgaaggaaag atcaaaggaa gtttctgatc ttctatccca aaaagcatac     1920
ttctacgttt gcggagacgc cgcacatatg gcacgtgaag tgaacactgt gttagcacag     1980
atcatagcag aaggccgtgg tgtatcagaa gccaagggtg aggaaattgt caaaaacatg     2040
agatcagcaa atcaatacca agtgtgttct gatttcgtaa ctttacactg taaagagaca     2100
acatacgcga attcagaatt gcaagaggat gtctggagtt aa                       2142
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SEQ ID NO:67

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gcttacttca ccaaaggtaa attgtggggt gttactaagg atccatacgc taatggtttt       120
gctgctggtg gtgcttctaa accaggtaga actagaaata tcgttgaagc catggaagaa       180
tctggtaaga actgtgttgt tttctacggt tctcaaactg gtactgctga agattatgct       240
tccagattgg ctaaagaagg taagagtaga ttcggtttga acaccatgat tgccgatttg       300
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ttggctacct acggtgaagg tgaacctact gataatgctg ttgacttcta cgaattcatt       420
accggtgaag atgcttcttt caacgaaggt aatgatccac cattgggtaa cttgaattac       480
gttgcttttg gtttgggtaa caacacctac gaacattaca actccatggt tagaaacgtc       540
aacaaggctt tggaaaaatt gggtgctcat agaattggtg aagctggtga aggtgatgat       600
ggtgctggta ctatggaaga agatttttttg gcttggaaag acccaatgtg ggaagccttg       660
gctaaaaaga tgggtttgga agaaagagaa gctgtctacg aacctatttt cgccattaac       720
gaaagagatg atttgacccc tgaagccaat gaagtttatt tgggtgaacc taacaagttg       780
cacttggaag gtactgctaa aggtccattc aattctcaca acccatatat tgctccaatc       840
gccgaatctt acgaattatt ctctgctaag gatagaaact gcttgcacat ggaaattgac       900
atctctggtt ctaatttgaa gtacgaaacc ggtgatcata ttgccatttg gccaactaat       960
ccaggtgaag aagttaacaa gttcttggac atcttggact tgtccggtaa acaacattct      1020
gttgttactg ttaaggcctt ggaacctaca gctaaagttc cttttccaaa tccaactacc      1080
tacgatgcca ttttgagata ccatttggaa atttgcgctc cagtctctag acaattcgtt      1140
tctactttgg ctgcttttgc tccaaacgat gatattaagg ctgaaatgaa cagattgggt      1200
tccgataagg attacttcca cgaaaaaact ggtccacact actacaacat tgctagattt      1260
ttggcctctg tctctaaagg tgaaaagtgg actaagattc cattctccgc tttcattgaa      1320
ggtttgacta agttgcaacc tagatattac tccatctcct cctcatcttt ggttcaacct      1380
aagaagatct ctattaccgc cgttgttgaa tcccaacaaa ttccaggtag agatgatcct      1440
tttagaggtg ttgctaccaa ttacttgttc gccttgaaac aaaagcaaaa cggtgatcca      1500
aatcctgctc catttggtca atcttatgaa ttgactggtc caagaaacaa gtacgatggt      1560
attcatgttc cagttcacgt tagacactct aactttaagt tgccatctga tccaggtaag      1620
ccaattatca tgattggtcc aggtactggt gttgctccat tcagaggttt tgttcaagaa      1680
agagctaagc aagctagaga tggtgttgaa gttggtaaaa ccttgttgtt cttcggttgt      1740
agaaagtcca ctgaagattt catgtaccaa aaagaatggc aagaatacaa agaagcctta      1800
ggtgacaagt tcgaaatgat tactgccttc tcaagagaag gttctaagaa ggtttacgtc      1860
caacacagat tgaaagaaag atccaaagaa gtctccgatt tgttgtctca aaaggcctac      1920
ttttacgttt gtggtgatgc tgctcatatg gccagagaag ttaatactgt tttggcccaa      1980
attatcgctg aaggtagagg tgtatctgaa gctaagggtg aagaaatcgt taagaacatg      2040
agatccgcca atcaatacca agtttgctct gattttgtta ccttgcactg taaagaaacc      2100
acctacgcta attccgaatt gcaagaagat gtttggtcct aa                        2142
```

SEQ ID NO:68

```
MEASYLYISI LLLLASYLFT TQLRRKSANL PPTVFPSIPI IGHLYLLKKP LYRTLAKIAA        60
KYGPILQLQL GYRRVLVISS PSAAEECFTN NDVIFANRPK TLFGKIVGGT SLGSLSYGDQ       120
WRNLRRVASI EILSVHRLNE FHDIRVDENR LLIRKLRSSS SPVTLITVFY ALTLNVIMRM       180
ISGKRYFDSG DRELEEEGKR FREILDETLL LAGASNVGDY LPILNWLGVK SLEKKLIALQ       240
KKRDDFFQGL IEQVRKSRGA KVGKGRKTMI ELLLSLQESE PEYYTDAMIR SFVLGLLAAG       300
SDTSAGTMEW AMSLLVNHPH VLKKAQAEID RVIGNNRLID ESDIGNIPYI GCIINETLRL       360
YPAGPLLFPH ESSADCVISG YNIPRGTMLI VNQWAIHHDP KVWDDPETFK PERFQGLEGT       420
RDGFKLMPFG SGRRGCPGEG LAIRLLGMTL GSVIQCFDWE RVGDEMVDMT EGLGVTLPKA       480
VPLVAKCKPR SEMTNLLSEL                                                   500
```

SEQ ID NO:69

```
MQSESVEAST IDLMTAVLKD TVIDTANASD NGDSKMPPAL AMMFEIRDLL LILTTSVAVL        60
VGCFVVLVWK RSSGKKSGKE LEPPKIVVPK RRLEQEVDDG KKKVTIFFGT QTGTAEGFAK       120
ALFEEAKARY EKAAFKVIDL DDYAADLDEY AEKLKKETYA FFFLATYGDG EPTDNAAKFY       180
KWFTEGDEKG VWLQKLQYGV FGLGNRQYEH FNKIGIVVDD GLTEQGAKRI VPVGLGDDDQ       240
SIEDDFSAWK ELVWPELDLL LRDEDDKAAA TPYTAAIPEY RVVFHDKPDA FSDDHTQTNG       300
HAVHDAQHPC RSNVAVKKEL HTPESDRSCT HLEFDISHTG LSYETGDHVG VYCENLIEVV       360
EEAGKLLGLS TDTYFSLHID NEDGSPLGGP SLQPPFPPCT LRKALTNYAD LLSSPKKSTL       420
LALAAHASDP TEADRLRFLA SREGKDEYAE WVVANQRSLL EVMEAFPSAR PPLGVFFAAV       480
APRLQPRYYS ISSSPKMEPN RIHVTCALVY EKTPAGRIHK GICSTWMKNA VPLTESQDCS       540
WAPIFVRTSN FRLPIDPKVP VIMIGPGTGL APFRGFLQER LALKESGTEL GSSILFFGCR       600
NRKVDYIYEN ELNNFVENGA LSELDVAFSR DGPTKEYVQH KMTQKASEIW NMLSEGAYLY       660
VCGDAKGMAK DVHRTLHTIV QEQGSLDSSK AELYVKNLQM SGRYLRDVW                   709
```

SEQ ID NO:70

```
MASITHFLQD FQATPFATAF AVGGVSLLIF FFFIRGFHST KKNEYYKLPP VPVVPGLPVV        60
GNLLQLKEKK PYKTFLRWAE IHGPIYSIRT GASTMVVVNS THVAKEAMVT RFSSISTRKL       120
SKALELLTSN KSMVATSDYN EFHKMVKKYI LAELLGANAQ KRHRIHRDTL IENVLNKLHA       180
HTKNSPLQAV NFRKIFESEL FGLAMKQALG YDVDSLFVEE LGTTLSREEI YNVLVSDMLK       240
GAIEVDWRDF FPYLKWIPNK SFEMKIQRLA SRRQAVMNSI VKEQKKSIAS GKGENCYLNY       300
LLSEAKTLTE KQISILAWET IIETADTTVV TTEWAMYELA KNPKQQDRLY NEIQNVCGTD       360
KITEEHLSKL PYLSAVFHET LRKYSPSPLV PLRYAHEDTQ LGGYYVPAGT EIAVNIYGCN       420
MDKNQWETPE EWKPERFLDE KYDPMDMYKT MSFGSGKRVC AGSLQASLIA CTSIGRLVQE       480
FEWRLKDGEV ENVDTLGLTT HKLYPMQAIL QPRN                                   514
```

SEQ ID NO:71

```
MASMISLLLG FVVSSFLFIF FLKKLLFFFS RHKMSEVSRL PSVPVPGFPL IGNLLQLKEK        60
KPHKTFTKWS ELYGPIYSIK MGSSSLIVLN SIETAKEAMV SRFSSISTRK LSNALTVLTC       120
NKSMVATSDY DDFHKFVKRC LLNGLLGANA QERKRHYRDA LIENVTSKLH AHTRNHPQEP       180
VNFRAIFEHE LFGVALKQAF GKDVESIYVK ELGVTLSRDE IFKVLVHDMM EGAIDVDWRD       240
FFPYLKWIPN NSFEARIQQK HKRRLAVMNA LIQDRLNQND SESDDDCYLN FLMSEAKTLT       300
MEQIAILVWE TIIETADTTL VTTEWAMYEL AKHQSVQDRL FKEIQSVCGG EKIKEEQLPR       360
LPYVNGVFHE TLRKYSPAPL VPIRYAHEDT QIGGYHIPAG SEIAINIYGC NMDKKRWERP       420
EEWWPERFLE DRYESSDLHK TMAFGAGKRV CAGALQASLM AGIAIGRLVQ EFEWKLRDGE       480
EENVDTYGLT SQKLYPLMAI INPRRS                                            506
```

SEQ ID NO:72

```
MDMMGIEAVP FATAVVLGGI SLVVLIFIRR FVSNRKRSVE GLPPVPDIPG LPLIGNLLQL        60
KEKKPHKTFA RWAETYGPIF SIRTGASTMI VLNSSEVAKE AMVTRFSSIS TRKLSNALKI       120
LTFDKCMVAT SDYNDFHKMV KGFILRNVLG APAQKRHRCH RDTLIENISK YLHAHVKTSP       180
LEPVVLKKIF ESEIFGLALK QALGKDIESI YVEELGTTLS REEIFAVLVV DPMAGAIEVD       240
WRDFFPYLSW IPNKSMEMKI QRMDFRRGAL MKALIGEQKK RIGSGEEKNS YIDFLLSEAT       300
TLTEKQIAML IWETIIEISD TTLVTSEWAM YELAKDPNRQ EILYREIHKV CGSNKLTEEN       360
LSKLPYLNSV FHETLRKYSP APMVPVRYAH EDTQLGGYHI PAGSQIAINI YGCNMNKKQW       420
ENPEEWKPER FLDEKYDLMD LHKTMAFGGG KRVCAGALQA MLIACTSIGR FVQEFEWKLM       480
GGEEENVDTV ALTSQKLHPM QAIIKARE                                          508
```

SEQ ID NO:73

```
MAELDTLDIV VLGVIFLGTV AYFTKGKLWG VTKDPYANGF AAGGASKPGR TRNIVEAMEE        60
SGKNCVVFYG SQTGTAEDYA SRLAKEGKSR FGLNTMIADL EDYDFDNLDT VPSDNIVMFV       120
LATYGEGEPT DNAVDFYEFI TGEDASFNEG NDPPLGNLNY VAFGLGNNTY EHYNSMVRNV       180
NKALEKLGAH RIGEAGEGDD GAGTMEEDFL AWKDPMWEAL AKKMGLEERE AVYEPIFAIN       240
ERDDLTPEAN EVYLGEPNKL HLEGTAKGPF NSHNPYIAPI AESYELFSAK DRNCLHMEID       300
ISGSNLKYET GDHIAIWPTN PGEEVNKFLD ILDLSGKQHS VVTVKALEPT AKVPFPNPTT       360
YDAILRYHLE ICAPVSRQFV STLAAFAPND DIKAEMNRLG SDKDYFHEKT GPHYYNIARF       420
LASVSKGEKW TKIPFSAFIE GLTKLQPRYY SISSSSLVQP KKISITAVVE SQQIPGRDDP       480
FRGVATNYLF ALKQKQNGDP NPAPFGQSYE LTGPRNKYDG IHVPVHVRHS NFKLPSDPGK       540
PIIMIGPGTG VAPFRGFVQE RAKQARDGVE VGKTLLFFGC RKSTEDFMYQ KEWQEYKEAL       600
GDKFEMITAF SREGSKKVYV QHRLKERSKE VSDLLSQKAY FYVCGDAAHM AREVNTVLAQ       660
IIAEGRGVSE AKGEEIVKNM RSANQYQVCS DFVTLHCKET TYANSELQED VWS               713
```

SEQ ID NO:74

```
MKVSPFEFMS AIIKGRMDPS NSSFESTGEV ASVIFENREL VAILTTSIAV MIGCFVVLMW        60
RRAGSRKVKN VELPKPLIVH EPEPEVEDGK KKVSIFFGTQ TGTAEGFAKA LADEAKARYE       120
KATFRVVDLD DYAADDDQYE EKLKNESFAV FLLATYGDGE PTDNAARFYK WFAEGKERGE       180
WLQNLHYAVF GLGNRQYEHF NKIAKVADEL LEAQGGNRLV KVGLGDDDQC IEDDFSAWRE       240
SLWPELDMLL RDEDDATTVT TPYTAAVLEY RVVFHDSADV AAEDKSWINA NGHAVHDAQH       300
PFRSNVVVRK ELHTSASDRS CSHLEFNISG SALNYETGDH VGVYCENLTE TVDEALNLLG       360
LSPETYFSIY TDNEDGTPLG GSSLPPPFPS CTLRTALTRY ADLLNSPKKS ALLALAAHAS       420
NPVEADRLRY LASPAGKDEY AQSVIGSQKS LLEVMAEFPS AKPPLGVFFA AVAPRLQPRF       480
YSISSSPRMA PSRIHVTCAL VYDKMPTGRI HKGVCSTWMK NSVPMEKSHE CSWAPIFVRQ       540
SNFKLPAESK VPIIMVGPGT GLAPFRGFLQ ERLALKESGV ELGPSILFFG CRNRRMDYIY       600
EDELNNFVET GALSELVIAF SREGPTKEYV QHKMAEKASD IWNLISEGAY LYVCGDAKGM       660
AKDVHRTLHT IMQEQGSLDS SKAESMVKNL QMNGRYLRDV W                           701
```

SEQ ID NO:75

```
MATLLEHFQA MPFAIPIALA ALSWLFLFYI KVSFFSNKSA QAKLPPVPVV PGLPVIGNLL        60
QLKEKKPYQT FTRWAEEYGP IYSIRTGAST MVVLNTTQVA KEAMVTRYLS ISTRKLSNAL       120
KILTADKCMV AISDYNDFHK MIKRYILSNV LGPSAQKRHR SNRDTLRANV CSRLHSQVKN       180
SPREAVNFRR VFEWELFGIA LKQAFGKDIE KPIYVEELGT TLSRDEIFKV LVLDIMEGAI       240
EVDWRDFFPY LRWIPNTRME TKIQRLYFRR KAVMTALINE QKKRIASGEE INCYIDFLLK       300
EGKTLTMDQI SMLLWETVIE TADTTMVTTE WAMYEVAKDS KRQDRLYQEI QKVCGSEMVT       360
EEYLSQLPYL NAVFHETLRK HSPAALVPLR YAHEDTQLGG YYIPAGTEIA INIYGCNMDK       420
HQWESPEEWK PERFLDPKFD PMDLYKTMAF GAGKRVCAGS LQAMLIACPT IGRLVQEFEW       480
KLRDGEEENV DTVGLTTHKR YPMHAILKPR S                                      511
```

SEQ ID NO:76

```
MQSDSVKVSP FDLVSAAMNG KAMEKLNASE SEDPTTLPAL KMLVENRELL TLFTTSFAVL        60
IGCLVFLMWR RSSSKKLVQD PVPQVIVVKK KEKESEVDDG KKKVSIFYGT QTGTAEGFAK       120
ALVEEAKVRY EKTSFKVIDL DDYAADDDEY EEKLKKESLA FFFLATYGDG EPTDNAANFY       180
KWFTEGDDKG EWLKKLQYGV FGLGNRQYEH FNKIAIVVDD KLTEMGAKRL VPVGLGDDDQ       240
CIEDDFTAWK ELVWPELDQL LRDEDDTSVT TPYTAAVLEY RVVYHDKPAD SYAEDQTHTN       300
GHVVHDAQHP SRSNVAFKKE LHTSQSDRSC THLEFDISHT GLSYETGDHV GVYSENLSEV       360
VDEALKLLGL SPDTYFSVHA DKEDGTPIGG ASLPPPFPPC TLRDALTRYA DVLSSPKKVA       420
LLALAAHASD PSEADRLKFL ASPAGKDEYA QWIVANQRSL LEVMQSFPSA KPPLGVFFAA       480
VAPRLQPRYY SISSSPKMSP NRIHVTCALV YETTPAGRIH RGLCSTWMKN AVPLTESPDC       540
SQASIFVRTS NFRLPVDPKV PVIMIGPGTG LAPFRGFLQE RLALKESGTE LGSSIFFFGC       600
RNRKVDFIYE DELNNFVETG ALSELIVAFS REGTAKEYVQ HKMSQKASDI WKLLSEGAYL       660
YVCGDAKGMA KDVHRTLHTI VQEQGSLDSS KAELYVKNLQ MSGRYLRDVW                  710
```

SEQ ID NO:77

```
MSKSNSMNST SHETLFQQLV LGLDRMPLMD VHWLIYVAFG AWLCSYVIHV LSSSSTVKVP        60
VVGYRSVFEP TWLLRLRFVW EGGSIIGQGY NKFKDSIFQV RKLGTDIVII PPNYIDEVRK       120
LSQDKTRSVE PFINDFAGQY TRGMVFLQSD LQNRVIQQRL TPKLVSLTKV MKEELDYALT       180
KEMPDMKNDE WVEVDISSIM VRLISRISAR VFLGPEHCRN QEWLTTTAEY SESLFITGFI       240
LRVVPHILRP FIAPLLPSYR TLLRNVSSGR RVIGDIIRSQ QGDGNEDILS WMRDAATGEE       300
KQIDNIAQRM LILSLASIHT TAMTMTHAMY DLCACPEYIE PLRDEVKSVV GASGWDKTAL       360
NRFHKLDSFL KESQRFNPVF LLTFNRIYHQ SMTLSDGTNI PSGTRIAVPS HAMLQDSAHV       420
```

```
PGPTPPTEFD GFRYSKIRSD SNYAQKYLFS MTDSSNMAFG YGKYACPGRF YASNEMKLTL       480
AILLLQFEFK LPDGKGRPRN ITIDSDMIPD PRARLCVRKR SLRDE                      525
```

SEQ ID NO:78

```
MEDPTVLYAC LAIAVATFVV RWYRDPLRSI PTVGGSDLPI LSYIGALRWT RRGREILQEG        60
YDGYRGSTFK IAMLDRWIVI ANGPKLADEV RRRPDEELNF MDGLGAFVQT KYTLGEAIHN       120
DPYHVDIIRE KLTRGLPAVL PDVIEELTLA VRQYIPTEGD EWVSVNCSKA ARDIVARASN       180
RVFVGLPACR NQGYLDLAID FTLSVVKDRA IINMFPELLK PIVGRVVGNA TRNVRRAVPF       240
VAPLVEERRR LMEEYGEDWS EKPNDMLQWI MDEAASRDSS VKAIAERLLM VNFAAIHTSS       300
NTITHALYHL AEMPETLQPL REEIEPLVKE EGWTKAAMGK MWWLDSFLRE SQRYNGINIV       360
SLTRMADKDI TLSDGTFLPK GTLVAVPAYS THRDDAVYAD ALVFDPFRFS RMRAREGEGT       420
KHQFVNTSVE YVPFGHGKHA CPGRFFAANE LKAMLAYIVL NYDVKLPGDG KRPLNMYWGP       480
TVLPAPAGQV LFRKRQVSL                                                    499
```

SEQ ID NO:79

```
MDAVTGLLTV PATAITIGGT AVALAVALIF WYLKSYTSAR RSQSNHLPRV PEVPGVPLLG        60
NLLQLKEKKP YMTFTRWAAT YGPIYSIKTG ATSMVVVSSN EIAKEALVTR FQSISTRNLS       120
KALKVLTADK TMVAMSDYDD YHKTVKRHIL TAVLGPNAQK KHRIHRDIMM DNISTQLHEF       180
VKNNPEQEEV DLRKIFQSEL FGLAMRQALG KDVESLYVED LKITMNRDEI FQVLVVDPMM       240
GAIDVDWRDF FPYLKWVPNK KFENTIQQMY IRREAVMKSL IKEHKKRIAS GEKLNSYIDY       300
LLSEAQTLTD QQLLMSLWEP IIESSDTTMV TTEWAMYELA KNPKLQDRLY RDIKSVCGSE       360
KITEEHLSQL PYITAIFHET LRRHSPVPII PLRHVHEDTV LGGYHVPAGT ELAVNIYGCN       420
MDKNVWENPE EWNPERFMKE NETIDFQKTM AFGGGKRVCA GSLQALLTAS IGIGRMVQEF       480
EWKLKDMTQE EVNTIGLTTQ MLRPLRAIIK PRI                                    513
```

SEQ ID NO:80

```
atggaagtaa cagtagctag tagtgtagcc ctgagcctgg tctttattag catagtagta        60
agatgggcat ggagtgtggt gaattgggtg tggtttaagc cgaagaagct ggaaagattt       120
ttgagggagc aaggccttaa aggcaattcc tacaggtttt tatatggaga catgaaggag       180
aactctatcc tgctcaaaca agcaagatcc aaacccatga acctctccac ctcccatgac       240
atagcacctc aagtcacccc ttttgtcgac caaaccgtga aagcttacgg taagaactct       300
tttaattggg ttggccccat accaagggtg aacataatga atccagaaga tttgaaggac       360
gtcttaacaa aaaatgttga ctttgttaag ccaatatcaa acccacttat caagttgcta       420
gctacaggta ttgcaatcta tgaaggtgag aaatggacta aacacagaag gattatcaac       480
ccaacattcc attcggagag gctaaagcgt atgttacctt catttcacca aagttgtaat       540
gagatggtca aggaatggga gagcttggtg tcaaaagagg gttcatcatg tgagttggat       600
gtctggcctt ttcttgaaaa tatgtcggca gatgtgatct cgagaacagc atttggaact       660
agctacaaaa aaggacagaa aatctttgaa ctcttgagag agcaagtaat atatgtaacg       720
aaaggctttc aaagttttta cattccagga tggaggtttc tcccaactaa gatgaacaag       780
aggatgaatg agattaacga agaaataaaa ggattaatca ggggtattat aattgacaga       840
gagcaaatca ttaaggcagg tgaagaaacc aacgatgact tattaggtgc acttatggag       900
tcaaacttga aggacattcg ggaacatggg aaaaacaaca aaaatgttgg gatgagtatt       960
gaagatgtaa ttcaggagtg taagctgttt tactttgctg ggcaagaaac cacttcagtg      1020
ttgctggctt ggacaatggt tttacttggt caaaatcaga actggcaaga tcgagcaaga      1080
caagaggttt tgcaagtctt tggaagcagc aagccagatt ttgatggtct agctcacctt      1140
aaagtcgtaa ccatgatttt gcttgaagtt cttcgattat acccaccagt cattgaactt      1200
attcgaacca ttcacaagaa aacacaactt gggaagctct cactaccaga aggagttgaa      1260
gtccgcttac caacactgct cattcaccat gacaaggaac tgtggggtga tgatgcaaac      1320
cagttcaatc cagagaggtt ttcggaagga gtttccaaag caacaaagaa ccgactctca      1380
ttcttccccc tcggagccgg tccacgcatt tgcattggac agaacttttc tatgatggaa      1440
gcaaagttgg ccttagcatt gatcttgcaa cacttcacct ttgagctttc tccatctcat      1500
gcacatgctc cttcccatcg tataacccct caaccacagt atggtgttcg tatcatttta      1560
catcgacgtt ag                                                         1572
```

SEQ ID NO:81

```
atggaagtca ctgtcgcctc ttctgtcgct ttatccttag tcttcatttc cattgtcgtc        60
agatgggctt ggtccgttgt caactgggtt tggttcaaac caaagaagtt ggaaagattc       120
ttgagagagc aaggtttgaa gggtaattct tatagattct tgtacggtga catgaaggaa       180
aattctattt tgttgaagca agccagatcc aaaccaatga acttgtctac ctctcatgat       240
attgctccac aagttactcc attcgtcgat caaactgtta aagcctacgg taagaactct       300
```

```
ttcaattggg ttggtccaat tcctagagtt aacatcatga acccagaaga tttgaaggat      360
gtcttgacca agaacgttga cttcgttaag ccaatttcca acccattgat taaattgttg      420
gctactggta ttgccattta cgaaggtgaa aagtggacta agcatagaag aatcatcaac      480
cctaccttcc actctgaaag attgaagaga atgttaccat ctttccatca atcctgtaat      540
gaaatggtta aggaatggga atccttggtt tctaaagaag gttcttcttg cgaattggat      600
gtttggccat tcttggaaaa tatgtctgct gatgtcattt ccagaaccgc tttcggtacc      660
tcctacaaga agggtcaaaa gattttcgaa ttgttgagag agcaagttat ttacgttacc      720
aagggtttcc aatccttcta catcccaggt tggagattct tgccaactaa aatgaacaag      780
cgtatgaacg agatcaacga agaaattaaa ggtttgatca gaggtattat tatcgacaga      840
gaacaaatta ttaaagctgg tgaagaaacc aacgatgatt tgttgggtgc tttgatggag      900
tccaacttga aggatattag agaacatggt aagaacaaca agaatgttgg tatgtctatt      960
gaagatgtta ttcaagaatg taagttattc tacttcgctg gtcaagagac cacttctgtt     1020
ttgttagcct ggactatggt cttgttaggt caaaaccaaa attggcaaga tagagctaga     1080
caagaagttt tgcaagtctt cggttcttcc aagccagact ttgatggttt ggcccacttg     1140
aaggttgtta ctatgatttt gttagaagtt ttgagattgt acccaccagt cattgagtta     1200
atcagaacca ttcataaaaa gactcaattg ggtaaattat ctttgccaga aggtgttgaa     1260
gtcagattac caaccttgtt gattcaccac gataaggaat tatggggtga cgacgctaat     1320
caatttaatc cagaaagatt ttccgaaggt gtttccaagg ctaccaaaaa ccgtttgtcc     1380
ttcttcccat ttggtgctgg tccacgtatt tgtatcggtc aaaacttttc catgatggaa     1440
gccaagttgg ctttggcttt aatcttgcaa cacttcactt tcgaattgtc tccatcccat     1500
gcccacgctc cttctcatag aatcacttta caaccacaat acggtgtcag aatcatctta     1560
cacagaagat aa                                                        1572
```

SEQ ID NO:82

```
MEVTVASSVA LSLVFISIVV RWAWSVVNWV WFKPKKLERF LREQGLKGNS YRFLYGDMKE       60
NSILLKQARS KPMNLSTSHD IAPQVTPFVD QTVKAYGKNS FNWVGPIPRV NIMNPEDLKD      120
VLTKNVDFVK PISNPLIKLL ATGIAIYEGE KWTKHRRIIN PTFHSERLKR MLPSFHQSCN      180
EMVKEWESLV SKEGSSCELD VWPFLENMSA DVISRTAFGT SYKKGQKIFE LLREQVIYVT      240
KGFQSFYIPG WRFLPTKMNK RMNEINEEIK GLIRGIIIDR EQIIKAGEET NDDLLGALME      300
SNLKDIREHG KNNKNVGMSI EDVIQECKLF YFAGQETTSV LLAWTMVLLG QNQNWQDRAR      360
QEVLQVFGSS KPDFDGLAHL KVVTMILLEV LRLYPPVIEL IRTIHKKTQL GKLSLPEGVE      420
VRLPTLLIHH DKELWGDDAN QFNPERFSEG VSKATKNRLS FFPFGAGPRI CIGQNFSMME      480
AKLALALILQ HFTFELSPSH AHAPSHRITL QPQYGVRIIL HRR                        523
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SEQ ID NO:83

```
MENKTETTVR RRRRIILFPV PFQGHINPIL QLANVLYSKG FSITIFHTNF NKPKTSNYPH       60
FTFRFILDND PQDERISNLP THGPLAGMRI PIINEHGADE LRRELELLML ASEEDEEVSC      120
LITDALWYFA QSVADSLNLR RLVLMTSSLF NFHAHVSLPQ FDELGYLDPD DKTRLEEQAS      180
GFPMLKVKDI KSAYSNWQIL KEILGKMIKQ TKASSGVIWN SFKELEESEL ETVIREIPAP      240
SFLIPLPKHL TASSSSLLDH DRTVFQWLDQ QPPSSVLYVS FGSTSEVDEK DFLEIARGLV      300
DSKQSFLWVV RPGFVKGSTW VEPLPDGFLG ERGRIVKWVP QQEVLAHGAI GAFWTHSGWN      360
STLESVCEGV PMIFSDFGLD QPLNARYMSD VLKVGVYLEN GWERGEIANA IRRVMVDEEG      420
EYIRQNARVL KQKADVSLMK GGSSYESLES LVSYISSL                              458
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SEQ ID NO:84

```
MDAMATTEKK PHVIFIPFPA QSHIKAMLKL AQLLHHKGLQ ITFVNTDFIH NQFLESSGPH       60
CLDGAPGFRF ETIPDGVSHS PEASIPIRES LLRSIETNFL DRFIDLVTKL PDPPTCIISD      120
GFLSVFTIDA AKKLGIPVMM YWTLAACGFM GFYHIHSLIE KGFAPLKDAS YLTNGYLDTV      180
IDWVPGMEGI RLKDFPLDWS TDLNDKVLMF TTEAPQRSHK VSHHIFHTFD ELEPSIIKTL      240
SLRYNHIYTI GPLQLLLDQI PEEKKQTGIT SLHGYSLVKE EPECFQWLQS KEPNSVVYVN      300
FGSTTVMSLE DMTEFGWGLA NSNHYFLWII RSNLVIGENA VLPPELEEHI KKRGFIASWC      360
SQEKVLKHPS VGGFLTHCGW GSTIESLSAG VPMICWPYSW DQLTNCRYIC KEWEVGLEMG      420
TKVKRDEVKR LVQELMGEGG HKMRNKAKDW KEKARIAIAP NGSSSLNIDK MVKEITVLAR      480
```

SEQ ID NO:85

```
MATSDSIVDD RKQLHVATFP WLAFGHILPY LQLSKLIAEK GHKVSFLSTT RNIQRLSSHI       60
SPLINVVQLT LPRVQELPED AEATTDVHPE DIPYLKKASD GLQPEVTRFL EQHSPDWIIY      120
DYTHYWLPSI AASLGISRAH FSVTTPWAIA YMGPSADAMI NGSDGRTTVE DLTTPPKWFP      180
```

```
FPTKVCWRKH DLARLVPYKA PGISDGYRMG LVLKGSDCLL SKCYHEFGTQ WLPLLETLHQ       240
VPVVPVGLLP PEIPGDEKDE TWVSIKKWLD GKQKGSVVYV ALGSEVLVSQ TEVVELALGL       300
ELSGLPFVWA YRKPKGPAKS DSVELPDGFV ERTRDRGLVW TSWAPQLRIL SHESVCGFLT       360
HCGSGSIVEG LMFGHPLIML PIFGEIPRNE EDGCLTKESV ARSLRSVVVE KEGEIYKANA       420
RELSKIYNDT KVEKEYVSQF VDYLEKNARA VAIDHES                                457
```

SEQ ID NO:86

```
MDSGYSSSYA AAAGMHVVIC PWLAFGHLLP CLDLAQRLAS RGHRVSFVST PRNISRLPPV        60
RPALAPLVAF VALPLPRVEG LPDGAESTND VPHDRPDMVE LHRRAFDGLA APFSEFLGTA       120
CADWVIVDVF HHWAAAAALE HKVPCAMMLL GSAHMIASIA DRRLERAETE SPAAAGQGRP       180
AAAPTFEVAR MKLIRTKGSS GMSLAERFSL TLSRSSLVVG RSCVEFEPET VPLLSTLRGK       240
PITFLGLMPP LHEGRREDGE DATVRWLDAQ PAKSVVYVAL GSEVPLGVEK VHELALGLEL       300
AGTRFLWALR KPTGVSDADL LPAGFEERTR GRGVVATRWV PQMSILAHAA VGAFLTHCGW       360
NSTIEGLMFG HPLIMLPIFG DQGPNARLIE AKNAGLQVAR NDGDGSFDRE GVAAAIRAVA       420
VEEESSKVFQ AKAKKLQEIV ADMACHERYI DGFIQQLRSY KD                          462
```

SEQ ID NO:87

```
MSSSSSSSTS MIDLMAAIIK GEPVIVSDPA NASAYESVAA ELSSMLIENR QFAMIVTTSI        60
AVLIGCIVML VWRRSGSGNS KRVEPLKPLV IKPREEEIDD GRKKVTIFFG TQTGTAEGFA       120
KALGEEAKAR YEKTRFKIVD LDDYAADDDE YEEKLKKEDV AFFFLATYGD GEPTDNAARF       180
YKWFTEGNDR GEWLKNLKYG VFGLGNRQYE HFNKVAKVVD DILVEQGAQR LVQVGLGDDD       240
QCIEDDFTAW REALWPELDT ILREEGDTAV ATPYTAAVLE YRVSIHDSED AKFNDITLAN       300
GNGYTVFDAQ HPYKANVAVK RELHTPESDR SCIHLEFDIA GSGLTMKLGD HVGVLCDNLS       360
ETVDEALRLL DMSPDTYFSL HAEKEDGTPI SSSLPPPFPP CNLRTALTRY ACLLSSPKKS       420
ALVALAAHAS DPTEAERLKH LASPAGKDEY SKWVVESQRS LLEVMAEFPS AKPPLGVFFA       480
GVAPRLQPRF YSISSSPKIA ETRIHVTCAL VYEKMPTGRI HKGVCSTWMK NAVPYEKSEK       540
LFLGRPIFVR QSNFKLPSDS KVPIIMIGPG TGLAPFRGFL QERLALVESG VELGPSVLFF       600
GCRNRRMDFI YEEELQRFVE SGALAELSVA FSREGPTKEY VQHKMMDKAS DIWNMISQGA       660
YLYVCGDAKG MARDVHRSLH TIAQEQGSMD STKAEGFVKN LQTSGRYLRD VW               712
```

SEQ ID NO:88

```
MATSDSIVDD RKQLHVATFP WLAFGHILPY LQLSKLIAEK GHKVSFLSTT RNIQRLSSHI        60
SPLINVVQLT LPRVQELPED AEATTDVHPE DIPYLKKASD GLQPEVTRFL EQHSPDWIIY       120
DYTHYWLPSI AASLGISRAH FSVTTPWAIA YMGPSADAMI NGSDGRTTVE DLTTPPKWFP       180
FPTKVCWRKH DLARLVPYKA PGISDGYRMG MVLKGSDCLL SKCYHEFGTQ WLPLLETLHQ       240
VPVVPVGLLP PEIPGDEKDE TWVSIKKWLD GKQKGSVVYV ALGSEALVSQ TEVVELALGL       300
ELSGLPFVWA YRKPKGPAKS DSVELPDGFV ERTRDRGLVW TSWAPQLRIL SHESVCGFLT       360
HCGSGSIVEG LMFGHPLIML PIFGDQPLNA RLLEDKQVGI EIPRNEEDGC LTKESVARSL       420
RSVVVEKEGE IYKANARELS KIYNDTKVEK EYVSQFVDYL EKNARAVAID HES              473
```

SEQ ID NO:89

```
atggctactt ctgattccat cgttgacgat agaaagcaat tgcatgttgc tacttttcca        60
tggttggctt tcggtcatat tttgccatac ttgcaattgt ccaagttgat tgctgaaaag       120
ggtcacaagg tttcattctt gtctaccacc agaaacatcc aaagattgtc ctctcatatc       180
tccccattga tcaacgttgt tcaattgact ttgccaagag tccaagaatt gccagaagat       240
gctgaagcta ctactgatgt tcatccagaa gatatccctt acttgaaaaa ggcttccgat       300
ggtttacaac cagaagttac tagattcttg gaacaacatt ccccagattg gatcatctac       360
gattatactc attactggtt gccatccatt gctgcttcat tgggtatttc tagagcccat       420
ttctctgtta ctactccatg ggctattgct tatatgggtc catctgctga tgctatgatt       480
aacggttctg atggtagaac taccgttgaa gatttgacta ctccaccaaa gtggtttcca       540
tttccaacaa aagtctgttg gagaaaacac gatttggcta gattggttcc atacaaagct       600
ccaggtattt ctgatggtta cagaatgggt atggttttga aaggttccga ttgcttgttg       660
tctaagtgct atcatgaatt cggtactcaa tggttgcctt tgttggaaac attgcatcaa       720
gttccagttg ttccagtagg tttgttgcca ccagaaattc caggtgacga aaaagacgaa       780
acttgggttt ccatcaaaaa gtggttggat ggtaagcaaa agggttctgt tgtttatgtt       840
gctttgggtt ccgaagcttt ggtttctcaa accgaagttg ttgaattggc tttgggtttg       900
gaattgtctg gtttgccatt tgtttgggct tacagaaaac ctaaaggtcc agctaagtct       960
gattctgttg aattgccaga tggtttcgtt gaaagaacta gagatagagg tttggtttgg      1020
acttcttggg ctccacaatt gagaattttg tctcatgaat ccgtctgtgg tttcttgact      1080
cattgtggtt ctggttctat cgttgaaggt ttgatgtttg gtcacccatt gattatgttg      1140
```

```
ccaatctttg gtgaccaacc attgaacgct agattattgg aagataagca agtcggtatc      1200
gaaatcccaa gaaatgaaga agatggttgc ttgaccaaag aatctgttgc tagatctttg      1260
agatccgttg tcgttgaaaa agaaggtgaa atctacaagg ctaacgctag agaattgtcc      1320
aagatctaca acgataccaa ggtcgaaaaa gaatacgttt cccaattcgt tgactacttg      1380
gaaaagaatg ctagagctgt tgccattgat catgaatctt ga                         1422
```

SEQ ID NO:90

```
atggaagctt ctagagcatc ttgtgttgct ttgtgtgttg tttgggtttc catcgttatt        60
actttggctt ggagagtttt gaattgggtc tggttaagac caaaaaagtt ggaaagatgc       120
ttgagagaac aaggtttgac tggtaactct tacagattgt tgttcggtga taccaaggac       180
ttgtctaaga tgttggaaca aactcaatcc aagcctatca agttgtctac ctctcatgat       240
attgctccaa gagttactcc attcttccat agaactgtta actccaacgg taagaactct       300
tttgtttgga tgggtccaat tccaagagtc catattatga accctgaaga tttgaaggac       360
gctttcaaca gacatgatga tttccataag accgtcaaga acccaattat gaagtctcca       420
ccaccaggta tagttggtat tgaaggtgaa caatgggcca aacatagaaa gattattaac       480
ccagccttcc acttggaaaa gttgaaaggt atggttccaa tcttctacca atcctgctct       540
gaaatgatta acaagtggga atccttggtt tccaaagaat cttcctgtga attggatgtc       600
tggccatatt tggaaaactt cacctccgat gttatttcca gagctgcttt tggttcttct       660
tacgaagaag gtagaaagat cttccaatta ttgagagaag aagccaaggt ttactccgtt       720
gctttgagat ctgtttacat tccaggttgg agattcttgc caactaagca aaacaaaaag       780
accaaagaaa tccacaacga aatcaagggt ttgttgaagg gtatcatcaa caagagagaa       840
gaagctatga aggctggtga agctacaaaa gatgatttgt tgggtatctt gatggaatcc       900
aacttcagag aaatccaaga acacggtaac aacaagaatg ccggtatgtc tattgaagat       960
gttatcggtg aatgcaagtt gttctacttt gctggtcaag aaactacctc cgttttgttg      1020
gtttggacca tgattttgtt gtcccaaaat caagattggc aagctagagc tagagaagaa      1080
gtcttgaaag ttttcggttc taacatccca acctacgaag aattgtctca cttgaaggtt      1140
gtcactatga tcttgttgga agtattgaga ttatacccat ccgttgttgc attgccaaga      1200
actactcata agaaaactca attgggtaaa ttgtccttgc cagctggtgt tgaagtttct      1260
ttgccaattt tgttagtcca ccacgacaaa gaattgtggg gtgaagatgc taatgaattc      1320
aagccagaaa gattctccga aggtgtttct aaagctacca agaacaagtt cacttacttg      1380
ccatttggtg gtggtccaag aatatgtatt ggtcaaaatt tcgctatggt cgaagctaaa      1440
ttggctttgg ctttgatctt gcaacatttc gctttcgaat tgtcaccatc ttatgctcat      1500
gctccatctg ctgttattac attgcaacca caatttggtg cccatatcat cttgcataag      1560
agataac                                                               1567
```

SEQ ID NO:91

```
MEASRASCVA LCVVWVSIVI TLAWRVLNWV WLRPKKLERC LREQGLTGNS YRLLFGDTKD        60
LSKMLEQTQS KPIKLSTSHD IAPRVTPFFH RTVNSNGKNS FVWMGPIPRV HIMNPEDLKD       120
AFNRHDDFHK TVKNPIMKSP PPGIVGIEGE QWAKHRKIIN PAFHLEKLKG MVPIFYQSCS       180
EMINKWESLV SKESSCELDV WPYLENFTSD VISRAAFGSS YEEGRKIFQL LREEAKVYSV       240
ALRSVYIPGW RFLPTKQNKK TKEIHNEIKG LLKGIINKRE EAMKAGEATK DDLLGILMES       300
NFREIQEHGN NKNAGMSIED VIGECKLFYF AGQETTSVLL VWTMILLSQN QDWQARAREE       360
VLKVFGSNIP TYEELSHLKV VTMILLEVLR LYPSVVALPR TTHKKTQLGK LSLPAGVEVS       420
LPILLVHHDK ELWGEDANEF KPERFSEGVS KATKNKFTYL PFGGGPRICI GQNFAMVEAK       480
LALALILQHF AFELSPSYAH APSAVITLQP QFGAHIILHK R                          521
```

SEQ ID NO:92

```
ASWVAVLSVV WVSMVIAWAW RVLNWVWLRP KKLEKCLREQ GLAGNSYRLL FGDTKDLSKM        60
LEQTQSKPIK LSTSHDIAPH VTPFFHQTVN SYGKNSFVWM GPIPRVHIMN PEDLKDTFNR       120
HDDFHKVVKN PIMKSLPQGI VGIEGEQWAK HRKIINPAFH LEKLKGMVPI FYRSCSEMIN       180
KWESLVSKES SCELDVWPYL ENFTSDVISR AAFGSSYEEG RKIFQLLREE AKIYTVAMRS       240
VYIPGWRFLP TKQNKKAKEI HNEIKGLLKG IINKREEAMK AGEATKDDLL GILMESNFRE       300
IQEHGNNKNA GMSIEDVIGE CKLFYFAGQE TTSVLLVWTM VLLSQNQDWQ ARAREEVLQV       360
FGSNIPTYEE LSQLKVVTMI LLEVLRLYPS VVALPRTTHK KTQLGKLSLP AGVEVSLPIL       420
LVHHDKELWG EDANEFKPER FSEGVSKATK NQFTYFPFGG GPRICIGQNF AMMEAKLALS       480
LILRHFALEL SPLYAHAPSV TITLQPQYGA HIILHKR                                517
```

SEQ ID NO:93

```
MEASRPSCVA LSVVLVSIVI AWAWRVLNWV WLRPNKLERC LREQGLTGNS YRLLFGDTKE        60
ISMMVEQAQS KPIKLSTTHD IAPRVIPFSH QIVYTYGRNS FVWMGPTPRV TIMNPEDLKD       120
```

```
AFNKSDEFQR AISNPIVKSI SQGLSSLEGE KWAKHRKIIN PAFHLEKLKG MLPTFYQSCS       180
EMINKWESLV FKEGSREMDV WPYLENLTSD VISRAAFGSS YEEGRKIFQL LREEAKFYTI       240
AARSVYIPGW RFLPTKQNKR MKEIHKEVRG LLKGIINKRE DAIKAGEAAK GNLLGILMES       300
NFREIQEHGN NKNAGMSIED VIGECKLFYF AGQETTSVLL VWTLVLLSQN QDWQARAREE       360
VLQVFGTNIP TYDQLSHLKV VTMILLEVLR LYPAVVELPR TTYKKTQLGK FLLPAGVEVS       420
LHIMLAHHDK ELWGEDAKEF KPERFSEGVS KATKNQFTYF PFGAGPRICI GQNFAMLEAK       480
LALSLILQHF TFELSPSYAH APSVTITLHP QFGAHFILHK R                           521
```

SEQ ID NO:94

```
CVALSVVLVS IVIAWAWRVL NWVWLRPNKL ERCLREQGLT GNSYRLLFGD TKEISMMVEQ        60
AQSKPIKLST THDIAPRVIP FSHQIVYTYG RNSFVWMGPT PRVTIMNPED LKDAFNKSDE       120
FQRAISNPIV KSISQGLSSL EGEKWAKHRK IINPAFHLEK LKGMLPTFYQ SCSEMINKWE       180
SLVFKEGSRE MDVWPYLENL TSDVISRAAF GSSYEEGRKI FQLLREEAKF YTIAARSVYI       240
PGWRFLPTKQ NKRMKEIHKE VRGLLKGIIN KREDAIKAGE AAKGNLLGIL MESNFREIQE       300
HGNNKNAGMS IEDVIGECKL FYFAGQETTS VLLVWTLVLL SQNQDWQARA REEVLQVFGT       360
NIPTYDQLSH LKVVTMILLE VLRLYPAVVE LPRTTYKKTQ LGKFLLPAGV EVSLHIMLAH       420
HDKELWGEDA KEFKPERFSE GVSKATKNQF TYFPFGAGPR ICIGQNFAML EAKLALSLIL       480
QHFTFELSPS YAHAPSVTIT LHPQFGAHFI LHKR                                   514
```

SEQ ID NO:95

```
MGPIPRVHIM NPEDLKDTFN RHDDFHKVVK NPIMKSLPQG IVGIEGDQWA KHRKIINPAF        60
HLEKLKGMVP IFYQSCSEMI NIWKSLVSKE SSCELDVWPY LENFTSDVIS RAAFGSSYEE       120
GRKIFQLLRE EAKVYTVAVR SVYIPGWRFL PTKQNKKTKE IHNEIKGLLK GIINKREEAM       180
KAGEATKDDL LGILMESNFR EIQEHGNNKN AGMSIEDVIG ECKLFYFAGQ ETTSVLLVWT       240
MVLLSQNQDW QARAREEVLQ VFGSNIPTYE ELSHLKVVTM ILLEVLRLYP SVVALPRTTH       300
KKTQLGKLSL PAGVEVSLPI LLVHHDKELW GEDANEFKPE RFSEGVSKAT KNQFTYFPFG       360
GGPRICIGQN FAMMEAKLAL SLILQHFTFE LSPQYSHAPS VTITLQPQYG AHLILHKR         418
```

SEQ ID NO:96

```
atggaagcat caagggctag ttgtgttgcg ctatgtgttg tttgggtgag catagtaatt        60
acattggcat ggagggtgct gaattgggtg tggttgaggc caaagaaact agaaagatgc       120
ttgagggagc aaggccttac aggcaattct tacaggcttt tgtttggaga caccaaggat       180
ctctcgaaga tgctggaaca aacacaatcc aaacccatca aactctccac ctcccatgat       240
atagcgccac gagtcacccc atttttccat cgaactgtga actctaatgg caagaattct       300
tttgtttgga tgggccctat accaagagtg cacatcatga atccagaaga tttgaaagat       360
gccttcaaca gacatgatga ttttcataag acagtaaaaa atcctatcat gaagtctcca       420
ccaccgggca ttgtaggcat tgaaggtgag caatgggcta aacacagaaa gattatcaac       480
ccagcattcc atttagagaa gctaaagggt atggtaccaa tattttacca aagttgtagc       540
gagatgatta acaaatggga gagcttggtg tccaaagaga gttcatgtga gttggatgtg       600
tggccttatc ttgaaaattt taccagcgat gtgatttccc gagctgcatt tggaagtagc       660
tatgaagagg gaaggaaaat atttcaacta ctaagagagg aagcaaaagt ttattcggta       720
gctctacgaa gtgtttacat tccaggatgg aggtttctac caaccaagca gaacaagaag       780
acgaaggaaa ttcacaatga aattaaaggc ttacttaagg gcattataaa taaaagggaa       840
gaggcgatga aggcagggga agccactaaa gatgacttac taggaatact tatggagtcc       900
aacttcaggg aaattcagga acatgggaac aacaaaaatg ctggaatgag tattgaagat       960
gtaattggag agtgtaagtt gttttacttt gctgggcaag agaccacttc ggtgttgctt      1020
gtttggacaa tgattttact aagccaaaat caggattggc aagctcgtgc aagagaagag      1080
gtcttgaaag tctttggaag caacatccca acctatgaag agctaagtca cctaaaagtt      1140
gtgaccatga ttttacttga agttcttcga ttatacccat cagtcgttgc gcttcctcga      1200
accactcaca agaaaacaca gcttggaaaa ttatcattac cagctggagt ggaagtctcc      1260
ttgcccatac tgcttgttca ccatgacaaa gagttgtggg gtgaggatgc aaatgagttc      1320
aagccagaga ggttttcaga gggagtttca aaggcaacaa agaacaaatt tacatactta      1380
cctttcggag ggggtccaag gatttgcatt ggacaaaact ttgccatggt ggaagctaaa      1440
ttggccttgg ccctgatttt acaacacttt gcctttgagc tttctccatc ctatgctcat      1500
gctccttctg cagttataac ccttcaacct caatttggtg ctcatatcat tttgcataaa      1560
cgttga                                                                 1566
```

SEQ ID NO:97

```
atgtcctcca actccgattt ggtcagaaga ttggaatctg ttttgggtgt ttctttcggt        60
```

```
ggttctgtta ctgattccgt tgttgttatt gctaccacct ctattgcttt ggttatcggt       120
gttttggttt tgttgtggag aagatcctct gacagatcta gagaagttaa gcaattggct       180
gttccaaagc cagttactat cgttgaagaa gaagatgaat tcgaagttgc ttctggtaag       240
accagagttt ctatttttcta cggtactcaa actggtactg ctgaaggttt tgctaaggct      300
ttggctgaag aaatcaaagc cagatacgaa aaagctgccg ttaaggttat tgatttggat       360
gattacacag ccgaagatga caaatacggt gaaaagttga agaaagaaac tatggccttc       420
ttcatgttgg ctacttatgg tgatggtgaa cctactgata atgctgctag attttacaag       480
tggttcaccg aaggtactga tagaggtgtt tggttggaac atttgagata cggtgtattc       540
ggtttgggta acagacaata cgaacacttc aacaagattg ccaaggttgt tgatgatttg       600
ttggttgaac aaggtgccaa gagattggtt actgttggtt tgggtgatga tgatcaatgc       660
atcgaagatg atttctccgc ttggaaagaa gccttgtggc cagaattgga tcaattattg       720
caagatgata ccaacaccgt ttctactcca tacactgctg ttattccaga atacagagtt       780
gttatccacg atccatctgt tacctcttat gaagatccat actctaacat ggctaacggt       840
aatgcctctt acgatattca tcatccatgt agagctaacg ttgccgtcca aaaagaattg       900
cataagccag aatctgacag aagttgcatc catttggaat tcgatatttt cgctactggt       960
ttgacttacg aaaccggtga tcatgttggt gtttacgctg ataattgtga tgatactgta      1020
gaagaagccg ctaagttgtt gggtcaacca ttggatttgt tgttctccat tcataccgat      1080
aacaacgacg gtacttcttt gggttcttct ttgccaccac catttccagg tccatgtact      1140
ttgagaactg ctttggctag atatgccgat ttgttgaatc caccaaaaaa ggctgctttg      1200
attgctttag ctgctcatgc tgatgaacca tctgaagctg aaagattgaa gttcttgtca      1260
tctccacaag gtaaggacga atattctaaa tgggttgtcg gttcccaaag atccttggtt      1320
gaagttatgg ctgaatttcc atctgctaaa ccaccattgg gtgtattttt tgctgctgtt      1380
gttcctagat tgcaacctag atattactcc atctcttcca gtccaagatt tgctccacat      1440
agagttcatg ttacttgcgc tttggtttat ggtccaactc caactggtag aattcacaga      1500
ggtgtatgtt cattctggat gaagaatgtt gtcccattgg aaaagtctca aaactgttct      1560
tgggccccaa ttttcatcag acaatctaat ttcaagttgc cagccgatca ttctgttcca      1620
atagttatgg ttggtccagg tactggttta gctcctttta gaggtttctt acaagaaaga      1680
ttggccttga aagaagaagg tgctcaagtt ggtcctgctt tgttgttttt tggttgcaga      1740
aacagacaaa tggacttcat ctacgaagtc gaattgaaca actttgtcga acaaggtgct      1800
ttgtccgaat tgatcgttgc tttttcaaga gaaggtccat ccaaagaata cgtccaacat      1860
aagatggttg aaaaggcagc ttacatgtgg aacttgattt ctcaaggtgg ttacttctac      1920
gtttgtggtg atgctaaagg tatggctaga gatgttcata gaacattgca taccatcgtc      1980
caacaagaag aaaaggttga ttctaccaag gccgaatcca tcgttaagaa attgcaaatg      2040
gacggtagat acttgagaga tgtttggtga                                      2070
```

SEQ ID NO:98

```
MSSNSDLVRR LESVLGVSFG GSVTDSVVVI ATTSIALVIG VLVLLWRRSS DRSREVKQLA        60
VPKPVTIVEE EDEFEVASGK TRVSIFYGTQ TGTAEGFAKA LAEEIKARYE KAAVKVIDLD       120
DYTAEDDKYG EKLKKETMAF FMLATYGDGE PTDNAARFYK WFTEGTDRGV WLEHLRYGVF       180
GLGNRQYEHF NKIAKVVDDL LVEQGAKRLV TVGLGDDDQC IEDDFSAWKE ALWPELDQLL       240
QDDTNTVSTP YTAVIPEYRV VIHDPSVTSY EDPYSNMANG NASYDIHHPC RANVAVQKEL       300
HKPESDRSCI HLEFDIFATG LTYETGDHVG VYADNCDDTV EEAAKLLGQP LDLLFSIHTD       360
NNDGTSLGSS LPPPFPGPCT LRTALARYAD LLNPPKKAAL IALAAHADEP SEAERLKFLS       420
SPQGKDEYSK WVVGSQRSLV EVMAEFPSAK PPLGVFFAAV VPRLQPRYYS ISSSPRFAPH       480
RVHVTCALVY GPTPTGRIHR GVCSFWMKNV VPLEKSQNCS WAPIFIRQSN FKLPADHSVP       540
IVMVGPGTGL APFRGFLQER LALKEEGAQV GPALLFFGCR NRQMDFIYEV ELNNFVEQGA       600
LSELIVAFSR EGPSKEYVQH KMVEKAAYMW NLISQGGYFY VCGDAKGMAR DVHRTLHTIV       660
QQEEKVDSTK AESIVKKLQM DGRYLRDVW                                         689
```

SEQ ID NO:99

```
atggatgctg tgacgggttt gttaactgtc ccagcaaccg ctataactat tggtggaact        60
gctgtagcat tggcggtagc gctaatcttt tggtacctga aatcctacac atcagctaga       120
agatcccaat caaatcatct tccaagagtg cctgaagtcc caggtgttcc attgttagga       180
aatctgttac aattgaagga gaaaaagcca tacatgactt ttacgagatg ggcagcgaca       240
tatggaccta tctatagtat caaaactggg gctacaagta tggttgtggt atcatctaat       300
gagatagcca aggaggcatt ggtgaccaga ttccaatcca tatctacaag gaacttatct       360
aaagccctga aagtacttac agcagataag acaatggtcg caatgtcaga ttatgatgat       420
tatcataaaa cagttaagag acacatactg accgccgtct tgggtcctaa tgcacagaaa       480
aagcatagaa ttcacagaga tatcatgatg gataacatat ctactcaact tcatgaattc       540
gtgaaaaaca acccagaaca ggaagaggta gaccttagaa aaatctttca atctgagtta       600
ttcggcttag ctatgagaca agccttagga aaggatgttg aaagtttgta cgttgaagac       660
ctgaaaatca ctatgaatag agacgaaatc tttcaagtcc ttgttgttga tccaatgatg       720
ggagcaatcg atgttgattg gagagacttc tttccatacc taaagtgggt cccaaacaaa       780
```

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aagttcgaaa atactattca acaaatgtac atcagaagag aagctgttat gaaatcttta      840
atcaaagagc acaaaaagag aatagcgtca ggcgaaaagc taaatagtta tatcgattac      900
cttttatctg aagctcaaac tttaaccgat cagcaactat tgatgtcctt gtgggaacca      960
atcattgaat cttcagatac aacaatggtc acaacagaat gggcaatgta cgaattagct     1020
aaaaacccta aattgcaaga taggttgtac agagacatta agtccgtctg tggatctgaa     1080
aagataaccg aagagcatct atcacagctg ccttacatta cagctatttt ccacgaaaca     1140
ctgagaagac actcaccagt tcctatcatt cctctaagac atgtacatga agataccgtt     1200
ctaggcggct accatgttcc tgctggcaca gaacttgccg ttaacatcta cggttgcaac     1260
atggacaaaa acgtttggga aaatccagag gaatggaacc cagaaagatt catgaaagag     1320
aatgagacaa ttgattttca aaagacgatg gccttcggtg gtggtaagag agtttgtgct     1380
ggttccttgc aagccctttt aactgcatct attgggattg ggagaatggt tcaagagttc     1440
gaatggaaac tgaaggatat gactcaagag gaagtgaaca cgataggcct aactacacaa     1500
atgttaagac cattgagagc tattatcaaa cctaggatcc catcaagacc aagtcctagt     1560
accgaacaat ctgcaaaaaa agttagaaaa aaagcagaaa atgcacacaa tactccattg     1620
ctagttcttt atggttctaa tatgggaaca gcggaaggaa cggccaggga tctagctgac     1680
atagctatgt ccaagggatt tgccccgcaa gtagcaaccc tggattccca tgcaggtaac     1740
ttgccaagag aaggtgctgt tctaatagtt accgctagct acaatgggca cctccagat      1800
aatgcgaagc agttcgtcga ttggttagat caagcatcag cagatgaagt taagggtgtt     1860
agatactctg tttttggatg tggagataag aattgggcca ccacatatca gaaggttccg     1920
gctttcatcg atgaaatgct tgctgcaaaa ggggctgaaa atatagcaga tcgtggtgag     1980
gccgacgcaa gcgacgattt tgagggtacc tatgaggagt ggagagagca catgtggtct     2040
gatgttgccg cgtattttaa tctagacata gaaaattctg aagacaataa aagtgcctta     2100
cttcttcaat tcgtcgatag tgctgcggac atgcccttag caaagatgca tggagccttt     2160
tcaacgaacg tagtagccag taaggaactt caacaaccag gtagtgccag aagtacacgt     2220
cacttggaaa ttgaattacc aaaagaggca tcctaccaag aaggtgacca tcttggtgta     2280
atcccaagaa actacgaagg tatagtcaat agggtaacgg caagatttgg gctggatgca     2340
agccaacaga taagactaga agcagaagaa gaaaaattgg cgcaccttcc actagcgaag     2400
acagtatccg ttgaagaatt attgcaatac gtggaattgc aggatcccgt cactagaacg     2460
caattgagag ctatggcagc aaagactgtt tgtccacctc acaaggttga acttgaagct     2520
ctacttgaaa aacaagcata caaagagcaa gtgctagcaa agagactaac catgttagaa     2580
ttgctggaaa aatacccggc atgcgaaatg gaattctccg aatttatcgc gttgttgcca     2640
agtattcgtc ccaggtatta ctcaatttca tcttcaccaa gggttgacga gaaacaggca     2700
tctattaccg tatctgtggt ctctggagaa gcttggagtg gttacggaga atacaagggt     2760
attgcttcca attatcttgc agaactgcag gaaggggata caattacctg ctttatttct     2820
actcctcaat cagaatttac tcttccgaag gatccagaaa ctccgttaat tatggtaggt     2880
ccgggaacag gagtcgcccc tttcagaggc tttgtgcaag caaggaagca actaaaagaa     2940
cagggacaaa gtctgggtga ggcacatcta tatttcggtt gcagatctcc gcatgaggat     3000
tacttatacc aagaagaact tgaaaacgcc caatcagaag gtattatcac cttgcatact     3060
gcattcagta gaatgccaaa ccagccgaaa acttacgtac agcatgttat ggagcaagat     3120
ggtaagaagt taattgagct tttggataag ggcgcccact tctacatttg cggcgacgga     3180
tcccaaatgg cgcctgccgt tgaagccacc ttgatgaaat catatgcaga tgttcatcaa     3240
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aaagatgttt ggtaa                                                     3315
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SEQ ID NO:100

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NLLQLKEKKP YMTFTRWAAT YGPIYSIKTG ATSMVVVSSN EIAKEALVTR FQSISTRNLS      120
KALKVLTADK TMVAMSDYDD YHKTVKRHIL TAVLGPNAQK KHRIHRDIMM DNISTQLHEF      180
VKNNPEQEEV DLRKIFQSEL FGLAMRQALG KDVESLYVED LKITMNRDEI FQVLVVDPMM      240
GAIDVDWRDF FPYLKWVPNK KFENTIQQMY IRREAVMKSL IKEHKKRIAS GEKLNSYIDY      300
LLSEAQTLTD QQLLMSLWEP IIESSDTTMV TTEWAMYELA KNPKLQDRLY RDIKSVCGSE      360
KITEEHLSQL PYITAIFHET LRRHSPVPII PLRHVHEDTV LGGYHVPAGT ELAVNIYGCN      420
MDKNVWENPE EWNPERFMKE NETIDFQKTM AFGGGKRVCA GSLQALLTAS IGIGRMVQEF      480
EWKLKDMTQE EVNTIGLTTQ MLRPLRAIIK PRIPSRPSPS TEQSAKKVRK KAENAHNTPL      540
LVLYGSNMGT AEGTARDLAD IAMSKGFAPQ VATLDSHAGN LPREGAVLIV TASYNGHPPD      600
NAKQFVDWLD QASADEVKGV RYSVFGCGDK NWATTYQKVP AFIDEMLAAK GAENIADRGE      660
ADASDDFEGT YEEWREHMWS DVAAYFNLDI ENSEDNKSAL LLQFVDSAAD MPLAKMHGAF      720
STNVVASKEL QQPGSARSTR HLEIELPKEA SYQEGDHLGV IPRNYEGIVN RVTARFGLDA      780
SQQIRLEAEE EKLAHLPLAK TVSVEELLQY VELQDPVTRT QLRAMAAKTV CPPHKVELEA      840
LLEKQAYKEQ VLAKRLTMLE LLEKYPACEM EFSEFIALLP SIRPRYYSIS SSPRVDEKQA      900
SITVSVVSGE AWSGYGEYKG IASNYLAELQ EGDTITCFIS TPQSEFTLPK DPETPLIMVG      960
PGTGVAPFRG FVQARKQLKE QGQSLGEAHL YFGCRSPHED YLYQEELENA QSEGIITLHT     1020
AFSRMPNQPK TYVQHVMEQD GKKLIELLDK GAHFYICGDG SQMAPAVEAT LMKSYADVHQ     1080
VSEADARLWL QQLEEKGRYA KDVW                                            1104
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SEQ ID NO:101

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atggatgctg tgacgggttt gttaactgtc ccagcaaccg ctataactat tggtggaact      60
gctgtagcat tggcggtagc gctaatcttt tggtacctga aatcctacac atcagctaga     120
agatcccaat caaatcatct tccaagagtg cctgaagtcc caggtgttcc attgttagga     180
aatctgttac aattgaagga gaaaaagcca tacatgactt ttacgagatg ggcagcgaca     240
tatggaccta tctatagtat caaaactggg gctacaagta tggttgtggt atcatctaat     300
gagatagcca aggaggcatt ggtgaccaga ttccaatcca tatctacaag gaacttatct     360
aaagccctga aagtacttac agcagataag acaatggtcg caatgtcaga ttatgatgat     420
tatcataaaa cagttaagag acacatactg accgccgtct tgggtcctaa tgcacagaaa     480
aagcatagaa ttcacagaga tatcatgatg gataacatat ctactcaact tcatgaattc     540
gtgaaaaaca acccagaaca ggaagaggta gaccttagaa aaatctttca atctgagtta     600
ttcggcttag ctatgagaca agccttagga aaggatgttg aaagtttgta cgttgaagac     660
ctgaaaatca ctatgaatag agacgaaatc tttcaagtcc ttgttgttga tccaatgatg     720
ggagcaatcg atgttgattg gagagacttc tttccatacc taaagtgggt cccaaacaaa     780
aagttcgaaa atactattca acaaatgtac atcagaagag aagctgttat gaaatcttta     840
atcaaagagc acaaaaagag aatagcgtca ggcgaaaagc taaatagtta tatcgattac     900
cttttatctg aagctcaaac tttaaccgat cagcaactat tgatgtcctt gtgggaacca     960
atcattgaat cttcagatac aacaatggtc acaacagaat gggcaatgta cgaattagct    1020
aaaaacccta aattgcaaga taggttgtac agagacatta agtccgtctg tggatctgaa    1080
aagataaccg aagagcatct atcacagctg ccttacatta cagctatttt ccacgaaaca    1140
ctgagaagac actcaccagt tcctatcatt cctctaagac atgtacatga agataccgtt    1200
ctaggcggct accatgttcc tgctggcaca gaacttgccg ttaacatcta cggttgcaac    1260
atggacaaaa acgtttggga aaatccagag gaatggaacc cagaaagatt catgaaagag    1320
aatgagacaa ttgattttca aaagacgatg gccttcggtg gtggtaagag agtttgtgct    1380
ggttccttgc aagccctttt aactgcatct attgggattg ggagaatggt tcaagagttc    1440
gaatggaaac tgaaggatat gactcaagag gaagtgaaca cgataggcct aactacacaa    1500
atgttaagac cattgagagc tattatcaaa cctaggatcc catcaagacc aagtcctagt    1560
accgaacaat ctgcaaaaaa agttagaaaa aaagcagaaa atgcacacaa tactccattg    1620
ctagttcttt atggttctaa tatgggaaca gcggaaggaa cggccaggga tctagctgac    1680
atagctatgt ccaagggatt tgccccgcaa gtagcaaccc tggattccca tgcaggtaac    1740
ttgccaagag aaggtgctgt tctaatagtt accgctagct acaatgggca ccctccagat    1800
aatgcgaagc agttcgtcga ttggttagat caagcatcag cagatgaagt taagggtgtt    1860
agatactctg tttttggatg tggagataag aattgggcca ccacatatca gaaggttccg    1920
gctttcatcg atgaaatgct tgctgcaaaa ggggctgaaa atatagcaga tcgtggtgag    1980
gccgacgcaa gcgacgattt tgagggtacc tatgaggagt ggagagagca catgtggtct    2040
gatgttgccg cgtattttaa tctagacata gaaaattctg aagacaataa aagtgcctta    2100
cttcttcaat tcgtcgatag tgctgcggac atgcccttag caaagatgca tggagccttt    2160
tcaacgaacg tagtagccag taaggaactt caacaaccag gtagtgccag aagtacacgt    2220
cacttggaaa ttgaattacc aaaagaggca tcctaccaag aaggtgacca tcttggtgta    2280
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agccaacaga taagactaga agcagaagaa gaaaaattgg cgcaccttcc actagcgaag    2400
acagtatccg ttgaagaatt attgcaatac gtggaattgc aggatcccgt cactagaacg    2460
caattgagag ctatggcagc aaagactgtt tgtccacctc acaaggttga acttgaagct    2520
ctacttgaaa aacaagcata caaagagcaa gtgctagcaa agagactaac catgttagaa    2580
ttgctggaaa aatacccggc atgcgaaatg gaattctccg aatttatcgc gttgttgcca    2640
agtattcgtc ccaggtatta ctcaatttca tcttcaccaa gggttgacga gaaacaggca    2700
tctattaccg tatctgtggt ctctggagaa gcttggagtg gttacggaga atacaagggt    2760
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ccgggaacag gagtcgcccc tttcagaggc tttgtgcaag caaggaagca actaaaagaa    2940
cagggacaaa gtctgggtga ggcacatcta tatttcggtt gcagatctcc gcatgaggat    3000
tacttatacc aagaagaact tgaaaacgcc caatcagaag gtattatcac cttgcatact    3060
gcattcagta gaatgccaaa ccagccgaaa acttacgtac agcatgttat ggagcaagat    3120
ggtaagaagt taattgagct tttggataag ggcgcccact tctacatttg cggcgacgga    3180
tcccaaatgg cgcctgccgt tgaagccacc ttgatgaaat catatgcaga tgttcatcaa    3240
gtttcagaag cggacgcccg tctttggtta caacaactag aggagaaagg aaggtatgca    3300
aaagatgttg cttaa                                                    3315
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SEQ ID NO:102

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NLLQLKEKKP YMTFTRWAAT YGPIYSIKTG ATSMVVVSSN EIAKEALVTR FQSISTRNLS     120
KALKVLTADK TMVAMSDYDD YHKTVKRHIL TAVLGPNAQK KHRIHRDIMM DNISTQLHEF     180
VKNNPEQEEV DLRKIFQSEL FGLAMRQALG KDVESLYVED LKITMNRDEI FQVLVVDPMM     240
```

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GAIDVDWRDF FPYLKWVPNK KFENTIQQMY IRREAVMKSL IKEHKKRIAS GEKLNSYIDY      300
LLSEAQTLTD QQLLMSLWEP IIESSDTTMV TTEWAMYELA KNPKLQDRLY RDIKSVCGSE      360
KITEEHLSQL PYITAIFHET LRRHSPVPII PLRHVHEDTV LGGYHVPAGT ELAVNIYGCN      420
MDKNVWENPE EWNPERFMKE NETIDFQKTM AFGGGKRVCA GSLQALLTAS IGIGRMVQEF      480
EWKLKDMTQE EVNTIGLTTQ MLRPLRAIIK PRIPSRPSPS TEQSAKKVRK KAENAHNTPL      540
LVLYGSNMGT AEGTARDLAD IAMSKGFAPQ VATLDSHAGN LPREGAVLIV TASYNGHPPD      600
NAKQFVDWLD QASADEVKGV RYSVFGCGDK NWATTYQKVP AFIDEMLAAK GAENIADRGE      660
ADASDDFEGT YEEWREHMWS DVAAYFNLDI ENSEDNKSAL LLQFVDSAAD MPLAKMHGAF      720
STNVVASKEL QQPGSARSTR HLEIELPKEA SYQEGDHLGV IPRNYEGIVN RVTARFGLDA      780
SQQIRLEAEE EKLAHLPLAK TVSVEELLQY VELQDPVTRT QLRAMAAKTV CPPHKVELEA      840
LLEKQAYKEQ VLAKRLTMLE LLEKYPACEM EFSEFIALLP SIRPRYYSIS SSPRVDEKQA      900
SITVSVVSGE AWSGYGEYKG IASNYLAELQ EGDTITCFIS TPQSEFTLPK DPETPLIMVG      960
PGTGVAPFRG FVQARKQLKE QGQSLGEAHL YFGCRSPHED YLYQEELENA QSEGIITLHT     1020
AFSRMPNQPK TYVQHVMEQD GKKLIELLDK GAHFYICGDG SQMAPAVEAT LMKSYADVHQ     1080
VSEADARLWL QQLEEKGRYA KDVA                                            1104
```

SEQ ID NO:103

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atcaaaactg gggctacaag tatggttgtg gtatcatcta atgagatagc caaggaggca      180
ttggtgacca gattccaatc catatctaca aggaacttat ctaaagccct gaaagtactt      240
acagcagata agacaatggt cgcaatgtca gattatgatg attatcataa aacagttaag      300
agacacatac tgaccgccgt cttgggtcct aatgcacaga aaaagcatag aattcacaga      360
gatatcatga tggataacat atctactcaa cttcatgaat tcgtgaaaaa caacccagaa      420
caggaagagg tagaccttag aaaaatcttt caatctgagt tattcggctt agctatgaga      480
caagccttag gaaaggatgt tgaaagtttg tacgttgaag acctgaaaat cactatgaat      540
agagacgaaa tctttcaagt ccttgttgtt gatccaatga tgggagcaat cgatgttgat      600
tggagagact tctttccata cctaaagtgg gtcccaaaca aaaagttcga aaatactatt      660
caacaaatgt acatcagaag agaagctgtt atgaaatctt taatcaaaga gcacaaaaag      720
agaatagcgt caggcgaaaa gctaaatagt tatatcgatt acctttttatc tgaagctcaa      780
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acaacaatgg tcacaacaga atgggcaatg tacgaattag ctaaaaaccc taaattgcaa      900
gataggttgt acagagacat taagtccgtc tgtggatctg aaaagataac cgaagagcat      960
ctatcacagc tgccttacat tacagctatt ttccacgaaa cactgagaag acactcacca     1020
gttcctatca ttcctctaag acatgtacat gaagataccg ttctaggcgg ctaccatgtt     1080
cctgctggca cagaacttgc cgttaacatc tacggttgca acatggacaa aaacgtttgg     1140
gaaaatccag aggaatggaa cccagaaaga ttcatgaaag agaatgagac aattgatttt     1200
caaaagacga tggccttcgg tggtggtaag agagtttgtg ctggttcctt gcaagccctt     1260
ttaactgcat ctattgggat tgggagaatg gttcaagagt tcgaatggaa actgaaggat     1320
atgactcaag aggaagtgaa cacgataggc ctaactacac aaatgttaag accattgaga     1380
gctattatca aacctaggat cccatcaaga ccaagtccta gtaccgaaca atctgcaaaa     1440
aaagttagaa aaaaagcaga aaatgcacac aatactccat tgctagttct ttatggttct     1500
aatatgggaa cagcggaagg aacggccagg gatctagctg acatagctat gtccaaggga     1560
tttgccccgc aagtagcaac cctggattcc catgcaggta acttgccaag agaaggtgct     1620
gttctaatag ttaccgctag ctacaatggg caccctccag ataatgcgaa gcagttcgtc     1680
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tgtggagata agaattgggc caccacatat cagaaggttc cggctttcat cgatgaaatg     1800
cttgctgcaa aaggggctga aaatatagca gatcgtggtg aggccgacgc aagcgacgat     1860
tttgagggta cctatgagga gtggagagag cacatgtggt ctgatgttgc cgcgtatttt     1920
aatctagaca tagaaaattc tgaagacaat aaaagtgcct tacttcttca attcgtcgat     1980
agtgctgcgg acatgccctt agcaaagatg catggagcct tttcaacgaa cgtagtagcc     2040
agtaaggaac ttcaacaacc aggtagtgcc agaagtacac gtcacttgga aattgaatta     2100
ccaaaagagg catcctacca agaaggtgac catcttggtg taatcccaag aaactacgaa     2160
ggtatagtca atagggtaac ggcaagattt gggctggatg caagccaaca gataagacta     2220
gaagcagaag aagaaaaatt ggcgcacctt ccactagcga agacagtatc cgttgaagaa     2280
ttattgcaat acgtggaatt gcaggatccc gtcactagaa cgcaattgag agctatggca     2340
gcaaagactg tttgtccacc tcacaaggtt gaacttgaag ctctacttga aaaacaagca     2400
tacaaagagc aagtgctagc aaagagacta accatgttag aattgctgga aaaatacccg     2460
gcatgcgaaa tggaattctc cgaatttatc gcgttgttgc caagtattcg tcccaggtat     2520
tactcaattt catcttcacc aagggttgac gagaaacagg catctattac cgtatctgtg     2580
gtctctggag aagcttggag tggttacgga gaatacaagg gtattgcttc caattatctt     2640
gcagaactgc aggaagggga tacaattacc tgctttattt ctactcctca atcagaattt     2700
actcttccga aggatccaga aactccgtta attatggtag gtccgggaac aggagtcgcc     2760
cctttcagag gctttgtgca agcaaggaag caactaaaag aacagggaca aagtctgggt     2820
gaggcacatc tatatttcgg ttgcagatct ccgcatgagg attacttata ccaagaagaa     2880
```

```
cttgaaaacg cccaatcaga aggtattatc accttgcata ctgcattcag tagaatgcca      2940
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cttttggata agggcgccca cttctacatt tgcggcgacg gatcccaaat ggcgcctgcc      3060
gttgaagcca ccttgatgaa atcatatgca gatgttcatc aagtttcaga agcggacgcc      3120
cgtctttggt tacaacaact agaggagaaa ggaaggtatg caaaagatgt ttggtaa         3177
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SEQ ID NO:104

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MPRVPEVPGV PLLGNLLQLK EKKPYMTFTR WAATYGPIYS IKTGATSMVV VSSNEIAKEA        60
LVTRFQSIST RNLSKALKVL TADKTMVAMS DYDDYHKTVK RHILTAVLGP NAQKKHRIHR       120
DIMMDNISTQ LHEFVKNNPE QEEVDLRKIF QSELFGLAMR QALGKDVESL YVEDLKITMN       180
RDEIFQVLVV DPMMGAIDVD WRDFFPYLKW VPNKKFENTI QQMYIRREAV MKSLIKEHKK       240
RIASGEKLNS YIDYLLSEAQ TLTDQQLLMS LWEPIIESSD TTMVTTEWAM YELAKNPKLQ       300
DRLYRDIKSV CGSEKITEEH LSQLPYITAI FHETLRRHSP VPIIPLRHVH EDTVLGGYHV       360
PAGTELAVNI YGCNMDKNVW ENPEEWNPER FMKENETIDF QKTMAFGGGK RVCAGSLQAL       420
LTASIGIGRM VQEFEWKLKD MTQEEVNTIG LTTQMLRPLR AIIKPRIPSR PSPSTEQSAK       480
KVRKKAENAH NTPLLVLYGS NMGTAEGTAR DLADIAMSKG FAPQVATLDS HAGNLPREGA       540
VLIVTASYNG HPPDNAKQFV DWLDQASADE VKGVRYSVFG CGDKNWATTY QKVPAFIDEM       600
LAAKGAENIA DRGEADASDD FEGTYEEWRE HMWSDVAAYF NLDIENSEDN KSALLLQFVD       660
SAADMPLAKM HGAFSTNVVA SKELQQPGSA RSTRHLEIEL PKEASYQEGD HLGVIPRNYE       720
GIVNRVTARF GLDASQQIRL EAEEEKLAHL PLAKTVSVEE LLQYVELQDP VTRTQLRAMA       780
AKTVCPPHKV ELEALLEKQA YKEQVLAKRL TMLELLEKYP ACEMEFSEFI ALLPSIRPRY       840
YSISSSPRVD EKQASITVSV VSGEAWSGYG EYKGIASNYL AELQEGDTIT CFISTPQSEF       900
TLPKDPETPL IMVGPGTGVA PFRGFVQARK QLKEQGQSLG EAHLYFGCRS PHEDYLYQEE       960
LENAQSEGII TLHTAFSRMP NQPKTYVQHV MEQDGKKLIE LLDKGAHFYI CGDGSQMAPA      1020
VEATLMKSYA DVHQVSEADA RLWLQQLEEK GRYAKDVW                              1058
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SEQ ID NO:105

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atgccaagag tgcctgaagt cccaggtgtt ccattgttag gaaatctgtt acaattgaag        60
gagaaaaagc catacatgac ttttacgaga tgggcagcga catatggacc tatctatagt       120
atcaaaactg gggctacaag tatggttgtg gtatcatcta atgagatagc caaggaggca       180
ttggtgacca gattccaatc catatctaca aggaacttat ctaaagccct gaaagtactt       240
acagcagata agacaatggt cgcaatgtca gattatgatg attatcataa aacagttaag       300
agacacatac tgaccgccgt cttgggtcct aatgcacaga aaaagcatag aattcacaga       360
gatatcatga tggataacat atctactcaa cttcatgaat tcgtgaaaaa caacccagaa       420
caggaagagg tagaccttag aaaaatcttt caatctgagt tattcggctt agctatgaga       480
caagccttag gaaaggatgt tgaaagtttg tacgttgaag acctgaaaat cactatgaat       540
agagacgaaa tctttcaagt ccttgttgtt gatccaatga tgggagcaat cgatgttgat       600
tggagagact tctttccata cctaaagtgg gtcccaaaca aaaagttcga aaatactatt       660
caacaaatgt acatcagaag agaagctgtt atgaaatctt taatcaaaga gcacaaaaag       720
agaatagcgt caggcgaaaa gctaaatagt tatatcgatt acctttttatc tgaagctcaa       780
actttaaccg atcagcaact attgatgtcc ttgtgggaac caatcattga atcttcagat       840
acaacaatgg tcacaacaga atgggcaatg tacgaattag ctaaaaaccc taaattgcaa       900
gataggttgt acagagacat taagtccgtc tgtggatctg aaaagataac cgaagagcat       960
ctatcacagc tgccttacat tacagctatt ttccacgaaa cactgagaag acactcacca      1020
gttcctatca ttcctctaag acatgtacat gaagataccg ttctaggcgg ctaccatgtt      1080
cctgctggca cagaacttgc cgttaacatc tacggttgca acatggacaa aaacgtttgg      1140
gaaaatccag aggaatggaa cccagaaaga ttcatgaaag agaatgagac aattgatttt      1200
caaaagacga tggccttcgg tggtggtaag agagtttgtg ctggttcctt gcaagccctt      1260
ttaactgcat ctattgggat tgggagaatg gttcaagagt tcgaatggaa actgaaggat      1320
atgactcaag aggaagtgaa cacgataggc ctaactacac aaatgttaag accattgaga      1380
gctattatca aacctaggat cccatcaaga ccaagtccta gtaccgaaca atctgcaaaa      1440
aaagttagaa aaaaagcaga aaatgcacac aatactccat tgctagttct ttatggttct      1500
aatatgggaa cagcggaagg aacggccagg gatctagctg acatagctat gtccaaggga      1560
tttgccccgc aagtagcaac cctggattcc catgcaggta acttgccaag agaaggtgct      1620
gttctaatag ttaccgctag ctacaatggg caccctccag ataatgcgaa gcagttcgtc      1680
gattggttag atcaagcatc agcagatgaa gttaagggtg ttagatactc tgtttttgga      1740
tgtggagata agaattgggc caccacatat cagaaggttc cggctttcat cgatgaaatg      1800
cttgctgcaa aaggggctga aaatatagca gatcgtggtg aggccgacgc aagcgacgat      1860
tttgagggta cctatgagga gtggagagag cacatgtggt ctgatgttgc cgcgtatttt      1920
aatctagaca tagaaaattc tgaagacaat aaaagtgcct tacttcttca attcgtcgat      1980
agtgctgcgg acatgccctt agcaaagatg catggagcct tttcaacgaa cgtagtagcc      2040
agtaaggaac ttcaacaacc aggtagtgcc agaagtacac gtcacttgga aattgaatta      2100
ccaaaagagg catcctacca agaaggtgac catcttggtg taatcccaag aaactacgaa      2160
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ggtatagtca atagggtaac ggcaagattt gggctggatg caagccaaca gataagacta      2220
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ttattgcaat acgtggaatt gcaggatccc gtcactagaa cgcaattgag agctatggca      2340
gcaaagactg tttgtccacc tcacaaggtt gaacttgaag ctctacttga aaaacaagca      2400
tacaaagagc aagtgctagc aaagagacta accatgttag aattgctgga aaaatacccg      2460
gcatgcgaaa tggaattctc cgaatttatc gcgttgttgc caagtattcg tcccaggtat      2520
tactcaattt catcttcacc aagggttgac gagaaacagg catctattac cgtatctgtg      2580
gtctctggag aagcttggag tggttacgga gaatacaagg gtattgcttc caattatctt      2640
gcagaactgc aggaagggga tacaattacc tgctttattt ctactcctca atcagaattt      2700
actcttccga aggatccaga aactccgtta attatggtag gtccgggaac aggagtcgcc      2760
cctttcagag gctttgtgca agcaaggaag caactaaaag aacagggaca aagtctgggt      2820
gaggcacatc tatatttcgg ttgcagatct ccgcatgagg attacttata ccaagaagaa      2880
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aaccagccga aaacttacgt acagcatgtt atggagcaag atggtaagaa gttaattgag      3000
cttttggata agggcgccca cttctacatt tgcggcgacg gatcccaaat ggcgcctgcc      3060
gttgaagcca ccttgatgaa atcatatgca gatgttcatc aagtttcaga agcggacgcc      3120
cgtctttggt tacaacaact agaggagaaa ggaaggtatg caaaagatgt tgcttaa         3177
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SEQ ID NO:106

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DIMMDNISTQ LHEFVKNNPE QEEVDLRKIF QSELFGLAMR QALGKDVESL YVEDLKITMN       180
RDEIFQVLVV DPMMGAIDVD WRDFFPYLKW VPNKKFENTI QQMYIRREAV MKSLIKEHKK       240
RIASGEKLNS YIDYLLSEAQ TLTDQQLLMS LWEPIIESSD TTMVTTEWAM YELAKNPKLQ       300
DRLYRDIKSV CGSEKITEEH LSQLPYITAI FHETLRRHSP VPIIPLRHVH EDTVLGGYHV       360
PAGTELAVNI YGCNMDKNVW ENPEEWNPER FMKENETIDF QKTMAFGGGK RVCAGSLQAL       420
LTASIGIGRM VQEFEWKLKD MTQEEVNTIG LTTQMLRPLR AIIKPRIPSR PSPSTEQSAK       480
KVRKKAENAH NTPLLVLYGS NMGTAEGTAR DLADIAMSKG FAPQVATLDS HAGNLPREGA       540
VLIVTASYNG HPPDNAKQFV DWLDQASADE VKGVRYSVFG CGDKNWATTY QKVPAFIDEM       600
LAAKGAENIA DRGEADASDD FEGTYEEWRE HMWSDVAAYF NLDIENSEDN KSALLLQFVD       660
SAADMPLAKM HGAFSTNVVA SKELQQPGSA RSTRHLEIEL PKEASYQEGD HLGVIPRNYE       720
GIVNRVTARF GLDASQQIRL EAEEEKLAHL PLAKTVSVEE LLQYVELQDP VTRTQLRAMA       780
AKTVCPPHKV ELEALLEKQA YKEQVLAKRL TMLELLEKYP ACEMEFSEFI ALLPSIRPRY       840
YSISSSPRVD EKQASITVSV VSGEAWSGYG EYKGIASNYL AELQEGDTIT CFISTPQSEF       900
TLPKDPETPL IMVGPGTGVA PFRGFVQARK QLKEQGQSLG EAHLYFGCRS PHEDYLYQEE       960
LENAQSEGII TLHTAFSRMP NQPKTYVQHV MEQDGKKLIE LLDKGAHFYI CGDGSQMAPA      1020
VEATLMKSYA DVHQVSEADA RLWLQQLEEK GRYAKDVA                              1058
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SEQ ID NO:107

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caattgaaag aaaagaagcc ataccaaacc ttcactagat gggctgaaga atatggtcca       240
atctactcta ttagaactgg tgcttctact atggttgtct tgaacactac tcaagttgcc       300
aaagaagcta tggttaccag atacttgtct atctctacca gaaagttgtc caacgccttg       360
aaaattttga ccgctgataa gtgcatggtt gccatttctg attacaacga tttccacaag       420
atgatcaaga gatatatctt gtctaacgtt ttgggtccat ctgcccaaaa aagacataga       480
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tctccaagag aagctgtcaa ctttagaaga gttttcgaat gggaattatt cggtatcgct       600
ttgaaacaag ccttcggtaa ggatattgaa aagccaatct acgtcgaaga attgggtact       660
actttgtcca gagatgaaat cttcaaggtt ttggtcttgg acattatgga aggtgccatt       720
gaagttgatt ggagagattt tttcccatac ttgcgttgga ttcccaaacac cagaatggaa       780
actaagatcc aaagattata ctttagaaga aaggccgtta tgaccgcctt gattaacgaa       840
caaaagaaaa gaattgcctc cggtgaagaa atcaactgct acatcgattt cttgttgaaa       900
gaaggtaaga ccttgaccat ggaccaaatc tctatgttgt tgtgggaaac cgttattgaa       960
actgctgata ccacaatggt tactactgaa tgggctatgt acgaagttgc taaggattct      1020
aaaagacaag acagattata ccaagaaatc caaaaggtct gcggttctga aatggttaca      1080
gaagaatact tgtcccaatt gccatacttg aatgctgttt tccacgaaac tttgagaaaa      1140
cattctccag ctgctttggt tccattgaga tatgctcatg aagatactca attgggtggt      1200
tattacattc cagccggtac tgaaattgcc attaacatct acggttgcaa catggacaaa      1260
caccaatggg aatctccaga agaatggaag ccagaaagat ttttggatcc taagtttgac      1320
ccaatggact tgtacaaaac tatggctttt ggtgctggta aaagagtttg cgctggttct      1380
ttacaagcta tgttgattgc ttgtccaacc atcggtagat tggttcaaga atttgaatgg      1440
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aagttgagag atggtgaaga agaaaacgtt gatactgttg gtttgaccac ccataagaga      1500
tatccaatgc atgctatttt gaagccaaga tctccatcaa gaccaagtcc tagtaccgaa      1560
caatctgcaa aaaaagttag aaaaaaagca gaaaatgcac acaatactcc attgctagtt      1620
ctttatggtt ctaatatggg aacagcggaa ggaacggcca gggatctagc tgacatagct      1680
atgtccaagg gatttgcccc gcaagtagca accctggatt cccatgcagg taacttgcca      1740
agagaaggtg ctgttctaat agttaccgct agctacaatg ggcaccctcc agataatgcg      1800
aagcagttcg tcgattggtt agatcaagca tcagcagatg aagttaaggg tgttagatac      1860
tctgtttttg gatgtggaga taagaattgg gccaccacat atcagaaggt tccggctttc      1920
atcgatgaaa tgcttgctgc aaaaggggct gaaaatatag cagatcgtgg tgaggccgac      1980
gcaagcgacg attttgaggg tacctatgag gagtggagag agcacatgtg gtctgatgtt      2040
gccgcgtatt ttaatctaga catagaaaat tctgaagaca ataaaagtgc cttacttctt      2100
caattcgtcg atagtgctgc ggacatgccc ttagcaaaga tgcatggagc cttttcaacg      2160
aacgtagtag ccagtaagga acttcaacaa ccaggtagtg ccagaagtac acgtcacttg      2220
gaaattgaat taccaaaaga ggcatcctac caagaaggtg accatcttgg tgtaatccca      2280
agaaactacg aaggtatagt caatagggta acggcaagat ttgggctgga tgcaagccaa      2340
cagataagac tagaagcaga agaagaaaaa ttggcgcacc ttccactagc gaagacagta      2400
tccgttgaag aattattgca atacgtggaa ttgcaggatc ccgtcactag aacgcaattg      2460
agagctatgg cagcaaagac tgtttgtcca cctcacaagg ttgaacttga agctctactt      2520
gaaaaacaag catacaaaga gcaagtgcta gcaaagagac taaccatgtt agaattgctg      2580
gaaaaatacc cggcatgcga aatggaattc tccgaattta tcgcgttgtt gccaagtatt      2640
cgtcccaggt attactcaat ttcatcttca ccaagggttg acgagaaaca ggcatctatt      2700
accgtatctg tggtctctgg agaagcttgg agtggttacg gagaatacaa gggtattgct      2760
tccaattatc ttgcagaact gcaggaaggg gatacaatta cctgctttat ttctactcct      2820
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acaggagtcg ccccttcag aggctttgtg caagcaagga agcaactaaa agaacaggga      2940
caaagtctgg gtgaggcaca tctatatttc ggttgcagat ctccgcatga ggattactta      3000
taccaagaag aacttgaaaa cgcccaatca gaaggtatta tcaccttgca tactgcattc      3060
agtagaatgc caaaccagcc gaaaacttac gtacagcatg ttatggagca agatggtaag      3120
aagttaattg agcttttgga taagggcgcc cacttctaca tttgcggcga cggatcccaa      3180
atggcgcctg ccgttgaagc caccttgatg aaatcatatg cagatgttca tcaagtttca      3240
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gtttggtaa                                                             3309
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SEQ ID NO:108

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KILTADKCMV AISDYNDFHK MIKRYILSNV LGPSAQKRHR SNRDTLRANV CSRLHSQVKN       180
SPREAVNFRR VFEWELFGIA LKQAFGKDIE KPIYVEELGT TLSRDEIFKV LVLDIMEGAI       240
EVDWRDFFPY LRWIPNTRME TKIQRLYFRR KAVMTALINE QKKRIASGEE INCYIDFLLK       300
EGKTLTMDQI SMLLWETVIE TADTTMVTTE WAMYEVAKDS KRQDRLYQEI QKVCGSEMVT       360
EEYLSQLPYL NAVFHETLRK HSPAALVPLR YAHEDTQLGG YYIPAGTEIA INIYGCNMDK       420
HQWESPEEWK PERFLDPKFD PMDLYKTMAF GAGKRVCAGS LQAMLIACPT IGRLVQEFEW       480
KLRDGEEENV DTVGLTTHKR YPMHAILKPR SPSRPSPSTE QSAKKVRKKA ENAHNTPLLV       540
LYGSNMGTAE GTARDLADIA MSKGFAPQVA TLDSHAGNLP REGAVLIVTA SYNGHPPDNA       600
KQFVDWLDQA SADEVKGVRY SVFGCGDKNW ATTYQKVPAF IDEMLAAKGA ENIADRGEAD       660
ASDDFEGTYE EWREHMWSDV AAYFNLDIEN SEDNKSALLL QFVDSAADMP LAKMHGAFST       720
NVVASKELQQ PGSARSTRHL EIELPKEASY QEGDHLGVIP RNYEGIVNRV TARFGLDASQ       780
QIRLEAEEEK LAHLPLAKTV SVEELLQYVE LQDPVTRTQL RAMAAKTVCP PHKVELEALL       840
EKQAYKEQVL AKRLTMLELL EKYPACEMEF SEFIALLPSI RPRYYSISSS PRVDEKQASI       900
TVSVVSGEAW SGYGEYKGIA SNYLAELQEG DTITCFISTP QSEFTLPKDP ETPLIMVGPG       960
TGVAPFRGFV QARKQLKEQG QSLGEAHLYF GCRSPHEDYL YQEELENAQS EGIITLHTAF      1020
SRMPNQPKTY VQHVMEQDGK KLIELLDKGA HFYICGDGSQ MAPAVEATLM KSYADVHQVS      1080
EADARLWLQQ LEEKGRYAKD VW                                               1102
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SEQ ID NO:109

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caagctaaat tgccaccagt tccagttgtt ccaggtttgc cagttattgg taatttgttg       180
caattgaaag aaaagaagcc ataccaaacc ttcactagat gggctgaaga atatggtcca       240
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aaagaagcta tggttaccag atacttgtct atctctacca gaaagttgtc caacgccttg       360
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atgatcaaga gatatatctt gtctaacgtt ttgggtccat ctgcccaaaa aagacataga       480
```

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gaagaatact tgtcccaatt gccatacttg aatgctgttt tccacgaaac tttgagaaaa     1140
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tattacattc cagccggtac tgaaattgcc attaacatct acggttgcaa catggacaaa     1260
caccaatggg aatctccaga agaatggaag ccagaaagat ttttggatcc taagtttgac     1320
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tatccaatgc atgctatttt gaagccaaga tctccatcaa gaccaagtcc tagtaccgaa     1560
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ctttatggtt ctaatatggg aacagcggaa ggaacggcca gggatctagc tgacatagct     1680
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aagcagttcg tcgattggtt agatcaagca tcagcagatg aagttaaggg tgttagatac     1860
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gcaagcgacg attttgaggg tacctatgag gagtggagag agcacatgtg gtctgatgtt     2040
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caattcgtcg atagtgctgc ggacatgccc ttagcaaaga tgcatggagc cttttcaacg     2160
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cagataagac tagaagcaga agaagaaaaa ttggcgcacc ttccactagc gaagacagta     2400
tccgttgaag aattattgca atacgtggaa ttgcaggatc ccgtcactag aacgcaattg     2460
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gaaaaacaag catacaaaga gcaagtgcta gcaaagagac taaccatgtt agaattgctg     2580
gaaaaatacc cggcatgcga aatggaattc tccgaattta tcgcgttgtt gccaagtatt     2640
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acaggagtcg ccccttcag aggctttgtg caagcaagga agcaactaaa agaacaggga     2940
caaagtctgg gtgaggcaca tctatatttc ggttgcagat ctccgcatga ggattactta     3000
taccaagaag aacttgaaaa cgcccaatca gaaggtatta tcaccttgca tactgcattc     3060
agtagaatgc caaaccagcc gaaaacttac gtacagcatg ttatggagca agatggtaag     3120
aagttaattg agcttttgga taagggcgcc cacttctaca tttgcggcga cggatcccaa     3180
atggcgcctg ccgttgaagc caccttgatg aaatcatatg cagatgttca tcaagtttca     3240
gaagcggacg cccgtctttg gttacaacaa ctagaggaga aaggaaggta tgcaaaagat     3300
gttgcttaa                                                            3309
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SEQ ID NO:110

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QLKEKKPYQT FTRWAEEYGP IYSIRTGAST MVVLNTTQVA KEAMVTRYLS ISTRKLSNAL      120
KILTADKCMV AISDYNDFHK MIKRYILSNV LGPSAQKRHR SNRDTLRANV CSRLHSQVKN      180
SPREAVNFRR VFEWELFGIA LKQAFGKDIE KPIYVEELGT TLSRDEIFKV LVLDIMEGAI      240
EVDWRDFFPY LRWIPNTRME TKIQRLYFRR KAVMTALINE QKKRIASGEE INCYIDFLLK      300
EGKTLTMDQI SMLLWETVIE TADTTMVTTE WAMYEVAKDS KRQDRLYQEI QKVCGSEMVT      360
EEYLSQLPYL NAVFHETLRK HSPAALVPLR YAHEDTQLGG YYIPAGTEIA INIYGCNMDK      420
HQWESPEEWK PERFLDPKFD PMDLYKTMAF GAGKRVCAGS LQAMLIACPT IGRLVQEFEW      480
KLRDGEEENV DTVGLTTHKR YPMHAILKPR SPSRPSPSTE QSAKKVRKKA ENAHNTPLLV      540
LYGSNMGTAE GTARDLADIA MSKGFAPQVA TLDSHAGNLP REGAVLIVTA SYNGHPPDNA      600
KQFVDWLDQA SADEVKGVRY SVFGCGDKNW ATTYQKVPAF IDEMLAAKGA ENIADRGEAD      660
ASDDFEGTYE EWREHMWSDV AAYFNLDIEN SEDNKSALLL QFVDSAADMP LAKMHGAFST      720
NVVASKELQQ PGSARSTRHL EIELPKEASY QEGDHLGVIP RNYEGIVNRV TARFGLDASQ      780
QIRLEAEEEK LAHLPLAKTV SVEELLQYVE LQDPVTRTQL RAMAAKTVCP PHKVELEALL      840
EKQAYKEQVL AKRLTMLELL EKYPACEMEF SEFIALLPSI RPRYYSISSS PRVDEKQASI      900
```

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TVSVVSGEAW SGYGEYKGIA SNYLAELQEG DTITCFISTP QSEFTLPKDP ETPLIMVGPG      960
TGVAPFRGFV QARKQLKEQG QSLGEAHLYF GCRSPHEDYL YQEELENAQS EGIITLHTAF     1020
SRMPNQPKTY VQHVMEQDGK KLIELLDKGA HFYICGDGSQ MAPAVEATLM KSYADVHQVS     1080
EADARLWLQQ LEEKGRYAKD VA                                              1102
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SEQ ID NO:111

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ttgtctatct ctaccagaaa gttgtccaac gccttgaaaa ttttgaccgc tgataagtgc      240
atggttgcca tttctgatta caacgatttc cacaagatga tcaagagata tatcttgtct      300
aacgttttgg gtccatctgc ccaaaaaaga catagatcta acagagatac cttgagagcc      360
aacgtttgtt ctagattgca ttcccaagtt aagaactctc caagagaagc tgtcaacttt      420
agaagagttt tcgaatggga attattcggt atcgctttga aacaagcctt cggtaaggat      480
attgaaaagc caatctacgt cgaagaattg ggtactactt tgtccagaga tgaaatcttc      540
aaggttttgg tcttggacat tatggaaggt gccattgaag ttgattggag agatttttc       600
ccatacttgc gttggattcc aaacaccaga atggaaacta agatccaaag attatacttt      660
agaagaaagg ccgttatgac cgccttgatt aacgaacaaa agaaaagaat tgcctccggt      720
gaagaaatca actgctacat cgatttcttg ttgaaagaag gtaagacctt gaccatggac      780
caaatctcta tgttgttgtg ggaaaccgtt attgaaactg ctgataccac aatggttact      840
actgaatggg ctatgtacga agttgctaag gattctaaaa gacaagacag attataccaa      900
gaaatccaaa aggtctgcgg ttctgaaatg gttacagaag aatacttgtc ccaattgcca      960
tacttgaatg ctgttttcca cgaaactttg agaaaacatt ctccagctgc tttggttcca     1020
ttgagatatg ctcatgaaga tactcaattg ggtggttatt acattccagc cggtactgaa     1080
attgccatta acatctacgg ttgcaacatg gacaaacacc aatgggaatc tccagaagaa     1140
tggaagccag aaagattttt ggatcctaag tttgacccaa tggacttgta caaaactatg     1200
gcttttggtg ctggtaaaag agtttgcgct ggttctttac aagctatgtt gattgcttgt     1260
ccaaccatcg gtagattggt tcaagaattt gaatggaagt tgagagatgg tgaagaagaa     1320
aacgttgata ctgttggttt gaccacccat aagagatatc caatgcatgc tattttgaag     1380
ccaagatctc catcaagacc aagtcctagt accgaacaat ctgcaaaaaa agttagaaaa     1440
aaagcagaaa atgcacacaa tactccattg ctagttcttt atggttctaa tatgggaaca     1500
gcggaaggaa cggccaggga tctagctgac atagctatgt ccaagggatt tgccccgcaa     1560
gtagcaaccc tggattccca tgcaggtaac ttgccaagag aaggtgctgt tctaatagtt     1620
accgctagct acaatgggca ccctccagat aatgcgaagc agttcgtcga ttggttagat     1680
caagcatcag cagatgaagt taagggtgtt agatactctg tttttggatg tggagataag     1740
aattgggcca ccacatatca gaaggttccg gctttcatcg atgaaatgct tgctgcaaaa     1800
gggcctgaaa atatagcaga tcgtggtgag gccgacgcaa gcgacgattt tgagggtacc     1860
tatgaggagt ggagagagca catgtggtct gatgttgccg cgtattttaa tctagacata     1920
gaaaattctg aagacaataa aagtgcctta cttcttcaat tcgtcgatag tgctgcggac     1980
atgcccttag caaagatgca tggagccttt tcaacgaacg tagtagccag taaggaactt     2040
caacaaccag gtagtgccag aagtacacgt cacttggaaa ttgaattacc aaaagaggca     2100
tcctaccaag aaggtgacca tcttggtgta atcccaagaa actacgaagg tatagtcaat     2160
agggtaacgg caagatttgg gctggatgca agccaacaga taagactaga agcagaagaa     2220
gaaaaattgg cgcaccttcc actagcgaag acagtatccg ttgaagaatt attgcaatac     2280
gtggaattgc aggatcccgt cactagaacg caattgagag ctatggcagc aaagactgtt     2340
tgtccacctc acaaggttga acttgaagct ctacttgaaa aacaagcata caaagagcaa     2400
gtgctagcaa agagactaac catgttagaa ttgctggaaa aatacccggc atgcgaaatg     2460
gaattctccg aatttatcgc gttgttgcca agtattcgtc ccaggtatta ctcaatttca     2520
tcttcaccaa gggttgacga gaaacaggca tctattaccg tatctgtggt ctctggagaa     2580
gcttggagtg gttacggaga atacaagggt attgcttcca attatcttgc agaactgcag     2640
gaaggggata caattacctg ctttatttct actcctcaat cagaatttac tcttccgaag     2700
gatccagaaa ctccgttaat tatggtaggt ccgggaacag gagtcgcccc tttcagaggc     2760
tttgtgcaag caaggaagca actaaaagaa cagggacaaa gtctgggtga ggcacatcta     2820
tatttcggtt gcagatctcc gcatgaggat tacttatacc aagaagaact tgaaaacgcc     2880
caatcagaag gtattatcac cttgcatact gcattcagta gaatgccaaa ccagccgaaa     2940
acttacgtac agcatgttat ggagcaagat ggtaagaagt taattgagct tttggataag     3000
ggcgcccact tctacatttg cggcgacgga tcccaaatgg cgcctgccgt tgaagccacc     3060
ttgatgaaat catatgcaga tgttcatcaa gtttcagaag cggacgcccg tctttggtta     3120
caacaactag aggagaaagg aaggtatgca aaagatgttg cttaa                     3165
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SEQ ID NO:112

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MVPGLPVIGN LLQLKEKKPY QTFTRWAEEY GPIYSIRTGA STMVVLNTTQ VAKEAMVTRY       60
LSISTRKLSN ALKILTADKC MVAISDYNDF HKMIKRYILS NVLGPSAQKR HRSNRDTLRA      120
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NVCSRLHSQV KNSPREAVNF RRVFEWELFG IALKQAFGKD IEKPIYVEEL GTTLSRDEIF       180
KVLVLDIMEG AIEVDWRDFF PYLRWIPNTR METKIQRLYF RRKAVMTALI NEQKKRIASG       240
EEINCYIDFL LKEGKTLTMD QISMLLWETV IETADTTMVT TEWAMYEVAK DSKRQDRLYQ       300
EIQKVCGSEM VTEEYLSQLP YLNAVFHETL RKHSPAALVP LRYAHEDTQL GGYYIPAGTE       360
IAINIYGCNM DKHQWESPEE WKPERFLDPK FDPMDLYKTM AFGAGKRVCA GSLQAMLIAC       420
PTIGRLVQEF EWKLRDGEEE NVDTVGLTTH KRYPMHAILK PRSPSRPSPS TEQSAKKVRK       480
KAENAHNTPL LVLYGSNMGT AEGTARDLAD IAMSKGFAPQ VATLDSHAGN LPREGAVLIV       540
TASYNGHPPD NAKQFVDWLD QASADEVKGV RYSVFGCGDK NWATTYQKVP AFIDEMLAAK       600
GAENIADRGE ADASDDFEGT YEEWREHMWS DVAAYFNLDI ENSEDNKSAL LLQFVDSAAD       660
MPLAKMHGAF STNVVASKEL QQPGSARSTR HLEIELPKEA SYQEGDHLGV IPRNYEGIVN       720
RVTARFGLDA SQQIRLEAEE EKLAHLPLAK TVSVEELLQY VELQDPVTRT QLRAMAAKTV       780
CPPHKVELEA LLEKQAYKEQ VLAKRLTMLE LLEKYPACEM EFSEFIALLP SIRPRYYSIS       840
SSPRVDEKQA SITVSVVSGE AWSGYGEYKG IASNYLAELQ EGDTITCFIS TPQSEFTLPK       900
DPETPLIMVG PGTGVAPFRG FVQARKQLKE QGQSLGEAHL YFGCRSPHED YLYQEELENA       960
QSEGIITLHT AFSRMPNQPK TYVQHVMEQD GKKLIELLDK GAHFYICGDG SQMAPAVEAT      1020
LMKSYADVHQ VSEADARLWL QQLEEKGRYA KDVA                                  1054
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SEQ ID NO:113

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atgaccagtt tgtccaaaag cttcatgcag agtggacgaa tctgcgcagc atgtttctat        60
ctgttattca cactactttc aattccaatc tcgtttaaag ttggtggttt ggaatgcggg       120
ctttccttca cggtgacact gttcacttta tatttcataa ctacgactct taacgtgttg       180
gcaagacgac atggaggaag actatacatt ttttttacca actgtctgta ttactcacaa       240
cattttatca ttgcatcttt gctatacctg tttttgtctg gattttctaa tgatgagttg       300
ggaaacgttc tgaaaaataa atataatgag tcggagtcgt tcctggaagc tttgaaaaat       360
agcttgaatt ccaatcaaat taactacgtc ttatattatt actactatcg atttgttgta       420
caaccgtggc aattcgtgct taccaagtcc acacctttt ttactctatc ggaaggtttt       480
ttcactattt tagccattca ggccgtcggg gaaactaata gatggttatc aaatgacttg       540
aattcaaaca cgtggattat ttcctcattg ttaacctccg gaggtgtgat taccgcatcg       600
ctgtactatt tgtatcggat ttatgtcacc cccatatggc cgttatccat ccaaacggcg       660
tccttattag gacttgtttt gtctatggta tgtggactgg ggttgtatgg tattgtgagt       720
caaaaaggat ccgtcataga gagctcttta ttttttgcgt atattgttcg ttgtatttat       780
gaaatttccc ccaaattagc tactaccgcg actgatgaaa ttttaaattt gttcaaagac       840
gtctggcaga aacatcaaag aaatctgccc acagctgaca atcttttgtg ctactttcat       900
aatgtcatat tgaaaaatgc agaggtgtta tgggggtcct ttattcctag aggaagaaag       960
aaaaccggtg attttcatga taaactcatt agcattctat cattcgaaaa agtatccttg      1020
atatctaaac cattttggaa atttttcaag aatttcacct ttagtgttcc gctatccatt      1080
aatgaatttt gtcaagttac aattaagatg gcaagcgaat cagtttcccc agctatagta      1140
atcaatttat gctttagagt tctgatgttt tactcggcaa cgaggattat tccagcatta      1200
caaagaaaaa atgacaaaca gttgcgcaag agtcgcagga tcatgaaggg attgtattgg      1260
tacagtcctt gcatattaat tgctatgtat actcacctga ttttacaata ttcaggtgag      1320
ctaaagaaag acctgtgcat atggggttgc agtgaaaagt ggtttggcgt agatcaacca      1380
gaaattatag tagattcatg gggattttgg aactggtgca acattttctg tactattttg      1440
gtatacgcta cagaattaat aggttctggt agttga                                1476
```

SEQ ID NO:114

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MTSLSKSFMQ SGRICAACFY LLFTLLSIPI SFKVGGLECG LSFTVTLFTL YFITTTLNVL        60
ARRHGGRLYI FFTSCLYYSQ HFIIASLLYL FLSGFSNDEL GNVLKNKYNE SESFLEALKN       120
SLNSNQINYV LYYYYYRFVV QPWQFVLTKS TPFFTLSEGF FTILAIQAVG ETNRWLSNDL       180
NSNTWIISSL LTSGGVITAS LYYLYRIYVT PIWPLSIQTA SLLGFVLSMV CGLGLYGIVS       240
QKGSVIESSL FFAYIVRCIY EISPKLATTA TDEILNLFKD VWQKHQRNLP TADNLLCYFH       300
NVILKNAEVL WGSFIPRGRK KTGDFHDKLI SILSFEKVSL ISKPFWKFFK NFTFSVPLSI       360
NEFCQVTIKM ASESVSPAIV INLCFRVLMF YSATRIIPAL QRKNDKQLRK SRRIMKGLYW       420
YSPCILIAMY THLILQYSGE LKKDLCIWGC SEKWFGVDQP EIIVDSWGFW NWCNIFCTIL       480
VYATELIGSG S                                                            491
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SEQ ID NO:115

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agatctttat gaagacatag ctgcagaaga aaaagcaaga gctacatatc aatggttaat        60
tgatatatca gatgatcccg atttaaacga cagcttacga tttttacgag aaagagagat       120
tgttcactca cagcggttcc gcgaggccgt ggagatttta aaagatgaca gagacaggaa       180
gaaaatcttt taactagtaa aaaaacatcc cccttggcga atgcaaacga aaggagggat       240
gtttttttgtt gtgactgcgt tgattatgcg ctagaactgc agtgacaaga aacaaccttt       300
aatttccctt caacatcttt ccaaactcgc gtataactgt attcacctcc aatagattca       360
```

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ccggttgcca gtgccccatt taacgctact tttgtaacgg taacggcaag ttcttgaaac       420
agtttaactt cttgttccaa cacttccatg cccgctatat caagactttt tgaacgatga       480
acatttatat cttcttcttt tgacaaccat tgcccaaggt gattcacaaa aataagctca       540
tctgaaagta attcttctaa tagctctatg ttattagaaa gcatggctga gcgaagcatt       600
tcttcgtatt ctataactct tgcttgattc atttttaatc ctcctttacg ccttgtgtaa       660
ctcttttcta tttccacgtt gcttttcctt taaacttctt tcattaataa ttcgtgctaa       720
attatgttaa tagaggggat aagtggacta attttctgta agcactaaat attctgaaat       780
actctgttaa ttacctttaa atggtataaa attagaatga aagaaccttt tctttccact       840
tttctagtta tctttttact attaagatgc agtttttttat acttgtaatt gtagcggaat      900
gaacgttcat tccgtttttg aaaagaggtg ataaagtgga atctactcca acaaaacaaa       960
aagcgatttt ttctgcttcg cttctgctgt ttgcagaaag agggtttgat gcaaccacga      1020
tgccaatgat tgcagagaat gccaaagtag gagcaggaac aatttatcgc tactttaaaa      1080
ataaagaaag ccttgtaaat gaattattcc aacagcacgt aaacgagttt ttacagtgca      1140
ttgaaagcgg tctggcaaac gagagagatg gataccgaga tgggtttcat catatctttg      1200
aaggtatggt gacatttact aaaaaccatc ctcgtgctct tggatttatt aaaactcata      1260
gccaaggaac ttttttaaca gaagagagcc gcttagcata tcaaaagctg gtggaatttg      1320
tttgtacgtt cttcagagaa ggacaaaagc aaggtgtgat tagaaatctt cctgaaaatg      1380
cgctaattgc tattttattt ggaagtttca tggaagtata tgaaatgatt gaaaatgact      1440
acttatcttt aactgatgaa cttcttaccg gtgtagaaga gagtctgtgg gcagcactta      1500
gcagacaatc atgaaactta acaagtgaaa gagggataac atgacaatta aagaaatgcc      1560
tcagccaaaa acgtttggag agcttaaaaa tttaccgtta ttaaaacacag ataaaccggt     1620
tcaagctttg atgaaaattg cggatgaatt aggagaaatc tttaaattcg aggcgcctgg      1680
tcgtgtaacg cgctacttat caagtcagcg tctaattaaa gaagcatgcg atgaatcacg      1740
ctttgataaa aacttaagtc aagcgcttaa atttgtacgt gattttgcag gagacgggtt      1800
atttacaagc tggacgcatg aaaaaaattg gaaaaaagcg cataatatct tacttccaag      1860
cttcagtcag caggcaatga aaggctatca tgcgatgatg gtcgatatcg ccgtgcagct      1920
tgttcaaaag tgggagcgtc taaatgcaga tgagcatatt gaagtaccgg aagacatgac      1980
acgtttaacg cttgatacaa ttggtctttg cggctttaac tatcgcttta acagctttta      2040
ccgagatcag cctcatccat ttattacaag tatggtccgt gcactggatg aagcaatgaa      2100
caagctgcag cgagcaaatc cagacgaccc agcttatgat gaaaacaagc gccagtttca      2160
agaagatatc aaggtgatga acgacctagt agataaaatt attgcagatc gcaaagcaag      2220
cggtgaacaa agcgatgatt tattaacgca tatgctaaac ggaaaagatc cagaaacggg      2280
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cgaaacaaca agtggtcttt tatcatttgc gctgtatttc ttagtgaaaa atccacatgt      2400
attacaaaaa gcagcagaag aagcagcacg agttctagta gatcctgttc caagctacaa      2460
acaagtcaaa cagcttaaat atgtcggcat ggtcttaaac gaagcgctgc gcttatggcc      2520
aactgctcct gcgttttccc tatatgcaaa agaagatacg gtgcttggag gagaatatcc      2580
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gcagcatgcg tttaaaccgt ttggaaacgg tcagcgtgcg tgtatcggtc agcagttcgc      2760
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tgaaacgctt gccgctaaag gggcagaaaa catcgctgac cgcggtgaag cagatgcaag      3360
cgacgacttt gaaggcacat atgaagaatg gcgtgaacat atgtggagtg acgtagcagc      3420
ctactttaac ctcgacattg aaaacagtga agataataaa tctactcttt cacttcaatt      3480
tgtcgacagc gccgcggata tgccgcttgc gaaaatgcac ggtgcgtttt caacgaacgt      3540
cgtagcaagc aaagaacttc aacagccagg cagtgcacga agcacgcgac atcttgaaat      3600
tgaacttcca aaagaagctt cttatcaaga aggagatcat ttaggtgtta ttcctcgcaa      3660
ctatgaagga atagtaaacc gtgtaacagc aaggttcggc ctagatgcat cacagcaaat      3720
ccgtctggaa gcagaagaag aaaaattagc tcatttgcca ctcgctaaaa cagtatccgt      3780
agaagagctt ctgcaatacg tggagcttca agatcctgtt acgcgcacgc agcttcgcgc      3840
aatggctgct aaaacggtct gcccgccgca taaagtagag cttgaagcct tgcttgaaaa      3900
gcaagcctac aaagaacaag tgctggcaaa acgtttaaca atgcttgaac tgcttgaaaa      3960
atacccggcg tgtgaaatga aattcagcga atttatcgcc cttctgccaa gcatacgccc      4020
gcgctattac tcgatttctt catcacctcg tgtcgatgaa aaacaagcaa gcatcacggt      4080
cagcgttgtc tcaggagaag cgtggagcgg atatggagaa tataaaggaa ttgcgtcgaa      4140
ctatcttgcc gagctgcaag aaggagatac gattacgtgc tttatttcca caccgcagtc      4200
agaatttacg ctgccaaaag accctgaaac gccgcttatc atggtcggac cgggaacagg      4260
cgtcgcgccg tttagaggct ttgtgcaggc gcgcaaacag ctaaaagaac aaggacagtc      4320
acttggagaa gcacatttat acttcggctg ccgttcacct catgaagact atctgtatca      4380
```

```
agaagagctt gaaaacgccc aaagcgaagg catcattacg cttcataccg ctttttctcg      4440
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gattgaactt cttgatcaag gagcgcactt ctatatttgc ggagacggaa gccaaatggc      4560
acctgccgtt gaagcaacgc ttatgaaaag ctatgctgac gttcaccaag tgagtgaagc      4620
agacgctcgc ttatggctgc agcagctaga agaaaaaggc cgatacgcaa aagacgtgtg      4680
ggctgggtaa attaaaaaga ggctaggata aaagtagttt agttggttga aggaagatcc      4740
gaacgatgaa tcgttcggat ctttttattg gtagagtaaa cgtagatttc atctatttag      4800
tgacttgtag cggttgattg gagggcaagg tgaagactcc aatcaaccgc ggtgtcacat      4860
gcaagccata cgaaattcat ttctcccatt tattcgtctt ttgtccccac ttaattttta      4920
tagcgcctta acgtttcttc tgcgtgacag cagatct                               4957
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SEQ ID NO:116

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MTIKEMPQPK TFGELKNLPL LNTDKPVQAL MKIADELGEI FKFEAPGRVT RYLSSQRLIK        60
EACDESRFDK NLSQALKFVR DFAGDGLFTS WTHEKNWKKA HNILLPSFSQ QAMKGYHAMM       120
VDIAVQLVQK WERLNADEHI EVPEDMTRLT LDTIGLCGFN YRFNSFYRDQ PHPFITSMVR       180
ALDEAMNKLQ RANPDDPAYD ENKRQFQEDI KVMNDLVDKI IADRKASGEQ SDDLLTHMLN       240
GKDPETGEPL DDENIRYQII TFLIAGHETT SGLLSFALYF LVKNPHVLQK AAEEAARVLV       300
DPVPSYKQVK QLKYVGMVLN EALRLWPTAP AFSLYAKEDT VLGGEYPLEK GDELMVLIPQ       360
LHRDKTIWGD DVEEFRPERF ENPSAIPQHA FKPFGNGQRA CIGQQFALHE ATLVLGMMLK       420
HFDFEDHTNY ELDIKETLTL KPEGFVVKAK SKKIPLGGIP SPSTEQSAKK VRKKAENAHN       480
TPLLVLYGSN MGTAEGTARD LADIAMSKGF APQVATLDSH AGNLPREGAV LIVTASYNGH       540
PPDNAKQFVD WLDQASADEV KGVRYSVFGC GDKNWATTYQ KVPAFIDETL AAKGAENIAD       600
RGEADASDDF EGTYEEWREH MWSDVAAYFN LDIENSEDNK STLSLQFVDS AADMPLAKMH       660
GAFSTNVVAS KELQQPGSAR STRHLEIELP KEASYQEGDH LGVIPRNYEG IVNRVTARFG       720
LDASQQIRLE AEEEKLAHLP LAKTVSVEEL LQYVELQDPV TRTQLRAMAA KTVCPPHKVE       780
LEALLEKQAY KEQVLAKRLT MLELLEKYPA CEMKFSEFIA LLPSIRPRYY SISSSPRVDE       840
KQASITVSVV SGEAWSGYGE YKGIASNYLA ELQEGDTITC FISTPQSEFT LPKDPETPLI       900
MVGPGTGVAP FRGFVQARKQ LKEQGQSLGE AHLYFGCRSP HEDYLYQEEL ENAQSEGIIT       960
LHTAFSRMPN QPKTYVQHVM EQDGKKLIEL LDQGAHFYIC GDGSQMAPAV EATLMKSYAD      1020
VHQVSEADAR LWLQQLEEKG RYAKDVWAG                                        1049
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SEQ ID NO:117

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aatactccat tgctagttct ttatggttct aatatgggaa cagcggaagg aacggccagg       120
gatctagctg acatagctat gtccaaggga tttgccccgc aagtagcaac cctggattcc       180
catgcaggta acttgccaag agaaggtgct gttctaatag ttaccgctag ctacaatggg       240
caccctccag ataatgcgaa gcagttcgtc gattggttag atcaagcatc agcagatgaa       300
gttaagggtg ttagatactc tgtttttgga tgtggagata agaattgggc caccacatat       360
cagaaggttc cggctttcat cgatgaaatg cttgctgcaa aaggggctga aaatatagca       420
gatcgtggtg aggccgacgc aagcgacgat tttgagggta cctatgagga gtggagagag       480
cacatgtggt ctgatgttgc cgcgtatttt aatctagaca tagaaaattc tgaagacaat       540
aaaagtgcct tacttcttca attcgtcgat agtgctgcgg acatgccctt agcaaagatg       600
catggagcct tttcaacgaa cgtagtagcc agtaaggaac ttcaacaacc aggtagtgcc       660
agaagtacac gtcacttgga aattgaatta ccaaaagagg catcctacca agaaggtgac       720
catcttggtg taatcccaag aaactacgaa ggtatagtca atagggtaac ggcaagattt       780
gggctggatg caagccaaca gataagacta gaagcagaag aagaaaaatt ggcgcacctt       840
ccactagcga agacagtatc cgttgaagaa ttattgcaat acgtggaatt gcaggatccc       900
gtcactagaa cgcaattgag agctatggca gcaaagactg tttgtccacc tcacaaggtt       960
gaacttgaag ctctacttga aaaacaagca tacaaagagc aagtgctagc aaagagacta      1020
accatgttag aattgctgga aaaatacccg gcatgcgaaa tggaattctc cgaatttatc      1080
gcgttgttgc caagtattcg tcccaggtat tactcaattt catcttcacc aagggttgac      1140
gagaaacagg catctattac cgtatctgtg gtctctggag aagcttggag tggttacgga      1200
gaatacaagg gtattgcttc caattatctt gcagaactgc aggaagggga tacaattacc      1260
tgctttattt ctactcctca atcagaattt actcttccga aggatccaga aactccgtta      1320
attatggtag gtccgggaac aggagtcgcc cctttcagag gctttgtgca agcaaggaag      1380
caactaaaag aacagggaca aagtctgggt gaggcacatc tatatttcgg ttgcagatct      1440
ccgcatgagg attacttata ccaagaagaa cttgaaaacg cccaatcaga aggtattatc      1500
accttgcata ctgcattcag tagaatgcca aaccagccga aaacttacgt acagcatgtt      1560
atggagcaag atggtaagaa gttaattgag cttttggata agggcgccca cttctacatt      1620
tgcggcgacg gatcccaaat ggcgcctgcc gttgaagcca ccttgatgaa atcatatgca      1680
gatgttcatc aagtttcaga agcggacgcc cgtctttggt tacaacaact agaggagaaa      1740
ggaaggtatg caaaagatgt ttggtaa                                          1767
```

SEQ ID NO:118

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HAGNLPREGA VLIVTASYNG HPPDNAKQFV DWLDQASADE VKGVRYSVFG CGDKNWATTY       120
QKVPAFIDEM LAAKGAENIA DRGEADASDD FEGTYEEWRE HMWSDVAAYF NLDIENSEDN       180
KSALLLQFVD SAADMPLAKM HGAFSTNVVA SKELQQPGSA RSTRHLEIEL PKEASYQEGD       240
HLGVIPRNYE GIVNRVTARF GLDASQQIRL EAEEEKLAHL PLAKTVSVEE LLQYVELQDP       300
VTRTQLRAMA AKTVCPPHKV ELEALLEKQA YKEQVLAKRL TMLELLEKYP ACEMEFSEFI       360
ALLPSIRPRY YSISSSPRVD EKQASITVSV VSGEAWSGYG EYKGIASNYL AELQEGDTIT       420
CFISTPQSEF TLPKDPETPL IMVGPGTGVA PFRGFVQARK QLKEQGQSLG EAHLYFGCRS       480
PHEDYLYQEE LENAQSEGII TLHTAFSRMP NQPKTYVQHV MEQDGKKLIE LLDKGAHFYI       540
CGDGSQMAPA VEATLMKSYA DVHQVSEADA RLWLQQLEEK GRYAKDVW                    588
```

SEQ ID NO:119

```
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aatactccat tgctagttct ttatggttct aatatgggaa cagcggaagg aacggccagg       120
gatctagctg acatagctat gtccaaggga tttgccccgc aagtagcaac cctggattcc       180
catgcaggta acttgccaag agaaggtgct gttctaatag ttaccgctag ctacaatggg       240
caccctccag ataatgcgaa gcagttcgtc gattggttag atcaagcatc agcagatgaa       300
gttaagggtg ttagatactc tgtttttgga tgtggagata agaattgggc caccacatat       360
cagaaggttc cggctttcat cgatgaaatg cttgctgcaa aaggggctga aaatatagca       420
gatcgtggtg aggccgacgc aagcgacgat tttgagggta cctatgagga gtggagagag       480
cacatgtggt ctgatgttgc cgcgtatttt aatctagaca tagaaaattc tgaagacaat       540
aaaagtgcct tacttcttca attcgtcgat agtgctgcgg acatgccctt agcaaagatg       600
catggagcct tttcaacgaa cgtagtagcc agtaaggaac ttcaacaacc aggtagtgcc       660
agaagtacac gtcacttgga aattgaatta ccaaaagagg catcctacca agaaggtgac       720
catcttggtg taatcccaag aaactacgaa ggtatagtca atagggtaac ggcaagattt       780
gggctggatg caagccaaca gataagacta gaagcagaag aagaaaaatt ggcgcacctt       840
ccactagcga agacagtatc cgttgaagaa ttattgcaat acgtggaatt gcaggatccc       900
gtcactagaa cgcaattgag agctatggca gcaaagactg tttgtccacc tcacaaggtt       960
gaacttgaag ctctacttga aaaacaagca tacaaagagc aagtgctagc aaagagacta      1020
accatgttag aattgctgga aaaatacccg gcatgcgaaa tggaattctc cgaatttatc      1080
gcgttgttgc caagtattcg tcccaggtat tactcaattt catcttcacc aagggttgac      1140
gagaaacagg catctattac cgtatctgtg gtctctggag aagcttggag tggttacgga      1200
gaatacaagg gtattgcttc caattatctt gcagaactgc aggaagggga tacaattacc      1260
tgctttattt ctactcctca atcagaattt actcttccga aggatccaga aactccgtta      1320
attatggtag gtccgggaac aggagtcgcc cctttcagag gctttgtgca agcaaggaag      1380
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ccgcatgagg attacttata ccaagaagaa cttgaaaacg cccaatcaga aggtattatc      1500
accttgcata ctgcattcag tagaatgcca aaccagccga aaacttacgt acagcatgtt      1560
atggagcaag atggtaagaa gttaattgag cttttggata agggcgccca cttctacatt      1620
tgcggcgacg gatcccaaat ggcgcctgcc gttgaagcca ccttgatgaa atcatatgca      1680
gatgttcatc aagtttcaga agcggacgcc cgtctttggt tacaacaact agaggagaaa      1740
ggaaggtatg caaaagatgt tgcttaa                                          1767
```

SEQ ID NO:120

```
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QKVPAFIDEM LAAKGAENIA DRGEADASDD FEGTYEEWRE HMWSDVAAYF NLDIENSEDN       180
KSALLLQFVD SAADMPLAKM HGAFSTNVVA SKELQQPGSA RSTRHLEIEL PKEASYQEGD       240
HLGVIPRNYE GIVNRVTARF GLDASQQIRL EAEEEKLAHL PLAKTVSVEE LLQYVELQDP       300
VTRTQLRAMA AKTVCPPHKV ELEALLEKQA YKEQVLAKRL TMLELLEKYP ACEMEFSEFI       360
ALLPSIRPRY YSISSSPRVD EKQASITVSV VSGEAWSGYG EYKGIASNYL AELQEGDTIT       420
CFISTPQSEF TLPKDPETPL IMVGPGTGVA PFRGFVQARK QLKEQGQSLG EAHLYFGCRS       480
PHEDYLYQEE LENAQSEGII TLHTAFSRMP NQPKTYVQHV MEQDGKKLIE LLDKGAHFYI       540
CGDGSQMAPA VEATLMKSYA DVHQVSEADA RLWLQQLEEK GRYAKDVA                    588
```

SEQ ID NO:121

```
ccatcaaga                                                               9
```

SEQ ID NO:122

PSR 3

WHAT IS CLAIMED IS:

1. A recombinant host comprising one or more of:

(a) a gene encoding an ent-kaurene oxidase (KO) polypeptide;

(b) a gene encoding a cytochrome P450 reductase (CPR) polypeptide; and/or

(c) a gene encoding an ent-kaurenoic **acid** hydroxylase (KAH) polypeptide;

wherein at least one of the genes is a recombinant gene; and

wherein the recombinant host is capable of producing a steviol glycoside precursor.

2. A recombinant host comprising:

(a) a gene encoding a geranylgeranyi diphosphate synthase (GGPPS) polypeptide;

(b) a gene encoding an ent-copalyi diphosphate synthase (CDPS) polypeptide;

(c) a gene encoding an ent-kaurene synthase (KS) polypeptide

(d) a gene encoding an ent-kaurene oxidase (KO) polypeptide;

(e) a gene encoding a cytochrome P450 reductase (CPR) polypeptide; and

(f) a gene encoding an ent-kaurenoic acid hydroxylase (KAH) polypeptide;

wherein at least one of the **genes** is **a** recombinant gene; and

wherein the recombinant host is capable of producing steviol.

3. The recombinant host of claims 1 or 2, wherein:

(a) the KO polypeptide comprises a KO polypeptide having at least 60% identity to an amino acid sequence set forth in SEQ ID NO:72 or SEQ ID NO:75; at least 65% identity to an amino acid sequence set forth in SEQ ID NO:54; at least 70% identity to an amino acid sequence set forth in SED ID NO: 70, SEQ ID NO:71, or

SEQ ID NO:79; at least 40% identity to an amino acid sequence set forth in SEQ ID NO:77; or at least 50% identity to an amino acid sequence set forth in SEQ ID NO:78;

(b) the CPR polypeptide comprises a CPR polypeptide having at least 70% identity to an amino acid sequences set forth in SEQ ID NO:69, SEQ ID NO:74, SEQ ID NO:76, or SEQ ID NO:87; at least 80% identity to an amino acid sequence set forth in SEQ ID NO:73; at least 85% identity to an amino acid sequence set forth in SEQ ID NO:22; at least 65% identity to an amino acid sequence set forth in SEQ ID NO:28; or at least 50% identity to an amino acid sequence set forth in SEQ ID NO:98; and/or

(c) the KAH polypeptide comprises a KAH polypeptide having at least 40% identity to an amino acid sequence set forth in SEQ ID NO:82; at least 50% identity to an amino acid sequence set forth in SEQ ID NO:91 ; or at least 60% identity to an amino acid sequence set forth in SEQ ID NO:68.

4. A recombinant host comprising one or more of:

(a) a gene encoding a KO polypeptide having at least 60% identity to an amino acid sequence set forth in SEQ ID NO:75;

(b) a gene encoding a KAH polypeptide having at least 40% identity to an amino acid sequence set forth in SEQ ID NO:82; and/or

(c) a gene encoding a CPR polypeptide having at least 50% identity to an amino acid sequence set forth in SEQ ID NO:98;

wherein at least one of the **genes** is a recombinant gene; and

wherein the recombinant host is capable of producing a steviol glycoside precursor.

5. A recombinant host comprising one or more of:

(a) a gene encoding a KO polypeptide having at least 70% identity to an amino acid sequence set forth in SEQ ID NO:70;

(b) a gene encoding a KAH polypeptide having at least 40% identity to an amino acid sequence set forth in SEQ ID NO:82; and/or

(c) a gene encoding a CPR polypeptide having at least 50% identity to an amino acid sequence set forth in SEQ ID NO:98;

wherein at least one of the genes is a recombinant gene; and

wherein the recombinant host is capable of producing a steviol glycoside precursor.

6. The recombinant host of claim 4 or 5, wherein the host further comprises a gene encoding a KO polypeptide having at least 65% identity to an amino acid sequence set forth in SEQ ID NO:54.

7. The recombinant host of any one of claims 4-6, wherein the host further comprises a gene encoding a KAH polypeptide having at least 60% identity to an amino acid sequence set forth in SEQ ID NO:68.

8. The recombinant host of any one of claims 4-7, wherein the host further comprises a gene encoding a KO polypeptide having at least 70% identity to an amino acid sequence set forth in SEQ ID NO:79.

9. The recombinant host of any one of claims 1 or 3-8, wherein the host further comprises one or more of:

(a) a gene encoding a geranylgeranyl diphosphate synthase (GGPPS) polypeptide;

(b) a gene encoding an ent-copalyl diphosphate synthase (CDPS) polypeptide; and/or

(c) a gene encoding an ent-kaurene synthase (KS) polypeptide;

wherein at least one of the genes is a recombinant gene; and

wherein the recombinant host is capable of producing a steviol glycoside precursor.

10. The recombinant host of claim 9, wherein:

(a) the GGPPS polypeptide comprises a polypeptide having at least 70% identity to an amino acid sequence set forth in SEQ ID NO:49;

(b) the CDPS polypeptide comprises a polypeptide having at least 70% identity to an amino acid sequence set forth in SEQ ID NO:37; and/or

(c) the KS polypeptide comprises a polypeptide having at least 40% identity to an amino acid sequence set forth in SEQ ID NO:6.

11. The recombinant host of claims 1-10, wherein the host further comprises a gene encoding an endoplasmic reticulum membrane polypeptide.

12. The recombinant host of claim 11, wherein the endoplasmic reticulum membrane polypeptide comprises an Inheritance of cortical ER protein 2 (ICE2) polypeptide having at least 50% identity to the amino acid sequence set forth in SEQ ID NO:114.

13. The recombinant host of any one of claim 1-10, wherein the KO polypeptide is a fusion construct.

14. The recombinant host of claim 13, wherein the fusion construct comprises a polypeptide having at least 60% identity to an amino acid sequence set forth in SEQ ID NO:118 or SEQ ID NO:120.

15. The recombinant host of claim 13 or claim 14, wherein the fusion construct has at least 50% identity to an amino acid sequence set forth in SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 104, SEQ ID NO: 106, SEQ ID NO:108, SEQ ID NO:110, or SEQ ID NO:112.

16. The recombinant host of any one of claims 1-15, wherein the host further comprises one or more of:

(a) a gene encoding a UGT85C polypeptide;

(b) a gene encoding a UGT76G polypeptide;

(c) a gene encoding a UGT74G1 polypeptide;

(d) a gene encoding a UGT91 D2 functional homolog polypeptide; and/or

(e) a gene encoding an EUGT11 polypeptide;

wherein at least one of the genes is a recombinant gene; and

wherein the host is capable of producing a steviol glycoside.

17. The recombinant host of claim 16, wherein:

(a) the UGT85C2 polypeptide comprises a polypeptide having at least 55% identity to an amino acid sequence set forth in SEQ ID NO:30;

(b) the UGT76G1 polypeptide comprises a polypeptide having at least 50% identity to an amino acid sequence set forth in SEQ ID NO:83;

(c) the UGT74G1 polypeptide comprises a polypeptide having at least 55% identity to an amino acid sequence set forth in SEQ ID NO:29;

(d) the UGT91 D2 functional homolog polypeptide comprises a UGT91D2 polypeptide having 90% or greater identity to the amino acid sequence set forth in SEQ ID NO:84 or a UGT91D2e-b polypeptide having 90% or greater identity to the amino acid sequence set forth in SEQ ID NO:88; and/or

(e) the EUGT1 1 polypeptide comprises a polypeptide having at least 65% identity to an amino acid sequence set forth in SEQ ID NO:86.

18. The recombinant host of any one of claims 1-17, wherein the recombinant host comprises a plant cell, a mammalian cell, an insect cell, a fungal cell, or a bacterial cell.

19. The recombinant host of claim 18, wherein the bacterial cell comprises *Escherichia* bacteria cells, *Lactobacillus* bacteria cells, *Lactococcus* bacteria cells, *Cornebacterium* bacteria cells, *Acetobacter* bacteria cells, *Acinetobacter* bacteria cells, or *Pseudomonas* bacterial cells.

20. The recombinant host of claim 18, wherein the fungal cell comprises a yeast cell.

21. The recombinant host of claim 20, wherein the yeast cell is a cell from *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Yarrowia lipolytica, Candida glabrata, Ashbya gossypii, Cyberlindnera jadinii, Pichia pastoris, Kluyveromyces lactis, Hansenula polymorpha, Candida boidinii, Arxula adeninivorans, Xanthophyllomyces dendrorhous,* or *Candida albicans* species.

22. The recombinant host of claim 21, wherein the yeast cell is a *Saccharomycete.*

23. The recombinant host of claim 22, wherein the yeast cell is a cell from the *Saccharomyces cerevisiae* species.

24. A method of producing a steviol glycoside or a steviol glycoside precursor, comprising:

(a) growing the recombinant host of any one of claims 1-23 in a culture medium, under conditions in which any of the genes disclosed in any one of claims 1-23 are expressed;

wherein the **steviol** glycoside or the steviol glycoside precursor is synthesized by said host; and/or

(b) optionally quantifying the steviol glycoside or the steviol glycoside precursor; and/or

(c) optionally isolating the steviol glycoside or the steviol glycoside precursor.

25. The method of claim 24, wherein the steviol glycoside comprises steviol-13-O-glucoside (13-SMG), steviol-1,2-bioside, steviol-1,3-bioside, steviol-19-O-glucoside (19-SMG), stevioside, 1,3-stevioside, rubusoside, Rebaudioside A (RebA), Rebaudioside B (RebB), Rebaudioside C (RebC), Rebaudioside D (RebD), Rebaudioside E (RebE), Rebaudioside F (RebF), Rebaudioside M (RebM), Rebaudioside Q (RebQ), Rebaudioside I (Rebl), dulcoside A, di-glycosylated steviol, tri-glycosylated steviol, tetra-glycosylated steviol, penta-glycosylated steviol, hexa-glycosylated steviol, hepta-glycosylated steviol, or isomers thereof.

26. The steviol glycoside or the steviol glycoside precursor produced by the recombinant host of any one of claims 1-23 or the method of claim 24 or claim 25, wherein the steviol glycoside or steviol glycoside precursor accumulates to a detectable concentration when cultured under said conditions.

27. A steviol glycoside composition produced by the host of any one of claims 1-23 or the method of claim 24 or claim 25, wherein the composition has an undetectable concentration of stevia plant-derived contaminants.

28. A steviol glycoside composition produced by the host of any one of claims 1-23 or the method of claim 24 or claim 25, wherein the composition has a steviol glycoside composition enriched for RebD or RebM relative to the steviol glycoside composition of a wild-type Stevia plant.

Figure 1

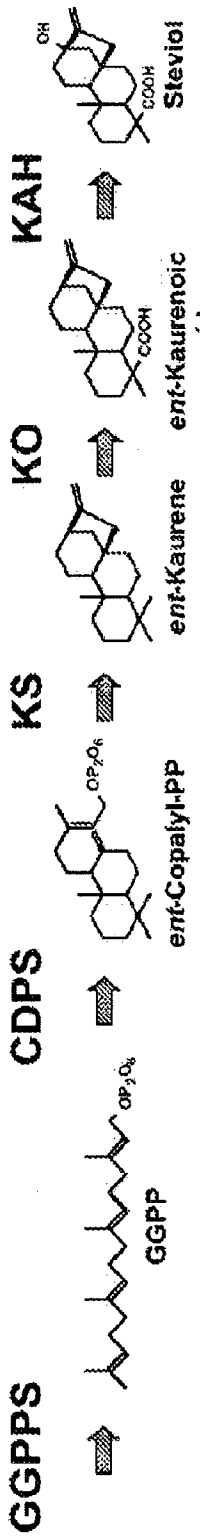

GGPPS
GGPP
CDPS
ent-Copalyl-PP
KS
ent-Kaurene
KO
ent-Kaurenoic acid
KAH
Steviol
COOH
OH

Figure 2

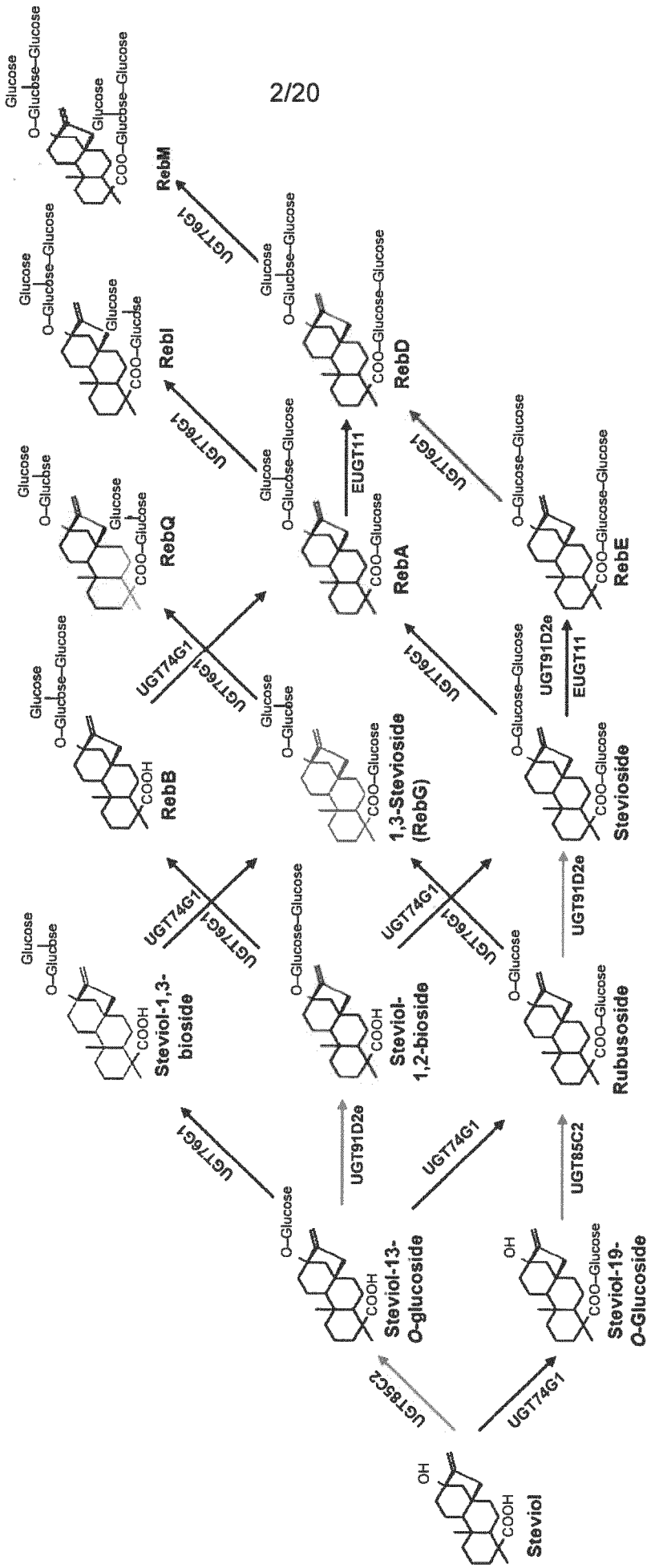

Steviol
UGT85C2
UGT74G1
Steviol-13-O-glucoside
Steviol-19-O-Glucoside
UGT76G1
UGT91D2e
UGT74G1
UGT85C2
Steviol-1,3-bioside
Steviol-1,2-bioside
Rubusoside
UGT76G1
UGT74G1
UGT76G1
UGT91D2e
UGT91D2e
RebB
1,3-Stevioside (RebG)
Stevioside
UGT76G1
UGT74G1
UGT76G1
EUGT11
EUGT11
RebQ
RebA
RebE
UGT76G1
UGT76G1
UGT76G1
RebI
RebD
RebM

Figure 3

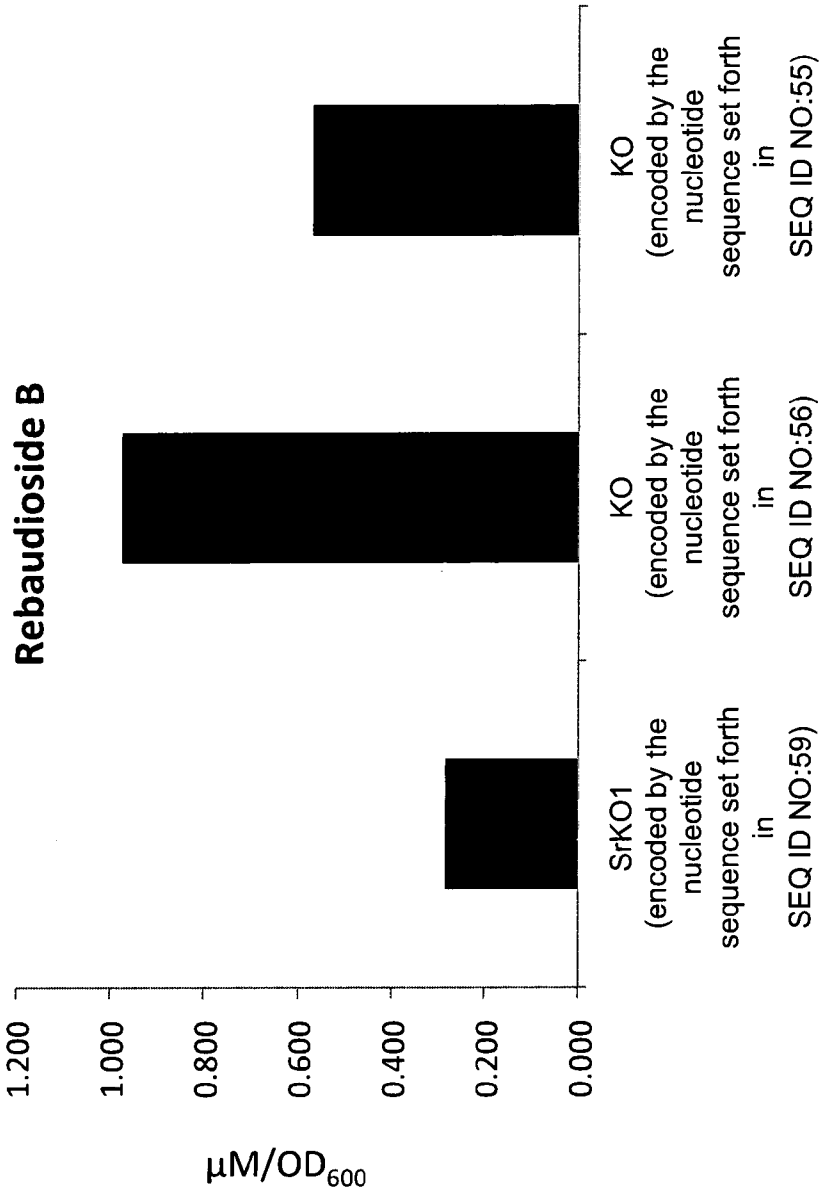
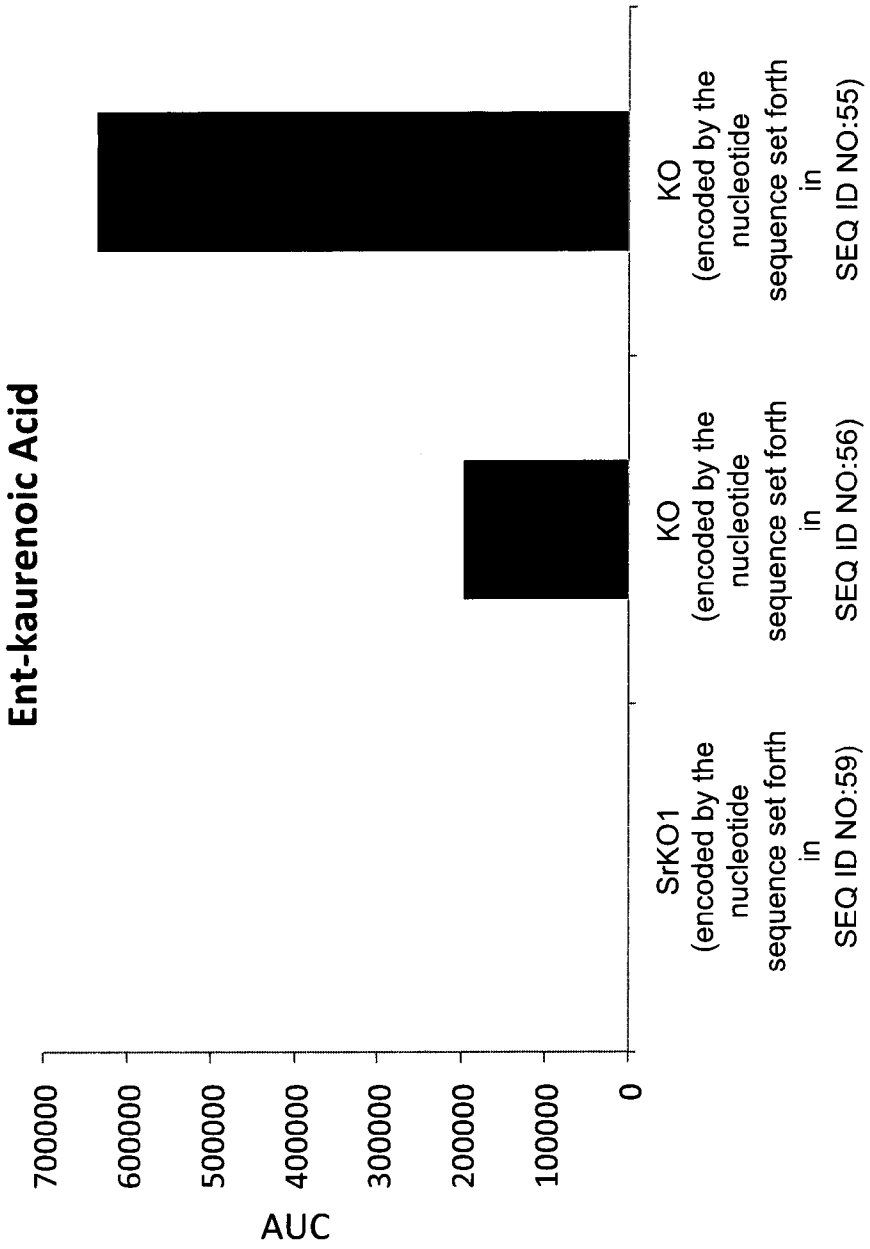

Rebaudioside B
1.200
1.000
0.800
0.600
0.400
0.200
0.000
µM/OD600
SrKO1 (encoded by the nucleotide sequence set forth in SEQ ID NO:59)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:56)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:55)

Figure 4


Ent-kaurenoic Acid
AUC
700000
600000
500000
400000
300000
200000
100000
0
SrKO1 (encoded by the nucleotide sequence set forth in SEQ ID NO:59)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:56)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:55)

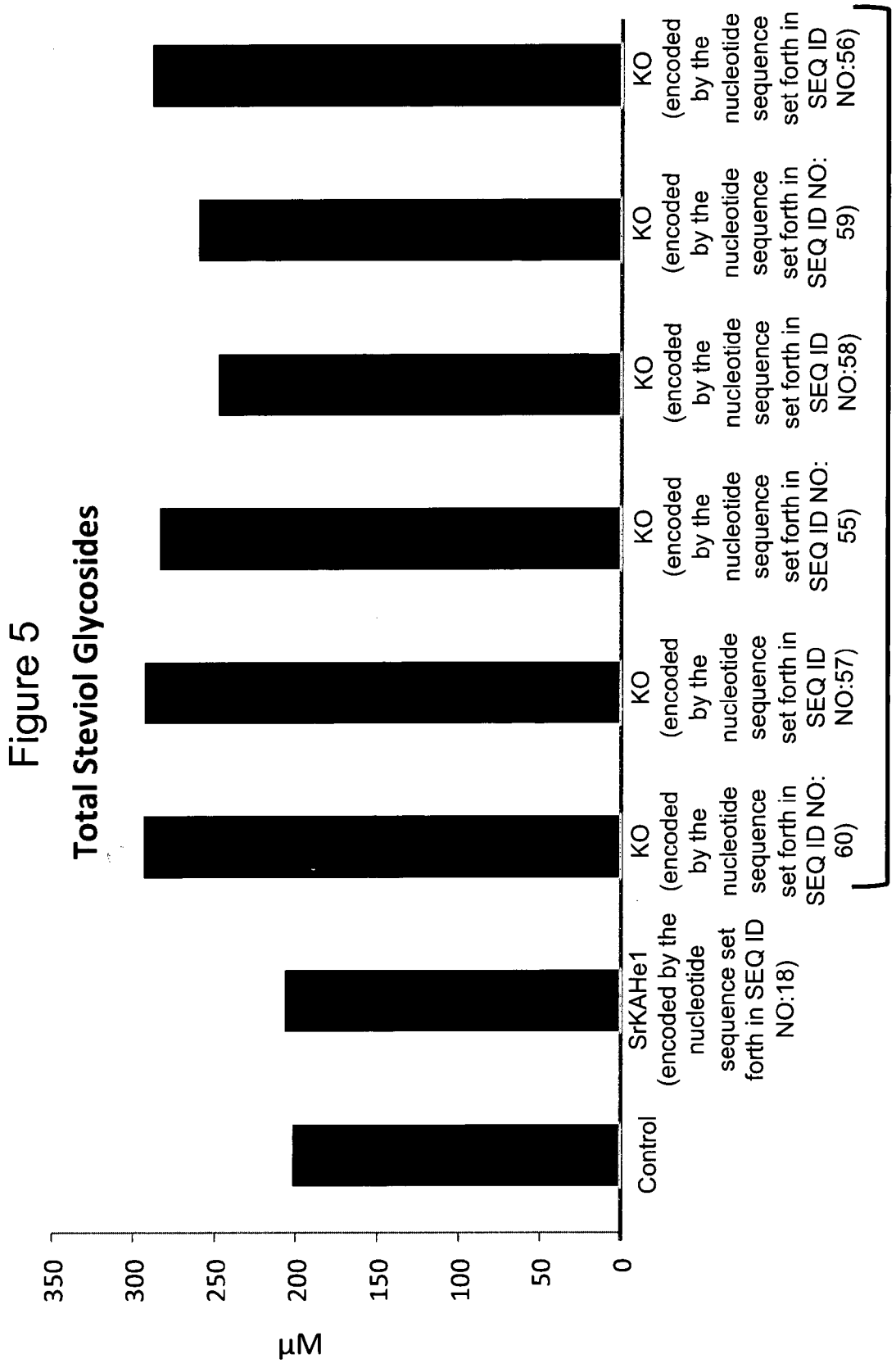


Figure 5
Total Steviol Glycosides
µM
350
300
250
200
150
100
50
0
Control
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO: 60)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:57)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO: 55)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:58)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO: 59)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:56)
+ SrKAHe1 (SEQ ID NO:18)

Figure 6

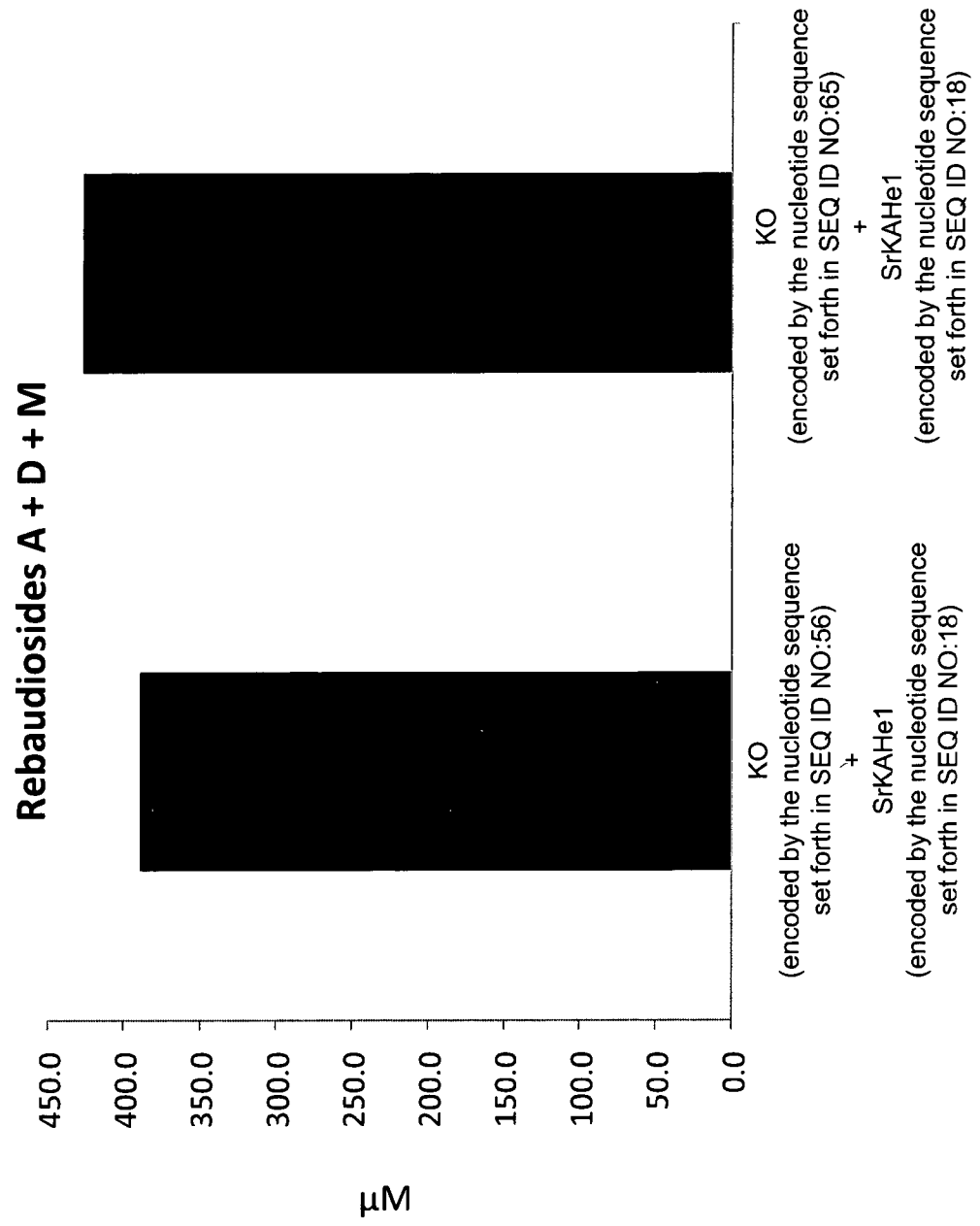

Rebaudiosides A + D + M
450.0
400.0
350.0
300.0
250.0
200.0
150.0
100.0
50.0
0.0
µM
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:56) + SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:65) + SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18)

Figure 7

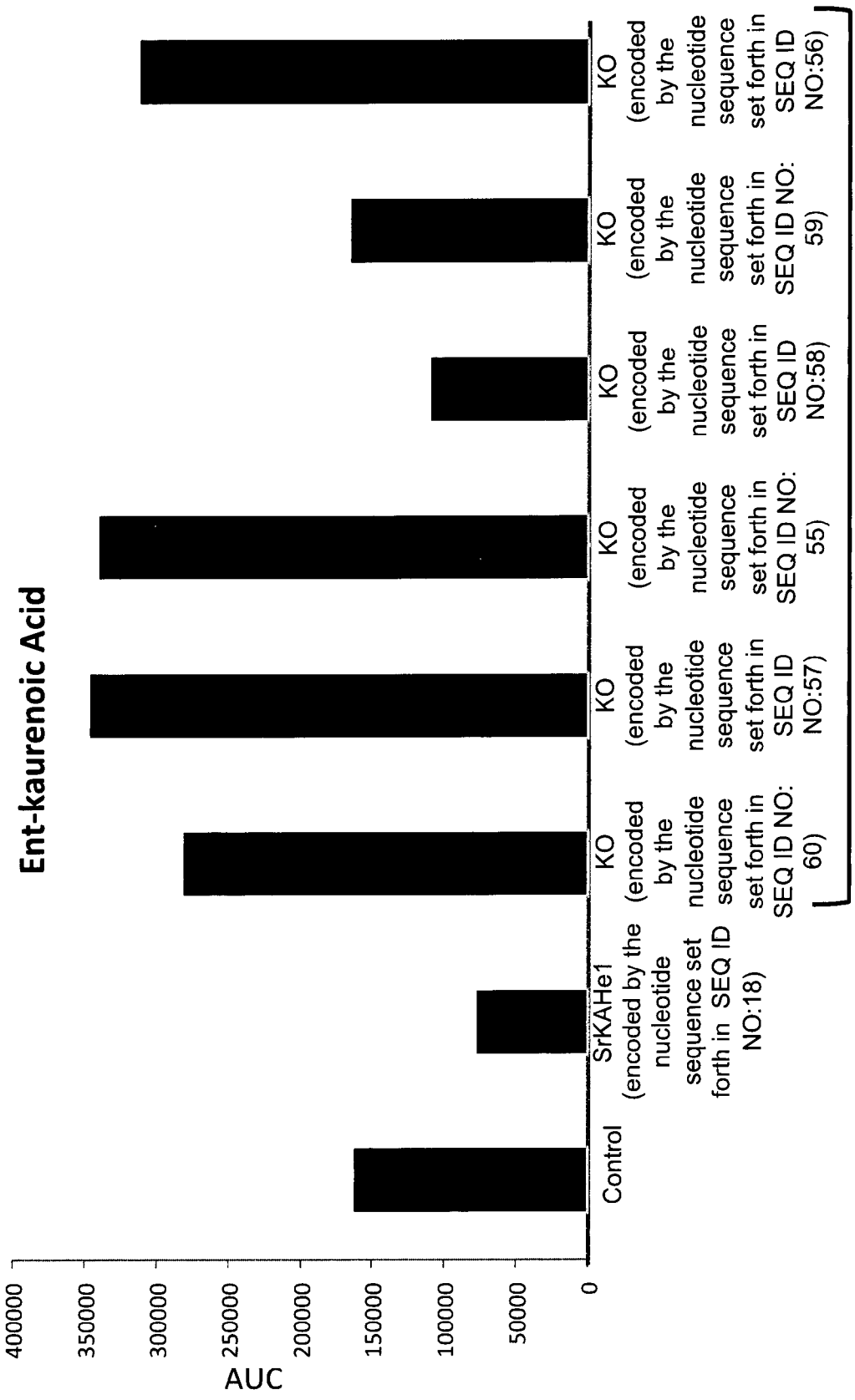

Ent-kaurenoic Acid
AUC
400000
350000
300000
250000
200000
150000
100000
50000
0
Control
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO: 60)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:57)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO: 55)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:58)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO: 59)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:56)
+ SrKAHe1 (SEQ ID NO:18)

Figure 8

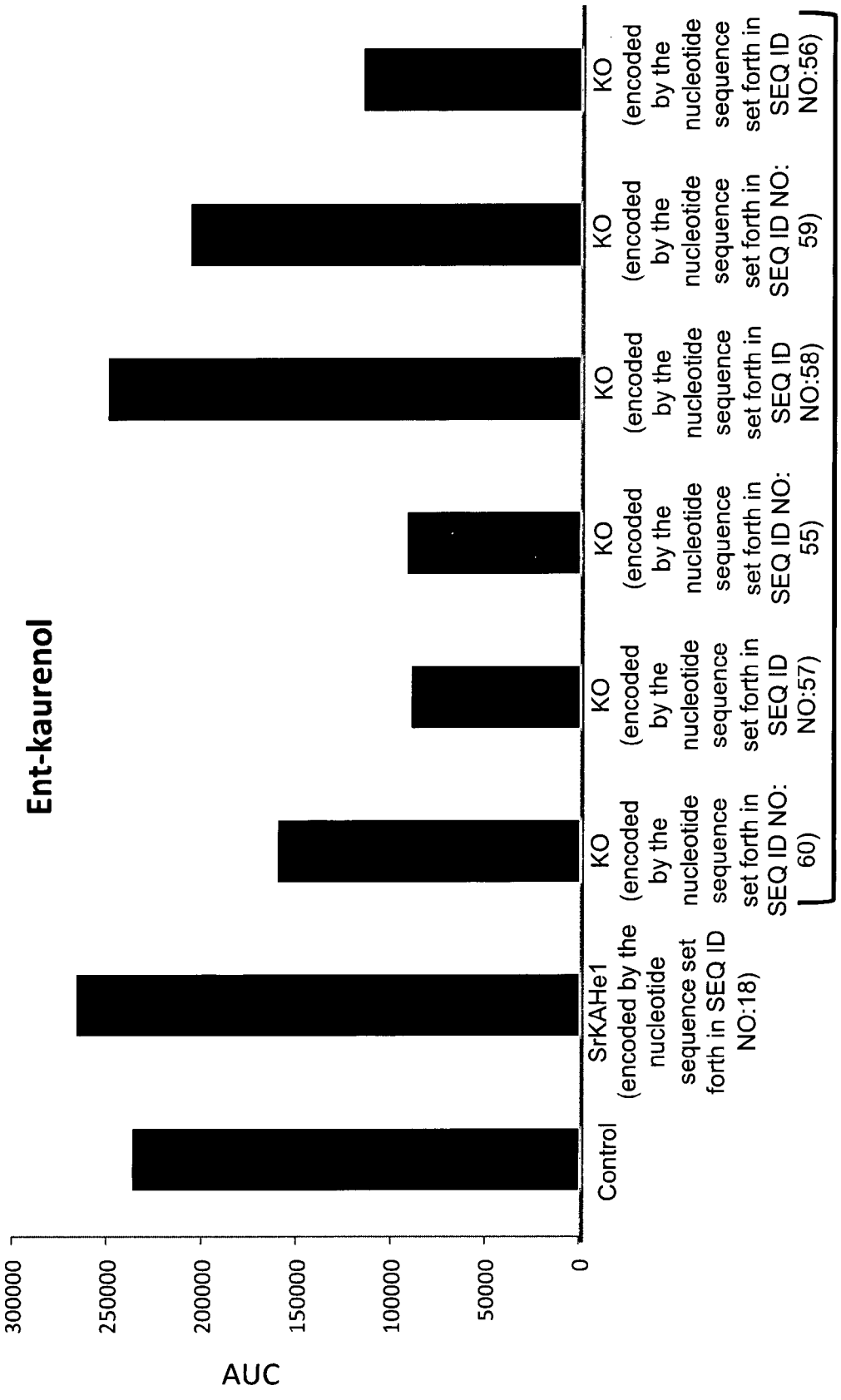

Ent-kaurenol
AUC
300000
250000
200000
150000
100000
50000
0
Control
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO: 60)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:57)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO: 55)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:58)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO: 59)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:56)
+ SrKAHe1 (SEQ ID NO:18)

Figure 9

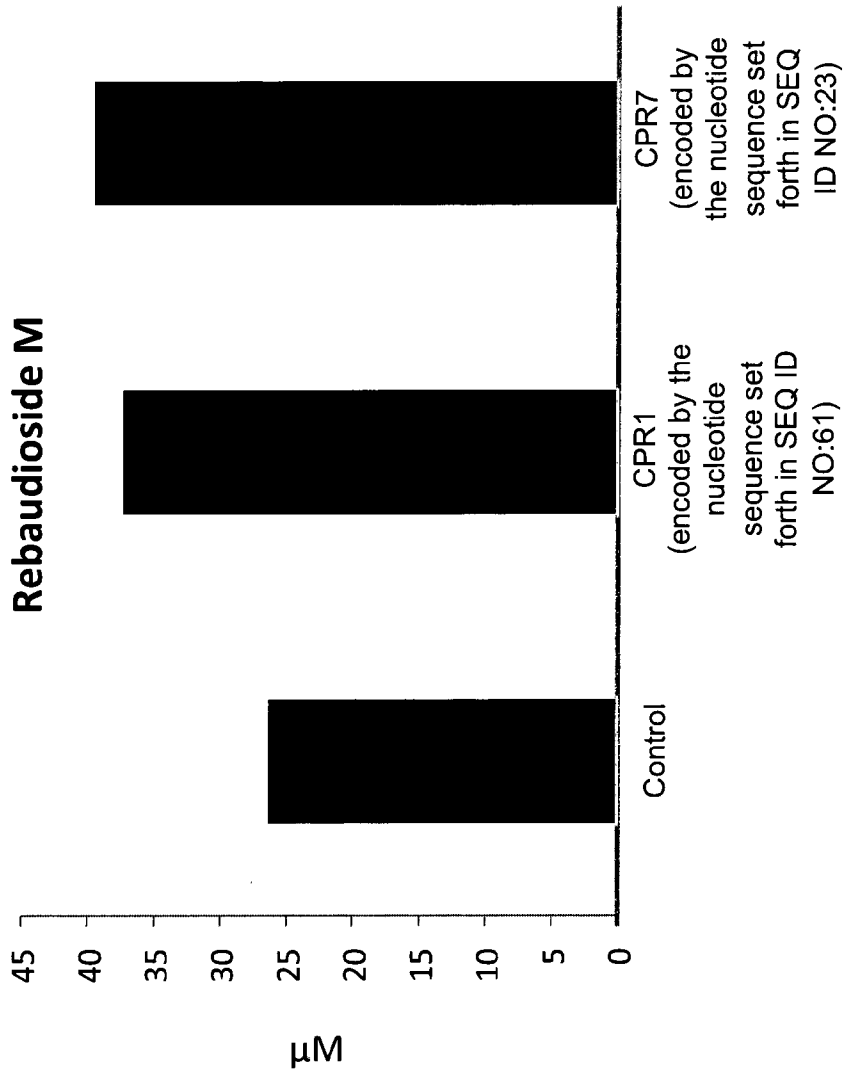

Rebaudioside M
45
40
35
30
25
20
15
10
5
0
µM
Control
CPR1 (encoded by the nucleotide sequence set forth in SEQ ID NO:61)
CPR7 (encoded by the nucleotide sequence set forth in SEQ ID NO:23)

Figure 10

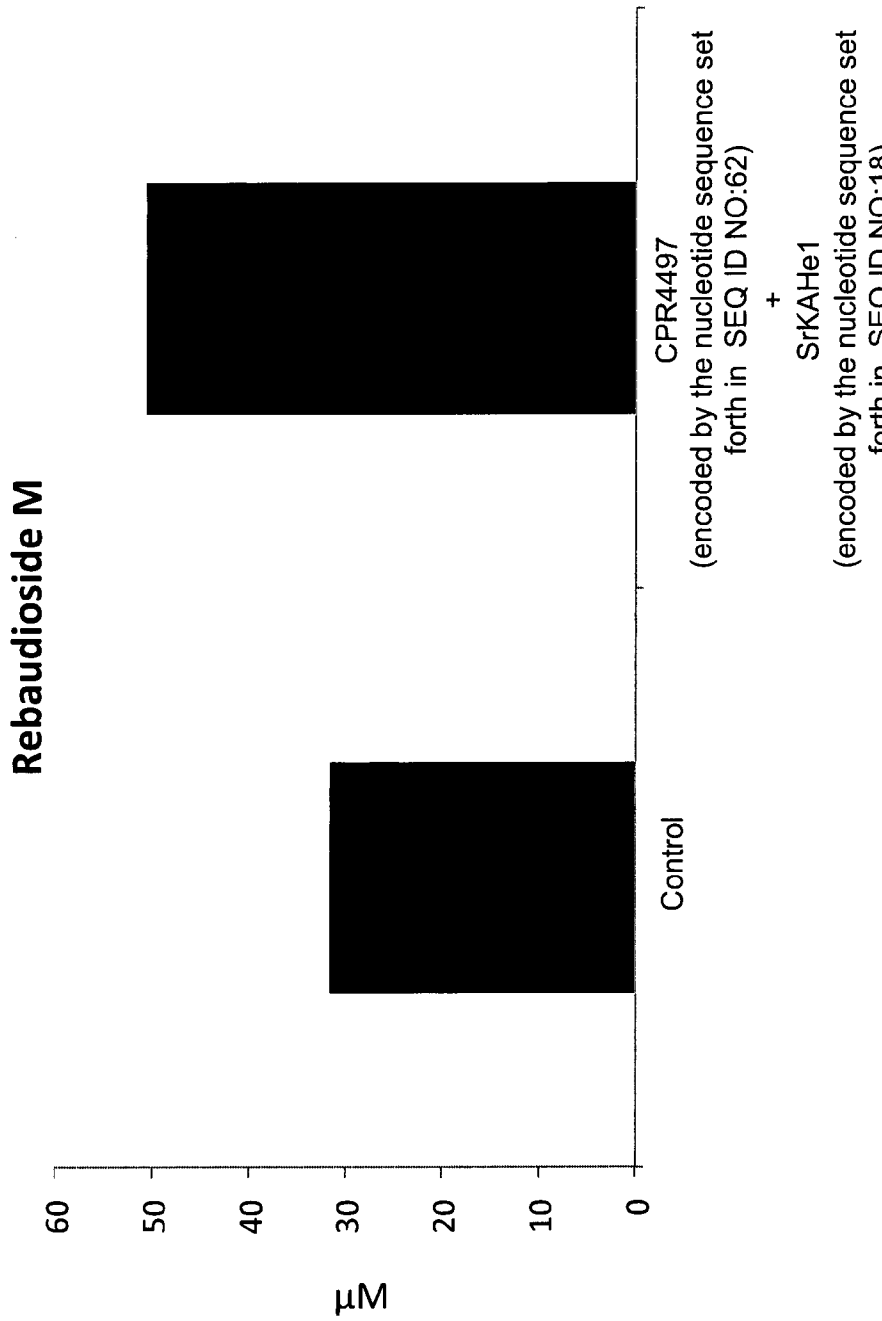

Rebaudioside M
60
50
40
30
20
10
0
µM
Control
CPR4497
(encoded by the nucleotide sequence set forth in SEQ ID NO:62)
+
SrKAHe1
(encoded by the nucleotide sequence set forth in SEQ ID NO:18)

Figure 11A

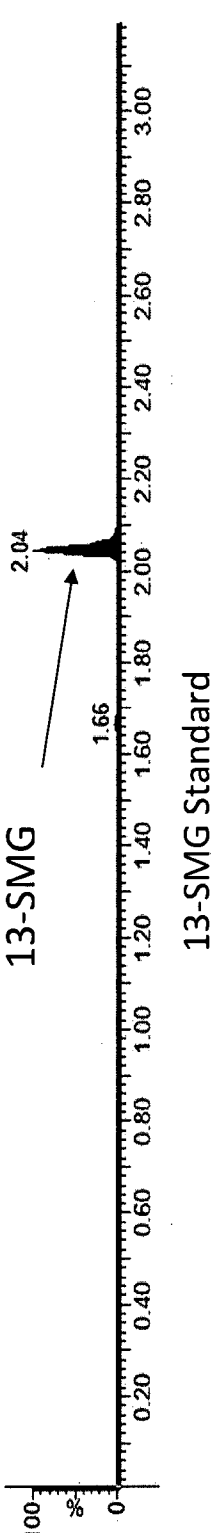
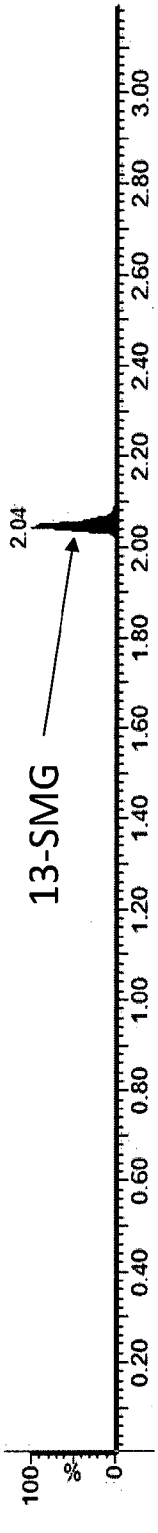


Figure 11B



S. cerevisiae expressing KAH encoded by nucleotide sequence set forth in SEQ ID NO:80

Figure 12

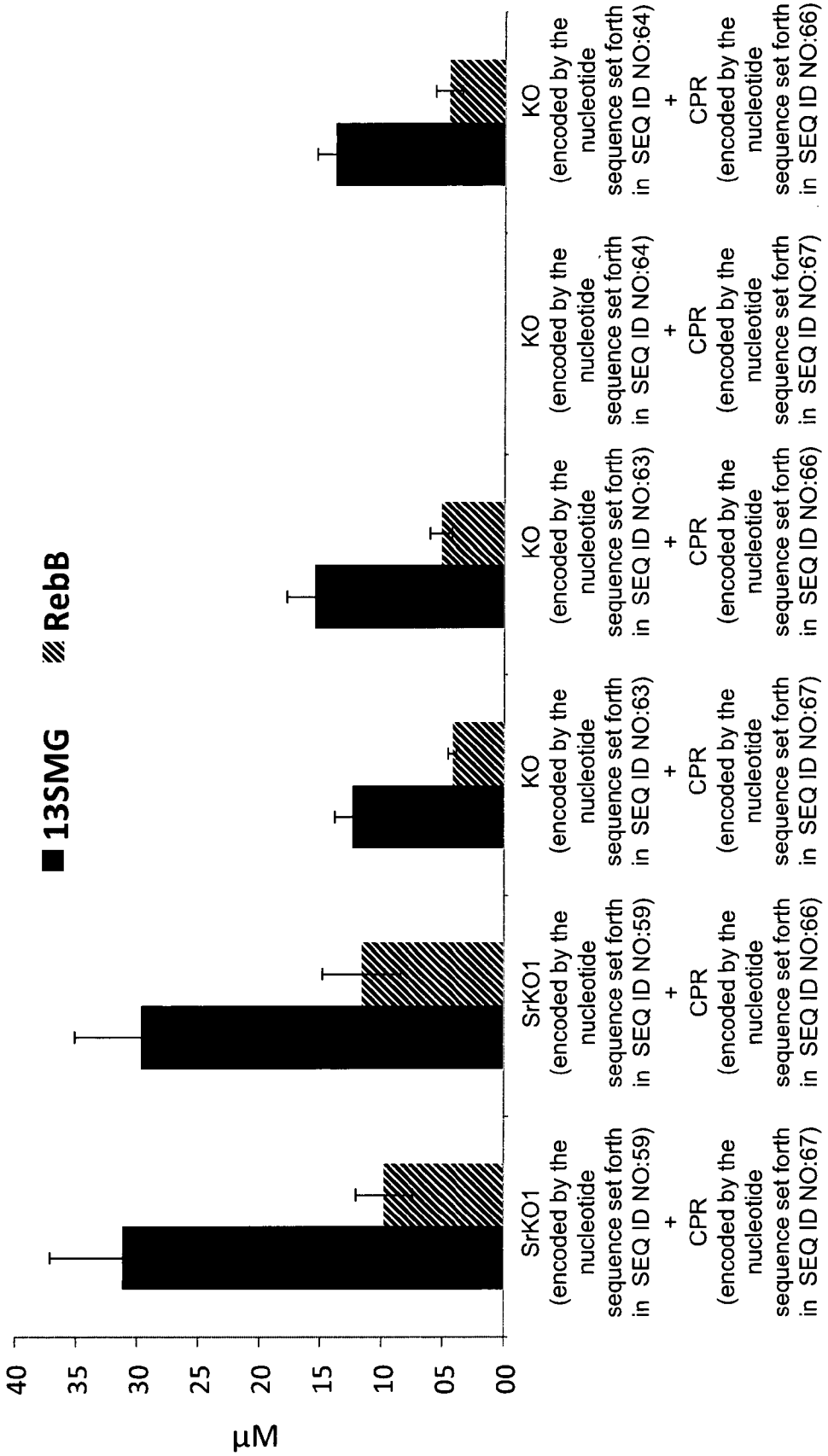

13SMG
RebB
µM
00
05
10
15
20
25
30
35
40
SrKO1 (encoded by the nucleotide sequence set forth in SEQ ID NO:67) + CPR (encoded by the nucleotide sequence set forth in SEQ ID NO:66)
SrKO1 (encoded by the nucleotide sequence set forth in SEQ ID NO:59) + CPR (encoded by the nucleotide sequence set forth in SEQ ID NO:66)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:67) + CPR (encoded by the nucleotide sequence set forth in SEQ ID NO:66)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:63) + CPR (encoded by the nucleotide sequence set forth in SEQ ID NO:66)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:64) + CPR (encoded by the nucleotide sequence set forth in SEQ ID NO:67)
KO (encoded by the nucleotide sequence set forth in SEQ ID NO:64) + CPR (encoded by the nucleotide sequence set forth in SEQ ID NO:66)

Figure 13

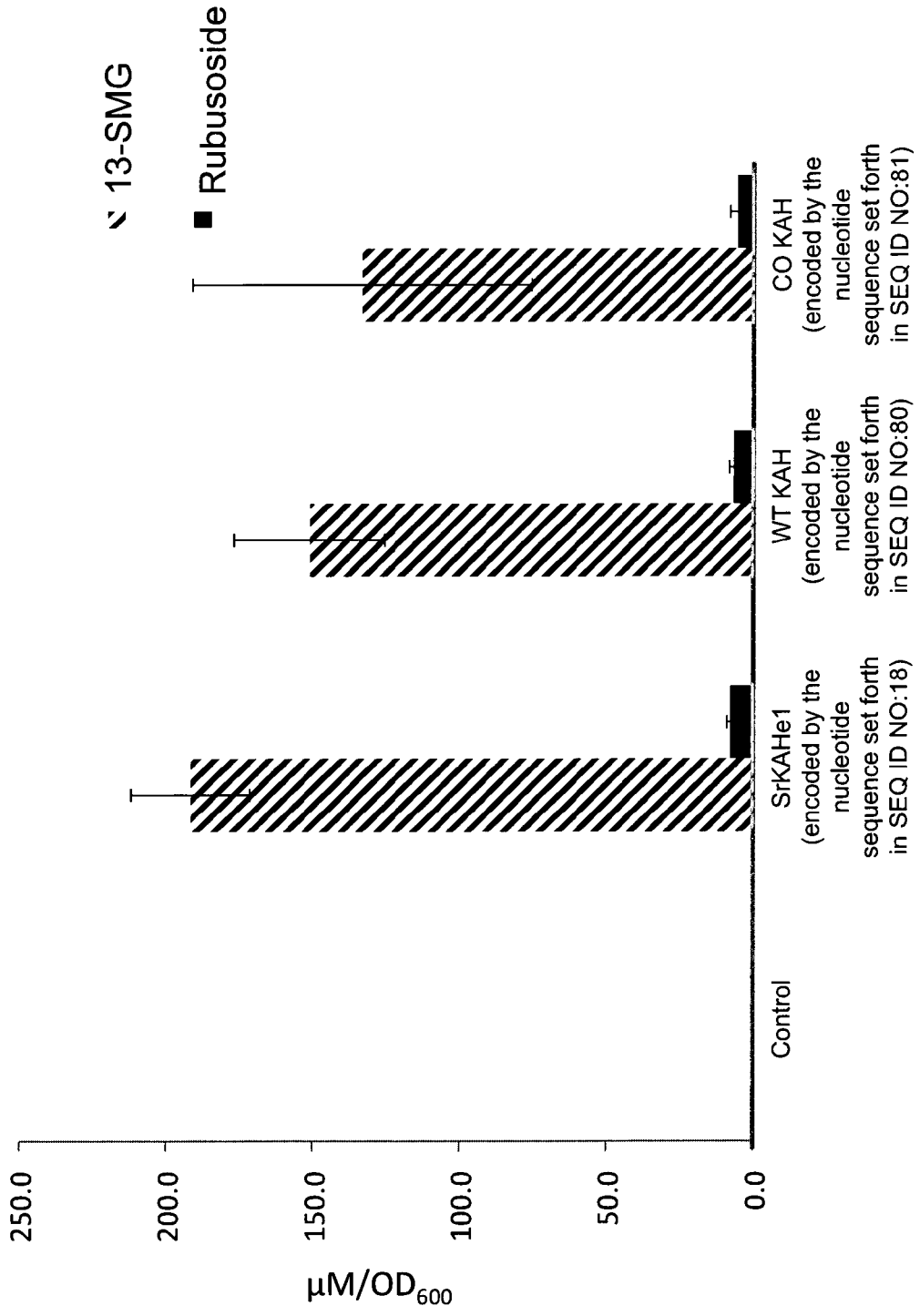

13-SMG
Rubusoside
250.0
200.0
150.0
100.0
50.0
0.0
µM/OD600
Control
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18)
WT KAH (encoded by the nucleotide sequence set forth in SEQ ID NO:80)
CO KAH (encoded by the nucleotide sequence set forth in SEQ ID NO:81)

Figure 14

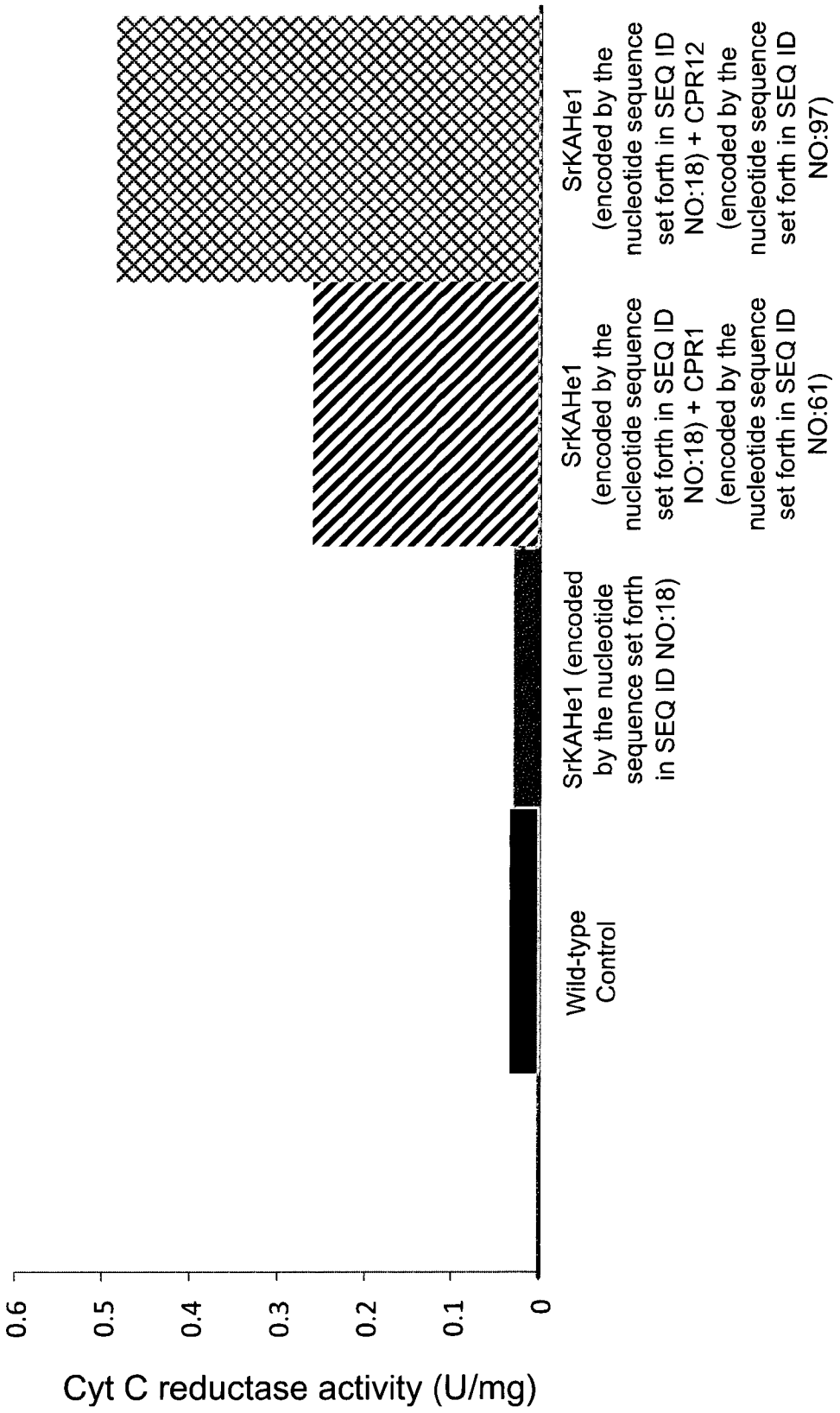

Cyt C reductase activity (U/mg)
0.6
0.5
0.4
0.3
0.2
0.1
0
Wild-type Control
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18)
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18) + CPR1 (encoded by the nucleotide sequence set forth in SEQ ID NO:61)
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18) + CPR12 (encoded by the nucleotide sequence set forth in SEQ ID NO:97)

Figure 15A

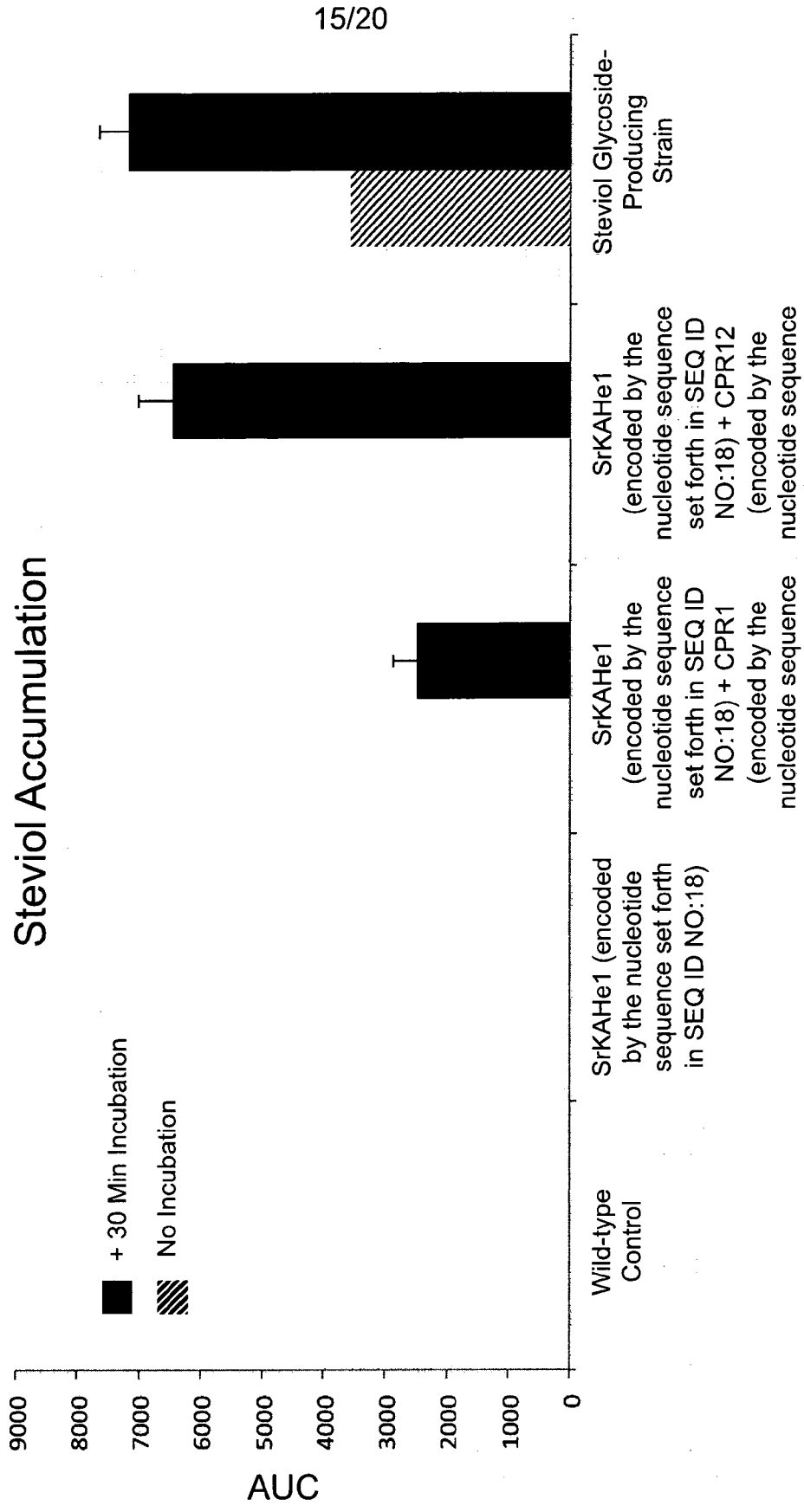

Steviol Accumulation
AUC
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
+ 30 Min Incubation
No Incubation
Wild-type Control
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18)
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18) + CPR1 (encoded by the nucleotide sequence set forth in SEQ ID NO:61)
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18) + CPR12 (encoded by the nucleotide sequence set forth in SEQ ID NO:97)
Steviol Glycoside-Producing Strain

Figure 15B

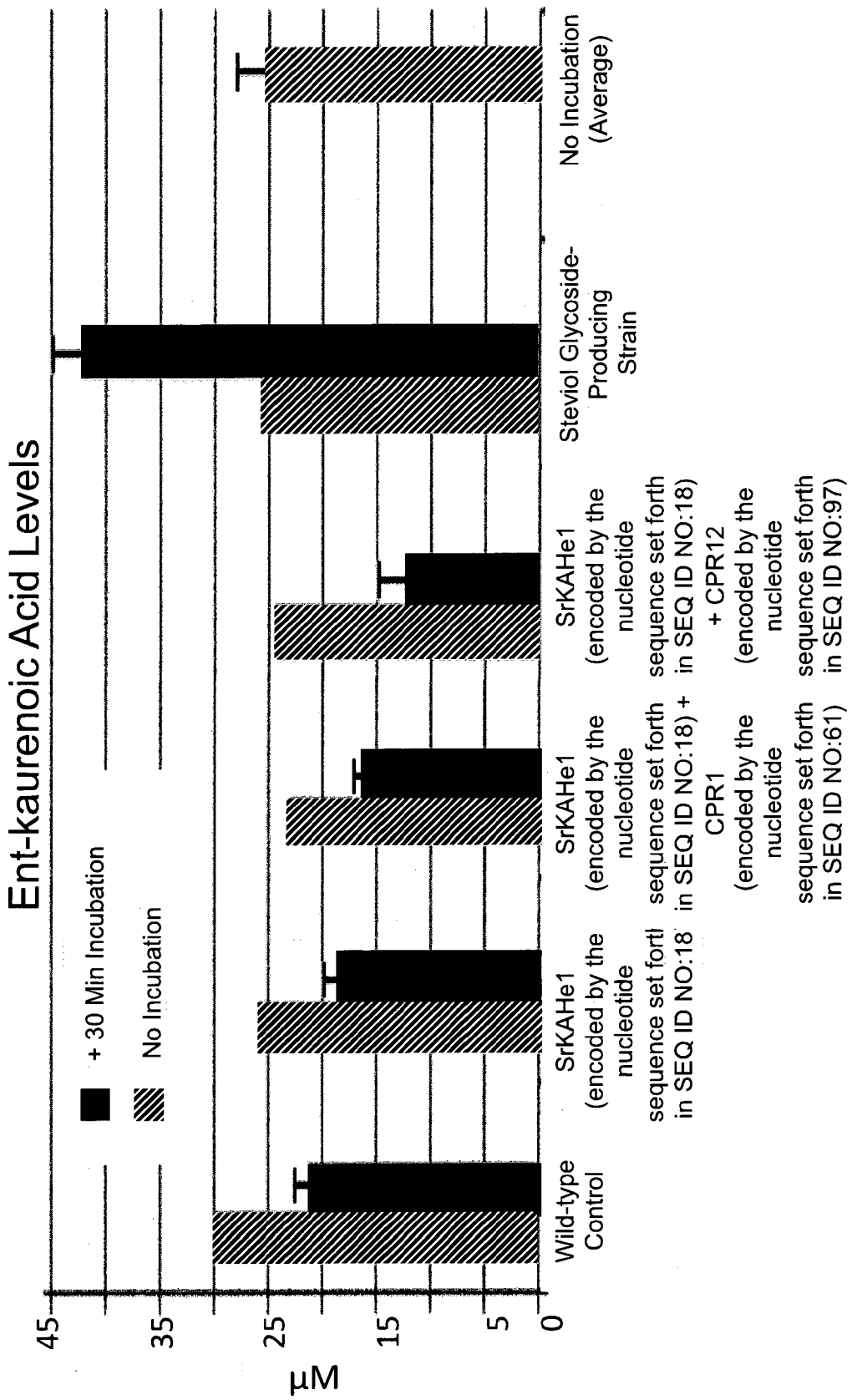

Ent-kaurenoic Acid Levels
+ 30 Min Incubation
No Incubation
µM
45
35
25
15
5
0
Wild-type Control
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18) + CPR1 (encoded by the nucleotide sequence set forth in SEQ ID NO:61)
SrKAHe1 (encoded by the nucleotide sequence set forth in SEQ ID NO:18) + CPR12 (encoded by the nucleotide sequence set forth in SEQ ID NO:97)
Steviol Glycoside-Producing Strain
No Incubation (Average)

Figure 16A

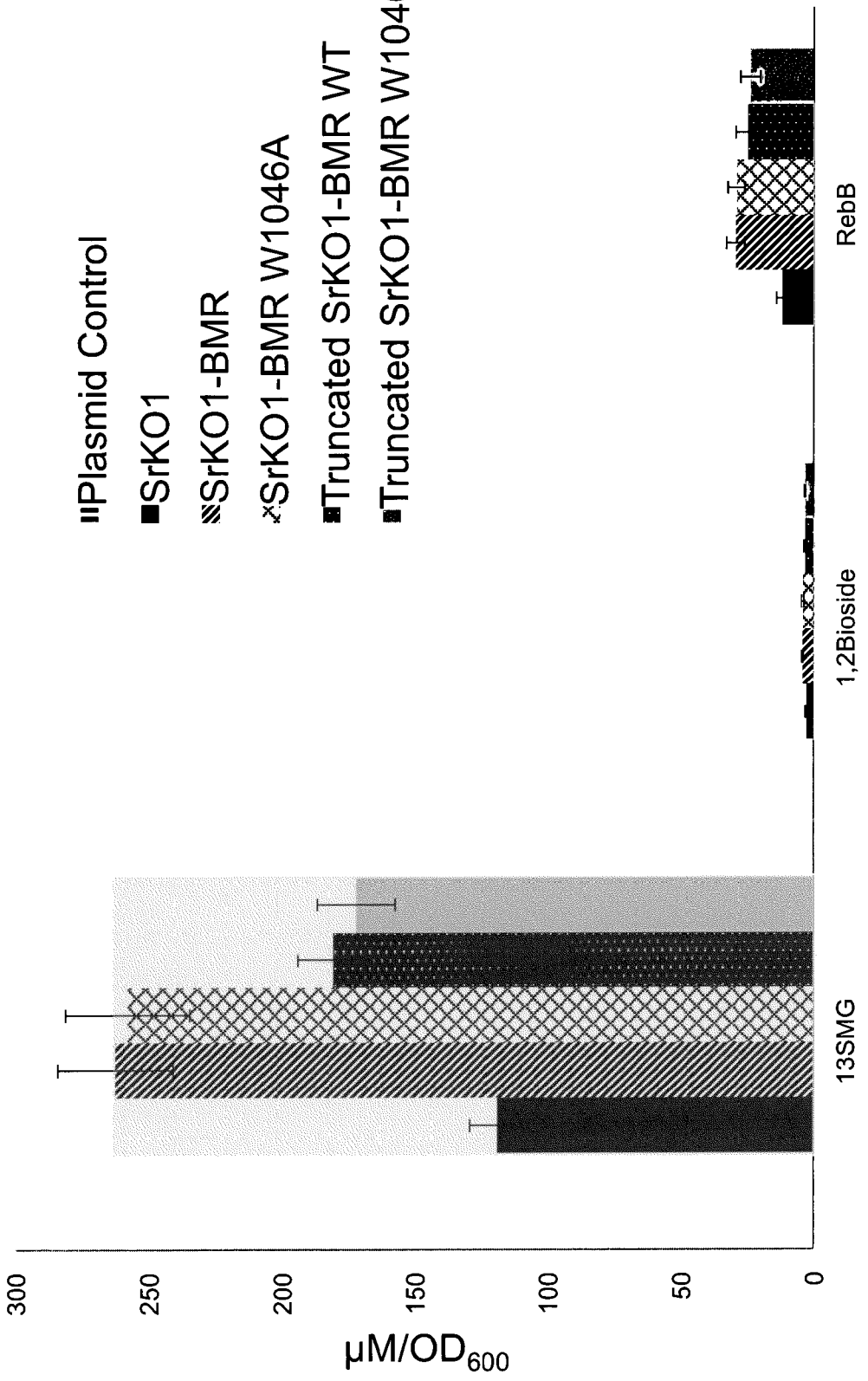

Plasmid Control
SrKO1
SrKO1-BMR
SrKO1-BMR W1046A
Truncated SrKO1-BMR WT
Truncated SrKO1-BMR W1046A
300
250
200
150
100
50
0
µM/OD600
13SMG
1,2Bioside
RebB

Figure 16B

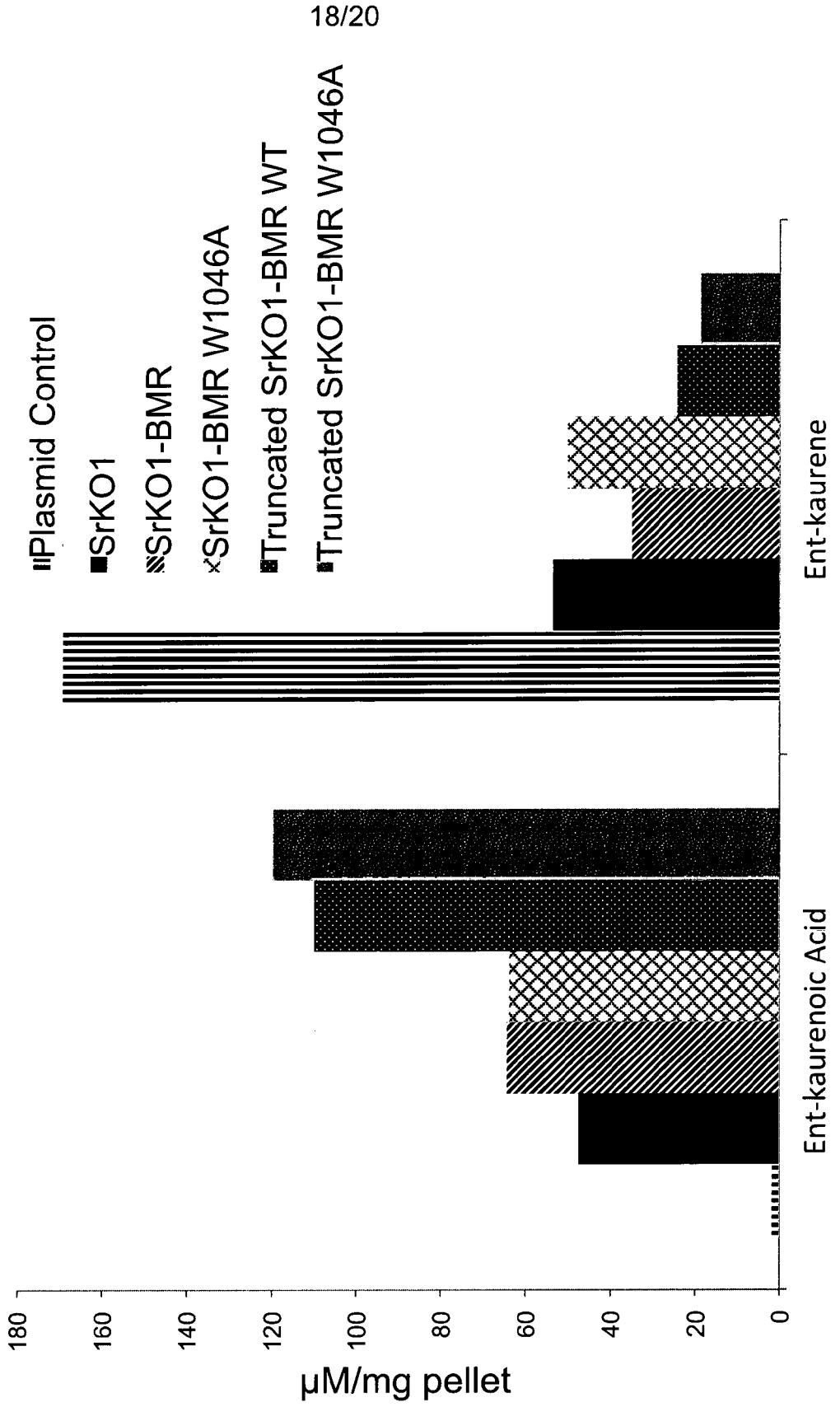

Plasmid Control
SrKO1
SrKO1-BMR
SrKO1-BMR W1046A
Truncated SrKO1-BMR WT
Truncated SrKO1-BMR W1046A
Ent-kaurene
Ent-kaurenoic Acid
180
160
140
120
100
80
60
40
20
0
µM/mg pellet

Figure 16C

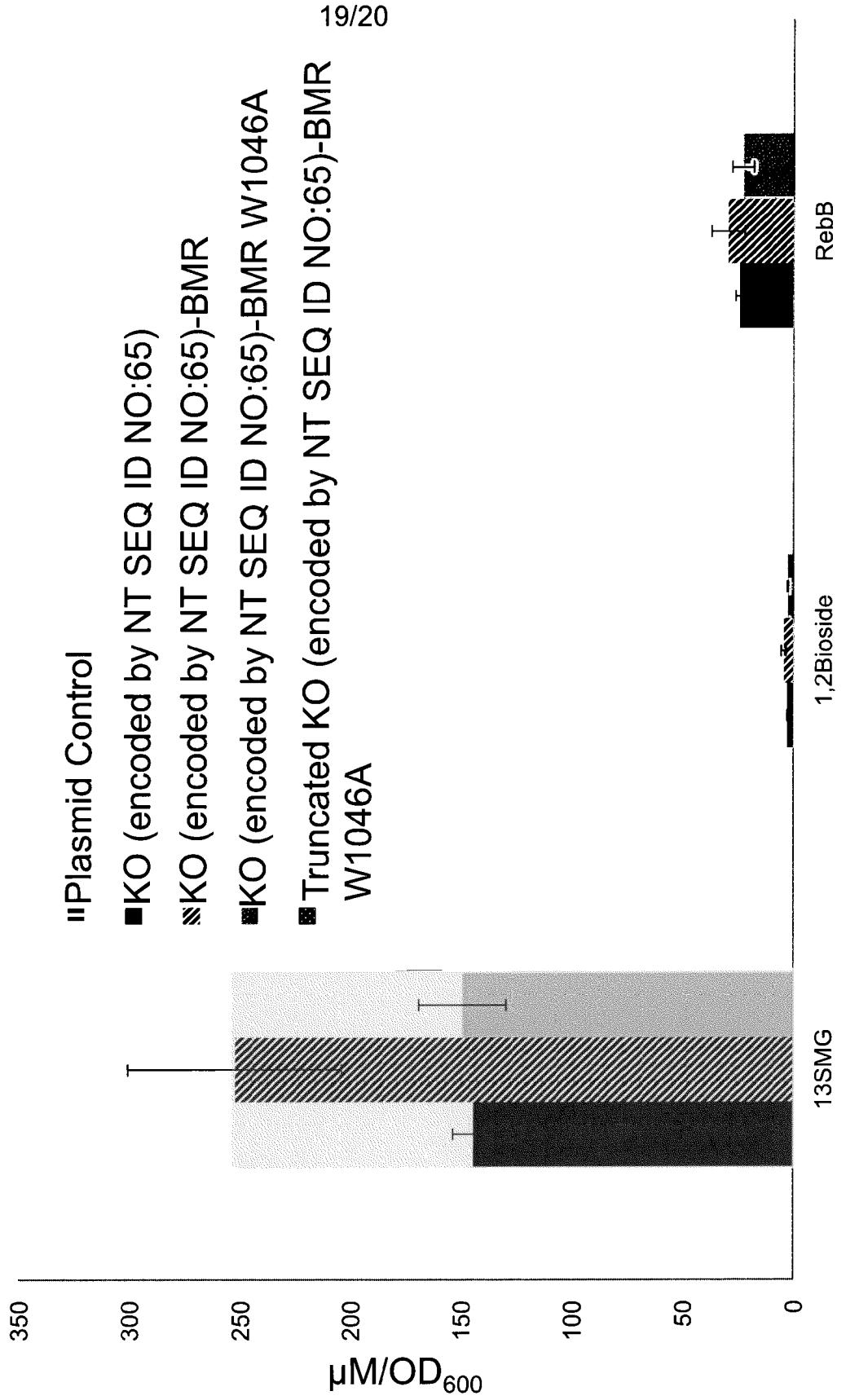
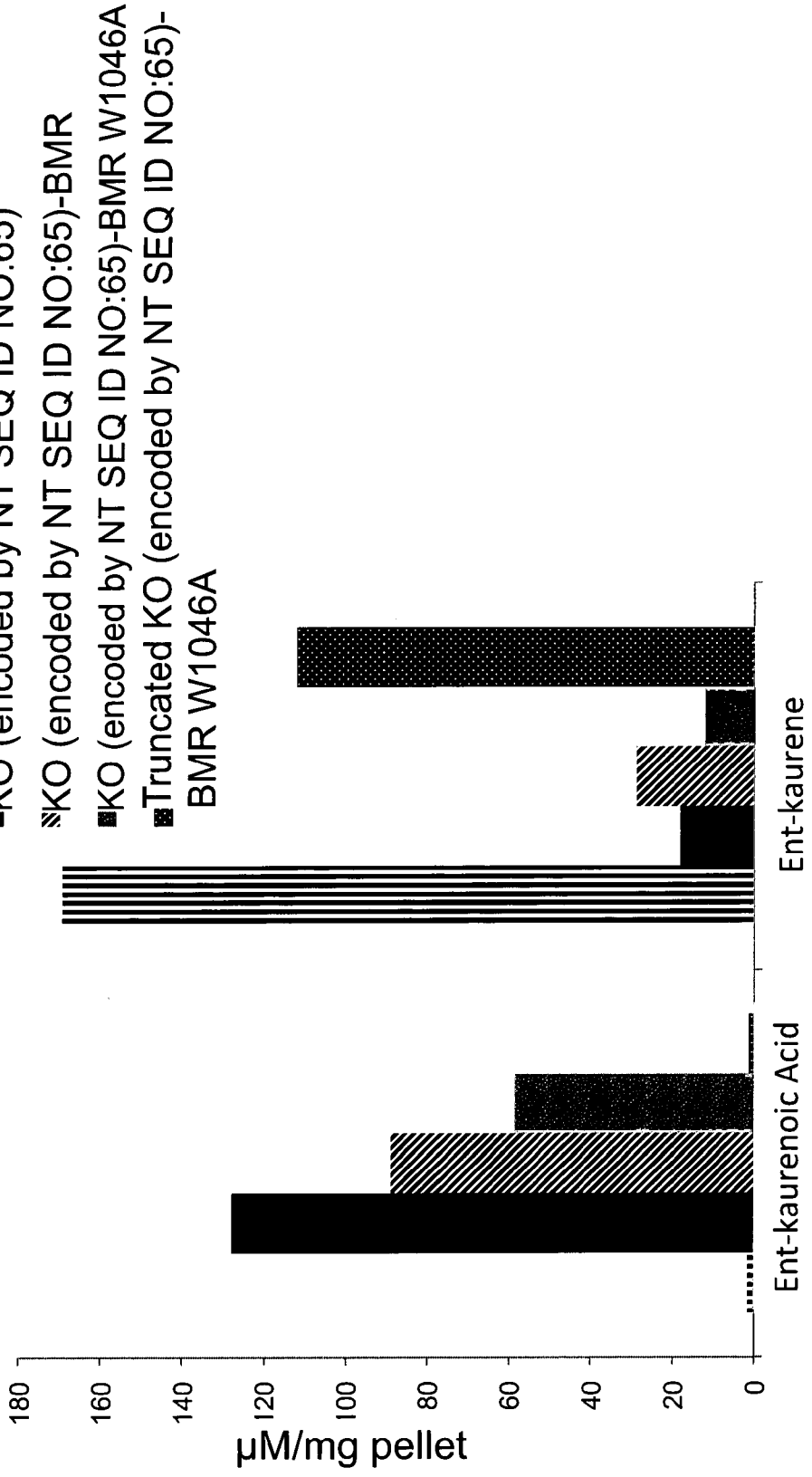

Plasmid Control
KO (encoded by NT SEQ ID NO:65)
KO (encoded by NT SEQ ID NO:65)-BMR
KO (encoded by NT SEQ ID NO:65)-BMR W1046A
Truncated KO (encoded by NT SEQ ID NO:65)-BMR W1046A
µM/OD600
350
300
250
200
150
100
50
0
13SMG
1,2Bioside
RebB

Figure 16D


Plasmid Control
KO (encoded by NT SEQ ID NO:65)
KO (encoded by NT SEQ ID NO:65)-BMR
KO (encoded by NT SEQ ID NO:65)-BMR W1046A
Truncated KO (encoded by NT SEQ ID NO:65)-BMR W1046A
180
160
140
120
100
80
60
40
20
0
µM/mg pellet
Ent-kaurenoic Acid
Ent-kaurene