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High Activity Mutants of Butyrylcholinesterase for Cocaine Hydrolysis

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(54) **HIGH ACTIVITY MUTANTS OF BUTYRYLCHOLINESTERASE FOR COCAINE HYDROLYSIS**

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(51) **Int. Cl.**

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(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

PUBLICATIONS

Brimijoin, S. et al., Neuropsychopharmacology 2008, 33, 2715-2725.

Xie, W.; Altamirano, C. V.; Bartels, C. F.; Speirs, R. J.; Cashman, J. R.; Lockridge, O. Mol. Pharmacol. 1999, 55, 83.

Xue, L.; Ko, M.-C.; Tong, M.; Yang, W.; Hou, S.; Fang, L.; Liu, J.; Zheng, F.; Woods, J. H.; Tai, H.-H.; Zhan, C.-G. “Design, preparation, and characterization of high-activity mutants of human butyrylcholinesterase specific for detoxification of cocaine”, Mol. Pharmacol. 2011, 79, 290-297.

Yang, W.; Pan, Y.; Fang, L.; Gao, D.; Zheng, F.; Zhan, C.-G. “Free-energy perturbation simulation on transition states and high-activity mutants of human butyrylcholinesterase for (−)-cocaine hydrolysis”, J. Phys. Chem. B 2010, 114, 10889-10896.

Yang, W.; Xue, L.; Fang, L.; Zhan, C.-G. “Characterization of a high-activity mutant of human butyrylcholinesterase against (−)-cocaine”, Chemico-Biological Interactions, 2010, 187, 148-152.

Zheng, F.; Yang, W.; Xue, L.; Hou, S.; Liu, J.; Zhan, C.-G. “Design of high-activity mutants of human butyrylcholinesterase against (−)-cocaine: structural and energetic factors affecting the catalytic efficiency”, Biochemistry 2010, 49, 9113-9119.

Zheng, F.; Yang, W.; Ko, M.-C.; Liu, J.; Cho, H.; Gao, D.; Tong, M.; Tai, H.-H.; Woods, J. H.; Zhan, C.-G. “Most Efficient Cocaine Hydrolase Designed by Virtual Screening of Transition States”, J. Am. Chem. Soc. 2008, 130, 12148-12155.

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(57) **ABSTRACT**

Butyrylcholinesterase (BChE) polypeptide variants of the presently-disclosed subject matter have enhanced catalytic efficiency for (−)-cocaine, as compared to wild-type BChE. Pharmaceutical compositions of the presently-disclosed subject matter include a BChE polypeptide variant having an enhanced catalytic efficiency for (−)-cocaine. A method of the presently-disclosed subject matter for treating a cocaine-induced condition includes administering to an individual an effective amount of a BChE polypeptide variant, as disclosed herein, to lower blood cocaine concentration.

2 Claims, No Drawings

HIGH ACTIVITY MUTANTS OF BUTYRYLCHOLINESTERASE FOR COCAINE HYDROLYSIS

RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application Ser. No. 61/443,932 filed Feb. 17, 2011, and is a division of U.S. patent application Ser. No. 14/061,405 filed Oct. 23, 2013, now allowed, which is a division of U.S. patent application Ser. No. 13/399,406 filed Feb. 17, 2012, now issued as U.S. Pat. No. 8,592,193. The entire disclosures contained in each of these Applications are incorporated herein by this reference.

GOVERNMENT INTEREST

Subject matter described herein was made with government support under Grant Number R01DA013930 awarded by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH). The government has certain rights in the described subject matter.

TECHNICAL FIELD

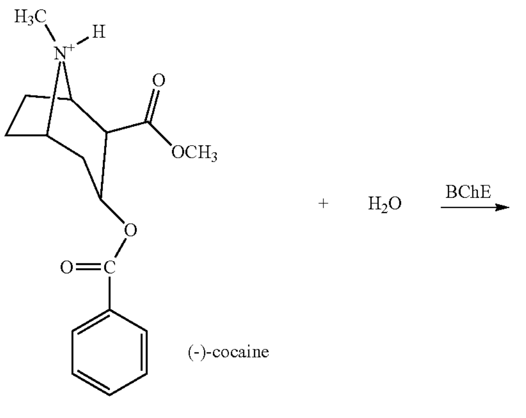
The presently-disclosed subject matter relates to butyrylcholinesterase variant polypeptides, and in particular, butyrylcholinesterase mutants having amino acid substitutions.

INTRODUCTION

Cocaine abuse is a major medical and public health problem that continues to defy treatment. The disastrous medical and social consequences of cocaine addiction, such as violent crime, loss in individual productivity, illness, and death, have made the development of an effective pharmacological treatment a high priority. However, cocaine mediates its reinforcing and toxic effects by blocking neurotransmitter reuptake and the classical pharmacodynamic approach has failed to yield small-molecule receptor/transporter antagonists due to the difficulties inherent in blocking a blocker. An alternative to pharmacodynamic approach is to interfere with the delivery of cocaine to its receptors/transporters and accelerate its metabolism in the body.

The dominant pathway for cocaine metabolism in primates is butyrylcholinesterase (BChE)-catalyzed hydrolysis at the benzoyl ester group (Scheme 1).

Scheme 1. Schematic representation of BChE-catalyzed hydrolysis at the benzoyl ester group.



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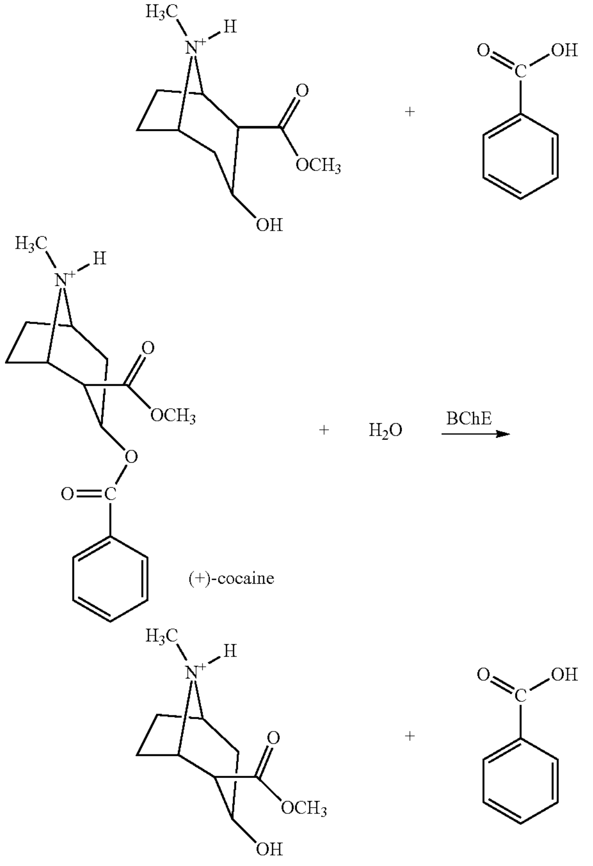

Only 5% of the cocaine is deactivated through oxidation by the liver microsomal cytochrome P450 system. Cocaine hydrolysis at benzoyl ester group yields ecgonine methyl ester, whereas the oxidation produces norcocaine. The metabolite ecgonine methyl ester is a biologically inactive metabolite, whereas the metabolite norcocaine is hepatotoxic and a local anesthetic. In human beings, more than 90% of cocaine is metabolized by BChE. BChE is synthesized in the liver and widely distributed in the body, including plasma, brain, and lung. Extensive experimental studies in animals and humans demonstrate that enhancement of BChE activity by administration of exogenous enzyme substantially decreases cocaine half-life.

Enhancement of cocaine metabolism by administration of BChE has been recognized to be a promising pharmacokinetic approach for treatment of cocaine abuse and dependence. However, the catalytic activity of this plasma enzyme is three orders-of-magnitude lower against the naturally occurring (−)-cocaine than that against the biologically inactive (+)-cocaine enantiomer. (+)-cocaine can be cleared from plasma in seconds and prior to partitioning into the central nervous system (CNS), whereas (−)-cocaine has a plasma half-life of approximately 45-90 minutes (for a relatively low dose of cocaine), long enough for manifestation of the CNS effects which peak in minutes. Under the overdose condition, BChE is saturated with (−)-cocaine and, thus, the plasma half-life of (−)-cocaine will be longer. Hence, BChE mutants with high activity against (−)-cocaine are highly desired for use in humans. Although some BChE mutants with increased catalytic activity over wild-type BChE have previously been generated, there exists a need for mutant BChE with even higher catalytic activity.

SUMMARY

The presently-disclosed subject matter meets some or all of the above-identified needs, as will become evident to those of ordinary skill in the art after a study of information provided in this document.

This Summary describes several embodiments of the presently-disclosed subject matter, and in many cases lists variations and permutations of these embodiments. This Summary is merely exemplary of the numerous and varied embodiments. Mention of one or more representative features of a given embodiment is likewise exemplary. Such an embodiment can typically exist with or without the feature(s) mentioned; likewise, those features can be applied to other embodiments of the presently-disclosed subject matter, whether listed in this Summary or not. To avoid excessive repetition, this Summary does not list or suggest all possible combinations of such features.

The presently-disclosed subject matter includes butyrylcholinesterase (BChE) polypeptide variants. In some embodiments the amino acid sequence of the BChE polypeptide variant includes an amino acid sequence selected from the group consisting of: SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, and 46 as set forth herein. The presently-disclosed subject matter further includes nucleic acid molecules that encodes a BChE polypeptide variant, including the nucleic acid sequence selected from the group consisting of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, and 45.

The presently-disclosed subject matter further includes a pharmaceutical composition that includes a butyrylcholinesterase polypeptide variant and a suitable pharmaceutical carrier.

The presently-disclosed subject matter further includes a method of treating a cocaine-induced condition, which includes administering to an individual an effective amount of BChE polypeptide variant or functional fragment thereof, or a pharmaceutical composition comprising a BChE polypeptide variant or functional fragment thereof, as described herein, to lower blood cocaine concentration. In some embodiments, the BChE polypeptide variant exhibits a one-hundred-fold or more increase in cocaine hydrolysis catalytic efficiency compared to wild-type butyrylcholinesterase.

The presently-disclosed subject matter further includes a method of treating a cocaine-induced condition, which includes administering to an individual an effective amount of a BChE nucleotide variant, i.e., a nucleotide molecule encoding a BChE polypeptide variant or functional fragment thereof as disclosed herein.

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

SEQ ID NO: 1 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 2;

SEQ ID NO: 2 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227S, S287G, A328W, and Y332G;

SEQ ID NO: 3 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 4;

SEQ ID NO: 4 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227T, S287G, A328W, and Y332G;

SEQ ID NO: 5 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 6;

SEQ ID NO: 6 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227M, S287G, A328W, and Y332G;

SEQ ID NO: 7 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 8;

SEQ ID NO: 8 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227C, S287G, A328W, and Y332G;

SEQ ID NO: 9 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 10;

SEQ ID NO: 10 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227A, P285N, S287G, A328W, and Y332G;

SEQ ID NO: 11 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 12;

SEQ ID NO: 12 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227P, P285A, S287G, A328W, and Y332G;

SEQ ID NO: 13 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 14;

SEQ ID NO: 14 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227S, P285Q, S287G, A328W, and Y332G;

SEQ ID NO: 15 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 16;

SEQ ID NO: 16 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227S, P285S, S287G, A328W, and Y332G;

SEQ ID NO: 17 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 18;

SEQ ID NO: 18 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227S, P285G, S287G, A328W, and Y332G;

SEQ ID NO: 19 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 20;

SEQ ID NO: 20 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227P, P285S, L286M, S287G, A328W, and Y332G;

SEQ ID NO: 21 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 22;

SEQ ID NO: 22 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227A, P285S, S287G, A328W, and E441D;

SEQ ID NO: 23 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 24;

SEQ ID NO: 24 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227A, P285A, S287G, A328W, and E441D;

SEQ ID NO: 25 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 26;

SEQ ID NO: 26 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227P, L286M, S287G, A328W, and Y332G;

SEQ ID NO: 27 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 28;

SEQ ID NO: 28 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227G, P285A, S287G, A328W, and Y332G;

SEQ ID NO: 29 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 30;

SEQ ID NO: 30 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227G, P285G, S287G, A328W, and Y332G;

SEQ ID NO: 31 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 32;

SEQ ID NO: 32 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227G, P285Q, S287G, A328W, and Y332G;

SEQ ID NO: 33 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 34;

SEQ ID NO: 34 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227G, P285S, S287G, A328W, and Y332G;

SEQ ID NO: 35 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 36;

SEQ ID NO: 36 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227A, P285E, S287G, A328W, and Y332G;

SEQ ID NO: 37 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 38;

SEQ ID NO: 38 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227P, P285N, S287G, A328W, and Y332G;

SEQ ID NO: 39 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 40;

SEQ ID NO: 40 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227S, P285A, S287G, A328W, and Y332G;

SEQ ID NO: 41 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 42;

SEQ ID NO: 42 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227S, P285N, S287G, A328W, and Y332G;

SEQ ID NO: 43 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 44;

SEQ ID NO: 44 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227S, L286M, S287G, A328W, and Y332G;

SEQ ID NO: 45 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 46;

SEQ ID NO: 46 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227G, L286M, S287G, A328W, and Y332G;

DESCRIPTION OF EXEMPLARY EMBODIMENTS

The details of one or more embodiments of the presently-disclosed subject matter are set forth in this document. Modifications to embodiments described in this document, and other embodiments, will be evident to those of ordinary skill in the art after a study of the information provided in this document. The information provided in this document, and particularly the specific details of the described exemplary embodiments, is provided primarily for clearness of understanding and no unnecessary limitations are to be understood therefrom. In case of conflict, the specification of this document, including definitions, will control.

The presently-disclosed subject matter includes butyrylcholinesterase (BChE) polypeptide variants. The BChE polypeptide variants disclosed herein each have enhanced catalytic efficiency for (−)-cocaine, as compared to wild-type BChE. The presently-disclosed subject matter further includes a pharmaceutical composition including a butyrylcholinesterase polypeptide variant, as described herein, and a suitable pharmaceutical carrier. The presently-disclosed subject matter further includes a method of treating a cocaine-induced condition comprising administering to an individual an effective amount of a butyrylcholinesterase polypeptide variant of functional fragement there of, or a BChE nucleotide variant, i.e., a nucleotide molecule encoding a BChE polypeptide variant or functional fragment thereof, as disclosed herein, to lower blood cocaine concentration. A cocaine-induced condition includes conditions resulting from the administration/use of cocaine, including, for example, treatment for an addiction to cocaine. For example, a polypeptide or nucleotide, as described herein, could be administered prior to the use of cocaine as part of an addiction treatment strategy.

In some embodiments, the BChE polypeptide variant is selected from a BChE polypeptide variants set forth in Table 1. Table 1 also includes the SEQ ID NOs associated with the identified BChE polypeptide variants, as well as a summary of the approximate fold increase in catalytic efficiency against (−)-cocaine for the identified BChE polypeptide variants, as compared to wild-type BChE.

TABLE 1

BChE Polypeptide Variants and Associated SEQ ID NOs

Variant No.	Amino Acid Substitution										
	199	227	285	286	287	328	332	441	C.E.[a]	N.A. SEQ ID NO:	A.A. SEQ ID NO:
1	A199S	F227S	—	—	S287G	A328W	Y332G	—	2750	1	2
2	A199S	F227T	—	—	S287G	A328W	Y332G	—	1780	3	4
3	A199S	F227M	—	—	S287G	A328W	Y332G	—	1310	5	6
4	A199S	F227C	—	—	S287G	A328W	Y332G	—	1290	7	8
5	A199S	F227A	P285N	—	S287G	A328W	Y332G	—	2790	9	10
6	A199S	F227P	P285A	—	S287G	A328W	Y332G	—	2810	11	12
7	A199S	F227S	P285Q	—	S287G	A328W	Y332G	—	4260	13	14
8	A199S	F227S	P285S	—	S287G	A328W	Y332G	—	2430	15	16
9	A199S	F227S	P285G	—	S287G	A328W	Y332G	—	2480	17	18
10	A199S	F227P	P285S	L286M	S287G	A328W	Y332G	—	2710	19	20
11	A199S	F227A	P285S	—	S287G	A328W	—	E441D	2280	21	22
12	A199S	F227A	P285A	—	S287G	A328W	—	E441D	1980	23	24
13	A199S	F227P	—	L286M	S287G	A328W	Y332G	—	1140	25	26
14	A199S	F227G	P285A	—	S287G	A328W	Y332G	—	3130	27	28
15	A199S	F227G	P285G	—	S287G	A328W	Y332G	—	3445	29	30
16	A199S	F227G	P285Q	—	S287G	A328W	Y332G	—	2515	31	32
17	A199S	F227G	P285S	—	S287G	A328W	Y332G	—	3980	33	34
18	A199S	F227A	P285E	—	S287G	A328W	Y332G	—	2180	35	36
19	A199S	F227P	P285N	—	S287G	A328W	Y332G	—	2640	37	38
20	A199S	F227S	P285A	—	S287G	A328W	Y332G	—	2450	39	40
21	A199S	F227S	P285N	—	S287G	A328W	Y332G	—	2040	41	42
22	A199S	F227S	—	L286M	S287G	A328W	Y332G	—	1774	43	44
23	A199S	F227G	—	L286M	S287G	A328W	Y332G	—	1535	45	46

[a] Catalytic Efficiency (k_{cat}/K_m) against (—)-cocaine (Approx Fold Increase); The approximate ratio of the k_{cat}/K_m value for the BChE mutant to that for the wild-type BChE against (—)-cocaine.

The terms “polypeptide”, “protein”, and “peptide”, which are used interchangeably herein, refer to a polymer of the protein amino acids, or amino acid analogs, regardless of its size or function. Although “protein” is often used in reference to relatively large polypeptides, and “peptide” is often used in reference to small polypeptides, usage of these terms in the art overlaps and varies. The term “polypeptide” as used herein refers to peptides, polypeptides, and proteins, unless otherwise noted. The terms “protein”, “polypeptide”, and “peptide” are used interchangeably herein when referring to a gene product. Thus, exemplary polypeptides include gene products, naturally occurring proteins, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing.

The term “variant” refers to an amino acid sequence that is different from the reference polypeptide by one or more amino acids, e.g., one or more amino acid substitutions. For example a butyrylcholinesterase (BChE) polypeptide variant differs from wild-type BChE by one or more amino acid substitutions, i.e., mutations.

The terms “polypeptide fragment” or “fragment”, when used in reference to a reference polypeptide, refers to a polypeptide in which amino acid residues are deleted as compared to the reference polypeptide itself, but where the remaining amino acid sequence is usually identical to the corresponding positions in the reference polypeptide. Such deletions can occur at the amino-terminus, carboxy-terminus of the reference polypeptide, or alternatively both. A fragment can also be a “functional fragment,” in which case the fragment retains some or all of the activity of the reference polypeptide as described herein. For example, a functional fragment of a particular BChE polypeptide variant retains some or all of the cocaine hydrolysis activity, i.e., the catalytic efficiency for (−)-cocaine, of the particular BChE polypeptide variant. In this regard, the term “BChE polypeptide variant” is inclusive of functional fragments of the BChE polypeptide variant. Such fragments are typically are at least about 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, or 550 amino acids long. One or more residues from about 1 to 67 and/or one or more residues from about 443 to 574 can be removed without substantially affecting the catalytic activity of the BChE polypeptide variant. As such, the term “BChE polypeptide variant” is inclusive of functional fragments wherein one or more residues from 1 to 67 and/or one or more residues from 443 to 574 is truncated relative to the full-length BChE polypeptide variant. In some embodiments, the fragment includes residues from 1 to 529. See Brimijoin, S. et al., *Neuropsychopharmacology* 2008, 33, 2715-2725).

The BChE polypeptide variant (e.g., SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, and 46) can be formulated in a pharmaceutical composition along with a suitable pharmaceutical carrier known to one skilled in the art.

The present BChE variant polypeptides can be used in treating a cocaine-induced condition by administering to an individual, an effective amount of a BChE variant polypeptides, (e.g., SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, and 46), to lower blood cocaine concentration. The BChE polypeptide variant can be administered in the form of a pharmaceutical composition in which the BChE polypeptide variant is included with a suitable pharmaceutical carrier. Treatment of a cocaine-induced condition using one of the aforementioned BChE polypeptide variants can be in a manner that will be understood by those skilled in the art.

The preferred dose for administration of a BChE polypeptide variant or pharmaceutical composition in accordance with the presently-described subject matter is that amount which will be effective in lowering (−)-cocaine concentration in a patient’s bloodstream, and one would readily recognize that this amount will vary greatly depending on the nature of cocaine consumed, e.g., injected or inhaled, and the condition of a patient. An "effective amount" of butyrylcholinesterase polypeptide variant or pharmaceutical composition to be used in accordance with the presently-disclosed subject matter is intended to mean a nontoxic but sufficient amount of the agent, such that the desired prophylactic or therapeutic effect is produced. Thus, the exact amount of the enzyme or a particular agent that is required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition being treated, the particular carrier or adjuvant being used and its mode of administration, and the like. Similarly, the dosing regimen should also be adjusted to suit the individual to whom the composition is administered and will once again vary with age, weight, metabolism, etc. of the individual. Accordingly, the "effective amount" of any particular butyrylcholinesterase polypeptide variant, or pharmaceutical composition thereof, will vary based on the particular circumstances, and an appropriate effective amount may be determined in each case of application by one of ordinary skill in the art using only routine experimentation.

The presently-disclosed subject matter is further illustrated by the following specific but non-limiting examples. The following examples may include compilations of data that are representative of data gathered at various times during the course of development and experimentation related to the presently-disclosed subject matter.

EXAMPLES

Embodiments of the BChE polypeptide variants of the presently-disclosed subject matter were made and studied using the following experimental procedure.

Site-directed mutagenesis of human BChE cDNA was performed by the QuikChange method of Braman, J.; Papworth, C.; Greener, A. *Methods Mol. Biol.* 1996, 57, 5731, incorporated herein by this reference. Mutations were generated from wild-type human BChE in a pRc/CMV expression plasmid in accordance with Xie, W.; Altamirano, C. V.; Bartels, C. F.; Speirs, R. J.; Cashman, J. R.; Lockridge, O. *Mol. Pharmacol.* 1999, 55, 83, each of which is incorporated herein by this reference. The expression plasmid pRc/CMV was kindly provided by Dr. O. Lockridge, University of Nebraska Medical Center (Omaha, Nebr.).

Using plasmid DNA as template and primers with specific base-pair alterations, mutations were made by polymerase chain reaction with Pfu DNA polymerase, for replication fidelity. The PCR product was treated with Dpn I endonuclease to digest the parental DNA template. Cloned pfu DNA polymerase and Dpn I endonuclease were obtained from Stratagene (La Jolla, Calif.). Modified plasmid DNA was transformed into *Escherichia coli*, amplified, and purified. The DNA sequences of the mutants were confirmed by DNA sequencing. All oligonucleotides were synthesized by the Integrated DNA Technologies, Inc. The QIAprep Spin Plasmid Miniprep Kit and Qiagen plasmid purification kit and QIAquick PCR purification kit were obtained from Qiagen (Santa Clarita, Calif.).

BChE mutants were expressed in human embryonic kidney cell line 293T/17. Cells were grown to 80-90% confluence in 6-well dishes and then transfected by Lipofectamine 2000 complexes of 4 μg plasmid DNA per each well. Cells were incubated at 37° C. in a CO_2 incubator for 24 hours and cells were moved to 60-mm culture vessel and cultured for four more days. The culture medium [10% fetal bovine serum in Dulbecco's modified Eagle's medium (DMEM)] was harvested for a BChE activity assay.

Human embryonic kidney 293T/17 cells were from ATCC (Manassas, Va.). Dulbecco's modified Eagle's medium (DMEM) was purchased from Fisher Scientific (Fairlawn, N.J.). Oligonucleotide primers were synthesized by the Integrated DNA Technologies and Analysis Facility of the University of Kentucky. 3,3',5,5'-Tetramethylbenzidine (TMB) was obtained from Sigma (Saint Louis, Mo.). Anti-butyrylcholinesterase (mouse monoclonal antibody, Product # HAH002-01) was purchased from AntibodyShop (Gentofte, Denmark) and Goat anti-mouse IgG HRP conjugate from Zymed (San Francisco, Calif.).

To measure cocaine and benzoic acid, the product of cocaine hydrolysis by BChE, sensitive radiometric assays based on toluene extraction of [^{3}H]-(−)-cocaine labeled on its benzene ring were used in accordance with Zheng, F.; Yang, W.; Ko, M.-C.; Liu, J.; Cho, H.; Gao, D.; Tong, M.; Tai, H.-H.; Woods, J. H.; Zhan, C.-G. "Most Efficient Cocaine Hydrolase Designed by Virtual Screening of Transition States", *J. Am. Chem. Soc.* 2008, 130, 12148-12155, which is incorporated herein by this reference. ^{3}H-(−)-cocaine (50 Ci/mmol) was purchased from PerkinElmer Life Sciences (Boston, Mass.).

In brief, to initiate reactions, 100 nCi of [^{3}H]-(−)-cocaine was mixed with 100 μl of culture medium. Reactions proceeded at room temperature (25° C.) with varying concentrations of (−)-cocaine. Reactions were stopped by adding 300 μl of 0.02 M HCl, which neutralized the liberated benzoic acid while ensuring a positive charge on the residual cocaine. [^{3}H]benzoic acid was extracted by 1 ml of toluene and measured by scintillation counting. Finally, the measured (−)-cocaine concentration-dependent radiometric data were analyzed by using the standard Michaelis-Menten kinetics so that the catalytic efficiency (k_{cat}/K_M) was determined, along with the use of an enzyme-linked immunosorbent assay (ELISA) described by Zheng, F.; Yang, W.; Ko, M.-C.; Liu, J.; Cho, H.; Gao, D.; Tong, M.; Tai, H.-H.; Woods, J. H.; Zhan, C.-G. "Most Efficient Cocaine Hydrolase Designed by Virtual Screening of Transition States", *J. Am. Chem. Soc.* 2008, 130, 12148-12155.

The catalytic efficiencies (k_{cat}/K_M) of the BChE polypeptide variants were found to be between about 1000 to about 4000 times the k_{cat}/K_M value ($9.11\times10^5 M^{-1}$ min^{-1}) of the wild-type BChE.

Enzyme-linked immunosorbent assays (ELISA) were preformed as follows. The ELISA buffers used were the same as those described in the literature such as Brock, A.; Mortensen, V.; Loft, A. G. R.; Nergaard-Pedersen, B. *J. Clin. Chem. Clin. Biochem.* 1990, 28, 221-224; and Khattab, A. D.; Walker, C. H.; Johnston, G.; Siddiqui, M. K. Saphier, P. W. *Environmental Toxicology and Chemistry* 1994, 13, 1661-1667, both of which are incorporated herein by this reference. The coating buffer was 0.1 M sodium carbonate/bicarbonate buffer, pH 9.5. The diluent buffer (EIA buffer) was potassium phosphate monobasic/potassium phosphate monohydrate buffer, pH 7.5, containing 0.9% sodium chloride and 0.1% bovine serum albumin. The washing buffer (PBS-T) was 0.01 M potassium phosphate monobasic/potassium phosphate monohydrate buffer, pH 7.5, containing 0.05% (v/v) Tween-20. All the assays were performed in triplicate. Each well of an ELISA microtiter plate was filled with 100 μl of the mixture buffer consisting of 20 μl culture medium and 80 μl coating buffer. The plate was covered and incubated overnight at 4° C. to allow the antigen to bind to the plate. The solutions were then removed and the wells were washed four times with PBS-T. The washed wells were filled with 200 μl diluent buffer and kept shaking for 1.5 h at room temperature (25° C.). After washing with PBS-T for four times, the wells were filled with 100 μl antibody (1:8000) and were incubated for 1.5 h, followed by washing for four times. Then, the wells were filled with 100 μl goat anti-mouse IgG HRP conjugate complex diluted to a final 1:3000 dilution, and were incubated at room temperature for 1.5 h, followed by washing for four times. The enzyme reactions were started by addition of 100 μl substrate (TMB) solution. The reactions were stopped after 15 min by the addition of 100 μl of 2 M sulfuric acid, and the absorbance was read at 460 nm using a Bio-Rad ELISA plate reader.

While the terms used herein are believed to be well understood by one of ordinary skill in the art, the definitions set forth herein are provided to facilitate explanation of the presently-disclosed subject matter.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the presently-disclosed subject matter belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the presently-disclosed subject matter, representative methods, devices, and materials are now described.

Following long-standing patent law convention, the terms “a”, “an”, and “the” refer to “one or more” when used in this application, including the claims. Thus, for example, reference to “a cell” includes a plurality of such cells, and so forth.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about”. Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and claims are approximations that can vary depending upon the desired properties sought to be obtained by the presently-disclosed subject matter.

As used herein, the term “about,” when referring to a value or to an amount of mass, weight, time, volume, concentration or percentage is meant to encompass variations of in some embodiments ±50%, in some embodiments ±40%, in some embodiments ±30%, in some embodiments ±20%, in some embodiments ±10%, in some embodiments ±5%, in some embodiments ±1%, in some embodiments ±0.5%, and in some embodiments ±0.1% from the specified amount, as such variations are appropriate to perform the disclosed method.

As used herein, ranges can be expressed as from “about” one particular value, and/or to “about” another particular value. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

Throughout this document, various references are mentioned. All such references are incorporated herein by reference.

SEQUENCE LISTING

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Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
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Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
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Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
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Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
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Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
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Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
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Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
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Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
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Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
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Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
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Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
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Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
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Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
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Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
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Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
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Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
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Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
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Gly Ser Thr Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
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Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Gly Val
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Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
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Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
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Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
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Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
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Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
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Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
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Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
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<223> OTHER INFORMATION: synthesized

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Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Met Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350
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Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 7
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 7

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttcctg caatgctcct tgggcggtaa catctcttta tgaagctagg     720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata     780
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atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga ctcctttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722


<210> SEQ ID NO 8
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 8

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
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        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Cys Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 9
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized
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<400> SEQUENCE: 9

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt     60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga    120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa    180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag    240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca    300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact    360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt    420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga    600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660

attctgcaaa gtggttccgc taatgctcct tgggcggtaa catctcttta tgaagctagg    720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga ctaacttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722


<210> SEQ ID NO 10
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 10

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45
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Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Ala Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Asn Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
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465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 11
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 11

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttcccc gaatgctcct tgggcggtaa catctcttta tgaagctagg     720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata     780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc     840

ccctatggga ctgctttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact     900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt     960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat    1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga    1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag    1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc    1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat    1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat    1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag    1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca    1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat    1500
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ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                        1722


<210> SEQ ID NO 12
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 12

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Pro Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Ala Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320
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Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 13
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 13

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660
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attctgcaaa gtggttcctc caatgctcct tgggcggtaa catctcttta tgaagctagg    720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga ctcagttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                       1722


<210> SEQ ID NO 14
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 14

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175
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Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Ser Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Gln Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 15
<211> LENGTH: 1722
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 15

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt 60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga 120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa 180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag 240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca 300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact 360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt 420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct 480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa 540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga 600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc 660

attctgcaaa gtggttcctc caatgctcct tgggcggtaa catctcttta tgaagctagg 720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata 780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc 840

ccctatggga cttccttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact 900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt 960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat 1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga 1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag 1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc 1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat 1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat 1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag 1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca 1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga 1560

ttctggacat catttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc 1722

<210> SEQ ID NO 16
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 16

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1 5 10 15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro

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            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Ser Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Ser Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445
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Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 17
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 17

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttcctc caatgctcct tgggcggtaa catctcttta tgaagctagg     720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata     780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc     840

ccctatggga ctggtttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact     900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt     960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat    1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga    1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag    1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc    1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat    1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat    1320
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gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa    1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722


<210> SEQ ID NO 18
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 18

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Ser Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Gly Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
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    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570
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<210> SEQ ID NO 19
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 19

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gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480
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gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga    600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660

attctgcaaa gtggttcccc gaatgctcct tgggcggtaa catctcttta tgaagctagg    720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga cttccatggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722


<210> SEQ ID NO 20
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 20

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140
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Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Pro Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Ser Met Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
```

565 570

<210> SEQ ID NO 21
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 21

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt 60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga 120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa 180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag 240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca 300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact 360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt 420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct 480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa 540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga 600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc 660

attctgcaaa gtggttccgc taatgctcct tgggcggtaa catctcttta tgaagctagg 720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata 780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc 840

ccctatggga cttccttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact 900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt 960

gttaataaag atgaagggac atggttttta gtctacggtg ctcctggctt cagcaaagat 1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga 1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag 1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg ggattataa tttcatatgc 1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat 1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat 1320

gacattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag 1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca 1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga 1560

ttctggacat catttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc 1722

<210> SEQ ID NO 22
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 22

```
Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Ala Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Ser Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Tyr Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415
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Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Asp Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 23
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 23

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt     60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga    120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa    180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag    240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca    300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact    360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt    420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga    600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660

attctgcaaa gtggttccgc taatgctcct tgggcggtaa catctcttta tgaagctagg    720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga ctgctttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtctacggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200
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cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gacattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                       1722


<210> SEQ ID NO 24
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 24

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Ala Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270
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Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Ala Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Tyr Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Asp Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 25
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 25

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360
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ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt    420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga    600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660

attctgcaaa gtggttcccc gaatgctcct tgggcggtaa catctcttta tgaagctagg    720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga ctcctatggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                       1722


<210> SEQ ID NO 26
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 26

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
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        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Pro Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Met Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540
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Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 27
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 27

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttccgg taatgctcct tgggcggtaa catctcttta tgaagctagg     720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata     780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc     840

ccctatggga ctgctttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact     900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt     960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat    1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga    1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag    1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc    1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat    1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat    1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag    1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca    1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat    1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga    1560

ttctggacat catttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa    1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa    1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                       1722


<210> SEQ ID NO 28
<211> LENGTH: 574
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 28

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Gly Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Ala Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
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385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 29
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 29

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttccgg taatgctcct tgggcggtaa catctcttta tgaagctagg     720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata     780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc     840

ccctatggga ctggtttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact     900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt     960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat    1020
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aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                       1722


<210> SEQ ID NO 30
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 30

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Gly Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240
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Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Gly Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 31
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 31

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180
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tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag    240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca    300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact    360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt    420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga    600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660

attctgcaaa gtggttccgg taatgctcct tgggcggtaa catctcttta tgaagctagg    720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga ctcagttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722
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<210> SEQ ID NO 32
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 32

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Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95
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Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Gly Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Gln Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510
```

```
Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 33
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 33

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt     60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga    120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa    180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag    240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca    300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact    360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt    420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga    600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660

attctgcaaa gtggttccgg taatgctcct tgggcggtaa catctcttta tgaagctagg    720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga cttccttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722
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<210> SEQ ID NO 34
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 34

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Gly Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Ser Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365
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Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570
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<210> SEQ ID NO 35
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 35

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttccgc taatgctcct tgggcggtaa catctcttta tgaagctagg     720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata     780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc     840

ccctatggga ctgaattggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact     900
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gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722
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<210> SEQ ID NO 36
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 36

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
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    210                 215                 220

Gly Ser Ala Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Glu Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 37
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 37

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60
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tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga    120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa    180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag    240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca    300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact    360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt    420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga    600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660

attctgcaaa gtggttcccc gaatgctcct tgggcggtaa catctcttta tgaagctagg    720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga ctaacttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722


<210> SEQ ID NO 38
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 38

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60
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Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Pro Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Asn Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
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                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 39
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 39

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttcctc caatgctcct tgggcggtaa catctcttta tgaagctagg     720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata     780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc     840

ccctatggga ctgctttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact     900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt     960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat    1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga    1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag    1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc    1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat    1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat    1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag    1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca    1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat    1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga    1560
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ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722


<210> SEQ ID NO 40
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 40

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Ser Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Ala Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335
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Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570
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<210> SEQ ID NO 41
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 41

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttcctc caatgctcct tgggcggtaa catctcttta tgaagctagg     720
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aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc    840

ccctatggga ctaacttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt    960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat   1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga   1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaaatat  1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat catttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722


<210> SEQ ID NO 42
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 42

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190
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Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Ser Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Asn Leu Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 43
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 43

```
gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttcctc caatgctcct tgggcggtaa catctcttta tgaagctagg     720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata     780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc     840

ccctatggga ctcctatggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact     900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt     960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat    1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga    1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag    1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc    1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat    1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat    1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag    1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca    1440

aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat    1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga    1560

ttctggacat catttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa    1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa    1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                        1722
```

<210> SEQ ID NO 44
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 44

```
Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
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        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Ser Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Met Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460
```

```
Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570


<210> SEQ ID NO 45
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 45

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60

tttggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga     120

cttcgattca aaaagccaca gtctctgacc aagtggtctg atatttggaa tgccacaaaa     180

tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag     240

atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca     300

gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact     360

ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt     420

gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct     480

gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa     540

aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga     600

gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc     660

attctgcaaa gtggttccgg taatgctcct tgggcggtaa catctcttta tgaagctagg     720

aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata     780

atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc     840

ccctatggga ctcctatggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact     900

gacatgccag acatattact tgaacttgga caatttaaaa aaacccagat tttggtgggt     960

gttaataaag atgaagggac atggttttta gtcggtggtg ctcctggctt cagcaaagat    1020

aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt ttttccagga    1080

gtgagtgagt ttggaaagga atccatcctt tttcattaca cagactgggt agatgatcag    1140

agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc    1200

cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat    1260

tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat    1320

gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag    1380

gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca    1440
```

```
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500

ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620

tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680

tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                      1722


<210> SEQ ID NO 46
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthesized

<400> SEQUENCE: 46

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1               5                   10                  15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
            20                  25                  30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
        35                  40                  45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
    50                  55                  60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65                  70                  75                  80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85                  90                  95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
            100                 105                 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115                 120                 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
    130                 135                 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145                 150                 155                 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165                 170                 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
            180                 185                 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195                 200                 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
    210                 215                 220

Gly Ser Gly Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225                 230                 235                 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
                245                 250                 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
            260                 265                 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Met Gly Val
        275                 280                 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
    290                 295                 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
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                        -continued
305                 310                 315                 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
                325                 330                 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
            340                 345                 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
        355                 360                 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
    370                 375                 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
385                 390                 395                 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
                405                 410                 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
            420                 425                 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
        435                 440                 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
    450                 455                 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465                 470                 475                 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
                485                 490                 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
            500                 505                 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
        515                 520                 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
    530                 535                 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545                 550                 555                 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
                565                 570
```

The invention claimed is:

1. An isolated nucleic acid molecule comprising a nucleic acid sequence which encodes a butyrylcholinesterase polypeptide variant, comprising the nucleic acid sequence of SEQ ID NO: 13.

2. An isolated nucleic acid molecule comprising a nucleic acid sequence which encodes a butyrylcholinesterase polypeptide variant comprising the amino acid sequence of SEQ ID NO: 14.

* * * * *