

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
31 July 2003 (31.07.2003)

PCT

(10) International Publication Number
WO 03/062268 A2

(51) International Patent Classification⁷: **C07K 14/00**

(21) International Application Number: PCT/US03/01451

(22) International Filing Date: 16 January 2003 (16.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/349,117	16 January 2002 (16.01.2002)	US
60/376,337	29 April 2002 (29.04.2002)	US
60/388,895	14 June 2002 (14.06.2002)	US
60/411,988	19 September 2002 (19.09.2002)	US

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(81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CORTICOTROPIN RELEASING FACTOR 2 RECEPTOR AGONISTS

(57) Abstract: Isolated corticotropin releasing factor derivatives, and nucleic acids encoding the same, are effective for treating corticotropin releasing factor 2 receptor modulated disorders such as muscular dystrophy.



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CORTICOTROPIN RELEASING FACTOR 2 RECEPTOR AGONISTS

FIELD OF INVENTION

This invention relates to the use of novel peptides, and nucleic acids encoding the same, to treat CRF₂R modulated disorders.

BACKGROUND

CRFR and ligands

There are at least two corticotropin releasing factor (CRF) receptors identified to date (CRF₁R and CRF₂R) which belong to G-protein coupled receptor (GPCR) class. Agonist activation of CRF₁R or CRF₂R leads to G_{αs} activation of adenylate cyclase. Adenylate cyclase catalyzes the formation of cAMP, which in turn has multiple effects including the activation of protein kinase A, intracellular calcium release and activation of mitogen-activated protein kinase (MAP kinase). In other studies, the enhancement of intracellular inositol triphosphate synthesis, after agonist activation of CRF receptors, suggests that CRFRs also couple to G_{αq}.

CRF₁R and CRF₂R have been cloned from human, rat, mouse, chicken, cow, catfish, frog and sheep. CRF₁R and CRF₂R each have a unique distribution patterns. In humans three isoforms, alpha, beta and gamma, of the CRF₂R receptor have been cloned. Homologs for alpha and beta CRF₂R have been identified in rat.

Several ligands/agonists of the CRFRs are known and include corticotropin releasing factor (or hormone, CRF, CRH), urocortin I, urocortin II (or stresscopin related peptide), urocortin III (or stresscopin), urotensin I, sauvagine and other related peptides. Corticotropin releasing factor binds to and activates CRF₁R and CRF₂R. CRF is a major modulator of the body's responses to stress. This 41-amino acid peptide presides over a panoply of neuronal, endocrine, and immune processes as the primary regulator of the hypothalamus-pituitary-adrenal hormonal axis (HPA axis). In addition, there is substantial sequence homology between all known ligands of CRFR. Further, two CRF₂R selective ligands have been identified, urocortin II (or stresscopin related peptide) and urocortin III (stresscopin). These peptides have been identified from multiple mammalian and fish species.

The CRF receptors can be distinguished, from non-CRFRs, pharmacologically through the use of receptor selective agonists and antagonists. These selective agonists and antagonist,

along with the CRFR knockout mice, have been useful in determining which CRF receptor mediates a particular biological response.

The role of CRF₁R has been fairly well established. Mice in which the CRF₁R gene has been ablated (CRF₁R knockout) demonstrate an impaired stress response and reduced anxiety-like behavior. CRF₁R is a major mediator of the HPA axis. Specifically, CRF, which is released from the hypothalamus and transported to the anterior pituitary via the hypothalamic-hypophyseal portal system, interacts with the CRF₁R present on cells located in the anterior pituitary. Agonist activation of the CRF₁R results in release of ACTH from the cells of the anterior pituitary into the systemic circulation. The released ACTH binds the ACTH receptor present on cells located in the adrenal cortex, resulting in the release of adrenal hormones including corticosteroids. Corticosteroids mediate many effects including, but not limited to, immune system suppression via a mechanism, which involves thymic and splenic atrophy. Thus activation of the CRF₁R indirectly results in the down-regulation of the immune system via activation of the HPA axis.

The role of CRF₂R is less well established. Mice in which the CRF₂R gene has been ablated (CRF₂R knockout) demonstrate an impaired or reduced food intake following stimulation with urocortin, lack of vasodilation, but a normal stress response. Experiments with CRF₂R demonstrated that CRF₂R is responsible for the hypotensive/vasodilatory effects of CRFR agonists and for the reduction in food intake observed following treatment of mice with CRFR agonists.

Skeletal Muscle Atrophy and Hypertrophy

In addition, CRF₂R is involved in the modulation of skeletal muscle atrophy and the induction of hypertrophy. Skeletal muscle is a plastic tissue, which readily adapts to changes in either physiological demand for work or metabolic need. Hypertrophy refers to an increase in skeletal muscle mass while skeletal muscle atrophy refers to a decrease in skeletal muscle mass. Acute skeletal muscle atrophy is traceable to a variety of causes including, but not limited to: disuse due to surgery, bed rest, or broken bones; denervation/nerve damage due to spinal cord injury, autoimmune disease, or infectious disease; glucocorticoid use for unrelated conditions; sepsis due to infection or other causes; nutrient limitation due to illness or starvation; and space travel. Skeletal muscle atrophy occurs through normal biological processes, however, in certain medical situations this normal biological process results in a debilitating level of muscle atrophy. For example, acute skeletal muscle atrophy presents a significant limitation in the rehabilitation of patients from immobilizations, including, but not limited to, those accompanying an orthopedic procedure. In such cases, the rehabilitation period required to reverse the skeletal

muscle atrophy is often far longer than the period of time required to repair the original injury. Such acute disuse atrophy is a particular problem in the elderly, who may already suffer from substantial age-related deficits in muscle function and mass, because such atrophy can lead to permanent disability and premature mortality.

Skeletal muscle atrophy can also result from chronic conditions such as cancer cachexia, chronic inflammation, AIDS cachexia, chronic obstructive pulmonary disease (COPD), congestive heart failure, genetic disorders, e.g., muscular dystrophies, neurodegenerative diseases and sarcopenia (age associated muscle loss). In these chronic conditions, skeletal muscle atrophy can lead to premature loss of mobility, thereby adding to the disease-related morbidity.

Little is known regarding the molecular processes which control atrophy or hypertrophy of skeletal muscle. While the initiating trigger of the skeletal muscle atrophy is different for the various atrophy initiating events, several common biochemical changes occur in the affected skeletal muscle fiber, including a decrease in protein synthesis and an increase in protein degradation and changes in both contractile and metabolic enzyme protein isozymes characteristic of a slow (highly oxidative metabolism/slow contractile protein isoforms) to fast (highly glycolytic metabolism/fast contractile protein isoforms) fiber switch. Additional changes in skeletal muscle, which occur, include the loss of vasculature and remodeling of the extracellular matrix. Both fast and slow switch muscle demonstrate atrophy under the appropriate conditions, with the relative muscle loss depending on the specific atrophy stimuli or condition. Importantly, all these changes are coordinately regulated and are switched on or off depending on changes in physiological and metabolic need.

The processes by which atrophy and hypertrophy occur are conserved across mammalian species. Multiple studies have demonstrated that the same basic molecular, cellular, and physiological processes occur during atrophy in both rodents and humans. Thus, rodent models of skeletal muscle atrophy have been successfully utilized to understand and predict human atrophy responses. For example, atrophy induced by a variety of means in both rodents and humans results in similar changes in muscle anatomy, cross-sectional area, function, fiber type switching, contractile protein expression, and histology. In addition, several agents have been demonstrated to regulate skeletal muscle atrophy in both rodents and in humans. These agents include anabolic steroids, growth hormone, insulin like growth factor I, beta-adrenergic agonists, and CRF₂R agonists. Together, these data demonstrate that skeletal muscle atrophy results from common mechanisms in both rodents and humans.

While some agents have been shown to regulate skeletal muscle atrophy and are approved for use in humans for this indication, these agents have undesirable side effects such as hypertrophy of cardiac muscle, neoplasia, hirsutism, androgenization of females, increased morbidity and mortality, liver damage, hypoglycemia, musculoskeletal pain, increased tissue turgor, tachycardia, and edema. Currently, there are no highly effective and selective treatments for either acute or chronic skeletal muscle atrophy. Thus, there is a continuing need to identify other therapeutic agents, which treat skeletal muscle atrophy.

Muscular Dystrophies

Muscular dystrophies encompass a group of inherited, progressive muscle disorders, distinguished clinically by the selective distribution of skeletal muscle weakness. The two most common forms of muscle dystrophy are Duchenne and Becker dystrophies, each resulting from the inheritance of a mutation in the dystrophin gene, which is located at the Xp21 locus. Other dystrophies include, but are not limited to, limb-girdle muscular dystrophy which results from mutation of multiple genetic loci including the p94 calpain, adhalin, γ -sarcoglycan, and β -sarcoglycan loci; fascioscapulohumeral (Landouzy-Dejerine) muscular dystrophy, myotonic dystrophy, and Emery-Dreifuss muscular dystrophy. The symptoms of Duchenne muscular dystrophy, which occurs almost exclusively in males, include a waddling gait, toe walking, lordosis, frequent falls, and difficulty in standing up and climbing stairs. Symptoms start at about 3-7 years of age with most patients confined to a wheelchair by 10-12 years and many die at about 20 years of age due to respiratory complications. Current treatment for Duchenne muscular dystrophy includes administration of prednisone (a corticosteroid drug), which while not curative, slows the decline of muscle strength and delays disability. Corticosteroids, such as prednisone, are believed to act by blocking the immune cell activation and infiltration which are precipitated by muscle fiber damage resulting from the disease. Unfortunately, corticosteroid treatment also results in skeletal muscle atrophy which negates some of the potential benefit of blocking the immune response in these patients. Thus, there is a continuing need to identify therapeutic agents which slow the muscle fiber damage and delay the onset of disability in patients with muscular dystrophies, but cause a lesser degree of skeletal muscle atrophy than current therapies.

SUMMARY OF THE INVENTION

The present invention provides isolated peptides that are CRF₂R agonists. Specifically, the invention provides an isolated peptide, or nucleic acid encoding the same, that are CRF, urocortin I, urocortin II, urocortin III, sauvagine, urotensin I or related peptide derivatives. The invention also provides for pharmaceutical composition comprising a safe and effective amount of an isolated peptide of the present invention and a pharmaceutically acceptable excipient. The invention further provides a kit comprising an isolated peptide in unit dose form and usage instructions.

The administration of a peptide, or nucleic acid encoding the same, pharmaceutical composition, or kit of the present invention, to a subject in need thereof, is effective for the treatment of CRF₂R modulated disorders such as muscle atrophy or wasting. The invention also provides for an antibody that is specific to the peptides of the present invention. Lastly, the invention provides for the use of a peptide of the present invention, or nucleic acid encoding the same, in the manufacture of a medicament for the treatment of a CRF₂R modulated disorder in a subject in need thereof.

The present invention encompasses isolated non-native peptides according to the Formula (I):

alpha – beta – gamma – delta – epsilon – zeta – eta – theta

(I)

wherein:

(a) alpha comprises a sequence of a formula $X_1X_2X_3X_4X_5X_6$; wherein:

X_1 , X_2 and X_3 are each selected from the group consisting of nil, A, E, D G, N, P, Q, S, T, and Z;

X_4 is selected from the group consisting of F, I, L, P, T, and V;

X_5 is selected from the group consisting of A, I, P, S, T, and V;

X_6 is selected from the group consisting of I, L, M, and N;

(b) beta comprises a sequence of a formula SX_8DX_{10} ; wherein: X_8 and X_{10} are each independently selected from the group consisting of I, L, and V;

(c) gamma comprises a sequence of a formula $X_{11}X_{12}X_{13}$; wherein: X_{11} is selected from a group consisting of P, T, V, and S, and X_{12} and X_{13} are each independently selected from the group consisting of A, Naphthylalanine (Represented as B), C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, and Y;

(d) delta comprises a sequence of a formula $X_{14}X_{15}X_{16}$, wherein:

- X_{14} is selected from the group consisting of I, L, and M;
 X_{15} is selected from the group consisting of L and M; and
 X_{16} is selected from the group consisting of S, N, Q, and R;
- (e) epsilon comprises a sequence of a formula $X_{17}X_{18}X_{19}X_{20}X_{21}$, wherein:
 X_{17} is selected from the group consisting of V, I, L, T, K, E, N, and Q;
 X_{18} is selected from the group consisting of L, M, V, A, and T;
 X_{19} is selected from the group consisting of I, F, L, and M;
 X_{20} is selected from the group consisting of D, E, N, and H; and
 X_{21} is selected from the group consisting of L, V, I, Q, M, and R;
- (f) zeta comprises a sequence of a formula $X_{22}X_{23}X_{24}X_{25}$, wherein:
 X_{22} is selected from the group consisting of nil, A, D, E, S, and T;
 X_{23} is selected from the group consisting of nil, K, and R;
 X_{24} is selected from the group consisting of nil, A, H, M, N, Q, T, and Y;
 X_{25} is selected from the group consisting of nil, E, D, I, K, N, Q, and R;
- (g) eta comprises a sequence of the formula $X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}$, wherein:
 X_{26} is selected from the group consisting of A, D, G, H, K, N, Q, and S;
 X_{27} is selected from the group consisting of A, E, I, L, M, and Q;
 X_{28} is selected from the group consisting of A, H, K, Q, R, and V;
 X_{29} is selected from the group consisting of A, E, K, N, M, and Q;
 X_{30} is selected from the group consisting of H, K, N, Q, and R;
 X_{31} is selected from the group consisting of A and K;
- (h) theta comprises a sequence of the formula $X_{32}X_{33}NX_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}$, wherein:
 X_{32} is selected from the group consisting of A, E, H, and T;
 X_{33} is selected from the group consisting of A, D, E, I, L, N, Q, R, S, and T;
 X_{35} is selected from the group consisting of A and R;
 X_{36} is selected from the group consisting of E, H, I, K, L, N, Q, and R;
 X_{37} is selected from the group consisting of F, I, L, M, and Y;
 X_{38} is selected from the group consisting of L, F, and M;
 X_{39} is selected from the group consisting of A, D, E, N, and Q;
 X_{40} is selected from the group consisting of A, D, E, H, I, K, N, Q, R, S, and T;
 X_{41} is selected from the group consisting of A, F, I, and V; and variants thereof.

All documents cited are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

SEQUENCE LISTING DESCRIPTION

Table 1 describes various proteins and protein fragment sequences that bind to CRF receptors. These selected sequences are included with the corresponding Genbank or Derwent accession number(s) and the animal species from which it is reported, as well as accession numbers for related nucleotide sequences that encode identical, or nearly identical, amino acid sequences. These known and novel sequences of the invention are further presented in the sequence listing.

Table 1

Sequence Description	amino acid SEQ ID NO:	Species	Genbank (GB), Swiss-Prot (SP) or Derwent (D) Accession No. for nucleotide sequence	Related Genbank (GB) or Derwent (D) Accession Nos.
urocortin I fragment	2	<i>Homo sapiens</i>	Fragment of AF038633 (GB) amino acid residues 83-122	AC109828 (GB) AX015619 (GB) AV708591 (GB) AV708591 (GB) AAZ35707 (D) AAT73432 (D)
urocortin II fragment	4	<i>Homo sapiens</i>	Fragment of AF320560 (GB) amino acid residues 72-109	

urocortin III fragment	6	<i>Homo sapiens</i>	Fragment of AF361943 (GB) amino acid residue 118-157	AY026949 (GB)
corticotropin releasing hormone fragment	8	<i>Homo sapiens</i>	Fragment of V00571 (GB) amino acid residues 154-194	AC090195(GB) AC090196 (GB) BC002599(GB) AC021240 (GB) E00245 (GB)
corticotropin releasing factor fragment	10	<i>Ovis sp.</i>	E00212 (GB)	J00803 (GB) M22853 (GB)
sauvagine	11	<i>Phyllomedusa sauvagei</i>	P01144 (SP)	

DESCRIPTION OF THE INVENTION

Glossary of Terms

The following is a list of definitions for terms used herein.

“Agonist” means any compound, including, but not limited to, antibodies, that activates a receptor. For example, CRFR agonists include, but are not limited to CRF, urocortin, urocortin II, urocortin III, urotensin I, sauvagine and related analogs.

“Antibody”, in its various grammatical forms, means immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site which specifically binds an antigen. As used herein, “isolated antibody,” means an antibody which has been partially or completely separated from the proteins and naturally occurring organic molecules with which it is naturally associated.

“Binding affinity” means the propensity for a ligand to interact with a receptor and is inversely related to the dissociation constant for a specific CRF ligand-CRFR interaction. The dissociation constant can be measured directly via standard saturation, competition, or kinetics binding techniques or indirectly via pharmacological techniques involving functional assays and endpoints.

“Chimeric antibody” means an antibody that contains structural elements from two or more different antibody molecules, i.e., from different animal species. Chimeric antibodies include, but are not limited to, antibodies known as “humanized antibodies” which include, but

are not limited to, chimeric antibodies generated by the technique known as complementarity determining region grafting.

“CRF” means corticotropin releasing factor which is the same as corticotropin releasing hormone (CRH). Exemplary CRF peptides include r/h CRF and ovine CRF (*see* U.S. Pat. No. 4,415,558), and the like.

“CRF analog” means substances which act as ligands of CRFRs. Suitable CRF analogs can be obtained from a variety of vertebrate species and include, but are not limited to, substances such as sauvagine (*see, e.g.,* U.S. Pat. No. 4,605,642), urotensin (*see, e.g.,* U.S. Pat. Nos. 4,908,352; and 4,533,654), mouse urocortin II, human urocortin-related peptide (Reyes, T.M. et al., *Proc. Nat’l Acad Sci* 98:2843-2848 (2001)), urocortin (*see, e.g.,* WO 97/00063), human urocortin II (stresscopin related peptide), human urocortin III (stresscopin), pufferfish URP 1, pufferfish URP II, urotensin I, and the CRF analogs described in U.S. Pat. Nos: 4,415,558; 4,489,163; 4,594,329; 4,605,642; 5,109,111; 5,235,036; 5,278,146; 5,439,885; 5,493,006; 5,663,292; 5,824,771; 5,844,074; and 5,869,450. Specific CRF analogs include hUcnI (human urocortin I, AF038633 (GB)); hUroII (human urocortin II or stresscopin related peptide)(AF320560); hUroIII (human urocortin III or stresscopin, AF361943); hCRF (human corticotropin releasing factor)(V00571(GB)); oCRF (sheep corticotropin releasing factor E00212 (GB)); Svg (sauvagine, P01144 (SP)).

“CRFR agonist” means a compound or molecule which has the ability to activate CRF₁R, CRF₂R, or both.

“CRFR” means CRF₁R or CRF₂R. The term “CRFR ” also includes truncated and/or mutated proteins wherein regions of the receptor molecule not required for ligand binding or signaling have been deleted or modified.

“CRF₁R” means any isoforms of CRF₁R from any animal species. The CRF₁R has previously been referred to as CRF-RA, PC-CRF, CRF, (Perrin, M.H., et al. *Endocrinology* 133:3058-3061 (1993), Chen, R., et al. *Proc. Natl. Acad. Sci.USA* 90:8967-8971 (1993), Chang, C-P. et al., *Neuron* 11:1187-1195 (1993), Kishimoto, T., et al., *Proc. Natl. Acad. Sci.USA*, 92:1108-1112 (1995) and, Vita, N. et al., *FEBS Lett.* 335: 1-5 (1993)) or the CRH receptor.

The definition of CRF₁R includes, but is not limited to, those receptors for which the cDNA or genomic sequence encoding the receptor has been deposited in a sequence database. These sequences include Accession Nos.: X72304, E11431, L23332, I92584, T37068, T28968, Q81952, L23333, NM_004382, AF180301, T28970, L25438, L24096, I92586, Q81954, AH006791, NM_007762, X72305, AF054582, Y14036, AF229359, AF229361, AB055434 and

L41563. The nucleotide and protein sequences of these receptors are available from GenBank or Derwent.

“CRF₂R” means any isoform of CRF₂R from any animal species. CRF₂R has also been referred to as HM-CRF, CRF-RB, (Kishimoto, T., et al., *Proc. Natl. Acad. Sci. USA*, 92:1108-1112 (1995) and Perrin, M. et al. *Proc. Natl. Acad. Sci. USA* 92:2969-2973 (1995)).

The definition of CRF₂R receptor includes, but is not limited to, those receptors for which the DNA sequence encoding the receptor has been deposited in a sequence database. These sequences include Accession Nos.: U34587, E12752, NM_001883, T12247, T66508, AF011406, AF019381, U16253, T12244, T28972, U17858, NM_009953, Y14037 and AF229360. The nucleotide and protein sequences of these receptors are available from GenBank or Derwent.

“Inhibit” means to partially or completely block a particular process or activity. For example, a compound inhibits skeletal muscle atrophy if it either completely or partially prevents muscle atrophy.

“Isolated peptide” means a peptide molecule is said to be “isolated” when physical, mechanical or chemical methods are employed to remove the peptide from cellular constituents that are normally associated with the protein. A skilled artisan can readily employ standard purification methods to obtain an isolated peptide.

“Isolated nucleic acid” means a nucleic acid molecule is substantially separated from contaminant nucleic acid molecules encoding other polypeptides. Purification and sequence identification techniques are well known in the art.

As used herein, two DNA sequences are said to be “operably associated” if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of a promoter region to direct the transcription of the coding sequences, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. For example, a coding sequence and regulatory sequences are operably associated when they are covalently linked in such a way as to place the transcription of the coding sequence under the influence or control of the regulatory sequences. Thus, a promoter region is operably associated with a coding sequence when the promoter region is capable of effecting transcription of that DNA sequence such that the resulting transcript is capable of being translated into the desired peptide.

“Selective agonist” means that the agonist generally has greater, preferably has significantly greater, activity toward a certain receptor(s) compared with other receptors, not that it is completely inactive with regard to other receptors.

“Sequence Identity” or “Homology” at the amino acid or nucleotide sequence level is determined by BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx, tblastn and tblastx (Altschul *et al.* (1997) *Nucleic Acids Res.* 25, 3389-3402 and Karlin *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87, 2264-2268) which are tailored for sequence similarity searching. The approach used by the BLAST program is to first consider similar segments, with gaps (non-contiguous) and without gaps (contiguous), between a query sequence and a database sequence, then to evaluate the statistical significance of all matches that are identified and finally to summarize only those matches which satisfy a preselected threshold of significance. For a discussion of basic issues in similarity searching of sequence databases, see Altschul *et al.* (1994) *Nature Genetics* 6, 119-129. The search parameters for histogram, descriptions, alignments, expect (*i.e.*, the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter (low complexity) are at the default settings. The default scoring matrix used by blastp, blastx, tblastn, and tblastx is the BLOSUM62 matrix (Henikoff *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89, 10915-10919), recommended for query sequences over 85 nucleotides or amino acids in length.

For blastn, the scoring matrix is set by the ratios of M (*i.e.*, the reward score for a pair of matching residues) to N (*i.e.*, the penalty score for mismatching residues), wherein the default values for M and N are +5 and -4, respectively. Four blastn parameters were adjusted as follows: Q=10 (gap creation penalty); R=10 (gap extension penalty); wink=1 (generates word hits at every winkth position along the query); and gapw=16 (sets the window width within which gapped alignments are generated). The equivalent Blastp parameter settings were Q=9; R=2; wink=1; and gapw=32. A Bestfit comparison between sequences, available in the GCG package version 10.0, uses DNA parameters GAP=50 (gap creation penalty) and LEN=3 (gap extension penalty) and the equivalent settings in protein comparisons are GAP=8 and LEN=2.

“Skeletal muscle hypertrophy” means an increase in skeletal muscle mass or skeletal muscle function or both.

“Skeletal muscle atrophy” means the same as “muscle wasting” and means a decrease in skeletal muscle mass or skeletal muscle function or both.

In describing protein structure and function, reference is made to amino acids comprising the protein. The amino acids may also be referred to by their conventional abbreviations, as

shown: A = Ala = Alanine; T = Thr = Threonine; V = Val = Valine; C = Cys = Cysteine; L = Leu = Leucine; Y = Tyr = Tyrosine; I = Ile = Isoleucine; N = Asn = Asparagine; P = Pro = Proline; Q = Gln Glutamine; F = Phe = Phenylalanine; D = Asp = Aspartic Acid; W = Trp = Tryptophan; E = Glu = Glutamic Acid; M = Met = Methionine; K = Lys = Lysine; G = Gly = Glycine; R = Arg = Arginine; S = Ser = Serine; H = His = Histidine. The letter Z = Glx = Pyrrolidone carboxylic acid, is used to indicate N-terminal glutamic acid or glutamine that has formed an internal cyclic lactam. This has been described in the sequence listing under "MODIFIED_RES" feature where appropriate. The letter B is used in the specification to designate Naphthylalanine, a modification of Alanine in certain peptides and has been indicated in the sequence listing under the "miscellaneous feature" in the sequence listing in the peptide sequences where it occurs. Abbreviation "Ac" has been used to indicate modified acetylated NH₂-terminus in the specification and has been described under the "MODIFIED_RES" feature where appropriate. The peptides of the invention are also modified to have amide group at the carboxy-terminus. This is indicated in the sequence listing under "MODIFIED_RES" feature. In order to designate a deletion or an absence of an amino acid in context of the natural homolog, a "--" or "nil" is used throughout the application.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the arts of protein chemistry, pharmacology, or molecular biology. The methods, materials and examples described herein are not intended to be limiting. Other methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention.

Peptides

The present invention encompasses isolated non-native peptides according to the Formula (I):

alpha – beta – gamma – delta – epsilon – zeta – eta – theta

(I)

In Formula (I), alpha comprises a sequence of a formula X₁X₂X₃X₄X₅X₆; wherein: X₁, X₂ and X₃ are each selected from the group consisting of nil, A, E, D G, N, P, Q, S, T and Z; X₄ is selected from the group consisting of F, I, L, P, T, and V; X₅ is selected from the group consisting of A, I, P, S, T and V; and X₆ is selected from the group consisting of I, L, M, and N. In one aspect of the invention, alpha comprises a sequence of the formula X₁X₂X₃X₄X₅X₆; wherein X₁ is

nil, X_2 is selected from the group consisting of D, E and Z; X_3 is selected from the group consisting of D, G and N; X_4 is selected from the group consisting of L and P; X_5 is selected from the group consisting of P and S; and X_6 is selected from the group consisting of I, L, M and N. In one embodiment, alpha further comprises the sequence selected from the group consisting of -EDLPL (SEQ ID NO: 388), -DNPSL (SEQ ID NO: 389), -DDPPL (SEQ ID NO: 390), -ZGPPI (SEQ ID NO: 391), ---PSL, and ---IVL, wherein "-" denotes nil. In another embodiment, alpha comprises the sequence -ZGPPI. In another embodiment, alpha comprises the sequence -DNPSL. In another embodiment, alpha comprises the sequence ---IVL. In another embodiment, alpha comprises the sequence ---PSL.

In another aspect of the invention, alpha comprises the formula $X_1X_2X_3X_4X_5X_6$; wherein X_1 is nil; X_2 is nil; X_3 is nil; X_4 is selected from the group consisting of F, I, L, P and V; X_5 is selected from the group consisting of A, I, S, T and V; X_6 is L. In one embodiment, alpha comprises a sequence selected from the group consisting of ---IVL, ---FTL, ---LTL, ---FAL, ---VIL, and ---PSL. In another embodiment, alpha comprises the sequence ---IVL.

In yet another aspect of the invention, alpha comprises a sequence selected from the group consisting of SQEPPI (SEQ ID NO: 392), SEEPPI (SEQ ID NO: 393), -DNPSL, ---IVL, -TKFTL (SEQ ID NO: 394), -ZGPPI, SQEIVL (SEQ ID NO: 395), SEEIVL (SEQ ID NO: 396), DNPIVL (SEQ ID NO: 397), TKIVL (SEQ ID NO: 398), ZGIVL (SEQ ID NO: 399), SDNPSL (SEQ ID NO: 401), STKFTL (SEQ ID NO: 402), SZGPPI (SEQ ID NO: 403), and NDDPPI (SEQ ID NO: 404).

In yet another aspect of the invention, alpha may be preceded by a polyhistidine (HHHHHH, SEQ ID NO: 400) or other peptide tag that may be useful in the purification or detection of the peptides of the invention.

In Formula (I), beta comprises a sequence of a formula SX_8DX_{10} , wherein X_8 and X_{10} are each selected from the group consisting of I, L and V. In one embodiment, beta comprises the sequence selected from the group consisting of SIDL (SEQ ID NO: 405), SLDV (SEQ ID NO: 406), SLDL (SEQ ID NO: 407), SIDI (SEQ ID NO: 408), and SIDV (SEQ ID NO: 409). In another embodiment beta comprises the sequence further selected from the group consisting of SIDL and SLDV. In yet another embodiment, beta comprises the sequence SIDL. In yet another embodiment, beta comprises the sequence SLDV. In yet another embodiment, beta comprises the sequence SIDV.

In Formula (I), gamma comprises a sequence of a formula $X_{11}X_{12}X_{13}$; wherein X_{11} is P, T, V, or S, and X_{12} and X_{13} are each selected from the group consisting of A, B (Naphthylalanine),

C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, and Y. In one embodiment of the invention X_{11} is P. In another embodiment, gamma comprises the sequence selected from the group consisting of PAB, PAF, PAH, PAQ, PAY, PFB, PFE, PFF, PFG, PFH, PFI, PFL, PFQ, PFV, PFW, PFY, PGY, PHB, PHF, PHH, PHQ, PHW, PHY, PIA, PIB, PID, PIE, PIF, FIG, PIH, PII, PIL, PIQ, PIR, PIT, PIV, PIW, PIY, PKY, PLB, PLE, PLF, PLG, PLH, PLI, PLL, PLQ, PLV, PLW, PLY, PNY, PQB, PQF, PQH, PQI, PQL, PQQ, PQV, PQW, PQY, PRY, PSY, PTB, PTE, PTF, PTH, PTI, PTL, PTV, PTW, PTY, PVB, PVY, PWF, PWH, PWQ, PWW, PWY, PYB, PYF, PYH, PYI, PYL, PYQ, PYT, PYV, PYW, PYY, SLE, SLG, SIG, and VIG. In yet another embodiment of the invention, gamma comprises the sequence selected from the group consisting of PFE, PFG, PFH, PFQ, PFY, PLE, PLG, PLH, PLQ, PLY, PTE, PTH, PTY, PIE, PIH, PIQ, PIY, FIG, PTN and PTS. In yet another embodiment, gamma comprises the sequence selected from the group consisting of PFE, PFG, PFH, PFQ, PFY, PLE, PLG, PLH, PLQ, PLY, PTE, PTH, PTY, PIE, PIH, PIQ, PIY, PYY, PFE, PTW, PQY, PHY, PII, PIL, PTI, PTF, PTL, PIV, PIT, PTV and PIE. In yet another embodiment, gamma comprises the sequence selected from the group consisting of FIG, PTN, PTS, and FIG. In yet another embodiment, gamma comprises of sequence selected from PFQ, PYW, PLQ, FIG, PLY, PUY, PTY, FIG, PLL, PLF, and PFF. In yet another embodiment, gamma comprises the sequence FIG. In yet another embodiment, gamma comprises PFQ.

In Formula (I), delta comprises a sequence of a formula $X_{14}X_{15}X_{16}$, wherein X_{14} is selected from the group consisting of I, L, and M; X_{15} is selected from the group consisting of L and M; and X_{16} is selected from the group consisting of S, N, Q, and R. In one embodiment, delta comprises a sequence selected from the group consisting of ILS, IMN, LLQ, LLR, and MLR. In one embodiment, delta comprises the sequence LLQ or LLR.

In Formula (I), epsilon comprises a sequence of a formula $X_{17}X_{18}X_{19}X_{20}X_{21}$, wherein, X_{17} is selected from the group consisting of V, I, L, T, K, E, N, and Q; X_{18} is selected from the group consisting of L, M, V, A, and T; X_{19} is selected from the group consisting of I, F, L, and M; X_{20} is selected from the group consisting of D, E, N, and H; and X_{21} is selected from the group consisting of L, V, I, Q, M, and R. In one embodiment, epsilon comprises a sequence selected from the group consisting of VLIDL (SEQ ID NO: 410), VLFDV (SEQ ID NO: 411), VLIEI (SEQ ID NO: 412), ILFNI (SEQ ID NO: 413), LLIEI (SEQ ID NO: 414), LLFNI (SEQ ID NO: 415), ILLEQ (SEQ ID NO: 416), ILIEI (SEQ ID NO: 417), ILLEI (SEQ ID NO: 418), TLLEL (SEQ ID NO: 419), KMIEI (SEQ ID NO: 420), KVIEI (SEQ ID NO: 421), EVLEM (SEQ ID NO: 422), EMIEI (SEQ ID NO: 423), EVIEI (SEQ ID NO: 424), EAIEI (SEQ ID NO: 425),

ETIEI (SEQ ID NO: 426), EIIEI (SEQ ID NO: 427), ELIEI (SEQ ID NO: 428), NMIEM (SEQ ID NO: 429), NMIHR (SEQ ID NO: 430), NMIHM (SEQ ID NO: 431), QMMEM (SEQ ID NO: 432), and LLFNI (SEQ ID NO: 433). In one embodiment of the invention, epsilon comprises the sequence selected from the group consisting of VLIDL, VLFDV, ILFNI, LLFNI, ILLEQ, TLLEL and KMIEI. In another embodiment, epsilon comprises the sequence selected from the group consisting of VLIDL, VLFDV, ILFNI and ILLEQ. In yet another embodiment, epsilon comprises the sequence selected from the group consisting of KMIEI or ILLEQ. In yet another embodiment, epsilon comprises the sequence KVIEI, KMIEI, ILLEI, ILLEQ, or TLLEL. In yet another embodiment, epsilon comprises the sequence KMIEI. In yet another embodiment, epsilon comprises the sequence ILLEQ.

In Formula (I), zeta comprises a sequence of a formula $X_{22}X_{23}X_{24}X_{25}$, wherein X_{22} is selected from the group consisting of nil, A, D, E, S and T; X_{23} is selected from the group consisting of nil, K and R; X_{24} is selected from the group consisting of nil, A H, M, N, Q, T and Y; and X_{25} is selected from the group consisting of nil, E, D, I, K, N, Q and R. In one embodiment of the invention, zeta comprises a sequence of the formula $X_{22}X_{23}X_{24}X_{25}$; wherein X_{22} is selected from the group consisting of nil, D and E; X_{23} is selected from the group consisting of nil, K and R; X_{24} is selected from the group consisting of nil, A H, M, N, Q, T and Y; X_{25} is selected from the group consisting of nil, E, D, I, K, N, Q and R. In another embodiment, zeta comprises a sequence selected from the group consisting of SRAE (SEQ ID NO: 434), EKAR (SEQ ID NO: 435), ERAR (SEQ ID NO: 436), EKQE (SEQ ID NO: 437), TKDR (SEQ ID NO: 438), TKAD (SEQ ID NO: 439), AKAR (SEQ ID NO: 440), AKQR (SEQ ID NO: 441), ERQR (SEQ ID NO: 442), AKAE (SEQ ID NO: 443), ERAE (SEQ ID NO: 444), ARQR (SEQ ID NO: 445), EKQR (SEQ ID NO: 446), TKAN (SEQ ID NO: 447), TKAR (SEQ ID NO: 448), EAAR (SEQ ID NO: 449), ERQE (SEQ ID NO: 450), ARAD (SEQ ID NO: 451), EKTQ (SEQ ID NO: 452), ARAR (SEQ ID NO: 453), ARAE (SEQ ID NO: 454), ARQE (SEQ ID NO: 455), AKQE (SEQ ID NO: 456), TRAD (SEQ ID NO: 457), AKAD (SEQ ID NO: 458), TRAR (SEQ ID NO: 459), EKQQ (SEQ ID NO: 520), --RR, --AA, -AAR, ---R, -RAR, ---A, --AR, -ARA, -R-R, A-AR, A-A-, A---, ARA- and ----. In yet another embodiment, zeta comprises a sequence selected from the group consisting of EKAR, ERAR, EKQE and TKDR. In yet another embodiment, zeta comprises EKQE, EKTQ, ARAR, or EKAR.

In Formula (I), eta comprises a sequence of a formula $X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}$, wherein: X_{26} is selected from the group consisting of A, D, G, H, K, N, Q, and S; X_{27} is selected from the group consisting of A, E, I, L, M and Q; X_{28} is selected from the group consisting of A, H, K, Q,

R and V; X_{29} is selected from the group consisting of A, E, K, M, N and Q; X_{30} is selected from the group consisting of H, K, N, Q and R; and X_{31} is selected from the group consisting of A and K. In one embodiment of the invention, eta comprises a sequence selected from the group consisting of AAREQA (SEQ ID NO: 460); KEKKRK (SEQ ID NO: 461); SQRERA (SEQ ID NO: 462), KEKQQA (SEQ ID NO: 463), and QLAQQA (SEQ ID NO: 464) AARNQA (SEQ ID NO: 521), KERNQA (SEQ ID NO: 522), KEKNQA (SEQ ID NO: 523), KQRERA (SEQ ID NO: 524), KERERA (SEQ ID NO: 525), KEKERA (SEQ ID NO: 526), KEKQRA (SEQ ID NO: 527), AEAAAK (SEQ ID NO: 528), AAHAAA (SEQ ID NO: 529), and HAHABA (SEQ ID NO: 530). In yet another embodiment, eta comprises a sequence selected from the group consisting of AAREQA, and KEKKRK. In yet still another embodiment, eta comprises the sequence AAREQA. In yet still another embodiment, eta comprises a sequence selected from the group consisting of SQRERA and KEKQQA. In yet another embodiment, eta comprises the sequence KEKQQA.

In Formula (I), theta comprises a sequence of the formula $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}$, wherein X_{32} is selected from the group consisting of A, E, H and T; X_{33} is selected from the group consisting of A, D, E, I, L, N, Q, R, S and T; X_{35} is selected from the group consisting of A and R; X_{36} is selected from the group consisting of E, H, I, K, L, N, Q and R; X_{37} is selected from the group consisting of F, I, L, M and Y; X_{38} is selected from the group consisting of L, F and M; X_{39} is selected from the group consisting of A, D, E, N and Q; X_{40} is selected from the group consisting of A, D, E, H, I, K, N, Q, R, S and T; X_{41} is selected from the group consisting of A, F, I and V. In one embodiment of the invention, theta comprises a sequence of the formula $X_{32}X_{33}NX_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}$, wherein X_{32} is selected from the group consisting of A, E and T; X_{33} is selected from the group consisting of A, D, E, N, Q, S and T; X_{35} is selected from the group consisting of A and R; X_{36} is selected from the group consisting of H, I, L, N, Q and R; X_{37} is selected from the group consisting of F, I, L, M, and Y; X_{38} is selected from the group consisting of L, F and M; X_{39} is selected from the group consisting of A, D, E, N and Q; X_{40} is selected from the group consisting of nil, A, D, H, Q, R, S and T; X_{41} is selected from the group consisting of I and V. In another embodiment, theta comprises a sequence selected from the group consisting of AANRLLDVT (SEQ ID NO: 465), AAQEQLAHV (SEQ ID NO: 466), ANNAELLAIE (SEQ ID NO: 467), ANNAHLLAHI (SEQ ID NO: 468), ANNAKLLAKI (SEQ ID NO: 469), ANNALLLATI (SEQ ID NO: 470), ANNALLLDTI (SEQ ID NO: 471), ANNANLLANI (SEQ ID NO: 472), ANNAQLLAHI (SEQ ID NO: 473), ANNAQLLAQI (SEQ ID NO: 474), ANNARILARV (SEQ ID NO: 475),

ANNARLLARI (SEQ ID NO: 476), ANNARLLDTI (SEQ ID NO: 477), ANNRLLLATI (SEQ ID NO: 478), ANNRLLLDTI (SEQ ID NO: 479), EQNAHIFAHV (SEQ ID NO: 480), EQNAQIFAHV (SEQ ID NO: 481), EQNARIFARV (SEQ ID NO: 482), EQNRIIFDSV (SEQ ID NO: 483), ETNARILARV (SEQ ID NO: 484), HAQAHILAHV (SEQ ID NO: 485), HSNRKIIDIA (SEQ ID NO: 486), HSNRKLLDIA (SEQ ID NO: 487), HSNRKLMEII (SEQ ID NO: 488), HTNARILARV (SEQ ID NO: 489), TNNRLLLATV (SEQ ID NO: 490), TNNRLLLDTI (SEQ ID NO: 491), TSNRKLMEII (SEQ ID NO: 492), TTNARILARN (SEQ ID NO: 493), TTNARILARV (SEQ ID NO: 494), TTNARLLATV (SEQ ID NO: 495), TTNARLLDRV (SEQ ID NO: 496), TTNARLLDTV (SEQ ID NO: 497), TTNRLLLARV (SEQ ID NO: 498), TTNRLLLATV (SEQ ID NO: 499), TTNRLLLDTV (SEQ ID NO: 500), TTQARILARV (SEQ ID NO: 501), and TTVARILARV (SEQ ID NO: 502). In yet another embodiment, theta comprises a sequence selected from the group consisting of TTNARILARV, ANNALLLDTI, ANNALLLATI, TTNARLLDTV and TTNARLLDRV. In yet another embodiment, theta comprises the sequence ANNARLLDTI, ANNARLLARI, ANNALLLDTI, ANNALLLATI, TTNARLLDRV, TTNARILARV, ANNRLLLDTI, EQNARIFARV, EQNAHIFAHV, and EQNAQIFAHV. One skilled in the art will readily appreciate that theta encompasses the C-terminus end of the peptide.

The peptides of the invention have also been described as a peptide of 41 amino acids with certain preferred sequences. Following peptide strings have been specifically exemplified: ZGPPISIDLP (SEQ ID NO: 503) for residues X₂-X₁₁, LLRK (SEQ ID NO: 504) for residues X₁₄-X₁₇, IEIEKQEKEKQQA (SEQ ID NO: 505) for residues X₁₉-X₃₁, PLSID (SEQ ID NO: 506) for residues X₄-X₉, and LLRTLLELEKTQSQRERAEQNA (SEQ ID NO: 507) for residues X₁₄-X₃₅.

Variants of the disclosed peptides, and nucleotide sequences encoding the same, are also encompassed by the present invention. As used herein, "variants," means those peptides, polypeptides or proteins, or nucleotide sequences encoding the same, that are substantially similar to those peptides described by Formula (I) and which may be used as CRF₂R agonists. A peptide of Formula (I) may be altered in various ways to yield a variant of those encompassed by the present invention including amino acid substitutions, deletions, truncations, insertions, and modifications. Methods for such manipulations are generally known in the art. For example, variants can be prepared by mutations in the nucleotide sequences encoding the same. Methods for mutagenesis and nucleotide sequence alterations are well known in the art. See, for example, Kunkel (1985) *Proc. Natl. Acad. Sci. USA* 82:488-492; Kunkel et al. (1987) *Methods in Enzymol.* 154:367-382; U.S. Pat. No. 4,873,192; Walker and Gaastra, eds. (1983) *Techniques in Molecular*

Biology (MacMillan Publishing Company, New York) and the references cited therein. In one embodiment of the variant, the substitution(s) of the peptide of Formula (I) is conservative in that it minimally disrupts the biochemical properties of the variant. Thus, where mutations are introduced to substitute amino acid residues, positively charged residues (H, K, and R) preferably are substituted with positively charged residues; negatively charged residues (D and E) preferably are substituted with negatively-charged residues; and neutral non-polar residues (A, F, I, L, M, P, V, and W) preferably are substituted with neutral non-polar residues. In another embodiment of the variant, the overall charge, structure or hydrophobic/hydrophilic properties of the peptide can be altered without substantially adversely affecting CRF₂R agonism. In still another embodiment, the variant is an active fragment of a peptide of Formula (I). In yet another embodiment of a variant, a peptide of Formula (I) is modified by acetylation, carboxylation, phosphorylation, glycosylation, ubiquitination, and labeling, whether accomplished by *in vivo* or *in vitro* enzymatic treatment of the protein or by the synthesis of the peptide using modified amino acids. Common non-limiting examples of modifications to amino acids include phosphorylation of tyrosine, serine, and threonine residues; methylation of lysine residue; acetylation of lysine residues; hydroxylation of proline and lysine residues; carboxylation of glutamic acid residues; glycosylation of serine, threonine, or asparagine residues; and ubiquitination of lysine residues. The variant can also include other domains, such as epitope tags and His tags (e.g., the peptide can be a fusion protein).

In yet another embodiment, peptide mimics of a peptide of Formula (I) are encompassed within the meaning of variant. As used herein, "mimic," means an amino acid or an amino acid analog that has the same or similar function characteristics of an amino acid. Thus, for example, an arginine analog can be a mimic of arginine if the analog contains a side chain having a positive charge at physiologic pH, as is characteristic of the guanidinium side chain reactive group of arginine. Examples of organic molecules that can be suitable mimics are listed at Table 1 of U.S. Pat. No. 5,807,819. Generally, a variant, or nucleic acid sequence encoding the same, of the present invention will have at least 70%, generally, 80%, preferably up to 90%, more preferably 95%, even more preferably 97%, still even more preferably 98%, and most preferably 99% sequence identity to its respective native amino acid sequence. Fusion proteins, or N-terminal, C-terminal or internal extensions, deletions, or insertions into the peptide sequence shall not be construed as affecting homology.

Use of the Peptides of the Invention as CRF₂R Agonists

The peptides of the invention are useful for the treatment of a variety of diseases, disorders, and conditions that are modulated by CRF₂R or by CRF₂R activity. As used herein, the terms “disease,” “disorder” and “condition” are used interchangeably. As used herein, a disorder described by the terms “modulated by CRF₂R,” or “modulated by CRF₂R activity” refers to a disorder, condition or disease where CRF₂R activity is an effective means of alleviating the disorder or one or more of the biological manifestations of the disease or disorder; or interferes with one or points in the biological cascade either leading to the disorder or responsible for the underlying disorder; or alleviates one or more symptoms of the disorder. Thus, disorders subject to “modulation” include those for which: (1) The lack of CRF₂R activity is a “cause” of this disorder or one or more of the biological manifestations, whether the activity was altered genetically, by infection, by irritation, by internal stimulus or by some other cause; (2) The disease or disorder or the observable manifestation or manifestations of the disease or disorder are alleviated by CRF₂R activity (the lack of CRF₂R activity need not be causally related to the disease or disorder or the observable manifestations thereof); (3) CRF₂R activity interferes with part of the biochemical or cellular cascade that results in or relates to the disease or disorder. In this respect, the CRF₂R activity alters the cascade, and thus controls the disease, condition, or disorder.

In one embodiment of the invention, the peptides of the present invention have none or only weak CRF₁R agonist activity. Thus, the peptides of the present invention are particularly useful for the treatment of CRF₂R modulated disorders. One such CRF₂R modulated disorder is skeletal muscle atrophy. Skeletal muscle atrophy may be induced by disuse due to surgery, bed rest, broken bones; denervation/nerve damage due to spinal cord injury; autoimmune disease; infectious disease; glucocorticoid use for unrelated conditions; sepsis due to infection or other causes; nutrient limitation due to illness or starvation; cancer cachexia; chronic inflammation; acquired immunodeficiency syndrome (AIDS); cachexia; chronic obstructive pulmonary disease (COPD); congestive heart failure; sarcopenia and genetic disorders; e.g., muscular dystrophies, neurodegenerative diseases.

In another embodiment, the treatment of a CRF₂R modulated disorder results in an increase of skeletal mass and function. Diseases and conditions affecting skeletal muscle mass and function include, but not limited to, skeletal muscle atrophy or wasting including acute atrophy/wasting resulting from disuse due to illness, surgery, bed rest or accident; nerve damage

due to spinal cord injury, autoimmune disease, or infectious disease; glucocorticoid use for unrelated conditions; sepsis due to infection or other causes; nutrient limitation due to illness or starvation; and space travel: and chronic atrophy/wasting including cancer cachexia, chronic inflammation, AIDS cachexia, COPD, congestive heart failure, genetic disorders, e.g., muscular dystrophies, neurodegenerative diseases and sarcopenia (age associated muscle loss).

In yet another embodiment, the treatment of a CRF₂R modulated disorder includes disorders affecting bone. Diseases and conditions affecting bone include, but not limited to, bone loss resulting from disuse due to illness, surgery, bed rest or accident; nerve damage due to spinal cord injury, autoimmune disease, or infectious disease; glucocorticoid use for unrelated conditions; sepsis due to infection or other causes; nutrient limitation due to illness or starvation; and space travel. Age and hormone related bone loss (osteoporosis) are also included.

In yet another embodiment, the treatment of a CRF₂R modulated disorder includes disorders affecting the heart and circulatory system including but not limited to hypertension, congestive heart failure, damage to the heart resulting from heart attack, ischemia reperfusion injury, stroke, migraine, memory loss, Alzheimer's disease, dementia, and the like.

In yet another embodiment, the treatment of a CRF₂R modulated disorder includes disorder affecting the joints including but not limited to arthritis in particular osteoarthritis and rheumatoid arthritis.

In yet another embodiment, the treatment of a CRF₂R modulated disorder includes metabolic diseases including obesity and diabetes.

In yet another embodiment, the treatment of a CRF₂R modulated disorder includes: pain reduction; swelling reduction; allergic reactions, allergy; reducing body temperature; suppressing appetite; congestive heart failure; stress and anxiety; altering undesirably low levels of adrenocorticotrophic hormone ("ACTH") secretion; controlling appetite, arousal, and cognitive functions; and preventing long term effects of stress, such as anxiety disorders, anorexia nervosa and melancholic depression.

The term "treatment" is herein to mean that, at a minimum, administration of a peptide of the present invention that mitigates a CRF₂R modulated disorder in a mammalian subject, preferably in humans. Thus, the term "treatment" includes: preventing a CRF₂R modulated disorder from occurring in a mammal, particularly when the mammal is predisposed to acquiring the CRF₂R modulated disorder, but has not yet been diagnosed with the disease; inhibiting the CRF₂R modulated disorder; and/or alleviating or reversing the CRF₂R modulated disorder. Insofar as the methods of the present invention are directed to preventing the CRF₂R modulated

disorder, it is understood that the term “prevent” does not require that the CRF₂R modulated disorder be completely thwarted (see Webster’s Ninth Collegiate Dictionary). Rather, as used herein, the term “preventing” refers to the ability of the skilled artisan to identify a population that is susceptible to CRF₂R modulated disorders, such that administration of the peptides and kits of the present invention may occur prior to the onset of the symptoms of the CRF₂R modulated disorder. The population that is at risk for a particular CRF₂R modulated disorder is readily identifiable. For example, the population that is at risk for developing muscular dystrophy can be determined by identifying mutations in genes characteristic of the disorder. For example, and previously discussed, Duchenne and Becker dystrophies results from the inheritance of a mutation in the dystrophy gene, which is located at the Xp21 locus. Those individuals of a population that possess these mutations are at risk of developing muscular dystrophy. Thus, the patient population is identifiable and could receive the administration of a composition or unit dose form of a kit of the present invention before progression of the disease. Thus, progression of muscular atrophy or wasting in such individuals would be “prevented.”

Nucleic Acid Molecules

The present invention further provides nucleic acid molecules that encode the peptides of Formula (I) and variants thereof, preferably in isolated form. As used herein, “nucleic acid” is defined as RNA or DNA that encodes a peptide of the present invention as defined above, or is complementary to a nucleic acid sequence encoding such peptides. Specifically contemplated are genomic DNA, cDNA, mRNA and antisense molecules, as well as nucleic acids based on alternative backbones or including alternative bases whether derived from natural sources or synthesized.

The present invention further provides a fragment of an encoding nucleic acid molecule. As used herein, a fragment of an encoding nucleic acid molecule refers to a small portion of the entire protein coding sequence. The size of the fragment will be determined by the intended use. For example, if the fragment is chosen so as to encode an active portion of a peptide of the present invention, the fragment will need to be large enough to encode the functional regions of the peptide.

Fragments of the encoding nucleic acid molecules of the present invention (*i.e.*, synthetic oligonucleotides) that are used as probes or specific primers for the polymerase chain reaction (PCR), or to synthesize gene sequences encoding peptides of the invention, can easily be synthesized by chemical techniques, for example, the phosphotriester method of Matteucci et al.,

J. Am. Chem. Soc., 103:3185-3191 (1981) or using automated synthesis methods. In addition, larger DNA segments can readily be prepared by well-known methods, such as synthesis of a group of oligonucleotides that define various modular segments of the gene, followed by ligation of oligonucleotides to build the complete modified gene.

The encoding nucleic acid molecules of the present invention may further be modified so as to contain a detectable label for diagnostic and probe purposes. A variety of such labels are known in the art and can readily be employed with the encoding molecules herein described. Suitable labels include, but are not limited to, biotin, radiolabeled nucleotides and the like. A skilled artisan can readily employ any such label to obtain labeled variants of the nucleic acid molecules of the invention. Modifications to the primary structure itself by deletion, addition, or alteration of the amino acids incorporated into the protein sequence during translation can be made without destroying the activity of the protein. Such substitutions or other alterations result in proteins having an amino acid sequence encoded by a nucleic acid falling within the contemplated scope of the present invention.

Preparation of Peptides or Cell Lines Expressing Peptides

The peptides of the present invention can be prepared for a variety of uses, including, but not limited to, use as pharmaceutical reagents for the treatment of CRF₂R modulated disorders. It will be clear to one of skill in the art that, for certain embodiments of the invention, purified peptides will be most useful, while for other embodiments cell lines expressing the peptides will be most useful.

Because the peptides of Formula (I) are short polypeptides, the skilled artisan will recognize that peptides of the present invention may be synthesized by direct synthesis, rather than by recombinant means, using techniques well known in the art. See Bodanszky, *Principles of Peptide Synthesis*, Springer-Verlag, Heidelberg (1984); and such as via solid-phase synthesis, see, e.g., Merrifield, *J. Am. Chem. Soc.*, 85:2149-54 (1963); Barany et al., *Int. J. Peptide Protein Res.*, 30:705-739 (1987); and U.S. Pat. No. 5,424,398.

For example, the peptides can be synthesized with either an Applied Biosystem, Inc. (ABI) Model 433 automated synthesizer or a multi-reactor synthesizer (model Symphony™) from Protein Technology, Inc (PTI). As to peptides synthesized with the ABI synthesizer, all reagents are purchased from ABI (except piperidine which is purchased from Aldrich). Fmoc amino acids are purchased from ABI (except Fmoc-L-Pyr which is purchased from Chem-Impek). Rink Amide resins are purchased from Nova Chemicals. Standard 0.1 mmole FastMoc chemistry

with single coupling is used. The general Fmoc chemistry protocol for SPPS (solid phase peptide synthesis) includes: 1) cleavage of the Fmoc protection groups with piperidine; 2) activation of the carboxyl group of amino acids; and 3) coupling the activated amino acids to the amino-terminal of the resin bound peptide chain to form peptide bonds. Amino acids are activated with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU). A dry protected amino acid in a cartridge (1.0 mmol) is dissolved in a solution of HBTU, N,N-diisopropylethylamine (DIEA), and 1-hydroxybenzotriazole (HOBt) in N,N-dimethylformamide (DMF) with additional N-methylpyrrolidone (NMP) added. The activated Fmoc amino acid is formed almost instantaneously and the solution is transferred directly to the reaction vessel. The step of Fmoc deprotection is monitored and controlled by conductivity measurement. The peptide chain is built on a Rink Amide resin since the C-terminal amide is needed. The final product is washed extensively with NMP and dichloromethane (DCM).

As to peptides synthesized with the PTI multiple synthesizer, all the Fmoc amino acids are purchased from NovaBiochem (except Fmoc-Pyr which is purchased from Chem-Impex). Standard 0.05 mmole Fmoc synthesis protocols are used for syntheses. Fmoc amino acids (0.4 mmol) are dissolved in a solution of HBTU (200 mM), N-methylmorpholine (NMM, 0.4 M) and N,N-dimethylformamide (DMF) with additional N-methylpyrrolidone (NMP) added. The activated Fmoc amino acid is formed almost instantaneously and the solution is transferred directly to the reaction vessel. The step of Fmoc deprotection is conducted twice. The peptide chain is built on a Rink Amide resin since the C-terminal amide is needed. The final synthesis product is washed extensively with NMP and dichloromethane (DCM).

The newly synthesized peptides are deprotected. The resins containing synthesized peptides are unloaded from the synthesizer and briefly air-dried. Using 1.5-2.0 ml of the cleavage cocktail (comprising 95% trifluoroacetic acid (TFA), 2.5% ethanodithiol, 2.5% thioanisol, 2.5% phenol (W/V) in water) for 4 hours at room temperature, the peptides are cleaved off the resin and at the same time, the side chain protection groups [O-t-butyl (OtBu) for Asp, Glu, Tyr, Thr and Ser; Pentamethylchroman-6-sulfonyl (Pmc) for Arg, t-butoxycarbonyl (Boc) for Trp and Lys; trityl (Trt) for His, Asn and Gln] are removed under the deprotection condition. The cleavage solution is separated from the resin by filtration. The filtrate is then diluted with 15 ml of water. Six rounds of ether extraction are performed to clean the peptide product. The peptide is lyophilized and stored at -20°C before purification.

The deprotected peptides are purified and characterized. The peptide powder is dissolved in 50% acetic acid solution and injected onto a Vydac 1.0 cm I.D. 25 cm length C-8

column with 5 μm particle size, and 300 Å pore size for purification. A Beckman System Gold high performance liquid chromatography (HPLC) system with dual wavelength (220 nm and 280 nm) ultraviolet detector is used. A linear gradient of acetonitrile is programmed and introduced to the column to separate the peptide product from other substances. The elute is collected by a Pharmacia fraction collector, and the individual separation fractions were subjected to both analytical HPLC and (matrix assisted laser desorption ionization time of flight mass spectroscopy) MALDI-TOF MS for characterization to ensure the identity and purity.

The use of recombinant DNA technology in the preparation of the peptides, or of cell lines expressing these peptides, is also contemplated. Such recombinant methods are well known in the art. Methods for generating rDNA molecules are well known in the art, for example, see Sambrook et al., *Molecular Cloning - A Laboratory Manual*, Cold Spring Harbor Laboratory Press (1989). To express recombinant peptides of the present invention, an expression vector that comprises a nucleic acid which encodes the polypeptide of interest under the control of one or more regulatory elements, is prepared. The sequence of nucleic acids encoding the peptides of the present invention can be deduced from the peptide sequences discussed or claimed herein.

By methods well known in the art, the isolated nucleic acid molecule encoding the peptide of interest may be ligated into a suitable expression vector. The host-expression vector systems that may be used for purposes of the invention include, but are not limited to: microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA, or cosmid DNA expression vectors containing nucleotide sequences encoding the peptides of the present invention; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing nucleotide sequences encoding the peptides of the present invention; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing nucleotide sequences encoding the peptides of the present invention; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, tobacco mosaic virus) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing nucleotide sequences encoding the peptides of the present invention; or mammalian cell systems (e.g., COS, CHO, HEK293, NIH3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., retrovirus LTR) and also containing nucleotide sequences encoding the peptides of the present invention.

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the peptide being expressed. For example, when a large

quantity of such protein is needed, vectors which direct the expression of high levels of protein products are desirable. One skilled in the art is able to generate such vector constructs and purify the proteins by a variety of methodologies including selective purification technologies such as fusion protein selective columns and antibody columns, and non-selective purification technologies.

In an insect protein expression system, the baculovirus *A. californica* nuclear polyhedrosis virus (AcNPV), is used as a vector to express foreign genes in *S. frugiperda* cells. In this case, nucleotide sequences encoding the peptides of the present invention are cloned into non-essential regions of the virus and placed under the control of an AcNPV promoter. The recombinant viruses are then used to infect cells in which the inserted gene is expressed and the protein is purified by one of many techniques known to one skilled in the art.

In mammalian host cells, a number of viral-based expression systems may be utilized. Utilization of these expression systems often requires the creation of specific initiation signals in the vectors for efficient translation of the inserted nucleotide sequences. This is particularly important if a portion of the nucleotide sequence used does not contain the endogenous initiation signal. The placement of this initiation signal, in frame with the coding region of the inserted nucleotide sequence, as well as the addition of transcription and translation enhancing elements and the purification of the recombinant protein, are achieved by one of many methodologies known to one skilled in the art. Also important in mammalian host cells is the selection of an appropriate cell type which is capable of the necessary post translational modifications of the recombinant protein. Such modifications, for example, cleavage, phosphorylation, glycosylation, acetylation, etc., require the selection of the appropriate host cell which contains the modifying enzymes. Such host cells include, but are not limited to, CHO, HEK293, NIH3T3, COS, etc. and are known by those skilled in the art.

For long term, high expression of recombinant proteins, stable expression is preferred. For example, cell lines that stably express peptides of the present invention may be engineered. One of skill in the art, following known methods such as electroporation, calcium phosphate transfection, or liposome-mediated transfection, can generate a cell line that stably expresses the peptides of the present invention. This is usually accomplished by transfecting cells using expression vectors which contain appropriate expression control elements (e.g., promoter sequences, enhancer sequences, transcriptional termination sequences, polyadenylation sites, translational start sites, etc.), a selectable marker, and the gene of interest. The selectable marker may either be contained within the same vector, as the gene of interest, or on a separate vector,

which is co-transfected with the peptide encoding sequence-containing vector. The selectable marker in the expression vector may confer resistance to the selection and allows cells to stably integrate the vector into their chromosomes and to grow to form foci which in turn can be cloned and expanded into cell lines. Alternatively, the expression vector may allow selection of the cell expressing the selectable marker utilizing a physical attribute of the marker, i.e., expression of Green Fluorescent Protein (GFP) allows for selection of cells expressing the marker using fluorescence activated cell sorting (FACS) analysis.

One of skill in the art is able to select an appropriate cell type for transfection in order to allow for selection of cells into which the sequence of interest has been successfully integrated. For example, where the selectable marker is herpes simplex virus thymidine kinase, hypoxanthine-guanine phosphoribosyltransferase or adenine phosphoribosyltransferase, the appropriate cell type would be tk-, hgp^rt- or ap^rt- cells, respectively. Or, normal cells can be used where the selectable marker is dhfr, gpt, neo or hyg^ro which confer resistance to methotrexate, mycophenolic acid, G-418 or hygromycin, respectively.

Preparation of Antibodies

Antibodies that selectively recognize one or more epitopes of the peptides of the present invention are also encompassed by the invention. Such antibodies include, e.g., polyclonal antibodies, monoclonal antibodies, chimeric antibodies, human antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, molecules produced using a Fab expression library, human antibodies (polyclonal or monoclonal) produced in transgenic mice and epitope binding fragments of any of the above.

The antibodies can be utilized in conjunction with gene therapy techniques to evaluate, for example, the expression of the peptides of the present invention either in cells or directly in patient tissues in which these genes have been introduced.

For the production of antibodies, a variety of host animals may be immunized by injection with peptides of the present invention, anti-peptide antibody, anti-peptide analog antibody, or immunogenic fragments thereof by methods well known in the art. For preparation of an anti-idiotypic antibody the immunogen is an anti-peptide antibody or anti-peptide analog antibody. Production of anti-idiotypic antibodies is described, for example, in US Patent No. 4,699,880. Suitable host animals include, but are not limited to, rabbits, mice, goats, sheep and horses. Immunization techniques are well known in the art. Polyclonal antibodies can be purified from the serum of the immunized animals, or monoclonal antibodies can be generated by

methods that are well known in the art. These techniques include, but are not limited to, the well-known hybridoma techniques of Kohler and Milstein, human B-cell hybridoma techniques, and the EBV hybridoma technology. Monoclonal antibodies may be of any immunoglobulin class, including IgG, IgE, IgM, IgA, and IgD containing either kappa or lambda light chains. Techniques of producing and using chimeric antibodies are known in the art, and are described in, for example, U.S. Pat. Nos. 5,807,715; 4,816,397; 4,816,567; 5,530,101; 5,585,089; 5,693,761; 5,693,762; 6,180,370; and 5,824,307.

Assays Determining CRF₂R Selectivity

The pharmacological activity and selectivity of the peptides of present invention can be determined using published test procedures. See, e.g., U.S. Pat. Appl. No. 09/799978. Because CRF₂R and CRF₁R are homologous proteins, it is expected that a certain proportion of agonists for CRF₂R will also function as agonists of CRF₁R. As discussed above, activation of CRF₁R induces activation of the HPA axis since increased corticosteroid production leads to skeletal muscle atrophy. In most cases in which an increase in muscle mass or function is desired, it is not desirable to activate the HPA axis. When selecting a peptide useful for the treatment of a CRF₂R modulated disorder, which is not related to muscular dystrophy, it is preferable that the peptide be selective for CRF₂R. Preferably the peptide exhibits 10-fold selectivity for CRF₂R versus CRF₁R (i.e., 10-fold more active against CRF₂R than against CRF₁R), more preferably 100-fold selectivity and most preferably 1000-fold or greater selectivity. As published studies have demonstrated a benefit of corticosteroid therapy in the treatment of muscular dystrophies, it may be beneficial that a CRF₂R agonist retain some level of CRF₁R agonism when used to treat muscular dystrophies. Thus, for the treatment of muscular dystrophies, a peptide of lower selectivity that activates the CRF₂R as well as the CRF₁R, over a similar concentration range, is preferred. Preferably the peptide is 100-fold selective for CRF₂R versus CRF₁R, more preferably 10-fold selective and most preferably not selective for CRF₂R versus CRF₁R (i.e., the activity of the candidate compound is substantially similar for CRF₂R and CRF₁R). Also, in this case, it may be more preferable that the peptide is full agonist for CRF₂R while being a partial agonist for CRF₁R. Such a peptide would therefore have a built-in limit to the maximum degree of cortisol elevation and potential for muscle atrophy, while the anti-atrophy effect modulated through the CRF₂R could be enhanced by increasing the dose. One of skill in the art would be able to readily determine whether a peptide is a full or partial agonist of the CRF₁R or CRF₂R using methods known in the art.

Because it is desirable to discriminate binding between CRF₂R, as compared with CRF₁R, the assays described above may be conducted using a cell, or membrane from a cell, which expresses only CRF₂R or the assays can be conducted with a recombinant source of CRF₂R. Cells expressing both forms of CRFR may be modified using homologous recombination to inactivate or otherwise disable the CRF₁R gene. Alternatively, if the source of CRFR contains more than one CRFR type, the background signal produced by the receptor which is not of interest must be subtracted from the signal obtained in the assay. The background response can be determined by a number of methods, including elimination of the signal from the CRFR which is not of interest by use of antisense, antibodies or selective antagonists. Known antagonists of CRFRs include, but are not limited to, antalarmin (CRF₁R selective), antisauvagine-30 (CRF₂R selective) and astressin (nonselective for CRF₁R / CRF₂R).

To determine whether a peptide activates CRF₂R and/or CRF₁R, the assays are typically cell-based; however, cell-free assays are known which are able to differentiate agonist and antagonist binding as described above. Cell-based assays include the steps of contacting cells which express CRF₁R or CRF₂R with a peptide of the present invention or control and measuring activation of the CRFR by measuring the expression or activity of components of the CRFR signal transduction pathways.

As described in the background section above, CRFRs appear to couple through several different pathways including G_{os}, G_{oq} or G_{oi}, depending upon the cell type. It is thought that agonist activation of CRFR allows the receptor to signal via any of these pathways, provided that the necessary pathway components are present in the particular cell type. Thus, to assay a particular peptide of the present invention for CRFR activation, an assay can use any of the signal transduction pathways as the readout even if the relevant cell type for treatment, *in vivo*, couples CRFR to skeletal muscle atrophy via a different pathway. One of ordinary skill in the art would recognize that an assay would be effective for identifying useful peptide agonists independent of the pathway by which receptor activation was measured. Assays for measuring activation of these signaling pathways are known in the art.

For example, after contact with a peptide of the present invention, lysates of the cells can be prepared and assayed for induction of cAMP. cAMP is induced in response to G_{os} activation. Because G_{os} is activated by receptors other than CRFR and because a test peptide may be exerting its effect through CRFRs or by another mechanism, two control comparisons are relevant for determining whether the peptide increases levels of cAMP via activation of a CRFR. One control compares the cAMP level of cells contacted with the peptide and the cAMP level of

cells contacted with a control compound (i.e., the vehicle in which the peptide is dissolved). If the peptide increases cAMP levels relative to the control compound this indicates that the peptide is increasing cAMP by some mechanism. The other control compares the cAMP levels of a CRFR expressing cell line and a cell line that is essentially the same except that it does not express the CRFR, where both of the cell lines have been treated with the peptide. If the peptide elevates cAMP levels in the CRFR expressing cell line relative to the cell line that does not express CRFRs, this is an indication that the peptide elevates cAMP via activation of the CRFRs.

In one example, cAMP induction is measured with the use of DNA constructs containing the cAMP responsive element linked to any of a variety of reporter genes can be introduced into cells expressing CRFRs. Such reporter genes include, but are not limited to, chloramphenicol acetyltransferase (CAT), luciferase, glucuronide synthetase, growth hormone, fluorescent proteins (e.g., Green Fluorescent Protein), or alkaline phosphatase. Following exposure of the cells to the peptide, the level of reporter gene expression can be quantitated to determine the peptide's ability to increase cAMP levels and thus determine the peptide's ability to activate the CRFR.

The cells useful in this assay are the same as for the CRFR binding assay described above, except that cells utilized in the activation assays preferably express a functional receptor which gives a statistically significant response to CRF or one or more CRF analog. In addition to using cells expressing full length CRFRs, cells can be engineered which express CRFRs containing the ligand binding domain of the receptor coupled to, or physically modified to contain, reporter elements or to interact with signaling proteins. For example, a wild type CRFR or CRFR fragment can be fused to a G-protein resulting in activation of the fused G-protein upon agonist binding to the CRFR portion of the fusion protein. Siefert, R. et al., *Trends Pharmacol. Sci.*, 20: 383-389 (1999). The cells should also preferably possess a number of characteristics, depending on the readout, to maximize the inductive response by CRF or the CRF analog, for example, for detecting a strong induction of a CRE reporter gene; (a) a low natural level of cAMP; (b) G proteins capable of interacting with CRFRs; (c) a high level of adenylyl cyclase; (d) a high level of protein kinase A; (e) a low level of phosphodiesterases; and (f) a high level of cAMP response element binding protein would be advantageous. To increase the response to CRF or a CRF analog, host cells could be engineered to express a greater amount of favorable factors or a lesser amount of unfavorable factors. In addition, alternative pathways for induction of the CRE reporter could be eliminated to reduce basal levels.

Assays to Determine Pharmacological Activity

The pharmacological activity of the peptides of present invention can be determined using published test procedures. For example, models of skeletal muscle atrophy or hypertrophy include both *in vitro* cell culture models and *in vivo* animal models of skeletal muscle atrophy.

In vitro models of skeletal muscle atrophy are known in the art. Such models are described, for example, in Vandeburgh, H.H., *In Vitro*, 24:609-619 (1988), Vandeburgh, H.H. et al., *J. Biomechanics*, 24 Suppl 1:91-99 (1991), Vandeburgh, H.H. et al., *In Vitro Cell. Dev. Biol.*, 24(3):166-174 (1988), Chromiak, J.A., et al., *In Vitro Cell. Dev. Biol. Anim.*, 34(9):694-703 (1998), Shansky, J., et al., *In Vitro Cell. Dev. Biol. Anim.*, 33(9):659-661 (1997), Perrone, C.E. et al., *J. Biol. Chem.*, 270(5):2099-2106 (1995), Chromiak, J.A. and Vandeburgh, H.H., *J. Cell. Physiol.*, 159(3):407-414 (1994), and Vandeburgh, H.H. and Karlisch, P., *In Vitro Cell. Dev. Biol.*, 25(7):607-616 (1989).

A variety of animal models for skeletal muscle atrophy are known in the art, such as those described in the following references: Herbison, G.J., et al. *Arch. Phys. Med. Rehabil.*, 60:401-404 (1979), Appell, H.J. *Sports Medicine* 10:42-58 (1990), Hasselgren, P-O. and Fischer, J.E. *World J. Surg.*, 22:203-208 (1998), Agbenyega, E.T. and Wareham, A.C. *Comp. Biochem. Physiol.*, 102A:141-145 (1992), Thomason, D.B. and Booth, F.W. *J. Appl. Physiol.*, 68:1-12 (1990), Fitts, R.H., et al. *J. Appl. Physiol.*, 60:1946-1953 (1986), Bramanti, P., et al. *Int. J. Anat. Embryol.* 103:45-64 (1998), Cartee, G.D. *J. Gerontol. A Biol. Sci. Med. Sci.*, 50:137-141 (1995), Cork, L.C., et al. *Prog. Clin. Biol. Res.*, 229:241-269 (1987), Booth, F.W. and Gollnick, P.D. *Med. Sci. Sports Exerc.*, 15:415-420 (1983), Bloomfield, S.A. *Med. Sci. Sports Exerc.*, 29:197-206 (1997). Preferred animals for these models are mice and rats. These models include, for example, models of disuse-induced atrophy such as casting or otherwise immobilizing limbs, hind limb suspension, complete animal immobilization, and reduced gravity situations. Models of nerve damage induced atrophy include, for example, nerve crush, removal of sections of nerves which innervate specific muscles, toxin application to nerves and infection of nerves with viral, bacterial or eukaryotic infectious agents. Models of glucocorticoid-induced atrophy include application of atrophy-inducing doses of exogenous glucocorticoid to animals, and stimulation of endogenous corticosteroid production, for example, by application of hormones that activate the hypothalamus-pituitary-adrenal (HPA) axis. Models of sepsis-induced atrophy include, for example, inoculation with sepsis-inducing organisms such as bacteria, treatment of the animal with immune-activating compounds such as bacterial cell wall extract or endotoxin, and puncture of intestinal walls. Models of cachexia-induced atrophy include, for example, inoculation of an

animal with tumorigenic cells with cachexia forming potential, infection of an animal with infectious agents (such as viruses which cause AIDS) which result in cachexia and treatment of an animal with hormones or cytokines such as CNTF, TNF, IL-6, IL-1, etc. which induce cachexia. Models of heart failure-induced atrophy include the manipulation of an animal so that heart failure occurs with concomitant skeletal muscle atrophy. Neurodegenerative disease-induced atrophy models include autoimmune animal models such as those resulting from immunization of an animal with neuronal components. Muscular dystrophy-induced models of atrophy include natural or man-made genetically induced models of muscular dystrophy such as the mutation of the dystrophin gene which occurs in the Mdx mouse.

Animal models of skeletal muscle hypertrophy include, for example, models of increased limb muscle use due to inactivation of the opposing limb, reweighing following a disuse atrophy inducing event, reutilization of a muscle which atrophied because of transient nerve damage, increased use of selective muscles due to inactivation of a synergistic muscle (e.g., compensatory hypertrophy), increased muscle utilization due to increased load placed on the muscle and hypertrophy resulting from removal of the glucocorticoid after glucocorticoid-induced atrophy. Preferred animal atrophy models include the sciatic nerve denervation atrophy model, glucocorticoid-induced atrophy model, and the leg casting disuse atrophy model that are described in further detail below.

The sciatic nerve denervation atrophy model involves anesthetizing the animal followed by the surgical removal of a short segment of either the right or left sciatic nerve, e.g., in mice the sciatic nerve is isolated approximately at the midpoint along the femur and a 3-5 mm segment is removed. This denervates the lower hind limb musculature resulting in atrophy of these muscles. Typically, innervation to the biceps femoris is left intact to provide satisfactory motion of the knee for virtually normal ambulation. Typically, in untreated animals, muscle mass of the denervated muscles is reduced 30-50% ten days following denervation. Following denervation, test peptides are administered e.g., by injection or by continuous infusion, e.g., via implantation of an osmotic minipump (e.g., Alzet, Palo Alto, CA), to determine their effect on denervation induced skeletal muscle atrophy. At various times following denervation, the animals are euthanized and lower leg muscles are dissected rapidly from both the denervated and nondenervated legs, the muscles, cleaned of tendons and connective tissue, are weighed. The extent of atrophy in the affected muscles is analyzed, for example, by measuring muscle mass, muscle cross-sectional area, myofiber cross-sectional area or contractile protein content.

The glucocorticoid-induced atrophy model involves the administration of a glucocorticoid to the test animal, e.g., 1.2 mg/kg/day of dexamethasone in the drinking water. Typically, in untreated animals, skeletal muscle mass is reduced 30-50% following ten days of dexamethasone administration. Concomitantly with, or following glucocorticoid administration, test peptides are administered e.g., by injection or by continuous infusion to determine their effect on glucocorticoid-induced skeletal muscle atrophy. At various times following glucocorticoid administration, the extent of atrophy in the affected muscles is analyzed as described above for the denervation model.

The leg casting disuse atrophy model involves casting one hind leg of an animal from the knee down through the foot. Typically, muscle mass is reduced 20-40% after ten days of casting. Following casting, test peptides are administered by injection or by continuous infusion via implantation of an osmotic minipump (e.g., Alzet, Palo Alto, CA) to determine their effect on leg casting induced skeletal muscle atrophy. At various times following leg casting, the extent of atrophy in the affected muscles is analyzed as described above for the denervation model.

Bone activity of the subject peptides can be conveniently demonstrated using an assay designed to test the ability of the subject compounds to increase bone volume, mass, or density. An example of such assays is the ovariectomized rat assay.

In the ovariectomized rat assay, six-month old rats are ovariectomized, aged 2 months, and then dosed once a day subcutaneously with a test compound. Upon completion of the study, bone mass and/or density can be measured by dual energy x-ray absorptometry (DXA) or peripheral quantitative computed tomography (pQCT), or micro computed tomography (mCT). Alternatively, static and dynamic histomorphometry can be used to measure the increase in bone volume or formation.

Compositions

Another aspect of this invention is compositions which comprise: (a) a safe and effective amount of a peptide of the present invention; and (b) a pharmaceutically-acceptable carrier. Standard pharmaceutical formulation techniques are used, such as those disclosed in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pa., latest edition.

A "safe and effective amount" means an amount of the peptide of the invention sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (such as toxicity, irritation, or allergic response) in an animal, preferably a mammal, more preferably a human subject, in need thereof,

commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the subject, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the peptide therein, and the dosage regimen desired for the composition. One skilled in the art may use the following teachings to determine a "safe and effective amount" in accordance with the present invention. Spilker B., *Guide to Clinical Studies and Developing Protocols*, Raven Press Books, Ltd., New York, 1984, pp. 7-13, 54-60; Spilker B., *Guide to Clinical Trials*, Raven Press, Ltd., New York, 1991, pp. 93-101; Craig C., and R. Stitzel, eds., *Modern Pharmacology*, 2d ed., Little, Brown and Co., Boston, 1986, pp. 127-33; T. Speight, ed., *Avery's Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics*, 3d ed., Williams and Wilkins, Baltimore, 1987, pp. 50-56; R. Tallarida, R. Raffa and P. McGonigle, *Principles in General Pharmacology*, Springer-Verlag, New York, 1988, pp. 18-20.

In addition to the subject peptide, the compositions of the subject invention contain a pharmaceutically acceptable carrier. The term "pharmaceutically-acceptable carrier," as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to an animal, preferably a mammal, more preferably a human. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject peptide, and with each other, in a manner such that there is no interaction that would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal, preferably a mammal, more preferably a human being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tweens®; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents;

tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the peptide is to be administered.

If the subject peptide is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with a blood-compatible colloidal suspending agent, the pH of which has been adjusted to about 7.4.

In particular, pharmaceutically-acceptable carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

The compositions of this invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition of this invention containing an amount of a Formula (I) peptide that is suitable for administration to an animal, preferably a mammal, more preferably a human subject, in a single dose, according to good medical practice. These compositions preferably contain from about 0.1 mg (milligrams) to about 1000 mg, more preferably from about 0.5 mg to about 500 mg, more preferably from about 1 mg to about 30 mg, of a peptide of Formula (I).

The compositions of this invention may be in any of a variety of forms, suitable, for example, for oral, rectal, topical, nasal, ocular or parenteral administration. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the CRF₂R agonist activity of the peptides of Formula (I). The amount of carrier employed in conjunction with the Formula (I) peptide is sufficient to provide a practical quantity of material for administration per unit dose of the Formula (I) peptide. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references,: *Modern Pharmaceutics*, Chapters 9 and 10 (Banker & Rhodes,

editors, 1979); Lieberman et al., *Pharmaceutical Dosage Forms: Tablets* (1981); and Ansel, *Introduction to Pharmaceutical Dosage Forms* 2d Edition (1976).

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of the peptide. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, and containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art. In general, the formulation will include the peptide, and inert ingredients which allow for protection against the stomach environment, and release of the biologically active material in the intestine.

The peptide of Formula (I) may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the protein molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the protein and increase in circulation time in the body. Examples of such moieties include: polyethylene glycol, copolymers of ethylene glycol and

propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. Newmark et al., *J. Appl. Biochem.*, 4:185-189 (1982). Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. Preferred for pharmaceutical usage, as indicated above, are polyethylene glycol moieties.

The location of release may be the stomach, the small intestine (the duodenum, the jejunum, or the ileum), or the large intestine. One skilled in the art has available formulations which will not dissolve in the stomach, yet will release the material in the duodenum or elsewhere in the intestine. Preferably, the release will avoid the deleterious effects of the stomach environment, either by protection of the peptide (or variant) or by release of the biologically active material beyond the stomach environment, such as in the intestine.

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

Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, Avicel[®] RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Compositions of the subject invention may optionally include other active agents. Non-limiting examples of active agents are listed in WO 99/15210.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal, suppository, nasal and pulmonary dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compositions of this invention can also be administered topically to a subject, e.g., by the direct laying on or spreading of the composition on the epidermal or epithelial tissue of the subject, or transdermally via a "patch." An example of a suitable patch applicator is described in U.S. Patent Application Serial No. 10/054113. Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions preferably comprise a safe and effective amount, usually at least about 0.1%, and preferably from about 1% to about 5%, of the peptide. Suitable carriers for topical administration preferably remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the peptide. The carrier may include pharmaceutically-acceptable emollients, emulsifiers, thickening agents, solvents and the like.

Methods of Administration

This invention also provides methods of treating CRF₂R modulated disorders in a human or other animal subject, by administering a safe and effective amount of a peptide to said subject. The methods of the invention are useful in preventing or treating disorders described above.

Compositions of this invention can be administered topically or systemically. Systemic application includes any method of introducing a peptide of Formula (I) into the tissues of the body, e.g., intra-articular (especially in treatment of rheumatoid arthritis), intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, nasal, pulmonary, sublingual, rectal, and oral administration.

The specific dosage of the peptide to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific peptide used, the treatment indication, the ability of the peptide to reach minimum inhibitory concentrations at the site of the tissue in need of treatment, the personal attributes of the subject (such as weight), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

Topical administration can be used to deliver the peptide systemically, or to treat a subject locally. The amounts of the peptide to be topically administered depends upon such

factors as skin sensitivity, type and location of the tissue to be treated, the composition and carrier (if any) to be administered, the particular peptide to be administered, as well as the particular disorder to be treated and the extent to which systemic (as distinguished from local) effects are desired.

The peptides of the present invention can be targeted to specific locations where treatment is needed by using targeting ligands. For example, to focus a peptide to treat muscular dystrophy, the peptide is conjugated to an antibody or fragment thereof which is immunoreactive with a skeletal muscle marker as is generally understood in the art. The targeting ligand can also be a ligand suitable for a receptor which is present on skeletal muscle. Any targeting ligand which specifically reacts with a marker for the intended target tissue can be used. Methods for coupling the invention compound to the targeting ligand are well known and are similar to those described below for coupling to carrier.

A peptide of Formula (I) may be administered via a controlled release. For example, the peptide may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, subcutaneous depot injection containing a biodegradable material, or other modes of administration. In one embodiment, a pump may be used Langer et al., eds., *Medical Applications of Controlled Release*, CRC Pres., Boca Raton, Fla. (1974); Sefton, *CRC Crit. Rev. Biomed. Eng.*, 14:201 (1987); Buchwald et al., *Surgery*, 88:507 (1980); Saudek et al., *N. Engl. J. Med.*, 321:574 (1989). In another embodiment, polymeric materials can be used. Langer, 1974, supra; Sefton, 1987, supra; Smolen et al., eds., *Controlled Drug Bioavailability, Drug Product Design and Performance*, Wiley, N.Y. (1984); Ranger et al., *J. Macromol. Sci. Rev. Macromol. Chem.*, 23:61 (1983); see also Levy et al., *Science*, 228:190 (1985); During et al., *Ann. Neurol.*, 25:351 (1989); Howard et al., *J. Neurosurg.*, 71:105 (1989). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target thus requiring only a fraction of the systemic dose. See, e.g., Goodson, in *Medical Applications of Controlled Release*, vol. 2, pp. 115-138 (1984). In yet another embodiment, a polymer-based drug-delivery system wherein drugs are delivered from polymer or lipid systems. These systems deliver a drug by three general mechanisms: (1) diffusion of the drug species from or through the system; (2) a chemical or enzymatic reaction leading to degradation of the system, or cleavage of the drug from the system; and (3) solvent activation, either through osmosis or swelling of the system. Suitable systems are described in review articles: Langer, Robert, "Drug delivery and targeting," *Nature*: 392 (Supp):5-10 (1996); Kumar, Majeti N. V., "Nano and Microparticles as Controlled Drug Delivery Devices," *J Pharm Pharmaceut Sci*, 3(2):234-258 (2000); Brannon-

Peppas, "Polymers in Controlled Drug Delivery," Medical Plastics and Biomaterials, (Nov. 1997). See also, Langer, 1990, *supra*; Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Langer, *Science*, 249:1527-1533 (1990). Suitable systems may include: Atrigel™ drug delivery system from Atrix Labs; DepoFoam™ from SkyPharma; polyethylene glycol-based hydrogels from Infimed Therapeutics, Inc.; ReGel™, SQZGel™ oral, HySolv™ and ReSolv™ solubilizing drug-delivery systems from MacroMed; ProGelz™ from ProGelz' Products; and ProLease™ injectable from Alkermes.

In all of the foregoing, of course, the peptides of the invention can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication.

Gene Therapy

Expression vectors may be used to introduce the nucleic acids of the invention into a cell as part of gene therapy. Such vectors generally have convenient restriction sites located near the promoter sequence to provide for the insertion of nucleic acid sequences. Transcription cassettes may be prepared comprising a transcription initiation region, the target gene or fragment thereof, and a transcriptional termination region. The transcription cassettes may be introduced into a variety of vectors, *e.g.*, plasmid, retrovirus, lentivirus, adenovirus and the like, where the vectors are able to transiently or stably be maintained in the cells, usually for a period of at least about one day, more usually for a period of at least about several days to several weeks.

The proteins and nucleic acids of the invention may be introduced into tissues or host cells by any number of routes, including viral infection, microinjection, or fusion of vesicles. Jet injection may also be used for intramuscular administration, as described by Furth et al., *Anal. Biochem.*, 205:365-368 (1992). The DNA may be coated onto gold microparticles, and delivered intradermally by a particle bombardment device, or "gene gun" as described in the literature. See, *e.g.*, Tang et al., *Nature* 356:152-154 (1992), where gold microprojectiles are coated with DNA, then bombarded into skin cells.

Kits

The present invention includes a kit for preventing or treating a CRF₂R modulated disorder comprising: (a) a peptide of Formula (I) in a unit dose form; and (b) usage instructions. Such a kit preferably includes a number of unit dosages. Such kits can include a card having

dosages oriented in the order of their intended use. An example of such a kit is a “blister pack.” Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Example of a kit is described in WO 01/45636. Treatments schedules are within the purview of those skilled in the medicinal arts. Non-limiting examples include once daily, weekly, biweekly, monthly, or bimonthly.

EXAMPLES

Example 1

Savagine and other non-selective CRFR agonists are generally not effective in treating CRF₂R modulated disorders because these agonists also activate CRF₁R thereby resulting in undesirable side effects.

Table 2 reflects comparative CRF binding for native sequence fragments of human urocortin I (hUcnI), human urocortin II (hUroII), human urocortin III (hUroIII), human corticotropin releasing factor (hCRF), ovine corticotropin (oCRF), and savagine (Svg) designated as SEQ ID NO: 2, 4, 6, 8, 10 and 11, respectively.

Table 2

SEQ ID NO	PEPTIDE	CRF₂R EC₅₀ (nM) (Emax%)	CRF₁R EC₅₀ (nM) (Emax%)
2	hUcnI	3.52 (100)	9.00 (100)
4	hUroII	3.64 (98)	>100 (9)
6	hUroIII	>100 (60)	>1000 (10.25)
8	hCRF	49.25 (100)	19.95 (87)
10	oCRF	>100 (33)	27.35 (98)
11	Svg	6.03 (95)	17.60 (100)

Example 2

Table 3 reflects comparative CRF binding of various embodiments of the invention.

Table 3

SEQ ID NO	CRF₂R EC₅₀ (nM) (Emax%)	CRF₁R EC₅₀ (nM) (Emax%)
1	31.50 (100)	783 (64)
3	12.13 (88)	1000 (12)
5	100 (12)	100 (9)
7	100 (19)	100 (4)
9	100 (34)	100 (10)
12	9.72 (91)	928 (73)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
13	3.88 (79)	97.65 (69)
14	6.33 (90)	109.00 (92)
15	6.56 (97)	85.30 (86)
16	7.88 (86)	136.00 (98)
17	10.20 (96)	260.50 (98)
18	5.29 (97)	106.00 (100)
19	7.42 (75)	232.50 (83)
20	7.81 (99)	906.00 (60)
21	8.46 (96)	908.00 (88)
22	8.33 (100)	1000.00 (64)
23	10.20 (100)	1000.00 (82)
24	43.15 (100)	>1000 (18)
25	80.95 (81.90)	677.00 (92.35)
26	91.75 (86)	>1000 (16)
27	10.70 (96)	325 (100)
28	100 (15)	>1000 (2)
29	16.00 (100)	>1000 (79)
30	18.70 (85.50)	100.45 (100)
31	30.75 (100)	>1000 (18)
32	20.25 (98)	606 (94)
34	>100 (45)	>1000 (11)
35	15.55 (88)	>1000 (74)
36	14.75 (73)	>1000 (33)
37	>100 (51)	>1000 (5)
38	71.90 (91)	>1000 (11)
39	58.17 (94)	1000 (63)
40	6.95 (93)	102.5 (99)
41	18.30 (100)	>1000 (43)
42	>100 (88)	>1000 (10)
43	>100 (67)	>1000 (10)
44	19.15 (87)	943.50 (64)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
45	>100 (44)	>1000 (7)
46	>100 (100)	>1000 (17)
47	>100 (66)	1000 (12)
48	100 (14)	1000 (21)
49	>100 (37)	>1000 (15)
50	19.04 (94)	>1000 (42)
51	20.65 (100)	>1000 (48)
52	>100 (10)	>1000 (13)
53	>100 (95)	>1000 (19)
54	100 (11)	1000 (10)
55	7.95 (95)	11.60 (92)
56	50.35 (87)	>100 (14)
57	>100 (46)	>100 (12)
58	71.60 (100)	>100 (16)
59	>100 (27)	>100 (10)
60	>100 (44)	>100 (8)
61	>100 (89)	>100 (12)
63	67.35 (100)	73.15 (34)
64	63.30 (94)	68.90 (57)
65	67.90 (64)	>100 (16)
67	10.02 (50)	44.17 (96)
68	38.55 (74)	>100 (33)
69	5.85 (81)	34.50 (88)
70	18.25 (82)	>100 (8)
71	94.80 (56)	>100 (6)
72	>100 (55)	>100 (4)
73	>100 (11)	>100 (11)
74	54.97 (100)	>100 (7)
75	>100 (52)	>100 (5)
76	91.45 (76)	>100 (7)
77	43.35 (100)	>100 (5)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
78	24.65 (78)	>100 (6)
79	22.30 (100)	>100 (8)
80	6.53 (88)	>100 (55)
81	4.30 (73)	60.90 (81)
82	10.87 (90)	96.20 (85)
83	1.91 (81)	52.17 (96)
84	1.77 (100)	82.23 (99)
85	2.34 (100)	11.00 (84)
86	100 (8.10)	100 (4.60)
87	100 (14.65)	100 (5.30)
88	100 (12.60)	100 (11.15)
89	100 (12.70)	
90	100 (12.25)	100 (4.00)
91	100 (7.10)	100 (4.00)
92	100 (15.85)	100 (4.60)
93	100 (6.40)	100 (5.00)
94	100 (6.15)	100 (7.30)
95	100 (8.25)	100 (5.55)
96	100 (12.50)	100 (16.30)
97	100 (7.60)	100 (4.25)
98	100 (5.50)	100 (4.00)
99	100 (4.35)	100 (4.35)
100	100 (9.85)	100 (6.25)
101	100 (6.95)	100 (7.35)
102	100 (13.50)	100 (7.80)
103	100 (4.85)	100 (5.75)
104	100 (4.50)	100 (11.10)
105	100 (9.15)	100 (5.20)
106	100 (6.10)	100 (4.80)
107	12.13 (87.90)	1000 (12.40)
108	79.00 (97)	>100 (3)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
109	11.83 (91.67)	100 (6.70)
110	10.96 (100)	>100 (9)
111	10.95 (99)	>100 (9)
112	12.30 (100)	>100 (10)
113	11.30 (98)	>100 (4)
114	3.42 (100)	>100 (6)
115	13.60 (98)	>100 (7)
116	100 (26.45)	100 (4.80)
117	9.41 (98.85)	100 (7.80)
118	14.60 (100)	>100 (5)
119	3.57 (95)	>100 (3)
120	69.90 (100)	100 (7)
121	5.67 (91)	>100 (3)
122	3.31 (97)	1000 (10.7)
123	3.49 (93.75)	>1000 (9.60)
124	3.49 (94)	>100 (6)
125	4.47 (99)	>100 (9)
126	13.00 (91)	>100 (7)
127	7.79 (94)	>100 (6)
128	2.85 (98)	>100 (8)
129	3.83 (92)	>100 (12)
130	8.57 (92)	>100 (9)
131	5.25 (91)	>100 (8)
132	7.53 (88)	>100 (8)
133	12.22 (88)	>100 (4)
134	>100 (19)	>100 (7)
135	>100 (76)	>100 (6)
136	23.40 (68)	>100 (8)
137	36.90 (100)	>100 (4)
138	59.00 (46)	>100 (5)
139	42.60 (60)	>100 (4)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
141	>100 (29)	>100 (7)
142	9.08 (77.00)	43.45 (85.35)
143	11.05 (85.50)	232.00 (100)
144	9.16 (85.53)	567 (100)
145	7.80 (69.00)	196.50 (91.30)
146	8.20 (84.50)	103 (100)
147	6.75 (94.00)	101.60 (96.00)
148	9.45 (51.50)	295.00 (100)
149	26.20 (95.50)	1000 (40.70)
150	34.65 (70.50)	1000 (5.70)
151	36.75 (96.00)	1000 (19.90)
152	>100 (19)	>100 (4)
153	9.28 (97)	>100 (7)
154	10.30 (100)	>100 (7)
155	20.60 (94)	40.65 (16)
156	9.29 (79)	>100 (6)
157	42.00 (60.65)	100 (91.00)
158	6.37 (89)	>100 (15)
159	90.77 (62)	>100 (9)
160	9.15 (87)	>100 (10)
161	>100 (88)	>100 (77)
162	>100 (7)	>100 (11)
163	4.49 (96)	>100 (13)
164	2.24 (92)	>100 (26)
165	>100 (75)	>100 (19)
166	3.7 (99)	437.5 (95)
167	13.0 (100)	1000.0 (15)
168	4.9 (75)	1000.0 (52)
169	17.8 (93)	978.0 (26)
170	75.0 (83)	1000.0 (9)
171	17.6 (100)	206.0 (99)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
172	13.5 (100)	1000.0 (68)
173	100 (65.20)	1000 (6.05)
174	4.42 (97.2)	1000.0 (29.10)
175	5.42 (92.15)	1000.0 (34.8)
176	12.60 (90.25)	1000.0 (26.9)
177	5.63 (97.65)	613.0 (69.2)
178	5.17 (96.45)	1000.0 (55.70)
179	10.22 (92.5)	477.0 (78.90)
180	3.14 (95.7)	125.0 (99.3)
181	5.22 (97.75)	154.0 (100)
182	7.21 (91.4)	409.0 (89.7)
183	7.93 (100)	415 (57.5)
184	3.72 (96.45)	486.0 (77.35)
185	8.98 (100)	358.5 (95.8)
186	25.05 (100)	323 (100)
187	10.3 (100)	31.6 (72)
188	14.6 (100)	162.5 (96)
189	7.0 (96)	62.2 (57)
190	39.60 (31)	>100 (9)
191	8.3 (100)	63.7 (65)
192	66.8 (97)	562.0 (99)
193	10.1 (97)	265.5 (95)
194	5.0 (96)	106.0 (94)
195	18.8	103.0 (93)
196	27.7 (97)	447.0 (96)
197	48.1 (94)	
198	29.9 (100)	
199	8.5 (92)	706.5 (93)
200	8.8 (100)	188.5 (99)
201	5.0 (100)	99.6 (80)
202	8.7 (99)	403.5 (100)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
203	5.2 (94)	76.2 (86)
204	3.6 (93)	32.1 (74)
205	25.0 (93)	126.5 (88)
206	30.5 (97)	696.5 (97)
207	61.4 (96)	465.5 (88)
208	5.6 (88)	64.9 (81)
209	7.4 (93)	26.4 (80)
210	10.2 (97)	43.5 (90)
211	59.5 (100)	826.0 (37)
212	21.3 (100)	445.0 (100)
213	22.3 (99)	1000.0 (76)
214	74.30 (60)	100 (4)
215	4.0 (100)	187.5 (100)
216	9.9 (90)	49.8 (98)
217	4.7 (95)	94.7 (100)
218	4.8 (96)	98.4 (100)
219	7.8 (98)	80.9 (100)
220	4.1 (98)	63.6 (81)
221	8.5 (100)	236.5 (100)
222	9.4 (100)	384.5 (95)
223	3.0 (92)	48.1 (81)
224	26.9 (100)	1000.0 (27)
225	4.8 (89)	219.5 (97)
226	7.6 (100)	315.0 (95)
227	33.6 (95)	918.0 (18)
228	7.1 (100)	275.5 (100)
229	10.3 (100)	298.0 (100)
230	8.1 (100)	219.0 (100)
231	5.9 (100)	94.0 (100)
232	45.3 (100)	1000.0 (7)
233	46.1 (95)	1000 (11)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
234	20.6 (100)	434.3 (96)
235	25.7 (100)	806.5 (70)
236	40.4 (97)	1000.0 (15)
237	22.2 (93)	1000.0 (18)
238	16.7 (100)	753.0 (88)
239	13.2 (100)	587.0 (80)
240	22.0 (100)	915.0 (80)
241	12.6 (99)	307.5 (99)
242	29.0 (94)	358.5 (99)
243	16.8 (100)	440.5 (96)
244	8.8 (98)	299.5 (100)
245	7.5 (93)	381.0 (100)
246	38.8 (100)	1000.0 (33)
247	18.8 (100)	1000.0 (34)
248	19.6 (98)	1000.0 (32)
249	12.2 (92)	1000.0 (50)
250	19.7 (100)	137.5 (99)
251	11.8 (100)	926.0 (80)
252	22.3 (100)	226.5 (100)
253	41.8 (86)	1000.0 (42)
254	100.0 (36)	708.0 (6)
255	7.0 (100)	33.3 (84)
256	12.6 (100)	253.5 (100)
257	100 (72.60)	744.50 (83.50)
258	100 (49.30)	1000 (23.65)
259	100 (64.95)	819.50 (83.60)
260	100 (89.35)	834.00 (89.70)
261	100 (95.30)	274 (100)
262	100 (92.25)	408 (100)
263	36.17 (93.03)	802.50 (71.95)
264	100.00 (66.30)	704.50 (100)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
265	100.00 (23.35)	1000.00 (9.30)
266	100.00 (19.35)	1000.00 (4.45)
267	100.00 (44.20)	1000.00 (22.80)
268	100.00 (59.05)	1000.00 (14.15)
269	100.00 (77.30)	1000.00 (44.30)
270	100.00 (19.30)	1000.00 (7.85)
271	48.10 (68.95)	815.00 (80.65)
272	23.30 (100.00)	1000.00 (51.10)
273	31.30 (100.00)	1000.00 (59.30)
274	13.80 (100.00)	508.00 (80.90)
275	46.60 (100.00)	1000.00 (38.30)
276	22.10 (100.00)	1000.00 (75.70)
277	28.20 (100.00)	1000.00 (39.90)
278	19.55 (100.00)	1000.00 (48.70)
279	13.10 (100.00)	1000.00 (93.00)
280	100.00 (82.30)	1000.00 (11.80)
281	100.00 (78.80)	1000.00 (12.20)
282	25.80 (60.75)	1000.00 (21.75)
283	10.55 (71.95)	635.00 (100.00)
284	100.00 (100.00)	1000.00 (27.70)
285	13.95 (97.10)	1000.00 (11.10)
286	13.50 (92.45)	1000.00 (19.20)
287	11.31 (100.00)	1000.00 (51.75)
288	14.70 (100.00)	838.00 (31.65)
289	12.16 (97.30)	1000.00 (69.55)
290	100.00 (100.00)	1000.00 (6.40)
291	100.00 (63.75)	1000.00 (4.75)
292	100.00 (86.10)	1000.00 (7.00)
293	40.30 (87.00)	520.50 (95.30)
294	100.00 (100.00)	1000.00 (13.60)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
295	55.05 (67.60)	1000.00 (5.30)
296	6.66 (65)	100 (4)
297	100.00 (88.30)	1000.00 (27.250)
298	82.00 (98.85)	1000.00 (20.05)
299	46.40 (71.55)	1000.00 (10.20)
300	17.10 (100.00)	1000.00 (7.95)
301	50.45 (88.40)	690.00 (84.10)
302	36.20 (100.00)	366.50 (100.00)
303	27.25 (100.00)	581.50 (100.00)
304	19.30 (92.55)	115.50 (100.00)
305	35.45 (95.20)	1000.00 (59.55)
306	27.55 (100.00)	608.00 (97.65)
307	5.82 (96.55)	78.40 (92.65)
308	3.30 (72.80)	63.45 (100.00)
309	5.55 (99.90)	107.50 (96.35)
310	8.70 (87.55)	1000.00 (45.30)
311	11.65 (100.00)	1000.00 (29.70)
312	14.05 (95.00)	869.50 (62.00)
313	11.05 (95.00)	704.00 (87.100)
314	10.35 (99.75)	978.50 (82.40)
315	9.35 (81.70)	454.50 (100.00)
316	10.15 (94.50)	221.50 (92.35)
317	9.30 (88.35)	187.50 (100.00)
318	9.95 (95.40)	134.50 (92.85)
319	8.50 (95.00)	106.00 (88.30)
320	19.05 (100.00)	718.00 (68.75)
321	19.55 (86.80)	1000.00 (33.80)
322	23.05 (96.45)	1000.00 (10.65)
323	19.60 (100.00)	1000.00 (36.90)
324	17.20 (100.00)	1000.00 (46.60)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
325	11.67 (100)	100 (5)
326	33.70 (100.00)	1000.00 (30.10)
327	28.40 (100.00)	1000.00 (36.50)
328	11.70 (95.70)	1000.00 (30.70)
329	5.15 (98.30)	1000.00 (98.40)
330	6.00 (93.65)	1000.00 (86.80)
331	9.85 (100.00)	1000.00 (78.65)
332	9.95 (100.00)	1000.00 (61.30)
333	9.85 (96.90)	1000.00 (43.80)
334	13.15 (93.55)	1000.00 (82.60)
335	28.05 (90.95)	1000.00 (49.45)
336	17.80 (100.00)	1000.00 (59.90)
337	23.95 (86.65)	1000.00 (36.45)
338	19.30 (77.55)	1000.00 (41.10)
339	100.00 (47.90)	1000.00 (13.20)
340	7.99 (100.00)	739.50 (95.95)
341	8.83 (95.50)	850.50 (82.35)
342	20.25 (92.25)	1000.00 (19.65)
343	13.60 (96.55)	783.00 (62.50)
344	4.30 (94.47)	650.00 (77.65)
345	39.70 (100.00)	1000.00 (18.75)
346	8.48 (97.75)	1000.00 (59.00)
347	22.35 (95.65)	1000.00 (48.75)
348	5.77 (90.40)	630.00 (86.05)
349	13.75 (100)	1000 (44.20)
350	11.59 (98.10)	1000 (48.00)
351	12.93 (97.37)	1000 (85.70)
352	8.26 (83.65)	780 (82.60)
353	4.75 (89.90)	229.50 (92.25)
354	6.48 (100)	1000 (13.40)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
355	6.03 (95)	18 (100)
356	83.05(16)	1000 (9)
357	6.44 (100)	331 (100)
358	5.56 (100)	99 (100)
359	23.10 (100)	230 (100)
360	6.12 (93)	157 (100)
361	6.37 (99)	149 (100)
362	4.39 (100)	386 (100)
363	25.15 (100)	1000 (20)
364	13.20 (100)	1000 (27)
365	23.45 (94)	1000 (21)
366	100.00 (46)	1000 (9)
367	100.00 (18)	1000 (6)
368	50.35 (91)	1000 (6)
369	100.00 (18)	1000 (4)
370	51.05 (75)	1000 (33)
371	6.62 (97)	1000 (22)
372	14.20 (100)	1000 (13)
373	11.54 (100)	1000 (9)
374	15.75 (91)	1000 (11)
375	11.50 (100)	1000 (22)
376	52.55 (100)	1000 (8)
377	19.25 (83)	1000 (25)
378	14.88 (100)	1000 (36)
379	70.55 (94)	1000 (8)
380	19.00 (100)	1000 (16)
381	12.73 (99)	1000 (27)
382	39.45 (100)	1000 (8)
383	9.31 (96)	1000 (55)
384	7.10 (97.30)	1000 (70.30)

SEQ ID NO	CRF ₂ R EC ₅₀ (nM) (E _{max} %)	CRF ₁ R EC ₅₀ (nM) (E _{max} %)
385	10.25 (100)	1000 (46)
386	8.70 (96)	1000 (78.25)
387	17.85 (100)	1000 (50.10)

Example 3

Increased *In Vivo* Efficacy

The peptides of the present invention exhibit extended biological availability, particularly under conditions of low dosing, as compared to known native sequences, e.g., UroII peptide fragment (SEQ ID NO: 4).

The half-life of a peptide in a subject can be determined, for example, by high performance liquid chromatography (HPLC) of serum samples collected from the subject at various times following administration of the peptide. One skilled in the art would know how to select appropriate elution buffers for HPLC based on the physicochemical properties of a particular peptide.

A non-limiting example of an *in vivo* study to determine efficacy is herein described. Mice are dosed by intravenous (IV) (1000 ug/kg) and subcutaneous (SC) (1000 ug/kg) routes with a peptide of Formula (I). Blood samples are obtained at various time points (IV = 0, 2, 10, 30 min and 1, 2, 4 and 6 h; and SC = 0, 0.25, 0.5, 1, 2, 4, and 6 h) post dosing in microcentrifuge tubes containing sodium heparin. The blood samples are further processed to obtain plasma which is stored at -70°C until analyzed.

Plasma standards are prepared. Spiking solution of a peptide of Formula (I) covering a concentration range from 50 ng/mL to 100 µg/mL are prepared in methanol on the analysis day by serial dilution of a previously prepared 1 mg/mL peptide of Formula (I) methanolic stock solution. Similarly, the internal standard (ISTD), stable isotope labeled h-Unc-II, spiking solution is prepared by serial dilution of a stored 1 mg/mL ISTD stock solution to give a final concentration of 5 µg/mL on the day of analysis. Working plasma standards covering a mass range from 0.5 to 100 ng are prepared by adding 10 µL of the appropriate peptide of Formula (I) spiking solution into tubes already containing 10 µL of a 5 µg/mL ISTD solution, 100 µL of dd-water and 100 µL of blank rat plasma. The working standards are prepared for analysis as described below.

Quality control (QC) samples are prepared. A QC stock solution is prepared at the 50 ng/mL level by adding 25 μ L of a 1 μ g/mL a peptide of Formula (I) spiking solution into 475 μ L of blank, heparinized rat plasma contained in a plastic vial. Working QC samples are prepared by adding 100 μ L of the QC stock solution (50 ng/mL) into tubes already containing 10 μ L of a 5 μ g/mL ISTD solution and 100 μ L of dd-water. The working QC sample was prepared for analysis as described below.

Study samples are prepared. On the day of analysis, the samples are thawed at room temperature and an aliquot of the sample was added to a tube already containing 10 μ L of a 5 μ g/mL ISTD solution, 100 μ L of dd-water and an aliquot of blank, heparinized rat plasma. The volume of the sample and the blank rat plasma are such that the total volume of plasma is equal to 100 μ L.

The working standards, working QC samples and study samples are prepared for analysis by adding 400 μ L of acetonitrile to tubes containing each of these, capping, vortexing, centrifuging and isolating the supernatant. An aliquot (300 μ L) of the supernatant is dried under N_2 and reconstituted in 50 μ L of methanol/water (50/50).

The prepared working standards, working QC samples and study samples are analyzed by gradient reversed-phase high performance liquid chromatography (RP-HPLC) separation followed by sample introduction through electron spray ionization (ESI) with mass spectroscopy / mass spectroscopy (MS/MS) detection using selected reaction monitoring (SRM) in the positive ion mode. An SRM channel is monitored for h-Unc-II and the ISTD.

The dose solutions from the pharmacokinetic study are diluted with methanol and analyzed by RP-HPLC with ultraviolet detection. The concentrations of the peptide of Formula (I) in the dose solutions are calculated by interpolation from a linear regression curve constructed from known standards.

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

What is claimed is:

1. A non-native peptide comprising the sequence

-X₂X₃PSLSIDX₁₀PX₁₂X₁₃X₁₄LLRTLLELEKTQSQRERAEQNAX₃₆IFAX₄₀V

wherein;

X₂ is selected from nil and D;

X₃ is selected from nil and N;

X₁₀ is selected from L and V;

X₁₂ is selected from L, and F;

X₁₃ is selected from L, F, and Y;

X₁₄ through X₃₅ comprises the sequence

X₃₆ is selected from R, H, and Q;

X₄₀ is selected from H and R;

and variants thereof.

1. The peptide according to Claim 1, wherein;
X₂X₃ are selected from the group consisting of DN, and --.
2. The peptide according to Claim 1, wherein;
X₁₂X₁₃ are selected from the group consisting of LL, LF, FF, and LY.
3. The peptide according to Claim 2, wherein;
X₁₂X₁₃ are selected from the group consisting of LL, LF, FF, and LY.
4. The peptide according to Claim 4, wherein;
X₁₀ is selected from the group consisting of L, and V.
5. The peptide according to Claim 5, wherein;
X₃₆ is selected from the group consisting of R, H, and Q.
6. The peptide according to Claim 6, wherein;
X₄₀ is selected from the group consisting of H and R.

7. The peptide according to Claim 1, selected from the group consisting of SEQ ID NO: 324, 328, 331, 333, 334, 341, 384, 385, 386, and 387.
8. A method of preventing or treating a CRF₂R modulated disorder comprising administering to a host in need of such treatment a safe and effective amount of a peptide of Claim 1.
9. An isolated nucleic acid encoding a peptide of any of the preceding claims.
10. An isolated antibody specific for a peptide of any of the preceding claims.
11. A pharmaceutical composition comprising:
 - a. a safe and effective amount of a peptide of any of the preceding claims; and
 - b. a pharmaceutically acceptable carrier.
12. A kit for preventing or treating a CRF₂R modulated disorder comprising:
 - a. a peptide of any of the preceding claims in a unit dose form; and
 - b. usage instruction.

SEQUENCE LISTING

<110> The Procter & Gamble Company
 Isfort, Robert J
 Mazur, Wieslaw A

<120> Corticotropin Releasing Factor 2 Receptor Agonists

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 20 25 30

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 20 25 30

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 1 5 10 15

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 20 25 30

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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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 1 5 10 15

Glu Gln Thr Lys Gln Glu Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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Thr Lys Phe Thr Leu Ser Leu Asp Val Pro Thr Asn Ile Met Asn Leu
 1 5 10 15

Leu Phe Asn Ile Ala Lys Ala Lys Asn Leu Arg Ala Gln Ala Ala Ala
 20 25 30

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 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

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Ser Glu Glu Pro Pro Ile Ser Leu Asp Leu Thr Phe His Leu Leu Arg
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Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Gln Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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Asn Arg Leu Leu Leu Asp Thr Ile
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Asn Arg Leu Leu Leu Ala Thr Val
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Asn Arg Leu Leu Leu Asp Thr Ile
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 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
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Asn Arg Leu Leu Leu Asp Thr Val
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Asn Arg Leu Leu Leu Asp Thr Val
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Asn Arg Leu Leu Leu Ala Arg Val
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 20 25 30

Asn Ala Arg Leu Leu Asp Arg Val
 35 40

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Asn Arg Leu Leu Leu Asp Thr Ile
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20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
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<400> 64

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Asn Tyr Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
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Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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 <223> AMIDATION

<400> 65

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Arg Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn

20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Gly Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 67

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Glu Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
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<223> AMIDATION

<400> 68

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gly Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 69

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe His Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 70

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Tyr Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<223> AMIDATION

<400> 71

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Glu Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<223> AMIDATION

<400> 72

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Gln Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 73

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Gly Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 74

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 75

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Gly Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 76

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Glu Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<223> AMIDATION

<400> 77

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile His Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

<210> 78

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Gln Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Tyr Leu Leu Arg Lys
 1 5 10 15

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 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Gln Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 81

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Tyr Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr
35

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<400> 82

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Glu Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

<210> 83
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<400> 83

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 85

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

<210> 86

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<223> AMIDATION

<400> 86

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Thr Ile Gly Leu Leu Arg
 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

<210> 87

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<223> AMIDATION

<400> 87

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Thr Ile His Leu Leu Arg

1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

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<400> 88

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Thr Phe Gly Leu Leu Arg
1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
35 40

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<400> 89

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Leu Glu Leu Leu Arg
1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

<210> 90
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Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Leu Gly Leu Leu Arg
 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

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<400> 91

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Phe Gln Leu Leu Arg
 1 5 10 15

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 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

<210> 92
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<400> 92

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 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Ile Ile Asp Ile Ala
 35 40

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<400> 93

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 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

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Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Ile His Leu Leu Arg
 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

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<400> 95

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Leu Gln Leu Leu Arg
 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

<210> 96
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<400> 96

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1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
35 40

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<400> 97

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Phe Glu Leu Leu Arg
1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
35 40

<210> 98
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Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Thr Gly Leu Leu Arg
 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

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Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Thr His Leu Leu Arg
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Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

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Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Ile Gln Leu Leu Arg
 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

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<400> 101

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Leu Tyr Leu Leu Arg
 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

<210> 102
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<400> 102

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Leu His Leu Leu Arg
 1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
35 40

<210> 103
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<400> 103

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Phe Gly Leu Leu Arg
1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
35 40

<210> 104
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<400> 104

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Phe His Leu Leu Arg
1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
35 40

<210> 105

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<400> 105

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Thr Gln Leu Leu Arg
1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
35 40

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<400> 106

Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Pro Thr Tyr Leu Leu Arg
1 5 10 15

Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
35 40

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<223> AMIDATION

<400> 107

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Gln Glu Lys Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
20 25 30

Arg Ile Leu Ala Arg Val
35

<210> 108

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<400> 108

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Gln Thr Lys Ala Asp Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
20 25 30

Arg Ile Leu Ala Arg Val
35

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<400> 109

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Ala Lys Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
 35

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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Ala Lys Gln Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Gln Glu Arg Gln Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
20 25 30

Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Gln Ala Lys Ala Glu Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
20 25 30

Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Glu Arg Ala Glu Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Ala Arg Gln Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Glu Lys Gln Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Thr Lys Ala Asn Ala Ala Arg Glu Gln Ala Thr Thr Val Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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 1 5 10 15

Glu Gln Thr Lys Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val

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 1 5 10 15

Glu Gln Glu Arg Gln Glu Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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Glu Gln Glu Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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 1 5 10 15

Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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Glu Gln Ala Arg Ala Glu Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
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Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Ala Arg Gln Glu Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
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Arg Ile Leu Ala Arg Val
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Glu Gln Ala Lys Gln Glu Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
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Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Gln Glu Lys Gln Glu Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
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Arg Ile Leu Ala Arg Val
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1 5 10 15

Glu Gln Thr Arg Ala Asp Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
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Arg Ile Leu Ala Arg Val
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Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
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Glu Gln Thr Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
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Arg Ile Leu Ala Arg Val
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Arg Ile Leu Ala Arg Val
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Glu Gln Ala Arg Ala Asp Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
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Arg Ile Leu Ala Arg Val
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Glu Gln Ala Lys Ala Asp Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
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Arg Ile Leu Ala Arg Val
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Glu Gln Glu Lys Glu Lys Lys Arg Lys Glu Thr Asn Ala Arg Ile Leu
 20 25 30

Ala Arg Val
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Glu Gln Arg Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala Arg Ile
20 25 30

Leu Ala Arg Val
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Glu Gln Ala Ala Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala Arg Ile
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Leu Ala Arg Val
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Glu Gln Ala Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala Arg
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Ile Leu Ala Arg Val
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Glu Gln Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala Arg Ile Leu
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Ala Arg Val
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Ile Leu Ala Arg Val
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Glu Gln Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala Arg Ile Leu Ala
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Arg Val

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Ala Arg Val
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 1 5 10 15

Glu Gln Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala Arg Ile
 20 25 30

Leu Ala Arg Val
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 1 5 10 15

Glu Gln Ala Arg Ala Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala Arg
 20 25 30

Ile Leu Ala Arg Val
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<400> 142

Glx Gly Pro Pro Ile Ser Ile Asp Leu Ser Leu Glu Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
35 40

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<400> 143

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Glu Leu Leu Arg Lys

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Met  Ile  Glu  Ile  Glu  Lys  Gln  Glu  Lys  Glu  Lys  Gln  Gln  Ala  Thr  Thr
          20              25              30

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Asn  Ala  Arg  Ile  Leu  Ala  Arg  Val
          35              40

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<400> 144

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Gln Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
35 40

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<400> 145

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu His Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe His Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Tyr Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Tyr Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
35 40

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20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Tyr Leu Leu Arg Lys
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 20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
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Ser Gln Glu Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Arg
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Glu Val Leu Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Leu Asp Ile Ala
 35 40

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Glx Gly Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Ile
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Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn Asn Arg

20 25 30

Leu Leu Leu Asp Thr Ile
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
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Glu Met Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His Ser Asn Arg
20 25 30

Lys Leu Leu Asp Ile Ala
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Met Ile Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr
 20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
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Ser Gln Glu Pro Pro Ile Ser Leu Asp Leu Thr Phe His Leu Leu Arg
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Glu Val Leu Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr
 20 25 30

Thr Asn Ala Arg Ile Leu Ala Arg Val
 35 40

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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
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Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn Asn Arg
 20 25 30

Leu Leu Leu Asp Thr Ile

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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
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Glu Gln Thr Lys Ala Asp Gln Leu Ala Gln Gln Ala His Ser Asn Arg
20 25 30

Lys Leu Leu Asp Ile Ala
35

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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Thr Leu Leu
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Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln Asn Arg
20 25 30

Ile Ile Phe Asp Ser Val
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Ser Glu Glu Pro Pro Ile Ser Leu Asp Leu Thr Phe His Leu Leu Arg
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Glu Val Leu Glu Met Ala Arg Ala Glu Gln Leu Ala Gln Gln Ala His
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Thr Asn Ala Arg Ile Leu Ala Arg Val
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Ser Glu Glu Pro Pro Ile Ser Leu Asp Val Pro Ile Gly Leu Leu Gln
 1 5 10 15

Glu Val Leu Glu Met Ala Arg Ala Glu Gln Leu Ala Gln Gln Ala His
 20 25 30

Ser Asn Arg Lys Leu Met Glu Ile Ile
 35 40

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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Ser Asn Arg
20 25 30

Lys Leu Met Glu Ile Ile
35

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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Met Ala Arg Ala Glu Gln Leu Ala Gln Gln Ala His Ser Asn Arg
20 25 30

Lys Leu Met Glu Ile Ile
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Glu Val Leu
 1 5 10 15

Glu Met Ala Arg Ala Glu Gln Leu Ala Gln Gln Ala His Ser Asn Arg
 20 25 30

Lys Leu Met Glu Ile Ile
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Ile
 1 5 10 15

Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu

1 5 10 15

Glu Gln Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
 35

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Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Ile
1 5 10 15

Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Thr Thr Asn
20 25 30

Ala Arg Ile Leu Ala Arg Val
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<400> 169

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Thr Tyr Leu Leu Arg Ile
 1 5 10 15

Leu Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
 20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Thr Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
 20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Phe Gln Leu Leu Arg Ile
 1 5 10 15

Leu Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
 20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Phe Gln Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
 20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
 35 40

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<400> 173

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Thr Tyr Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Ile Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Gln Leu Leu Arg Thr
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Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Tyr Leu Leu Arg Thr
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Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Phe Leu Leu Arg Thr
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Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu His Leu Leu Arg Thr
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Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
35 40

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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Phe Leu Leu Leu Arg Thr
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Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
35 40

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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Phe Ile Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
35 40

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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Phe Tyr Leu Leu Arg Thr
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Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Phe Phe Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Phe His Leu Leu Arg Thr
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Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro His Trp Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Trp Phe Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Ile Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Val Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Leu Leu Leu Arg Lys

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn

20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Trp Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Val Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Ile Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Phe Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Leu Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Val Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Gln Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Ile Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
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 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Gln Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Leu Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Ile Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 205

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro His His Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ala His Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 207

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 208

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 209

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Trp His Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 210

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Trp Gln Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 211

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ala Gln Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 212

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro His Gln Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 213

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Trp Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 214

Ile Val Leu Ser Leu Asp Val Val Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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<223> AMIDATION

<400> 215

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Trp Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<223> AMIDATION

<400> 216

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Trp Trp Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 217

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Trp Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 218

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Trp Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 219

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro His Phe Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<400> 220

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Phe Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<223> AMIDATION

<400> 221

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Phe Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<223> AMIDATION

<400> 222

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ala Phe Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<223> AMIDATION

<400> 223

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Phe Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 224

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

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<400> 225

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Ala Thr Ile
 35 40

<210> 226
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<400> 226

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

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<400> 227

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

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<400> 228

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

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<400> 229

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
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<400> 230

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

<210> 231

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<223> AMIDATION

<400> 231

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Phe	Tyr	Leu	Leu	Arg	Lys
1				5					10					15	

Met	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Ala	Asn
			20					25					30		

Asn	Ala	Leu	Leu	Leu	Ala	Thr	Ile
		35					40

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<223> AMIDATION

<400> 232

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Thr	Tyr	Leu	Leu	Arg	Lys
1				5					10					15	

Met	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Ala	Asn
			20					25					30		

Asn	Ala	Leu	Leu	Leu	Asp	Thr	Ile
		35					40

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<223> AMIDATION

<400> 233

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Tyr Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
35 40

<210> 234
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<223> AMIDATION

<400> 234

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Glu Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile

35

40

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 <223> AMIDATION

<400> 235

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Leu	Glu	Leu	Leu	Arg	Lys
1				5					10					15	

Met	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Ala	Asn
			20				25						30		

Asn	Ala	Leu	Leu	Leu	Asp	Thr	Ile
		35					40

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 <222> (40)..(40)
 <223> AMIDATION

<400> 236

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Ile	Tyr	Leu	Leu	Arg	Lys
1				5					10					15	

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

<210> 237
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<400> 237

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 238
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<223> AMIDATION

<400> 238

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu His Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Leu Leu Asp Thr Val
35 40

<210> 239

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<223> AMIDATION

<400> 239

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu His Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Leu Leu Asp Arg Val
35 40

<210> 240

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<400> 240

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

<210> 241
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 <223> AMIDATION

<400> 241

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 242
 <211> 40
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<222> (40)..(40)

<223> AMIDATION

<400> 242

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Tyr Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Leu Leu Asp Thr Val
35 40

<210> 243

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<222> (40)..(40)

<223> AMIDATION

<400> 243

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Tyr Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Leu Leu Asp Arg Val
35 40

<210> 244
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<220>
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<222> (40)..(40)
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<400> 244

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Tyr Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
35 40

<210> 245
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<222> (40)..(40)
<223> AMIDATION

<400> 245

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Tyr Leu Leu Arg Lys

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1           5           10           15
Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
          20          25          30

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Asn Ala Leu Leu Leu Ala Thr Ile
35 40

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<220>
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<223> AMIDATION

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<400> 246

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Gln Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Leu Leu Asp Thr Val
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Gln Leu Leu Glu Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
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Asn Ala Arg Leu Leu Asp Arg Val
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Gln Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Gln Leu Leu Glu Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
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Asn Ala Leu Leu Leu Ala Thr Ile
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
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Asn Arg Leu Leu Leu Ala Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
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Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Tyr Leu Leu Arg Ile
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Asn Arg Leu Leu Leu Asp Thr Ile
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
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Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
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 20 25 30

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

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Asn Asp Asp Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg
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Asn Met Ile Glu Met Ala Arg Ile Glu Asn Glu Arg Glu Gln Ala Gly
 20 25 30

Leu Asn Ala Lys Tyr Leu Ala Glu Val
 35 40

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Asn Asp Asp Pro Pro Ile Ser Ile Asp Leu Pro Leu His Leu Leu Arg
 1 5 10 15

Asn Met Ile Glu Met Ala Arg Ile Glu Asn Glu Arg Glu Gln Ala Gly
 20 25 30

Leu Asn Ala Lys Tyr Leu Ala Glu Val
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Asn Asp Asp Pro Pro Ile Ser Ile Asp Leu Pro Phe Leu Leu Leu Arg
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20 25 30

Leu Asn Ala Lys Tyr Leu Ala Glu Val
35 40

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Asn Met Ile Glu Met Ala Arg Ile Glu Asn Glu Arg Glu Gln Ala Gly
20 25 30

Leu Asn Ala Lys Tyr Leu Ala Glu Val
35 40

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Asn Asp Asp Pro Pro Ile Ser Ile Asp Leu Pro Phe His Leu Leu Arg
1 5 10 15

Asn Met Ile Glu Met Ala Arg Ile Glu Asn Glu Arg Glu Gln Ala Gly
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Leu Asn Ala Lys Tyr Leu Ala Glu Val
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Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Tyr Tyr Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
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Asn Asp Asp Pro Pro Ile Ser Ile Asp Leu Pro Phe Phe Leu Leu Arg
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Asn Met Ile Glu Met Ala Arg Ile Glu Asn Glu Arg Glu Gln Ala Gly
 20 25 30

Leu Asn Ala Lys Tyr Leu Ala Glu Val
 35 40

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Asn Met Ile Glu Met Ala Arg Ile Glu Asn Glu Arg Glu Gln Ala Gly
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Leu Asn Ala Lys Tyr Leu Ala Glu Val
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Asn Met Ile Glu Met Ala Arg Ile Glu Asn Glu Arg Glu Gln Ala Gly
 20 25 30

Leu Asn Ala Lys Tyr Leu Ala Glu Val
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Leu Asn Ala Lys Tyr Leu Ala Glu Val
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Leu Asn Ala Lys Tyr Leu Ala Glu Val
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20 25 30

Leu Asn Ala Lys Tyr Leu Ala Glu Val
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Asn Met Ile Glu Met Ala Arg Ile Glu Asn Glu Arg Glu Gln Ala Gly
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Leu Asn Ala Lys Tyr Leu Ala Glu Val
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Asn Asp Asp Pro Pro Ile Ser Ile Asp Leu Pro Leu Tyr Leu Leu Arg
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Asn Met Ile Glu Met Ala Arg Ile Glu Asn Glu Arg Glu Gln Ala Gly
 20 25 30

Leu Asn Ala Lys Tyr Leu Ala Glu Val
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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Glu Leu Leu Ala Glu Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Gln Leu Leu Ala His Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Lys Leu Leu Ala Lys Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Asn Leu Leu Ala Asn Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Gln Leu Leu Ala Gln Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala His Leu Leu Ala His Ile
35 40

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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Asp Thr Ile
 35 40

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Asn Ala Arg Leu Leu Ala Arg Ile
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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Phe Leu Leu Arg Lys
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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Phe Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
 35 40

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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Trp Leu Leu Arg Lys
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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
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<400> 285

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Ile Leu Leu Arg Lys
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 20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
 35 40

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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
 35 40

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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn

20 25 30

Asn Ala Arg Leu Leu Ala Arg
35

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Gln Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Ala Arg
35

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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Trp Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
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Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Ile Leu Leu Arg Lys
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Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
35 40

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Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
 35 40

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 <223> AMIDATION

<400> 292

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Trp Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
 35 40

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<223> AMIDATION

<400> 293

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Gln	Ile	Leu	Leu	Arg	Lys
1				5				10						15	

Val	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Ala	Asn
		20					25						30		

Asn	Arg	Leu	Leu	Leu	Asp	Thr	Ile
		35					40

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<223> AMIDATION

<400> 294

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Gln	Ile	Leu	Leu	Arg	Lys
1				5				10						15	

Val	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Ala	Asn
		20					25						30		

Asn	Ala	Arg	Leu	Leu	Ala	Arg	Ile
		35					40

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 <223> AMIDATION

<400> 295

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Ile Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
 35 40

<210> 296
 <211> 44
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<220>
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<220>
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 <222> (44)..(44)
 <223> AMIDATION

<400> 296

His His His His His His Ile Val Leu Ser Leu Asp Val Pro Ile Gly
 1 5 10 15

Leu Leu Gln Ile Leu Leu Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu
 20 25 30

Gln Ala Thr Thr Asn Ala Arg Ile Leu Ala Arg Asn
 35 40

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 <223> AMIDATION

<400> 297

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Ile Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

<210> 298
 <211> 40
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 <222> (40)..(40)
 <223> AMIDATION

<400> 298

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Phe Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 299
 <211> 40
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 <223> AMIDATION

<400> 299

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Ile Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 300
 <211> 38
 <212> PRT
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<220>
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 <222> (38)..(38)
 <223> AMIDATION

<400> 300

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Lys Val Ile
 1 5 10 15

Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
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<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 301

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Thr Ala Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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<222> (40)..(40)

<223> AMIDATION

<400> 302

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Gln Ala Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

<210> 303

<211> 40

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<223> PYRROLIDONE CARBOXYLIC ACID

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<222> (40)..(40)

<223> AMIDATION

<400> 303

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ala Ala Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

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 <222> (40)..(40)
 <223> AMIDATION

<400> 304

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro His Ala Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

<210> 305
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<220>
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<222> (40)..(40)
<223> AMIDATION

<400> 305

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Val Ala Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

<210> 306
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<220>
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<222> (40)..(40)
<223> AMIDATION

<400> 306

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Ile Ala Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

<210> 307
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<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 307

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Ala Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

<210> 308
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<400> 308

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Ala Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 309

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Ala Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

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<400> 310

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Trp Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
35 40

<210> 311
<211> 40
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<222> (40)..(40)
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<400> 311

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr Trp Leu Leu Arg Lys

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1              5              10              15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
          20              25              30

Asn Ala Leu Leu Leu Asp Thr Ile
      35              40

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<223> AMIDATION
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<400> 312

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr His Leu Leu Arg Lys
1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
35 40

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<210> 313
<211> 40
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<222> (40)..(40)
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<400> 313

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr His Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 314
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 <223> AMIDATION

<400> 314

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

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 <223> AMIDATION

<400> 315

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Tyr His Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr
 35

<210> 316
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<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 316

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Phe Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

<210> 317
 <211> 40

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 <222> (40)..(40)
 <223> AMIDATION

<400> 317

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Phe Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 318
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<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 318

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Phe Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

<210> 319
 <211> 40
 <212> PRT
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<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 319

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Phe Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 320
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 <222> (40)..(40)
 <223> AMIDATION

<400> 320

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Gln Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
 20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
 35 40

<210> 321
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 <223> PYRROLIDONE CARBOXYLIC ACID

<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 321

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
 1 5 10 15

Thr Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
 20 25 30

Asn Ala Arg Leu Leu Asp Arg Val
 35 40

<210> 322
 <211> 38
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<220>
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 <222> (38)..(38)
 <223> AMIDATION

<400> 322

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Lys Met Ile
 1 5 10 15

Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
 35

<210> 323
 <211> 40
 <212> PRT
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 <222> (40)..(40)
 <223> AMIDATION

<400> 323

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Glu Ile Phe Ala Glu Val
 35 40

<210> 324
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 <222> (40)..(40)
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<400> 324

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Gln Ile Phe Ala His Val
 35 40

<210> 325
 <211> 38
 <212> PRT
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<220>
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 <222> (38)..(38)
 <223> AMIDATION

<400> 325

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Glu Lys Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
 35

<210> 326
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 <222> (40)..(40)
 <223> AMIDATION

<400> 326

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Asn Ile Phe Ala Asn Val

35

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<210> 327
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 <222> (40)..(40)
 <223> AMIDATION

<400> 327

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Gln Ile Phe Ala Gln Val
 35 40

<210> 328
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<220>
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 <222> (40)..(40)
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<400> 328

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala His Ile Phe Ala His Val
 35 40

<210> 329
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 <222> (40)..(40)
 <223> AMIDATION

<400> 329

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Phe Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
 35 40

<210> 330
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 <222> (40)..(40)
 <223> AMIDATION

<400> 330

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Ile Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
 35 40

<210> 331
 <211> 38
 <212> PRT
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<220>
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<220>
<221> MOD_RES
<222> (38)..(38)
<223> AMIDATION

<400> 331

Pro Ser Leu Ser Ile Asp Leu Pro Leu Phe Leu Leu Arg Thr Leu Leu
1 5 10 15

Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln Asn Ala
20 25 30

Arg Ile Phe Ala Arg Val
35

<210> 332
<211> 38
<212> PRT
<213> Artificial

<220>
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<220>
<221> MOD_RES
<222> (38)..(38)
<223> AMIDATION

<400> 332

Pro Ser Leu Ser Ile Asp Leu Pro Leu Ile Leu Leu Arg Thr Leu Leu
1 5 10 15

Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln Asn Ala
20 25 30

Arg Ile Phe Ala Arg Val
35

<210> 333
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<220>
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<222> (38)..(38)
<223> AMIDATION

<400> 333

Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Arg Thr Leu Leu
 1 5 10 15

Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln Asn Ala
 20 25 30

Arg Ile Phe Ala Arg Val
 35

<210> 334

<211> 40

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<213> Artificial

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<222> (40)..(40)

<223> AMIDATION

<400> 334

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Phe Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
 35 40

<210> 335

<211> 40

<212> PRT

<213> Artificial

<220>

<223> Artificial

<220>

<221> MOD_RES

<222> (40)..(40)

<223> AMIDATION

<400> 335

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Ile Leu Leu Arg Thr

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1              5              10              15
Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
      20              25              30
Asn Ala Arg Ile Phe Ala Arg Val
      35              40

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<210> 336
<211> 40
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<220>
<223> Artificial
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<220>
<221> MOD_RES
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<223> AMIDATION
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<400> 336

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Phe Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Asp Arg Val
35 40

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<210> 337
<211> 40
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<220>
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<220>
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<222> (40) .. (40)
<223> AMIDATION

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<400> 337

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Ile Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Asp Arg Val
 35 40

<210> 338
 <211> 40
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<220>
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 <223> AMIDATION

<400> 338

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Arg Ile Phe Asp Arg Val
 35 40

<210> 339
 <211> 40
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<220>
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 <223> AMIDATION

<400> 339

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Gln Tyr Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

<210> 340
<211> 40
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<220>
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<222> (40)..(40)
<223> AMIDATION

<400> 340

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Ala Arg Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
35 40

<210> 341
<211> 40
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<223> AMIDATION

<400> 341

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
35 40

<210> 342
<211> 40
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 <223> AMIDATION

<400> 342

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Gln Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

<210> 343
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<220>
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 <223> AMIDATION

<400> 343

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Phe Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

<210> 344
 <211> 38
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<222> (38)..(38)
<223> AMIDATION

<400> 344

Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr Leu Leu
1 5 10 15

Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln Asn Ala
20 25 30

Ile Ile Phe Ala Ser Val
35

<210> 345
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<220>
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<222> (40)..(40)
<223> AMIDATION

<400> 345

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Ile Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
35 40

<210> 346
<211> 40
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<223> AMIDATION

<400> 346

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

<210> 347

<211> 40

<212> PRT

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<222> (1)..(1)

<223> ACETYLTATION

<220>

<221> MOD_RES

<222> (40)..(40)

<223> AMIDATION

<400> 347

Asp Asn Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Ile Ile Phe Ala Ser Val
 35 40

<210> 348

<211> 38

<212> PRT

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<222> (1)..(1)

<223> ACETYLTATION

<220>
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 <222> (38)..(38)
 <223> AMIDATION

<400> 348

Pro Ser Leu Ser Ile Asp Leu Pro Leu Leu Leu Arg Thr Leu Leu
 1 5 10 15

Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln Asn Ala
 20 25 30

Ile Ile Phe Ala Ser Val
 35

<210> 349
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<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 349

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Gln Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 350
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 <212> PRT
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<223> PYRROLIDONE CARBOXYLIC ACID

<220>

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<222> (40)..(40)

<223> AMIDATION

<400> 350

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Phe	Gln	Leu	Leu	Arg	Lys
1				5				10						15	

Val	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Ala	Asn
			20					25					30		

Asn	Ala	Leu	Leu	Leu	Asp	Thr	Ile
		35					40

<210> 351

<211> 40

<212> PRT

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<223> PYRROLIDONE CARBOXYLIC ACID

<220>

<221> MOD_RES

<222> (40)..(40)

<223> AMIDATION

<400> 351

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Phe	Gln	Leu	Leu	Arg	Lys
1				5				10						15	

Val	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Thr	Thr
			20					25					30		

Asn	Ala	Arg	Leu	Leu	Asp	Arg	Val
		35					40

<210> 352
 <211> 40
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 <223> PYRROLIDONE CARBOXYLIC ACID

<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 352

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 353
 <211> 40
 <212> PRT
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 <223> PYRROLIDONE CARBOXYLIC ACID

<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 353

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Leu Tyr Leu Leu Arg Lys
 1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
 20 25 30

Asn Ala Arg Ile Leu Ala Arg Val
 35 40

<210> 354
 <211> 38
 <212> PRT
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 <222> (1)..(1)
 <223> ACETYLATION

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 <222> (38)..(38)
 <223> AMIDATION

<400> 354

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
 35

<210> 355
 <211> 40
 <212> PRT
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<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 355

Glx Gly Pro Pro Ile Ser Ile Asp Leu Ser Leu Glu Leu Leu Arg Lys
1 5 10 15

Met Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
35 40

<210> 356

<211> 39

<212> PRT

<213> Artificial

<220>

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<222> (39)..(39)

<223> AMIDATION

<400> 356

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
20 25 30

Arg Ile Leu Ala Arg Val Met
35

<210> 357

<211> 40

<212> PRT

<213> Artificial

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<221> MOD_RES

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<223> PYRROLIDONE CARBOXYLIC ACID

<220>

<221> MOD_RES

<222> (40)..(40)

<223> AMIDATION

<400> 357

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
1 5 10 15

Leu Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
35 40

<210> 358

<211> 39

<212> PRT

<213> Artificial

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<222> (1)..(1)

<223> PYRROLIDONE CARBOXYLIC ACID

<220>

<221> MOD_RES

<222> (39)..(39)

<223> AMIDATION

<400> 358

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Ile
1 5 10 15

Leu Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Leu Leu Leu Ala Thr
35

<210> 359

<211> 40

<212> PRT

<213> Artificial

<220>

<223> Artificial

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<222> (1)..(1)

<223> PYRROLIDONE CARBOXYLIC ACID

<220>

<221> MOD_RES

<222> (40)..(40)

<223> AMIDATION

<400> 359

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Phe	Gln	Leu	Leu	Arg	Glu
1				5					10					15	

Val	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Ala	Asn
		20					25						30		

Asn	Ala	Leu	Leu	Leu	Ala	Thr	Ile
		35					40

<210> 360

<211> 40

<212> PRT

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<220>

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<222> (1)..(1)

<223> PYRROLIDONE CARBOXYLIC ACID

<220>

<221> MOD_RES

<222> (40)..(40)

<223> AMIDATION

<400> 360

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Leu	Pro	Phe	Gln	Leu	Leu	Arg	Leu
1				5					10					15	

Leu	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Ala	Asn
		20					25						30		

Asn	Ala	Leu	Leu	Leu	Ala	Thr	Ile
		35					40

<210> 361

<211> 40

<212> PRT

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 <223> PYRROLIDONE CARBOXYLIC ACID

<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 361

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Val
 1 5 10 15

Leu Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 362
 <211> 40
 <212> PRT
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<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 362

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
 1 5 10 15

Ile Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile

35

40

<210> 363
<211> 40
<212> PRT
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<220>
<221> MOD_RES
<222> (40)..(40)
<223> AMIDATION

<400> 363

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
1 5 10 15

Ala Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr
20 25 30

Asn Ala Arg Leu Leu Asp Arg Val
35 40

<210> 364
<211> 40
<212> PRT
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<220>
<221> MOD_RES
<222> (40)..(40)
<223> AMIDATION

<400> 364

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
1 5 10 15

Ala Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Ala Thr Ile
 35 40

<210> 365
 <211> 40
 <212> PRT
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<220>
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 <222> (40)..(40)
 <223> AMIDATION

<400> 365

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro Phe Gln Leu Leu Arg Lys
 1 5 10 15

Ala Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Leu Leu Leu Asp Thr Ile
 35 40

<210> 366
 <211> 38
 <212> PRT
 <213> Artificial

<220>
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<220>
 <221> MOD_RES
 <222> (38)..(38)
 <223> AMIDATION

<400> 366

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu

```

1              5              10              15

Glu Lys Ala Ala Ala Glu Ala Glu Ala Ala Ala Lys Ala Ala Gln Glu
      20              25              30

Gln Ile Leu Ala His Val
      35

<210> 367
<211> 38
<212> PRT
<213> Artificial

<220>
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<220>
<221> MOD_RES
<222> (38)..(38)
<223> AMIDATION

<400> 367

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1              5              10              15

Glu Gln Ala Arg His Ala Ala Ala His Ala Ala Ala His Ala Gln Ala
      20              25              30

His Ile Leu Ala His Val
      35

<210> 368
<211> 39
<212> PRT
<213> Artificial

<220>
<223> Artificial

<220>
<221> MOD_RES
<222> (39)..(39)
<223> AMIDATION

<400> 368

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1              5              10              15

Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
      20              25              30

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Arg Ile Leu Ala Arg Val Met
35

<210> 369
<211> 38
<212> PRT
<213> Artificial

<220>
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<220>
<221> MOD_RES
<222> (38)..(38)
<223> AMIDATION

<400> 369

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Gln Ala Arg His Ala His Ala His Ala His Ala His Ala Gln Ala
20 25 30

His Ile Leu Ala His Val
35

<210> 370
<211> 38
<212> PRT
<213> Artificial

<220>
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<220>
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<222> (38)..(38)
<223> AMIDATION

<400> 370

Ile Val Leu Ser Leu Asp Val Ser Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
20 25 30

Arg Ile Leu Ala Arg Val
35

<210> 371
 <211> 38
 <212> PRT
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<220>
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<220>
 <221> MOD_RES
 <222> (38)..(38)
 <223> AMIDATION

<400> 371

Ile Val Leu Ser Leu Asp Val Pro Ile His Leu Leu Gln Ile Leu Leu
 1 5 10 15

Glu Gln Ala Arg Ala Arg Ala Ala Arg Glu Gln Ala Thr Thr Asn Ala
 20 25 30

Arg Ile Leu Ala Arg Val
 35

<210> 372
 <211> 40
 <212> PRT
 <213> Artificial

<220>
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 <223> PYRROLIDONE CARBOXYLIC ACID

<220>
 <221> MOD_RES
 <222> (40)..(40)
 <223> AMIDATION

<400> 372

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Tyr Trp Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Asp Thr Ile
 35 40

<210> 373
<211> 40
<212> PRT
<213> Artificial

<220>
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<220>
<221> MOD_RES
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<223> PYRROLIDONE CARBOXYLIC ACID

<220>
<221> MOD_RES
<222> (40)..(40)
<223> AMIDATION

<400> 373

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Tyr Trp Leu Leu Arg Lys
1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
35 40

<210> 374
<211> 40
<212> PRT
<213> Artificial

<220>
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<223> PYRROLIDONE CARBOXYLIC ACID

<220>
<221> MOD_RES
<222> (40)..(40)
<223> AMIDATION

<400> 374

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Tyr Gln Leu Leu Arg Lys
1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Asp Thr Ile
 35 40

<210> 375
 <211> 40
 <212> PRT
 <213> Artificial

<220>
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<220>
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 <222> (1)..(1)
 <223> PYRROLIDONE CARBOXYLIC ACID

<220>
 <221> MOD_RES
 <222> (40)..(40)
 <223> AMIDATION

<400> 375

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Tyr Gln Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
 35 40

<210> 376
 <211> 40
 <212> PRT
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 <222> (1)..(1)
 <223> PYRROLIDONE CARBOXYLIC ACID

<220>
 <221> MOD_RES
 <222> (40)..(40)
 <223> AMIDATION

<400> 376

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Tyr His Leu Leu Arg Lys
1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Asp Thr Ile
35 40

<210> 377

<211> 40

<212> PRT

<213> Artificial

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<222> (1)..(1)

<223> PYRROLIDONE CARBOXYLIC ACID

<220>

<221> MOD_RES

<222> (40)..(40)

<223> AMIDATION

<400> 377

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Tyr His Leu Leu Arg Lys
1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
35 40

<210> 378

<211> 40

<212> PRT

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<222> (1)..(1)

<223> PYRROLIDONE CARBOXYLIC ACID

<220>

<221> MOD_RES

<222> (40)..(40)

<223> AMIDATION

<400> 378

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Tyr Tyr Leu Leu Arg Lys
1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
35 40

<210> 379

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<223> PYRROLIDONE CARBOXYLIC ACID

<220>

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<222> (40)..(40)

<223> AMIDATION

<400> 379

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Ile Tyr Leu Leu Arg Lys
1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
35 40

<210> 380

<211> 40

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<220>
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 <223> AMIDATION

<400> 380

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Leu Gln Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Asp Thr Ile
 35 40

<210> 381
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<220>
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 <223> AMIDATION

<400> 381

Glx Gly Pro Pro Ile Ser Ile Asp Val Pro Leu Gln Leu Leu Arg Lys
 1 5 10 15

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
 20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile

35

40

<210> 382
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 <223> AMIDATION

<400> 382

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Val	Pro	Phe	Gln	Leu	Leu	Arg	Lys
1				5					10					15	

Val	Ile	Glu	Ile	Glu	Lys	Gln	Glu	Lys	Glu	Lys	Gln	Gln	Ala	Ala	Asn
			20				25						30		

Asn	Ala	Arg	Leu	Leu	Asp	Thr	Ile
			35				40

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<220>
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 <223> AMIDATION

<400> 383

Glx	Gly	Pro	Pro	Ile	Ser	Ile	Asp	Val	Pro	Phe	Gln	Leu	Leu	Arg	Lys
1				5					10					15	

Val Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Ala Asn
20 25 30

Asn Ala Arg Leu Leu Ala Arg Ile
35 40

<210> 384
<211> 40
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<220>
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<222> (40)..(40)
<223> AMIDATION

<400> 384

Asp Asn Pro Ser Leu Ser Ile Asp Val Pro Leu Leu Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
35 40

<210> 385
<211> 40
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<223> AMIDATION

<400> 385

Asp Asn Pro Ser Leu Ser Ile Asp Val Pro Leu Phe Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
35 40

<210> 386
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<223> AMIDATION

<400> 386

Asp Asn Pro Ser Leu Ser Ile Asp Val Pro Phe Phe Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
35 40

<210> 387
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<223> AMIDATION

<400> 387

Asp Asn Pro Ser Leu Ser Ile Asp Val Pro Leu Tyr Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
35 40

<210> 388
<211> 5
<212> PRT
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<220>
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<400> 388

Glu Asp Leu Pro Leu
1 5

<210> 389
<211> 5
<212> PRT
<213> artificial

<220>
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<400> 389

Asp Asn Pro Ser Leu
1 5

<210> 390
<211> 5
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<220>
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<400> 390

Asp Asp Pro Pro Leu
1 5

<210> 391
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<400> 391

Glx Gly Pro Pro Ile
1 5

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<220>
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<400> 392

Ser Gln Glu Pro Pro Ile
1 5

<210> 393
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<220>
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<400> 393

Ser Glu Glu Pro Pro Ile
1 5

<210> 394
<211> 5
<212> PRT
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<220>
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<400> 394

Thr Lys Phe Thr Leu
1 5

<210> 395
<211> 6
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<220>
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<400> 395

Ser Gln Glu Ile Val Leu
1 5

<210> 396
<211> 6
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<220>
<223> artificial

<400> 396

Ser Glu Glu Ile Val Leu
1 5

<210> 397
<211> 6
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<220>
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<400> 397

Asp Asn Pro Ile Val Leu
1 5

<210> 398
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<212> PRT
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<220>
<223> artificial

<400> 398

Thr Lys Ile Val Leu
1 5

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<400> 399

Glx Gly Ile Val Leu
1 5

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<213> artificial

<220>

<223> artificial

<400> 400

His His His His His His
1 5

<210> 401

<211> 6

<212> PRT

<213> artificial

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<223> artificial

<400> 401

Ser Asp Asn Pro Ser Leu
1 5

<210> 402

<211> 6

<212> PRT

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<220>

<223> artificial

<400> 402

Ser Thr Lys Phe Thr Leu
1 5

<210> 403

<211> 6

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<220>

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<223> PYRROLIDONE CARBOXYLIC ACID

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Ser Glx Gly Pro Pro Ile
1 5

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<220>
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<400> 404

Asn Asp Asp Pro Pro Ile
1 5

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<220>
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<400> 405

Ser Ile Asp Leu
1

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<220>
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<400> 406

Ser Leu Asp Val
1

<210> 407
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<400> 407

Ser Leu Asp Leu
1

<210> 408
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<400> 408

Ser Ile Asp Ile
1

<210> 409

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<400> 409

Ser Ile Asp Val
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<211> 5

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<400> 410

Val Leu Ile Asp Leu
1 5

<210> 411

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<400> 411

Val Leu Phe Asp Val
1 5

<210> 412

<211> 5

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<213> artificial

<220>

<223> artificial

<400> 412

Val Leu Ile Glu Ile
1 5

<210> 413
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<220>
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<400> 413

Ile Leu Phe Asn Ile
1 5

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Leu Leu Ile Glu Ile
1 5

<210> 415
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<400> 415

Leu Leu Phe Asn Ile
1 5

<210> 416
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<400> 416

Ile Leu Leu Glu Gln
1 5

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Ile Leu Ile Glu Ile
1 5

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Ile Leu Leu Glu Ile
1 5

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<400> 419

Thr Leu Leu Glu Leu
1 5

<210> 420

<211> 5

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<220>

<223> artificial

<400> 420

Lys Met Ile Glu Ile
1 5

<210> 421

<211> 5

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<223> artificial

<400> 421

Lys Val Ile Glu Ile
1 5

<210> 422

<211> 5

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<220>

<223> artificial

<400> 422

Glu Val Leu Glu Met
1 5

<210> 423

<211> 5

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<223> artificial

<400> 423

Glu Met Ile Glu Ile
1 5

<210> 424

<211> 5

<212> PRT

<213> artificial

<220>

<223> artificial

<400> 424

Glu Val Ile Glu Ile
1 5

<210> 425

<211> 5

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<220>

<223> artificial

<400> 425

Glu Ala Ile Glu Ile
1 5

<210> 426
<211> 5
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<220>
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<400> 426

Glu Thr Ile Glu Ile
1 5

<210> 427
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<220>
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<400> 427

Glu Ile Ile Glu Ile
1 5

<210> 428
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<213> artificial

<220>
<223> artificial

<400> 428

Glu Leu Ile Glu Ile
1 5

<210> 429
<211> 5
<212> PRT
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<220>
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<400> 429

Asn Met Ile Glu Met
1 5

<210> 430
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<220>
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<400> 430

Asn Met Ile His Arg
1 5

<210> 431
<211> 5
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<213> artificial

<220>
<223> artificial

<400> 431

Asn Met Ile His Met
1 5

<210> 432
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<213> artificial

<220>
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<400> 432

Gln Met Met Glu Met
1 5

<210> 433
<211> 5
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<220>
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<400> 433

Leu Leu Phe Asn Ile
1 5

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<400> 434

Ser Arg Ala Glu
1

<210> 435
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<400> 435

Glu Lys Ala Arg
1

<210> 436
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<400> 436

Glu Arg Ala Arg
1

<210> 437
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<400> 437

Glu Lys Gln Glu
1

<210> 438
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<213> artificial

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<400> 438

Thr Lys Asp Arg
1

<210> 439
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<400> 439

Thr Lys Ala Asp
1

<210> 440
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<400> 440

Ala Lys Ala Arg
1

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Ala Lys Gln Arg
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Glu Arg Gln Arg
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Ala Lys Ala Glu
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<210> 444
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Glu Arg Ala Glu
1

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Ala Arg Gln Arg
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Glu Lys Gln Arg
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Thr Lys Ala Asn
1

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Thr Lys Ala Arg
1

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Glu Ala Ala Arg
1

<210> 450
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<400> 450

Glu Arg Gln Glu
1

<210> 451
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<400> 451

Ala Arg Ala Asp
1

<210> 452

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<400> 452

Glu Lys Thr Gln
1

<210> 453
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Ala Arg Ala Arg
1

<210> 454
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<400> 454

Ala Arg Ala Glu
1

<210> 455
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Ala Arg Gln Glu
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<400> 456

Ala Lys Gln Glu

1

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<223> artificial

<400> 457

Thr Arg Ala Asp

1

<210> 458

<211> 4

<212> PRT

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<220>

<223> artificial

<400> 458

Ala Lys Ala Asp

1

<210> 459

<211> 4

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<400> 459

Thr Arg Ala Arg

1

<210> 460

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<213> artificial

<220>

<223> artificial

<400> 460

Ala Ala Arg Glu Gln Ala

1 5

<210> 461
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<400> 461

Lys Glu Lys Lys Arg Lys
1 5

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<400> 462

Ser Gln Arg Glu Arg Ala
1 5

<210> 463
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<212> PRT
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<220>
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<400> 463

Lys Glu Lys Gln Gln Ala
1 5

<210> 464
<211> 6
<212> PRT
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<220>
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<400> 464

Gln Leu Ala Gln Gln Ala
1 5

<210> 465
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<223> AMIDATION

<400> 465

Ala Ala Asn Arg Leu Leu Leu Asp Thr Val
1 5 10

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<220>
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<223> AMIDATION

<400> 466

Ala Ala Gln Glu Gln Ile Leu Ala His Val
1 5 10

<210> 467
<211> 10
<212> PRT
<213> artificial

<220>
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<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 467

Ala Asn Asn Ala Glu Leu Leu Ala Glu Ile
1 5 10

<210> 468
<211> 10
<212> PRT

<213> artificial

<220>

<223> Artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 468

Ala Asn Asn Ala His Leu Leu Ala His Ile
1 5 10

<210> 469

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 469

Ala Asn Asn Ala Lys Leu Leu Ala Lys Ile .
1 5 10

<210> 470

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 470

Ala Asn Asn Ala Leu Leu Leu Ala Thr Ile
1 5 10

<210> 471

<211> 10

<212> PRT

<213> artificial

<220>
<223> artificial

<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 471

Ala	Asn	Asn	Ala	Leu	Leu	Leu	Asp	Thr	Ile
1				5					10

<210> 472
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<212> PRT
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<220>
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<222> (10)..(10)
<223> AMIDATION

<400> 472

Ala	Asn	Asn	Ala	Asn	Leu	Leu	Ala	Asn	Ile
1				5					10

<210> 473
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<212> PRT
<213> artificial

<220>
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<220>
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<222> (10)..(10)
<223> AMIDATION

<400> 473

Ala	Asn	Asn	Ala	Gln	Leu	Leu	Ala	His	Ile
1				5					10

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<220>
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<220>
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<222> (10)..(10)
<223> AMIDATION

<400> 474

Ala	Asn	Asn	Ala	Gln	Leu	Leu	Ala	Gln	Ile
1				5					10

<210> 475
<211> 10
<212> PRT
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<220>
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<220>
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<222> (10)..(10)
<223> AMIDATION

<400> 475

Ala	Asn	Asn	Ala	Arg	Ile	Leu	Ala	Arg	Val
1				5					10

<210> 476
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<212> PRT
<213> artificial

<220>
<223> artificial

<220>
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<222> (10)..(10)
<223> AMIDATION

<400> 476

Ala	Asn	Asn	Ala	Arg	Leu	Leu	Ala	Arg	Ile
1				5					10

<210> 477
<211> 10
<212> PRT
<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 477

Ala	Asn	Asn	Ala	Arg	Leu	Leu	Asp	Thr	Ile
1				5					10

<210> 478

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 478

Ala	Asn	Asn	Arg	Leu	Leu	Leu	Ala	Thr	Ile
1				5					10

<210> 479

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 479

Ala	Asn	Asn	Arg	Leu	Leu	Leu	Asp	Thr	Ile
1				5					10

<210> 480

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 480

Glu Gln Asn Ala His Ile Phe Ala His Val
1 5 10

<210> 481
<211> 10
<212> PRT
<213> artificial

<220>
<223> artificial

<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 481

Glu Gln Asn Ala Gln Ile Phe Ala His Val
1 5 10

<210> 482
<211> 10
<212> PRT
<213> artificial

<220>
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<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 482

Glu Gln Asn Ala Arg Ile Phe Ala Arg Val
1 5 10

<210> 483
<211> 10
<212> PRT
<213> artificial

<220>
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<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 483

Glu Gln Asn Arg Ile Ile Phe Asp Ser Val
1 5 10

<210> 484
<211> 10
<212> PRT
<213> artificial

<220>
<223> artificial

<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 484

Glu Thr Asn Ala Arg Ile Leu Ala Arg Val
1 5 10

<210> 485
<211> 10
<212> PRT
<213> artificial

<220>
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<220>
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<222> (10)..(10)
<223> AMIDATION

<400> 485

His Ala Gln Ala His Ile Leu Ala His Val
1 5 10

<210> 486
<211> 10
<212> PRT
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<220>
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<220>

<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 486

His Ser Asn Arg Lys Ile Ile Asp Ile Ala
1 5 10

<210> 487
<211> 10
<212> PRT
<213> artificial

<220>
<223> artificial

<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 487

His Ser Asn Arg Lys Leu Leu Asp Ile Ala
1 5 10

<210> 488
<211> 10
<212> PRT
<213> artificial

<220>
<223> artificial

<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 488

His Ser Asn Arg Lys Leu Met Glu Ile Ile
1 5 10

<210> 489
<211> 10
<212> PRT
<213> artificial

<220>
<223> artificial

<220>
<221> MOD_RES

<222> (10)..(10)
<223> AMIDATION

<400> 489

His	Thr	Asn	Ala	Arg	Ile	Leu	Ala	Arg	Val
1				5					10

<210> 490
<211> 10
<212> PRT
<213> artificial

<220>
<223> artificial

<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 490

Thr	Asn	Asn	Arg	Leu	Leu	Leu	Ala	Thr	Val
1				5					10

<210> 491
<211> 10
<212> PRT
<213> artificial

<220>
<223> artificial

<220>
<221> MOD_RES
<222> (10)..(10)
<223> AMIDATION

<400> 491

Thr	Asn	Asn	Arg	Leu	Leu	Leu	Asp	Thr	Ile
1				5					10

<210> 492
<211> 10
<212> PRT
<213> artificial

<220>
<223> artificial

<220>
<221> MOD_RES
<222> (10)..(10)

<223> AMIDATION

<400> 492

Thr	Ser	Asn	Arg	Lys	Leu	Met	Glu	Ile	Ile
1				5					10

<210> 493

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 493

Thr	Thr	Asn	Ala	Arg	Ile	Leu	Ala	Arg	Asn
1				5					10

<210> 494

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 494

Thr	Thr	Asn	Ala	Arg	Ile	Leu	Ala	Arg	Val
1				5					10

<210> 495

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 495

Thr	Thr	Asn	Ala	Arg	Leu	Leu	Ala	Thr	Val
1				5					10

<210> 496

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 496

Thr	Thr	Asn	Ala	Arg	Leu	Leu	Asp	Arg	Val
1				5					10

<210> 497

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 497

Thr	Thr	Asn	Ala	Arg	Leu	Leu	Asp	Thr	Val
1				5					10

<210> 498

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 498

Thr	Thr	Asn	Arg	Leu	Leu	Leu	Ala	Arg	Val
1				5					10

<210> 499

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 499

Thr	Thr	Asn	Arg	Leu	Leu	Leu	Ala	Thr	Val
1				5					10

<210> 500

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 500

Thr	Thr	Asn	Arg	Leu	Leu	Leu	Asp	Thr	Val
1				5					10

<210> 501

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 501

Thr Thr Gln Ala Arg Ile Leu Ala Arg Val
1 5 10

<210> 502

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (10)..(10)

<223> AMIDATION

<400> 502

Thr Thr Val Ala Arg Ile Leu Ala Arg Val
1 5 10

<210> 503

<211> 10

<212> PRT

<213> artificial

<220>

<223> artificial

<220>

<221> MOD_RES

<222> (1)..(1)

<223> PYRROLIDONE CARBOXYLIC ACID

<400> 503

Glx Gly Pro Pro Ile Ser Ile Asp Leu Pro
1 5 10

<210> 504

<211> 4

<212> PRT

<213> artificial

<220>

<223> artificial

<400> 504

Leu Leu Arg Lys
1

<210> 505

<211> 13
<212> PRT
<213> artificial

<220>
<223> artificial

<400> 505

Ile Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala
1 5 10

<210> 506
<211> 6
<212> PRT
<213> artificial

<220>
<223> artificial

<400> 506

Pro Ser Leu Ser Ile Asp
1 5

<210> 507
<211> 22
<212> PRT
<213> artificial

<220>
<223> artificial

<400> 507

Leu Leu Arg Thr Leu Leu Glu Leu Glu Lys Thr Gln Ser Gln Arg Glu
1 5 10 15

Arg Ala Glu Gln Asn Ala
20

<210> 508
<211> 37
<212> PRT
<213> Artificial

<220>
<223> Artificial

<220>
<221> MOD_RES
<222> (37)..(37)
<223> AMIDATION

<400> 508

Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu Glu
1 5 10 15

Ile Glu Lys Gln Glu Ala Ala Arg Asn Gln Ala Thr Thr Asn Ala Arg
20 25 30

Ile Leu Ala Arg Val
35

<210> 509
<211> 38
<212> PRT
<213> Artificial

<220>
<223> Artificial

<220>
<221> MOD_RES
<222> (38)..(38)
<223> AMIDATION

<400> 509

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Ile Glu Lys Gln Glu Lys Ala Arg Asn Gln Ala Thr Thr Asn Ala
20 25 30

Arg Ile Leu Ala Arg Val
35

<210> 510
<211> 38
<212> PRT
<213> Artificial

<220>
<223> Artificial

<220>
<221> MOD_RES
<222> (38)..(38)
<223> AMIDATION

<400> 510

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Ile Glu Lys Gln Glu Lys Glu Arg Asn Gln Ala Thr Thr Asn Ala

20 25 30

Arg Ile Leu Ala Arg Val
35

<210> 511
<211> 38
<212> PRT
<213> Artificial

<220>
<223> Artificial

<220>
<221> MOD_RES
<222> (38)..(38)
<223> AMIDATION

<400> 511

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Ile Glu Lys Gln Glu Lys Glu Lys Asn Gln Ala Thr Thr Asn Ala
20 25 30

Arg Ile Leu Ala Arg Val
35

<210> 512
<211> 38
<212> PRT
<213> Artificial

<220>
<223> Artificial

<220>
<221> MOD_RES
<222> (38)..(38)
<223> AMIDATION

<400> 512

Ile Val Leu Ser Leu Asp Val Pro Ile Gly Leu Leu Gln Ile Leu Leu
1 5 10 15

Glu Ile Glu Lys Gln Glu Lys Glu Lys Gln Gln Ala Thr Thr Asn Ala
20 25 30

Arg Ile Leu Ala Arg Val
35

<210> 513
 <211> 40
 <212> PRT
 <213> Artificial

<220>
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<220>
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 <222> (1)..(1)
 <223> PYRROLIDONE CARBOXYLIC ACID

<220>
 <221> MOD_RES
 <222> (40)..(40)
 <223> AMIDATION

<400> 513

Glx Gly Pro Pro Ile Ser Ile Asp Leu Ser Leu Glu Leu Leu Arg Ile
 1 5 10 15

Leu Leu Glu Gln Ala Arg Ala Arg Ala Ala Arg Asn Gln Ala Ala Asn
 20 25 30

Asn Arg Leu Leu Leu Asp Thr Ile
 35 40

<210> 514
 <211> 40
 <212> PRT
 <213> Artificial

<220>
 <223> Artificial

<220>
 <221> MOD_RES
 <222> (40)..(40)
 <223> AMIDATION

<400> 514

Asp Asn Pro Ser Leu Ser Ile Asp Val Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Gln Gln Ser Gln Arg Glu Arg Ala Glu Gln
 20 25 30

Asn Ala Arg Ile Phe Ala Arg Val

35

40

<210> 515
 <211> 40
 <212> PRT
 <213> Artificial

<220>
 <223> Artificial

<220>
 <221> MOD_RES
 <222> (40)..(40)
 <223> AMIDATION

<400> 515

Asp	Asn	Pro	Ser	Leu	Ser	Ile	Asp	Val	Pro	Leu	Leu	Leu	Leu	Arg	Thr
1				5					10					15	

Leu	Leu	Glu	Leu	Glu	Lys	Gln	Glu	Ser	Gln	Arg	Glu	Arg	Ala	Glu	Gln
			20					25					30		

Asn	Ala	Arg	Ile	Phe	Ala	Arg	Val
		35					40

<210> 516
 <211> 40
 <212> PRT
 <213> Artificial

<220>
 <223> Artificial

<220>
 <221> MOD_RES
 <222> (40)..(40)
 <223> AMIDATION

<400> 516

Asp	Asn	Pro	Ser	Leu	Ser	Ile	Asp	Val	Pro	Leu	Leu	Leu	Leu	Arg	Thr
1				5					10					15	

Leu	Leu	Glu	Leu	Glu	Lys	Gln	Glu	Lys	Gln	Arg	Glu	Arg	Ala	Glu	Gln
			20					25					30		

Asn	Ala	Arg	Ile	Phe	Ala	Arg	Val
		35					40

<210> 517
 <211> 40

<212> PRT
<213> Artificial

<220>
<223> Artificial

<220>
<221> MOD_RES
<222> (40)..(40)
<223> AMIDATION

<400> 517

Asp Asn Pro Ser Leu Ser Ile Asp Val Pro Leu Leu Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Gln Glu Lys Glu Arg Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
35 40

<210> 518
<211> 40
<212> PRT
<213> Artificial

<220>
<223> Artificial

<220>
<221> MOD_RES
<222> (40)..(40)
<223> AMIDATION

<400> 518

Asp Asn Pro Ser Leu Ser Ile Asp Val Pro Leu Leu Leu Leu Arg Thr
1 5 10 15

Leu Leu Glu Leu Glu Lys Gln Glu Lys Glu Lys Glu Arg Ala Glu Gln
20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
35 40

<210> 519
<211> 40
<212> PRT
<213> Artificial

<220>
<223> Artificial

<220>
 <221> MOD_RES
 <222> (40)..(40)
 <223> AMIDATION

<400> 519

Asp Asn Pro Ser Leu Ser Ile Asp Val Pro Leu Leu Leu Leu Arg Thr
 1 5 10 15

Leu Leu Glu Leu Glu Lys Gln Glu Lys Glu Lys Gln Arg Ala Glu Gln
 20 25 30

Asn Ala Arg Ile Phe Ala Arg Val
 35 40

<210> 520
 <211> 4
 <212> PRT
 <213> Artificial

<220>
 <223> Artificial

<400> 520

Glu Lys Gln Gln
 1

<210> 521
 <211> 6
 <212> PRT
 <213> Artificial

<220>
 <223> Artificial

<400> 521

Ala Ala Arg Asn Gln Ala
 1 5

<210> 522
 <211> 6
 <212> PRT
 <213> Artificial

<220>
 <223> Artificial

<400> 522

Lys Glu Arg Asn Gln Ala
 1 5

<210> 523
<211> 6
<212> PRT
<213> Artificial

<220>
<223> Artificial

<400> 523

Lys Glu Lys Asn Gln Ala
1 5

<210> 524
<211> 6
<212> PRT
<213> Artificial

<220>
<223> Artificial

<400> 524

Lys Gln Arg Glu Arg Ala
1 5

<210> 525
<211> 6
<212> PRT
<213> Artificial

<220>
<223> Artificial

<400> 525

Lys Glu Arg Glu Arg Ala
1 5

<210> 526
<211> 6
<212> PRT
<213> Artificial

<220>
<223> Artificial

<400> 526

Lys Glu Lys Glu Arg Ala
1 5

<210> 527
<211> 6
<212> PRT

<213> Artificial

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<223> Artificial

<400> 527

Lys Glu Lys Gln Arg Ala
1 5

<210> 528

<211> 6

<212> PRT

<213> Artificial

<220>

<223> Artificial

<400> 528

Ala Glu Ala Ala Ala Lys
1 5

<210> 529

<211> 6

<212> PRT

<213> Artificial

<220>

<223> Artificial

<400> 529

Ala Ala His Ala Ala Ala
1 5

<210> 530

<211> 6

<212> PRT

<213> Artificial

<220>

<223> Artificial

<400> 530

His Ala His Ala His Ala
1 5