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(54) **NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED HUMAN G PROTEIN-COUPLED RECEPTORS**

NICHT-ENDOGENE, KONSTITUTIV AKTIVIERTE, MENSCHLICHE, AN EIN G-PROTEIN GEKOPPELTE REZEPTOREN

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EP 1 121 431 B9

Description

FIELD OF THE INVENTION

[0001] The invention disclosed in this patent document relates to transmembrane receptors, and more particularly to human G protein-coupled receptors (GPCRs) which have been altered such that altered GPCRs are constitutively activated. Most preferably, the altered human GPCRs are used for the screening of therapeutic compounds.

BACKGROUND OF THE INVENTION

[0002] Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2% or 2,000 genes, are estimated to code for GPCRs. Of these, there are approximately 100 GPCRs for which the endogenous ligand that binds to the GPCR has been identified. Because of the significant time-lag that exists between the discovery of an endogenous GPCR and its endogenous ligand, it can be presumed that the remaining 1,900 GPCRs will be identified and characterized long before the endogenous ligands for these receptors are identified. Indeed, the rapidity by which the Human Genome Project is sequencing the 100,000 human genes indicates that the remaining human GPCRs will be fully sequenced within the next few years. Nevertheless, and despite the efforts to sequence the human genome, it is still very unclear as to how scientists will be able to rapidly, effectively and efficiently exploit this information to improve and enhance the human condition. The present invention is geared towards this important objective.

[0003] Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified are referred to as "orphan" receptors. This distinction is not merely semantic, particularly in the case of GPCRs. GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, 60% of all prescription pharmaceuticals have been developed. Thus, the orphan GPCRs are to the pharmaceutical industry what gold was to California in the late 19th century - an opportunity to drive growth, expansion, enhancement and development. A serious drawback exists, however, with orphan receptors relative to the discovery of novel therapeutics. This is because the traditional approach to the discovery and development of pharmaceuticals has required access to both the receptor and its endogenous ligand. Thus, heretofore, orphan GPCRs have presented the art with a tantalizing and undeveloped resource for the discovery of pharmaceuticals.

[0004] Under the traditional approach to the discovery ofpotential therapeutics, it is generally the case that the receptor is first identified. Before drug discovery efforts can be initiated, elaborate, time consuming and expensive procedures are typically put into place in order to identify, isolate and generate the receptor's endogenous ligand - this process can require from between 3 and ten years per receptor, at a cost of about $5million (U.S.) per receptor. These time and financial resources must be expended before the traditional approach to drug discovery can commence. This is because traditional drug discovery techniques rely upon so-called "competitive binding assays" whereby putative therapeutic agents are "screened" against the receptor in an effort to discover compounds that either block the endogenous ligand from binding to the receptor ("antagonists"), or enhance or mimic the effects of the ligand binding to the receptor ("agonists"). The overall objective is to identify compounds that prevent cellular activation when the ligand binds to the receptor (the antagonists), or that enhance or increase cellular activity that would otherwise occur if the ligand was properly binding with the receptor (the agonists). Because the endogenous ligands for orphan GPCRs are by definition not identified, the ability to discover novel and unique therapeutics to these receptors using traditional drug discovery techniques is not possible. The present invention, as will be set forth in greater detail below, overcomes these and other severe limitations created by such traditional drug discovery techniques.

[0005] GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each ofwhich spans the membrane (each span is identified by number, *i.e.,* transmembrane-1 (TM-1), transmebrane-2 (TM-2), etc.). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the receptor lies in the extracellular space outside of the cell. The general structure of G protein-coupled receptors is depicted in Figure 1.

[0006] Generally, when an endogenous ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region

and an intracellular "G-protein." Although other G proteins exist, currently, Gq, Gs, Gi, and Go are G proteins that have been identified. Endogenous ligand-activated GPCR coupling with the G-protein begins a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein. A principal focus of this invention is directed to the transmembrane-6 (TM6) region and the intracellular-3 (IC3) region of the GPCR.

[0007] Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. As shown schematically in Figure 2, a receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response.

[0008] A receptor may be stabilized in an active state by an endogenous ligand or a compound such as a drug. Recent discoveries, including but not exclusively limited to modifications to the amino acid sequence of the receptor, provide means other than endogenous ligands or drugs to promote and stabilize the receptor in the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of an endogenous ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

[0009] As noted above, the use of an orphan receptor for screening purposes has not been possible. This is because the traditional "dogma" regarding screening ofcompounds mandates that the ligand for the receptor be known. By definition, then, this approach has no applicability with respect to orphan receptors. Thus, by adhering to this dogmatic approach to the discovery of therapeutics, the art, in essence, has taught and has been taught to forsake the use of orphan receptors unless and until the endogenous ligand for the receptor is discovered. Given that there are an estimated 2,000 G protein coupled receptors, the majority of which are orphan receptors, such dogma castigates a creative, unique and distinct approach to the discovery of therapeutics.

[0010] Information regarding the nucleic acid and/or amino acid sequences of a variety ofGPCRs is summarized below in Table A. Because an important focus of the invention disclosed herein is directed towards orphan GPCRs, many of the below-cited references are related to orphan GPCRs. However, this list is not intended to imply, nor is this list to be construed, legally or otherwise, that the invention disclosed herein is only applicable to orphan GPCRs or the specific GPCRs listed below. Additionally, certain receptors that have been isolated are not the subject of publications per se; for example, reference is made to a G Protein-Coupled Receptor database on the "world-wide web" (neither the named inventors nor the assignee have any affiliation with this site) that lists GPCRs. Other GPCRs are the subject of patent applications owned by the present assignee and these are not listed below (including GPR3, GPR6 and GPR12; *see* U.S. Provisional Number 60/094879):

Table A

Receptor Name	Publication Reference
GPR1	23 Genomics 609 (1994)
GPR4	14 DNA and Cell Biology 25 (1995)
GPR5	14 DNA and Cell Biology 25 (1995)
GPR7	28 Genomics 84 (1995)
GPR8	28 Genomics 84 (1995)
GPR9	184 J. Exp. Med. 963 (1996)
GPR10	29 Genomics 335 (1995)
GPR15	32 Genomics 462 (1996)
GPR17	70 J Neurochem. 1357 (1998)
GPR18	42 Genomics 462 (1997)
GPR20	187 Gene 75 (1997)
GPR21	187 Gene 75 (1997)
GPR22	187 Gene 75 (1997)
GPR24	398 FEBS Lett. 253 (1996)
GPR30	45 Genomics 607 (1997)
GPR31	42 Genomics 519 (1997)
GPR32	50 Genomics 281 (1997)
GPR40	239 Biochem. Biophys. Res. Commun. 543 (1997)
GPR41	239 Biochem. Biophys. Res. Commun. 543 (1997)
GPR43	239 Biochem. Biophys. Res. Commun. 543 (1997)
APJ	136 Gene 355 (1993)
BLR1	22 Eur. J. Immunol. 2759 (1992)
CEPR	231 Biochem. Biophys. Res. Commun. 651 (1997)
EBI1	23 Genomics 643 (1994)
EBI2	67 J. Virol. 2209 (1993)
ETBR-LP2	424 FEBS Lett. 193 (1998)
GPCR-CNS	54 Brain Res. Mol. Brain Res. 152 (1998); 45 Genomics 68 (1997)
GPR-NGA	394 FEBS Lett. 325 (1996)
H9	386 FEBS Lett 219 (1996)
HBA954	1261 Biochim. Biophys. Acta 121 (1995)
HG38	247 Biochem. Biophys. Res. Commun. 266 (1998)
HM74	5 Int. Immunol. 1239 (1993)
OGR1	35 Genomics 397 (1996)
V28	163 Gene 295 (1995)

[0011] As will be set forth and disclosed in greater detail below, utilization of a mutational cassette to modify the endogenous sequence of a human GPCR leads to a constitutively activated version of the human GPCR. These non-endogenous, constitutively activated versions ofhuman GPCRs can be utilized, *inter alia,* for the screening of candidate compounds to directly identify compounds of, *e.g.*, therapeutic relevance.

[0012] WO 97/21731 discloses a consitutively active, non-endogenous version of an endogenous human GPCR, the CCK-B/gastrin receptor, which is characterised in that the valine residue, found at position 16 when counting from the endogenous proline residue within the transmembrane-6 region in a C-terminal to N-terminal direction, was altered to a non-endogenous glutamic acid residue.

[0013] WO 98/38217 discloses an alignment method for identifying in the sequences of GPCRs the amino acid equivalent to the alanine residue at position 293 of the alpha 1B-adrenergic receptor. It teaches to apply the alignment method to create contitutively active versions of other GPCRs.

SUMMARY OF THE INVENTION

[0014] The present invention provides a method for creating a non-endogenous, constitutively active version of an endogenous human G protein coupled receptor (GPCR), said endogenous GPCR comprising a transmembrane 6 region and an intracellular loop 3 region, the method comprising:

(a) selecting an endogenous human GPCR comprising a proline residue in the transmembrane 6 region;
(b) identifying the endogenous 16th amino acid residue from the proline residue of step (a), in a carboxy-terminus to amino-terminus direction;
(c) altering the identified amino acid residue of step (b) to a non-endogenous amino acid residue to create a non-endogenous version of the endogenous human GPCR; and
(d) determining if the non-endogenous version of the endogenous human GPCR of step (c) is constitutively active by measuring a difference in an intracellular signal measured for the non-endogenous version as compared with a signal induced by the endogenous GPCR.

[0015] Disclosed herein is a non-endogenous, human G protein-coupled receptor comprising (a) as a most preferred amino acid sequence region (C-terminus to N-terminus orientation) and/or (b) as a most preferred nucleic acid sequence region (3' to 5' orientation) transversing the transmembrane-6 (TM6) and intracellular loop-3 (IC3) regions of the GPCR:

(a)

$$P^1\ AA_{15}\ X$$

wherein:

(I) P^1 is an amino acid residue located within the TM6 region of the GPCR, where P^1 is selected from the group consisting of (i) the endogenous GPCR's proline residue, and (ii) a non-endogenous amino acid residue other than proline;
(2) AA_{15} are 15 amino acids selected from the group consisting of (a) the endogenous GPCR's amino acids (b) non-endogenous amino acid residues, and (c) a combination of the endogenous GPCR's amino acids and non-endogenous amino acids, excepting that none of the 15 endogenous amino acid residues that are positioned within the TM6 region of the GPCR is proline; and
(3) X is a non-endogenous amino acid residue located within the IC3 region of said GPCR, preferably selected from the group consisting of lysine, hisitidine and arginine, and most preferably lysine, excepting that when the endogenous amino acid at position X is lysine, then X is an amino acid other than lysine, preferably alanine;

and/or
(b)

$$P^{codon}\ (AA\text{-}codon)_{15}\ X_{codon}$$

wherein:

(1) P^{codon} is a nucleic acid sequence within the TM6 region of the GPCR, wherein P^{codon} encodes an amino acid selected from the group consisting of (i) the endogenous GPCR's proline residue, and (ii) a non-endogenous amino acid residue other than proline;
(2) $(AA\text{-}codon)_{15}$ are 15 codons encoding 15 amino acids selected from the group consisting of (a) the endogenous GPCR's amino acids (b) non-endogenous amino acid residues and (c) a combination of the endogenous GPCR's amino acids and non-endogenous amino acids, excepting that none of the 15 endogenous codons within the TM6 region of the GPCR encodes a proline amino acid residue; and

(3) X_{codon} is a nucleic acid encoding region residue located within the IC3 region of said GPCR, where X_{codon} encodes a non-endogenous amino acid, preferably selected from the group consisting of lysine, hisitidine and arginine, and most preferably lysine, excepting that when the endogenous encoding region at position X_{codon} encodes the amino acid lysine, then X_{codon} encodes an amino acid other than lysine, preferably alanine.

The terms endogenous and non-endogenous in reference to these sequence cassettes are relative to the endogenous GPCR. For example, once the endogenous proline residue is located within the TM6 region of a particular GPCR, and the 16th amino acid therefrom is identified for mutation to constitutively activate the receptor, it is also possible to mutate the endogenous proline residue (*i.e.*, once the marker is located and the 16th amino acid to be mutated is identified, one may mutate the marker itself), although it is most preferred that the proline residue not be mutated. Similarly, and while it is most preferred that AA_{15}be maintained in their endogenous forms, these amino acids may also be mutated. The only amino acid that must be mutated in the non-endogenous version of the human GPCR is X *i.e.,* the endogenous amino acid that is 16 residues from P^1 cannot be maintained in its endogenous form and must be mutated, as further disclosed herein. Stated again, while it is preferred that in the non-endogenous version of the human GPCR, P^1 and AA_{15} remain in their endogenous forms (*i.e.,* identical to their wild-type forms), once X is identified and mutated, any and/or all of P^1 and AA_{15} can be mutated. This applies to the nucleic acid sequences as well. In those cases where the endogenous amino acid at position X is lysine, then in the non-endogenous version of such GPCR, X is an amino acid other than lysine, preferably alanine.

[0016] Accordingly, and as a hypothetical example, if the endogenous GPCR has the following endogenous amino acid sequence at the above-noted positions:

P-AACCTTGGRRRDDDE –Q

then any of the following exemplary and hypothetical cassettes would fall within the scope of the disclosure (non-endogenous amino acids are set forth in bold):

P-AACCTTGGRRRDDDE –**K**

P-AACCTT**HIG**RRDDDE –**K**

P-A**DEE**TTGGRRRDDDE –**A**

P-**LLKFMSTWZLVAAPQ** –**K**

A-LLKFMSTWZLVAAPQ –K

It is also possible to add amino acid residues within AA_{15}, but such an approach is not particularly advanced. Indeed, in the most preferred embodiments, the only amino acid that differs in the non-endogenous version of the human GPCR as compared with the endogenous version of that GPCR is the amino acid in position X; mutation of this amino acid itself leads to constitutive activation of the receptor.

[0017] Thus, in particularly preferred embodiments, P^1 and P^{codon} are endogenous proline and an endogenous nucleic acid encoding region encoding proline, respectively; and X and X_{codon} are non-endogenous lysine or alanine and a non-endogenous nucleic acid encoding region encoding lysine or alanine, respectively, with lysine being most preferred. Because it is most preferred that the non-endogenous versions of the human GPCRs which incorporate these mutations are incorporated into mammalian cells and utilized for the screening of candidate compounds, the non-endogenous human GPCR incorporating the mutation need not be purified and isolated *per se (i.e.,* these are incorporated within

the cellular membrane of a mammalian cell), although such purified and isolated non-endogenous human GPCRs are well within the purview of this disclosure. Gene-targeted and transgenic non-human mammals (preferably rats and mice) incorporating the non-endogenous human GPCRs are also within the purview of this disclosure; in particular, gene-targeted mammals are most preferred in that these animals will incorporate the non-endogenous versions of the human GPCRs inplace of the non-human mammal's endogenous GPCR-encoding region (techniques for generating such non-human mammals to replace the non-human mammal's protein encoding region with a human encoding region are well known; see, for example, U.S. Patent No. 5,777,194.)

[0018] It has been discovered that these changes to an endogenous human GPCR render the GPCR constitutively active such that, as will be further disclosed herein, the non-endogenous, constitutively activated version of the human GPCR can be utilized for, *inter alia,* the direct screening of candidate compounds without the need for the endogenous ligand. Thus, methods for using these materials, and products identified by these methods are also within the purview of the following disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019]

Figure 1 shows a generalized structure of a G protein-coupled receptor with the numbers assigned to the trans-membrane helixes, the intracellular loops, and the exhacellular loops.

Figure 2 schematically shows the two states, active and inactive, for a typical G protein coupled receptor and the linkage of the active state to the second messenger transduction pathway.

Figure 3 is a sequence diagram of the preferred vector pCMV, including restriction enzymen site locations.

Figure 4 is a diagrammatic representation ofthe signal measured comparing pCMV, non-endogenous, constitutively active GPR30 inhibition of GPR6-mediated activation ofCRE-Luc reporter with endogenous GPR30 inhibition of GPR6-mediated activation of CRE-Luc reporter.

Figure 5 is a diagrammatic representation ofthe signal measured comparing pCMV, non-endogenous, constitutively activated GPR 17 inhibition of GPR3-mediated activation of CRE-Luc reporter with endogenous GPR17 inhibition of GPR3-mediated activation of CRE-Luc reporter.

Figure 6 provides diagrammatic results of the signal measured comparing control pCMV, endogenous APJ and non-endogenous APJ.

Figure 7 provides an illustration of IP_3 production from non-endogenous human 5-HT_{2A} receptor as compared to the endogenous version of this receptor.

Figure 8 are dot-blot format results for GPR1 (8A), GPR30 (8B) and APJ (8C).

DETAILED DESCRIPTION

[0020] The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

[0021] **AGONISTS** shall mean compounds that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

[0022] **AMINO ACID ABBREVIATIONS** used herein are set below:

ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I

(continued)

LEUCINE	LEU	L
LYSINE	LYS	K
METHIONINE	MET	M
PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

[0023] **PARTIAL AGONISTS** shall mean compounds which activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists

[0024] **ANTAGONIST** shall mean compounds that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. ANTAGONISTS do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

[0025] **CANDIDATE COMPOUND** shall mean a molecule (for example, and not limitation, a chemical compound) which is amenable to a screening technique. Preferably, the phrase "candidate compound" does not include compounds which were publicly known to be compounds selected from the group consisting of inverse agonist, agonist or antagonist to a receptor, as previously determined by an indirect identification process ("indirectly identified compound"); more preferably, not including an indirectly identified compound which has previously been determined to have therapeutic efficacy in at least one mammal; and, most preferably, not including an indirectly identified compound which has previously been determined to have therapeutic utility in humans.

[0026] **CODON** shall mean a grouping of three nucleotides (or equivalents to nucleotides) which generally comprise a nucleoside (adenosine (A), guanosine (G), cytidine (C), uridine (U) and thymidine (T)) coupled to a phosphate group and which, when translated, encodes an amino acid.

[0027] **COMPOUND EFFICACY** shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity. A preferred means of detecting compound efficacy is via measurement of, *e.g.,* [^{35}S]GTPγS binding, as further disclosed in the Example section of this patent document.

[0028] **CONSTITUTIVELY ACTIVATED RECEPTOR** shall mean a receptor subject to constitutive receptor activation, In accordance with the invention disclosed herein, a non-endogenous, human constitutively activated G protein-coupled receptor is one that has been mutated to include the amino acid cassette $P^1AA_{15}X$, as set forth in greater detail below.

[0029] **CONSTITUTIVE RECEPTOR ACTIVATION** shall mean stabilization of a receptor in the active state by means other than binding of the receptor with its endogenous ligand or a chemical equivalent thereof. Preferably, a G protein-coupled receptor subjected to constitutive receptor activation in accordance with the invention disclosed herein evidences at least a 10% difference in response (increase or decrease, as the case may be) to the signal measured for constitutive activation as compared with the endogenous form of that GPCR, more preferably, about a 25% difference in such comparative response, and most preferably about a 50% difference in such comparative response. When used for the purposes of directly identifying candidate compounds, it is most preferred that the signal difference be at least about 50% such that there is a sufficient difference between the endogenous signal and the non-endogenous signal to differentiate between selected candidate compounds. In most instances, the "difference" will be an increase in signal; however, with respect to Gs-coupled GPCRS, the "difference" measured is preferably a decrease, as will be set forth in greater detail below.

[0030] **CONTACT** or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

[0031] **DIRECTLY IDENTIFYING** or **DIRECTLY IDENTIFIED**, in relationship to the phrase "candidate compound", shall mean the screening of a candidate compound against a constitutively activated G protein-coupled receptor, and assessing the compound efficacy of such compound. This phrase is, under no circumstances, to be interpreted or understood to be encompassed by or to encompass the phrase "indirectly identifying" or "indirectly identified."

[0032] **ENDOGENOUS** shall mean a material that is naturally produced by the genome of the species. ENDOGENOUS

in reference to, for example and not limitation, GPCR, shall mean that which is naturally produced by a human, an insect, a plant, a bacterium, or a virus. By contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by the genome of a species. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when mutated by using the cassettes disclosed herein and thereafter becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For example, and not limitation, in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system whereby the receptor is expressed on the cell-surface of a mammalian cell. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

[0033] **HOST CELL** shall mean a cell capable of having a Plasmid and/or Vector incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as an autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. Preferably, for the purposes of the invention disclosed herein, the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

[0034] **INDIRECTLY IDENTIFYING** or **INDIRECTLY IDENTIFIED** means the traditional approach to the drug discovery process involving identification of an endogenous ligand specific for an endogenous receptor, screening of candidate compounds against the receptor for determination of those which interfere and/or compete with the ligand-receptor interaction, and assessing the efficacy of the compound for affecting at least one second messenger pathway associated with the activated receptor.

[0035] **INHIBIT** or **INHIBITING,** in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

[0036] **INVERSE AGONISTS** shall mean compounds which bind to either the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

[0037] **KNOWN RECEPTOR** shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has been identified.

[0038] **LIGAND** shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

[0039] **MUTANT** or **MUTATION** in reference to an endogenous receptor's nucleic acid and/or amino acid sequence shall mean a specified change or changes to such endogenous sequences such that a mutated form of an endogenous, non-constitutively activated receptor evidences constitutive activation of the receptor. In terms of equivalents to specific sequences, a subsequent mutated form of a human receptor is considered to be equivalent to a first mutation of the human receptor if (a) the level of constitutive activation of the subsequent mutated form of the receptor is substantially the same as that evidenced by the first mutation of the receptor; and (b) the percent sequence (amino acid and/or nucleic acid) homology between the subsequent mutated form of the receptor and the first mutation of the receptor is at least about 80%, more preferably at least about 90% and most preferably at least 95%. Ideally, and owing to the fact that the most preferred cassettes disclosed herein for achieving constitutive activation includes a single amino acid and/or codon change between the endogenous and the non-endogenous forms of the GPCR (i.e. X or X_{codon}), the percent sequence homology should be at least 98%.

[0040] **ORPHAN RECEPTOR** shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has not been identified or is not known.

[0041] **PHARMACEUTICAL COMPOSITION** shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[0042] PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purpose of replication and/or expression of the cDNA as a protein.

[0043] **STIMULATE** or **STIMULATING,** in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

[0044] **TRANSVERSE** or **TRANSVERSING**, in reference to either a defined nucleic acid sequence or a defined amino acid sequence, shall mean that the sequence is located within at least two different and defined regions. For example, in an amino acid sequence that is 10 amino acid moieties in length, where 3 of the 10 moieties are in the TM6 region of a GPCR and the remaining 7 moieties are in the IC3 region of the GPCR, the 10 amino acid moiety can be described

as transversing the TM6 and IC3 regions of the GPCR.

[0045] **VECTOR** in reference to cDNA shall mean a circular DNA capable of incorporating at least one cDNA and capable of incorporation into a Host Cell.

[0046] The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

A. Introduction

[0047] The traditional study of receptors has always proceeded from the a priori assumption (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized is that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand. This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

[0048] Screening candidate compounds against non-endogenous, constitutively activated GPCRs allows for the direct identification of candidate compounds which act at these cell surface receptors, without requiring any prior knowledge or use of the receptor's endogenous ligand. By determining areas within the body where the endogenous version of such GPCRs are expressed and/or over-expressed, it is possible to determine related disease/disorder states which are associated with the expression and/or over-expression of these receptors; such an approach is disclosed in this patent document.

B. Disease/Disorder Identification and/or Selection

[0049] Most preferably, inverse agonists to the non-endogenous, constitutively activated GPCRs can be identified using the materials of this invention. Such inverse agonists are ideal candidates as lead compounds in drug discovery programs for treating diseases related to these receptors. Because of the ability to directly identify inverse agonists, partial agonists or agonists to these receptors, thereby allowing for the development of pharmaceutical compositions, a search, for diseases and disorders associated with these receptors is possible. For example, scanning both diseased and normal tissue samples for the presence of these receptor now becomes more than an academic exercise or one which might be pursued along the path of identifying, in the case of an orphan receptor, an endogenous ligand. Tissue scans can be conducted across a broad range of healthy and diseased tissues. Such tissue scans provide a preferred first step in associating a specific receptor with a disease and/or disorder.

[0050] Preferably, the DNA sequence of the endogenous GPCR is used to make a probe for either radiolabeled cDNA or RT-PCR identification of the expression of the GPCR in tissue samples. The presence of a receptor in a diseased tissue, or the presence of the receptor at elevated or decreased concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with that disease. Receptors can equally well be localized to regions of organs by this technique. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

C. A "Human GPCR Proline Marker" Algorithm and the Creation of Non-Endogenous, Constitutively-Active Human GPCRs

[0051] Among the many challenges facing the biotechnology arts is the unpredictability in gleaning genetic information from one species and correlating that information to another species- nowhere in this art does this problem evidence more annoying exacerbation than in the genetic sequences that encode nucleic acids and proteins. Thus, for consistency and because of the highly unpredictable nature of this art, the following invention is limited, in terms of mammals, to human GPCRs - applicability of this invention to other mammalian species, while a potential possibility, is considered beyond mere rote application.

[0052] In general, when attempting to apply common "rules" from one related protein sequence to another or from one species to another, the art has typically resorted to sequence alignment, *i.e.,* sequences are linearized and attempts are then made to find regions of commonality between two or more sequences. While useful, this approach does not always prove to result in meaningful information. In the case of GPCRs, while the general structural motif is identical for

all GPCRs, the variations in lengths of the TMs, ECs and ICs make such alignment approaches from one GPCR to another difficult at best. Thus, while it may be desirable to apply a consistent approach to, e.g., constitutive activation from one GPCR to another, because of the great diversity in sequence length, fidelity, etc from one GPCR to the next, a generally applicable, and readily successful mutational alignment approach is in essence not possible. In an analogy, such an approach is akin to having a traveler start a journey at point A by giving the traveler dozens of different maps to point B, without any scale or distance markers on any of the maps, and then asking the traveler to find the shortest and most efficient route to destination B only by using the maps. In such a situation, the task can be readily simplified by having (a) a common "place-marker" on each map, and (b) the ability to measure the distance from the place-marker to destination B - this, then, will allow the traveler to select the most efficient from starting-point A to destination B.

[0053] In essence, a feature of the invention is to provide such coordinates within human GPCRs that readily allows for creation of a constitutively active form of the human GPCRs.

[0054] As those in the art appreciate, the transmembrane region of a cell is highly hydrophobic; thus, using standard hydrophobicity plotting techniques, those in the art are readily able to determine the TM regions of a GPCR, and specifically TM6 (this same approach is also applicable to determining the EC and IC regions of the GPCR). It has been discovered that within the TM6 region of human GPCRs, a common proline residue (generally near the middle of TM6), acts as a constitutive activation "marker." By counting 15 amino acids from the proline marker, the 16th amino acid (which is located in the IC3 loop), when mutated from its endogenous form to a non-endogenous form, leads to constitutive activation of the receptor. For convenience, we refer to this as the "Human GPCR Proline Marker" Algorithm. Although the non-endogenous amino acid at this position can be any of the amino acids, most preferably, the non-endogenous amino acid is lysine. While not wishing to be bound by any theory, we believe that this position itself is unique and that the mutation at this location impacts the receptor to allow for constitutive activation.

[0055] We note that, for example, when the endogenous amino acid at the 16th position is already lysine (as is the case with GPR4 and GPR32), then in order for X to be a non-endogenous amino acid, it must be other than lysine; thus, in those situations where the endogenous GPCR has an endogenous lysine residue at the 16th position, the non-endogenous version of that GPCR preferably incorporates an amino acid other than lysine, preferably alanine, histidine and arginine, at this position. Of further note, it has been determined that GPR4 appears to be linked to Gs and active in its endogenous form (data not shown).

[0056] Because there are only 20 naturally occurring amino acids (although the use of non-naturally occurring amino acids is also viable), selection of a particular non-endogenous amino acid for substitution at this 16th position is viable and allows for efficient selection of a non-endogenous amino acid that fits the needs of the investigator. However, as noted, the more preferred non-endogenous amino acids at the 16th position are lysine, hisitidine, arginine and alanine, with lysine being most preferred. Those of ordinary skill in the art are credited with the ability to readily determine proficient methods for changing the sequence of a codon to achieve a desired mutation.

[0057] It has also been discovered that occasionally, but not always, the proline residue marker will be preceded in TM6 by W2 *(i.e.,* W2P^{1}AA$_{15}$X) where W is tryptophan and 2 is any amino acid residue.

[0058] Our discovery, amongst other things, negates the need for unpredictable and complicated sequence alignment approaches commonly used by the art. Indeed, the strength of our discovery, while an algorithm in nature, is that it can be applied in a facile manner to human GPCRs, with dexterous simplicity by those in the art, to achieve a unique and highly useful end-product, *i.e.,* a constitutively activated version of a human GPCR. Because many years and significant amounts of money will be required to determine the endogenous ligands for the human GPCRs that the Human Genome project is uncovering, the disclosed invention not only reduces the time necessary to positively exploit this sequence information, but at significant cost-savings. This approach truly validates the importance of the Human Genome Project because it allows for the utilization of genetic information to not only understand the role of the GPCRs in, e.g., diseases, but also provides the opportunity to improve the human condition.

D. Screening of Candidate Compounds

1. Generic GPCR screening assay techniques

[0059] When a G protein receptor becomes constitutively active, it couples to a G protein (*e.g.*, Gq, Gs, Gi, Go) and stimulates release and subsequent binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors, including the non-endogenous, human constitutively active GPCRs of the present invention, continue to exchange GDP for GTP. A non-hydrolyzable analog of GTP, [^{35}S]GTPγS, can be used to monitor enhanced binding to G proteins present on membranes which express constitutively activated receptors. It is reported that [^{35}S] GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the

system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

B 2. Specific GPCR screening assay techniques

[0060] C Once candidate compounds are identified using the "generic" G protein-coupled receptor assay (*i.e.*, an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

a. Gs and Gi.

[0061] Gs stimulates the enzyme adenylyl cyclase. Gi (and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple the Gi (or Go) protein are associated with decreased cellular levels of cAMP. *See, generally,* "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to the receptor (*i.e.*, such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription factor (CREB) which then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, e.g., β-galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes the accumulation of cAMP that then activates the gene and expression of the reporter protein. The reporter protein such as β-galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995). With respect to GPCRs that link to Gi (or Go), and thus decrease levels of cAMP, an approach to the screening of, e.g., inverse agonists, based upon utilization of receptors that link to Gs (and thus increase levels of cAMP) is disclosed in the Example section with respect to GPR17 and GPR30.

b. Go and Gq.

[0062] Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP_2, releasing two intracellular messengers: diacycloglycerol (DAG) and inistol 1,4,5-triphoisphate (IP_3). Increased accumulation of IP_3 is associated with activation of Gq- and Go-associated receptors. *See, generally,* "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Assays that detect IP_3 accumulation can be utilized to determine if a candidate compound is, *e.g.,* an inverse agonist to a Gq- or Go-associated receptor *(i.e.,* such a compound would decrease the levels of IP_3). Gq-associated receptors can also been examined using an AP1 reporter assay in that Gq-dependent phospholipase C causes activation of genes containing AP1 elements; thus, activated Gq-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will evidence an increase in such expression. Commercially available assays for such detection are available.

E. Medicinal Chemistry

[0063] Generally, but not always, direct identification of candidate compounds is preferably conducted in conjunction with compounds generated via combinatorial chemistry techniques, whereby thousands of compounds are randomly prepared for such analysis. Generally, the results of such screening will be compounds having unique core structures; thereafter, these compounds are preferably subjected to additional chemical modification around a preferred core structure(s) to further enhance the medicinal properties thereof. Such techniques are known to those in the art and will not be addressed in detail in this patent document.

F. Pharmaceutical Compositions

[0064] Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers are available to those in

the art; for example, *see* Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Oslo et al., eds.)

G. Other Utility

[0065] Although a preferred use of the non-endogenous versions of the disclosed human GPCRs is for the direct identification of candidate compounds as inverse agonists, agonists or partial agonists (preferably for use as pharmaceutical agents), these receptors can also be utilized in research settings. For example, in vitro and in vivo systems incorporating these receptors can be utilized to further elucidate and understand the roles of the receptors in the human condition, both normal and diseased, as well understanding the role of constitutive activation as it applies to understanding the signaling cascade. A value in these non-endogenous receptors is that their utility as a research tool is enhanced in that, because of their unique features, the disclosed receptors can be used to understand the role of a particular receptor in the human body before the endogenous ligand therefor is identified. Other uses of the disclosed receptors will become apparent to those in the art based upon, *inter alia,* a review of this patent document.

EXAMPLES

[0066] The following examples are presented for purposes of elucidation, and not limitation, of the present invention. Following the teaching of this patent document that a mutational cassette may be utilized in the IC3 loop of human GPCRs based upon a position relative to a proline residue in TM6 to constitutively activate the receptor, and while specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. Particular approaches to sequence mutations are within the purview of the artisan based upon the particular needs of the artisan.

Example 1

Preparation of Endogenous Human GPCRs

[0067] A variety of GPCRs were utilized in the Examples to follow. Some endogenous human GPCRs were graciously provided in expression vectors (as acknowledged below) and other endogenous human GPCRs were synthesized *de novo* using publicly-available sequence information.

1. GPR1 (GenBank Accession Number: U13666)

[0068] The human cDNA sequence for GPR1 was provided in pRcCMV by Brian O'Dowd (University of Toronto). GPR1 cDNA (1.4kB fragment) was excised from the pRcCMV vector as a NdeI-XbaI fragment and was subcloned into the NdeI-XbaI site of pCMV vector *(see* Figure 3). Nucleic acid (SEQ.ID.NO.: 1) and amino acid (SEQ.ID.NO.: 2) sequences for human GPR1 were thereafter determined and verified.

2. GPR4 (GenBank Accession Numbers: L36148, U35399, U21051)

[0069] The human cDNA sequence for GPR4 was provided in pRcCMV by Brian O'Dowd (University of Toronto). GPR 1 cDNA (1.4kB fragment) was excised from the pRcCMV vector as an ApaI(blunted)-XbaI fragment and was subcloned (with most of the 5' untranslated region removed) into HindIII(blunted)-XbaI site of pCMV vector. Nucleic acid (SEQ.ID.NO.: 3) and amino acid (SEQ.ID.NO.: 4) sequences for human GPR4 were thereafter determined and verified.

3. GPR5 (GenBank Accession Number: L36149)

[0070] The cDNA for human GPR5 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM ofeach primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 64°C for 1min; and 72 °C for 1.5 min. The 5' PCR primer contained an EcoRI site with the sequence:

5'-TATGAATTCAGATGCTCTAAACGTCCCTGC-3' (SEQ.ID.NO.: 5)

and the 3' primer contained BamHI site with the sequence:

5'-TCCGGATCCACCTGCACCTGCGCCTGCACC-3' (SEQ.ID.NO.: 6).

The 1.1 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site of PCMV expression vector. Nucleic acid (SEQ.ID.NO.: 7) and amino acid (SEQ.ID.NO.: 8) sequences for human GPR5 were thereafter determined and verified.

4. GPR7 (GenBank Accession Number: U22491)

[0071] The cDNA for human GPR7 was generated and cloned into pCMV expression vector as follows: PCR condition-PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 62°C for 1min; and 72°C for 1min and 20 sec. The 5'PCR primer contained a Hindin site with the sequence:

5'-GCAAGCTTGGGGGACGCCAGGTCGCCGGCT-3' (SEQ.ID.NO.: 9)

and the 3' primer contained a BamHI site with the sequence:

5'-GCGGATCCGGACGCTGGGGGAGTCAGGCTGC-3' (SEQ.ID.NO.: 10).

The 1.1 kb PCR fragment was digested with HindIII and BamHI and cloned into HindIII-BamHI site ofpCMV expression vector. Nucleic acid (SEQ.ID.NO.: 11) and amino acid (SEQ.ID.NO.: 12) sequences for human GPR7 were thereafter determined and verified.

5. GPR8 (GenBank Accession Number: U22492)

[0072] The cDNA for human GPR8 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 62°C for 1 min; and 72 °C for 1min and 20 sec. The 5' PCR primer contained an EcoRI site with the sequence:

5'-CGGAATTCGTCAACGGTCCCAGCTACAATG-3' (SEQ.ID.NO.: 13).

and the 3' primer contained a BamHI site with the sequence:

5'-ATGGATCCCAGGCCCTTCAGCACCGCAATAT-3'(SEQ.ID.NO.: 14).

The 1.1 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site of PCMV expression vector. All 4 cDNA clones sequenced contained a possible polymorphism involving a change of amino acid 206 from Arg to Gln. Aside from this difference, nucleic acid (SEQ.ID.NO.:15) and amino acid (SEQ.ID.NO.: 16) sequences for human GPR8 were thereafter determined and verified.

6. GPR9 (GenBank Accession Number: X95876)

[0073] The cDNA for human GPR9 was generated and cloned into pCMV expression vector as follows: PCR was

performed using a clone (provided by Brian O'Dowd) as template and pfu polymerase (Stratagene) with the buffer system provided by the manufacturer supplemented with 10% DMSO, 0.25 μM of each primer, and 0.5 mM of each of the 4 nucleotides. The cycle condition was 25 cycles of: 94°C for 1 min; 56°C for 1mm; and 72 °C for 2.5 min. The 5' PCR primer contained an EcoRI site with the sequence:

5'-ACGAATTCAGCCATGGTCCTTGAGGTGAGTGACCACCAAGTGCTAAAT-3'

(SEQ.ID.NO.: 17)

and the 3' primer contained a BamHI site with the sequence:

5'-GAGGATCCTGGAATGCGGGGAAGTCAG-3' (SEQ.ID.NO.: 18).

The 1.2 kb PCR fragment was digested with EcoRI and cloned into EcoRI-SmaI site of PCMV expression vector. Nucleic acid (SEQ.ID.NO.: 19) and amino acid (SEQ.ID.NO.: 20) sequences for human GPR9 were thereafter determined and verified.

7. GPR9-6 (GenBank Accession Number: U45982)

[0074] The cDNA for human GPR9-6 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 62°C for 1min; and 72°C for 1 min and 20 sec. The 5' PCR primer was kinased with the sequence:

5'-TTAAGCTTGACCTAATGCCATCTTGTGTCC-3' (SEQ.ID.NO.: 21)

and the 3' primer contained a BamHI site with the sequence:

5'-TTGGATCCAAAAGAACCATGCACCTCAGAG-3' (SEQ.ID.NO.: 22).

The 1.2 kb PCR fragment was digested with BamHI and cloned into EcoRV-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 23) and amino acid (SEQ.m.NO.: 24) sequences for human GPR9-6 were thereafter determined and verified.

8. GPR10 (GenBank Accession Number: U32672)

[0075] The human cDNA sequence for GPR10 was provided in pRcCMV by Brian O'Dowd (University of Toronto). GPR10 cDNA (1.3kB fragment) was excised from the pRcCMV vector as an EcoRI-XbaI fragment and was subcloned into EcoRI-XbaI site of pCMV vector. Nucleic acid (SEQ.ID.NO.: 25) and amino acid (SEQ.ID.NO.: 26) sequences for human GPR10 were thereafter determined and verified.

9. GPR15 (GenBank Accession Number: U34806)

[0076] The human cDNA sequence for GPR15 was provided in pCDNA3 by Brian O'Dowd (University of Toronto). GPR15 cDNA (1.5kB fragment) was excised from the pCDNA3 vector as a HindIII-Bam fragment and was subcloned into HindIII-Bam site of pCMV vector. Nucleic acid (SEQ.ID.NO.: 27) and amino acid (SEQ.ID.NO.: 28) sequences for human GPR15 were thereafter determined and verified.

10. GPR17 (GenBank Accession Number: Z94154)

[0077] The cDNA for human GPR17 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 56°C for 1min and 72 °C for 1 min and 20 sec. The 5' PCR primer contained an EcoRI site with the sequence: 5'-CTAGAATTCTGACTCCAGCCAAAGCATGAAT-3' (SEQ.ID.NO.: 29)and the 3' primer contained a BamHI site with the sequence:

5'-GCTGGATCCTAAACAGTCTGCGCTCGGCCT-3' (SEQ.ID.NO.: 30).

The 1.1 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 31) and amino acid (SEQ.ID.NO.: 32) sequences for human GPR17 were thereafter determined and verified.

11. GPR18 (GenBank Accession Number: L42324)

[0078] The cDNA for human GPR18 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each ofthe 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 54°C for 1min; and 72 °C for 1min and 20 sec. The 5' PCR primer was kinased with the sequence:

5'-ATAAGATGATCACCCTGAACAATCAAGAT -3' (SEQ.ID.NO.: 33)

and the 3' primer contained an EcoRI site with the sequence:

5'-TCCGAATTCATAACATTTCACTGTTTATATTGC-3' (SEQ.ID.NO.: 34).

The 1.0 kb PCR fragment was digested with EcoRI and cloned into blunt-EcoRI site of pCMV expression vector. All 8 cDNA clones sequenced contained 4 possible polymorphisms involving changes of amino acid 12 from Thr to Pro, amino acid 86 from Ala to Glu, amino acid 97 from Ile to Leu and amino acid 310 from Leu to Met. Aside from these changes, nucleic acid (SEQ.ID.NO.: 35) and amino acid (SEQ.ID.NO.: 36) sequences for human GPR18 were thereafter determined and verified.

12. GPR20 (GenBank Accession Number: U66579)

[0079] The cDNA for human GPR20 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 62°C for 1min; and 72 °C for 1 min and 20 sec. The 5' PCR primer was kinased with the sequence:

5'-CCAAGCTTCCAGGCCTGGGGTGTGCTGG-3' (SEQ.ID.NO.: 37)

and the 3' primer contained a BamHI site with the sequence:

5'-ATGGATCCTGACCTTCGGCCCCTGGCAGA-3' (SEQ.ID.NO.: 38).

The 1.2 kb PCR fragment was digested with BamHI and cloned into EcoRV-BamHI site of PCMV expression vector.

Nucleic acid (SEQ.ID.NO.: 39) and amino acid (SEQ.ID.NO.: 40) sequences for human GPR20 were thereafter determined and verified.

13. GPR21 (GenBank Accession Number: U66580)

[0080] The cDNA for human GPR21 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 62°C for 1min; and 72 °C for 1 min and 20 sec. The 5' PCR primer was kinased with the sequence:

5'-GAGAATTCACTCCTGAGCTCAAGATGAACT-3' (SEQ.ID.NO.: 41)

and the 3' primer contained a BamHI site with the sequence:

5'-CGGGATCCCCGTAACTGAGCCACTTCAGAT-3' (SEQ.ID.NO.: 42).

The 1.1 kb PCR fragment was digested with BamHI and cloned into EcoRV-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 43) and amino acid (SEQ.ID.NO.: 44) sequences for human GPR21 were thereafter determined and verified.

14. GPR22 (GenBank Accession Number: U66581)

[0081] The cDNA for human GPR22 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 50°C for 1min; and 72 °C for 1.5 min. The 5' PCR primer was kinased with the sequence:

5'-TCCCCCGGGAAAAAAACCAACTGCTCCAAA-3' (SEQ.ID.NO.: 45)

and the 3' primer contained a BamHI site with the sequence:

5'-TAGGATCCATTTGAATGTGGATTTGGTGAAA-3' (SEQ.ID.NO.: 46).

The 1.38 kb PCR fragment was digested with BamHI and cloned into EcoRV-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 47) and amino acid (SEQ.ID.NO.: 48) sequences for human GPR22 were thereafter determined and verified.

15. GPR24 (GenBank Accession Number: U71092)

[0082] The cDNA for human GPR24 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM ofeach primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 56°C for 1min; and 72 °C for 1 min and 20 sec. The 5' PCR primer contains a HindIII site with the sequence:

5'-GTGAAGCTTGCCTCTGGTGCCTGCAGGAGG-3' (SEQ.ID.NO.: 49)

and the 3' primer contains an EcoRI site with the sequence:

5'-GCAGAATTCCCGGTGGCGTGTTGTGGTGCCC-3' (SEQ.ID.NO.: 50).

The 1.3 kb PCR fragment was digested with HindIII and EcoRI and cloned into HindIII-EcoRI site of pCMV expression vector. The nucleic acid (SEQ.ID.NO.: 51) and amino acid sequence (SEQ.ID.NO.: 52) for human GPR24 were thereafter determined and verified.

16. GPR30 (GenBank Accession Number: U63917)

[0083] The cDNA for human GPR30 was generated and cloned as follows: the coding sequence of GPR30 (1128bp in length) was amplified from genomic DNA using the primers:

5'-GGCGGATCCATGGATGTGACTTCCCAA-3' (SEQ.ID.NO.: 53)

and

5'-GGCGGATCCCTACACGGCACTGCTGAA-3' (SEQ.ID.NO.: 54).

The amplified product was then cloned into a commercially available vector, pCR2.1 (Invitrogen), using a "TOPO-TA Cloning Kit" (Invitrogen, #K4500-01), following manufacturer instructions. The full-length GPR30 insert was liberated by digestion with BamH1, separated from the vector by agarose gel electrophoresis, and purified using a Sephaglas Band-prep™ Kit (Pharmacia, # 27-9285-01) following manufacturer instructions. The nucleic acid (SEQ.ID.NO.: 55) and amino acid sequence (SEQ.ID.NO.: 56) for human GPR30 were thereafter determined and verified.

17. GPR31 (GenBank Accession Number: U65402)

[0084] The cDNA for human GPR31 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 58°C for 1min; and 72 °C for 2 min. The 5' PCR primer contained an EcoRI site with the sequence:

5'-AAGGAATTCACGGCCGGGTGATGCCATTCCC-3' (SEQ.ID.NO.: 57)

and the 3' primer contained a BamHI site with the sequence:

5'-GGTGGATCCATAAACACGGGCGTTGAGGAC -3' (SEQ.ID.NO.: 58).

The 1.0 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 59) and amino acid (SEQ.ID.NO.: 60) sequences for human GPR31 were thereafter determined and verified.

18. GPR32 (GenBank Accession Number: AF045764)

[0085] The cDNA for human GPR32 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 56°C for 1min; and 72 °C for 1 min and 20 sec. The 5' PCR primer contained an EcoRI site with the sequence:

5'-TAAGAATTCCATAAAAATTATGGAATGG-3' (SEQ.ID.NO.:243)

and the 3' primer contained a BamHI site with the sequence:

5'-CCAGGATCCAGCTGAAGTCTTCCATCATTC-3' (SEQ.ID.NO.: 244).

The 1.1 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site ofpCMV expression vector. Nucleic acid (SEQ.ID.NO.: 245) and amino acid (SEQ.ID.NO.: 246) sequences for human GPR32 were thereafter determined and verified.

19. GPR40 (GenBank Accession Number: AF024687)

[0086] The cDNA for human GPR40 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min, 65°C for 1min and 72 °C for 1 min and 10 sec. The 5' PCR primer contained an EcoRI site with the sequence

5'-GCAGAATTCGGCGGCCCCATGGACCTGCCCCC-3' (SEQ.ID.NO.: 247)

and the 3' primer contained a BamHI site with the sequence

5'-GCTGGATCCCCCGAGCAGTGGCGTTACTTC-3' (SEQ.ID.NO.: 248).

The 1 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site ofpCMV expression vector. Nucleic acid (SEQ.ID.NO.: 249) and amino acid (SEQ.ID.NO.: 250) sequences for human GPR40 were thereafter determined and verified.

20. GPR41 (GenBank Accession Number AF024688)

[0087] The cDNA for human GPR41 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 65°C for 1min and 72 °C for 1 min and 10 sec. The 5' PCR primer contained an HindIII site with the sequence:

5'-CTCAAGCTTACTCTCTCTCACCAGTGGCCAC-3' (SEQ.ID.NO.: 251)

and the 3' primer was kinased with the sequence

5'-CCCTCCTCCCCCGGAGGACCTAGC-3' (SEQ.ID.NO.: 252).

The 1 kb PCR fragment was digested with HindIII and cloned into HindIII-blunt site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 253) and amino acid (SEQ.ID.NO.: 254) sequences for human GPR41 were thereafter determined and verified.

21. GPR43 (GenBank Accession Number AF024690)

[0088] The cDNA for human GPR43 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 65°C for 1min; and 72 °C for 1 min and 10 sec. The 5' PCR primer contains an HindIII site with the sequence:

5'-TTTAAGCTTCCCCTCCAGGATGCTGCCGGAC-3' (SEQ.ID.NO.: 255)

and the 3' primer contained an EcoRI site with the sequence:

5'-GGCGAATTCTGAAGGTCCAGGGAAACTGCTA-3' (SEQ.ID.NO. 256).

The 1 kb PCR fragment was digested with HindIII and EcoRI and cloned into HindIII-EcoRI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 257) and amino acid (SEQ.ID.NO.: 258) sequences for human GPR43 were thereafter determined and verified.

22. APJ (GenBank Accession Number: U03642)

[0089] Human APJ cDNA (in pRcCMV vector) was provided by Brian O'Dowd (University of Toronto). The human APJ cDNA was excised from the pRcCMV vector as an EcoRI-XbaI (blunted) fragment and was subcloned into EcoRI-SmaI site of pCMV vector. Nucleic acid (SEQ.ID.NO.: 61) and amino acid (SEQ.ID.NO.:62) sequences for human APJ were thereafter determined and verified.

23. BLR1 (GenBank Accession Number: X68149)

[0090] The cDNA for human BLR1 was generated and cloned into pCMV expression vector as follows: PCR was performed using thymus cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 62°C for 1min; and 72 °C for 1 min and 20 sec. The 5' PCR primer contained an EcoRI site with the sequence:

5'-TGAGAATTCTGGTGACTCACAGCCGGCACAG-3' (SEQ.ID.NO.: 63):

and the 3' primer contained a BamHI site with the sequence:
5'-GCCGGATCCAAGGAAAAGCAGCAATAAAAGG-3' (SEQ.ID.NO.: 64). The 1.2 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 65) and amino acid (SEQ.ID.NO.: 66) sequences for human BLR1 were thereafter determined and verified.

24. CEPR (GenBank Accession Number: U77827)

[0091] The cDNA for human CEPR was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 65°C for 1min; and 72 °C for 1 min and 20 sec. The 5' PCR primer was kinased with the sequence:

5'-CAAAGCTTGAAAGCTGCACGGTGCAGAGAC-3' (SEQ.ID.NO.:67)

and the 3' primer contained a BamHI site with the sequence:

5'-GCGGATCCCGAGTCACACCCTGGCTGGGCC-3' (SEQ.ID.NO.: 68).

The 1.2 kb PCR fragment was digested with BamHI and cloned into EcoRV-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 69) and amino acid (SEQ.ID.NO.: 70) sequences for human CEPR were thereafter determined and verified.

25. EBI1 (GenBank Accession Number: L31581)

[0092] The cDNA for human EBI1 was generated and cloned into pCMV expression vector as follows: PCR was performed using thymus cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 62°C for 1min; and 72 °C for 1 min and 20 sec. The 5' PCR primer contained an EcoRI site with the sequence:

5'-ACAGAATTCCTGTGTGGTTTTACCGCCCAG-3' (SEQ.ID.NO.: 71)

and the 3' primer contained a BamHI site with the sequence:

5'-CTCGGATCCAGGCAGAAGAGTCGCCTATGG-3' (SEQ.ID.NO.: 72).

The 1.2 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site of PCMV expression vector. Nucleic acid (SEQ.ID.NO.: 73) and amino acid (SEQ.ID.NO.: 74) sequences for human EBI1 were thereafter determined and verified.

26. EBI2 (GenBank Accession Number: L08177)

[0093] The cDNA for human EBI2 was generated and cloned into pCMV expression vector as follows: PCR was performed using cDNA clone (graciously provided by Kevin Lynch, University of Virginia Health Sciences Center; the vector utilized was not identified by the source) as template and pfu polymerase (Stratagene) with the buffer system provided by the manufacturer supplemented with 10% DMSO, 0.25 μM of each primer, and 0.5 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 60°C for 1min; and 72°C for 1 min and 20 sec. The 5' PCR primer contained an EcoRI site with the sequence:

5'-CTGGAATTCACCTGGACCACCACCAATGGATA-3' (SEQ.ID.NO.: 75)

and the 3' primer contained a BamHI site with the sequence

5'-CTCGGATCCTGCAAAGTTTGTCATACAG TT-3' (SEQ.ID.NO.: 76).

The 1.2 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BarnHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 77) and amino acid (SEQ.ID.NO.: 78) sequences for human EBI2 were thereafter determined and verified.

27. ETBR-LP2 (GenBank Accession Number: D38449)

[0094] The cDNA for human ETBR-LP2 was generated and cloned into pCMV expression vector as follows: PCR was performed using brain cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of:

94°C for 1 min; 65°C for 1min; and 72 °C for 1.5 min. The 5' PCR contained an EcoRI site with the sequence:

5'-CTGGAATTCTCCTGCTCATCCAGCCATGCGG -3' (SEQ.ID.NO.: 79)

and the 3' primer contained a BamHI site with the sequence:

5'-CCTGGATCCCCACCCCTACTGGGGCCTCAG -3' (SEQ.ID.NO.: 80).

The 1.5 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 81) and amino acid (SEQ.ID.NO.: 82) sequences for human ETBR-LP2 were thereafter determined and verified.

28. GHSR (GenBank Accession Number: U60179)

[0095] The cDNA for human GHSR was generated and cloned into pCMV expression vector as follows: PCR was performed using hippocampus cDNA as template and TaqPlus Precision polymerase (Stratagene) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 68°C for 1 min; and 72 °C for 1 min and 10 sec. For first round PCR, the 5' PCR primer sequence was:

5'-ATGTGGAACGCGACGCCCAGCG-3' (SEQ.ID.NO.: 83)

and the 3' primer sequence was:

5'-TCATGTATTAATACTAGATTCT-3' (SEQ.ID.NO.: 84).

Two microliters of the first round PCR was used as template for the second round PCR where the 5' primer was kinased with sequence:

5'-TACCATGTGGAACGCGACGCCCAGCGAAGAGCCGGGGT-3'(SEQ.ID.NO.:85)

and the 3' primer contained an EcoRI site with the sequence:

5'-CGGAATTCATGTATTAATACTAGATTCTGTCCAGGCCCG-3'(SEQ.ID.NO.:86).

The 1.1 kb PCR fragment was digested with EcoRI and cloned into blunt-EcoRI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 87) and amino acid (SEQ.ID.NO.: 88) sequences for human GHSR were thereafter determined and verified.

29. GPCR-CNS (GenBank Accession Number: AFO17262)

[0096] The cDNA for human GPCR-CNS was generated and cloned into pCMV expression vector as follows: PCR was performed using brain cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 65°C for 1min; and 72°C for 2 min. The 5' PCR primer contained a HindIII site with the sequence:

5'-GCAAGCTTGTGCCCTCACCAAGCCATGCGAGCC-3' (SEQ.ID.NO.: 89)

and the 3' primer contained an EcoRI site with the sequence:

5'-CGGAATTCAGCAATGAGTTCCGACAGAAGC-3' (SEQ.ID.NO.: 90).

The 1.9 kb PCR fragment was digested with HindIII and EcoRI and cloned into HindIII-EcoRI site of pCMV expression vector. All nine clones sequenced contained a potential polymorphism involving a S284C change. Aside from this difference, nucleic acid (SEQ.ID.NO.: 91) and amino acid (SEQ.ID.NO.: 92) sequences for human GPCR-CNS were thereafter determined and verified.

30. GPR-NGA (GenBank Accession Number: U55312)

[0097] The cDNA for human GPR-NGA was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 56°C for 1 min and 72°C for 1.5 min. The 5' PCR primer contained an EcoRI site with the sequence:

5'-CAGAATTCAGAGAAAAAAAGTGAATATGGTTTTT-3' (SEQ.ID.NO.: 93)

and the 3' primer contained a BamHI site with the sequence:

5'-TTGGATCCCTGGTGCATAACAATTGAAAGAAT-3' (SEQ.ID.NO.: 94).

The 1.3 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 95) and amino acid (SEQ.ID.NO.: 96) sequences for human GPR-NGA were thereafter determined and verified.

31. H9 (GenBank Accession Number: U52219)

[0098] The cDNA for human HB954 was generated and cloned into pCMV expression vector as follows: PCR was performed using pituitary cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min, 62°C for 1min and 72 °C for 2 min. The 5' PCR primer contains a HindIII site with the sequence:

5'-GGAAAGCTTAACGATCCCCAGGAGCAACAT-3' (SEQ.ID.NO.: 97)

and the 3' primer contains a BamHI site with the sequence:

5'-CTGGGATCCTACGAGAGCATTTTTCACACAG-3' (SEQ.ID.NO.: 98).

The 1.9 kb PCR fragment was digested with HindIII and BamHI and cloned into HindIII-BamHI site of pCMV expression vector. When compared to the published sequences, a different isoform with 12 bp in frame insertion in the cytoplasmic tail was also identified and designated "H9b." Both isoforms contain two potential polymorphisms involving changes of amino acid P320S and amino acid G448A. Isoform H9a contained another potential polymorphism of amino acid S493N, while isoform H9b contained two additional potential polymorphisms involving changes of amino acid 1502T and amino

acid A532T (corresponding to amino acid 528 of isoform H9a). Nucleic acid (SEQ.ID.NO.: 99) and amino acid (SEQ.ID.NO.: 100) sequences for human H9 were thereafter determined and verified (in the section below, both isoforms were mutated in accordance with the Human GPCR Proline Marker Algorithm).

32. HB954 (GenBank Accession Number: D38449)

[0099] The cDNA for human HB954 was generated and cloned into pCMV expression vector as follows: PCR was performed using brain cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0 25 μM of each primer, and 02 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 58°C for 1 min and 72°C for 2 min. The 5' PCR contained a HindIII site with the sequence:

5'-TCCAAGCTTCGCCATGGGACATAACGGGAGCT -3' (SEQ.ID.NO.: 101)

and the 3' primer contained an EcoRI site with the sequence:

5'-CGTGAATTCCAAGAATTTACAATCCTTGCT -3' (SEQ.ID.NO.: 102).

The 1.6 kb PCR fragment was digested with HindIII and EcoRI and cloned into HindIII-EcoRI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 103) and amino acid (SEQ.ID.NO.: 104) sequences for human HB954 were thereafter determined and verified.

33. HG38 (GenBank Accession Number: AF062006)

[0100] The cDNA for human HG38 was generated and cloned into pCMV expression vector as follows: PCR was performed using brain cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 56°C for 1min and 72 °C for 1 min and 30 sec. Two PCR reactions were performed to separately obtain the 5' and 3' fragment. For the 5' fragment, the 5' PCR primer contained an HindIII site with the sequence:

5'-CCCAAGCTTCGGGCACCATGGACACCTCCC-3' (SEQ.ID.NO.: 259)

and the 3' primer contained a BamHIsite with the sequence:

5'-ACAGGATCCAAATGCACAGCACTGGTAAGC-3' (SEQ.ID.NO.: 260).

This 5' 1.5 kb PCR fragment was digested with HindIII and BamHI and cloned into an HindIII-BamHI site of pCMV. For the 3' fragment, the 5' PCR primer was kinased with the sequence: 5'-CTATAACTGGGTIACATGGTTTAAC-3' (SEQ.ID.NO. 261) and the 3' primer contained an EcoRI site with the sequence:

5'-TTTGAATTCACATATTAATTAGAGACATGG-3' (SEQ.ID.NO.: 262).

The 1.4 kb 3' PCR fragment was digested with EcoRI and subcloned into a blunt-EcoRI site of pCMV vector. The 5' and 3' fragments were then ligated together through a common EcoR V site to generate the full length cDNA clone. Nucleic acid (SEQ.ID.NO.: 263) and amino acid (SEQ.ID.NO.: 264) sequences for human HG38 were thereafter determined and verified.

34. HM74 (GenBank Accession Number: D10923)

[0101] The cDNA for human HM74 was generated and cloned into pCMV expression vector as follows: PCR was performed using either genomic DNA or thymus cDNA (pooled) as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 65°C for 1 min; and 72°C for 1 min and 20 sec. The 5' PCR primer contained an EcoRI site with the sequence:

5'-GGAGAATTCACTAGGCGAGGCGCTCCATC-3' (SEQ.ID.NO.: 105)

and the 3' primer was kinased with the sequence:

5'-GGAGGATCCAGGAAACCTTAGGCCGAGTCC-3' (SEQ.ID.NO.:106).

The 1.3 kb PCR fragment was digested with EcoRI and cloned into EcoRI-SmaI site of pCMV expression vector. Clones sequenced revealed a potential polymorphism involving a N94K change. Aside from this difference, nucleic acid (SEQ.ID.NO.: 107) and amino acid (SEQ.ID.NO.: 108) sequences for human HM74 were thereafter determined and verified.

35. MIG (GenBank Accession Numbers: AF044600 and AFO44601)

[0102] The cDNA for human MIG was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and TaqPlus Precision polymerase (Stratagene) for first round PCR or pfu polymerase (Stratagene) for second round PCR with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM (TaqPlus Precision) or 0.5 mM (pfu) of each of the 4 nucleotides. When pfu was used, 10% DMSO was included in the buffer. The cycle condition was 30 cycles of: 94°C for 1 min; 65°C for 1min; and 72 °C for: (a) 1 min for first round PCR; and (b) 2 min for second round PCR. Because there is an intron in the coding region, two sets of primers were separately used to generate overlapping 5' and 3' fragments. The 5' fragment PCR primers were:

5'-ACCATGGCTTGCAATGGCAGTGCGGCCAGGGGGCACT-3' (external sense)

(SEQ.ID.NO.: 109)

and

5'-CGACCAGGACAAACAGCATCTTGGTCACTTGTCTCCGGC-3'(internal antisense)

(SEQ.ID.NO.: 110).

[0103] The 3' fragment PCR primers were:

5'-GACCAAGATGCTGTTTGTCCTGGTCGTGGTGTTTGGCAT-3' (internal sense)

(SEQ.ID.NO.: 111)

and

5'-CGGAATTCAGGATGGATCGGTCTCTTGCTGCGCCT-3' (external antisense with an EcoRI site) (SEQ.ID.NO.: 112).

The 5' and 3' fragments were ligated together by using the first round PCR as template and the kinased external sense primer and external antisense primer to perform second round PCR. The 1.2 kb PCR fragment was digested with EcoRI and cloned into the blunt-EcoRI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 113) and amino acid (SEQ. 1D.NO.: 114) sequences for human MIG were thereafter determined and verified.

36. OGR1 (GenBank Accession Number: U48405)

[0104] The cDNA for human OGR1 was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 65°C for 1min; and 72 °C for 1 min and 20 sec. The 5' PCR primer was kinased with the sequence:

5'-GGAAGCTTCAGGCCCAAAGATGGGGAACAT-3' (SEQ.ID.NO.: 115):

and the 3' primer contained a BamHI site with the sequence:

5'-GTGGATCCACCCGCGGAGGACCCAGGCTAG -3' (SEQ.ID.NO.: 116).

The 1.1 kb PCR fragment was digested with BamHI and cloned into the EcoRV-BamHI site ofpCMV expression vector. Nucleic acid (SEQ.ID.NO.: 117) and amino acid (SEQ.ID.NO.: 118) sequences for human OGR1 were thereafter determined and verified.

37. Serotonin $5HT_{2A}$

[0105] The cDNA encoding endogenous human $5HT_{2A}$ receptor was obtained by RT-PCR using human brain poly-A^+ RNA; a 5' primer from the 5' untranslated region with an Xho I restriction site:

5'-GACCTCGAGTCCTTCTACACCTCATC-3' (SEQ.ID.NO: 119)

and a 3' primer from the 3' untranslated region containing an Xba I site:

5'-TGCTCTAGATTCCAGATAGGTGAAAACTTG-3' (SEQ.ID.NO: 120)

PCR was performed using either TaqPlus™ precision polymerase (Stratagene) or rTth™ polymerase (Perkin Elmer) with the buffer system provided by the manufacturers, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 57 °C for 1min; and 72°C for 2 min. The 1.5 kb PCR fragment was digested with Xba 1 and subcloned into Eco RV-Xba 1 site of pBluescript. The resulting cDNA clones were fully sequenced and found to encode two amino acid changes from the published sequences. The first one was a T25N mutation in the N-terminal extracellular domain; the second is an H452Y mutation. Because cDNA clones derived from two independent PCR reactions using Taq polymerase from two different commercial sources (TaqPlus™ from Stratagene and rTth™ Perkin Elmer) contained the same two mutations, these mutations are likely to represent sequence polymorphisms rather than PCR errors. With these exceptions, the nucleic acid (SEQ.ID.NO.: 121) and amino acid (SEQ.ID.NO.: 122) sequences for human $5HT_{2A}$ were thereafter determined and verified.

38. Serotonin $5HT_{2C}$

[0106] The cDNA encoding endogenous human $5HT_{2C}$ receptor was obtained from human brain poly-A^+ RNA by RT-PCR. The 5' and 3' primers were derived from the 5' and 3' untranslated regions and contained the following sequences:

5'-GACCTCGAGGTTGCTTAAGACTGAAGC-3' (SEQ.ID.NO.: 123)

5'-ATTTCTAGACATATGTAGCTTGTACCG-3' (SEQ.ID.NO.: 124)

Nucleic acid (SEQ.ID.NO.: 125) and amino acid (SEQ.ID.NO.: 126) sequences for human $5HT_{2C}$ were thereafter determined and verified.

39. V28 (GenBank Accession Number: U20350)

[0107] The cDNA for human V28 was generated and cloned into pCMV expression vector as follows: PCRwas performed using brain cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each of the 4 nucleotides. The cycle condition was 30 cycles of: 94°C for 1 min; 65°C for 1min; and 72 °C for 1 min and 20 sec. The 5' PCR primer contained a HindIII site with the sequence:

5'-GGTAAGCTTGGCAGTCCACGCCAGGCCTTC-3' (SEQ.ID.NO.: 127)

and the 3' primer contained an EcoRI site with the sequence:

5'-TCCGAATTCTCTGTAGACACAAGGCTTTGG-3' (SEQ.ID.NO.: 128)

The 1.1 kb PCR fragment was digested with HindIII and EcoRI and cloned into HindIII-EcoRI site ofpCMV expression vector. Nucleic acid (SEQ.ID.NO.:129) and amino acid (SEQ.ID.NO.: 130) sequences for human V28 were thereafter determined and verified.

Example 2

PREPARATION OF NON-ENDOGENOUS HUMAN GPCRS

1. Site-Direrted Mutagenesis

[0108] Mutagenesis based upon the Human GPCR Proline Marker approach disclosed herein was performed on the foregoing endogenous human GPCRs using Transformer Site-Directed Mutagenesis Kit (Clontech) according to the manufacturer instructions. For this mutagenesis approach, a Mutation Probe and a Selection Marker Probe (unless otherwise indicated, the probe of SEQ.ID.NO.: 132 was the same throughout) were utilized, and the sequences of these for the specified sequences are listed below in Table B (the parenthetical number is the SEQ. ID.NO.). For convenience, the codon mutation incorporated into the human GPCR is also noted, in standard form:

Table B

Receptor Identifier (Codon Mutation)	Mutation Probe Sequence (5'-3') (SEQ.ID.NO.)	Selection Marker Probe Sequence (5'-3') (SEQ.ID.NO.)
GPR1 (F245K)	GATCTCCAGTAGGCATAAGT GGACAATTCTGG (131)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAG (132)
GPR4 (K223A)	AGAAGGCCAAGATCGCGCGG CTGGCCCTCA (133)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR5 (V224K)	CGGCGCCACCGCACGAAAAA GCTCATCTTC	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT

	(134)	
GPR7 (T250K)	GCCAAGAAGCGGGTGAAGTT CCTGGTGGTGGCA (135)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR8 (T259K)	CAGGCGGAAGGTGAAAGTCC TGGTCCTCGT (136)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR9 (M254K)	CGGCGCCTGCGGGCCAAGCG GCTGGTGGTGGTG (137)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR9-6 (L241K)	CCAAGCACAAAGCCAAGAAA GTGACCATCAC (138)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR10 (F276K)	GCGCCGGCGCACCAAATGCT TGCTGGTGGT (139)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR15 (I240K)	CAAAAAGCTGAAGAAATCTA AGAAGATCATCTTTATTGTCG (140)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR17 (V234K)	CAAGACCAAGGCAAAACGCA TGATCGCCAT (141)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR18 (I231K)	GTCAAGGAGAAGTCCAAAAG GATCATCATC (142)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR20 (M240K)	CGCCGCGTGCGGGCCAAGCA GCTCCTGCTC (143)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR21 (A251K)	CCTGATAAGCGCTATAAAAT GGTCCTGTTTCGA (144)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR22 (F312K)	GAAAGACAAAAGAGAGTCA AGAGGATGTCTTTATTG (145)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR24 (T304K)	CGGAGAAAGAGGGTGAAAC GCACAGCCATCGCC (146)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR30 (L258K)	alternate approach; *see* below	alternate approach; *see* below
GPR31 (Q221K)	AAGCTTCAGCGGGCCAAGGC ACTGGTCACC (147)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR32 (K255A)	CATGCCAACCGGCCCGCGAG GCTGCTGCTGGT (279)	ACCAGCAGCAGCCTCGCGGG CCGGTTGGCATG (280)
GPR40 (A223K)	CGGAAGCTGCGGGCCAAATG GGTGGCCGGC (265)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR41	CAGAGGAGGGTGAAGGGGCT GTTGGCG	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT

(A223K)	(266)	
GPR43 (V221K)	GGCGGCGCCGAGCCAAGGGG CTGGCTGTGG (267)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
APJ (L247K)	alternate approach; *see* below	alternate approach; *see* below
BLR1 (V258K)	CAGCGGCAGAAGGCAAAAA GGGTGGCCATC (148)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
CEPR (L258K)	CGGCAGAAGGCGAAGCGCAT GATCCTCGCG (149)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
EBI1 (I262K)	GAGCGCAACAAGGCCAAAA AGGTGATCATC (150)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
EBI2 (L243K)	GGTGTAAACAAAAAGGCTAA AAACACAATTATTCTTATT (151)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
ETBR-LP2 (N358K)	GAGAGCCAGCTCAAGAGCAC CGTGGTG (152)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GHSR (V262K)	CCACAAGCAAACCAAGAAAA TGCTGGCTGT (153)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPCR-CNS (N491K)	CTAGAGAGTCAGATGAAGTG TACAGTAGTGGCAC (155)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
GPR-NGA (I275K)	CGGACAAAAGTGAAAACTAA AAAGATGTTCCTCATT (156)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
H9a and H9b (F236K)	GCTGAGGTTCGCAATAAACT AACCATGTTTGTG (157)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
HB954 (H265K)	GGGAGGCCGAGCTGAAAGCC ACCCTGCTC (158)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
HG38 (V765K)	GGGACTGCTCTATGAAAAAA CACATTGCCCTG (268)	CATCAAGTGTATCATGTGCC AAGTACGCCC (154)
HM74 (I230K)	CAAGATCAAGAGAGCCAAAA CCTTCATCATG (159)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
MIG (T273K)	CCGGAGACAAGTGAAGAAG ATGCTGTTTGTC (160)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
OGR1 (Q227K)	GCAAGGACCAGATCAAGCGG CTGGTGCTCA (161)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT
Serotonin $5HT_{2A}$ (C322K)	alternate approach; *see* below	alternate approach; *see* below
Serotonin $5HT_{2C}$ (S310K)	alternate approach; *see* below	alternate approach; *see* below

V28 (I230K)	CAAGAAAGCCAAAGCCAAG AAACTGATCCTTCTG (162)	CTCCTTCGGTCCTCCTATCGT TGTCAGAAGT

The non-endogenous human GPCRs were then sequenced and the derived and verified nucleic acid and amino acid sequences are listed in the accompanying "Sequence Listing" appendix to this patent document, as summarized in Table C below:

Table C

Mutated GPCR	Nucleic Acid Sequence Listing	Amino Acid Sequence Listing
GPR1 (F245K)	SEQ.ID.NO.: 163	SEQ.ID.NO.: 164
GPR4 (K223A)	SEQ.ID.NO.: 165	SEQ.ID.NO.: 166
GPR5 (V224K)	SEQ.ID.NO.: 167	SEQ.ID.NO.: 168
GPR7 (T250K)	SEQ.ID.NO.: 169	SEQ.ID.NO.: 170
GPR8 (T259K)	SEQ.ID.NO.: 171	SEQ.ID.NO.: 172
GPR9 (M254K)	SEQ.ID.NO.: 173	SEQ.ID.NO.: 174
GPR9-6 (L241K)	SEQ.ID.NO.: 175	SEQ.ID.NO.: 176
GPR10 (F276K)	SEQ.ID.NO.: 177	SEQ.ID.NO.: 178
GPR15 (I240K)	SEQ.ID.NO.: 179	SEQ.ID.NO.: 180
GPR17 (V234K)	SEQ.ID.NO.: 181	SEQ.ID.NO.: 182
GPR18 (I231K)	SEQ.ID.NO.: 183	SEQ.ID.NO.: 184
GPR20 (M240K)	SEQ.ID.NO.: 185	SEQ.ID.NO.: 186
GPR21 (A251K)	SEQ.ID.NO.: 187	SEQ.ID.NO.: 188
GPR22 (F312K)	SEQ.ID.NO.: 189	SEQ.ID.NO.: 190
GPR24 (T304K))	SEQ.ID.NO.: 191	SEQ.ID.NO.: 192
GPR30	SEQ.ID.NO.: 193	SEQ.ID.NO.: 194
(L258K)		
GPR31 (Q221K)	SEQ.ID.NO.: 195	SEQ.ID.NO.: 196
GPR32	SEQ.ID.NO.: 269	SEQ.ID.NO.: 270

(continued)

Mutated GPCR	Nucleic Acid Sequence Listing	Amino Acid Sequence Listing
(K255A)		
GPR40 (A223K)	SEQ.ID.NO.: 271	SEQ.ID.NO.: 272
GPR41 (A223K)	SEQ.ID.NO.: 273	SEQ.ID.NO.: 274
GPR43 (V221K)	SEQ.ID.NO.: 275	SEQ.ID.NO.: 276
APJ (L247K)	SEQ.ID.NO.: 197	SEQ.ID.NO.: 198
BLR1 (V258K)	SEQ.ID.NO.: 199	SEQ.ID.NO.: 200
CEPR (L258K)	SEQ.ID.NO.: 201	SEQ.ID.NO.: 202
EBII (I262K)	SEQ.ID.NO.: 203	SEQ.ID.NO.: 204
EBI2 (L243K)	SEQ.ID.NO.: 205	SEQ.ID.NO.: 206
ETBR-LP2 (N358K)	SEQ.ID.NO.: 207	SEQ.ID.NO.: 208
GHSR (V262K)	SEQ.ID.NO.: 209	SEQ.ID.NO.: 210
GPCR-CNS (N491K)	SEQ.ID.NO.: 211	SEQ.ID.NO.: 212
GPR-NGA (I275K)	SEQ.ID.NO.: 213	SEQ.ID.NO.: 214
H9a (F236K)	SEQ.ID.NO.: 215	SEQ.ID.NO.: 216
H9b (F236K)	SEQ.ID.NO.: 217	SEQ.ID.NO.: 218
HB954 (H265K)	SEQ.ID.NO.: 219	SEQ.ID.NO.: 220
HG38 (V765K)	SEQ.ID.NO.: 277	SEQ.ID.NO.: 278
HM74 (I230K)	SEQ.ID.NO.: 221	SEQ.ID.NO.: 222
MIG (T273K)	SEQ.ID.NO.: 223	SEQ.ID.NO.: 224
OGR1 (Q227K)	SEQ.ID.NO.: 225	SEQ.ID.NO.: 226
Serotonin $5HT_{2A}$ (C322K)	SEQ.ID.NO.: 227	SEQ.ID.NO.: 228
Serotonin $5HT_{2C}$ (S310K)	SEQ.ID.NO.: 229	SEQ.ID.NO.: 230

(continued)

Mutated GPCR	Nucleic Acid Sequence Listing	Amino Acid Sequence Listing
V28 (I230K)	SEQ.ID.NO.: 231	SEQ.ID.NO.: 232

2. Alternate Mutation Approaches for Employment of the Proline Marker Algorithm: APJ; Serotonin $5HT_{2A}$; Serotonin $5HT_{2C}$; and GPR30

[0109] Although the above site-directed mutagenesis approach is particularly preferred, other approaches can be utilized to create such mutations; those skilled in the art are readily credited with selecting approaches to mutating a GPCR that fits within the particular needs of the artisan.

α***. APJ***

[0110] Preparation of the non-endogenous, human APJ receptor was accomplished by mutating L247K. Two oligonucleotides containing this mutation were synthesized:

5'- GGCTTAAGAGCATCATCGTGGTGCTGGTG-3' (SEQ.ID.NO.: 233)

5'-GTCACCACCAGCACCACGATGATGCTCTTAAGCC-3' (SEQ.ID.NO.: 234)

The two oligonucleotides were annealed and used to replace the NaeI-BstEII fragment of human, endogenous APJ to generate the non-endogenous, version of human APJ.

b. Serotonin $5HT_{2A}$

[0111] cDNA containing the point mutation C322K was constructed by utilizing the restriction enzyme site Sph I which encompasses amino acid 322. A primer containing the C322K mutation:

5'-CAAAGAAAGTACTGGGCATCGTCTTCTTCCT-3' (SEQ.ID.NO: 235)

was used along with the primer from the 3' untranslated region of the receptor:

5'-TGCTCTAGATTCCAGATAGGTGAAAA CTTG-3' (SEQ.ID.NO.: 236)

to perform PCR (under the conditions described above). The resulting PCR fragment was then used to replace the 3' end of endogenous $5HT_{2A}$ cDNA through the T4 polymerase blunted Sph I site.

c. Serotonin $5HT_{2C}$

[0112] The cDNA containing a S310K mutation was constructed by replacing the Sty I restriction fragment containing amino acid 310 with synthetic double stranded oligonucleotides that encode the desired mutation. The sense strand sequence utilized had the following sequence:

5'-CTAGGGGCACCATGCAGGCTATCAACAATGAAAGAAAAGCTAAGAAAGTC-3'

(SEQ. ID.NO.: 237)

and the antisense strand sequence utilized had the following sequence:

5'-CAAGGACTTTCTTAGCTTTTCTTTCATTGTTGATAGCCTGCATGGTGCCC-3' (SEQ. ID. NO.: 238)

d. GPR30

[0113] Prior to generating non-endogenous GPR30, several independentpCR2.1/GPR30 isolates were sequenced in their entirety in order to identify clones with no PCR-generated mutations. A clone having no mutations was digested with EcoR1 and the endogenous GPR30 cDNA fragment was transferred into the CMV-driven expression plasmid pCI-neo (Promega), by digesting pCI-Neo with EcoRI and subcloning the EcoRI-liberated GPR30 fragment from pCR2.1/GPR30, to generate pCI/GPR30. Thereafter, the leucine at codon 258 was mutated to a lysine using a QuickChange™ Site-Directed Mutagenesis Kit (Stratagene, #200518), according to manufacturer's instructions, and the following primers:

5'-CGGCGGCAGAAGGCGAAACGCATGATCCTCGCGGT-3' (SEQ.ID.NO.: 239)

and

5'-ACCGCGAGGATCATGCGTTTCGCCTTCTGC CGCCG-3' (SEQ.ID.NO.: 240)

Example 3

Receptor (Endogenous and Mutated) Expression

[0114] Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary pathways that have evolved for mammalian systems - thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan.

[0115] Unless otherwise noted herein, the following protocol was utilized for the expression of the endogenous and non-endogenous human GPCRs. Table D lists the mammalian cell and number utilized (per 150mm plate) for GPCR expression.

Table D

Receptor Name (Endogenous or Non-Endogenous)	Mammalian Cell (Number Utilized)
GPR17	293 (2 x 10^4)
GPR30	293 (4 x 10^4)
APJ	COS-7 (5X10^6)
ETBR-LP2	293 (1 x 10^7)

(continued)

Receptor Name (Endogenous or Non-Endogenous)	Mammalian Cell (Number Utilized)
	293T (1 x 10^7)
GHSR	293 (1 x 10^7) 293T (1 x 10^7)
MIG	293 (1 x 10^7)
Serotonin $5HT_{2A}$	293T (1 x 10^7)
Serotonin $5HT_{2c}$	293T (1 x 10^7)

[0116] On day one, mammalian cells were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 20μg DNA (*e.g.*, pCMV vector; pCMV vector with endogenous receptor cDNA, and pCMV vector with non-endogenous receptor cDNA.) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B was prepared by mixing 120μl lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B were then admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated cells were washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4ml of the transfection mixture was then added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture was then removed by aspiration, followed by the addition of 25ml of DMEM/ 10% Fetal Bovine Serum. Cells were then incubated at 37°C/5% CO_2. After 72hr incubation, cells were then harvested and utilized for analysis.

1. Gi-Coupled Receptors: Co-Transfection with Gs-Coupled Receptors

[0117] In the case of GPR30, it has been determined that this receptor couples the G protein Gi. Gi is known to inhibit the enzyme adenylyl cyclase, which is necessary for catalyzing the conversion of ATP to cAMP. Thus, a non-endogenous, constitutively activated form of GPR30 would be expected to be associated with decreased levels of cAMP. Assay confirmation of a non-endogenous, constitutively activated form of GPR30 directly viameasurement of decreasing levels of cAMP, while viable, can be preferably measured by cooperative use of a Gs-coupled receptor. For example, a receptor that is Gs-coupled will stimulate adenylyl cyclase, and thus will be associated with an increase in cAMP. The assignee of the present application has discovered that the orphan receptor GPR6 is an endogenous, constitutively activated GPCR. GPR6 couples to the Gs protein. Thus when co-transfected, one can readily verify that a putative GPR30-mutation leads to constitutive activation thereof: *i.e.,* an endogenous, constitutively activated GPR6/endogenous, non-constitutively activated GPR30 cell will evidence an elevated level of cAMP when compared with an endogenous, constitutively active GPR6/non-endogenous, constitutively activated GPR30 (the latter evidencing a comparatively lower level of cAMP). Assays that detect cAMP can be utilized to determine if a candidate compound is *e.g.*, an inverse agonist to a Gs-associated receptor (*i. e.,* such a compound would decrease the levels of cAMP) or a Gi-associated receptor (or a Go-associated receptor) (*i.e.*, such a candidate compound would increase the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a preferred approach relies upon the use of anti-cAMP antibodies. Another approach, and most preferred, utilizes a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription factor (CREB) which then binds to the promoter at specific sites called cAMP response elements and drives the expression ofthe gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, *e.g.*, β-galactosidase or luciferase. Thus, an activated receptor such as GPR6 causes the accumulation of cAMP which then activates the gene and expression of the reporter protein. Most preferably, 293 cells are co-transfected with GPR6 (or another Gs-linked receptor) and GPR30 (or another Gi-linked receptor) plasmids, preferably in a 1:1 ratio, most preferably in a 1:4 ratio. Because GPR6 is an endogenous, constitutively active receptorthat stimulates the production of cAMP, GPR6 strongly activates the reporter gene and its expression. The reporter protein such as β-galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995). Co-transfection of endogenous, constitutively active GPR6 with endogenous, non-constitutively active GPR30 evidences an increase in the luciferase reporter protein. Conversely, co-transfection of endogenous, constitutively active GPR6 with non-endogenous, constitutively active GPR30 evidences a drastic decrease in expression of luciferase. Several reporter plasmids are known and available in the art for measuring a second messenger assay. It is considered well within the skilled artisan to determine an appropriate reporter plasmid for a particular gene expression based primarily upon the particular need of the artisan. Although a variety of cells are available for expression, mammalian cells are most preferred, and of these types, 293 cells are most preferred. 293 cells were transfected with the reporter plasmid pCRE-Luc/GPR6 and non-endogenous, constitutively

activated GPR30 using a Mammalian Transfection™ Kit (Stratagene, #200285) $CaPO_4$ precipitation protocol according to the manufacturer's instructions (*see,* 28 Genomics 347 (1995) for the published endogenous GPR6 sequence). The precipitate contained 400ng reporter, 80ng CMV-expression plasmid (having a 1:4 GPR6 to endogenous GPR30 or non-endogenous GPR30 ratio) and 20ng CMV-SEAP (a transfection control plasmid encoding secreted alkaline phosphatase). 50% of the precipitate was split into 3 wells of a 96-well tissue culture dish (containing $4X10^4$ cells/well); the remaining 50% was discarded. The following morning, the media was changed. 48 hr after the start of the transfection, cells were lysed and examined for luciferase activity using a Luclite™ Kit (Packard, Cat. # 6016911) and Trilux 1450 Microbeta™ liquid scintillation and luminescence counter (Wallac) as per the vendor's instructions. The data were analyzed using GraphPad Prism 2.0a (GraphPad Software Inc.).

[0118] With respect to GPR17, which has also been determined to be Gi-linked, a modification of the foregoing approach was utilized, based upon, *inter alia,* use of another Gs-linked endogenous receptor, GPR3 (*see* 23 Genomics 609 (1994) and 24 Genomics 391 (1994)). Most preferably, 293 cells are utilized. These cells were plated-out on 96 well plates at a density of 2×10^4 cells per well and were transfected using Lipofectamine Reagent (BRL) the following day according to manufacturer instructions. A DNA/lipid mixture was prepared for each 6-well transfection as follows: 260ng of plasmid DNA in 100μl of DMEM were gently mixed with 2μl of lipid in 100μl of DMEM (the 260ng of plasmid DNA consisted of 200ng of a 8xCRE-Luc reporterplasmid (*see* below), 50ng ofpCMV comprising endogenous receptor or non-endogenous receptor or pCMV alone, and 10ng of a GPRS expression plasmid (GPRS in pcDNA3 (Invitrogen)). The 8XCRE-Luc reporter plasmid was prepared as follows: vector SRIF-β-gal was obtained by cloning the rat somatostatin promoter (-71/+51) at BglV-HindIII site in the pβgal-Basic Vector (Clontech). Eight (8) copies of cAMP response element were obtained by PCR from an adenovirus template AdpCF126CCRE8 (*see* 7 Human Gene Therapy 1883 (1996)) and cloned into the SRIF-β-gal vector at the Kpn-BglV site, resulting in the 8xCRE-β-gal reporter vector. The 8xCRE-Luc reporter plasmid was generated by replacing the beta-galactosidase gene in the 8xCRE-β-gal reporter vector with the luciferase gene obtained from the pGL3-basic vector (Promega) at the HindIII-BamHI site. Following 30min. incubation at room temperature, the DNA/lipid mixture was diluted with 400 μl of DMEM and 100μl of the diluted mixture was added to each well. 100 μl of DMEM with 10% FCS were added to each well after a 4hr incubation in a cell culture incubator. The next morning the transfected cells were changed with 200 μl/well of DMEM with 10% FCS. Eight (8) hours later, the wells were changed to 100 μl /well of DMEM without phenol red, after one wash with PBS. Luciferase activity were measured the next day using the LucLite™ reporter gene assay kit (Packard) following manufacturer instructions and read on a 1450 MicroBeta™ scintillation and luminescence counter (Wallac).

[0119] Figure 4 evidences that constitutively active GPR30 inhibits GPR6-mediated activation of CRE-Luc reporter in 293 cells. Luciferase was measured at about 4.1 relative light units in the expression vector pCMV. Endogenous GPR30 expressed luciferase at about 8.5 relative light units, whereas the non-endogenous, constitutively active GPR30 (L258K), expressed luciferase at about 3.8 and 3.1 relative light units, respectively. Co-transfection of endogenous GPR6 with endogenous GPR30, at a 1:4 ratio, drastically increased luciferase expression to about 104.1 relative light units. Co-transfection of endogenous GPR6 with non-endogenous GPR30 (L258K), at the same ratio, drastically decreased the expression, which is evident at about 18.2 and 29.5 relative light units, respectively. Similar results were observed with respect to GPR17 with respect to co-transfection with GPR3, as set forth in Figure 5.

Example 3

ASSAYS FOR DETERMINATION OF CONSTITUTIVE ACTIVITY OF NON-ENDOGENOUS GPCRS

A. Membrane Binding Assays

1. [^{3S}S]GTPγS Assay

[0120] When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. Constitutively activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [^{35}S]GTPγS, can be utilized to demonstrate enhanced binding of [^{35}S] GTPγS to membranes expressing constitutively activated receptors. The advantage of using [^{35}S]GTPγS binding to measure constitutive activation is that: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

[0121] The assay utilizes the ability of G protein coupled receptors to stimulate [^{35}S]GTPγS binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to known, orphan and constitutively activated G protein-coupled receptors. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

The [^{35}S]GTPγS assay was incubated in 20 mM HEPES and between 1 and about 20mM $MgCl_2$ (this amount can be adjusted for optimization of results, although 20mM is preferred) pH 7.4, binding buffer with between about 0.3 and about 1.2 nM [^{35}S]GTPγS (this amount can be adjusted for optimization of results, although 1.2 is preferred) and 12.5 to 75 μg membrane protein (*e.g.* COS-7 cells expressing the receptor; this amount can be adjusted for optimization, although 75μg is preferred) and 1 μM GDP (this amount can be changed for optimization) for 1 hour. Wheatgerm agglutinin beads (25 μl; Amersham) were then added and the mixture was incubated for another 30 minutes at room temperature. The tubes were then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter.

[0122] A less costly but equally applicable alternative has been identified which also meets the needs of large scale screening. Flash plates™ and Wallac™ scintistrips may be utilized to format a high throughput [^{35}S]GTPγS binding assay. Furthermore, using this technique, the assay can be utilized for known GPCRs to simultaneously monitor tritiated ligand binding to the receptor at the same time as monitoring the efficacy via [^{35}S]GTPγS binding. This is possible because the Wallac beta counter can switch energy windows to look at both tritium and ^{35}S-1abeled probes. This assay may also be used to detect other types of membrane activation events resulting in receptor activation. For example, the assay may be used to monitor ^{32}P phosphorylation of a variety of receptors (both G protein coupled and tyrosine kinase receptors). When the membranes are centrifuged to the bottom of the well, the bound [^{35}S]GTPγS or the ^{32}P-phosphorylated receptor will activate the scintillant which is coated of the wells. Scinti® strips (Wallac) have been used to demonstrate this principle. In addition, the assay also has utility for measuring ligand binding to receptors using radioactively labeled ligands. In a similar manner, when the radiolabeled bound ligand is centrifuged to the bottom of the well, the scintistrip label comes into proximity with the radiolabeled ligand resulting in activation and detection.

[0123] Representative results of graph comparing Control (pCMV), Endogenous APJ and Non-Endogenous APJ, based upon the foregoing protocol, are set forth in Figure 6.

2. Adenylyl Cyclase

[0124] A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays was modified for use with crude plasma membranes. The Flash Plate wells contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells was quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in membranes that express the receptors.

[0125] Transfected cells were harvested approximately three days after transfection. Membranes were prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$. Homogenization was performed on ice using a Brinlanan Polytron™ for approximately 10 seconds. The resulting homogenate was centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet was then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet can be stored at -80°C until utilized. On the day of measurement, the membrane pellet was slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCL_2$ (these amounts can be optimized, although the values listed herein are prefereed), to yield a final protein concentration of 0.60mg/ml (the resuspended membranes were placed on ice until use).

[0126] cAMP standards and Detection Buffer (comprising 2 μCi of tracer [^{125}I cAMP (100 μl] to 11 ml Detection Buffer) were prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM $MgCl_2$, 20mM (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 μM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer can be stored on ice until utilized. The assay was initiated by addition of 50ul of assay buffer followed by addition of 50ul of membrane suspension to the NEN Flash Plate. The resultant assay mixture is incubated for 60 minutes at room temperature followed by addition of 100ul of detection buffer. Plates are then incubated an additional 2-4 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well are extrapolated from a standard cAMP curve which is contained within each assay plate. The foregoing assay was utilized with respect to analysis of MIG.

B. Reporter-Based Assays

1. CREB Reporter Assay (Gs-associated receptors)

[0127] A method to detect Gs stimulation depends on the known property of the transcription factor CREB, which is activated in a cAMP-dependent manner. A PathDetect CREB trans-Reporting System (Stratagene, Catalogue # 219010) was utilized to assay for Gs coupled activity in 293 or 293T cells. Cells were transfected with the plasmids components of this above system and the indicated expression plasmid encoding endogenous or mutant receptor using a Mammalian Transfection Kit (Stratagene, Catalogue #200285) according to the manufacurer's instructions. Briefly, 400 ng pFR-Luc (luciferase reporter plasmid containing Gal4 recognition sequences), 40 ng pFA2-CREB (Gal4-CREB fusion protein

containing the Gal4 DNA-binding domain), 80 ng CMV-receptor expression plasmid (comprising the receptor) and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) were combined in a calcium phosphate precipitate as per the Kit's instructions. Half of the precipitate was equally distributed over 3 wells in a 96-well plate, kept on the cells overnight, and replaced with fresh medium the following morning. Forty-eight (48) hr after the start of the transfection, cells were treated and assayed for luciferase activity as set forth with resepct to the GPR30 system, above. This assay was used with respect to GHSR.

2. AP1 reporter assay (Gq-associated receptors)

[0128] Ae method to detect Gq stimulation depends on the known property ofGq-dependent phospholipase C to cause the activation of genes containing AP 1 elements in their promoter. A Pathdetect AP-1 cis-Reporting System (Stratagene, Catalogue # 219073) was utilized following the protocl set forth above with respect to the CREB reporter assay, except that the components of the calcium phosphate precipitate were 410 ng pAP1-Luc, 80 ng receptor expression plasmid, and 20 ng CMV-SEAP. This assay was used with respect to ETBR-LP2

C. Intracellular IP3 Accumulation Assay

[0129] On day 1, cells comprising the serotonin receptors (endogenous and mutated) were plated onto 24 well plates, usually 1×10^5 cells/well. On day 2 cells were transfected by firstly mixing 0.25ug DNA in 50 ul serumfree DMEM/well and 2 ul lipofectamine in 50 μl serumfree DMEM/well. The solutions were gently mixed and incubated for 15-30 min at room temperature. Cells were washed with 0.5 ml PBS and 400 μl of serum free media was mixed with the transfection media and added to the cells. The cells were then incubated for 3-4 hrs at 37°C/5%CO_2 and then the transfection media was removed and replaced with 1ml/well of regular growth media. On day 3 the cells were labeled with ^{3}H-myo-inositol. Briefly, the media was removed the cells were washed with 0.5 ml PBS. Then 0.5 ml inositol-free/serumfree media (GIBCO BRL) was added/well with 0.25 μCi of ^{3}H-myo-inositol / well and the cells were incubated for 16-18 hrs o/n at 37°C/5%CO_2. On Day 4 the cells were washed with 0.5 ml PBS and 0.45 ml of assay medium was added containing inositol-free/serum free media 10 μM pargyline 10 mM lithium chloride or 0.4 ml of assay medium and 50 ul of 10x ketanserin (ket) to final concentration of 10μM. The cells were then incubated for 30 min at 37°C. The cells were then washed with 0.5 ml PBSand 200 ul of fresh/icecold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) was added/well. The solution was kept on ice for 5-10 min or until cells were lysed and then neutralized by 200 μl of fresh/ice cold neutralization sol. (7.5 % HCL). The lysate was then transferred into 1.5 ml eppendorf tubes and 1 ml of chloroform/methanol (1:2) was added/tube. The solution was vortexed for 15 sec and the upper phase was applied to a Biorad AG1-X8 anion exchange resin (100-200 mesh). Firstly, the resin was washed with water at 1:1.25 W/V and 0.9 ml of upper phase was loaded onto the column. The column was washed with 10 mls of 5 mM myo-inositol and 10 ml of 5 mM Na-borate/60mM Na-formate. The inositol tris phosphates were eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns were regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with dd H_2O and stored at 4°C in water.

[0130] Figure 7 provides an illustration ofIP3 production from the human 5-HT_{2A} receptor that incorporates the C322K mutation. While these results evidence that the Proline Mutation Algorithm approach constitutively activates this receptor, for purposes of using such a receptor for screening for identification of potential therapeutics, a more robust difference would be preferred. However, because the activated receptor can be utilized for understanding and elucidating the role of constitutive activation and for the identification of compounds that can be further examined, we believe that this difference is itself useful in differentiating between the endogenous and non-endogenous versions of the human $5HT_{2A}$ receptor.

D. Result Summary

[0131] The results for the GPCRs tested are set forth in Table E where the Per-Cent Increase indicates the percentage difference in results observed for the non-endogenous GPCR as compared to the endogenous GPCR; these values are followed by parenthetical indications as to the type of assay utilized. Additionally, the assay sytem utilized is parenthetically listed (and, in cases where different Host Cells were used, both are listed). As these results indicate, a variety of assays can be utilized to determine constitutive activity of the non-endogenous versions ofthe human GPCRs. Those skilled in the art, based upon the foregoing and with reference to information available to the art, are creditied with theability to selelect and/ot maximize a particular assay approach that suites the particualr needs of the investigator.

Table E

Receptor Identifier (Codon Mutation)	Per-Cent Difference
GPR17 (V234K)	74.5 (CRE-Luc)
GPR30 (L258K)	71.6 (CREB)
APJ (L247K)	49.0 (GTPγS)
ETBR-LP2 (N358K)	48.4(AP1-Luc - 293) 61.1(AP1-Luc – 293T)
GHSR (V262K)	58.9(CREB – 293) 35.6(CREB – 293T)
MIG (I230K)	39 (cAMP)
Serotonin $5HT_{2A}$ (C322K)	33.2 (IP_3)
Serotonin $5HT_{2C}$ (S310K)	39.1(IP_3)

Example 6

Tissue Distribution of Endogenous Orphan GPCRs

[0132] Using a commercially available human-tissue dot-blot format, endogenous orphan GPCRs were probed for a determination ofthe areas where such receptors are localized. Except as indicate below, the entire receptor cDNA (radiolabelled) was used as the probe: radiolabeled probe was generated using the complete receptor cDNA (excised from the vector) using a Prime-It II™ Random Primer Labeling Kit (Stratagene, #300385), according to manufacturer's instructions. A human RNA Master Blot™ (Clontech, #7770-1) was hybridized with the GPCR radiolabeled probe and washed under stringent conditions according manufacturer's instructions. The blot was exposed to Kodak BioMax Autoradiography film overnight at-80°C.

[0133] Representative dot-blot format results are presented in Figure 8 for GPR1 (8A), GPR30 (8B), and APJ (8C), with results being summarized for all receptors in Table F

Table F

GPCR	Tissue Distribution (highest levels, relative to other tissues in the dot-blot)
GPR1	Placenta, Ovary, Adrenal
GPR4	Broad; highest in Heart, Lung, Adrenal, Thyroid, Spinal Cord
GPR5	Placenta, Thymus, Fetal Thymus Lesser levels in spleen, fetal spleen
GPR7	Liver, Spleen, Spinal Cord, Placenta
GPR8	No expression detected
GPR9-6	Thymus, Fetal Thymus Lesser levels in Small Intestine
GPR18 .	Spleen, Lymph Node, Fetal Spleen, Testis
GPR20	Broad
GPR21	Broad; very low abundance
GPR22	Heart, Fetal Heart Lesser levels in Brain
GPR30	Stomach
GPR31	Broad
BLR1	Spleen
CEPR	Stomach, Liver, Thyroid, Putamen
EBI1	Pancreas Lesser levels in Lymphoid Tissues
EBI2	Lymphoid Tissues, Aorta, Lung, Spinal Cord
ETBR-LP2	Broad; Brain Tissue
GPCR-CNS	Brain Lesser levels in Testis, Placenta
GPR-NGA	Pituitary Lesser levels in Brain
H9	Pituitary
HB954	Aorta, Cerebellum Lesser levels in most other tissues
HM74	Spleen, Leukocytes, Bone marrow, Mammary Glands, Lung, Trachea
MIG	Low levels in Kidney, Liver, Pancreas, Lung, Spleen
ORG1	Pituitary, Stomach, Placenta
V28	Brain. Spleen, Peripheral Leukocytes

[0134] Based upon the foregoing information, it is noted that human GPCRs can also be assessed for distribution in diseased tissue; comparative assessments between "normal" and diseased tissue can then be utilized to determine the potential for over-expression or under-expression of a particular receptor in a diseased state. In those circumstances where it is desirable to utilize the non-endogenous versions of the human GPCRs for the purpose of screening to directly identify candidate compounds ofpotential therapeutic relevance, it is noted that inverse agonists are useful in the treatment of diseases and disorders where a particular human GPCR is over-expressed, whereas agonists or partial agonists are useful in the treatment of diseases and disorders where a particular human GPCR is under-expressed.

[0135] As desired, more detailed, cellular localization of the receptors, using techniques well-known to those in the art (*e.g.*, in-situ hybridization) can be utilized to identify particualr cells within these tissues where the receptor of interest is expressed.

[0136] As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the scope of the claims.

[0137] Although a variety of expression vectors are available to those in the art, for purposes of utilization for both the endogenous and non-endogenous human GPCRs, it is most preferred that the vector utilized be pCMV.

SEQUENCE LISTING

[0138]

(1) GENERAL INFORMATION:

(i) APPLICANT: Behan, Dominic P. Chalmers, Derek T. Liaw, Chen W.

(ii) TITLE OF INVENTION: Non-Endogenous, Constitutively Activated Human G Protein-Coupled Orphan Receptors

(iii) NUMBER OF SEQUENCES: 280

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Arena Pharmaceuticals, Inc.
(B) STREET: 6166 Nancy Ridge Drive
(C) CITY: San Diego
(D) STATE: CA
(E) COUNTRY: USA
(F) ZIP: 92122

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Burgoon, Richard P.
(B) REGISTRATION NUMBER: 34,787

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (619)453-7200
(B) TELEFAX: (619)453-7210

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1068 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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ATGGAAGATT TGGAGGAAAC ATTATTTGAA GAATTTGAAA ACTATTCCTA TGACCTAGAC     60

TATTACTCTC TGGAGTCTGA TTTGGAGGAG AAAGTCCAGC TGGGAGTTGT TCACTGGGTC    120

TCCCTGGTGT TATATTGTTT GGCTTTTGTT CTGGGAATTC CAGGAAATGC CATCGTCATT    180

TGGTTCACGG GGCTCAAGTG GAAGAAGACA GTCACCACTC TGTGGTTCCT CAATCTAGCC    240

ATTGCGGATT TCATTTTTCT TCTCTTTCTG CCCCTGTACA TCTCCTATGT GGCCATGAAT    300

TTCCACTGGC CCTTTGGCAT CTGGCTGTGC AAAGCCAATT CCTTCACTGC CCAGTTGAAC    360

ATGTTTGCCA GTGTTTTTTT CCTGACAGTG ATCAGCCTGG ACCACTATAT CCACTTGATC    420

CATCCTGTCT TATCTCATCG GCATCGAACC CTCAAGAACT CTCTGATTGT CATTATATTC    480

ATCTGGCTTT TGGCTTCTCT AATTGGCGGT CCTGCCCTGT ACTTCCGGGA CACTGTGGAG    540

TTCAATAATC ATACTCTTTG CTATAACAAT TTTCAGAAGC ATGATCCTGA CCTCACTTTG    600

ATCAGGCACC ATGTTCTGAC TTGGGTGAAA TTTATCATTG GCTATCTCTT CCCTTTGCTA    660

ACAATGAGTA TTTGCTACTT GTGTCTCATC TTCAAGGTGA AGAAGCGAAC AGTCCTGATC    720

TCCAGTAGGC ATTTCTGGAC AATTCTGGTT GTGGTTGTGG CCTTTGTGGT TTGCTGGACT    780

CCTTATCACC TGTTTAGCAT TTGGGAGCTC ACCATTCACC ACAATAGCTA TTCCCACCAT    840

GTGATGCAGG CTGGAATCCC CCTCTCCACT GGTTTGGCAT TCCTCAATAG TTGCTTGAAC    900

CCCATCCTTT ATGTCCTAAT TAGTAAGAAG TTCCAAGCTC GCTTCCGGTC CTCAGTTGCT    960

GAGATACTCA AGTACACACT GTGGGAAGTC AGCTGTTCTG GCACAGTGAG TGAACAGCTC   1020

AGGAACTCAG AAACCAAGAA TCTGTGTCTC CTGGAAACAG CTCAATAA                1068
```

(3) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 355 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Met Glu Asp Leu Glu Glu Thr Leu Phe Glu Glu Phe Glu Asn Tyr Ser
1               5                  10                  15

Tyr Asp Leu Asp Tyr Tyr Ser Leu Glu Ser Asp Leu Glu Glu Lys Val
            20                  25                  30

Gln Leu Gly Val Val His Trp Val Ser Leu Val Leu Tyr Cys Leu Ala
        35                  40                  45
```

```
Phe Val Leu Gly Ile Pro Gly Asn Ala Ile Val Ile Trp Phe Thr Gly
    50                  55                  60

Leu Lys Trp Lys Lys Thr Val Thr Thr Leu Trp Phe Leu Asn Leu Ala
65                  70                  75                  80

Ile Ala Asp Phe Ile Phe Leu Leu Phe Leu Pro Leu Tyr Ile Ser Tyr
                85                  90                  95

Val Ala Met Asn Phe His Trp Pro Phe Gly Ile Trp Leu Cys Lys Ala
            100                 105                 110

Asn Ser Phe Thr Ala Gln Leu Asn Met Phe Ala Ser Val Phe Phe Leu
        115                 120                 125

Thr Val Ile Ser Leu Asp His Tyr Ile His Leu Ile His Pro Val Leu
    130                 135                 140

Ser His Arg His Arg Thr Leu Lys Asn Ser Leu Ile Val Ile Ile Phe
145                 150                 155                 160

Ile Trp Leu Leu Ala Ser Leu Ile Gly Gly Pro Ala Leu Tyr Phe Arg
                165                 170                 175

Asp Thr Val Glu Phe Asn Asn His Thr Leu Cys Tyr Asn Asn Phe Gln
            180                 185                 190

Lys His Asp Pro Asp Leu Thr Leu Ile Arg His His Val Leu Thr Trp
        195                 200                 205

Val Lys Phe Ile Ile Gly Tyr Leu Phe Pro Leu Leu Thr Met Ser Ile
    210                 215                 220

Cys Tyr Leu Cys Leu Ile Phe Lys Val Lys Lys Arg Thr Val Leu Ile
225                 230                 235                 240

Ser Ser Arg His Phe Trp Thr Ile Leu Val Val Val Val Ala Phe Val
                245                 250                 255

Val Cys Trp Thr Pro Tyr His Leu Phe Ser Ile Trp Glu Leu Thr Ile
            260                 265                 270

His His Asn Ser Tyr Ser His His Val Met Gln Ala Gly Ile Pro Leu
        275                 280                 285

Ser Thr Gly Leu Ala Phe Leu Asn Ser Cys Leu Asn Pro Ile Leu Tyr
    290                 295                 300

Val Leu Ile Ser Lys Lys Phe Gln Ala Arg Phe Arg Ser Ser Val Ala
305                 310                 315                 320

Glu Ile Leu Lys Tyr Thr Leu Trp Glu Val Ser Cys Ser Gly Thr Val
                325                 330                 335

Ser Glu Gln Leu Arg Asn Ser Glu Thr Lys Asn Leu Cys Leu Leu Glu
```

340 345 350

Thr Ala Gln
355

(4) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1089 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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ATGGGCAACC ACACGTGGGA GGGCTGCCAC GTGGACTCGC GCGTGGACCA CCTCTTTCCG   60
CCATCCCTCT ACATCTTTGT CATCGGCGTG GGGCTGCCCA CCAACTGCCT GGCTCTGTGG  120
GCGGCCTACC GCCAGGTGCA ACAGCGCAAC GAGCTGGGCG TCTACCTGAT GAACCTCAGC  180
ATCGCCGACC TGCTGTACAT CTGCACGCTG CCGCTGTGGG TGGACTACTT CCTGCACCAC  240
GACAACTGGA TCCACGGCCC CGGGTCCTGC AAGCTCTTTG GGTTCATCTT CTACACCAAT  300
ATCTACATCA GCATCGCCTT CCTGTGCTGC ATCTCGGTGG ACCGCTACCT GGCTGTGGCC  360
CACCCACTCC GCTTCGCCCG CCTGCGCCGC GTCAAGACCG CCGTGGCCGT GAGCTCCGTG  420
GTCTGGGCCA CGGAGCTGGG CGCCAACTCG GCGCCCCTGT TCCATGACGA GCTCTTCCGA  480
GACCGCTACA ACCACACCTT CTGCTTTGAG AAGTTCCCCA TGGAAGGCTG GGTGGCCTGG  540
ATGAACCTCT ATCGGGTGTT CGTGGGCTTC CTCTTCCCGT GGGCGCTCAT GCTGCTGTCG  600
TACCGGGGCA TCCTGCGGGC CGTGCGGGGC AGCGTGTCCA CCGAGCGCCA GGAGAAGGCC  660
AAGATCAAGC GGCTGGCCCT CAGCCTCATC GCCATCGTGC TGGTCTGCTT TGCGCCCTAT  720
CACGTGCTCT TGCTGTCCCG CAGCGCCATC TACCTGGGCC GCCCCTGGGA CTGCGGCTTC  780
GAGGAGCGCG TCTTTTCTGC ATACCACAGC TCACTGGCTT TCACCAGCCT CAACTGTGTG  840
GCGGACCCCA TCCTCTACTG CCTGGTCAAC GAGGGCGCCC GCAGCGATGT GGCCAAGGCC  900
CTGCACAACC TGCTCCGCTT TCTGGCCAGC GACAAGCCCC AGGAGATGGC CAATGCCTCG  960
CTCACCCTGG AGACCCCACT CACCTCCAAG AGGAACAGCA CAGCCAAAGC CATGACTGGC 1020
AGCTGGGCGG CCACTCCGCC TTCCCAGGGG GACCAGGTGC AGCTGAAGAT GCTGCCGCCA 1080
GCACAATGA                                                         1089
```

(5) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 362 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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Met Gly Asn His Thr Trp Glu Gly Cys His Val Asp Ser Arg Val Asp
1               5                  10                  15

His Leu Phe Pro Pro Ser Leu Tyr Ile Phe Val Ile Gly Val Gly Leu
            20                  25                  30

Pro Thr Asn Cys Leu Ala Leu Trp Ala Ala Tyr Arg Gln Val Gln Gln
        35                  40                  45

Arg Asn Glu Leu Gly Val Tyr Leu Met Asn Leu Ser Ile Ala Asp Leu
    50                  55                  60

Leu Tyr Ile Cys Thr Leu Pro Leu Trp Val Asp Tyr Phe Leu His His
65                  70                  75                  80

Asp Asn Trp Ile His Gly Pro Gly Ser Cys Lys Leu Phe Gly Phe Ile
                85                  90                  95

Phe Tyr Thr Asn Ile Tyr Ile Ser Ile Ala Phe Leu Cys Cys Ile Ser
            100                 105                 110

Val Asp Arg Tyr Leu Ala Val Ala His Pro Leu Arg Phe Ala Arg Leu
        115                 120                 125

Arg Arg Val Lys Thr Ala Val Ala Val Ser Ser Val Val Trp Ala Thr
    130                 135                 140

Glu Leu Gly Ala Asn Ser Ala Pro Leu Phe His Asp Glu Leu Phe Arg
145                 150                 155                 160

Asp Arg Tyr Asn His Thr Phe Cys Phe Glu Lys Phe Pro Met Glu Gly
                165                 170                 175

Trp Val Ala Trp Met Asn Leu Tyr Arg Val Phe Val Gly Phe Leu Phe
            180                 185                 190

Pro Trp Ala Leu Met Leu Leu Ser Tyr Arg Gly Ile Leu Arg Ala Val
        195                 200                 205

Arg Gly Ser Val Ser Thr Glu Arg Gln Glu Lys Ala Lys Ile Lys Arg
    210                 215                 220

Leu Ala Leu Ser Leu Ile Ala Ile Val Leu Val Cys Phe Ala Pro Tyr
```

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225                 230                 235                 240

His Val Leu Leu Leu Ser Arg Ser Ala Ile Tyr Leu Gly Arg Pro Trp
                245                 250                 255

Asp Cys Gly Phe Glu Glu Arg Val Phe Ser Ala Tyr His Ser Ser Leu
            260                 265                 270

Ala Phe Thr Ser Leu Asn Cys Val Ala Asp Pro Ile Leu Tyr Cys Leu
        275                 280                 285

Val Asn Glu Gly Ala Arg Ser Asp Val Ala Lys Ala Leu His Asn Leu
    290                 295                 300

Leu Arg Phe Leu Ala Ser Asp Lys Pro Gln Glu Met Ala Asn Ala Ser
305                 310                 315                 320

Leu Thr Leu Glu Thr Pro Leu Thr Ser Lys Arg Asn Ser Thr Ala Lys
                325                 330                 335

Ala Met Thr Gly Ser Trp Ala Ala Thr Pro Pro Ser Gln Gly Asp Gln
            340                 345                 350

Val Gln Leu Lys Met Leu Pro Pro Ala Gln
        355                 360
```

(6) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
TATGAATTCA GATGCTCTAA ACGTCCCTGC                                    30
```

(7) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TCCGGATCCA CCTGCACCTG CGCCTGCACC 30

(8) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1002 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

ATGGAGTCCT CAGGCAACCC AGAGAGCACC ACCTTTTTTT ACTATGACCT TCAGAGCCAG 60

CCGTGTGAGA ACCAGGCCTG GGTCTTTGCT ACCCTCGCCA CCACTGTCCT GTACTGCCTG 120

GTGTTTCTCC TCAGCCTAGT GGGCAACAGC CTGGTCCTGT GGGTCCTGGT GAAGTATGAG 180

AGCCTGGAGT CCCTCACCAA CATCTTCATC CTCAACCTGT GCCTCTCAGA CCTGGTGTTC 240

GCCTGCTTGT TGCCTGTGTG GATCTCCCCA TACCACTGGG GCTGGGTGCT GGGAGACTTC 300

CTCTGCAAAC TCCTCAATAT GATCTTCTCC ATCAGCCTCT ACAGCAGCAT CTTCTTCCTG 360

ACCATCATGA CCATCCACCG CTACCTGTCG GTAGTGAGCC CCCTCTCCAC CCTGCGCGTC 420

CCCACCCTCC GCTGCCGGGT GCTGGTGACC ATGGCTGTGT GGGTAGCCAG CATCCTGTCC 480

TCCATCCTCG ACACCATCTT CCACAAGGTG CTTTCTTCGG GCTGTGATTA TTCCGAACTC 540

ACGTGGTACC TCACCTCCGT CTACCAGCAC AACCTCTTCT TCCTGCTGTC CCTGGGGATT 600

ATCCTGTTCT GCTACGTGGA GATCCTCAGG ACCCTGTTCC GCTCACGCTC CAAGCGGCGC 660

CACCGCACGG TCAAGCTCAT CTTCGCCATC GTGGTGGCCT ACTTCCTCAG CTGGGGTCCC 720

TACAACTTCA CCCTGTTTCT GCAGACGCTG TTTCGGACCC AGATCATCCG GAGCTGCGAG 780

GCCAAACAGC AGCTAGAATA CGCCCTGCTC ATCTGCCGCA ACCTCGCCTT CTCCCACTGC 840

TGCTTTAACC CGGTGCTCTA TGTCTTCGTG GGGGTCAAGT TCCGCACACA CCTGAAACAT 900

GTTCTCCGGC AGTTCTGGTT CTGCCGGCTG CAGGCACCCA GCCCAGCCTC GATCCCCCAC 960

TCCCCTGGTG CCTTCGCCTA TGAGGGCGCC TCCTTCTACT GA 1002

(9) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 333 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

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Met Glu Ser Ser Gly Asn Pro Glu Ser Thr Thr Phe Phe Tyr Tyr Asp
1               5                  10                  15

Leu Gln Ser Gln Pro Cys Glu Asn Gln Ala Trp Val Phe Ala Thr Leu
            20                  25                  30

Ala Thr Thr Val Leu Tyr Cys Leu Val Phe Leu Leu Ser Leu Val Gly
        35                  40                  45

Asn Ser Leu Val Leu Trp Val Leu Val Lys Tyr Glu Ser Leu Glu Ser
    50                  55                  60

Leu Thr Asn Ile Phe Ile Leu Asn Leu Cys Leu Ser Asp Leu Val Phe
65                  70                  75                  80

Ala Cys Leu Leu Pro Val Trp Ile Ser Pro Tyr His Trp Gly Trp Val
                85                  90                  95

Leu Gly Asp Phe Leu Cys Lys Leu Leu Asn Met Ile Phe Ser Ile Ser
            100                 105                 110

Leu Tyr Ser Ser Ile Phe Phe Leu Thr Ile Met Thr Ile His Arg Tyr
        115                 120                 125

Leu Ser Val Val Ser Pro Leu Ser Thr Leu Arg Val Pro Thr Leu Arg
    130                 135                 140

Cys Arg Val Leu Val Thr Met Ala Val Trp Val Ala Ser Ile Leu Ser
145                 150                 155                 160

Ser Ile Leu Asp Thr Ile Phe His Lys Val Leu Ser Ser Gly Cys Asp
                165                 170                 175

Tyr Ser Glu Leu Thr Trp Tyr Leu Thr Ser Val Tyr Gln His Asn Leu
            180                 185                 190

Phe Phe Leu Leu Ser Leu Gly Ile Ile Leu Phe Cys Tyr Val Glu Ile
        195                 200                 205

Leu Arg Thr Leu Phe Arg Ser Arg Ser Lys Arg Arg His Arg Thr Val
    210                 215                 220

Lys Leu Ile Phe Ala Ile Val Val Ala Tyr Phe Leu Ser Trp Gly Pro
225                 230                 235                 240

Tyr Asn Phe Thr Leu Phe Leu Gln Thr Leu Phe Arg Thr Gln Ile Ile
                245                 250                 255

Arg Ser Cys Glu Ala Lys Gln Gln Leu Glu Tyr Ala Leu Leu Ile Cys
            260                 265                 270

Arg Asn Leu Ala Phe Ser His Cys Cys Phe Asn Pro Val Leu Tyr Val
        275                 280                 285
```

```
Phe Val Gly Val Lys Phe Arg Thr His Leu Lys His Val Leu Arg Gln
    290                 295                 300

Phe Trp Phe Cys Arg Leu Gln Ala Pro Ser Pro Ala Ser Ile Pro His
305                 310                 315                 320

Ser Pro Gly Ala Phe Ala Tyr Glu Gly Ala Ser Phe Tyr
                325                 330
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(10) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

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GCAAGCTTGG GGGACGCCAG GTCGCCGGCT                                    30
```

(11) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

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GCGGATCCGG ACGCTGGGGG AGTCAGGCTG C                                  31
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(12) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 987 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

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ATGGACAACG CCTCGTTCTC GGAGCCCTGG CCCGCCAACG CATCGGGCCC GGACCCGGCG    60

CTGAGCTGCT CCAACGCGTC GACTCTGGCG CCGCTGCCGG CGCCGCTGGC GGTGGCTGTA   120

CCAGTTGTCT ACGCGGTGAT CTGCGCCGTG GGTCTGGCGG GCAACTCCGC CGTGCTGTAC   180


GTGTTGCTGC GGGCGCCCCG CATGAAGACC GTCACCAACC TGTTCATCCT CAACCTGGCC   240

ATCGCCGACG AGCTCTTCAC GCTGGTGCTG CCCATCAACA TCGCCGACTT CCTGCTGCGG   300

CAGTGGCCCT TCGGGGAGCT CATGTGCAAG CTCATCGTGG CTATCGACCA GTACAACACC   360

TTCTCCAGCC TCTACTTCCT CACCGTCATG AGCGCCGACC GCTACCTGGT GGTGTTGGCC   420

ACTGCGGAGT CGCGCCGGGT GGCCGGCCGC ACCTACAGCG CCGCGCGCGC GGTGAGCCTG   480

GCCGTGTGGG GGATCGTCAC ACTCGTCGTG CTGCCCTTCG CAGTCTTCGC CCGGCTAGAC   540

GACGAGCAGG GCCGGCGCCA GTGCGTGCTA GTCTTTCCGC AGCCCGAGGC CTTCTGGTGG   600

CGCGCGAGCC GCCTCTACAC GCTCGTGCTG GGCTTCGCCA TCCCCGTGTC CACCATCTGT   660

GTCCTCTATA CCACCCTGCT GTGCCGGCTG CATGCCATGC GGCTGGACAG CCACGCCAAG   720

GCCCTGGAGC GCGCCAAGAA GCGGGTGACC TTCCTGGTGG TGGCAATCCT GGCGGTGTGC   780

CTCCTCTGCT GGACGCCCTA CCACCTGAGC ACCGTGGTGG CGCTCACCAC CGACCTCCCG   840

CAGACGCCGC TGGTCATCGC TATCTCCTAC TTCATCACCA GCCTGACGTA CGCCAACAGC   900

TGCCTCAACC CCTTCCTCTA CGCCTTCCTG GACGCCAGCT TCCGCAGGAA CCTCCGCCAG   960

CTGATAACTT GCCGCGCGGC AGCCTGA                                       987
```

(13) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 328 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Met Asp Asn Ala Ser Phe Ser Glu Pro Trp Pro Ala Asn Ala Ser Gly
1               5                  10                  15

Pro Asp Pro Ala Leu Ser Cys Ser Asn Ala Ser Thr Leu Ala Pro Leu
            20                  25                  30

Pro Ala Pro Leu Ala Val Ala Val Pro Val Val Tyr Ala Val Ile Cys
        35                  40                  45

Ala Val Gly Leu Ala Gly Asn Ser Ala Val Leu Tyr Val Leu Leu Arg
    50                  55                  60

Ala Pro Arg Met Lys Thr Val Thr Asn Leu Phe Ile Leu Asn Leu Ala
65                  70                  75                  80
```

```
Ile Ala Asp Glu Leu Phe Thr Leu Val Leu Pro Ile Asn Ile Ala Asp
                85                  90                  95

Phe Leu Leu Arg Gln Trp Pro Phe Gly Glu Leu Met Cys Lys Leu Ile
            100                 105                 110

Val Ala Ile Asp Gln Tyr Asn Thr Phe Ser Ser Leu Tyr Phe Leu Thr
        115                 120                 125

Val Met Ser Ala Asp Arg Tyr Leu Val Val Leu Ala Thr Ala Glu Ser
    130                 135                 140

Arg Arg Val Ala Gly Arg Thr Tyr Ser Ala Ala Arg Ala Val Ser Leu
145                 150                 155                 160

Ala Val Trp Gly Ile Val Thr Leu Val Val Leu Pro Phe Ala Val Phe
                165                 170                 175

Ala Arg Leu Asp Asp Glu Gln Gly Arg Arg Gln Cys Val Leu Val Phe
            180                 185                 190

Pro Gln Pro Glu Ala Phe Trp Trp Arg Ala Ser Arg Leu Tyr Thr Leu
        195                 200                 205

Val Leu Gly Phe Ala Ile Pro Val Ser Thr Ile Cys Val Leu Tyr Thr
    210                 215                 220

Thr Leu Leu Cys Arg Leu His Ala Met Arg Leu Asp Ser His Ala Lys
225                 230                 235                 240

Ala Leu Glu Arg Ala Lys Lys Arg Val Thr Phe Leu Val Val Ala Ile
                245                 250                 255

Leu Ala Val Cys Leu Leu Cys Trp Thr Pro Tyr His Leu Ser Thr Val
            260                 265                 270

Val Ala Leu Thr Thr Asp Leu Pro Gln Thr Pro Leu Val Ile Ala Ile
        275                 280                 285

Ser Tyr Phe Ile Thr Ser Leu Thr Tyr Ala Asn Ser Cys Leu Asn Pro
    290                 295                 300

Phe Leu Tyr Ala Phe Leu Asp Ala Ser Phe Arg Arg Asn Leu Arg Gln
305                 310                 315                 320

Leu Ile Thr Cys Arg Ala Ala Ala
                325
```

(14) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CGGAATTCGT CAACGGTCCC AGCTACAATG 30

(15) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

ATGGATCCCA GGCCCTTCAG CACCGCAATA T 31

(16) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1002 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
ATGCAGGCCG CTGGGCACCC AGAGCCCCTT GACAGCAGGG GCTCCTTCTC CCTCCCCACG    60

ATGGGTGCCA ACGTCTCTCA GGACAATGGC ACTGGCCACA ATGCCACCTT CTCCGAGCCA   120

CTGCCGTTCC TCTATGTGCT CCTGCCCGCC GTGTACTCCG GGATCTGTGC TGTGGGGCTG   180

ACTGGCAACA CGGCCGTCAT CCTTGTAATC CTAAGGGCGC CCAAGATGAA GACGGTGACC   240

AACGTGTTCA TCCTGAACCT GGCCGTCGCC GACGGGCTCT TCACGCTGGT ACTGCCCGTC   300

AACATCGCGG AGCACCTGCT GCAGTACTGG CCCTTCGGGG AGCTGCTCTG CAAGCTGGTG   360

CTGGCCGTCG ACCACTACAA CATCTTCTCC AGCATCTACT TCCTAGCCGT GATGAGCGTG   420

GACCGATACC TGGTGGTGCT GGCCACCGTG AGGTCCCGCC ACATGCCCTG GCGCACCTAC   480

CGGGGGGCGA AGGTCGCCAG CCTGTGTGTC TGGCTGGGCG TCACGGTCCT GGTTCTGCCC   540

TTCTTCTCTT TCGCTGGCGT CTACAGCAAC GAGCTGCAGG TCCCAAGCTG TGGGCTGAGC   600

TTCCCGTGGC CCGAGCGGGT CTGGTTCAAG GCCAGCCGTG TCTACACTTT GGTCCTGGGC   660

TTCGTGCTGC CCGTGTGCAC CATCTGTGTG CTCTACACAG ACCTCCTGCG CAGGCTGCGG   720

GCCGTGCGGC TCCGCTCTGG AGCCAAGGCT CTAGGCAAGG CCAGGCGGAA GGTGACCGTC   780

CTGGTCCTCG TCGTGCTGGC CGTGTGCCTC CTCTGCTGGA CGCCCTTCCA CCTGGCCTCT   840

GTCGTGGCCC TGACCACGGA CCTGCCCCAG ACCCCACTGG TCATCAGTAT GTCCTACGTC   900

ATCACCAGCC TCACGTACGC CAACTCGTGC CTGAACCCCT TCCTCTACGC CTTTCTAGAT   960

GACAACTTCC GGAAGAACTT CCGCAGCATA TTGCGGTGCT GA                      1002
```

(17) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 333 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Met Gln Ala Ala Gly His Pro Glu Pro Leu Asp Ser Arg Gly Ser Phe
1               5                  10                  15

Ser Leu Pro Thr Met Gly Ala Asn Val Ser Gln Asp Asn Gly Thr Gly
            20                  25                  30

His Asn Ala Thr Phe Ser Glu Pro Leu Pro Phe Leu Tyr Val Leu Leu
        35                  40                  45

Pro Ala Val Tyr Ser Gly Ile Cys Ala Val Gly Leu Thr Gly Asn Thr
    50                  55                  60

Ala Val Ile Leu Val Ile Leu Arg Ala Pro Lys Met Lys Thr Val Thr
65                  70                  75                  80

Asn Val Phe Ile Leu Asn Leu Ala Val Ala Asp Gly Leu Phe Thr Leu
                85                  90                  95

Val Leu Pro Val Asn Ile Ala Glu His Leu Leu Gln Tyr Trp Pro Phe
            100                 105                 110

Gly Glu Leu Leu Cys Lys Leu Val Leu Ala Val Asp His Tyr Asn Ile
        115                 120                 125

Phe Ser Ser Ile Tyr Phe Leu Ala Val Met Ser Val Asp Arg Tyr Leu
    130                 135                 140

Val Val Leu Ala Thr Val Arg Ser Arg His Met Pro Trp Arg Thr Tyr
145                 150                 155                 160

Arg Gly Ala Lys Val Ala Ser Leu Cys Val Trp Leu Gly Val Thr Val
                165                 170                 175
```

```
Leu Val Leu Pro Phe Phe Ser Phe Ala Gly Val Tyr Ser Asn Glu Leu
            180                 185                 190

Gln Val Pro Ser Cys Gly Leu Ser Phe Pro Trp Pro Glu Arg Val Trp
        195                 200                 205

Phe Lys Ala Ser Arg Val Tyr Thr Leu Val Leu Gly Phe Val Leu Pro
    210                 215                 220

Val Cys Thr Ile Cys Val Leu Tyr Thr Asp Leu Leu Arg Arg Leu Arg
225                 230                 235                 240

Ala Val Arg Leu Arg Ser Gly Ala Lys Ala Leu Gly Lys Ala Arg Arg
                245                 250                 255

Lys Val Thr Val Leu Val Leu Val Val Leu Ala Val Cys Leu Leu Cys
            260                 265                 270

Trp Thr Pro Phe His Leu Ala Ser Val Val Ala Leu Thr Thr Asp Leu
        275                 280                 285

Pro Gln Thr Pro Leu Val Ile Ser Met Ser Tyr Val Ile Thr Ser Leu
    290                 295                 300

Thr Tyr Ala Asn Ser Cys Leu Asn Pro Phe Leu Tyr Ala Phe Leu Asp
305                 310                 315                 320

Asp Asn Phe Arg Lys Asn Phe Arg Ser Ile Leu Arg Cys
                325                 330
```

(18) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
ACGAATTCAG CCATGGTCCT TGAGGTGAGT GACCACCAAG TGCTAAAT                48
```

(19) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GAGGATCCTG GAATGCGGGG AAGTCAG 27

(20) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1107 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION SEQ ID NO:19:

ATGGTCCTTG AGGTGAGTGA CCACCAAGTG CTAAATGACG CCGAGGTTGC CGCCCTCCTG 60

GAGAACTTCA GCTCTTCCTA TGACTATGGA GAAAACGAGA GTGACTCGTG CTGTACCTCC 120

CCGCCCTGCC CACAGGACTT CAGCCTGAAC TTCGACCGGG CCTTCCTGCC AGCCCTCTAC 180

AGCCTCCTCT TTCTGCTGGG GCTGCTGGGC AACGGCGCGG TGGCAGCCGT GCTGCTGAGC 240

CGGCGGACAG CCCTGAGCAG CACCGACACC TTCCTGCTCC ACCTAGCTGT AGCAGACACG 300

CTGCTGGTGC TGACACTGCC GCTCTGGGCA GTGGACGCTG CCGTCCAGTG GGTCTTTGGC 360

TCTGGCCTCT GCAAAGTGGC AGGTGCCCTC TTCAACATCA ACTTCTACGC AGGAGCCCTC 420

CTGCTGGCCT GCATCAGCTT TGACCGCTAC CTGAACATAG TTCATGCCAC CCAGCTCTAC 480

CGCCGGGGGC CCCCGGCCCG CGTGACCCTC ACCTGCCTGG CTGTCTGGGG GCTCTGCCTG 540

CTTTTCGCCC TCCCAGACTT CATCTTCCTG TCGGCCCACC ACGACGAGCG CCTCAACGCC 600

ACCCACTGCC AATACAACTT CCCACAGGTG GGCCGCACGG CTCTGCGGGT GCTGCAGCTG 660

GTGGCTGGCT TTCTGCTGCC CCTGCTGGTC ATGGCCTACT GCTATGCCCA CATCCTGGCC 720

GTGCTGCTGG TTTCCAGGGG CCAGCGGCGC CTGCGGGCCA TGCGGCTGGT GGTGGTGGTC 780

GTGGTGGCCT TTGCCCTCTG CTGGACCCCC TATCACCTGG TGGTGCTGGT GGACATCCTC 840

ATGGACCTGG GCGCTTTGGC CCGCAACTGT GGCCGAGAAA GCAGGGTAGA CGTGGCCAAG 900

TCGGTCACCT CAGGCCTGGG CTACATGCAC TGCTGCCTCA ACCCGCTGCT CTATGCCTTT 960

GTAGGGGTCA AGTTCCGGGA GCGGATGTGG ATGCTGCTCT TGCGCCTGGG CTGCCCCAAC 1020

CAGAGAGGGC TCCAGAGGCA GCCATCGTCT TCCCGCCGGG ATTCATCCTG GTCTGAGACC 1080

TCAGAGGCCT CCTACTCGGG CTTGTGA 1107

(21) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 368 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Met Val Leu Glu Val Ser Asp His Gln Val Leu Asn Asp Ala Glu Val
1               5                  10                  15

Ala Ala Leu Leu Glu Asn Phe Ser Ser Ser Tyr Asp Tyr Gly Glu Asn
            20                  25                  30

Glu Ser Asp Ser Cys Cys Thr Ser Pro Pro Cys Pro Gln Asp Phe Ser
        35                  40                  45

Leu Asn Phe Asp Arg Ala Phe Leu Pro Ala Leu Tyr Ser Leu Leu Phe
    50                  55                  60

Leu Leu Gly Leu Leu Gly Asn Gly Ala Val Ala Ala Val Leu Leu Ser
65                  70                  75                  80

Arg Arg Thr Ala Leu Ser Ser Thr Asp Thr Phe Leu Leu His Leu Ala
                85                  90                  95

Val Ala Asp Thr Leu Leu Val Leu Thr Leu Pro Leu Trp Ala Val Asp
            100                 105                 110

Ala Ala Val Gln Trp Val Phe Gly Ser Gly Leu Cys Lys Val Ala Gly
        115                 120                 125

Ala Leu Phe Asn Ile Asn Phe Tyr Ala Gly Ala Leu Leu Leu Ala Cys
    130                 135                 140

Ile Ser Phe Asp Arg Tyr Leu Asn Ile Val His Ala Thr Gln Leu Tyr
145                 150                 155                 160

Arg Arg Gly Pro Pro Ala Arg Val Thr Leu Thr Cys Leu Ala Val Trp
                165                 170                 175

Gly Leu Cys Leu Leu Phe Ala Leu Pro Asp Phe Ile Phe Leu Ser Ala
            180                 185                 190

His His Asp Glu Arg Leu Asn Ala Thr His Cys Gln Tyr Asn Phe Pro
        195                 200                 205

Gln Val Gly Arg Thr Ala Leu Arg Val Leu Gln Leu Val Ala Gly Phe
    210                 215                 220

Leu Leu Pro Leu Leu Val Met Ala Tyr Cys Tyr Ala His Ile Leu Ala
225                 230                 235                 240
```

```
Val Leu Leu Val Ser Arg Gly Gln Arg Arg Leu Arg Ala Met Arg Leu
                245                 250                 255

Val Val Val Val Val Val Ala Phe Ala Leu Cys Trp Thr Pro Tyr His
            260                 265                 270

Leu Val Val Leu Val Asp Ile Leu Met Asp Leu Gly Ala Leu Ala Arg
        275                 280                 285

Asn Cys Gly Arg Glu Ser Arg Val Asp Val Ala Lys Ser Val Thr Ser
    290                 295                 300

Gly Leu Gly Tyr Met His Cys Cys Leu Asn Pro Leu Leu Tyr Ala Phe
305                 310                 315                 320

Val Gly Val Lys Phe Arg Glu Arg Met Trp Met Leu Leu Leu Arg Leu
                325                 330                 335

Gly Cys Pro Asn Gln Arg Gly Leu Gln Arg Gln Pro Ser Ser Ser Arg
            340                 345                 350

Arg Asp Ser Ser Trp Ser Glu Thr Ser Glu Ala Ser Tyr Ser Gly Leu
        355                 360                 365
```

(22) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
TTAAGCTTGA CCTAATGCCA TCTTGTGTCC                                    30
```

(23) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
TTGGATCCAA AAGAACCATG CACCTCAGAG                                    30
```

(24) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1074 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
ATGGCTGATG ACTATGGCTC TGAATCCACA TCTTCCATGG AAGACTACGT TAACTTCAAC    60

TTCACTGACT TCTACTGTGA GAAAAACAAT GTCAGGCAGT TTGCGAGCCA TTTCCTCCCA   120

CCCTTGTACT GGCTCGTGTT CATCGTGGGT GCCTTGGGCA ACAGTCTTGT TATCCTTGTC   180

TACTGGTACT GCACAAGAGT GAAGACCATG ACCGACATGT TCCTTTTGAA TTTGGCAATT   240

GCTGACCTCC TCTTTCTTGT CACTCTTCCC TTCTGGGCCA TTGCTGCTGC TGACCAGTGG   300

AAGTTCCAGA CCTTCATGTG CAAGGTGGTC AACAGCATGT ACAAGATGAA CTTCTACAGC   360

TGTGTGTTGC TGATCATGTG CATCAGCGTG GACAGGTACA TTGCCATTGC CCAGGCCATG   420

AGAGCACATA CTTGGAGGGA GAAAAGGCTT TTGTACAGCA AAATGGTTTG CTTTACCATC   480

TGGGTATTGG CAGCTGCTCT CTGCATCCCA GAAATCTTAT ACAGCCAAAT CAAGGAGGAA   540

TCCGGCATTG CTATCTGCAC CATGGTTTAC CCTAGCGATG AGAGCACCAA ACTGAAGTCA   600

GCTGTCTTGA CCCTGAAGGT CATTCTGGGG TTCTTCCTTC CCTTCGTGGT CATGGCTTGC   660

TGCTATACCA TCATCATTCA CACCCTGATA CAAGCCAAGA AGTCTTCCAA GCACAAAGCC   720

CTAAAAGTGA CCATCACTGT CCTGACCGTC TTTGTCTTGT CTCAGTTTCC CTACAACTGC   780

ATTTTGTTGG TGCAGACCAT TGACGCCTAT GCCATGTTCA TCTCCAACTG TGCCGTTTCC   840

ACCAACATTG ACATCTGCTT CCAGGTCACC CAGACCATCG CCTTCTTCCA CAGTTGCCTG   900

AACCCTGTTC TCTATGTTTT TGTGGGTGAG AGATTCCGCC GGGATCTCGT GAAAACCCTG   960

AAGAACTTGG GTTGCATCAG CCAGGCCCAG TGGGTTTCAT TTACAAGGAG AGAGGGAAGC  1020

TTGAAGCTGT CGTCTATGTT GCTGGAGACA ACCTCAGGAG CACTCTCCCT CTGA         1074
```

(25) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 357 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
Met Ala Asp Asp Tyr Gly Ser Glu Ser Thr Ser Ser Met Glu Asp Tyr
1               5                  10                  15

Val Asn Phe Asn Phe Thr Asp Phe Tyr Cys Glu Lys Asn Asn Val Arg
            20                  25                  30

Gln Phe Ala Ser His Phe Leu Pro Pro Leu Tyr Trp Leu Val Phe Ile
        35                  40                  45

Val Gly Ala Leu Gly Asn Ser Leu Val Ile Leu Val Tyr Trp Tyr Cys
    50                  55                  60

Thr Arg Val Lys Thr Met Thr Asp Met Phe Leu Leu Asn Leu Ala Ile
65                  70                  75                  80

Ala Asp Leu Leu Phe Leu Val Thr Leu Pro Phe Trp Ala Ile Ala Ala
                85                  90                  95

Ala Asp Gln Trp Lys Phe Gln Thr Phe Met Cys Lys Val Val Asn Ser
            100                 105                 110

Met Tyr Lys Met Asn Phe Tyr Ser Cys Val Leu Leu Ile Met Cys Ile
        115                 120                 125

Ser Val Asp Arg Tyr Ile Ala Ile Ala Gln Ala Met Arg Ala His Thr
    130                 135                 140

Trp Arg Glu Lys Arg Leu Leu Tyr Ser Lys Met Val Cys Phe Thr Ile
145                 150                 155                 160

Trp Val Leu Ala Ala Ala Leu Cys Ile Pro Glu Ile Leu Tyr Ser Gln
                165                 170                 175

Ile Lys Glu Glu Ser Gly Ile Ala Ile Cys Thr Met Val Tyr Pro Ser
            180                 185                 190

Asp Glu Ser Thr Lys Leu Lys Ser Ala Val Leu Thr Leu Lys Val Ile
        195                 200                 205

Leu Gly Phe Phe Leu Pro Phe Val Val Met Ala Cys Cys Tyr Thr Ile
    210                 215                 220

Ile Ile His Thr Leu Ile Gln Ala Lys Lys Ser Ser Lys His Lys Ala
225                 230                 235                 240

Leu Lys Val Thr Ile Thr Val Leu Thr Val Phe Val Leu Ser Gln Phe
                245                 250                 255

Pro Tyr Asn Cys Ile Leu Leu Val Gln Thr Ile Asp Ala Tyr Ala Met
            260                 265                 270

Phe Ile Ser Asn Cys Ala Val Ser Thr Asn Ile Asp Ile Cys Phe Gln
        275                 280                 285
```

```
Val Thr Gln Thr Ile Ala Phe Phe His Ser Cys Leu Asn Pro Val Leu
    290                 295                 300

Tyr Val Phe Val Gly Glu Arg Phe Arg Arg Asp Leu Val Lys Thr Leu
305                 310                 315                 320

Lys Asn Leu Gly Cys Ile Ser Gln Ala Gln Trp Val Ser Phe Thr Arg
                325                 330                 335

Arg Glu Gly Ser Leu Lys Leu Ser Ser Met Leu Leu Glu Thr Thr Ser
            340                 345                 350

Gly Ala Leu Ser Leu
        355
```

(26) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1110 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
ATGGCCTCAT CGACCACTCG GGGCCCCAGG GTTTCTGACT TATTTTCTGG GCTGCCGCCG    60

GCGGTCACAA CTCCCGCCAA CCAGAGCGCA GAGGCCTCGG CGGGCAACGG GTCGGTGGCT   120

GGCGCGGACG CTCCAGCCGT CACGCCCTTC CAGAGCCTGC AGCTGGTGCA TCAGCTGAAG   180

GGGCTGATCG TGCTGCTCTA CAGCGTCGTG GTGGTCGTGG GGCTGGTGGG CAACTGCCTG   240

CTGGTGCTGG TGATCGCGCG GGTGCCGCGG CTGCACAACG TGACGAACTT CCTCATCGGC   300

AACCTGGCCT TGTCCGACGT GCTCATGTGC ACCGCCTGCG TGCCGCTCAC GCTGGCCTAT   360

GCCTTCGAGC CACGCGGCTG GGTGTTCGGC GGCGGCCTGT GCCACCTGGT CTTCTTCCTG   420

CAGCCGGTCA CCGTCTATGT GTCGGTGTTC ACGCTCACCA CCATCGCAGT GGACCGCTAC   480

GTCGTGCTGG TGCACCCGCT GAGGCGCGCA TCTCGCTGCG CCTCAGCCTA CGCTGTGCTG   540

GCCATCTGGG CGCTGTCCGC GGTGCTGGCG CTGCCGCCCG CCGTGCACAC CTATCACGTG   600

GAGCTCAAGC CGCACGACGT GCGCCTCTGC GAGGAGTTCT GGGGCTCCCA GGAGCGCCAG   660

CGCCAGCTCT ACGCCTGGGG GCTGCTGCTG GTCACCTACC TGCTCCCTCT GCTGGTCATC   720

CTCCTGTCTT ACGTCCGGGT GTCAGTGAAG CTCCGCAACC GCGTGGTGCC GGGCTGCGTG   780

ACCCAGAGCC AGGCCGACTG GGACCGCGCT CGGCGCCGGC GCACCTTCTG CTTGCTGGTG   840

GTGGTCGTGG TGGTGTTCGC CGTCTGCTGG CTGCCGCTGC ACGTCTTCAA CCTGCTGCGG   900

GACCTCGACC CCCACGCCAT CGACCCTTAC GCCTTTGGGC TGGTGCAGCT GCTCTGCCAC   960

TGGCTCGCCA TGAGTTCGGC CTGCTACAAC CCCTTCATCT ACGCCTGGCT GCACGACAGC  1020

TTCCGCGAGG AGCTGCGCAA ACTGTTGGTC GCTTGGCCCC GCAAGATAGC CCCCCATGGC  1080

CAGAATATGA CCGTCAGCGT GGTCATCTGA                                    1110
```

(27) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 369 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Met Ala Ser Ser Thr Thr Arg Gly Pro Arg Val Ser Asp Leu Phe Ser
1               5                  10                  15

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

Ser Ala Gly Asn Gly Ser Val Ala Gly Ala Asp Ala Pro Ala Val Thr
        35                  40                  45

Pro Phe Gln Ser Leu Gln Leu Val His Gln Leu Lys Gly Leu Ile Val
    50                  55                  60

Leu Leu Tyr Ser Val Val Val Val Val Gly Leu Val Gly Asn Cys Leu
65                  70                  75                  80

Leu Val Leu Val Ile Ala Arg Val Pro Arg Leu His Asn Val Thr Asn
                85                  90                  95

Phe Leu Ile Gly Asn Leu Ala Leu Ser Asp Val Leu Met Cys Thr Ala
            100                 105                 110

Cys Val Pro Leu Thr Leu Ala Tyr Ala Phe Glu Pro Arg Gly Trp Val
        115                 120                 125

Phe Gly Gly Gly Leu Cys His Leu Val Phe Phe Leu Gln Pro Val Thr
    130                 135                 140

Val Tyr Val Ser Val Phe Thr Leu Thr Thr Ile Ala Val Asp Arg Tyr
145                 150                 155                 160

Val Val Leu Val His Pro Leu Arg Arg Ala Ser Arg Cys Ala Ser Ala
                165                 170                 175
```

```
Tyr Ala Val Leu Ala Ile Trp Ala Leu Ser Ala Val Leu Ala Leu Pro
            180                 185                 190

Pro Ala Val His Thr Tyr His Val Glu Leu Lys Pro His Asp Val Arg
        195                 200                 205

Leu Cys Glu Glu Phe Trp Gly Ser Gln Glu Arg Gln Arg Gln Leu Tyr
    210                 215                 220

Ala Trp Gly Leu Leu Leu Val Thr Tyr Leu Leu Pro Leu Leu Val Ile
225                 230                 235                 240

Leu Leu Ser Tyr Val Arg Val Ser Val Lys Leu Arg Asn Arg Val Val
                245                 250                 255

Pro Gly Cys Val Thr Gln Ser Gln Ala Asp Trp Asp Arg Ala Arg Arg
            260                 265                 270

Arg Arg Thr Phe Cys Leu Leu Val Val Val Val Val Val Phe Ala Val
        275                 280                 285

Cys Trp Leu Pro Leu His Val Phe Asn Leu Leu Arg Asp Leu Asp Pro
    290                 295                 300

His Ala Ile Asp Pro Tyr Ala Phe Gly Leu Val Gln Leu Leu Cys His
305                 310                 315                 320

Trp Leu Ala Met Ser Ser Ala Cys Tyr Asn Pro Phe Ile Tyr Ala Trp
                325                 330                 335

Leu His Asp Ser Phe Arg Glu Glu Leu Arg Lys Leu Leu Val Ala Trp
            340                 345                 350

Pro Arg Lys Ile Ala Pro His Gly Gln Asn Met Thr Val Ser Val Val
        355                 360                 365

Ile
```

(28) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1083 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
ATGGACCCAG AAGAAACTTC AGTTTATTTG GATTATTACT ATGCTACGAG CCCAAACTCT    60

GACATCAGGG AGACCCACTC CCATGTTCCT TACACCTCTG TCTTCCTTCC AGTCTTTTAC   120
```

```
ACAGCTGTGT TCCTGACTGG AGTGCTGGGG AACCTTGTTC TCATGGGAGC GTTGCATTTC   180

AAACCCGGCA GCCGAAGACT GATCGACATC TTTATCATCA ATCTGGCTGC CTCTGACTTC   240

ATTTTTCTTG TCACATTGCC TCTCTGGGTG GATAAAGAAG CATCTCTAGG ACTGTGGAGG   300

ACGGGCTCCT TCCTGTGCAA AGGGAGCTCC TACATGATCT CCGTCAATAT GCACTGCAGT   360

GTCCTCCTGC TCACTTGCAT GAGTGTTGAC CGCTACCTGG CCATTGTGTG GCCAGTCGTA   420

TCCAGGAAAT TCAGAAGGAC AGACTGTGCA TATGTAGTCT GTGCCAGCAT CTGGTTTATC   480

TCCTGCCTGC TGGGGTTGCC TACTCTTCTG TCCAGGGAGC TCACGCTGAT TGATGATAAG   540

CCATACTGTG CAGAGAAAAA GGCAACTCCA ATTAAACTCA TATGGTCCCT GGTGGCCTTA   600

ATTTTCACCT TTTTTGTCCC TTTGTTGAGC ATTGTGACCT GCTACTGTTG CATTGCAAGG   660

AAGCTGTGTG CCCATTACCA GCAATCAGGA AAGCACAACA AAAAGCTGAA GAAATCTATA   720

AAGATCATCT TTATTGTCGT GGCAGCCTTT CTTGTCTCCT GGCTGCCCTT CAATACTTTC   780

AAGTTCCTGG CCATTGTCTC TGGGTTGCGG CAAGAACACT ATTTACCCTC AGCTATTCTT   840

CAGCTTGGTA TGGAGGTGAG TGGACCCTTG GCATTTGCCA ACAGCTGTGT CAACCCTTTC   900

ATTTACTATA TCTTCGACAG CTACATCCGC CGGGCCATTG TCCACTGCTT GTGCCCTTGC   960

CTGAAAAACT ATGACTTTGG GAGTAGCACT GAGACATCAG ATAGTCACCT CACTAAGGCT  1020

CTCTCCACCT TCATTCATGC AGAAGATTTT GCCAGGAGGA GGAAGAGGTC TGTGTCACTC  1080

TAA                                                                1083
```

(29) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 360 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Met Asp Pro Glu Glu Thr Ser Val Tyr Leu Asp Tyr Tyr Tyr Ala Thr
1               5                  10                  15

Ser Pro Asn Ser Asp Ile Arg Glu Thr His Ser His Val Pro Tyr Thr
            20                  25                  30

Ser Val Phe Leu Pro Val Phe Tyr Thr Ala Val Phe Leu Thr Gly Val
        35                  40                  45
```

Leu Gly Asn Leu Val Leu Met Gly Ala Leu His Phe Lys Pro Gly Ser
50 55 60

Arg Arg Leu Ile Asp Ile Phe Ile Ile Asn Leu Ala Ala Ser Asp Phe
65 70 75 80

Ile Phe Leu Val Thr Leu Pro Leu Trp Val Asp Lys Glu Ala Ser Leu
85 90 95

Gly Leu Trp Arg Thr Gly Ser Phe Leu Cys Lys Gly Ser Ser Tyr Met
100 105 110

Ile Ser Val Asn Met His Cys Ser Val Leu Leu Leu Thr Cys Met Ser
115 120 125

Val Asp Arg Tyr Leu Ala Ile Val Trp Pro Val Val Ser Arg Lys Phe
130 135 140

Arg Arg Thr Asp Cys Ala Tyr Val Val Cys Ala Ser Ile Trp Phe Ile
145 150 155 160

Ser Cys Leu Leu Gly Leu Pro Thr Leu Leu Ser Arg Glu Leu Thr Leu
165 170 175

Ile Asp Asp Lys Pro Tyr Cys Ala Glu Lys Lys Ala Thr Pro Ile Lys
180 185 190

Leu Ile Trp Ser Leu Val Ala Leu Ile Phe Thr Phe Phe Val Pro Leu
195 200 205

Leu Ser Ile Val Thr Cys Tyr Cys Cys Ile Ala Arg Lys Leu Cys Ala
210 215 220

His Tyr Gln Gln Ser Gly Lys His Asn Lys Lys Leu Lys Lys Ser Ile
225 230 235 240

Lys Ile Ile Phe Ile Val Val Ala Ala Phe Leu Val Ser Trp Leu Pro
245 250 255

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

His Tyr Leu Pro Ser Ala Ile Leu Gln Leu Gly Met Glu Val Ser Gly
275 280 285

Pro Leu Ala Phe Ala Asn Ser Cys Val Asn Pro Phe Ile Tyr Tyr Ile
290 295 300

Phe Asp Ser Tyr Ile Arg Arg Ala Ile Val His Cys Leu Cys Pro Cys
305 310 315 320

Leu Lys Asn Tyr Asp Phe Gly Ser Ser Thr Glu Thr Ser Asp Ser His
325 330 335

Leu Thr Lys Ala Leu Ser Thr Phe Ile His Ala Glu Asp Phe Ala Arg

340 345 350

Arg Arg Lys Arg Ser Val Ser Leu
355 360

(30) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

CTAGAATTCT GACTCCAGCC AAAGCATGAA T 31

(31) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GCTGGATCCT AAACAGTCTG CGCTCGGCCT 30

(32) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1020 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
ATGAATGGCC TTGAAGTGGC TCCCCCAGGT CTGATCACCA ACTTCTCCCT GGCCACGGCA    60

GAGCAATGTG GCCAGGAGAC GCCACTGGAG AACATGCTGT TCGCCTCCTT CTACCTTCTG   120

GATTTTATCC TGGCTTTAGT TGGCAATACC CTGGCTCTGT GGCTTTTCAT CCGAGACCAC   180

AAGTCCGGGA CCCCGGCCAA CGTGTTCCTG ATGCATCTGG CCGTGGCCGA CTTGTCGTGC   240

GTGCTGGTCC TGCCCACCCG CCTGGTCTAC CACTTCTCTG GGAACCACTG GCCATTTGGG   300

GAAATCGCAT GCCGTCTCAC CGGCTTCCTC TTCTACCTCA ACATGTACGC CAGCATCTAC   360

TTCCTCACCT GCATCAGCGC CGACCGTTTC CTGGCCATTG TGCACCCGGT CAAGTCCCTC   420

AAGCTCCGCA GGCCCCTCTA CGCACACCTG GCCTGTGCCT TCCTGTGGGT GGTGGTGGCT   480

GTGGCCATGG CCCCGCTGCT GGTGAGCCCA CAGACCGTGC AGACCAACCA CACGGTGGTC   540

TGCCTGCAGC TGTACCGGGA GAAGGCCTCC CACCATGCCC TGGTGTCCCT GGCAGTGGCC   600

TTCACCTTCC CGTTCATCAC CACGGTCACC TGCTACCTGC TGATCATCCG CAGCCTGCGG   660

CAGGGCCTGC GTGTGGAGAA GCGCCTCAAG ACCAAGGCAG TGCGCATGAT CGCCATAGTG   720

CTGGCCATCT TCCTGGTCTG CTTCGTGCCC TACCACGTCA ACCGCTCCGT CTACGTGCTG   780

CACTACCGCA GCCATGGGGC CTCCTGCGCC ACCCAGCGCA TCCTGGCCCT GGCAAACCGC   840

ATCACCTCCT GCCTCACCAG CCTCAACGGG GCACTCGACC CCATCATGTA TTTCTTCGTG   900

GCTGAGAAGT TCCGCCACGC CCTGTGCAAC TTGCTCTGTG GCAAAAGGCT CAAGGGCCCG   960

CCCCCCAGCT TCGAAGGGAA AACCAACGAG AGCTCGCTGA GTGCCAAGTC AGAGCTGTGA  1020
```

(33) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 339 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
Met Asn Gly Leu Glu Val Ala Pro Pro Gly Leu Ile Thr Asn Phe Ser
1               5                  10                  15

Leu Ala Thr Ala Glu Gln Cys Gly Gln Glu Thr Pro Leu Glu Asn Met
            20                  25                  30

Leu Phe Ala Ser Phe Tyr Leu Leu Asp Phe Ile Leu Ala Leu Val Gly
        35                  40                  45

Asn Thr Leu Ala Leu Trp Leu Phe Ile Arg Asp His Lys Ser Gly Thr
    50                  55                  60

Pro Ala Asn Val Phe Leu Met His Leu Ala Val Ala Asp Leu Ser Cys
65                  70                  75                  80

Val Leu Val Leu Pro Thr Arg Leu Val Tyr His Phe Ser Gly Asn His
                85                  90                  95

Trp Pro Phe Gly Glu Ile Ala Cys Arg Leu Thr Gly Phe Leu Phe Tyr
```

```
                100                 105                 110

Leu Asn Met Tyr Ala Ser Ile Tyr Phe Leu Thr Cys Ile Ser Ala Asp
        115                 120                 125

Arg Phe Leu Ala Ile Val His Pro Val Lys Ser Leu Lys Leu Arg Arg
    130                 135                 140

Pro Leu Tyr Ala His Leu Ala Cys Ala Phe Leu Trp Val Val Val Ala
145                 150                 155                 160

Val Ala Met Ala Pro Leu Leu Val Ser Pro Gln Thr Val Gln Thr Asn
                165                 170                 175

His Thr Val Val Cys Leu Gln Leu Tyr Arg Glu Lys Ala Ser His His
            180                 185                 190

Ala Leu Val Ser Leu Ala Val Ala Phe Thr Phe Pro Phe Ile Thr Thr
        195                 200                 205

Val Thr Cys Tyr Leu Leu Ile Ile Arg Ser Leu Arg Gln Gly Leu Arg
    210                 215                 220

Val Glu Lys Arg Leu Lys Thr Lys Ala Val Arg Met Ile Ala Ile Val
225                 230                 235                 240

Leu Ala Ile Phe Leu Val Cys Phe Val Pro Tyr His Val Asn Arg Ser
                245                 250                 255

Val Tyr Val Leu His Tyr Arg Ser His Gly Ala Ser Cys Ala Thr Gln
            260                 265                 270

Arg Ile Leu Ala Leu Ala Asn Arg Ile Thr Ser Cys Leu Thr Ser Leu
        275                 280                 285

Asn Gly Ala Leu Asp Pro Ile Met Tyr Phe Phe Val Ala Glu Lys Phe
    290                 295                 300

Arg His Ala Leu Cys Asn Leu Leu Cys Gly Lys Arg Leu Lys Gly Pro
305                 310                 315                 320

Pro Pro Ser Phe Glu Gly Lys Thr Asn Glu Ser Ser Leu Ser Ala Lys
                325                 330                 335

Ser Glu Leu
```

(34) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

ATAAGATGAT CACCCTGAAC AATCAAGAT 29

(35) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

TCCGAATTCA TAACATTTCA CTGTTTATAT TGC 33

(36) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 996 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```
ATGATCACCC TGAACAATCA AGATCAACCT GTCACTTTTA ACAGCTCACA TCCAGATGAA    60

TACAAAATTG CAGCCCTTGT CTTCTATAGC TGTATCTTCA TAATTGGATT ATTTGTTAAC   120

ATCACTGCAT TATGGGTTTT CAGTTGTACC ACCAAGAAGA GAACCACGGT AACCATCTAT   180

ATGATGAATG TGGCATTAGT GGACTTGATA TTTATAATGA CTTTACCCTT TCGAATGTTT   240

TATTATGCAA AAGATGCATG GCCATTTGGA GAGTACTTCT GCCAGATTAT TGGAGCTCTC   300

ACAGTGTTTT ACCCAAGCAT TGCTTTATGG CTTCTTGCCT TTATTAGTGC TGACAGATAC   360

ATGGCCATTG TACAGCCGAA GTACGCCAAA GAACTTAAAA ACACGTGCAA AGCCGTGCTG   420

GCGTGTGTGG GAGTCTGGAT AATGACCCTG ACCACGACCA CCCCTCTGCT ACTGCTCTAT   480

AAAGACCCAG ATAAAGACTC CACTCCCGCC ACCTGCCTCA AGATTTCTGA CATCATCTAT   540

CTAAAAGCTG TGAACGTGCT GAACCTCACT CGACTGACAT TTTTTTTCTT GATTCCTTTG   600

TTCATCATGA TTGGGTGCTA CTTGGTCATT ATTCATAATC TCCTTCACGG CAGGACGTCT   660

AAGCTGAAAC CCAAAGTCAA GGAGAAGTCC ATAAGGATCA TCATCACGCT GCTGGTGCAG   720

GTGCTCGTCT GCTTTATGCC CTTCCACATC TGTTTCGCTT TCCTGATGCT GGGAACGGGG   780

GAGAACAGTT ACAATCCCTG GGGAGCCTTT ACCACCTTCC TCATGAACCT CAGCACGTGT   840

CTGGATGTGA TTCTCTACTA CATCGTTTCA AAACAATTTC AGGCTCGAGT CATTAGTGTC   900

ATGCTATACC GTAATTACCT TCGAAGCCTG CGCAGAAAAA GTTTCCGATC TGGTAGTCTA   960

AGGTCACTAA GCAATATAAA CAGTGAAATG TTATGA                              996
```

(37) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 331 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```
Met Ile Thr Leu Asn Asn Gln Asp Gln Pro Val Thr Phe Asn Ser Ser
1               5                  10                  15

His Pro Asp Glu Tyr Lys Ile Ala Ala Leu Val Phe Tyr Ser Cys Ile
            20                  25                  30

Phe Ile Ile Gly Leu Phe Val Asn Ile Thr Ala Leu Trp Val Phe Ser
        35                  40                  45

Cys Thr Thr Lys Lys Arg Thr Thr Val Thr Ile Tyr Met Met Asn Val
    50                  55                  60

Ala Leu Val Asp Leu Ile Phe Ile Met Thr Leu Pro Phe Arg Met Phe
65                  70                  75                  80

Tyr Tyr Ala Lys Asp Ala Trp Pro Phe Gly Glu Tyr Phe Cys Gln Ile
                85                  90                  95

Ile Gly Ala Leu Thr Val Phe Tyr Pro Ser Ile Ala Leu Trp Leu Leu
            100                 105                 110

Ala Phe Ile Ser Ala Asp Arg Tyr Met Ala Ile Val Gln Pro Lys Tyr
        115                 120                 125

Ala Lys Glu Leu Lys Asn Thr Cys Lys Ala Val Leu Ala Cys Val Gly
    130                 135                 140

Val Trp Ile Met Thr Leu Thr Thr Thr Thr Pro Leu Leu Leu Leu Tyr
145                 150                 155                 160

Lys Asp Pro Asp Lys Asp Ser Thr Pro Ala Thr Cys Leu Lys Ile Ser
                165                 170                 175
```

```
Asp Ile Ile Tyr Leu Lys Ala Val Asn Val Leu Asn Leu Thr Arg Leu
            180                 185                 190

Thr Phe Phe Phe Leu Ile Pro Leu Phe Ile Met Ile Gly Cys Tyr Leu
        195                 200                 205

Val Ile Ile His Asn Leu Leu His Gly Arg Thr Ser Lys Leu Lys Pro
    210                 215                 220

Lys Val Lys Glu Lys Ser Ile Arg Ile Ile Ile Thr Leu Leu Val Gln
225                 230                 235                 240

Val Leu Val Cys Phe Met Pro Phe His Ile Cys Phe Ala Phe Leu Met
                245                 250                 255

Leu Gly Thr Gly Glu Asn Ser Tyr Asn Pro Trp Gly Ala Phe Thr Thr
            260                 265                 270

Phe Leu Met Asn Leu Ser Thr Cys Leu Asp Val Ile Leu Tyr Tyr Ile
        275                 280                 285

Val Ser Lys Gln Phe Gln Ala Arg Val Ile Ser Val Met Leu Tyr Arg
    290                 295                 300

Asn Tyr Leu Arg Ser Leu Arg Arg Lys Ser Phe Arg Ser Gly Ser Leu
305                 310                 315                 320

Arg Ser Leu Ser Asn Ile Asn Ser Glu Met Leu
                325                 330
```

(38) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```
CCAAGCTTCC AGGCCTGGGG TGTGCTGG                                  28
```

(39) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

ATGGATCCTG ACCTTCGGCC CCTGGCAGA 29

(40) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1077 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

ATGCCCTCTG TGTCTCCAGC GGGGCCCTCG GCCGGGGCAG TCCCCAATGC CACCGCAGTG 60

ACAACAGTGC GGACCAATGC CAGCGGGCTG GAGGTGCCCC TGTTCCACCT GTTTGCCCGG 120

CTGGACGAGG AGCTGCATGG CACCTTCCCA GGCCTGTGCG TGGCGCTGAT GGCGGTGCAC 180

GGAGCCATCT TCCTGGCAGG GCTGGTGCTC AACGGGCTGG CGCTGTACGT CTTCTGCTGC 240

CGCACCCGGG CCAAGACACC CTCAGTCATC TACACCATCA ACCTGGTGGT GACCGATCTA 300

CTGGTAGGGC TGTCCCTGCC CACGCGCTTC GCTGTGTACT ACGGCGCCAG GGGCTGCCTG 360

CGCTGTGCCT TCCCGCACGT CCTCGGTTAC TTCCTCAACA TGCACTGCTC CATCCTCTTC 420

CTCACCTGCA TCTGCGTGGA CCGCTACCTG GCCATCGTGC GGCCCGAAGG CTCCCGCCGC 480

TGCCGCCAGC CTGCCTGTGC CAGGGCCGTG TGCGCCTTCG TGTGGCTGGC CGCCGGTGCC 540

GTCACCCTGT CGGTGCTGGG CGTGACAGGC AGCCGGCCCT GCTGCCGTGT CTTTGCGCTG 600

ACTGTCCTGG AGTTCCTGCT GCCCCTGCTG GTCATCAGCG TGTTTACCGG CCGCATCATG 660

TGTGCACTGT CGCGGCCGGG TCTGCTCCAC CAGGGTCGCC AGCGCCGCGT GCGGGCCATG 720

CAGCTCCTGC TCACGGTGCT CATCATCTTT CTCGTCTGCT TCACGCCCTT CCACGCCCGC 780

CAAGTGGCCG TGGCGCTGTG GCCCGACATG CCACACCACA CGAGCCTCGT GGTCTACCAC 840

GTGGCCGTGA CCCTCAGCAG CCTCAACAGC TGCATGGACC CCATCGTCTA CTGCTTCGTC 900

ACCAGTGGCT TCCAGGCCAC CGTCCGAGGC CTCTTCGGCC AGCACGGAGA GCGTGAGCCC 960

AGCAGCGGTG ACGTGGTCAG CATGCACAGG AGCTCCAAGG GCTCAGGCCG TCATCACATC 1020

CTCAGTGCCG GCCCTCACGC CCTCACCCAG GCCCTGGCTA ATGGGCCCGA GGCTTAG 1077

(41) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 358 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

```
Met Pro Ser Val Ser Pro Ala Gly Pro Ser Ala Gly Ala Val Pro Asn
1               5                  10                  15

Ala Thr Ala Val Thr Thr Val Arg Thr Asn Ala Ser Gly Leu Glu Val
            20                  25                  30

Pro Leu Phe His Leu Phe Ala Arg Leu Asp Glu Glu Leu His Gly Thr
        35                  40                  45

Phe Pro Gly Leu Cys Val Ala Leu Met Ala Val His Gly Ala Ile Phe
    50                  55                  60

Leu Ala Gly Leu Val Leu Asn Gly Leu Ala Leu Tyr Val Phe Cys Cys
65                  70                  75                  80

Arg Thr Arg Ala Lys Thr Pro Ser Val Ile Tyr Thr Ile Asn Leu Val
                85                  90                  95

Val Thr Asp Leu Leu Val Gly Leu Ser Leu Pro Thr Arg Phe Ala Val
            100                 105                 110

Tyr Tyr Gly Ala Arg Gly Cys Leu Arg Cys Ala Phe Pro His Val Leu
        115                 120                 125

Gly Tyr Phe Leu Asn Met His Cys Ser Ile Leu Phe Leu Thr Cys Ile
    130                 135                 140

Cys Val Asp Arg Tyr Leu Ala Ile Val Arg Pro Glu Ala Pro Ala Ala
145                 150                 155                 160

Cys Arg Gln Pro Ala Cys Ala Arg Ala Val Cys Ala Phe Val Trp Leu
                165                 170                 175

Ala Ala Gly Ala Val Thr Leu Ser Val Leu Gly Val Thr Gly Ser Arg
            180                 185                 190

Pro Cys Cys Arg Val Phe Ala Leu Thr Val Leu Glu Phe Leu Leu Pro
        195                 200                 205

Leu Leu Val Ile Ser Val Phe Thr Gly Arg Ile Met Cys Ala Leu Ser
    210                 215                 220

Arg Pro Gly Leu Leu His Gln Gly Arg Gln Arg Arg Val Arg Ala Met
225                 230                 235                 240

Gln Leu Leu Leu Thr Val Leu Ile Ile Phe Leu Val Cys Phe Thr Pro
                245                 250                 255
```

```
Phe His Ala Arg Gln Val Ala Val Ala Leu Trp Pro Asp Met Pro His
            260                 265                 270

His Thr Ser Leu Val Val Tyr His Val Ala Val Thr Leu Ser Ser Leu
        275                 280                 285

Asn Ser Cys Met Asp Pro Ile Val Tyr Cys Phe Val Thr Ser Gly Phe
    290                 295                 300

Gln Ala Thr Val Arg Gly Leu Phe Gly Gln His Gly Glu Arg Glu Pro
305                 310                 315                 320

Ser Ser Gly Asp Val Val Ser Met His Arg Ser Ser Lys Gly Ser Gly
                325                 330                 335

Arg His His Ile Leu Ser Ala Gly Pro His Ala Leu Thr Gln Ala Leu
            340                 345                 350

Ala Asn Gly Pro Glu Ala
        355
```

(42) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

```
GAGAATTCAC TCCTGAGCTC AAGATGAACT                                    30
```

(43) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

```
CGGGATCCCC GTAACTGAGC CACTTCAGAT                                    30
```

(44) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1050 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

```
ATGAACTCCA CCTTGGATGG TAATCAGAGC AGCCACCCTT TTTGCCTCTT GGCATTTGGC    60

TATTTGGAAA CTGTCAATTT TTGCCTTTTG GAAGTATTGA TTATTGTCTT TCTAACTGTA   120

TTGATTATTT CTGGCAACAT CATTGTGATT TTTGTATTTC ACTGTGCACC TTTGTTGAAC   180

CATCACACTA CAAGTTATTT TATCCAGACT ATGGCATATG CTGACCTTTT TGTTGGGGTG   240

AGCTGCGTGG TCCCTTCTTT ATCACTCCTC CATCACCCCC TTCCAGTAGA GGAGTCCTTG   300

ACTTGCCAGA TATTTGGTTT TGTAGTATCA GTTCTGAAGA GCGTCTCCAT GGCTTCTCTG   360

GCCTGTATCA GCATTGATAG ATACATTGCC ATTACTAAAC CTTTAACCTA TAATACTCTG   420

GTTACACCCT GGAGACTACG CCTGTGTATT TTCCTGATTT GGCTATACTC GACCCTGGTC   480

TTCCTGCCTT CCTTTTTCCA CTGGGGCAAA CCTGGATATC ATGGAGATGT GTTTCAGTGG   540

TGTGCGGAGT CCTGGCACAC CGACTCCTAC TTCACCCTGT TCATCGTGAT GATGTTATAT   600

GCCCCAGCAG CCCTTATTGT CTGCTTCACC TATTTCAACA TCTTCCGCAT CTGCCAACAG   660

CACACAAAGG ATATCAGCGA AAGGCAAGCC CGCTTCAGCA GCCAGAGTGG GGAGACTGGG   720

GAAGTGCAGG CCTGTCCTGA TAAGCGCTAT GCCATGGTCC TGTTTCGAAT CACTAGTGTA   780

TTTTACATCC TCTGGTTGCC ATATATCATC TACTTCTTGT TGGAAAGCTC CACTGGCCAC   840

AGCAACCGCT TCGCATCCTT CTTGACCACC TGGCTTGCTA TTAGTAACAG TTTCTGCAAC   900

TGTGTAATTT ATAGTCTCTC CAACAGTGTA TTCCAAAGAG GACTAAAGCG CCTCTCAGGG   960

GCTATGTGTA CTTCTTGTGC AAGTCAGACT ACAGCCAACG ACCCTTACAC AGTTAGAAGC  1020

AAAGGCCCTC TTAATGGATG TCATATCTGA                                    1050
```

(45) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 349 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Met Asn Ser Thr Leu Asp Gly Asn Gln Ser Ser His Pro Phe Cys Leu

```
1               5                  10                  15
Leu Ala Phe Gly Tyr Leu Glu Thr Val Asn Phe Cys Leu Leu Glu Val
            20                  25                  30
Leu Ile Ile Val Phe Leu Thr Val Leu Ile Ile Ser Gly Asn Ile Ile
        35                  40                  45
Val Ile Phe Val Phe His Cys Ala Pro Leu Leu Asn His His Thr Thr
    50                  55                  60
Ser Tyr Phe Ile Gln Thr Met Ala Tyr Ala Asp Leu Phe Val Gly Val
65                  70                  75                  80
Ser Cys Val Val Pro Ser Leu Ser Leu Leu His His Pro Leu Pro Val
                85                  90                  95
Glu Glu Ser Leu Thr Cys Gln Ile Phe Gly Phe Val Val Ser Val Leu
            100                 105                 110
Lys Ser Val Ser Met Ala Ser Leu Ala Cys Ile Ser Ile Asp Arg Tyr
        115                 120                 125
Ile Ala Ile Thr Lys Pro Leu Thr Tyr Asn Thr Leu Val Thr Pro Trp
    130                 135                 140
Arg Leu Arg Leu Cys Ile Phe Leu Ile Trp Leu Tyr Ser Thr Leu Val
145                 150                 155                 160
Phe Leu Pro Ser Phe Phe His Trp Gly Lys Pro Gly Tyr His Gly Asp
                165                 170                 175
Val Phe Gln Trp Cys Ala Glu Ser Trp His Thr Asp Ser Tyr Phe Thr
            180                 185                 190
Leu Phe Ile Val Met Met Leu Tyr Ala Pro Ala Ala Leu Ile Val Cys
        195                 200                 205
Phe Thr Tyr Phe Asn Ile Phe Arg Ile Cys Gln Gln His Thr Lys Asp
    210                 215                 220
Ile Ser Glu Arg Gln Ala Arg Phe Ser Ser Gln Ser Gly Glu Thr Gly
225                 230                 235                 240
Glu Val Gln Ala Cys Pro Asp Lys Arg Tyr Ala Met Val Leu Phe Arg
                245                 250                 255
Ile Thr Ser Val Phe Tyr Ile Leu Trp Leu Pro Tyr Ile Ile Tyr Phe
            260                 265                 270
Leu Leu Glu Ser Ser Thr Gly His Ser Asn Arg Phe Ala Ser Phe Leu
        275                 280                 285
Thr Thr Trp Leu Ala Ile Ser Asn Ser Phe Cys Asn Cys Val Ile Tyr
    290                 295                 300
```

```
Ser Leu Ser Asn Ser Val Phe Gln Arg Gly Leu Lys Arg Leu Ser Gly
305                 310                 315                 320

Ala Met Cys Thr Ser Cys Ala Ser Gln Thr Thr Ala Asn Asp Pro Tyr
                325                 330                 335

Thr Val Arg Ser Lys Gly Pro Leu Asn Gly Cys His Ile
            340                 345
```

(46) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

```
TCCCCCGGGA AAAAAACCAA CTGCTCCAAA                                    30
```

(47) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```
TAGGATCCAT TTGAATGTGG ATTTGGTGAA A                                  31
```

(48) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1302 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

```
ATGTGTTTTT CTCCCATTCT GGAAATCAAC ATGCAGTCTG AATCTAACAT TACAGTGCGA     60

GATGACATTG ATGACATCAA CACCAATATG TACCAACCAC TATCATATCC GTTAAGCTTT    120

CAAGTGTCTC TCACCGGATT TCTTATGTTA GAAATTGTGT TGGGACTTGG CAGCAACCTC    180

ACTGTATTGG TACTTTACTG CATGAAATCC AACTTAATCA ACTCTGTCAG TAACATTATT    240

ACAATGAATC TTCATGTACT TGATGTAATA ATTTGTGTGG GATGTATTCC TCTAACTATA    300

GTTATCCTTC TGCTTTCACT GGAGAGTAAC ACTGCTCTCA TTTGCTGTTT CCATGAGGCT    360

TGTGTATCTT TTGCAAGTGT CTCAACAGCA ATCAACGTTT TTGCTATCAC TTTGGACAGA    420

TATGACATCT CTGTAAAACC TGCAAACCGA ATTCTGACAA TGGGCAGAGC TGTAATGTTA    480

ATGATATCCA TTTGGATTTT TTCTTTTTTC TCTTTCCTGA TTCCTTTTAT TGAGGTAAAT    540

TTTTTCAGTC TTCAAAGTGG AAATACCTGG GAAAACAAGA CACTTTTATG TGTCAGTACA    600

AATGAATACT ACACTGAACT GGGAATGTAT TATCACCTGT TAGTACAGAT CCCAATATTC    660

TTTTTCACTG TTGTAGTAAT GTTAATCACA TACACCAAAA TACTTCAGGC TCTTAATATT    720

CGAATAGGCA CAAGATTTTC AACAGGGCAG AAGAAGAAAG CAAGAAAGAA AAAGACAATT    780

TCTCTAACCA CACAACATGA GGCTACAGAC ATGTCACAAA GCAGTGGTGG GAGAAATGTA    840

GTCTTTGGTG TAAGAACTTC AGTTTCTGTA ATAATTGCCC TCCGGCGAGC TGTGAAACGA    900

CACCGTGAAC GACGAGAAAG ACAAAAGAGA GTCTTCAGGA TGTCTTTATT GATTATTTCT    960

ACATTTCTTC TCTGCTGGAC ACCAATTTCT GTTTTAAATA CCACCATTTT ATGTTTAGGC   1020

CCAAGTGACC TTTTAGTAAA ATTAAGATTG TGTTTTTTAG TCATGGCTTA TGGAACAACT   1080

ATATTTCACC CTCTATTATA TGCATTCACT AGACAAAAAT TTCAAAAGGT CTTGAAAAGT   1140

AAAATGAAAA AGCGAGTTGT TTCTATAGTA GAAGCTGATC CCCTGCCTAA TAATGCTGTA   1200

ATACACAACT CTTGGATAGA TCCCAAAAGA AACAAAAAAA TTACCTTTGA AGATAGTGAA   1260

ATAAGAGAAA AACGTTTAGT GCCTCAGGTT GTCACAGACT AG                       1302
```

(49) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 433 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

```
Met Cys Phe Ser Pro Ile Leu Glu Ile Asn Met Gln Ser Glu Ser Asn
1               5                  10                  15

Ile Thr Val Arg Asp Asp Ile Asp Asp Ile Asn Thr Asn Met Tyr Gln
            20                  25                  30
```

Pro Leu Ser Tyr Pro Leu Ser Phe Gln Val Ser Leu Thr Gly Phe Leu
35 40 45

Met Leu Glu Ile Val Leu Gly Leu Gly Ser Asn Leu Thr Val Leu Val
50 55 60

Leu Tyr Cys Met Lys Ser Asn Leu Ile Asn Ser Val Ser Asn Ile Ile
65 70 75 80

Thr Met Asn Leu His Val Leu Asp Val Ile Ile Cys Val Gly Cys Ile
85 90 95

Pro Leu Thr Ile Val Ile Leu Leu Leu Ser Leu Glu Ser Asn Thr Ala
100 105 110

Leu Ile Cys Cys Phe His Glu Ala Cys Val Ser Phe Ala Ser Val Ser
115 120 125

Thr Ala Ile Asn Val Phe Ala Ile Thr Leu Asp Arg Tyr Asp Ile Ser
130 135 140

Val Lys Pro Ala Asn Arg Ile Leu Thr Met Gly Arg Ala Val Met Leu
145 150 155 160

Met Ile Ser Ile Trp Ile Phe Ser Phe Phe Ser Phe Leu Ile Pro Phe
165 170 175

Ile Glu Val Asn Phe Phe Ser Leu Gln Ser Gly Asn Thr Trp Glu Asn
180 185 190

Lys Thr Leu Leu Cys Val Ser Thr Asn Glu Tyr Tyr Thr Glu Leu Gly
195 200 205

Met Tyr Tyr His Leu Leu Val Gln Ile Pro Ile Phe Phe Phe Thr Val
210 215 220

Val Val Met Leu Ile Thr Tyr Thr Lys Ile Leu Gln Ala Leu Asn Ile
225 230 235 240

Arg Ile Gly Thr Arg Phe Ser Thr Gly Gln Lys Lys Lys Ala Arg Lys
245 250 255

Lys Lys Thr Ile Ser Leu Thr Thr Gln His Glu Ala Thr Asp Met Ser
260 265 270

Gln Ser Ser Gly Gly Arg Asn Val Val Phe Gly Val Arg Thr Ser Val
275 280 285

Ser Val Ile Ile Ala Leu Arg Arg Ala Val Lys Arg His Arg Glu Arg
290 295 300

Arg Glu Arg Gln Lys Arg Val Phe Arg Met Ser Leu Leu Ile Ile Ser
305 310 315 320

Thr Phe Leu Leu Cys Trp Thr Pro Ile Ser Val Leu Asn Thr Thr Ile

```
                    325                 330                 335

Leu Cys Leu Gly Pro Ser Asp Leu Leu Val Lys Leu Arg Leu Cys Phe
            340                 345                 350

Leu Val Met Ala Tyr Gly Thr Thr Ile Phe His Pro Leu Leu Tyr Ala
        355                 360                 365

Phe Thr Arg Gln Lys Phe Gln Lys Val Leu Lys Ser Lys Met Lys Lys
    370                 375                 380

Arg Val Val Ser Ile Val Glu Ala Asp Pro Leu Pro Asn Asn Ala Val
385                 390                 395                 400

Ile His Asn Ser Trp Ile Asp Pro Lys Arg Asn Lys Lys Ile Thr Phe
                405                 410                 415

Glu Asp Ser Glu Ile Arg Glu Lys Arg Leu Val Pro Gln Val Val Thr
            420                 425                 430

Asp
```

(50) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```
GTGAAGCTTG CCTCTGGTGC CTGCAGGAGG                                    30
```

(51) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

```
GCAGAATTCC CGGTGGCGTG TTGTGGTGCC C                                  31
```

(52) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1209 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

```
ATGTTGTGTC CTTCCAAGAC AGATGGCTCA GGGCACTCTG GTAGGATTCA CCAGGAAACT    60
CATGGAGAAG GGAAAAGGGA CAAGATTAGC AACAGTGAAG GGAGGGAGAA TGGTGGGAGA   120
GGATTCCAGA TGAACGGTGG GTCGCTGGAG GCTGAGCATG CCAGCAGGAT GTCAGTTCTC   180
AGAGCAAAGC CCATGTCAAA CAGCCAACGC TTGCTCCTTC TGTCCCCAGG ATCACCTCCT   240
CGCACGGGGA GCATCTCCTA CATCAACATC ATCATGCCTT CGGTGTTCGG CACCATCTGC   300
CTCCTGGGCA TCATCGGGAA CTCCACGGTC ATCTTCGCGG TCGTGAAGAA GTCCAAGCTG   360
CACTGGTGCA ACAACGTCCC CGACATCTTC ATCATCAACC TCTCGGTAGT AGATCTCCTC   420
TTTCTCCTGG GCATGCCCTT CATGATCCAC CAGCTCATGG GCAATGGGGT GTGGCACTTT   480
GGGGAGACCA TGTGCACCCT CATCACGGCC ATGGATGCCA ATAGTCAGTT CACCAGCACC   540
TACATCCTGA CCGCCATGGC CATTGACCGC TACCTGGCCA CTGTCCACCC CATCTCTTCC   600
ACGAAGTTCC GGAAGCCCTC TGTGGCCACC CTGGTGATCT GCCTCCTGTG GGCCCTCTCC   660
TTCATCAGCA TCACCCCTGT GTGGCTGTAT GCCAGACTCA TCCCCTTCCC AGGAGGTGCA   720
GTGGGCTGCG GCATACGCCT GCCCAACCCA GACACTGACC TCTACTGGTT CACCCTGTAC   780
CAGTTTTTCC TGGCCTTTGC CCTGCCTTTT GTGGTCATCA CAGCCGCATA CGTGAGGATC   840
CTGCAGCGCA TGACGTCCTC AGTGGCCCCC GCCTCCCAGC GCAGCATCCG GCTGCGGACA   900
AAGAGGGTGA CCCGCACAGC CATCGCCATC TGTCTGGTCT TCTTTGTGTG CTGGGCACCC   960
TACTATGTGC TACAGCTGAC CCAGTTGTCC ATCAGCCGCC CGACCCTCAC CTTTGTCTAC  1020
TTATACAATG CGGCCATCAG CTTGGGCTAT GCCAACAGCT GCCTCAACCC CTTTGTGTAC  1080
ATCGTGCTCT GTGAGACGTT CCGCAAACGC TTGGTCCTGT CGGTGAAGCC TGCAGCCCAG  1140
GGGCAGCTTC GCGCTGTCAG CAACGCTCAG ACGGCTGACG AGGAGAGGAC AGAAAGCAAA  1200
GGCACCTGA                                                          1209
```

(53) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 402 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```
Met Leu Cys Pro Ser Lys Thr Asp Gly Ser Gly His Ser Gly Arg Ile
1               5                  10                  15

His Gln Glu Thr His Gly Glu Gly Lys Arg Asp Lys Ile Ser Asn Ser
            20                  25                  30

Glu Gly Arg Glu Asn Gly Gly Arg Gly Phe Gln Met Asn Gly Gly Ser
        35                  40                  45

Leu Glu Ala Glu His Ala Ser Arg Met Ser Val Leu Arg Ala Lys Pro
    50                  55                  60

Met Ser Asn Ser Gln Arg Leu Leu Leu Leu Ser Pro Gly Ser Pro Pro
65                  70                  75                  80

Arg Thr Gly Ser Ile Ser Tyr Ile Asn Ile Ile Met Pro Ser Val Phe
                85                  90                  95

Gly Thr Ile Cys Leu Leu Gly Ile Ile Gly Asn Ser Thr Val Ile Phe
            100                 105                 110

Ala Val Val Lys Lys Ser Lys Leu His Trp Cys Asn Asn Val Pro Asp
        115                 120                 125

Ile Phe Ile Ile Asn Leu Ser Val Val Asp Leu Leu Phe Leu Leu Gly
    130                 135                 140

Met Pro Phe Met Ile His Gln Leu Met Gly Asn Gly Val Trp His Phe
145                 150                 155                 160

Gly Glu Thr Met Cys Thr Leu Ile Thr Ala Met Asp Ala Asn Ser Gln
                165                 170                 175

Phe Thr Ser Thr Tyr Ile Leu Thr Ala Met Ala Ile Asp Arg Tyr Leu
            180                 185                 190

Ala Thr Val His Pro Ile Ser Ser Thr Lys Phe Arg Lys Pro Ser Val
        195                 200                 205

Ala Thr Leu Val Ile Cys Leu Leu Trp Ala Leu Ser Phe Ile Ser Ile
    210                 215                 220

Thr Pro Val Trp Leu Tyr Ala Arg Leu Ile Pro Phe Pro Gly Gly Ala
225                 230                 235                 240

Val Gly Cys Gly Ile Arg Leu Pro Asn Pro Asp Thr Asp Leu Tyr Trp
                245                 250                 255
```

```
Phe Thr Leu Tyr Gln Phe Phe Leu Ala Phe Ala Leu Pro Phe Val Val
            260                 265                 270

Ile Thr Ala Ala Tyr Val Arg Ile Leu Gln Arg Met Thr Ser Ser Val
        275                 280                 285

Ala Pro Ala Ser Gln Arg Ser Ile Arg Leu Arg Thr Lys Arg Val Thr
    290                 295                 300

Arg Thr Ala Ile Ala Ile Cys Leu Val Phe Phe Val Cys Trp Ala Pro
305                 310                 315                 320

Tyr Tyr Val Leu Gln Leu Thr Gln Leu Ser Ile Ser Arg Pro Thr Leu
                325                 330                 335

Thr Phe Val Tyr Leu Tyr Asn Ala Ala Ile Ser Leu Gly Tyr Ala Asn
            340                 345                 350

Ser Cys Leu Asn Pro Phe Val Tyr Ile Val Leu Cys Glu Thr Phe Arg
        355                 360                 365

Lys Arg Leu Val Leu Ser Val Lys Pro Ala Ala Gln Gly Gln Leu Arg
    370                 375                 380

Ala Val Ser Asn Ala Gln Thr Ala Asp Glu Glu Arg Thr Glu Ser Lys
385                 390                 395                 400

Gly Thr
```

(54) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```
GGCGGATCCA TGGATGTGAC TTCCCAA                                    27
```

(55) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

GGCGGATCCC TACACGGCAC TGCTGAA 27

(56) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1128 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

ATGGATGTGA CTTCCCAAGC CCGGGGCGTG GGCCTGGAGA TGTACCCAGG CACCGCGCAC 60

GCTGCGGCCC CCAACACCAC CTCCCCCGAG CTCAACCTGT CCCACCCGCT CCTGGGCACC 120

GCCCTGGCCA ATGGGACAGG TGAGCTCTCG GAGCACCAGC AGTACGTGAT CGGCCTGTTC 180

CTCTCGTGCC TCTACACCAT CTTCCTCTTC CCCATCGGCT TTGTGGGCAA CATCCTGATC 240

CTGGTGGTGA ACATCAGCTT CCGCGAGAAG ATGACCATCC CCGACCTGTA CTTCATCAAC 300

CTGGCGGTGG CGGACCTCAT CCTGGTGGCC GACTCCCTCA TTGAGGTGTT CAACCTGCAC 360

GAGCGGTACT ACGACATCGC CGTCCTGTGC ACCTTCATGT CGCTCTTCCT GCAGGTCAAC 420

ATGTACAGCA GCGTCTTCTT CCTCACCTGG ATGAGCTTCG ACCGCTACAT CGCCCTGGCC 480

AGGGCCATGC GCTGCAGCCT GTTCCGCACC AAGCACCACG CCCGGCTGAG CTGTGGCCTC 540

ATCTGGATGG CATCCGTGTC AGCCACGCTG GTGCCCTTCA CCGCCGTGCA CCTGCAGCAC 600

ACCGACGAGG CCTGCTTCTG TTTCGCGGAT GTCCGGGAGG TGCAGTGGCT CGAGGTCACG 660

CTGGGCTTCA TCGTGCCCTT CGCCATCATC GGCCTGTGCT ACTCCCTCAT TGTCCGGGTG 720

CTGGTCAGGG CGCACCGGCA CCGTGGGCTG CGGCCCCGGC GGCAGAAGGC GCTCCGCATG 780

ATCCTCGCGG TGGTGCTGGT CTTCTTCGTC TGCTGGCTGC CGGAGAACGT CTTCATCAGC 840

GTGCACCTCC TGCAGCGGAC GCAGCCTGGG GCCGCTCCCT GCAAGCAGTC TTTCCGCCAT 900

GCCCACCCCC TCACGGGCCA CATTGTCAAC CTCGCCGCCT TCTCCAACAG CTGCCTAAAC 960

CCCCTCATCT ACAGCTTTCT CGGGGAGACC TTCAGGGACA AGCTGAGGCT GTACATTGAG 1020

CAGAAAACAA ATTTGCCGGC CCTGAACCGC TTCTGTCACG CTGCCCTGAA GGCCGTCATT 1080

CCAGACAGCA CCGAGCAGTC GGATGTGAGG TTCAGCAGTG CCGTGTGA 1128

(57) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 375 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

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

Gly Thr Ala His Ala Ala Ala Pro Asn Thr Thr Ser Pro Glu Leu Asn
            20                  25                  30

Leu Ser His Pro Leu Leu Gly Thr Ala Leu Ala Asn Gly Thr Gly Glu
        35                  40                  45

Leu Ser Glu His Gln Gln Tyr Val Ile Gly Leu Phe Leu Ser Cys Leu
    50                  55                  60

Tyr Thr Ile Phe Leu Phe Pro Ile Gly Phe Val Gly Asn Ile Leu Ile
65                  70                  75                  80

Leu Val Val Asn Ile Ser Phe Arg Glu Lys Met Thr Ile Pro Asp Leu
                85                  90                  95

Tyr Phe Ile Asn Leu Ala Val Ala Asp Leu Ile Leu Val Ala Asp Ser
            100                 105                 110

Leu Ile Glu Val Phe Asn Leu His Glu Arg Tyr Tyr Asp Ile Ala Val
        115                 120                 125

Leu Cys Thr Phe Met Ser Leu Phe Leu Gln Val Asn Met Tyr Ser Ser
    130                 135                 140

Val Phe Phe Leu Thr Trp Met Ser Phe Asp Arg Tyr Ile Ala Leu Ala
145                 150                 155                 160

Arg Ala Met Arg Cys Ser Leu Phe Arg Thr Lys His His Ala Arg Leu
                165                 170                 175

Ser Cys Gly Leu Ile Trp Met Ala Ser Val Ser Ala Thr Leu Val Pro
            180                 185                 190

Phe Thr Ala Val His Leu Gln His Thr Asp Glu Ala Cys Phe Cys Phe
        195                 200                 205

Ala Asp Val Arg Glu Val Gln Trp Leu Glu Val Thr Leu Gly Phe Ile
    210                 215                 220

Val Pro Phe Ala Ile Ile Gly Leu Cys Tyr Ser Leu Ile Val Arg Val
225                 230                 235                 240

Leu Val Arg Ala His Arg His Arg Gly Leu Arg Pro Arg Arg Gln Lys
```

```
                    245                 250                 255

Ala Leu Arg Met Ile Leu Ala Val Val Leu Val Phe Phe Val Cys Trp
            260                 265                 270

Leu Pro Glu Asn Val Phe Ile Ser Val His Leu Leu Gln Arg Thr Gln
        275                 280                 285

Pro Gly Ala Ala Pro Cys Lys Gln Ser Phe Arg His Ala His Pro Leu
    290                 295                 300

Thr Gly His Ile Val Asn Leu Ala Ala Phe Ser Asn Ser Cys Leu Asn
305                 310                 315                 320

Pro Leu Ile Tyr Ser Phe Leu Gly Glu Thr Phe Arg Asp Lys Leu Arg
                325                 330                 335

Leu Tyr Ile Glu Gln Lys Thr Asn Leu Pro Ala Leu Asn Arg Phe Cys
            340                 345                 350

His Ala Ala Leu Lys Ala Val Ile Pro Asp Ser Thr Glu Gln Ser Asp
        355                 360                 365

Val Arg Phe Ser Ser Ala Val
    370                 375
```

(58) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

```
AAGGAATTCA CGGCCGGGTG ATGCCATTCC C                                  31
```

(59) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

GGTGGATCCA TAAACACGGG CGTTGAGGAC 30

(60) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 960 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

ATGCCATTCC CAAACTGCTC AGCCCCCAGC ACTGTGGTGG CCACAGCTGT GGGTGTCTTG 60

CTGGGGCTGG AGTGTGGGCT GGGTCTGCTG GGCAACGCGG TGGCGCTGTG GACCTTCCTG 120

TTCCGGGTCA GGGTGTGGAA GCCGTACGCT GTCTACCTGC TCAACCTGGC CCTGGCTGAC 180

CTGCTGTTGG CTGCGTGCCT GCCTTTCCTG GCCGCCTTCT ACCTGAGCCT CCAGGCTTGG 240

CATCTGGGCC GTGTGGGCTG CTGGGCCCTG CGCTTCCTGC TGGACCTCAG CCGCAGCGTG 300

GGGATGGCCT TCCTGGCCGC CGTGGCTTTG GACCGGTACC TCCGTGTGGT CCACCCTCGG 360

CTTAAGGTCA ACCTGCTGTC TCCTCAGGCG GCCCTGGGGG TCTCGGGCCT CGTCTGGCTC 420

CTGATGGTCG CCCTCACCTG CCCGGGCTTG CTCATCTCTG AGGCCGCCCA GAACTCCACC 480

AGGTGCCACA GTTTCTACTC CAGGGCAGAC GGCTCCTTCA GCATCATCTG GCAGGAAGCA 540

CTCTCCTGCC TTCAGTTTGT CCTCCCCTTT GGCCTCATCG TGTTCTGCAA TGCAGGCATC 600

ATCAGGGCTC TCCAGAAAAG ACTCCGGGAG CCTGAGAAAC AGCCCAAGCT TCAGCGGGCC 660

CAGGCACTGG TCACCTTGGT GGTGGTGCTG TTTGCTCTGT GCTTTCTGCC CTGCTTCCTG 720

GCCAGAGTCC TGATGCACAT CTTCCAGAAT CTGGGGAGCT GCAGGGCCCT TTGTGCAGTG 780

GCTCATACCT CGGATGTCAC GGGCAGCCTC ACCTACCTGC ACAGTGTCGT CAACCCCGTG 840

GTATACTGCT TCTCCAGCCC CACCTTCAGG AGCTCCTATC GGAGGGTCTT CCACACCCTC 900

CGAGGCAAAG GGCAGGCAGC AGAGCCCCCA GATTTCAACC CCAGAGACTC CTATTCCTGA 960

(61) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 319 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Met Pro Phe Pro Asn Cys Ser Ala Pro Ser Thr Val Val Ala Thr Ala

```
1               5                  10                  15
Val Gly Val Leu Leu Gly Leu Glu Cys Gly Leu Gly Leu Leu Gly Asn
            20                  25                  30
Ala Val Ala Leu Trp Thr Phe Leu Phe Arg Val Arg Val Trp Lys Pro
        35                  40                  45
Tyr Ala Val Tyr Leu Leu Asn Leu Ala Leu Ala Asp Leu Leu Leu Ala
    50                  55                  60
Ala Cys Leu Pro Phe Leu Ala Ala Phe Tyr Leu Ser Leu Gln Ala Trp
65                  70                  75                  80
His Leu Gly Arg Val Gly Cys Trp Ala Leu Arg Phe Leu Leu Asp Leu
                85                  90                  95
Ser Arg Ser Val Gly Met Ala Phe Leu Ala Ala Val Ala Leu Asp Arg
            100                 105                 110
Tyr Leu Arg Val Val His Pro Arg Leu Lys Val Asn Leu Leu Ser Pro
        115                 120                 125
Gln Ala Ala Leu Gly Val Ser Gly Leu Val Trp Leu Leu Met Val Ala
    130                 135                 140
Leu Thr Cys Pro Gly Leu Leu Ile Ser Glu Ala Ala Gln Asn Ser Thr
145                 150                 155                 160
Arg Cys His Ser Phe Tyr Ser Arg Ala Asp Gly Ser Phe Ser Ile Ile
                165                 170                 175
Trp Gln Glu Ala Leu Ser Cys Leu Gln Phe Val Leu Pro Phe Gly Leu
            180                 185                 190
Ile Val Phe Cys Asn Ala Gly Ile Ile Arg Ala Leu Gln Lys Arg Leu
        195                 200                 205
Arg Glu Pro Glu Lys Gln Pro Lys Leu Gln Arg Ala Gln Ala Leu Val
    210                 215                 220
Thr Leu Val Val Val Leu Phe Ala Leu Cys Phe Leu Pro Cys Phe Leu
225                 230                 235                 240
Ala Arg Val Leu Met His Ile Phe Gln Asn Leu Gly Ser Cys Arg Ala
                245                 250                 255
Leu Cys Ala Val Ala His Thr Ser Asp Val Thr Gly Ser Leu Thr Tyr
            260                 265                 270
Leu His Ser Val Val Asn Pro Val Val Tyr Cys Phe Ser Ser Pro Thr
        275                 280                 285
Phe Arg Ser Ser Tyr Arg Arg Val Phe His Thr Leu Arg Gly Lys Gly
    290                 295                 300
```

Gln Ala Ala Glu Pro Pro Asp Phe Asn Pro Arg Asp Ser Tyr Ser
305 310 315

(62) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1143 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

```
ATGGAGGAAG GTGGTGATTT TGACAACTAC TATGGGGCAG ACAACCAGTC TGAGTGTGAG     60

TACACAGACT GGAAATCCTC GGGGGCCCTC ATCCCTGCCA TCTACATGTT GGTCTTCCTC    120

CTGGGCACCA CGGGAAACGG TCTGGTGCTC TGGACCGTGT TTCGGAGCAG CCGGGAGAAG    180

AGGCGCTCAG CTGATATCTT CATTGCTAGC CTGGCGGTGG CTGACCTGAC CTTCGTGGTG    240

ACGCTGCCCC TGTGGGCTAC CTACACGTAC CGGGACTATG ACTGGCCCTT TGGGACCTTC    300

TTCTGCAAGC TCAGCAGCTA CCTCATCTTC GTCAACATGT ACGCCAGCGT CTTCTGCCTC    360

ACCGGCCTCA GCTTCGACCG CTACCTGGCC ATCGTGAGGC CAGTGGCCAA TGCTCGGCTG    420

AGGCTGCGGG TCAGCGGGGC CGTGGCCACG GCAGTTCTTT GGGTGCTGGC CGCCCTCCTG    480

GCCATGCCTG TCATGGTGTT ACGCACCACC GGGGACTTGG AGAACACCAC TAAGGTGCAG    540

TGCTACATGG ACTACTCCAT GGTGGCCACT GTGAGCTCAG AGTGGGCCTG GGAGGTGGGC    600

CTTGGGGTCT CGTCCACCAC CGTGGGCTTT GTGGTGCCCT TCACCATCAT GCTGACCTGT    660

TACTTCTTCA TCGCCCAAAC CATCGCTGGC CACTTCCGCA AGGAACGCAT CGAGGGCCTG    720

CGGAAGCGGC GCCGGCTGCT CAGCATCATC GTGGTGCTGG TGGTGACCTT TGCCCTGTGC    780

TGGATGCCCT ACCACCTGGT GAAGACGCTG TACATGCTGG GCAGCCTGCT GCACTGGCCC    840

TGTGACTTTG ACCTCTTCCT CATGAACATC TTCCCCTACT GCACCTGCAT CAGCTACGTC    900

AACAGCTGCC TCAACCCCTT CCTCTATGCC TTTTTCGACC CCCGCTTCCG CCAGGCCTGC    960

ACCTCCATGC TCTGCTGTGG CCAGAGCAGG TGCGCAGGCA CCTCCCACAG CAGCAGTGGG   1020

GAGAAGTCAG CCAGCTACTC TTCGGGGCAC AGCCAGGGGC CCGGCCCCAA CATGGGCAAG   1080

GGTGGAGAAC AGATGCACGA GAAATCCATC CCCTACAGCC AGGAGACCCT TGTGGTTGAC   1140

TAG                                                                 1143
```

(63) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 380 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

```
Met Glu Glu Gly Gly Asp Phe Asp Asn Tyr Tyr Gly Ala Asp Asn Gln
1               5                  10                  15

Ser Glu Cys Glu Tyr Thr Asp Trp Lys Ser Ser Gly Ala Leu Ile Pro
            20                  25                  30

Ala Ile Tyr Met Leu Val Phe Leu Leu Gly Thr Thr Gly Asn Gly Leu
        35                  40                  45

Val Leu Trp Thr Val Phe Arg Ser Ser Arg Glu Lys Arg Arg Ser Ala
    50                  55                  60

Asp Ile Phe Ile Ala Ser Leu Ala Val Ala Asp Leu Thr Phe Val Val
65                  70                  75                  80

Thr Leu Pro Leu Trp Ala Thr Tyr Thr Tyr Arg Asp Tyr Asp Trp Pro
                85                  90                  95

Phe Gly Thr Phe Phe Cys Lys Leu Ser Ser Tyr Leu Ile Phe Val Asn
            100                 105                 110

Met Tyr Ala Ser Val Phe Cys Leu Thr Gly Leu Ser Phe Asp Arg Tyr
        115                 120                 125

Leu Ala Ile Val Arg Pro Val Ala Asn Ala Arg Leu Arg Leu Arg Val
    130                 135                 140

Ser Gly Ala Val Ala Thr Ala Val Leu Trp Val Leu Ala Ala Leu Leu
145                 150                 155                 160

Ala Met Pro Val Met Val Leu Arg Thr Thr Gly Asp Leu Glu Asn Thr
                165                 170                 175

Thr Lys Val Gln Cys Tyr Met Asp Tyr Ser Met Val Ala Thr Val Ser
            180                 185                 190

Ser Glu Trp Ala Trp Glu Val Gly Leu Gly Val Ser Ser Thr Thr Val
        195                 200                 205

Gly Phe Val Val Pro Phe Thr Ile Met Leu Thr Cys Tyr Phe Phe Ile
    210                 215                 220

Ala Gln Thr Ile Ala Gly His Phe Arg Lys Glu Arg Ile Glu Gly Leu
```

```
225                 230                 235                 240

Arg Lys Arg Arg Arg Leu Leu Ser Ile Ile Val Val Leu Val Val Thr
                245                 250                 255

Phe Ala Leu Cys Trp Met Pro Tyr His Leu Val Lys Thr Leu Tyr Met
            260                 265                 270

Leu Gly Ser Leu Leu His Trp Pro Cys Asp Phe Asp Leu Phe Leu Met
        275                 280                 285

Asn Ile Phe Pro Tyr Cys Thr Cys Ile Ser Tyr Val Asn Ser Cys Leu
    290                 295                 300

Asn Pro Phe Leu Tyr Ala Phe Phe Asp Pro Arg Phe Arg Gln Ala Cys
305                 310                 315                 320

Thr Ser Met Leu Cys Cys Gly Gln Ser Arg Cys Ala Gly Thr Ser His
                325                 330                 335

Ser Ser Ser Gly Glu Lys Ser Ala Ser Tyr Ser Ser Gly His Ser Gln
            340                 345                 350

Gly Pro Gly Pro Asn Met Gly Lys Gly Gly Glu Gln Met His Glu Lys
        355                 360                 365

Ser Ile Pro Tyr Ser Gln Glu Thr Leu Val Val Asp
    370                 375                 380
```

(64) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

```
TGAGAATTCT GGTGACTCAC AGCCGGCACA G                              31
```

(65) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GCCGGATCCA AGGAAAAGCA GCAATAAAAG G 31

(66) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1119 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

ATGAACTACC CGCTAACGCT GGAAATGGAC CTCGAGAACC TGGAGGACCT GTTCTGGGAA 60

CTGGACAGAT TGGACAACTA TAACGACACC TCCCTGGTGG AAAATCATCT CTGCCCTGCC 120

ACAGAGGGTC CCCTCATGGC CTCCTTCAAG GCCGTGTTCG TGCCCGTGGC CTACAGCCTC 180

ATCTTCCTCC TGGGCGTGAT CGGCAACGTC CTGGTGCTGG TGATCCTGGA GCGGCACCGG 240

CAGACACGCA GTTCCACGGA GACCTTCCTG TTCCACCTGG CCGTGGCCGA CCTCCTGCTG 300

GTCTTCATCT TGCCCTTTGC CGTGGCCGAG GGCTCTGTGG GCTGGGTCCT GGGGACCTTC 360

CTCTGCAAAA CTGTGATTGC CCTGCACAAA GTCAACTTCT ACTGCAGCAG CCTGCTCCTG 420

GCCTGCATCG CCGTGGACCG CTACCTGGCC ATTGTCCACG CCGTCCATGC CTACCGCCAC 480

CGCCGCCTCC TCTCCATCCA CATCACCTGT GGGACCATCT GGCTGGTGGG CTTCCTCCTT 540

GCCTTGCCAG AGATTCTCTT CGCCAAAGTC AGCCAAGGCC ATCACAACAA CTCCCTGCCA 600

CGTTGCACCT TCTCCCAAGA GAACCAAGCA GAAACGCATG CCTGGTTCAC CTCCCGATTC 660

CTCTACCATG TGGCGGGATT CCTGCTGCCC ATGCTGGTGA TGGGCTGGTG CTACGTGGGG 720

GTAGTGCACA GGTTGCGCCA GGCCCAGCGG CGCCCTCAGC GGCAGAAGGC AGTCAGGGTG 780

GCCATCCTGG TGACAAGCAT CTTCTTCCTC TGCTGGTCAC CCTACCACAT CGTCATCTTC 840

CTGGACACCC TGGCGAGGCT GAAGGCCGTG GACAATACCT GCAAGCTGAA TGGCTCTCTC 900

CCCGTGGCCA TCACCATGTG TGAGTTCCTG GGCCTGGCCC ACTGCTGCCT CAACCCCATG 960

CTCTACACTT TCGCCGGCGT GAAGTTCCGC AGTGACCTGT CGCGGCTCCT GACCAAGCTG 1020

GGCTGTACCG GCCCTGCCTC CCTGTGCCAG CTCTTCCCTA GCTGGCGCAG GAGCAGTCTC 1080

TCTGAGTCAG AGAATGCCAC CTCTCTCACC ACGTTCTAG 1119

(67) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 372 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

```
Met Asn Tyr Pro Leu Thr Leu Glu Met Asp Leu Glu Asn Leu Glu Asp
1               5                  10                  15

Leu Phe Trp Glu Leu Asp Arg Leu Asp Asn Tyr Asn Asp Thr Ser Leu
            20                  25                  30

Val Glu Asn His Leu Cys Pro Ala Thr Glu Gly Pro Leu Met Ala Ser
        35                  40                  45

Phe Lys Ala Val Phe Val Pro Val Ala Tyr Ser Leu Ile Phe Leu Leu
    50                  55                  60

Gly Val Ile Gly Asn Val Leu Val Leu Val Ile Leu Glu Arg His Arg
65                  70                  75                  80

Gln Thr Arg Ser Ser Thr Glu Thr Phe Leu Phe His Leu Ala Val Ala
                85                  90                  95

Asp Leu Leu Leu Val Phe Ile Leu Pro Phe Ala Val Ala Glu Gly Ser
            100                 105                 110

Val Gly Trp Val Leu Gly Thr Phe Leu Cys Lys Thr Val Ile Ala Leu
        115                 120                 125

His Lys Val Asn Phe Tyr Cys Ser Ser Leu Leu Leu Ala Cys Ile Ala
    130                 135                 140

Val Asp Arg Tyr Leu Ala Ile Val His Ala Val His Ala Tyr Arg His
145                 150                 155                 160

Arg Arg Leu Leu Ser Ile His Ile Thr Cys Gly Thr Ile Trp Leu Val
                165                 170                 175

Gly Phe Leu Leu Ala Leu Pro Glu Ile Leu Phe Ala Lys Val Ser Gln
            180                 185                 190

Gly His His Asn Asn Ser Leu Pro Arg Cys Thr Phe Ser Gln Glu Asn
        195                 200                 205

Gln Ala Glu Thr His Ala Trp Phe Thr Ser Arg Phe Leu Tyr His Val
    210                 215                 220

Ala Gly Phe Leu Leu Pro Met Leu Val Met Gly Trp Cys Tyr Val Gly
225                 230                 235                 240

Val Val His Arg Leu Arg Gln Ala Gln Arg Arg Pro Gln Arg Gln Lys
```

```
                    245                 250                 255

Ala Val Arg Val Ala Ile Leu Val Thr Ser Ile Phe Phe Leu Cys Trp
            260                 265                 270

Ser Pro Tyr His Ile Val Ile Phe Leu Asp Thr Leu Ala Arg Leu Lys
        275                 280                 285

Ala Val Asp Asn Thr Cys Lys Leu Asn Gly Ser Leu Pro Val Ala Ile
    290                 295                 300

Thr Met Cys Glu Phe Leu Gly Leu Ala His Cys Cys Leu Asn Pro Met
305                 310                 315                 320

Leu Tyr Thr Phe Ala Gly Val Lys Phe Arg Ser Asp Leu Ser Arg Leu
                325                 330                 335

Leu Thr Lys Leu Gly Cys Thr Gly Pro Ala Ser Leu Cys Gln Leu Phe
            340                 345                 350

Pro Ser Trp Arg Arg Ser Ser Leu Ser Glu Ser Glu Asn Ala Thr Ser
        355                 360                 365

Leu Thr Thr Phe
    370
```

(68) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

```
CAAAGCTTGA AAGCTGCACG GTGCAGAGAC                                    30
```

(69) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

```
GCGGATCCCG AGTCACACCC TGGCTGGGCC                                    30
```

(70) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1128 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

```
ATGGATGTGA CTTCCCAAGC CCGGGGCGTG GGCCTGGAGA TGTACCCAGG CACCGCGCAG    60

CCTGCGGCCC CCAACACCAC CTCCCCCGAG CTCAACCTGT CCCACCCGCT CCTGGGCACC   120

GCCCTGGCCA ATGGGACAGG TGAGCTCTCG GAGCACCAGC AGTACGTGAT CGGCCTGTTC   180

CTCTCGTGCC TCTACACCAT CTTCCTCTTC CCCATCGGCT TTGTGGGCAA CATCCTGATC   240

CTGGTGGTGA ACATCAGCTT CCGCGAGAAG ATGACCATCC CCGACCTGTA CTTCATCAAC   300

CTGGCGGTGG CGGACCTCAT CCTGGTGGCC GACTCCCTCA TTGAGGTGTT CAACCTGCAC   360

GAGCGGTACT ACGACATCGC CGTCCTGTGC ACCTTCATGT CGCTCTTCCT GCAGGTCAAC   420

ATGTACAGCA GCGTCTTCTT CCTCACCTGG ATGAGCTTCG ACCGCTACAT CGCCCTGGCC   480

AGGGCCATGC GCTGCAGCCT GTTCCGCACC AAGCACCACG CCCGGCTGAG CTGTGGCCTC   540

ATCTGGATGG CATCCGTGTC AGCCACGCTG GTGCCCTTCA CCGCCGTGCA CCTGCAGCAC   600

ACCGACGAGG CCTGCTTCTG TTTCGCGGAT GTCCGGGAGG TGCAGTGGCT CGAGGTCACG   660

CTGGGCTTCA TCGTGCCCTT CGCCATCATC GGCCTGTGCT ACTCCCTCAT TGTCCGGGTG   720

CTGGTCAGGG CGCACCGGCA CCGTGGGCTG CGGCCCCGGC GGCAGAAGGC GCTCCGCATG   780

ATCCTCGCGG TGGTGCTGGT CTTCTTCGTC TGCTGGCTGC CGGAGAACGT CTTCATCAGC   840

GTGCACCTCC TGCAGCGGAC GCAGCCTGGG GCCGCTCCCT GCAAGCAGTC TTTCCGCCAT   900

GCCCACCCCC TCACGGGCCA CATTGTCAAC CTCACCGCCT TCTCCAACAG CTGCCTAAAC   960

CCCCTCATCT ACAGCTTTCT CGGGGAGACC TTCAGGGACA AGCTGAGGCT GTACATTGAG  1020

CAGAAAACAA ATTTGCCGGC CCTGAACCGC TTCTGTCACG CTGCCCTGAA GGCCGTCATT  1080

CCAGACAGCA CCGAGCAGTC GGATGTGAGG TTCAGCAGTG CCGTGTAG               1128
```

(71) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 375 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

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

Gly Thr Ala Gln Pro Ala Ala Pro Asn Thr Thr Ser Pro Glu Leu Asn
            20                  25                  30

Leu Ser His Pro Leu Leu Gly Thr Ala Leu Ala Asn Gly Thr Gly Glu
        35                  40                  45

Leu Ser Glu His Gln Gln Tyr Val Ile Gly Leu Phe Leu Ser Cys Leu
    50                  55                  60

Tyr Thr Ile Phe Leu Phe Pro Ile Gly Phe Val Gly Asn Ile Leu Ile
65                  70                  75                  80

Leu Val Val Asn Ile Ser Phe Arg Glu Lys Met Thr Ile Pro Asp Leu
                85                  90                  95

Tyr Phe Ile Asn Leu Ala Val Ala Asp Leu Ile Leu Val Ala Asp Ser
            100                 105                 110

Leu Ile Glu Val Phe Asn Leu His Glu Arg Tyr Tyr Asp Ile Ala Val
        115                 120                 125

Leu Cys Thr Phe Met Ser Leu Phe Leu Gln Val Asn Met Tyr Ser Ser
    130                 135                 140

Val Phe Phe Leu Thr Trp Met Ser Phe Asp Arg Tyr Ile Ala Leu Ala
145                 150                 155                 160

Arg Ala Met Arg Cys Ser Leu Phe Arg Thr Lys His His Ala Arg Leu
                165                 170                 175

Ser Cys Gly Leu Ile Trp Met Ala Ser Val Ser Ala Thr Leu Val Pro
            180                 185                 190

Phe Thr Ala Val His Leu Gln His Thr Asp Glu Ala Cys Phe Cys Phe
        195                 200                 205

Ala Asp Val Arg Glu Val Gln Trp Leu Glu Val Thr Leu Gly Phe Ile
    210                 215                 220

Val Pro Phe Ala Ile Ile Gly Leu Cys Tyr Ser Leu Ile Val Arg Val
225                 230                 235                 240

Leu Val Arg Ala His Arg His Arg Gly Leu Arg Pro Arg Arg Gln Lys
                245                 250                 255

Ala Leu Arg Met Ile Leu Ala Val Val Leu Val Phe Phe Val Cys Trp
            260                 265                 270
```

```
Leu Pro Glu Asn Val Phe Ile Ser Val His Leu Leu Gln Arg Thr Gln
        275                 280                 285

Pro Gly Ala Ala Pro Cys Lys Gln Ser Phe Arg His Ala His Pro Leu
    290                 295                 300

Thr Gly His Ile Val Asn Leu Thr Ala Phe Ser Asn Ser Cys Leu Asn
305                 310                 315                 320

Pro Leu Ile Tyr Ser Phe Leu Gly Glu Thr Phe Arg Asp Lys Leu Arg
                325                 330                 335

Leu Tyr Ile Glu Gln Lys Thr Asn Leu Pro Ala Leu Asn Arg Phe Cys
            340                 345                 350

His Ala Ala Leu Lys Ala Val Ile Pro Asp Ser Thr Glu Gln Ser Asp
        355                 360                 365

Val Arg Phe Ser Ser Ala Val
    370                 375
```

(72) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

```
ACAGAATTCC TGTGTGGTTT TACCGCCCAG                                    30
```

(73) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

```
CTCGGATCCA GGCAGAAGAG TCGCCTATGG                                    30
```

(74) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1137 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

```
ATGGACCTGG GGAAACCAAT GAAAAGCGTG CTGGTGGTGG CTCTCCTTGT CATTTTCCAG    60
GTATGCCTGT GTCAAGATGA GGTCACGGAC GATTACATCG GAGACAACAC CACAGTGGAC   120
TACACTTTGT TCGAGTCTTT GTGCTCCAAG AAGGACGTGC GGAACTTTAA AGCCTGGTTC   180
CTCCCTATCA TGTACTCCAT CATTTGTTTC GTGGGCCTAC TGGGCAATGG GCTGGTCGTG   240
TTGACCTATA TCTATTTCAA GAGGCTCAAG ACCATGACCG ATACCTACCT GCTCAACCTG   300
GCGGTGGCAG ACATCCTCTT CCTCCTGACC CTTCCCTTCT GGGCCTACAG CGCGGCCAAG   360
TCCTGGGTCT TCGGTGTCCA CTTTTGCAAG CTCATCTTTG CCATCTACAA GATGAGCTTC   420
TTCAGTGGCA TGCTCCTACT TCTTTGCATC AGCATTGACC GCTACGTGGC CATCGTCCAG   480
GCTGTCTCAG CTCACCGCCA CCGTGCCCGC GTCCTTCTCA TCAGCAAGCT GTCCTGTGTG   540
GGCATCTGGA TACTAGCCAC AGTGCTCTCC ATCCCAGAGC TCCTGTACAG TGACCTCCAG   600
AGGAGCAGCA GTGAGCAAGC GATGCGATGC TCTCTCATCA CAGAGCATGT GGAGGCCTTT   660
ATCACCATCC AGGTGGCCCA GATGGTGATC GGCTTTCTGG TCCCCCTGCT GGCCATGAGC   720
TTCTGTTACC TTGTCATCAT CCGCACCCTG CTCCAGGCAC GCAACTTTGA GCGCAACAAG   780
GCCATCAAGG TGATCATCGC TGTGGTCGTG GTCTTCATAG TCTTCCAGCT GCCCTACAAT   840
GGGGTGGTCC TGGCCCAGAC GGTGGCCAAC TTCAACATCA CCAGTAGCAC CTGTGAGCTC   900
AGTAAGCAAC TCAACATCGC CTACGACGTC ACCTACAGCC TGGCCTGCGT CCGCTGCTGC   960
GTCAACCCTT TCTTGTACGC CTTCATCGGC GTCAAGTTCC GCAACGATCT CTTCAAGCTC  1020
TTCAAGGACC TGGGCTGCCT CAGCCAGGAG CAGCTCCGGC AGTGGTCTTC CTGTCGGCAC  1080
ATCCGGCGCT CCTCCATGAG TGTGGAGGCC GAGACCACCA CCACCTTCTC CCCATAG      1137
```

(75) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 378 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

```
Met Asp Leu Gly Lys Pro Met Lys Ser Val Leu Val Val Ala Leu Leu
1               5                  10                  15

Val Ile Phe Gln Val Cys Leu Cys Gln Asp Glu Val Thr Asp Asp Tyr
            20                  25                  30

Ile Gly Asp Asn Thr Thr Val Asp Tyr Thr Leu Phe Glu Ser Leu Cys
        35                  40                  45

Ser Lys Lys Asp Val Arg Asn Phe Lys Ala Trp Phe Leu Pro Ile Met
    50                  55                  60

Tyr Ser Ile Ile Cys Phe Val Gly Leu Leu Gly Asn Gly Leu Val Val
65                  70                  75                  80

Leu Thr Tyr Ile Tyr Phe Lys Arg Leu Lys Thr Met Thr Asp Thr Tyr
                85                  90                  95

Leu Leu Asn Leu Ala Val Ala Asp Ile Leu Phe Leu Leu Thr Leu Pro
            100                 105                 110

Phe Trp Ala Tyr Ser Ala Ala Lys Ser Trp Val Phe Gly Val His Phe
        115                 120                 125

Cys Lys Leu Ile Phe Ala Ile Tyr Lys Met Ser Phe Phe Ser Gly Met
    130                 135                 140

Leu Leu Leu Leu Cys Ile Ser Ile Asp Arg Tyr Val Ala Ile Val Gln
145                 150                 155                 160

Ala Val Ser Ala His Arg His Arg Ala Arg Val Leu Leu Ile Ser Lys
                165                 170                 175

Leu Ser Cys Val Gly Ile Trp Ile Leu Ala Thr Val Leu Ser Ile Pro
            180                 185                 190

Glu Leu Leu Tyr Ser Asp Leu Gln Arg Ser Ser Ser Glu Gln Ala Met
        195                 200                 205

Arg Cys Ser Leu Ile Thr Glu His Val Glu Ala Phe Ile Thr Ile Gln
    210                 215                 220

Val Ala Gln Met Val Ile Gly Phe Leu Val Pro Leu Leu Ala Met Ser
225                 230                 235                 240

Phe Cys Tyr Leu Val Ile Ile Arg Thr Leu Leu Gln Ala Arg Asn Phe
                245                 250                 255

Glu Arg Asn Lys Ala Ile Lys Val Ile Ile Ala Val Val Val Val Phe
            260                 265                 270

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

```
Ala Asn Phe Asn Ile Thr Ser Ser Thr Cys Glu Leu Ser Lys Gln Leu
    290                 295                 300

Asn Ile Ala Tyr Asp Val Thr Tyr Ser Leu Ala Cys Val Arg Cys Cys
305                 310                 315                 320

Val Asn Pro Phe Leu Tyr Ala Phe Ile Gly Val Lys Phe Arg Asn Asp
                325                 330                 335

Leu Phe Lys Leu Phe Lys Asp Leu Gly Cys Leu Ser Gln Glu Gln Leu
            340                 345                 350

Arg Gln Trp Ser Ser Cys Arg His Ile Arg Arg Ser Ser Met Ser Val
        355                 360                 365

Glu Ala Glu Thr Thr Thr Thr Phe Ser Pro
    370                 375
```

(76) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

```
CTGGAATTCA CCTGGACCAC CACCAATGGA TA                                32
```

(77) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```
CTCGGATCCT GCAAAGTTTG TCATACAGTT                                   30
```

(78) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1085 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```
ATGGATATAC AAATGGCAAA CAATTTTACT CCGCCCTCTG CAACTCCTCA GGGAAATGAC    60
TGTGACCTCT ATGCACATCA CAGCACGGCC AGGATAGTAA TGCCTCTGCA TTACAGCCTC   120
GTCTTCATCA TTGGGCTCGT GGGAAACTTA CTAGCCTTGG TCGTCATTGT TCAAAACAGG   180
AAAAAAATCA ACTCTACCAC CCTCTATTCA ACAAATTTGG TGATTTCTGA TATACTTTTT   240
ACCACGGCTT TGCCTACACG AATAGCCTAC TATGCAATGG GCTTTGACTG GAGAATCGGA   300
GATGCCTTGT GTAGGATAAC TGCGCTAGTG TTTTACATCA ACACATATGC AGGTGTGAAC   360
TTTATGACCT GCCTGAGTAT TGACCGCTTC ATTGCTGTGG TGCACCCTCT ACGCTACAAC   420
AAGATAAAAA GGATTGAACA TGCAAAAGGC GTGTGCATAT TTGTCTGGAT TCTAGTATTT   480
GCTCAGACAC TCCCACTCCT CATCAACCCT ATGTCAAAGC AGGAGGCTGA AAGGATTACA   540
TGCATGGAGT ATCCAAACTT TGAAGAAACT AAATCTCTTC CCTGGATTCT GCTTGGGGCA   600
TGTTTCATAG GATATGTACT TCCACTTATA ATCATTCTCA TCTGCTATTC TCAGATCTGC   660
TGCAAACTCT TCAGAACTGC CAAACAAAAC CCACTCACTG AGAAATCTGG TGTAAACAAA   720
AAGGCTCTCA ACACAATTAT TCTTATTATT GTTGTGTTTG TTCTCTGTTT CACACCTTAC   780
CATGTTGCAA TTATTCAACA TATGATTAAG AAGCTTCGTT TCTCTAATTT CCTGGAATGT   840
AGCCAAAGAC ATTCGTTCCA GATTTCTCTG CACTTTACAG TATGCCTGAT GAACTTCAAT   900
TGCTGCATGG ACCCTTTTAT CTACTTCTTT GCATGTAAAG GGTATAAGAG AAAGGTTATG   960
AGGATGCTGA AACGGCAAGT CAGTGTATCG ATTTCTAGTG CTGTGAAGTC AGCCCCTGAA  1020
GAAAATTCAC GTGAAATGAC AGAAACGCAG ATGATGATAC ATTCCAAGTC TTCAAATGGA  1080
AAGTGA                                                             1086
```

(79) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 361 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Met Asp Ile Gln Met Ala Asn Asn Phe Thr Pro Pro Ser Ala Thr Pro
1 5 10 15

```
Gln Gly Asn Asp Cys Asp Leu Tyr Ala His His Ser Thr Ala Arg Ile
            20                  25                  30

Val Met Pro Leu His Tyr Ser Leu Val Phe Ile Ile Gly Leu Val Gly
        35                  40                  45

Asn Leu Leu Ala Leu Val Val Ile Val Gln Asn Arg Lys Lys Ile Asn
    50                  55                  60

Ser Thr Thr Leu Tyr Ser Thr Asn Leu Val Ile Ser Asp Ile Leu Phe
65                  70                  75                  80

Thr Thr Ala Leu Pro Thr Arg Ile Ala Tyr Tyr Ala Met Gly Phe Asp
                85                  90                  95

Trp Arg Ile Gly Asp Ala Leu Cys Arg Ile Thr Ala Leu Val Phe Tyr
            100                 105                 110

Ile Asn Thr Tyr Ala Gly Val Asn Phe Met Thr Cys Leu Ser Ile Asp
        115                 120                 125

Arg Phe Ile Ala Val Val His Pro Leu Arg Tyr Asn Lys Ile Lys Arg
    130                 135                 140

Ile Glu His Ala Lys Gly Val Cys Ile Phe Val Trp Ile Leu Val Phe
145                 150                 155                 160

Ala Gln Thr Leu Pro Leu Leu Ile Asn Pro Met Ser Lys Gln Glu Ala
                165                 170                 175

Glu Arg Ile Thr Cys Met Glu Tyr Pro Asn Phe Glu Glu Thr Lys Ser
            180                 185                 190

Leu Pro Trp Ile Leu Leu Gly Ala Cys Phe Ile Gly Tyr Val Leu Pro
        195                 200                 205

Leu Ile Ile Ile Leu Ile Cys Tyr Ser Gln Ile Cys Cys Lys Leu Phe
    210                 215                 220

Arg Thr Ala Lys Gln Asn Pro Leu Thr Glu Lys Ser Gly Val Asn Lys
225                 230                 235                 240

Lys Ala Leu Asn Thr Ile Ile Leu Ile Ile Val Val Phe Val Leu Cys
                245                 250                 255

Phe Thr Pro Tyr His Val Ala Ile Ile Gln His Met Ile Lys Lys Leu
            260                 265                 270

Arg Phe Ser Asn Phe Leu Glu Cys Ser Gln Arg His Ser Phe Gln Ile
        275                 280                 285

Ser Leu His Phe Thr Val Cys Leu Met Asn Phe Asn Cys Cys Met Asp
    290                 295                 300

Pro Phe Ile Tyr Phe Phe Ala Cys Lys Gly Tyr Lys Arg Lys Val Met
```

```
305                 310                 315                 320

Arg Met Leu Lys Arg Gln Val Ser Val Ser Ile Ser Ser Ala Val Lys
                325                 330                 335

Ser Ala Pro Glu Glu Asn Ser Arg Glu Met Thr Glu Thr Gln Met Met
            340                 345                 350

Ile His Ser Lys Ser Ser Asn Gly Lys
        355                 360
```

(80) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

```
CTGGAATTCT CCTGCTCATC CAGCCATGCG G                              31
```

(81) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

```
CCTGGATCCC CACCCCTACT GGGGCCTCAG                                30
```

(82) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1446 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

ATGCGGTGGC TGTGGCCCCT GGCTGTCTCT CTTGCTGTGA TTTTGGCTGT GGGGCTAAGC 60

AGGGTCTCTG GGGGTGCCCC CCTGCACCTG GGCAGGCACA GAGCCGAGAC CCAGGAGCAG 120

CAGAGCCGAT CCAAGAGGGG CACCGAGGAT GAGGAGGCCA AGGGCGTGCA GCAGTATGTG 180

CCTGAGGAGT GGGCGGAGTA CCCCCGGCCC ATTCACCCTG CTGGCCTGCA GCCAACCAAG 240

CCCTTGGTGG CCACCAGCCC TAACCCCGAC AAGGATGGGG GCACCCCAGA CAGTGGGCAG 300

GAACTGAGGG GCAATCTGAC AGGGGCACCA GGGCAGAGGC TACAGATCCA GAACCCCCTG 360

TATCCGGTGA CCGAGAGCTC CTACAGTGCC TATGCCATCA TGCTTCTGGC GCTGGTGGTG 420

TTTGCGGTGG GCATTGTGGG CAACCTGTCG GTCATGTGCA TCGTGTGGCA CAGCTACTAC 480

CTGAAGAGCG CCTGGAACTC CATCCTTGCC AGCCTGGCCC TCTGGGATTT TCTGGTCCTC 540

TTTTTCTGCC TCCCTATTGT CATCTTCAAC GAGATCACCA AGCAGAGGCT ACTGGGTGAC 600

GTTTCTTGTC GTGCCGTGCC CTTCATGGAG GTCTCCTCTC TGGGAGTCAC GACTTTCAGC 660

CTCTGTGCCC TGGGCATTGA CCGCTTCCAC GTGGCCACCA GCACCCTGCC CAAGGTGAGG 720

CCCATCGAGC GGTGCCAATC CATCCTGGCC AAGTTGGCTG TCATCTGGGT GGGCTCCATG 780

ACGCTGGCTG TGCCTGAGCT CCTGCTGTGG CAGCTGGCAC AGGAGCCTGC CCCCACCATG 840

GGCACCCTGG ACTCATGCAT CATGAAACCC TCAGCCAGCC TGCCCGAGTC CCTGTATTCA 900

CTGGTGATGA CCTACCAGAA CGCCCGCATG TGGTGGTACT TTGGCTGCTA CTTCTGCCTG 960

CCCATCCTCT TCACAGTCAC CTGCCAGCTG GTGACATGGC GGGTGCGAGG CCCTCCAGGG 1020

AGGAAGTCAG AGTGCAGGGC CAGCAAGCAC GAGCAGTGTG AGAGCCAGCT CAACAGCACC 1080

GTGGTGGGCC TGACCGTGGT CTACGCCTTC TGCACCCTCC CAGAGAACGT CTGCAACATC 1140

GTGGTGGCCT ACCTCTCCAC CGAGCTGACC CGCCAGACCC TGGACCTCCT GGGCCTCATC 1200

AACCAGTTCT CCACCTTCTT CAAGGGCGCC ATCACCCCAG TGCTGCTCCT TTGCATCTGC 1260

AGGCCGCTGG GCCAGGCCTT CCTGGACTGC TGCTGCTGCT GCTGCTGTGA GGAGTGCGGC 1320

GGGGCTTCGG AGGCCTCTGC TGCCAATGGG TCGGACAACA AGCTCAAGAC CGAGGTGTCC 1380

TCTTCCATCT ACTTCCACAA GCCCAGGGAG TCACCCCCAC TCCTGCCCCT GGGCACACCT 1440

TGCTGA 1446

(83) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 481 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
Met Arg Trp Leu Trp Pro Leu Ala Val Ser Leu Ala Val Ile Leu Ala
1               5                  10                  15

Val Gly Leu Ser Arg Val Ser Gly Gly Ala Pro Leu His Leu Gly Arg
            20                  25                  30

His Arg Ala Glu Thr Gln Glu Gln Gln Ser Arg Ser Lys Arg Gly Thr
        35                  40                  45

Glu Asp Glu Glu Ala Lys Gly Val Gln Gln Tyr Val Pro Glu Glu Trp
    50                  55                  60

Ala Glu Tyr Pro Arg Pro Ile His Pro Ala Gly Leu Gln Pro Thr Lys
65                  70                  75                  80

Pro Leu Val Ala Thr Ser Pro Asn Pro Asp Lys Asp Gly Gly Thr Pro
                85                  90                  95

Asp Ser Gly Gln Glu Leu Arg Gly Asn Leu Thr Gly Ala Pro Gly Gln
            100                 105                 110

Arg Leu Gln Ile Gln Asn Pro Leu Tyr Pro Val Thr Glu Ser Ser Tyr
        115                 120                 125

Ser Ala Tyr Ala Ile Met Leu Leu Ala Leu Val Val Phe Ala Val Gly
    130                 135                 140

Ile Val Gly Asn Leu Ser Val Met Cys Ile Val Trp His Ser Tyr Tyr
145                 150                 155                 160

Leu Lys Ser Ala Trp Asn Ser Ile Leu Ala Ser Leu Ala Leu Trp Asp
                165                 170                 175

Phe Leu Val Leu Phe Phe Cys Leu Pro Ile Val Ile Phe Asn Glu Ile
            180                 185                 190

Thr Lys Gln Arg Leu Leu Gly Asp Val Ser Cys Arg Ala Val Pro Phe
        195                 200                 205

Met Glu Val Ser Ser Leu Gly Val Thr Thr Phe Ser Leu Cys Ala Leu
    210                 215                 220

Gly Ile Asp Arg Phe His Val Ala Thr Ser Thr Leu Pro Lys Val Arg
225                 230                 235                 240

Pro Ile Glu Arg Cys Gln Ser Ile Leu Ala Lys Leu Ala Val Ile Trp
                245                 250                 255

Val Gly Ser Met Thr Leu Ala Val Pro Glu Leu Leu Leu Trp Gln Leu
            260                 265                 270

Ala Gln Glu Pro Ala Pro Thr Met Gly Thr Leu Asp Ser Cys Ile Met
```

```
                275                 280                 285

Lys Pro Ser Ala Ser Leu Pro Glu Ser Leu Tyr Ser Leu Val Met Thr
290                 295                 300

Tyr Gln Asn Ala Arg Met Trp Trp Tyr Phe Gly Cys Tyr Phe Cys Leu
305                 310                 315                 320

Pro Ile Leu Phe Thr Val Thr Cys Gln Leu Val Thr Trp Arg Val Arg
                325                 330                 335

Gly Pro Pro Gly Arg Lys Ser Glu Cys Arg Ala Ser Lys His Glu Gln
            340                 345                 350

Cys Glu Ser Gln Leu Asn Ser Thr Val Val Gly Leu Thr Val Val Tyr
        355                 360                 365

Ala Phe Cys Thr Leu Pro Glu Asn Val Cys Asn Ile Val Val Ala Tyr
370                 375                 380

Leu Ser Thr Glu Leu Thr Arg Gln Thr Leu Asp Leu Leu Gly Leu Ile
385                 390                 395                 400

Asn Gln Phe Ser Thr Phe Phe Lys Gly Ala Ile Thr Pro Val Leu Leu
                405                 410                 415

Leu Cys Ile Cys Arg Pro Leu Gly Gln Ala Phe Leu Asp Cys Cys Cys
            420                 425                 430

Cys Cys Cys Cys Glu Glu Cys Gly Gly Ala Ser Glu Ala Ser Ala Ala
        435                 440                 445

Asn Gly Ser Asp Asn Lys Leu Lys Thr Glu Val Ser Ser Ser Ile Tyr
450                 455                 460

Phe His Lys Pro Arg Glu Ser Pro Pro Leu Leu Pro Leu Gly Thr Pro
465                 470                 475                 480

Cys
```

(84) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

```
ATGTGGAACG CGACGCCCAG CG                                              22
```

(85) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

TCATGTATTA ATACTAGATT CT 22

(86) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

TACCATGTGG AACGCGACGC CCAGCGAAGA GCCGGGGT 38

(87) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

CGGAATTCAT GTATTAATAC TAGATTCTGT CCAGGCCCG 39

(88) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1101 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```
ATGTGGAACG CGACGCCCAG CGAAGAGCCG GGGTTCAACC TCACACTGGC CGACCTGGAC     60

TGGGATGCTT CCCCCGGCAA CGACTCGCTG GGCGACGAGC TGCTGCAGCT CTTCCCCGCG    120

CCGCTGCTGG CGGGCGTCAC AGCCACCTGC GTGGCACTCT TCGTGGTGGG TATCGCTGGC    180

AACCTGCTCA CCATGCTGGT GGTGTCGCGC TTCCGCGAGC TGCGCACCAC CACCAACCTC    240

TACCTGTCCA GCATGGCCTT CTCCGATCTG CTCATCTTCC TCTGCATGCC CCTGGACCTC    300

GTTCGCCTCT GGCAGTACCG GCCCTGGAAC TTCGGCGACC TCCTCTGCAA ACTCTTCCAA    360

TTCGTCAGTG AGAGCTGCAC CTACGCCACG GTGCTCACCA TCACAGCGCT GAGCGTCGAG    420

CGCTACTTCG CCATCTGCTT CCCACTCCGG GCCAAGGTGG TGGTCACCAA GGGGCGGGTG    480

AAGCTGGTCA TCTTCGTCAT CTGGGCCGTG GCCTTCTGCA GCGCCGGGCC CATCTTCGTG    540

CTAGTCGGGG TGGAGCACGA GAACGGCACC GACCCTTGGG ACACCAACGA GTGCCGCCCC    600

ACCGAGTTTG CGGTGCGCTC TGGACTGCTC ACGGTCATGG TGTGGGTGTC CAGCATCTTC    660

TTCTTCCTTC CTGTCTTCTG TCTCACGGTC CTCTACAGTC TCATCGGCAG GAAGCTGTGG    720

CGGAGGAGGC GCGGCGATGC TGTCGTGGGT GCCTCGCTCA GGGACCAGAA CCACAAGCAA    780

ACCGTGAAAA TGCTGGCTGT AGTGGTGTTT GCCTTCATCC TCTGCTGGCT CCCCTTCCAC    840

GTAGGGCGAT ATTTATTTTC CAAATCCTTT GAGCCTGGCT CCTTGGAGAT TGCTCAGATC    900

AGCCAGTACT GCAACCTCGT GTCCTTTGTC CTCTTCTACC TCAGTGCTGC CATCAACCCC    960

ATTCTGTACA ACATCATGTC CAAGAAGTAC CGGGTGGCAG TGTTCAGACT TCTGGGATTC   1020

GAACCCTTCT CCCAGAGAAA GCTCTCCACT CTGAAAGATG AAAGTTCTCG GGCCTGGACA   1080

GAATCTAGTA TTAATACATG A                                              1101
```

(89) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 366 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

```
Met Trp Asn Ala Thr Pro Ser Glu Glu Pro Gly Phe Asn Leu Thr Leu
1               5                  10                  15

Ala Asp Leu Asp Trp Asp Ala Ser Pro Gly Asn Asp Ser Leu Gly Asp
            20                  25                  30
```

Glu Leu Leu Gln Leu Phe Pro Ala Pro Leu Leu Ala Gly Val Thr Ala
35 40 45

Thr Cys Val Ala Leu Phe Val Val Gly Ile Ala Gly Asn Leu Leu Thr
50 55 60

Met Leu Val Val Ser Arg Phe Arg Glu Leu Arg Thr Thr Thr Asn Leu
65 70 75 80

Tyr Leu Ser Ser Met Ala Phe Ser Asp Leu Leu Ile Phe Leu Cys Met
85 90 95

Pro Leu Asp Leu Val Arg Leu Trp Gln Tyr Arg Pro Trp Asn Phe Gly
100 105 110

Asp Leu Leu Cys Lys Leu Phe Gln Phe Val Ser Glu Ser Cys Thr Tyr
115 120 125

Ala Thr Val Leu Thr Ile Thr Ala Leu Ser Val Glu Arg Tyr Phe Ala
130 135 140

Ile Cys Phe Pro Leu Arg Ala Lys Val Val Val Thr Lys Gly Arg Val
145 150 155 160

Lys Leu Val Ile Phe Val Ile Trp Ala Val Ala Phe Cys Ser Ala Gly
165 170 175

Pro Ile Phe Val Leu Val Gly Val Glu His Glu Asn Gly Thr Asp Pro
180 185 190

Trp Asp Thr Asn Glu Cys Arg Pro Thr Glu Phe Ala Val Arg Ser Gly
195 200 205

Leu Leu Thr Val Met Val Trp Val Ser Ser Ile Phe Phe Phe Leu Pro
210 215 220

Val Phe Cys Leu Thr Val Leu Tyr Ser Leu Ile Gly Arg Lys Leu Trp
225 230 235 240

Arg Arg Arg Arg Gly Asp Ala Val Val Gly Ala Ser Leu Arg Asp Gln
245 250 255

Asn His Lys Gln Thr Val Lys Met Leu Ala Val Val Val Phe Ala Phe
260 265 270

Ile Leu Cys Trp Leu Pro Phe His Val Gly Arg Tyr Leu Phe Ser Lys
275 280 285

Ser Phe Glu Pro Gly Ser Leu Glu Ile Ala Gln Ile Ser Gln Tyr Cys
290 295 300

Asn Leu Val Ser Phe Val Leu Phe Tyr Leu Ser Ala Ala Ile Asn Pro
305 310 315 320

Ile Leu Tyr Asn Ile Met Ser Lys Lys Tyr Arg Val Ala Val Phe Arg

```
                    325                 330                 335

Leu Leu Gly Phe Glu Pro Phe Ser Gln Arg Lys Leu Ser Thr Leu Lys
            340                 345                 350

Asp Glu Ser Ser Arg Ala Trp Thr Glu Ser Ser Ile Asn Thr
        355                 360                 365
```

(90) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

```
GCAAGCTTGT GCCCTCACCA AGCCATGCGA GCC                              33
```

(91) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

```
CGGAATTCAG CAATGAGTTC CGACAGAAGC                                  30
```

(92) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1842 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

```
ATGCGAGCCC CGGGCGCGCT TCTCGCCCGC ATGTCGCGGC TACTGCTTCT GCTACTGCTC    60

AAGGTGTCTG CCTCTTCTGC CCTCGGGGTC GCCCCTGCGT CCAGAAACGA AACTTGTCTG   120

GGGGAGAGCT GTGCACCTAC AGTGATCCAG CGCCGCGGCA GGGACGCCTG GGGACCGGGA   180

AATTCTGCAA GAGACGTTCT GCGAGCCCGA GCACCCAGGG AGGAGCAGGG GGCAGCGTTT   240
```

CTTGCGGGAC CCTCCTGGGA CCTGCCGGCG GCCCCGGGCC GTGACCCGGC TGCAGGCAGA 300

GGGGCGGAGG CGTCGGCAGC CGGACCCCCG GGACCTCCAA CCAGGCCACC TGGCCCCTGG 360

AGGTGGAAAG GTGCTCGGGG TCAGGAGCCT TCTGAAACTT TGGGGAGAGG GAACCCCACG 420

GCCCTCCAGC TCTTCCTTCA GATCTCAGAG GAGGAAGAGA AGGGTCCCAG AGGCGCTGGC 480

ATTTCCGGGC GTAGCCAGGA GCAGAGTGTG AAGACAGTCC CCGGAGCCAG CGATCTTTTT 540

TACTGGCCAA GGAGAGCCGG GAAACTCCAG GGTTCCCACC ACAAGCCCCT GTCCAAGACG 600

GCCAATGGAC TGGCGGGGCA CGAAGGGTGG ACAATTGCAC TCCCGGGCCG GGCGCTGGCC 660

CAGAATGGAT CCTTGGGTGA AGGAATCCAT GAGCCTGGGG GTCCCCGCCG GGGAAACAGC 720

ACGAACCGGC GTGTGAGACT GAAGAACCCC TTCTACCCGC TGACCCAGGA GTCCTATGGA 780

GCCTACGCGG TCATGTGTCT GTCCGTGGTG ATCTTCGGGA CCGGCATCAT TGGCAACCTG 840

GCGGTGATGA GCATCGTGTG CCACAACTAC TACATGCGGA GCATCTCCAA CTCCCTCTTG 900

GCCAACCTGG CCTTCTGGGA CTTTCTCATC ATCTTCTTCT GCCTTCCGCT GGTCATCTTC 960

CACGAGCTGA CCAAGAAGTG GCTGCTGGAG GACTTCTCCT GCAAGATCGT GCCCTATATA 1020

GAGGTCGCTT CTCTGGGAGT CACCACTTTC ACCTTATGTG CTCTGTGCAT AGACCGCTTC 1080

CGTGCTGCCA CCAACGTACA GATGTACTAC GAAATGATCG AAAACTGTTC CTCAACAACT 1140

GCCAAACTTG CTGTTATATG GGTGGGAGCT CTATTGTTAG CACTTCCAGA AGTTGTTCTC 1200

CGCCAGCTGA GCAAGGAGGA TTTGGGGTTT AGTGGCCGAG CTCCGGCAGA AAGGTGCATT 1260

ATTAAGATCT CTCCTGATTT ACCAGACACC ATCTATGTTC TAGCCCTCAC CTACGACAGT 1320

GCGAGACTGT GGTGGTATTT TGGCTGTTAC TTTTGTTTGC CCACGCTTTT CACCATCACC 1380

TGCTCTCTAG TGACTGCGAG GAAAATCCGC AAAGCAGAGA AAGCCTGTAC CCGAGGGAAT 1440

AAACGGCAGA TTCAACTAGA GAGTCAGATG AACTGTACAG TAGTGGCACT GACCATTTTA 1500

TATGGATTTT GCATTATTCC TGAAAATATC TGCAACATTG TTACTGCCTA CATGGCTACA 1560

GGGGTTTCAC AGCAGACAAT GGACCTCCTT AATATCATCA GCCAGTTCCT TTTGTTCTTT 1620

AAGTCCTGTG TCACCCCAGT CCTCCTTTTC TGTCTCTGCA AACCCTTCAG TCGGGCCTTC 1680

ATGGAGTGCT GCTGCTGTTG CTGTGAGGAA TGCATTCAGA AGTCTTCAAC GGTGACCAGT 1740

GATGACAATG ACAACGAGTA CACCACGGAA CTCGAACTCT CGCCTTTCAG TACCATACGC 1800

CGTGAAATGT CCACTTTTGC TTCTGTCGGA ACTCATTGCT GA 1842

(93) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 613 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

```
Met Arg Ala Pro Gly Ala Leu Leu Ala Arg Met Ser Arg Leu Leu Leu
1               5                  10                  15

Leu Leu Leu Leu Lys Val Ser Ala Ser Ser Ala Leu Gly Val Ala Pro
            20                  25                  30

Ala Ser Arg Asn Glu Thr Cys Leu Gly Glu Ser Cys Ala Pro Thr Val
        35                  40                  45

Ile Gln Arg Arg Gly Arg Asp Ala Trp Gly Pro Gly Asn Ser Ala Arg
    50                  55                  60

Asp Val Leu Arg Ala Arg Ala Pro Arg Glu Glu Gln Gly Ala Ala Phe
65                  70                  75                  80

Leu Ala Gly Pro Ser Trp Asp Leu Pro Ala Ala Pro Gly Arg Asp Pro
                85                  90                  95

Ala Ala Gly Arg Gly Ala Glu Ala Ser Ala Ala Gly Pro Pro Gly Pro
            100                 105                 110

Pro Thr Arg Pro Pro Gly Pro Trp Arg Trp Lys Gly Ala Arg Gly Gln
        115                 120                 125

Glu Pro Ser Glu Thr Leu Gly Arg Gly Asn Pro Thr Ala Leu Gln Leu
    130                 135                 140

Phe Leu Gln Ile Ser Glu Glu Glu Glu Lys Gly Pro Arg Gly Ala Gly
145                 150                 155                 160

Ile Ser Gly Arg Ser Gln Glu Gln Ser Val Lys Thr Val Pro Gly Ala
                165                 170                 175

Ser Asp Leu Phe Tyr Trp Pro Arg Arg Ala Gly Lys Leu Gln Gly Ser
            180                 185                 190

His His Lys Pro Leu Ser Lys Thr Ala Asn Gly Leu Ala Gly His Glu
        195                 200                 205

Gly Trp Thr Ile Ala Leu Pro Gly Arg Ala Leu Ala Gln Asn Gly Ser
    210                 215                 220

Leu Gly Glu Gly Ile His Glu Pro Gly Gly Pro Arg Arg Gly Asn Ser
225                 230                 235                 240
```

```
Thr Asn Arg Arg Val Arg Leu Lys Asn Pro Phe Tyr Pro Leu Thr Gln
                245                 250                 255

Glu Ser Tyr Gly Ala Tyr Ala Val Met Cys Leu Ser Val Val Ile Phe
            260                 265                 270

Gly Thr Gly Ile Ile Gly Asn Leu Ala Val Met Ser Ile Val Cys His
        275                 280                 285

Asn Tyr Tyr Met Arg Ser Ile Ser Asn Ser Leu Leu Ala Asn Leu Ala
    290                 295                 300

Phe Trp Asp Phe Leu Ile Ile Phe Phe Cys Leu Pro Leu Val Ile Phe
305                 310                 315                 320

His Glu Leu Thr Lys Lys Trp Leu Leu Glu Asp Phe Ser Cys Lys Ile
                325                 330                 335

Val Pro Tyr Ile Glu Val Ala Ser Leu Gly Val Thr Thr Phe Thr Leu
            340                 345                 350

Cys Ala Leu Cys Ile Asp Arg Phe Arg Ala Ala Thr Asn Val Gln Met
        355                 360                 365

Tyr Tyr Glu Met Ile Glu Asn Cys Ser Ser Thr Thr Ala Lys Leu Ala
    370                 375                 380

Val Ile Trp Val Gly Ala Leu Leu Leu Ala Leu Pro Glu Val Val Leu
385                 390                 395                 400

Arg Gln Leu Ser Lys Glu Asp Leu Gly Phe Ser Gly Arg Ala Pro Ala
                405                 410                 415

Glu Arg Cys Ile Ile Lys Ile Ser Pro Asp Leu Pro Asp Thr Ile Tyr
            420                 425                 430

Val Leu Ala Leu Thr Tyr Asp Ser Ala Arg Leu Trp Trp Tyr Phe Gly
        435                 440                 445

Cys Tyr Phe Cys Leu Pro Thr Leu Phe Thr Ile Thr Cys Ser Leu Val
    450                 455                 460

Thr Ala Arg Lys Ile Arg Lys Ala Glu Lys Ala Cys Thr Arg Gly Asn
465                 470                 475                 480

Lys Arg Gln Ile Gln Leu Glu Ser Gln Met Asn Cys Thr Val Val Ala
                485                 490                 495

Leu Thr Ile Leu Tyr Gly Phe Cys Ile Ile Pro Glu Asn Ile Cys Asn
            500                 505                 510

Ile Val Thr Ala Tyr Met Ala Thr Gly Val Ser Gln Gln Thr Met Asp
        515                 520                 525

Leu Leu Asn Ile Ile Ser Gln Phe Leu Leu Phe Phe Lys Ser Cys Val
```

```
     530                 535                 540

Thr Pro Val Leu Leu Phe Cys Leu Cys Lys Pro Phe Ser Arg Ala Phe
545                 550                 555                 560

Met Glu Cys Cys Cys Cys Cys Cys Glu Glu Cys Ile Gln Lys Ser Ser
                565                 570                 575

Thr Val Thr Ser Asp Asp Asn Asp Asn Glu Tyr Thr Thr Glu Leu Glu
            580                 585                 590

Leu Ser Pro Phe Ser Thr Ile Arg Arg Glu Met Ser Thr Phe Ala Ser
        595                 600                 605

Val Gly Thr His Cys
    610
```

(94) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

```
CAGAATTCAG AGAAAAAAAG TGAATATGGT TTTT                              34
```

(95) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

```
TTGGATCCCT GGTGCATAAC AATTGAAAGA AT                                32
```

(96) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1248 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

```
ATGGTTTTTG CTCACAGAAT GGATAACAGC AAGCCACATT TGATTATTCC TACACTTCTG    60
GTGCCCCTCC AAAACCGCAG CTGCACTGAA ACAGCCACAC CTCTGCCAAG CCAATACCTG   120
ATGGAATTAA GTGAGGAGCA CAGTTGGATG AGCAACCAAA CAGACCTTCA CTATGTGCTG   180
AAACCCGGGG AAGTGGCCAC AGCCAGCATC TTCTTTGGGA TTCTGTGGTT GTTTTCTATC   240
TTCGGCAATT CCCTGGTTTG TTTGGTCATC CATAGGAGTA GGAGGACTCA GTCTACCACC   300
AACTACTTTG TGGTCTCCAT GGCATGTGCT GACCTTCTCA TCAGCGTTGC CAGCACGCCT   360
TTCGTCCTGC TCCAGTTCAC CACTGGAAGG TGGACGCTGG GTAGTGCAAC GTGCAAGGTT   420
GTGCGATATT TTCAATATCT CACTCCAGGT GTCCAGATCT ACGTTCTCCT CTCCATCTGC   480
ATAGACCGGT TCTACACCAT CGTCTATCCT CTGAGCTTCA AGGTGTCCAG AGAAAAAGCC   540
AAGAAAATGA TTGCGGCATC GTGGATCTTT GATGCAGGCT TTGTGACCCC TGTGCTCTTT   600
TTCTATGGCT CCAACTGGGA CAGTCATTGT AACTATTTCC TCCCCTCCTC TTGGGAAGGC   660
ACTGCCTACA CTGTCATCCA CTTCTTGGTG GGCTTTGTGA TTCCATCTGT CCTCATAATT   720
TTATTTTACC AAAAGGTCAT AAAATATATT TGGAGAATAG GCACAGATGG CCGAACGGTG   780
AGGAGGACAA TGAACATTGT CCCTCGGACA AAAGTGAAAA CTATCAAGAT GTTCCTCATT   840
TTAAATCTGT TGTTTTTGCT CTCCTGGCTG CCTTTTCATG TAGCTCAGCT ATGGCACCCC   900
CATGAACAAG ACTATAAGAA AAGTTCCCTT GTTTTCACAG CTATCACATG GATATCCTTT   960
AGTTCTTCAG CCTCTAAACC TACTCTGTAT TCAATTTATA ATGCCAATTT TCGGAGAGGG  1020
ATGAAAGAGA CTTTTTGCAT GTCCTCTATG AAATGTTACC GAAGCAATGC CTATACTATC  1080
ACAACAAGTT CAAGGATGGC CAAAAAAAAC TACGTTGGCA TTTCAGAAAT CCCTTCCATG  1140
GCCAAAACTA TTACCAAAGA CTCGATCTAT GACTCATTTG ACAGAGAAGC CAAGGAAAAA  1200
AAGCTTGCTT GGCCCATTAA CTCAAATCCA CCAAATACTT TTGTCTAA               1248
```

(97) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 415 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

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

Pro Thr Leu Leu Val Pro Leu Gln Asn Arg Ser Cys Thr Glu Thr Ala
            20                  25                  30

Thr Pro Leu Pro Ser Gln Tyr Leu Met Glu Leu Ser Glu Glu His Ser
        35                  40                  45

Trp Met Ser Asn Gln Thr Asp Leu His Tyr Val Leu Lys Pro Gly Glu
    50                  55                  60

Val Ala Thr Ala Ser Ile Phe Phe Gly Ile Leu Trp Leu Phe Ser Ile
65                  70                  75                  80

Phe Gly Asn Ser Leu Val Cys Leu Val Ile His Arg Ser Arg Arg Thr
                85                  90                  95

Gln Ser Thr Thr Asn Tyr Phe Val Val Ser Met Ala Cys Ala Asp Leu
            100                 105                 110

Leu Ile Ser Val Ala Ser Thr Pro Phe Val Leu Leu Gln Phe Thr Thr
        115                 120                 125

Gly Arg Trp Thr Leu Gly Ser Ala Thr Cys Lys Val Val Arg Tyr Phe
    130                 135                 140

Gln Tyr Leu Thr Pro Gly Val Gln Ile Tyr Val Leu Leu Ser Ile Cys
145                 150                 155                 160

Ile Asp Arg Phe Tyr Thr Ile Val Tyr Pro Leu Ser Phe Lys Val Ser
                165                 170                 175

Arg Glu Lys Ala Lys Lys Met Ile Ala Ala Ser Trp Ile Phe Asp Ala
            180                 185                 190

Gly Phe Val Thr Pro Val Leu Phe Phe Tyr Gly Ser Asn Trp Asp Ser
        195                 200                 205

His Cys Asn Tyr Phe Leu Pro Ser Ser Trp Glu Gly Thr Ala Tyr Thr
    210                 215                 220

Val Ile His Phe Leu Val Gly Phe Val Ile Pro Ser Val Leu Ile Ile
225                 230                 235                 240

Leu Phe Tyr Gln Lys Val Ile Lys Tyr Ile Trp Arg Ile Gly Thr Asp
                245                 250                 255

Gly Arg Thr Val Arg Arg Thr Met Asn Ile Val Pro Arg Thr Lys Val
            260                 265                 270

Lys Thr Ile Lys Met Phe Leu Ile Leu Asn Leu Leu Phe Leu Leu Ser
        275                 280                 285
```

```
Trp Leu Pro Phe His Val Ala Gln Leu Trp His Pro His Glu Gln Asp
    290                 295                 300

Tyr Lys Lys Ser Ser Leu Val Phe Thr Ala Ile Thr Trp Ile Ser Phe
305                 310                 315                 320

Ser Ser Ser Ala Ser Lys Pro Thr Leu Tyr Ser Ile Tyr Asn Ala Asn
                325                 330                 335

Phe Arg Arg Gly Met Lys Glu Thr Phe Cys Met Ser Ser Met Lys Cys
            340                 345                 350

Tyr Arg Ser Asn Ala Tyr Thr Ile Thr Thr Ser Ser Arg Met Ala Lys
        355                 360                 365

Lys Asn Tyr Val Gly Ile Ser Glu Ile Pro Ser Met Ala Lys Thr Ile
    370                 375                 380

Thr Lys Asp Ser Ile Tyr Asp Ser Phe Asp Arg Glu Ala Lys Glu Lys
385                 390                 395                 400

Lys Leu Ala Trp Pro Ile Asn Ser Asn Pro Pro Asn Thr Phe Val
                405                 410                 415
```

(98) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

```
GGAAAGCTTA ACGATCCCCA GGAGCAACAT                                    30
```

(99) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

```
CTGGGATCCT ACGAGAGCAT TTTTCACACA G                                  31
```

(100) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1842 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

ATGGGGCCCA CCCTAGCGGT TCCCACCCCC TATGGCTGTA TTGGCTGTAA GCTACCCCAG 60

CCAGAATACC CACCGGCTCT AATCATCTTT ATGTTCTGCG CGATGGTTAT CACCATCGTT 120

GTAGACCTAA TCGGCAACTC CATGGTCATT TTGGCTGTGA CGAAGAACAA GAAGCTCCGG 180

AATTCTGGCA ACATCTTCGT GGTCAGTCTC TCTGTGGCCG ATATGCTGGT GGCCATCTAC 240

CCATACCCTT TGATGCTGCA TGCCATGTCC ATTGGGGGCT GGGATCTGAG CCAGTTACAG 300

TGCCAGATGG TCGGGTTCAT CACAGGGCTG AGTGTGGTCG GCTCCATCTT CAACATCGTG 360

GCAATCGCTA TCAACCGTTA CTGCTACATC TGCCACAGCC TCCAGTACGA ACGGATCTTC 420

AGTGTGCGCA ATACCTGCAT CTACCTGGTC ATCACCTGGA TCATGACCGT CCTGGCTGTC 480

CTGCCCAACA TGTACATTGG CACCATCGAG TACGATCCTC GCACCTACAC CTGCATCTTC 540

AACTATCTGA ACAACCCTGT CTTCACTGTT ACCATCGTCT GCATCCACTT CGTCCTCCCT 600

CTCCTCATCG TGGGTTTCTG CTACGTGAGG ATCTGGACCA AAGTGCTGGC GGCCCGTGAC 660

CCTGCAGGGC AGAATCCTGA CAACCAACTT GCTGAGGTTC GCAATTTTCT AACCATGTTT 720

GTGATCTTCC TCCTCTTTGC AGTGTGCTGG TGCCCTATCA ACGTGCTCAC TGTCTTGGTG 780

GCTGTCAGTC CGAAGGAGAT GGCAGGCAAG ATCCCCAACT GGCTTTATCT TGCAGCCTAC 840

TTCATAGCCT ACTTCAACAG CTGCCTCAAC GCTGTGATCT ACGGGCTCCT CAATGAGAAT 900

TTCCGAAGAG AATACTGGAC CATCTTCCAT GCTATGCGGC ACCCTATCAT ATTCTTCCCT 960

GGCCTCATCA GTGATATTCG TGAGATGCAG GAGGCCCGTA CCCTGGCCCG CGCCCGTGCC 1020

CATGCTCGCG ACCAAGCTCG TGAACAAGAC CGTGCCCATG CCTGTCCTGC TGTGGAGGAA 1080

ACCCCGATGA ATGTCCGGAA TGTTCCATTA CCTGGTGATG CTGCAGCTGG CCACCCCGAC 1140

CGTGCCTCTG GCCACCCTAA GCCCCATTCC AGATCCTCCT CTGCCTATCG CAAATCTGCC 1200

TCTACCCACC ACAAGTCTGT CTTTAGCCAC TCCAAGGCTG CCTCTGGTCA CCTCAAGCCT 1260

GTCTCTGGCC ACTCCAAGCC TGCCTCTGGT CACCCCAAGT CTGCCACTGT CTACCCTAAG 1320

CCTGCCTCTG TCCATTTCAA GGGTGACTCT GTCCATTTCA AGGGTGACTC TGTCCATTTC 1380

```
AAGCCTGACT CTGTTCATTT CAAGCCTGCT TCCAGCAACC CCAAGCCCAT CACTGGCCAC  1440

CATGTCTCTG CTGGCAGCCA CTCCAAGTCT GCCTTCAGTG CTGCCACCAG CCACCCTAAA  1500

CCCATCAAGC CAGCTACCAG CCATGCTGAG CCCACCACTG CTGACTATCC CAAGCCTGCC  1560

ACTACCAGCC ACCCTAAGCC CGCTGCTGCT GACAACCCTG AGCTCTCTGC CTCCCATTGC  1620

CCCGAGATCC CTGCCATTGC CCACCCTGTG TCTGACGACA GTGACCTCCC TGAGTCGGCC  1680

TCTAGCCCTG CCGCTGGGCC CACCAAGCCT GCTGCCAGCC AGCTGGAGTC TGACACCATC  1740

GCTGACCTTC CTGACCCTAC TGTAGTCACT ACCAGTACCA ATGATTACCA TGATGTCGTG  1800

GTTGTTGATG TTGAAGATGA TCCTGATGAA ATGGCTGTGT GA                      1842
```

(101) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 613 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

```
Met Gly Pro Thr Leu Ala Val Pro Thr Pro Tyr Gly Cys Ile Gly Cys
1               5                  10                  15

Lys Leu Pro Gln Pro Glu Tyr Pro Pro Ala Leu Ile Ile Phe Met Phe
            20                  25                  30

Cys Ala Met Val Ile Thr Ile Val Val Asp Leu Ile Gly Asn Ser Met
        35                  40                  45

Val Ile Leu Ala Val Thr Lys Asn Lys Lys Leu Arg Asn Ser Gly Asn
    50                  55                  60

Ile Phe Val Val Ser Leu Ser Val Ala Asp Met Leu Val Ala Ile Tyr
65                  70                  75                  80

Pro Tyr Pro Leu Met Leu His Ala Met Ser Ile Gly Gly Trp Asp Leu
                85                  90                  95

Ser Gln Leu Gln Cys Gln Met Val Gly Phe Ile Thr Gly Leu Ser Val
            100                 105                 110

Val Gly Ser Ile Phe Asn Ile Val Ala Ile Ala Ile Asn Arg Tyr Cys
        115                 120                 125

Tyr Ile Cys His Ser Leu Gln Tyr Glu Arg Ile Phe Ser Val Arg Asn
    130                 135                 140
```

```
Thr Cys Ile Tyr Leu Val Ile Thr Trp Ile Met Thr Val Leu Ala Val
145                 150                 155                 160

Leu Pro Asn Met Tyr Ile Gly Thr Ile Glu Tyr Asp Pro Arg Thr Tyr
                165                 170                 175

Thr Cys Ile Phe Asn Tyr Leu Asn Asn Pro Val Phe Thr Val Thr Ile
            180                 185                 190

Val Cys Ile His Phe Val Leu Pro Leu Leu Ile Val Gly Phe Cys Tyr
        195                 200                 205

Val Arg Ile Trp Thr Lys Val Leu Ala Ala Arg Asp Pro Ala Gly Gln
    210                 215                 220

Asn Pro Asp Asn Gln Leu Ala Glu Val Arg Asn Phe Leu Thr Met Phe
225                 230                 235                 240

Val Ile Phe Leu Leu Phe Ala Val Cys Trp Cys Pro Ile Asn Val Leu
                245                 250                 255

Thr Val Leu Val Ala Val Ser Pro Lys Glu Met Ala Gly Lys Ile Pro
            260                 265                 270

Asn Trp Leu Tyr Leu Ala Ala Tyr Phe Ile Ala Tyr Phe Asn Ser Cys
        275                 280                 285

Leu Asn Ala Val Ile Tyr Gly Leu Leu Asn Glu Asn Phe Arg Arg Glu
    290                 295                 300

Tyr Trp Thr Ile Phe His Ala Met Arg His Pro Ile Ile Phe Phe Pro
305                 310                 315                 320

Gly Leu Ile Ser Asp Ile Arg Glu Met Gln Glu Ala Arg Thr Leu Ala
                325                 330                 335

Arg Ala Arg Ala His Ala Arg Asp Gln Ala Arg Glu Gln Asp Arg Ala
            340                 345                 350

His Ala Cys Pro Ala Val Glu Glu Thr Pro Met Asn Val Arg Asn Val
        355                 360                 365

Pro Leu Pro Gly Asp Ala Ala Ala Gly His Pro Asp Arg Ala Ser Gly
    370                 375                 380

His Pro Lys Pro His Ser Arg Ser Ser Ser Ala Tyr Arg Lys Ser Ala
385                 390                 395                 400

Ser Thr His His Lys Ser Val Phe Ser His Ser Lys Ala Ala Ser Gly
                405                 410                 415

His Leu Lys Pro Val Ser Gly His Ser Lys Pro Ala Ser Gly His Pro
            420                 425                 430

Lys Ser Ala Thr Val Tyr Pro Lys Pro Ala Ser Val His Phe Lys Gly
```

```
                435                 440                 445

Asp Ser Val His Phe Lys Gly Asp Ser Val His Phe Lys Pro Asp Ser
    450                 455                 460

Val His Phe Lys Pro Ala Ser Ser Asn Pro Lys Pro Ile Thr Gly His
465                 470                 475                 480

His Val Ser Ala Gly Ser His Ser Lys Ser Ala Phe Ser Ala Ala Thr
                485                 490                 495

Ser His Pro Lys Pro Ile Lys Pro Ala Thr Ser His Ala Glu Pro Thr
            500                 505                 510

Thr Ala Asp Tyr Pro Lys Pro Ala Thr Thr Ser His Pro Lys Pro Ala
        515                 520                 525

Ala Ala Asp Asn Pro Glu Leu Ser Ala Ser His Cys Pro Glu Ile Pro
    530                 535                 540

Ala Ile Ala His Pro Val Ser Asp Asp Ser Asp Leu Pro Glu Ser Ala
545                 550                 555                 560

Ser Ser Pro Ala Ala Gly Pro Thr Lys Pro Ala Ala Ser Gln Leu Glu
                565                 570                 575

Ser Asp Thr Ile Ala Asp Leu Pro Asp Pro Thr Val Val Thr Thr Ser
            580                 585                 590

Thr Asn Asp Tyr His Asp Val Val Val Val Asp Val Glu Asp Asp Pro
        595                 600                 605

Asp Glu Met Ala Val
    610
```

(102) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

```
TCCAAGCTTC GCCATGGGAC ATAACGGGAG CT                              32
```

(103) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

CGTGAATTCC AAGAATTTAC AATCCTTGCT 30

(104) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1548 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

```
ATGGGACATA ACGGGAGCTG GATCTCTCCA AATGCCAGCG AGCCGCACAA CGCGTCCGGC    60
GCCGAGGCTG CGGGTGTGAA CCGCAGCGCG CTCGGGGAGT TCGGCGAGGC GCAGCTGTAC   120
CGCCAGTTCA CCACCACCGT GCAGGTCGTC ATCTTCATAG GCTCGCTGCT CGGAAACTTC   180
ATGGTGTTAT GGTCAACTTG CCGCACAACC GTGTTCAAAT CTGTCACCAA CAGGTTCATT   240
AAAAACCTGG CCTGCTCGGG GATTTGTGCC AGCCTGGTCT GTGTGCCCTT CGACATCATC   300
CTCAGCACCA GTCCTCACTG TTGCTGGTGG ATCTACACCA TGCTCTTCTG CAAGGTCGTC   360
AAATTTTTGC ACAAAGTATT CTGCTCTGTG ACCATCCTCA GCTTCCCTGC TATTGCTTTG   420
GACAGGTACT ACTCAGTCCT CTATCCACTG GAGAGGAAAA TATCTGATGC CAAGTCCCGT   480
GAACTGGTGA TGTACATCTG GGCCCATGCA GTGGTGGCCA GTGTCCCTGT GTTTGCAGTA   540
ACCAATGTGG CTGACATCTA TGCCACGTCC ACCTGCACGG AAGTCTGGAG CAACTCCTTG   600
GGCCACCTGG TGTACGTTCT GGTGTATAAC ATCACCACGG TCATTGTGCC TGTGGTGGTG   660
GTGTTCCTCT TCTTGATACT GATCCGACGG GCCCTGAGTG CCAGCCAGAA GAAGAAGGTC   720
ATCATAGCAG CGCTCCGGAC CCCACAGAAC ACCATCTCTA TTCCCTATGC CTCCCAGCGG   780
GAGGCCGAGC TGCACGCCAC CCTGCTCTCC ATGGTGATGG TCTTCATCTT GTGTAGCGTG   840
CCCTATGCCA CCCTGGTCGT CTACCAGACT GTGCTCAATG TCCCTGACAC TTCCGTCTTC   900
TTGCTGCTCA CTGCTGTTTG GCTGCCCAAA GTCTCCCTGC TGGCAAACCC TGTTCTCTTT   960
CTTACTGTGA ACAAATCTGT CCGCAAGTGC TTGATAGGGA CCCTGGTGCA ACTACACCAC  1020
CGGTACAGTC GCCGTAATGT GGTCAGTACA GGGAGTGGCA TGGCTGAGGC CAGCCTGGAA  1080

CCCAGCATAC GCTCGGGTAG CCAGCTCCTG GAGATGTTCC ACATTGGGCA GCAGCAGATC  1140
TTTAAGCCCA CAGAGGATGA GGAAGAGAGT GAGGCCAAGT ACATTGGCTC AGCTGACTTC  1200
CAGGCCAAGG AGATATTTAG CACCTGCCTC GAGGGAGAGC AGGGGCCACA GTTTGCGCCC  1260
TCTGCCCCAC CCCTGAGCAC AGTGGACTCT GTATCCCAGG TGGCACCGGC AGCCCCTGTG  1320
GAACCTGAAA CATTCCCTGA TAAGTATTCC CTGCAGTTTG GCTTTGGGCC TTTTGAGTTG  1380
CCTCCTCAGT GGCTCTCAGA GACCCGAAAC AGCAAGAAGC GGCTGCTTCC CCCCTTGGGC  1440
AACACCCCAG AAGAGCTGAT CCAGACAAAG GTGCCCAAGG TAGGCAGGGT GGAGCGGAAG  1500
ATGAGCAGAA ACAATAAAGT GAGCATTTTT CCAAAGGTGG ATTCCTAG               1548
```

(105) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 515 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

```
Met Gly His Asn Gly Ser Trp Ile Ser Pro Asn Ala Ser Glu Pro His
1               5                  10                  15

Asn Ala Ser Gly Ala Glu Ala Ala Gly Val Asn Arg Ser Ala Leu Gly
            20                  25                  30

Glu Phe Gly Glu Ala Gln Leu Tyr Arg Gln Phe Thr Thr Thr Val Gln
        35                  40                  45

Val Val Ile Phe Ile Gly Ser Leu Leu Gly Asn Phe Met Val Leu Trp
    50                  55                  60

Ser Thr Cys Arg Thr Thr Val Phe Lys Ser Val Thr Asn Arg Phe Ile
65                  70                  75                  80

Lys Asn Leu Ala Cys Ser Gly Ile Cys Ala Ser Leu Val Cys Val Pro
                85                  90                  95

Phe Asp Ile Ile Leu Ser Thr Ser Pro His Cys Cys Trp Trp Ile Tyr
            100                 105                 110

Thr Met Leu Phe Cys Lys Val Val Lys Phe Leu His Lys Val Phe Cys
        115                 120                 125

Ser Val Thr Ile Leu Ser Phe Pro Ala Ile Ala Leu Asp Arg Tyr Tyr
    130                 135                 140
```

Claims

1. A method for creating a non-endogenous, constitutively active version of an endogenous human G protein coupled receptor (GPCR), said endogenous GPCR comprising a transmembrane 6 region and an intracellular loop 3 region, the method comprising:

   (a) selecting an endogenous human GPCR comprising a proline residue in the transmembrane 6 region;
   (b) identifying the endogenous 16th amino acid residue from the proline residue of step (a), in a carboxy-terminus to amino-terminus direction;
   (c) altering the identified amino acid residue of step (b) to a non-endogenous amino acid residue to create a non-endogenous version of the endogenous human GPCR; and
   (d) determining if the non-endogenous version of the endogenous human GPCR of step (c) is constitutively active by measuring a difference in an intracellular signal measured for the non-endogenous version as compared with a signal induced by the endogenous GPCR.

2. A method for directly identifying a compound selected from the group consisting of inverse agonist, agonist and partial agonist to a non-endogenous, constitutively activated human G protein coupled receptor, said receptor comprising a transmembrane 6 region and an intracellular loop 3 region, the method comprising steps (a) to (d) of claim

1 and further comprising the steps:

(e) contacting a candidate compound with a non-endogenous, constitutively active GPCR identified in step (d); and
(f) determining, by measurement of the compound efficacy at said contacted receptor, whether said compound is an inverse agonist, agonist or partial agonist of said receptor.

3. The method of claim 1 wherein the amino acid residue that is two residues from said proline residue in the transmembrane 6 region, in a carboxy-terminus to amino-terminus direction, is tryptophan.

4. The method of any one of claims 1 to 3 wherein the endogenous 16th amino acid residue from said proline residue in a carboxy-terminus to amino-terminus direction has been altered to a lysine residue.

5. The method of any one of claims 1 to 3 wherein the endogenous 16th amino acid residue from said proline residue in a carboxy-terminus to amino-terminus direction has been altered to an alanine residue.

6. The method of any one of claims 1 to 3 wherein the endogenous 16th amino acid residue from said proline residue in a carboxy-terminus to amino-terminus direction has been altered to an arginine residue.

7. The method of any one of claims 1 to 3 wherein the endogenous 16th amino acid residue from said proline residue in a carboxy-terminus to amino-terminus direction has been altered to a histidine residue.

8. A method for creating a non-endogenous, constitutively active version of an endogenous human G protein coupled receptor (GPCR), said endogenous GPCR comprising a transmembrane 6 region and an intracellular loop 3 region, the method comprising:

(a) providing a polynucleotide, said polynucleotide encoding an endogenous human GPCR, said endogenous GPCR comprising a transmembrane 6 region and an intracellular loop 3 region, said transmembrane 6 region comprising a proline residue;
(b) identifying the codon of said polynucleotide corresponding to the endogenous 16th amino acid residue from said proline residue of said GPCR of step (a), in a carboxy-terminus to amino-terminus direction;
(c) altering said identified codon of step (b) to encode a non-endogenous amino acid residue, to provide a non-endogenous polynucleotide;
(d) expressing said non-endogenous polynucleotide in a host cell, thereby providing a non-endogenous version of the endogenous human GPCR; and
(e) determining if the non-endogenous version of the endogenous human GPCR of step (d) is constitutively active by measuring a difference in an intracellular signal measured for the non-endogenous version as compared with a signal induced by the endogenous GPCR.

9. The method of claim 8 wherein the amino acid residue that is two residues from said proline residue in the transmembrane 6 region, in a carboxy-terminus to amino-terminus direction, is tryptophan.

10. The method of claim 8 or claim 9 wherein said identified codon of step (b) has been altered to be a codon encoding lysine.

11. The method of claim 8 or claim 9 wherein said identified codon of step (b) has been altered to be a codon encoding alanine.

12. The method of claim 8 or claim 9 wherein said identified codon of step (b) has been altered to be a codon encoding arginine.

13. The method of claim 8 or claim 9 wherein said identified codon of step (b) has been altered to be a codon encoding histidine.

14. The method of claim 2 wherein the directly identified compound is an inverse agonist.

15. The method of claim 2 wherein the directly identified compound is an agonist.

16. The method of claim 2 wherein the directly identified compound is a partial agonist.

17. The method of claim 2, further comprising the step (g) of formulating the compound into a pharmaceutical composition.

Patentansprüche

1. Verfahren zum Erzeugen einer nicht-endogenen, konstitutiv aktiven Version eines endogenen humanen G-Protein-gekoppelten Rezeptors (GPCR), wobei der endogene GPCR eine Transmembran-6-Region und eine intrazelluläre Schleifen-3-Region umfasst, wobei das Verfahren umfasst:

   (a) Auswählen eines endogenen humanen GPCR, umfassend einen Prolinrest in der Transmembran-6-Region;
   (b) Identifizieren des endogenen 16. Aminosäurerestes des Prolinrestes von Schritt (a) in Richtung vom Carboxyterminus zum Aminoterminus;
   (c) Verändern des in Schritt (b) identifizierten Aminosäurerestes zu einem nicht-endogenen Aminosäurerest zum Erzeugen einer nicht-endogenen Version des endogenen humanen GPCR, und
   (d) Feststellen, ob die nicht-endogene Version des endogenen humanen GPCR von Schritt (c) konstitutiv aktiv ist, indem ein Unterschied eines für die nicht-endogene Version gemessenen intrazellulären Signals im Vergleich zu einem von dem endogenen GPCR induzierten Signal gemessen wird.

2. Verfahren zum direkten Identifizieren einer Verbindung, die aus der Gruppe ausgewählt ist, welche aus einem inversen Agonisten, Agonisten und partiellen Agonisten eines nicht-endogenen, konstitutiv aktivierten humanen G-Protein-gekoppelten Rezeptor besteht, wobei der Rezeptor eine Transmembran-6-Region und eine intrazelluläre Schleifen-3-Region umfasst, wobei das Verfahren Schritt (a) bis (d) von Anspruch 1 umfasst und des weiteren folgende Schritte umfasst:

   (e) In-Berührung-Bringen einer Kandidatenverbindung mit einem in Schritt (d) identifizierten nicht-endogenen, konstitutiv aktiven GPCR, und
   (f) Feststellen durch Messen der Verbindungswirksamkeit an dem berührten Rezeptor, ob es sich bei der Verbindung um einen inversen Agonisten, Agonisten oder partiellen Agonisten des Rezeptors handelt.

3. Verfahren nach Anspruch 1, wobei der Aminosäurerest, der sich in Richtung vom Carboxyterminus zum Aminoterminus zwei Reste von dem Prolinrest in der Transmembran-6-Region befindet, Tryptophan ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei der endogene 16. Aminosäurerest des Prolinrestes in einer Richtung vom Carboxyterminus zum Aminoterminus zu einem Lysinrest geändert wurde.

5. Verfahren nach einem der Ansprüche 1 bis 3, wobei der endogene 16. Aminosäurerest des Prolinrestes in einer Richtung vom Carboxyterminus zum Aminoterminus zu einem Alaninrest geändert wurde.

6. Verfahren nach einem der Ansprüche 1 bis 3, wobei der endogene 16. Aminosäurerest des Prolinrestes in einer Richtung vom Carboxyterminus zum Aminoterminus zu einem Argininrest geändert wurde.

7. Verfahren nach einem der Ansprüche 1 bis 3, wobei der endogene 16. Aminosäurerest des Prolinrestes in einer Richtung vom Carboxyterminus zum Aminoterminus zu einem Histidinrest geändert wurde.

8. Verfahren zum Erzeugen einer nicht-endogenen, konstitutiv aktiven Version eines endogenen humanen G-Protein-gekoppelten Rezeptors (GPCR), wobei der endogene GPCR eine Transmembran-6-Region und eine intrazelluläre Schleifen-3-Region umfasst, wobei das Verfahren umfasst:

   (a) Bereitstellen eines Polynukleotids, wobei das Polynukleotid einen endogenen humanen GPCR kodiert, wobei der endogene GPCR eine Transmembran-6-Region und eine intrazelluläre Schleifen-3-Region umfasst, wobei die Transmembran-6-Region einen Prolinrest umfasst;
   (b) Identifizieren des Kodons des Polynukleotids, das dem endogenen 16. Aminosäurerest des Prolinrestes des GPCR von Schritt (a) in Richtung vom Carboxyterminus zum Aminoterminus entspricht.
   (c) Verändern des in Schritt (b) identifizierten Kodons, um einen nicht-endogenen Aminosäurerest zu kodieren, um ein nicht-endogenes Polynukleotid bereit zu stellen.
   (d) Exprimieren des nicht-endogenen Polynukleotids in einer Wirtszelle, womit eine nicht-endogene Version

des endogenen humanen GPCR bereit gestellt wird, und
(e) Feststellen, ob die nicht-endogene Version des endogenen humanen GPCR von Schritt (d) konstitutiv aktiv ist, indem ein Unterschied eines für die nicht-endogene Version gemessenen intrazellulären Signals im Vergleich zu einem von dem endogenen GPCR induzierten Signal gemessen wird.

9. Verfahren nach Anspruch 8, wobei der Aminosäurerest, der sich in Richtung vom Carboxyterminus zum Aminoterminus zwei Reste von dem Prolinrest in der Transmembran-6-Region befindet, Tryptophan ist.

10. Verfahren nach Anspruch 8 oder Anspruch 9, wobei das in Schritt (b) identifizierte Kodon zu einem Kodon verändert wurde, das Lysin kodiert.

11. Verfahren nach Anspruch 8 oder Anspruch 9, wobei das in Schritt (b) identifizierte Kodon zu einem Kodon verändert wurde, das Alanin kodiert.

12. Verfahren nach Anspruch 8 oder Anspruch 9, wobei das in Schritt (b) identifizierte Kodon zu einem Kodon verändert wurde, das Arginin kodiert.

13. Verfahren nach Anspruch 8 oder Anspruch 9, wobei das in Schritt (b) identifizierte Kodon zu einem Kodon verändert wurde, das Histidin kodiert.

14. Verfahren nach Anspruch 2, wobei die direkt identifizierte Verbindung ein inverser Agonist ist.

15. Verfahren nach Anspruch 2, wobei die direkt identifizierte Verbindung ein Agonist ist.

16. Verfahren nach Anspruch 2, wobei die direkt identifizierte Verbindung ein partieller Agonist ist.

17. Verfahren nach Anspruch 2, das des Weiteren den Schritt (g) des Formulierens der Verbindung in eine pharmazeutische Zusammensetzung umfasst.

Revendications

1. Méthode de création d'une version constitutivement active non endogène d'un récepteur couplé aux protéines-G humain endogène RCPG, ledit RCPG endogène comprenant une région 6 transmembranaire et une région 3 de boucle intracellulaire, la méthode comprenant :

(a) sélectionner un RCPG humain endogène comprenant un résidu de proline dans la région 6 transmembranaire ;
(b) identifier le résidu du 16ème acide aminé endogène du résidu de proline de l'étape (a), dans le sens de l'extrémité carboxy vers l'extrémité amino;
(c) transformer le résidu d'acide aminé identifié de l'étape (b) en un résidu d'acide aminé non endogène pour créer une version non endogène du RCPG humain endogène; et
(d) déterminer si la version non endogène du RCPG endogène humain de l'étape (c) est constitutivement active en mesurant une différence dans un signal intracellulaire mesuré pour la version non endogène comparativement à un signal induit par le RCPG endogène

2. Méthode d'identification directe d'un composé choisi dans le groupe consistant en un agoniste inverse, un agoniste et un agoniste partiel d'un récepteur couplé aux protéines-G activé, ledit récepteur comprenant une région 6 transmembranaire et une région 3 de boucle intracellulaire, la méthode comprenant les étapes (a) à (d) de la revendication 1 et comprenant en outre les étapes :

(e) mettre en contact un composé candidat avec un RCPG constitutivement actif non endogène identifié dans l'étape (d) ; et
(f) déterminer, en mesurant l'efficacité du composé au contact dudit récepteur, si ledit composé est un agoniste inverse, un agoniste ou un agoniste partiel dudit récepteur.

3. Méthode selon la revendication 1, dans laquelle le résidu d'acide aminé, c'est-à-dire deux résidus dudit résidu de proline dans la région 6 transmembranaire, dans le sens de l'extrémité carboxy vers l'extrémité amino, est le tryp-

tophane

4. Méthode l'une quelconque des revendications 1 à 3 dans laquelle le résidu du 16ème acide aminé endogène dudit résidu de proline dans le sens de l'extrémité carboxy vers l'extrémité amino a été transformé en résidu de lysine.

5. Méthode l'une quelconque des revendications 1 à 3 dans laquelle le résidu du 16ème acide aminé endogène dudit résidu de proline dans le sens de l'extrémité carboxy vers l'extrémité amino a été transformé en résidu d'alanine.

6. Méthode l'une quelconque des revendications 1 à 3 dans laquelle le résidu du 16ème acide aminé endogène dudit résidu de proline dans le sens de l'extrémité carboxy vers l'extrémité amino a été transformé en résidu d'arginine.

7. Méthode l'une quelconque des revendications 1 à 3 dans laquelle le résidu du 16ème acide aminé endogène dudit résidu de proline dans le sens de l'extrémité carboxy vers l'extrémité amino a été transformé en résidu d'histidine.

8. Méthode de création d'une version constitutivement active non endogène d'un récepteur couplé aux protéines-G humain endogène RCPG, ledit RCPG endogène comprenant une région 6 transmembranaire et une région 3 de boucle intracellulaire, la méthode comprenant :

(a) fournir un polynucléotide, ledit polynucléotide codant un RCPG humain endogène, ledit RCPG endogène comprenant une région 6 transmembranaire et une région 3 de boucle intracellulaire, ladite région 6 transmembranaire comprenant un résidu de proline ;
(b) identifier le codon dudit polynucléotide correspondant au résidu du 16ème acide aminé endogène dudit résidu de proline de ladite étape (a) de RCPG, dans le sens de l'extrémité carboxy vers l'extrémité amino ;
(c) transformer ledit codon identifié de l'étape (b) pour coder un résidu d'acide aminé non endogène, pour fournir un polynucléotide non endogène ;
(d) faire exprimer ledit polynucléotide non endogène dans une cellule hôte, et fournir par ce moyen une version non endogène du RCPG humain endogène ; et
(e) déterminer si la version non endogène de l'étape (d) du RCPG humain endogène est constitutivement active en mesurant une différence dans un signal intracellulaire mesuré pour la version non endogène par rapport à un signal induit par le RCPG endogène.

9. Méthode selon la revendication 8, dans laquelle le résidu de l'acide aminé, c'est à dire deux résidus dudit résidu de proline dans la région 6 transmembranaire, dans le sens de l'extrémité carboxy vers l'extrémité amino, est le tryptophane.

10. Méthode selon la revendication 8 ou la revendication 9 dans laquelle ledit codon identifié de l'étape (b) a été transformé pour être un codon codant la lysine

11. Méthode selon la revendication 8 ou la revendication 9 dans laquelle ledit codon identifié de l'étape (b) a été transformé pour en faire un codon codant l'alanine

12. Méthode selon la revendication 8 ou la revendication 9 dans laquelle ledit codon identifié de l'étape (b) a été transformé pour en faire un codon codant l'arginine

13. Méthode selon la revendication 8 ou la revendication 9 dans laquelle ledit codon identifié de l'étape (b) a été transformé pour en faire un codon codant l'histidine.

14. Méthode de la revendication 2 dans laquelle le composé directement identifié est un agoniste inverse.

15. Méthode de la revendication 2 dans laquelle le composé directement identifié est un agoniste.

16. Méthode de la revendication 2 dans laquelle le composé directement identifié est un agoniste partiel.

17. Méthode de la revendication 2, comprenant en outre l'étape (g) de formulation du composé en une composition pharmaceutique.

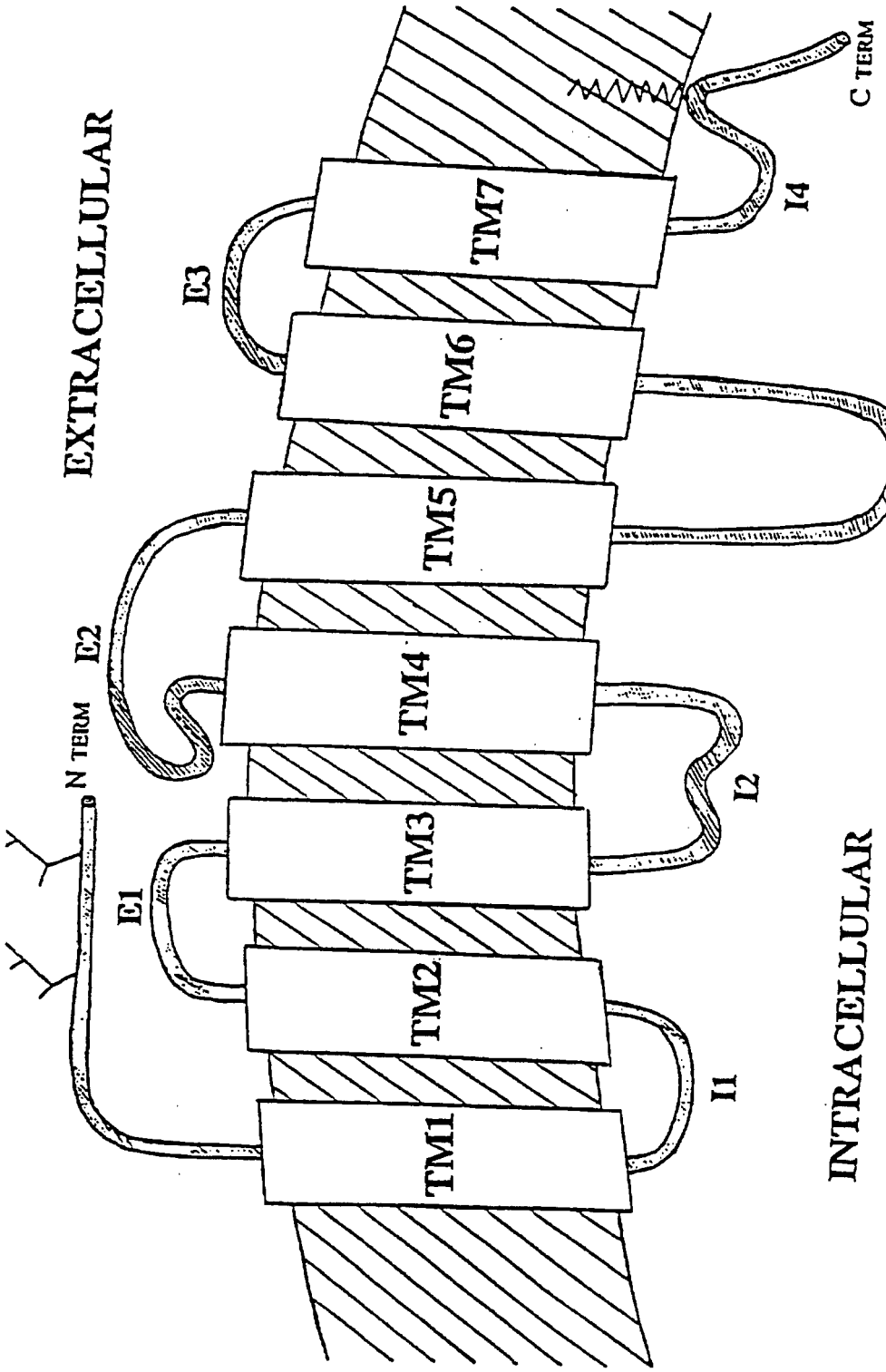

EXTRACELLULAR
INTRACELLULAR
N TERM
C TERM
TM1
TM2
TM3
TM4
TM5
TM6
TM7
E1
E2
E3
I1
I2
I3
I4

FIGURE 1

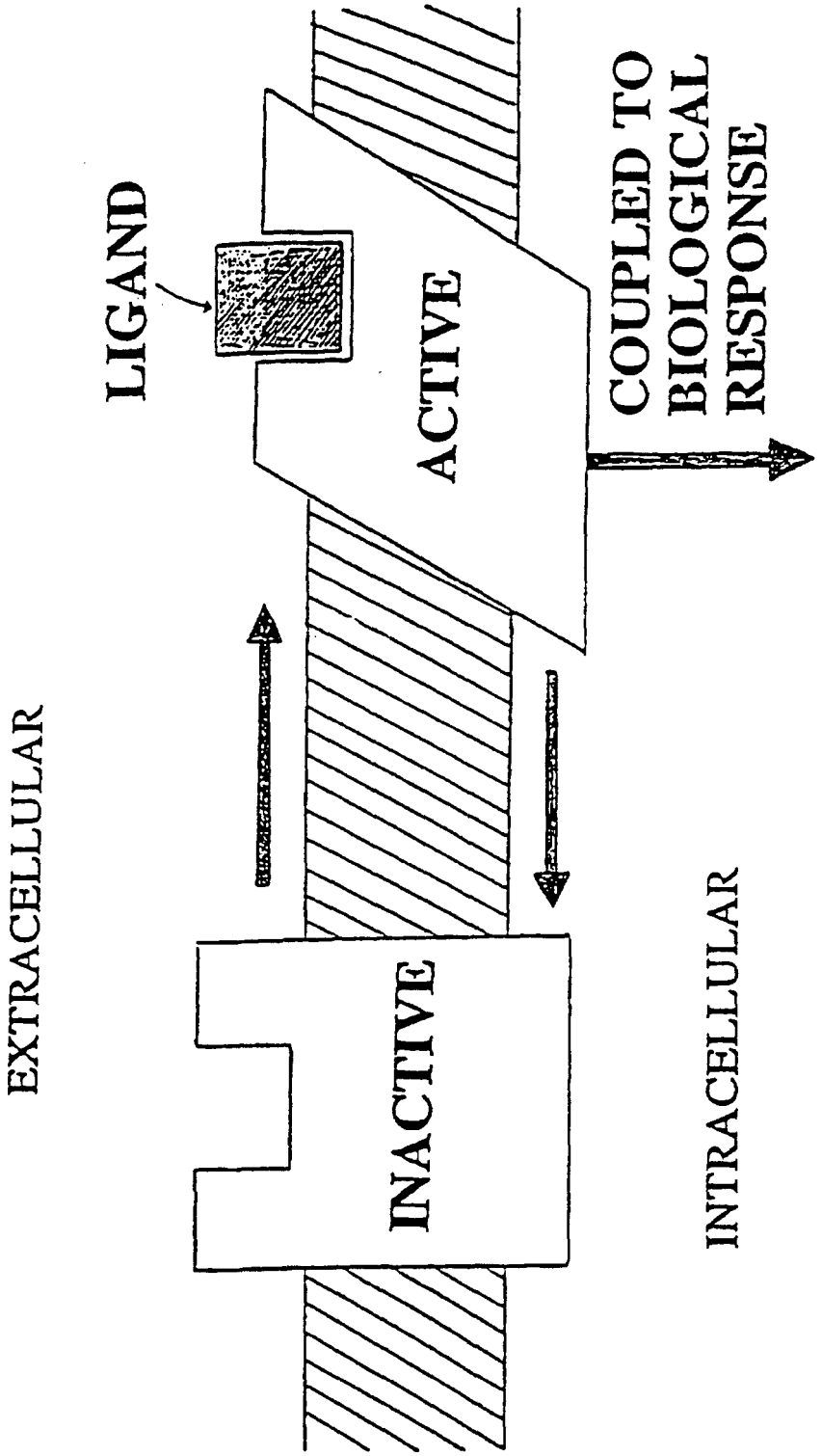

LIGAND
ACTIVE
COUPLED TO
BIOLOGICAL
RESPONSE
EXTRACELLULAR
INACTIVE
INTRACELLULAR

FIGURE 2

pCMV Sequence and Restriction Site

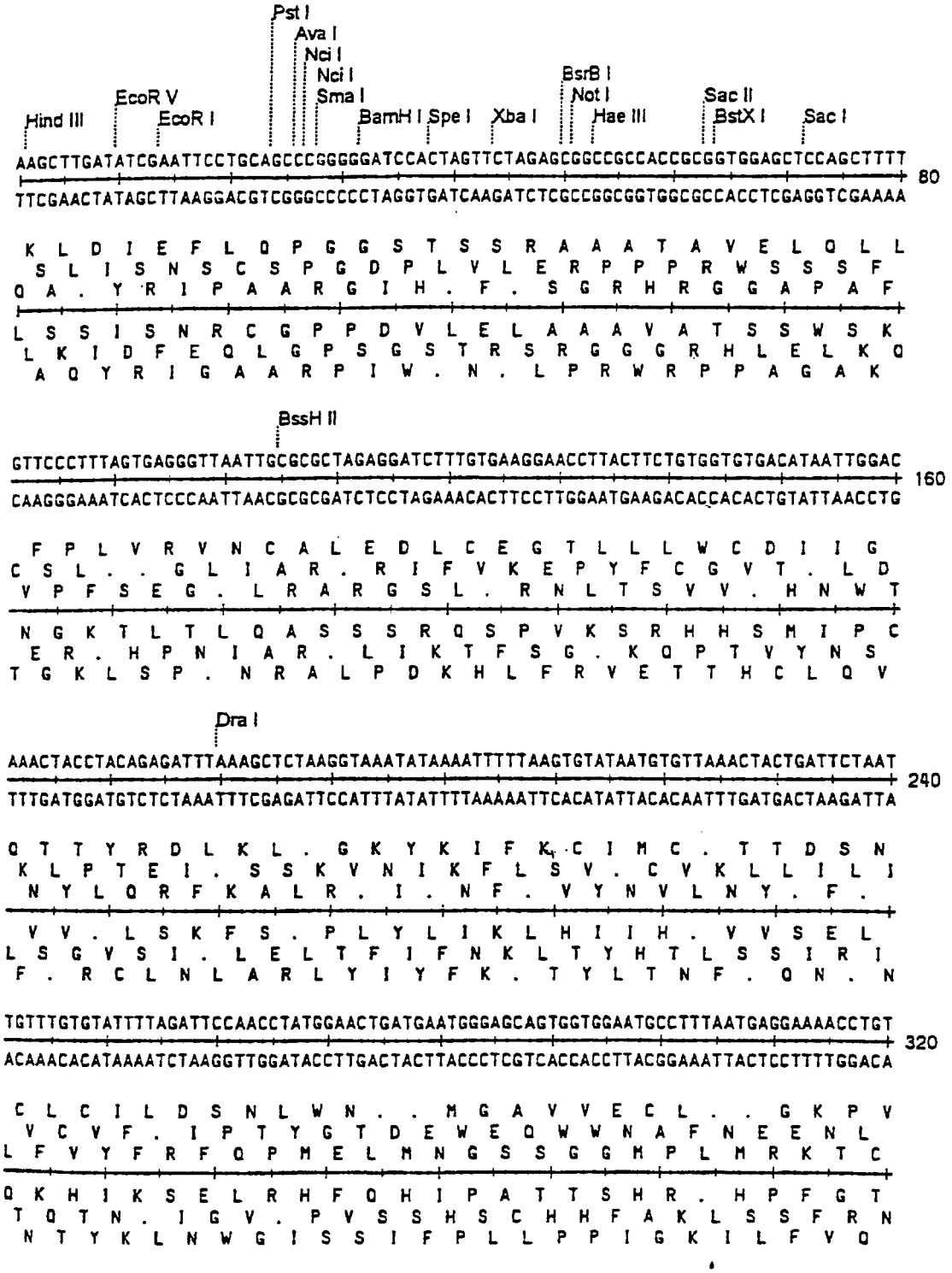


FIGURE 3A

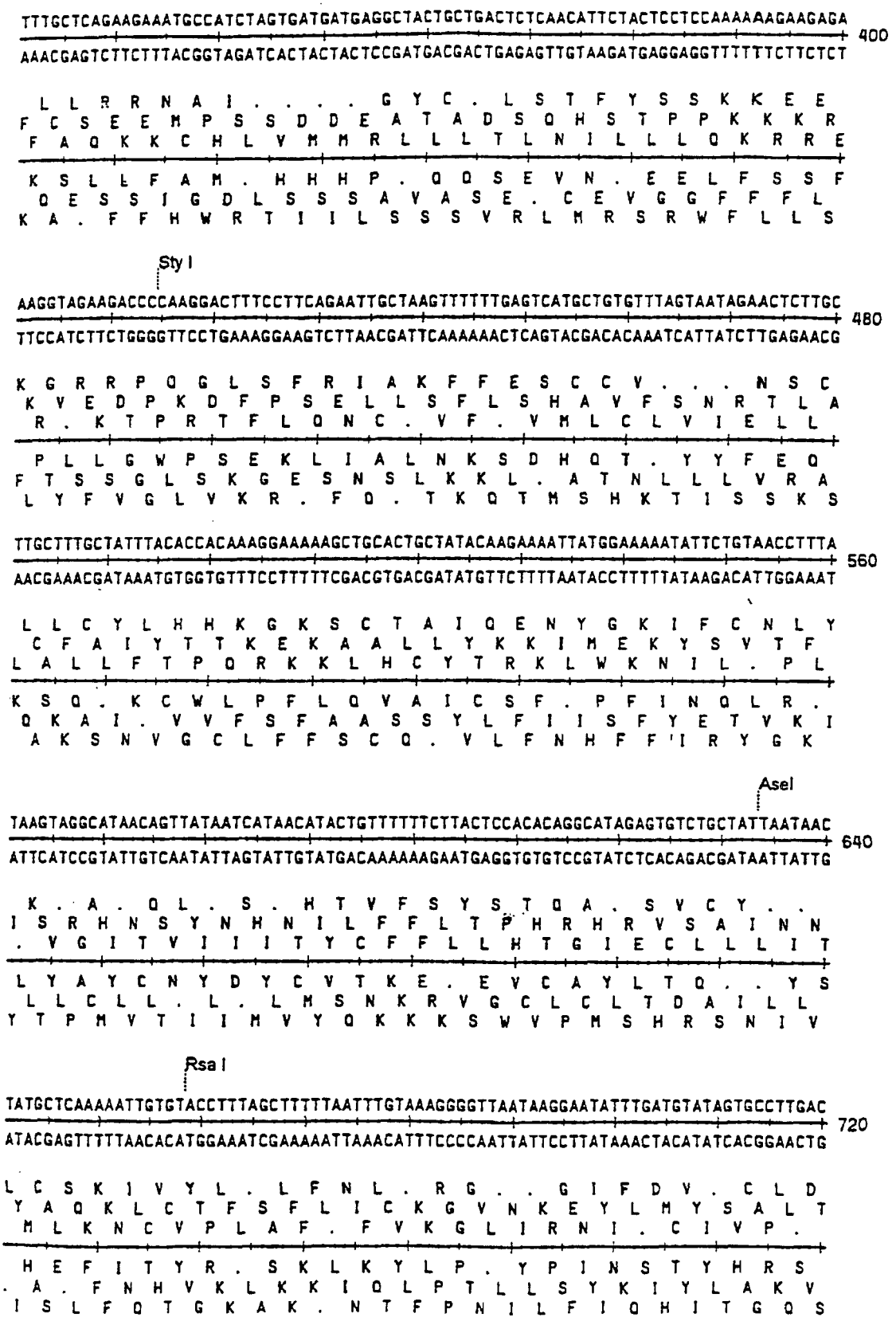


FIGURE 3B

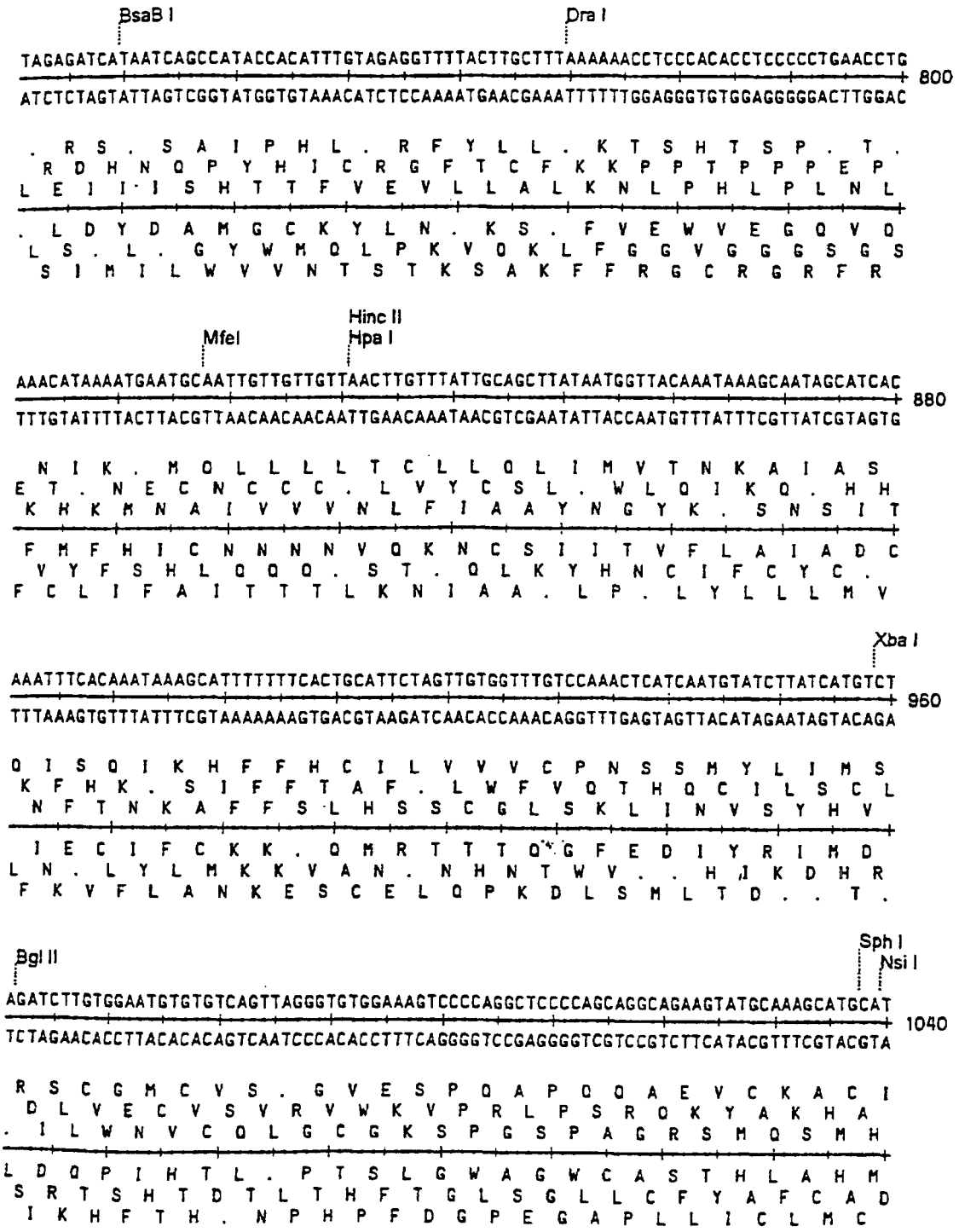

BsaB I
Dra I
TAGAGATCATAATCAGCCATACCACATTTGTAGAGGTTTTACTTGCTTTAAAAAACCTCCCACACCTCCCCCTGAACCTG
800
ATCTCTAGTATTAGTCGGTATGGTGTAAACATCTCCAAAATGAACGAAATTTTTTGGAGGGTGTGGAGGGGGACTTGGAC
Mfe I
Hinc II
Hpa I
AAACATAAAATGAATGCAATTGTTGTTGTTAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAATAGCATCAC
880
TTTGTATTTTACTTACGTTAACAACAACAATTGAACAAATAACGTCGAATATTACCAATGTTTATTTCGTTATCGTAGTG
Xba I
AAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTGTCCAAACTCATCAATGTATCTTATCATGTCT
960
TTTAAAGTGTTTATTTCGTAAAAAAAGTGACGTAAGATCAACACCAAACAGGTTTGAGTAGTTACATAGAATAGTACAGA
Bgl II
Sph I
Nsi I
AGATCTTGTGGAATGTGTGTCAGTTAGGGTGTGGAAAGTCCCCAGGCTCCCCAGCAGGCAGAAGTATGCAAAGCATGCAT
1040
TCTAGAACACCTTACACACAGTCAATCCCACACCTTTCAGGGGTCCGAGGGGTCGTCCGTCTTCATACGTTTCGTACGTA

FIGURE 3C

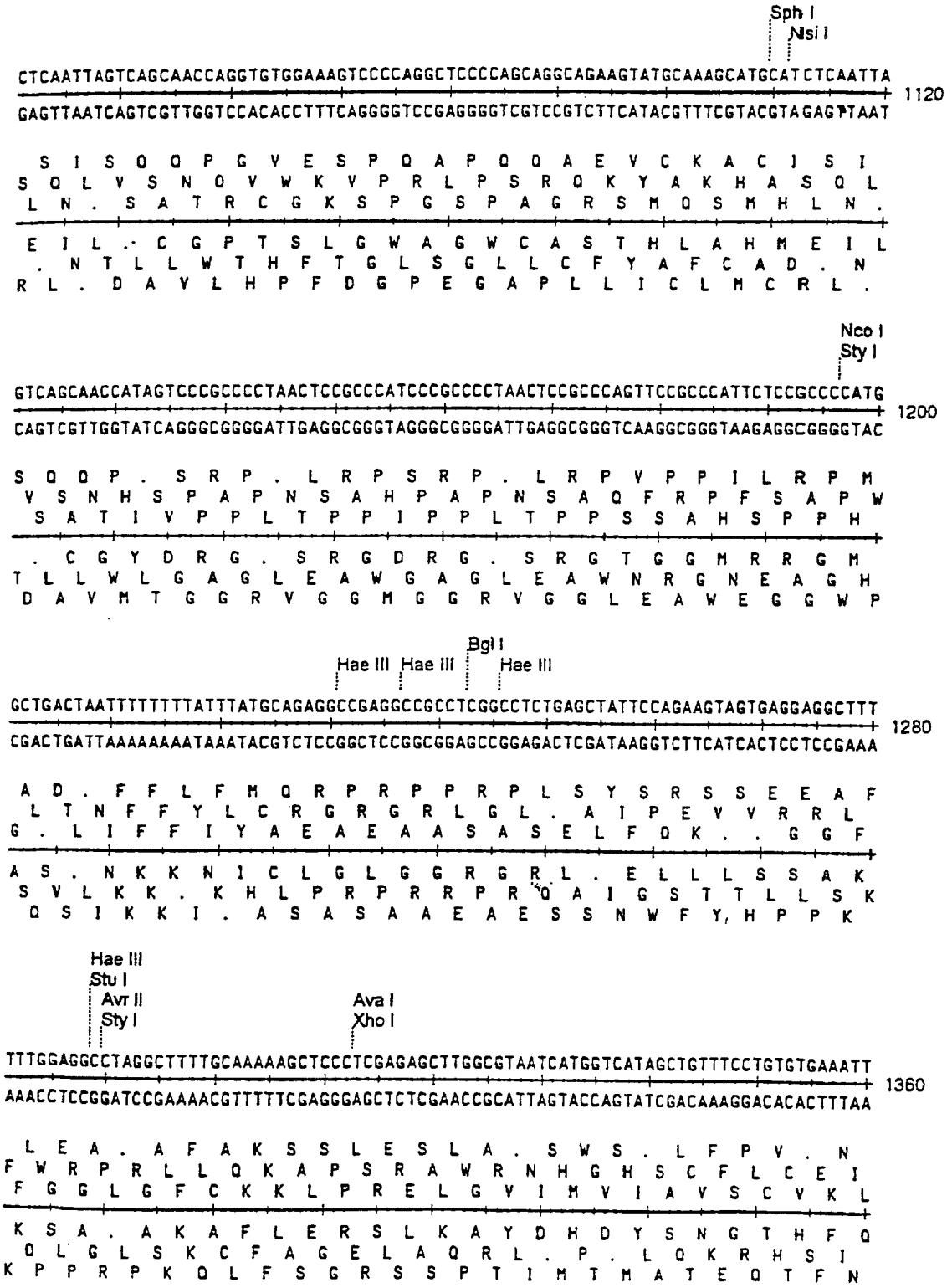

Sph I
Nsi I
CTCAATTAGTCAGCAACCAGGTGTGGAAAGTCCCCAGGCTCCCCAGCAGGCAGAAGTATGCAAAGCATGCATCTCAATTA
GAGTTAATCAGTCGTTGGTCCACACCTTTCAGGGGTCCGAGGGGTCGTCCGTCTTCATACGTTTCGTACGTAGAGTTAAT
1120
S I S Q Q P G V E S P Q A P Q Q A E V C K A C I S I
S Q L V S N Q V W K V P R L P S R Q K Y A K H A S Q L
L N . S A T R C G K S P G S P A G R S M Q S M H L N .
E I L . C G P T S L G W A G W C A S T H L A H M E I L
. N T L L W T H F T G L S G L L C F Y A F C A D . N
R L . D A V L H P F D G P E G A P L L I C L M C R L .
Nco I
Sty I
GTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATG
CAGTCGTTGGTATCAGGGCGGGGATTGAGGCGGGTAGGGCGGGGATTGAGGCGGGTCAAGGCGGGTAAGAGGCGGGGTAC
1200
S Q Q P . S R P . L R P S R P . L R P V P P I L R P M
V S N H S P A P N S A H P A P N S A Q F R P F S A P W
S A T I V P P L T P P I P P L T P P S S A H S P P H
. C G Y D R G . S R G D R G . S R G T G G M R R G M
T L L W L G A G L E A W G A G L E A W N R G N E A G H
D A V M T G G R V G G M G G R V G G L E A W E G G W P
Bgl I
Hae III
Hae III
Hae III
GCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTT
CGACTGATTAAAAAAAATAAATACGTCTCCGGCTCCGGCGGAGCCGGAGACTCGATAAGGTCTTCATCACTCCTCCGAAA
1280
A D . F F L F M Q R P R P P R P L S Y S R S S E E A F
L T N F F Y L C R G R G R L G L . A I P E V V R R L
G . L I F F I Y A E A E A A S A S E L F Q K . . G G F
A S . N K K N I C L G L G G R G R L . E L L L S S A K
S V L K K . K H L P R P R R P R Q A I G S T T L L S K
Q S I K K I . A S A S A A E A E S S N W F Y, H P P K
Hae III
Stu I
Avr II
Sty I
Ava I
Xho I
TTTGGAGGCCTAGGCTTTTGCAAAAAGCTCCCTCGAGAGCTTGGCGTAATCATGGTCATAGCTGTTTCCTGTGTGAAATT
AAACCTCCGGATCCGAAAACGTTTTTCGAGGGAGCTCTCGAACCGCATTAGTACCAGTATCGACAAAGGACACACTTTAA
1360
L E A . A F A K S S L E S L A . S W S . L F P V . N
F W R P R L L Q K A P S R A W R N H G H S C F L C E I
F G G L G F C K K L P R E L G V I M V I A V S C V K L
K S A . A K A F L E R S L K A Y D H D Y S N G T H F Q
Q L G L S K C F A G E L A Q R L . P . L Q K R H S I
K P P R P K Q L F S G R S S P T I M T M A T E Q T F N

FIGURE 3D

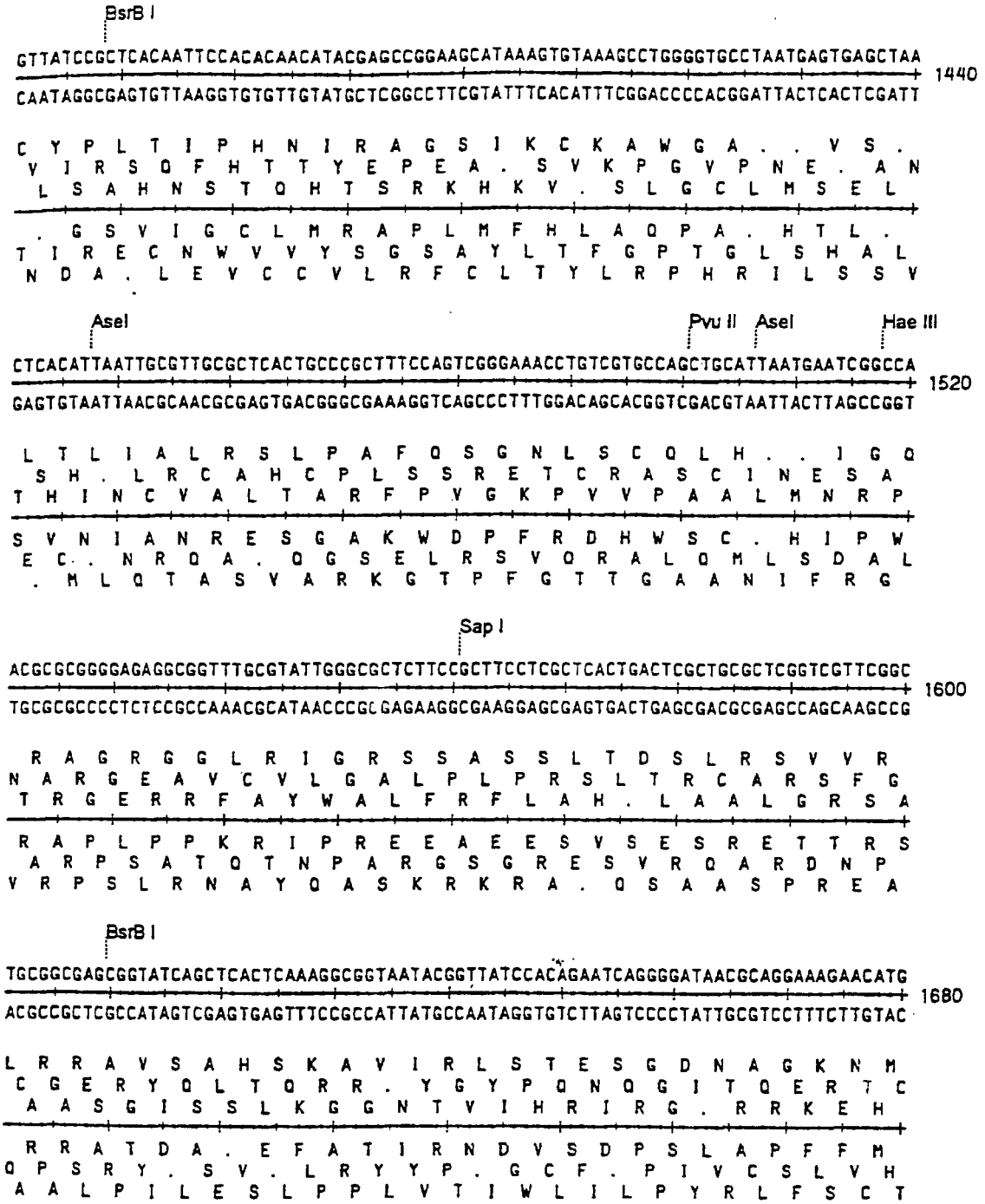

BsrB I
GTTATCCGCTCACAATTCCACACAACATACGAGCCGGAAGCATAAAGTGTAAAGCCTGGGGTGCCTAATGAGTGAGCTAA
CAATAGGCGAGTGTTAAGGTGTGTTGTATGCTCGGCCTTCGTATTTCACATTTCGGACCCCACGGATTACTCACTCGATT
1440
C Y P L T I P H N I R A G S I K C K A W G A . . V S .
V I R S Q F H T T Y E P E A . S V K P G V P N E . A N
L S A H N S T Q H T S R K H K V . S L G C L M S E L
. G S V I G C L M R A P L M F H L A Q P A . H T L .
T I R E C N W V V Y S G S A Y L T F G P T G L S H A L
N D A . L E V C C V L R F C L T Y L R P H R I L S S V
AseI
Pvu II
AseI
Hae III
CTCACATTAATTGCGTTGCGCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGCCAGCTGCATTAATGAATCGGCCA
GAGTGTAATTAACGCAACGCGAGTGACGGGCGAAAGGTCAGCCCTTTGGACAGCACGGTCGACGTAATTACTTAGCCGGT
1520
L T L I A L R S L P A F Q S G N L S C Q L H . . I G Q
S H . L R C A H C P L S S R E T C R A S C I N E S A
T H I N C V A L T A R F P V G K P V V P A A L M N R P
S V N I A N R E S G A K W D P F R D H W S C . H I P W
E C . N R Q A . Q G S E L R S V Q R A L Q M L S D A L
. M L Q T A S V A R K G T P F G T T G A A N I F R G
Sap I
ACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGC
TGCGCGCCCCTCTCCGCCAAACGCATAACCCGCGAGAAGGCGAAGGAGCGAGTGACTGAGCGACGCGAGCCAGCAAGCCG
1600
R A G R G G L R I G R S S A S S L T D S L R S V V R
N A R G E A V C V L G A L P L P R S L T R C A R S F G
T R G E R R F A Y W A L F R F L A H . L A A L G R S A
R A P L P P K R I P R E E A E E S V S E S R E T T R S
A R P S A T Q T N P A R G S G R E S V R Q A R D N P
V R P S L R N A Y Q A S K R K R A . Q S A A S P R E A
BsrB I
TGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATG
ACGCCGCTCGCCATAGTCGAGTGAGTTTCCGCCATTATGCCAATAGGTGTCTTAGTCCCCTATTGCGTCCTTTCTTGTAC
1680
L R R A V S A H S K A V I R L S T E S G D N A G K N M
C G E R Y Q L T Q R R . Y G Y P Q N Q G I T Q E R T C
A A S G I S S L K G G N T V I H R I R G . R R K E H
R R A T D A . E F A T I R N D V S D P S L A P F F M
Q P S R Y . S V . L R Y Y P . G C F . P I V C S L V H
A A L P I L E S L P P L V T I W L I L P Y R L F S C T

FIGURE 3E

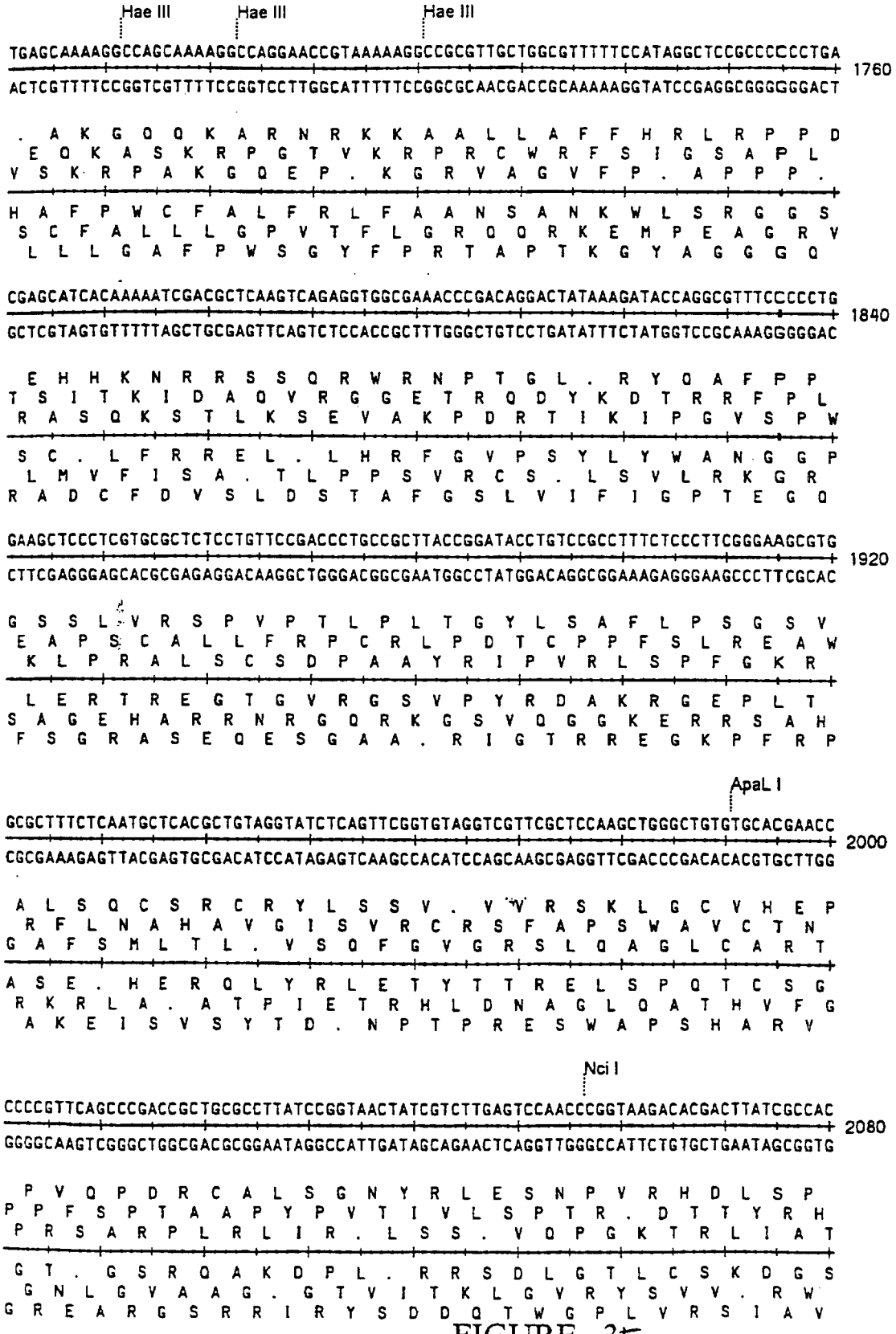
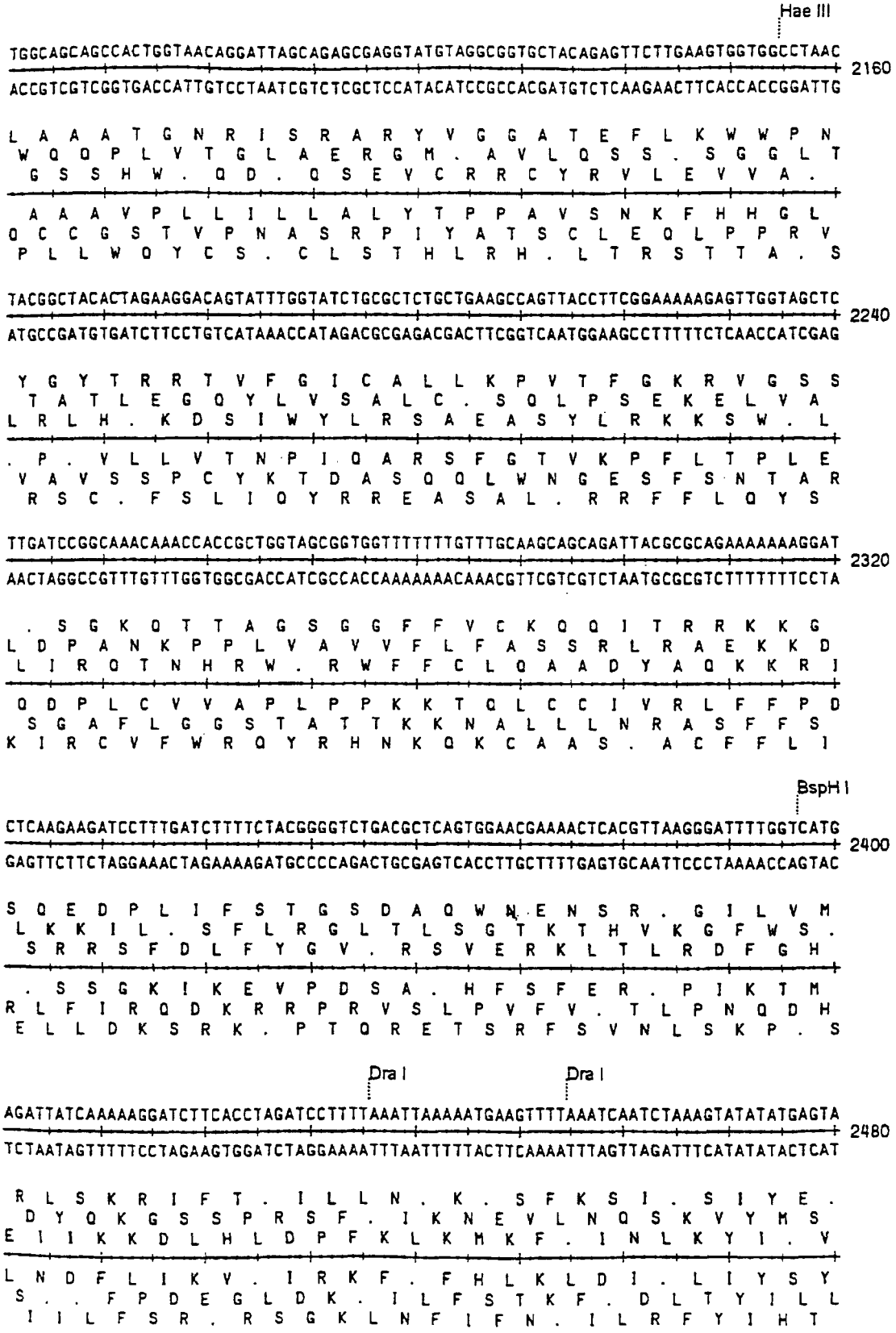

Hae III
Hae III
Hae III
TGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGA
ACTCGTTTTCCGGTCGTTTTCCGGTCCTTGGCATTTTTCCGGCGCAACGACCGCAAAAAGGTATCCGAGGCGGGGGGACT
1760
. A K G Q Q K A R N R K K A A L L A F F H R L R P P D
E Q K A S K R P G T V K R P R C W R F S I G S A P L
V S K R P A K G Q E P . K G R V A G V F P . A P P P .
H A F P W C F A L F R L F A A N S A N K W L S R G G S
S C F A L L L G P V T F L G R Q Q R K E M P E A G R V
L L L G A F P W S G Y F P R T A P T K G Y A G G G Q
CGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTG
GCTCGTAGTGTTTTTAGCTGCGAGTTCAGTCTCCACCGCTTTGGGCTGTCCTGATATTTCTATGGTCCGCAAAGGGGGAC
1840
E H H K N R R S S Q R W R N P T G L . R Y Q A F P P
T S I T K I D A Q V R G G E T R Q D Y K D T R R F P L
R A S Q K S T L K S E V A K P D R T I K I P G V S P W
S C . L F R R E L . L H R F G V P S Y L Y W A N G G P
L M V F I S A . T L P P S V R C S . L S V L R K G R
R A D C F D V S L D S T A F G S L V I F I G P T E G Q
GAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTG
CTTCGAGGGAGCACGCGAGAGGACAAGGCTGGGACGGCGAATGGCCTATGGACAGGCGGAAAGAGGGAAGCCCTTCGCAC
1920
G S S L V R S P V P T L P L T G Y L S A F L P S G S V
E A P S C A L L F R P C R L P D T C P P F S L R E A W
K L P R A L S C S D P A A Y R I P V R L S P F G K R
L E R T R E G T G V R G S V P Y R D A K R G E P L T
S A G E H A R R N R G Q R K G S V Q G G K E R R S A H
F S G R A S E Q E S G A A . R I G T R R E G K P F R P
ApaL I
GCGCTTTCTCAATGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGCACGAACC
CGCGAAAGAGTTACGAGTGCGACATCCATAGAGTCAAGCCACATCCAGCAAGCGAGGTTCGACCCGACACACGTGCTTGG
2000
A L S Q C S R C R Y L S S V . V V R S K L G C V H E P
R F L N A H A V G I S V R C R S F A P S W A V C T N
G A F S M L T L . V S Q F G V G R S L Q A G L C A R T
A S E . H E R Q L Y R L E T Y T T R E L S P Q T C S G
R K R L A . A T P I E T R H L D N A G L Q A T H V F G
A K E I S V S Y T D . N P T P R E S W A P S H A R V
Nci I
CCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCAC
GGGGCAAGTCGGGCTGGCGACGCGGAATAGGCCATTGATAGCAGAACTCAGGTTGGGCCATTCTGTGCTGAATAGCGGTG
2080
P V Q P D R C A L S G N Y R L E S N P V R H D L S P
P P F S P T A A P Y P V T I V L S P T R . D T T Y R H
P R S A R P L R L I R . L S S . V Q P G K T R L I A T
G T . G S R Q A K D P L . R R S D L G T L C S K D G S
G N L G V A A G . G T V I T K L G V R Y S V V . R W
G R E A R G S R R I R Y S D D Q T W G P L V R S I A V

FIGURE 3F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TGGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAAC
ACCGTCGTCGGTGACCATTGTCCTAATCGTCTCGCTCCATACATCCGCCACGATGTCTCAAGAACTTCACCACCGGATTG
2160
L A A A T G N R I S R A R Y V G G A T E F L K W W P N
W Q Q P L V T G L A E R G M . A V L Q S S . S G G L T
G S S H W . Q D . Q S E V C R R C Y R V L E V V A .
A A A V P L L I L L A L Y T P P A V S N K F H H G L
Q C C G S T V P N A S R P I Y A T S C L E Q L P P R V
P L L W Q Y C S . C L S T H L R H . L T R S T T A . S
TACGGCTACACTAGAAGGACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTC
ATGCCGATGTGATCTTCCTGTCATAAACCATAGACGCGAGACGACTTCGGTCAATGGAAGCCTTTTTCTCAACCATCGAG
2240
Y G Y T R R T V F G I C A L L K P V T F G K R V G S S
T A T L E G Q Y L V S A L C . S Q L P S E K E L V A
L R L H . K D S I W Y L R S A E A S Y L R K K S W . L
. P . V L L V T N P I Q A R S F G T V K P F L T P L E
V A V S S P C Y K T D A S Q Q L W N G E S F S N T A R
R S C . F S L I Q Y R R E A S A L . R R F F L Q Y S
TTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGAT
AACTAGGCCGTTTGTTTGGTGGCGACCATCGCCACCAAAAAAACAAACGTTCGTCGTCTAATGCGCGTCTTTTTTTCCTA
2320
. S G K Q T T A G S G G F F V C K Q Q I T R R K K G
L D P A N K P P L V A V V F L F A S S R L R A E K K D
L I R Q T N H R W . R W F F C L Q A A D Y A Q K K R I
Q D P L C V V A P L P P K K T Q L C C I V R L F F P D
S G A F L G G S T A T T K K N A L L L N R A S F F S
K I R C V F W R Q Y R H N K Q K C A A S . A C F F L I
BspH I
CTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATG
GAGTTCTTCTAGGAAACTAGAAAAGATGCCCCAGACTGCGAGTCACCTTGCTTTTGAGTGCAATTCCCTAAAACCAGTAC
2400
S Q E D P L I F S T G S D A Q W N E N S R . G I L V M
L K K I L . S F L R G L T L S G T K T H V K G F W S .
S R R S F D L F Y G V . R S V E R K L T L R D F G H
. S S G K I K E V P D S A . H F S F E R . P I K T M
R L F I R Q D K R R P R V S L P V F V . T L P N Q D H
E L L D K S R K . P T Q R E T S R F S V N L S K P . S
Dra I
Dra I
AGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTA
TCTAATAGTTTTTCCTAGAAGTGGATCTAGGAAAATTTAATTTTTACTTCAAAATTTAGTTAGATTTCATATATACTCAT
2480
R L S K R I F T . I L L N . K . S F K S I . S I Y E .
D Y Q K G S S P R S F . I K N E V L N Q S K V Y M S
E I I K K D L H L D P F K L K M K F . I N L K Y I . V
L N D F L I K V . I R K F . F H L K L D I . L I Y S Y
S . . F P D E G L D K . I L F S T K F . D L T Y I L L
I I L F S R . R S G K L N F I F N . I L R F Y I H T

FIGURE 3G

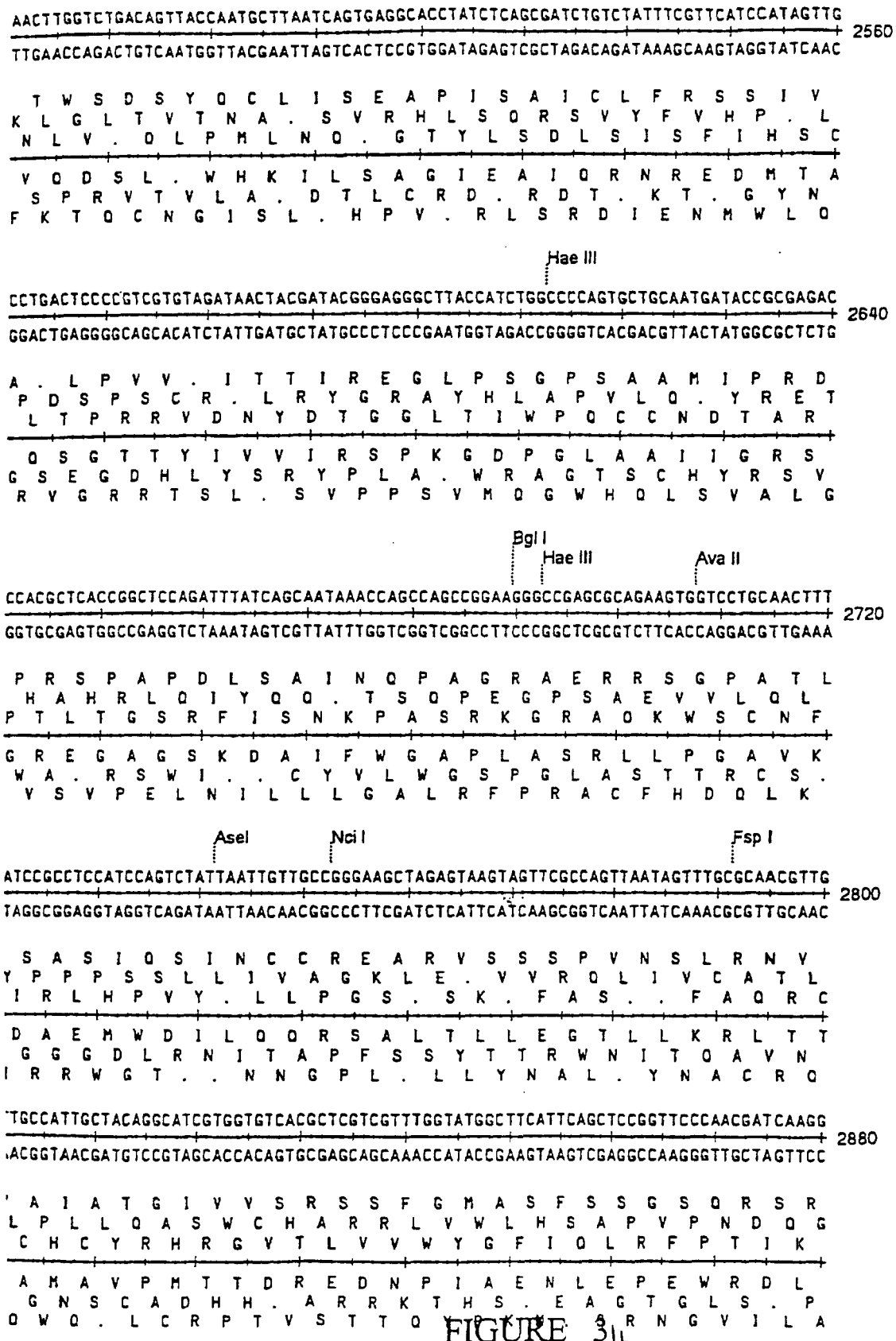

Hae III
Bgl I
Hae III
Ava II
AseI
Nci I
Fsp I
2560
2640
2720
2800
2880

FIGURE 34

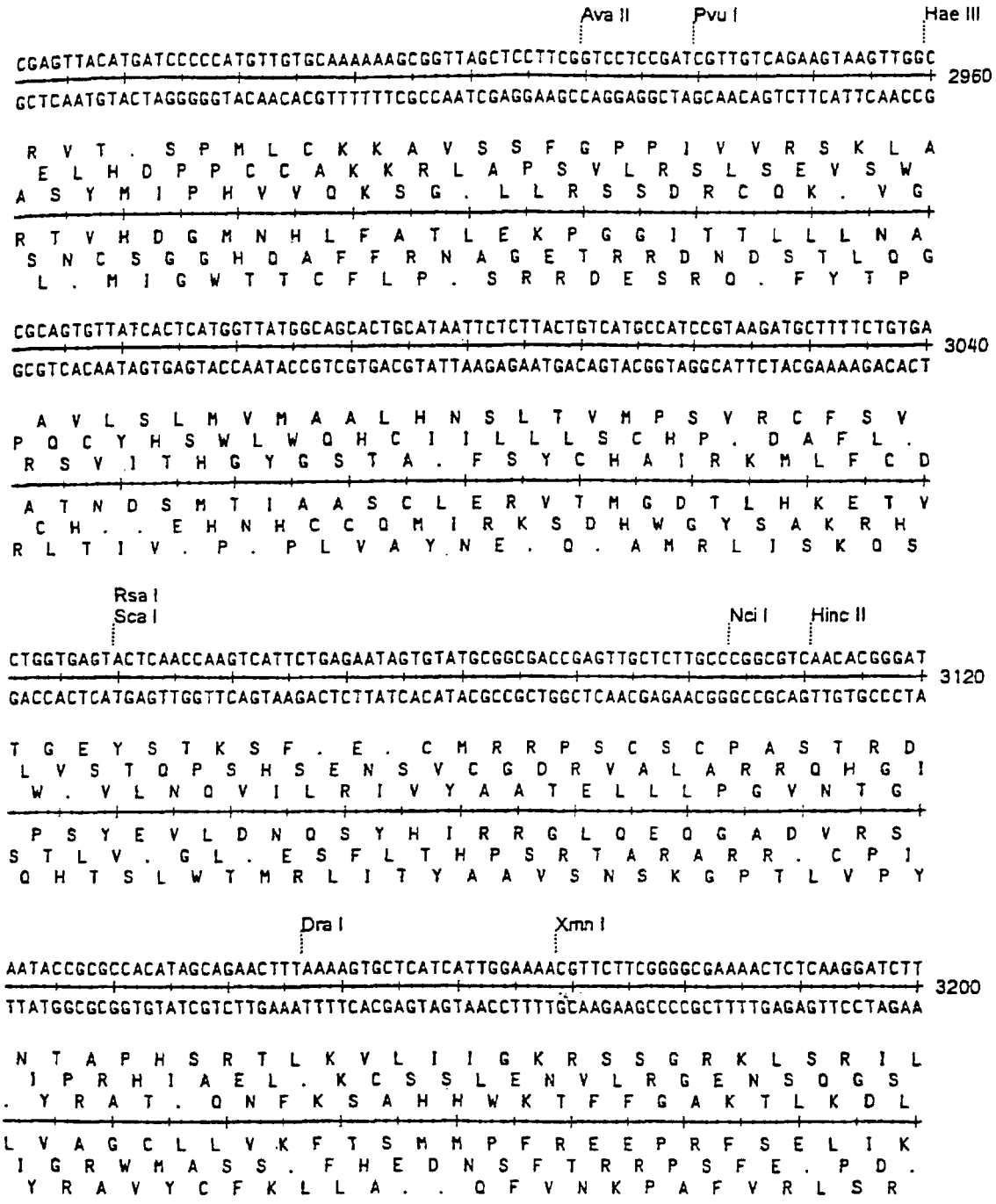

Ava II
Pvu I
Hae III
2960
3040
Rsa I
Sca I
Nci I
Hinc II
3120
Dra I
Xmn I
3200

FIGURE 3I

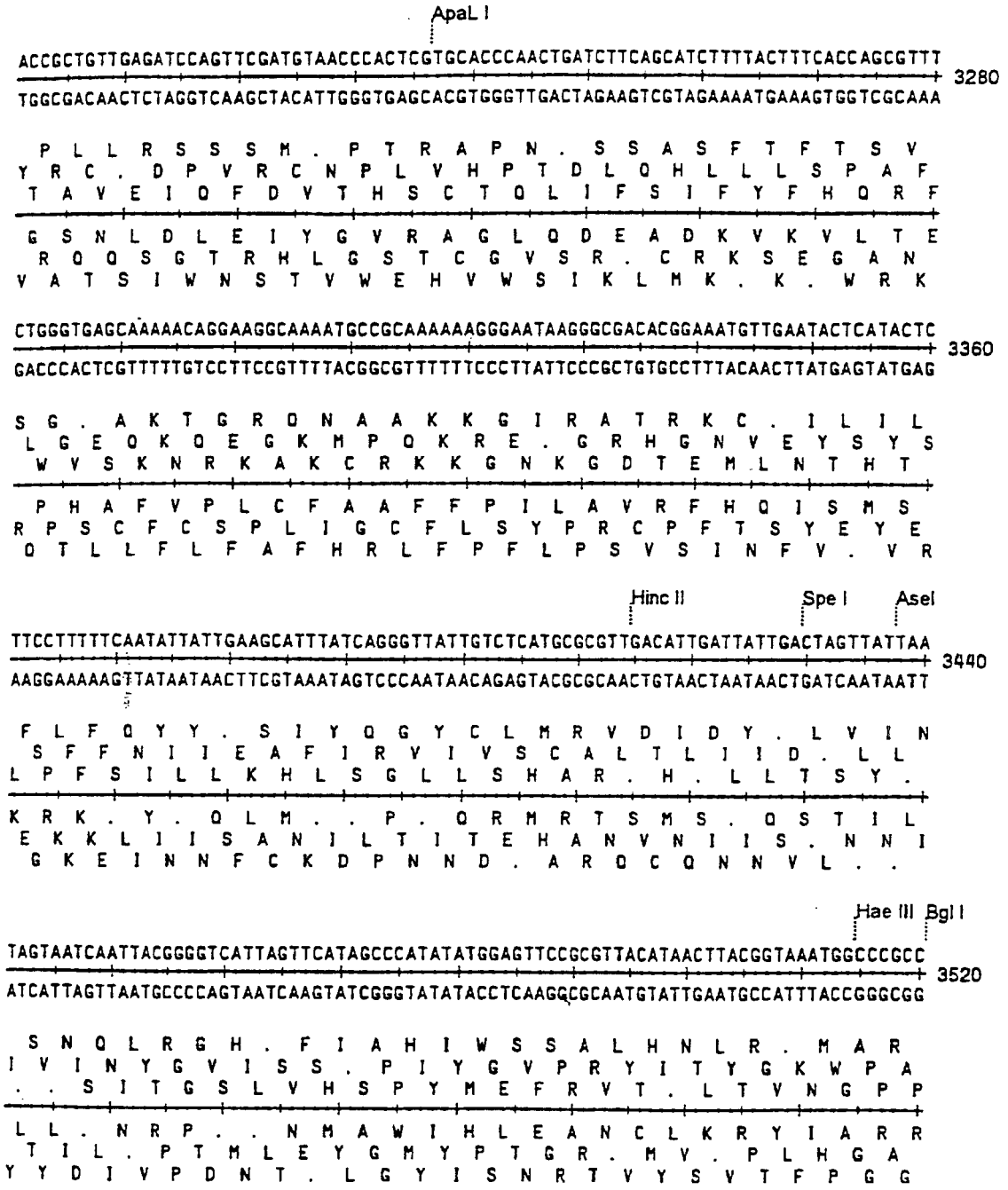

ApaL I
ACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTT
TGGCGACAACTCTAGGTCAAGCTACATTGGGTGAGCACGTGGGTTGACTAGAAGTCGTAGAAAATGAAAGTGGTCGCAAA
3280
P L L R S S S M . P T R A P N . S S A S F T F T S V
Y R C . D P V R C N P L V H P T D L Q H L L L S P A F
T A V E I Q F D V T H S C T Q L I F S I F Y F H Q R F
G S N L D L E I Y G V R A G L Q D E A D K V K V L T E
R Q Q S G T R H L G S T C G V S R . C R K S E G A N
V A T S I W N S T V W E H V W S I K L M K . K . W R K
CTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCATACTC
GACCCACTCGTTTTTGTCCTTCCGTTTTACGGCGTTTTTTCCCTTATTCCCGCTGTGCCTTTACAACTTATGAGTATGAG
3360
S G . A K T G R Q N A A K K G I R A T R K C . I L I L
L G E Q K Q E G K M P Q K R E . G R H G N V E Y S Y S
W V S K N R K A K C R K K G N K G D T E M L N T H T
P H A F V P L C F A A F F P I L A V R F H Q I S M S
R P S C F C S P L I G C F L S Y P R C P F T S Y E Y E
Q T L L F L F A F H R L F P F L P S V S I N F V . V R
Hinc II
Spe I
AseI
TTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGCGCGTTGACATTGATTATTGACTAGTTATTAA
AAGGAAAAAGTTATAATAACTTCGTAAATAGTCCCAATAACAGAGTACGCGCAACTGTAACTAATAACTGATCAATAATT
3440
F L F Q Y Y . S I Y Q G Y C L M R V D I D Y . L V I N
S F F N I I E A F I R V I V S C A L T L I I D . L L
L P F S I L L K H L S G L L S H A R . H . L L T S Y .
K R K . Y . Q L M . . P . Q R M R T S M S . Q S T I L
E K K L I I S A N I L T I T E H A N V N I I S . N N I
G K E I N N F C K D P N N D . A R Q C Q N N V L . .
Hae III
BglI
TAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCC
ATCATTAGTTAATGCCCCAGTAATCAAGTATCGGGTATATACCTCAAGGCGCAATGTATTGAATGCCATTTACCGGGCGG
3520
S N Q L R G H . F I A H I W S S A L H N L R . M A R
I V I N Y G V I S S . P I Y G V P R Y I T Y G K W P A
. . S I T G S L V H S P Y M E F R V T . L T V N G P P
L L . N R P . . N M A W I H L E A N C L K R Y I A R R
T I L . P T M L E Y G M Y P T G R . M V . P L H G A
Y Y D I V P D N T . L G Y I S N R T V Y S V T F P G G

FIGURE 3J

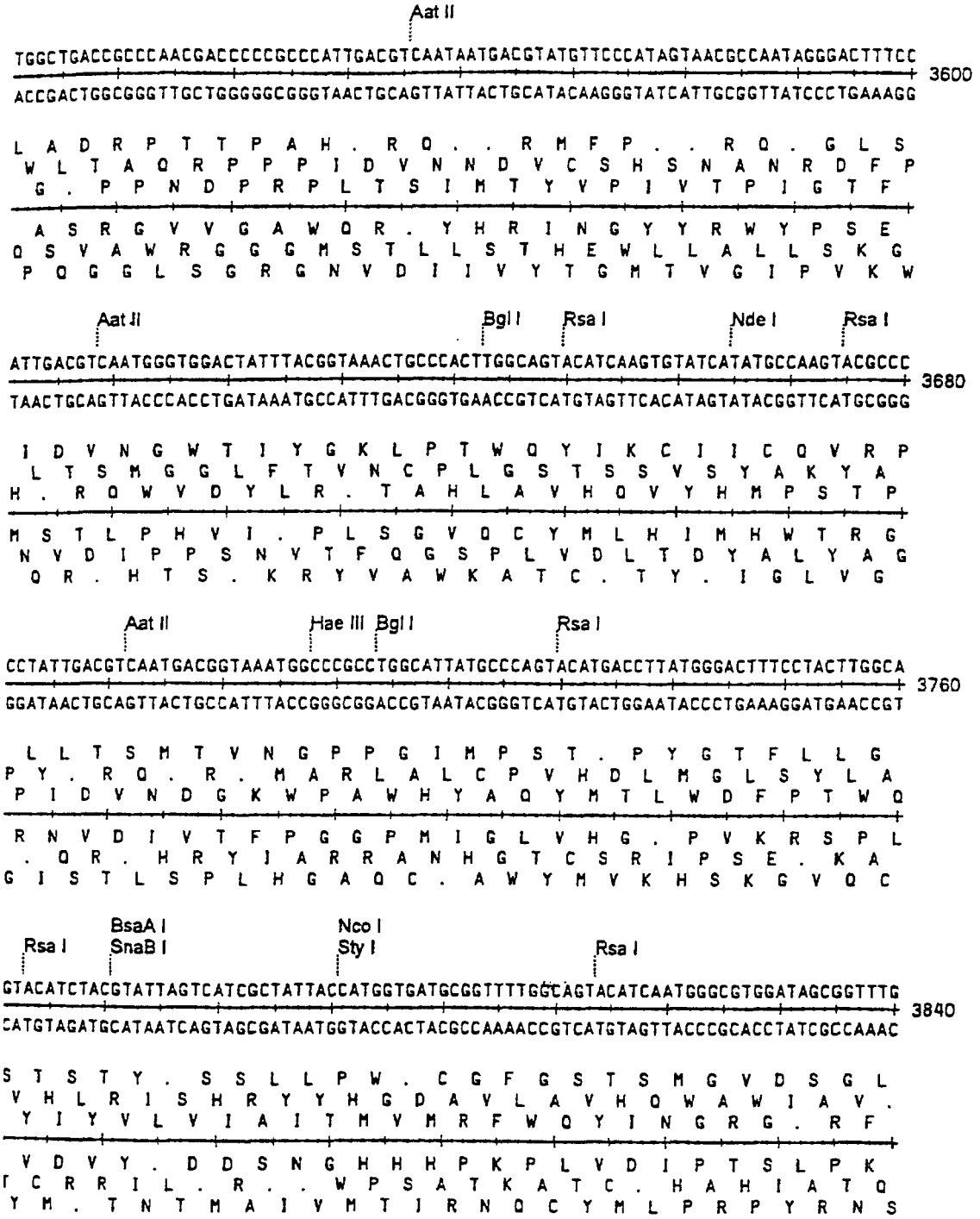

Aat II
TGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCC
ACCGACTGGCGGGTTGCTGGGGGCGGGTAACTGCAGTTATTACTGCATACAAGGGTATCATTGCGGTTATCCCTGAAAGG
3600
L A D R P T T P A H . R Q . . R M F P . . R Q . G L S
W L T A Q R P P P I D V N N D V C S H S N A N R D F P
G . P P N D P R P L T S I M T Y V P I V T P I G T F
A S R G V V G A W Q R . Y H R I N G Y Y R W Y P S E
Q S V A W R G G G M S T L L S T H E W L L A L L S K G
P Q G G L S G R G N V D I I V Y T G M T V G I P V K W
Aat II
Bgl I
Rsa I
Nde I
Rsa I
ATTGACGTCAATGGGTGGACTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCC
TAACTGCAGTTACCCACCTGATAAATGCCATTTGACGGGTGAACCGTCATGTAGTTCACATAGTATACGGTTCATGCGGG
3680
I D V N G W T I Y G K L P T W Q Y I K C I I C Q V R P
L T S M G G L F T V N C P L G S T S S V S Y A K Y A
H . R Q W V D Y L R . T A H L A V H Q V Y H M P S T P
M S T L P H V I . P L S G V Q C Y M L H I M H W T R G
N V D I P P S N V T F Q G S P L V D L T D Y A L Y A G
Q R . H T S . K R Y V A W K A T C . T Y . I G L V G
Aat II
Hae III
Bgl I
Rsa I
CCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCA
GGATAACTGCAGTTACTGCCATTTACCGGGCGGACCGTAATACGGGTCATGTACTGGAATACCCTGAAAGGATGAACCGT
3760
L L T S M T V N G P P G I M P S T . P Y G T F L L G
P Y . R Q . R . M A R L A L C P V H D L M G L S Y L A
P I D V N D G K W P A W H Y A Q Y M T L W D F P T W Q
R N V D I V T F P G G P M I G L V H G . P V K R S P L
. Q R . H R Y I A R R A N H G T C S R I P S E . K A
G I S T L S P L H G A Q C . A W Y M V K H S K G V Q C
Rsa I
BsaA I
SnaB I
Nco I
Sty I
Rsa I
GTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTG
CATGTAGATGCATAATCAGTAGCGATAATGGTACCACTACGCCAAAACCGTCATGTAGTTACCCGCACCTATCGCCAAAC
3840
S T S T Y . S S L L P W . C G F G S T S M G V D S G L
V H L R I S H R Y Y H G D A V L A V H Q W A W I A V .
Y I Y V L V I A I T M V M R F W Q Y I N G R G . R F
V D V Y . D D S N G H H H P K P L V D I P T S L P K
C R R I L . R . . W P S A T K A T C . H A H I A T Q
Y M . T N T M A I V M T I R N Q C Y M L P R P Y R N S

FIGURE 3K

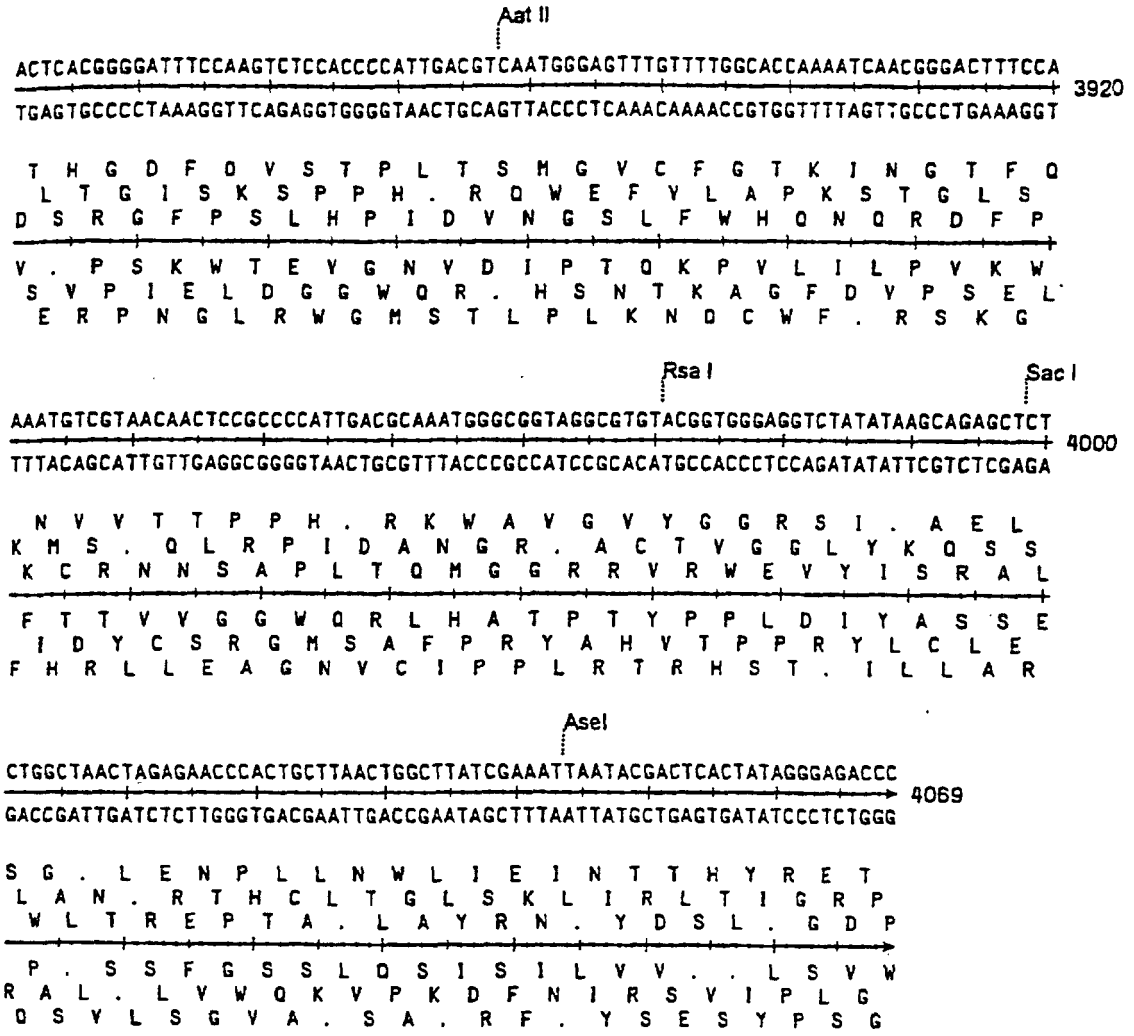

Aat II
ACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCA
TGAGTGCCCCTAAAGGTTCAGAGGTGGGGTAACTGCAGTTACCCTCAAACAAAACCGTGGTTTTAGTTGCCCTGAAAGGT
3920
T H G D F Q V S T P L T S M G V C F G T K I N G T F Q
L T G I S K S P P H . R Q W E F Y L A P K S T G L S
D S R G F P S L H P I D V N G S L F W H Q N Q R D F P
V . P S K W T E Y G N Y D I P T Q K P V L I L P V K W
S V P I E L D G G W Q R . H S N T K A G F D V P S E L
E R P N G L R W G M S T L P L K N D C W F . R S K G
Rsa I
Sac I
AAATGTCGTAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCT
TTTACAGCATTGTTGAGGCGGGGTAACTGCGTTTACCCGCCATCCGCACATGCCACCCTCCAGATATATTCGTCTCGAGA
4000
N V V T T P P H . R K W A V G V Y G G R S I . A E L
K M S . Q L R P I D A N G R . A C T V G G L Y K Q S S
K C R N N S A P L T Q M G G R R V R W E V Y I S R A L
F T T V V G G W Q R L H A T P T Y P P L D I Y A S S E
I D Y C S R G M S A F P R Y A H V T P P R Y L C L E
F H R L L E A G N V C I P P L R T R H S T . I L L A R
AseI
CTGGCTAACTAGAGAACCCACTGCTTAACTGGCTTATCGAAATTAATACGACTCACTATAGGGAGACCC
GACCGATTGATCTCTTGGGTGACGAATTGACCGAATAGCTTTAATTATGCTGAGTGATATCCCTCTGGG
4069
S G . L E N P L L N W L I E I N T T H Y R E T
L A N . R T H C L T G L S K L I R L T I G R P
W L T R E P T A . L A Y R N . Y D S L . G D P
P . S S F G S S L Q S I S I L V V . . L S V W
R A L . L V W Q K V P K D F N I R S V I P L G
Q S Y L S G V A . S A . R F . Y S E S Y P S G

FIGURE 3L

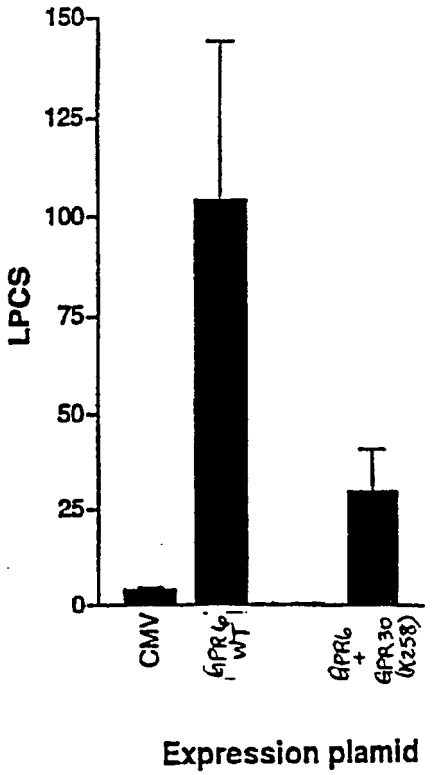

150
125
100
75
50
25
0
LPCS
CMV
GPR6 WT
GPR6 + GPR30 (K258)
Expression plamid

FIGURE 4

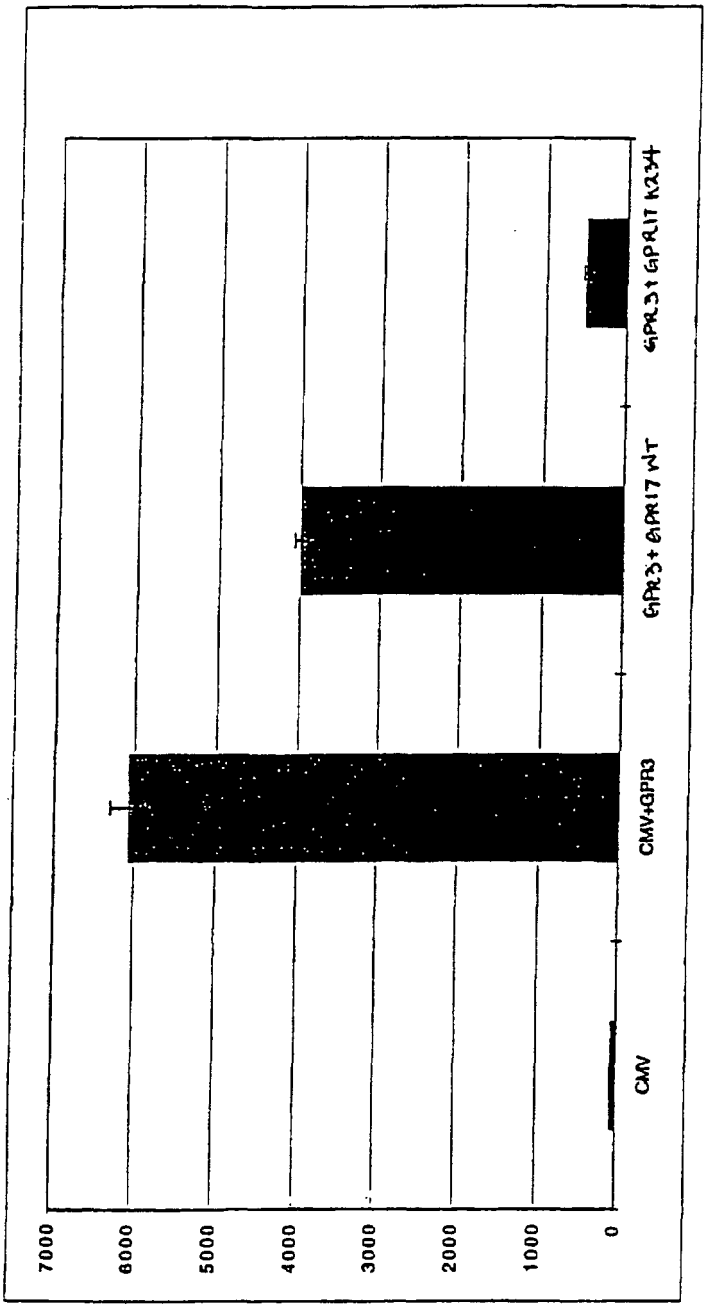

7000
6000
5000
4000
3000
2000
1000
0
CMV
CMV+GPR3
GPR3+GPR17 WT
GPR3+GPR17 K234

FIGURE 5

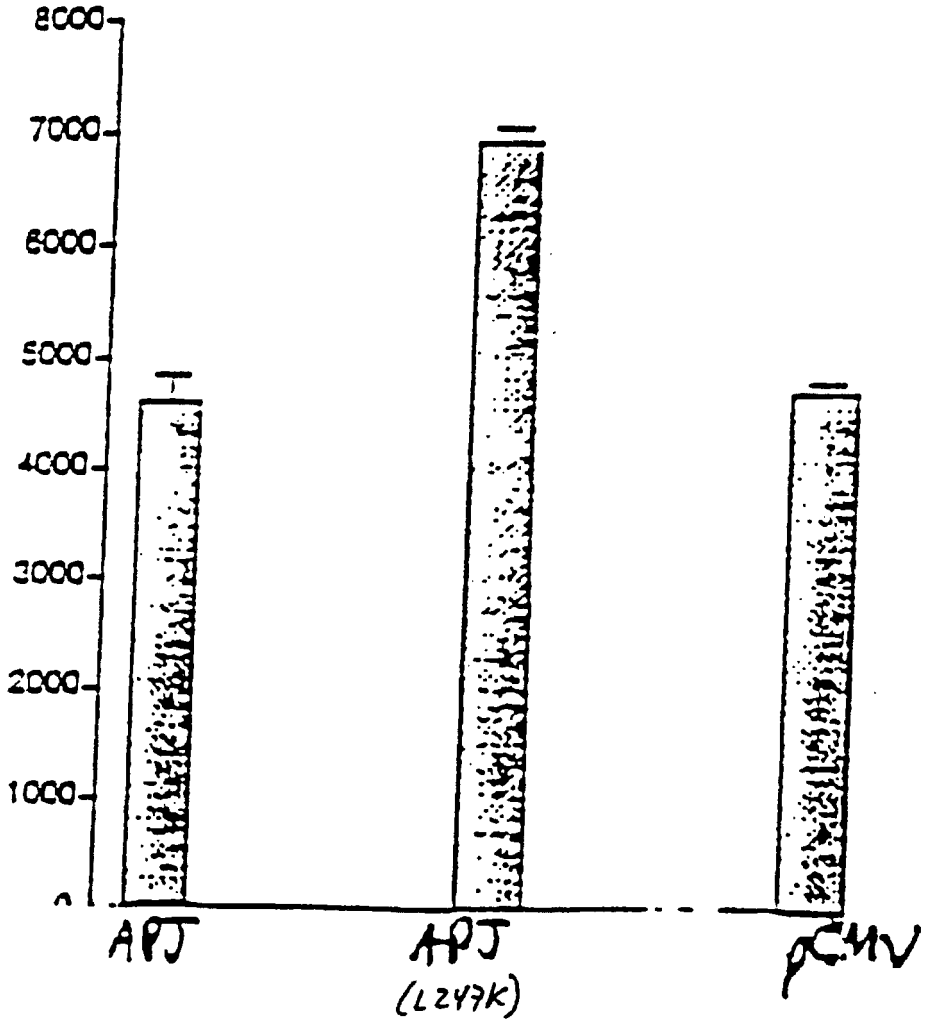


FIGURE 6

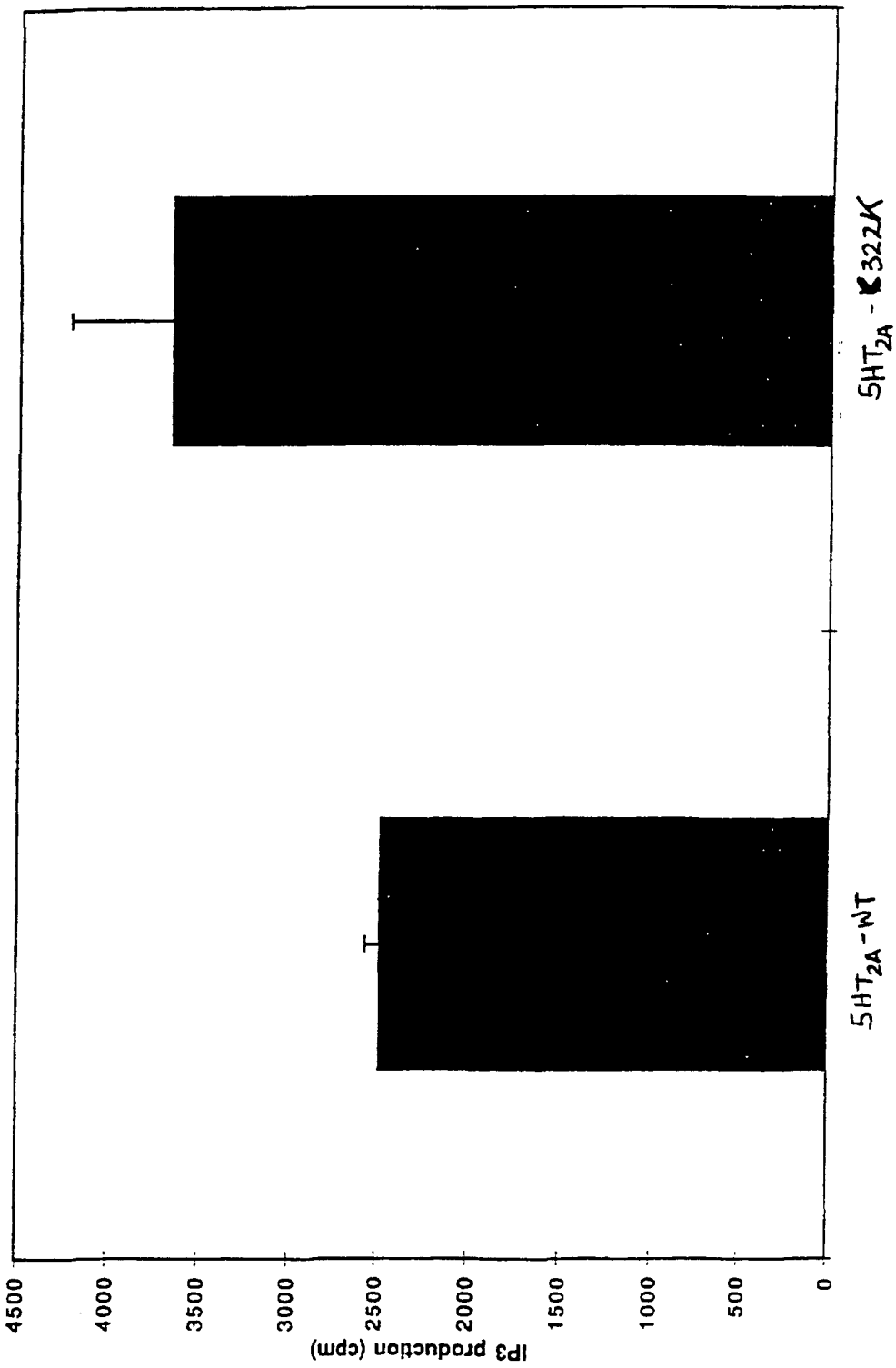

IP3 production (cpm)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
5HT2A - K322K
5HT2A-WT

FIGURE 7

FIGURE 8A

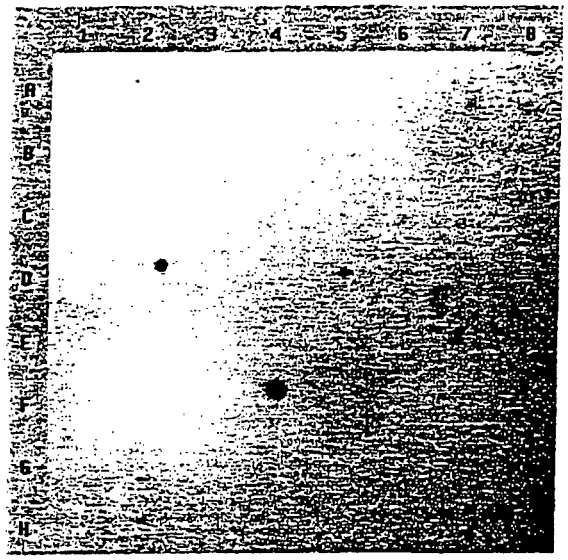
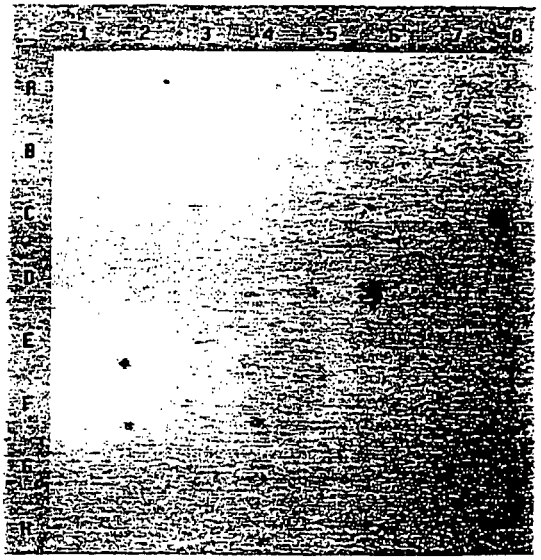


FIGURE 8B



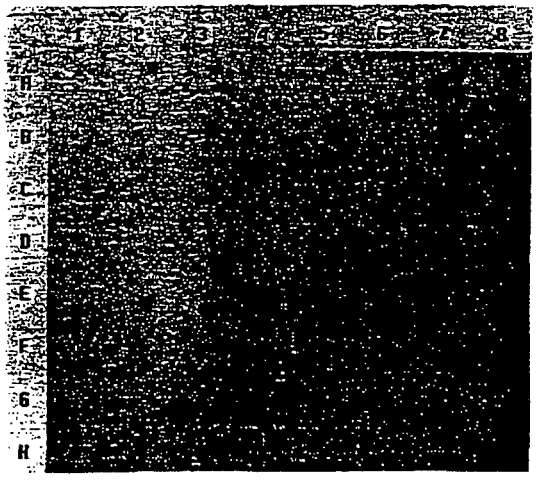


FIGURE 8C