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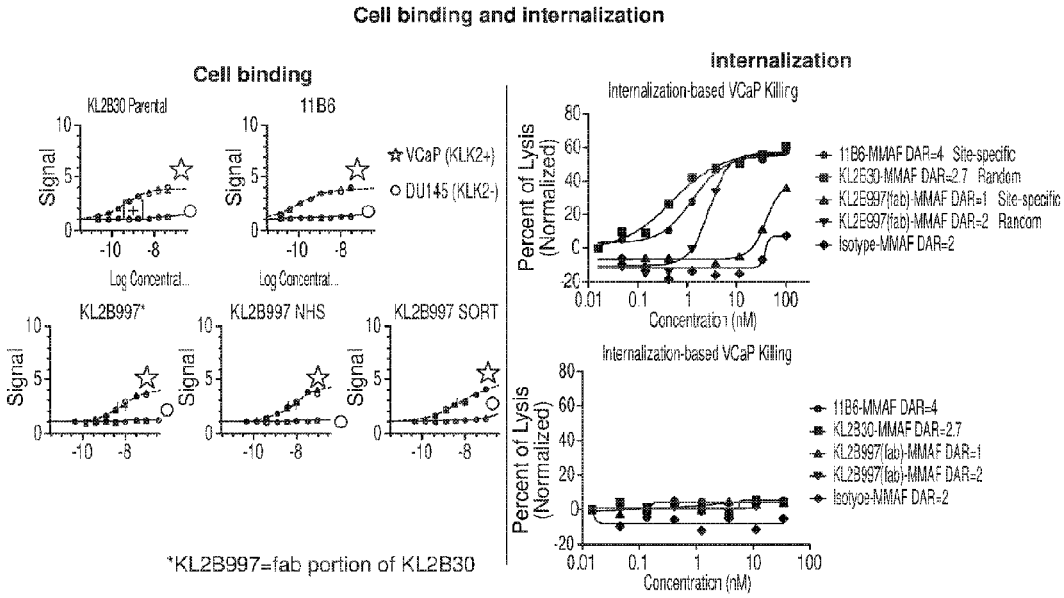


FIG. 1

(57) Abstract: Provided herein are immunoconjugates, such as radioimmunoconjugates, comprising a therapeutic moiety conjugated to an antibody or antigen binding domain with binding specificity for hK2. In certain embodiments, the hK2-specific immunoconjugate demonstrates a short half-life. Also provided herein are methods of using the immunoconjugates for selectively targeting cancer cells and for treating diseases such as prostate cancer.

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IMMUNOCONJUGATES COMPRISING KALLIKREIN RELATED PEPTIDASE 2 ANTIGEN BINDING DOMAINS AND THEIR USES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Application No. 63/142,147, filed on January 27, 2021, and U.S. Provisional Application No. 63/144,586, filed on February 2, 2021, the contents of which are incorporated by reference herein, in their entireties and for all purposes.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on January 20, 2022, is named JBI6462WOPCT1_Seq Listing.txt and is 755 KB in size.

TECHNICAL FIELD

The invention provides immunoconjugates, such as radioconjugates, comprising antigen binding domains that bind kallikrein related peptidase 2 (hK2) protein, and methods of making and using them.

BACKGROUND OF THE INVENTION

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for about 14% of the total new cancer cases and about 6% of the total cancer deaths in males worldwide. The course of prostate cancer from diagnosis to death is best categorized as a series of clinical stages based on the extent of disease, hormonal status, and absence or presence of detectable metastases: localized disease, rising levels of prostate-specific antigen (PSA) after radiation therapy or surgery with no detectable metastases, and clinical metastases in the non-castrate or castrate stage. Although surgery, radiation, or a combination of both can be curative for patients with localized disease, a significant proportion of these patients have recurrent disease as evidenced by a rising level of PSA, which can lead to the development of metastases, especially in the high-risk group—a transition to the lethal stage of the disease.

Androgen depletion therapy (ADT) is the standard treatment with a generally predictable outcome: decline in PSA, a period of stability in which the tumor does not proliferate, followed by rising PSA and regrowth as castration-resistant disease. Historically, ADT has been the standard of care for patients with metastatic prostate cancer.

Kallikrein related peptidase 2 (hK2, HK2) is a trypsin-like enzyme with androgen receptor (AR)-driven expression specific to prostate tissue and prostate cancer. hK2 expression is restricted to the prostate and prostate cancer tissue, however it has recently been demonstrated that hK2 was detectable in breast cancer lines and primary patient samples after appropriate activation of the AR-pathway by steroid hormones (U.S. Pat. Publ. No. 2018/0326102). Retrograde release of catalytically inactive hK2 into the blood occurs when the highly structured organization of the prostate is compromised upon hypertrophy or malignant transformation.

There remains a need for next generation hK2-targeted therapies for therapeutic and diagnostic purposes.

BRIEF SUMMARY OF THE INVENTION

Embodiments of the present invention relate to an anti-hk2 radioconjugate comprising an antigen binding domain conjugated with a chelator that binds radiometals for therapeutic use or imaging. According to particular embodiments, the anti-hK2 radioconjugate comprising an antigen binding domain has a shorter half-life compared to an anti-hK2 radioconjugate comprising a full-length antibody.

In many cases the circulating half-life of immunoglobulin G (IgG) in humans is approximately 10–21 days. The Fc domain in an intact IgG is capable of binding to the neonatal Fc receptor (FcRn), leading to antibody recycling and minimal endosomal degradation. FcRn plays a key role in serum IgG homeostasis as well as in placental transfer of IgG molecules from mother to fetus. Following pinocytosis, the acidic environment of the early endosome allows for binding of IgG (as well as albumin) to FcRn, which provides protection from degradation and facilitates trafficking of IgG back to the extracellular environment, where the molecules dissociate back into circulation upon exposure to physiological pH.

The circulating half-life of an antigen binding domain, such as a Fab, tends to be much shorter than that of an IgG. As the Fab fragment lacks the Fc domain, the FcRn mediated

enhanced half-life mechanism is lacking, thus the Fab alone has a shorter half-life (for example, less than 24 hours, or less than 12 hours, and in some cases about 2-3 hours).

An embodiment of the present invention provides immunoconjugate comprising a therapeutic moiety conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

According to certain embodiments, the therapeutic moiety is a cytotoxic agent.

According to certain embodiments, the therapeutic moiety is an imaging agent.

According to certain embodiments, the therapeutic moiety comprises a radiometal. Non-limiting examples of suitable radiometals include ^{225}Ac, ^{177}Lu, ^{32}P, ^{47}Sc, ^{67}Cu, ^{77}As, ^{89}Sr, ^{90}Y, ^{99}Tc, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{131}I, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{255}Fm, ^{227}Th, ^{177}Lu, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, and ^{111}In.

According to certain embodiments, the therapeutic moiety is a cytotoxic agent comprising ^{225}Ac.

According to certain embodiments, the therapeutic moiety is an imaging agent comprising ^{111}In.

According to certain embodiments, the therapeutic moiety comprises a radiometal complex, wherein the radiometal complex comprises the radiometal bound to a chelator, and wherein the chelator is conjugated to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

According to certain embodiments, the chelator is 1,4,7,10-tetraazacyclododecane-1,4,7,10,tetraacetic acid (DOTA), S-2-(4-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), 1,4,8,11-tetraazacyclodocedan-1,4,8,11-tetraacetic acid (TETA), 3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-4-(S)-(4-isothiocyanatobenzyl)-3,6,9-triacetic acid (PCTA), 5-S-(4-aminobenzyl)-1-oxa-4,7,10- triazacyclododecane-4,7,10-tris(acetic acid) (DO3A), or a derivative thereof.

According to certain embodiments, the chelator is DOTA.

According to certain embodiments, the chelator is H_2bp18c6 or a H_2bp18c6 derivative.

According to certain embodiments, the radiometal complex is a radiocomplex of Formula (I-m), or Formula (II-m), or Formula (III-m) as described herein, wherein R_{11} comprises the

antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2) and M is the radiometal.

According to certain embodiments, the radiometal complex is a radiometal complex of Formula (IV-m), or Formula (V-m), or Formula (VI-m) as described herein, wherein R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2) and M+ is the radiometal.

According to certain embodiments, the therapeutic moiety is an auristatin derivative, such as MMAE (monomethyl auristatin E) or MMAF (monomethyl auristatin F).

According to certain embodiments, the antigen binding domain that binds hK2 is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb or a VHH.

According to certain embodiments, the antigen binding domain with binding specificity for hK2 is a Fab.

According to certain embodiments, the antigen binding domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NO: 170 (SYYWS), SEQ ID NO: 171 (YIYYSGSTNYNPSLKS), SEQ ID NO: 172 (TTIFGVVTPNFYYGMDV), SEQ ID NO: 173 (RASQGISSYLA), SEQ ID NO: 174 (AASTLQS) and SEQ ID NO: 175 (QQLNSYPLT), respectively.

According to certain embodiments, the antigen binding domain that binds hK2 comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 (QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGTTVTVSS), and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163 (DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK).

According to certain embodiments, the antigen binding domain that binds hK2 comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.

According to certain embodiments, the antigen binding domain is a Fab that comprises: A) a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ

ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or B) a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

According to certain embodiments, the immunoconjugate is a short half-life immunoconjugate.

According to certain embodiments, a method of treating an hK2-expressing cancer in a subject, comprises administering to the subject a therapeutically effective amount of the immunoconjugate according to any of the foregoing embodiments.

According to certain embodiments, a method of reducing the amount of hK2-expressing tumor cells in a subject, comprises administering to the subject a therapeutically effective amount of the immunoconjugate according to any of the foregoing embodiments.

According to certain embodiments, a method of treating prostate cancer in a subject comprises administering to the subject a therapeutically effective amount of the immunoconjugate according to any of the foregoing embodiments.

According to certain embodiments, the prostate cancer is relapsed, refractory, malignant or castration resistant prostate cancer, or any combination thereof.

According to certain embodiments, the prostate cancer is metastatic castration-resistant prostate cancer.

According to certain embodiments, a method of detecting the presence of prostate cancer in a subject, comprising administering the immunoconjugate according to any of the foregoing embodiments to a subject suspected to have prostate cancer and visualizing the biological structures to which the conjugate is bound (e.g., by computerized tomography or positron emission tomography), thereby detecting the presence of prostate cancer, wherein the immunoconjugate preferably comprises an imaging agent, such as 111-In or 64-Cu. According to certain embodiments, the method comprises conjugating the therapeutic moiety to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

According to certain embodiments, a method of making a radioimmunoconjugate as described herein comprises binding a radiometal to a chelator that is conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

According to certain embodiments, a short half-life radioimmunoconjugate comprises a radiometal complex, wherein the radiometal complex comprises ^{225}Ac bound to a chelator,

and wherein the chelator is conjugated to a Fab with binding specificity for hK2, said Fab comprising: a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively. According to certain embodiments, said Fab comprises a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

DETAILED DESCRIPTION OF THE DRAWINGS

The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings. It should be understood that the invention is not limited to the precise embodiments shown in the drawings.

In the drawings:

FIG. 1 shows cell binding and internalization of an immunoconjugate of the present invention, comprising the KL2B30 Fab (identified as KL2B997) conjugated to MMAF (monomethyl auristatin F), in hK2-expressing VCaP cells.

FIG. 2 shows amino acid sequences (heavy chain and light chain sequences) of KL2B997 and KL2B1251. KL2B997 has a His-tag and a sortase tag (underlined in FIG. 2) on the heavy chain, and KL2B1251 is tagless.

DETAILED DESCRIPTION OF THE INVENTION

Various publications, articles and patents are cited or described in the background and throughout the specification; each of these references is herein incorporated by reference in its entirety. Discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is for the purpose of providing context for the invention. Such discussion is not an admission that any or all of these matters form part of the prior art with respect to any inventions disclosed or claimed.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning commonly understood to one of ordinary skill in the art to which this invention pertains. Otherwise, certain terms cited herein have the meanings as set in the specification. All patents, published patent applications and publications cited herein are incorporated by reference as if set forth fully herein

As used herein, the conjunctive term “and/or” between multiple recited elements is understood as encompassing both individual and combined options. For instance, where two

elements are conjoined by "and/or", a first option refers to the applicability of the first element without the second. A second option refers to the applicability of the second element without the first. A third option refers to the applicability of the first and second elements together. Any one of these options is understood to fall within the meaning, and therefore satisfy the requirement of the term "and/or" as used herein. Concurrent applicability of more than one of the options is also understood to fall within the meaning, and therefore satisfy the requirement of the term "and/or."

In an attempt to help the reader of the application, the description has been separated into various paragraphs or sections, or is directed to various embodiments of the application. These separations should not be considered as disconnecting the substance of a paragraph or section or embodiments from the substance of another paragraph or section or embodiments. To the contrary, one skilled in the art will understand that the description has broad application and encompasses all the combinations of the various sections, paragraphs and sentences that can be contemplated. The discussion of any embodiment is meant only to be exemplary and is not intended to suggest that the scope of the disclosure, including the claims, is limited to these examples.

As used herein, the use of a numerical range expressly includes all possible subranges, all individual numerical values within that range, including integers within such ranges and fractions of the values unless the context clearly indicates otherwise.

When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list, and every combination of that list, is a separate embodiment. For example, a list of embodiments presented as "A, B, or C" is to be interpreted as including the embodiments, "A," "B," "C," "A or B," "A or C," "B or C," or "A, B, or C."

As used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a cell" includes a combination of two or more cells, and the like.

The transitional terms "comprising," "consisting essentially of," and "consisting of" are intended to connote their generally accepted meanings in the patent vernacular; that is, (i) "comprising," which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; (ii) "consisting of" excludes any element, step, or ingredient not specified in the claim; and (iii)

"consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Embodiments described in terms of the phrase "comprising" (or its equivalents) also provide as embodiments those independently described in terms of "consisting of" and "consisting essentially of."

"About" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system.

"Antibody-dependent cellular cytotoxicity", "antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to the mechanism of inducing cell death that depends upon the interaction of antibody-coated target cells with effector cells possessing lytic activity, such as natural killer cells (NK), monocytes, macrophages and neutrophils via Fc gamma receptors (FcγR) expressed on effector cells.

"Antibody-dependent cellular phagocytosis" or "ADCP" refers to the mechanism of elimination of antibody-coated target cells by internalization by phagocytic cells, such as macrophages or dendritic cells.

"Antigen" refers to any molecule (e.g., protein, peptide, polysaccharide, glycoprotein, glycolipid, nucleic acid, portions thereof, or combinations thereof) capable of being bound by an antigen binding domain or a T-cell receptor capable of mediating an immune response. Exemplary immune responses include antibody production and activation of immune cells, such as T cells, B cells or NK cells. Antigens may be expressed by genes, synthetized, or purified from biological samples such as a tissue sample, a tumor sample, a cell or a fluid with other biological components, organisms, subunits of proteins/antigens, killed or inactivated whole cells or lysates.

"Antigen binding fragment" or "antigen binding domain" refers to a portion of an isolated protein that binds an antigen. Antigen binding fragments may be synthetic, enzymatically obtainable or genetically engineered polypeptides and include portions of an immunoglobulin that bind an antigen, such as the VH, the VL, the VH and the VL, Fab, Fab', $F(ab')_2$, Fd and Fv fragments, domain antibodies (dAb) consisting of one VH domain or one VL domain, shark variable IgNAR domains, camelized VH domains, VHH domains, minimal

recognition units consisting of the amino acid residues that mimic the CDRs of an antibody, such as FR3-CDR3-FR4 portions, the HCDR1, the HCDR2 and/or the HCDR3 and the LCDR1, the LCDR2 and/or the LCDR3, alternative scaffolds that bind an antigen, and multispecific proteins comprising the antigen binding fragments. Antigen binding fragments (such as VH and VL) may be linked together via a synthetic linker to form various types of single antibody designs where the VH/VL domains may pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chains, to form a monovalent antigen binding domain, such as single chain Fv (scFv) or diabody. As used herein, an "antigen binding fragment" or "antigen binding domain" does not refer to a full-length antibody having an Fc region.

"Antibodies" is meant in a broad sense and includes immunoglobulin molecules including monoclonal antibodies including murine, human, humanized and chimeric monoclonal antibodies, antigen binding fragments, multispecific antibodies, such as bispecific, trispecific, tetraspecific , dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the immunoglobulin molecule that comprises an antigen binding site of the required specificity. "Full length antibodies" are comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds as well as multimers thereof (e.g. IgM). Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region (comprised of domains CH1, hinge, CH2 and CH3). Each light chain is comprised of a light chain variable region (VL) and a light chain constant region (CL). The VH and the VL regions may be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-to-carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. Immunoglobulins may be assigned to five major classes, IgA, IgD, IgE, IgG and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4. Antibody light chains of any vertebrate species may be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

"Cancer" refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the

formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream. A "cancer" or "cancer tissue" can include a tumor.

"Complementarity determining regions" (CDR) are antibody regions that bind an antigen. There are three CDRs in the VH (HCDR1, HCDR2, HCDR3) and three CDRs in the VL (LCDR1, LCDR2, LCDR3). CDRs may be defined using various delineations such as Kabat (Wu et al. (1970) J Exp Med 132: 211-50; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991), Chothia (Chothia et al. (1987) J Mol Biol 196: 901-17), IMGT (Lefranc et al. (2003) Dev Comp Immunol 27: 55-77) and AbM (Martin and Thornton J Bmol Biol 263: 800-15, 1996). The correspondence between the various delineations and variable region numbering is described (see e.g. Lefranc et al. (2003) Dev Comp Immunol 27: 55-77; Honegger and Pluckthun, J Mol Biol (2001) 309:657-70; International ImMunoGeneTics (IMGT) database; Web resources, http://www_imgt_org). Available programs such as abYsis by UCL Business PLC may be used to delineate CDRs. The term "CDR", "HCDR1", "HCDR2", "HCDR3", "LCDR1", "LCDR2" and "LCDR3" as used herein includes CDRs defined by any of the methods described supra, Kabat, Chothia, IMGT or AbM, unless otherwise explicitly stated in the specification.

"Decrease," "lower," "lessen," "reduce," or "abate" refers generally to the ability of a test molecule to mediate a reduced response (*i.e.*, downstream effect) when compared to the response mediated by a control or a vehicle. Exemplary responses are T cell expansion, T cell activation or T-cell mediated tumor cell killing or binding of a protein to its antigen or receptor, enhanced binding to a Fcγ or enhanced Fc effector functions such as enhanced ADCC, CDC and/or ADCP. Decrease may be a statistically significant difference in the measured response between the test molecule and the control (or the vehicle), or a decrease in the measured response, such as a decrease of about 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 30 fold or more, such as 500, 600, 700, 800, 900 or 1000 fold or more (including all integers and decimal points in between and above 1, e.g., 1.5, 1.6, 1.7. 1.8, etc.).

"Differentiation" refers to a method of decreasing the potency or proliferation of a cell or moving the cell to a more developmentally restricted state.

"Encode" or "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates

for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

"Enhance," "promote," "increase," "expand" or "improve" refers generally to the ability of a test molecule to mediate a greater response (*i.e.,* downstream effect) when compared to the response mediated by a control or a vehicle. Exemplary responses are T cell expansion, T cell activation or T-cell mediated tumor cell killing or binding of a protein to its antigen or receptor, enhanced binding to a Fcγ or enhanced Fc effector functions such as enhanced ADCC, CDC and/or ADCP. Enhance may be a statistically significant difference in the measured response between the test molecule and control (or vehicle), or an increase in the measured response, such as an increase of about 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 30 fold or more, such as 500, 600, 700, 800, 900 or 1000 fold or more (including all integers and decimal points in between and above 1, e.g., 1.5, 1.6, 1.7. 1.8, etc.).

"Epitope" refers to a portion of an antigen to which an antibody specifically binds. Epitopes typically consist of chemically active (such as polar, non-polar or hydrophobic) surface groupings of moieties such as amino acids or polysaccharide side chains and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. An epitope may be composed of contiguous and/or discontinuous amino acids that form a conformational spatial unit. For a discontinuous epitope, amino acids from differing portions of the linear sequence of the antigen come in close proximity in 3-dimensional space through the folding of the protein molecule. Antibody "epitope" depends on the methodology used to identify the epitope.

"Expansion" refers to the outcome of cell division and cell death.

"Express" and "expression" refers the to the well-known transcription and translation occurring in cells or *in vitro.* The expression product, *e.g.,* the protein, is thus expressed by the cell or *in vitro* and may be an intracellular, extracellular or a transmembrane protein.

"Expression vector" refers to a vector that can be utilized in a biological system or in a reconstituted biological system to direct the translation of a polypeptide encoded by a polynucleotide sequence present in the expression vector.

"dAb" or "dAb fragment" refers to an antibody fragment composed of a VH domain (Ward et al., Nature 341:544 546 (1989)).

"Fab" or "Fab fragment" or "Fab region" refers to an antibody region that binds to antigens. A conventional IgG usually comprises two Fab regions, each residing on one of the two arms of the Y-shaped IgG structure. Each Fab region is typically composed of one variable region and one constant region of each of the heavy and the light chain. More specifically, the variable region and the constant region of the heavy chain in a Fab region are VH and CH1 regions, and the variable region and the constant region of the light chain in a Fab region are VL and CL regions. The VH, CH1, VL, and CL in a Fab region can be arranged in various ways to confer an antigen binding capability according to the present disclosure. For example, VH and CH1 regions can be on one polypeptide, and VL and CL regions can be on a separate polypeptide, similarly to a Fab region of a conventional IgG. Alternatively, VH, CH1, VL and CL regions can all be on the same polypeptide and oriented in different orders.

"$F(ab')_2$" or "$F(ab')_2$ fragment" refers to an antibody fragment containing two Fab fragments connected by a disulfide bridge in the hinge region.

"Fd" or "Fd fragment" refers to an antibody fragment composed of VH and CH1 domains.

"Fv" or "Fv fragment" refers to an antibody fragment composed of the VH and the VL domains from a single arm of the antibody. Fv fragments lack the constant regions of Fab (CH1 and CL) regions. The VH and VL in Fv fragments are held together by non-covalent interactions.

"Fc" polypeptide" of a dimeric Fc refers to one of the two polypeptide forming the dimeric Fc domain. For example, an Fc polypeptide of a dimeric IgG FC comprises an IgG CH2 and an IgG CH3 constant domain sequence).

"Full length antibody" is comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds as well as multimers thereof (e.g. IgM). Each heavy chain is comprised of a heavy chain variable domain (VH) and a heavy chain constant domain, the heavy chain constant domain comprised of subdomains CH1, hinge, CH2 and CH3. Each light chain is

comprised of a light chain variable domain (VL) and a light chain constant domain (CL). The VH and the VL may be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-to-carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4.

"Host cell" refers to any cell that contains a heterologous nucleic acid. An exemplary heterologous nucleic acid is a vector (*e.g.*, an expression vector).

"Human antibody" refers to an antibody that is optimized to have minimal immune response when administered to a human subject. Variable regions of human antibody are derived from human immunoglobulin sequences. If human antibody contains a constant region or a portion of the constant region, the constant region is also derived from human immunoglobulin sequences. Human antibody comprises heavy and light chain variable regions that are "derived from" sequences of human origin if the variable regions of the human antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Such exemplary systems are human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice or rats carrying human immunoglobulin loci. "Human antibody" typically contains amino acid differences when compared to the immunoglobulins expressed in humans due to differences between the systems used to obtain the human antibody and human immunoglobulin loci, introduction of somatic mutations or intentional introduction of substitutions into the frameworks or CDRs, or both. Typically, "human antibody" is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical in amino acid sequence to an amino acid sequence encoded by human germline immunoglobulin or rearranged immunoglobulin genes. In some cases, "human antibody" may contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik et al., (2000) J Mol Biol 296:57-86, or a synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example as described in Shi et al., (2010) J Mol Biol 397:385-96, and in Int. Patent Publ. No. WO2009/085462. Antibodies in which at least one CDR is derived from a non-human species are not included in the definition of "human antibody".

"Humanized antibody" refers to an antibody in which at least one CDR is derived from non-human species and at least one framework is derived from human immunoglobulin sequences. Humanized antibody may include substitutions in the frameworks so that the frameworks may not be exact copies of expressed human immunoglobulin or human immunoglobulin germline gene sequences.

"In combination with" means that two or more therapeutic agents are be administered to a subject together in a mixture, concurrently as single agents or sequentially as single agents in any order.

"Isolated" refers to a homogenous population of molecules (such as synthetic polynucleotides or polypeptides) which have been substantially separated and/or purified away from other components of the system the molecules are produced in, such as a recombinant cell, as well as a protein that has been subjected to at least one purification or isolation step. "Isolated" refers to a molecule that is substantially free of other cellular material and/or chemicals and encompasses molecules that are isolated to a higher purity, such as to 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% purity.

"Kallikrein related peptidase 2" or "hK2" (also referred to herein as KLK2) refers to a known protein which is also called kallikrein-2, grandular kallikrein 2, or HK2. hK2 is produced as a preproprotein and cleaved during proteolysis to generate active protease. All hK2 isoforms and variants are encompassed in "hK2". The amino acid sequences of the various isoforms are retrievable from GenBank accession numbers NP_005542.1, NP_001002231.1 and NP_001243009. The amino acid sequence of a full length hK2 is shown in SEQ ID NO: 62. The sequence includes the signal peptide (residues 1-18) and the pro-peptide region (residues 19-24).

SEQ ID NO: 62

MWDLVLSIALSVGCTGAVPLIQSRIVGGWECEKHSQPWQVAVYSHGWAHCGGVLVHPQWV
LTAAHCLKKNSQVWLGRHNLFEPEDTGQRVPVSHSFPHPLYNMSLLKHQSLRPDEDSSHD
LMLLRLSEPAKITDVVKVLGLPTQEPALGTTCYASGWGSIEPEEFLRPRSLQCVSLHLLS
NDMCARAYSEKVTEFMLCAGLWTGGKDTCGGDSGGPLVCNGVLQGITSWGPEPCALPEKP
AVYTKVVHYRKWIKDTIAANP

"Modulate" refers to either enhanced or decreased ability of a test molecule to mediate an enhanced or a reduced response (*i.e.*, downstream effect) when compared to the response mediated by a control or a vehicle.

"Monoclonal antibody" refers to an antibody obtained from a substantially homogenous population of antibody molecules, i.e., the individual antibodies comprising the population are identical except for possible well-known alterations such as removal of C-terminal lysine from the antibody heavy chain or post-translational modifications such as amino acid isomerization or deamidation, methionine oxidation or asparagine or glutamine deamidation. Monoclonal antibodies typically bind one antigenic epitope. A bispecific monoclonal antibody binds two distinct antigenic epitopes. Monoclonal antibodies may have heterogeneous glycosylation within the antibody population. Monoclonal antibody may be monospecific or multispecific such as bispecific, monovalent, bivalent or multivalent.

"Operatively linked" and similar phrases, when used in reference to nucleic acids or amino acids, refers to the operational linkage of nucleic acid sequences or amino acid sequence, respectively, placed in functional relationships with each other. For example, an operatively linked promoter, enhancer elements, open reading frame, 5' and 3' UTR, and terminator sequences result in the accurate production of a nucleic acid molecule (e.g., RNA) and in some instances to the production of a polypeptide (i.e., expression of the open reading frame). Operatively linked peptide refers to a peptide in which the functional domains of the peptide are placed with appropriate distance from each other to impart the intended function of each domain.

The term "paratope" refers to the area or region of an antibody molecule which is involved in binding of an antigen and comprise residues that interact with an antigen. A paratope may composed of continuous and/or discontinuous amino acids that form a conformational spatial unit. The paratope for a given antibody can be defined and characterized at different levels of details using a variety of experimental and computational methods. The experimental methods include hydrogen/deuterium exchange mass spectrometry (HX-MS). The paratope will be defined differently depending on the mapping method employed.

"Pharmaceutical combination" refers to a combination of two or more active ingredients administered either together or separately.

"Pharmaceutical composition" refers to a composition that results from combining an active ingredient and a pharmaceutically acceptable carrier.

"Pharmaceutically acceptable carrier" or "excipient" refers to an ingredient in a pharmaceutical composition, other than the active ingredient, which is nontoxic to a subject. Exemplary pharmaceutically acceptable carriers are a buffer, stabilizer or preservative.

"Polynucleotide" or "nucleic acid" refers to a synthetic molecule comprising a chain of nucleotides covalently linked by a sugar-phosphate backbone or other equivalent covalent chemistry. cDNA is a typical example of a polynucleotide. Polynucleotide may be a DNA or a RNA molecule.

"Prevent," "preventing," "prevention," or "prophylaxis" of a disease or disorder means preventing that a disorder occurs in a subject.

"Proliferation" refers to an increase in cell division, either symmetric or asymmetric division of cells.

"Promoter" refers to the minimal sequences required to initiate transcription. Promoter may also include enhancers or repressor elements which enhance or suppress transcription, respectively.

"Protein" or "polypeptide" are used interchangeably herein are refers to a molecule that comprises one or more polypeptides each comprised of at least two amino acid residues linked by a peptide bond. Protein may be a monomer, or may be protein complex of two or more subunits, the subunits being identical or distinct. Small polypeptides of less than 50 amino acids may be referred to as "peptides". Protein may be a heterologous fusion protein, a glycoprotein, or a protein modified by post-translational modifications such as phosphorylation, acetylation, myristoylation, palmitoylation, glycosylation, oxidation, formylation, amidation, citrullination, polyglutamylation, ADP-ribosylation, pegylation or biotinylation. Protein may be recombinantly expressed.

"Recombinant" refers to polynucleotides, polypeptides, vectors, viruses and other macromolecules that are prepared, expressed, created or isolated by recombinant means.

"Regulatory element" refers to any cis-or trans acting genetic element that controls some aspect of the expression of nucleic acid sequences.

"Relapsed" refers to the return of a disease or the signs and symptoms of a disease after a period of improvement after prior treatment with a therapeutic.

"Refractory" refers to a disease that does not respond to a treatment. A refractory disease can be resistant to a treatment before or at the beginning of the treatment, or a refractory disease can become resistant during a treatment.

"Single chain Fv" or "scFv" refers to a fusion protein comprising at least one antibody fragment comprising a light chain variable region (VL) and at least one antibody fragment comprising a heavy chain variable region (VH), wherein the VL and the VH are contiguously linked via a polypeptide linker, and capable of being expressed as a single chain polypeptide. Unless specified, as used herein, a scFv may have the VL and VH variable regions in either order, e.g., with respect to the N- terminal and C-terminal ends of the polypeptide, the scFv may comprise VL-linker-VH or may comprise VH-linker-VL.

"$(scFv)_2$" or "tandem scFv" or "bis-scFv" fragments refers to a fusion protein comprising two light chain variable region (VL) and two heavy chain variable region (VH), wherein the two VL and the two VH regions are contiguously linked via polypeptide linkers, and capable of being expressed as a single chain polypeptide. The two VL and two VH regions fused by peptide linkers form a bivalent molecule VL_A-linker-VH_A-linker-VL_B-linker-VH_B to form two binding sites, capable of binding two different antigens or epitopes concurrently.

"Specifically binds," "specific binding," "specifically binding" or "binds" refer to a protein molecule binding to an antigen or an epitope within the antigen with greater affinity than for other antigens. Typically, the protein molecule binds to the antigen or the epitope within the antigen with an equilibrium dissociation constant (K_D) of about $1x10^{-7}$ M or less, for example about $5x10^{-8}$ M or less, about $1x10^{-8}$ M or less, about $1x10^{-9}$ M or less, about $1x10^{-10}$ M or less, about $1x10^{-11}$ M or less, or about $1x10^{-12}$ M or less, typically with the K_D that is at least one hundred fold less than its K_D for binding to a non-specific antigen (e.g., BSA, casein). In the context of the prostate neoantigens described here, "specific binding" refers to binding of the protein molecule to the prostate neoantigen without detectable binding to a wild-type protein the neoantigen is a variant of. As used herein, an antibody or antigen binding domain "with binding specificity for hK2" refers to an antibody or antigen binding domain that specifically binds to hK2, respectively.

"Subject" includes any human or nonhuman animal. "Nonhuman animal" includes all vertebrates, *e.g.*, mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats,

horses, cows, chickens, amphibians, reptiles, etc. The terms "subject" and "patient" can be used interchangeably herein.

"T cell" and "T lymphocyte" are interchangeable and used synonymously herein. T cell includes thymocytes, naïve T lymphocytes, memory T cells, immature T lymphocytes, mature T lymphocytes, resting T lymphocytes, or activated T lymphocytes. A T cell can be a T helper (Th) cell, for example a T helper 1 (Th1) or a T helper 2 (Th2) cell. The T cell can be a helper T cell (HTL; $CD4^+$ T cell) $CD4^+$ T cell, a cytotoxic T cell (CTL; $CD8^+$ T cell), a tumor infiltrating cytotoxic T cell (TIL; $CD8^+$ T cell), $CD4^+CD8^+$ T cell, or any other subset of T cells. Also included are "NKT cells", which refer to a specialized population of T cells that express a semi-invariant αβ T-cell receptor, but also express a variety of molecular markers that are typically associated with NK cells, such as NK1.1. NKT cells include $NK1.1^+$ and $NK1.1^-$, as well as $CD4^+$, $CD4^-$, $CD8^+$ and $CD8^-$ cells. The TCR on NKT cells is unique in that it recognizes glycolipid antigens presented by the MHC I-like molecule CD Id. NKT cells can have either protective or deleterious effects due to their abilities to produce cytokines that promote either inflammation or immune tolerance. Also included are "gamma-delta T cells (γδ T cells)," which refer to a specialized population that to a small subset of T cells possessing a distinct TCR on their surface, and unlike the majority of T cells in which the TCR is composed of two glycoprotein chains designated α- and β-TCR chains, the TCR in γδ T cells is made up of a γ-chain and a δ-chain . γδ T cells can play a role in immunosurveillance and immunoregulation and were found to be an important source of IL-17 and to induce robust $CD8^+$ cytotoxic T cell response. Also included are "regulatory T cells" or "Tregs" which refer to T cells that suppress an abnormal or excessive immune response and play a role in immune tolerance. Tregs are typically transcription factor Foxp3-positive $CD4^+$T cells and can also include transcription factor Foxp3-negative regulatory T cells that are IL-10-producing $CD4^+$T cells.

"Therapeutically effective amount" or "effective amount" used interchangeably herein, refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Example indicators of an effective therapeutic or combination of therapeutics that include, for example, improved well-

being of the patient, reduction of a tumor burden, arrested or slowed growth of a tumor, and/or absence of metastasis of cancer cells to other locations in the body.

"Transduction" refers to the introduction of a foreign nucleic acid into a cell using a viral vector.

"Treat," "treating" or "treatment" of a disease or disorder such as cancer refers to accomplishing one or more of the following: reducing the severity and/or duration of the disorder, inhibiting worsening of symptoms characteristic of the disorder being treated, limiting or preventing recurrence of the disorder in subjects that have previously had the disorder, or limiting or preventing recurrence of symptoms in subjects that were previously symptomatic for the disorder.

"Tumor cell" or a "cancer cell" refers to a cancerous, pre-cancerous or transformed cell, either *in vivo*, *ex vivo*, or in tissue culture, that has spontaneous or induced phenotypic changes. These changes do not necessarily involve the uptake of new genetic material. Although transformation may arise from infection with a transforming virus and incorporation of new genomic nucleic acid, uptake of exogenous nucleic acid or it can also arise spontaneously or following exposure to a carcinogen, thereby mutating an endogenous gene. Transformation/cancer is exemplified by morphological changes, immortalization of cells, aberrant growth control, foci formation, proliferation, malignancy, modulation of tumor specific marker levels, invasiveness, tumor growth in suitable animal hosts such as nude mice, and the like, *in vitro*, *in vivo*, and *ex vivo*.

"Variant," "mutant" or "altered" refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications, for example one or more substitutions, insertions or deletions.

The numbering of amino acid residues in the antibody constant region throughout the specification is according to the EU index as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991), unless otherwise explicitly stated.

Mutations in the Ig constant regions are referred to as follows: L351Y_F405A_Y407V refers to L351Y, F405A and Y407V mutations in one immunoglobulin constant region. L351Y_F405A_Y407V/T394W refers to L351Y, F405A and Y407V mutations in the first Ig

constant region and T394W mutation in the second Ig constant region, which are present in one multimeric protein.

"VHH" refers to a single-domain antibody or nanobody, exclusively composed of the antigen binding domain of a heavy chain. A VHH single domain antibody lacks the light chain and the CH1 domain of the heavy chain of conventional Fab region.

CHEMICAL NOMENCLATURE

Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium. Compounds comprising radioisotopes such as tritium, C^{14}, P^{32} and S^{35} are thus within the scope of the present technology. Procedures for inserting such labels into the compounds of the present technology will be readily apparent to those skilled in the art based on the disclosure herein.

The term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that all normal valencies are maintained and that the substitution results in a stable compound. When a particular group is "substituted," that group can have one or more substituents, preferably from one to five substituents, more preferably from one to three substituents, most preferably from one to two substituents, independently selected from the list of substituents. For example, "substituted" refers to an organic group as defined below (e.g., an alkyl group) in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Thus, a substituted group is substituted with one or more substituents, unless otherwise specified. In some embodiments, a substituted group is substituted with 1, 2, 3, 4, 5, or 6 substituents. Examples of substituent groups include: halogens (i.e., F, Cl, Br, and I); hydroxyls; alkoxy, alkenoxy, aryloxy, aralkyloxy, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, and heterocyclylalkoxy groups; carbonyls (oxo); carboxylates; esters; urethanes; oximes; hydroxylamines; alkoxyamines; aralkoxyamines; thiols; sulfides; sulfoxides; sulfones; sulfonyls; pentafluorosulfanyl (i.e., SFs), sulfonamides; amines; N-oxides; hydrazines; hydrazides; hydrazones; azides; amides; ureas; amidines; guanidines; enamines; imides; isocyanates; isothiocyanates; cyanates; thiocyanates; imines; nitro groups; nitriles (i.e., CN); and the like. The term "independently" when used in reference to substituents, means that when

more than one of such substituents is possible, such substituents can be the same or different from each other.

Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups also include rings and ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups may also be substituted with substituted or unsubstituted alkyl, alkenyl, and alkynyl groups as defined below.

As used herein, Cm-Cn, such as C_1-C_{11}, C_1-C_8, or C_1-C_6 when used before a group refers to that group containing m to n carbon atoms.

Alkyl groups include straight chain and branched chain alkyl groups having from 1 to 12 carbon atoms, and typically from 1 to 10 carbons or, in some embodiments, from 1 to 8, 1 to 6, or 1 to 4 carbon atoms. Examples of straight chain alkyl groups include groups such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, tert-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. Alkyl groups may be substituted or unsubstituted. Representative substituted alkyl groups may be substituted one or more times with substituents such as those listed above, and include without limitation haloalkyl (e.g., trifluoromethyl), hydroxyalkyl, thioalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, carboxyalkyl, and the like.

Cycloalkyl groups include mono-, bi- or tricyclic alkyl groups having from 3 to 12 carbon atoms in the ring(s), or, in some embodiments, 3 to 10, 3 to 8, or 3 to 4, 5, or 6 carbon atoms. Exemplary monocyclic cycloalkyl groups include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 3 to 6, or 3 to 7. Bi- and tricyclic ring systems include both bridged cycloalkyl groups and fused rings, such as, but not limited to, bicyclo[2.1.1]hexane, adamantyl, decalinyl, and the like. Cycloalkyl groups may be substituted or unsubstituted. Substituted cycloalkyl groups may be substituted one or more times with, non-hydrogen and non-carbon groups as defined above. However, substituted cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups may be mono-substituted or substituted more than once, such as,

but not limited to, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups, which may be substituted with substituents such as those listed above.

Cycloalkylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a cycloalkyl group as defined above. In some embodiments, cycloalkylalkyl groups have from 4 to 16 carbon atoms, 4 to 12 carbon atoms, and typically 4 to 10 carbon atoms. Cycloalkylalkyl groups may be substituted or unsubstituted. Substituted cycloalkylalkyl groups may be substituted at the alkyl, the cycloalkyl or both the alkyl and cycloalkyl portions of the group. Representative substituted cycloalkylalkyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

Alkenyl groups include straight and branched chain alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Alkenyl groups have from 2 to 12 carbon atoms, and typically from 2 to 10 carbons or, in some embodiments, from 2 to 8, 2 to 6, or 2 to 4 carbon atoms. In some embodiments, an alkenyl can have one carbon-carbon double bond, or multiple carbon-carbon double bonds, such as 2, 3, 4 or more carbon-carbon double bonds. Examples of alkenyl groups include, but are not limited to methenyl, ethenyl, propenyl, butenyl, etc. Alkenyl groups may be substituted or unsubstituted. Representative substituted alkenyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

Cycloalkenyl groups include cycloalkyl groups as defined above, having at least one double bond between two carbon atoms. Cycloalkenyl group can be a mono- or polycyclic alkyl group having from 3 to 12, more preferably from 3 to 8 carbon atoms in the ring(s) and comprising at least one double bond between two carbon atoms. Cycloalkenyl groups may be substituted or unsubstituted. In some embodiments the cycloalkenyl group may have one, two or three double bonds or multiple carbon-carbon double bonds, such as 2, 3, 4, or more carbon-carbon double bonds.but does not include aromatic compounds. Cycloalkenyl groups have from 3 to 14 carbon atoms, or, in some embodiments, 5 to 14 carbon atoms, 5 to 10 carbon atoms, or even 5, 6, 7, or 8 carbon atoms. Examples of cycloalkenyl groups include cyclohexenyl, cyclopentenyl, cyclohexadienyl, cyclobutadienyl, and cyclopentadienyl.

Cycloalkenylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkenyl group as defined above.

Cycloalkenylalkyl groups may be substituted or unsubstituted. Substituted cycloalkenylalkyl groups may be substituted at the alkyl, the cycloalkenyl or both the alkyl and cycloalkenyl portions of the group. Representative substituted cycloalkenylalkyl groups may be substituted one or more times with substituents such as those listed above.

Alkynyl groups include straight and branched chain alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. Alkynyl groups have from 2 to 12 carbon atoms, and typically from 2 to 10 carbons or, in some embodiments, from 2 to 8, 2 to 6, or 2 to 4 carbon atoms. In some embodiments, the alkynyl group has one, two, or three carbon-carbon triple bonds. Examples include, but are not limited to -C=CH, -C=CCH_3, -CH_2C=CCH_3, -C=$CCH_2CH(CH_2CH_3)_2$, among others. Alkynyl groups may be substituted or unsubstituted. A terminal alkyne has at least one hydrogen atom bonded to a triply bonded carbon atom. Representative substituted alkynyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or trisubstituted with substituents such as those listed above. A “cyclic alkyne” or “cycloalkynyl” is a cycloalkyl ring comprising at least one triple bond between two carbon atoms. Examples of cyclic alkynes or cycloalkynyl groups include, but are not limited to, cyclooctyne, bicyclononyne (BCN), difluorinated cyclooctyne (DIFO), dibenzocyclooctyne (DIBO), keto-DIBO, biarylazacyclooctynone (BARAC), dibenzoazacyclooctyne (DIBAC), dimethoxyazacyclooctyne (DIMAC), difluorobenzocyclooctyne (DIFBO), monobenzocyclooctyne (MOBO), and tetramethoxy DIBO (TMDIBO).

Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms. Aryl groups herein include monocyclic, bicyclic and tricyclic ring systems. Thus, aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, fluorenyl, phenanthrenyl, anthracenyl, indenyl, indanyl, pentalenyl, and naphthyl groups. In some embodiments, aryl groups contain 6-14 carbons, and in others from 6 to 12 or even 6-10 carbon atoms in the ring portions of the groups. In some embodiments, the aryl groups are phenyl or naphthyl. Aryl groups may be substituted or unsubstituted. The phrase "aryl groups" includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like). Representative substituted aryl groups may be monosubstituted or substituted more than once. For example, monosubstituted aryl groups include, but are not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or naphthyl groups, which may be substituted with substituents such as

those listed above. Aryl moieties are well known and described, for example, in Lewis, R. J., ed., *Hawley's Condensed Chemical Dictionary*, 13th Edition, John Wiley & Sons, Inc., New York (1997). An aryl group can be a single ring structure (i.e., monocyclic) or comprise multiple ring structures (i.e., polycyclic) that are fused ring structures. Preferably, an aryl group is a monocyclic aryl group.

Alkoxy groups are hydroxyl groups (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of a substituted or unsubstituted alkyl group as defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, and the like. Examples of branched alkoxy groups include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, isohexoxy, and the like. Examples of cycloalkoxy groups include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. Alkoxy groups may be substituted or unsubstituted. Representative substituted alkoxy groups may be substituted one or more times with substituents such as those listed above.

Similarly, alkylthio or thioalkoxy refers to an -SR group in which R is an alkyl attached to the parent molecule through a sulfur bridge, for example, -S-methyl, -S-ethyl, etc. Representative examples of alkylthio include, but are not limited to, $-SCH_3$, $-SCH_2CH_3$, etc.

The term "halogen" as used herein refers to bromine, chlorine, fluorine, or iodine. Correspondingly, the term “halo” means fluoro, chloro, bromo, or iodo. In some embodiments, the halogen is fluorine. In other embodiments, the halogen is chlorine or bromine.

The terms “hydroxy” and “hydroxyl” can be used interchangeably and refer to –OH.

The term “carboxy” refers to –COOH.

The term “cyano” refers to –CN.

The term “nitro” refers to $-NO_2$.

The term “isothiocyanate” refers to -N=C=S.

The term “isocyanate” refers to -N=C=O.

The term “azido” refers to $-N_3$.

The term “amino” refers to $–NH_2$. The term “alkylamino” refers to an amino group in which one or both of the hydrogen atoms attached to nitrogen is substituted with an alkyl group. An alkylamine group can be represented as $-NR_2$ in which each R is independently a hydrogen or alkyl group. For example, alkylamine includes methylamine ($-NHCH_3$), dimethylamine ($-N(CH_3)_2$), $-NHCH_2CH_3$, etc. The term “aminoalkyl” as used herein is intended to include both

branched and straight-chain saturated aliphatic hydrocarbon groups substituted with one or more amino groups. Representative examples of aminoalkyl groups include, but are not limited to, -CH_2NH_2, -$CH_2CH_2NH_2$, and –$CH_2CH(NH_2)CH_3$.

As used herein, "amide" refers to –$C(O)N(R)_2$, wherein each R is independently an alkyl group or a hydrogen. Examples of amides include, but are not limited to, -$C(O)NH_2$, -$C(O)NHCH_3$, and –$C(O)N(CH_3)_2$.

The terms "hydroxylalkyl" and "hydroxyalkyl" are used interchangeably, and refer to an alkyl group substituted with one or more hydroxyl groups. The alkyl can be a branched or straight-chain aliphatic hydrocarbon. Examples of hydroxylalkyl include, but are not limited to, hydroxylmethyl (-CH_2OH), hydroxylethyl (-CH_2CH2OH), etc.

As used herein, the term "heterocyclyl" includes stable monocyclic and polycyclic hydrocarbons that contain at least one heteroatom ring member, such as sulfur, oxygen, or nitrogen. As used herein, the term "heteroaryl" includes stable monocyclic and polycyclic aromatic hydrocarbons that contain at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl can be monocyclic or polycyclic, e.g., bicyclic or tricyclic. Each ring of a heterocyclyl or heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. Heteroaryl groups which are polycyclic, e.g., bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings can be aromatic or non-aromatic. The heterocyclyl or heteroaryl group can be attached at any available nitrogen or carbon atom of any ring of the heterocyclyl or heteroaryl group. Preferably, the term "heteroaryl" refers to 5- or 6-membered monocyclic groups and 9- or 10-membered bicyclic groups which have at least one heteroatom (O, S, or N) in at least one of the rings, wherein the heteroatom-containing ring preferably has 1, 2, or 3 heteroatoms, more preferably 1 or 2 heteroatoms, selected from O, S, and/or N. The nitrogen heteroatom(s) of a heteroaryl can be substituted or unsubstituted. Additionally, the nitrogen and sulfur heteroatom(s) of a heteroaryl can optionally be oxidized (i.e., N→O and $S(O)_r$, wherein r is 0, 1 or 2).

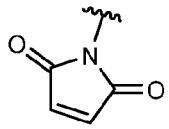
The term "ester" refers to -$C(O)_2R$, wherein R is alkyl.

The term "carbamate" refers to -$OC(O)NR_2$, wherein each R is independently alkyl or hydrogen.

The term "aldehyde" refers to -C(O)H.

The term "carbonate" refers to -OC(O)OR, wherein R is alkyl.

The term "maleimide" refers to a group with the chemical formula $H_2C_2(CO)_2NH$. The term "maleimido" refers to a maleimide group covalently linked to another group or molecule. Preferably, a maleimido group is N-linked, for example:



The term "acyl halide" refers to -C(O)X, wherein X is halo (e.g., Br, Cl). Exemplary acyl halides include acyl chloride (-C(O)Cl) and acyl bromide (-C(O)Br).

In accordance with convention used in the art:



is used in structural formulas herein to depict the bond that is the point of attachment of the moiety, functional group, or substituent to the core, parent, or backbone structure, such as an antigen binding domain of the present invention.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R groups, then said group can be optionally substituted with up to three R groups, and at each occurrence, R is selected independently from the definition of R.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent can be bonded to any atom on the ring.

As used herein, the term "radiometal ion" or "radioactive metal ion" or "radioisotope" or "radiometal" refers to one or more isotopes of the elements that emit particles and/or photons. Any radiometal ion known to those skilled in the art in view of the present disclosure can be used in the invention. Non-limiting examples of radioisotopes that may be used for therapeutic applications in accordance with the present invention include, e.g., beta or alpha emitters, such as, e.g., ^{225}Ac, ^{177}Lu, ^{32}P, ^{47}Sc, ^{67}Cu, ^{77}As, ^{89}Sr, ^{90}Y, ^{99}Tc, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{131}I, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{255}Fm and ^{227}Th. Other non-limiting examples of radioisotopes that may be used as imaging agents in accordance with the present invention include gamma-emitting radioisotopes,

such as, e.g., ^{177}Lu, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, and ^{111}In. In certain embodiments, the radiometal ion is a "therapeutic emitter," meaning a radiometal ion that is useful as a therapeutic agent, e.g., as a cytotoxic agent that is capable of reducing or inhibiting the growth of, or in particular killing, a cancer cell, such as a prostate cancer cell. Examples of therapeutic emitters include, but are not limited to, beta or alpha emitters, such as, ^{132}La, ^{135}La, ^{134}Ce, ^{144}Nd, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{177}Lu, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{225}Ac, ^{255}Fm and ^{227}Th, ^{226}Th, ^{230}U. Preferably, a radiometal ion used in the invention is an alpha-emitting radiometal ion, such as actinium-225 (^{225}Ac).

A "radiometal complex" as used herein refers to a complex comprising a radiometal ion associated with a chelator that is a macrocyclic compound. Typically, a radiometal ion is bound to or coordinated to a macrocyclic compound via coordinate bonding. Heteroatoms of the macrocyclic ring can participate in coordinate bonding of a radiometal ion to a macrocycle compound. A macrocycle compound can be substituted with one or more substituent groups, and the one or more substituent groups can also participate in coordinate bonding of a radiometal ion to a macrocycle compound in addition to, or alternatively to the heteroatoms of the macrocyclic ring.

Immunoconjugates

Embodiments of the present invention relate to compositions and methods for targeting hK2 with a short half-life Fab-based radioconjugate to achieve efficacious tumor cell death in prostate cancer patients; preferably, such radioconjugates comprise a Fab (instead of a full-length antibody) and demonstrate an improved safety profile (e.g., as measured by bone marrow toxicity) compared to full-length antibody-based radioconjugates. Embodiments of the Fab-based radioconjugates of the present invention target hK2-expressing prostate cancer cells and demonstrate a short half-life.

As used herein, an "immunoconjugate" refers to an antibody, or an antigen binding domain, that is conjugated (joined, e.g., bound via a covalent bond) to a second molecule, such as a toxin, drug, radiometal ion, chelator, radiometal complex, etc. A "radioimmunoconjugate" (also referred to herein as a "radioconjugate") in particular is an immunoconjugate in which an antibody or antigen binding domain is labeled with a radiometal or conjugated to a radiometal complex.

According to embodiments of the present invention, an immunoconjugate comprises a therapeutic moiety conjugated to an antigen binding domain of the present invention that has binding specificity for hK2. As used herein, a "therapeutic moiety" that forms part of an immunoconjugate may be useful in therapeutic applications and/or imaging applications, i.e., as a therapeutic agent (e.g., a cytotoxic agent) and/or an imaging agent, respectively. For example, therapeutic moieties of the present invention may comprise radiometals. It is noted that certain radiometals may be used as therapeutic agents (e.g., ^{225}Ac) and/or as imaging agents (e.g., ^{111}In). A suitable therapeutic agent is one that is capable of reducing or inhibiting the growth of, or in particular killing, a cancer cell, such as a prostate cancer cell. In certain embodiments, radioconjugates comprising a radioisotope conjugated to an antigen binding domain can deliver a cytotoxic payload with the ability to emit alpha and/or beta particles in the vicinity of a tumor by binding onto cancer cells' surface antigens and initiating cell death.

According to preferred embodiments, the present invention relates to short half-life immunoconjugates (e.g. short half-life radioimmunococonjugates). As used herein, a "short half-life immunoconjugate" refers to an immunoconjugate comprising an antigen binding domain (e.g., a Fab), wherein the immunoconjugate has an *in vivo* half-life that is shorter than the *in vivo* half-life of a comparator immunoconjugate, wherein the comparator immunoconjugate is identical to the short half-life immunoconjugate except the antigen binding domain of the comparator immunoconjugate is replaced with a full-length antibody comprising the antigen binding domain (e.g., a full-length IgG comprising an Fc region and the antigen binding domain). In certain embodiments, a short half-life immunoconjugate of the present invention has a half-life of 36 hours or less, or 24 hours or less, or 12 hours or less, or 6 hours or less, or 3 hours or less. For example, a short half-life immunoconjugate of the present invention may have a half-life from about 1 hour to about 36 hours, or from about 1 hour to about 24 hours, or from about 1 hour to about 12 hours, or from about 1 hour to about 6 hours, or from about 1 hour to about 3 hours, or from about 2 hours to about 3 hours.

Actinium-225 (^{225}Ac) is an alpha-emitting radioisotope that is of particular interest for medical applications. Another radioisotope of interest for medical applications is Lutetium-177 (^{177}Lu), which emits both gamma-irradiation suitable for imaging and medium-energy beta-irradiation suitable for radiotherapy. Non-limiting examples of radioisotopes that may be used for therapeutic applications in accordance with the present invention include, e.g., beta or alpha

emitters, such as, e.g., ^{225}Ac, ^{177}Lu, ^{32}P, ^{47}Sc, ^{67}Cu, ^{77}As, ^{89}Sr, ^{90}Y, ^{99}Tc, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{131}I, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{255}Fm and ^{227}Th. Other non-limiting examples of radioisotopes that may be used as imaging agents in accordance with the present invention include gamma-emitting radioisotopes, such as, e.g., ^{177}Lu, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, and ^{111}In.

In certain embodiments, the therapeutic moiety is a cytotoxic agent that is an auristatin derivative, such as MMAE (monomethyl auristatin E) or MMAF (monomethyl auristatin F). For example, the auristatin derivative may be attached to the antibody or antigen binding domain of the invention through the N (amino) terminus or the C (carboxyl) terminus of the peptidic drug moiety (WO02/088172), or via any cysteine engineered into the antibody or antigen binding domain.

Anti-hK2 Antibodies and Antigen Binding Domains

As described herein, embodiments of the present invention relate to an immunoconjugate comprising a therapeutic moiety conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2). According to certain embodiments, the antigen binding domain is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb or a VHH. According to a preferred embodiment, the antigen binding domain with binding specificity for hK2 is a Fab.

According to certain embodiments, the antigen binding domain that binds hK2 (e.g., a Fab) comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively.

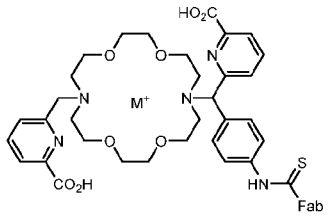
According to certain embodiments, the antigen binding domain that binds hK2 (e.g., a Fab) comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163. For example, the antigen binding domain that binds hK2 (e.g., a Fab) comprises a VH which is at least 95% identical to the VH of SEQ ID NO: 162 and a VL which is at least 95% identical to the VL of SEQ ID NO: 163. According to certain embodiments, the antigen binding domain that binds hK2 (e.g., a Fab) comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.

According to certain embodiments, the antigen binding domain is a "KL2B30 Fab," also referred to as "Fab of KL2B30," which is a Fab that comprises (a) a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or (b) a VH which is at least 95% identical, or 100% identical, to SEQ ID NO: 162 and a VL which is at least 95% identical, or 100% identical, to SEQ ID NO: 163.

Non-limiting examples of KL2B30 Fabs include KL2B997 and KL2B1251, which are described in the example section below. The heavy chain and light chain sequences of KL2B997 and KL2B1251 are provided in FIG. 2. KL2B997 has a His-tag and a sortase tag (underlined in FIG. 2) on the heavy chain, and KL2B1251 is tagless.

In some embodiments, an immunoconjugate of the present invention comprises an antigen binding domain that comprises VL, VH or CDRs having amino acid sequences of certain antibodies described below, selected from the group consisting of m11B6, hu11B6, HCF3-LCD6, HCG5-LCB7, KL2B357, KL2B358, KL2B359, KL2B360, KL2B413, KL2B30, KL2B53, KL2B242, KL2B467 and KL2B494. The foregoing antibodies and antigen binding domains, and methods of making them, are described in PCT/IB2020/056972, which is incorporated by reference herein.

An embodiment of the present invention provides a radioimmunoconjugate having the following structure (which does not show the lysine residue of the Fab that is linked to the phenylthiourea moiety):

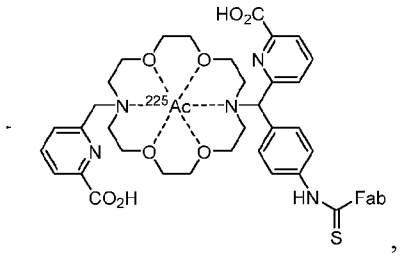


(also referred to as TOPA-[C7]-phenylthiourea-Fab),

wherein M^+ is a radioisotope, such as actinium-225(^{225}Ac), and

wherein the Fab has binding specificity for hK2, such as a KL2B30 Fab (e.g., KL2B997 or KL2B1251). The Fab preferably comprises (a) a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or (b) a VH which is at least 95% identical, or 100% identical, to SEQ ID NO: 162 and a VL which is at least 95% identical, or 100% identical, to SEQ ID NO: 163.

An embodiment of the present invention provides a radioimmunoconjugate having the following structure (which does not show the lysine residue of the Fab that is linked to the phenylthiourea moiety):



,

wherein the Fab has binding specificity for hK2, such as a KL2B30 Fab (e.g., KL2B997 or KL2B1251). The Fab preferably comprises (a) a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or (b) a VH which is at least 95% identical, or 100% identical, to SEQ ID NO: 162 and a VL which is at least 95% identical, or 100% identical, to SEQ ID NO: 163.

Specific Enumerated Embodiments

Exemplary enumerated embodiments of the present invention are provided below.

1. An immunoconjugate comprising: a therapeutic moiety conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).
2. The immunoconjugate of embodiment 1, wherein the therapeutic moiety is a cytotoxic agent.
3. The immunoconjugate of embodiment 1, wherein the therapeutic moiety is an imaging agent.
4. The immunoconjugate of any of embodiments 1-3, wherein the therapeutic moiety comprises a radiometal.
5. The immunoconjugate of embodiment 4, wherein the radiometal is selected from the group consisting of ^{225}Ac, ^{177}Lu, ^{32}P, ^{47}Sc, ^{67}Cu, ^{77}As, ^{89}Sr, ^{90}Y, ^{99}Tc, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{131}I, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{255}Fm, ^{227}Th, ^{177}Lu, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, and ^{111}In.
6. The immunoconjugate of embodiment 1, wherein the therapeutic moiety is a cytotoxic agent comprising ^{225}Ac.
7. The immunoconjugate of embodiment 1, wherein the therapeutic moiety is an imaging agent comprising ^{111}In or ^{64}Cu.

8. The immunoconjugate according to any of embodiments 4-7, wherein the therapeutic moiety comprises a radiometal complex, wherein the radiometal complex comprises the radiometal bound to a chelator, and wherein the chelator is conjugated to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).
9. The immunoconjugate according to embodiment 8, wherein the chelator is 1,4,7,10-tetraazacyclododecane-1,4,7,10,tetraacetic acid (DOTA), S-2-(4-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), 1,4,8,11-tetraazacyclodocedan-1,4,8,11-tetraacetic acid (TETA), 3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-4-(S)-(4-isothiocyanatobenzyl)-3,6,9-triacetic acid (PCTA), 5-S-(4-aminobenzyl)-1-oxa-4,7,10-triazacyclododecane-4,7,10-tris(acetic acid) (DO3A), or a derivative thereof.
10. The immunoconjugate according to embodiment 8, wherein the chelator is DOTA or NOTA or a derivative thereof.
11. The immunoconjugate according to embodiment 8, wherein the chelator is H_2bp18c6 or a H_2bp18c6 derivative.
12. The immunoconjugate according to embodiment 8, wherein the radiometal complex is a radiocomplex of Formula (I-m), or Formula (II-m), or Formula (III-m) as described herein, wherein R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2) and M is the radiometal.
13. The immunoconjugate according to embodiment 8, wherein the radiometal complex is a radiometal complex of Formula (IV-m), or Formula (V-m), or Formula (VI-m) as described herein, wherein R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2) and M+ is the radiometal.
14. The immunoconjugate of embodiment 1, wherein the therapeutic moiety is an auristatin derivative.
15. The immunoconjugate of embodiment 14, wherein the therapeutic moiety is MMAE (monomethyl auristatin E).
16. The immunoconjugate of embodiment 14, wherein the therapeutic moiety is MMAF (monomethyl auristatin F).
17. The immunoconjugate according to any of embodiments 1-16 or 51-56, wherein the antigen binding domain that binds hK2 is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb or a VHH.

18. The immunoconjugate according to any of embodiments 1-16 or 51-56, wherein the antigen binding domain with binding specificity for hK2 is a Fab.
19. The immunoconjugate according to any of embodiments 1-18 or 51-56, wherein the antigen binding domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NO: 170 (SYYWS), SEQ ID NO: 171 (YIYYSGSTNYNPSLKS), SEQ ID NO: 172 (TTIFGVVTPNFYYGMDV), SEQ ID NO: 173 (RASQGISSYLA), SEQ ID NO: 174 (AASTLQS) and SEQ ID NO: 175 (QQLNSYPLT), respectively.
20. The immunoconjugate according to any of embodiments 1-19 or 51-56, wherein the antigen binding domain that binds hK2 comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 (QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGTTVTVSS), and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163 (DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK).
21. The immunoconjugate according to any of embodiments 1-19 or 51-56, wherein the antigen binding domain that binds hK2 comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.
22. The immunoconjugate according to any of embodiments 1-18 or 51-56, wherein the antigen binding domain is a Fab that comprises:
    a. a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or
    b. a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.
23. The immunoconjugate according to any of embodiments 1-22 or 51-56, wherein the immunoconjugate is a short half-life immunoconjugate.
24. A method of treating an hK2-expressing cancer in a subject, comprising administering to the subject a therapeutically effective amount of the immunoconjugate according to any of embodiments 1-23 or 51-56.

25. A method of reducing the amount of hK2-expressing tumor cells in a subject, comprising administering to the subject a therapeutically effective amount of the immunoconjugate according to any of embodiments 1-23 or 51-56.
26. A method of treating prostate cancer in a subject, comprising administering to the subject a therapeutically effective amount of the immunoconjugate according to any of embodiments 1-23 or 51-56.
27. The method of embodiment 26, wherein the prostate cancer is relapsed, refractory, malignant or castration resistant prostate cancer, or any combination thereof.
28. The method of embodiment 26, wherein the prostate cancer is metastatic castration-resistant prostate cancer.
29. A method of detecting the presence of prostate cancer in a subject, comprising administering the immunoconjugate according to any of embodiments 1-23 or 51-56 to a subject suspected to have prostate cancer and visualizing the biological structures to which the conjugate is bound (e.g., by computerized tomography or positron emission tomography), thereby detecting the presence of prostate cancer, wherein the immunoconjugate preferably comprises an imaging agent, such as 111-In or 64-Cu.
30. A method of making an immunoconjugate according to any of embodiments 1-23 or 51-56 comprising: conjugating the therapeutic moiety to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).
31. A method of making a radioimmunoconjugate comprising binding a radiometal to a chelator that is conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).
32. The method of embodiment 31, wherein the chelator is DOTA or NOTA or a derivative thereof.
33. The method of embodiment 31, wherein the chelator is H_2bp18c6 or a H_2bp18c6 derivative.
34. The method of embodiment 31, wherein the chelator is selected from the group consisting of chelators of Formula (I), Formula (II) and Formula (III) as described herein, wherein R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).
35. The method of embodiment 31, wherein the chelator is selected from the group consisting of chelators of Formula (IV), Formula (V) and Formula (VI) as described herein, wherein R_4

comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

36. The method according to any of embodiments 31-35, wherein the antigen binding domain that binds hK2 is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb or a VHH.

37. The method according to any of embodiments 31-35, wherein the antigen binding domain that binds hK2 is a Fab.

38. The method according to any of embodiments 31-37, wherein the antigen binding domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively.

39. The method according to any of embodiments 31-38, wherein the antigen binding domain that binds hK2 comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163.

40. The method according to any of embodiments 31-38, wherein the antigen binding domain that binds hK2 comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.

41. The method according to any of embodiments 31-37, wherein the antigen binding domain is a Fab that comprises:

a. a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or

b. a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

42. A short half-life radioimmunoconjugate comprising a radiometal complex, wherein the radiometal complex comprises ^{225}Ac bound to a chelator, and wherein the chelator is conjugated to a Fab with binding specificity for hK2, said Fab comprising: a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively.

43. The short half-life radioimmunoconjugate of embodiment 42, said Fab comprising a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

44. The short half-life radioimmunoconjugate of embodiment 42 or embodiment 43, wherein the chelator is DOTA or NOTA or a derivative thereof.

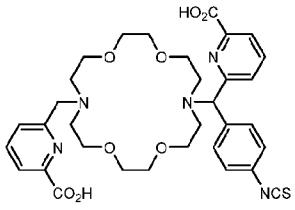
45. The short half-life radioimmunoconjugate of embodiment 42 or embodiment 43, wherein the chelator is H_2bp18c6 or a H_2bp18c6 derivative.

46. The short half-life radioimmunoconjugate of embodiment 42 or embodiment 43, wherein the radiometal complex is selected from the group consisting of chelators of Formula (I-m), Formula (II-m) and Formula (III-m) as described herein, wherein R_{11} comprises the Fab with binding specificity for hK2.

47. The short half-life radioimmunoconjugate of embodiment 42 or embodiment 43, wherein the radiometal complex is selected from the group consisting of chelators of Formula (IV-m), Formula (V-m) and Formula (VI-m) as described herein, wherein R_4 comprises the Fab with binding specificity for hK2.

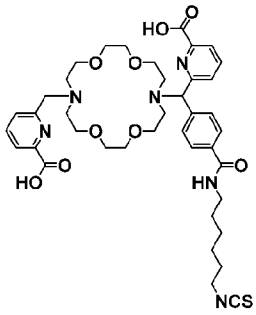
48. The method according to any of embodiments 31-37 further comprising conjugating the chelator to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2) prior to binding the radiometal to the chelator.

49. The method according to embodiment 48, wherein the chelator has the structure of



prior to conjugating the chelator to the antigen binding domain.

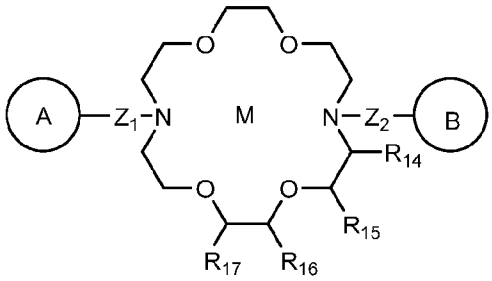
50. The method according to embodiment 48, wherein the chelator has the structure of



prior to conjugating the chelator to the antigen binding domain.

51. The immunoconjugate according to embodiment 8, wherein the radiometal complex is a radiometal complex of Formula (I-m),

wherein the radiometal complex of Formula (I-m) has the following structure:



(I-m)

wherein:

M is the radiometal, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

each of ring A and ring B is independently a 6-10 membered aryl or a 5-10 membered heteroaryl, wherein each of ring A and ring B is optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, -OR_{13}, -SR_{13}, , -$(CH_2)_pCOOR_{13}$, -$OC(O)R_{13}$, -$N(R_{13})_2$, -$CON(R_{13})_2$, -NO_2, -CN -$OC(O)N(R_{13})_2$, and X;

each of Z_1 and Z_2 is independently –$(C(R_{12})_2)_m$- or –$(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$-;

each X is independently -L_1-R_{11};

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

each R_{13} is independently hydrogen or alkyl;

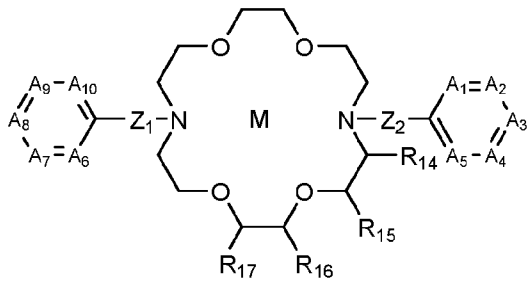
each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X; provided that the radiometal complex comprises at least one X, and

when X is present on ring A or ring B, L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen.

52. The immunoconjugate according to embodiment 8, wherein the radiometal complex is a radiometal complex of Formula (II-m),

wherein the radiometal complex of Formula (II-m) has the following structure:



(II-m)

wherein:

M is the radiometal, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

A_1 is N or CR_1 or is absent;

A_2 is N or CR_2;

A_3 is N or CR_3;

A_4 is N or CR_4;

A_5 is N or CR_5;

A_6 is N or CR_6 or is absent;

A_7 is N or CR_7;

A_8 is N or CR_8;

A_9 is N or CR_9;

A_{10} is N or CR_{10};

provided that no more than three of A_1, A_2, A_3, A_4, and A_5 are N, and no more than three of A_6, A_7, A_8, A_9, and A_{10} are N;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl,

heterocyclyl, heteroaryl, -OR_{13}, -SR_{13}, -$(CH_2)_pCOOR_{13}$, -$OC(O)R_{13}$, -$N(R_{13})_2$, -$CON(R_{13})_2$, -NO_2, -CN -$OC(O)N(R_{13})_2$, and -X,

or, alternatively, any two directly adjacent R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are taken together with the atoms to which they are attached to form a five or six-membered substituted or unsubstituted carbocyclic or nitrogen-containing ring;

each of Z_1 and Z_2 is independently $–(C(R_{12})_2)_m-$ or $–(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;

each X is independently -L_1-R_{11};

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

each R_{13} is independently hydrogen or alkyl;

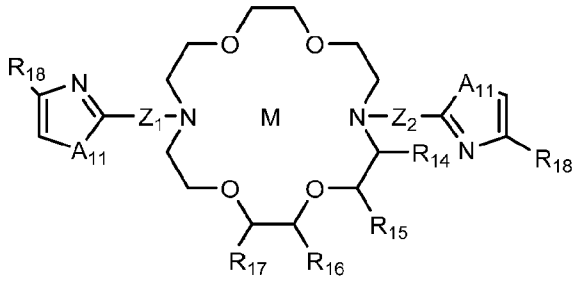
each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X;

provided that the radiometal complex comprises at least one X, and when any one of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is X, then L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen.

53. The immunoconjugate according to embodiment 8, wherein the radiometal complex is a radiometal complex of Formula (III-m),

wherein the radiometal complex of Formula (III-m) has the following structure:



(III-m)

wherein:

M is the radiometal, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

each A_{11} is independently O, S, NMe, or NH;

each of Z_1 and Z_2 is independently $-(C(R_{12})_2)_m-$ or $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;

each X is independently $-L_1-R_{11}$;

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

each R_{13} is independently hydrogen or alkyl;

each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

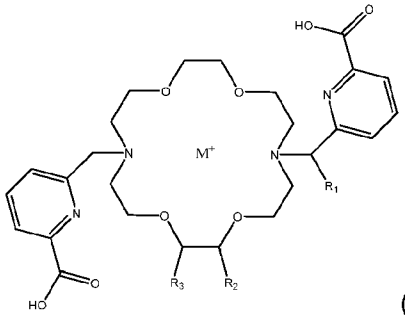
or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X; and

each R_{18} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, , $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN $-OC(O)N(R_{13})_2$, and -X,

provided that the radiometal complex comprises at least one X, and when R_{18} is X, then L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen.

54. The immunoconjugate according to embodiment 8, wherein the radiometal complex is a radiometal complex of Formula (IV-m),

wherein the radiometal complex of Formula (IV-m) has the following structure:



(IV-m)

or a pharmaceutically acceptable salt thereof, wherein:

M^+ is the radiometal, preferably selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

R_1 is hydrogen and R_2 is $-L_1-R_4$;

alternatively, R_1 is $-L_1-R_4$ and R_2 is hydrogen;

R_3 is hydrogen;

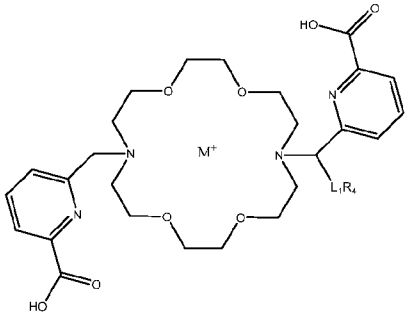
alternatively, R_2 and R_3 are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl, wherein the 5- or 6-membered cycloalkyl is optionally substituted with $-L_1-R_4$;

L_1 is absent or a linker;

R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

55. The immunoconjugate according to embodiment 8, wherein the radiometal complex is a radiometal complex of Formula (V-m),

wherein the radiometal complex of Formula (V-m) has the following structure:



(V-m)

or a pharmaceutically acceptable salt thereof, wherein:

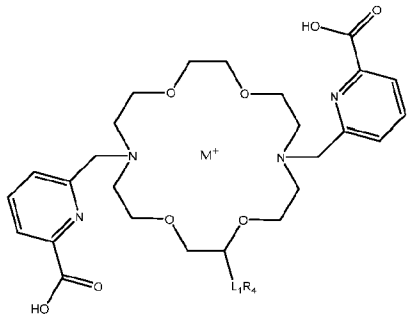
M^+ is the radiometal, preferably selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 (^{226}Th^{4+}), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

L_1 is absent or a linker;

R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

56. The immunoconjugate according to embodiment 8, wherein the radiometal complex is a radiometal complex of Formula (VI-m),

wherein the radiometal complex of Formula (VI-m) has the following structure:



(VI-m)

or a pharmaceutically acceptable salt thereof, wherein:

M^+ is the radiometal, preferably selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or

^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

L_1 is absent or a linker; and

R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

57. An immunoconjugate comprising: a therapeutic moiety conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2), wherein the antigen binding domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NO: 170 (SYYWS), SEQ ID NO: 171 (YIYYSGSTNYNPSLKS), SEQ ID NO: 172 (TTIFGVVTPNFYYGMDV), SEQ ID NO: 173 (RASQGISSYLA), SEQ ID NO: 174 (AASTLQS) and SEQ ID NO: 175 (QQLNSYPLT), respectively.

58. The immunoconjugate of embodiment 57, wherein the antigen binding domain that binds hK2 comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 (QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGTTVTVSS), and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163 (DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK).

59. The immunoconjugate according to embodiment 57, wherein the antigen binding domain that binds hK2 comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.

60. The immunoconjugate according to any of embodiments 57-59, wherein the therapeutic moiety is a cytotoxic agent.

61. The immunoconjugate according to any of embodiments 57-59, wherein the therapeutic moiety is an imaging agent.

62. The immunoconjugate according to any of embodiments 57-59, wherein the therapeutic moiety comprises a radiometal.

63. The immunoconjugate of embodiment 62, wherein the radiometal is selected from the group consisting of ^{225}Ac, ^{177}Lu,^{32}P, ^{47}Sc, ^{67}Cu, ^{77}As, ^{89}Sr, ^{90}Y, ^{99}Tc, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{131}I, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{255}Fm, ^{227}Th, ^{177}Lu, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, and ^{111}In.

64. The immunoconjugate according to any of embodiments 57-59, wherein the therapeutic moiety is a cytotoxic agent comprising ^{225}Ac.

65. The immunoconjugate according to any of embodiments 57-59, wherein the therapeutic moiety is an imaging agent comprising ^{111}In or ^{64}Cu.

66. The immunoconjugate according to any of embodiments 62-65, wherein the therapeutic moiety comprises a radiometal complex, wherein the radiometal complex comprises the radiometal bound to a chelator, and wherein the chelator is conjugated to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

67. The immunoconjugate according to embodiment 66, wherein the chelator is 1,4,7,10-tetraazacyclododecane-1,4,7,10,tetraacetic acid (DOTA), S-2-(4-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), 1,4,8,11-tetraazacyclodocedan-1,4,8,11-tetraacetic acid (TETA), 3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-4-(S)-(4-isothiocyanatobenzyl)-3,6,9-triacetic acid (PCTA), 5-S-(4-aminobenzyl)-1-oxa-4,7,10-triazacyclododecane-4,7,10-tris(acetic acid) (DO3A), or a derivative thereof.

68. The immunoconjugate according to embodiment 66, wherein the chelator is DOTA or NOTA or a derivative thereof.

69. The immunoconjugate according to embodiment 66, wherein the chelator is H_2bp18c6 or a H_2bp18c6 derivative.

70. The immunoconjugate according to embodiment 66, wherein the radiometal complex is a radiocomplex of Formula (I-m), or Formula (II-m), or Formula (III-m) as described herein, wherein R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2) and M is the radiometal.

71. The immunoconjugate according to embodiment 66, wherein the radiometal complex is a radiometal complex of Formula (IV-m), or Formula (V-m), or Formula (VI-m) as described herein, wherein R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2) and M+ is the radiometal.

72. The immunoconjugate according to any of embodiments 57-71, wherein the antigen binding domain with binding specificity for hK2 is a Fab.

Chelators

According to particular embodiments, the present invention relates to immunoconjugates, such as radioimmunoconjugates, comprising a chelator, preferably a chelator to which radiometals can be chelated via coordinate bonding. According to particular embodiments, chelators of the invention refer to a chelator to which a metal, preferably a radiometal, can be complexed to form a radiometal complex. Preferably, the chelator is a macrocyclic compound. In certain embodiments, a chelator comprises a macrocycle or a macrocyclic ring containing one or more heteroatoms, e.g., oxygen and/or nitrogen as ring atoms.

According to particular embodiments, the chelator comprises a macrocyclic chelating moiety. Examples of macrocyclic chelating moieties include, without limitation, 1,4,7,10-tetraazacyclododecane-1,4,7,10,tetraacetic acid (DOTA), S-2-(4-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), 1,4,8,11-tetraazacyclodocedan-1,4,8,11-tetraacetic acid (TETA), 3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-4-(S)-(4-isothiocyanatobenzyl)-3,6,9-triacetic acid (PCTA), 5-S-(4-aminobenzyl)-1-oxa-4,7,10-triazacyclododecane-4,7,10-tris(acetic acid) (DO3A), or a derivative thereof. In some aspects, the chelator is 1,4,7,10-tetraazacyclododecane-1,4,7,10,tetraacetic acid (DOTA). In other aspects, the chelator is S-2-(4-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA). In further aspects, the chelator is 1,4,8,11-tetraazacyclodocedan-1,4,8,11-tetraacetic acid (TETA). In yet other aspects, the chelator is 3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-4-(S)-(4-isothiocyanatobenzyl)-3,6,9-triacetic acid (PCTA). In still further aspects, the chelator is 5-S-(4-aminobenzyl)-1-oxa-4,7,10- triazacyclododecane-4,7,10-tris(acetic acid) (DO3A). In other aspects, the chelator is DOTA, DFO, DTPA, NOTA, or TETA.

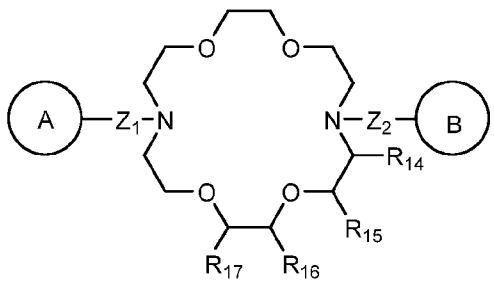
In certain embodiments the chelator comprises NOTA or a derivative thereof.

In certain embodiments, the chelator comprises a macrocycle that is a derivative of 4,13-diaza-18-crown-6. 4,13-Diaza-18-crown-6 may be prepared in a variety of ways (*See, e.g.*, Gatto et al., *Org. Synth.* 1990, 68, 227; DOI: 10.15227/orgsyn.068.0227). According to further embodiments of the present invention, the chelator is H_2bp18c6 or a H_2bp18c6 derivative, such

as those described in WO2020/229974. H_2bp18c6 refers to N,N'-bis[(6-carboxy-2-pyridil)methyl]-4,13-diaza-18-crown-6, as described herein. H_2bp18c6 and H_2bp18c6 derivatives are also described, for example, in Thiele et al. "An Eighteen-Membered Macrocyclic Ligand for Actinium-225 Targeted Alpha Therapy" *Angew. Chem. Int. Ed.* (2017) 56, 14712-14717, and Roca-Sabio et al. "Macrocyclic Receptor Exhibiting Unprecedented Selectivity for Light Lanthanides" *J. Am. Chem. Soc.* (2009) 131, 3331-3341, which are incorporated by reference herein. Additional chelators suitable for use in accordance with the present invention are described in WO2018/183906 and WO2020/106886, which are incorporated by reference herein. As used herein, the term "TOPA" refers to the macrocycle known in the art as H_2bp18c6 and may alternatively be referred to as N,N'-bis[(6-carboxy-2-pyridil)methyl]-4,13-diaza-18-crown-6 (*see, e.g.,* Roca-Sabio et al.).

CHELATORS OF FORMULAE (I), (II) and (III)

Additional chelators suitable for use in accordance with the present invention are described in WO2020/229974, which is incorporated by reference herein. According to particular embodiments, *e.g.,* as described in WO2020/229974, the chelator has the structure of Formula (I):



(I)

wherein:

each of ring A and ring B is independently a 6-10 membered aryl or a 5-10 membered heteroaryl, wherein each of ring A and ring B is optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, , $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN $-OC(O)N(R_{13})_2$, and X;

each of Z_1 and Z_2 is independently $-(C(R_{12})_2)_m-$ or $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;

each X is independently -L_1-R_{11};

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} is a nucleophilic moiety or an electrophilic moiety, or R_{11} comprises an antigen binding domain;

each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

each R_{13} is independently hydrogen or alkyl;

each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X;

provided that the chelator comprises at least one X, and when X is present on ring A or ring B, L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen.

According to embodiments of the invention, a chelator comprises at least one X group, wherein X is -L_1-R_{11}, wherein L_1 is absent or a linker, and R_{11} is an electrophilic moiety or a nucleophilic moiety, or R_{11} comprises an antigen binding domain. When R_{11} is a nucleophilic or electrophilic moiety, such moiety can be used for attachment of the chelator to an antigen binding domain, directly or indirectly via a linker. According to preferred embodiments, R_{11} comprises an antibody or antigen binding domain with binding specificity for hK2, such as the Fab of KL2B30.

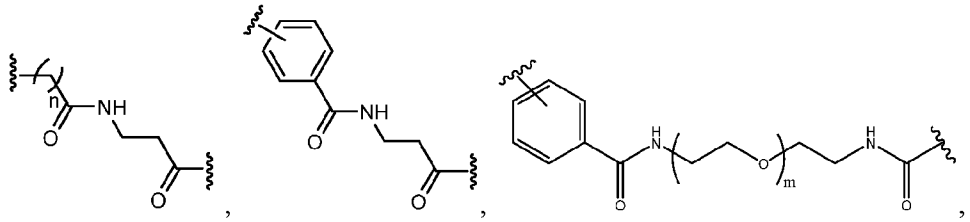
In certain embodiments, a chelator comprises a single X group, and preferably L_1 of the X group is a linker.

A chelator of the invention can be substituted with X at any one of the carbon atoms of the macrocyclic ring, the Z_1 or Z_2 position, or on ring A or ring B, provided that when ring or ring B comprises an X group, L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen (i.e., at least one of the carbon atoms of Z_1, Z_2, and/or the carbons of the macrocyclic ring is substituted for instance with an alkyl group, such as methyl or ethyl). Preferably, substitution at

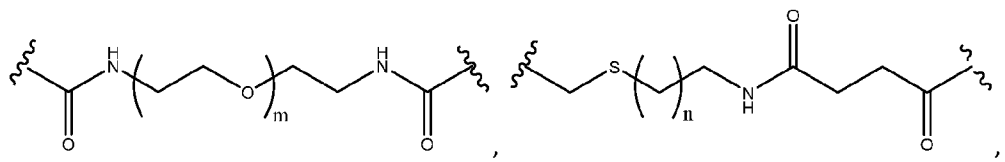
such positions does not affect the chelation efficiency of the chelator for radiometal ions, particularly ^{225}Ac, and in some embodiments, the substitutions can enhance chelation efficiency.

In some embodiments, L_1 is absent. When L_1 is absent, R_{11} is directly bound (e.g., via covalent linkage) to the chelator.

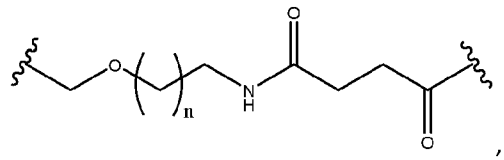
In some embodiments, L_1 is a linker. As used herein, the term "linker" refers to a chemical moiety that joins a chelator to a nucleophilic moiety, electrophilic moiety, or antigen binding domain. Any suitable linker known to those skilled in the art in view of the present disclosure can be used in the invention. The linkers can contain, for example, a substituted or unsubstituted alkyl, a substituted or unsubstituted heteroalkyl moiety, a substituted or unsubstituted aryl or heteroaryl, a polyethylene glycol (PEG) linker, a peptide linker, a sugar-based linker, or a cleavable linker, such as a disulfide linkage or a protease cleavage site such as valine-citrulline- p-aminobenzyl (PAB). Exemplary linker structures suitable for use in the invention include, but are not limited to:



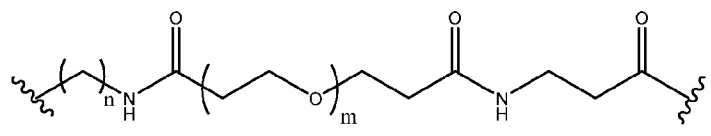
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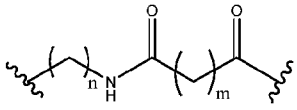
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,



, and


, wherein n is an integer of 0 to 10, preferably an integer of 1 to 4; and m is an integer of 0 to 12, preferably an integer of 0 to 6.

In some embodiments, R_{11} is a nucleophilic moiety or an electrophilic moiety. A "nucleophilic moiety" or "nucleophilic group" refers to a functional group that donates an electron pair to form a covalent bond in a chemical reaction. An "electrophilic moiety" or "electrophilic group" refers to a functional group that accepts an electron pair to form a covalent bond in a chemical reaction. Nucleophilic groups react with electrophilic groups, and *vice versa*, in chemical reactions to form new covalent bonds. Reaction of the nucleophilic group or electrophilic group of a chelator of the invention with an antigen binding domain or other chemical moiety (e.g., linker) comprising the corresponding reaction partner allows for covalent linkage of the antigen binding domain or chemical moiety to the chelator of the invention.

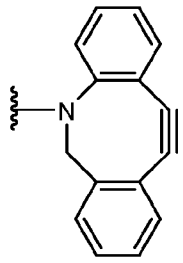
Exemplary examples of nucleophilic groups include, but are not limited to, azides, amines, and thiols. Exemplary examples of electrophilic groups include, but are not limited to amine-reactive groups, thiol-reactive groups, alkynyls and cycloalkynyls. An amine-reactive group preferably reacts with primary amines, including primary amines that exist at the N-terminus of each polypeptide chain and in the side-chain of lysine residues. Examples of amine-reactive groups suitable for use in the invention include, but are not limited to, N-hydroxy succinimide (NHS), substituted NHS (such as sulfo-NHS), isothiocyanate (-NCS), isocyanate (-NCO), esters, carboxylic acid, acyl halides, amides, alkylamides, and tetra- and per-fluoro phenyl ester. A thiol-reactive group reacts with thiols, or sulfhydryls, preferably thiols present in the side-chain of cysteine residues of polypeptides. Examples of thiol-reactive groups suitable for use in the invention include, but are not limited to, Michael acceptors (e.g., maleimide), haloacetyl, acyl halides, activated disulfides, and phenyloxadiazole sulfone.

In particular embodiments, R_{11} is $-NH_2$, -NCS (isothiocyanate), -NCO (isocyanate), $-N_3$ (azido), alkynyl, cycloalkynyl, carboxylic acid, ester, amido, alkylamide, maleimido, acyl halide, tetrazine, or trans-cyclooctene, more particularly -NCS, -NCO, $-N_3$, alkynyl, cycloalkynyl, $-C(O)R_{13}$, $-COOR_{13}$, $-CON(R_{13})_2$, maleimido, acyl halide (e.g., -C(O)Cl, -C(O)Br), tetrazine, or trans-cyclooctene wherein each R_{13} is independently hydrogen or alkyl.

In some embodiments, R_{11} is an alkynyl, cycloalkynyl, or azido group thus allowing for attachment of the chelator to an antigen binding domain or other chemical moiety (e.g., linker) using a click chemistry reaction. In such embodiments, the click chemistry reaction that can be performed is a Huisgen cycloaddition or 1,3-dipolar cycloaddition between an azido ($-N_3$) and an alkynyl or cycloalkynyl group to form a 1,2,4-triazole linker or moiety. In one embodiment, the chelator comprises an alkynyl or cycloalkynyl group and the antigen binding domain or other chemical moiety comprises an azido group. In another embodiment, the chelator comprises an azido group and the antigen binding domain or other chemical moiety comprises an alkynyl or cycloalkynyl group.

In certain embodiments, R_{11} is an alkynyl group, more preferably a terminal alkynyl group or cycloalkynyl group that is reactive with an azide group, particularly via strain-promoted azide-alkyne cycloaddition (SPAAC). Examples of cycloalkynyl groups that can react with azide groups via SPAAC include, but are not limited to cyclooctynyl or a bicyclononynyl (BCN), difluorinated cyclooctynyl (DIFO), dibenzocyclooctynyl (DIBO), keto-DIBO, biarylazacyclooctynonyl (BARAC), dibenzoazacyclooctynyl (DIBAC, DBCO, ADIBO), dimethoxyazacyclooctynyl (DIMAC), difluorobenzocyclooctynyl (DIFBO), monobenzocyclooctynyl (MOBO), and tetramethoxy dibenzocyclooctynyl (TMDIBO).

In a particular embodiment, R_{11} is dibenzoazacyclooctynyl (DIBAC, DBCO, ADIBO), which has the following structure:



. In such embodiments in which R_{11} is DBCO, the DBCO can be covalently linked to a chelator directly or indirectly via a linker, and is preferably attached to the chelator indirectly via a linker.

In some embodiments, R_{11} comprises an antigen binding domain. The antigen binding domain can be linked to the chelator directly via a covalent linkage, or indirectly via a linker. In preferred embodiments, the antigen binding domain is an antibody or antigen binding fragment thereof. According to preferred embodiments, R_{11} comprises an antigen binding domain with binding specificity for hK2, such as the Fab of KL2B30.

According to embodiments of the invention, each of ring A and ring B is independently a 6-10 membered aryl or a 5-10 membered heteroaryl. In alternative embodiments, it is contemplated that each of ring A and ring B is an optionally substituted heterocyclyl ring, such as oxazoline. Each of ring A and ring B can be optionally and independently substituted with one or more substituent groups independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN $-OC(O)N(R_{13})_2$, and X. Examples of 6-10 membered aryl groups suitable for this purpose include, but are not limited to, phenyl and naphthyl. Examples of 5 to 10 membered heteroaryl groups suitable for this purpose include, but are not limited to pyridinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, and imidazolyl. Examples of suitable substituents of the 5 to 10 membered heteroaryl and 6 to 10 membered aryl groups include, but are not limited to -COOH, tetrazolyl, and $-CH_2COOH$. In preferred embodiments, a substituent group is -COOH or tetrazolyl, which is an isostere of -COOH.

In certain embodiments, each of ring A and ring B are independently and optionally substituted with one or more carboxyl groups, including but not limited to, -COOH and $-CH_2COOH$.

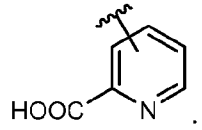
In certain embodiments, each of ring A and ring B are independently and optionally substituted with tetrazolyl.

In one embodiment, ring A and ring B are the same, e.g., both ring A and ring B are pyridinyl. In another embodiment, ring A and ring B are different, e.g., one of ring A and ring is pyridinyl and the other is phenyl.

In a particular embodiment, both ring A and ring B are pyridinyl substituted with -COOH.

In a particular embodiment, both ring A and ring B are pyridinyl substituted with tetrazolyl.

In another particular embodiment, both ring A and ring B are picolinic acid groups having the following structure:



.

According to embodiments of the invention, each of Z_1 and Z_2 is independently –$(C(R_{12})_2)_m$- or –$(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$-; each X is independently -L_1-R_{11}; each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; each n is independently 0, 1, 2, 3, 4, or 5; and each m is independently 1, 2, 3, 4, or 5.

In some embodiments, each R_{12} is independently hydrogen or alkyl, more preferably hydrogen, -CH_3, or -CH_2CH_3.

In some embodiments, each R_{12} is hydrogen.

In some embodiments, both Z_1 and Z_2 are –$(CH_2)_m$-, wherein each m is preferably 1. In such embodiments, a carbon atom of the macrocyclic ring, ring A, or ring B is substituted with an X group.

In some embodiments, one of Z_1 and Z_2 is -$(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$- and the other is –$(CH_2)_m$-.

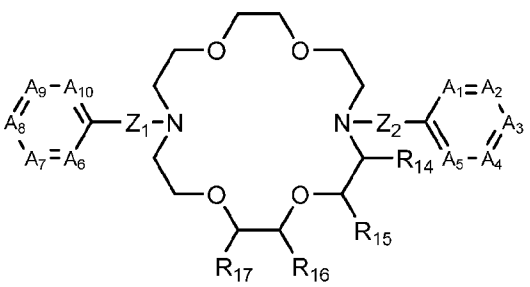
In some embodiments, one of Z_1 and Z_2 -$(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$- and the other is –$(CH_2)_m$-; each n is 0; m is 1; X is -L_1-R_{11}; and L_1 is a linker.

In some embodiments, both Z_1 and Z_2 are –$(CH_2)_m$-; each m is independently 0, 1, 2, 3, 4, or 5, preferably each m is 1; and one of R_{14}, R_{15}, R_{16}, and R_{17} is X, and the rest of R_{14}, R_{15}, R_{16}, and R_{17} are each hydrogen.

In some embodiments, R_{14} and R_{15} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring (i.e., cyclopentyl or cyclohexyl). Such 5- or 6-membered cycloalkyl ring can be substituted with an X group.

In some embodiments R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring (i.e., cyclopentyl or cyclohexyl). Such 5- or 6-membered cycloalkyl ring can be substituted with an X group.

In certain embodiments, a chelator has the structure of Formula (II):



(II)

wherein:

A_1 is N or CR_1 or is absent;

A_2 is N or CR_2;

A_3 is N or CR_3;

A_4 is N or CR_4;

A_5 is N or CR_5;

A_6 is N or CR_6 or is absent;

A_7 is N or CR_7;

A_8 is N or CR_8;

A_9 is N or CR_9;

A_{10} is N or CR_{10};

provided that no more than three of A_1, A_2, A_3, A_4, and A_5 are N, and no more than three of A_6, A_7, A_8, A_9, and A_{10} are N;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN, $-OC(O)N(R_{13})_2$, and -X,

or, alternatively, any two directly adjacent R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are taken together with the atoms to which they are attached to form a five or six-membered substituted or unsubstituted carbocyclic or nitrogen-containing ring;

and Z_1, Z_2, X, n, m, p, L_1, and R_{11}-R_{17} are as described above for formula (I),

provided that the chelator comprises at least one X, and when any one of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is X, then L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen.

In some embodiments, any two directly adjacent R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are taken together with the atoms to which they are attached to form a five or six-membered substituted or unsubstituted carbocyclic or nitrogen-containing ring. Examples of such carbocyclic rings that can be formed include, but are not limited to, naphthyl. Examples of such nitrogen-containing rings that can be formed include, but are not limited to, quinolinyl. The

carbocyclic or nitrogen-containing rings can be unsubstituted or substituted with one or more suitable substituents, e.g., -COOH, -CH_2COOH, tetrazolyl etc.

In some embodiments, L_1 is absent. When L_1 is absent, R_{11} is directly bound (e.g., via covalent linkage) to the chelator.

In some embodiments, L_1 is a linker. Any suitable linker known to those skilled in the art in view of the present disclosure can be used in the invention, such as those described above.

In some embodiments, one of A_1, A_2, A_3, A_4, and A_5 is nitrogen, one of A_1, A_2, A_3, A_4, and A_5 is carbon substituted with -COOH and the rest are CH, i.e., forming a pyridinyl ring substituted with carboxylic acid.

In some embodiments, one of A_6, A_7, A_8, A_9, and A_{10} is nitrogen, one of A_6, A_7, A_8, A_9, and A_{10} is carbon substituted with -COOH, and the rest are CH, i.e., forming a pyridinyl ring substituted with carboxylic acid.

In one embodiment, at least one of R_1, R_2, R_3, R_4 and R_5 is -COOH. In one embodiment, at least one of R_6, R_7, R_8, R_9, and R_{10} is -COOH. In another embodiment, at least one of R_1, R_2, R_3, R_4 and R_5 is -COOH; and at least one of R_6, R_7, R_8, R_9, and R_{10} is -COOH.

In some embodiments, each of A_1 and A_{10} is nitrogen; A_2 is CR_2 and R_2 is -COOH; A_9 is CR_9 and R_9 is -COOH; each of A_3-A_8 is CR_2, CR_3, CR_4, CR_5, CR_6, CR_7, and CR_8, respectively; and each of R_3 to R_8 is hydrogen.

In some embodiments, one of A_1, A_2, A_3, A_4, and A_5 is nitrogen, one of A_1, A_2, A_3, A_4, and A_5 is carbon substituted with tetrazolyl and the rest are CH.

In some embodiments, one of A_6, A_7, A_8, A_9, and A_{10} is nitrogen, one of A_6, A_7, A_8, A_9, and A_{10} is carbon substituted with tetrazolyl, and the rest are CH.

In one embodiment, at least one of R_1, R_2, R_3, R_4 and R_5 is tetrazolyl. In one embodiment, at least one of R_6, R_7, R_8, R_9, and R_{10} is tetrazolyl. In another embodiment, at least one of R_1, R_2, R_3, R_4 and R_5 is tetrazolyl; and at least one of R_6, R_7, R_8, R_9, and R_{10} is tetrazolyl.

In some embodiments, each R_{12} is hydrogen.

In some embodiments, R_{11} is an alkynyl group or cycloalkynyl group, preferably cyclooctynyl or a cyclooctynyl derivative, e.g., DBCO.

In particular embodiments of a chelator of formula (II):

each of A_1 and A_{10} is nitrogen;

A_2 is CR_2 and R_2 is -COOH;

A_9 is CR_9 and R_9 is -COOH;

each of A_3-A_8 is CR_2, CR_3, CR_4, CR_5, CR_6, CR_7, and CR_8, respectively;

each of R_3 to R_8 is hydrogen;

one of Z_1 and Z_2 is $-(CH_2)_m-$ and the other of Z_1 and Z_2 is $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;

R_{12} is hydrogen;

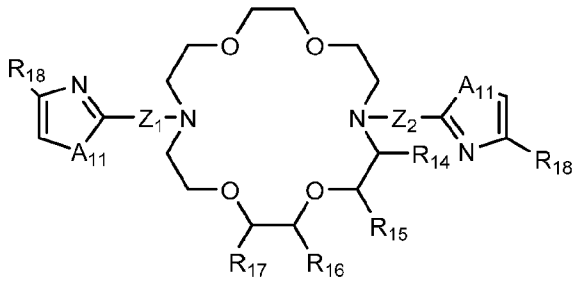
m is 1;

each n is 0;

X is $-L_1-R_{11}$, wherein L_1 is a linker and $-R_{11}$ is an electrophilic group, e.g., cyclooctynyl or cyclooctynyl derivative such as DBCO; and

each of R_{14}-R_{17} is hydrogen, or alternatively R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring.

In certain embodiments, a chelator has the structure of formula (III):



(III)

wherein:

each A_{11} is independently O, S, NMe, or NH;

each R_{18} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, $-COOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN $-OC(O)N(R_{13})_2$, and -X,

and Z_1, Z_2, X, n, m, L_1, R_{11}-R_{17} are as described above for formula (I),

provided that the chelator comprises at least one X, and when R_{18} is X, then L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen.

In some embodiments, each A_{11} is the same, and each A_{11} is O, S, NMe, or NH. For example, each A_{11} can be S. In other embodiments, each A_{11} is different and each is independently selected from O, S, NMe, and NH.

In some embodiments, each R_{18} is independently $-(CH_2)_p$-$COOR_{13}$ or tetrazolyl, wherein R_{13} is hydrogen and each p is independently 0 or 1.

In some embodiments, each R_{18} is -COOH.

In some embodiments, each R_{18} is $-CH_2COOH$.

In some embodiments, each R_{18} is tetrazolyl.

In particular embodiments of a chelator of formula (III):

each R_{18} is COOH;

one of Z_1 and Z_2 is $-(CH_2)_m$- and the other of Z_1 and Z_2 is $-(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$-;

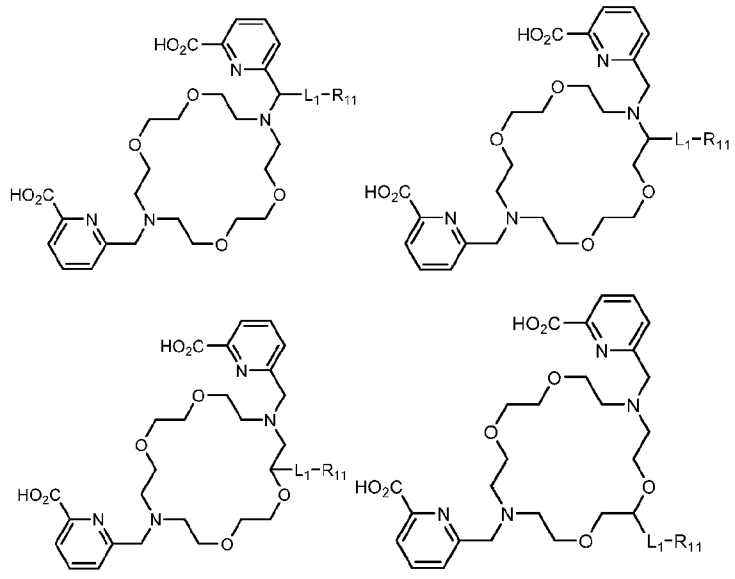
R_{12} is hydrogen;

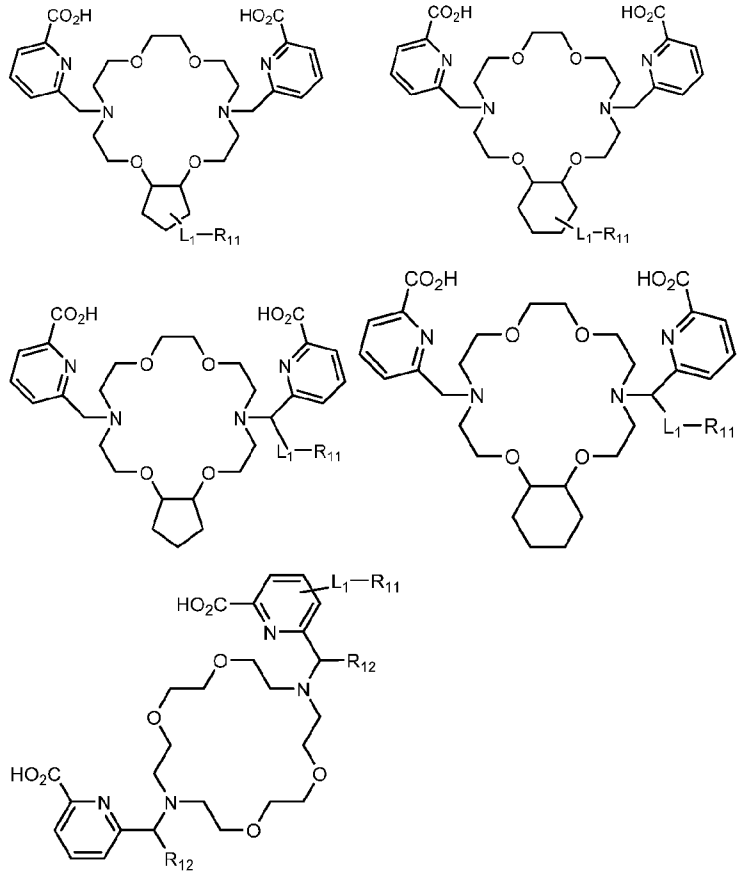
m is 1; each n is 0;

X is $-L_1$-R_{11}, wherein L_1 is a linker and $-R_{11}$ is an electrophilic group, e.g., cyclooctynyl or cyclooctynyl derivative such as DBCO, or BCN; and

each of R_{14}-R_{17} is hydrogen, or alternatively R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring.

In particular embodiments of the invention, a chelator is selected from the group consisting of:





wherein:

L_1 is absent or a linker;

R_{11} is a nucleophilic moiety or an electrophilic moiety, or R_{11} comprises an antigen binding domain (e.g., the Fab of KL2B30); and

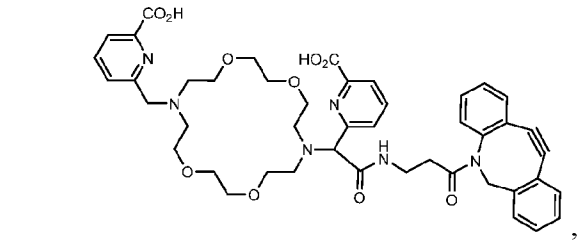
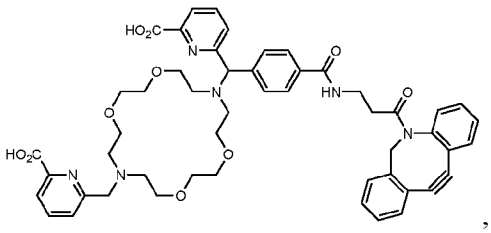
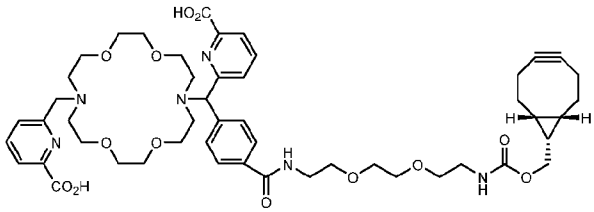
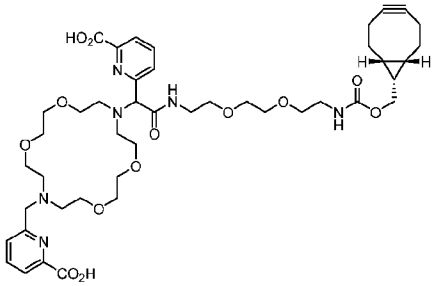
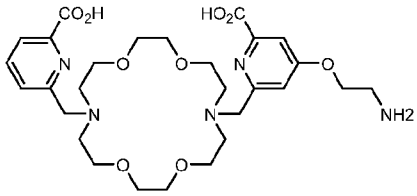
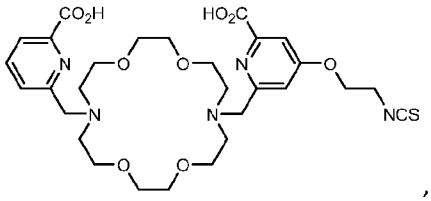
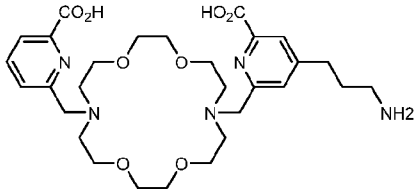
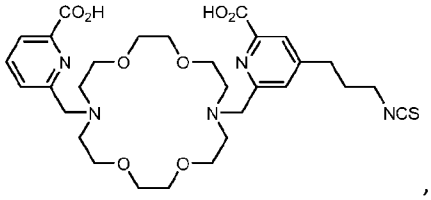
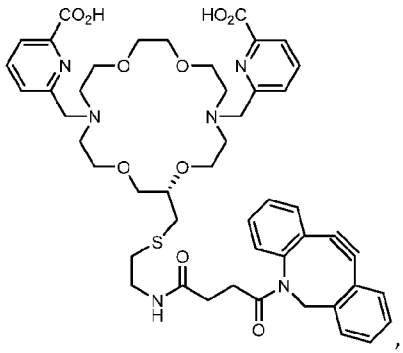
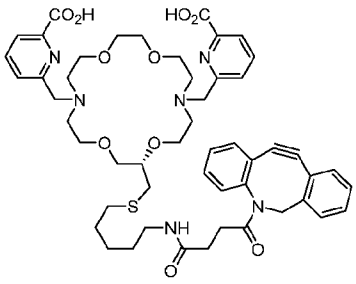
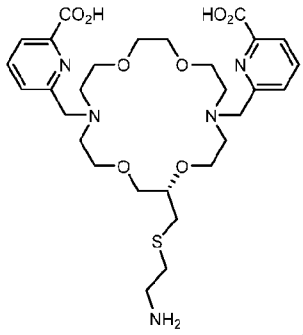
each R_{12} is independently hydrogen, $-CH_3$, or $-CH_2CH_3$, provided at least one R_{12} is $-CH_3$ or $-CH_2CH_3$.

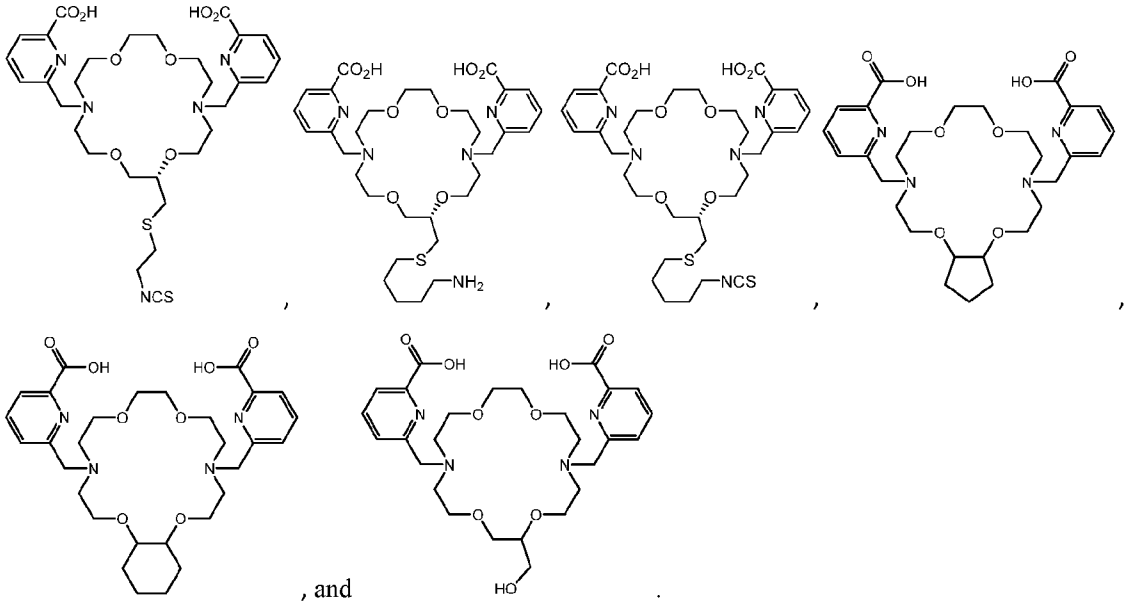
In some embodiments, R_{11} is $-NH_2$, -NCS, -NCO, $-N_3$, alkynyl, cycloalkynyl, $-C(O)R_{13}$, $-COOR_{13}$, $-CON(R_{13})_2$, maleimido, acyl halide, tetrazine, or trans-cyclooctene.

In certain embodiments, R_{11} is cyclooctynyl or a cyclooctynyl derivative selected from the group consisting of bicyclononynyl (BCN), difluorinated cyclooctynyl (DIFO), dibenzocyclooctynyl (DIBO), keto-DIBO, biarylazacyclooctynonyl (BARAC), dibenzoazacyclooctynyl (DIBAC, DBCO, ADIBO), dimethoxyazacyclooctynyl (DIMAC), difluorobenzocyclooctynyl (DIFBO), monobenzocyclooctynyl (MOBO), and tetramethoxy dibenzocyclooctynyl (TMDIBO).

Preferably, R_{11} is an alkynyl group or cycloalkynyl group, more preferably a cycloalkynyl group, e.g., DBCO or BCN.

Exemplary chelators of the invention include, but are not limited to:


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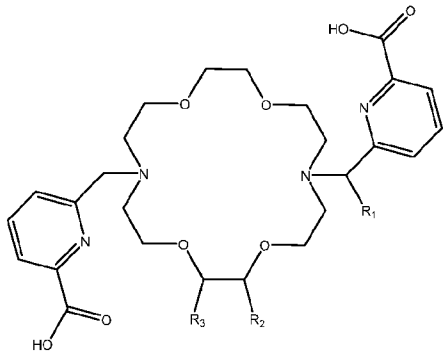
, and .

Such chelators can be covalently attached to an antigen binding domain to form immunoconjugates or radioimmunoconjugates by reacting the chelator with an azide-labeled antigen binding domain to form a 1,2,3-triazole linker via a click chemistry reaction as described in WO2020/229974.

Chelators of the invention can be produced by any method known in the art in view of the present disclosure. For example, the pendant aromatic/heteroaromatic groups can be attached to the macrocyclic ring portion by methods known in the art, such as those exemplified and described in WO2020/229974.

CHELATORS OF FORMULAE (IV), (V) and (VI)

In an embodiment, the chelator is directed to a compound of formula (IV)



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen and R_2 is $-L_1-R_4$;

alternatively, R_1 is -L_1-R_4 and R_2 is hydrogen;

R_3 is hydrogen;

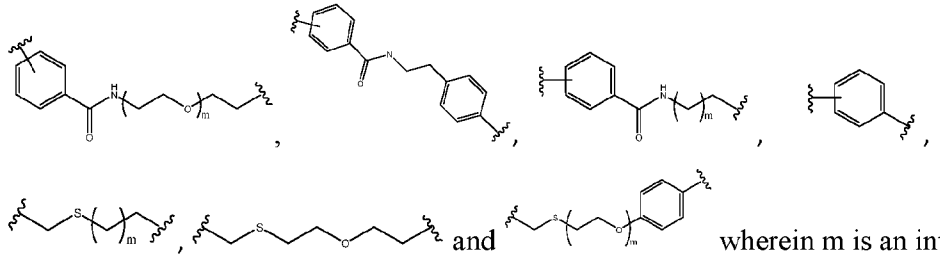
alternatively, R_2 and R_3 are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl, wherein the 5- or 6-membered cycloalkyl is optionally substituted with -L_1-R_4;

L_1 is absent or a linker; and

R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain (e.g., the Fab of KL2B30).

In some embodiments, L_1 is absent. When L_1 is absent, R_4 is directly bound (e.g., via covalent linkage) to the compound.

In some embodiments, L_1 is a linker. As used herein, the term "linker" refers to a chemical moiety that joins a compound of the invention to a nucleophilic moiety, electrophilic moiety, or antigen binding domain. Any suitable linker known to those skilled in the art in view of the present disclosure can be used in the invention. The linkers can have, for example, a substituted or unsubstituted alkyl, a substituted or unsubstituted heteroalkyl moiety, a substituted or unsubstituted aryl or heteroaryl, a polyethylene glycol (PEG) linker, a peptide linker, a sugar-based linker, or a cleavable linker, such as a disulfide linkage or a protease cleavage site such as valine-citrulline- p-aminobenzyl (PAB). Exemplary linker structures suitable for use in the invention include, but are not limited to:



wherein m is an integer of 0 to 12.

In some embodiments, R_4 is a nucleophilic moiety or an electrophilic moiety. A "nucleophilic moiety" or "nucleophilic group" refers to a functional group that donates an electron pair to form a covalent bond in a chemical reaction. An "electrophilic moiety" or "electrophilic group" refers to a functional group that accepts an electron pair to form a covalent bond in a chemical reaction. Nucleophilic groups react with electrophilic groups, and *vice versa*, in chemical reactions to form new covalent bonds. Reaction of the nucleophilic group or

electrophilic group of a compound of the invention with an antigen binding domain or other chemical moiety (e.g., linker) comprising the corresponding reaction partner allows for covalent linkage of the antigen binding domain or chemical moiety to the compound of the invention.

Exemplary examples of nucleophilic groups include, but are not limited to, azides, amines, and thiols. Exemplary examples of electrophilic groups include, but are not limited to amine-reactive groups, thiol-reactive groups, alkynyls and cycloalkynyls. An amine-reactive group preferably reacts with primary amines, including primary amines that exist at the N-terminus of each polypeptide chain and in the side-chain of lysine residues. Examples of amine-reactive groups suitable for use in the invention include, but are not limited to, N-hydroxy succinimide (NHS), substituted NHS (such as sulfo-NHS), isothiocyanate (-NCS), isocyanate (-NCO), esters, carboxylic acid, acyl halides, amides, alkylamides, and tetra- and per-fluoro phenyl ester. A thiol-reactive group reacts with thiols, or sulfhydryls, preferably thiols present in the side-chain of cysteine residues of polypeptides. Examples of thiol-reactive groups suitable for use in the invention include, but are not limited to, Michael acceptors (e.g., maleimide), haloacetyl, acyl halides, activated disulfides, and phenyloxadiazole sulfone.

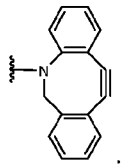
In certain embodiments, R_4 is $-NH_2$, -NCS (isothiocyanate), -NCO (isocyanate), $-N_3$ (azido), alkynyl, cycloalkynyl, carboxylic acid, ester, amido, alkylamide, maleimido, acyl halide, tetrazine, or trans-cyclooctene, more particularly -NCS, -NCO, $-N_3$, alkynyl, cycloalkynyl, $-C(O)R_{13}$, $-COOR_{13}$, $-CON(R_{13})_2$, maleimido, acyl halide (e.g., -C(O)Cl, -C(O)Br), tetrazine, or trans-cyclooctene wherein each R_{13} is independently hydrogen or alkyl.

In some embodiments, R_4 is an alkynyl, cycloalkynyl, or azido group thus allowing for attachment of the compound of the invention to an antigen binding domain or other chemical moiety (e.g., linker) using a click chemistry reaction. In such embodiments, the click chemistry reaction that can be performed is a Huisgen cycloaddition or 1,3-dipolar cycloaddition between an azido ($-N_3$) and an alkynyl or cycloalkynyl group to form a 1,2,4-triazole linker or moiety. In one embodiment, the compound of the invention comprises an alkynyl or cycloalkynyl group and the antigen binding domain or other chemical moiety comprises an azido group. In another embodiment, the compound of the invention comprises an azido group and the antigen binding domain or other chemical moiety comprises an alkynyl or cycloalkynyl group.

In certain embodiments, R_4 is an alkynyl group, more preferably a terminal alkynyl group or cycloalkynyl group that is reactive with an azide group, particularly via strain-promoted azide-

alkyne cycloaddition (SPAAC). Examples of cycloalkynyl groups that can react with azide groups via SPAAC include, but are not limited to cyclooctynyl or a bicyclononynyl (BCN), difluorinated cyclooctynyl (DIFO), dibenzocyclooctynyl (DIBO), keto-DIBO, biarylazacyclooctynonyl (BARAC), dibenzoazacyclooctynyl (DIBAC, DBCO, ADIBO), dimethoxyazacyclooctynyl (DIMAC), difluorobenzocyclooctynyl (DIFBO), monobenzocyclooctynyl (MOBO), and tetramethoxy dibenzocyclooctynyl (TMDIBO).

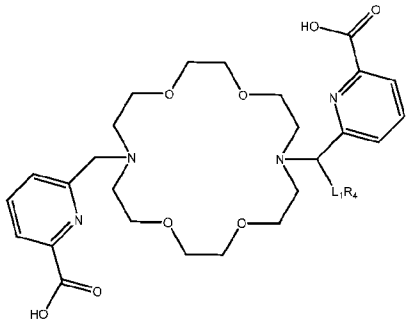
In certain embodiments, R_4 is dibenzoazacyclooctynyl (DIBAC, DBCO, ADIBO), which has the following structure:



. In embodiments in which R_4 is DBCO, the DBCO can be covalently linked to a compound directly or indirectly via a linker, and is preferably attached to the compound indirectly via a linker.

In certain embodiments, R_4 comprises an antigen binding domain. The antigen binding domain can be linked to the compound directly via a covalent linkage, or indirectly via a linker. In preferred embodiments, the antigen binding domain has binding specificity for hK2, such as the Fab of KL2B30.

In another embodiment, the chelator is directed to a compound of formula (V):



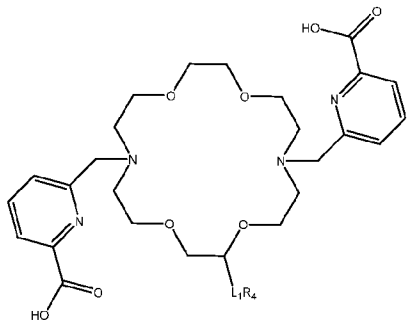
(V)

or a pharmaceutically acceptable salt thereof, wherein:

L_1 is absent or a linker; and

R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain.

In another embodiment the chelator is a compound of formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof, wherein:

L_1 is absent or a linker; and

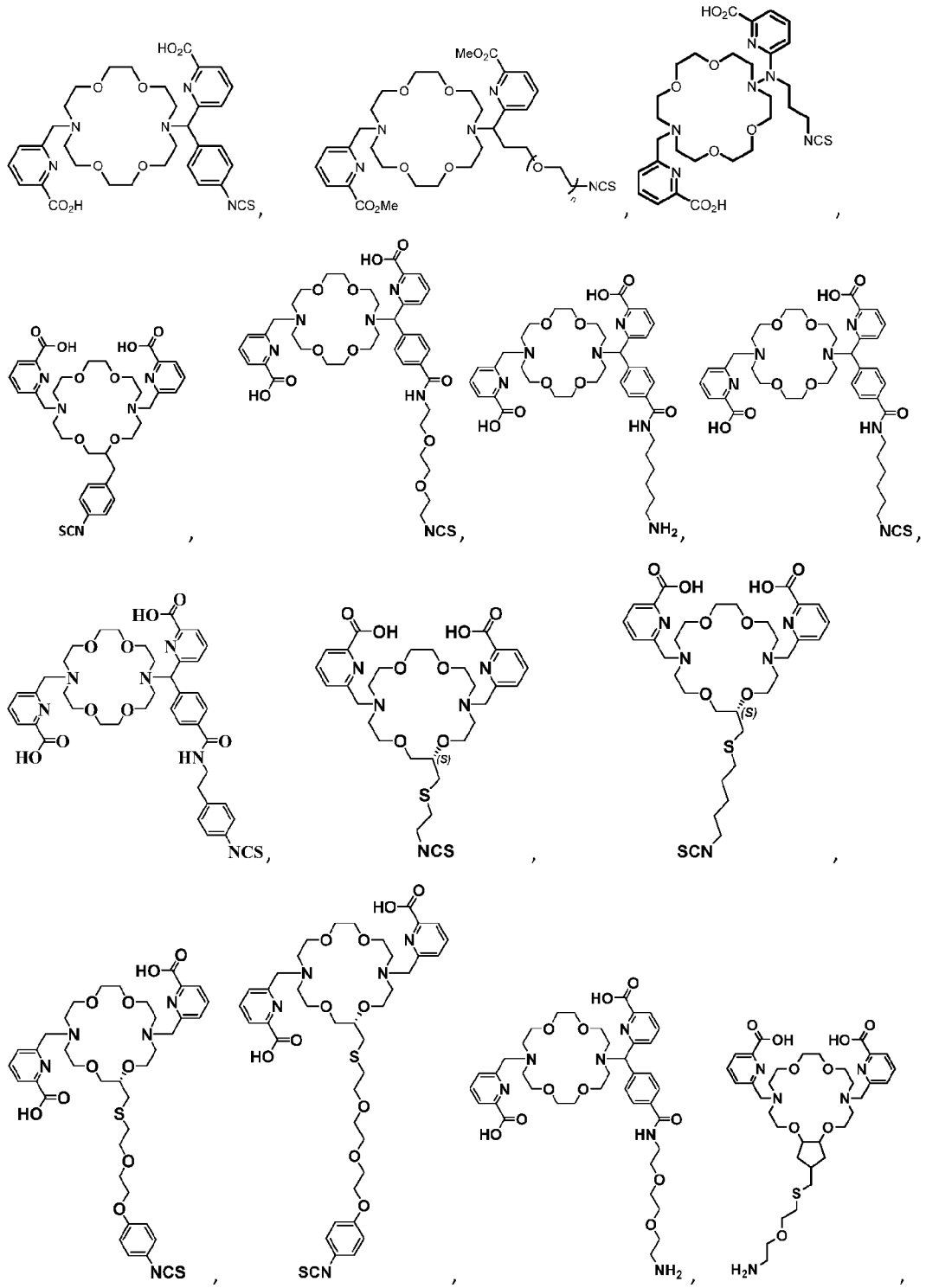
R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain (e.g., the Fab of KL2B30).

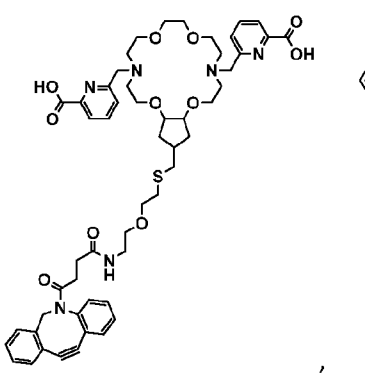
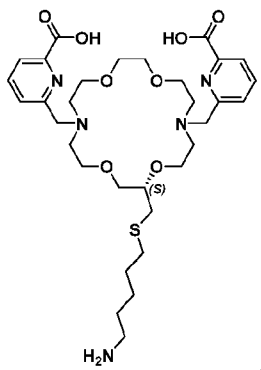
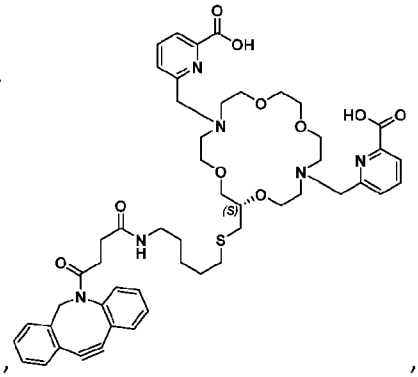
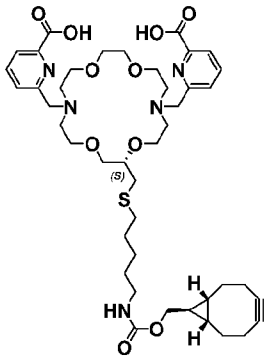
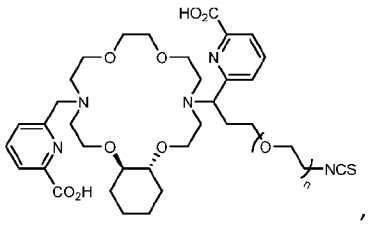
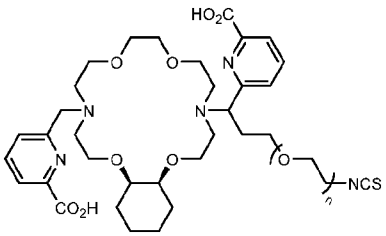
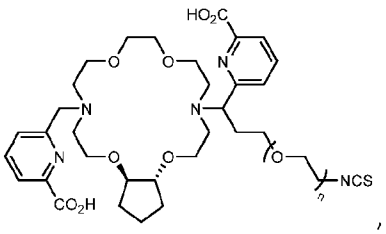
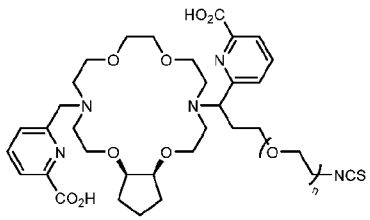
In another embodiment, the invention is directed to a compound, wherein: R_1 is -L_1-R_4; R_2 and R_3 are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl; L_1 is absent or a linker; and R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain; or a pharmaceutically acceptable salt thereof.

In a further embodiment, the invention is directed to a compound, wherein R_1 is H; R_2 and R_3 are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl substituted with -L_1-R_4; L_1 is absent or a linker; and R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain; or a pharmaceutically acceptable salt thereof:

Additional embodiments include those wherein R_4 is an antigen binding domain. According to preferred embodiments, R_4 comprises an antigen binding domain with binding specificity for hK2, such as the Fab of KL2B30.

In an embodiment, the chelators are any one or more independently selected from the group consisting of :




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, wherein n is 1-10.

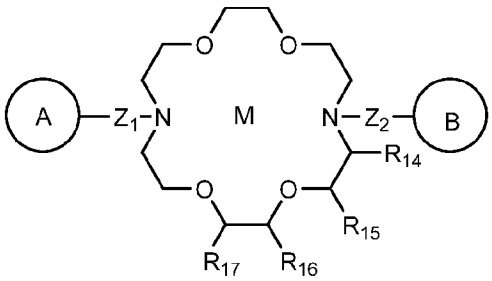
Said chelators can be covalently attached to an antigen binding domain (e.g., the Fab of KL2B30) to form immunoconjugates or radioimmunoconjugates by reacting the compound with an azide-labeled antigen binding domain to form a 1,2,3-triazole linker, e.g., via a click chemistry reaction as described in WO2020/229974.

Chelators, radiometal complexes and radioimmunoconjugates of the present invention can be produced by any method known in the art in view of the present disclosure; for example, the pendant aromatic/heteroaromatic groups can be attached to the macrocyclic ring portion by methods known in the art, such as those exemplified and described in WO2020/229974.

Radiometal Complexes

In another general aspect, the invention relates to a radiometal complex comprising a radiometal ion coordinated to a chelator of the invention via coordinate bonding. Any of the chelators of the invention described herein can comprise a radiometal ion. Preferably, the radiometal ion is an alpha-emitting radiometal ion, more preferably ^{225}Ac. Chelators of the invention can robustly chelate radiometal ions, particularly ^{225}Ac at any specific activity irrespective of metal impurities, thus forming a radiometal complex having high chelation stability *in vivo* and *in vitro* and which is stable to challenge agents, e.g., diethylene triamine pentaacetic acid (DTPA).

According to embodiments of the invention, a radiometal complex has the structure of formula (I-m):



wherein the variable groups are as defined above in the chelators of the invention, e.g., the chelator of formula (I); and M is a radiometal ion. The radiometal ion M is bound to the chelator via coordinate bonding to form the radiometal complex. Heteroatoms of the macrocyclic ring of the chelator as well as any functional groups of the pendant arms (i.e., -Z_1-ring A and/or -Z_2-ring B) can participate in coordinate bonding of the radiometal ion.

Any of the chelators of formula (I) described above can be used to form radiometal complexes of formula (I-m).

In certain embodiments, the radiometal ion M is an alpha-emitting radiometal ion Preferably, the alpha-emitting radiometal ion is ^{225}Ac.

According to embodiments of the invention, a radiometal complex comprises at least one X group, wherein X is -L_1-R_{11}, wherein L_1 is absent or a linker, and R_{11} is an electrophilic moiety or a nucleophilic moiety, or R_{11} comprises an antigen binding domain (e.g., the Fab of KL2B30). When R_{11} is a nucleophilic or electrophilic moiety, such moiety can be used for attachment of the radiometal complex to an antigen binding domain, directly or indirectly via a linker.

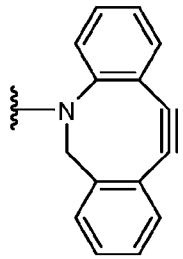
In certain embodiments, a radiometal comprises a single X group, and preferably L_1 of the X group is a linker.

In particular embodiments, R_{11} is $-NH_2$, -NCS (isothiocyanate), -NCO (isocyanate), $-N_3$ (azido), alkynyl, cycloalkynyl, carboxylic acid, ester, amido, alkylamide, maleimido, acyl halide, tetrazine, or trans-cyclooctene, more particularly -NCS, -NCO, $-N_3$, alkynyl, cycloalkynyl, -$C(O)R_{13}$, -$COOR_{13}$, -$CON(R_{13})_2$, maleimido, or acyl halide (e.g., -C(O)Cl or -C(O)Br), wherein each R_{13} is independently hydrogen or alkyl.

In some embodiments, R_{11} is an alkynyl, cycloalkynyl, or azido group thus allowing for attachment of the chelator to an antigen binding domain or other chemical moiety (e.g., linker) using a click chemistry reaction.

In certain embodiments, R_{11} is an alkynyl group, more preferably a terminal alkynyl group or cycloalkynyl group that is reactive with an azido group, particularly via strain-promoted azide-alkyne cycloaddition (SPAAC). Examples of cycloalkynyl groups that can react with azide groups via SPAAC include, but are not limited to cyclooctynyl or a cyclooctynyl derivative, such as bicyclononynyl (BCN), difluorinated cyclooctynyl (DIFO), dibenzocyclooctynyl (DIBO), keto-DIBO, biarylazacyclooctynonyl (BARAC), dibenzoazacyclooctynyl (DIBAC, DBCO, ADIBO), dimethoxyazacyclooctynyl (DIMAC), difluorobenzocyclooctynyl (DIFBO), monobenzocyclooctynyl (MOBO), and tetramethoxy dibenzocyclooctynyl (TMDIBO).

In a particular embodiment, R_{11} is dibenzoazacyclooctynyl (DIBAC, DBCO, ADIBO), which has the following structure:



In such embodiments in which R_{11} is DBCO, the DBCO can be covalently linked to a radiometal complex directly or indirectly via a linker, and is preferably attached to the radiometal complex indirectly via a linker.

In another particular embodiment, R_{11} is bicyclononynyl (BCN).

According to embodiments of the invention, each of ring A and ring B is independently a 6-10 membered aryl or a 5-10 membered heteroaryl. In alternative embodiments, it is contemplated that each of ring A and ring B is an optionally substituted heterocyclyl ring, such as oxazoline. Each of ring A and ring B can be optionally and independently substituted with one or more substituent groups independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN $-OC(O)N(R_{13})_2$, and X. Examples of 6-10 membered aryl groups suitable for this purpose include, but are not limited to, phenyl and naphthyl. Examples of 5 to 10 membered heteroaryl groups suitable for this purpose include, but are not limited to pyridinyl, isothiazolyl, isoxazolyl, and imidazolyl. Examples of suitable substituents of the 5 to 10 membered heteroaryl and 6 to 10 membered aryl groups include, but are not limited to -COOH, tetrazolyl, and $-CH_2COOH$.

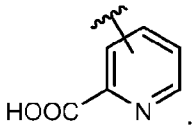
In certain embodiments, each of ring A and ring B are independently and optionally substituted with one or more carboxyl groups, including but not limited to, -COOH and $-CH_2COOH$.

In one embodiment, ring A and ring B are the same, e.g., both ring A and ring B are pyridinyl. In another embodiment, ring A and ring B are different, e.g., one of ring A and ring is pyridinyl and the other is phenyl.

In a particular embodiment, both ring A and ring B are pyridinyl substituted with -COOH.

In a particular embodiment, both ring A and ring B are pyridinyl substituted with tetrazolyl.

In another particular embodiment, both ring A and ring B are picolinic acid groups having the following structure:



According to embodiments of the invention, each of Z_1 and Z_2 is independently –$(C(R_{12})_2)_m$- or –$(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$-; each X is independently -L_1-R_{11}; each n is independently 0, 1, 2, 3, 4, or 5; and each m is independently 1, 2, 3, 4, or 5.

In some embodiments, both Z_1 and Z_2 are –$(CH_2)_m$-, wherein each m is preferably 1. In such embodiments, a carbon atom of the macrocyclic ring, ring A, or ring B is substituted with an X group.

In some embodiments, one of Z_1 and Z_2 is -$(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$- and the other is –$(CH_2)_m$-.

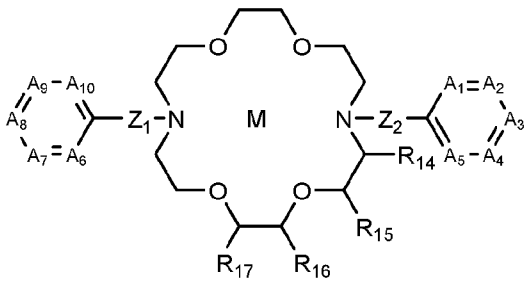
In some embodiments, one of Z_1 and Z_2 -$(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$- and the other is –$(CH_2)_m$-; each n is 0; m is 1; X is -L_1-R_{11}; and L_1 is a linker.

In some embodiments, both Z_1 and Z_2 are –$(CH_2)_m$-; each m is independently 0, 1, 2, 3, 4, or 5, preferably each m is 1; and one of R_{14}, R_{15}, R_{16}, and R_{17} is X, and the rest of R_{14}, R_{15}, R_{16}, and R_{17} are each hydrogen.

In some embodiments, R_{14} and R_{15} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring (e.g., cyclopentyl or cyclohexyl). Such 5- or 6-membered cycloalkyl ring can be substituted with an X group.

In some embodiments R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring (e.g., cyclopentyl or cyclohexyl). Such 5- or 6-membered cycloalkyl ring can be substituted with an X group.

In certain embodiments a radiometal complex has the structure of formula (II-m):



(II-m)

wherein the variable groups are as defined above in the chelators of the invention, e.g., the chelator of formula (II); and M is a radiometal ion, preferably an alpha-emitting radiometal ion, more preferably ^{225}Ac.

Any of the chelators of formula (II) described above can be used to form radiometal complexes of formula (II-m).

In some embodiments, one of A_1, A_2, A_3, A_4, and A_5 is nitrogen, one of A_1, A_2, A_3, A_4, and A_5 is carbon substituted with -COOH and the rest are CH, i.e., forming a pyridinyl ring substituted with carboxylic acid.

In some embodiments, one of A_6, A_7, A_8, A_9, and A_{10} is nitrogen, one of A_6, A_7, A_8, A_9, and A_{10} is carbon substituted with -COOH, and the rest are CH, i.e., forming a pyridinyl ring substituted with carboxylic acid.

In one embodiment, at least one of R_1, R_2, R_3, R_4 and R_5 is -COOH. In one embodiment, at least one of R_6, R_7, R_8, R_9, and R_{10} is -COOH. In another embodiment, at least one of R_1, R_2, R_3, R_4 and R_5 is -COOH; and at least one of R_6, R_7, R_8, R_9, and R_{10} is -COOH.

In some embodiments, each of A_1 and A_{10} is nitrogen; A_2 is CR_2 and R_2 is -COOH; A_9 is CR_9 and R_9 is -COOH; each of A_3-A_8 is CR_2, CR_3, CR_4, CR_5, CR_6, CR_7, and CR_8, respectively; and each of R_3 to R_8 is hydrogen.

In one embodiment, at least one of R_1, R_2, R_3, R_4 and R_5 is tetrazolyl. In one embodiment, at least one of R_6, R_7, R_8, R_9, and R_{10} is tetrazolyl. In another embodiment, at least one of R_1, R_2, R_3, R_4 and R_5 is tetrazolyl; and at least one of R_6, R_7, R_8, R_9, and R_{10} is tetrazolyl.

In some embodiments, each R_{12} is hydrogen.

In some embodiments, R_{11} is an alkynyl group or cycloalkynyl group, preferably cyclooctynyl or a cyclooctynyl derivative, e.g., DBCO.

In particular embodiments of a radiometal complex of formula (II-m):

M is ^{225}Ac;

each of A_1 and A_{10} is nitrogen;

A_2 is CR_2 and R_2 is -COOH;

A_9 is CR_9 and R_9 is -COOH;

each of A_3-A_8 is CR_2, CR_3, CR_4, CR_5, CR_6, CR_7, and CR_8, respectively;

each of R_3 to R_8 is hydrogen;

one of Z_1 and Z_2 is $-(CH_2)_m-$ and the other of Z_1 and Z_2 is $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;

R_{12} is hydrogen;

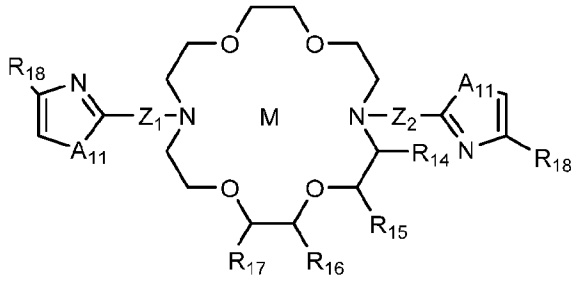
m is 1;

each n is 0;

X is $-L_1-R_{11}$, wherein L_1 is a linker and $-R_{11}$ is an electrophilic group, e.g., cyclooctynyl or cyclooctynyl derivative such as DBCO; and

each of R_{14}-R_{17} is hydrogen, or alternatively R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring.

In certain embodiments, a radiometal complex has the structure of formula (III-m):



(III-m)

wherein the variable groups are as defined above in the chelators of the invention, e.g., the chelator of formula (III); and M is a radiometal ion, preferably an alpha-emitting radiometal ion, more preferably ^{225}Ac.

Any of the chelators of formula (III) described above can be used to form radiometal complexes of formula (III-m).

In some embodiments, each A_{11} is the same, and each A_{11} is O, S, NMe, or NH. For example, each A_{11} can be S. In other embodiments, each A_{11} is different and each is independently selected from O, S, NMe, and NH.

In some embodiments, each R_{18} is independently $-(CH_2)_p-COOR_{13}$, wherein R_{13} is hydrogen and each p is independently 0 or 1.

In some embodiments, each R_{18} is -COOH.

In some embodiments, each R_{18} is $-CH_2COOH$.

In some embodiments, each R_{18} is tetrazolyl.

In particular embodiments of a radiometal complex of formula (III-m):

each R_{18} is COOH;

one of Z_1 and Z_2 is $-(CH_2)_m-$ and the other of Z_1 and Z_2 is $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;

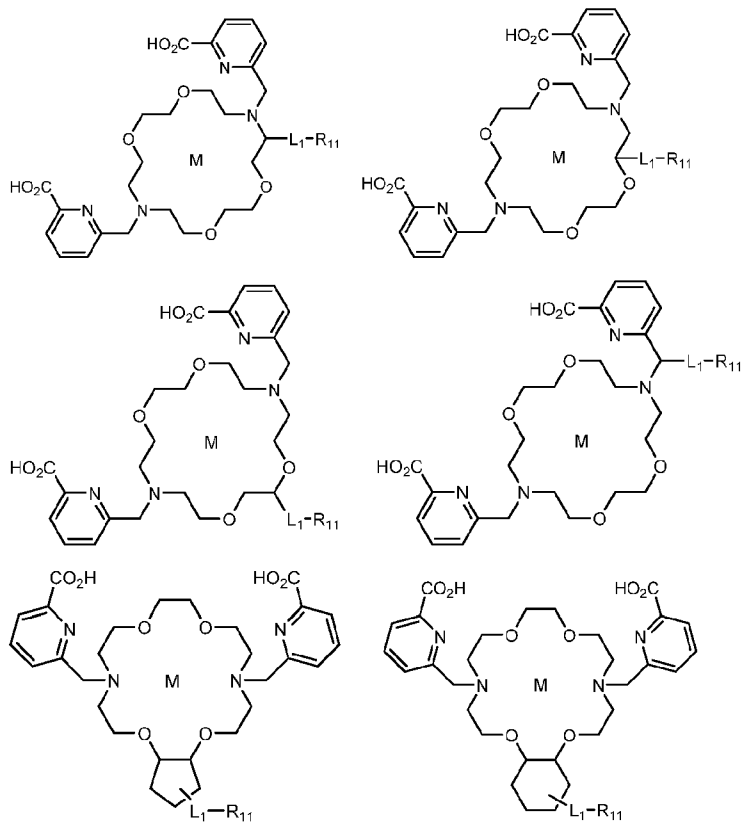
R_{12} is hydrogen;

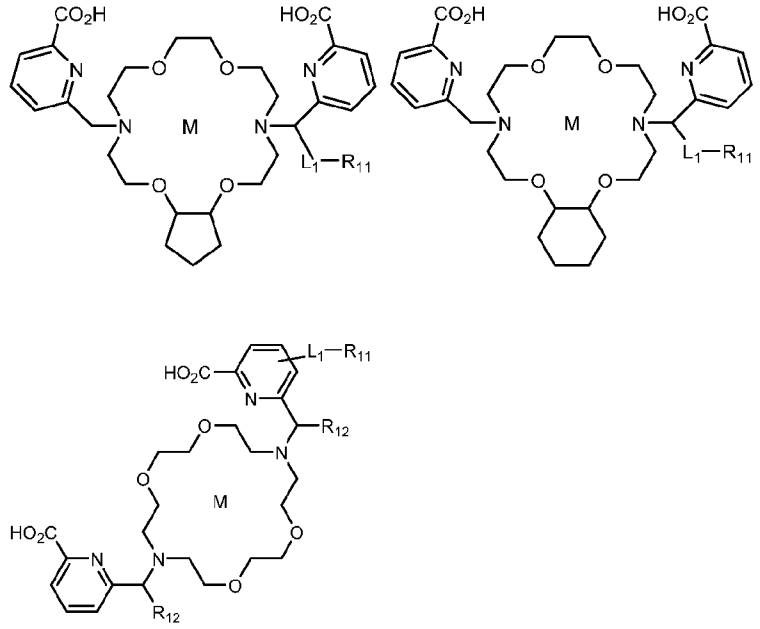
m is 1;each n is 0;

X is $-L_1-R_{11}$, wherein L_1 is a linker and $-R_{11}$ is an electrophilic group, e.g., cyclooctynyl or cyclooctynyl derivative such as DBCO; and

each of $R_{14}-R_{17}$ is hydrogen, or alternatively R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring.

In particular embodiments of the invention, a radiometal complex has one of the following structures:





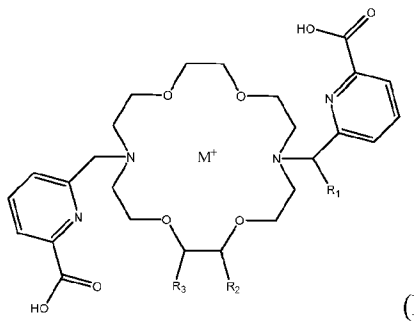
wherein:

M is actinium-225 (^{225}Ac), L_1 is absent or a linker;

R_{11} is a nucleophilic moiety or an electrophilic moiety, or R_{11} comprises an antigen binding domain (e.g., the Fab of KL2B30); and

each R_{12} is independently hydrogen, $-CH_3$, or $-CH_2CH_3$, provided at least one R_{12} is $-CH_3$ or $-CH_2CH_3$.

In certain embodiments, the invention is directed to a radiometal complex structure of formula (IV-m):



(IV-m)

or a pharmaceutically acceptable salt thereof, wherein:

M^+ is a radiometal ion, wherein M^+ is selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255

(^{255}Fm), thorium-227 (^{227}Th), thorium-226 (^{226}Th^{4+}), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

R_1 is hydrogen and R_2 is -L_1-R_4;

alternatively, R_1 is -L_1-R_4 and R_2 is hydrogen;

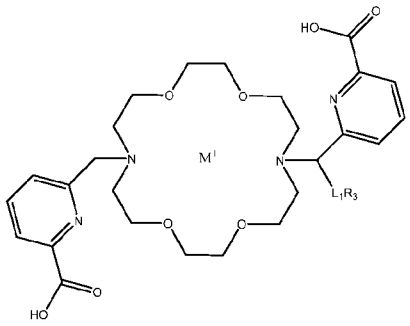
R_3 is hydrogen;

alternatively, R_2 and R_3 are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl, wherein the 5- or 6-membered cycloalkyl is optionally substituted with -L_1-R_4;

L_1 is absent or a linker;

R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain (e.g., the Fab of KL2B30).

In another embodiment, the invention is directed to a radiometal complex of formula (V-m):



(V-m)

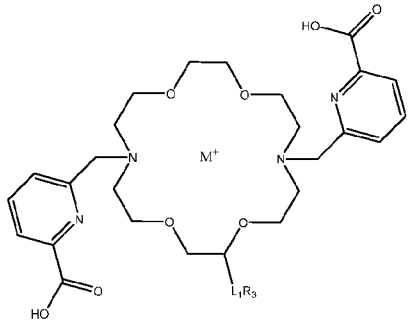
or a pharmaceutically acceptable salt thereof, wherein:

M^+ is a radiometal ion, wherein M^+ is selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 (^{226}Th^{4+}), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

L_1 is absent or a linker;

R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain (e.g., the Fab of KL2B30).

In another embodiment, the invention is directed to a compounds of formula (VI-m):



(VI-m)

or a pharmaceutically acceptable salt thereof, wherein:

M^+ is a radiometal ion, wherein M^+ is selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);L_1 is absent or a linker; and

R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain (e.g., the Fab of KL2B30).

In another embodiment, the invention is directed to a is radiometal complex wherein:

M^+ is a radiometal ion, wherein M^+ is selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);R_1 is -L_1-R_4;

R_2 and R_3 are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl;

L_1 is absent or a linker; and

R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain (e.g., the Fab of KL2B30);
or a pharmaceutically acceptable salt thereof.

In a further embodiment, the invention is directed to a radiometal complex wherein

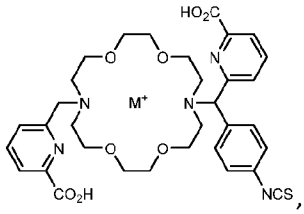
M^+ is a radiometal ion, wherein M^+ is selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);R_1 is H;

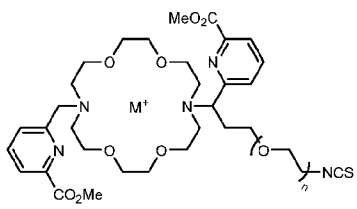
R_2 and R_3 are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl substituted with -L_1-R_4;

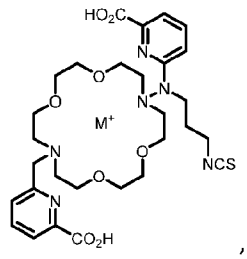
L_1 is absent or a linker; and

R_4 is a nucleophilic moiety, an electrophilic moiety, or an antigen binding domain (e.g., the Fab of KL2B30);
or a pharmaceutically acceptable salt thereof.

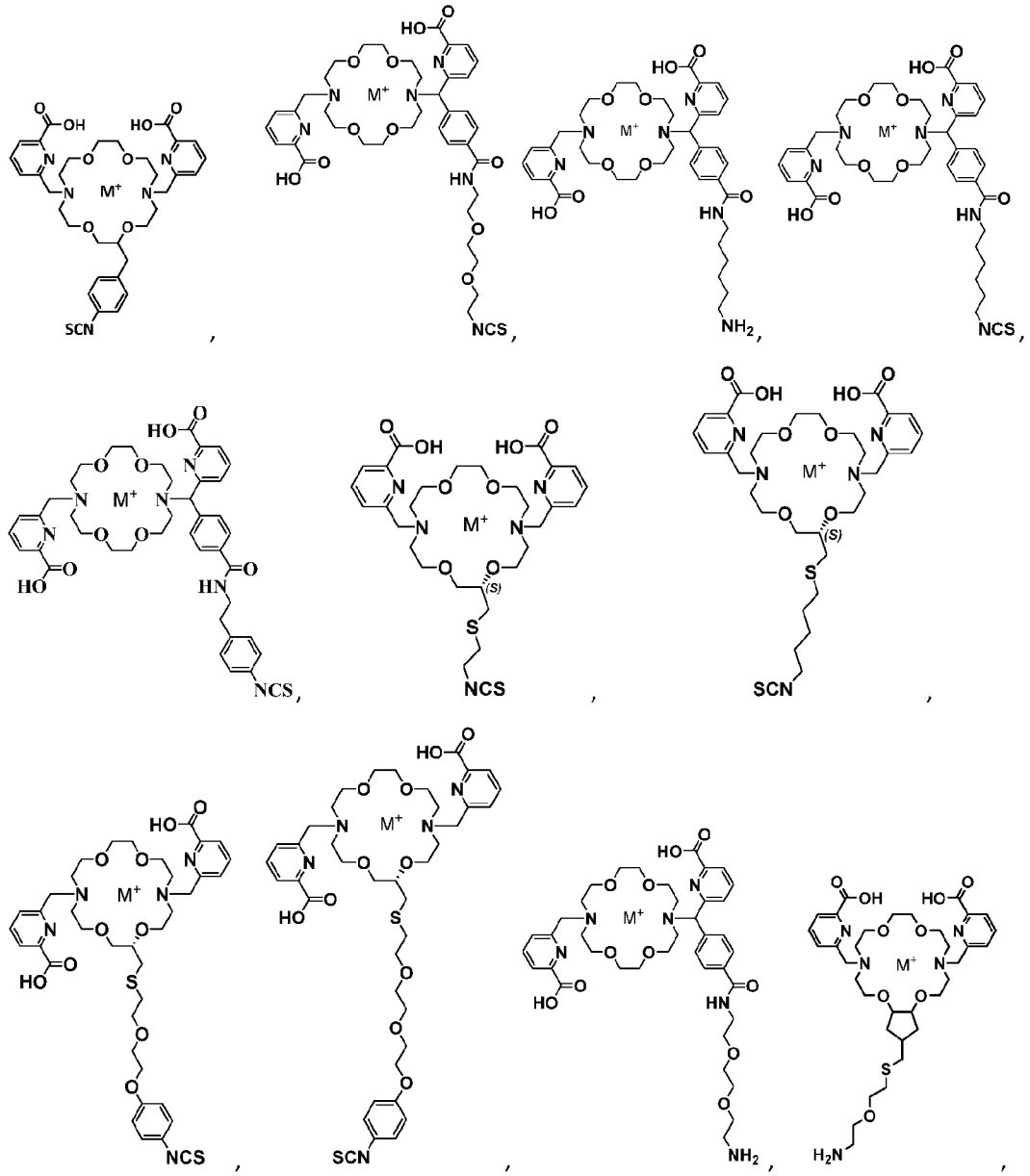
In certain embodiments, the invention is directed to any one or more radiometal complexes selected from the group consisting of:

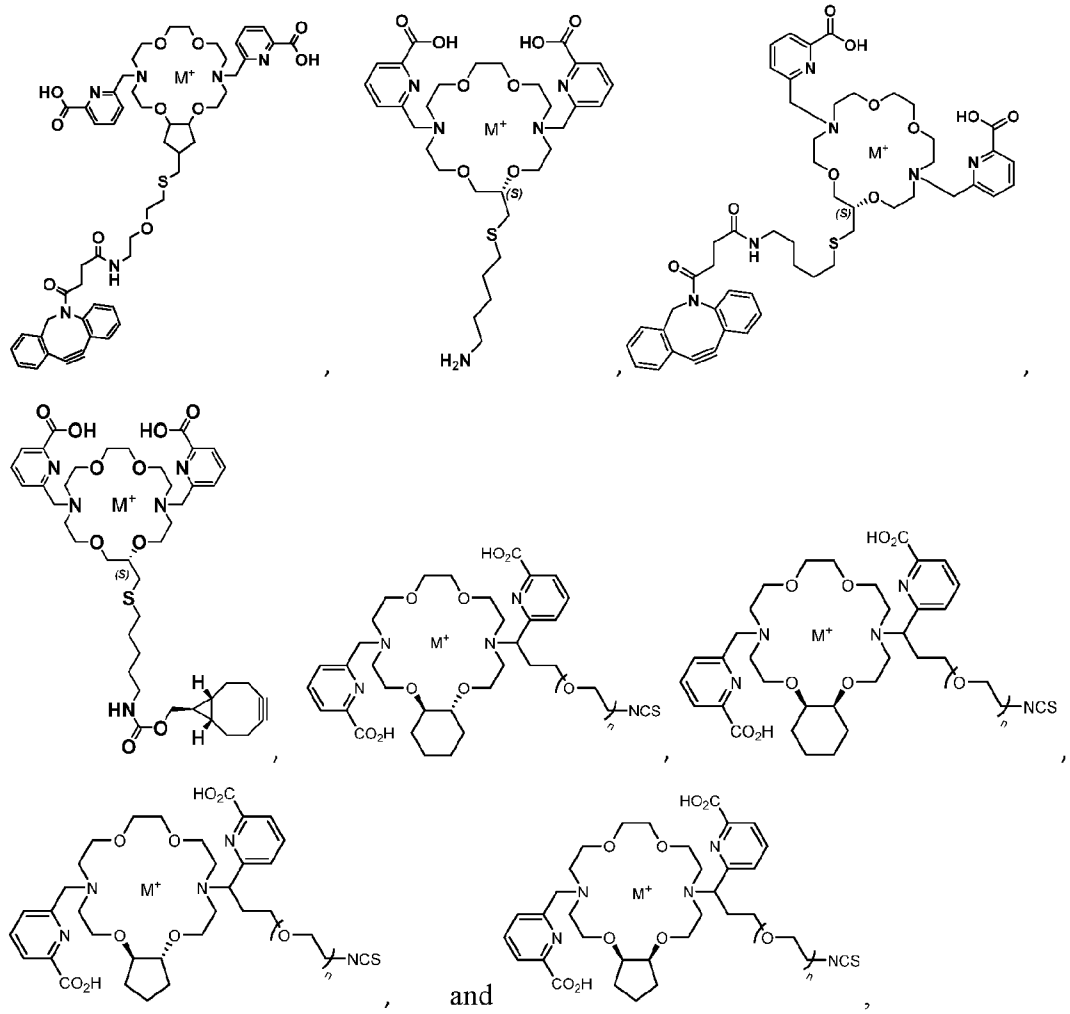


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wherein n is 1-10 and M^+ is a radiometal ion, wherein M^+ is selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U).

Radiometal complexes can be produced by any method known in the art in view of the present disclosure. For example, a chelator of the invention can be mixed with a radiometal ion and the mixture incubated to allow for formation of the radiometal complex. In an exemplary embodiment, a chelator is mixed with a solution of $^{225}Ac(NO_3)_3$ to form a radiocomplex comprising ^{225}Ac bound to the chelator via coordinate bonding. As described above, chelators of in the invention efficiently chelate radiometals, particularly ^{225}Ac. Thus, in particular

embodiments, a chelator of the invention is mixed with a solution of ^{225}Ac ion at a ratio by concentration of chelator to ^{225}Ac ion of 1:1000, 1:500, 1:400, 1:300, 1:200, 1:100, 1:50, 1:10, or 1:5, preferably 1:5 to 1:200, more preferably 1:5 to 1:100. Thus, in some embodiments, the ratio of a chelator of the invention to ^{225}Ac which can be used to form a radiometal complex is much lower than that which can be achieved with other known ^{225}Ac chelators, e.g., DOTA. The radiocomplex can be characterized by instant thin layer chromatography (e.g., iTLC-SG), HPLC, LC-MS, etc. Exemplary methods are described, for example, in WO2020/229974.

Additional Embodiments of Immunoconjugates and Radioimmunoconjugates

As described herein, chelators and radiometal complexes of the invention can be conjugated to (i.e., covalently linked to) antigen binding domains, such as an immune substance to produce immunoconjugates and/or radioimmunoconjugates that are suitable, for example, for medicinal applications in subjects, e.g., humans, such as targeted radiotherapy. Using the chelators and radiometal complexes of the invention, antigen binding domains, particularly antibodies or antigen binding fragments thereof that can bind specifically to targets of interest (such as cancer cells), can be site-specifically labeled with radiometal ions to produce radioimmunoconjugates. In particular, using the chelators and/or radiometal complexes of the invention, radioimmunoconjugates having high yield chelation of radiometal ions, particularly ^{225}Ac, and desired chelator-antibody ratio (CAR) can be produced. According to particular embodiments, methods of the present invention provide an average CAR of less than 10, less than 8, less than 6, or less than 4; or a CAR of between about 2 to about 8, or about 2 to about 6, or about 2 to about 4, or about 2 to about 3; or a CAR of about 2, or about 3, or about 4, or about 5, or about 6, or about 7, or about 8.

According to embodiments of the invention, an immunoconjugate comprises a chelator of the invention, e.g., a chelator of formula (I), formula (II), or formula (III) as described herein, covalently linked to an antibody or antigen binding fragment thereof (e.g., the Fab of KL2B30), preferably via a linker. Numerous modes of attachment with different linkages between the chelator and antibody or antigen binding fragment thereof are possible depending on the reactive functional groups (i.e., nucleophiles and electrophiles) on the chelator and antibody or antigen binding fragment thereof.

According to embodiments of the invention, a radioimmunoconjugate comprises a radiometal complex of the invention, e.g., a radiometal complex of formula (I-m), formula (II-m), or formula (III-m) as described herein, covalently linked to an antibody or antigen binding fragment thereof (e.g., the Fab of KL2B30), preferably via a linker.

Any of the chelators or radiometal complexes of the invention, such as those described herein, can be used to produce immunoconjugates or radioimmunoconjugates of the invention.

In some embodiments, a radiometal complex of a radioimmunoconjugate of the invention comprises an alpha-emitting radiometal ion coordinated to the chelator moiety of the radiocomplex. Preferably, the alpha-emitting radiometal ion is ^{225}Ac.

In particular embodiments, an antibody or antigen binding fragment thereof is linked to a radiocomplex via a triazole moiety to form a radioimmunoconjugate of the invention.

In particular embodiments, the antibody or antigen binding fragment in an immunoconjugate or radioimmunoconjugate of the application can bind specifically to a tumor antigen. Preferably, the antibody or antigen binding fragment binds specifically to hK2.

Immunoconjugates and radioimmunoconjugates of the invention can be prepared by any method known in the art in view of the present disclosure for conjugating ligands, e.g., antibodies, to chelators, including chemical and/or enzymatic methods. For example, immunoconjugates and radioimmunoconjugates can be prepared by a coupling reaction, including by not limited to, formation of esters, thioesters, or amides from activated acids or acyl halides; nucleophilic displacement reactions (e.g., such as nucleophilic displacement of a halide ring or ring opening of a strained ring system); azide-alkyne Huisgen cycloaddition (e.g., 1,3-dipolar cycloaddition between an azide and alkyne to form a 1,2,3-triazole linker); thiolyne addition; imine formation; Diels-Alder reactions between tetrazines and trans-cyclooctene (TCO); and Michael additions (e.g., maleimide addition). Numerous other modes of attachment, with different linkages, are possible depending on the reactive functional group used. The attachment of a ligand can be performed on a chelator that is coordinated to a radiometal ion, or on a chelator which is not coordinated to a radiometal ion.

According to an embodiment, a radioimmunoconjugate can be produced by covalently linking a radiometal complex of the invention to an antibody or antigen binding fragment thereof by, for example, a click chemistry reaction. Alternatively, a radioimmunoconjugate can be produced by first preparing an immunoconjugate of the invention by covalently linking a

chelator of the invention to an antibody or antigen-binding fragment thereof by, for example, a click chemistry reaction; the immunoconjugate can subsequently be labeled with a radiometal ion to produce a radioimmunoconjugate (referred to as "one-step direct radiolabeling"). Both residue-specific and site-specific methods of conjugation can be used to produce immunoconjugate and radioimmunoconjugates of the invention. Such methods are described, for example, in WO2020/229974.

According to embodiments of the invention, a method of producing a radioimmunoconjugate comprises reacting a chelator or radiocomplex of the invention, wherein R_{11} is a nucleophilic or electrophilic moiety, with an antibody or antigen binding fragment thereof (e.g., the Fab of KL2B30), or a modified antibody or antigen binding fragment thereof comprising a nucleophilic or electrophilic moiety.

In one embodiment, a method comprises reacting a chelator of the invention with an antibody or antigen binding fragment thereof, or a modified antibody or antigen binding fragment thereof comprising a nucleophilic or electrophilic functional group, to form an immunoconjugate having a covalent linkage between the chelator and antibody or antigen binding fragment thereof, or modified antibody or antigen binding fragment thereof, and reacting the immunoconjugate with a radiometal ion such that the radiometal ion binds the chelator of the immunoconjugate via coordinate binding, thereby forming the radioimmunoconjugate. This embodiment may be referred to as a "one-step direct radiolabeling" method because there is only one chemical reaction step involving the radiometal.

In another embodiment, a method comprises reacting a radiocomplex of the invention with an antibody or antigen binding fragment thereof, or a modified antibody or antigen binding fragment thereof comprising a nucleophilic or electrophilic functional group, thereby forming the radioimmunoconjugate. This embodiment may be referred to as a "click radiolabeling" method. A modified antibody or antigen binding fragment thereof can be produced by any method known in the art in view of the present disclosure, e.g., by labeling an antibody at a particular residue with a biorthogonal reactive functional group using one or more of the above described methods, or by site-specifically incorporating an unnatural amino acid (e.g., azido- or alkynyl-amino acid) into an antibody using one or more of the above described methods. The degree of labeling (DOL), sometimes called degree of substitution (DOS), is a particularly useful parameter for characterizing and optimizing bioconjugates, such as antibody modified by unnatural amino acid.

It is expressed as an average number of the unnatural amino acid coupled to a protein molecule (e.g. an antibody), or as a molar ratio in the form of label/protein. The DOL can be determined from the absorption spectrum of the labeled antibody by any known method in the filed.

In certain embodiments, as described herein, immunoconjugates and radioimmunoconjugates of the invention are prepared using a click chemistry reaction. For example, radioimmunoconjugates of the invention can be prepared using a click chemistry reaction referred to as "click radiolabeling". Click radiolabeling uses click chemistry reaction partners, preferably an azide and alkyne (e.g., cyclooctyne or cyclooctyne derivative) to form a covalent triazole linkage between the radiocomplex (radiometal ion bound to the chelator) and antibody or antigen binding fragment thereof. Click radiolabeling methods of antibodies are described in, e.g., International Patent Application No. PCT/US18/65913, entitled "Radiolabeling of Polypeptides" of which the relevant description is incorporated herein by reference. In other embodiments referred to as "one-step direct radiolabeling," an immunoconjugate is prepared using a click chemistry reaction between an antibody or antigen binding fragment thereof and a chelator; the immunoconjugate is then contacted with a radiometal ion to form the radioimmunoconjugate.

According to an embodiment, a method of preparing a radioimmunoconjugate comprises binding a radiometal ion to a chelator of the invention (e.g., via coordinate bonding).

An embodiment of the "one-step direct radiolabeling" method may be described as a method of preparing a radioimmunoconjugate comprising: contacting an immunoconjugate (i.e., polypeptide-chelator complex) with a radiometal ion to thereby form the radioimmunoconjugate, wherein the immunoconjugate comprises a chelator of the present invention. According to particular embodiments, the immunoconjugate has been formed via a click chemistry reaction between the chelator of the present invention and the polypeptide. According to particular embodiments, the radioimmunoconjugate has been formed without metal-free conditions (e.g., without any step(s) of removing or actively excluding common metal impurities from the reaction mixture). This is contrary to certain conventional methods in which it is necessary to radiolabel an antibody under strict metal-free conditions to avoid competitive (non-productive) chelation of common metals such as iron, zinc and copper, which introduce significant challenges into the production process.

In a particular embodiment, a method of preparing a radioimmunoconjugate of the invention comprises a "one-step direct radiolabeling" method comprising:

(i) providing a modified polypeptide comprising the polypeptide (e.g., antibody or antigen binding fragment thereof) covalently linked to a first click reaction partner (e.g., an azido group);

(ii) providing a chelator complex comprising a chelator of the present invention covalently linked to a second click reaction partner (e.g., an alkynyl group or cycloalkynyl group);

(iii) contacting the modified polypeptide with the chelator complex under a condition to allow the first click reaction partner (e.g., azido group) to react with the second click reaction partner (e.g., alkynyl group or cycloalkynyl group) to thereby form a polypeptide-chelator complex (i.e., immunoconjugate); and

(iv) contacting the polypeptide-chelator complex with a radiometal ion to thereby prepare the radioimmunoconjugate (wherein the radioimmunoconjugate comprises the polypeptide labeled with the radiometal ion, e.g., a modified antibody or antigen binding fragment thereof labeled with an alpha-emitting radiometal ion bound to the chelator via coordinate bonding).

According to particular embodiments, step (iv) is performed without metal-free conditions.

In an alternative embodiment, a method of preparing a radioimmunoconjugate comprises a "click radiolabeling" method comprising:

(i) providing a modified antibody or antigen binding fragment thereof comprising the antibody or antigen binding fragment thereof covalently linked to an azido group;

(ii) providing a radiocomplex comprising an alpha-emitting radiometal ion bound to a chelator via coordinate bonding, wherein the chelator is covalently linked to an alkynyl group or cycloalkynyl group; and

(iii) contacting the modified antibody or antigen binding fragment thereof with the radiocomplex under a condition to allow the azido group to react with the alkynyl group or cycloalkynyl group to thereby prepare the radioimmunoconjugate.

Conditions for carrying out click chemistry reactions are known in the art, and any conditions for carrying out click chemistry reactions known to those skilled in the art in view of

the present disclosure can be used in the invention. Examples of conditions include, but are not limited to, incubating the modified polypeptide and the radiocomplex at a ratio of 1:1 to 1000:1 at a pH of 4 to 10 and a temperature of 20°C to 70°C.

The click radiolabeling methods described above allow for chelation of the radiometal ion under low or high pH and/or high temperature conditions to maximize efficiency, which can be accomplished without the risk of inactivating the alkyne reaction partner. The efficient chelation and efficient SPAAC reaction between an azide-labeled antibody or antigen binding fragment thereof and the radiocomplex allows radioimmunoconjugates to be produced with high radiochemical yield even with low azide: antibody ratios. The only step in which trace metals must be excluded is the radiometal ion chelation to the chelating moiety; the antibody production, purification, and conjugation steps do not need to be conducted under metal free conditions.

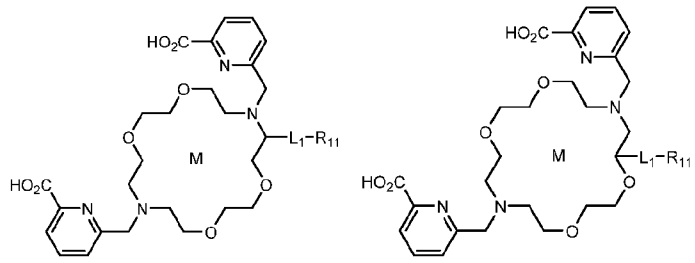
Chelators and radiometal complexes of the invention can also be used in the production of site-specific radiolabeled polypeptides, e.g., antibodies. The click radiolabeling methods described herein facilitate site-specific production of radioimmunoconjugates by taking advantage of established methods to install azide groups site-specifically on antibodies (Li, X., et al. Preparation of well-defined antibody-drug conjugates through glycan remodeling and strain-promoted azide-alkyne cycloadditions. *Angew Chem Int Ed Engl*, 2014. 53(28): p. 7179-82; Xiao, H., et al., Genetic incorporation of multiple unnatural amino acids into proteins in mammalian cells. *Angew Chem Int Ed Engl*, 2013. 52(52): p. 14080-3). Methods of attaching molecules to proteins or antibodies in a site-specific manner are known in the art, and any method of site-specifically labeling an antibody known to those skilled in the art can be used in the invention in view of the present disclosure. Examples of methods to site-specifically modify antibodies suitable for use in the invention include, but are not limited to, incorporation of engineered cysteine residues (e.g., THIOMAB™), use of non-natural amino acids or glycans (e.g., seleno cysteine, p-AcPhe, formylglycine generating enzyme (FGE, SMARTag™), etc.), and enzymatic methods (e.g., use of glycotransferase, endoglycosidase, microbial or bacterial transglutaminase (MTG or BTG), sortase A, etc.).

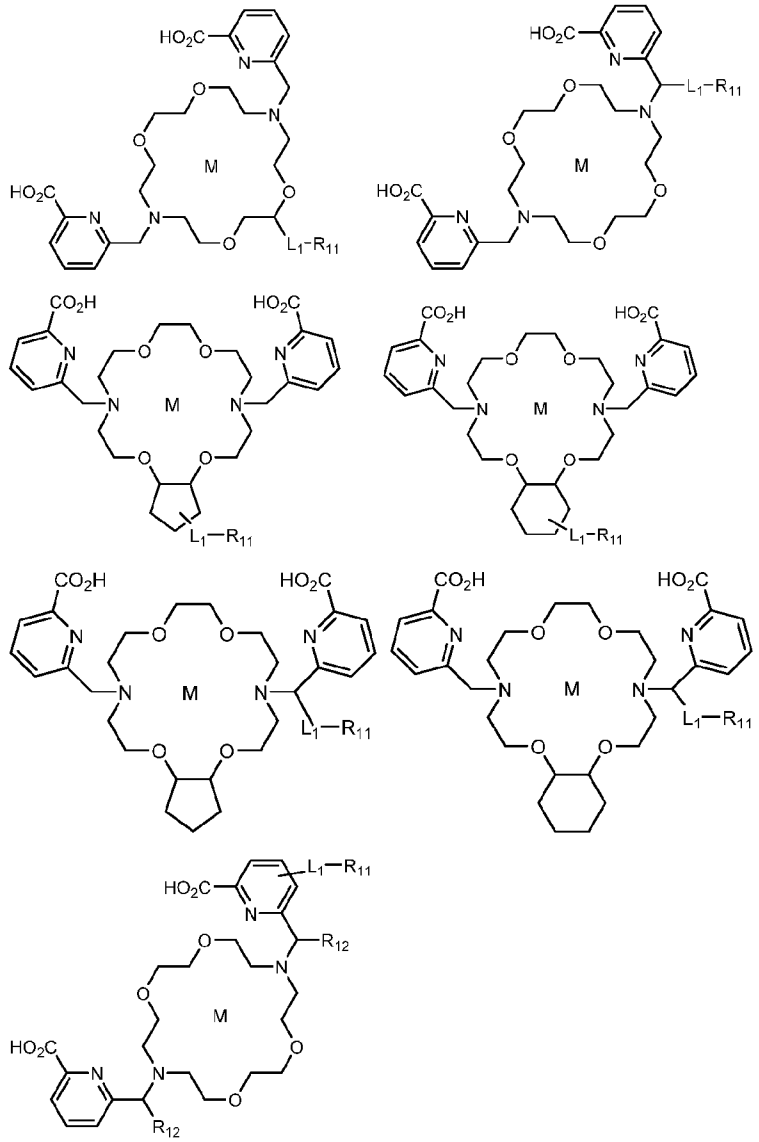
In some embodiments, a modified antibody or antigen binding fragment thereof for use in producing an immunoconjugate or radioimmunoconjugate of the invention is obtained by trimming the antibody or antigen binding fragment thereof with a bacterial endoglycosidase

specific for the β-1,4 linkage between a core GlcNac residue in an Fc-glycosylation site of the antibody, such as GlycINATOR (Genovis), which leaves the inner most GlcNAc intact on the Fc, allowing for the site-specific incorporation of azido sugars at that site. The trimmed antibody or antigen binding fragment thereof can then be reacted with an azide-labeled sugar, such as UDP-N-azidoacetylgalactosamine (UDP-GalNAz) or UDP-6-azido 6-deoxy GalNAc, in the presence of a sugar transferase, such as GalT galactosyltransferase or GalNAc transferase, to thereby obtain the modified antibody or antigen binding fragment thereof.

In other embodiments, a modified antibody or antigen binding fragment thereof for use in producing an immunoconjugate or radioimmunoconjugate of the invention is obtained by deglycosylating the antibody or antigen binding fragment thereof with an amidase. The resulting deglycosylated antibody or antigen binding fragment thereof can then be reacted with an azido amine, preferably 3-azido propylamine, 6-azido hexylamine, or any azido-linker-amine or any azido-alkyl/heteroalkyl-amine, such as an azido-polyethylene glycol (PEG)-amine, for example, O-(2-aminoethyl)-O′-(2-azidoethyl)tetraethylene glycol, O-(2-aminoethyl)-O′-(2-azidoethyl)pentaethylene glycol, O-(2-aminoethyl)-O′-(2-azidoethyl)triethylene glycol, etc., or in the presence of a microbial transglutaminase to thereby obtain the modified antibody or antigen binding fragment thereof.

Any radiometal complex described herein can be used to produce a radioimmunoconjugate of the invention. In particular embodiments, the radiometal complex has the structure of formula (I-m), formula (II-m), or formula (III-m). In particular embodiments, the radiometal complex has a structure selected from the group consisting of:



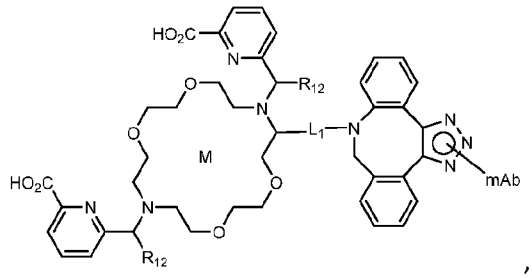


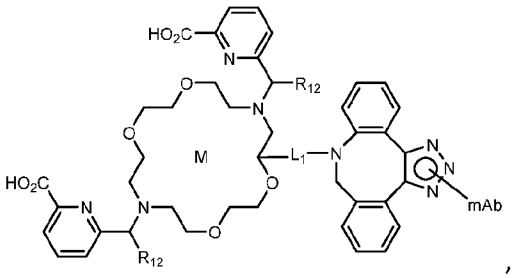
wherein M is a radiometal ion, preferably an alpha-emitting radiometal ion, more preferably actinium-225 (^{225}Ac), R_{11} is cyclooctynyl or a cyclooctynyl derivative, such as bicyclononynyl (BCN), difluorinated cyclooctynyl (DIFO), dibenzocyclooctynyl (DIBO), keto-DIBO, biarylazacyclooctynonyl (BARAC), dibenzoazacyclooctynyl (DIBAC, DBCO, ADIBO), dimethoxyazacyclooctynyl (DIMAC), difluorobenzocyclooctynyl (DIFBO), monobenzocyclooctynyl (MOBO), and tetramethoxy dibenzocyclooctynyl (TMDIBO).

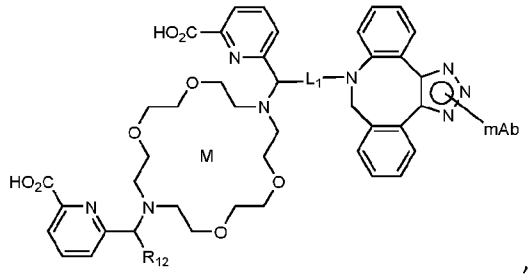
In some embodiments, an antibody or antigen binding fragment thereof is covalently linked to an azido group using any method for chemical or enzymatic modification of antibodies

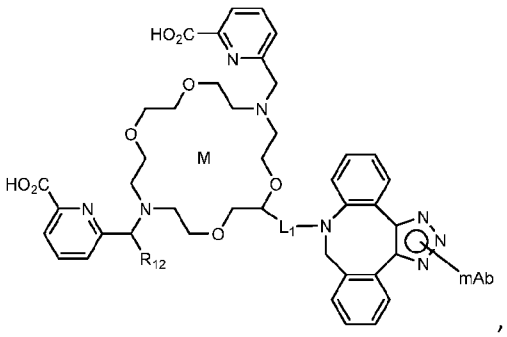
and polypeptides known to those skilled in the art in view of the present disclosure. The azido-labeled antibody or antigen binding fragment thereof is reacted with a chelator or radiometal complex of the invention comprising an alkynyl or cycloalkynyl group, preferably a cyclooctynyl group and more preferably DBCO under conditions sufficient for the azido and alkynyl or cycloalkynyl group to undergo a click chemistry reaction to form a 1,2,3-triazole moiety.

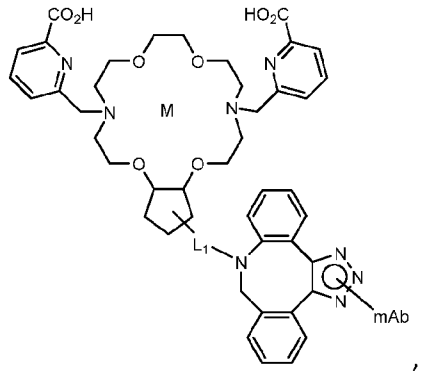
In particular embodiments, the radiommunoconjugates of the application include, but are not limited to:

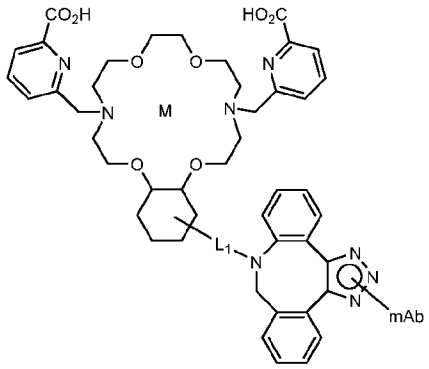


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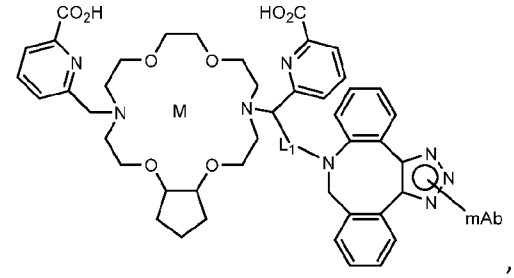
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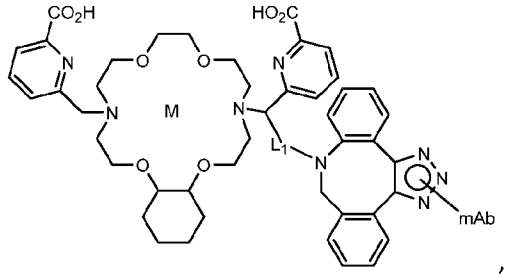
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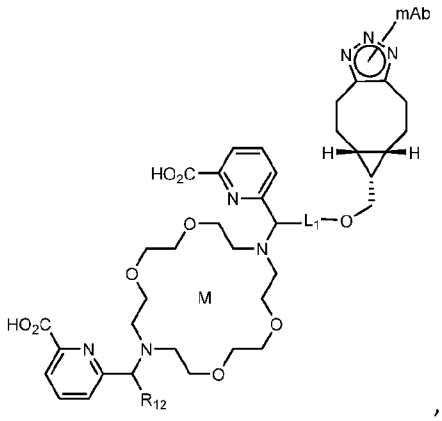
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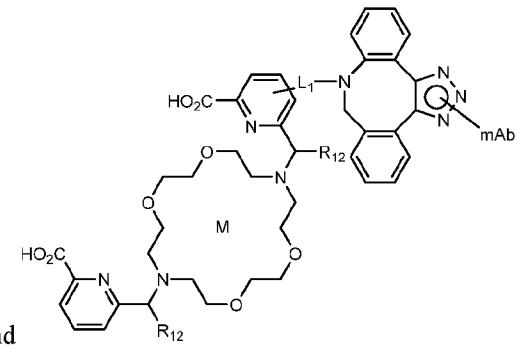
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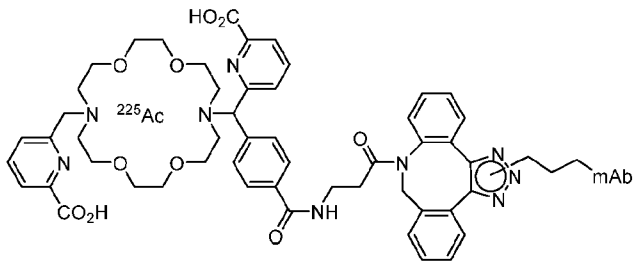
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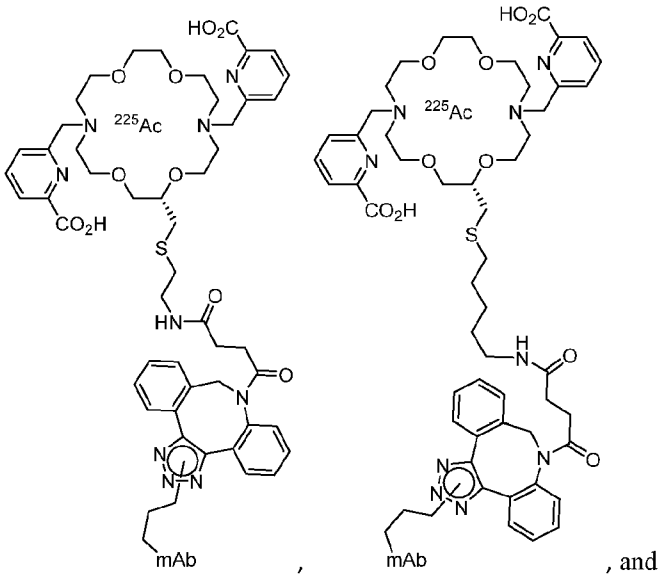
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wherein "mAb" is an antibody or antigen binding domain (e.g., the Fab of KL2B30); L_1 is absent or a linker, preferably a linker; each R_{12} is independently hydrogen, CH_3 or CH_2CH_3, provided at least one R_{12} is $-CH_3$ or $-CH_2CH_3$; and M is an alpha-emitting radionuclide, preferably ^{225}Ac.

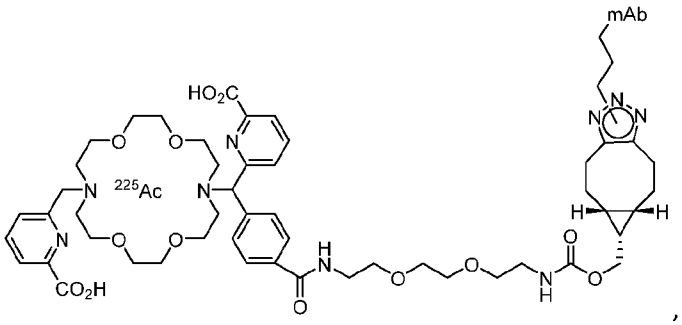
Examples of radiommunoconjugates of the application include, but are not limited to:



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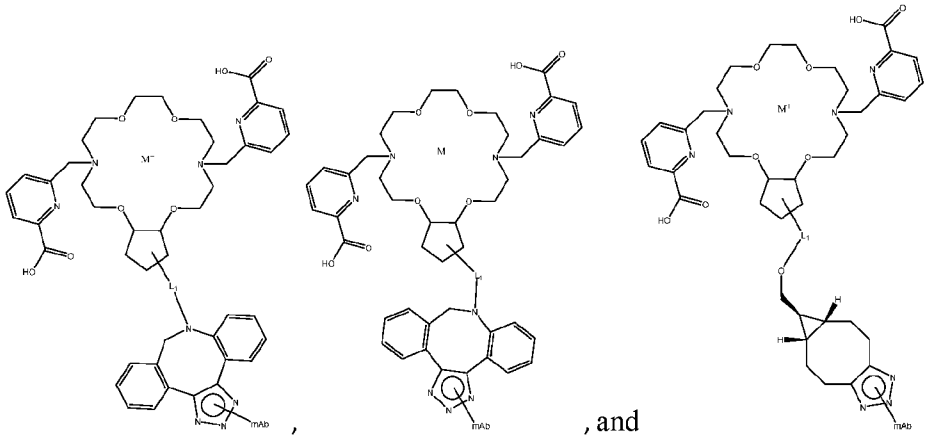
, and



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wherein "mAb" preferably refers to an antibody or antigen binding domain that has binding specificity for hK2, such as the Fab of KL2B30, or otherwise described herein.

In certain embodiments, the radioimmunoconjugate is any one or more structures independently selected from the group consisting of:



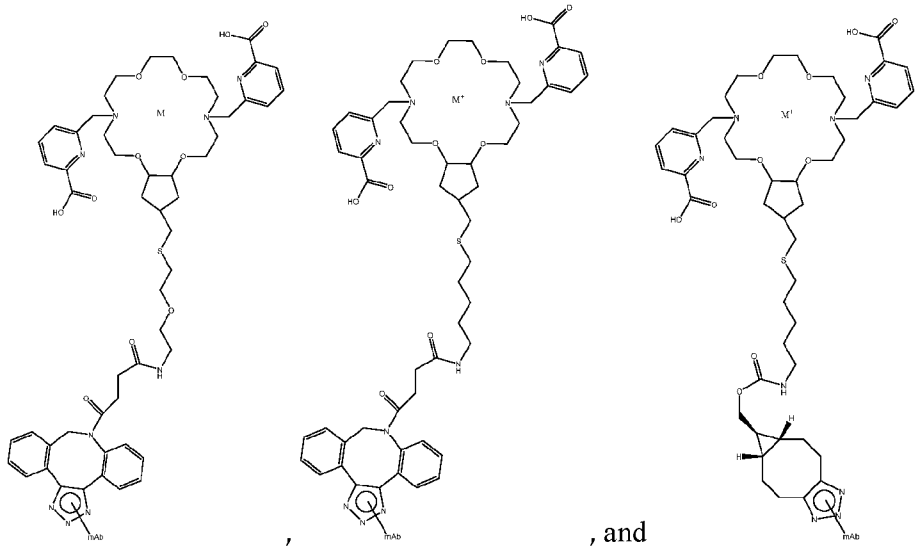
wherein:

M^+ is a radiometal ion, wherein M^+ is selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 (^{226}Th^{4+}), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

L_1 is absent or a linker; and

wherein "mAb" preferably refers to an antibody or antigen binding domain that has binding specificity for hK2, such as the Fab of KL2B30, or otherwise described herein.

In another embodiment, the radioimmunoconjugate is any one or more selected from the group consisting of:



, , and wherein "mAb" preferably refers to an antibody or antigen binding domain that has binding specificity for hK2, such as the Fab of KL2B30, or otherwise described herein.

Radioimmunoconjugates produced by the methods described herein can be analyzed using methods known to those skilled in the art in view of the present disclosure. For example, LC/MS analysis can be used to determine the ratio of the chelator to the labeled polypeptide, e.g., antibody or antigen binding fragment thereof; analytical size-exclusion chromatography can be used to determine the oligomeric state of the polypeptides and polypeptide conjugates, e.g., antibody and antibody conjugates; radiochemical yield can be determined by instant thin layer chromatography (e.g., iTLC-SG), and radiochemical purity can be determined by size-exclusion HPLC.

Pharmaceutical Compositions and Methods of Use

In another general aspect, the invention relates to a pharmaceutical composition comprising a chelator, radiometal complex, an immunoconjugate, or radioimmunoconjugate of the invention, and a pharmaceutically acceptable carrier. The pharmaceutical composition may comprise one or more pharmaceutically acceptable excipients.

In one embodiment, a pharmaceutical composition comprises a radiometal complex of the invention, and a pharmaceutically acceptable carrier.

In another embodiment, a pharmaceutical composition comprises a radioimmunoconjugate of the invention, and a pharmaceutically acceptable carrier.

As used herein, the term "carrier" refers to any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, oil, lipid, lipid containing vesicle, microsphere, liposomal encapsulation, or other material well known in the art for use in pharmaceutical formulations. It will be understood that the characteristics of the carrier, excipient or diluent will depend on the route of administration for a particular application. As used herein, the term "pharmaceutically acceptable carrier" refers to a non-toxic material that does not interfere with the effectiveness of a composition according to the invention or the biological activity of a composition according to the invention. According to particular embodiments, in view of the present disclosure, any pharmaceutically acceptable carrier suitable for use in an antibody-based, or a radiocomplex-based pharmaceutical composition can be used in the invention.

According to particular embodiments, the compositions described herein are formulated to be suitable for the intended route of administration to a subject. For example, the compositions described herein can be formulated to be suitable for parenteral administration, e.g., intravenous, subcutaneous, intramuscular or intratumoral administration.

In other general aspects, the invention relates to methods of selectively targeting neoplastic cells for radiotherapy and treating neoplastic diseases or disorders. Any of the radiocomplexes or radioimmunoconjugates, and pharmaceutical compositions thereof described herein can be used in the methods of the invention.

A "neoplasm" is an abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Neoplasms can be benign (not cancer) or malignant (cancer). A neoplasm is also referred to as a tumor. A neoplastic disease or disorder is a disease or disorder associated with a neoplasm, such as cancer. Examples of neoplastic disease or disorders include, but are not limited to, disseminated cancers and solid tumor cancers.

According to an embodiment, a method of treating prostate cancer (e.g., metastatic prostate cancer, or metastatic castration-resistant prostate cancer) in a subject in need thereof comprises administering to the subject a therapeutically effective amount of a radioimmunoconjugate as described herein, wherein the radioimmunoconjugate comprises a radiometal complex as described herein conjugated to an antigen binding domain with binding specificity for hK2, such as the KL2B30 Fab.

In an embodiment of the invention, a method of selectively targeting neoplastic cells for radiotherapy comprises administering to a subject in need thereof a radioimmunoconjugate or pharmaceutical composition of the invention to the subject.

In an embodiment of the invention, a method of treating a neoplastic disease or disorder comprises administering to a subject in need thereof a radioimmunoconjugate or pharmaceutical composition of the invention to the subject.

In an embodiment of the invention, a method of treating cancer in a subject in need thereof comprises administering to the subject in need thereof a radioimmunoconjugate or pharmaceutical composition of the invention to the subject.

Radioimmunoconjugates carry radiation directly to, for example, cells, etc., targeted by the antigen binding domain. Preferably, the radioimmunoconjugates carry alpha-emitting radiometal ions, such as ^{225}Ac. Upon targeting, alpha particles from the alpha-emitting radiometal ions, e.g., ^{225}Ac and daughters thereof, are delivered to the targeted cells and cause a cytotoxic effect thereto, thereby selectively targeting neoplastic cells for radiotherapy and/or treating the neoplastic disease or disorder.

Pre-targeting approaches for selectively targeting neoplastic cells for radiotherapy and for treating a neoplastic disease or disorder are also contemplated by the invention. According to a pre-targeting approach, an azide-labeled antibody or antigen binding fragment thereof is dosed, binds to cells bearing the target antigen of the antibody, and is allowed to clear from circulation over time or removed with a clearing agent. Subsequently, a radiocomplex of the invention, preferably a radiocomplex comprising a cyclooctyne or cyclooctyne derivative, e.g., DBCO, is administered and undergoes a SPAAC reaction with azide-labeled antibody bound at the target site, while the remaining unbound radiocomplex clears rapidly from circulation. The pre-targeting technique provides a method of enhancing radiometal ion localization at a target site in a subject.

In other embodiments, a modified polypeptide, e.g., azide-labeled antibody or antigen binding fragment thereof, and a radiocomplex of the invention are administered to a subject in need of targeted radiotherapy or treatment of a neoplastic disease or disorder in the same composition, or in different compositions.

In some embodiments, a therapeutically effective amount of a radioimmunoconjugate or pharmaceutical composition of the invention is administered to a subject to treat a neoplastic disease or disorder in the subject, such as cancer.

In other embodiments of the invention, radioimmunoconjugates and pharmaceutical compositions of the invention can be used in combination with other agents that are effective for treatment of neoplastic diseases or disorders.

Also provided are radioimmunoconjugates and pharmaceutical compositions as described herein for use in selectively targeting neoplastic cells for radiotherapy and/or for treating a neoplastic disease or disorder and/or for diagnosing a neoplastic disease or disorder; and use of a radioimmunoconjugate or pharmaceutical compositions as described herein in the manufacture of a medicament for selectively targeting neoplastic cells for radiotherapy and/or for treating a neoplastic disease or disorder.

EXAMPLES

The following examples of the invention are to further illustrate the nature of the invention. It should be understood that the following examples do not limit the invention and that the scope of the invention is to be determined by the appended claims.

Synthesis of Chelators and Immunoconjugates (Examples 1-21)

Methods of synthesis for embodiments of chelators described herein are provided, for example, in WO2020/229974, which is incorporated by reference herein. Additional synthetic methods are provided in PCT/IB2021/060350, which is incorporated by reference herein, and below in Examples 1-21.

In Examples 1-21, some synthesis products are listed as having been isolated as a residue. It will be understood by one of ordinary skill in the art that the term "residue" does not limit the physical state in which the product was isolated and may include, for example, a solid, an oil, a foam, a gum, a syrup, and the like.

Abbreviations used in the specification, particularly the Schemes and Examples, are as listed in the Table A, below:

Table A: Abbreviations

ADP	=	Adenosine Diphosphate

Alexa633 tracer	=	Alexa Fluor® 633 Hydrazide Tracer (ThermoFisher)
BSA	=	Bovine Serum Albumin
ACN or MeCN	=	Acetonitrile
ATP	=	Adenosine Triphosphate
BINAP	=	(2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl)
Brij™-35	=	Polyethylene glycol hexadecyl ether
DBCO	=	Dibenzocyclooctyl
DCM	=	Dichloromethane
DIPEA or DIEA	=	Diisopropylethylamine
DMF	=	N,N-Dimethylformamide
DMSO	=	Dimethylsulfoxide
DPPF or dppf	=	1,1'-Bis(diphenylphosphino)ferrocene
DTPA	=	Diethylene triamine pentaacetic acid
DTT	=	Dithiothrietol
EDTA	=	Ethylenediaminetetracetic acid
eGFR	=	Estimated Glomular Filtration Rate
EtOH	=	Ethanol
F12 medium	=	Gibco® F12 Nutrient Medium (ThermoFisher)
FBS	=	Fetal Bovine Serum
G418	=	Geneticin® (G418) Sulfate
GFR	=	Glomular Filtration Rate
GLP-1	=	Glucagon-like peptide 1
GRK2	=	G protein-coupled Receptor Kinase 2

HATU	=	(1-[Bis(dimethylamino)methylene-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HBSS	=	GIBCO® Hank's Balanced Salt Solution
HEPES	=	4-(2-Hydroxyethyl)-1-Piperizine Ethane Sulfonic Acid
HPLC	=	High Pressure Liquid Chromatography
HTRF	=	Homogeneous Time Resolved Fluorescence
IFG	=	Impaired fasting glucose
IGT	=	Impaired glucose tolerance
LCMS or LC/MS	=	Liquid chromatography-mass spectrometry
LDA	=	Lithium diisopropylamide
LiHMDS	=	Lithium bis(trimethylsilyl)amide
MeOH	=	Methanol
mesyl or Ms	=	Methylsulfonyl (i.e. $-SO_2-CH_3$)
mesylate or OMs	=	Methanesulfonate (i.e. $-O-SO_2-CH_3$)
MOM	=	Methoxy methyl
Ms or mesyl	=	$-SO_2-CH_3$
MsCl	=	Mesyl Chloride (i.e. CH_3-SO_2-Cl)
$NaBH(OAc)_3$	=	Sodium triacetoxyborohydride
NAFLD	=	Non-alcoholic fatty liver disease
Na_2SO_4	=	Sodium Sulfate
NASH	=	Non-alcoholic steatohepatitis
NBS	=	N-Bromosuccinimide
$NH(PMB)_3$	=	tris(4-methoxybenzyl)-λ^4-azane
NMO	=	4-Methylmorpholine N-oxide

NMP	=	N-Methyl-2-pyrrolidone
NMR	=	Nuclear Magnetic Resonance
OMs or mesylate	=	Methanesulfonate (i.e. -O-SO_2-CH_3)
OTf or triflate	=	Trifluoromethanesulfonate
OTs or tosylate	=	*p*-Toluenesulfonate
Pd/C	=	Palladium on carbon
$Pd(dba)_2$	=	Bis(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	=	[1,1'-Bis(diphenylphosphino)ferrocene] Palladium (II) Dichloride
$Pd(dppf)Cl_2•CHCl_3$	=	[1,1′-Bis(diphenylphosphino) ferrocene]chloropalladium complex with chloroform
$(1\text{-nap})_3P$ or $P(1\text{-nap})_3$	=	*Tri*(*1*-naphthyl)*phosphine*
$Pd(OAc)_2$	=	Palladium (II) acetate
$Pd(OH)_2$	=	Palladium hydroxide
$Pd(OH)_2/C$	=	Palladium hydroxide on carbon (Pearlman's Catalyst)
$Pd(PPh_3)_4$	=	Tetrakis(triphenylphosphine) palladium (0)
PEG	=	Polyethylene Glycol
PMB	=	4-Methoxybenzyl ether
PPh_3	=	Triphenylphosphine
SNS	=	Sympathetic Nervous System
TBAB	=	Tetra-n-butylammonium bromide
TBAF	=	Tetra-n-butylammonium fluoride
TBAI	=	Tetra-n-butylammonium iodide
TBSOTf	=	*Tert*-butyldimethylsilyl trifluoromethanesulfonate

TEA	=	Triethylamine
Tf or trifyl	=	Trifluoromethylsulfonyl (i.e. $-SO_2-CF_3$)
TFA	=	Trifluoroacetic Acid
THF	=	Tetrahydrofuran
THP	=	2-Tetrahydropyranyl
TLC	=	Thin Layer Chromatography
TMS	=	Trimethylsilyl
$TMSN_3$	=	Trimethylsilyl azide
Tosylate or OTs	=	*p*-Toluenesulfonate
TOPA	=	6,6'-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid = H2bp18c6
Ts or tosyl	=	-*p*-Toluenesulfonyl chloride
p-TsCl	=	*p*-Toluenesulfonyl chloride
Tween-20®	=	Nonionic detergent (Sigma Aldrich)

As used herein, unless otherwise noted, the term "isolated form" shall mean that the compound is present in a form which is separate from any solid mixture with another compound(s), solvent system or biological environment. In an embodiment of the present invention, any of the compounds as herein described are present in an isolated form.

As used herein, unless otherwise noted, the term "substantially pure form" shall mean that the mole percent of impurities in the isolated compound is less than about 5 mole percent, preferably less than about 2 mole percent, more preferably, less than about 0.5 mole percent, most preferably, less than about 0.1 mole percent. In an embodiment of the present invention, the compound of formula (I) is present as a substantially pure form.

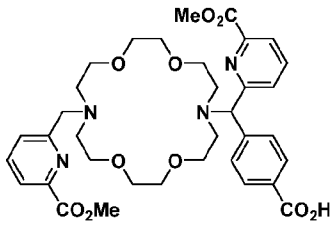
As used herein, unless otherwise noted, the term "substantially free of a corresponding salt form(s)" when used to described the compound of formula (I) shall mean that mole percent

of the corresponding salt form(s) in the isolated base of formula (I) is less than about 5 mole percent, preferably less than about 2 mole percent, more preferably, less than about 0.5 mole percent, most preferably less than about 0.1 mole percent. In an embodiment of the present invention, the compound of formula (I) is present in a form which is substantially free of corresponding salt form(s).

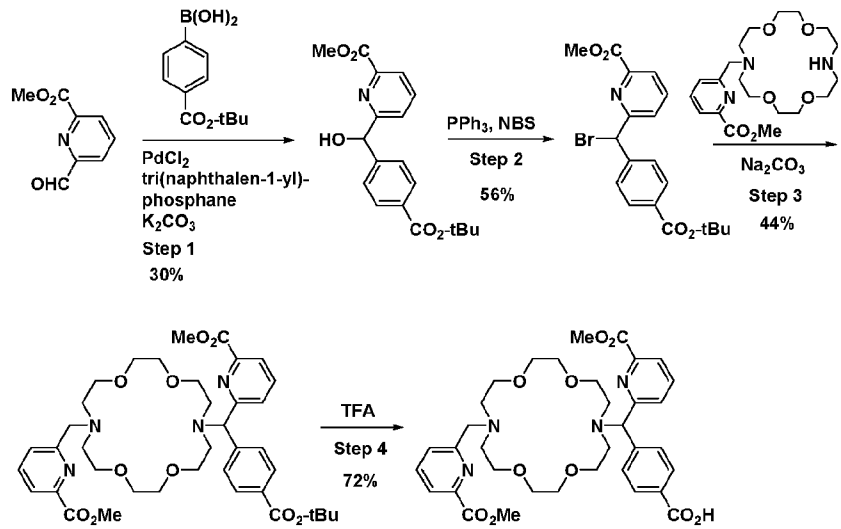
Example 1

4-((6-(methoxycarbonyl)pyridin-2-yl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)benzoic acid

(TOPA-[C-7]-Phenyl-carboxylic acid)



Scheme 1



Step 1: To a mixture of methyl 6-formylpicolinate (4.00 g, 24.2 mmol), (4-(*tert*-butoxycarbonyl)phenyl)boronic acid (10.7 g, 48.5 mmol), $PdCl_2$ (0.21 g, 1.2 mmol), tri(naphthalen-1-yl)phosphine (0.50 g, 1.2 mmol) and potassium carbonate (10.0 g, 72.7 mmol) under nitrogen at -78 °C in a 500 mL three neck round bottom flask was added tetrahydrofuran (100 mL) in one portion. The mixture was purged with nitrogen and stirred at room temperature for 30 min, then heated at 65 °C for 24 h. The reaction mixture was cooled room temperature and filtered through a pad of Celite and the filtrate was concentrated to dryness. The crude product was purified by silica gel chromatography (0-50% EtOAc/petroleum ether) to afford methyl 6-((4-(tert-butoxycarbonyl)phenyl)(hydroxy)methyl)picolinate as a yellow oil (2.5 g, 30% yield).

Step 2: A stir bar, methyl 6-((4-(tert-butoxycarbonyl)phenyl)(hydroxy)methyl)picolinate (2.50 g, 7.30 mmol), PPh_3 (3.43 g, 13.1 mmol), N-bromosuccinimide (2.13 g, 12.0 mmol) and dichloromethane (30 mL) were added to a 250 mL three neck round bottom flask under nitrogen atmosphere at room temperature and stirred for 1 h. The reaction solution was loaded onto a silica gel column and chromatography (0-30% EtOAc/ petroleum ether) gave compound methyl 6-(bromo(4-(tert-butoxycarbonyl)phenyl)methyl)picolinate (1.65 g, 56% yield) as a yellow oil.

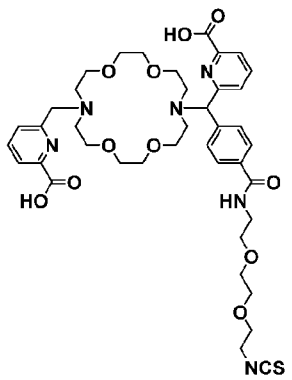
Step 3: A stir bar, methyl 6-(bromo(4-(tert-butoxycarbonyl)phenyl)methyl)picolinate (1.52 g, 3.69 mmol), methyl 6-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (1.50 g, 3.69 mmol), Na_2CO_3 (1.17 g, 11.1 mmol), and acetonitrile (30 mL) were added to a 250 mL three neck round-bottomed flask, and the resultant heterogeneous mixture was heated at 90 °C for 16 h under nitrogen atmosphere. Subsequently reaction mixture was cooled to room temperature, filtered through a pad of Celite, and concentrated to dryness in vacuo to give the crude product. The crude product was purified by silica gel chromatography (0-10% MeOH/dichloromethane) to afford methyl 6-((4-(tert-butoxycarbonyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate as a brown oil (1.2 g, 44%).

Step 4: A stir bar, methyl 6-((4-(tert-butoxycarbonyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (1.2 g, 1.6 mmol), TFA (0.62 mL, 8.1 mmol) and DCM (20 mL) were added to a 100 mL three neck round bottom flask at r.t. and stirred for 1 h. Reaction mixture was concentrated to dryness and the resultant crude product was subjected to preparative HPLC (Column: XBRIDGE C18 (19 X 150 mm) 5.0 μm; Mobile phase: 0.1% TFA in water/ACN; Flow Rate: 15.0 mL/min) to give TOPA-

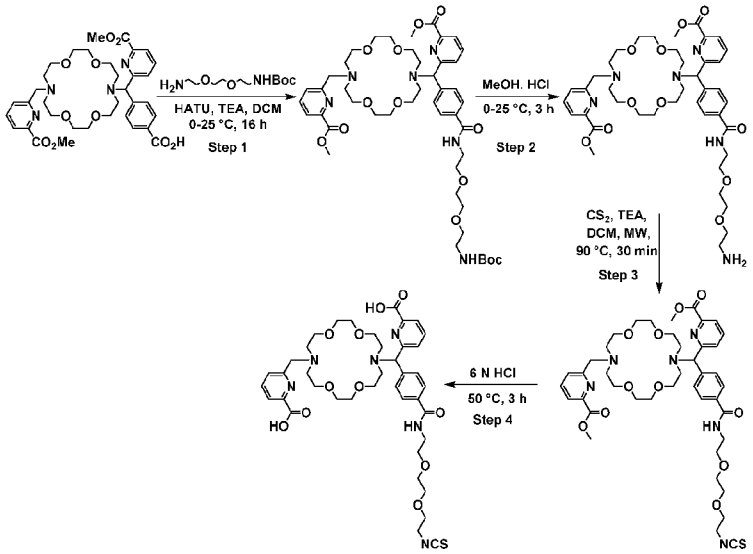
[C-7]-Phenyl-carboxylic acid (0.8 g, 72%) as brown oil. LC-MS APCI: Calculated for $C_{35}H_{44}N_4O_{10}$ 680.31; Observed *m/z* $[M+H]^+$ 681.5. Purity by LC-MS: 99.87%. Purity by HPLC: 97.14% (97.01% at 210 nm, 97.20% at 254 nm and 97.21% at 280 nm; Column: Atlantis dC18 (250 X4.6 mm), 5 µm; Mobile phase A: 0.1% TFA in water, Mobile phase B: acetonitrile; Flow rate: 1.0 mL/min.%. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.12-8.07 (m, 4H), 8.00-7.98 (m, 2H), 7.75-7.73 (m, 4H), 6.10 (s, 1H), 4.67 (s, 2H), 3.96 (s, 3H), 3.91 (s, 3H), 3.82 (s, 8H), 3.56 (s, 8H), 3.52 (s, 8H).

Example 2

6-((16-((6-Carboxypyridin-2-yl)(4-((2-(2-(2-isothiocyanatoethoxy)ethoxy)ethyl)carbamoyl)phenyl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid



Scheme 2



Step 1: A stir bar, 4-((6-(methoxycarbonyl)pyridin-2-yl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)benzoic acid (0.40 g, 0.60 mmol), *tert*-butyl (2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamate (0.15 g, 0.60 mmol), triethylamine (0.18 g, 0.76 mmol), HATU (0.33 g, 0.90 mmol), and DCM (4.0 mL) were added to a 25 mL three neck round-bottomed flask at 0 °C under nitrogen atmosphere. The mixture was stirred overnight at room temperature. The reaction was treated with water (10 mL) and extracted with dichloromethane (10 mL x 3). The combined extracts were washed with 10% aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield an oil, which was purified by silica gel chromatography (0-10% MeOH/DCM) to yield methyl 6-((4-((2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.18 g).

Step 2: A stir bar, methyl 6-((4-((2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.18 g, 0.20 mmol), MeOH (1.8 mL), and HCl in methanol (4 M, 1.0 mL, 4.0 mmol) were added to a 10 mL single-neck round-bottomed flask at 0 °C, then warmed to room temperature and stirred for 2 h. The volatiles were removed in vacuo to yield methyl 6-((4-((2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamoyl)phenyl)(16-((6-

(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.15 g), which was used without purification.

Step 3: A stir bar, methyl 6-((4-((2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.10 g, 0.12 mmol), triethylamine (37 mg, 0.37 mmol), dry DCM (2 mL), and carbon disulfide (14 mg, 0.18 mmol) were added to a pressure vial at room temperature under a nitrogen atmosphere. The vial was subjected to microwave-irradiation (150 W power) at 90 °C for 30 min. The vial was then cooled to room temperature, the reaction mixture diluted with dichloromethane (10 mL), and then washed successively with water (5 mL), 1 M HCl (5 mL), and water (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield methyl 6-((4-((2-(2-(2-isothiocyanatoethoxy)ethoxy)ethyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (100 mg), which was used without purification.

Step 4: A stir bar, methyl 6-((4-((2-(2-(2-isothiocyanatoethoxy)ethoxy)ethyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.10 g, 0.12 mmol), and aqueous HCl (6 N, 0.4 mL, 2.34 mmol) were added to a 10 mL single-neck round-bottomed flask, and stirred at 50 °C for 3 h. The reaction mixture was cooled to room temperature, concentrated to dryness in vacuo to yield an oil, which was purified by preparative HPLC (Column: XBRIDGE C18 19 X 150 mm, 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield 6-((16-((6-carboxypyridin-2-yl)(4-((2-(2-(2-isothiocyanatoethoxy)ethoxy)ethyl)carbamoyl)phenyl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid (5.0 mg). LC-MS APCI: Calculated for $C_{40}H_{52}N_6O_{11}S$: 824.34; Observed m/z $[M+H]^+$ 824.8. ^1H NMR (400 MHz, CD_3OD): δ 8.22 – 8.20 (m, 2H), 8.14-8.05 (m, 2H), 7.94 (d, J = 8.00 Hz, 2H), 7.79 (d, J = 8.00 Hz, 2H), 7.73 -7.67 (m, 2H), 6.16 (s, 1H), 4.77 (s, 2H), 3.93-4.00 (m, 8H), 3.59-3.70 (m, 27H), 3.47 – 3.44 (m, 2H).

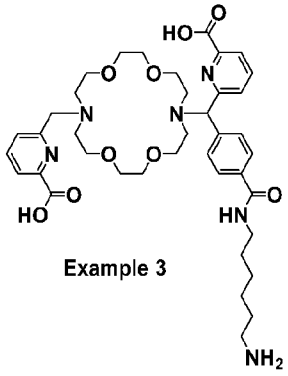
Example 3

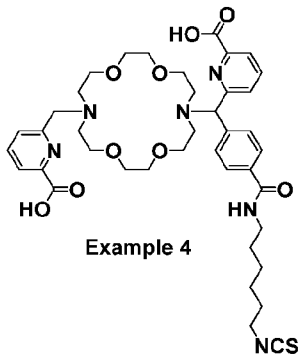
6-((4-((6-Aminohexyl)carbamoyl)phenyl)(16-((6-carboxypyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid

and

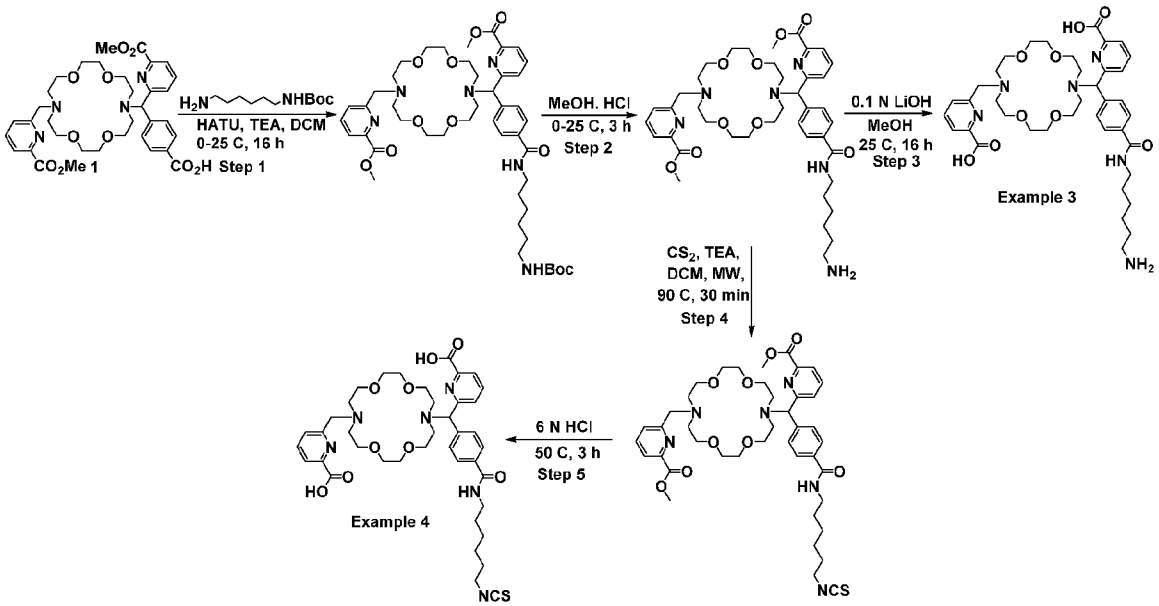
Example 4

6-((16-((6-Carboxypyridin-2-yl)(4-((6-isothiocyanatohexyl)carbamoyl)phenyl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid





Scheme 3



Step 1: A stir bar, 4-((6-(methoxycarbonyl)pyridin-2-yl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)benzoic acid (0.12 g, 0.18 mmol), *tert*-butyl (6-aminohexyl)carbamate (38 mg, 0.18 mmol), triethylamine (54 mg, 0.54 mmol), HATU (0.10 g, 0.27 mmol), and DCM (4.0 mL) were added to a 25 mL three-neck round-bottomed flask at 0 °C under a nitrogen atmosphere. The reaction mixture was then

brought to room temperature and stirred overnight. The reaction mixture was then treated with water (10 mL) and extracted with dichloromethane (10 mL x 3). The combined extracts were washed with 10% aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield an oil. The oil was purified via silica gel chromatography (0-10% MeOH/DCM) to yield methyl 6-((4-((6-((*tert*-butoxycarbonyl)amino)hexyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (70 mg) as a gummy oil.

Step 2: A stir bar, methyl 6-((4-((6-((*tert*-butoxycarbonyl)amino)hexyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (70 mg, 0.080 mmol), MeOH (1.5 mL), and HCl in methanol (4 M, 0.4 mL, 1.6 mmol) were added to a 25 mL round-bottomed flask at 0 °C, which was subsequently brought to room temperature and stirred for 2 h. The volatiles were removed in vacuo to yield methyl 6-((4-((6-aminohexyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (30 mg), which was used without purification.

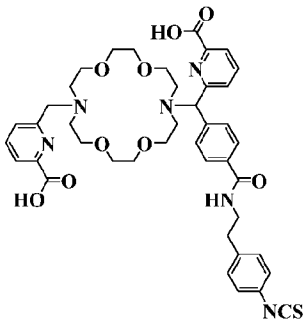
Step 3: A stir bar, methyl 6-((4-((6-aminohexyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (30 mg, 0.038 mmol), aqueous LiOH (1.1 mL, 0.1 N, 0.11 mmol), and MeOH (1.0 mL) were added to an 8 mL reaction vial and stirred overnight at room temperature. The reaction mixture was then treated with acetic acid until pH~6.5, and subsequently concentrated to dryness in vacuo at room temperature. The resultant product was subjected to preparative HPLC (Column: XBRIDGE C18 19 x 150 mm, 5.0 µm; Mobile phase: 10 mM ammonium acetate in water/ACN; Flow Rate: 15.0 mL/min) to yield **Example 3:** 6-((4-((6-aminohexyl)carbamoyl)phenyl)(16-((6-carboxypyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid (10 mg). LC-MS APCI: Calculated for $C_{39}H_{54}N_6O_9$; 750.40; Observed m/z $[M+H]^+$ 751.3. ^1H NMR (400 MHz, CD_3OD): δ 8.22 (d, J = 1.60 Hz, 2H), 8.21-8.06 (m, 2H), 7.92 (d, J = 8.40 Hz, 2H), 7.80 (d, J = 8.40 Hz, 2H), 7.75-7.69 (m, 2H), 6.20 (s, 1H), 4.70 (s, 2H), 4.02-3.92 (m, 8H), 3.76-3.62 (m, 14H), 3.51-3.32 (m, 4H), 2.93 (t, J = 8.00 Hz, 2H), 1.67-1.64 (m, 4H), 1.46-1.45 (m, 4H).

Step 4: A stir bar, methyl 6-((4-((6-aminohexyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.10 g, 0.13 mmol), triethylamine (39 mg, 0.38 mmol), dry DCM (2 mL), and carbon disulfide (15 mg, 0.19 mmol) were added to a pressure vial at room temperature under a nitrogen atmosphere. The vial was subjected to microwave irradiation (150 W power) at 90 °C for 30 min. The vial was then cooled to room temperature and the reaction mixture diluted with dichloromethane (10 mL), washed with water (5 mL), 1 M HCl (5 mL), and water (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield methyl 6-((4-((6-isothiocyanatohexyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.1 g), which was used without purification.

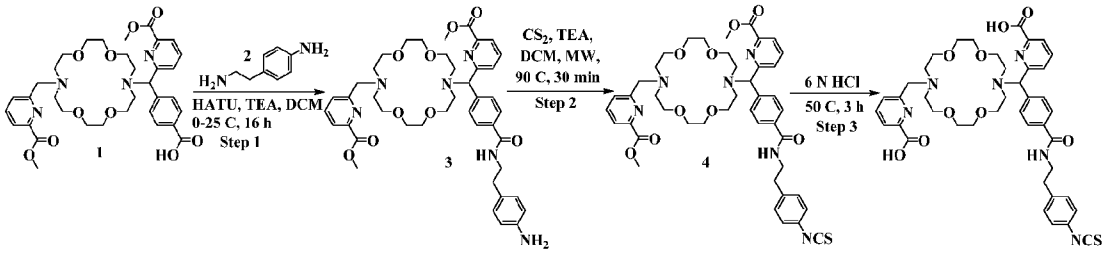
Step 5: A stir bar, methyl 6-((4-((6-isothiocyanatohexyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.10 g, 0.12 mmol), and aqueous HCl (6 N, 0.4 mL, 2.4 mmol) were added to a 10 mL round-bottomed flask, and then stirred at 50 °C for 3 h. The reaction mixture was then cooled to room temperature and concentrated to dryness in vacuo to yield a residue, which was purified by preparative HPLC (Column: XBRIDGE C18 19 X 150 mm, 3.5 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 2.0 mL/min) to yield **Example 4:** 6-((16-((6-carboxypyridin-2-yl)(4-((6-isothiocyanatohexyl)carbamoyl)phenyl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid (15 mg). LC-MS APCI: Calculated for $C_{40}H_{52}N_6O_9S$: 792.35; Observed m/z $[M+H]^+$ 792.8. ^1H NMR (400 MHz, CD_3OD): δ 8.23-8.20 (m, 2H), 8.15-8.06 (m, 2H), 7.92 (d, J = 8.40 Hz, 2H), 7.79 (d, J = 8.40 Hz, 2H), 7.74 – 7.68 (m, 2H), 6.17 (s, 1H), 4.77 (s, 2H), 4.01-3.93 (m, 8H), 3.75-3.56 (m, 16H), 3.42-3.33 (m, 5H), 1.74-1.64 (m, 4H), 1.50-1.44 (m, 4H).

Example 5

6-((16-((6-Carboxypyridin-2-yl)(4-((4-isothiocyanatophenethyl)carbamoyl)phenyl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid



Scheme 4



Step 1: A stir bar, 4-((6-(methoxycarbonyl)pyridin-2-yl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)benzoic acid (0.25 g, 0.37 mmol), 4-(2-aminoethyl)aniline (60 mg, 0.37 mmol), TEA (0.11 g, 0.15 mL, 1.1 mmol), HATU (0.21 g, 0.55 mmol), and DCM (5 mL) were added to a 25 mL three neck round-bottomed flask at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature, and then treated with water (10 mL),and extracted with dichloromethane (10 mL x3). The combined extracts were washed with 10% aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield a product which was purified by silica gel chromatography (0-10% MeOH/DCM) to yield methyl 6-((4-((4-aminophenethyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.12 g).

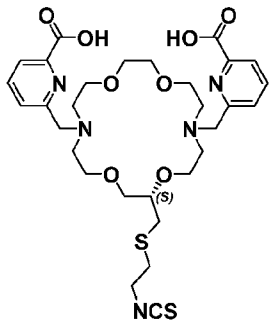
Step 2: A stir bar, methyl 6-((4-((4-aminophenethyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.12 g, 0.15 mmol), TEA (45 mg, 65 µL, 0.45 mmol), DCM (3 mL), and CS_2 (17 mg, 0.23 mmol) were added to a 10 mL microwave pressure vial at room temperature under a nitrogen atmosphere. The reaction mixture was subjected to microwave-irradiation (150 W power) at 90 °C for 30 min. The reaction mixture was then cooled to room temperature, diluted with dichloromethane (10 mL), washed successively with water (5 mL), 1 M HCl (5 mL), and water

(5 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness to yield methyl 6-((4-((4-isothiocyanatophenethyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.12 g), which was used without purification.

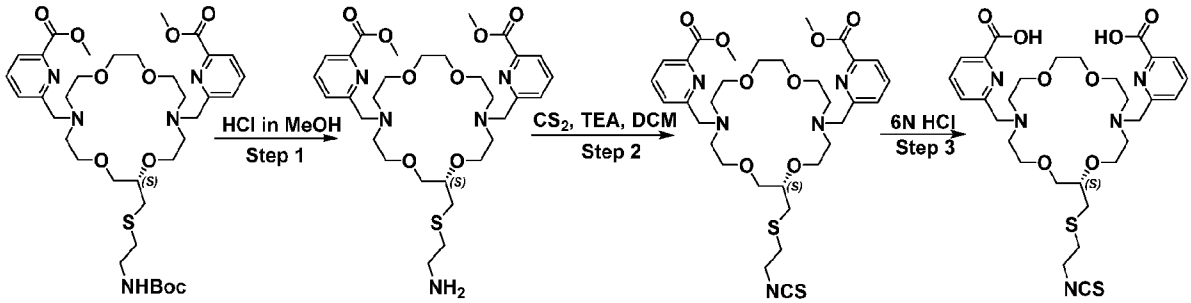
Step 3: A stir bar, methyl 6-((4-((4-isothiocyanatophenethyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.12 g, 0.14 mmol), and aqueous HCl (0.50 mL, 6 N, 2.8 mmol) were added to a 10 mL single-neck round-bottomed flask and stirred at 50 °C for 3 h. The reaction mixture was cooled to room temperature, concentrated to dryness in vacuo, and the crude product was subjected to preparative HPLC (Column: XBRIDGE C18 19 X 150 mm, 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield 6-((16-((6-carboxypyridin-2-yl)(4-((4-isothiocyanatophenethyl)carbamoyl)phenyl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid (30 mg). LC-MS APCI: Calculated for $C_{42}H_{48}N_5O_{10}S$; 812.32; Observed m/z $[M+H]^+$ 812.9. ^1H NMR (400 MHz, CD_3OD): δ 8.22 (d, J = 0.80 Hz, 2H), 8.06-8.21 (m, 2H), 7.85 (d, J = 8.40 Hz, 2H), 7.68-7.78 (m, 4H), 7.31 (d, J = 8.40 Hz, 2H), 7.21 (d, J = 2.00 Hz, 2H), 6.18 (s, 1H), 4.77 (s, 2H), 3.70-4.00 (m, 7H), 3.60-3.67 (m, 16H), 3.44-3.49 (m, 2H), 2.90-3.10 (m, 3H).

Example 6

(*S*)-6,6'-((2-(((2-Isothiocyanatoethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid



Scheme 5



Step 1: A stir bar, **1** (methyl 6-((4-((tert-butoxycarbonyl)amino)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate) (0.10 g, 0.15 mmol), MeOH (0.5 mL) and HCl in methanol (4 M, 0.6 mL, 4.0 mmol) were added to a 25 mL single-neck round-bottomed flask at 0 °C and then brought to room temperature and stirred for 2 h. The volatiles were removed in vacuo to yield dimethyl 6,6'-((2-(((2-aminoethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (55 mg), which was used in the next step without purification.

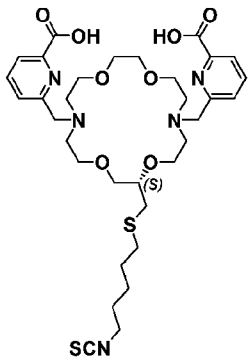
Step 2: A stir bar, dimethyl 6,6'-((2-(((2-aminoethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (50 mg, 0.10 mmol), triethylamine (24 mg, 0.24 mmol), DCM (2 mL) and carbon disulfide (12 mg, 0.16 mmol) were added to a microwave vial at room temperature under a nitrogen atmosphere. The vial was subjected to microwave-irradiation (150 W power) at 90 °C for 30 min. The vial was then cooled to room temperature and the reaction mixture diluted with dichloromethane (10 mL), washed successively with water (5 mL), 1M HCl (5 mL), water (5 mL), dried over anhydrous Na_2SO_4, concentrated to dryness and was subjected to silica gel chromatography (0-10% MeOH/DCM) to yield dimethyl 6,6'-((2-(((2-isothiocyanatoethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate as a yellow solid (20 mg).

Step 3: A stir bar, dimethyl 6,6'-((2-(((2-isothiocyanatoethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (20 mg, 0.030 mmol) and aqueous HCl (6 N, 0.1 mL, 0.6 mmol) were added to a 10 mL single-neck round-bottomed flask

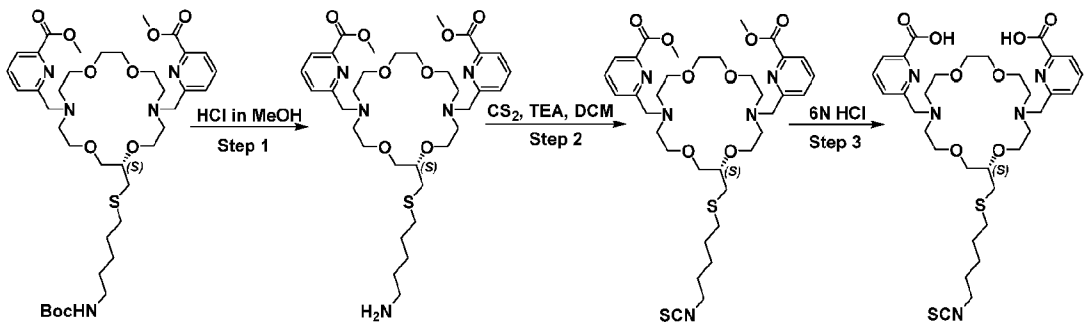
and stirred at room temperature overnight. The reaction mixture was concentrated to dryness in vacuo, and the resultant residue was subjected to preparative HPLC (Column: XBRIDGE C18 (19 X 150 mm) 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield (*S*)-6,6'-((2-(((2-isothiocyanatoethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (6 mg). LC-MS APCI: Calculated for $C_{30}H_{41}N_5O_8S_2$: 663.24; Observed *m/z* $[M+H]^+$ 664.2. ^1H NMR (400 MHz, DMSO-*d*6): δ 9.78 (s, 1H), 8.10 (s, 4H), 7.78 (d, *J* = 6.00 Hz, 2H), 4.69 (s, 4H), 3.96-3.52 (m, 23H), 2.85 (t, *J* = 6.40 Hz, 2H), 2.70 (t, *J* = 8.00 Hz, 2H) .

Example 7

(*S*)-6,6'-((2-(((5-Isothiocyanatopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid



Scheme 6



Step 1: A stir bar, dimethyl 6,6'-((2-(((5-((*tert*-butoxycarbonyl)amino)pentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 g,

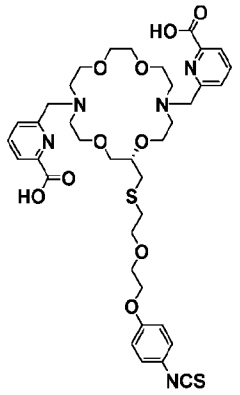
0.15 mmol), MeOH (0.5 mL), and HCl in methanol (4 M, 0.6 mL, 4.0 mmol) were added to a 25 mL single-neck round-bottomed flask at 0 °C and brought to room temperature and stirred for 2 h. The volatiles were then removed in vacuo to yield dimethyl 6,6'-((2-(((5-aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (70 mg), which was used without purification.

Step 2: A stir bar, dimethyl 6,6'-((2-(((5-aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (70 mg, 0.10 mmol), triethylamine (20 mg, 0.20 mmol) dry DCM (2 mL) and carbon disulfide (15 mg, 0.20 mmol) were added to a microwave vial at room temperature under a nitrogen atmosphere. The reaction mixture was subjected to microwave-irradiation (150 W power) at 90 °C for 30 min. The vial was brought to room temperature and the reaction mixture was diluted with dichloromethane (10 mL), washed successively with water (5 mL), 1M HCl (5 mL), and water (5 mL), dried over anhydrous sodium sulphate (Na_2SO_4), filtered and concentrated to dryness to yield a residue. The residue was subjected to silica gel chromatography (0-10% MeOH/DCM) to yield dimethyl 6,6'-((2-(((5-isothiocyanatopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(S)-dipicolinate as a yellow solid (30 mg).

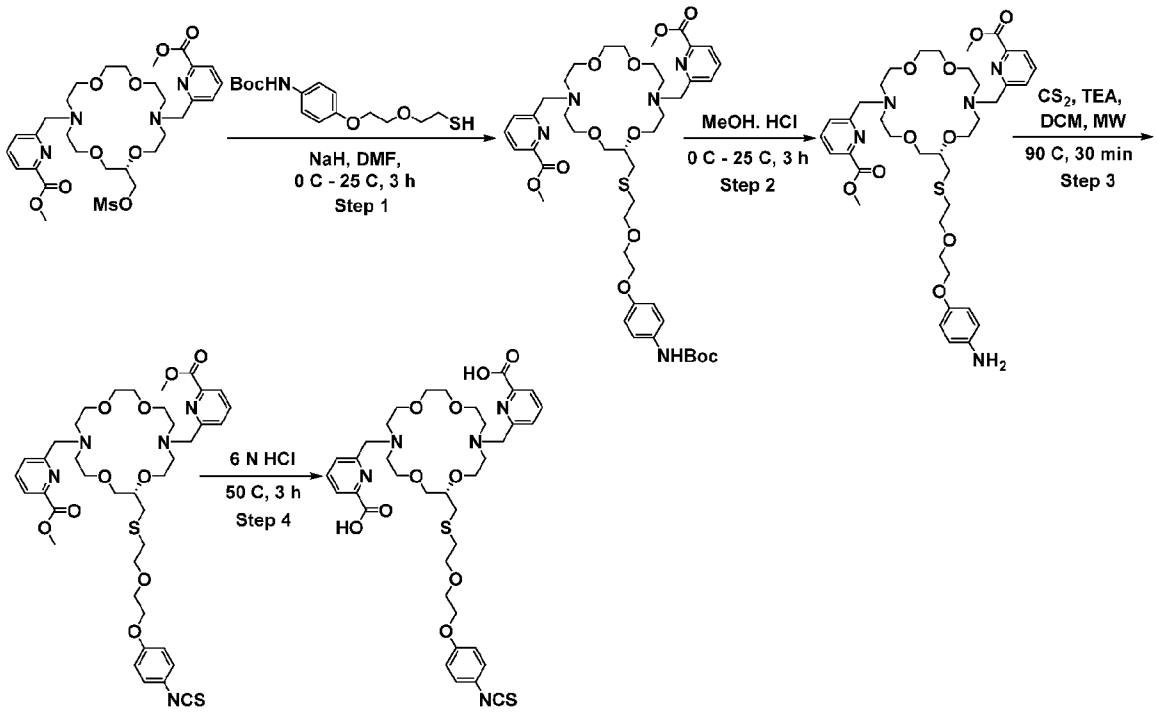
Step 3: A stir bar, dimethyl 6,6'-((2-(((5-isothiocyanatopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(S)-dipicolinate (30 mg, 0.040 mmol), and aqueous HCl (6 N, 0.2 mL, 0.8 mmol) were added to a 10 mL single-neck round-bottomed flask and stirred overnight at room temperature. The reaction mixture was concentrated to dryness in vacuo, and the concentrate was purified by HPLC (Column: XBRIDGE C18 19 X 150 mm, 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield (*S*)-6,6'-((2-(((5-isothiocyanatopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (12 mg). LC-MS APCI: Calculated for $C_{33}H_{47}N_5O_8S_2$: 705.29; Observed *m/z* $[M+H]^+$ 706.2. ^1H NMR (400 MHz, DMSO-d_6): δ 13.40 (s, 1H), 9.90 (s, 1H), 8.17-8.09 (m, 4H), 7.78 (d, J = 6.80 Hz, 2H), 4.70 (s, 4H), 3.93-3.17 (m, 27H), 2.68-2.67 (m, 2H), 1.64-1.60 (m, 2H), 1.53-1.49 (m, 2H), 1.40-1.38 (m, 2H)..

Example 8

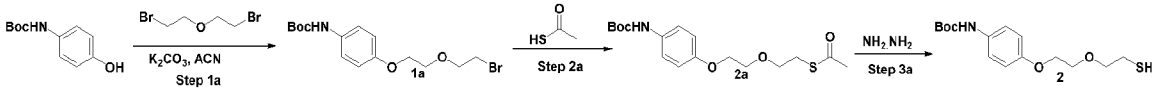
(*S*)-6,6'-((2-(((2-(2-(4-Isothiocyanatophenoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid



Scheme 7



Scheme 7a



Scheme 7a, Step 1a: A stir bar, *tert*-butyl (4-hydroxyphenyl)carbamate (4.5 g, 22 mmol), 1-bromo-2-(2-bromoethoxy)ethane (5.0 g, 22 mmol), K_2CO_3 (4.6 g, 43 mmol) and ACN (45 mL) were added to a 250 mL three-neck round-bottomed flask under nitrogen atmosphere, and the resultant reaction mixture was heated at 80 °C for 16 h under nitrogen atmosphere. Reaction mixture was cooled to room temperature, filtered through Celite®, and concentrated to dryness in vacuo to yield a concentrate which was purified by silica gel chromatography (0-20% EtOAc/pet ether) to afford product *tert*-butyl (4-(2-(2-bromoethoxy)ethoxy)phenyl)carbamate (2.0 g,).

Step 2a: A stir bar, *tert*-butyl (4-(2-(2-bromoethoxy)ethoxy)phenyl)carbamate (2.0 g, 5.6 mmol), ethanethioic S-acid (0.42 g, 5.6 mmol), K_2CO_3 (1.5 g, 11 mmol) and ACN (50 mL) were added to a 250 mL three-neck round-bottomed flask under nitrogen atmosphere. The reaction mixture stirred at 80 °C for 2 h, and then cooled to room temperature, filtered through Celite®, and concentrated to dryness in vacuo. The concentrate was purified using neutral alumina chromatography (0-50% EtOAc/pet ether) to yield *S*-(2-(2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)ethoxy)ethyl) ethanethioate (1.8 g).

Step 3a: A stir bar, *S*-(2-(2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)ethoxy)ethyl) ethanethioate (1.8 g, 5.1 mmol), ethanol (20 mL) and hydrazine monohydrate (0.24 g, 0.24 mL, 7.6 mmol) were added to a 250 mL single-neck round-bottomed flask under nitrogen, and stirred at 80 °C for 1 h. The reaction mixture was then cooled to room temperature and concentrated to dryness in vacuo, to yield a concentrate which was purified via silica gel chromatography (5-10% EtOAc/pet ether) to yield *tert*-butyl (4-(2-(2-mercaptoethoxy)ethoxy)phenyl)carbamate (0.5 g) as a colorless oil.

Scheme 7, Step 1: A solution consisting of *tert*-butyl (4-(2-(2-mercaptoethoxy)ethoxy)phenyl)carbamate (0.40 g, 1.0 mmol) and DMF (3.0 mL) was added dropwise over 5 minutes to a 50 mL three-neck round-bottomed flask containing a suspension of sodium hydride (0.060 g, 60% in mineral oil, 1.5 mmol) in DMF (3.0 mL) at 0 °C and a under nitrogen atmosphere. Once addition was complete, the reaction mixture was warmed to room temperature and stirred for 15 minutes. The mixture was re-cooled to 0 °C and a solution consisting of dimethyl 6,6'-((2-(((methylsulfonyl)oxy)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.5 g, 0.7 mmol) and DMF (3.0 mL) was added dropwise. Once addition was complete, the reaction mixture was slowly warmed to room temperature and stirred

1.5 h. The reaction was slowly treated with sat. NH_4Cl (0.2 mL) and then concentrated to dryness to yield an oil. The oil was purified by preparative HPLC (Column: XBRIDGE C18 19 X 150 mm 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield dimethyl 6,6'-((2-(((2-(2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.15 g) as a brown oil.

Step 2: A stir bar, dimethyl 6,6'-((2-(((2-(2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.15 g, 0.16 mmol), MeOH (1.0 mL) and HCl in methanol (4 M, 0.80 mL, 3.2 mmol) were added to a 25 mL single-neck round-bottomed flask at 0 °C and then brought to room temperature. and stirred for 3 h. The volatiles were removed in vacuo to yield dimethyl 6,6'-((2-(((2-(2-(4-aminophenoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 g), which was used without purification.

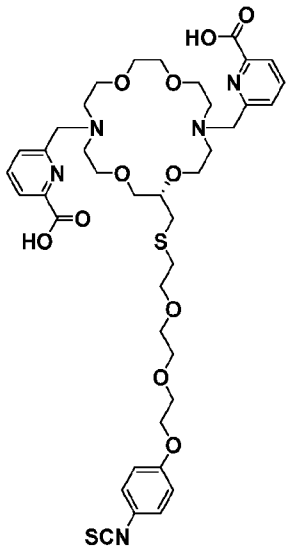
Step 3: A stir bar, dimethyl 6,6'-((2-(((2-(2-(4-aminophenoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 g, 0.15 mmol), triethylamine (46 mg, 0.46 mmol), dry DCM (3 mL) and carbon disulfide (17 mg, 0.22 mmol) were added to a pressure vial at room temperature under nitrogen atmosphere. The reaction mixture was subjected to microwave-irradiation (150 W power) at 90 °C for 30 min. The reaction mixture was cooled to room temperature and was diluted with dichloromethane (10 mL), washed successively with water (5 mL), 1M HCl (5 mL), and water (5 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness to yield dimethyl 6,6'-((2-(((2-(2-(4-isothiocyanatophenoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 g), which was used in the without purification.

Step 4: A stir bar, dimethyl 6,6'-((2-(((2-(2-(4-isothiocyanatophenoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 g, 0.15 mmol) and aqueous HCl (6 N, 0.51 mL, 3.1 mmol) were added to a 10 mL single-neck round-bottomed flask and stirred at 50 °C for 3 h. The reaction mixture was cooled to room temperature, concentrated to dryness in vacuo, and the concentrate was purified via preparative HPLC (Column: XBRIDGE C18 19 X 150 mm 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield (*S*)-6,6'-((2-(((2-(2-(4-

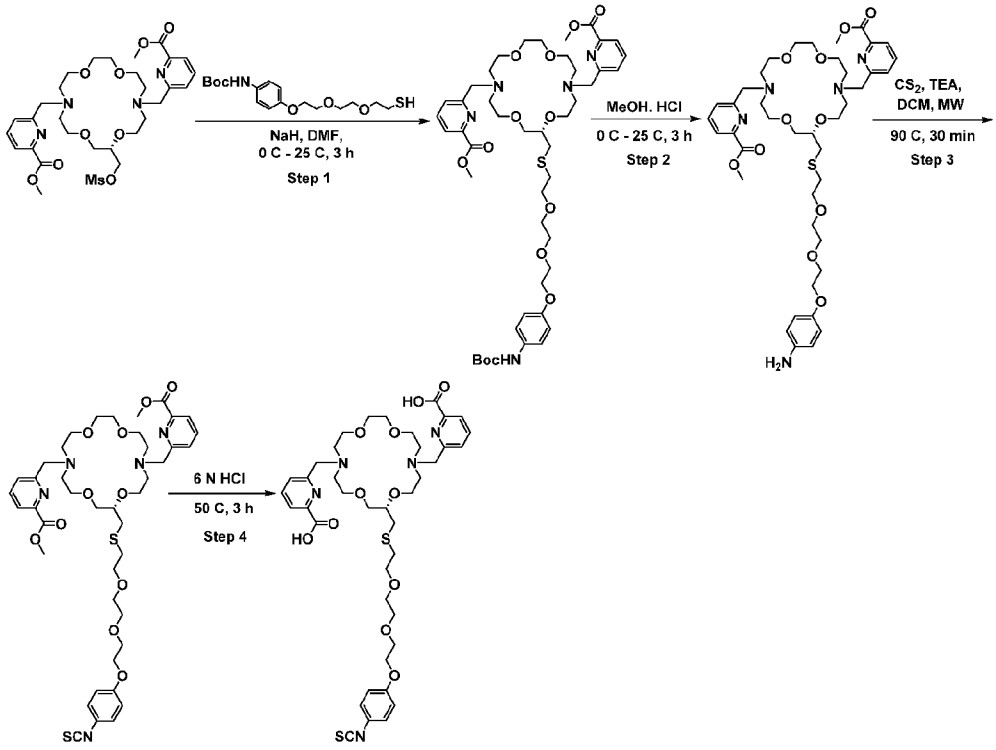
isothiocyanatophenoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (40 mg, 37%). LC-MS APCI: Calculated for $C_{38}H_{49}N_5O_{10}S_2$: 799.29; Observed *m/z* $[M+H]^+$ 799.9. ^1H NMR (400 MHz, CD_3OD): δ 8.23-8.20 (m, 2H), 8.15-8.09 (m, 2H), 7.74-7.71 (m, 2H), 7.19 (d, *J* = 8.80 Hz, 2H), 6.92 (d, *J* = 9.20 Hz, 2H), 4.81 (s, 2H), 4.77 (s, 2H), 4.09-4.11 (m, 4H), 3.92-3.95 (m, 6H), 3.79 (t, *J* = 4.00 Hz, 3H), 3.66-3.71 (m, 16H), 2.70-2.76 (m, 4H).

Example 9

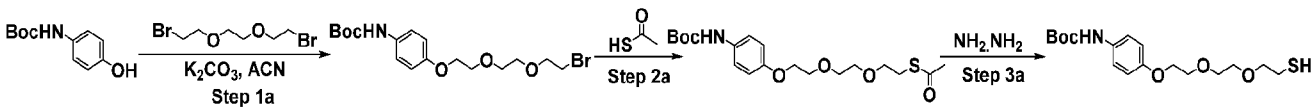
(*S*)-6,6'-((2-(((2-(2-(2-(4-Isothiocyanatophenoxy)ethoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid



Scheme 8



Scheme 8a



Scheme 8a, Step 1a: A stir bar, tert-butyl (4-hydroxyphenyl)carbamate (3.5 g, 17 mmol), 1,2-bis(2-bromoethoxy)ethane (4.6 g, 17 mmol), K_2CO_3 (4.6 g, 33 mmol) and ACN (40 mL) were added to a 250 mL three-neck round-bottomed flask, and then stirred at 80 °C for 48 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered through Celite® and concentrated to dryness in vacuo to yield a concentrate, which was purified via silica gel chromatography (0-10% MeOH/DCM) to yield *tert*-butyl (4-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)phenyl)carbamate (4.0 g) as a brown oil.

Step 2a: A stir bar, *tert*-butyl (4-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)phenyl)carbamate (4.0 g, 9.9 mmol), ethanethioic S-acid (0.75 g, 9.9 mmol), K_2CO_3 (2.7 g, 20 mmol) and ACN (50 mL) were added to a 250 mL three-neck round-bottomed flask under a nitrogen atmosphere, and the reaction mixture was heated at 60 °C for 2 h under a nitrogen atmosphere. The reaction mixture

was cooled to room temperature, filtered through Celite®, concentrated to dryness in vacuo and the concentrate was purified by alumina chromatography (0-50% EtOAc/Pet Ether) to yield *S*-(2-(2-(2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)ethoxy)ethoxy)ethyl) ethanethioate (3.0 g) as brown oil.

Step 3a: A stir bar, *S*-(2-(2-(2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)ethoxy)ethoxy)ethyl) ethanethioate (3.0 g, 7.5 mmol), ethanol (50 mL) and hydrazine monohydrate (0.36 g, 0.36 mL, 11 mmol) were added to a 250 mL single-neck round-bottomed flask under nitrogen, and stirred at 80 °C for 1 h. The reaction mixture was cooled to room temperature, concentrated to dryness in vacuo, and the concentrate was purified by silica gel chromatography (5-10% EtOAc/pet ether) to yield *tert*-butyl (4-(2-(2-(2-mercaptoethoxy)ethoxy)ethoxy)phenyl)carbamate (1.0 g) as a colorless oil.

Scheme 7, Step 1: A solution consisting of *tert*-butyl (4-(2-(2-(2-mercaptoethoxy)ethoxy)ethoxy)phenyl)carbamate (0.40 g, 1.0 mmol) and DMF (3.0 mL) was added dropwise over 5 minutes to a 50 mL three-neck round-bottomed flask containing a suspension of sodium hydride (0.060 g, 60% in mineral oil, 1.5 mmol) in DMF (3.0 mL) at 0 °C under nitrogen atmosphere. Once addition was complete, the reaction mixture brought to room temperature and stirred continuously for 15 minutes. The mixture was re-cooled to 0 °C and a solution consisting of dimethyl 6,6'-((2-(((methylsulfonyl)oxy)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.5 g, 0.7 mmol) and DMF (3.0 mL) was added dropwise over 10 minutes. Once addition was complete, the reaction mixture was slowly warmed to room temperature and stirred for 1.5 h. The reaction mixture was then slowly treated with sat. aqueous NH_4Cl (0.2 mL) and concentrated to dryness to yield an oil. The oil was purified by preparative HPLC (Column: XBRIDGE C18 (19 X 150 mm) 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield dimethyl 6,6'-((2-(((2-(2-(2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)ethoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.15 g, 21%) as a brown oil.

Step 2: A stir bar, dimethyl 6,6'-((2-(((2-(2-(2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)ethoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.15 mg, 0.16 mmol), MeOH (1.0 mL) and HCl in methanol (4 M, 0.80 mL, 3.2 mmol) were added to a 25 mL single-neck round-bottomed flask at 0 °C. The reaction mixture was allowed to warm to room temperature

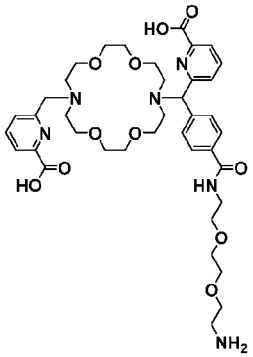
and stirred for 3 h. The volatiles were removed in vacuo to give yield dimethyl 6,6'-((2-(((2-(2-(2-(4-aminophenoxy)ethoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 g), which was used in the next step without purification.

Step 3: A stir bar, dimethyl 6,6'-((2-(((2-(2-(2-(4-aminophenoxy)ethoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 g, 0.14 mmol), triethylamine (44 mg, 0.43 mmol) dry DCM (5 mL) and carbon disulfide (17 mg, 0.22 mmol) were added to a microwave vial at room temperature under a nitrogen atmosphere. The reaction mixture subjected to microwave irradiation (150 W power) at 90 °C for 30 min. The reaction mixture was then cooled to room temperature, diluted with dichloromethane (10 mL), washed successively with water (5 mL), 1M HCl (5 mL), and water (5 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness to yield dimethyl 6,6'-((2-(((2-(2-(2-(4-isothiocyanatophenoxy)ethoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 g), which was used in the next step without purification.

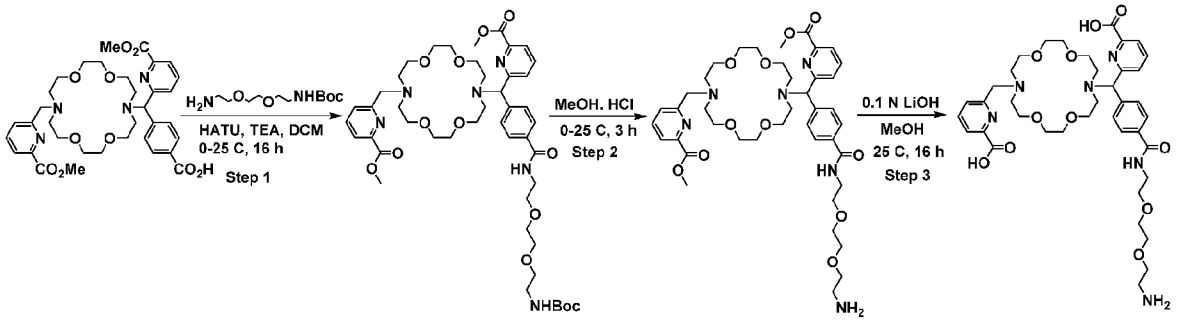
Step 4: A stir bar, dimethyl 6,6'-((2-(((2-(2-(2-(4-isothiocyanatophenoxy)ethoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 mg, 0.14 mmol) and aqueous HCl (6 N, 0.50 mL, 2.8 mmol) were added to a 10 mL single-neck round-bottomed flask and stirred at 50 °C for 3 h. The reaction mixture was cooled to room temperature, concentrated to dryness in vacuo to yield a residue which was purified by preparative HPLC (Column: XBRIDGE C18 19 X 150 mm 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield (*S*)-6,6'-((2-(((2-(2-(2-(4-isothiocyanatophenoxy)ethoxy)ethoxy)ethyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (50 mg). LC-MS APCI: Calculated for $C_{40}H_{53}N_5O_{11}S_2$: 843.32; Observed *m/z* $[M+H]^+$ 843.9. ^1H NMR (400 MHz, CD_3OD): δ 8.24-8.21 (m, 2H), 8.21-8.11 (m, 2H), 7.74 (d, *J* = 7.60 Hz, 2H), 7.23-7.20 (m, 2H), 6.97-6.95 (m, 2H), 4.84-4.79 (m, 5H), 4.14-4.12 (m, 4H), 3.97-3.94 (m, 6H), 3.83-3.59 (m, 23H), 2.75-2.67 (m, 4H).

Example 10

6-((4-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)carbamoyl)phenyl)(16-((6-carboxypyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid



Scheme 9



Step 1: A stir bar, 4-((6-(methoxycarbonyl)pyridin-2-yl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)benzoic acid (0.40 g, 0.60 mmol), *tert*-butyl (2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamate (0.15 g, 0.60 mmol), triethylamine (0.18 g, 0.76 mmol), HATU (0.33 g, 0.90 mmol), and DCM (4.0 mL) were added to a 25 mL three-neck round-bottomed flask at 0 °C under a nitrogen atmosphere. The mixture was stirred overnight at room temperature and diluted with water (10 mL),and extracted with dichloromethane (10 mL x 3). The combined extracts were washed with 10% aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield a concentrate, which was purified via silica gel chromatography (0-10% MeOH/DCM) to yield methyl 6-((4-((2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.18 g).

Step 2: A stir bar, methyl 6-((4-((2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.18 g, 0.20 mmol), MeOH (1.8 mL), and HCl in methanol (4 M, 1.0 mL, 4.0 mmol) were added to a 10 mL single-neck round-bottomed flask at 0 °C, and then brought to room temperature and stirred for 2 h. The volatiles were removed in vacuo to yield methyl 6-((4-((2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.15 g), which was used without purification.

Step 3: A stir bar, methyl 6-((4-((2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamoyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (0.1 g, 0.1 mmol), aqueous LiOH (3 mL, 0.1 N, 0.3 mmol), and MeOH (1.0 mL) were added to an 8 mL reaction vial at room temperature and stirred overnight. The reaction mixture was adjusted to pH~6.5 with acetic acid, and then concentrated to dryness in vacuo at room temperature to yield a concentrate, which was purified via preparative HPLC (Column: XBRIDGE C18 19 X 150 mm, 5.0 µm; Mobile phase: 0.1% TFA in water/ACN; Flow Rate: 15.0 mL/min) to yield 6-((4-((2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamoyl)phenyl)(16-((6-carboxypyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid (40 mg). LC-MS APCI: Calculated for $C_{39}H_{54}N_6O_{11}$; 782.39; Observed m/z [M+H]+ 783.0.

Example 11

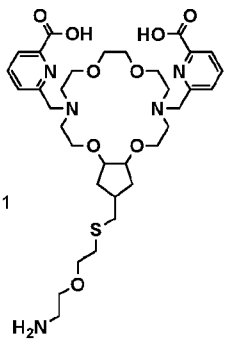
6,6'-((18-(((2-(2-Aminoethoxy)ethyl)thio)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinic acid

and

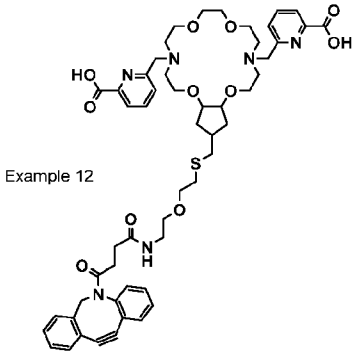
Example 12

N-acyl-DBCO tagged 6,6'-((18-(((2-(2-Aminoethoxy)ethyl)thio)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinic acid

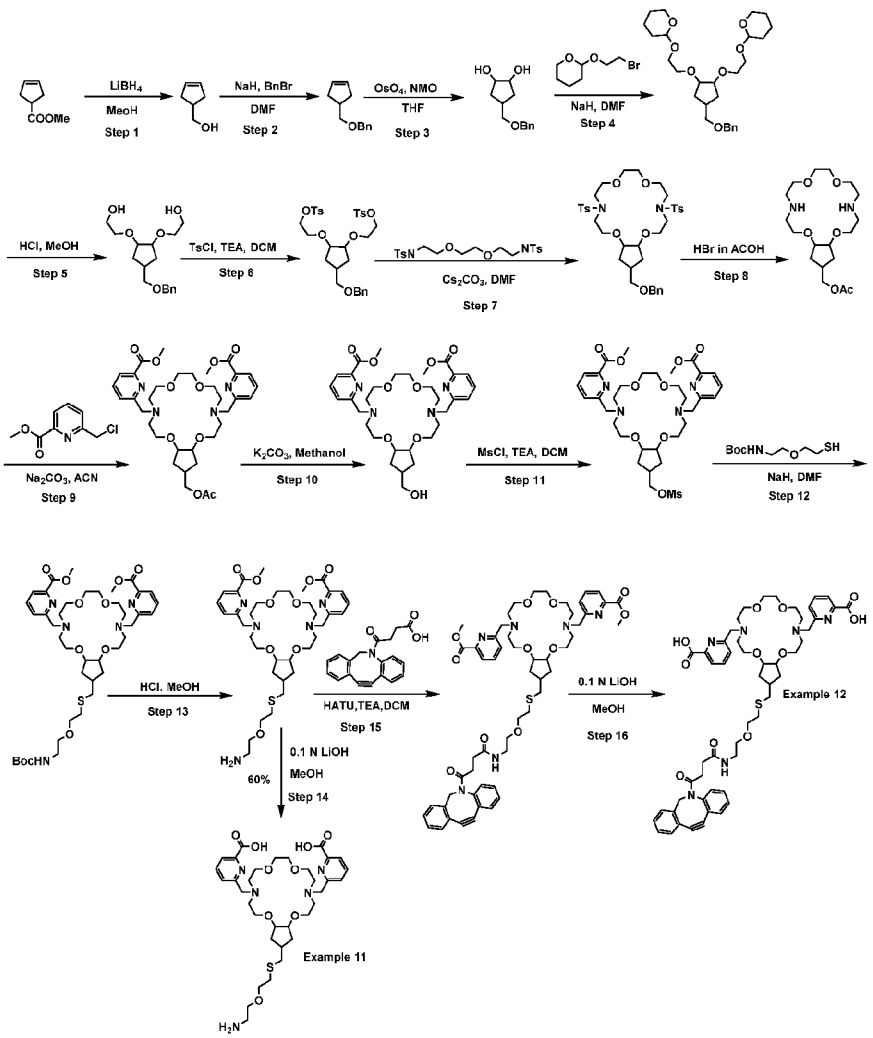
Example 11



Example 12



Scheme 10



Step 1: A stir bar, methyl cyclopent-3-ene-1-carboxylate (25.0 g, 198 mmol), THF (600 mL), methanol (12.6 g, 16.0 mL, 397 mmol) and lithium borohydride (198 mL, 2.0 M in THF, 397 mmol) were added to a 3000 mL three-neck round-bottomed flask at 0 °C. Once addition was complete, the reaction mixture was stirred at 70 °C for 6 h. The reaction mixture was then cooled to room temperature, slowly treated with ice water (250 mL), cooled further to 0 °C, brought to pH~2 with 1.5 N HCl (pH~2) and then extracted with DCM (1000 mL x 3). The combined extracts were washed with water (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to yield a concentrate which was purified by silica gel chromatography (50-80% EtOAc/pet ether) to yield cyclopent-3-en-1-ylmethanol (13.8g).

Step 2 : A solution consisting of cyclopent-3-en-1-ylmethanol (13.7 g, 139 mmol) and DMF (50 mL) was added dropwise over 30 min into a 1000 mL three-neck round-bottomed flask

containing a suspension of sodium hydride (6.69 g, 60% in mineral oil, 167 mmol) in DMF (50 mL) at 0 °C under nitrogen atmosphere. Once addition was complete, the reaction mixture was slowly warmed to room temperature and stirring continued for 30 min. The mixture was then re-cooled to 0 °C and treated dropwise over 15 min with a solution consisting of benzyl bromide (19.8 g, 167 mmol) and DMF (50 mL). Once addition was complete, the reaction mixture was slowly warmed to room temperature and then stirred for 16 h. The reaction mixture was slowly treated with sat. aqueous NH_4Cl (50 mL) and then extracted with ethyl acetate (1000 mL x 3). The combined extracts were washed with water (500 mL x 3), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield a concentrate. The concentrate was purified by silica gel chromatography (0-20% EtOAc/pet ether) to yield ((cyclopent-3-en-1-ylmethoxy)methyl)benzene (21.0 g).

Step 3: A stir bar, NMO (38.0 g, 50% wt in H_2O, 158 mmol), THF (180 mL) and osmium tetroxide (16.2 g, 3.21 mL, 2.5% wt% in *t*-butanol, 0.158 mmol) were added to a 1000 mL three-neck round-bottomed flask at 0 °C. The reaction mixture was brought to room temperature, stirred for 10 min and re-cooled to 0 °C. Once cooled, the mixture was treated dropwise over 15 min with a solution of ((cyclopent-3-en-1-ylmethoxy)methyl)benzene (20.0 g, 158 mmol) and THF (180 mL). The reaction was brought to room temperature and stirred for 16 h before it was slowly treated with sat. aqueous $NaHCO_3$ (100 mL) and extracted with DCM (1000 mL x 3). The combined extracts were washed with water (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield a concentrate, which was purified via silica gel chromatography (0-20% EtOAc/pet ether) to yield an isomeric mixture of 4-((benzyloxy)methyl)cyclopentane-1,2-diol as a colorless oil. The isomers were separated via SFC (Instrument: PIC 100; Column: Chiralpak OXH (250 x 30) mm, 5µm; Mobile phase: CO_2: 0.5% isopropyl amine in IPA (60:40); Total flow: 70 g/min; Back pressure: 100 bar; Wave length: 220 nm; Cycle time: 8.0 min) yielded both *cis*-1,2 isomers of 4-((benzyloxy)methyl)cyclopentane-1,2-diol: 1st eluting isomer (10 g) and 2nd eluting isomer (5 g).

Step 4: A solution consisting of the 1st-eluting isomer of 4-((benzyloxy)methyl)cyclopentane-1,2-diol (10.0 g, 45.0 mmol) and DMF (60 mL) was added dropwise over 1 h to a 250 mL three-neck round-bottomed flask containing a suspension of sodium hydride (8.62 g, 60% in mineral oil, 225 mmol) in DMF (60 mL) at 0 °C under a nitrogen atmosphere. Once addition was complete, the reaction mixture brought to room temperature and stirred for 30 min. The mixture

was then re-cooled to 0 °C and treated dropwise over 15 min with a solution consisting of 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (47.0 g, 225 mmol) and DMF (60 mL). Once addition was complete, the reaction mixture was slowly warmed to room temperature and stirred for 2 h. The mixture was then slowly treated with sat. aqueous NH_4Cl (50 mL) and then extracted with ethyl acetate (500 mL x 3). The combined extracts were washed with water (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield an oil, which was purified by silica gel chromatography (0-30% EtOAc/pet ether)to yield 2,2'-((((4-((benzyloxy)methyl)cyclopentane-1,2-diyl)bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(tetrahydro-2*H*-pyran) (21.0 g).

Step 5: A stir bar, 2,2'-((((4-((benzyloxy)methyl)cyclopentane-1,2-diyl)bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(tetrahydro-2*H*-pyran) (29.0 g, 61.0 mmol), MeOH (200 mL) and HCl in 1,4-dioxane (4 M, 3.0 mL, 12.0 mmol) were added to a 1000 mL three-neck round-bottomed flask and then heated at reflux for 1 h. The flask was then cooled to room temperature and the volatiles removed in vacuo to yield 2,2'-((4-((benzyloxy)methyl)cyclopentane-1,2-diyl)bis(oxy))bis(ethan-1-ol) (20.0 g) as a residue, which was used without purification.

Step 6: A stir bar, 2,2'-((4-((benzyloxy)methyl)cyclopentane-1,2-diyl)bis(oxy))bis(ethan-1-ol) (20.0 g) (20.0 g, 64.4 mmol), DCM (200 mL) and triethylamine (32.6 mL, 322 mmol) were added to a 1000 mL round-bottomed flask under a nitrogen atmosphere, and the resulting mixture was cooled to 10 °C. The mixture was then treated with pTsCl (36.9 g, 193 mmol) which was added portion-wise and then brought to room temperature. Once addition was complete the reaction mixture was stirred for 16 h during which time a precipitate formed. The mixture was then diluted with DCM (500 mL), washed with cold aq. HCl (1 M, 500 mL x 3) and ice-cold water (500 mL x 2), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield a residue which was purified via silica gel chromatography (0-30% EtOAc/pet ether) to yield ((4-((benzyloxy)methyl)cyclopentane-1,2-diyl)bis(oxy))bis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (26.0 g).

Step 7: A stir-bar, *N*,*N*'-((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(4-methylbenzenesulfonamide) (21.0 g, 42.0 mmol), Cs_2CO_3 (41.3 g, 126 mmol) and dry DMF (250 mL) were added to a 2000 mL three-neck round-bottomed flask under nitrogen atmosphere, and the resultant heterogeneous mixture stirred at room temperature for 1.5 h. The mixture was then treated dropwise with a solution consisting of ((4-((benzyloxy)methyl)cyclopentane-1,2-

diyl)bis(oxy))bis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (26.0 g, 42.0 mmol) and DMF (250 mL) over a period of 2 h. Stirring was continued for 20 h, before the mixture was concentrated to dryness in vacuo to yield a paste-like solid. The paste was suspended in DCM (1000 mL), stirred for 30 min, and filtered by vacuum filtration. The filtrate was concentrated to dryness in vacuo to yield a concentrate, which was purified by silica gel chromatography (0-40% EtOAc/pet ether) to yield 18-((benzyloxy)methyl)-4,13-ditosyltetradecahydro-2*H*,11*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine (24 g).

Step 8: A HOAc solution of HBr (50%, 112 mL, 695 mmol) was added to a 500 mL round-bottomed flask containing a stir bar and 18-((benzyloxy)methyl)-4,13-ditosyltetradecahydro-2*H*,11*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine (24.0 g, 32.8 mmol) under a nitrogen atmosphere. The mixture was stirred at room temperature until homogeneous and then treated with phenol (16.3 g, 174 mmol). The reaction mixture was then heated at 60 °C for 6 h, before cooling to room temperature and concentrating to dryness in vacuo to yield a concentrate. The concentrate was purified via reverse-phase column chromatography (Column: Revelris C18-330 g; Mobile phase A: 0.1% TFA in water, Mobile phase B: acetonitrile; Flow rate: 60 mL/min) to yield (tetradecahydro-2*H*,11*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecin-18-yl)methyl acetate (8.0 g).

Step 9: A stir bar, (tetradecahydro-2*H*,11*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecin-18-yl)methyl acetate (8.0 g, 21 mmol), methyl 6-(chloromethyl)picolinate (12.2 g, 53.2 mmol), Na_2CO_3 (11.1 g, 106 mmol) and acetonitrile (100 mL) were added to a 500 mL three-neck round-bottomed flask under a nitrogen atmosphere, and the resultant heterogeneous mixture heated at 90 °C for 16 h under a nitrogen atmosphere. The resulting mixture was then cooled to room temperature, filtered through a pad of Celite®, and the filtrate concentrated to dryness in vacuo to yield a concentrate. The concentrate was subjected to silica gel chromatography (0-10% MeOH/DCM) to yield dimethyl 6,6'-((18-(acetoxymethyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (5.0 g).

Step 10 : A stir bar, dimethyl 6,6'-((18-(acetoxymethyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (5.0 g, 7.4 mmol), K_2CO_3 (0.10 g, 0.74 mmol) and methanol (50

mL) were added to a 250 mL round-bottomed flask under nitrogen atmosphere, and the resulting mixture was stirred at room temperature for 10 min. The mixture was then concentrated to dryness in vacuo and the resulting residue purified by silica gel chromatography (0-10% MeOH/DCM) to yield 6,6'-((18-(hydroxymethyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (3.0 g).

Step 11: A stir bar, 6,6'-((18-(hydroxymethyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (2.0 g, 3.1 mmol), DCM (20 mL) and triethylamine (1.2 g, 9.5 mmol) were added to a 100 mL three-neck round-bottomed flask under a nitrogen atmosphere, and the resulting mixture cooled to 10 °C. The mixture was treated with MsCl (0.48 g, 6.3 mmol) portion wise, and once addition was complete, the reaction vessel was brought to room temperature and stirred for 30 minutes, during which time a precipitate formed. The heterogeneous mixture was then diluted with DCM (50 mL), washed with cold aq. HCl (1 M, 50 mL x 3) and ice-cold water (50 mL x 2), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield a gummy solid. The gummy solid was purified by neutral alumina column chromatography (0-10% MeOH/DCM) to yield dimethyl 6,6'-((18-(((methylsulfonyl)oxy)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (1.5 g).

Step 12: A solution consisting of dimethyl 6,6'-((18-(((methylsulfonyl)oxy)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (0.69 g, 3.2 mmol) and DMF (5 mL)was added dropwise over 5 minutes to a 25 mL three-neck round-bottomed flask containing a suspension of sodium hydride (162 mg, 60% in mineral oil, 4.22 mmol) in DMF (0.5 mL), at 0 °C under nitrogen atmosphere. Once addition was complete, the reaction mixture was brought to room temperature and stirred 15 minutes. The reaction mixture was then re-cooled to 0 °C and treated dropwise over 5 minutes with a solution consisting of *tert*-butyl (2-(2-mercaptoethoxy)ethyl)carbamate (1.50 g, 2.11 mmol) and DMF (3 mL). Once addition was complete, the reaction mixture was slowly warmed to room temperature and then stirred for 1 h. The reaction was then slowly treated with sat.

NH_4Cl and subsequently extracted with ethyl acetate (10 mL x 3). The combined extracts were washed with water (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield an oil. The oil was purified via preparative HPLC (Column: XBRIDGE C18 19 X 150 m) 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (0.2 g).

Step 13: A stir bar, cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (0.20 g, 0.24 mmol), MeOH (1.0 mL), and HCl in methanol (4 M, 1.2 mL, 4.8 mmol) were added to a 25 mL single-neck round-bottomed flask at 0 °C and the resulting mixture brought to room temperature, and stirred for 2 h. The volatiles were removed in vacuo to yield dimethyl 6,6'-((18-(((2-(2-aminoethoxy)ethyl)thio)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (150 mg), which was used without purification.

Step 14: A stir bar, dimethyl 6,6'-((18-(((2-(2-aminoethoxy)ethyl)thio)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (40 mg, 0.054 mmol), aqueous LiOH (1.6 mL, 0.1 N, 0.16 mmol) and MeOH (0.5 mL) were added to an 8 mL reaction vial at room temperature and the resulting mixture was stirred overnight. The pH of the reaction mixture was adjusted with acetic acid to pH~6.5 and then concentrated to dryness in vacuo at room temperature, and the resultant concentrate was purified by preparative HPLC (Column: XBRIDGE C18 19 X 150 mm 5.0 µm; Mobile phase: 10Mm Ammonium Acetate in water/ACN; Flow Rate: 15.0 mL/min) to yield

Example 11: 6,6'-((18-(((2-(2-aminoethoxy)ethyl)thio)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinic acid(23 mg). LC-MS APCI: Calculated for $C_{34}H_{51}N_5O_9S$; 705.34; Observed m/z $[M+H]^+$ 706.4.

Step 15: A stir bar, dimethyl 6,6'-((18-(((2-(2-aminoethoxy)ethyl)thio)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (70 mg, 0.95 mmol), 11,12-Didehydro-γ-oxodibenz[b,f]azocine-5(6H)-butanoic acid (29 mg, 0.95 mmol), triethylamine (29 mg, 0.76 mmol), HATU (54 mg, 0.14 mmol) and DCM (0.5 mL) were added to a 25 mL three-neck round-bottomed flask at 0 °C under a nitrogen atmosphere. The resulting mixture was brought to room temperature and stirred

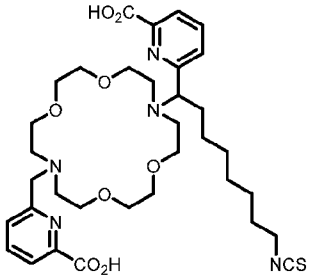
overnight. The reaction mixture was diluted with water (10 mL) and the extracted with dichloromethane (10 mL x 3). The combined extracts were washed with 10% aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield an oil. The oil was purified via silica gel chromatography (0-10% MeOH/DCM) to yield *N*-acyl-DBCO tagged dimethyl 6,6'-((18-(((2-(2-aminoethoxy)ethyl)thio)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (10 mg).

Step 16: A stir bar, *N*-acyl-DBCO tagged dimethyl 6,6'-((18-(((2-(2-aminoethoxy)ethyl)thio)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinate (10 mg, 0.01 mmol), aqueous LiOH (0.3 mL, 0.1 N, 0.03 mmol) and methanol (0.25 mL) were added to an 8 mL reaction vial at room temperature and the resultant mixture stirred overnight. The reaction mixture was adjusted to pH~6.5 with acetic acid, concentrated to dryness in vacuo at room temperature, and the resultant concentrate was purified by preparative HPLC (Column: XBRIDGE C18 (19 X 150 mm) 5.0 µm; Mobile phase: 10Mm Ammonium Acetate in water/ACN; Flow Rate: 15.0 mL/min) to yield

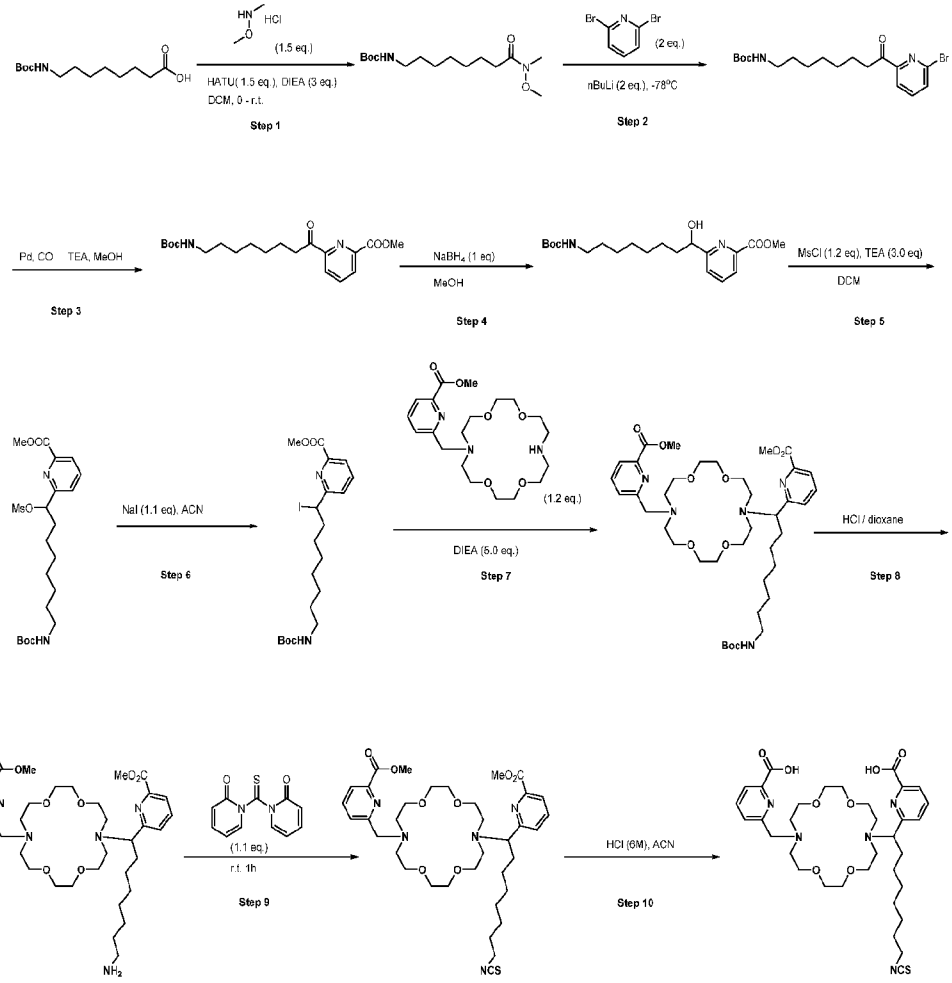
Example 12: *N*-acyl-DBCO tagged 6,6'-((18-(((2-(2-aminoethoxy)ethyl)thio)methyl)tetradecahydro-4*H*,13*H*,17*H*-cyclopenta[*b*][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-4,13-diyl)bis(methylene))dipicolinic acid(3 mg). LC-MS APCI: Calculated for $C_{53}H_{64}N_6O_{11}S$; 992.44; Observed m/z $[M-H]^-$: 991.4.

Example 13

6-((16-(1-(6-carboxypyridin-2-yl)-8-isothiocyanatooctyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid



Scheme 11



5 **Step 1**: Into a 500-mL 3-necked round-bottom flask, purged and maintained under an inert atmosphere of nitrogen, was placed a solution of 8-((*tert*-butoxycarbonyl)amino)octanoic acid (20.0 g, 77.1 mmol) in dichloromethane (200 mL), N, O-dimethylhydroxylamine (7.0 g, 115 mmol), diisopropylethylamine (29.90 g, 231 mmol). This was followed by the addition of HATU

(43.9 g, 115 mmol) with stirring at 0°C. The resulting solution was stirred for 1 h. at room temperature. The reaction was then quenched by the addition of 200 mL of water. The resulting solution was extracted with dichloromethane (100 mL X 2). The combined organic layers were washed sequentially with HCl (1 M) (300 mL X 2), NH_4CO_3 aqueous solution (400 mL X 3) and bine (400 mL). After it was dried over anhydrous Na_2SO4, it was concentrated to give *tert*-butyl (8-(methoxy(methyl)amino)-8-oxooctyl)carbamate (15.4 g, 66% yield) as light-yellow oil.

Step 2: Into a 500-mL 3-necked round-bottom flask, purged and maintained under an inert atmosphere of nitrogen, was placed a solution of 2,6-dibromopyridine (23.0 g, 927 mmol) in THF (400 mL). It was cooled to -78 °C and *n*-BuLi (60.4 mL, 927 mmol) was added dropwise quickly. After stirring for 10 min, an addition of tert-butyl (8-(methoxy(methyl)amino)-8-oxooctyl)carbamate (14.0 g, 463.5 mmol) in THF (40 mL) was added dropwise with stirring at -78 °C. The resulting solution was stirred for 30 min. at room temperature. The reaction was quenched by the addition of 500 mL of water. The resulting solution was extracted with ethyl acetate (200 mL X 2). The combined organic layers were washed with brine (400 mL), dried over anhydrous sodium sulfate and concentrated to give the crude product. Chromatography on silica gel ((0-10% ethyl acetate in petroleum ether) gave *tert*-butyl (8-(6-bromopyridin-2-yl)-8-oxooctyl)carbamate (11.8 g, 50% yield) as light yellow solid.

Step 3: Into a 1-L high pressure reactor, maintained with an inert atmosphere of nitrogen, was placed a solution of *tert*-butyl (8-(6-bromopyridin-2-yl)-8-oxooctyl)carbamate (11.5 g, 28.8 mmol, 1.0 eq.) in MeOH (500 mL), followed by $Pd(dppf)Cl_2$ (2.1 g, 2.88 mmol), TEA (8.7 g, 86.4 mmol). Then CO (20 atm) was introduced in. The resulting solution was stirred for 16 h at 100 °C. The reaction solution was filtered and used for next step directly.

Step 4: The MeOH solution received from above was cooled to 0 °C and $NaBH_4$ (1.08 g, 28.8 mmol) was added. The resulting solution was stirred for 1 h. at room temperature. The reaction was quenched by the addition of 500 mL of NH_4CO_3 aqueous solution and extracted with ethyl acetate (300 mL X 2). The combined organic layers were washed with brine (600 mL), dried over anhydrous Na_2SO_4 and concentrated to give methyl 6-(8-((*tert*-butoxycarbonyl)amino)-1-hydroxyoctyl)picolinate (10 g) as brown oil.

Step 5: Into a 250-mL 3-necked round-bottom flask, purged and maintained under an inert atmosphere of nitrogen, was placed a solution of methyl 6-(8-((*tert*-butoxycarbonyl)amino)-1-hydroxyoctyl)picolinate (10 g) in DCM (100 mL). After it was cooled to 0°C, TEA (7.9 g, 78.9

mmol) and mesyl chloride (3.6 g, 31.5 mmol) were added. The resulting solution was stirred for 1 h. at room temperature. The mixture was concentrated under vacuum. MeCN (100 mL) was added and concentrated under vacuum. The crude product methyl 6-(8-((tert-butoxycarbonyl)amino)-1-((methylsulfonyl)oxy)octyl)picolinate went straight to the next step.

Step 6: To a solution of the above crude product methyl 6-(8-((*tert*-butoxycarbonyl)amino)-1-((methylsulfonyl)oxy)octyl)picolinate in ACN (100 mL) was added NaI (4.3 g, 28.9 mmol). The resulting solution was stirred for 1 h at 80 °C. The mixture was filtered and concentrated. The crude product was purified by Flash-Prep-HPLC: Column C18 ; mobile phase, H_2O/ACN=50/50% to H_2O/ACN=20/80% in 30 min; It gave 4 g of methyl 6-(8-((*tert*-butoxycarbonyl)amino)-1-iodooctyl)picolinate as brown oil.

Step 7: To a solution of methyl 6-(8-((*tert*-butoxycarbonyl)amino)-1-iodooctyl)picolinate (3.0 g, 6.12 mmol,) in DCM (200 mL) were added methyl 6-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (3.0 g, 7.34 mmol), diisopropylethylamine (3.9 g, 30.61 mmol). The resulting solution was stirred for 16 h at 80 °C. The reaction was concentrated. The crude product was purified by Flash-Prep-HPLC: Column C18; mobile phase, A: H_2O (0.05% TFA), B: CAN; 20% B to 40% B in 20 min. It gave 1.9 g of methyl 6-(8-((*tert*-butoxycarbonyl)amino)-1-(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)octyl)picolinate as brown oil.

Step 8: To a stirred solution of methyl 6-(8-((*tert*-butoxycarbonyl)amino)-1-(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)octyl)picolinate (1.7 g, 2.19 mmol, 77% on LCMS) in DCM (8.5 mL) at 0°C was added HCl/dioxane dropwise. The resulting solution was stirred for 1 h. at room temperature. The reaction was quenched by the portion wise addition of NH_4CO_3 aqueous solution (20 mL X 3). The resulting solution was extracted with dichloromethane (100 mL X 2). The combined organic layers were washed brine (400 mL), dried over anhydrous Na_2SO_4 and concentrated to give 1.3 g of methyl 6-(8-amino-1-(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)octyl)picolinate as brown oil.

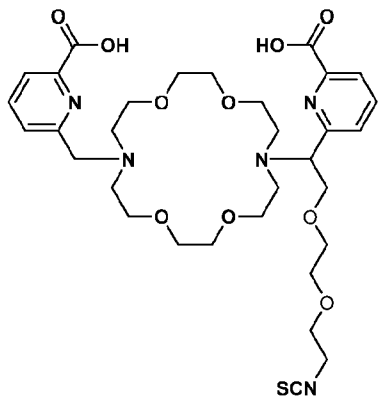
Step 9: To a solution of methyl 6-(8-amino-1-(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)octyl)picolinate (1.0 g, 1.48 mmol) in DCM (17 mL) under N_2 was added 1,1'-thiocarbonylbis(pyridin-2(1H)-one) (0.38 g, 1.63 mmol). The resulting solution was stirred for 1 h at room temperature. It was concentrated to give 1.6 g of

methyl 6-((16-(1-(6-(methoxycarbonyl)pyridin-2-yl)-8-thiocyanatooctyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate as brown oil.

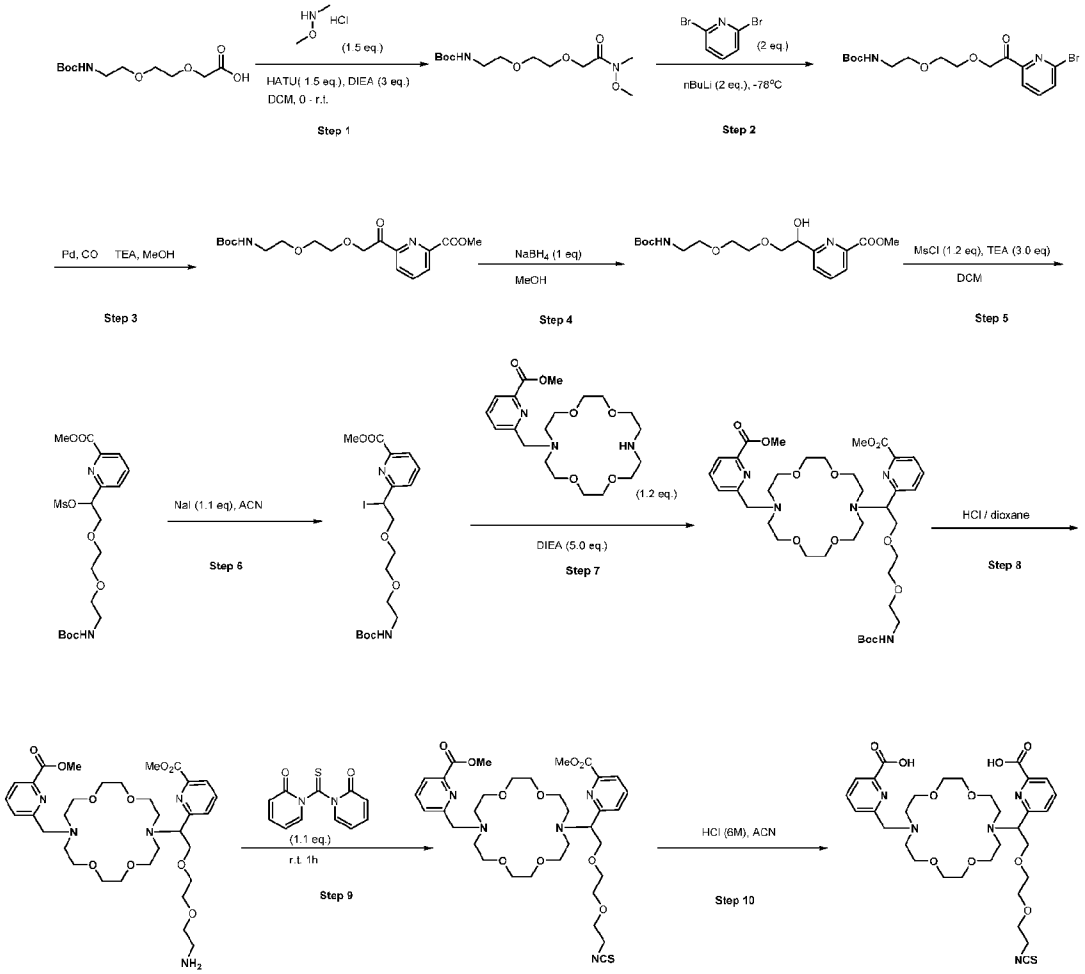
Step 10: To a solution of methyl 6-((16-(1-(6-(methoxycarbonyl)pyridin-2-yl)-8-thiocyanatooctyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (1.40 g, 1.42 mmol) in ACN (4 mL) was added HCl (6 M) (7 mL). The resulting solution was stirred for 5 h at 50 °C in an oil bath. It was diluted with 10 mL of H_2O. The crude product was purified by Flash-Prep-HPLC: Column, C18; mobile phase, A: H_2O (0.05% TFA), B: ACN, 20% B to 36% B in 20 min; Detector UV@210nm. The product fractions were concentrated to remove ACN. The aqueous was adjust to pH to 7~8 with $NaHCO_3$ aqueous solution. It was purified again on Flash-Prep-HPLC: Column, C18; mobile phase, A: H_2O, B: ACN, 95% B to 100% B in 20 min. The product solution was concentrated to remove CAN and then lyophilized. It gave 190 mg of 6-((16-(1-(6-carboxypyridin-2-yl)-8-thiocyanatooctyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid as a brown solid. ^1H NMR (300 MHz, D_2O) δ 7.91 (s, 4H), 7.54 (s, 2H), 4.52 (d, J = 17.9 Hz, 3H), 3.77 (d, J = 9.3 Hz, 8H), 3.56 – 3.41 (m, 18H), 2.11 (s, 2H), 1.51 (s, 2H), 1.17 (s, 7H), 0.97 (s, 1H). MS (ES, m/z): 688.3 ($M + H^+$).

Example 14

6-((16-(1-(6-carboxypyridin-2-yl)-2-(2-(2-isothiocyanatoethoxy)ethoxy)ethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid



Scheme 12



Step 1: To a stirred solution of 2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-oic acid (10.00 g, 37.98 mmol) and diisopropylethylamine (14.73 g, 113.94 mmol) in dichloromethane (100 mL) at 0 °C under nitrogen atmosphere was added [Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (15.16 g, 39.88 mmol), *N,O*-dimethyl hydroxylamine (5.55 g, 56.97 mmol) dropwise. After the resulting mixture was stirred for 1 h at room temperature, it was poured to saturated NH4Cl (aq.). The resulting mixture was extracted with dichloromethane (100 mL X 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by chromatography: Column, C18; mobile phase A: H_2O with 0.05% TFA, B: ACN; gradient 20% B to 40% B in 20 minutes; Detector: UV@210 nm. It gave

tert-butyl (3-methyl-4-oxo-2,6,9-trioxa-3-azaundecan-11-yl)carbamate (9.90 g. 85% yield) as light yellow oil.

Step 2: To a solution of 2,6-dibromo-pyridine (13.3 g, 56.1 mmol) in THF (260 mL) in a 500 ml 3-necked round-bottom flask at -78 °C under nitrogen atmosphere was added *n*-BuLi (28.0 mL, 56.1 mmol) dropwise. The solution was stirred at -78 °C for 10 min. A solution of *tert*-butyl (3-methyl-4-oxo-2,6,9-trioxa-3-azaundecan-11-yl)carbamate (7.0 g, 28.0 mmol) in THF (30 mL) was added dropwise to the reaction solution at -78 °C and the mixture was stirred at room temperature for 30 min. The reaction was quenched by the addition of water/ice (200 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (100 mL X 3). The combined extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography: Column, C18; mobile phase, mobile phase A: H_2O with 0.05% TFA, B: ACN; gradient 38% B to 58% B in 20 minutes; Detector: UV@210 nm. It gave to *tert*-butyl (2-(2-(2-(6-bromopyridin-2-yl)-2-oxoethoxy)ethoxy)ethyl)carbamate (4.6 g, 50% yield) as a yellow solid. MS (ES, *m/z*): 425, 427 ($M + Na^+$).

Step 3: To a 250-mL high pressure reactor were added *tert*-butyl (2-(2-(2-(6-bromopyridin-2-yl)-2-oxoethoxy)ethoxy)ethyl)carbamate (4.0 g, 18.1 mmol), triethylamine (5.5 g, 54.3 mmol), $Pd(dppf)Cl_2$ (1.3 g, 1.8 mmol) and MeOH (40 mL). The reaction solution was evacuated and backfilled with N_2. Then CO (10 atm) was introduced in. The resulting solution was stirred at 100 °C for overnight. The reaction mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified by chromatography: Column, C18; mobile phase A: H_2O with 0.05% TFA, B: ACN; gradient 38% B to 58% B in 20 minutes; Detector: UV@210 nm. It gave methyl 6-(2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-oyl)picolinate (2.4 g, 63% yield) as a brown oil. MS (ES, *m/z*): 405 ($M + Na^+$).

Step 4: To a solution of methyl 6-(2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-oyl)picolinate (2.30 g, 6.01 mmol) in MeOH (46 mL) under N_2 atmosphere at 0 °C was added $NaBH_4$ (0.23 g, 6.01 mmol). The resulting solution was stirred for 1 h at room temperature and quenched by the addition of 50 mL of saturated NH_4HCO_3 (aq.). The resulting solution was extracted with ethyl acetate (30 mL X 2). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4 and concentrated. It gave 2.2 g of the crude product methyl 6-(13-hydroxy-2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)picolinate as brown oil.

Step 5: To a solution of methyl 6-(13-hydroxy-2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)picolinate (2.2 g, 5.72 mmol) in dichloromethane (22 mL) at 0 °C under N_2 atmosphere were added triethylamine (1.74 g, 17.16 mmol) and MsCl (0.79 g, 6.86 mmol). The resulting solution was stirred for 1 h at room temperature and quenched with H_2O (22 mL). The resulting mixture was extracted with dichloromethane (20 mL X 2). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and concentrated. It gave 2.2 g of the crude product methyl 6-(2,2-dimethyl-13-((methylsulfonyl)oxy)-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)picolinate as brown oil.

Step 6: To a solution of methyl 6-(2,2-dimethyl-13-((methylsulfonyl)oxy)-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)picolinate (2.2 g, 4.75 mmol) in ACN (22 mL) under N_2 atmosphere was added NaI (0.78 g, 5.23 mmol). The resulting solution was stirred for 1 h at 80 °C. The mixture was filtered and concentrated. The crude product was purified by chromatography: Column, C18; mobile phase A: H_2O, B: ACN; gradient 50% B to 80% B in 30 min; Detector: UV@210 nm. It gave methyl 6-(13-iodo-2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)picolinate (1.2 g) as brown oil. MS (ES, *m/z*): 517 ($M + Na^+$), 495 ($M + H^+$).

Step 7: A solution of methyl 6-(13-iodo-2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)picolinate (840 mg, 1.69 mmol) and methyl 6-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (839 mg, 2.03 mmol) in ACN (16.8 mL) was stirred for overnight at 80 °C under nitrogen atmosphere. The cooled reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography: Column, C18; mobile phase A: H_2O, B: ACN; gradient 40% B to 60% B in 20 min; Detector: UV@210 nm. It gave methyl 6-((16-(13-(6-(methoxycarbonyl)pyridin-2-yl)-2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (450 mg) as a brown oil. MS (ES, *m/z*): 700 ($M + Na^+$), 678 ($M + H^+$).

Step 8: To a solution of methyl 6-((16-(13-(6-(methoxycarbonyl)pyridin-2-yl)-2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (450 mg, 579 mmol) in dichloromethane (2.5 mL) at 0 °C was added HCl/dioxane (2.5 ml, 4 M). The resulting solution was stirred for 20 min at room temperature. The reaction was quenched by the addition of saturated Na_2CO_3 (aq.). The aqueous layer was extracted with DCM: IPA (5: 1) (30 mL X 2). The combined organic layers were dried over

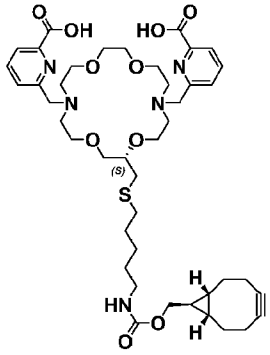
anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product methyl 6-(2-(2-(2-aminoethoxy)ethoxy)-1-(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)ethyl)picolinate (330 mg). The crude product was used directly in the next step.

Step 9: A solution of methyl 6-(2-(2-(2-aminoethoxy)ethoxy)-1-(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)ethyl)picolinate (300 mg, 0.44 mmol) and 1-(2-oxopyridine-1-carbothioyl) pyridin-2-one (113.08 mg, 0.48 mmol) in dichloromethane (3 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to afford the crude product methyl 6-(2-(2-(2-isothiocyanatoethoxy)ethoxy)-1-(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)ethyl)picolinate (380 mg). The crude product was used directly in the next step.

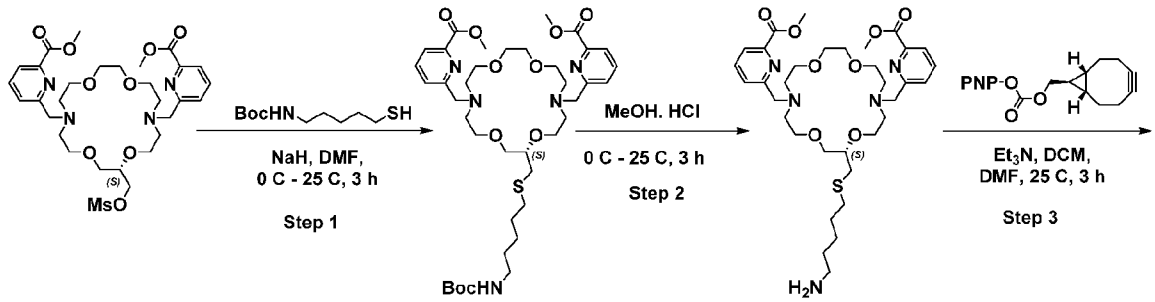
Step 10: A solution of methyl 6-(2-(2-(2-isothiocyanatoethoxy)ethoxy)-1-(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)ethyl)picolinate (380 mg, 0.52 mmol) and HCl (1.9 mL, 6 M) in dichloromethane (1.9 mL) was stirred for 3 h at 50 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure and was basified to pH 6-7 with saturated $NaHCO_3$ (aq.). The residue was purified by chromatography: Column, C18; mobile phase A: H_2O with 0.05% TFA, B: ACN, gradient 20% B to 36% B in 20 min; Detector: UV@210nm. Then, the product fractions were concentrated under vacuum to remove MeCN. The solution was purified again by chromatography: Column, C18; mobile phase A: H_2O, B: ACN, gradient 95% B to 100% B in 20 min. The solution was concentrated to remove most MeCN and the aqueous solution was lyophilized to give 6-((16-(1-(6-carboxypyridin-2-yl)-2-(2-(2-isothiocyanatoethoxy)ethoxy)ethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid (130 mg) as brown solid. ^1H NMR (300 MHz, D_2O) 8.03 – 7.84 (m, 2H), 7.57 (dd, J = 22.3, 7.4 Hz, 1H), 5.00 (s, 0H), 4.59 (s, 1H), 4.20 (dd, J = 23.4, 9.5 Hz, 1H), 3.82 (d, J = 15.4 Hz, 4H), 3.70 – 3.58 (m, 6H), 3.58 – 3.49 (m, 6H). MS (ES, *m/z*): 692.3 ($M + H^+$).

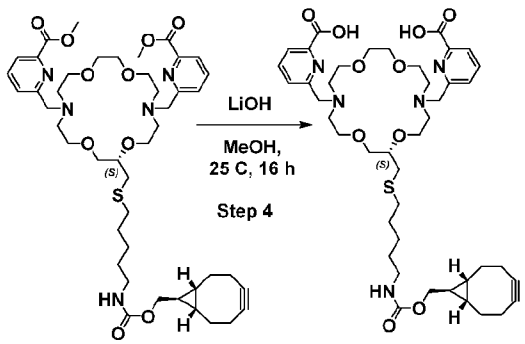
Example 15

6,6'-(((*S*)-2-(((5-(((((1*R*,8*S*,9*r*)-Bicyclo[6.1.0]non-4-yn-9-yl)methoxy)carbonyl)amino)pentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid



Scheme 13





Step 1: A solution consisting of *tert*-butyl (5-mercaptopentyl)carbamate (0.30 g, 1.0 mmol) and DMF (3.0 mL) was added dropwise over 5 minutes to a 50 mL three-neck round-bottomed flask containing a suspension of sodium hydride (0.07 g, 60% in mineral oil, 2 mmol) in DMF (3.0 mL) at 0 °C and under a nitrogen atmosphere. Once addition was complete, the reaction mixture was

brought to room temperature and stirring continued for 15 minutes. The reaction mixture was then re-cooled to 0 °C and treated dropwise over 10 minutes with a solution consisting of dimethyl 6,6'-((2-(((methylsulfonyl)oxy)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.6 g, 0.9 mmol) and DMF (3.0 mL). Once addition was complete, the reaction mixture was slowly warmed to room temperature and stirring continued for 1.5 h. The reaction mixture was then carefully treated with sat. aqueous NH_4Cl (1.0 mL) and concentrated to dryness to give an oil. The oil was subjected to preparative HPLC (Column: XBRIDGE C18 19 X 150 mm, 5.0 µm; Mobile phase: 0.1% TFA in water/acetonitrile; Flow Rate: 15.0 mL/min) to yield dimethyl 6,6'-((2-(((5-((*tert*-butoxycarbonyl)amino)pentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.25 g).

Step 2: A stir bar, dimethyl 6,6'-((2-(((5-((*tert*-butoxycarbonyl)amino)pentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.25 g, 0.32 mmol), MeOH (1.0 mL), and HCl in methanol (4 M, 1.5 mL, 6.3 mmol) were added to a 25 mL round-bottomed flask at 0 °C, which was subsequently brought to room temperature and the mixture stirred for 3 h. The volatiles were then removed in vacuo to yield dimethyl 6,6'-((2-(((5-aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.21 g), which was used without purification.

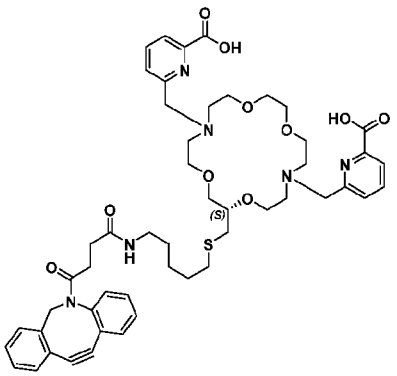
Step 3: A stir bar, dimethyl 6,6'-((2-(((5-aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.15 g, 0.22 mmol), ((1*R*,8*S*,9*r*)-bicyclo[6.1.0]non-4-yn-9-yl)methyl 4-nitrophenyl carbonate (68 mg, 0.22 mmol), triethylamine (66 mg, 0.65 mmol), and a mixture of DCM (2 mL) and DMF (0.1 mL) were added to a 25 mL three-neck round-bottomed flask at 0 °C under a nitrogen atmosphere. The resultant mixture was gradually warmed to room temperature and stirred overnight. The mixture was then concentrated to dryness to give dimethyl 6,6'-(((*S*)-2-(((5-(((((1*R*,8*S*,9*r*)-bicyclo[6.1.0]non-4-yn-9-yl)methoxy)carbonyl)amino)pentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinate (0.1 g), which was used without purification.

Step 4: A stir bar, dimethyl 6,6'-(((*S*)-2-(((5-(((((1*R*,8*S*,9*r*)-bicyclo[6.1.0]non-4-yn-9-yl)methoxy)carbonyl)amino)pentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-

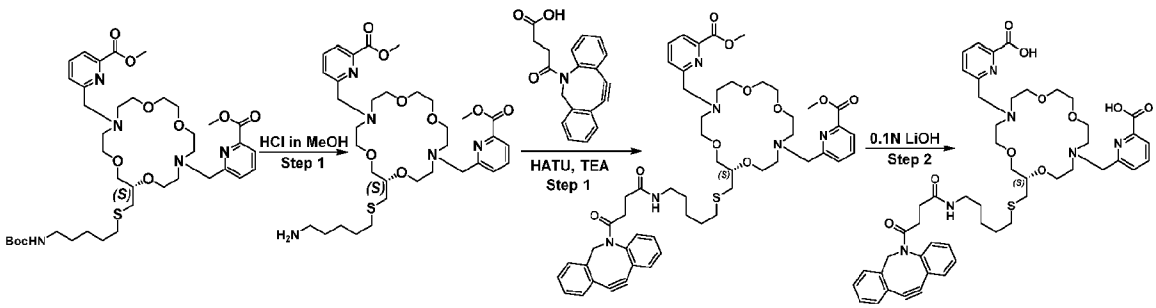
7,16-diyl)bis(methylene))dipicolinate (0.10 g, 0.12 mmol), aqueous LiOH (3.5 mL, 0.1 N, 0.35 mmol), and MeOH (0.5 mL) were added to a 8 mL reaction vial and the resultant mixture stirred overnight at room temperature. The reaction mixture was then treated with acetic acid until pH~6.5, and subsequently concentrated to dryness in vacuo at room temperature to yield an oil, which was purified via preparative HPLC (Column: XBRIDGE C18 19 x 150 mm, 5.0 µm; Mobile phase: 0.1% Formic acid in H_2O/ACN; Flow Rate: 15.0 mL/min) to yield 6,6'-(((S)-2-(((5-(((((1*R*,8*S*,9*r*)-bicyclo[6.1.0]non-4-yn-9-yl)methoxy)carbonyl)amino)pentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (42 mg).

Example 16

N-acyl-DBCO tagged 6,6'-((2-(((5-Aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinic acid



Scheme 14



Step 1: A stir bar, dimethyl 6,6'-((2-(((5-((*tert*-butoxycarbonyl)amino)pentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (0.12 g, 0.15 mmol), MeOH (0.5 mL), and HCl in methanol (4 M, 0.75 mL, 3.0 mmol) were added to a

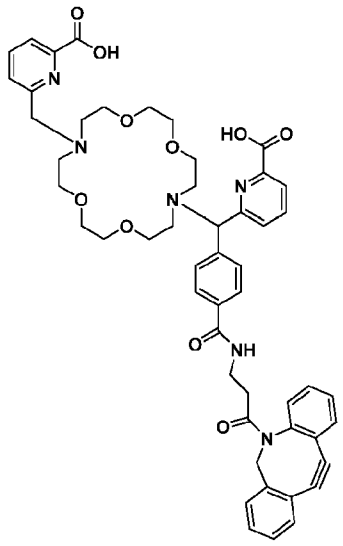
25 mL round-bottomed flask at 0 °C and then brought to room temperature and stirred for 2 h. The volatiles were removed in vacuo to yield dimethyl 6,6'-((2-(((5-aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (70 mg), which was used without purification.

[0001] **Step 2**: A stir bar, dimethyl 6,6'-((2-(((5-aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (50 mg, 0.070 mmol), 11,12-Didehydro-γ-oxodibenz[b,f]azocine-5(6H)-butanoic acid(20 mg, 0.070 mmol), triethylamine (21 mg, 0.21 mmol), HATU (38 mg, 0.10 mmol), and DCM (0.5 mL) were added to a 25 mL three-neck round-bottomed flask at 0 °C under a nitrogen atmosphere, and subsequently brought to room temperature and stirred overnight. The reaction mixture was treated with water (10 mL) and extracted with dichloromethane (10 mL x 3), and the combined extracts washed with 10% aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield an oil. The oil was purified via silica gel chromatography (0-10% MeOH/DCM) to yield *N*-acyl-DBCO tagged dimethyl 6,6'-((2-(((5-aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (16 mg).

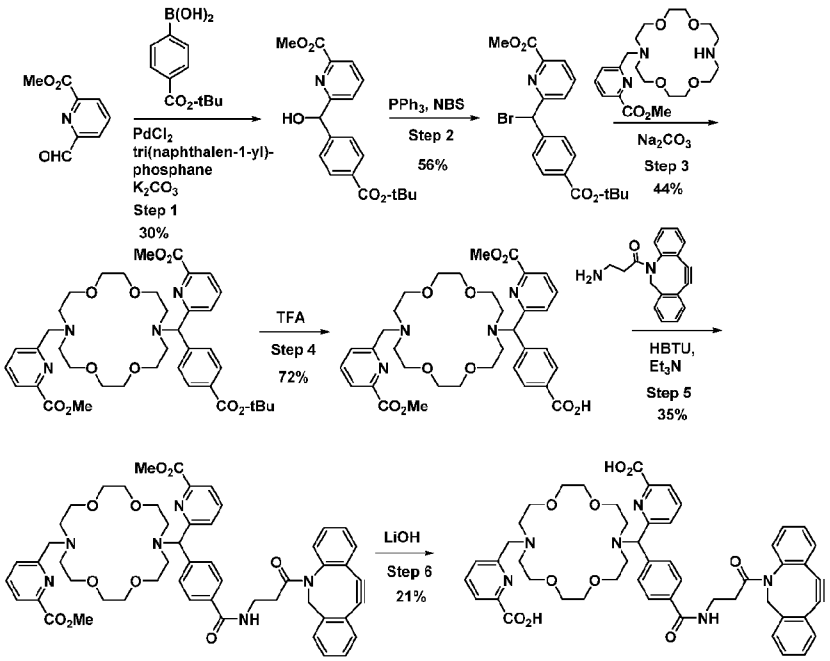
Step 3: A stir bar, *N*-acyl-DBCO tagged dimethyl 6,6'-((2-(((5-aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinate (16 mg, 0.016 mmol), aqueous LiOH (0.49 mL, 0.1 N, 0.049 mmol), and MeOH (0.25 mL) were added to an 8 mL reaction vial and the mixture stirred at room temperature overnight. The reaction mixture was then treated with acetic acid until pH~6.5, and concentrated to dryness in vacuo at room temperature to yield a concentrate, which was purified via preparative HPLC (Column: XBRIDGE C18 19 X 150 mm 5.0 µm; Mobile phase: 10 mM Ammonium Acetate in water/ACN; Flow Rate: 15.0 mL/min) to yield N-acyl-DBCO tagged 6,6'-((2-(((5-aminopentyl)thio)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))(*S*)-dipicolinic acid (5 mg) as an off-white solid. LC-MS APCI: Calculated for $C_{51}H_{62}N_6O_{10}S$; 950.42; Observed *m/z* $[M+H]^+$ 951.4. ^1H NMR (400 MHz, D_2O): δ 7.81-7.75 (m, 4H), 7.52-7.17 (m, 10H), 4.97-4.90 (m, 1H), 4.80 (s, 4H), 4.14 (s, 3H), 3.77-3.46 (m, 16H), 3.10 (s, 7H), 2.83-2.80 (m, 2H), 2.55-2.53 (m, 2H), 2.42-2.38 (m, 3H), 2.11-2.08 (m, 3H), 1.39-1.35 (m, 2H), 1.20-1.10 (m, 4H).

Example 17

N-acyl-DBCO tagged 6-((4-((6-Aminoethyl)carbamoyl)phenyl)16-((6-carboxypyridin-2-yl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid (TOPA-[C7]-benzimido-DBCO)



Scheme 15



Step 1: To a mixture of methyl 6-formylpicolinate (4.00 g, 24.2 mmol), (4-(*tert*-butoxycarbonyl)phenyl)boronic acid (10.7 g, 48.5 mmol), $PdCl_2$ (0.21 g, 1.2 mmol), tri(naphthalen-1-yl)phosphine (0.50 g, 1.2 mmol) and potassium carbonate (10.0 g, 72.7 mmol) under nitrogen at -78 °C in a 500 mL three neck round bottom flask was added tetrahydrofuran (100 mL) in one portion. The mixture was purged with nitrogen and stirred at r.t. for 30 min, then heated at 65 °C for 24 h. The reaction mixture was cooled r.t. and filtered through a pad of Celite® and the filtrate was concentrated to dryness. The crude product was subjected to silica gel chromatography (0-50% EtOAc/petether) to afford methyl 6-((4-(tert-butoxycarbonyl)phenyl)(hydroxy)methyl)picolinate as a yellow oil (2.5 g, 30%).

Step 2: A stir bar, methyl 6-((4-(tert-butoxycarbonyl)phenyl)(hydroxy)methyl)picolinate (2.50 g, 7.30 mmol), PPh_3 (3.43 g, 13.1 mmol), *N*-bromosuccinimide (2.13 g, 12.0 mmol) and DCM (30 mL) were taken in a 250 mL three neck round bottom flask under nitrogen atmosphere at r.t. and stirred for 1 h. The reaction solution was loaded onto a silica gel column and purified using 0-30% ethyl acetate in petroleum ether to get compound methyl 6-(bromo(4-(tert-butoxycarbonyl)phenyl)methyl)picolinate (1.65 g, 56%) as a yellow oil.

Step 3: A stir bar, methyl 6-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (1.52 g, 3.69 mmol), 6-(bromo(4-(tert-butoxycarbonyl)phenyl)methyl)picolinate (1.50 g, 3.69 mmol), Na_2CO_3 (1.17 g, 11.1 mmol), and acetonitrile (30 mL) were added to a 250 mL three neck round-bottomed flask, and the resultant heterogeneous mixture was heated at 90 °C for 16 h under nitrogen atmosphere. Subsequently reaction mass was cooled to r.t., filtered through a pad of Celite®, and concentrated to dryness in vacuo to give the crude product. The crude product was subjected to silica gel chromatography (0-10% MeOH/DCM) to afford methyl 6-((4-(tert-butoxycarbonyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate as a brown oil (1.2 g, 44%).

Step 4: A stir bar, methyl 6-((4-(tert-butoxycarbonyl)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (1.2 g, 1.6 mmol), TFA (0.62 mL, 8.1 mmol) and DCM (20 mL) were added to a 100 mL three neck round bottom flask at r.t. and stirred for 1 h. Reaction mixture was concentrated to dryness and the resultant crude product was subjected to preparative HPLC (Column: XBRIDGE C18 (19 X 150 mm) 5.0 µm; Mobile phase: 0.1% TFA in water/ACN; Flow Rate: 15.0 mL/min) to give 4-((6-

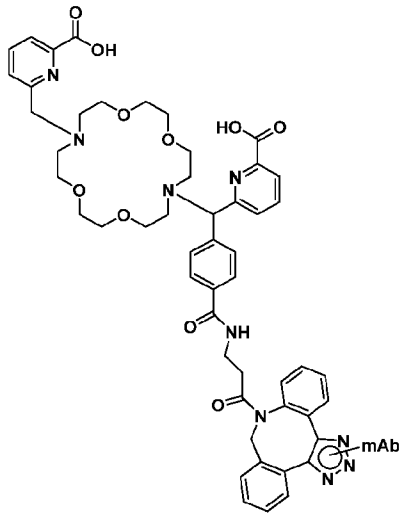
(methoxycarbonyl)pyridin-2-yl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)benzoic acid (0.8 g, 72%) as brown oil. **LC-MS APCI:** Calculated for $C_{35}H_{44}N_4O_{10}$ 680.31; Observed *m/z* $[M+H]^+$ 681.5. Purity by LC-MS: 99.87%. **Purity by HPLC**: 97.14% (97.01% at 210 nm, 97.20% at 254 nm and 97.21% at 280 nm; Column: Atlantis dC18 (250 X4.6 mm), 5 µm; Mobile phase A: 0.1% TFA in water, Mobile phase B: acetonitrile; Flow rate: 1.0 mL/min.%. **^{1}H NMR** (400 MHz, DMSO-d6): δ 8.12-8.07 (m, 4H), 8.00-7.98 (m, 2H), 7.75-7.73 (m, 4H), 6.10 (s, 1H), 4.67 (s, 2H), 3.96 (s, 3H), 3.91 (s, 3H), 3.82 (s, 8H), 3.56 (s, 8H), 3.52 (s, 8H).

[0002] Step 5: A stir bar, 4-((6-(methoxycarbonyl)pyridin-2-yl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)benzoic acid (0.25 g, 0.37 mmol), DBCO (0.10 g, 0.37 mmol), triethylamine (0.16 mL, 1.1 mmol), HBTU (0.21 g, 0.55 mmol) and DCM (10 mL) were added to a 25 mL three neck round-bottom flask at 0 °C under nitrogen atmosphere at r.t. and stirred for 16 h. The reaction was quenched with water (20 mL) and it was extracted with DCM (3 X 20 mL). The combined extracts were washed with 10% aqueous $NaHCO_3$ solution (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to afford the crude product as an oil. The crude product was subjected to silica gel chromatography (0-10% MeOH/DCM) to give TOPA dimethyl ester-[C7]-phenyl-DBCO (0.12 g, 35%) as a colorless gummy oil.

Step 6: A stir bar, TOPA dimethyl ester-[C7]-phenyl-DBCO (0.1 g, 0.1 mmol), aqueous $LiOH.H_2O$ (3 mL, 0.1 N, 0.3 mmol) and THF/MeOH/H_2O (4:1:1 v/v/v, 2 mL) were added to a 8 mL reaction vial at r.t. and it was allowed to stir for 2 h. The reaction mixture was neutralized with aqueous HCl (1N) to P^H~6.5. The reaction mixture was concentrated to dryness in vacuo at room temperature, and the resultant crude product was subjected to preparative HPLC (Column: XBRIDGE C18 (19 X 150 mm) 5.0 µm; Mobile phase: 10Mm Ammonium Acetate in water/ACN; Flow Rate: 15.0 mL/min) to give TOPA-[C7]-phenyl-DBCO (20 mg, 21%) as an off-white solid. **LC-MS APCI**: Calculated for $C_{51}H_{54}N_6O_{10}$ 910.39; Observed *m/z* $[M-H]^+$ 909.3. Purity by LC-MS: 92.47% . **Purity by HPLC**: 90.68% (88.04% at 210 nm, 90.43% at 254 nm and 93.56% at 280 nm; Column: XBRIDGE C8 (50 X 4.6 mm), 3.5 µm; Mobile phase A: 10mM Ammonium bicarbonate in water, Mobile phase B: acetonitrile; Flow rate: 1.0 mL/min. **^{1}H NMR** (400 MHz, DMSO-d6): δ 7.84-7.82 (m, 4H), 7.60-7.29 (m, 12H), 7.13-7.10 (m, 2H), 5.12-5.02 (m, 2H), 3.97 (s, 2H), 3.59-3.44 (m, 20H), 2.85 (s, 4H), 2.73-2.68 (m, 6H).

Example 18

TOPA-[C7]-benzyimido-DBCO-triazole-PSMB-127 Antibody Conjugate



Step 1. *Azide modification of mAb and Click reaction*: PSMB127 was site-selectively modified with 100x molar excess of 3-azido propylamine and microbial transglutaminase (MTG; Activa TI) at 37 ° C. The addition of two azides on the heavy chains of the mAb was monitored by intact mass ESI-TOF LC-MS on an Agilent G224 instrument. Excess 3-azido propylamine and MTG was removed and azide modified mAb (azido-mAb) was purified using a 1mL GE Healthcare MabSelect column. Azido-mAb is eluted from the resin using 100 mM sodium citrate pH 3.0 and subsequently exchanged into 20 mM Hepes, 100 mM NaCl pH 7.5 using 7K Zeba ® desalting columns. 10x molar excess of TOPA-[C7]-phenyl-DBCO was reacted with site specific azide-PSMB127 (DOL = 2) at 37 °C for 1 hour without shaking. Completion of the DBCO-azide click reaction was monitored by intact mass spectrometry. Excess free chelator was removed by desalting the conjugate over a Zeba ®7K desalting column into 20 mM Hepes, 100 mM NaCl pH 7.5 followed by three sequential 15x dilution and concentration steps in 20 mM Hepes, 100 mM NaCl pH 7.5 using a 30K MWCO Amicon concentrator device by spinning at 3800 x g. This provided the final site specific TOPA-[C7]-phenyl-DBCO-PSMB127 conjugate with CAR = 2. The final conjugate was confirmed to be monomeric by analytical size

exclusion chromatography on a Tosoh TSKgel G3000SWxl 7.8mm x 30cm, 5 u column; column temperature: room temperature; the column was eluted with DPBS buffer (1x, without calcium and magnesium); flow rate: 0.7 mL/min; 18 min run; injection volume: 18 µL.

Step 2. *Chelation:* Stock solutions of the following metal salts were prepared in pure water:

Salt	Catalog #	Concentration
Cerium (III) Chloride	Sigma Cat # 429406	10 mM
Neodymium (III) chloride hexahydrate	Sigma Cat # 289183	10 mM
Terbium (III) chloride	Sigma Cat # 451304	10mM
Lutetium (III) chloride	Sigma Cat # 450960	10mM
Thulium (III) chloride	Sigma Cat # 451304	10mM
Yttrium (III) chloride	Sigma Cat # 451363	10mM
Holmium (III) chloride	Sigma Cat # 450901	10mM

Metal solutions were added to the TOPA-[C7]-phenyl-DBCO-PSMB127 in 5x molar excess (6.8 uM antibody, 34 uM metal ion) in 10 mM sodium acetate buffer pH 5.2 and incubated for 2 hours at 37C. Excess metal was removed by desalting with a Zeba ® column (ThermoFisher ®) followed by two cycles of 10x dilution and concentration in a 50K MWCO Amicon concentrator (EMD Millipore ®). Chelation was assessed by intact and reduced mass LC-MS.

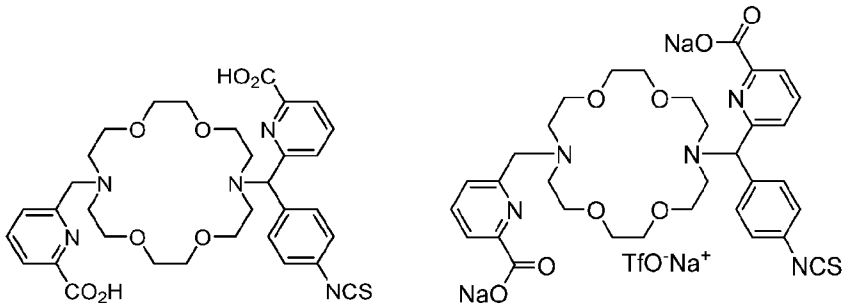
Step 3. *Stability Determination:* To determine stability of the chelate, DTPA challenge was performed. 50 uL of the sample (6.3 uM antibody) was combined with 50 uL of 10mM DTPA pH 6.5 and incubated at 37C overnight. Chelation was assessed by intact and reduced mass LC-MS. LC-MS was performed on an Agilent 1260 HPLC system connected to an Agilent G6224 MS-TOF Mass Spectrometer. LC was run on an Agilent RP-mAb C4 column (2.1 x 50 mm, 3.5 micron) at a flow rate of 1 mL/min with the mobile phase 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (Sigma-Aldrich Cat# 34688) (B) and a gradient of 20% B (0-2 min), 20-60% B (2-3 min), 60-80% B (3-5.5 min). The instrument was operated in positive electro-spray ionization mode and scanned from m/z 600 to 6000. Mass to charge spectrum was deconvoluted using the Maximum Entropy algorithm, and relative amounts of the relevant species were estimates by peak heights of the deconvoluted masses. Instrument settings included: capillary voltage 3500V; fragmentor 175V; skimmer 65V; gas temperature 325C; drying gas

flow 5.0 L/min; nebulizer pressure 30 psig; acquisition mode range 100-7000 with 0.42 scan rate.

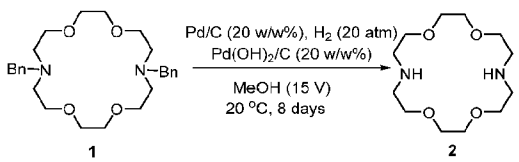
Changes in MW relative to the TOPA-[C7]-phenyl-DBCO-PSMB127 were observed for the cerium and neodymium samples. The intact mass of the conjugate incubated with cerium showed an increase in MW of 139 (20 % by peak area) or 276 (77 %) Da corresponding to the addition of 1 or 2 cerium ions. After DTPA challenge, the masses remained similar with similar abundance (30 and 67% for the +138 and +274 species).

Example 19

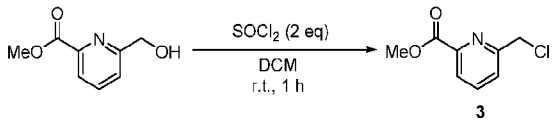
6-((16-((6-carboxypyridin-2-yl)(4-isothiocyanatophenyl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid (H2bp18c6-benzyl-phenyl) (TOPA-[C7]-phenylisothiocyanate and Sodium salt forms



Compound **2** was prepared in an analogous manner to existing literature methods see. J. Org. Chem; 1987, 52, 5172.

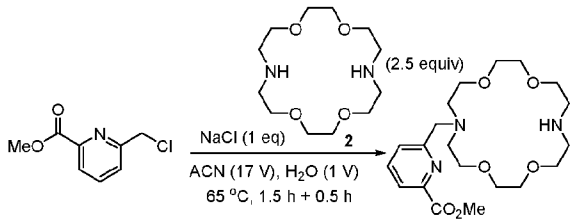


Compound **3** was prepared in an analogous manner to existing literature methods see. Chemistry – a European Journal; 2015, 21, 10179.



3

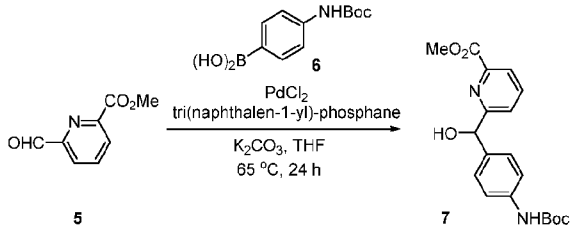
Preparation of Compound 4:



3 4

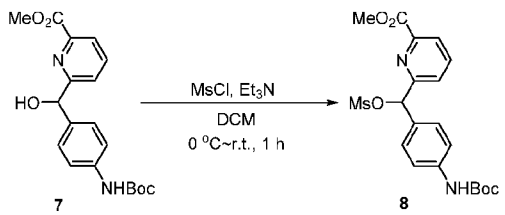
1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (494g, 1.88mol, 2.5 equiv.), NaCl (44.1g, 0.75 mol, 1.0 equiv.), H_2O (140 mL, 1 volume with respect to compound **3**) and acetonitrile (2.1L, 15 volumes) were charged to a 10 L reactor under N_2 atmosphere at 15-20°C the heated to 65°C. To the resulting mixture was added a solution of compound **3** (140g, 0.75mol) in acetonitrile (280ml, 2 volumes) dropwise over 1 hour 65°C. The solution was aged at 65°C for 0.5 hours. LCMS analysis of the mixture showed the reaction was completed. The mixture was cooled to room temperature and concentrated under vacuum. Acetone (700ml, 5 volumes) was added to the mixture and the suspension was stirred for an additional 1 hour. The mixture was filtered (the filtered solid was unreacted compound **2**). The filtrate was concentrated under vacuum, then dissolved in DCM (1.4L, 10 volumes). The organic phase was washed with water (3 x 750mL) and the organic phase was dried over Na_2SO_4 then concentrated under vacuum to yield compound **4**, 212g (63% yield, assay: 85% w/w). LCMS: (ES,m/z): 412.15 $[M+H]^+$ ^{1}H-NMR (300MHz, DMSO-d_6, *ppm*): δ 7.98 – 7.87 (m, 2H), 7.81 (dd, J = 6.4, 2.6 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 2H), 3.61 – 3.38 (m, 16H), 2.77 (dt, J = 19.0, 5.2 Hz, 8H).

Preparation of Compound 7:



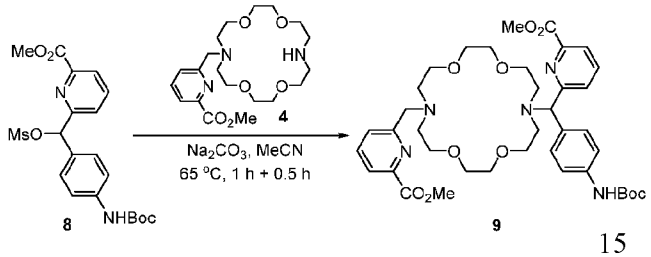
Methyl 6-formylpicolinate **5** (250g, 1.0 equiv.), (4-((tert-butoxycarbonyl)amino)phenyl)boronic acid **6** (538g, 1.5 equiv.) and degassed THF (6.5 L, 26 volumes with respect to **5**) were charged into a 10 L reactor under N_2 atmosphere at 15-20°C. This was followed by the addition of $PdCl_2$ (14.0g, 0.05 equiv.), tri(naphthalen-1-yl)-phosphane (31 g, 0.05 equiv.) and K_2CO_3 (650 g, 3.1 equiv.). The resulting solution was stirred at 20°C for 0.5 hours. The Mixture was then heated to 65°C and aged for 17 hours. Analysis by LCMS showed this reaction was complete. The resulting solution was cooled at room temperature and was diluted with ice water (2.5L, 10 volumes) and ethyl acetate (5L, 20 volumes). The mixture was stirred then filtered through a celite pad. The solution was allowed to separate, and the aqueous lower layer was discarded. The organic phase was washed with the water (2 x 1.5L, 12 volumes). The layers were separated, and the organic layer was dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was treated with heptane (1.25L, 5 Volumes) and the resulting suspension was stirred for 0.5 hours. The mixture was filtered, and the filter cake was washed with n-heptane (500ml, 2 volumes) to yield 530 g (98% yield, LCAP purity: 90%) of desired product **7** as yellow solid, which was used directly in the next step without further purification. LCMS: (ES,m/z): 381.10 $[M+Na]^+$ ^{1}H-NMR (300MHz, DMSO-d_6, *ppm*): δ 9.27 (s, 1H), 8.03 – 7.85 (m, 2H), 7.79 (dd, J = 7.7, 1.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.13 (d, J = 4.0 Hz, 1H), 5.72 (d, J = 3.9 Hz, 1H), 3.87 (s, 3H), 1.46 (s, 9H).

Preparation of Compound 8;



Methyl 6-((4-((tert-butoxycarbonyl)amino)phenyl)(hydroxy)methyl)picolinate **7** (310g, 1.0 equiv.), triethylamine (219g, 2.5 equiv.) and DCM (6.2L, 20 volumes with respect to **7**) were charged into a 10L reactor under nitrogen atmosphere at 15-20°C and the solution was cooled to 0°C. Methanesulfonyl chloride (99.2g, 1.0 equiv.) was added dropwise over 30 min maintaining the temperature at 0°C. The cooling bath was removed, and the temperature was allowed to reach ambient temperature and was then aged for 1 hour at this temperature. The solution was concentrated under vacuum at 10-15°C and the residue was then dissolved in acetonitrile (438ml, 2 volumes). The resulting solution was concentrated under vacuum to yield 518g (crude) of desired product **8**. This crude product was used for the next step directly without further purification.

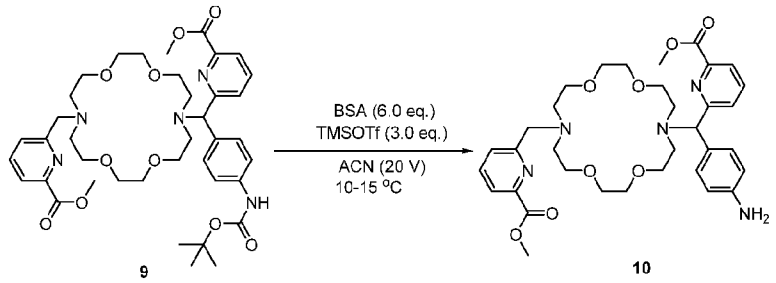
Preparation of Compound 9:



Methyl 6-((4-((tert-butoxycarbonyl)amino)phenyl)-((methylsulfonyl)oxy)methyl)picolinate **8** (212g, 1.0 equiv. 85% purity by Q-NMR), Na_2CO_3 (137.6 g, 3.0 equiv.) and acetonitrile (3.56 L, 20 volumes with respect to **8**) were charged into a 10L reactor under a nitrogen atmosphere at room temperature then the mixture was heated to 65°C and aged for 1 hour. A solution of methyl 6-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate **4** (377.8g, 2.0 equiv.) in acetonitrile (3L, 10 volumes) was added dropwise over 0.5 hours at 65 °C. The mixture was aged at this temperature until HPLC analysis showed this reaction was completed. The resulting solution was cooled at room temperature then filtered, and the filter cake was washed by MeOH (2 x 1 volume). The filtrate was concentrated under vacuum and the resulting residue was dissolved in EA (700 mL), then silica gel (800g, type: ZCX-2, 100-200 mesh, 2.11 w/w) was added. The mixture was concentrated under vacuum whilst maintaining the temperature below 35°C. Silica gel (9.6kg, type: ZCX-2, 100-200 mesh, 26.3 w/w) was charged to the column, followed by the prepared dry silica gel containing adsorbed crude **9**. The column was eluted with

ethyl acetate:petroleum ether:dichloromethane (3:3:1) / methanol:dichloromethane (1:1) (gradient from 100:0 to 90:10 with sample collection every 4L ± 0.5 L). The fractions were analyzed by TLC (ethyl acetate:petroleum ether:dichloromethane:methanol = 4:4:1:1). The product bearing fractions were combined and concentrated to yield 260g of compound **9** as yellow solid (HPLC: 94%, QNMR: 92%). An additional 70g of compound **9** was afforded as yellow oil (HPLC: 75%, QNMR: 60%). LCMS (ES, m/z): 752.30 $[M+H]^+$ Observed *m/z* ^{1}H-NMR (400MHz, $CDCl_3$, *ppm*): δ 7.53 – 7.32 (m, 3H), 7.28 – 7.18 (m, 3H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.09 (s, 1H), 4.63 (s, 1H), 3.48 (s, 3H), 3.44 (bs, 5H), 3.17 – 2.92 (m, 16H), 2.38 (dq, *J* = 25.0, 7.2, 6.8 Hz, 8H), 0.97 (s, 9H).

Preparation of Compound 10:

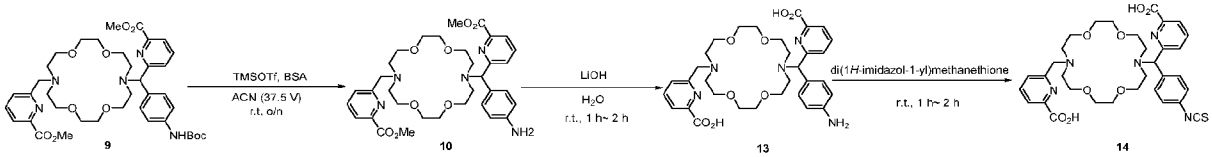


9 10

Compound **9** (260g, QNMR: 92%, 1.0 equiv.), N,O-bis(trimethylsilyl)acetamide (BSA, 6.0 equiv.) and acetonitrile (4L, 15 volumes) were charged into a 10L reactor under nitrogen atmosphere at 15-20 °C. The mixture was stirred for 40 min at 20 °C. A solution of TMSOTf (212.9g, 3.0 equiv.) in acetonitrile (1.3L, 5 volumes) was charged dropwise over 0.5 hours maintain the internal temperature between 15-20°C. The solution was aged for 1 hour at 15-20°C. When process analysis (sample preparation 0.1 mL system + 0.9 mL ACN + one drop of diisopropylethylamine) showed complete conversion of staring material the mixture was quenched with diisoproylethylamine (617g, 15.0 equiv.) maintain a temperature between 5-10 °C. The mixture was stirred for 20 minutes at 5-10°C, then a saturated aqueous NH_4Cl solution (2.6L, 10 volumes) was charged maintaining a temperature between 5-10°C. The mixture was aged for an additional 30 minutes at this temperature. The aqueous phase (contained solids) was collected and was extracted with 2-MeTHF (520ml, 2 volumes). The organic phases were combined and checked for water content by KF (KF: 9.18%), then dried with anhydrous Na_2SO_4 (500 g, 10.0 equiv.). The solids were removed by filtration and the filter cake was washed by

acetonitrile (2 x 520ml, 2 volumes). The filtrates were then dried with anhydrous Na_2SO_4 (500 g, 10.0 equiv.). After filtration, the filter cake was washed by acetonotrile (2 x 520 ml, 2 volumes) and water content was checked by KF (KF: 8.15%). The acetonitrile/2-MeTHF stream of **10** was used for next step directly. (The product was not stable to LCMS conditions).

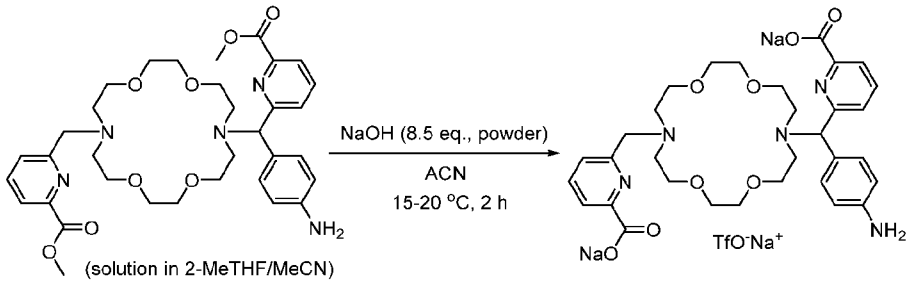
Preparation of Compound 14 (Free Acid)



Methyl 6-((4-((tert-butoxycarbonyl)amino)phenyl)(16-((6-(methoxycarbonyl)pyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinate (6.0g, 1.0 equiv.) and BSA (9.7g, 6.0 equiv.) and MeCN (120mL, 20 volumes with respect to **9**) were charged to a 500 mL reactor under nitrogen atmosphere at room temperature. A solution of TMSOTf (5.4g, 2.3 equiv.) in MeCN (120mL, 20 volumes) was added dropwise over 30 min at room temperature. The mixture was aged for overnight at room temperature. Analysis of the mixture (sample preparation 0.1 mL system + 0.9 mL ACN + one drop of diisopropylethylamine) showed the reaction had reached completion. The mixture was quenched with diisoproylethylamine (15.4g, 15.0 equiv.) maintain a temperature between 0-5°C. The mixture was stirred for 5 minutes at 0-5°C, then a saturated aqueous NH_4Cl solution (60mL, 10 volumes) was charged dropwise maintaining a temperature between 0-5°C. The aqueous phase was removed by extraction and the organic phase was collected and used for next step directly. The organic phase was charged to 500 mL 3-necked round bottle bottom bottle, a solution of LiOH (1.15g, 6.0 equiv.) in water (60mL, 10 V) was added to the solution at room temperature. The solution was stirred for 1 hour at this temperature. Analysis of the mixture (sample preparation, 0.1 mL system + 0.9 mL acetonitrile) showed not fully conversion. Another portion of LiOH (576mg, 3.0 equiv.) was added and the solution was stirred for another 1 hour at room temperature. Analysis of the mixture (sample preparation, 0.1 mL system + 0.9 mL acetonitrile) showed the reaction had reached completion. Then, TCDI (5.6g, 3.9 equiv.) was added and the solution was stirred for 1 hour at room temperature. Analysis of the mixture (sample preparation, 0.1 mL system + 0.9 mL acetonitrile) showed not fully conversion. Another portion of TCDI (2.8g, 2.0 equiv.) was added and the solution was stirred for another 1 hour at room temperature.

Analysis of the mixture (sample preparation, 0.1 mL system + 0.9 mL acetonitrile) showed the reaction had reached completion. The reaction solution was separated by reversal phase Combi-Flash. Method: column C18, A solution H_2O (Containing 0.01% formic acid), B solution ACN. 5% to 35% in 40 min, flow (100 mL/min), product in 20 min-25 min. Collect a solution. The solution was concentrated to remove ACN and separated by reversal phase Combi-Flash again. Method: column C18, A solution H_2O, B solution ACN. 5% 10 min ,5% to 35% in 5 min 95% 10 min, flow (100 mL/min), product in 13 min-25 min. Collect a solution. The solution was concentrated under vacuum at <20 °C and dried by lyophilization. This result in 2.5g (47% yield in 3 steps) compound **14** as a yellow solid. Compound **14** (6-((16-((6-carboxypyridin-2-yl)(4-isothiocyanatophenyl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)picolinic acid) required storage at -80 °C. LCMS: (ES, *m/z*): 666.3 $[M+H]^+$ ^{1}H-NMR: (400 MHz, D_2O, *ppm*): 7.94-7.84 (m, 4H), 7.56-7.40 (m, 4H), 7.16-7.14 (m, 2H), 5.83 (s, 1H), 4.56 (s, 2H), 3.80-3.75 (m, 8H), 3.60-3.49 (m, 14H), 3.36-3.33 (m, 2H).

Preparation of Compound 11 (Sodium salt):

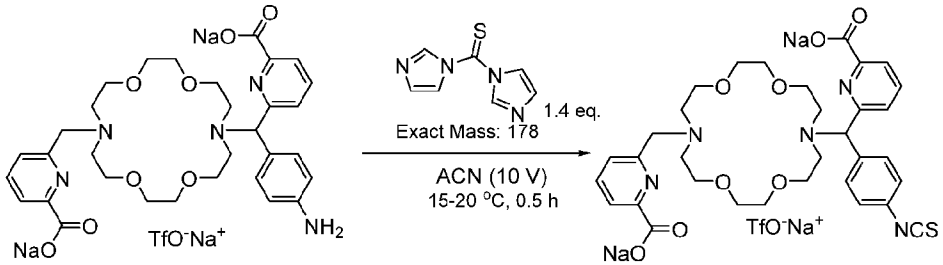


10 **11**

The prepared solution of compound **10** in ACN and 2-MeTHF was charged to a 10L 4-necked reaction and the solution was cooled to 5-10°C. Powdered NaOH (56.9g, 4.5 equiv.) was added maintaining the temperature between 5-10°C. The solution was stirred for 0.5 hours at 15-20°C. Analysis of the mixture (sample preparation, 0.1 mL system + 0.9 mL acetonitrile) showed no conversion. Additional powdered NaOH (25.3g, 2.0 equiv.) was added at 5-10 °C. The solution was aged for an additional 0.5 hours at 15-20°C. A second IPC was analyzed and showed there was 50% conversion. A final charge of powdered NaOH (25.3 g, 2.0 equiv.) was added at 5-10°C. The mixture was stirred for additional 0.5 hours at 15-20°C. Analysis showed complete conversion of the starting material **10**. The mixture was filtered, and the filter cake was washed by acetonitrile (2 x 520ml, 2 volumes). The final solution (~7.5 L, 28.8 voluems) was

concentrated to 1-2 volumes maintaining a temperature between 15-20°C. The residue was then treated with acetonitrile (2L, 7.7 volumes) and the water content was checked by KF (KF: 5.7%). The mixture was filtered, and the filter cake was washed by ACN (2 x 520ml, 2 volumes). The solution was then concentrated to 1-2 V under vacuum at 15-20°C. The water content was again checked by KF (KF: 5.5%). The solution was diluted with acetonitrile (390ml, 1.5 volumes), and was added dropwise over 0.5 hours into MTBE (2.6L, 10 volumes) maintaining a temperature between 15-20°C. The solvents were decanted to leave a viscous oil which was redissolved in acetonitrile (520ml, 2 volumes) and added into MTBE (2.6L, 10 volumes). This process was repeated a further four times. To yield a viscous oil which was finally dissolved in acetonitrile (520ml, 2 volumes) and dried, then concentrated at 15-20°C under reduced pressure. Residual solvents were then removed by evaporation with an oil pump at 15-20°C. After drying 335 g of compound **11** was afforded as an off-yellow solid (QNMR: 70 %, 87 % overall yield over the two steps). LCMS (ES,m/z): 624.3 $[M\text{-}TfONa\text{-}2Na+3H]^+$ ^{1}H-NMR (300MHz, Methanol-d_4, *ppm*): δ 7.97 (dd, J = 7.8, 2.1 Hz, 2H), 7.84 (t, J = 7.7 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.36 (dd, J = 7.8, 1.1 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 3.96 (s, 1H), 3.83-3.36 (m, 18H), 3.03 – 2.62 (m, 6H), 2.55 (d, J = 14.3 Hz, 2H).

Preparation of Compound 12 (TOPA-[C7]-phenylisothiocyanate sodium salt):



11 **12**

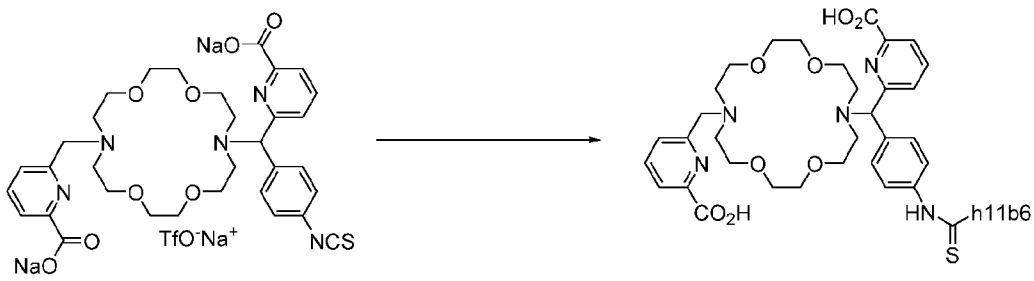
TCDI (68.7g, 1.4 equiv.) and acetonitrile (2.6L, 8 volumes) were charged to a 10L reactor under nitrogen atmosphere at 15-20°C. A solution of compound **11** (330 g, Na^+ salt, QNMR: 70 %, 1.0 equiv.) in acetonitrile (660 mL, 2 volumes) was added dropwise over 30 min maintaining a temperature between 15-20 °C. The mixture was aged for 0.5 hours at 15-20°C. Analysis of the mixture (sample preparation:30 µL system + 300 µL ACN + a drop of water) showed the reaction had reached completion. The water content was checked by KF (KF: 0.19%). The system was dried and concentrated at 15-20 °C under reduced pressure. The

resulting residue was dissolved in acetonitrile (945ml, 2.9 volumes) and the water content was measured by KF (KF: 0.34%). isopropyl acetate (660ml, 2 volumes) was charged to the solution over 40 minutes at 15-20 °C. No nucleation was observed, and additional isopropyl acetate (6.6L, 18 volumes) was charged dropwise slowly in 40 min at 15-20 °C leading to precipitation of the product **12** which was collected by filtration as an off yellow solid. The solid was dissolved in acetonitrile (330ml, 1 volume) and IPAc (6.6L, 20 volumes) was charged dropwise slowly in 40 min at 15-20 °C. The mixture was filtered to yield 230g of product as an off-yellow solid (LCAP: 80.99%, QNMR: 59%, 10% IPAc). The wet cake was dried under vacuum in 2 hours at 15-20°C, to give 224g of crude **12** as an off-yellow solid (LCAP: 80.9%, QNMR: 60.4%, ~6% IPAc). The crude **12** was redissolved in acetonitrile (330ml, 1 volumes) and isopropyl acetate (412ml, 1.25 volumes) was charged dropwise slowly in 40 min at 15-20 °C. The resulting mixture was filtered, and **12** was collected (30.5 g, HPLC = 60.9%, assay: 25.5%). The mother liquors were diluted with isopropyl acetate (6.6L, 20 volumes) added over 40 minutes at 15-20 °C. The mixture was filtered, and the cake was dried to afford 173.5 g of crude product **12** as an off-yellow solid (LCAP: 85.4%, QNMR: 66%, 3.9% IPAc, RRT1.19 = 3.9%). 190 g of crude **12** product was dissolved in 760 mL of acetonitrile:isopropyl acetate (2:1) and the mixture was passed through a silica gel column (380g, 2 x). The silica was flushed with acetonitrile:isopropyl acetate (2:1, 5.7L) and then 12L acetonitrile (very little product). Product containing fraction were the concentrated to afford 118g of product **12** as an off-yellow solid (LCAP: 95%). The silica pad was then flushed with MeCN/H_2O (12L, 10:1). The solvents were removed in vacuo to afford and additional 60 g crude 12 as an off-yellow solid which was dissolved in acetonitrile (1.5L), stirred for 30 min then filtered. The mother liquor were then concentrated to afford 24g of crude **12** as an off-yellow solid (LCAP = 92%). crude **12** (118 g) and crude **12** (24 g) prepared as above were dissolved in acetonitrile (330ml, 1 volume) and isopropyl acetate (6.6L, 20 volumes) was charge dropwise over 40 min 15-20 °C. The mixture was then filtered to afford 133g of 12 product as off-yellow solid of suitable purity (LCAP: 95%, QNMR: 60.8%, 7.8% IPAc). Note, compound **12** required storage at -20 °C. LCMS: (ES,m/z): 666.61 [M-TfONa-2Na+3H]$^+$ ^{1}H-NMR: (400MHz, methanol-d_4, *ppm*): δ 8.00 (ddd, J = 13.8, 7.7, 1.0 Hz, 2H), 7.84 (dt, J = 20.4, 7.7 Hz, 2H), 7.58 – 7.49 (m, 2H), 7.40 (dd, J = 7.6, 1.0 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.28 – 7.20 (m, 1H), 4.96 (hept, J = 6.3 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.83 (d, J = 15.1 Hz,

1H), 3.70 – 3.52 (m, 11H), 3.55 – 3.39 (m, 4H), 3.07 – 2.73 (m, 6H), 2.62 (dt, J = 15.1, 3.6 Hz, 2H).

Example 20

TOPA-[C7]-phenylthiourea-h11B6 Antibody Conjugate



(In the TOPA-[C7]-phenylthiourea-h11B6 Antibody Conjugate depicted above, the structure does not show the lysine residue of h11b6 that is linked to the phenylthiourea moiety.)

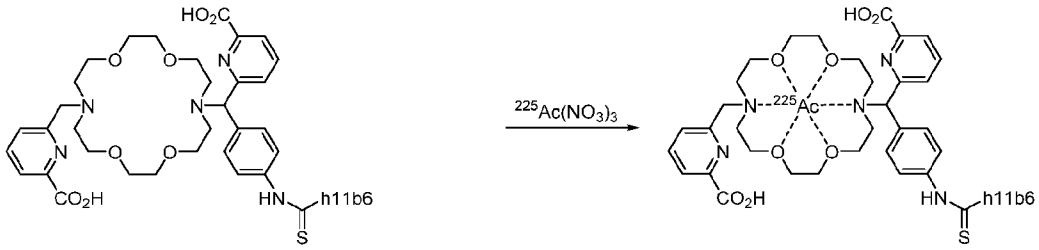
TOPA-[C7]-phenylthiourea *modification of mAb:*

h11b6 mAb (10.2 mg/ml) was diluted to 1mg/ml in 10mM sodium acetate pH 5.2 buffer. Directly prior to conjugation, pH was adjusted to pH 9 with sodium bicarbonate buffer (VWR 144-55-8). pH was confirmed with pH paper. Then, 10x molar excess of disodium salt TOPA-[C7]-phenylisothiocyanate sodium salt (50mM stock dissolved in water) was added to the *h11b6* mAb, and the mixture of antibody and TOPA-[C7]-phenylisothiocyanate sodium salt was incubated at room temperature without shaking for approximately 1 hour. The addition of TOPA-[C7]-phenylisothiocyanate sodium salt was monitored by intact mass ESI-TOF LC-MS on an Agilent ® G224 instrument until the CAR value was between 1.5-2.0. The mixture was then immediately quenched by addition of 1M Tris pH 8.5 (Teknova T1085) to a final concentration of 100 mM. Excess free chelator was removed by desalting the reaction into 10mM sodium acetate pH 5.2 using a 7K Zeba ® desalting column. To confirm no excess chelator was present, 3x rounds of sample dilution to 15mls followed by concentration to 1ml using a 50,000MWCO Amicon concentrator device was performed. Sample was then concentrated to its final concentration for radiolabeling. The final conjugate was confirmed to be monomeric by analytical size exclusion chromatography on a Tosoh TSKgel G3000SWxl 7.8mm

x 30cm, 5 u column; column temperature: room temperature; the column was eluted 0.2M sodium phosphate pH 6.8; flow rate: 0.8 mL/min; 18 min run; injection volume: 18ul.

Example 21

Ac-225 labeled TOPA-[C7]-phenylthiourea-h11B6 antibody conjugate



(In the Ac-225 labeled TOPA-[C7]-phenylthiourea-h11B6 Antibody Conjugate depicted above, the structure does not show the lysine residue of h11b6 that is linked to the phenylthiourea moiety.)

(i) *Labeling of TOPA-[C7]-phenylthiourea-h11B6 with Ac-225 in 3M NaOAc buffer*:

To a solution of NaOAc (3 M in H_2O, 60 µL) in a plastic vial were added sequentially Ac-225 (10 mCi/mL in 0.1 N HCl, 15 µL) and TOPA-[C7]-phenylthiourea-h11B6 (1.13 mg/mL in 10 mM NaOAc pH=5.5, 441 uL, 0.5 mg). After mixing, the pH was ~ 6.5 by pH paper. The vial was left standing still at 37 °C for 2 hr.

iTLC of the labeling reaction mixture:

0.5 µL of the labeling reaction mixture was loaded onto an iTLC-SG, which was developed with 10 mM EDTA (pH 5-6). The dried iTLC-SG was left at room temperature for overnight before it was scanned on a Bioscan AR-2000 radio-TLC scanner. Under the elution conditions described herein, TOPA-[C7]-phenylthiourea-h11B6 bound Ac-225 stayed at the origin and any free Ac-225 would migrate with the solvent to the solvent front. Scanning of the iTLC showed 99.9% TOPA-[C7]-phenylthiourea-h11B6 bound Ac-225.

DTPA challenge of the labeling reaction mixture:

0.5 uL of the labeling reaction mixture was also mixed with 10mM DTPA (pH=6.5, 15 µL) at 37°C. After 30 min, 10 uL of the mixture was spotted on iTLC-SG and developed by 10 mM EDTA. The dried iTLC-SG was left at room temperature for overnight before it was scanned on a Bioscan AR-2000 radio-TLC scanner. Under the elution conditions described herein, TOPA-

[C7]-phenylthiourea-h11B6 chelated Ac-225 stayed at the origin and any free Ac-225 would migrate with the solvent to the solvent front. Scanning of the iTLC showed 99.7% TOPA-[C7]-phenylthiourea-h11B6 chelated Ac-225.

Purification on PD10 column:

The PD-10 resin was conditioned in NaOAc buffer solution by passing 5 mL X 3 of NaOAc buffer (25 mM NaOAc, 0.04% PS-20, pH 5.5) through column and discarding the washings. The entire labeling reaction mixture was applied to the reservoir of the column and the eluate collected in pre-numbered plastic tubes. The reaction vial was washed with 0.2 mL X 3 NaOAc buffer (25 mM NaOAc, 0.04% PS-20, pH 5.5) and the washings pipetted into the reservoir of the PD-10 column and the eluate collected. Each tube contained ~1 mL of the eluate. Continued application of NaOAc buffer (25 mM NaOAc, 0.04% PS-20, pH 5.5) into the reservoir of the PD-10 column occurred until a total elution volume of 10 mL was reached. The radiochemical purity of fractions collected were checked by iTLC: 10 uL of each collected fraction was spotted on iTLC-SG and developed with 10 mM EDTA. The dried iTLC-SG was left at room temperature for overnight before it was scanned on a Bioscan AR-2000 radio-TLC scanner. Pure fraction should have no radioactivity signal at the solvent front of the iTLC-SG.

DTPA challenge of the purified ^{225}Ac-TOPA-[C7]-phenylthiourea-h11B6 :

10 µL of fraction #3 collected after PD-10 column was mixed with 15 µL of 10 mM DTPA solution (pH 6.5), and incubated for 30 min. 10 µL of the mixture was loaded onto an iTLC-SG, which was developed with 10 mM EDTA and dried overnight. It was scanned on a Bioscan AR-2000 radio-TLC scanner. No radioactivity signal was observed at the solvent front of the iTLC-SG indicating that there was no free Ac-225 in the fraction #3.

HPLC analysis of the purified ^{225}Ac-TOPA-[C7]-phenylthiourea-h11B6 :

The fraction #3 collected after PD-10 column was analyzed by HPLC. HPLC method: Tosoh TSKgel G3000SWxl 7.8 mm x 30 cm, 5 µm column; column temperature: room temperature; the column was eluted with DPBS buffer (X1, without calcium and magnesium); flow rate: 0.7 mL/min; 20 min run; injection volume: 40 µL. After HPLC, the fractions were collected in time intervals of 30 seconds or 1 minute. The collected HPLC fractions were left at room temperature overnight. The radioactivity in each of the collected fractions was counted in a gamma counter. The HPLC radio trace was constructed from the radioactivity in each HPLC fraction. HPLC

radio trace showed a radioactive peak corresponding to the TOPA-[C7]-phenylthiourea-h11B6 peak on HPLC UV trace.

(ii) *Labeling of TOPA-[C7]-phenylthiourea-h11B6 at higher concentration with Ac-225 in 1.5 M NaOAc buffer*:

To a solution of NaOAc (1.5 M in H_2O with 0.04% PS-20, 63 μL) in a plastic vial were added sequentially Ac-225 (10 mCi/mL in 0.1 N HCl, 10 μL) and TOPA-[C7]-phenylthiourea-h11B6 (9.36 mg/mL in 10 mM NaOAc pH=5.2, 0.04% PS-20, 36 uL, 337 μg). After mixing, the pH was ~ 6.5 by pH paper. The vial was left standing still at 37 °C for 2 hr.

iTLC of the labeling reaction mixture:

0.5 μL of labeling reaction mixture was then loaded onto an iTLC-SG, which was developed with 10 mM EDTA. The dried iTLC-SG was left at room temperature for overnight before it was scanned on a Bioscan AR-2000 radio-TLC scanner. Under the elution conditions described herein, TOPA-[C7]-phenylthiourea-h11B6 bounded Ac-225 stayed at the origin and any free Ac-225 would migrate with the solvent to the solvent front. Scanning of the iTLC showed 99.9% TOPA-[C7]-phenylthiourea-h11B6 bonded Ac-225.

DTPA challenge of the labeling reaction mixture:

0.5 uL of the labeling reaction mixture was also mixed with 10mM DTPA (pH=6.5, 15 μL) at 37°C. After 30 min, 10 uL of the mixture was spotted on iTLC-SG and developed by 10 mM EDTA. The dried iTLC-SG was left at room temperature for overnight before it was scanned on a Bioscan AR-2000 radio-TLC scanner. Under the elution conditions described herein, TOPA-[C7]-phenylthiourea-h11B6 chelated Ac-225 stayed at the origin and any free Ac-225 would migrate with the solvent to the solvent front. Scanning of the iTLC showed 99.9% TOPA-[C7]-phenylthiourea-h11B6 chelated Ac-225.

(iii) *Labeling of TOPA-[C7]-phenylthiourea-h11B6 at higher concentration with Ac-225 in 1 M NaOAc buffer*:

To a solution of NaOAc (1.0 M in H_2O with 0.04% PS-20, 63 μL) in a plastic vial were added sequentially Ac-225 (10 mCi/mL in 0.1 N HCl, 10 μL) and TOPA-[C7]-phenylthiourea-h11B6 (9.36 mg/mL in 10 mM NaOAc pH=5.2, 0.04% PS-20, 36 uL, 337 μg). After mixing, the pH was ~ 6.5 by pH paper. The vial was left standing still at 37 °C for 2 hr.

iTLC of the labeling reaction mixture:

0.5 μL of labeling reaction mixture was then loaded onto an iTLC-SG, which was developed with 10 mM EDTA. The dried iTLC-SG was left at room temperature for overnight before it was scanned on a Bioscan AR-2000 radio-TLC scanner. Under the elution conditions described herein, TOPA-[C7]-phenylthiourea-h11B6 bound Ac-225 stayed at the origin and any free Ac-225 would migrate with the solvent to the solvent front. Scanning of the iTLC showed 99.9% TOPA-[C7]-phenylthiourea-h11B6 bonded Ac-225.

DTPA challenge of the labeling reaction mixture:

0.5 uL of the labeling reaction mixture was also mixed with 10mM DTPA (pH=6.5, 15 μL) at 37°C. After 30 min, 10 uL of the mixture was spotted on iTLC-SG and developed by 10 mM EDTA. The dried iTLC-SG was left at room temperature for overnight before it was scanned on a Bioscan AR-2000 radio-TLC scanner. Under the elution conditions described herein, TOPA-[C7]-phenylthiourea-h11B6 chelated Ac-225 stayed at the origin and any free Ac-225 would migrate with the solvent to the solvent front. Scanning of the iTLC showed 99.9% TOPA-[C7]-phenylthiourea-h11B6 chelated Ac-225.

Labeling of TOPA-[C7]-phenylthiourea-h11B6 at higher concentration with Ac-225 in 25 mM NaOAc with 0.4% tween-20, pH 5.5:

To a solution of NaOAc (25 mM in H_2O with 0.04% PS-20, pH 5.5, 10 μL) in a plastic vial were added sequentially Ac-225 (10 mCi/mL in 0.1 N HCl, 5 μL), TOPA-[C7]-phenylthiourea-h11B6 (10.4 mg/mL in 10 mM NaOAc pH=5.2, 16 uL, 166 μg) and NaOH (0.1 M, 5 μL). After mixing, the pH was ~ 6.0 by pH paper. The vial was left standing still at 37 °C for 2 hr.

iTLC of the labeling reaction mixture:

0.5 μL of labeling reaction mixture was then loaded onto an iTLC-SG, which was developed with 10 mM EDTA. The dried iTLC-SG was left at room temperature for overnight before it was scanned on a Bioscan AR-2000 radio-TLC scanner. Under the elution conditions described herein, TOPA-[C7]-phenylthiourea-h11B6 bound Ac-225 stayed at the origin and any free Ac-225 would migrate with the solvent to the solvent front. Scanning of the iTLC showed 99.9% TOPA-[C7]-phenylthiourea-h11B6 bonded Ac-225.

DTPA challenge of the labeling reaction mixture:

0.5 uL of the labeling reaction mixture was also mixed with 10mM DTPA (pH=6.5, 15 μL) at 37°C. After 30 min, 10 uL of the mixture was spotted on iTLC-SG and developed by 10 mM EDTA. The dried iTLC-SG was left at room temperature for overnight before it was scanned on

a Bioscan AR-2000 radio-TLC scanner. Under the elution conditions described herein, TOPA-[C7]-phenylthiourea-h11B6 chelated Ac-225 stayed at the origin and any free Ac-225 would migrate with the solvent to the solvent front. Scanning of the iTLC showed 99.8% TOPA-[C7]-phenylthiourea-h11B6 chelated Ac-225.

Reaction conditions for labeling of TOPA-[C7]-phenylthiourea-h11B6 with Ac-225

TOPA-[C7]-phenylthiourea-h11B6 in buffer	Buffer for Labeling reaction	Radiochemical yield (iTLC)	DTPA challenge
1.13 mg/mL in 10 mM NaOAc pH=5.5	3 M NaOAc	> 99 %	> 99 %
9.36 mg/mL in 10 mM NaOAc, pH=5.2; 0.04% PS-20	1.5 M NaOAc, 0.04% PS-20	> 99 %	> 99 %
9.36 mg/mL in 10 mM NaOAc, pH=5.2; 0.04% PS-20	1.0 M NaOAc, 0.04% PS-20	> 99 %	> 99 %
10.4 mg/mL in 10 mM NaOAc, pH=5.2	25 mM in NaOAc, 0.04% PS-20, pH 5.5	> 99 %	> 99 %

EXAMPLE 22 — GENERATION OF ANTI-KLK2 ANTIBODIES

Antibody Generation Using Transgenic Mice (Ablexis®) and Transgenic Rats (OmniRat®) Expressing Human Immunoglobulin Loci

The OmniRat® contains a chimeric human/rat IgH locus (comprising 22 human VHs, all human D and JH segments in natural configuration linked to the rat CH locus) together with fully human IgL loci (12 Vκs linked to Jκ-Cκ and 16 Vλs linked to Jλ-Cλ) (*see*, *e.g.*, Osborn, *et al.*, *J Immunol*, 2013, 190(4): 1481-90). Accordingly, the rats exhibit reduced expression of rat immunoglobulin, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity chimeric human/rat IgG monoclonal antibodies with fully human variable regions. The preparation and use of OmniRat®, and the genomic modifications carried by such rats, is described in International Publication No. WO14/093908.

Ablexis® mice generate antibodies having human variable domains linked to human CH1 and CL domains, chimeric human/mouse hinge regions, and mouse Fc regions. Ablexis Kappa Mouse and Lambda Mouse strains are distinguished by which of their heavy chains are human or mouse as noted below. Antibodies produced by the Kappa Mouse lack sequences derived from mouse VH, DH and JH exons and mouse Vκ, Jκ and Cκ exons. The endogenous mouse Igλ is active in the Kappa Mouse. The human Igκ chains comprise approximately 90-95% of the naïve repertoire and mouse Igλ chains comprise approximately 5-10% of the naïve repertoire in this strain. Antibodies produced by the Lambda Mouse lack sequences derived from mouse VH, DH and JH exons and mouse Vλ, Jλ and Cλ exons. The endogenous mouse Igκ is active in the Lambda Mouse. The human Igλ chains comprise approximately 40% of the naïve repertoire and mouse Igκ chains comprise approximately 60% of the naïve repertoire. The preparation and use of Ablexis®, and the genomic modifications carried by such mice, is described in International Publication No. WO11/123708.

Ablexis® mice and OmniRats® rats were immunized with soluble full length KLK2 protein (human kallikrein-2 6-His protein, with an amino acid sequence of VPLIEGRIVGGWECEKHSQPWQVAVYSHGWAHCGGVLVHPQWVLTAAHCLKKNSQVWLGR HNLFEPEDTGQRVPVSHSFPHPLYNMSLLKHQSLRPDEDSSHDLMLLRLSEPAKITDVVKVLGL PTQEPALGTTCYASGWGSIEPEEFLRPRSLQCVSLHYSEKVTEFMLCAGLWTGGKDTCGGDSG GPLVCNGVLQGITSWGPEPCALPEKPAVYTKVVHYRKWIKDTIAANPHHHHHH (SEQ ID NO: 454).

Lymphocytes from Ablexis mice and OniRats rats were extracted from lymph nodes and fusions performed by cohorts. Cells were combined and sorted for CD138 expression. Hybridoma screening was performed in high throughput miniaturized MSD format using soluble hK2 antigen. Approximately >300 samples were identified to be hK2 binders. The binding of >300 anti-hKLK2 supernatant samples to human KLK2 protein was measured by single cycle kinetics method by Biacore 8K SPR. Additionally the supernatant samples were tested for binding to human KLK3 protein as well. In parallel, supernatants were also tested for binding to KLK2 expressing cell lines VCap and negative cell line DU145 by Flow Cytometry. Selected cell binders were moved forward to scFv conversion in both VH-VL and VL/VH orientation and thermal stability tests as described above. KL2B413, KL2B30, KL2B53 and KL2B242 resulted from the Ablexis mice immunization campaign. KL2B467 and KL2B494 resulted from the OmniRat immunization campaign.

Antibodies generated through the various immunization and humanization campaigns described above were expressed in a fab format, a mAb format, a scFv format in the VH-linker-VL orientation or a scFv format in VL-linker-VH orientation and were further analyzed as described below. The linker sequence of SEQ ID NO: 7 described above was used to conjugate the VH/VL regions.

Example 23. Structural characterization of anti KLK2 antibodies

Sequences of antibody variable domains and scFv antibody fragments which showed highest performance in intracellular assay are provided herein. Variable domains were expressed in a Fab format, a scFv format in the VH-linker-VL orientation or a scFv format in VL-linker-VH orientation.

Variable domains VH, VL and CDRs

Table 3 shows the VH and VL amino acid sequences of selected anti-hK2 antibodies. **Table 4** shows the Kabat HCDR1, HCDR2 and HCDR3 of selected anti-hK2 selected antibodies. **Table 5** shows the Kabat LCDR1, LCDR2 and LCDR3 of the selected anti-hK2 antibodies. **Table 6** shows the AbM HCDR1, HCDR2 and HCDR3 of selected anti-hK2 antibodies. **Table 7** shows the AbM LCDR1, LCDR2 and LCDR3 of the anti-hK2. **Table 8** summarizes the variable domain sequence and SEQ ID NO of selected hK2 antibodies. **Table 9** shows the protein and DNA SEQ ID NOs for the VH and VL regions.

Table 3. VH and VL amino acid sequences of selected anti-hK2 antibodies.

Ab name	VH name	VH amino acid Sequence	VH SEQ ID NO:	VL name	VL amino acid sequence	VL SEQ ID NO:
m11B6	m11B6_VH	DVQLQESGPGLVKPSQSLSLTCTVTGNSITSDYAWNWIRQFPGNRLEWMGYISYSGSTTYSPSLKSRFSITRDTSKNQFFLQLNSVTPEDTATYFCATGYYYGSGFWGQGTLVTVSS	125	m11B6_VL	DIVLTQSPASLAVSLGQRATISCRASESVEYFGTSLMHWYRQKPGQPPKLLIYAASNVESGVPARFSGSGSGTDFSLNIQPVEEDDFSMYFCQQTRKVPYTFGGGTKLEIK	124
h11B6	hu11B6_VH	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQGTLVTVSS	5	hu11B6_VL	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIK	2

HCF3-LCD6	HCF3_VH	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGTLVTVSS	6	LCD6_VL	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIK	1
HCG5-LCB7	HCG5_VH	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGTLVTVSS	4	LCB7_VL	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIK	3
KL2B357	KL2B357_VH	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSS	159	KL2B357_VL	DIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQTRKVPYTFGGGTKVEIK	160
KL2B358	KL2B358_VH	QVQLQESGPGLVPSQTLSLTCTVSGNTSDYAWNWIRQPPKGLEWIGYISYSGSTYNPSLKSRVTISRTSKNQFSLKLSSVTADTAVYYCATGYYGSGFWGQGTLVTSS	161	KL2B358_VL	EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIK	140
KL2B359	KL2B359_VH	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKRLEWIGYISYSGSTTYNPS	139	KL2B359_VL	EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSG	140

		LKSRVTISRDTSK NQFSLKLSSVTAA DTAVYYCATGYY YGSGFWGQGTLV TVSS			SGTDFTLTISSVEPE DFAVYFCQQTRKV PYTFGGGTKVEIK	
KL2B360	KL2B360_ VH	QVQLQESGPGLV KPSQTLSLTCTVS GNSITSDYAWNW IRQFPGKGLEWIG YISYSGSTTYNPS LKSRVTISRDTSK NQFSLKLSSVTAA DTAVYYCATGYY YGSGFWGQGTLV TVSS	159	KL2B360_ VL	EIVLTQSPATLSLSP GERATLSCRASESV EYFGTSLMHWYQQ KPGQPPRLLIYAAS NVESGIPARFSGSG SGTDFTLTISSVEPE DFAVYFCQQTRKV PYTFGGGTKVEIK	140
KL2B413	KL2B413_ VH	EVQLVESGGGLV QPGGSLRLSCAAS GFTFSSYWMTWV RQAPGKGLEWV ANIKQDGSERYY VDSVKGRFTISRD NAKNSLYLQMNS LRAEDTAVYYCA RDQNYDILTGHY GMDVWGQGTTV TVSS	137	KL2B413_ VL	EIVLTQSPSFLSASV GDRVTITCRASQGI SSYLSWYQQKPGK APKLLIYATSTLQS GVPSRFSGSGSGTE FTLTISSLQPEDFAT YYCQQLNSYPRTF GQGTKVEIK	138
KL2B30	KL2B30_V H	QVQLQESGPGLV KPSETLSLTCTVS GGSISSYYWSWIR QPPGKGLEWIGYI YYSGSTNYNPSL KSRVTISVDTSKN QFSLKLSSVTAAD TAVYYCAGTTIF GVVTPNFYYGMD VWGQGTTVTVSS	162	KL2B30_V L	DIQMTQSPSFLSAS VGDRVTITCRASQG ISSYLAWYQQKPG KAPKFLIYAASTLQ SGVPSRFSGSGSGT EFTLTISSLQPEDFA TYYCQQLNSYPLTF GGGTKVEIK	163

KL2B53	KL2B53_VH	EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDGSKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCARESGWSHYYYYGMDVWGQGTMVTVSS	164	KL2B53_VL	DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIK	165
KL2B242	KL2B242_VH	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWGQGTLVTVSS	166	KL2B242_VL	SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVL	167
KL2B467	KL2B467_VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAFDYWGQGTQVTVSS	168	KL2B467_VL	QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTV	169
KL2B494	KL2B494_VH	QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALLYDGMDVWGQGTMVTVSS	204	KL2B494_VL	SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVL	205

KL2B242 LC_C33S	KL2B242_ VH	QVQLQESGPGLV KPSETLSLTCTVS GGSISSYYWSWL RQPAGSGLEWIG RLYVSGFTNYNP SLKSRVTLSLDPS RNQLSLKLSSVTA ADTAVYYCAGDS GNYWGWFDPWG QGTLVTVSS	166	KL2B242L C_C33S_V L	SYELTQPPSVSVSP GETASITCSGDQLG ENYASWYQQKPGQ SPVLVIYQDSKRPS GIPERFSGSNSGNT ATLTISGTQALDEA DYYCQAWDNSIVV FGGGTKLTVL	444

Table 4. Kabat HCDR1, HCDR2 and HCDR3 amino acid sequences of selected anti-KLK2 antibodies.

	Kabat HCDR1		Kabat HCDR2		Kabat HCDR3	
Ab name	Sequence	SEQ ID NO	Sequence	SEQ ID NO	Sequence	SEQ ID NO
m11B6	SDYAWN	63	YISYSGSTTYSPSLKS	64	GYYYGSGF	66
hu11B6	SDYAWN	63	YISYSGSTTYNPSLKS	65	GYYYGSGF	66
HCF3-LCD6	SDYAWN	63	YISYSGSTTYNPSLKS	65	GYYYGSGF	66
HCG5-LCB7	SDYAWN	63	YISYSGSTTYNPSLKS	65	GYYYGSGF	66
KL2B357	SDYAWN	63	YISYSGSTTYNPSLKS	65	GYYYGSGF	66
KL2B358	SDYAWN	63	YISYSGSTTYNPSLKS	65	GYYYGSGF	66
KL2B359	SDYAWN	63	YISYSGSTTYNPSLKS	65	GYYYGSGF	66
KL2B360	SDYAWN	63	YISYSGSTTYNPSLKS	65	GYYYGSGF	66
KL2B413	SYWMT	141	NIKQDGSERYYVDSV KG	142	DQNYDILTGHY GMDV	143
KL2B30	SYYWS	170	YIYYSGSTNYNPSLKS	171	TTIFGVVTPNFY YGMDV	172
KL2B53	SYDIH	176	IISYDGSKKDYTDSVK G	177	ESGWSHYYYY GMDV	178
KL2B242	SYYWS	170	RLYVSGFTNYNPSLKS	183	DSGNYWGWFD P	184
KL2B467	YYGMH	188	FISYDGSNKYYADSV KG	189	LPYSGSYWAFD Y	190
KL2B494	HYAMS	206	TIGGSGGSTYYADSVK G	207	PHIVMVTALLY DGMDV	208

Table 5. Kabat LCDR1, LCDR2 and LCDR3 amino acid sequences of selected anti-hK2 antibodies.

	Kabat LCDR1		Kabat LCDR2		Kabat LCDR3	
Ab name	Sequence	SEQ ID NO	Sequence	SEQ ID NO	Sequence	SEQ ID NO
m11B6	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
hu11B6	KASESVEYFGTSLMH	68	AASNRES	70	QQTRKVPYT	71
HCF3-LCD6	KASESVEYFGTSLMH	68	AASNRES	70	QQTRKVPYT	71
HCG5-LCB7	KASESVEYFGTSLMH	68	AASNRES	70	QQTRKVPYT	71
KL2B357	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
KL2B358	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
KL2B359	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
KL2B360	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
KL2B413	RASQGISSYLS	144	ATSTLQS	145	QQLNSYPRT	146
KL2B30	RASQGISSYLA	173	AASTLQS	174	QQLNSYPLT	175
KL2B53	RASQDISNYLA	179	AASTLHS	180	QKYNSAPYT	181
KL2B242	SGDQLGENYAC	185	QDSKRPS	186	QAWDNSIVV	187
KL2B467	GGDNIGSKSVH	191	DNSDRPS	192	QVWDSSSDHPVV	193
KL2B494	GGNNIGSKSVH	182	DDSDRPS	470	QVWDSSSDHVV	209

Table 6. AbM HCDR1, HCDR2 and HCDR3 amino acid sequences of selected anti-hK2 antibodies.

	AbM HCDR1		AbM HCDR2		AbM HCDR3	
Ab name	Sequence	SEQ ID NO	Sequence	SEQ ID NO	Sequence	SEQ ID NO
m11B6	GNSITSDYAWN	72	YISYSGSTT	73	GYYYGSGF	66
hu11B6	GNSITSDYAWN	72	YISYSGSTT	73	GYYYGSGF	66
HCF3-LCD6	GNSITSDYAWN	72	YISYSGSTT	73	GYYYGSGF	66
HCG5-LCB7	GNSITSDYAWN	72	YISYSGSTT	73	GYYYGSGF	66
KL2B357	GNSITSDYA	72	YISYSGSTT	73	GYYYGSGF	66

	WN					
KL2B358	GNSITSDYAWN	72	YISYSGSTT	73	GYYYGSGF	66
KL2B359	GNSITSDYAWN	72	YISYSGSTT	73	GYYYGSGF	66
KL2B360	GNSITSDYAWN	72	YISYSGSTT	73	GYYYGSGF	66
KL2B413	GFTFSSYWMT	147	NIKQDGSERY	148	DQNYDILTGHYGMDV	143
KL2B30	GGSISSYYWS	194	YIYYSGSTN	195	TTIFGVVTPNFYYGMDV	172
KL2B53	GFTFSSYDIH	196	IISYDGSKKD	197	ESGWSHYYYYGMDV	178
KL2B242	GGSISSYYWS	198	RLYVSGFTN	199	DSGNYWGWFDP	184
KL2B467	GFTFSYY	200	FISYDGSNKY	201	LPYSGSYWAFDY	190
KL2B494	GFTFSHYAMS	216	TIGGSGGSTYY	217	PHIVMVTALLYDGMDV	218

Table 7. AbM LCDR1, LCDR2 and LCDR3 amino acid sequences of selected anti-hK2 antibodies.

	AbM LCDR1		AbM LCDR2		AbM LCDR3	
Ab name	Sequence	SEQ ID NO	Sequence	SEQ ID NO	Sequence	SEQ ID NO
m11B6	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
hu11B6	KASESVEYFGTSLMH	68	AASNRES	70	QQTRKVPYT	71
HCF3-LCD6	KASESVEYFGTSLMH	68	AASNRES	70	QQTRKVPYT	71
HCG5-LCB7	KASESVEYFGTSLMH	68	AASNRES	70	QQTRKVPYT	71
KL2B357	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
KL2B358	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
KL2B359	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
KL2B360	RASESVEYFGTSLMH	67	AASNVES	69	QQTRKVPYT	71
KL2B413	RASQGISSYLS	144	ATSTLQS	145	QQLNSYPRT	146
KL2B30	RASQGISSYLA	173	AASTLQS	174	QQLNSYPLT	175
KL2B53	RASQDISNYLA	179	AASTLHS	180	QKYNSAPYT	181

KL2B242	SGDQLGENYAC	185	QDSKRPS	186	QAWDNSIVV	187
KL2B467	GGDNIGSKSVH	191	DNSDRPS	192	QVWDSSSDHPVV	193
KL2B494	GGNNIGSKSVH	182	DDSDRPS	470	QVWDSSSDHVV	209

Table 8. Amino acid sequences and SEQ ID NO summary of the variable domains of selected anti-hK2 antibodies

Antibody name	Region	Amino acid sequence	SEQ ID NO:
m11B6	HCDR1	SDYAWN	63
	HCDR2	YISYSGSTTYSPSLKS	64
	HCDR3	GYYYGSGF	66
	LICDR1	RASESVEYFGTSLMH	67
	LCDR2	AASNVES	69
	LCDR3	QQTRKVPYT	71
	VH (m11B6_VH)	DVQLQESGPGLVKPSQSLSLTCTVTGNSITSDYAWN WIRQFPGNRLEWMGYISYSGSTTYSPSLKSRFSITRD TSKNQFFLQLNSVTPEDTATYFCATGYYYGSGFWG QGTLVTVSS	125
	VL (m11B6_VL)	DIVLTQSPASLAVSLGQRATISCRASESVEYFGTSLM HWYRQKPGQPPKLLIYAASNVESGVPARFSGSGSG TDFSLNIQPVEEDDFSMYFCQQTRKVPYTFGGGTKL EIK	124
h11B6	HCDR1	SDYAWN	63
	HCDR2	YISYSGSTTYNPSLKS	65
	HCDR3	GYYYGSGF	66
	LICDR1	KASESVEYFGTSLMH	68
	LCDR2	AASNRES	70
	LCDR3	QQTRKVPYT	71
	VH (hu11B6_VH)	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN WIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSR DTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGF WGQGTLVTVSS	5
	VL (hu11B6_VL)	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKL EIK	2
HCF3-LCD6	HCDR1	SDYAWN	63
	HCDR2	YISYSGSTTYNPSLKS	65
	HCDR3	GYYYGSGF	66
	LICDR1	KASESVEYFGTSLMH	68
	LCDR2	AASNRES	70
	LCDR3	QQTRKVPYT	71
	VH (HCF3_VH)	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN WIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRD	6

		TSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWG QGTLVTVSS	
	VL (LCD6_VL)	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSG TDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKL EIK	1
HCG5-LCB7	HCDR1	SDYAWN	63
	HCDR2	YISYSGSTTYNPSLKS	65
	HCDR3	GYYYGSGF	66
	LICDR1	KASESVEYFGTSLMH	68
	LCDR2	AASNRES	70
	LCDR3	QQTRKVPYT	71
	VH (HCG5_VH)	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN WIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISR DTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFW GQGTLVTVSS	4
	VL (LCB7_VL)	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSG TDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTK LEIK	3
KL2B357	HCDR1	SDYAWN	63
	HCDR2	YISYSGSTTYNPSLKS	65
	HCDR3	GYYYGSGF	66
	LICDR1	RASESVEYFGTSLMH	67
	LCDR2	AASNVES	69
	LCDR3	QQTRKVPYT	71
	VH (KL2B357_VH)	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWN WIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRD TSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFW GQGTLVTVSS	159
	VL (KL2B_357_VL)	DIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNVESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYFCQQTRKVPYTFGGGTKV EIK	160
KL2B358	HCDR1	SDYAWN	63
	HCDR2	YISYSGSTTYNPSLKS	65
	HCDR3	GYYYGSGF	66
	LICDR1	RASESVEYFGTSLMH	67
	LCDR2	AASNVES	69
	LCDR3	QQTRKVPYT	71
	VH (KL2B358_VH)	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWN WIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTISRD TSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFW GQGTLVTVSS	161
	VL (KL2B_358_VL)	EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLM HWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGT DFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEI K	140
KL2B359	HCDR1	SDYAWN	63
	HCDR2	YISYSGSTTYNPSLKS	65

	HCDR3	GYYYGSGF	66
	LICDR1	RASESVEYFGTSLMH	67
	LCDR2	AASNVES	69
	LCDR3	QQTRKVPYT	71
	VH (KL2B359_VH)	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWN WIRQFPGKRLEWIGYISYSGSTTYNPSLKSRVTISRD TSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFW GQGTLVTVSS	139
	VL (KL2B_359_VL)	EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLM HWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGT DFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEI K	140
KL2B360	HCDR1	SDYAWN	63
	HCDR2	YISYSGSTTYNPSLKS	65
	HCDR3	GYYYGSGF	66
	LICDR1	RASESVEYFGTSLMH	67
	LCDR2	AASNVES	69
	LCDR3	QQTRKVPYT	71
	VH (KL2B360_VH)	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWN WIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRD TSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFW GQGTLVTVSS	159
	VL (KL2B_360_VL)	EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLM HWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGT DFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEI K	140
KL2B413	HCDR1	SYWMT	141
	HCDR2	NIKQDGSERYYVDSVKG	142
	HCDR3	DQNYDILTGHYGMDV	143
	LICDR1	RASQGISSYLS	144
	LCDR2	ATSTLQS	145
	LCDR3	QQLNSYPRT	146
	VH (KL2B413_VH)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMT WVRQAPGKGLEWVANIKQDGSERYYVDSVKGRFT ISRDNAKNSLYLQMNSLRAEDTAVYYCARDQNYDI LTGHYGMDVWGQGTTVTVSS	137
	VL (KL2B_413_VL)	EIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQ QKPGKAPKLLIYATSTLQSGVPSRFSGSGSGTEFTLT ISSLQPEDFATYYCQQLNSYPRTFGQGTKVEIK	138
KL2B30	HCDR1	SYYWS	170
	HCDR2	YIYYSGSTNYNPSLKS	171
	HCDR3	TTIFGVVTPNFYYGMDV	172
	LICDR1	RASQGISSYLA	173
	LCDR2	AASTLQS	174
	LCDR3	QQLNSYPLT	175
	VH (KL2B30_VH)	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSW IRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFY YGMDVWGQGTTVTVSS	162
	VL	DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWY	163

	(KL2B30_VL)	QQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTL TISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK	
KL2B53	HCDR1	SYDIH	176
	HCDR2	IISYDGSKKDYTDSVKG	177
	HCDR3	ESGWSHYYYYGMDV	178
	LICDR1	RASQDISNYLA	179
	LCDR2	AASTLHS	180
	LCDR3	QKYNSAPYT	181
	VH (KL2B53_VH)	EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHW VRQAPGKGLEWVAIISYDGSKKDYTDSVKGRFTISR DNSKNTLYLQMDSLRVED SAVYSCARESGWSHYYYYGMDVWGQGTMVTVSS	164
	VL (KL2B53_VL)	DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWY QQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFT LTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIK	165
KL2B242	HCDR1	SYYWS	170
	HCDR2	RLYVSGFTNYNPSLKS	183
	HCDR3	DSGNYWGWFDP	184
	LICDR1	SGDQLGENYAC	185
	LCDR2	QDSKRPS	186
	LCDR3	QAWDNSIVV	187
	VH (KL2B242_VH)	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSW LRQPAGSGLEWIGRLYVSGFTNYNPSLKSRVTLSLD PSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWF DPWGQGTLVTVSS	166
	VL (KL2B242_VL)	SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQ QKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLT ISGTQALDEADYYCQAWDNSIVVFGGGTKLTVL	167
KL2B467	HCDR1	YYGMH	188
	HCDR2	FISYDGSNKYYADSVKG	189
	HCDR3	LPYSGSYWAFDY	190
	LICDR1	GGDNIGSKSVH	191
	LCDR2	DNSDRPS	192
	LCDR3	QVWDSSSDHPVV	193
	VH (KL2B467_VH)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMH WVRQAPGKGLEWVAFISYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSY WAFDYWGQGTQVTVSS	168
	VL (KL2B467_VL)	QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQ QKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATL TISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVT V	169
KL2B494	HCDR1	HYAMS	206
	HCDR2	TIGGSGGSTYYADSVKG	207
	HCDR3	PHIVMVTALLYDGMDV	208
	LCDR1	GGNNIGSKSVH	182
	LCDR2	DDSDRPS	470
	LCDR3	QVWDSSSDHVV	209
	VH	QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMS	204

	(KL2B494_VH)	WVRQAPGKGLEWVSTIGGSGGSTYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMV TALLYDGMDVWGQGTMVTVSS	
	VL (KL2B494_VL)	SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQ QKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATL TISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTV L	205

Table 9. SEQ ID NO of Protein and DNA sequences of the VH and VL domains of selected hK2 antibodies.

Antibody	VH Protein SEQ ID NO:	VL Protein SEQ ID NO	VH cDNA SEQ ID NO:	VL cDNA SEQ ID NO:
m11B6	125	124	225	237
hu11B6	5	2	226	238
HCF3-LCD6	6	1	227	239
HCG5-LCB7	4	3	228	240
KL2B357	159	160	229	241
KL2B358	161	140	230	242
KL2B359	139	140	231	242
KL2B360	159	140	229	242
KL2B413	137	138	232	243
KL2B30	162	163	233	244
KL2B53	164	165	234	245
KL2B242	166	167	235	246
KL2B467	168	169	236	247
KL2B494	204	205	263	271

SEQ ID NO:225 (m11B6 VH cDNA)
GATGTGCAGCTTCAGGAGTCTGGACCCGGACTTGTTAAACCAAGTCAGTCTCTGTCCCTGAC
CTGTACCGTCACCGGCAACAGCATCACAAGCGATTACGCATGGAACTGGATCAGGCAGTTCC
CTGGAAATCGACTCGAATGGATGGGCTACATTTCATACTCCGGTTCAACCACTTACTCTCCAT
CCTTGAAATCTAGGTTCAGCATCACCCGTGATACCTCAAAGAACCAATTTTTTCTGCAACTG
AATAGCGTAACTCCAGAGGACACAGCCACATATTTCTGCGCCACTGGGTATTACTATGGCTC
AGGTTTCTGGGGTCAGGGCACTCTCGTCACCGTCAGCAGC

SEQ ID NO: 226 (hu11B6 VH cDNA)

CAGGTCCAACTGCAAGAGAGCGGACCGGGCCTGGTAAAGCCATCCGACACATTGTCCCTGA
CGTGTGCGGTAAGTGGAAACTCTATCACTAGCGACTATGCGTGGAATTGGATAAGACAACC
GCCGGGCAAGGGGCTGGAATGGATAGGATATATCAGCTATTCCGGTTCTACGACATACAATC
CTTCCCTGAAAAGCAGAGTCACTATGTCACGCGACACGTCCAAGAATCAGTTCTCATTGAAA
TTGTCATCCGTAACGGCCGTTGACACTGCGGTTTATTATTGCGCAACCGGATATTACTACGGC
TCTGGTTTTTGGGGACAGGGAACACTTGTTACTGTTAGTTCA

SEQ ID:NO 227 (HCF3-LCD6 VH cDNA)
CAGGTGCAGCTGCAGGAGAGCGGCCCAGGCCTGGTGAAGCCAAGCGACACCCTGAGCCTGA
CCTGCGCCGTGAGCGGCAACAGCATCACCAGCGACTACGCCTGGAACTGGATCCGCCAGTTC
CCAGGCAAGGGCCTGGAGTGGATCGGCTACATCAGCTACAGCGGCAGCACCACCTACAACC
CAAGCCTGAAGAGCCGCGTCACCATCAGCCGCGACACCAGCAAGAACCAGTTCAGCCTGAA
GCTGAGCAGCGTGACCCCTGTGGACACCGCCGTGTACTACTGCGCCACCGGCTACTACTACG
GCAGCGGCTTCTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC

SEQ ID NO: 228 (HCG5-LCB7 VH cDNA)
CAGGTGCAGCTGCAGGAGAGCGGCCCAGGCCTGGTGAAGCCAAGCGACACCCTGAGCCTGA
CCTGCGCCGTGAGCGGCAACAGCATCACCAGCGACTACGCCTGGAACTGGATCCGCCAGTTC
CCAGGCAAGGGCCTGGAGTGGATGGGCTACATCAGCTACAGCGGCAGCACCACCTACAACC
CAAGCCTGAAGAGCCGCGTCACCATCAGCCGCGACACCAGCAAGAACCAGTTCAGCCTGAA
GCTGAGCAGCGTGACCCCTGTGGACACCGCCGTGTACTACTGCGCCACCGGCTACTACTACG
GCAGCGGCTTCTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC

SEQ ID NO: 229 (KL2B357, KL2B360 VH cDNA)
CAGGTTCAGCTGCAAGAGTCTGGACCAGGCCTGGTCAAGCCCTCTCAGACCCTGTCTCTGAC
CTGTACCGTGTCCGGCAACTCCATCACCTCTGACTACGCCTGGAACTGGATTCGGCAGTTCC
CTGGCAAGGGCCTTGAGTGGATCGGCTACATCTCCTACTCCGGTTCCACCACCTACAACCCC
AGCCTGAAGTCCCGGGTCACCATCTCCCGCGACACCTCCAAGAACCAGTTCTCCCTGAAGCT
GTCCTCCGTGACCGCTGCTGATACCGCCGTGTACTACTGTGCCACCGGCTACTACTACGGCTC
CGGCTTTTGGGGACAGGGCACACTGGTTACCGTGTCTAGT

SEQ ID NO: 230 (KL2B358 VH cDNA)
CAGGTTCAGCTGCAAGAGTCTGGACCAGGCCTGGTCAAGCCCTCTCAGACCCTGTCTCTGAC
CTGTACCGTGTCCGGCAACTCCATCACCTCTGACTACGCCTGGAACTGGATTCGGCAGCCAC
CTGGCAAGGGCCTTGAGTGGATCGGCTACATCTCCTACTCCGGTTCCACCACCTACAACCCC
AGCCTGAAGTCCCGGGTCACCATCTCCCGCGACACCTCCAAGAACCAGTTCTCCCTGAAGCT
GTCCTCCGTGACCGCTGCTGATACCGCCGTGTACTACTGTGCCACCGGCTACTACTACGGCTC
CGGCTTTTGGGGACAGGGCACACTGGTTACCGTGTCTAGT

SEQ ID NO: 231 (KL2B359 VH cDNA)
CAGGTTCAGCTGCAAGAGTCTGGACCAGGCCTGGTCAAGCCCTCTCAGACCCTGTCTCTGAC
CTGTACCGTGTCCGGCAACTCCATCACCTCTGACTACGCCTGGAACTGGATTCGGCAGTTCC
CTGGCAAGCGCCTTGAGTGGATCGGCTACATCTCCTACTCCGGTTCCACCACCTACAACCCC
AGCCTGAAGTCCCGGGTCACCATCTCCCGCGACACCTCCAAGAACCAGTTCTCCCTGAAGCT
GTCCTCCGTGACCGCTGCTGATACCGCCGTGTACTACTGTGCCACCGGCTACTACTACGGCTC
CGGCTTTTGGGGACAGGGCACACTGGTTACCGTGTCTAGT

SEQ ID NO: 232 (KL2B413 VH cDNA)
GAGGTGCAACTTGTGGAGAGCGGCGGAGGTCTGGTCCAACCCGGAGGAAGTCTCCGTCTCT
CCTGTGCTGCTAGTGGCTTCACTTTCAGCTCATATTGGATGACATGGGTGAGACAAGCCCCA

GGAAAGGGGCTCGAGTGGGTAGCTAACATTAAACAGGACGGCTCCGAACGGTACTATGTTG
ATTCTGTGAAGGGACGGTTCACTATATCCAGGGATAATGCAAAAAATTCACTCTATCTTCAA
ATGAACTCACTCAGAGCAGAGGACACTGCCGTGTATTATTGCGCCAGGGATCAAAATTATGA
CATACTGACCGGTCATTATGGAATGGATGTTTGGGGCCAGGGAACAACCGTTACCGTCTCAA
GT

SEQ ID NO:233 (KL2B30 VH cDNA)
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCA
CCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTGGATCCGGCAGCCCCCA
GGGAAGGGACTGGAGTGGATTGGATATATCTATTACAGTGGGAGCACCAACTACAACCCCT
CCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTG
AGCTCTGTGACCGCTGCGGACACGGCCGTGTATTACTGTGCGGGGACTACGATTTTTGGAGT
GGTTACCCCCAACTTCTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT
CCTCA

SEQ ID NO: 234 (KL2B53 VH cDNA)
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
CCTGTGTAGCCTCTGGATTCACCTTCAGTAGTTATGACATACACTGGGTCCGCCAGGCTCCA
GGCAAGGGGCTGGAGTGGGTGGCAATTATTTCATATGATGGAAGTAAAAAAGACTATACAG
ACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAA
ATGGACAGCCTGAGAGTTGAGGACTCGGCTGTGTATTCCTGTGCGAGAGAAAGTGGCTGGTC
CCACTACTACTATTACGGTATGGACGTCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

SEQ ID NO: 235 (KL2B242 VH cDNA)
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCA
CCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTATTGGAGCTGGCTCCGGCAGCCCGCC
GGGTCGGGACTGGAGTGGATTGGGCGTTTATATGTCAGTGGGTTCACCAACTACAACCCCTC
CCTCAAGAGTCGAGTCACCTTGTCACTAGACCCGTCCAGGAACCAGTTGTCCCTGAAACTGA
GTTCTGTGACCGCCGCGGACACGGCCGTATATTATTGTGCGGGAGATAGTGGGAACTACTGG
GGTTGGTTCGACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

SEQ ID NO: 236 (KL2B467 VH cDNA)
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
CCTGTGCAGCCTCTGGATTCACCTTCAGTTACTATGGCATGCACTGGGTCCGCCAGGCTCCA
GGCAAGGGGCTGGAGTGGGTGGCATTTATATCATATGATGGAAGTAATAAATACTATGCAG
ACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAA
ATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCCCACCTCCCTTATAGTGG
GAGCTACTGGGCCTTTGACTACTGGGGCCAGGGAACCCAGGTCACCGTCTCTTCA

SEQ ID NO: 263 (KL2B494 VH cDNA)
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCT
CCTGTGCAGCCTCTGGATTCACCTTTAGTCATTATGCCATGAGCTGGGTCCGCCAGGCTCCAG
GGAAGGGGCTGGAGTGGGTCTCAACTATTGGTGGTAGTGGTGGTAGCACATACTACGCAGA
CTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAA
TGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAACCTCATATTGTAATG
GTGACTGCTCTTCTCTACGACGGTATGGACGTCTGGGGCCAAGGGACAATGGTCACCGTCTC
CTCA

SEQ ID NO: 237 (m11B6 VL cDNA)
GACATTGTGCTGACACAGAGTCCAGCATCCTTGGCAGTATCTTTGGGGCAGCGGGCAACAAT
TTCATGCCGTGCATCTGAAAGTGTGGAGTATTTTGGAACTTCTCTTATGCACTGGTATCGCCA

GAAGCCTGGGCAGCCTCCCAAACTCCTTATATATGCCGCTTCCAACGTGGAGTCCGGAGTAC
CAGCACGCTTTTCCGGCTCTGGGTCCGGCACAGACTTTTCCCTCAATATCCAACCTGTTGAAG
AAGACGATTTTTCCATGTATTTTTGCCAACAGACACGCAAGGTTCCATATACATTCGGCGGC
GGCACTAAACTTGAGATCAAA

SEQ ID NO: 238 (hu11B6 VL cDNA)
GACATAGTCTTGACTCAGAGCCCGGATTCCCTTGCTGTGTCTCTGGGAGAACGAGCTACGAT
CAACTGCAAGGCAAGTGAATCCGTAGAATACTTCGGGACATCATTGATGCATTGGTATCAAC
AGAAACCGGGGCAACCGCCCAAATTGCTGATATATGCGGCTAGTAATAGAGAATCAGGAGT
ACCGGATAGGTTTAGTGGTTCAGGATCAGGTACAGATTTCACCCTGACAATAAGTAGCTTGC
AAGCCGAAGACGTAGCAGTGTATTACTGCCAACAAACCCGAAAGGTGCCATATACGTTTGG
ACAGGGTACAAAGTTGGAAATCAAA

SEQ ID NO: 239 (HCF3-LCD6 VL cDNA)
GACATCGTGCTGACCCAGAGCCCAGACAGCCTGGCCGTGAGCCTGGGCGAGCGCGCCACCA
TCAACTGCAAGGCCAGCGAGAGCGTGGAGTACTTCGGCACCAGCCTGATGCACTGGTACCA
GCAGAAGCCAGGCCAGCCACCAAAGCTGCTGATCTACGCTGCCAGCAACCGCGAGAGCGGC
GTGCCAGACCGCTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCCAGAGCG
TGCAGGCCGAGGACGTCTCCGTGTACTTCTGCCAGCAGACCCGCAAGGTGCCATACACCTTC
GGCCAGGGCACCAAGCTGGAGATCAAG

SEQ ID NO: 240 (HCG5-LCB7 VL cDNA)
GACATCGTGCTGACCCAGAGCCCAGACAGCCTGGCCGTGAGCCTGGGCGAGCGCGCCACCA
TCAACTGCAAGGCCAGCGAGAGCGTGGAGTACTTCGGCACCAGCCTGATGCACTGGTACCA
GCAGAAGCCAGGCCAGCCACCAAAGCTGCTGATCTACGCTGCCAGCAACCGCGAGAGCGGC
GTGCCAGACCGCTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCG
TGCAGGCCGAGGACGTCGCCGTGTACTACTGCCAGCAGACCCGCAAGGTGCCATACACCTTC
GGCCAGGGCACCAAGCTGGAGATCAAG

SEQ ID NO: 241 (KL2B357 VL cDNA)
GACATCGTGCTGACCCAGTCTCCAGACTCTCTGGCTGTGTCTCTGGGCGAGAGAGCCACCAT
CAACTGCAGAGCCTCCGAGTCCGTGGAATACTTCGGCACCTCTCTGATGCACTGGTACCAGC
AGAAGCCCGGCCAGCCTCCTAAGCTGCTGATCTACGCCGCCTCCAACGTGGAATCTGGCGTG
CCCGATAGATTTTCCGGCTCTGGCTCTGGCACCGACTTTACCCTGACCATCAGCTCTCTGCAG
GCCGAGGATGTGGCCGTGTACTTCTGTCAGCAGACCCGGAAGGTGCCCTACACATTTGGCGG
CGGAACAAAGGTGGAAATCAAG

SEQ ID NO: 242 (KL2B358, KL2B359, KL2B360 VL cDNA)
GAGATCGTGCTGACCCAGTCTCCTGCCACACTGTCACTGTCTCCAGGCGAGAGAGCCACCCT
CTCTTGTAGAGCCTCCGAGTCCGTGGAATACTTCGGCACCTCTCTGATGCACTGGTACCAGC
AGAAGCCCGGCCAGCCTCCTAGACTGCTGATCTACGCCGCCTCCAACGTCGAATCTGGCATC
CCCGCTAGATTCTCCGGCTCTGGCTCTGGCACAGACTTTACCCTGACCATCTCCTCCGTGGAA
CCCGAGGATTTCGCTGTGTACTTTTGCCAGCAGACCCGGAAGGTGCCCTACACATTTGGCGG
CGGAACAAAGGTGGAAATCAAG

SEQ ID NO: 243 (KL2B413 VL cDNA)
GAAATCGTACTGACCCAGTCCCCTTCTTTCTTGAGTGCATCAGTTGGGGATAGAGTGACCAT
TACTTGTAGAGCATCTCAAGGTATTTCTTCATACTTGTCTTGGTATCAACAAAAACCTGGCAA
GGCACCCAAACTCTTGATCTACGCCACCTCTACATTGCAAAGTGGGGTTCCTTCTAGGTTTTC
AGGCTCCGGCTCTGGTACCGAGTTCACCCTCACTATAAGCAGTCTCCAACCTGAAGATTTCG

CTACTTATTATTGTCAGCAGCTTAATTCTTATCCCCGAACCTTTGGTCAAGGAACTAAGGTCG
AGATCAAA

SEQ ID NO: 244 (KL2B30 VL cDNA)
GACATCCAGATGACCCAGTCTCCTTCCTTCCTGTCTGCATCTGTAGGAGACAGAGTCACCAT
CACTTGCCGGGCCAGTCAGGGCATTAGCAGTTATTTAGCCTGGTATCAGCAAAAACCAGGGA
AAGCCCCTAAGTTCCTGATCTATGCTGCATCCACTTTGCAAAGTGGGGTCCCATCAAGGTTC
AGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTT
TGCAACTTATTACTGTCAACAGCTTAATAGTTACCCTCTCACTTTCGGCGGAGGGACCAAGG
TGGAAATCAAA

SEQ ID NO: 245 (KL2B53 VL cDNA)
GACATCGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCAT
CACTTGCCGGGCGAGTCAGGACATTAGCAATTATTTAGCCTGGTATCAGCAGAAACCAGGG
AAAGTTCCTAAGTTCCTGATCTATGCTGCATCCACTTTGCACTCTGGGGTCCCATCTCGGTTC
AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGT
TGCAACTTATTACTGTCAAAAGTATAACAGTGCCCCGTACACTTTTGGCCAAGGGACACGAC
TGGAGATTAAA

SEQ ID NO: 246 (KL2B242 VL cDNA)
TCCTATGAGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGAGAGACAGCCAGCATCAC
CTGCTCTGGAGATCAATTGGGGGAAAATTATGCTTGCTGGTATCAGCAGAAGCCAGGCCAGT
CCCCTGTGTTGGTCATCTATCAAGATAGTAAGCGGCCCTCAGGGATCCCTGAGCGATTCTCT
GGCTCCAACTCTGGGAACACAGCCACTCTGACCATCAGCGGGACCCAGGCTCTGGATGAGG
CTGACTATTACTGTCAGGCGTGGGACAACAGTATTGTGGTATTCGGCGGAGGGACCAAGCTG
ACCGTCCTA

SEQ ID NO: 247 (KL2B467 VL cDNA)
CAGTCTGTGCTGACTCAGCCACCCTCGGTGTCAGTGGCCCCCGGGCAGACGGCCAGTATTAC
CTGTGGGGGAGACAACATTGGAAGTAAAAGTGTGCACTGGTACCAGCAGAAGCCAGGCCAG
GCCCCTGTGCTGGTCGTCTATGATAATAGCGACCGGCCCTCAGGGATCCCTGAGCGATTCTC
TGGCTCCAACTCTGGGACCACGGCCACCCTGACCATCAGCAGGGTCGAAGCCGGGGATGAG
GCCGACTATTACTGTCAGGTGTGGGATAGTAGTAGTGATCATCCTGTGGTATTCGGCGGAGG
GACCAAGGTCACCGTCCTA

SEQ ID: 271 (KLK2B494_VL DNA)
TCTTCTGAGCTGACTCAGCCACCCTCGGTGTCAGTGGCCCCAGGACAGACGGCCAGGATTAC
CTGTGGGGGAAACAACATTGGAAGTAAAAGTGTGCACTGGTACCAGCAGAAGCCAGGCCAG
GCCCCTGTGCTGGTCGTCTATGATGATAGCGACCGGCCCTCAGGGATCCCTGAGCGATTCTC
TGGCTCCAACTCTGGGAACACGGCCACCCTGACCATCAGCAGGGTCGAAGCCGGGGATGAG
GCCGACTATTACTGTCAGGTGTGGGATAGTAGTAGTGATCATGTGGTATTCGGCGGAGGGAC
CAAGCTGACCGTCCTA

Fab-Fc and scFvs

The hK2 specific VH/VL regions were engineered as VH-CH1-hinge CH2-CH3 and VL-CL and expressed as IgG2 or IgG4 or were engineered as scFvs in either the VH-Linker-VL or VL-linker-VH orientations. The linker that is used in the scFv was the linker of SEQ ID NO: 7 described above. The

scFv were used to generate bispecific antibodies as described in Example 7 or to generated CAR as described in Example 11.

Table 10 shows the HC amino acid sequences of selected anti-hK2 antibodies in the mAb format. **Table 11** shows the LC amino acid sequences of selected anti-hK2 antibodies in a mAb. **Table 12** summaries the HC and LC DNA SEQ ID NOs of selected anti-hK2 antibodies in the mAb format. **Table 13** shows the amino acid sequences of selected scFvs in VH-linker-VL or VL-linker-VH orientation.

Table 10. Amino acid sequence of the HC (VH-CH1-hinge CH2-CH3) of selected anti-hK2 antibodies in a mAb format.

HK2 HEAVY CHAIN	HC PROTEIN SEQ ID NO:	HC AMINO ACID SEQUENCE
m11B6_HC	202	DVQLQESGPGLVKPSQSLSLTCTVTGNSITSDYAWNWIRQFP GNRLEWMGYISYSGSTTYSPSLKSRFSITRDTSKNQFFLQLNS VTPEDTATYFCATGYYYGSGFWGQGTLVTVSSAKTTAPSVY PLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVH TFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVD KKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLS PIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKP KGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVE WTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGK
h11B6_HC	203	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPP GKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSS VTAVDTAVYYCATGYYYGSGFWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
KL2B30_HC	210	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGK GLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVT AADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGTTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGF

		YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
K2B53_HC	211	EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPG KGLEWVAIISYDGSKKDYTDSVKGRFTISRDNSKNTLYLQM DSLRVEDSAVYSCARESGWSHYYYYGMDVWGQGTMVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
KL2B242_HC	212	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAG SGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPSRNQLSLKLSSV TAADTAVYYCAGDSGNYWGWFDPWGQGTLVTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
KL2B467_HC	213	QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQA PGKGLEWVAFISYDGSNKYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAHLPYSGSYWAFDYWGQGTQVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFP PKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
KL2B494_HC	219	QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAP GKGLEWVSTIGGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKPHIVMVTALLYDGMDVWGQGTMV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI

		CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Table 11. Amino acid sequences of the LC (VL-CL) of selected anti-hK2 antibodies in a mAb (Fab-Fc) format.

HK2 LIGHT CHAIN	LC PROTEIN SEQ ID NO:	LC AMINO ACID SEQUENCE
m11B6_LC	214	DIVLTQSPASLAVSLGQRATISCRASESVEYFGTSLMHWYRQKPGQP PKLLIYAASNVESGVPARFSGSGSGTDFSLNIQPVEEDDFSMYFCQQ TRKVPYTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLN NFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTK DEYERHNSYTCEATHKTSTSPIVKSFNRNEC
h11B6_LC	215	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQ PPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQ QTRKVPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
KL2B30_LC	221	DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFL IYAASTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYP LTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
KL2B53_LC	222	DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFL IYAASTLHSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAP YTFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
KL2B242_LC	223	SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVI YQDSKRPSGIPERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSI VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECS
KL2B467_LC	224	QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLV VYDNSDRPSGIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSS SDHPVVFGGGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLIS DFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPE QWKSHRSYSCQVTHEGSTVEKTVAPTECS
KL2B494_LC	220	SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLV VYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDS SSDHVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLIS

		DFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPE QWKSHRSYSCQVTHEGSTVEKTVAPTECS

Table 12. SEQ ID Nos of the cDNA sequences of HC and LC of selected hK2 antibodies

Antibody	HC Protein SEQ ID NO:	LC Protein SEQ ID NO:	HC cDNA SEQ ID NO:	LC cDNA SEQ ID NO:
m11B6	202	214	284	296
hu11B6	203	215	285	297
KL2B30	210	221	292	450
KL2B53	211	222	293	451
KL2B242	212	223	294	305
KL2B467	213	224	295	306
KL2B494	219	220	274	282

Table 13. Amino acid sequences of the variable domain of selected anti-hK2 scFvs antibodies in VH-linker-VL (HL) or in VL-linker-VH (LH) format.

scFv name	Acronym	Amino acid sequence of scFv	SEQ ID NO:
scFv1	HCG5_LDC6_HL	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN WIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRD TSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWG QGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSP DSLAVSLGERATINCKASESVEYFGTSLMHWYQQKP GQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSV QAEDVSVYFCQQTRKVPYTFGQGTKLEIK	8
scFv2	HCG5_hu11B6_HL	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN WIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRD TSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWG QGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSP DSLAVSLGERATINCKASESVEYFGTSLMHWYQQKP GQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCQQTRKVPYTFGQGTKLEIK	9
scFv3	HCF3_hu11B6_HL	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN WIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDT SKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQ GTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPD SLAVSLGERATINCKASESVEYFGTSLMHWYQQKPG QPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQ AEDVAVYYCQQTRKVPYTFGQGTKLEIK	10

scFv4	HCG5_LCB7_HL	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN WIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRD TSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWG QGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSP DSLAVSLGERATINCKASESVEYFGTSLMHWYQQKP GQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSV QAEDVAVYYCQQTRKVPYTFGQGTKLEIK	11
scFv5	LCD6_HCG5_LH	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGT DFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEI KGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS DTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMG YISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTP VDTAVYYCATGYYYGSGFWGQGTLVTVSS	12
scFv6	hu11B6_HCF3_LH	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGT DFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEI KGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS DTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYI SYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVD TAVYYCATGYYYGSGFWGQGTLVTVSS	13
scFv7	hu11B6_HCG5_L H	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGT DFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEI KGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS DTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMG YISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTP VDTAVYYCATGYYYGSGFWGQGTLVTVSS	14
scFv8	LCB7_HCF3_LH	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGT DFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLE IKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS DTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYI SYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVD TAVYYCATGYYYGSGFWGQGTLVTVSS	15
scFv9	LCB7_HCG5_LH	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGT DFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLE IKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS DTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMG YISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTP VDTAVYYCATGYYYGSGFWGQGTLVTVSS	16
scFv10	LCD6_HCF3_LH	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGT DFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEI KGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS DTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYI SYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVD TAVYYCATGYYYGSGFWGQGTLVTVSS	17
scFv11	hu11B6_LCB7_HL	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN	18

		WIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRD TSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWG QGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSP DSLAVSLGERATINCKASESVEYFGTSLMHWYQQKP GQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSV QAEDVAVYYCQQTRKVPYTFGQGTKLEIK	
scFv12	hu11B6_LCD6_HL	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN WIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRD TSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWG QGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSP DSLAVSLGERATINCKASESVEYFGTSLMHWYQQKP GQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSV QAEDVSVYFCQQTRKVPYTFGQGTKLEIK	19
scFv13	hu11B6_HL	QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWN WIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRD TSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWG QGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSP DSLAVSLGERATINCKASESVEYFGTSLMHWYQQKP GQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCQQTRKVPYTFGQGTKLEIK	20
scFv14	LCD6_hu11B6_LH	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGT DFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEI KGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS DTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYI SYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAV DTAVYYCATGYYYGSGFWGQGTLVTVSS	21
scFv15	hu11B6_LH	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGT DFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEI KGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS DTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYI SYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAV DTAVYYCATGYYYGSGFWGQGTLVTVSS	22
scFv16	LCB7_hu11B6_LH	DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGT DFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLE IKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS DTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYI SYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAV DTAVYYCATGYYYGSGFWGQGTLVTVSS	23
scFv17	KL2B413_HL	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMT WVRQAPGKGLEWVANIKQDGSERYYVDSVKGRFTI SRDNAKNSLYLQMNSLRAEDTAVYYCARDQNYDIL TGHYGMDVWGQGTTVTVSSGGSEGKSSGSGSESKS TGGSEIVLTQSPSFLSASVGDRVTITCRASQGISSYLS WYQQKPGKAPKLLIYATSTLQSGVPSRFSGSGSGTEF	133

		TLTISSLQPEDFATYYCQQLNSYPRTFGQGTKVEIK	
scFv18	KL2B413_LH	EIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQQ KPGKAPKLLIYATSTLQSGVPSRFSGSGSGTEFTLTIS SLQPEDFATYYCQQLNSYPRTFGQGTKVEIKGGSEG KSSGSGSESKSTGGSEVQLVESGGGLVQPGGSLRLSC AASGFTFSSYWMTWVRQAPGKGLEWVANIKQDGSE RYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARDQNYDILTGHYGMDVWGQGTTVTVSS	134
scFv19	KL2B359_HL	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWN WIRQFPGKRLEWIGYISYSGSTTYNPSLKSRVTISRDT SKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQ GTLVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPAT LSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQ PPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPE DFAVYFCQQTRKVPYTFGGGTKVEIK	135
scFv20	KL2B359_LH	EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMH WYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDF TLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKG GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTL SLTCTVSGNSITSDYAWNWIRQFPGKRLEWIGYISYS GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTA VYYCATGYYYGSGFWGQGTLVTVSS	136
scFv21	KL2B357_HL	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWN WIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDT SKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQ GTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPD SLAVSLGERATINCRASESVEYFGTSLMHWYQQKPG QPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISSLQ AEDVAVYFCQQTRKVPYTFGGGTKVEIK	318
scFv22	KL2B357_LH	DIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLM HWYQQKPGQPPKLLIYAASNVESGVPDRFSGSGSGT DFTLTISSLQAEDVAVYFCQQTRKVPYTFGGGTKVEI KGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPS QTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYI SYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAA DTAVYYCATGYYYGSGFWGQGTLVTVSS	319
scFv23	KL2B358_HL	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWN WIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDT SKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQ GTLVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPAT LSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQ PPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPE DFAVYFCQQTRKVPYTFGGGTKVEIK	320
scFv24	KL2B358_LH	EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMH WYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDF TLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKG GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTL SLTCTVSGNSITSDYAWNWIRQPPGKGLEWIGYISYS GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTA VYYCATGYYYGSGFWGQGTLVTVSS	321

scFv25	KL2B360_HL	QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWN WIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDT SKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQ GTLVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPAT LSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQ PPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPE DFAVYFCQQTRKVPYTFGGGTKVEIK	322
scFv26	KL2B360_LH	EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMH WYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDF TLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKG GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTL SLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYS GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTA VYYCATGYYYGSGFWGQGTLVTVSS	323
scFv27	KL2B467_HL	QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMH WVRQAPGKGLEWVAFISYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSY WAFDYWGQGTQVTVSSGGSEGKSSGSGSESKSTGG SQSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWY QQKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATL TISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVT V	324
scFv28	KL2B467_LH	QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQ QKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLT ISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTV GGSEGKSSGSGSESKSTGGSQVQLVESGGGVVQPGR SLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFI SYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLR AEDTAVYYCAHLPYSGSYWAFDYWGQGTQVTVSS	325
scFv39	KL2B494_HL	QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMS WVRQAPGKGLEWVSTIGGSGGSTYYADSVKGRFTIS RDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTA LLYDGMDVWGQGTMVTVSS GGSEGKSSGSGSESKSTGGSSSELTQPPSVSVAPGQT ARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSD RPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQV WDSSSDHVVFGGGTKLTVL	308
scFv40	KL2B494_LH	SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQ QKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLT ISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVL GGSEGKSSGSGSESKSTGGSQVQLVESGGGLVQPGG SLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIG GSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCAKPHIVMVTALLYDGMDVWGQGTMVT VSS	316
scFv41	KL2B30_HL	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWI RQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYY GMDVWGQGTTVTVSSGGSEGKSSGSGSESKSTGGS DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQ	404

		QKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTI SSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK	
scFv42	KL2B30_LH	DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQ QKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTI SSLQPEDFATYYCQQLNSYPLTFGGGTKVEIKGGSEG KSSGSGSESKSTGGSQVQLQESGPGLVKPSETLSLTC TVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNY NPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCA GTTIFGVVTPNFYYGMDVWGQGTTVTVSS	405
scFv43	KL2B53_HL	EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHW VRQAPGKGLEWVAIISYDGSKKDYTDSVKGRFTISR DNSKNTLYLQMDSLRVEDSAVYSCARESGWSHYYY YGMDVWGQGTMVTVSSGGSEGKSSGSGSESKSTGG SDIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWY QQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTL TISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIK	406
scFv44	KL2B53_LH	DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQ QKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTI SSLQPEDVATYYCQKYNSAPYTFGQGTRLEIKGGSE GKSSGSGSESKSTGGSEVQLVESGGGVVQPGRSLRL SCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDGS KKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVEDSA VYSCARESGWSHYYYYGMDVWGQGTMVTVSS	407
scFv45	KL2B242_HL	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWL RQPAGSGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPS RNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDP WGQGTLVTVSSGGSEGKSSGSGSESKSTGGSSYELT QPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQ SPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQA LDEADYYCQAWDNSIVVFGGGTKLTVL	408
scFv46	KL2B242_LH	SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQ QKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTI SGTQALDEADYYCQAWDNSIVVFGGGTKLTVLGGS EGKSSGSGSESKSTGGSQVQLQESGPGLVKPSETLSL TCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGF TNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAV YYCAGDSGNYWGWFDPWGQGTLVTVSS	409

Example 24. Biophysical characterization of anti-hK2 antibodies

Affinity and thermal stability of anti-hK2 antibodies.

Affinity of selected hK2 antibodies for soluble hK2 was measured by surface plasmon resonance (SPR). SPR is a label-free technique to study the strength of an interaction between two binding partners by measuring the change in mass upon complex formation and dissociation. Antibodies were captured on a sensor chip coated with an anti-Fc antibody followed by injection of soluble hK2 at various concentrations and specified association and dissociation times. Post dissociation, the surface was regenerated with an appropriate solution to prepare for the next interaction. Kinetic information (on-rate

and off-rate constants) were extracted by fitting sensorgrams to the 1:1 Langmuir model. Binding affinity (K_D) are reported as the ratio of rate constants (k_{off}/k_{on}). K_D values of selected hK2 antibodies are listed in **Table 14.**

Thermal stability was determined by Differential Scanning Fluorimetry (NanoDSF) using an automated Prometheus instrument. NanoDSF was used to measure T_m of molecules at a concentration of 0.5 mg/mL in Phosphate Buffered Saline, pH 7.4. Measurements were made by loading samples into 24 well capillary from a 384 well sample plate. Duplicate runs were performed for each sample. The thermal scans span from 20°C to 95°C at a rate of 1.0°C/minute. Intrinsic tryptophan and tyrosine fluorescence were monitored at the emission wavelengths of 330 nm and 350 nm, and the F350/F330 nm ratio were plotted against temperature to generate unfolding curves. Measured Tm values are listed in **Table 14**.

Table 14. K_D and Tm of selected molecules

Molecule	K_D (nM)	Tm (°C)
KL2B413 (scFv-LH-Fc)	34.3	67
KL2B359 (scFv-LH-Fc)	0.7 – 1	67
KL2B30 (Fab)	0.460	>70
KL2B242 (Fab)	0.040	>70
KL2B53 (Fab)	0.080	>70
KL2B467 (Fab)	0.078	>70
KL2B494 (Fab)	0.053	>70

KL2B413 scFv generated from the Ablexis immunization campaign had a thermal stability (Tm) of 67°C as measured by Nano DSF and a binding affinity (K_D) to human hK2 of about 34 nM. Clone KL2B359 obtained for the re-humanization campaign and which had maintained a binding affinity similar to murine 11B6 was converted to scFv-Fc and CAR-T for additional profiling. KL2B359 scFv shows a Tm of 67°C and a binding affinity (K_D) to hK2 of ~0.7 – 1nM. KL2B30, KL2B242, KL2B53, KL2B467 and KL2B494 Fab showed binding affinities below 0.5 nM and Tm values above 70°C.

Epitope mapping

The epitope and paratope of selected anti-hK2 antibodies and anti-hK2/CD3 bispecific antibodies were determined by hydrogen-deuterium exchange mass spectrometry (HDX-MS). Human KLK2 antigen was used for epitope and paratope mapping experiment.

Briefly, purified KLK2 antigen was incubated with and without anti-hK2 antibodies or anti-hK2/CD3 bispecific antibodies in deuterium oxide labeling buffer. The hydrogen-deuterium exchange (HDX) mixture was quenched at different time point by the addition of 8 M urea, 1M TCEP, pH 3.0. The quenched sample was passed over an immobilized pepsin/FPXIII column at 600 µL/min equilibrated with buffer A (1% acetonitrile, 0.1% FA in H2O) at room temperature. Peptic fragments were loaded onto a reverse phase trap column at 600 µL/min with buffer A and desalted for 1 min (600 µL buffer A). The desalted fragments were separated by a C18 column with a linear gradient of 8% to 35% buffer B (95% acetonitrile, 5% H2O, 0.0025% TFA) at 100 µL/min over 20 min and analyzed by mass spectrometry. Mass spectrometric analyses were carried out using an LTQ™ Orbitrap Fusion Lumos mass spectrometer (Thermo Fisher Scientific) with the capillary temperature at 275 °C, resolution 150,000, and mass range (m/z) 300 – 1,800. BioPharma Finder 3.0 (Thermo Fisher Scientific) was used for the peptide identification of non-deuterated samples prior to the HDX experiments. HDExaminer version 2.5 (Sierra Analytics, Modesto, CA) was used to extract centroid values from the MS raw data files for the HDX experiments.

Incubation of hK2 antibodies, hu11B6, KL2B494, KL2B467, KL2B30, KL2B413 and KL2B53 with soluble hK2 protein resulted in different patterns of hydrogen exchange and overall protection. The protected segments were mapped onto the sequence of hK2 antigen to visualize the binding epitopes. KL2B494, KL2B467 and KL2B30 bound to common sequences of (i) residues 174-178 (**SEQ ID NO: 111**, KVTEF) (e.g., KL2B494, KL2B467 and KL2B30 bound at least three of the residues of SEQ ID NO: 111, namely, the KVT residues at 174-176) and (ii) residues 230-234 (**SEQ ID NO: 112**, HYRKW) (e.g., KL2B494, KL2B467 and KL2B30 bound at least three of the residues of SEQ ID NO: 112, namely, the HYR residues at 230-232). KL2B413 also bound all residues of SEQ ID NO: 111 and the KW residues of SEQ ID NO: 112. An embodiment of the present invention provides an isolated protein comprising an antigen binding domain that binds hK2, wherein said antigen binding domain binds to hK2 within epitopes having sequences of SEQ ID NO: 111 and SEQ ID NO: 112; for example, said antigen binding domain binds to all residues, or at least four residues, or at least three residues of SEQ ID NO: 111 and binds to all residues, or at least four residues, or at least three residues of SEQ ID NO: 112.

KL2B53 showed a different pattern of protection and bound to a sequence consisting of residues 27-32 (Seq ID NO: **113**, SHGWAH), 60-75 (**SEQ ID NO: 114**, RHNLFEPEDTGQRVP) and 138-147 (**SEQ ID NO: 115**, GWGSIEPEE).

According to an embodiment, an isolated anti-hK2/anti-CD3 protein (e.g., hu11B6, KL2B494, KL2B467, KL2B30, KL2B413, or KL2B53) comprises an hk2-specific antigen binding domain that specifically binds to a discontinuous epitope (i.e., epitopes whose residues are distantly placed in the

sequence) of hK2 comprising one or more amino acid sequences selected from the group consisting of SEQ ID NO: 111, 112, 113, 114, and 115.

The paratope of anti-hK2 antibodies hu11B6, KL2B494, KL2B467, KL2B413 and anti-hK2/CD3 bispecific antibodies KLCB113 and KLCB80 were identified based on significant differences in deuterium uptake from the HDExaminer residue plots. KL2BB494 comprises three paratope regions two of which are located in the KL2B494 heavy chain variable domain (GFTFSH (SEQ ID NO: 455) and TAVYYCAKPHIVMVTAL (SEQ ID NO: 456)) and a single paratope region located within the light chain variable domain (YDDSDRPSGIPER (SEQ ID NO: 457)). KL2B467 comprises three paratope regions, two of which are located in the KL2B467 heavy chain variable domain (FTFSY (SEQ ID NO: 458) and GSYWAFDY (SEQ ID NO: 459)) and a single paratope region within the light chain variable domain (DNSD (SEQ ID NO: 460)). Hu11B6 comprises a single epitope region located in the heavy chain (GNSITSDYA (SEQ ID NO: 461)). KL2B413 comprises two paratope regions located in the heavy chain variable domain (GFTF (SEQ ID NO: 462) and ARDQNYDIL (SEQ ID NO: 463)). KL2B30 of bispecific KLCB80 comprise a paratope region locate in the heavy chain (comprising amino acid residues TIF and VTPNF (SEQ ID NO: 464)) and a paratope region located in the light chain (YAASTLQSG (SEQ ID NO: 465)). KL2B53 of bispecific KLCB113 comprise a single paratope region locate in the heavy chain (comprising amino acid residues ESGWSHY (SEQ ID NO: 466)).

Example 25 – MMAF Conjugation to KL2B30 Fab

Immunoconjugates of the present invention were made by conjugating the KL2B30 Fab (identified as KL2B997) to MMAF. Conjugation was performed via random conjugation and site-specific conjugation; such methods are described, for example, in WO2020/229974. As described herein, KL2B997 (the Fab of KL2B30) comprises a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and KL2B997 comprises a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

In FIG. 1, the term "DAR" is "drug-to-antibody ratio", which refers to the number of drug molecules, i.e., MMAF, attached to the antibody moiety, i.e., KL2B997. The number of drug molecules bound per antibody moiety or the degree of labeling is a parameter commonly used in the art and is designated "DAR" for "drug-antibody ratio."

To evaluate target cell binding of the KL2B30 Fab with different conjugation variants, VCaP cells were used as hK2-postive target cells and DU145 cells were used as hK2-negative cells. KL2B30 parental antibody (comprising a heavy chain and light chain of SEQ ID NO: 210 and SEQ ID NO: 221, respectively) and hu11B6 (an anti-hK2 antibody, also referred to herein as

h11B6, comprising a heavy chain and light chain of SEQ ID NO: 203 and SEQ ID NO: 215, respectively) were included as positive controls. The h11B6 antibody is described in U.S. Patent No. 10,100,125, which is incorporated by reference herein. An anti-Human F(ab')2 fragment specific secondary detection antibody was used for detecting Fab-based binding. Test antibodies were incubated with target cells at 4 °C for 60 minutes and detected by secondary staining. Cell binding was quantified by flow cytometry based on secondary antibody binding signal and gated from on live cells. Results indicated positive and dose-dependent cell binding using all three tested methods, which included un-conjugated KL2B997, random conjugation of KL2B997 and site-specific conjugation of KL2B997 (depicted in FIG. 1 as KL2B997*, KL2B997 NHS and KL2B997 SORT). KL2B30 Fab was shown to bind specifically to hK2-positive VCaP cells and not to hK2-negative DU145 cells. As shown in FIG. 1, results showed the KL2B30 Fab binds to hK2-expressing VCaP cells and can internalize and trigger internalization-based cell killing when conjugated with MMAF.

The immunoconjugates described above were made via random conjugation and site-specific conjugation. For site-specific conjugation, 2.1 mgs of h11B6 at 2 mg/mL in 1x dPBS (Thermo Fisher 14190144) was deglycosylated with 5ul of Rapid PNGaseF (NEB # P0711S) overnight at 37°C. Bacterial transglutaminase (bTG; Activa TI from Ajinomoto) was added to 30% w/v along with a 1000x molar excess of the amino-PEG4-(PEG3-azide)2 branched substrate (CP-2051 Conju-Probe LLC) and incubated overnight at room temperature. The azide-modified mAb was purified on an AKTA Avant instrument equipped with a 1ml Mabselect column (GE 11003493) and exchanged into 1x dPBS with 10 mL Zeba desalting columns (Thermo Fisher). DBCO-PEG4-vc-PAB-MMAF (Levena Biopharma) was added in 10x molar excess and reaction was monitored by LC-MS until reaching drug:antibody ratio of 4. The final h11B6-vcMMAF ADC was purified on a Zeba desalting column followed by concentration and diafiltration with an Amicon concentrator.

For random conjugation, KL2B30 was first reacted with to NHS-PEG4-azide (Thermo Fisher Cat # 26130). To 1.5mgs of KL2B30 at 1 mg/ml in 1x dPBS was added 30ul of 1M pH 9 sodium bicarbonate (BDH #144-55-8) and immediately followed by the addition of a 7x molar ratio of NHS-PEG4-azide. Reaction was monitored by mass spectrometry until the degree of labeling reached 2-2.5 and then quenched by addition of Tris pH 8.5 (Teknova T1085) to a final concentration of 100 mM. Following removal of unreacted NHS-PEG4-azide, a 10x molar

excess of DBCO-PEG4-vc-PAB-MMAF was added and incubated for 1 hour at 37°C. Final ADC (DAR = 2.7) was purified by 10 ml Zeba desalt column followed by concentration and diafiltration with an Amicon concentrator.

The KL2B997 site-specific ADC (antibody-drug conjugate) was prepared by conjugation via the sortase tag. 1 mg of KL2B997 at 1 mg/ml was incubated with S. pyogenes sortase A enzyme (2 uM) [reference to Chen et al. PNAS 2011:11399], and an excess of Gly3-vcMMAF (Levena Biopharma) in 50 mM Tris pH 7.5, 150 mM NaCl, 10 mM CaCl2 buffer. Reaction was incubated at for 1 hour at 37°C. The conjugate as purified on a 1 mL HisTrap column (Cytiva 17524701) on an AKTA Avant instrument. The ADC was further purified over a 24 ml Superdex 75 10/300 (Cytiva 29148721) in 1x dPBS to remove any aggregate or residual substrates.

KL2B997 randomly conjugated ADC was prepared by addition of NHS-PEG4-azide followed by reaction with DBCO-vcMMAF as described above.

Example 26 – TOPA-KL2B1251 Fab

A method of conjugating a KL2B30 Fab (identified as KL2B1251) to TOPA is provided below.

Preparation of TOPA-KL2B1251.

Random TOPA modification of Fab: KL2B1251 Fab was diluted to 1mg/ml in sterile 1xdPBS. Adjusted the pH of the mAb to 9.0 with sodium bicarbonate buffer pH 9 (VWR 144-55-8). Then, 8x molar excess of TOPA (TOPA-phenyl-NCS (intermediate); 50mM stock dissolved in DMSO) was added, and the pool was incubated at room temperature without shaking for approximately 1 hour. The addition of TOPA was monitored by intact mass ESI-TOF LC-MS on an Agilent G224 instrument until the CAR value was between 1.5-2.0. Pool was quenched by addition of 1M Tris pH 8.5 (Teknova T1085) to a final concentration of 100 mM. Excess free chelator was removed by successive rounds of desalting and eluting 15mls of conjugate pool at a time over a 55ml HiPrep 26/10 desalting column (17508701 – Cytiva). Equilibration and elution all performed in 1xdPBS. Sample was then concentrated to 2mls. To confirm no excess chelator was present, 3x rounds of sample dilution to 15mls followed by concentration to 1ml using a 50,000MWCO Amicon concentrator device was performed. The final conjugate was confirmed to be monomeric by analytical size exclusion chromatography on a Tosoh TSKgel G3000SWxl 7.8mm x 30cm, 5 u column; column temperature: room

temperature; the column was eluted 0.2M sodium phosphate pH 6.8; flow rate: 0.8 mL/min; 18 min run; injection volume: 18ul.

It is understood that the examples and embodiments described herein are for illustrative purposes only, and that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the spirit and scope of the invention as defined by the appended claims.

CLAIMS

What is claimed is:

1. An immunoconjugate comprising: a therapeutic moiety conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

2. The immunoconjugate according to claim 1, wherein the therapeutic moiety is a cytotoxic agent.

3. The immunoconjugate according to claim 1, wherein the therapeutic moiety is an imaging agent.

4. The immunoconjugate according to any of claims 1-3, wherein the therapeutic moiety comprises a radiometal.

5. The immunoconjugate according to claim 4, wherein the radiometal is selected from the group consisting of ^{225}Ac, ^{177}Lu, ^{32}P, ^{47}Sc, ^{67}Cu, ^{77}As, ^{89}Sr, ^{90}Y, ^{99}Tc, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{131}I, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{255}Fm, ^{227}Th, ^{177}Lu, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, and ^{111}In.

6. The immunoconjugate of claim 1, wherein the therapeutic moiety is a cytotoxic agent comprising ^{225}Ac.

7. The immunoconjugate of claim 1, wherein the therapeutic moiety is an imaging agent comprising ^{111}In.

8. The immunoconjugate according to any of claims 4-7, wherein the therapeutic moiety comprises a radiometal complex, wherein the radiometal complex comprises the radiometal bound to a chelator, and wherein the chelator is conjugated to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

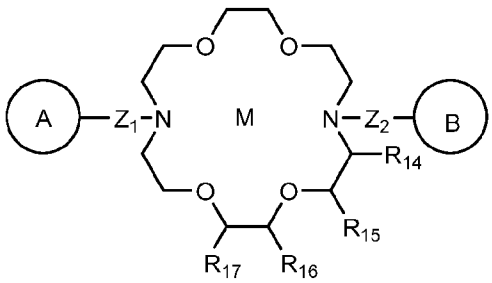
9. The immunoconjugate according to claim 8, wherein the chelator is 1,4,7,10-tetraazacyclododecane-1,4,7,10,tetraacetic acid (DOTA), S-2-(4-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), 1,4,8,11-tetraazacyclodocedan-1,4,8,11-tetraacetic acid (TETA), 3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-4-(S)-(4-isothiocyanatobenzyl)-3,6,9-triacetic acid (PCTA), 5-S-(4-aminobenzyl)-1-oxa-4,7,10-triazacyclododecane-4,7,10-tris(acetic acid) (DO3A), or a derivative thereof.

10. The immunoconjugate according to claim 8, wherein the chelator is DOTA.

11. The immunoconjugate according to claim 8, wherein the chelator is H_2bp18c6 or a H_2bp18c6 derivative.

12. The immunoconjugate according to claim 8, wherein the radiometal complex is a radiometal complex of Formula (I-m), or Formula (II-m), or Formula (III-m),

wherein the radiometal complex of Formula (I-m) has the following structure:



(I-m)

wherein:

M is the radiometal, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

each of ring A and ring B is independently a 6-10 membered aryl or a 5-10 membered heteroaryl, wherein each of ring A and ring B is optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, -OR_{13}, -SR_{13}, , -$(CH_2)_pCOOR_{13}$, -$OC(O)R_{13}$, -$N(R_{13})_2$, -$CON(R_{13})_2$, -NO_2, -CN -$OC(O)N(R_{13})_2$, and X;

each of Z_1 and Z_2 is independently –$(C(R_{12})_2)_m$- or –$(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$-;

each X is independently -L_1-R_{11};

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

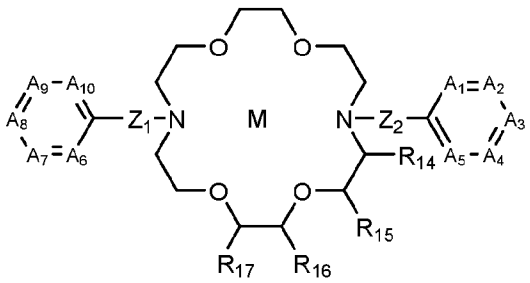
each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

each R_{13} is independently hydrogen or alkyl;

each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X; provided that the radiometal complex comprises at least one X, and when X is present on ring A or ring B, L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen;

wherein the radiometal complex of Formula (II-m) has the following structure:



(II-m)

wherein:

M is the radiometal, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

A_1 is N or CR_1 or is absent;

A_2 is N or CR_2;

A_3 is N or CR_3;

A_4 is N or CR_4;

A_5 is N or CR_5;

A_6 is N or CR_6 or is absent;

A_7 is N or CR_7;

A_8 is N or CR_8;

A_9 is N or CR_9;

A_{10} is N or CR_{10};

provided that no more than three of A_1, A_2, A_3, A_4, and A_5 are N, and no more than three of A_6, A_7, A_8, A_9, and A_{10} are N;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN $-OC(O)N(R_{13})_2$, and -X,

or, alternatively, any two directly adjacent R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are taken together with the atoms to which they are attached to form a five or six-membered substituted or unsubstituted carbocyclic or nitrogen-containing ring;

each of Z_1 and Z_2 is independently $-(C(R_{12})_2)_m-$ or $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;

each X is independently $-L_1-R_{11}$;

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

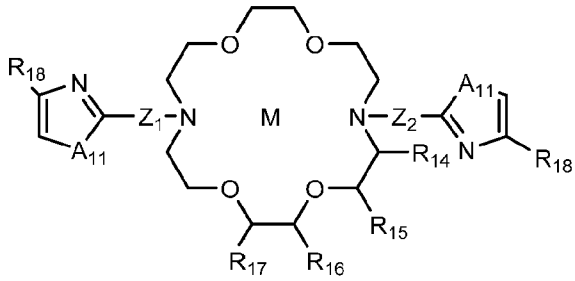
each R_{13} is independently hydrogen or alkyl;

each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X;

provided that the radiometal complex comprises at least one X, and when any one of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is X, then L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen;

wherein the radiometal complex of Formula (III-m) has the following structure:



(III-m)

wherein:

M is the radiometal, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

each A_{11} is independently O, S, NMe, or NH;

each of Z_1 and Z_2 is independently $-(C(R_{12})_2)_m-$ or $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;

each X is independently $-L_1-R_{11}$;

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

each R_{13} is independently hydrogen or alkyl;

each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

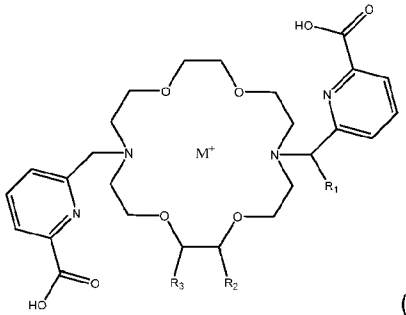
or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X; and

each R_{18} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, , $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN $-OC(O)N(R_{13})_2$, and -X,

provided that the radiometal complex comprises at least one X, and when R_{18} is X, then L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen.

13. The immunoconjugate according to claim 8, wherein the radiometal complex is a radiometal complex of Formula (IV-m), or Formula (V-m), or Formula (VI-m),

wherein the radiometal complex of Formula (IV-m) has the following structure:



(IV-m)

or a pharmaceutically acceptable salt thereof, wherein:

M^+ is the radiometal, preferably selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

R_1 is hydrogen and R_2 is -L_1-R_4;

alternatively, R_1 is -L_1-R_4 and R_2 is hydrogen;

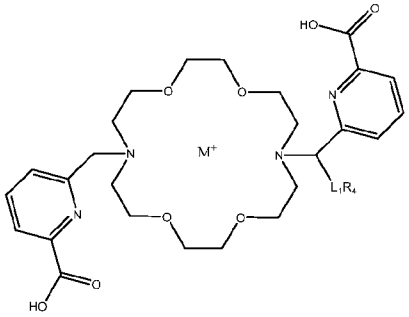
R_3 is hydrogen;

alternatively, R_2 and R_3 are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl, wherein the 5- or 6-membered cycloalkyl is optionally substituted with -L_1-R_4;

L_1 is absent or a linker;

R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

wherein the radiometal complex of Formula (V-m) has the following structure:



(V-m)

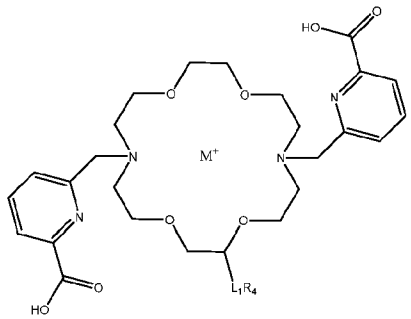
or a pharmaceutically acceptable salt thereof, wherein:

M^+ is the radiometal, preferably selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

L_1 is absent or a linker;

R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

wherein the radiometal complex of Formula (VI-m) has the following structure:



(VI-m)

or a pharmaceutically acceptable salt thereof, wherein:

M^+ is the radiometal, preferably selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134

(^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

L_1 is absent or a linker; and

R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

14. The immunoconjugate of claim 1, wherein the therapeutic moiety is an auristatin derivative.

15. The immunoconjugate of claim 14, wherein the therapeutic moiety is MMAE (monomethyl auristatin E).

16. The immunoconjugate of claim 14, wherein the therapeutic moiety is MMAF (monomethyl auristatin F).

17. The immunoconjugate according to any of claims 1-16, wherein the antigen binding domain that binds hK2 is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb or a VHH.

18. The immunoconjugate according to any of claims 1-16, wherein the antigen binding domain with binding specificity for hK2 is a Fab.

19. The immunoconjugate according to any of claims 1-18, wherein the antigen binding domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively.

20. The immunoconjugate according to any of claims 1-19, wherein the antigen binding domain that binds hK2 comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163.

21. The immunoconjugate according to any of claims 1-19, wherein the antigen binding domain that binds hK2 comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.

22. The immunoconjugate according to any of claims 1-18, wherein the antigen binding domain is a Fab that comprises:

a. a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or

b. a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

23. The immunoconjugate according to any of claims 1-22, wherein the immunoconjugate is a short half-life immunoconjugate.

24. A method of treating an hK2-expressing cancer in a subject, comprising administering to the subject a therapeutically effective amount of the immunoconjugate according to any of claims 1-23.

25. A method of reducing the amount of hK2-expressing tumor cells in a subject, comprising administering the immunoconjugate according to any of claims 1-23 to the subject for a time sufficient to reduce the amount of hK2-expressing tumor cells.

26. A method of treating prostate cancer in a subject, comprising administering to the subject a therapeutically effective amount of the immunoconjugate according to any of claims 1-23.

27. The method of claim 26, wherein the prostate cancer is relapsed, refractory, malignant or castration resistant prostate cancer, or any combination thereof.

28. The method of claim 26, wherein the prostate cancer is metastatic castration-resistant prostate cancer.

29. A method of detecting the presence of prostate cancer in a subject, comprising administering the immunoconjugate according to any of claims 1-23 to a subject suspected to have prostate cancer and visualizing the biological structures to which the conjugate is bound, thereby detecting the presence of prostate cancer.

30. A method of making an immunoconjugate according to any of claims 1-23 comprising: conjugating the therapeutic moiety to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

31. A method of making a radioimmunoconjugate comprising binding a radiometal to a chelator that is conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

32. The method of claim 31, wherein the chelator is DOTA.

33. The method of claim 31, wherein the chelator is H_2bp18c6 or a H_2bp18c6 derivative.

34. The method of claim 31, wherein the chelator is selected from the group consisting of chelators of Formula (I), Formula (II) and Formula (III) as described herein,

wherein R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2)

35. The method of claim 31, wherein the chelator is selected from the group consisting of chelators of Formula (IV), Formula (V) and Formula (VI) as described herein, wherein R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

36. The method according to any of claims 31-35, wherein the antigen binding domain that binds hK2 is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb or a VHH.

37. The method according to any of claims 31-35, wherein the antigen binding domain that binds hK2 is a Fab.

38. The method according to any of claims 31-37, wherein the antigen binding domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively.

39. The method according to any of claims 31-38, wherein the antigen binding domain that binds hK2 comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163.

40. The method according to any of claims 31-38, wherein the antigen binding domain that binds hK2 comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.

41. The method according to any of claims 31-37, wherein the antigen binding domain is a Fab that comprises:

a. a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or

b. a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163

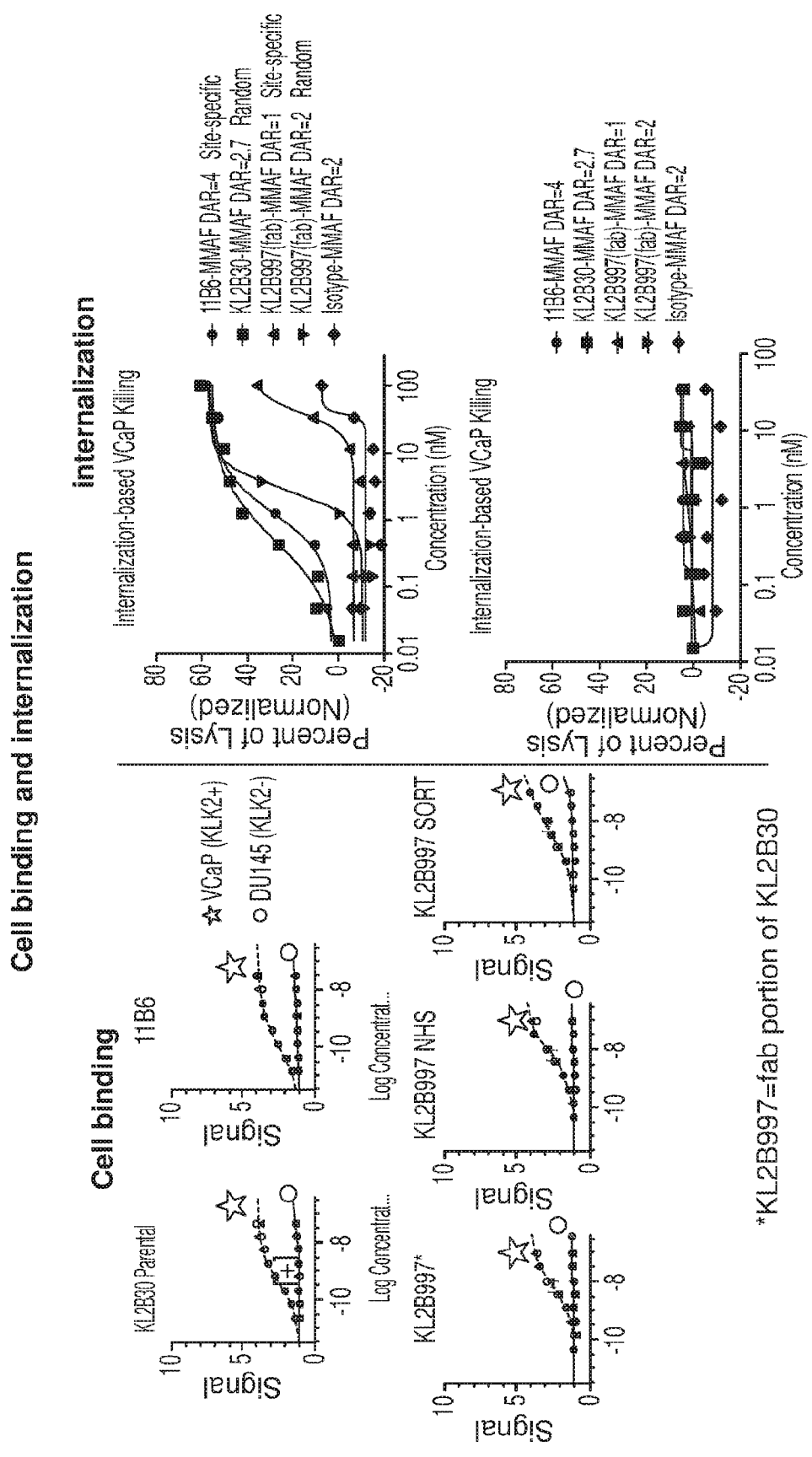

Cell binding and internalization
Cell binding
internalization
KL2B30 Parental
11B6
KL2B997*
KL2B997 NHS
KL2B997 SORT
VCaP (KLK2+)
DU145 (KLK2-)
Signal
Log Concentrat...
Internalization-based VCaP Killing
Percent of Lysis (Normalized)
Concentration (nM)
11B6-MMAF DAR=4 Site-specific
KL2B30-MMAF DAR=2.7 Random
KL2B997(fab)-MMAF DAR=1 Site-specific
KL2B997(fab)-MMAF DAR=2 Random
Isotype-MMAF DAR=2
*KL2B997=fab portion of KL2B30

FIG. 1

FIG. 2

Heavy Chain (HC) and Light Chain (LC) Sequences of KL2B997 and KL2B1251

KL2B997

HC (SEQ ID NO. 472)

QVQLQESGPG LVKPSETLSL TCTVSGGSIS SYYWSWIRQP PGKGLEWIGY IYYSGSTNYN PSLKSRVTIS VDTSKNQFSL
KLSSVTAADT AVYYCAGTTI FGVVTPNFYY GMDVWGQGTT VTVSSASTKG PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE
PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THTGSGSGSH
HHHHHGSGLP ETGG

LC (SEQ ID NO. 473)

DIQMTQSPSF LSASVGDRVT ITCRASQGIS SYLAWYQQKP GKAPKFLIYA ASTLQSGVPS RFSGSGSGTE FTLTISSLQP
EDFATYYCQQ LNSYPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ
ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

KL2B1251

HC (SEQ ID NO. 474)

QVQLQESGPG LVKPSETLSL TCTVSGGSIS SYYWSWIRQP PGKGLEWIGY IYYSGSTNYN PSLKSRVTIS VDTSKNQFSL
KLSSVTAADT AVYYCAGTTI FGVVTPNFYY GMDVWGQGTT VTVSSASTKG PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE
PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KKVEPKSC

LC (SEQ ID NO. 475)

DIQMTQSPSF LSASVGDRVT ITCRASQGIS SYLAWYQQKP GKAPKFLIYA ASTLQSGVPS RFSGSGSGTE FTLTISSLQP
EDFATYYCQQ LNSYPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ
ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

SEQUENCE LISTING

<110> JANSSEN BIOTECH, INC.

<120> IMMUNOCONJUGATES COMPRISING KALLIKREIN RELATED PEPTIDASE 2 ANTIGEN BINDING DOMAINS AND THEIR USES

<130> JBI6462WOPCT1

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<150> 63/144,586
<151> 2021-02-02

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1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gln
65 70 75 80

Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

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Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

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polypeptide

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Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

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polypeptide

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Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
        35   40   45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

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<213> Artificial Sequence

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      polypeptide

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

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35   40   45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

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Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Val Thr Val Ser Ser
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Thr Gly Gly Ser
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<220>
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1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
35 40 45

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Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160

Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ser Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240
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Gln Gly Thr Lys Leu Glu Ile Lys
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<213> Artificial Sequence

<220>
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Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
115 120 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
130 135 140

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Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160


Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175


Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190


Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205


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


Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240


Gln Gly Thr Lys Leu Glu Ile Lys
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            20                  25                  30


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

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160

Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Leu Glu Ile Lys
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20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
115 120 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
130 135 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145 150 155 160

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Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175


Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190


Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205


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


Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240


Gln Gly Thr Lys Leu Glu Ile Lys
                245
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            20                  25                  30


Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


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

Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser
                245
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polypeptide

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20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
115 120 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
130 135 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145 150 155 160

```
Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175


Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190


Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205


Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220


Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240


Gly Thr Leu Val Thr Val Ser Ser
                245
```

<210> 14
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 14

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


Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30


Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly Val Pro Asp
    50                  55                  60
```

```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser
                245
```

<210> 15
<211> 248

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 15
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
115 120 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
130 135 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145 150 155 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
165 170 175

```
Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190


Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205


Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220


Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240


Gly Thr Leu Val Thr Val Ser Ser
                245


<210> 16
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 16
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15


Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30


Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


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


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80
```

```
Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser
                245
```

<210> 17
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 17
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gln
65 70 75 80

Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
115 120 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
130 135 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145 150 155 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
165 170 175

```
Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190


Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205


Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220


Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240


Gly Thr Leu Val Thr Val Ser Ser
                245


<210> 18
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 18
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30


Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80
```

```
Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160

Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 19
<211> 248
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 19

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

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160

Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190
```

```
Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205


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


Ser Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240


Gln Gly Thr Lys Leu Glu Ile Lys
                245


<210> 20
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 20
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30


Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125


Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140


Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160


Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175


Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190


Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205


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


Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240


Gln Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 21
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 21
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20   25   30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gln
65   70   75   80

Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln Gln Thr Arg
                85   90   95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100   105   110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115   120   125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130   135   140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145   150   155   160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
                165   170   175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180   185   190

```
Pro Ser Leu Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205


Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val
    210                 215                 220


Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240


Gly Thr Leu Val Thr Val Ser Ser
                245


<210> 22
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 22
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15


Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30


Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


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


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80


Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85                  90                  95
```

```
Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser
                245
```

<210> 23
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 23

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

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80

Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205
```

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val
    210   215   220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225   230   235   240

Gly Thr Leu Val Thr Val Ser Ser
                245

<210> 24
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 24
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1   5   10   15

Ile Gln Ala

<210> 25
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 25
Thr Ser Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1   5   10   15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
            20   25   30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
35 40 45

<210> 26
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 26
Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys
20

<210> 27
<211> 42
<212> PRT
<213> Homo sapiens

<400> 27
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> 28
<211> 112
<212> PRT
<213> Homo sapiens

<400> 28
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
1 5 10 15

```
Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
            20                  25                  30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
        35                  40                  45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
    50                  55                  60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65                  70                  75                  80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
                85                  90                  95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
            100                 105                 110
```

<210> 29
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 29

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15

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

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
        35                  40                  45

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
    50                  55                  60
```

```
Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65                  70                  75                  80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
        115                 120                 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
    130                 135                 140

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190

Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205

Tyr Ala Ala Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gln Ser Val Gln Ala
225                 230                 235                 240

Glu Asp Val Ser Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            260                 265
```

<210> 30
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 30
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

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

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
35 40 45

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

Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65 70 75 80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
130 135 140

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu
145 150 155 160

```
Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175


Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190


Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205


Tyr Ala Ala Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
225                 230                 235                 240


Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr
                245                 250                 255


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            260                 265


<210> 31
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 31
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


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


Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
        35                  40                  45
```

```
Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65                  70                  75                  80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
        115                 120                 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
    130                 135                 140

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190

Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205

Tyr Ala Ala Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
225                 230                 235                 240
```

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr
245 250 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
260 265

<210> 32
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 32
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

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

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
35 40 45

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

Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65 70 75 80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
115 120 125

```
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
    130                 135                 140

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190

Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205

Tyr Ala Ala Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
225                 230                 235                 240

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            260                 265
```

<210> 33
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 33

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15
```

```
Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val
        35                  40                  45

Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly
65                  70                  75                  80

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95

Thr Ile Gln Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln
            100                 105                 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro
            180                 185                 190

Gly Lys Gly Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205

Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220
```

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp
225 230 235 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
245 250 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
260 265

<210> 34
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 34
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
20 25 30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val
35 40 45

Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
50 55 60

Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly
65 70 75 80

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
85 90 95

Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln
100 105 110

```
Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro
            180                 185                 190

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205

Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp
225                 230                 235                 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265
```

<210> 35
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 35
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1   5   10   15

Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
            20   25   30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val
        35   40   45

Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50   55   60

Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly
65   70   75   80

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85   90   95

Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln
            100   105   110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
        115   120   125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130   135   140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145   150   155   160

Leu Val Lys Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
                165   170   175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro
            180   185   190

```
Gly Lys Gly Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205


Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220


Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp
225                 230                 235                 240


Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265
```

<210> 36
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 36

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30


Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val
        35                  40                  45


Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60


Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly
65                  70                  75                  80
```

```
Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95

Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln
            100                 105                 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro
            180                 185                 190

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205

Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp
225                 230                 235                 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265
```

<210> 37
<211> 267

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 37
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
20 25 30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val
35 40 45

Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
50 55 60

Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly
65 70 75 80

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
85 90 95

Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln
100 105 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
115 120 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
130 135 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145 150 155 160

Leu Val Lys Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
165 170 175

```
Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro
            180                 185                 190


Gly Lys Gly Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205


Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220


Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp
225                 230                 235                 240


Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265
```

<210> 38
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 38

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30


Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val
        35                  40                  45


Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60
```

```
Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly
65                  70                  75                  80

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95

Thr Ile Gln Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln
            100                 105                 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro
            180                 185                 190

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205

Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp
225                 230                 235                 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255
```

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
260 265

<210> 39
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 39
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

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

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
35 40 45

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65 70 75 80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
130 135 140

```
Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu
145                 150                 155                 160


Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175


Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190


Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205


Tyr Ala Ala Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
225                 230                 235                 240


Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr
                245                 250                 255


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            260                 265


<210> 40
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 40
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


Ile Gln Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30
```

```
Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
        35                  40                  45

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65                  70                  75                  80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
        115                 120                 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
    130                 135                 140

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190

Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205

Tyr Ala Ala Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gln Ser Val Gln Ala
225                 230                 235                 240
```

Glu Asp Val Ser Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr
245 250 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
260 265

<210> 41
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 41
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

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

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
35 40 45

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65 70 75 80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
115 120 125

```
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
    130                 135                 140

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190

Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205

Tyr Ala Ala Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
225                 230                 235                 240

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            260                 265
```

<210> 42
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 42

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15
```

```
Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val
        35                  40                  45

Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly
65                  70                  75                  80

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95

Thr Ile Gln Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln
            100                 105                 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro
            180                 185                 190

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205
```

```
Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Met Ser Arg Asp Thr
    210                 215                 220

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp
225                 230                 235                 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265
```

<210> 43
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 43

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15

Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val
        35                  40                  45

Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly
65                  70                  75                  80

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95
```

```
Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln
            100                 105                 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro
            180                 185                 190

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205

Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Met Ser Arg Asp Thr
    210                 215                 220

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp
225                 230                 235                 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265
```

<210> 44
<211> 267
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 44

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                  10                  15


Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30


Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val
        35                  40                  45


Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60


Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Arg Glu Ser Gly
65                  70                  75                  80


Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95


Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln
            100                 105                 110


Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
        115                 120                 125


Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140


Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160


Leu Val Lys Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
                165                 170                 175


Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro
            180                 185                 190
```

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
195 200 205

Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Met Ser Arg Asp Thr
210 215 220

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp
225 230 235 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
245 250 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
260 265

<210> 45
<211> 154
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 45
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
35 40 45

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
50 55 60

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
65 70 75 80

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
85 90 95

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
100 105 110

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
115 120 125

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
130 135 140

Ala Leu His Met Gln Ala Leu Pro Pro Arg
145 150

<210> 46
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 46
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

```
Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160

Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ser Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Leu Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270
```

```
Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 47
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 47
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
115 120 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
130 135 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145 150 155 160

```
Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Leu Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350
```

```
Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 48
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 48

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

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30
```

```
Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160

Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240
```

```
Gln Gly Thr Lys Leu Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
               245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430
```

```
Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445


Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460


Met Gln Ala Leu Pro Pro Arg
465                 470


<210> 49
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 49
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30


Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110
```

```
Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160

Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Leu Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320
```

```
Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 50
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 50
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20   25   30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gln
65   70   75   80

Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln Gln Thr Arg
                85   90   95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100   105   110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115   120   125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130   135   140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145   150   155   160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165   170   175

Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180   185   190

```
Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400
```

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
405 410 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
420 425 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
435 440 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
450 455 460

Met Gln Ala Leu Pro Pro Arg
465 470

<210> 51
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 51
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

```
Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270
```

```
Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 52
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 52
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
115 120 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
130 135 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145 150 155 160

```
Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350
```

```
Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 53
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 53

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

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30
```

```
Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80

Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240
```

```
Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430
```

```
Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445


Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460


Met Gln Ala Leu Pro Pro Arg
465                 470


<210> 54
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 54
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15


Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30


Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


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


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80


Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85                  90                  95


Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110
```

```
Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320
```

```
Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 55
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 55

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

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gln
65                  70                  75                  80

Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190
```

```
Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Pro Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400
```

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
405 410 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
420 425 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
435 440 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
450 455 460

Met Gln Ala Leu Pro Pro Arg
465 470

<210> 56
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 56
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

```
Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160

Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Leu Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270
```

```
Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 57
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 57
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
115 120 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
130 135 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145 150 155 160

```
Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ser Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Leu Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350
```

```
Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 58
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 58

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

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30
```

```
Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160

Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ala Val Tyr Tyr Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240
```

```
Gln Gly Thr Lys Leu Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
               245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430
```

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435   440   445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450   455   460

Met Gln Ala Leu Pro Pro Arg
465   470

<210> 59
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 59
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20   25   30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gln
65   70   75   80

Ser Val Gln Ala Glu Asp Val Ser Val Tyr Phe Cys Gln Gln Thr Arg
                85   90   95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100   105   110

```
Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320
```

```
Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 60
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 60
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20   25   30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65   70   75   80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85   90   95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100   105   110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115   120   125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130   135   140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145   150   155   160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
                165   170   175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180   185   190

```
Pro Ser Leu Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400
```

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
405 410 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
420 425 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
435 440 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
450 455 460

Met Gln Ala Leu Pro Pro Arg
465 470

<210> 61
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 61
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

```
Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Asp Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270
```

```
Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 62
<211> 261
<212> PRT
<213> Homo sapiens

<400> 62
Met Trp Asp Leu Val Leu Ser Ile Ala Leu Ser Val Gly Cys Thr Gly
1   5   10   15

Ala Val Pro Leu Ile Gln Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20   25   30

Lys His Ser Gln Pro Trp Gln Val Ala Val Tyr Ser His Gly Trp Ala
        35   40   45

His Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50   55   60

His Cys Leu Lys Lys Asn Ser Gln Val Trp Leu Gly Arg His Asn Leu
65   70   75   80

Phe Glu Pro Glu Asp Thr Gly Gln Arg Val Pro Val Ser His Ser Phe
                85   90   95

Pro His Pro Leu Tyr Asn Met Ser Leu Leu Lys His Gln Ser Leu Arg
            100   105   110

Pro Asp Glu Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
        115   120   125

Pro Ala Lys Ile Thr Asp Val Val Lys Val Leu Gly Leu Pro Thr Gln
    130   135   140

Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
145   150   155   160

Glu Pro Glu Glu Phe Leu Arg Pro Arg Ser Leu Gln Cys Val Ser Leu
                165   170   175

```
His Leu Leu Ser Asn Asp Met Cys Ala Arg Ala Tyr Ser Glu Lys Val
            180                 185                 190


Thr Glu Phe Met Leu Cys Ala Gly Leu Trp Thr Gly Gly Lys Asp Thr
        195                 200                 205


Cys Gly Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln
    210                 215                 220


Gly Ile Thr Ser Trp Gly Pro Glu Pro Cys Ala Leu Pro Glu Lys Pro
225                 230                 235                 240


Ala Val Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr
                245                 250                 255


Ile Ala Ala Asn Pro
            260
```

<210> 63
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 63
```
Ser Asp Tyr Ala Trp Asn
1               5
```

<210> 64
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 64

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

<210> 65
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 65
Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 66
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 66
Gly Tyr Tyr Tyr Gly Ser Gly Phe
1 5

<210> 67
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 67
Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His
1 5 10 15

<210> 68
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 68
Lys Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His
1 5 10 15

<210> 69
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 69
Ala Ala Ser Asn Val Glu Ser
1 5

<210> 70
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 70
Ala Ala Ser Asn Arg Glu Ser
1 5

<210> 71
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 71
Gln Gln Thr Arg Lys Val Pro Tyr Thr
1 5

<210> 72
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 72
Gly Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn
1 5 10

<210> 73
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 73
Tyr Ile Ser Tyr Ser Gly Ser Thr Thr
1 5

<210> 74
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (1)..(1)
<223> D or E

<220>
<221> MOD_RES
<222> (9)..(9)
<223> D or A

<220>
<221> MOD_RES
<222> (10)..(10)
<223> S or T

<220>
<221> MOD_RES
<222> (12)..(12)
<223> A or S

<220>
<221> MOD_RES
<222> (13)..(13)
<223> V or L

<220>
<221> MOD_RES
<222> (15)..(15)
<223> L or P

<220>
<221> MOD_RES
<222> (21)..(21)
<223> I or L

<220>
<221> MOD_RES
<222> (22)..(22)
<223> N or S

<220>
<221> MOD_RES
<222> (24)..(24)
<223> R or K

<220>
<221> MOD_RES
<222> (49)..(49)
<223> K or R

<220>
<221> MOD_RES
<222> (58)..(58)
<223> V or R

<220>
<221> MOD_RES
<222> (62)..(62)
<223> V or I

<220>
<221> MOD_RES
<222> (64)..(64)
<223> A or D

<220>
<221> MOD_RES
<222> (80)..(80)
<223> Q or S

<220>
<221> MOD_RES
<222> (82)..(82)
<223> L or V

<220>
<221> MOD_RES
<222> (83)..(83)
<223> Q or E

<220>
<221> MOD_RES
<222> (85)..(85)
<223> P or A

<220>
<221> MOD_RES
<222> (88)..(88)
<223> F or V

<220>
<221> MOD_RES
<222> (89)..(89)
<223> A or S

<220>
<221> MOD_RES
<222> (92)..(92)
<223> Y or F

<220>
<221> MOD_RES
<222> (105)..(105)
<223> Q or G

<220>
<221> MOD_RES
<222> (109)..(109)
<223> L or V

<400> 74
Xaa Ile Val Leu Thr Gln Ser Pro Xaa Xaa Leu Xaa Xaa Ser Xaa Gly
1   5   10   15

Glu Arg Ala Thr Xaa Xaa Cys Xaa Ala Ser Glu Ser Val Glu Tyr Phe
            20   25   30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45

Xaa Leu Leu Ile Tyr Ala Ala Ser Asn Xaa Glu Ser Gly Xaa Pro Xaa
    50   55   60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Xaa
65   70   75   80

Ser Xaa Xaa Gln Xaa Glu Asp Xaa Xaa Val Tyr Xaa Cys Gln Gln Thr
                85   90   95

Arg Lys Val Pro Tyr Thr Phe Gly Xaa Gly Thr Lys Xaa Glu Ile Lys
            100   105   110

<210> 75
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (16)..(16)
<223> D or Q

<220>
<221> MOD_RES
<222> (23)..(23)
<223> A or T

<220>

<221> MOD_RES
<222> (41)..(41)
<223> P or F

<220>
<221> MOD_RES
<222> (45)..(45)
<223> G or R

<220>
<221> MOD_RES
<222> (49)..(49)
<223> I or M

<220>
<221> MOD_RES
<222> (70)..(70)
<223> I or M

<220>
<221> MOD_RES
<222> (88)..(88)
<223> A or P

<220>
<221> MOD_RES
<222> (89)..(89)
<223> V or A

<400> 75
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Xaa
1   5   10   15

Thr Leu Ser Leu Thr Cys Xaa Val Ser Gly Asn Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Xaa Pro Gly Lys Xaa Leu Glu Trp
        35   40   45

Xaa Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Xaa Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Xaa Xaa Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 76
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 76
Gly Gly Gly Ser Gly Gly Gly Ser
1 5

<210> 77
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 77
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10

<210> 78
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 78

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1   5   10   15

<210> 79
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 79
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1   5   10   15

Gly Gly Gly Ser
            20

<210> 80
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 80
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1   5   10   15

<210> 81
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 81
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser
            20

<210> 82
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 82
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
            20   25

<210> 83
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 83
Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
1   5   10   15

Lys Gly

<210> 84
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 84

Ile Arg Pro Arg Ala Ile Gly Gly Ser Lys Pro Arg Val Ala
1 5 10

<210> 85
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 85
Gly Lys Gly Gly Ser Gly Lys Gly Gly Ser Gly Lys Gly Gly Ser
1 5 10 15

<210> 86
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 86
Gly Gly Lys Gly Ser Gly Gly Lys Gly Ser Gly Gly Lys Gly Ser
1 5 10 15

<210> 87
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 87
Gly Gly Gly Lys Ser Gly Gly Gly Lys Ser Gly Gly Gly Lys Ser
1 5 10 15

<210> 88
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 88
Gly Lys Gly Lys Ser Gly Lys Gly Lys Ser Gly Lys Gly Lys Ser
1 5 10 15

<210> 89
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 89
Gly Gly Gly Lys Ser Gly Gly Lys Gly Ser Gly Lys Gly Gly Ser
1 5 10 15

<210> 90
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 90
Gly Lys Pro Gly Ser Gly Lys Pro Gly Ser Gly Lys Pro Gly Ser
1 5 10 15

<210> 91
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 91
Gly Lys Pro Gly Ser Gly Lys Pro Gly Ser Gly Lys Pro Gly Ser Gly
1 5 10 15

Lys Pro Gly Ser
            20

<210> 92
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 92
Gly Lys Gly Lys Ser Gly Lys Gly Lys Ser Gly Lys Gly Lys Ser Gly
1   5   10   15

Lys Gly Lys Ser
            20

<210> 93
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 93
Ser Thr Ala Gly Asp Thr His Leu Gly Gly Glu Asp Phe Asp
1   5   10

<210> 94
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 94
Gly Glu Gly Gly Ser Gly Glu Gly Gly Ser Gly Glu Gly Gly Ser
1   5   10   15

<210> 95
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 95
Gly Gly Glu Gly Ser Gly Gly Glu Gly Ser Gly Gly Glu Gly Ser
1 5 10 15

<210> 96
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 96
Gly Glu Gly Glu Ser Gly Glu Gly Glu Ser Gly Glu Gly Glu Ser
1 5 10 15

<210> 97
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 97
Gly Gly Gly Glu Ser Gly Gly Glu Gly Ser Gly Glu Gly Gly Ser
1 5 10 15

<210> 98
<211> 20
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 98
Gly Glu Gly Glu Ser Gly Glu Gly Glu Ser Gly Glu Gly Glu Ser Gly
1 5 10 15

Glu Gly Glu Ser
20

<210> 99
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 99
Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
1 5 10 15

Lys Gly

<210> 100
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 100
Pro Arg Gly Ala Ser Lys Ser Gly Ser Ala Ser Gln Thr Gly Ser Ala
1 5 10 15

Pro Gly Ser

<210> 101
<211> 19

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 101
Gly Thr Ala Ala Ala Gly Ala Gly Ala Ala Gly Gly Ala Ala Ala Gly
1 5 10 15

Ala Ala Gly

<210> 102
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 102
Gly Thr Ser Gly Ser Ser Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly
1 5 10 15

Gly Gly Gly

<210> 103
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 103
Gly Lys Pro Gly Ser Gly Lys Pro Gly Ser Gly Lys Pro Gly Ser Gly
1 5 10 15

Lys Pro Gly Ser
20

<210> 104
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 104
Gly Ser Gly Ser
1

<210> 105
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 105
Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
1 5 10

<210> 106
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 106
Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
1 5 10 15

Ala Pro Ala Pro
20

<210> 107
<211> 32

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 107
Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Ala
1 5 10 15

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

<210> 108
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 108
Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
1 5 10 15

<210> 109
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 109
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

```
Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50                  55                  60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Ala Leu Val
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly
225                 230
```

<210> 110
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 110
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Met Thr
130 135 140

Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

```
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175


Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190


Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205


Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220


Ser Leu Ser Leu Ser Pro Gly
225                 230


<210> 111
<211> 5
<212> PRT
<213> Homo sapiens

<400> 111
Lys Val Thr Glu Phe
1               5


<210> 112
<211> 5
<212> PRT
<213> Homo sapiens

<400> 112
His Tyr Arg Lys Trp
1               5


<210> 113
<211> 6
<212> PRT
<213> Homo sapiens

<400> 113
Ser His Gly Trp Ala His
1               5
```

<210> 114
<211> 15
<212> PRT
<213> Homo sapiens

<400> 114
Arg His Asn Leu Phe Glu Pro Glu Asp Thr Gly Gln Arg Val Pro
1 5 10 15

<210> 115
<211> 9
<212> PRT
<213> Homo sapiens

<400> 115
Gly Trp Gly Ser Ile Glu Pro Glu Glu
1 5

<210> 116
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 116
Asn Asn Asn Ala Ala Trp Ser
1 5

<210> 117
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 117
Arg Thr Tyr Tyr Arg Ser Lys Trp Leu Tyr Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 118
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 118
Gly Tyr Ser Ser Ser Phe Asp Tyr
1 5

<210> 119
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 119
Thr Gly Thr Ser Ser Asn Ile Gly Thr Tyr Lys Phe Val Ser
1 5 10

<210> 120
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 120
Glu Val Ser Lys Arg Pro Ser
1 5

<210> 121
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 121
Val Ser Tyr Ala Gly Ser Gly Thr Leu Leu
1 5 10

<210> 122
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 122
Gln Val Gln Leu Gln Gln Ser Gly Pro Arg Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 123
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 123
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Gln Ala Asp Tyr His Cys Val Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 124
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 124
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

```
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30

Gly Thr Ser Leu Met His Trp Tyr Arg Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile Gln
65                  70                  75                  80

Pro Val Glu Glu Asp Asp Phe Ser Met Tyr Phe Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

<210> 125
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 125

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Arg Leu Glu Trp
        35                  40                  45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Ser Pro Ser Leu
    50                  55                  60
```

```
Lys Ser Arg Phe Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80


Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95


Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115


<210> 126
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 126
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1               5                   10                  15


<210> 127
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 127
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
1               5                   10


<210> 128
<211> 62
<212> PRT
<213> Artificial Sequence
```

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 128
Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro Arg Cys
1 5 10 15

Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
20 25 30

Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu
35 40 45

Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
50 55 60

<210> 129
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 129
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro
1 5 10

<210> 130
<211> 330
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown:
wild-type IgG1 sequence

<400> 130
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

```
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220
```

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240


Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255


Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270


Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285


Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300


Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320


Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330


<210> 131
<211> 326
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown:
      wild-type IgG2 sequence

<400> 131
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
```

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
        115                 120                 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    130                 135                 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145                 150                 155                 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
                165                 170                 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
            180                 185                 190

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

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

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225                 230                 235                 240
```

```
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                245                 250                 255


Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            260                 265                 270


Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
        275                 280                 285


Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    290                 295                 300


Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305                 310                 315                 320


Ser Leu Ser Pro Gly Lys
                325


<210> 132
<211> 327
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown:
      wild-type IgG4 sequence

<400> 132
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


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


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
            100                 105                 110


Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190


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


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


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270
```

```
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320


Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 133
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 133

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Trp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr Gly Met Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Ser Glu
        115                 120                 125

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser
    130                 135                 140

Glu Ile Val Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
145                 150                 155                 160

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
                165                 170                 175

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
            180                 185                 190

Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
        195                 200                 205

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
    210                 215                 220

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
225                 230                 235                 240

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
                245                 250
```

<210> 134
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 134

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Trp
145                 150                 155                 160

Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
                165                 170                 175

Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val Asp Ser Val Lys
            180                 185                 190
```

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
195 200 205

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
210 215 220

Arg Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr Gly Met Asp Val
225 230 235 240

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
245 250

<210> 135
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 135
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Arg Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro Glu Asp Phe
    210                 215                 220

Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gly Gly Thr Lys Val Glu Ile Lys
                245
```

<210> 136
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 136

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Arg
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205
```

```
Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
    210                 215                 220


Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240


Gly Thr Leu Val Thr Val Ser Ser
                245


<210> 137
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 137
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Trp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr Gly Met Asp
            100                 105                 110
```

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 138
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 138
Glu Ile Val Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20   25   30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 139
<211> 117
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 139
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Arg Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 140
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 140
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

```
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 141
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 141
```
Ser Tyr Trp Met Thr
1               5
```

<210> 142
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 142
```
Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val Asp Ser Val Lys
1               5                   10                  15
```

Gly

<210> 143
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 143
Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr Gly Met Asp Val
1 5 10 15

<210> 144
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 144
Arg Ala Ser Gln Gly Ile Ser Ser Tyr Leu Ser
1 5 10

<210> 145
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 145
Ala Thr Ser Thr Leu Gln Ser
1 5

<210> 146
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 146
Gln Gln Leu Asn Ser Tyr Pro Arg Thr
1 5

<210> 147
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 147
Gly Phe Thr Phe Ser Ser Tyr Trp Met Thr
1 5 10

<210> 148
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 148
Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr
1 5 10

<210> 149
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 149

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                  10                  15

Ile Gln Ala Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Trp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr
        115                 120                 125

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
145                 150                 155                 160

Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala
                165                 170                 175

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile
            180                 185                 190

Ser Ser Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
        195                 200                 205
```

```
Leu Leu Ile Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg
    210                 215                 220

Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser
225                 230                 235                 240

Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser
                245                 250                 255

Tyr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            260                 265                 270
```

<210> 150
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 150

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15

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

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile
        35                  40                  45

Ser Ser Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
    50                  55                  60

Leu Leu Ile Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg
65                  70                  75                  80

Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser
                85                  90                  95
```

```
Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser
            100                 105                 110

Tyr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly
        115                 120                 125

Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly
    130                 135                 140

Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
145                 150                 155                 160

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
                165                 170                 175

Ser Tyr Trp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
            180                 185                 190

Trp Val Ala Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val Asp
        195                 200                 205

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
    210                 215                 220

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
225                 230                 235                 240

Tyr Cys Ala Arg Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr Gly
                245                 250                 255

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            260                 265                 270
```

<210> 151
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 151
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

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

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
35 40 45

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

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65 70 75 80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
130 135 140

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu
145 150 155 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
165 170 175

```
Leu Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190


Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile
        195                 200                 205


Tyr Ala Ala Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly
    210                 215                 220


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro
225                 230                 235                 240


Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr
                245                 250                 255


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            260                 265


<210> 152
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 152
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


Ile Gln Ala Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu
            20                  25                  30


Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val
        35                  40                  45


Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60
```

```
Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly
65                  70                  75                  80

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95

Thr Ile Ser Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln
            100                 105                 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro
            180                 185                 190

Gly Lys Arg Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205

Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
225                 230                 235                 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265
```

<210> 153
<211> 474
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 153
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Ser Glu
115 120 125

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser
130 135 140

Glu Ile Val Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
145 150 155 160

```
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
                165                 170                 175

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
            180                 185                 190

Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
        195                 200                 205

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
    210                 215                 220

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
225                 230                 235                 240

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Ser Thr Pro Ala
                245                 250                 255

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
            260                 265                 270

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
        275                 280                 285

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
    290                 295                 300

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
305                 310                 315                 320

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
                325                 330                 335

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
            340                 345                 350
```

```
Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
        355                 360                 365


Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
    370                 375                 380


Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
385                 390                 395                 400


Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
                405                 410                 415


Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
            420                 425                 430


Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
        435                 440                 445


Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
    450                 455                 460


Ala Leu His Met Gln Ala Leu Pro Pro Arg
465                 470


<210> 154
<211> 474
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 154
Glu Ile Val Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30
```

```
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Trp
145                 150                 155                 160

Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
                165                 170                 175

Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
        195                 200                 205

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
    210                 215                 220

Arg Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr Gly Met Asp Val
225                 230                 235                 240
```

```
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Thr Ser Thr Pro Ala
                245                 250                 255

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
            260                 265                 270

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
        275                 280                 285

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
    290                 295                 300

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
305                 310                 315                 320

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
                325                 330                 335

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
            340                 345                 350

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
        355                 360                 365

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
    370                 375                 380

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
385                 390                 395                 400

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
                405                 410                 415

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
            420                 425                 430
```

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
        435   440   445

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
    450   455   460

Ala Leu His Met Gln Ala Leu Pro Pro Arg
465   470

<210> 155
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 155
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Arg Leu Glu Trp
        35   40   45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100   105   110

```
Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro Glu Asp Phe
    210                 215                 220

Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gly Gly Thr Lys Val Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320
```

```
Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 156
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 156
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
            20   25   30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65   70   75   80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Thr Arg
                85   90   95

Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
            100   105   110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115   120   125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130   135   140

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
145   150   155   160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Arg
                165   170   175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180   185   190

```
Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400
```

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
405 410 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
420 425 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
435 440 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
450 455 460

Met Gln Ala Leu Pro Pro Arg
465 470

<210> 157
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<220>
<221> MOD_RES
<222> (4)..(4)
<223> L or M

<220>
<221> MOD_RES
<222> (9)..(9)
<223> G or S

<220>
<221> MOD_RES
<222> (10)..(10)
<223> I or S

<220>
<221> MOD_RES
<222> (13)..(13)

<223> V or A

<220>
<221> MOD_RES
<222> (15)..(15)
<223> P or V

<220>
<221> MOD_RES
<222> (17)..(17)
<223> E or D

<220>
<221> MOD_RES
<222> (20)..(20)
<223> S or T

<220>
<221> MOD_RES
<222> (21)..(21)
<223> F or I

<220>
<221> MOD_RES
<222> (22)..(22)
<223> S or T

<220>
<221> MOD_RES
<222> (40)..(40)
<223> T or P

<220>
<221> MOD_RES
<222> (41)..(41)
<223> N or G

<220>
<221> MOD_RES
<222> (42)..(42)
<223> G or K

<220>
<221> MOD_RES
<222> (43)..(43)
<223> S or A

<220>
<221> MOD_RES
<222> (45)..(45)

<223> R or K

<220>
<221> MOD_RES
<222> (49)..(49)
<223> K or Y

<220>
<221> MOD_RES
<222> (58)..(58)
<223> I or V

<220>
<221> MOD_RES
<222> (76)..(76)
<223> N or S

<220>
<221> MOD_RES
<222> (78)..(78)
<223> V or L

<220>
<221> MOD_RES
<222> (80)..(80)
<223> S or P

<220>
<221> MOD_RES
<222> (83)..(83)
<223> I or F

<220>
<221> MOD_RES
<222> (85)..(85)
<223> D or T

<220>
<221> MOD_RES
<222> (92)..(92)
<223> N or G

<220>
<221> MOD_RES
<222> (100)..(100)
<223> G or Q

<400> 157
Asp Ile Gln Xaa Thr Gln Ser Pro Xaa Xaa Leu Ser Xaa Ser Xaa Gly
1 5 10 15

Xaa Arg Val Xaa Xaa Xaa Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20   25   30

Ile His Trp Tyr Gln Gln Lys Xaa Xaa Xaa Xaa Pro Xaa Leu Leu Ile
        35   40   45

Xaa Tyr Ala Ser Glu Ser Ile Ser Gly Xaa Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Xaa Ser Xaa Gln Xaa
65   70   75   80

Glu Asp Xaa Ala Xaa Tyr Tyr Cys Gln Gln Ser Xaa Ser Trp Pro Tyr
                85   90   95

Thr Phe Gly Xaa Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 158
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 158
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1   5   10   15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20   25   30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50   55   60

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

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

Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 159
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 159

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80
```

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 160
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 160
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly Val Pro Asp
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 161
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 161
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 162
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 162
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20   25   30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50   55   60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65   70   75   80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met
            100   105   110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120   125

<210> 163
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 163
Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 164
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 164
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

```
Leu Gln Met Asp Ser Leu Arg Val Glu Asp Ser Ala Val Tyr Ser Cys
                85                  90                  95


Ala Arg Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210> 165
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 165
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Phe Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105
```

<210> 166
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 166
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Leu Arg Gln Pro Ala Gly Ser Gly Leu Glu Trp Ile
35 40 45

Gly Arg Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Leu Ser Leu Asp Pro Ser Arg Asn Gln Leu Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Gly Asp Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 167
<211> 106
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 167
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Glu
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Leu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Asn Ser Ile Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 168
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 168
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala His Leu Pro Tyr Ser Gly Ser Tyr Trp Ala Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 169
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 169
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asn Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Pro Val Val Phe Gly Gly Gly Thr Lys Val Thr Val
100 105

<210> 170
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 170
Ser Tyr Tyr Trp Ser
1 5

<210> 171
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 171
Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 172
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 172

Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met Asp
1   5   10   15

Val

<210> 173
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 173
Arg Ala Ser Gln Gly Ile Ser Ser Tyr Leu Ala
1   5   10

<210> 174
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 174
Ala Ala Ser Thr Leu Gln Ser
1   5

<210> 175
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 175
Gln Gln Leu Asn Ser Tyr Pro Leu Thr
1   5

<210> 176
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 176
Ser Tyr Asp Ile His
1 5

<210> 177
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 177
Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr Asp Ser Val Lys
1 5 10 15

Gly

<210> 178
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 178
Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 179
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 179
Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Ala
1 5 10

<210> 180
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 180
Ala Ala Ser Thr Leu His Ser
1 5

<210> 181
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 181
Gln Lys Tyr Asn Ser Ala Pro Tyr Thr
1 5

<210> 182
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 182
Gly Gly Asn Asn Ile Gly Ser Lys Ser Val His
1 5 10

<210> 183
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 183
Arg Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 184
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 184
Asp Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro
1 5 10

<210> 185
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 185
Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala Cys
1 5 10

<210> 186
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 186
Gln Asp Ser Lys Arg Pro Ser
1 5

<210> 187
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 187
Gln Ala Trp Asp Asn Ser Ile Val Val
1 5

<210> 188
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 188
Tyr Tyr Gly Met His
1 5

<210> 189
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 189
Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 190
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 190
Leu Pro Tyr Ser Gly Ser Tyr Trp Ala Phe Asp Tyr
1 5 10

<210> 191
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 191
Gly Gly Asp Asn Ile Gly Ser Lys Ser Val His
1 5 10

<210> 192
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 192
Asp Asn Ser Asp Arg Pro Ser
1 5

<210> 193
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 193
Gln Val Trp Asp Ser Ser Ser Asp His Pro Val Val
1 5 10

<210> 194
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 194
Gly Gly Ser Ile Ser Ser Tyr Tyr Trp Ser
1 5 10

<210> 195
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 195
Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn
1 5

<210> 196
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 196
Gly Phe Thr Phe Ser Ser Tyr Asp Ile His
1 5 10

<210> 197
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 197
Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp
1 5 10

<210> 198
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 198
Gly Gly Ser Ile Ser Ser Tyr Tyr Trp Ser
1 5 10

<210> 199
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 199
Arg Leu Tyr Val Ser Gly Phe Thr Asn
1 5

<210> 200
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 200
Gly Phe Thr Phe Ser Tyr Tyr
1 5

<210> 201
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 201
Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr
1 5 10

<210> 202
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 202
Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Arg Leu Glu Trp
35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Ser Pro Ser Leu
50 55 60

Lys Ser Arg Phe Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65 70 75 80

```
Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu
        115                 120                 125

Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys
    130                 135                 140

Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn Ser
145                 150                 155                 160

Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr Trp
            180                 185                 190

Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr
        195                 200                 205

Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys
    210                 215                 220

Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser
                245                 250                 255

Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp
            260                 265                 270
```

```
Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln
        275                 280                 285

Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser
    290                 295                 300

Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys
305                 310                 315                 320

Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile
                325                 330                 335

Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro
            340                 345                 350

Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met
        355                 360                 365

Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn
    370                 375                 380

Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn
                405                 410                 415

Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu
            420                 425                 430

His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
        435                 440                 445
```

<210> 203
<211> 447
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 203

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


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30


Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Met Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125


Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140


Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160


Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175


Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190
```

```
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380
```

```
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400


Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415


Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430


His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> 204
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 204

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
            20                  25                  30


Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

Ala Lys Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120 125

<210> 205
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 205
Ser Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 206
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 206
His Tyr Ala Met Ser
1 5

<210> 207
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 207
Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 208
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 208
Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met Asp Val
1 5 10 15

<210> 209
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 209
Gln Val Trp Asp Ser Ser Ser Asp His Val Val
1   5   10

<210> 210
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 210
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20   25   30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50   55   60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65   70   75   80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met
            100   105   110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115   120   125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
    130   135   140

```
Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys
        195                 200                 205

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
    210                 215                 220

Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser
                325                 330                 335
```

```
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Leu Gly Lys
    450
```

<210> 211
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 211

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
```

```
Asp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asp Ser Leu Arg Val Glu Asp Ser Ala Val Tyr Ser Cys
                85                  90                  95

Ala Arg Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

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

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
    210                 215                 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225                 230                 235                 240
```

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
            260                 265                 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430
```

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

Gly Lys
450

<210> 212
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 212
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Leu Arg Gln Pro Ala Gly Ser Gly Leu Glu Trp Ile
35 40 45

Gly Arg Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Leu Ser Leu Asp Pro Ser Arg Asn Gln Leu Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Gly Asp Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

```
Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
                325                 330                 335
```

```
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350


Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365


Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380


Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400


Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415


Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430


Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440                 445


<210> 213
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 213
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
            20                  25                  30


Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala His Leu Pro Tyr Ser Gly Ser Tyr Trp Ala Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225                 230                 235                 240
```

```
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445
```

Pro Gly Lys
    450

<210> 214
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 214
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
            20   25   30

Gly Thr Ser Leu Met His Trp Tyr Arg Gln Lys Pro Gly Gln Pro Pro
        35   40   45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly Val Pro Ala
    50   55   60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile Gln
65   70   75   80

Pro Val Glu Glu Asp Asp Phe Ser Met Tyr Phe Cys Gln Gln Thr Arg
                85   90   95

Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100   105   110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
        115   120   125

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
    130   135   140

```
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145                 150                 155                 160


Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175


Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
            180                 185                 190


His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
        195                 200                 205


Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
    210                 215


<210> 215
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 215
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15


Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30


Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


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


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80
```

```
Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Thr Arg
                85                  90                  95


Lys Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110


Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125


Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140


Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160


Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175


Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190


His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205


Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 216
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 216

```
Gly Phe Thr Phe Ser His Tyr Ala Met Ser
1               5                   10
```

<210> 217
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 217
Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr
1 5 10

<210> 218
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 218
Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met Asp Val
1 5 10 15

<210> 219
<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 219
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

```
Ser Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240
```

```
Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
    290                 295                 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445
```

Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 220
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 220
Ser Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 221
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 221
Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

```
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 222
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 222

```
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15
```

```
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Phe Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205
```

Phe Asn Arg Gly Glu Cys
    210

<210> 223
<211> 212
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 223
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Glu
1   5   10   15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala
            20   25   30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
        35   40   45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50   55   60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Leu
65   70   75   80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Asn Ser Ile Val Val
                85   90   95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
            100   105   110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
        115   120   125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
    130   135   140

```
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145                 150                 155                 160


Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
                165                 170                 175


Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
            180                 185                 190


Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
        195                 200                 205


Thr Glu Cys Ser
    210


<210> 224
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 224
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1               5                   10                  15


Thr Ala Ser Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Ser Val
            20                  25                  30


His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
        35                  40                  45


Asp Asn Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60


Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65                  70                  75                  80
```

```
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
                85                  90                  95

Pro Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Gln Pro
            100                 105                 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205

Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> 225
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polynucleotide

<400> 225
gatgtgcagc ttcaggagtc tggacccgga cttgttaaac caagtcagtc tctgtccctg       60

acctgtaccg tcaccggcaa cagcatcaca agcgattacg catggaactg gatcaggcag      120
```

ttccctggaa atcgactcga atggatgggc tacatttcat actccggttc aaccacttac 180

tctccatcct tgaaatctag gttcagcatc acccgtgata cctcaaagaa ccaatttttt 240

ctgcaactga atagcgtaac tccagaggac acagccacat atttctgcgc cactgggtat 300

tactatggct caggtttctg gggtcagggc actctcgtca ccgtcagcag c 351

<210> 226
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 226
caggtccaac tgcaagagag cggaccgggc ctggtaaagc catccgacac attgtccctg 60

acgtgtgcgg taagtggaaa ctctatcact agcgactatg cgtggaattg gataagacaa 120

ccgccgggca aggggctgga atggatagga tatatcagct attccggttc tacgacatac 180

aatccttccc tgaaaagcag agtcactatg tcacgcgaca cgtccaagaa tcagttctca 240

ttgaaattgt catccgtaac ggccgttgac actgcggttt attattgcgc aaccggatat 300

tactacggct ctggtttttg gggacaggga acacttgtta ctgttagttc a 351

<210> 227
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 227
caggtgcagc tgcaggagag cggcccaggc ctggtgaagc caagcgacac cctgagcctg 60

acctgcgccg tgagcggcaa cagcatcacc agcgactacg cctggaactg gatccgccag 120

ttcccaggca agggcctgga gtggatcggc tacatcagct acagcggcag caccacctac 180

aacccaagcc tgaagagccg cgtcaccatc agccgcgaca ccagcaagaa ccagttcagc 240

ctgaagctga gcagcgtgac ccctgtggac accgccgtgt actactgcgc caccggctac 300

tactacggca gcggcttctg gggccagggc accctggtga ccgtgagcag c 351

<210> 228
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 228
caggtgcagc tgcaggagag cggcccaggc ctggtgaagc caagcgacac cctgagcctg 60

acctgcgccg tgagcggcaa cagcatcacc agcgactacg cctggaactg gatccgccag 120

ttcccaggca agggcctgga gtggatgggc tacatcagct acagcggcag caccacctac 180

aacccaagcc tgaagagccg cgtcaccatc agccgcgaca ccagcaagaa ccagttcagc 240

ctgaagctga gcagcgtgac ccctgtggac accgccgtgt actactgcgc caccggctac 300

tactacggca gcggcttctg gggccagggc accctggtga ccgtgagcag c 351

<210> 229
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 229
caggttcagc tgcaagagtc tggaccaggc ctggtcaagc cctctcagac cctgtctctg 60

acctgtaccg tgtccggcaa ctccatcacc tctgactacg cctggaactg gattcggcag 120

ttccctggca agggccttga gtggatcggc tacatctcct actccggttc caccacctac 180

aaccccagcc tgaagtcccg ggtcaccatc tcccgcgaca cctccaagaa ccagttctcc 240

ctgaagctgt cctccgtgac cgctgctgat accgccgtgt actactgtgc caccggctac 300

tactacggct ccggcttttg gggacagggc acactggtta ccgtgtctag t 351

<210> 230
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 230
caggttcagc tgcaagagtc tggaccaggc ctggtcaagc cctctcagac cctgtctctg 60

acctgtaccg tgtccggcaa ctccatcacc tctgactacg cctggaactg gattcggcag 120

ccacctggca agggccttga gtggatcggc tacatctcct actccggttc caccacctac 180

aaccccagcc tgaagtcccg ggtcaccatc tcccgcgaca cctccaagaa ccagttctcc 240

ctgaagctgt cctccgtgac cgctgctgat accgccgtgt actactgtgc caccggctac 300

tactacggct ccggcttttg gggacagggc acactggtta ccgtgtctag t 351

<210> 231
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 231
caggttcagc tgcaagagtc tggaccaggc ctggtcaagc cctctcagac cctgtctctg 60

acctgtaccg tgtccggcaa ctccatcacc tctgactacg cctggaactg gattcggcag 120

ttccctggca agcgccttga gtggatcggc tacatctcct actccggttc caccacctac 180

aaccccagcc tgaagtcccg ggtcaccatc tcccgcgaca cctccaagaa ccagttctcc 240

ctgaagctgt cctccgtgac cgctgctgat accgccgtgt actactgtgc caccggctac 300

tactacggct ccggcttttg gggacagggc acactggtta ccgtgtctag t 351

<210> 232
<211> 372
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 232
gaggtgcaac ttgtggagag cggcggaggt ctggtccaac ccggaggaag tctccgtctc 60

tcctgtgctg ctagtggctt cactttcagc tcatattgga tgacatgggt gagacaagcc 120

ccaggaaagg ggctcgagtg ggtagctaac attaaacagg acggctccga acggtactat 180

gttgattctg tgaagggacg gttcactata tccagggata atgcaaaaaa ttcactctat 240

cttcaaatga actcactcag agcagaggac actgccgtgt attattgcgc cagggatcaa 300

aattatgaca tactgaccgg tcattatgga atggatgttt ggggccaggg aacaaccgtt 360

accgtctcaa gt 372

<210> 233
<211> 375
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 233
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattggatat atctattaca gtgggagcac caactacaac 180

ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcggg gactacgatt 300

tttggagtgg ttaccccaa cttctactac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> 234
<211> 369
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 234
gaggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgtag cctctggatt caccttcagt agttatgaca tacactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcaatt atttcatatg atggaagtaa aaaagactat 180

acagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatgg acagcctgag agttgaggac tcggctgtgt attcctgtgc gagagaaagt 300

ggctggtccc actactacta ttacggtatg gacgtctggg gccaagggac aatggtcacc 360

gtctcttca 369

<210> 235
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 235
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactatt ggagctggct ccggcagccc 120

gccgggtcgg gactggagtg gattgggcgt ttatatgtca gtgggttcac caactacaac 180

ccctccctca agagtcgagt caccttgtca ctagacccgt ccaggaacca gttgtccctg 240

aaactgagtt ctgtgaccgc cgcggacacg gccgtatatt attgtgcggg agatagtggg 300

aactactggg gttggttcga cccctggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 236
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 236
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt tactatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcattt atatcatatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc ccacctccct 300

tatagtggga gctactgggc ctttgactac tggggccagg gaacccaggt caccgtctct 360

tca 363

<210> 237
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 237
gacattgtgc tgacacagag tccagcatcc ttggcagtat ctttggggca gcgggcaaca 60

atttcatgcc gtgcatctga aagtgtggag tattttggaa cttctcttat gcactggtat 120

cgccagaagc ctgggcagcc tcccaaactc cttatatatg ccgcttccaa cgtggagtcc 180

ggagtaccag cacgctttc cggctctggg tccggcacag acttttccct caatatccaa 240

cctgttgaag aagacgattt ttccatgtat ttttgccaac agacacgcaa ggttccatat 300

acattcggcg gcggcactaa acttgagatc aaa 333

<210> 238
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 238
gacatagtct tgactcagag cccggattcc cttgctgtgt ctctgggaga acgagctacg 60

atcaactgca aggcaagtga atccgtagaa tacttcggga catcattgat gcattggtat 120

caacagaaac cggggcaacc gcccaaattg ctgatatatg cggctagtaa tagagaatca 180

ggagtaccgg ataggtttag tggttcagga tcaggtacag atttcaccct gacaataagt 240

agcttgcaag ccgaagacgt agcagtgtat tactgccaac aaacccgaaa ggtgccatat 300

acgtttggac agggtacaaa gttggaaatc aaa 333

<210> 239
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 239
gacatcgtgc tgacccagag cccagacagc ctggccgtga gcctgggcga gcgcgccacc 60

atcaactgca aggccagcga gagcgtggag tacttcggca ccagcctgat gcactggtac 120

cagcagaagc caggccagcc accaaagctg ctgatctacg ctgccagcaa ccgcgagagc 180

ggcgtgccag accgcttcag cggcagcggc agcggcaccg acttcaccct gaccatccag 240

agcgtgcagg ccgaggacgt ctccgtgtac ttctgccagc agacccgcaa ggtgccatac 300

accttcggcc agggcaccaa gctggagatc aag 333

<210> 240
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 240
gacatcgtgc tgacccagag cccagacagc ctggccgtga gcctgggcga gcgcgccacc 60

atcaactgca aggccagcga gagcgtggag tacttcggca ccagcctgat gcactggtac 120

cagcagaagc caggccagcc accaaagctg ctgatctacg ctgccagcaa ccgcgagagc 180

ggcgtgccag accgcttcag cggcagcggc agcggcaccg acttcaccct gaccatcagc 240

agcgtgcagg ccgaggacgt cgccgtgtac tactgccagc agacccgcaa ggtgccatac 300

accttcggcc agggcaccaa gctggagatc aag 333

<210> 241
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 241
gacatcgtgc tgacccagtc tccagactct ctggctgtgt ctctgggcga gagagccacc 60

atcaactgca gagcctccga gtccgtggaa tacttcggca cctctctgat gcactggtac 120

cagcagaagc ccggccagcc tcctaagctg ctgatctacg ccgcctccaa cgtggaatct 180

ggcgtgcccg atagattttc cggctctggc tctggcaccg actttaccct gaccatcagc 240

tctctgcagg ccgaggatgt ggccgtgtac ttctgtcagc agacccggaa ggtgccctac 300

acatttggcg gcggaacaaa ggtggaaatc aag 333

<210> 242
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 242
gagatcgtgc tgacccagtc tcctgccaca ctgtcactgt ctccaggcga gagagccacc 60

ctctcttgta gagcctccga gtccgtggaa tacttcggca cctctctgat gcactggtac 120

cagcagaagc ccggccagcc tcctagactg ctgatctacg ccgcctccaa cgtcgaatct 180

ggcatccccg ctagattctc cggctctggc tctggcacag actttaccct gaccatctcc 240

tccgtggaac ccgaggattt cgctgtgtac ttttgccagc agacccggaa ggtgccctac 300

acatttggcg gcggaacaaa ggtggaaatc aag 333

<210> 243
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 243
gaaatcgtac tgacccagtc cccttctttc ttgagtgcat cagttgggga tagagtgacc 60

attacttgta gagcatctca aggtatttct tcatacttgt cttggtatca acaaaaacct 120

ggcaaggcac ccaaactctt gatctacgcc acctctacat tgcaaagtgg ggttccttct 180

aggttttcag gctccggctc tggtaccgag ttcaccctca ctataagcag tctccaacct 240

gaagatttcg ctacttatta ttgtcagcag cttaattctt atccccgaac ctttggtcaa 300

ggaactaagg tcgagatcaa a 321

<210> 244
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 244
gacatccaga tgacccagtc tccttccttc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggccagtca gggcattagc agttatttag cctggtatca gcaaaaacca 120

gggaaagccc ctaagttcct gatctatgct gcatccactt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcaacag cttaatagtt accctctcac tttcggcgga 300

gggaccaagg tggaaatcaa a 321

<210> 245
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 245
gacatcgtga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcgagtca ggacattagc aattatttag cctggtatca gcagaaacca 120

gggaaagttc ctaagttcct gatctatgct gcatccactt tgcactctgg ggtcccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagatgttg caacttatta ctgtcaaaag tataacagtg ccccgtacac ttttggccaa 300

gggacacgac tggagattaa a 321

<210> 246
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 246
tcctatgagc tgactcagcc accctcagtg tccgtgtccc caggagagac agccagcatc 60

acctgctctg gagatcaatt gggggaaaat tatgcttgct ggtatcagca gaagccaggc 120

cagtcccctg tgttggtcat ctatcaagat agtaagcggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctctg 240

gatgaggctg actattactg tcaggcgtgg gacaacagta ttgtggtatt cggcggaggg 300

accaagctga ccgtccta 318

<210> 247
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 247
cagtctgtgc tgactcagcc accctcggtg tcagtggccc ccgggcagac ggccagtatt 60

acctgtgggg gagacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcgt ctatgataat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaccacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcatcc tgtggtattc 300

ggcggaggga ccaaggtcac cgtccta 327

<210> 248
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 248
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp

65 70 75 80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 249
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 249
Asp Ile Leu Leu Thr Gln Ser Pro Gly Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser Asn Ser Trp Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

100 105

<210> 250
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 250
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 251
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 251
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20   25   30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 252
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 252
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20   25   30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 253
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 253
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 254
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 254
Asp Ile Leu Leu Thr Gln Ser Pro Gly Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 255
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

peptide

<400> 255
Arg Tyr Asn Met Asn
1 5

<210> 256
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 256
Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 257
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 257
Gly Trp Gly Pro Phe Asp Tyr
1 5

<210> 258
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 258
Arg Ala Arg Gln Ser Ile Gly Thr Ala Ile His

1 5 10

<210> 259
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 259
Tyr Ala Ser Glu Ser Ile Ser
1 5

<210> 260
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 260
Gln Gln Ser Asn Ser Trp Pro Tyr Thr
1 5

<210> 261
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 261
Gln Gln Ser Gly Ser Trp Pro Tyr Thr
1 5

<210> 262
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 262
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65 70 75 80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

```
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380
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Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 263
<211> 375
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 263
caggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagt cattatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcaact attggtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaacctcat 300

attgtaatgg tgactgctct tctctacgac ggtatggacg tctggggcca agggacaatg 360

gtcaccgtct cctca 375

<210> 264
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 264
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20   25   30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65   70   75   80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85   90   95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115   120   125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130   135   140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145   150   155   160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165   170   175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180   185   190

```
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
            340                 345                 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400
```

```
Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415


Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430


Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> 265
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 265
Asp Ile Leu Leu Thr Gln Ser Pro Gly Ile Leu Ser Val Ser Pro Gly
1               5                   10                  15


Glu Arg Val Ser Phe Ser Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20                  25                  30


Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35                  40                  45


Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


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


Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser Asn Ser Trp Pro Tyr
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110
```

```
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210> 266
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 266
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20                  25                  30


Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

```
Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 267
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 267
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

```
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210> 268
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 268
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20                  25                  30


Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110
```

```
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210> 269
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 269
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20                  25                  30


Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

```
Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 270
<211> 214
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 270

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


Glu Arg Val Ser Phe Ser Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20                  25                  30


Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35                  40                  45


Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


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


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


Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190
```

```
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210
```

<210> 271
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 271
tcttctgagc tgactcagcc accctcggtg tcagtggccc caggacagac ggccaggatt 60

acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcgt ctatgatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcatgt ggtattcggc 300

ggagggacca agctgaccgt ccta 324

<210> 272
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 272
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Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Ile Gly Thr Tyr
            20                  25                  30
```

```
Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
        35                  40                  45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Gln Ala Asp Tyr His Cys Val Ser Tyr Ala Gly Ser
                85                  90                  95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> 273

<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 273
gaggtgcaac tggtggagtc tgggggaggc ctggtcaagc ctgggggGTC cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agatataaca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcatcc attagtacta gtagtaatta catatactac 180

gcagactcag tgaagggccg attcaccttc tccagagaca acgccaagaa ctcactggat 240

ctgcaaatga gcggcctgag agccgaggac acggctattt attactgtac gagaggctgg 300

gggccttttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 274
<211> 1365
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 274
caggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggGTC cctgagactc 60

tcctgtgcag cctctggatt cacctttagt cattatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcaact attggtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaacctcat 300

attgtaatgg tgactgctct tctctacgac ggtatggacg tctggggcca agggacaatg 360

gtcaccgtct cctcagcctc caccaagggc ccatcggtct tccccctggc accctcctcc 420

aagagcacct ctgggggcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa 480

ccggtgacgg tgtcgtggaa ctcaggcgcc ctgaccagcg gcgtgcacac cttcccggct 540

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcagc 600

ttgggcaccc agacctacat ctgcaacgtg aatcacaagc ccagcaacac caaggtggac 660

aagaaagttg agcccaaatc ttgtgacaaa actcacacat gcccaccgtg cccagcacct 720

gaagccgccg ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 780

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 840

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 900

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 960

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1020

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc 1080

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1140

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1200

accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg 1260

gacaagagca gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1320

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1365

<210> 275
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 275
caggtgcagc tgcagcagtc tggccctaga ctcgtgcggc cttcccagac cctgtctctg 60

acctgtgcca tctccggcga ctccgtgttc aacaacaacg ccgcctggtc ctggatccgg 120

cagagccctt ctagaggcct ggaatggctg ggccggacct actaccggtc caagtggctg 180

tacgactacg ccgtgtccgt gaagtcccgg atcaccgtga accctgacac ctcccggaac 240

cagttcaccc tgcagctgaa ctccgtgacc cctgaggaca ccgccctgta ctactgcgcc 300

agaggctact cctcctcctt cgactattgg ggccagggca ccctcgtgac cgtgtcctct 360

<210> 276
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 276
gatatacttc ttacccagag tcccggcatc ctctccgtta gccctgggga gagagtctca 60

ttctcatgcc gagccagaca gtcaattggt accgcaatac actggtatca acagcggacc 120

aatggttctc cccgacttct gataaagtac gcatcagaat caattagtgg aataccatca 180

agatttagtg gctcagggag tggaaccgat tttactctga ccatcaactc agtggaatct 240

gaggacattg ccgactacta ctgtcaacaa agcaatagtt ggccatatac cttcggaggc 300

ggaactaaat tggagataaa a 321

<210> 277
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 277
gacatccaga tgacacagtc accttctagt ttgtctgctt ctgtaggcga ccgtgtaact 60

atcacctgtc gagcccgtca aagtattggt actgccattc actggtacca acaaaaacct 120

ggcaaagctc caaaactctt gatctactat gcctccgaaa gcatatcagg ggtcccaagc 180

agattctcag gcagtggcag tggcactgac ttcactctca ccatttctag cgtgcaacca 240

gaggacttcg ccacttatta ctgccaacag tcagggagct ggccctacac cttcggccaa 300

ggtacaaaac tggagatcaa a 321

<210> 278
<211> 321

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 278
gacatacaaa tgacacaatc accctcttct ctttctgcaa gcgttggcga ccgtgtcact 60

atcacttgtc gagcccgcca gtccataggt actgccattc actggtatca acagaagcct 120

ggcaaggctc ccaaactcct gattaagtat gccagcgaga gcatttccgg cgtaccttca 180

agattttccg gctccggtag tgggacagat ttcactctca ctatatctag cctccaacca 240

gaagatttcg ccacttacta ctgtcaacaa tcaggttcat ggccttacac tttcggccag 300

gggacaaaat tggagatcaa g 321

<210> 279
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 279
gacatccaaa tgactcaatc acctagcagc ctctccgcct ccgttggaga tagagtgaca 60

ataacttgcc gagcccggca aagtatcgga actgctattc actggtatca acaaaaacct 120

ggaaaggcac ctaagctctt gattaaatac gcttctgagt ccatctccgg cgtgccttca 180

cgattcagcg gcagcggtag tggtactgac tttaccctca ctattagttc tgttcagcca 240

gaggacttcg caacttatta ctgccaacag agtggttcct ggccatacac ttttggccag 300

gggactaaat tggaaatcaa a 321

<210> 280
<211> 321
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 280
gacatccaaa tgactcaaag cccctctagt ttgagtgcat ctgtaggtga ccgggtaaca 60

atcacctgcc gtgcccggca aagtataggt actgcaatcc actggtacca gcaaaaaccc 120

ggcaaagcac caaagctgct catatactat gctagtgaga gcatttctgg cgttcctagt 180

cgattttctg gatcagggag tggaactgat tttacactga caatcagcag cctccaaccc 240

gaagacttcg ccacctacta ttgtcagcag tctgggtcct ggccttacac attcggtcaa 300

ggaactaaat tggagatcaa a 321

<210> 281
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 281
gacattttgc tgacacagag ccctggtatc ctctcagtca gtccagggga acgcgtttca 60

tttagctgcc gtgctcgaca gagcattggg accgcaatcc actggtacca acaaagaact 120

aacggttcac cacggctttt gattaagtat gcctccgaat ccatcagtgg cattcctagt 180

cgtttttctg gatcaggatc aggcaccgac tttactctca caattaatag tgtcgaaagt 240

gaggacattg cagactatta ttgtcagcaa tccggttcct ggccctatac ttttggtggt 300

ggtactaagt tggaaattaa a 321

<210> 282
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 282

tcttctgagc tgactcagcc accctcggtg tcagtggccc caggacagac ggccaggatt 60

acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcgt ctatgatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcatgt ggtattcggc 300

ggagggacca agctgaccgt cctaggtcag cccaaggctg cacccagtgt cactctgttc 360

ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 420

ttctacccgg gagccgtgac agtggcctgg aaggccgata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

<210> 283
<211> 329
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 283
agtctgctct gacccagcct gcctccgtgt ctggctctcc cggccagtcc atcaccatca 60

gctgtaccgg cacctcctcc aacatcggca cctacaagtt cgtgtcctgg tatcagcagc 120

accccgacaa ggcccccaaa gtgctgctgt acgaggtgtc caagcggccc tctggcgtgt 180

cctccagatt ctccggctcc aagtctggca acaccgcctc cctgaccatc agcggactgc 240

aggctgagga ccaggccgac taccactgtg tgtcctacgc tggctctggc accctgctgt 300

ttggcggagg caccaagctg accgtgctg 329

<210> 284
<211> 1341
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 284
gatgtgcagc ttcaggagtc tggacccgga cttgttaaac caagtcagtc tctgtccctg 60

acctgtaccg tcaccggcaa cagcatcaca agcgattacg catggaactg gatcaggcag 120

ttccctggaa atcgactcga atggatgggc tacatttcat actccggttc aaccacttac 180

tctccatcct tgaaatctag gttcagcatc acccgtgata cctcaaagaa ccaatttttt 240

ctgcaactga atagcgtaac tccagaggac acagccacat atttctgcgc cactgggtat 300

tactatggct caggtttctg gggtcagggc actctcgtca ccgtcagcag cgccaaaaca 360

acagcaccaa gtgtctatcc actggcccct gtgtgtggag atacaactgg ctcctcggtg 420

actctaggat gcctggtcaa gggttatttc cctgagccag tgaccttgac ctggaactct 480

ggatccctgt ccagtggtgt gcacaccttc ccagctgtcc tgcagtctga cctctacacc 540

ctcagcagct cagtgactgt aacctcgagc acctggccca gccagtccat cacctgcaat 600

gtggcccacc cggcaagcag caccaaggtg gacaagaaaa ttgagcccag agggcccaca 660

atcaagccct gtcctccatg caaatgccca gcacctaacc tcttgggtgg accatccgtc 720

ttcatcttcc ctccaaagat caaggatgta ctcatgatct ccctgagccc catagtcaca 780

tgtgtggtgg tggatgtgag cgaggatgac ccagatgtcc agatcagctg gtttgtgaac 840

aacgtggaag tacacacagc tcagacacaa acccatagag aggattacaa cagtactctc 900

cgggtggtca gtgccctccc catccagcac caggactgga tgagtggcaa ggagttcaaa 960

tgcaaggtca acaacaaaga cctcccagcg cccatcgaga gaaccatctc aaaacccaaa 1020

gggtcagtaa gagctccaca ggtatatgtc ttgcctccac cagaagaaga gatgactaag 1080

aaacaggtca ctctgacctg catggtcacc gacttcatgc ctgaagacat ttacgtggag 1140

tggaccaaca acgggaaaac agagctaaac tacaagaaca ctgaaccagt cctggactct 1200

gatggttctt acttcatgta cagcaagctg agagtggaaa agaagaactg ggtggaaaga 1260

aatagctact cctgttcagt ggtccacgag ggtctgcaca atcaccacac gactaagagc 1320

ttctcccgga ctccgggtaa a 1341

<210> 285
<211> 1341
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 285
caggtccaac tgcaagagag cggaccgggc ctggtaaagc catccgacac attgtccctg 60

acgtgtgcgg taagtggaaa ctctatcact agcgactatg cgtggaattg gataagacaa 120

ccgccgggca aggggctgga atggatagga tatatcagct attccggttc tacgacatac 180

aatccttccc tgaaaagcag agtcactatg tcacgcgaca cgtccaagaa tcagttctca 240

ttgaaattgt catccgtaac ggccgttgac actgcggttt attattgcgc aaccggatat 300

tactacggct ctggtttttg gggacaggga acacttgtta ctgttagttc agcctccacc 360

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 720

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 780

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 840

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 900

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 960

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1140

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1200

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcagatg gcagcagggg 1260

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320

ctctccctgt ctccgggtaa a 1341

<210> 286

<400> 286
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<210> 287

<400> 287
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<210> 288

<400> 288
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<210> 289

<400> 289
000

<210> 290

<400> 290
000

<210> 291

<400> 291
000

<210> 292
<211> 1356
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 292
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattggatat atctattaca gtgggagcac caactacaac 180

ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcggg gactacgatt 300

tttggagtgg ttaccccaa cttctactac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctcagcttc caccaagggc ccatccgtct tccccctggc gccctgctcc 420

aggagcacct ccgagagcac agccgccctg ggctgcctgg tcaaggacta cttccccgaa 480

ccggtgacgg tgtcgtggaa ctcaggcgcc ctgaccagcg gcgtgcacac cttcccggct 540

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcagc 600

ttgggcacga aaacctacac ttgcaacgta gatcacaagc ccagcaacac caaggtggac 660

aagagagttg agtccaaata tggtccccca tgcccaccat gcccagcacc tgaggccgcc 720

gggggaccat cagtcttcct gttcccccca aaacccaagg acactctcat gatctcccgg 780

acccctgagg tcacgtgcgt ggtggtggac gtgagccagg aagaccccga ggtccagttc 840

aactggtacg tggatggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 900

ttcaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaac 960

ggcaaggagt acaagtgcaa ggtctccaac aaaggcctcc cgtcctccat cgagaaaacc 1020

atctccaaag ccaaagggca gccccgagag ccacaggtgt acaccctgcc cccatcccag 1080

gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctaccccagc 1140

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1200

cccgtgctgg actccgacgg ctccttcttc ctctacagca ggctaaccgt ggacaagagc 1260

agatggcagg aggggaatgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1320

tacacacaga agagcctctc cctgtctctg ggtaaa 1356

<210> 293
<211> 1350
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 293
gaggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgtag cctctggatt caccttcagt agttatgaca tacactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcaatt atttcatatg atggaagtaa aaaagactat 180

acagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatgg acagcctgag agttgaggac tcggctgtgt attcctgtgc gagagaaagt 300

ggctggtccc actactacta ttacggtatg gacgtctggg gccaagggac aatggtcacc 360

gtctcttcag cttccaccaa gggcccatcc gtcttccccc tggcgccctg ctccaggagc 420

acctccgaga gcacagccgc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 480

acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 540

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 600

acgaaaacct acacttgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaga 660

gttgagtcca aatatggtcc cccatgccca ccatgcccag cacctgaggc cgccggggga 720

ccatcagtct tcctgttccc cccaaaaccc aaggacactc tcatgatctc ccggacccct 780

gaggtcacgt gcgtggtggt ggacgtgagc caggaagacc ccgaggtcca gttcaactgg 840

tacgtggatg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagttcaac 900

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaacggcaag 960

gagtacaagt gcaaggtctc caacaaaggc ctcccgtcct ccatcgagaa aaccatctcc 1020

aaagccaaag ggcagccccg agagccacag gtgtacaccc tgcccccatc ccaggaggag 1080

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctaccc cagcgacatc 1140

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 1200

ctggactccg acggctcctt cttcctctac agcaggctaa ccgtggacaa gagcagatgg 1260

caggagggga atgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacaca 1320

cagaagagcc tctccctgtc tctgggtaaa 1350

<210> 294
<211> 1338
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 294
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactatt ggagctggct ccggcagccc 120

gccgggtcgg gactggagtg gattgggcgt ttatatgtca gtgggttcac caactacaac 180

ccctccctca agagtcgagt caccttgtca ctagacccgt ccaggaacca gttgtccctg 240

aaactgagtt ctgtgaccgc cgcggacacg gccgtatatt attgtgcggg agatagtggg 300

aactactggg gttggttcga cccctggggc cagggaaccc tggtcaccgt ctcctcagct 360

tccaccaagg gcccatccgt cttccccctg gcgccctgct ccaggagcac ctccgagagc 420

acagccgccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 480

aactcaggcg ccctgaccag cggcgtgcac accttcccgg ctgtcctaca gtcctcagga 540

ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac gaaaacctac 600

acttgcaacg tagatcacaa gcccagcaac accaaggtgg acaagagagt tgagtccaaa 660

tatggtcccc catgcccacc atgcccagca cctgaggccg ccgggggacc atcagtcttc 720

ctgttccccc caaaacccaa ggacactctc atgatctccc ggaccctga ggtcacgtgc 780

gtggtggtgg acgtgagcca ggaagacccc gaggtccagt tcaactggta cgtggatggc 840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agttcaacag cacgtaccgt 900

gtggtcagcg tcctcaccgt cctgcaccag gactggctga acggcaagga gtacaagtgc 960

aaggtctcca acaaaggcct cccgtcctcc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag agccacaggt gtacaccctg cccccatccc aggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1200

ggctccttct tcctctacag caggctaacc gtggacaaga gcagatggca ggaggggaat 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacaca gaagagcctc 1320

tccctgtctc tgggtaaa 1338

<210> 295
<211> 1353
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 295
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt tactatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcattt atatcatatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc ccacctccct 300

tatagtggga gctactgggc ctttgactac tggggccagg gaacccaggt caccgtctct 360

tcagcctcca ccaagggccc atcggtcttc cccctggcac cctcctccaa gagcacctct 420

gggggcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480

tcgtggaact caggcgccct gaccagcggc gtgcacacct tcccggctgt cctacagtcc 540

tcaggactct actcctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag 600

acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gaaagttgag 660

cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgccggg 720

ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 780

cctgaggtca catgcgtggt ggtgagcgtg agccacgaag accctgaggt caagttcaac 840

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 900

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 960

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag cccccatcga gaaaaccatc 1020

tccaaagcca aggggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 1080

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 1140

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1200

gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcaga 1260

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1320

acgcagaaga gcctctccct gtctccgggt aaa 1353

<210> 296
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 296
gacattgtgc tgacacagag tccagcatcc ttggcagtat ctttggggca gcgggcaaca 60

atttcatgcc gtgcatctga aagtgtggag tattttggaa cttctcttat gcactggtat 120

cgccagaagc ctgggcagcc tcccaaactc cttatatatg ccgcttccaa cgtggagtcc 180

ggagtaccag cacgcttttc cggctctggg tccggcacag acttttccct caatatccaa 240

cctgttgaag aagacgattt ttccatgtat ttttgccaac agacacgcaa ggttccatat 300

acattcggcg gcggcactaa acttgagatc aaacgggctg atgctgcacc gactgtgtcc 360

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 420

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 480

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 540

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 600

actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgt 654

<210> 297
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 297
gacatagtct tgactcagag cccggattcc cttgctgtgt ctctgggaga acgagctacg 60

atcaactgca aggcaagtga atccgtagaa tacttcggga catcattgat gcattggtat 120

caacagaaac cggggcaacc gcccaaattg ctgatatatg cggctagtaa tagagaatca 180

ggagtaccgg ataggtttag tggttcagga tcaggtacag atttcaccct gacaataagt 240

agcttgcaag ccgaagacgt agcagtgtat tactgccaac aaacccgaaa ggtgccatat 300

acgtttggac agggtacaaa gttggaaatc aaacgtacgg tggctgcacc atctgtcttc 360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 420

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt 654

<210> 298

<400> 298
000

<210> 299

<400> 299
000

<210> 300

<400> 300
000

<210> 301

<400> 301
000

<210> 302

<400> 302
000

<210> 303
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 303
gatattcaaa tgacccagtc accatcattc ctgtccgcct cagtgggaga tcgcgtcact 60

attacttgtc gtgctagcca ggggatatca tcatatttgg cttggtatca acaaaagcca 120

ggaaaggccc caaaattcct tatatatgca gctagtacac tccagagtgg tgttcctagc 180

cggttctctg gcagcggctc agggaccgag ttcaccctga caatctccag cttgcagccc 240

gaagactttg caacctacta ttgccagcaa ctgaactcct atcctctgac tttcggggga 300

ggaaccaagg ttgagattaa acggacagtg gccgctcctt ccgtgttcat cttcccacct 360

tccgacgagc agctgaagtc cggcacagct tctgtcgtgt gcctgctgaa caacttctac 420

cctcgggaag ccaaggtgca gtggaaggtg gacaatgccc tgcagtccgg caactcccaa 480

gagtctgtga ccgagcagga ctccaaggac agcacctaca gcctgtcctc cacactgacc 540

ctgtccaagg ccgactacga gaagcacaag gtgtacgcct gcgaagtgac ccatcagggc 600

ctgtctagcc ctgtgaccaa gtctttcaac cggggcgagt gt 642

<210> 304
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 304
gatattgtaa tgactcagtc accctcttca ctgagtgcat cagtaggtga tcgcgttacc 60

atcacttgcc gtgccagtca agacatttca aattaccttg catggtacca acaaaagccc 120

ggaaaagtgc caaagttttt gatttatgcc gcttcaacac tccattcagg agtgccctct 180

cgtttcagtg gatctggcag tggcaccgat tttactctca caataagcag tctccagcct 240

gaggatgtag ccacctatta ttgccaaaaa tataattcag ccccctatac ttttggacag 300

ggcacacgcc ttgagattaa acggacagtg gccgctcctt ccgtgttcat cttcccacct 360

tccgacgagc agctgaagtc cggcacagct tctgtcgtgt gcctgctgaa caacttctac 420

cctcgggaag ccaaggtgca gtggaaggtg gacaatgccc tgcagtccgg caactcccaa 480

gagtctgtga ccgagcagga ctccaaggac agcacctaca gcctgtcctc cacactgacc 540

ctgtccaagg ccgactacga gaagcacaag gtgtacgcct gcgaagtgac ccatcagggc 600

ctgtctagcc ctgtgaccaa gtctttcaac cggggcgagt gt 642

<210> 305
<211> 636
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 305
tcctatgagc tgactcagcc accctcagtg tccgtgtccc caggagagac agccagcatc 60

acctgctctg gagatcaatt gggggaaaat tatgcttgct ggtatcagca gaagccaggc 120

cagtcccctg tgttggtcat ctatcaagat agtaagcggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctctg 240

gatgaggctg actattactg tcaggcgtgg gacaacagta ttgtggtatt cggcggaggg 300

accaagctga ccgtcctagg tcagcccaag gctgcaccca gtgtcactct gttcccgccc 360

tcctctgagg agcttcaagc caacaaggcc acactggtgt gtctcataag tgacttctac 420

ccgggagccg tgacagtggc ctggaaggcc gatagcagcc ccgtcaaggc gggagtggag 480

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaagggagc 600

accgtggaga agacagtggc ccctacagaa tgttca 636

<210> 306
<211> 645
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 306
cagtctgtgc tgactcagcc accctcggtg tcagtggccc ccgggcagac ggccagtatt 60

acctgtgggg gagacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120

caggcccctg tgctggtcgt ctatgataat agcgaccggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaccacggcc accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcatcc tgtggtattc 300

ggcggaggga ccaaggtcac cgtcctaggt cagcccaagg ctgcacccag tgtcactctg 360

ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt 420

gacttctacc cgggagccgt gacagtggcc tggaaggccg atagcagccc cgtcaaggcg 480

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600

gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca 645

<210> 307

<400> 307
000

<210> 308
<211> 253
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 308
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Ser
115 120 125

```
Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly
    130                 135                 140

Ser Ser Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly
145                 150                 155                 160

Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser
                165                 170                 175

Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val
            180                 185                 190

Tyr Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly
        195                 200                 205

Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala
    210                 215                 220

Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp
225                 230                 235                 240

His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 309
<211> 107
<212> PRT
<213> Homo sapiens

<400> 309

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45
```

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 310

<400> 310
000

<210> 311
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 311
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtcggcga ccgcgtgacc 60

atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatctactac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cgtgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gcgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 312
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 312
gacatacaaa tgacacaatc accctcttct ctttctgcaa gcgttggcga ccgtgtcact 60

atcacttgtc gagcccgcca gtccataggt actgccattc actggtatca acagaagcct 120

ggcaaggctc ccaaactcct gattaagtat gccagcgaga gcatttccgg cgtaccttca 180

agattttccg gctccggtag tgggacagat ttcactctca ctatatctag cctccaacca 240

gaagatttcg ccacttacta ctgtcaacaa tcaggttcat ggccttacac tttcggccag 300

gggacaaaat tggagatcaa gcggacagtg gccgctcctt ccgtgttcat cttcccacct 360

tccgacgagc agctgaagtc cggcacagct tctgtcgtgt gcctgctgaa caacttctac 420

cctcgggaag ccaaggtgca gtggaaggtg gacaatgccc tgcagtccgg caactcccaa 480

gagtctgtga ccgagcagga ctccaaggac agcacctaca gcctgtcctc cacactgacc 540

ctgtccaagg ccgactacga gaagcacaag gtgtacgcct gcgaagtgac ccatcagggc 600

ctgtctagcc ctgtgaccaa gtctttcaac cggggcgagt gt 642

<210> 313
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 313
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtcggcga ccgcgtgacc 60

atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatcaagtac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cgtgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gcgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 314
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 314
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtcggcga ccgcgtgacc 60

atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatctactac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gcgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 315
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 315
gacatcttgc tgactcagtc tccaggcatc ctgtctgtga gtccaggaga aagagtcagt 60

ttctcctgca gggccagaca gagcattggc acagccatac actggtatca gcaaagaaca 120

aatggttctc caaggcttct cataaagtat gcttctgagt ctatctctgg gatcccttcc 180

aggtttagcg gcagtggatc agggacagat tttactctta ccatcaacag tgtggagtct 240

gaagatattg cagattatta ctgtcaacaa agtgggagct ggccgtacac gttcggaggg 300

gggaccaagc tggaaataaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 316
<211> 253
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 316
Ser Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

```
Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
        35                  40                  45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
                85                  90                  95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Ser Glu
            100                 105                 110

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser
        115                 120                 125

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
    130                 135                 140

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
145                 150                 155                 160

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                165                 170                 175

Ser Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
            180                 185                 190

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
        195                 200                 205

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
```

210 215 220

Ala Lys Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met
225 230 235 240

Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
245 250

<210> 317
<211> 648
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 317
cagtctgctc tgacccagcc tgcctccgtg tctggctctc ccggccagtc catcaccatc 60

agctgtaccg gcacctcctc caacatcggc acctacaagt tcgtgtcctg gtatcagcag 120

caccccgaca aggcccccaa agtgctgctg tacgaggtgt ccaagcggcc ctctggcgtg 180

tcctccagat tctccggctc caagtctggc aacaccgcct ccctgaccat cagcggactg 240

caggctgagg accaggccga ctaccactgt gtgtcctacg ctggctctgg caccctgctg 300

tttggcggag gcaccaagct gaccgtgctg ggtcagccca aggctgcacc cagtgtcact 360

ctgttcccgc cctcctctga ggagcttcaa gccaacaagg ccacactggt gtgtctcata 420

agtgacttct acccgggagc cgtgacagtg gcctggaagg ccgatagcag ccccgtcaag 480

gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 540

tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg 600

catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttca 648

<210> 318
<211> 248
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 318

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30


Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125


Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
    130                 135                 140


Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145                 150                 155                 160


Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175


Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190
```

```
Ser Asn Val Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205


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


Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240


Gly Gly Thr Lys Val Glu Ile Lys
                245
```

<210> 319
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 319

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


Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30


Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly Val Pro Asp
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80


Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln Thr Arg
                85                  90                  95
```

```
Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser
                245
```

<210> 320
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 320
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35   40   45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115   120   125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130   135   140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145   150   155   160

Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165   170   175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala
            180   185   190

Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser
195 200 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro Glu Asp Phe
210 215 220

Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225 230 235 240

Gly Gly Thr Lys Val Glu Ile Lys
245

<210> 321
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 321
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Thr Arg
85 90 95

```
Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser
                245
```

<210> 322
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 322

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205
```

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro Glu Asp Phe
210 215 220

Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225 230 235 240

Gly Gly Thr Lys Val Glu Ile Lys
245

<210> 323
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 323
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
100 105 110

```
Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125


Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140


Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
145                 150                 155                 160


Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175


Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190


Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205


Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
    210                 215                 220


Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240


Gly Thr Leu Val Thr Val Ser Ser
                245


<210> 324
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 324
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala His Leu Pro Tyr Ser Gly Ser Tyr Trp Ala Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser
        115                 120                 125

Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Gln Ser Val
    130                 135                 140

Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Ser
145                 150                 155                 160

Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Ser Val His Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asn Ser
            180                 185                 190

Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly
        195                 200                 205
```

Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp Glu Ala
210 215 220

Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His Pro Val Val
225 230 235 240

Phe Gly Gly Gly Thr Lys Val Thr Val
245

<210> 325
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 325
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asn Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Pro Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Gly Gly Ser Glu
100 105 110

```
Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser
        115                 120                 125


Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
    130                 135                 140


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
145                 150                 155                 160


Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                165                 170                 175


Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
            180                 185                 190


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
        195                 200                 205


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
    210                 215                 220


Ala His Leu Pro Tyr Ser Gly Ser Tyr Trp Ala Phe Asp Tyr Trp Gly
225                 230                 235                 240


Gln Gly Thr Gln Val Thr Val Ser Ser
                245


<210> 326
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 326
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
        115                 120                 125

Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
    130                 135                 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145                 150                 155                 160

Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Glu Ser Ile Ser
            180                 185                 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Ser Ser Val Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220
```

```
Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415
```

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420   425   430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435   440   445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450   455   460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465   470   475

<210> 327
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 327
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20   25   30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85   90   95

```
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300
```

```
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475
```

<210> 328
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 328
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65 70 75 80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
115 120 125

Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
130 135 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145 150 155 160

Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro
165 170 175

```
Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Glu Ser Ile Ser
            180                 185                 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Ser Ser Val Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220

Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys
```

<210> 329
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 329

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20                  25                  30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro
65                  70                  75                  80
```

```
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser
```

<210> 330
<211> 243
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 330

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80


Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95


Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110


Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
        115                 120                 125


Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
    130                 135                 140


Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145                 150                 155                 160


Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro
                165                 170                 175


Gly Lys Ala Pro Lys Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser
            180                 185                 190
```

```
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205


Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220


Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240


Glu Ile Lys
```

<210> 331
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 331

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20                  25                  30


Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85                  90                  95
```

```
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser
```

<210> 332
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 332
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20   25   30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65   70   75   80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85   90   95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110

Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
        115   120   125

Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
    130   135   140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145   150   155   160

Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro
                165   170   175

Gly Lys Ala Pro Lys Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser
            180   185   190

```
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Ser Ser Val Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220

Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys
```

<210> 333
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 333

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20                  25                  30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85                  90                  95
```

```
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser
```

<210> 334
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 334

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
        115                 120                 125

Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
    130                 135                 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145                 150                 155                 160

Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Glu Ser Ile Ser
            180                 185                 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205
```

```
Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220


Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240


Glu Ile Lys
```

<210> 335
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 335

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20                  25                  30


Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110
```

```
Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125


Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140


Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160


Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175


Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190


Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205


Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220


Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240


Val Ser Ser
```

<210> 336
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 336

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
        115                 120                 125

Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Leu Leu Thr Gln Ser Pro
    130                 135                 140

Gly Ile Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe Ser Cys Arg
145                 150                 155                 160

Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Arg Thr
                165                 170                 175

Asn Gly Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser
            180                 185                 190

Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205
```

Leu Thr Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr Tyr Cys
210 215 220

Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu
225 230 235 240

Glu Ile Lys

<210> 337
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 337
Asp Ile Leu Leu Thr Gln Ser Pro Gly Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
100 105 110

```
Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125


Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140


Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160


Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175


Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190


Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205


Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220


Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240


Val Ser Ser
```

<210> 338
<211> 432
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 338

```
Phe Lys Ile Pro Ile Glu Glu Leu Glu Asp Arg Val Phe Val Asn Cys
1               5                   10                  15
```

```
Asn Thr Ser Ile Thr Trp Val Glu Gly Thr Val Gly Thr Leu Leu Ser
            20                  25                  30

Asp Ile Thr Arg Leu Asp Leu Gly Lys Arg Ile Leu Asp Pro Arg Gly
        35                  40                  45

Ile Tyr Arg Cys Asn Gly Thr Asp Ile Tyr Lys Asp Lys Glu Ser Thr
    50                  55                  60

Val Gln Val His Tyr Arg Met Gly Ser Ala Asp Asp Ala Lys Lys Asp
65                  70                  75                  80

Ala Ala Lys Lys Asp Asp Ala Lys Lys Asp Asp Ala Lys Lys Asp Gly
                85                  90                  95

Ser Asp Gly Asn Glu Glu Met Gly Gly Ile Thr Gln Thr Pro Tyr Lys
            100                 105                 110

Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr Cys Pro Gln Tyr Pro
        115                 120                 125

Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys Asn Ile Gly Gly Asp
    130                 135                 140

Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp His Leu Ser Leu Lys
145                 150                 155                 160

Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr Val Cys Tyr Pro Arg
                165                 170                 175

Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu Tyr Leu Arg Ala Arg
            180                 185                 190

Val Ser Pro Pro Ser Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
        195                 200                 205

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
    210                 215                 220
```

```
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
225                 230                 235                 240

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
                245                 250                 255

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
            260                 265                 270

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
        275                 280                 285

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
    290                 295                 300

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
305                 310                 315                 320

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
                325                 330                 335

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
            340                 345                 350

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
        355                 360                 365

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
    370                 375                 380

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
385                 390                 395                 400

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
                405                 410                 415
```

Gly Gly Leu Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
420 425 430

<210> 339
<211> 426
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 339
Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr Gln Thr Pro Tyr Lys
1 5 10 15

Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr Cys Pro Gln Tyr Pro
20 25 30

Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys Asn Ile Gly Gly Asp
35 40 45

Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp His Leu Ser Leu Lys
50 55 60

Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr Val Cys Tyr Pro Arg
65 70 75 80

Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu Tyr Leu Arg Ala Arg
85 90 95

Val Gly Ser Ala Asp Asp Ala Lys Lys Asp Ala Ala Lys Lys Asp Asp
100 105 110

Ala Lys Lys Asp Asp Ala Lys Lys Asp Gly Ser Gln Ser Ile Lys Gly
115 120 125

Asn His Leu Val Lys Val Tyr Asp Tyr Gln Glu Asp Gly Ser Val Leu
130 135 140

```
Leu Thr Cys Asp Ala Glu Ala Lys Asn Ile Thr Trp Phe Lys Asp Gly
145                 150                 155                 160

Lys Met Ile Gly Phe Leu Thr Glu Asp Lys Lys Lys Trp Asn Leu Gly
                165                 170                 175

Ser Asn Ala Lys Asp Pro Arg Gly Met Tyr Gln Cys Lys Gly Ser Gln
            180                 185                 190

Asn Lys Ser Lys Pro Leu Gln Val Tyr Tyr Arg Met Gly Ser Gly Ser
        195                 200                 205

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    210                 215                 220

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
225                 230                 235                 240

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
                245                 250                 255

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
            260                 265                 270

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        275                 280                 285

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
    290                 295                 300

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
305                 310                 315                 320

Gln Val Tyr Thr Phe Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
                325                 330                 335

Val Ser Leu Arg Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            340                 345                 350
```

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        355   360   365

Lys Pro Val Leu Asp Ser Asp Gly Ser Phe Arg Leu Glu Ser Arg Leu
    370   375   380

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
385   390   395   400

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                405   410   415

Leu Ser Gly Gly His His His His His His
            420   425

<210> 340
<211> 805
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 340
Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr Gln Thr Pro Tyr Lys
1   5   10   15

Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr Cys Pro Gln Tyr Pro
            20   25   30

Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys Asn Ile Gly Gly Asp
        35   40   45

Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp His Leu Ser Leu Lys
    50   55   60

Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr Val Cys Tyr Pro Arg
65   70   75   80

```
Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu Tyr Leu Arg Ala Arg
               85                  90                  95

Val Gly Ser Ala Asp Asp Ala Lys Lys Asp Ala Ala Lys Lys Asp Asp
            100                 105                 110

Ala Lys Lys Asp Asp Ala Lys Lys Asp Gly Ser Gln Ser Ile Lys Gly
        115                 120                 125

Asn His Leu Val Lys Val Tyr Asp Tyr Gln Glu Asp Gly Ser Val Leu
    130                 135                 140

Leu Thr Cys Asp Ala Glu Ala Lys Asn Ile Thr Trp Phe Lys Asp Gly
145                 150                 155                 160

Lys Met Ile Gly Phe Leu Thr Glu Asp Lys Lys Lys Trp Asn Leu Gly
                165                 170                 175

Ser Asn Ala Lys Asp Pro Arg Gly Met Tyr Gln Cys Lys Gly Ser Gln
            180                 185                 190

Asn Lys Ser Lys Pro Leu Gln Val Tyr Tyr Arg Met Gly Gly Gly Ser
        195                 200                 205

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
    210                 215                 220

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
225                 230                 235                 240

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
                245                 250                 255

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
            260                 265                 270
```

```
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
        275                 280                 285

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
    290                 295                 300

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
305                 310                 315                 320

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
                325                 330                 335

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
            340                 345                 350

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
        355                 360                 365

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
    370                 375                 380

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
385                 390                 395                 400

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
                405                 410                 415

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
            420                 425                 430

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
        435                 440                 445

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
    450                 455                 460

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
465                 470                 475                 480
```

```
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
                485                 490                 495

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
            500                 505                 510

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
        515                 520                 525

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
    530                 535                 540

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
545                 550                 555                 560

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
                565                 570                 575

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
            580                 585                 590

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
        595                 600                 605

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
    610                 615                 620

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
625                 630                 635                 640

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
                645                 650                 655

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
            660                 665                 670
```

```
Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
        675                 680                 685

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
    690                 695                 700

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
705                 710                 715                 720

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
                725                 730                 735

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
            740                 745                 750

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
        755                 760                 765

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
    770                 775                 780

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Gly Ser His His His
785                 790                 795                 800

His His His His His
                805
```

<210> 341
<211> 9
<212> PRT
<213> Homo sapiens

<400> 341
```
Pro Gln Tyr Pro Gly Ser Glu Ile Leu
1               5
```

<210> 342
<211> 262
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 342
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65 70 75 80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
115 120 125

Ser Lys Ser Thr Asp Ile Leu Leu Thr Gln Ser Pro Gly Ile Leu Ser
130 135 140

Val Ser Pro Gly Glu Arg Val Ser Phe Ser Cys Arg Ala Arg Gln Ser
145 150 155 160

Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro
165 170 175

```
Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser
            180                 185                 190


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
        195                 200                 205


Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220


Ser Trp Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
225                 230                 235                 240


Pro Gly Gly Gln His His His His His His Gly Ala Tyr Pro Tyr Asp
                245                 250                 255


Val Pro Asp Tyr Ala Ser
            260
```

<210> 343
<211> 262
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 343

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

```
Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
        115                 120                 125

Ser Lys Ser Thr Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser
145                 150                 155                 160

Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220

Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
225                 230                 235                 240

Pro Gly Gly Gln His His His His His His Gly Ala Tyr Pro Tyr Asp
                245                 250                 255

Val Pro Asp Tyr Ala Ser
            260
```

<210> 344
<211> 262
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 344
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65 70 75 80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
115 120 125

Ser Lys Ser Thr Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser
145 150 155 160

```
Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175


Lys Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser
            180                 185                 190


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205


Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220


Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
225                 230                 235                 240


Pro Gly Gly Gln His His His His His His Gly Ala Tyr Pro Tyr Asp
                245                 250                 255


Val Pro Asp Tyr Ala Ser
            260
```

<210> 345
<211> 262
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 345

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
        115                 120                 125

Ser Lys Ser Thr Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser
145                 150                 155                 160

Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Val Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220

Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
225                 230                 235                 240
```

```
Pro Gly Gly Gln His His His His His His Gly Ala Tyr Pro Tyr Asp
                245                 250                 255


Val Pro Asp Tyr Ala Ser
            260


<210> 346
<211> 262
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 346
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80


Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95


Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110


Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
        115                 120                 125
```

```
Ser Lys Ser Thr Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser
145                 150                 155                 160

Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Val Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly
    210                 215                 220

Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
225                 230                 235                 240

Pro Gly Gly Gln His His His His His His Gly Ala Tyr Pro Tyr Asp
                245                 250                 255

Val Pro Asp Tyr Ala Ser
            260
```

<210> 347
<211> 262
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 347

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
        115                 120                 125

Ser Lys Ser Thr Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser
145                 150                 155                 160

Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly
    210                 215                 220
```

Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
225 230 235 240

Pro Gly Gly Gln His His His His His His Gly Ala Tyr Pro Tyr Asp
245 250 255

Val Pro Asp Tyr Ala Ser
260

<210> 348
<211> 262
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 348
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65 70 75 80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

```
Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
        115                 120                 125

Ser Lys Ser Thr Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser
145                 150                 155                 160

Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Val Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly
    210                 215                 220

Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
225                 230                 235                 240

Pro Gly Gly Gln His His His His His His Gly Ala Tyr Pro Tyr Asp
                245                 250                 255

Val Pro Asp Tyr Ala Ser
            260
```

<210> 349
<211> 262
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 349
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20   25   30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65   70   75   80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85   90   95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110

Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
        115   120   125

Ser Lys Ser Thr Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
    130   135   140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser
145   150   155   160

Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165   170   175

Lys Leu Leu Ile Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser
            180   185   190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
195 200 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly
210 215 220

Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly
225 230 235 240

Pro Gly Gly Gln His His His His His His Gly Ala Tyr Pro Tyr Asp
245 250 255

Val Pro Asp Tyr Ala Ser
260

<210> 350
<211> 262
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 350
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65 70 75 80

```
Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
        115                 120                 125

Ser Lys Ser Thr Asp Ile Leu Leu Thr Gln Ser Pro Gly Ile Leu Ser
    130                 135                 140

Val Ser Pro Gly Glu Arg Val Ser Phe Ser Cys Arg Ala Arg Gln Ser
145                 150                 155                 160

Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro
                165                 170                 175

Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
        195                 200                 205

Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser Gly
    210                 215                 220

Ser Trp Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
225                 230                 235                 240

Pro Gly Gly Gln His His His His His His Gly Ala Tyr Pro Tyr Asp
                245                 250                 255

Val Pro Asp Tyr Ala Ser
            260
```

<210> 351
<211> 479

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 351
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
20 25 30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Thr Arg
85 90 95

Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
100 105 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
115 120 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
130 135 140

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
145 150 155 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Arg
165 170 175

```
Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr
                245                 250                 255

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
            260                 265                 270

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
        275                 280                 285

Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro
    290                 295                 300

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
305                 310                 315                 320

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
                325                 330                 335

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
            340                 345                 350

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
        355                 360                 365
```

```
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu
    370                 375                 380

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu Cys
385                 390                 395                 400

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
                405                 410                 415

Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp
            420                 425                 430

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
        435                 440                 445

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
    450                 455                 460

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475


<210> 352
<211> 482
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 352
Glu Ile Val Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

```
Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Trp
145                 150                 155                 160

Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
                165                 170                 175

Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
        195                 200                 205

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
    210                 215                 220

Arg Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr Gly Met Asp Val
225                 230                 235                 240

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser Ser
                245                 250                 255
```

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
            260                 265                 270

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
        275                 280                 285

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His
    290                 295                 300

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
305                 310                 315                 320

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
                325                 330                 335

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
            340                 345                 350

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
        355                 360                 365

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
    370                 375                 380

Tyr Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
385                 390                 395                 400

Leu Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
                405                 410                 415

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro
            420                 425                 430

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
        435                 440                 445
```

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
    450   455   460

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
465   470   475   480

Pro Gly

<210> 353
<211> 481
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 353
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1   5   10   15

Thr Ala Ser Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Ser Val
            20   25   30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
        35   40   45

Asp Asn Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50   55   60

Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65   70   75   80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
                85   90   95

Pro Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Gly Ser
            100   105   110

```
Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly
        115                 120                 125

Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly
    130                 135                 140

Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr
145                 150                 155                 160

Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
                165                 170                 175

Val Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser
            180                 185                 190

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
        195                 200                 205

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
    210                 215                 220

Cys Ala His Leu Pro Tyr Ser Gly Ser Tyr Trp Ala Phe Asp Tyr Trp
225                 230                 235                 240

Gly Gln Gly Thr Gln Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
                245                 250                 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            260                 265                 270

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        275                 280                 285

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
    290                 295                 300

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
305                 310                 315                 320
```

```
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                325                 330                 335

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            340                 345                 350

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        355                 360                 365

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385                 390                 395                 400

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                405                 410                 415

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
            420                 425                 430

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        435                 440                 445

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    450                 455                 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465                 470                 475                 480

Gly
```

<210> 354
<211> 454
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 354
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175

```
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
    290                 295                 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380
```

```
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu
385                 390                 395                 400


Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415


Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445


Leu Ser Leu Ser Pro Gly
    450


<210> 355
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 355
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20                  25                  30


Tyr Trp Ser Trp Leu Arg Gln Pro Ala Gly Ser Gly Leu Glu Trp Ile
        35                  40                  45


Gly Arg Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Leu Ser Leu Asp Pro Ser Arg Asn Gln Leu Ser Leu
65                  70                  75                  80
```

```
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Gly Asp Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp
            260                 265                 270
```

```
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Leu
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445
```

<210> 356
<211> 452
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 356

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Asp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asp Ser Leu Arg Val Glu Asp Ser Ala Val Tyr Ser Cys
                85                  90                  95


Ala Arg Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125


Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140


Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160


Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175


Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190
```

```
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
225                 230                 235                 240

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val
            260                 265                 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350

Gln Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365

Val Ser Leu Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380
```

```
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445


Leu Ser Pro Gly
    450
```

<210> 357
<211> 484
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 357

```
Ser Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1               5                   10                  15


Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
            20                  25                  30


His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
        35                  40                  45


Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60


Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65                  70                  75                  80
```

```
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
                85                  90                  95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Ser Glu
            100                 105                 110

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser
        115                 120                 125

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
    130                 135                 140

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
145                 150                 155                 160

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                165                 170                 175

Ser Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
            180                 185                 190

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
        195                 200                 205

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
    210                 215                 220

Ala Lys Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met
225                 230                 235                 240

Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Glu Pro Lys
                245                 250                 255

Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
            260                 265                 270

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        275                 280                 285
```

```
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val
    290                 295                 300

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
305                 310                 315                 320

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
                325                 330                 335

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            340                 345                 350

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        355                 360                 365

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    370                 375                 380

Gln Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
385                 390                 395                 400

Val Ser Leu Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                405                 410                 415

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp
            420                 425                 430

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        435                 440                 445

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    450                 455                 460

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
465                 470                 475                 480
```

Leu Ser Pro Gly

<210> 358
<211> 445
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 358
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65 70 75 80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

```
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro
            340                 345                 350
```

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355   360   365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370   375   380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385   390   395   400

Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405   410   415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420   425   430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435   440   445

<210> 359
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 359
Gln Val Gln Leu Gln Gln Ser Gly Pro Arg Leu Val Arg Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Phe Asn Asn
            20   25   30

Asn Ala Ala Trp Ser Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Leu Tyr Asp Tyr Ala
    50   55   60

```
Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65                  70                  75                  80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
                85                  90                  95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255
```

```
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Val Tyr Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly
```

<210> 360
<211> 474
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 360
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
100 105 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
115 120 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
130 135 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145 150 155 160

```
Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350
```

```
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470
```

<210> 361
<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 361

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20                  25                  30
```

```
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240
```

```
Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
               245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
    290                 295                 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
               325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu
385                 390                 395                 400

Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
               405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430
```

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 362
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 362
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
100 105 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
115 120 125

```
Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335
```

```
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475
```

<210> 363
<211> 1437
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 363
gagattgttc tcacccaatc cccagctact ctctctcttt cacccggtga gcgggcaacc 60

ctctcctgta gagccagcga gagcgtggag tattttggca catccctgat gcactggtat 120

cagcaaaaac caggacaacc ccccagactc ctcatatatg ccgcctcaaa tgtcgagagt 180

gggatacctg cacggttttc aggaagcggc agcggtactg acttcacatt gactatatcc 240

tctgtagagc cagaggattt tgcagtctac ttctgccagc aaactaggaa ggttccatat 300

acttttgggg gcggtacaaa agttgagata aagggcggct ccgagggcaa gagcagcggc 360

agcggcagcg agagcaagag caccggcggc agccaagtac agctccagga gtcaggacct 420

gggctcgtca aaccatctca gacattgtcc ctgacatgca cagtttccgg caacagtatt 480

acttccgact atgcttggaa ttggatcagg caattcccag gaaagcggct cgagtggata 540

ggttatattt cttactctgg atctactacc tacaatccca gtttgaagtc tcgcgtgaca 600

attagccggg acacatcaaa aaatcaattc tcacttaaac ttagttctgt aaccgctgcc 660

gatacagccg tgtactactg cgccactggt tattattatg gaagcggatt ttgggggcaa 720

ggaactttgg tgaccgtctc ttccgagccc aaatctagcg acaaaactca cacatgtcca 780

ccgtgcccag cacctgaagc agcaggggga ccgtcagtct tcctcttccc cccaaaaccc 840

aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt gagcgtgagc 900

cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 960

aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 1020

gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 1080

ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 1140

gtgtacgtgc tgcccccatc ccgggaggag atgaccaaga accaggtcag cctgctgtgc 1200

ctggtcaaag gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg 1260

gagaacaact acctcacctg gcctcccgtg ctggactccg acggctcctt cttcctctac 1320

agcaagctca ccgtggacaa gtctagatgg cagcagggga acgtcttctc atgctccgtg 1380

atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggt 1437

<210> 364
<211> 1356
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 364
gaggtacaac ttgtcgaaag tggcggtgga gtcgtccagc ctgggcgatc acttcgcctc 60

tcctgtgtag cctctggttt cactttctca tcttacgaca tacactgggt ccgccaggca 120

cctggtaagg ggctggagtg ggttgccatc attagttacg atggctccaa aaaagattac 180

accgatagcg taaagggcag atttaccatt tccagggata attcaaagaa caccctgtat 240

ctgcaaatgg acagcctccg cgtcgaagac tctgcagttt atagctgtgc cagggagtca 300

ggctggtccc attattacta ttatggtatg gacgtttggg gccagggaac catggtcact 360

gttagttcag cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc 420

acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 480

acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 540

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 600

acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 660

gttgagccca aatcttgtga caaaactcac acatgtccac cgtgcccagc acctgaagca 720

gcaggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 780

cggacccctg aggtcacatg cgtggtggtg agcgtgagcc acgaagaccc tgaggtcaag 840

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 900

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 960

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1020

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacgtgct gcccccatcc 1080

cgggaggaga tgaccaagaa ccaggtcagc ctgctgtgcc tggtcaaagg cttctatccc 1140

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta cctcacctgg 1200

cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1260

tctagatggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1320

cactacacgc agaagagcct ctccctgtct ccgggt 1356

<210> 365
<211> 1443
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 365
cagagcgtac ttacccagcc tcccagcgtg tctgtagccc caggacagac agccagtatt 60

acatgcggtg gtgacaatat aggttccaaa tccgtgcatt ggtaccagca gaagccaggg 120

caagctcccg tgctcgtggt atatgataat tccgaccgcc cttccggcat tcccgaacgg 180

tttagtggtt caaattcagg caccacagca actctgacca taagcagagt cgaagctgga 240

gacgaagccg actactactg tcaggtatgg gactctagta gtgaccaccc tgtcgtcttc 300

ggtgggggaa ccaaagtgac cgttctgggc ggctccgagg gcaagagcag cggcagcggc 360

agcgagagca agagcaccgg cggcagccag gtccagctcg tagaaagtgg gggcggcgta 420

gttcagccag gcaggagtct ccggctgagt tgtgcagcca gcggctttac tttttcctac 480

tatggaatgc actgggtacg tcaggcaccc ggcaaaggtt tggagtgggt cgcattcatt 540

tcttatgatg gatcaaataa gtattatgcc gatagtgtaa agggcagatt tacaataagt 600

cgagacaact caaagaacac tctctacctc caaatgaata gtcttcgggc agaggatact 660

gcagtgtact attgtgctca tcttccttat tccggttctt actgggcatt cgattattgg 720

gggcaaggga cacaagttac cgtgtctagc gagcccaaat ctagcgacaa aactcacaca 780

tgtccaccgt gcccagcacc tgaagcagca gggggaccgt cagtcttcct cttccccca 840

aaacccaagg acaccctcat gatctcccgg acccctgagg tcacatgcgt ggtggtgagc 900

gtgagccacg aagaccctga ggtcaagttc aactggtacg tggacggcgt ggaggtgcat 960

aatgccaaga caaagccgcg ggaggagcag tacaacagca cgtaccgtgt ggtcagcgtc 1020

ctcaccgtcc tgcaccagga ctggctgaat ggcaaggagt acaagtgcaa ggtctccaac 1080

aaagccctcc cagcccccat cgagaaaacc atctccaaag ccaaagggca gccccgagaa 1140

ccacaggtgt acgtgctgcc cccatcccgg gaggagatga ccaagaacca ggtcagcctg 1200

ctgtgcctgg tcaaaggctt ctatcccagc gacatcgccg tggagtggga gagcaatggg 1260

cagccggaga acaactacct cacctggcct cccgtgctgg actccgacgg ctccttcttc 1320

ctctacagca agctcaccgt ggacaagtct agatggcagc aggggaacgt cttctcatgc 1380

tccgtgatgc atgaggctct gcacaaccac tacacgcaga agagcctctc cctgtctccg 1440

ggt 1443

<210> 366
<211> 1452
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 366
agcagcgaat tgacccaacc accttccgtc agcgtcgcac cagggcaaac cgcccgcatc 60

acatgcggtg ggaacaatat aggaagcaaa tctgtccact ggtaccagca aaaaccagga 120

caagcccctg ttctggtcgt ctatgatgac agcgacagac caagtggtat tcccgagaga 180

ttctccggta gcaactctgg aaatacagct actttgacca tctccagagt tgaggctggt 240

gacgaggcag attactattg ccaggtctgg gacagctcca gcgaccacgt cgtattcggt 300

ggcgggacca agctgactgt gctgggcggc tccgagggca agagcagcgg cagcggcagc 360

gagagcaaga gcaccggcgg cagccaggtg cagttggtag agtcaggagg gggcctcgtt 420

caacctggtg gcagcctccg tttgtcttgt gctgccagtg gatttacttt cagtcactac 480

gcaatgagct gggtgagaca agcacctggc aagggccttg agtgggtctc cactatcggc 540

ggttcagggg ggagcactta ctacgctgac tctgtaaaag gtcgctttac tatatctaga 600

gataactcta aaaacacact ctacttgcag atgaacagcc tgcgagccga agatacagcc 660

gtgtactact gcgccaagcc tcatattgta atggtcactg ccctcttgta tgatggcatg 720

gatgtttggg gccaagggac aatggtgaca gtctcaagcg agcccaaatc tagcgacaaa 780

actcacacat gtccaccgtg cccagcacct gaagcagcag ggggaccgtc agtcttcctc 840

ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacatgcgtg 900

gtggtgagcg tgagccacga agaccctgag gtcaagttca actggtacgt ggacggcgtg 960

gaggtgcata atgccaagac aaagccgcgg gaggagcagt acaacagcac gtaccgtgtg 1020

gtcagcgtcc tcaccgtcct gcaccaggac tggctgaatg gcaaggagta caagtgcaag 1080

gtctccaaca aagccctccc agcccccatc gagaaaacca tctccaaagc caaagggcag 1140

ccccgagaac cacaggtgta cgtgctgccc ccatcccggg aggagatgac caagaaccag 1200

gtcagcctgc tgtgcctggt caaaggcttc tatcccagcg acatcgccgt ggagtgggag 1260

agcaatgggc agccggagaa caactacctc acctggcctc ccgtgctgga ctccgacggc 1320

tccttcttcc tctacagcaa gctcaccgtg gacaagtcta gatggcagca ggggaacgtc 1380

ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc 1440

ctgtctccgg gt 1452

<210> 367
<211> 1362
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 367
caggttcaac ttcaagaatc cgggccaggt ctggtcaagc cttcagagac tttgtccctt 60

acttgcacag tgagcggtgg ctctatctca agttactact ggtcatggat acggcagccc 120

ccaggaaagg ggcttgagtg gattgggtac atttattact cagggtcaac aaactacaat 180

ccctccctca aatcccgagt gacaattagt gtcgatacat ctaaaaacca gttttccctg 240

aaattgagct cagtcaccgc agctgatact gcagtctatt attgtgctgg cacaacaatc 300

ttcggggtag taactccaaa cttctactac gggatggacg tgtgggggca aggaacaacc 360

gtaacagtaa gtagtgcctc caccaagggc ccatcggtct tcccccctggc accctcctcc 420

aagagcacct ctgggggcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa 480

ccggtgacgg tgtcgtggaa ctcaggcgcc ctgaccagcg gcgtgcacac cttcccggct 540

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcagc 600

ttgggcaccc agacctacat ctgcaacgtg aatcacaagc ccagcaacac caaggtggac 660

aagaaagttg agcccaaatc ttgtgacaaa actcacacat gtccaccgtg cccagcacct 720

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 780

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 840

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 900

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 960

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1020

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgctgccc 1080

ccatcccggg aggagatgac caagaaccag gtcagcctgc tgtgcctggt caaaggcttc 1140

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacctc 1200

acctggcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg 1260

gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1320

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gt 1362

<210> 368
<211> 1356
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 368
gaggtacaac ttgtcgaaag tggcggtgga gtcgtccagc ctgggcgatc acttcgcctc 60

tcctgtgtag cctctggttt cactttctca tcttacgaca tacactgggt ccgccaggca 120

cctggtaagg ggctggagtg ggttgccatc attagttacg atggctccaa aaaagattac 180

accgatagcg taaagggcag atttaccatt tccagggata attcaaagaa caccctgtat 240

ctgcaaatgg acagcctccg cgtcgaagac tctgcagttt atagctgtgc cagggagtca 300

ggctggtccc attattacta ttatggtatg gacgtttggg gccagggaac catggtcact 360

gttagttcag cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc 420

acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 480

acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 540

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 600

acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 660

gttgagccca aatcttgtga caaaactcac acatgtccac cgtgcccagc acctgaagca 720

gcaggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 780

cggacccctg aggtcacatg cgtggtggtg agcgtgagcc acgaagaccc tgaggtcaag 840

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 900

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 960

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1020

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacgtgct gcccccatcc 1080

cgggaggaga tgaccaagaa ccaggtcagc ctgctgtgcc tggtcaaagg cttctatccc 1140

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta cctcacctgg 1200

cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1260

tctagatggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1320

cactacacgc agaagagcct ctccctgtct ccgggt 1356

<210> 369
<211> 1344
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 369

caagtacaac ttcaagagtc tggccctggg cttgttaagc cctcagagac cttgtcactg 60

acctgtaccg tatcaggcgg gtcaatttca tcttactact ggagttggct tcgtcagcct 120

gccggatctg gactggagtg gataggtaga ctgtatgttt ccggctttac aaattacaac 180

ccatctttga aaagccgtgt gactctcagc ctcgaccctt ctcggaatca actttcactt 240

aaattgtctt ctgttacagc tgccgacact gcagtatatt attgtgcagg ggactcaggc 300

aactattggg gatggtttga tccttggggg caggggaccc tggtaaccgt gagttctgcc 360

tccaccaagg gcccatcggt cttccccctg gcaccctcct ccaagagcac ctctgggggc 420

acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 480

aactcaggcg ccctgaccag cggcgtgcac accttcccgg ctgtcctaca gtcctcagga 540

ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac 600

atctgcaacg tgaatcacaa gcccagcaac accaaggtgg acaagaaagt tgagcccaaa 660

tcttgtgaca aaactcacac atgtccaccg tgcccagcac ctgaagcagc agggggaccg 720

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 780

gtcacatgcg tggtggtgag cgtgagccac gaagaccctg aggtcaagtt caactggtac 840

gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc 900

acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 960

tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 1020

gccaaagggc agccccgaga accacaggtg tacgtgctgc ccccatcccg ggaggagatg 1080

accaagaacc aggtcagcct gctgtgcctg gtcaaaggct tctatcccag cgacatcgcc 1140

gtggagtggg agagcaatgg gcagccggag aacaactacc tcacctggcc tcccgtgctg 1200

gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagtc tagatggcag 1260

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1320

aagagcctct ccctgtctcc gggt 1344

<210> 370
<211> 1365
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 370
caggttcagc tgcaagagtc tggccctggc ctggtcaagc cttccgagac actgtctctg 60

acctgcaccg tgtctggcgg ctccatctcc tcctactact ggtcctggat cagacagcct 120

cctggcaaag gcctggaatg gatcggctac atctactact ccggctccac caactacaac 180

cccagcctga agtccagagt gaccatctcc gtggacacct ccaagaacca gttctccctg 240

aagctgtcct ccgtgaccgc tgctgatacc gccgtgtact attgtgctgg caccaccatc 300

ttcggcgtgg tcacccctaa cttctactac ggcatggacg tgtggggcca aggcacaaca 360

gtgacagtct cttctgcctc caccaagggt ccatcggtct tcccccctggc accctcctcc 420

aagagcacct ctgggggcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa 480

ccggtgacgg tgtcgtggaa ctcaggcgcc ctgaccagcg gcgtgcacac cttcccggct 540

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcagc 600

ttgggcaccc agacctacat ctgcaacgtg aatcacaagc ccagcaacac caaggtggac 660

aagaaagttg agcccaaatc ttgtgacaaa actcacactt gtccaccgtg cccagcacct 720

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 780

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 840

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 900

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 960

tggctgaatg gcaaggagta caagtgcaag gtgtccaaca aagccctccc agcccccatc 1020

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgctgccc 1080

ccatcccggg aggagatgac caagaaccag gtcagcctgc tgtgcctggt caaaggcttc 1140

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacctc 1200

acctggcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg 1260

gacaagtcca gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1320

cacaaccact acacgcagaa gtctctctcc ctgtctccgg gaaaa 1365

<210> 371
<211> 1335
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 371
gaggtgcaac tggtggagtc tgggggaggc ctggtcaagc ctgggggggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agatataaca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcatcc attagtacta gtagtaatta catatactac 180

gcagactcag tgaagggccg attcaccttc tccagagaca acgccaagaa ctcactggat 240

ctgcaaatga gcggcctgag agccgaggac acggctattt attactgtac gagaggctgg 300

gggccttttg actactgggg ccagggaacc ctggtcaccg tctcctcagc ctccaccaag 360

ggcccatcgg tcttcccccct ggcaccctcc tccaagagca cctctggggg cacagcggcc 420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 600

gtgaatcaca agcccagcaa caccaaggtg gacaagaaag ttgagcccaa atcttgtgac 660

aaaactcaca catgtccacc gtgcccagca cctgaagcag caggggggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc 780

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gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt 900

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag aaccacaggt gtacgtgtac cccccatccc gggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1200

ggctccttcg ccctcgtgag caagctcacc gtggacaagt ctagatggca gcaggggaac 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

tccctgtctc cgggt 1335

<210> 372
<211> 1347
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 372
caggtgcagc tccaacagag tggtcccaga ctcgtgagac cctctcaaac actcagtttg 60

acttgtgcca tctcaggcga ttcagttttc aacaacaatg cagcttggag ctggattagg 120

cagtcaccta gtcgcggtct tgaatggctt gggcgtacat actatcgctc taaatggttg 180

tatgattacg ctgtgtccgt gaagagccga atcaccgtaa accctgatac ctccaggaat 240

cagttcacat tgcaactgaa tagtgtgact cccgaggata ctgcactcta ttattgtgcc 300

cgaggatata gcagtagctt cgactattgg ggacaaggga cactcgttac cgttagttca 360

gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg 420

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 540

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc 600

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc 660

aaatcttgtg acaaaactca cacatgtcca ccgtgcccag cacctgaagc agcaggggga 720

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 780

gaggtcacat gcgtggtggt gagcgtgagc cacgaagacc ctgaggtcaa gttcaactgg 840

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 900

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 960

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 1020

aaagccaaag ggcagccccg agaaccacag gtgtacgtgt acccccccatc ccgggaggag 1080

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 1140

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 1200

ctggactccg acggctcctt cgccctcgtg agcaagctca ccgtggacaa gtctagatgg 1260

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1320

cagaagagcc tctccctgtc tccgggt 1347

<210> 373
<211> 1422
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 373
gacatacaaa tgacacaatc accctcttct ctttctgcaa gcgttggcga ccgtgtcact 60

atcacttgtc gagcccgcca gtccataggt actgccattc actggtatca acagaagcct 120

ggcaaggctc ccaaactcct gattaagtat gccagcgaga gcatttccgg cgtaccttca 180

agattttccg gctccggtag tgggacagat ttcactctca ctatatctag cctccaacca 240

gaagatttcg ccacttacta ctgtcaacaa tcaggttcat ggccttacac tttcggccag 300

gggacaaaat tggagatcaa gggcggctcc gagggcaaga gcagcggcag cggcagcgag 360

agcaagagca ccggcggcag cgaggtgcaa ctggtggagt ctgggggagg cctggtcaag 420

cctgggggt ccctgagact ctcctgtgca gcctctggat tcaccttcag tagatataac 480

atgaactggg tccgccaggc tccagggaag gggctggagt gggtctcatc cattagtact 540

agtagtaatt acatatacta cgcagactca gtgaagggcc gattcacctt ctccagagac 600

aacgccaaga actcactgga tctgcaaatg agcggcctga gagccgagga cacggctatt 660

tattactgta cgagaggctg ggggcctttt gactactggg gccagggaac cctggtcacc 720

gtctcctcag agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcgccc tcgtgagcaa gctcaccgtg 1320

gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gt 1422

<210> 374
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 374
gacatccaga tgacccagtc tccatcctct ctgtccgcct ctgtgggcga cagagtgacc 60

attacctgcc gggccagaca gtctatcggc accgctatcc actggtatca gcagaagcct 120

ggcaaggccc ctaagctgct gattaagtac gcctccgagt ccatctccgg cgtgccctcc 180

agattttctg gctctggatc tggcaccgac tttaccctga caatctccag cctgcagcct 240

gaggacttcg ccacctacta ctgtcagcag tccggctctt ggccttacac ctttggtcag 300

ggcaccaagc tggaaatcaa gggcggatct gagggaaagt ccagcggctc cggcagcgaa 360

agcaagtcca ccggcggaag cgaggtgcag ctggttgaat ctggcggagg actggttaag 420

cctggcggct ctctgagact gtcttgtgct gcttctggct tcaccttcag ccggtacaac 480

atgaactggg tccgacaggc tcctggcaaa ggcctggaat gggtgtcctc catctccacc 540

tccagcaact acatctacta cgccgactcc gtgaagggca gattcacctt ctccagagac 600

aacgccaaga actccctgga cctgcagatg tctggcctga gagctgagga caccgctatc 660

tactactgca ccagaggctg gggacccttc gattattggg gccagggaac cctggtcacc 720

gtgtcatctg agcccaaatc tagcgacaaa actcacactt gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtgtccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcgccc tcgtgagcaa gctcaccgtg 1320

gacaagtcca gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gtctctctcc ctgtctccgg gaaaa 1425

<210> 375
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 375
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
        115                 120                 125

Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
    130                 135                 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145                 150                 155                 160

Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Lys Ala Pro Lys Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser
            180                 185                 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220
```

```
Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415
```

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420   425   430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435   440   445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450   455   460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465   470   475

<210> 376
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 376
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20   25   30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
                85   90   95

```
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300
```

```
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475
```

<210> 377
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 377
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65 70 75 80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
115 120 125

Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
130 135 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145 150 155 160

Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro
165 170 175

```
Gly Lys Ala Pro Lys Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser
            180                 185                 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Ser Ser Val Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220

Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380
```

```
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400


Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415


Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430


Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445


Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460


Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475


<210> 378
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 378
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


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


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 379
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 379

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80
```

```
Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
        115                 120                 125

Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
    130                 135                 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145                 150                 155                 160

Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Glu Ser Ile Ser
            180                 185                 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220

Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285
```

```
Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475
```

<210> 380
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 380
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
100 105 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
115 120 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
130 135 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145 150 155 160

```
Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365
```

```
Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475
```

<210> 381
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 381

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ser Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp
65                  70                  75                  80

Leu Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Thr Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser
        115                 120                 125

Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Leu Leu Thr Gln Ser Pro
    130                 135                 140

Gly Ile Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe Ser Cys Arg
145                 150                 155                 160

Ala Arg Gln Ser Ile Gly Thr Ala Ile His Trp Tyr Gln Gln Arg Thr
                165                 170                 175

Asn Gly Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser
            180                 185                 190

Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr Tyr Cys
    210                 215                 220

Gln Gln Ser Gly Ser Trp Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240
```

```
Glu Ile Lys Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445
```

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450   455   460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465   470   475

<210> 382
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 382
Asp Ile Leu Leu Thr Gln Ser Pro Gly Ile Leu Ser Val Ser Pro Gly
1   5   10   15

Glu Arg Val Ser Phe Ser Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
            20   25   30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35   40   45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50   55   60

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

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
            100   105   110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115   120   125

```
Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320
```

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
325 330 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
340 345 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
355 360 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
370 375 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385 390 395 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
405 410 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
420 425 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
435 440 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
450 455 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470 475

<210> 383

<400> 383
000

<210> 384
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 384
gaggtgcagc tggtggagag cggtggcggt ctggtgaagc caggtggcag cctgcgcctg 60

agctgtgccg ccagcggttt caccttcagc cgctacaaca tgaactgggt gcgccaagcc 120

ccaggcaagg gcctggagtg ggtgagcagc atcagcacca gcagcaacta catctactac 180

gccgacagcg tgaagggccg cttcaccttc agccgcgaca acgccaagaa cagcctggac 240

ctgcagatga gcggtctgcg cgccgaggac accgccatct actactgcac ccgcggttgg 300

ggcccattcg actactgggg ccagggcacc ctggtgaccg tgagcagcgg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catccagatg 420

acccagagcc caagcagcct gagcgccagc gtcggcgacc gcgtgaccat cacctgtcgt 480

gcccgccaga gcatcggcac cgccatccac tggtaccagc agaagccagg caaggcccca 540

aagctgctga tctactacgc cagcgagagc atcagcggtg tgccaagccg cttcagcggc 600

agcggcagcg gcaccgactt caccctgacc atcagcagcg tgcagccaga ggacttcgcc 660

acctactact gccagcagag cggcagctgg ccatacacct tcggccaggg caccaagctg 720

gagatcaag 729

<210> 385
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 385
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtcggcga ccgcgtgacc 60

atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatctactac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cgtgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gggcggatct gagggaaagt ccagcggctc cggcagcgaa 360

agcaagtcca ccggcggaag cgaggtgcag ctggtggaga gcggtggcgg tctggtgaag 420

ccaggtggca gcctgcgcct gagctgtgcc gccagcggtt tcaccttcag ccgctacaac 480

atgaactggg tgcgccaagc cccaggcaag ggcctggagt gggtgagcag catcagcacc 540

agcagcaact acatctacta cgccgacagc gtgaagggcc gcttcacctt cagccgcgac 600

aacgccaaga acagcctgga cctgcagatg agcggtctgc gcgccgagga caccgccatc 660

tactactgca cccgcggttg gggcccattc gactactggg gccagggcac cctggtgacc 720

gtgagcagc 729

<210> 386
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 386
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agctgtgccg ccagcggttt caccttcagc cgctacaaca tgaactgggt gcgccaagcc 120

ccaggcaagg gcctggagtg ggtgagcagc atcagcacca gcagcaacta catctactac 180

gccgacagcg tgaagggccg cttcaccttc agccgcgaca acgccaagaa cagcctggac 240

ctgcagatga gcggtctgcg cgccgaggac accgccatct actactgcac ccgcggttgg 300

ggcccattcg actactgggg ccagggcacc ctggtgaccg tgagcagcgg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catccagatg 420

acccagagcc caagcagcct gagcgccagc gtcggcgacc gcgtgaccat cacctgtcgt 480

gcccgccaga gcatcggcac cgccatccac tggtaccagc agaagccagg caaggcccca 540

aagctgctga tcaagtacgc cagcgagagc atcagcggtg tgccaagccg cttcagcggc 600

agcggcagcg gcaccgactt caccctgacc atcagcagcc tgcagccaga ggacttcgcc 660

acctactact gccagcagag cggcagctgg ccatacacct tcggccaggg caccaagctg 720

gagatcaag 729

<210> 387
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 387
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtcggcga ccgcgtgacc 60

atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatcaagtac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gggcggatct gagggaaagt ccagcggctc cggcagcgaa 360

agcaagtcca ccggcggaag cgaggtgcag ctggtggaga gcggtggcgg tctggtgaag 420

ccaggtggca gcctgcgcct gagctgtgcc gccagcggtt tcaccttcag ccgctacaac 480

atgaactggg tgcgccaagc cccaggcaag ggcctggagt gggtgagcag catcagcacc 540

agcagcaact acatctacta cgccgacagc gtgaagggcc gcttcacctt cagccgcgac 600

aacgccaaga acagcctgga cctgcagatg agcggtctgc gcgccgagga caccgccatc 660

tactactgca cccgcggttg gggcccattc gactactggg gccagggcac cctggtgacc 720

gtgagcagc 729

<210> 388
<211> 729
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 388
gaggtgcagc tggtggagag cggtggcggt ctggtgaagc caggtggcag cctgcgcctg 60

agctgtgccg ccagcggttt caccttcagc cgctacaaca tgaactgggt gcgccaagcc 120

ccaggcaagg gcctggagtg ggtgagcagc atcagcacca gcagcaacta catctactac 180

gccgacagcg tgaagggccg cttcaccttc agccgcgaca acgccaagaa cagcctggac 240

ctgcagatga gcggtctgcg cgccgaggac accgccatct actactgcac ccgcggttgg 300

ggcccattcg actactgggg ccagggcacc ctggtgaccg tgagcagcgg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catccagatg 420

acccagagcc caagcagcct gagcgccagc gtcggcgacc gcgtgaccat cacctgtcgt 480

gcccgccaga gcatcggcac cgccatccac tggtaccagc agaagccagg caaggcccca 540

aagctgctga tcaagtacgc cagcgagagc atcagcggtg tgccaagccg cttcagcggc 600

agcggcagcg gcaccgactt caccctgacc atcagcagcg tgcagccaga ggacttcgcc 660

acctactact gccagcagag cggcagctgg ccatacacct tcggccaggg caccaagctg 720

gagatcaag 729

<210> 389
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 389
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atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatcaagtac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cgtgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gggcggatct gagggaaagt ccagcggctc cggcagcgaa 360

agcaagtcca ccggcggaag cgaggtgcag ctggtggaga gcggtggcgg tctggtgaag 420

ccaggtggca gcctgcgcct gagctgtgcc gccagcggtt tcaccttcag ccgctacaac 480

atgaactggg tgcgccaagc cccaggcaag ggcctggagt gggtgagcag catcagcacc 540

agcagcaact acatctacta cgccgacagc gtgaagggcc gcttcacctt cagccgcgac 600

aacgccaaga acagcctgga cctgcagatg agcggtctgc gcgccgagga caccgccatc 660

tactactgca cccgcggttg gggcccattc gactactggg gccagggcac cctggtgacc 720

gtgagcagc 729

<210> 390
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 390
gaggtgcagc tggtggagag cggtggcggt ctggtgaagc caggtggcag cctgcgcctg 60

agctgtgccg ccagcggttt caccttcagc cgctacaaca tgaactgggt gcgccaagcc 120

ccaggcaagg gcctggagtg ggtgagcagc atcagcacca gcagcaacta catctactac 180

gccgacagcg tgaagggccg cttcaccttc agccgcgaca acgccaagaa cagcctggac 240

ctgcagatga gcggtctgcg cgccgaggac accgccatct actactgcac ccgcggttgg 300

ggcccattcg actactgggg ccagggcacc ctggtgaccg tgagcagcgg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catccagatg 420

acccagagcc caagcagcct gagcgccagc gtcggcgacc gcgtgaccat cacctgtcgt 480

gcccgccaga gcatcggcac cgccatccac tggtaccagc agaagccagg caaggcccca 540

aagctgctga tctactacgc cagcgagagc atcagcggtg tgccaagccg cttcagcggc 600

agcggcagcg gcaccgactt caccctgacc atcagcagcc tgcagccaga ggacttcgcc 660

acctactact gccagcagag cggcagctgg ccatacacct tcggccaggg caccaagctg 720

gagatcaag 729

<210> 391
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 391
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtcggcga ccgcgtgacc 60

atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatctactac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gggcggatct gagggaaagt ccagcggctc cggcagcgaa 360

agcaagtcca ccggcggaag cgaggtgcag ctggtggaga gcggtggcgg tctggtgaag 420

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agcagcaact acatctacta cgccgacagc gtgaagggcc gcttcacctt cagccgcgac 600

aacgccaaga acagcctgga cctgcagatg agcggtctgc gcgccgagga caccgccatc 660

tactactgca cccgcggttg gggcccattc gactactggg gccagggcac cctggtgacc 720

gtgagcagc 729

<210> 392
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 392
gaggtgcaac tggtggagtc tgggggaggc ctggtcaagc ctgggggGtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agatataaca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcatcc attagtacta gtagtaatta catatactac 180

gcagactcag tgaagggccg attcaccttc tccagagaca acgccaagaa ctcactggat 240

ctgcaaatga gcggcctgag agccgaggac acggctattt attactgtac gagaggctgg 300

gggccttttg actactgggg ccagggaacc ctggtcaccg tctcctcagg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catcttgctg 420

actcagtctc caggcatcct gtctgtgagt ccaggagaaa gagtcagttt ctcctgcagg 480

gccagacaga gcattggcac agccatacac tggtatcagc aaagaacaaa tggttctcca 540

aggcttctca taaagtatgc ttctgagtct atctctggga tcccttccag gtttagcggc 600

agtggatcag ggacagattt tactcttacc atcaacagtg tggagtctga agatattgca 660

gattattact gtcaacaaag tgggagctgg ccgtacacgt tcggaggggg gaccaagctg 720

gaaataaaa 729

<210> 393
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 393
gacatcttgc tgactcagtc tccaggcatc ctgtctgtga gtccaggaga aagagtcagt 60

ttctcctgca gggccagaca gagcattggc acagccatac actggtatca gcaaagaaca 120

aatggttctc caaggcttct cataaagtat gcttctgagt ctatctctgg gatcccttcc 180

aggtttagcg gcagtggatc agggacagat tttactctta ccatcaacag tgtggagtct 240

gaagatattg cagattatta ctgtcaacaa agtgggagct ggccgtacac gttcggaggg 300

gggaccaagc tggaaataaa aggcggatct gagggaaagt ccagcggctc cggcagcgaa 360

agcaagtcca ccggcggaag cgaggtgcaa ctggtggagt ctgggggagg cctggtcaag 420

cctgggggt ccctgagact ctcctgtgca gcctctggat tcaccttcag tagatataac 480

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agtagtaatt acatatacta cgcagactca gtgaagggcc gattcacctt ctccagagac 600

aacgccaaga actcactgga tctgcaaatg agcggcctga gagccgagga cacggctatt 660

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gtctcctca 729

<210> 394
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 394
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agctgtgccg ccagcggttt caccttcagc cgctacaaca tgaactgggt gcgccaagcc 120

ccaggcaagg gcctggagtg ggtgagcagc atcagcacca gcagcaacta catctactac 180

gccgacagcg tgaagggccg cttcaccttc agccgcgaca acgccaagaa cagcctggac 240

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ggcccattcg actactgggg ccagggcacc ctggtgaccg tgagcagcgg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catccagatg 420

acccagagcc caagcagcct gagcgccagc gtcggcgacc gcgtgaccat cacctgtcgt 480

gcccgccaga gcatcggcac cgccatccac tggtaccagc agaagccagg caaggcccca 540

aagctgctga tctactacgc cagcgagagc atcagcggtg tgccaagccg cttcagcggc 600

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gagatcaagg agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

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gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 395
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 395
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atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatctactac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cgtgcagcca 240

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tactactgca cccgcggttg gggcccattc gactactggg gccagggcac cctggtgacc 720

gtgagcagcg agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

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gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 396
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 396
gaggtgcagc tggtggagag cggtggcggt ctggtgaagc caggtggcag cctgcgcctg 60

agctgtgccg ccagcggttt caccttcagc cgctacaaca tgaactgggt gcgccaagcc 120

ccaggcaagg gcctggagtg ggtgagcagc atcagcacca gcagcaacta catctactac 180

gccgacagcg tgaagggccg cttcaccttc agccgcgaca acgccaagaa cagcctggac 240

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ggcccattcg actactgggg ccagggcacc ctggtgaccg tgagcagcgg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catccagatg 420

acccagagcc caagcagcct gagcgccagc gtcggcgacc gcgtgaccat cacctgtcgt 480

gcccgccaga gcatcggcac cgccatccac tggtaccagc agaagccagg caaggcccca 540

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gagatcaagg agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

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gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 397
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 397

gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtcggcga ccgcgtgacc 60

atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatcaagtac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagcca 240

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aacgccaaga acagcctgga cctgcagatg agcggtctgc gcgccgagga caccgccatc 660

tactactgca cccgcggttg gggcccattc gactactggg gccagggcac cctggtgacc 720

gtgagcagcg agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcgccc tcgtgagcaa gctcaccgtg 1320

gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 398
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 398
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agctgtgccg ccagcggttt caccttcagc cgctacaaca tgaactgggt gcgccaagcc 120

ccaggcaagg gcctggagtg ggtgagcagc atcagcacca gcagcaacta catctactac 180

gccgacagcg tgaagggccg cttcaccttc agccgcgaca acgccaagaa cagcctggac 240

ctgcagatga gcggtctgcg cgccgaggac accgccatct actactgcac ccgcggttgg 300

ggcccattcg actactgggg ccagggcacc ctggtgaccg tgagcagcgg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catccagatg 420

acccagagcc caagcagcct gagcgccagc gtcggcgacc gcgtgaccat cacctgtcgt 480

gcccgccaga gcatcggcac cgccatccac tggtaccagc agaagccagg caaggcccca 540

aagctgctga tcaagtacgc cagcgagagc atcagcggtg tgccaagccg cttcagcggc 600

agcggcagcg gcaccgactt caccctgacc atcagcagcg tgcagccaga ggacttcgcc 660

acctactact gccagcagag cggcagctgg ccatacacct tcggccaggg caccaagctg 720

gagatcaagg agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcgccc tcgtgagcaa gctcaccgtg 1320

gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 399
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 399
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtcggcga ccgcgtgacc 60

atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatcaagtac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cgtgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gggcggatct gagggaaagt ccagcggctc cggcagcgaa 360

agcaagtcca ccggcggaag cgaggtgcag ctggtggaga gcggtggcgg tctggtgaag 420

ccaggtggca gcctgcgcct gagctgtgcc gccagcggtt tcaccttcag ccgctacaac 480

atgaactggg tgcgccaagc cccaggcaag ggcctggagt gggtgagcag catcagcacc 540

agcagcaact acatctacta cgccgacagc gtgaagggcc gcttcacctt cagccgcgac 600

aacgccaaga acagcctgga cctgcagatg agcggtctgc gcgccgagga caccgccatc 660

tactactgca cccgcggttg gggcccattc gactactggg gccagggcac cctggtgacc 720

gtgagcagcg agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcgccc tcgtgagcaa gctcaccgtg 1320

gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 400
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 400
gaggtgcagc tggtggagag cggtggcggt ctggtgaagc caggtggcag cctgcgcctg 60

agctgtgccg ccagcggttt caccttcagc cgctacaaca tgaactgggt gcgccaagcc 120

ccaggcaagg gcctggagtg ggtgagcagc atcagcacca gcagcaacta catctactac 180

gccgacagcg tgaagggccg cttcaccttc agccgcgaca acgccaagaa cagcctggac 240

ctgcagatga gcggtctgcg cgccgaggac accgccatct actactgcac ccgcggttgg 300

ggcccattcg actactgggg ccagggcacc ctggtgaccg tgagcagcgg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catccagatg 420

acccagagcc caagcagcct gagcgccagc gtcggcgacc gcgtgaccat cacctgtcgt 480

gcccgccaga gcatcggcac cgccatccac tggtaccagc agaagccagg caaggcccca 540

aagctgctga tctactacgc cagcgagagc atcagcggtg tgccaagccg cttcagcggc 600

agcggcagcg gcaccgactt caccctgacc atcagcagcc tgcagccaga ggacttcgcc 660

acctactact gccagcagag cggcagctgg ccatacacct tcggccaggg caccaagctg 720

gagatcaagg agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcgccc tcgtgagcaa gctcaccgtg 1320

gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 401
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 401
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atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatctactac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gggcggatct gagggaaagt ccagcggctc cggcagcgaa 360

agcaagtcca ccggcggaag cgaggtgcag ctggtggaga gcggtggcgg tctggtgaag 420

ccaggtggca gcctgcgcct gagctgtgcc gccagcggtt tcaccttcag ccgctacaac 480

atgaactggg tgcgccaagc cccaggcaag ggcctggagt gggtgagcag catcagcacc 540

agcagcaact acatctacta cgccgacagc gtgaagggcc gcttcacctt cagccgcgac 600

aacgccaaga acagcctgga cctgcagatg agcggtctgc gcgccgagga caccgccatc 660

tactactgca cccgcggttg gggcccattc gactactggg gccagggcac cctggtgacc 720

gtgagcagcg agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcgccc tcgtgagcaa gctcaccgtg 1320

gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 402
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 402
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tcctgtgcag cctctggatt caccttcagt agatataaca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcatcc attagtacta gtagtaatta catatactac 180

gcagactcag tgaagggccg attcaccttc tccagagaca acgccaagaa ctcactggat 240

ctgcaaatga gcggcctgag agccgaggac acggctattt attactgtac gagaggctgg 300

gggccttttg actactgggg ccagggaacc ctggtcaccg tctcctcagg cggatctgag 360

ggaaagtcca gcggctccgg cagcgaaagc aagtccaccg gcggaagcga catcttgctg 420

actcagtctc caggcatcct gtctgtgagt ccaggagaaa gagtcagttt ctcctgcagg 480

gccagacaga gcattggcac agccatacac tggtatcagc aaagaacaaa tggttctcca 540

aggcttctca taaagtatgc ttctgagtct atctctggga tcccttccag gtttagcggc 600

agtggatcag ggacagattt tactcttacc atcaacagtg tggagtctga agatattgca 660

gattattact gtcaacaaag tgggagctgg ccgtacacgt tcggaggggg gaccaagctg 720

gaaataaaag agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcgccc tcgtgagcaa gctcaccgtg 1320

gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 403
<211> 1425
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 403
gacatcttgc tgactcagtc tccaggcatc ctgtctgtga gtccaggaga aagagtcagt 60

ttctcctgca gggccagaca gagcattggc acagccatac actggtatca gcaaagaaca 120

aatggttctc caaggcttct cataaagtat gcttctgagt ctatctctgg gatcccttcc 180

aggtttagcg gcagtggatc agggacagat tttactctta ccatcaacag tgtggagtct 240

gaagatattg cagattatta ctgtcaacaa agtgggagct ggccgtacac gttcggaggg 300

gggaccaagc tggaaataaa aggcggatct gagggaaagt ccagcggctc cggcagcgaa 360

agcaagtcca ccggcggaag cgaggtgcaa ctggtggagt ctgggggagg cctggtcaag 420

cctgggggt ccctgagact ctcctgtgca gcctctggat tcaccttcag tagatataac 480

atgaactggg tccgccaggc tccagggaag gggctggagt gggtctcatc cattagtact 540

agtagtaatt acatatacta cgcagactca gtgaagggcc gattcacctt ctccagagac 600

aacgccaaga actcactgga tctgcaaatg agcggcctga gagccgagga cacggctatt 660

tattactgta cgagaggctg ggggcctttt gactactggg gccagggaac cctggtcacc 720

gtctcctcag agcccaaatc tagcgacaaa actcacacat gtccaccgtg cccagcacct 780

gaagcagcag ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtgagcg tgagccacga agaccctgag 900

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta cgtgtacccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcgccc tcgtgagcaa gctcaccgtg 1320

gacaagtcta gatggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaa 1425

<210> 404
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 404
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Ser
115 120 125

Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly
130 135 140

```
Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val
145                 150                 155                 160


Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser
                165                 170                 175


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu
            180                 185                 190


Ile Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
        195                 200                 205


Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
    210                 215                 220


Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro
225                 230                 235                 240


Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                245                 250


<210> 405
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 405
Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30


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

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Gln
        115                 120                 125

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
    130                 135                 140

Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr Tyr
145                 150                 155                 160

Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
                165                 170                 175

Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
            180                 185                 190

Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys
        195                 200                 205

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Gly
    210                 215                 220

Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met Asp
225                 230                 235                 240
```

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
245 250

<210> 406
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 406
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asp Ser Leu Arg Val Glu Asp Ser Ala Val Tyr Ser Cys
85 90 95

Ala Arg Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Ser Glu Gly
115 120 125

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp
130 135 140

```
Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
145                 150                 155                 160


Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu
                165                 170                 175


Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Phe Leu Ile Tyr
            180                 185                 190


Ala Ala Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
        195                 200                 205


Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
    210                 215                 220


Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Tyr Thr
225                 230                 235                 240


Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
                245                 250


<210> 407
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 407
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Phe Leu Ile
        35                  40                  45
```

```
Tyr Ala Ala Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser
    130                 135                 140

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

Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
                165                 170                 175

Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
        195                 200                 205

Gln Met Asp Ser Leu Arg Val Glu Asp Ser Ala Val Tyr Ser Cys Ala
    210                 215                 220

Arg Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly Met Asp Val Trp
225                 230                 235                 240

Gly Gln Gly Thr Met Val Thr Val Ser Ser
                245                 250
```

<210> 408
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 408
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Leu Arg Gln Pro Ala Gly Ser Gly Leu Glu Trp Ile
35 40 45

Gly Arg Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Leu Ser Leu Asp Pro Ser Arg Asn Gln Leu Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Gly Asp Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly
115 120 125

Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Ser Tyr Glu Leu Thr
130 135 140

Gln Pro Pro Ser Val Ser Val Ser Pro Gly Glu Thr Ala Ser Ile Thr
145 150 155 160

```
Cys Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala Cys Trp Tyr Gln Gln
                165                 170                 175


Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr Gln Asp Ser Lys Arg
            180                 185                 190


Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr
        195                 200                 205


Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Leu Asp Glu Ala Asp Tyr
    210                 215                 220


Tyr Cys Gln Ala Trp Asp Asn Ser Ile Val Val Phe Gly Gly Gly Thr
225                 230                 235                 240


Lys Leu Thr Val Leu
                245
```

<210> 409
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 409

```
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Glu
1               5                   10                  15


Thr Ala Ser Ile Thr Cys Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala
            20                  25                  30


Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
        35                  40                  45


Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60
```

```
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Leu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Asn Ser Ile Val Val
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Ser Glu Gly Lys
            100                 105                 110

Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Gln Val
        115                 120                 125

Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu
    130                 135                 140

Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr Tyr Trp
145                 150                 155                 160

Ser Trp Leu Arg Gln Pro Ala Gly Ser Gly Leu Glu Trp Ile Gly Arg
                165                 170                 175

Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg
            180                 185                 190

Val Thr Leu Ser Leu Asp Pro Ser Arg Asn Gln Leu Ser Leu Lys Leu
        195                 200                 205

Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Gly Asp
    210                 215                 220

Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu
225                 230                 235                 240

Val Thr Val Ser Ser
                245
```

<210> 410
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 410
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

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

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
35 40 45

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

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65 70 75 80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
130 135 140

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu
145 150 155 160

```
Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175


Ile Asn Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190


Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205


Tyr Ala Ala Ser Asn Val Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
225                 230                 235                 240


Glu Asp Val Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr
                245                 250                 255


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            260                 265


<210> 411
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 411
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


Ile Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30


Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val
        35                  40                  45
```

```
Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly
65                  70                  75                  80

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95

Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln
            100                 105                 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro
            180                 185                 190

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205

Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
225                 230                 235                 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255
```

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
260 265

<210> 412
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 412
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

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

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
35 40 45

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65 70 75 80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
130 135 140

```
Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu
145                 150                 155                 160


Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175


Leu Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190


Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile
        195                 200                 205


Tyr Ala Ala Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly
    210                 215                 220


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro
225                 230                 235                 240


Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr
                245                 250                 255


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            260                 265


<210> 413
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 413
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


Ile Gln Ala Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu
            20                  25                  30
```

```
Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val
        35                  40                  45

Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly
65                  70                  75                  80

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95

Thr Ile Ser Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln
            100                 105                 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro
            180                 185                 190

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205

Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220
```

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
225 230 235 240

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
245 250 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
260 265

<210> 414
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 414
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

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

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
35 40 45

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

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
65 70 75 80

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

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
100 105 110

```
Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
        115                 120                 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser
    130                 135                 140

Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu
            180                 185                 190

Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile
        195                 200                 205

Tyr Ala Ala Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro
225                 230                 235                 240

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr
                245                 250                 255

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            260                 265
```

<210> 415
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 415

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15

Ile Gln Ala Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu
            20                  25                  30

Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val
        35                  40                  45

Glu Tyr Phe Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly
65                  70                  75                  80

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
                85                  90                  95

Thr Ile Ser Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln
            100                 105                 110

Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
        115                 120                 125

Ile Lys Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser
    130                 135                 140

Lys Ser Thr Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
145                 150                 155                 160

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly
                165                 170                 175

Asn Ser Ile Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro
            180                 185                 190

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr
        195                 200                 205
```

```
Thr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr
    210                 215                 220


Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
225                 230                 235                 240


Thr Ala Val Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe
                245                 250                 255


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265


<210> 416
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 416
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


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


Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
        35                  40                  45


Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu
    50                  55                  60


Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro
65                  70                  75                  80


Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln
                85                  90                  95
```

```
Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Ala Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr
        115                 120                 125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser
145                 150                 155                 160

Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser
                165                 170                 175

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
            180                 185                 190

Ile Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
        195                 200                 205

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
225                 230                 235                 240

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn
                245                 250                 255

Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            260                 265                 270
```

<210> 417
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 417
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Ile Gln Ala Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala
20 25 30

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile
35 40 45

Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
50 55 60

Phe Leu Ile Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg
65 70 75 80

Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser
85 90 95

Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser
100 105 110

Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly
115 120 125

Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly
130 135 140

Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro
145 150 155 160

Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser
165 170 175

```
Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
            180                 185                 190


Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser
        195                 200                 205


Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
    210                 215                 220


Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
225                 230                 235                 240


Cys Ala Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr
                245                 250                 255


Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            260                 265                 270


<210> 418
<211> 269
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 418
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


Ile Gln Ala Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30


Pro Gly Arg Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe
        35                  40                  45


Ser Ser Tyr Asp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60
```

```
Glu Trp Val Ala Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asp Ser Leu Arg Val Glu Asp Ser Ala Val
            100                 105                 110

Tyr Ser Cys Ala Arg Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly
        115                 120                 125

Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly
145                 150                 155                 160

Gly Ser Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
                165                 170                 175

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser
            180                 185                 190

Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Phe
        195                 200                 205

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

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
225                 230                 235                 240

Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala
                245                 250                 255

Pro Tyr Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            260                 265
```

<210> 419
<211> 269
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 419
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

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

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile
35 40 45

Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys
50 55 60

Phe Leu Ile Tyr Ala Ala Ser Thr Leu His Ser Gly Val Pro Ser Arg
65 70 75 80

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
85 90 95

Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser
100 105 110

Ala Pro Tyr Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Gly Gly
115 120 125

Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly
130 135 140

Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro
145 150 155 160

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


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


Trp Val Ala Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr Asp
        195                 200                 205


Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
    210                 215                 220


Leu Tyr Leu Gln Met Asp Ser Leu Arg Val Glu Asp Ser Ala Val Tyr
225                 230                 235                 240


Ser Cys Ala Arg Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly Met
                245                 250                 255


Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
            260                 265


<210> 420
<211> 264
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 420
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


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


Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
        35                  40                  45
```

```
Ser Ser Tyr Tyr Trp Ser Trp Leu Arg Gln Pro Ala Gly Ser Gly Leu
    50                  55                  60

Glu Trp Ile Gly Arg Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro
65                  70                  75                  80

Ser Leu Lys Ser Arg Val Thr Leu Ser Leu Asp Pro Ser Arg Asn Gln
                85                  90                  95

Leu Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Ala Gly Asp Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro Trp
        115                 120                 125

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys
    130                 135                 140

Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Ser Tyr
145                 150                 155                 160

Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Glu Thr Ala
                165                 170                 175

Ser Ile Thr Cys Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala Cys Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr Gln Asp
        195                 200                 205

Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser
    210                 215                 220

Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Leu Asp Glu
225                 230                 235                 240
```

Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Asn Ser Ile Val Val Phe Gly
245 250 255

Gly Gly Thr Lys Leu Thr Val Leu
260

<210> 421
<211> 264
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 421
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Ile Gln Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
20 25 30

Pro Gly Glu Thr Ala Ser Ile Thr Cys Ser Gly Asp Gln Leu Gly Glu
35 40 45

Asn Tyr Ala Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu
50 55 60

Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65 70 75 80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
85 90 95

Gln Ala Leu Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Asn Ser
100 105 110

Ile Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Ser
115 120 125

```
Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly
    130                 135                 140

Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser
145                 150                 155                 160

Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser
                165                 170                 175

Tyr Tyr Trp Ser Trp Leu Arg Gln Pro Ala Gly Ser Gly Leu Glu Trp
            180                 185                 190

Ile Gly Arg Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro Ser Leu
        195                 200                 205

Lys Ser Arg Val Thr Leu Ser Leu Asp Pro Ser Arg Asn Gln Leu Ser
    210                 215                 220

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
225                 230                 235                 240

Ala Gly Asp Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro Trp Gly Gln
                245                 250                 255

Gly Thr Leu Val Thr Val Ser Ser
            260
```

<210> 422
<211> 268
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 422

```
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15
```

```
Ile Gln Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Tyr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala His Leu Pro Tyr Ser Gly Ser Tyr Trp Ala Phe Asp
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Glu
    130                 135                 140

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser
145                 150                 155                 160

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
                165                 170                 175

Thr Ala Ser Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Ser Val
            180                 185                 190

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
        195                 200                 205

Asp Asn Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    210                 215                 220
```

Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
225 230 235 240

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
245 250 255

Pro Val Val Phe Gly Gly Gly Thr Lys Val Thr Val
260 265

<210> 423
<211> 287
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 423
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Ile Gln Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala
20 25 30

Pro Gly Gln Thr Ala Ser Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser
35 40 45

Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
50 55 60

Val Val Tyr Asp Asn Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe
65 70 75 80

Ser Gly Ser Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val
85 90 95

Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser
100 105 110

```
Ser Asp His Pro Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Gly
        115                 120                 125

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
    130                 135                 140

Gly Gly Ser Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala
145                 150                 155                 160

Ala Gln Ser Ile Gln Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly
                165                 170                 175

Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
            180                 185                 190

Phe Thr Phe Ser Tyr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly
        195                 200                 205

Lys Gly Leu Glu Trp Val Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys
    210                 215                 220

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
225                 230                 235                 240

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
                245                 250                 255

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

Ala Phe Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        275                 280                 285
```

<210> 424
<211> 253
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 424
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Ser
115 120 125

Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly
130 135 140

Ser Ser Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly
145 150 155 160

Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser
165 170 175

```
Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val
            180                 185                 190


Tyr Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly
        195                 200                 205


Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala
    210                 215                 220


Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp
225                 230                 235                 240


His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 425
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 425
Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15


Ile Gln Ala Ser Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala
            20                  25                  30


Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser
        35                  40                  45


Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
    50                  55                  60


Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80
```

```
Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val
                85                  90                  95

Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser
            100                 105                 110

Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
        115                 120                 125

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
145                 150                 155                 160

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
                165                 170                 175

Ser His Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            180                 185                 190

Glu Trp Val Ser Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
        195                 200                 205

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
    210                 215                 220

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys Pro His Ile Val Met Val Thr Ala Leu Leu Tyr
                245                 250                 255

Asp Gly Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
            260                 265                 270
```

<210> 426
<211> 471

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 426
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
115 120 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
130 135 140

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
145 150 155 160

Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
165 170 175

```
Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Val Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

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

Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gly Gly Thr Lys Val Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365
```

```
Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 427
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 427

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

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val Glu Tyr Phe
            20                  25                  30

Gly Thr Ser Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45
```

```
Lys Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly Val Pro Asp
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln Thr Arg
                85                  90                  95

Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly
            100                 105                 110

Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
        115                 120                 125

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
    130                 135                 140

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile
145                 150                 155                 160

Thr Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly
                165                 170                 175

Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn
            180                 185                 190

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn
        195                 200                 205

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
    210                 215                 220

Tyr Tyr Cys Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255
```

```
Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445
```

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450   455   460

Met Gln Ala Leu Pro Pro Arg
465   470

<210> 428
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 428
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35   40   45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115   120   125

```
Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro Glu Asp Phe
    210                 215                 220

Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gly Gly Thr Lys Val Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335
```

```
Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 429
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 429

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15
```

```
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205
```

```
Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro Glu Asp Phe
    210                 215                 220

Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gly Gly Thr Lys Val Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415
```

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
420 425 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
435 440 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
450 455 460

Met Gln Ala Leu Pro Pro Arg
465 470

<210> 430
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 430
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
        115                 120                 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro Glu Asp Phe
    210                 215                 220

Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gly Gly Thr Lys Val Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285
```

```
Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    370                 375                 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385                 390                 395                 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                405                 410                 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            420                 425                 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        435                 440                 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    450                 455                 460

Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 431
<211> 471

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 431
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asn Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Tyr Tyr Tyr Gly Ser Gly Phe Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly
115 120 125

Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
130 135 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145 150 155 160

Arg Ala Ser Glu Ser Val Glu Tyr Phe Gly Thr Ser Leu Met His Trp
165 170 175

```
Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Ala Ala
            180                 185                 190

Ser Asn Val Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro Glu Asp Phe
    210                 215                 220

Ala Val Tyr Phe Cys Gln Gln Thr Arg Lys Val Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gly Gly Thr Lys Val Glu Ile Lys Thr Ser Thr Pro Ala Pro Arg Pro
                245                 250                 255

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
            260                 265                 270

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
        275                 280                 285

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
    290                 295                 300

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
305                 310                 315                 320

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                325                 330                 335

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            340                 345                 350

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
        355                 360                 365
```

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
370 375 380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
385 390 395 400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
405 410 415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
420 425 430

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
435 440 445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
450 455 460

Met Gln Ala Leu Pro Pro Arg
465 470

<210> 432
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 432
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

```
Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Ser
        115                 120                 125

Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly
    130                 135                 140

Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val
145                 150                 155                 160

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser
                165                 170                 175

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu
            180                 185                 190

Ile Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
        195                 200                 205

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
    210                 215                 220

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro
225                 230                 235                 240

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Thr Ser Thr Pro
                245                 250                 255
```

```
Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
            260                 265                 270

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
        275                 280                 285

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
    290                 295                 300

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
305                 310                 315                 320

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
                325                 330                 335

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
            340                 345                 350

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
        355                 360                 365

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
    370                 375                 380

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
385                 390                 395                 400

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
                405                 410                 415

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
            420                 425                 430

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
        435                 440                 445
```

```
His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
    450                 455                 460


Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
465                 470                 475


<210> 433
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 433
Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110


Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Gln
        115                 120                 125
```

```
Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
    130                 135                 140

Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr Tyr
145                 150                 155                 160

Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
                165                 170                 175

Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
            180                 185                 190

Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys
        195                 200                 205

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Gly
    210                 215                 220

Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met Asp
225                 230                 235                 240

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Thr Ser Thr Pro
                245                 250                 255

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
            260                 265                 270

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
        275                 280                 285

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
    290                 295                 300

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
305                 310                 315                 320

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
                325                 330                 335
```

```
Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
            340                 345                 350

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
        355                 360                 365

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
    370                 375                 380

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
385                 390                 395                 400

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
                405                 410                 415

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
            420                 425                 430

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
        435                 440                 445

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
    450                 455                 460

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
465                 470                 475
```

<210> 434
<211> 473
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 434

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asp Ser Leu Arg Val Glu Asp Ser Ala Val Tyr Ser Cys
                85                  90                  95

Ala Arg Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Ser Glu Gly
        115                 120                 125

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp
    130                 135                 140

Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
145                 150                 155                 160

Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu
                165                 170                 175

Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Phe Leu Ile Tyr
            180                 185                 190

Ala Ala Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
        195                 200                 205
```

```
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
    210                 215                 220

Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Tyr Thr
225                 230                 235                 240

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

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
            260                 265                 270

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
        275                 280                 285

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
    290                 295                 300

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
305                 310                 315                 320

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
                325                 330                 335

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
            340                 345                 350

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
        355                 360                 365

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
    370                 375                 380

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
385                 390                 395                 400

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
                405                 410                 415
```

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
420 425 430

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
435 440 445

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
450 455 460

Leu His Met Gln Ala Leu Pro Pro Arg
465 470

<210> 435
<211> 473
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 435
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Phe Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Tyr
85 90 95

```
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Gly Gly Ser Glu Gly
            100                 105                 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser
    130                 135                 140

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

Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
                165                 170                 175

Ile Ile Ser Tyr Asp Gly Ser Lys Lys Asp Tyr Thr Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
        195                 200                 205

Gln Met Asp Ser Leu Arg Val Glu Asp Ser Ala Val Tyr Ser Cys Ala
    210                 215                 220

Arg Glu Ser Gly Trp Ser His Tyr Tyr Tyr Tyr Gly Met Asp Val Trp
225                 230                 235                 240

Gly Gln Gly Thr Met Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro
                245                 250                 255

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
            260                 265                 270

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
        275                 280                 285
```

```
Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
    290                 295                 300

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
305                 310                 315                 320

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
                325                 330                 335

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
            340                 345                 350

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
        355                 360                 365

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
    370                 375                 380

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
385                 390                 395                 400

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
                405                 410                 415

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
            420                 425                 430

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
        435                 440                 445

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
    450                 455                 460

Leu His Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 436
<211> 468

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 436
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Leu Arg Gln Pro Ala Gly Ser Gly Leu Glu Trp Ile
35 40 45

Gly Arg Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Leu Ser Leu Asp Pro Ser Arg Asn Gln Leu Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Gly Asp Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly
115 120 125

Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Ser Tyr Glu Leu Thr
130 135 140

Gln Pro Pro Ser Val Ser Val Ser Pro Gly Glu Thr Ala Ser Ile Thr
145 150 155 160

Cys Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala Cys Trp Tyr Gln Gln
165 170 175

```
Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr Gln Asp Ser Lys Arg
            180                 185                 190

Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr
        195                 200                 205

Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Leu Asp Glu Ala Asp Tyr
    210                 215                 220

Tyr Cys Gln Ala Trp Asp Asn Ser Ile Val Val Phe Gly Gly Gly Thr
225                 230                 235                 240

Lys Leu Thr Val Leu Thr Ser Thr Pro Ala Pro Arg Pro Pro Thr Pro
                245                 250                 255

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
            260                 265                 270

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
        275                 280                 285

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
    290                 295                 300

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
305                 310                 315                 320

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
                325                 330                 335

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
            340                 345                 350

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
        355                 360                 365
```

```
Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
    370                 375                 380

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
385                 390                 395                 400

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
                405                 410                 415

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
            420                 425                 430

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
        435                 440                 445

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
    450                 455                 460

Leu Pro Pro Arg
465
```

<210> 437
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 437

```
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Glu
1               5                   10                  15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala
            20                  25                  30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
        35                  40                  45
```

```
Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Leu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Asn Ser Ile Val Val
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Ser Glu Gly Lys
            100                 105                 110

Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Gln Val
        115                 120                 125

Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu
    130                 135                 140

Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr Tyr Trp
145                 150                 155                 160

Ser Trp Leu Arg Gln Pro Ala Gly Ser Gly Leu Glu Trp Ile Gly Arg
                165                 170                 175

Leu Tyr Val Ser Gly Phe Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg
            180                 185                 190

Val Thr Leu Ser Leu Asp Pro Ser Arg Asn Gln Leu Ser Leu Lys Leu
        195                 200                 205

Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Gly Asp
    210                 215                 220

Ser Gly Asn Tyr Trp Gly Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu
225                 230                 235                 240

Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg Pro Pro Thr Pro
                245                 250                 255
```

```
Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
            260                 265                 270

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
        275                 280                 285

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
    290                 295                 300

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
305                 310                 315                 320

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
                325                 330                 335

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
            340                 345                 350

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
        355                 360                 365

Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
    370                 375                 380

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
385                 390                 395                 400

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
                405                 410                 415

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
            420                 425                 430

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
        435                 440                 445
```

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
    450   455   460

Leu Pro Pro Arg
465

<210> 438
<211> 472
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 438
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala His Leu Pro Tyr Ser Gly Ser Tyr Trp Ala Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser
        115   120   125

```
Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Gln Ser Val
    130                 135                 140

Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Ser
145                 150                 155                 160

Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Ser Val His Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asn Ser
            180                 185                 190

Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly
        195                 200                 205

Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp Glu Ala
    210                 215                 220

Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His Pro Val Val
225                 230                 235                 240

Phe Gly Gly Gly Thr Lys Val Thr Val Thr Ser Thr Pro Ala Pro Arg
                245                 250                 255

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
            260                 265                 270

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
        275                 280                 285

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
    290                 295                 300

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
305                 310                 315                 320

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
                325                 330                 335
```

```
Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
            340                 345                 350

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
        355                 360                 365

Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    370                 375                 380

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
385                 390                 395                 400

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                405                 410                 415

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
            420                 425                 430

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
        435                 440                 445

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
    450                 455                 460

His Met Gln Ala Leu Pro Pro Arg
465                 470
```

<210> 439
<211> 472
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 439

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1               5                   10                  15
```

```
Thr Ala Ser Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Ser Val
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
        35                  40                  45

Asp Asn Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
                85                  90                  95

Pro Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Gly Gly Ser Glu
            100                 105                 110

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser
        115                 120                 125

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
    130                 135                 140

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
145                 150                 155                 160

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                165                 170                 175

Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
            180                 185                 190

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
        195                 200                 205
```

```
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
    210                 215                 220

Ala His Leu Pro Tyr Ser Gly Ser Tyr Trp Ala Phe Asp Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Gln Val Thr Val Ser Ser Thr Ser Thr Pro Ala Pro Arg
                245                 250                 255

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
            260                 265                 270

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
        275                 280                 285

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
    290                 295                 300

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
305                 310                 315                 320

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
                325                 330                 335

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
            340                 345                 350

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
        355                 360                 365

Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    370                 375                 380

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
385                 390                 395                 400

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                405                 410                 415
```

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
420 425 430

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
435 440 445

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
450 455 460

His Met Gln Ala Leu Pro Pro Arg
465 470

<210> 440
<211> 476
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 440
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Lys Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Ser
        115                 120                 125

Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly
    130                 135                 140

Ser Ser Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly
145                 150                 155                 160

Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser
                165                 170                 175

Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val
            180                 185                 190

Tyr Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly
        195                 200                 205

Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala
    210                 215                 220

Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp
225                 230                 235                 240

His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Ser Thr
                245                 250                 255

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
            260                 265                 270

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
        275                 280                 285
```

```
His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
    290                 295                 300

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

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
                325                 330                 335

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
            340                 345                 350

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
        355                 360                 365

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
    370                 375                 380

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
385                 390                 395                 400

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
                405                 410                 415

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
            420                 425                 430

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
        435                 440                 445

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
    450                 455                 460

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
465                 470                 475
```

<210> 441
<211> 476

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 441
Ser Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Ser Glu
100 105 110

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser
115 120 125

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
130 135 140

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
145 150 155 160

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
165 170 175

```
Ser Thr Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
            180                 185                 190

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
        195                 200                 205

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
    210                 215                 220

Ala Lys Pro His Ile Val Met Val Thr Ala Leu Leu Tyr Asp Gly Met
225                 230                 235                 240

Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Thr Ser Thr
                245                 250                 255

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
            260                 265                 270

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
        275                 280                 285

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
    290                 295                 300

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

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
                325                 330                 335

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
            340                 345                 350

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
        355                 360                 365
```

```
Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
    370                 375                 380

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
385                 390                 395                 400

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
                405                 410                 415

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
            420                 425                 430

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
        435                 440                 445

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
    450                 455                 460

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
465                 470                 475
```

<210> 442
<211> 207
<212> PRT
<213> Homo sapiens

<400> 442

```
Met Gln Ser Gly Thr His Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1               5                   10                  15

Val Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr
            20                  25                  30

Gln Thr Pro Tyr Lys Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr
        35                  40                  45

Cys Pro Gln Tyr Pro Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys
    50                  55                  60
```

```
Asn Ile Gly Gly Asp Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp
65                  70                  75                  80


His Leu Ser Leu Lys Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr
                85                  90                  95


Val Cys Tyr Pro Arg Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu
            100                 105                 110


Tyr Leu Arg Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp Val Met
        115                 120                 125


Ser Val Ala Thr Ile Val Ile Val Asp Ile Cys Ile Thr Gly Gly Leu
    130                 135                 140


Leu Leu Leu Val Tyr Tyr Trp Ser Lys Asn Arg Lys Ala Lys Ala Lys
145                 150                 155                 160


Pro Val Thr Arg Gly Ala Gly Ala Gly Gly Arg Gln Arg Gly Gln Asn
                165                 170                 175


Lys Glu Arg Pro Pro Pro Val Pro Asn Pro Asp Tyr Glu Pro Ile Arg
            180                 185                 190


Lys Gly Gln Arg Asp Leu Tyr Ser Gly Leu Asn Gln Arg Arg Ile
        195                 200                 205


<210> 443
<211> 104
<212> PRT
<213> Homo sapiens

<400> 443
Asp Gly Asn Glu Glu Met Gly Gly Ile Thr Gln Thr Pro Tyr Lys Val
1               5                   10                  15


Ser Ile Ser Gly Thr Thr Val Ile Leu Thr Cys Pro Gln Tyr Pro Gly
            20                  25                  30
```

Ser Glu Ile Leu Trp Gln His Asn Asp Lys Asn Ile Gly Gly Asp Glu
        35   40   45

Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp His Leu Ser Leu Lys Glu
    50   55   60

Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr Val Cys Tyr Pro Arg Gly
65   70   75   80

Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu Tyr Leu Arg Ala Arg Val
                85   90   95

Cys Glu Asn Cys Met Glu Met Asp
            100

<210> 444
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 444
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Glu
1   5   10   15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala
            20   25   30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
        35   40   45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50   55   60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Leu
65   70   75   80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Asn Ser Ile Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 445
<211> 212
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 445
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Glu
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Gln Leu Gly Glu Asn Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Leu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Asn Ser Ile Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

```
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
    130                 135                 140

Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145                 150                 155                 160

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
                165                 170                 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
            180                 185                 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
        195                 200                 205

Thr Glu Cys Ser
    210
```

<210> 446
<211> 636
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 446

```
agttatgagc tgactcaacc acccagtgtc agcgtatccc caggagaaac tgcctctata       60

acatgcagcg gagaccagtt gggagaaaat tacgcctcct ggtaccaaca gaagcctgga      120

caaagtcctg tcctcgttat ttatcaagat tctaaacgtc cctctgggat ccccgaacga      180

ttctccggct ctaactctgg gaataccgct accttgacaa taagtggtac acaggcactt      240

gatgaagctg attattactg ccaggcatgg gataacagca ttgtggtttt cgggggcggc      300

accaaactca cagttctcgg tcagcccaag gctgcaccca gtgtcactct gttcccgccc      360

tcctctgagg agcttcaagc caacaaggcc acactggtgt gtctcataag tgacttctac      420

ccgggagccg tgacagtggc ctggaaggcc gatagcagcc ccgtcaaggc gggagtggag      480
```

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaagggagc 600

accgtggaga agacagtggc ccctacagaa tgttca 636

<210> 447
<211> 106
<212> PRT
<213> Homo sapiens

<400> 447
Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> 448
<211> 9
<212> PRT
<213> Homo sapiens

<400> 448
Gly Ser Asp Glu Asp His Leu Ser Leu
1 5

<210> 449
<211> 6
<212> PRT
<213> Homo sapiens

<400> 449
Pro Arg Gly Ser Lys Pro
1   5

<210> 450
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polynucleotide

<400> 450
gacatccaga tgacccagtc tccttccttc ctgtctgcat ctgtaggaga cagagtcacc   60

atcacttgcc gggccagtca gggcattagc agttatttag cctggtatca gcaaaaacca   120

gggaaagccc ctaagttcct gatctatgct gcatccactt tgcaaagtgg ggtcccatca   180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct   240

gaagattttg caacttatta ctgtcaacag cttaatagtt accctctcac tttcggcgga   300

gggaccaagg tggaaatcaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca   360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat   420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag   480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg   540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc   600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt   642

<210> 451
<211> 642
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 451
gacatcgtga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcgagtca ggacattagc aattatttag cctggtatca gcagaaacca 120

gggaaagttc ctaagttcct gatctatgct gcatccactt tgcactctgg ggtcccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagatgttg caacttatta ctgtcaaaag tataacagtg ccccgtacac ttttggccaa 300

gggacacgac tggagattaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 452
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 452
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtcggcga ccgcgtgacc 60

atcacctgtc gtgcccgcca gagcatcggc accgccatcc actggtacca gcagaagcca 120

ggcaaggccc caaagctgct gatcaagtac gccagcgaga gcatcagcgg tgtgccaagc 180

cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag agcggcagct ggccatacac cttcggccag 300

ggcaccaagc tggagatcaa gcgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 453
<211> 475
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 453
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Gly Thr Ala
20 25 30

Ile His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ser Trp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Ser Glu Gly
100 105 110

Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Glu
115 120 125

```
Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Asn
145                 150                 155                 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Thr Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Phe Ser Arg Asp Asn Ala Lys Asn Ser Leu Asp Leu
        195                 200                 205

Gln Met Ser Gly Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys Thr
    210                 215                 220

Arg Gly Trp Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Ser Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320
```

```
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475
```

<210> 454
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 454

```
Val Pro Leu Ile Glu Gly Arg Ile Val Gly Gly Trp Glu Cys Glu Lys
1               5                  10                  15

His Ser Gln Pro Trp Gln Val Ala Val Tyr Ser His Gly Trp Ala His
            20                  25                  30

Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala His
        35                  40                  45

Cys Leu Lys Lys Asn Ser Gln Val Trp Leu Gly Arg His Asn Leu Phe
    50                  55                  60

Glu Pro Glu Asp Thr Gly Gln Arg Val Pro Val Ser His Ser Phe Pro
65                  70                  75                  80

His Pro Leu Tyr Asn Met Ser Leu Leu Lys His Gln Ser Leu Arg Pro
                85                  90                  95

Asp Glu Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu Pro
            100                 105                 110

Ala Lys Ile Thr Asp Val Val Lys Val Leu Gly Leu Pro Thr Gln Glu
        115                 120                 125

Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile Glu
    130                 135                 140

Pro Glu Glu Phe Leu Arg Pro Arg Ser Leu Gln Cys Val Ser Leu His
145                 150                 155                 160

Tyr Ser Glu Lys Val Thr Glu Phe Met Leu Cys Ala Gly Leu Trp Thr
                165                 170                 175

Gly Gly Lys Asp Thr Cys Gly Gly Asp Ser Gly Gly Pro Leu Val Cys
            180                 185                 190

Asn Gly Val Leu Gln Gly Ile Thr Ser Trp Gly Pro Glu Pro Cys Ala
        195                 200                 205
```

Leu Pro Glu Lys Pro Ala Val Tyr Thr Lys Val Val His Tyr Arg Lys
210 215 220

Trp Ile Lys Asp Thr Ile Ala Ala Asn Pro His His His His His His
225 230 235 240

<210> 455
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 455
Gly Phe Thr Phe Ser His
1 5

<210> 456
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 456
Thr Ala Val Tyr Tyr Cys Ala Lys Pro His Ile Val Met Val Thr Ala
1 5 10 15

Leu

<210> 457
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 457
Tyr Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg
1   5   10

<210> 458
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 458
Phe Thr Phe Ser Tyr
1   5

<210> 459
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 459
Gly Ser Tyr Trp Ala Phe Asp Tyr
1   5

<210> 460
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 460
Asp Asn Ser Asp
1

<210> 461
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 461
Gly Asn Ser Ile Thr Ser Asp Tyr Ala
1 5

<210> 462
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 462
Gly Phe Thr Phe
1

<210> 463
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 463
Ala Arg Asp Gln Asn Tyr Asp Ile Leu
1 5

<210> 464
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 464

Val Thr Pro Asn Phe
1 5

<210> 465
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 465
Tyr Ala Ala Ser Thr Leu Gln Ser Gly
1 5

<210> 466
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 466
Glu Ser Gly Trp Ser His Tyr
1 5

<210> 467
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 467
Val Pro Leu Ile Glu Gly Arg Ile Val Gly Gly Trp Glu Cys Glu Lys
1 5 10 15

His Ser Gln Pro Trp Gln Val Ala Val Tyr Ser His Gly Trp Ala His
20 25 30

```
Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala His
        35                  40                  45

Cys Leu Lys Lys Asn Ser Gln Val Trp Leu Gly Arg His Asn Leu Phe
    50                  55                  60

Glu Pro Glu Asp Thr Gly Gln Arg Val Pro Val Ser His Ser Phe Pro
65                  70                  75                  80

His Pro Leu Tyr Asn Met Ser Leu Leu Lys His Gln Ser Leu Arg Pro
                85                  90                  95

Asp Glu Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu Pro
            100                 105                 110

Ala Lys Ile Thr Asp Val Val Lys Val Leu Gly Leu Pro Thr Gln Glu
        115                 120                 125

Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile Glu
    130                 135                 140

Pro Glu Glu Phe Leu Arg Pro Arg Ser Leu Gln Cys Val Ser Leu His
145                 150                 155                 160

Leu Leu Ser Asn Asp Met Cys Ala Arg Ala Tyr Ser Glu Lys Val Thr
                165                 170                 175

Glu Phe Met Leu Cys Ala Gly Leu Trp Thr Gly Gly Lys Asp Thr Cys
            180                 185                 190

Gly Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln Gly
        195                 200                 205

Ile Thr Ser Trp Gly Pro Glu Pro Cys Ala Leu Pro Glu Lys Pro Ala
    210                 215                 220

Val Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr Ile
225                 230                 235                 240
```

Ala Ala Asn Pro

<210> 468
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 468
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Thr Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Arg Tyr Phe Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gln Asn Tyr Asp Ile Leu Thr Gly His Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
130 135 140

```
Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190

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

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
    210                 215                 220

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
            260                 265                 270

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
                325                 330                 335
```

```
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Leu Gly Lys
    450
```

<210> 469
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 469

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30
```

```
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 470
<211> 7

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 470
Asp Asp Ser Asp Arg Pro Ser
1 5

<210> 471
<211> 1338
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 471
gaggtgcagc tggtggagag cggtggcggt ctggtgaagc caggtggcag cctgcgcctg 60

agctgtgccg ccagcggttt caccttcagc cgctacaaca tgaactgggt gcgccaagcc 120

ccaggcaagg gcctggagtg ggtgagcagc atcagcacca gcagcaacta catctactac 180

gccgacagcg tgaagggccg cttcaccttc agccgcgaca acgccaagaa cagcctggac 240

ctgcagatga gcggtctgcg cgccgaggac accgccatct actactgcac ccgcggttgg 300

ggcccattcg actactgggg ccagggcacc ctggtgaccg tgagcagcgc ctccaccaag 360

ggcccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc 420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 600

gtgaatcaca agcccagcaa caccaaggtg gacaagaaag ttgagcccaa atcttgtgac 660

aaaactcaca catgtccacc gtgcccagca cctgaagcag caggggggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc 780

gtggtggtga gcgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt 900

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag aaccacaggt gtacgtgtac cccccatccc gggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1200

ggctccttcg ccctcgtgag caagctcacc gtggacaagt ctagatggca gcaggggaac 1260

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tccctgtctc cgggtaaa 1338

<210> 472
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<223> KL2B997 HC

<400> 472

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

```
                85                  90                  95

Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Gly Ser Gly Ser Gly Ser His
225                 230                 235                 240

His His His His His Gly Ser Gly Leu Pro Glu Thr Gly Gly
                245                 250
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<210> 473
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> KL2B997 LC

<400> 473

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


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190
```

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195   200   205

Phe Asn Arg Gly Glu Cys
    210

<210> 474
<211> 228
<212> PRT
<213> Artificial Sequence

<220>
<223> KL2B1251 HC

<400> 474

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20   25   30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50   55   60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65   70   75   80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Gly Thr Thr Ile Phe Gly Val Val Thr Pro Asn Phe Tyr Tyr Gly Met
            100   105   110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115   120   125

```
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140


Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160


Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175


Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190


Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205


Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220


Pro Lys Ser Cys
225


<210>  475
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  KL2B1251 LC

<400>  475

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


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
        35                  40                  45
```

```
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```