tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

For intravenous, intramuscular, subcutaneous, or intraperitoneal administration, the compound may be combined with a sterile aqueous solution which is preferably isotonic with the blood of the recipient. Such formulations may be prepared by dissolving solid active ingredient in water containing physiologically compatible substances such as sodium chloride, glycine, and the like, and having a buffered pH compatible with physiological conditions to produce an aqueous solution, and rendering said solution sterile. The formulations may be present in unit or multi-dose containers such as sealed ampoules or vials.

If the neoplasia is localized in the G.I. tract, the compound may be formulated with acid-stable, base-labile coatings known in the art which begin to dissolve in the high pH small intestine. Formulation to enhance

local pharmacologic effects and reduce systemic uptake are preferred.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably made isotonic. Preparations for injections may also be formulated by suspending or emulsifying the compounds in non-aqueous solvent, such as vegetable oil, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol.

Formulations for topical use include known gels, creams, oils, and the like. For aerosol delivery, the compounds may be formulated with known aerosol exipients, such as saline, and administered using commercially available nebulizers. Formulation in a fatty acid source may be used to enhance biocompatibility. Aerosol delivery is the preferred method of delivery for epithelial neoplasias of the lung for prevention application.

For rectal administration, the active ingredient may be formulated into suppositories using bases which are solid at room temperature and melt or dissolve at body temperature. Commonly used bases include coca butter, glycerinated gelatin, hydrogenated vegetable oil, polyethylene glycols of various molecular weights, and fatty esters of polyethylene stearate.

The dosage form and amount can be readily established by reference to known treatment or prophylactic regiments. The amount of therapeutically active compound that is administered and the dosage

regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, the location of the neoplasia, as well as the pharmacokinetic properties of the individual treated, and thus may vary widely. The dosage will generally be lower if the compounds are administered locally rather than systemically, and for prevention rather than for treatment. Such treatments may be administered as often as necessary and for the period of time judged necessary by the treating physician. One of skill in the art will appreciate that the dosage regime or therapeutically effective amount of the inhibitor to be administrated may need to be optimized for each individual. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 200 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably from about 1 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

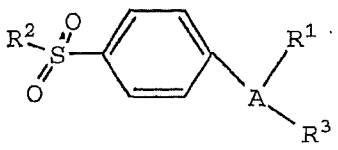
Human uroguanylin cDNA has been cloned in bacteria, and chemically synthesized by solid phase peptide synthesis. Uroguanylin peptide can be chemically synthesized by using the procedure as described in U.S. patent number 5,489,670 *Human Uroguanylin* and in U.S. patent number 5,140,102 *Pentadecapeptide, guanylin, which stimulates intestinal guanylate cyclase*. Peptides similar to uroguanylin peptides have been identified in mouse, rat, porcine, and bovine species. The

functionally active domain in most of these peptides are highly conserved. Therefore, the physiological functions of these peptides may be similar, and these peptides may be used as intestinal cancer preventative agents as well. Thus, as long as the functionally active domains of these peptides are conserved, substitutions in the non-active domains may be achieved with no change in the activity of the peptides.

In the present invention, the combination of any one or more of the following peptides; uroguanylin, human uroguanylin, pro-uroguanylin, and human pro-uroguanylin, guanylin, lymphoguanylin, prolymphoguanylin and heat stable enterotoxin, with any one of more of naturally occurring, or an extract of a natural occurring, or a chemically synthesized cyclooxygenase-2 inhibitor, preferably a selective cyclooxygenase-2 inhibitor or inhibitors is disclosed for the prevention, inhibition, or treatment of cancer in the intestinal tract by administration of an effective amount of such a combination to a subject in need of such treatment.

In such a combination, the cyclooxygenase inhibitor can be, by way of example, a COX-2 nonselective inhibitor or a COX-2 selective inhibitor. Examples of COX-2 nonselective inhibitors include the well-known compounds aspirin, acetaminophen, indomethacin, sulindac, etodolac, mefenamic acid, tolmetin, ketorolac, diclofenac, ibuprofen, naproxen, fenoprofen, ketoprofen, oxaprozin, flurbiprofen, piroxicam, tenoxicam, phenylbutazone, apazone, or nimesulide or a pharmaceutically acceptable salt or derivative or prodrug thereof. In a preferred embodiment of the invention the COX-2 nonselective inhibitor is selected from the group comprising aspirin, acetaminophen, indomethacin, ibuprofen, or naproxen.

In the preferred embodiments, the cyclooxygenase-2 inhibitor is selected from compounds of Formula I



I

wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R^1 is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

wherein R^2 is methyl or amino; and

wherein R^3 is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-

arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds which inhibit cyclooxygenase-2 consists of compounds of Formula I wherein A is selected from 5- or 6-member partially unsaturated heterocyclyl, 5- or 6-member unsaturated heterocyclyl, 9- or 10-member unsaturated condensed heterocyclyl, lower cycloalkenyl and phenyl; wherein R^1 is selected from 5- and 6-membered heterocyclyl, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R^2 is methyl or amino; and wherein R^3 is a radical selected from hydrido, oxo, cyano, carboxyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, halo, lower alkyl, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-

membered heterocyclyl, lower hydroxylalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl, lower alkylamino, lower aminoalkyl, lower alkylaminoalkyl, phenyloxy, and lower aralkoxy; or a pharmaceutically-acceptable salt thereof.

A more preferred class of compounds which inhibit cyclooxygenase-2 consists of compounds of Formula I wherein A is selected from oxazolyl, isoxazolyl, furyl, thienyl, dihydrofuryl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl, and pyridyl; wherein R^1 is selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals, and phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, hydroxyl, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, and methylthio; wherein R^2 is methyl or amino; and wherein R^3 is a radical selected from hydrido, oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, difluoromethyl,

trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxylmethyl, hydroxylpropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethyloxy, aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, benzyloxy, and phenyloxy; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;
1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

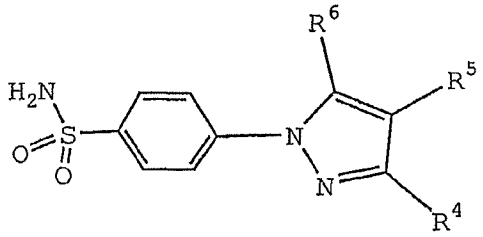
2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;
5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;
4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;
2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;
2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and
4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

A family of specific compounds of more particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; and
4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide.

A subclass of cyclooxygenase-2 inhibitors is selected from compounds of Formula II



II

wherein R^4 is selected from hydrido, alkyl, haloalkyl, alkoxycarbonyl, cyano, cyanoalkyl, carboxyl, aminocarbonyl, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, carboxyalkylaminocarbonyl, carboxyalkyl, aralkoxycarbonylalkylaminocarbonyl, aminocarbonylalkyl, alkoxycarbonylcyanoalkenyl and hydroxyalkyl;

wherein R^5 is selected from hydrido, alkyl, cyano, hydroxyalkyl, cycloalkyl, alkylsulfonyl and halo; and

wherein R^6 is selected from aralkenyl, aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfonyl, cyano, nitro, haloalkyl, alkyl, hydroxyl, alkenyl, hydroxyalkyl, carboxyl, cycloalkyl, alkylamino, dialkylamino, alkoxycarbonyl, aminocarbonyl, alkoxy, haloalkoxy, sulfamyl, heterocyclic and amino;

or a pharmaceutically-acceptable salt or derivative thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein R^4 is selected from hydrido, lower alkyl, lower haloalkyl, lower alkoxycarbonyl, cyano, lower cyanoalkyl, carboxyl, aminocarbonyl, lower alkylaminocarbonyl, lower cycloalkylaminocarbonyl, arylaminocarbonyl, lower carboxyalkylaminocarbonyl, lower aminocarbonylalkyl, lower aralkoxycarbonylalkylaminocarbonyl, lower carboxyalkyl, lower alkoxycarbonylcyanoalkenyl and lower hydroxyalkyl; wherein R^5 is selected from hydrido, lower alkyl, cyano, lower hydroxyalkyl, lower

cycloalkyl, lower alkylsulfonyl and halo; and wherein R^6 is selected from aralkenyl, aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfonyl, cyano, nitro, lower haloalkyl, lower alkyl, hydroxyl, lower alkenyl, lower hydroxyalkyl, carboxyl, lower cycloalkyl, lower alkylamino, lower dialkylamino, lower alkoxycarbonyl, aminocarbonyl, lower alkoxy, lower haloalkoxy, sulfamyl, five or six membered heterocyclic and amino; or a pharmaceutically-acceptable salt or derivative thereof.

A family of specific compounds of particular interest within Formula I consists of compounds, derivatives and pharmaceutically-acceptable salts thereof as follows:

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide; and
4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

A family of specific compounds of more particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts or derivatives thereof as follows:

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; and
4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

Derivatives are intended to encompass any compounds which are structurally related to the cyclooxygenase-2 inhibitors or which possess the substantially equivalent biologic activity. By way of example, such inhibitors may include, but are not limited to, prodrugs thereof.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached,

for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like. The terms "alkenyl", "lower alkenyl", embrace radicals having "cis"

and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl,

difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term

"aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl. The term "heterocyclyl" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclyl radicals. Examples of unsaturated heterocyclyl radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl,

pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclyl radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include

benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred

alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote NH_2O_2S-. The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl. The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes -(C=O)-. The term "aroyl" embraces aryl radicals with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl. The term "alkoxycarbonyl" means a

radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl porions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "heterocyclylalkyl" embraces saturated and partially unsaturated heterocyclyl-substituted alkyl radicals, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an

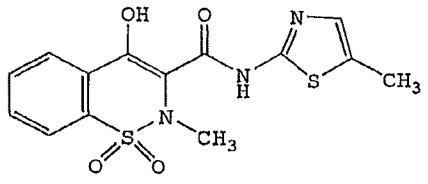
oxygen atom to an alkyl radical. The term "aralkylthio" embraces aralkyl radicals attached to a sulfur atom. The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical. The term "aminoalkyl" embraces alkyl radicals substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" embraces aralkyl radicals attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$. The term "alkylaminocarbonyl" denotes an aminocarbonyl group which has been

substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "alkylaminoalkyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical. The term "aryloxyalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent oxygen atom. The term "arylthioalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

The compounds utilized in the methods of the present invention may be present in the form of free bases or pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic,

aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, D-3-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

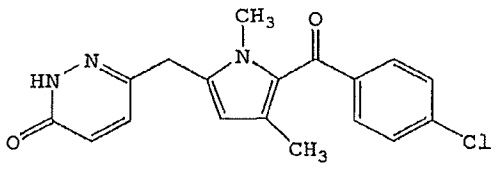
In another embodiment of the invention the cyclooxygenase inhibitor can be a cyclooxygenase-2 selective inhibitor, for example, the COX-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7) or a pharmaceutically acceptable salt or derivative or prodrug thereof.



B-1

In yet another embodiment of the invention the cyclooxygenase-2 selective inhibitor is the COX-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

Formula B-2 (CAS registry number 179382-91-3) or a pharmaceutically acceptable salt or derivative or prodrug thereof.



B-2

In a preferred embodiment of the invention the cyclooxygenase-2 selective inhibitor is a COX-2 selective inhibitor of the chromene structural class that is a substituted benzopyran or a substituted benzopyran analog selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the general Formula II shown below and possessing, by way of example and not limitation, the structures disclosed in Table 1, including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

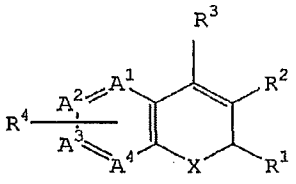
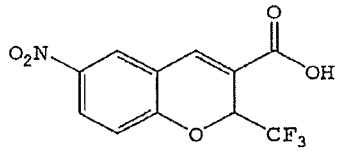
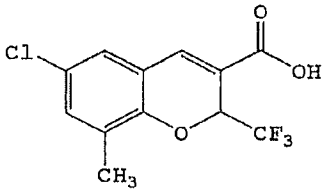
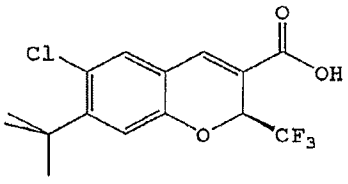
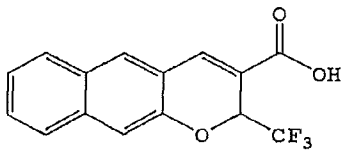
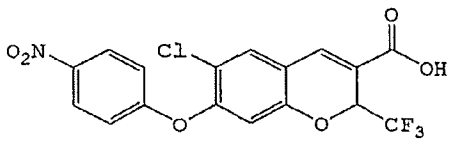
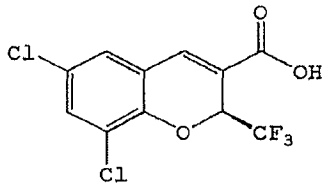
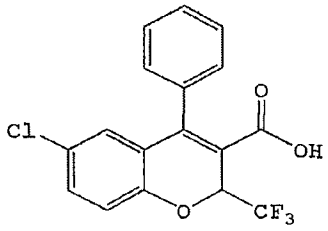
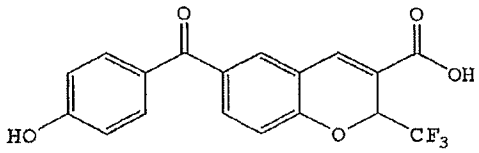
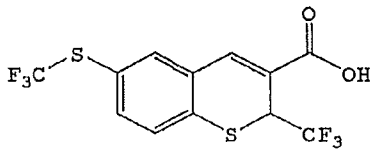
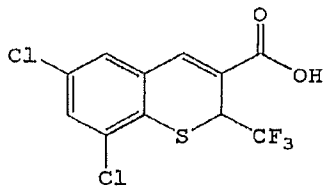
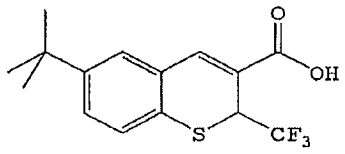
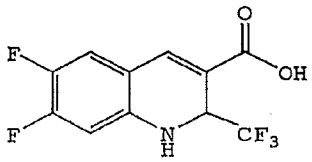
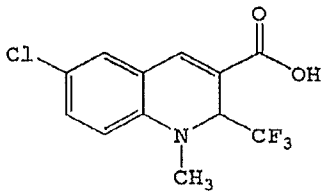


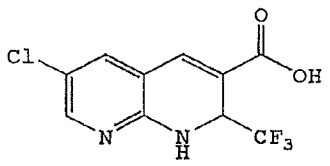
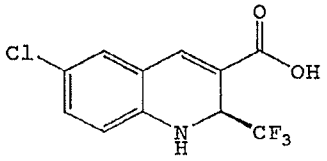
Table 1. Examples of Chromene COX-2 Selective Inhibitors as Embodiments

Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

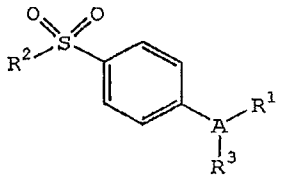
Compound Number	Structural Formula
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

In a more preferred embodiment of the invention the cycloxygenase-2 selective inhibitor is the substituted benzopyran (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, Formula B-8, or a pharmaceutically acceptable salt or derivative or prodrug thereof.

In a further preferred embodiment of the invention the cyclooxygenase inhibitor is selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of Formula III



III

wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R^1 is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

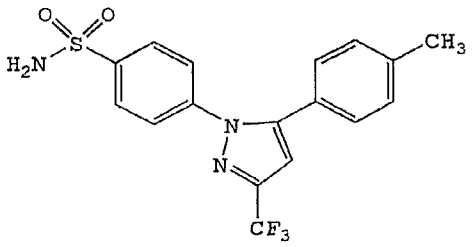
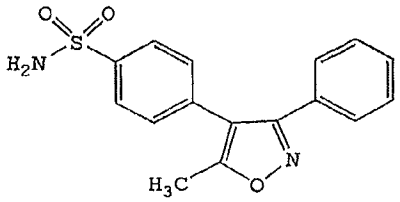
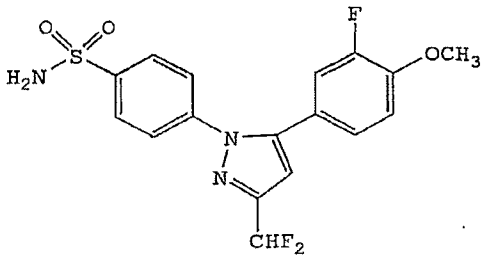
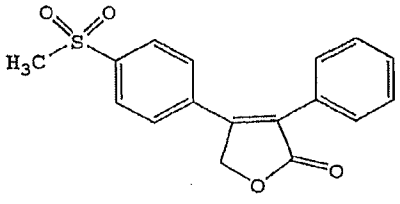
wherein R^2 is methyl or amino; and

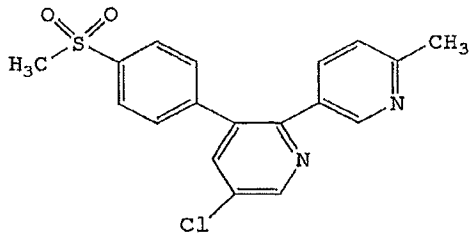
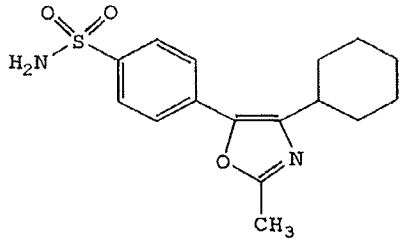
wherein R^3 is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl,

alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl; or a pharmaceutically acceptable salt or derivative thereof.

In a still more preferred embodiment of the invention the cyclooxygenase-2 selective inhibitor represented by the above Formula III is selected from the group of compounds, illustrated in Table 2, consisting of celecoxib (B-18), valdecoxib (B-19), deracoxib (B-20), rofecoxib (B-21), etoricoxib (MK-663; B-22), JTE-522 (B-23), or a pharmaceutically acceptable salt or derivative or prodrug thereof.

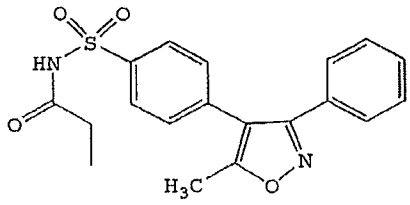
Table 2. Examples of Tricyclic COX-2 Selective Inhibitors as Embodiments

Compound Number	Structural Formula
B-18	
B-19	
B-20	
B-21	

Compound Number	Structural Formula
B-22	
B-23	

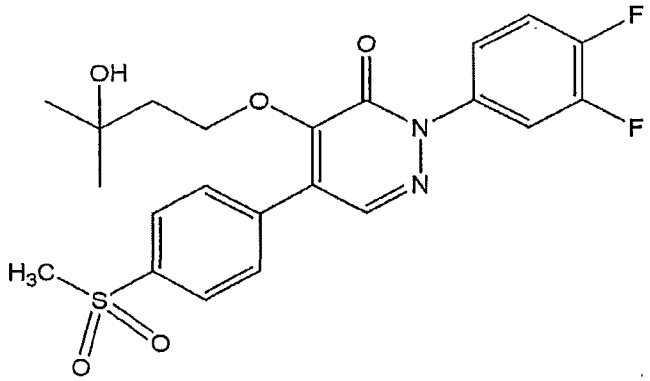
In an even more preferred embodiment of the invention the COX-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

In another highly preferred embodiment of the invention parecoxib, B-24, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, may be advantageously employed as a source of a cyclooxygenase inhibitor (US 5,932,598, herein incorporated by reference).



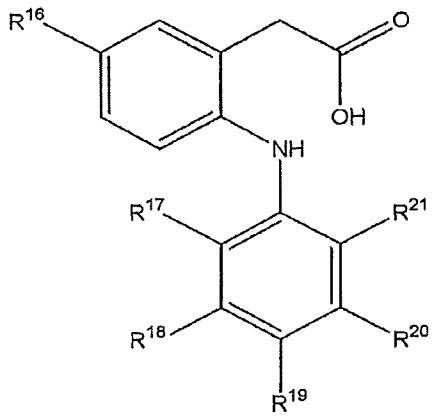
B-24

In another preferred embodiment of the invention, the compound ABT-963 having the formula B-25 that has been previously described in International Publication number WO 00/24719, is another tricyclic cyclooxygenase-2 selective inhibitor which may be advantageously employed.



B-25

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula V:



V

wherein R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided that R^{17}, R^{18}, R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H.

A particularly preferred phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 99/11605 is a compound that has the designation of COX189 (CAS RN 346670-74-4), and that has the structure shown in Formula V,

wherein R^{16} is ethyl;

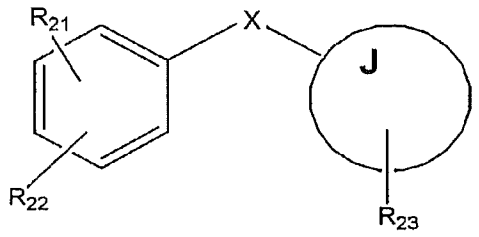
R^{17} and R^{19} are chloro;

R^{18} and R^{20} are hydrogen; and

and R^{21} is methyl.

Other preferred cyclooxygenase-2 selective inhibitors that can be used in the present invention

have the general structure shown in formula VI, where the J group is a carbocycle or a heterocycle. Particularly preferred embodiments have the structure:



VI

where:

X is O; J is 1-phenyl; R_{21} is 2-$NHSO_2CH_3$; R_{22} is 4-NO_2; and there is no R_{23} group, (nimesulide), and

X is O; J is 1-oxo-inden-5-yl; R_{21} is 2-F; R_{22} is 4-F; and R_{23} is 6-$NHSO_2CH_3$, (flosulide); and

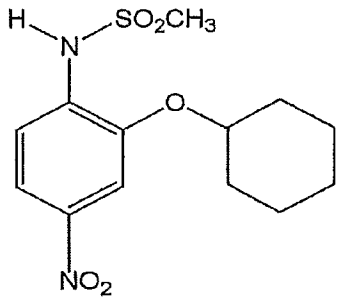
X is O; J is cyclohexyl; R_{21} is 2-$NHSO_2CH_3$; R_{22} is 5-NO_2; and there is no R_{23} group, (NS-398); and

X is S; J is 1-oxo-inden-5-yl; R_{21} is 2-F; R_{22} is 4-F; and R_{23} is 6-$N^-SO_2CH_3 \cdot Na^+$, (L-745337); and

X is S; J is thiophen-2-yl; R_{21} is 4-F; there is no R_{22} group; and R_{23} is 5-$NHSO_2CH_3$, (RWJ-63556); and

X is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R_{21} is 3-F; R_{22} is 4-F; and R_{23} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

Further information on the applications of N-(2-cyclohexyloxynitrophenyl)methane sulfonamide (NS-398, CAS RN 123653-11-2), having a structure as shown in formula B-26, have been described by, for example, Yoshimi, N. *et al.*, in

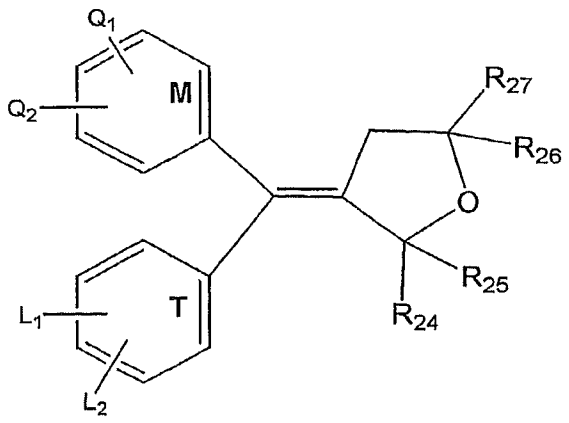


B-26

*Japanese J. Cancer Res., 90(4):*406 - 412 (1999); Falgueyret, J.-P. *et al.*, in *Science Spectra,* available at: http://www.gbhap.com/Science_Spectra/20-1-article.htm (06/06/2001); and Iwata, K. *et al.*, in *Jpn. J. Pharmacol., 75(2):*191 - 194 (1997).

An evaluation of the antiinflammatory activity of the cyclooxygenase-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther 282,* 1094-1101 (1997).

Other compounds useful as the cyclooxygenase-2 selective inhibitor in the present invention include diarylmethylidenefuran derivatives such as those described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **VII**:



VII

wherein:

the rings T and M independently are:

a phenyl radical,

a naphthyl radical,

a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or

a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q_1, Q_2, L_1 or L_2 is:

an $--S(O)_n--R$ group, in which n is an integer equal to 0, 1 or 2 and R is a

lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having 1 to 6 carbon atoms, or

an $-SO_2NH_2$ group;

and is located in the para position,

the others independently being:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a trifluoromethyl radical, or

a lower O-alkyl radical having 1 to 6 carbon atoms, or

Q_1 and Q_2 or L_1 and L_2 are a methylenedioxy group; and

R_{24}, R_{25}, R_{26} and R_{27} independently are:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R_{24}, R_{25} or R_{26}, R_{27} are an oxygen atom, or

R_{24}, R_{25} or R_{26}, R_{27}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

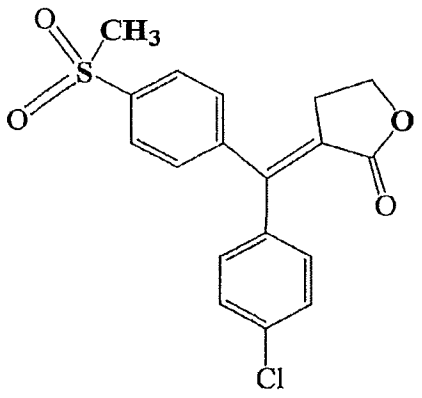
Particular materials that are included in this family of compounds, and which can serve as the cyclooxygenase-2 selective inhibitor in the present invention, include N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]

benzenesulfonamide.

Preferred cyclooxygenase-2 selective inhibitors that are useful in the present invention include the following individual compounds; darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381

(Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

Another preferred embodiment of the invention, is the compound BMS-347070, having the formula:



C-69

Information about S-33516, mentioned above, can be found in *Current Drugs Headline News*, at http://www.current-drugs.com/NEWS/Inflam1.htm, 10/04/2001, where it was reported that S-33516 is a tetrahydroisoinde derivative which has IC_{50} values of 0.1 and 0.001 mM against cyclooxygenase-1 and cyclooxygenase-2, respectively. In human whole blood, S-33516 was reported to have an ED_{50} = 0.39 mg/kg.

All references, patents or applications U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein.

The explanations and illustrations presented herein are intended to acquaint others skilled in the art with the invention, its principles, and its practical application. Those skilled in the art may adapt and apply the invention in its numerous forms, as may be best suited to the requirements of a particular use. Accordingly, the specific embodiments of the present invention as set forth are not intended as being exhaustive or limiting of the invention.

WHAT IS CLAIMED IS:

1. A method for the treatment or prevention of intestinal polyps in a subject, the method comprising administering to the subject an amount of a polypeptide and an amount of a cyclooxygenase-2 selective inhibitor wherein the amount of the polypeptide and the amount of the cyclooxygenase-2 selective inhibitor together comprise an intestinal polyp treating-effective amount of the polypeptide and the cyclooxygenase-2 selective inhibitor, wherein the polypeptide has the formula:

X_8-Asp -Asp -Cys $-X_1$ $-X_2$ -Cys $-X_3$ -Asn $-X_4$ $-X_5$ -Cys $-X_6$ $-X_7$ -Cys-X_9

and wherein each of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is an amino acid residue, X_8 and X_9 are independently hydrogen or at least one amino acid residue, and

the polypeptide is cross-linked by a disulfide bond between the cystine residue immediately adjacent the amine group of X_1 and the cystine residue immediately adjacent the amine group of X_6 and by a disulfide bond between the cystine residue immediately adjacent the amine group of X_3 and the cystine residue immediately adjacent the carboxy group of X_7.

2. A process of claim 1 wherein the polypeptide and cyclooxygenase-2 inhibitor are present as a single composition.

3. A process of claim 2 wherein the concentration of the peptide in the composition is at least 0.0001 percent by weight of the composition.

4. A process of claim 2 wherein the concentration of the peptide in the composition is at least 0.001 percent by weight of the composition.

5. A process of claim 2 wherein the concentration of the peptide in the composition is at least 0.01 percent by weight of the composition.

6. A process of claim 2 wherein the concentration of the peptide in the composition is at least 0.1 percent by weight of the composition.

7. A process of claim 2 wherein the concentration of the peptide in the composition is at least 1 percent by weight of the composition.

8. The process of claim 1 wherein said subject has been determined to have a genetic predisposition for the growth of polyps in the intestine.

9. The process of claim 1 wherein polyps have been identified in the intestine of said subject.

10. The process of claim 1 wherein said subject has been identified as having intestine cancer.

11. A process of claim 2 wherein the concentration of the peptide in the composition is at least 0.0001 percent by weight of the composition.

12. A process of claim 2 wherein the concentration of the peptide in the composition is at least 0.001 percent by weight of the composition.

13. A process of claim 2 wherein the concentration of the peptide in the composition is at least 0.01 percent by weight of the composition.

14. A process of claim 2 wherein the concentration of the peptide in the composition is at least 0.1 percent by weight of the composition.

15. A process of claim 2 wherein the concentration of the peptide in the composition is at least 1 percent by weight of the composition.

16. The process of claim 2 wherein said subject has been determined to have a genetic predisposition for the growth of polyps in the intestine.

17. The process of claim 2 wherein the polyps have been identified in the intestine of said subject.

18. The process of claim 2 wherein said subject has been identified as having intestine cancer.

19. The process of claim 1 wherein X_1 is selected from the group of amino acid residues consisting of aspartic acid, glutamic acid, glycine, lysine, asparagine, proline, glutamine, arginine, serine, and threonine.

20. The process of claim 1 wherein X_1 is selected from the group of amino acid residues consisting of glutamic acid, arginine, lysine, serine, aspartic acid, asparagine, glutamine, and glycine.

21. The process of claim 1 wherein X_1 is selected from the group of amino acid residues consisting of glutamic acid, aspartic acid, arginine, and lysine.

22. The process of claim 1 wherein X_1 is glutamic acid.

23. The process of claim 1 wherein X_2 is selected from the group of amino acid residues consisting of leucine, isoleucine, tyrosine, phenylalanine, tryptophan, valine, methionine, cysteine, alanine, histidine, proline, threonine, glycine, asparagine, and glutamine.

24. The process of claim 1 wherein X_2 is selected from the group of amino acid residues consisting of cysteine, phenylalanine, glycine, isoleucine, leucine, methionine, valine, and tyrosine.

25. The process of claim 1 wherein X_2 is selected from the group of amino acid residues consisting of leucine, isoleucine, tyrosine, valine, methionine.

26. The process of claim 1 wherein X_2 is selected from the group of amino acid residues consisting of leucine, and isoleucine.

27. The process of claim 1 wherein X_2 is leucine.

28. The process of claim 1 wherein X_3 is selected from the group of amino acid residues consisting of valine, isoleucine, leucine, tyrosine, phenylalanine, tryptophan, methionine, cysteine, alanine, histidine, proline, threonine, glycine, glutamine, asparagine, and serine.

29. The process of claim 1 wherein X_3 is selected from the group of amino acid residues consisting of valine, isoleucine, leucine, tyrosine, phenylalanine, methionine, cysteine, alanine, histidine, and proline.

30. The process of claim 1 wherein X_3 is selected from the group of amino acid residues consisting of valine, isoleucine, leucine, methionine, and cysteine.

31. The process of claim 1 wherein X_3 is valine.

32. The process of claim 1 wherein X_3 is isoleucine.

33. The process of claim 1 wherein X_4 is selected from the group of amino acid residues consisting of valine, isoleucine, leucine, tyrosine, phenylalanine, tryptophan, methionine, cysteine,

alanine, histidine, proline, threonine, glycine, glutamine, asparagine, and serine.

34. The process of claim 1 wherein X_4 is selected from the group of amino acid residues consisting of valine, isoleucine, leucine, tyrosine, phenylalanine, methionine, cysteine, alanine, histidine, and proline.

35. The process of claim 1 wherein X_4 is selected from the group of amino acid residues consisting of valine, isoleucine, leucine, methionine, and cysteine.

36. The process of claim 1 wherein X_4 is valine.

37. The process of claim 1 wherein X_5 is alanine, histidine, cysteine, methionine, valine, leucine, isoleucine, tyrosine, phenylalanine, proline, threonine, glycine, glutamine, asparagine, and serine.

38. The process of claim 1 wherein X_5 is selected from the group of amino acid residues consisting of alanine, histidine, cysteine, methionine, valine, proline, threonine, glycine, glutamine, asparagine, and serine.

39. The process of claim 1 wherein X_5 is selected from the group of amino acid residues consisting of alanine, histidine, cysteine, proline, threonine, glycine, glutamine, asparagine, and serine.

40. The process of claim 1 wherein X_5 is alanine.

41. The process of claim 1 wherein X_6 is selected from the group of amino acid residues consisting of threonine, proline, alanine, histidine, cysteine, methionine, valine, leucine, isoleucine, tyrosine, glycine, glutamine, asparagine, and serine.

42. The process of claim 1 wherein X_6 is selected from the group of amino acid residues consisting of threonine, proline, alanine, histidine, cysteine, methionine, glycine, glutamine, asparagine, and serine.

43. The process of claim 1 wherein X_6 is selected from the group of amino acid residues consisting of threonine, proline, alanine, histidine, and glycine.

44. The process of claim 1 wherein X_6 is threonine.

45. The process of claim 1 wherein X_7 is selected from the group of amino acid residues consisting of glycine, threonine, proline, alanine, histidine, cysteine, methionine, valine, leucine, isoleucine, glutamine, asparagine, serine, glutamic acid, and aspartic acid.

46. The process of claim 1 wherein X_7 is selected from the group of amino acid residues consisting of glycine, threonine, proline, alanine, histidine, cysteine, glutamine, asparagine, and serine.

47. The process of claim 1 wherein X_7 is selected from the group of amino acid residues consisting of glycine, threonine, proline, alanine, histidine, glutamine, asparagine, and serine.

48. The process of claim 1 wherein X_7 is glycine.

49. The process of claim 1 wherein the polypeptide is uroguanylin.

50. The process of claim 1 wherein the polypeptide is human uroguanylin.

51. The process of claim 1 wherein the composition comprises pro-uroguanylin.

52. The process of claim 1 wherein the composition comprises human pro-uroguanylin.

53. The process of claim 1 wherein the composition comprises guanylin.

54. The process of claim 1 wherein the composition comprises lymphoguanylin.

55. The process of claim 1 wherein the composition comprises prolymphoguanylin.

56. The process of claim 1 wherein the composition comprises heat stable enterotoxin.

57. The process of claim 1 wherein the composition comprises a polypeptide, which is degraded with endogenous proteases of the subject, into uroguanylin.

58. The process of claim 1 wherein about 0.5 mg to about 2 mg of the polypeptide is administered per kilogram of the subjects weight.

59. The process of claim 1 wherein the subject is human.

60. The process of claim 1 wherein said peptides are administered in a pharmaceutical composition which contains said peptide and one or more pharmacologically acceptable, inert or physiologically active diluents of adjuvants.

61. The process of claim 1 wherein X_1 is glutamic acid, X_2 is leucine, X_3 is isoleucine, X_4 is valine, X_5 is alanine, X_6 is threonine, and X_7 is glycine.

62. A process for the prevention, inhibition and treatment of cancer in the intestine of a subject, the process comprising administering to the subject the composition of claim 1.

63. A process for the prevention, inhibition and treatment of cancer in the intestine of a subject, the process comprising administering to the subject the composition of claim 2.

64. The process of claim 62 wherein the composition comprises uroguanylin.

65. The process of claim 63 wherein the composition comprises uroguanylin.

66. The process of claim 62 wherein the composition comprises pro-uroguanylin.

67. The process of claim 63 wherein the composition comprises pro-uroguanylin.

68. A process for retarding the development of polyps and prevention, inhibition and treatment of polyps in the intestine of a subject, the process comprising administering to the subject a composition comprising an agonist peptide or compound which binds to a guanylate cyclase receptor GC-C in the intestine of the subject, in combination with a cyclooxygenase-2 inhibitor.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 October 2002 (10.10.2002)

PCT

(10) International Publication Number
WO 02/078683 A1

(51) International Patent Classification[7]: A61K 31/00, 38/00, A01N 61/00, C12Q 1/00, C07K 2/00, 4/00, 5/00, 7/00, 14/00, 16/00, 17/00, G01N 33/53, 33/48, 33/567, 33/574

(21) International Application Number: PCT/US02/09551

(22) International Filing Date: 28 March 2002 (28.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/279,438	29 March 2001 (29.03.2001)	US
60/279,437	29 March 2001 (29.03.2001)	US
60/300,850	27 June 2001 (27.06.2001)	US
60/303,806	10 July 2001 (10.07.2001)	US
60/307,358	25 July 2001 (25.07.2001)	US
60/348,646	17 January 2002 (17.01.2002)	US

(71) Applicant: SYNERGY PHARMACEUTICALS, INC. [US/US]; Suite 450, Two Executive Drive, Somerset, NJ 08873 (US).

(72) Inventors: SHAILUBHAI, Kunwar; 600 Wick Lane, Blue Bell, PA 19422 (US). NIKIFOROVICH, Gregory; 751 Aramis Drive, St. Louis, mo 63141 (US). JACOB, Gary, S.; 12541 Mason Forest Drive, Creve Coeur, MO 63141 (US).

(74) Agents: SANZO, Michael, A. et al.; Pillsbury Winthrop LLP, 1600 Tysons Boulevard, McLean, VA 22102 (US).

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

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

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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

WO 02/078683 A1

(54) Title: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

(57) Abstract: A method of treatment of inflamed, pre-cancerous or cancerous tissue or polyps in a mammalian subject is disclosed. The treatment involves administration of a composition of at least one peptide agonist of a guanylate cyclase receptor and/or other small molecules that enhance intracellular production of cGMP. The at least one peptide agonist of a guanylate cyclase receptor may be administered either alone or in combination with an inhibitor of cGMP-dependent phosphodiesterase. The inhibitor may be a small molecule, peptide, protein or other compound that inhibits the degradation of cGMP. Without requiring a particular mechanism of action, this treatment may restore a healthy balance between proliferation and apoptosis in the subject's population of epithelial cells, and also suppress carcinogenesis. Thus, the method may be used to treat, <i>inter alia<i/>, inflammation, including gastrointestinal inflammatory disorders, general organ inflammation and asthma, and carcinogenesis of the lung, gastrointestinal tract, bladder, testis, prostate and pancreas, or polyps.

Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

Cross Reference to Related Applications

The present application claims the benefit of U.S. provisional application nos. 60/279,438, filed on March 29, 2001; 60/279,437, filed on March 29, 2001; 60/300,850, filed on June 27, 2001; 60/303,806, filed on July 10, 2001; 60/307,358, filed on July 25, 2001; and 60/348,646, filed on January 17, 2002.

Field of the Invention

The present invention relates to the therapeutic use of guanylate cyclase receptor agonists as a means for enhancing the intracellular production of cGMP. The agonists may be used either alone or in combination with inhibitors of cGMP-specific phosphodiesterase to prevent or treat cancerous, pre-cancerous and metastatic growths, particularly in the gastrointestinal tract and lungs. In addition, the agonists may be used in the treatment of inflammatory disorders such as ulcerative colitis and asthma.

Background of the Invention

Uroguanylin, guanylin and bacterial ST peptides are structurally related peptides that bind to a guanylate cyclase receptor and stimulate intracellular production of cyclic guanosine monophosphate (cGMP) (1-6). This results in the activation of the cystic fibrosis transmembrane conductance regulator (CFTR), an apical membrane channel for efflux of chloride from enterocytes lining the intestinal tract (1-6). Activation of CFTR and the subsequent enhancement of transepithelial secretion of chloride leads to stimulation of sodium and water secretion into the intestinal lumen. Therefore, by serving as paracrine regulators of CFTR activity, cGMP receptor agonists regulate fluid and electrolyte transport in the GI tract (1-6; US patent 5,489,670).

The process of epithelial renewal involves the proliferation, migration, differentiation, senescence, and eventual loss of GI cells in the lumen (7,8). The GI mucosa can be divided into three distinct zones based on the proliferation index of epithelial cells. One of these zones, the proliferative zone, consists of undifferentiated stem cells responsible for providing a constant source of new cells. The stem cells migrate upward toward the lumen to which they

are extruded. As they migrate, the cells lose their capacity to divide and become differentiated for carrying out specialized functions of the GI mucosa (9). Renewal of GI mucosa is very rapid with complete turnover occurring within a 24-48 hour period (9). During this process mutated and unwanted cells are replenished with new cells. Hence, homeostasis of the GI mucosa is regulated by continual maintenance of the balance between proliferation and apoptotic rates (8).

The rates of cell proliferation and apoptosis in the gut epithelium can be increased or decreased in a wide variety of different circumstances, *e.g.*, in response to physiological stimuli such as aging, inflammatory signals, hormones, peptides, growth factors, chemicals and dietary habits. In addition, an enhanced proliferation rate is frequently associated with a reduction in turnover time and an expansion of the proliferative zone (10). The proliferation index has been observed to be much higher in pathological cases of ulcerative colitis and other GI disorders (11). Thus, intestinal hyperplasia is the major promoter of gastrointestinal inflammation and carcinogenesis.

In addition to a role for uroguanylin and guanylin as modulators of intestinal fluid and ion secretion, these peptides may also be involved in the continual renewal of GI mucosa. Previously published data in WO 01/25266 suggests a peptide with the active domain of uroguanylin may function as an inhibitor of polyp development in the colon and may constitute a treatment of colon cancer. However, the mechanism by which this is claimed to occur is questionable in that WO 01/25266 teaches uroguanylin agonist peptides that bind specifically to a guanylate cyclase receptor, termed GC-C, that was first described as the receptor for *E. coli* heat-stable enterotoxin (ST) (4). Knockout mice lacking this guanylate cyclase receptor show resistance to ST in intestine, but effects of uroguanylin and ST are not disturbed in the kidney *in vivo* (3). These results were further supported by the fact that membrane depolarization induced by guanylin was blocked by genistein, a tyrosine kinase inhibitor, whereas hyperpolarization induced by uroguanylin was not effected (12,13). Taken together these data suggest that uroguanylin also binds to a currently unknown receptor, which is distinct from GC-C.

Other papers have reported that production of uroguanylin and guanylin is dramatically decreased in pre-cancerous colon polyps and tumor tissues (14-17). In addition, genes for both uroguanylin and guanylin have been shown to be localized to regions of the genome frequently

associated with loss of heterozygosity in human colon carcinoma (18-20). Taken together, these findings indicate that uroguanylin, guanylin and other peptides with similar activity may be used in the prevention or treatment of abnormal colon growths. This proposal is bolstered by a recent study demonstrating oral administration of uroguanylin inhibits polyp formation in mice (15,16).

Uroguanylin and guanylin peptides also appear to promote apoptosis by controlling cellular ion flux. Alterations in apoptosis have been associated with tumor progression to the metastatic phenotype. While a primary gastrointestinal (GI) cancer is limited to the small intestine, colon, and rectum, it may metastasize and spread to such localities as bone, lymph nodes, liver, lung, peritoneum, ovaries, brain. By enhancing the efflux of K^+ and influx of Ca^{++}, uroguanylin and related peptides may promote the death of transformed cells and thereby inhibit metastasis.

One of the clinical manifestations of reduced CFTR activity is the inflammation of airway passages (21). This effect may be due to CTFR regulating the expression of NF-kB, chemokines and cytokines (22-25). Recent reports have also suggested that the CFTR channel is involved in the transport and maintenance of reduced glutathione, an antioxidant that plays an important role in protecting against inflammation caused by oxidative stress (39). Enhancement of intracellular levels of cGMP by way of guanylate cyclase activation or by way of inhibition of cGMP-specific phosphodiesterase would be expected to down-regulate these inflammatory stimuli. Thus, uroguanylin-type agonists should be useful in the prevention and treatment of inflammatory diseases of the lung (*e.g.*, asthma), bowel (*e.g.*, ulcerative colitis and Crohn's disease), pancreas and other organs.

Overall, it may be concluded that agonists of guanylate cyclase receptor such as uroguanylin have potential therapeutic value in the treatment of a wide variety of inflammatory conditions, cancer (particularly colon cancer) and as anti-metastatic agents. The development of new agonists is therefore of substantial clinical importance.

Summary of the Invention

The present invention is based upon the development of new agonists of guanylate cyclase receptor, and new uses of naturally occurring agonists. The agonists are analogs of

uroguanylin, many of which have superior properties either in terms of improved receptor activation, stability, activity at low pH or reduced adverse effects. The peptides may be used to treat any condition that responds to enhanced intracellular levels of cGMP. Intracellular levels of cGMP can be increased by enhancing intracellular production of cGMP and/or by inhibition of its degradation by cGMP-specific phosphodiesterases. Among the specific conditions that can be treated or prevented are inflammatory conditions, cancer, polyps, and metastasis.

In its first aspect, the present invention is directed to a peptide consisting essentially of the amino acid sequence of any one of SEQ ID NOs:2-21 and to therapeutic compositions which contain these peptides. The term "consisting essentially of" includes peptides that are identical to a recited sequence identification number and other sequences that do not differ substantially in terms of either structure or function. For the purpose of the present application, a peptide differs substantially if its structure varies by more than three amino acids from a peptide of SEQ ID NOs:2-21 or if its activation of cellular cGMP production is reduced or enhanced by more than 50%. Preferably, substantially similar peptides should differ by no more than two amino acids and not differ by more than about 25% with respect to activating cGMP production. The most preferred peptide is a bicycle having the sequence of SEQ ID NO:20.

The peptides may be in a pharmaceutical composition in unit dose form, together with one or more pharmaceutically acceptable excipients. The term "unit dose form" refers to a single drug delivery entity, *e.g.*, a tablet, capsule, solution or inhalation formulation. The amount of peptide present should be sufficient to have a positive therapeutic effect when administered to a patient (typically, between 100 μg and 3 g). What constitutes a "positive therapeutic effect" will depend upon the particular condition being treated and will include any significant improvement in a condition readily recognized by one of skill in the art. For example, it may constitute a reduction in inflammation, a shrinkage of polyps or tumors, a reduction in metastatic lesions, etc.

The invention also encompasses combination therapy utilizing a guanylate cyclase receptor agonist administered either alone or together with an inhibitor of cGMP-dependent phosphodiesterase, an anti-inflammatory agent or an anticancer agent. These agents should be present in amounts known in the art to be therapeutically effective when administered to a

patient. Anti-neoplastic agents may include alkylating agents, epipodophyllotoxins, nitrosoureas, antimetabolites, vinca alkaloids, anthracycline antibiotics, nitrogen mustard agents, and the like. Particular anti-neoplastic agents may include tamoxifen, taxol, etoposide and 5-fluorouracil. Antiviral and monoclonal antibody therapies may be combined with chemotherapeutic compositions comprising at least one guanylate cyclase receptor agonist in devising a treatment regimen tailored to a patient's specific needs.

In another aspect, the invention is directed to a method for preventing, treating or retarding the onset of cancer, particularly cancer of epithelial cells, or polyps in a subject by administering a composition comprising an effective amount of a guanylate cyclase receptor agonist, preferably a synthetic guanylate cyclase receptor agonist. The term "effective amount" refers to sufficient agonist to measurably increase intracellular levels of cGMP. The term "synthetic" refers to a peptide created to bind a guanylate cyclase receptor, but containing certain amino acid sequence substitutions not present in known endogenous guanylate cyclase agonists, such as uroguanylin. The agonist should be a peptide selected from those defined by SEQ ID NOs:2-21 and which are listed in Tables 2 and 3. Also included in the invention are methods of treating primary cancers, other than primary colon cancer, by administering an effective dosage of a peptide selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide. Any known form of uroguanylin or guanylin can be used for this purpose, although the human peptides are preferred.

The invention also includes methods of preventing or treating tumor metastasis from a primary tumor mass. Metastatic tumor cells having guanylate cyclase receptors may be targeted by peptides generated according to the invention. In a preferred embodiment, the targeted receptor is found on cells of gastrointestinal (GI) cancers and on metastasized cells derived from those cancers. Such receptors are typically transmembrane proteins with an extracellular ligand-binding domain, a membrane-spanning domain, and an intracellular domain with guanylate cyclase activity. Although the invention is not bound by any particular mechanism of action, it is believed that the peptides will act by binding to these cellular receptors and inducing apoptosis. Metastatic tumors may also be treated by administering any known form of uroguanylin or guanylin (preferably human) or by administering *E. coli* ST peptide.

Peptides may be administered either alone or together with one or more inhibitors of cGMP dependent phosphodiesterase. Examples of cGMP dependent phosphodiesterase inhibitors include suldinac sulfone, zaprinast, and motapizone. Treatable forms of cancer include breast cancer, colorectal cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, and testicular cancer. Colon carcinogenesis may be prevented by inhibiting pre-cancerous colorectal polyp development via administration of a composition according to the invention. It is believed that the peptides should be especially effective with respect to the treatment of colon cancer and in preventing the metastasis of colon tumors.

In another aspect, the invention is directed to a method for treating, preventing, or retarding the onset of organ inflammation (*e.g.*, inflammation associated with the GI tract, asthma, nephritis, hepatitis, pancreatitis, bronchitis, or cystic fibrosis) of a subject by administering a composition comprising an agonist of a guanylate cyclase receptor that enhances intracellular production of cGMP. Preferred peptide agonists are selected from the group defined by SEQ ID NOs:2-21 shown in Tables 2 and 3, or uroguanylin, or guanylin, or *E.coli* ST peptide. These peptides may optionally be administered with one or more inhibitors of cGMP dependent phosphodiesterase, *e.g.*, suldinac sulfone, zaprinast, or motapizone. In a preferred embodiment, the invention is directed to a method of treating an inflammatory disorder in a mammalian gastrointestinal tract. The inflammatory disorder may be classified as an inflammatory bowel disease, and more particularly may be Crohn's disease or ulcerative colitis. Administration may be enteric, and employ formulations tailored to target enterocytes.

In a broader sense, the invention includes methods of inducing apoptosis in a patient by administering an effective amount of a peptide having the sequence of any one of SEQ ID NO:2 - SEQ ID NO:21, or uroguanylin, or guanylin or *E. coli* ST peptide. An "effective amount" of peptide, in this sense, refers to an amount sufficient to increase apoptosis in a target tissue. For example, sufficient peptide may be given to induce an increased rate of cell death in a neoplastic growth.

The most preferred peptide for use in the methods described above is the peptide defined by SEQ ID NO:20. The sequence is as follows (see also Table 3):

$$\underset{}{\text{Asn}^{1}}\ \underset{}{\text{Asp}^{2}}\ \underset{}{\text{Glu}^{3}}\ \underset{*}{\text{Cys}^{4}}\ \underset{}{\text{Glu}^{5}}\ \underset{}{\text{Leu}^{6}}\ \underset{**}{\text{Cys}^{7}}\ \underset{}{\text{Val}^{8}}\ \underset{}{\text{Asn}^{9}}\ \underset{}{\text{Val}^{10}}\ \underset{}{\text{Ala}^{11}}\ \underset{*}{\text{Cys}^{12}}\ \underset{}{\text{Thr}^{13}}\ \underset{}{\text{Gly}^{14}}\ \underset{**}{\text{Cys}^{15}}\ \underset{}{\text{Leu}^{16}}$$

and wherein there is one disulfide linkage between the cysteine at position 4 and the cysteine at position 12; and a second disulfide linkage between the cysteine at position 7 and the cysteine at position 15 (SEQ ID NO:20). This peptide has been found to have enhanced biological activity as an agonist of cGMP production due to its enhanced binding constant for the guanylate cyclase receptor, and is superior to uroguanylin with regard to temperature and protease stability and with regard to its biological activity at the physiologically favorable pH range (pH 6 to 7) in the large intestine.

The guanylate cyclase receptor agonists used in the methods described above may be administered either orally, systemically or locally. Dosage forms include preparations for inhalation or injection, solutions, suspensions, emulsions, tablets, capsules, topical salves and lotions, transdermal compositions, other known peptide formulations and pegylated peptide analogs. An effective dosage of the composition will typically be between about 1 μg and about 10 mg per kilogram body weight, preferably between about 10 μg to 5 mg of the compound per kilogram body weight. Adjustments in dosage will be made using methods that are routine in the art and will be based upon the particular composition being used and clinical considerations. Agonists may be administered as either the sole active agent or in combination with other drugs, *e.g.*, an inhibitor of cGMP-dependent phosphodiesterase. In all cases, additional drugs should be administered at a dosage that is therapeutically effective using the existing art as a guide. Drugs may be administered in a single composition or sequentially.

Detailed Description of the Invention

The present invention is based upon several concepts. The first is that there is a cGMP-dependent mechanism which regulates the balance between cellular proliferation and apoptosis and that a reduction in cGMP levels, due to a deficiency of uroguanylin/guanylin and/or due to the activation of cGMP-specific phosphodiesterases, is an early and critical step in neoplastic transformation. A second concept is that the release of arachidonic acid from membrane phospholipids, which leads to the activation of $cPLA_2$, COX-2 and possibly 5-lipoxygenase during the process of inflammation, is down-regulated by a cGMP-dependent mechanism, leading to reduced levels of prostaglandins and leukotrienes, and that increasing intracellular levels of cGMP may therefore produce an anti-inflammatory response. In addition, a cGMP-dependent mechanism, is thought to be involved in the control of proinflammatory processes. Therefore, elevating intracellular levels of cGMP may be used as a means of treating and

controlling inflammatory bowel diseases such as ulcerative colitis and Crohn's disease and other organ inflammation (*e.g.*, associated with asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis).

Without intending to be bound by any theory, it is envisioned that ion transport across the plasma membrane may prove to be an important regulator of the balance between cell proliferation and apoptosis that will be affected by compositions altering cGMP concentrations. Uroguanylin has been shown to stimulate K^+ efflux, Ca^{++} influx and water transport in the gastrointestinal tract (3). Moreover, atrial natriuretic peptide (ANP), a peptide that also binds to a specific guanylate cyclase receptor, has also been shown to induce apoptosis in rat mesangial cells, and to induce apoptosis in cardiac myocytes by a cGMP mechanism (26-29). It is believed that binding of the present agonists to a guanylate cyclase receptor stimulates production of cGMP. This ligand-receptor interaction, via activation of a cascade of cGMP-dependent protein kinases and CFTR, is then expected to induce apoptosis in target cells. Therefore, administration of the novel peptides defined by SEQ ID NOs:2-21, as shown in Tables 2 and 3, or uroguanylin, or guanylin or *E. coli* ST peptide is expected to eliminate or, at least retard, the onset of inflammatory diseases of the GI tract and general organ inflammation (*e.g.*, asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis).

In another aspect, the invention is directed to a method for preventing, treating or retarding the onset of cancer, particularly cancer of epithelial cells, in a subject by administering a composition comprising an effective amount of a guanylate cyclase receptor agonist, preferably a synthetic a guanylate cyclase receptor agonist. The term "effective amount" refers to sufficient agonist to measurably increase intracellular levels of cGMP. The term "synthetic" refers to a peptide created to bind a guanylate cyclase receptor, but containing certain amino acid sequence substitutions not present in known endogenous guanylate cyclase agonists, such as uroguanylin. The agonist should be a peptide selected from those defined by SEQ ID NOs:2-21 and which are listed in Tables 2 and 3. Also included in the invention are methods of treating primary and metastatic cancers, other than primary colon cancer, by administering an effective dosage of a peptide selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide. Any known form of uroguanylin or guanylin can be used for this purpose, although the human peptides are preferred.

The cGMP-dependent mechanism that regulates the balance between cellular proliferation and apoptosis in metastatic tumor cells may serve as a mechanism for targeting and treating metastatic tumors. The liver is the most common site of metastasis from a primary colorectal cancer. Toward later stages of disease, colorectal metastatic cells may also invade other parts of the body. It is important to note that metastatic cells originating from the primary site in the gastrointestinal tract typically continue to express guanylate cyclase receptors and therefore, these cells should be sensitive to apoptosis therapy mediated by intestinal guanylate cyclase receptors. Peptides having uroguanylin activity, when used either alone or in combination with specific inhibitors of cGMP-phosphodiesterase, also retard the onset of carcinogenesis in gut epithelium by restoring a healthy balance between cell proliferation and apoptosis via a cGMP-mediated mechanism.

As used herein, the term "guanylate cyclase receptor" refers to the class of guanylate cyclase receptors on any cell type to which the inventive agonist peptides or natural agonists described herein bind.

As used herein, the term "guanylate cyclase receptor-agonist" refers to peptides and/or other compounds that bind to a guanylate cyclase receptor and stimulate cGMP production. The term also includes all peptides that have amino acid sequences substantially equivalent to at least a portion of the binding domain comprising amino acid residues 3-15 of SEQ ID NO:1. This term also covers fragments and pro-peptides that bind to guanylate cyclase receptor and stimulate cGMP production. The term "substantially equivalent" refers to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide's ability to bind to a guanylate cyclase receptor and stimulate cGMP production.

Strategy and design of novel guanylate cyclase receptor agonists

Uroguanylin is a peptide secreted by the goblet and other epithelial cells lining the gastrointestinal mucosa as pro-uroguanylin, a functionally inactive form. The human pro-peptide is subsequently converted to the functionally active 16 amino acid peptide set forth in SEQ ID NO:1 (human uroguanylin sequence, see Table 2) in the lumen of the intestine by endogenous proteases. Since uroguanylin is a heat-resistant, acid-resistant, and proteolysis-resistant peptide, oral or systemic administration of this peptide and/or other peptides similar to

the functionally active 16 amino acid peptide sequence of SEQ ID NO:1 may be effectively employed in treatment methods.

Peptides similar to, but distinct from, uroguanylin are described below, including some which produce superior cGMP enhancing properties and/or other beneficial characteristics (*e.g.*, improved temperature stability, enhanced protease stability, or superior activity at preferred pH's) compared to previously known uroguanylin peptides. The peptides may be used to inhibit GI inflammation and for treating or preventing the onset of polyp formation associated with gut inflammation. Epithelial tissues susceptible to cancer cell formation may also be treated. The guanylate cyclase receptor agonists described have the amino acid sequences shown in Tables 2 and 3. The "binding domain" for agonist-receptor interaction includes the amino acid residues from 3-15 of SEQ ID NO:1.

Molecular modeling was applied to the design of novel guanylate cyclase receptor agonists using methods detailed in (30). It consisted of energy calculations for three compounds known to interact with guanylate cyclase receptors, namely for human uroguanylin, bicyclo [4,12; 7,15]Asn^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16} (UG, SEQ ID NO:1); human guanylin, bicyclo [4,12; 7,15]Pro^{1}-Gly^{2}-Thr^{3}-Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Tyr^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15} (GU, SEQ ID NO:22); and *E. coli* small heat-stable enterotoxin, tricyclo [6,10; 7,15; 11-18] Asn^{1}-Ser^{2}-Ser^{3}-Asn^{4}-Tyr^{5}-Cys^{6}-Cys^{7}-Glu^{8}-Leu^{9}-Cys^{10}-Cys^{11}-Asn^{12}-Pro^{13}-Ala^{14}-Cys^{15}-Thr^{16}-Gly^{17}-Cys^{18}-Tyr^{19} (ST, SEQ ID NO:23). Geometrical comparisons of all possible low-energy conformations for these three compounds were used to reveal the common 3D structures that served as the "templates" for the bioactive conformation, i.e., for the conformation presumably adopted by GU, UG and ST during interaction with receptor. It allowed designing novel analogs with significantly increased conformational population of the bioactive conformation at the expense of other low-energy conformations by selecting individual substitutions for various amino acid residues.

Energy calculations were performed by use of build-up procedures (30). The ECEPP/2 potential field (31,32) was used assuming rigid valence geometry with planar *trans*-peptide bonds, including that for Pro^{13} in ST. The ω angle in Pro^{13} was allowed to vary. Aliphatic and

aromatic hydrogens were generally included in united atomic centers of CH_n type; H^{α}-atoms and amide hydrogens were described explicitly.

The main calculation scheme involved several successive steps. First, the sequences of the two monocyclic model fragments (three fragments for ST), Ac-*cyclo* (Cys^i -...-Cys^j) -NMe, were considered, where all residues except Cys, Gly and Pro were replaced by alanines; the i and j values corresponded to the sequences of GU, UG and ST. At this step, all possible combinations of local minima for the peptide backbone for each amino acid residue were considered, *i.e.*, the minima in the Ramachandran map of *E, F, C, D, A* and A^* types (according to the notation in (33)) for the Ala residue; of E^*, F^*, C^*, D^*, *A, E, F, C D* and A^* types for the Gly residue; and of *F, C* and *A* types for Pro. For each backbone conformation, one optimal possibility to close a cycle employing the parabolic potential functions, intrinsic to the ECEPP force field, was found by checking an energy profile of rotation around the dihedral angle $\chi 1$ for the D-Cys residue.

Totally, as many as *ca.* 180,000 conformations for each of the cyclic moieties were considered. Then, the conformers satisfying the $E - E_{min} < \Delta E = 15$ kcal/mol criterion and differing by more than 40° in at least one value of any backbone dihedral angle were selected (from *ca.* 3,000 to 8,000 conformations for different model fragments). At the next step, the selected conformations of the matching monocyclic fragments were overlapped to create possible conformations of the bicyclic model fragments (the tricyclic fragments in the case of ST). Typically, this procedure yielded *ca.* 20,000–30,000 conformations. All these conformations were submitted for a new cycle of energy calculations, which resulted in 191 conformations satisfying the $E - E_{min} < \Delta E = 20$ kcal/mol criterion for the ST model fragment and in 6,965 conformations satisfying the same criterion for the GU/UG model fragment. After that, the missing side chains in the model fragments were restored, and energy calculations were performed again, the dihedral angle values of side chain groups (except the $\chi 1$ angle for the Cys residues) and of the terminal groups of the backbone being optimized before energy minimization to achieve their most favorable spatial arrangements, employing an algorithm previously described (34). For the UG 4-15 fragment, 632 conformations satisfied the criterion of $\Delta E = 20$ kcal/mol; 164 of them satisfied the more stringent criterion of $\Delta E = 12$ kcal/mol, which corresponds to the accepted criterion of 1 kcal/mol/residue (30). Subsequent elongation

of the UG 4-15 fragment to 3-16, and then to the entire UG molecule was performed by the same build-up procedure. Finally, 31 backbone conformations of UG were found as satisfying the criterion of $\Delta E = 16$ kcal/mol.

Geometrical comparison of conformers was performed in the following manner. The best fit in the superposition for the atomic centers in a pair of conformers was assessed to check the level of geometrical similarity between the two conformers, according to (35). The criterion for geometrical similarity was the rms value, which was calculated for a pair of conformations A and B as follows:

$$rms = (1/N)\,\Sigma^{N}_{i=1}\,[(x^{A}_{i} - x^{B}_{i})^2 + (y^{A}_{i} - y^{B}_{i})^2 + (z^{A}_{i} - z^{B}_{i})^2]^{1/2},$$

where N is the number of the C^{α}-atom pairs chosen for superposition, and x, y and z are the Cartesian coordinates. By the criterion of geometrical similarity of rms < 2.0 Å, low-energy conformations of the rigid conformational fragment UG 4-15 fell into seven conformational families. One of them consists of the same six conformers that are similar both to 1UYA and 1ETN; this family contains also the lowest-energy conformer of UG. (1UYA and 1ETN are the experimentally defined 3D structures of UG and ST, respectively, which are known to possess high biological activity (36,37); the 3D structures were available in the Protein Data Bank.)

Table 1. The values of dihedral angles (in degrees) for peptide backbone in the "template" conformation of UG

		Conformer's #					
Residue	Angle	1	3	9	22	25	27
Cys^4	ψ	-37	-41	-40	-55	-38	-54
Glu^5	ϕ	-71	-67	-72	-69	-68	-70
	ψ	-50	-47	-48	-33	-43	-22
Leu^6	ϕ	-86	-86	-85	-81	-88	-91
	ψ	163	165	160	153	160	156
Cys^7	ϕ	-79	-82	-79	-83	-79	-81
	ψ	74	68	78	67	75	72
Val^8	ϕ	-120	-114	-126	-124	-125	-128
	ψ	-65	-57	-62	-55	-60	-64
Asn^9	ϕ	-83	-95	-82	-88	-89	-82
	ψ	119	113	134	118	111	116

Val^{10}	ϕ	-84	-82	-97	-90	-82	-82
	ψ	-21	-13	-16	-4	-15	-16
Ala^{11}	ϕ	-79	-86	-87	-89	-85	-80
	ψ	-32	-21	-35	-35	-18	-27
Cys^{12}	ϕ	-86	-92	-78	-79	-95	-90
	ψ	-52	-53	-55	-57	-53	-54
Thr^{13}	ϕ	-129	-121	-127	-119	-118	-130
	ψ	111	153	141	155	141	119
Gly^{14}	ϕ	-64	-78	-78	-80	-78	-68
	ψ	83	64	68	62	67	78
Cys^{15}	ϕ	-139	-160	-150	-156	-78	-131

The dihedral angles ϕ and ψ, values that determine the overall 3D shape of this UG fragment, are similar (Table 1). It allowed performing preliminary design of new analogs aimed at stabilizing this particular family of conformations employing the known local conformational limitations imposed by various types of amino acids.

For instance, it is known that Gly is more conformationally flexible compared to any other L-amino acid residue, since Gly may adopt conformations with any of the four combinations of signs for ϕ and ψ, *i.e.*, -,+; -,-; +,+; and +,-. The last combination is sterically forbidden for the L-amino acids, as Ala. Therefore, substitution of Gly^{14} for Ala^{14} should limit conformational flexibility in position 14 preserving the conformations described in Table 1. Also, substitution for Aib (α-Me-Ala, di-α-methyl-alanine) should limit the local conformational flexibility by two regions only, namely for -,- and +,+, the first one being compatible with conformers of Ala^{11} in Table 1. Therefore, one more desirable substitution is Aib^{11}. In Pro, the ϕ value is fixed at -75°; this residue is also similar to valine by its hydrophobic properties. Therefore, Val^{10} may be replaced by Pro^{10}, which adds more local conformational constraints to the UG conformers in Table 1. Replacement by Pro also requires that the preceding residue possesses only positive ψ values; Asn^{9} in Table 1 fulfills this requirement. The Pro residue already exists in the corresponding position of ST. All suggested substitutions within SEQ ID NO:1 shown below (*e.g.*, Pro^{10}, Aib^{11} or Ala^{14}) do not change the chemical nature of the non-aliphatic amino acids (such as Asn, Asp or Thr), which may be

important for the actual interaction with receptor. The former substitutions should lead only to conformational limitations shifting conformational equilibrium in UG towards the suggested "template" 3-D shape.

Based on the 3D structures defined in Table 1, a three-dimensional pharmacophore for uroguanylin was defined, enabling the determination of distances between functional groups of uroguanylin thought to directly interact with the receptor. Those groups thought to directly interact with the receptor are side groups of residues in positions 3, 5, 9 and 13 of the backbone sequence. Preferably, the residues are Glu3, Glu5, Asn9, and Thr13, as shown in SEQ ID NO:2 and SEQ ID NO:20. Thus, a three dimensional pharmacophore of uroguanylin is described in which the spatial arrangement of the four side chains of the residues at positions 3, 5, 9 and 13 may be created such that the distances between these side chains enable optional biological activity. Those distances (measured as distances between Cβ atoms of corresponding residues) are as follows: from 5.7 to 7.6 Å for the 3-5 distance, from 4.0 to 6.0 Å for 3-9; from 7.7 to 8.3 Å for 3-13, from 9.4 to 9.5 Å for 5-9, from 9.4 to 9.5 Å for 5-13, and from 5.8 to 6.3 Å for 9-13.

The distances above depend only on conformations of the peptide backbone. In some cases, however, conformations of side chains themselves are also important. For instance, calculations showed that there is no conformational difference between the backbones of UG (SP301), [Glu^2]-UG (SP303), [Glu^3]-UG (SP304) and [Glu^2, Glu3]-UG (SP302) in terms of their low-energy conformations. However, there is a distinct difference in the spatial positions of the β-carboxyls of Asp and γ-carboxyls of Glu in position 3. Namely, γ-carboxyls of the Glu residues in position 3 are clearly stretched "outwards" of the bulk of the molecules farther than the corresponding β-carboxyls of the Asp residues. The above observation strongly suggests that the negatively charged carboxyl group of the side chain in position 3 specifically interacts with a positively charged binding site on the receptor; therefore, analogs containing Glu3 instead of Asp3 should be more active. At the same time, to ensure efficiency of this particular interaction, an entire system of the long-range electrostatic interactions between ligand and receptor should be well balanced. Since the Glu^2 side chain presents more conformational possibilities compared to the Asp^2 side chain, this balance may be slightly changed in SP302 (double substitution of Asp's for Glu's) compared to SP304 (single substitution of Asp^3 for Glu^3).

Compounds capable of adopting low-energy conformations described in Table 1 are listed in Table 2. All compounds are [4,12; 7,15] bicycles.

Table 2

1. Parent compound: uroguanylin

SEQ ID NO:1

Asn[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]

2. Compounds without modifications of cysteines:

Common sequence (SEQ ID NO:2):

Asn[1]-**Aaa[2]**-**Bbb[3]**-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-**Xxx[10]**-**Yyy[11]**-Cys[12]-Thr[13]-**Zzz[14]**-Cys[15]-Leu[16]

where Aaa = Asp, Glu; Bbb = Asp, Glu

with the exception that Aaa and Bbb are not both Asp in same molecule

And where Xxx = Val, Pro; Yyy = Ala, Aib; Zzz = Gly, Ala

3. Compounds with mercaptoproline (Mpt) substituted for cysteine in position 7:

Common sequence (SEQ ID NO:3):

Asn[1]-**Aaa[2]**-**Bbb[3]**-Cys[4]-Glu[5]-Leu[6]-**Mpt[7]**-Val[8]-Asn[9]-**Xxx[10]**-**Yyy[11]**-Cys[12]-Thr[13]-**Zzz[14]**-Cys[15]-Leu[16]

where Aaa = Asp, Glu; Bbb = Asp, Glu

where Xxx = Val, Pro; Yyy = Ala, Aib; Zzz = Gly, Ala

4. Compounds with penicillamines (β,β-dimethylcysteines, Pen) substituted for cysteines:

Common sequence (SEQ ID NO:4):

Asn[1]-**Aaa[2]**-**Bbb[3]**-**Kkk[4]**-Glu[5]-Leu[6]-**Lll[7]**-Val[8]-Asn[9]-**Xxx[10]**-**Yyy[11]**-**Mmm[12]**-Thr[13]-**Zzz[14]**-**Nnn[15]**-Leu[16]

where Aaa = Asp, Glu; Bbb = Asp, Glu

where Xxx = Val, Pro; Yyy = Ala, Aib; Zzz = Gly, Ala

and Kkk, Lll, Mmm and Nnn are either Cys or Pen (except not all are Cys in the same conformer)

5. Compounds with lactam bridges substituted for disulfide bridges:

Common sequence (SEQ ID NO:5):

Asn[1]-**Aaa[2]**-**Bbb[3]**-**Kkk[4]**-Glu[5]-Leu[6]-**Lll[7]**-Val[8]-Asn[9]-**Xxx[10]**-**Yyy[11]**-**Mmm[12]**-Thr[13]-**Zzz[14]**-**Nnn[15]**-Leu[16]

where Aaa = Asp, Glu; Bbb = Asp, Glu

where Xxx = Val, Pro; Yyy = Ala, Aib; Zzz = Gly, Ala;

and all combinations of the following (Dpr is diaminopropionic acid):

Kkk is Dpr and Mmm is either Asp or Glu;

Kkk is either Asp or Glu, and Mmm is Dpr;

Lll is either Cys or Pen;

Nnn is either Cys or Pen;

or:

Lll is Dpr and Nnn is either Asp or Glu;

Lll is either Asp or Glu, and Nnn is Dpr;

Kkk is either Cys or Pen;

Mmm is either Cys or Pen.

Some of the peptides shown in Table 2 contain 16 amino acid residues in which cysteine residues form disulfide bridges between Cys[4] and Cys[12], and Cys[7] and Cys[15], respectively. These peptides differ from the peptide sequences described in WO 01/25266, and are designed on the basis of peptide conformation and energy calculations.

In addition, peptides, varying in length from 13 to 16 amino acids, shown in Table 3, are designed, based on energy calculations and three-dimensional structures, to promote stabilization of the biologically active conformer and minimize or eliminate interconversion to biologically inactive conformers. These peptides are also designed to promote stability against proteolysis and higher temperatures. The design of these peptides involves modifications of amino acid residues that contain ionic charges at lower pH values, such as glutamic and aspartic acids.

Table 3

SEQ ID NO:6	X1 Glu Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:7	X1 Glu Asp Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:8	X1 Asp Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:9	X1 Asp Asp Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:10	X1 Glu Glu Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:11	X1 Asp Glu Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:12	X1 Glu Asp Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:13	X1 Asp Asp Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:14	X1 Glu Glu Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:15	X1 Asp Glu Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:16	X1 Glu Asp Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9
SEQ ID NO: 17	Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9
SEQ ID NO: 18	Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys
SEQ ID NO: 19	X1 Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
SEQ ID NO:20	Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
SEQ ID NO:21	Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

X1 to X9 can be any amino acid. The disulfide bridges are formed between Cys residues at 4 and 12 and between 7 and 15, respectively. SEQ ID NO:18 represents the minimum length requirement for these peptides to bind a guanylate cyclase receptor.

Pharmaceutical Compositions and Formulations

The guanylate cyclase receptor agonists of the present invention (Table 2; SEQ ID NOs:2-5 and Table 3; SEQ ID NOs:6-21), as well as uroguanylin, guanylin and/or bacterial enterotoxin ST, may be combined or formulated with various excipients, vehicles or adjuvants for oral, local or systemic administration. Peptide compositions may be administered in solutions, powders, suspensions, emulsions, tablets, capsules, transdermal patches, ointments, or other formulations. Formulations and dosage forms may be made using methods well known

in the art (see, *e.g.*, Remington's Pharmaceutical Sciences, 16th ed., A. Oslo ed., Easton, PA (1980)).

Inhibitors of cGMP-dependent phosphodiesterase may be small molecules, peptides, proteins or other compounds that specifically prevent the degradation of cGMP. Inhibitory compounds include suldinac sulfone, zaprinast, motapizone and other compounds that block the enzymatic activity of cGMP-specific phosphodiesterases. One or more of these compounds may be combined with a guanylate cyclase receptor agonist exemplified in SEQ ID NOs:2-21, uroguanylin, guanylin and *E. coli* ST peptide.

The selection of carriers (*e.g.*, phosphate-buffered saline or PBS) and other components suitable for use in compositions is well within the level of skill in this art. In addition to containing one or more guanylate cyclase receptor agonists, such compositions may incorporate pharmaceutically acceptable carriers and other ingredients known to facilitate administration and/or enhance uptake. Other formulations, such as microspheres, nanoparticles, liposomes, pegylated protein or peptide, and immunologically-based systems may also be used. Examples include formulations employing polymers (*e.g.*, 20% w/v polyethylene glycol) or cellulose, or enteric formulations and pegylated peptide analogs for increasing systemic half-life and stability.

Treatment Methods

The term "treatment" refers to reducing or alleviating symptoms in a subject, preventing symptoms from worsening or progressing, or preventing disease development. For a given subject, improvement in a symptom, its worsening, regression, or progression may be determined by any objective or subjective measure typically employed by one of skill in the art. Efficacy of the treatment in the case of cancer may be measured as an improvement in morbidity or mortality (*e.g.*, lengthening of the survival curve for a selected population). Thus, effective treatment would include therapy of existing disease, control of disease by slowing or stopping its progression, prevention of disease occurrence, reduction in the number or severity of symptoms, or a combination thereof. The effect may be shown in a controlled study using one or more statistically significant criteria.

Combination therapy with one or more medical/surgical procedures and/or at least one other chemotherapeutic agent may be practiced with the invention. Other suitable agents useful in combination therapy include anti-inflammatory drugs such as, for example, steroids or non-steroidal anti-inflammatory drugs (NSAIDS), such as aspirin and the like. Prophylactic methods for preventing or reducing the incidence of relapse are also considered treatment.

Cancers expected to be responsive to compositions include breast, colorectal, lung, ovarian, pancreatic, prostatic, renal, stomach, bladder, liver, esophageal and testicular carcinoma. Further examples of diseases involving cancerous or precancerous tissues that should be responsive to a therapeutic comprising at least one guanylate cyclase receptor agonist include: carcinoma (*e.g.*, basal cell, basosquamous, Brown-Pearce, ductal, Ehrlich tumor, in situ, Krebs, Merkel cell, small or non-small cell lung, oat cell, papillary, bronchiolar, squamous cell, transitional cell, Walker), leukemia (*e.g.*, B-cell, T-cell, HTLV, acute or chronic lymphocytic, mast cell, myeloid), histiocytoma, histiocytosis, Hodgkin disease, non-Hodgkin lymphoma, plasmacytoma, reticuloendotheliosis, adenoma, adeno-carcinoma, adenofibroma, adenolymphoma, ameloblastoma, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, sclerosing angioma, angiomatosis, apudoma, branchioma, malignant carcinoid syndrome, carcinoid heart disease, carcinosarcoma, cementoma, cholangioma, cholesteatoma, chondrosarcoma, chondroblastoma, chondrosarcoma, chordoma, choristoma, craniopharyngioma, chrondroma, cylindroma, cystadenocarcinoma, cystadenoma, cystosarcoma phyllodes, dysgerminoma, ependymoma, Ewing sarcoma, fibroma, fibro-sarcoma, giant cell tumor, ganglioneuroma, glioblastoma, glomangioma, granulosa cell tumor, gynandroblastoma, hamartoma, hemangioendothelioma, hemangioma, hemangio-pericytoma, hemangiosarcoma, hepatoma, islet cell tumor, Kaposi sarcoma, leiomyoma, leiomyosarcoma, leukosarcoma, Leydig cell tumor, lipoma, liposarcoma, lymphangioma, lymphangiomyoma, lymphangiosarcoma, medulloblastoma, meningioma, mesenchymoma, mesonephroma, mesothelioma, myoblastoma, myoma, myosarcoma, myxoma, myxosarcoma, neurilemmoma, neuroma, neuroblastoma, neuroepithelioma, neurofibroma, neurofibromatosis, odontoma, osteoma, osteosarcoma, papilloma, paraganglioma, paraganglioma nonchromaffin, pinealoma, rhabdomyoma, rhabdomyosarcoma, Sertoli cell tumor, teratoma, theca cell tumor, and other diseases in which cells have become dysplastic, immortalized, or transformed.

A bolus of the inventive composition may be administered over a short time. Once a day is a convenient dosing schedule to treat, *inter alia*, one of the above-mentioned disease states. Alternatively, the effective daily dose may be divided into multiple doses for purposes of administration, for example, two to twelve doses per day. The dose level selected for use will depend on the bioavailability, activity, and stability of the compound, the route of administration, the severity of the disease being treated, and the condition of the subject in need of treatment. It is contemplated that a daily dosage will typically be between about 10 μg and about 2 mg (*e.g.*, about 100 μg to 1 mg) of the compound per kilogram body weight. The amount of compound administered is dependent upon factors known to a person skilled in this art such as, for example, chemical properties of the compound, route of administration, location and type of cancer, and the like. The subject mammal may be any animal or human patient. Thus, both veterinary and medical treatments are envisioned according to the invention.

The invention will be further described by the following non-limiting example.

EXAMPLE

Materials and Methods

Cell Culture: Human T84 colon carcinoma cells were obtained from the American Type Culture Collection at passage 52. Cells were grown in a 1:1 mixture of Ham's F-12 medium and Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 100 U penicillin/ml, and 100 μg/ml streptomycin. The cells were fed fresh medium every third day and split at a confluence of approximately 80%.

T84 cell-based assay for determining the intracellular levels of cGMP: Peptide analogs were custom synthesized by Multiple Peptide Systems, San Diego, CA., and by Princeton Biomolecules, Langhorne, PA. Biological activity of the synthetic peptides was assayed as previously reported (15). Briefly, the confluent monolayers of T-84 cells in 24-well plates were washed twice with 250 μl of DMEM containing 50 mM HEPES (pH 7.4), pre-incubated at 37°C for 10 min with 250 μl of DMEM containing 50 mM HEPES (pH 7.4) and 1 mM isobutylmethylxanthine (IBMX), followed by incubation with peptide analogs (0.1 nM to 10 μM) for 30 min. The medium was aspirated, and the reaction was terminated by the addition of

3% perchloric acid. Following centrifugation, and neutralization with 0.1 N NaOH, the supernatant was used directly for measurements of cGMP using an ELISA kit (Caymen Chemical, Ann Arbor, MI.).

Results

Peptides shown in Table 4 were custom synthesized and purified (>95% purity) using a published procedure (38). Peptide analogs were evaluated in the T84 cell-based assay for their ability to enhance intracellular levels of cGMP. As shown in Table 4, SP304 (SEQ ID NO:20) gave the greatest enhancement of intracellular cGMP of all the analogs tested. SP316 (SEQ ID NO:21) was second in effectiveness, whereas the biological activities of SP301, SP302 and SP303 were all somewhat weaker. The peptide analogs SP306 and SP310 were not active in this assay. These results indicate that SP304 is the most potent peptide for enhancing cGMP. These results also suggest that the cysteine residue at position 7 cannot be substituted with penicillamine as a component of the [7,15] disulfide linkage, and that the Asn residue at position 9 cannot be changed to a Gln.

Table 4: Peptide agonists evaluated for biological activity in the T84 cell bioassay.

SEQ ID NO.*	Compound Code	cGMP Level** (pmol/well)
1	SP 301	205
6	SP 302	225
7	SP 303	195
20	SP 304	315
14	SP 306	0
4	SP 310	0
21	SP 316	275

* SEQ ID's for SP301, SP304 and SP316 are the precise amino acid sequences for these analogs as given in the text.

** Intracellular cGMP level observed in T84 cells following treatment with 1 micromolar solution of the respective peptide agonist for 30 minutes. The value observed for SP304 was statistically significant with a $p > 0.5$.

To examine heat stability, 10 micromolar solutions of peptide analogs were heated at 95°C for up to 90 minutes. At specific times during the treatment, samples were tested for their biological activity in the T84 cell-based assay. Biological activity of SP301, SP302, SP303 and SP304 did not change significantly after 60 minutes of heating. After 90 minutes, the activities of SP301, SP302 and SP303 were reduced to about 80% of their original values, whereas the biological activity of SP304 remained unaltered. This indicates that SP304 is more stable to heat denaturation compared to the other peptides tested. Based on energy calculations and 3D structure, we expected that the negatively charged carboxyl group of the side chain in position 3 of SEQ ID NO:1 specifically interacts with a positively charged binding site on the receptor. In the case where this interaction can be enhanced, analogs containing Glu3 instead of Asp3 should be more active, as was found to be the case with SP304. At the same time, to ensure efficiency of this particular interaction, an entire system of the long-range electrostatic interactions between ligand and receptor should be well balanced. Since the Glu^2 side chain presents more conformational possibilities compared to the Asp^2 side chain, this balance may be slightly changed in SP302 (double substitution of Asp's for Glu's) compared to SP304 (single substitution of Asp^3 for Glu^3). Indeed, biological activity of SP 304 is the best amongst the analogs evaluated.

Synthetic peptides SP301, SP302, SP303 and SP304 were also tested for their activities at different pH values of the T84 cell-based assay. Whereas all of these peptides showed enhanced intracellular production of cGMP at pH's ranging from 5 to 7, SP304 showed the greatest enhancement in the range between 6.5 and 7. It is important to note that the physiological pH of the large intestine is in a similar range, and, therefore, SP304 would be expected to be especially efficacious for colon cancer treatment.

We also evaluated peptides used either alone or in combination with inhibitors of cGMP dependent phosphodiesterase (*e.g.*, zaprinast or sulindac sulfone) in T84 cell-based assays for enhancement of intracellular levels of cGMP. Combinations of an inhibitor of cGMP dependent phosphodiesterase with SP304 displayed a dramatic effect in enhancing cGMP levels in these experiments. Synthetic peptide SP304 substantially increased the cGMP level over the level reached in the presence of either zaprinast or sulindac sulfone alone. Treatment of wells with SP304 in combination with either Zaprinast or sulindac sulfone resulted in synergistic increases in intracellular cGMP levels. These increases were statistically

significant, with p values of <0.5. These data indicate that treatments combining a peptide agonist of a guanylate cyclase receptor with one or more inhibitors of cGMP dependent phosphodiesterase result in a greater than additive increase in cGMP concentrations.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to those of ordinary skill in the art that various changes and modifications can be made without departing from the spirit and scope of the invention.

References

1. Currie, *et al.*, *Proc. Nat'l Acad. Sci. USA 89*:947-951 (1992).
2. Hamra, *et al.*, *Proc. Nat'l Acad. Sci. USA 90*:10464-10468 (1993).
3. Forte, L., *Reg. Pept. 81*:25-39 (1999).
4. Schulz, *et al.*, *Cell 63*:941-948 (1990).
5. Guba, *et al.*, *Gastroenterology 111*:1558-1568 (1996).
6. Joo, *et al.*, *Am. J. Physiol. 274*:G633-G644 (1998).
7. Evan, *et al.*, *Nature (London) 411*:342-348 (2001).
8. Eastwood, G., *J. Clin. Gastroenterol. 14*:S29-33 (1992).
9. Lipkin, M. *Arch. Fr. Mal. Appl Dig. 61*:691-693 (1972).
10. Wong, *et al.*, *Gut 50*:212-217 (2002).
11. Potten, *et al.*, *Stem Cells 15*:82-93.
12. Basoglu, *et al.*, in: Proceedings of the Second FEPS Congress, June 29-July 4, 1999, Prague, Czech Republic., http://www.lf2.cuni.cz/physiolres/feps/basoglu.htm.
13. Sindic, *et al.*, *J. Biol. Chem. March 11, 2002, manuscript M110627200 (in press).*
14. Zhang, *et al.*, *Science 276*:1268-1272 (1997).
15. Shailubhai, *et al.*, *Cancer Res. 60*:5151-5157 (2000).

16. Shailubhai, *et al.*, In: Proceedings of the 1999 AACR·NCI·EORTC International Conference. Nov. 1999, Abstract # 0734.

17. Cohen, *et al.*, *Lab. Invest. 78*:101-108 (1998).

18. Sciaky, *et al.*, *Genomics 26*:427-429 (1995).

19. Whitaker, *et al.*, *Genomics 45*:348-354 (1997).

20. Leister, *et al.*, *Cancer Res. 50*:7232-7235 (1990).

21. Cheng, *et al.*, *Cell 63*:827-834 (1990).

22. Welsh, *et al.*, *Cell 73*:1251-1254 (1993).

23. Weber, *et al.*, *Am. J. Physiol. Lung Cell Mol. Physiol. 281(1)*:L71-78 (2001).

24. Venkatakrishnan, *et al.*, *Am. J. Respir. Cell Mol. Biol. 23(3)*:396-403 (2000).

25. Hudson, *et al.*, *Free Radic. Biol. Med. 30*:1440-1461 (2001).

26. Bhakdi, *et al.*, *Infect. Immun. 57*:3512-3519 (1989).

27. Hughes, *et al.*, *J. Biol. Chem. 272*:30567-30576 (1997).

28. Cermak, *et al.*, *Pflugers Arch. 43*:571-577 (1996).

29. Wu, *et al.*, *J. Biol. Chem. 272*:14860-14866 (1997).

30. Nikiforovich, G., *Int. J. Pept. Prot. Res. 44*:513-531 (1994).

31. Dunfield, *et al.*, *J. Phys. Chem. 82*:2609-2616 (1978).

32. Nemethy, *et al.*, *J. Phys. Chem. 87*:1883-1887 (1983).

33. Zimmerman, *et al.*, *Biopolymers 16*:811-843 (1977).

34. Nikiforovich, *et al.*, *Biopolymers 31*:941-955 (1991).

35. Nyburg, S., *Acta Crystallographica B30 (part 1)*:251-253 (1974).

36. Chino, *et al.*, *FEBS Letters 421*:27-31 (1998).

37. Schulz, *et al.*, *J. Peptide Res. 52*:518-525 (1998).

38. Klodt, *et al.*, *J. Peptide Res. 50*:222-230 (1997).

39. Shailubhai, I., *Curr. Opin. Drug Discov. Devel. 5*:261-268 (2002)

What is Claimed is:

1. A peptide consisting essentially of the amino acid sequence of any one of SEQ ID NO:2 - SEQ ID NO:21.

2. The peptide of claim 1, wherein said peptide is a (4,12; 7,15) bicycle having the sequence of SEQ ID NO:20.

3. The peptide of either claim 1 or claim 2, wherein said peptide consists of the amino acid sequence of any one of SEQ ID NO:2-SEQ ID NO:21.

4. A method for preventing or treating primary or metastatic cancer or polyps in a patient comprising administering to said patient an effective dosage of a guanylate cyclase receptor agonist having the sequence of any one of SEQ ID NO:2 - SEQ ID NO:21.

5. A method for treating metastatic cancer in a patient comprising administering to said patient an effective dosage of a guanylate cyclase receptor agonist selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide.

6. A method for treating primary cancers other than colon cancer in a patient, comprising administering to said patient an effective dosage of a guanylate cyclase receptor agonist selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide.

7. The method of claim 4, wherein said peptide is a (4,12; 7,15) bicyclic peptide having the sequence of SEQ ID NO:20.

8. The method of claim 4, wherein said primary cancer is a member selected from the group consisting of the breast, colon, rectum, lung, ovary, pancreas, bladder, prostate, kidney or testis.

9. The method of any one of claims 4-8, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

10. A method of treating a patient for colon cancer or polyps comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with uroguanylin, guanylin or *E. coli* ST peptide.

11. The method of claim 9 and 10, wherein said cGMP-dependent phosphodiesterase inhibitor is selected from the group consisting of suldinac sulfone, zaprinast, and motapizone.

12. A method for preventing or treating inflammation in a patient comprising administering to said patient an effective dosage of a guanylate cyclase receptor agonist having the sequence of any one of: SEQ ID NO:2 - SEQ ID NO:21; uroguanylin; guanylin; or *E. coli* ST peptide.

13. The method of claim 12, wherein said peptide is a (4,12; 7,15) bicyclic peptide having the sequence of SEQ ID NO:20.

14. The method of claim 12, wherein said inflammation is an inflammatory disaese selected from the group consisting of: asthma; nephritis, hepatitis, pancreatitis, bronchitis and cystic fibrosis.

15. The method of claim 12, wherein said patient is treated for an inflammatory disorder of the gastrointestinal tract.

16. The method of claim 15, wherein said inflammatory disorder of the gastrointestinal tract is an inflammatory bowel disease selected from the group consisting of: ulcerative colitis and Crohn's disease.

17. The method of claim 12, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

18. The method of claim 17, wherein said cGMP-dependent phosphodiesterase is selected from the group consisting of suldinac sulfone, zaprinast, and motapizone.

19. A method of treating a patient for primary or metastatic cancer, polyps or inflammation comprising administering to said patient:

a) a guanylate cyclase receptor agonist peptide having the sequence of any one of: SEQ ID NOs:2-21; uroguanylin; guanylin; or *E. coli* ST peptide; and

b) at least one compound selected from the group consisting of: a cGMP-dependent phosphodiesterase inhibitor; an anti-inflammatory agent; an antiviral agent; and an anticancer agent;

wherein said guanylate cyclase receptor agonist and said compound are each administered in a therapeutically effective amount.

20. A pharmaceutical composition in unit dose form comprising a guanylate cyclase receptor agonist peptide having the sequence of any one of SEQ ID NOs:2-21 present in a therapeutically effective amount.

21. A pharmaceutical composition in unit dose form comprising:

a) a guanylate cyclase receptor agonist peptide having the sequence of any one of: SEQ ID NOs:2-21; uroguanylin; guanylin; or *E. coli* ST peptide; and

b) at least one compound selected from the group consisting of: a cGMP-dependent phosphodiesterase inhibitor, an anti-inflammatory agent, an antiviral agent and an anticancer agent;

wherein said guanylate cyclase receptor agonist and said compound are each present in a therapeutically effective amount.

22. The pharmaceutical composition of either claim 20 or 21, wherein the unit dose form is selected from the group consisting of a tablet, a capsule, a solution or inhalation formulation.

23. The pharmaceutical composition of either claim 20 nor 21, further comprising one or more excipients.

24. A method of inducing apoptosis in the cells of a subject, comprising administering to said subject an effective amount of agonist peptide having the sequence of any one of SEQ ID NO:2 - SEQ ID NO:21.

25. A method of inducing apoptosis in the cells of a subject, comprising administering to said subject an effective amount of uroguanylin, guanylin or *E. coli* ST peptide for cancers other than colon cancer.

26. A peptide conjugate comprising polyethylene glycol (PEG) attached to a peptide having the sequence of any of: SEQ ID NO:2 - SEQ ID NO:21; uroguanylin; guanylin; or *E. coli* ST peptide.

27. A method of treating cancer, inflammation or polyps in a patient comprising administering to said patient a therapeutically effective amount of the peptide conjugate of claim 26.

SEQUENCE LISTING

<110> SYNERGY PHARMACEUTICALS

<120> GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

<130> 81361/141030

<140>
<141>

<160> 23

<170> PatentIn Ver. 2.1

<210> 1
<211> 16
<212> PRT
<213> Homo sapiens

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<400> 1
Asn Asp Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 2
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (2)
<223> Asp or Glu

<220>
<221> MOD_RES
<222> (3)
<223> Asp or Glu

<220>

<221> MOD_RES
<222> (10)
<223> Val or Pro

<220>
<221> MOD_RES
<222> (11)
<223> Ala or Aib

<220>
<221> MOD_RES
<222> (14)
<223> Gly or Ala

<400> 2
Asn Xaa Xaa Cys Glu Leu Cys Val Asn Xaa Xaa Cys Thr Xaa Cys Leu
1 5 10 15

<210> 3
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (2)
<223> Asp or Glu

<220>
<221> MOD_RES
<222> (3)
<223> Asp or Glu

<220>
<221> MOD_RES
<222> (7)
<223> Mpt

<220>
<221> MOD_RES
<222> (10)
<223> Val or Pro

<220>
<221> MOD_RES
<222> (11)
<223> Ala or Aib

<220>
<221> MOD_RES

<222> (14)
<223> Gly or Ala

<400> 3
Asn Xaa Xaa Cys Glu Leu Xaa Val Asn Xaa Xaa Cys Thr Xaa Cys Leu
1 5 10 15

<210> 4
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (2)
<223> Asp or Glu

<220>
<221> MOD_RES
<222> (3)
<223> Asp or Glu

<220>
<221> MOD_RES
<222> (4)
<223> Cys or Pen

<220>
<221> MOD_RES
<222> (7)
<223> Cys or Pen

<220>
<221> MOD_RES
<222> (10)
<223> Val or Pro

<220>
<221> MOD_RES
<222> (11)
<223> Ala or Aib

<220>
<221> MOD_RES
<222> (12)
<223> Cys or Pen

<220>
<221> MOD_RES
<222> (14)

<223> Gly or Ala

<220>
<221> MOD_RES
<222> (15)
<223> Cys or Pen

<400> 4
Asn Xaa Xaa Xaa Glu Leu Xaa Val Asn Xaa Xaa Xaa Thr Xaa Xaa Leu
1 5 10 15

<210> 5
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (2)
<223> Asp or Glu

<220>
<221> MOD_RES
<222> (3)
<223> Asp or Glu

<220>
<221> MOD_RES
<222> (4)
<223> Dpr, Cys, Pen, Asp or Glu

<220>
<221> MOD_RES
<222> (7)
<223> Dpr, Cys, Pen, Asp or Glu

<220>
<221> MOD_RES
<222> (10)
<223> Val or Pro

<220>
<221> MOD_RES
<222> (11)
<223> Ala or Aib

<220>
<221> MOD_RES
<222> (12)
<223> Dpr, Cys, Pen, Asp or Glu

<220>
<221> MOD_RES
<222> (14)
<223> Gly or Ala

<220>
<221> MOD_RES
<222> (15)
<223> Dpr, Cys, Pen, Asp or Glu

<400> 5
Asn Xaa Xaa Xaa Glu Leu Xaa Val Asn Xaa Xaa Xaa Thr Xaa Xaa Leu
1 5 10 15

<210> 6
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 6

Xaa Glu Glu Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 7
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 7
Xaa Glu Asp Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 8
<211> 16
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 8
Xaa Asp Glu Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 9
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 9
Xaa Asp Asp Cys Xaa Xaa Cys Xaa Tyr Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 10
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES

<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 10
Xaa Glu Glu Cys Xaa Xaa Cys Xaa Tyr Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 11
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)

<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 11
Xaa Asp Glu Cys Xaa Xaa Cys Xaa Tyr Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 12
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 12
Xaa Glu Asp Cys Xaa Xaa Cys Xaa Tyr Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 13
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 13
Xaa Asp Asp Cys Xaa Xaa Cys Xaa Gln Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 14
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 14
Xaa Glu Glu Cys Xaa Xaa Cys Xaa Gln Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 15
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES

<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 15
Xaa Asp Glu Cys Xaa Xaa Cys Xaa Gln Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 16
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (10)..(11)

<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(14)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (16)
<223> Any amino acid

<400> 16
Xaa Glu Asp Cys Xaa Xaa Cys Xaa Gln Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 17
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (2)..(10)

<220>
<221> DISULFID
<222> (5)..(13)

<220>
<221> MOD_RES
<222> (3)..(4)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (11)..(12)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (14)
<223> Any amino acid

<400> 17
Glu Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10

<210> 18
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (2)..(10)

<220>
<221> DISULFID
<222> (5)..(13)

<220>
<221> MOD_RES
<222> (3)..(4)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (11)..(12)
<223> Any amino acid

<400> 18
Glu Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys
1 5 10

<210> 19
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (3)..(11)

<220>
<221> DISULFID
<222> (6)..(14)

<220>
<221> MOD_RES
<222> (1)
<223> Any amino acid
<220>

<221> MOD_RES
<222> (4)..(5)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (7)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (9)..(10)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (12)..(13)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (15)
<223> Any amino acid

<400> 19
Xaa Glu Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 20
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<400> 20
Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 21
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide

<220>
<221> DISULFID
<222> (2)..(10)

<220>
<221> DISULFID
<222> (5)..(13)

<400> 21
Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10

<210> 22
<211> 15
<212> PRT
<213> Homo sapiens

<220>
<221> DISULFID
<222> (4)..(12)

<220>
<221> DISULFID
<222> (7)..(15)

<400> 22
Pro Gly Thr Cys Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys
1 5 10 15

<210> 23
<211> 19
<212> PRT
<213> Escherichia coli

<220>
<221> DISULFID
<222> (6)..(10)

<220>
<221> DISULFID
<222> (7)..(15)

<220>
<221> DISULFID
<222> (11)..(18)

<400> 23
Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/09551

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/00, 38/00; A01N 61/00; C12Q 1/00; C07K 2/00, 4/00, 5/00, 7/00, 14/00, 16/00, 17/00; G01N 33/53, 33/48, 33/567, 574

US CL : 435/4, 7.1, 7.21, 7.23; 436/64; 514/1, 2, 10, 14; 530/300, 317

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/4, 7.1, 7.21, 7.23; 436/64; 514/1, 2, 10, 14; 530/300, 317

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

GenCore, EAST, WEST, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HILL, O. et al. A new human guanylate cyclase-activating peptide (GCAP-II, uroguanylin): precursor cDNA and colonic expression. Biochimica et Biophysica Acta, 1995, Vol 1253, pages 146-149.	1-27
Y,P	US 6,235,782 B1 (PAMUKCU et at) 22 May 2001 (22.05.2001)	9-11, 19 and 21-23
X	US 5,879,656 (WALDMAN) 9 March 1999 (9.3.1999)	5 and 6
---		---
Y		9-11, 19, 21-23 and 25-27
Y	US 5,578,709 (WOISZWILLO) 26 November 1996 (26.11.1996)	26 and 27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 August 2002 (08.08.2002)	18 SEP 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Alana M. Harris, Ph.D. Telephone No. (703)308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
12. Dezember 2002 (12.12.2002)

PCT

(10) Internationale Veröffentlichungsnummer
WO 02/098912 A3

(51) Internationale Patentklassifikation[7]: C07K 14/47, A61P 11/00, A61K 38/17, G01N 33/68, A61M 15/00

(21) Internationales Aktenzeichen: PCT/DE02/02040

(22) Internationales Anmeldedatum: 5. Juni 2002 (05.06.2002)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
101 27 119.0 5. Juni 2001 (05.06.2001) DE

(71) Anmelder und
(72) Erfinder: CETIN, Yalcin [DE/DE]; Boschhof 2, 30655 Hannover (DE). SAVAS, Yüksel [DE/DE]; Salzgitterstrasse 23, 38268 Lengede (DE).

(74) Anwalt: LÄUFER, Martina; Gramm, Lins & Partner GbR, Freundallee 13, 30173 Hannover (DE).

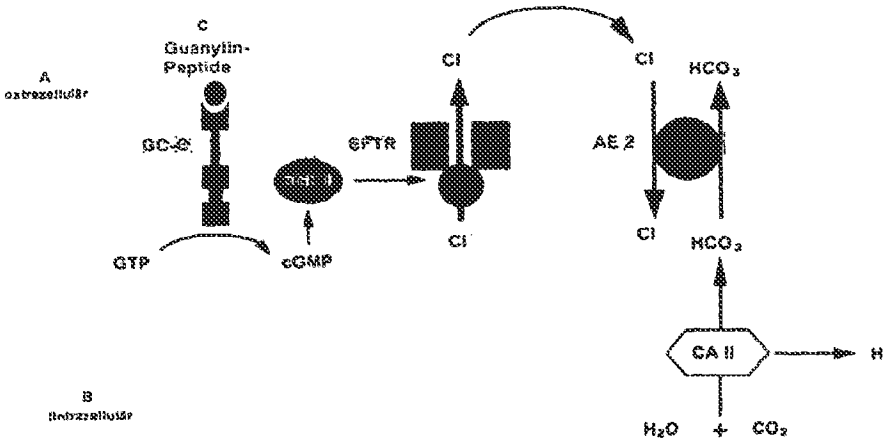
(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT,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

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

[Fortsetzung auf der nächsten Seite]

(54) Title: GUANYLATE-CYCLASE C LIGAND, ADMINISTERED VIA THE AIRWAYS, FOR THE TREATMENT OF RESPIRATORY AIRWAY PROBLEMS

(54) Bezeichnung: LUFTSEITIG VERABREICHTE GUANYLAT CYCLASE C LIGANDEN FÜR ATEMWEGSERKRANKUNGEN



(57) Abstract: The invention relates to the use of a guanylate cyclase C activated peptide for the treatment of respiratory airway problems and problems associated with ventilation disorder and/or mucous secretion disorders via the airways, in addition to a medicament which is fed via the airways. The invention also relates to an inhalation device which contains the medicament and a method for diagnosing the illnesses associated with inhalation disorders and mucous secretion disorders in the airways, by detecting a guanylate cyclase C activated peptide. The peptides which are used are guanylin, uroguanylin and lymphoguanylin or a heat resistant enterotoxin.

[Fortsetzung auf der nächsten Seite]

WO 02/098912 A3

eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Erklärungen gemäß Regel 4.17:

— *hinsichtlich der Berechtigung des Anmelders, ein Patent zu beantragen und zu erhalten (Regel 4.17 Ziffer ii) für die folgenden Bestimmungsstaaten AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *Erfindererklärung (Regel 4.17 Ziffer iv) nur für US*

Veröffentlicht:

— *mit internationalem Recherchenbericht*

(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 31. Juli 2003

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(57) Zusammenfassung: Es wird die Verwendung eines Guanylat Cyclase C aktivierenden Peptids für die Behandlung von Atemwegserkrankungen und Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimhautsekretion einhergehen, über die Luftwege vorgeschlagen, sowie eines Arzneimittels, das über die Luftwege zugeführt wird. Des weiteren wird eine Inhalationsvorrichtung, die das Arzneimittel enthält, angegeben und ein Verfahren zur Diagnose von Erkrankungen, die mit Ventilationsstörungen und Störungen der Schleimhaut in den Atemwegen einhergehen, durch Nachweis eines Gualylat Cyclase C aktivierenden Peptids. Als Peptide werden Guanylin, Uroguanylin und Lymphoguanylin oder ein hitzebeständiges Enterotoxin eingesetzt.

INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/DE 02/02040

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/47 A61P11/00 A61K38/17 G01N33/68 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, MEDLINE, EMBASE, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OHBAYASHI HIROYUKI ET AL: "Both inhalant and intravenous uroguanylin inhibit leukotriene C4-induced airway changes." PEPTIDES (NEW YORK), vol. 21, no. 10, October 2000 (2000-10), pages 1467-1472, XP002230927 ISSN: 0196-9781 abstract page 1467, left-hand column -page 1468, left-hand column, paragraph 2 page 1468, right-hand column, paragraph 2 page 1468, right-hand column, last paragraph page 1469, right-hand column, last paragraph -page 1470, left-hand column, line 6 page 1470, right-hand column, paragraph 1 - paragraph 2 figures 1,2 -/--	1-3,5-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2003	04/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hars, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 195 43 628 A (FORSSMANN WOLF GEORG) 28 May 1997 (1997-05-28) claims 1,2,10,17,19	4,12-15
A	OHBAYASHI HIROYUKI ET AL: "Effects of uroguanylin and guanylin against antigen-induced bronchoconstriction and airway microvascular leakage in sensitized guinea-pigs." LIFE SCIENCES, vol. 62, no. 20, 10 April 1998 (1998-04-10), pages 1833-1844, XP002230928 ISSN: 0024-3205 abstract page 1834, paragraph 1 - paragraph 2 page 1841, paragraph 2 -page 1842, paragraph 4	1-15
A	HOENSCHEID M ET AL: "Guanylin activates chloride currents in H441 lung epithelial cells." PFLUEGERS ARCHIV EUROPEAN JOURNAL OF PHYSIOLOGY, vol. 441, no. 6 Supplement, 2001, page R270 XP009005486 Joint Congress of the Scandinavian and the German Physiological Societies;Berlin, Germany; March 10-13, 2001 ISSN: 0031-6768 the whole document	1-15
A	CETIN YALCIN ET AL: "Bronchiolar nonciliated secretory (Clara) cells: Source of guanylin in the mammalian lung." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 92, no. 13, 1995, pages 5925-5929, XP002230929 1995 ISSN: 0027-8424 abstract page 5925, left-hand column, last paragraph -right-hand column, paragraph 1 page 5928, left-hand column, line 18 -right-hand column, line 7 page 5929, left-hand column	1-15

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ZHANG ZHI HAO ET AL: "The airway-epithelium: A novel site of action by guanylin." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 244, no. 1, 6 March 1998 (1998-03-06), pages 50-56, XP002230930 ISSN: 0006-291X abstract page 50, right-hand column, paragraph 2 page 55, left-hand column, last paragraph -right-hand column	1-15
A	ABDEL-RAZEL T ET AL: "Smooth muscle relaxation by guanylin: Implications for mediator role of cyclic GMP in vascular and airway smooth muscle relaxation." FASEB JOURNAL, vol. 8, no. 4-5, 1994, page A556 XP009005528 Experimental Biology 94, Parts I and II;Anaheim, California, USA; April 24-28, 1994 ISSN: 0892-6638 the whole document	1-15
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; April 1999 (1999-04) FORTE LEONARD R ET AL: "Lymphoguanylin: Cloning and characterization of a unique member of the guanylin peptide family." Database accession no. PREV199900204569 XP002230932 cited in the application abstract & ENDOCRINOLOGY, vol. 140, no. 4, April 1999 (1999-04), pages 1800-1806, ISSN: 0013-7227	1-15
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 2000 (2000-07) CHEN YAHONG ET AL: "The changes of guanylin in plasma and lung tissue from asthmatic guinea pigs." Database accession no. PREV200000544836 XP002230933 abstract & ZHONGHUA JIEHE HE HUXI ZAZHI, vol. 23, no. 7, July 2000 (2000-07), pages 410-412, ISSN: 1001-0939	1-15

-/—

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	KULAKSIZ HASAN ET AL: "Clara cell impact in air-side activation of CFTR in small pulmonary airways." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 99, no. 10, 14 May 2002 (2002-05-14), pages 6796-6801, XP002230931 http://www.pnas.org May 14, 2002 ISSN: 0027-8424 cited in the application abstract page 6801, right-hand column, last paragraph	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DE 02/02040

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

See supplemental sheet FURTHER INFORMATION PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See supplemental sheet FURTHER INFORMATION PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION

Continuation of I.1

Although Claims 12-15 relate to a diagnostic method practiced on the human or animal body, the search was carried out on the basis of the alleged properties of the compound or composition.

Continuation of I.1

PCT Rule 39.1(iv) – diagnostic methods practiced on the human or animal body.

Continuation of I.2

The current Claims 1, 2, 4-6, 8-12, 14, 15 relate to peptides characterized in each case by a desirable characteristic or property, namely the activation of guanylate cyclase C, or relate to compounds similar to the peptides guanylin, uroguanylin, lymphoguanylin or heat-resistant enterotoxin, also characterized by the activation of guanylate cyclase C.
The claims therefore encompass all products, etc., that have this characteristic or property, but the application provides support by the description (PCT Article 5) for only a limited number of such products, etc. In the present case the claims lack the proper support and the application lacks the requisite disclosure to such an extent that it appears impossible to carry out a meaningful search covering the entire range of protection sought. Moreover, the claims also lack the requisite clarity (PCT Article 6) since they attempt to define the product in terms of the desired result. This lack of clarity too is such that it is impossible to carry out a meaningful search covering the entire scope of protection sought. Therefore, the search was directed to the parts of the claims that appear to be clear, supported or disclosed in the above sense, that is the parts concerning the peptides guanylin, uroguanylin, lymphoguanylin and heat-resistant enterotoxin (according to Claims 3, 7 and 13 and SEQ ID 1-7).

The applicant is advised that claims or parts of claims relating to inventions in respect of which no international search report has been established normally cannot be the subject of an international preliminary examination (PCT Rule 66.1(e)). In its capacity as International Preliminary Examining Authority the EPO generally will not carry out a preliminary examination for subjects that have not been searched. This also applies to cases where the claims were amended after receipt of the international search report (PCT Article 19) or where the applicant submits new claims in the course of the procedure under PCT Chapter II.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. tional Application No
PCT/DE 02/02040

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19543628 A	28-05-1997	DE 19543628 A1	28-05-1997
		AU 1031397 A	19-06-1997
		WO 9720049 A1	05-06-1997

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/DE 02/02040

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 C07K14/47 A61P11/00 A61K38/17 G01N33/68 A61M15/00

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 C07K A61M

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
BIOSIS, MEDLINE, EMBASE, EPO-Internal, WPI Data, PAJ

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	OHBAYASHI HIROYUKI ET AL: "Both inhalant and intravenous uroguanylin inhibit leukotriene C4-induced airway changes." PEPTIDES (NEW YORK), Bd. 21, Nr. 10, Oktober 2000 (2000-10), Seiten 1467-1472, XP002230927 ISSN: 0196-9781 Zusammenfassung Seite 1467, linke Spalte -Seite 1468, linke Spalte, Absatz 2 Seite 1468, rechte Spalte, Absatz 2 Seite 1468, rechte Spalte, letzter Absatz Seite 1469, rechte Spalte, letzter Absatz -Seite 1470, linke Spalte, Zeile 6 Seite 1470, rechte Spalte, Absatz 1 - Absatz 2 Abbildungen 1,2 ---- -/--	1-3,5-11

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist
"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist
"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann nahellegend ist
"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
13. Februar 2003	04/03/2003

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hars, J

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	DE 195 43 628 A (FORSSMANN WOLF GEORG) 28. Mai 1997 (1997-05-28) Ansprüche 1,2,10,17,19	4,12-15
A	OHBAYASHI HIROYUKI ET AL: "Effects of uroguanylin and guanylin against antigen-induced bronchoconstriction and airway microvascular leakage in sensitized guinea-pigs." LIFE SCIENCES, Bd. 62, Nr. 20, 10. April 1998 (1998-04-10), Seiten 1833-1844, XP002230928 ISSN: 0024-3205 Zusammenfassung Seite 1834, Absatz 1 - Absatz 2 Seite 1841, Absatz 2 -Seite 1842, Absatz 4	1-15
A	HOENSCHEID M ET AL: "Guanylin activates chloride currents in H441 lung epithelial cells." PFLUEGERS ARCHIV EUROPEAN JOURNAL OF PHYSIOLOGY, Bd. 441, Nr. 6 Supplement, 2001, Seite R270 XP009005486 Joint Congress of the Scandinavian and the German Physiological Societies;Berlin, Germany; March 10-13, 2001 ISSN: 0031-6768 das ganze Dokument	1-15
A	CETIN YALCIN ET AL: "Bronchiolar nonciliated secretory (Clara) cells: Source of guanylin in the mammalian lung." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, Bd. 92, Nr. 13, 1995, Seiten 5925-5929, XP002230929 1995 ISSN: 0027-8424 Zusammenfassung Seite 5925, linke Spalte, letzter Absatz -rechte Spalte, Absatz 1 Seite 5928, linke Spalte, Zeile 18 -rechte Spalte, Zeile 7 Seite 5929, linke Spalte	1-15

-/--

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	ZHANG ZHI HAO ET AL: "The airway-epithelium: A novel site of action by guanylin." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, Bd. 244, Nr. 1, 6. März 1998 (1998-03-06), Seiten 50-56, XP002230930 ISSN: 0006-291X Zusammenfassung Seite 50, rechte Spalte, Absatz 2 Seite 55, linke Spalte, letzter Absatz -rechte Spalte	1-15
A	ABDEL-RAZEL T ET AL: "Smooth muscle relaxation by guanylin: Implications for mediator role of cyclic GMP in vascular and airway smooth muscle relaxation." FASEB JOURNAL, Bd. 8, Nr. 4-5, 1994, Seite A556 XP009005528 Experimental Biology 94, Parts I and II;Anaheim, California, USA; April 24-28, 1994 ISSN: 0892-6638 das ganze Dokument	1-15
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; April 1999 (1999-04) FORTE LEONARD R ET AL: "Lymphoguanylin: Cloning and characterization of a unique member of the guanylin peptide family." Database accession no. PREV199900204569 XP002230932 in der Anmeldung erwähnt Zusammenfassung & ENDOCRINOLOGY, Bd. 140, Nr. 4, April 1999 (1999-04), Seiten 1800-1806, ISSN: 0013-7227	1-15
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; Juli 2000 (2000-07) CHEN YAHONG ET AL: "The changes of guanylin in plasma and lung tissue from asthmatic guinea pigs." Database accession no. PREV200000544836 XP002230933 Zusammenfassung & ZHONGHUA JIEHE HE HUXI ZAZHI, Bd. 23, Nr. 7, Juli 2000 (2000-07), Seiten 410-412, ISSN: 1001-0939	1-15

-/--

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
P,A	KULAKSIZ HASAN ET AL: "Clara cell impact in air-side activation of CFTR in small pulmonary airways." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, Bd. 99, Nr. 10, 14. Mai 2002 (2002-05-14), Seiten 6796-6801, XP002230931 http://www.pnas.org May 14, 2002 ISSN: 0027-8424 in der Anmeldung erwähnt Zusammenfassung Seite 6801, rechte Spalte, letzter Absatz	1-15

INTERNATIONALER RECHERCHENBERICHT

nationales Aktenzeichen
PCT/DE 02/02040

Feld I Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 2 auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. [X] Ansprüche Nr. –
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich

siehe Zusatzblatt WEITERE ANGABEN PCT/ISA/210

2. [X] Ansprüche Nr. –
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich

siehe Zusatzblatt WEITERE ANGABEN PCT/ISA/210

3. [ ] Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld II Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 3 auf Blatt 1)

Die Internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. [ ] Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche.

2. [ ] Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die Behörde nicht zur Zahlung einer solchen Gebühr aufgefordert.

3. [ ] Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.

4. [ ] Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

[ ] Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.

[ ] Die Zahlung zusätzlicher Recherchengebühren erfolgte ohne Widerspruch.

WEITERE ANGABEN PCT/ISA/ 210

Fortsetzung von Feld I.1

Obwohl die Ansprüche 12-15 sich auf ein Diagnostizierverfahren, das am menschlichen/tierischen Körper vorgenommen wird, beziehen, wurde die Recherche durchgeführt und gründete sich auf die angeführten Wirkungen der Verbindung/Zusammensetzung.

Fortsetzung von Feld I.1

Regel 39.1(iv) PCT - Diagnostizierverfahren, die am menschlichen oder tierischen Körper vorgenommen werden

---

Fortsetzung von Feld I.2

Die geltenden Patentansprüche 1,2,4-6,8-12,14,15 beziehen sich auf Peptide, jeweils charakterisiert durch eine erstrebenswerte Eigenheit oder Eigenschaft, nämlich die Aktivierung von Guanylat Cyclase C beziehungsweise beziehen sich auf den Peptiden Guanylin, Uroguanylin, Lymphoguanylin oder hitzebeständigem Enterotoxin ähnlichen Verbindungen, ebenfalls charakterisiert durch die Aktivierung von Guanylat Cyclase C. Die Patentansprüche umfassen daher alle Produkte etc., die diese Eigenheit oder Eigenschaft aufweisen, wohingegen die Patentanmeldung Stütze durch die Beschreibung im Sinne von Art. 5 PCT nur für eine begrenzte Zahl solcher Produkte etc. liefert. Im vorliegenden Fall fehlen den Patentansprüchen die entsprechende Stütze bzw. der Patentanmeldung die nötige Offenbarung in einem solchen Maße, daß eine sinnvolle Recherche über den gesamten erstrebten Schutzbereich unmöglich erscheint. Desungeachtet fehlt den Patentansprüchen auch die in Art. 6 PCT geforderte Klarheit, nachdem in ihnen versucht wird, das Produkt über das jeweils erstrebte Ergebnis zu definieren. Auch dieser Mangel an Klarheit ist dergestalt, daß er eine sinnvolle Recherche über den gesamten erstrebten Schutzbereich unmöglich macht. Daher wurde die Recherche auf die Teile der Patentansprüche gerichtet, welche im o.a. Sinne als klar, gestützt oder offenbart erscheinen, nämlich die Teile betreffend die Peptide Guanylin, Uroguanylin, Lymphoguanylin und hitzebeständiges Enterotoxin (entsprechend der Ansprüche 3,7 und 13 und den SEQ ID 1-7).

Der Anmelder wird darauf hingewiesen, daß Patentansprüche, oder Teile von Patentansprüchen, auf Erfindungen, für die kein internationaler Recherchenbericht erstellt wurde, normalerweise nicht Gegenstand einer internationalen vorläufigen Prüfung sein können (Regel 66.1(e) PCT). In seiner Eigenschaft als mit der internationalen vorläufigen Prüfung beauftragte Behörde wird das EPA also in der Regel keine vorläufige Prüfung für Gegenstände durchführen, zu denen keine Recherche vorliegt. Dies gilt auch für den Fall, daß die Patentansprüche nach Erhalt des internationalen Recherchenberichtes geändert wurden (Art. 19 PCT), oder für den Fall, daß der Anmelder im Zuge des Verfahrens gemäß Kapitel II

WEITERE ANGABEN PCT/ISA/ 210

PCT neue Patentansprüche vorlegt.

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/DE 02/02040

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
DE 19543628 A	28-05-1997	DE 19543628 A1	28-05-1997
		AU 1031397 A	19-06-1997
		WO 9720049 A1	05-06-1997

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 August 2004 (19.08.2004)

PCT

(10) International Publication Number
WO 2004/069165 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2004/002390

(22) International Filing Date: 28 January 2004 (28.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/443,098	28 January 2003 (28.01.2003)	US
60/471,288	15 May 2003 (15.05.2003)	US
60/519,460	12 November 2003 (12.11.2003)	US

(71) Applicant *(for all designated States except US)*: **MICROBIA, INC.** [US/US]; 320 Bent Street, Cambridge, MA 02141 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CURRIE, Mark, G.** [US/US]; 18 Hall Avenue, Sterling, MA 01564 (US). **MAHAJAN-MIKLOS, Shalina** [/US]; 14 Holland Street, Needham, MA 02492 (US).

(74) Agent: **MEIKLEJOHN, Anita, L.**; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

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

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

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

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

(54) **Title:** METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

(57) **Abstract:** The present invention features compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), Crohn's disease, ulcerative colitis, Inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudo-obstruction), and disorders and conditions associated with constipation, e.g., constipation associated with use of opiate pain killers, post-surgical constipation, and constipation associated with neuropathic disorders as well as other conditions and disorders using peptides and other agents that activate the guanylate cyclase C (GC-C) receptor.

WO 2004/069165 A2

Methods and Compositions for the Treatment of Gastrointestinal Disorders

TECHNICAL FIELD

This invention relates to methods and compositions for treating various disorders, including gastrointestinal disorders, obesity, congestive heart failure and benign prostatic hyperplasia.

BACKGROUND

Irritable bowel syndrome (IBS) is a common chronic disorder of the intestine that affects 20 to 60 million individuals in the US alone (Lehman Brothers, Global Healthcare-Irritable bowel syndrome industry update, September 1999). IBS is the most common disorder diagnosed by gastroenterologists (28% of patients examined) and accounts for 12% of visits to primary care physicians (Camilleri 2001, Gastroenterology 120:652-668). In the US, the economic impact of IBS is estimated at $25 billion annually, through direct costs of health care use and indirect costs of absenteeism from work (Talley 1995, Gastroenterology 109:1736-1741). Patients with IBS have three times more absenteeism from work and report a reduced quality of life. Sufferers may be unable or unwilling to attend social events, maintain employment, or travel even short distances (Drossman 1993, Dig Dis Sci 38:1569-1580). There is a tremendous unmet medical need in this population since few prescription options exist to treat IBS.

Patients with IBS suffer from abdominal pain and a disturbed bowel pattern. Three subgroups of IBS patients have been defined based on the predominant bowel habit: constipation-predominant (c-IBS), diarrhea-predominant (d-IBS) or alternating between the two (a-IBS). Estimates of individuals who suffer from c-IBS range from 20-50% of the IBS patients with 30% frequently cited. In contrast to the other two subgroups that have a similar gender ratio, c-IBS is more common in women (ratio of 3:1) (Talley et al. 1995, Am J Epidemiol 142:76-83).

The definition and diagnostic criteria for IBS have been formalized in the "Rome Criteria" (Drossman et al. 1999, Gut 45:Suppl II: 1-81), which are well accepted in clinical practice. However, the complexity of symptoms has not been explained by anatomical abnormalities or metabolic changes. This has led to the classification of IBS as a functional GI disorder, which is diagnosed on the basis of the Rome criteria and limited evaluation to exclude organic disease.(Ringel et al. 2001, Annu Rev Med 52: 319-338). IBS is considered to be a "biopsychosocial" disorder resulting from a combination of three interacting mechanisms: altered bowel motility, an increased sensitivity of the intestine or colon to pain stimuli (visceral sensitivity) and psychosocial factors (Camilleri 2001, Gastroenterology 120:652-668). Recently, there has been increasing evidence for a role of inflammation in etiology of IBS. Reports indicate that subsets of IBS patients have small but significant increases in colonic inflammatory and mast cells, increased inducible nitric oxide (NO) and synthase (iNOS) and altered expression of inflammatory cytokines (reviewed by Talley 2000, Medscape Coverage of DDW week).

SUMMARY

The present invention features compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), Crohn's disease, ulcerative colitis, Inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudo-obstruction), and disorders and conditions associated with constipation, e.g., constipation associated with use of opiate pain killers, post-surgical constipation, and constipation associated with neuropathic disorders as well as other conditions and disorders. The compositions feature peptides that activate the guanylate cyclase C (GC-C) receptor.

The present invention also features compositions and related methods for treating obesity, congestive heart failure and benign prostatic hyperplasia (BPH).

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are useful because they can increase gastrointestinal motility.

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are useful, in part, because they can decrease inflammation.

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are also useful because they can decrease gastrointestinal pain or visceral pain.

The invention features pharmaceutical compositions comprising certain peptides that are capable of activating the guanylate-cyclase C (GC-C) receptor. Also within the invention are pharmaceutical compositions comprising a peptide of the invention as well as combination compositions comprising a peptide of the invention and a second therapeutic agent, e.g., an agent for treating constipation (e.g., SPI-0211; Sucampo Pharmaceuticals, Inc.; Bethesda, MD) or some other gastrointestinal disorder. Examples of a second therapeutic agent include: acid reducing agents such as proton pump inhibitors and H2 receptor blockers, pro-motility agents such as 5HT receptor agonists (e.g. Zelnorm®), anti-inflammatory agents, antispasmodics, antidepressants, centrally-acting analgesic agents such as opiod receptor agonists, opiod receptor antagonists, agents for the treatment of Inflammatory bowel disease, Crohn's disease and ulcerative colitis (e.g., Traficet-EN™ (ChemoCentryx, Inc.; San Carlos, CA) agents that treat gastrointestinal or visceral pain and cGMP phosphodiesterase inhibitors (motapizone, zaprinast, and suldinac sulfone). Thus, for example, the pharmaceutical compositions can include an analgesic agent selected from the group consisting of: Ca channel blockers (e.g., ziconotide), 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HT1 receptor antagonists), opioid receptor agonists (e.g., loperamide, fedotozine, and fentanyl, naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine, morphine, diphenyloxylate, enkephalin pentapeptide, and

trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033), CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists (e.g., talnetant, osanetant (SR-142801)), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid and cannabanoid receptor agonists (e.g., arvanil), sialorphin, sialorphin-related peptides comprising the amino acid sequence QHNPR (SEQ ID NO:) for example, VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:), compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1), loperamide, Tyr-Arg (kyotorphin), CCK receptor agonists (caerulein), conotoxin peptides, peptide analogs of thymulin, loxiglumide, dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) and other analgesic peptides or compounds can be used with or linked to the peptides of the invention.

The invention includes methods for treating various gastrointestinal disorders by administering a peptide that acts as a partial or complete agonist of the GC-C receptor. The peptide includes at least six cysteines that form three disulfide bonds. In certain embodiments the disulfide bonds are replaced by other covalent cross-links and in some cases the cysteines are substituted by other residues to provide for alternative covalent cross-links. The peptides may also include at least one trypsin or chymotrypsin cleavage site and/or a carboxy-terminal analgesic peptide or small molecule, e.g., AspPhe or some other analgesic peptide. When present within the peptide, the analgesic peptide or small molecule may be preceded by a chymotrypsin or trypsin cleavage site that allows release of the analgesic peptide or small molecule. The peptides and methods of the invention are also useful for treating pain and inflammation associated with various disorders, including gastrointestinal disorders. Certain peptides include a functional chymotrypsin or trypsin cleavage site located so as to allow inactivation of the peptide upon cleavage. Certain peptides having a functional cleavage site undergo cleavage and gradual inactivation in the digestive tract, and this is desirable in some circumstances. In certain peptides, a functional chymotrypsin site is altered, increasing the stability of the peptide *in vivo*.

The invention includes methods for treating other disorders such as congestive heart failure and benign prostatic hyperplasia by administering a peptide or small molecule (parenterally or orally) that acts as an agonist of the GC-C receptor. Such agents can be used in combination with natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

The invention features methods and compositions for increasing intestinal motility. Intestinal motility involves spontaneous coordinated dissentions and contractions of the stomach, intestines, colon and rectum to move food through the gastrointestinal tract during the digestive process.

In certain embodiments the peptides include either one or two or more contiguous negatively charged amino acids (e.g., Asp or Glu) or one or two or more contiguous positively charged residues (e.g., Lys or Arg) or one or two or more contiguous positively or negatively charged amino acids at the carboxy terminus. In these embodiments all of the flanking amino acids at the carboxy terminus are either positively or negatively charged. In other embodiments the carboxy terminal charged amino acids are preceded by a Leu. For example, the following amino acid sequences can be added to the carboxy terminus of the peptide: Asp; Asp Lys; Lys Lys Lys Lys Lys Lys; Asp Lys Lys Lys Lys Lys Lys; Leu Lys Lys; and Leu Asp. It is also possible to simply add Leu at the carboxy terminus.

In a first aspect, the invention features a peptide comprising, consisting of, or consisting essentially of the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing. In certain embodiments Xaa_8, Xaa_9, Xaa_{12}, Xaa_{13}, Xaa_{14}, Xaa_{17}, and Xaa_{19} can be any amino acid. In certain embodiments Xaa_5 is Asn, Trp, Tyr, Asp, or Phe. In other embodiments, Xaa_5 can also be Thr or Ile. In other embodiments Xaa_5 is Tyr, Asp or Trp. In some embodiments Xaa_8 is Glu, Asp, Gln,

Gly or Pro. In other embodiments Xaa_8 is Glu; in some embodiments Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe in some embodiments Xaa_9 is Leu, Ile, Val, Lys, Arg, Trp, Tyr or Phe.

In certain embodiments, an amino acid can be replace by a non-naturally occurring amino acid or a naturally or non-naturally occurring amino acid analog. For example, an aromatic amino acid can be replaced by 3,4-dihydroxy-L-phenylalanine, 3-iodo-L-tyrosine, triiodothyronine, L-thyroxine, phenylglycine (Phg) or nor-tyrosine (norTyr). Phg and norTyr and other amino acids including Phe and Tyr can be substituted by, e.g., a halogen, -CH3, -OH, $-CH_2NH_3$, -C(O)H, $-CH_2CH_3$, -CN, $-CH_2CH_2CH_3$, -SH, or another group.

In some embodiments Xaa_{12} is Asn, Tyr, Asp or Ala. In other embodiments Xaa_{12} is Asn. In some embodiments Xaa_{13} is Ala, Pro or Gly, and in other embodiments it is Pro. In some embodiments Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, or Asp, and in other embodiments it is Ala or Gly, and in still other embodiments it is Ala. In some embodiments Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is selected from Trp, Tyr, Phe, Asn and Leu or Xaa_{19} is selected from Trp, Tyr, and Phe or Xaa_{19} is selected from Leu, Ile and Val; or Xaa_{19} is His or Xaa_{19} is selected from Trp, Tyr, Phe, Asn, Ile, Val, His and Leu; and Xaa_{20} Xaa_{21} is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or Xaa_{19} Xaa_{20} Xaa_{21} is missing. The invention also features methods for treating a gastrointestinal disorder (e.g., a gastrointestinal motility disorder, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction), obesity, congestive heart failure or benign prostatic hyperplasia by administering a composition comprising an aforementioned peptide

When Xaa_9 is Trp, Tyr or Phe or when Xaa_{16} is Trp the peptide has a potentially functional chymotrypsin cleavage site that is located at a position where cleavage will inactivate GC-C receptor binding by the peptide. When Xaa_9 is Lys or Arg or when Xaa_{16} is Lys or Arg, the peptide has a potentially functional trypsin cleavage site that

is located at a position where cleavage will inactivate GC-C receptor binding by the peptide.

When Xaa_{19} is Trp, Tyr or Phe, the peptide has a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide carboxy-terminal to Xaa_{19}. When Xaa_{19} is Leu, Ile or Val, the peptide can have a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide amino-terminal to Xaa_{19}. At relatively high pH the same effect is seen when Xaa_{19} is His. When Xaa_{19} is Lys or Arg, the peptide has a trypsin cleavage site that is located at a position where cleavage will liberate portion of the peptide carboxy-terminal to Xaa_{19}. Thus, if the peptide includes an analgesic peptide carboxy-terminal to Xaa_{19}, the peptide will be liberated in the digestive tract upon exposure to the appropriate protease. Among the analgesic peptides which can be included in the peptide are: AspPhe (as $Xaa_{20}Xaa_{21}$), endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance P and other analgesic peptides described herein. These peptides can, for example, be used to replace $Xaa_{20}Xaa_{21}$.

When Xaa_1 or the amino-terminal amino acid of the peptide of the invention (e.g., Xaa_2 or Xaa_3) is Trp, Tyr or Phe, the peptide has a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide amino-terminal to Xaa_1 (or Xaa_2 or Xaa_3) along with Xaa_1, Xaa_2 or Xaa_3. When Xaa_1 or the amino-terminal amino acid of the peptide of the invention (e.g., Xaa_2 or Xaa_3) is Lys or Arg, the peptide has a trypsin cleavage site that is located at a position where cleavage will liberate portion of the peptide amino-terminal to Xaa_1 along with Xaa_1, Xaa_2 or Xaa_3). When Xaa_1 or the amino-terminal amino acid of the peptide of the invention is Leu, Ile or Val, the peptide can have a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide amino-terminal to Xaa_1. At relatively high pH the same effect is seen when Xaa_1 is His. Thus, for example, if the peptide includes an analgesic peptide amino-terminal to Xaa_1, the peptide will be liberated in the digestive tract upon exposure to the appropriate protease. Among the analgesic peptides which can be included in the

peptide are: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance p and other analgesic peptides described herein.

When fully folded, disulfide bonds are present between: Cys_6 and Cys_{11}; Cys_7 and Cys_{15}; and Cys_{10} and Cys_{18}. The peptides of the invention bear some sequence similarity to ST peptides. However, they include amino acid changes and/or additions that improve functionality. These changes can, for example, increase or decrease activity (e.g., increase or decrease the ability of the peptide to stimulate intestinal motility), alter the ability of the peptide to fold correctly, the stability of the peptide, the ability of the peptide to bind the GC-C receptor and/or decrease toxicity. In some cases the peptides may function more desirably than wild-type ST peptide. For example, they may limit undesirable side effects such as diarrhea and dehydration.

In some embodiments one or both members of one or more pairs of Cys residues which normally form a disulfide bond can be replaced by homocysteine, 3-mercaptoproline (Kolodziej et al. 1996 Int J Pept Protein Res 48:274); β, β dimethylcysteine (Hunt et al. 1993 Int J Pept Protein Res 42:249) or diaminopropionic acid (Smith et al. 1978 J Med Chem 21:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

In addition, one or more disulfide bonds can be replaced by alternative covalent cross-links, e.g., an amide bond, an ester linkage, an alkyl linkage, a thio ester linkage, a lactam bridge, a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate ester linkage, an alkyl linkage, and alkenyl linkage, an ether, a thioether linkage, or an amino linkage. For example, Ledu et al. (Proceedings Nat'l Acad. Sci. 100:11263-78, 2003) described methods for preparing lactam and amide cross-links. Schafmeister et al. (J. Am. Chem. Soc. 122:5891, 2000) describes stable, all carbon cross-links. In some cases, the generation of such alternative cross-links requires replacing the Cys residues with other residues such as Lys or Glu or non-naturally occurring amino acids.

In the case of a peptide comprising the sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing and/or the sequence Xaa_{19} Xaa_{20} Xaa_{21} is missing, the peptide can still contain additional carboxyterminal or amino terminal amino acids or both. For example, the peptide can include an amino terminal sequence that facilitates recombinant production of the peptide and is cleaved prior to administration of the peptide to a patient. The peptide can also include other amino terminal or carboxyterminal amino acids. In some cases the additional amino acids protect the peptide, stabilize the peptide or alter the activity of the peptide. In some cases some or all of these additional amino acids are removed prior to administration of the peptide to a patient. The peptide can include 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70 80, 90, 100 or more amino acids at its amino terminus or carboxy terminus or both. The number of flanking amino acids need not be the same. For example, there can be 10 additional amino acids at the amino terminus of the peptide and none at the carboxy terminus.

In one embodiment the peptide comprises the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; and Xaa_{20} Xaa_{21} is AspPhe or is missing. Where Xaa_{20} Xaa_{21} and/or Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 are missing, there may be additional flanking amino acids in some embodiments.

In a second aspect, the invention also features a therapeutic or prophylactic method comprising administering a peptide comprising the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn, Trp, Tyr, Asp, Ile, Thr, or Phe; Xaa_8 is Glu, Asp, Gln, Gly or Pro; Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn, Tyr, Asp or Ala; Xaa_{13} is Pro or Gly; Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, and Asp; Xaa_{16} is Thr, Ala, Asn,

Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is Trp, Tyr, Phe or Leu; and Xaa_{20} Xaa_{21} is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or Xaa_{19} Xaa_{20} Xaa_{21} is missing.

In certain embodiments of the therapeutic or prophylactic methods: the peptide comprises the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr, or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp or Xaa_{16} is any amino acid or Xaa_{16} is Thr, Ala, Lys, Arg, Trp or Xaa_{16} is any non-aromatic amino acid; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; and Xaa_{20} Xaa_{21} is AspPhe or is missing.

In certain embodiments, the invention features, a purified polypeptide comprising the amino acid sequence (II):

Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Asn_{12} Pro_{13} Ala_{14} Cys_{15} Xaa_{16} Gly_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein

Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn;

Xaa_8 is Glu or Asp;

Xaa_9 is Leu, Ile, Val, Trp, Tyr or Phe;

Xaa_{16} is Thr, Ala, Trp;

Xaa_{19} is Trp, Tyr, Phe or Leu or is missing; and Xaa_{20} Xaa_{21} is AspPhe.

In various preferred embodiments the invention features a purified polypeptide comprising the amino acid sequence (II): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Asn_{12} Pro_{13} Ala_{14} Cys_{15} Xaa_{16} Gly_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein, Xaa_9 is Leu, Ile or Val and Xaa_{16} is Trp, Tyr or Phe; Xaa_9 is Trp, Tyr or Phe, and Xaa_{16} is Thr or Ala; Xaa_{19} is Trp, Tyr, Phe and Xaa_{20} Xaa_{21} is AspPhe; and Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn; the peptide comprises fewer than 50, 40, 30 or 25 amino acids; fewer than five amino acid precede Cys_6.

The peptides can be co-administered with or linked, e.g., covalently linked to any of a variety of other peptides including analgesic peptides or analgesic compounds. For example, a therapeutic peptide of the invention can be linked to an analgesic agent selected from the group consisting of: Ca channel blockers (e.g., ziconotide), complete or partial 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HT1 receptor antagonists), complete or partial 5HT receptor agonists including 5HT3, 5HT4 (for example tegaserod, mosapride and renzapride) and 5HT1 receptor agonists, CRF receptor agonists (NBI-34041), β-3 adrenoreceptor agonists, opioid receptor agonists (e.g., loperamide, fedotozine, and fentanyl, naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine, morphine, diphenyloxylate, enkephalin pentapeptide, asimadoline, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033), CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists (e.g., talnetant, osanetant (SR-142801)), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid and cannabanoid receptor agonists (e.g., arvanil), sialorphin, sialorphin-related peptides comprising the amino acid sequence QHNPR (SEQ ID NO:) for example, VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:), compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1), loperamide, Tyr-Arg (kyotorphin), CCK receptor agonists (caerulein), conotoxin peptides, pepetide analogs of thymulin, loxiglumide, dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) and other analgesic peptides or compounds can be used with or linked to the peptides of the invention.

Amino acid, non-amino acid, peptide and non-peptide spacers can be interposed between a peptide that is a GC-C receptor agonsit and a peptide that has some other biological function, e.g., an analgesic peptide or a peptide used to treat obesity. The linker can be one that is cleaved from the flanking peptides *in vivo* or one that remains linked to the flanking peptides *in vivo*. For example, glycine, beta-alanine, glycyl-glycine, glycyl-beta-alanine, gamma-aminobutyric acid, 6-aminocaproic acid, L-

phenylalanine, L-tryptophan and glycil-L-valil-L-phenylalanine can be used as a spacer (Chaltin et al. 2003 Helvetica Chimica Acta 86:533-547; Caliceti et al. 1993 FARMCO 48:919-32) as can polyethylene glycols (Butterworth et al. 1987 J. Med. Chem 30:1295-302) and maleimide derivatives (King et al. 2002 Tetrahedron Lett. 43:1987-1990). Various other linkers are described in the literature (Nestler 1996 Molecular Diversity 2:35-42; Finn et al. 1984 Biochemistry 23:2554-8; Cook et al. 1994 Tetrahedron Lett. 35:6777-80; Brokx et al. 2002 Journal of Controlled Release 78:115-123; Griffin et al. 2003 J. Am. Chem. Soc. 125:6517-6531; Robinson et al. 1998 Proc. Natl. Acad. Sci. USA 95:5929-5934.

The peptides can include the amino acid sequence of a peptide that occurs naturally in a vertebrate (e.g., mammalian) species or in a bacterial species. In addition, the peptides can be partially or completely non-naturally occurring peptides. Also within the invention are peptidomimetics corresponding to the peptides of the invention. In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, chronic constipation, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, Crohn's disease, ulcerative colitis, Irritable bowel syndrome, colonic pseudo-obstruction, obesity, congestive heart failure, or benign prostatic hyperplasia; the composition is administered orally; the peptide comprises 30 or fewer amino acids, the peptide comprises 20 or fewer amino acids, and the peptide comprises no more than 5 amino acids prior to Cys_6; the peptide comprises 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, or 30 or fewer amino acids. In other embodiments, the peptide comprises 20 or fewer amino acids. In other embodiments the peptide comprises no more than 20, 15, 10, or 5 peptides subsequent to Cys_{18}. In certain embodiments Xaa_{19} is a chymotrypsin or trypsin cleavage site and an analgesic peptide is present immediately following Xaa_{19}.

In a third aspect, the invention features a method for treating a patient suffering from constipation. Clinically accepted criteria that define constipation range from the

frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001, Aliment Pharmacol Ther 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung's disease and Cystic fibrosis. Constipation may also be the result of surgery (postoperative ileus) or due to the use of drugs such as analgesics (like opiods), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

The method comprising administering a composition comprising a purified polypeptide comprising the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn, Trp, Tyr, Asp, Ile, Thr, or Phe; Xaa_8 is Glu, Asp, Gln, Gly or Pro; Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn, Tyr, Asp or Ala; Xaa_{13} is Pro or Gly; Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, and Asp; Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is Trp, Tyr, Phe or Leu; Xaa_{19} is Lys or Arg; Xaa_{20} Xaa_{21} is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or Xaa_{19} Xaa_{20} Xaa_{21} is missing.

In one embodiment of the method, the peptide comprises the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; Xaa_{19} is Lys or Arg; Xaa_{20} Xaa_{21} is AspPhe or is missing.

In various preferred embodiments, the constipation is associated with use of a therapeutic agent; the constipation is associated with a neuropathic disorder; the constipation is post-surgical constipation (postoperative ileus); and the constipation associated with a gastrointestinal disorder; the constipation is idiopathic (functional constipation or slow transit constipation); the constipation is associated with neuropathic, metabolic or endocrine disorder (e.g., diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung's disease or cystic fibrosis). Constipation may also be the result of surgery (postoperative ileus) or due the use of drugs such as analgesics (e.g., opiods), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In a fourth aspect, the invention features a method for treating a patient suffering a gastrointestinal disorder, the method comprising administering to the patient a composition comprising a purified polypeptide comprising the amino acid sequence (I): $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5\ Cys_6\ Cys_7\ Xaa_8\ Xaa_9\ Cys_{10}\ Cys_{11}\ Xaa_{12}\ Xaa_{13}\ Xaa_{14}\ Cys_{15}\ Xaa_{16}\ Xaa_{17}\ Cys_{18}\ Xaa_{19}\ Xaa_{20}\ Xaa_{21}$ wherein: $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5$ is Asn Ser Ser Asn Tyr or is missing or $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4$ is missing and Xaa_5 is Asn, Trp, Tyr, Asp, Ile, Thr, or Phe; Xaa_8 is Glu, Asp, Gln, Gly or Pro; Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn, Tyr, Asp or Ala; Xaa_{13} is Pro or Gly; Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, and Asp; Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is Trp, Tyr, Phe or Leu; Xaa_{19} is Lys or Arg;$Xaa_{20}\ Xaa_{21}$ is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or $Xaa_{19}\ Xaa_{20}\ Xaa_{21}$ is missing.

In one embodiment of the method, the peptide comprises the amino acid sequence (I): $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5\ Cys_6\ Cys_7\ Xaa_8\ Xaa_9\ Cys_{10}\ Cys_{11}\ Xaa_{12}\ Xaa_{13}\ Xaa_{14}\ Cys_{15}\ Xaa_{16}\ Xaa_{17}\ Cys_{18}\ Xaa_{19}\ Xaa_{20}\ Xaa_{21}$ wherein: $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5$ is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; Xaa_{19} is Lys or Arg; $Xaa_{20}\ Xaa_{21}$ is AspPhe or is missing.

In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, chronic constipation, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, Crohn's disease, ulcerative colitis, Inflammatory bowel disease, colonic pseudo-obstruction, obesity, congestive heart failure, or benign prostatic hyperplasia.

In various preferred embodiments, Xaa_9 is Leu, Ile or Val and Xaa_{16} is Trp, Tyr or Phe; Xaa_9 is Trp, Tyr or Phe and Xaa_{16} is Thr or Ala; Xaa_{19} is Trp, Tyr, Phe; Xaa_{19} is Lys or Arg;Xaa_{20} Xaa_{21} is AspPhe; Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn.

In a fifth aspect, the invention features a method for increasing gastrointestinal motility in a patient, the method comprising: administering to the patient a composition comprising a purified polypeptide comprising the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn, Trp, Tyr, Asp, Ile, Thr, or Phe; Xaa_8 is Glu, Asp, Gln, Gly or Pro; Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn, Tyr, Asp or Ala; Xaa_{13} is Pro or Gly; Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, and Asp; Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is Trp, Tyr, Phe or Leu; Xaa_{19} is Lys or Arg; Xaa_{20} Xaa_{21} is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or Xaa_{19} Xaa_{20} Xaa_{21} is missing.

In one embodiment the peptide comprises the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is

Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; Xaa_{19} is Lys or Arg; Xaa_{20} Xaa_{21} is AspPhe or is missing.

In a sixth aspect, the invention features a method for increasing the activity of an intestinal guanylate cyclase (GC-C) receptor in a patient, the method comprising: administering to the patient a composition comprising a purified polypeptide comprising the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn, Trp, Tyr, Asp, Ile, Thr, or Phe; Xaa_8 is Glu, Asp, Gln, Gly or Pro; Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn, Tyr, Asp or Ala; Xaa_{13} is Pro or Gly; Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, and Asp; Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is Trp, Tyr, Phe or Leu; Xaa_{19} is Lys or Arg; Xaa_{20} Xaa_{21} is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or Xaa_{19} Xaa_{20} Xaa_{21} is missing.

In one embodiment the peptide comprises the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; Xaa_{19} is Lys or Arg; Xaa_{20} Xaa_{21} is AspPhe or is missing.

In a seventh aspect, the invention features an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence: (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn, Trp, Tyr, Asp, Ile, Thr, or Phe; Xaa_8 is Glu, Asp, Gln, Gly or Pro; Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn, Tyr, Asp or Ala; Xaa_{13} is Pro or Gly; Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, and Asp; Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is Trp, Tyr, Phe

or Leu; Xaa_{19} is Lys or Arg; $Xaa_{20}Xaa_{21}$ is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or $Xaa_{19}Xaa_{20}Xaa_{21}$ is missing.

In one embodiment the peptide comprises the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; Xaa_{19} is Lys or Arg; $Xaa_{20}Xaa_{21}$ is AspPhe or is missing.

In an eighth aspect the invention features a method for treating constipation, the method comprising administering an agonist of the intestinal guanylate cyclase (GC-C) receptor. In various embodiments: the agonist is a peptide, the peptide includes four Cys that form two disulfide bonds, and the peptide includes six Cys that form three disulfide bonds.

In a ninth aspect, the invention features a method for treating a gastrointestinal disorder, a gastrointestinal motility disorder, irritable bowel syndrome, chronic constipation, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, Crohn's disease, ulcerative colitis, Inflammatory bowel disease, obesity, congestive heart failure, or benign prostatic hyperplasia, the method comprising administering an agonist of the intestinal guanylate cyclase (GC-C) receptor either orally, by rectal suppository, or parenterally. In various embodiments: the agonist is a peptide, the peptide includes four Cys that form two disulfide bonds, and the peptide includes six Cys that form three disulfide bonds.

In a tenth aspect, the invention features a method for treating a gastrointestinal disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, chronic constipation, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction,

colonic pseudo-obstruction, Crohn's disease, ulcerative colitis, Inflammatory bowel disease, the method comprising administering an agonist of the intestinal guanylate cyclase (GC-C) receptor. In various embodiments the composition is administered orally; the peptide comprises 30 or fewer amino acids, the peptide comprises 20 or fewer amino acids, and the peptide comprises no more than 5 amino acids prior to Cys_5.

In various embodiments: the agonist is a peptide, the peptide includes four Cys that form two disulfide bonds, and the peptide includes six Cys that form three disulfide bonds.

In an eleventh aspect, the invention features a method for treating obesity, the method comprising administering an agonist of the intestinal guanylate cyclase (GC-C) receptor. In various embodiments: the agonist is a peptide, the peptide includes four Cys that form two disulfide bonds, and the peptide includes six Cys that form three disulfide bonds.

In a twelfth aspect, the invention features a method for treating obesity, the method comprising administering a polypeptide comprising the amino acid sequence: (I): $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5\ Cys_6\ Cys_7\ Xaa_8\ Xaa_9\ Cys_{10}\ Cys_{11}\ Xaa_{12}\ Xaa_{13}\ Xaa_{14}\ Cys_{15}\ Xaa_{16}\ Xaa_{17}\ Cys_{18}\ Xaa_{19}\ Xaa_{20}\ Xaa_{21}$ wherein: $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5$ is Asn Ser Ser Asn Tyr or is missing or $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4$ is missing and Xaa_5 is Asn, Trp, Tyr, Asp, Ile, Thr, or Phe; Xaa_8 is Glu, Asp, Gln, Gly or Pro; Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn, Tyr, Asp or Ala; Xaa_{13} is Pro or Gly; Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, and Asp; Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is Trp, Tyr, Phe or Leu; and $Xaa_{20}\ Xaa_{21}$ is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or $Xaa_{19}\ Xaa_{20}\ Xaa_{21}$ is missing. The peptide can be administered alone or in combination with another agent for the treatment of obesity, e.g., sibutramine or another agent, e.g., an agent described herein..

In one embodiment the peptide comprises the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; and Xaa_{20} Xaa_{21} is AspPhe or is missing.

In a thirteenth aspect, the invention features a pharmaceutical composition comprising a polypeptide described herein.

In a fourteenth aspect, the invention features a method for treating congestive heart failure, the method comprising: administering to the patient a composition comprising a purified polypeptide comprising the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn, Trp, Tyr, Asp, Ile, Thr, or Phe; Xaa_8 is Glu, Asp, Gln, Gly or Pro; Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn, Tyr, Asp or Ala; Xaa_{13} is Pro or Gly; Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, and Asp; Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is Trp, Tyr, Phe or Leu; and Xaa_{20} Xaa_{21} is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or Xaa_{19} Xaa_{20} Xaa_{21} is missing. The peptide can be administered in combination with another agent for treatment of congestive heart failure, for example, a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

In one embodiment the peptide comprises the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; Xaa_{19} is Lys or Arg; Xaa_{20} Xaa_{21} is AspPhe or is missing.

In a fifteenth aspect, the invention features a method for treating benign prostatic hyperplasia, the method comprising: administering to the patient a composition comprising a purified polypeptide comprising the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing and Xaa_5 is Asn, Trp, Tyr, Asp, Ile, Thr, or Phe; Xaa_8 is Glu, Asp, Gln, Gly or Pro; Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn, Tyr, Asp or Ala; Xaa_{13} is Pro or Gly; Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, and Asp; Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp; Xaa_{17} is Gly, Pro or Ala; Xaa_{19} is Trp, Tyr, Phe or Leu; Xaa_{19} is Lys or Arg; Xaa_{20} Xaa_{21} is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or Xaa_{19} Xaa_{20} Xaa_{21} is missing.

The peptide can be administered in combination with another agent for treatment of BPH, for example, a 5-alpha reductase inhibitor (e.g., finasteride) or an alpha adrenergic inhibitor (e.g., doxazosine).

In one embodiment the peptide comprises the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; and Xaa_{20} Xaa_{21} is AspPhe or is missing.

In a sixteenth aspect, the invention features a method for treating or reducing pain, including visceral pain, pain associated with a gastrointestinal disorder or pain associated with some other disorder, the method comprising: administering to a patient a composition comprising a purified polypeptide comprising the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21}, e.g., a purified polypeptide comprising an amino acid sequence disclosed herein.

In a seventeenth aspect, the invention features a method for treating inflammation, including inflammation of the gastrointestinal tract, e.g., inflammation associated with a gastrointestinal disorder or infection or some other disorder, the method comprising: administering to a patient a composition comprising a purified polypeptide comprising the amino acid sequence (I): $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5\ Cys_6\ Cys_7\ Xaa_8\ Xaa_9\ Cys_{10}\ Cys_{11}\ Xaa_{12}\ Xaa_{13}\ Xaa_{14}\ Cys_{15}\ Xaa_{16}\ Xaa_{17}\ Cys_{18}\ Xaa_{19}\ Xaa_{20}\ Xaa_{21}$, e.g., a purified polypeptide comprising an amino acid sequence disclosed herein.

In certain embodiments the peptide includes a peptide comprising or consisting of the amino acid sequence $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5$ Cys Cys Glu Xaa_9 Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr $Xaa_{20}\ Xaa_{21}$ (II) (SEQ ID NO:____) wherein Xaa_9 is any amino acid, wherein Xaa_9 is any amino acid other than Leu, wherein Xaa_9 is selected from Phe, Trp and Tyr; wherein Xaa_9 is selected from any other natural or non-natural aromatic amino acid, wherein Xaa_9 is Tyr; wherein $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5$ is Asn Ser Ser Asn Tyr; wherein Xaa_1, Xaa_2, Xaa_3, Xaa_4, and Xaa_5 are missing; wherein Xaa_1, Xaa_2, Xaa_3 and Xaa_4 are missing; wherein Xaa_1, Xaa_2 and Xaa_3 are missing; wherein Xaa_1 and Xaa_2 are missing; wherein Xaa_1 is missing; wherein $Xaa_{20}\ Xaa_{21}$ is AspPhe or is missing or Xaa_{20} is Asn or Glu and Xaa_{21} is missing or $Xaa_{19}\ Xaa_{20}\ Xaa_{21}$ is missing. In the case of a peptide comprising the sequence (I): $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5\ Cys_6\ Cys_7\ Xaa_8\ Xaa_9\ Cys_{10}\ Cys_{11}\ Xaa_{12}\ Xaa_{13}\ Xaa_{14}\ Cys_{15}\ Xaa_{16}\ Xaa_{17}\ Cys_{18}\ Xaa_{19}\ Xaa_{20}\ Xaa_{21}$ wherein: $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5$ is missing and/or the sequence $Xaa_{19}\ Xaa_{20}\ Xaa_{21}$ is missing peptide can still contain additional carboxyterminal or amino terminal amino acids or both

Among the useful peptides are peptides comprising, consisting of or consisting essentially of the amino acid sequence $Xaa_1\ Xaa_2\ Xaa_3\ Xaa_4\ Xaa_5$ Cys Cys Glu Xaa_9 Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr $Xaa_{20}\ Xaa_{21}$ (II) (SEQ ID NO:---) are the following peptides:
Gln Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Thr Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Leu Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Ile Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Ser Ser Gln Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Gln Ser Ser Gln Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Ser Ser Gln Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---).

Asn Ser Ser Asn Tyr Cys Cys Glu Ala Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Asn Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Asp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Cys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Gln Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Glu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Gly Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu His Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Ile Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Met Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Pro Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Thr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Asn Ser Ser Asn Tyr Cys Cys Glu Val Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Ala Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Asn Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Asp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Cys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Gln Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Glu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Gly Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu His Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Ile Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Met Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Pro Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Thr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)
Cys Cys Glu Val Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:)

In an eighteenth aspect, the invention features a method for treating congestive heart failure, the method comprising administering a complete or partial agonist of the intestinal guanylate cyclase (GC-C) receptor. The agonist can be administered in combination with another agent for treatment of congestive heart failure, for example, a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

In a nineteenth aspect, the invention features a method for treating BPH, the method comprising administering a complete or partial agonist of the intestinal guanylate cyclase (GC-C) receptor. The agonist can be administered in combination with another agent for treatment of BPH, for example, a 5-alpha reductase inhibitor (e.g., finasteride) or an alpha adrenergic inhibitor (e.g., doxazosine).

In a twentieth aspect, the invention features a method for treating obesity, the method comprising administering a complete or partial agonist of the intestinal guanylate cyclase (GC-C) receptor. The agonist can be administered in combination with another agent for treatment of obesity, for example, gut hormone fragment peptide YY_{3-36} (PYY_{3-36})(*N. Engl. J. Med.* 349:941, 2003; ikpeapge daspeelnry yaslrhylnl vtrqry) glp-1 (glucagon-like peptide-1), exendin-4 (an inhibitor of glp-1), sibutramine, phentermine, phendimetrazine, benzphetamine hydrochloride (Didrex), orlistat (Xenical), diethylpropion hydrochloride (Tenuate), fluoxetine (Prozac), bupropion, ephedra, chromium, garcinia cambogia, benzocaine, bladderwrack (focus vesiculosus), chitosan, nomame herba, galega (Goat's Rue, French Lilac), conjugated linoleic acid, L-carnitine, fiber (psyllium, plantago, guar fiber), caffeine, dehydroepiandrosterone, germander (teucrium chamaedrys), B-hydroxy-β-methylbutyrate, and pyruvate. A peptide useful for treating obesity can be administered as a co-therapy with a peptide of the invention either as a distinct molecule or as part of a fusion protein with a peptide of the invention. Thus, for example, PYY_{3-36} can be fused to the carboxy or amino terminus of a peptide of the

invention. Such a fusion protein can include a chymostrypsin or trypsin cleavage site that can permit cleavage to separate the two peptides.

The peptides and agonist of the intestinal guanylate cyclase (GC-C) receptor can be used to treat constipation or decreased intestinal motility, slow digestion or slow stomach emptying. The peptides can be used to relieve one or more symptoms of IBS (bloating, pain, constipation), GERD (acid reflux into the esophagus), functional dyspepsia, or gastroparesis (nausea, vomiting, bloating, delayed gastric emptying) and other disorders described herein..

The details of one or more embodiments of the invention are set forth in the accompanying description. All of the publications, patents and patnet applications are hereby incorporated by reference.

FIGURES

Figure 1a depicts the results of LCMS analysis of recombinant MM-416776 peptide and MD-915 peptide.

Figures 1b and c depict the results of LCMS analysis of synthetic MD-1100 peptide and the blank.

Figure 2 depicts the results of the intestinal GC-C receptor activity assay of synthetic MM-416776 peptide, MD-915 peptide and two different MD-1100 peptides.

Figure 3a depicts the effect of recombinant MM-416776 peptide and Zelnorm® in a murine gastrointestinal transit model.

Figure 3b depicts the effect of synthetic MD-1100 peptide and Zelnorm® in an acute murine gastrointestinal transit model.

Figure 3b depicts the effect of synthetic MD-1100 peptide and Zelnorm® in an chronic murine gastrointestinal transit model.

Figures 4a and 4b depict the effect of peptides MD-915, MD-1100, and MM-416776 in an acute murine gastrointestinal transit model.

Figure 4c depicts the effect of MD-1100 peptide in a chronic murine gastrointestinal transit model.

Figure 5a depicts the effect of MM-416776 peptide and Zelnorm® in a suckling mouse intestinal secretion model.

Figure 5b depicts the effects of MD-1100 and Zelnorm® in a mouse intestinal secretion model.

Figures 6a and 6b depict the effects of MM 416776, MD-1100 and MD-915 peptides in a mouse intestinal secretion model.

Figure 7 shows the results of experiment in which MD-1100 activity was analyzed in the TNBS colonic distention model.

Figures 8a and 8b show the effects of differing doses of MD-915 and MD-1100 in the PBQ writhing assay.

Figure 9 shows the results of Kd determination analysis using MD-1100 in a competitive radioligand binding assay.

Figures 10a and 10b show bioavailability data for IV and orally administered MD-1100 as detected by an ELISA assay and LCMS.

DETAILED DESCRIPTION

The peptides of the invention bind to the intestinal guanylate cyclase (GC-C) receptor, a key regulator of fluid and electrolyte balance in the intestine. When stimulated, this

receptor, which is located on the apical membrane of the intestinal epithelial surface, causes an increase in intestinal epithelial cyclic GMP (cGMP). This increase in cGMP is believed to cause a decrease in water and sodium absorption and an increase in chloride and potassium ion secretion, leading to changes in intestinal fluid and electrolyte transport and increased intestinal motility. The intestinal GC-C receptor possesses an extracellular ligand binding region, a transmembrane region, an intracellular protein kinase-like region and a cyclase catalytic domain. Proposed functions for the GC-C receptor are fluid and electrolyte homeostasis, the regulation of epithelial cell proliferation and the induction of apoptosis (Shalubhai 2002 Curr Opin Drug Dis Devel 5:261-268).

In addition to being expressed in the intestine by gastrointestinal epithelial cells, GC-C is expressed in extra-intestinal tissues including kidney, lung, pancreas, pituitary, adrenal, developing liver (reviewed in Vaandrager 2002, Mol Cell Biochem 230:73-83) and male and female reproductive tissues (reviewed in Vaandrager 2002 *Mol Cell Biochem* 230:73-83)) This suggests that the GC-C receptor agonists can be used in the treatment of disorders outside the GI tract, for example, congestive heart failure and benign prostatic hyperplasia.

Ghrelin, a peptide hormone secreted by the stomach, is a key regulator of appetite in humans. Ghrelin expression levels are regulated by fasting and by gastric emptying (Kim et al., 2003, Neuroreprt 14:1317-20; Gualillo et al., 2003, FEBS Letts 552: 105-9). Thus, by increasing gastrointestinal motility, GC-C receptor agonists may also be used to regulate obesity.

In humans, the GC-C receptor is activated by guanylin (Gn) (U.S. Patent 5,96,097), uroguanylin (Ugn) (U.S. Patent 5,140,102) and lymphoguanylin (Forte et al., 1999, *Endocrinology* 140:1800-1806). Interestingly, these agents are 10-100 fold less potent than a class of bacterially derived peptides, termed ST (reviewed in Gianella 1995 J Lab Clin Med 125:173-181). ST peptides are considered super agonists of GC-C and are very resistant to proteolytic degradation.

ST peptide is capable of stimulating the enteric nervous system (Rolfe et al., 1994, J Physiolo 475: 531-537; Rolfe et al., 1999, Gut 44: 615-619; Nzegwu et al., 1996, Exp Physiol 81: 313-315). Also, cGMP has been reported to have anitnociceptive effects in multiple animal models of pain (Lazaro Ibanez et al., 2001, Eur J Pharmacol 426: 39-44; Soares et al., 2001, British J Pharmacol 134: 127-131; Jain et al., 2001, Brain Res 909:170-178; Amarante et al., 2002, Eur J Pharmacol 454:19-23). Thus, GC-C agonists may have both an analgesic as well an anti-inflammatory effect.

In bacteria, ST peptides are derived from a preproprotein that generally has at least 70 amino acids. The pre and pro regions are cleaved as part of the secretion process, and the resulting mature protein, which generally includes fewer than 20 amino acids, is biologically active.

Among the known bacterial ST peptides are: *E. coli* ST Ib (Moseley et al. (1983) *Infect. Immun.* 39:1167) having the mature amino acid sequence Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:__); *E. coli* ST Ia (So and McCarthy (1980) *Proc. Natl. Acad. Sci.* USA 77:4011) having the mature amino acid sequence Asn Thr Phe Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Ala Gly Cys Tyr (SEQ ID NO:__); *E. coli* ST I* (Chan and Giannella (1981) *J. Biol. Chem.* 256:7744) having the mature amino acid sequence Asn Thr Phe Tyr Cys Cys Glu Leu Cys Cys Tyr Pro Ala Cys Ala Gly Cys Asn (SEQ ID NO:___); *C.freundii* ST peptide (Guarino et al. (1989) *Infect. Immun.* 57:649) having the mature amino acid sequence Asn Thr Phe Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Ala Gly Cys Tyr (SEQ ID NO:__); *Y. enterocolitica* ST peptides, Y-ST(Y-STa), Y-STb, and Y-STc (reviewed in Huang et al. (1997) *Microb. Pathog.* 22:89) having the following pro-form amino acid sequences: Gln Ala Cys Asp Pro Pro Ser Pro Pro Ala Glu Val Ser Ser Asp Trp Asp Cys Cys Asp Val Cys Cys Asn Pro Ala Cys Ala Gly Cys (SEQ ID NO:___) (as well as a Ser-7 to Leu-7 variant of Y-STa (SEQ ID NO:___), (Takao et al. (1985) *Eur. J. Biochem.* 152:199)); Lys Ala Cys Asp Thr Gln Thr Pro Ser Pro Ser Glu Glu Asn Asp Asp Trp Cys Cys Glu Val Cys Cys Asn Pro Ala Cys Ala Gly Cys (SEQ ID NO:___); Gln Glu Thr Ala Ser Gly Gln Val Gly Asp Val Ser Ser Ser Thr Ile Ala Thr Glu Val Ser Glu Ala Glu Cys Gly Thr Gln Ser Ala Thr

Thr Gln Gly Glu Asn Asp Trp Asp Trp Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Phe Gly Cys (SEQ ID NO:___), respectively; *Y. kristensenii* ST peptide having the mature amino acid sequence Ser Asp Trp Cys Cys Glu Val Cys Cys Asn Pro Ala Cys Ala Gly Cys (SEQ ID NO:___); V. *cholerae* non-01 ST peptide (Takao et al. (1985) *FEBS lett.* 193:250) having the mature amino acid sequence Ile Asp Cys Cys Glu Ile Cys Cys Asn Pro Ala Cys Phe Gly Cys Leu Asn (SEQ ID NO:__); and *V. mimicus* ST peptide (Arita (1991) et al. *FEMS Microbiol. Lett.* 79:105) having the mature amino acid sequence Ile Asp Cys Cys Glu Ile Cys Cys Asn Pro Ala Cys Phe Gly Cys Leu Asn (SEQ ID NO:__). The Table below provides sequences of all or a portion of a number of mature ST peptides.

GenBank® Accession	**GenBank® GI**	**Sequence**
QHECIB	69638	NSSNYCCELCCNPACTGCY(SEQ ID NO:__)
P01559	123711	NTFYCCELCCNPACAGCY(SEQ ID NO:__)
AAA24653	147878	NTFYCCELCCNPACAPCY(SEQ ID NO:__)
P01560	123707	NTFYCCELCCYPACAGCN(SEQ ID NO:__)
AAA27561	295439	IDCCEICCNPACFGCLN(SEQ ID NO:__)
P04429	123712	IDCCEICCNPACFGCLN(SEQ ID NO:__)
S34671	421286	IDCCEICCNPACF(SEQ ID NO:__)
CAA52209	395161	IDCCEICCNPACFG(SEQ ID NO:__)
A54534	628844	IDCCEICCNPACFGCLN(SEQ ID NO:__)
AAL02159	15592919	IDRCEICCNPACFGCLN(SEQ ID NO:__)
AAA18472	487395	DWDCCDVCCNPACAGC(SEQ ID NO:__)
S25659	282047	DWDCCDVCCNPACAGC(SEQ ID NO:__)
P74977	3913874	NDDWCCEVCCNPACAGC(SEQ ID NO:__)

BAA23656	2662339	WDWCCELCCNPACFGC(SEQ ID NO:__)
P31518	399947	SDWCCEVCCNPACAGC(SEQ ID NO:__)

The immature (including pre and pro regions) form of *E. coli* ST-1A (ST-P) protein has the sequence: mkklmlaifisvlsfpsfsqstesldsskekitletkkcdvvknnsekksenmnntfyccelccnpacagcy (SEQ ID NO:___; see GenBank® Accession No. P01559 (gi:123711). The pre sequence extends from aa 1-19. The pro sequence extends from aa 20-54. The mature protein extends from 55-72. The immature (including pre and pro regions) form of *E. coli* ST-1B (ST-H) protein has the sequence: mkksilfiflsvlsfspfaqdakpvesskekitleskkcniakksnksgpesmnssnyccelccnpactgcy (SEQ ID NO:___; see GenBank® Accession No. P07965 (gi:3915589). The immature (including pre and pro regions) form of *Y. enterocolitica* ST protein has the sequence: mkkivfvlvlmlssfgafgqetvsgqfsdalstpitaevykqacdpplppaevssdwdccdvccnpacagc (SEQ ID NO:___; see GenBank® Accession No. S25659 (gi:282047).

The peptides of the invention, like the bacterial ST peptides, have six Cys residues. These six Cys residues form three disulfide bonds in the mature and active form of the peptide. If the six Cys residues are identified, from the amino to carboxy terminus of the peptide, as A, B, C, D, E, and F, then the disulfide bonds form as follows: A-D, B-E, and C-F. The formation of these bonds is thought to be important for GC-C receptor binding. Certain of the peptides of the invention include a potentially functional chymotrypsin cleavage site, e.g., a Trp, Tyr or Phe located between either Cys B and Cys D or between Cys E and Cys F. Cleavage at either chymotrypsin cleavage site reduces or eliminates the ability of the peptide to bind to the GC-C receptor.

In the human body an inactive form of chymotrypsin, chymotrypsinogen is produced in the pancreas. When this inactive enzyme reaches the small intestine it is converted to active chymotrypsin by the excision of two di-peptides. Active chymotrypsin can potentially cleave peptides at the peptide bond on the carboxy-terminal side of Trp, Tyr or Phe. The presence of active chymotrypsin in the intestinal tract can potentially

lead to cleavage of certain of the peptides of the invention having an appropriately positioned functional chymotrypsin cleavage site. It is expected that chymotrypsin cleavage will moderate the action of a peptide of the invention having an appropriately positioned chymotrypsin cleavage site as the peptide passes through the intestinal tract.

Trypsinogen, like chymotrypsin, is a serine protease that is produced in the pancreas and is present in the digestive tract. The active form, trypsin, will cleave peptides having a Lys or Arg. The presence of active trypsin in the intestinal tract can lead to cleavage of certain of the peptides of the invention having an appropriately positioned functional trypsin cleavage site. It is expected that chymotrypsin cleavage will moderate the action of a peptide of the invention having an appropriately positioned trypsin cleavage site as the peptide passes through the intestinal tract.

Many gastrointestinal disorders, including IBS, are associated with abdominal or visceral pain. Certain of the peptides of the invention include analgesic or antinociceptive tags such as the carboxy-terminal sequence AspPhe immediately following a Trp, Tyr or Phe that creates a functional chymotrypsin cleavage site or following Lys or Arg that creates a functional trypsin cleavage site. Chymotrypsin in the intestinal tract can potentially cleave such peptides immediately carboxy terminal to the Trp, Phe or Tyr residue, releasing the dipeptide, AspPhe. This dipeptide has been shown to have analgesic activity in animal models (Abdikkahi et al. 2001, Fundam Clin Pharmacol 15:117-23; Nikfar et al 1997, 29:583-6; Edmundson et al 1998, Clin Pharmacol Ther 63:580-93). In this manner such peptides can treat both pain and inflammation. Other analgesic peptides can be present at the carboxy terminus of the peptide (following a functional cleavage site) including: endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance P.
A number of the useful peptides are based on the core sequence: Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr. To create a variant having a potentially functional chymotrypsin cleavage site capable of inactivating the peptide, either the Leu (underlined) or the Thr (underlined) can be replaced by Trp, Phe or Tyr or both the Leu and the Thr can be replaced by (independently) Trp, Phe or Tyr. To create a

variant having an analgesic di-peptide, the core sequence is followed by Asp Phe. The carboxy terminal Tyr in the core sequence can allow the Asp Phe dipeptide to be released by chymotrypsin in the digestive tract. The core sequence can be optionally be preceded by Asn Ser Ser Asn Tyr or Asn.

Thus, useful variants based on the core sequence include:

Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MM-416776)

Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr (SEQ ID NO:---)

Asn Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---; MD-915)

Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MM416774)

Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr (SEQ ID NO:---)

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MD-1100)

Asn Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr (SEQ ID NO:---)

Asn Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---)

Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe

(SEQ ID NO:---)

Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr Asp Phe

(SEQ ID NO:---)

Asn Ser Ser Asn Tyr Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe

(SEQ ID NO:---)

Asn Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe

(SEQ ID NO:---)

Asn Ser Ser Asn Tyr Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe

(SEQ ID NO:---)

Asn Ser Ser Asn Tyr Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe

(SEQ ID NO:---)

Asn Ser Ser Asn Tyr Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe

(SEQ ID NO:---)

Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Asn Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Asn Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Asn Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Asn Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Asn Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Asn Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

Asn Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---)

In some cases, the peptides of the invention are produced as a prepro protein that includes the amino terminal leader sequence: mkksilfiflsvlsfspfaqdakpvesskekitleskkcniakksnksgpesmn. Where the peptide is produced by a bacterial cell, e.g., *E. coli*, the forgoing leader sequence will be cleaved and the mature peptide will be efficiently secreted from the bacterial cell. U.S. Patent No. 5,395,490 describes vectors, expression systems and methods for the efficient production of ST peptides in bacterial cells and methods for achieving efficient secretion of mature ST peptides. The vectors, expression systems and methods described in U.S. Patent No. 5,395,490 can be used to produce the ST peptides and variant ST peptides of the present invention

Variant Peptides

The invention includes variant peptides which can include one, two, three, four, five, six, seven, eight, nine, or ten (in some embodiments fewer than 5 or fewer than 3 or 2 or fewer) amino acid substitutions compared to SEQ ID NOs:____ to ___. The substitution(s) can be conservative or non-conservative. The naturally-occurring amino acids can be substituted by D-isomers of any amino acid, non-natural amino acids, and other groups. A conservative amino acid substitution results in the alteration of an amino acid for a similar acting amino acid, or amino acid of like charge, polarity, or hydrophobicity. At some positions, even conservative amino acid

substitutions can reduce the activity of the peptide. Among the naturally occurring amino acid substitutions generally considered conservative are:

For Amino Acid	Code	Replace with any of
Alanine	Ala	Gly, Cys, Ser
Arginine	Arg	Lys, His
Asparagine	Asn	Asp, Glu, Gln,
Aspartic Acid	Asp	Asn, Glu, Gln
Cysteine	Cys	Met, Thr, Ser
Glutamine	Gln	Asn, Glu, Asp
Glutamic Acid	Glu	Asp, Asn, Gln
Glycine	Gly	Ala
Histidine	His	Lys, Arg
Isoleucine	Ile	Val, Leu, Met
Leucine	Leu	Val, Ile, Met
Lysine	Lys	Arg, His
Methionine	Met	Ile, Leu, Val
Phenylalanine	Phe	Tyr, His, Trp
Proline	Pro	
Serine	Ser	Thr, Cys, Ala
Threonine	Thr	Ser, Met, Val
Tryptophan	Trp	Phe, Tyr
Tyrosine	Tyr	Phe, His
Valine	Val	Leu, Ile, Met

In some circumstances it can be desirable to treat patients with a variant peptide that binds to and activates intestinal GC-C receptor, but is less active than the non-variant form the peptide. This reduced activity can arise from reduced affinity for the receptor or a reduced ability to activate the receptor once bound or reduced stability of the peptide.

In some peptides pairs of Cys residues which normally form a disulfide bond one or both members of the pair can be replaced by homocysteine, 3-mercaptoproline (Kolodziej et al. 1996 Int J Pept Protein Res 48:274); β, β dimethylcysteine (Hunt et al. 1993 Int J Pept Protein Res 42:249) or diaminopropionic acid (Smith et al. 1978 J Med Chem 21:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

Production of peptides

Useful peptides can be produced either in bacteria including, without limitation, *E. coli*, or in other existing systems for peptide or protein production (e.g., *Bacillus subtilis,* baculovirus expression systems using Drosophila Sf9 cells, yeast or filamentous fungal expression systems, mammalian cell expression systems), or they can be chemically synthesized.

If the peptide or variant peptide is to be produced in bacteria, e.g., *E. coli*, the nucleic acid molecule encoding the peptide will preferably also encode a leader sequence that permits the secretion of the mature peptide from the cell. Thus, the sequence encoding the peptide can include the pre sequence and the pro sequence of, for example, a naturally-occurring bacterial ST peptide. The secreted, mature peptide can be purified from the culture medium.

The sequence encoding a peptide of the invention is preferably inserted into a vector capable of delivering and maintaining the nucleic acid molecule in a bacterial cell. The DNA molecule may be inserted into an autonomously replicating vector (suitable vectors include, for example, pGEM3Z and pcDNA3, and derivatives thereof). The vector nucleic acid may be a bacterial or bacteriophage DNA such as bacteriophage lambda or M13 and derivatives thereof. Construction of a vector containing a nucleic acid described herein can be followed by transformation of a host cell such as a bacterium. Suitable bacterial hosts include but are not limited to, *E. coli, B. subtilis*, *Pseudomonas*, *Salmonella*. The genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences. A variety of transcriptional control sequences are well known to those in the art. The expression vector can also include a translation regulatory sequence (e.g., an untranslated 5' sequence, an untranslated 3' sequence, or an internal ribosome entry site). The vector can be capable of autonomous replication or it can integrate into host DNA to ensure stability during peptide production.

The protein coding sequence that includes a peptide of the invention can also be fused to a nucleic acid encoding a polypeptide affinity tag, e.g., glutathione S-transferase (GST), maltose E binding protein, protein A, FLAG tag, hexa-histidine, myc tag or the influenza HA tag, in order to facilitate purification. The affinity tag or reporter fusion joins the reading frame of the peptide of interest to the reading frame of the gene encoding the affinity tag such that a translational fusion is generated. Expression of the fusion gene results in translation of a single polypeptide that includes both the peptide of interest and the affinity tag. In some instances where affinity tags are utilized, DNA sequence encoding a protease recognition site will be fused between the reading frames for the affinity tag and the peptide of interest.

Genetic constructs and methods suitable for production of immature and mature forms of the peptides and variants of the invention in protein expression systems other than bacteria, and well known to those skilled in the art, can also be used to produce peptides in a biological system.

Mature peptides and variants thereof can be synthesized by the solid-phase method using an automated peptide synthesizer. For example, the peptide can be synthesized on Cyc(4-CH_2 Bxl)-OCH_2-4-(oxymethyl)-phenylacetamidomethyl resin using a double coupling program. Protecting groups must be used appropriately to create the correct disulfide bond pattern. For example, the following protecting groups can be used: t-butyloxycarbonyl (alpha-amino groups); acetamidomethyl (thiol groups of Cys residues B and E); 4-methylbenyl (thiol groups of Cys residues C and F); benzyl (y-carboxyl of glutamic acid and the hydroxyl group of threonine, if present); and bromobenzyl (phenolic group of tyrosine, if present). Coupling is effected with symmetrical anhydride of t-butoxylcarbonylamino acids or hydroxybenzotriazole ester (for asparagine or glutamine residues), and the peptide is deprotected and cleaved from the solid support in hydrogen fluoride, dimethyl sulfide, anisole, and p-thiocresol using 8/1/1/0.5 ratio (v/v/v/w) at 0°C for 60 min. After removal of hydrogen fluoride and dimethyl sulfide by reduced pressure and anisole and p-thiocresol by extraction with ethyl ether and ethyl acetate sequentially, crude peptides are extracted with a mixture of 0.5M sodium phosphate buffer, pH 8.0 and N, N-

dimethylformamide using 1/1 ratio, v/v. The disulfide bond for Cys residues B and E is the formed using dimethyl sulfoxide (Tam et al. (1991) *J. Am. Chem. Soc.* 113:6657-62). The resulting peptide is the purified by reverse-phase chromatography. The disulfide bond between Cys residues C and F is formed by first dissolving the peptide in 50% acetic acid in water. Saturated iodine solution in glacial acetic acid is added (1 ml iodine solution per 100 ml solution). After incubation at room temperature for 2 days in an enclosed glass container, the solution is diluted five-fold with deionized water and extracted with ethyl ether four times for removal of unreacted iodine. After removal of the residual amount of ethyl ether by rotary evaporation the solution of crude product is lyophilized and purified by successive reverse-phase chromatography.

Intestinal GC-C receptor binding assay

The ability of peptides and other agents to bind to the intestinal GC-C receptor can be tested as follows. Cells of the T84 human colon carcinoma cell line (American Type Culture Collection (Bethesda, Md.) are grown to confluence in 24-well culture plates with a 1:1 mixture of Ham's F12 medium and Dulbecco's modified Eagle's medium (DMEM), supplemented with 5% fetal calf serum. Cells used in the assay are typically between passages 54-60. Briefly, T84 cell monolayers in 24-well plates are washed twice with 1 ml of binding buffer (DMEM containing 0.05% bovine serum albumin and 25 mM HEPES, pH 7.2), then incubated for 30 min at 37°C in the presence of mature radioactively labeled *E. coli* ST peptide and the test material at various concentrations. The cells are then washed four times with 1 ml of DMEM and solubilized with 0.5 ml/well 1N NaOH. The level of radioactivity in the solubilized material is then determined using standard methods.

Example 1: Preparation of variant ST peptides and wild-type ST peptide

1a: Preparation of recombinant variant ST peptides and wild-type ST peptide

A variant ST peptide, referred to as MD-915, was reproduced recombinantly and tested in an animal model. MD-915 has the sequence: Asn Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---). A peptide having the sequence of the wild-type ST peptide was also created (MM-416776).

MD-915 and MM-416776 peptides were produced as preproproteins using vectors produced as follows. A sequence encoding a heat-stable enterotoxin pre-pro sequence was amplified from pGK51/pGSK51 (ATCC 67728) using oligonucleotide MO3514 (5' CACACCATATGAAGAAATCAATATTATTTATTTTTCTTTCTG 3' (SEG ID NO:)) and oligonucelotide MO3515 (5' CACACCTCGAGTTAGGTCTCCATGCTTTCAGGACCACTTTTATTAC 3' (SEQ ID NO: __)). The amplification product fragment was digested with NdeI/XhoI and ligated to the T7 expression vector, pET26b(+) (Novagen) digested with NdeI/XhoI thereby creating plasmid MB3976. The region encoding the pre-pro protein was sequenced and found to encode the amino acid sequence: mkksilfiflsvlsfspfaqdakpagsskekitleskkcnivkk**s**n**k**s**g**pesm (SEQ ID NO: __) which differs from the amino acid sequence of heat-stable enterotoxin a2 precursor (sta2; mkksilfiflsvlsfspfaqdakpagsskekitleskkcnivkknnesspesm (SEQ ID NO:___); GenBank® Accession No. Q47185, GI: 3913876) at three positions (indicated by underlining and bold text) near the C-terminus. To create expression vectors with the pre-pro sequence, complementary oligos encoding each ST peptide variant or wild-type ST peptide were annealed and cloned into the MB3976 expression vector. To create MB3984 (encoding MM-416776 peptide full length wild-type ST peptide as a prepro protein), containing the amino acid sequence, NSSNYCCELCCNPACTGCY (SEQ ID NO:___) fused downstream of the pre-pro sequence, MB 3976 was digested with BsaI/XhoI and ligated to annealed oligos MO3621 (5' GCATGAATAGTAGCAATTACTGCTGTGAATTGTGTTGTAATCCTGCTTGTAC CGGGTGCTATTAATAAC 3' (SEQ ID NO:__)) and MO3622 (5' TCGAGTTATTAATAGCACCCGGTACAAGCAGGATTACAACACAATTCACAG CAGTAATTGCTACTATTC 3'(SEQ ID NO:__)). To create MB3985 (encoding MD-915 as a prepro protein) containing the following amino acid sequence, NSSNYCCEYCCNPACTGCY fused downstream of the pre-pro sequence, MB 3976

was digested with BsaI/XhoI and ligated to annealed oligos MO3529 (5' GCATGAATAGTAGCAATTACTGCTGTGAATATTGTTGTAATCCTGCTTGTACC GGGTGCTATTAATAAC 3' (SEQ ID NO:__)) and MO3530 (5' TCGAGTTATTAATAGCACCCGGTACAAGCAGGATTACAACAATATTCACAGC AGTAATTGCTACTATTC 3'(SEQ ID NO:__)).

The MD-915 peptide and the MM-416776 peptide were produced as follows. The expression vectors were transformed into *E. coli* bacterial host BL21 λ DE3 (Invitrogen). A single colony was innoculated and grown shaking overnight at 30°C in L broth + 25 mg/l kanamycin. The overnight culture was added to 3.2 L of batch medium (Glucose 25 g/l, Caseamino Acids 5 g/l, Yeast Extract 5 g/l, KH_2PO_4 13.3 g/l, $(NH_4)_2HPO_4$ 4 g/l, $MgSO_4$-$7H_20$ 1.2 g/l, Citric Acid 1.7 g/l, EDTA 8.4 mg/l, $CoCl_2$-$6H_2O$ 2.5 mg/l, $MnCl_2$-$4H_2O$ 15 mg/l, $CuCl_2$-$4H_20$ 1.5 mg/l, H_3BO_3 3 mg/l, Na_2MoO_4-$2H_20$ 2.5 mg/l, Zn Acetate-$2H_20$ 13 mg/l, Ferric Citrate 100 mg/l, Kanamycin 25 mg/l, Antifoam DF_20_4 1 ml/l) and fermented using the following process parameters : pH 6.7 - control with base only (28% NH_4OH), 30°C, aeration : 5 liters per minute. After the initial consumption of batch glucose (based on monitoring dissolved oxygen (DO) levels), 1.5 L of feed medium (Glucose 700 g/l, Caseamino Acids 10 g/l, Yeast Extract 10 g/l, $MgSO_4$-$7H_20$ 4 g/l, EDTA 13 mg/l, $CoCl_2$-$6H_2O$ 4 mg/l, $MnCl_2$-$4H_2O$ 23.5 mg/l, $CuCl_2$-$4H_20$ 2.5 mg/l, H_3BO_3 5 mg/l, Na_2MoO_4-$2H_20$ 4 mg/l, Zn Acetate-$2H_20$ 16 mg/l, Ferric Citrate 40 mg/l, Antifoam DF_20_4 1 ml/l) was added at a feed rate controlled to maintain 20% DO. IPTG was added to 0.2 mM 2 hours post feed start. The total run time was approximately 40-45 hours (until feed exhaustion).

Cells were collected by centrifugation at 5,000 g for 10 minutes. The cell pellet was discarded and the supernatant was passed through a 50 Kd ultrafiltration unit. The 50 Kd filtrate (0.6 liters) was loaded onto a 110 ml Q-Sepharose fast Flow column (Amersham Pharmacia, equilibrated with 20 mM Tris-HCl pH 7.5) at a flow rate of 400 ml/hour. The column was washed with six volumes of 20 mM Tris-HCl pH 7.5 and proteins were eluted with 50 mM acetic acid collecting 50 ml fractions. Fractions containing ST peptide variant or wild-type ST peptide were pooled and the solvent

was removed by rotary evaporation. The dried proteins were resuspended in 10 ml of 8% acetic acid, 0.1% trifluoroacetic acid (TFA) and loaded onto a Varian Polaris C18-A column (250 X 21.2 mm 10 μm, equilibrated in the same buffer) at a flow rate of 20 ml/min. The column was washed with 100 ml of 8% methanol, 0.1% TFA and developed with a gradient (300 ml) of 24 to 48% methanol, 0.1% TFA, collecting 5-ml fractions. Fractions containing peptide were pooled and the solvent was removed by rotary evaporation. The peptides were dissolved in 0.1%TFA and lyophilized.

The MD-915 peptide and MM-416776 peptide fractions were analyzed by standard LCMS and HPLC. LCMS analysis revealed that MD-915 is more homogeneous than MM-416776 (see Figure 1a; note that MD-915 peptide exhibits fewer peaks (Panel B) than MM-416776 (Panel A)).

1b: Preparation of synthetic variant ST peptides and wild-type ST peptide

Peptides were chemically synthesized by a commercial peptide synthesis company. Varying yields of peptides were obtained depending on the efficiency of chemical synthesis. Thus, the four peptides, in decreasing order of yield were: Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--;MD-1100), 10-20% yield; Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--;MM416774); Asn Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MD-915); Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--MM-416776), <5% yield. Thus the specific amino acid changes introduced into the peptides can create improved manufacturing properties.

Figure 1b shows the total ion chromatograph profile of synthetically manufactured MD-1100. Figure 1c shows the total ion chromatograph profile of the control blank sample. There is one major peak present in the MD-1100 sample that is not also present in the control sample. Quantitative analysis suggests the MD-1100 is >98% pure.

Example 2: Activation of the intestinal GC-C receptor by a variant ST peptide and ST peptide

The ability of MD-915, MM-416776, and MD-1100 to activate the intestinal GC-C receptor was assessed in an assay employing the T84 human colon carcinoma cell line (American Type Culture Collection (Bethesda, Md.). For the assays cells were grown to confluency in 24-well culture plates with a 1:1 mixture of Ham's F12 medium and Dulbecco's modified Eagle's medium (DMEM), supplemented with 5% fetal calf serum and were used at between passages 54 and 60.

Briefly, monolayers of T84 cells in 24-well plates were washed twice with 1 ml/well DMEM, then incubated at 37°C for 10 min with 0.45 ml DMEM containing 1 mM isobutylmethylxanthine (IBMX), a cyclic nucleotide phosphodiesterase inhibitor. Test peptides (50µl) were then added and incubated for 30 minutes at 37°C. The media was aspirated and the reaction was then terminated by the addition of ice cold 0.5 ml of 0.1N HCl. The samples were held on ice for 20 minutes and then evaporated to dryness using a heat gun or vacuum centrifugation. The dried samples were resuspended in 0.5ml of phosphate buffer provided in the Cayman Chemical Cyclic GMP EIA kit (Cayman Chemical, Ann Arbor, MI). Cyclic GMP was measured by EIA according to procedures outlined in the Cayman Chemical Cyclic GMP EIA kit.

Figure 2 shows the activity of chemically synthesized peptide variants in this GC-C receptor activity assay. In this assay, MM-416776 and two different MD-1100 peptides (MD-1100(a) and MD-1100(b), synthesized by two different methods) had activity comparable to MM-416776. MD-915 and MM-416776 peptide were chemically synthesized in a manner identical to that of MD-1100(b).

Example 3: MD-915 and MM-416776 increase intestinal transit in mice

In order to determine whether the peptides increase the rate of gastrointestinal transit, the peptides and controls were tested using a murine gastrointestinal transit (GIT)

assay (Moon et al. *Infection and Immunity* 25:127, 1979). In this assay, charcoal, which can be readily visualized in the gastrointestinal tract is administered to mice after the administration of a test compound. The distance traveled by the charcoal is measured and expressed as a percentage of the total length of the colon.

Mice were fasted with free access to water for 12 to 16 hours before the treatment with peptide or control buffer. The peptides were orally administered at 1μg/kg – 1mg/kg of peptide in buffer (20mM Tris pH 7.5) 7 minutes before being given an oral dose of 5% Activated Carbon (Aldrich 242276-250G). Control mice were administered buffer only before being given a dose of Activated Carbon. After 15 minutes, the mice were sacrificed and their intestines from the stomach to the cecum were dissected. The total length of the intestine as well as the distance traveled from the stomach to the charcoal front was measured for each animal and the results are expressed as the percent of the total length of the intestine traveled by the charcoal front. All results are reported as the average of 10 mice ± standard deviation. A comparison of the distance traveled by the charcoal between the mice treated with peptide versus the mice treated with vehicle alone was performed using a Student's t test and a statistically significant difference was considered for $P<0.05$. P-values are calculated using a two-sided T-Test assuming unequal variances.

As can be seen in Figure 3a, b, wild-type ST peptide (MM-416776, (Sigma-Aldrich, St Louis, MO; 0.1 mg/kg), synthetically manufactured MD-1100 and Zelnorm® (0.1 mg/kg), a drug approved for IBS that is an agonist for the serotonin receptor 5HT4, increase gastrointestinal transit rate in this model. Figure 4a shows the result of a study demonstrating that intestinal transit rate increases with an increasing dosage of either recombinantly synthesized MM-416776 or MD-915. Figure 4b shows the results of a study demonstrating both chemically synthesized MM-416776 or MD-1100 peptide increase intestinal transit rates more than either Tris buffer alone or an equivalent dose of Zelnorm®.

The identical experiment was performed to determine if MD-1100 is effective in a chronic dosing treatment regimen. Briefly, 8 week old CD1 female mice are dosed

orally once a day for 5 days with either MD-1100 (0.06mg/kg or 0.25mg/kg in 20mM Tris pH 7.5) or vehicle alone (20mM Tris pH 7.5). On the 5th day, a GIT assay is performed identical to that above except 200µl of a 10% charcoal solution is administered. Figure 4c shows the results of a study demonstrating both chemically synthesized MD-1100 or Zelnorm® are effective in a mouse gastrointestinal motility assay upon chronic dosing (daily for 5 days). The results are shown side by side with acute dosing (1 day).

Example 4: MD-915 peptide and MM-416776 peptide increase intestinal secretion in suckling mice (SuMi assay)

MM-416776 peptide and MD-915 were tested for their ability to increase intestinal secretion using a suckling mouse model of intestinal secretion. In this model a test compound is administered to suckling mice that are between 7 and 9 days old. After the mice are sacrificed, the gastrointestinal tract from the stomach to the cecum is dissected ("guts"). The remains ("carcass") as well as the guts are weighed and the ratio of guts to carcass weight is calculated. If the ratio is above 0.09, one can conclude that the test compound increases intestinal secretion. Figure 5a shows a dose response curve for wild-type ST peptide (MM-416776) in this model. Figure 5b shows dose response curve for the MD-1100 peptide in this model. These data show that wild-type ST peptide (purchased from TDT, Inc. West Chester, PA) and the MD-1100 peptide increase intestinal secretion. The effect of Zelnorm® was also studied. As can be seen from Figure 5, Zelnorm® at 0.2 mg/kg does not increase intestinal secretion in this model. Figure 6a shows a dose response curve for the recombinant MM-416776 peptide described above and the recombinant MD-915 peptide described above. As can be seen from Figure 6a, both peptides increase intestinal secretion in this model. Similarly figure 6b shows a dose response curve for chemically synthesized MD-915, MD-1100 and MM-416776 as well as wild-type ST peptide (purchased from Sigma-Aldrich, St Louis, MO).

Colonic hyperalgesia animal models

Hypersensitivity to colorectal distension is common in patients with IBS and may be responsible for the major symptom of pain. Both inflammatory and non-inflammatory animal models of visceral hyperalgesia to distension have been developed to investigate the effect of compounds on visceral pain in IBS.

I. Trinitrobenzenesulphonic acid (TNBS)-induced rectal allodynia model

Male Wistar rats (220-250 g) were premedicated with 0.5 mg/kg of acepromazine injected intraperitoneally (IP) and anesthetized by intramuscular administration of 100 mg/kg of ketamine. Pairs of nichrome wire electrodes (60 cm in length and 80 μm in diameter) were implanted in the striated muscle of the abdomen, 2 cm laterally from the white line. The free ends of electrodes were exteriorized on the back of the neck and protected by a plastic tube attached to the skin. Electromyographic (EMG) recordings were started 5 days after surgery. Electrical activity of abdominal striated muscle was recorded with an electroencephalograph machine (Mini VIII, Alvar, Paris, France) using a short time constant (0.03 sec.) to remove low-frequency signals (<3 Hz).

Ten days post surgical implantation, trinitrobenzenesulphonic acid (TNBS) was administered to induce rectal inflammation. TNBS (80 mg kg^{-1} in 0.3 ml 50 % ethanol) was administered intrarectally through a silicone rubber catheter introduced at 3 cm from the anus under light diethyl-ether anesthesia, as described (Morteau et al. 1994 Dig Dis Sci 39:1239). Following TNBS administration, rats were placed in plastic tunnels where they were severely limited in mobility for several days before colorectal distension (CRD). Experimental compound was administered one hour before CRD which was performed by insertion into the rectum, at 1 cm of the anus, a 4 cm long balloon made from a latex condom (Gue et al, 1997 *Neurogastroenterol. Motil.* 9:271). The balloon was fixed on a rigid catheter taken from an embolectomy probe (Fogarty). The catheter attached balloon was fixed at the base of the tail. The balloon, connected to a barostat, was inflated progressively by step of 15 mmHg, from

0 to 60 mmHg, each step of inflation lasting 5 min. Evaluation of rectal sensitivity, as measured by EMG, was performed before (1-2 days) and 3 days following rectal instillation of TNBS.

The number of spike bursts that corresponds to abdominal contractions was determined per 5 min periods. Statistical analysis of the number of abdominal contractions and evaluation of the dose-effects relationships was performed by a one way analysis of variance (ANOVA) followed by a post-hoc (Student or Dunnett tests) and regression analysis for ED50 if appropriate.
Figure 7 shows the results of experiment in which MD-1100 activity was analyzed in the TNBS colorectal model. Significant decreases in abdominal response are observed at 0.3 μg/kg and 3 μg/kg MD-1100. These results demonstrate that MD-1100 reduces pain associated with colorectal distension in this animal model.

II. Stress-induced hyperalgesia model

Male Wistar Rats (200-250 g) are surgically implanted with nichrome wire electrodes as in the TNBS model. Ten days post surgical implantation, partial restraint stress (PRS), is performed as described by Williams et al. for two hours (Williams et al. 1988 Gastroenterology 64:611). Briefly, under light anesthesia with ethyl-ether, the foreshoulders, upper forelimbs and thoracic trunk are wrapped in a confining harness of paper tape to restrict, but not prevent body movements. Control sham-stress animals are anaesthetized but not wrapped. Thirty minutes before the end of the PRS session, the animals are administered test-compound or vehicle. Thirty minutes to one hour after PRS completion, the CRD distension procedure is performed as described above for the TNBS model with barostat at pressures of 15, 30, 45 and 60mm Hg. Statistical analysis on the number of bursts is determined and analyzed as in the TNBS model above.

Phenylbenzoquinone-induced writhing model

The PBQ-induced writhing model can be used to assess pain control activity of the peptides and GC-C receptor agonists of the invention. This model is described by

Siegmund et al. (1957 Proc. Soc. Exp. Bio. Med. 95:729-731). Briefly, one hour after oral dosing with a test compound, e.g., a peptide, morphine or vehicle, 0.02% phenylbenzoquinone (PBQ) solution (12.5 mL/kg) is injected by intraperitoneal route into the mouse. The number of stretches and writhings are recorded from the 5^{th} to the 10^{th} minute after PBQ injection, and can also be counted between the 35^{th} and 40^{th} minute and between the 60^{th} and 65^{th} minute to provide a kinetic assessment. The results are expressed as the number of stretches and writhings (mean ± SEM) and the percentage of variation of the nociceptive threshold calculated from the mean value of the vehicle-treated group. The statistical significance of any differences between the treated groups and the control group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software.

Figures 8a and 8b show the effect of different doses of MD-915 and MD-1100 in the PBQ writhing assay. Indomethacin, an NSAID (nonsteroidal anti-inflammatory drug) with known pain control activity, was used as the positive control in the assay. Significant reductions in writhings were observed for MD-915 (1 mg/kg dose) and MD-1100 (2.5 mg/kg dose) compared to the vehicle control. Loss of efficacy at the highest dose tested has also been observed for multiple other compounds (such as 5HT-3 antagonists) tested in similar assays. The results of this study suggest that both MD-915 and MD-1100 have antinociceptive effects in this visceral pain model comparable to the intermediate doses of indomethacin.

Example 5: MD-1100 Kd determination

To determine the affinity of MD-1100 for GC-C receptors found in rat intestinal mucosa, a competition binding assay was performed using rate intestinal epithelial cells. Epithelial cells from the small intestine of rats were obtained as described by Kessler et al. (*J. Biol. Chem.* 245: 5281-5288 (1970)). Briefly, animals were sacrificed and their abdominal cavities exposed. The small intestine was rinsed with 300 ml ice cold saline or PBS. 10 cm of the small intestine measured at 10 cm from the pylorus was removed and cut into 1 inch segments. Intestinal mucosa was

extruded from the intestine by gentle pressure between a piece of parafilm and a P-1000 pipette tip. Intestinal epithelial cells were placed in 2 ml PBS and pipetted up and down with a 5 ml pipette to make a suspension of cells. Protein concentration in the suspension was measured using the Bradford method (*Anal. Biochem.* 72: 248-254 (1976)).

A competition binding assay was performed based on the method of Giannella et al. (*Am. J. Physiol.* 245: G492-G498) between [^{125}I] labeled MM-416776 and MD-1100. The assay mixture contained: 0.5 ml of DME with 20 mM HEPES-KOH pH 7.0, 0.9 mg of the cell suspension listed above, 21.4 fmol [^{125}I]-MM-416776 (42.8 pM), and different concentrations of competitor MD-1100 (0.01 to 1000 nM). The mixture was incubated at room temperature for 1 hour, and the reaction stopped by applying the mixture to GF/B glass-fiber filters (Whatman). The filters were washed with 5 ml ice-cold PBS and radioactivity was measured. Figure 9 shows that the Kd for MD-1100 in this assay is 4.5 nm. %B/Bo is the percentage of the ratio of radioactivity trapped in each sample (B) compared to the radioactivity retained in a control sample with no cold competitor (Bo). Giannella et al. (*Am. J. Physiol.*245: G492-G498) observed that the Kd for wild-type ST peptide in this same assay was ~13 nm.

Example 6: Pharmacokinetic properties of MD-1100

To study the pharmacokinetics of MD-1100, absorbability studies in mice were performed by administering MD-1100 intravaneously via tail vein injection or orally by gavage to 8-week-old CD1 mice. Serum was collected from the animals at various time points and tested for the presence of MD-1100 using a competitive enzyme-linked immunoabsorbent assay (Oxoid, ST EIA kit, Cat#TD0700). The assay utilized monoclonal antibodies against ST peptide (antibodies are provided in the Oxoid kit) and synthetically manufactured MD-1100. Figure 10a show absorption data for intravenously and orally administered MD-1100 as detected by the ELISA assay. MD-1100 appears to be minimally systemically absorbed and is < 2.2% bioavailable.

A similar bioavailability study was performed in which LCMS rather than ELISA was used to detect MD-1100. Initially, serum samples were extracted from the whole blood of exposed and control mice, then injected directly (10mL) onto an in-line solid phase extraction (SPE) column (Waters Oasis HLB 25mm column, 2.0 x 15mm direct connect) without further processing. The sample on the SPE column was washed with a 5% methanol, 95% dH_2O solution (2.1 mL/min, 1.0 minute), then loaded onto an analytical column using a valve switch that places the SPE column in an inverted flow path onto the analytical column (Waters Xterra MS C8 5mm IS column, 2.1 x 20mm). The sample was eluted from the analytical column with a reverse phase gradient (Mobile Phase A: 10 mM ammonium hydroxide in dH_2O, Mobile Phase B: 10 mM ammonium hydroxide in 80% acetonitrile and 20% methanol; 20% B for the first 3 minutes then ramping to 95% B over 4 min. and holding for 2 min., all at a flow rate of 0.4 mL/min.). At 9.1 minutes, the gradient returns to the initial conditions of 20%B for 1 min. MD-1100 eluted from the analytical column at 1.45 minutes, and was detected by triple-quadrapole mass spectrometry (MRM, 764 (+2 charge state)>182 (+1 charge state) Da; cone voltage = 30V; collision = 20 eV; parent resolution = 2 Da at base peak; daughter resolution = 2 Da at base peak). Instrument response was converted into concentration units by comparison with a standard curve using known amounts of chemically synthesized MD-1100 prepared and injected in mouse serum using the same procedure.

Figure 10b shows absorption data for IV and orally administered MD-1100 as detected by LCMS. In this assay, MD-1100 appears similarly minimally systemically absorbed and is < 0.11 % bioavailable.

Administration of peptides and GC-C receptor agonists

For treatment of gastrointestinal disorders, the peptides and agonists of the invention are preferably administered orally, e.g., as a tablet, gel, paste, slurry, liquid, powder or in some other form. Orally administered compositions can include binders, flavoring agents, and humectants. The peptides and agonists can be co-administered with other agents used to treat gastrointestinal disorders including but not limited to acid suppressing agents such as Histamine-2 receptor agonists (H2As) and proton pump inhibitors (PPIs). The peptides and agonists can also be administered by rectal suppository. For the treatment of disorders outside the gastrointestinal tract such as congestive heart failure and benign prostatic hypertrophy, peptides and agonists are preferably administered parenterally or orally.

The peptides described herein can be used alone or in combination with other agents. For example, the peptides can be administered together with an analgesic peptide or compound. The analgesic peptide or compound can be covalently attached to a peptide described herein or it can be a separate agent that is administered together with or sequentially with a peptide described herein in a combination therapy.

Combination therapy can be achieved by administering two or more agents, e.g., a peptide described herein and an analgesic peptide or compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

The agents, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, etc.

The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO 01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628); poly(ε-caprolactone) to create a sustained release formulation. Such formulations can be used to implants that release a peptide or another agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (see, e.g., U.S. 6,620,422). Other sustained release formulations are described in EP 0 467 389 A2, WO 93/241150, U.S. 5,612,052; WO 97/40085, WO 94/155587, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, and U.S. 5,445,832. In such sustained release formulations microparticles of peptide are combined with microparticles of polymer. One or more sustained release implants can be placed in the large intestine, the small intestine or both.

The agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, or by other routes. The agents can be administered orally, e.g., as a tablet, gel, paste, slurry, liquid, powder or in some other form. Orally administered compositions can include binders, flavoring agents, and humectants. The agents can be included in dentifrices or oral washes. Thus, oral formulations can include abrasives and foaming agents. The agents can also be administered transdermally or in the form a suppository.

The agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means.

Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences (18th Edition, Mack Publishing Company, 1995).

The agents described herein and combination therapy agents can be packaged as a kit that includes single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation.

Analgesic Agents

The peptides described herein can be used in combination therapy with an analgesic agent, e.g., an analgesic compound or an analgesic peptide. The analgesic agent can optionally be covalently attached to a peptide described herein. Among the useful

analgesic agents are: Ca channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HT1 receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NK1 receptor antagonists, CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabanoid receptor agonists, and sialorphin. Analgesics agents in the various classes are described in the literature.

Among the useful analgesic peptides are sialorphin-related peptides, including those comprising the amino acid sequence QHNPR (SEQ ID NO:), including: VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:). Sialorphin-related peptides bind to neprilysin and inhibit neprilysin-mediated breakdown of substance P and Met-enkephalin. Thus, compounds or peptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the peptides of the invention in a co-therapy or linked to the peptides of the invention, e.g., by a covalent bond. Sialophin and related peptides are described in U.S. Patent 6,589,750; U.S. 20030078200 A1; and WO 02/051435 A2.

Opioid receptor antagonists and agonists can be administered with the peptides of the invention in co-therapy or linked to the peptide of the invention, e.g., by a covalent bond. For example, opioid receptor antagonists such as naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine are thought to be useful in the treatment of IBS. It can be useful to formulate opioid antagonists of this type is a delayed and sustained release formulation such that initial release of the antagonist is in the mid to distal small intestine and/or ascending colon. Such antagonists are described in WO 01/32180 A2. Enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-homoserine) is an agonist of the mu and delta opioid receptors and is thought to be useful for increasing intestinal motility (*Eur. J. Pharm.* 219:445, 1992), and this peptide can be used in conjunction with the peptides of the invention. Also useful is trimebutine which is thought to bind to mu/delta/kappa opioid receptors and activate release of motilin and

modulate the release of gastrin, vasoactive intestinal peptide, gastrin and glucagons. Kappa opioid receptor agonists such as fedotozine, ketocyclazocine, and compounds described in WO 03/097051 A2 can be used with or linked to the peptides of the invention. In addition, mu opioid receptor agonists such as morphine, diphenyloxylate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1) and loperamide can be used.

Tyr-Arg (kyotorphin) is a dipeptide that acts by stimulating the release of met-enkephalins to elicit an analgesic effect (*J. Biol. Chem* 262:8165, 1987). Kyotorphin can be used with or linked to the peptides of the invention.

CCK receptor agonists such as caerulein from amphibians and other species are useful analgesic agents that can be used with or linked to the peptides of the invention.

Conotoxin peptides represent a large class of analgesic peptides that act at voltage gated Ca channels, NMDA receptors or nicotinic receptors. These peptides can be used with or linked to the peptides of the invention.

Peptide analogs of thymulin (FR Application 2830451) can have analgesic activity and can be used with or linked to the peptides of the invention.

CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) can have analgesic activity and can be used with or linked to the peptides of the invention.

Other useful analgesic agents include 5-HT4 agonists such as tegaserod/zelnorm and lirexapride. Such agonists are described in: EP1321142 A1, WO 03/053432A1, EP 505322 A1, EP 505322 B1, US 5,510,353, EP 507672 A1, EP 507672 B1, and US 5,273,983.

Calcium channel blockers such as ziconotide and related compounds described in, for example, EP625162B1, US 5,364,842, US 5,587,454, US 5,824,645, US 5,859,186,

US 5,994,305, US 6,087,091, US 6,136,786, WO 93/13128 A1, EP 1336409 A1, EP 835126 A1, EP 835126 B1, US 5,795,864, US 5,891,849, US 6,054,429, WO 97/01351 A1, can be used with or linked to the peptides of the invention.

Various antagonists of the NK-1, NK-2, and NK-3 receptors (for a review see Giardina et al. 2003 *Drugs* 6:758) can be can be used with or linked to the peptides of the invention.

NK1 receptor antagonists such as: aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-14033 and related compounds described in, for example, EP 873753 A1, US 20010006972 A1, US 20030109417 A1, WO 01/52844 A1, can be used with or linked to the peptides of the invention.

NK-2 receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi-Synthelabo), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc) can be used with or linked to the peptides of the invention.

NK3 receptor antagonists such as osanetant (Sanofi-Synthelabo), talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 A1, WO 97/21680 A1, US 6,277,862, WO 98/11090, WO 95/28418, WO 97/19927, and Boden et al. (*J Med Chem.* 39:1664-75, 1996) can be used with or linked to the peptides of the invention.

Norepinephrine-serotonin reuptake inhibitors such as milnacipran and related compounds described in WO 03/077897 A1 can be used with or linked to the peptides of the invention.

Vanilloid receptor antagonists such as arvanil and related compounds described in WO 01/64212 A1 can be used with or linked to the peptides of the invention.

Where the analgesic is a peptide and is covalently linked to a peptide described herein the resulting peptide may also include at least one trypsin or chymotrypsin cleavage site. When present within the peptide, the analgesic peptide may be preceded by (if it is at the carboxy terminus) or followed by (if it is at the amino terminus) a chymotrypsin or trypsin cleavage site that allows release of the analgesic peptide.

In addition to sialorphin-related peptides, analgesic peptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, zicnotide, and substance P.

Methods of Treatment

The peptides of the invention can be used for the treatment or prevention of cancer, pre-cancerous growths, or metastatic growths. For example, they can be used for the prevention or treatment of: colorectal/local metastasized colorectal cancer, gastrointestinal tract cancer, lung cancer, cancer or pre-cancerous growths or metastatic growths of epithelial cells, polyps, breast, colorectal, lung, ovarian, pancreatic, prostatic, renal, stomach, bladder, liver, esophageal and testicular carcinoma, carcinoma (e.g., basal cell, basosquamous, Brown-Pearce, ductal carcinoma, Ehrlich tumor, Krebs, Merkel cell, small or non-small cell lung, oat cell, papillary, bronchiolar, squamous cell, transitional cell, Walker), leukemia (e.g., B-cell, T-cell, HTLV, acute or chronic lymphocytic, mast cell, myeloid), histiocytonia, histiocytosis, Hodgkin's disease, non-Hodgkin's lymphoma, plasmacytoma, reticuloendotheliosis, adenoma, adeno-carcinoma, adenofibroma, adenolymphoma, ameloblastoma, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, sclerosing angioma, angiomatosis, apudoma, branchionia, malignant carcinoid syndrome, carcinoid heart disease, carcinosarcoma, cementoma, cholangioma, cholesteatoma, chondrosarcoma, chondroblastoma, chondrosarcoma, chordoma, choristoma, craniopharyngioma, chrondrorna, cylindroma, cystadenocarcinoma, cystadenoma, cystosarconia phyllodes, dysgenninoma, ependymoma, Ewing sarcoma, fibroma, fibrosarcoma, giant cell tumor, ganglioneuroma, glioblastoma, glomangioma, granulosa cell tumor, gynandroblastoma, hamartoma,

hemangioendothelioma, hemangioma, hemangio-pericytoma, hemangiosarcoma, hepatoma, islet cell tumor, Kaposi sarcoma, leiomyoma, leiomyosarcoma, leukosarcoma, Leydig cell tumor, lipoma, liposarcoma, lymphaugioma, lymphangiomyoma, lymphangiosarcoma, medulloblastoma, meningioma, mesenchymoma, mesonephroma, mesothelioma, myoblastoma, myoma, myosarcoma, myxoma, myxosarcoma, neurilemmoma, neuroma, neuroblastoma, neuroepithelioma, neurofibroma, neurofibromatosis, odontoma, osteoma,, osteosarcoma, papilloma, paraganglioma, paraganglionia. nonchroinaffin, pinealoma, rhabdomyoma, rhabdomyosarcoma, Sertoli cell tumor, teratoma, theca cell tumor, and other diseases in which cells have become dysplastic, immortalized, or transformed.

The peptides of the invention can be used for the treatment or prevention of: Familial Adenomatous Polyposis (FAP) (autosomal dominant syndrome) that precedes colon cancer, hereditary nonpolyposis colorectal cancer (HNPCC), and inherited autosomal dominant syndrome.

For treatment or prevention of cancer, pre-cancerous growths and metastatic growths, the peptides can be used in combination therapy with radiation or chemotherapeutic agents, an inhibitor of a cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor (a number of selective cyclooxygenase-2 inhibitors are described in WO02062369, hereby incorporated by reference).

The peptides can be for treatment or prevention of inflammation. Thus, they can be used alone or in combination with inhibitor of cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor for treatment of: organ inflammation, IBD (e.g, Crohn's disease, ulcerative colitis), asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis, ischemic bowel diseases, intestinal inflammations/allergies, coeliac disease, proctitis, eosnophilic gastroenteritis, mastocytosis, and other inflammatory disorders.

The peptides can also be used to treat or prevent insulin-related disorders, for example: II diabetes mellitus, hyperglycemia, obesity, disorders associated with

disturbances in glucose or electrolyte transport and insulin secretion in cells, or endocrine disorders. They can be also used in insulin resistance treatment and post-surgical and non-post surgery decrease in insulin responsiveness.

The peptides can be used to prevent or treat respiratory disorders, including, inhalation, ventilation and mucus secretion disorders, pulmonary hypertension, chronic obstruction of vessels and airways, and irreversible obstructions of vessels and bronchi.

The peptides can be used in combination therapy with a phosphodiesterase inhibitor (examples of such inhibitors can be found in US Patent No. 6,333,354, hereby incorporated by reference).

The peptides can also be used to prevent or treat: retinopathy, nephropathy, diabetic angiopathy, and edema formation

The peptides can also be used to prevent or treat neurological disorders, for example, headache, anxiety, movement disorders, aggression, psychosis, seizures, panic attacks, hysteria, sleep disorders, depression, schizoaffective disorders, sleep apnea, attention deficit syndromes, memory loss, and narcolepsy. They may also be used as a sedative.

The peptides and detectabley labeled peptides can be used as markers to identify, detect, stage, or diagnosis diseases and conditions of the small intestine, including: Crohn's disease, colitis, inflammatory bowel disease, tumors, benign tumors, such as benign stromal tumors, adenoma, angioma, adenomatous (pedunculated and sessile) polyps, malignant, carcinoid tumors, endocrine cell tumors, lymphoma, adenocarcinoma, foregut, midgut, and hindgut carcinoma, gastroinstestinal stromal tumor (GIST), such as leiomyorna, cellular leiomyoma, leiomyoblastoma, and leiomyosarcoma, gastrointestinal autonomic nerve tumor, malabsorption syndromes, celiac diseases, diverticulosis, Meckel's diverticulurn, colonic diverticula, megacolon, Hirschsprung's disease, irritable bowel syndrome, mesenteric ischemia, ischemic

colitis, colorectal cancer, colonic polyposis, polyp syndrome, intestinal adenocarcinoma, Liddle syndrome, Brody myopathy, infantile convulsions, and choreoathetosis

The peptides can be conjugated to another molecule (e.g, a diagnostic or therapeutic molecule) to target cells bearing the GCC receptor, e.g., cystic fibrosis lesions and specific cells lining the intestinal tract. Thus, they can be used to target radioactive moieties or therapeutic moieties to the intestine to aid in imaging and diagnosing or treating colorectal/metastasized or local colorectal cancer and to deliver normal copies of the p53 tumor suppressor gene to the intestinal tract.

The peptides can be used alone or in combination therapy to treat erectile dysfunction.

The peptides can be used alone or in combination therapy to treat inner ear disorders, e.g., to treat Meniere's disease, including symptoms of the disease such as vertigo, hearing loss, tinnitus, sensation of fullness in the ear, and to maintain fluid homeostasis in the inner ear.

The peptides can be used alone or in combination therapy to treat disorders associated with fluid and sodium retention, e.g., diseases of the electrolyte-water/electrolyte transport system within the kidney, gut and urogenital system, congestive heart failure, hypertension, hypotension, liver cirrhosis, and nephrotic syndrome. In addition they can be used to facilitate diuresis or control intestinal fluid.

The peptides can be used alone or in combination therapy to treat disorders associated with bicarbonate secreion, e.g., Cystic Fibrosis.

The peptides can be used alone or in combination therapy to treat disorders associated with liver cell regeneration.

What is claimed is:

1. A purified peptide comprising the amino acid sequence (I): Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Cys_6 Cys_7 Xaa_8 Xaa_9 Cys_{10} Cys_{11} Xaa_{12} Xaa_{13} Xaa_{14} Cys_{15} Xaa_{16} Xaa_{17} Cys_{18} Xaa_{19} Xaa_{20} Xaa_{21} wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is Asn Ser Ser Asn Tyr or is missing or Xaa_1 Xaa_2 Xaa_3 Xaa_4 is missing.

2. The purified peptide of claim 1 wherein Xaa_5 is Asn, Trp, Tyr, Asp, or Phe.

3. The purified peptide of claim 1 wherein Xaa_5 is Thr or Ile.

4. The purified peptide of claim 1 wherein Xaa_5 is Tyr, Asp or Trp.

5. The purified peptide of claim 1 wherein Xaa_8 is Glu, Asp, Gln, Gly or Pro.

6. The purified peptide of claim 1 wherein Xaa_9 is Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe.

7. The purified peptide of claim 1 wherein Xaa_9 is Leu, Ile, Val, Lys, Arg, Trp, Tyr or Phe.

8. The purified peptide of claim 1 wherein Xaa_{12} is Asn, Tyr, Asp or Ala.

9. The purified peptide of claim 1 wherein Xaa_{13} is Ala, Pro or Gly.

10. The purified peptide of claim 1 wherein Xaa_{14} is Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, or Asp.

11. The purified peptide of claim 1 wherein Xaa_{16} is Thr, Ala, Asn, Lys, Arg, Trp.

12. The purified peptide of claim 1 wherein Xaa_{17} is Gly, Pro or Ala.

13. The purified peptide of claim 1 wherein Xaa_{19} is Trp, Tyr, Phe, Asn or Leu.

14. The purified peptide of claim 1 wherein Xaa_{19} is Lys or Arg.

15. The purified peptide of claim 1 wherein Xaa_{20} Xaa_{21} is AspPhe or Xaa_{20} is Asn or Glu and Xaa_{21} is missing.

16. A purified peptide comprising the amino acid sequence: Asn Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---; MD-915).

17. A purified peptide comprising the amino acid sequence: Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MD-1100).

18. A purified peptide consisting of the amino acid sequence: Asn Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---; MD-915).

19. A purified peptide consisting of the amino acid sequence: Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MD-1100).

20. A method for treating a gastrointestinal disorder in a patient comprising administering a purified peptide comprising the amino acid sequence: Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MM-416776).

21. A method for treating a gastrointestinal disorder in a patient comprising administering a purified peptide comprising the amino acid sequence: Asn Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr

(SEQ ID NO:---; MD-915).

22. A method for treating a gastrointestinal disorder in a patient comprising administering a purified peptide comprising the amino acid sequence: Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MM416774)

23. A method for treating a gastrointestinal disorder in a patient comprising administering a purified peptide comprising the amino acid sequence: Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MD-1100).

24. A purified polypeptide comprising an amino acid sequence of any of:
Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr (SEQ ID NO:--);
Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr (SEQ ID NO:---);
Asn Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);
Asn Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr (SEQ ID NO:---);
Asn Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);
Asn Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);
Asn Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);
Asn Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);
Asn Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);
Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe
(SEQ ID NO:---);
Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr Asp Phe
(SEQ ID NO:---);
Asn Ser Ser Asn Tyr Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe
(SEQ ID NO:---);

Asn Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe
(SEQ ID NO:---);
Asn Ser Ser Asn Tyr Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe
(SEQ ID NO:---);
Asn Ser Ser Asn Tyr Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe
(SEQ ID NO:---);
Asn Ser Ser Asn Tyr Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe
(SEQ ID NO:---);
Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);
Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr Asp Phe (SEQ ID NO:---);
Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);
Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);
Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);
Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);
Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:--);
Asn Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:--);
Asn Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Trp Gly Cys Tyr Asp Phe (SEQ ID NO:---);
Asn Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);

Asn Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);

Asn Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);

Asn Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);

Asn Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr Asp Phe (SEQ ID NO:---);

Gln Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);

Asn Thr Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);

Asn Leu Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);

Asn Ile Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);

Asn Ser Ser Gln Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);

Ser Ser Asn Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);

Gln Ser Ser Gln Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);

Ser Ser Gln Tyr Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:---);

Asn Ser Ser Asn Tyr Cys Cys Glu Ala Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Asn Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Asp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Cys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Gln Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Glu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Gly Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu His Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Ile Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Met Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Pro Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Thr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Asn Ser Ser Asn Tyr Cys Cys Glu Val Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Cys Cys Glu Ala Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Cys Cys Glu Arg Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Cys Cys Glu Asn Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Cys Cys Glu Asp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Cys Cys Glu Cys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Cys Cys Glu Gln Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);

Cys Cys Glu Glu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Gly Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu His Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Ile Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Lys Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Met Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Pro Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Thr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Trp Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Cys Cys Glu Val Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:);
Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MM-416776); and
Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr (SEQ ID NO:--; MM416774).

25. A method for treating a gastrointestinal disorder in a patient comprising administering the peptide of claim 1.

26. A method for treating a gastrointestinal disorder in a patient comprising administering the peptide of claim 24.

27. The method of any of claims 20 – 26 wherein the gastrointestinal disorder is a gastrointestinal motility disorder.

28. The method of any of claims 20 – 26 wherein the gastrointestinal disorder is selected from the group consisting of a gastrointestinal motility disorder, irritable bowel syndrome, chronic constipation, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction,

colonic pseudo-obstruction, Crohn's disease, ulcerative colitis, and inflammatory bowel disease.

29. A method for treating obesity comprising administering the peptide of any of claims 1, 16-19, and 24.

30. A method for treating congestive heart failure comprising administering the peptide of any of claims 1, 16-19, and 24.

31. A method for treating benign prostatic hyperplasia comprising administering the peptide of any of claims 1, 16-19, and 24.

32. The purified peptide of any of claims 1, 16, 17, and 24 wherein the polypeptide comprises the amino acid sequence DF; QHNPR (SEQ ID NO:); VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); or RQHNPR (SEQ ID NO:) fused to its amino terminus or its caboxy terminus.

33. The purified peptide of any of claims 1, 16, 17, and 24 wherein the purified polypeptide comprises the amino acid sequence of an analgesic peptide selected from the group consisting of endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance P fused to its amino terminus or its carboxy terminus.

34. The purified peptide of any of claims 1, 16, 17, and 24 wherein the polypeptide includes no more than 10 additional amino acids at its amino terminus or carboxy terminus or both and wherein the polypeptide is a guanylate cyclase receptor agonist.

35. The purified peptide of claim 1 wherein wherein: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 is missing; Xaa_8 is Glu; Xaa_9 is Leu, Ile, Lys, Arg, Trp, Tyr or Phe; Xaa_{12} is Asn; Xaa_{13} is Pro; Xaa_{14} is Ala; Xaa_{16} is Thr, Ala, Lys, Arg, Trp; Xaa_{17} is Gly; Xaa_{19} is Tyr or Leu; and Xaa_{20} Xaa_{21} is AspPhe or is missing.

36. A method for treating a patient suffering from constipation, the method comprising administering the polypeptide of any of claims 1, 16-23 and 28.

37. A method for increasing the activity of an intestinal guanylate cyclase (GC-C) receptor in a patient, the method comprising administering the polypeptide of any of claims 1, 16-19 and 24.

38. A method for treating a gastrointestinal disorder in a patient comprising administering a GC-C receptor agonist.

39. The method of claim 38 wherein the gastrointestinal disorder is a gastrointestinal motility disorder.

40. The method of claim 38 wherein the gastrointestinal disorder is selected from the group consisting of a gastrointestinal motility disorder, irritable bowel syndrome, chronic constipation, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, Crohn's disease, ulcerative colitis, and inflammatory bowel disease.

41. A method for treating obesity comprising administering a GC-C receptor agonist.

42. A method for treating congestive heart failure comprising administering a GC-C receptor agonist.

43. A method for treating benign prostatic hyperplasia comprising administering a GC-C receptor agonist.

44. A method for treating visceral pain comprising administering a GC-C receptor agonist.

45. A method for treating inflammation comprising administering a GC-C receptor agonist.

46. A method for treating constipation comprising administering a GC-C receptor agonist.

47. A method for treating visceral pain comprising administering the polypeptide of any of claims 1, 16-19 and 24.

48. A method for treating inflammation comprising administering the polypeptide of any of claims 1, 16-19 and 24.

49. A method for treating cystic fibrosis comprising administering the polypeptide of any of claims 1, 16-19 and 24.

50. A method for treating cystic fibrosis comprising administering a GC-C receptor agonist.

51. A pharmaceutical composition comprising the peptide of any of claims 1, 16-19 and 24 and a pharmaceutically acceptable carrier.

52. A pharmaceutical composition comprising the peptide of any of claims 1, 16-19 and 24 surrounded by an enteric coating.

53. A controlled release pharmaceutical composition comprising the peptide of any of claims 1, 16-19 and 24 and a biodegradable polymeric matrix.

54. A pharmaceutical composition comprising the peptide of any of claims 1, 16-19 and 24, an analgesic agent and a pharmaceutically acceptable carrier.

55. A pharmaceutical composition comprising the peptide of any of claims 1, 16-19 and 24, a phosphodiesterase inhibitor and a pharmaceutically acceptable carrier.

56. A method for treating cancer, a respiratory disorder, a neurological disorder, a disorder associated with fluid and sodium retention, a disorder associated with carbonate imbalance, erectile dysfunction, an insulin-related disorder, or an inner ear disorder, the method comprising administering the peptide of any of claims 1, 16-19 and 24.

57. A method for treating cancer, a respiratory disorder, a neurological disorder, a disorder associated with fluid and sodium retention, a disorder associated with carbonate imbalance, erectile dysfunction, an insulin-related disorder, or an inner ear disorder, the method comprising administering a GC-C receptor agonist.

58. A method of producing the peptide of any of claims 16-19 and 24, comprising providing a cell harboring a nucleic acid molecule encoding the polypeptide, culturing the cell under conditions in which the peptide is expressed, and isolating the expressed peptide.

59. A method of producing the peptide of any of claims 16-19 and 24, comprising chemically synthesizing the peptide and they purifying the synthesized peptide.

60. A pharmaceutical composition comprising the peptide of any of claims 1, 16-19 and 24 and a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide, a C-type natriuretic peptide, a diuretic, or an inhibitor of angiotensin converting enzyme.

61. A pharmaceutical composition comprising the peptide of any of claims 1, 16-19 and 24 and a 5-alpha reductase inhibitor or an alpha adrenergic inhibitor.

62. A pharmaceutical composition comprising the peptide of any of claims 1, 16-19 and 24 and gut hormone fragment peptide YY_{3-36}, glp-1 (glucagon-like peptide-1), exendin-4 (an inhibitor of glp-1), sibutramine, phentermine, phendimetrazine, benzphetamine hydrochloride (Didrex), orlistat (Xenical), diethylpropion hydrochloride (Tenuate), fluoxetine (Prozac), bupropion, ephedra, chromium, garcinia cambogia, benzocaine, bladderwrack (focus vesiculosus), chitosan, nomame herba, galega (Goat's Rue, French Lilac), conjugated linoleic acid, L-carnitine, fiber (psyllium, plantago, guar fiber), caffeine, dehydroepiandrosterone, germander (teucrium chamaedrys), B-hydroxy-β-methylbutyrate, or pyruvate.

63. A pharmaceutical composition comprising a GC-C receptor agonist and a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide, a C-type natriuretic peptide, a diuretic, or an inhibitor of angiotensin converting enzyme.

64. A pharmaceutical composition comprising a GC-C receptor agonist and a 5-alpha reductase inhibitor or an alpha adrenergic inhibitor.

65. A pharmaceutical composition comprising a GC-C receptor agonist and gut hormone fragment peptide YY_{3-36}, glp-1 (glucagon-like peptide-1), exendin-4 (an inhibitor of glp-1), sibutramine, phentermine, phendimetrazine, benzphetamine hydrochloride (Didrex), orlistat (Xenical), diethylpropion hydrochloride (Tenuate), fluoxetine (Prozac), bupropion, ephedra, chromium, garcinia cambogia, benzocaine, bladderwrack (focus vesiculosus), chitosan, nomame herba, galega (Goat's Rue, French Lilac), conjugated linoleic acid, L-carnitine, fiber (psyllium, plantago, guar fiber), caffeine, dehydroepiandrosterone, germander (teucrium chamaedrys), B-hydroxy-β-methylbutyrate, or pyruvate.

66. A method for treating congestive heart failure comprising administering the peptide of any of claims 1, 16-19 and 24 and a natriuretic peptide

such as atrial natriuretic peptide, brain natriuretic peptide, a C-type natriuretic peptide, a diuretic, or an inhibitor of angiotensin converting enzyme.

67. A method for treating benign prostatic hyperplasia comprising administering the peptide of any of claims 1, 16-19 and 24 and a 5-alpha reductase inhibitor or an alpha adrenergic inhibitor.

68. A method for treating obesity comprising administering the peptide of any of claims 1, 16-19 and 24 and gut hormone fragment peptide YY_{3-36}, glp-1 (glucagon-like peptide-1), exendin-4 (an inhibitor of glp-1), sibutramine, phentermine, phendimetrazine, benzphetamine hydrochloride (Didrex), orlistat (Xenical), diethylpropion hydrochloride (Tenuate), fluoxetine (Prozac), bupropion, ephedra, chromium, garcinia cambogia, benzocaine, bladderwrack (focus vesiculosus), chitosan, nomame herba, galega (Goat's Rue, French Lilac), conjugated linoleic acid, L-carnitine, fiber (psyllium, plantago, guar fiber), caffeine, dehydroepiandrosterone, germander (teucrium chamaedrys), B-hydroxy-β-methylbutyrate, or pyruvate.

69. A method for treating congestive heart failure comprising administering a GC-C receptor agonist and a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide, a C-type natriuretic peptide, a diuretic, or an inhibitor of angiotensin converting enzyme.

70. A method for treating benign prostatic hyperplasia comprising a GC-C receptor agonist and a 5-alpha reductase inhibitor or an alpha adrenergic inhibitor.

71. A method for treating obesity comprising administering a GC-C receptor agonist and gut hormone fragment peptide YY_{3-36}, glp-1 (glucagon-like peptide-1), exendin-4 (an inhibitor of glp-1), sibutramine, phentermine, phendimetrazine, benzphetamine hydrochloride (Didrex), orlistat (Xenical), diethylpropion hydrochloride (Tenuate), fluoxetine (Prozac), bupropion, ephedra, chromium, garcinia cambogia, benzocaine, bladderwrack (focus vesiculosus),

chitosan, nomame herba, galega (Goat's Rue, French Lilac), conjugated linoleic acid, L-carnitine, fiber (psyllium, plantago, guar fiber), caffeine, dehydroepiandrosterone, germander (teucrium chamaedrys), B-hydroxy-β-methylbutyrate, or pyruvate.

Figure 1a. LCMS analysis of recombinant peptide variants

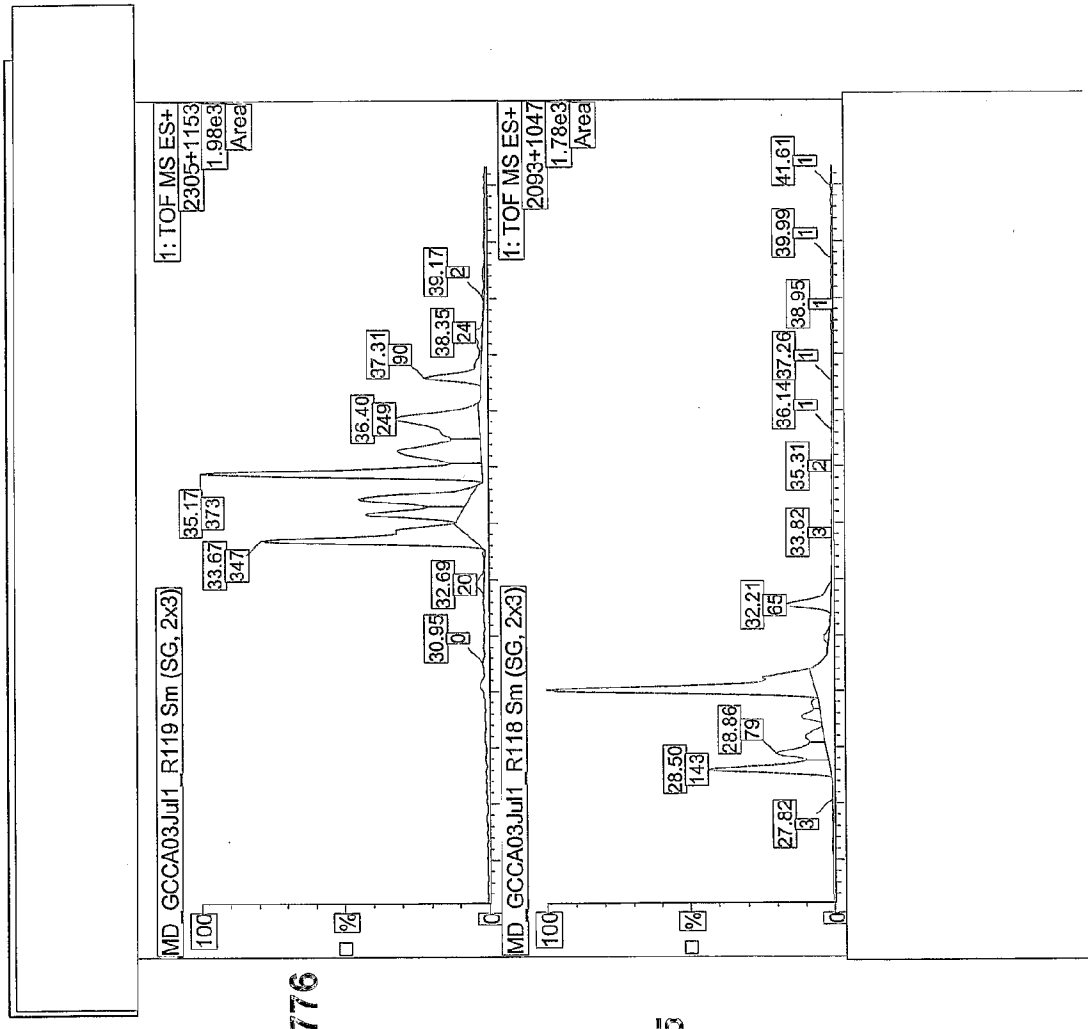


Figure 1b: LCMS analysis of synthetic MD-1100 (Total Ion Chromatograph (TIC))

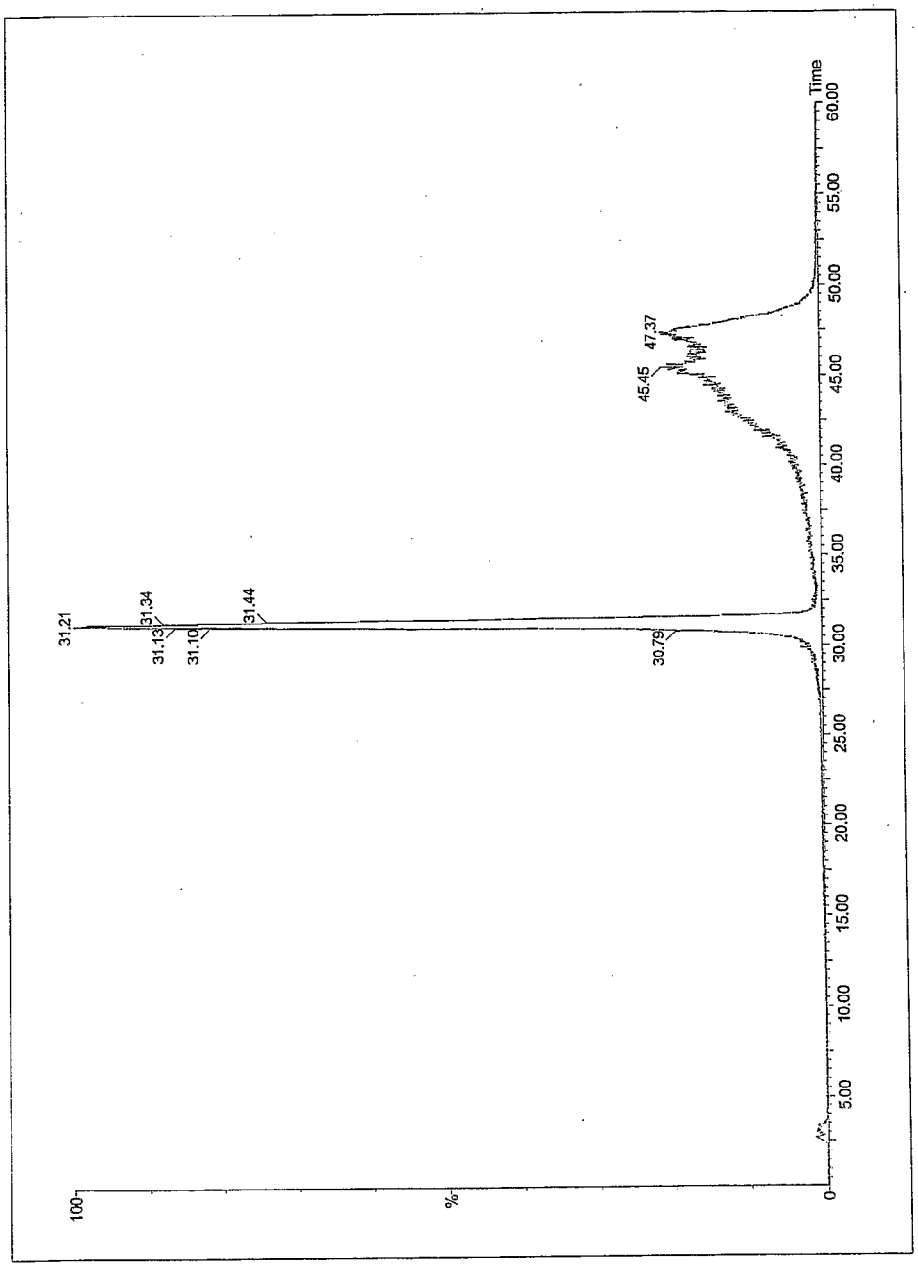


Figure 1c: LCMS analysis (Total Ion Chromatograph of blank used in MD-1100 analysis)

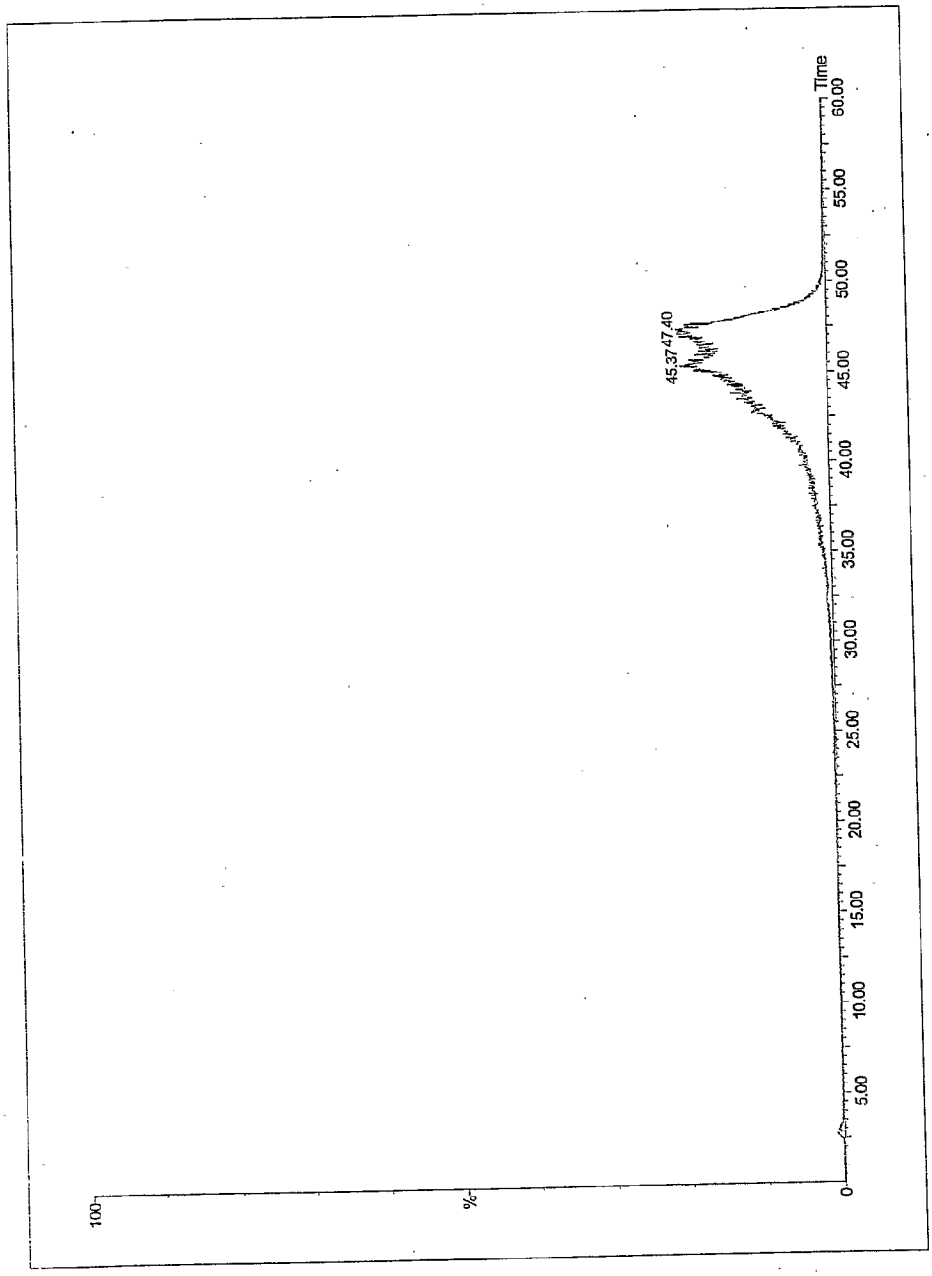


Figure 2. Chemically synthesized peptides in the Intestinal GC-C Receptor Activity Assay

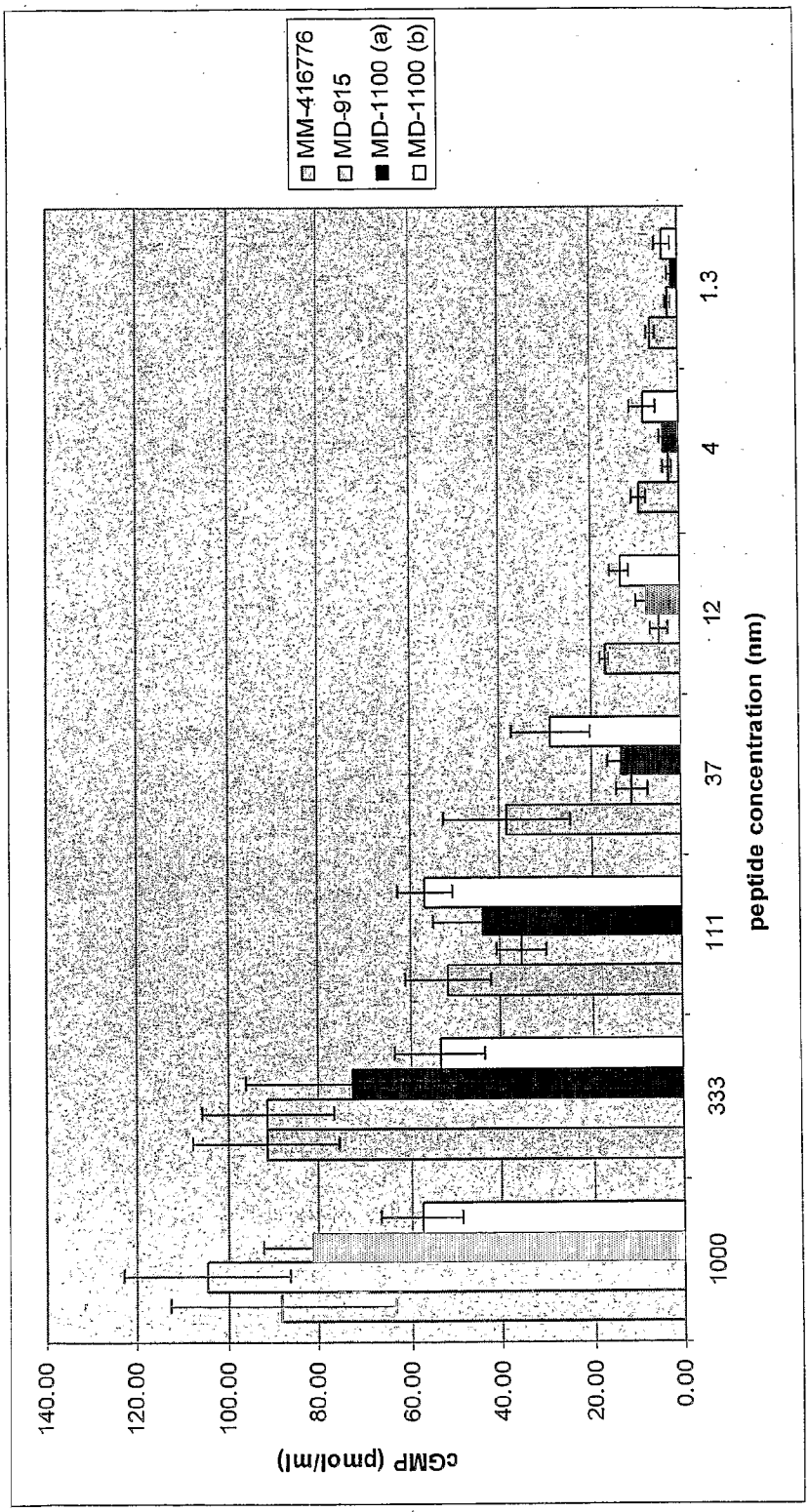


Figure 3a. MM-416776 vs Zelnorm® in an acute Mouse Gastrointestinal Transit Model (GIT)

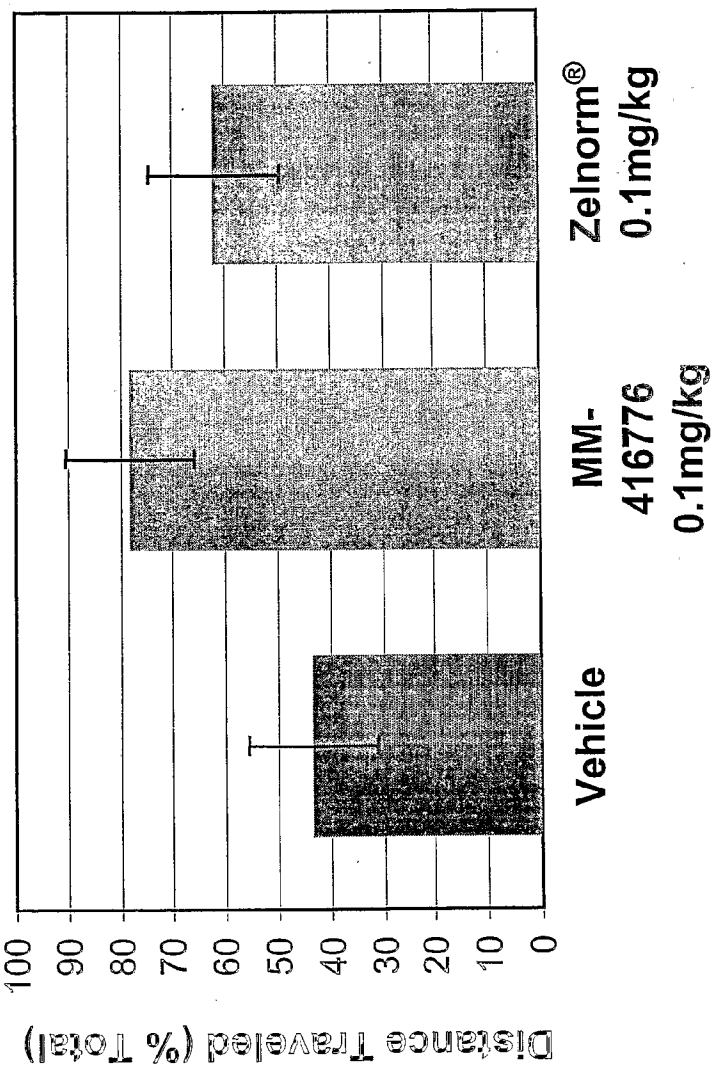


Figure 3b: MD-1100 vs. Zelnorm® in an acute Mouse Gastrointestinal Transit Model

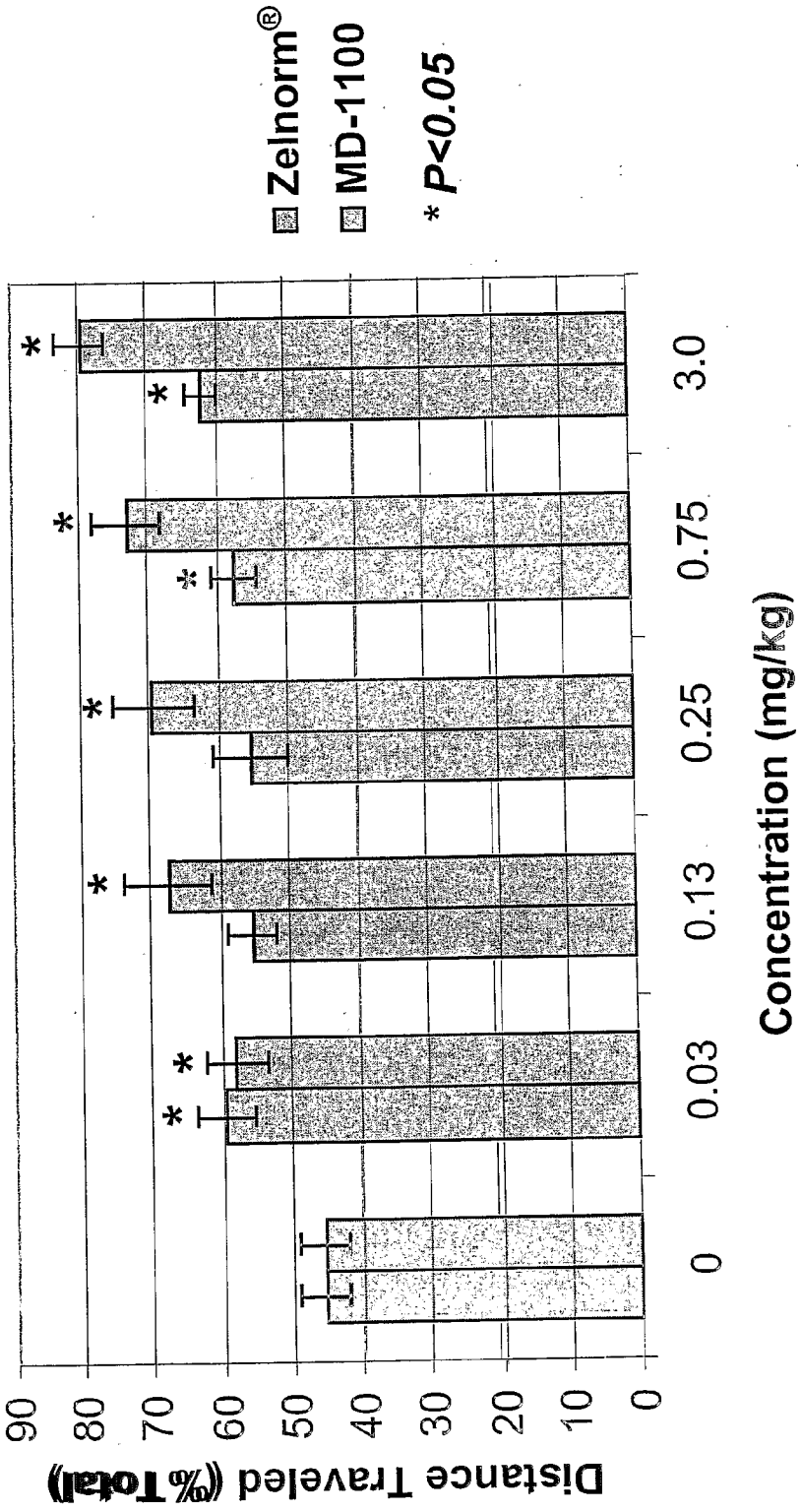


Figure 4a. Purified MD-915 and MM-416776 in GIT Model

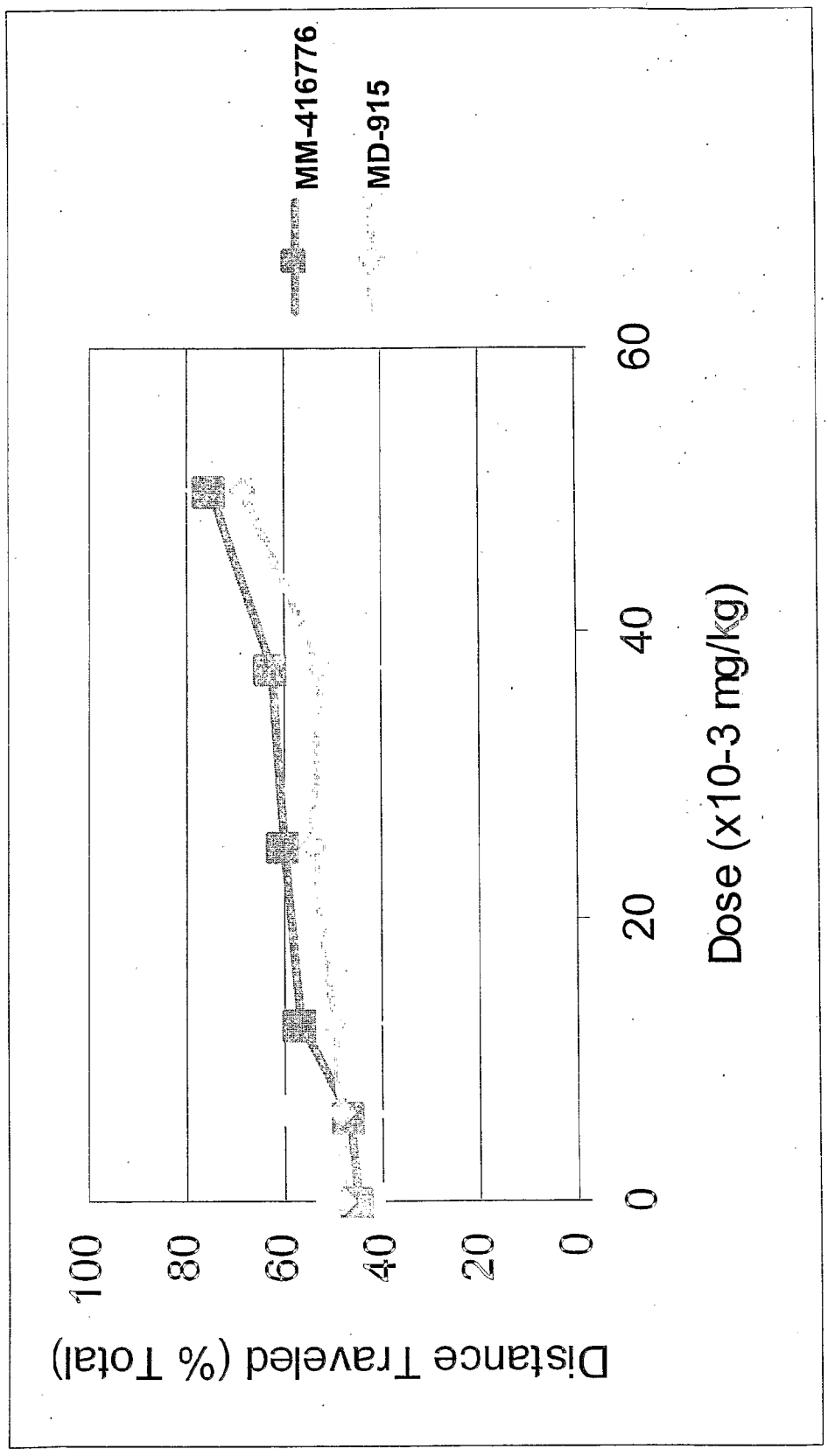
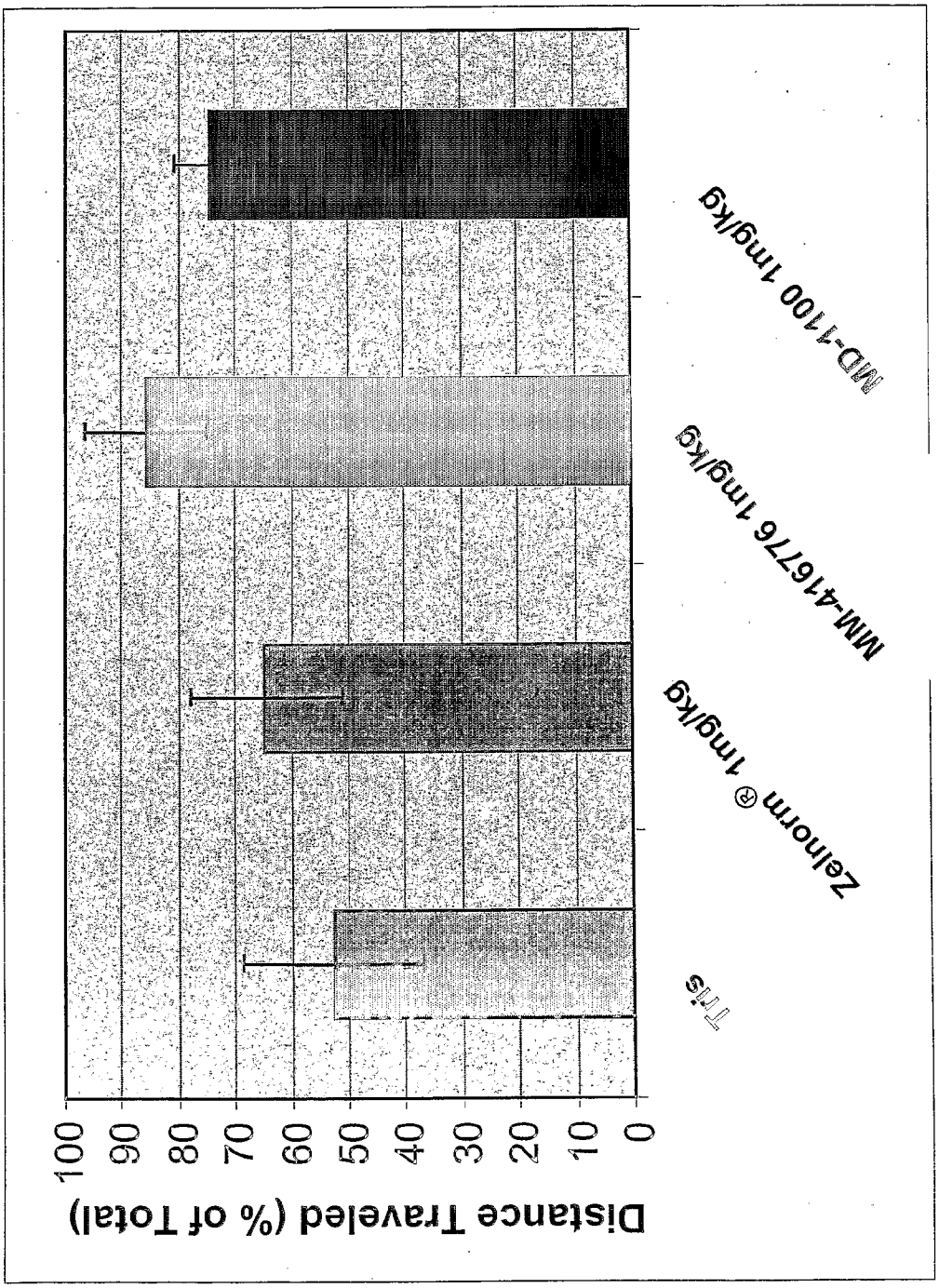


Figure 4b. Chemically Synthesized Peptides in GIT Model



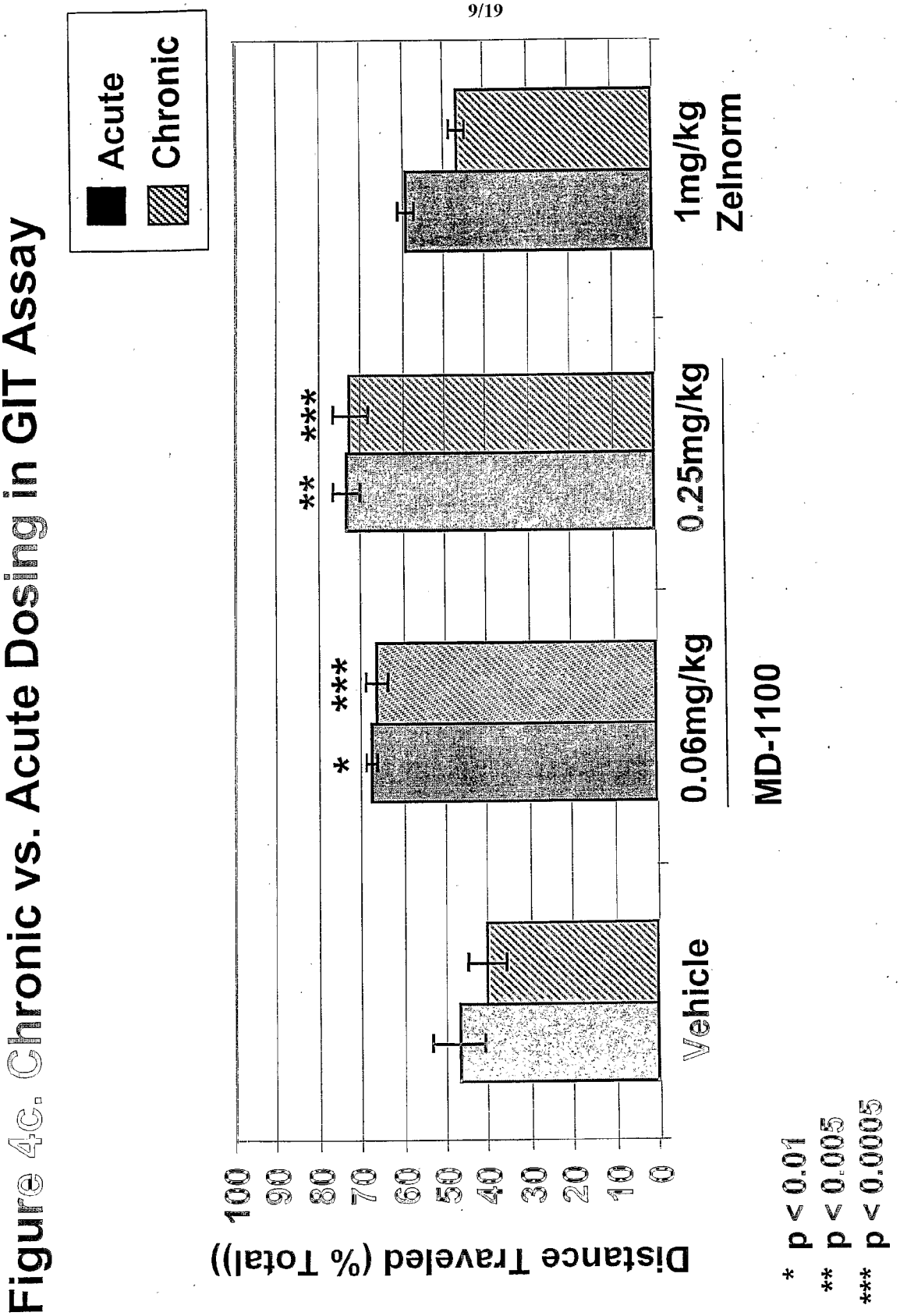


Figure 4c. Chronic vs. Acute Dosing in GIT Assay

Figure 5a. MM-416776 vs Zelnorm® in a Mouse Intestinal Secretion Model

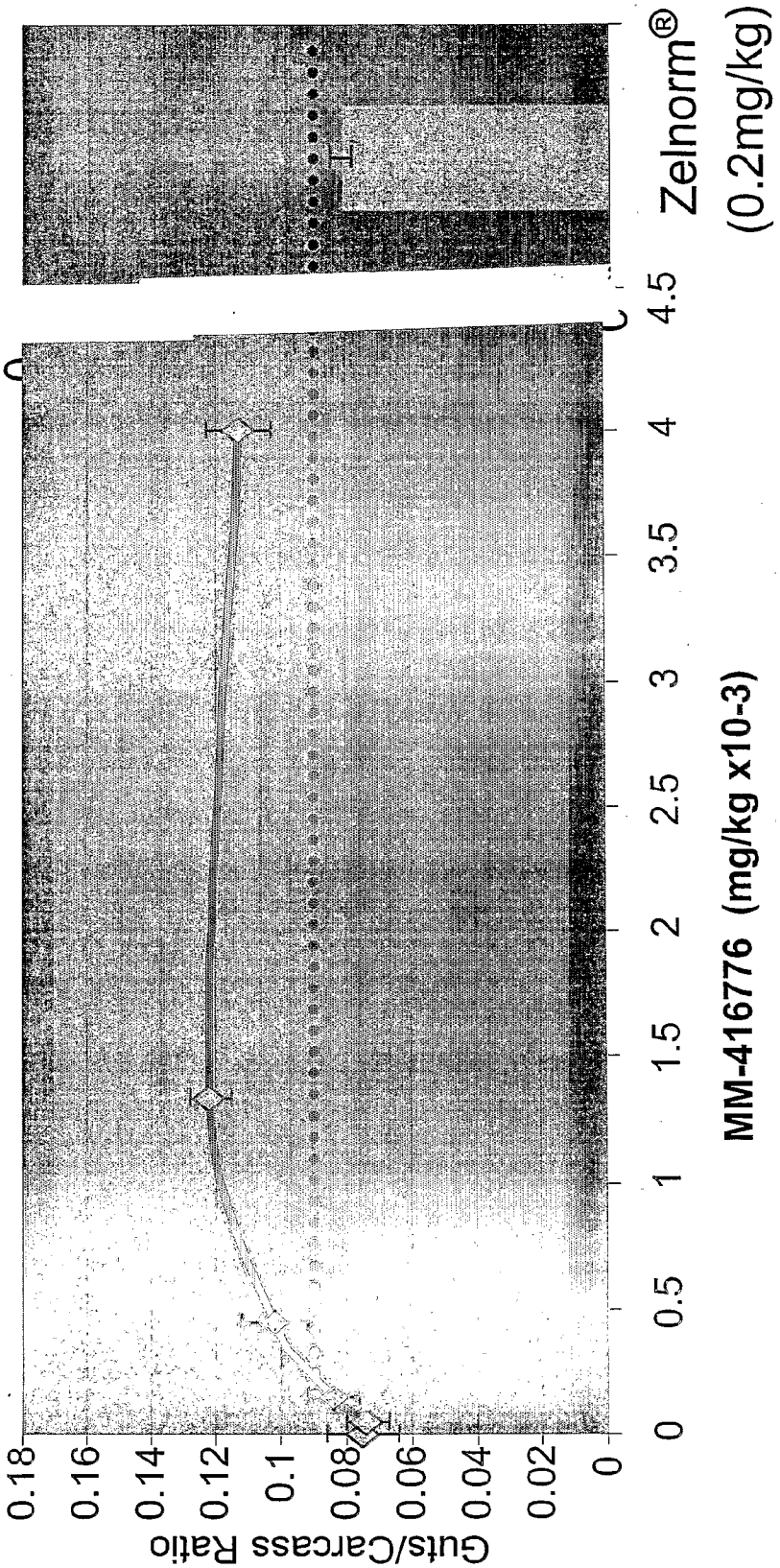


Figure 5b: MD-1100 vs Zelnorm® in Mouse Intestinal Secretion Model

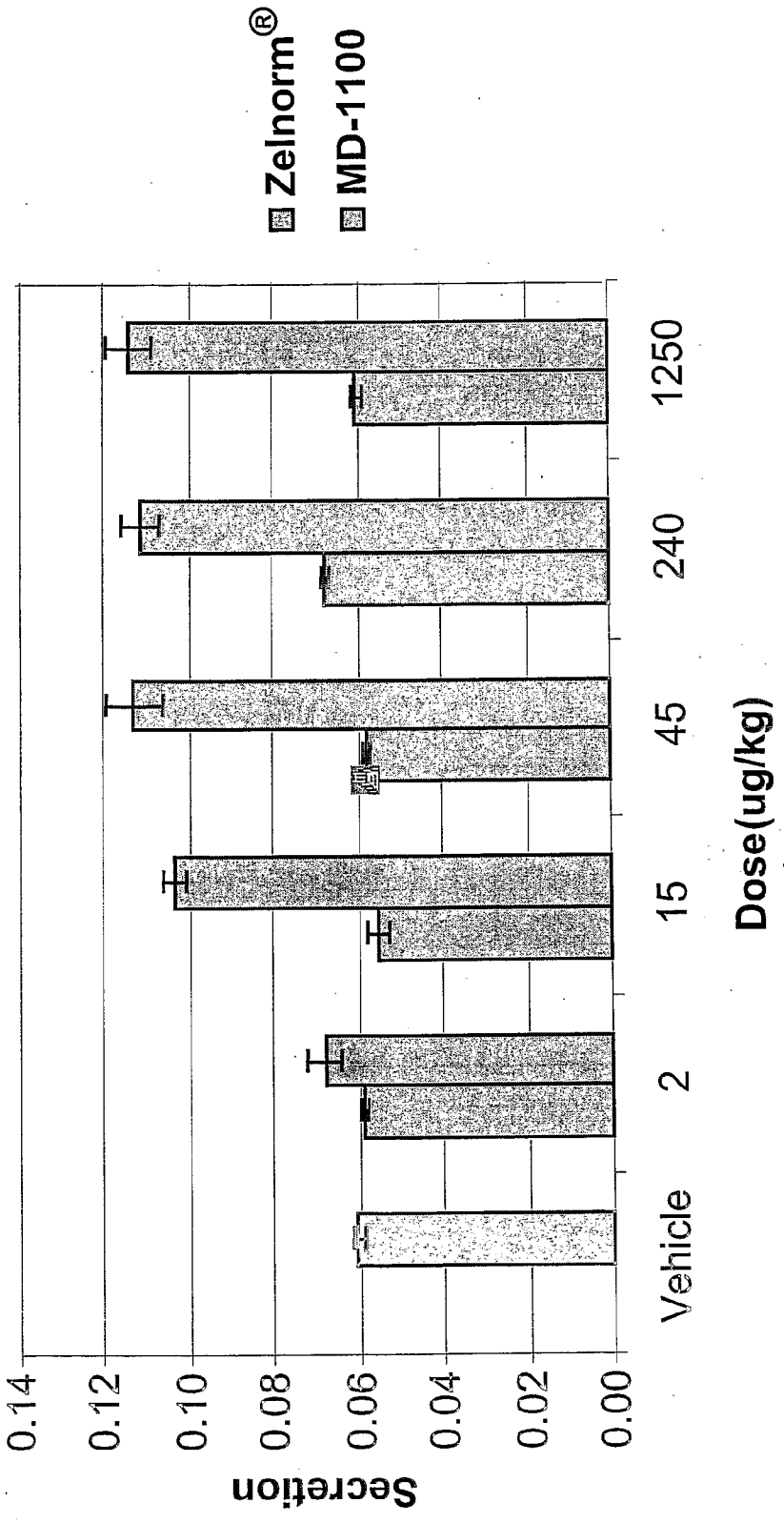


Figure 6a. Recombinantly generated MD-915 and MM-416776 in Mouse Intestinal Secretion Model

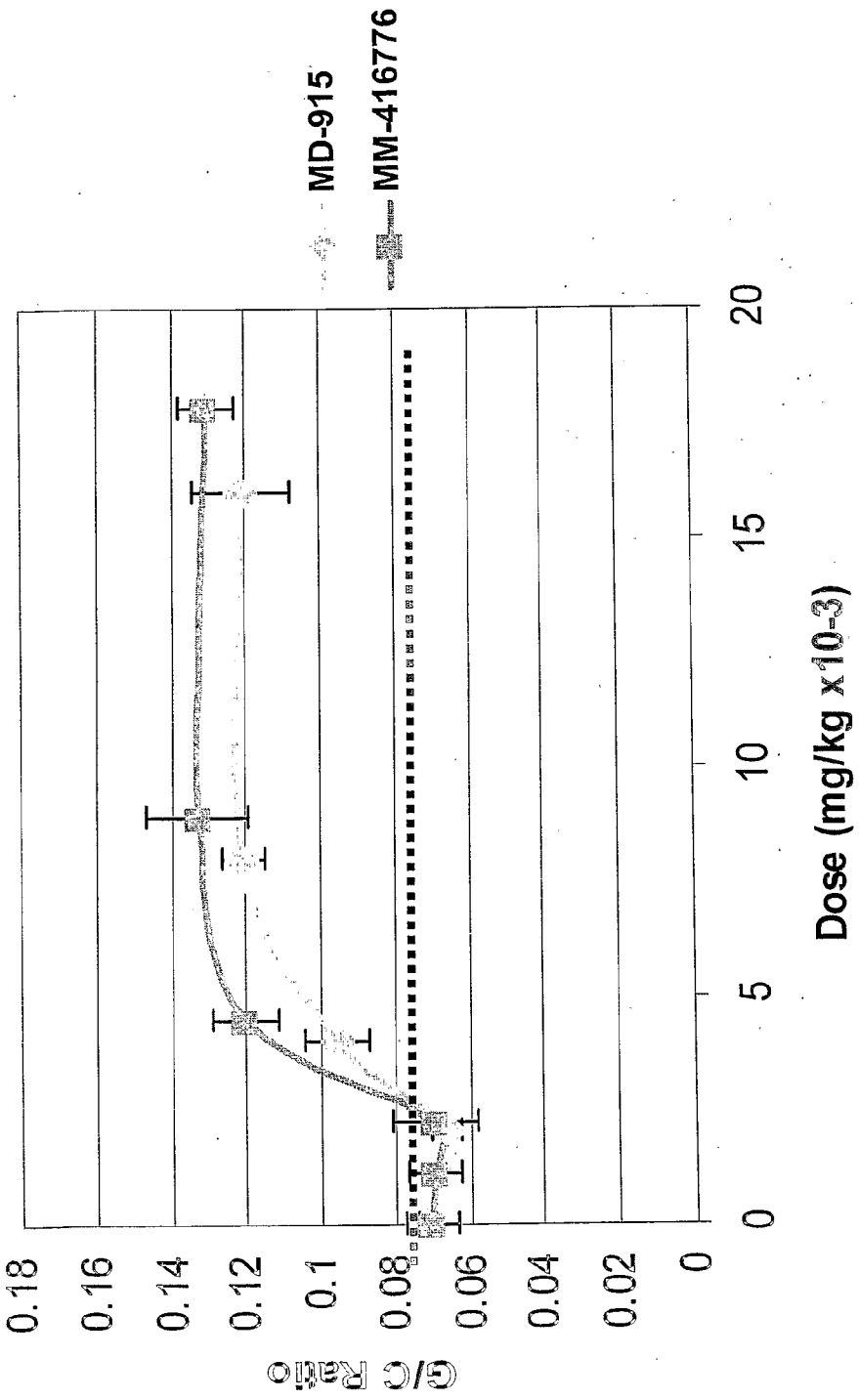


Figure 6b. Chemically synthesized peptides in Mouse Intestinal Secretion Model

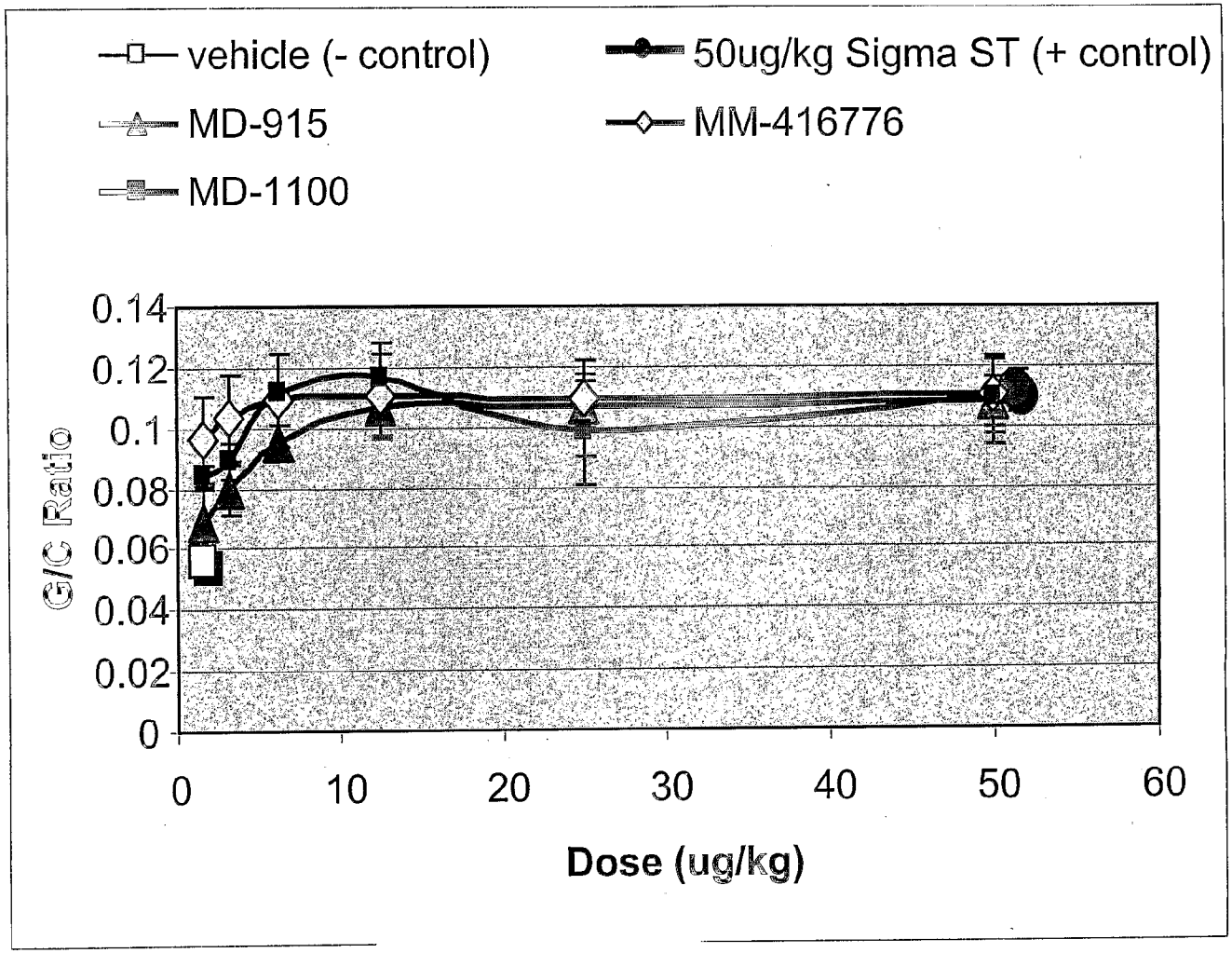
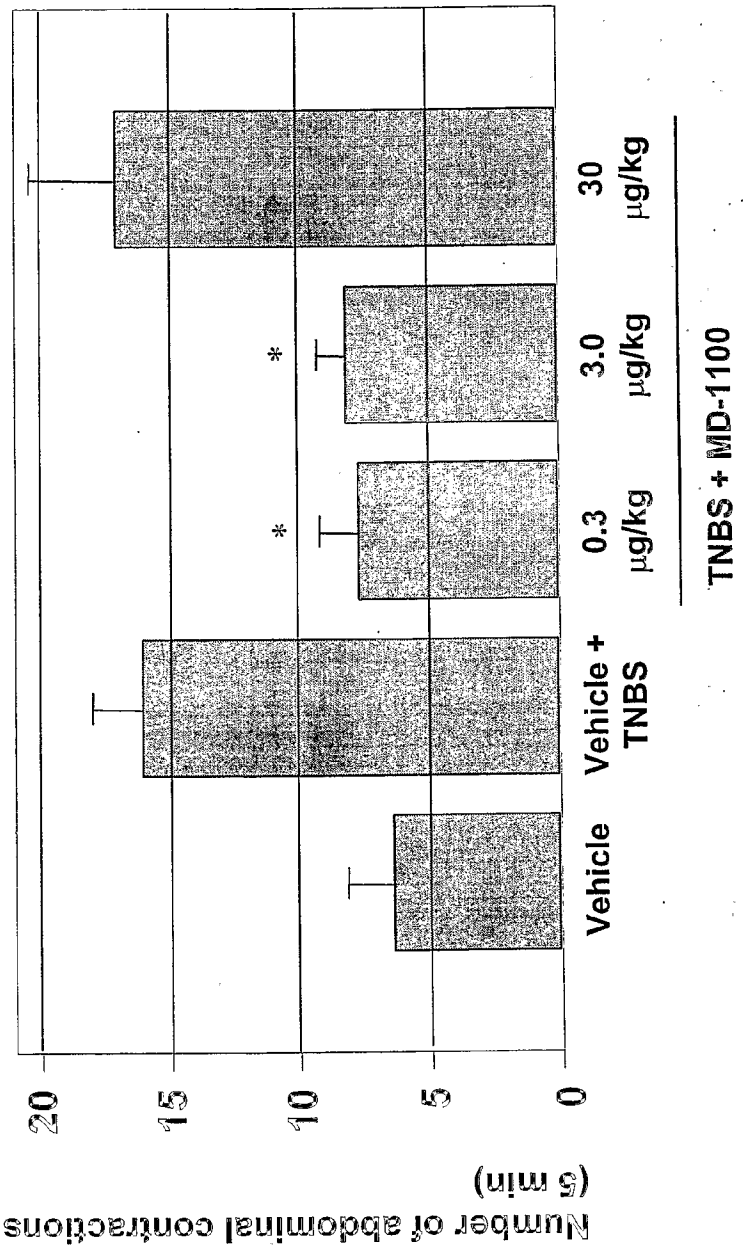


Figure 7: Effect of MD-1100 on pain in a rat TNBS Colorectal Distention Assay



* $p<0.05$ as compared to "vehicle" value

Figure 8a: Visceral Antinociceptive Effects of MD-915 in a Mouse Writhing Assay

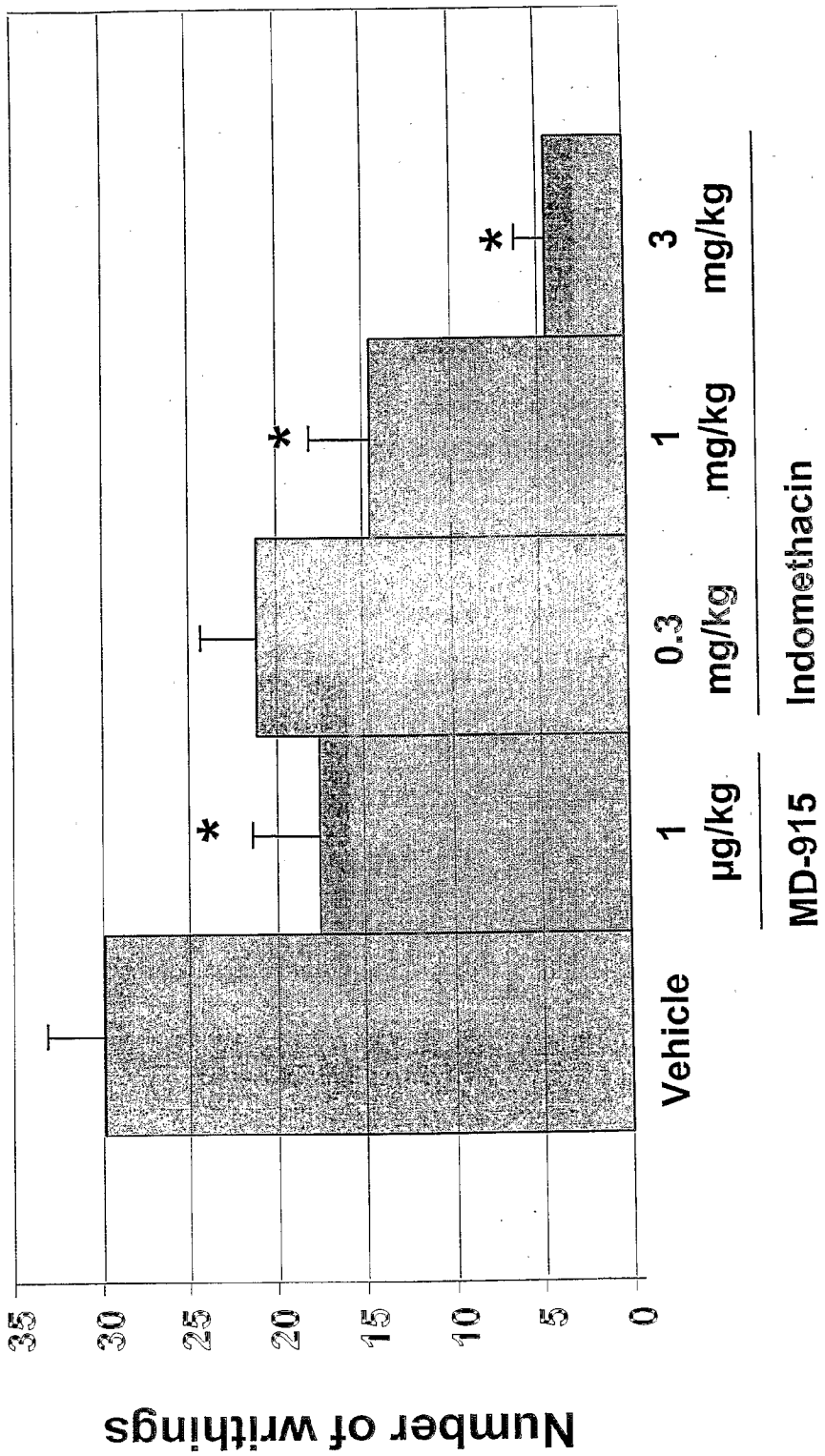


Figure 8b: Visceral Antinociceptive Effects of MD-1100 in a Mouse Writhing Assay

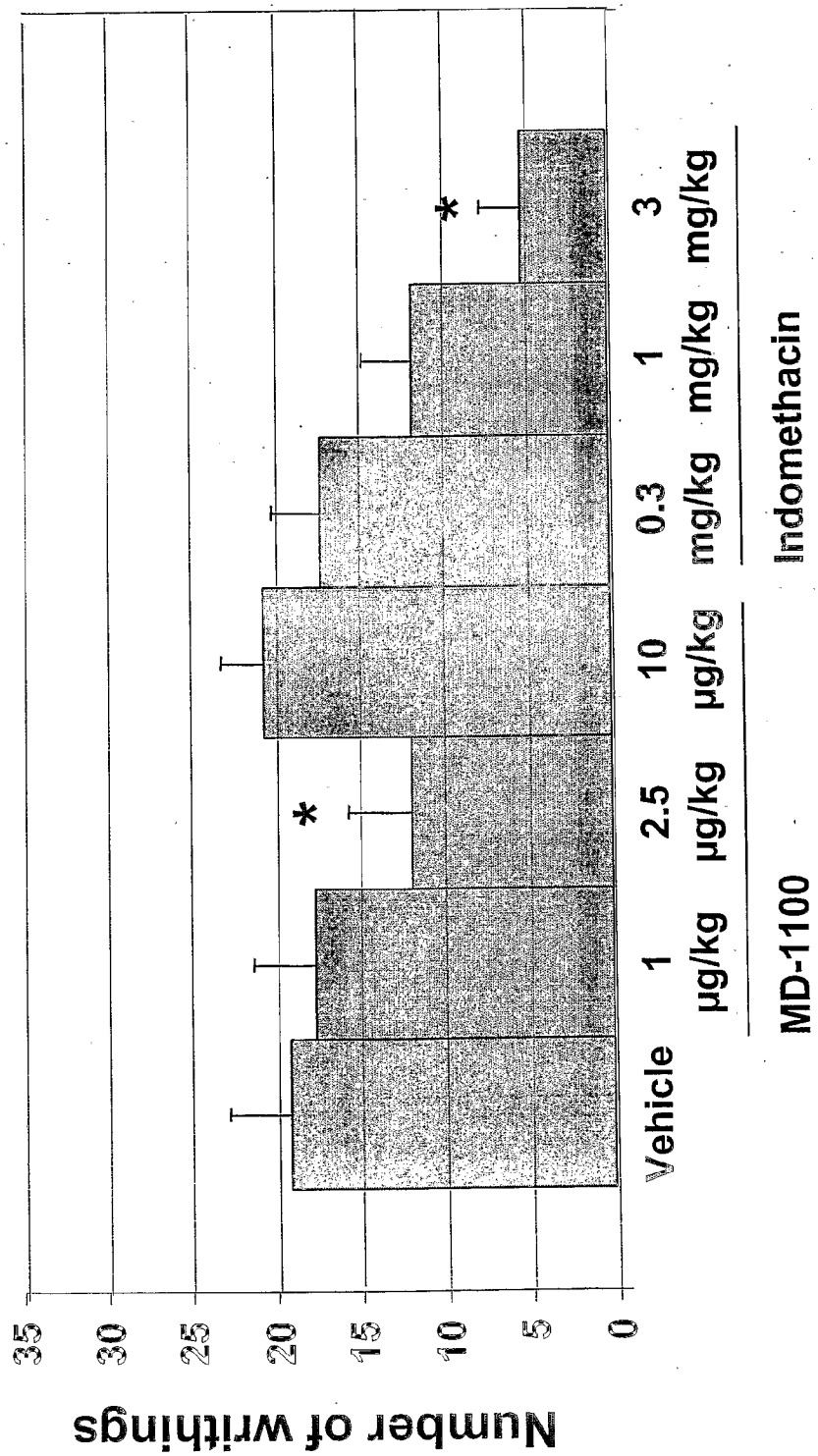


Figure 9: Competitive Radioligand Binding of MD-1100

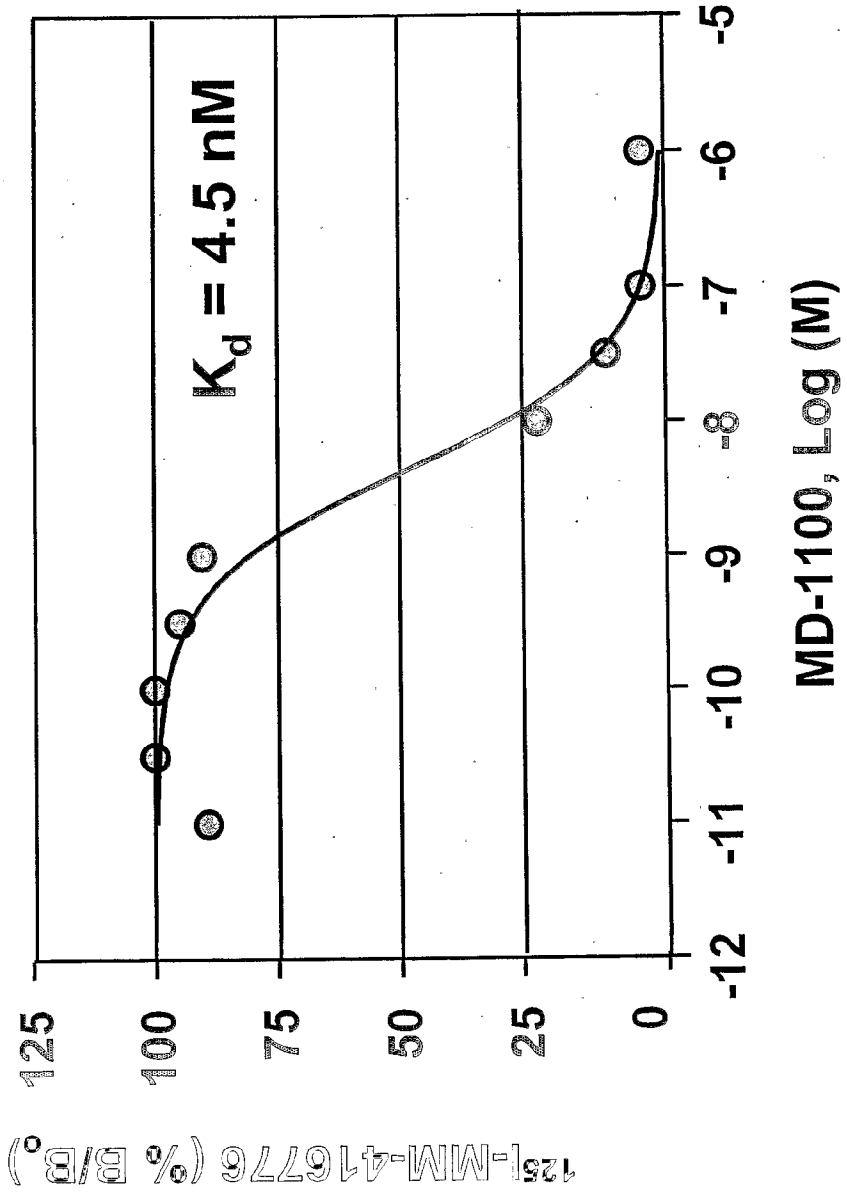
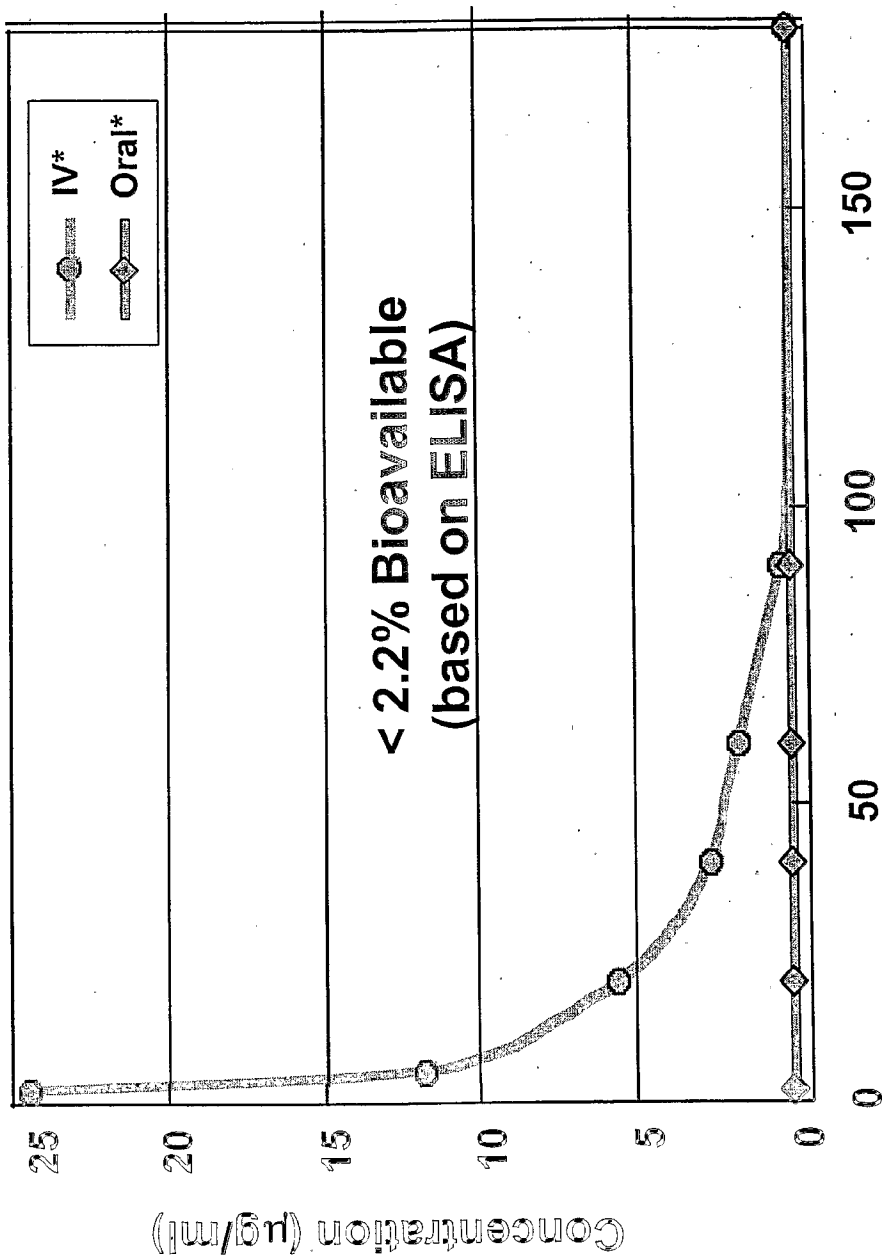
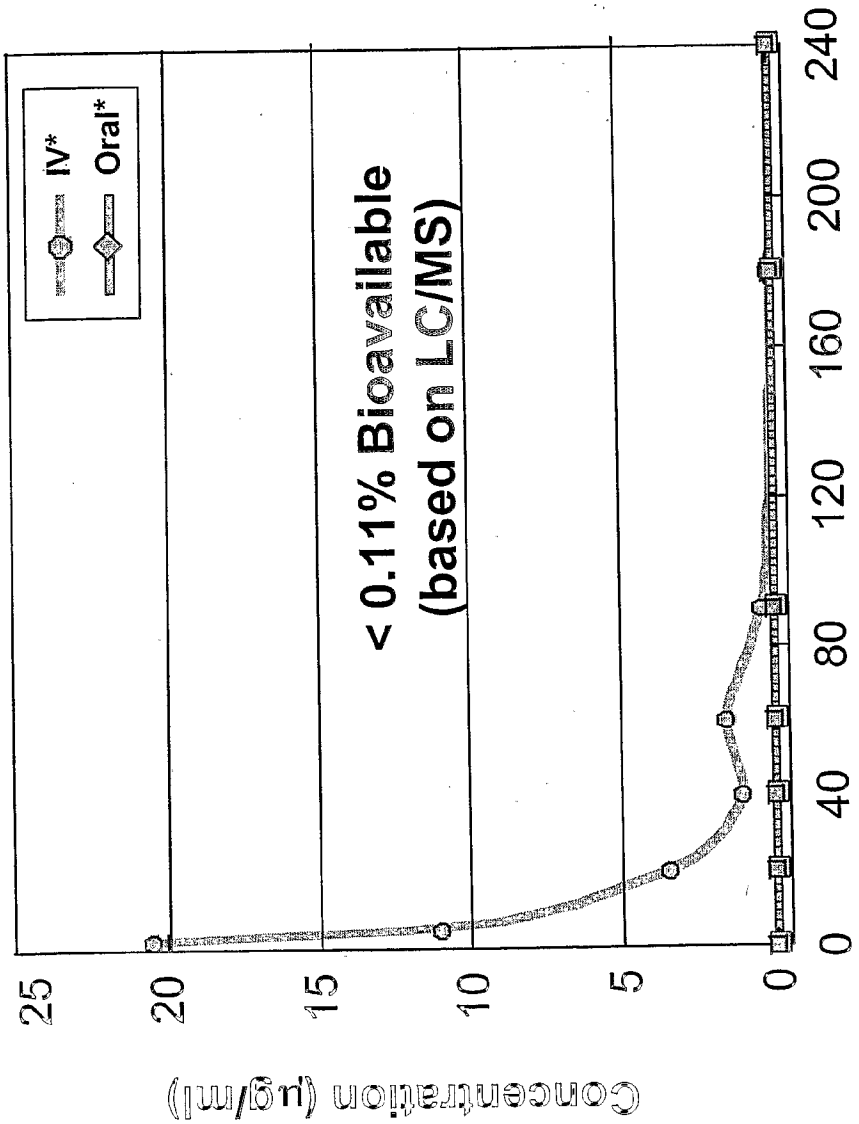


Figure 10a: Minimum Systemic Absorption of MD-1100 (based on ELISA)



* Limit of detection 0.061 µg/ml (40 nM)
Dosing at 10 mg/kg

Figure 10b: Minimum Systemic Absorption of MD-1100 (based on LC/MS)



- Limit of detection 0.00063 µg/mL (0.6 nM)
- Dosing at 10 mg/kg

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 February 2005 (24.02.2005)

PCT

(10) International Publication Number
WO 2005/016244 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2004/018751

(22) International Filing Date: 14 June 2004 (14.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/478,492	13 June 2003 (13.06.2003)	US
60/532,361	23 December 2003 (23.12.2003)	US
60/571,386	14 May 2004 (14.05.2004)	US

(71) Applicant *(for all designated States except US)*: **MICROBIA, INC.** [US/US]; 320 Bent Street, Cambridge, MA 02141 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CURRIE, Mark, G.** [US/US]; 18 Hall Avenue, Sterling, MA 01564 (US). **MAHAJAN-MIKLOS, Shalina** [IN/US]; 14 Holland Street, Needham, MA 02492 (US). **LI, Jing, Sun** [US/US]; 41 Fenno Street, Cambridge, MA 02138 (US).

(74) Agent: **MEIKLEJOHN, Anita, L.**; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,

[Continued on next page]

(54) Title: METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys

Human Guanylin (SEQ ID NO:)

--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

(57) Abstract: Compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), duodenogastric reflux, Crohn's disease, ulcerative colitis, inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudoobstruction), and disorders and conditions associated with constipation, e.g., constipation associated with use of opiate pain killers, post-surgical constipation, and constipation associated with neuropathic disorders as well as other conditions and disorders are described. The compositions feature peptides that activate the guanylate cyclase C (GC-C) receptor.

WO 2005/016244 A2

ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:

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

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

METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

TECHNICAL FIELD

This invention relates to methods and compositions for treating gastrointestinal disorders, obesity, congestive heart failure, benign prostatic hyperplasia and other disorders.

BACKGROUND

Irritable bowel syndrome (IBS) is a common chronic disorder of the intestine that affects 20 to 60 million individuals in the US alone (Lehman Brothers, Global Healthcare-Irritable Bowel Syndrome Industry Update, September 1999). IBS is the most common disorder diagnosed by gastroenterologists (28% of patients examined) and accounts for 12% of visits to primary care physicians (Camilleri 2001 *Gastroenterology* 120:652-668). In the US, the economic impact of IBS is estimated at $25 billion annually, through direct costs of health care use and indirect costs of absenteeism from work (Talley 1995 Gastroenterology 109:1736-1741). Patients with IBS have three times more absenteeism from work and report a reduced quality of life. Sufferers may be unable or unwilling to attend social events, maintain employment, or travel even short distances (Drossman 1993 *Dig Dis Sci* 38:1569-1580). There is a tremendous unmet medical need in this population since few prescription options exist to treat IBS.

Patients with IBS suffer from abdominal pain and a disturbed bowel pattern. Three subgroups of IBS patients have been defined based on the predominant bowel habit: constipation-predominant (c-IBS), diarrhea-predominant (d-IBS) or alternating between the two (a-IBS). Estimates of individuals who suffer from c-IBS range from 20-50% of the IBS patients with 30% frequently cited. In contrast to the other two subgroups that have a similar gender ratio, c-IBS is more common in women (ratio of 3:1) (Talley et al. 1995 *Am J Epidemiol* 142:76-83).

The definition and diagnostic criteria for IBS have been formalized in the "Rome Criteria" (Drossman et al. 1999 *Gut* 45:Suppl II:1-81), which are well accepted in clinical practice. However, the complexity of symptoms has not been explained by anatomical abnormalities or

metabolic changes. This has led to the classification of IBS as a functional GI disorder, which is diagnosed on the basis of the Rome criteria and limited evaluation to exclude organic disease(Ringel et al. 2001 *Annu Rev Med* 52: 319-338). IBS is considered to be a "biopsychosocial" disorder resulting from a combination of three interacting mechanisms: altered bowel motility, an increased sensitivity of the intestine or colon to pain stimuli (visceral sensitivity) and psychosocial factors (Camilleri 2001 *Gastroenterology* 120:652-668). Recently, there has been increasing evidence for a role of inflammation in the etiology of IBS. Reports indicate that subsets of IBS patients have small but significant increases in colonic inflammatory and mast cells, increased inducible nitric oxide (NO) and synthase (iNOS) and altered expression of inflammatory cytokines (reviewed by Talley 2000, Medscape Coverage of DDW Week).

SUMMARY OF THE INVENTION

The present invention features compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), duodenogastric reflux, Crohn's disease, ulcerative colitis, inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudoobstruction), and disorders and conditions associated with constipation, e.g., constipation associated with use of opiate pain killers, post-surgical constipation, and constipation associated with neuropathic disorders as well as other conditions and disorders. The compositions feature peptides that activate the guanylate cyclase C (GC-C) receptor.

The present invention also features compositions and related methods for treating obesity, congestive heart failure and benign prostatic hyperplasia (BPH).

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are useful because they can increase gastrointestinal motility.

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are useful, in part, because they can decrease inflammation.

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are also useful because they can decrease gastrointestinal pain or visceral pain.

The invention features pharmaceutical compositions comprising certain peptides that are capable of activating the guanylate-cyclase C (GC-C) receptor. Also within the invention are pharmaceutical compositions comprising a peptide of the invention as well as combination compositions comprising a peptide of the invention and one or more additional therapeutic agents, e.g., an agent for treating constipation (e.g., a chloride channel activator such as SPI-0211; Sucampo Pharmaceuticals, Inc.; Bethesda, MD, a laxative such as MiraLax; Braintree Laboratories, Braintree MA) or some other gastrointestinal disorder. Examples of additional therapeutic agents include: acid reducing agents such as proton pump inhibitors (e.g. omeprazole, esomeprazole, lansoprazole, pantorazole and rabeprazole), H2 receptor blockers (e.g., cimetidine, ranitidine, famotidine and nizatidine), pro-motility agents such as motilin agonists (e.g., GM-611 or mitemcinal fumarate), 5HT receptor agonists (e.g. 5HT4 receptor agonists such as Zelnorm®; 5HT3 receptor agonists such as MKC-733), 5HT receptor antagonists (e.g., 5HT1, 5HT2, 5HT3 (e.g., alosetron), 5HT4 receptor antagonists, muscarinic receptor agonists, anti-inflammatory agents, antispasmodics, antidepressants, centrally-acting analgesic agents such as opioid receptor agonists, opioid receptor antagonists (e.g., naltrexone), agents for the treatment of Inflammatory bowel disease, Crohn's disease and ulcerative colitis (e.g., Traficet-EN™ (ChemoCentryx, Inc.; San Carlos, CA)), agents that treat gastrointestinal or visceral pain, and cGMP phosphodiesterase inhibitors (e.g., motapizone, zaprinast, and suldinac sulfone). The peptides of the invention can also be used in combination with agents such as tianeptine (Stablon®) and other agents described in U.S. 6,683,072, (E)-4 (1,3bis(cyclohexylmethyl)-1,2,34,-tetrahydro-2,6-diono-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester and related compounds described in WO 02/067942. The peptides can also be used in combination with treatments entailing the administration of microorganisms useful in the treatment of gastrointestinal disorders such as IBS. Probactrix®

(The BioBalance Corporation; New York, NY) is one example of a formulation that contains microorganisms useful in the treatment of gastrointestinal disorders. The peptides can also be used in combination with purgatives that draw fluids to the intestine (e.g., Visicol®, a combination of sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrate.

In addition, the pharmaceutical compositions can include one or more agents selected from the group consisting of: Ca channel blockers (e.g., ziconotide), complete or partial 5HT receptor antagonists (for example 5HT3 (e.g., alosetron, ATI-7000; Aryx Thearpeutics, Santa Clara CA), 5HT4, 5HT2, and 5HT1 receptor antagonists), complete or partial 5HT receptor agonists including 5HT3, 5HT2, 5HT4 (e.g., tegaserod, mosapride and renzapride), 5HT1 receptor agonists, CRF receptor agonists (NBI-34041), β-3 adrenoreceptor agonists, opioid receptor agonists (e.g., loperamide, fedotozine, and fentanyl, naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine, morphine, diphenyloxylate, enkephalin pentapeptide, asimadoline, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033), CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists (e.g., talnetant, osanetant (SR-142801), SSR-241586), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid and cannabanoid receptor agonists (e.g., arvanil), sialorphin, sialorphin-related peptides comprising the amino acid sequence QHNPR (SEQ ID NO:) for example, VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:), compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1), loperamide, Tyr-Arg (kyotorphin), CCK receptor agonists (caerulein), conotoxin peptides, peptide analogs of thymulin, loxiglumide, dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774). These peptides and compounds can be administered with the peptides of the invention (simultaneously or sequentially). They can also be covalently linked to a peptide of the invention to create therapeutic conjugates.

The invention includes methods for treating various gastrointestinal disorders by administering a peptide that acts as a partial or complete agonist of the GC-C receptor. The peptide contains up to four cysteines that form one or two disulfide bonds. In certain embodiments the disulfide bonds are replaced by other covalent cross-links and in some cases the cysteines are substituted by other residues to provide for alternative covalent cross-links. The peptides may also include at least one trypsin or chymotrypsin cleavage site and/or a carboxy-terminal analgesic peptide or small molecule, e.g., AspPhe or some other analgesic peptide. When present within the peptide, the analgesic peptide or small molecule may be preceded by a chymotrypsin or trypsin cleavage site that allows release of the analgesic peptide or small molecule. The peptides and methods of the invention are also useful for treating pain and inflammation associated with various disorders, including gastrointestinal disorders. Certain peptides include a functional chymotrypsin or trypsin cleavage site located so as to allow inactivation of the peptide upon cleavage. Certain peptides having a functional cleavage site undergo cleavage and gradual inactivation in the digestive tract, and this is desirable in some circumstances. In certain peptides, a functional chymotrypsin site is altered, increasing the stability of the peptide *in vivo*(e.g., guanylin).

The invention includes methods for treating other disorders such as congestive heart failure and benign prostatic hyperplasia by administering a peptide or small molecule (parenterally or orally) that acts as an agonist of the GC-C receptor. Such agents can be used in combination with natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

The invention features methods and compositions for increasing intestinal motility. Intestinal motility involves spontaneous coordinated distentions and contractions of the stomach, intestines, colon and rectum to move food through the gastrointestinal tract during the digestive process.

The peptide can contain additional carboxy terminal or amino terminal amino acids or both. For example, the peptide can include an amino terminal sequence that facilitates recombinant production of the peptide and is cleaved prior to administration of the peptide to a patient. The

peptide can also include other amino terminal or carboxy terminal amino acids. In some cases the additional amino acids protect the peptide, stabilize the peptide or alter the activity of the peptide. In some cases some or all of these additional amino acids are removed prior to administration of the peptide to a patient. The peptide can include 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70 80, 90, 100 or more amino acids at its amino terminus or carboxy terminus or both. The number of flanking amino acids need not be the same. For example, there can be 10 additional amino acids at the amino terminus of the peptide and none at the carboxy terminus.

In certain embodiments the peptides include either one or two or more contiguous negatively charged amino acids (e.g., Asp or Glu) or one or two or more contiguous positively charged residues (e.g., Lys or Arg) or one or two or more contiguous positively or negatively charged amino acids at the carboxy terminus. In these embodiments all of the flanking amino acids at the carboxy terminus are either positively or negatively charged. In other embodiments the carboxy terminal charged amino acids are preceded by a Leu. For example, the following amino acid sequences can be added to the carboxy terminus of the peptide: Asp; Asp Lys; Lys Lys Lys Lys Lys Lys; Asp Lys Lys Lys Lys Lys Lys; Leu Lys Lys; and Leu Asp. It is also possible to simply add Leu at the carboxy terminus.

In a first aspect, the invention features a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is a) any amino acid, b) Phe, Tyr, Asn, Trp, c) an amino acid other than Phe, Trp, or Tyr, d) non-aromatic amino acid or e) is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr;

Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing; and

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

In some embodiments, Xaa_1 is preceded by Lys or Tyr.

In certain embodiments, a Cys is replaces by any amino acid other than Cys. Certain such polypeptides will have fewer disulfide bonds.

In a related aspect the invention features a composition comprising a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein: Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing; Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing; Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu; Xaa_5 is Asp, Ile or Glu; Xaa_6 is Ile, Trp or Leu; Xaa_7 is Cys, Ser, or Tyr; Xaa_8 is Ala, Val, Thr, Ile, Met or is missing; Xaa_9 is Phe, Tyr, Asn, Trp, an amino acid other than Phe, Trp, or Tyr, is a non-aromatic amino acid or is missing; Xaa_{10} is Ala, Val, Met, Thr or Ile; Xaa_{11} is Ala or Val; Xaa_{13} is Ala or Thr; Xaa_{14} is Gly, Ala or Ser; Xaa_{15} is Cys, Tyr or is missing; and Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser and a pharmaceutically acceptable carrier. In related aspects, the invention features a pharmaceutically acceptable tablet, pill, capsule comprising the peptide.

In a related aspect, the invention features a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Asn, any amino acid or is missing;

Xaa_2 is Asp, Glu, any amino acid or is missing;

Xaa_3 is Asp or Glu;

Xaa_5 is any amino acid or Glu;

Xaa_6 is any amino acid or Leu;

Xaa_7 is Cys;

Xaa_8 is any amino acid or Val;

Xaa_9 is Asn, Gln, Tyr;

Xaa_{10} is is any amino acid or Val;

Xaa_{11} is any amino acid or Ala;

Xaa_{13} is is any amino acid or Thr;

Xaa_{14} is is any amino acid or Gly;

Xaa_{15} is Cys;

Xaa_{16} is any amino acid, Leu or missing

In a related aspect, the invention features a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Asn_1 Xaa_2 Xaa_3 Xaa_4 Glu_5 Leu_6 Xaa_7 Val_8 Asn_9 Xaa_{10} Xaa_{11} Xaa_{12} Thr_{13} Xaa_{14} Xaa_{15} Leu_{16} (SEQ ID NO:__)

Xaa_2 is Asp or Glu;

Xaa_3 is Asp or Glu;

Xaa_4 is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_7 is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_{10} is Val or Pro;

Xaa_{11} is Ala or Aib (alpha-aminoisobutyric acid);

Xaa_{12} is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu; and

In certain embodiments, where Xaa_{15} is other than Cys or is missing, Xaa_7 is Ser or an amino acid other than Cys.

In certain embodiments 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 of Xaa_1, Xaa_2,Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, Xaa_{10}, Xaa_{11}, Xaa_{13}, Xaa_{14}, and Xaa_{16} are any amino acid other than Cys.

In certain embodiments, Xaa_9 is any amino acid other than Gln. In other embodiments where Xaa_2 and Xaa_3 are Glu, Xaa_9 is any amino acid other than Gln.

In certain embodiments Xaa_1 and Xaa_2 are missing; Xaa_3 is Thr; Xaa_5 is Glu; Xaa_6 is Ile or Leu; Xaa_8 is Ala, Val, or Ile; Xaa_9 is Phe or Tyr; Xaa_{10} is Ala or Val; Xaa_{11} is Ala; Xaa_{13} is Ala or Thr; Xaa_{14} is Gly; and Xaa_{16} is Trp, Tyr, Phe, Lys, Arg or is missing.

In certain embodiments the polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) is not cleaved after Xaa_9 by chymotrypsin. In these embodiments wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, or Gly, or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is either: a) any amino acid other than Phe and Tyr, b) any amino acid other than Phe, Tyr, and Trp, c) any amino acid other than Phe, Tyr, Trp, Ile, Leu and Val; d) any amino acid other than Phe, Tyr, Trp, Ile, Leu, Val, and His; d) any non-aromatic amino acid or e) is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr;

Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing; and

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

In addition, the invention features variants of Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) that is not cleaved after Xaa_9 by chymotrypsin due to the addition of an amino terminal lysine. An example of such a molecule is a human guanylin variant having an amino terminal lysine: KPGTCEICAYAACTGC (SEQ ID NO:).

In certain embodiments of the peptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) that is not cleaved after Xaa_9 by chymotrypsin, Xaa_7 and Xaa_{15} are both Cys.

Also within the invention are variants of PGTCEICAYAACTGC (human guanylin) (SEQ ID NO:) wherein Y is substituted by any amino acid other than a) Phe; b) any amino acid other than Phe and Trp; c) any amino acid other than Phe, Trp, Ile, Leu and Val; d) any amino acid other than Phe, Trp, Ile, Leu, Val and His; e) any non-aromatic amino acid or f) is missing.

In certain embodiments the polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) is not cleaved after Xaa_9 by either chymotrypsin or trypsin. In these embodiments wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, or Gly, or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is either: a) any amino acid other than Lys, Arg, Phe and Tyr, b) any amino acid other than Lys, Arg, Phe, Tyr, and Trp, c) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu and Val; d) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu, Val, and His; or e) is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr;

Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing; and

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

In certain embodiments of the peptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) that is not cleaved after Xaa_9 by chymotrypsin or trypsin, Xaa_7 and Xaa_{15} are both Cys.

Useful variants of PGTCEICAYAACTGC (human guanylin) (SEQ ID NO:) that should not be cleaved by chymotrypsin include:

PGTCEICASAACTGC (SEQ ID NO:)

PGTCEICATAACTGC (SEQ ID NO:)

PGTCEICANAACTGC (SEQ ID NO:)

PGTCEICAQAACTGC (SEQ ID NO:)

PGTCEICARAACTGC (SEQ ID NO:)

PGTCEICAEAACTGC (SEQ ID NO:)

PGTCEICADAACTGC (SEQ ID NO:)

PGTCEICAGAACTGC (SEQ ID NO:)

PGTCEICAAAACTGC (SEQ ID NO:)

PGTCEICAMAACTGC (SEQ ID NO:).

Additional variants which are not likely to be cleaved by chymotrypsin under certain conditions include:

PGTCEICAIAACTGC (SEQ ID NO:)

PGTCEICALAACTGC (SEQ ID NO:)

PGTCEICAVAACTGC (SEQ ID NO:)

PGTCEICAHAACTGC (SEQ ID NO:)

The invention also features deletion variants of any of the peptides described herein in which one, two, three or four amino acids, other than a Cys, are deleted. Where two (or more) amino acids are deleted and the peptide comprises the sequence: Cys_a Xaa Xaa Cys_b Xaa Xaa Xaa Xaa Cys_c Xaa Xaa Cys_d, in some embodiments two or more deletions can be located between Cys_a and Cys_b or between Cys_b and Cys_c or between Cys_c and Cys_d. Thus, there can be two or more deletions between two Cys. However, in other embodiments there is at most one deletion between each Cys, i.e., there is no more than one deletion between each of Cys_a and Cys_b, Cys_b and Cys_c, and Cys_c and Cys_d. Thus, the invention includes any of the peptides described herein comprising the sequence Cys_a Xaa Xaa Cys_b Xaa Xaa Xaa Xaa Cys_c Xaa Xaa Cys_d wherein: a) one amino acid between Cys_a and Cys_b is deleted; b) one amino acid between Cys_b and Cys_c is deleted; c) one amino acid between Cys_c and Cys_d is deleted; d) one amino acid between Cys_a and Cys_b is deleted and one amino acid between Cys_b and Cys_c is deleted; e) one amino acid between Cys_a and Cys_b is deleted and one amino acid between Cys_c and Cys_d is deleted; f) one amino acid between Cys_b and Cys_c is deleted and one amino acid between Cys_c and Cys_d is deleted; or g) one amino acid between Cys_a and Cys_b is deleted, one amino acid between Cys_b and Cys_c is deleted, and one amino acid between Cys_c and Cys_d is deleted. In addition, one or more amino acids preceding Cys_a and/or one or more amino acids following Cys_d can be deleted. The various deletion variants are peptides that bind to and/or activate the GC-C receptor.

The invention also features deletion variants of any of the peptides described herein in which one, two, three or four amino acids (or non-natural amino acids or natural or non-natural amino acid analogs), other than a Cys (or an amino acid substituted for Cys, e.g., an amino acid capable of forming a covalent bond to another amino acid) is deleted. Thus, additional variants include those in which a Cys is substituted by an amino acid capable of forming a covalent linkage with another amino acid (e.g., a Cys or a substitute therefore). Such amino acids include: Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid).

FIG. 1 includes deletion variants of human guanylin in which one, two, three or four amino acids are deleted. The deleted amino acids are between Cys_a and Cys_d as well as amino terminal to Cys_a.

The invention also features insertion variants of any of the peptides described herein in which one, two, three or four amino acids are inserted.

Where two (or more) amino acids are inserted and the peptide comprises the sequence: Cys_a Xaa Xaa Cys_b Xaa Xaa Xaa Xaa Cys_c Xaa Xaa Cys_d, in some embodiments two or more insertions can be located between Cys_a and Cys_b or between Cys_b and Cys_c or between Cys_c and Cys_d. However, in other embodiments there is at most one insertion between each of Cys_a and Cys_b or between Cys_b and Cys_c or between Cys_c and Cys_d. Thus, the invention includes any of the peptides described herein comprising the sequence Cys_a Xaa Xaa Cys_b Xaa Xaa Xaa Xaa Cys_c Xaa Xaa Cys_d wherein: a) one amino acid is inserted between Cys_a and Cys_b; b) one amino acid is inserted between Cys_b and Cys_c; c) one amino acid is inserted between Cys_c and Cys_d; d) one amino acid is inserted between Cys_a and Cys_b and one amino acid is inserted between Cys_b and Cys_c; e) one amino acid is inserted between Cys_a and Cys_b and one amino acid is inserted between Cys_c and Cys_d; f) one amino acid is inserted between Cys_b and Cys_c and one amino acid is inserted between Cys_c and Cys_d or g) one amino acid is inserted between Cys_a and Cys_b, one amino acid is inserted between Cys_b and Cys_c, and one amino acid is inserted between Cys_c and Cys_d . In addition, one or more amino acids can be inserted preceding Cys_a and/or one or more amino acids can be inserted following Cys_d. The insertions can be any natural or non-natural occurring amino acid (e.g., Gly or Ala) or amino acid analog and where there are more than one insertions present, they can be the same or different. The various deletion variants are peptides that bind to and/or activate the GC-C receptor.

For example, the invention includes the following insertion variants of PGTCGEICAYAACTGC (human guanylin) (SEQ ID NO:) include:

PGTCEGICAYAACTGC (SEQ ID NO:)
PGTCEIGCAYAACTGC (SEQ ID NO:)

PGTCEICGAYAACTGC (SEQ ID NO:)
PGTCEICAGYAACTGC (SEQ ID NO:)
PGTCEICAYGAACTGC (SEQ ID NO:)
PGTCEICAYAGACTGC (SEQ ID NO:)
PGTCEICAYAAGCTGC (SEQ ID NO:)
PGTCEICAYAACGTGC (SEQ ID NO:)
PGTCEICAYAACTGGC (SEQ ID NO:)
PGTCAEICAYAACTGC (SEQ ID NO:)
PGTCEAICAYAACTGC (SEQ ID NO:)
PGTCEIACAYAACTGC (SEQ ID NO:)
PGTCEICAAYAACTGC (SEQ ID NO:)
PGTCEICAYAAACTGC (SEQ ID NO:)
PGTCEICAYAACATGC (SEQ ID NO:)
PGTCEICAYAACTAGC (SEQ ID NO:)
PGTCEICAYAACTGAC (SEQ ID NO:)
PGTCAEICAAYAACTGC (SEQ ID NO:)
PGTCEAICAAYAACTGC (SEQ ID NO:)
PGTCEIACAAYAACTGC (SEQ ID NO:)

Other insertion variants of human guanylin can have up to four amino acids (i.e., 0, 1, 2, 3 or 4 natural or non-natural amino acids) inserted after each of the 15 amino acids in human guanylin. Thus, the invention includes peptides having the sequence: Pro $Xaa_{(0-4)}$ Gly $Xaa_{(0-4)}$ Thr $Xaa_{(0-4)}$ Cys $Xaa_{(0-4)}$ Glu $Xaa_{(0-4)}$ Ile $Xaa_{(0-4)}$ Cys $Xaa_{(0-4)}$ Ala $Xaa_{(0-4)}$ Tyr $Xaa_{(0-4)}$ Ala $Xaa_{(0-4)}$ Ala $Xaa_{(0-4)}$ Cys $Xaa_{(0-4)}$ Thr $Xaa_{(0-4)}$ Gly $Xaa_{(0-4)}$ Cys $Xaa_{(0-4)}$ (SEQ ID NO:). The inserted amino acids can be any amino acid and can be the same or different. In certain embodiments the inserted amino acids are all Gly or all Ala or a combination of Gly and Ala.

FIG. 2 depicts insertion variants of human guanylin in which one, two, three or four amino acids are inserted. The inserted amino acids are between Cys_a and Cys_d as well as amino terminal to Cys_a and carboxy terminal to Cys_d.

The invention also features variants of peptides having the sequence Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1), e.g., variants of PGTCEICAYAACTGC human guanylin (SEQ ID NO:) in which up to four amino acids are deleted and/or up to four amino acids are inserted. The insertions and deletions can be between Cys4 and Cys12 in SEQ ID NO:1 or they can be amino terminal to Cys4 and/or carboxy terminal to Cys12 in SEQ ID NO:1

When Xaa_{16} is Trp, Tyr or Phe, the peptide has a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide carboxy-terminal to Xaa_{16}. When Xaa_{16} is Lys or Arg, the peptide has a trypsin cleavage site that is located at a position where cleavage will liberate portion of the peptide carboxy-terminal to Xaa_{16}. Thus, if the peptide includes an analgesic peptide carboxy-terminal to Xaa_{16}, the peptide will be liberated in the digestive tract upon exposure to the appropriate protease. Among the analgesic peptides which can be included in the peptide are: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance P and other analgesic peptides described herein.

When Xaa_1 or the amino-terminal amino acid of the peptide of the invention (e.g., Xaa_2 or Xaa_3) is Trp, Tyr or Phe, the peptide has a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide amino-terminal to Xaa_1 (or Xaa_2 or Xaa_3) along with Xaa_1, Xaa_2 or Xaa_3. When Xaa_1 or the amino-terminal amino acid of the peptide of the invention (e.g., Xaa_2 or Xaa_3) is Lys or Arg, the peptide has a trypsin cleavage site that is located at a position where cleavage will liberate portion of the peptide amino-terminal to Xaa_1 along with Xaa_1, Xaa_2 or Xaa_3). Thus, for example, if the peptide includes an analgesic peptide amino-terminal to Xaa_1, the peptide will be liberated in the digestive tract upon exposure to the appropriate protease. Among the analgesic peptides which can be included in the peptide are: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance p and other analgesic peptides described herein.

The peptides can linked, e.g., covalently linked to any of a variety of other analgesic peptides or analgesic compounds. Thus, a peptide described herein can be linked to a second therapeutic

agent, e.g., an agent for treating constipation (e.g., a chloride channel activator such as SPI-0211; Sucampo Pharmaceuticals, Inc.; Bethesda, MD, a laxative such as MiraLax; Braintree Laboratories, Braintree MA) or some other gastrointestinal disorder. Examples of a second therapeutic agent include: acid reducing agents such as proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, pantorazole and rabeprazole), H2 receptor blockers (e.g., cimetidine, ranitidine, famotidine and nizatidine), pro-motility agents such as motilin agonists (e.g., GM-611 or mitemcinal fumarate), 5HT receptor agonists (e.g., 5HT4 receptor agonists such as Zelnorm®; 5HT3 receptor agonists such as MKC-733), 5HT receptor antagonists (e.g., 5HT1, 5HT2, 5HT3 (e.g., alosetron), 5HT4 receptor antagonists, muscarinic receptor agonists, anti-inflammatory agents, antispasmodics, antidepressants, centrally-acting analgesic agents such as opioid receptor agonists, opioid receptor antagonists (e.g., naltrexone), agents for the treatment of Inflammatory bowel disease, Crohn's disease and ulcerative colitis (e.g., Traficet-EN™ (ChemoCentryx, Inc.; San Carlos, CA), agents that treat gastrointestinal or visceral pain, and cGMP phosphodiesterase inhibitors (motapizone, zaprinast, and suldinac sulfone). The peptides of the invention can also be linked to agents such a tianeptine (Stablon®) and other agents described in U.S. 6,683,072; (E)-4 (1,3bis(cyclohexylmethyl)-1,2,34,-tetrahydro-2,6-diono-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester and related compounds described in WO 02/067942. The peptides can be linked to an agent selected from the group consisting of: Ca channel blockers (e.g., ziconotide), complete or partial 5HT receptor antagonists (for example 5HT3 (e.g., alosetron, ATI-7000; Aryx Thearpeutics, Santa Clara CA), 5HT4, 5HT2, and 5HT1 receptor antagonists), complete or partial 5HT receptor agonists including 5HT3, 5HT2, 5HT4 (e.g., tegaserod, mosapride and renzapride) and 5HT1 receptor agonists, CRF receptor agonists (NBI-34041), β-3 adrenoreceptor agonists, opioid receptor agonists (e.g., loperamide, fedotozine, and fentanyl, naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine, morphine, diphenyloxylate, enkephalin pentapeptide, asimadoline, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033), CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists (e.g., talnetant, osanetant (SR-142801), SSR-241586), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid and cannabanoid receptor agonists (e.g., arvanil), sialorphin, sialorphin-related peptides

comprising the amino acid sequence QHNPR (SEQ ID NO:) for example, VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:), compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1), loperamide, Tyr-Arg (kyotorphin), CCK receptor agonists (caerulein), conotoxin peptides, pepetide analogs of thymulin, loxiglumide, dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) and other analgesic peptides or compounds.

Amino acid, non-amino acid, peptide and non-peptide spacers can be interposed between a peptides of the invention and a peptide that has some other biological function, e.g., an analgesic peptide or a peptide used to treat obesity. The linker can be one that is cleaved from the flanking peptides *in vivo* or one that remains linked to the flanking peptides *in vivo*. For example, glycine, beta-alanine, glycyl-glycine, glycyl-beta-alanine, gamma-aminobutyric acid, 6-aminocaproic acid, L-phenylalanine, L-tryptophan and glycil-L-valil-L-phenylalanine can be used as a spacer (Chaltin et al. 2003 Helvetica Chimica Acta 86:533-547; Caliceti et al. 1993 FARMCO 48:919-32) as can polyethylene glycols (Butterworth et al. 1987 J. Med. Chem 30:1295-302) and maleimide derivatives (King et al. 2002 Tetrahedron Lett. 43:1987-1990). Various other linkers are described in the literature (Nestler 1996 Molecular Diversity 2:35-42; Finn et al. 1984 Biochemistry 23:2554-8; Cook et al. 1994 Tetrahedron Lett. 35:6777-80; Brokx et al. 2002 Journal of Controlled Release 78:115-123; Griffin et al. 2003 J. Am. Chem. Soc. 125:6517-6531; Robinson et al. 1998 Proc. Natl. Acad. Sci. USA 95:5929-5934.

The peptides can include the amino acid sequence of a peptide that occurs naturally in a vertebrate (e.g., mammalian) species or in a bacterial species. In addition, the peptides can be partially or completely non-naturally occurring peptides. Also within the invention are peptidomimetics corresponding to the peptides of the invention.

When fully folded, disulfide bonds are present between the first and third cysteines and between the second and fourth cysteines, e.g., there is a disulfide bond between Cys_4 and Cys_{12} and a

disulfide bond between Xaa_7 and Xaa_{15} (when Xaa_7 is a Cys and Xaa_{15} is a Cys). In some embodiments, the peptide has only one disulfide bond, e.g., between the first and third cysteines (i.e., Cys_4 and Cys_{12}; corresponds to the first and second cysteines when Xaa_7 is other than Cys). In certain embodiments one or more Cys can be replaced by Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or some other amino acid that can covalently link to another amino acid (e.g., Cys, Mpt, Pen or Dpr). In some embodiments, one or both members of a pair of Cys residues which normally form a disulfide bond can be replaced by homocysteine, 3-mercaptoproline (Kolodziej et al. 1996 *Int J Pept Protein Res* 48:274); β, β dimethylcysteine (Hunt et al. 1993 *Int J Pept Protein Res* 42:249) or diaminopropionic acid (Smith et al. 1978 *J Med Chem* 21:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

In addition, one or more disulfide bonds can be replaced by alternative covalent cross-links, e.g., an amide bond, an ester linkage, an alkyl linkage, a thio ester linkage, a lactam bridge, a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate ester linkage, an alkyl linkage, and alkenyl linkage, an ether, a thioether linkage, or an amino linkage. For example, Ledu et al. (Proceedings Nat'l Acad. Sci. 100:11263-78, 2003) described methods for preparing lactam and amide cross-links. Schafmeister et al. (J. Am. Chem. Soc. 122:5891, 2000) describes stable, all carbon cross-links. In some cases, the generation of such alternative cross-links requires replacing the Cys residues with other residues such as Lys or Glu or non-naturally occurring amino acids.

In certain embodiments one or more amino acids can be replaced by a non-naturally occurring amino acid or a naturally or non-naturally occurring amino acid analog. For example, an aromatic amino acid can be replaced by 3,4-dihydroxy-L-phenylalanine, 3-iodo-L-tyrosine, triiodothyronine, L-thyroxine, phenylglycine (Phg) or nor-tyrosine (norTyr). Phg and norTyr and other amino acids including Phe and Tyr can be substituted by, e.g., a halogen, -CH3, -OH, -CH_2NH_3, -C(O)H, -CH_2CH_3, -CN, -$CH_2CH_2CH_3$, -SH, or another group.

Further examples of unnatural amino acids include: an unnatural analogue of tyrosine; an unnatural analogue of glutamine; an unnatural analogue of phenylalanine; an unnatural analogue

of serine; an unnatural analogue of threonine; an alkyl, aryl, acyl, azido, cyano, halo, hydrazine, hydrazide, hydroxyl, alkenyl, alkynl, ether, thiol, sulfonyl, seleno, ester, thioacid, borate, boronate, phospho, phosphono, phosphine, heterocyclic, enone, imine, aldehyde, hydroxylamine, keto, or amino substituted amino acid, or any combination thereof; an amino acid with a photoactivatable cross-linker; a spin-labeled amino acid; a fluorescent amino acid; an amino acid with a novel functional group; an amino acid that covalently or noncovalently interacts with another molecule; a metal binding amino acid; a metal-containing amino acid; a radioactive amino acid; a photocaged and/or photoisomerizable amino acid; a biotin or biotin-analogue containing amino acid; a glycosylated or carbohydrate modified amino acid; a keto containing amino acid; amino acids comprising polyethylene glycol or polyether; a heavy atom substituted amino acid (e.g., an amino acid containing deuterium, tritium, ^{13}C, ^{15}N, or ^{18}O); a chemically cleavable or photocleavable amino acid; an amino acid with an elongated side chain; an amino acid containing a toxic group; a sugar substituted amino acid, e.g., a sugar substituted serine or the like; a carbon-linked sugar-containing amino acid; a redox-active amino acid; an α.-hydroxy containing acid; an amino thio acid containing amino acid; an α, α disubstituted amino acid; a β-amino acid; a cyclic amino acid other than proline; an O-methyl-L-tyrosine; an L-3-(2-naphthyl)alanine; a 3-methyl-phenylalanine; a *p*-acetyl-L-phenylalanine; an 0-4-allyl-L-tyrosine; a 4-propyl-L-tyrosine; a tri-O-acetyl-GlcNAcβ-serine; an L-Dopa; a fluorinated phenylalanine; an isopropyl-L-phenylalanine; a p-azido-L-phenylalanine; a p-acyl-L-phenylalanine; a p-benzoyl-L-phenylalanine; an L-phosphoserine; a phosphonoserine; a phosphonotyrosine; a p-iodo-phenylalanine; a 4-fluorophenylglycine; a p-bromophenylalanine; a p-amino-L-phenylalanine; a isopropyl-L-phenylalanine; L-3-(2-naphthyl)alanine; an amino-, isopropyl-, or O-allyl-containing phenylalanine analogue; a dopa, O-methyl-L-tyrosine; a glycosylated amino acid; a p-(propargyloxy)phenylalanine, dimethyl-Lysine, hydroxy-proline, mercaptopropionic acid, methyl-lysine, 3-nitro-tyrosine, norleucine, pyro-glutamic acid, Z (Carbobenzoxyl), ε-Acetyl-Lysine, β-alanine, aminobenzoyl derivative, aminobutyric acid (Abu), citrulline, aminohexanoic acid, aminoisobutyric acid, cyclohexylalanine, d-cyclohexylalanine, hydroxyproline, nitro-arginine, nitro-phenylalanine, nitro-tyrosine, norvaline, octahydroindole carboxylate, ornithine, penicillamine, tetrahydroisoquinoline, acetamidomethyl protected amino

acids and a pegylated amino acid. Further examples of unnatural amino acids can be found in U.S. 20030108885, U.S. 20030082575, and the references cited therein.

In some embodiments, an amino acid can be replaced by a naturally-occurring, non-essential amino acid, e.g., taurine.

Methods to manufacture peptides containing unnatural amino acids can be found in, for example, U.S. 20030108885, U.S. 20030082575, Deiters et al., J Am Chem Soc. (2003) 125:11782-3, Chin et al., Science (2003) 301:964-7, and the references cited therein.

Peptides that include non-natural amino acids can also be prepared using the methods described in WO02086075.

The peptides of the invention can be modified using standard modifications. Modifications may occur at the amino (N-), carboxy (C-) terminus, internally or a combination of any of the preceeding. In one aspect of the invention, there may be more than one type of modification on the peptide. Modifications include but are not limited to: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, formylation, myristoylation, palmitoylation, phosphorylation (Ser, Tyr or Thr), stearoylation, succinylation, sulfurylation and cyclisation (via disulfide bridges or amide cyclisation), and modification by Cy3 or Cy5. The peptides of the invention may also be modified by 2, 4-dinitrophenyl (DNP), DNP-lysin, modification by 7-Amino-4-methyl-coumarin (AMC), flourescein, NBD (7-Nitrobenz-2-Oxa-1,3-Diazole), p-nitro-anilide, rhodamine B, EDANS (5-((2-aminoethyl)amino)naphthalene-1- sulfonic acid), dabcyl, dabsyl, dansyl, texas red, FMOC, and Tamra (Tetramethylrhodamine). The peptides of the invention may also be conjugated to, for example, BSA or KLH (Keyhole Limpet Hemocyanin).

The invention also features a purified polypeptide comprising, consisting of or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is any amino acid or is missing;

Xaa_2 is any amino acid or is missing;

Xaa_3 is any amino acid or is missing;

Xaa_5 is Glu;

Xaa_6 is Tyr, Trp, Phe or Leu;

Xaa_7 is Cys;

Xaa_8 is any of the 20 naturally-occurring amino acids other than Cys or is missing;

Xaa_9 is any of the 20 naturally-occurring amino acids;

Xaa_{10} is Pro or Gly;

Xaa_{11} is any of the 20 naturally-occurring amino acids;

Xaa_{13} is Thr, Val or Gly;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys; and

Xaa_{16} is any of the 20 naturally-occurring amino acids or is missing.

In various embodiments: Xaa_9 is Asn; Xaa_{11} is Ala or Thr; Xaa_8 is missing; and Xaa_{16} is Tyr.

In other embodiments Xaa_4 is immediately preceded by an amino acid sequence seleted from: Ser His Thr; Pro Ser Thr; Thr; Pro Asp Pro; Ile Ala Glu Asp Ser His Thr; Ile Ala Gln Asp Pro Ser Thr; Ala Asn Thr; Asn Thr; Asp Pro Asn Thr; Lys Asn Thr; Pro Asn Thr; Ile Ala Gln Asp Pro Asn Thr; Lys Pro Asn Thr; Asp Pro Gly Thr; Glu Asp Pro Gly Thr; Pro Gly Thr; Pro Ala Thr; Val Ala Ala Arg Ala Asp Leu; Gly Asp Asp; Asn Asp Glu; Gln Glu Asp; Asn Asp Asp; Arg Thr Ile Ala Asn Asp Asp; Thr Ile Ala Asn Asp Asp; Asp Asp; Arg Thr Met Asp Asn Asp Glu; Arg Thr Ile Ala Gly Asp Asp; Arg Thr Ile Ala Asn Asp; Asp; Glu Asp; Arg Ser Ile Ser Gln Glu Asp; Thr Asp Glu; Arg Thr Ile Ala Thr Asp Glu; Glu; Ile Ile Thr Pro Pro Asp Pro; Gln Glu Leu; Lys Asp Asp; Gln Glu Glu; Arg Tyr Ile Asn Gln Glu Glu; Ala Ser Ser Tyr Ala Ser; and Thr Ser Ser Tyr Ala Ser.

The invention further features a purified polypeptide comprising, consisting of or consisting essentially the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is: a) Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing; b)

preceded by Lys or Tyr; c) any amino acid; d) missing; e) any amino acid other than Cys; or f) Lys or Arg;

Xaa_2 is: a) His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing; b) His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing; c) Asp, Glu, any amino acid or is missing; d) Asp or Glu; e) any amino acid other than Cys; e) Glu; f) missing; g) Trp, Tyr or Phe; or h) Lys or Arg;

Xaa_3 is: a) Thr, Asp, Ser, Glu, Pro, Val or Leu; Asp or Glu; b) any amino acid other than Cys; c) Glu; d) Thr; e) Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing; f) Trp, Tyr or Phe; or g) Lys or Arg;

Xaa_4 is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu;

Xaa_5 is: a) any amino acid; b) Glu, Asp, Gln, Gly or Pro; c) Glu; d) Glu or Asp; e) Asp, Ile or Glu; f) any amino acid; or g) any amino acid other than Cys;

Xaa_6 is: a) Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; b) Leu, Ile, Val, Lys, Arg, Trp, Tyr or Phe; Leu, Ile, Lys, Arg, Trp, Tyr or Phe; c) Leu, Ile, Val, Trp, Tyr or Phe; d) Trp, Tyr, Phe or Leu; e) Leu, Ile or Val; f) Ile, Trp or Leu; g) Trp, Tyr or Phe; h) Ile or Leu; i) Tyr; j) any amino acid; k) any amino acid except Leu; l) any natural or non-natural aromatic amino acid; or m) any amino acid other than Cys;

Xaa_7 is: a) Cys, Ser, or Tyr; Cys; b) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; c) Ser; or d) an amino acid other than Cys;

Xaa_8 is: a) Ala, Val, or Ile; b) Ala, Val, Thr, Ile, Met or is missing; c) any amino acid; d) Val; e) any amino acid other than Cys; or f) missing;

Xaa_9 is: a) any amino acid; b) any amino acid other than Phe and Tyr; c) any amino acid other than Phe, Tyr, and Trp; d) any amino acid other than Phe, Tyr, Trp, Ile, Leu and Val; e) any amino acid other than Phe, Tyr, Trp, Ile, Leu, Val, and His; f) any amino acid other than Gln; g) any amino acid other than Lys, Arg, Phe, Tyr, and Trp; h) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu and Val; i) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu, Val, and His; j) any non-aromatic amino acid; k) missing; l) Phe, Tyr, Asn, or Trp; m) Asn, Tyr, Asp or Ala; n) Asn, Gln, or Tyr; o) Phe or Tyr; p) Asn; or q) any amino acid other than Cys;

Xaa_{10} is: a) Ala, Pro or Gly; b) Pro or Gly; c) Pro; d) Ala, Val, Met, Thr or Ile; e) any amino acid; f) Val; g) Val or Pro; h) Ala or Val; i) any amino acid other than Cys; j) Pro; or k) Gly;

Xaa_{11} is: a) any amino acid; b) Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, or Asp; c) Ala or Gly; d) Ala; e) Ala or Val; f) any amino acid; g) Ala or Aib (alpha-aminoisobutyric acid); h) any amino acid other than Cys; i) Ala or Thr; or j) Thr.

Xaa_{12} is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu; or b) any amino acid other than Cys;

Xaa_{13} is: a) Thr, Ala, Asn, Lys, Arg, or Trp; b) Thr, Ala, Lys, Arg, or Trp; c) any amino acid; d) any non-aromatic amino acid; e) Thr, Ala, or Trp; f) Trp, Tyr or Phe; g) Thr or Ala; h) any amino acid; i) Thr; j) any amino acid other than Cys; k) Thr, Val, or Gly; l) Thr or Val, m) Thr or Gly, n) Val or Thr; o) Val; p) Thr; or q) Gly;

Xaa_{14} is: a) Gly, Pro or Ala; b) Gly; c) any amino acid; d) Gly, Ala or Ser; e) Gly or Ala; f) any amino acid other than Cys; or g) Ala;

Xaa_{15} is: a) Cys, Tyr or is missing; b) Cys; c) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, Glu; or d) any amino acid other than Cys or is missing; and

Xaa_{16} is: a) Trp, Tyr, Phe, Asn, Ile, Val, His or Leu; b) Trp, Tyr, Phe, Asn or Leu; c) Trp, Tyr, Phe or Leu; d) Trp, Tyr, or Phe; e) Leu, Ile or Val; f) His, Leu or Ser; g) Tyr or Leu; Lys or Arg; h) His; i) any amino acid, j) Leu, or missing; k) Trp, Tyr, Phe, Lys, Arg or is missing; l) missing; m) any amino acid other than Cys; or n) Tyr.

Also featured is purified polypeptide comprising, consiting of or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is any amino acid or is missing;

Xaa_2 is any amino acid or is missing;

Xaa_3 is any amino acid or is missing;

Xaa_4 is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_5 is Glu;

Xaa_6 is Tyr, Trp, Phe or Leu;

Xaa_7 is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_8 is any amino acid other than Cys or is missing;

Xaa_9 is any amino acid;

Xaa_{10} is Pro or Gly;

Xaa_{11} is any amino acid;

Xaa_{12} is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_{13} is Thr, Val or Gly;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; and

Xaa_{16} is any amino acid or is missing.

The various peptides can be present with a counterion. Useful counterions include salts of: acetate, benzenesulfonate, benzoate, calcium edetate, camsylate, carbonate, citrate, edetate (EDTA), edisylate, embonate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, iodide, bromide, chloride, hydroxynaphthoate, isethionate, lactate, lactobionate, estolate, maleate, malate, mandelate, mesylate, mucate, napsylate, nitrate, pantothenate, phosphate, salicylate, stearate, succinate, sulfate, tartarate, theoclate, acetamidobenzoate, adipate, alginate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, camphorate, caprate, caproate, caprylate, cinnamate, cyclamate, dichloroacetate, formate, gentisate, glucuronate, glycerophosphate, glycolate, hippurate, fluoride, malonate, napadisylate, nicotinate, oleate, orotate, oxalate, oxoglutarate, palmitate, pectinate, pectinate polymer, phenylethylbarbiturate, picrate, propionate, pidolate, sebacate, rhodanide, tosylate, tannate

In a second aspect, the invention also features a therapeutic or prophylactic method comprising administering a composition comprising a purified peptide comprising, consisting essentially or consisting of the amino acid sequence of SEQ ID NO:1. For the treatment of gastrointestinal disorders, the peptide can be administered orally, by rectal suppository or parenterally.

In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, obesity, congestive heart failure, or benign prostatic hyperplasia; the composition is administered orally; the peptide comprises 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, or 30 or fewer amino acids. In other embodiments, the peptide comprises 20 or fewer amino acids, and the peptide comprises no more than 5 amino acids prior to Cys_4. In other embodiments the peptide comprises no more than 20, 15, 10, or 5 peptides subsequent to Cys_{15}. In certain embodiments Xaa_{16} is a chymotrypsin or trypsin cleavage site and an analgesic peptide is present immediately following Xaa_{16}.

Among the useful peptides are those comprising, consisting of or consisting essentially of any of the following amino acid sequences:

SHTCEICAFAACAGC (opossum guanylin) (SEQ ID NO:);

PGTCEICAYAACTGC (human guanylin) (SEQ ID NO:);

PSTCEICAYAACAGC (pig guanylin) (SEQ ID NO:);

PNTCEICAYAACTGC (rat guanylin) (SEQ ID NO:);

PDPCEICANAACTGCL (European eel guanylin, inferred) (SEQ ID NO:);

NDDCELCVNVACTGCL (human uroguanylin) (SEQ ID NO:);

QEECELCINMACTGY (opossum lymphoguanylin) (SEQ ID NO:);

GDDCELCVNVACTGCS (pig uroguanylin) (SEQ ID NO:);

NDECELCVNIACTGC (guinea pig uroguanylin) (SEQ ID NO:);

TDECELCINVACTGC (rat uroguanylin) (SEQ ID NO:);

QEDCELCINVACTGC (opossum uroguanylin) (SEQ ID NO:);

MPSTQYIRRPASSYASCIWCTTACASCHGRTTKPSLAT (EAST 1) (SEQ ID NO:);

MPSTQYIRRPASSYASCIWCATACASCHGRTTKPSLAT (SEQ ID NO:);

MPSTQYIRRPTSSYASCIWCATACASCHGRTTKPSLAT (SEQ ID NO:);

MPSTQYIRRPTSSYASCIWCATVCASCHGRTTKPSLAT (SEQ ID NO:);

MPSTQYIRRPASSYASCIWYATACASCHGRTTEPSLAT (SEQ ID NO:);

QEECELSINMACTGY (opossum lymphoguanylin analog) (SEQ ID NO:);

YDECEICMFAACTGC (Japanese eel guanylin) (SEQ ID NO:);

VCEICAFAACTGC (Zebrafish guanylin, inferred) (SEQ ID NO:);

ADLCEICAFAACTGCL (Japenese eel renoguanylin, inferred) (SEQ ID NO:);

PGTCEICAYAACTGCL (SEQ ID NO:);

PGTCEICAYAACTGCLKK (SEQ ID NO:);

PNTCEICAYAACTGCKKKKKK (SEQ ID NO:);

PNTCEICAYAACTGCD (SEQ ID NO:);

PNTCEICAYAACTGCDK (SEQ ID NO:);

YPNTCEICAYAACTGC (SEQ ID NO:);

KNTCEICAYAACTGC (SEQ ID NO:);

KPNTCEICAYAACTGC (SEQ ID NO:);

EDPGTCEICAYAACTGC (SEQ ID NO:);

VTVQDG NFSFSLESVK KLKDLQEPQE PRVGKLRNFA PIPGEPVVPI LCSNPNFPEE LKPLCKEPNA QEILQRLEEIAEDPGTCEICAYAACTGC (SEQ ID NO:);

DPGTCEICAYAACTGC (SEQ ID NO:);

MNAFLLSALC LLGAWAALAG GVTVQDGNFS FSLESVKKLK DLQEPQEPRV GKLRNFAPIP GEPVVPILCS NPNFPEELKP LCKEPNAQEI LQRLEEIAED PGTCEICAYAACTGC (SEQ ID NO:);

MNAFLLFALC LLGAWAALAG GVTVQDGNFS FSLEPRVGKL RNFAPIPGEP VVPILCSNPN FPEELKPLCK EPNAQEILQR LEEIAEDPGTCEICAYAACTGC (SEQ ID NO:);

TGSMNAFLLF ALCLLGAWAA LAGGVTVQDG NFSFSLEPRV GKLRNFAPIP GEPVVPILCS NPNFPEELKP LCKEPNAQEI LQRLEEIAEDPGTCEICAYAACTGCLEG (SEQ ID NO:);

NDECELCVNVACTGCL (SEQ ID NO:);

ECELCVNVACTGCL (SEQ ID NO:);

EDCELCINVACTGC (SEQ ID NO:);

NDDCELCVACTGCL (SEQ ID NO:);

FKTLRTIANDDCELCVNVACTGCL (SEQ ID NO:);

FKTLRTIANDDCLCVNVACTGCL (SEQ ID NO:);

DDCELCVNVACTGCL (SEQ ID NO:);

DCELCVNVACTGCL (SEQ ID NO:);

CELCVNVACTGCL (SEQ ID NO:);

KDDCELCVNVACTGCL (SEQ ID NO:);

PNTCEICANPACTGC (SEQ ID NO.).

The peptides can include the amino acid sequence of a peptide that occurs naturally in a vertebrate (e.g., mammalian) species or in a bacterial species. In addition, the peptides can be partially or completely non-naturally occurring peptides.

In a third aspect, the invention features a method for treating a patient suffering from constipation, the method comprising administering a composition comprising a peptide comprising, consisting essentially or consisting of the amino acid sequence of SEQ ID NO:1. Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001 *Aliment Pharmacol Ther* 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease and cystic fibrosis. Constipation may also be the result of surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In various embodiments, the constipation is associated with use of a therapeutic agent; the constipation is associated with a neuropathic disorder; the constipation is post-surgical constipation; the constipation is associated with a gastrointestinal disorder; the constipation is idiopathic (functional constipation or slow transit constipation); the constipation is associated

with neuropathic, metabolic or endocrine disorder (e.g., diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease or cystic fibrosis). Constipation may also be the result of surgery or due to the use of drugs such as analgesics (e.g., opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In a fourth aspect, the invention features a method for treating a patient suffering a gastrointestinal disorder, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction; Crohn's disease, ulcerative colitis, Inflammatory bowel disease , colonic pseudo-obstruction, obesity, congestive heart failure, and benign prostatic hyperplasia.

In a fifth aspect, the invention features a method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In a sixth aspect, the invention features a method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In a seventh aspect, the invention features a method for increasing the activity of an intestinal guanylate cyclase (GC-C) receptor in a patient, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In an eighth aspect, the invention features an isolated nucleic acid molecule comprising a nucleotide sequence encoding a peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In a ninth aspect, the invention features a composition comprising a purified polypeptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. In an embodiment, the composition is a pharmaceutical composition.

In a tenth aspect, the invention features a method for treating obesity, the method comprising administering a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. The peptide can be administered in combination with one or more agents for treatment of obesity, for example, gut hormone fragment peptide YY_{3-36} (PYY_{3-36}) (*N. Engl. J. Med.* 349:941, 2003; ikpeapge daspeelnry yaslrhylnl vtrqry) or a variant thereof, glp-1 (glucagon-like peptide-1), exendin-4 (an inhibitor of glp-1), sibutramine, phentermine, phendimetrazine, benzphetamine hydrochloride (Didrex), orlistat (Xenical), diethylpropion hydrochloride (Tenuate), fluoxetine (Prozac), bupropion, ephedra, chromium, garcinia cambogia, benzocaine, bladderwrack (focus vesiculosus), chitosan, nomame herba, galega (Goat's Rue, French Lilac), conjugated linoleic acid, L-carnitine, fiber (psyllium, plantago, guar fiber), caffeine, dehydroepiandrosterone, germander (teucrium chamaedrys), B-hydroxy-β-methylbutyrate, ATL-962 (Alizyme PLC), and pyruvate. A peptide useful for treating obesity can be administered as a co-therapy with a peptide of the invention either as a distinct molecule or as part of a fusion protein with a peptide of the invention. Thus, for example, PYY_{3-36} can be fused to the carboxy or amino terminus of a peptide of the invention. Such a fusion protein can include a chymostrypsin or trypsin cleavage site that can permit cleavage to separate the two peptides. A peptide useful for treating obesity can be administered as a co-therapy with electrostimulation (U.S. 20040015201).

In an eleventh aspect, the invention features a method for treating congestive heart failure, the method comprising: administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. The peptide can be administered in combination with one or more agents for treatment of congestive heart failure, for example, a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

In a twelfth aspect, the invention features a method for treating benign prostatic hyperplasia, the method comprising: administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. The peptide can be administered in combination with one or more agents for treatment of BPH, for example, a 5-alpha reductase inhibitor (e.g., finasteride) or an alpha adrenergic inhibitor (e.g., doxazosine).

In a thirteenth aspect, the invention features a method for treating a patient suffering a gastrointestinal disorder, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor. In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, and colonic pseudo-obstruction.

In a fourteenth aspect, the invention features a method for treating a patient suffering from constipation, the method comprising administering a composition comprising a complete or partial agonist of the GC-C receptor.

In a fifteenth aspect, the invention features a method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

In a sixteenth aspect, the invention features a method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

In a seventeenth aspect, the invention features a method for treating congestive heart failure, the method comprising administering a complete or partial agonist of the GC-C receptor. GC-C agonists can act in the kidney and adrenal gland to control natriuresis, kaliuresis, and diuresis thereby reducing the build-up of fluid associated with congestive heart failure (Lorenz et al. *J Clin Invest* 112:1138, 2003; Carrithers et al. *Kidney Int* 65:40, 2004). The agonist can be administered in combination with one or more agents for treatment of congestive heart failure, for example, a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

In an eighteenth aspect, the invention features a method for treating BPH, the method comprising administering a complete or partial agonist of the GC-C receptor. GC-C agonists acting in the prostate can reduce cellular hypertrophy and complications associated with cellular hypertrophy. The agonist can be administered in combination with one or more agents for treatment of BPH, for example, a 5-alpha reductase inhibitor (e.g., finasteride) or an alpha adrenergic inhibitor (e.g., doxazosine).

In a nineteenth aspect, the invention features a method for treating obesity, the method comprising administering a complete or partial agonist of the GC-C receptor. The agonist can be administered in combination with one or more agents for treatment of obesity, for example, sibutramine.

The peptides and agonists of the GC-C receptor can be used to treat constipation or decreased intestinal motility, slow digestion or slow stomach emptying. The peptides can be used to relieve one or more symptoms of IBS (bloating, pain, constipation), GERD (acid reflux into the esophagus), duodenogastric reflux, functional dyspepsia, or gastroparesis (nausea, vomiting, bloating, delayed gastric emptying) and other disorders described herein.

Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001, Aliment Pharmacol Ther 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung's disease and cystic fibrosis. Constipation may also be the result of surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In a twentieth aspect, the invention features isolated nucleic acid molecules comprising or consisting of a sequence encoding a peptide of the invention. The invention also features vectors, e.g., expression vectors that include such nucleic acid molecules and can be used to express a peptide of the invention in a cultured cell (e.g., a eukaryotic cell or a prokaryotic cell). The vector can further include one or more regulatory elements, e.g., a heterologous promoter or elements required for translation operably linked to the sequence encoding the peptide. In some cases the nucleic acid molecule will encode an amino acid sequence that includes the amino acid sequence of a peptide of the invention. For example, the nucleic acid molecule can encode a preprotein or a preproprotein that can be processed to produce a peptide of the invention.

A vector that includes a nucleotide sequence encoding a peptide of the invention or a peptide or polypeptide comprising a peptide of the invention may be either RNA or DNA, single- or double-stranded, prokaryotic, eukaryotic, or viral. Vectors can include transposons, viral vectors, episomes, (e.g., plasmids), chromosomes inserts, and artificial chromosomes (e.g. BACs or YACs). Suitable bacterial hosts for expression of the encode peptide or polypeptide include, but are not limited to, *E. coli*. Suitable eukaryotic hosts include yeast such as *S. cerevisiae*, other fungi, vertebrate cells, invertebrate cells (e.g., insect cells), plant cells, human cells, human tissue cells, and whole eukaryotic organisms. (e.g., a transgenic plant or a transgenic animal). Further, the vector nucleic acid can be used to generate a virus such as vaccinia or baculovirus.

As noted above the invention includes vectors and genetic constructs suitable for production of a peptide of the invention or a peptide or polypeptide comprising such a peptide. Generally, the genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences. A variety of transcriptional control sequences are well known to those in the art and may be functional in, but are not limited to, a bacterium, yeast, plant, or animal cell. The expression vector can also include a translation regulatory sequence (e.g., an untranslated 5' sequence, an untranslated 3' sequence, a poly A addition site, or an internal ribosome entry site), a splicing sequence or splicing regulatory sequence, and a transcription termination sequence. The vector can be capable of autonomous replication or it can integrate into host DNA.

The invention also includes isolated host cells harboring one of the forgoing nucleic acid molecules and methods for producing a peptide by culturing such a cell and recovering the peptide or a precursor of the peptide. Recovery of the peptide or precursor may refer to collecting the growth solution and need not involve additional steps of purification. Proteins of the present invention, however, can be purified using standard purification techniques, such as, but not limited to, affinity chromatography, thermaprecipitation, immunoaffinity chromatography, ammonium sulfate precipitation, ion exchange chromatography, filtration, electrophoresis and hydrophobic interaction chromatography.

In a twenty first aspect, the invention features a method of increasing the level of cyclic guanosine 3'-monophosphate (cGMP) in an organ, tissue (e.g, the intestinal mucosa), or cell (e.g., a cell bearing GC-A receptor) by administering a composition that includes a peptide of the invention.

The details of one or more embodiments of the invention are set forth in the accompanying description and claims. The publications and patents referenced herein are incorporated by reference.

DRAWINGS

FIG.1 depicts deletion variants of human guanylin in which one, two, three or four amino acids are deleted. The deleted amino acids are between Cys_a and Cys_d as well as amino terminal to Cys_a.

FIG. 2 depicts insertion variants of human guanylin in which one, two, three or four amino acids are inserted. The inserted amino acids are between Cys_a and Cys_d as well as amino terminal to Cys_a and carboxy terminal to Cys_d.

FIG. 3 depicts various polypeptides which include the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein: Xaa_1 is any amino acid or is missing; Xaa_2 is any amino acid or is missing; Xaa_3 is any amino acid or is missing; Xaa_5 is Glu; Xaa_6 is Tyr, Trp, Phe or Leu; Xaa_7 is Cys; Xaa_8 is any of the 20 naturally-occurring amino acids other than Cys or is missing; Xaa_9 is any of the 20 naturally-occurring amino acids; Xaa_{10} is Pro or Gly; Xaa_{11} is any of the 20 naturally-occurring amino acids; Xaa_{13} is Thr, Val or Gly; Xaa_{14} is Gly or Ala; Xaa_{15} is Cys; and Xaa_{16} is any of the 20 naturally-occurring amino acids or is missing.

DETAILED DESCRIPTION

The peptides of the invention bind to the guanylate cyclase (GC-C) receptor, a key regulator of fluid and electrolyte balance in the intestine and kidney. When stimulated, this receptor, which is located on the apical membrane of the intestinal epithelial surface, causes an increase in intestinal epithelial cyclic GMP (cGMP). This increase in cGMP is believed to cause a decrease in water and sodium absorption and an increase in chloride and potassium ion secretion, leading to changes in intestinal fluid and electrolyte transport and increased intestinal motility. The

intestinal GC-C receptor possesses an extracellular ligand binding region, a transmembrane region, an intracellular protein kinase-like region and a cyclase catalytic domain. Proposed functions for the GC-C receptor are the fluid and electrolyte homeostasis, the regulation of epithelial cell proliferation and the induction of apoptosis (Shaibhubhai 2002 *Curr Opin Drug Dis Devel* 5:261-268).

In addition to being expressed in gastrointestinal epithelial cells, GC-C is expressed in extra-intestinal tissues including kidney, lung, pancreas, pituitary, adrenal, developing liver, heart and male and female reproductive tissues (reviewed in Vaandrager 2002 *Mol Cell Biochem* 230:73-83). This suggests that the GC-C receptor agonists can be used in the treatment of disorders outside the GI tract, for example, congestive heart failure and benign prostatic hyperplasia.

Ghrelin, a peptide hormone secreted by the stomach, is a key regulator of appetite in humans. Ghrelin expression levels are regulated by fasting and by gastric emptying. (Kim et al., 2003, Neuroreprt 14:1317-20; Gualillo et al., 2003, FEBS Letts 552: 105-9). Thus, by increasing gastrointestinal motility, GC-C receptor agonists may also be used to regulate obesity.

In humans, the GC-C receptor is activated by guanylin (Gn) (U.S. Patent 5,96,097), uroguanylin (Ugn) (U.S. Patent 5,140,102) and lymphoguanylin (Forte et al. 1999 *Endocrinology* 140:1800-1806).

Many gastrointestinal disorders, including IBS, are associated with abdominal or visceral pain. Certain of the peptides of the invention include the analgesic or anti-nociceptive tags such as the carboxy-terminal sequence AspPhe immediately following a Trp, Tyr or Phe (i.e., a chymotrypsin cleavage site) or following Lys or Arg (a trypsin cleavage site). Chymotrypsin in the intestinal tract will cleave such peptides immediately carboxy terminal to the Trp, Phe or Tyr residue, releasing the dipeptide, AspPhe. This dipeptide has been shown to have analgesic activity is animal models (Abdikkahi et al. 2001 *Fundam Clin Pharmacol* 15:117-23; Nikfar et al 1997, 29:583-6; Edmundson et al 1998 *Clin Pharmacol Ther* 63:580-93). In this manner such peptides can treat both pain and inflammation. Other analgesic peptides can be present at the carboxy terminus of the peptide (following a cleavage site) including: endomorphin-1,

endomorphin-2, nocistatin, dalargin, lupron, and substance P. As described in greater detail below, various analgesic peptides and compounds can be covalently linked to or used in combination therapy with the therapeutic peptides described herein.

In the human body an inactive form of chymotrypsin, chymotrypsinogen is produced in the pancreas. When this inactive enzyme reaches the small intestine it is converted to active chymotrypsin by the excision of two di-peptides. Active chymotrypsin will cleave peptides at the peptide bond on the carboxy-terminal side of Trp, Tyr or Phe. The presence of active chymotrypsin in the intestinal tract will lead to cleavage of certain of the peptides of the invention having an appropriately positioned chymotrypsin cleavage site. Certain of the peptides of the invention include a Trp, Tyr or Phe immediately followed by a carboxy-terminal analgesic peptide. It is expected that chymotrypsin cleavage will release the analgesic peptide from peptide of the invention having an appropriately positioned chymotrypsin cleavage site as the peptide passes through the intestinal tract.

Trypsinogen, like chymotrypsin, is a serine protease that is produced in the pancreas and is present in the digestive tract. The active form, trypsin, will cleave peptides having a Lys or Arg. The presence of active trypsin in the intestinal tract will lead to cleavage of certain of the peptides of the invention having an appropriately positioned trypsin cleavage site. It is expected that chymotrypsin cleavage will release the analgesic peptide from peptide of the invention having an appropriately positioned trypsin cleavage site as the peptide passes through the intestinal tract.

In some cases, the peptides of the invention are produced as a prepro protein. The prepro protein can include any suitable prepro sequence, including, for example, mnafllsalc llgawaalag gvtvqdgnfs fslesvkklk dlqepqeprv gklrnfapip gepvvpilcs npnfpeelkp lckepnaqei lqrleeiaed (SEQ ID NO:) and mgcraasgll pgvavvllll lqstqsvyiq yqgfrvqles mkklsdleaq wapsprlqaq sllpavchhp alpqdlqpvc asqeassifk tlrtia (SEQ ID NO:) or a bacterial leader sequence such as: mkksilfiflsvlsfspfaqdakpvesskekitleskkcniakksnksgpesmn. Where the peptide is produced by a bacterial cell, e.g., *E. coli*, the forgoing leader sequence will be cleaved and the mature peptide will be efficiently secreted from the bacterial cell. U.S. Patent No. 5,395,490 describes vectors,

expression systems and methods for the efficient production of certain mature peptides having disulfide bonds in bacterial cells and methods for achieving efficient secretion of such mature peptides. The vectors, expression systems and methods described in U.S. Patent No. 5,395,490 can be used to produce the polypeptides of the present invention.

Variant Peptides

The invention includes variant peptides that can include one, two, three, four, or five or more (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) amino acid substitutions compared to any of the peptides described above. The substitution(s) can be conservative or non-conservative. The naturally-occurring amino acids can be substituted by D-isomers of any amino acid, non-natural amino acids, natural and non-natural amino acid analogs, and other groups. A conservative amino acid substitution results in the alteration of an amino acid for a similar acting amino acid, or amino acid of like charge, polarity, or hydrophobicity. At some positions, even conservative amino acid substitutions can reduce the activity of the peptide. A conservative substitution can substitute a naturally-occurring amino acid for a non-naturally-occurring amino acid. Among the naturally occurring amino acid substitutions generally considered conservative are:

For Amino Acid	Code	Replace with any of
Alanine	Ala	Gly, Cys, Ser
Arginine	Arg	Lys, His
Asparagine	Asn	Asp, Glu, Gln,
Aspartic Acid	Asp	Asn, Glu, Gln
Cysteine	Cys	Met, Thr, Ser
Glutamine	Gln	Asn, Glu, Asp
Glutamic Acid	Glu	Asp, Asn, Gln
Glycine	Gly	Ala
Histidine	His	Lys, Arg
Isoleucine	Ile	Val, Leu, Met
Leucine	Leu	Val, Ile, Met
Lysine	Lys	Arg, His
Methionine	Met	Ile, Leu, Val
Phenylalanine	Phe	Tyr, His, Trp
Proline	Pro	
Serine	Ser	Thr, Cys, Ala
Threonine	Thr	Ser, Met, Val
Tryptophan	Trp	Phe, Tyr
Tyrosine	Tyr	Phe, His
Valine	Val	Leu, Ile, Met

In some circumstances it can be desirable to treat patients with a variant peptide that binds to and activates intestinal GC-C receptor, but is less active or more active than the non-variant form of the peptide. Reduced activity can arise from reduced affinity for the receptor or a reduced ability to activate the receptor once bound or reduced stability of the peptide. Increased activity can arise from increased affinity for the receptor or an increased ability to activate the receptor once bound or increased stability of the peptide.

In some peptides one or both members of one or both pairs of Cys residues which normally form a disulfide bond can be replaced by homocysteine, 3-mercaptoproline (Kolodziej et al. 1996 *Int J Pept Protein Res* 48:274); β, β dimethylcysteine (Hunt et al. 1993 *Int J Pept Protein Res* 42:249) or diaminopropionic acid (Smith et al. 1978 *J Med Chem* 21:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

Production of peptides

Useful peptides can be produced either in bacteria including, without limitation, *E. coli*, or in other existing systems for peptide or protein production (e.g., *Bacillus subtilis,* baculovirus expression systems using Drosophila Sf9 cells, yeast or filamentous fungal expression systems, mammalian cell expression systems), or they can be chemically synthesized.

If the peptide or variant peptide is to be produced in bacteria, e.g., *E. coli*, the nucleic acid molecule encoding the peptide may also encode a leader sequence that permits the secretion of the mature peptide from the cell. Thus, the sequence encoding the peptide can include the pre sequence and the pro sequence of, for example, a naturally-occurring bacterial ST peptide. The secreted, mature peptide can be purified from the culture medium.

The sequence encoding a peptide of the invention is can be inserted into a vector capable of delivering and maintaining the nucleic acid molecule in a bacterial cell. The DNA molecule may be inserted into an autonomously replicating vector (suitable vectors include, for example, pGEM3Z and pcDNA3, and derivatives thereof). The vector nucleic acid may be a bacterial or bacteriophage DNA such as bacteriophage lambda or M13 and derivatives thereof. Construction of a vector containing a nucleic acid described herein can be followed by transformation of a host cell such as a bacterium. Suitable bacterial hosts include but are not limited to, *E. coli,* B *subtilis*, *Pseudomonas*, *Salmonella*. The genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences. A variety of transcriptional control sequences are well known to those in the art. The expression vector can also include a translation regulatory sequence (e.g., an untranslated 5' sequence, an untranslated 3' sequence, or an internal ribosome entry site). The vector can be capable of autonomous replication or it can integrate into host DNA to ensure stability during peptide production.

The protein coding sequence that includes a peptide of the invention can also be fused to a nucleic acid encoding a polypeptide affinity tag, e.g., glutathione S-transferase (GST), maltose E binding protein, protein A, FLAG tag, hexa-histidine, myc tag or the influenza HA tag, in order to facilitate purification. The affinity tag or reporter fusion joins the reading frame of the peptide of interest to the reading frame of the gene encoding the affinity tag such that a translational fusion is generated. Expression of the fusion gene results in translation of a single polypeptide that includes both the peptide of interest and the affinity tag. In some instances where affinity tags are utilized, DNA sequence encoding a protease recognition site will be fused between the reading frames for the affinity tag and the peptide of interest.

Genetic constructs and methods suitable for production of immature and mature forms of the peptides and variants of the invention in protein expression systems other than bacteria, and well known to those skilled in the art, can also be used to produce peptides in a biological system.

Mature peptides and variants thereof can be synthesized by the solid-phase method using an automated peptide synthesizer. For example, the peptide can be synthesized on Cyc(4-CH_2 Bxl)-OCH_2-4-(oxymethyl)-phenylacetamidomethyl resin using a double coupling program. Protecting groups must be used appropriately to create the correct disulfide bond pattern. For example, the following protecting groups can be used: t-butyloxycarbonyl (alpha-amino groups); acetamidomethyl (thiol groups of Cys residues B and E); 4-methylbenyl (thiol groups of Cys residues C and F); benzyl (y-carboxyl of glutamic acid and the hydroxyl group of threonine, if present); and bromobenzyl (phenolic group of tyrosine, if present). Coupling is effected with symmetrical anhydride of t-butoxylcarbonylamino acids or hydroxybenzotriazole ester (for asparagine or glutamine residues), and the peptide is deprotected and cleaved from the solid support in hydrogen fluoride, dimethyl sulfide, anisole, and p-thiocresol using 8/1/1/0.5 ratio (v/v/v/w) at 0°C for 60 min. After removal of hydrogen fluoride and dimethyl sulfide by reduced pressure and anisole and p-thiocresol by extraction with ethyl ether and ethyl acetate sequentially, crude peptides are extracted with a mixture of 0.5M sodium phosphate buffer, pH 8.0 and N,N-dimethylformamide using 1/1 ratio, v/v. The disulfide bond for Cys residues B and E is the formed using dimethyl sulfoxide (Tam et al. (1991) *J. Am. Chem. Soc.* 113:6657-62). The resulting peptide is the purified by reverse-phase chromatography. The disulfide bond

between Cys residues C and F is formed by first dissolving the peptide in 50% acetic acid in water. Saturated iodine solution in glacial acetic acid is added (1 ml iodine solution per 100 ml solution). After incubation at room temperature for 2 days in an enclosed glass container, the solution is diluted five-fold with deionized water and extracted with ethyl ether four times for removal of unreacted iodine. After removal of the residual amount of ethyl ether by rotary evaporation the solution of crude product is lyophilized and purified by successive reverse-phase chromatography.

Intestinal GC-C Receptor Binding and Activity Assays

The ability of peptides, variant peptides and other compounds to bind to and activate the intestinal GC-C receptor can be tested using the T84 human colon carcinoma cell line (American Type Culture Collection (Bethesda, Md.).

Briefly, cells are grown to confluency in 24-well culture plates with a 1:1 mixture of Ham's F12 medium and Dulbecco's modified Eagle's medium (DMEM), supplemented with 5% fetal calf serum and are used at between passages 54 and 60.

Monolayers of T84 cells in 24-well plates are washed twice with 1 ml/well DMEM, then incubated at 37°C for 10 min with 0.45 ml DMEM containing 1 mM isobutylmethylxanthine (IBMX), a cyclic nucleotide phosphodiesterase inhibitor. Test peptides (50µl) are then added and incubated for 30 minutes at 37°C. The media is aspirated and the reaction is terminated by the addition of ice cold 0.5 ml of 0.1N HCl. The samples are held on ice for 20 minutes and then evaporated to dryness using a heat gun or vacuum centrifugation. The dried samples are resuspended in 0.5ml of phosphate buffer provided in the Cayman Chemical Cyclic GMP EIA kit (Cayman Chemical, Ann Arbor, MI). Cyclic GMP is measured by EIA according to procedures outlined in the Cayman Chemical Cyclic GMP EIA kit.

For the binding assay, T84 cell monolayers in 24-well plates are washed twice with 1 ml of binding buffer (DMEM containing 0.05% bovine serum albumin and 25 mM HEPES, pH 7.2), then incubated for 30 min at 37°C in the presence of mature radioactively labeled *E. coli* ST

peptide and the test material at various concentrations. The cells are then washed 4 times with 1 ml of DMEM and solubilized with 0.5 ml/well 1N NaOH. The level of radioactivity in the solubilized material is then determined using standard methods.

Murine gastrointestinal transit (GIT) assay

In order to determine whether a test compound or a peptide, increases the rate of gastrointestinal transit, the test compound can be tested in the murine gastrointestinal transit (GIT) assay (Moon et al. *Infection and Immunity* 25:127, 1979). In this assay, charcoal, which can be readily visualized in the gastrointestinal tract is administered to mice after the administration of a test compound. The distance traveled by the charcoal is measured and expressed as a percentage of the total length of the colon.

Mice are fasted with free access to water for 12 to 16 hours before the treatment with peptide or control buffer. The peptides are orally administered at 1μg/kg – 1mg/kg of peptide in buffer (20mM Tris pH 7.5) seven minutes before being given an oral dose of 5% Activated Carbon (Aldrich 242276-250G). Control mice are administered buffer only before being given a dose of Activated Carbon. After 15 minutes, the mice are sacrificed and their intestines from the stomach to the cecum are dissected. The total length of the intestine as well as the distance traveled from the stomach to the charcoal front is measured for each animal and the results are expressed as the percent of the total length of the intestine traveled by the charcoal front. Results are reported as the average of 10 mice ± standard deviation. A comparison of the distance traveled by the charcoal between the mice treated with peptide versus the mice treated with vehicle alone is performed using a Student's t test and a statistically significant difference is considered for $P<0.05$. Positive controls for this assay may include commercially available wild-type ST peptide (Sigma-Aldrich, St Louis, MO) and Zelnorm®, a drug approved for IBS that is an agonist for the serotonin receptor 5HT4.

Suckling mouse model of intestinal secretion (SuMi assay)

The peptides of the invention can be tested for their ability to increase intestinal secretion using a suckling mouse model of intestinal secretion. In this model a test compound is administered to

suckling mice that are between seven and nine days old. After the mice are sacrificed, the gastrointestinal tract from the stomach to the cecum is dissected ("guts"). The remains ("carcass") as well as the guts are weighed and the ratio of guts to carcass weight is calculated. If the ratio is above 0.09, one can conclude that the test compound increases intestinal secretion. Controls for this assay may include wild-type ST peptide and Zelnorm®

Phenylbenzoquinone-induced writhing model

The PBQ-induced writhing model can be used to assess pain control activity of the peptides and GC-C receptor agonists of the invention. This model is described by Siegmund et al. (1957 Proc. Soc. Exp. Bio. Med. 95:729-731). Briefly, one hour after oral dosing with a test compound, e.g., a peptide, morphine or vehicle, 0.02% phenylbenzoquinone (PBQ) solution (12.5 mL/kg) is injected by intraperitoneal route into the mouse. The number of stretches and writhings are recorded from the 5^{th} to the 10^{th} minute after PBQ injection, and can also be counted between the 35^{th} and 40^{th} minute and between the 60^{th} and 65^{th} minute to provide a kinetic assessment. The results are expressed as the number of stretches and writhings (mean ± SEM) and the percentage of variation of the nociceptive threshold calculated from the mean value of the vehicle-treated group. The statistical significance of any differences between the treated groups and the control group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software.

Colonic hyperalgesia animal models

Hypersensitivity to colorectal distension is a common feature in patients with IBS and may be responsible for the major symptom of pain. Both inflammatory and non-inflammatory animal models of visceral hyperalgesia to distension have been developed to investigate the effect of compounds on visceral pain in IBS.

I. Trinitrobenzenesulphonic acid (TNBS)-induced rectal allodynia model

Male Wistar rats (220-250 g) are premedicated with 0.5 mg/kg of acepromazine injected intraperitoneally (IP) and anesthetized by intramuscular administration of 100 mg/kg of

ketamine. Pairs of nichrome wire electrodes (60 cm in length and 80 μm in diameter) are implanted in the striated muscle of the abdomen, 2 cm laterally from the white line. The free ends of electrodes are exteriorized on the back of the neck and protected by a plastic tube attached to the skin. Electromyographic (EMG) recordings are started 5 days after surgery. Electrical activity of abdominal striated muscle is recorded with an electroencephalograph machine (Mini VIII, Alvar, Paris, France) using a short time constant (0.03 sec.) to remove low-frequency signals (<3 Hz).

Ten days post surgical implantation, trinitrobenzenesulphonic acid (TNBS) is administered to induce rectal inflammation. TNBS (80 mg kg^{-1} in 0.3 ml 50 % ethanol) is administered intrarectally through a silicone rubber catheter introduced at 3 cm from the anus under light diethyl-ether anesthesia, as described (Morteau et al. 1994 Dig Dis Sci 39:1239). Following TNBS administration, rats are placed in plastic tunnels where they are severely limited in mobility for several days before colorectal distension (CRD). Experimental compound is administered one hour before CRD which is performed by insertion into the rectum, at 1 cm of the anus, a 4 cm long balloon made from a latex condom (Gue et al, 1997 *Neurogastroenterol. Motil.* 9:271). The balloon is fixed on a rigid catheter taken from an embolectomy probe (Fogarty). The catheter attached balloon is fixed at the base of the tail. The balloon, connected to a barostat is inflated progressively by step of 15 mmHg, from 0 to 60 mmHg, each step of inflation lasting 5 min. Evaluation of rectal sensitivity, as measured by EMG, is performed before (1-2 days) and 3 days following rectal instillation of TNBS.

The number of spike bursts that corresponds to abdominal contractions is determined per 5 min periods. Statistical analysis of the number of abdominal contractions and evaluation of the dose-effects relationships is performed by a one way analysis of variance (ANOVA) followed by a post-hoc (Student or Dunnett tests) and regression analysis for ED50 if appropriate.

II. Stress-induced hyperalgesia model

Male Wistar Rats (200-250 g) are surgically implanted with nichrome wire electrodes as in the TNBS model. Ten days post surgical implantation, partial restraint stress (PRS), is performed as

described by Williams et al. for two hours (Williams et al. 1988 Gastroenterology 64:611). Briefly, under light anaesthesia with ethyl-ether, the foreshoulders, upper forelimbs and thoracic trunk are wrapped in a confining harness of paper tape to restrict, but not prevent body movements. Control sham-stress animals are anaesthetized but not wrapped. Thirty minutes before the end of the PRS session, the animals are administered test-compound or vehicle. Thirty minutes to one hour after PRS completion, the CRD distension procedure is performed as described above for the TNBS model with barostat at pressures of 15, 30, 45 and 60mm Hg. Statistical analysis on the number of bursts is determined and analyzed as in the TNBS model above.

Administration of peptides and GC-C receptor agonists

For treatment of gastrointestinal disorders, the peptides and agonists of the invention are can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, pellet, gel, paste, syrup, bolus, electuary, slurry, capsule; powder; granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a liposomal formulation (see, e.g., EP 736299) or in some other form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The peptides and agonists can be co-administered with other agents used to treat gastrointestinal disorders including but not limited to acid suppressing agents such as Histamine-2 receptor agonists (H2As) and proton pump inhibitors (PPIs). The peptides and agonists can also be administered by rectal suppository. For the treatment of disorders outside the gastrointestinal tract such as congestive heart failure and benign prostatic hypertrophy, peptides and agonists can be administered parenterally or orally.

The peptides described herein can be used alone or in combination with other agents. For example, the peptides can be administered together with one or more analgesic peptides or compounds. The analgesic peptide and/or compound can be covalently attached to a peptide

described herein or it can be a separate agent that is administered together with or sequentially with a peptide described herein in a combination therapy.

Combination therapy can be achieved by administering two or more agents, e.g., a peptide described herein and an analgesic peptide or compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

The agents, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. Any such optional ingredient must be compatible with the compound of the invention to insure the stability of the formulation.

The composition may contain other additives as needed, including for exanple lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and peptides and proteins, for example albumen.

Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as:

BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch (*e.g.*, STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™, such as, AVICEL-PH-101™, -103™ and -105™, sold by FMC Corporation, Marcus Hook, PA, USA), or mixtures thereof,

FILLERS: talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, or mixtures thereof,

DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose,

croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums, or mixtures thereof,

LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof,

ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof,

ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, and

COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, or mixtures thereof.

The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO

01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ε-caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Such formulations can be used to implants that release a peptide or another agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (see, e.g., U.S. 6,620,422). Other sustained release formulations and polymers for use in such formulations are described in EP 0 467 389 A2, WO 93/24150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 9726015, WO 97/04744, and. US20020019446. In such sustained release formulations microparticles of peptide are combined with microparticles of polymer. One or more sustained release implants can be placed in the large intestine, the small intestine or both. U.S. 6,011,011 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (i.e. PEG 300 and PEG 400) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled release of the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326 151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1,U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224.

The agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, intraperitoneal injection, topical, sublingual, intraarticular (in the joints), intradermal, buccal, ophthalmic (including intraocular), intranasaly (including using a cannula), or by other routes. The agents can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, gel, pellet, paste, syrup, bolus, electuary, slurry, capsule, powder, granules, as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a micellar formulation (see, e.g. WO 97/11682) via a liposomal formulation (see, e.g., EP 736299,WO 99/59550 and WO 97/13500), via formulations described in WO 03/094886 or in some other

form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The agents can also be administered transdermally (i.e. via reservoir-type or matrix-type patches, microneedles, thermal poration, hypodermic needles, iontophoresis, electroporation, ultrasound or other forms of sonophoresis, jet injection, or a combination of any of the preceding methods (Prausnitz et al. 2004, Nature Reviews Drug Discovery 3:115-124)). The agents can be administered using high-velocity transdermal particle injection techniques using the hydrogel particle formulation described in U.S. 20020061336. Additional particle formulations are described in WO 00/45792, WO 00/53160, and WO 02/19989. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisosorbide can be found in WO 89/04179. WO 96/11705 provides formulations suitable for transdermal adminisitration. The agents can be administered in the form a suppository or by other vaginal or rectal means. The agents can be administered in a transmembrane formulation as described in WO 90/07923. The agents can be administered non-invasively via the dehydrated particles described in U.S. 6,485,706. The agent can be administered in an enteric-coated drug formulation as described in WO 02/49621. The agents can be administered intranassaly using the formulation described in U.S. 5,179,079. Formulations suitable for parenteral injection are described in WO 00/62759. The agents can be administered using the casein formulation described in U. S. 20030206939 and WO 00/06108. The agents can be administered using the particulate formulations described in U.S. 20020034536.

The agents, alone or in combination with other suitable components, can be administered by pulmonary route utilizing several techniques including but not limited to intratracheal instillation (delivery of solution into the lungs by syringe), intratracheal delivery of liposomes, insufflation (administration of powder formulation by syringe or any other similar device into the lungs) and aerosol inhalation. Aerosols (e.g., jet or ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs)) can also be used in intranasal applications. Aerosol formulations are stable dispersions or suspensions of solid material and liquid droplets in a

gaseous medium and can be placed into pressurized acceptable propellants, such as hydrofluroalkanes (HFAs, i.e. HFA-134a and HFA-227, or a mixture thereof), dichlorodifluoromethane (or other chlorofluocarbon propellants such as a mixture of Propellants 11, 12, and/or 114), propane, nitrogen, and the like. Pulmonary formulations may include permeation enhancers such as fatty acids, and saccharides, chelating agents, enzyme inhibitors (e.g., protease inhibitors), adjuvants (e.g., glycocholate, surfactin, span 85, and nafamostat), preservatives (e.g., benzalkonium chloride or chlorobutanol), and ethanol (normally up to 5% but possibly up to 20%, by weight). Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of the dispersion. Pulmonary formulations may also include surfactants which include but are not limited to bile salts and those described in U.S. 6,524,557 and references therein. The surfactants described in U.S. 6,524,557, e.g., a C8-C16 fatty acid salt, a bile salt, a phospholipid, or alkyl saccaride are advantageous in that some of them also reportedly enhance absorption of the peptide in the formulation. Also suitable in the invention are dry powder formulations comprising a therapeutically effective amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler. Absorption enhancers which can be added to dry powder formulations of the present invention include those described in U.S. 6,632,456. WO 02/080884 describes new methods for the surface modification of powders. Aerosol formulations may include U.S. 5,230,884, U.S. 5,292,499, WO 017/8694, WO 01/78696, U.S. 2003019437, U. S. 20030165436, and WO 96/40089 (which includes vegetable oil). Sustained release formulations suitable for inhalation are described in U.S. 20010036481A1, 20030232019A1, and U.S. 20040018243A1 as well as in WO 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885. Pulmonary formulations containing microparticles are described in WO 03/015750, U.S. 20030008013, and WO 00/00176. Pulmonary formulations containing stable glassy state powder are described in U.S. 20020141945 and U.S. 6,309,671. Other aerosol formulations are described in EP 1338272A1 WO 90/09781, U. S. 5,348,730, U.S. 6,436,367, WO 91/04011, and U.S. 6,294,153 and U.S. 6,290,987 describes a liposomal based formulation that can be administered via aerosol or other means. Powder formulations for inhalation are described in U.S. 20030053960 and WO 01/60341. The agents can be administered intranasally as described in U.S. 20010038824.

Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

The agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). The formulations may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means.

The agent can be fused to immunoglobulins or albumin, or incorporated into a lipsome to improve half-life. The agent can also be conjugated to polyethylene glycol (PEG) chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris and Chess, Nature Reviews Drug Discovery 2: 214-221 and the references therein. The peptides of the invention may also be conjugated to, for example, alkyl groups (e.g., C1-C20 straight or branched alkyl groups); fatty acid radicals; and combinations of PEG, alkyl groups and fatty acid radicals (see U.S. Patent 6,309,633; Soltero et al., 2001 Innovations in Pharmaceutical Technology 106-110). The agent

can be administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences International). The agents can be delivered transmucosally (i.e. across a mucosal surface such as the vagina, eye or nose) using formulations such as that described in U.S. 5,204,108. The agents can be formulated in microcapsules as described in WO 88/01165. The agent can be administered intra-orally using the formulations described in U.S. 20020055496, WO 00/47203, and U.S. 6,495,120. The agent can be delivered using nanoemulsion formulations described in WO 01/91728A2.

Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences (18th Edition, Mack Publishing Company, 1995).

The agents described herein and combination therapy agents can be packaged as a kit that includes single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation.

Methods to increase chemical and/or physical stability of the agents the described herein are found in U.S. 6,541,606, U.S. 6,068,850, U.S. 6,124,261, U.S. 5,904,935, and WO 00/15224, U.S. 20030069182 (via the additon of nicotinamide), U.S. 20030175230A1, U.S. 20030175230A1, U.S. 20030175239A1, U.S. 20020045582, U.S. 20010031726, WO 02/26248, WO 03/014304, WO 98/00152A1, WO 98/00157A1, WO 90/12029, WO 00/04880, and WO 91/04743, WO 97/04796 and the references cited therein.

Methods to increase bioavailability of the agents described herein are found in U.S. 6,008,187, U.S. 5,424,289, U.S. 20030198619, WO 90/01329, WO 01/49268, WO 00/32172, and WO 02/064166. Glycyrrhizinate can also be used as an absorption enhancer (see, e.g., EP397447). WO 03/004062 discusses Ulex europaeus I (UEAI) and UEAI mimetics which may be used to target the agents of the invention to the GI tract.

Analgesic Agents

The peptides described herein can be used in combination therapy with an analgesic agent, e.g., an analgesic compound or an analgesic peptide. The analgesic agent can optionally be covalently attached to a peptide described herein. Among the useful analgesic agents are: Ca channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HT1 receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NK1 receptor antagonists, CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabanoid receptor agonists, and sialorphin. Analgesics agents in the various classes are described in the literature.

Among the useful analgesic peptides are sialorphin-related peptides, including those comprising the amino acid sequence QHNPR (SEQ ID NO:), including: VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:). Sialorphin-related peptides bind to neprilysin and inhibit neprilysin-mediated breakdown of substance P and Met-enkephalin. Thus, compounds or peptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the peptides of the invention in a co-therapy or linked to the peptides of the invention, e.g., by a covalent bond. Sialophin and related peptides are described in U.S. Patent 6,589,750; U.S. 20030078200 A1; and WO 02/051435 A2.

Opioid receptor antagonists and agonists can be administered with the peptides of the invention in co-therapy or linked to the peptide of the invention, e.g., by a covalent bond. For example, opioid receptor antagonists such as naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine are thought to be useful in the treatment of IBS. It can be useful to formulate opioid antagonists of this type is a delayed and sustained release formulation such that initial release of the antagonist is in the mid to distal small intestine and/or ascending colon. Such antagonists are described in WO 01/32180 A2. Enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-homoserine) is an agonist of the mu and delta opioid receptors and is thought to be useful for increasing intestinal motility (Eur. J. Pharm. 219:445, 1992), and this peptide can be used in conjunction with the peptides of the invention. Also useful is trimebutine which is thought to bind to mu/delta/kappa opioid receptors and activate release of motilin and modulate the release of gastrin, vasoactive intestinal peptide, gastrin and glucagons. Kappa opioid receptor agonists such as fedotozine, ketocyclazocine, and compounds described in WO 03/097051 A2 can be used with or linked to the peptides of the invention. In addition, mu opioid receptor agonists such as morphine, diphenyloxylate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1) and loperamide can be used.

Tyr-Arg (kyotorphin) is a dipeptide that acts by stimulating the release of met-enkephalins to elicit an analgesic effect (J. Biol. Chem. 262:8165, 1987). Kyotorphin can be used with or linked to the peptides of the invention.

CCK receptor agonists such as caerulein from amphibians and other species are useful analgesic agents that can be used with or linked to the peptides of the invention.

Conotoxin peptides represent a large class of analgesic peptides that act at voltage gated Ca channels, NMDA receptors or nicotinic receptors. These peptides can be used with or linked to the peptides of the invention.

Peptide analogs of thymulin (FR 2830451) can have analgesic activity and can be used with or linked to the peptides of the invention.

CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) can have analgesic activity and can be used with or linked to the peptides of the invention.

Other useful analgesic agents include 5-HT4 agonists such as tegaserod/zelnorm and lirexapride. Such agonists are described in: EP1321142 A1, WO 03/053432A1, EP 505322 A1, EP 505322 B1, U.S. 5,510,353, EP 507672 A1, EP 507672 B1, and U.S. 5,273,983.

Calcium channel blockers such as ziconotide and related compounds described in, for example, EP 625162B1, U.S. 5,364,842, U.S. 5,587,454, U.S. 5,824,645, U.S. 5,859,186, U.S. 5,994,305, U.S. 6,087,091, U.S. 6,136,786, WO 93/13128 A1, EP 1336409 A1, EP 835126 A1, EP 835126 B1, U.S. 5,795,864, U.S. 5,891,849, U.S. 6,054,429, WO 97/01351 A1, can be used with or linked to the peptides of the invention.

Various antagonists of the NK-1, NK-2, and NK-3 receptors (for a review see Giardina et al. 2003 *Drugs* 6:758) can be can be used with or linked to the peptides of the invention.

NK1 receptor antagonists such as: aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-14033 and related compounds described in, for example, EP 873753 A1, U.S. 20010006972 A1, U.S. 20030109417 A1, WO 01/52844 A1, can be used with or linked to the peptides of the invention.

NK-2 receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi-Synthelabo), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc) can be used with or linked to the peptides of the invention.

NK3 receptor antagonists such as osanetant (Sanofi-Synthelabo), talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 A1, WO 97/21680 A1, U.S. 6,277,862, WO 98/11090, WO 95/28418, WO 97/19927, and Boden et al. (*J Med Chem.* 39:1664-75, 1996) can be used with or linked to the peptides of the invention.

Norepinephrine-serotonin reuptake inhibitors such as milnacipran and related compounds described in WO 03/077897 A1 can be used with or linked to the peptides of the invention.

Vanilloid receptor antagonists such as arvanil and related compounds described in WO 01/64212 A1 can be used with or linked to the peptides of the invention.

Where the analgesic is a peptide and is covalently linked to a peptide described herein the resulting peptide may also include at least one trypsin or chymotrypsin cleavage site. When present within the peptide, the analgesic peptide may be preceded by (if it is at the carboxy terminus) or followed by (if it is at the amino terminus) a chymotrypsin or trypsin cleavage site that allows release of the analgesic peptide.

In addition to sialorphin-related peptides, analgesic peptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, zicnotide, and substance P.

Methods of Treatment

The peptides of the invention can be used alone or in combination therapy for the treatment or prevention of cancer, pre-cancerous growths, or metastatic growths. For example, they can be used for the prevention or treatment of: colorectal/local metastasized colorectal cancer, gastrointestinal tract cancer, lung cancer, cancer or pre-cancerous growths or metastatic growths of epithelial cells, polyps, breast, colorectal, lung, ovarian, pancreatic, prostatic, renal, stomach, bladder, liver, esophageal and testicular carcinoma, carcinoma (e.g., basal cell, basosquamous, Brown-Pearce, ductal carcinoma, Ehrlich tumor, Krebs, Merkel cell, small or non-small cell lung, oat cell, papillary, bronchiolar, squamous cell, transitional cell, Walker), leukemia (e.g., B-

cell, T-cell, HTLV, acute or chronic lymphocytic, mast cell, myeloid), histiocytonia, histiocytosis, Hodgkin's disease, non-Hodgkin's lymphoma, plasmacytoma, reticuloendotheliosis, adenoma, adeno-carcinoma, adenofibroma, adenolymphoma, ameloblastoma, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, sclerosing angioma, angiomatosis, apudoma, branchionia, malignant carcinoid syndrome, carcinoid heart disease, carcinosarcoma, cementoma, cholangioma, cholesteatoma, chondrosarcoma, chondroblastoma, chondrosarcoma, chordoma, choristoma, craniopharyngioma, chrondrorna, cylindroma, cystadenocarcinoma, cystadenoma, cystosarconia phyllodes, dysgenninoma, ependymoma, Ewing sarcoma, fibroma, fibrosarcoma, giant cell tumor, ganglioneuroma, glioblastoma, glomangioma, granulosa cell tumor, gynandroblastoma, hamartoma, hemangioendothelioma, hemangioma, hemangio-pericytoma, hemangiosarcoma, hepatoma, islet cell tumor, Kaposi sarcoma, leiomyoma, leiomyosarcoma, leukosarcoma, Leydig cell tumor, lipoma, liposarcoma, lymphaugioma, lymphangiomyoma, lymphangiosarcoma, medulloblastoma, meningioma, mesenchymoma, mesonephroma, mesothelioma, myoblastoma, myoma, myosarcoma, myxoma, myxosarcoma, neurilemmoma, neuroma, neuroblastoma, neuroepithelioma, neurofibroma, neurofibromatosis, odontoma, osteoma,, osteosarcoma, papilloma, paraganglioma, paraganglionia. nonchroinaffin, pinealoma, rhabdomyoma, rhabdomyosarcoma, Sertoli cell tumor, teratoma, theca cell tumor, and other diseases in which cells have become dysplastic, immortalized, or transformed.

The peptides of the invention can be used alone or in combination therapy for the treatment or prevention of: Familial Adenomatous Polyposis (FAP) (autosomal dominant syndrome) that precedes colon cancer, hereditary nonpolyposis colorectal cancer (HNPCC), and inherited autosomal dominant syndrome.

For treatment or prevention of cancer, pre-cancerous growths and metastatic growths, the peptides can be used alone or in combination therapy with radiation or chemotherapeutic agents, an inhibitor of a cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor (a number of selective cyclooxygenase-2 inhibitors are described in WO02062369, hereby incorporated by reference).

The peptides can be for treatment or prevention of inflammation. Thus, they can be used alone or in combination with inhibitors of cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor for treatment of: organ inflammation, IBD (e.g, Crohn's disease, ulcerative colitis), asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis, ischemic bowel diseases, intestinal inflammations/allergies, coeliac disease, proctitis, eosnophilic gastroenteritis, mastocytosis, and other inflammatory disorders.

The peptides can also be used alone or in combination therapy to treat or prevent insulin-related disorders, for example: II diabetes mellitus, hyperglycemia, obesity, disorders associated with disturbances in glucose or electrolyte transport and insulin secretion in cells, or endocrine disorders. They can be also used in insulin resistance treatment and post-surgical and non-post surgery decrease in insulin responsiveness.

The peptides can be used alone or in combination therapy to prevent or treat respiratory disorders, including, inhalation, ventilation and mucus secretion disorders, pulmonary hypertension, chronic obstruction of vessels and airways, and irreversible obstructions of vessels and bronchi.

The peptides can be used in combination therapy with a phosphodiesterase inhibitor (examples of such inhibitors can be found in U.S. 6,333,354, hereby incorporated by reference).

The peptides can also be used alone or in combination therapy to prevent or treat: retinopathy, nephropathy, diabetic angiopathy, and edema formation

The peptides can also be used alone or in combination therapy to prevent or treat neurological disorders, for example, headache, anxiety, movement disorders, aggression, psychosis, seizures, panic attacks, hysteria, sleep disorders, depression, schizoaffective disorders, sleep apnea, attention deficit syndromes, memory loss, and narcolepsy. They may also be used as a sedative.

The peptides and detectabley labeled peptides can be used as markers to identify, detect, stage, or diagnosis diseases and conditions of the small intestine, including:
Crohn's disease, colitis, inflammatory bowel disease, tumors, benign tumors, such as benign stromal tumors, adenoma, angioma, adenomatous (pedunculated and sessile) polyps, malignant, carcinoid tumors, endocrine cell tumors, lymphoma, adenocarcinoma, foregut, midgut, and hindgut carcinoma, gastroinstestinal stromal tumor (GIST), such as leiomyorna, cellular leiomyoma, leiomyoblastoma, and leiomyosarcoma, gastrointestinal autonomic nerve tumor, malabsorption syndromes, celiac diseases, diverticulosis, Meckel's diverticulum, colonic diverticula, megacolon, Hirschsprung's disease, irritable bowel syndrome, mesenteric ischemia, ischemic colitis, colorectal cancer, colonic polyposis, polyp syndrome, intestinal adenocarcinoma, Liddle syndrome, Brody myopathy, infantile convulsions, and choreoathetosis

The peptides can be conjugated to another molecule (e.g, a diagnostic or therapeutic molecule) to target cells bearing the GCC receptor, e.g., cystic fibrosis lesions and specific cells lining the intestinal tract. Thus, they can be used to target radioactive moieties or therapeutic moieties to the intestine to aid in imaging and diagnosing or treating colorectal/metastasized or local colorectal cancer and to deliver normal copies of the p53 tumor suppressor gene to the intestinal tract.

The peptides can be used alone or in combination therapy to treat erectile dysfunction.

The peptides can be used alone or in combination therapy to treat inner ear disorders, e.g., to treat Meniere's disease, including symptoms of the disease such as vertigo, hearing loss, tinnitus, sensation of fullness in the ear, and to maintain fluid homeostasis in the inner ear.

The peptides can be used alone or in combination therapy to treat disorders associated with fluid and sodium retention, e.g., diseases of the electrolyte-water/electrolyte transport system within the kidney, gut and urogenital system, congestive heart failure, hypertension, hypotension, liver cirrhosis, and nephrotic syndrome. In addition they can be used to facilitate diuresis or control intestinal fluid.

The peptides can be used alone or in combination therapy to treat disorders associated with chloride or bicarbonate secretion, e.g., Cystic Fibrosis.

The peptides can be used alone or in combination therapy to treat disorders associated with bile secretion. In addition, they can be used to facilitate or control chloride and bile fluid secretion in the gall bladder.

The peptides can be used alone or in combination therapy to treat disorders associated with liver cell regeneration.

What is claimed is:

1. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is a) any amino acid, b) Phe, Tyr, Asn, Trp, c) an amino acid other than Phe, Trp, or Tyr, d) non-aromatic amino acid or e) is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr;

Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing; and

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

2. The purified polypeptide of claim 1 wherein Xaa_1 is preceded by Lys or Tyr.

3. A composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier.

4. A composition comprising a polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is Phe, Tyr, Asn, Trp, an amino acid other than Phe, Trp, or Tyr, is a non-aromatic amino acid or is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr; Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing;

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser

and a pharmaceutically acceptable carrier.

5. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Asn, any amino acid or is missing;

Xaa_2 is Asp, Glu, any amino acid or is missing;

Xaa_3 is Asp or Glu;

Xaa_5 is any amino acid or Glu;

Xaa_6 is any amino acid or Leu;

Xaa_7 is Cys;

Xaa_8 is any amino acid or Val;

Xaa_9 is Asn, Gln, Tyr;

Xaa_{10} is is any amino acid or Val;

Xaa_{11} is any amino acid or Ala;

Xaa_{13} is is any amino acid or Thr;

Xaa_{14} is is any amino acid or Gly;

Xaa_{15} is Cys;

Xaa_{16} is any amino acid, Leu or missing

6. A purified polypeptide comprising the amino acid sequence: Asn_1 Xaa_2 Xaa_3 Xaa_4 Glu_5 Leu_6 Xaa_7 Val_8 Asn_9 Xaa_{10} Xaa_{11} Xaa_{12} Thr_{13} Xaa_{14} Xaa_{15} Leu_{16} (SEQ ID NO:__)

Xaa_2 is Asp or Glu;

Xaa_3 is Asp or Glu;

Xaa_4 is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_7 is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_{10} is Val or Pro;

Xaa_{11} is Ala or Aib (alpha-aminoisobutyric acid);

Xaa_{12} is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu; and

7. The polypeptide of claim 1 wherein Xaa_{15} is other than Cys or is missing and Xaa_7 is Ser or an amino acid other than Cys.

8. The polypeptide of claim 1 wherein at least 5 of Xaa_1, Xaa_2,Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, Xaa_{10}, Xaa_{11}, Xaa_{13}, Xaa_{14}, and Xaa_{16} are any amino acid other than Cys.

9. The polypeptide of claim 1 wherein: Xaa_9 is any amino acid other than Gln.

10. The polypeptide of claim 1 wherein Xaa_2 and Xaa_3 are Glu.

11. A polypeptide comprising the amino acid sequence of claim 1 wherein the polypeptide is not cleaved after Xaa_9 by chymotrypsin.

12. The polypeptide of claim 1 wherein the polypeptide does not comprise the amino acid sequence PGTCEICAYAACTGC.

13. A purified polypeptide comprising the amino acid sequence KPGTCEICAYAACTGC.

14. A purified polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe;

b) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe and Trp;

c) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe, Trp, Ile, Leu and Val;

d) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe, Trp, Ile, Leu, Val and His;

e) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any non-aromatic amino acid or

f) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is missing.

15. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

PGTCEICASAACTGC (SEQ ID NO:)
PGTCEICATAACTGC (SEQ ID NO:)
PGTCEICANAACTGC (SEQ ID NO:)
PGTCEICAQAACTGC (SEQ ID NO:)
PGTCEICARAACTGC (SEQ ID NO:)
PGTCEICAEAACTGC (SEQ ID NO:)
PGTCEICADAACTGC (SEQ ID NO:)
PGTCEICAGAACTGC (SEQ ID NO:)
PGTCEICAAAACTGC (SEQ ID NO:)
PGTCEICAMAACTGC (SEQ ID NO:)
PGTCEICAIAACTGC (SEQ ID NO:)
PGTCEICALAACTGC (SEQ ID NO:)
PGTCEICAVAACTGC (SEQ ID NO:) and

PGTCEICAHAACTGC (SEQ ID NO:)

16. A purified polypeptide comprising an amino acid sequence shown in Figure 1.

17. A purified polypeptide comprising an amino acid sequence shown in Figure 2 wherein Xaa is any amino acid.

18. The purified polypeptide of claim 17 wherein Xaa is any amino acid other than Cys.

19. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

PGTCEGICAYAACTGC (SEQ ID NO:)
PGTCEIGCAYAACTGC (SEQ ID NO:)
PGTCEICGAYAACTGC (SEQ ID NO:)
PGTCEICAGYAACTGC (SEQ ID NO:)
PGTCEICAYGAACTGC (SEQ ID NO:)
PGTCEICAYAGACTGC (SEQ ID NO:)
PGTCEICAYAAGCTGC (SEQ ID NO:)
PGTCEICAYAACGTGC (SEQ ID NO:)
PGTCEICAYAACTGGC (SEQ ID NO:)
PGTCAEICAYAACTGC (SEQ ID NO:)
PGTCEAICAYAACTGC (SEQ ID NO:)
PGTCEIACAYAACTGC (SEQ ID NO:)
PGTCEICAAYAACTGC (SEQ ID NO:)
PGTCEICAYAAACTGC (SEQ ID NO:)
PGTCEICAYAACATGC (SEQ ID NO:)
PGTCEICAYAACTAGC (SEQ ID NO:)
PGTCEICAYAACTGAC (SEQ ID NO:)
PGTCAEICAAYAACTGC (SEQ ID NO:)
PGTCEAICAAYAACTGC (SEQ ID NO:) and

PGTCEIACAAYAACTGC (SEQ ID NO:).

20. The polypeptide of claim 1 further comprising an amino acid sequence selected from: Asp Phe, the amino acid sequence of endomorphin-1, the amino acid sequence of endomorphin-2, the amino acid sequence of nocistatin, the amino acid sequence of dalargin, the amino acid sequence of lupron, and the amino acid sequence of substance P.

21. A method for treating a gastrointestinal disorder comprising administering a composition comprising the purified polypeptide of claim 1.

22. The method of claim 21 wherein the gastrointestinal disorder is: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, or colonic pseudo-obstruction.

23. A method for treating obesity comprising administering a composition comprising the purified polypeptide of claim 1.

24. A method for treating congestive heart failure comprising administering a composition comprising the purified polypeptide of claim 1.

25. A method for treating benign prostatic hyperplasia comprising administering a composition comprising the purified polypeptide of claim 1.

26. A method for treating constipation comprising administering a composition comprising the purified polypeptide of claim 1

27. The method of claim 21 wherein the polypeptide does not comprise the amino acid sequence PGTCEICAYAACTGC or the amino acid sequence

NDDCELCVNVACTGCL.

28. A method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient the polypeptide of claim 1.

29. A method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient the polypeptide of claim 1.

30. A method for increasing the activity of an intestinal guanylate cyclase (GC-C) receptor in a patient, the method comprising administering to the patient the polypeptide of claim 1.

31. A method for treating a patient suffering a gastrointestinal disorder, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

32. A method for treating a patient suffering from constipation, the method comprising administering a composition comprising a complete or partial agonist of the GC-C receptor.

33. A method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

34. A method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

35. A method for treating congestive heart failure, the method comprising administering a complete or partial agonist of the GC-C receptor.

36. A method for treating benign prostatic hyperplasia, the method comprising administering a complete or partial agonist of the GC-C receptor.

37. A method for treating obesity, the method comprising administering a complete or partial agonist of the GC-C receptor.

38. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is any amino acid or is missing;

Xaa_2 is any amino acid or is missing;

Xaa_3 is any amino acid or is missing;

Xaa_5 is Glu;

Xaa_6 is Tyr, Trp, Phe or Leu;

Xaa_7 is Cys;

Xaa_8 is any of the 20 naturally-occurring amino acids other than Cys or is missing;

Xaa_9 is any of the 20 naturally-occurring amino acids;

Xaa_{10} is Pro or Gly;

Xaa_{11} is any of the 20 naturally-occurring amino acids;

Xaa_{13} is Thr, Val or Gly;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys; and

Xaa_{16} is any of the 20 naturally-occurring amino acids or is missing.

39. The purified polypeptide of claim 38 wherein Xaa_9 is Asn.

40. The purified polypeptide of claim 38 wherein Xaa_{11} is Ala or Thr.

41. The purified polypeptide of claim 38 wherein Xaa_8 is missing.

42. The purified polypeptide of claim 38 wherein Xaa_{16} is Tyr.

43. The purified polypeptide of claim 38 wherein Xaa_4 is immediately preceded by an amino acid sequence seleted from: Ser His Thr; Pro Ser Thr; Thr; Pro Asp Pro; Ile Ala Glu Asp Ser His

Thr; Ile Ala Gln Asp Pro Ser Thr; Ala Asn Thr; Asn Thr; Asp Pro Asn Thr; Lys Asn Thr; Pro Asn Thr; Ile Ala Gln Asp Pro Asn Thr; Lys Pro Asn Thr; Asp Pro Gly Thr; Glu Asp Pro Gly Thr; Pro Gly Thr; Pro Ala Thr; Val Ala Ala Arg Ala Asp Leu; Gly Asp Asp; Asn Asp Glu; Gln Glu Asp; Asn Asp Asp; Arg Thr Ile Ala Asn Asp Asp; Thr Ile Ala Asn Asp Asp; Asp Asp; Arg Thr Met Asp Asn Asp Glu; Arg Thr Ile Ala Gly Asp Asp; Arg Thr Ile Ala Asn Asp; Asp; Glu Asp; Arg Ser Ile Ser Gln Glu Asp; Thr Asp Glu; Arg Thr Ile Ala Thr Asp Glu; Glu; Ile Ile Thr Pro Pro Asp Pro; Gln Glu Leu; Lys Asp Asp; Gln Glu Glu; Arg Tyr Ile Asn Gln Glu Glu; Ala Ser Ser Tyr Ala Ser; and Thr Ser Ser Tyr Ala Ser.

44. A pharmaceutical composition comprising the polypeptide of claim 38 and a pharmaceutically acceptable carrier.

45. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is: a) Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing; b) preceded by Lys or Tyr; c) any amino acid; d) missing; e) any amino acid other than Cys; or f) Lys or Arg;

Xaa_2 is: a) His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing; b) His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing; c) Asp, Glu, any amino acid or is missing; d) Asp or Glu; e) any amino acid other than Cys; e) Glu; f) missing; g) Trp, Tyr or Phe; or h) Lys or Arg;

Xaa_3 is: a) Thr, Asp, Ser, Glu, Pro, Val or Leu; Asp or Glu; b) any amino acid other than Cys; c) Glu; d) Thr; e) Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing; f) Trp, Tyr or Phe; or g) Lys or Arg;

Xaa_4 is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu;

Xaa_5 is: a) any amino acid; b) Glu, Asp, Gln, Gly or Pro; c) Glu; d) Glu or Asp; e) Asp, Ile or Glu; f) any amino acid; or g) any amino acid other than Cys;

Xaa_6 is: a) Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; b) Leu, Ile, Val, Lys, Arg, Trp, Tyr or Phe; Leu, Ile, Lys, Arg, Trp, Tyr or Phe; c) Leu, Ile, Val, Trp, Tyr or Phe; d) Trp, Tyr, Phe or Leu; e) Leu, Ile or Val; f) Ile, Trp or Leu; g) Trp, Tyr or Phe; h) Ile or Leu; i) Tyr; j) any

amino acid; k) any amino acid except Leu; l) any natural or non-natural aromatic amino acid; or m) any amino acid other than Cys;

Xaa_7 is: a) Cys, Ser, or Tyr; Cys; b) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; c) Ser; or d) an amino acid other than Cys;

Xaa_8 is: a) Ala, Val, or Ile; b) Ala, Val, Thr, Ile, Met or is missing; c) any amino acid; d) Val; e) any amino acid other than Cys; or f) missing;

Xaa_9 is: a) any amino acid; b) any amino acid other than Phe and Tyr; c) any amino acid other than Phe, Tyr, and Trp; d) any amino acid other than Phe, Tyr, Trp, Ile, Leu and Val; e) any amino acid other than Phe, Tyr, Trp, Ile, Leu, Val, and His; f) any amino acid other than Gln; g) any amino acid other than Lys, Arg, Phe, Tyr, and Trp; h) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu and Val; i) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu, Val, and His; j) any non-aromatic amino acid; k) missing; l) Phe, Tyr, Asn, or Trp; m) Asn, Tyr, Asp or Ala; n) Asn, Gln, or Tyr; o) Phe or Tyr; p) Asn; or q) any amino acid other than Cys;

Xaa_{10} is: a) Ala, Pro or Gly; b) Pro or Gly; c) Pro; d) Ala, Val, Met, Thr or Ile; e) any amino acid; f) Val; g) Val or Pro; h) Ala or Val; i) any amino acid other than Cys; j) Pro; or k) Gly;

Xaa_{11} is: a) any amino acid; b) Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, or Asp; c) Ala or Gly; d) Ala; e) Ala or Val; f) any amino acid; g) Ala or Aib (alpha-aminoisobutyric acid); h) any amino acid other than Cys; i) Ala or Thr; or j) Thr.

Xaa_{12} is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu; or b) any amino acid other than Cys;

Xaa_{13} is: a) Thr, Ala, Asn, Lys, Arg, or Trp; b) Thr, Ala, Lys, Arg, or Trp; c) any amino acid; d) any non-aromatic amino acid; e) Thr, Ala, or Trp; f) Trp, Tyr or Phe; g) Thr or Ala; h) any amino acid; i) Thr; j) any amino acid other than Cys; k) Thr, Val, or Gly; l) Thr or Val, m) Thr or Gly, n) Val or Thr; o) Val; p) Thr; or q) Gly;

Xaa_{14} is: a) Gly, Pro or Ala; b) Gly; c) any amino acid; d) Gly, Ala or Ser; e) Gly or Ala; f) any amino acid other than Cys; or g) Ala;

Xaa_{15} is: a) Cys, Tyr or is missing; b) Cys; c) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, Glu; or d) any amino acid other than Cys or is missing; and

Xaa_{16} is: a) Trp, Tyr, Phe, Asn, Ile, Val, His or Leu; b) Trp, Tyr, Phe, Asn or Leu; c) Trp, Tyr, Phe or Leu; d) Trp, Tyr, or Phe; e) Leu, Ile or Val; f) His, Leu or Ser; g) Tyr or Leu; Lys or Arg; h) His; i) any amino acid, j) Leu, or missing; k) Trp, Tyr, Phe, Lys, Arg or is missing; l) missing; m) any amino acid other than Cys; or n) Tyr.

46. A composition comprising the polypeptide of claim 45 and a pharmaceutically acceptable carrier.

47. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is any amino acid or is missing;

Xaa_2 is any amino acid or is missing;

Xaa_3 is any amino acid or is missing;

Xaa_4 is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_5 is Glu;

Xaa_6 is Tyr, Trp, Phe or Leu;

Xaa_7 is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_8 is any amino acid other than Cys or is missing;

Xaa_9 is any amino acid;

Xaa_{10} is Pro or Gly;

Xaa_{11} is any amino acid;

Xaa_{12} is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_{13} is Thr, Val or Gly;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; and

Xaa_{16} is any amino acid or is missing.

FIG. 1 (sheet 1 of 13)

Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys

Human Guanylin (SEQ ID NO:)

--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 2 of 13)

--- Gly --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 3 of 13)

--- Gly Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)

FIG. 1 (sheet 4 of 13)

--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 5 of 13)

Pro --- --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 6 of 13)

Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG 1 (sheet 7 of 13)

Pro --- Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 8 of 13)

Pro Gly --- Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG.1 (sheet 9 of 13)

Pro Gly --- Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 10 of 13)

Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 11 of 13)

Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 12 of 13)

Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 13 of 13)

Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)

FIG. 2 (sheet 1 of 91)

Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 2 of 91)

Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 3 of 91)

Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)

FIG. 2 (sheet 4 of 91)

```
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO: )
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO: )
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Xaa' Thr Xaa' Xaa' Cys Gly Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
```

FIG. 2 (sheet 5 of 91)

Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' (SEQ ID NO:)

FIG. 2 (sheet 6 of 91)

Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 7 of 91)

```
Pro Gly Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa'   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys             (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys        (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys        (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys        (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'   (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys        (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
```

FIG. 2 (sheet 8 of 91)

Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 9 of 91)

Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 10 of 91)

Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 11 of 91)

Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 12 of 91)

```
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
```

FIG. 2 (sheet 13 of 91)

Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 14 of 91)

Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 15 of 91)

Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 16 of 91)

Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 17 of 91)

Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)

FIG. 2 (sheet 18 of 91)

```
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa'       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys            (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Xaa' Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa'       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys            (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys       (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Xaa' Cys  (SEQ ID NO: )
```

FIG. 2 (sheet 19 of 91)

Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)

FIG. 2 (sheet 20 of 91)

Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' Xaa' (SEQ ID NO:)

Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 21 of 91)

Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)

FIG. 2 (sheet 22 of 91)

```
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Ala Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Ala Ala Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
```

FIG. 2 (sheet 23 of 91)

Pro Gly Thr Xaa' Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)

FIG. 2 (sheet 24 of 91)

```
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys      (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys      (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys      (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Cys Thr Gly Cys     (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys     (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Cys Thr Gly Cys    (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys     (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Cys Thr Gly Cys    (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
```

FIG. 2 (sheet 25 of 91)

Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 26 of 91)

Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 27 of 91)

```
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa'   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys        (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa'   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys        (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa'   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys        (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa'   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'        (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa'   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys             (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys        (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys        (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'   (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys        (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys   (SEQ ID NO: )
```

FIG. 2 (sheet 28 of 91)

```
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys     (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Xaa' Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO: )
```

FIG. 2 (sheet 29 of 91)

Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 30 of 91)

Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:).
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 31 of 91)

```
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys                (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa'     (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys               (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa'          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys               (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Ala Cys Thr Gly Cys          (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Xaa' Ala Ala Cys Thr Gly Cys     (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys Xaa'    (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Xaa' Xaa' Cys Thr Gly Cys    (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Xaa' Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO: )
```

FIG. 2 (sheet 32 of 91)

```
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa'  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys            (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys       (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys       (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys       (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys       (SEQ ID NO: )
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys  (SEQ ID NO: )
```

FIG. 2 (sheet 33 of 91)

Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 34 of 91)

Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 35 of 91)

Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 36 of 91)

Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 37 of 91)

Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 38 of 91)

Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 39 of 91)

Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 40 of 91)

Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 41 of 91)

Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 42 of 91)

```
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa'  (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys      (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'      (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys          (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Xaa' Ala Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Xaa' Ala Tyr Ala Ala Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
```

FIG. 2 (sheet 43 of 91)

Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)

FIG. 2 (sheet 44 of 91)

Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 45 of 91)

Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)

FIG. 2 (sheet 46 of 91)

Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 2 (sheet 47 of 91)

Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)

FIG. 2 (sheet 48 of 91)

Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Xaa' Thr Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Xaa' Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Xaa' Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Xaa' Cys	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' Xaa'	(SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys	(SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys	(SEQ ID NO:)

FIG. 2 (sheet 49 of 91)

Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)

FIG. 2 (sheet 50 of 91)

Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)