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(54) **Title:** CARBOHYDRATE-BASED DRUG DELIVERY POLYMERS AND CONJUGATES THEREOF

(57) **Abstract:** Provided herein are water-soluble carbohydrate polymers which are monoderivatized at their reducing terminus, such that the carbohydrate polymers can be selectively conjugated at a single location. Also provided are methods of preparation and conjugation of the monoderivatized carbohydrate polymers.

## Carbohydrate-Based Drug Delivery Polymers and Conjugates Thereof

### Background of the Invention

In recent years, human therapeutics have expanded past traditional small molecule drugs and into the realm of biopharmaceuticals. The discovery of novel proteins and peptides has led to the development of numerous protein and polypeptide biopharmaceuticals. Unfortunately, proteins and polypeptides, when utilized as therapeutics, often exhibit properties that make them extremely difficult to formulate or administer, such as short circulating half lives, immunogenicity, proteolytic degradation, and low solubility.

There is significant interest in using naturally occurring biopolymers as drug delivery and/or conjugating agents, as they are generally safe and because they are biodegradable. Both of these factors are very significant in selecting a polymer for drug delivery, as polymer safety and clearance rank among the most important issues in selecting a delivery polymer. Solubility in serum and in aqueous media is often very important for drug manufacture and drug delivery. By far the most successful water soluble polymer in use for drug delivery is polyethylene glycol (PEG) (see e.g. Harris, J.M. (1985), "Laboratory Synthesis of Polyethylene Glycol Derivatives", *JMS-Rev. Macromol. Chem. Phys.* **C25**: 325-373; Harris, J.M. and Chess, R.B. (2003), "Effect of PEGylation on Pharmaceuticals", *Nature Reviews Drug Discovery* **2**: 214-221; Roberts, M.J., Bentley, M.D., and Harris, J.M. (2002), "Chemistry for peptide and protein PEGylation", *Adv. Drug Del. Rev.* **54**: 459-476; Pasut, G., Guiotto, A., and Veronese, F.M. (2004), "Protein, peptide and non-peptide drug PEGylation for therapeutic application", *Expert Opin. Ther. Patents* **14**:1-36; Filpula, D. and Zhao, H. (2008), "Releasable PEGylation of proteins with customized linkers", *Adv. Drug Del. Rev.* **60**: 29-49; Zhao, X and Harris, J.M. (1997), "Novel degradable poly(ethylene glycol) esters for drug delivery", In: Harris J.M. and Zalipsky S. (eds): *Poly(ethylene glycol) chemistry and biological applications*, American Chemical Society, Washington, DC, 458-472.)

Attempts have also been made to use carbohydrates for conjugation with and delivery of drugs. The most prominent examples are hydroxyethyl starch (HES) and polysialic acid (PSA). HES, a derivative of naturally occurring starch (amylopectin & amylose), has been described as the polymer of choice as a polyfunctional carrier for oligopeptide-polymer conjugates. It is non-toxic and nonimmunogenic and is degraded by  $\alpha$ -amylase in the body.

HES is recommended as a polyfunctional carrier, since it has a large number of functional groups (primarily hydroxyl groups), making monofunctionalization virtually

impossible. Thus, activation of HES for attachment of drug moieties provides a polyfunctional polymer with a diversity of sites; i.e. some polymer molecules have more functional sites than other polymer molecules, and the overall result is a polydisperse distribution of reactive sites. This is often acceptable for smaller drug molecules, where several drug molecules per polymer strand may be acceptable, as long as biodistribution is not affected by the polydisperse character of the conjugate. However, it is undesirable for larger molecules such as proteins, where a single protein molecule per polymer moiety is highly desired. In fact, in many cases, e.g. with very large proteins like Factor VIII, multiple polymer molecules may be desired to protect the protein. While PEGs are very suitable for such applications, because they can readily be engineered to provide only one active group per polymer molecule, it is very difficult to selectively activate only one functional group of a carbohydrate polymer.

Polysialic acid (PSA) and hyaluronic acid (HA) are acid carbohydrates that have also been promoted for drug delivery. However, the very high biodegradability of HA is problematic, as it is generally inadequately stable *in vivo* to be a good delivery agent. HA also suffers from its strong targeting properties which consistently steer it toward certain biotargets. PSA has enjoyed more recent attention. Like HES, however, PSA is only reasonably useful when polyfunctionality is acceptable. Thus, to this point, polysaccharides have not presented a significant commercial threat to the use of PEGs (PEGylation) for modification of the pharmacological properties of drugs; i.e. relatively little product development activity has occurred, and there are no launched products.

Another issue that must be dealt with in employing carbohydrates for drug delivery is control of molecular weight. It is possible, for example, to manufacture PEG with fairly precise control of molecular weight and polydispersity. Thus, it is common to see commercially available PEGs having moderate molecular weights (i.e. 20 – 40 kD) with a polydispersity of 1.10 or less. Since carbohydrates are biologically derived, often with variable molecular weights, obtaining a specific molecular weight for drug delivery is difficult. With respect to molecular weight distribution, commercially available dextrans often have polydispersity values of 2.0 or greater, or around 1.25-1.35 for purified materials.

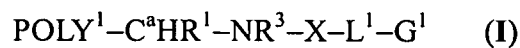
Thus, there remains a need to overcome these barriers of polyfunctionality and polydispersity in order to take advantage of the desirable properties of these naturally occurring polymers.

## **Summary**

In one aspect, the invention provides a method of selectively monoderivatizing a water-soluble carbohydrate polymer at its reductive terminus, wherein said reductive terminus comprises a hemiacetal or ketal group or the corresponding aldehyde or ketone functionality, the method comprising:

contacting said carbohydrate polymer with a heterobifunctional oxyamine or hydrazine reagent, effective to produce a monoderivatized carbohydrate derivative having a functional group, not selected from oxyamine and hydrazine, linked via an oxyimine or hydrazone moiety at said terminus.

The method may further comprise reducing the double bond of said oxyimine or hydrazone moiety. Thus, the monoderivatized carbohydrate polymer may have a structure



where

$\text{POLY}^1$  is said carbohydrate polymer and  $\text{C}^a$  is the anomeric carbon atom of said terminal hemiacetal or ketal group or corresponding aldehyde or ketone functionality;

$\text{R}^1$  is H or hydroxymethyl;

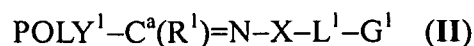
$\text{X}$  is oxygen or  $\text{NR}^2$ , where  $\text{R}^2$  is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl, and is preferably H or methyl, and more preferably H;

$\text{R}^3$  is H or methyl, and is typically H;

$\text{L}^1$  is a linker group, and

$\text{G}^1$  is an optionally protected functional group, not selected from oxyamine and hydrazine.

When the reduction step is not carried out, the 4. The method of claim 1, wherein the monoderivatized carbohydrate derivative monoderivatized carbohydrate polymer may have a structure



where:

$\text{POLY}^1$  is said carbohydrate polymer and  $\text{C}^a$  is the anomeric carbon atom of said terminal hemiacetal or ketal group or corresponding aldehyde or ketone functionality;

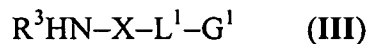
$\text{R}^1$  is H or hydroxymethyl;

$\text{X}$  is oxygen or  $\text{NR}^2$ , where  $\text{R}^2$  is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl, and is preferably H or methyl, and more preferably H;

$\text{L}^1$  is said linker group, and

G<sup>1</sup> is said optionally protected functional group, not selected from oxyamine and hydrazine.

The heterobifunctional oxyamine or hydrazine reagent used for such monoderivatization typically has the structure



where:

X is oxygen or NR<sup>2</sup>, where R<sup>2</sup> is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl, and is preferably H or methyl, and more preferably H;

R<sup>3</sup> is H or methyl, and is generally H;

L<sup>1</sup> is a linker group, and

G<sup>1</sup> is an optionally protected functional group, not selected from oxyamine and hydrazine, which is unreactive under the conditions of said contacting.

In selected embodiments, X is oxygen (an oxyamine reagent) or NR<sup>2</sup>, e.g. NH<sub>2</sub> (a hydrazine reagent). X may also be sulfur.

R<sup>1</sup> may be hydroxymethyl, when POLY<sup>1</sup> is a ketose, or hydrogen, when POLY<sup>1</sup> is an aldose, such as a dextran or a chitosan. POLY<sup>1</sup> generally has a molecular weight in the range of 200 Da to 2,000,000 Da. Molecular weights such as 5KDa, 10KDa, 20KDa, 40KDa, and 70KDa, for example, are typical.

L<sup>1</sup> is a linker as defined further below. Preferably, L<sup>1</sup> consists of moieties selected from alkylene, -CH<sub>2</sub>CH<sub>2</sub>O-, amide, carbamate, and combinations thereof; more preferably, L<sup>1</sup> consists of alkylene moieties, -CH<sub>2</sub>CH<sub>2</sub>O- moieties, and combinations thereof. Generally, L<sup>1</sup> is 1 to about 20 atoms in length, and may be 3-12, or 3-8 atoms in length.

The functional group G<sup>1</sup> may be selected from amine, hydroxy, thiol, carboxylic acid, carboxylic acid ester, imide ester, orthoester, carbonate, isocyanate, isothiocyanate, aldehyde, acetal, ketone, ketal, thione, alkenyl, acrylate, methacrylate, acrylamide, sulfone, maleimide, disulfide, iodo, epoxy, sulfonate, thiosulfonate, silane, alkoxy silane, halosilane, and phosphoramidate; and in selected embodiments is selected from amine, hydroxy, thiol, carboxylic acid, carboxylic acid ester, imide ester, orthoester, carbonate, isocyanate, aldehyde, acetal, ketone, ketal, and maleimide.

The preparation method may also include a step of purifying the carbohydrate polymer. In particular, when the heterobifunctional reagent comprises an oxyamine or hydrazine at one terminus and a carboxylic acid or amine group at the other terminus, effective to produce a monoderivatized water-soluble carbohydrate polymer having a single terminal carboxylic

acid or amine group, the method may further comprise purifying the amine- or carboxylic acid-terminated carbohydrate polymer by ion exchange chromatography.

In a related aspect, the invention provides a monofunctional water-soluble carbohydrate-based reagent having the structure



where:

POLY<sup>1</sup> is a water-soluble carbohydrate polymer having a terminal anomeric carbon atom, where C<sup>a</sup> is said terminal anomeric carbon atom;

--- represents a double bond when x=0 and a single bond when x=1;

R<sup>1</sup> is H or hydroxymethyl;

X is oxygen or NR<sup>2</sup>, where R<sup>2</sup> is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl, and is preferably H or methyl, and more preferably H;

R<sup>3</sup> is H or methyl, and is typically H;

L<sup>1</sup> is a linker group, and

G<sup>1</sup> is a functional group, in reactive or protected form, not selected from oxyamine and hydrazine.

In selected embodiments, the carbohydrate reagent has a double bond represented by ---, such that x=0. In other embodiments, e.g. where the double bond is subjected to reduction, the carbohydrate reagent has a single bond represented by ---, such that x=1.

Selected embodiments of the components represented by X, R<sup>1</sup>, POLY<sup>1</sup>, L<sup>1</sup>, and G<sup>1</sup> are as described above.

Exemplary carbohydrate reagents include the reagent having a structure designated herein as dextran-O-(carboxymethyl)oxyimine (**2**); the reagent having a structure designated herein as oxyimine-linked dextran-butanoic acid (**7**); the reagent having a structure designated herein as oxyimine-linked dextran(40K)-butyraldehyde (**16**); the reagent having a structure designated herein as oxyimine-linked chitosan tetra(ethylene glycol) maleimidopropionamide (**22**); and the reagent having a structure designated herein as oxyimine-linked chitosan butanoic acid (**23**). The carbohydrate component in any of these structures may have any of a variety of molecular weights. The reagents also include protected versions of the terminal functional groups.

In another aspect, the invention provides a method of preparing a water-soluble carbohydrate reagent having a single terminal carboxylic acid group, the method comprising

oxidizing a water-soluble carbohydrate polymer, such as a dextran, having a terminal acetal or aldehyde group under mild conditions, effective to produce an oxidized carbohydrate having a single terminal carboxylic acid group and having substantially the same molecular weight as the carbohydrate prior to oxidation. Such conditions include reaction with iodine (I<sub>2</sub>) and a hydroxide base as described herein.

The method may further comprise the step of purifying the carbohydrate reagent by ion exchange chromatography, such that the purified carbohydrate reagent is substantially free of unreacted carbohydrate and overoxidized byproducts. Such purification may also be effective to significantly reduce the polydispersity of the monocarboxylic acid reagent relative to that of the carbohydrate prior to oxidation.

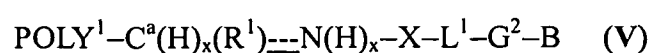
In accordance with this method, the invention provides a water-soluble carbohydrate reagent, preferably a dextran, having a single terminal functional group which is a carboxylic acid. The carboxyl carbon of the carboxylic acid is the terminal anomeric carbon of the starting carbohydrate. Such carbohydrate monocarboxylic acids may have a molecular weight of 200 Da to 2,000,000 Da.

Also provided are the corresponding carboxylic acid derivatives, which can be readily prepared from the carbohydrate monocarboxylic acid. The carboxylic acid derivative may be selected from ester, activated ester, thioester, anhydride, amide, acid halide, nitrile, carbamate, carbonate, isocyanate, and isothiocyanate.

Also provided is a conjugate comprising the water-soluble carbohydrate monocarboxylic acid or derivative and a covalently attached biologically active molecule, which may be prepared by reaction of the carbohydrate monocarboxylic acid or derivative with a biologically active molecule having a suitable reactive group. In one embodiment, the biologically active molecule is a protein or peptide, where the reactive group is typically an amine.

In one embodiment, the biologically active molecule is insulin. Accordingly, the invention provides a method of reducing blood glucose levels in a diabetic subject, including a human subject, by administering a dextran monocarboxylic acid-insulin conjugate.

The invention also provides conjugates of a water-soluble carbohydrate reagent and a biologically active molecule, having the structure



where

POLY<sup>1</sup> is a water-soluble carbohydrate polymer having a terminal anomeric carbon atom, where C<sup>a</sup> is said terminal anomeric carbon atom;

--- represents a double bond when x=0 and a single bond when x=1;

R<sup>1</sup> is H or hydroxymethyl;

X is oxygen or NR<sup>2</sup>, where R<sup>2</sup> is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl;

L<sup>1</sup> is a linker group, and

G<sup>2</sup> is a covalent bond comprising a residue or converted form of functional group G<sup>1</sup>, not selected from oxyamine and hydrazine, following reaction with a corresponding functional group on biomolecule B.

Selected embodiments of the components represented by the variables in structure (V) include those disclosed for structure (IV) above.

In selected embodiments, POLY<sup>1</sup> is a chitosan. In further embodiments of this type, the biologically active molecule is an oligonucleotide, such as an RNA.

In other embodiments, POLY<sup>1</sup> is a dextran. Exemplary dextran conjugates include conjugates of proteins or peptides, such as conjugates of lysozyme, protegrin-1, C-peptide, and insulin as described herein. In one embodiment, the biologically active molecule is insulin, which may be a partially acetylated insulin. Such conjugates include having the structure disclosed herein as **20**. The dextran component in this conjugate may vary in molecular weight. In a preferred embodiment, the carbohydrate is dextran(40KDa).

In a related aspect, the invention provides a method of reducing blood glucose levels in a diabetic subject, including a human subject, by administering a dextran-insulin conjugate having the structure designated as **20** herein.

These and other aspects of the invention will become apparent upon review of the following description and accompanying figures.

### **Brief Description of the Drawings**

Figure 1 shows gels produced by SDS-PAGE analysis (4-12% gel) of purified dextran-butyraldehyde-40K-protegrin-1, as described in Example 16. Dextran perturbs the gel migration of the dextran-peptide conjugate; the conjugate's band location is not indicative of its size. The marker (M) molecular weight unit is kDa.

Figure 2 shows a MALDI-TOF spectrum for mono-Dextran<sub>40K</sub>-C-peptide(S20C) conjugate, prepared as described in Example 17. The peaks at 43.2 kDa and 22.0 kDa agree with molecular weights of the singly and doubly charged forms of the conjugated peptide.

Figure 3 shows gels produced by SDS-PAGE (4-12% Bis-Tris-Nu-PAGE, Invitrogen) analysis of purified dextran-butyraldehyde-40K-insulin, produced by conjugation of Dextran<sub>40K</sub> tetraethylene glycol butyraldehyde (16) with acetylated insulin, as described in Example 18B. Lane 1: Dextran-butyraldehyde-40K-insulin purified and concentrated by anion-exchange chromatography; Lane 2: Purified and concentrated dextran-butyraldehyde-40K-insulin after precipitation from water/DMSO with acetonitrile.

Figure 4 shows the results of the *in vitro* competition binding assay described in Example 19, where the *in vitro* affinity for the insulin receptor of the insulin-dextran conjugate (20b) was evaluated.

Figure 5 shows the effect of insulin and dextran-conjugated insulin on blood glucose levels in db/db diabetic mice, as described in Example 20.

## **Detailed Description of the Invention**

### **I. Definitions**

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular polymers, synthetic techniques, active agents, and the like, as such may vary.

As used in this specification and in the claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a polymer" includes a single polymer as well as two or more of the same or different polymers, reference to "a conjugate" refers to a single conjugate as well as two or more of the same or different conjugates, reference to "an excipient" includes a single excipient as well as two or more of the same or different excipients, and the like.

"Optional" and "optionally" mean that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions described below.

As used herein, the terms "therapeutic peptide" and "therapeutic peptides" mean one or more peptides having demonstrated or potential use in treating, preventing, or ameliorating one or more diseases, disorders, or conditions in a subject in need thereof, as well as related peptides. These terms may be used to refer to therapeutic peptides prior to conjugation to a water-soluble polymer as well as following the conjugation. Therapeutic peptides include, but are not limited to, those disclosed herein, including in Table 1. Therapeutic peptides

include peptides found to have use in treating, preventing, or ameliorating one or more diseases, disorders, or conditions after the time of filing of this application. Related peptides include fragments of therapeutic peptides, therapeutic peptide variants, and therapeutic peptide derivatives that retain some or all of the therapeutic activities of the therapeutic peptide. As will be known to one of skill in the art, as a general principle, modifications may be made to peptides that do not alter, or only partially abrogate, the properties and activities of those peptides. In some instances, modifications may be made that result in an increase in therapeutic activities. Thus, in the spirit of the invention, the terms "therapeutic peptide" or "therapeutic peptides" are meant to encompass modifications to the therapeutic peptides defined and/or disclosed herein that do not alter, only partially abrogate, or increase the therapeutic activities of the parent peptide.

The term "therapeutic activity" as used herein refers to a demonstrated or potential biological activity whose effect is consistent with a desirable therapeutic outcome in humans, or to desired effects in non-human mammals or in other species or organisms. A given therapeutic peptide may have one or more therapeutic activities, however the term "therapeutic activities" as used herein may refer to a single therapeutic activity or multiple therapeutic activities. "Therapeutic activity" includes the ability to induce a response *in vitro*, and may be measured *in vivo* or *in vitro*. For example, a desirable effect may be assayed in cell culture, or by clinical evaluation, EC<sub>50</sub> assays, IC<sub>50</sub> assays, or dose response curves. *In vitro* or cell culture assays, for example, are commonly available and known to one of skill in the art for many therapeutic peptides as defined and/or disclosed herein. Therapeutic activity includes treatment, which may be prophylactic or ameliorative, or prevention of a disease, disorder, or condition. Treatment of a disease, disorder or condition can include improvement of a disease, disorder or condition by any amount, including elimination of a disease, disorder or condition.

As used herein, the terms "peptide," "polypeptide," and "protein," refer to polymers comprised of amino acid monomers linked by amide bonds. Peptides may include the standard 20  $\alpha$ -amino acids that are used in protein synthesis by cells (*i.e.* natural amino acids), as well as non-natural amino acids (non-natural amino acids may be found in nature, but not used in protein synthesis by cells, *e.g.*, ornithine, citrulline, and sarcosine, or may be chemically synthesized), amino acid analogs, and peptidomimetics. Spatola, (1983) in *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*, Weinstein, ed., Marcel Dekker, New York, p. 267. The amino acids may be D- or L-optical isomers. Peptides may be formed by a condensation or coupling reaction between the  $\alpha$ -carbon carboxyl group of

one amino acid and the amino group of another amino acid. The terminal amino acid at one end of the chain (amino terminal) therefore has a free amino group, while the terminal amino acid at the other end of the chain (carboxy terminal) has a free carboxyl group. Alternatively, the peptides may be non-linear, branched peptides or cyclic peptides. Moreover, the peptides may optionally be modified or protected with a variety of functional groups or protecting groups, including on the amino and/or carboxy terminus.

Amino acid residues in peptides are abbreviated as follows: Phenylalanine is Phe or F; Leucine is Leu or L; Isoleucine is Ile or I; Methionine is Met or M; Valine is Val or V; Serine is Ser or S; Proline is Pro or P; Threonine is Thr or T; Alanine is Ala or A; Tyrosine is Tyr or Y; Histidine is His or H; Glutamine is Gln or Q; Asparagine is Asn or N; Lysine is Lys or K; Aspartic Acid is Asp or D; Glutamic Acid is Glu or E; Cysteine is Cys or C; Tryptophan is Trp or W; Arginine is Arg or R; and Glycine is Gly or G.

The terms "therapeutic peptide fragment" or "fragments of therapeutic peptides" refer to a polypeptide that comprises a truncation at the amino-terminus and/or a truncation at the carboxyl-terminus of a therapeutic peptide as defined herein. The terms "therapeutic peptide fragment" or "fragments of therapeutic peptides" also encompasses amino-terminal and/or carboxyl-terminal truncations of therapeutic peptide variants and therapeutic peptide derivatives. Therapeutic peptide fragments may be produced by synthetic techniques known in the art or may arise from *in vivo* protease activity on longer peptide sequences. It will be understood that therapeutic peptide fragments retain some or all of the therapeutic activities of the therapeutic peptides.

As used herein, the terms "therapeutic peptide variants" or "variants of therapeutic peptides" refer to therapeutic peptides having one or more amino acid substitutions, including conservative substitutions and non-conservative substitutions, amino acid deletions (either internal deletions and/or C- and/or N- terminal truncations), amino acid additions (either internal additions and/or C- and/or N- terminal additions, *e.g.*, fusion peptides), or any combination thereof. Variants may be naturally occurring (*e.g.* homologs or orthologs), or non-natural in origin. The term "therapeutic peptide variants" may also be used to refer to therapeutic peptides incorporating one or more non-natural amino acids, amino acid analogs, and peptidomimetics. It will be understood that, in accordance with the invention, therapeutic peptide fragments retain some or all of the therapeutic activities of the therapeutic peptides.

The terms "therapeutic peptide derivatives" or "derivatives of therapeutic peptides" as used herein refer to therapeutic peptides, therapeutic peptide fragments, and therapeutic

peptide variants that have been chemically altered other than through covalent attachment of a water-soluble polymer. It will be understood that, in accordance with the invention, therapeutic peptide derivatives retain some or all of the therapeutic activities of the therapeutic peptides.

"PEG", "polyethylene glycol" and "poly(ethylene glycol)" as used herein, are meant to encompass any water-soluble poly(ethylene oxide). Typically, PEGs comprise the following structure  $-\text{O}(\text{CH}_2\text{CH}_2\text{O})_m-$  where (m) is 2 to 4000. As used herein, PEG also includes  $-(\text{CH}_2\text{CH}_2\text{O})_m-$  and  $-\text{CH}_2\text{CH}_2-\text{O}(\text{CH}_2\text{CH}_2\text{O})_m-\text{CH}_2\text{CH}_2-$ , depending upon whether or not the terminal oxygens have been displaced. When the PEG further comprises a spacer moiety (to be described in greater detail below), the atoms comprising the spacer moiety, when covalently attached to a water-soluble polymer segment, do not result in the formation of an oxygen-oxygen bond (i.e., an  $-\text{O}-\text{O}-$  or peroxide linkage). The term "PEG" includes structures having various terminal or "end capping" groups and so forth. The term "PEG" also means a polymer that contains a majority, that is to say, greater than 50%, of  $-\text{CH}_2\text{CH}_2\text{O}-$  monomeric subunits. With respect to specific forms, the PEG can take any number of a variety of molecular weights, as well as structures or geometries such as "branched," "linear," "forked," "multifunctional," "dendrimeric", and the like.

The terms "end-capped" or "terminally capped" are interchangeably used herein to refer to a terminal or endpoint of a polymer having an end-capping moiety. Typically, although not necessarily, the end-capping moiety comprises a hydroxy or  $\text{C}_{1-20}$  alkoxy group. Thus, examples of end-capping moieties include alkoxy (e.g., methoxy, ethoxy and benzyloxy), as well as aryl, heteroaryl, cyclo, heterocyclo, and the like. In addition, saturated, unsaturated, substituted and unsubstituted forms of each of the foregoing are envisioned. Moreover, the end-capping group can also be a silane. The end-capping group can also advantageously comprise a detectable label. When the polymer has an end-capping group comprising a detectable label, the amount or location of the polymer and/or the moiety (e.g., active agent) of interest to which the polymer is coupled to can be determined by using a suitable detector. Such labels include, without limitation, fluorescers, chemiluminescers, moieties used in enzyme labeling, colorimetric (e.g., dyes), metal ions, radioactive moieties, and the like. Suitable detectors include photometers, films, spectrometers, and the like.

"Non-naturally occurring", with respect to a polymer or water-soluble polymer, indicates that the polymer in its entirety is not found in nature. A non-naturally occurring polymer or water-soluble polymer may, however, contain one or more subunits or portions of a subunit that are naturally occurring, so long as the overall polymer structure is not found in nature.

A "water-soluble polymer" is any polymer that is soluble in water at room temperature. Typically, a water-soluble polymer will transmit at least about 75%, more preferably at least about 95% of light, transmitted by the same solution after filtering. On a weight basis, a water-soluble polymer will preferably be at least about 35% (by weight) soluble in water, more preferably at least about 50% (by weight) soluble in water, still more preferably about 70% (by weight) soluble in water, and still more preferably about 85% (by weight) soluble in water. It is still more preferred, however, that the water-soluble polymer is about 95% (by weight) soluble in water and most preferred that the water-soluble polymer is completely soluble in water.

"Molecular weight", in the context of a water-soluble polymer of the invention, such as PEG, can be expressed as either a number average molecular weight or a weight average molecular weight. Unless otherwise indicated, all references to molecular weight herein refer to the weight average molecular weight. Both molecular weight determinations, number average and weight average, can be made using gel permeation chromatography or other liquid chromatography techniques. Other methods for measuring molecular weight can also be used, such as end-group analysis or colligative properties (e.g., freezing-point depression, boiling-point elevation, or osmotic pressure) to determine number average molecular weight, or light scattering techniques, ultracentrifugation or viscometry to determine weight average molecular weight. The polymers of the invention are typically polydisperse (i.e., number average molecular weight and weight average molecular weight of the polymers are not equal), possessing low polydispersity values of preferably less than about 1.2, more preferably less than about 1.15, still more preferably less than about 1.10, yet still more preferably less than about 1.05, and most preferably less than about 1.03.

An "organic radical" as used includes, for example, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl and substituted aryl.

"Alkyl" refers to a hydrocarbon chain, typically ranging from about 1 to 20 atoms in length. Such hydrocarbon chains are preferably but not necessarily saturated and may be branched or straight chain, although typically straight chain is preferred. Exemplary alkyl groups include ethyl, propyl, butyl, pentyl, isooctyl, decyl, 3-ethyl-3-pentyl, 2-methyl-1-hexyl, and the like. As used herein, "alkyl" includes cycloalkyl, when three or more carbon atoms are referenced, and lower alkyl. "Alkylene" refers to an unsaturated bivalent radical (e.g.  $-(CH_2)_n-$ ).

"Lower alkyl" refers to an alkyl group containing from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, and may be straight chain or branched, as exemplified by methyl, ethyl,

*n*-butyl, *iso*-butyl, and *tert*-butyl. When a group is defined as "alkyl" herein, lower alkyl is generally a preferred embodiment.

"Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon chain, including bridged, fused, or spiro cyclic compounds, preferably made up of 3 to about 12 carbon atoms, more preferably 3 to about 8.

"Alkoxy" refers to an -O-R group, wherein R is alkyl or substituted alkyl, preferably C<sub>1</sub>-C<sub>20</sub> alkyl (e.g., methoxy, ethoxy, propoxy, benzyl, perfluorobutyl, etc.), preferably C<sub>1</sub>-C<sub>7</sub> alkyl, more preferably C<sub>1</sub>-C<sub>7</sub> alkyl. "Alkoxyalkyl" refers to an -R-O-R group, where R is as defined above, and is preferably unsubstituted C<sub>1</sub>-C<sub>7</sub> alkyl.

"Aminoalkyl" refers to an -NHR or -NR<sub>2</sub> group, where R is alkyl as defined above, and is preferably unsubstituted C<sub>1</sub>-C<sub>7</sub> alkyl, and the two R groups in -NR<sub>2</sub> may be the same or different. The two R groups may also form a five- to seven-membered ring.

"Iminoalkyl(ene)" refers to an -R'-N=R" group, where R" represents CH<sub>2</sub>, CHR, or CR<sub>2</sub>, where each R is alkyl as defined above, and the two R groups in -CR<sub>2</sub> may be the same or different. R' is alkyl as defined above, i.e. an sp<sup>2</sup> hybridized carbon, or alkylene, i.e. an sp<sup>2</sup> hybridized carbon forming one member of a double bond. An R in CHR or CR<sub>2</sub> taken together with the R' may form a five- to seven-membered ring.

As used herein, "alkenyl" refers to a branched or unbranched hydrocarbon group of 2 to 15 atoms in length, containing at least one double bond, such as ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, isobutenyl, octenyl, decenyl, tetradecenyl, and the like.

The term "alkynyl" as used herein refers to a branched or unbranched hydrocarbon group of 2 to 15 atoms in length, containing at least one triple bond, ethynyl, *n*-butynyl, isopentynyl, octynyl, decynyl, and so forth.

"Aliphatic" refers to a group containing carbon and hydrogen which is not aromatic. As used herein, it can refer to linear, branched, or cyclic groups. It can refer to saturated or unsaturated groups, with saturated groups generally being preferred.

"Aryl" means one or more aromatic rings, each of 5 or 6 core carbon atoms. Aryl includes multiple aryl rings that may be fused, as in naphthyl, or unfused, as in biphenyl. Aryl rings may also be fused or unfused with one or more cyclic hydrocarbon, heteroaryl, or heterocyclic rings. As used herein, "aryl" includes heteroaryl. An aromatic moiety (e.g., Ar<sup>1</sup>, Ar<sup>2</sup>, and so forth), means a structure containing aryl.

"Heteroaryl" is an aryl group containing from one to four heteroatoms, preferably N, O, or S, or a combination thereof. Heteroaryl rings may also be fused with one or more cyclic hydrocarbon, heterocyclic, aryl, or heteroaryl rings.

"Heterocycle" or "heterocyclic" means one or more rings of 5-12 atoms, preferably 5-7 atoms, with or without unsaturation or aromatic character and having at least one ring atom which is not a carbon. Preferred heteroatoms include sulfur, oxygen, and nitrogen.

"Substituted heteroaryl" is heteroaryl having one or more non-interfering groups as substituents.

"Substituted heterocycle" is a heterocycle having one or more side chains formed from non-interfering substituents.

"Non-interfering substituents" are those groups that, when present in a molecule, are typically non-reactive with other functional groups contained within the molecule. Such groups include: lower alkyl, lower alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, e.g., cyclopropyl, cyclobutyl, and the like; halo, e.g., fluoro, chloro, bromo, and iodo; cyano; phenyl; substituted phenyl; and the like. For substitutions on a phenyl ring, the substituents may be in any orientation (i.e., ortho, meta, or para). Preferred non-interfering substituents include lower alkyl, lower alkoxy, cyclopropyl, fluoro, chloro, and cyano.

The term "substituted" as in, for example, "substituted alkyl," refers to a moiety (e.g., an alkyl group) substituted with one or more non-interfering substituents, such as, but not limited to: C<sub>3</sub>-C<sub>8</sub> cycloalkyl, e.g., cyclopropyl, cyclobutyl, and the like; halo, e.g., fluoro, chloro, bromo, and iodo; cyano; alkoxy, lower phenyl (e.g., 0-2 substituted phenyl); substituted phenyl; and the like. "Substituted aryl" is aryl having one or more non-interfering groups as a substituent. For substitutions on a phenyl ring, the substituents may be in any orientation (i.e., ortho, meta, or para).

As used herein, the "halo" designator (e.g., fluoro, chloro, iodo, bromo, and so forth) is generally used when the halogen is attached to a molecule, while the suffix "ide" (e.g., fluoride, chloride, iodide, bromide, and so forth) is used when the halogen exists in its independent ionic form (e.g., such as when a leaving group leaves a molecule).

"Electrophile" refers to an ion or atom or collection of atoms, that may be ionic, having an electrophilic center, i.e., a center that is electron seeking, capable of reacting with a nucleophile.

"Nucleophile" refers to an ion or atom or collection of atoms that may be ionic having a nucleophilic center, i.e., a center that is seeking an electrophilic center or with an electrophile.

A basic or acidic reactant described herein includes neutral, charged, and any corresponding salt forms thereof.

As used herein, the term "ionizable hydrogen atom" ("H<sub>α</sub>") means a hydrogen atom that can be removed in the presence of a base, often a hydroxide or amine base. Typically, the

"ionizable hydrogen atom" (" $H_{\alpha}$ ") will be a hydrogen atom attached to a carbon atom that, in turn, is attached to one or more aromatic moieties or another group or groups that in some way stabilize the carbanion that would form from loss of the ionizable hydrogen atom as a proton (or the transition state leading to said carbanion).

As used herein, the term "carboxylic acid" is a moiety having a  $-C(O)OH$  functional group, as well as moieties that are derivatives of a carboxylic acid, such derivatives including, for example, protected carboxylic acids. Thus, unless the context clearly dictates otherwise, the term carboxylic acid includes not only the acid form, but corresponding esters and protected forms as well. With regard to protecting groups suited for a carboxylic acid and any other functional group described herein, reference is made to Greene *et al.*, "PROTECTIVE GROUPS IN ORGANIC SYNTHESIS", 3<sup>rd</sup> Edition, John Wiley and Sons, Inc., New York, 1999.

The term "reactive" or "activated" when used in conjunction with a particular functional group, refers to a reactive functional group that reacts readily with an electrophile or a nucleophile on another molecule. This is in contrast to those groups that require strong catalysts or highly impractical reaction conditions in order to react (i.e., a "nonreactive" or "inert" group).

The terms "protected" or "protecting group" or "protective group" refer to the presence of a moiety (i.e., the protecting group) that prevents or blocks reaction of a particular chemically reactive functional group in a molecule under certain reaction conditions. The protecting group will vary depending upon the type of chemically reactive functional group being protected as well as the reaction conditions to be employed and the presence of additional reactive or protecting groups in the molecule, if any. Protecting groups known in the art can be found in Greene *et al.*, *supra*.

As used herein, the term "functional group" or any synonym thereof is meant to encompass protected forms thereof. In particular, recitation of specific functional groups such as carboxylic acids, aldehydes, or hydroxyl groups encompasses protected forms thereof.

"Multifunctional", in the context of a polymer of the invention, means a polymer having 3 or more functional groups contained therein, where the functional groups may be the same or different. Multifunctional polymers of the invention will typically contain from about 3-100 functional groups, or from 3-50 functional groups, or from 3-25 functional groups, or from 3-15 functional groups, or from 3 to 10 functional groups, or will contain 3, 4, 5, 6, 7, 8, 9 or 10 functional groups within the polymer. A "difunctional" polymer means a polymer having two

functional groups contained therein, either the same (i.e., homodifunctional) or different (i.e., heterodifunctional).

"Branched," in reference to the geometry or overall structure of a polymer, refers to polymer having 2 or more polymer "arms." A branched polymer may possess 2 polymer arms, 3 polymer arms, 4 polymer arms, 6 polymer arms, 8 polymer arms or more. One particular type of highly branched polymer is a dendritic polymer or dendrimer, which, for the purposes of the invention, is considered to possess a structure distinct from that of a branched polymer.

A "dendrimer" or dendritic polymer is a globular, size monodisperse polymer in which all bonds emerge radially from a central focal point or core with a regular branching pattern and with repeat units that each contribute a branch point. Dendrimers exhibit certain dendritic state properties such as core encapsulation, making them unique from other types of polymers.

In the context of the present description, the definition of a variable provided with respect to one structure or formula is applicable to the same variable repeated in a different structure, unless the context dictates otherwise. Thus, for example, the definition of "POLY," "a spacer moiety," "R<sup>el</sup>" and so forth with respect to a polymer can be equally applicable to a water-soluble polymer conjugate provided herein.

The terms "spacer" or "spacer moiety" (which may also be referred to as a linker or linker moiety) are used herein to refer to an atom or a collection of atoms optionally used to link one moiety to another, such as a water-soluble polymer segment to a functional moiety in a polymeric reagent. The spacer moieties of the invention are preferably hydrolytically stable but may include one or more physiologically hydrolyzable or enzymatically degradable linkages. Exemplary spacer moieties are described further below.

A "physiologically cleavable" or "hydrolyzable" bond is a relatively weak bond that reacts with water (i.e., is hydrolyzed) under physiological conditions. The tendency of a bond to hydrolyze in water will depend not only on the general type of linkage connecting two central atoms but also on the substituents attached to these central atoms. Appropriate hydrolytically unstable or weak linkages include, but are not limited to, carboxylate ester, phosphate ester, anhydrides, acetals, ketals, acyloxyalkyl ether, imines, ortho esters, peptides and oligonucleotides.

A "degradable linkage" includes, but is not limited to, a physiologically cleavable bond, a hydrolyzable bond, and an enzymatically degradable linkage. Thus, a "degradable linkage" is a linkage that may undergo either hydrolysis or cleavage by some other mechanism (e.g.,

enzyme-catalyzed, acid-catalyzed, base-catalyzed, and so forth) under physiological conditions. For example, a "degradable linkage" can involve an elimination reaction that has a base abstraction of a proton, (e.g., an ionizable hydrogen atom, H<sub>a</sub>), as the driving force.

An "enzymatically degradable linkage" means a linkage that is subject to degradation by one or more enzymes.

A "hydrolytically stable" linkage or bond refers to a chemical bond, typically a covalent bond, that is substantially stable in water, that is to say, does not undergo hydrolysis under physiological conditions to any appreciable extent over an extended period of time. Examples of hydrolytically stable linkages include but are not limited to the following: carbon-carbon bonds (e.g., in aliphatic chains), ethers, amides, urethanes (carbamates), and the like. Generally, a hydrolytically stable linkage is one that exhibits a rate of hydrolysis of less than about 1-2% per day under physiological conditions. Hydrolysis rates of representative chemical bonds can be found in most standard chemistry textbooks. It must be pointed out that some linkages can be hydrolytically stable or hydrolyzable, depending upon (for example) adjacent and neighboring atoms and ambient conditions. One of ordinary skill in the art can determine whether a given linkage or bond is hydrolytically stable or hydrolyzable in a given context by, for example, placing a linkage-containing molecule of interest under conditions of interest and testing for evidence of hydrolysis (e.g., the presence and amount of two molecules resulting from the cleavage of a single molecule). Other approaches known to those of ordinary skill in the art for determining whether a given linkage or bond is hydrolytically stable or hydrolyzable can also be used.

As used herein, "drug release rate" means a rate (stated as a half-life) in which half of the total amount of polymer-active agent conjugates in a system will cleave into the active agent and a polymeric residue.

The terms "active agent," "biologically active agent" and "pharmacologically active agent" are used interchangeably herein and are defined to include any agent, drug, compound, composition of matter or mixture that provides some pharmacologic, often beneficial, effect that can be demonstrated *in-vivo* or *in vitro*. This includes foods, food supplements, nutrients, nutraceuticals, drugs, proteins, vaccines, antibodies, vitamins, and other beneficial agents. As used herein, these terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient.

"Pharmaceutically acceptable excipient" or "pharmaceutically acceptable carrier" refers to an excipient that can be included in the compositions of the invention and that causes no significant adverse toxicological effects to the patient.

"Pharmacologically effective amount," "physiologically effective amount," and "therapeutically effective amount" are used interchangeably herein to mean the amount of a polymer-active agent conjugate, typically present in a pharmaceutical preparation, that is needed to provide a desired level of active agent and/or conjugate in the bloodstream or in a target tissue. The exact amount will depend upon numerous factors, e.g., the particular active agent, the components and physical characteristics of the pharmaceutical preparation, intended patient population, patient considerations, and the like, and can readily be determined by one of ordinary skill in the art, based upon the information provided herein and available in the relevant literature.

The term "patient" refers to a living organism suffering from or prone to a condition that can be prevented or treated by administration of a conjugate as provided herein, and includes both humans and animals.

## **II. Carbohydrate-Based Reagents**

Because of their very low toxicity and immunogenicity, carbohydrate polymers are attractive candidates for use in conjugating to biologically active molecules for drug delivery. However, because carbohydrates are generally very large polydisperse polymers with hundreds or even thousands of reactive functional groups, controlling the degree of functionality and the polydispersity are important considerations in such applications of carbohydrates.

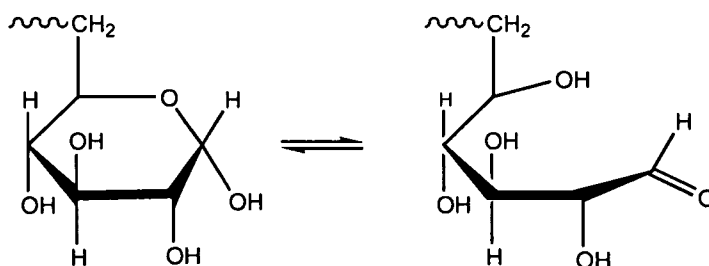
Carbohydrate polymers, which may also be referred to as polysaccharides, include naturally occurring polysaccharides and materials derived from naturally occurring polysaccharides. Water soluble polymers are preferred. Well known examples are dextran, glycogen, and amylose, as well as chitosan (deacetylated chitin), which is a positively charged carbohydrate. The polymers can be obtained in a large range of molecular weights. For the present application, molecular weights in the range of 200 Da to 2,000,000 Da are contemplated, depending on the intended use of the carbohydrate reagent. Molecular weights such as 5KDa, 10KDa, 20KDa, 40KDa, and 70KDa, for example, are typical.

Dextran is one of the most important polysaccharides for medical and industrial applications. It is produced primarily from sucrose by bacterial strains and structurally is a poly(glucose) having an  $\alpha$ -(1-6) linked D-glucose main chain. It is commercially available in a variety of molecular weights, though generally with high polydispersity values.

Several existing dextran derivatives, used mainly for modification of small molecular weight drugs, are based on activation of hydroxyl groups present in each repeating unit of the polymer. This type of activation is not suitable for the single point attachment of a drug moiety; thus it is not applicable to protein modification, where a polymer having only one active group on the polymer chain is desired.

Chitosan, a carbohydrate polymer formed by deacetylation of the naturally occurring chitin, is particularly useful in certain drug delivery applications because it is a cationic polymer, having an amine group on each repeating unit.

The present disclosure is directed to monofunctional carbohydrate reagents for drug conjugation, prepared by activation of the reducing end (i.e. the anomeric carbon) of carbohydrates such as dextran. As is well known for aldoses in general, the reducing terminus of dextran can be represented in the closed ring acetal (pyranose) form or the open-chain aldehyde form, as follows:

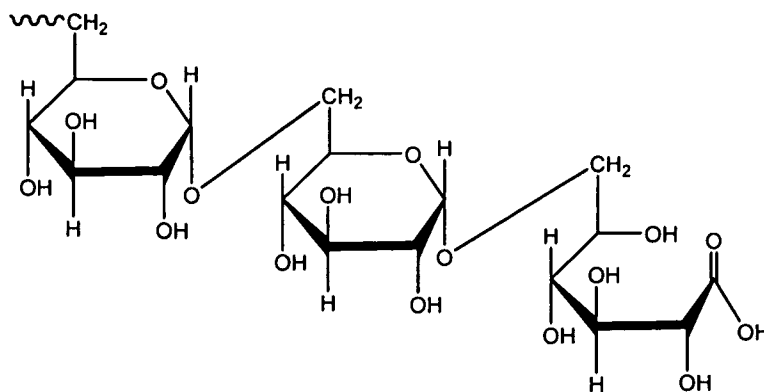


where the aldehyde carbon is the anomeric carbon. A similar conversion between closed ring forms (pyranose or furanose) and open chain (keto) forms exists for ketoses, where the open chain form terminates in  $-C(O)-CH_2OH$ .

Particular embodiments of the monofunctional carbohydrate polymers of the invention are described in the following sections. The terms “monoderivatized” and “monofunctional” in this context may be used interchangeably and refer to the fact that the carbohydrate polymer is modified such that it may be selectively conjugated at a single location, in this case a single terminus bearing a functional group.

#### A. Monocarboxylic Acid and Carboxylic Acid Derivatives

In one embodiment, a water soluble carbohydrate polymer terminating in an aldose group, such as dextran, is selectively oxidized at the reductive end of the polymer under mild conditions, effective to produce a single carboxylic acid functionality, without modifying the remaining structure of the polymer. The monoacid dextran reagent is designated (1) herein.



(1)

Suitable oxidation conditions include iodine ( $I_2$ ) and a hydroxide base, e.g. NaOH, such as described in Examples 1, 3, and 5 below. In general, oxidation conditions are such that the ratio of the desired monocarboxylic acid product to overoxidized side products (such as polymer oxidized at internal sites, including cleaved chain products) is greater than 15:1, preferably greater than 25:1, and more preferably greater than 50:1. Thus, the molecular weight of the oxidized polymer is essentially unchanged. Furthermore, the ratio of desired monocarboxylic acid product to dicarboxylic acid product is preferably greater than 25:1. The total conversion is preferably greater than 70-80%; that is, less than 20-30% of unreacted dextran remains. For example, the conditions described in Example 5 below produced a reaction mixture containing 3.1% of dextran diacid, 83.9% of dextran monoacid, and 13.0% of unreacted dextran. The procedure is effective on higher molecular weight water soluble carbohydrate polymers, as shown for dextran having a molecular weight of 40,000 in Examples 3 and 5.

Further to this embodiment, the polydispersity of a carbohydrate polymer can be significantly reduced by purifying the monocarboxylic product, prepared as described above, by ion exchange chromatography. A demonstration of the process using dextran (40K) monocarboxylic acid, designated herein as (1b), is given in Example 4. In another instance, a dextran monocarboxylic acid having a polydispersity of 2.34 was obtained from a starting dextran (molecular weight 6KDa) having a polydispersity of 3.27 by mild oxidation, as described herein, followed by ion exchange chromatography.

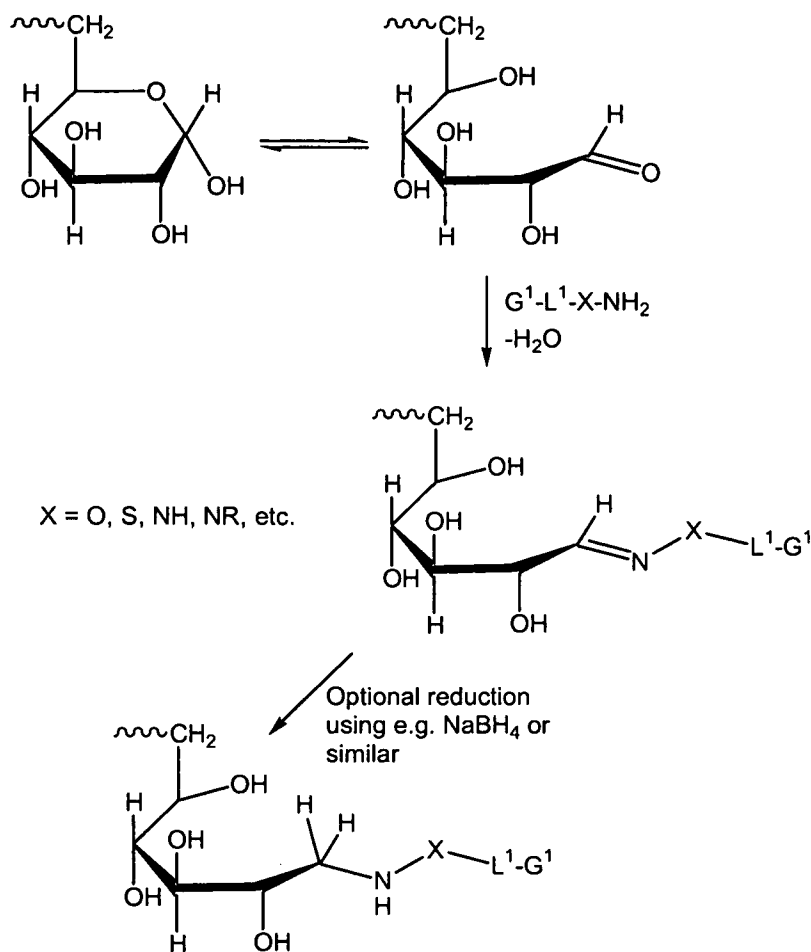
Preferred polydispersities are less than 2.5, preferably less than 2.0, and more preferably less than 1.5. In some embodiments, polydispersities may be less than 1.35, or less than 1.20.

The low polydispersity carbohydrate monocarboxylic acid also provides access to a

range of low polydispersity carbohydrate carboxylic acid derivatives. Such derivatives and their preparation are well known in the art and include functionalities such as ester, activated ester, thioester, anhydride, amide, acid halide, nitrile, carbamate, carbonate, isocyanate, and isothiocyanate. These can of course be further converted to any number of different functionalities by well known methods. Thus, for example, with appropriate linkers, carboxylic acids are readily converted into useful reactive groups such as maleimides, aldehydes, and active disulfides, e.g. orthopyridyl disulfides (OPPS).

#### B. Monoderivatization with Heterobifunctional Oxyamines or Hydrazines

In a further embodiment, a heterobifunctional reagent comprising, at one terminus, a highly nucleophilic amine such as an oxyamine or hydrazine is selectively reacted with the reductive end of a carbohydrate polymer, preferably the aldehyde end of an aldose. The other terminus of the reagent bears a different functional group (i.e., not an oxyamine or hydrazine) that is either protected or is otherwise unreactive under the conditions of the reaction. Such reactions produce oxyimine or hydrazone linkages, as shown in the scheme below, to the carbohydrate moiety, with a distinct functional group, indicated by  $G^1$ , where  $L^1$  is a linker as described below, at the new terminus. Because of the presence of the heterogroup, X (which may also be sulfur) adjacent the C=N bond, these linkages are generally stable except to certain acid-catalyzed hydrolytic procedures. If more stability is desired, the product may be further converted in a reduction step, as also shown in the scheme below.



Accordingly, the invention provides a monofunctional water-soluble carbohydrate-based reagent having the structure



where:

POLY<sup>1</sup> is a water-soluble carbohydrate polymer having a terminal anomeric carbon atom, where C<sup>a</sup> is said terminal anomeric carbon atom;

--- represents a double bond when x=0 and a single bond when x=1;

R<sup>1</sup> is H or hydroxymethyl;

X is oxygen or NR<sup>2</sup>, where R<sup>2</sup> is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl, and is preferably H or methyl, and more preferably H;

R<sup>3</sup> is H or methyl, and is typically H;

L<sup>1</sup> is a linker group, and

G<sup>1</sup> is a functional group, in reactive or protected form, not selected from oxyamine and hydrazine.

In selected embodiments, the carbohydrate reagent has a double bond represented by  $\text{---}$ , such that  $x=0$ . In other embodiments, e.g. where the double bond is subjected to reduction, the carbohydrate reagent has a single bond represented by  $\text{---}$ , such that  $x=1$ .

In selected embodiments, X is oxygen (an oxyamine reagent) or  $\text{NR}^2$ , e.g.  $\text{NH}_2$  (a hydrazine reagent). X may also be sulfur.

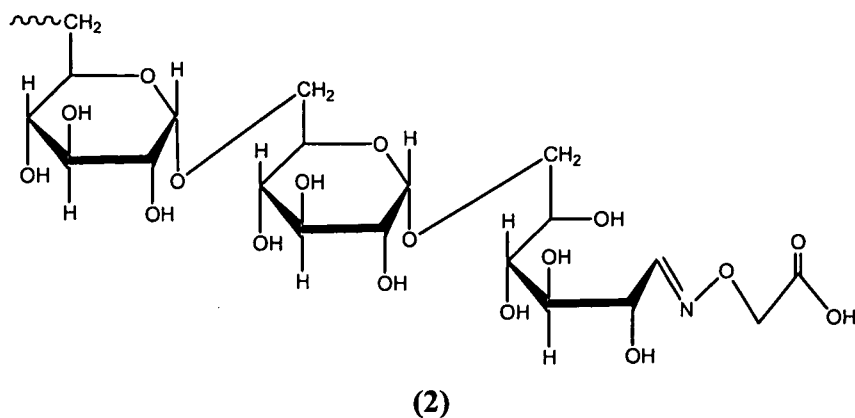
$\text{R}^1$  may be hydroxymethyl, when  $\text{POLY}^1$  is a ketose, or hydrogen, when  $\text{POLY}^1$  is an aldose, such as a dextran or a chitosan.  $\text{POLY}^1$  generally has a molecular weight in the range of 200 Da to 2,000,000 Da. Molecular weights such as 5KDa, 10KDa, 20KDa, 40KDa, and 70KDa, for example, are typical.

$\text{L}^1$  is a linker as defined further below. Preferably,  $\text{L}^1$  consists of moieties selected from alkylene,  $\text{-CH}_2\text{CH}_2\text{O-}$ , amide, carbamate, and combinations thereof; more preferably,  $\text{L}^1$  consists of alkylene moieties,  $\text{-CH}_2\text{CH}_2\text{O-}$  moieties, and combinations thereof. Generally,  $\text{L}^1$  is 1 to about 20 atoms in length, and may be 3-12, or 3-8 atoms in length.

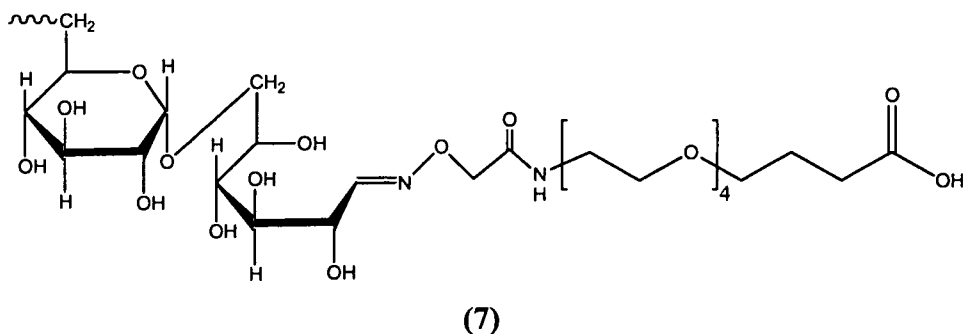
The functional group  $\text{G}^1$  may be selected from amine, hydroxy, thiol, carboxylic acid, carboxylic acid ester, imide ester, orthoester, carbonate, isocyanate, isothiocyanate, aldehyde, acetal, ketone, ketal, thione, alkenyl, acrylate, methacrylate, acrylamide, sulfone, maleimide, disulfide, iodo, epoxy, sulfonate, thiosulfonate, silane, alkoxy silane, halosilane, and phosphoramidate; and in selected embodiments is selected from amine, hydroxy, thiol, carboxylic acid, carboxylic acid ester, imide ester, orthoester, carbonate, isocyanate, aldehyde, acetal, ketone, ketal, and maleimide.

The preparation method may also include a step of purifying the carbohydrate polymer. In particular, when the heterobifunctional reagent comprises an oxyamine or hydrazine at one terminus and a carboxylic acid or amine group at the other terminus, effective to produce a monoderivatized water-soluble carbohydrate polymer having a single terminal carboxylic acid or amine group, the method may further comprise purifying the amine- or carboxylic acid-terminated carbohydrate polymer by ion exchange chromatography.

A particularly useful embodiment is that in which  $\text{G}^1$  is a carboxyl group. For example, the reaction of O-(carboxymethyl)hydroxylamine with dextran gives dextran-O-(carboxymethyl)oxyimine, designated herein as (2), as described in Example 6. In this case,  $\text{L}^1$  is an alkylene (methylene) linker.

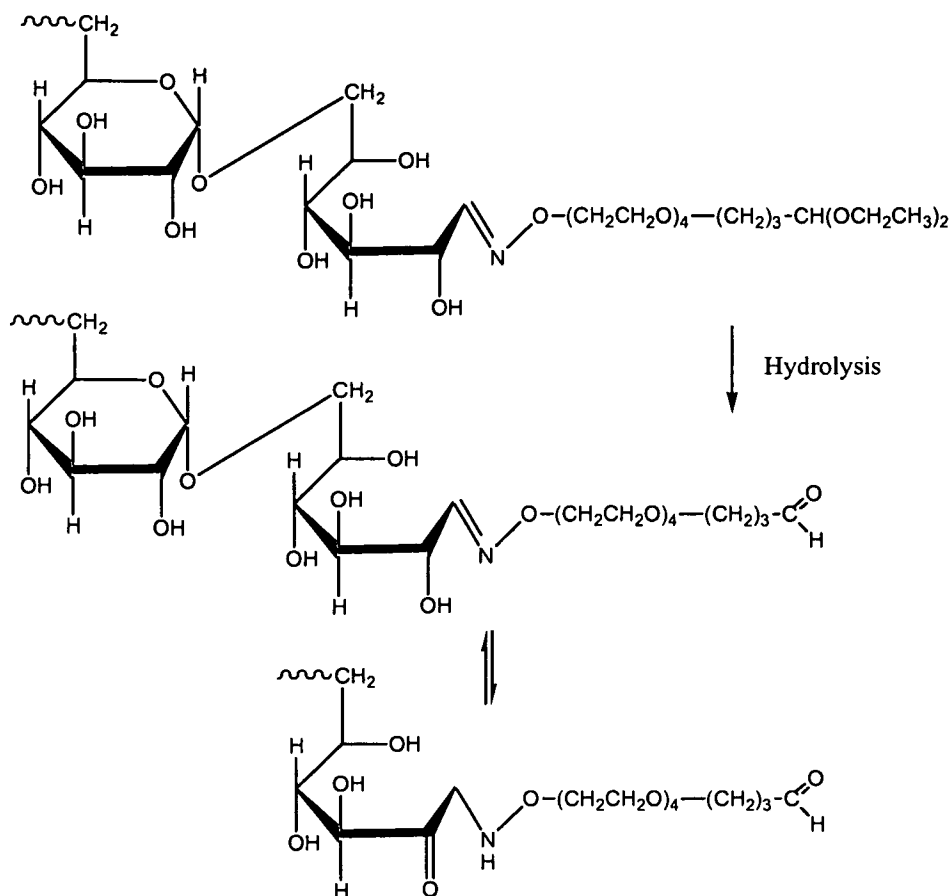


In another example, a reagent containing an oxyamine group connected by an oligo(ethylene glycol)-alkylene linker to a butanoic acid group can be used to provide a butanoic acid having an extended linker to the polysaccharide, as shown in Example 8 below. The dextran reagent is designated herein as (7). Such reagents can be purified to low polydispersities by ion exchange chromatography.



In further embodiments, additional heterobifunctional reagents having linkers based on oligomers, e.g. tetraethylene glycol, attached to having highly nucleophilic amines, such as hydrazines or oxyamines, are used to prepare a variety of polysaccharide reagents. These reagents include an optionally protected functional group that may ultimately be activated for reaction with a drug moiety. For example, preparation of a protected aldehyde-terminated dextran reagent, oxyimine-linked dextran butyraldehyde (16), is described in Example 13.

The hydroxy-imine moiety in these reagents may rearrange to an amino ketone moiety, as shown in the scheme below.



### C. Linker Moieties

As described above, the reagents disclosed herein may include a linker moiety, designated  $L^1$ . A linker may be used to connect polymer segments making up the component POLY to each other.

A linker is typically but is not necessarily linear in nature. The overall length of the linker will typically range between 1 to about 40 atoms, where by length is meant the number of atoms in a single chain, not counting substituents. For instance,  $-\text{CH}_2-$  counts as one atom with respect to overall linker length, and  $-\text{CH}_2\text{CH}(\text{CH}_3)\text{O}-$  counts as 3 atoms in length. Preferably, a linker will have a length of about 1 to about 20 atoms, or, more preferably, from about 2 to about 15 atoms; e.g. 3 to 8 atoms.

Illustrative linkers are those corresponding to either of the following structures:

$-(\text{CH}_2)_c-\text{D}_e-(\text{CH}_2)_f-$  or  $-(\text{CH}_2)_p-\text{M}_r-\text{C}(\text{O})-\text{K}_s-(\text{CH}_2)_q-$ ; where  $c$  is 0 to 8; "D" is O, NH, or S;  $e$  is 0 or 1;  $f$  is 0 to 8;  $p$  is 0 to 8; "M" is  $-\text{NH}$  or O; "K" is NH or O;  $q$  is 0 to 8, and  $r$  and  $s$  are each independently 0 or 1.

Other exemplary linker moieties include, but are not limited to, the following:  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{S}(\text{O}_2)-$ ,  $-\text{S}(\text{O})-$ ,  $-\text{NH}-\text{S}(\text{O}_2)-$ ,  $-\text{S}(\text{O}_2)-\text{NH}-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{O}-\text{CH}=\text{CH}-$ ,  $-\text{C}(\text{O})-\text{NH}-$ ,  $-\text{NH}-\text{C}(\text{O})-\text{NH}-$ ,  $-\text{O}-\text{C}(\text{O})-\text{NH}-$ ,  $-\text{C}(\text{S})-$ ,  $-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,

-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -O-CH<sub>2</sub>-, -CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-O-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-O-,  
 -O-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-O-,  
 -O-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-O-, -S-CH<sub>2</sub>-, -CH<sub>2</sub>-S-, -S-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-S-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-S-, -S-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-S-, -S-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-S-, -C(O)-NH-CH<sub>2</sub>-, -C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-, -C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-,  
 -C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-,  
 -NH-C(O)-CH<sub>2</sub>-C(O)-NH-, -NH-C(O)-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-,  
 -NH-C(O)-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-, -NH-C(O)-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-,  
 -NH-C(O)-CH=CH-C(O)-NH-, -C(O)-O-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)-O-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-C(O)-O-CH<sub>2</sub>-,  
 -C(O)-O-CH<sub>2</sub>-CH<sub>2</sub>-, -NH-C(O)-CH<sub>2</sub>-, -CH<sub>2</sub>-NH-C(O)-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-NH-C(O)-CH<sub>2</sub>-,  
 -NH-C(O)-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-NH-C(O)-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-NH-C(O)-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -C(O)-NH-CH<sub>2</sub>-, -C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-, -O-C(O)-NH-CH<sub>2</sub>-, -O-C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -NH-CH<sub>2</sub>-, -NH-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-NH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-NH-CH<sub>2</sub>-, -C(O)-CH<sub>2</sub>-,  
 -C(O)-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-C(O)-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-C(O)-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-C(O)-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-NH-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-NH-C(O)-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-NH-C(O)-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C(O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-NH-C(O)-CH<sub>2</sub>-CH<sub>2</sub>-, bivalent cycloalkyl, and amino acids.

Also included are -N(R<sup>6</sup>)-, where R<sup>6</sup> is H or an organic radical selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl and substituted aryl; and -NH-C(O)-O-(CH<sub>2</sub>)<sub>h</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>j</sub>- or -O-C(O)-NH-(CH<sub>2</sub>)<sub>h</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>j</sub>-, where (h) is zero to six, and (j) is zero to 20. Other specific spacer moieties have the following structures: -C(O)-NH-(CH<sub>2</sub>)<sub>1-6</sub>-NH-C(O)-, -NH-C(O)-NH-(CH<sub>2</sub>)<sub>1-6</sub>-NH-C(O)-, and -O-C(O)-NH-(CH<sub>2</sub>)<sub>1-6</sub>-NH-C(O)-, wherein the subscript values following each methylene indicate the number of methylenes contained in the structure, e.g., (CH<sub>2</sub>)<sub>1-6</sub> means that the structure can contain 1, 2, 3, 4, 5 or 6 methylenes.

A linker may include combinations of two or more of any of the foregoing.

In the reagents and/or conjugates of structures I-V herein, the linker preferably includes a carbon atom attached to the atom X (generally oxygen or nitrogen), which may be part of, for example, an alkyl or alkylene group, or a carbonyl carbon. A linker can comprise a single functional group such as an amide, an ester, a urethane (carbamate), or a urea, preferably containing methylene or other alkylene groups flanking one or both sides of the functional group. Alternatively, a linker may contain a combination of functional groups, which can be the same or different. A linker can be an alkylene chain, optionally containing one or more oxygen or sulfur atoms (i.e., an ether or thioether linkage). Also included are alkylene chains containing a nitrogen atom (i.e. an amine linkage.)

Preferably, the linker is hydrolytically stable, and may contain one or more of the following functional groups: amide, urethane, ether, thioether, or urea. However, hydrolytically degradable linkages, such as carboxylate ester, phosphate ester, orthoester, anhydride, imine, acetal, ketal, oligonucleotide, or peptide, may also be present.

Additionally, any of the above spacer moieties may further include an ethylene oxide oligomer chain comprising 1 to 20 ethylene oxide monomer units (i.e.,  $-(\text{CH}_2\text{CH}_2\text{O})_{1-20}$ ). That is, the ethylene oxide oligomer chain can occur before or after the spacer moiety, and optionally in between any two atoms of a spacer moiety comprised of two or more atoms.

#### D. Functional Groups

As described above, the reagents of structures I-IV include a functional group  $G^1$  which is useful for forming a conjugate of the polymer, e.g., with a pharmacologically active agent, surface, solid support, or the like. The functional group typically comprises an electrophilic or nucleophilic group that provides for covalent attachment of a desired agent to the carbohydrate polymer.

Preferred nucleophilic groups include amine, hydroxy, and thiol, particularly amine.

Examples of electrophilic functional groups include carboxylic acid, carboxylic ester, particularly imide esters, orthoester, carbonate, isocyanate, isothiocyanate, aldehyde, ketone, thione, alkenyl, acrylate, methacrylate, acrylamide, sulfone, maleimide, disulfide, iodo, epoxy, sulfonate, thiosulfonate, silane, alkoxy silane, halosilane, and phosphoramidate. More specific examples of these groups include succinimidyl ester or carbonate, imidazolyl ester or carbonate, benzotriazole ester or carbonate, vinyl sulfone, chloroethylsulfone, vinylpyridine, pyridyl disulfide, iodoacetamide, glyoxal, dione, mesylate, tosylate, and tresylate (2,2,2-trifluoroethanesulfonate).

Also included are sulfur analogs of several of these groups, such as thione, thione hydrate, thioketal, etc., as well as hydrates or protected derivatives of any of the above

moieties (e.g. aldehyde hydrate, hemiacetal, acetal, ketone hydrate, hemiketal, ketal, thioketal, thioacetal). Another useful conjugation reagent is 2-thiazolidine thione.

The term "carboxylic acid derivative" encompasses various functional groups that include a carbonyl group with an attached heteroatom, such as ester, thioester, anhydride, amide, acid halide, nitrile, carbamate, carbonate, isocyanate, and isothiocyanate. An "activated derivative" of a carboxylic acid refers to a carboxylic acid derivative which reacts readily with nucleophiles, generally much more readily than the underivatized carboxylic acid. Activated carboxylic acids include, for example, acid halides (such as acid chlorides), anhydrides, carbonates, and esters. Such esters (referred to as active or activated esters) include imide esters, of the general form  $-(CO)O-N[(CO)-]_2$ ; for example, N-hydroxysuccinimidyl (NHS) esters or N-hydroxyphthalimidyl esters. Also preferred are imidazolyl esters and benzotriazole esters. Particularly preferred are activated propionic acid or butanoic acid esters, as described in co-owned U.S. Patent No. 5,672,662. These include groups of the form  $-(CH_2)_{2-3}C(=O)O-Q$ , where Q is preferably selected from N-succinimide, N-sulfosuccinimide, N-phthalimide, N-glutarimide, N-tetrahydrophthalimide, N-norbornene-2,3-dicarboximide, benzotriazole, 7-azabenzotriazole, and imidazole.

Other preferred electrophilic groups include succinimidyl carbonate, maleimide, benzotriazole carbonate, glycidyl ether, imidazolyl carbonate, p-nitrophenyl carbonate, acrylate, tresylate, aldehyde, and orthopyridyl disulfide.

These electrophilic groups are subject to reaction with nucleophiles, e.g. hydroxy, thio, or amino groups, to produce various bond types. For example, carboxylic acids and activated derivatives thereof, which include orthoesters, succinimidyl esters, imidazolyl esters, and benzotriazole esters, react with the above types of nucleophiles to form esters, thioesters, and amides, respectively, of which amides are the most hydrolytically stable. Carbonates, including succinimidyl, imidazolyl, and benzotriazole carbonates, will react with hydroxyl or amino groups to form further carbonates or carbamates, respectively. Isocyanates ( $R-N=C=O$ ) react with hydroxyl or amino groups to form, respectively, carbamate ( $RNH-C(O)-OR'$ ) or urea ( $RNH-C(O)-NHR'$ ) linkages. Phosphoramidites can be reacted with hydroxyl reagents, followed by oxidation, to form phosphate esters (as in conventional oligonucleotide synthesis).

Aldehydes, ketones, glyoxals, diones and their hydrates or alcohol adducts (i.e. aldehyde hydrate, hemiacetal, acetal, ketone hydrate, hemiketal, and ketal) are preferably reacted with amines, followed by reduction of the resulting imine, if desired, to give an amine linkage (reductive amination). Alternatively, these groups can be reacted with hydroxyl containing

groups, to form further acetals, ketals, etc. In these cases, the linkages formed are subject to hydrolytic degradation, which may be desirable, as discussed further below.

Several of the electrophilic functional groups include electrophilic double bonds to which nucleophilic groups, such as thiols, can be added, to form, for example, thioether bonds. These groups include maleimides, vinyl sulfones, vinyl pyridine, acrylates, methacrylates, and acrylamides. Other groups comprise leaving groups which can be displaced by a nucleophile; these include chloroethyl sulfone, pyridyl disulfides (which include a cleavable S-S bond), iodoacetamide, mesylate, tosylate, thiosulfonate, and tresylate. Epoxides react by ring opening by a nucleophile, to form, for example, an ether or amine bond. Silanes, including halosilanes and alkoxy silanes, react with hydroxy- or oxide-containing compounds, or surfaces such as glass, to form siloxanes.

### **III. Conjugation Method**

In accordance with the invention, methods of forming stable conjugates of monoderivatized carbohydrate polymers with biologically active molecules (e.g. drugs) are provided. Accordingly, the invention provides a method of conjugating a monoderivatized carbohydrate polymer with a target compound, the method comprising: reacting a reagent of structure(s) I, II or IV, having a terminal functional group  $G^1$ , or a reagent as described in section IIA above, having a terminal carboxylic acid or carboxylic acid derivative, with a biologically active molecule having a corresponding functional group, which is reactive with  $G^1$  or with said carboxylic acid or carboxylic acid derivative, to form a stable covalent bond between the reagent and the biologically active molecule.

Functional groups and corresponding functional group with which they are reactive are known in the art and include those described in section IID above. In one embodiment, the functional group on the biologically active molecule is an amine, as is common in protein conjugations.

In general, preferred embodiments of the method employ preferred embodiments of the reagents as described herein.

#### **A. Reaction Conditions for Conjugation**

Suitable solvents for carrying out the conjugation reaction include buffers such as aqueous sodium phosphate, sodium acetate, sodium carbonate, phosphate buffered saline (PBS), sodium borate, and N-(2-hydroxyethyl) piperazine-N'-(2-ethanesulfonic acid) (HEPES). For conjugation to a protein, the polymeric reagent is typically added to the protein-containing solution at an equimolar amount or at a molar excess relative to target

protein. Molar excesses of carbohydrate reagent relative to target protein are typically in the range of about 2 to 50, preferably in the range of 2 to 20, and most preferably in the range of 2 to 5. The conjugation reaction is typically carried out at temperatures at or below about room temperature (25°C), although temperatures may range from about -15°C to about 100°C, more preferably from about 4°C to 37°C, for approximately one to 24 hours. Exemplary conjugation reactions are described in Examples 14 and 16-18 below.

Conditions for conjugation to a small molecule, e.g. amphotericin B or other amine-containing molecules as discussed below, will vary according to the small molecule being modified. Typically, however, the conjugation is conducted using a slight molar excess of polymeric reagent relative to small molecule, e.g., about 1.2-1.5, to about a 5 to 10-fold molar excess. In some instances, depending upon the molecule, the small molecule drug may actually be used in excess, such as when the carbohydrate-small molecule conjugate precipitates in the reaction solvent, e.g., ether, while the unreacted drug remains in solution.

The exact reaction time is determined by monitoring the progress of the reaction over time. Progress of the reaction is typically monitored by withdrawing aliquots from the reaction mixture at various time points and analyzing the reaction mixture by SDS-PAGE or MALDI-TOF mass spectrometry or any other suitable analytical method.

#### B. Characterization and Optional Separation of Conjugates

The strategy for purification of the final conjugate reaction mixture will depend upon a number of factors, such as the molecular weight of the polymer employed, the particular protein, and the residual activity and *in vivo* properties of the conjugate species.

Conjugates having different molecular weights can be isolated using gel filtration chromatography. Gel filtration columns suitable for carrying out this type of separation include Superdex<sup>®</sup> and Sephadex<sup>®</sup> columns available from Amersham Biosciences. Selection of a particular column will depend upon the desired fractionation range desired. Elution is generally carried out using a non-amine based buffer, such as phosphate, acetate, or the like. The collected fractions may be analyzed by a number of different methods, for example, (i) OD at 280 nm for protein content, (ii) BSA protein analysis, (iii) iodine testing for PEG content, or (iv) by running an SDS PAGE gel, followed by staining with barium iodide.

Carbohydrate polymers having carboxylic acid termini, prepared as described herein, can be purified by ion exchange chromatography, as demonstrated in the Examples below. This process can produce reagents having low polydispersities, an important feature for drug delivery.

Separation of positional isomers (i.e. conjugates having polymers attached to different locations on a protein), generally not achievable by molecular weight-based methods, can often be carried out by reverse phase chromatography using e.g. an RP-HPLC C18 column (Amersham Biosciences or Vydac).

#### C. Conjugation to Proteins: Random and N-Terminal Selective

Generally, the polymeric reagents of the invention can be used to selectively target the modification of the N-terminus of a protein, under conditions that differentiate the reactivity of the  $\alpha$ -amine at the N-terminal amino acid. Reaction conditions for preparing an N-terminally modified protein or peptide include (i) dissolving the protein or peptide to be modified in a non-amine-containing buffer (e.g., at a pH range from about 4 to about 6.5, preferably from about 5 to 6.5, most preferably at a pH of about 5 to 5.5), (ii) adding to the protein or peptide solution a polymeric reagent ( $\alpha$ -hydroxy aldehyde or ketone) of the invention, and (iii) allowing the protein or peptide and polymeric reagent to react to form the conjugate.

Reaction under conditions of higher pH can be used for random attachment of a polymeric reagent ( $\alpha$ -hydroxy aldehyde or ketone). More specifically, to covalently attach a polymeric reagent to any number of lysine residues that are surface accessible, a protein or peptide (such as those exemplary biomolecules provided below) is typically reacted with a polymeric reagent of the invention in a non-amine-containing buffer at mild pH, generally ranging from about 5 to 8, more preferably from about 6.5 to 8. Non-amine containing buffers are preferred, since the amino-groups in the buffer can compete with protein amino groups for coupling to the polymeric reagent. A suitable non-amine containing buffer is selected having an appropriate pK for the desired pH range for conducting the conjugation chemistry. The coupling reaction generally takes anywhere from minutes to several hours (e.g., from 5 minutes to 24 hours or more), and on average, coupling is achieved between about 0.2 and 4 hours.

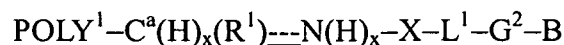
The degree of modification, that is, the number of polymeric reagents that are covalently attached at available sites on the target molecule, can be increased by increasing, either independently or simultaneously, any one or more of: molar ratio of polymeric reagent to protein or peptide, temperature, reaction time, and pH.

#### IV. Polymeric Conjugates

In accordance with the invention, polymeric conjugates, comprising a reagent as

disclosed herein conjugated to a biologically active molecule (e.g. drug), preferably a single such molecule, are provided. (In some cases, multiple carbohydrate polymers may be attached to a single biologically active molecule.) The conjugates are prepared by reaction of a reagent of structure(s) I, II or IV, having a terminal functional group  $G^1$ , or a reagent as described in section IIA above, having a terminal carboxylic acid or carboxylic acid derivative, with a biologically active molecule having a corresponding functional group, which is reactive with  $G^1$  or with said carboxylic acid or carboxylic acid derivative, to form a stable covalent bond between the reagent and the biologically active molecule.

Conjugates formed using reagents of structure IV thereby typically have the structure



where

$\text{POLY}^1$  is a water-soluble carbohydrate polymer having a terminal anomeric carbon atom, where  $\text{C}^a$  is said terminal anomeric carbon atom;

--- represents a double bond when  $x=0$  and a single bond when  $x=1$ ;

$\text{R}^1$  is H or hydroxymethyl;

X is oxygen or  $\text{NR}^2$ , where  $\text{R}^2$  is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl;

$\text{L}^1$  is a linker group, and

$\text{G}^2$  is a covalent bond comprising a residue or converted form of functional group  $\text{G}^1$ , following reaction with a corresponding functional group on biomolecule B.

Conjugates of dextran with several proteins (lysozyme, protegrin-1, C-peptide, and insulin), in accordance with the invention, is described in Examples 14 and 16-18 below. Biological activity of the dextran-insulin conjugate (designated **20b**) *in vitro* and *in vivo* is described in Examples 19 and 20, respectively. Conjugation of chitosan with a single stranded RNA is described in Example 23.

## V. The Conjugated Biologically Active Agent

The biologically active agent conjugated to a polymeric reagent of the invention may fall into one of a number of structural classes, including but not limited to small molecules (including difficultly soluble small molecules), peptides, polypeptides, proteins, polysaccharides, steroids, nucleotides, oligonucleotides, polynucleotides, fats, electrolytes, and the like. In one embodiment, the molecule either possesses a native amino group or is modified to contain at least one reactive amino group. As noted above, the working

Examples below describe conjugates of the proteins lysozyme, protegrin-1, C-peptide, and insulin.

The agent may be a therapeutic substance selected from, for example, hypnotics and sedatives, psychic energizers, tranquilizers, respiratory drugs, anticonvulsants, muscle relaxants, antiparkinson agents (dopamine antagonists), analgesics, anti-inflammatories, antianxiety drugs (anxiolytics), appetite suppressants, antimigraine agents, muscle contractants, anti-infectives (antibiotics, antivirals, antifungals, vaccines) antiarthritics, antimalarials, antiemetics, anepileptics, bronchodilators, cytokines, growth factors, anti-cancer agents, antithrombotic agents, antihypertensives, cardiovascular drugs, antiarrhythmics, antioxidants, anti-asthma agents, hormonal agents including contraceptives, sympathomimetics, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, anticoagulants, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, antienteritis agents, vaccines, antibodies, diagnostic agents, and contrasting agents.

Specific examples of active agents suitable for covalent attachment to a polymer of the invention include asparaginase, amdoxovir (DAPD), antide, becaplermin, calcitonins, cyanovirin, denileukin difitox, erythropoietin (EPO), EPO agonists (e.g., peptides from about 10-40 amino acids in length and comprising a particular core sequence as described in WO 96/40749), dornase  $\alpha$ , erythropoiesis stimulating protein (NESP), coagulation factors such as Factor V, Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor XII, Factor XIII, von Willebrand factor; ceredase, cerezyme,  $\alpha$ -glucosidase, collagen, cyclosporin, alpha defensins, beta defensins, exedin-4, granulocyte colony stimulating factor (GCSF), thrombopoietin (TPO),  $\alpha$ -1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), fibrinogen, filgrastim, growth hormones human growth hormone (hGH), growth hormone releasing hormone (GHRH), GRO-beta, GRO-beta antibody, bone morphogenic proteins such as bone morphogenic protein-2, bone morphogenic protein-6, OP-1; acidic fibroblast growth factor, basic fibroblast growth factor, CD-40 ligand, heparin, human serum albumin, low molecular weight heparin (LMWH), interferons such as interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, consensus interferon; interleukins and interleukin receptors such as interleukin-1 receptor, interleukin-2, interleukin-2 fusion proteins, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-4 receptor, interleukin-6, interleukin-8, interleukin-12, interleukin-13 receptor, interleukin-17 receptor; lactoferrin and lactoferrin

fragments, luteinizing hormone releasing hormone (LHRH), insulin, pro-insulin, insulin analogues (e.g., mono-acylated insulin as described in U.S. Pat. No. 5,922,675), amylin, C-peptide, somatostatin, somatostatin analogs including octreotide, vasopressin, follicle stimulating hormone (FSH), influenza vaccine, insulin-like growth factor (IGF), insulintropin, macrophage colony stimulating factor (M-CSF), plasminogen activators such as alteplase, urokinase, reteplase, streptokinase, pamiteplase, lanoteplase, and tenetelase; nerve growth factor (NGF), osteoprotegerin, platelet-derived growth factor, tissue growth factors, transforming growth factor-1, vascular endothelial growth factor, leukemia inhibiting factor, keratinocyte growth factor (KGF), glial growth factor (GGF), T Cell receptors, CD molecules/antigens, tumor necrosis factor (TNF), monocyte chemoattractant protein-1, endothelial growth factors, parathyroid hormone (PTH), glucagon-like peptide, somatotropin, thymosin alpha 1, thymosin alpha 1 IIB/IIIa inhibitor, thymosin beta 10, thymosin beta 9, thymosin beta 4, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 (very late antigen-4), VLA-4 inhibitors, bisphosphonates, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyribonuclease (Dnase), bactericidal/permeability increasing protein (BPI), and anti-CMV antibody. Exemplary monoclonal antibodies include etanercept (a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kD TNF receptor linked to the Fc portion of IgG1), abciximab, afelimomab, basiliximab, daclizumab, infliximab, ibritumomab tiuexetan, mitumomab, muromonab-CD3, iodine 131 tositumomab conjugate, olizumab, rituximab, and trastuzumab (herceptin).

Additional agents suitable for covalent attachment to a polymer of the invention include but are not limited to amifostine, amiodarone, aminocaproic acid, aminohippurate sodium, aminoglutethimide, aminolevulinic acid, aminosalicic acid, amsacrine, anagrelide, anastrozole, asparaginase, anthracyclines, bexarotene, bicalutamide, bleomycin, buserelin, busulfan, cabergoline, capecitabine, carboplatin, carmustine, chlorambucin, cilastatin sodium, cisplatin, cladribine, clodronate, cyclophosphamide, cyproterone, cytarabine, camptothecins, 13-cis retinoic acid, all trans retinoic acid; dacarbazine, dactinomycin, daunorubicin, deferoxamine, dexamethasone, diclofenac, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, estramustine, etoposide, exemestane, fexofenadine, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, epinephrine, L-Dopa, hydroxyurea, idarubicin, ifosfamide, imatinib, irinotecan, itraconazole, goserelin, letrozole, leucovorin, levamisole, lisinopril, lovathyroxine sodium, lomustine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, metaraminol bitartrate,

methotrexate, metoclopramide, mexiletine, mitomycin, mitotane, mitoxantrone, naloxone, nicotine, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, pilcamycin, porfimer, prednisone, procarbazine, prochlorperazine, ondansetron, raltitrexed, sirolimus, streptozocin, tacrolimus, tamoxifen, temozolomide, teniposide, testosterone, tetrahydrocannabinol, thalidomide, thioguanine, thiotepa, topotecan, tretinoin, valrubicin, vinblastine, vincristine, vindesine, vinorelbine, dolasetron, granisetron; formoterol, fluticasone, leuprolide, midazolam, alprazolam, amphotericin B, podophylotoxins, nucleoside antivirals, aroyl hydrazones, sumatriptan; macrolides such as erythromycin, oleandomycin, troleandomycin, roxithromycin, clarithromycin, davercin, azithromycin, flurithromycin, dirithromycin, josamycin, spiromycin, midecamycin, leucomycin, miocamycin, rokitamycin, andazithromycin, and swinolide A; fluoroquinolones such as ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, alatrofloxacin, moxifloxacin, norfloxacin, enoxacin, grepafloxacin, gatifloxacin, lomefloxacin, sparfloxacin, temafloxacin, pefloxacin, amifloxacin, fleroxacin, tosufloxacin, prulifloxacin, irloxacin, pazufloxacin, clinafloxacin, and sitafloxacin; aminoglycosides such as gentamicin, netilmicin, paramecin, tobramycin, amikacin, kanamycin, neomycin, streptomycin, vancomycin, teicoplanin, rampolanin, mideplanin, colistin, daptomycin, gramicidin, colistimethate; polymixins such as polymixin B, capreomycin, bacitracin, penems; penicillins including penicillinase-sensitive agents such as penicillin G and penicillin V; penicillinase-resistant agents such as methicillin, oxacillin, cloxacillin, dicloxacillin, floxacillin, and nafcillin; gram negative microorganism active agents such as ampicillin, amoxicillin, and hetacillin, cillin, and galampicillin; antipseudomonal penicillins such as carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin; cephalosporins such as cefpodoxime, cefprozil, ceftbuten, ceftizoxime, ceftriaxone, cephalothin, cephapirin, cephalixin, cephradine, cefoxitin, cefamandole, cefazolin, cephaloridine, cefaclor, cefadroxil, cephaloglycin, cefuroxime, ceforamide, cefotaxime, cefatrizine, cephaetrile, cefepime, cefixime, cefonicid, cefoperazone, cefotetan, cefinetazole, ceftazidime, loracarbef, and moxalactam; monobactams such as aztreonam; and carbapenems such as imipenem, meropenem, pentamidine isethiouate, albuterol sulfate, lidocaine, metaproterenol sulfate, beclomethasone dipropionate, triamcinolone acetamide, budesonide acetone, fluticasone, ipratropium bromide, flunisolide, cromolyn sodium, and ergotamine tartrate; taxanes such as paclitaxel; SN-38, and tyrphostines.

Preferred small molecules for coupling to a polymeric reagent of the invention are those having at least one amino group. Preferred molecules include aminohippurate sodium, amphotericin B, doxorubicin, aminocaproic acid, aminolevulinic acid, aminosalicyclic acid,

metaraminol bitartrate, pamidronate disodium, daunorubicin, levothyroxine sodium, lisinopril, cilastatin sodium, mexiletine, cephalexin, deferoxamine, and amifostine.

Preferred peptides or proteins for coupling to a polymeric reagent of the invention include EPO, IFN-alpha, IFN-beta, IFN-gamma, consensus IFN, Factor VII, Factor VIII, Factor IX, IL-2, remicade (infliximab), Rituxan (rituximab), Enbrel (etanercept), Synagis (palivizumab), Reopro (abciximab), Herceptin (trastuzimab), tPA, Cerizyme (imiglucerase), Hepatitis-B vaccine, rDNAse, alpha-1 proteinase inhibitor, GCSF, GMCSF, hGH, insulin, FSH,an PTH.

**Table 1**

This table lists the SEQ ID NOs., names, sequences, and known or suspected therapeutic activities of various peptides described herein. The SEQ ID NOs. 1-301 describe sequences that are required to be provided with the Sequence Listing and are therefore appended with the instant Specification. In some instances, these peptides contain features that are either inconsistent with or not amenable to inclusion in the Sequence Listing. For example, a sequence with less than four-amino acids; a sequence with a D-amino acid; or certain modification that cannot be described in the Sequence Listing presently, and therefore are not provided in the Sequence Listing. However, for the ease of use and description, a SEQ ID NO. has been provided to these peptides (i.e., SEQ ID NOs: 302-469).

(-NH<sub>2</sub> indicates amidation at the C-terminus; Ac indicates acetylation; other modifications are as described herein and in the specification; SIN indicates Sequence Identification Number)

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
1	carperitide	ANP	SLRRSSCFGGRMDRIGAQSLGCSNFRY; human alpha-atrial natriuretic peptide; Atriopeptin-28 (human);	Cardio stimulant Respiratory
2	alpha-neoendorphin	Endorphin	H-Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys-OH	Analgesic, other
3	A-3847	Insulin	gi 386828 gb AAA59172.1  insulin [Homo sapiens] MALWMRLPLLALLALWGPDPAAAFVFNQHLCSHL VEALYLVCGERGFFYTPKTRAEEDLQVGQVELGGG PGAGSLQPLALEGSLQKRGIVEQCCTSICSLYQLENYC N	Antidiabetic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
4	A-4114	Insulin	MALWMRLPLLLALLALWGPDPAAAFVNQHLCSGSHLV EALYLVCGERGFFYTPKTRREAEDLQVGGVELGG	Antidiabetic
5	A-68552		GPGAGSLQPLALEGSLQKRKRGIVEQCCTSICSLYQLENY CN	Anorectic/Antiobesity
302 and 303	A-75998		[Ac-D-2NaI1-D-4ClPhe2-D-3Pal3-NMeTyr5-D-Lys(Nic)6-Lys(Isp)8-D-Ala10]GnRH; N-acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-seryl-N-methyltyrosyl-D-N(epsilon)-nicotinyllysyl-leucyl-N(epsilon)-isopropyllysyl-prolyl-alaninamide acetate	Releasing hormone Reproductive/gonadal, general
6	AN-1792	beta-amyloid peptide	g 8176533 gb AAB26264.2  beta-amyloid peptide precursor; beta APP [Homo sapiens] GSGLTNIKTEEIASEVKMDAEFRHDSGYEVHHQKLVFFA EDVGSNKGAIIGLMVGGVVVVIATVIIIIVMLK KQYTSNHHGVVE	Cognition enhancer
7	AAMP-1		MESESGAAADTPPLETLSFHGDEEIEVVELDPGPPD PDDL AQEMEDVDFEEEEEEEGNEEGWVLEPQEGVVG SMEGPDSEVTFALHSASVFCVSLDPKTNLAVTGGE DDKAFVWRLSDGELLFECAGHKDSVTCAGFSDSTLV	Anticoagulant Anti-inflammatory Immunological Anticancer, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			ATGDMGSLKVVWQVDTKEEVWSFEAGDLEWMEWH PRAPVLLAGTAGDNTWMWKVPNGDCKTFQGPNCPAT CGRVLPDGKRAVVGIEDGTIRIWDLKQGSPIHVLKGT EGHQPLTCVAANQDGSILITGSVDCQAKLVSATGK VVGFRPETVASQPSLGESESESNVESLGFCSVMPL AAVGYLDGTLAIYDLATQTLRHQCQHQSGIVQLLWEA GTAVVYTCSLDGIVRLWDARTGRLLTDYRGHTAEILDF ALSKDALVVTSTGDHKAKVFCVQRPDR	Vulnery
8	Exenatide	GLP-1	HEGTFTSDLKQMEEEAVRLFIEWLKNGGPSSGAPPP S	Antidiabetic Anorectic/Antiobesity
9	AC-625		Acetyl-ATQRLANELVRLQTYPRTNVGSNTY-NH <sub>2</sub>	Antihypertensive, renin system Symptomatic antidiabetic
10	ACTH		gi 80861463 ref NP_001030333.1  proopiomelanocortin preproprotein [Homo sapiens] MPRSCCSRSRSGALLLALLQASMEVRGWCESSQCQDL TTESNLLCIRACKPDLAETPMFPGNGDEQPLTENPR KYVMGHFRWDRFGRNRNSSSSGSSGAGQKREDVSAGE DCGPLPEGGPEPRSDGAKPGPREGKRSYSMEHFRWGK	Adrenal and pituitary disorders

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			PVGKRRPVKVPNGAEDESAEAFLEFKRELTGQRL REGDGPDDGAGAQADLEHSLLVAAEKKDEGPY RMEHFRWGSPPKDKRYGGFMTSEKSTPLVTLFKNAII KNAYKKGE	
11	AIDS therapeutic vaccine		gi 288842 emb CAA78890.1 V3 loop [Human immunodeficiency virus type 1] CTRPSNNTRKSIPVGP GKALYATGAIIGNIRQAHC	Therapeutic vaccine
12	AIDS therapy		gi 5081475 gb AAD39400.1 AF128998_1 gag [Human immunodeficiency virus type 1] MGARASVLSGGKLDKWEKIRLRPGGKKTYYLKHIVW ASRELERFAVNPGLLETGGGCKQILVQLQPSLQTGSEE LKSLYNAVATLYCVHQGIEVRDTKEALDKIEEEQNKSK KKAQQAADTGNSSQVSQNYPIVQNLQGGQMVHQAIS PRTLNAWVKVIEEKAFSPFVPMFSALSEGATPQDLNT MLNTVGGHQAAMQMLKETINEEAAEWDRLHPAHAG PNAPGQMPREPRGSDIAGTTSTLQEQIGWMTSNPPVPV GEYKRWIILGLNKIVRMYSPV SILDIRQGPKEPFRDYV DRFYKTLRAEQASQDVKNWMTETLLVQNANPDCKTI LKALGPAATLEEMMTACQGVGGPSPHKARILAEAMSQ	Antiviral, anti-HIV

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
13 and 14	Allotrap-2702		<p>VTSPANIMQRGNFRNQRKTIKCFNCGKEGHLARHC                      RAPRKKGCWKCGRGHQMKDCTERQANFLGKIWPS                      HKGRPGNFLQSRPEPTAPPEESFRFGEETTPPQKQEPL                      PSQKQETIDKDYPLASLSLFGNDPSLQ</p> <p>Allotrap 1258; Allotrap 2702; Allotrap E; Allotrap G;                      RDP58; peptide Bc-1ni;                      NLRIALR/RLAIRLN</p>	Immunosuppressant
15 and 16	Alzheimer's imaging agent		<p>H-                      DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV-OH; or                      H-                      DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVIA-OH</p>	Imaging agent
17	AM-425		<p>g 4504991 ref NP_002300.1  leukemia inhibitory factor (cholinergic differentiation factor) [Homo sapiens]                      MKVLAAGVVPLLLVHWHKGAGSPLPITPVNATCAIR                      HPCHNNLMNQIRSQLAQLNGSANALFILYTYAQGEPPF                      NNLDKLCGPNVTDPPPFHANGTEKAKLVELYRIVVYL                      GTSLGNITRDQKILNPSALSLSKLNATADILRGLLSNV</p>	Antiarthritic, immunological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
304	AN-238		LCRLCSKYHVGHVDTYGPDTSGKDVFKKKLGCQL LGKYKQIIAVLAQAF L-Threoninamide, N-[5-[2-[(2S,4S)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-(2,3-dihydro-1H-pyrrol-1-yl)-alpha-L-lyxo-hexopyranosyl]oxy]-2-naphthaceny]]-2-oxoethoxy]-1,5-dioxopentyl]-D-phenylalanyl-L-cysteiny]-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteiny]-, cyclic (2-7)-disulfide	Somatostatin Anticancer, hormonal
305	AV-9		[D-Arg]9-NH <sub>2</sub>	Antiviral, other
8	AZM-134	GLP-1	HGEFTTSDLKQMEEEAVRLFIEWLKNGGPSSGAPPP S	Anorectic/Antiobesity Antidiabetic
18	Addressin		gi 109633022 ref NP_570116.2  mucosal vascular addressin cell adhesion molecule 1 isoform a precursor [Homo sapiens] MDFGLALLLAGLLGLLLGQSLQVKPLQVEPPEPVAV ALGASRQLTCRLACADRASVQWRGLDTSLGAVQSD TGRSVLTVRNASLSAAGTRVVCVSGCGGRFTFQHTVQLL VYAFPDLTVSPAALVPGDPEVACTAHKVTVPDPNALS	Recombinant, other Anti-inflammatory

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
306	ambamustine		FSLVGGQLEGAQALGPEVQEEEEEPQGGDEDVLFVRV TERWRLPPLGTPVPALYCQATMRLPGLLESHRQAIPV LHSPTSPEPPDTSPEPDTSPEPDTSPEPDTSPEPDTSPE PPDKTSPEPAPQQGSTHTPRSPGSTRRRRPEISQAGPTQ GEVPTGSSKPAQDQLPAALWTSSAVLGLLLALPTYH LWKRCRHLAEDDTHPPASLRLLPQVSAWAGLRGTGQ VGISPS	Anticancer, alkylating Anticancer, antimetabolite
19	amylin antagonists		DTTVEPAPSCVTLYQSWRYSQADNGCAETVTVKVV YEDDTEGLCYAVAPGQITTVGDGYIGSHGHARYLARC L	Antidiabetic
20	anaritide analogues	ANP	g I178638 gb AAA35529.1  atrial natriuretic peptide MSSFSTTTVSFLLLLAFQLLQTRANPMPYNAVSNADL MDFKNLLDHLKEMPLEDEVVPPQVLSDPNNEEGAA LSPLPEVPPWTGEVSPAQRDGGALGRPWSSDRSAL LKSKLRALLTAPRSLRRSSCFGGRMDRIGAQSGLGCNS FRY	Antihypertensive, diuretic
21-28	anti-		As disclosed in U.S. Patent No. 5,470,831:	Anti-inflammatory

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
	inflammatory peptide		Thr-Thr-Ser-Gln-Val-Arg-Pro-Arg Val-Lys-Thr-Thr-Ser-Gln-Val-Arg-Pro-Arg. Ser-Gln-Val-Arg-Pro-Arg Val-Arg-Pro-Arg Thr-Thr-Ser-Gln-Val-Arg-Pro-Arg-His-Ile-Thr. Thr-Thr-Ser-Gln-Val Thr-Ser-Gln-Val-Arg Thr-Thr-Ser-Gly-Ile-His-Pro-Lys	Immunosuppressant Multiple sclerosis treatment Antiarthritic, other Stomatological Dermatological
307	antiinflammins		L-Leucine, N-[N-[N-[N-[N2-[N2-[N-(N-L-histidyl)-L-alpha-aspartyl)-L-methionyl]-L-asparaginy]-L-lysyl]-L-valyl]-L-leucyl]-L-alpha-aspartyl]-	Anti-inflammatory
308	antifungal tripeptides		tripeptides of N3-4-methoxyfumaryl and di- and tripeptides of N3-D-trans 2,3-epoxysuccinamoyl-L-2,3-diaminopropanoic acid	Antifungal
29	Gastrimmune		G17-DT; G17DT (vaccine); Gastrimmune; Glu-Gly-Pro-Trip-Leu-Glu-Glu-Glu-Glu-diphtheria toxoid; anti-gastrin 17 immunogen; gastrin 17 vaccine; gastrin-17-diphtheria toxoid conjugate	Anticancer, immunological
30	antithrombin		gi 312673 emb CAA51292.1  Hirudin [Hirudinaria	Antithrombotic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
	polypeptides		manillensis] MFSLKLFVFLAVCICVSAVSYTDCATESGQNYCLCV GGNLCGGGKHCEMDGSGNKCVDGEGTPKPKSQT EGDFEEDILN	Anticoagulant
31	antiviral peptides		NH <sub>2</sub> -Tyr-Ala-Gly-Ala-Val-Val-Asn-Asp-Leu-COOH	Antiviral, other
32	apolipoprotein		gi 671882 emb CAA28583.1  apolipoprotein [Homo sapiens] MKLLAATVLLLTICLEGALVRRQAKEPCVESLSQYF QTVTDYGKDLMEKVKSPQLQAEAKSYFEKSKE QLTPLIKKAGTELNVFLSYFVELGTHPATQ	Hypolipaeamic/Antiatherosc lerosis
33	arthritis antigen		gi 46369603 gb AAS89650.1  secreted antigen 8.5A precursor [Mycobacterium bovis BCG] MQLVDRVRGAVTGMRRLLVVGAVGAALVSGLVGAVG GTATAGAFSRPGLPVEYLQVPSPSMGRDIKVFQFQSGG ANSPALYLLDGLRAQDDDFSGWDINTPAFEWYDQSGLS VVMFVGGQSSFYSDWYQPACCGKAGCQTYKWETFLTS ELPGWLQANRHVKPTGSVVGLSMAASSALLTALYHP QQFVYAGAMSGLLDPSQAMGPTLIGLAMGDAGGYK ASDMWGPKEPAWQRNDPLLNVGKLIANNTRVWVY	Recombinant, other Antiarthritic, immunological Immunosuppressant

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
309	Avorelin		CGNGKPSDLGGNNLPAKFLLEGFVRTSNIKFDAYNAG GGHNGVDFDPDSGTHSWEYWG AQLNAMKPD LQRAL GATPNTGPAPQGA 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-2-methyl-D-tryptophyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide	Releasing hormone Anticancer, hormonal Menstruation disorders
310	B-956		N-[8(R)-Amino-2(S)-benzyl-5(S)-isopropyl-9-sulfanyl-3(Z),6(E)-nonadienoyl]-L-methionine	Anticancer, other
311	BCH-2687		L-Tyrosyl-D-arginyl-L-phenylalanyl-L-phenylalaninamide	Analgesic, other
34	BCH-2763		L-Leucine, D-phenylalanyl-L-prolyl-5-aminopentanoyl-5-aminopentanoyl-L-alpha-aspartyl-L-phenylalanyl-L-alpha-glutamyl-L-prolyl-L-isoleucyl-L-prolyl-; BCH-2763; Phe-Pro-(NH(CH <sub>2</sub> ) <sub>4</sub> CO) <sub>2</sub> -Asp-Phe-Glu-Pro-Ile-Pro-Leu; phenylalanyl-prolyl-(NH(CH <sub>2</sub> ) <sub>4</sub> CO) <sub>2</sub> -aspartyl-phenylalanyl-glutamyl-prolyl-isoleucyl-prolyl-leucine	Antithrombotic Anticoagulant
312	frakefamide		L-phenylalaninamide, L-tyrosyl-D-alanyl-4-fluoro-L-phenylalanyl-	Analgesic, other
313	BIM-22015		Glycinamide, D-alanyl-L-glutaminy-L-tyrosyl-L-phenylalanyl-L-arginyl-L-tryptophyl-	ACTH Neurological

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
35	BIM-26028		Pyroglutamyl-glutaminy-arginyl-leucyl-glycyl-asparaginy- glutaminy-tryptyl-alanyl-valyl-glycyl-histidiny-leucyl- leucyl-NH <sub>2</sub>	Releasing hormone Respiratory Anorectic/Antiobesity Anticancer, hormonal
314	BIM-44002		L-Tyrosinamide, L-phenylalanyl-L-norleucyl-L-histidyl-L- asparaginy-L-leucyl-D-tryptophyl-L-lysyl-L-histidyl-L- leucyl-L-seryl-L-seryl-L-norleucyl-L-alpha-glutamyl-L- arginyl-L-valyl-L-alpha.-glutamyl-L-tryptophyl-L-leucyl-L- arginyl-L-lysyl-L-lysyl-L-leucyl-L-glutaminy-L-alpha- aspartyl-L-valyl-L-histidyl-L-asparaginy-	Hormone Osteoporosis treatment
36	BIO-1211		L-Proline, N-((4-(((2- methylphenyl)aminocarbonyl)amino)phenyl)acetyl)-L- leucyl-L-alpha-aspartyl-L-valyl- ; BIO-1211; N-((4-(((2- methylphenyl)amino)carbonyl)amino)phenyl)acetyl)-leucyl- aspartyl-valyl-proline	Antiasthma GI inflammatory/bowel disorders Multiple sclerosis treatment
37	BPC-15		BPC 15; BPC-15; BPC-157; booly protection compound 15; L-Valine, glycyl-L-alpha-glutamyl-L-prolyl-L-prolyl-L- prolylglycyl-L-lysyl-L-prolyl-L-alanyl-L-alpha-aspartyl-L- alpha-aspartyl-L-alanylglycyl-L-leucyl-	Anti-inflammatory

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
315	bivalirudin		L-Leucine, D-phenylalanyl-L-prolyl-L-arginyl-L-prolylglycylglycylglycyl-L-asparaginyglycyl-L-alpha-aspartyl-L-phenylalanyl-L-alpha-glutamyl-L-alpha-glutamyl-L-isoleucyl-L-prolyl-L-alpha-glutamyl-L-tyrosyl-; D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycylglycylglycyl-glycyl-L-asparagyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucine trifluoroacetate (salt) hydrate	Anticoagulant Antianginal
38	bombesin antagonist		5-oxoPro-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-MetNH <sub>2</sub> [CAS], Bombesin 14; Bombesin Dihydrochloride; Dihydrochloride, Bombesin	Anticancer, other
39	brain natriuretic peptide	BNP	SPKMQGSGCFGRKMDRISSSSSGLGCKVLRH	COPD treatment, cardiac
41	C-peptide analogues	C-peptide	Glu-Ala-Glu-Asp-Leu-Gln-Val-Gly-Gln-Val-Glu-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser-Leu-Gln-Pro-Leu-Ala-Leu-Glu-Gly-Ser-Leu-Gln	Symptomatic antidiabetic Ophthalmological Neurological
316	C5a antagonist		Me-Phe-Lys-Pro-D-Cha-L-Cha-D-Phe	Anti-inflammatory
42	CBT-101		L-Cysteinamide, L-asparaginy-L-leucylglycyl-L-valyl-S-[(acetylamino)methyl]-, monoacetate	Antiglaucoma

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43	CCK(27-32)		Tyr(SO <sub>3</sub> )-Met-Gly-Trp-Met-Asp; CBZ-CCK (27-32)-NH <sub>2</sub> ; cholecystokinin (27-32) amide, benzoyloxycarbonyl-, D-Trp	Analgesic, obesity, other
44	CD4		CD4 (81-92), D-Ile; CD4 (81-92), D-Tyr; CD4 (81-92), D-Tyr,D-Cys,D-Glu(5); CD4(81-92); TYICEVEDQKEE; Thr-Tyr-Ile-Cys-Glu-Val-Glu-Asp-Gln-Lys-Glu-Glu; threonyl-tyrosyl-isoleucyl-cysteiny-glutamyl-valyl-glutamyl-aspartyl-glutaminy-l-lysyl-glutamyl-glutamic acid	Antiviral, anti-HIV
317	CEE-04-420		Lys-D-Pro-Thr and Lys-D-Pro-Val	Analgesic, other
45	CEP-079		gi 108796063 ref NP_001007140.2  insulin-like growth factor 2 isoform 1 precursor [Homo sapiens] MGIPMGKSMMLVLLTFLAFASCCIAAYRPSSETLCGGELV DTLQFVCGDRGFYFSRPASRVSRRGIVEEC CFRSCDLALLETYCATPAKSERDVSPTPTVLPDNFPRY PVGKFFQYDTWKQSTQRLRRGLPALRRRGGH VLAKELEAFREAKRRRLJALPTQDPAHGAPPEMAS NRK	Ophthalmological
318	mifamurtide		L-Alaninamide, N-(N-acetylmuramoyl)-L-alanyl-D-alpha-glutaminy-N-[4-hydroxy-10-oxo-7-[(1-oxohexadecyl)oxy]-3,5,9-trioxa-4-phosphapentacos-1-yl]-, P-oxide,	Anticancer, immunological

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46	CGRP analogues	CGRP	monosodium salt, (R)- ACDTATCVTHRLAGLLSRGGVVKNNFVPTNVGSKAF -NH <sub>2</sub>	Hormone Cardiovascular
47	rusalotide acetate		gi 4503635 ref NP_000497.1  coagulation factor II preproprotein [Homo sapiens] MAHVRGLQLPGCLALALCSLVHSQHVLAPQQARS LLQVRRRANTFLEEVRKGNLERECVEETCSYEEAFEA LESSTATDVFWAKYTACETARTPRDKLAACLEGNCAE GLGTNYRGHVNITRSGIECQLWRSRYPHKPEINSTTHP GADLQENFCRNPDSSTTGPWCYTDTPTVRRQECIPV CGQDQVTVAMTPRSEGSSVNLSPLEQCVPDRGQQYQ GRLAVTTHGLPCLAWASAQAKALSKHQDFNSAVQLVE NFCRNPDGDEEGVWCYVAGKPGDFGYCDLNYCEEAV EEETGDGLDESDRAIEGRATATSEYQTFNPRFTFGSGE ADCGLRPLFEKKSLEDKTERELLESYIDGRIVEGSDAEI GMSPWQVMLFRKSPQELLCGASLISDRWVLTAAHCLL YPPWDKNFTENDLLVRIGKHSRTRYERNIEKISMLEKI YIHPRYNWRENDRDIALMKLKKPVAFSDYIHPVCLP DRETAASLLQAGYKGRVTGWGNLKETWTANVKGKQ	Musculoskeletal Vulnerary Symptomatic antidiabetic Cardiovascular Anti-infective, other Ophthalmological

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48	CKS-17		PSVLQVNLPIVERPVCKDSTRIRITDNNMFCAGYKPDE GKRGDACEGDSGGPFVMSPFNNRWYQMGIWSWGE GCDRDGKYGFYTHVFRLLKWKVIDQFGE L-Leucine, L-leucyl-L-glutaminy-L-asparaginy-L-arginyl- L-arginylglycyl-L-leucyl-L-alpha-aspartyl-L-leucyl-L- leucyl-L-phenylalanyl-L-leucyl-L-lysyl-L-alpha- glutamylglycylglycyl- ; CKS-17; CKS-17 peptide	Immunosuppressant Anticancer, immunological
10	corticotropin acetate	corticotropin	gi 80861463 ref NP_001030333.1  proopiomelanocortin preproprotein [Homo sapiens] MPRSCCSRSGALLALLQASMEVRGWCLLESSQCQDL TTESNLLECIRACKPDLSAETPMFPGNGDEQPLTENPR KYVMGHRWDRFRRNSSSSGSSGAGQKREDVSAGE DCGPLPEGGPEPRSDGAKPGREGKRYSMEHFRWGK PVGKKRRPVK VYPNGAEDESAEAFLEFKRELTGQRL REGDGPDPADDGAGAQADLEHSLLVAAEKKDEGPY RMEHFRWGSPPKDKRYGGFMTSEKSTPLVTLFKNAII KNAYKKGE	Neuroprotective Asthma Anti-inflammatory
49	CT-112		L-Arginine, L-threonyl-L-threonyl-L-seryl-L-glutaminy-L- valyl-L-arginyl-L-prolyl- ; 5-(3-ethoxy-4-pentyloxyphenyl)-	Antiarthritic, immunological

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50	CTAP-III		2,4-thiazolidinedione phenylalanyl--cysteinyll--tyrosyl-tryptophyl-arginyl-threonyl-penicillaminyll-threoninamide; rCTAP-III-Leu-21 (des 1-15); somatostatin analog CTAP	Vulneryary Antiarthritic, other Musculoskeletal Recombinant, other
51	CVFM		Cys-Val-Phe-Met	Anticancer, other
52 and 53	calcitonin	calcitonin	CGNLSTCMLGTYTQDFNKFHTFPQTAIGVGAP (human) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH <sub>2</sub> (salmon)	Formulation, oral, other Hormone Osteoporosis treatment
54	calciseptine		sp P22947 TXCAS_DENPO Calciseptin OS=Dendroaspis polylepis polylepis PE=1 SV=1 RICYIHKASLPRATKTCVENTCYKMFIRTQREYISERGC GCPTAMWPYQTECCCKGDRCNK	Antihypertensive, other
52 and 53	calcitonin analogues	calcitonin	CGNLSTCMLGTYTQDFNKFHTFPQTAIGVGAP (human) H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH <sub>2</sub> (salmon)	Hormone Osteoporosis treatment
55	calphobindin I		gi 186680508 ref NM_001154.3  Homo sapiens annexin A5	Ophthalmological,

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			(ANXA5), MAQVLRGTVTDFPGRADERADAETLRKAMKGLGTDEE SILTLTSRNAQRQEISA AFKTLFGRDLLDDLLKSELTG KFEKLIVALMKPSRLYDAYELKHALKGAGTNEKVLTEI IASRTPEELRAIKQVYEEYGSSEDDVVGDTSYYQR MLVLLQANRDPDAGIDEAQVEQDAQALFQAGELK WGTDEEKFITFGTRSVSHLRKVFDKYM TISGFQIEETI DRETSGNLEQLLAVVKSIRSIPAYLAETLYAMKGAG TDDHTLIRVMVSRSEIDLNFNIRKEFRKNFATSLYSMIKG DTSGDYKKALLLCCGEDD	Vulnerary
319	cargutocin		1,6-Dicarboxytocin, 1-butanoic acid-7-glycine-	Labour inducer
320	casokefamide		L-Tyrosinamide, L-tyrosyl-D-alanyl-L-phenylalanyl-D-alanyl-	Antidiarrhoeal
56	cekropin-P		sp P14661 CECP1_PIG Cecropin-P1 OS=Sus scrofa PE=1 SV=1 SWLSKTAKKLENSAKKRISEGIAIAIQGGPR	Antibacterial, other
57	tasidotin hydrochloride		N,N-Dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-propyl-L-proline-tert-butylamide	Anticancer, other
58	ceruletide		Pyr-Gln-Asp-Tyr(SO3H)-Thr-Gly-Trp-Met-Asp-Phe-C(O)-	Analgesic, other

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	diethylamine		NH <sub>2</sub>	Gastroprokinetic
321	cetrotrelax acetate		D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N5-(aminocarbonyl)-D-ol-L-leucyl-L-arginyl-L-prolyl-	Fertility enhancer Prostate disorders Menstruation disorders Anticancer, hormonal
59	corticoliberin	corticoliberin	SQEPPISLDLTFHLLREVLEMTKADQLAQQAHSNRKLL DIA	Releasing hormone
322	D-22213		L-Histidinamide, N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-L-glutaminy-L-tryptophyl-L-alanyl-L-valylglycyl-N-[1-[[[1-(aminocarbonyl)-3-methylbutyl]amino]methyl]-3-methylbutyl]-, [1(R),6[S-(R*,R*)]]-, monoacetate	Anticancer, other
323	DAP inhibitors		L-AP-L-Ala and L-Ala-L-Ala-DL-AP;	Antibacterial, other
60	DP-640	insulin	L-Tyrosinamide, β-alanyl-L-arginylglycyl-L-phenylalanyl-L-phenylalanyl-, diacetate (salt)	Insulin Antidiabetic
61	DP-107		L-Leucine, L-methionyl-L-threonyl-L-leucyl-L-threonyl-L-valyl-L-glutaminy-L-alanyl-L-arginyl-L-glutaminy-L-leucyl-L-leucyl-L-seryl-L-glutaminy-L-isoleucyl-L-valyl-L-glutaminy-L-glutaminy-L-glutaminy-L-aspariny-L-	Antiviral, anti-HIV

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62	DU-728		asparaginy]L-leucyl-L-leucyl-L-arginyl-L-alanyl-L-isoleucyl-L-alpha.-glutamyl-L-alanyl-L-glutaminy]L-glutaminy]L-histidy]L-leucyl-L-leucyl-L-glutaminy]L-leucyl-L-threony]L-valyl-L-tryptophylglycyl-L-isoleucyl-L-lysyl-L-glutaminy]L-	Antithrombotic
63	Dynorphin A		Arg-Gly-Asp-Ser H-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln-OH	Analgesic, other Neuroprotective Dependence treatment
64	defensins		gi 181535 gb AAA52304.1  defensin precursor MRTLAILAAILLVALQAQEPLQARADEVAAPAEQIAA DIPEVVVSLAWDESLAPKHPGSRKKNMDCYCRIPACIA GERRYGTICYQGRLWAFCC	Antibiotic, other Antifungal Vulnerary
324	detirelix		D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-tyrosyl-N6-[bis(ethylamino)methylene]-D-lysyl-L-leucyl-L-arginyl-L-prolyl-	Releasing hormone Abortifacient Male contraceptive
65	disagregin		gi 545738 gb AAB30092.1  disagregin=fibrinogen receptor antagonist [Ornithodoros moubata=tick, salivary gland,	Antithrombotic Cardiovascular

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66 and 65	E-2078		Peptide, 60 aa] SDDKCCQGRPMYGCREDDDSVFGWTYDSNHGQCWKG SYCKHRRQPSNYFASQQECRNTCGA D-Leucinamide, N-methyl-L-tyrosylglycyl-L-phenylalanyl-L-leucyl-L-arginyl-N2-methyl-L-arginyl-N-ethyl- SDDKCCQGRPMYGCREDDDSVFGWTYDSNHGQCWKG SYCKHRRQPSNYFASQQECRNTCGA	Analgesic, other
67	ELS-1 ecallantide		Arg-Lys-Glu Glu-Ala-Met-His-Ser-Phe-Cys-Ala-Phe-Lys-Ala-Asp-Asp-Gly-Pro-Cys-Arg-Ala-Ala-His-Pro-Arg-Trp-Phe-Phe-Asn-Ile-Phe-Thr-Arg-Gln-Cys-Glu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Gln-Asn-Arg-Phe-Glu-Ser-Leu-Glu-Glu-Cys-Lys-Lys-Met-Cys-Thr-Arg-Asp	Immunostimulant, other Angioedema, Anti-inflammatory, Haemostatic, Antiarthritic, other
325	ES-1005		bis-(1-naphthyl)methylacetyl-His-Sta-Leu-E-Lys diHCl	Antihypertensive, renin system
326	efegatran		L-prolinamide, N-methyl-D-phenylalanyl-n-(4-((aminoiminomethyl)amino)-1-formylbutyl), (S)- gi 999146 gb AAB34627.1  elafin [Homo sapiens]	Antithrombotic Antianginal Respiratory

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69	derivatives		MRASSFLIVVFLIAGTLVLE H-Ala-Gln-Glu-Pro-Val-Lys-Gly-Pro-Val-Ser-Thr-Lys-Pro-Gly-Ser-Cys-Pro-Ile-Ile-Leu-Ile-Arg-Cys-Ala-Met-Leu-Asn-Pro-Pro-Asn-Arg-Cys-Leu-Lys-Asp-Thr-Asp-Cys-Pro-Gly-Ile-Lys-Lys-Cys-Cys-Glu-Gly-Ser-Cys-Gly-Met-Ala-Cys-Phe-Val-Pro-Gln-OH (Disulfide bonds between Cys16-Cys45, Cys23-Cys49, Cys32-Cys44, Cys38-Cys53)	COPD treatment Antiarthritic, other
70 and 52	elcatonin	calcitonin	Ser-Asn-Leu-Ser-Thr-Asn-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Val-Gly-Ala-Gly-Thr-Pro-NH <sub>2</sub> CGNLSTCMLGTYTQDFNKFHTFPQTAIGVGAP (human)	Hormone Osteoporosis treatment Analgesic, other
71	eledoisin		5-oxo-L-Pro-L-Ser-L-Lys-L-Asp-L-Ala-L-Phe-L-Ala-L-isoleucylglycyl-L-Leu-L-methionin-amide	Ophthalmological
3	encapsulated insulin	insulin	gi 386828 gb AAA59172.1  insulin [Homo sapiens] MALWMRLRLPLALLALWGPDPAAAFVNQHLCGSHLVE ALYLVCGGERGFFYTPKTRREAEDLQVQVELGGGPGA GSLQPLALEGSLQKRGIVEQCCTSIKSLYQLENYCN	Formulation, optimized, nanoparticles Insulin Antidiabetic
72	endorphin, β-		YGGFMTSEKSTPLVTLFKNAIKNAYKKGE	Analgesic, other
72	endorphin,		YGGFMTSEKSTPLVTLFKNAIKNAYKKGE	Analgesic, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
73	pancreatic endothelial cell growth factor		<p>gi 189701 gb AAA60043.1  endothelial cell growth factor</p> <p>MAALMTPGTGAPPAPGDFSGEGSQGLPDPSPPEPKQLP</p> <p>ELIRMKRDGGRLSEADIRGFVAAVVNGSAQGAQIGAM</p> <p>LMAIRLRGMDLEETSVLTLQALAQSGQQLEWPEAWRQ</p> <p>QLVDKHSTGGVGDVKVSLVLPALAAACGCKVPMISGR</p> <p>GLGHTGGTLDKLESIPGFNVIQSPEQMQLLDQAGCCI</p> <p>VGQSEQLVPADGILYAARDVVTATVDSLPLITASILSKKL</p> <p>VEGLSALVVVDVKFGGAAVFPNQEARELAKTLVGVG</p> <p>ASLGLRVA AALTAMDKPLGRCVGHAVEVEEALLCMD</p> <p>GAGPPDLRDLVTTLGGALLWLSGHAGTQAQGAARVA</p> <p>AALDDGSALGRFERMLAAQQGVDPGLARALCSGSPAE</p> <p>RRQLLPRAREQEELLAPADGTVELVRLALPLALVHEL</p> <p>GAGRSRAGEPLRLGVGAELLVDVGGQLRRRGTTPWLRV</p> <p>HRDGPALSQPQSRALQEALVLSDRAPFAAPSPFAELVL</p> <p>PPQQ</p>	Cardiovascular
74	eptifibatide		MAP-HAR-GLY-ASP-TRP-PRO-CYS-NH <sub>2</sub>	Antianginal Cardiovascular
327	examorelin	GHRP	L-Lysinamide, L-histidyl-2-methyl-D-tryptophyl-L-alanyl-L-	Releasing hormone

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
75	FG-005		tryptophyl-D-phenylalanyl-SMR1-QHNPR	Vulnery Cardiovascular Male sexual dysfunction
328	FR-113680		L-Phenylalaninamide, N-acetyl-L-threonyl-L-formyl-D-tryptophyl-N-methyl-N-(phenylmethyl)-	Antiasthma
76	fibronectin-related peptide		Gly-Arg-Gly-Asp-Ser	Anticancer, other
329	G-4120		L-Cysteine, N-(mercaptoacetyl)-D-tyrosyl-L-arginylglycyl-L-alpha-aspartyl-, cyclic (1-5)-sulfide, S-oxide	Antithrombotic
330	EP-51216		2S)-6-amino-2-[[[(2R)-2-[[[(2R)-2-(4-aminobutanoylamino)-3-(2-methyl-1H-indol-3-yl)propanoyl]amino]-3-(2-methyl-1H-indol-3-yl)propanoyl]amino]-3-(2-methyl-1H-indol-3-yl)propanoyl]amino]hexanamide	GH Releasing hormone Vulnery, endocrine
8	GLP-1 + exendin-4	GLP-1	HGEGTFTSDLKQMEEEAVRLFIEWLKNGGPSSGAPPP S	Antidiabetic
77	GM-1986		YYWIGIR	Anti-inflammatory
78	GnRH-associated	GnRH	gi 133908612 ref NP_001076580.1  gonadotropin-releasing hormone 1 precursor [Homo sapiens]	Antiprolactin Menstruation disorders

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	peptide		MKPIQKLLAGLILTWCVGCSQHWYSGLRPGGKRD AENLIDSFQEIVKEVGQLAETQRFECTTHQPRSPRLDL KGALESLIEEETGQKKI	Fertility enhancer
79	GRF1-44		gi 1103484 ref NP_066567.1  growth hormone releasing hormone preproprotein [Homo sapiens] MPLWVFFFVILTLNSSSHCSPPPLTLRMRRYADAIFTN SYRKV	Musculoskeletal
80	GRF	GHRF	gi 337133 gb AA52609.1  growth hormone releasing factor MPLWVFFFVILTLNSSSHCSPPPLTLRMRRYADAIFTN SYRKVGLQLSARKLLQDIMSRQQGESNQERGARL GRQVDSMWAEQKQMELESILVALLQKHRNSQG	Idiopathic growth hormone deficiency; cachexia
331	GYKJ-14451		L-Prolinamide, N-[(1,1-dimethylethoxy)carbonyl]-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-formylbutyl]-, (S)-	Antithrombotic
81	galanin		gi 1247490 emb CAA01907.1  galanin [Homo sapiens] MARGSALLLASLLLAALSASAGLWSPAKEKRGWTL NSAGYLLGPHAVGNHRFSFDKNGLTSKRELRPEDDMK PGSFDRSIPENNIMRTIIEFLSFLHLKEAGALDRLLDLPA AASSEDIERS	Releasing hormone

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82	gastrin antagonists		(benzyloxycarbonyl)-L-Glu-L-Ala-L-Tyr-Gly-L-Tyr-L-Met-L-aspartic acid amide	Antiulcer
332	glaspimod		N2,N2'-[2,7-Bis(pyroglutamyl-glutamyl-aspartylamino)-octanedioyl]bis(lysine)	Immunomodulator, anti-infective Immunostimulant, other Radio/chemoprotective
83	glicentin		gi 12598783 sp P01275.3 GLUC_HUMAN Glucagon precursor [Contains: Glicentin; Glicentin-related polypeptide (GRPP); Oxyntomodulin (OXY) (OXM); Glucagon; Glucagon-like peptide 1 (GLP-1); Glucagon-like peptide 1(7-37) (GLP-1(7-37)); Glucagon-like peptide 1(7-36) (GLP-1(7-36)); Glucagon-like peptide 2 (GLP-2)] MKSIYFVAGLFVMLVQGSWQRSIQDTEEKSRFSASQ ADPLSDPDQMNEKRRHSQGTFTSDYSKYLDSSRAQD FVQWLMNTKRNRRNNIAKRHDEFERHAEGTFTSDVSS YLEGQAAKEFIAWLVKGRGRRDFPEEVAIVEELGRRH ADGFSDEMNTILDNLAARDFINWLIQKITDRK	Insulin Antiulcer Antidiabetic
84	glucagon		H <sub>2</sub> N-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-	hypoglycemia Diagnostic

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84	glucagon	glucagon	Leu-Met-Asn-Thr-COOH His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr	Hypoglycemia
85	gonadorelin analogues	gonadorelin	gi 121522 sp P01148.1 GON1_HUMAN Progonadoliberin-1 precursor (Progonadoliberin I) [Contains: Gonadoliberin-1 (Gonadoliberin I) (Luteinizing hormone-releasing hormone I) (LH-RH I) (Gonadotropin-releasing hormone I) (GnRH-I) (Luliberin I) (Gonadorelin); GnRH-associated peptide I (GnRH-associated peptide I)] MKPIQKLLAGLILLTWCVEGCSSQHWSYGLRPGGKRD AENLIDSFQEIVKEVGQLAETQRFECTTHQPRSPRLDL KGALESLEEETGQKKI	Female contraceptive; enometiosis, uterine leiomyoma, precocious puberty, prostate and breast cancer
333	gonadorelin antagonist		[Ac-DNAL1(2),4FDPhe2,D-Trp3,D-Arg6]-LHRH	Female contraceptive; enometiosis, uterine leiomyoma, precocious puberty, prostate and breast cancer
86	gonadorelin	gonadorelin	5-oxo-L-His-L-Trp-L-Ser-L-Tyr-Gly-L-Leu-L-Arg-L-Pro-	Female contraceptive;

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			glycinamide	enometriosis, uterine leiomyoma, precocious puberty, prostate and breast cancer
334	goralatlade		L-Proline, 1-[N2-[N-(N-acetyl-L-seryl)-L- $\alpha$ -aspartyl]-L-lysyl]-	Haematological Immunological Radio/chemoprotective
335	H-142		L-Lysine, N2-[N-[N-[4-methyl-2-[[N-[N-[1-(N-L-prolyl-L-histidyl)-L-prolyl]-L-phenylalanyl]-L-histidyl]amino]pentyl]-L-valyl]-L-isoleucyl]-L-histidyl]-, (S)-	Antihypertensive, renin system
336	15B2		L-Tyrosinamide, N-methyl-L-valyl-N-[2-(4-hydroxyphenyl)-1-phosphonoethyl]-	Antihypertensive, renin system
87	iseganan hydrochloride		L-Argininamide, L-arginylglycylglycyl-L-leucyl-L-cysteinyl-L-tyrosyl-L-cysteinyl-L-arginylglycyl-L-arginyl-L-phenylalanyl-L-cysteinyl-L-valyl-L-cysteinyl-L-valylglycyl-, cyclic (5-14),(7-12)-bis(disulfide) hydrochloride	Antibacterial, other Antifungal Antiviral, other
88	netamiftide		L-Tryptophanamide, 4-fluoro-L-phenylalanyl-(4R)-4-hydroxy-L-prolyl-L-arginylglycyl-, bis(trifluoroacetate)	Antidepressant Anxiolytic

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337	icrocaptive		(salt) L-Arginine, glycyl-N2-ethyl-L-lysyl-L-prolyl-	Cardiovascular Septic shock treatment
338	icatibant		L-Arginine, D-arginyl-L-arginyl-L-prolyl-trans-4-hydroxy-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-D-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-(2 $\alpha$ ,3 $\alpha$ ,7 $\alpha$ )-octahydro-1H-indole-2-carbonyl-	Cardiovascular Hepatoprotective Vulnerary
339	AG-1776		3-[2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl]-5,5-dimethyl-N-(2-methylbenzyl)thiazolidine-4(R)-carboxamide	Antiviral, anti-HIV
340	pralmorelin		L-Lysinamide, D-alanyl-3-(2-naphthalenyl)-D-alanyl-L-alanyl-L-tryptophyl-D-phenylalanyl-	Diagnostic Releasing hormone
89	katacalcin	calcitonin	gi 115478 sp P01258.1 CALC_HUMAN Calcitonin precursor [Contains: Calcitonin; Katacalcin (Calcitonin carboxyl-terminal peptide) (CCP) (PDN-21)] MGFQKFSPFLALSILVLLQAGSLHAAPFRSALESSPADP ATLSEDEARLLLAALVQDYVQMKASELEQEEREGSS LDSPRSKRCGNLSTCMLGTYTQDFNKFHFTFPQTAIGV GAPGKKRDMSSDLERDHRPHVSMQPAN	Osteoporosis treatment Hormone Recombinant, other

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341	ketomethylurea s		N-[N-[3-benzoylamino-4-phenyl-2-oxobutyl]-N-methylaminocarbonyl]proline	Antihypertensive, renin system
90	L-346670		N-L-arginyl-8-L-methionine-21a-L-phenylalanine-21b-L-arginine-21c-L-tyrosine-	Antihypertensive, diuretic
91	L-364210		N-isovaleryl-L-histidyl-L-prolyl-L-phenylalanyl-L-histidyl-(3S,4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid)-L-leucyl-L-phenylalanylamide	Antihypertensive, renin system
342	L-659837		L-Phenylalanine, N-[2-(3-amino-2-oxo-1-pyrrolidinyl)-4-methyl-1-oxopentyl]-L-methionyl-L-glutamyl-L-tryptophyl-, cyclic (4-1)-peptide, [S-(R*,S*)]-	Analgesic, other
343	L-693549		5(S)-(tert-butoxycarbonylamino)-4(S)-hydroxy-N-[2(R)-hydroxyindan-1(S)-yl]-2(R)-[4-(3-hydroxypropyl)benzyl]-6-phenylhexamide	Antiviral, anti-HIV
344	L-709049		L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-(2-carboxy-1-formylethyl)-, (S)-	Anti-inflammatory
92	LDV-containing peptides		4-((N'-2-methylphenyl)ureido)phenylalanyl-leucyl-alpha-aspartyl-valyl-prolyl-alanyl-alanyl-lysine	Anticancer, other
	Lys-Phe		L-Phenylalanine, N-L-lysyl-	Haematological Antisickling

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
93	lagatide		D-Alaninamide, L-prolyl-L-valyl-L-threonyl-L-lysyl-L-prolyl-L-glutaminyll-	Antidiarrhoeal
94	laminin A peptide		seryl-isoleucyl-lysyl-valyl-alanyl-valinamide	Anticancer, other Neurological
95	laminin		tyrosyl-isoleucyl-glycyl-serylarginine	Anticancer, other
345	lanreotide	somatostatin	L-Threoninamide, 3-(2-naphthalenyl)-D-alanyl-L-cysteinyll-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyll-, cyclic (2-7)-disulfide ; L-Threoninamide, 3-(1-naphthalenyl)-D-alanyl-L-cysteinyll-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyll-, cyclic (2-7)-disulfide	Acromegaly Anticancer, hormonal Cardiovascular Antidiarrhoeal
346	leuprolide acetate		Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	Formulation, implant Anticancer, hormonal Menstruation disorders
347	MCI-826		Butanoic acid, 2,2-diethyl-4-[[3-[2-[4-(1-methylethyl)-2-thiazolyl]ethenyl]phenyl]amino]-4-oxo-, (E)-	Antiasthma
96	omiganan pentahydrochloride		L-lysineamide, L-isoleucyl-L-leucyl-L-arginyl-L-tryptophyll-L-prolyl-L-tryptophyl-L-tryptophyl-L-prolyl-L-tryptophyll-L-arginyl-L-tryptophyl-L-tryptophyll-L-tryptophyll-L-arginyl, pentahydrochloride	Peptide antibiotic
97-100	MBP		g 68509940 ref NP_001020272.1  Golli-mbp isoform 1	Multiple sclerosis

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			<p>[Homo sapiens]                      MGNHAGKRELNAEKASTNSETNRGESEKKNLNGELS                      RTTSEDNEVFGEADANQNNGTSSQDTAVTDSKRTADP                      KNAWQDAHPADPGSRPHLIRLFSRDAPGREDNTFKDR                      PSEDELQTIQEDSAATSESLDVMSAQKRPQRHGSKY                      LATASTMDHARHGFLPRHRDTGILDSIGRFFGGDRGAP                      KRGGKDSHHPARTAHYGSLPQKSHGRTQDENPVVHF                      FKNIVTPRTPPSQKGRGLSLRFSWGAEGQRPQFGY                      GGRADYKSAHKGFGVDAQGTLKIFKLGGRDSRS                      GSPMARR                      gi 68509938 ref NP_001020271.1  Golli-mbp isoform 2                      [Homo sapiens]                      MGNHAGKRELNAEKASTNSETNRGESEKKNLNGELS                      RTTSEDNEVFGEADANQNNGTSSQDTAVTDSKRTADP                      KNAWQDAHPADPGSRPHLIRLFSRDAPGREDNTFKDR                      PSEDELQTIQEDSAATSESLDVMSAQKRPQRHGSKY                      LATASTMDHARHGFLPRHRDTGILDSIGRFFGGDRGAP                      KRGGKVSSEE                      gi 68509930 ref NP_001020252.1  myelin basic protein</p>	<p>treatment                      Immunosuppressant</p>

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			isoform 1 [Homo sapiens] MASQKRPSQRHGSKYLATASTMDHARHGFLPRHRDT GILDSIGRFFGGDRGAPKRGSGKVPWLKGRSPLPSHA RSQGLCNMYKDSHHPARTAHYGSLPQKSHGRTQDE NPVVHFFKNIVTPPPSQGKGRGLSLRFSWGAEGQ RPFGEYGGRASDYKSAHKGFGKGVDAQGTLSKIFKLG GRDSRSGSPMARR gi 4505123 ref NP_002376.1  myelin basic protein isoform 2 [Homo sapiens] MASQKRPSQRHGSKYLATASTM	
348	MDL-104238		N-[4-(4-morpholinylcarbonyl)benzoyl]-L-valyl-N'- [3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-2- azetamide	Anti-inflammatory
349	MDL-28050		D-Glutamic acid, N-[N-[N-[N-[1-[N-[1-[N-(3- carboxy-1-oxopropyl)-L-tyrosyl]-L-alpha-glutamyl]-L- prolyl]-L-isoleucyl]-L-prolyl]-L-alpha-glutamyl]-L-alpha- glutamyl]-L-alanyl]-3-cyclohexyl-L-alanyl]-	Antithrombotic Anticoagulant
101	MMP inhibitors		FN 439; FN-439; H2N-C6H4-CO-Gly-Pro-Leu-Ala-NHOH; MMP-inhibitor I; p-NH <sub>2</sub> -Bz-Gly-Pro-D-Leu-D-Ala-NHOH	Antiarthritic, Anticancer, Anti-inflammatory

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
350	MR-988		N-pivaloyl-leucyl-gamma-aminobutyric acid	Antiepileptic
351	meritatie		Glycine, N-[N-[N-(mercaptoacetyl)glycyl]glycyl]-	Diagnostic
352	metkephamide		L-Methioninamide, L-tyrosyl-D-alanyl-glycyl-L-phenylalanyl-N2-methyl-, monoacetate (salt)	Analgesic, other
353	murabutide		D-Glutamine, N2-[N-(N-acetyl-muramoyl)-L-alanyl]-, butyl ester	Immunomodulator, anti-infective Anticancer, immunological Immunostimulant, other
354	muramyl dipeptide derivatives		D-alpha-Glutamine, N2-[N-(N-acetyl-muramoyl)-L-alanyl]-	Immunomodulator, anti-infective Anticancer, immunological Immunostimulant, other
355	NPY24-36		N-acetyl[Leu-28Leu-31]NPY24-36	Antihypertensive
102	NAGA		Asn-Ala-Gly-Ala	Analgesic, other
356	tiplimotide		L-Proline, D-alanyl-L-lysyl-L-prolyl-L-valyl-L-valyl-L-histidyl-L-leucyl-L-phenylalanyl-L-alanyl-L-asparagyl-L-isoleucyl-L-valyl-L-threonyl-L-prolyl-L-arginyl-L-threonyl-	Multiple sclerosis treatment
103	opebecan		gi 157276599 refNP_001716.2 bactericidal/permeability-increasing protein precursor [Homo sapiens]	Recombinant, other Antibacterial, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			<p>MRENMARGPCNAPRWASLMVLVAIGTAVTAAVNPGV  VVRISQKGLDYASQQGTAALQKELKRIKIPDYSDSFKI  KHLGKGHYSFYSDIREFQLPSSQISMVNPVGLKFSIS  NANIKISGKWKAQKRFLKMSGNFDLSIEGMSISADLK  LGSNPTSGKPTITCSSSSHINSVHVHISKSKVGVWLIQL  FHKKIESALRNKMNSQVCEKVTNSVSELQPYFQTLP  VMTKIDSVAGINYGLVAPPATTAETLDVQMKGEFYSEN  HHNPPFPAPPVMEFPAHDRMVYLGSLDYFFNTAGLV  YQEAGVLKMTLRDDMIPKESKFRLLTKFFGTFLPEVA  KKFPNMKIQIHVSASTPPHLSVQPTGLTFYPAVDVQAF  AVLPNSSLASLFLIGMHTTGSMEEVSAESNRLVGEKLD  RLLLELKHSNIGPFPVELLQDIMNYIVPILVLRVNEKL  QKGFPLPTPARVQLYNNVVLQPHQNFLFLFGADVYVK</p>	<p>GI inflammatory/bowel disorders  Vulnerary  Anti-inflammatory  Symptomatic antidiabetic  Ophthalmological</p>
104 and 105	liraglutide	GLP-1	<p>Glycine, L-histidyl-L-alanyl-L-alpha-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-valyl-L-seryl-L-tyrosyl-L-leucyl-L-alpha-glutamylglycyl-L-glutaminy-L-alanyl-L-alanyl-N6-[N-(1-oxohexadecyl)-L-gamma-glutamyl]-L-lysyl-L-alpha-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-</p>	<p>Antidiabetic  Anorectic/Antiobesity</p>

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
106	Nona CCK		L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-SFKIKHLGKGHYSFYSM DIREFQLPSSQISMV PNVGLKFSISNANIKISGKWKAKQRFLKMSGNFDLSIEGMSISADLKLGSNPTSGKPTITCSSSHINSVHVHISKSKVGWLIQLFHKKIESALRNKMNSQVCEKVT	Diagnostic Neuroleptic Anorectic/Antiobesity Antidepressant
107 and 108	NP-06		Cysteiny l-leucyl-glycyl-valyl-glycyl-seryl-cysteiny l-asparaginy l-aspartyl-phenylalanyl-alanyl-glycyl-cysteiny l-glycyl-tyrosyl-alanyl-isoleucyl-valyl-cysteiny l-phenylalanyl-tryptophan S-3.1-S-3.13:S-3.7-S-3.19-bis(disulfide)N-2.1-C-4.9-lactam NSVSELQPYFQTL PVMTKIDS VAGIN YGLVAPPATTAETL DVQMKGEFYSENHNNPPPFAPPVMEFPAA	Antiviral, anti-HIV
109	NPC-18545		Bradykinin, N2-D-arginyl-3-(trans-4-hydroxy-L-proline)-7-(D-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid)-8-[L-(2alpha,3aß,7a.beta.)-octahydro-1H-indole-2-carboxylic	Anti-inflammatory

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
110	Nva-FMDP		acid]- HDRMVYLGSDYFFNTAGLVYQEAGVLKMTLRDDMI PKESKFRLLTKFFGTFLPEVAKKFPNMKIQIHVS Nva-N3-4-methoxyfumaryl-L-2,3-diaminopropanoic acid ASTPPHLSVQPTGLTFYPVDVQAFVAVLPNSSLASFLI GMHTTGSMEVSAESNRLVGELKLDRLLELK	Antifungal
111	nacartocin		6-Carbaoxytocin, 1-(3-mercaptopropanoic acid)-2-(4-ethyl-L-phenylalanine)- HSNIGPPVELLQDIMNYIVPILVLP RVNEK LQKGFPLP TPARVQLYNVVLQPHQNFLFGADVYK	Hormone Labour inducer Antihypertensive, diuretic
112	natural peptide		U.S. Patent No. 5,288,708 Partial N terminal sequence: H <sub>2</sub> N-Gly-Glu-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-... --COOH	Antitumor Hepatoprotective Vulnerary Anti-inflammatory Antiparkinsonian Urological
39	nesiritide citrate	BNP	SPKMVQSGGCFGRKMDRISSSSSGLGCKVLRRH	Cardio stimulant Vasodilator, coronary
113-141	neurotrophic		U.S. Patent No. 5,545,719:	Cognition enhancer

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
	factors		<p>AspLeuGlnValPheVal; GlyGluLysLysAsp;                      AlaThrHisGluSer;                      CysLeuProValSerGly;LeuProValSerGlySer;                      ProCysHisAlaProPro; GlyGlyHisAspLeuGluSerGly;                      AspAspLeuGlnValPhe 15 ProLeuThrSerGly 15                      LeulleHisPheGluGluGlyVal 15 (2) INFORMATION FOR                      SEQ ID NO:11: (i) SEQUENCE CHARACTERISTICS: (A)                      LENGTH: 7 amino acids (B) TYPE: amino acid (D)                      TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v)                      FRAGMENT TYPE: internal (xi) SEQUENCE                      DESCRIPTION: SEQ ID NO:11: GlyGluPheSerTyrAspSer                      15 (2) INFORMATION FOR SEQ ID NO:12: (i)                      SEQUENCE CHARACTERISTICS: (A) LENGTH: 7 amino                      acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii)                      MOLECULE TYPE: peptide (v) FRAGMENT TYPE:                      internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:                      HisAlaProProLeuThrSer 15 (2) INFORMATION FOR SEQ                      ID NO:13: (i) SEQUENCE CHARACTERISTICS: (A)                      LENGTH: 7 amino acids (B) TYPE: amino acid (D)</p>	Neuroprotective

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			<p>TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v)                      FRAGMENT TYPE: internal (xi) SEQUENCE                      DESCRIPTION: SEQ ID NO:13: AspLeuGluSerGlyGluPhe                      15 (2) INFORMATION FOR SEQ ID NO:14: (i)                      SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino                      acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii)                      MOLECULE TYPE: peptide (v) FRAGMENT TYPE:                      internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:                      GlyGluPheSerValCysAspSer 15 (2) INFORMATION FOR                      SEQ ID NO:15: (i) SEQUENCE CHARACTERISTICS: (A)                      LENGTH: 10 amino acids (B) TYPE: amino acid (D)                      TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v)                      FRAGMENT TYPE: internal (xi) SEQUENCE                      DESCRIPTION: SEQ ID NO:15:                      LysLysGlyGluPheSerValAlaAspSer 1510 (2)                      INFORMATION FOR SEQ ID NO:16: (i) SEQUENCE                      CHARACTERISTICS: (A) LENGTH: 9 amino acids (B)                      TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE                      TYPE: peptide (v) FRAGMENT TYPE: internal (xi)</p>	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			<p>SEQUENCE DESCRIPTION: SEQ ID NO:16:                      LysLysGlyGluPheTyrCysSerArg 15 (2) INFORMATION FOR SEQ ID NO:17: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 13 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:                      GlyLeuArgValArgValTrpAsnGlyLysPheProLys 1510 (2) INFORMATION FOR SEQ ID NO:18: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 16 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:                      GlyValAlaPheGluGluAlaProAspHisSerPheLeuPhe 151015 (2) INFORMATION FOR SEQ ID NO:19: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 7 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:</p>	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			<p>GlyGlyHisAspLeuSerGly 15 (2) INFORMATION FOR SEQ ID NO:20: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:</p> <p>GlyGlyHisAspLeuGluSerGly 15 (2) INFORMATION FOR SEQ ID NO:21: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 14 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:</p> <p>GlyGlyHisAspLeuGluSerGlyGluPheSerTyrAspSer 1510 (2) INFORMATION FOR SEQ ID NO:22: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 14 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:</p> <p>GlyGlySerAspLeuSerGlyGluPheSerValCysAspSer 1510 (2)</p>	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			<p>INFORMATION FOR SEQ ID NO:23: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23: GlyGlySerAspLeuSerGlyGlyGluPheSerValCysAspSer 151015 (2) INFORMATION FOR SEQ ID NO:24: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24: GlyGlySerAspLeuSerGlyGlyGluPheSerValAlaAspSer 151015 (2) INFORMATION FOR SEQ ID NO:25: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 14 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25: GlyGlySerAspLeuSerGlyGlyGluPheSerValAlaAspSer 1510 (2) INFORMATION FOR SEQ ID NO:26: (i) SEQUENCE</p>	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			<p>CHARACTERISTICS: (A) LENGTH: 6 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26: GluThrLeuGlnPheArg 15 (2) INFORMATION FOR SEQ ID NO:27: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27: LysLysGluThrLeuGlnPheArg 15 (2) INFORMATION FOR SEQ ID NO:28: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28: GluThrLeuGlnPheArgLysLys 15 (2) INFORMATION FOR SEQ ID NO:29: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 9 amino acids (B) TYPE: amino acid (D)</p>	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
357	nifalotide		<p>TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v)</p> <p>FRAGMENT TYPE: internal (xi) SEQUENCE</p> <p>DESCRIPTION: SEQ ID NO:29: LysAlaSerThrThrThrAsnTyrThr 15</p> <p>L-Prolinamide, L-tyrosyl-4-(methylsulfinyl)-D-2-aminobutanoyl-glycyl-4-nitro-L-phenylalanyl-</p>	<p>Antidiarrhoeal</p> <p>Analgesic, other</p>
358	Org-2766		<p>L-Phenylalanine, 4-(methylsulfonyl)-L-2-aminobutanoyl-L-alpha-glutamyl-L-histidyl-L-phenylalanyl-D-lysyl-</p>	<p>ACTH</p> <p>Symptomatic antidiabetic</p> <p>Radio/chemoprotective</p> <p>Neurological</p>
359	Org-30035		<p>L-Phenylalanine, glycylglycyl-L-phenylalanyl-4-(methylsulfonyl)-L-2-aminobutanoyl-D-lysyl-</p>	<p>Neuroleptic</p> <p>Anxiolytic</p>
360	octreotide	somatostatin	<p>L-Cysteinamide, D-phenylalanyl-L-cysteinyll-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]-; L-Cysteinamide, D-phenylalanyl-L-cysteinyll-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-(2-hydroxy-1-(hydroxymethyl)propyl)-, cyclic (2-7)-disulfide, (R-(R*,R*))-</p>	<p>Acromegaly</p> <p>Antidiarrhoeal</p> <p>Anticancer, hormonal</p>

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
142	osteogenic growth peptide		Glycine, L-alanyl-L-leucyl-L-lysyl-L-arginyl-L-glutamylglycyl-L-arginyl-L-threonyl-L-leucyl-L-tyrosylglycyl-L-phenylalanylglycyl-	Osteoporosis treatment
143	P-113		Angiotensin II, 1-(N-methylglycine)-5-L-valine-8-L-alanine-[CAS]; (Sar(1),Ala(8))ANGII; (Sar1, Val5,Ala8)Angiotensin II; 1 Sar 8 Ala Angiotensin II; 1 Sarcosine 8 Alanine Angiotensin II; 1-Sar-8-Ala Angiotensin II; 1-Sar-8-Ala-angiotensin II; 1-Sarcosine-8-Alanine Angiotensin II; Acetate, Hydrated Saralasin; Angiotensin II, 1-Sar-8-Ala; Angiotensin II, 1-Sarcosine-8-Alanine; Anhydrous Saralasin Acetate; Hydrated Saralasin Acetate; P-113; P-113 Acetate; Sar Arg Val Tyr Val His Pro Ala; Sar-Arg-Val-Tyr-Val-His-Pro-Ala; Saralasin Acetate; Saralasin Acetate, Anhydrous; Saralasin Acetate, Hydrated; angiotensin II, Sar(1)-Ala(8)-angiotensin II, sarcosyl(1)-alanine(8)-	Stomatological Antibacterial, other Antifungal
361	PACAP 27		Pituitary adenylate cyclase-activating peptide-27	Antiviral, anti-HIV
362	PAPP		N-(dibenzoyloxphosphophionyl)-L-alanyl-L-prolyl-L-proline	Antihypertensive, other
363	PD-83176		CBZ-his-tyr(OBn)-ser(OBn)-trp-D-ala-NH <sub>2</sub>	Anticancer, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
364	PD-122264		N-[(1,1-dimethylethoxy)carbonyl]-alpha-methyltryptophyl-L-phenylalaninamide	Anorectic/Antiobesity Analgesic, other
365	PD-132002		DL-Serinamide, N-(4-morpholinylsulfonyl)-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]-O-methyl-3-oxo-, [1S-(1R*,2S*,3R*)]-	Antihypertensive, renin system
144	Penetratin		U.S. Patent Nos. 5,888,762 and 6,080,762; PCT Pub. Nos. WO/2000/29427 and WO/2000/01417: NH <sub>2</sub> -Arg Lys Arg Gly Arg Gln Thr Tyr Thr Arg Tyr Gln Thr Leu Glu Leu Glu Lys Glu Phe His Phe Asn Arg Tyr Leu Thr Arg Arg Arg Arg Ile Glu Ile Ala His Ala Leu Cys Leu Thr Glu Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys Glu Asn-COOH.	Formulation technology
366	PL-030		Glycinamide, L-tyrosyl-L-prolyl-N-methyl-L-phenylalanyl-D-prolyl-	Analgesic, other
367	POL-443		Z-prolyl-leucyl-tryptophan	Antihypertensive, renin system
368	POL-509		L-Tryptophan, N-[N-(5-oxo-L-prolyl)-L-leucyl]-, methyl ester-	Immunostimulant, other
369	PPA		D-phenylalanine-L-proline-L-arginylchloromethane	Anticoagulant

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
145	PR-39		L-Prolinamide, L-arginyl-L-arginyl-L-arginyl-L-prolyl-L-arginyl-L-prolyl-L-prolyl-L-tyrosyl-L-leucyl-L-prolyl-L-arginyl-L-prolyl-L-phenylalanyl-L-phenylalanyl-L-prolyl-L-arginyl-L-leucyl-L-prolyl-L-arginyl-L-isoleucyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-prolyl-L-arginyl-L-phenylalanyl-L-prolyl-L-arginyl-L-phenylalanyl-	Diagnostic Antithrombotic Antibacterial, other
146	tigapotide triflutate		L-Threonine, L-alpha-glutamyl-L-tryptophyl-L-glutaminyll-threonyl-L-alpha-aspartyl-L-asparaginyll-S-[(acetylamino)methyl]-L-cysteinyll-L-alpha-glutamyl-L-threonyll-S-[(acetylamino)methyl]-L-cysteinyll-L-tyrosyl-L-alpha-glutamyl-, mono(trifluoroacetate)	Anticancer, other
370	PT-14		L-Lysinamide, N-acetyl-L-norleucyl-L-alpha-aspartyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-, cyclic (2-7)-peptide	Male sexual dysfunction Female sexual dysfunction
147	PT-5	somatostatin	gi 21619156 gb AAH32625.1  Somatostatin [Homo sapiens]	Anticancer, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
148	semparatide	PTHrP	<p>MLSCRLQCALAALSIVLALGCVTGAPSDPRLRQFLQK                      SLAAAAGKQELAKYFLAELLSEPNQTENDALEPEDLS                      QAAEQDEMRLQLRSANSNPAMAPRERKAGCKNFFW                      KTFTSC</p> <p>gi 131542 sp P12272.1 PTHR_HUMAN Parathyroid hormone-related protein precursor (PTH-rP) (PTHrP) [Contains: PTHrP[1-36]; PTHrP[38-94]; Osteostatin (PTHrP[107-139])]</p> <p>MQRRLVQQWSVAVFLLSYAVPSCGRSVEGLSRRLLKRA                      VSEHQLLHDKGKSIQDLRRRFFLHLLIAEIHAEIRATS                      EVSPNSKPSNTKNHPVFGSDDEGRYLTQETNKVETY                      KEQPLKTPGKKKKGKPGKRKKEKRRRTRSAWLDS                      GVTGSGLEGDHLSDTSTTSLELDSRRH</p>	<p>Hormone</p> <p>Osteoporosis treatment</p>
149	parathyroid hormone fragments	PTH	<p>SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF</p>	<p>Osteoporosis treatment</p>
150	enfuvirtide		<p>L-Phenylalaninamide, N-acetyl-L-tyrosyl-L-threonyl-L-seryl-L-leucyl-L-isoleucyl-L-histidyl-L-seryl-L-leucyl-L-isoleucyl-L-alpha-glutamyl-L-alpha-glutamyl-L-seryl-L-</p>	<p>Antiviral, anti-HIV</p>

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
151	pentapeptide 6A		glutamyl-L-asparagyl-L-glutamyl-L-glutamyl-L-alpha-glutamyl-L-lysyl-L-asparagyl-L-alpha-glutamyl-L-glutamyl-L-alpha-glutamyl-L-leucyl-L-alpha-glutamyl-L-leucyl-L-alpha-aspartyl-L-lysyl-L-tryptophyl-L-alanyl-L-seryl-L-leucyl-L-tryptophyl-L-asparagyl-L-tryptophyl-	Vasodilator, coronary
371	pentigetide		Ala-Arg-Pro-Ala-Lys  L-Arginine, N2-[1-[N-(N-L-alpha-aspartyl-L-seryl)-L-alpha-aspartyl]-L-prolyl]-	Antiallergic, non-asthma Ophthalmological Antiasthma
372	peptide analogues		N1,N3-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(2-methoxyacetamido)-N1-methylisophthalamide	Ophthalmological Antiarthritic, other Antiulcer Antihypertensive, other Multiple sclerosis treatment COPD treatment
373	peptide G		[Arg(6),D-Trp(7,9),MePhe(8)]substance P	Anticancer, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
374	peptide T analogue		D-Ala1-peptide T	Antiviral, anti-HIV
375	peptide T		L-Threonine, N-[N-[N2-[N-[N-(N-L-alanyl-L-seryl)-L-threonyl]-L-threonyl]-L-threonyl]-L-asparaginy]-L-tyrosyl]-	Analgesic, other Antiviral, other Antiarthritic, other GI inflammatory/bowel disorders Anti-inflammatory
152	pramlintide		1,2-Dithia-5,8,11,14,17-pentaazacycloicosane, cyclic peptide derivative U.S. Patent No. 5,998,367 gi 10066209 gb AAE39671.1  Sequence 1 from patent US 5998367 KCNTATCATQRLANFLVHSSNNFNGAILSSSTNVGSNTY;	Antidiabetic Anorectic/Antiobesity
376	pranlukast		Benzamide, N-[4-oxo-2-(1H-tetrazol-5-yl)-4H-1-benzopyran-8-yl]-4-(4-phenylbutoxy)-; 8-(4 (4-phenylbutoxy)benzoyl)amino-2-(tetrazol-5'-yl)-4-oxo-4H-1-benzopyran	Antiasthma Antiallergic, non-asthma
3	proinsulin	proinsulin	gi 59036749 gb AAW83741.1  proinsulin [Homo sapiens]	Antidiabetic

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377	protirelin	TRH	MALWMRLPLLALLALWGPDPAAAFVNQHLCGSHLV EALYLVCGERGFFYTPKTRREAEDLQVGQVELGGGPG AGSLQPLALEGSLQKRGIVEQCCTSICSLYQLENYCN L-Prolinamide, 5-oxo-L-prolyl-L-histidyl- ; 2-Nle-3-Prot- protirelin; TRH, Nle(2)-Prot(3)-; pyroglutamyl-norleucyl- proline thioamide	Releasing hormone Diagnostic
378	protirelin	TRH	prolinamide, 5-oxo-L-prolyl-L-histidyl-	Releasing hormone Cognition enhancer
153	Ro-25-1553		L-Threoninamide, N-acetyl-L-histidyl-L-seryl-L-alpha- aspartyl-L-alanyl-L-valyl-L-phenylalanyl-L-threonyl-L- alpha-glutamyl-L-asparaginyll-L-tyrosyl-L-threonyl-L-lysyl- L-leucyl-L-arginyl-L-lysyl-L-glutaminyll-L-norleucyl-L- alanyl-L-alanyl-L-lysyl-L-tyrosyl-L-leucyl-L- asparaginyll-L-alpha-aspartyl-L-leucyl-L-lysyl-L- lysylglycylglycyl-, (25-21)-lactam	Antiasthma Anti-inflammatory
379	RWJ-51438		N-methylphenylalanyl-N-(4-(aminoiminomethyl)amino)-l- (((6-carboxy-2-benzothiazolyl)carbonyl)butyl)prolinamide	Antithrombotic
380	TRH	TRH	L-Prolinamide, 5-oxo-L-prolyl-L-histidyl-3,3-dimethyl- ; pyroGlu-His-Pro-NH <sub>2</sub> (or 5-oxo-L-prolyl-L-histidyl-L-	Diagnostic Thyroid hormone

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
154	renin inhibitors		prolinamide)	Releasing hormone
381	romurtide		Boc-Leu-Lys-Arg-Met-Pro-OMe L-Lysine, N2-[N2-[N-(N-acetylmuramoyl)-L-alanyl]-D-alpha-glutamyl]-N6-(1-oxooctadecyl)- ; L-Lysine, N2-(N2-(N-(N-acetylmuramoyl)-L-alanyl)-D-alpha-glutamyl)-N6-(1-oxooctadecyl)-	Radio/chemoprotective Immunostimulant, other
382	S-17162		L-Tryptophan, N-[(2,3-dihydroxypropoxy)hydroxyphosphinyl]-L-leucyl-, disodium salt	Urological
383	S-2441		L-Argininamide, D-prolyl-L-phenylalanyl-N-heptyl-	Antimigraine Antigout Septic shock treatment
384	SDZ-CO-611	somatostatin	L-Cysteinamide, N-(1-deoxy-4-O-.alpha.-D-glucopyranosyl-D-fructopyranos-1-yl)-D-phenylalanyl-L-cysteiny-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2.fwdarw.7)-disulfide, [R-(R*, R*)]-	Somatostatin
385	SK&F-101926		L-Argininamide, O-ethyl-N-[(1-mercaptocyclohexyl)acetyl]-D-tyrosyl-L-phenylalanyl-L-valyl-L-asparaginy-L-	Antihypertensive, diuretic

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386	SK&F-110679		cysteiny-L-prolyl-, cyclic (1-5)-disulfide His-D-Trp-Ala-Trp-D-Phe-LysNH <sub>2</sub>	Releasing hormone Vulnerary
387	edotreotide		[N-[2-[4,7-Bis[(carboxy-kappaO)methyl]-10-(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl-kappaN1,kappaN4,kappaN10]acetyl]-D-phenylalanyl-L-cysteiny-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteiny-L-threoninol cyclic (2-7)-disulfidato(3-)]yttrium	Anticancer, hormonal
155	SP-1		pGlu-Glu-Asp-Cys-Lys	Anticancer, other
156	SPAAT		L-Lysine, L-methionyl-L-phenylalanyl-L-leucyl-L-alpha-glutamyl-L-alanyl-L-isoleucyl-L-prolyl-L-methionyl-L-seryl-L-isoleucyl-L-prolyl-L-alpha-glutamyl-L-valyl-L-lysyl-L-phenylalanyl-L-asparaginy-L-lysyl-L-prolyl-L-phenylalanyl-L-valyl-L-phenylalanyl-L-leucyl-L-methionyl-L-isoleucyl-L-alpha-glutamyl-L-asparaginy-L-threonyl-L-lysyl-L-seryl-L-prolyl-L-leucyl-L-phenylalanyl-L-methionylglycyl-L-lysyl-L-valyl-L-valyl-L-asparaginy-L-prolyl-L-threonyl-L-glutaminy-	COPD treatment
388	SR-41476		Z-Tyr-Val-Sta-Ala-Sta-OMe	Antiviral, anti-HIV

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
389	SR-42128		1-[N-(3-methyl-1-oxobutyl)-L-phenylalanine]-2-L-norleucine-	Antihypertensive, renin system
157	SR-42654		isoval-phe-norleu-sta-ala-sta-lys	Antihypertensive, renin system
147	SRIF-A	somatostatin	gi 21619156 gb AAH32625.1  Somatostatin [Homo sapiens] MLSCRLQCALAALSIVLALGCVTGAPSDPRLRQFLQK SLAAAAGKQELAKYFLAELLSEPNQTENDALEPEDLS QAAEQDEMRLQLRSANSNPAMAPRERKAGCKNFFW KTFTSC	Somatostatin Haemostatic Alimentary/Metabolic, other
158	calcitonin	calcitonin	8-D-tryptophan-14-D-cysteinesomatostatin (sheep) CSNLSTCVLGKLSQELHKLQTYPRNTGSGTP	Osteoporosis treatment
390	salmon calcitonin	calcitonin	11,18-Arg-14-Lys-salmon calcitonin; 11,18-arginyl-14-lysine-salmon calcitonin; Arg-Lys-Arg-CT; calcitonin, salmon, arginyl(11,18)-lysine(14)-	Osteoporosis treatment
159	sermorelin		Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH <sub>2</sub>	Idiopathic growth hormone deficiency Imaging agent
391	saralasin acetate		1-Sar-8-Ala-angiotensin; Angiotensin II, 1-(N-	Antihypertensive, renin



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164	PTR-3173	somatostatin	NSYRKVLGQLSARKLLQDIMSRQQGESNQERGARAR LGRQVDSMWAEQKQMELESILVALLQKHSRNSQG Cyclic[(R)-βMeNphe-Phe-DTrp-Lys-Thr-Phe], MPLWVFFFVILTLSNSSHCSPPPPLTLRMRRYADAIFTN SYRKVLGQLSARKLLQDIMSRQQGESNQERG	Acogaly Symptomatic antidiabetic Ophthalmological Urological Anticancer, hormonal
165	somatostatin analogue	somatostatin	des-(Ala1,Gly2)-(D-Trp8,D-Asu(3,14))-somatostatin, ARARLGRQVDSMWAEQKQMELESILVALLQKHSRNS QG	Acromegaly Antidiabetic Diagnostic
392	somatostatin analogues	somatostatin	cyclo-(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe)-somatostatin	Acromegaly Antidiabetic
393	somatostatin	somatostatin	3,14-Dicarbomatostatin, 1-de-L-alanine-2-deglycine-3- butanoic acid-11-L-tyrosine-	Acromegaly
394	somatostatin	somatostatin	3,14-Dicarbomatostatin, 1-de-L-alanine-2-deglycine-3- butanoic acid-11-L-tyrosine-	Acromegaly
395	syndyphalin		Glycinamide, L-tyrosyl-4-(methylsulfinyl)-D-2- aminobutanoyl-N-methyl-N-(2-phenylethyl)-	Analgesic, other
166	synthetic		gi 109948285 ref NP_001035971.1  poly(A) binding protein,	Antiulcer

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	peptide BPC		cytoplasmic 1-like 2B [Homo sapiens] MASLYVGDHLHPEVTEAMLYEKFPAGPILSIRICRDKIT RRLGYAYVNYQQPVDAKRALETNFDVVIKG RPVRIMWSQRDPSLRKSGVGNVFIKNLGKTIDNKALY NIFSAFGNILSCKVACDEKPKGYGVHFQKQE SAERAIDVMNGMFLNYRKIFVGRFKSHKEREAEERGA WARQSTSADVKDFEEDTDEEATLR	Hepatoprotective Vulneryary Anti-inflammatory Antiparkinsonian Musculoskeletal
167	T22		L-Argininamide, L-arginyl-L-arginyl-L-tryptophyl-L-cysteiny-L-tyrosyl-L-arginyl-L-lysyl-L-cysteiny-L-tyrosyl-L-lysylglycyl-L-tyrosyl-L-cysteiny-L-tyrosyl-L-arginyl-L-lysyl-L-cysteiny-, cyclic (4-17),(8-13)-bis(disulfide)	Antiviral, anti-HIV
396	Tc-99m depreotide		Technetium-99Tc, (cyclo(L-homocysteiny-L-N-methyl-L-phenylalanyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl) (1-1')-thioether with 3-((mercaptoacetyl)amino)-L-alanyl-L-lysyl-L-cysteiny-L-lysynamidato(3-))oxo-, (SP-5-24)-	Imaging agent
397	Tc-99m-P280		13, 13'-[Oxybis[methylene(2,5-dioxo-1,3-pyrrolidinediyl)]]bis[N-(mercaptoacetyl)-D-tyrosyl-S-(3-aminopropyl)-L-cysteinyglycyl-L-alpha-aspartyl-L-cysteinyglycylglycyl-S-[(acetylamino)mehtyl]-L-	Imaging agent Antithrombotic

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398	TEI-1345		cysteinyglycyl-S-[(acetylamino)methyl-L-cysteinyglycylglycyl-L-cysteinamide], cyclic (1 --> 5), (1' --> 5'), -bis(sulfide)	Anti-inflammatory
168	THF		(7E)-8-(2-naphthyl)-5,6-trans-5,6-methano-7-octenyl 3-(3,4-dimethoxyphenyl)-2-propenoate Leu-Glu-Asp-Gly-Pro-Lys-Phe-Leu;leucyl-glutamyl-aspartyl-glycyl-proly-lysyl-phenylalanyl-leucine	Immunomodulator, anti-infective, Immunostimulant, anti-AIDS
169	Theradigm-HBV		Dipalmitoyl-Lys-Ser-Ser-Gln-Tyr-Ile-Lys-Ala-Asn-Ser-Lys-Phe-Ile-Gly-Ile-Thr-Glu-Ala-Ala-Phe-Leu-Pro-Ser-Asp-Phe-Phe-Pro-Ser-Val-OH	Immunomodulator, anti-infective Immunostimulant
80	tesamorelin acetate	GHRF	gi 337133 gb AAA52609.1  growth hormone releasing factor MPLWVFFFVILTLNSSSHCSPPPPLTLRMRRYADAIFTN SYRKVLGQLSARKLLQDIMSRQQGESNQERGARARL GRQVDSMWAEQKQMELESILVALLQKHRNSQG (3E)-Hex-3-enoylsomatoliberin (human) acetate (salt)	Musculoskeletal, COPD, Hypnotic/Sedative, Immunostimulant, Antidiabetic, Anabolic, Symptomatic antidiabetic, Vulnerary
170	TP-9201		L-Cysteinamide, N-acetyl-L-cysteinyl-L-asparaginyl-L-	Neuroprotective,

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			prolyl-L-arginylglycyl-L-alpha-aspartyl-O-methyl-L-tyrosyl-L-arginyl-, cyclic (1-9)-disulfide	Antithrombotic, Antianginal, Cardiovascular
399	TRH analogues	TRH	pyroGlu-His-Pro-NH <sub>2</sub> (or 5-oxo-L-prolyl-L-histidyl-L-prolinamide)	Cognition enhancer
400	TT-235		[β,β-(3-Thiapentamethylene)-β-sulfany]propionic acid, D-Trp2, Pen6, Arg8]-oxytocin acetate	Labour inhibitor
401	tabilautide		L-Lysinamide, 6-carboxy-N6-[N-(1-oxododecyl)-L-alanyl]-D-gamma-glutamyl]-, (S)-	Immunomodulator, anti-infective Radio/chemoprotective Immunostimulant, other
171 and 172	terlipressin		N-[N-(N-glycylglycyl)glycyl]-8-L-lysine- ; Gly-Gly-Gly-8-Lys-vasopressin; N-(alpha)-glycyl-glycyl-8-lysine vasopressin; Gly-Gly-Gly-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH <sub>2</sub> ; N-(N-(N-glycylglycyl)glycyl)-8-L-lysinevasopressin	Haemostatic; GI bleeding
171 and 172	terlipressin		N-[N-(N-glycylglycyl)glycyl]-8-L-lysine- ; Gly-Gly-Gly-8-Lys-vasopressin; N-(alpha)-glycyl-glycyl-8-lysine vasopressin; Gly-Gly-Gly-c[Cys-Tyr-Phe-Gln-Asn-Cys]-	Haemostatic; GI bleeding

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
402	teverelix		Pro-Lys-Gly-NH <sub>2</sub> D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N6-(aminocarbonyl)-D-lysyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl-	Anticancer, hormonal Prostate disorders Menstruation disorders Fertility enhancer Male contraceptive
403	thymopentin		L-Tyrosine, N-[N-(N2-L-arginyl-L-lysyl)-L-alpha-aspartyl]-L-valyl]- ; L-Tyrosine, N-(N-(N2-L-arginyl-L-lysyl)-L-alpha-aspartyl)-L-valyl)-	Immunostimulant, other Immunomodulator, anti-infective
404	triletide		L-Histidine, N-[N-(N-acetyl-L-phenylalanyl)-L-phenylalanyl]-, methyl ester	Antitumor
405	tuftsin		L-Arginine, N2-[1-(N2-L-threonyl-L-lysyl)-L-prolyl]-	Anticancer, immunological Immunostimulant, other
173	Uroguanylin		Guanylin (rat reduced), 1-L-glutamine-2-L-glutamic acid-3-L-aspartic acid-6-L-leucine-8-L-isoleucine-9-L-asparagine-10-L-valine-	Alimentary/Metabolic, other Antidiarrhoeal Diagnostic
174	VIC		gi 6681267 refNP_031929.1 endothelin 3 [Mus musculus] MEPGLWLLGLTVTSAAGLVPCPQSGDGRASVSQGP	Gastroprokinetic

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175	VIP derivative		<p>PEAGSERGCEETVAGPGERIVSPTVALPAQESAGQER                      AGRSGKQEDKGLPAHHRPRRCTCFTYKDKCECVYYC                      HLDIIWINTPEQTPYGLSNYRESLRKRS LGPVPESSQ                      PSPWTRLRRCM GADDKACAHFCA RTRDVTSYSGRA                      ERPAAEEMRETGGPRQLMSRTDKAHRP</p> <p>gi 5803023 ref NP_006807.1  lectin, mannose-binding 2                      [Homo sapiens]                      MA AEGWIWRWGWGRRCLGRPGLLGP GPPTPLFLL                      LLLGSVTADITDGNSEHLKREHSLIKPYQGVGSSSMPL                      WDFQGSTMLTSQYVRLTPDERSKEGIWNHQPCFLKD                      WEMHVHFKVHGTGKKNLHGDGIALWYTRDRRLVPGP                      VFGSKDNFHGLAIFLDTPNDETTERTVFPYISVMVNNG                      SLSYDHSKDRWTELAGCTADFRNRDHD TFLAVRYSR                      GR LTVMTDLEDKNEWKNCIDITGVRLPTGY YFGASAG                      TGD LSDNHDIISMKLFQLMVEHTPDEESIDWTKIEPSV                      NFLKSPKDNVDDPTGNFRSGPLTGW RVFLLLCALLGI                      VVCAVVGAVVFQKRQERNKRFY</p>	<p>Antiasthma                      Vasodilator, peripheral</p>
147	vapreotide, immediate-	somatostatin	<p>gi 21619156 gb AAH32625.1  Somatostatin [Homo sapiens]                      MLSCR LQCALAALSIVLALGCVTGAPSDPRLRQLQK</p>	<p>Formulation, modified-                      release, immediate</p>

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	release		SLAAAAGKQELAKYFLAELLSEPNQTENDALEPEDLS QAAEQDEMRLQLRSANSNPAMAPRERKAGCKNFFW KTFTSC L-Tryptophanamide, D-phenylalanyl-L-cysteiny-L-tyrosyl- D-tryptophyl-L-lysyl-L-valyl-L-cysteinyL-, cyclic (2-7)- disulfide-	Somatostatin Haemostatic Anticancer, hormonal Antidiarrhoeal GI inflammatory/bowel disorders
406	Pharmaprojects No. 1269		L-Proline, 1-[N-[N-[1-[4-(4-hydroxyphenyl)-1-oxobutyl]-L- prolyl]-alpha.-methyl-DL-phenylalanyl]glycyl]-	Vasodilator, renal
407	Pharmaprojects No. 1583		N(alpha)-((3S)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3- carbonyl)-L-histidyl-L-prol inamide	Neuroleptic Antiparkinsonian
408	Pharmaprojects No. 1626		D-2-phenylglycyl-D-2-phenylglycine	Anticancer, immunological Immunostimulant, other
409	Pharmaprojects No. 1779		N-acyl-D-glutamyl-l-meso-diaminopimelyl-l-lysine tripeptide derivatives	Immunomodulator, anti- infective Immunostimulant, other
176	Pharmaprojects No. 1876		Thr-Asp-Ser-Phe-Val-Gly-Leu-Methionylamide	Antihypertensive, other
410	Pharmaprojects No. 1913		L-leucyl-D-methionyl-glycyl-N-(2-adamantyl)-L- phenylalanylamide	Antihypertensive, renin system

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
177	Pharmaprojects No. 1939		Lys-Pro-Gly-Glu-Pro-Gly-Pro-Lys	Anticoagulant
178-182, 178, 183-185 and 178	Pharmaprojects No. 2063		U.S. Patent No. 4,461,724 and European Patent No. EP0078228: GSHK; ASHK; A <sub>D</sub> SHK; LSHK; TSHK; YSHK; GSHKCH <sub>3</sub> COOH.H <sub>2</sub> O; SAR-SHK; PSHK; (PYR)ESHK; WSHK; GSHK.2TosOH	Antiulcer Antithrombotic
411	Pharmaprojects No. 2363		N-methyl-D-Phe-Pro-Arg-H	Antithrombotic
186	Pharmaprojects No. 2388		N-3-(4-hydroxyphenyl)propionyl-Pro-Hyp-Gly-Ala-Gly	Antiarrhythmic
412	Pharmaprojects No. 2425		Glp-lys-NH <sub>2</sub> -L-mandelate	Anticancer, immunological Immunostimulant, other
413	Pharmaprojects No. 3341		D-1-Tiq-Pro-Arg-H-sulfate	Antithrombotic
414	Pharmaprojects No. 3415		(2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'- isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl)]methyl-6- phenyl-2-phenylmethyl-hexanamide	Antiviral, anti-HIV
415	Pharmaprojects No. 4004		Piv-1-Ser-Leu-GABA, and Piv-Ser-Leu-GABA	Neurological

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416	Pharmaprojects No. 4323		(1R,4aR,8aR)-1,2,3,4,5,6,7,8-perhydroisoquinolin-1-carbonyl-(L)-prolinyl-(L)-arimine aldehyde	Antithrombotic Anticoagulant
187, and 417	Pharmaprojects No. 491		H-Trp-Ala-Ser-Gly-L-Asn-OH & H-Trp-D-Ala-Ser-Gly-Asp(OH) <sub>2</sub>	Hypnotic/Sedative Antidepressant Neuroprotective
188	Pharmaprojects No. 4975		H <sub>2</sub> N-Asp-Ala-Asp-Pro-Arg-Gln-Tyr-Ala-COOH	Anti-inflammatory
418	Pharmaprojects No. 5200		2-Amino-N-{1-(R)-benzyloxymethyl-2-[4-(morpholine-4-carbonyl)-4-phenyl-piperidin-1-yl]-2-oxo-ethyl}-isobutyramide	Osteoporosis treatment
419	Pharmaprojects No. 5356		4-chloro-phenylcarbonyl-thienylalanyl-leucyl-phenylalanine	Anti-inflammatory Anti-infective, other
420	DMP-444		synthetic cyclic pentapeptide (cyclo(D-Val-NMeArg-Gly-Asp-Mamb)) with a tethered hydrazinonicotinyI (HYNIC) chelator for radiolabelling with <sup>99m</sup> Tc	Imaging agent
189	RIP-3		MSCVKLWPSGAPAPLVSIEELENQELVKGKGGFTVFR AQHRKWGYDVAVKIVNSKAISREVKAMASLDNEFVL RLEGVIEKVNWDQDPKPALVTKFMENGLSGLLQSQC PRPWLLCRLLEKVVLMGFYLDHQNPNVLLHRDLKPS	Anticancer, other

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			NVLLDPELVKLAADFGLSTFQGSQSGTSGGEGGTL GYLAPELVVNRKASTASDVYSGILMWAVLAGREV ELPTESLVYEAVCNQRNRPDLAELPQAGPETPGLGL KELMQLCWSSEPKDRPSFQECLPKTDEVFQMVENNMM NAAVSTVKDFLSQLRSSNRFRFIPESGQGGTMDGFRR TIENQHSRNDVMVSEWLNKLNLEPPSSVPKCKPSLT KRSRAQEEQVPQAWTAGTSSDSMAQPPQTPETSTFRN QMPSPTSTGTPSPGPRGNQGAERQGMNWSCRTPEPNP VTGRPLVNIYNCVGVQGDNNYLTMQQTALPTWGL APSGKGRGLQHPPVGSQEGPKDPEAWSRPQGWYNH SGK	
421	Pharmaprojects No. 955		N-(N-acetyl-L-isoleucyl-L-tyrosyl)-(-)-1-amino-2-(4-hydroxyphenyl)ethylphosphonic acid	Antihypertensive, other
422	leupropride		6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	Formulation, modified-release, Anticancer
190	edratide		L-glycyl-L-tyrosyl-L-tyrosyl-L-tryptophyl-L-seryl-L-tryptophyl-L-isoleucyl-L-arginyl-L-glutamyl-L-prolyl-L-prolyl-L-glycyl-L-lysyl-L-glycyl-L-glutamyl-L-glutamyl-L-tryptophyl-L-isoleucyl-L-glycine	Immunosuppressant

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
423	Prosaptide TX14(A)		H-Thr-D-Ala-Leu-Ile-Asp-Asn-Ala-Thr-Glu-Glu-Ile-Leu-Tyr-OH	Symptomatic antidiabetic Neurological Analgesic, other
8	GLP-1	GLP-1	HGEGTFTSDLKQMEEEAVRLFIEWLKNGGPSSGAPPP S	Antidiabetic
160	secretin		His-Ser-Asp-Gly-Thr-Phe-OMe; histidyl-seryl-aspartyl-glycyl-threonyl-phenylalanine-O-methyl-	Hormone, Diagnostic, GI inflammatory/bowel disorders, Neurological, Neuroleptic
147	BIM-23190	somatostatin	gi 21619156 gb AAH32625.1  Somatostatin [Homo sapiens] MLSCRLQCALAALSIVLALGCVTGAPSDPRLRQFLQK SLAAAAGKQELAKYFLAELLSEPNQTENDALEPEDLS QAAEQDEMRLLELQRSANSNPAMAPRERKAGCKNFFW KTFTSC L-Threoninamide, N-[[4-(2-hydroxyethyl)-1-piperazinyl]acetyl]-D-phenylalanyl-L-cysteiny-L-tyrosyl-D-tryptophyl-L-lysyl-(2S)-2-aminobutanoyl-L-cysteinyL-cyclic (2-7)-disulfide	Acromegaly Antidiabetic
424	leuprorelin		6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	Formulation, Anticancer

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191	$\beta$ -amyloid peptides	beta-amyloid peptide	gi 8176533 gb AAB26264.2  beta-amyloid peptide precursor; beta APP [Homo sapiens] GSLTNIKTEEISEVKMDAEFRHDSGYEVHHQKLVFFA EDVGSNKGAIIGLMVGGGVIAIVIIITLVMLK KQYTSNHHGVVE	Cognition enhancer
425	oglutamide disodium		L-tryptophan, L-alpha-glutamyl-, disodium salt	Immunomodulator, anti-infective Anticancer, immunological
192	HAV peptide matrix		leucyl-arginyl-alanyl-histidyl-alanyl-valyl-aspartyl-valyl-asparagyl-glycinamide	Neurological
149	PTH 1-34	PTH	SVSEIQLMHNLGKHLNSMERVEWLKKLQDVHNF	Hormone
	leuprorelin		6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	Anticancer
193	TRP-2		H-Leu-Leu-Pro-Gly-Gly-Arg-Pro-Tyr-Arg-OH	Anticancer, immunological
426	gotolimod		(2R)-2-amino-5-[[[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino]-5-oxopentanoic acid	Immunostimulant, other Immunomodulator, anti-infective Anticancer, immunological Stomatological
194	angiotensin-II	Angiotensin	gi 28710 emb CAA77513.1  angiotensin II [Homo sapiens]	Vulnerary

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		II	MILNSSTEDGIKRIQDDCPKAGRHNIFVMIPTLYSIHFV VGIFGNSLVVIVYFYMKLKTVASVFLNLALADLCFL LTLPLWAVYTAMEYRWPFGNYLCKIASASVSFNLYASV FLTCLSIDRYLAIVHPMKSRRLRRTMLVAKVTCIIWLL AGLASLPAIIHRNVFFIENTNITVCAFHYESQNSTLPIGL GLTKNILGFLFPFLIILTSYTLIWKALKKAYEIQKNKPR NDDIFKIIMAIVLFFFFSWPHQIFTFLDVLIQLGIIRDCR IADIVDTAMPITICIAYFNCLNPLFYGFLGKFKRYFL QLLKYIPPKAKSHSNLSTKMSTLSYRPSDDNVSSSTKKP APCFEVE	Symptomatic antidiabetic
195	omiganan		L-lysineamide, L-isoleucyl-L-leucyl-L-arginyl-L-tryptophyl-L-prolyl-L-tryptophyl-L-tryptophyl-L-tryptophyl-L-arginyl-L-arginyl, pentahydrochloride	Formulation, dermal, topical Peptide antibiotic Antiacne
427	leuprorelin		6-D-leucine-9-(N-ethyl-L-prolineamide)-10-deglycinamide-	Transmucosal, nasal, Menstruation disorders, Anticancer, hormonal, Fertility enhancer
428	delmitide		D-Tyrosinamide, D-arginyl-D-norleucyl-D-norleucyl-D-	GI inflammatory/bowel

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	acetate		norleucyl-D-arginyl-D-norleucyl-D-norleucyl-D-norleucylglycyl-monoacetate	disorders, Radio/chemoprotective, Antipsoriasis, Antipruritic/inflam, allergic, Multiple sclerosis treatment, Alimentary /Metabolic, other, Antiviral, anti-HIV, Antiasthma, COPD treatment, Respiratory Stomatological
196	cat PAD		MRGALLVLALLVTQALGVKMAETCPIFYDVFFAVANG NELLDLSLTKVNATEPERTAMKKIQDCYVENGLISRV LDGLVMTTISSSKDCMGEAVQNTVEDLKLNTLGR	Antiasthma Antiallergic, non-asthma
429	NOV-002		bis-(gamma-L-glutamy)-L-cysteiny-bis-glycin disodium salt	Anticancer, immunological Radio/chemosensitizer Antidote
430	GPG-NH2		glycyl-prolyl-glycine amide	Antiviral, anti-HIV
431	ABT-510		NAc-Sar-Gly-ValDalloleThrNValleArgProNHE	Anticancer, other

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8	CJC-1131	GLP-1	HGEGTFTSDLKQMEEEAVRLFIEWLKNGGPSSGAPPS S	Antidiabetic
432	desmopressin		Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine-	Formulation, oral, Hormone, Antidiabetic, Urological
197	metastin		MNSLVSWQLLLFLCATHFGEPLKVASVGNRPTGQQ LESGLLAPGEOQLPCTERKPAATARLRRGTLSLPPPE SSGSPQQGLSAPHSRQIPAPQGAVLVQREKDLPNYNW NSFGLRFGKREAAPGNHGRSAGRG	Anticancer, other
433	leuprorelin		5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl- D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)	Anticancer
434	SGS-111		N-phenylacetylprolylglycine ethyl ester	Cognition enhancer Neuroprotective
435	taltobulin		(4S)-4-[[[(2S)-3,3-dimethyl-2-[[[(2S)-3-methyl-2- (methylamino)-3- phenylbutanoyl]amino]butanoyl]methylamino]-2,5- dimethylhex-2-enoic acid	Anticancer, other
436	leuprolide		6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-	inhalable, systemic,

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103	XOMA-629		<p>gi 157276599 ref NP_001716.2  bactericidal/permeability-increasing protein precursor [Homo sapiens]  MRENMARGPCNAPRWASLMVLAIGTAVTAAVNP  GVVVRISQKGLDYASQQGTAALQKELKRIKIPDYSDSFKI  KHLGKGHYSFYSMDIREFQLPSSQISMVFNVGLKFSIS  NANIKISGKWKAQKRFLKMSGNFDSLIEGMSISADLK  LGSNPTSGKPTTITCSSSHINSVHVHISKSKVGWLIQL  FHKKIESALRNKMNSQVCEKVTNSVSELQPYFQTLP  VMTKIDSVAGINYGLVAPPATTAETLDVQMKGEFYSEN  HHNPPFPAPPVMEFPAHADMVYVYGLSDYFFNTAGLV  YQEAGVLKMTLRDDMIPKESKFRLLTKFFGTFLPEVA  KKFPNMKIQIHVSASTPPHLSVQPTGLTFYPAVDVQAF  AVLPNSSLASLFLIGMHTTGSMEVSAESNRLV  GELKLDRLLELKHSNIGPPVELLQDIMNYIVPILVPRVNEKL  QKGFPLTPARVQLYNVVLQPHQNFLFLFGADV  VYK</p>	<p>Anticancer, Menstruation disorders  Antiacne  Anti-infective, other</p>
198	synthetic erythropoiesis		<p>gi 8393713 ref NP_058651.1  Sep (O-phosphoserine)  tRNA:Sec (selenocysteine) tRNA synthase isoform 1 [Homo</p>	<p>Antianaemic  Radio/chemoprotective</p>

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	pro		<p>sapiens]  MSTSYGCFWRRFIHGIGRSGDISAVQPKAAGSSLLNKI  TNSLVLDIIKLAGVHTVANCVVPMATGMSLTLCLFLTL  RHKRPKAKYIIWPRIDQKSCFKSMITAGFEPVVIENVLE  GDELRTDLKAVEAKVQELGPDCLCIHSTTSCFAPRVP  DRLEELAVICANYDIPHIVNNAYGVQSSKCMHLIQQG  ARVGRIDAFVQSLDKNFVMPVGGAIAGFNDSFIQEIS  KMYPRASASPSLDVLITLSSLGNSGYKLLKERKEM  FSYLSNQIKKLLSEAYNERLLHTPHNPISLAMTLKTLDE  HRDKAVTQLGSMFLTKQVSGARVPLGSMQTVSGYT  FRGFMSTNNYPCAYLNAASAIGMKMQDVDFINRL  DRCLKAVRKRKESDDNYDKTEDVDIEEMALKLDN  VLLDTYQDA  SS</p>	
191	β-amyloid vaccine	beta-amyloid peptide	<p>gi 8176533 gb AAB26264.2  beta-amyloid peptide precursor;  beta APP [Homo sapiens]  GSGLTNIKTEEISEVKMDAEFRHDSGYEVHHQKLVFFA  EDVGSNKGAIIGLMVGGGVVIATVVIITLVMLKKQYTSN  HHGVVE</p>	Cognition enhancer

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437	sincalide		1-De-(5-oxo-L-proline)-2-de-L-glutamine-5-L-methioninecaerulein	Imaging agent Alimentary/Metabolic
438	albiglutide		([8-glycine]human glucagon-like peptide 1-(7-36)-peptidyl)([8-glycine]human glucagon-like peptide 1-(7-36)-peptidyl)(human serum albumin (585 residues))	Antidiabetic Anorectic/Antiobesity
199	SB-144		gi 13899257 ref NP_113622.1 transmembrane and ubiquitin-like domain containing 1 [Homo sapiens] MTLIEGVGDEVTVLFSVLAACLLVLALAWVSTHTAEGG DPLPQPSGTTPSQPSAAMAATDSMRGEAPGAETPSLR HRGQAAQPEPSTGTATPPADSPQEPLVLRKFLNDSE QVARAWPHDTIGSLKRTQFPGREQQVRLIYQQQLLGD DTQTLGSLHLPNCVHLCHVSTRVGPNNPPCGSEPG PSGLEIGSLLPLLLLLLLLLLWYCCIQYRPFPLTATLGL AGFTLLSLLAFAMYRP	Anticancer, other Radio/chemosensitizer
200	exenatide LAR		L-histidylglycyl-L-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutaminyll-L-methionyl-L-glutamyl-L-glutamyl-L-glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tryptophyl-L-leucyl-	Antidiabetic

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201	BA-058	PTHrP	<p>L-lysyl-L-asparaginyglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide</p> <p>gi 131542 sp P12272.1 PTHR_HUMAN Parathyroid hormone-related protein precursor (PTH-rP) (PTHrP) [Contains: PTHrP[1-36]; PTHrP[38-94]; Osteostatin (PTHrP[107-139])]</p> <p>MQRRLVQQWSVAVFLLSYAVPSCGRSVEGLSRLKRA VSEHQLLHDKGKSIQDLRRRFFLHLLAEIHTAEIRATS EVSPNSKSPNTKNHPVRFSGDDEGRYLIQETNKVET YKEQPLKTPGKKKKGKPGKRKEQEKKKRRRTRSAWLD SGVTGSGLEGDHLSDTSTTSLELDSRRH</p>	Osteoporosis treatment
8	BIM-51077	GLP-1	<p>HGEGFTSDLKQMEEEAVRLFIEWLKNKNGPSSGAPPP</p> <p>S</p> <p>[(aminoisobutyric acid) 8,35]hGLP-1(1-36)NH<sub>2</sub>, has the same amino acid sequence as human GLP-1(7-36 amide) except for the replacement of amino acids 8 and 35 with α-aminoisobutyric acid (Aib) to reduce protease susceptibility.</p>	Antidiabetic
202	TM-701		<p>H-Met-Cys-Met-Pro-Cys-Phe-Thr-Thr-Asp-His-Gln-Met-</p>	Anticancer, other

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439	CZEN-002		Ala-Arg-Lys-Cys-Asp-Asp-Cys-Cys-Gly-Gly-Lys-Gly-Arg-Gly-Lys-Cys-Tyr-Gly-Pro-Gln-Cys-Leu-Cys-Arg-NH <sub>2</sub> (Disulfide bridge: 2-19, 5-28, 16-33, 20-35) [dNaI(2')-7,Phe-12]-α-MSH 6-13	Radio/chemosensitizer  Antifungal, Antibacterial, other, Antiviral, anti-HIV, Immunosuppressant, Metabolic and enzyme disorders, Anti- inflammatory, Antiarthritic, otherGI inflammatory/bowel disorders
203	ZP-120		Ac-RYYRWKKKKKKK-NH <sub>2</sub>	Cardiostimulant
204	CTT		H-Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys-OH	Formulation technology
205	PYY3-36		g 71361686 ref NP_004151.2  peptide YY [Homo sapiens] MVFVRRPWPALTTVLLALLVCLGALVDAYPIKPEAPRE DASPEELNRYASYSLRHYLNLVTRQRYGKRDGPDLLS KTFFPDGEDRPVRSRSEGPLDW	Anorectic/Antiobesity
	AEZS-130		EP1572 UMV1843 [Aib-DTrp-DgTrp-CHO]	Growth hormone

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206	AL-108		H-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-OH	Anabolic Musculoskeletal
202	TM-801		H-Met-Cys-Met-Pro-Cys-Phe-Thr-Thr-Asp-His-Gln-Met-Ala-Arg-Lys-Cys-Asp-Cys-Cys-Gly-Gly-Lys-Gly-Arg-Gly-Lys-Cys-Tyr-Gly-Pro-Gln-Cys-Leu-Cys-Arg-NH <sub>2</sub> (Disulfide bridge: 2-19, 5-28, 16-33, 20-35)	Neuroprotective Cognition enhancer Antiparkinsonian Ophthalmological
202	TM-901		H-Met-Cys-Met-Pro-Cys-Phe-Thr-Thr-Asp-His-Gln-Met-Ala-Arg-Lys-Cys-Asp-Cys-Cys-Gly-Gly-Lys-Gly-Arg-Gly-Lys-Cys-Tyr-Gly-Pro-Gln-Cys-Leu-Cys-Arg-NH <sub>2</sub> (Disulfide bridge: 2-19, 5-28, 16-33, 20-35)	Imaging agent
440	S-0373	TRH	pyroGlu-His-Pro-NH <sub>2</sub> (or 5-oxo-L-prolyl-L-histidyl-L-prolinamide)	Anticancer, other Imaging agent
205	PYY3-36		gi 71361686 ref NP_004151.2  peptide YY [Homo sapiens] MVFVRRPWPALTTVLLALLVCLGALVDAYPIKPEAPRE	Neurological Psychostimulant Antiparkinsonian Formulation, oral, other Anorectic/Antiobesity

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207	XG-101		<p>DASPEELNRYASYLRHYLNLVTRQRYGKRDPDTLLS                      KTFPPDGEDRPVRSRSEGPLDW</p> <p>gi 4885433 ref NP_005447.1  mitogen-activated protein kinase 8 interacting protein 1 [Homo sapiens]                      MAERESGGLGGGAASPPAASPFLGLHIASPPNFRRLTHD                      ISLEEFEDLSEITDECGLSQCKDTLSLRPPRAGLLSA                      GGGGAGSRLQAEMQLMDLIDATGDTPGAEDDEEDDD                      EERAARRPGAGPPKAESGQEPASRGQGQSQSQGPG                      SGDTYRKRPTTLNLFQVPRSQDTLNNNSLGGKHSW                      QDRVSRSSPLKTGEQTPHEHICLSDELPPQSGPAPT                      DRGTSTDSPCRRSTATQMAPPGGPPAAPPGRGHSR                      DRIHYQADVRLATEEYIYLPVQRPDAAEPTSAFLPPT                      ESRMSVSSDDPAAYPSTAGRPHPSISEEEEEGFDCCLSSP                      ERAEPPGGGWRGSLGEP PPPPRASLSSDTSALSYSVK                      YTLV VDEHAQLELVSLRPCFGDY SDESDSATVYDNCA                      SVSSPYESAIGEEYEEAPRPQPPACLSEDPDEPDVHF                      SKKFLNVFMSGRSRSSAESFGLFSCIINGEEQEQT                      HRA                      IFRFVPRHEDELELVDDPLLVELQAEDYWEAYNMR                      TGARGVFPAYYAEVTKPEHMAALAKNSDWVDQFR</p>	<p>Immunological                      Cardiovascular                      Neuroprotective                      Immunosuppressant</p>

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208	XG-102		<p>VKFLGSVQVPYHKGNDVLC AAMQKIATTRRLTVHFN                      PPSSCVLEISVRGVKIGVKADDSQEA KGNKCSHFFQLK                      NISFCGYHPKNNKYFGFITKHPADHRFACHVFVSEDST                      KALAESVGRAQQFYKQFVEYTCPTEDIYLE</p> <p>gi 4885433 ref NP_005447.1  mitogen-activated protein kinase 8 interacting protein 1 [Homo sapiens]                      MAERESGGLGGGAASPPAASPFLGLHIASPPNFRLLTHD                      ISLEEFEDLSEITDECGISLQCKDTLSLRPPRAGLLSA                      GGGAGSRLQAEMLQMDLIDATGDTPGAEDDEEDDD                      EERAARRPGAGPPKAESGQEPASRGQGGQSQSQGPG                      SGDTYRPKRPTTLNLFPPQVPRSQDTLNNNSLGKKHSW                      QDRVSRSSSPLKTGEQTPPHEHICLSDELPPQSGPAPT                      DRGTSTDSPCRRSTATQMAPPGGPPAAPGGGRGHSR                      DRIHYQADVRLEATEEYIYLPVQRPPDAAEPTSAFLPPT                      ESRMSVSSDDPDPAAYPSTAGRPHPSISEEEEEGFDCCLSSP                      ERAEPPGGGWGSLGEP PPPRASLSSDTSALSYSVVK                      YTLVVDEHAQLELVSLRPFCDYSDSDSATVYDNCA                      SVSSPYESAIGEEYEEAPRPQPPACLSESDSTPDEPDVHF                      SKKFLNVFMGRSRSSSAESFGLFSCIINGEEQEETHRA</p>	<p>Neuroprotective                      Cardiovascular                      Otological                      Ophthalmological                      Antiparkinsonian                      Immunosuppressant</p>

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441	lanreotide SR		IFRFVPRHEDELELEVDPLLVLELQAEDYWYEAYNMR TGARGVFPAYYAIEVTKPEPEHMAALAKNSDWVDQFR VKFLGSVQVPYHKGNLCAAMQKIATRRRLTVHFN PPSSCVLEISVRGVKGVKADDSQEAQKGNKCSHFFQLK NISFCGYHPKNNKYFGFITKHPADHRFACHVFVSEDST KALAESVGRAFQQFYKQFVEYTCPTEDIYLE L-Threonamide,3-(2-naphthalenyl)-D-alanyl-L-cysteinyL-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyL-, cyclic (2-7)-disulfide	Formulation, modified-release, other Somatostatin Antihypertensive, other
209	OGP-(10-14)-L		H-Tyrosine-Glycine-Phenylalanine-Glycine-Glycine-OH	Haematological Musculoskeletal
210	WP9QY		cyclo(Tyr-Cys-Trp-Ser-Gln-Tyr-Leu-Cys-Tyr); cyclo(tyrosyl-cysteinyL-tryptophyl-seryl-glutaminyL-tyrosyl-leucyl-cysteinyL-tyrosyl)	Antiarthritic, other Anti-inflammatory
211	aviptadil		His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn	Antihypertensive, other Respiratory Immunosuppressant
212	AL-209		Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala	Neuroprotective

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442	octreotide		L-Cysteinamide, D-phenylalanyl-L-cysteiny-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]-	Cognition enhancer Ophthalmological Formulation, implant Formulation, modified-release, >24hr Somatostatin
213	CDX-110		Leu-Glu-Glu-Lys-Lys-Gly-Asn-Tyr-Val-Val-Thr-Asp-His-Cys-KLH	Recombinant vaccine Anticancer, immunological
444	desmopressin		Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine-	Hormone, Urological, Reproductive/gonadal, general
445	obinopitide		[34-L-glutamine]pancreatic hormone (human)	Anorectic/Antiobesity
	Insulin		Insulin (ox), 8A-L-threonine-10A-L-isoleucine-30B-L-threonine-	solubility-enhanced Insulin
171	terlipressin		N-(N-(N-glycylglycyl)glycyl)-8-L-lysinevasopressin [CAS]; Gly-Gly-Gly-8-Lys-vasopressin; N-(alpha)-glycyl-glycyl-glycyl-8-lysine vasopressin; Remestyp; TGLVP; glipressin; glycylipressin; glypressin; terlypressin; triglycyl lysine vasopressin; triglycyl-(8-lysine)vasopressin;	Hepatoprotective, Urological, Gi bleeding

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
214	ZT-153		triglycylvasopressin; vasopressin, tri-Gly-8-Lys-Asn-Phe-Gly-Ala-Ile-Leu; NFGAIL; asparagyl-phenylalanyl-glycyl-alanyl-isoleucyl-leucine; islet amyloid polypeptide (22-27)	Antidiabetic
215, 215 and 216	FGLL		gi 42544189 ref NP_004458.3  fibrinogen-like 1 precursor [Homo sapiens] MAKVFSFILVTTALTMGREISALEDCAQEQMRLRAQV RLLETRVKQQQVKIKQLLENEVQFLDKGDENTVIDL GSKRQYADCSEIFNDGYKLSGFYKIKPLQSPAEFVYC DMSDGGGWTVIQRRSDGSENFNRGWKDYENGFNF VQKHGEYWLGKNLHFLTQEDYTLKIDLADFEKNS RYAQYKNFKVGDENFYELNIGEYSGTAGDSLGNFH PEVQWASHQRMKFSWDRDHDNIEGNC AEEDQSG WWFNCHSANLNGVYYS GPYTAKTDNGIVWYTWHG WWYSLKSVVMKIRPNDFIPNVI	Cognition enhancer Neurological
			gi 42544200 ref NP_963846.1  fibrinogen-like 1 precursor [Homo sapiens] MAKVFSFILVTTALTMGREISALEDCAQEQMRLRAQV	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			RLLETRVKQQQVKIKQLLENEVQFLDKGDENTVIDL GSKRQYADCSEIFNDGYKLSGFYKIKPLQSPAEFVYC DMSDGGGWTVIQRSDGSENFNRGWKDYENGFNF VQKHGEYWLGNKNLHFLTQEDYTLKIDLADFEKNS RYAYKNFKVGVDEKNFYELNIGEYSGTAGDSLGNFH PEVQWWASHQRMKFSTWDRDHDNYEGNCAEEDQSG WWFNCHSANLNGVYSGPYTAKTDNGIVWYTWHG WWYSLKSVVMKIRPNDIFPNVI  gi 42544198 ref NP_671736.2  fibrinogen-like 1 precursor [Homo sapiens] MAKVFSFILVTTALTMGREISALEDCAQEQMRLRAQV RLLETRVKQQQVKIKQLLENEVQFLD	
217	ST-03		gi 386634 gb AAB27460.1 01-ST-3=heat-stable enterotoxin [Vibrio cholerae, 01, Peptide, 19 aa]  NLIDCCEICCNPAFCGLN	Recombinant growth factor Musculoskeletal Osteoporosis treatment
446	cetrorelix acetate		D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-	Formulation, modified-release, >24hr

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
218	neurodegenerative ther		tyrosyl-N5-(aminocarbonyl)-D-ol-L-leucyl-L-arginyl-L-prolyl-alpha toxin, Naja; cobra alpha toxin; cobra toxin alpha; toxin alpha, cobra; gi 64054 emb CAA26373.1  unnamed protein product [Laticauda semifasciata] MKTLLTLVVVTIVCLDLGYTRICFNHQSSQPQTTKTC SPGESSCYNKQWSDFRGTIIERGCGCPTVKPGIKLSCC ESEVCNN	Menstruation disorders
			gi 4519816 dbj BAA75752.1  short chain neurotoxin [Laticauda semifasciata] MKTLLTLVVVTIVCLDLGYTRICFNHQSSQPQTTKTC SPGESSCYNKQWSDFRGTIIERGCGCPTVKPGIKLSCC ESEVCNN gi 32140561 dbj BAC78199.1  erabutoxin a [Laticauda semifasciata] MKTLLTLVVVTIVCLDLGYTRICFNHQSSQPQTTKTC	Cognition enhancer

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219	CT-319		<p>SPGESSCYNKQWSDFRGTIERGCCGPTVKPGIKLSCC ESEVCNN</p> <p>gi 32140563 dbj BAC78200.1  erabutoxin a [Laticauda semifasciata]</p> <p>MKTLTLLVVTIVCLDLGYTRICFNHQSSQPQTTKTC SPGESSCYNKQWSDFRGTIERGCCGPTVKPGIKLSCC ESEVCNN</p> <p>MSNKKIHKIKLQIPGGKANPAPPALGAAGVNIMGF CKEFNAATQDRPGDLLPVVIT VYSDKTFSFVMKQSPVSSLIKKALGLESGSKIPNRNKV GKLTRAQITVIAEQMKMDVV LLESAERMVEGTARSMGVDVE</p>	Antiviral, anti-HIV
447	Peptide T		<p>L-Threonine, N-(N-(N2-(N-(N-(N-D-alanyl-L-seryl)-L-threonyl)-L-threonyl)-L-threonyl)-L-asparaginy)-L-tyrosyl)-[CAS]; HIV Peptide T; Peptide T, HIV</p>	<p>Antipsoriasis</p> <p>Multiple sclerosis treatment</p> <p>Cognition enhancer</p> <p>Musculoskeletal</p>
220 and	APP-018		pallidin [Mus musculus]	Hypolipaeamic/Antiatherosc

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
221			<p>gi 9790039 ref NP_062762.1 [9790039]                      MSVPEPPPPDGVLTGPSDSLEAGEPTPGLSDTSPDEGLI                      EDFPVDDRAVEHLVGGLLSHY                      LPDLQRSKRALQELTQNQVLLDTLEQEISKFKECHS                      MLDINALFTEAKHYHAKLVTIK                      EMLLLHEKTSKLRALKLQKQRQREELEREQQREK                      EFEREKQLTAKPAKRT</p> <p>envelope glycoprotein [Human immunodeficiency virus type 1]</p> <p>gi 4205319 gb AAD11044.1 [4205319]                      KLTPLCVTLNCTDLDLRNTNNTTTEERGERMKNCSFN                      ITTNIIRDYQKEYALFYKLDVIP                      IKEDNTSDNTSYRLISCNTSVITQACPKIS</p>	Ierosis
222	somatotropin		<p>gi 60651145 gb AAX31661.1 somatotropin [Bubalus bubalis]                      AFPAMSLSSLFANAFLRAQHLHLQAADTFKFEFERTYI                      PEGQRYSIQNTQVAFCFSETIPA</p>	Formulation, transmucosal, nasal Growth hormone Anabolic Reproductive/gonadal,

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
448	heparin		<p>PTGKNEAQQKSDLELLRISLLLIQSWLGPLQLSRVFT                      NSLVFGTSDRVYEKLLKDLLEEGI                      LALMRELEDGTPRAGQILKRTYDKFDTNMRSDALL                      KNYGLLSCFRKDLHKTETYLVRVMKRRRFGAECASF</p> <p>6-[5-acetamido-4,6-dihydroxy-2-(sulfooxymethyl)oxan-3-yl]oxy-3-[5-(6-carboxy-4,5-dihydroxy-3-sulfooxoxan-2-yl)oxy-6-(hydroxymethyl)-3-(sulfoamino)-4-sulfooxoxan-2-yl]oxy-4-hydroxy-5-sulfooxoxane-2-carboxylic acid</p>	<p>general</p> <p>Formulation, transmucosal, nasal</p> <p>Anticoagulant</p>
46	CGRP	CGRP	<p>ACDTATCVTHRLAGLLRSRGGVVKNNFVPTNVGSKAF-NH<sub>2</sub></p>	<p>Cardiovascular</p> <p>Cardiostimulant</p>
449	YM-216391		<p>A concise total synthesis of the unusual oxazole-based cyclopeptide structure YM-216391, which also establishes the stereochemistry of the natural product i.e. 1, is described.</p> <p>The unusual polyoxazole-thiazole-based cyclopeptide 1, designated YM-216391, was recently isolated from <i>Streptomyces nobilis</i>.<sup>1</sup> It shares both a structural and biological homology with the potent telomerase inhibitor telomestatin 2 which is showing promise in cancer</p>	<p>Anticancer, other</p>

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
223	FGLm		<p>chemotherapy.2 The structure of YM-216391 comprises a continuum of five azoles which have their origins in serine, cysteine and phenylalanine, linked via a glycine- valine- isoleucine tripeptide tether. The complete stereochemical assignment of YM-216391 has not been established. In this communication we describe a concise total synthesis of the cyclopeptide, which not only confirms its unique structure but also allows the assignment of its stereochemistry, shown in formula 1. Thus, the 2,4-disubstituted oxazoles 3 and 4 and the trisubstituted oxazole 5 were first elaborated</p> <p>LSENDEWTQDRKP</p>	<p>Cognition enhancer Neurological</p>
224	prohanin		<p>NPFPTWRKRP</p>	<p>Analgesic, other</p>
225	heart failure therapy	NP	<p>gi 189079 gb AAA36355.1  natriuretic peptide</p> <p>MDPQTAPSRALLLLFLHLAFLGGRSHPLGSPGSASDL ETSGLQEQRNHLQGKLSLQVEQTSLEPLQES PRPTGVWKSREVATEGIRGHRKMVLYTLRAPRSPKMV QGSGCFGRKMDRISSSSGLGCKVLRRH</p>	<p>Cardiostimulant</p>

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450	SEN-304		D-[(chG)Y-(chG)(chG)(MeL)]-NH <sub>2</sub> , where chG is R-cyclohexylglycine	Cognition enhancer Anti-inflammatory
451	Primacoll		Synthetic growth factor	Musculoskeletal
452	Octreotide		L-Cysteinamide, D-phenylalanyl-L-cysteiny-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]-	Formulation, modified-release, >24hr Symptomatic antidiabetic Ophthalmological Somatostatin
453	ALS-02		Glycine, N-(aminoiminomethyl)-N-methyl-	Neuroprotective
200	exendin-4, PC-DAC	GLP-1	L-histidylglycyl-L-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutaminy-L-methionyl-L-glutamyl-L-glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tryptophyl-L-leucyl-L-lysyl-L-asparaginyglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide	Antidiabetic
226	Exenatide		g 1916067 gb AAB51130.1  exendin 4 [Heloderma suspectum]	Formulation, transmucosal, nasal

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
225	Cardeva	BNP	<p>MKIIILWLCVFGFLATLFPISWQMPVESGLSSEDSASSE                      SFASKIKRHGEGTFTSDLSKQMEEEAVRLFIEWLKNKGG                      PSSGAPPPSG</p> <p>g 113836 sp P16860.1 ANFB_HUMAN Natriuretic peptides                      B precursor [Contains: Gamma-brain natriuretic peptide;                      Brain natriuretic peptide 32 (BNP-32)]                      MDPQTAPSRALLLLFLHLAFLGGRSHPLGSPGSASDL                      ETSQLQEQRNHLQKLSLELQVEQTSLEPLQES                      PRPTGVVKSREVATEGIRGHRKMVLYTLRAPRSPKMOV                      QGSGCFGRKMDRISSSSGLGCKVLRH</p>	Antidiabetic
227	Alloferon		<p>H-His-Gly-Val-Ser-Gly-His-Gly-Gln-His-Gly-Val-His-Gly-                      OH</p>	Cardiostimulant
454	PAC-G31P		<p>AMCF-I; Alveolar Macrophage Chemotactic Factor I;                      Alveolar Macrophage Chemotactic Factor-I; Anionic                      Neutrophil Activating Peptide; Anionic Neutrophil-                      Activating Peptide; CXCL8 Chemokine; CXCL8                      Chemokines; CXCL8, Chemokine; Chemokine CXCL8;                      Chemokine, CXCL8; Chemokines, CXCL8; Chemotactic                      Factor, Macrophage Derived; Chemotactic Factor,</p>	Immunomodulator, anti- infective  Recombinant interleukin Respiratory Antiasthma COPD treatment

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			Macrophage-Derived; Chemotactic Factor, Neutrophil; Chemotactic Factor, Neutrophil, Monocyte-Derived; Chemotactic Peptide-Interleukin-8, Granulocyte; Granulocyte Chemotactic Peptide Interleukin 8; Granulocyte Chemotactic Peptide-Interleukin-8; IL-8; Interleukin 8; Lymphocyte-Derived Neutrophil-Activating Peptide; Macrophage-Derived Chemotactic Factor; Monocyte-Derived Neutrophil Chemotactic Factor; Monocyte-Derived Neutrophil-Activating Peptide; Neutrophil Activating Peptide, Lymphocyte Derived; Neutrophil Activating Peptide, Monocyte Derived; Neutrophil Activation Factor; Neutrophil Chemotactic Factor; Neutrophil-Activating Peptide, Anionic; Neutrophil-Activating Peptide	
228	PAC-525		Ac-KWRRWRWI-NH <sub>2</sub>	Antibacterial, other
229, 230 and 230	PAC-113		Lys-Phe-His-Glu-Lys-His-His-Ser-His-Arg-Gly-Tyr  histatin 10, human; histatin 11, human; histatin 12, human; histatin 3, human; histatin 4, human; histatin 5, human; histatin 6, human; histatin 7, human; histatin 8, human;	Antifungal

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			histatin 9, human; histatin-3 (1-24), human; histatin-3 (1-25), human; histatin-3 (12-24), human; histatin-3 (12-25), human; histatin-3 (12-32), human; histatin-3 (13-25), human; histatin-3 (5-11), human; histatin-3 (5-12), human; lysyl-phenylalanyl-histidyl-histidyl-lysyl-histidyl-histidyl-seryl-histidyl-arginyl-glycyl-tyrosine  gi 4557653 ref NP_000191.1  histatin 3 [Homo sapiens] MKFFVFA LILALMLSM TGADSHAKRRHHGYKRFHEK HHSRGRYSNYLYDN	
231	MLIF		Met-Gln-Cys-Asn-Ser U.S. Patent No. 6,524,591	Anti-inflammatory
454	carfilzomib		L-Phenylalaninamide, (alphaS)-alpha-[(4-morpholinylacetyl)amino]benzenebutanoyl-L-leucyl-N-[(1S)-3-methyl-1-[[[(2R)-2-methyloxiranyl]carbonyl]butyl]-	Anticancer, other
232	NAFB001		gi 63025222 ref NP_000651.3  transforming growth factor, beta 1 [Homo sapiens] MPPSGLRLPLLLPLLLWLLVTPRPAAGLSTCKTIDM ELVKKRRIEARGQILSKRLRLASPPSQGEVPP	Ophthalmological Hepatoprotective

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			GPLPEAVLALYNSTRDRVAGESAEPEPEPEADYYAKEV TRVLMVETHNEYDKFKQSTHSIYMFNTSEL REAVPEPVLLSRAELRLRLKLVQHVVELYQKYSNN SWRYLSNRL LAPSDSPEWLSFDVTVGVVRQWLSR GGEIEGFRLSAHCSDSRDNTLQVDINGFTTGRRLD TIHGMRPFLLMATPLERAQHLQSSRRRAL DTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGY HANFCLGPCPYIWSLDTQYSKVLALYNQHNPGA SAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSC KCS [PIR]	
233	IL12-NGR		H-Cys-Asn-Gly-Arg-Cys-Gly-OH (Disulfide bridge: 1-5)	Recombinant, other Cytokine Anticancer, immunological
234 and 235	enterostatin		Val-Pro-Val-Asp; Val-Pro-Asp-Pro-Arg	Anorectic/Antiobesity
455	octreotide		L-Cysteineamide, D-phenylalanyl-L-cysteiny]-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]-	Formulation, modified-release, >24hr Somatostatin

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
150	enfuvirtide		L-Phenylalaninamide, N-acetyl-L-tyrosyl-L-threonyl-L-seryl-L-leucyl-L-isoleucyl-L-histidyl-L-seryl-L-leucyl-L-isoleucyl-L-alpha-glutamyl-L-alpha-glutamyl-L-seryl-L-glutamyl-L-asparaginy-L-glutaminy-L-glutaminy-L-alpha-glutamyl-L-alpha-glutamyl-L-lysyl-L-asparaginy-L-alpha-glutamyl-L-glutaminy-L-alpha-glutamyl-L-leucyl-L-leucyl-L-leucyl-L-alpha-glutamyl-L-glutamyl-L-leucyl-L-alpha-aspartyl-L-lysyl-L-tryptophyl-L-alanyl-L-seryl-L-leucyl-L-tryptophyl-L-asparaginy-L-tryptophyl-	Formulation, parenteral, needle-free Antiviral, anti-HIV
236	PR-21		gi 2213924 gb AAB61615.1  neural cell adhesion molecule [Homo sapiens] MLQTKDLIWTLFFLGTAVSLQVDIVPSQGEISVGESKFF LCQVAGDAKDKDISWFSPNGEKLTPNQQRIS VWVWDDSSSTLTIYNANIDDA GIYKCVVTGEDGSESE ATVNVKIFQKLMFKNAPTPQEFREGEDAVIVCD VVSSLPTIIWKHKGRDVILKDDVRFIFLSNNYLPPIGI KKTDEGTYRCEGRILARGEINFNDIQVIVNV PPTIQRQNVNATANLQQSVTLVCD AEGFPPTMSW TKDGEQEQEEHDEKYLFSDDSSHLTIKKVVDKN	Neurological Cognition enhancer

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237	AC-163794	GIP	HEAENICIAENKVGEDATIHLLKVFQAKPQITYVEDQTA MELAEQVILTVEASGDHIPYITWWTSTWQI gi 183221 gb AAA53192.1  gastric inhibitory polypeptide precursor MVATKTFALLLLSLFLAVGLGKKEGHFSLPSLPVGS HAKVSSPQPRGPRYAEGTFISDYSIAMDKIHQ QDFVNWLLAQKKNNDWKHNITQREARALELASQA NRKEEEAVEPQSSPAKNPSEDELLRDLQLQELLAC LLDQTNLCRLRSR;	Antidiabetic
456	glucagon		Glucagon (1-29); Glukagon; HG Factor; HG-Factor; Hyperglycemic Glycogenolytic Factor; Hyperglycemic- Glycogenolytic Factor; Proglucagon (33-61)	Formulation, transdermal, systemic hypoglycemia
457	Insulin		Insulin (ox), 8A-L-threonine-10A-L-iso-leucine-30B-L-threonine-	Formulation, oral, other Formulation, optimized, nanoparticles Antidiabetic
458	Dekafin-2		DNA Synthesis Factor; Fibroblast Growth Factor; Fibroblast Growth Regulatory Factor; Growth Factor, Fibroblast; Growth Factors, Fibroblast	Anticancer, other

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
238 and 239	relaxin		(1) Glu-Leu-Tyr-Ser-Ala-Leu-Ala-Asn-Lys-Cys-Cys-His-Val-Gly-Cys-Thr-Lys-Arg-Ser-Leu-Ala-Arg-Phe-Cys  (2) H-Asp-Ser-Trp-Met-Glu-Glu-Val-Ile-Lys-Leu-Cys-Gly-Arg-Glu-Leu-Val-Arg-Ala-Gln-Ile-Ala-Ile-Cys-Gly-Met-Ser-Thr-Ser  Cys 11 of each chain form disulfide bond; cys 24 of the first chain forms disulfide bond with cys 23 of chain 2	Recombinant hormone  Hormone  Labour inducer  Antihypertensive, other
459	rhNRG-1		Differentiation Factor, neu; GGF Protein; Glial Growth Factor; Heregulin; NDF Protein; NRG1 Protein; Neuregulin 1; neu Differentiation Factor	Recombinant, other  Cardiostimulant
240	c-peptide analogue	C-peptide	Glu-Ala-Glu-Asp-Leu-Gln-Val-Gly-Gln-Val-Glu-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser-Leu-Gln-Pro-Leu-Ala-Leu-Glu-Gly-Ser-Leu-Gln	Symptomatic antidiabetic
241	SB-101		gi 30353933 gb AAH52287.1  CD44 protein [Homo sapiens] MDKFWHAAAWGLCLVPLSLAQIDLNITCRFAGVFHV EKNGRYSISRTEAADLCKAFNSTLPTMAQMEKAL SIGFETCSST	Recombinant, other  Anticancer, other
242	Britistatin		gi 66270695 gb AAAY43681.1  disintegrin isoform D-1 [Bitis	Antithrombotic

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243	echistatin		arietans] SPPVCGNKILEQGEDCDGSPANCQDRCCNAATCKLT PGSQCNYGECDDQCRFKKAGTVCRIARGDWNDDYCT GKSSDCPWNH gi 208338 gb AAA72777.1  echistatin MECEGPCCRNCKFLKEGTICKRARGDDLDDYCNCK TCDCPRNPHKGPAT	Antithrombotic
244	gastrin		gi 4503923:20-101 gastrin preproprotein [Homo sapiens] EASWKPRSQQPDAPLGTGANRDLELPWLEQQGPASH HRRQLGPPHVLVADPSKKQGPWLEEEAYGWMD FGRRAEDEN	diabetes
245	herpes simplex vaccine		gi 9629447:1-23 envelope glycoprotein D [Human herpesvirus 1] MGGAAARLGAVILFVIVGLHGV	Prophylactic vaccine
246	neurotensin		gi 5453816:152-163 neurotensin/neuromedin N preproprotein [Homo sapiens] LYENKPRRPYIL	Analgesic, other
247	nociceptin		gi 5453922 ref NP_006219.1  prepronociceptin [Homo sapiens]	Neurological Cognition enhancer

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
248	oxyntomodulin		<p>MKVLLCDLLLSLFSSVFSSCQRDCLTCQEKLHPALDS                      FDLEVCILECEEKVFPSPLWTPCTKVMARSSWQLSPAA                      PEHVAALYQPRASEMQHLRRMPRVSRLFQEEPEP                      GMEEAGEMEQLQKRFGGFTGARKSARKLANQKR                      FSEFMRQYLVLSMQSSQRRRTLHQGNV</p> <p>sp P01275.3 GLUC_HUMAN:53-89 Glucagon precursor                      [Contains: Glicentin; Glicentin-related polypeptide (GRPP);                      Oxyntomodulin (OXY) (OXM)]</p> <p>HSQGTFTSDYSKYLDSRRAQDFVQWLMNTKRNRNII                      A</p>	Obesity; Antiulcer
249	pancreastatin		<p>gi 164417:256-304 chromogranin A precursor                      GWPQAPAMDGAGKTGAEEAQPEGKGAREHSRQEEEE                      EETAGAPQGLFRG</p>	Antidiabetic
250	relaxin	Relaxin	<p>gi 5902052 ref NP_008842.1  relaxin 1 preproprotein [Homo sapiens]                      MPRLFLHLLLEFCLLLNQFSRAVAAKWKDDVIKLCGR                      ELVRAQIAICGMSTWSKRSLSQEDAPQTPRPVAEIVPSF                      INKDTETIIIMLEFIANLPPELKAALSERQPSLPELQQYV                      PALKDSNLSFEEFKLIRNRQSEAAADSNPSELKYLGLD</p>	Recombinant hormone Hormone Labour inducer

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
251	secretin		THSQKRRPYVALFEKCCCLIGCTKRSLAKYC gi 11345450:28-54 secretin preproprotein [Homo sapiens] HSDGTFSELSRLREGARLQRLQLGLV	Haemostatic; diagnostic of pancreatic dysfunction, asthma, COPD, others
252	TIMP		MAPFEPLASGILLLLWLIAPSRACCTCVPPHPQTAFNCNSD LVIRAKFVGTPEVNQTTLYQRYEIKMTKMYKGFQALG DAADIRFVYTPAMESVCGYFHRSHNRSEEFLLIAGKLLQ DGLLHITCSFVAPWNSLSLAQRRGFTKTYTVGCEECT VFPCLSPCKLQSGTHCLWTDQLLQSEKGFQSRHLAC LPREGLCTWQSLRSQIA	Recombinant, other Vulnerary Antiarthritic, other Stomatological
252	TIMP		MAPFEPLASGILLLLWLIAPSRACCTCVPPHPQTAFNCNSD LVIRAKFVGTPEVNQTTLYQRYEIKMTKMYKGFQALG DAADIRFVYTPAMESVCGYFHRSHNRSEEFLLIAGKLLQ DGLLHITCSFVAPWNSLSLAQRRGFTKTYTVGCEECT VFPCLSPCKLQSGTHCLWTDQLLQSEKGFQSRHLAC LPREGLCTWQSLRSQIA	Recombinant, other Antiarthritic, other Stomatological
253	tendamistat		Asp-Thr-Thr-Val-Ser-Glu-Pro-Ala-Pro-Ser-Cys-Val-Thr- Leu-Tyr-Gln-Ser-Trp-Arg-Tyr-Ser-Gln-Ala-Asp-Asn-Gly- Cys-Ala-Gln-Thr-Val-Thr-Val-Lys-Val-Val-Tyr-Glu-Asp-	Antidiabetic

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254	thymosin $\beta$ 4		<p>Asp-Thr-Glu-Gly-Leu-Cys-Tyr-Ala-Val-Ala-Pro-Gly-Gln-Ile-Thr-Thr-Val-Gly-Asp-Gly-Tyr-Ile-Gly-Ser-His-Gly-His-Ala-Arg-Tyr-Leu-Ala-Arg-Cys-Leu</p> <p>gi 11056061 ref NP_066932.1  thymosin, beta 4 [Homo sapiens]</p> <p>MSDKPDMAEIEKFDKSKLKKTTETQKNPLPSKETIEQE</p> <p>KQAGES</p>	<p>Vulnerary</p> <p>Ophthalmological</p> <p>Symptomatic antidiabetic</p> <p>Dermatological</p> <p>Cardiovascular</p> <p>Septic shock treatment</p> <p>Antiasthma</p>
255	urodilatin		<p>Thr-Ala-Pro-Arg-Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr</p>	<p>Cardiostimulant</p> <p>Urological</p> <p>Antiasthma</p>
256	Pharmaprojects No. 6236		<p>Gly-Ser-Arg-Ala-His-Ser-Ser-His-Leu-Lys</p>	<p>Anticancer, other</p> <p>Antiarrhythmic</p> <p>Antiparkinsonian</p> <p>Cognition enhancer</p> <p>Neuroprotective</p>
257	ANUP-1		<p>Glu-Leu-Lys-Cys-Tyr-Thr-Cys-Lys-Glu-Pro-Met-Thr-Ser-</p>	<p>Anticancer, other</p>

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
			Ala-Ala-Cys	
258	DML-4983		Asp-Ala-His-Lys	Cardiovascular
460	Glypromate		Gly-Pro-Glu	Neuroprotective
259	CD-NP		Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Ile Ser Ser Ser Ser Gly Leu Gly Cys Pro Ser Leu Arg Asp Pro Arg Pro Asn Ala Pro Ser Thr Ser Ala	Cardiostimulant
260	Kisspeptin-54		GTSLSPPESSGSPQQPGLSAPHSRQIPAPQGAVLVQRE KDLPNYNWNSFGLRF-NH2	Cancer metastasis, angiogenesis
261	Kisspeptin-14		DLPNYNWNFSGLRF-NH2	Cancer metastasis, angiogenesis
262	Kisspeptin-13		LPNYNWNFSGLRF-NH2	Cancer metastasis, angiogenesis
263	Kisspeptin-10		YNWNSFGLRF-NH2	Cancer metastasis, angiogenesis
264	Ziconotide		CKGKGAKCSRLMYDCCTGSCRSKGC	
461	Biphalin		Tyr-D-Ala-Gly-Phe-NH-NH-Phe-Gly-D-Ala-Tyr	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
39	Nesiritide	Brain Natriuretic peptide (BNP)	SPKMVQSGGCFGRKMDRISSSSGLGCKVLRHH	
40	CD-NP		GLSKGCFGLKLDRI GSMGLGCP SLRDRPNAPSTSA	
265	Protegrin-1	Cytolytic	RGRLCYCRRRRCVGR-NH2	antibiotic
266	V681		Ac-KWKSFLKTFKSAVKTVLHTALKAISS-NH2	
462	V681 (V13A <sub>D</sub> )		Ac-KWKSFLKTFKSA(AD)KTVLHTALKAISS-NH2	'(AD)' discloses the D-configuration of Alanine
267	V681 des A12		KWKSFLKTFKSVKTVLHTALKAISS	
268	V681 V13K		KWKSFLKTFKSAKKTVLHTALKAISS	
269	V681 V13K, T15K		KWKSFLKTFKSAKKKVLHTALKAISS	
270	GLP-2	GLP	HADGFSDEMNTILDNLAARDFINWLIQTKITD	
271	GLP-2 (A2G)	GLP	HGDGFSDEMNTILDNLAARDFINWLIQTKITD	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
272	GLP-2 (A2G/C34)	GLP	HGDGFSDEMNTILDNLAARDFINWLIQTKITDC	
273	AOD-9604	Human Growth Hormone	LRIVQCASVEGSCGFY	Musculoskeletal, COPD, Hypnotic/Sedative, Immunostimulant, Antidiabetic, Anabolic, Symptomatic antidiabetic, Vulnerary
274	Ac-AOD- 9604(S8K)	Human Growth Hormone	Ac-LRIVQCAKVEGSCGFY	Musculoskeletal, COPD, Hypnotic/Sedative, Immunostimulant, Antidiabetic, Anabolic, Symptomatic antidiabetic, Vulnerary
275	Ac-AOD- 9604(K17)	Human Growth Hormone	Ac-LRIVQCASVEGSCGFYK	Musculoskeletal, COPD, Hypnotic/Sedative, Immunostimulant, Antidiabetic, Anabolic, Symptomatic antidiabetic,

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
276	C-peptide	Insulin	EAEDLQVGQVELGGGPGAGSLQPLALEGSLQ	Vulnerary
463	CR845	Opioids	<p>peripherally-selective kappa</p> <div style="border: 1px solid black; padding: 10px; margin: 10px 0;"> </div> <p>opioid receptor agonists</p> <p>D-Phe-D-Phe-D-Leu-D-Lys-[<math>\square</math>-(4-aminopiperidine-4-carboxylic acid)]-OH</p>	acute and chronic pain of visceral, inflammatory and neuropathic origin, and for the treatment of pruritis (itch)
277	Protegrin-2	Cytolytic	RGGRLLCYCRRRRFCICV	antibiotic
278	Protegrin-3	Cytolytic	RGGGLCYCRRRRFCVCGRG	antibiotic

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
279	Protegrin-4	Cytolytic	RGRLCYCRGWICFCVGRG	antibiotic
280	Protegrin-5	Cytolytic	RGRLCYCRPRFCVCVGRG	antibiotic
281	Preprotegrin	Cytolytic	METQRASLCLGRWSLWLLLLGLVVPSSASAQALSYREA VLRVDRRLNEQSSEANLYRLELDQPPKADEDPPGTPK PVSFTVKETVCPRPTRQPPELDFKENGGRVKQCVCVGT TLDQIKDPLDITCNEVQGVRRGLCYCRPRFCVCVGR G	antibiotic
248	Oxyntomodulin		HSQGTFTSDYSKYLDSRRAQDFVQWLMNTKRRNNI A	
276	C-peptide		EAEDLQVGQVELGGPGAGSLQPLALEGSLQ	
282	C-peptide mutant		EGSLC	
283	Human Opioid Growth Factor	Enkephalin	Tyr-Gly-Gly-Phe-Met	
284	cholecystokinin		RDY(SO <sub>3</sub> -)TGW(Nle)DF	
285	Dynorphin A		YGGFLRRIRPKLK	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
464	Pralmorelin (GHRFA)		D-Ala-D-2-Nal-Ala-Trp-D-Phe-Lys-NH <sub>2</sub>	
286	Aniridine		RSSCFGRRMDRIGAQSLGCNSFRY	
287	Vessel dilator proANP31-67		EVVPPQVLSDPNEEAGAALSPLPEVPPWTGEVSPAQR	
465	Peptide G		Arg-Pro-Lys-Pro-Gln-Arg-D-Trp-MePhe-D-Trp-Leu-Met	
466	Tiplimotide		D - Ala - lys - pro - val - val - his - leu - phe - ala - asp - ile - val - thr - pro - arg - thr - pro	
288	Desirudin (63-desulfohirudin)		VVYTDCTESQNLCLCEGSNVCGQGNKCILGSDGEK NQCVTGEGTPKPQSHNDGDFEEIPEEYLQ	
467	Examorelin		His-DTrp(2-Me)-Ala-Trp-DPhe-Lys-NH <sub>2</sub>	
172	Terlipressin	Vesopressin	Gly-Gly-Gly-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH <sub>2</sub>	
289	Osteogenic Growth Factor (WT)		ALKRQGRPLYGFGG	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
290	Osteogenic Growth Factor (10-14)		YGFGG	
291	Myelin Basic Protein peptide		Ac-ASQKRPSQRHG	
292	Myelin Basic Protein peptide Ac1-11[4Y]		Ac-ASQYRPSQRHG	
293	Gonadorelin (24-33)		pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly CONH2	
468	Bremelanotide	Alpha-MSH	Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]-OH	
294	Islet Neogenesis associated peptide (INGAP)		GLHDPSHGTLPNGSG	Diabetes
295	Urocortin II		IVLSLDVPIGLLLQILLEQARARAAREQATTNARILARVG	

SEQ ID NO:	Name	Family	Sequence and/or other Identifying Information	Therapeutic Activity
296	A6 (anti-angiogenic peptide)		HC CH3CO-NH2-KPSSPPEE-CONH2	
297	Obestatin		H-Phe-Asn-Ala-Pro-Phe-Asp-Val-Gly-Ile-Lys-Leu-Ser-Gly-Val-Gln-Tyr-Gln-Gln-His-Ser-Gln-Ala-Leu-NH2	
298	ITF-1697		Gly-Lys(Et)-Pro-Arg	
299	CNP (C-type natriuretic peptide)		GLSKGCFGLKLDLRIGMSGLGC	
300	Osteocalcin		YLYQWLGAPVYPDPLEPRREVCELNPDDELADHIG FQEAYRRFYGPV	Diabetes
301			EAEDLQVQVELGGPGAGCLQPLALEGSLQ	
469	D4F-APO1 mimetic peptide		Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH <sub>2</sub>	

The above exemplary biologically active agents are meant to encompass, where applicable, analogues, agonists, antagonists, inhibitors, isomers, and pharmaceutically acceptable salt forms thereof. In reference to peptides and proteins, the invention is intended to encompass synthetic, recombinant, native, glycosylated, and non-glycosylated forms, as well as biologically active fragments thereof. The above biologically active proteins are additionally meant to encompass variants having one or more amino acids substituted, deleted, or the like, as long as the resulting variant protein possesses at least a certain degree of activity of the parent (native) protein.

The reactive polymeric reagents of the invention may be attached, either covalently or non-covalently, to a number of solid entities including films, chemical separation and purification surfaces, solid supports, metal/metal oxide surfaces, such as gold, titanium, tantalum, niobium, aluminum, steel, and their oxides, and silicon oxide. Additionally, the polymers of the invention may also be used in biochemical sensors, bioelectronic switches, and gates. The polymeric reagents of the invention may also be employed as carriers for peptide synthesis, for the preparation of polymer-coated surfaces and polymer grafts, to prepare polymer-ligand conjugates for affinity partitioning, to prepare cross-linked or non-cross-linked hydrogels, and to prepare polymer-cofactor adducts for bioreactors.

## **VI. Pharmaceutical Compositions and Administration Methods**

The invention also includes pharmaceutical preparations comprising a conjugate as provided herein in combination with a pharmaceutical excipient. Generally, the conjugate itself will be in a solid form (e.g., a precipitate), which can be combined with a suitable pharmaceutical excipient that can be in either solid or liquid form. The pharmaceutical preparations encompass all types of formulations and in particular those that are suited for injection, e.g., powders that can be reconstituted as well as suspensions and solutions.

Exemplary excipients include, without limitation, those selected from the group consisting of carbohydrates, inorganic salts, antimicrobial agents, antioxidants, surfactants, buffers, acids, bases, and combinations thereof.

A carbohydrate such as a sugar, a derivatized sugar such as an alditol, aldonic acid, an esterified sugar, and/or a sugar polymer may be present as an excipient. Specific carbohydrate excipients include, for example: monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol,

maltitol, lactitol, xylitol, sorbitol (glucitol), pyranosyl sorbitol, myoinositol, and the like.

The excipient can also include an inorganic salt or buffer such as citric acid, sodium chloride, potassium chloride, sodium sulfate, potassium nitrate, sodium phosphate monobasic, sodium phosphate dibasic, and combinations thereof.

The preparation may also include an antimicrobial agent for preventing or deterring microbial growth. Nonlimiting examples of antimicrobial agents suitable for the present invention include benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate, thimersol, and combinations thereof.

An antioxidant can be present in the preparation as well. Antioxidants are used to prevent oxidation, thereby preventing the deterioration of the conjugate or other components of the preparation. Suitable antioxidants for use in the present invention include, for example, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite, and combinations thereof.

A surfactant may be present as an excipient. Exemplary surfactants include: polysorbates, such as "Tween 20" and "Tween 80," and pluronics such as F68 and F88 (both of which are available from BASF, Mount Olive, N.J.); sorbitan esters; lipids, such as phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines (although preferably not in liposomal form), fatty acids and fatty esters; steroids, such as cholesterol; and chelating agents, such as EDTA, zinc and other such suitable cations.

Acids or bases may be present as an excipient in the preparation. Nonlimiting examples of acids that can be used include those acids selected from the group consisting of hydrochloric acid, acetic acid, phosphoric acid, citric acid, malic acid, lactic acid, formic acid, trichloroacetic acid, nitric acid, perchloric acid, phosphoric acid, sulfuric acid, fumaric acid, and combinations thereof. Examples of suitable bases include, without limitation, bases selected from the group consisting of sodium hydroxide, sodium acetate, ammonium hydroxide, potassium hydroxide, ammonium acetate, potassium acetate, sodium phosphate, potassium phosphate, sodium citrate, sodium formate, sodium sulfate, potassium sulfate, potassium fumarate, and combinations thereof.

The amount of the conjugate (i.e., the conjugate formed between the active agent and the polymer described herein) in the composition will vary depending on a number of factors, but will optimally be a therapeutically effective dose when the composition is stored in a unit dose container (e.g., a vial). In addition, the pharmaceutical preparation can be housed in a

syringe. A therapeutically effective dose can be determined experimentally by repeated administration of increasing amounts of the conjugate in order to determine which amount produces a clinically desired endpoint.

The amount of any individual excipient in the composition will vary depending on the activity of the excipient and particular needs of the composition. Typically, the optimal amount of any individual excipient is determined through routine experimentation, i.e., by preparing compositions containing varying amounts of the excipient (ranging from low to high), examining the stability and other parameters, and then determining the range at which optimal performance is attained with no significant adverse effects. Generally, however, the excipient will be present in the composition in an amount of about 1% to about 99% by weight, preferably from about 5%-98% by weight, more preferably from about 15-95% by weight of the excipient, with concentrations less than 30% by weight most preferred.

These foregoing pharmaceutical excipients along with other excipients are described in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, N.J. (1998), and Kibbe, A. H., Handbook of Pharmaceutical Excipients, 3rd Edition, American Pharmaceutical Association, Washington, D.C., 2000.

The pharmaceutical preparations of the present invention are typically, although not necessarily, administered via injection and are therefore generally liquid solutions or suspensions immediately prior to administration. The conjugates can be administered injected parenterally by intravenous injection, or less preferably by intramuscular or by subcutaneous injection. Suitable formulation types for parenteral administration include ready-for-injection solutions, dry powders for combination with a solvent prior to use, suspensions ready for injection, dry insoluble compositions for combination with a vehicle prior to use, and emulsions and liquid concentrates for dilution prior to administration, among others.

The pharmaceutical preparation can also take other forms such as syrups, creams, ointments, tablets, powders, and the like. Other modes of administration are also included, such as pulmonary, rectal, transdermal, transmucosal, oral, intrathecal, subcutaneous, intra-arterial, and so forth.

The invention also provides methods for administering a conjugate as provided herein to a patient suffering from a condition that is responsive to treatment with the conjugated agent. The method comprises administering, generally via injection, a therapeutically effective amount of the conjugate (preferably provided as part of a pharmaceutical preparation). The

actual dose to be administered will vary depend upon the age, weight, and general condition of the subject, as well as the severity of the condition being treated, the judgment of the health care professional, and conjugate being administered. Therapeutically effective amounts are known to those skilled in the art and/or are described in the pertinent reference texts and literature. Generally, a therapeutically effective amount will range from about 0.001 mg to 100 mg, preferably in doses from 0.01 mg/day to 75 mg/day, and more preferably in doses from 0.10 mg/day to 50 mg/day.

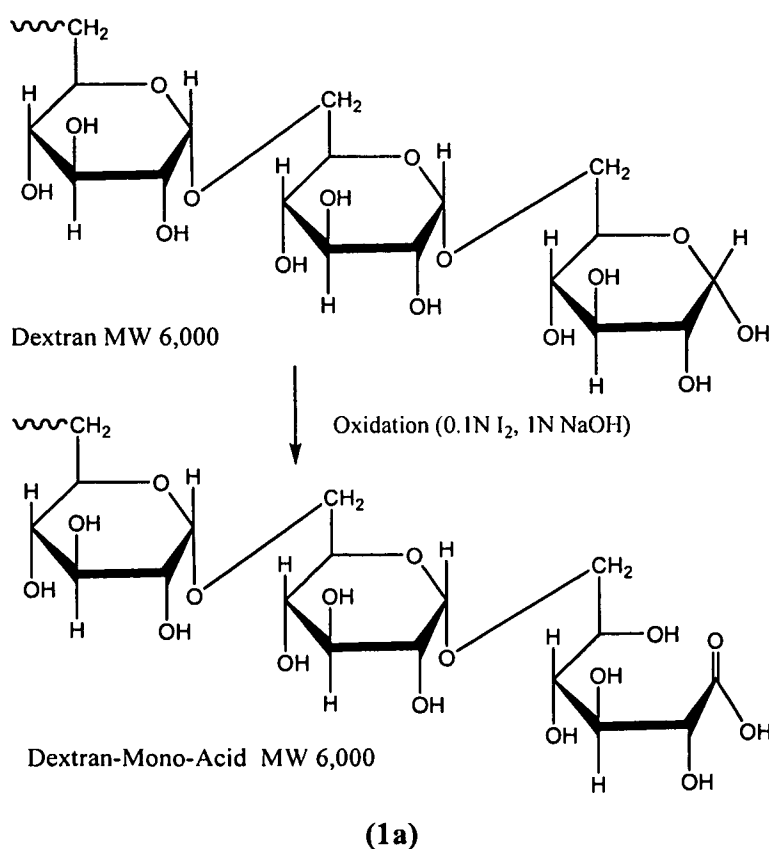
Optimally, cleavage of the water-soluble polymer portion, which may be desirable to facilitate clearance from the body, can be facilitated through the incorporation of one or more physiologically cleavable and/or enzymatically degradable linkages such as urethane, amide, carbonate or ester-containing linkages, as described above, into the polymer component. In this way, clearance of the conjugate (via cleavage of individual water-soluble polymer portions) can be modulated by selecting the polymer molecular size and the type of linkage that would provide the desired clearance properties. One of ordinary skill in the art can determine the proper molecular size of the polymer as well as the cleavable functional group. Clearance properties can be evaluated by preparing a series of polymer derivatives with different polymer weights and cleavable functional groups, and then obtaining clearance profiles (e.g., through periodic blood or urine sampling) by administering the polymer derivatives to a patient and taking periodic blood and/or urine sampling.

## EXPERIMENTAL

### Materials

Dextran obtained from *Leuconostoc ssp.*, having a molecular weight ~ 6,000, was purchased from Fluka Chemical Corp. and used for exploratory experiments. For drug delivery applications, where higher molecular weights are desired, dextran having molecular weights of 40 and 70 kDa was obtained from Pharmacosmos, located in Holbaek, Denmark. These higher molecular weight starting materials had polydispersity (PDI) values of 1.25 – 1.35.

### Example 1: Preparation of dextran(6K)-monocarboxylic acid (1a) by mild oxidation



To a solution of Dextran 6 (10.0 g; Mw = 6353, Mn = 2,717, Mw/Mn = 2.34; Fluka, product number 31388) in deionized water (12.0 ml) was added 0.1N iodine solution (2.0 ml) followed by slow addition of 1.0N sodium hydroxide solution until the solution became clear. This addition of iodine solution followed by slow addition of sodium hydroxide solution was repeated 18 times. The total amounts of added iodine solution and sodium hydroxide solution

were 40.0 ml and 5.0 ml, respectively. The reaction mixture was dialyzed against deionized water using dialysis cassettes having a 3500 kD cutoff (Pierce). Water was distilled off under reduced pressure, and the wet product was dried under vacuum overnight. Yield 9.2 g. Anion exchange chromatography showed that the product contained 46.1% of dextran monocarboxylic acid (1) and 51.9% of unreacted dextran.

Example 2: Purification of dextran (6K)-monocarboxylic acid (1a) by anion exchange chromatography

A sample of the product from Example 1 (1.0 g; containing 46.1% of dextran acid and 51.9% of unreacted dextran) was dissolved in deionized water (100 ml) and applied to a DEAE Sepharose FF column (10 ml). The column was then washed with deionized water. The product adsorbed on the column was eluted with 10% ammonia. Ammonia and water were distilled off from the eluate under reduced pressure, and the residue was dried under vacuum, giving 0.2 g of white solid product. Anion exchange chromatography showed that the product contained 99.1% of dextran monocarboxylic acid (1a) and 0.9% of dextran.

Example 3: Preparation of dextran(40K)-monocarboxylic acid (1b) by mild oxidation

To a solution of Dextran 40 (10.0 g;  $M_w = 46,021$ ,  $M_n = 22,617$ ,  $M_w/M_n = 2.03$ ; Sigma-Aldrich) in deionized water (12.0 ml) was added 0.1N iodine solution (2.0 ml) followed by slow addition of 1.0N sodium hydroxide solution until the solution became clear. This addition of iodine solution followed by slow addition of sodium hydroxide solution was repeated several times. The total amounts of added iodine solution and sodium hydroxide solution were 34.0 ml and 5.1 ml, respectively. The reaction mixture was dialyzed against deionized water using dialysis cassettes having a 3500 MW cutoff (Pierce). Water was then distilled off under reduced pressure, and the wet product was dried under vacuum overnight. Yield 9.3 g. Anion exchange chromatography showed that the product contained 36.4 % of dextran-diacid, 59.3 % of dextran-monoacid (1b), and 4.3% of unreacted dextran.

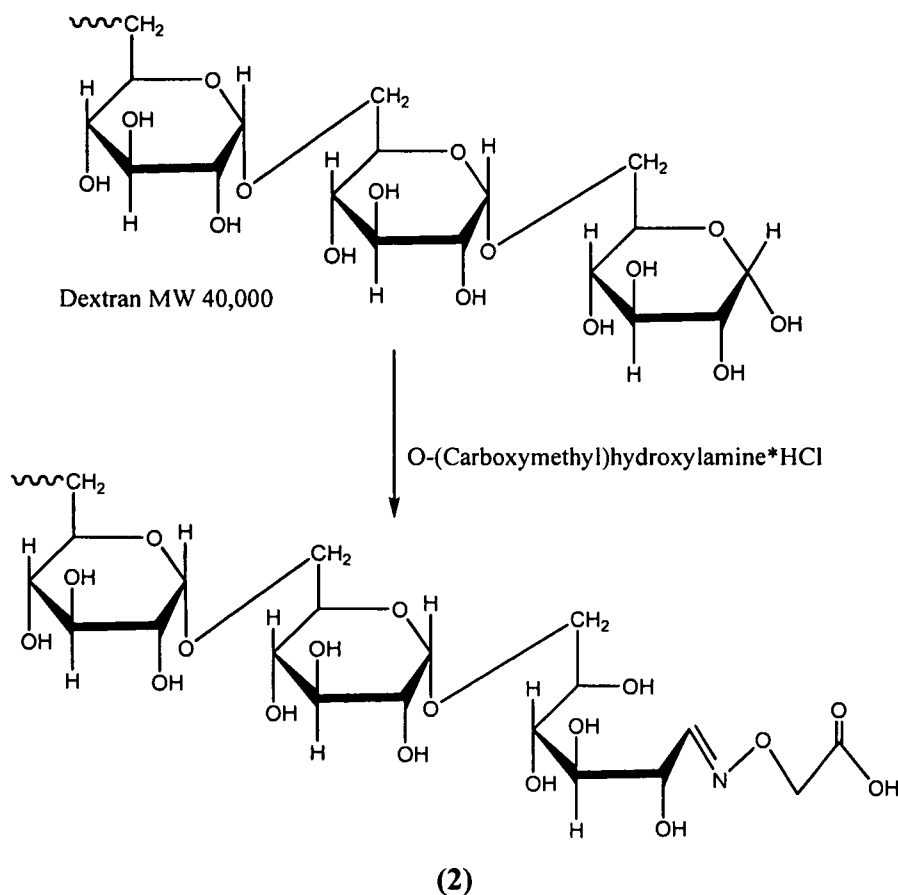
Example 4: Purification of dextran(40K)- monocarboxylic acid (1b) by anion exchange chromatography

A sample of the product from Example 3 (5.0 g) was dissolved in deionized water (250 ml) and applied to a DEAE Sepharose FF column (50 ml). The column was then washed with deionized water. The following fractions were collected:

Fraction #	Volume (ml)	Dextran-Diacid, %	Dextran-Monoacid ( <b>1b</b> ), %	Dextran, %
1	25	0	0	0
2	25	0	0	100
3	25	0	0	100
4	25	0	0	100
5	25	0	36.0	64.0
6	25	4.1	81.4	14.5
7	25	8.9	79.6	11.5
8	25	14.4	80.3	5.3
9	25	12.7	82.1	5.2
10	25	15.3	80.0	4.7
11	25	0	100	0

Example 5: Preparation of dextran(40K)- monocarboxylic acid (**1b**) by controlled oxidation of dextran monitored by ion exchange chromatography

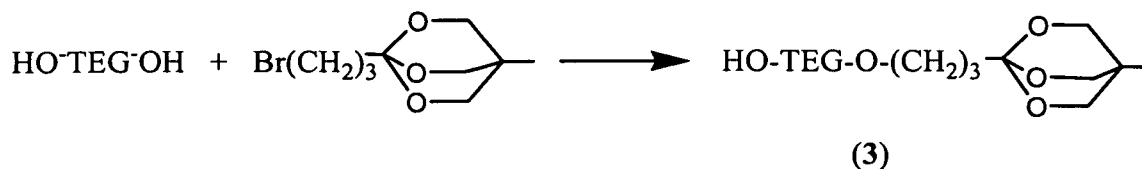
To a solution of Dextran 40 (10.0 g; Mw = 46,021, Mn = 22,617, Mw/Mn = 2.03; Sigma-Aldrich) in deionized water (12.0 ml) was added 0.1N iodine solution (2.0 ml) followed by slow addition of 1.0N sodium hydroxide solution (~ 0.25 ml) until the solution became clear. Ion exchange chromatography showed that the reaction mixture at that point contained 25.3 % of dextran monoacid and 74.7% of unreacted dextran. The addition of iodine solution (2.0 ml) followed by slow addition of sodium hydroxide solution was repeated two more times. At this stage, ion exchange chromatography showed that the reaction mixture contained 50.7% of dextran monoacid and 49.3% of unreacted dextran. After addition of a fourth portion of iodine solution (2.0 ml) followed by slow addition of sodium hydroxide, ion exchange chromatography showed that the reaction mixture contained 84.9% of dextran monoacid and 15.1% of unreacted Dextran. A fifth addition of iodine solution (2.0 ml) followed by slow addition of sodium hydroxide produced a reaction mixture containing 3.1% of dextran diacid, 83.9% of dextran monoacid, and 13.0% of unreacted dextran. This final reaction mixture was diluted with deionized water (500 ml) and the obtained solution was filtered through a desalting column containing 120 ml of Amberlite IR-120 and 120 ml of Amberlite IRA-67 ion exchange resin. Water was then distilled off under reduced pressure from the filtrate, and the wet product was dried under vacuum overnight. Yield 8.5 g.

**Example 6: Preparation of dextran(40K)-O-(carboxymethyl)oxyimine (2)**

To a solution of Dextran 40 (2.5 g; Mw = 46,021, Mn = 22,617, Mw/Mn = 2.03; Sigma-Aldrich) in 0.1M sodium acetate buffer (pH = 5.5) was added O-(carboxymethyl)hydroxylamine hemihydrochloride (0.1 g; Sigma-Aldrich). The pH was readjusted to 5.2 and the mixture was stirred overnight at room temperature. Ion exchange chromatography showed that the product contained 77.1% of dextran(40K)-O-(carboxymethyl)oxyimine (2) and 22.9% of unreacted dextran.

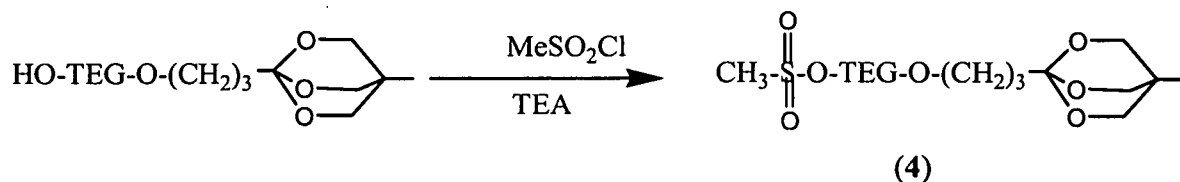
**Example 7: Preparation of tetra(ethylene glycol)- $\alpha$ -amino- $\omega$ -butanoic acid, orthoester (5)**

This reagent can be used to prepare a carboxy-terminated carbohydrate derivative, as shown in Example 8 below.

**A. Tetra(ethylene glycol)-monobutanoic acid, orthoester (3)**

A solution of tetra(ethylene glycol) (97.1 g, 0.5 mole) in toluene (200 ml) was azeotropically dried by distilling off toluene under reduced pressure. The dried tetra(ethylene glycol) was dissolved in anhydrous toluene (180 ml), and 1.0 M solution of potassium tert-butoxide in tert-butanol (120 ml, 0.12 moles) and 1-(3-bromopropyl)-4-methyl-3,6,7-trioxabicyclo[2,2,2]octane (25.1 g, 0.1 mole) were added. The mixture was placed under an argon atmosphere, heated to 70°C and stirred overnight. After cooling to room temperature, the mixture was filtered and the solvents were distilled off under reduced pressure. The crude product was dissolved in 1000 ml of deionized water and the disubstituted product was removed by extraction with ethyl acetate (2 x 100 ml). Sodium chloride (100g) was added and the product was extracted with dichloromethane (200, 100, and 100 ml). The extract was dried (MgSO<sub>4</sub>) and the solvent was distilled off under reduced pressure. The crude product (3) (26.6 g) was dissolved in 300 ml of deionized water and extracted with dichloromethane (200, 100, and 50 ml). The extract was dried (MgSO<sub>4</sub>) and the solvent was distilled off under reduced pressure. Yield: 23.4 g. NMR (d<sub>6</sub>-DMSO): 0.74 ppm (s, -CH<sub>3</sub>, orthoester) 1.56 ppm (m, -CH<sub>2</sub>-CH<sub>2</sub> -orthoester), 3.51 ppm (bm, -OCH<sub>2</sub>CH<sub>2</sub>O-), 3.80 ppm (s, -CH<sub>2</sub>, orthoester), 4.58 ppm (t, -OH). Purity: ~100%.

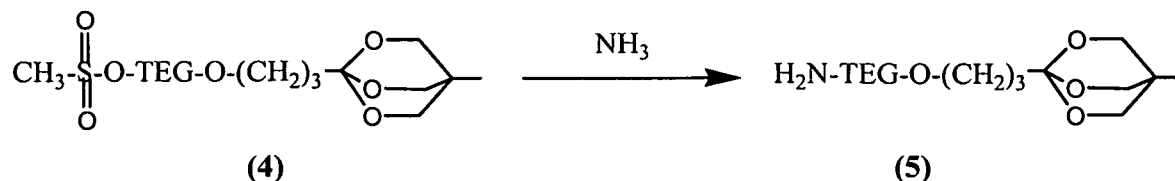
B. Tetra(ethylene glycol)- $\alpha$ -mesylate- $\omega$ -butanoic acid, orthoester (4)



A mixture of tetra(ethylene glycol) monobutanoic acid orthoester (3) (20 g, 0.0549 moles), prepared in step A above, and toluene (200 ml) was azeotropically dried by distilling off toluene under reduced pressure. The dried tetra(ethylene glycol) monobutanoic acid orthoester was dissolved in anhydrous toluene (200 ml). Then, 40 ml of anhydrous dichloromethane and 15.4 ml of triethylamine (0.1105 moles) were added to the solution followed by the dropwise addition of 7.4 g of methanesulfonyl chloride (0.0646 moles) dissolved in dichloromethane (80 ml) while maintaining the solution temperature at 0-5 °C. The solution was stirred an additional 2h at room temperature under argon atmosphere. The resulting mixture was filtered, sodium carbonate (2 g) was added, and the mixture was stirred 1.0 h. Finally the solution was filtered and the solvents distilled off under reduced pressure.

Yield: 23.2 g. NMR ( $d_6$ -DMSO): 0.74 ppm (s, -CH<sub>3</sub>, orthoester) 1.56 ppm (m, -CH<sub>2</sub>-CH<sub>2</sub>-orthoester), 3.18 ppm (s, CH<sub>3</sub>-methanesulfonate), 3.51 ppm (bm, -OCH<sub>2</sub>CH<sub>2</sub>O-), 3.67 ppm (m, -CH<sub>2</sub>-CH<sub>2</sub>-methanesulfonate), 3.80 ppm (s, -CH<sub>2</sub>, orthoester), 4.31 ppm (m, -CH<sub>2</sub>-methanesulfonate). Purity: ~100%.

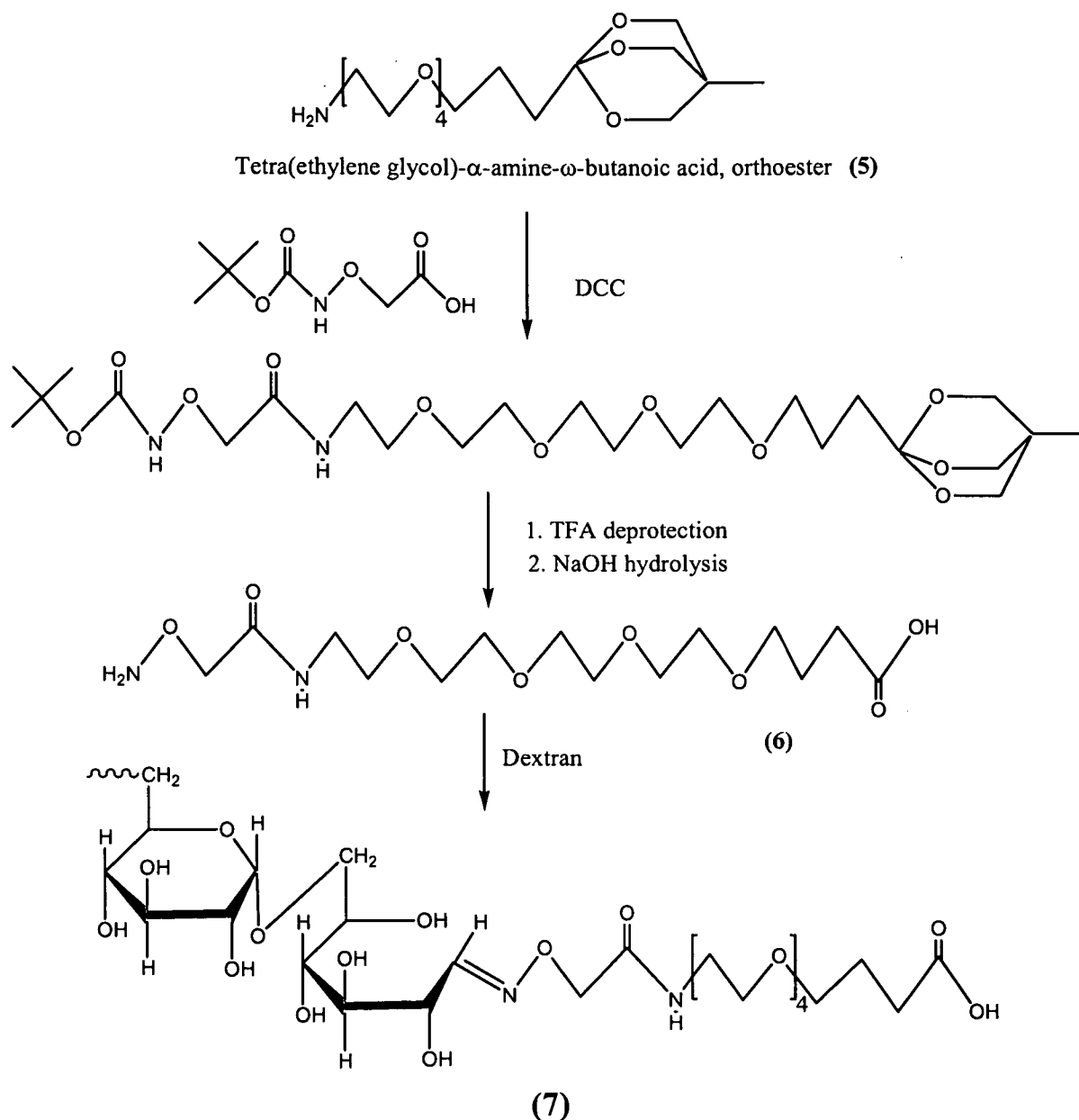
C. Tetra(ethylene glycol)- $\alpha$ -amine- $\omega$ -butanoic acid, orthoester (5)



A mixture of tetra(ethylene glycol)- $\alpha$ -mesylate- $\omega$ -butanoic acid orthoester (4) (23.2 g), prepared in step B above, ethyl alcohol (100 ml), and concentrated ammonia (1000 ml) was stirred for 88h at room temperature. The reaction mixture was extracted with dichloromethane (600, 400, and 400 ml), the extract was dried (MgSO<sub>4</sub>), and the solvent was distilled off under reduced pressure. Yield 19.5 g. NMR (D<sub>2</sub>O): 0.74 ppm (s, -CH<sub>3</sub>, orthoester) 1.63 ppm (m, -CH<sub>2</sub>-CH<sub>2</sub>-orthoester), 2.71 ppm (t, -CH<sub>2</sub>-amine), 3.58 ppm (bm, -OCH<sub>2</sub>CH<sub>2</sub>O-), 3.67 ppm (m, -CH<sub>2</sub>-CH<sub>2</sub>-methanesulfonate), 3.89 ppm (s, -CH<sub>2</sub>, orthoester). Purity: ~100%.

Example 8: Preparation of oxyimine-linked dextran(40K)-butanoic Acid (7)

This reagent was prepared according to the following scheme, described in greater detail below:



A. Preparation of tetra(ethylene glycol)- $\alpha$ -aminooxyacetamide- $\omega$ -butanoic acid (6)

To a solution of (Boc-aminooxy)acetic acid (2.0 g, 0.0105 moles; Sigma-Aldrich), N-hydroxysuccinimide (1.20 g, 0.0105 moles), 1-hydroxybenzotriazole (0.30 g, 0.0022 moles) in anhydrous  $\text{CH}_2\text{Cl}_2$  (100 ml) cooled to  $\sim 5^\circ\text{C}$ , N,N-dicyclohexylcarbodiimide (1.70 g, 0.0115 moles) dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (30 ml) was added and the mixture was stirred 1h at  $5\text{--}15^\circ\text{C}$ . Tetra(ethylene glycol)- $\alpha$ -amine- $\omega$ -butanoic acid orthoester (5), prepared as described in Example 7 (4.0 g, 0.0109 moles), and triethylamine (3.80 ml) were then added, and the mixture was stirred overnight at room temperature under nitrogen atmosphere. The mixture was filtered and the solvent was distilled off. The residue was

dissolved in deionized water (80 ml) and the product was extracted with dichloromethane. The extract was dried and the solvent was distilled off under reduced pressure, giving 4.8 g of the Boc- and orthoester-protected linker as a liquid product.

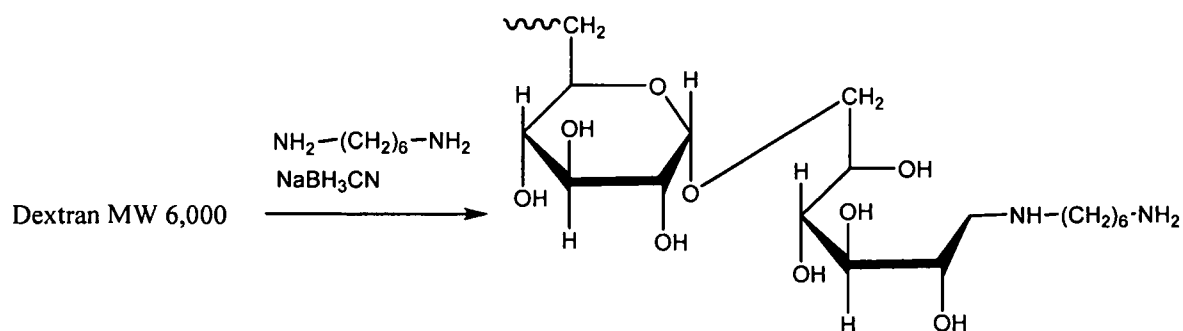
The Boc- and orthoester-protected linker, prepared as described above (4.8 g), was dissolved in a mixture of trifluoroacetic acid (30 ml) and anhydrous dichloromethane (30 ml). The resulting solution was stirred 2 h at room temperature, after which time the dichloromethane and trifluoroacetic acid were distilled off under reduced pressure. The residue was dissolved in deionized water (40 ml) and 1.0M sodium hydroxide was added to adjust the pH to 12.2. The mixture was stirred 2 h, keeping the pH 12.1 - 12.3 by periodical addition of 0.1M sodium hydroxide. The pH was then adjusted to 7.5, and a portion of water was distilled off under reduced pressure, giving 12.2 g of concentrated solution of tetra(ethylene glycol) linker (6) containing terminal oxyamine and butanoic acid groups.

**B. Reaction of heterobifunctional Reagent (6) with dextran(40K)**

To a solution of Dextran 40 (2.5 g; Mw = 46,021, Mn = 22,617, Mw/Mn = 2.03; Sigma-Aldrich) in 0.1M sodium acetate buffer, pH = 5.5, a solution of tetra(ethylene glycol)- $\alpha$ -aminooxyacetamide- $\omega$ -butanoic acid (6) (from part A above) was added. The pH was readjusted to 5.2 with acetic acid and the mixture was stirred overnight at room temperature. The solution was dialyzed 3 times against DI water using Dialysis Cassette MW CO 3.5K (Pierce). The water was then distilled off under reduced pressure. The wet crude product (7) was dried under vacuum overnight, giving 2.2 g of white solid. NMR analysis performed in D<sub>2</sub>O showed that the substitution of end groups of dextran with butanoic acid groups was 38.6%.

**Example 9: Purification of oxyimine-linked dextran(40K)-butanoic Acid (7)**

The crude functionalized dextran (7) from step B (1.8 g) was dissolved in deionized water (180 ml) and applied to a DEAE Sepharose FF column (50 ml). The column was then washed with deionized water. The material adsorbed on the column product was eluted with 10% NaCl solution. The eluate (100 ml) was dialyzed 4 times against DI water using Dialysis Cassette MW CO 3.5K (Pierce). The water was distilled off under reduced pressure, and the wet product was dried under vacuum overnight, giving 0.5 g of purified (7) as a white solid. NMR analysis performed in D<sub>2</sub>O showed that the substitution of end groups of dextran with butanoic acid groups in the purified product was ~100 %.

**Example 10: Preparation of dextran(6K)-hexamethylenediamine (8)**

A mixture of hexamethylenediamine (1.8 g), sodium cyanoborohydride (1.2 g), acetic acid (0.44 ml) and DMSO (12 ml) was warmed to 85°C. Dextran 40 (1.5 g; Mw = 46,021, Mn = 22,617, Mw/Mn = 2.03; Sigma-Aldrich) was added slowly during 3 h, and the mixture was stirred 24 h at 85°C. After cooling to room temperature, the reaction mixture was dialyzed 3 times against DI water using Dialysis Cassette MW CO 3.5K (Pierce). The water was distilled off under reduced pressure, and the wet product (8) was dried under vacuum overnight. The product was purified using cation exchange chromatography. NMR analysis performed in D<sub>2</sub>O showed that the substitution of end groups of dextran with amine groups was 38.6%.

**Example 11: Preparation of heterobifunctional reagent di(ethylene glycol)- $\alpha$ -amino- $\omega$ -oxyamine (11)****A. Preparation of CBZ-NH-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>-OH (9)**

To 2-(2-aminoethoxy)ethanol (20 g) dissolved in dichloromethane (200 ml) was added stepwise triethylamine (26.5 ml) and benzyloxy(carbonyloxy)succinimide (47.47 g). The reaction mixture was stirred overnight at room temperature. The solvent was distilled off under reduced pressure and the residue was dissolved in deionized water (500 ml). The insoluble layer was separated, and the aqueous layer was mixed with 50 g of NaCl and the pH adjusted to 5.0 with 5 % H<sub>3</sub>PO<sub>4</sub>. The product was extracted with dichloromethane (100 ml, 50 ml, and 50 ml) and the extract was dried with MgSO<sub>4</sub>, filtered, and evaporated to dryness under reduced pressure. The residue was dried under vacuum overnight, then combined with the previously separated insoluble layer and dissolved in dichloromethane (300 ml). The solution was washed with 5-% aqueous NaCl solution (3 x 50 ml) and dried with MgSO<sub>4</sub>. The solvent was distilled under reduced pressure, and the residue was dried overnight under vacuum, giving 40 g of the desired product.

**B. Preparation of CBZ-NH-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>-O(SO<sub>2</sub>)CH<sub>3</sub> (10)**

CBZ- Methanesulfonyl chloride (7.1 ml) dissolved in anhydrous dichloromethane (70 ml) was slowly added to the product (9) of step A, and the mixture was stirred overnight at room temperature under nitrogen atmosphere. The mixture was filtered, stirred 1h with solid Na<sub>2</sub>CO<sub>3</sub> (26.6 g), and refiltered. The filtrate was concentrated under reduced pressure, the residue was re-dissolved in toluene (150 ml), and the resulting solution was filtered and concentrated by distillation under reduced pressure. The residue was dried overnight under vacuum, giving 24 g of the desired product (10).

C. Preparation of CBZ-NH-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>-ONH<sub>2</sub> (11)

CBZ-NH-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>-O(SO<sub>2</sub>)CH<sub>3</sub> (10) (24 g), prepared as described in step B, was dissolved in CH<sub>3</sub>CN (240 ml), and *endo*-N-hydroxy-5-norbomene-2,3-dicarboximide (20.5 g) followed by diisopropylethylamine (39.5 ml) was added. The reaction mixture was refluxed at 93 °C overnight under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered and the solvent distilled off under reduced pressure. The residue was dissolved in dichloromethane (200 ml), and the solution was washed with 0.1 M phosphate buffer (pH 5.0, 2 x 100 ml) and dried with (MgSO<sub>4</sub>). The solvent was distilled off under reduced pressure, the residue was dissolved in ethyl alcohol (150 ml), and butylamine (28.0 ml) was added. The mixture was stirred overnight at 90°C under nitrogen atmosphere. The solution was filtered and the solvent was distilled off under reduced pressure. The crude product was dissolved in 100 mM phosphate buffer, pH = 4.5 (120 ml), and the solution was filtered. The impurities were removed by extraction with ethyl ether (3 x 20 ml). NaCl (15 g) was added, the pH was readjusted to 9 with 1.0 M NaOH, and the product was extracted with dichloromethane (3 x 50 ml). The extract was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure giving (11) as a clear liquid product.

Example 12: Preparation of tetra(ethylene glycol)-α-oxyamino-ω-butyraldehyde, diethyl acetal (14)

This reagent can be used to prepare an aldehyde-terminated carbohydrate derivative, as shown in Example 13 below.

A. Tetra(ethylene glycol) mono-butyraldehyde, diethyl acetal (12)

A mixture of tetra(ethylene glycol) (97.1 g, 0.500 moles) and toluene (200 ml) was azeotropically dried by distilling off toluene under reduced pressure. The dried tetra(ethylene glycol) was dissolved in anhydrous toluene (180 ml), and a 1.0 M solution of potassium tert-butoxide in tert-butanol (120.0 ml, 0.120 moles) and 4-chlorobutyraldehyde diethyl acetal (18.1 g, 0.100 moles) were added. The mixture was stirred at 90°C overnight under argon

atmosphere. After cooling to room temperature, the mixture was filtered and the solvents were distilled off under reduced pressure. The crude product was dissolved in 1000 ml deionized water and the resulting solution was filtered through activated carbon. Sodium chloride (10g) was added and the product was extracted with dichloromethane (250, 200, and 150 ml). The extract was dried ( $\text{MgSO}_4$ ) and the solvent was distilled off under reduced pressure. Yield: 20.3 g. NMR ( $d_6$ -DMSO): 1.10 ppm (t,  $\text{CH}_3$ -C-) 1.51 ppm (m, C- $\text{CH}_2$ - $\text{CH}_2$ -), 3.49 ppm (bm,  $-\text{OCH}_2\text{CH}_2\text{O}-$ ), 4.46 ppm (t,  $-\text{CH}$ , acetal), 4.58 ppm (t,  $-\text{OH}$ ). Purity: ~100%.

**B. Tetra(ethylene glycol)- $\alpha$ -mesylate- $\omega$ -butyraldehyde diethyl acetal (13)**

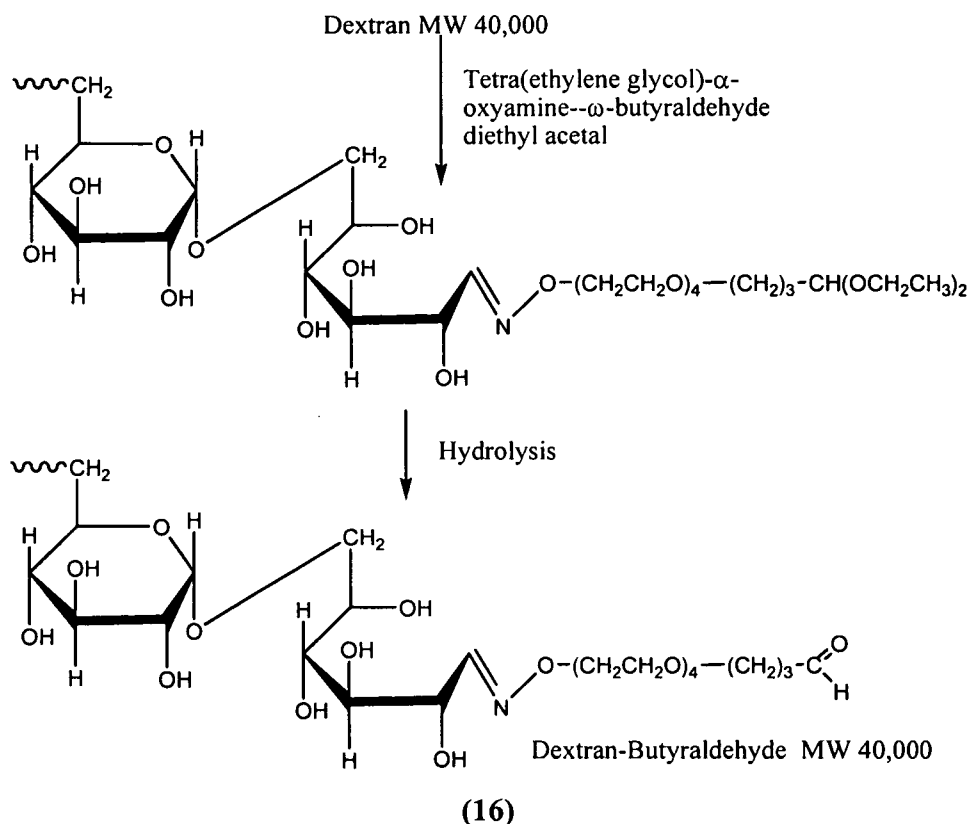
A mixture of tetra(ethylene glycol) mono-butylaldehyde diethyl acetal (12) (12.5g, 0.037 moles), prepared in step A above, and toluene (120 ml) was azeotropically dried by distilling off toluene under reduced pressure. The dried tetra(ethylene glycol) mono-butylaldehyde, diethyl acetal was dissolved in anhydrous toluene (100 ml). To the solution was added 20 ml of anhydrous dichloromethane and 5.7 ml of triethylamine (0.041 moles). Then 4.5g of methanesulfonyl chloride (0.039 moles) was added dropwise. The solution was stirred at room temperature under nitrogen atmosphere overnight. Sodium carbonate (5 g) was added, and the mixture was stirred 1h. The solution was filtered and solvents were distilled off under reduced pressure. NMR ( $d_6$ -DMSO): 1.10 ppm (t,  $\text{CH}_3$ -C-) 1.51 ppm (m, C- $\text{CH}_2$ - $\text{CH}_2$ -), 3.17 ppm (s,  $\text{CH}_3$ - methanesulfonate), 3.49 ppm (bm,  $-\text{OCH}_2\text{CH}_2\text{O}-$ ), 4.30 ppm (m,  $-\text{CH}_2$ - methanesulfonate), 4.46 ppm (t,  $-\text{CH}$ , acetal). Purity: ~100%.

**C. Tetra(ethylene glycol)- $\alpha$ -oxyamino- $\omega$ -butyraldehyde diethyl acetal (14)**

To a solution of tetra(ethylene glycol)- $\alpha$ -mesylate- $\omega$ -butylaldehyde diethyl acetal (13) (20.0 g), prepared in step B above, in anhydrous acetonitrile (200 ml), *endo*-N-hydroxy-5-norbornene-2,3-dicarboximide (13.0 g) and diisopropylethylamine (21.0 ml) was added and the mixture was stirred at 90°C overnight under nitrogen atmosphere. The solution was filtered and the solvent was distilled off under reduced pressure. The residue was dissolved in ethyl alcohol (100 ml) and butylamine (26.0 ml) was added. The mixture was stirred 6 h at 90°C under nitrogen atmosphere. The solution was filtered and the solvent was distilled off under reduced pressure. The crude product was dissolved in 100 mM phosphate buffer, pH = 5.0 (200 ml), and the solution was filtered. The impurities were removed by extraction with ethyl ether (3 x 25 ml). NaCl (20g) was then added, the pH was readjusted to 9 with 1.0 M

NaOH, and the product was extracted with dichloromethane (3 x 50 ml). The extract was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure, giving 18 g of clear viscous water white liquid product. NMR (DMSO-d<sub>6</sub>): 1.11 ppm (t, CH<sub>3</sub>-C-) 1.51 ppm (m, C-CH<sub>2</sub>-CH<sub>2</sub>-), 3.47 ppm (bm, -OCH<sub>2</sub>CH<sub>2</sub>O-), 4.56 ppm (t, -CH, acetal), 5.97 ppm (s, H<sub>2</sub>N-O-). Purity: ~100%.

**Example 13: Preparation of oxyimine-linked dextran(40K)-butyraldehyde (16)**



**A. Oxyimine-linked dextran(40K)-butyraldehyde diethyl acetal (15)**

To a solution of Dextran 40 (2.5 g; Mw = 46,021, Mn = 22,617, Mw/Mn = 2.03; Sigma-Aldrich) in 0.1M sodium acetate buffer, pH = 5.2 (20 ml), tetra(ethylene glycol)-α-oxyamino-ω-butyraldehyde diethyl acetal (14) (0.30 g), prepared as described in Example 12, was added. The pH was readjusted to 5.2 and the mixture was stirred overnight at room temperature. The solution was dialyzed 3 times against DI water using Dialysis Cassette MW CO 3.5K (Pierce). The water was then distilled off under reduced pressure. The wet product was dried under vacuum overnight, giving 2.3 g of a white solid. NMR analysis performed in D<sub>2</sub>O showed that the substitution of end groups of dextran with butyraldehyde diethyl acetal groups was 78.9%.

**B. Oxyimine-linked dextran(40K)-Butyraldehyde (16)**

Dextran(40K)-butyraldehyde diethyl acetal (0.336 g), prepared in step A above, was dissolved in 2 ml of 10 mM phosphate buffer (pH = 7.2), and the pH was adjusted to 2.0 with 5% phosphoric acid. The mixture was stirred 1.5 h. The pH was then readjusted to 6.5 with 1.0 N sodium hydroxide. The obtained solution of (16) was used directly for the dextran modification of lysozyme.

**Example 14: Reaction of oxyimine-linked dextran(40K)-butyraldehyde (16) with lysozyme**

To the solution of oxyimine-linked dextran(40K)-butyraldehyde (16) obtained as described in Example 13 above, lysozyme (6 mg; Sigma-Aldrich) was added, and the mixture was stirred for 15 min, followed by addition of 0.21 ml of 0.1 M aqueous solution of sodium cyanoborohydride (Sigma-Aldrich). The mixture was stirred overnight at room temperature. HPLC analysis showed that Dextran-Lysozyme conjugate (17) was formed.

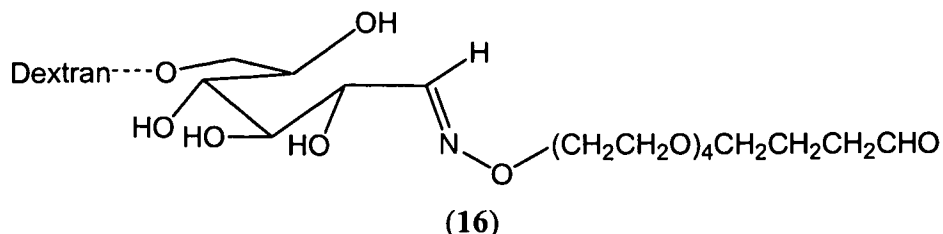
**Example 15: Larger scale preparation of oxyimine-linked dextran(40K)-butyraldehyde (16)****A. Oxyimine-linked dextran(40K)butyraldehyde diethyl acetal (15)**

To a solution of Dextran 40 (130 g; Mw = 40,210, Mn = 30,931, Mw/Mn = 1.3; Pharmacosmos A/S, Denmark) in 0.1M sodium acetate buffer, pH = 5.2 (780 ml), tetra(ethylene glycol)- $\alpha$ -oxyamino- $\omega$ -butyraldehyde diethyl acetal (14) (20.3 g), prepared as described in Example 12 above, was added. The pH was readjusted to 5.2 with acetic acid and the mixture was stirred overnight at room temperature. The crude product was precipitated with isopropyl alcohol, collected by vacuum filtration and dried. The precipitation process was repeated two more times to remove all unreacted reagent. The yield of the solid dry product (15) was 114 g. NMR analysis performed in D<sub>2</sub>O showed that the substitution of end groups of dextran with butyraldehyde diethyl acetal groups was ~85%.

**B. Oxyimine-linked dextran(40K)-Butyraldehyde (16)**

Dextran(40K)-butyraldehyde diethyl acetal (114 g), prepared in step A above, was dissolved in 1100 ml of deionized water and the pH was adjusted to 3.0 with 10% phosphoric acid, and the mixture was stirred for 1 h. The pH was then readjusted to 6.8 with 1.0 N sodium hydroxide. The solution was concentrated to dryness under reduced pressure, the crude product was redissolved in 600 ml of deionized water, and the solution was lyophilized, giving 108 g of white solid product. NMR analysis performed in D<sub>2</sub>O showed that the substitution of end groups of dextran with butyraldehyde groups was ~ 80%.

**Example 16: Conjugation of protegrin-1 with oxyimine-linked dextran<sub>40K</sub> tetraethylene glycol butyraldehyde (16)**



Stock solutions of 0.3 mg/mL protegrin-1 and 55 mg/mL dextran tetraethylene glycol (TEG) butyraldehyde 40K (16), both in 50 mM HEPES, pH 7.0, were prepared. To initiate a reaction, both stock solutions were brought to 25°C and then mixed in equal volumes. The reaction mixture was stirred at 25°C. After 1 hour reaction, 100 μM sodium cyanoborohydride (final concentration) was added and the reaction was allowed to proceed for an additional 4 hours.

The dextran-protegrin-1 conjugate (18) was purified from the reaction mixture by cation-exchange chromatography using CM Sepharose (GE Healthcare). Thus, upon completion of the conjugation reaction, the reaction mixture was diluted 10-fold with water and loaded onto a column packed with CM Sepharose resin. The resin was washed with buffer B (10 mM HEPES, pH 7, 1M NaCl) and equilibrated with buffer A (10 mM HEPES, pH 7) prior to sample loading. After loading, the column was washed with 2 column volumes buffer A. Conjugated and nonconjugated peptides were eluted in a linear gradient of 0-100% buffer B in 10 column volumes at a flow rate of 7 mL/min.

Fractions containing dextran-butyraldehyde-40K-protegrin-1 were pooled, dialyzed against water, lyophilized and stored at -80°C. SDS-PAGE analysis (4-12% gel) of the purified dextran-butyraldehyde-40K-protegrin-1 conjugate (18) is shown in Fig. 1. Dextran perturbs the gel migration of the dextran-peptide conjugate; the conjugate's band location is not indicative of its size.

**Example 17: Conjugation of C-peptide (S20C) with oxyimine-linked dextran<sub>40K</sub> tetraethylene glycol butyraldehyde (16)**

Stock solutions of 2 mg/mL C-peptide(S20C) and 200 mg/mL oxyimine-linked dextran tetraethylene glycol (TEG)-butyraldehyde 40K (16), both in 500 mM HEPES, pH 7.0, were prepared. To initiate a reaction, both stock solutions were brought to 25°C and then mixed in equal volumes. The reaction mixture was stirred at 25°C. After 1 hour reaction, 10 mM

sodium cyanoborohydride (final concentration) was added, and the reaction was allowed to proceed for an additional 16 hours.

The dextran-C-peptide(S20C) conjugate (19) was purified from the reaction mixture by anion-exchange chromatography using Q HP Sepharose resin (GE Healthcare). Thus, upon completion of the conjugation reaction, the reaction mixture was diluted 2-fold with water and loaded onto a column packed with the Sepharose resin. The resin was washed with buffer B (10 mM HEPES, pH 7, 1M NaCl) and equilibrated with buffer A (10 mM HEPES, pH 7) prior to sample loading. After loading, the column was washed with 2 CV buffer A. Conjugated and nonconjugated peptides were eluted in a linear gradient of 0-100% buffer B in 10 CV at a flow rate of 8 mL/min. A conjugate-containing fraction collected during chromatography with Q HP Sepharose was diluted 10-fold with water and re-loaded onto the Q column in order to concentrate the conjugate. The conjugate (19) was eluted with 100% buffer B.

Fractions collected during both anion exchange chromatography runs were analyzed using reversed-phase HPLC. An Agilent Poroshell 300-SB-C8 column was used with a flow rate of 0.2 ml/min and a column temperature of 50°C. Detection was carried out at 215 nm. The column was equilibrated in 0% Mobile Phase B, and conjugate separation was achieved using the gradient timetable shown below:

Time (min)	% Mobile phase A (0.1% TFA in water)	% Mobile phase B (0.85% TFA in CH <sub>3</sub> CN)
0.00	100.0	0.0
5.00	70.0	30.0
15.00	40.0	60.0
20.00	20.0	80.0

The concentrated purified conjugate (19) collected from the second anion exchange chromatography run was dialyzed against water and frozen at -80°C. The purity of the mono-dextran conjugate (19) was >93% by RP-HPLC analysis, and the mass as determined by MALDI-TOF was within the expected range (Fig. 2).

Example 18: Conjugation of insulin with oxyimine-linked dextran<sub>40K</sub> tetraethylene glycol butyraldehyde (16)

Insulin contains three primary amine groups, all of which can undergo a reductive amination reaction with an aldehyde. Reactions of insulin with oxyimine-linked dextran<sub>40K</sub> tetraethylene glycol butyraldehyde (**16**) therefore produce a mixture of mono-, di- and tri-conjugated peptides. The relative yields of these products depend primarily on the molar ratios of insulin and the dextran reagent used in the reactions, and the reaction conditions (*e.g.*, reaction time and temperature). The relative yield of the mono-conjugated peptide was determined to be very low unless reaction conditions were selected in which the majority of the insulin remained unreacted. Thus, in order to increase the relative and absolute yields of mono-conjugated insulin, a fraction of the amine groups on the peptide were blocked by acetylation prior to reacting the peptide and the dextran reagent. This example will describe the conjugation of both non-acetylated and partially acetylated insulin.

A. Conjugation of non-acetylated insulin with oxyimine-linked dextran<sub>40K</sub> tetraethylene glycol butyraldehyde (**16**)

Stock solutions of 2 mg/ml insulin and 42/mL oxyimine-linked dextran-butyRALD-40K (**16**) were prepared in DMSO/TEA (95%:5%, v/v). To initiate a reaction, both stock solutions were brought to ambient temperature and then mixed in equal volumes. After 5 min reaction with stirring at ambient temperature, 1 M sodium cyanoborohydride was added, to a final concentration of 20 mM, and the reaction was allowed to proceed with continued stirring for 22 hours at ambient temperature.

The product dextran-butyRALD-40K-insulin (**20a**) was purified from the reaction mixture by anion-exchange chromatography using Q Sepharose FF (GE Healthcare). Thus, upon completion of the conjugation reaction, the reaction mixture was diluted 15-fold with 20 mM HEPES (pH 7) and the mixture was loaded onto a column packed with Q Sepharose FF resin. The resin was washed with Buffer B (20 mM HEPES, 1.0 M sodium chloride, pH 7) and equilibrated with Buffer A (20 mM HEPES, pH 7) prior to sample loading. After loading, the resin was washed with 5 column volumes Buffer A. Conjugated and nonconjugated peptides were eluted using a linear gradient of 0-100% Buffer B over 10 column volumes at a flow rate of 150 cm/h.

B. Conjugation of partially acetylated insulin with oxyimine-linked dextran<sub>40K</sub> tetraethylene glycol butyraldehyde (**16**)

Stock solutions of 2.5 mg/mL (430  $\mu$ M) insulin, 2.24 mg/mL (8.62 mM) sulfo-N-hydroxysuccinimide (NHS)-acetate, and 138 mg/mL (3.45 mM) oxyimine-linked dextran-butyRALD-40K were prepared in DMSO/TEA (95%:5%, v/v), DMSO, and DMSO/TEA (99.35%:0.65%, v/v), respectively. To initiate an acetylation reaction of insulin, in which a

fraction of the amine groups on the peptide are acetylated, the insulin and sulfo-NHS-acetate stock solutions were brought to ambient temperature and mixed at a 4:1 ratio (v/v).

After 30 min acetylation reaction with stirring, conjugation of the peptide with dextran-butyrald-40K (16) was initiated by the drop-wise addition of an equal volume of stock solution of (16) to the acetylation reaction mixture under vigorous stirring. Tween-20 was then added, to a final concentration of 0.05% (v/v), and the reaction mixture was brought to 37°C with stirring. After 20 minutes, 1 M sodium cyanoborohydride was added, to a final concentration of 17 mM, and the reaction was allowed to proceed with continued stirring for an additional 20 hours at 37°C.

The product dextran-butyrald-40K-insulin was purified from the reaction mixture by anion-exchange chromatography using Q Sepharose FF (GE Healthcare). Thus, upon completion of the conjugation reaction, the reaction mixture was diluted 1:3 with 20 mM HEPES (pH 7) and the mixture was loaded onto a column packed with Q Sepharose FF resin. The resin was washed with Buffer B (20 mM HEPES, 1.0 M sodium chloride, pH 7) and equilibrated with Buffer A (20 mM HEPES, pH 7) prior to sample loading. After loading, the resin was washed with 10 column volumes Buffer A. Conjugated and nonconjugated peptides were eluted using a two-step gradient consisting of 0 to 25% Buffer B over 25 column volumes and 25% to 75% Buffer B over 5 column volumes at a flow rate of 90 cm/h.

Fractions containing lower molecular weight, less substituted conjugates were identified by SDS-PAGE. These fractions were pooled, diluted 10-fold with 20 mM HEPES, pH 7 (Buffer A), and applied to a second column packed with Q Sepharose FF resin for sample concentration. The resin was washed with Buffer B and equilibrated with Buffer A prior to sample loading. Dextran-butyrald-40K-insulin was eluted using a linear gradient of 0-75% Buffer B over 3 column volumes at a flow rate of 90 cm/h.

Fractions containing dextran-butyrald-40K-insulin were pooled and lyophilized. These fractions were shown SDS-PAGE analysis of the pooled fractions to contain a significant amount of nonconjugated insulin (Figure 3, Lane 1). The nonconjugated insulin can be removed by selective precipitation of the conjugate from a water/DMSO solution (50/50, v/v) through the addition of an organic solvent (for example, acetonitrile). Dextran-butyrald-40K-insulin is less soluble than nonconjugated insulin in organic solvents and precipitates upon addition of an organic solvent. Thus, lyophilized dextran-butyrald-40K-insulin was dissolved in water, to a peptide concentration of 2 mg/mL, and an equal volume of DMSO was added to the solution. After thorough mixing, acetonitrile was added drop-wise until the

composition of the mixture was 25% water, 25% DMSO, and 50% acetonitrile (v/v/v). Precipitated conjugated insulin was collected by centrifugation and re-dissolved in water. SDS-PAGE analysis showed that the final concentration of nonconjugated insulin in this product was less than 1% of the total peptide amount (Figure 3, Lane 2). The redissolved conjugate (**20b**) was lyophilized and stored at -80°C.

Example 19: Receptor binding: *In vitro* binding of the insulin-dextran conjugate.

The *in vitro* affinity for the insulin receptor of the insulin-dextran conjugate (**20b**), prepared as described in Example 18, was evaluated using radioligand binding assays in CHO cells that stably express the recombinant human insulin receptor (CHO-hIR). CHO-hIR cells were plated in 24 well plates and washed with assay buffer containing 120 mM NaCl, 5 mM KCl, 1.2 mM MgSO<sub>4</sub>, 9 mM Glucose, 10 mM HEPES, 0.5% BSA, pH 8.0. The insulin-dextran conjugate was 98% pure and contained up to 2% of free and acetylated insulin.

Competition binding assays were conducted by incubating CHO-hIR cells with increasing concentrations of insulin, insulin-dextran conjugate (**20b**), and glycine dextran and a fixed concentration (100 pM) of <sup>125</sup>I-labelled recombinant human insulin for 4 hours at 4°C. Cells were washed to remove unbound ligands and solubilized with 0.2 N NaOH, and bound radioactivity was counted using a gamma counter. Non-specific binding was measured in the presence of excess cold insulin, and subtraction of this value from the total binding yielded the specific binding at each test compound concentration. IC<sub>50</sub> values were obtained from non-linear regression analysis of specific binding versus concentration curves.

The results of the *in vitro* competition binding assay are shown in Figure 4. Insulin and the Dextran-TEG-butyraldehyde-40K acetyl insulin conjugate (**20b**) bound to the insulin receptor with IC<sub>50</sub> values of 4.3 nM and 174.9 nM respectively. Dextran conjugation thus resulted in a 40-fold reduction in the binding affinity of insulin. The dextran itself did not display specific binding to the insulin receptor at concentrations up to 1 μM.

Example 20: *In vivo* effect of dextran-conjugated insulin on blood glucose levels in db/db diabetic mice

Summary: Dextran conjugated insulin (**20b**) (250 μg/mouse) was administered by i.p. injection into diabetic mice having elevated blood glucose levels. Blood glucose levels were measured at different time points after dosing. PBS saline solution and Dextran equivalent doses were administered as negative controls, and insulin (50 μg/mouse) was injected as

positive control. Insulin (5 µg/mouse) was also given to a group of db/db mice to determine whether the presence of ~2% free insulin in the 250 µg Dextran-insulin prep (i.e. ~ 5 µg) would have an effect.

Study Procedure: Animals were acclimated to researcher's handling procedures. Baseline glucose levels were measured prior to drug administration. Outlier animals with glucose level <300 or >600 mg/dL were excluded from the study. Animals were assigned randomly to different groups, as follows:

Group	Test Article	Route	Dose	Dose Volume	# Animals
1	PBS	ip	-	100 ul	4
2	Dextran-Insulin	ip	250ug/mouse	100 ul	5
3	Insulin	ip	50 ug/mouse	100 ul	5
4	Insulin	ip	5 ug/mouse	100 ul	5
5	Dextran	ip	1.75 mg/mouse	100 ul	5

At different time points (1, 2, 4, 8, and 24 hrs), blood was collected by tail clipping, and glucose level was measured using a One Touch® Ultra glucometer (Johnson & Johnson; Life Scan Ltd.)

Results: Glucose levels in db/db mice after drug administration are listed in Table 1 and plotted in Figure 5. As shown, Dextran-Insulin conjugate (**20b**) (250 ug/mouse) reduced glucose level from 495±32 mg/dL at time 0 to 263±39 mg/dL at 1hr (47% reduction) and to 192±36 mg/dL at 2 hrs after administration (61% reduction). Insulin (50 ug/mouse) produced a 53% and 67% reduction at 1 and 2 hrs, respectively, after injection; and insulin (5 ug/mouse) produced a 48% and 31% reduction at 1 and 2 hrs, respectively, after injection.

PBS and Dextran injections were not observed to decrease db/db mice glucose levels throughout the course of the study.

The data shows that the Dextran-Insulin conjugate produced a prolonged effect in comparison with the 5 µg/mouse insulin injections (i.e. 61% vs. 31% reduction at 2 hr).

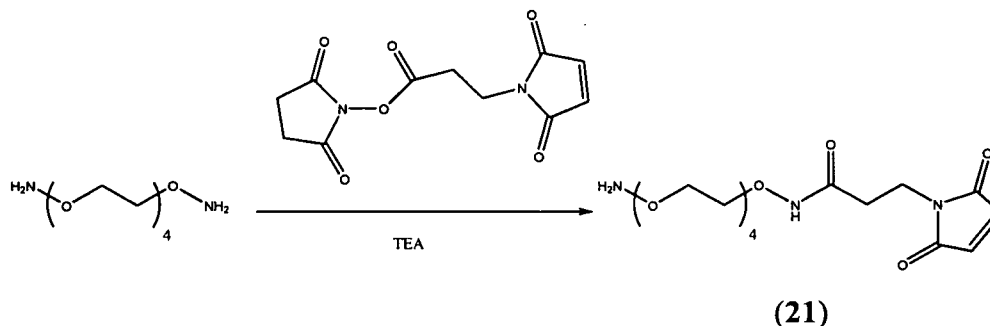
Table 1: Glucose levels in db/db mice after compound administration.

Time (hr)	<u>PBS (N=4)</u>		<u>Dex-Ins 250ug (N=4)</u>		<u>Ins 50ug (N=5)</u>		<u>Ins 5ug (N=5)</u>		<u>Dextran 1.75mg (N=5)</u>	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
0	486	51	495	32	445	29	510	37	485	31
1	528	54	263	39	210	16	265	51	565	32
2	582	9	192	36	150	15	352	60	565	22
4	597	1	462	30	550	25	587	9	562	27
8	577	14	494	10	558	23	538	30	540	36

24	560	24	517	24	541	19	538	36	531	40
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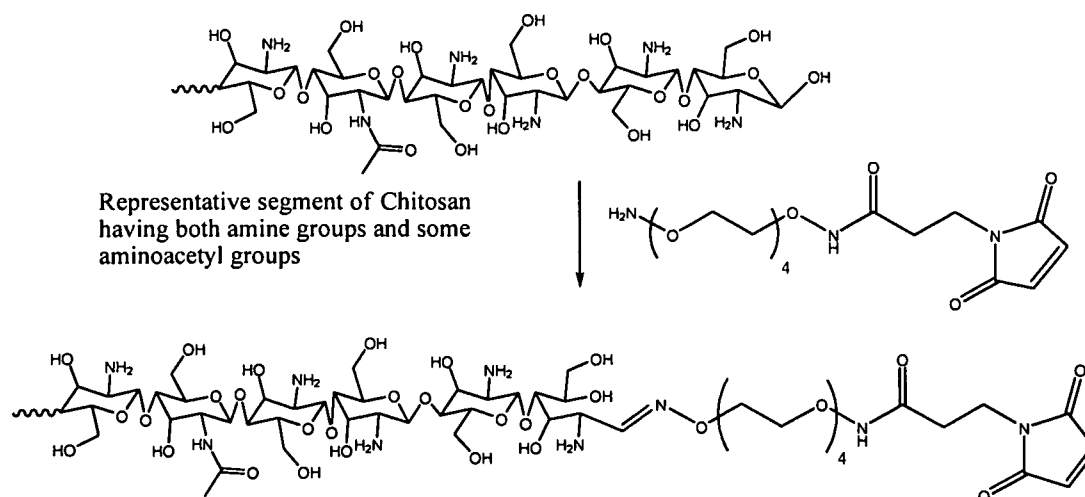
**Example 21: Preparation of oxyimine-linked chitosan (3-5K) tetra(ethylene glycol) maleimidopropionamide (22)**

**A. Preparation of  $\alpha$ -oxyaminoacetamide-tetra(ethylene glycol)- $\omega$ -maleimidopropionamide (21)**



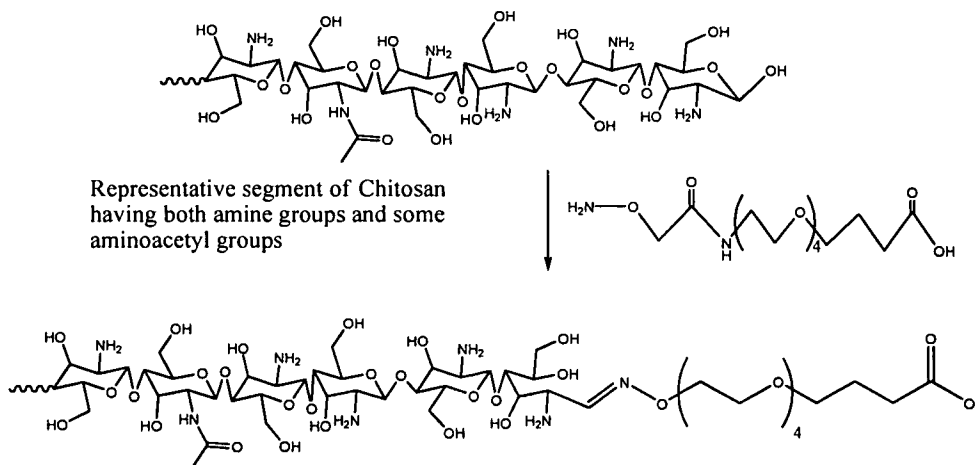
To a solution of  $\alpha,\omega$ -bis-oxyaminotetra(ethylene glycol) (2.0g) and triethylamine (1.0 ml) in acetonitrile (20 ml) was added dropwise a ten-fold excess of 3-maleimidopropionic acid, N-succinimidyl ester (Pierce) while stirring and maintaining the liquid temperature at  $\sim 25^\circ\text{C}$ . After stirring for an additional 2 hours, the solids were filtered off and the solvent was removed by vacuum distillation. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and extracted with water. The  $\text{CH}_2\text{Cl}_2$  extract was evaporated and distilled water was added to dissolve the residue. This solution, containing a mixture of the desired product and a large amount of bis-TEG-maleimide, was chromatographed on a POROS cation exchange resin to provide 0.26 g of the desired product **21**. This product was used directly in the next step.

**B. Preparation of oxyimine-linked chitosan (3-5K) tetra(ethylene glycol) maleimidopropionamide (22)**



## (22)

To a solution of chitosan 3-5K (Kitto Life, Kyongki-Do, Korea, 0.1 g; MW = 3000-5000 by GPC) in 0.5M sodium phosphate buffer, pH = 5 (2 mL),  $\alpha$ -oxyaminoacetamide-tetra(ethylene glycol)- $\omega$ -maleimidopropionamide (prepared in step A above, 0.060 g) was added. Slowly to the solution, acetonitrile (2 mL) was added. The mixture was stirred overnight at 70°C. The reaction mixture was cooled to room temperature and dialyzed for 3 hours against DI water using Dialysis Cassette MWCO 3500 (Pierce). The water was distilled off under reduced pressure. The wet product was dried under vacuum overnight giving 0.13 g of **22** as a yellowish solid. NMR analysis performed in D<sub>2</sub>O showed that the substitution of end groups of chitosan with maleimide substitution was  $\geq 90\%$ .

Example 22: Preparation of oxyimine-linked chitosan (10K)-butanoic acid (23)

To a solution of chitosan (10K) (0.2 g, Kitto Life, Kyongki-Do, Korea, containing ~ 15% acetyl groups, ave. MW = 10000 by GPC) in 0.1M sodium acetate buffer, pH = 5.5, a solution of tetra(ethylene glycol) linker containing oxyamine group and butanoic acid group (from Example 8 above) was added. The pH was readjusted to 5.2 with acetic acid and the mixture was stirred overnight at room temperature. The solution was dialyzed 3 times against DI water using Dialysis Cassette MW CO 10000K (Pierce). The water was distilled off under reduced pressure. The wet product was dried under vacuum overnight giving 2.2 g of **23** as a white solid. NMR analysis performed in D<sub>2</sub>O showed that the substitution of end groups of chitosan with butanoic acid groups was ~26%.

Example 23: ssRNA-C<sub>6</sub>-SS-Mal-TEG-Chitosan Conjugate (24)

The title conjugate was produced by the reduction of 5'capped-RNA (5'-C6-S-SC6-AmCAmACmAGmACmUUmUAmAUmGUmAA-3', Tri-Link BioTechnologies, San Diego,

CA) with Tris (2-Carboxyethyl) phosphine Hydrochloride (TCEP·HCl) followed by the coupling with chitosan (3-5K) tetra(ethylene glycol)maleimidopropionamide **22**, produced in Example 21. To reduce 5'-capped-RNA, a 0.015 mL solution containing 0.003 mL 5'-capped-RNA, 0.003 mL, 1 M, EPPS, pH 8.5 and 0.007 mL 64 mM TCEP·HCl was incubated at 25 °C without stirring for 60 minutes. After 60 minutes incubation, 0.015 mL reaction mixture was loaded on a desalting column (pre-equilibrated with 20 mM HEPES, 50 mM NaCl, pH 7.4) and rinsed with 0.045 mL buffer (20 mM HEPES, 50 mM NaCl, pH 7.4). A total of 0.06 mL solution containing RNA with free thiol group (5'-HSC6-AmCAmACmAGmACmUUmUAmAUmGUmAA-3') was collected.

To couple reduced RNA with the maleimide, 0.005-mL of reduced oligo from the above reaction was mixed with 0.005-ML solution containing the maleimide. The reaction mixture was incubated at 25 °C without stirring for three hours. Analysis of the reaction mixture by ion-exchange HPLC revealed a new peak attributable to the title conjugate.

**CLAIMS**

1. A method of selectively monoderivatizing a water-soluble carbohydrate polymer at its reductive terminus, wherein said reductive terminus comprises a hemiacetal or ketal group or the corresponding aldehyde or ketone functionality, the method comprising:

contacting said carbohydrate polymer with a heterobifunctional oxyamine or hydrazine reagent, effective to produce a monoderivatized carbohydrate derivative having a functional group, not selected from oxyamine and hydrazine, linked via an oxyimine or hydrazone moiety at said terminus.

2. The method of claim 1, further comprising reducing the double bond of said oxyimine or hydrazone moiety.

3. The method of claim 2, wherein said monoderivatized carbohydrate derivative has the structure



where

POLY<sup>1</sup> is said carbohydrate polymer and C<sup>a</sup> is the anomeric carbon atom of said terminal hemiacetal or ketal group or corresponding aldehyde or ketone functionality;

R<sup>1</sup> is H or hydroxymethyl;

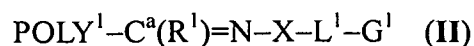
X is oxygen or NR<sup>2</sup>, where R<sup>2</sup> is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl;

R<sup>3</sup> is H or methyl;

L<sup>1</sup> is a linker group, and

G<sup>1</sup> is an optionally protected functional group, not selected from oxyamine and hydrazine.

4. The method of claim 1, wherein the monoderivatized carbohydrate derivative has the structure



where:

POLY<sup>1</sup> is said carbohydrate polymer and C<sup>a</sup> is the anomeric carbon atom of said terminal hemiacetal or ketal group or corresponding aldehyde or ketone functionality;

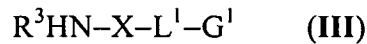
R<sup>1</sup> is H or hydroxymethyl;

X is oxygen or NR<sup>2</sup>, where R<sup>2</sup> is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl;

L<sup>1</sup> is said linker group, and

G<sup>1</sup> is said optionally protected functional group, not selected from oxyamine and hydrazine.

5. The method of claim 1, wherein the heterobifunctional oxyamine or hydrazine reagent has the structure



where:

X is oxygen or NR<sup>2</sup>, where R<sup>2</sup> is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl;

R<sup>3</sup> is H or methyl;

L<sup>1</sup> is a linker group, and

G<sup>1</sup> is an optionally protected functional group, not selected from oxyamine and hydrazine, which is unreactive under the conditions of said contacting.

6. The method of claim 5, where R<sup>3</sup> is H.

7. The method of claim 4, wherein X is oxygen.

8. The method of claim 4, wherein X is NR<sup>2</sup>.

9. The method of claim 8, where R<sup>2</sup> is hydrogen.

10. The method of claim 4, wherein R<sup>1</sup> is hydrogen.

11. The method of claim 10, wherein POLY<sup>1</sup> is a dextran or a chitosan.

12. The method of claim 4, wherein L<sup>1</sup> consists of moieties selected from alkylene, -CH<sub>2</sub>CH<sub>2</sub>O-, amide, carbamate, and combinations thereof.

13. The method of claim 12, wherein L<sup>1</sup> consists of alkylene moieties, -CH<sub>2</sub>CH<sub>2</sub>O- moieties, and combinations thereof.

14. The method of claim 4, wherein  $L^1$  is 1-20 atoms in length.
15. The method of claim 4, wherein  $G^1$  is selected from amine, hydroxy, thiol, carboxylic acid, carboxylic acid ester, imide ester, orthoester, carbonate, isocyanate, isothiocyanate, aldehyde, acetal, ketone, ketal, thione, alkenyl, acrylate, methacrylate, acrylamide, sulfone, maleimide, disulfide, iodo, epoxy, sulfonate, thiosulfonate, silane, alkoxy silane, halosilane, and phosphoramidate
16. The method of claim 15, wherein  $G^1$  is selected from amine, hydroxy, thiol, carboxylic acid, carboxylic acid ester, imide ester, orthoester, carbonate, isocyanate, aldehyde, acetal, ketone, ketal, and maleimide.
17. The method of claim 1, wherein  $POLY^1$  has a molecular weight of 200 Da to 2,000,000 Da.
18. The method of claim 1, wherein said heterobifunctional reagent comprises an oxyamine or hydrazine at one terminus and a carboxylic acid or amine group at the other terminus, effective to produce a monoderivatized water-soluble carbohydrate polymer having a single terminal carboxylic acid or amine group;  
 further comprising the step of purifying the amine- or carboxylic acid-terminated carbohydrate polymer by ion exchange chromatography.

19. A monofunctional water-soluble carbohydrate-based reagent having the structure



where:

$POLY^1$  is a water-soluble carbohydrate polymer having a terminal anomeric carbon atom, where  $C^a$  is said terminal anomeric carbon atom;

$---$  represents a double bond when  $x=0$  and a single bond when  $x=1$ ;

$R^1$  is H or hydroxymethyl;

$X$  is oxygen or  $NR^2$ , where  $R^2$  is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl;

$R^3$  is H or methyl;

$L^1$  is a linker group, and

$G^1$  is a functional group, in reactive or protected form, not selected from oxyamine and hydrazine.

20. The reagent of claim 19, wherein  $\text{---}$  represents a double bond, such that  $x=0$ .
21. The reagent of claim 19, wherein  $\text{---}$  represents a single bond, such that  $x=1$ .
22. The reagent of claim 19, wherein  $R^3$  is H.
23. The reagent of claim 19, wherein X is oxygen.
24. The reagent of claim 19, wherein X is  $NR^2$ .
25. The reagent of claim 19, wherein  $R^1$  is hydrogen.
26. The reagent of claim 19, wherein  $POLY^1$  is a dextran.
27. The reagent of claim 19, wherein  $POLY^1$  is a chitosan.
28. The reagent of claim 19, wherein  $L^1$  consists of moieties selected from alkylene,  $-\text{CH}_2\text{CH}_2\text{O}-$ , amide, carbamate, and combinations thereof.
29. The reagent of claim 28, wherein  $L^1$  consists of alkylene moieties,  $-\text{CH}_2\text{CH}_2\text{O}-$  moieties, and combinations thereof.
30. The reagent of claim 19, wherein  $L^1$  is 1-20 atoms in length.
31. The reagent of claim 19, wherein  $G^1$  is selected from amine, hydroxy, thiol, carboxylic acid, carboxylic acid ester, imide ester, orthoester, carbonate, isocyanate, isothiocyanate, aldehyde, acetal, ketone, ketal, thione, alkenyl, acrylate, methacrylate, acrylamide, sulfone, maleimide, disulfide, iodo, epoxy, sulfonate, thiosulfonate, silane, alkoxy silane, halosilane, and phosphoramidate

32. The reagent of claim 31, wherein G<sup>1</sup> is selected from amine, hydroxy, thiol, carboxylic acid, carboxylic acid ester, imide ester, orthoester, carbonate, isocyanate, aldehyde, acetal, ketone, ketal, and maleimide.
33. The reagent of claim 19, wherein POLY<sup>1</sup> has a molecular weight of 200 Da to 2,000,000 Da.
34. A reagent as recited in claim 26, wherein said reagent has a structure designated herein as dextran-O-(carboxymethyl)oxyimine (2).
35. A reagent as recited in claim 26, wherein said reagent has a structure designated herein as oxyimine-linked dextran-butanoic acid (7).
36. A reagent as recited in claim 26, wherein said reagent has a structure designated herein as oxyimine-linked dextran-butyraldehyde (16).
37. A reagent as recited in claim 27, wherein said reagent has a structure designated herein as oxyimine-linked chitosan tetra(ethylene glycol) maleimidopropionamide (22).
38. A reagent as recited in claim 27, wherein said reagent has a structure designated herein as oxyimine-linked chitosan butanoic acid (23).
39. A method of preparing a water-soluble carbohydrate reagent having a single terminal carboxylic acid group, the method comprising  
oxidizing a water-soluble carbohydrate polymer having a terminal acetal or aldehyde group under mild conditions, effective to produce an oxidized carbohydrate having a single terminal carboxylic acid group and having substantially the same molecular weight as the carbohydrate prior to oxidation.
40. The method of claim 39, further comprising the step of purifying the carbohydrate reagent by ion exchange chromatography,  
wherein the purified carbohydrate reagent is substantially free of unreacted carbohydrate and overoxidized byproducts.

41. The method of claim 40, wherein the purified carbohydrate reagent has a polydispersity of less than 1.5.
42. The method of claim 39, wherein said conditions comprise reaction with iodine (I<sub>2</sub>) and a hydroxide base.
43. The method of claim 39, wherein said carbohydrate is dextran.
44. A water-soluble carbohydrate reagent having a single terminal functional group which is a carboxylic acid or carboxylic acid derivative.
45. The carbohydrate reagent of claim 44, wherein the carboxyl carbon of said carboxylic acid or carboxylic acid derivative is the anomeric carbon.
46. The carbohydrate reagent of claim 44, having a polydispersity of less than 1.5.
47. The carbohydrate reagent of claim 44, having a molecular weight of 200 Da to 2,000,000 Da.
48. The carbohydrate reagent of claim 44, wherein the carbohydrate is dextran.
49. The carbohydrate reagent of claim 44, wherein said carboxylic acid derivative is selected from ester, activated ester, thioester, anhydride, amide, acid halide, nitrile, carbamate, carbonate, isocyanate, and isothiocyanate.
50. A conjugate comprising the water-soluble carbohydrate reagent of claim 44 and a covalently attached biologically active molecule.
51. The conjugate of claim 50, wherein the biologically active molecule is a protein or peptide.
52. A conjugate of a water-soluble carbohydrate reagent and a biologically active molecule, having the structure



where

POLY<sup>1</sup> is a water-soluble carbohydrate polymer having a terminal anomeric carbon atom, where C<sup>a</sup> is said terminal anomeric carbon atom;

--- represents a double bond when x=0 and a single bond when x=1;

R<sup>1</sup> is H or hydroxymethyl;

X is oxygen or NR<sup>2</sup>, where R<sup>2</sup> is hydrogen, methyl, lower alkyl, cycloalkyl, or aryl;

L<sup>1</sup> is a linker group, and

G<sup>2</sup> is a covalent bond comprising a residue or converted form of functional group G<sup>1</sup>, not selected from oxyamine and hydrazine, following reaction with a corresponding functional group on biomolecule B.

53. The conjugate of claim 52, where POLY<sup>1</sup> is a dextran.
54. The conjugate of claim 52, where POLY<sup>1</sup> is a chitosan.
55. The conjugate of claim 53, where the biologically active molecule is a protein or peptide.
56. The conjugate of claim 55, where the biologically active molecule is selected from lysozyme, protegrin-1, C-peptide, and insulin.
57. The conjugate of claim 56, where the biologically active molecule is insulin.
58. The conjugate of claim 54, where the biologically active molecule is an oligonucleotide.

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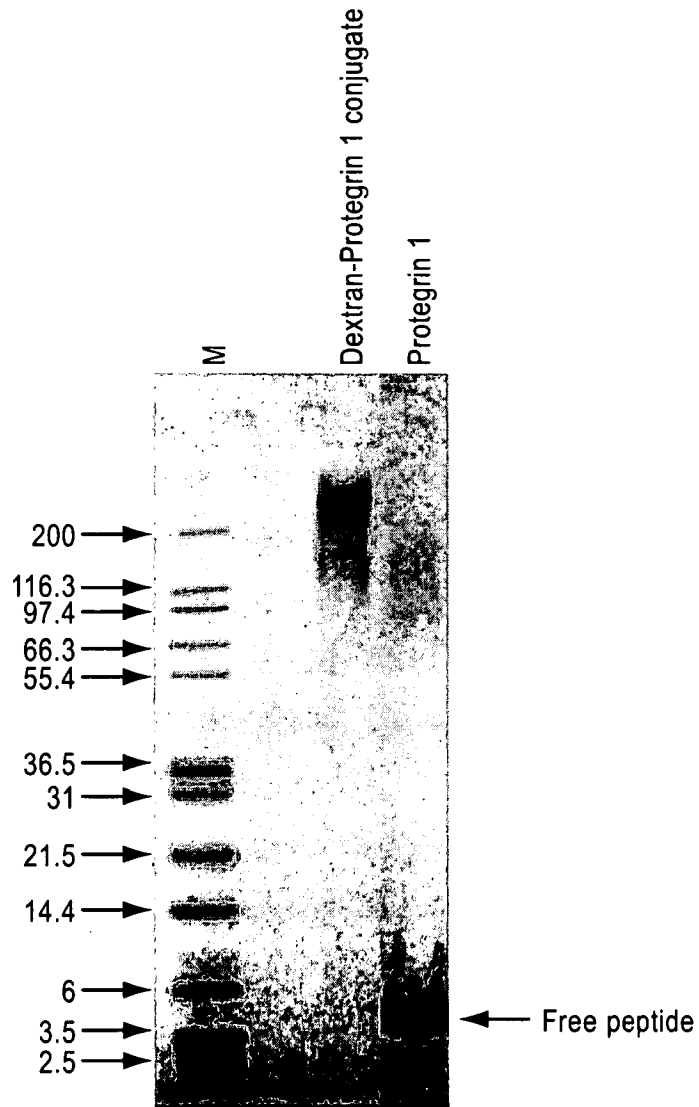


FIG. 1

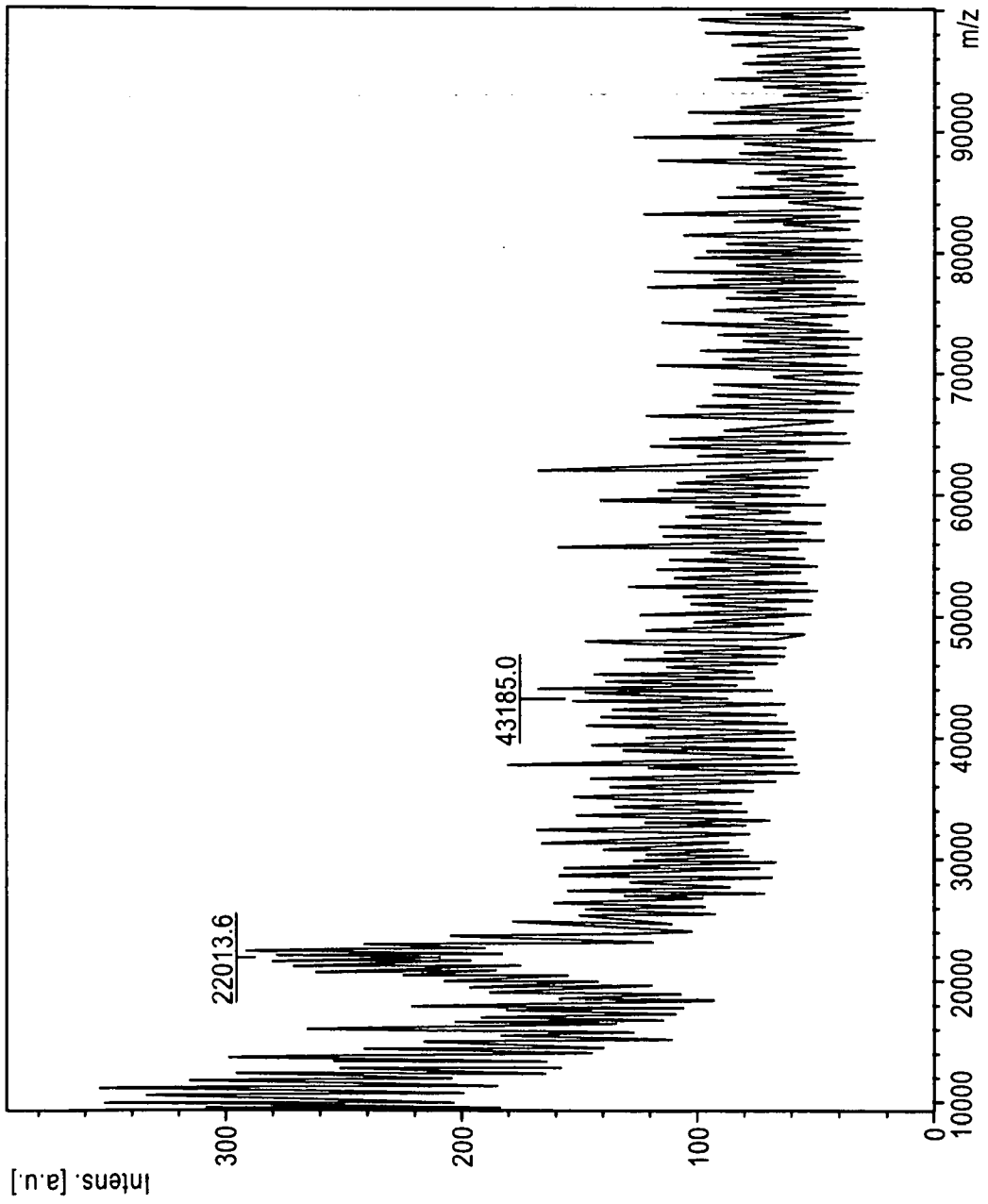


FIG. 2

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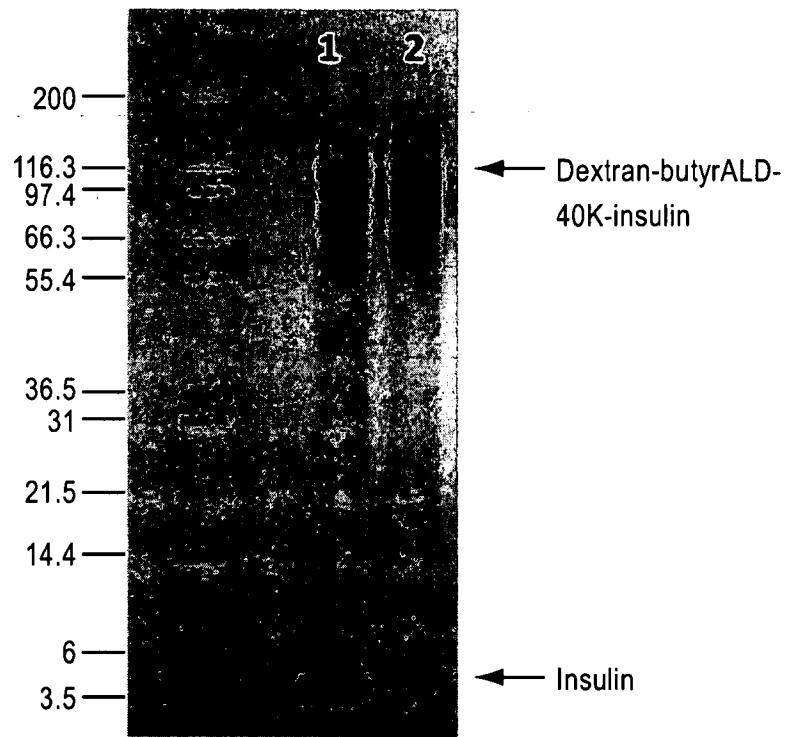


FIG. 3

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COMPETITION BINDING ASSAY  
CHO-hIR (Clone 4.1)  
02Sep09

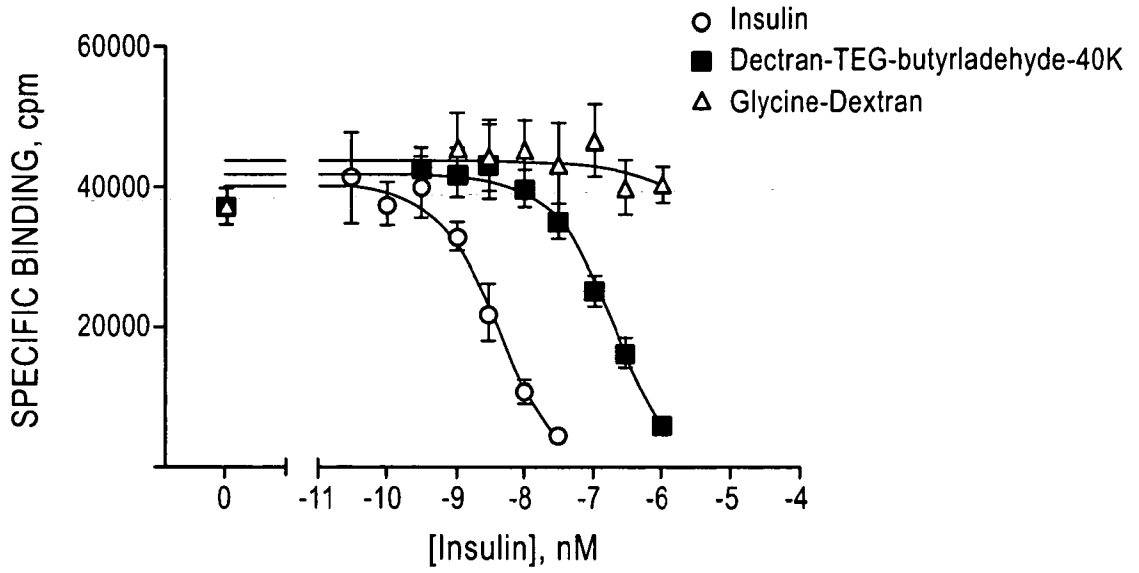


FIG. 4

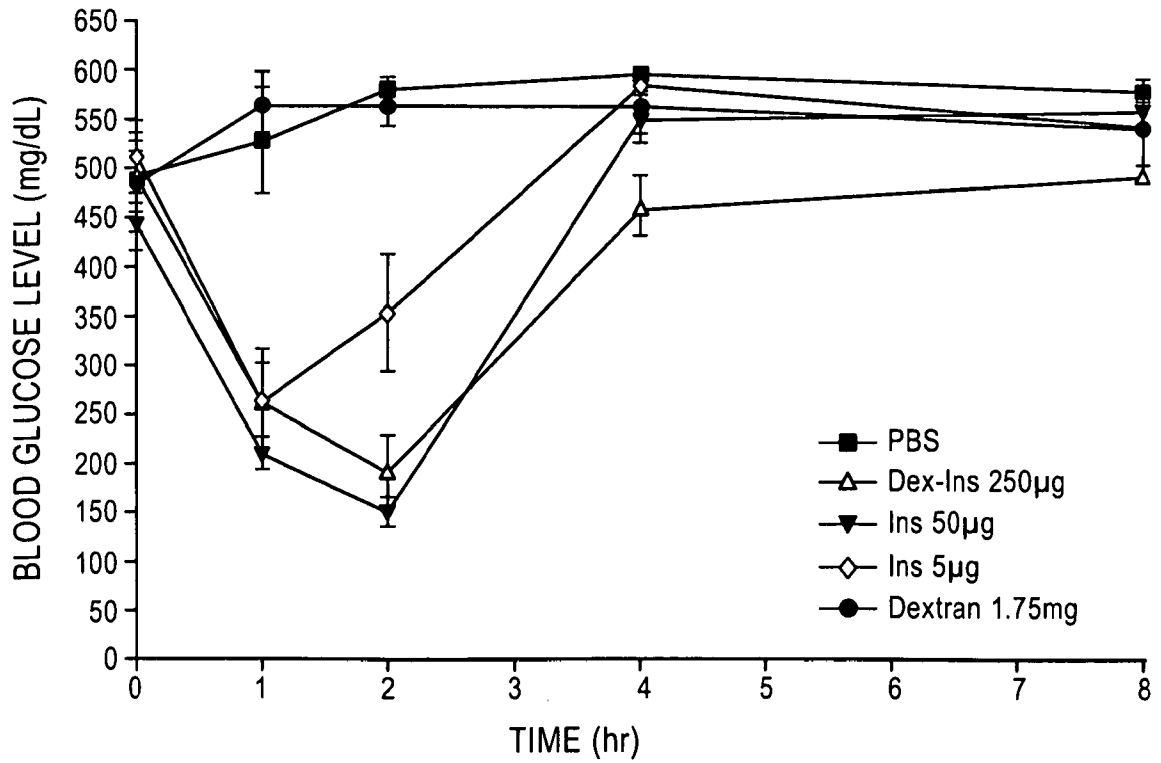


FIG. 5