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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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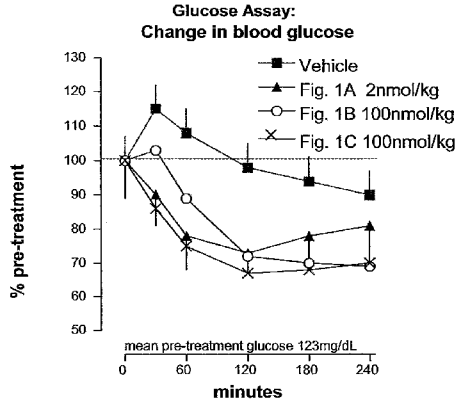
(54) Title: N-TERMINUS CONFORMATIONALLY CONSTRAINED GLP-1 RECEPTOR AGONIST COMPOUNDS

Figure 1A HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2

Figure 1B H-dAla-PGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2

Figure 1C H-dAla-PGTFTSDLSKQLEEEAVRLFIEFLKN-NH_2

Figure 1D



(57) Abstract: The disclosure provides N-terminus conformationally constrained compounds, which may comprise peptide mimetics and/or amino acid substitutions, which may be used in peptides, such as GLP-1 receptor agonist compounds, to induce a β-turn secondary structure at the N- terminus. The N-terminus conformationally constrained compounds may be used for research purposes; to produce GLP-1 receptor agonist compounds having improved GLP-1 receptor binding activity, enzymatic stability, or in vivo glucose lowering activity; and to develop GLP-1 receptor agonist compounds which have fewer amino acid residues. The disclosure also provides GLP-1 receptor agonist compounds, such as exendins, exendin analogs, GLP-1 (7-37), GLP-1(7- 37) analogs, comprising the N-terminus conformationally constrained compounds. The compounds are useful for treating various diseases, such as diabetes and obesity. The disclosure also provides methods for chemically synthesizing the N-terminus conformationally constrained compounds.

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N-Terminus Conformationally Constrained GLP-1 Receptor Agonist Compounds

Related Applications

This application claims priority to US Application No. 61/165,604 filed April 1, 2009.

Field

Provided herein are N-terminus conformationally constrained GLP-1 receptor agonist compounds and therapeutic methods for their use.

Background

Peptides and proteins play critical roles in the regulation of biological processes. Peptides, for example, play a regulatory role as hormones and inhibitors, and are also involved in immunological recognition. The significant biological role of peptides makes it important to understand their interactions with the receptors to which they bind.

The determination of the receptor-bound conformation of a peptide is invaluable for the rational design of peptide analogs. Marshall et al, *Ann. Rep. Med. Chem.*, 13:227-238 (1978) disclose that peptides are characteristically highly flexible molecules, the structures of which are strongly influenced by the environment in which they reside. Thus, peptides are not generally useful for determining their receptor-bound conformation.

As no approach is available to predict which new ligand-receptor interactions will lead to antagonists and which will lead to agonists of greater or less potency, it is necessary to perform classical structure-function studies in a systematic way to provide information about the specific amino acid residues and functional groups in a peptide that are important to biological activity. Studies of this nature can utilize conformationally constrained peptide mimetics. For example, Hruby, *Trends Pharmacol. Sci.*, 8:336-339 (1987) suggests that conformational constraints can provide information about the different requirements that a receptor has for a ligand to be an agonist or antagonist.

Generally, peptide mimetics can be defined as structures which serve as appropriate substitutes for peptides in interactions with receptors and enzymes. The development of rational approaches for discovering peptide mimetics is a major goal of medicinal chemistry. Such development has been attempted both by empirical screening approaches and by specific synthetic design. Specific design of peptide mimetics has utilized both peptide backbone modifications and chemical mimics of peptide secondary structures. The beta-turn has been

implicated as an important site for molecular recognition in many biologically active peptides. Consequently, peptides containing conformationally constrained mimetics of beta-turns are particularly desirable.

There is a need in the art for new GLP-1 receptor agonist compounds that have good stability, resistance to degradation, and good glucagon-like peptide-1 (GLP-1) receptor binding activity and in vivo glucose lowering activity. To solve these needs, the disclosure herein provides, among other things, novel N-terminus conformationally constrained compounds, novel N-terminus conformationally constrained GLP-1 receptor agonist compounds containing modifications, such as peptide mimetics and/or amino acid substitutions, that provide a conformationally constrained N-terminus that results in improved GLP-1 receptor binding and in vivo blood glucose lowering activity.

Summary

It was previously believed that the N-terminus of exendin-4 and exendin analogs was a random coil. It has now been unexpectedly discovered that the N-terminus shows a high beta-turn characteristic in a specific site, and therefore mimics the receptor bound conformation of this region of the peptides. The disclosure herein is based on this discovery.

Provided herein are N-terminus conformationally constrained compounds having the formula: $Xaa_1Xaa_2Xaa_3$-Z and $Xaa_1Xaa_2Xaa_3Xaa_4$-Z, where the substituents are defined herein. These N-terminus conformationally constrained compounds may induce a β-turn conformational constraint at the N-terminus when they are used in GLP-1 receptor agonist compounds. The N-terminus conformationally constrained compounds may be used for therapeutic purposes (e.g., treat diabetes); for research purposes; and to produce GLP-1 receptor agonist compounds having improved GLP-1 receptor binding activity, enzymatic stability, and improved in vivo glucose lowering activity. The disclosure provides pharmaceutical compositions comprising therapeutically effective amounts of the N-terminus conformationally constrained compounds. The disclosure also provides methods for synthesizing the N-terminus conformationally constrained compounds.

Provided herein are GLP-1 receptor agonist compounds, such as exendins, exendin analogs, GLP-1(7-37), and GLP-1(7-37) analogs, comprising an N-terminus conformationally constrained compound having the formula $Xaa_1Xaa_2Xaa_3$- or $Xaa_1Xaa_2Xaa_3Xaa_4$-, where the substituents are defined herein. In one embodiment, the GLP-1 receptor agonist compounds

comprise $Xaa_1Xaa_2Xaa_3Xaa_4$, where the substituents are defined herein, at positions 1-4 at the N-terminus. In one embodiment, the GLP-1 receptor agonist compounds comprise $Xaa_1Xaa_2Xaa_3$, where the substituents are defined herein, at positions 1-3 at the N-terminus. The disclosure provides pharmaceutical compositions comprising therapeutically effective amounts of these N-terminus conformationally-constrained GLP-1 receptor agonist compounds.

Provided herein are exendins and exendin analogs having the formula:

$Xaa_1Xaa_2Xaa_3Xaa_4$TFTSDLSKQXaa_{14}EEEAVRLFIEXaa_{25}LKN-Z;

$Xaa_1Xaa_2Xaa_3Xaa_4$TFTSDLSKQXaa_{14}EEEAVRLFIEXaa_{25}LK-R_{10}-Z;

$Xaa_1Xaa_2Xaa_3Xaa_4$TFTSDLSKQXaa_{14}EEEAVRLFIEXaa_{25}LKNGGPSSGAPPPS-Z;

where Xaa_{14}, Xaa_{25}, R_{10}, and Z are defined herein; and at least one of Xaa_1, Xaa_2, Xaa_3, and Xaa_4 are modifications, such as peptide mimetics and/or amino acid substitutions, that induce a conformational constraint at the N-terminus. The disclosure provides pharmaceutical compositions comprising therapeutically effective amounts of these exendin analogs.

Provided herein are GLP-1(7-37) and GLP-1(7-37) analogs having the formula:

$Xaa_1Xaa_2Xaa_3Xaa_4$TFTSDVSSYXaa_{14}EGQAAKEFIAXaa_{25}LVXaa_{28}GRXaa_{31}-Z;

where Xaa_{14}, Xaa_{25}, Xaa_{28}, Xaa_{31}, and Z are as defined herein; and at least one of Xaa_1, Xaa_2, Xaa_3, and Xaa_4 are modifications, such as peptide mimetics and/or amino acid substitutions, that induce a conformational constraint at the N-terminus. The disclosure provides pharmaceutical compositions comprising therapeutically effective amounts of these GLP-1(7-37) analogs.

Provided herein are GLP-1 receptor agonist compounds, such as exendins, exendin analogs, GLP-1(7-37), and GLP-1(7-37) analogs wherein position 1 comprises an imidazole ring (e.g., His) and position 3 is proline; where the GLP-1 receptor agonist compounds bind in a RIN cell membrane receptor binding assay with an affinity of less than 1 nM (or less than 0.1 nM).

The disclosure provides methods for treating diabetes; treating insulin resistance; treating postprandial hyperglycemia; lowering blood glucose levels; lowering HbA1c levels; stimulating insulin release; reducing gastric motility; delaying gastric emptying; reducing food intake; reducing appetite; reducing weight; treating overweight; and treating obesity in patients in need by administering therapeutically effective amounts of the N-terminus conformationally constrained compounds and/or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein.

Brief Description of the Figures

Figure 1: **Figure 1A** is exendin-4 amide; **Figure 1B** is dAla^2,Pro^3-exendin-4 amide, and **Figure 1C** is dAla^2,Pro^3,Leu^{14},Phe^{25}-exendin-4 (1-28) amide. **Figure 1D** is a graph showing the change in blood glucose in mice administered the compounds shown in **Figures 1A-C** based on the in vivo blood glucose assay described in Example 17. The compounds were injected IP at t=0 immediately following a baseline sample in 2-hour fasted NIH/Swiss mice. Blood glucose samples were taken at t=30, 60, 120, 180, and 240 minutes with a ONETOUCH® ULTRA® (LifeScan, Inc., Milpitas, CA).

Figure 2: **Figure 2A** is an exendin analog, described, e.g., in WO 2007/139941. **Figures 2B-J** show the exendin analog of **Figure 2A** having a modification at Glu^3. R_1 is GTFTSDLSKQLEEEAVRLFIEWLKQGGPSKEIIS-NH_2. **Figure 2K** shows the exendin analog of **Figure 2A** having modifications at Gly^{2}Glu^3. **Figures 2L-2U** show N-terminus conformationally constrained compounds. **Figures 2B-J** provide examples of exendin analogs containing the N-terminus conformationally constrained compounds shown in **Figures 2L-2U**.

Figures 3A-G are dAla^2,Pro^3-exendin-4 (**Figure 3A**), Ala^2,Pro^3-exendin-4 (**Figure 3B**), Pro^3,Ala^4-exendin-4 (**Figure 3C**), Ala^2,Pro^3,Ala^4-exendin-4 (**Figure 3D**), Pro^3,dAla^4-exendin-4 (**Figure 3E**), Val^2,Pro^3-exendin-4 (**Figure 3F**), and NMeAla^2,Pro^3-exendin-4 (**Figure 3G**). The compound in **Figure 1B** and **3A** are the same.

Figure 4 is a graph showing the change in blood glucose in mice administered the compounds shown in **Figures 3G**, **2I**, and **2B** based on the in vivo blood glucose assay described in Example 17. The compounds were injected IP at t=0 immediately following a baseline sample in 2-hour fasted NIH/Swiss mice. Blood glucose samples were taken at t=30, 60, 120, 180, and 240 minutes with a ONETOUCH® ULTRA® (LifeScan, Inc., Milpitas, CA).

Figure 5: **Figure 5A** is Leu^{14},Phe^{25}-exendin-4(1-28), described in WO 2007/139941. Leu^{14},Phe^{25}-exendin-4(1-28) refers to amino acid residues 1-28 in exendin-4 (i.e., exendin-4(1-28), where the amino acid residue at position 14 in exendin-4 is replaced with Leu (i.e., Leu^{14}), and the amino acid residue at position 25 is replaced with Phe (i.e., Phe^{25}). **Figures 5B-G** show the exendin analog of **Figure 5A** having a modification at Glu^3 or Gly^{2}Glu^3 at the N-terminus. R_4 is GTFTSDLSKQLEEEAVRLFIEFLKN-NH_2.

Figures 6A-E show the exendin analog of **Figure 5A** having a modification at Gly^{2}Glu^3 or Gly^{2}Glu^{3}Gly^4 at the N-terminus. The C-terminal amino acid in each compound shown in

Figures 6A-E is amidated.

Figure 7 is a graph showing the change in blood glucose in mice administered the compounds shown in **Figures 6A**, **8B**, **6E**, **1C**, **5B**, and **5A** based on the in vivo blood glucose assay described in Example 17. The compounds were injected IP at t=0 immediately following a baseline sample in 2-hour fasted NIH/Swiss mice. Blood glucose samples were taken at t=30, 60, 120, 180, and 240 minutes with a ONETOUCH® ULTRA® (LifeScan, Inc., Milpitas, CA).

Figure 8: **Figures 8A-D** show the exendin analog in **Figure 5A** having modifications at $Gly^2Glu^3Gly^4$ at the N-terminus., where the C-terminal amino acid is amidated. **Figures 8E-H** show the exendin analog in **Figure 2A** having modifications at $Gly^2Glu^3Gly^4$ at the N-terminus.

Figure 9: **Figures 9A-H** show the exendin analog in **Figure 5A** having a modification at Gly^2Glu^3 or $Gly^2Glu^3Gly^4$ at the N-terminus. Each compound in **Figures 9A-H** is amidated at the C-terminal amino acid. **Figure 9I** is a graph showing the change in blood glucose in mice administered the compounds shown in **Figures 9B, 9C, 9D, 9F, 5A**, and **1C** based on the in vivo blood glucose assay described in Example 17. The compounds were injected IP at t=0 immediately following a baseline sample in 2-hour fasted NIH/Swiss mice. Blood glucose samples were taken at t=30, 60, 120, 180, and 240 minutes with a ONETOUCH® ULTRA® (LifeScan, Inc., Milpitas, CA).

Figures 10A-I show the exendin analog in **Figure 5A** having a modification at His^1 at the N-terminus. R_4 is $Xaa_2Xaa_3GTFTSDLSKQLEEEAVRLFIEFLKN\text{-}NH_2$, where Xaa_2 is Gly, dAla, or Aib; and Xaa_3 is Glu or Pro. Alternatively, R_4 is $Xaa_2Xaa_3GTFTSDLSKQLEEEA$ VRLFIEWLKNGGPSSGAPPPS-NH_2, where Xaa_2 is Gly, dAla, or Aib; and Xaa_3 is Glu or Pro; provided that Xaa_3 is not Glu when Xaa_2 is Gly, or Xaa_2 is not Gly when Xaa_3 is Glu. Alternatively, R_4 is $Xaa_2Xaa_3GTFTSDLSKQLEEEAVRLFIEWLKQGGPSKEIIS\text{-}OH$, where Xaa_2 is Gly, dAla, or Aib; and Xaa_3 is Glu or Pro.

Figures 11A-B show exendin-4 of **Figure 1A** having a modification at His^1 at the N-terminus. R_2 is GEGTFTSDLSKQLEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2.

Figure 12 shows the compound of **Figure 10E** with an amino acid substitution of Trp^{25}. The compound in Figure 12 is amidated at the C-terminal amino acid residue.

Figure 13 shows an exendin analog having a modification at $His^1Gly^2Glu^3$. The compound in Figure 13 is amidated at the C-terminal amino acid residue.

Figure 14: **Figure 14A** is a generic structure (where Xaa_2 is, e.g., Gly, dAla, or Aib;

and the other substituents are defined herein) of an exendin analog of **Figure 1A, 2A, or 5A** having modifications at $His^1Gly^2Glu^3$ at the N-terminus, where R is a peptide, such as any one of the following: GTFTSDLSKQLEEEAVRLFIEFLKN-NH_2; GTFTSDLSKQLEEEAV-RLFIEWLKQGGPSKEIIS-OH; or GTFTSDLSKQLEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2. Aib is α-methylalanine. **Figures 14B-C** are examples of compounds from the structure in **Figure 14A** that have modifications at His^1 and Glu^3. The compounds in **Figures 14B-C** are amidated at the C-terminal amino acid residue. **Figure 14D** provides the generic structure (where Xaa_2 is Gly, dAla, or Aib; and the other substituents are defined herein) of an N-terminus conformationally constrained compound. **Figures 14E-R** are exendin analogs comprising an N-terminus conformationally constrained compound. R_1 is GTFTSDLSKQLEEEAVRLF IEWLKQGGPSKEIIS-OH. R_4 is GTFTSDLSKQLEEEAVRLFIEFLKN-NH_2. R_5 is PGTFTSDLSKQLEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2.

Figures 15A-D are exendin analogs that comprise isomers of nipecotic acid as the N-terminus conformationally constrained compound. R_1 is FTSDLSKQLEEEAVRLFI EWLKQGGPSKEIIS-NH_2.

Figure 16: Figures 16A-H are exendin analogs containing a modification at the N-terminus. R_1 is FTSDLSKQLEEEAVRLFIEWLKQGGPSKEIIS-OH. R_2 is FTSDLSKQLE EEAVRLFIEWLKNGGPSSGAPPPS-NH_2. R_3 is FTSDVSSYLEGQAAKEFIAWLVKGRG-NH_2. **Figures 16I-L** are exendin analogs containing a modification at the N-terminus. The modification is designed to mimic amino acid residues $His^1Gly^2Glu^3$. R_4 is GTFTSDLSKQLEE EAVRLFIEFLKN-NH_2.

Figure 17: Figures 17A-F are exendin analogs containing a thiazolidine-proline peptide mimetics at Gly^2Glu^3. R_4 is GTFTSDLSKQLEEEAVRLFIEFLKN-NH_2. **Figures 17G-N** are exendin analogs having a modification at His^1 and containing a thiazolidine peptide mimetic at Gly^2Glu^3. R_1, R_2, and R_3 are each independently hydrogen, methyl, or ethyl. In this embodiment, Xaa_3 is Glu, Asp, Pro, or Gly. R_4 is GTFTSDLSKQLEEEAVRLFIEFLKN-NH_2.

Figure 18: Figure 18A is a process for preparing (5,5)-Glu-Gly-OH, a dipeptide mimetic that can be used to induce a β-turn conformational constraint, for example, at the N-terminus in a GLP-1 receptor agonist compound. **Figure 18B** is a generic structure of the compound that can be produced by the process shown in **Figure 18A**. The skilled artisan can choose compounds with different stereochemistries during the reaction process to provide for

various stereochemistries in the final product. * represents a chiral carbon atom.

Figure 19: **Figure 19A** is a process for preparing γ-lactam Glu-Gly-OH, a dipeptide mimetic that can be used to induce a β-turn conformational constraint, for example, at the N-terminus in a GLP-1 receptor agonist compound. **Figure 19B** is a generic structure of the compound that can be produced by the process shown in **Figure 19A**. The skilled artisan can choose compounds with different stereochemistries during the reaction process to provide for various stereochemistries in the final product. * represents a chiral carbon atom.

Figure 20: **Figure 20A** is a process for preparing (6,5)-Asp-Gly-OH, a dipeptide mimetic that can be used to induce a β-turn conformational constraint, for example, at the N-terminus in a GLP-1 receptor agonist compound. **Figure 20B** is a generic structure of the compound that can be produced by the process shown in **Figure 20A**. The skilled artisan can choose compounds with different stereochemistries during the reaction process to provide for various stereochemistries in the final product. * represents a chiral carbon atom.

Figure 21: **Figure 21A** is a process for preparing δ-lactam Asp-Gly-OH and Asp-Ala-OH, both of which are dipeptide mimetics that can be used to induce a β-turn conformational constraint, for example, at the N-terminus in a GLP-1 receptor agonist compound. **Figure 21B** is a generic structure of the compound that can be produced by the process shown in **Figure 21A**. The skilled artisan can choose compounds with different stereochemistries during the reaction process to provide for various stereochemistries in the final product. * represents a chiral carbon atom.

Figure 22 is a process for preparing a peptide mimetic which can be used to induce a β-turn conformational constraint, for example, at the N-terminus in a GLP-1 receptor agonist compound.

Detailed Description

"GLP-1 receptor agonist compounds" refer to compounds that elicit a biological activity of an exendin reference peptide (e.g., exendin-4) or a GLP-1(7-37) reference peptide when evaluated by art-known measures such as receptor binding studies or in vivo blood glucose assays as described, e.g., Examples 16 and 17, and by Hargrove et al, *Regulatory Peptides*, 141:113-119 (2007), the disclosure of which is incorporated by reference herein. GLP-1 receptor agonist compounds include, for example, native exendins, exendin analogs, native GLP-1, GLP-1 analogs, GLP-1(7-37), and GLP-1(7-37) analogs.

The term "exendin" includes naturally occurring (or synthetic versions of naturally occurring) exendin peptides that are found in the salivary secretions of the Gila monster. Exendin-3 (HSDGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2) is present in the salivary secretions of *Heloderma horridum* and exendin-4 (**Figure 1A**) is present in the salivary secretions of *Heloderma suspectum*. Exendins include the amidated forms, the acid form, the pharmaceutically acceptable salt form, and any other physiologically active form of the molecule. In one embodiment, the term exendin can be used interchangeably with the term "exendin agonist."

"Exendin analog" refers to peptides, peptides containing peptide mimetics, amino acid substitutions, and/or other modifications, peptides containing the N-terminus conformationally constrained compounds described herein, and/or other chemical moieties, or other compounds which elicit a biological activity similar to that of an exendin reference peptide (e.g., exendin-4), when evaluated by art-known measures such as receptor binding assays or in vivo blood glucose assays as described, e.g., Examples 16 and 17, and by Hargrove et al, *Regulatory Peptides*, 141:113-119 (2007), the disclosure of which is incorporated by reference herein. Preferably, the exendin analogs will bind in such receptor binding assays with an affinity of less than 1 μM; an affinity of less than 5 nM; an affinity of less than 1 nM, or an affinity of less than 0.1 nM. In one embodiment, the term "exendin analog" refers to a peptide that has an amino acid sequence with 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions, insertions, deletions, or a combination of two or more thereof, when compared to the amino acid sequence of exendin-4 shown in **Figure 1A**. In other embodiment, the term "exendin analog" refers to a peptide that has at least 85%, at least 88%, at least 90%, at least 93%, at least 95%, or at least 98% sequence identity to the amino acid sequence of exendin-4 shown in **Figure 1A**. Exendin analogs include the amidated forms, the acid form, the pharmaceutically acceptable salt form, and any other physiologically active form of the molecule. In one embodiment, the term exendin analog can be used interchangeably with the term "exendin agonist analog."

"GLP-1(7-37) analogs" refers to peptides, peptides containing peptide mimetics and/or other modifications, peptides containing the N-terminus conformationally constrained compounds described herein, and/or other chemical moieties, or other compounds which elicit a biological activity similar to that of GLP-1(7-37), when evaluated by art-known measures such as receptor binding assays or in vivo blood glucose assays as described, e.g., Examples 16 and

17, and by Hargrove et al, *Regulatory Peptides*, 141:113-119 (2007), the disclosure of which is incorporated by reference herein. In one embodiment, the term "GLP-1(7-37) analog" refers to a peptide that has an amino acid sequence with 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions, insertions, deletions, or a combination of two or more thereof, when compared to the amino acid sequence of GLP-1(7-37). In one embodiment, the GLP-1(7-37) analog is GLP-1(7-36). GLP-1(7-37) analogs include the amidated forms, the acid form, the pharmaceutically acceptable salt form, and any other physiologically active form of the molecule.

"N-Terminus conformationally constrained GLP-1 receptor agonist compounds" refers to compounds in which one, two, three, or four of the amino acid residues at positions 1-4 at the N-terminus of "GLP-1 receptor agonist compounds" (e.g., exendins, exendin analogs, GLP-1, GLP-1 analogs, GLP-1(7-37), GLP-1(7-37) analogs) have been modified or substituted with amino acids (e.g., natural and/or non-natural amino acids), peptidomimetics, or beta-turn dipetidemimetics. This substitution(s) or modification(s) to the N-terminus of the parent GLP-1 receptor agonist compound changes the flexible random coil structure of this specific region into a more rigid secondary structure with beta-turn characteristics.

The glycine residues at positions 2 and 4 at the N-terminus of exendin-4 may indicate the presence of a β-turn in this region. In order to produce a conformationally constrained N-terminus, exendin analogs having a mimetic or other structural modification that restricted the conformational flexibility of the His^1 side chain were synthesized. Restricting the flexibility of the His^1 side chain was hypothesized to provide structural information about the possible bioactive conformation of GLP-1 receptor agonist compounds and thus enhance GLP-1 receptor binding, in vivo blood glucose lowering activity, and enzymatic stability.

An Ala scan of exendin-4 showed that the Glu^3 residue was important for biological activity. Additionally, Glu^3 or Asp^3 are present in many members of the super-family of glucagon-related peptides, which indicates the importance of an acidic side chain at that residue. It was postulated that the negative charge of Glu^3 or Asp^3 interacted through an ionic bond with the positive charge of the His^1 side chain to position the key imidazole ring of the His^1 side chain in the right space for interaction with the GLP-1 receptor. It was thus proposed that a β-turn would be formed by the sequence $Gly^2Glu^3Gly^4Thr^5$ in the super-family of glucagon related peptides, such as exendin-4 and exendin analogs.

In order to maintain the negative charge of Glu^3, thought to be essential for biological

activity, β-turn peptide mimetics were synthesized to mimic the amino acid residues Glu^3Gly^4. In one embodiment, the disclosure provides N-terminus conformationally constrained compounds of **Formula (F)**:

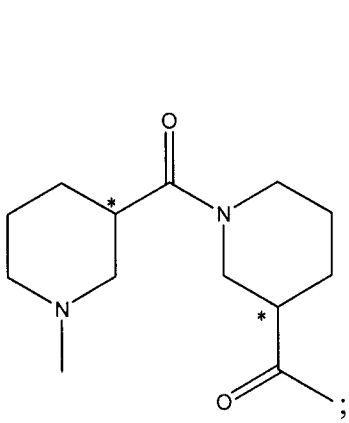
$$Xaa_1Xaa_2Xaa_3\text{-}Z;$$

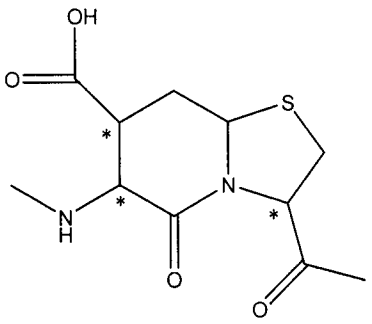
wherein:

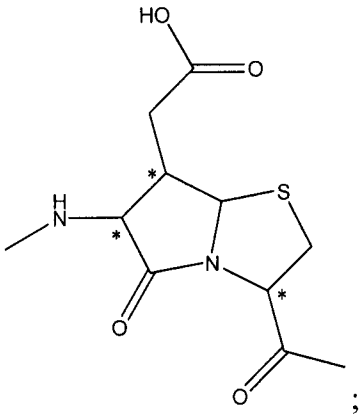
Xaa_1 is a compound of Formula (1), as described herein;

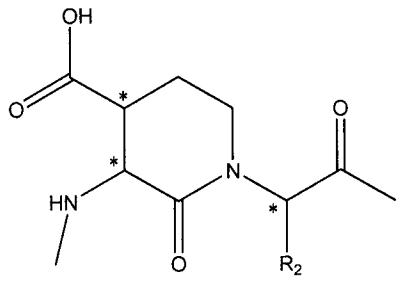
Xaa_2 is Gly, Ala, dAla, or Aib;

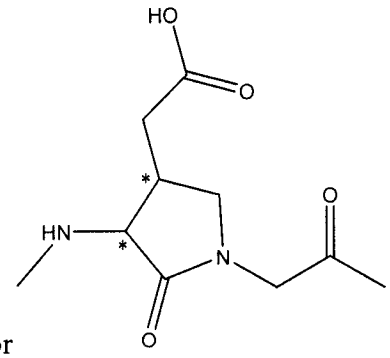
Xaa_3 is:


;


;


;


; or


;

wherein * indicates a chiral carbon atom; and R_2 is hydrogen or a $C_{1\text{-}4}$ alkyl (e.g., methyl, ethyl); and

Z is: (i) OH;

(ii) NH_2;

(iii) $TFTSDLSKQXaa_{14}EEEAVRLFIEXaa_{25}LKN\text{-}Z_1$;

(iv) $TFTSDLSKQXaa_{14}EEEAVRLFIEXaa_{25}LKNGGPSSGAPPPS\text{-}Z_1$;

(v) $TFTSDLSKQXaa_{14}EEEAVRLFIEXaa_{25}LK\text{-}R_{10}\text{-}Z_1$; or

(vi) $TFTSDVSSYXaa_{14}EGQAAKEFIAXaa_{25}LVXaa_{28}GRXaa_{31}\text{-}Z_1$;

wherein:

$\mathbf{Z_1}$ is OH or NH_2;

$\mathbf{Xaa_{14}}$ is Leu or Met;

$\mathbf{Xaa_{25}}$ is Phe or Trp;

$\mathbf{Xaa_{28}}$ is Lys or Arg;

$\mathbf{Xaa_{31}}$ is Gly or absent; and

$\mathbf{R_{10}}$ is QGGPSKEIIS; QGGPSSGAPPPS; NG; NGG; NGGP; NGGPS; NGGPSS; NGGPSSG; NGGPSSGA; NGGPSSGAP; NGGPSSGAPP; NGGPSSGAPPP; NGGPSSGAPPS; NGGPSSGAPPSK; NGGPSSGAPPS$(K)_{2\text{-}6}$; NGGPSSGAPPPSK; or NK.

When Z is OH or NH_2, the compounds of **Formula (F)** are N-terminus conformationally constrained compounds. When Z is (iii), (iv), (v) or (vi), the compounds of **Formula (F)** are N-terminus conformationally constrained GLP-1 receptor agonist compounds.

Exemplary compounds of **Formula (F)** include the compounds in **Figures 15A-D** and **16A-H**, each of which may be optionally amidated at the C-terminal amino acid residue. The reaction schemes for preparing the compounds are shown, e.g., in **Figures 18-20**.

Additional studies were undertaken to restrict the N-terminus conformation of GLP-1 receptor agonist compounds and it was unexpectedly discovered that the β-turn in GLP-1 receptor agonist compounds, such as exendin and exendin analogs, was provided by $His^1Gly^2Glu^3Gly^4$. Thus, GLP-1 receptor agonist compounds were produced to constrain or mimic a β-turn defined by residues $His^1Gly^2Glu^3Gly^4$ in exendin-4 and other GLP-1 receptor agonist compounds; or to constrain or mimic a β-turn defined by residues $His^1Ala^2Glu^3Gly^4$ in GLP-1, GLP-1 analogs, GLP-1(7-37), or GLP-1(7-37) analogs.

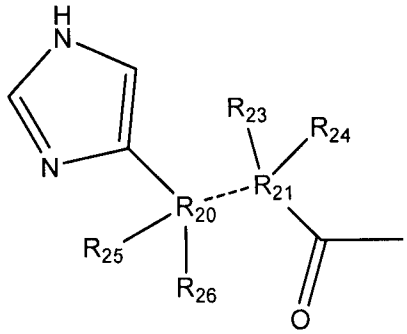
Provided herein are N-terminus conformationally constrained compounds of **Formula (A)**: $Xaa_1Xaa_2Xaa_3Xaa_4$-Z.

In one embodiment, the disclosure provides the compound of **Formula (A)**:

$$Xaa_1Xaa_2Xaa_3Xaa_4\text{-}Z;$$

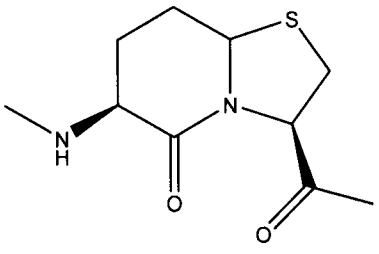
wherein:

$\mathbf{Xaa_1}$ is a compound of Formula (1):



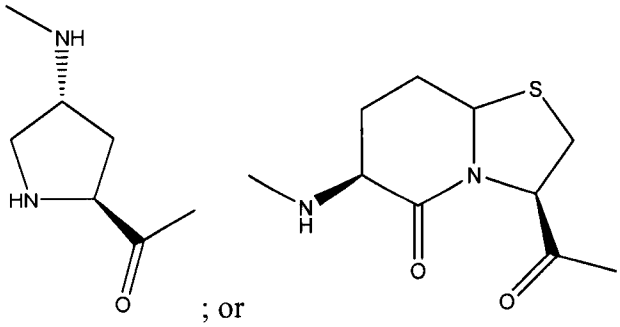
wherein R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23}, R_{24}, R_{25} and R_{26} are each independently absent, hydrogen, hydroxyl, C_{1-4} alkyl, carboxyl, or C_{1-4} alkoxy; ------ is a single bond or a double bond; and R_{21} is a chiral or achiral carbon atom;

Xaa_2 is Gly, dAla, Aib, Ala, Val, NMeAla, a compound of Formula (3), as described herein; or a compound of Formula (4) and described herein; and Xaa_2 is absent when Xaa_3 is:



;

Xaa_3 is Pro; a compound of Formula (2), as described herein; a compound of Formula (3), as described herein; a Compound of Formula (4), as described herein;



; or

Xaa_4 is Gly, dAla, or Aib; and

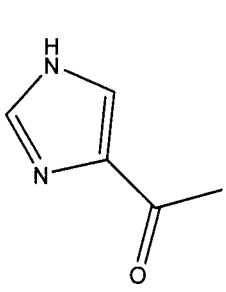
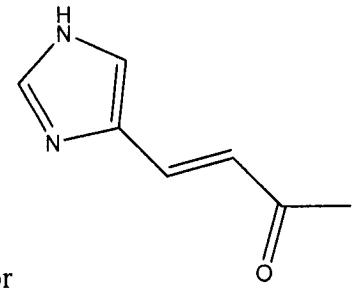
Z is OH or NH_2. In other embodiments, **Xaa_3** is Pro. In other embodiments, **Xaa_2** is dAla, Aib, Ala, Val, NMeAla, a compound of Formula (3), or a compound of Formula (4).

In other embodiments, the disclosure provides the compound of **Formula (A)**:

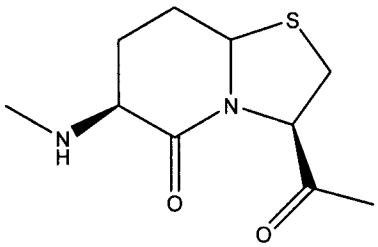
$$Xaa_1Xaa_2Xaa_3Xaa_4\text{-}Z;$$

wherein:

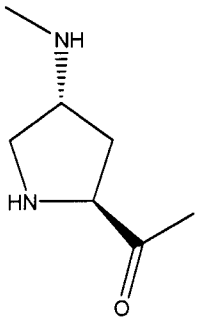
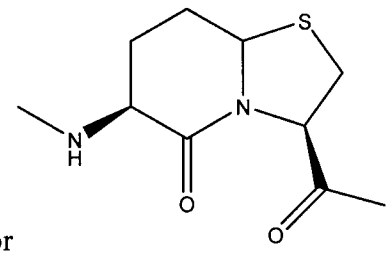
Xaa_1 is


(1j) or

(1m);

Xaa$_2$ is Gly, dAla, Aib, Ala, Val, NMeAla, a compound of Formula (3), as described herein; or a compound of Formula (4), as described herein; and Xaa$_2$ is absent when Xaa$_3$ is:


;

Xaa$_3$ is Glu; Pro; a compound of Formula (2), as described herein; a compound of Formula (3), as described herein; a Compound of Formula (4), as described herein;


; or


Xaa$_4$ is Gly, dAla, or Aib; and

Z is OH or NH_2.

Also provided herein are N-terminus conformationally constrained GLP-1 receptor agonist compounds of **Formula (B)-(E)**:

(B) Xaa$_1$Xaa$_2$Xaa$_3$Xaa$_4$TFTSDLSKQXaa$_{14}$EEEAVRLFIEXaa$_{25}$LKN-Z;

(C) Xaa$_1$Xaa$_2$Xaa$_3$Xaa$_4$TFTSDLSKQXaa$_{14}$EEEAVRLFIEXaa$_{25}$LK-R$_{10}$-Z;

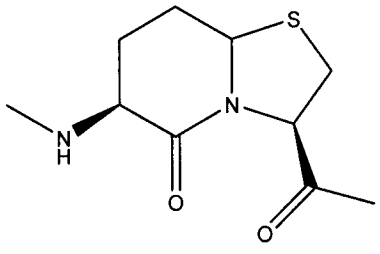
(D) Xaa$_1$Xaa$_{2a}$Xaa$_3$Xaa$_4$TFTSDLSKQXaa$_{14}$EEEAVRLFIEXaa$_{25}$LKNGGPSSGAPPPS-Z;

(E) Xaa$_1$Xaa$_2$Xaa$_3$Xaa$_4$TFTSDVSSYXaa$_{14}$EGQAAKEFIAXaa$_{25}$LVXaa$_{28}$GRXaa$_{31}$-Z.

The substituents for the compounds of **Formula (A), (B), (C), (D)**, and **(E)** are as follows:

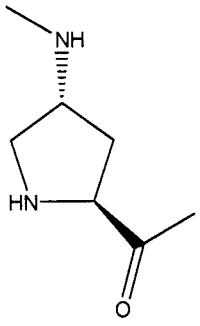
Xaa$_1$ is a compound of Formula (1), as described herein;

Xaa$_2$ is Gly; dAla; Aib; Ala; Val; NMeAla; a compound of Formula (3), as described herein; or a compound of Formula (4), as described herein; and **Xaa$_2$** is absent when **Xaa$_3$** is:

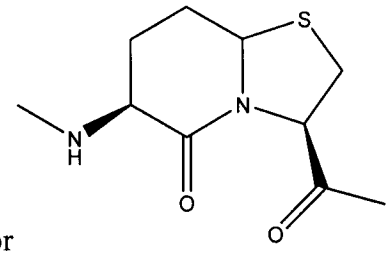


;

Xaa$_3$ is Pro; Glu; Asp; a compound of Formula (2), as described herein; a compound of Formula (3), as described herein; a Compound of Formula (4), as described herein;



; or



Xaa$_4$ is Gly, dAla, or Aib;

Xaa$_{14}$ is Leu or Met;

Xaa$_{25}$ is Phe or Trp;

Xaa$_{28}$ is Lys or Arg;

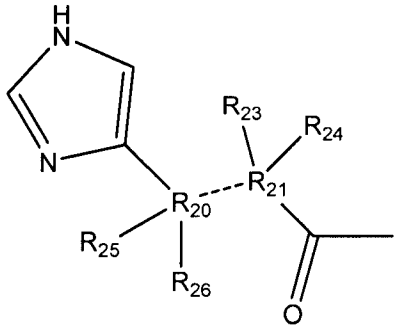
Xaa$_{31}$ is Gly or absent;

R$_{10}$ is QGGPSKEIIS; QGGPSSGAPPPS; NG; NGG; NGGP; NGGPS; NGGPSS; NGGPSSG; NGGPSSGA; NGGPSSGAP; NGGPSSGAPP; NGGPSSGAPPP; NGGPSSGAPPS; NGGPSSGAPPSK; NGGPSSGAPPS(K)$_{2\text{-}5}$; NGGPSSGAPPPSK; or NK; and

Z is OH or NH_2.

The compounds of **Formula (A)-(E)** may optionally be in the form of a pharmaceutically acceptable salt.

The compound of **Formula (1)** is:



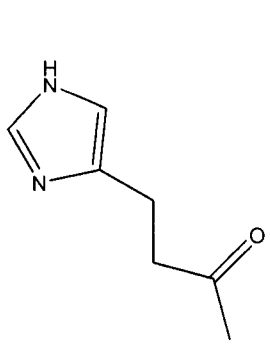
Formula (1)

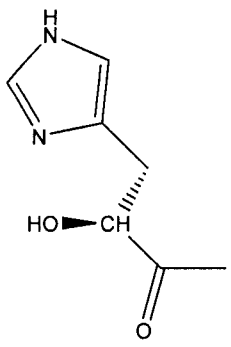
wherein R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23}, R_{24}, R_{25} and R_{26} are each independently absent, hydrogen, hydroxyl, C_{1-4} alkyl, carboxyl, amino, or C_{1-4} alkoxy; ------ is a single bond or a double bond; and R_{21} is a chiral or achiral carbon atom.

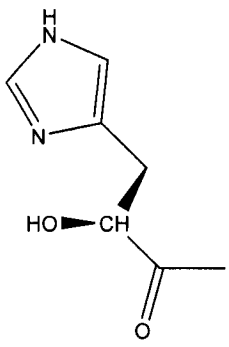
In one embodiment for the compound of **Formula (1)**, R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23} and R_{24} are each independently absent, hydrogen, hydroxy, a C_{1-4} alkyl, carboxyl, or a C_{1-4} alkoxy; R_{25} and R_{26} are each independently absent, hydrogen, hydroxy, a C_{1-4} alkyl, carboxyl, amino, or a C_{1-4} alkoxy; ------ is a single bond or a double bond; and R_{21} is a chiral or achiral carbon atom.

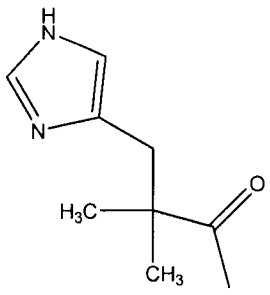
In one embodiment for the compound of **Formula (1)**, R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23} and R_{24} are each independently absent, hydrogen, hydroxy, methyl, ethyl, or carboxyl; R_{25} and R_{26} are each independently absent or hydrogen; ------ is a single bond or a double bond; and R_{21} is a chiral or achiral carbon atom.

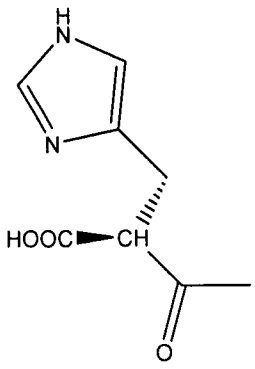
In one embodiment, the compound of **Formula (1)** is a compound of Formula (1a), (1b), (1c), (1d), (1e), (1f), (1g), (1h), (1j), (1k), (1m), or (1n):

 (1a);

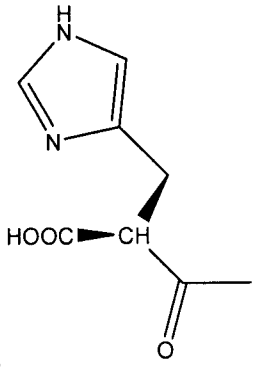
 (1b);

 (1c);

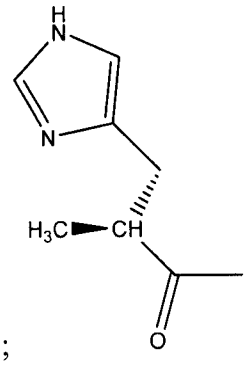
 (1d);



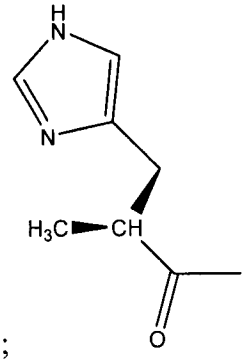
(1e);



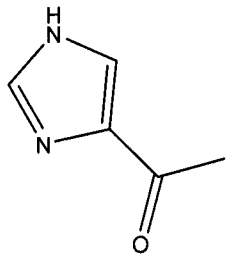
(1f);



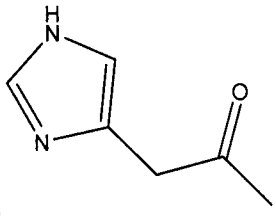
(1g);



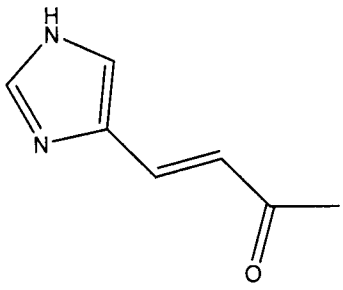
(1h);



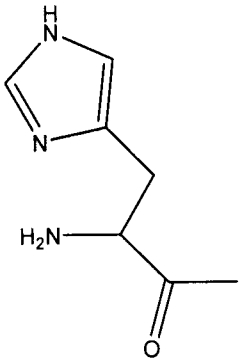
(1j);



(1k);



(1m); or



(1n).

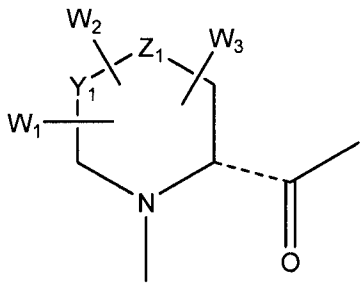
In one embodiment, the compound of **Formula (1)** is a compound of Formula (1a), (1b), (1c), (1d), (1e), (1f), (1g), (1h), (1j), (1k), or (1m).

In one embodiment, the compound of **Formula (1)** is a compound of Formula (1a), (1b), (1c), (1d), (1e), (1f), (1g), (1h), or (1k).

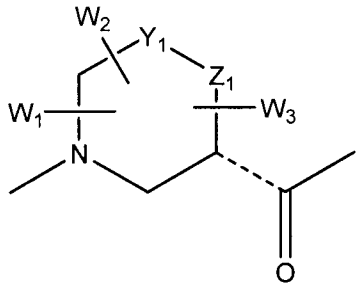
In one embodiment, the compound of **Formula (1)** is a compound of Formula (1j) or (1m).

In one embodiment, the compound of **Formula (1)** is a compound of Formula (1n).

The compounds of **Formula (2)** and **Formula (3)** are:



Formula (2),



Formula (3)

wherein Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyl, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is ◄ or ''''''''''.

In one embodiment for the Compounds of **Formula (2)** and **(3)**, Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is ◄ or ''''''''''.

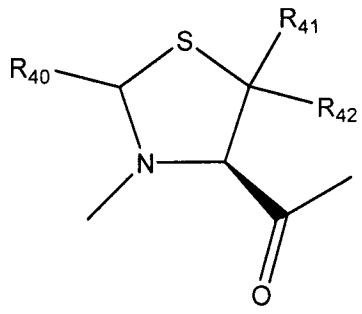
In one embodiment for the Compounds of **Formula (2)** and **(3)**, Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is ◄ or ''''''''''.

In one embodiment for the Compounds of **Formula (2)** and **(3)**, ------ is ◄.

In one embodiment for the Compounds of **Formula (2)**, Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl; and ------ is ◄.

In one embodiment for the Compounds of **Formula (3)**, Y_1 and Z_1 are each independently a single bond or carbon; and W_1, W_2 and W_3 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl; and ------ is ◄.

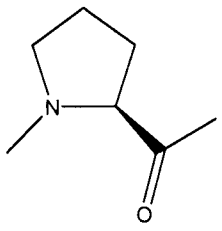
In one embodiment, the compound of **Formula (2)** is a compound of Formula (2Z):



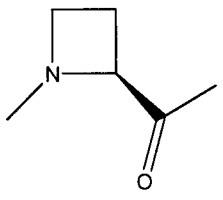
Formula (2Z)

wherein R_{40}, R_{41}, and R_{42} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl (preferably methyl or ethyl). Exemplary compounds of Formula (2Z) include compounds of Formula (2d), (2e), (2f), (2g), and (2h) described below.

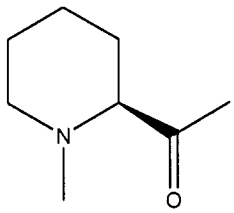
In one embodiment, the compound of **Formula (2)** is a compound of Formula (2a), (2b), (2c), (2d), (2e), (2f), (2g), (2h), or (2j):



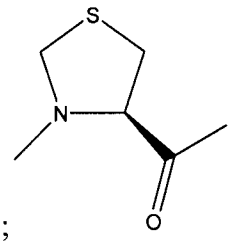
(2a);



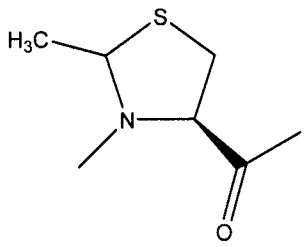
(2b);



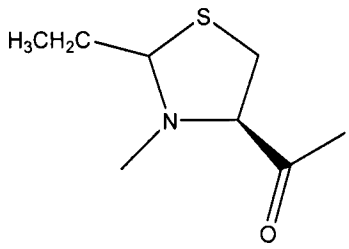
(2c);



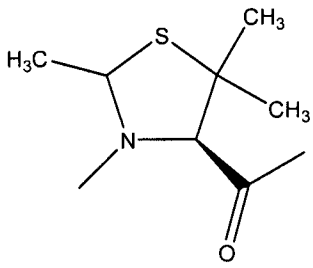
(2d);



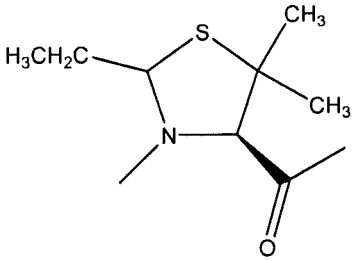
(2e);



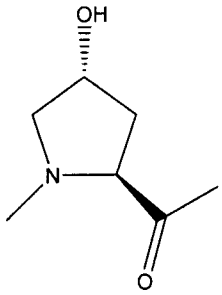
(2f);



(2g);



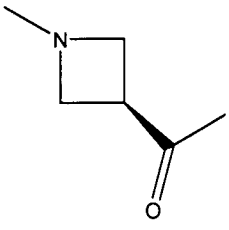
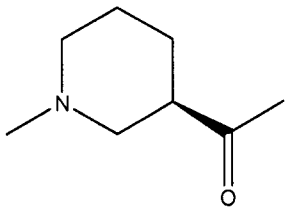
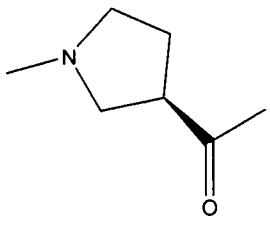
(2h); or



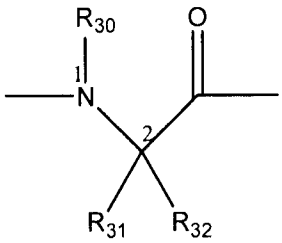
(2j).

In one embodiment, the compound of **Formula (2)** is a compound of Formula (2d), (2e), (2f), (2g), or (2h).

In one embodiment, the compound of **Formula (3)** is a compound of Formula (3a), (3b), or (3c):


(3a);

(3b); or

(3c).

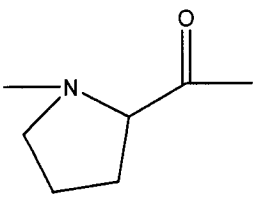
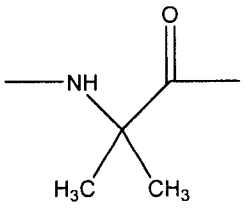
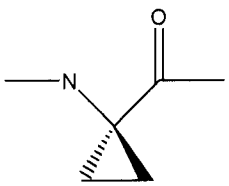
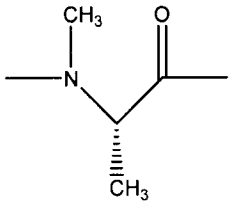
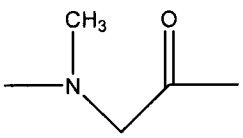
The compound of **Formula (4)** is:



wherein R_{30}, R_{31}, and R_{32} are each independently hydrogen or a C_{1-4} alkyl; or R_{30} and R_{31}, together with the nitrogen[1] and the carbon[2], form a 5- membered or 6-membered heterocyclic ring; or R_{31} and R_{32}, together with the carbon[2], form a 3-, 4-, or 5-membered carbocyclic ring.

In one embodiment for the compound of **Formula (4)**, R_{30}, R_{31}, and R_{32} are each independently hydrogen, methyl, or ethyl; or R_{30} and R_{31}, together with the nitrogen[1] and carbon[2], form a 5- membered or 6-membered heterocyclic ring; or R_{31} and R_{32}, together with the carbon[2], form a 3-, or 4-membered carbocyclic ring;

In one embodiment, the compound of **Formula (4)** is a compound of Formula (4a), (4b), (4c), (4d), or (4e):


(4a);

(4b);

(4c);

(4d);

(4e).

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_2** is dAla, Aib, Ala, Val, or NMeAla.

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_2** is a compound of Formula (3).

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_2** is a compound of

Formula (4).

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_2** is Gly.

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_2** is dAla.

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_2** is dAla or Aib.

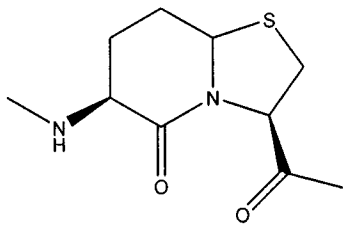
In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_3** is Pro.

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_3** is Glu.

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_3** is a compound of Formula (2), as described herein.

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_3** is a compound of Formula (3), as described herein.

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_2** is absent and **Xaa_3** is



.

In one embodiment for the Compounds of **Formula (A)-(F)**, **Xaa_4** is Gly or dAla.

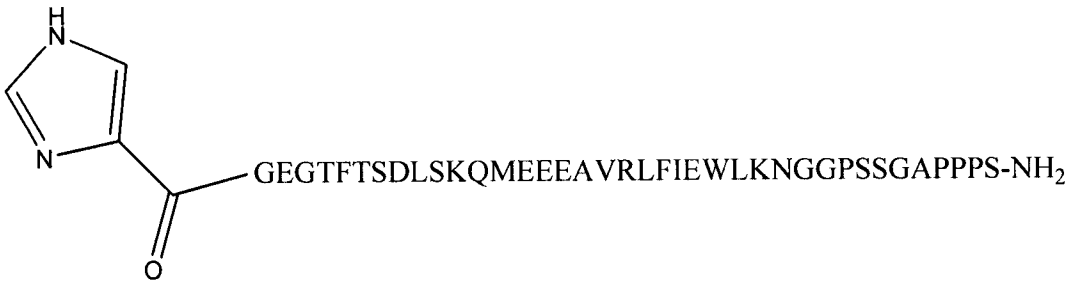
In one embodiment for the Compounds of **Formula (A)-(F)**, **Z** is NH_2.

For the Compounds of **Formula (A)-(F)**: in one embodiment **R_{10}** is QGGPSKEIIS; in one embodiment **R_{10}** is NG; in one embodiment **R_{10}** is NGG; in one embodiment **R_{10}** is NGGP; in one embodiment **R_{10}** is NGGPS; in one embodiment **R_{10}** is NGGPSS; in one embodiment **R_{10}** is NGGPSSG; in one embodiment **R_{10}** is NGGPSSGA; in one embodiment **R_{10}** is NGGPSSGAP; in one embodiment **R_{10}** is NGGPSSGAPP; in one embodiment **R_{10}** is NGGPSSGAPPP; in one embodiment **R_{10}** is NGGPSSGAPPS; in one embodiment **R_{10}** is NGGPSSGAPPSK; in one embodiment **R_{10}** is NGGPSSGAPPS$(K)_{2\text{-}5}$; in one embodiment **R_{10}** is NGGPSSGAPPPSK; and in one embodiment **R_{10}** is NK; and in one embodiment **R_{10}** is QGGPSSGAPPPS.

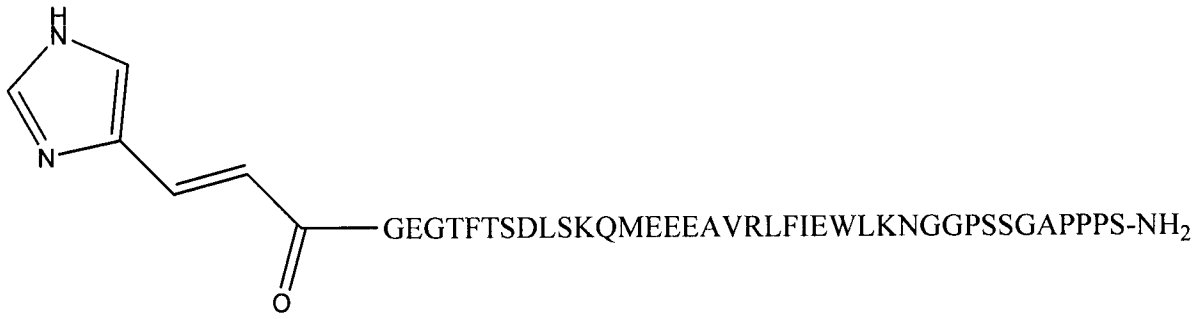
For the Compounds of **Formula (A)-(F)**: in one embodiment **Xaa_{14}** is Met and **Xaa_{25}** is Trp; in one embodiment **Xaa_{14}** is Leu and **Xaa_{25}** is Phe; in one embodiment **Xaa_{14}** is Met and **Xaa_{25}** is Phe; and in one embodiment **Xaa_{14}** is Leu and **Xaa_{25}** is Trp.

With respect to the compounds of **Formula (D)**, Xaa_2, Xaa_3, Xaa_{14}, and Xaa_{25} cannot simultaneously be Gly, Glu, Met, and Trp, respectively, except when the compound of **Formula (1)** is a compound of Formula 1(j) or 1(m). Thus, when Xaa_2, Xaa_3, Xaa_{14}, and Xaa_{25} are Gly,

Glu, Met, and Trp, respectively, the compound of **Formula (D)** may be one of the following:



; or



.

In one embodiment, the N-terminus conformationally constrained GLP-1 receptor agonist compound may be Pro^3-exendin-4; Pro^3,Leu^{14}-exendin-4; Pro^3,Leu^{14},Phe^{25}-exendin-4; Pro^3-exendin-4(1-28); Pro^3,Leu^{14}-exendin-4(1-28); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-28); Pro^3-exendin-4(1-36); Pro^3,Leu^{14}-exendin-4(1-36); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-36); or HGPGTFTSDLSKQLEEEAVRLFIEWLKQGGPSKEIIS, each of which may optionally be amidated and which may optionally be in the form of a pharmaceutically acceptable salt.

In one embodiment, the N-terminus conformationally constrained GLP-1 receptor agonist compound may be Pro^3-exendin-3; Pro^3-exendin-4(1-29); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-29); Pro^3-exendin-4(1-30); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-30); Pro^3-exendin-4(1-31); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-31); Pro^3-exendin-4(1-32); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-32); Pro^3-exendin-4(1-33); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-33); Pro^3-exendin-4(1-34); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-34); Pro^3-exendin-4(1-35); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-35); Pro^3-exendin-4(1-37); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-37); Pro^3-exendin-4(1-38); or Pro^3,Leu^{14},Phe^{25}-exendin-4(1-38), each of which may optionally be amidated and which may optionally be in the form of a pharmaceutically acceptable salt.

Examples of the compounds of **Formula (A), (B), (C), (D)**, and **(E)** are shown in **Figures 1B-C, 2A-U, 3A-G, 5B-G, 6A-E, 8A-H, 9A-H, 10A-I, 11A-B, 12, 13, 14A-Q, 15C-D, 16I-L,** and **17A-N**.

The N-terminus conformationally constrained compounds (e.g., compounds of **Formula (A)** and **(F)**) and the N-Terminus conformationally constrained GLP-1 receptor agonist compounds (e.g., compounds of **Formula (B)-(F)**) described herein (collectively referred to as "the compounds") can optionally be covalently linked to one or more polymers to provide beneficial biological properties to the compounds. Such beneficial properties may include conferring another therapeutic property to the compounds; increasing the in vivo half life of the compounds; decreasing the rate of clearance of the compounds by the kidney; decreasing the immunogenicity of the compounds; decreasing the proteolysis rate of the compounds; or increasing the stability of the compounds. Exemplary polymers that can be covalently linked to the compounds include peptides, polyethylene glycols, albumin, fatty acids, dextran, polyamino acids, alkyl chains, immunoglobulins, signaling moieties, gelatin, polyvinyl pyrrolidone, polyvinyl alcohol, N-(2-hydroxypropyl)-methacrylamide, and the like. In one embodiment, two or more polymers (e.g., peptides, polyethylene glycols, albumin, fatty acids, dextran, polyamino acids, alkyl chains, immunoglobulins, gelatin, polyvinyl pyrrolidone, polyvinyl alcohol, N-(2-hydroxypropyl)-methacrylamide) are covalently attached together and linked to the N-terminus conformation constrained compounds described herein. For example, the two more polymers that are linked together may be polyethylene glycol(s) and fatty acid(s) or a peptide, polyethylene glycol(s), and fatty acids.

In one embodiment, the compounds are linked to another peptide to provide additional therapeutic benefits. Such peptides include amylin, amylin agonist analogs (e.g., amylin analogs that function as amylin agonists), PYY, PYY analogs, GIP, GIP analogs, leptin, metraleptin, leptin analogs, metraleptin analogs, and the like. Hybrid peptides comprising the compounds and another therapeutic peptide are described, for example, in WO 2005/077072 and WO 2007/022123, the disclosures of which are incorporated by reference herein.

In one embodiment, compounds are linked to one, two, or three polyethylene glycols. In one embodiment, the compounds are linked to one polyethylene glycol. The polyethylene glycol can have a molecular weight from about 200 daltons to about 80,000 daltons; from about 5,000 from about 10,000 daltons to about 60,000 daltons; from about 10,000 daltons to about 50,000 daltons; or from about 15,000 daltons to about 40,000 daltons. The polyethylene glycol may be linear or branched.

In one embodiment, compounds are linked to one or two polyethylene glycols, where the

polyethylene glycol is further linked to a lipophilic moiety. In one embodiment, the polyethylene glycol may have a molecular weight from about 200 to about 7,000 daltons or from about 500 to about 5,000 daltons. The lipophilic moiety may be an alkyl group (e.g., C_{1-20} alkyl group; C_{1-10} alkyl group; C_{1-6} alkyl group; C_{1-4} alkyl group), a fatty acid (e.g., C_{4-28} fatty acid; C_{4-20} fatty acid; C_{4-10} fatty acid), cholesteryl, adamantyl, and the like. The alkyl group may be linear or branched, preferably linear. In one embodiment, the fatty acid is an acetylated fatty acid or an esterified fatty acid. The –(polyethylene glycol)-(lipophilic moiety) may be linked to the compound at a C-terminal amino acid residue, an N-terminal amino acid residue, an internal amino acid residue (e.g., an internal Lys amino acid residue), or a combination thereof (e.g., the compound is linked at the N-terminal and C-terminal amino acid residues via a lysine residue). Examplary peptides linked to such groups are shown in Example 20.

In one embodiment, the compounds are linked to a polyamino acid. Exemplary polyamino acids include poly-lysine, poly-aspartic acid, poly-serine, poly-glutamic acid, and the like. The polyamino acid may be in the D or L form, preferably the L form. The polyamino acids may comprise from 1 to 12 amino acid residues; from 2 to 10 amino acid residues; or from 2 to 6 amino acid residues.

In one embodiment, compounds are linked to a fatty acid. The fatty acid may be a C_4-C_{28} fatty acid chain, a C_8-C_{24} fatty acid chain, or a C_{10}-C_{20} fatty acid chain. In one embodiment, the fatty acid is an acetylated fatty acid. In one embodiment, the fatty acid is an esterified fatty acid.

In one embodiment, the compounds are linked to albumin. The albumin may be a recombinant albumin, serum albumin, or recombinant serum albumin. In another embodiment, the compounds are linked to an albumin-fatty acid (i.e., an albumin linked to a fatty acid).

In one embodiment, the compounds are linked to an immunoglobulin or an immunoglobulin Fc region. The immunoglobulin may be IgG, IgE, IgA, IgD, or IgM. In one embodiment, the compounds are linked to an IgG Fc region or an IgM Fc region. The immunoglobulin Fc region is (i) the heavy chain constant region 2(C_H2) of an immunoglobulin; (ii) the heavy chain constant region 3(C_H3) of an immunoglobulin; or (iii) both the heavy chain constant regions 2(C_H2) and 3(C_H3) of an immunoglobulin. The immunoglobulin Fc region may further comprise the hinge region at the heavy chain constant region. Other embodiments for the immunoglobulin Fc region that can be linked to exendin analog peptides are described in WO 2008/082274, the disclosure of which is incorporated by reference herein.

In one embodiment, the compounds are linked to one or more signalling moieties. Exemplary signalling moieties include, biotin, antigens, antibodies, receptors, enzymes, chemiluminescent groups, photoreactive groups, fluorescent groups, heavy metal-containing compounds (e.g., ferritin), and the like.

When the compounds described herein are covalently linked to one or more polymers, such as those described herein, any linking group known in the art can be used. The linking group may comprise any chemical group(s) suitable for linking the peptide to the polymer. Alternatively, compounds can be directly attached to the polymer without any linking group. Exemplary linking groups include amino acids, maleimido groups, dicarboxylic acid groups, succinimide groups, or a combination of two or more thereof. Methods for linking peptides to one or more polymers are known in the art and described, for example, in US Patent No. 6,329,336; US Patent No. 6,423,685; US Patent No. 6,924,264; WO 2005/077072, WO 2007/022123, WO 2007/053946; WO 2008/058461; and WO 2008/082274, the disclosures of which are incorporated by reference herein.

The compounds described herein may be prepared using biological, chemical, and/or recombinant DNA techniques that are known in the art. Exemplary methods are described in US Patent No. 6,872,700; WO 2007/139941; WO 2007/140284; WO 2008/082274; WO 2009/011544; and US Publication No. 2007/0238669, the disclosures of which are incorporated herein by reference. Other methods for preparing the compounds are set forth herein.

The compounds described herein may be prepared using standard solid-phase peptide synthesis techniques, such as an automated or semiautomated peptide synthesizer. Typically, using such techniques, an alpha-N-carbamoyl protected amino acid and an amino acid attached to the growing peptide chain on a resin are coupled at room temperature in an inert solvent (e.g., dimethylformamide, N-methylpyrrolidinone, methylene chloride, and the like) in the presence of coupling agents (e.g., dicyclohexylcarbodiimide, 1-hydroxybenzo- triazole, and the like) in the presence of a base (e.g., diisopropylethylamine, and the like). The alpha-N-carbamoyl protecting group is removed from the resulting peptide-resin using a reagent (e.g., trifluoroacetic acid, piperidine, and the like) and the coupling reaction repeated with the next desired N-protected amino acid to be added to the peptide chain. Suitable N-protecting groups are well known in the art, such as t-butyloxycarbonyl (tBoc) fluorenylmethoxycarbonyl (Fmoc), and the like. The solvents, amino acid derivatives and 4-methylbenzhydryl-amine resin used in the peptide

synthesizer may be purchased from Applied Biosystems Inc. (Foster City, Calif.).

Solid phase peptide synthesis may be carried out with an automatic peptide synthesizer (Model 430A, Applied Biosystems Inc., Foster City, Calif.) using the NMP/HOBt (Option 1) system and tBoc or Fmoc chemistry (See Applied Biosystems User's Manual for the ABI 430A Peptide Synthesizer, Version 1.3B Jul. 1, 1988, section 6, pp. 49-70, Applied Biosystems, Inc., Foster City, Calif.) with capping. Boc-peptide-resins may be cleaved with HF (-5°C to 0°C, 1 hour). The peptide may be extracted from the resin with alternating water and acetic acid, and the filtrates lyophilized. The Fmoc-peptide resins may be cleaved according to standard methods (e.g., Introduction to Cleavage Techniques, Applied Biosystems, Inc., 1990, pp. 6-12). Peptides may be also be assembled using an Advanced Chem Tech Synthesizer (Model MPS 350, Louisville, Ky.).

Peptides may be purified by RP-HPLC (preparative and analytical) using a Waters Delta Prep 3000 system. A C4, C8 or C18 preparative column (10μ, 2.2X25 cm; Vydac, Hesperia, Calif.) may be used to isolate peptides, and purity may be determined using a C4, C8 or C18 analytical column (5μ, 0.46X25 cm; Vydac). Solvents (A=0.1% TFA/water and B=0.1% TFA/CH_3CN) may be delivered to the analytical column at a flow rate of 1.0 ml/min and to the preparative column at 15 ml/min. Amino acid analyses may be performed on the Waters Pico Tag system and processed using the Maxima program. Peptides may be hydrolyzed by vapor-phase acid hydrolysis (115°C, 20-24 h). Hydrolysates may be derivatized and analyzed by standard methods (Cohen et al, The Pico Tag Method: A Manual of Advanced Techniques for Amino Acid Analysis, pp. 11-52, Millipore Corporation, Milford, Mass. (1989)). Fast atom bombardment analysis may be carried out by M-Scan, Incorporated (West Chester, Pa.). Mass calibration may be performed using cesium iodide or cesium iodide/glycerol. Plasma desorption ionization analysis using time of flight detection may be carried out on an Applied Biosystems Bio-Ion 20 mass spectrometer.

The compounds described herein may also be prepared using recombinant DNA techniques using methods known in the art, such as Sambrook et al., Molecular Cloning: A Laboratory Manual, 2d Ed., Cold Spring Harbor (1989). Non-peptide compounds may be prepared by art-known methods. For example, phosphate-containing amino acids and peptides containing such amino acids, may be prepared using methods known in the art, such as described in Bartlett et al, Biorg. Chem., 14:356-377 (1986).

The disclosure also provides pharmaceutical compositions comprising at least one of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein and a pharmaceutically acceptable carrier. The N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds can be present in the pharmaceutical composition in a therapeutically effective amount and can be present in an amount to provide a minimum blood plasma level for therapeutic efficacy.

Pharmaceutical compositions containing the compounds described herein may be provided for peripheral administration, such as parenteral (e.g., subcutaneous, intravenous, intramuscular), topical, nasal, or oral administration. Suitable pharmaceutically acceptable carriers and their formulation are described in standard formulation treatises, such as Remington's Pharmaceutical Sciences by Martin; and Wang et al, Journal of Parenteral Science and Technology, Technical Report No. 10, Supp. 42:2S (1988).

The compounds described herein can be provided in parenteral compositions for injection or infusion. They can, for example, be suspended in water; an inert oil, such as a vegetable oil (e.g., sesame, peanut, olive oil, and the like); or other pharmaceutically acceptable carrier. In one embodiment, the compounds are suspended in an aqueous carrier, for example, in an isotonic buffer solution at a pH of about 3.0 to 8.0, or about 3.0 to 5.0. The compositions may be sterilized by conventional sterilization techniques or may be sterile filtered. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH buffering agents. Useful buffers include for example, acetic acid buffers. A form of repository or "depot" slow release preparation may be used so that therapeutically effective amounts of the preparation are delivered into the bloodstream over many hours or days following subcutaneous injection, transdermal injection or other delivery method. The desired isotonicity may be accomplished using sodium chloride or other pharmaceutically acceptable agents such as dextrose, boric acid, sodium tartrate, propylene glycol, polyols (such as mannitol and sorbitol), or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions.

The compounds can also be formulated as pharmaceutically acceptable salts (e.g., acid addition salts) and/or complexes thereof. Pharmaceutically acceptable salts are non-toxic salts at the concentration at which they are administered. Pharmaceutically acceptable salts include acid

addition salts such as those containing sulfate, hydrochloride, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, and quinic acid. Such salts may be prepared by, for example, reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the ions of an existing salt for another ion on a suitable ion exchange resin.

Carriers or excipients can also be used to facilitate administration of the compounds. Examples of carriers and excipients include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents.

If desired, solutions of the above compositions may be thickened with a thickening agent such as methyl cellulose. They may be prepared in emulsified form, either water in oil or oil in water. Any of a wide variety of pharmaceutically acceptable emulsifying agents may be employed including, for example, acacia powder, a non-ionic surfactant (such as a Tween), or an ionic surfactant (such as alkali polyether alcohol sulfates or sulfonates, e.g., a Triton).

Compositions may be prepared by mixing the ingredients following generally accepted procedures. For example, the selected components may be simply mixed in a blender or other standard device to produce a concentrated mixture which may then be adjusted to the final concentration and viscosity by the addition of water or thickening agent and possibly a buffer to control pH or an additional solute to control tonicity.

The therapeutically effective amount of the compounds described herein to treat the diseases described herein will typically be from about 0.01 μg to about 5 mg; about 0.1 μg to about 2.5 mg; about 1 μg to about 1 mg; about 1 μg to about 50 μg; or about 1 μg to about 25 μg. Alternatively, the therapeutically effective amount of the GLP-1 receptor agonist compounds may be from about 0.001 μg to about 100 μg based on the weight of a 70 kg patient; or from about 0.01 μg to about 50 μg based on the weight of a 70 kg patient. These therapeutically effective doses may be administered once/day, twice/day, thrice/day, once/week, biweekly, or

once/month, depending on the formulation. The exact dose to be administered is determined, for example, by the formulation, such as an immediate release formulation or an extended release formulation. For transdermal, nasal or oral dosage forms, the dosage may be increased from about 5-fold to about 10-fold.

The compounds described herein and pharmaceutical compositions comprising the compounds are useful for treating diabetes. The diabetes can be Type I diabetes, Type II diabetes, or gestational diabetes. The methods for treating diabetes provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to treat diabetes in the patient.

The compounds described herein and pharmaceutical compositions comprising the compounds are useful for treating insulin resistance and stimulating insulin release. The methods for treating insulin resistance provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to treat insulin resistance in the patient. The methods for treating stimulating insulin release provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to stimulate insulin release in the patient.

The compounds described herein and pharmaceutical compositions comprising the compounds are useful for treating postprandial hyperglycemia. The methods for treating postprandial hyperglycemia provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to treat postprandial hyperglycemia in the patient.

The compounds described herein and pharmaceutical compositions comprising the compounds are useful for lowering blood glucose levels and lowering HbA1c levels. The methods for lowering blood glucose levels provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds

described herein to lower blood glucose levels in the patient. In one embodiment, the blood glucose levels can be fasting blood glucose levels. The methods for lowering HbA1c levels provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to lower HbA1c levels in the patient. HbA1c levels are generally a long-term measure of a patient's blood glucose levels.

The compounds described herein and pharmaceutical compositions comprising the compounds are useful for reducing gastric motility and delaying gastric emptying. The methods for reducing gastric motility provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to reduce gastric motility in the patient. The methods for delaying gastric emptying provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to delay gastric emptying in the patient.

The compounds described herein and pharmaceutical compositions comprising the compounds are useful for reducing food intake, reducing appetite, increasing satiety, and reducing weight. The methods for reducing food intake provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to reduce food intake in the patient. The methods for reducing appetite provide or increasing satiety administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to reduce appetite in the patient. The methods for treating reducing weight provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to reduce weight in the patient. In the methods described herein, the patient may be in need of a reduced

intake in food, of a reduced appetite, or of reduced weight. In other methods described herein, the patient may be desirous of having a reduced intake in food, of having a reduced appetite, or of having a reduced weight. The patient may be of any weight, and can be overweight or obese.

The compounds described herein and pharmaceutical compositions comprising the compounds are useful for treating overweight and obesity. The methods for treating overweight provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to treat overweight in the patient. The methods for treating obesity provide administering to a patient in need thereof a therapeutically effective amount of one or more of the N-terminus conformationally constrained compounds or the N-terminus conformationally constrained GLP-1 receptor agonist compounds described herein to treat obesity in the patient.

The disclosure also provides drug delivery devices having at least one therapeutically effective dose of the compounds described herein or the pharmaceutical composition containing the compounds described herein. The drug delivery devices can be single or multiple-use vials, single or multiple-use pharmaceutical pens, single or multiple-use cartridges, and the like. In one embodiment, the drug delivery devices contain the compounds or pharmaceutical compositions described herein in amounts capable of providing a patient with from about 7 to about 40 doses or enough doses to last about one week or about one month.

Examples

The following examples are for purposes of illustration only and are not intended to limit the scope of the claims.

Example 1: Preparation of Compound in Figure 16A

A calculated 100 μmol of Fmoc-Ser(OtBu)-Wang resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and the peptide elongation was carried out following standard Fmoc peptide synthesis protocol up to residue Thr^5. The resulting peptide-resin intermediate (0.3 g, 0.0927 mmol) was swollen in dimethylformamide (DMF) and to the slurry was added compound **7** (0.110 g, 2.2 eq), followed by O-(benzotriazol-1-yl)-N,N,N',N' tetramethyluronium hexafluorophosphate (HBTU) (0.035 g, 2.2 eq), N-hydroxybenzotriazole (HOBt) (0.03 g, 2.2 eq) and methylmorpholine (NMM) (0.04 mL, 4.4 eq). After 3 hours, the resin was washed with DMF 6x, treated with 20% piperidine in DMF 2x25 min and washed with

DMF 6x. The above cycle was repeated with Fmoc-Ala-OH and Fmoc-His(Trt)-OH followed by cleavage of the peptide from the resin with 10 ml TFA/H_2O/PhOH/TIPS (95:2:2:1) (TFA is trifluoroacetic acid; TIPS is triisopropylsilyl), precipitated by methyl-*tert*-Butyl ether and the obtained residue applied to a reverse-phase high performance liquid chromatography (HPLC) column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compound as a white powder (16.4 mg, 6%): Retention time in reverse phase-high performance liquid chromatography (RP-HPLC) (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 9.78 min; Calculated mass for $C_{189}H_{294}N_{48}O_{60}S$ $(M+H)^+$ 4231.84, found by liquid chromatography/mass spectrometry (LC-MS) 1411.3 $(M+3H)^{3+}$, 1059.6 $(M+4H)^{4+}$, 2117.2 $(M+2H)^{2+}$.

Example 2: Preparation of Compound in Figure 16B

A calculated 100 μmol of Fmoc-Ser(OtBu)-Wang resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and the peptide elongation was carried out following standard Fmoc peptide synthesis protocol up to residue Thr^5. The resulting peptide-resin intermediate (0.3 g, 0.0927 mmol) was swollen in DMF and to the slurry was added compound **24** (0.122 g, 2.2 eq), followed by HBTU (0.035 g, 2.2 eq), HOBt (0.03 g, 2.2 eq) and NMM (0.04 mL, 4.4 eq). After 3 hours, the resin was washed with DMF 6x, treated with 20% piperidine in DMF 2x25 min and washed with DMF 6x. The above cycle was repeated with Fmoc-His(Trt)-OH followed by cleavage of the peptide from the resin with 10 ml TFA/H_2O/PhOH/TIPS (95:2:2:1), precipitated by methyl-*tert*-Butyl ether. The obtained crude peptide was dissolved in 1.5 mL of MeOH:ACN (1:1) (ACN is acetonitrile), followed by addition of 2M LiOH (0.6 mL) and the reaction stirred at RT for 6h. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compound as a white powder (15 mg, 6%): Retention time in RP-HPLC (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 9.82 min; Calculated mass for $C_{188}H_{294}N_{48}O_{60}$ $(M+H)^+$ 4186.72, found by LC-MS 1396.7 $(M+3H)^{3+}$, 1048.6 $(M+4H)^{4+}$, 2114.2 $(M+2H)^{2+}$.

Example 3: Preparation of Compound in Figure 16C

A calculated 100 μmol of Fmoc-Ser(OtBu)-Wang resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and the peptide elongation was carried out following standard Fmoc peptide synthesis protocol up to residue Thr^5. The resulting peptide-resin

intermediate (0.3 g, 0.0927 mmol) was swollen in DMF and to the slurry was added compound **18** (0.131 g, 2.2 eq), followed by HBTU (0.035 g, 2.2 eq), HOBt (0.03 g, 2.2 eq) and NMM (0.04 mL, 4.4 eq). After 3 hours, the resin was washed with DMF 6x, treated with 20% piperidine in DMF 2x25 min and washed with DMF 6x. The above cycle was repeated with Fmoc-His(Trt)-OH followed by cleavage of the peptide from the resin with 10 ml $TFA/H_2O/PhOH/TIPS$ (95:2:2:1), precipitated by methyl-*tert*-Butyl ether. The obtained crude peptide was dissolved in 1.5 mL of MeOH:ACN (1:1), followed by addition of 2M LiOH (0.6 mL) and the reaction stirred at RT for 6h. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compound as a white powder (19.7 mg, 8%): Retention time in RP-HPLC (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 8.58 min; Calculated mass for $C_{189}H_{294}N_{48}O_{60}S$ $(M+H)^+$ 4230.80, found by LC-MS 1411. $(M+3H)^{3+}$, 1059.6 $(M+4H)^{4+}$, 2117.2 $(M+2H)^{2+}$.

Example 4: Preparation of Compound in Figure 16E

The synthesis of this compound was accomplished following the same experimental procedure as described for Example 3. The only difference was the sequence of the peptide-resin intermediate, starting with Rink-amide resin. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compound as a white powder (15.7 mg, 7%): Retention time in RP-HPLC (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 8.25 min; Calculated mass for $C_{188}H_{286}N_{48}O_{60}S$ $(M+H)^+$ 4238.74, found by LC-MS 1414.8 $(M+3H)^{3+}$, 1061.6 $(M+4H)^{4+}$, 2121.2 $(M+2H)^{2+}$.

Example 5: Preparation of Compound in Figure 16D

A calculated 100 μmol of Fmoc-Ser(OtBu)-Wang resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and the peptide elongation was carried out following standard Fmoc peptide synthesis protocol up to residue Thr^5. The resulting peptide-resin intermediate (0.3 g, 0.0927 mmol) was swollen in DMF and to the slurry was added compound **11** (0.100 g, 2.2 eq), followed by HBTU (0.035 g, 2.2 eq), HOBt (0.03 g, 2.2 eq) and NMM (0.04 mL, 4.4 eq). After 3 h, the resin was washed with DMF 6x, treated with 20% piperidine in DMF 2x25 min and washed with DMF 6x. The above cycle was repeated with Fmoc-Ala-OH and Fmoc-His(Trt)-OH followed by cleavage of the peptide from the resin with 10 ml $TFA/H_2O/PhOH/TIPS$ (95:2:2:1), precipitated by methyl-*tert*-Butyl ether and the obtained residue applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over

30 min gradient) to afford the titled compound as a white powder (20.3 mg, 10%): Retention time in RP-HPLC (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 9.74 min; Calculated mass for $C_{188}H_{294}N_{48}O_{60}$ $(M+H)^+$ 4186.72, found by LC-MS 1396.7 $(M+3H)^{3+}$, 1048.6 $(M+4H)^{4+}$, 2114.2 $(M+2H)^{2+}$.

Example 6: Preparation of Compound in Figure 16F

A calculated 100 μmol of Fmoc-Ser(OtBu)-Wang resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and the peptide elongation was carried out following standard Fmoc peptide synthesis protocol up to residue Thr^5. The resulting peptide-resin intermediate (0.3 g, 0.0927 mmol) was swollen in DMF and to the slurry was added compound **21** (0.125 g, 2.2 eq), followed by HBTU (0.035 g, 2.2 eq), HOBt (0.03 g, 2.2 eq) and NMM (0.04 mL, 4.4 eq). After 3 h, the resin was washed with DMF 6x, treated with 20% piperidine in DMF 2x25 min and washed with DMF 6x. The above cycle was repeated with Fmoc-His(Trt)-OH followed by cleavage of the peptide from the resin with 10 ml TFA/H_2O/PhOH/TIPS (95:2:2:1), precipitated by methyl-*tert*-Butyl ether. The obtained crude peptide was dissolved in 1.5 mL of MeOH:ACN (1:1), followed by addition of 2M LiOH (0.6 mL) and the reaction stirred at RT for 6h. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compound as a white powder (8 mg, 4%): Retention time in RP-HPLC (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 7.93 min; Calculated mass for $C_{189}H_{296}N_{48}O_{60}$ $(M+H)^+$ 4200.75, found by LC-MS 1401.8 $(M+3H)^{3+}$, 1051.6 $(M+4H)^{4+}$, 2102.2 $(M+2H)^{2+}$.

Example 7: Preparation of Compound in Figure 16G

The synthesis of this compound was accomplished following the same experimental procedure as described for Example 3. The only difference was the sequence of the peptide-resin intermediate. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compound as a white powder (27.4 mg, 18%): Retention time in RP-HPLC (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 8.25 min; Calculated mass for $C_{153}H_{228}N_{40}O_{47}S$ $(M+H)^+$ 3411.83, found by LC-MS 1138.6 $(M+3H)^{3+}$, 854.5 $(M+4H)^{4+}$, 1707.9 $(M+2H)^{2+}$.

Example 8: Preparation of (5,5)-Glu-Gly-OH as shown in Figure 18

Preparation of Boc-Asp(OBn)-OMe: Boc-Asp(OBn)-OH 2.4 g (1 equiv, 7.45 mmol) was dissolved in 17 mL of dry DMF in a 100 mL round-bottom flask. Finely ground K_2CO_3 (1.5 g,

11 mmol) was added to the solution to form a suspension. The mixture was cooled to 0°C in an ice-bath over five minutes. MeI (1 mL, 15 mmol) was then added to the mixture over 20 seconds under a positive flow of nitrogen. A yellow color developed within 30 min. The resulting mixture was stirred for 3 hours. The ice-bath was removed and 25 mL of water were added and the mixture left standing at room temperature 2 hours. The mixture was then treated with 30 mL of water and extracted with 3x25 mL AcOEt. The organics were washed with saturated $NaHCO_3$ 1X, brine 3x, dried over Na_2SO_4 filtered and concentrated to yield a yellow oil. This material was passed through a short silica column (eluting w/ AcOEt), after concentration of the pure fractions 2.42 g of Boc-Asp(OBn)-OMe as a yellow oil was obtained (98% yield). ^1H NMR (DMSO d6, 500 mHz): δ 7.36 (m, 5H), 5.10 (s, 2H), 4.40 (q, 1H), 3.6 (s, 3H), 2.80 (dd, 1H), 2.72 (dd, 1H), 1.38 (s, 9H). LCMS (C_{18}, 2-98% CH_3CN in 0.1% TFA/H_2O over 6 min); Calculated mass for $C_{17}H_{23}NO_6$ $(M+H)^+$ 338.23, found by LC-MS 338.2.

Preparation of Compound **1** in **Figure 18**: Boc-Asp(OBn)-OMe (26.4 g, 78.3 mmol) was dissolved in a 500 mL round-bottom flask with 110 mL of dry THF and the mixture cooled at negative 42°C. To this mixture was added lithium bis(trimethylsilyl)amide (LiHMDS) (173 mL, 1 M solution, 2.2 eq). This solution was stirred under a gentle argon flow for 45 min followed by slow addition (via syringe) of *tert*-butyl bromo acetate (14.5 mL, 1.25 eq). Thin layer chromatography (TLC) (Hex:AcOEt, 8/2) showed after 4 h > 95% of expected product. The reaction was quenched by addition of saturated NH_4Cl (70 mL). The mixture was evaporated and the residue re-dissolved with 100 mL of dichloromethane (DCM). The emulsion formed was separated by standing overnight. The organics were collected and washed with saturated NH_4Cl 2x, brine 1X, dried over Na_2SO_4, filtered and concentrated to give Compound 1 as a red orange oil. Flash chromatography (Hex:AcOEt, 7:3) gave 27.4 g of a yellow oil (78% yield). ^1H NMR (DMSO d6, 500 mHz): δ 7.35 (m, 5H), 5.08 (s, 2H), 4.57 (dd, 1H), 4.05 (m, 1H), 3.52 (s, 3H), 1.39 (s, 9H), 1.34 (s, 9H). LCMS (C_{18}, 2-98% CH_3CN in 0.1% TFA/H_2O over 6 min); Calculated mass for $C_{23}H_{33}NO_8$ $(M+H)^+$ 452.23, found by LC-MS 452.2.

Preparation of Compound **2** in **Figure 18**. Compound **2** is *tert*-butyl-(1S,2R)-2-[(carboxy)-3-*tert*-butoxycarbonyl)-1-metoxhycarbonyl)]propylcarbamate. Compound **1** (5.8 g, 12.8 mmol) was dissolved in 30 mL of a 6:4 mixture of MeOH/THF. Argon was bubbled in the catalyst for 5 minutes, followed by incorporation of two hydrogen balloons attached via syringe to the reaction flask. After 4 hours, LCMS shows complete transformation. The crude mixture

was filtrated through celite and concentrated to yield 5.25 g of Compound **2** as an orange oil which was used without further purification in the next step. Calculated mass for $C_{16}H_{27}NO_8$ $(M+H)^+$ 362.23, found by LC-MS 362.2.

Preparation of Compound **3** in **Figure 18**. Compound **3** is *tert*-butyl-(1S,2R)-2-[(benzylthio)-carbonyl)-3-*tert*-butoxycarbonyl)-1-metoxhycarbonyl)]propylcarbamate. Compound **2** (2.1 g, 5.8 mmol) was dissolved with DCM (7 mL). To this clear mixture was added ethylthiol (0.4 g, 1.1 eq) and 4-dimethylaminopyridine (DMAP) (0.07 g, 0.1 eq). To the clear solution was added dicyclohexyl carbodiimide (DCC) (1.3 g, 1.1 eq) as a solid and the mixture was stirred at room temperature for 5 hours. The mixture was diluted with DCM (40 mL) and washed with 1N HCl (2x), dried over Na_2SO_4, filtered and concentrated to give 2.15 g of Compound **3** as a yellow oil, which was used without further purification in the next step. Calculated mass for $C_{18}H_{31}NO_7S$ $(M+H)^+$ 406.13, found by LC-MS 406.2.

Preparation of Compound **4** in **Figure 18**. Compound **4** is *tert*-butyl-(1S,2R)-3-(*tert*-butoxcarbonyl)-1-(methoxycarbonyl)-2-formylpropylcarbamate. To Compound **3** (5.9 g, 14.5 mmol) and Pd-C 10% wt (0.35 g) were added acetone (36 mL) and the mixture cooled down to about 4-8°C. To this mixture was added drop wise, under positive flow of Argon, triethylsilyl (TES) (11.5 mL, 5 eq). After addition of TES the mixture was kept at 10-15°C. After 3.5 hours LCMS showed no more starting material. The mixture was filtrated through celite, and the solution concentrated to give 6.6 g of Compound **4** as a green oil which was used without further purification in the next step. Calculated mass for $C_{16}H_{27}NO_7$ $(M+H)^+$ 346.13, found by LC-MS 346.2.

Preparation of Compound **5** in **Figure 18**. Compound **5** is methyl-[3S,4R,8R]-1-Aza-3-*tert*-butoxycarbonyl-4-(*tert*-butoxycarbonyl)methyl)-2-oxo-6-thiabicyclic[3.3.0]-octane-8-carboxylate. To Compound **4** (1.3 g, 3.76 mmol), L-Cys-OH-HCl (0.98 g, 1.5 eq) and 4 °A molecular sieves (2 g) was added dry pyridine (10 mL) and the mixture stirred, under argon, at room temperature for 4 hours in high pressure vessel. After this time, 3.5 mL more of pyridine were added and the reaction was stirred at 50°C for 5 days. After this time, the crude mixture was filtered through celite, the solution was re-dissolved in AcOEt and washed with 2N HCl 2x, dried over Na_2SO_4, filtered and concentrated to yield 1.2 g of Compound **5** as a yellowish semisolid, which was used without further purification in the next step. Calculated mass for $C_{19}H_{30}N_2O_7S$ $(M+H)^+$ 431.13, found by LC-MS 431.2.

Preparation of Compound **6** in **Figure 18**. Compound **6** is [3S,4R,8R]-1-Aza-3-amino-4-(*tert*-butoxycarbonyl)methyl)-2-oxo-6-thiabicyclic[3.3.0]-octane-8-carboxylate. Crude Compound **5** was treated with 10 mL of a 50% TFA-DCM mixture at 0°C. The mixture was let to warm up at 10°C and stirred for 2.5 hours. The mixture is then concentrated and the residue re-dissolved with 5 mL of a 2M LiOH solution and stirred at room temperature for 2.5 hours. LCMS analysis showed complete transformation to Compound **6**. The reaction was concentrated and the residue passed through a short column packed with ion-exchange resin (H^+, Dowex), eluting with 1:1 MeOH /H_2O. The residue was concentrated and then lyophilized to give 1.8 g of crude Compound **6** as a yellow semisolid, which was used without further purification in the next step. Calculated mass for $C_{13}H_{20}N_2O_5S$ $(M+H)^+$ 317.13, found by LC-MS 317.2.

Preparation of Compound **7** in **Figure 18**. Compound **7** is the (5,5)-Glu-Gly bicylic dipeptide mimetic. Compound **7** is also referred to as [3S,4R,8R]-1-Aza-3-fluorenylmethyl-carbonyl-4-(*tert*-butoxycarbonyl)methyl)-2-oxo-6-thiabicyclic[3.3.0]-octane-8-carboxylate. Crude Compound **6** (1.2 g, 3.8 mmol) was dissolved in 17 mL of dry DCM. To this solution was added FmocOSu (1.8 g, 1.4 eq) followed by N,N-diisopropylethylamine (DIEA) (1.3 mL, 2 eq). The reaction was stirred at room temperature for 3 hours. To the mixture was added 50 mL of DCM and washed with 2M HCl 2x, brine 1x, dried over Na_2SO_4, filtered and concentrated to give 1.42 g of a yellow oil. Purification by flash chromatography using an increasing polarity solvent gradient (Hex:AcOEt 1:1 to DCM:MeOH 9:1) gave 0.150 g of pure Compound **7**. Calculated mass for $C_{28}H_{30}N_2O_7S$ $(M+H)^+$ 539.13, found by LC-MS 539.2.

Example 9: Preparation of Compound 11 in Figure 19

Compound **9** is 1-Aza-3-amino-*tert*-butoxylcarbonyl-4-(*tert*-butoxycarbonyl)methyl)-2-oxo-1-methoxyacetyl. Compound **4** was prepared as described above. A solution of Compound **4** (preparation described in Example 8) (4.1 g, 12 mmol) and the HCl salt of NH_2-Gly-OMe (1.66 g, 1.1 eq) in 20 mL of DMF were stirred at room temperature. To this mixture was added $NaBH(OAc)_3$ (5.0 g, 2 eq) dissolved in 18 mL of DMF. After 1 hour LCMS shows complete transformation to the desired secondary amine **8**. Calculated mass for $C_{19}H_{34}N_2O_8$ $(M+H)^+$ 419.1, found by LC-MS 419.2. To this crude mixture was added AcOEt (80 mL), washed with sat. $NaHCO_3$ 3x, water 1x, brine 1x, dried over Na_2SO_4, filtered and concentrated to give 3.9 g of a crude yellow oil. LCMS of this material showed that the five-member ring lactam (Compound

9) was formed during work-up. The residue was concentrated to give 3.9 g of crude Compound **9** as a yellow oil, which was used without further purification in the next step. Calculated mass for $C_{18}H_{30}N_2O_7$ $(M+H)^+$ 387.1, found by LC-MS 387.2.

Preparation of Compound **10** in **Figure 19**. Compound **10** is 1-amino-4-(*tert*-butoxy-carbonyl)methyl)-2-oxo-1-methoxyacetyl. Crude Compound **9** (3.8 g) was cooled at 10°C in an ice-water bath. To this stirred mixture was added in a drop wise manner 15 mL of a 50% solution of TFA in DCM. The mixture was stirred at that temperature for 2 h. LCMS showed a selective N-Boc deprotection. The mixture was concentrated to yield crude compound **10** as clear semisolid, which was used without further purification in the next step. Calculated mass for $C_{13}H_{22}N_2O_5$ $(M+H)^+$ 287.1, found by LC-MS 287.2.

Preparation of Compound **11** in **Figure 19**. Compound **11** is a γ-lactam-Glu-Gly bicyclic dipeptide mimetic which is 1-Aza-3-aminofluorenylmethylcarbonyl-4-(*tert*-butoxycarbonyl) methyl)-2-oxo-1-acetylcarboxylate. Crude Compound **10** (2.8 g, 9.8 mmol) was dissolved in 8 mL of a 1:1 mixture of dioxane/MeOH at room temperature. To this mixture was added 15 mL of a 2M LiOH (2.8 eq) and the mixture stirred at room temperature for 3 hours. The mixture was then concentrated and passed trough a short column of Dowex H^+ ion-exchange resin. The pooled fractions containing M+1= 273 by LCMS were collected and lyophilized. This crude material was then dissolved in DCM (40 mL) followed by addition of DIEA (3.5 mL, 2 eq) and FmocOSu (3.9 g, 1.2 eq). The mixture was stirred at room temperature for 3 hours. LCMS analysis shows no more starting material, thus to the reaction was added AcOEt (60 mL), washed with sat. $NaHCO_3$ 3x, water 1x, brine 1x, dried over Na_2SO_4, filtered and concentrated to give 2.5 g of a crude Compound **11**. The mixture was purified by flash chromatography using AcOEt:Hex (1:1). Collection of the pure fractions identified by LCMS gave 100 mg of pure Compound **11**. Calculated mass for $C_{27}H_{30}N_2O_7$ $(M+H)^+$ 495.1, found by LC-MS 495.2.

Example 10: Preparation of Compound 18 in Figure 20

Compound **1** (i.e., *tert*-buty1-l(1S,2R)-2-[(benzyloxy)carbonyl)-3-*tert*-butoxycarbonyl)-1-metoxhycarbonyl)]propylcarbamate) was prepared as described in Example 8 above.

Preparation of Compound **12** in **Figure 20**. Compound **12** is *tert*-Butyl-(1S,2R)-2-[(benzylcarboxylate)-3-carboxy)-1-metoxhycarbonyl)]propylcarbamate. To Compound **1** (13.9 g, 30.8 mmol) was added 45 mL of a 2M solution of HCl in diethyl ether. The clear yellow solution was stirred at room temperature for 18 hours. The mixture was triturated with cold ether

which gave a yellow foam. Drying of this solid gave 8.32 g (84% yield) of the hydrochloride salt intermediate which was used without further purification in the next step. This HCl salt crude (8.3 g, 25 mmol) was dissolved in THF (80 mL). To this clear solution was added TEA (7.6 mL, 2.2 eq) followed by Boc_2O (6.5 g, 1.2 eq). The mixture was stirred for 18 hours at room temperature. The mixture was then concentrated, re-dissolved in AcOEt (150 mL), washed with 1N HCl 2x, sat. NaCl 1x, dried over Na_2SO_4, filtered, concentrated and dried under high vacuum to yield Compound **12** as a brownish oil (11.1 g ,100% crude yield), which was used without further purification in the next step. Calculated mass for $C_{19}H_{25}NO_8$ $(M+H)^+$ 396.1, found by LC-MS 396.2.

Preparation of Compound **13** in **Figure 20**. Compound **13** is *tert*-Butyl-(1S,2R)-2-[(benzylcarboxylate)-3-ethylthiocarboxylate)-1-metoxhycarbonyl)]propylcarbamate. DCC (5.9 g, 1.1 eq) was added to a solution of crude Compound **12** (10.4 g, 26.2 mmol), EtSH (2.15 mL, 1.1 eq) and 4-dimethylaminopyridine (DMAP) (0.32 g, 0.1 eq) dissolved in DCM (28 mL). After 6 hours the mixture was concentrated, re-dissolved in AcOEt (150 mL) washed with 1N HCl 2x, sat. NaCl 1x, dried over Na_2SO_4, filtered, concentrated and dried under high vacuum to yield Compound **13** as a brown oil (7.6 g), which was used without further purification in the next step. Calculated mass for $C_{21}H_{29}NO_7S$ $(M+H)^+$ 440.1, found by LC-MS 440.2.

Preparation of Compound **14** in **Figure 20**. Compound **14** is (1S,2R)-2-[(benzyl-carboxylate)-3-ethylthiocarboxylate)-1-metoxhycarbonyl)]propylamine hydrochloride salt. Crude Compound **13** (7.6 g, 17.2 mmol) was dissolved in ethyl ether (8 mL), followed by addition of a 2N solution of HCl in diethyl ether (40 mL). The clear mixture was stirred at room temperature for 18 hours. The mixture was concentrated to give Compound **14** as an orange oil (7.5 g) which was used without further purification in the next step. Calculated mass for $C_{16}H_{21}NO_5S$ $(M+H)^+$ 338.1, found by LC-MS 338.2.

Preparation of Compound **15** in **Figure 20**. Compound **15** is (1S,2R)-2-[(benzyl-carboxylate)-3-ethylthiocarboxylate)-1-metoxhycarbonyl)]propyl-L-N-Boc-Ala. Crude Compound **14** (6.6 g, 17.7 mmol), Boc-L-Ala-OH (3.7 g, 1.1 eq) and 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoride (HATU) (12.1 g, 1.8 eq) were dissolved in ACN (150 mL). To this solution was added DIEA (6.1 mL, 2 eq) and the mixture was stirred at room temperature for 6 hours. The mixture was concentrated, re-dissolved in AcOEt (150 mL), washed with sat NH_4Cl 2x, sat. NaCl 1x, dried over Na_2SO_4, filtered, concentrated and dried

under high vacuum to yield compound **15** as a brown oil (16.5 g of crude). Purification by flash chromatography using Hex;AcOEt (6:4) gave pure compound **15** (3.55 g, 40% yield). Calculated mass for $C_{24}H_{34}N_2O_8S$ $(M+H)^+$ 511.1, found by LC-MS 511.2.

Preparation of Compound **16** in **Figure 20**. Compound **16** is (1S,2R)-2-[(benzyl-carboxylate)-3-formyl)-1-metoxhycarbonyl)]propyl-L-N-Boc-Ala. Triethylsilane (5.6 mL, 5 eq) was slowly added, under argon, to a solution of Compound **15** (3.5 g, 6.9 mmol) and Pd-C (0.6 g) dissolved in acetone (16 mL) in an ice bath (~4°C). After addition of TES the reaction was stirred at 10-20°C. After 4 hours, thin layer chromatography (TLC) showed complete transformation. The reaction was filtered and concentrated to give an off-green oil. Purification by flash chromatography using Hex;AcOEt (6:4) gave pure Compound **16** (2.9 g, 93% yield). Calculated mass for $C_{22}H_{30}N_2O_8$ $(M+H)^+$ 452.1, found by LC-MS 452.2.

Preparation of Compound **17** in **Figure 20**. Compound **17** is (3R,6S,7R)-7-(benzyloxy-carbonyl)-6-amino-(L-Boc-Ala)-hexahydro-5-oxo-2*H*-thiazolo[3,2-a]pyridine-3-carboxylic acid. In a high pressure vial crude Compound **16** (2 g, 4.55 mmol) was dissolved in dry pyridine (12 mL). To this mixture was added L-Cys-OH (0.88g, 1.6 eq) followed by addition of 2.7 g of activated 4°A molecular sieves (powder). The mixture was stirred vigorously at room temperature for 4 hours. Dry-pyridine (10 mL) was added to the mixture, the vial was capped and the mixture stirred at 50°C for 4 days. The mixture was then filtered through a bed of celite and washed with tetrahydrofuran (THF) and MeOH. The mixture was concentrated to give Compound **17** as yellow foam (1.6 g) which was used without further purification in the next step. Calculated mass for $C_{24}H_{31}N_3O_8S$ $(M+H)^+$ 522.1, found by LC-MS 522.2.

Preparation of Compound **18** in **Figure 20**. Compound **18** is (3R,6S,7R)-7-(benzyloxy-carbonyl)-6-amino-(L-Ala)-hexahydro-5-oxo-2*H*-thiazolo[3,2-a]pyridine-3-carboxylic acid. In a round bottom flask crude Compound **17** (1.6 g, 3.1 mmol) was dissolved in dioxane (15 mL) followed by addition of 4M HCl. The mixture was stirred at room temperature and after 3 hours LCMS analysis showed complete conversion to the free amine. The mixture was concentrated, dissolved with DCM, MeOH, concentrated again and then dried under high vacuum to give the hydrochloride salt as a brownish semisolid (1.5 g) which was used without further purification in the next step. Calculated mass for $C_{24}H_{31}N_3O_8S$ $(M+H)^+$ 522.1, found by LC-MS 522.2.

This HCl salt was dissolved in DCM (14 mL) followed by addition of DIEA (2 mL, 3.5 eq) and FmocOSu (1.2 g, 1.1 eq) in portions as solid. The mixture was stirred for 3 hours

showing complete transformation by LCMS. The mixture was concentrated, dissolved in AcOEt (60 mL), washed with 2N HCl 2x, brine, dried over Na_2SO_4, filtered and concentrated to give 2.1 g of a brownish oil. Purification by flash chromatography using Hex;AcOEt (5:95) followed by 100% MeOH gave pure compound **18** (0.821 g, 44% yield). Calculated mass for $C_{34}H_{33}N_3O_8S$ $(M+H)^+$ 644.1, found by LC-MS 644.2.

Example 11: Preparation of Compounds in Figure 21

Preparation of compound **16** has been described in Example 10.

Preparation of Compound **19** in **Figure 21**. Compound **19** is (1S,2R)- [2-(benzylcarboxylate)-3-formyl-4-(*tert*-butoxy-N-2-methyl acetyl)-1-(methoxycarbonyl)]butyl-L-N-Boc-Ala. Crude compound **16** (1.01 g, 2.24 mmol) and L-Ala-OtBu. HCl (0.449 g, 1.1 eq) were dissolved in DMF (4.5 mL) at room temperature. $NaBH(OAc)_3$ (0.95 g, 2 eq) was dissolved separately in DMF (4.5 mL) at room temperature, the two solutions were mixed and stirred at room temperature for about 2 hours. The reaction was washed with saturated $NaHCO_3$ solution 2x, water 1x, sat. NaCl 1x, dried over Na_2SO_4, filtered, concentrated to yield 0.92 g of Compound **19** as a colorless oil, which was used without further purification in the next step. Calculated mass for $C_{29}H_{45}N_3O_9$ $(M+H)^+$ 579.68, found by LC-MS 579.6.

Preparation of Compound **20** in **Figure 21**. Compound **20** is (1S,2R)-*tert*-butyl-[4-(benzylcarboxylate)-3-(N-L-Boc-Ala)-2-oxopiperidine)-1-methyl-1-yl]acetate. Crude Compound **19** (0.550 g, 0.95 mmol) was dissolved in DMF (3 mL), DIEA (0.445 mL, 2 eq) was heated using microwaves at 140°C for 20 min. The reaction was checked and then washed with 0.5M HCl 2x, water 1x, sat. NaCl 1x, dried over Na_2SO_4, filtered, concentrated to give 0.50 g of Compound **20** as a light brownish oil, which was used without further purification in the next step. Calculated mass for $C_{28}H_{41}N_3O_8$ $(M+H)^+$ 547.64, found by LC-MS 547.6.

Preparation of Compound **21** in **Figure 21**. Compound **21** is (1S,2R)-[4-(benzyl-carboxylate)-3-(N-L-Fmoc-Ala)-2-oxopiperidine)-1-methyl-1-yl]acetic acid. Crude Compound **20** (0.501 g, 0.91 mmol) was dissolved in 5 mL of 20% TFA in DCM and stirred for about an hour at room temperature. The reaction was concentrated and then dried under high vacuum to give the corresponding TFA salt as brownish oil (0.47 g) which was used without further purification in the next step. Calculated mass for $C_{19}H_{25}N_3O_6$ $(M+H)^+$ 505.64, found by LC-MS 505.6

This TFA salt (0.47 g, 0.91 mmol) was dissolved in aqueous 10% Na_2CO_3 solution (12

mL) and DMF (4 mL), and cooled down to 0°C. A solution of FmocOSu (0.472 g, 1.5 eq) in DMF (8 mL) was added dropwise to the cold aqueous solution. After 5 minutes the ice bath was removed and the reaction was stirred overnight, quenched by adding 40 mL water followed by washings with AcOEt. The aqueous layer was acidified using 2N HCl (pH=2) and washed with AcOEt 3x, NaCl 1x, dried over Na_2SO_4, filtered and concentrated. Purification was done by washing the crude compound with Hex:AcOEt (6:4) 2x at room temperature to give Compound **21** as light colored oil (0.290 g, 52% yield). Calculated mass for $C_{34}H_{35}N_3O_8$ $(M+H)^+$ 613.24, found by LC-MS 613.2.

Preparation of Compound **22** in **Figure 21**. Compound **22** is (1S,2R)-[2-(benzyl-carboxylate)-3-(formyl)-4-(*tert*-butoxy-N-acetyl)-1-(methoxycarbonyl)]butyl-L-N-Boc-Ala. Crude compound **16** (1.01 g, 2.24 mmol) and AcOH. NH_2-Gly-OtBu (0.478 g, 1.1 eq) were dissolved in dry DMF (4.5 mL) at room temperature. $NaBH(OAc)_3$ (0.95 g, 2 eq) was dissolved separately in dry DMF (4.5 mL) at room temperature, the two solutions were mixed and stirred at room temperature for about 2 hours. The reaction was washed with saturated $NaHCO_3$ solution 2x, water 1x, sat. NaCl 1x, dried over Na_2SO_4, filtered and concentrated to yield 1.09 g of Compound **22** as a colorless oil, which was used without further purification in the next step. Calculated mass for $C_{28}H_{43}N_3O_9$ $(M+H)^+$ 565.68, found by LC-MS 565.3.

Preparation of Compound **23** in **Figure 21**. Compound **23** is (1S,2R)-*tert*-butyl-[4-(benzylcarboxylate)-3-(N-L-Boc-Ala)-2-oxopiperidine)-1-yl]acetate. Crude compound **22** (0.550 g, 0.95 mmol) was dissolved in DMF (3 mL), DIEA (0.445 mL, 2 eq) and then heated using microwaves at 140°C for 20 min (Biotage™, Initiator8). The reaction was checked by LCMS. The reaction crude was washed with 0.5M HCl 2x, water 1x, sat. NaCl 1x, dried over Na_2SO_4, filtered and concentrated to yield 0.41 g of Compound **23** as a light brownish oil, which was used without further purification in the next step. Calculated mass for $C_{27}H_{39}N_3O_8$ $(M+H)^+$ 533.64, found by LC-MS 533.6.

Preparation of Compound **24** in **Figure 21**. Compound **24** is (1S,2R)-[4-(benzyl-carboxylate)-3-(N-L-Fmoc-Ala)-2-oxopiperidine)-1-yl]acetic acid. Crude Compound **23** (0.41 g, 0.76 mmol) was dissolved in 5 mL of 20% TFA in DCM; reaction was stirred for about an hour at room temperature. The reaction was concentrated and then dried under high vacuum to give the corresponding TFA salt as a brownish oil (0.45 g) which was used without further purification in the next step. Calculated mass for $C_{18}H_{23}N_3O_6$ $(M+H)^+$ 491.3, found by LC-MS

491.4

This TFA salt (0.45 g, 0.92 mmol) was dissolved in aqueous 10% Na_2CO_3 solution (12 mL) and DMF (4 mL), and cooled down to 0°C. A solution of FmocOSu (0.472 g, 1.5 eq) in DMF (8 mL) was added dropwise to the cold aqueous solution. After 5 min, the ice bath was removed and the reaction was stirred overnight, then quenched by adding about 40 mL water, followed by washings with AcOEt. The aqueous layer was acidified using 2N HCl (pH=2) and washed with AcOEt 3x, NaCl 1x, dried over Na_2SO_4, filtered, concentrated. Purification was done by washing the crude compound with Hex: AcOEt (6:4) 2x at room temperature giving Compound **24** as light colored oil (0.15 g, 27% yield). Calculated mass for $C_{33}H_{33}N_3O_8$ $(M+H)^+$ 599.6, found by LC-MS 599.4.

Example 12: Preparation of Compounds in Figures 1A, 2A, and 5A.

The compound in Figure 1A may be prepared following the methods described, e.g., in US Patent No. 6,872,700, the disclosure of which is incorporated by reference. The compounds in Figures 2A and 5A may be prepared following the methods described, e.g., in WO 2007/139941, the disclosure of which is incorporated by reference.

Example 13: Preparation of Compounds in Figures 1B-C, 2B-U, 3A-G, 5B-G, 6A-E, 10A-I, 11A-C, 12, 13A-B, 14B-C, 14E-R

For each compound in Figures 1B, 1C, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 5B, 5C, 5D, 6A, 6B, 6C, 6D, and 6E, a calculated 100 μmol of Fmoc-Ser(OtBu)-Wang resin or Fmoc Rink amide resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and peptide elongation was carried out following standard Fmoc peptide synthesis protocol. If an unnatural amino acid was used at position 2 this was incorporated manually in a polypropylene syringe. Cleavage of the peptide from the resin was done with 10 mL TFA/H_2O/PhOH/TIPS (95:2:2:1), then precipitated by methyl-*tert*-Butyl ether. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compounds as white powders. All characterized by LC-MS. The compounds in Figures 2L-U, 5E-G, 10A-I, 13B, 14B-C and 14E-K will be prepared following the methods described in this example.

With respect to the compounds in **Figures 14L-R**, a calculated 100 μmol of Fmoc-Rink-amide resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and peptide elongation was carried out following standard Fmoc peptide synthesis protocol. If an unnatural

amino acid was used at position 2 this was incorporated manually in a polypropylene syringe. Only for the compounds in **Figures 14N-O**, this procedure was carried out under the following microwave-assisted conditions: A microwave vial was loaded with the corresponding peptide-resin intermediate (0.3 g, 0.14 mmol), Fmoc-AA-OH (4 eq), PyBrop (0.32 g, 4.8 eq), 2,6-lutidine (0.25 mL, 15 eq), dichloroethane (DCE) (2-3 mL) and DMF (about 0.3 mL). The vial was capped and heated with microwaves (Biotage™, Initiator8) at 100°C for 11 min. The resin was filtered, washed with DCE and MeOH. Cleavage of the peptide from the resin was done with 10 mL TFA/H_2O/PhOH/TIPS (95:2:2:1), then precipitated by methyl-*tert*-Butyl ether. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compounds as white powders. All characterized by LC-MS.

Example 14: Preparation of Compounds in Figures 8A-H

For the compounds in Figures 8B, 8C, 8D, 8E, 8F, 8G, and 8H, a calculated 100 mol of Fmoc-Ser(OtBu)-Wang or Fmoc-Rink-amide resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and the peptide elongation was carried out following standard Fmoc peptide synthesis protocol. The corresponding L- or D-Cys(Trt)-OH was introduced at positions 2 and 4. Cleavage of the peptide from the resin with 10 mL TFA/H_2O/PhOH/TIPS (95:2:2:1) then precipitated by methyl-*tert*-Butyl ether. The crude peptides were dried overnight under high vacuum.

Disulfide cylclization: Clear-OX resin (0.39 g, 3x molar excess) was swollen on DCM for 45 min at room temperature, then washed with DCM 2x, DMF 3x, MeOH 3x, deionized water 3x and finally H_2O:ACN (1:1) 3x. The corresponding crude peptide (0.1 g) was dissolved in degassed 1:1 v/v solution of 0.1M NH_4OAc buffer (pH=6.5)/ACN. The peptide solution was then added to the pre-swollen Clear-OX resin and the slurry was shacked at room temperature. After 2-3 hours the cyclization was complete. The resin was washed with a small amount of ACN/H_2O (1:1) solution, the filtrate concentrated to remove volatiles and then lyophilized. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compounds as white powders. All characterized by LC-MS. The compound in Figure 8A will be prepared following the methods described in this example.

Example 15: Preparation of Compounds in Figures 9A-H

For each compound in Figures 9A, 9B, 9C, 9D, 9E, 9G, and 9H, a calculated 100 μmol of Fmoc-Rink amide resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and the peptide elongation was carried out following standard Fmoc peptide synthesis protocol. The amino acid at position 2 of all these compounds was introduced by special coupling conditions. A microwave vial was loaded with the corresponding peptide-resin intermediate (0.3 g, 0.14 mmol), Fmoc-AA-OH (4 eq), PyBrop (0.32 g, 4.8 eq), 2,6-lutidine (0.25 mL, 15 eq), dichloroethane (DCE) (2-3 mL) and DMF (~0.3 mL). The vial was capped and heated with microwaves (Biotage™, Initiator8) at 100°C for 11 min. The resin was filtered, washed with DCE and MeOH. For some compounds the above process was repeated twice. The resin is then treated in a cycle of deprotection, coupling with Fmoc-His(Trt)-OH, HBTU and HOBt, deprotection. Cleavage of the peptide from the resin was done with 10 mL TFA/H_2O/PhOH/ TIPS (95:2:2:1), then precipitated by methyl-*tert*-Butyl ether. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compounds as white powders. All characterized by LC-MS. The compound in Figure 9F will be prepared following the methods described in this example.

Example 16: In Vitro Assay

The compounds shown in Table 1 below were analyzed in an in vitro functional assay at the GLP-1 receptor. The assay was conducted as follows: Membrane fractions were prepared from confluent cultures of RIN m5f cells. Compounds were serially diluted with an assay buffer, and then added to a 96-well assay plate containing RIN m5f cell membranes in an ATP/GTP mixture. Cyclase activities were determined by measuring the production of cAMP induced through GLP-1 receptor activation. Quantification of cAMP production was achieved through a competitive chemiluminescence assay with a biotinylated-cAMP probe using Perkin Elmer Fusion™-Alpha Microplate Analyzer (AlphaScreen™ technology). The compound EC_{50} values were obtained through fitting the concentration-response curves to a four-parameter logistic equation within GraphPad PRISM® software. The results of the assay are presented in Table 1 below.

Example 17: In Vivo Assay

Some compounds shown in Table 1 below were analyzed in an in vivo basal glucose lowering assay using the following procedure: A subcutaneous injection of either 200μl

phosphate-buffered saline (PBS) vehicle or test article was given immediately following baseline glucose (t=0) to NIH/Swiss female mice. Tail blood glucose samples were measured at t= 2 and 4 hours post dose using a OneTouch® Ultra® (LifeScan, Inc., a Johnson & Johnson Company, Milpitas, CA). Body weight was measured daily. Significant test sample effects were identified by ANOVA ($p<0.05$), followed by Dunnett's post test using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego CA). The results are presented in Table 1 below.

Table 1

Compound in Figure	Cyclase GLP-1 Receptor EC_{50} (nM)	In Vivo Glucose-Lowering Assay
1A	0.01	not tested
1B	0.004	not tested
1C	0.029	not tested
2A	0.008	greater than 3 hours
2B	0.0089	more than 4 hours
2C	6	not tested
2D	0.04	not tested
2E	2.15	not tested
2F	0.027	more than 4 hours
2G	0.89	not tested
2H	0.124	not tested
2I	0.054	more than 4 hours
2J	7.2	not tested
2K	0.29	similar to GLP-1
3A	0.007	more than 4 hours
3B	0.007	more than 2 hours
3C	0.022	not tested
3D	1.03	not tested
3E	0.06	more than 2 hours
3F	1.089	not tested
3G	0.065	similar to GLP-1
5A	1.83	more than 4 hours
5B	0.53	more than 4 hours
5C	1.056	not tested
5D	10.5	not tested

Compound in Figure	Cyclase GLP-1 Receptor EC_{50} (nM)	In Vivo Glucose-Lowering Assay
6A	0.144	similar to GLP-1
6B	0.52	not tested
6C	151.9	not tested
6D	0.282	not tested
6E	0.60	more than 4 hours
8B	1.26	similar to GLP-1
8C	968.6	not tested
8D	106.2	not tested
9A	0.21	not tested
9B	0.03	more than 4 hours
9C	0.05	more than 4 hours
9D	0.01	more than 4 hours
9E	133	not tested
9F	0.07	more than 4 hours
9G	1.9	not tested
9H	0.1	not tested
11A	0.155	not tested
11B	0.007	not tested
11C	0.011	not tested
12	0.028	not tested
13	0.274	not tested
14J	0.054	not tested
14K	3.5	not tested
14L	0.05	not tested
14M	0.2 (partial agonist)	not tested
14N	0.004	not tested
14O	0.24	not tested
14P	0.25	not tested
14Q	0.02	not tested
14R	0.41 (partial agonist)	not tested
15A	0.57	inactive
15B	1000	not tested
15C	2.46	inactive

Compound in Figure	Cyclase GLP-1 Receptor EC_{50} (nM)	In Vivo Glucose-Lowering Assay
15D	1.7	inactive
16A	0.52	inactive
16B	0.18	similar to GLP-1
16C	1.1	inactive
16D	1	inactive
16E	1	inactive
16F	0.61	about 30 minutes
16G	56	not tested
16H	1000	not tested
17A	105	not tested
17B	668	not tested
17C	10,000	not tested

Example 18: Preparation of Compounds in Figures 17A-F

A calculated 100 μmol of Rink amide resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and the peptide elongation was carried out following standard Fmoc peptide synthesis protocol up to residue Pro^3. The resulting peptide-resin intermediate (0.3 g, 0.0927 mmol) was swollen in DCM with around 5% DMF and to the slurry was added Fmoc-Cys(Trt)-OH (0.351 g, 4 eq), followed by Bromo-tris-pyrrolidino-phosphonium hexafluoro-phosphate (PyBrop) (0.34 g, 4.8 eq) and 2,6-lutidine (0.27 mL, 15 eq). The vial was capped and heated in a microwave apparatus (Biotage Initiator8) at 100°C for 11 min. The resin was filtered and washed with DMF 6x, treated with 20% piperidine in DMF 2x25 min and washed with DMF 6x, DCM 4x followed by treatment with 2%TFA/1.5% TIS in DCM 4x10 min. then washed with DCM 4x, DMF 2x and TMOF 3x. In a polypropylene syringe the resin is swollen in TMOF, followed by addition of compound **25** (0.2 g, 3 eq) and dry pyridine (0.06 mL, 5 eq). The resin was shaken at room temperature for 16 hours, followed by washings with TMOF 3x, DCM 3x, MeOH 3x and dried under high vacuum. Cleavage of the peptide from the resin was carried out with 10 ml TFA/H_2O/PhOH/TIPS (95:2:2:1) (TFA is trifluoroacetic acid; TIPS is triisopropyl-silyl), precipitated by methyl-*tert*-Butyl ether. The residue was dissolved in 0.8 ml of MeOH and 0.8 ml of ACN. To this solution 0.1 ml of DEA were added and the mixture stirred at room temperature overnight. The resulting residue was applied to a reverse-phase high performance

liquid chromatography (HPLC) column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford compound **17A** as a white powder (5.3 mg, 3%): Retention time in reverse phase-high performance liquid chromatography (RP-HPLC) (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 8.71 min; Calculated mass for $C_{146}H_{228}N_{38}O_{43}S$ $(M+H)^+$ 3235.74, found by liquid chromatography/mass spectrometry (LC-MS) 1079.6 $(M+3H)^{3+}$, 1619.9 $(M+2H)^{2+}$.

The synthesis of compounds **17B** and **17C** was performed similar as reported above for compound **17A**, with the difference of using Fmoc-D-Cys(Trt)-OH and Fmoc-Pen-OH, respectively. After purification compound **17B** was obtained as a white powder (8 mg, 7%): Retention time in reverse phase-high performance liquid chromatography (RP-HPLC) (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 8.55 min; Calculated mass for $C_{146}H_{228}N_{38}O_{43}S$ $(M+H)^+$ 3235.74, found by liquid chromatography/mass spectrometry (LC-MS) 1079.6 $(M+3H)^{3+}$, 1619.9 $(M+2H)^{2+}$. After purification compound **17C** was obtained as a white powder (1.5 mg, 3%): Retention time in reverse phase-high performance liquid chromatography (RP-HPLC) (C_{18}, 5-75% CH_3CN in 0.1% TFA/H_2O over 15 min) is 8.55 min; Calculated mass for $C_{148}H_{232}N_{38}O_{43}S$ $(M+H)^+$ 3263.79, found by liquid chromatography/mass spectrometry (LC-MS) 1089.6 $(M+3H)^{3+}$, 1632.9 $(M+2H)^{2+}$.

Example 19: Preparation of Compound 25

In a round bottom flask Fmoc-His(Boc)-OH (4 g, 1 eq) was dissolved in DCM (50 mL). To this solution was added DCC (1.9 g, 1.1 eq), EtSH (0.7 mL, 1.1 eq) and DMAP (0.102 g, 0.1 eq). The mixture was stirred at room temperature for 6 h. The reaction mixture was filtered and the solution concentrated to yield 4.9 g of an off-white solid. The crude product was purified by flash chromatography using Hex:AcOEt (1:1). After concentration of the pure fractions the corresponding thioester was obtained as a clear oil (3.6 g, 84%). The thioester (0.69 g, 1 eq) was dissolved in THF (11 mL) and stirred under Argon atmosphere for few minutes. To this solution was added Pd-C (0.180 g) and the mixture stirred under Argon for 10 min followed by dropwise addition of TES (0.75 mL, 3.5 eq) and the mixture stirred at room temperature. After 4 h one more equivalent of TES was added, one hour later the crude mixture was filtered through a bed of silica/celite and washed with THF. The filtrate was concentrated to give a dark brown oil, which was purified by flash chromatography in a short (20 mL) silica gel column using Hex:AcOEt (2:8). After concentration of the pure fractions compound **25** was obtained as a clear

semisolid (0.26 g, 50%).

Example 20: Modified Exendin Peptides

N-Terminus conformationally constrained GLP-1 receptor agonist compounds described herein were covalently linked to one or more polyethylene glycol and/or fatty acids, as described herein. In particular, the following twelve compounds 23A-L were prepared:

Compound 23A: 4-imidazopropionyl-dAla-PGTFTSDLSK^{12}QMEEEAVRLFIE-WLKNGGPSSGAPPPS-NH_2, wherein K^{12} was modified with -C(=O)-$CH_2(OCH_2CH_2)_2NH$-C(=O)CH_2-$(OCH_2CH_2)_2NH$-C(=O)-$(CH_2)_6$-CH_3.

Compound 23B: 4-imidazopropionyl-dAla-PGTFTSDLSK^{12}QMEEEAVRLFIE-WLKNGGPSSGAPPPS-NH_2, wherein K^{12} was modified with -C(=O)-$CH_2(OCH_2CH_2)_2NH$-C(=O)$CH_2(OCH_2CH_2)_2NH$-C(=O)-$CH(NH_2)$-$(CH_2)_7$-CH_3.

Compound 23C: 4-imidazopropionyl-dAla-PGTFTSDLSK^{12}QMEEEAVRLFIE-WLKNGGPSSGAPPPS-NH_2, wherein K^{12} was modified with -C(=O)-$CH_2(OCH_2CH_2)_2NH$-C(=O)$CH_2(OCH_2CH_2)_2NH$-C(=O)-CH[NH-C(=O)$(CH_2)_6CH_3$]-$(CH_2)_7$-CH_3.

Compound 23D: 4-imidazopropionyl-dAla-PGTFTSDLSK^{12}QMEEEAVRLFIE-WLKNGGPSSGAPPPS-NH_2, wherein K^{12} was modified with -C(=O)-$CH_2(OCH_2CH_2)_2NH$-C(=O)$CH_2(OCH_2CH_2)_2NH$-C(=O)-CH_2CH_2-CH[C(OH)(=O)]-NH-C(=O)-$(CH_2)_{16}$-[C(OH)(=O)].

Compound 23E: 4-imidazopropionyl-dAla-PGTFTSDLSKQMEEEAVRLFIEW-LK^{27}NGGPSSGAPPPS-NH_2, wherein K^{27} was modified with -C(=O)-$CH_2(OCH_2CH_2)_2NH$-C(=O)$CH_2(OCH_2CH_2)_2NH$-C(=O)-$(CH_2)_6$-CH_3.

Compound 23F: 4-imidazopropionyl-dAla-PGTFTSDLSKQMEEEAVRLFIEW-LK^{27}NGGPSSGAPPPS-NH_2, wherein K^{27} was modified with -C(=O)-$CH_2(OCH_2CH_2)_2NH$-C(=O)$CH_2(OCH_2CH_2)_2NH$-C(=O)-$CH(NH_2)$-$(CH_2)_7$-CH_3.

Compound 23G: 4-imidazopropionyl-dAla-PGTFTSDLSKQMEEEAVRLFIEW-LK^{27}NGGPSSGAPPPS-NH_2, wherein K^{27} was modified with -C(=O)-$CH_2(OCH_2CH_2)_2NH$-C(=O)$CH_2(OCH_2CH_2)_2NH$-C(=O)-CH[NH-C(=O)$(CH_2)_6CH_3$]-$(CH_2)_7$-CH_3.

Compound 23H: 4-imidazopropionyl-dAla-PGTFTSDLSKQMEEEAVRLFIEW-LK^{27}NGGPSSGAPPPS-NH_2, wherein K^{27} was modified with -C(=O)-$CH_2(OCH_2CH_2)_2NH$-C(=O)$CH_2(OCH_2CH_2)_2NH$-C(=O)-CH_2CH_2-CH[C(OH)(=O)]-NH-C(=O)-$(CH_2)_{16}$-[C(OH)(=O)].

Compound 23I: 4-imidazopropionyl-dAla-PGTFTSDLSKQMEEEAVRLFIEWLKN-GGPSSGAPPPS^{39}, wherein S^{39} was modified with -Lys(NH_2)-C(=O)-$CH_2(OCH_2CH_2)_2NH$-

$C(=O)CH_2(OCH_2CH_2)_2NH$-$C(=O)$-$(CH_2)_6$-CH_3.

Compound 23J: 4-imidazopropionyl-dAla-PGTFTSDLSKQMEEEAVRLFIEWLKN-GGPSSGAPPPS^{39}, wherein S^{39} was modified with -$Lys(NH_2)$-$C(=O)$-$CH_2(OCH_2CH_2)_2NH$-$C(=O)CH_2(OCH_2CH_2)_2NH$-$C(=O)$-$CH(NH_2)$-$(CH_2)_7$-CH_3.

Compound 23K: 4-imidazopropionyl-dAla-PGTFTSDLSKQMEEEAVRLFIEWLKN-GGPSSGAPPPS^{39}, wherein S^{39} was modified with -$Lys(NH_2)$-$C(=O)$-$CH_2(OCH_2CH_2)_2NH$-$C(=O)CH_2(OCH_2CH_2)_2NH$-$C(=O)$-$CH[NH$-$C(=O)(CH_2)_6CH_3]$-$(CH_2)_7$-CH_3.

Compound 23L: 4-imidazopropionyl-dAla-PGTFTSDLSKQMEEEAVRLFIEWLKN-GGPSSGAPPPS^{39}, wherein S^{39} was modified with -$C(=O)$-$CH_2(OCH_2CH_2)_2NH$-$C(=O)CH_2(OCH_2CH_2)_2NH$-$C(=O)$-CH_2CH_2-$CH[C(OH)(=O)]$-NH-$C(=O)$-$(CH_2)_{16}$-$[C(OH)(=O)]$.

For each of Compound Nos. 23A-L above, a calculated 100 μmol of Fmoc-Rink-amide resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and peptide elongation was carried out following standard Fmoc peptide synthesis protocol. The dAla at position 2 was incorporated manually in a polypropylene syringe. The orthogonal protection (alloc group) of the side chain group (Lys^{12}, Lys^{27} or Lys^{40}) was performed as follows: The peptide-resin was swollen in DCM and dimethylamino borane-complex (6eq) followed after about 3 minutes by tetrakis(triphenylphosphine)palladium(0) (0.1 eq). The resin was shaken for 15 minutes, washed with DCM 3x and the process repeated. Then, the resin was washed with DCM 3x, 10%DIEA in DCM 2x, DCM 3x and MeOH 2x. At this point, the peptide-resin gave a positive chloranil test. The resulting peptide-resin intermediate (0.3 g, 0.0927 mmol) was swollen in DMF and to the slurry was added the corresponding polyethylene glycol (2.2 eq), followed by HBTU (0.035 g, 2.2 eq), HOBt (0.03 g, 2.2 eq) and NMM (0.04 mL, 4.4 eq). After 3 hours, the resin was washed with DMF 6x, treated with 20% piperidine in DMF 2x25 min and washed with DMF 6x. The above cycle was repeated with a second Fmoc-(polyethylene glycol)-OH in most cases. The coupling of the corresponding fatty acid chain was done using two different microwave-assisted methods: the corresponding acyl chloride (5eq) and NMM (7eq) were added to the resin swollen in a 1:1 DMF:DCM mixture, and then heated using microwaves at 75°C for 20 min (Biotage™, Initiator8); or the corresponding carboxylic or dicarboxylic acid (5eq), HOAt (5eq) and DIC (5eq) were added to the slurry resin on DMF, and then heated using microwaves at 75°C for 15 min (Biotage™, Initiator8). Cleavage of the peptide from the resin was done with 10 mL TFA/H_2O/PhOH/TIPS (95:2:2:1), then precipitated by methyl-*tert*-Butyl

ether. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compounds as white powders. All were characterized by LC-MS.

Each of these compounds was analyzed in an in vitro functional assay at the GLP-1 receptor following the methods described in Example 16. The results are in Table 2:

Table 2

Compound	Cyclase GLP-1 Receptor EC_{50} (nM)
23A	0.027
23B	0.027
23C	0.06
23D	0.22
23E	0.3
23F	0.1
23G	0.7
23H	0.08
23I	0.01
23J	0.01
23K	0.02
23L	0.185

Example 21: Modified Exendin Peptides

N-Terminus conformationally constrained GLP-1 receptor agonist compounds described herein were covalently linked to one or more biotin, as described herein. In particular, the following compounds 24A-L were prepared:

Compound 24A: His-dAla-PGTFTSDLSKQMEEEAVRLFIEWL-Lys(biotin)-NGGPSSGAPPS-Lys[(NH_2)(biotin)].

Compound 24B: 4-imidazopropionyl-GEGTFTSDLSKQMEEEAVRLFIEWL-Lys(biotin)-NGGPSSGAPPS-Lys[(NH_2)(biotin)].

Compound 24C: 4-imidazopropionyl-GEGTFTSDLSKQMEEEAVRLFIEWLKN-Lys[(NH_2)(biotin)].

Compound 24D: 4-imidazopropionyl-APGTFTSDLSKQMEEEAVRLFIEWLKN-Lys[(NH_2)(biotin)].

Compound 24E: His-dAla-PGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-Lys(NH_2)-(O-CH_2-CH_2)$_2$-KAKAEAEAKAKAEAEA-biotin.

Compound 24F: His-dAla-PGTFTSDLSKQMEEEAVRLFIEWLE[-(O-CH_2-CH_2)$_2$-(biotin)]-NGGPSSGAPPPS-NH_2.

Compound 24G: His-dAla-PGTFTSDLSEK[-(O-CH_2-CH_2)$_2$-(biotin)]-QMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2.

For each of Compound Nos. 24A-G above, a calculated 100 μmol of Fmoc-Rink-amide resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and peptide elongation was carried out following standard Fmoc peptide synthesis protocol. If an unnatural amino acid was used at position 2 this was incorporated manually in a polypropylene syringe. The orthogonal protection (alloc group) of the side chain group (Lys^{27}, Lys^{28} or Lys^{40}) was performed as follows: The peptide-resin was swollen in DCM and dimethylamino borane-complex (6eq) followed after about 3 minutes by tetrakis(triphenylphosphine)palladium(0) (0.1 eq). The resin was shaken for 15 min, washed with DCM 3x and the process repeated. Then, the resin was washed with DCM 3x, 10%DIEA in DCM 2x, DCM 3x and MeOH 2x. At this point, the peptide-resin gave a positive chloranil test. The biotin moiety (one or two) was coupled to the free amino group using the standard solid-phase coupling conditions described above (HBTU, HOBt, NMM). Cleavage of the peptide from the resin was done with 10 mL TFA/H_2O/PhOH/TIPS (95:2:2:1), then precipitated by methyl-*tert*-Butyl ether. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compounds as white powders. All were characterized by LC-MS.

Each of these compounds was analyzed in an in vitro functional assay at the GLP-1 receptor following the methods described in Example 16. The results are in Table 3:

Table 3

Compound	Cyclase GLP-1 Receptor EC_{50} (nM)
24A	0.04
24B	0.03
24C	0.07
24D	0.77
24E	0.06

Compound	Cyclase GLP-1 Receptor EC_{50} (nM)
24F	0.06
24G	0.01

Example 22: Compounds of Figure 10

With respect to **Figure 10**, the following compounds 10J-10N were made:

10J: 4-imidazopropionyl-GPGTFTSDLSKQLEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2

10K: 4-imidazopropionyl-dAla-PGTFTSDLSKQLEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2

10L: 4-imidazopropionyl-Aib-PGTFTSDLSKQLEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2

10M: 4-imidazopropionyl-GEGTFTSDLSKQLEEEAVRLFIEWLKQGGPSKEIIS-OH

10N: 4-imidazopropionyl-dAla-PGTFTSDLSKQLEEEAVRLFIEWLKQGGPSKEIIS-OH

For each of Compounds 10J-N, a calculated 100 μmol of Fmoc-Rink-amide resin was weighed into a reaction vessel in a Symphony peptide synthesizer, and peptide elongation was carried out following standard Fmoc peptide synthesis protocol. If an unnatural amino acid was used at position 2 this was incorporated manually in a polypropylene syringe. Only for the compound in Figure 10L, this procedure was carried out under the following microwave-assisted conditions: a microwave vial was loaded with the corresponding peptide-resin intermediate (0.3 g, 0.14 mmol), Fmoc-AA-OH (4 eq), PyBrop (0.32 g, 4.8 eq), 2,6-lutidine (0.25 mL, 15 eq), dichloroethane (DCE) (2-3 mL) and DMF (~0.3 mL). The vial was capped and heated with microwaves (Biotage™, Initiator8) at 100°C for 11 min. The resin was filtered, washed with DCE and MeOH. Cleavage of the peptides from the resins was done with 10 mL TFA/H_2O/PhOH/TIPS (95:2:2:1), then precipitated by methyl-*tert*-Butyl ether. The crude was dissolved and applied to a reverse-phase HPLC column (C_{18}, 20-50% CH_3CN in 0.1% TFA/H_2O over 30 min gradient) to afford the titled compounds as white powders. All characterized by LC-MS.

Compounds 10J-L were analyzed in an in vitro functional assay at the GLP-1 receptor following the methods described in Example 16. The results are in Table 4:

Table 4

Compound	Cyclase GLP-1 Receptor EC_{50} (nM)
10J	0.1
10K	0.03
10L	0.005
10M	0.007
10N	0.01

All publications and patent applications are incorporated herein by reference. Although the foregoing has been described in detail for purposes of clarity of understanding, it will be apparent to one of ordinary skill in the art that changes and modifications may be made without departing from the spirit or scope of the disclosure or appended claims.

CLAIMS

What is claimed is:

1. The compound of Figure 1B or 1C.
2. The compound of Figure 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, or 2U.
3. The compound of Figure 3A, 3B, 3C, 3D, 3E, 3F, or 3G.
4. The compound of Figure 5B, 5C, 5D, 5E, 5F, or 5G.
5. The compound of Figure 6A, 6B, 6C, 6D, or 6E.
6. The compound of Figure 8A, 8B, 8C, 8D, 8E, 8F, 8G, or 8H.
7. The compound of Figure 9A, 9B, 9C, 9D, 9E, 9F, 9G, or 9H.
8. The compound of Figure 10A, 10B, 10C, 10D, 10E, 10F, 10G, 10H, or 10I; or Compound 10J, 10K, 10L, 10M, or 10N.
9. The compound of Figure 11A or 11B.
10. The compound of Figure 12.
11. The compound of Figure 13.
12. The compound of Figure 14A, 14B, 14C, 14D, 14E, 14F, 14G, 14H, 14I, 14J, 14K, 14L, 14M, 14N, 14O, 14P, or 14Q.
13. The compound of Figure 15A, 15B, 15C, or 15D.
14. The compound of Figure 16A, 16B, 16C, 16D, 16E, 16F, 16G, 16H, 16I, 16J, 16K, 16L, 18B, 19B, 20B, or 21B.
15. The compound of Figure 17A, 17B, 17C, 17D, 17E, 17F, 17G, 17H, 17I, 17J, 17K, 17L, 17M, or 17N.
16. A compound selected from the group consisting of Pro^3-exendin-4; Pro^3,Leu^{14}-exendin-4; Pro^3,Leu^{14},Phe^{25}-exendin-4; Pro^3-exendin-4(1-28); Pro^3,Leu^{14}-exendin-4(1-28); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-28); Pro^3-exendin-4(1-29); Pro^3,Leu^{14} -exendin-4(1-29); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-29); Pro^3-exendin-4(1-30); Pro^3,Leu^{14}-exendin-4(1-30); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-30); Pro^3-exendin-4(1-31); Pro^3,Leu^{14}-exendin-4(1-31); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-31); Pro^3-exendin-4(1-32); Pro^3,Leu^{14}-exendin-4(1-32); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-32); Pro^3-exendin-4(1-33); Pro^3,Leu^{14}-exendin-4(1-33); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-33); Pro^3-exendin-4(1-34); Pro^3,Leu^{14}-exendin-4(1-34); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-34); Pro^3-exendin-4(1-35); Pro^3,Leu^{14}-exendin-4(1-35);

Pro^3,Leu^{14},Phe^{25}-exendin-4(1-35); Pro^3-exendin-4(1-36); Pro^3,Leu^{14}-exendin-4(1-36); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-36); Pro^3-exendin-4(1-37); Pro^3,Leu^{14}-exendin-4(1-37); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-37); Pro^3-exendin-4(1-38); Pro^3,Leu^{14}-exendin-4(1-38); Pro^3,Leu^{14},Phe^{25}-exendin-4(1-38); Pro^3-exendin-3; and

HGPGTFTSDLSKQLEEEAVRLFIEWLKQGGPSKEIIS.

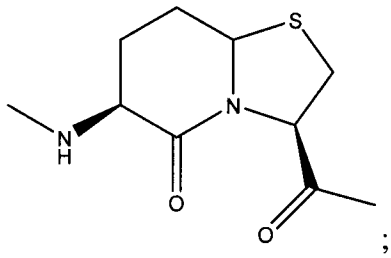
17. The compound of any one of Claims 1-16, wherein the C-terminal amino acid residue is amidated.

18. An exendin or an exendin analog, wherein the amino acid at position 3 is proline, and the C-terminal amino acid residue is optionally amidated.

19. The compound of Formula (A): $Xaa_1Xaa_2Xaa_3Xaa_4$-Z; wherein:

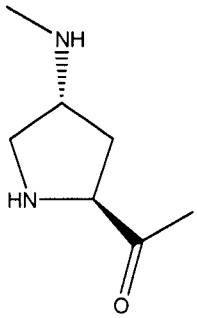
Xaa_1 is a compound of Formula (1);

Xaa_2 is Gly, dAla, Aib, Ala, Val, NMeAla, a compound of Formula (3), or a compound of Formula (4); and Xaa_2 is absent when Xaa_3 is:

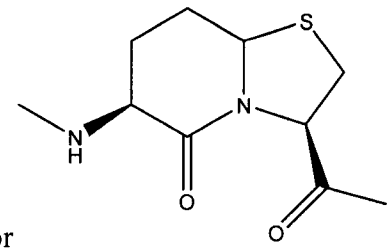


;

Xaa_3 is Pro; a compound of Formula (2); a compound of Formula (3); a Compound of Formula (4);



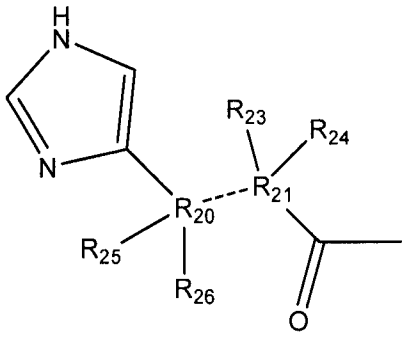
; or



Xaa_4 is Gly, dAla, or Aib; and

Z is OH or NH_2;

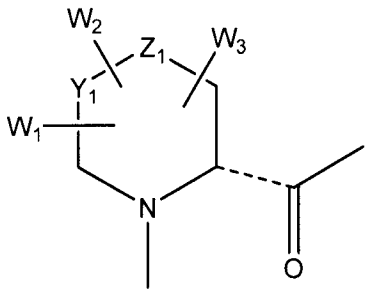
wherein the compound of Formula (1) is:



Formula (1)

wherein R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23}, R_{24}, R_{25} and R_{26} are each independently absent, hydrogen, hydroxyl, C_{1-6} alkyl, carboxyl, or C_{1-4} alkoxy; ------ is a single bond or a double bond; and R_{21} is a chiral or achiral carbon atom;

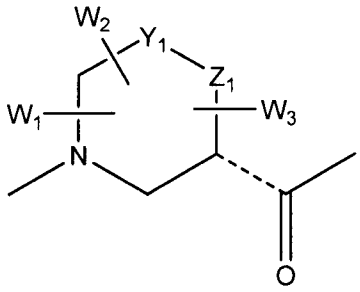
wherein the compound of Formula (2) is:



Formula (2)

wherein Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyl, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is  or ''''''''''';

wherein the compound of Formula (3) is:

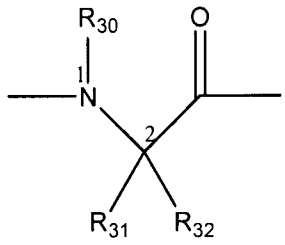


Formula (3)

wherein Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6}

alkoxy, hydroxyl, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is ▬ or ''''''''''; and

wherein the compound of Formula (4) is:



Formula (4)

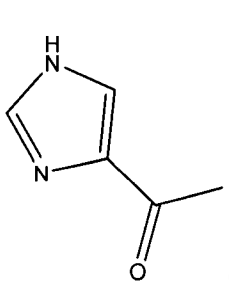
wherein R_{30}, R_{31}, and R_{32} are each independently hydrogen or a C_{1-6} alkyl; or R_{30} and R_{31}, together with the nitrogen[1] and the carbon[2], form a 5- membered or 6-membered heterocyclic ring; or R_{31} and R_{32}, together with the carbon[2], form a 3-, 4-, or 5-membered carbocyclic ring.

20. The compound of Claim 19, wherien Xaa_3 is Pro.

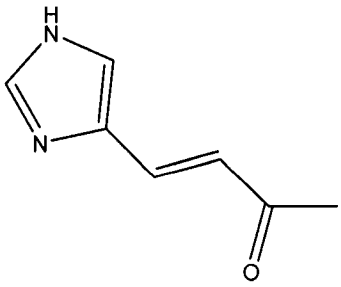
21. The compound of Claim 19, wherein Xaa_2 is dAla, Aib, Ala, Val, NMeAla, a compound of Formula (3), or a compound of Formula (4).

22. The compound of Formula (A): $Xaa_1Xaa_2Xaa_3Xaa_4$-Z; wherein:

Xaa_1 is

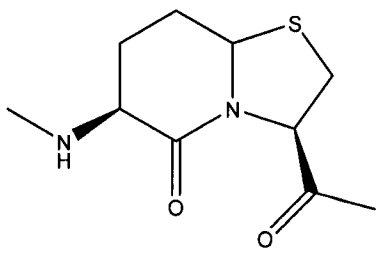


(1j) or



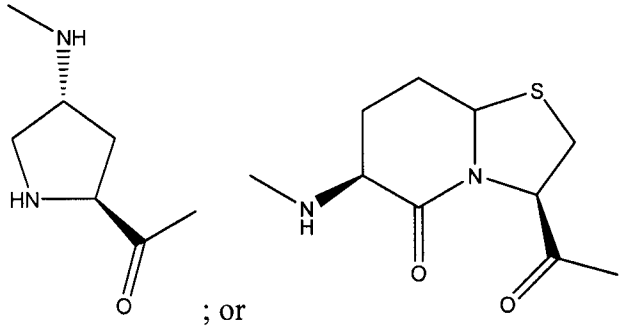
(1m);

Xaa_2 is Gly, dAla, Aib, Ala, Val, NMeAla, a compound of Formula (3), or a compound of Formula (4); and Xaa_2 is absent when Xaa_3 is:



;

Xaa$_3$ is Glu; Pro; a compound of Formula (2); a compound of Formula (3); a Compound of Formula (4);

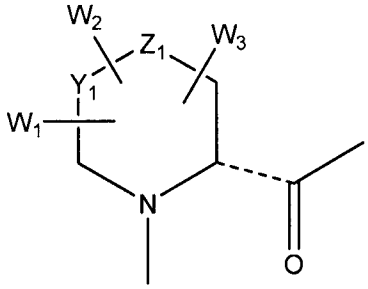


; or

Xaa$_4$ is Gly, dAla, or Aib; and

Z is OH or NH_2;

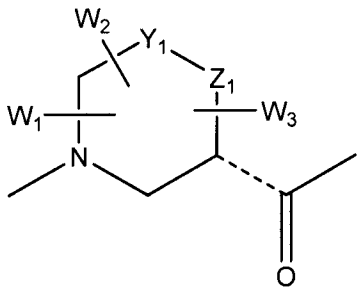
wherein the compound of Formula (2) is:



Formula (2)

wherein Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyl, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is ◀ or ⁞⁞⁞⁞⁞⁞⁞⁞⁞;

wherein the compound of Formula (3) is:

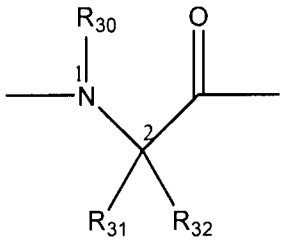


Formula (3)

wherein Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6}

alkoxy, hydroxyl, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is ▬ or ''''''''''; and

wherein the compound of Formula (4) is:



Formula (4)

wherein R_{30}, R_{31}, and R_{32} are each independently hydrogen or a C_{1-6} alkyl; or R_{30} and R_{31}, together with the nitrogen[1] and the carbon[2], form a 5- membered or 6-membered heterocyclic ring; or R_{31} and R_{32}, together with the carbon[2], form a 3-, 4-, or 5-membered carbocyclic ring.

23. A GLP-1 receptor agonist compound wherein the the amino acid residues at positions 1-4 of the GLP-1 receptor agonist compound are replaced with the compound of any one of Claims 19-22.

24. An exendin or an exendin analog wherein the the amino acid residues at positions 1-4 of the exendin or exendin analog are replaced with the compound of any one of Claims 19-22.

25. A GLP-1(7-37) or a GLP-1(7-37) analog wherein the the amino acid residues at positions 1-4 of the GLP-1(7-37) or a GLP-1(7-37) analog are replaced with the compound of any one of Claims 19-22.

26. A compound of Formula (B); Formula (C); or Formula (D):

(B) $Xaa_1Xaa_2Xaa_3Xaa_4$TFTSDLSKQXaa_{14}EEEAVRLFIEXaa_{25}LKN-Z;

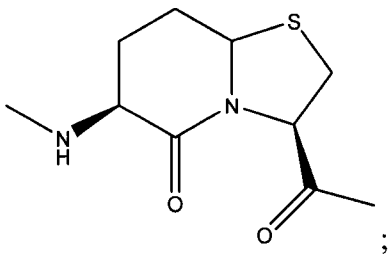
(C) $Xaa_1Xaa_2Xaa_3Xaa_4$TFTSDLSKQXaa_{14}EEEAVRLFIEXaa_{25}LK-R_{10}-Z; or

(D) $Xaa_1Xaa_{2a}Xaa_3$ Xaa_4TFTSDLSKQXaa_{14}EEEAVRLFIEXaa_{25}LKNGGPSSGAPPPS-Z;

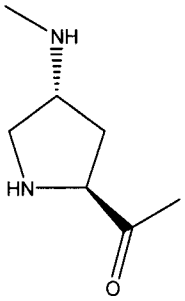
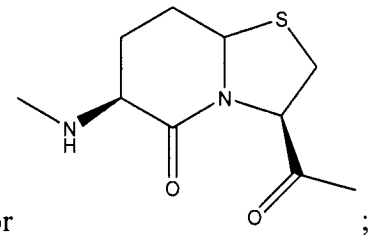
wherein:

Xaa_1 is a compound of Formula (1):

Xaa_2 is Gly, dAla, Aib, Ala, Val, NMeAla, a compound of Formula (3), or a compound of Formula (4); and Xaa_2 is absent when Xaa_3 is:


;

Xaa$_3$ is Pro; Glu; Asp; a compound of Formula (2); a compound of Formula (3); a Compound of Formula (4);


; or 
;

Xaa$_4$ is Gly, dAla, or Aib;

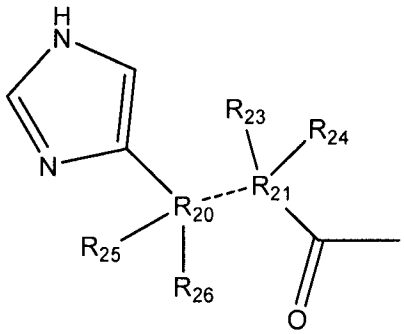
Xaa$_{14}$ is Leu or Met;

Xaa$_{25}$ is Phe or Trp;

R$_{10}$ is QGGPSKEIIS; NG; NGG; NGGP; NGGPS; NGGPSS; NGGPSSG; NGGPSSGA; NGGPSSGAP; NGGPSSGAPP; NGGPSSGAPPP; QGGPSSGAPPPS; NGGPSSGAPPS; NGGPSSGAPPSK; NGGPSSGAPPS(K)$_{2-5}$; NGGPSSGAPPPSK; or NK; and

Z is OH or NH_2;

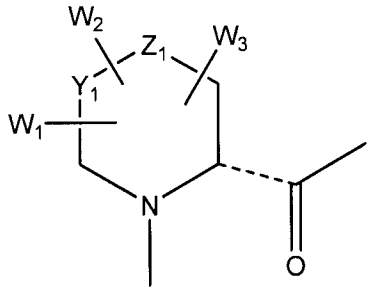
wherein the compound of Formula (1) is:


Formula (1)

wherein R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23}, R_{24}, R_{25} and R_{26} are each independently absent, hydrogen, hydroxyl, C_{1-6} alkyl, carboxyl, amino, or C_{1-6} alkoxy; ------ is a single bond or a double bond; and R_{21}

is a chiral or achiral carbon atom;

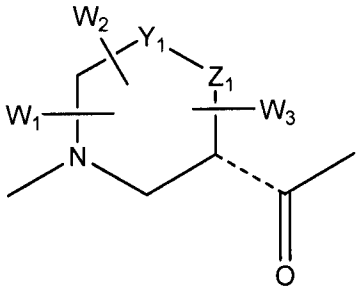
wherein the compound of Formula (2) is:



Formula (2)

wherein Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyl, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is ◀ or ''''''''''';

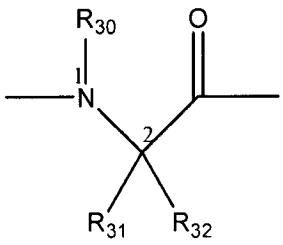
wherein the compound of Formula (3) is:



Formula (3)

wherein Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyl, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is ◀ or ''''''''''''; and

wherein the compound of Formula (4) is:



Formula (4)

wherein R_{30}, R_{31}, and R_{32} are each independently hydrogen or a C_{1-6} alkyl; or R_{30} and R_{31}, together with the nitrogen[1] and the carbon[2], form a 5- membered or 6-membered heterocyclic ring; or R_{31} and R_{32}, together with the carbon[2], form a 3-, 4-, or 5-membered carbocyclic ring.

27. The compound of Claim 26, wherein the compound is a compound of Formula (B).

28. The compound of Claim 26, wherein the compound is a compound of Formula (C).

29. The compound of Claim 26, wherein the compound is a compound of Formula (D).

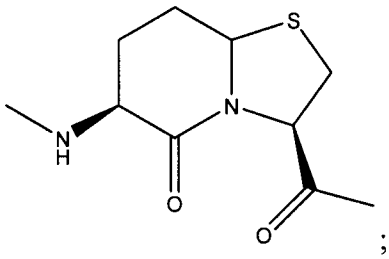
30. A compound of Formula (E):

$Xaa_1Xaa_2Xaa_3$ Xaa_4TFTSDVSSYXaa_{14}EGQAAKEFIAXaa_{25}LVXaa_{28}GRXaa_{31}-Z;

wherein:

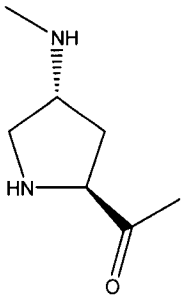
Xaa_1 is a compound of Formula (1);

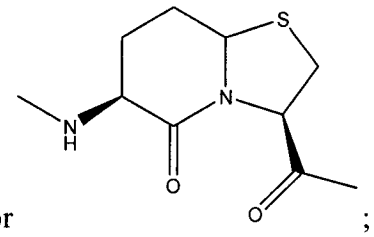
Xaa_2 is dAla, Aib, Val, NMeAla, a compound of Formula (3), or a compound of Formula (4); and Xaa_2 is absent when Xaa_3 is:



;

Xaa_3 is Pro; Glu; Asp; a compound of Formula (2); a compound of Formula (3); a Compound of Formula (4);



; or


;

Xaa_4 is Gly, dAla, or Aib;

Xaa_{14} is Leu or Met;

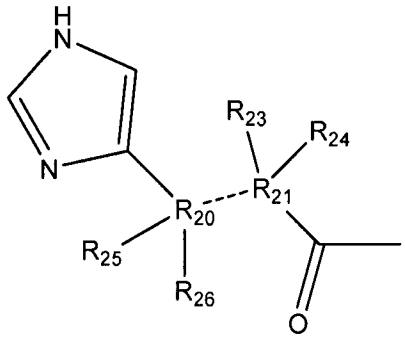
Xaa_{25} is Phe or Trp;

Xaa_{28} is Lys or Arg;

Xaa_{31} is Gly or absent; and

Z is OH or NH_2,

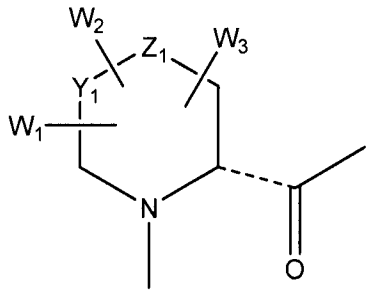
wherein the compound of Formula (1) is:



Formula (1)

wherein R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23}, R_{24}, R_{25} and R_{26} are each independently absent, hydrogen, hydroxyl, C_{1-6} alkyl, carboxyl, or C_{1-6} alkoxy; ------ is a single bond or a double bond; and R_{21} is a chiral or achiral carbon atom;

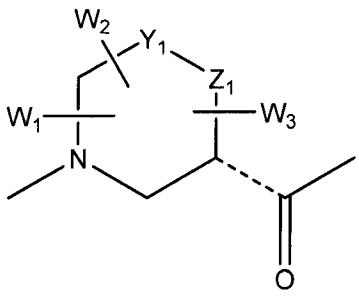
wherein the compound of Formula (2) is:



Formula (2)

wherein Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyl, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is or ''''''''''';

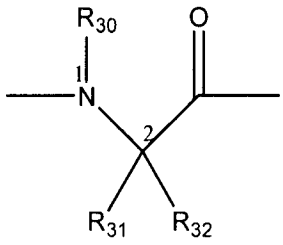
wherein the compound of Formula (3) is:



Formula (3)

wherein Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and W_1, W_2 and W_3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxyl, and amino; and when one Y_1 or Z_1 is sulfur, the sulfur may be bonded to two oxygen atoms to form a sulfonyl group; and ------ is ◀ or ''''''''''; and

wherein the compound of Formula (4) is:



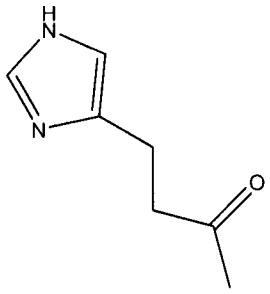
Formula (4)

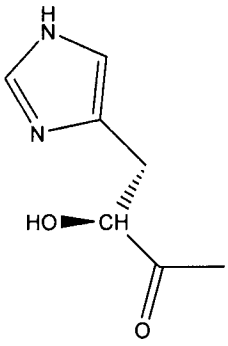
wherein R_{30}, R_{31}, and R_{32} are each independently hydrogen or a C_{1-6} alkyl; or R_{30} and R_{31}, together with the nitrogen[1] and the carbon[2], form a 5- membered or 6-membered heterocyclic ring; or R_{31} and R_{32}, together with the carbon[2], form a 3-, 4-, or 5-membered carbocyclic ring.

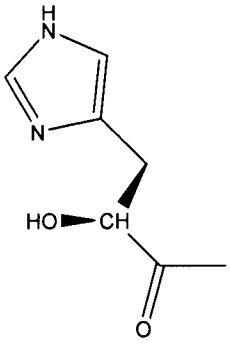
31. The compound of Claim 26, 27, 28, 29, or 30, wherein, for the compound of Formula (1), R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23} and R_{24} are each independently absent, hydrogen, hydroxy, a C_{1-4} alkyl, carboxyl, or a C_{1-4} alkoxy; R_{25} and R_{26} are each independently absent, hydrogen, hydroxy, a C_{1-4} alkyl, carboxyl, amino, or a C_{1-4} alkoxy; ------ is a single bond or a double bond; and R_{21} is a chiral or achiral carbon atom.

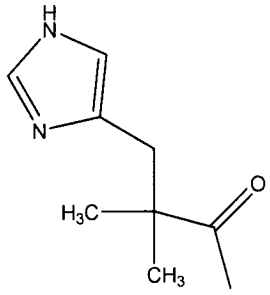
32. The compound of Claim 19, 26, 27, 28, 29, or 30, wherein, for the compound of Formula (1), R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23} and R_{24} are each independently absent, hydrogen, hydroxy, methyl, ethyl, or carboxyl; R_{25} and R_{26} are each independently absent or hydrogen; ------ is a single bond or a double bond; and R_{21} is a chiral or achiral carbon atom.

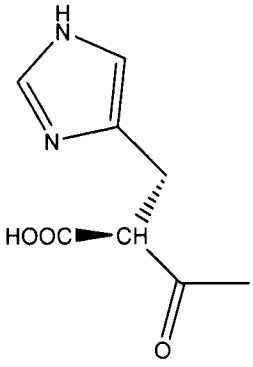
33. The compound of Claim 26, 27, 28, 29, or 30, wherein the compound of Formula (1) is a compound of Formula (1a), (1b), (1c), (1d), (1e), (1f), (1g), (1h), (1j), (1k), (1m), or (1n):

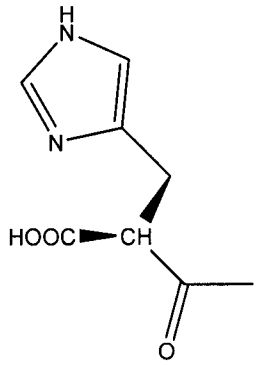

(1a);

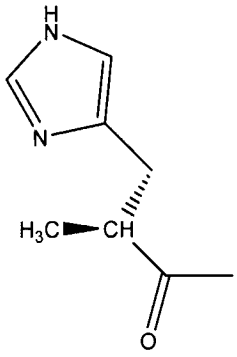

(1b);

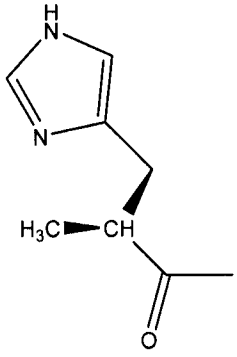

(1c);

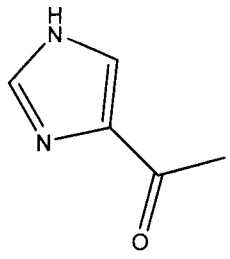

(1d);

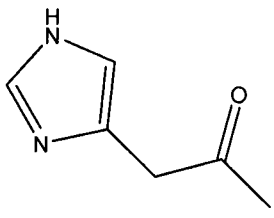

(1e);

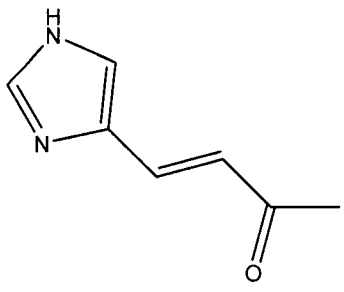

(1f);

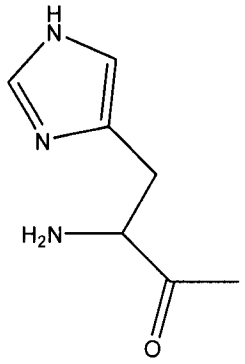

(1g);


(1h);


(1j);


(1k);


(1m);



or (1n).

34. The compound of Claim 19, 26, 27, 28, 29, or 30, wherein the compound of Formula (1) is a compound of Formula (1a), (1b), (1c), (1d), (1e), (1f), (1g), (1h), (1j), (1k), or (1m).

35. The compound of Claim 34, wherein the compound of Formula (1) is a compound of Formula (1a), (1b), (1c), (1d), (1e), (1f), (1g), (1h), or (1k).

36. The compound of Claim 34, wherein the compound of Formula (1) is a compound of Formula (1j) or (1m).

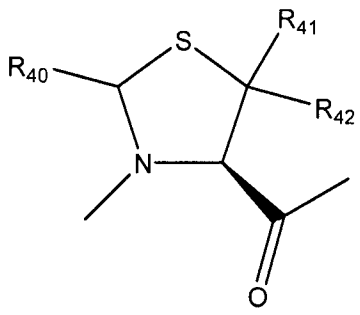
37. The compound of Claim 26, 27, 28, 29, or 30, wherein the compound of Formula (1) is a compound of Formula (1n).

38. The compound of any one of Claims 19, 22 and 26-30, wherein, for the compound of Formula (2), ------ is ◀.

39. The compound of any one of Claims 19, 22 and 26-30, wherein, for the compound of Formula (2), Y_1 and Z_1 are each independently a single bond, a carbon, or a sulfur; and each W_1 is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, and hydroxyl; and ------ is ◀.

40. The compound of Claim 39, wherein, for the compound of Formula (2), Y_1 and Z_1 are each independently a single bond or carbon.

41. The compound of any one of Claims 19, 22 and 26-30, wherein the compound of Formula (2) is a compound of Formula (2Z):

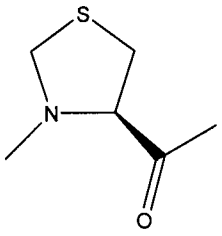
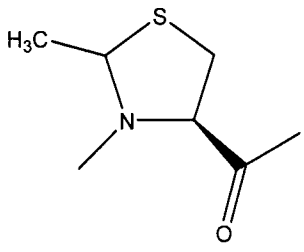
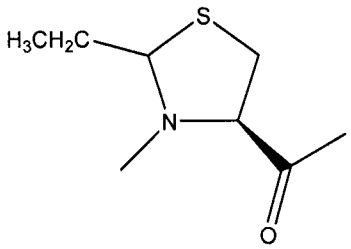
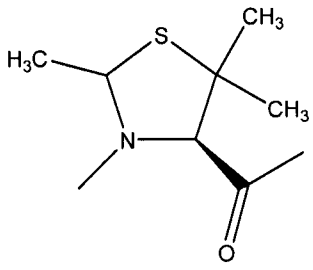
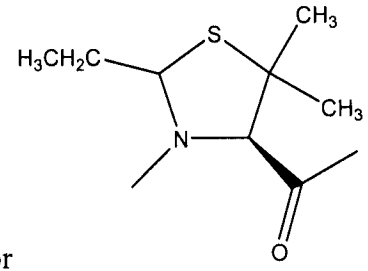


Formula (2Z)

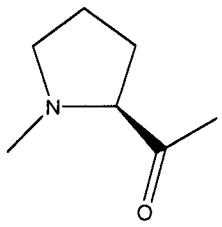
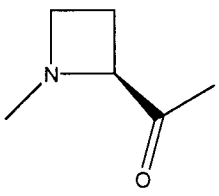
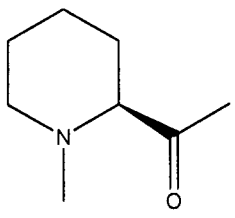
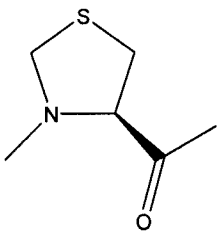
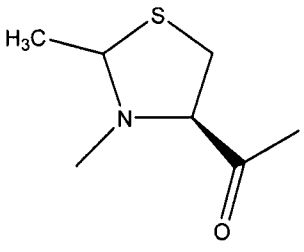
wherein R_{40}, R_{41}, and R_{42} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl.

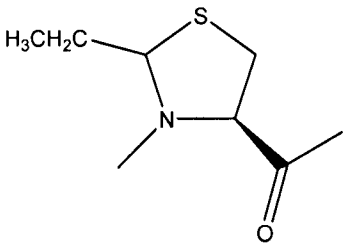
42. The compound of Claim 41, wherein, for the compound of Formula (2Z), R_{40}, R_{41}, and R_{42} are each independently selected from the group consisting of hydrogen, methyl, and ethyl.

43. The compound of Claim 41, wherein the compound of Formula (2Z) is a compound of Formula (2d), (2e), (2f), (2g), or (2h):

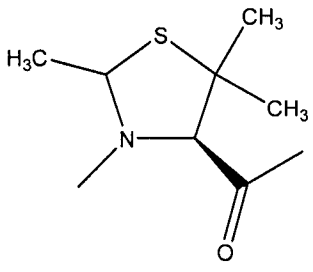

(2d);

(2e);

(2f);

(2g); or

(2h).

44. The compound of any one of Claims 19, 22 and 26-30, wherein the compound of Formula (2) is a compound of Formula (2a), (2b), (2c), (2d), (2e), (2f), (2g), (2h), or (2j):

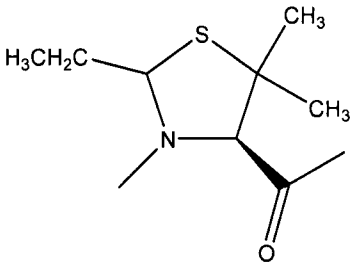

(2a);

(2b);

(2c);

(2d);

(2e);



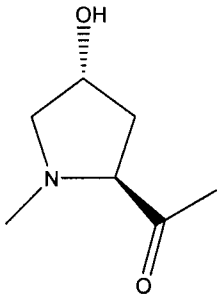
(2f);



(2g);



(2h); or

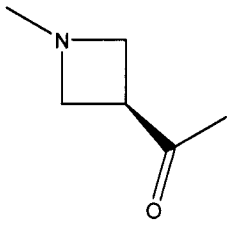


(2j).

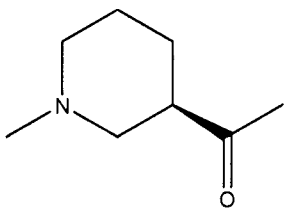
45. The compound of any one of Claims 19, 22 and 26-30, wherein, for the compound of Formula (3), ------ is ◀.

46. The compound of any one of Claims 19, 22 and 26-30, wherein, for the compound of Formula (3), Y_1 and Z_1 are each independently a single bond or carbon; and each W_1 is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, and hydroxyl; and ------ is ◀.

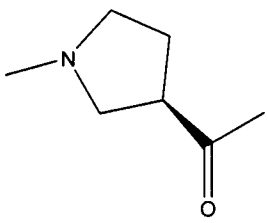
47. The compound of any one of Claims 19, 22 and 26-30, wherein the compound of Formula (3) is a compound of Formula (3a), (3b), or (3c):



(3a);



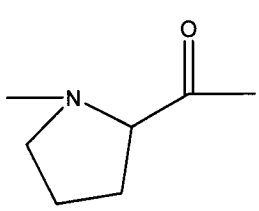
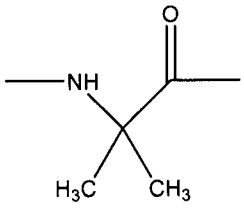
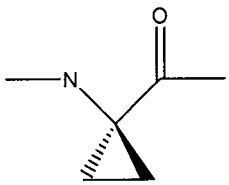
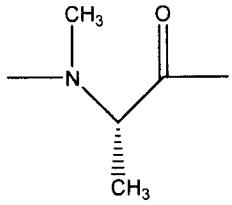
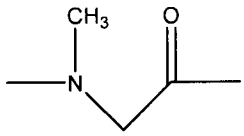
(3b); or



(3c).

48. The compound of any one of Claims 19, 22 and 26-30, wherein, for the compound of Formula (4), R_{30}, R_{31}, and R_{32} are each independently hydrogen, methyl, or ethyl; or R_{30} and R_{31}, together with the nitrogen[1] and carbon[2], form a 5- membered or 6-membered heterocyclic ring; or R_{31} and R_{32}, together with the carbon[2], form a 3-, or 4-membered carbocyclic ring.

49. The compound of any one of Claims 19, 22 and 26-30, wherein the compound of Formula (4) is a compound of Formula (4a), (4b), (4c), (4d), or (4e):


(4a);

(4b);

(4c);

(4d); or

(4e).

50. The compound of any one of Claims 19, 22 and 26-29, wherein Xaa_2 is dAla, Aib, Ala, Val, or NMeAla.

51. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_2 is a compound of Formula (3).

52. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_2 is a compound of Formula (4).

53. The compound of any one of Claims 19, 22 and 26-29, wherein Xaa_2 is Gly.

54. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_2 is dAla.

55. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_2 is Aib.

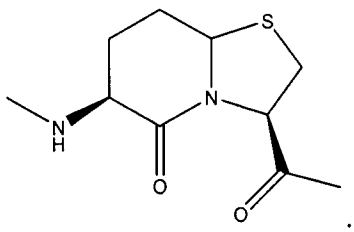
56. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_3 is Pro.

57. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_3 is Glu.

58. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_3 is a compound of Formula (2).

59. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_3 is a compound of Formula (3).

60. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_2 is absent and Xaa_3 is


.

61. The compound of any one of Claims 19, 22 and 26-30, wherein Xaa_4 is Gly or dAla.

62. The compound of any one of Claims 19, 22 and 26-30, wherein Z is NH_2.

63. The compound of any one of Claims 26-29, wherein R_{10} is QGGPSKEIIS.

64. The compound of any one of Claims 26-29, wherein R_{10} is NG or NK.

65. The compound of any one of Claims 26-29, wherein R_{10} is NGG.

66. The compound of any one of Claims 26-29, wherein R_{10} is NGGP.

67. The compound of any one of Claims 26-29, wherein R_{10} is NGGPS.

68. The compound of any one of Claims 26-29, wherein R_{10} is NGGPSS.

69. The compound of any one of Claims 26-29, wherein R_{10} is NGGPSSG.

70. The compound of any one of Claims 26-29, wherein R_{10} is NGGPSSGA.

71. The compound of any one of Claims 26-29, wherein R_{10} is NGGPSSGAP.

72. The compound of any one of Claims 26-29, wherein R_{10} is NGGPSSGAPP.

73. The compound of any one of Claims 26-29, wherein R_{10} is NGGPSSGAPPP.

74. The compound of any one of Claims 26-29, wherein R_{10} is QGGPSSGAPPPS.

75. The compound of any one of Claims 26-29, wherein R_{10} is NGGPSSGAPPS.

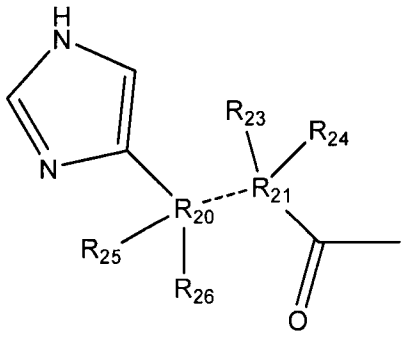
76. The compound of any one of Claims 26-29, wherein R_{10} is NGGPSSGAPPSK.

77. The compound of any one of Claims 26-29, wherein R_{10} is $NGGPSSGAPPS(K)_{2\text{-}5}$.

78. The compound of any one of Claims 26-29, wherein R_{10} is NGGPSSGAPPPSK.

79. A compound of Formula (F): $Xaa_1Xaa_2Xaa_3$-Z, wherein:

Xaa_1 is a compound of Formula (1):

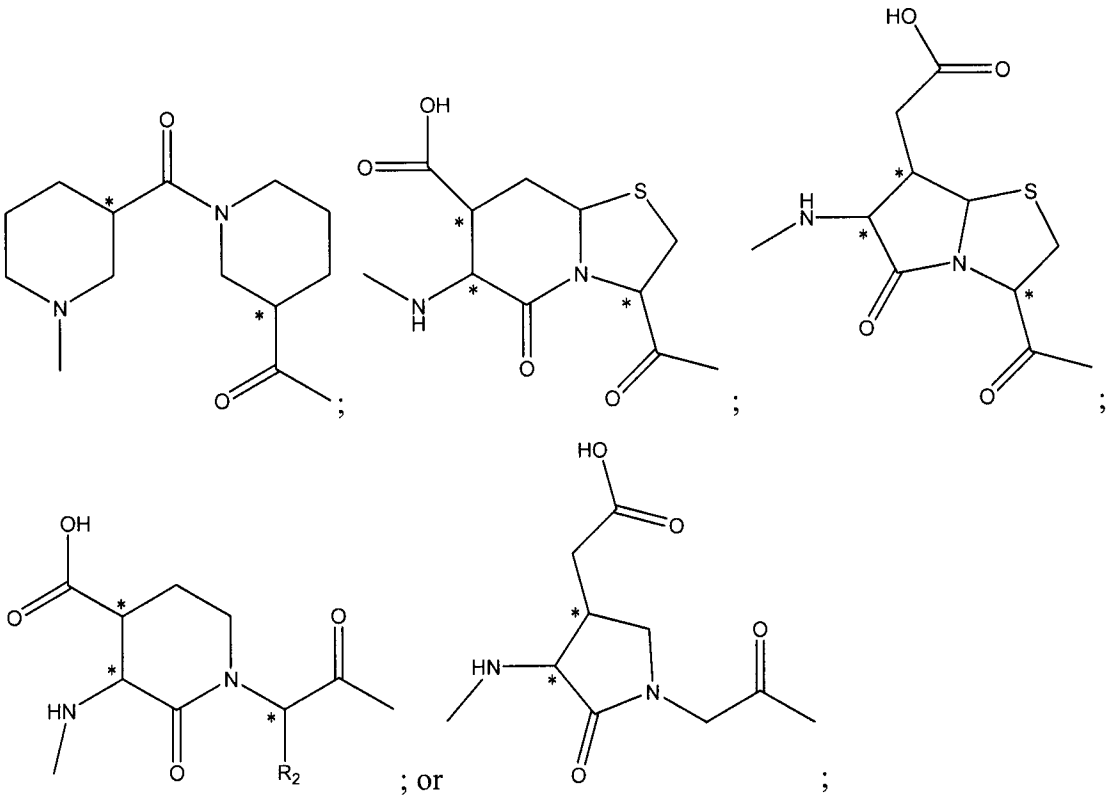


Formula (1)

wherein R_{20} and R_{21} are each independently a single bond or a carbon atom; R_{23}, R_{24}, R_{25} and R_{26} are each independently absent, hydrogen, hydroxyl, $C_{1\text{-}6}$ alkyl, carboxyl, amino, or $C_{1\text{-}6}$ alkoxy; ------ is a single bond or a double bond; and R_{21} is a chiral or achiral carbon atom;

Xaa_2 is Gly, Ala, dAla, or Aib;

Xaa_3 is:



wherein * indicates a chiral carbon atom; and R_2 is hydrogen or a C_{1-4} alkyl; and

Z is (i) OH;

(ii) NH_2;

(iii) TFTSDLSKQXaa$_{14}$EEEAVRLFIEXaa$_{25}$LKN-Z_1;

(iv) TFTSDLSKQXaa$_{14}$EEEAVRLFIEXaa$_{25}$LKNGGPSSGAPPPS-Z_1;

(v) TFTSDLSKQXaa$_{14}$EEEAVRLFIEXaa$_{25}$LK-R_{10}-Z_1; or

(vi) TFTSDVSSYXaa$_{14}$EGQAAKEFIAXaa$_{25}$LVXaa$_{28}$GRXaa$_{31}$- Z_1;

wherein: Z_1 is OH or NH_2; Xaa$_{14}$ is Leu or Met; Xaa$_{25}$ is Phe or Trp; Xaa$_{28}$ is Lys or Arg; Xaa$_{31}$ is Gly or absent; and R_{10} is QGGPSKEIIS; NG; NGG; NGGP; NGGPS; NGGPSS; NGGPSSG; NGGPSSGA; NGGPSSGAP; NGGPSSGAPP; NGGPSSGAPPP; NGGPSSGAPPS; NGGPSSGAPPSK; NGGPSSGAPPS(K)$_{2-6}$; NGGPSSGAPPPSK; or NK.

80. The compound of any one of Claims 1-79 which binds in a GLP-1 receptor binding assay with an affinity of less than 1 μM.

81. The compound of any one of Claims 1-79 which binds in a GLP-1 receptor binding assay with an affinity of less than 5 nM.

82. The compound of any one of Claims 1-79 which binds in a GLP-1 receptor binding assay

with an affinity of less than 1 nM.

83. The compound of any one of Claims 1-79 which binds in a GLP-1 receptor binding assay with an affinity of less than 0.1 nM.

84. The compound of any one of Claims 1-79 covalently linked to at least one immunoglobulin.

85. The compound of any one of Claims 1-79 covalently linked to at least one immunoglobulin Fc region.

86. The compound of any one of Claims 1-79 covalently linked to at least one dextran, gelatin, polyvinyl pyrrolidone, polyvinyl alcohol, or N-(2-hydroxypropyl)-methacrylamide.

87. The compound of any one of Claims 1-79 covalently linked to at least one polyethylene glycol.

88. The compound of Claim 87 wherein the polyethylene glycol is linked to a lipophilic moiety.

89. The compound of Claim 88 wherein the lipophilic moiety is an alkyl group, a fatty acid, a cholesteryl, or an adamantyl.

90. The compound of any one of Claims 1-79 covalently linked to at least one fatty acid.

91. The compound of any one of Claims 1-79 covalently linked to albumin.

92. The compound of Claim 91 wherein the albumin is linked to a fatty acid.

93. The compound of any one of Claims 1-79 covalently linked to a polyamino acid.

94. The compound of any one of Claims 1-79 covalently linked to at least one peptide selected from the group consisting of an amylin, an amylin analog, PYY, a PYY analog, GIP, a GIP analog, leptin, and a leptin analog.

95. A compound of 23A, 23B, 23C, 23D, 23E, 23F, 23G, 23H, 23I, 23J, 23K, 23L, 24A, 24B, 24C, 24D, 24E, 24F, or 24G.

96. The compound of any one of Claims 1-95 in the form of a pharmaceutically acceptable salt.

97. A pharmaceutical composition comprising a compound according to any one of Claims 1-96 and a pharmaceutically acceptable carrier.

98. A method for treating diabetes in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to treat diabetes in the patient.

99. The method of Claim 98, wherein the diabetes is Type 1 diabetes.

100. The method of Claim 98, wherein the diabetes is Type 2 diabetes.

101. The method of Claim 98, wherein the diabetes is gestational diabetes.

102. A method for treating insulin resistance in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to treat insulin resistance in the patient.

103. A method for treating postprandial hyperglycemia in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to treat postprandial hyperglycemia in the patient.

104. A method for lowering blood glucose levels in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to lower blood glucose levels in the patient.

105. A method for lowering HbA1c levels in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to lower HbA1c levels in the patient.

106. A method for stimulating insulin release in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to stimulate insulin release in the patient.

107. A method for reducing gastric motility in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to reduce gastric motility in the patient.

108. A method for delaying gastric emptying in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims

1-96 or the pharmaceutical composition of Claim 97 to delay gastric emptying in the patient.

109. A method for reducing food intake in a patient in need or desirous thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to reduce food intake in the patient.

110. A method for reducing appetite in a patient in need or desirous thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to reduce appetite in the patient.

111. A method for reducing weight in a patient in need or desirous thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to reduce weight in the patient.

112. A method for treating overweight in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to treat overweight in the patient.

113. A method for treating obesity in a patient in need thereof comprising administering a therapeutically effective amount of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97 to treat obesity in the patient.

114. The method of any one of Claims 98-113, wherein the therapeutically effective amount of the compound is from about 0.1 μg to about 5 mg.

115. The method of any one of Claims 98-113, wherein the therapeutically effective amount of the compound is from about 1 μg to about 2.5 mg.

116. The method of any one of Claims 98-113, wherein the therapeutically effective amount of the compound is from about 1 μg to about 1 mg.

117. The method of any one of Claims 98-113, wherein the therapeutically effective amount of the compound is from about 1 μg to about 50 μg.

118. The method of any one of Claims 98-113, wherein the therapeutically effective amount of the compound is from about 1 μg to about 25 μg.

119. The method of any one of Claims 98-113, wherein the therapeutically effective amount of the compound is from about 0.01 μg to about 100 μg based on the weight of a 70 kg patient.

120. The method of any one of Claims 98-113, wherein the therapeutically effective amount of

the compound is from about 0.01 μg to about 50 μg based on the weight of a 70 kg patient.

121. The method of any one of Claims 98-113, further comprising administering an effective amount of an amylin, an amylin analog, GIP, a GIP analog, PYY, a PYY analog, leptin, a leptin analog, or a combination of two or more thereof.

122. A drug delivery device comprising at least one therapeutically effective dose of the compound of any one of Claims 1-96 or the pharmaceutical composition of Claim 97.

123. The drug delivery device of Claim 122, wherein the drug delivery device is a vial, a pharmaceutical pen, or a cartridge.

124. The drug delivery device of Claim 121 or 122, comprising about a one month supply of therapeutically effective doses.|

125. A process of Figure 18, 19, 20, 21, or 22.

126. A process of Example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 18, or 19.

127. A GLP-1 receptor agonist compound comprising an imidazole ring at position 1 and a proline at position 3, wherein the compound binds in a RIN cell membrane receptor binding assay with an affinity of less than 1 nM.

128. The compound of Claim 127, wherin the imidazole ring at position 1 is histidine.

129. The compound of Claim 127, wherein the compound is an exendin analog or a GLP-1 analog.

130. The compound of Claim 127, wherein the compound binds in a RIN cell membrane receptor binding assay with an affinity of less than 0.1 nM.

Figure 1A HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2

Figure 1B H-dAla-PGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2

Figure 1C H-dAla-PGTFTSDLSKQLEEEAVRLFIEFLKN-NH_2

Figure 1D

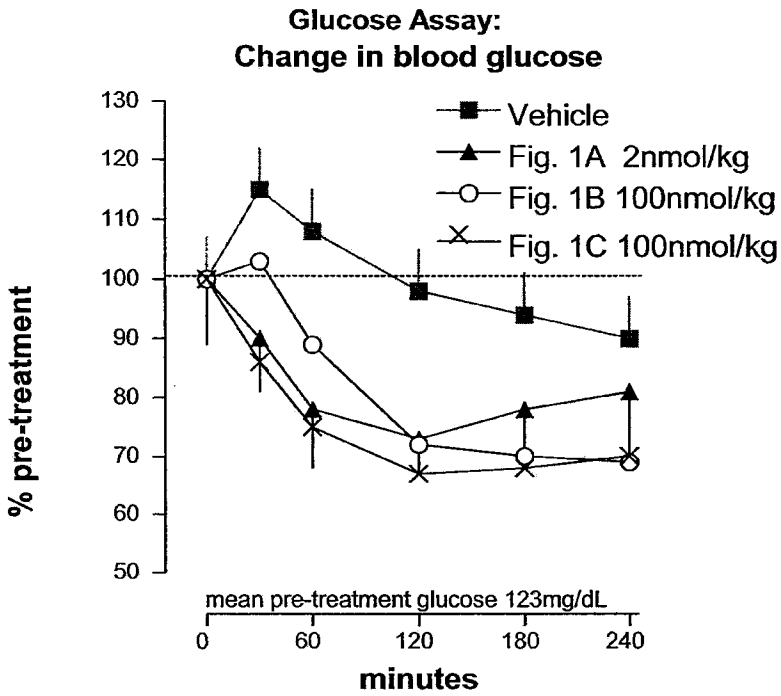


Figure 2A HGEGTFTSDLSKQLEEEAVRLFIEWLKQGGPSKEIIS

Figure 2B

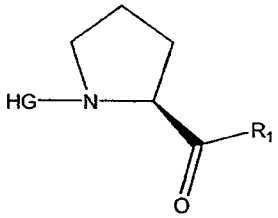


Figure 2C

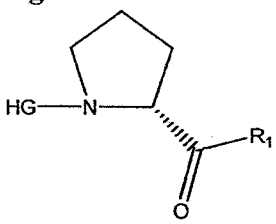


Figure 2D

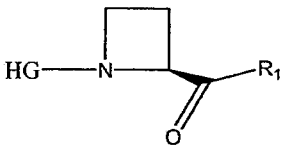


Figure 2E

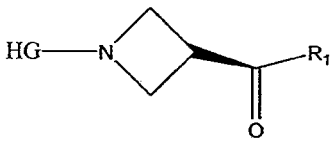


Figure 2F

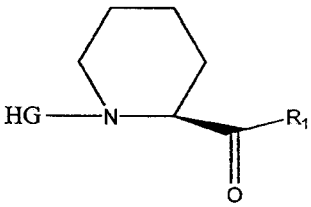


Figure 2G

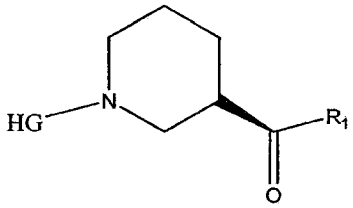


Figure 2H

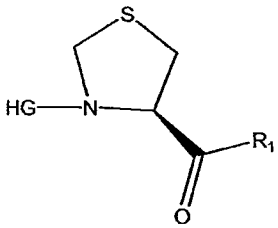


Figure 2I

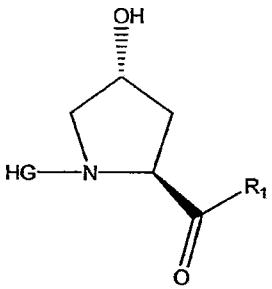


Figure 2J

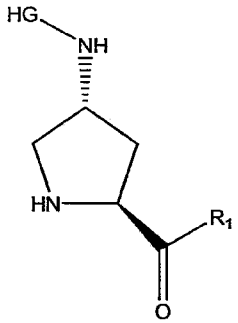


Figure 2K

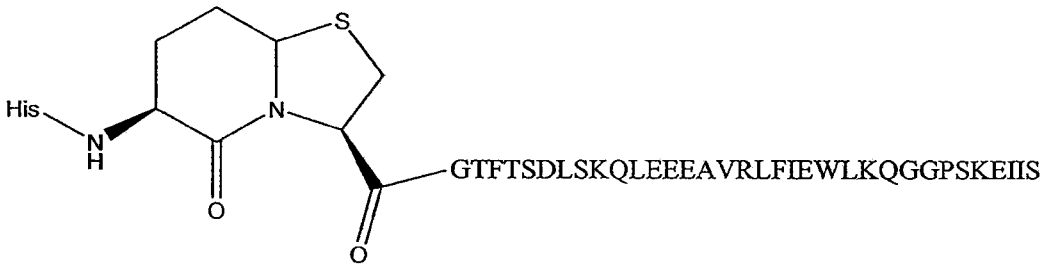


Figure 2L

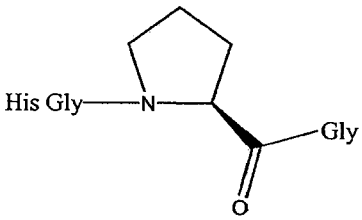


Figure 2M

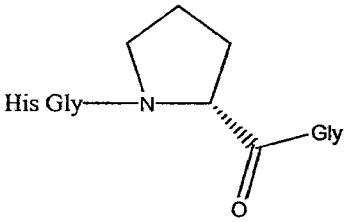


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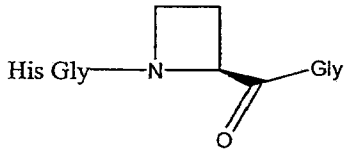


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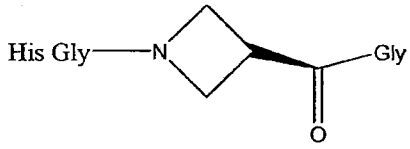


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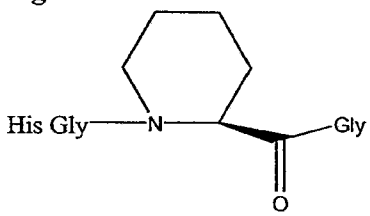


Figure 2Q

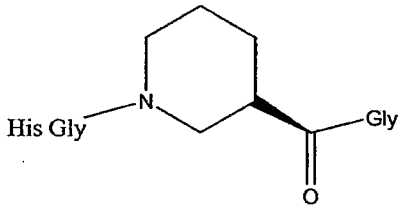


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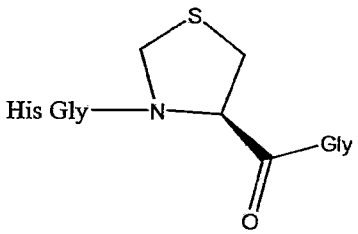


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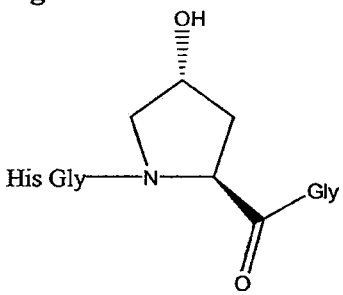


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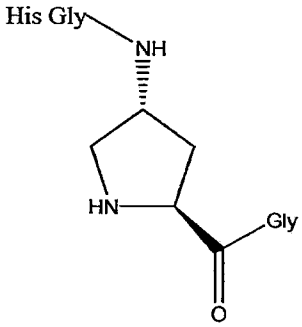


Figure 2U

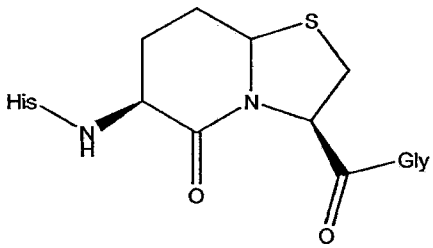


Figure 3A H-dAla-PGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2

Figure 3B HAPGT FTSDL SKQME EEAVR LFIEW LKNGG PSSGA PPPS-NH_2

Figure 3C HGPAT FTSDL SKQME EEAVR LFIEW LKNGG PSSGA PPPS-NH_2

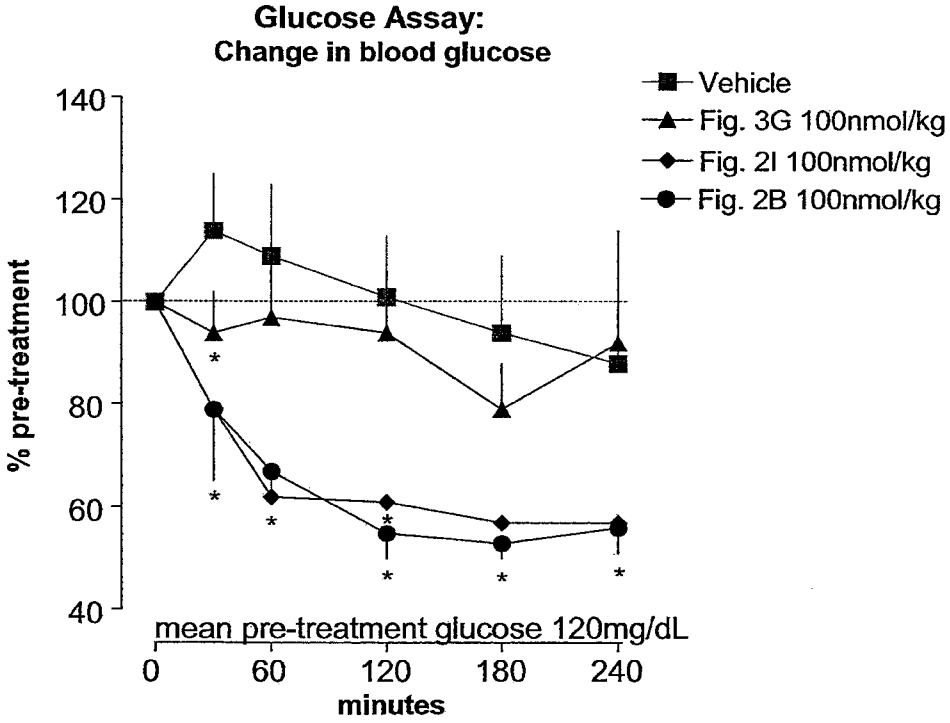
Figure 3D HAPAT FTSDL SKQME EEAVR LFIEW LKNGG PSSGA PPPS-NH_2

Figure 3E HGP-dAla-T FTSDL SKQME EEAVR LFIEW LKNGG PSSGA PPPS-NH_2

Figure 3F HVPGT FTSDL SKQME EEAVR LFIEW LKNGG PSSGA PPPS-NH_2

Figure 3G H-NMeAla-PGT FTSDL SKQME EEAVR LFIEW LKNGG PSSGA PPPS-NH_2

Figure 4



* p<0.05 v. vehicle control; ANOVA, Dunnett's test.

Figure 5A HGEGT FTSDL SKQLE EEAVR LFIEF LKN

Figure 5B

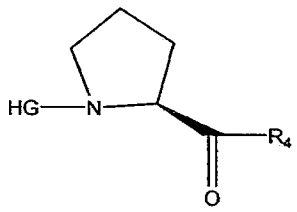


Figure 5C

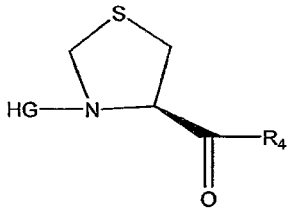


Figure 5D

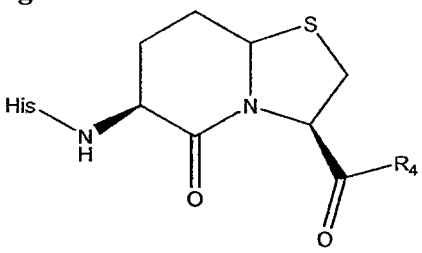


Figure 5E

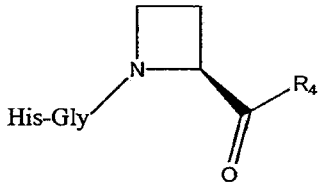


Figure 5F

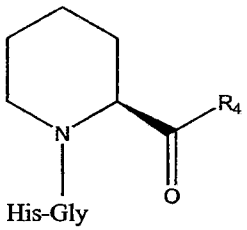


Figure 5G

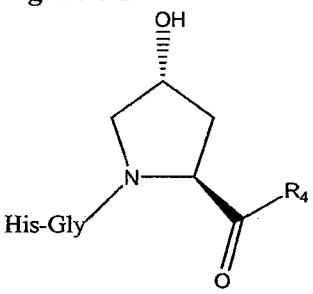


Figure 6A

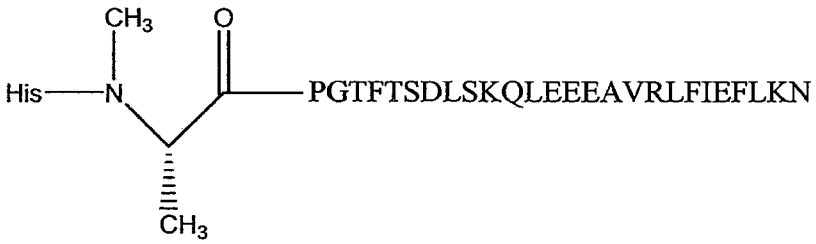


Figure 6B

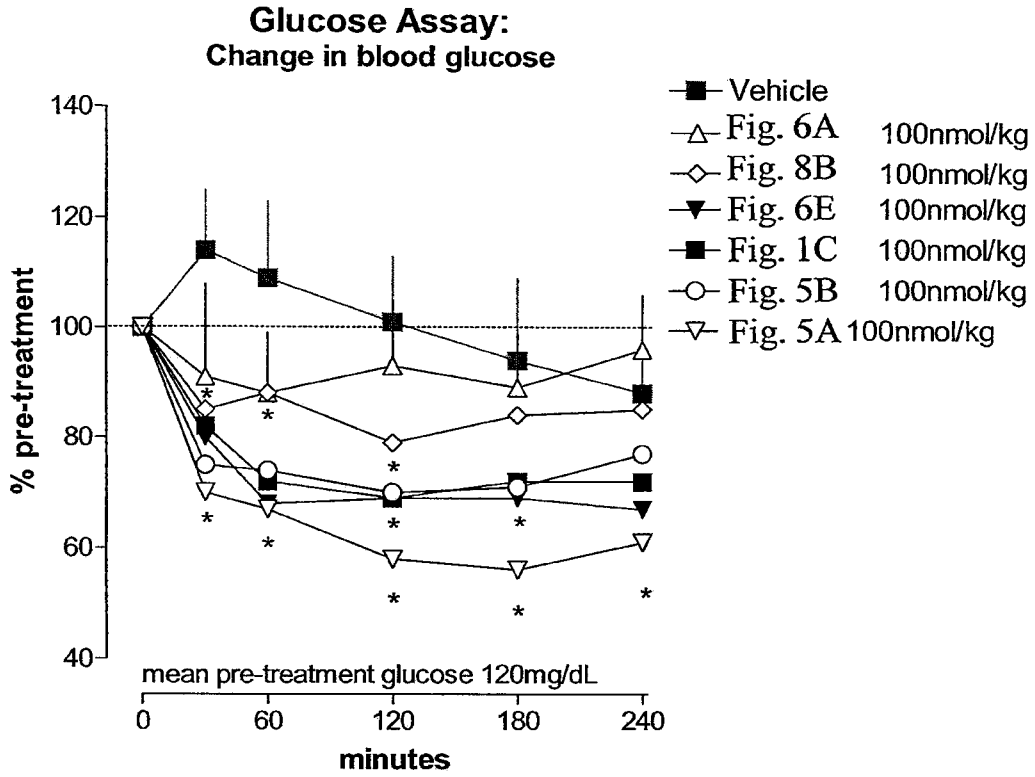


Figure 6C HVPGT FTSDL SKQLE EEAVR LFIEF LKN

Figure 6D HAPGT FTSDL SKQLE EEAVR LFIEF LKN

Figure 6E H-dAla-P-dAla-T FTSDL SKQLE EEAVR LFIEF LKN

Figure 7



Points represent mean ± sd.

* $p<0.05$ vs. vehicle control; ANOVA, Dunnett's test.

Figure 8A



Figure 8B



Figure 8C



Figure 8D



Figure 8E



Figure 8F



Figure 8G



Figure 8H



Figure 9A

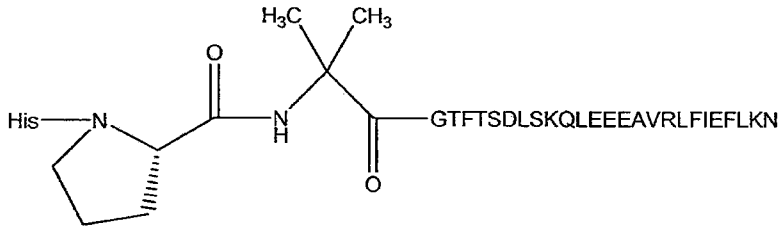


Figure 9B

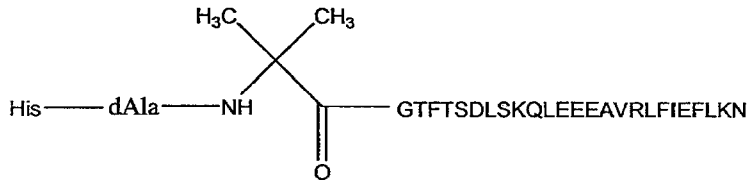


Figure 9C

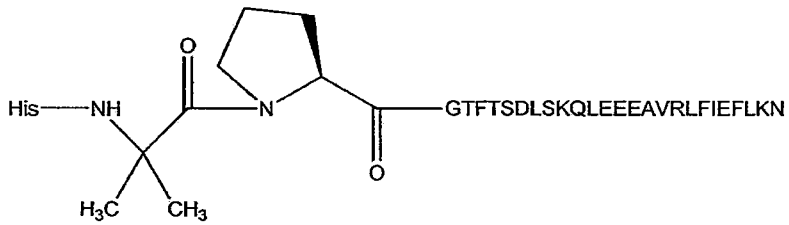


Figure 9D

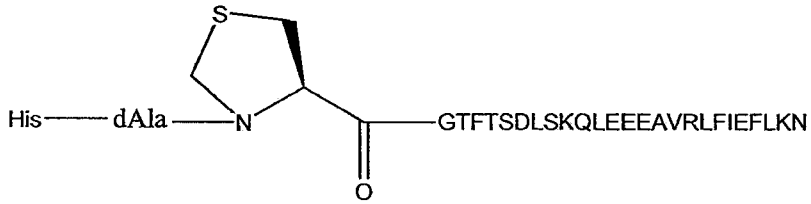


Figure 9E

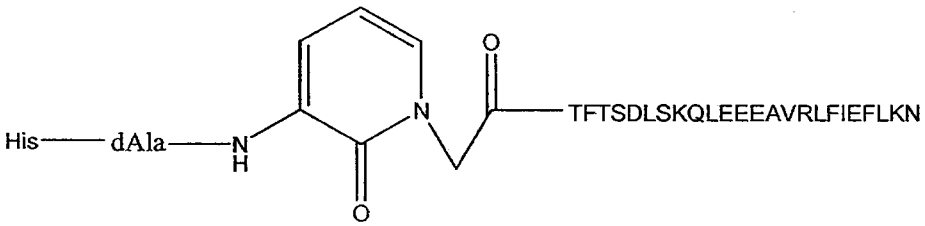


Figure 9F

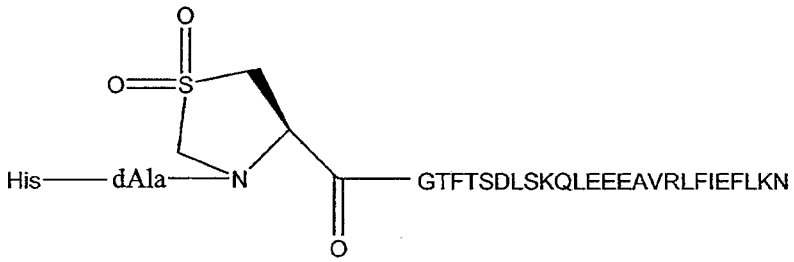


Figure 9G

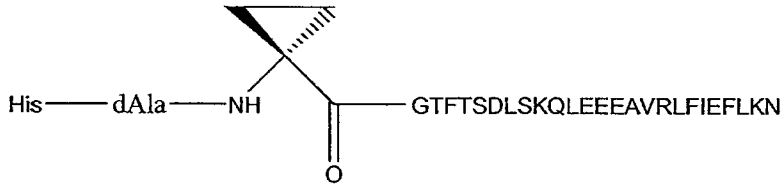


Figure 9H

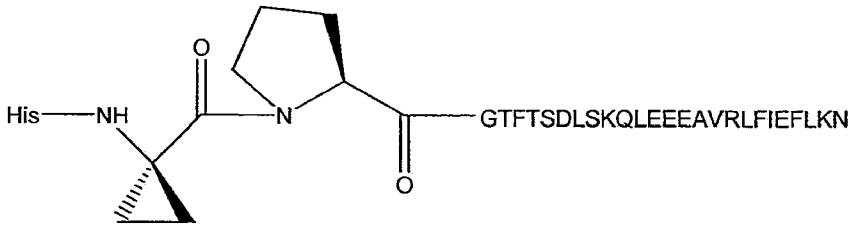
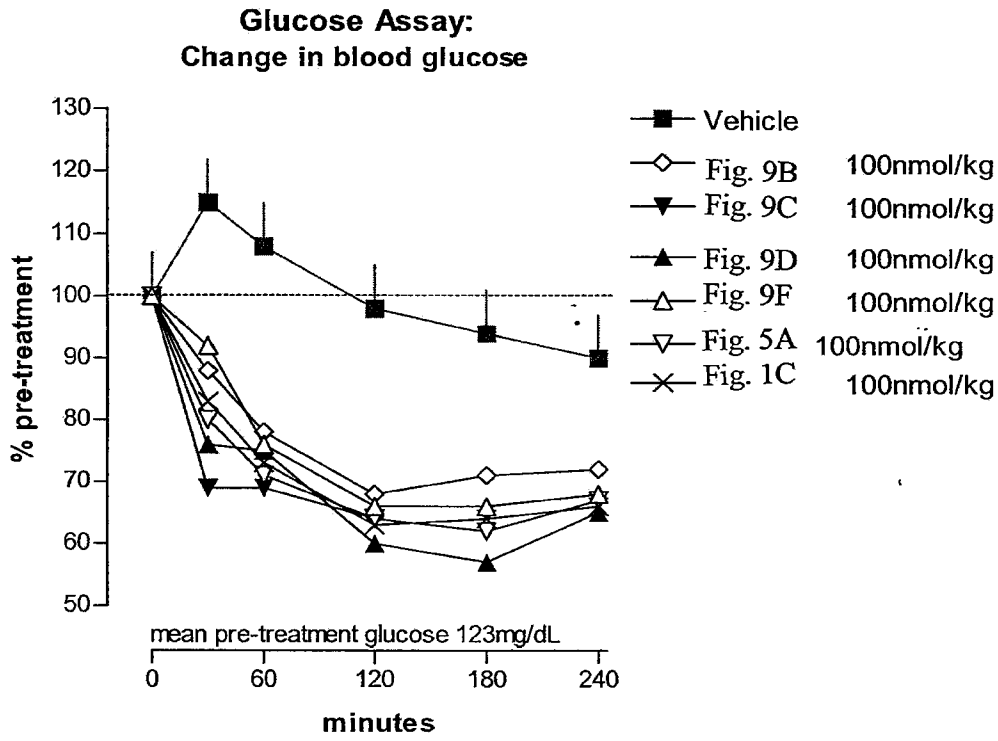


Figure 9I



Points represent mean ± sd.

Figure 10A

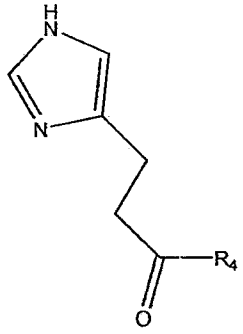


Figure 10B

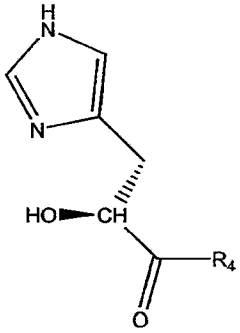


Figure 10C

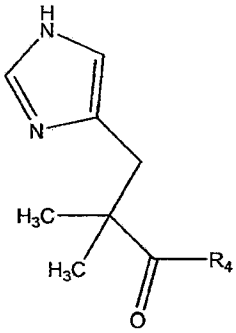


Figure 10D

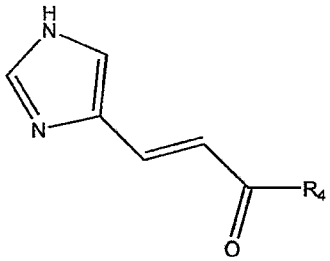


Figure 10E

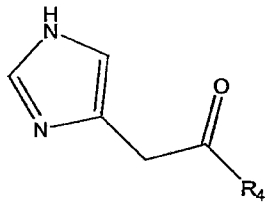


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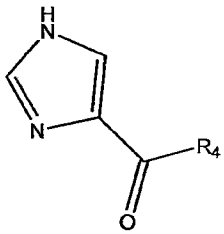


Figure 10G

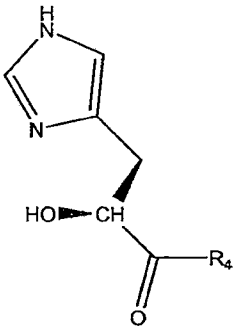


Figure 10H

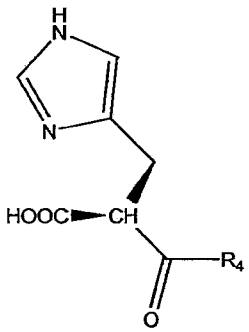


Figure 10I

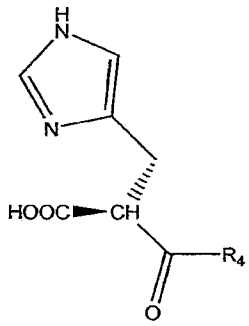


Figure 11A

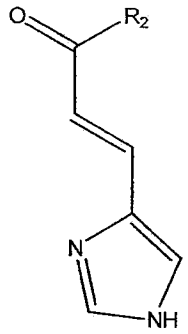


Figure 11B

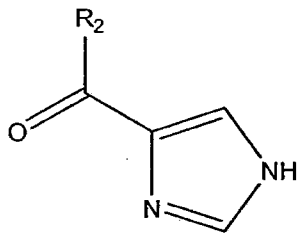


Figure 12

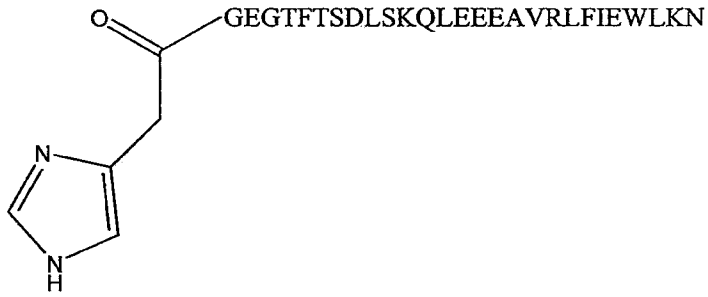


Figure 13

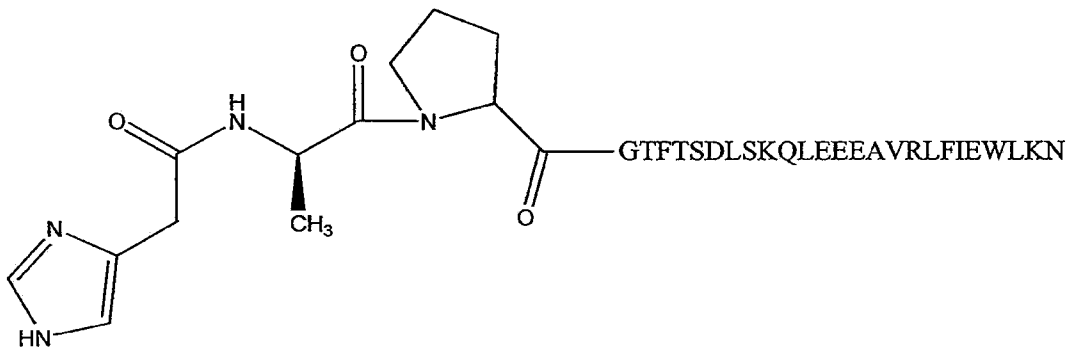


Figure 14A

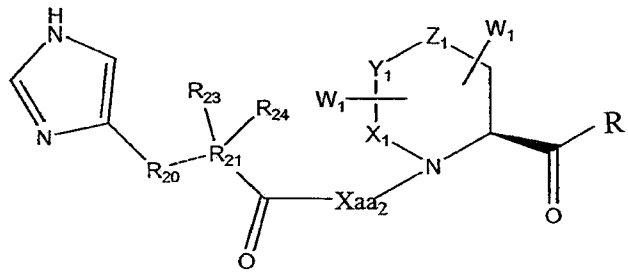


Figure 14B

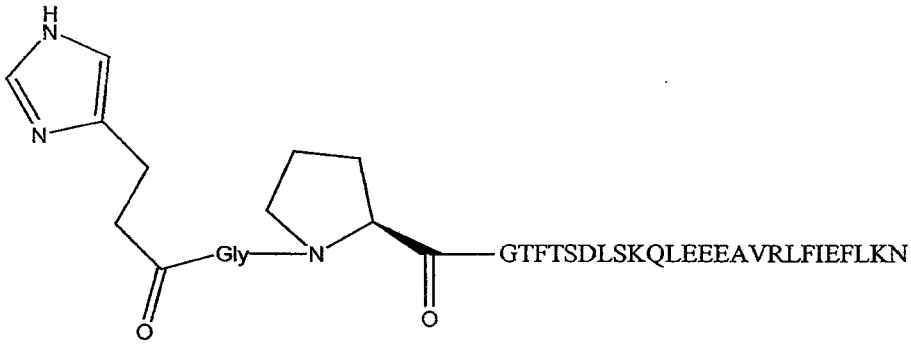


Figure 14C

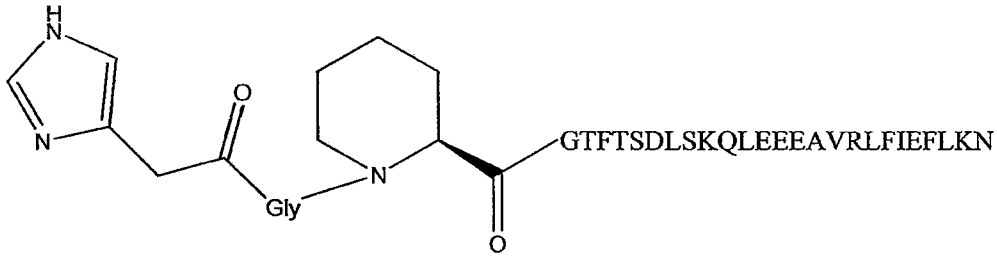


Figure 14D

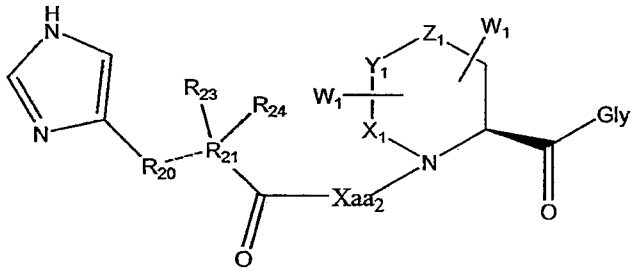


Figure 14E

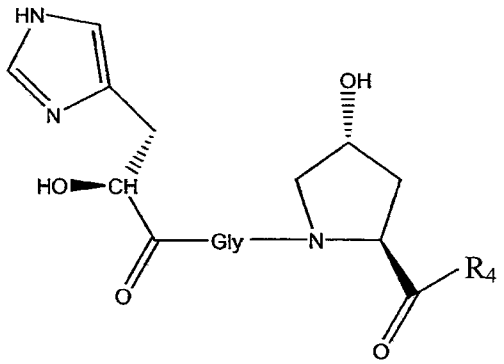


Figure 14F

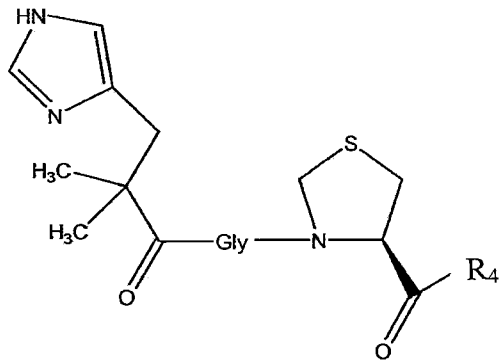


Figure 14G

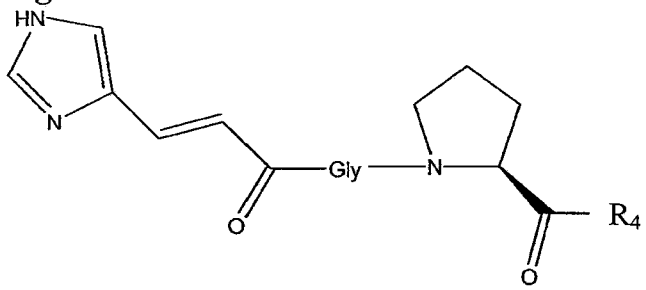


Figure 14H

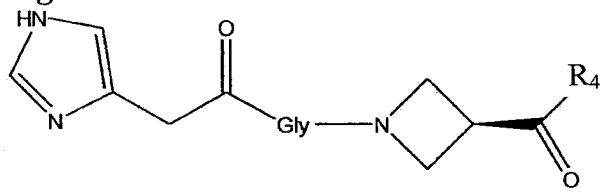


Figure 14I

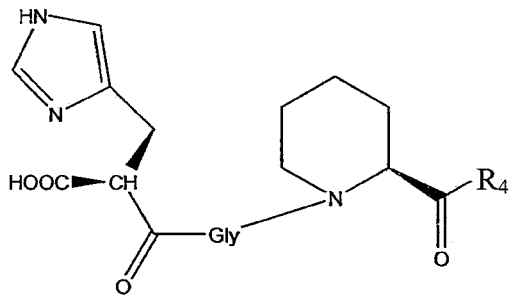


Figure 14J

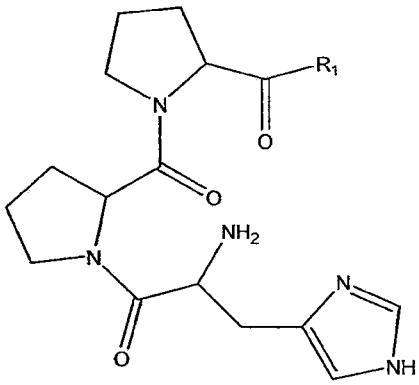


Figure 14K

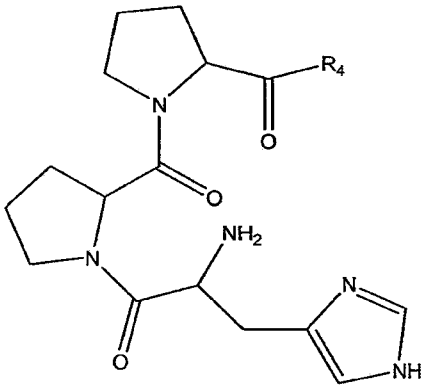


Figure 14L

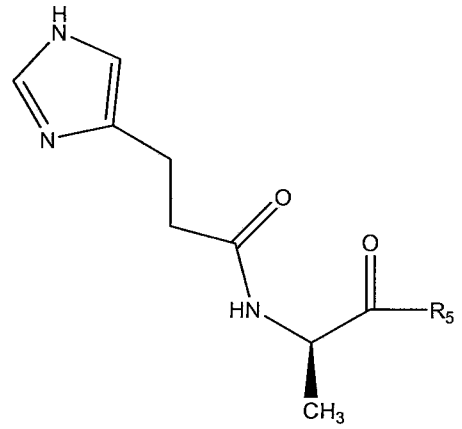


Figure 14M

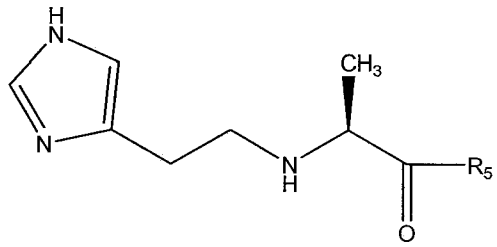


Figure 14N

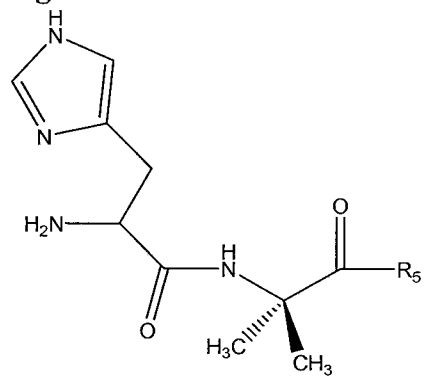


Figure 14O

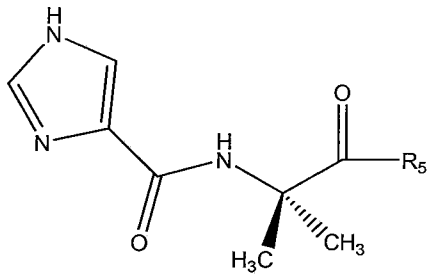


Figure 14Q
[βAla^2]-exendin-4-NH_2

Figure 14P

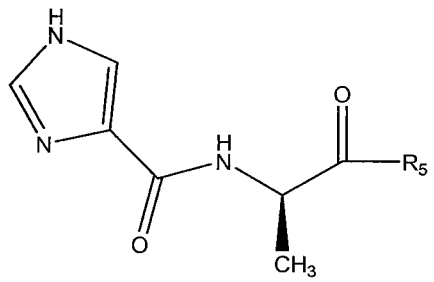


Figure 14R

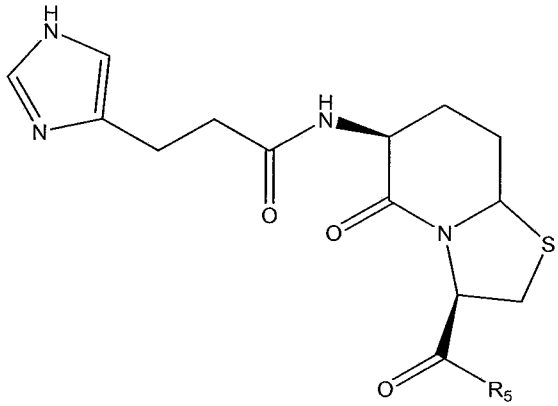


Figure 15A

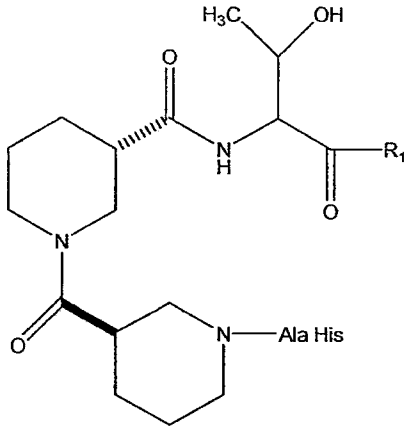


Figure 15B

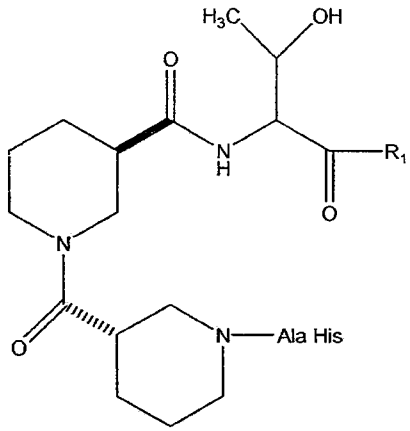


Figure 15C

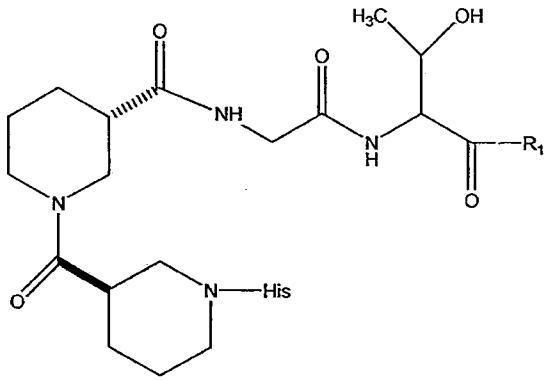


Figure 15D

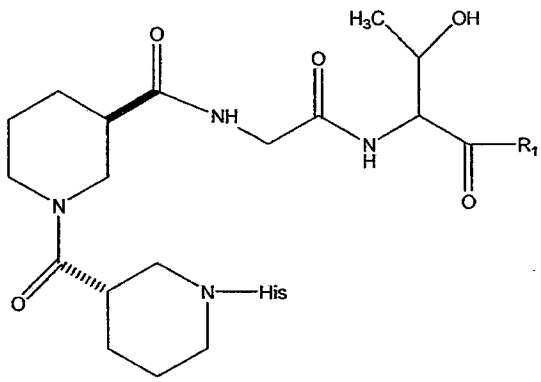


Figure 16A

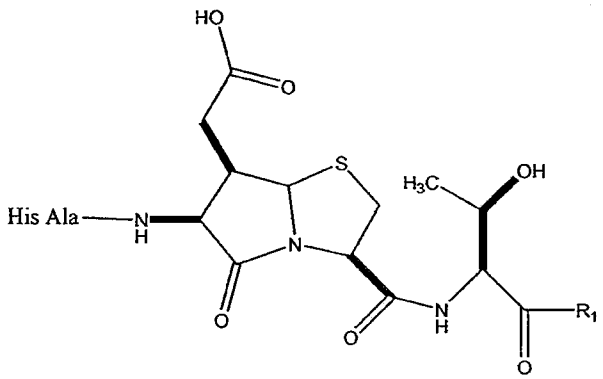


Figure 16B

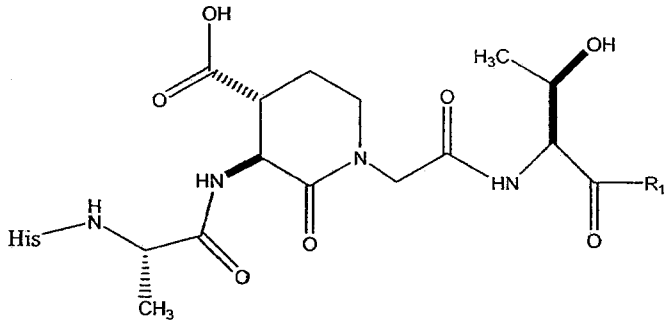


Figure 16C

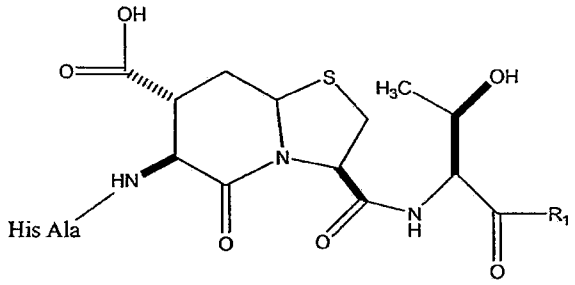


Figure 16D

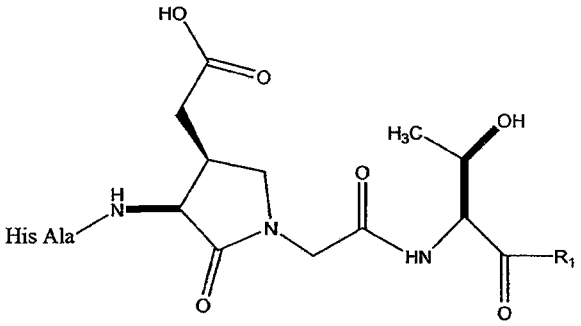


Figure 16E

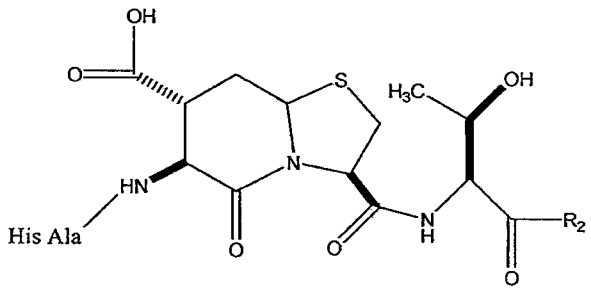


Figure 16F

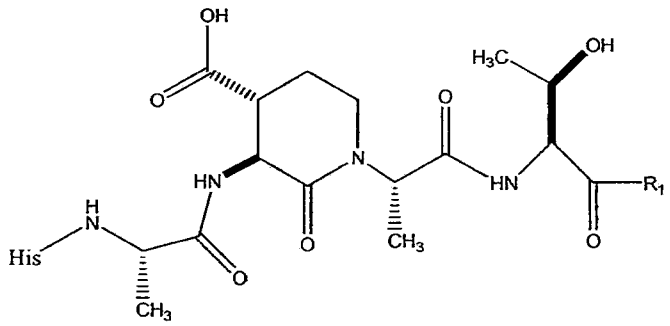


Figure 16G

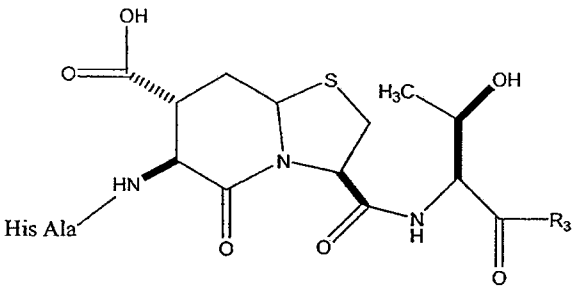


Figure 16H

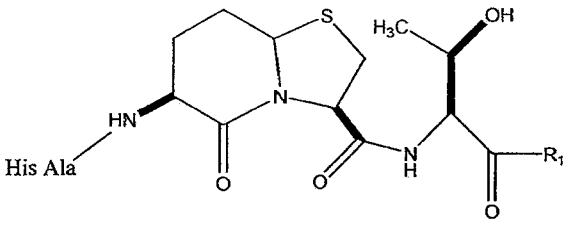


Figure 16I

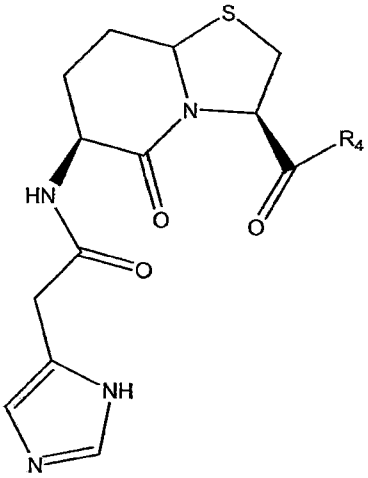


Figure 16J

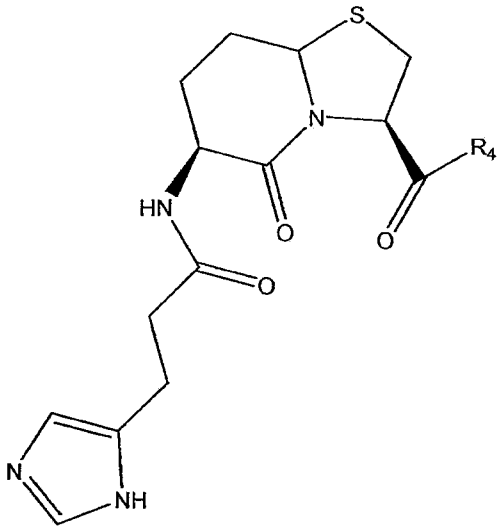


Figure 16K

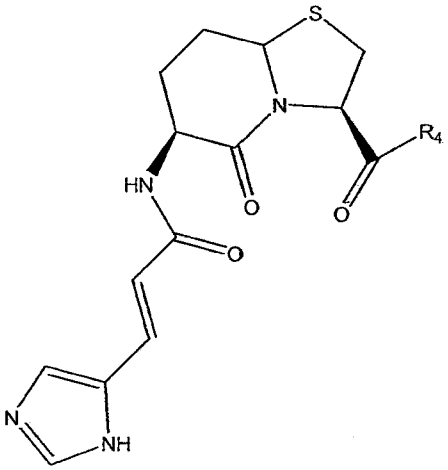


Figure 16L

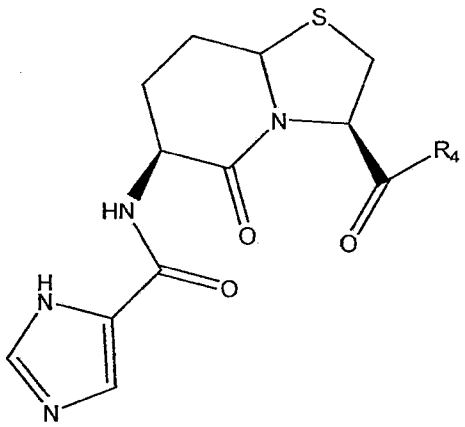


Figure 17A

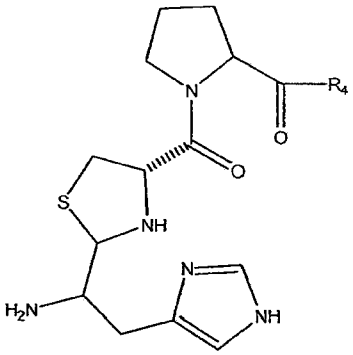


Figure 17B

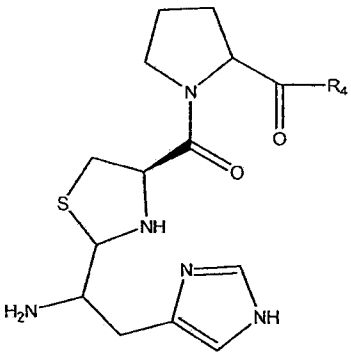


Figure 17C

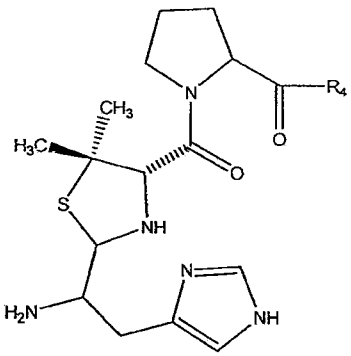


Figure 17D

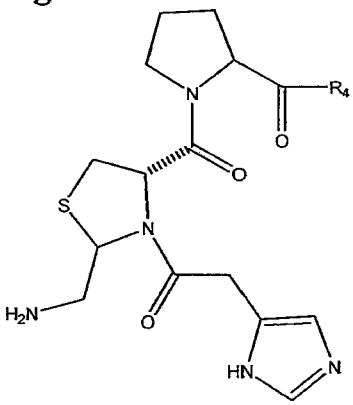


Figure 17E

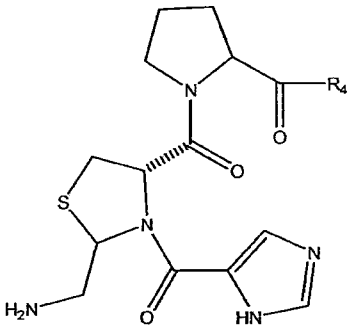


Figure 17F

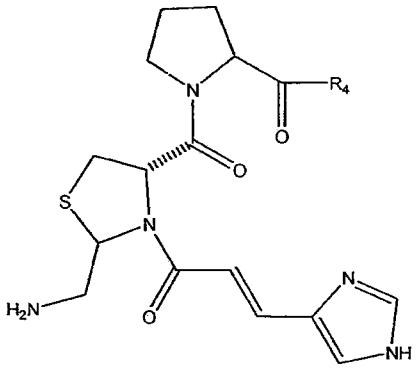


Figure 17G

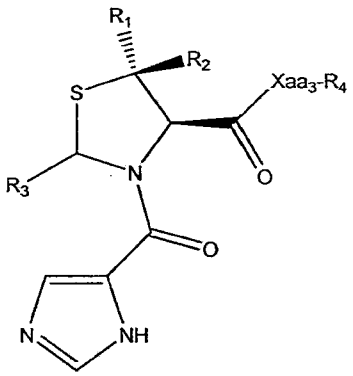


Figure 17H

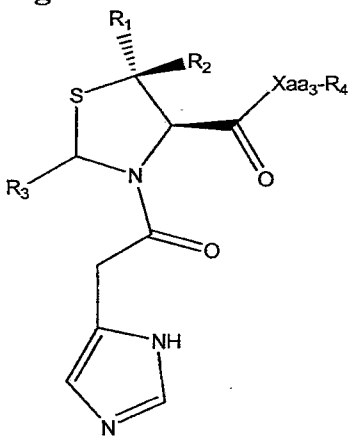


Figure 17I

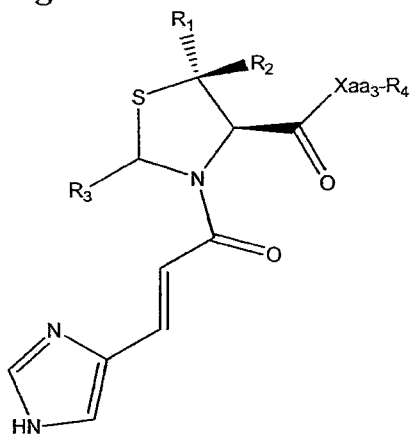


Figure 17J

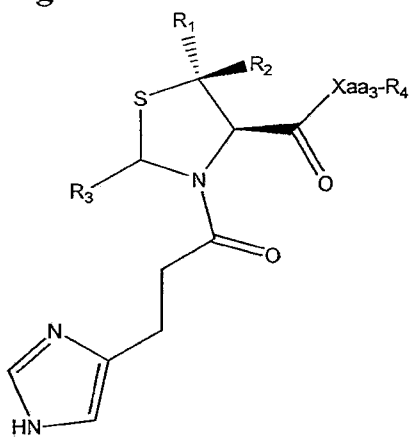


Figure 17K

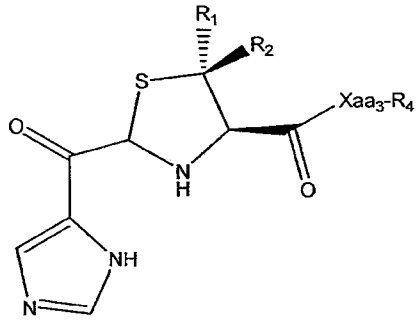


Figure 17L

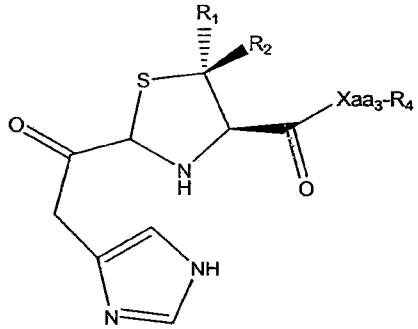


Figure 17M

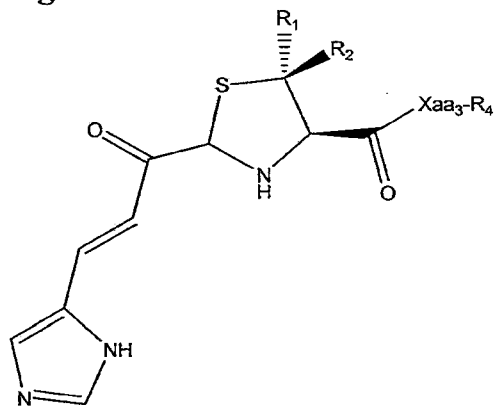


Figure 17N

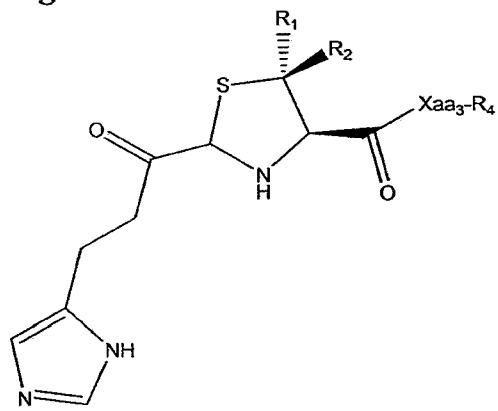


Figure 18A

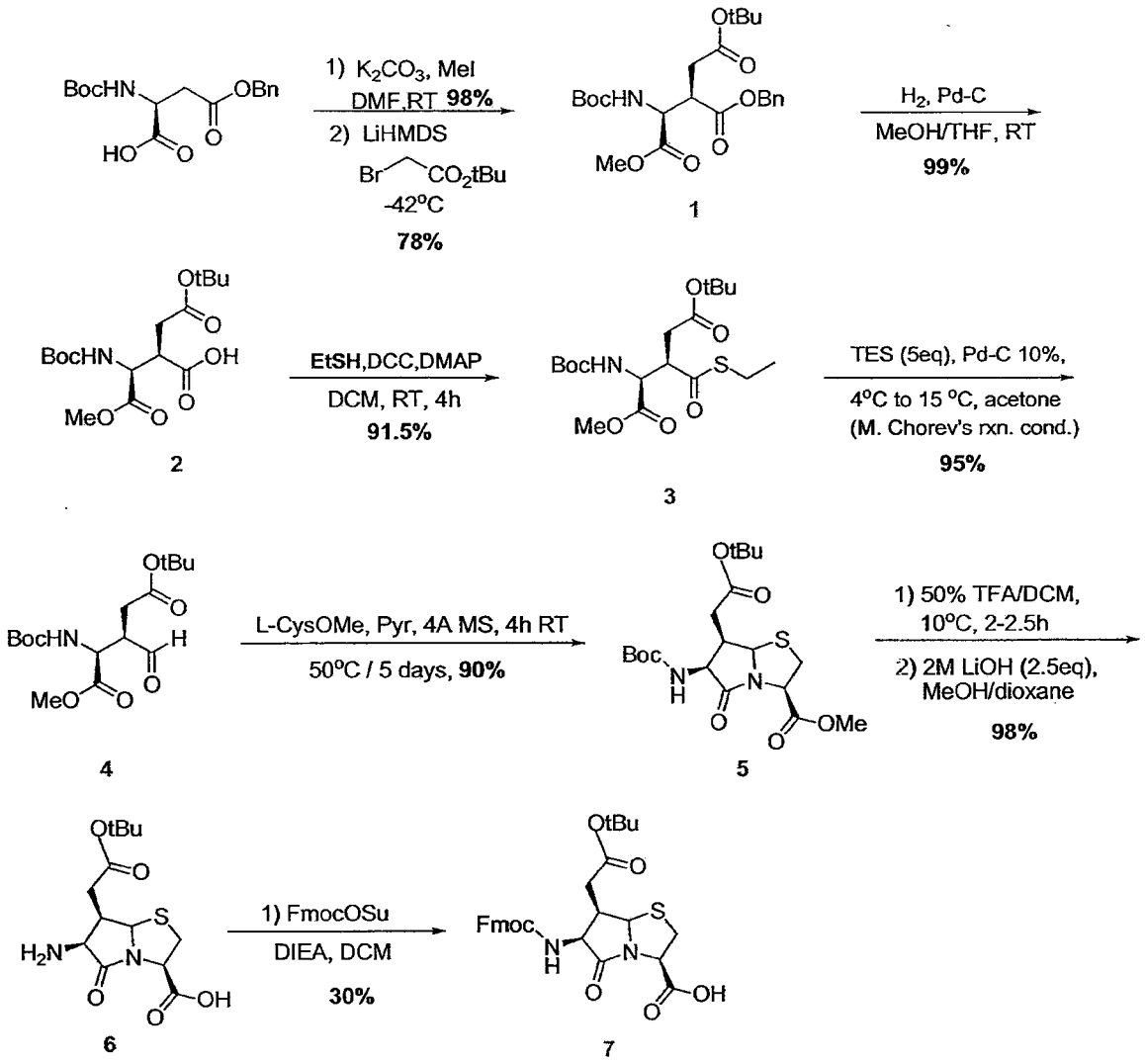


Figure 18B

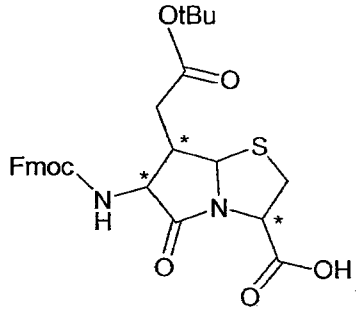


Figure 19A

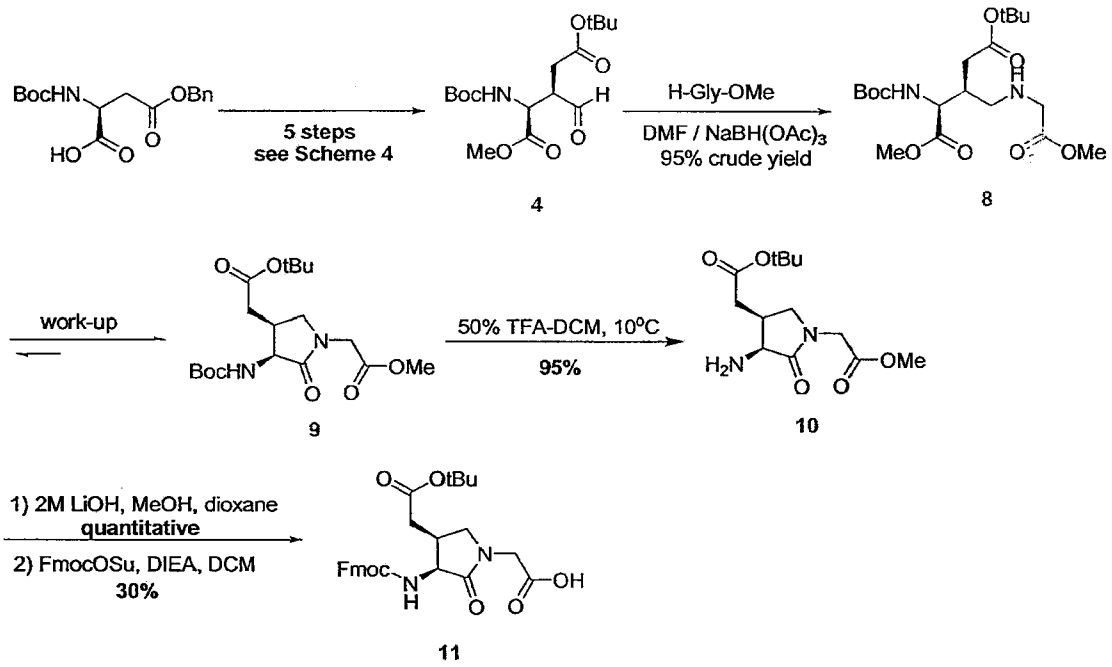


Figure 19B

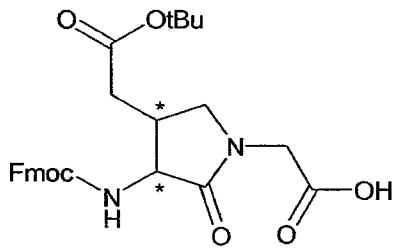


Figure 20A

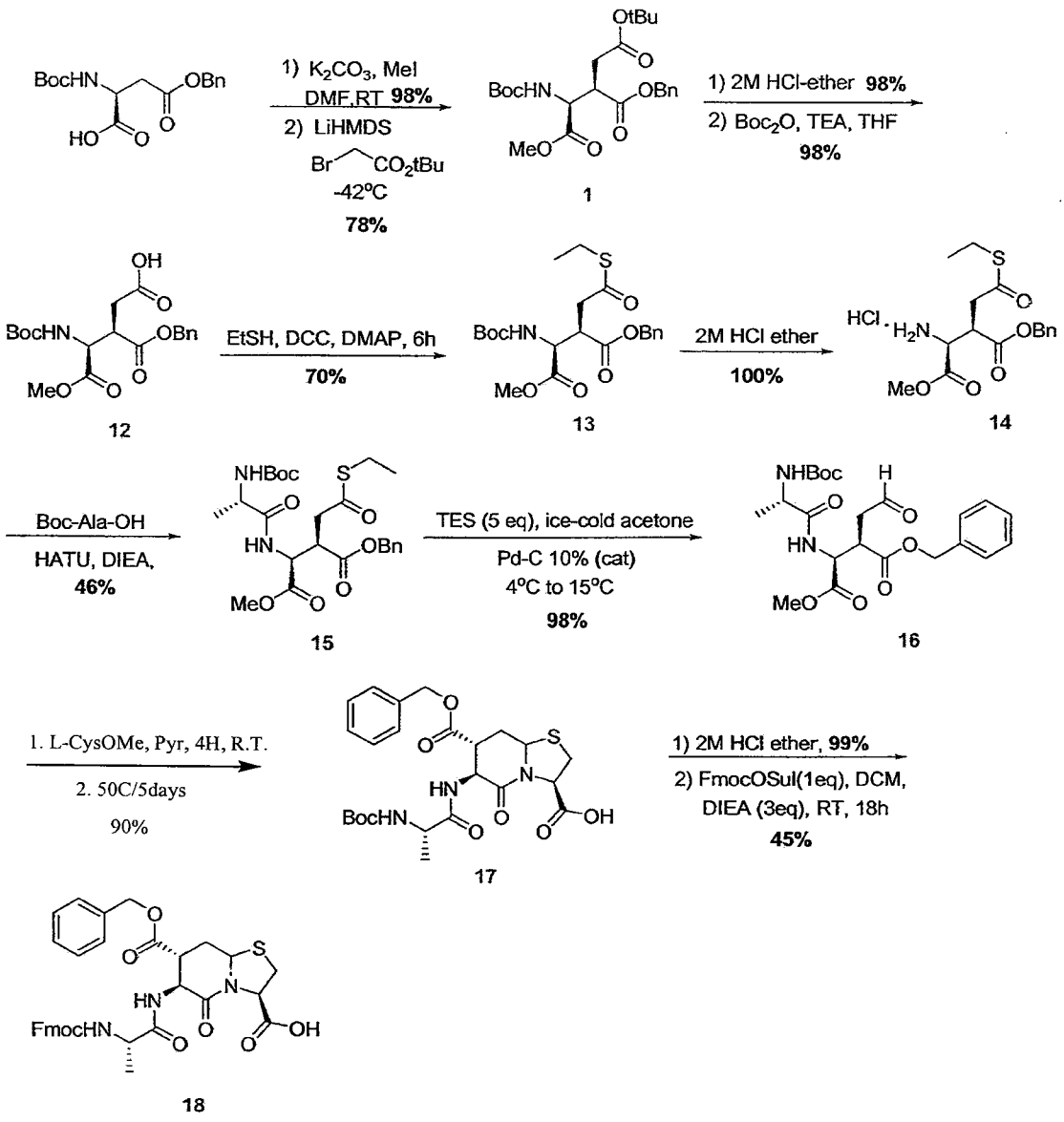


Figure 20B

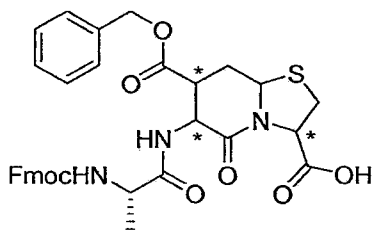


Figure 21A

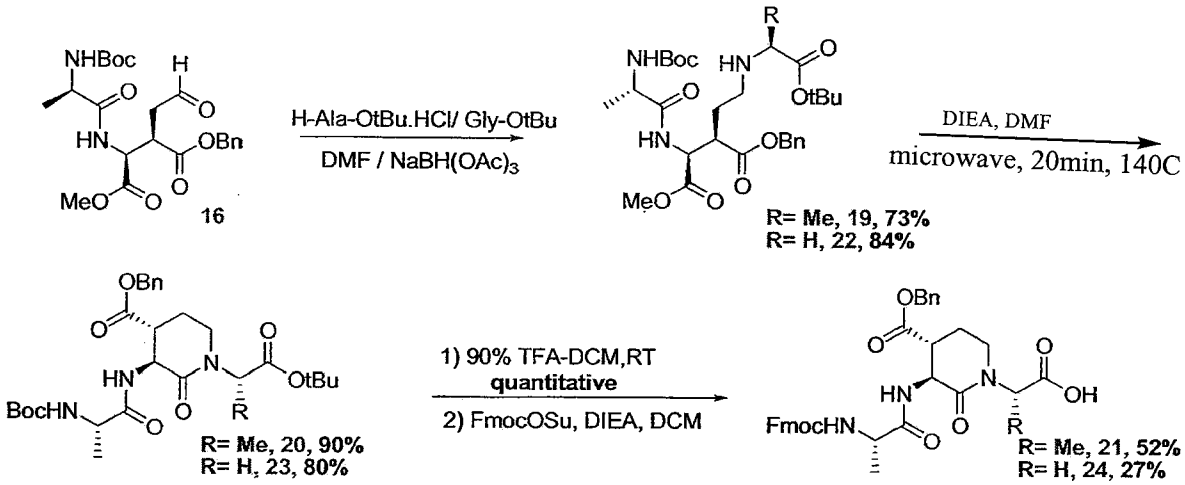


Figure 21B

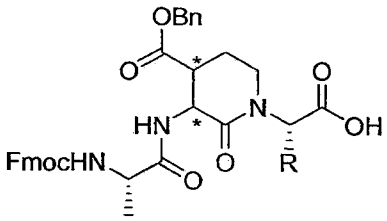


Figure 22

