Glucose is the main fuel for the human body, and blood glucose values are tightly regulated in healthy individuals. For example, between meals, blood glucose is near 5 mmol/L (mM), and when blood glucose concentrations rise after a meal, the value is quickly adjusted back toward 5 mM by the action of insulin. The hormone insulin is secreted from pancreatic beta cells, and when insulin binds to insulin receptors on cells in the body (for example muscle and fat), the cells are stimulated to absorb glucose by translocation of glucose transporters from storage vesicles to the cell surface (GLUT4). (Huang, S.H. et al. (2007) Cell Metabolism 5:237-252.)

People with diabetes may lose their ability to produce insulin due to autoimmunity against beta cells (type 1) or have low sensitivity to insulin in combination with impaired insulin secretion (type 2). For example, those with type 1 diabetes may rely on multiple daily insulin injections, both for basal coverage, typically once a day, and with meals (bolus) to control their glucose levels. (Polonsky, K.S. et al. (1988) The Journal of Clinical Investigation 81: 442-448.) Because glucose values can fluctuate unpredictably, perfect insulin dosing day after day is extremely difficult. Indeed, despite many technological advances in diabetes treatment, researchers are currently observing, partly due to lifestyle problems, a worsening of long-term glucose control and/or overall metabolic health.

Glucose sensors and glucose sensing insulin analogs are known in the art. *See*, e.g., WO 2016/179568 A1 and WO 2021/202802 A1. However, there is a need in the art to develop glucose sensors and glucose sensing insulins that have improved properties, such as binding to the insulin receptor and be proportionately responsive to different glucose concentrations and provide a graded and reversible response to changes in glucose levels under physiological conditions.

Thus, there is an unmet medical need for novel compounds, such as compounds which bind glucose and may be utilized in glucose-responsive insulin analogues/conjugates, that can control blood glucose levels.

Here, we disclose glucose sensors and glucose sensing insulin analogs that have improved properties, such as improved affinity for glucose at relatively low concentrations, improved affinity for the insulin receptor, and improved activation of the insulin receptor.

SUMMARY OF THE DISCLOSURE

The present disclosure provides, according to some examples, novel Z1c compounds (e.g., FF12, FF12A, FF12B, FF12C, FF12D, FF114, FF114A, FF114B, FF115, FF115A, FF115B, FF116, FF116A, FF116B, FF116C, FF116D, FF117, FF193A, FF203, FF225, FF225A, FF225B, and FF226) comprising aromatic boron-containing functionalities (e.g., F2, F5, and F10). In some examples, the present disclosure provides indirect linkers represented by

Formula $(X'')_{n1}$ where X" is as defined herein and each n1 is 1, 2, 3, 4, or 5 (e.g., as exemplified in Formulae FL3, FL5, FL5A, FL5B, and FL20-FL75). In some examples, the present disclosure provides novel Z1c-Linker(s) (e.g., Formulae FFL-1 to FFL-101) comprising aromatic boron-containing functionalities (e.g., F2, F5, and F10).

In some examples, the present disclosure provides compounds that comprise a drug substance (e.g., X1) and at least one Z1c with aromatic boron-containing functionalities. In some examples, the compounds disclosed comprise one or more scaffolds (e.g., FF scaffolds and Z1c-Linker scaffolds as exemplified in Formulae FFL-1 to FFL-101). In some examples, the compounds comprise a drug substance. In at least some examples, the drug substance is a polypeptide or a small-molecule.

In at least some examples, the disclosed compounds have at least two aromatic boron-containing functionalities. In some examples, the compounds are selective towards specific sugars, such as glucose, while showing reduced affinity for other sugars and wherein there is at least two aromatic boron-containing functionalities in the aromatic boron-containing portion of the compounds. In certain examples, the aromatic boron-containing portion may be covalently conjugated, directly or indirectly, to a drug substance comprising an amine, a drug substance that is covalently conjugated to an amine containing linker, or NH_2, or OH (e.g., where X1 is NH_2 or OH). In some examples, the drug substance is covalently conjugated to an amine containing linker and the amine group is conjugated to the aromatic boron-containing portion (Z1c). In certain examples, the aromatic boron-containing portion (Z1c) has an architecture comprising of tethering groups (FF formulae) and aromatic boron containing groups that collectively make the aromatic boron-containing portion of the disclosed compounds. In some examples, the aromatic boron-containing portion (Z1c) is covalently conjugated to an indirect linker (e.g, Formulae FL3, FL5, FL5A, FL5B, and FL20-FL75) and has an architecture comprising tethering groups (FF formulae), and aromatic boron containing groups that collectively make the aromatic boron-containing portion of the disclosed compounds.

In some examples, one or more Z1c may be linked (e.g., conjugated, connected) to a drug substance (e.g., X1) via one or more indirect linkers (e.g., Formulae FL3, FL5, FL5A, FL5B, and FL20-FL75 and/or one or more L- or D-amino acids connected together using amide or peptide bonds). In at least some examples, rotational constraining of the boron functionalities via the tethering group (e.g., FF formulae) enhances the binding affinity of the compounds (e.g., conjugates) towards specific diols (such as glucose) and away from other diols in the body and thereby provides selectivity to specific diols. In some examples, the compounds may exhibit therapeutic pharmacokinetics and/or pharmacodynamics in response to endogenous and/or exogenous small molecules in the body, such as glucose. Changes in the

physiological concentration of glucose, may result in the activation and/or release of the drug molecule or conversely, may result in the deactivation and/or sequestering of the drug molecule (e.g., a peptide hormone), and/or modulation of the activity of the drug molecule, through interaction of glucose with the boron-containing architectures conjugated to the drug molecule.

In some examples, the present disclosure provides a compound comprising X1 and one or more Z1c, or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or isotopic derivative thereof, wherein:

X1 comprises:

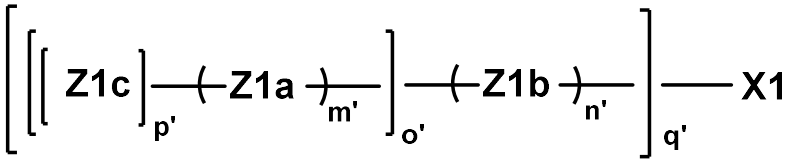
i. a drug substance comprising an amine;

ii. an amine configured to be covalently conjugated to a drug substance; or

iii. NH_2 or OH (e.g. X1 is NH_2 or OH);

wherein each Z1c is independently selected from Formulae FF12, FF12A, FF12B, FF12C, FF12D, FF114, FF114A, FF114B, FF115, FF115A, FF115B, FF116, FF116A, FF116B, FF116C, FF116D, FF117, FF193A, FF203, FF225, FF225A, FF225B, and FF226; and wherein each Z1c is covalently conjugated, directly or indirectly, to an amine in X1 or to NH_2 which X1 is NH_2 or to OH when X1 is OH.

In some examples, the present disclosure provides a compound represented by Formula I, or a stereoisomer or a mixture of stereoisomers, or pharmaceutically acceptable salt thereof:



(Formula I)

wherein:

X1 comprises:

i. a drug substance comprising an amine;

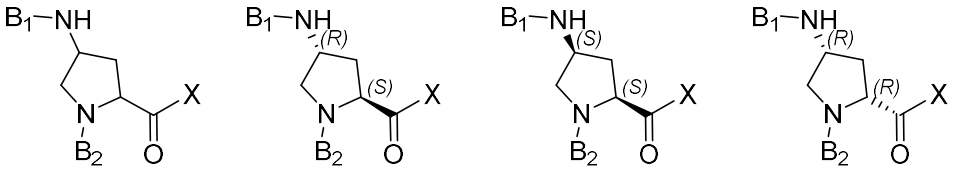
ii. an amine configured to be covalently conjugated to a drug substance; or

iii. NH_2 or OH (e.g. X1 is NH_2 or OH);

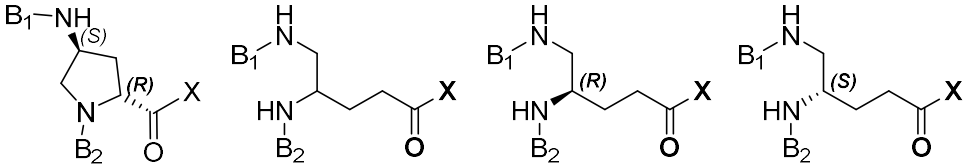
each Z1a independently comprises 1 to 50 amino acids connected together using amide or peptide bonds;

each Z1b is independently a small-molecule linker;

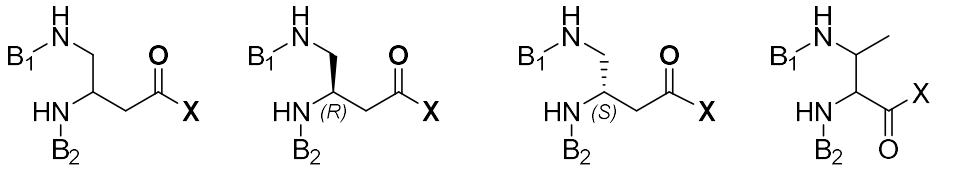
each Z1c is independently selected from Formulae FF12, FF12A, FF12B, FF12C, FF12D, FF114, FF114A, FF114B, FF115, FF115A, FF115B, FF116, FF116A, FF116B,



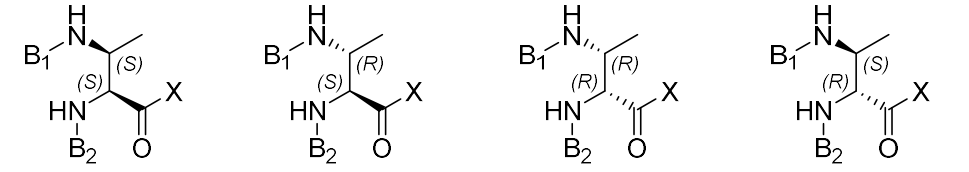
FF12 FF12A FF12B FF12C



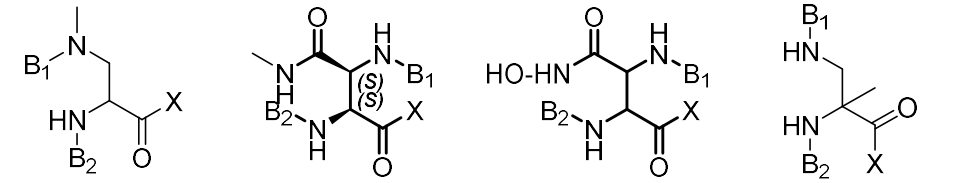
FF12D FF114 FF114A FF114B



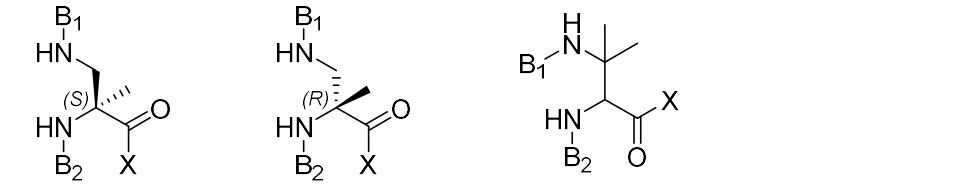
FF115 FF115A FF115B FF116



FF116A FF116B FF116C FF116D



FF117 FF193A FF203 FF225



FF225A FF225B FF226

,

wherein X represents a point of covalent attachment either directly to an amine of X1 or to NH_2 when X1 is NH_2 or to OH when X1 is OH or to an amine that is covalently conjugated directly or indirectly to X1; and wherein B_1 and B_2, which may be identical or different, each independently represent an aromatic boron-containing group; and wherein one or more positions of the compound of Formula I may comprise an isotope (e.g., ^{2}H or ^{14}C).

In some examples, X1 is OH or NH_2. In some examples, the compound disclosed herein (e.g., Formula I, Formula II) is conjugated directly or via an optional linker to a drug substance.

In some examples, the compound of Formula I comprises:

at least one Z1c covalently conjugated via the indirect linker to X1 or to Z1a, wherein the indirect linker is represented by Formula $(X'')_{n1}$,

each n1 is independently selected from 1, 2, 3, 4, and 5, and

each X" is independently selected from:

(i) an L- or D-amino acid, wherein an amine functional group of the L- or D-amino acid is covalently conjugated, directly or indirectly, to Z1c and an acid functional group of the L- or D- amino acid is conjugated, directly or indirectly, to X1 or to Z1a; and

(ii) Formulae FL3, FL5, FL5A, FL5B, FL20-FL68, and FL71-FL75 which comprise substituents R'' and Z'', and Formulae FL69 and FL70, which comprise substituents R'', Z'', A', and A'', and stereoisomers thereof;

wherein:

R'' represents a covalent bond, directly or indirectly, to Z1c;

Z'' represents a covalent bond, directly or indirectly, to X1 or to Z1a;

A' is selected from H, an alkyl group (e.g., C_1-C_6alkyl group), a saturated fatty acid, an unsaturated fatty acid, a cycloalkyl group (e.g., (C_3-C_6)cycloalkyl), a haloalkyl group (e.g., C_1-C_6haloalkyl group), an aryl group, and a heteroaryl group; and

A'' is selected from one of an alkyl group (e.g., C_1-C_6alkyl group), a substituted acyl group, acyl group terminating in an acid group, a saturated fatty acid, an unsaturated fatty acid, a cycloalkyl group (e.g., (C_3-C_6)cycloalkyl), a haloalkyl group (e.g., C_1-C_6 haloalkyl group), an aryl group, and a heteroaryl group;

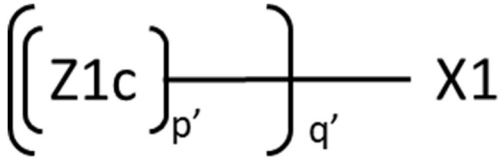
p is 1, 2, 3, 4, or 5,

q is 1, 2, 3, 4, or 5, and

any primary amine is optionally acetylated or alkylated.

In some examples, n1 is 1.

In some examples of the compound of Formula I, m'=0, n'=0, o'=0, and the compound is represented by Formula IC:



; wherein:

(Formula IC)

each p' is 1, 2, 3, or 4; and

each q' is 1, 2, 3, 4, or 5.

In some examples, each B_1 and B_2 is Formula F2.

In some examples, each Z1c is covalently conjugated to an indirect linker and each of the Z1c and the indirect linker in combination is selected from Formulae FFL-1 to FFL-101, which comprise substituent X; wherein X represents a point of covalent attachment either directly to an amine of X1 or to NH_2 when X1 is NH_2 or to OH when X1 is OH or to an amine that is covalently conjugated directly or indirectly to X1 or to an amine of Z1a.

In some examples, X1 is a polypeptide comprising an insulin receptor agonist having an A-chain and a B-chain.

In some examples, at least one Z1c comprises an alpha methyl group or a beta methyl group.

Also disclosed herein are methods of treatment. The disclosed methods may comprise treating a subject in need thereof, wherein the subject has a disease characterized by elevated glucose levels. The methods may comprise administering to a subject in need thereof a compound of Formula I, a pharmaceutically acceptable salt of a compound of Formula I, a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutical composition comprising a pharmaceutically acceptable salt of a compound of Formula I.

Also disclosed herein is a method of treating or preventing an endocrine and/or metabolic disease, in a subject in need thereof, comprising administering to said subject a compound of Formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof. In some examples, the compound of Formula (I) comprises a drug substance, wherein the drug substance is a polypeptide human hormone, an endocrine hormone, insulin, human insulin, glucagon, amylin, relaxin, GLP-1, oxyntomodulin, somatostatin, gastric inhibitory polypeptide, glucose-dependent insulinotropic polypeptide, a hybrid peptide comprising sequences from two or more human polypeptide hormones, or an analogue thereof.

In some examples, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, is administered simultaneously with a second agent or therapy. In some examples, the second agent is a drug substance, wherein the drug substance is a polypeptide human hormone, an endocrine hormone, insulin, human insulin, glucagon, amylin, relaxin, GLP-1, oxyntomodulin, somatostatin, gastric inhibitory polypeptide, glucose-dependent insulinotropic polypeptide, a hybrid peptide comprising sequences from two or more human polypeptide hormones, or an analogue thereof. In some examples, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition

comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, is administered concurrently with the second agent or therapy. In some examples, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, is administered sequentially with the second agent or therapy (e.g., where a compound of Formula (I) is administered initially and the second agent or therapy is administered subsequently or where the second agent or therapy is administered initially and the compound of Formula (I) is administered subsequently). In some examples, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, is administered in the same unit dosage form as the second agent or therapy. In some examples, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, is administered in a different unit dosage form from the second agent or therapy.

In at least one example, the pharmaceutical composition of the present disclosure may be for use in (or in the manufacture of medicaments for) the treatment of diseases characterized by elevated glucose in a subject such as diabetes. In at least one example, a therapeutically-effective amount of a pharmaceutical composition of the present disclosure may be administered to a subject diagnosed with diabetes or metabolic disease. In at least one example, the pharmaceutical composition of the present disclosure comprises at least one compound disclosed herein (e.g., Formula I, Z1c, Z1c-Linker) and at least one additional component selected from pharmaceutically acceptable carriers, pharmaceutically acceptable vehicles, and pharmaceutically acceptable excipients.

In some examples, the disclosed compounds comprise an insulin receptor agonist selected from insulin and an insulin analogue (e.g., where X1 is insulin or an insulin analogue). In some examples, X1 comprises an insulin having an A-chain and a B-chain, wherein the A-chain comprises a sequence selected from SEQ ID NOs 1, 25, 24051, and 24052, and the B-chain comprises a sequence selected from SEQ ID NOs 24060, 24061, 24062, 24063, 24064, and 25000–25397.

In some examples, X1 comprises an insulin having an A-chain and a B-chain, wherein:

the A-chain comprises a sequence selected from SEQ ID NOs 24051 and 24052,

the B-chain comprises a sequence selected from SEQ ID NOs 25095, 25229, 25232, 25236, 25305, 25308, 25312, and 25380-25397;

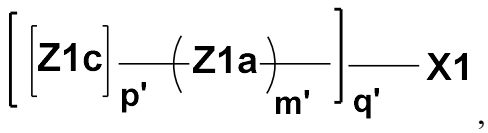
each Z1c is independently selected from FF12A, FF12B, FF12C, FF12D, FF116A, FF116B, FF116C, FF116D, and covalently conjugated either directly or via the indirect linker to one or more lysine residues in X1;

B_1 and B_2 is each F2; and

the indirect linker is independently selected from FL3, FL5, FL5A, FL5B, FL20-FL75, and stereoisomers thereof.

In some examples, the compound is selected from an insulin comprising an A-chain and a B-chain, wherein the A-chain comprises a sequence selected from SEQ ID NOs 24501 and 24502; and wherein the B-chain comprises a sequence selected from SEQ ID NOs 25229, 25232, 25305, 25308, 25312, 25236, 25095, and 25380-25397.

In an aspect, the present disclosure provides a compound of the following formula, or a stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof:



,

wherein:

X1 is a polypeptide comprising an insulin receptor agonist having an A-chain and a B-chain, wherein the A-chain comprises a sequence selected from SEQ ID NOs 1, 25, and 24051, and the B-chain comprises a sequence selected from SEQ ID NOs 24060, 24061, 24063, 25228, 25313, 25393, 25396, and 25397;

each Z1a independently comprises 1 to 50 amino acids connected together using amide or peptide bonds;

each Z1c is independently selected from Formulae FF12A, FF12B, FF114A, FF115A, FF116A, and FF225A, wherein each Z1c is covalently conjugated either directly or via an indirect linker to an amine of Z1a or to an amine of X1;

each m' is 0 or 1;

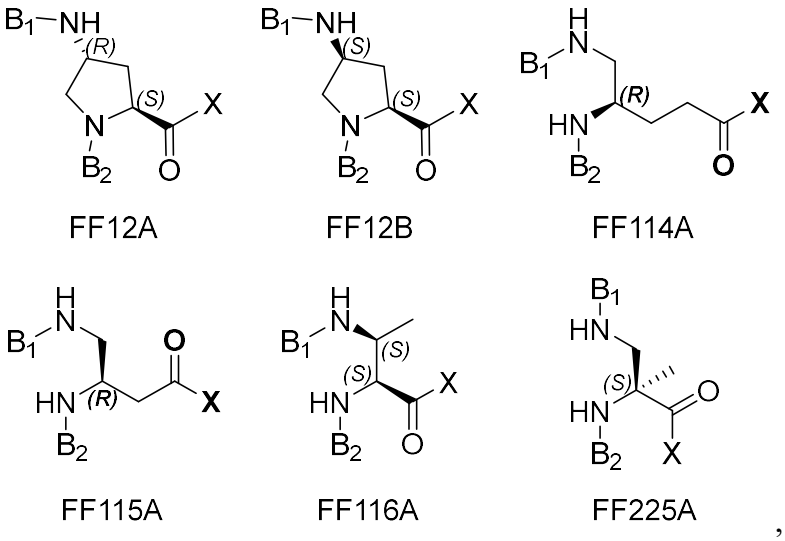
each p' is 1, 2, 3, 4, or 5; and

each q' is 1, 2, 3, 4, or 5, wherein when p' or q' is 2 or more, each corresponding Z1c is independently selected and may be the same or different and wherein when q' is 2 or more, each corresponding Z1a is independently selected and may be the same or different;

when m'=0, each Z1c is covalently conjugated either directly or via an indirect linker to an amine of X1, when m'=1 each Z1a is covalently conjugated via an amide or peptide bond to X1 and each Z1c is covalently conjugated either directly or via an indirect linker to an amine of Z1a;

and

wherein Formulae FF12A, FF12B, FF114A, FF115A, FF116A, and FF225A, are:



,

wherein X represents a point of covalent attachment either directly to an amine of X1 or to an amine that is covalently conjugated directly or indirectly to X1; and wherein B_1 and B_2, which may be identical or different, each independently represent an aromatic boron-containing group; and

wherein one or more positions of the compound may comprise an isotope.

In another aspect, the present disclosure provides a pharmaceutical composition comprising at least one compound as disclosed herein, or a stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides use of a compound as disclosed herein, or a stereoisomer or mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating diabetes, impaired glucose tolerance, hyperglycemia or metabolic syndrome.

In another aspect, the present disclosure provides a compound as disclosed herein, or a stereoisomer or mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, for use in therapy.

In some examples, the present disclosure provides a compound represented by Formula II, or a stereoisomer or a mixture of stereoisomers, or pharmaceutically acceptable salt thereof:

Z1c-Linker

(Formula II)

wherein the Z1c-Linker is selected from Formulae FFL-1 to FFL-101;

wherein X is selected from a leaving group (e.g., halogen, a N-hydroxysuccinimide (NHS) group, a 2,3,5,6-tetrafluorophenol (TFP) group, a pentafluorophenol (Pfp) group, or a sulfonate ester), NH_2, OH, and H; and

wherein B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group.

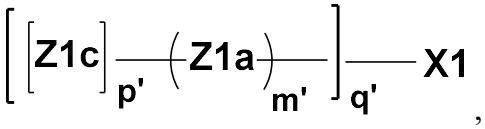
In some examples of the compound of Formula I, X1 comprises an insulin receptor agonist that is insulin or an insulin analogue having an A-chain and a B-chain. In some examples, one or more lysine residues and/or the N-terminus of the A- or B-chain are covalently conjugated as described by Formula I. In some examples the insulins or insulin analogues described herein are used as compounds (e.g., intermediate compounds) for the manufacture of conjugates described by Formula I. In some examples, the insulins or insulin analogues described herein are used in methods for preventing and/or treating an endocrine and/or metabolic disease, for example comprising administering any compound (e.g., modified insulin) of the examples described herein to a subject in need thereof, thereby treating the endocrine and/or metabolic disease.

DETAILED DESCRIPTION OF THE DISCLOSURE

While aromatic boron-containing compounds (e.g., groups) can bind to diol containing molecules, achieving selectivity using aromatic boron-containing compounds (which can act as

WHAT IS CLAIMED IS:

1. A compound of the following formula, or a stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof:



wherein:

X1 is a polypeptide comprising an insulin receptor agonist having an A-chain and a B-chain, wherein the A-chain comprises a sequence selected from SEQ ID NOs 1, 25, and 24051, and the B-chain comprises a sequence selected from SEQ ID NOs 24060, 24061, 24063, 25228, 25313, 25393, 25396, and 25397;

each Z1a independently comprises 1 to 50 amino acids connected together using amide or peptide bonds;

each Z1c is independently selected from Formulae FF12A, FF12B, FF114A, FF115A, FF116A, and FF225A, wherein each Z1c is covalently conjugated either directly or via an indirect linker to an amine of Z1a or to an amine of X1;

each m' is 0 or 1;

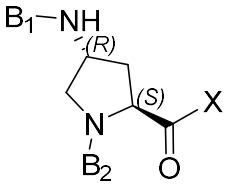
each p' is 1, 2, 3, 4, or 5; and

each q' is 1, 2, 3, 4, or 5, wherein when p' or q' is 2 or more, each corresponding Z1c is independently selected and may be the same or different and wherein when q' is 2 or more, each corresponding Z1a is independently selected and may be the same or different;

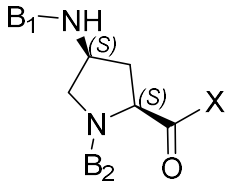
when m'=0, each Z1c is covalently conjugated either directly or via an indirect linker to an amine of X1, when m'=1 each Z1a is covalently conjugated via an amide or peptide bond to X1 and each Z1c is covalently conjugated either directly or via an indirect linker to an amine of Z1a;

and

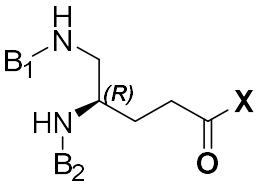
wherein Formulae FF12A, FF12B, FF114A, FF115A, FF116A, and FF225A, are:



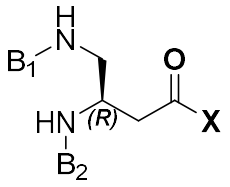
FF12A



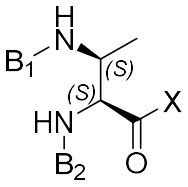
FF12B



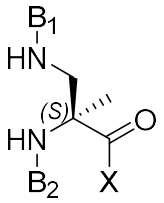
FF114A



FF115A



FF116A



FF225A ,

wherein X represents a point of covalent attachment either directly to an amine of X1 or to an amine that is covalently conjugated directly or indirectly to X1; and wherein B_1 and B_2, which may be identical or different, each independently represent an aromatic boron-containing group; and

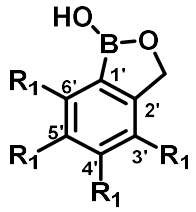
wherein one or more positions of the compound may comprise an isotope.

2. The compound of claim 1, wherein at least one Z1c comprises a beta methyl group.

3. The compound of claim 1, wherein at least one Z1c comprises an alpha methyl group.

4. The compound of claim 1, wherein the B_1 and the B_2 are each independently Formula F2,

wherein Formula F2 is:



(F2) ;

wherein:

a first R_1 represents (C=O)---* or $(CH_2)_m$(C=O)---*, wherein ---* represents the attachment point to the rest of Z1c, and m is 1, 2, 3, 4, 5, 6, or 7; and

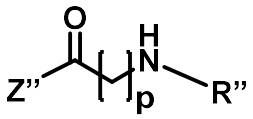
each remaining R_1 is independently selected from H, F, Cl, Br, I, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_{m''}CH_3$, $(SO_2)NH$-CH_3, $(SO_2)NH(CH_2)_{m''}CH_3$, and OCF_3, wherein m'' is 1, 2, 3 ,4, 5, 6, or 7.

5. The compound of claim 4, wherein the first R_1 is (C=O)---*.

6. The compound of claim 4, wherein (a) each remaining R_1 is independently selected from H, CF_3, and F; or (b) two remaining R_1 are H and one remaining R_1 is CF_3 or F.

7. The compound of claim 4, wherein each remaining R_1 is H.

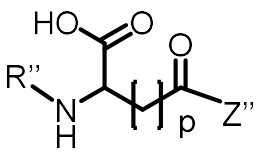
8. The compound of claim 1, wherein one or more Z1c is covalently conjugated to X1 via the indirect linker, and wherein each indirect linker is independently selected from



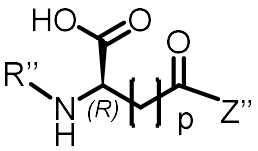
(FL3)

Formula FL3,

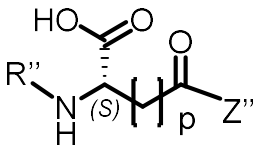
wherein p is 2 or 3;



(FL5)



(FL5A)



(FL5B)

Formulae FL5, FL5A, and FL5B,

wherein p is 1 or 2; and



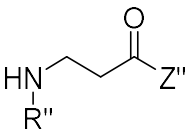
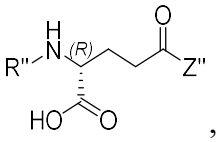
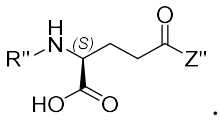
FL21 , or stereoisomers thereof;

wherein:

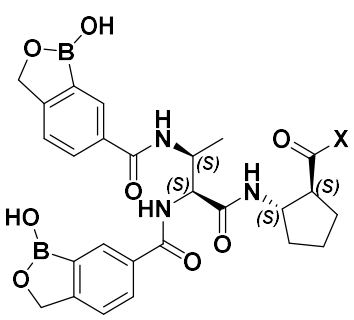
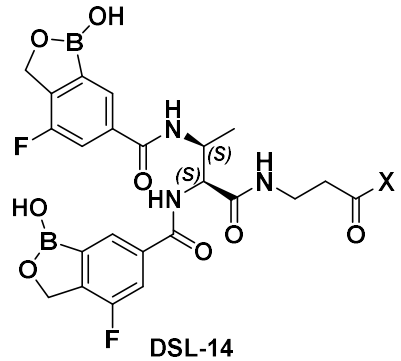
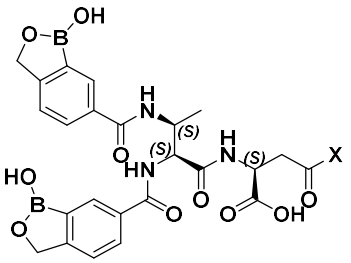
R'' represents a covalent bond, directly or indirectly, to Z1c; and

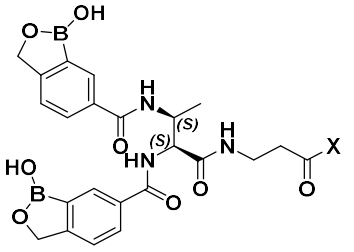
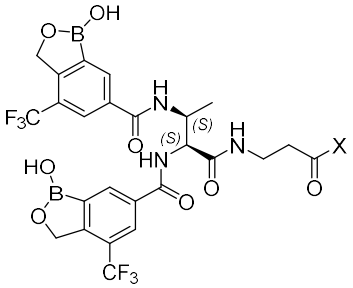
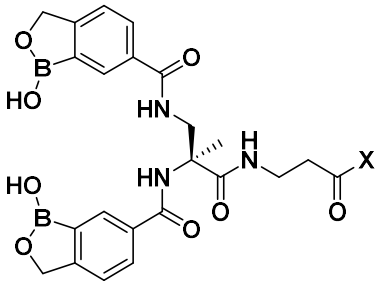
Z'' represents a covalent bond, directly or indirectly, to X1 or to Z1a.

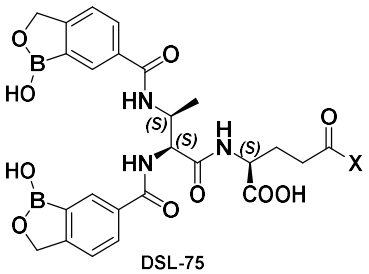
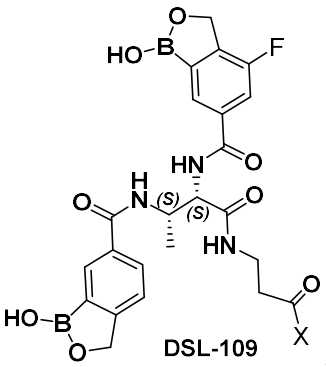
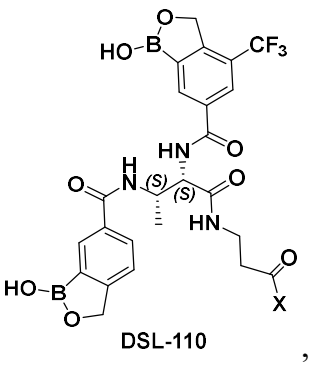
9. The compound of claim 8, wherein each indirect linker is selected from:


, 
, and 
.

10. The compound of claim 1, wherein each of the Z1c is covalently conjugated to the indirect linker to form a Z1c-Linker independently selected from:


DSL-9 , 
DSL-14 , 
DSL-18 ,

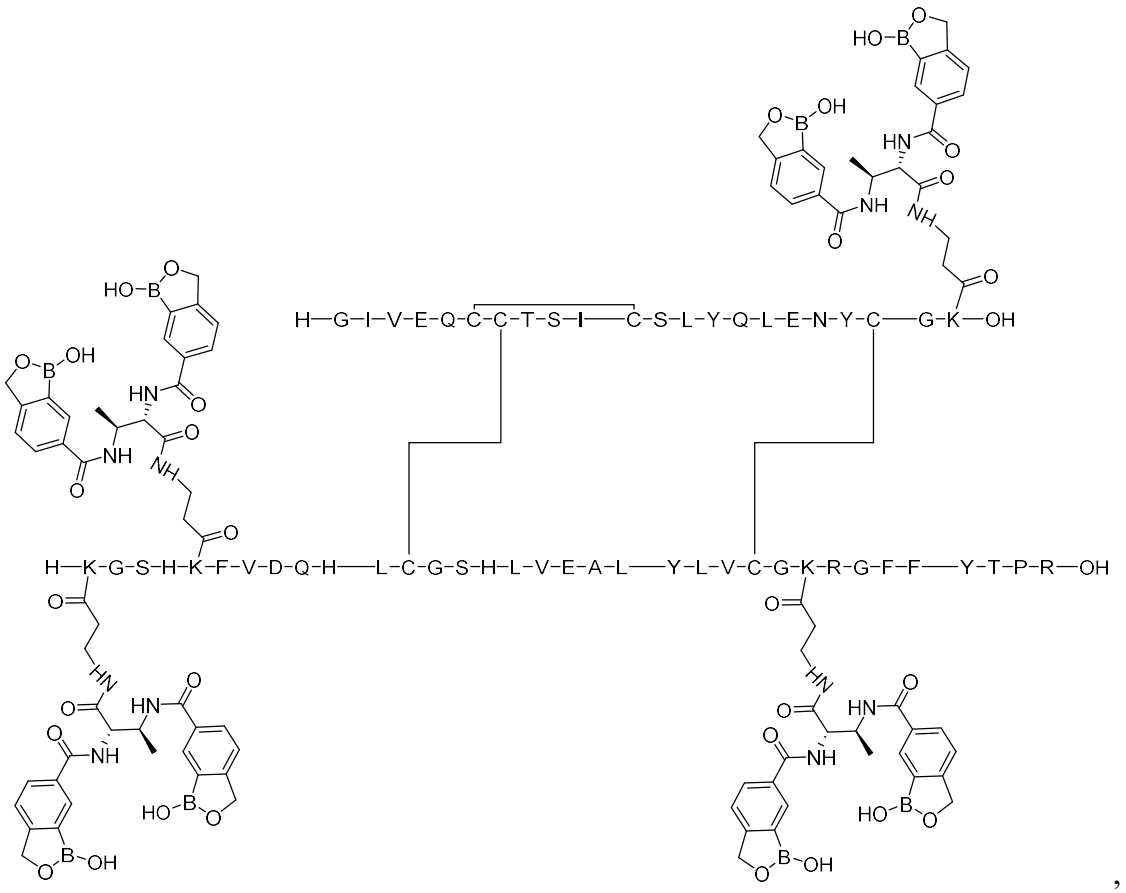

DSL-66 , 
DSL-69 , 
DSL-73 ,


DSL-75 , 
DSL-109 , and 
DSL-110 ,

wherein X represents a point of covalent attachment directly to the amine in X1.

11. The compound of claim 2, wherein the compound is

Example 3:

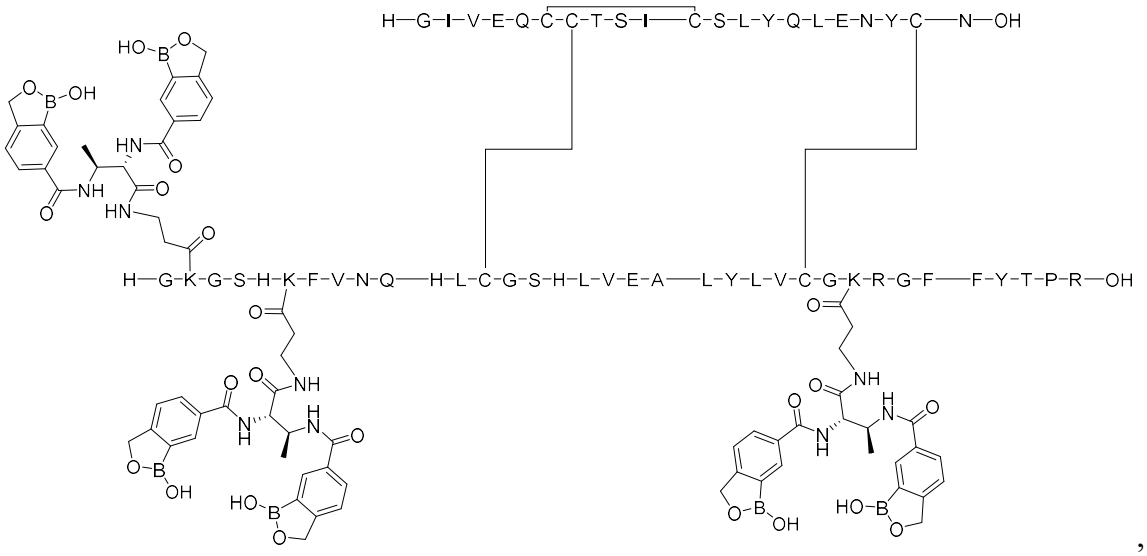


,

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 2, wherein the compound is

Example 19:

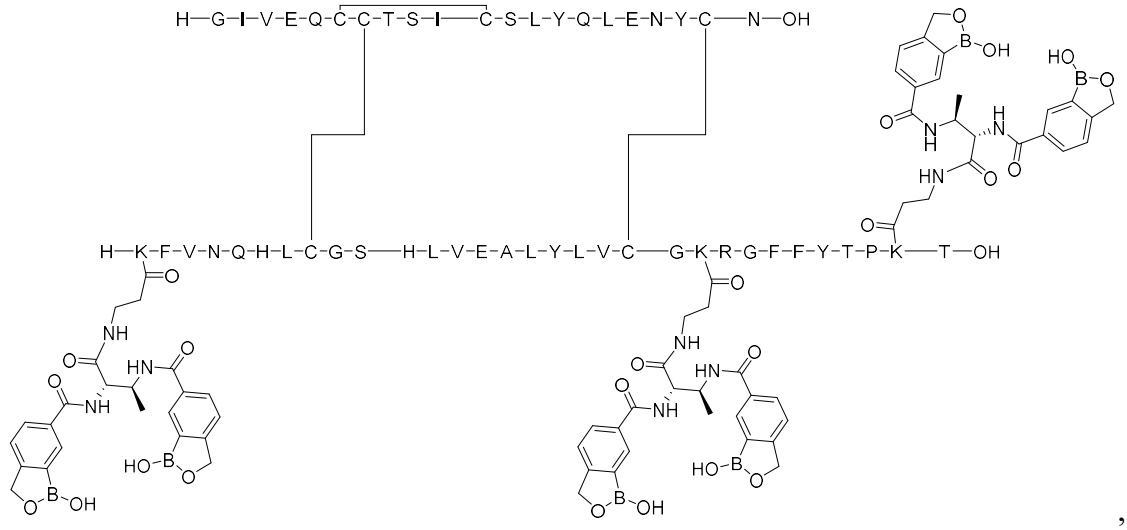


,

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 2, wherein the compound is

Example 23:

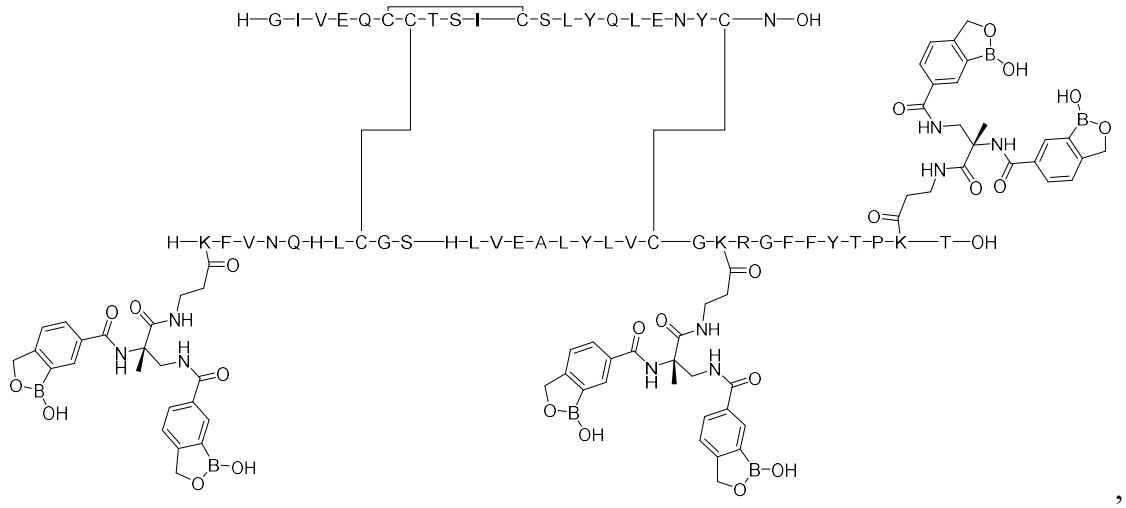


,

or a pharmaceutically acceptable salt thereof.

14. The compound of claim 3, wherein the compound is

Example 27:

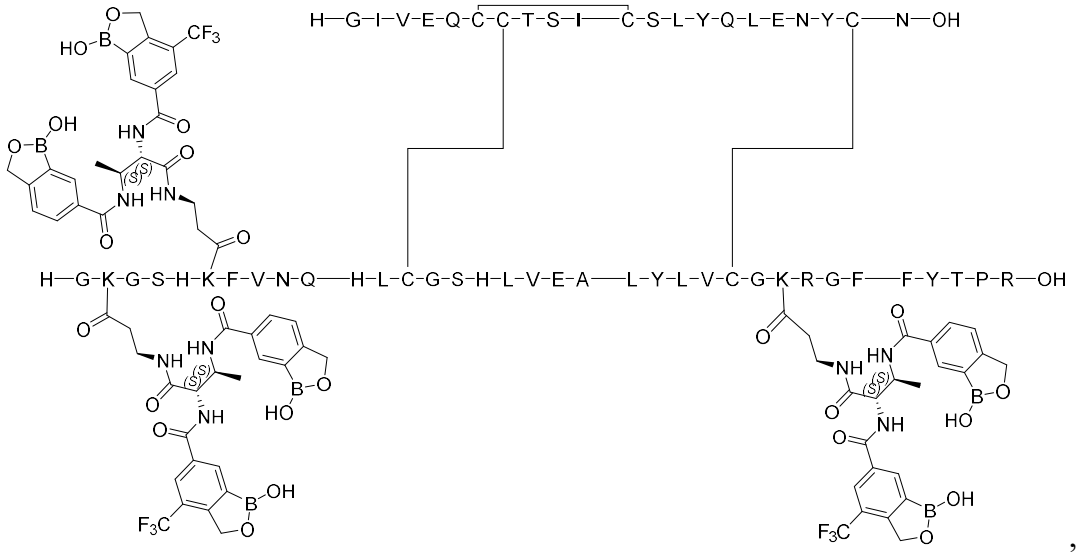


, or

a pharmaceutically acceptable salt thereof.

15. The compound of claim 2, wherein the compound is

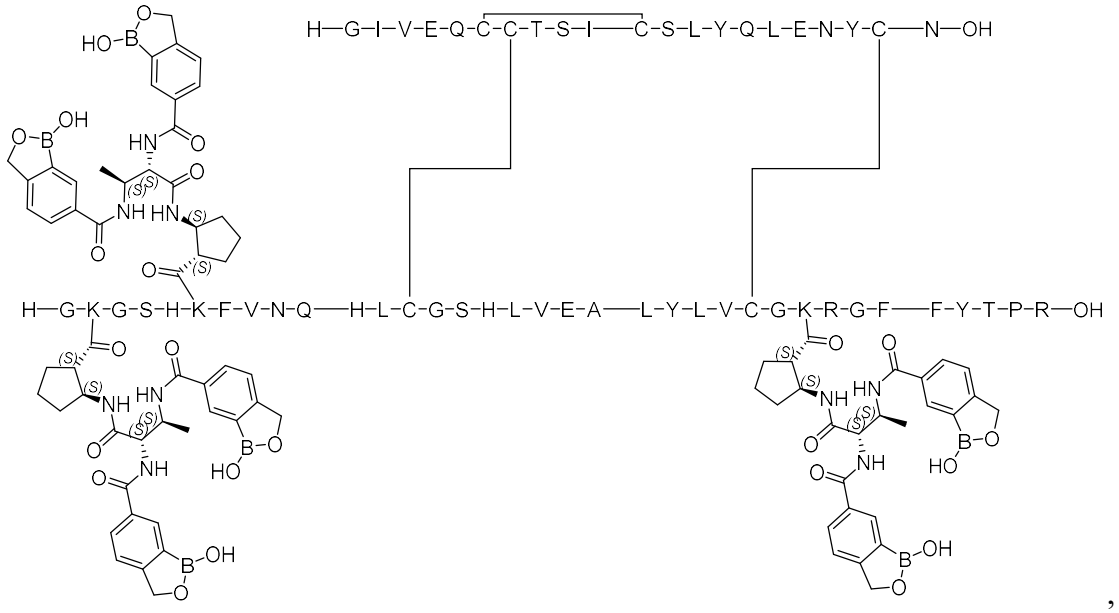
Example 41:



or a pharmaceutically acceptable salt thereof.

16. The compound of claim 2, wherein the compound is

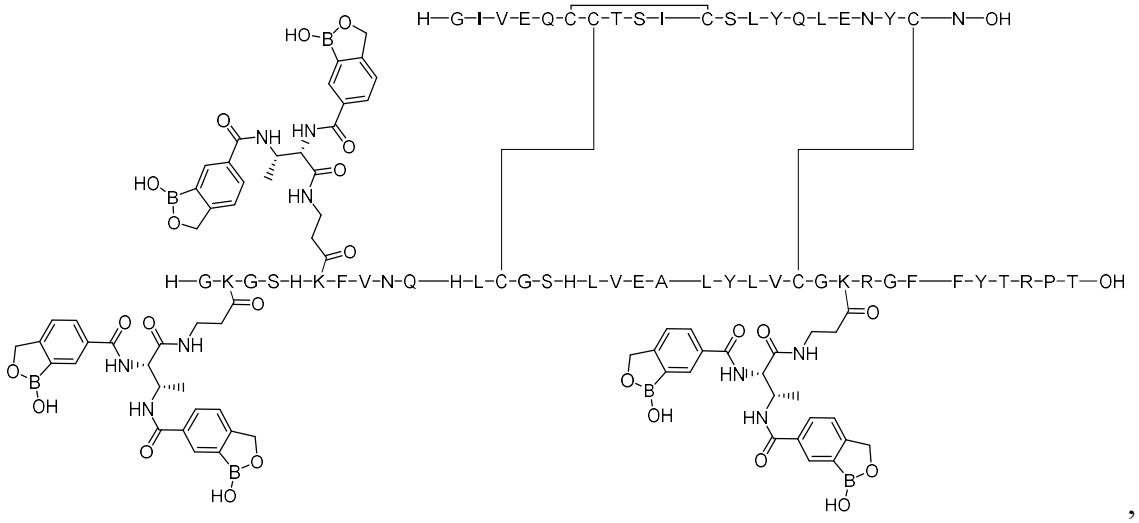
Example 44:



or a pharmaceutically acceptable salt thereof.

17. The compound of claim 2, wherein the compound is

Example 48:

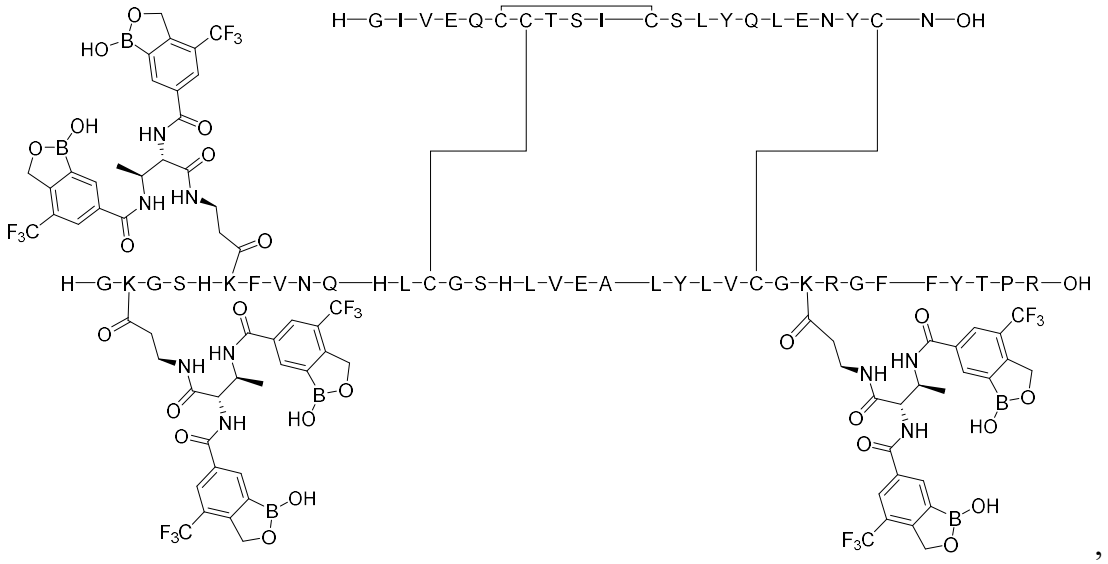


,

or a pharmaceutically acceptable salt thereof.

18. The compound of claim 2, wherein the compound is

Example 55:

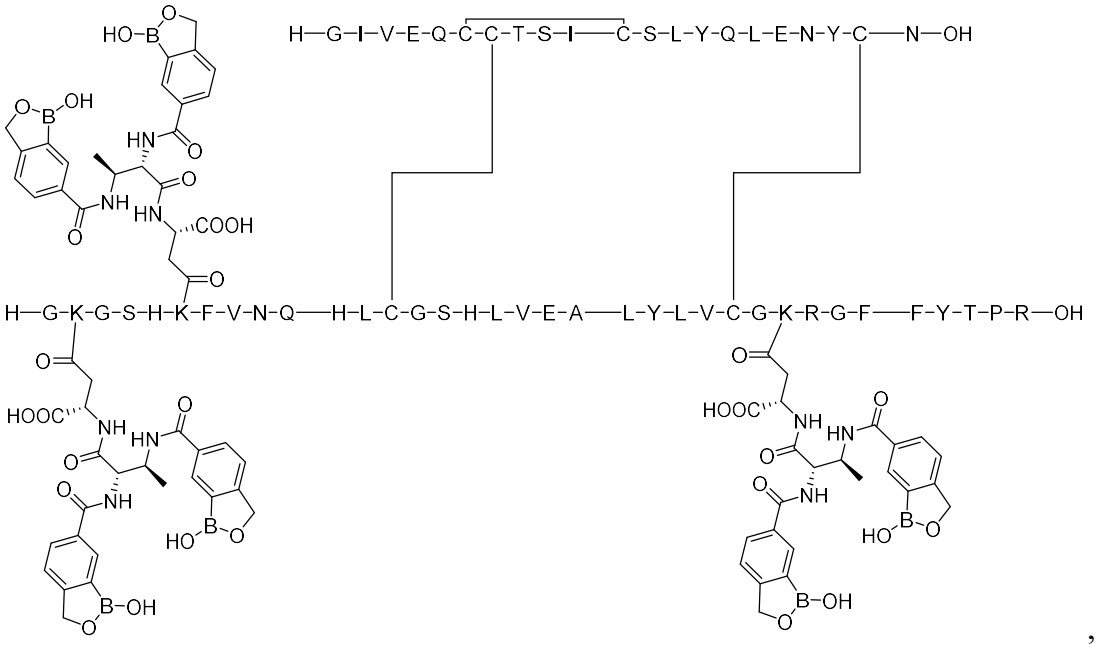


,

or a pharmaceutically acceptable salt thereof.

19. The compound of claim 2, wherein the compound is

Example 56:

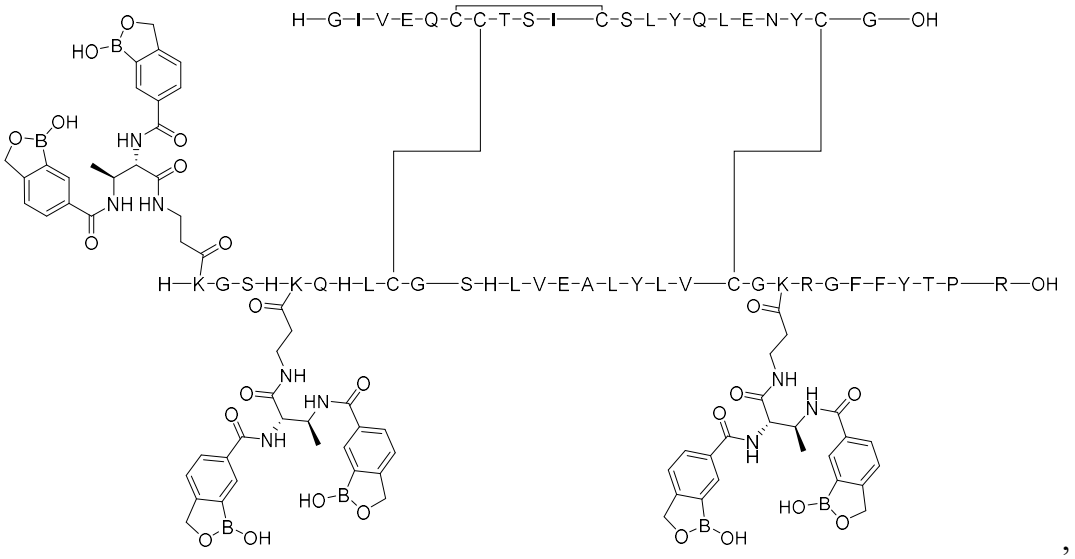


,

or a pharmaceutically acceptable salt thereof.

20. The compound of claim 2, wherein the compound is

Example 69:

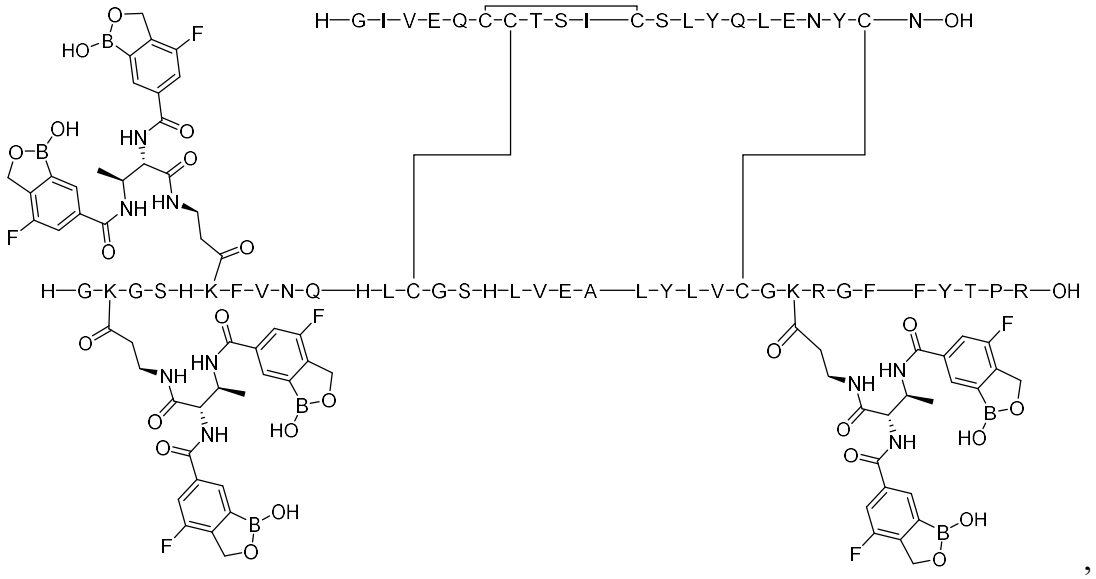


,

or a pharmaceutically acceptable salt thereof.

21. The compound of claim 2, wherein the compound is

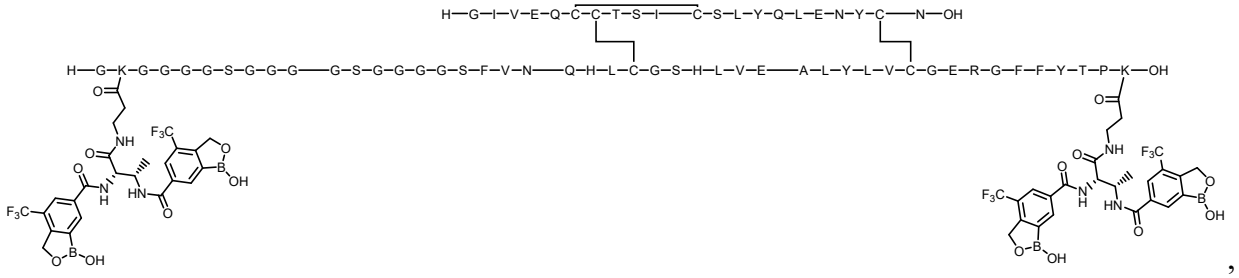
Example 76:



or a pharmaceutically acceptable salt thereof.

22. The compound of claim 2, wherein the compound is

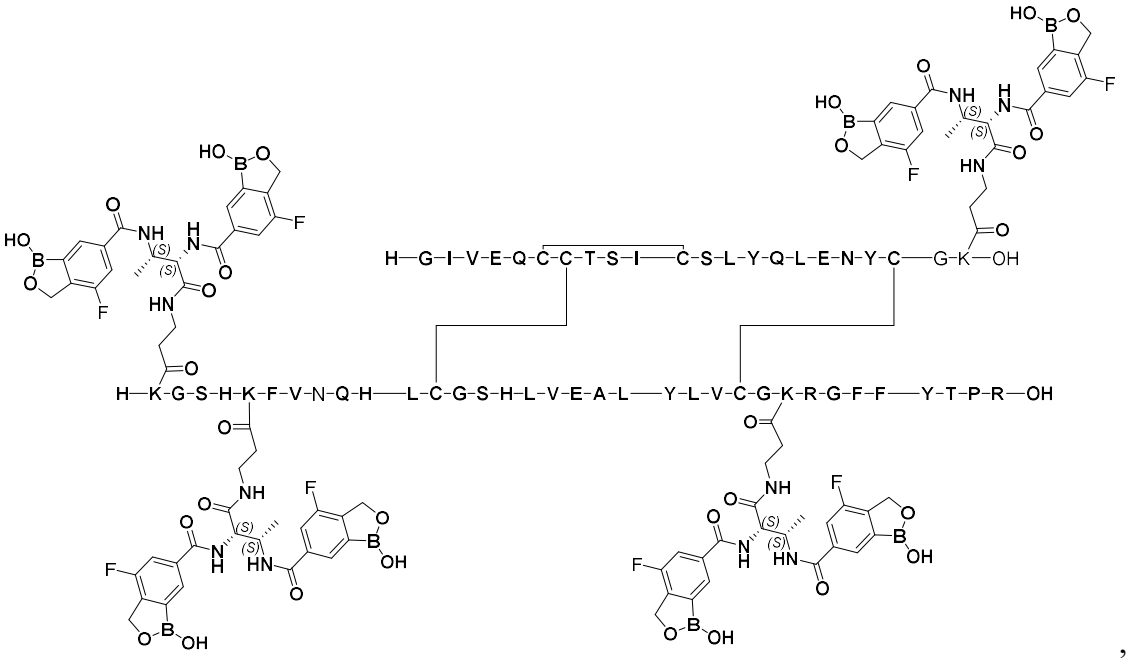
Example 131:



or a pharmaceutically acceptable salt thereof.

23. The compound of claim 2, wherein the compound is

Example 140:

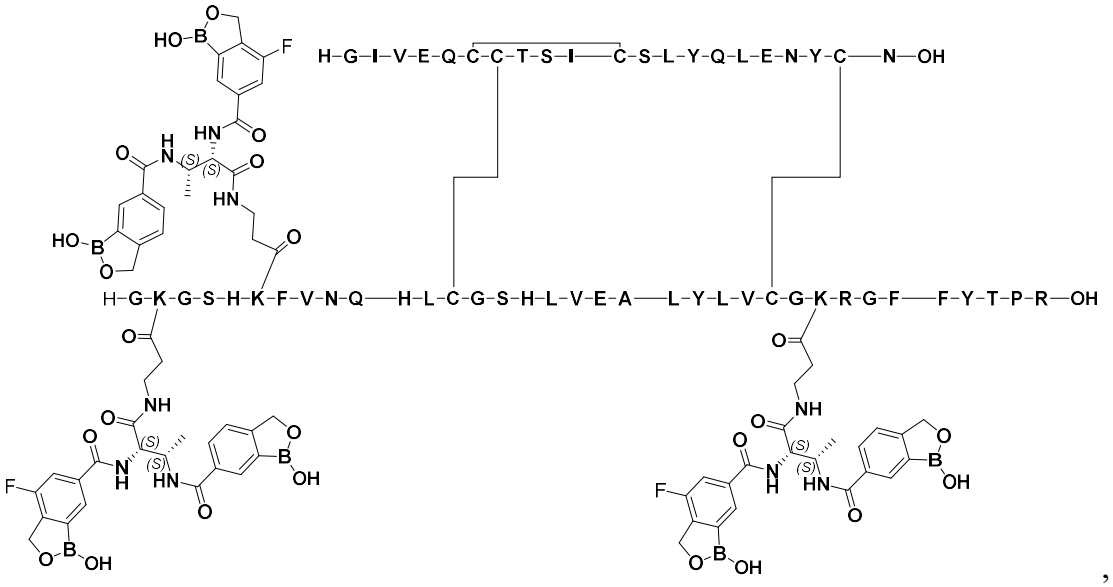


,

or a pharmaceutically acceptable salt thereof.

24. The compound of claim 2, wherein the compound is

Example 152

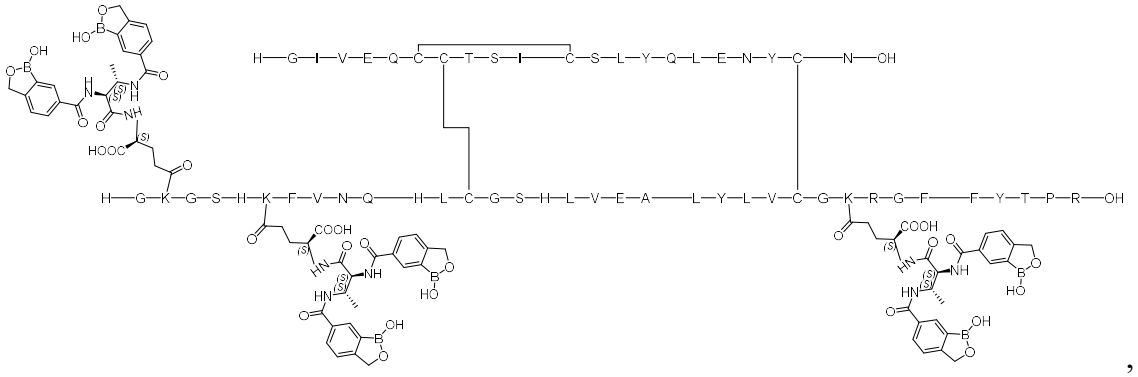


,

or a pharmaceutically acceptable salt thereof.

25. The compound of claim 2, wherein the compound is

Example 154

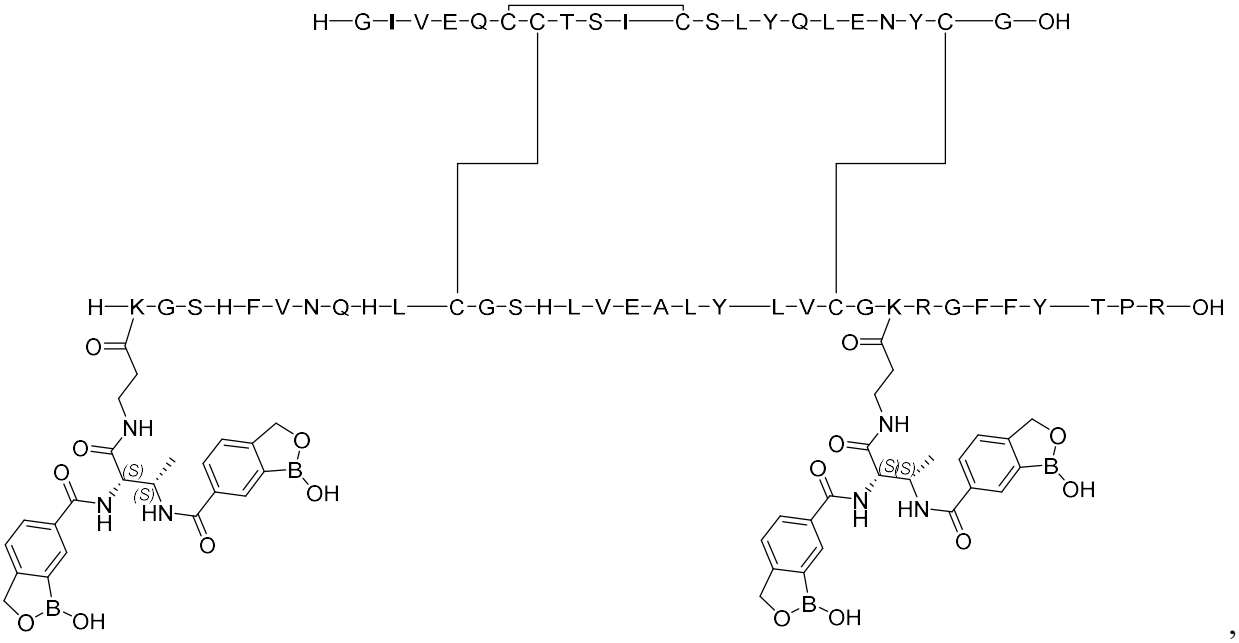


,

or a pharmaceutically acceptable salt thereof.

26. The compound of claim 2, wherein the compound is

Example 156:



,

or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising at least one compound according to claim 1, or a stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

28. Use of a compound of claim 1, or a stereoisomer or mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating diabetes, impaired glucose tolerance, hyperglycemia or metabolic syndrome.

29. A compound of claim 1, or a stereoisomer or mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, for use in therapy.