CONJUGATES FOR SELECTIVE RESPONSIVENESS TO VICINAL DIOLS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to and the benefit of U.S. Provisional Patent Application No. 63/002,662, filed March 31, 2020 and titled "INSULINS CONTAINING MODIFIED AMINO ACIDS," the entire content of which is incorporated herein by reference.

SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file titled "203819_ST25.txt," created March 30, 2021, and is 8795 bytes in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND

Boronic acids are generally considered Lewis acids that have a tendency to bind to hydroxyls, because, as Lewis acids, boronic acids can form complexes with Lewis bases such as, for example, hydroxide anions. Thus, molecules containing boronates including boronic acids have a general tendency to bind hydroxyl groups. This binding tendency can be used for detection of hydroxyl-containing groups by boronated labeling reagents wherein the boronate groups bind to the hydroxyls and, depending on the solvent and buffer conditions, the boronates can form hydrolysable boronate-ester bonds to the hydroxyl groups of hydroxyl containing molecules. The strength of the boronate ester bond and its reversibility is generally influenced by a variety of factors including the type of boronates, buffer conditions, and the composition of the hydroxyl group-containing molecules to which they bind.

SUMMARY

In one aspect, there is provided a compound represented by Formula I:

Z−R

(Formula I),

wherein, in Formula I,

R is selected from Formulae FF1-FF24; and

Z is selected from one of:

a) NH_2 or OH,

b) a covalent linkage, either directly or via an optional linker, to a drug substance,

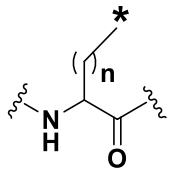
c) a covalent linkage, either directly or via the optional linker, to an N-terminal amine or an epsilon amino group of one or more amino acids in a polypeptide drug substance, and

d) a group represented by J-SCH_2—ø , J-$S(CH_2)_2$—ø, J—NH—ø, J—NH—(the optional linker)—ø, J—$S(CH_2)_kNH$—ø, or J—triazole$(CH_2)_kNH$—ø;

wherein —ø is the covalent bond towards R;

index k is an integer in the range of 3 to 14; and

J is an amino acid or one or more amino acids in a polypeptide drug substance, wherein each of the one or more amino acids in the polypeptide drug substance is represented by Formula I':



(Formula I'),

wherein, in Formula I',

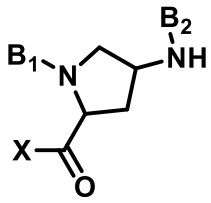
 and  indicate points of attachment to remaining portions of the polypeptide drug substance;

* indicates the point of attachment to the remaining portion of Z; and

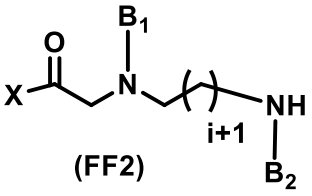
index n is an integer in the range of 1 to 8,

wherein for Formulae FF1-FF24:

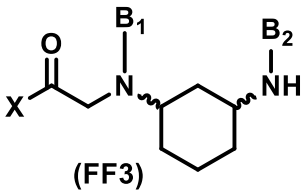
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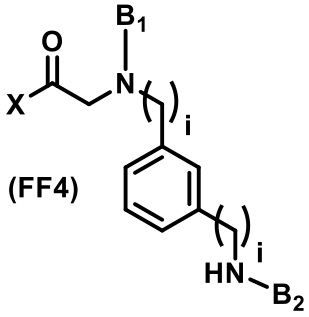
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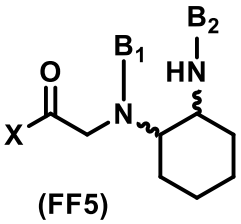
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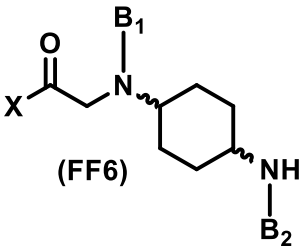
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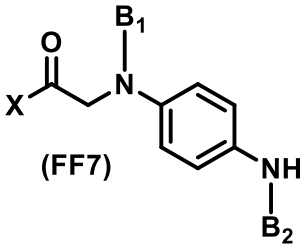
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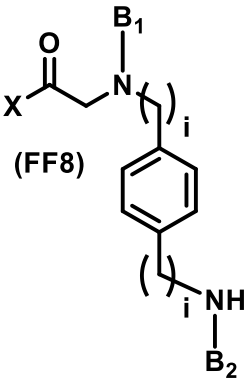
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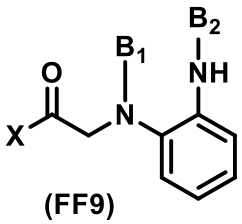
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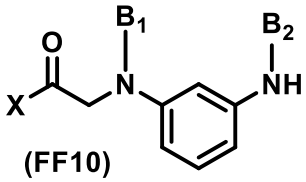
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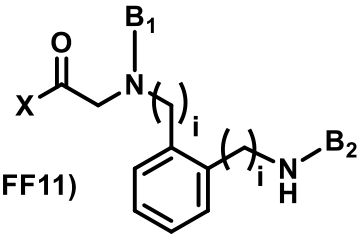
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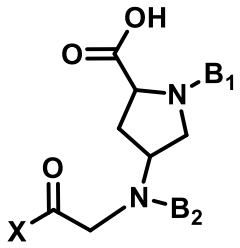
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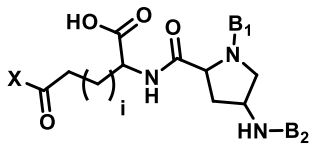


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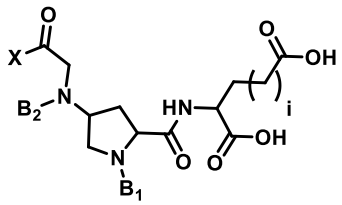


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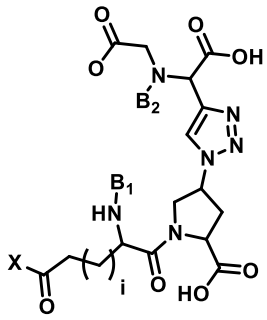
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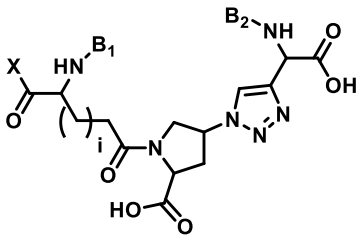
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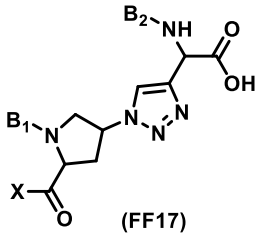
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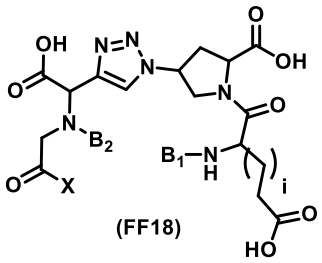
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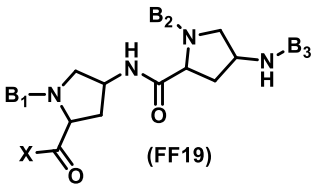
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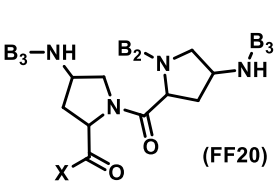
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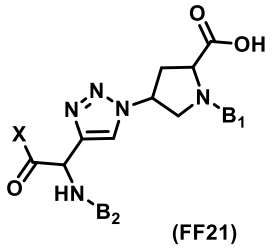
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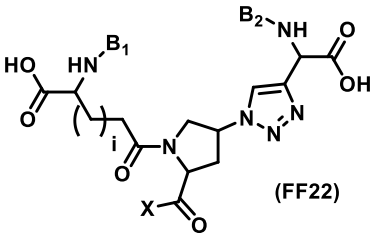
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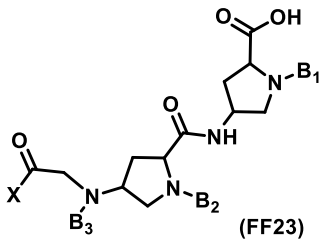
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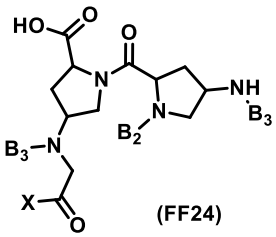
(FF21)



(FF22)



(FF23)



(FF24)

, wherein

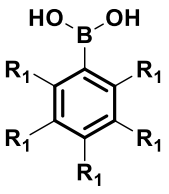
X represents a covalent linkage, either directly or via the optional linker, towards Z in Formula I;

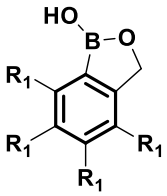
index i is an integer in the range of 1 to 20;

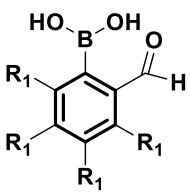
B_1 and B_2 are identical or different, and each independently represent a group selected from Formulae F1-F9; and

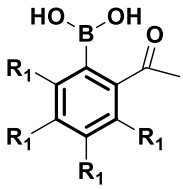
B_3 represents a group selected from Formulae F1-F11,

1d

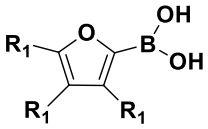

(F1)

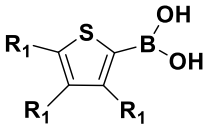

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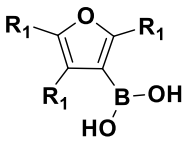

(F3)

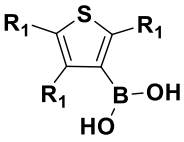

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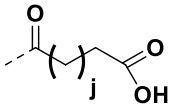

(F5)


(F6)


(F7)


(F8)


(F9)


F10


F11

, wherein, for each of Formulae F1-F9:

one R_1 represents (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R in Formula I;

none, one, or two R_1 each independently represent F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CF_3, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, —$(SO_2)NH(CH_2)_mCH_3$, or OCF_3,

index m is an integer in the range of 1 to 14;

one R_1 in F5 represents $B(OH)_2$, and

all remaining R_1 represent H, and

in Formula F10, index j is an integer in the range of 1 to 13.

In another aspect, there is provided a compound represented by Formula II:

Z−R

(Formula II),

wherein, in Formula II, either:

(i) R is selected from Formulae FF25-FF31;

B_1 and B_2 in FF25-FF31 are identical or different, and are each independently selected from Formulae F12-F19; and

Z is NH_2 and is not conjugated to any drug substance;

or

(ii) R is selected from Formulae FF25-FF31;

B_1 and B_2 are each independently selected from Formulae F20-F27; and

Z is selected from one of:

a) OH

b) a covalent linkage, either directly or via an optional linker, to a drug substance,

c) a covalent linkage, either directly or via the optional linker, to an N-terminal amine or an epsilon amino group of one or more amino acids in a polypeptide drug substance, and

d) a group represented by J-SCH_2—ø , J-$S(CH_2)_2$—ø, J—NH—ø, J—NH—(the optional linker)—ø, J—$S(CH_2)_kNH$—ø, or J—triazole$(CH_2)_kNH$—ø,

wherein —ø is the covalent bond towards R,

index k is an integer in the range of 3 to 14; and

J is an amino acid or one or more amino acids in a polypeptide drug substance, wherein each of the one or more amino acids in the polypeptide drug substance is represented by Formula II';

or

(iii) R is selected from Formulae FF32-FF33,

B_1 and B_2 in FF32 are each independently selected from Formulae F28-F35;

B_1 and B_2 in FF33 are each independently selected from Formulae F36-F43; and

Z is selected from one of:

a) a drug substance,

b) a covalent linkage, either directly or via an optional linker, to the N-terminal amine or the epsilon amino group of an amino acid in a polypeptide drug substance, and

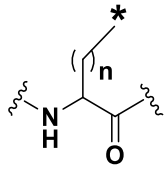
c) a group represented by J-SCH_2—ø , J-$S(CH_2)_2$—ø, J—NH—ø, J—NH—(the optional linker)—ø, J—$S(CH_2)_kNH$—ø, or J—triazole$(CH_2)_kNH$—ø,

wherein —ø is the covalent bond towards R,

index k is an integer in the range of 3 to 14; and

J is an amino acid or one or more amino acids in a polypeptide drug substance, wherein each of the one or more amino acids in the polypeptide drug substance is represented by Formula II';

wherein, for Formula II':



(Formula II'),

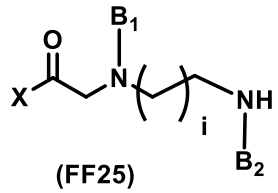
and indicate points of attachment to remaining portions of the polypeptide drug substance;

* indicates the point of attachment to the remaining portion of Z; and

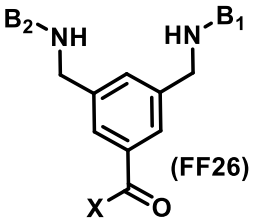
index n is an integer in the range of 1 to 8;

wherein for Formulae FF25-FF33:

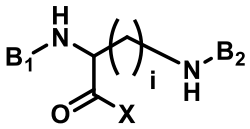
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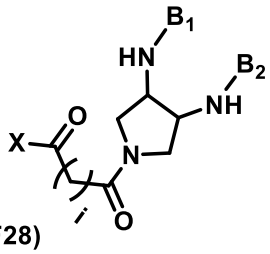
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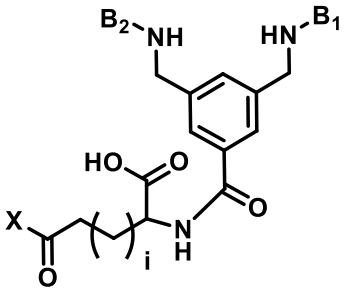
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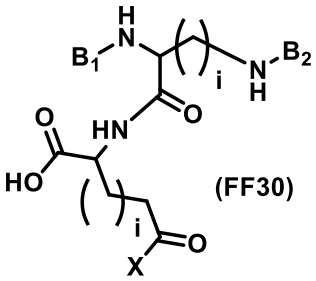
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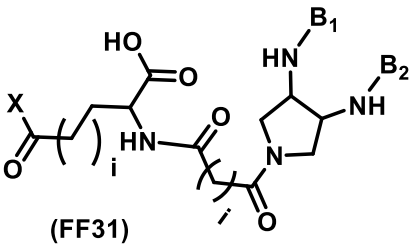
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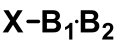
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(FF30)



(FF31)



(FF32)



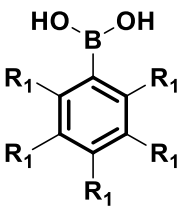
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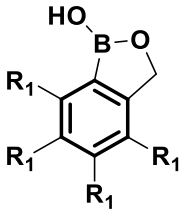
X represents a covalent linkage, either directly or via the optional linker, towards Z in Formula II; and

index i is an integer in the range of 1 to 20;

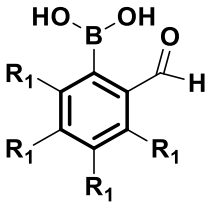
wherein, for each of Formulae F12-F19:



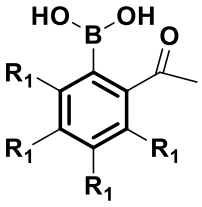
(F12)



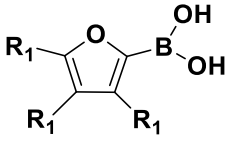
(F13)



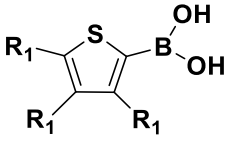
(F14)



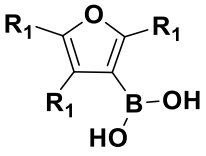
(F15)



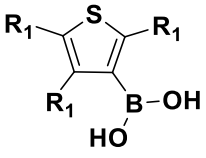
(F16)



(F17)



(F18)



(F19)

,

one R_1 from either B_1 or B_2 represents a covalent linkage, either directly or via an optional linker, to a drug substance;

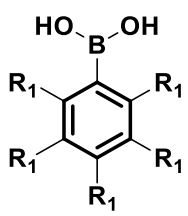
one R_1 in each of B_1 and B_2 is (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R in Formula II;

none, one, or two R_1 in each of B_1 and B_2 independently represent COOH, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CF_3, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, —$(SO_2)NH(CH_2)_mCH_3$ or OCF_3;

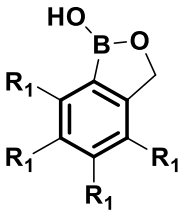
index m is an integer in the range of 1 to 14; and

all remaining R_1 represent H;

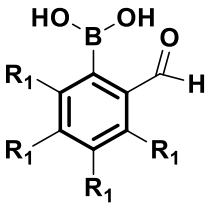
wherein, for each of Formulae F20-F25:



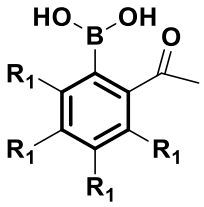
(F20)



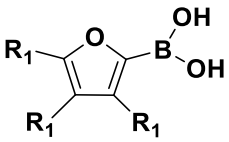
(F21)



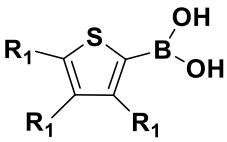
(F22)



(F23)



(F24)



(F25)

,

one R_1 is (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R in Formula II;

either:

(a) one or two R_1 on the same B_1 and/or B_2 represent COOH, wherein at least one COOH is not conjugated to a drug substance, and/or

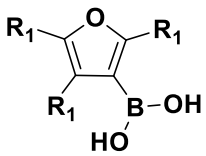
(b) one or two R_1 each independently represent NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, —$(SO_2)NH(CH_2)_mCH_3$, wherein index m is an integer in the range of 1 to 14, and

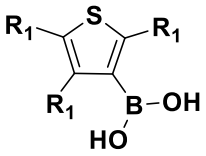
none, one, or two R_1 each independently represent NO_2, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CH_3, CF_3 or OCF_3, and

all remaining R_1 represent H;

1i

wherein, for each of Formulae F26-F27:


(F26)


(F27)

,

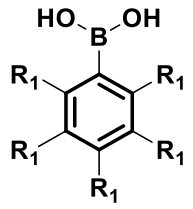
one R_1 is (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R in Formula II;

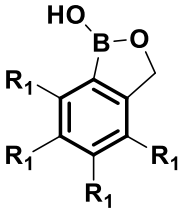
none, one, or two R_1 each independently represent COOH, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CF_3, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —(SO_2)NH CH_3, —$(SO_2)NH(CH_2)_mCH_3$ or OCF_3;

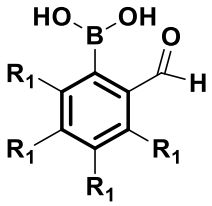
index m is an integer in the range of 1 to 14; and

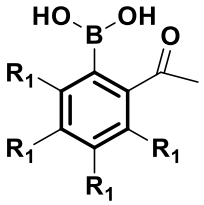
all remaining R_1 represent H;

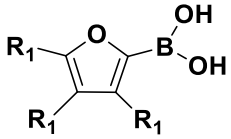
wherein, for each of Formulae F28-F35:

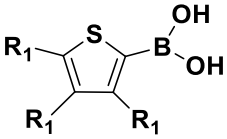

(F28)

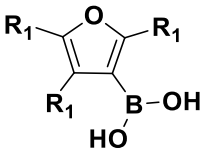

(F29)

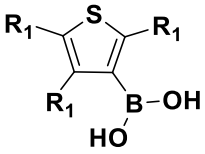

(F30)


(F31)


(F32)


(F33)


(F34)


(F35)

,

one R_1 in B_1 represents (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent linkage, either directly or via an optional linker, to Z in Formula II;

one R_1 for each of B_1 and B_2 is a covalent linkage between B_1 and B_2, wherein the covalent linkage is selected from –(S=O)–, –(S(=O)(=O)–, –(CF_2)–,–(C=O)–, —$(CH_2)_m$ $SCH_2CO(CH_2)_k$ —, —$(CH_2)_m$ $S(CH_2)_2CO(CH_2)_k$ —, and —$(CH_2)_m$ $(CO)NH(CH_2)_k$—;

either (i) two R_1 groups in B_2 are COOH and these two R_1 groups are not conjugated to a drug substance, or (ii) one or two R_1 in either B_1 and/or B_2 each independently represent NO_2, CH=O, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, or —$(SO_2)NH(CH_2)_mCH_3$;

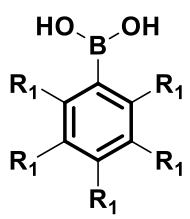
none, one, or two R_1 in either B_1 and/or B_2 each independently represent CH=O, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CH_3, CF_3, CHF_2, or OCF_3;

the remaining R_1 represent H;

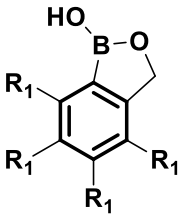
index k is an integer in the range of 1 to 7; and

index m is an integer in the range of 1 to 7;

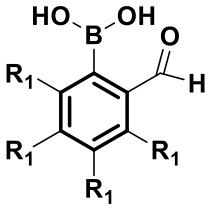
wherein, for each of Formulae F36-F43:



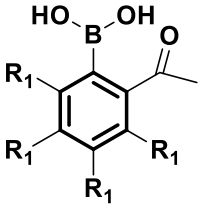
(F36)



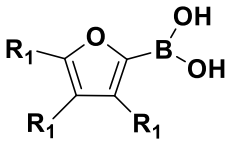
(F37)



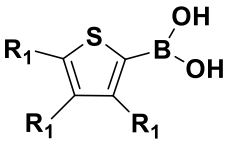
(F38)



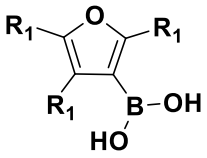
(F39)



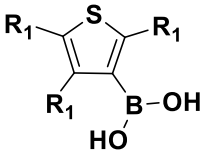
(F40)



(F41)



(F42)



(F43)

one R_1 for each of B_1 and B_2 is a covalent linkage to a sulfoximine group such that B_1 and B_2 are connected together by the sulfoximine group, and wherein the amino group of the sulfoximine is covalently linked, either directly through an acid containing linker or via an optional linker, to Z in Formula II;

either (i) two R_1 groups in B_1 and/or B_2 are COOH and these two R_1 groups are not conjugated to a drug substance, or (ii) one or two R_1 in either B_1 and/or B_2 each independently represent NO_2, CH=O, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, or —$(SO_2)NH(CH_2)_mCH_3$;

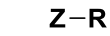
none, one, or two R_1 in either B_1 and/or B_2 each independently represent CH=O, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CH_3, CF_3, CHF_2, or OCF_3;

the remaining R_1 represent H;

index k is an integer in the range of 1 to 7; and

index m is an integer in the range of 1 to 7.

In another aspect, there is provided a compound comprising a drug substance, wherein the drug substance comprises an insulin and the insulin contains one or more modified amino acids represented by Formula III:



(Formula III),

wherein, in Formula III,

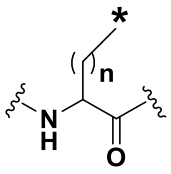
R is selected from Formulae FF1-FF24; and

Z is selected from an optional linker, J-SCH_2—ø , J-$S(CH_2)_2$—ø, J—NH—ø, J—NH(CO) linker—ø, J—$S(CH_2)_kNH$—ø, and J—triazole$(CH_2)_kNH$—ø,

wherein —ø is the covalent bond towards R,

index k is an integer in the range of 3 to 14; and

J is described by Formula III':



(Formula III'),

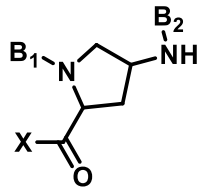
wherein, in Formula III':

 and  indicate points of attachment to remaining portions of the insulin;

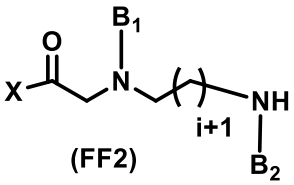
* indicates the point of attachment to the remaining portion of Z; and

index n is an integer in the range of 1 to 8;

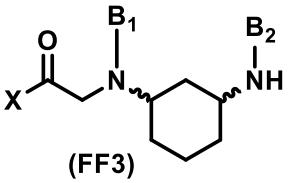
wherein for Formulae FF1-FF24:



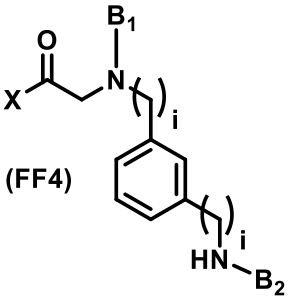
(FF1)



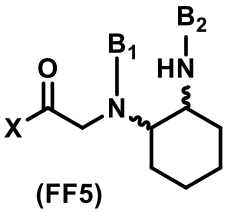
(FF2)



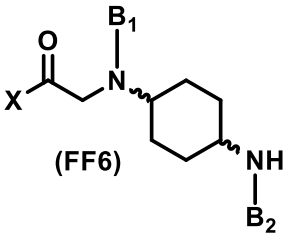
(FF3)



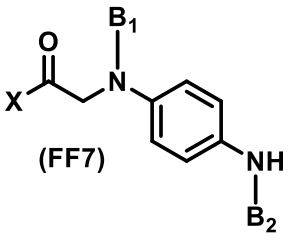
(FF4)



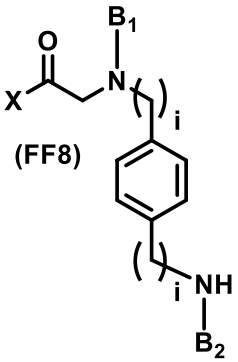
(FF5)



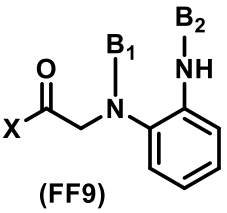
(FF6)



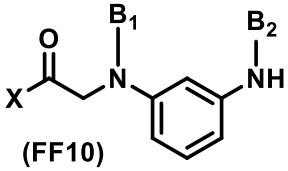
(FF7)



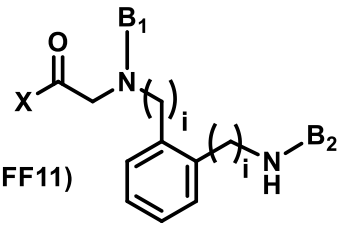
(FF8)



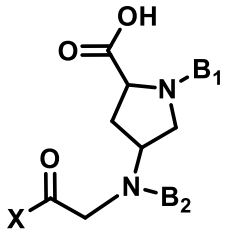
(FF9)



(FF10)

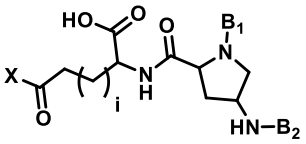


(FF11)

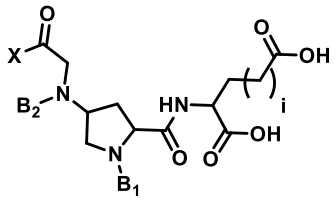


(FF12)

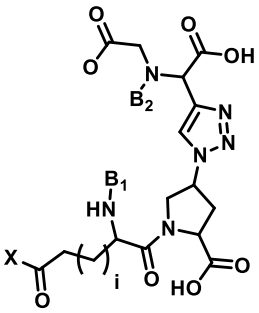
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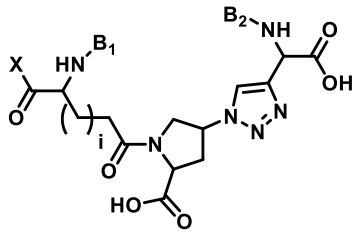
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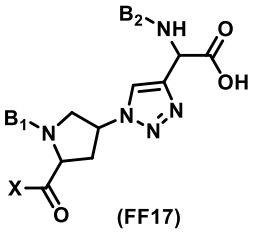
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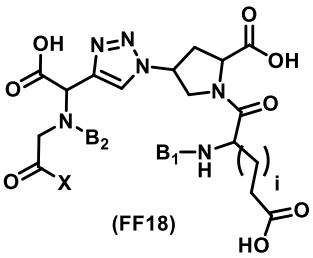
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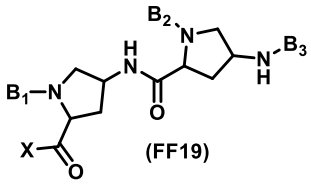
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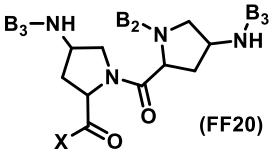
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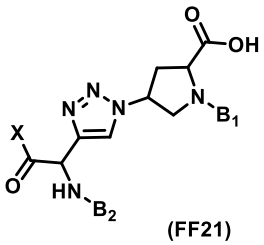
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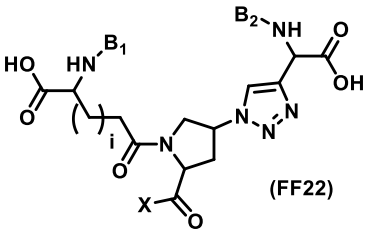
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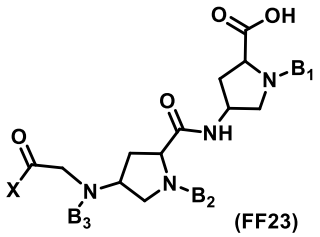
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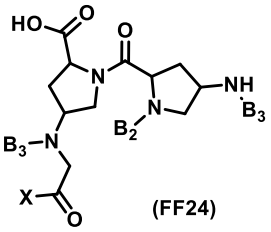
(FF21)



(FF22)



(FF23)



(FF24)

,

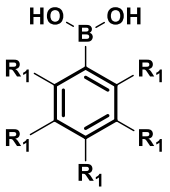
X represents a covalent linkage, either directly or via the optional linker, towards Z in Formula III;

index i is an integer in the range of 1 to 20;

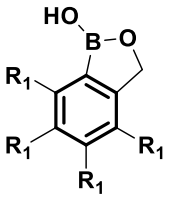
B_1 and B_2 are identical or different, and each independently represent a group selected from of Formulae F1-F9; and

B_3 represents a group selected from Formulae F1-F11;

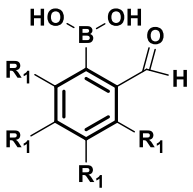
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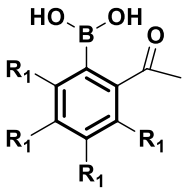
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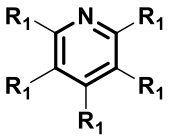
(F2)



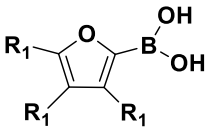
(F3)



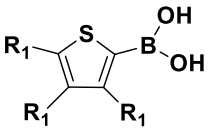
(F4)



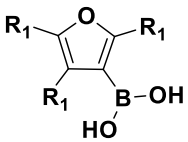
(F5)



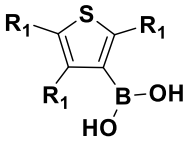
(F6)



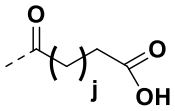
(F7)



(F8)



(F9)



F10



F11

, wherein, for each of Formulae F1-F9:

one R_1 represents (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R;

none, one, or two R_1 each independently represent F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CF_3, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH\ CH_3$, —$(SO_2)NH(CH_2)_mCH_3$ or OCF_3;

index m is an integer in the range of 1 to 14;

one R_1 in F5 represents $B(OH)_2$; and

all remaining R_1 represent H, and

in Formula F10, index j is an integer in the range of 1 to 13.

In another aspect, there is provided a conjugate comprising the compound as described above, wherein the compound as described above is conjugated, either directly or via an covalent linker, to a drug substance, provided that the conjugation is not through Z when Z is NH_2 in Formula II.

In another aspect, there is provided a method of manufacturing the compound as described above, wherein optionally, B_1 and B_2 are first conjugated to one of structures represented by FF1-FF33 and the resultant conjugate is then covalently linked to a drug

substance, or optionally, structures represented by FF1-FF33 are first conjugated to a drug substance and thereafter B_1 and B_2 are covalently linked to the corresponding structures in FF1-FF33.

In another aspect, there is provided a compound as described above for use in therapy.

In another aspect, there is provided a use of the compound as described above in the manufacture of a medicament for the treatment of a human subject, wherein the medicament is a therapeutic or prophylactic agent.

In another aspect, there is provided a modified insulin as described above, in which two or more amino acids of B-chain in range of B1 to B29 are replaced with natural or noncanonical or artificial amino acids.

In another aspect, there is provided a modified insulin as described above, wherein for Formula FF25 the index i is 0.

One or more ~~aspects~~ examples of ~~embodiments~~ examples of the present disclosure relate to boronated sensors that can simultaneously have a desirable selectivity or suitable affinity towards a specific vicinal diol, while having reduced affinity towards other diols. In certain ~~embodiments~~ examples the boronated

sensors can be used to modulate pharmacokinetic and pharmacodynamics of a drug substance in the body and in response to particular levels of specific vicinal diols.

One or more ~~embodiments~~ examples of the present disclosure include the following ~~embodiments~~ examples 1 to 15:

1. A compound represented by Formula I:

$$Z-R$$

(Formula I),

wherein, in Formula I,

R is selected from Formulae FF1-FF24; and

Z is selected from one of:

a) NH_2 or OH,

b) a covalent linkage, either directly or via an optional linker, to a drug substance,

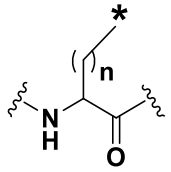
c) a covalent linkage, either directly or via the optional linker, to an N-terminal amine or an epsilon amino group of one or more amino acids in a polypeptide drug substance, and

d) a group represented by J-SCH_2—ø , J-$S(CH_2)_2$—ø, J—NH—ø, J—NH—(the optional linker)—ø, J—$S(CH_2)_kNH$—ø, or J—triazole$(CH_2)_kNH$—ø;

wherein —ø is the covalent bond towards R;

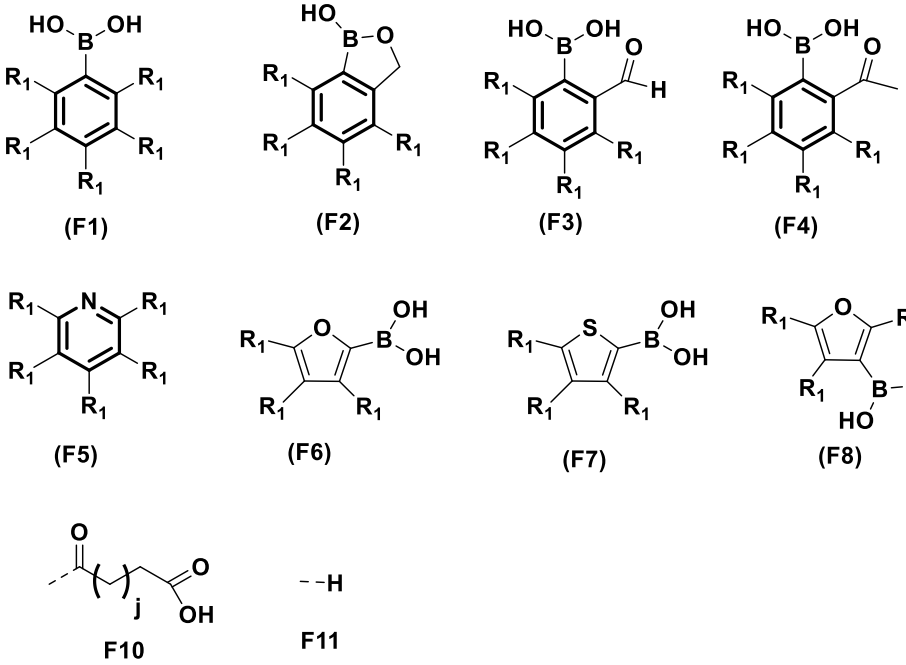
index k is an integer in the range of 3 to 14; and

J is an amino acid or one or more amino acids in a polypeptide drug substance, wherein each of the one or more amino acids in the polypeptide drug substance is represented by Formula I':



(Formula I'),

wherein, in Formula I',



,

wherein, for each of Formulae F1-F9:

one R_1 represents (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R;

none, one, or two R_1 each independently represent F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CF_3, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH\ CH_3$, — $(SO_2)NH(CH_2)_mCH_3$ or OCF_3;

index m is an integer in the range of 1 to 14;

one R_1 in F5 represents $B(OH)_2$; and

all remaining R_1 represent H, and

in Formula F10, index j is an integer in the range of 1 to 13.

4. The compound of any one of ~~embodiments~~ examples 1-3, wherein the optional linker is an L-or D-amino acid having at least one functional group directly conjugated to R, or the optional linker is selected from Formulae FL1-FL9:

5. The compound of any one of ~~embodiments~~ examples 1-3, wherein the compound is a drug substance that is additionally modified as described by ~~embodiments~~ examples 1-3 and/or wherein the one or more amines are each independently acetylated or alkylated.

6. The compound of any one of ~~embodiments~~ examples 1-3, wherein the drug substance is an insulin including human insulin or an analog thereof, and the insulin includes an A-chain and a B-chain.

7. The compound of any of ~~embodiments~~ examples 1-2, wherein the drug substance includes a polypeptide drug substance or a human peptide hormone.

8. The compound of ~~embodiment~~ example 6, wherein the insulin includes one or two peptide sequences each independently added to the A-chain and/or the B-chain of insulin, and each peptide sequence independently includes 1 to 20 continuous residues.

9. The compound of ~~embodiment~~ example 6, wherein the insulin includes 2 to 10 amino acids that are each independently modified as described by Formula I, II or III.

10. The compound of ~~embodiment~~ example 6, wherein the insulin includes one or more modifications each independently described by Formula I, II or III, wherein each of the one or more modifications is positioned:

(i) on the side chain of an amino acid and/or to the N-terminus of a polypeptide of up to 20 residues appended to the N- and/or C- terminus of the A-chain and/or the B-chain of insulin; and/or

(ii) within 4 residues of the B1, B21, B22, B29, A1, A22 or A3 residues in the insulin A- or B-chain; and/or

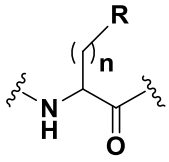
(iii) on the side chain of an amino acid and/or to the N-terminus of a polypeptide appended or integrated into the A-chain and or the B-chain of insulin, wherein the polypeptide includes the sequence $(X_2)_nX_1(X_2)_m$ wherein: X_1 is a lysine residue in which the side chain of the lysine residue is modified as described by Formulae I, II, or III; each X_2 is independanlty selected from the group of amino acids K, P, E, G, N, M, A, R, L, W, S, F, V, C, H, D, I, Y, Q, T or X_1; index m is an integer in the range of 0 to 20; and index n is an integer in the range of 0 to 18.

11. A conjugate including the compound according to any one of ~~embodiments~~ examples 1-2, wherein the compound according to any one of ~~embodiments~~ examples 1-2 is conjugated, either directly or via an covalent linker, to a drug substance, provided that the conjugation is not through Z when Z is NH_2 in Formula II.

12. The compound of any one of ~~embodiments~~ examples 1-3, wherein the compound of any one of ~~embodiments~~ examples 1-3 is used as an intermediate compound for the manufacture of any compounds in ~~embodiments~~ examples 1-11.

13. The compound of any one of ~~embodiments~~ examples 5-6, wherein the compound contains one or more modifications as described by Formulae IV, V or VI,

wherein for Formula IV:



(Formula IV),

and indicate points of attachment to remaining portions of the drug substance; index n is an integer in the range of 1 to 8; and

R is selected from the group consisting of Formulae F111, F222, F333, F444, and F555:

14. A method of manufacturing the compound of any one of ~~embodiments~~ examples 1-13, wherein optionally, B_1 and B_2 are first conjugated to one of structures represented by FF1-FF33 and the resultant conjugate is then covalently linked to a drug substance, or optionally, structures represented by FF1-FF33 are first conjugated to a drug substance and thereafter B_1 and B_2 are covalently linked to the corresponding structures in FF1-FF33.

15. A method of administering the compound of any one of ~~embodiments~~ examples 1-13 to a human subject as a therapeutic or prophylactic agent.

BRIEF DESCRIPTION OF THE DRAWINGS

The features and advantages of embodiments of the present disclosure will be better understood by reference to the following detailed description when considered in conjunction with the accompanying drawings.

FIGS. 1 to 24 are mass spectrum plots confirming the synthesis of Examples 1-24, respectively.

FIG 25 is a mass spectrum plot confirming the synthesis of modified insulin 1.

FIGS 26A is a mass spectrum plot confirming the synthesis of a modifying agent conjugated to modified insulin 2.

FIGS. 26B is a mass spectrum plot confirming the synthesis of modified insulin 2.

FIGS. 27-28 are mass spectrum plots confirming the synthesis of modified insulins 3 and 4, respectively.

DETAILED DESCRIPTION

The ability of sensors (e.g., molecular sensors) to selectively bind and respond to a specific vicinal diol in the body is facilitated by binding to the vicinal diol of interest while reducing binding to other diols or other vicinal diols. While most boronates bind to diol containing molecules, achieving selectivity using boronates (e.g., boronate-based sensors) is not always readily done; this is because of their general tendency to bind most diols, including cis

WHAT IS CLAIMED IS:

1. A compound represented by Formula I:



(Formula I),

wherein, in Formula I,

R is selected from Formulae FF1-FF24; and

Z is selected from one of:

a) NH_2 or OH,

b) a covalent linkage, either directly or via an optional linker, to a drug substance,

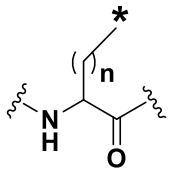
c) a covalent linkage, either directly or via the optional linker, to an N-terminal amine or an epsilon amino group of one or more amino acids in a polypeptide drug substance, and

d) a group represented by J-SCH_2—ø , J-$S(CH_2)_2$—ø, J—NH—ø, J—NH—(the optional linker)—ø, J—$S(CH_2)_kNH$—ø, or J—triazole$(CH_2)_kNH$—ø;

wherein —ø is the covalent bond towards R;

index k is an integer in the range of 3 to 14; and

J is an amino acid or one or more amino acids in a polypeptide drug substance, wherein each of the one or more amino acids in the polypeptide drug substance is represented by Formula I':



(Formula I'),

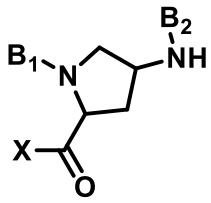
wherein, in Formula I',

 and  indicate points of attachment to remaining portions of the polypeptide drug substance;

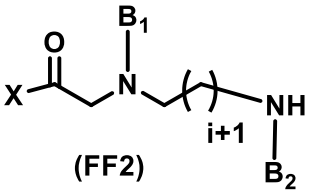
* indicates the point of attachment to the remaining portion of Z; and

index n is an integer in the range of 1 to 8,

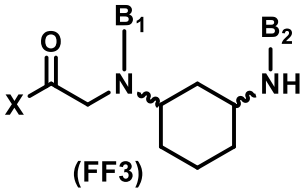
wherein for Formulae FF1-FF24:



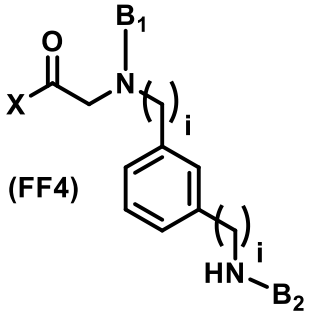
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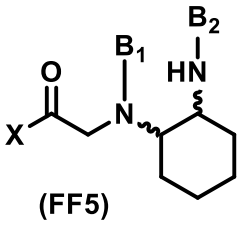
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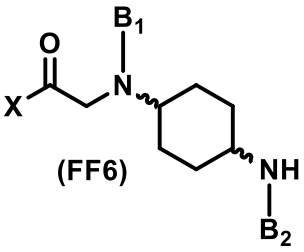
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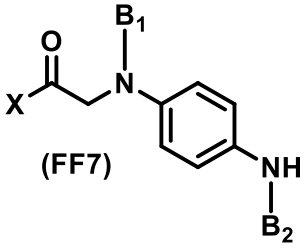
(FF4)



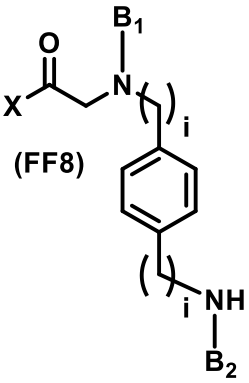
(FF5)



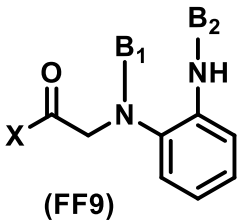
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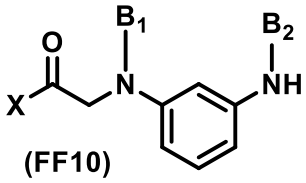
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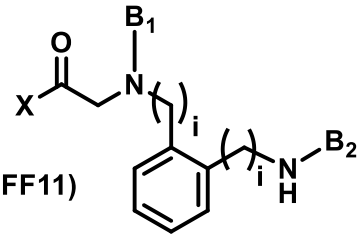
(FF8)



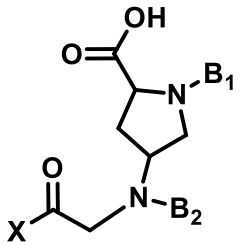
(FF9)



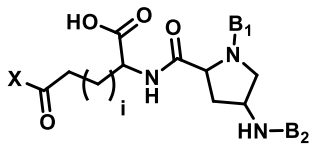
(FF10)



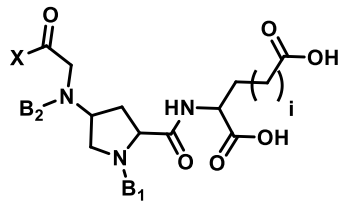
(FF11)



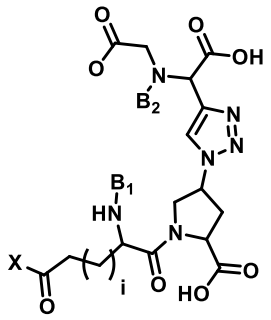
(FF12)



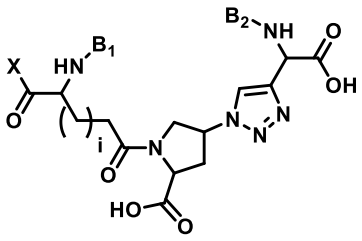
(FF13)



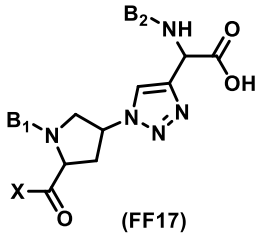
(FF14)



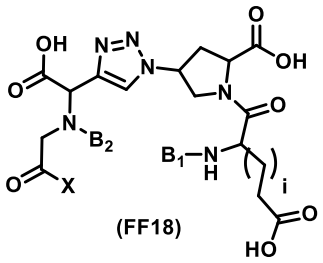
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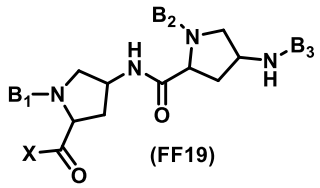
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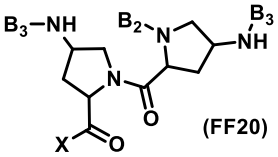
(FF17)



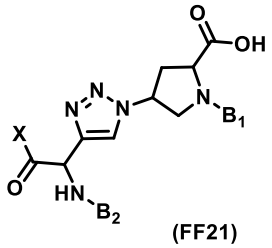
(FF18)



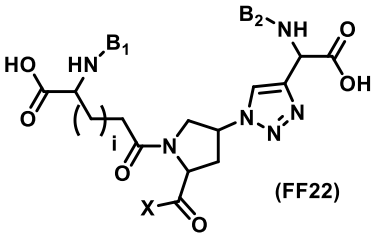
(FF19)



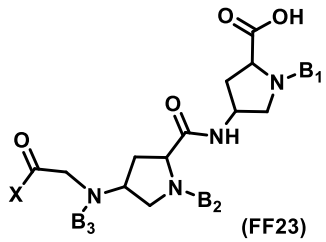
(FF20)



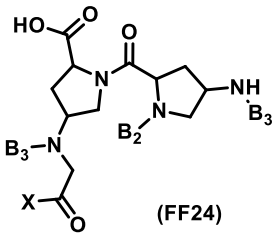
(FF21)



(FF22)



(FF23)



(FF24)

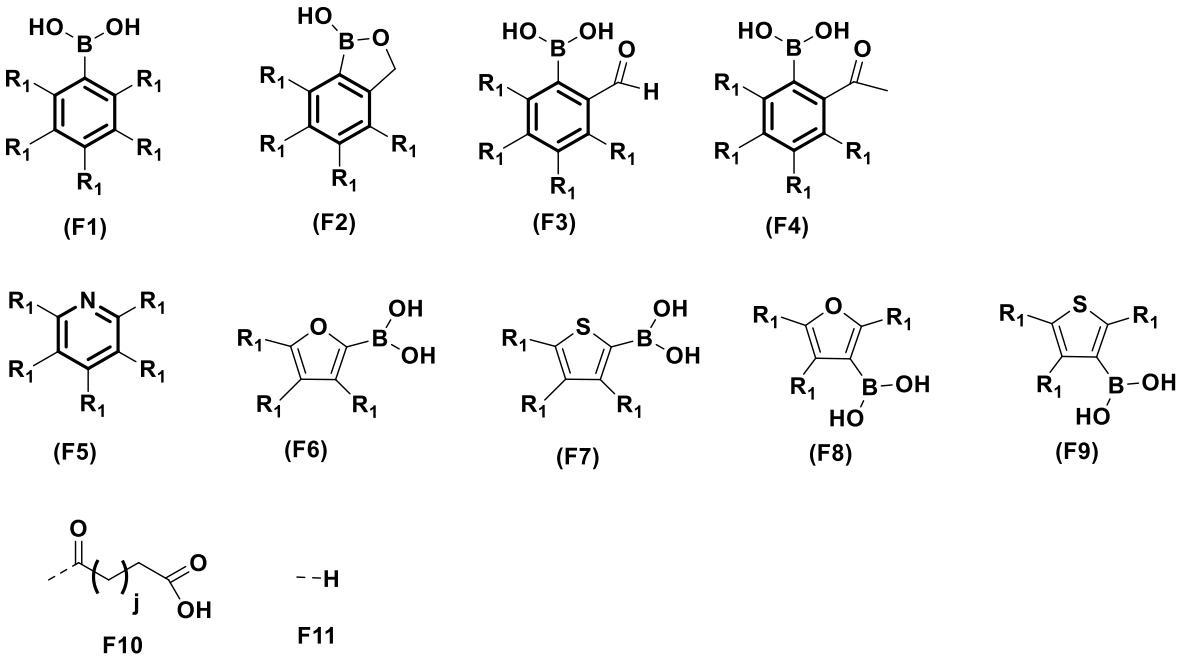
,

X represents a covalent linkage, either directly or via the optional linker, towards Z in Formula I;

index i is an integer in the range of 1 to 20;

B_1 and B_2 are identical or different, and each independently represent a group selected from Formulae F1-F9; and

B_3 represents a group selected from Formulae F1-F11,



,

wherein, for each of Formulae F1-F9:

one R_1 represents (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R in Formula I;

none, one, or two R_1 each independently represent F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CF_3, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH\ CH_3$, — $(SO_2)NH(CH_2)_mCH_3$, or OCF_3,

index m is an integer in the range of 1 to 14;

one R_1 in F5 represents $B(OH)_2$, and

all remaining R_1 represent H, and

in Formula F10, index j is an integer in the range of 1 to 13.

2. A compound represented by Formula II:



(Formula II),

wherein, in Formula II, either:

(i) R is selected from Formulae FF25-FF31;

B_1 and B_2 in FF25-FF31 are identical or different, and are each independently selected from Formulae F12-F19; and

Z is NH_2 and is not conjugated to any drug substance;

or

(ii) R is selected from Formulae FF25-FF31;

B_1 and B_2 are each independently selected from Formulae F20-F27; and

Z is selected from one of:

a) OH

b) a covalent linkage, either directly or via an optional linker, to a drug substance,

c) a covalent linkage, either directly or via the optional linker, to an N-terminal amine or an epsilon amino group of one or more amino acids in a polypeptide drug substance, and

d) a group represented by J-SCH_2—ø , J-$S(CH_2)_2$—ø, J—NH—ø, J—NH—(the optional linker)—ø, J—$S(CH_2)_k$NH—ø, or J—triazole$(CH_2)_k$NH—ø,

wherein —ø is the covalent bond towards R,

index k is an integer in the range of 3 to 14; and

J is an amino acid or one or more amino acids in a polypeptide drug substance, wherein each of the one or more amino acids in the polypeptide drug substance is represented by Formula II';

or

(iii) R is selected from Formulae FF32-FF33,

B_1 and B_2 in FF32 are each independently selected from Formulae F28-F35;

B_1 and B_2 in FF33 are each independently selected from Formulae F36-F43; and

Z is selected from one of:

a) a drug substance,

b) a covalent linkage, either directly or via an optional linker, to the N-terminal amine or the epsilon amino group of an amino acid in a polypeptide drug substance, and

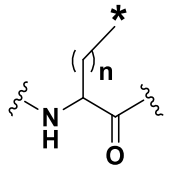
c) a group represented by J-SCH_2—ø , J-$S(CH_2)_2$—ø, J—NH—ø, J—NH—(the optional linker)—ø, J—$S(CH_2)_k$NH—ø, or J—triazole$(CH_2)_k$NH—ø,

wherein —ø is the covalent bond towards R,

index k is an integer in the range of 3 to 14; and

J is an amino acid or one or more amino acids in a polypeptide drug substance, wherein each of the one or more amino acids in the polypeptide drug substance is represented by Formula II';

wherein, for Formula II':



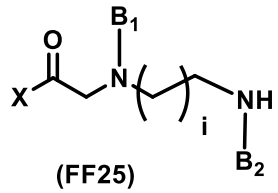
(Formula II'),

and indicate points of attachment to remaining portions of the polypeptide drug substance;

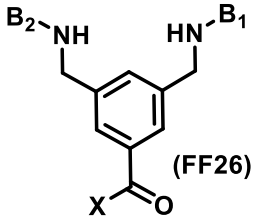
* indicates the point of attachment to the remaining portion of Z; and

index n is an integer in the range of 1 to 8;

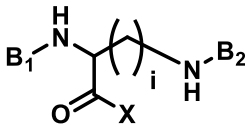
wherein for Formulae FF25-FF33:



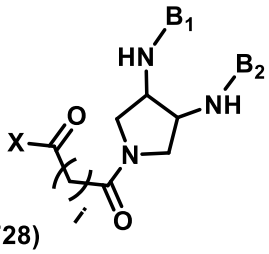
(FF25)



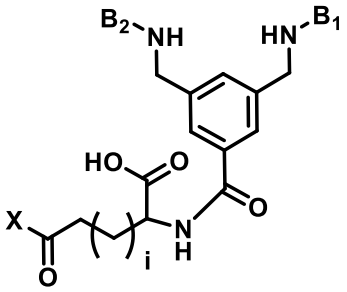
(FF26)



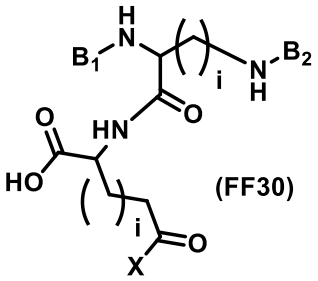
(FF27)



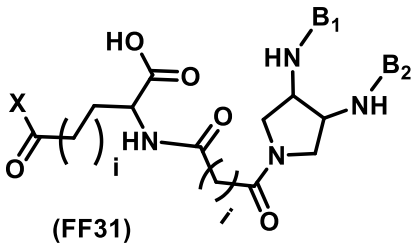
(FF28)



(FF29)



(FF30)



(FF31)

$X-B_1-B_2$

(FF32)

B_1-B_2

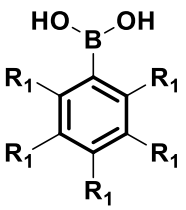
(FF33)

,

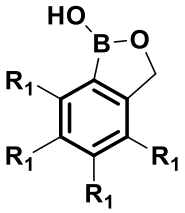
X represents a covalent linkage, either directly or via the optional linker, towards Z in Formula II; and

index i is an integer in the range of 1 to 20;

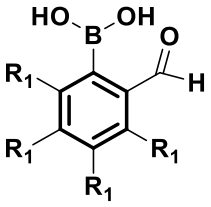
wherein, for each of Formulae F12-F19:



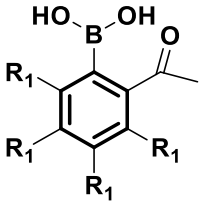
(F12)



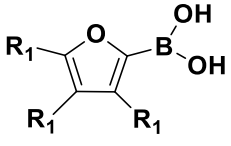
(F13)



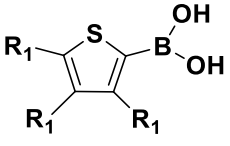
(F14)



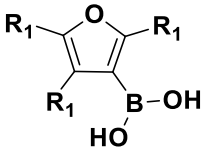
(F15)



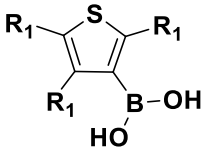
(F16)



(F17)



(F18)



(F19)

,

one R_1 from either B_1 or B_2 represents a covalent linkage, either directly or via an optional linker, to a drug substance;

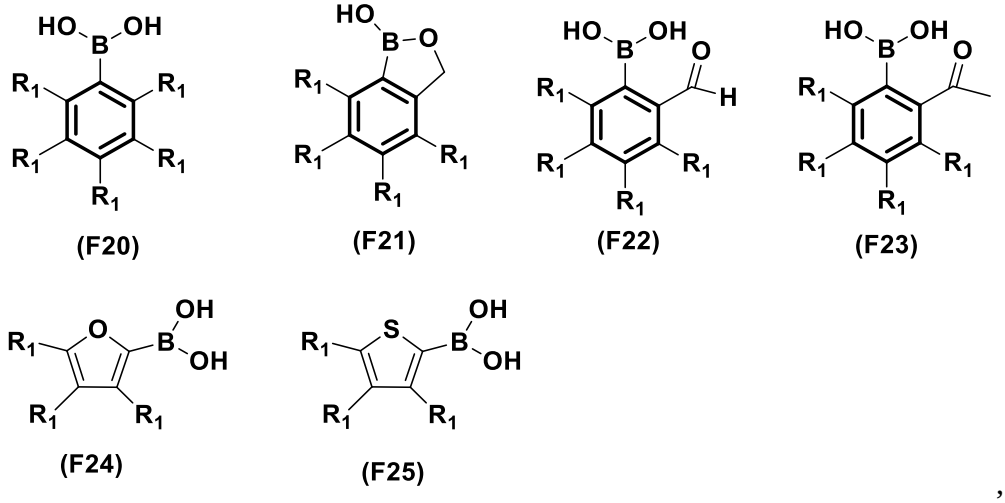
one R_1 in each of B_1 and B_2 is (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R in Formula II;

none, one, or two R_1 in each of B_1 and B_2 independently represent COOH, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CF_3, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, —$(SO_2)NH(CH_2)_mCH_3$ or OCF_3;

index m is an integer in the range of 1 to 14; and

all remaining R_1 represent H;

wherein, for each of Formulae F20-F25:



,

one R_1 is (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R in Formula II;

either:

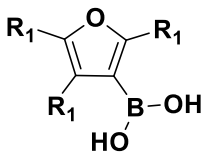
(a) one or two R_1 on the same B_1 and/or B_2 represent COOH, wherein at least one COOH is not conjugated to a drug substance, and/or

(b) one or two R_1 each independently represent NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, —$(SO_2)NH(CH_2)_mCH_3$, wherein index m is an integer in the range of 1 to 14, and

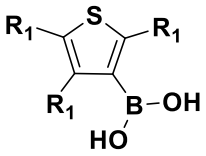
none, one, or two R_1 each independently represent NO_2, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CH_3, CF_3 or OCF_3, and

all remaining R_1 represent H;

wherein, for each of Formulae F26-F27:



(F26)



(F27)

,

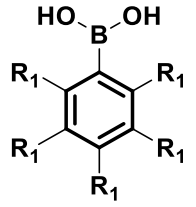
one R_1 is (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R in Formula II;

none, one, or two R_1 each independently represent COOH, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CF_3, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —(SO_2)NH CH_3, —$(SO_2)NH(CH_2)_mCH_3$ or OCF_3;

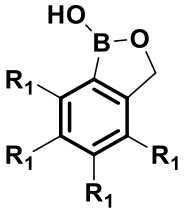
index m is an integer in the range of 1 to 14; and

all remaining R_1 represent H;

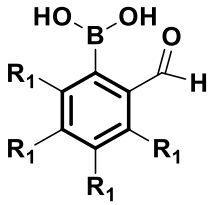
wherein, for each of Formulae F28-F35:



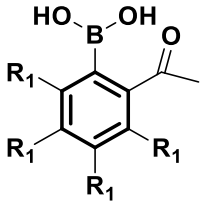
(F28)



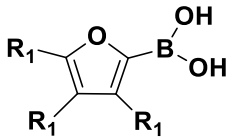
(F29)



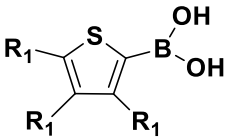
(F30)



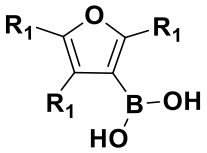
(F31)



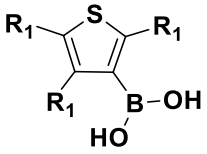
(F32)



(F33)



(F34)



(F35)

,

one R_1 in B_1 represents (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent linkage, either directly or via an optional linker, to Z in Formula II;

one R_1 for each of B_1 and B_2 is a covalent linkage between B_1 and B_2, wherein the covalent linkage is selected from –(S=O)–, –(S(=O)(=O)–, –(CF_2)–,–(C=O)–, —$(CH_2)_m$ $SCH_2CO(CH_2)_k$ —, —$(CH_2)_m$ $S(CH_2)_2CO(CH_2)_k$ —, and —$(CH_2)_m$ $(CO)NH(CH_2)_k$—;

either (i) two R_1 groups in B_2 are COOH and these two R_1 groups are not conjugated to a drug substance, or (ii) one or two R_1 in either B_1 and/or B_2 each independently represent NO_2, CH=O, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, or —$(SO_2)NH(CH_2)_mCH_3$;

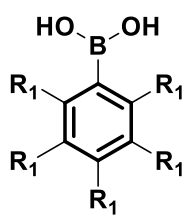
none, one, or two R_1 in either B_1 and/or B_2 each independently represent CH=O, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CH_3, CF_3, CHF_2, or OCF_3;

the remaining R_1 represent H;

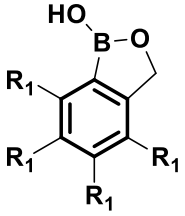
index k is an integer in the range of 1 to 7; and

index m is an integer in the range of 1 to 7;

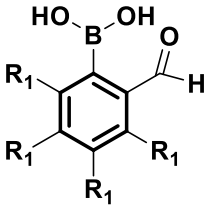
wherein, for each of Formulae F36-F43:



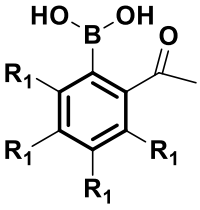
(F36)



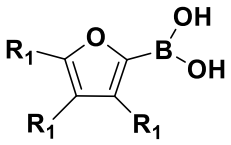
(F37)



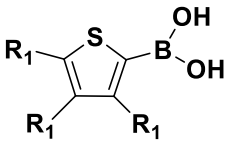
(F38)



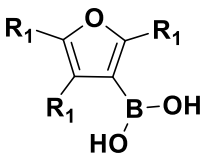
(F39)



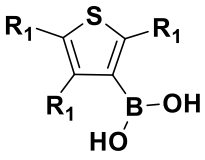
(F40)



(F41)



(F42)



(F43)

one R_1 for each of B_1 and B_2 is a covalent linkage to a sulfoximine group such that B_1 and B_2 are connected together by the sulfoximine group, and wherein the amino group of the sulfoximine is covalently linked, either directly through an acid containing linker or via an optional linker, to Z in Formula II;

either (i) two R_1 groups in B_1 and/or B_2 are COOH and these two R_1 groups are not conjugated to a drug substance, or (ii) one or two R_1 in either B_1 and/or B_2 each independently represent NO_2, CH=O, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, or —$(SO_2)NH(CH_2)_mCH_3$;

none, one, or two R_1 in either B_1 and/or B_2 each independently represent CH=O, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CH_3, CF_3, CHF_2, or OCF_3;

the remaining R_1 represent H;

index k is an integer in the range of 1 to 7; and

index m is an integer in the range of 1 to 7.

3. A compound comprising a drug substance, wherein the drug substance comprises an insulin and the insulin contains one or more modified amino acids represented by Formula III:

Z−R

(Formula III),

wherein, in Formula III,

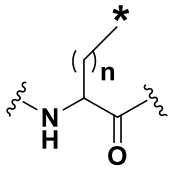
R is selected from Formulae FF1-FF24; and

Z is selected from an optional linker, J-SCH_2—ø , J-$S(CH_2)_2$—ø, J—NH—ø, J—NH(CO) linker—ø, J—$S(CH_2)_kNH$—ø, and J—triazole$(CH_2)_kNH$—ø,

wherein —ø is the covalent bond towards R,

index k is an integer in the range of 3 to 14; and

J is described by Formula III':



(Formula III'),

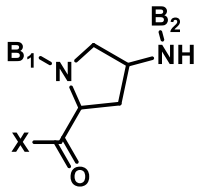
wherein, in Formula III':

 and  indicate points of attachment to remaining portions of the insulin;

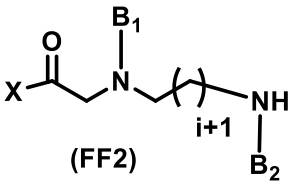
* indicates the point of attachment to the remaining portion of Z; and

index n is an integer in the range of 1 to 8;

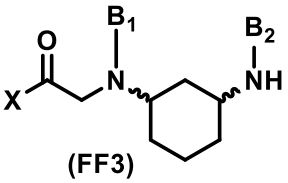
wherein for Formulae FF1-FF24:



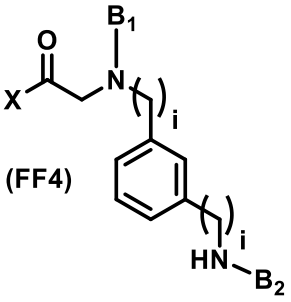
(FF1)



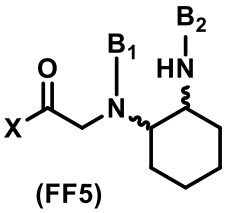
(FF2)



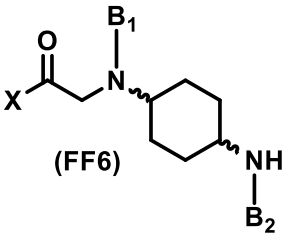
(FF3)



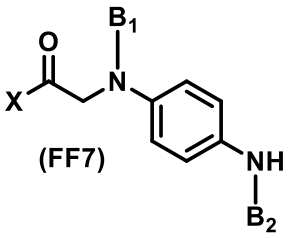
(FF4)



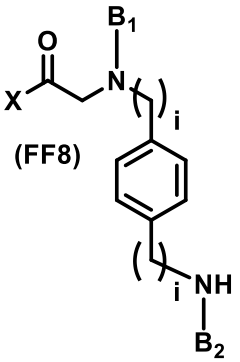
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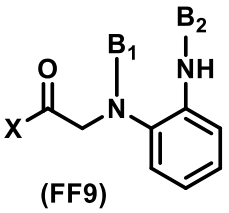
(FF6)



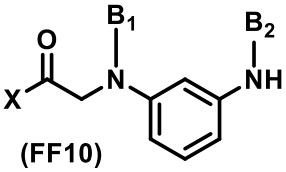
(FF7)



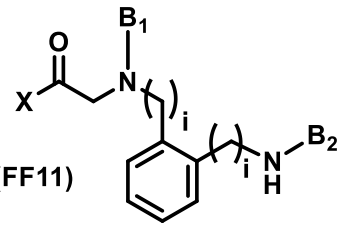
(FF8)



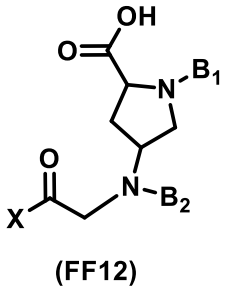
(FF9)



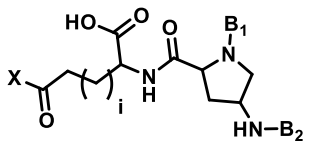
(FF10)



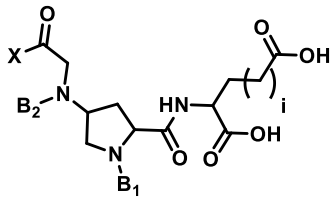
(FF11)



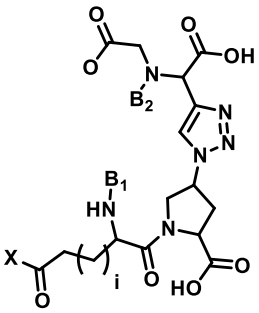
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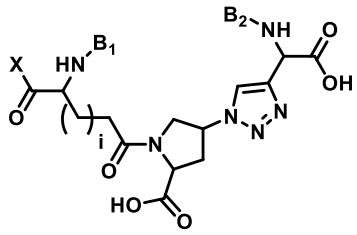
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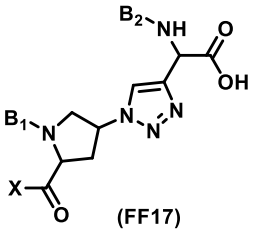
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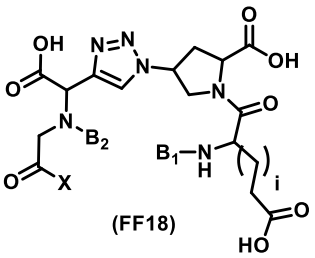
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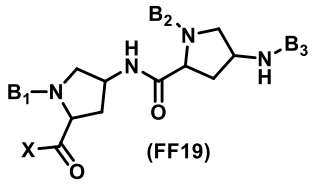
(FF16)



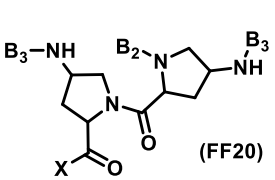
(FF17)



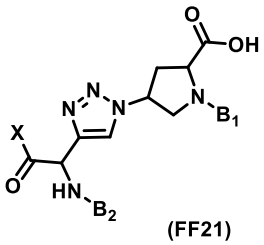
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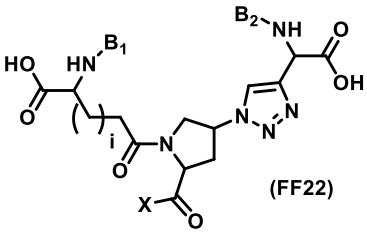
(FF19)



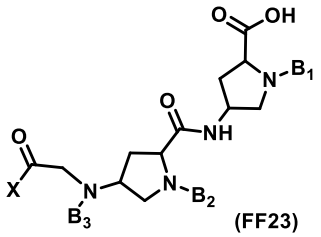
(FF20)



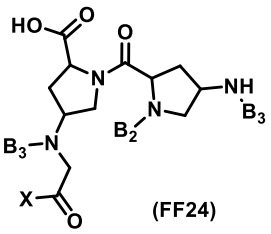
(FF21)



(FF22)



(FF23)



(FF24)

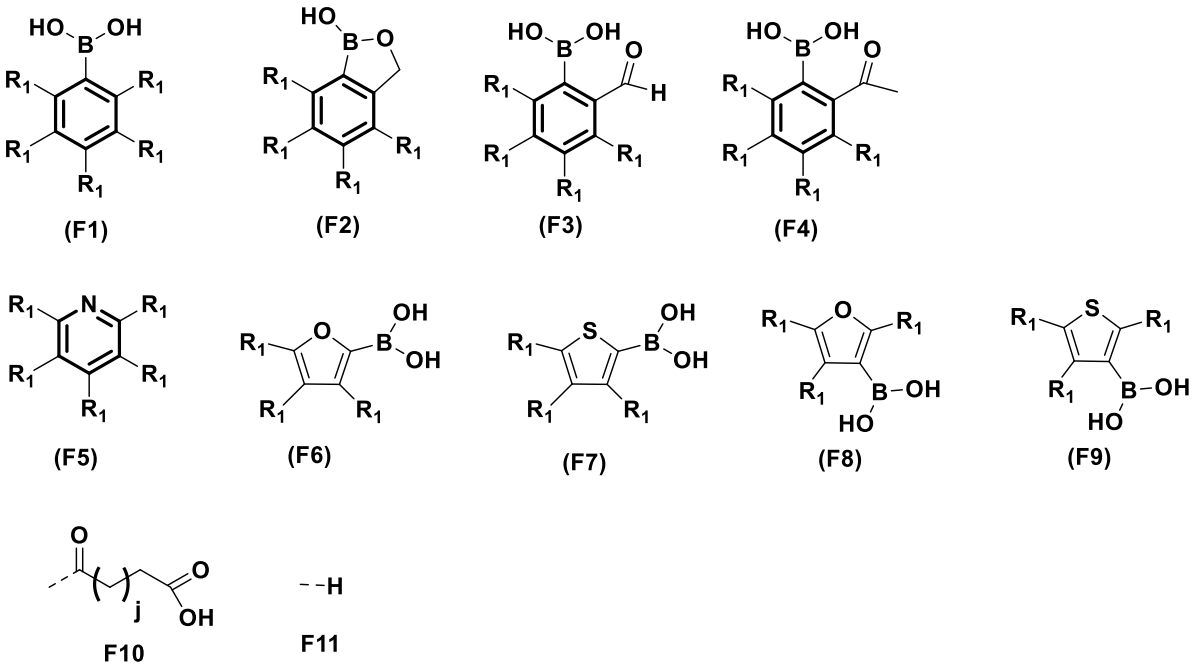
,

X represents a covalent linkage, either directly or via the optional linker, towards Z in Formula III;

index i is an integer in the range of 1 to 20;

B_1 and B_2 are identical or different, and each independently represent a group selected from of Formulae F1-F9; and

B_3 represents a group selected from Formulae F1-F11;



,

wherein, for each of Formulae F1-F9:

one R_1 represents (C=O)---, S(=O)(=O)---, $(CH_2)_m$(C=O)---, or $(CH_2)_m$---, wherein --- represents a covalent bond to the remainder of R;

none, one, or two R_1 each independently represent F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, SO_2CH_3, CF_3, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH\ CH_3$, — $(SO_2)NH(CH_2)_mCH_3$ or OCF_3;

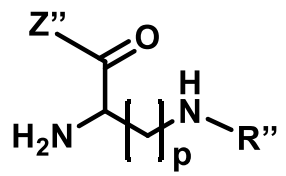
index m is an integer in the range of 1 to 14;

one R_1 in F5 represents $B(OH)_2$; and

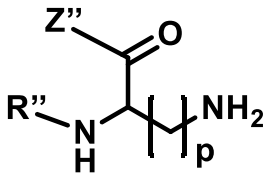
all remaining R_1 represent H, and

in Formula F10, index j is an integer in the range of 1 to 13.

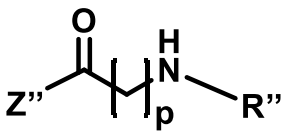
4. The compound of any one of claims 1-3, wherein the optional linker is an L-or D-amino acid having at least one functional group directly conjugated to R, or the optional linker is selected from Formulae FL1-FL9:



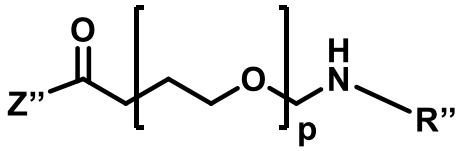
(FL1)



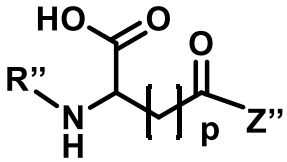
(FL2)



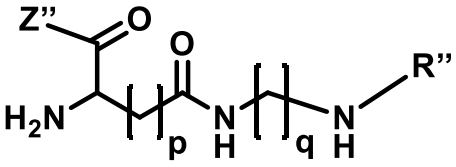
(FL3)



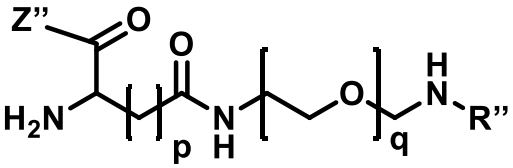
(FL4)



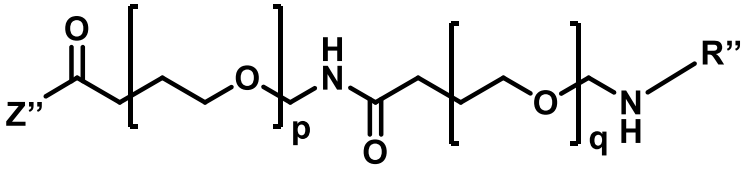
(FL5)



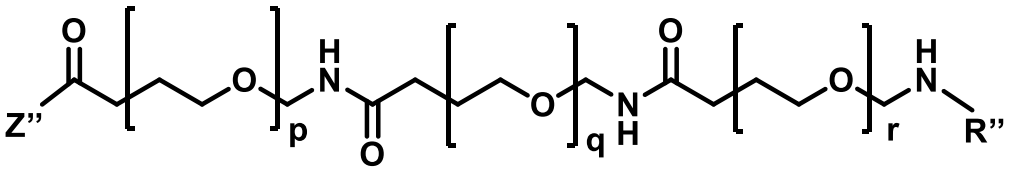
(FL6)



(FL7)



(FL8)



(FL9)

, wherein, in Formulae FL1-FL9:

Z'' represents a covalent bond towards Z;

R'' represents a covalent bond towards R;

p is an integer in the range of 1 to 5;

q is an integer in the range of 1 to 5; and

r is an integer in the range of 1 to 5.

5. The compound of any one of claims 1-3, wherein the compound is a drug substance that is additionally modified as described by claims 1-3 and/or wherein one or more amines are each independantly acetylated or alkylated.

6. The compound of any one of claims 1-3, wherein the drug substance is an insulin comprising human insulin or an analog thereof, and the insulin comprises an A-chain and a B-chain.

7. The compound of any of claims 1-2, wherein the drug substance comprises a polypeptide drug substance or a human peptide hormone.

8. The compound of claim 6, wherein the insulin comprises one or two peptide sequences each independently added to the A-chain and/or the B-chain of insulin, and each peptide sequence independently comprises 1 to 20 continuous residues.

9. The compound of claim 6, wherein the insulin comprises 2 to 10 amino acids that are each independently modified as described by Formula I, II or III.

10. The compound of claim 6, wherein the insulin comprises one or more modifications each independently described by Formula I, II or III, wherein each of the one or more modifications is positioned:

(i) on the side chain of an amino acid and/or to the N-terminus of a polypeptide of up to 20 residues appended to the N- and/or C- terminus of the A-chain and/or the B-chain of insulin; and/or

(ii) within 4 residues of the B1, B21, B22, B29, A1, A22 or A3 residues in the insulin A- or B-chain; and/or

(iii) on the side chain of an amino acid and/or to the N-terminus of a polypeptide appended or integrated into the A-chain and or the B-chain of insulin, wherein the polypeptide comprises the sequence $(X_2)_nX_1(X_2)_m$ wherein: X_1 is a lysine residue in which the side chain of the lysine residue is modified as described by Formulae I, II, or

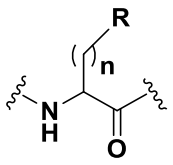
III; each X_2 is independanlty selected from the group of amino acids K, P, E, G, N, M, A, R, L, W, S, F, V, C, H, D, I, Y, Q, T or X_1; index m is an integer in the range of 0 to 20; and index n is an integer in the range of 0 to 18.

11. A conjugate comprising the compound according to any one of claims 1-2, wherein the compound according to any one of claims 1-2 is conjugated, either directly or via an covalent linker, to a drug substance, provided that the conjugation is not through Z when Z is NH_2 in Formula II.

12. The compound of any one of claims 1-3, wherein the compound of any one of claims 1-3 is used as an intermediate compound for the manufacture of any compounds in claims 1-11.

13. The compound of any one of claims 5-6, wherein the compound contains one or more modifications as described by Formulae IV, V or VI,

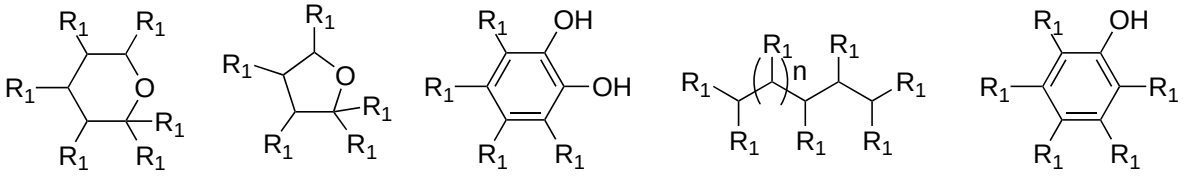
wherein for Formula IV:



(Formula IV),

and indicate points of attachment to remaining portions of the drug substance; index n is an integer in the range of 1 to 8; and

R is selected from the group consisting of Formulae F111, F222, F333, F444, and F555:



(F111) (F222) (F333) (F444) (F555),

wherein in Formulae F111, F222, F333, F444, and F555:

index n is an integer in the range of 1 to 8;

each carbon atom attached to an R^1 independently has (R) or (S) stereochemistry;

each R_1 is independently selected from —H, —OR^3, —$N(R^3)_2$, —SR^3, —OH, —OCH_3, —OR^5, $NHC(O)CH_3$, —CH_2R^3, —C(O)NHOH, —$NHC(O)CH_3$, —CH_2OH, —CH_2OR^5, —NH_2, —CH_2R^4, -OR^8, —R^6,—R^8, and —R^7,

each R^3 is independently selected from —H, acetyl, phosphate, —R^2, —SO_2R^2, —$S(O)R^2$, —$P(O)(OR^2)_2$, —$C(O)R^2$, —CO_2R^2, and —$C(O)N(R^2)_2$,

each R^2 is independently selected from —H, an optionally substituted $C_{1\text{-}6}$ aliphatic ring, an optionally substituted phenyl ring, an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms selected from nitrogen, oxygen, and sulfur, a 4-7 membered heterocyclic ring having 1-2 heteroatoms selected from nitrogen, oxygen, and sulfur, and an alkyl or amide covalent linkage to R in Formula IV,

each R^4 is independently selected from —H, —OH, —OR^3, —$N(R^3)_2$, —OR^5 and —SR^3;

each R^5 is independently selected from a mono-saccharide, a di-saccharide, a tri-saccharide, a pentose, and a hexose,

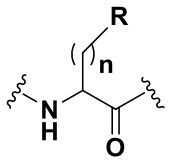
each R^6 is independently selected from —$NCOCH_2$—, —$(OCH_2CH_2)_n$—, a —O—$C_{1\text{-}9}$ alkylene group, and a substituted $C_{1\text{-}9}$ alkylene group in which one or more methylene groups are optionally replaced by —O—, —$(CH_2)_n$—, —OCH_2—, —$N(R^2)C(O)$—, —$N(R^2)C(O)N(R^2)$—, —SO_2—, —$SO_2N(R^2)$—, —$N(R^2)SO_2$—, —S—, —$N(R^2)$—, —C(O)—, —OC(O)—, —C(O)O—, —$C(O)N(R^2)$—, or —$N(R^2)SO_2N(R^2)$—, wherein index n is an integer in a range 1 to 8,

each R^7 is independently selected from —$N(R^2)_2$, —F, —Cl, —Br, —I, —SH, —OR^2, —SR^2, —NH_2, —N_3, —$C{\equiv}CR^2$, —$CH_2C{\equiv}CH$, —$C{\equiv}CH$, —CO_2R^2, —$C(O)R^2$,—OSO_2R^2 —$N(R^2)_2$, —OR^2, —SR^2 , —CH_3, —CH_2NH_2, and a direct linkage to R in Formula IV,

R^8 is (i) the sidechain of one of L-serine, D-serine, L-threonine, D-threonine, L-allothreonine, or D-allothreonine and corresponds to R in Formula IV, wherein index n=1 in Formula IV, (ii) an amide linkage to the C-terminus of lysine, cysteine, 2,3-diaminopropionic acid, or (iii) —$CH_2C(CH_2OH)_2CH_2NH_2$, and

structures F111, F222, F333, F444, and/or F555 optionally comprise one or more acetyl, acetylene, acetonide, and/or pinacol protecting groups;

wherein for Formula V:



(Formula V),

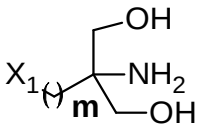
and indicate points of attachment to remaining portions of the drug substance;

index n is an integer in the range of 1 to 8;

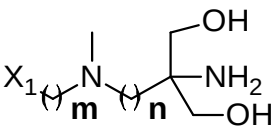
R represents X-Y,

wherein X is a covalent linkage selected from the group consisting of a triazole, an amide bond, an imine bond or a thioether bond;

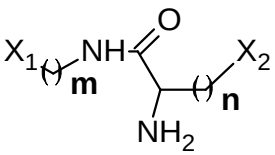
Y is selected from the group consisting of structures represented by Formulae F200-F203:



(F_{200})



(F_{201})



(F_{202}),

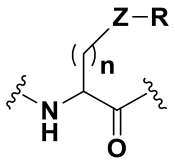
X_1 represents the covalent bond towards X;

X_2 represents SH, OH or NH_2;

index m is an integer in the range of 1 to 8; and

index n is an integer in the range of 1 to 8;

wherein for Formula VI:



(Formula VI),

and indicate points of attachment to remaining portions of the drug substance;

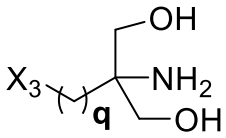
index n is an integer in the range of 1 to 8;

Z is selected from the group consisting of: an amino acid, —$(CH_2)_p$—, —$CH_2(OCH_2CH_2)_p$—, —SCH_2—, —$S(CH_2)_2$—, —NH—, —NH(CO)—, —(CO)NH—, —$S(CH_2)_kNH$—, —triazole—$(CH_2)_k$—NH—, a triazole, an amide bond, an imine bond, and a thioether bond;

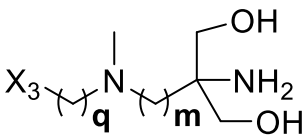
index k is an integer in the range of 3 to 5;

index p is an integer in the range of 1 to 8; and

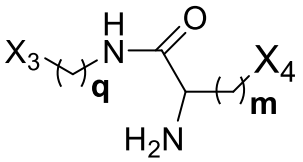
R is selected from the group consisting of structures represented by Formulae F203-F205:



(F203)



(F204)



(F205),

wherein X_3 represents the covalent bond towards Z;

X_4 represents SH, OH or NH_2

index q is an integer in the range of 1 to 8; and

index m is an integer in the range of 1 to 8.

14. A method of manufacturing the compound of any one of claims 1-13, wherein optionally, B_1 and B_2 are first conjugated to one of structures represented by FF1-FF33 and the resultant conjugate is then covalently linked to a drug substance, or optionally, structures represented by FF1-FF33 are first conjugated to a drug substance and thereafter B_1 and B_2 are covalently linked to the corresponding structures in FF1-FF33.

15. A compound of any one of claims 1-13 for use in therapy.

~~15.~~16. ~~A method of administering~~Use of the compound of any one of claims 1-13 in the manufacture of a medicament for the treatment of~~to~~ a human subject, wherein the medicament is ~~as~~ a therapeutic or prophylactic agent.

~~16.~~17. The compound of any of claims 1-13, wherein one or more amine groups are independently acetylated or alkylated.

~~17.~~18. The compound of claim 6, wherein the insulin includes two, three, or four modifications each independently described by Formulae I, II, or III.

~~18.~~19. The compound of claims 1-3, wherein the drug substance is a human polypeptide hormone or a peptide comprising at least 10% homology to one, two, three, or four different human peptide hormones and which includes dual or triple agonists, hybrid synthetic peptides based on one or more human polypeptide hormones or analogs thereof.

~~19.~~20. The compound of claims 1-3, in which the drug substance is insulin, and the amino acid at residue 21 of the B-chain is a modified amino acid represented by Formulae I, II, or III.

~~20.~~21. The compound of claims 1-3, in which the drug substance is insulin, and in which one or more residues that are within 4 residues of residue 22 of the B-chain of insulin are represented each independently by Formulae I, II, or III, and one or more additional residues in a polypeptide appended to the C- and/or N-terminus of B- and/or A-chain, is independently represented by Formulae I, II, or III.

~~21.~~22. The compound of claims 1-3, in which the drug substance is insulin, wherein the modified amino acids either replace an amino acid at a given residue in the peptide sequence of A- and/or the B-chain or the modified amino acids are appended to the peptide sequence of the A- and / or the B-chain either at the ends and/or inside the peptide sequences of the A- and / or the B-chain.

~~22.~~23. The compound of claims 1-3 and 13, in which the drug substance is insulin, and wherein the amino acid at residue 21 of the B-chain is a modified amino acid represented by Formulae IV, V or VI, and the residue at the C-terminus of the A-chain is represented by Formulae I, II, or III.

~~23.~~24. The compound of claims 1-3 and 13, in which the drug substance is insulin, in which one or more residues that are within 4 residues of C-terminus of the A-chain, or which are appended to the C-terminus of A-chain, are represented each independently by Formulae I, II, or III, and one or more residues that are within 4 residues of residue 22 of the B-chain are represented each independently by Formulae IV, V, or VI.

~~24.~~25. The compound of claims 1-3 and 13, in which the drug substance is insulin, in which one or more residues that are within 4 residues of C-terminus of the A-chain, or which are appended to the C-terminus of A-chain, are represented each independently by Formulae IV, V, or VI, and one or more residues that are within 4 residues of residue 22 of the B-chain are represented each independently by Formulae I, II, or III.

~~25.~~26. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein two modified amino acids are introduced to the B-chain of insulin at any position between the C-terminal cysteine of the B-chain and the C-terminus of B-chain, and two additional modified amino acids are introduced anywhere in the A-chain of insulin including being appended to one or both ends of the A-chain.

~~26.~~27. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein one or more residues that are (i) within 4 residues of residue 21 of the B-chain and/or (ii) within 6 residues of the N- or C-terminus of the A- and/or B-chain and/or (iii) within 4 residues of residue 13 of the A-chain and/or (iv) are represented each independently by Formulae I, II, III, IV, V, or VI, and one or more residues that are within 4 residues of the C-terminus of the A-chain are represented each independently by Formulae I, II, III, IV, V, or VI .

~~27.~~28. A modified insulin of any one of claims 1, 2, or 3, in which two or more amino acids of B-chain in range of B1 to B29 are replaced with natural or noncanonical or artificial amino acids.

~~28.~~29. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, in which one or more amino acids of A- or B-chain are replaced with natural or non-canonical amino acids.

~~29.~~30. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein the insulin is further conjugated either directly or through an optional linker to a polypeptide including up to 31 amino acids.

~~30.~~31. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein the insulin conjugated at the N- or C-terminus of the A- or B-chain to a polypeptide including up to 31 amino acids.

~~31.~~32. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein the insulin is conjugated at the N- or C-terminus of the A- or B-chain to a polypeptide including up to 31 amino acids and the polypeptide is connected to the insulin through a peptide bond.

~~32.~~33. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein the insulin is further conjugated either directly or through an optional linker to a polypeptide including up to 31 amino acids and wherein one or more pairs of the side chains of the polypeptide are covalently linked, and in certain embodiments thereof the covalent bond between the side chains is a bond selected from the group consisting of a triazole bond, a bond resulting from an azide-alkyne cycloaddition, a disulfide bond, a thioester bond, an oxime bond, an amide bond, a lactam bond, an ester bond, an olefin bond, an imine bond, an ester bond, and a thioether bond.

~~33.~~34. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein at least one primary or one secondary amine group in R in Formula I is covalently conjugated through an amide bond to a side chain of an L- and D- gamma-glutamic acid, and the N-terminus of the glutamic acid is covalently conjugated through an amide bond to an unsubstituted or monosubstituted diacid alkyl chain containing 3 to 16 carbons.

~~34.~~35. A modified insulin of claim 2, wherein for Formula FF25 the index i is 0.

~~35.~~36. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein between 1-10 amino acids are appended to the polypeptide sequence of insulin and these are appended N-terminal to residues 1 of the B-chain of insulin and wherein the residue that is inserted at N-terminal to residues 1 is a modified amino acid described by Formulae I, II or III.

~~36.~~37. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein between 1-10 amino acids are appended to the C-terminus of the B-chain of insulin and wherein the residue at position B29 of the insulin is a modified amino acid described by Formula I.

~~37.~~38. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, wherein up to 6 residues are appended to the polypeptide sequence of insulin and wherein at least two of those are modified amino acids described by Formulae I-VI.

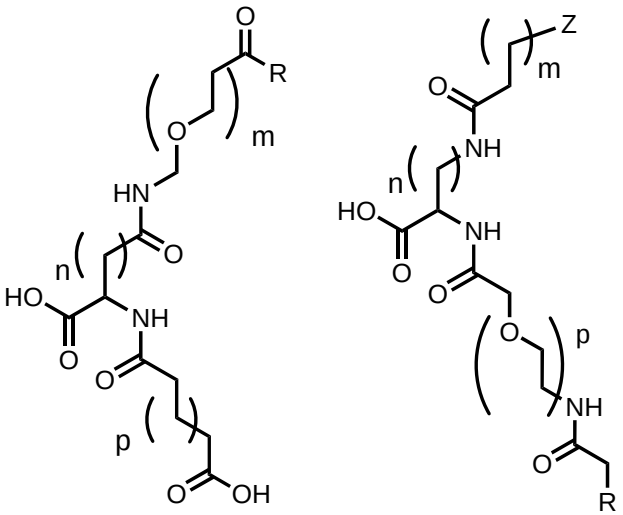
~~38.~~39. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, and the insulin is modified to have 4 or 5 intramolecular disulfide bonds.

~~39.~~40. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, and the insulin is linked to a polypeptide using an enzyme.

~~40.~~41. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, and the insulin is linked to a non-boronated polypeptide including up to 31 amino acids using an enzyme.

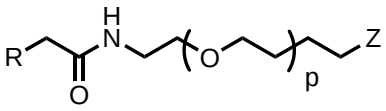
~~41.~~42. The compound of any one of claims 1-3 and 13, in which the drug substance is insulin, the insulin is linked to a polypeptide including up to 31 amino acids and the side chains of at least two amino acids in the polypeptide sequence are covalently linked together or through an optional linker.

~~42.~~43. The compound of any one of claims 1-3 and 13, wherein the drug substance is insulin and the insulin is covalently conjugated using an amide bond to structures described by Formulae F411-F416 or structures comprising a structure in which F411 is further covalently conjugated using amide bonds to structures described by Formulae F412-F416,

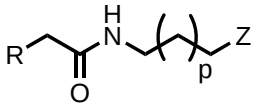


(F411)

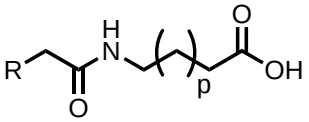
(F412)



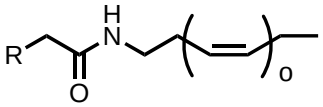
(F413)



(F414)



(F415)

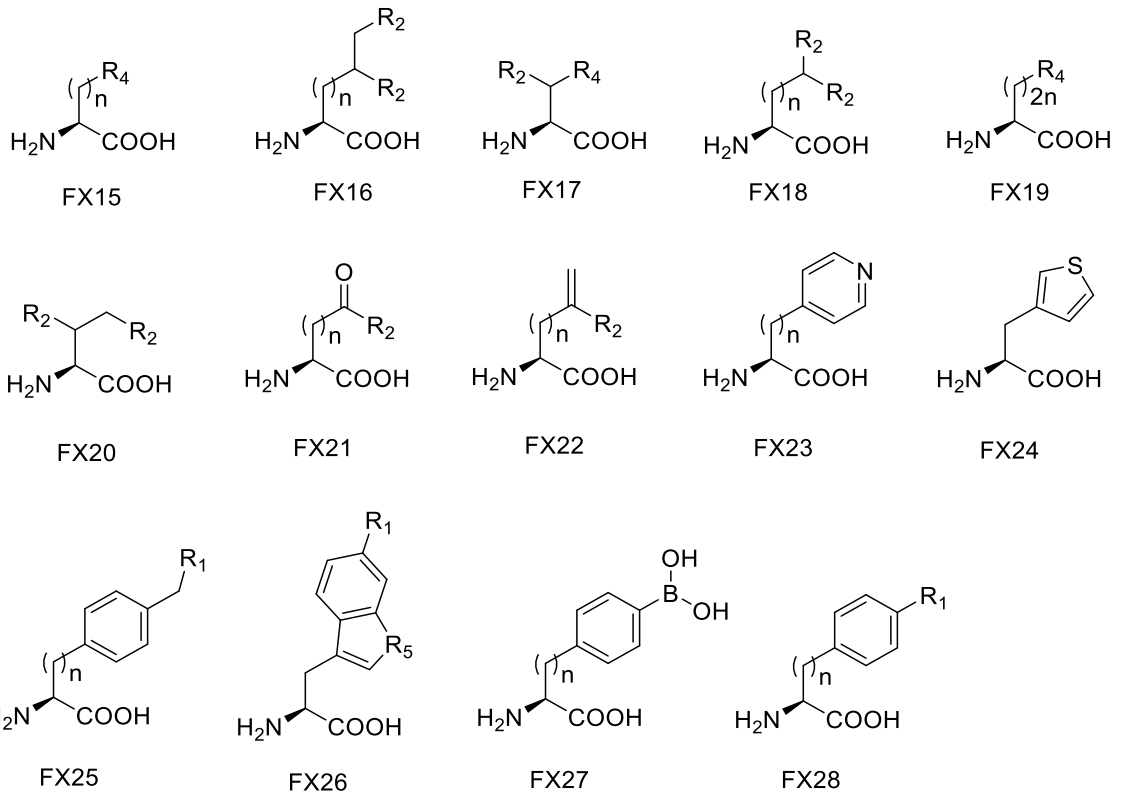


(F416)

,

wherein R represents a primary or secondary amine either in the N-terminus of the modified insulin, or, a primary or secondary amine in the side chains of a subset of amino acids in the modified insulin, and wherein the attachment to R is the point of attachment towards the modified insulin; index n represents an integer in the range of 1 to 14, index m represents an integer in the range of 1 to 12, index o represent an integer in the range of 1 to 6, index p represents an integer in the range of 1 to 12, Z represents one of –(C=O)-OH, -NH_2, a cholesterol, 7-OH cholesterol, 7,25-dihydroxycholesterol, cholic acid, chenodeoxycholic acid, lithocholic acid, deoxycholic acid, glycocholic acid, glycodeoxycholic acid, glycolithocholic acid, glycochenodeoxycholic acid, α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, αtocotrienol, β-tocotrienol, γ-tocotrienol or δ-tocotrienol.

~~43.~~44. The compound of any one of claims 1-3 and 13, wherein the drug substance includes one or more of structures represented by Formulae FX15-FX28:



,

wherein,

each R_1 is independently selected from H, NH_2, NO_2, Cl, CF_3, I, $COCH_3$, CN, C≡CH, N_3, or Br;

each R_2 is independently selected from CF_3, H, or CH_3;

each R_3 is independently selected from C≡CH, H, N_3, or a vinyl group;

each R_4 is independently selected from NH_2, R_2 or R_3;

each R_5 is independently selected from S or NH; and

the index n is an integer in the range of 1 to 4.