diols, including cis diols, to varying degrees. While improved binding affinity of boron-containing compounds towards a specific vicinal diol of interest may be achieved, this may result in a loss of selectivity.

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

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

Thus, there is an unmet medical need for novel compounds, such as glucose-responsive insulin analogues/conjugates, that can control blood glucose levels.

SUMMARY OF THE DISCLOSURE

In an aspect, there is provided a compound comprising X1 and one or more Z1c, or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or isotopic derivative thereof,

wherein:

X1 comprises:

i. NH_2 or OH;

ii. a drug substance comprising an amine;

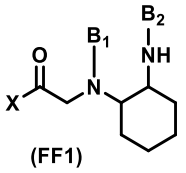
iii. a drug substance that is covalently conjugated to an amine containing linker; or

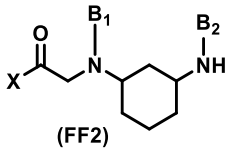
iv. an amine configured to be covalently conjugated to a drug substance;

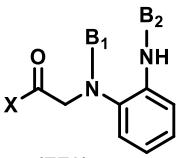
wherein each Z1c is independently selected from Formulae FF1-FF224;

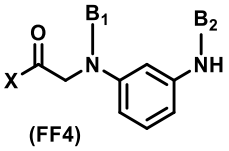
wherein each Z1c is covalently conjugated, directly or indirectly, to an amine in X1 or to OH when X1 is OH, and

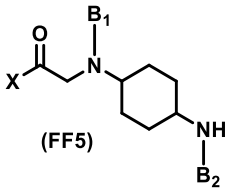
wherein Formulae FF1-FF48 are:

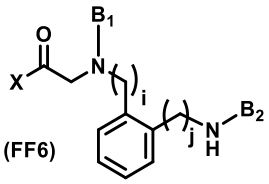

(FF1)

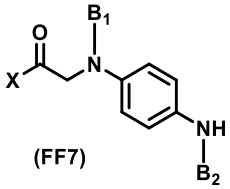

(FF2)

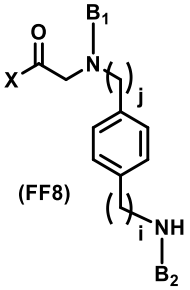

(FF3)

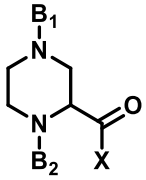

(FF4)

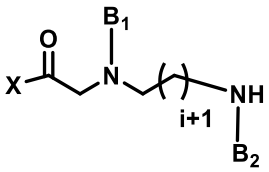

(FF5)

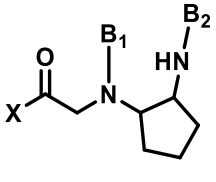

(FF6)

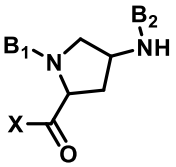

(FF7)

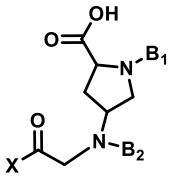

(FF8)

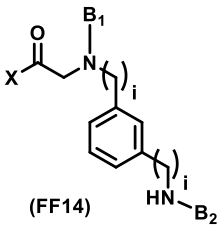

(FF9)

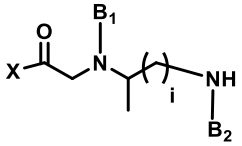

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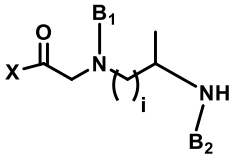

(FF11)


(FF12)

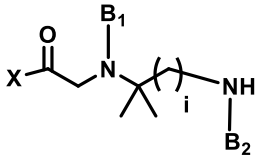

(FF13)


(FF14)

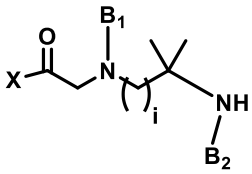

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(FF16)

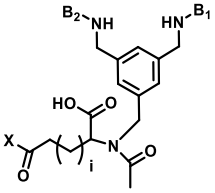
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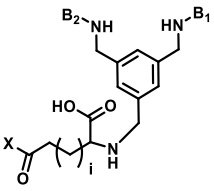
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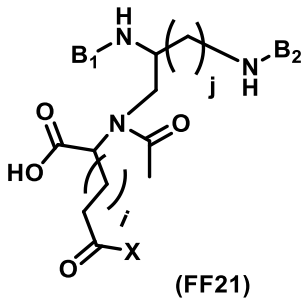
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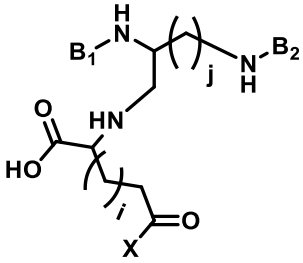
(FF19)



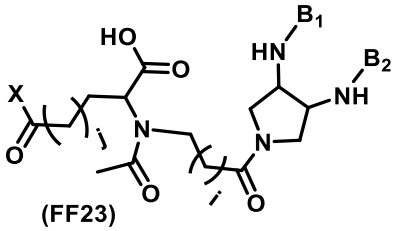
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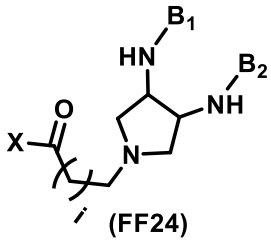
(FF21)



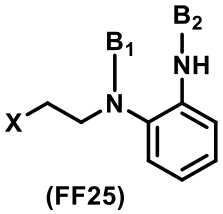
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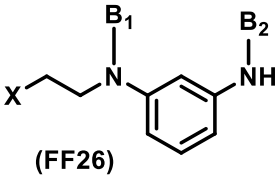
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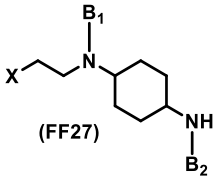
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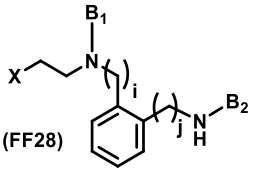
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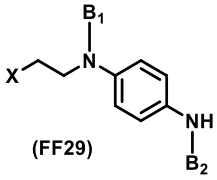
(FF26)



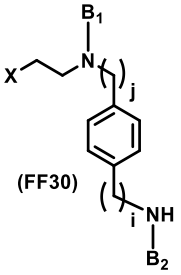
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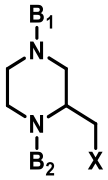
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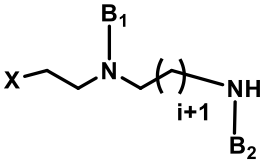
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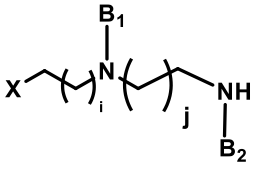
(FF30)



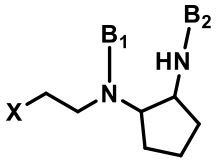
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(FF32)

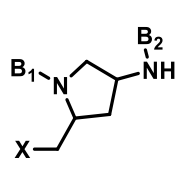


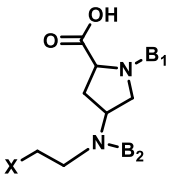
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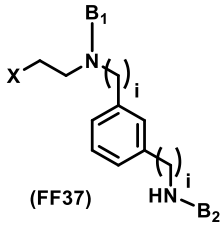


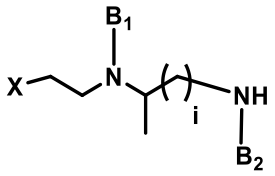
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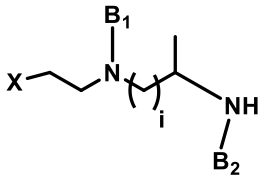
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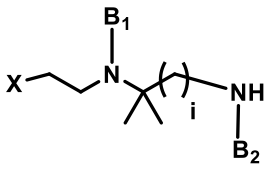

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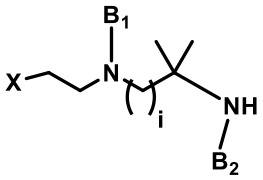

(FF36)

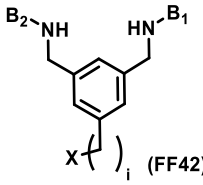

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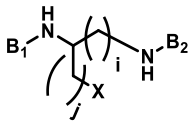

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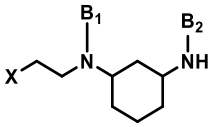

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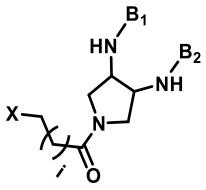

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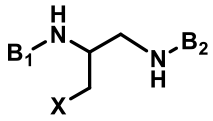

(FF41)

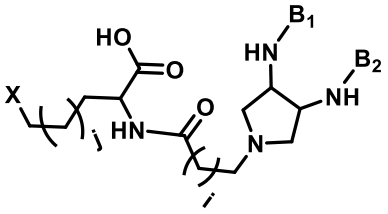

(FF42)

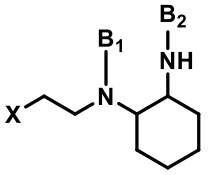

(FF43)


(FF44)


(FF45)


(FF46)


(FF47)


(FF48)

and

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

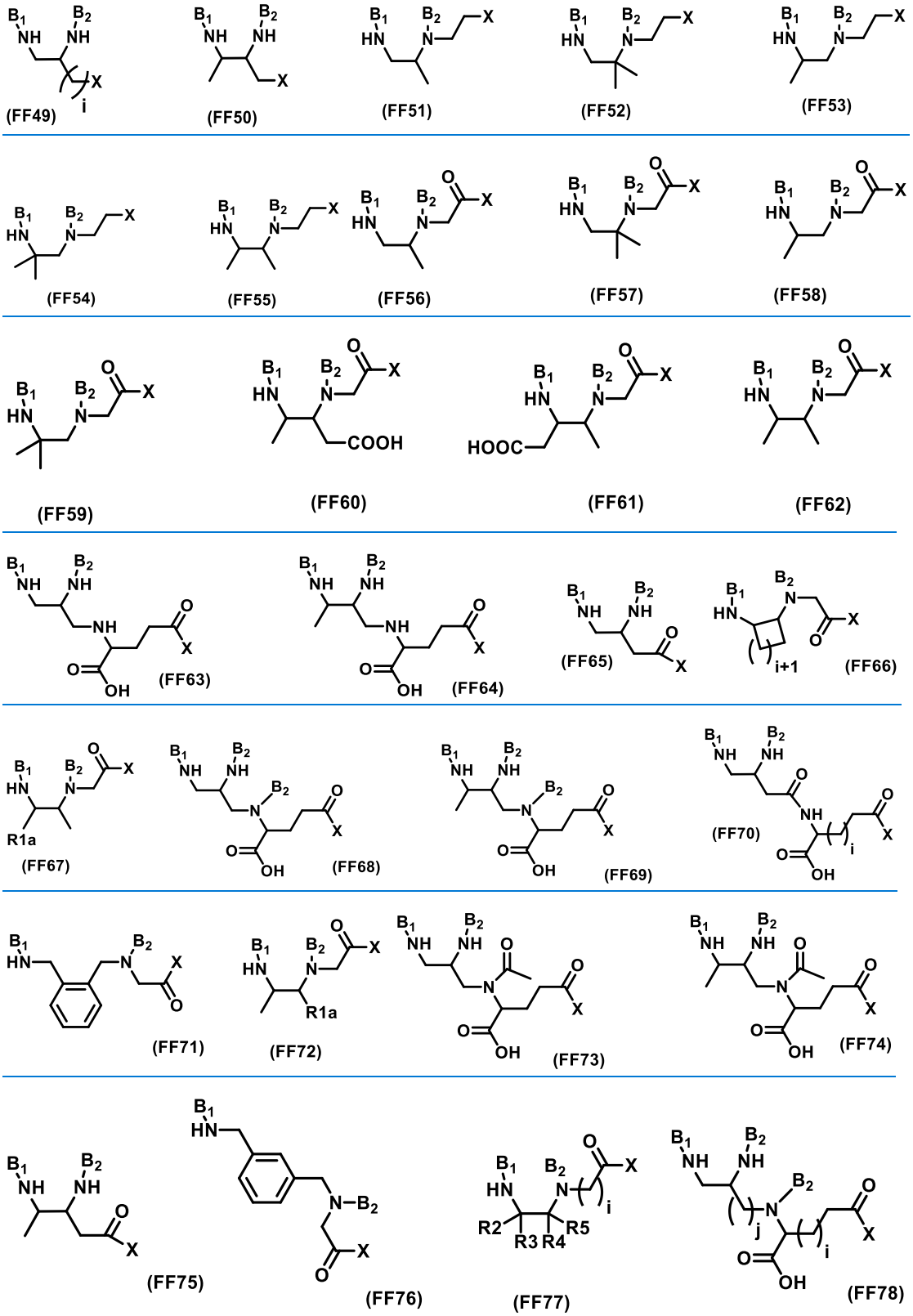
i is 1, 2, 3, 4, 5, 6, or 7;

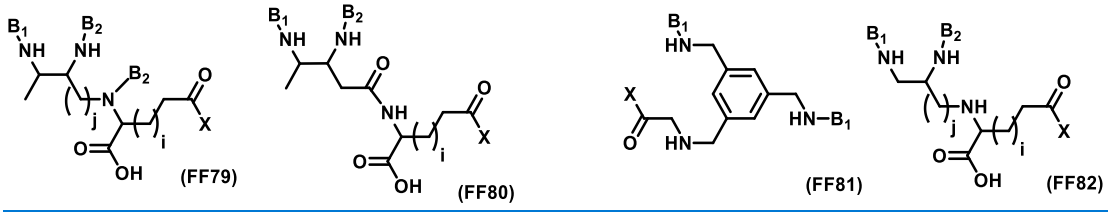
j is 1, 2, 3, 4, 5, 6, or 7; and

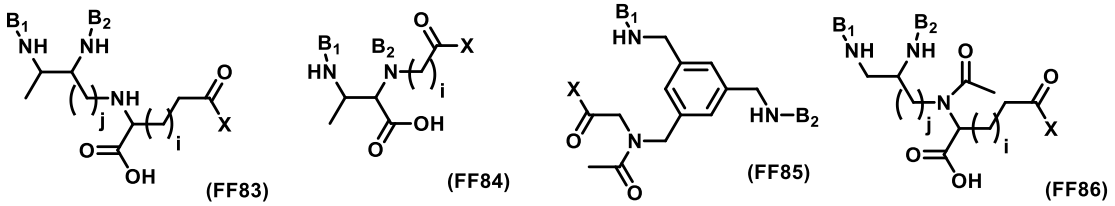
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group;

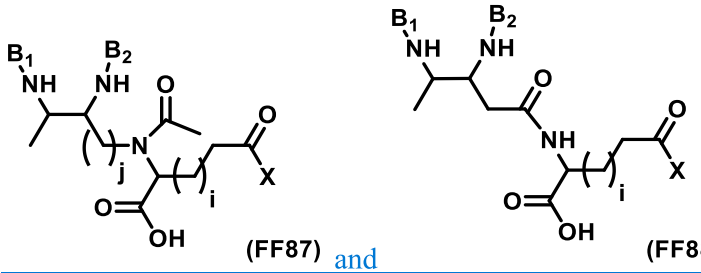
wherein Formulae FF49-FF88 are:

2d


(FF49)
(FF50)
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(FF70)
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(FF72)
(FF73)
(FF74)
(FF75)
(FF76)
(FF77)
(FF78)







and ;

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

i is 1, 2, 3, 4, 5, 6, or 7;

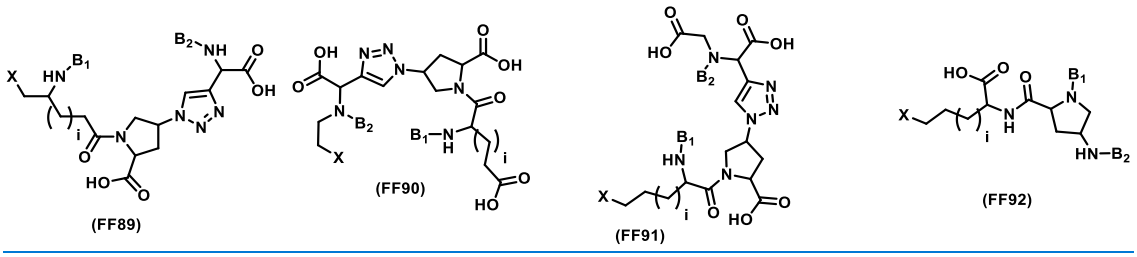
j is 1, 2, 3, 4, 5, 6, or 7;

R1a is selected from COOH, CH_3, H, and OH;

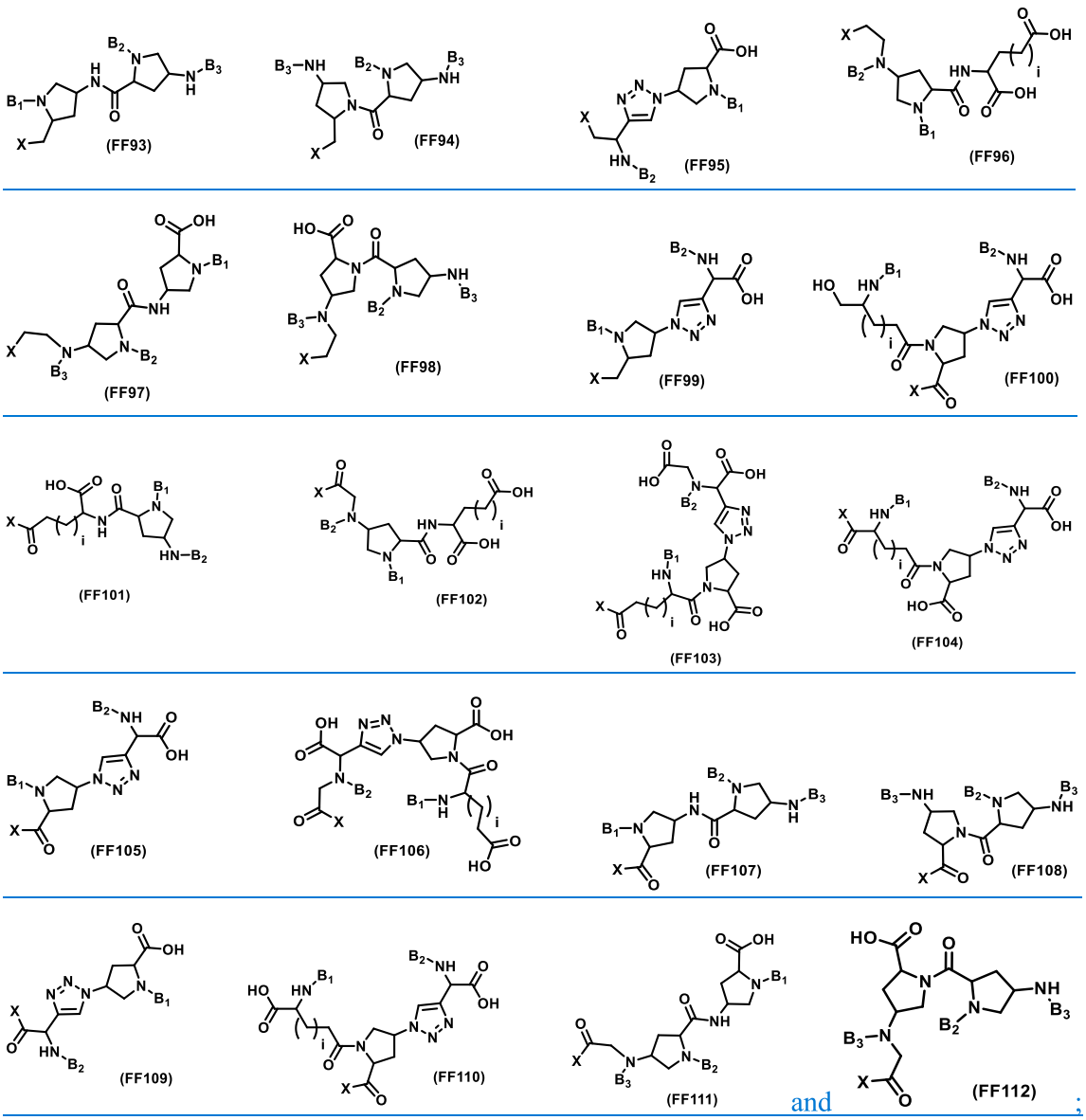
R2, R3, R4 and R5 are each independently selected from CH_3, H, OH, and COOH, and at least one of R2, R3, R4 and R5 is CH_3 or OH; and

B_1 and B_2, which may be identical or different, are each independently an aromatic boron-containing group;

wherein Formulae FF89-FF112 are:



2f



and ;

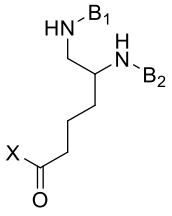
wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

i is 1, 2, 3, 4, 5, 6, or 7; and

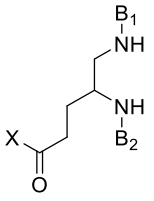
B_1, B_2 and B_3, which may be identical or different, are each independently an aromatic boron-containing group, a carboxylic acid derivative, or a H, wherein in each FF89-FF112 structure containing B1, B2 and B3 groups, at least two of the B1, B2 and B3 groups are independently an aromatic boron-containing group;

2g

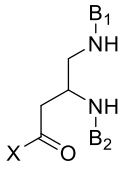
wherein Formulae FF113-FF136 are:



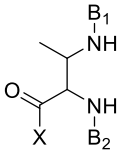
(FF113)



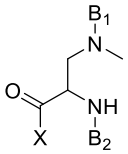
(FF114)



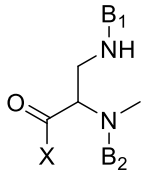
(FF115)



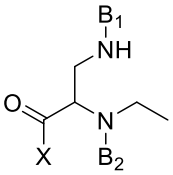
(FF116)



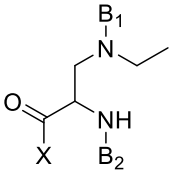
(FF117)



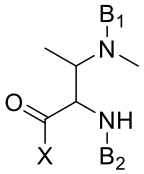
(FF118)



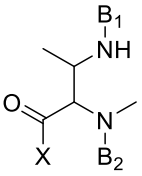
(FF119)



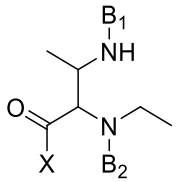
(FF120)



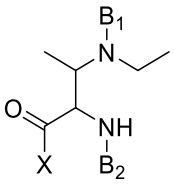
(FF121)



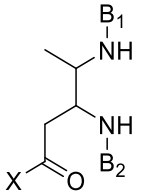
(FF122)



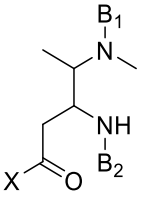
(FF123)



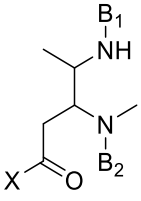
(FF124)



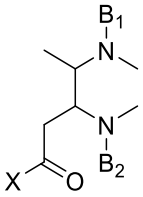
(FF125)



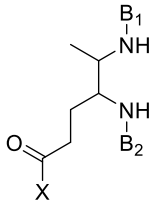
(FF126)



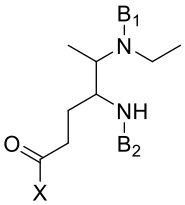
(FF127)



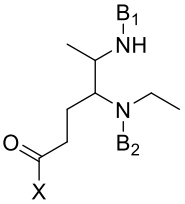
(FF128)



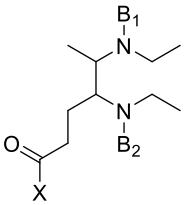
(FF129)



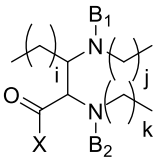
(FF130)



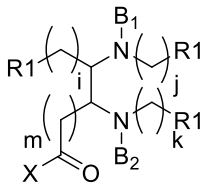
(FF131)



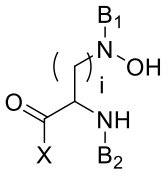
(FF132)



(FF133)

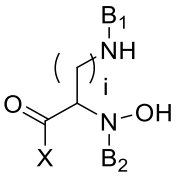


(FF134)



(FF135)

and



(FF136)

;

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

i is 1, 2, 3, 4, 5, 6, or 7;

j is 1, 2, 3, 4, 5, 6, or 7;

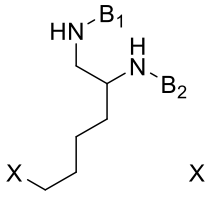
k is 1, 2, 3, 4, 5, 6, or 7;

m is 1, 2, 3, 4, 5, 6, or 7;

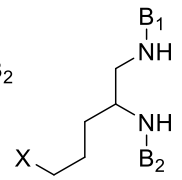
each R1 is independently selected from H, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each R1 optionally comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl, or aryl groups; and

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

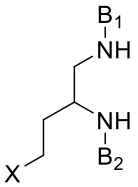
wherein Formulae FF137-FF160 are:



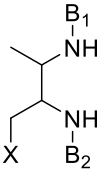
(FF137)



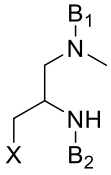
(FF138)



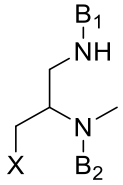
(FF139)



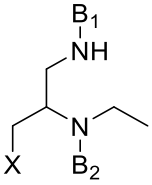
(FF140)



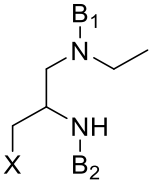
(FF141)



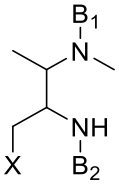
(FF142)



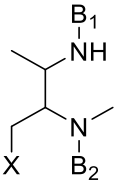
(FF143)



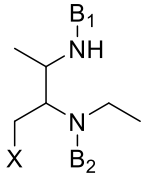
(FF144)



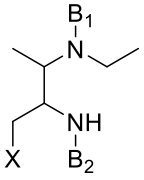
(FF145)



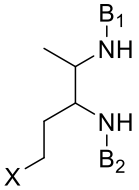
(FF146)



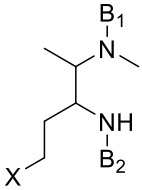
(FF147)



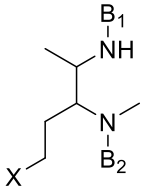
(FF148)



(FF149)

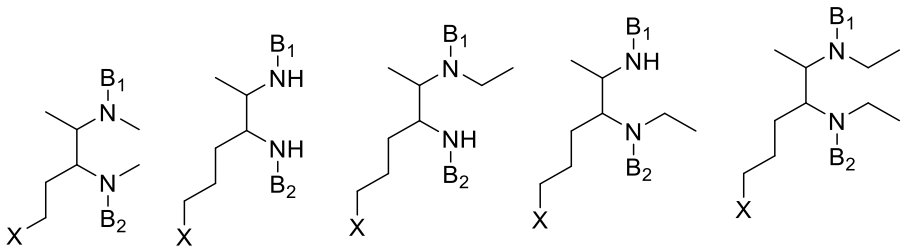


(FF150)

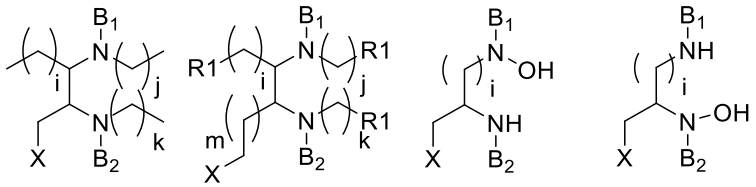


(FF151)

2i



(FF152) (FF153) (FF154) (FF155) (FF156)



(FF157) (FF158) (FF159) and (FF160) ;

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

i is 1, 2, 3, 4, 5, 6, or 7;

j is 1, 2, 3, 4, 5, 6, or 7;

k is 1, 2, 3, 4, 5, 6, or 7;

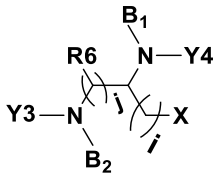
m is 1, 2, 3, 4, 5, 6, or 7;

each R1 is independently selected from H, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each R1 optionally comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl, or aryl groups; and

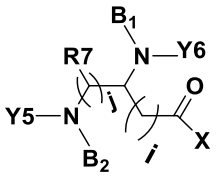
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group;

wherein Formulae FF161-FF164 are:

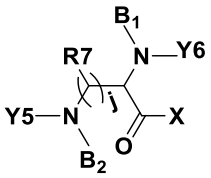
2j



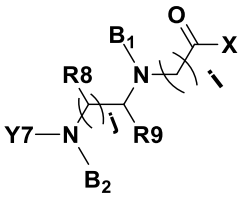
(FF161)



(FF162)



(FF163)



(FF164)

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

i is 1, 2, 3, 4, or 5;

j is 1, 2, 3, 4, or 5;

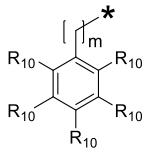
each R6, R7, R8, and R9 for different values of j is independently selected from H, CF_3, CH_3, CHF_2, and $(CH_2)_mCH_3$, wherein m is 1, 2, 3, 4, or 5;

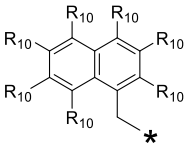
Y3, Y4, Y5, Y6 and Y7 are each independently selected from H, CH_2—X4, and Formulae IV-1 to IV-135;

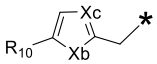
wherein X4 is selected from -COOH, $-(CH_2)_mCOOH$, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each X4 optionally comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl or aryl groups; wherein m is 1, 2, 3, 4, or 5;

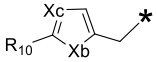
wherein at least one of Y5, Y6 and Y7 in Formulae FF162 and FF163 is not H and at least one of Y7, R8 and R9 in FF164 is not H; and

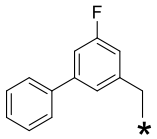
wherein Formulae IV-1 to IV-135 are:

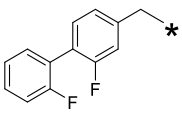

(IV-1)

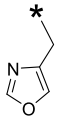

(IV-2)

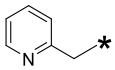

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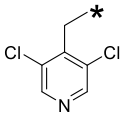

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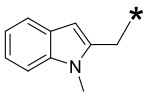

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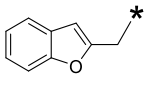

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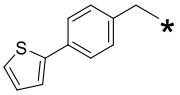

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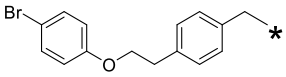

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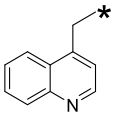

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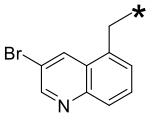

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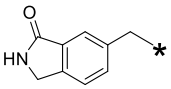

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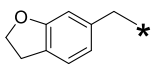

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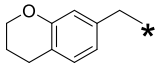

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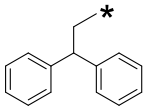

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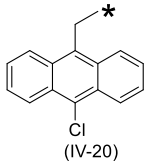

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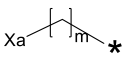

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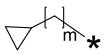

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(IV-18)

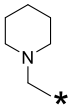

(IV-19)


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(IV-21)

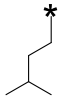

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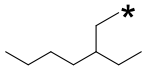

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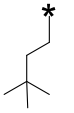

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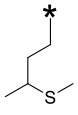

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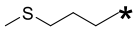

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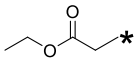

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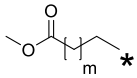

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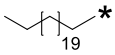

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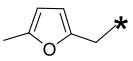

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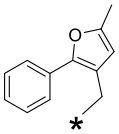

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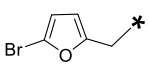

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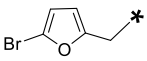

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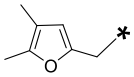

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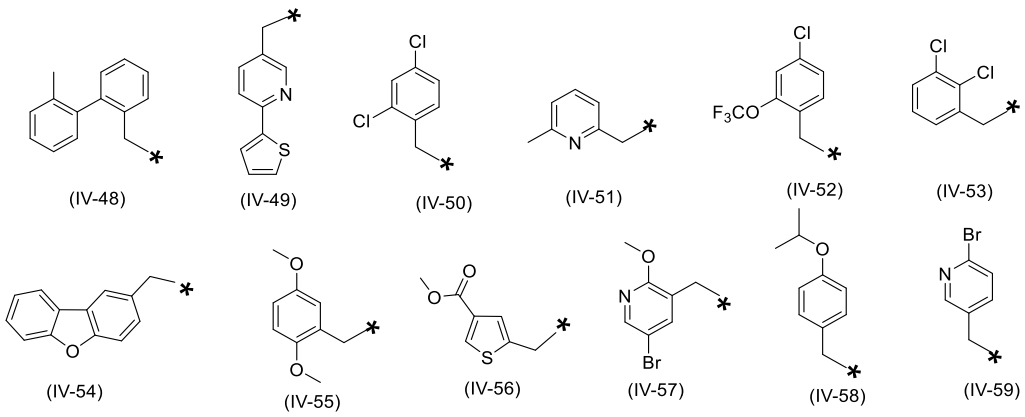
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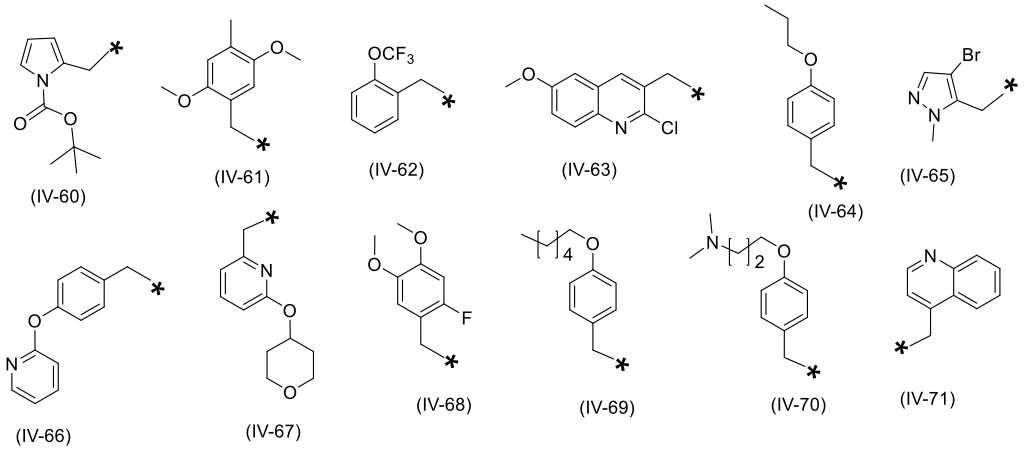
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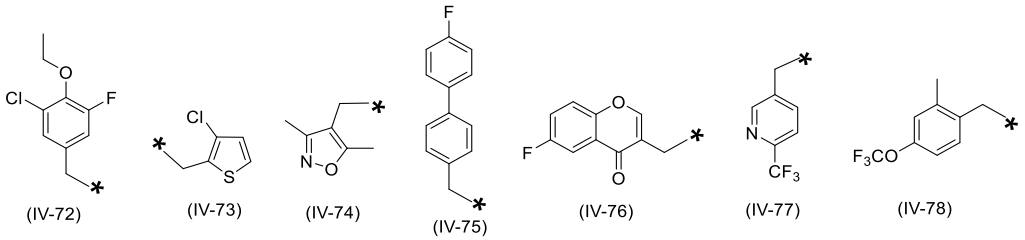
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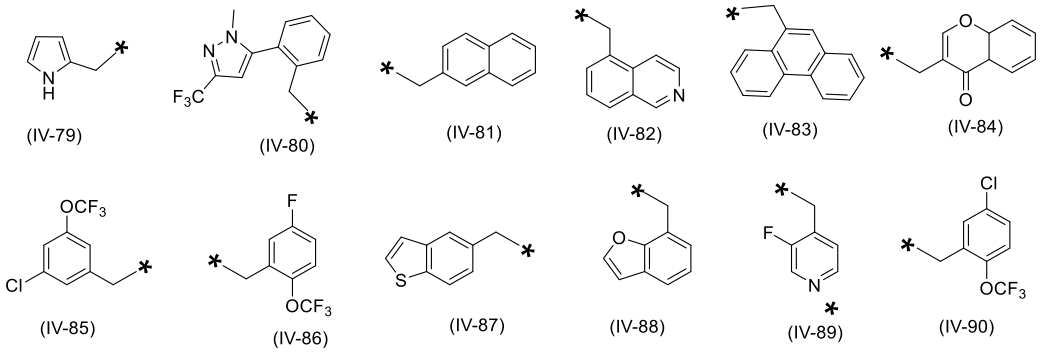
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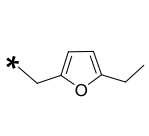

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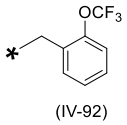

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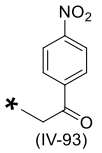

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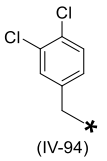

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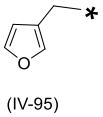
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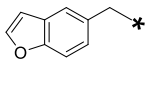

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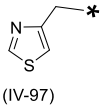

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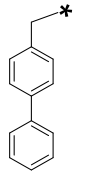

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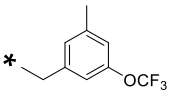

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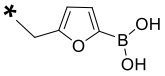

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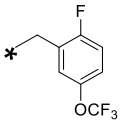

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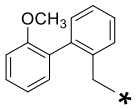

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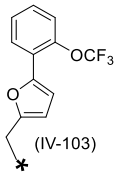

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(IV-99)

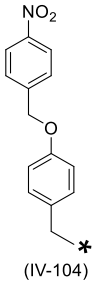

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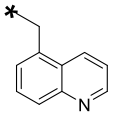

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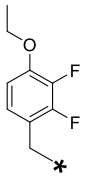

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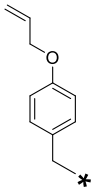

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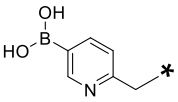
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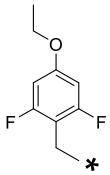

(IV-104)

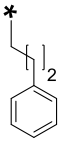

(IV-105)

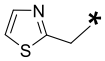

(IV-106)

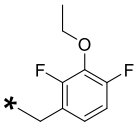

(IV-107)

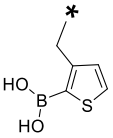

(IV-108)

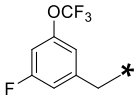

(IV-109)

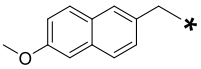

(IV-110)

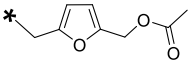

(IV-111)

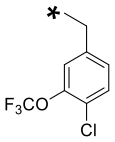

(IV-112)

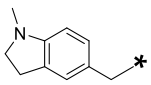

(IV-113)


(IV-114)

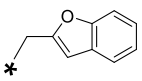

(IV-115)

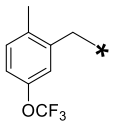

(IV-116)

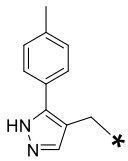

(IV-117)

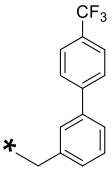

(IV-118)

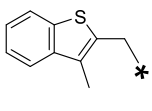

(IV-119)

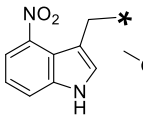

(IV-120)

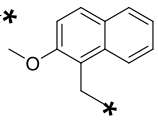

(IV-121)

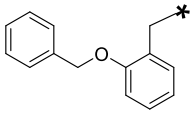

(IV-122)

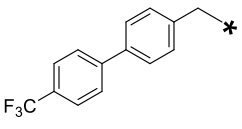

(IV-123)

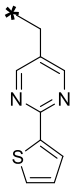

(IV-124)


(IV-125)


(IV-126)


(IV-127)


(IV-128)


(IV-129)


(IV-130)

(IV-131)

(IV-132)

(IV-133)

(IV-134)

and (IV-135) ;

2n

wherein Xa represents CH=O, CHF_2, CF_3, CH_2SH, COOH, CH_2OH, CH_2NO_2, CH_2NH_2, CH_3, $C(CH_3)_3$, $CH(CH_3)_2$, $CH((CH_2)_3\text{-}CH_3)_2$, or $CH(CH_2\text{-}CH_3)_2$;

Xb represents O, NH, CH_2, or S;

Xc represents CH or N;

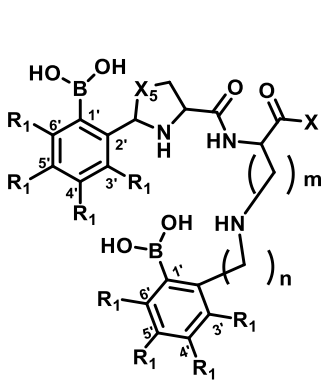
each R_{10} is independently selected from H, F, Cl, Br, CH_3, CF_3, CH=O, OH, COOH, and $(CH_2)_nCH_3$,

m is 1, 2, 3, 4, or 5; and n is 1, 2, 3, 4, or 5;

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

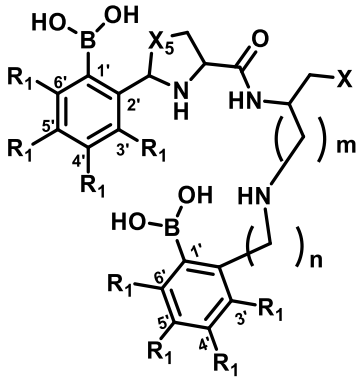
* in Formulae IV-1 to IV-135 represents a point of attachment to corresponding Formulae FF161-164;

wherein Formulae FF165-FF166 are:



(FF165)

and



(FF166)

;

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

m is 1, 2, 3, 4, 5, 6, or 7;

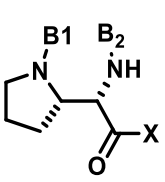
n is 1, 2, 3, 4, 5, 6, or 7;

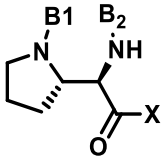
X5 is S, O, or NH; and

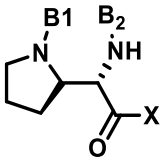
each R_1 is independently selected from H, F, Cl, Br, OH, $CH_2\text{-}NH_2$, NH_2, $(C=O)\text{-}NH_2$, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, $—(SO_2)NH\text{-}CH_3$, $—(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3, 4, 5, 6, or 7;

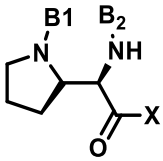
2o

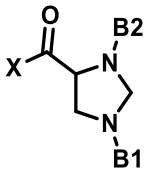
wherein Formulae FF167-FF192 are:

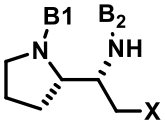

(FF167)

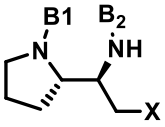

(FF168)

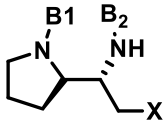

(FF169)

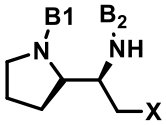

(FF170)

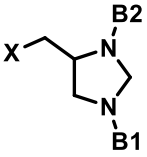

(FF171)

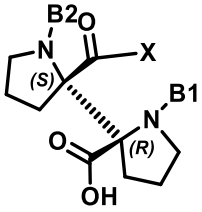

(FF172)

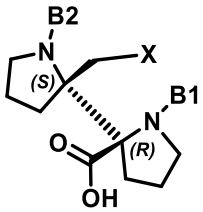

(FF173)

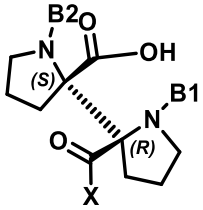

(FF174)

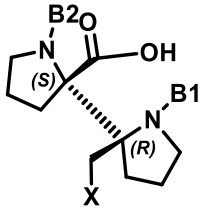

(FF175)

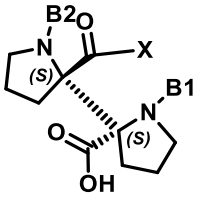

(FF176)

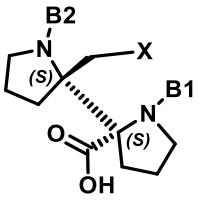

(FF177)

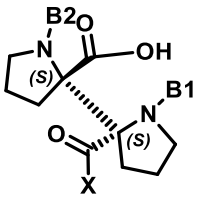

(FF178)

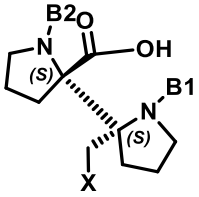

(FF179)

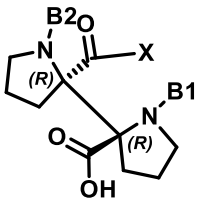

(FF180)

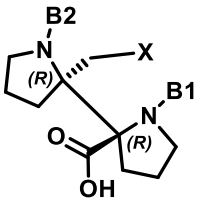

(FF181)

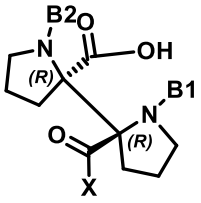

(FF182)

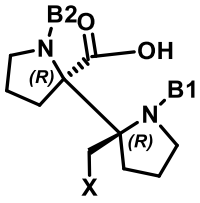

(FF183)

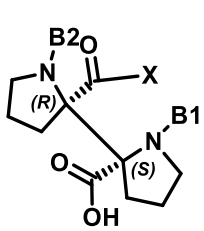

(FF184)

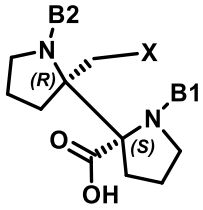

(FF185)

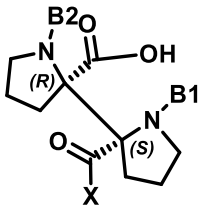

(FF186)

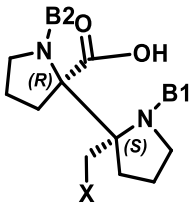

(FF187)


(FF188)


(FF189)


(FF190)

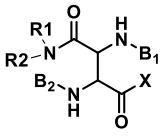

(FF191)

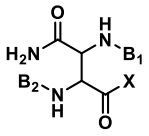

(FF192) and ;

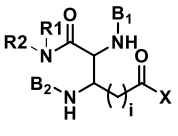
wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

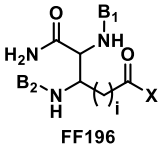
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group;

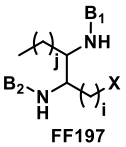
wherein Formulae FF193-FF209 are:

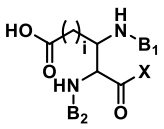

FF193

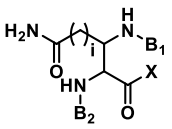

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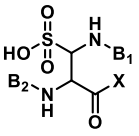

FF195

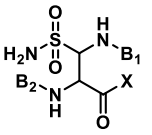

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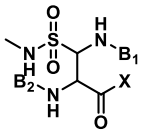

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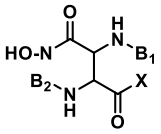

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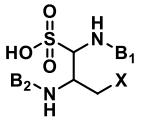

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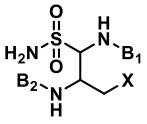

FF200

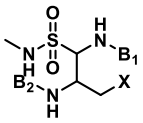

FF201

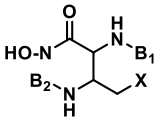

FF202

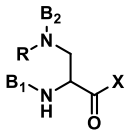

FF203

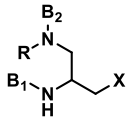

FF204


FF205


FF206


FF207


FF208


FF209 ;

wherein R in FF208 and FF209 is an alkyl, aryl or halide that is covalently conjugated through at least one CH_2 group to the amino group in the side chain of FF208 or FF209,

R1 and R2 are independently selected from H, CH_3, alkyl, and formulae IV-1 to IV-135;

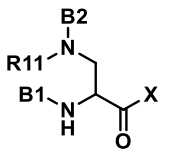
i is 1, 2, 3, 4, or 5;

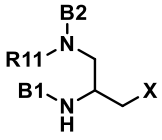
j is 1, 2, 3, 4, or 5; and

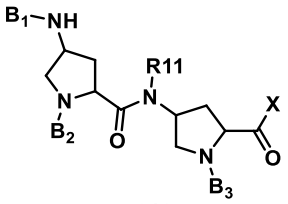
wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH; and

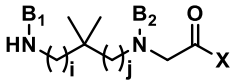
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group, and

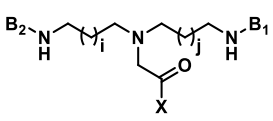
wherein Formulae FF210-FF224 are:

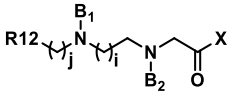

FF210

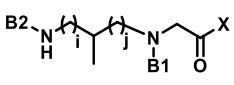

FF211

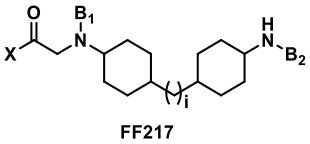

FF212

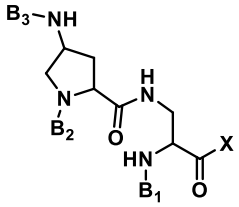

FF213

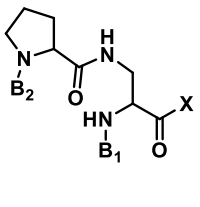

FF214

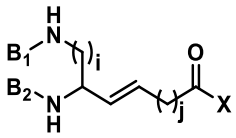

FF215

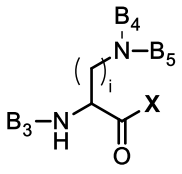

FF216

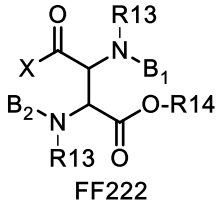

FF217

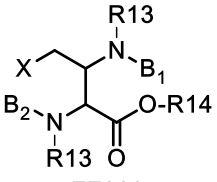

FF218


FF219


FF220


FF221


FF222


FF223


, and **FF224**;

wherein R11 in FF210 to FF212 is selected from Formulae IV-1 to IV-135 and R12 is selected from an amine, a hydroxyl, an alkyl, and a halide group;

wherein each R13 is independently selected from H, CH_3, alkyl, aryl and Formulae IV-1 to IV-135; R14 is selected from H, CH_3, alkyl, aryl and heteroaryl;

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

X'' represents a point of covalent attachment to an amine --N in the compound, wherein -- represents a single covalent bond to a CH_2 or CH group in the compound;

i is 1, 2, 3, 4, or 5;

j is 1, 2, 3, 4, or 5; and

wherein at least one primary or secondary amine in FF1-FF223 is optionally covalently conjugated to B_6; and

B_1, B_2, B_3, B_4, B_5, and B_6 each independently represents an aromatic boron-containing group, wherein in each FF structure containing B_1, B_2 and B_3 groups, at least two of the B1, B2 and B3 groups are independently an aromatic boron-containing group.

In another aspect, there is provided the use of the compound as defined above in the manufacture of a medicament as a therapeutic or prophylactic agent.

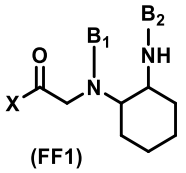
In another aspect, there is provided a method of making a compound as defined above, wherein the method comprises at least one alkylation and/or amidation step.

In another aspect, there is provided the use of a device or formulation comprising a compound as defined above and Examples 1-880 in the manufacture of a medicament for the treatment of a subject.

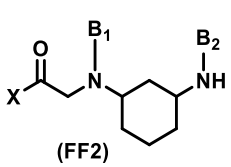
In another aspect ,there is provided the use of the compound as defined above or the composition or the mixture as defined above in the manufacture of a medicament for the treatment or prevention of diabetes, impaired glucose tolerance, hyperglycemia, or metabolic syndrome.

In another aspect, there is provided a compound selected from Formulae FF1-FF224:

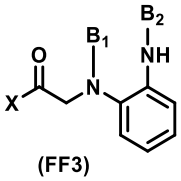
wherein Formulae FF1-FF48 are:



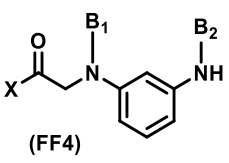
(FF1)



(FF2)

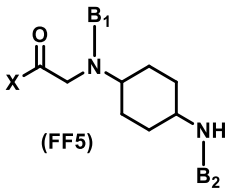


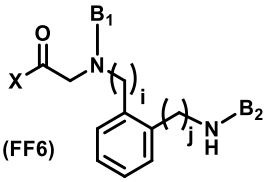
(FF3)

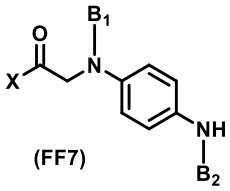


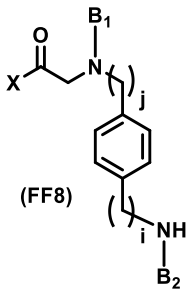
(FF4)

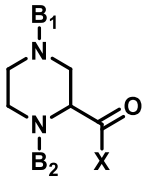
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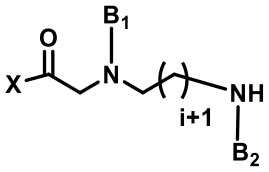

(FF5)

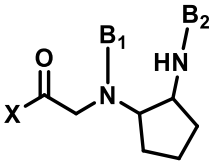

(FF6)

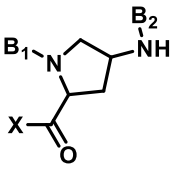

(FF7)

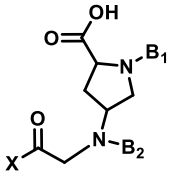

(FF8)

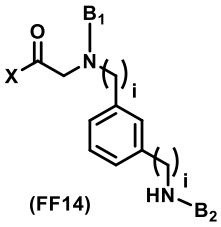

(FF9)

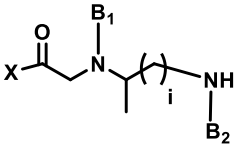

(FF10)

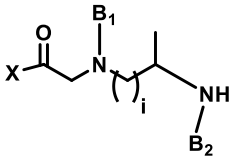

(FF11)

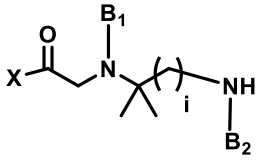

(FF12)

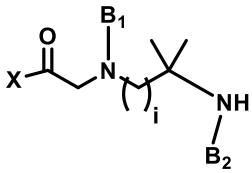

(FF13)

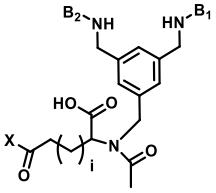

(FF14)

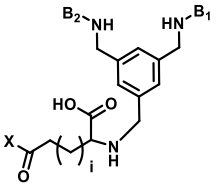

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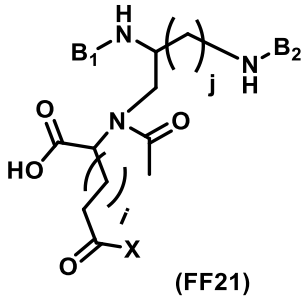

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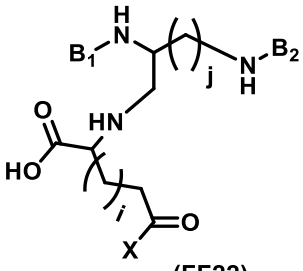

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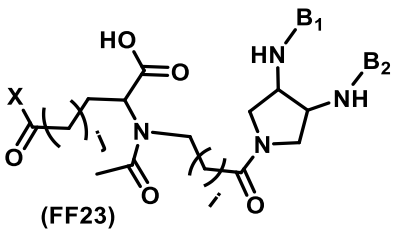

(FF18)


(FF19)

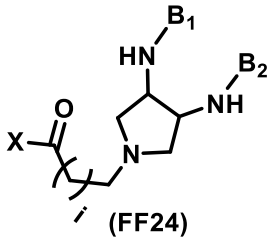

(FF20)

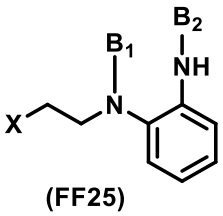

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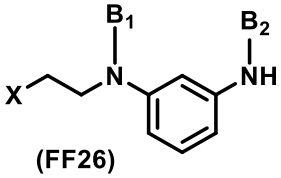

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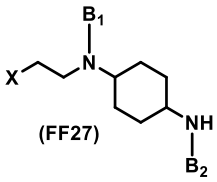

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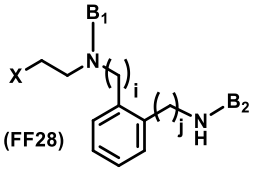
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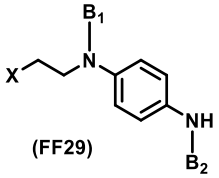

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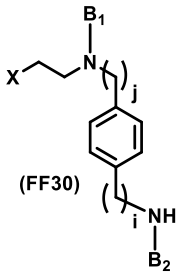

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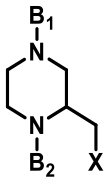

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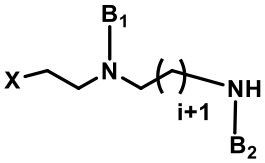

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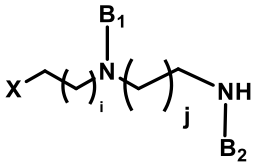

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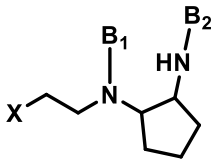

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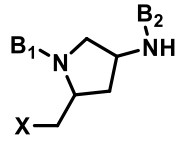

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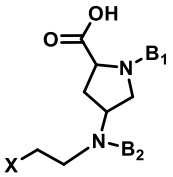

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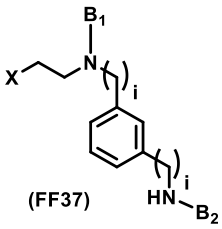

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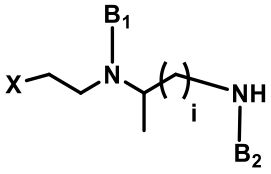

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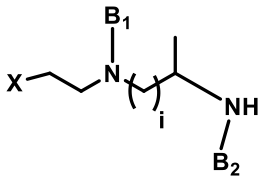

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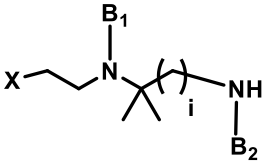

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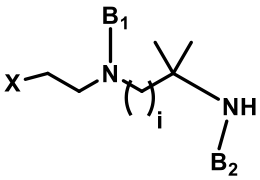

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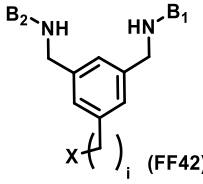

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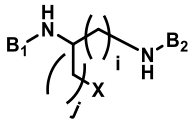

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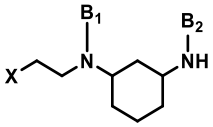

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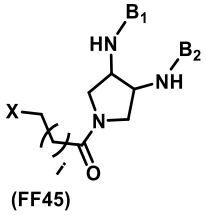

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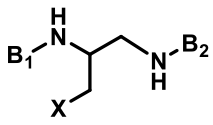

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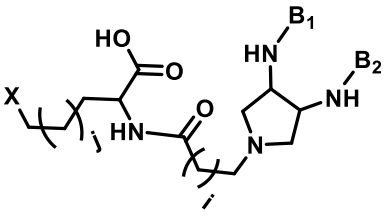

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(FF45)

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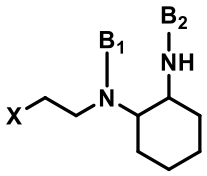


(FF46)



(FF47)

and



(FF48);

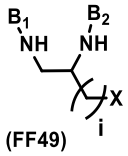
wherein X is selected from an amine, OH, and halogen; and

i is 1, 2, 3, 4, 5, 6, or 7;

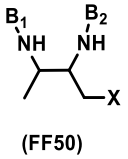
j is 1, 2, 3, 4, 5, 6, or 7; and

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

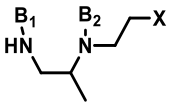
wherein Formulae FF49-FF88 are:



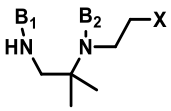
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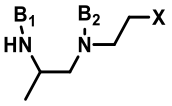
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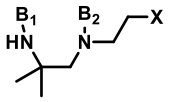
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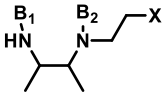
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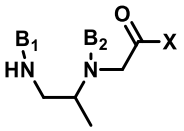
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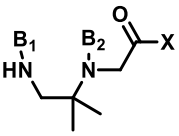
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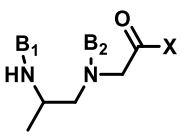
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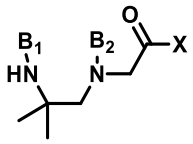
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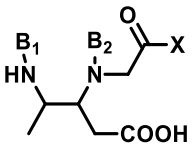
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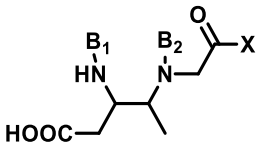
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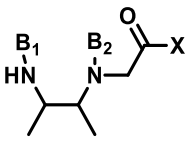
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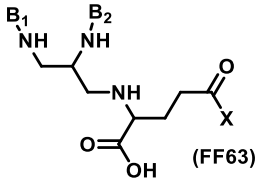
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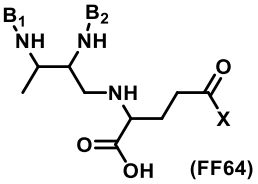
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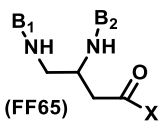
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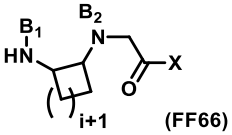
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(FF64)

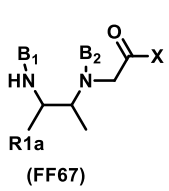


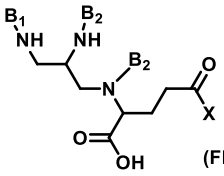
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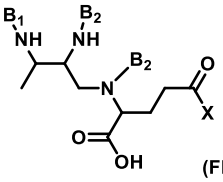


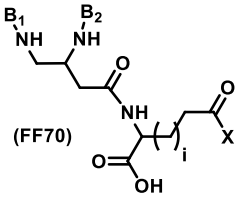
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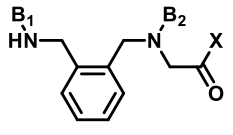
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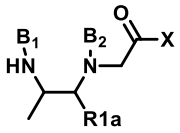

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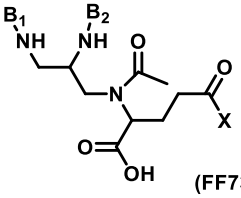

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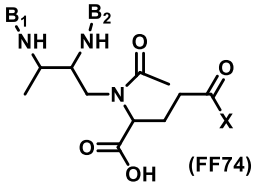

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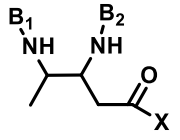

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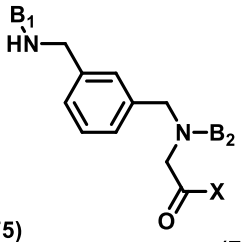

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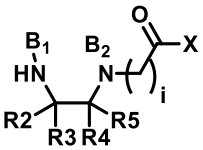

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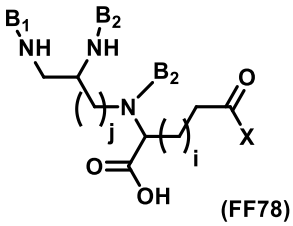

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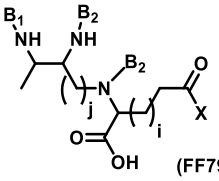

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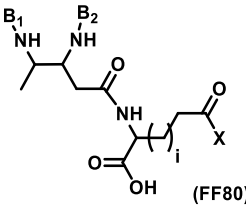

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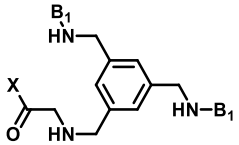

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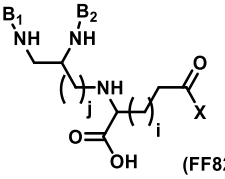

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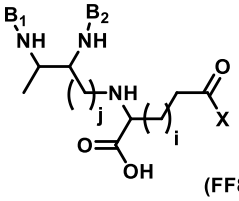

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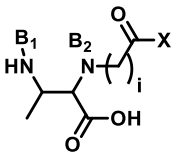

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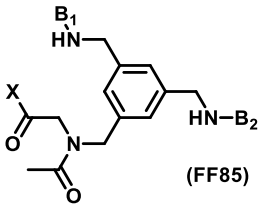

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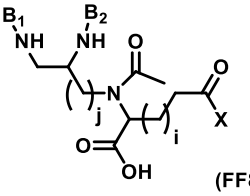

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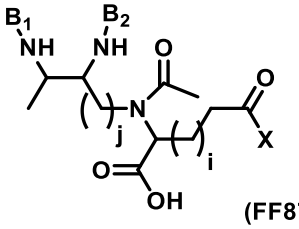

(FF82)

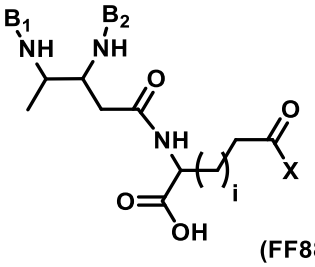

(FF83)


(FF84)


(FF85)


(FF86)


(FF87) and


(FF88) ;

wherein X is selected from an amine, OH, and halogen;

i is 1, 2, 3, 4, 5, 6, or 7;

2w

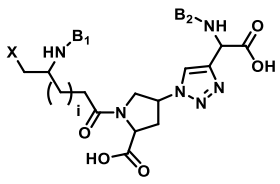
j is 1, 2, 3, 4, 5, 6, or 7;

R1a is selected from COOH, CH_3, H, and OH;

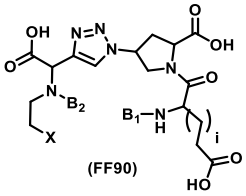
R2, R3, R4 and R5 is each independently selected from CH_3, H, OH, and COOH, and at least one of R2, R3, R4 and R5 is CH_3 or OH; and

B_1 and B_2, which may be identical or different, are each independently an aromatic boron-containing group; and

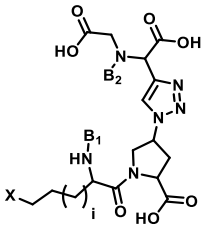
wherein Formulae FF89-FF112 are:



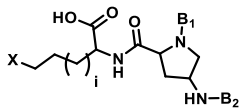
(FF89)



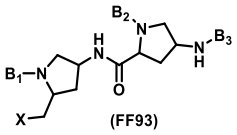
(FF90)



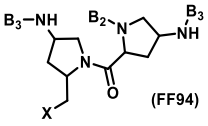
(FF91)



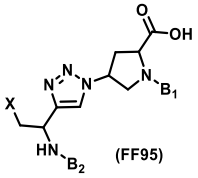
(FF92)



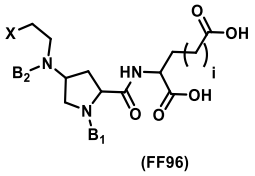
(FF93)



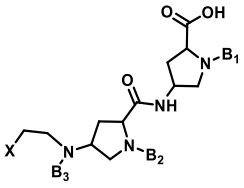
(FF94)



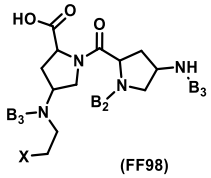
(FF95)



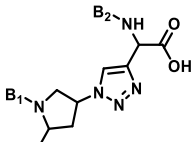
(FF96)



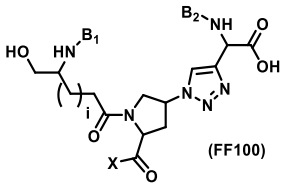
(FF97)



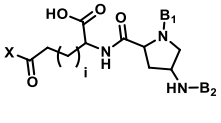
(FF98)



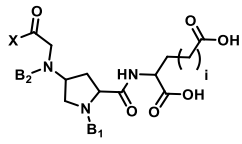
(FF99)



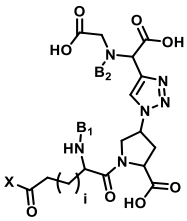
(FF100)



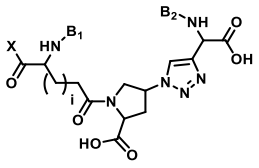
(FF101)



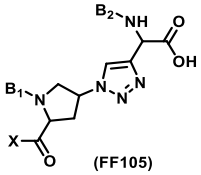
(FF102)



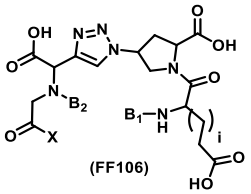
(FF103)



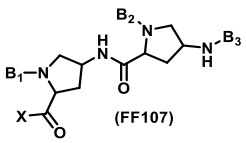
(FF104)



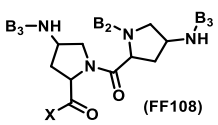
(FF105)



(FF106)

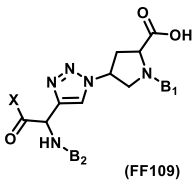


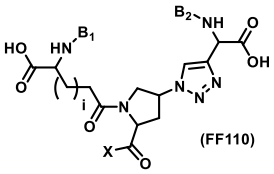
(FF107)

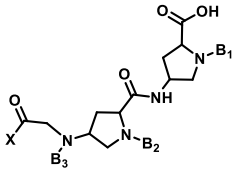


(FF108)

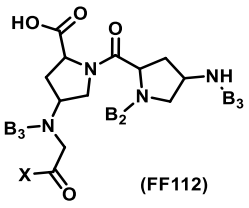
2x


(FF109)


(FF110)


(FF111)

and

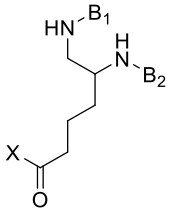

(FF112)

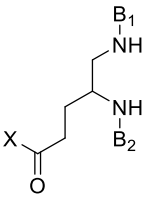
;

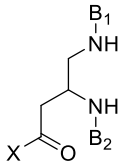
wherein X is selected from an amine, OH, and halogen;

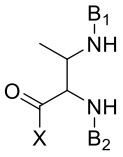
i is 1, 2, 3, 4, 5, 6, or 7; and

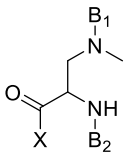
B_1, B_2 and B_3, which may be identical or different, each independently represents an aromatic boron-containing group, a carboxylic acid derivative, or a H, wherein at least two of B1, B2 and B3 in each FF structure are independently an aromatic boron-containing group; and wherein Formulae FF113-FF136 are:

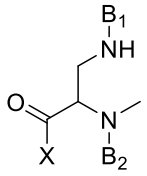

(FF113)

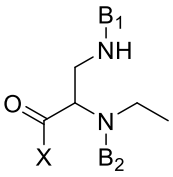

(FF114)

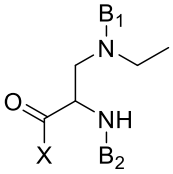

(FF115)

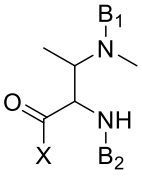

(FF116)

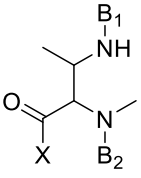

(FF117)

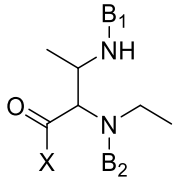

(FF118)

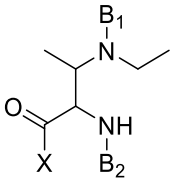

(FF119)

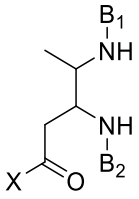

(FF120)

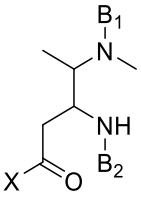

(FF121)

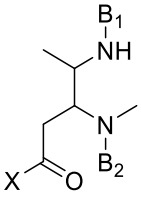

(FF122)

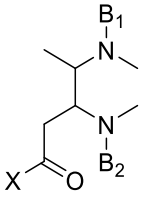

(FF123)


(FF124)

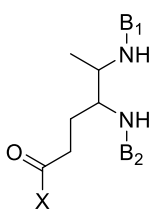

(FF125)

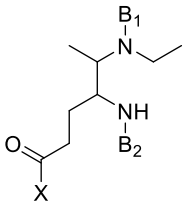

(FF126)

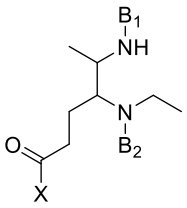

(FF127)

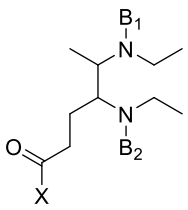

(FF128)

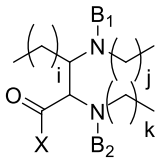
2y

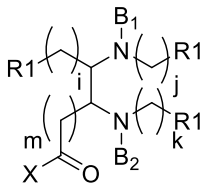

(FF129)

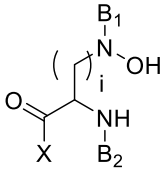

(FF130)


(FF131)

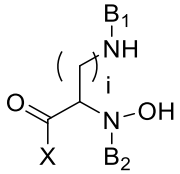

(FF132)


(FF133)


(FF134)


(FF135)

and


(FF136)

;

wherein X is selected from an amine, OH, and halogen;

i is 1, 2, 3, 4, 5, 6, or 7;

j is 1, 2, 3, 4, 5, 6, or 7;

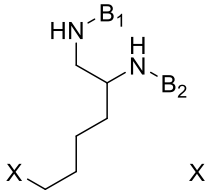
k is 1, 2, 3, 4, 5, 6, or 7;

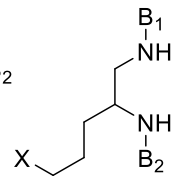
m is 1, 2, 3, 4, 5, 6, or 7;

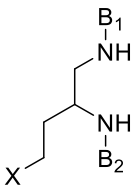
each R1 is independently selected from H, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each R1 optionally comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl or aryl groups; and

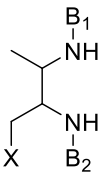
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group; and

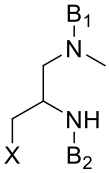
wherein Formulae FF137-FF160 are:


(FF137)

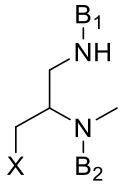

(FF138)

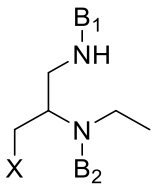

(FF139)

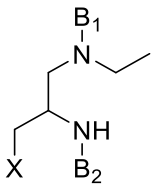

(FF140)

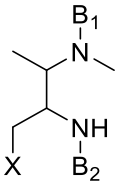

(FF141)

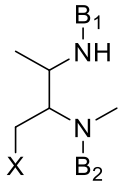
2z

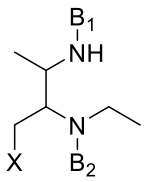

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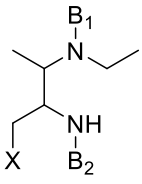

(FF143)

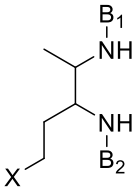

(FF144)

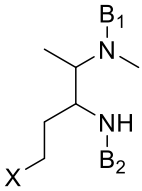

(FF145)

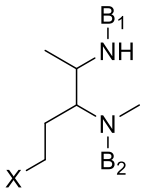

(FF146)

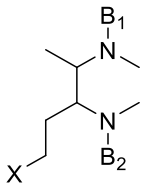

(FF147)

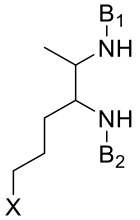

(FF148)

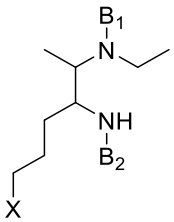

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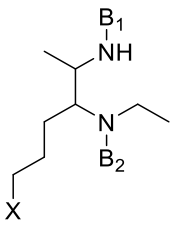

(FF150)

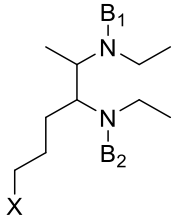

(FF151)

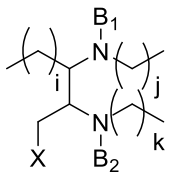

(FF152)

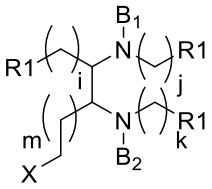

(FF153)

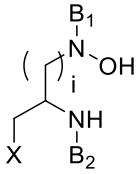

(FF154)

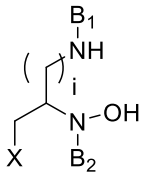

(FF155)


(FF156)


(FF157)


(FF158)


(FF159)


and (FF160) ;

wherein X is selected from an amine, OH, and halogen;

i is 1, 2, 3, 4, 5, 6, or 7;

j is 1, 2, 3, 4, 5, 6, or 7;

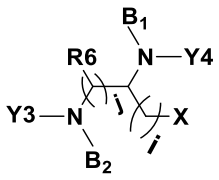
k is 1, 2, 3, 4, 5, 6, or 7;

m is 1, 2, 3, 4, 5, 6, or 7;

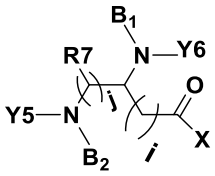
each R1 is independently selected from H, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each R1 optionally comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl or aryl groups; and

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

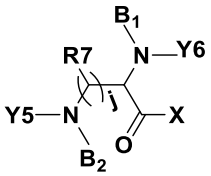
wherein Formulae FF161-FF164 are:



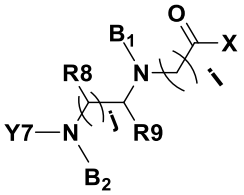
(FF161)



(FF162)



(FF163)



(FF164)

wherein X is selected from an amine, OH, and halogen;

i is 1, 2, 3, 4, or 5;

j is 1, 2, 3, 4, or 5;

each R6, R7, R8, and R9 for different values of j is independently selected from H, CF_3, CH_3, CHF_2, and $(CH_2)_mCH_3$, wherein m is 1, 2, 3, 4, or 5;

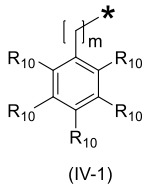
Y3, Y4, Y5, Y6 and Y7 are each independently selected from H, CH_2—X4, and Formulae IV-1 to IV-135;

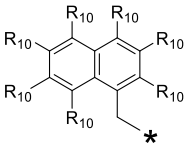
wherein X4 is selected from -COOH, $-(CH_2)_mCOOH$, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each optionally comprising one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl or aryl groups; wherein m is 1, 2, 3, 4, or 5;

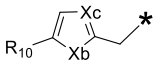
wherein at least one of Y5, Y6, and Y7 in Formulae FF162 and FF163 is not H and at least one of Y7, R8 and R9 in FF164 is not H; and

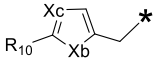
wherein Formulae IV-1 to IV-135 are:

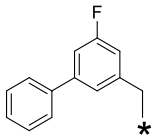
2ab

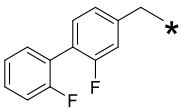

(IV-1)

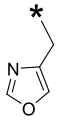

(IV-2)

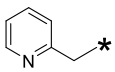

(IV-3)

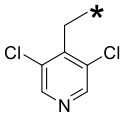

(IV-4)

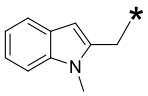

(IV-5)

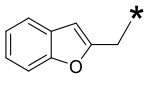

(IV-6)

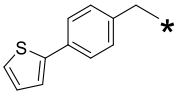

(IV-7)

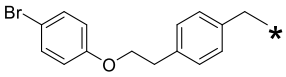

(IV-8)

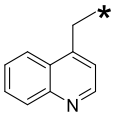

(IV-9)

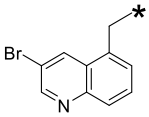

(IV-10)

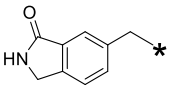

(IV-11)

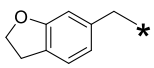

(IV-12)

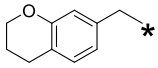

(IV-13)

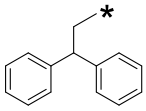

(IV-14)

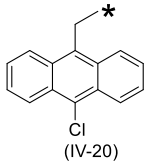

(IV-15)

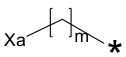

(IV-16)

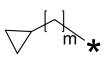

(IV-17)


(IV-18)

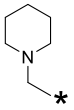

(IV-19)


(IV-20)


(IV-21)

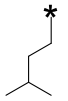

(IV-22)

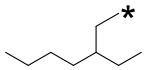

(IV-23)

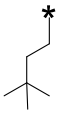

(IV-24)


(IV-25)

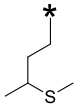

(IV-26)

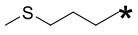

(IV-27)

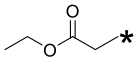

(IV-28)

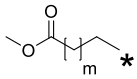

(IV-29)

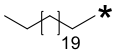

(IV-30)

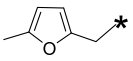

(IV-31)

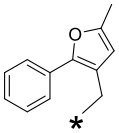

(IV-32)

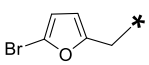

(IV-33)

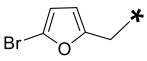

(IV-34)

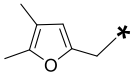

(IV-35)


(IV-36)


(IV-37)


(IV-38)


(IV-39)


(IV-40)

(IV-41)

(IV-42)

(IV-43)

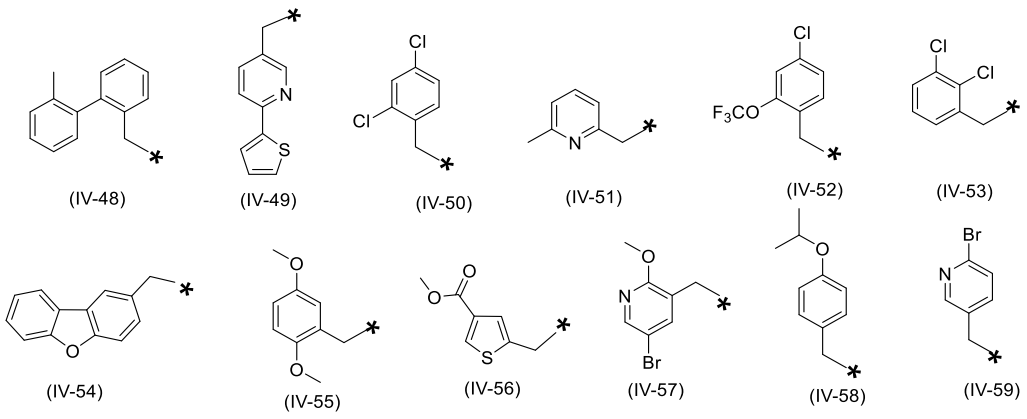
(IV-44)

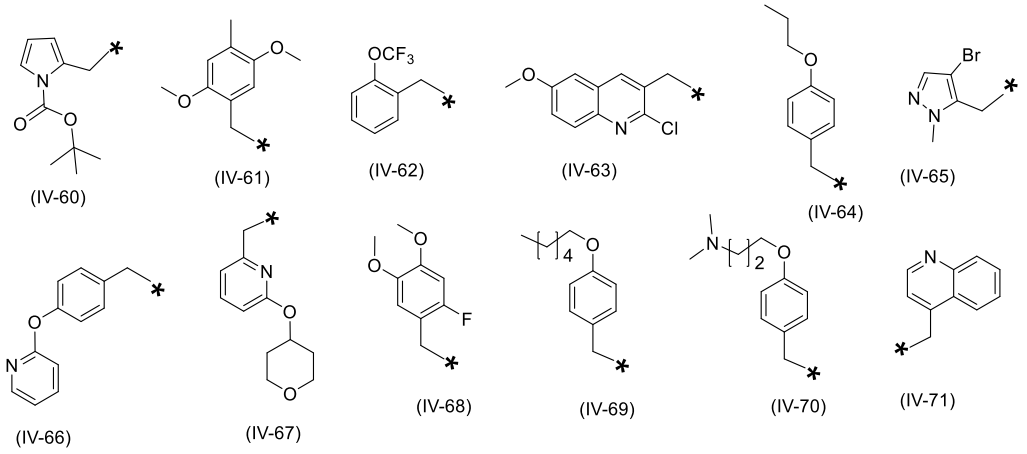
(IV-45)

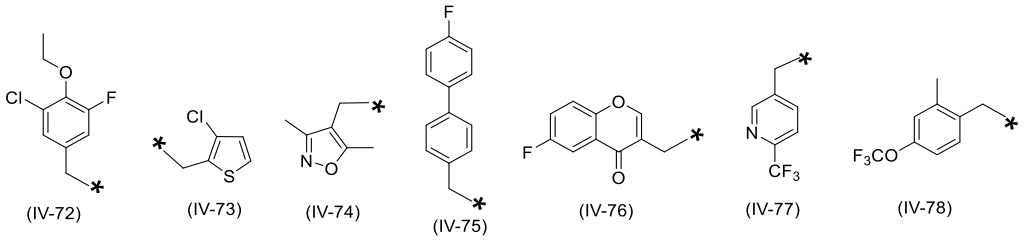
(IV-46)

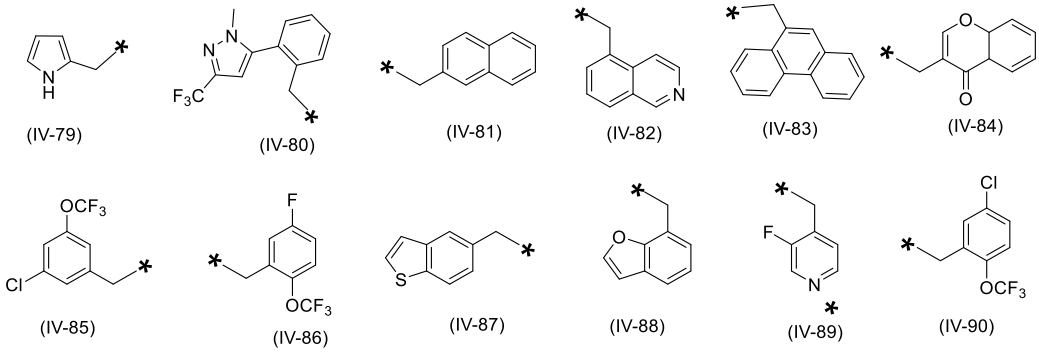
(IV-47)

2ac

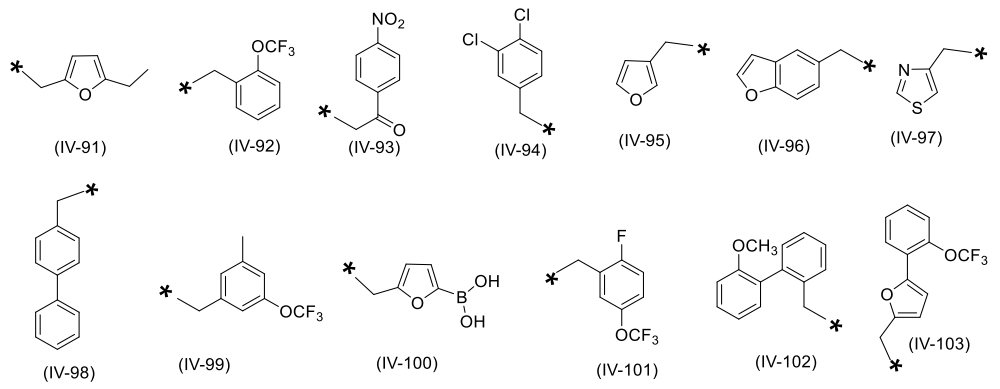

(IV-48)
(IV-49)
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(IV-59)

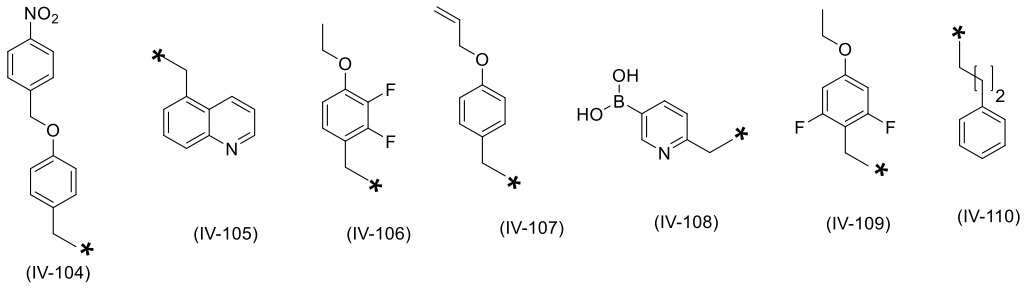

(IV-60)
(IV-61)
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(IV-71)

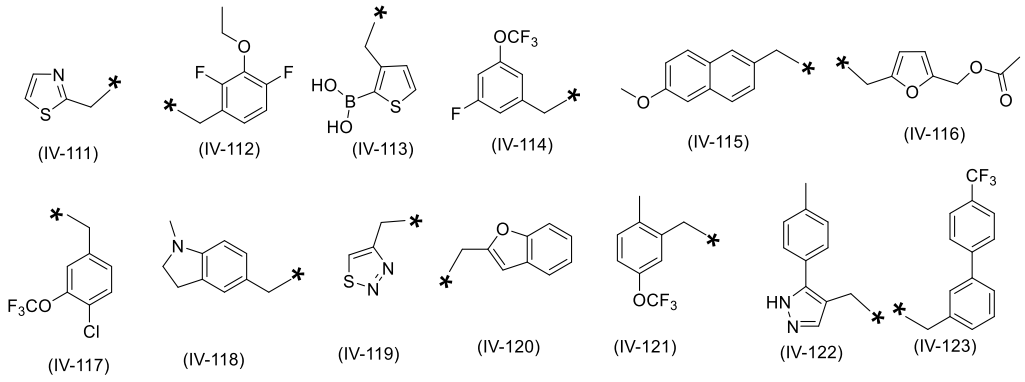

(IV-72)
(IV-73)
(IV-74)
(IV-75)
(IV-76)
(IV-77)
(IV-78)

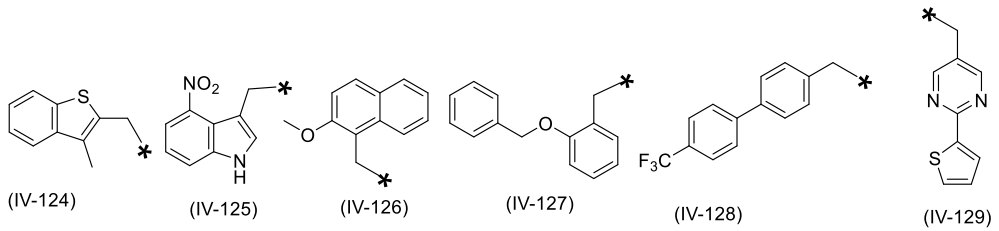

(IV-79)
(IV-80)
(IV-81)
(IV-82)
(IV-83)
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(IV-85)
(IV-86)
(IV-87)
(IV-88)
(IV-89)
(IV-90)

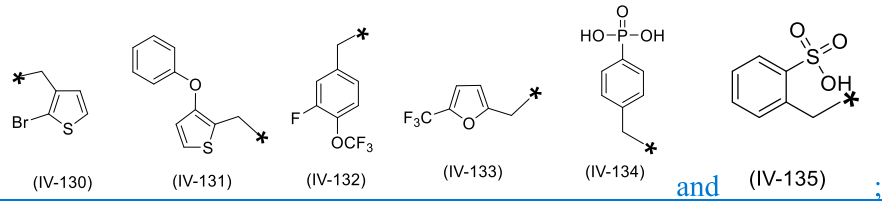
2ad











and ;

wherein:

2ae

Xa represents CH=O, CHF_2, CF_3, CH_2SH, COOH, CH_2OH, CH_2NO_2, CH_2NH_2, CH_3, $C(CH_3)_3$, $CH(CH_3)_2$, $CH((CH_2)_3\ CH_3)_2$, or $CH(CH_2\ CH_3)_2$;

Xb represents O, NH, CH_2, or S;

Xc represents CH or N;

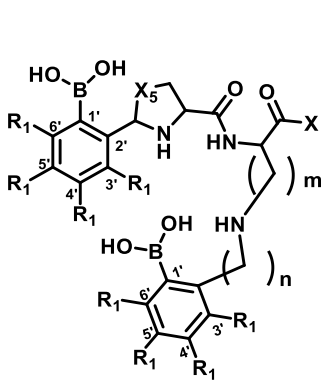
each R_{10} is independently selected from H, F, Cl, Br, CH_3, CF_3, CH=O, OH, COOH, and $(CH_2)_nCH_3$,

m is 1, 2, 3, 4, or 5; and n is 1, 2, 3, 4, or 5;

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

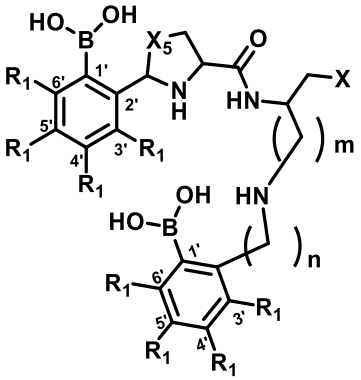
* in Formulae IV-1 to IV-135 represents the point of attachment to corresponding Formulae FF161-164; and

wherein Formulae FF165-FF166 are:



(FF165)

and



(FF166)

;

wherein X is selected from an amine, OH, and halogen;

m is 1, 2, 3, 4, 5, 6, or 7;

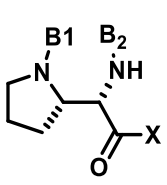
n is 1, 2, 3, 4, 5, 6, or 7;

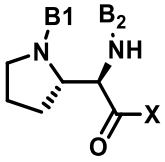
X5 is S, O, or NH; and

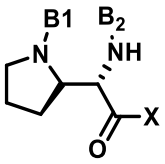
each R_1 is independently selected from H, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH\ CH_3$, —$(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3, 4, 5, 6, or 7; and

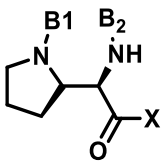
wherein Formulae FF167-FF192 are:

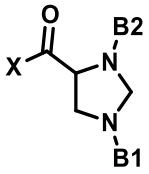
2af

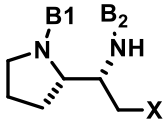

(FF167)

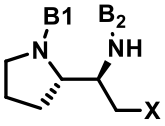

(FF168)

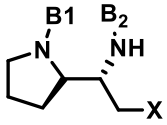

(FF169)

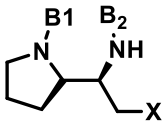

(FF170)

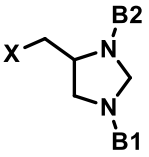

(FF171)

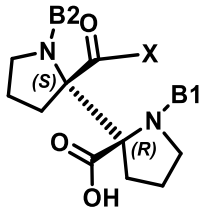

(FF172)

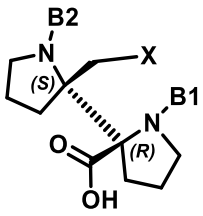

(FF173)

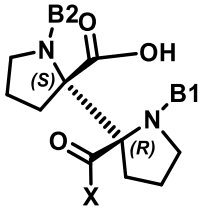

(FF174)

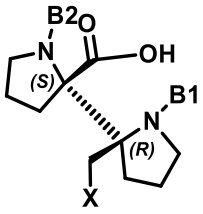

(FF175)

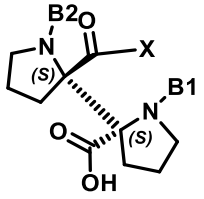

(FF176)

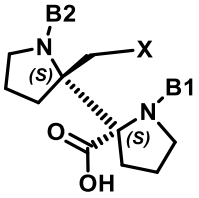

(FF177)

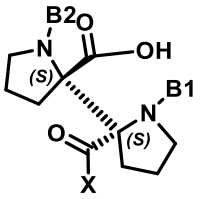

(FF178)

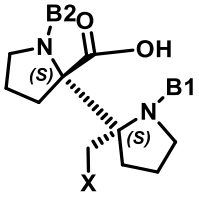

(FF179)

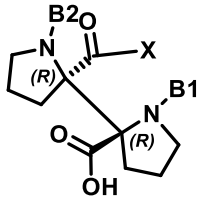

(FF180)

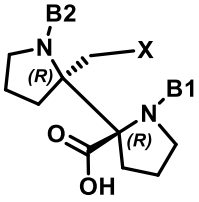

(FF181)

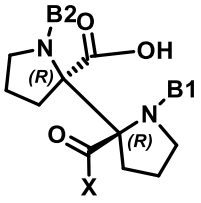

(FF182)

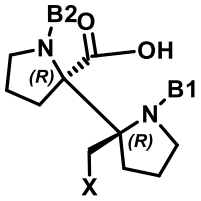

(FF183)


(FF184)

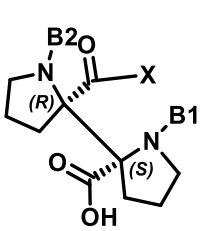

(FF185)

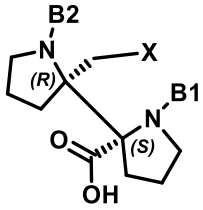

(FF186)

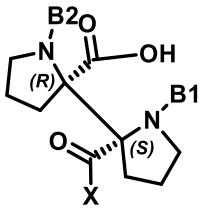

(FF187)

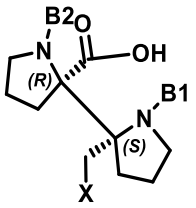

(FF188)

2ag


(FF189)


(FF190)


(FF191)

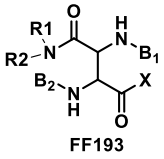

(FF192)

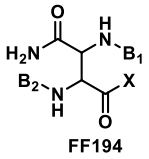
and ;

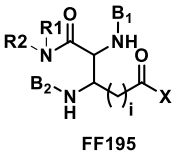
wherein X is selected from an amine, OH, and halogen;

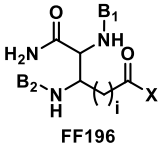
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group, and

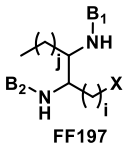
wherein Formulae FF193-FF209 are:

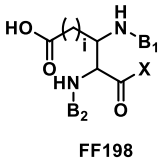

FF193

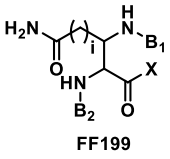

FF194

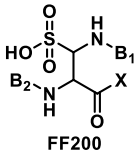

FF195

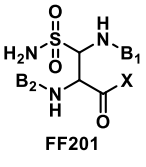

FF196


FF197


FF198

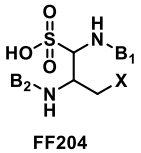

FF199


FF200


FF201

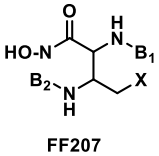

FF202

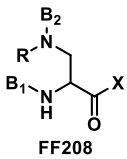

FF203

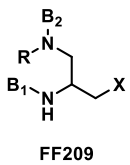

FF204


FF205


FF206


FF207


FF208


FF209

;

wherein R in FF208 and FF209 is an alkyl, aryl or halide that is covalently conjugated through at least one CH_2 group to the amino group in the side chain of FF208 or FF209;

R1 and R2 are independently selected from H, CH_3, alkyl, and formulae IV-1 to IV-135;

i is 1, 2, 3, 4, or 5;

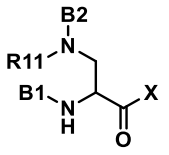
j is 1, 2, 3, 4, or 5; and

wherein X is selected from an amine, OH, and halogen; and

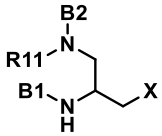
2ah

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

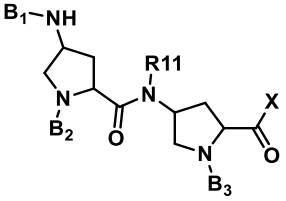
wherein Formulae FF210-FF224 are:



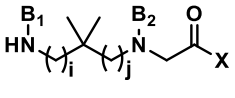
FF210



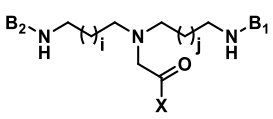
FF211



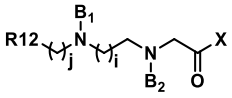
FF212



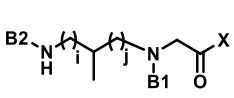
FF213



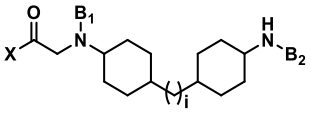
FF214



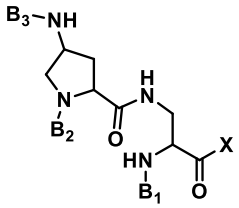
FF215



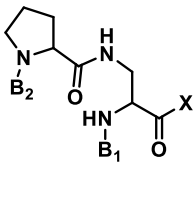
FF216



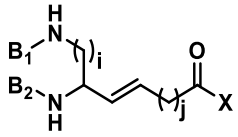
FF217



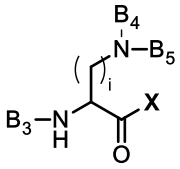
FF218



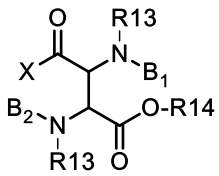
FF219



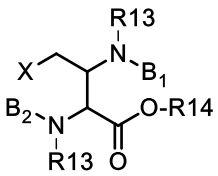
FF220



FF221



FF222



FF223



, and **FF224**;

wherein R11 in FF210 to FF212 is independently selected from Formulae IV-1 to IV-135 and R12 is selected from an amine, a hydroxyl, an alkyl, and a halide group;

wherein each R13 is independently selected from H, CH_3, alkyl, aryl, and formulae IV-1 to IV-135; R14 is selected from H, CH_3, alkyl, aryl, and heteroaryl;

wherein X is independently selected from an amine, OH, and halogen;

X'' is an amine;

i is 1, 2, 3, 4, or 5;

j is 1, 2, 3, 4, or 5; and

wherein at least one primary or secondary amine in FF1-FF223 is optionally covalently conjugated to B_6; and

B_1, B_2, B_3, B_4, B_5 and B_6 each independently represents an aromatic boron-containing group, wherein in each FF structure containing B1, B2 and B3 groups, at least two of the B1, B2 and B3 groups are independently an aromatic boron-containing group; and

when X is an amine in any one of Formulae FF1 to FF223, X is optionally acetylated or alkylated.

In another aspect, there is provided a human insulin analog, comprising an A-chain and a B-chain,

wherein the sequence of the A-chain comprises:

X_{aa}'X_{bb}'X_{cc}'X_{dd}'X_{ee}'X_{ff}'X_{gg}'VEQCCX$_{hh}$'X_{ii}'ICSLYQLENYCNX_{jj}'X_{kk}'X_{ll}'X_{mm}'X_{nn}'X_{oo}'X_{pp}' (SEQ ID NO:24015); and

wherein the sequence of the B-chain comprises:

(i)

$X_{aa}X_{bb}X_{cc}X_{dd}$KX$_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}$QHLCGSHLVEALYLVCX$_{oo}X_{pp}X_{qq}$GFFYT $X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24016),

wherein X_{aa}', X_{bb}', X_{cc}', X_{dd}', X_{ee}', X_{ff}', X_{gg}', X_{hh}', X_{ii}', X_{jj}', X_{kk}', X_{ll}', X_{mm}', X_{nn}', X_{oo}', X_{pp}', X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ee}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y and W,

(ii)

$X_{aa}X_{bb}X_{cc}X_{dd}$KPX$_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}X_{kk}X_{ll}X_{mm}X_{nn}$QHLCGSHLVEALYLVCX$_{oo}X_{pp}X_{qq}$GFFYT $X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24017),

wherein X_{aa}', X_{bb}', X_{cc}', X_{dd}', X_{ee}', X_{ff}', X_{gg}', X_{hh}', X_{ii}', X_{jj}', X_{kk}', X_{ll}', X_{mm}', X_{nn}', X_{oo}', X_{pp}', X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y and W, and wherein X_{ee} is selected from amino acid residues A, E, F, H, I, K, L, N, P, Q, R, S, T, V,Y and W,

(iii)

$X_{aa}X_{bb}X_{cc}X_{dd}$KX$_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}$QHLCGSHLVEALYLVCX$_{oo}X_{pp}X_{qq}$GFFYT $X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24018),

wherein X_{aa}', X_{bb}', X_{cc}', X_{dd}', X_{ee}', X_{ff}', X_{gg}', X_{hh}', X_{ii}', X_{jj}', X_{kk}', X_{ll}', X_{mm}', X_{nn}', X_{oo}', X_{pp}', X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ee}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A,

2aj

D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y , W and at least one of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} is present and at least one of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} is G,

(iv)

$X_{aa}X_{bb}X_{cc}X_{dd}KX_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}$QHLCGSHLVEALYLVC$X_{oo}X_{pp}X_{qq}$GFFYT$X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24019),

wherein $X_{aa'}$, $X_{bb'}$, $X_{cc'}$, $X_{dd'}$, $X_{ee'}$, $X_{ff'}$, $X_{gg'}$, $X_{hh'}$, $X_{ii'}$, $X_{jj'}$, $X_{kk'}$, $X_{ll'}$, $X_{mm'}$, $X_{nn'}$, $X_{oo'}$, $X_{pp'}$, X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ee}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y , W and at least one of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} is present and at least one of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} is S, or

(v)

$X_{aa}X_{bb}X_{cc}X_{dd}KX_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}$QHLCGSHLVEALYLVC$X_{oo}X_{pp}X_{qq}$GFFYT$X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24020),

wherein $X_{aa'}$, $X_{bb'}$, $X_{cc'}$, $X_{dd'}$, $X_{ee'}$, $X_{ff'}$, $X_{gg'}$, $X_{hh'}$, $X_{ii'}$, $X_{jj'}$, $X_{kk'}$, $X_{ll'}$, $X_{mm'}$, $X_{nn'}$, $X_{oo'}$, $X_{pp'}$, X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ee}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y , W and at least two of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} are present and at least one of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} is S, and another is G.

The present disclosure provides, according to some ~~embodiments~~examples, novel Z1c compounds (e.g., FF1-FF224) comprising aromatic boron-containing functionalities (e.g., F1-F12). In some ~~embodiment~~examples, the present disclosure provides compounds that comprise a drug substance (e.g., X1) and at least one Z1c with aromatic boron-containing functionalities (e.g., aromatic boron-containing groups, Z1c scaffolds comprising FF1-FF224 and F1-F12). In some ~~embodiment~~examples, the compounds disclosed comprise one or more molecular scaffolds (e.g., FF scaffolds). In some ~~embodiment~~examples, the compounds comprise a drug substance. In at least some ~~embodiment~~examples, the drug substance is a polypeptide or a small-molecule.

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

In some ~~embodiment~~examples, one or more Z1c may be linked (e.g., conjugated, connected) to a drug substance (e.g., X1) via one or more small-molecule linkers (e.g., Z1b) and/or one or more amino acids connected together using amide or peptide bonds (e.g., Z1a). In at least some ~~embodiment~~examples, rotational constraining of the boron functionalities via the tethering group (e.g., FF formulae) enhances the binding affinity of the compounds (e.g., conjugates) towards specific diols (such as glucose) and away from other diols in the body and thereby provides selectivity to specific diols. In some ~~embodiment~~examples, the compounds may exhibit therapeutic pharmacokinetics and/or pharmacodynamics in response to endogenous and/or exogenous small molecules in the body, such as glucose. Changes in the physiological concentration of glucose, result in the activation and/or release of the drug molecule or conversely, deactivation and/or sequestering of the drug molecule (e.g., a peptide hormone), and/or modulation of the activity of the drug molecule, through interaction of glucose with the boron-containing architectures conjugated to the drug molecule.

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

X1 comprises:

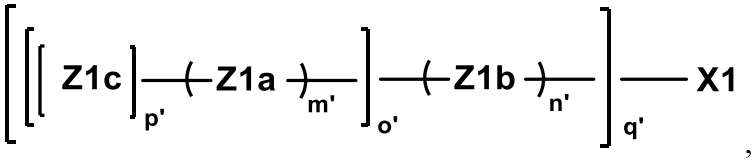
i. NH_2 or OH (e.g. X1 is NH_2 or OH);
ii. a drug substance comprising an amine;

iii. a drug substance that is covalently conjugated to an amine containing linker; or

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

wherein each Z1c is independently selected from Formulae FF1-FF224; and wherein each Z1c is covalently conjugated, directly or indirectly, to an amine in X1 or to OH when X1 is OH.

In some ~~embodiment~~examples, the compound is a molecular conjugate represented by Formula I, or a stereoisomer or a mixture of stereoisomers, or pharmaceutically acceptable salts:



(Formula I)

wherein X1 comprises:

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

ii. a polypeptide drug substance comprising an amine;

iii. a polypeptide drug substance that is covalently conjugated to an amine containing linker; or

iv. an amine configured to be covalently conjugated to a polypeptide drug substance;

each Z1c is independently selected from Formulae FF1-FF224 and covalently conjugated either directly, or via Z1a and/or Z1b, to X1;

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

each Z1b is a small-molecule linker;

each m' is independently 0 or 1;

each n' is independently 0 or a positive integer;

each o' is independently an integer of 1 or greater;

each p' is a positive integer; and

q' is a positive integer of at least 1 and not more than two times the total number of amine groups in X1, with the proviso that when any of n', o', p', or q' is 2 or more, the

corresponding groups Z1a, Z1b, and Z1c are independently selected and may be the same or different;

wherein each Z1c is independently covalently conjugated, directly or indirectly, to an amine of Z1a, to an amine of Z1b, or to X1; and wherein optionally the molecular conjugate may comprise one or more isotopes at any position of the molecular conjugate of Formula I.

In some ~~embodiment~~examples, X1 comprises human insulin or a human insulin analogue comprising an A-chain and a B-chain, wherein the A-chain comprises a sequence selected from SEQ ID NOs 1 and 3 to 33, and the B-chain comprises a sequence selected from SEQ ID NOs 2 and 34 to 74, 24047, and 24048;

each Z1c is independently selected from FF1, FF10, FF12, FF14, FF15, FF114, FF115, FF116, FF163, FF193, FF194, FF203, and FF221-FF224 and covalently conjugated either directly, or indirectly via a linker (an indirect linker), to Z1a and/or Z1b, or to X1;

each Z1a is independently absent or independently comprises a sequence selected from K, GK, KGSH (SEQ ID NO:24049), KGSHK (SEQ ID NO:4238), KNSTK (SEQ ID NO:5085), GKASHK (SEQ ID NO:12414), GKEEEK (SEQ ID NO:12677), GKEEHK (SEQ ID NO:12680), GKGHSK (SEQ ID NO:13120), GKGSH (SEQ ID NO:24050), GKGSHK (SEQ ID NO:13198), GKGSTK (SEQ ID NO:13205), GKHENK (SEQ ID NO:13271), GKNSHK (SEQ ID NO:13982), GKNSTK (SEQ ID NO:13989), GKQSSK (SEQ ID NO:14380), GKYQFK (SEQ ID NO:15128), GKGSKK (SEQ ID NO:24045), GKKPGKK (SEQ ID NO:24046), GKGPSK (SEQ ID NO:24044), GKPSHKP (SEQ ID NO:24043), and GSHKGSHK (SEQ ID NO:24042);

each said linker is selected from FL1, FL3, FL4, and FL5;

each m' is independently 0 or 1;

each n' is independently 0, 1, 2, or 3;

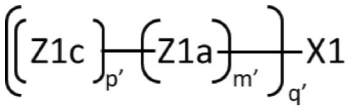
each o' is independently 1, 2, 3, 4, or 5;

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

q' is 1, 2, 3, or 4, wherein when any of n', o', p', or q' is 2 or more, the corresponding groups Z1a, Z1b, and Z1c are independently selected and may be the same or different; and

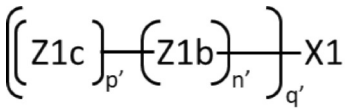
wherein each Z1c is independently covalently conjugated, directly or indirectly, to an amine of Z1a, to an amine of Z1b, or to X1.

In some ~~embodiment~~examples, the compound of Formula I is selected from:



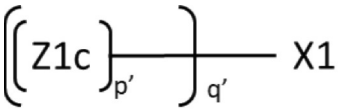
;

IA



; and

IB



.

IC

Also disclosed herein is a method of treating or preventing an endocrine and/or metabolic disease, in a subject in need thereof, comprising administering to said subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the polypeptide drug substance is a polypeptide hormone such as insulin, an insulin analog, an incretin or an incretin analog. In some ~~embodiment~~examples, the disease (e.g., disorder) is chosen from hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, metabolic syndrome X, or dyslipidemia, diabetes during pregnancy, pre-diabetes, Alzheimer's disease, MODY 1, MODY 2 or MODY 3 diabetes, mood disorders, and psychiatric disorders.

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

In at least one ~~embodiment~~example, the present disclosure is directed to a human insulin analog comprising an A-chain and a B-chain, wherein the sequence of the A-chain comprises:

D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y , W and at least one of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} is present and at least one of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} is S, or

(v)

$X_{aa}X_{bb}X_{cc}X_{dd}KX_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}$QHLCGSHLVEALYLVC$X_{oo}X_{pp}X_{qq}$GFFYT $X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24020),

wherein $X_{aa'}$, $X_{bb'}$, $X_{cc'}$, $X_{dd'}$, $X_{ee'}$, $X_{ff'}$, $X_{gg'}$, $X_{hh'}$, $X_{ii'}$, $X_{jj'}$, $X_{kk'}$, $X_{ll'}$, $X_{mm'}$, $X_{nn'}$, $X_{oo'}$, $X_{pp'}$, X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ee}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y , W and at least two of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} are present and at least one of X_{ee},X_{ff},X_{gg},X_{hh},X_{ii},X_{jj} is S, and another is G.

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

DETAILED DESCRIPTION OF THE DISCLOSURE

While aromatic boron-containing compounds (e.g., groups) can bind to diol containing molecules, achieving selectivity using aromatic boron-containing compounds (which can act as molecular sensors) is challenging because of their ability to bind various diols, including cis diols, to varying degrees. Improved binding affinity of aromatic boron-containing compounds (which can act as sensors) towards a specific vicinal diol of interest may result in a loss of selectivity.

Scaffolds that position the boron functionality (e.g., sensors) of the aromatic boron-containing compounds in a specific or particular ensemble of geometries can increase selectivity towards a specific vicinal diol while simultaneously maintaining affinity for the diol of interest. According to some embodiments, aromatic boron-containing compounds disclosed

WHAT IS CLAIMED IS:

1. A compound comprising X1 and one or more Z1c, or a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or isotopic derivative thereof,

wherein:

X1 comprises:

(i) NH_2 or OH;

(ii) a drug substance comprising an amine;

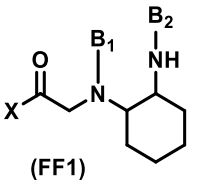
(iii) a drug substance that is covalently conjugated to an amine containing linker; or

(iv) an amine configured to be covalently conjugated to a drug substance;

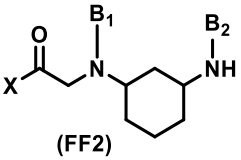
wherein each Z1c is independently selected from Formulae FF1-FF224;

wherein each Z1c is covalently conjugated, directly or indirectly, to an amine in X1 or to OH when X1 is OH, and

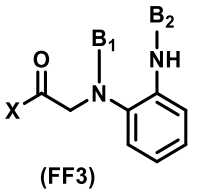
wherein Formulae FF1-FF48 are:



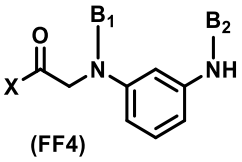
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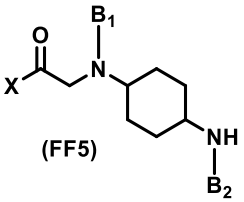
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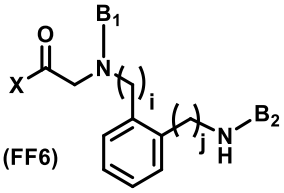
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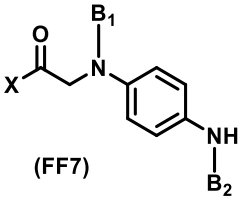
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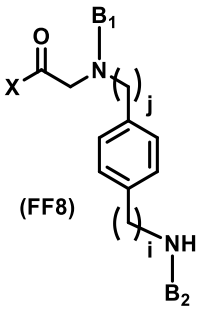
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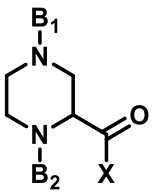
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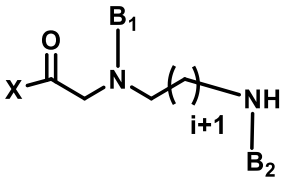
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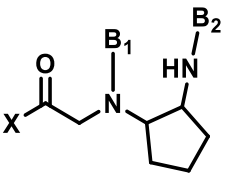
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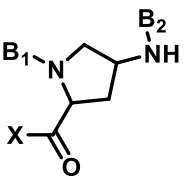
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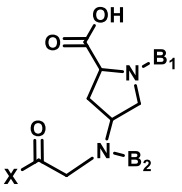
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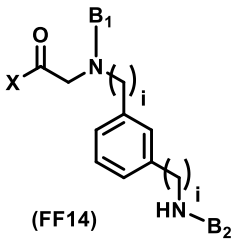
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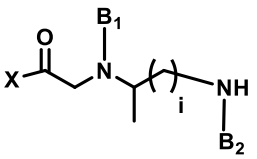
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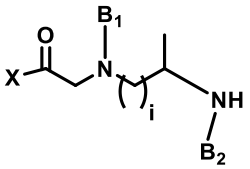
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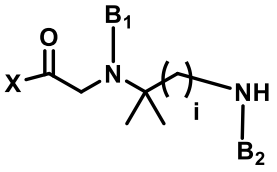
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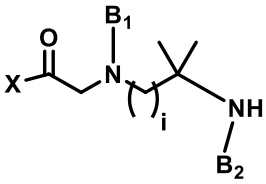
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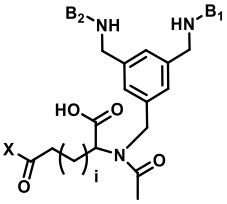
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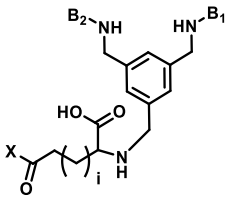
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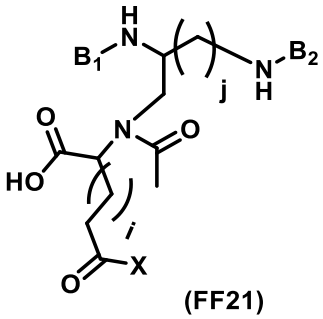
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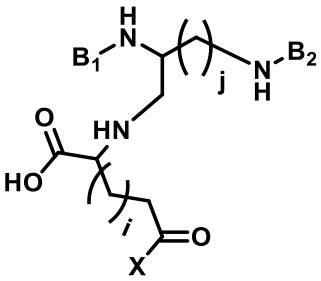
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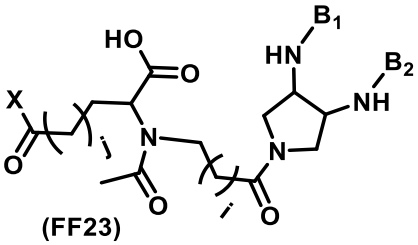
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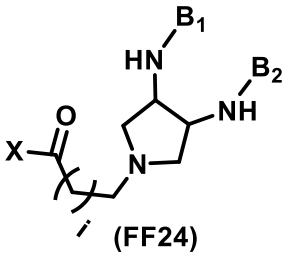
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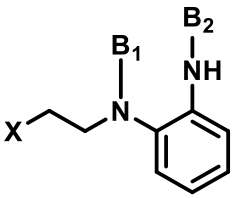
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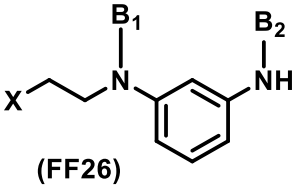
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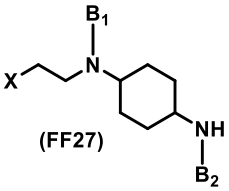
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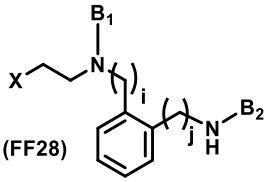
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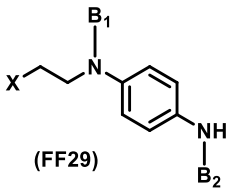
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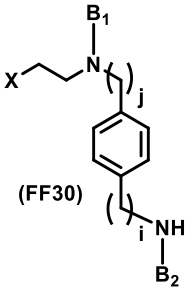
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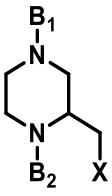
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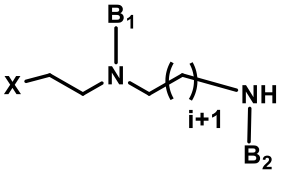
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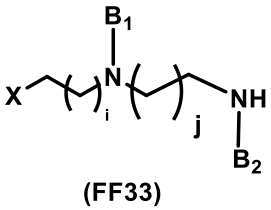
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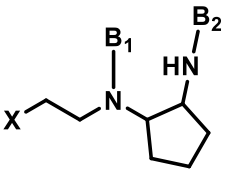
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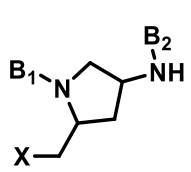
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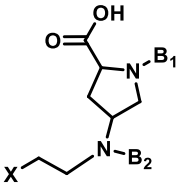


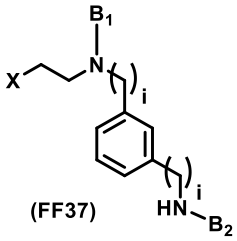
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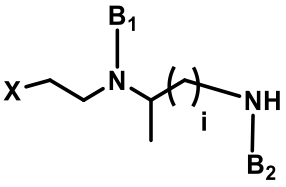


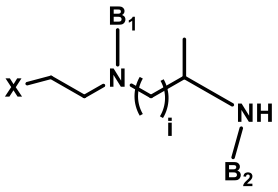
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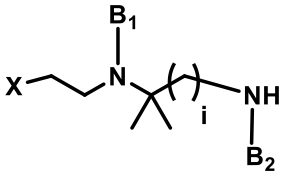

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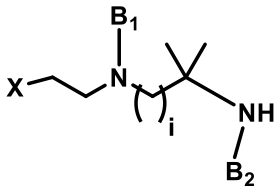

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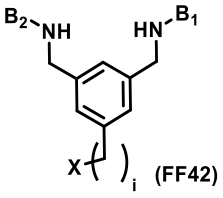

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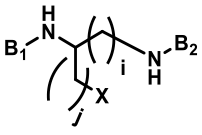

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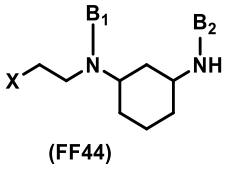

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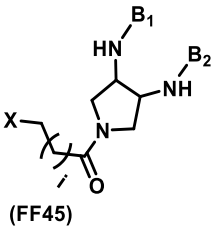

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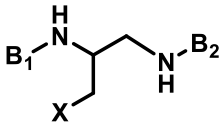

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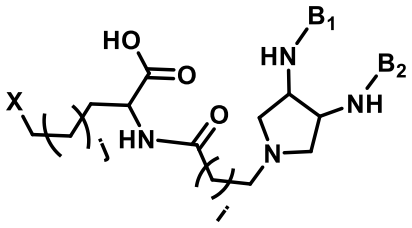

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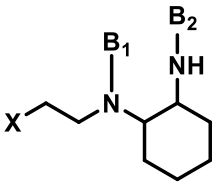

(FF44)


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(FF47)

and


(FF48);

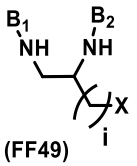
wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

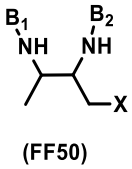
i is 1, 2, 3, 4, 5, 6, or 7;

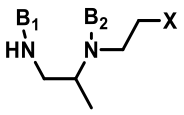
j is 1, 2, 3, 4, 5, 6, or 7; and

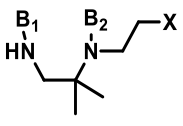
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group;

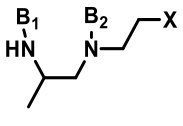
wherein Formulae FF49-FF88 are:

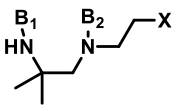

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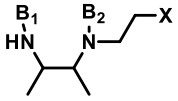

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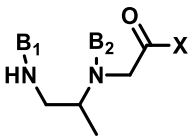

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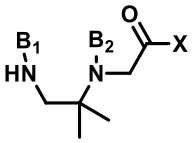

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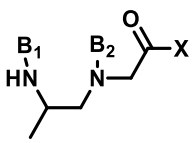

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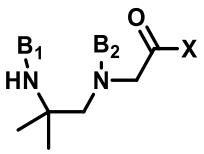

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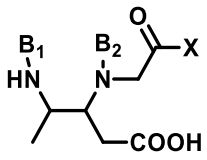

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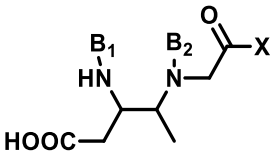

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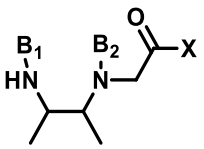

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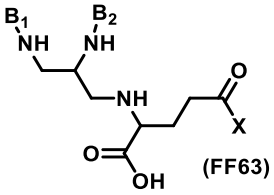

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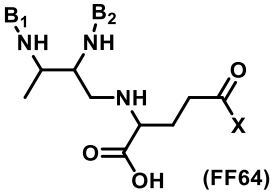

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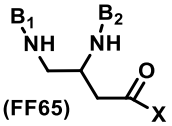

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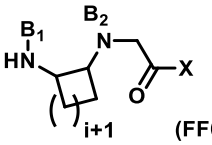

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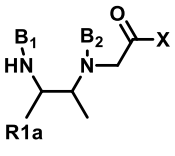

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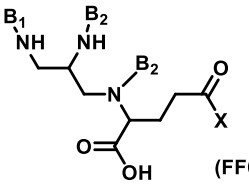

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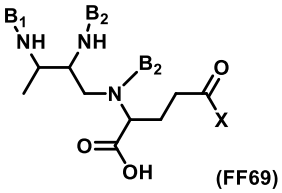

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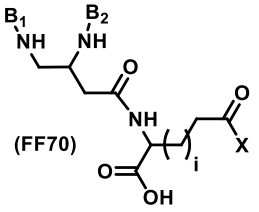

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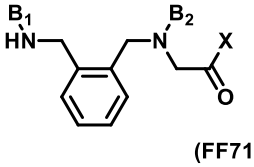

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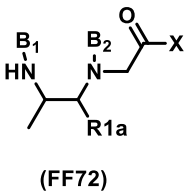

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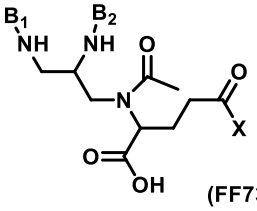

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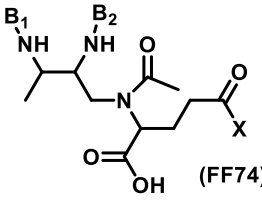

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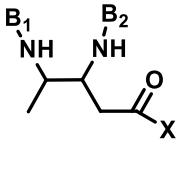

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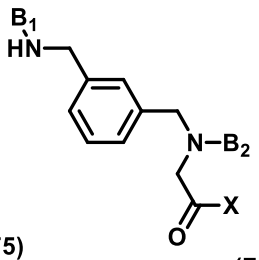

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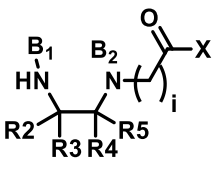

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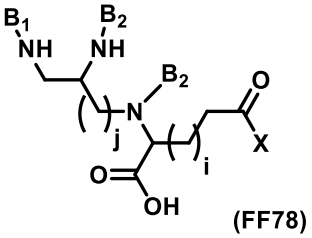

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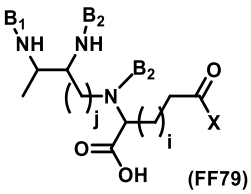

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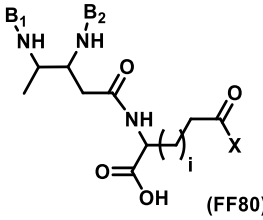

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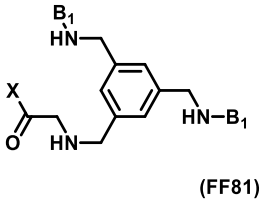

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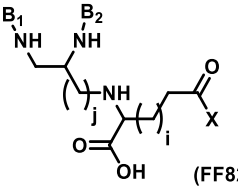

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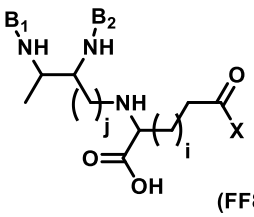

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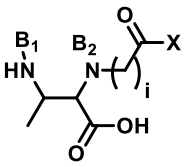

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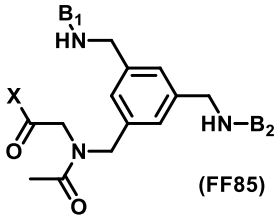

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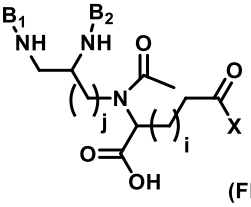

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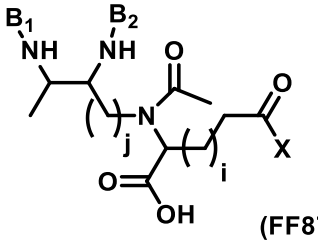

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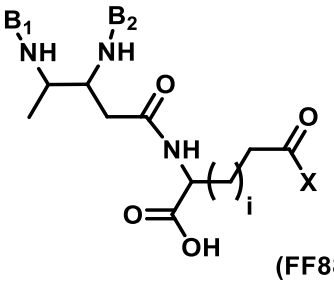

(FF83)


(FF84)


(FF85)


(FF86)


(FF87) and


(FF88);

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

i is 1, 2, 3, 4, 5, 6, or 7;

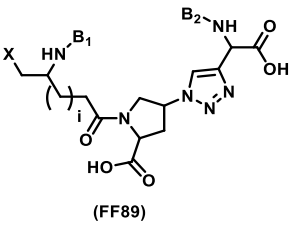
j is 1, 2, 3, 4, 5, 6, or 7;

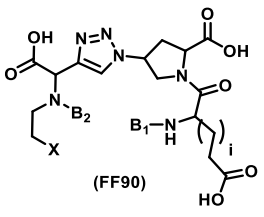
R1a is selected from COOH, CH_3, H, and OH;

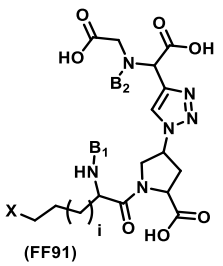
R2, R3, R4 and R5 are each independently selected from CH_3, H, OH, and COOH, and at least one of R2, R3, R4 and R5 is CH_3 or OH; and

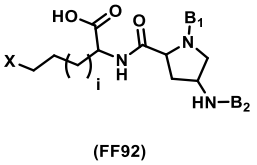
B_1 and B_2, which may be identical or different, are each independently an aromatic boron-containing group;

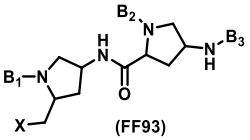
wherein Formulae FF89-FF112 are:

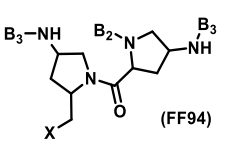

(FF89)

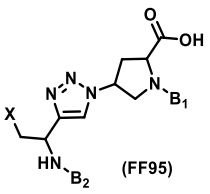

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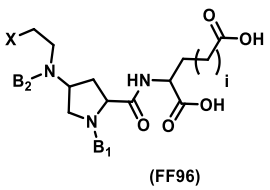

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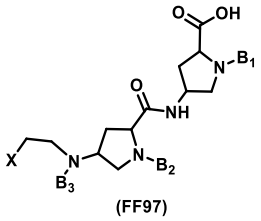

(FF92)

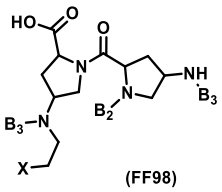

(FF93)

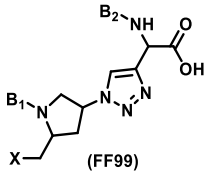

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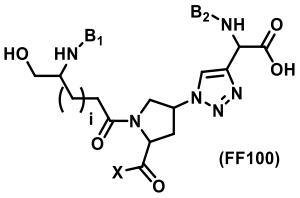

(FF95)

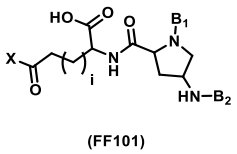

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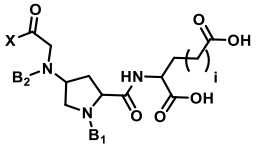

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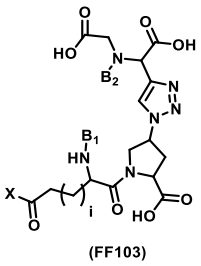

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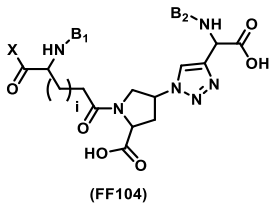

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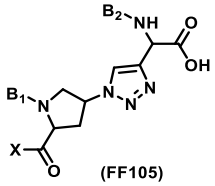

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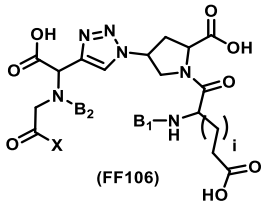

(FF101)

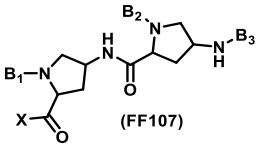

(FF102)

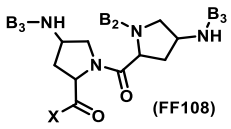

(FF103)

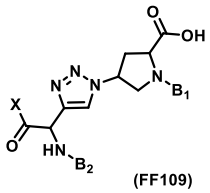

(FF104)

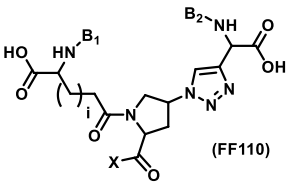

(FF105)

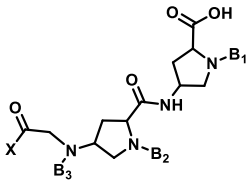

(FF106)


(FF107)

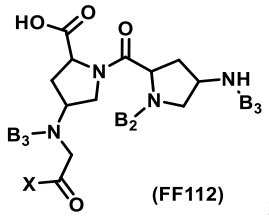

(FF108)


(FF109)


(FF110)


(FF111)

and


(FF112)

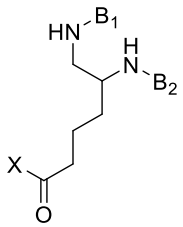
;

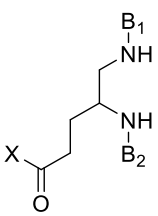
wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

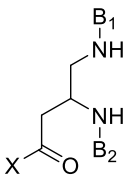
i is 1, 2, 3, 4, 5, 6, or 7; and

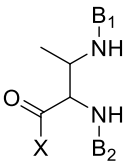
B_1, B_2 and B_3, which may be identical or different, are each independently an aromatic boron-containing group, a carboxylic acid derivative, or a H, wherein in each FF89-FF112 structure containing B1, B2 and B3 groups, at least two of the B1, B2 and B3 groups are independently an aromatic boron-containing group;

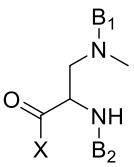
wherein Formulae FF113-FF136 are:

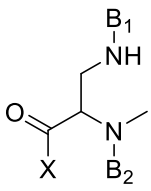

(FF113)


(FF114)

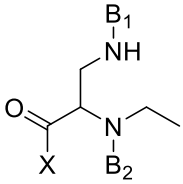

(FF115)


(FF116)

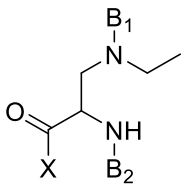

(FF117)



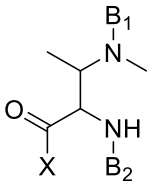
(FF118)



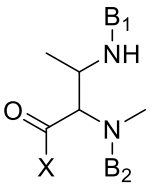
(FF119)



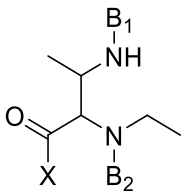
(FF120)



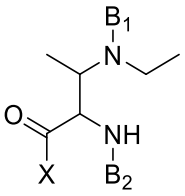
(FF121)



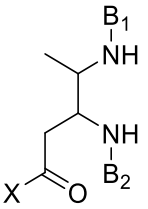
(FF122)



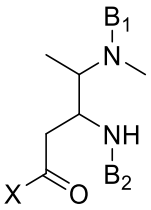
(FF123)



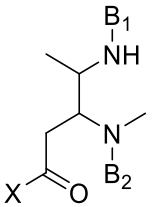
(FF124)



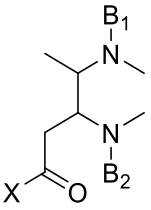
(FF125)



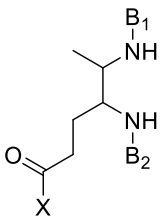
(FF126)



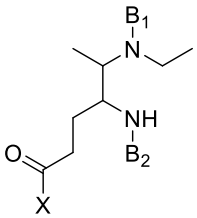
(FF127)



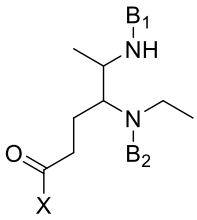
(FF128)



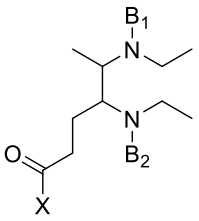
(FF129)



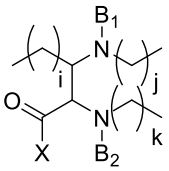
(FF130)



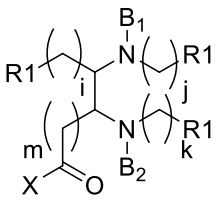
(FF131)



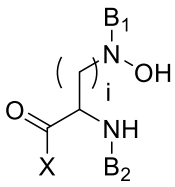
(FF132)



(FF133)

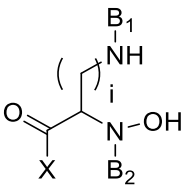


(FF134)



(FF135)

and



(FF136)

;

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

i is 1, 2, 3, 4, 5, 6, or 7;

j is 1, 2, 3, 4, 5, 6, or 7;

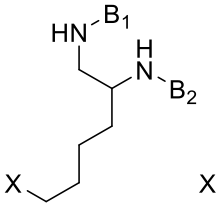
k is 1, 2, 3, 4, 5, 6, or 7;

m is 1, 2, 3, 4, 5, 6, or 7;

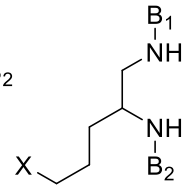
each R1 is independently selected from H, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each R1 optionally comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl, or aryl groups; and

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

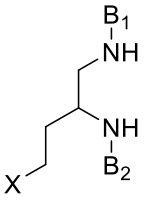
wherein Formulae FF137-FF160 are:



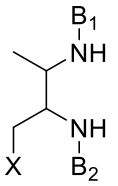
(FF137)



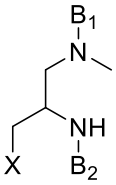
(FF138)



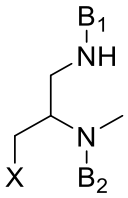
(FF139)



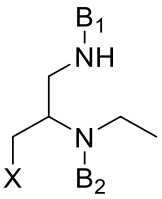
(FF140)



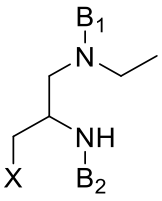
(FF141)



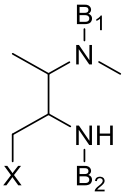
(FF142)



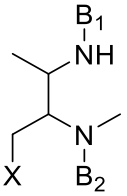
(FF143)



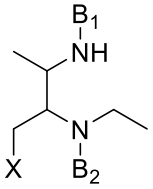
(FF144)



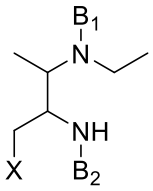
(FF145)



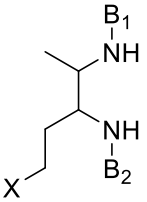
(FF146)



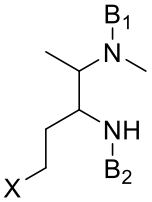
(FF147)



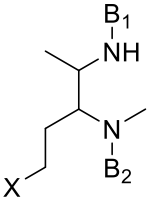
(FF148)



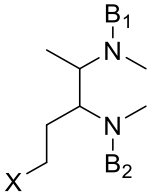
(FF149)



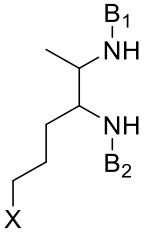
(FF150)



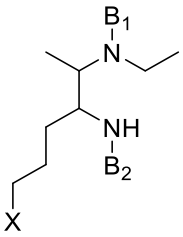
(FF151)



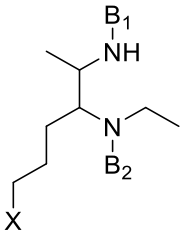
(FF152)



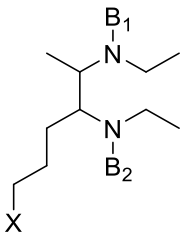
(FF153)



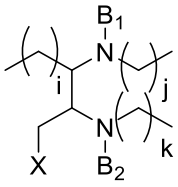
(FF154)



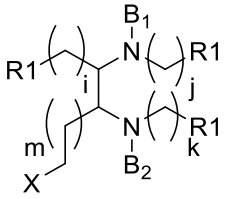
(FF155)



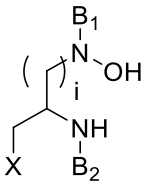
(FF156)



(FF157)

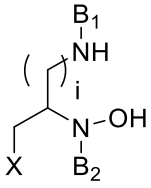


(FF158)



(FF159)

and



(FF160)

;

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

i is 1, 2, 3, 4, 5, 6, or 7;

j is 1, 2, 3, 4, 5, 6, or 7;

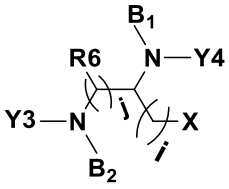
k is 1, 2, 3, 4, 5, 6, or 7;

m is 1, 2, 3, 4, 5, 6, or 7;

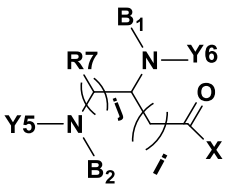
each R1 is independently selected from H, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each R1 optionally comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl, or aryl groups; and

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

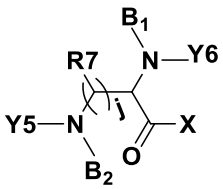
wherein Formulae FF161-FF164 are:



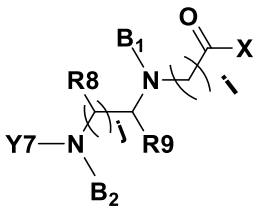
(FF161)



(FF162)



(FF163)



(FF164)

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

i is 1, 2, 3, 4, or 5;

j is 1, 2, 3, 4, or 5;

each R6, R7, R8, and R9 for different values of j is independently selected from H, CF_3, CH_3, CHF_2, and $(CH_2)_mCH_3$, wherein m is 1, 2, 3, 4, or 5;

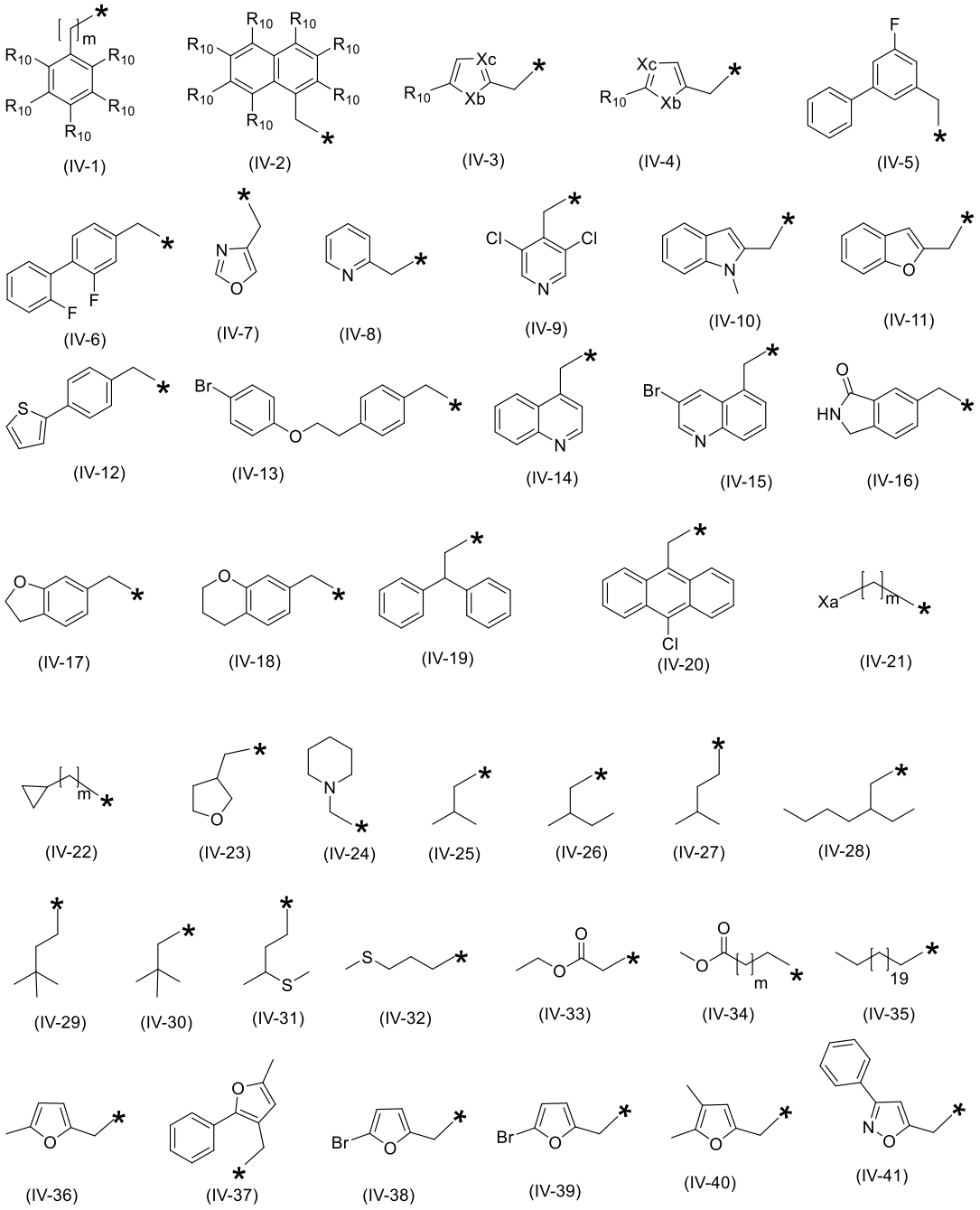
Y3, Y4, Y5, Y6 and Y7 are each independently selected from H, CH_2—X4, and Formulae IV-1 to IV-135;

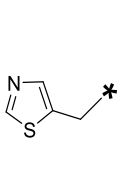
wherein X4 is selected from -COOH, $-(CH_2)_mCOOH$, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each X4 optionally

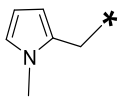
comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl or aryl groups; wherein m is 1, 2, 3, 4, or 5;

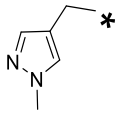
wherein at least one of Y5, Y6 and Y7 in Formulae FF162 and FF163 is not H and at least one of Y7, R8 and R9 in FF164 is not H; and

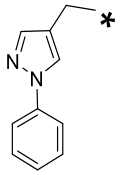
wherein Formulae IV-1 to IV-135 are:

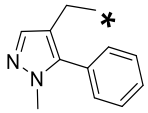


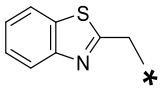

(IV-42)

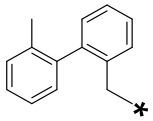

(IV-43)

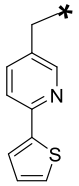

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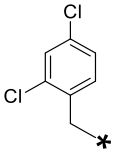

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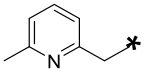

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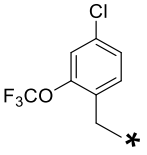

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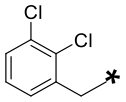

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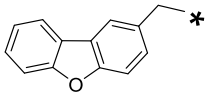

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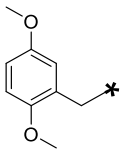

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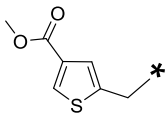

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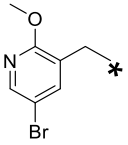

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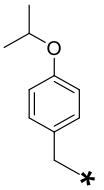

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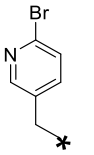

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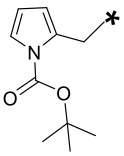

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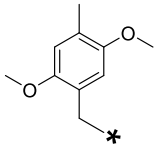

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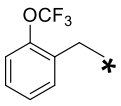

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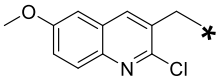

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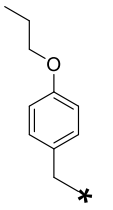

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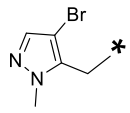

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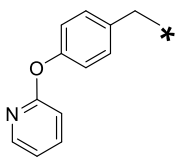

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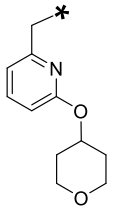

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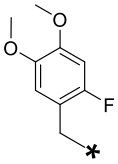

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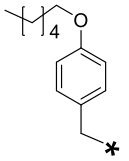

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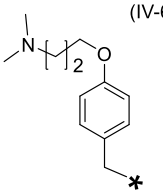

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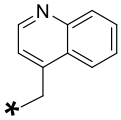

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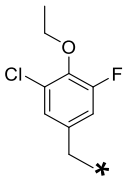

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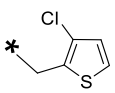

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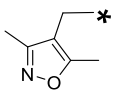

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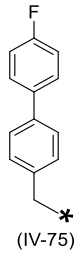

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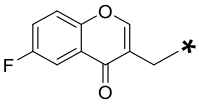

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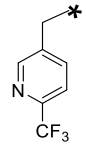

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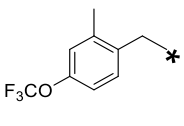

(IV-73)

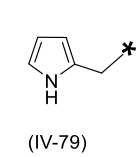

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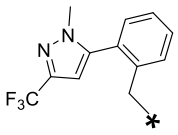

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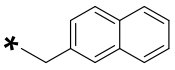

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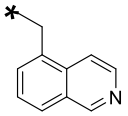

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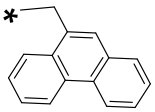

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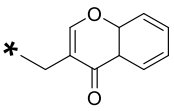

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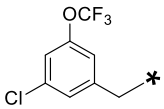

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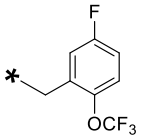

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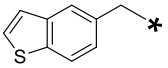

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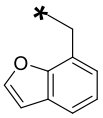

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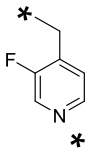

(IV-84)

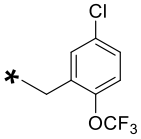

(IV-85)

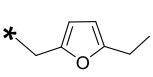

(IV-86)

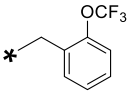

(IV-87)

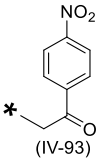

(IV-88)

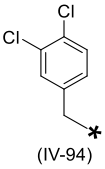

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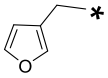

(IV-90)

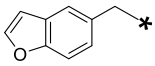

(IV-91)

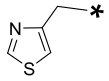

(IV-92)

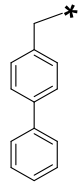

(IV-93)

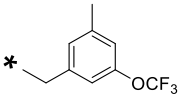

(IV-94)

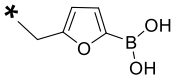

(IV-95)

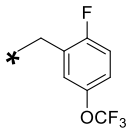

(IV-96)

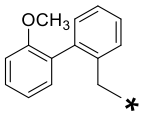

(IV-97)

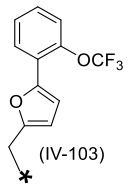

(IV-98)

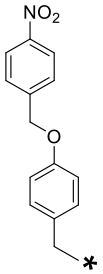

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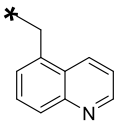

(IV-100)

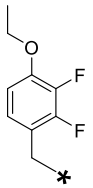

(IV-101)

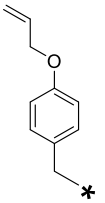

(IV-102)

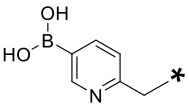

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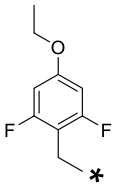

(IV-104)

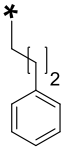

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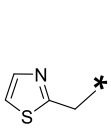

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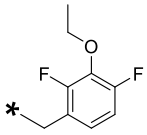

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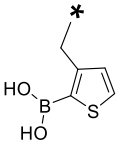

(IV-108)

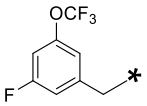

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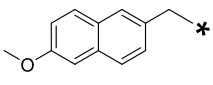

(IV-110)

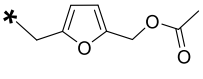

(IV-111)

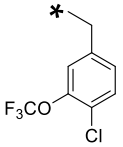

(IV-112)

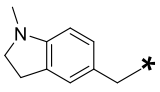

(IV-113)


(IV-114)


(IV-115)


(IV-116)


(IV-117)


(IV-118)

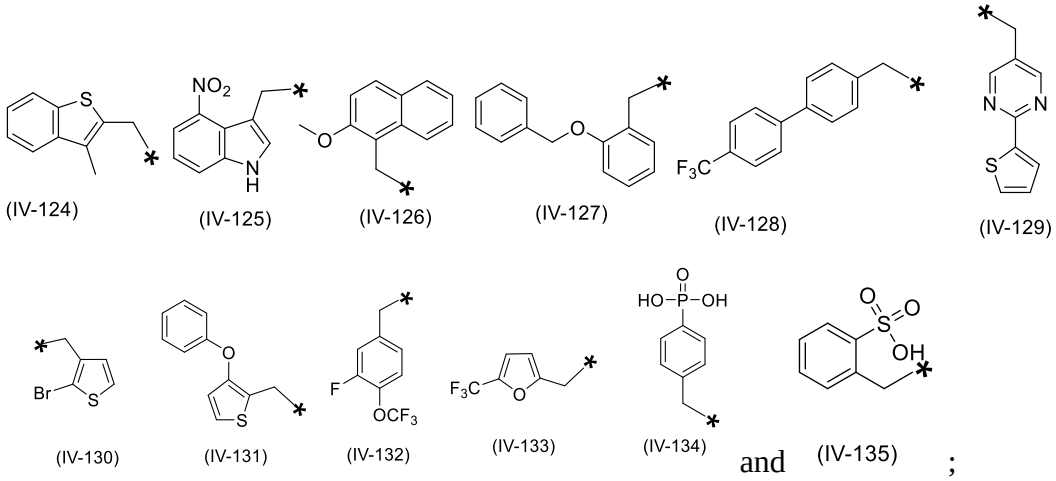
(IV-119)

(IV-120)

(IV-121)

(IV-122)

(IV-123)



and ;

wherein Xa represents CH=O, CHF_2, CF_3, CH_2SH, COOH, CH_2OH, CH_2NO_2, CH_2NH_2, CH_3, $C(CH_3)_3$, $CH(CH_3)_2$, $CH((CH_2)_3\text{-}CH_3)_2$, or $CH(CH_2\text{-}CH_3)_2$;

Xb represents O, NH, CH_2, or S;

Xc represents CH or N;

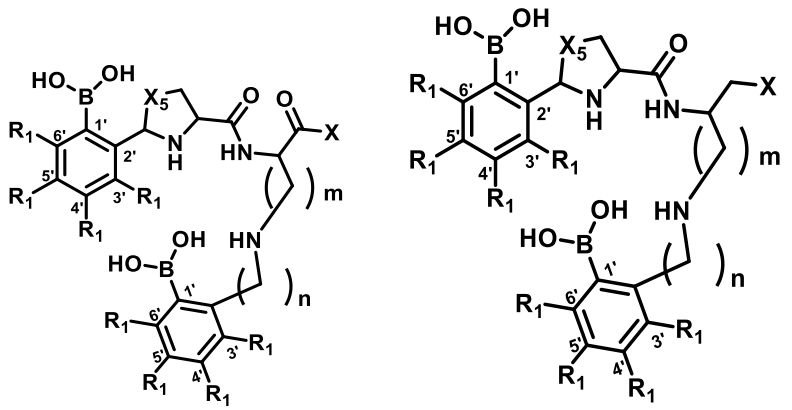
each R_{10} is independently selected from H, F, Cl, Br, CH_3, CF_3, CH=O, OH, COOH, and $(CH_2)_nCH_3$,

m is 1, 2, 3, 4, or 5; and n is 1, 2, 3, 4, or 5;

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

* in Formulae IV-1 to IV-135 represents a point of attachment to corresponding Formulae FF161-164;

wherein Formulae FF165-FF166 are:



(FF165) and **(FF166)** ;

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

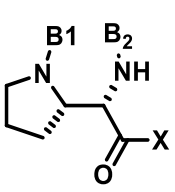
m is 1, 2, 3, 4, 5, 6, or 7;

n is 1, 2, 3, 4, 5, 6, or 7;

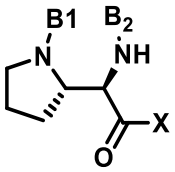
X5 is S, O, or NH; and

each R_1 is independently selected from H, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$-CH_3, —$(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3, 4, 5, 6, or 7;

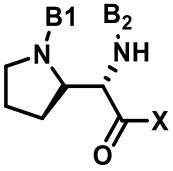
wherein Formulae FF167-FF192 are:



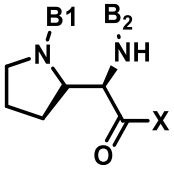
(FF167)



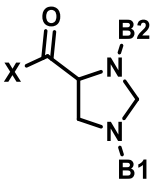
(FF168)



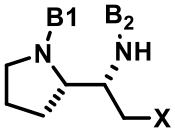
(FF169)



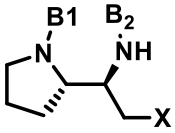
(FF170)



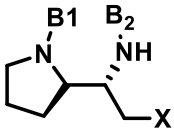
(FF171)



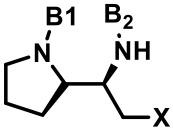
(FF172)



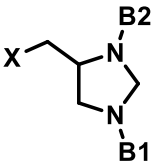
(FF173)



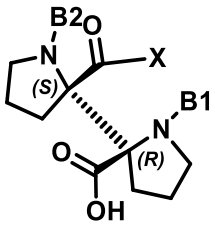
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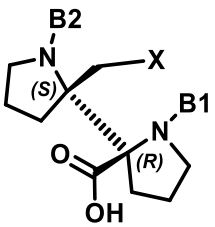
(FF175)



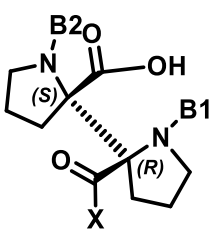
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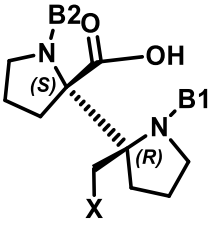
(FF177)



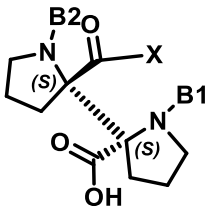
(FF178)



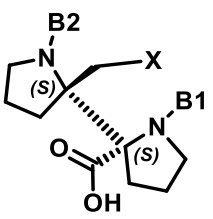
(FF179)



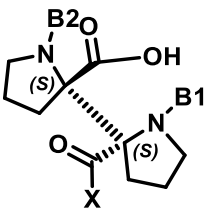
(FF180)



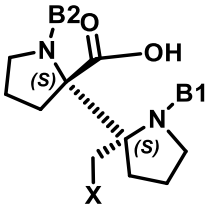
(FF181)



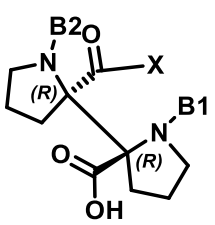
(FF182)

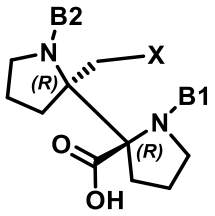


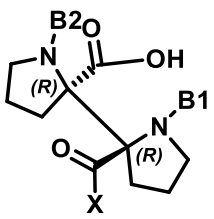
(FF183)

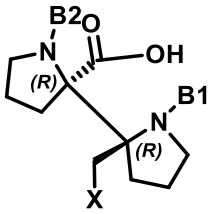


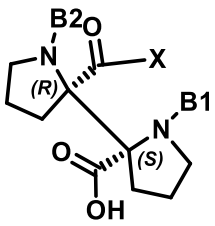
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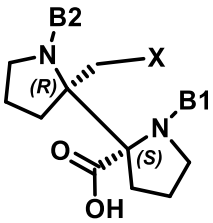

(FF185)

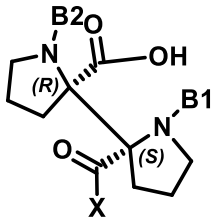

(FF186)


(FF187)

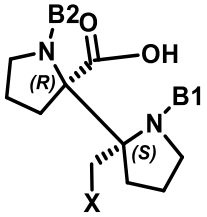

(FF188)


(FF189)


(FF190)


(FF191)

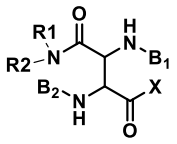
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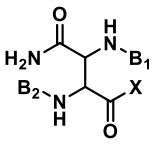

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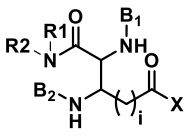
wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

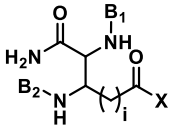
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group;

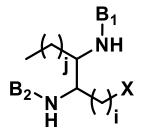
wherein Formulae FF193-FF209 are:

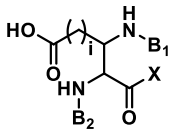

FF193

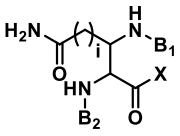

FF194

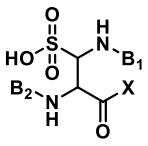

FF195

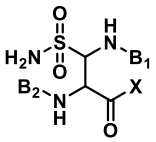

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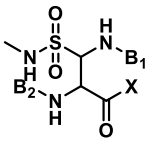

FF197

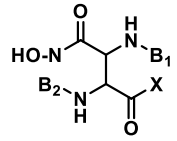

FF198

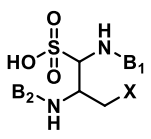

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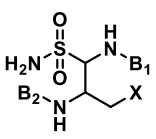

FF200

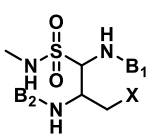

FF201

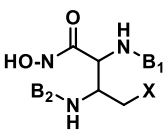

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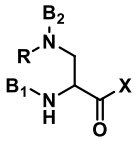

FF203

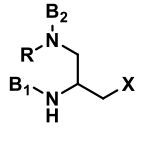

FF204


FF205


FF206


FF207


FF208


FF209

;

wherein R in FF208 and FF209 is an alkyl, aryl or halide that is covalently conjugated through at least one CH_2 group to the amino group in the side chain of FF208 or FF209,

R1 and R2 are independently selected from H, CH_3, alkyl, and formulae IV-1 to IV-135;

i is 1, 2, 3, 4, or 5;

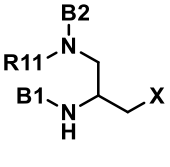
j is 1, 2, 3, 4, or 5; and

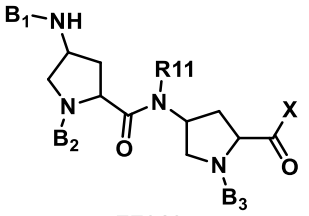
wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH; and

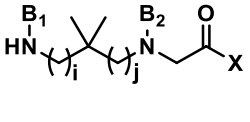
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group, and

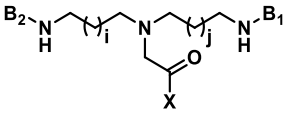
wherein Formulae FF210-FF224 are:

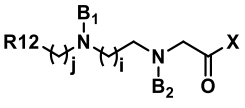

FF210

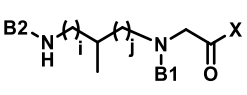

FF211

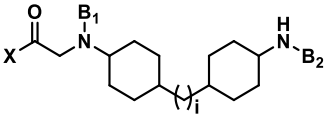

FF212

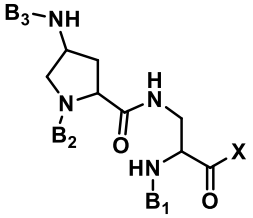

FF213

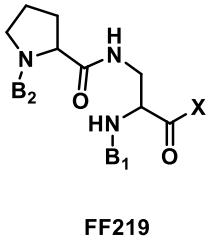

FF214

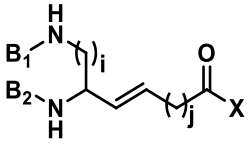

FF215

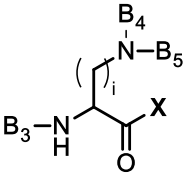

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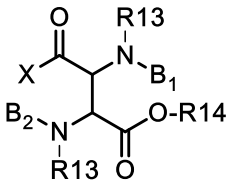

FF217

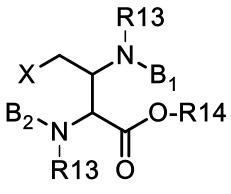

FF218


FF219


FF220


FF221


FF222


FF223


, and **FF224**;

wherein R11 in FF210 to FF212 is selected from Formulae IV-1 to IV-135 and R12 is selected from an amine, a hydroxyl, an alkyl, and a halide group;

wherein each R13 is independently selected from H, CH_3, alkyl, aryl and Formulae IV-1 to IV-135; R14 is selected from H, CH_3, alkyl, aryl and heteroaryl;

wherein X represents a point of covalent attachment either directly to an amine in X1 or to an amine that is covalently conjugated directly or indirectly to X1, or to OH when X1 is OH;

X'' represents a point of covalent attachment to an amine --N in the compound, wherein -- represents a single covalent bond to a CH_2 or CH group in the compound;

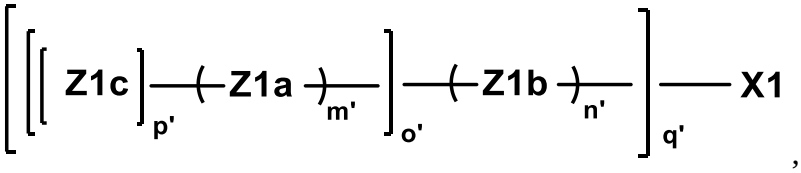
i is 1, 2, 3, 4, or 5;

j is 1, 2, 3, 4, or 5; and

wherein at least one primary or secondary amine in FF1-FF223 is optionally covalently conjugated to B_6; and

B_1, B_2, B_3, B_4, B_5, and B_6 each independently represents an aromatic boron-containing group, wherein in each FF structure containing B_1, B_2 and B_3 groups, at least two of the B1, B2 and B3 groups are independently an aromatic boron-containing group.

2. The compound of claim 1, wherein the compound is a molecular conjugate represented by Formula I, or a stereoisomer or a mixture of stereoisomers, or pharmaceutically acceptable salt thereof:



,

(Formula I)

wherein

X1 comprises:

(i) NH_2 or OH,

(ii) a polypeptide drug substance comprising an amine,

(iii) a polypeptide drug substance that is covalently conjugated to an amine containing linker, or

(iv) an amine configured to be covalently conjugated to a polypeptide drug substance;

each Z1c is independently selected from Formulae FF1-FF224 and covalently conjugated either directly, or via Z1a and/or Z1b, to X1;

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

each Z1b is independently a small-molecule linker;

each m' is independently 0 or 1;

each n' is independently 0 or a positive integer;

each o' is independently an integer greater than or equal to 1;

each p' is a positive integer; and

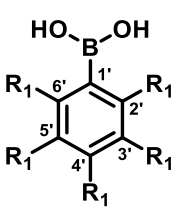
q' is a positive integer of at least 1 and not more than two times the total number of amine groups in X1, wherein when any of n', o', p', or q' is 2 or more, the corresponding groups Z1a, Z1b, and Z1c are independently selected and may be the same or different;

wherein each Z1c is independently covalently conjugated, directly or indirectly, to an amine of Z1a, to an amine of Z1b, or to X1; and

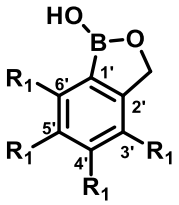
wherein optionally the molecular conjugate may comprise one or more isotopes at any position of the molecular conjugate of Formula I.

3. The compound of claim 1 or 2, wherein the compound comprises at least one of B_1, B_2 and B_3 independently selected from Formulae F1-F12 or wherein the compound comprises at least one of B_4, B_5 and B_6 independently selected from Formulae F1-F10,

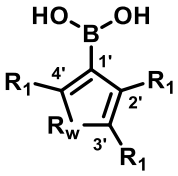
wherein Formulae F1-F10 are:



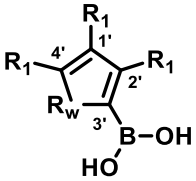
(F1)



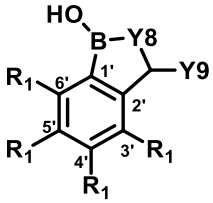
(F2)



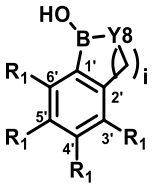
(F3)



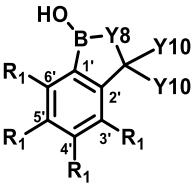
(F4)



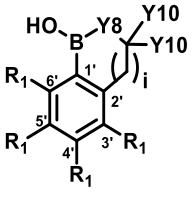
(F5)



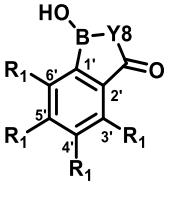
(F6)



(F7)

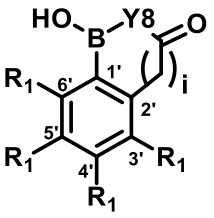


(F8)



(F9)

, and



(F10)

;

wherein for B_1, B_2, and B_3:

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

each remaining R_1 is independently selected from H, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$-CH_3, —$(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3 ,4, 5, 6, or 7;

wherein for B_4 and B_5:

one R_1 for B_4 represents $(CH_2)_m$---ø, wherein ---ø represents an attachment point to the rest of $Z1_C$ and one R_1 for B_5 represents (C=O)---*, S(=O)(=O)---*, $(CH_2)_m$(C=O)---*, or $(CH_2)_m$---*, wherein ---* represents an attachment point to the rest of $Z1_C$, and m is 1, 2, 3, 4, 5, 6, or 7; and

each remaining R_1 is independently selected from H, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$-CH_3, —$(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3 ,4, 5, 6, or 7;

wherein for B_6:

one R_1 for B_6 represents $(CH_2)_m$---ø, wherein ---ø represents an attachment point to the rest of the compound, and m is 1, 2, 3, 4, 5, 6, or 7; and

each remaining R_1 is independently selected from H, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$-CH_3, —$(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3 ,4, 5, 6, or 7;

wherein,

for Formulae F3-F4:

R_w is O or S;

for Formulae F5-F10:

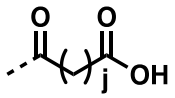
Y8 is selected from O, N, and NR, wherein R is an alkyl group or H;

Y9 is H, CH_3, or an alkyl group, provided that when Y8 is O, Y9 is a CH_3 or an alkyl group;

each Y10 is independently selected from H, CH_3, F, CF_3, and OCH_3; and

i is 1, 2, or 3; and

wherein Formulae F11-F12 are:



(F11)



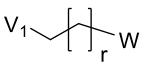
(F12),

j is 1, 2, 3, 4, 5, 6, or 7; and

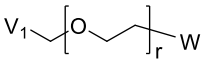
--- represents an attachment point to the rest of Z1c.

4. The compound of claim 2, wherein the compound comprises at least one Z1b selected from Formulae IIa-IIai and Formulae IIIa-IIIai,

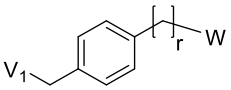
wherein Formulae IIa-IIai are:



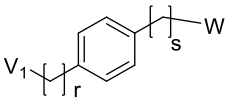
Formula IIa



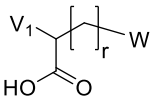
Formula IIb



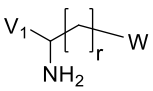
Formula IIc



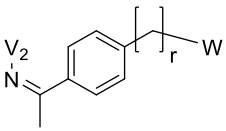
Formula IId



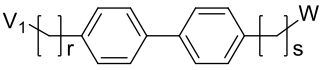
Formula IIe



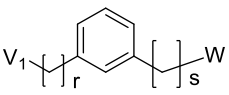
Formula IIf



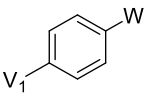
Formula IIg



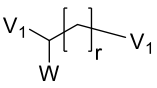
Formula IIh



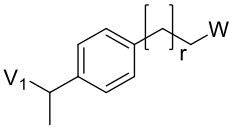
Formula IIi



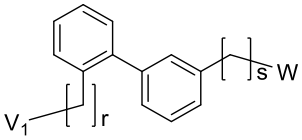
Formula IIj



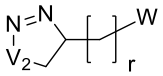
Formula IIk



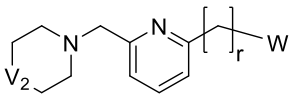
Formula III



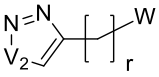
Formula IIm



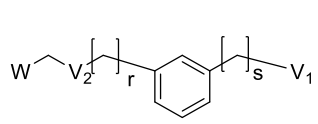
Formula IIn



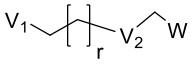
Formula IIo



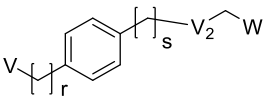
Formula IIp



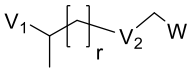
Formula IIq



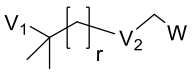
Formula IIr



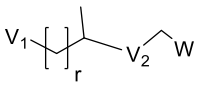
Formula IIs



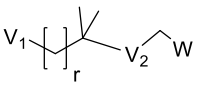
Formula IIt



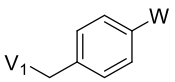
Formula IIu



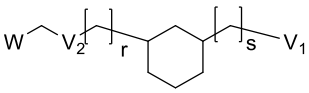
Formula IIv



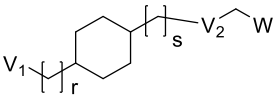
Formula IIw



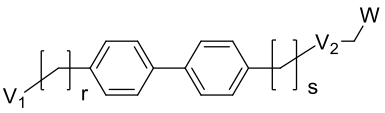
Formula IIx



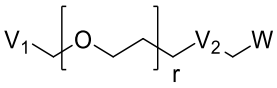
Formula IIy



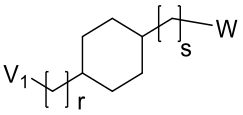
Formula IIz



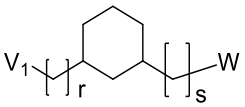
Formula IIaa



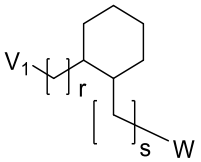
Formula IIab



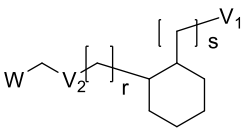
Formula IIac



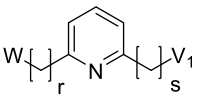
Formula IIad



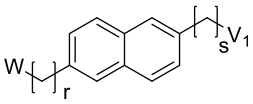
Formula IIae



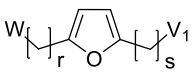
Formula IIaf



Formula IIag



Formula IIah



Formula IIai

and ;

wherein:

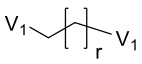
r is 0, 1, 2, 3, 4, or 5;

s is 0, 1, 2, 3, 4, or 5;

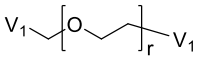
W represents CH_2---~ or (C=O)---~, wherein ---~ is a covalent linkage to X1; and

each V_1 is independently selected from NH---†, CH_2---†, and (C=O)---† and each V_2 is N---†, wherein ---† is a covalent linkage towards successive Z1b, Z1a or Z1c, provided that V_1 is NH---† when connected to Z1c; and the covalent linkages between Z1a and Z1b units each independently comprise an amine linkage or an amide linkage; and when n'=0 and m'=1, Z1a is directly conjugated to X1 by an amine linkage or amide linkage, and

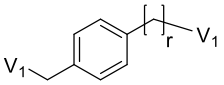
wherein Formulae IIIa-IIIai are:



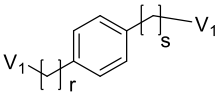
Formula IIIa



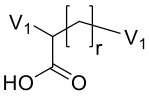
Formula IIIb



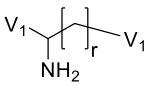
Formula IIIc



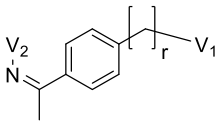
Formula IIId



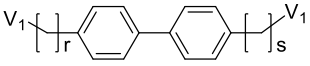
Formula IIIe



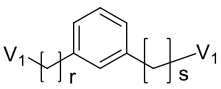
Formula IIIf



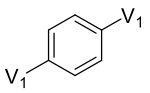
Formula IIIg



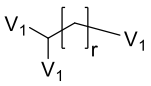
Formula IIIh



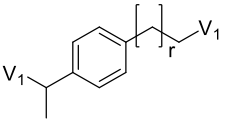
Formula IIIi



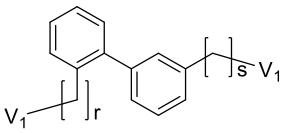
Formula IIIj



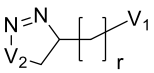
Formula IIIk



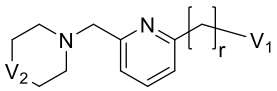
Formula IIIl



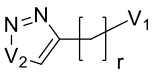
Formula IIIm



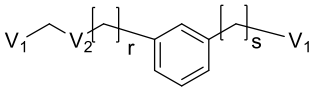
Formula IIIn



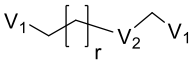
Formula IIIo



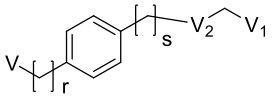
Formula IIIp



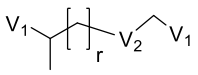
Formula IIIq



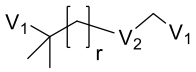
Formula IIIr



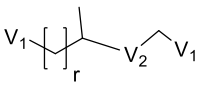
Formula IIIs



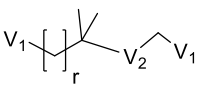
Formula IIIt



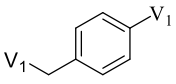
Formula IIIu



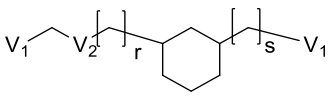
Formula IIIv



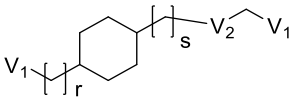
Formula IIIw



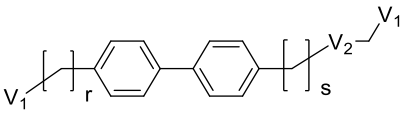
Formula IIIx



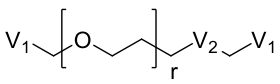
Formula IIIy



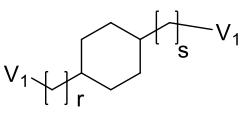
Formula IIIz



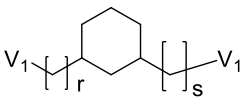
Formula IIIaa



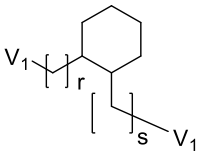
Formula IIIab



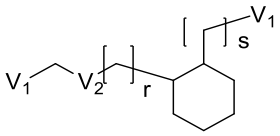
Formula IIIac



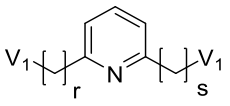
Formula IIIad



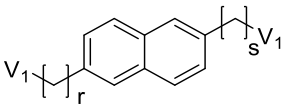
Formula IIIae



Formula IIIaf

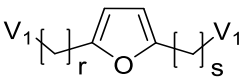


Formula IIIag



Formula IIIah

and



Formula IIIai ;

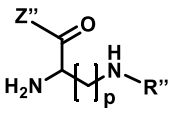
wherein:

r is 1, 2, 3, 4, or 5;

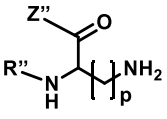
s is 1, 2, 3, 4, or 5; and

each V_1 is independently selected from NH---†, CH_2---†, and (C=O)---† and each V_2 is N---†, wherein ---† is a covalent linkage towards successive Z1b, Z1a or Z1c, provided that V_1 is NH---† when connected to Z1c; and the covalent linkages between Z1a and Z1b units each independently comprise an amine linkage or an amide linkage; and when n'=0 and m'=1, Z1a is directly conjugated to X1 by an amine linkage or amide linkage.

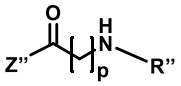
5. The compound of claim 1 or 2, wherein the at least one Z1c is covalently conjugated indirectly via a linker selected from (i) Formulae FL1-FL19:



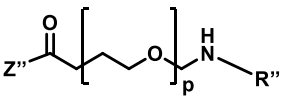
(FL1)



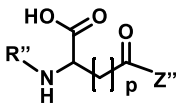
(FL2)



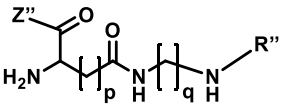
(FL3)



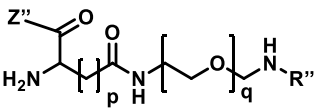
(FL4)



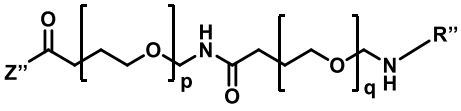
(FL5)



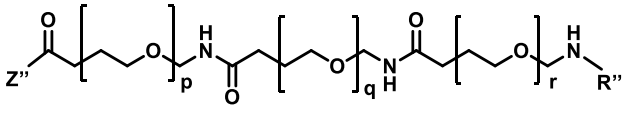
(FL6)



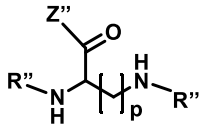
(FL7)



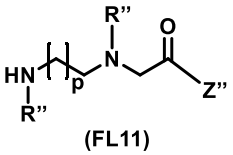
(FL8)



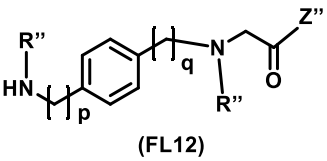
(FL9)



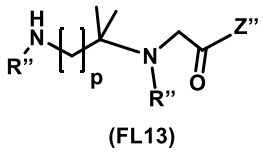
(FL10)



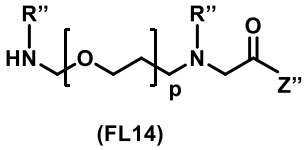
(FL11)



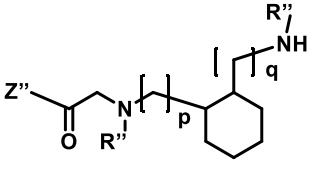
(FL12)



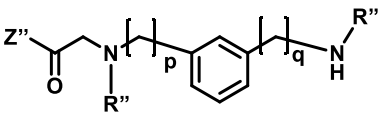
(FL13)



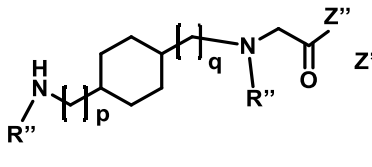
(FL14)



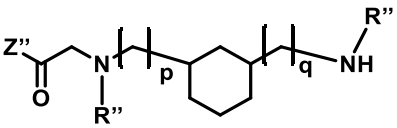
(FL15)



(FL16)

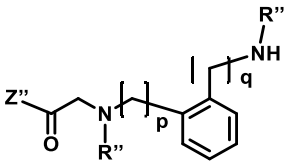


(FL17)



(FL18)

and



(FL19)

;

wherein, in Formulae FL1 to FL19:

Z’’ represents an attachment point toward X1;

R’’ represents an attachment point toward Z1c;

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

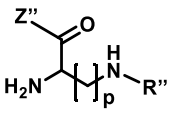
q is 1, 2, 3, 4, or 5,

r is 1, 2, 3, 4, or 5; and

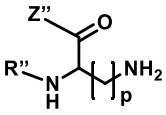
any primary amine is optionally acetylated or alkylated; and

(ii) an L- or D-amino acid comprising at least one amine group directly conjugated to Z1c, wherein an acid functional group of the amino acid is conjugated toward X1 in Formula I.

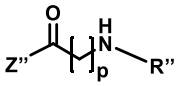
6. The compound of claim 2, wherein n’ is 1 and each of the Z1b is independently selected from (i) Formulae FL1-FL19:



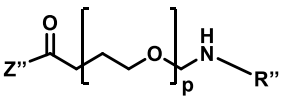
(FL1)



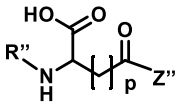
(FL2)



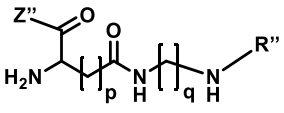
(FL3)



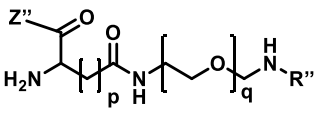
(FL4)



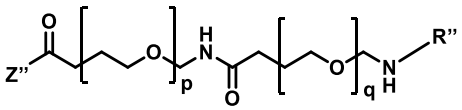
(FL5)



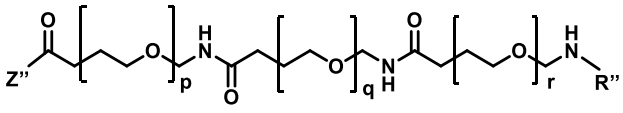
(FL6)



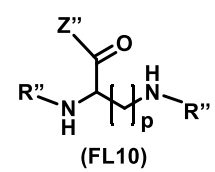
(FL7)

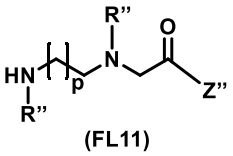


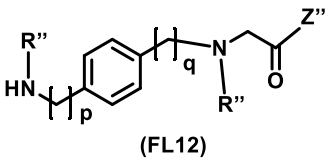
(FL8)

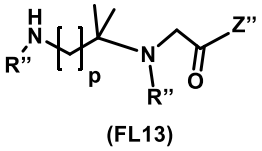


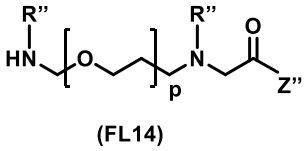
(FL9)

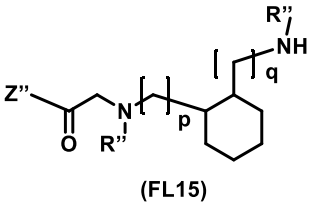

(FL10)

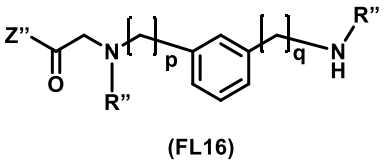

(FL11)

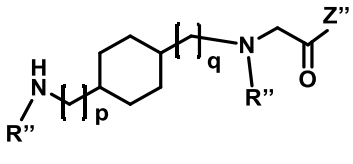

(FL12)

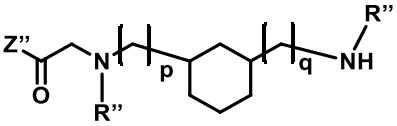

(FL13)

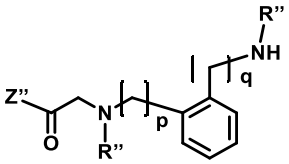

(FL14)


(FL15)


(FL16)


(FL17)


(FL18)


(FL19)

and ;

wherein, in Formulae FL1 to FL19:

Z'' represents an attachment point toward X1;

R'' represents an attachment point toward Z1c;

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

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

r is 1, 2, 3, 4, or 5; and

any primary amine is optionally acetylated or alkylated; and

(ii) an L- or D-amino acid comprising at least one amine group directly conjugated to Z1c, wherein an acid functional group of the amino acid is conjugated toward X1 in Formula I.

7. The compound of claim 1 or 2, wherein the compound comprises a drug substance comprising a human polypeptide hormone of the human pancreas, insulin, glucagon, GLP-1, a somatostatin, a gastric inhibitory polypeptide, a glucose-dependent insulinotropic polypeptide, a hybrid peptide comprising sequences from two or more human polypeptide hormones, or an analogue thereof.

8. The compound of claim 5, wherein:

X1 comprises human insulin or a human insulin analogue comprising an A-chain and a B-chain, wherein the A-chain comprises a sequence selected from SEQ ID

NOs 1 and 3 to 33, and the B-chain comprises a sequence selected from SEQ ID NOs 2 and 34 to 74, 24047, and 24048;

each Z1c is independently selected from FF1, FF10, FF12, FF14, FF15, FF114, FF115, FF116, FF163, FF193, FF194, FF203, and FF221-FF224 and covalently conjugated either directly, or indirectly via the linker, to Z1a and/or Z1b, or to X1;

each Z1a is independently absent or independently comprises a sequence selected from K, GK, KGSH (SEQ ID NO:24049), KGSHK (SEQ ID NO:4238), KNSTK (SEQ ID NO:5085), GKASHK (SEQ ID NO:12414), GKEEEK (SEQ ID NO:12677), GKEEHK (SEQ ID NO:12680), GKGHSK (SEQ ID NO:13120), GKGSH (SEQ ID NO:24050), GKGSHK (SEQ ID NO:13198), GKGSTK (SEQ ID NO:13205), GKHENK (SEQ ID NO:13271), GKNSHK (SEQ ID NO:13982), GKNSTK (SEQ ID NO:13989), GKQSSK (SEQ ID NO:14380), GKYQFK (SEQ ID NO:15128), GKGSKK (SEQ ID NO:24045), GKKPGKK (SEQ ID NO:24046), GKGPSK (SEQ ID NO:24044), GKPSHKP (SEQ ID NO:24043), and GSHKGSHK (SEQ ID NO:24042);

each said linker is selected from FL1, FL3, FL4, and FL5;

each m' is independently 0 or 1;

each n' is independently 0, 1, 2, or 3;

each o' is independently 1, 2, 3, 4, or 5;

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

q' is 1, 2, 3, or 4, wherein when any of n', o', p', or q' is 2 or more, the corresponding groups Z1a, Z1b, and Z1c are independently selected and may be the same or different; and

wherein each Z1c is independently covalently conjugated, directly or indirectly, to an amine of Z1a, to an amine of Z1b, or to X1.

9. The compound of claim 5 or 8, wherein:

X1 comprises the human insulin or human insulin analogue comprising an A-chain and a B-chain, wherein the A-chain comprises SEQ ID NO:1; and the B-chain is selected from SEQ ID NOs 2, 36, 24047, and 24048;

each Z1c is independently selected from FF1, FF10, FF12, FF14, FF15, FF114, FF115, FF116, FF193, FF194, FF203, and FF221-FF224 and covalently conjugated either directly, or indirectly via the linker, to Z1a and/or Z1b, or to X1;

each Z1a independently comprises a sequence selected from K, GK, KGSH (SEQ ID NO:24049), KGSHK (SEQ ID NO:4238), KNSTK (SEQ ID NO:5085), GKASHK (SEQ ID NO:12414), GKEEEK (SEQ ID NO:12677), GKEEHK (SEQ ID NO:12680), GKGHSK (SEQ

ID NO:13120), GKGSH (SEQ ID NO:24050), GKGSHK (SEQ ID NO:13198), GKGSTK (SEQ ID NO:13205), GKHENK (SEQ ID NO:13271), GKNSHK (SEQ ID NO:13982), GKNSTK (SEQ ID NO:13989), GKQSSK (SEQ ID NO:14380), GKYQFK (SEQ ID NO:15128), GKGSKK (SEQ ID NO:24045), GKKPGKK (SEQ ID NO:24046), GKGPSK (SEQ ID NO:24044), GKPSHKP (SEQ ID NO:24043), and GSHKGSHK (SEQ ID NO:24042);

each said linker is independently absent or independently selected from FL3 and FL5;

each m' is independently 0 or 1;

each n' is independently 0 or 2;

each o' is independently 1, 2, or 3;

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

q' is 1, 2, or 3, wherein when any of n', o', p', or q' is 2 or more, the corresponding groups Z1a, Z1b, and Z1c are independently selected and may be the same or different;

wherein each Z1c is independently covalently conjugated, directly or indirectly, to an amine of Z1a, to an amine of Z1b, or to X1.

10. The compound of any one of claims 2-9, wherein each of the Z1a is independently absent or independently comprises a sequence selected from K, GK, KGSH (SEQ ID NO:24049), GKGSH (SEQ ID NO:24050), KGSHK (SEQ ID NO:4238), and GKGSHK (SEQ ID NO:13198).

11. The compound of any one of claims 2-10, wherein each of the Z1c is independently selected from FF1, FF10, FF12, FF14, FF15, FF114, FF115, FF116, and FF221-FF224, and wherein the B_1 and the B_2 are independently selected from Formulae F1 and F2.

12. The compound of claim 11, wherein the B_1 and the B_2 are F2.

13. The compound of claim 12, wherein at least one R_1 in B_1 or B_2 is F or CF_3.

14. The compound of any one of claims 2-4 and 6-11, wherein Z1b is independently absent, FL3, or FL5.

15. The compound of any one of claims 1-14, wherein each of the Z1c is independently selected from FF10, FF12, FF116, FF221, FF222, and FF224.

16. The compound of any one of claims 2-4 and 6-7, wherein:

each B_1 and B_2 is F2 and is covalently conjugated to Z1c using an amide linkage,

each Z1b is independently absent; FL3 wherein p is 1, 2, or 3; or FL5 wherein p is 2, 3, or 4;

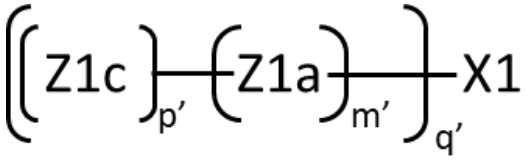
each FF is independently selected from FF10, FF12, FF116, FF134, FF163, FF193, FF203, FF221, FF222 and FF224; wherein each FF12 and FF222 has either (*S*,*R*) or (*S*,*S*) stereochemistry;

each Z1c is conjugated either directly or indirectly through FL3 or FL5 to the amine group in one or more lysine side chain in X1 or the N-terminus in X1; and

X1 is a polypeptide drug substance and/or an insulin optionally having from 0 to 4 residues replaced, inserted, or mutated to lysines, and wherein the lysines are each conjugated directly or indirectly to a Z1c.

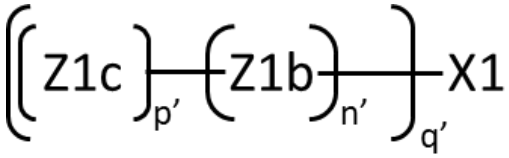
17. The compound of any one of claims 1-2, 8 and 9, wherein Z1c is FF224, n' is 0, and Z1a is an amine containing amino acid.

18. The compound of any one of claims 2-17, wherein the compound is selected from:



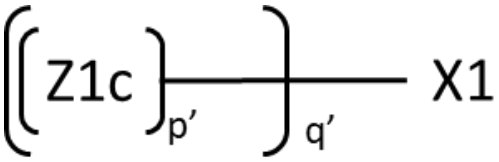
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IA



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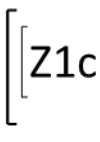
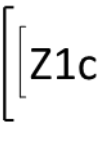
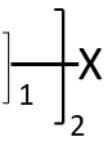
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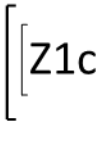
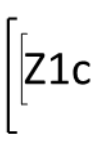
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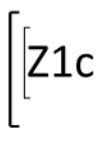
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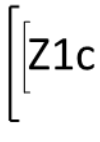
19. The compound of any one of claims 2-18, wherein the compound is selected from:

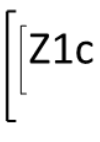




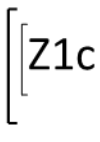
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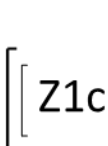
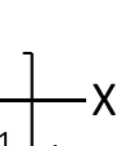

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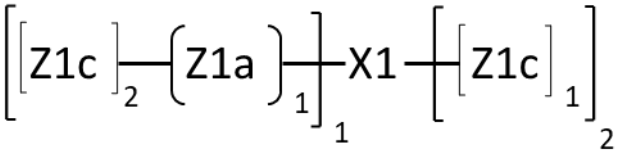

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;

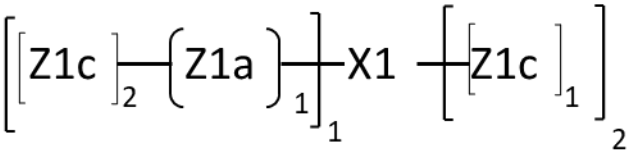

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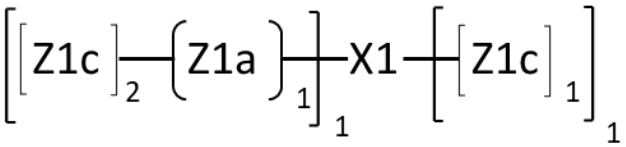


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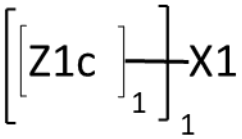


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20. The compound of claim 19, wherein the compound is selected from

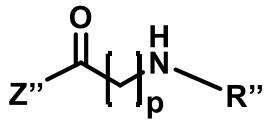


and



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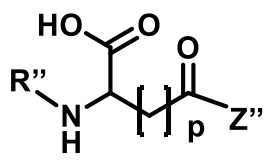
21. The compound of any one of claims 1-2 and 8-9, wherein Z1c is covalently conjugated directly to X1 via a linker, and wherein the linker is independently selected from gamma-glutamic acid, beta-alanine, and



(FL3)

Formula FL3,

wherein p is 1, 2, or 3; and



(FL5)

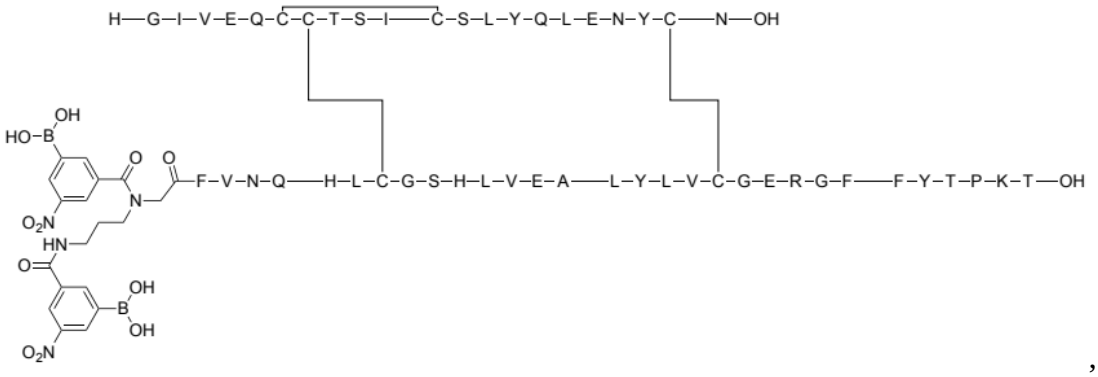
Formula FL5,

wherein p is 2, 3, or 4.

22. The compound of any one of claims 1-21, wherein X1 is OH or NH_2, and the compound further comprises a drug substance covalently conjugated directly or indirectly to the compound.

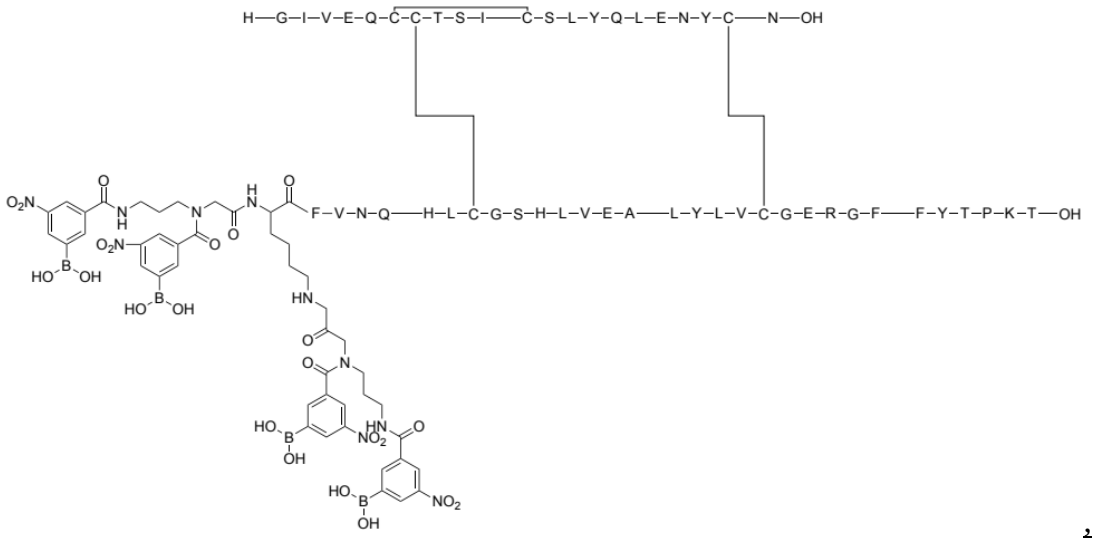
23. The compound of any one of claims 1-22, wherein the compound is selected from:

Example 315:



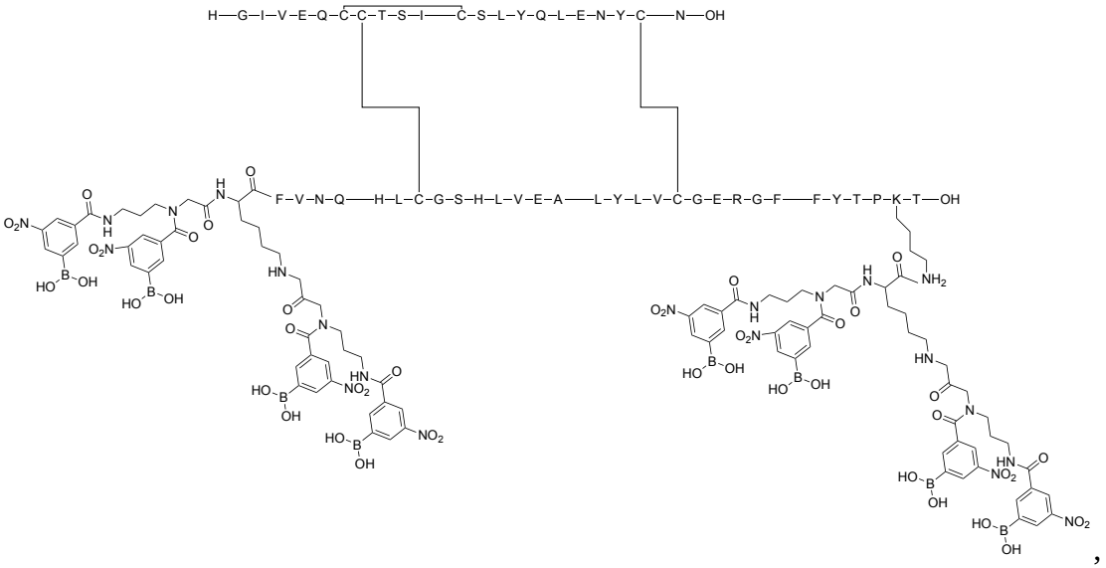
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Example 318:



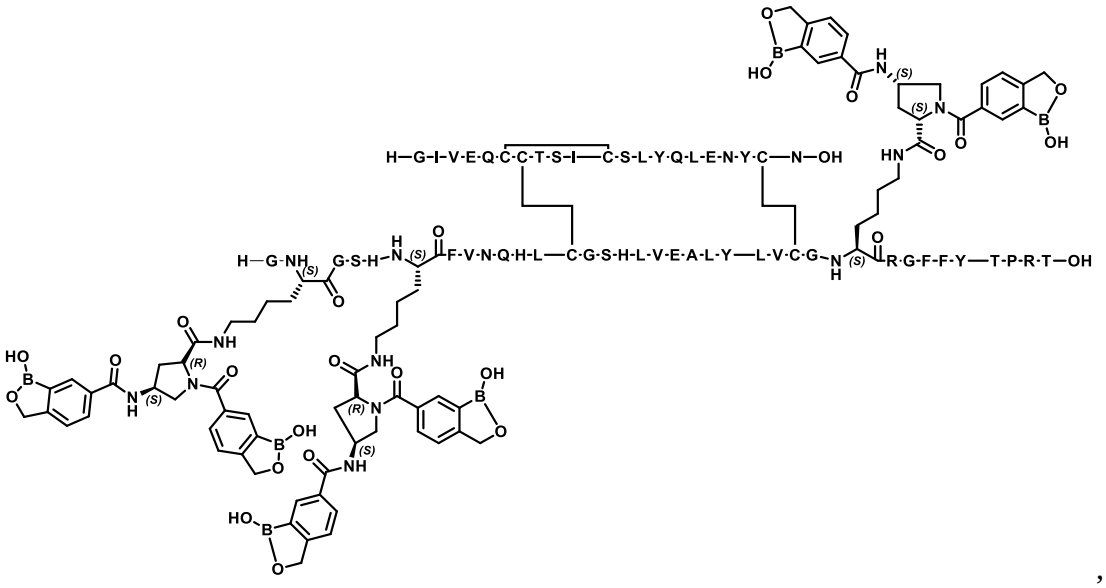
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Example 320:



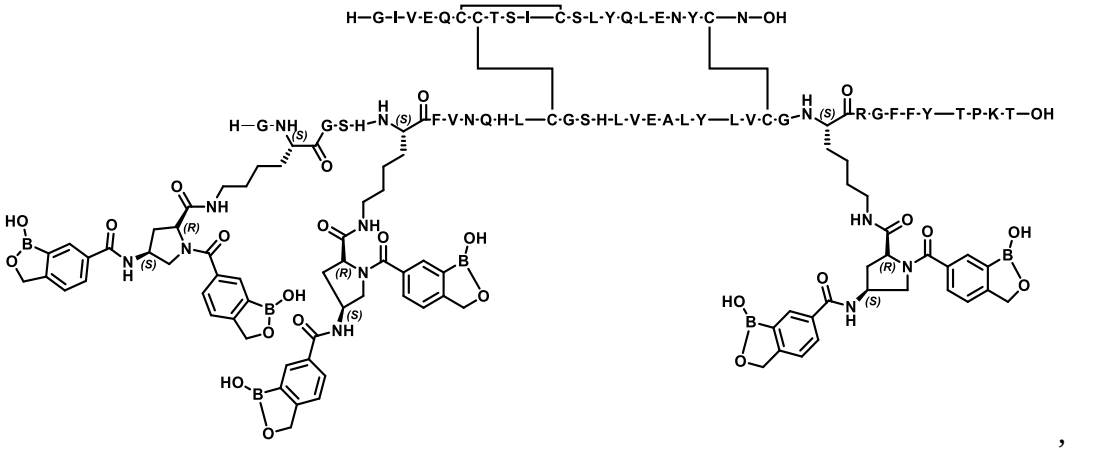
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Example 605:



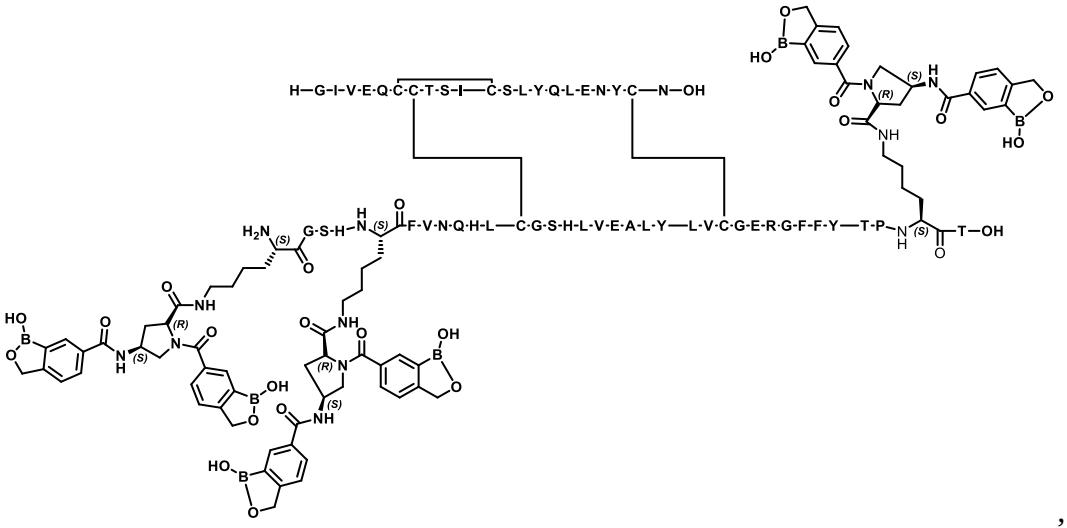
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Example 606:



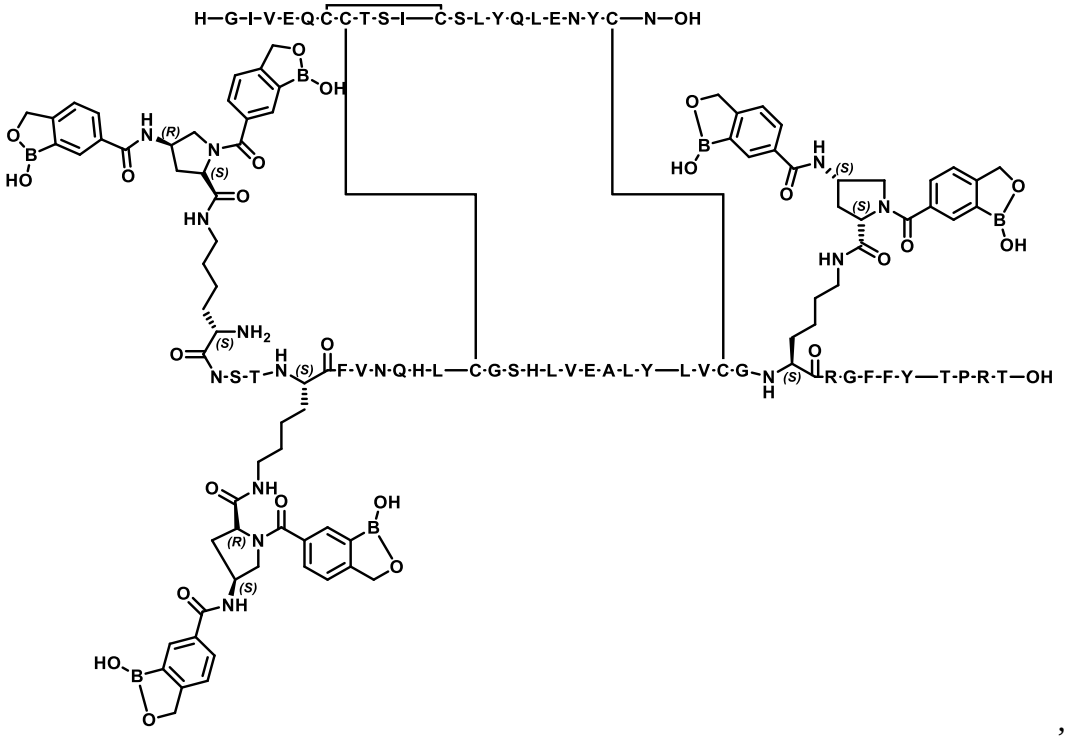
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Example 607:



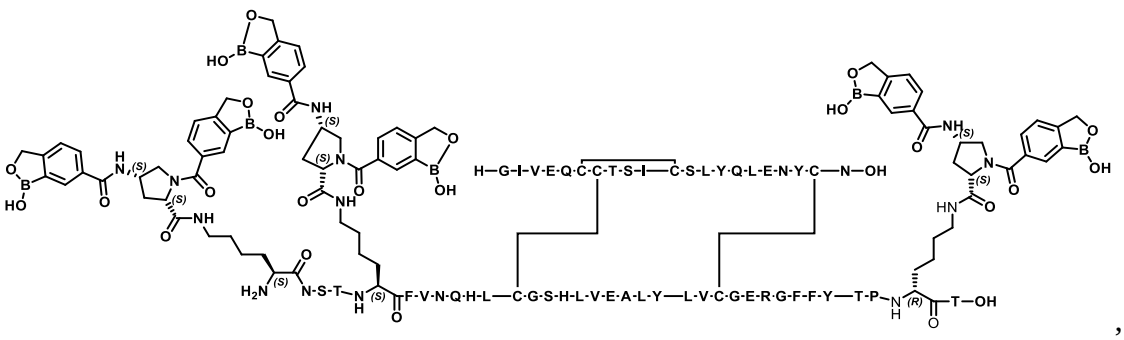
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Example 608:



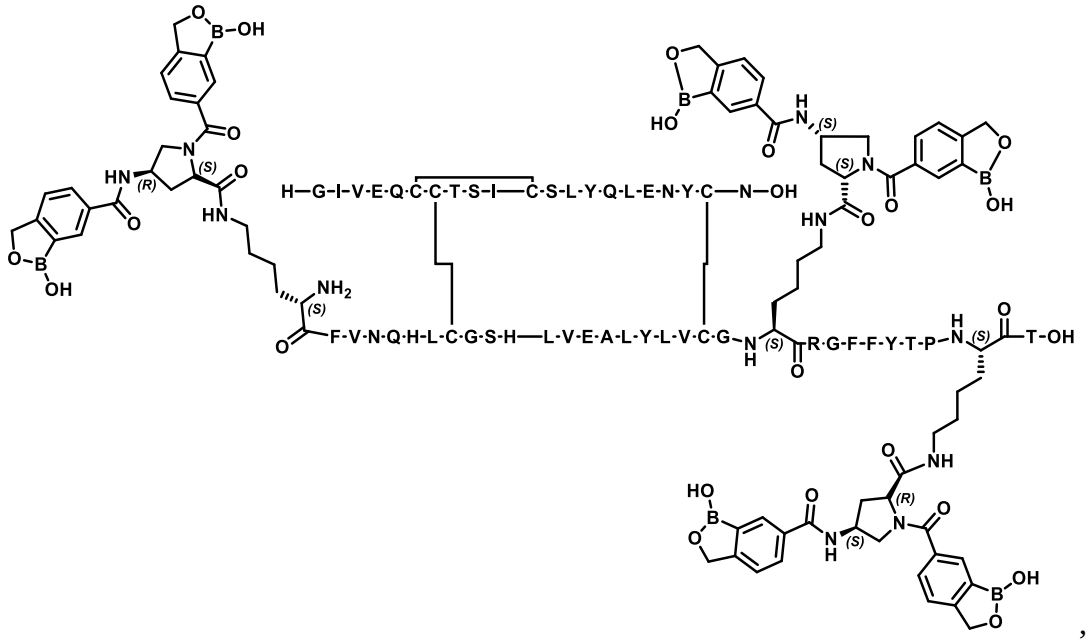
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Example 610:



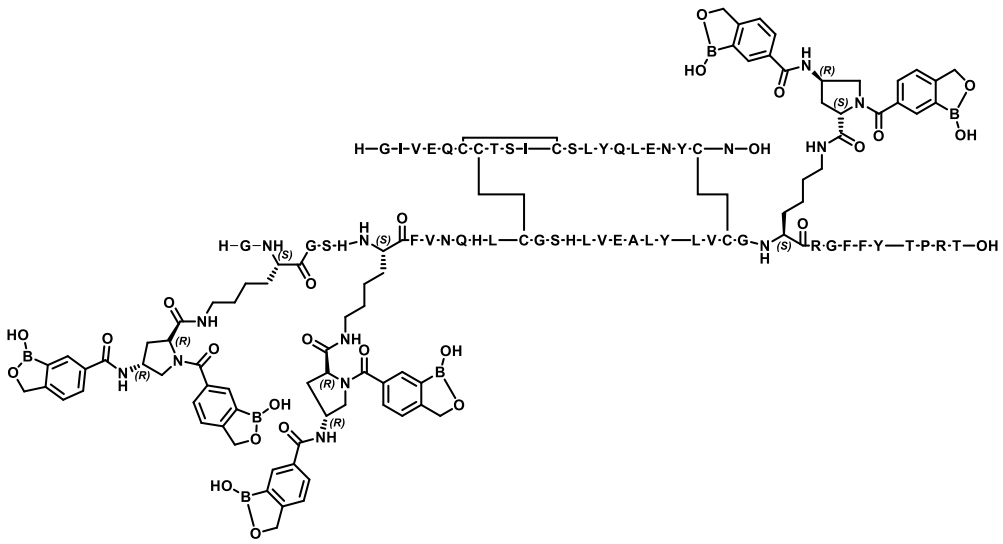
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Example 611:



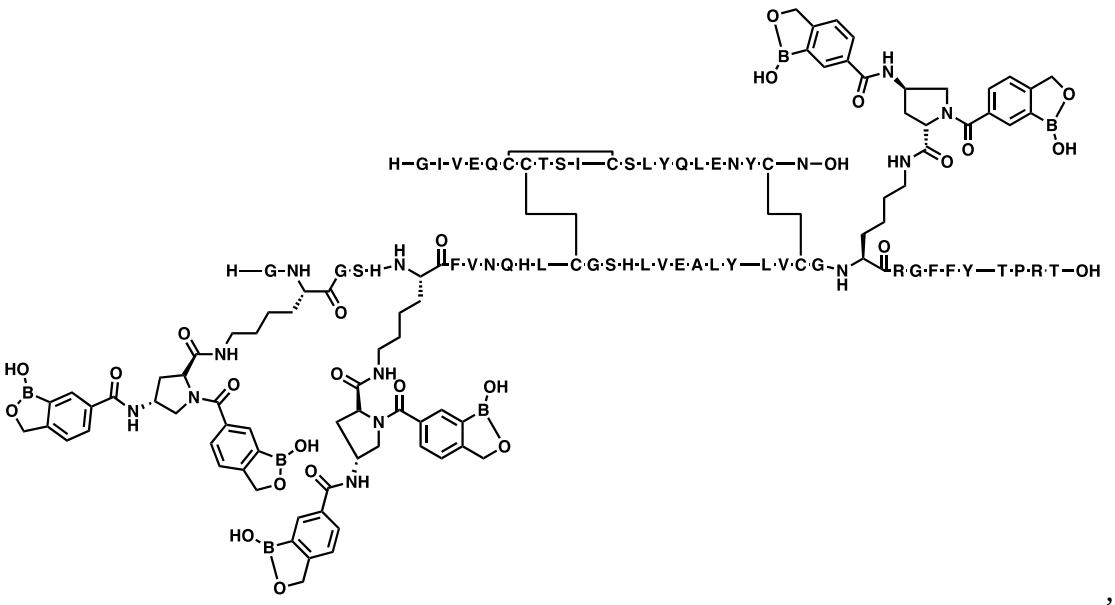
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Example 612:



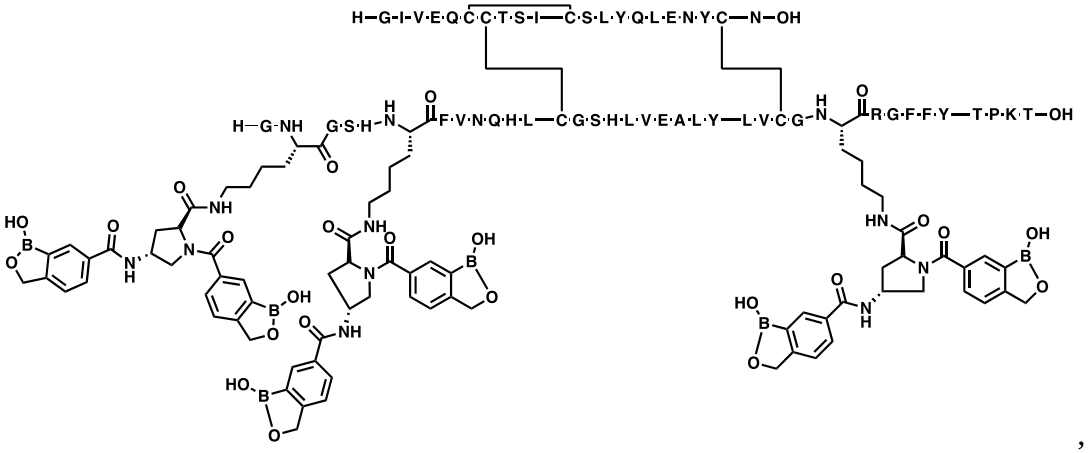
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Example 589:



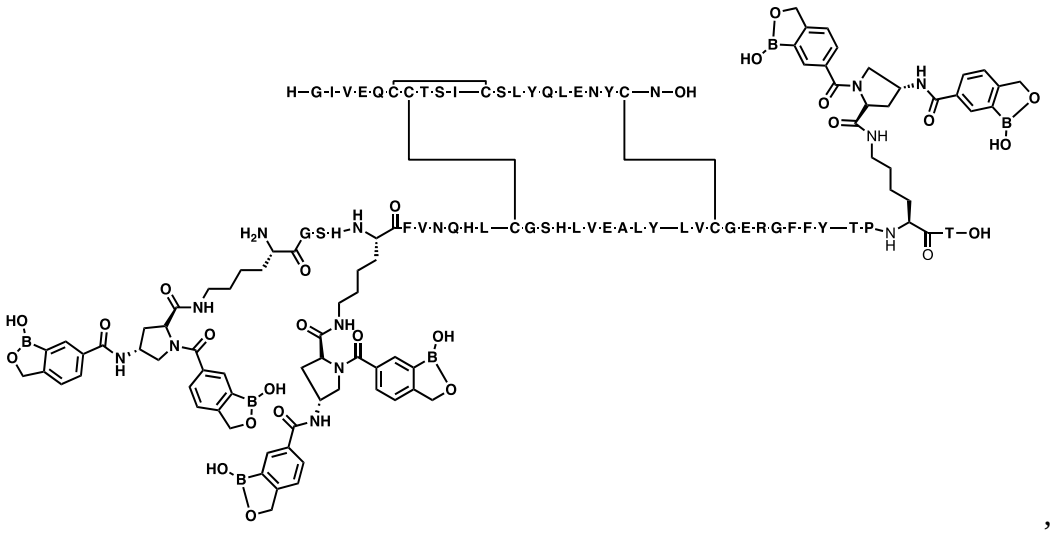
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Example 590:



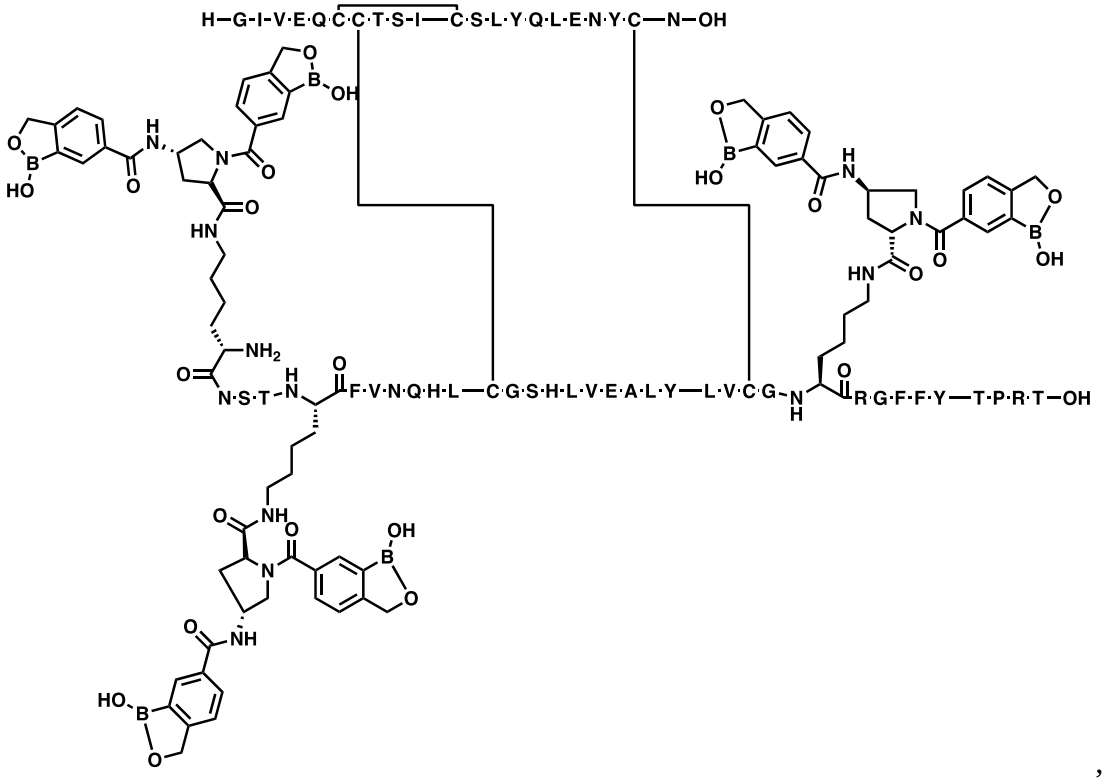
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Example 591:



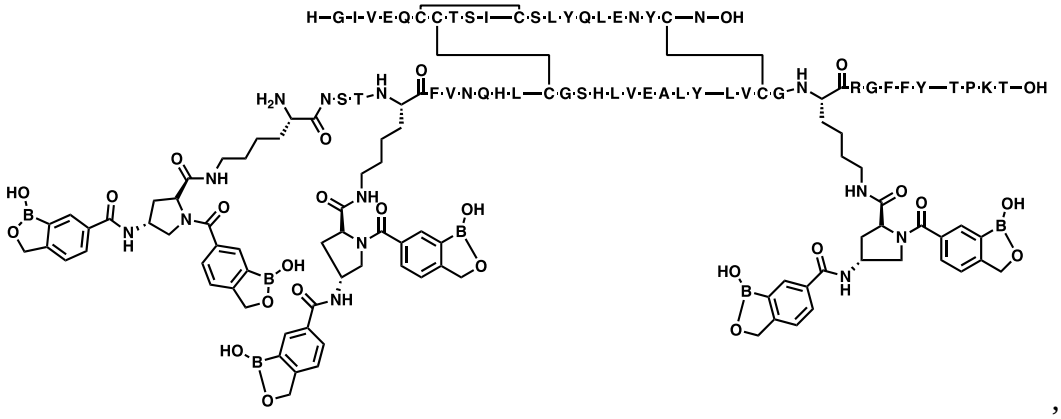
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Example 592:



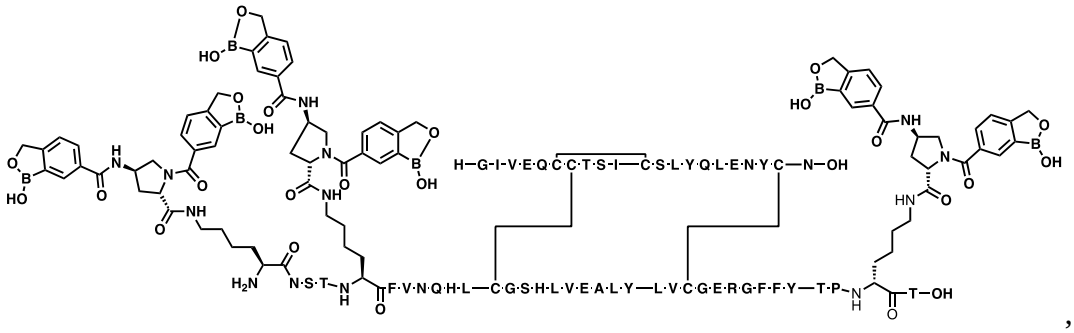
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Example 593:



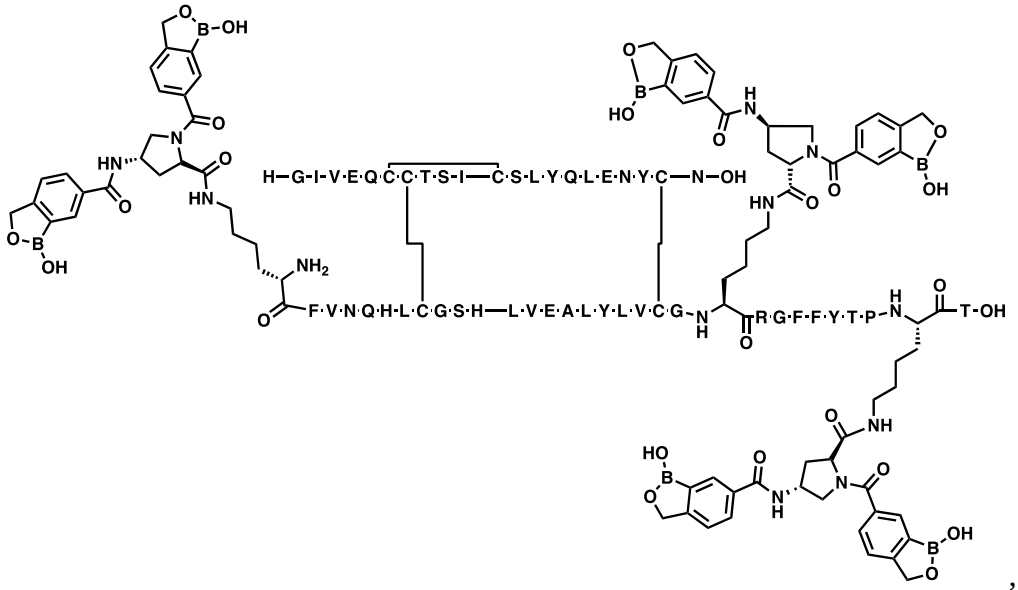
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Example 594:



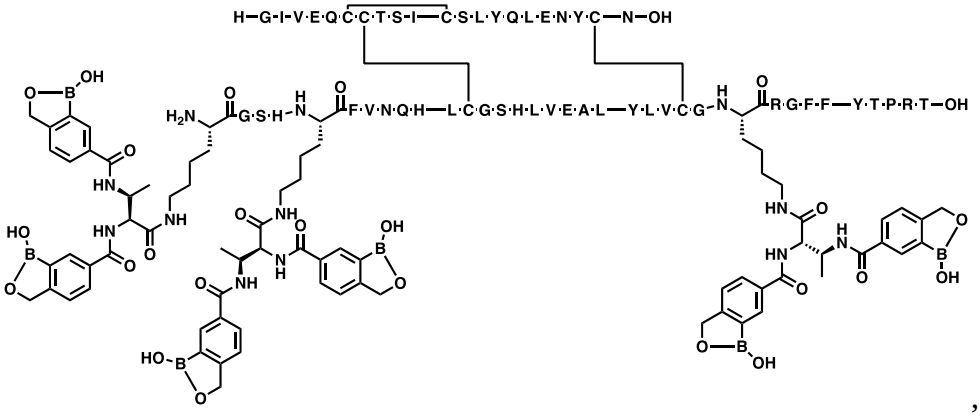
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Example 595:



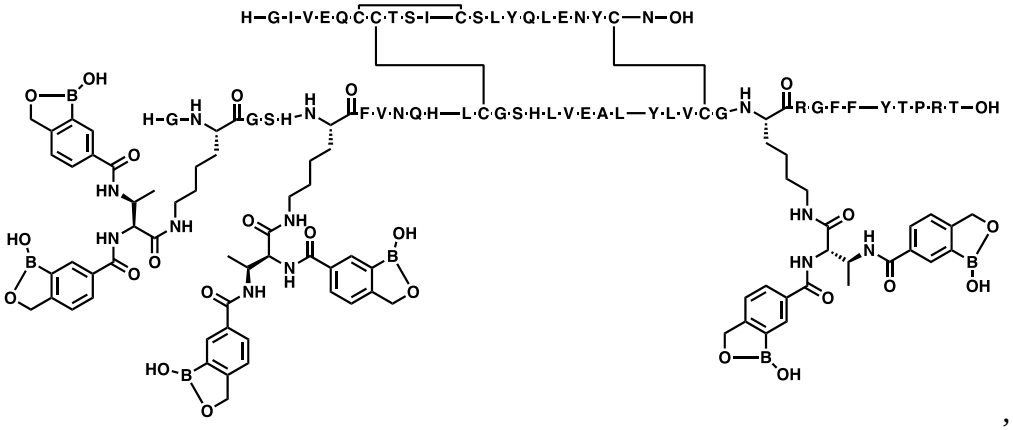
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Example 562:



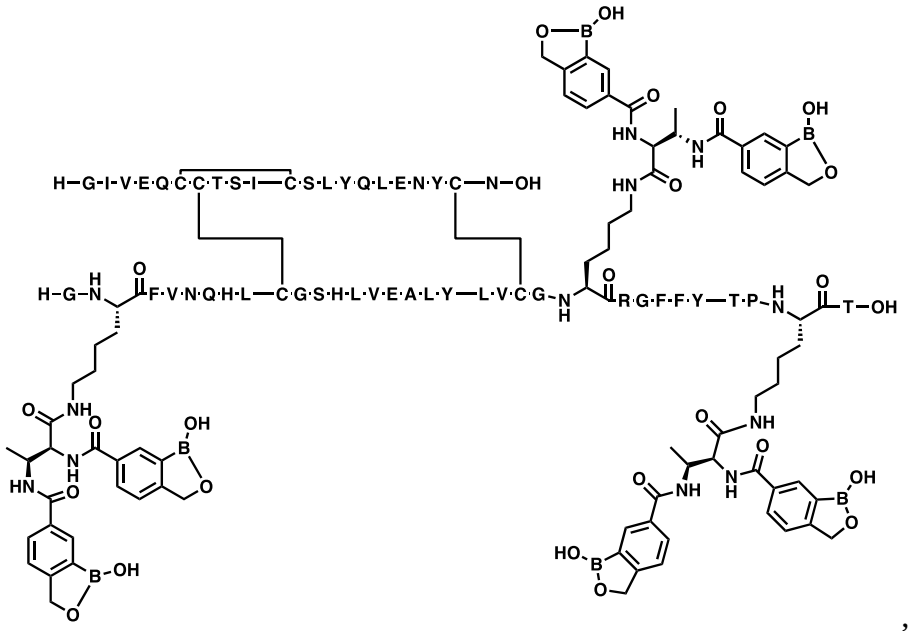
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Example 563:



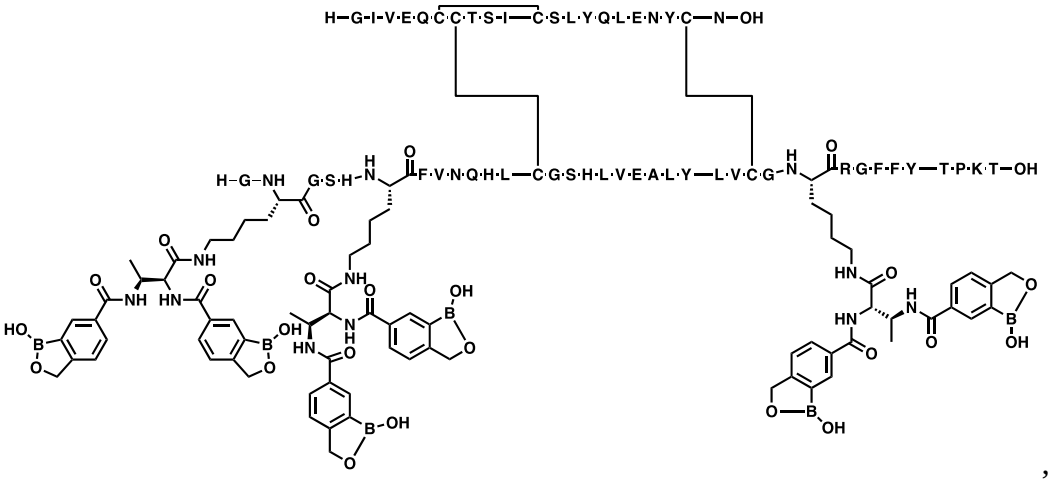
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Example 564:



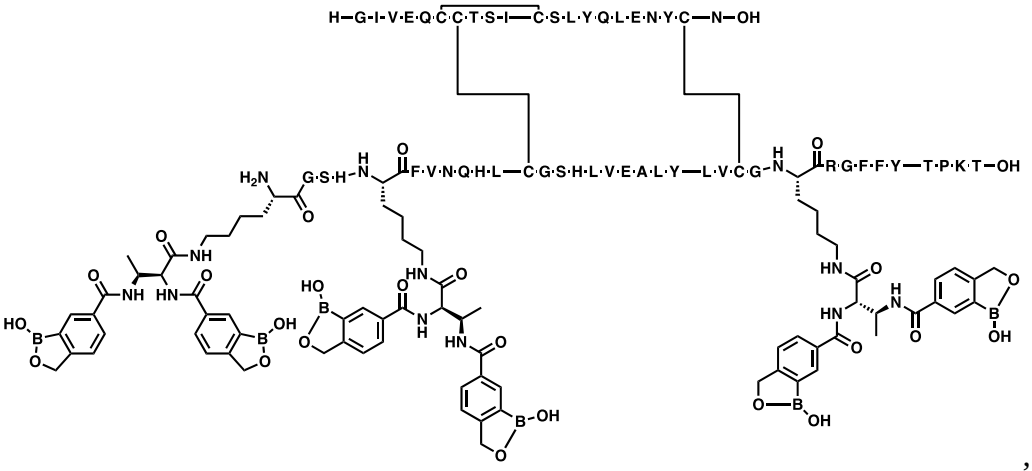
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Example 565:



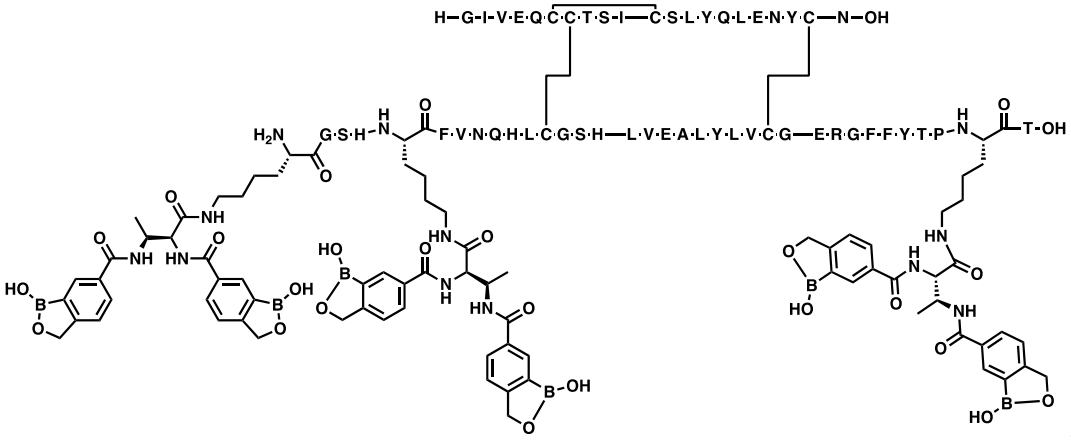
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Example 566:



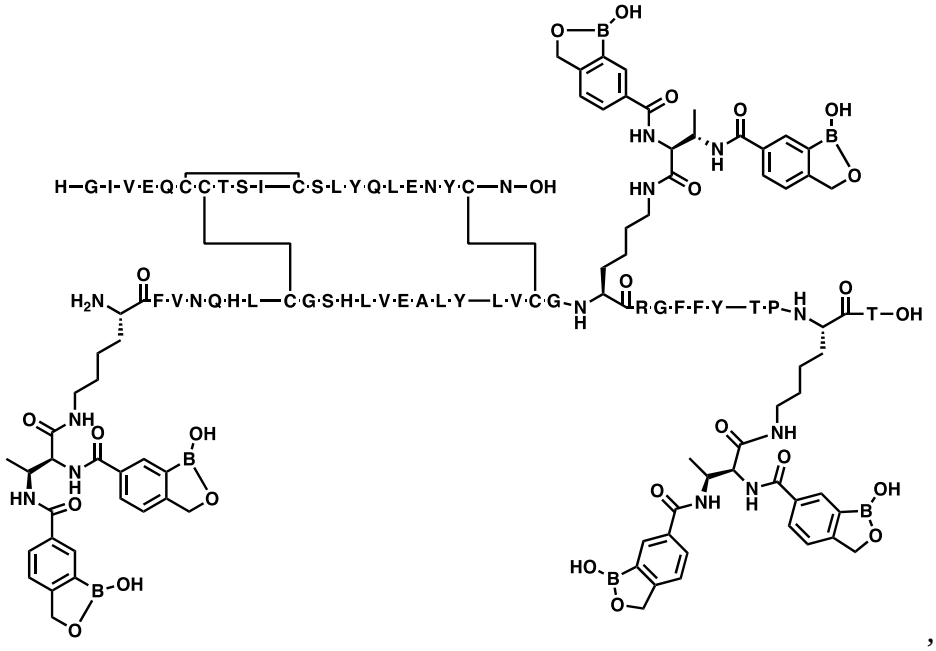
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Example 567:



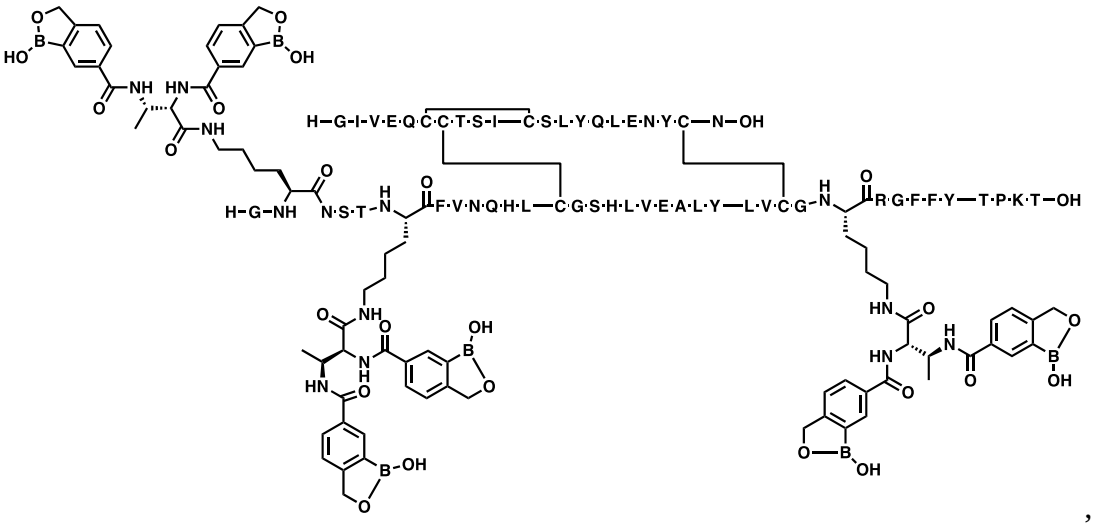
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Example 568:



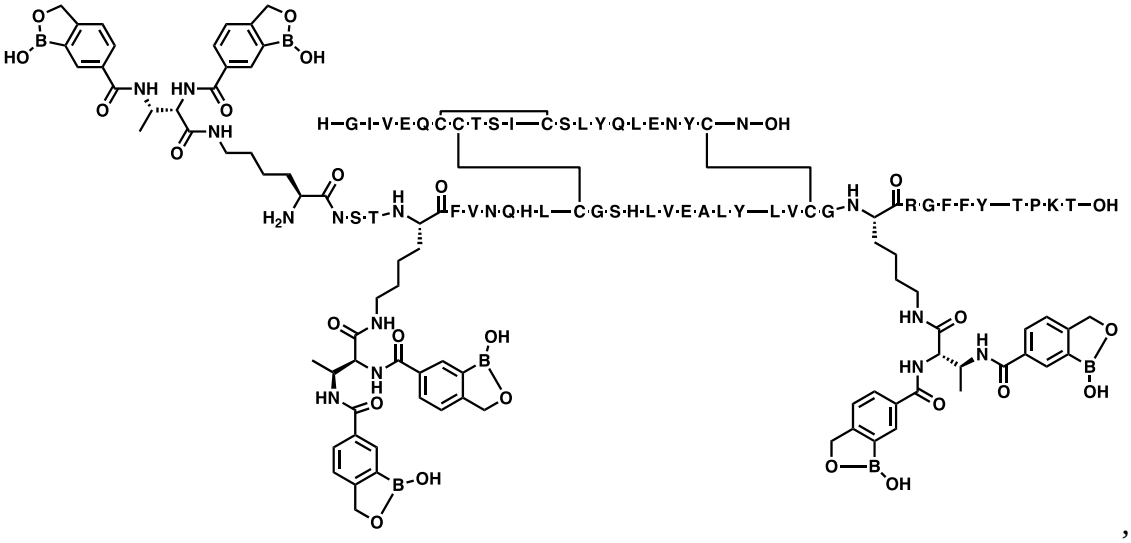
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Example 569:



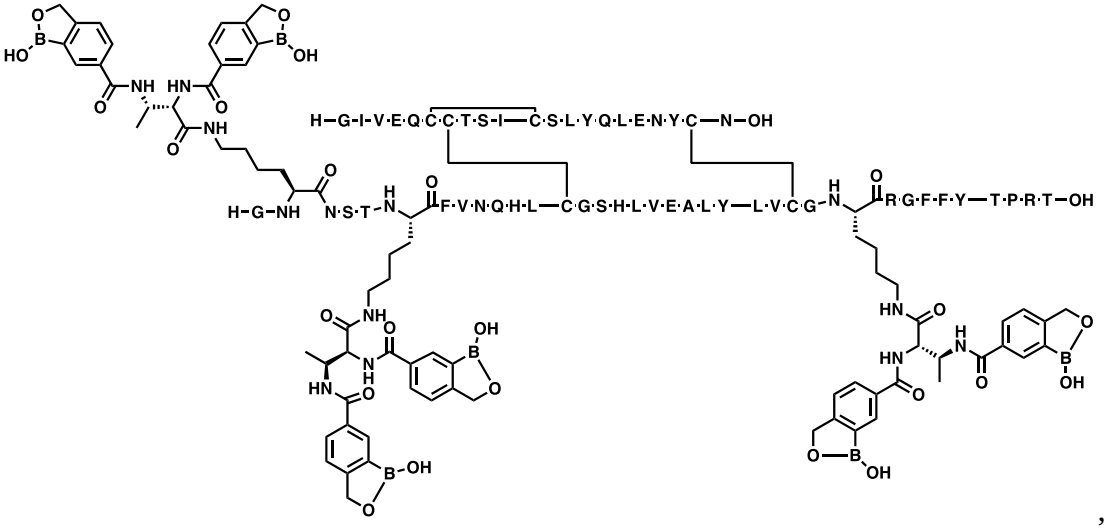
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Example 570:



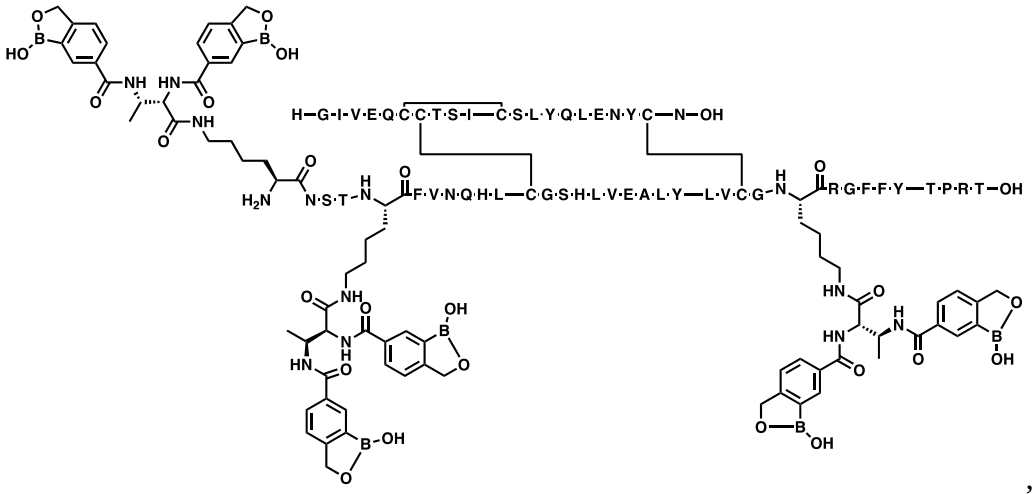
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Example 571:



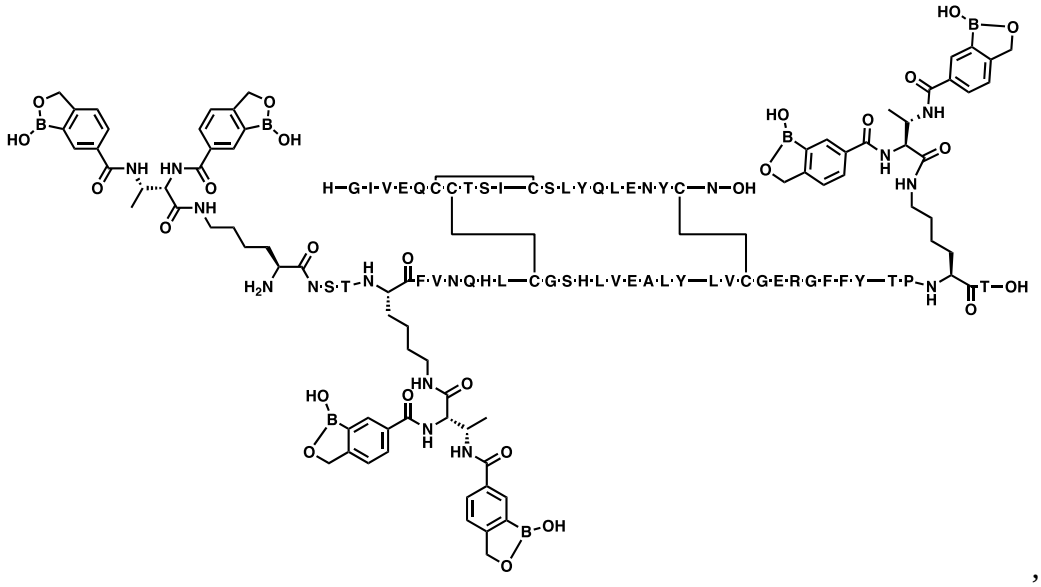
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Example 572:



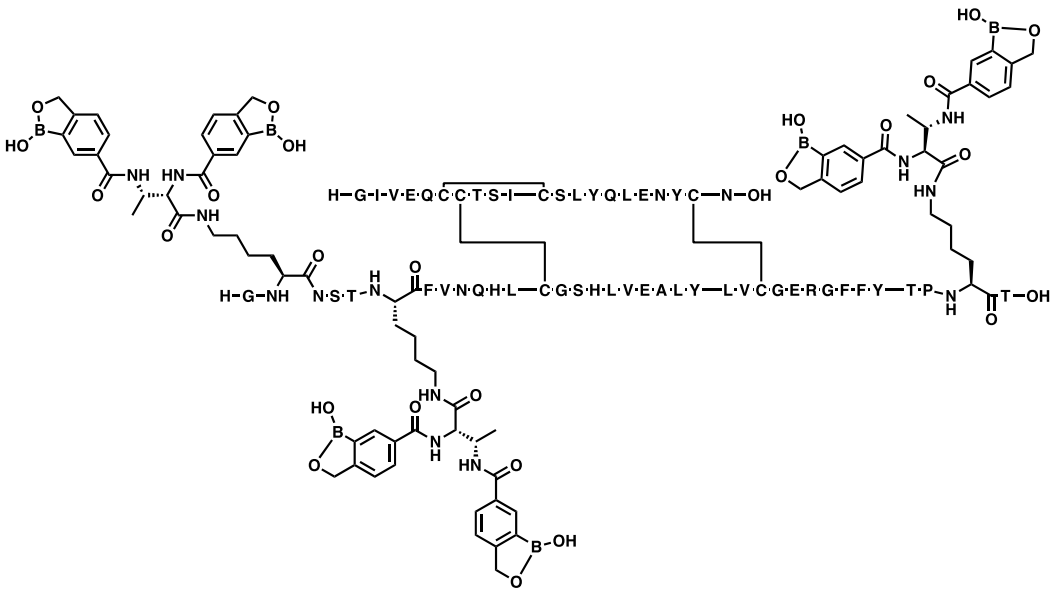
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Example 573:



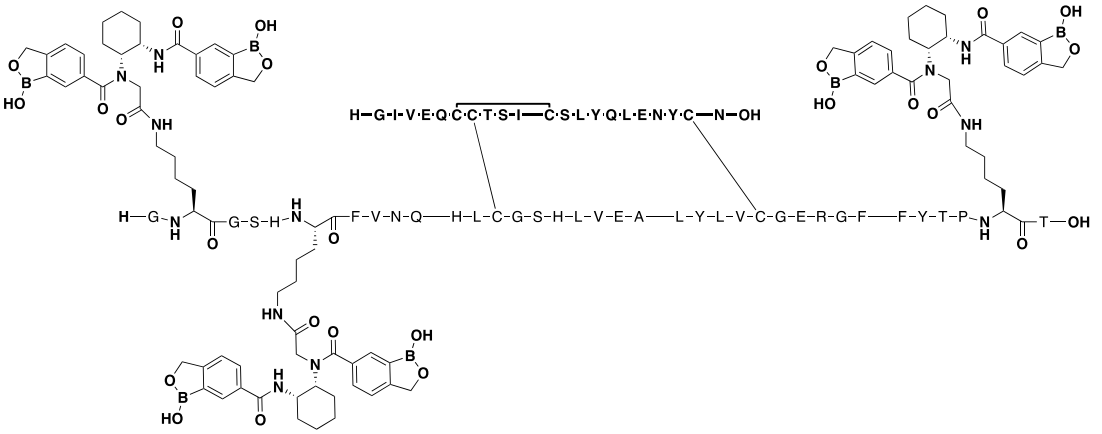
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Example 574:



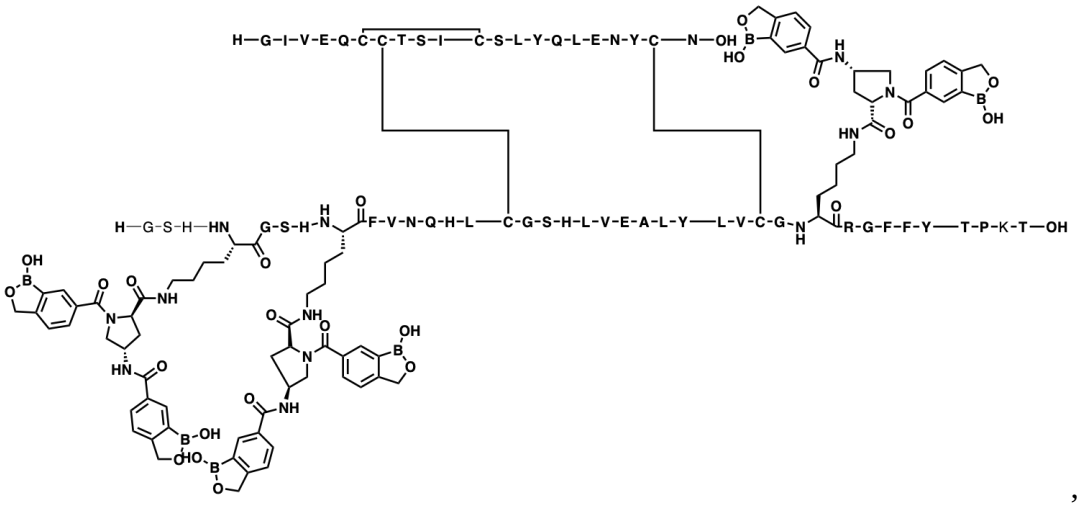
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Example 803:



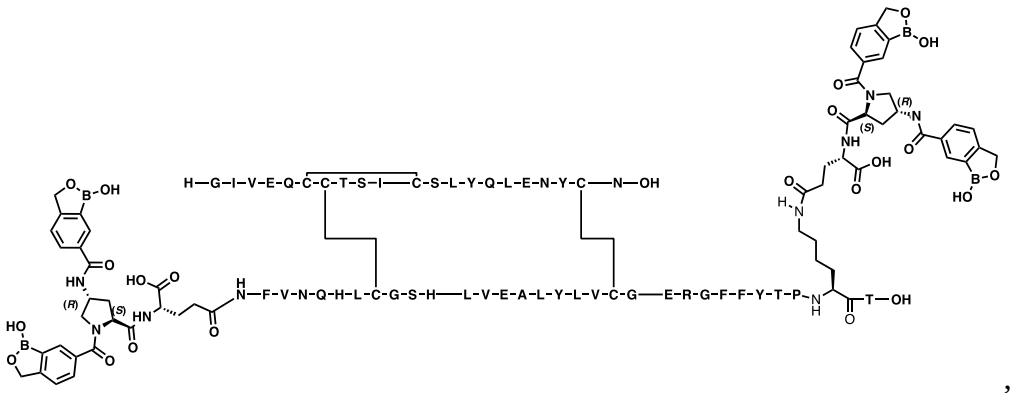
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Example 804:



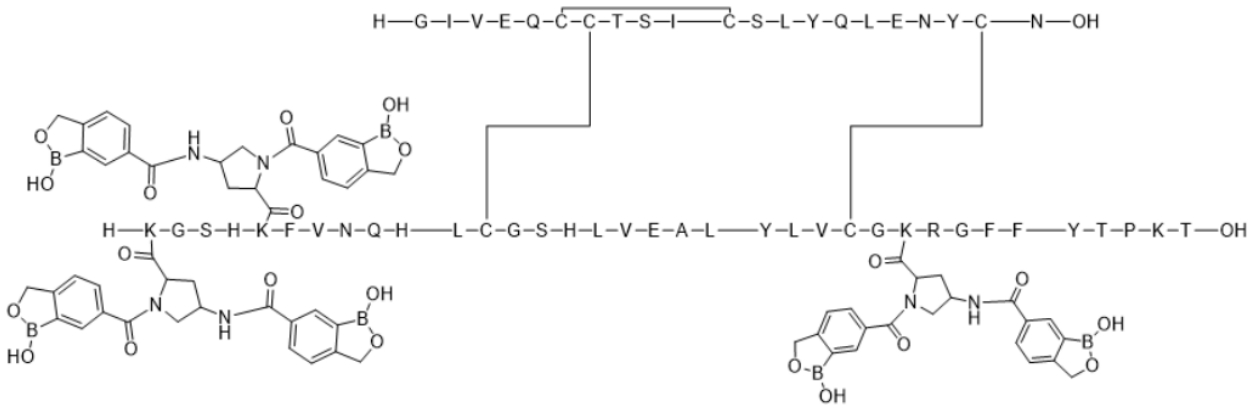
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Example 805:

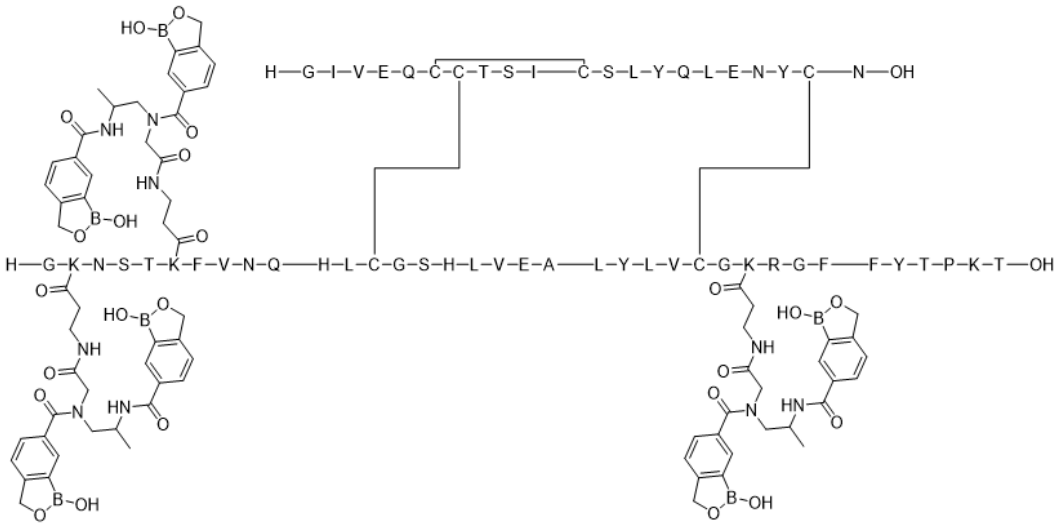


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Example 806:

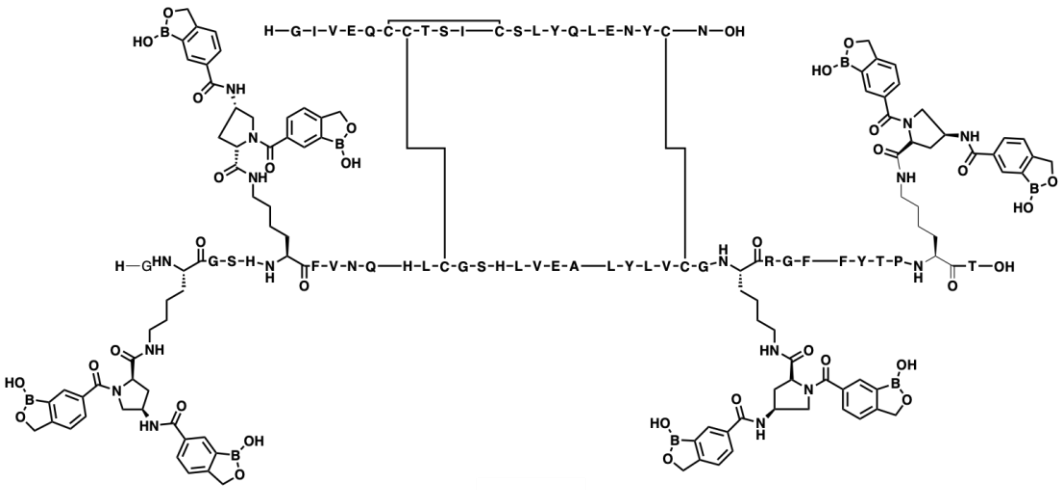


Example 807:



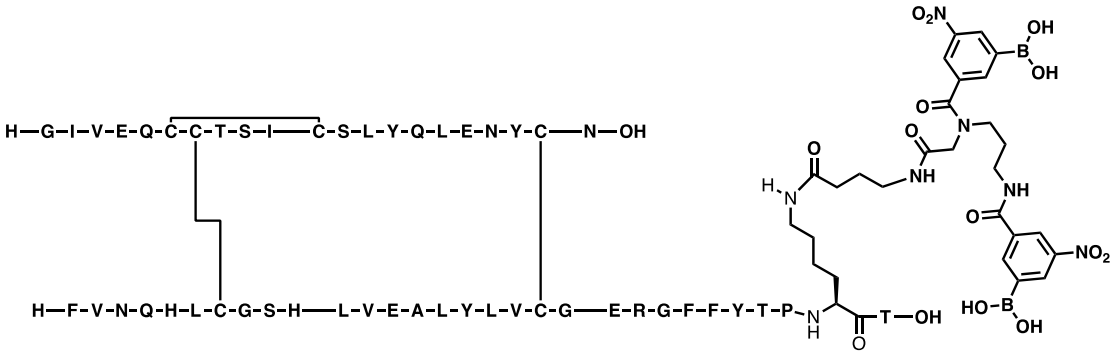
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Example 808:



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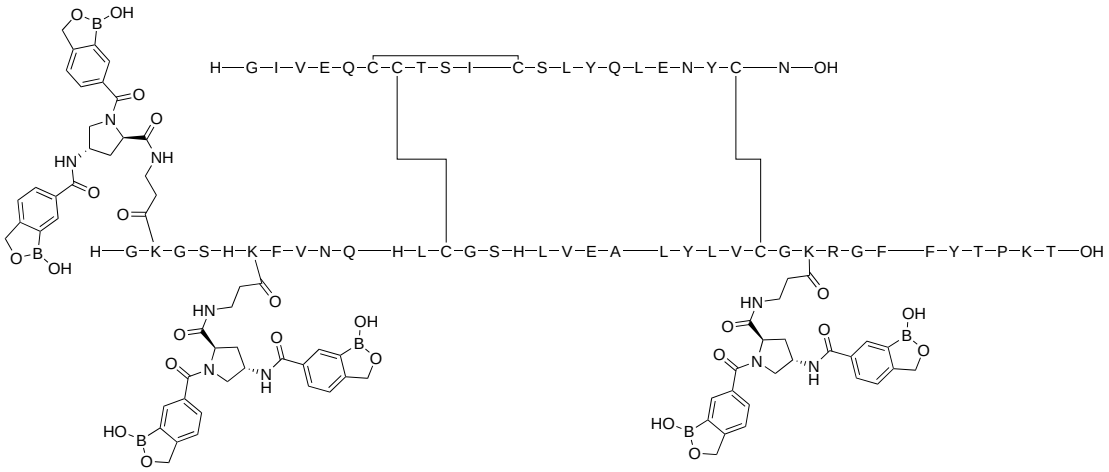
Example 809:



GSI - 094135

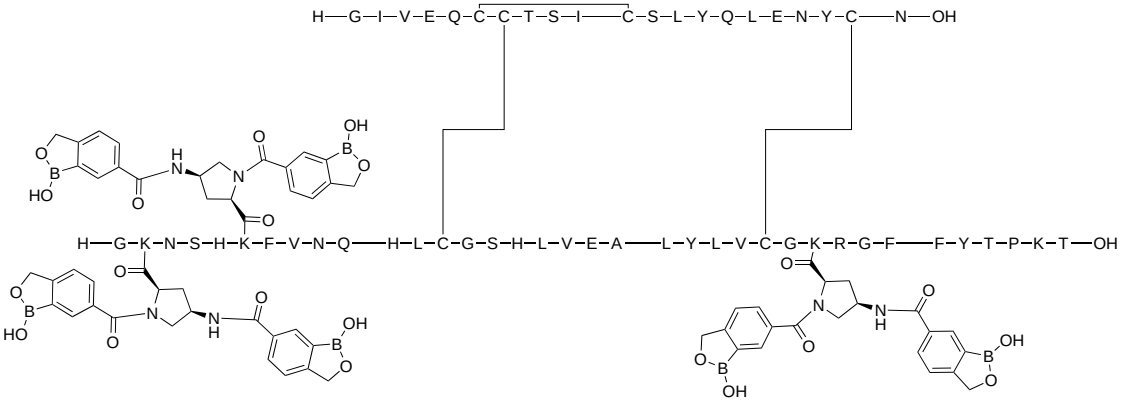
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Example 810:



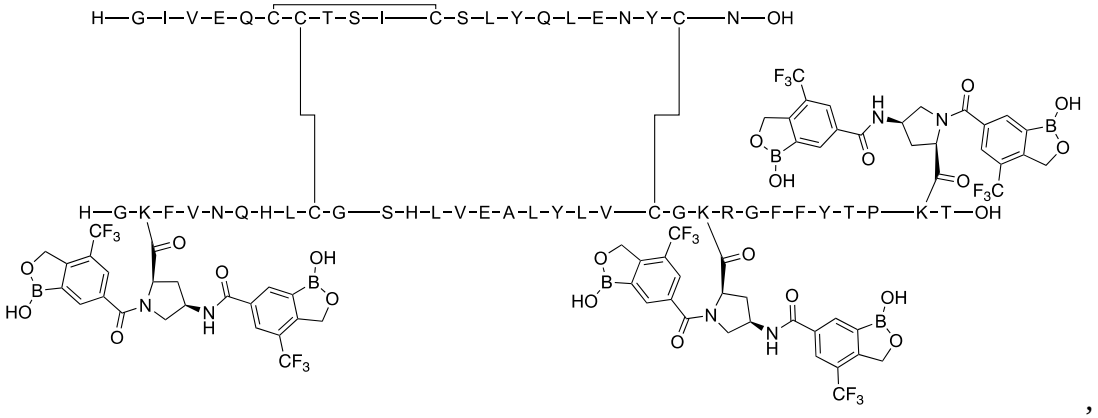
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Example 811:



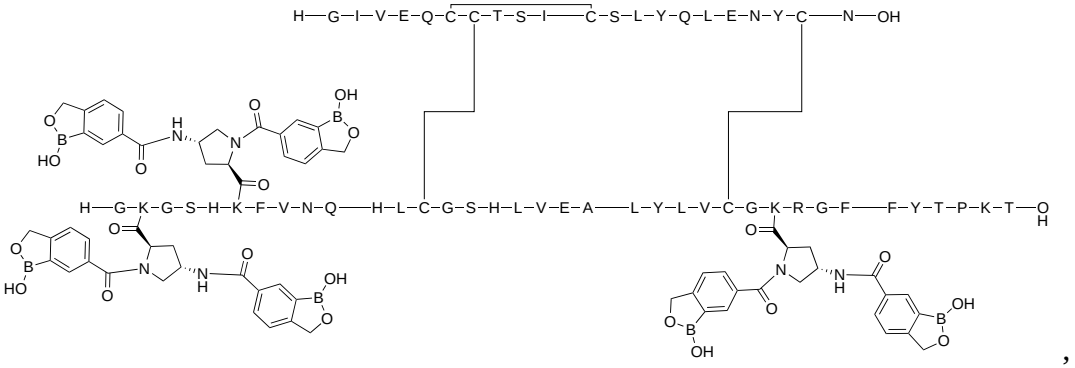
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Example 812:



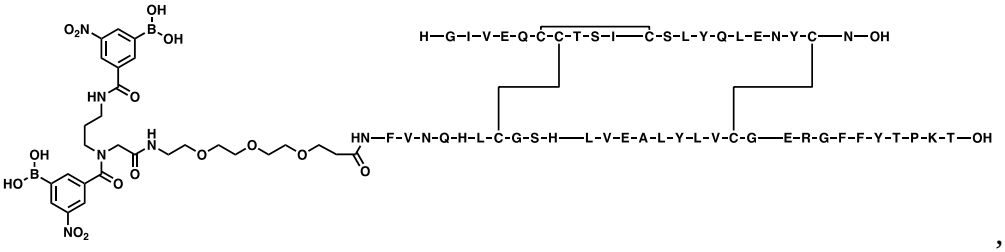
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Example 813:



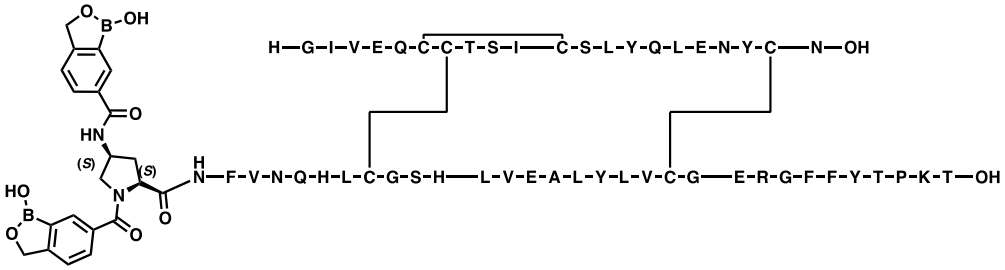
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Example 814:



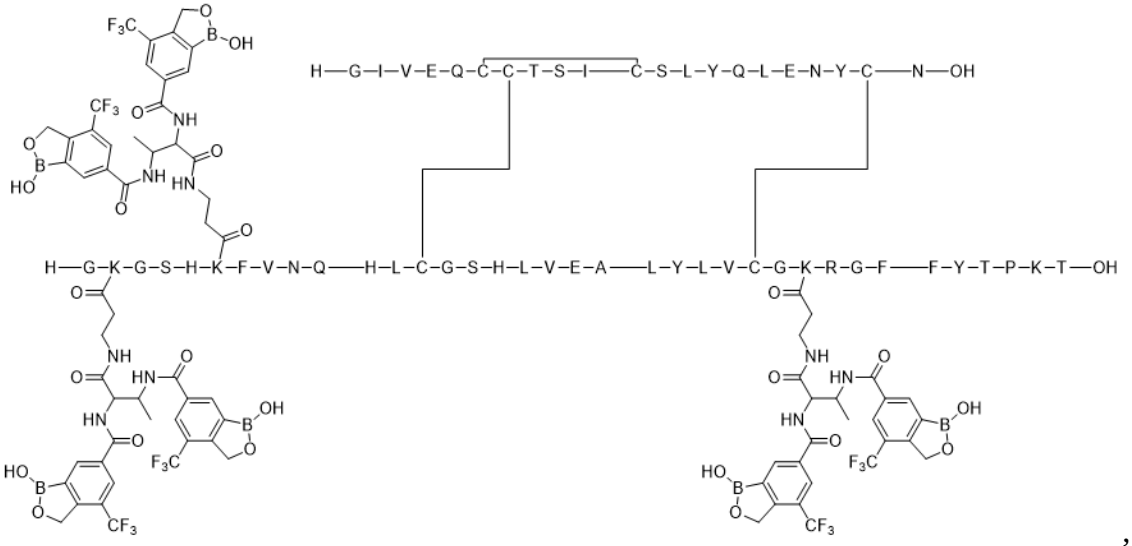
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Example 815:



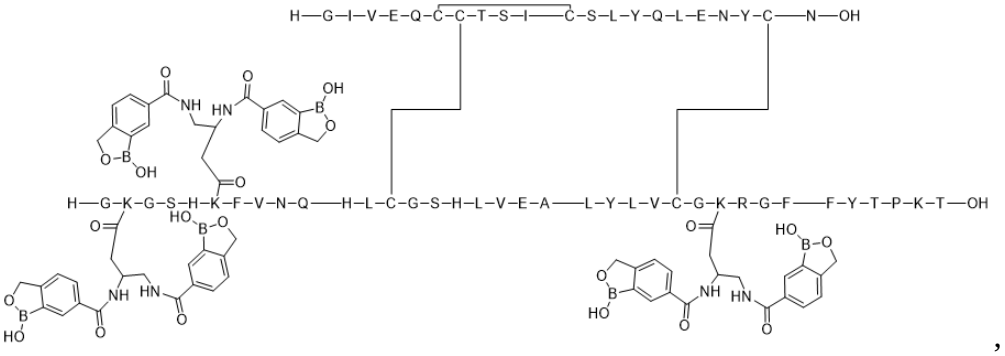
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Example 816:



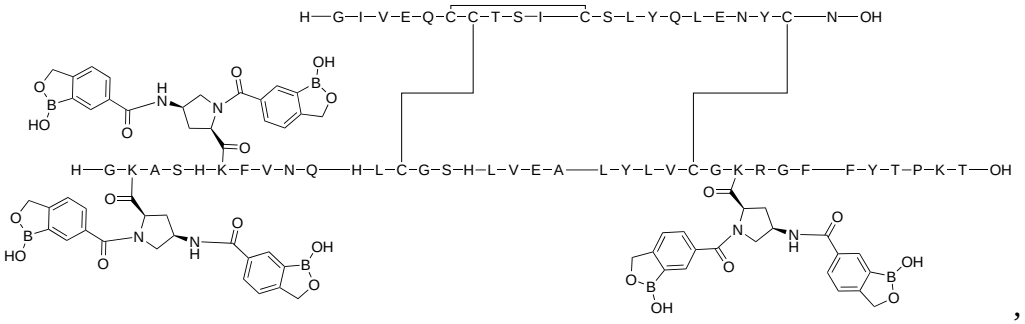
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Example 817:



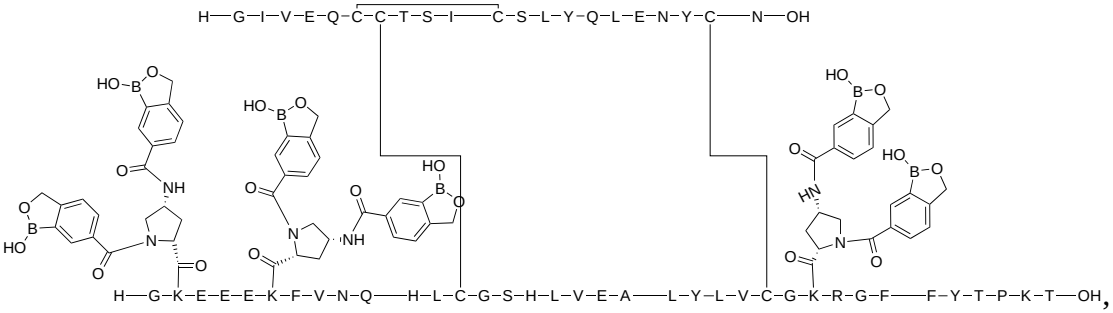
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Example 818:



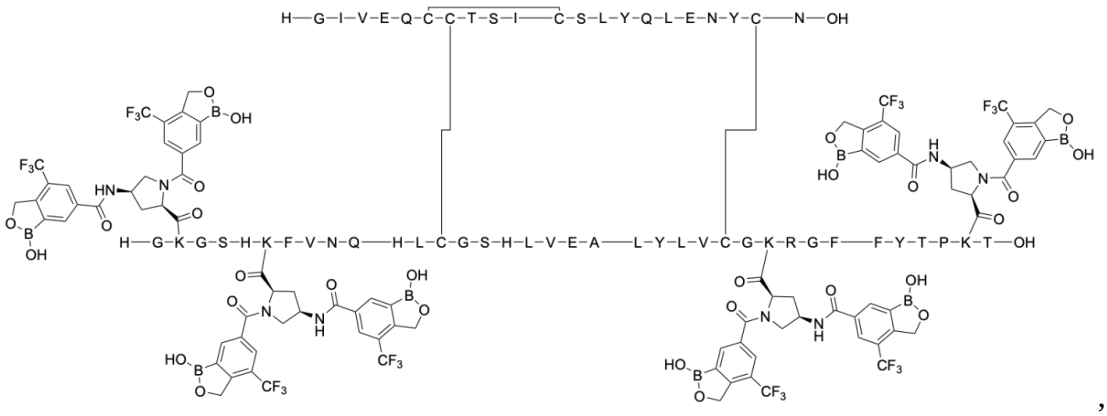
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Example 819:



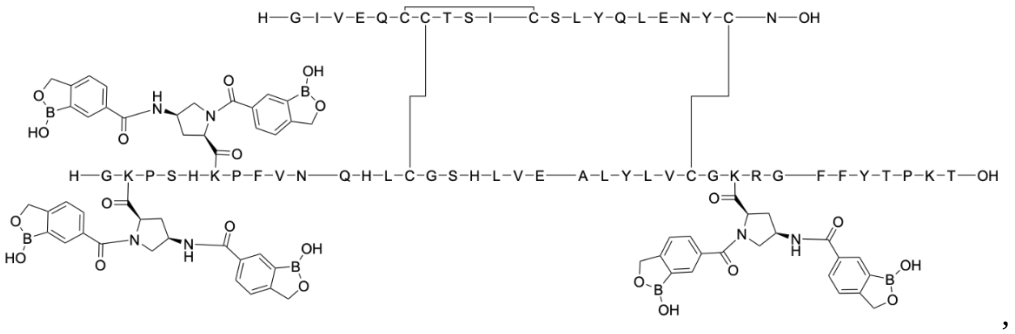
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Example 820:



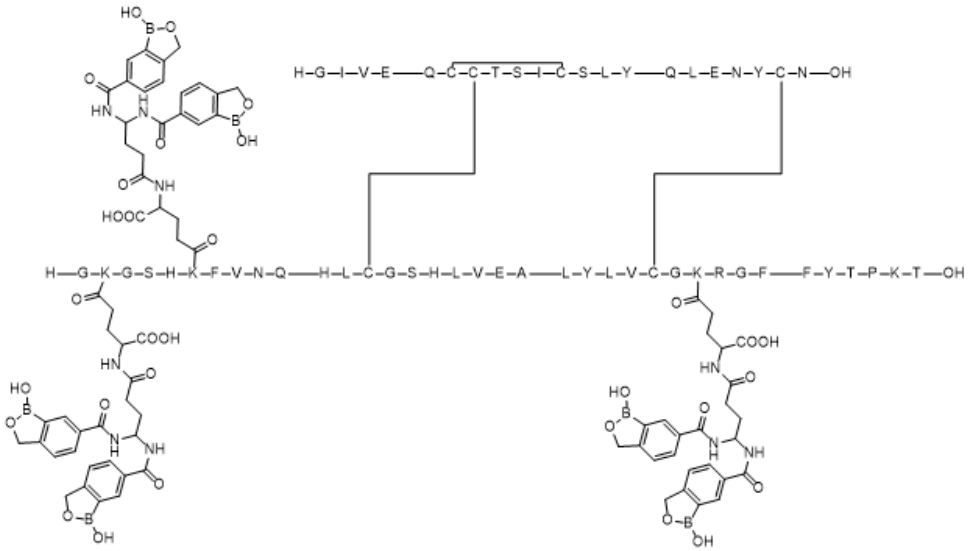
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Example 821:



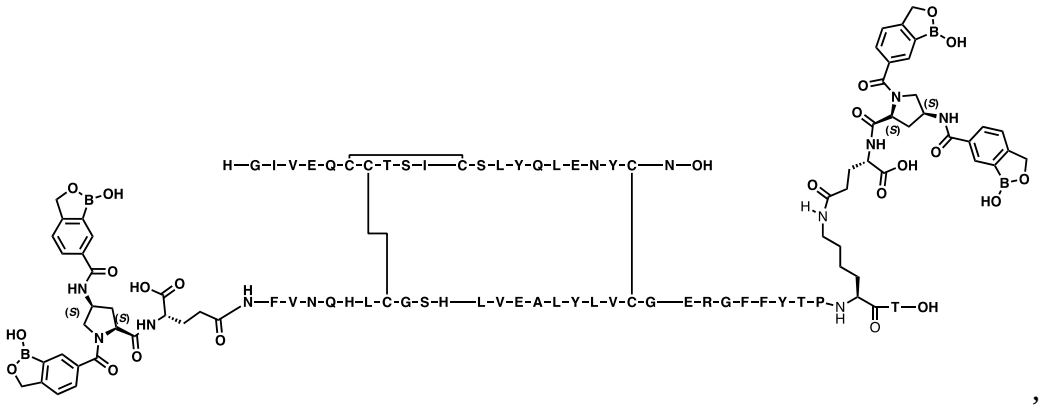
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Example 822:



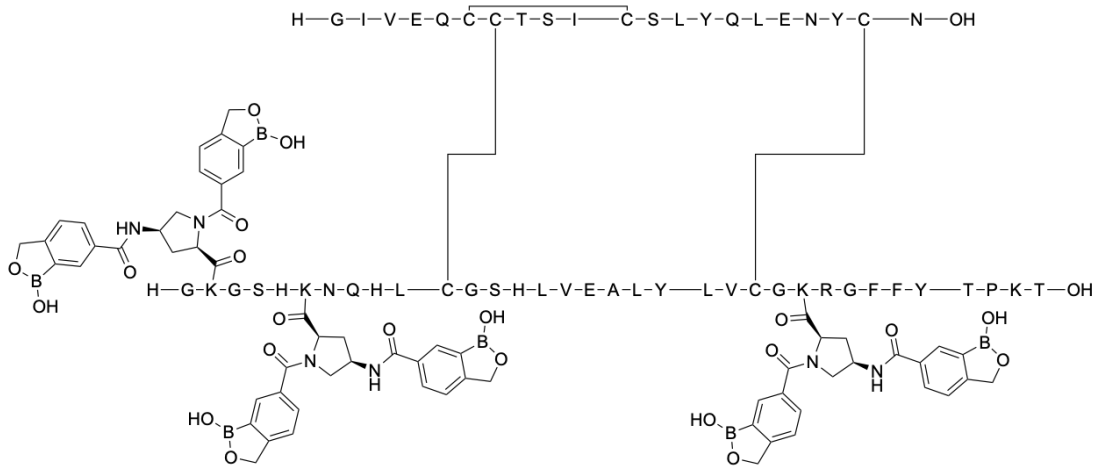
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Example 823:



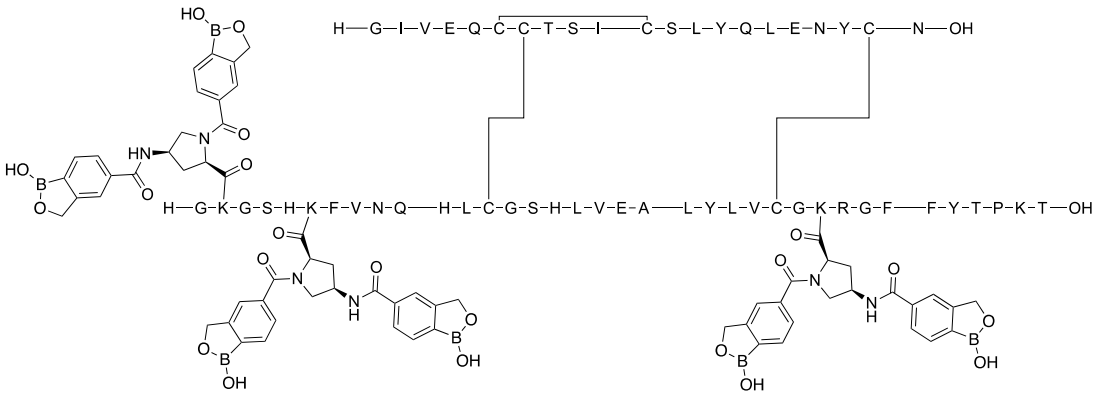
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Example 824:



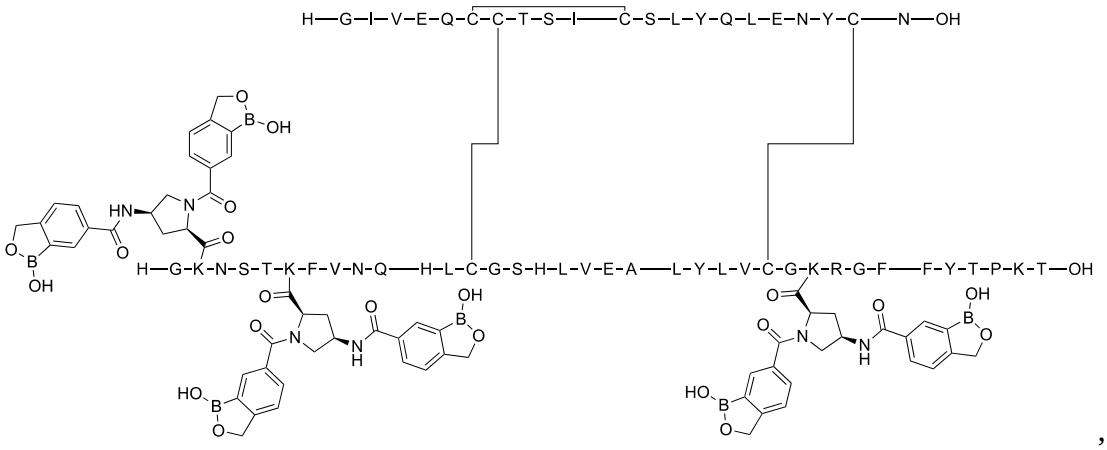
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Example 825:



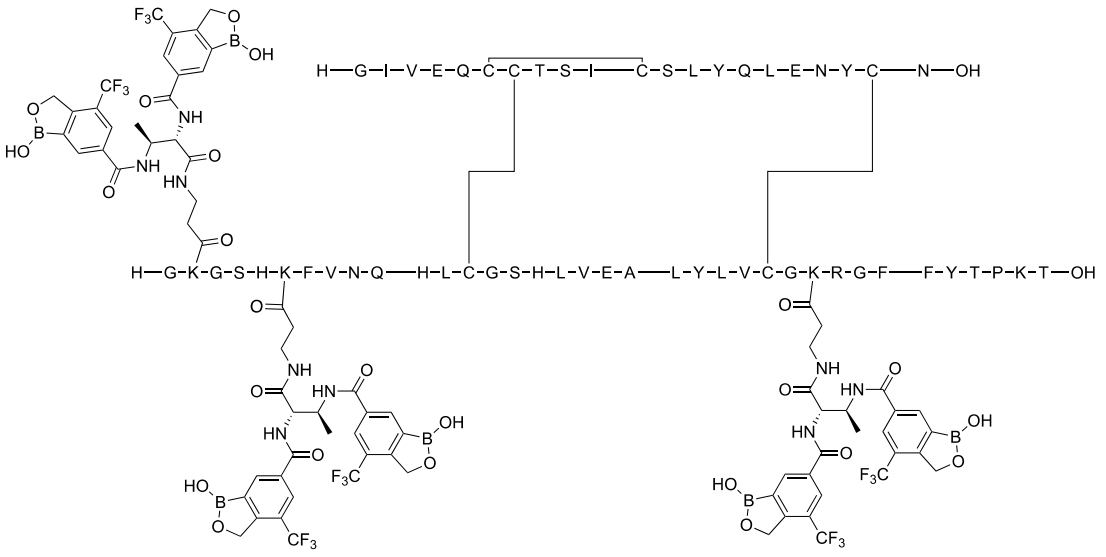
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Example 826:



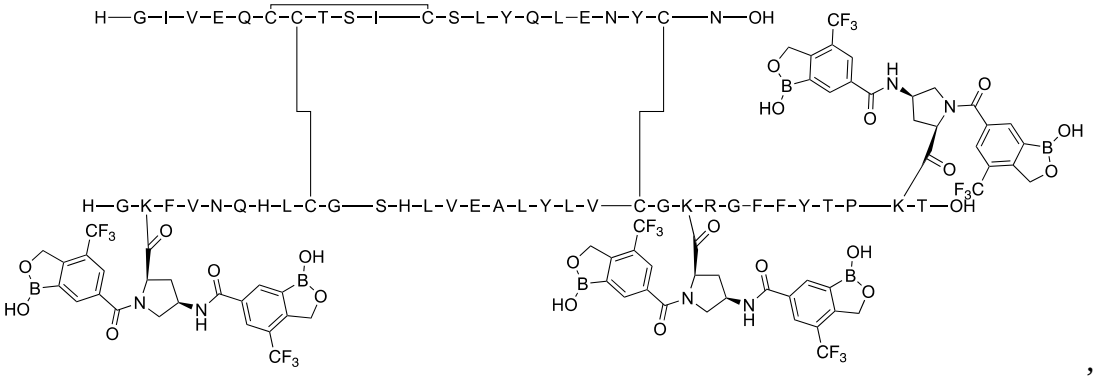
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Example 827:



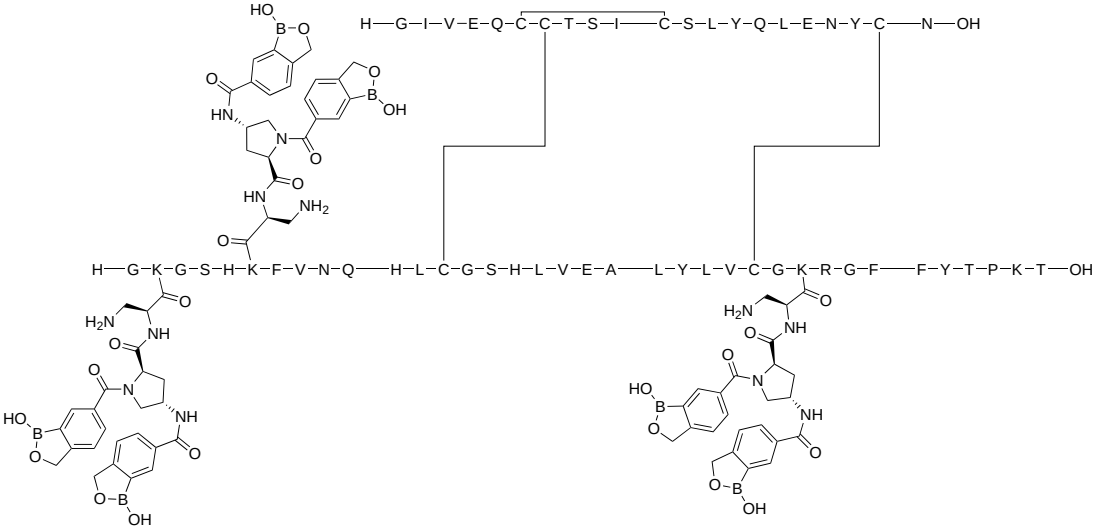
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Example 828:



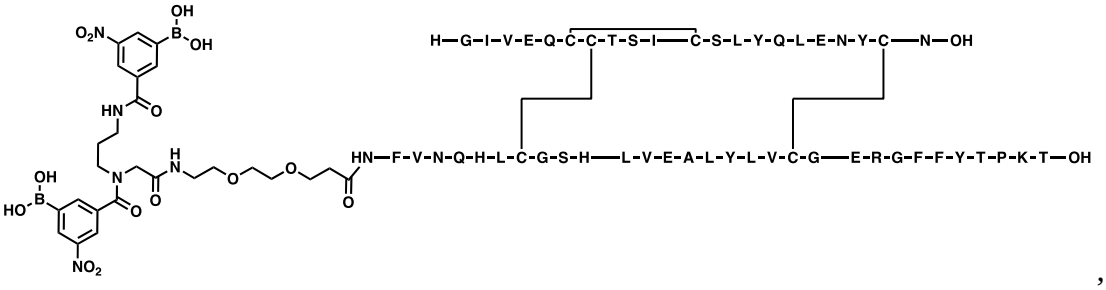
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Example 829:



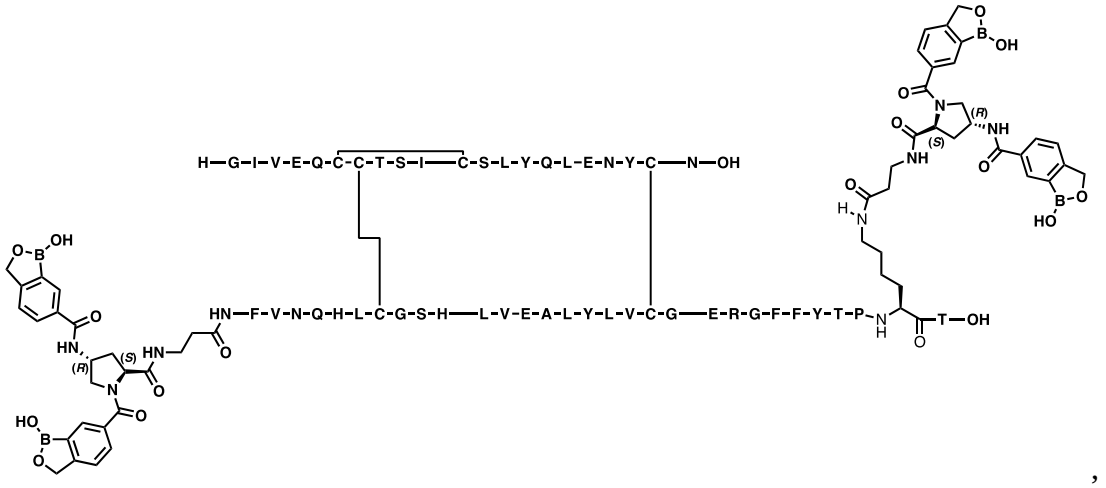
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Example 830:



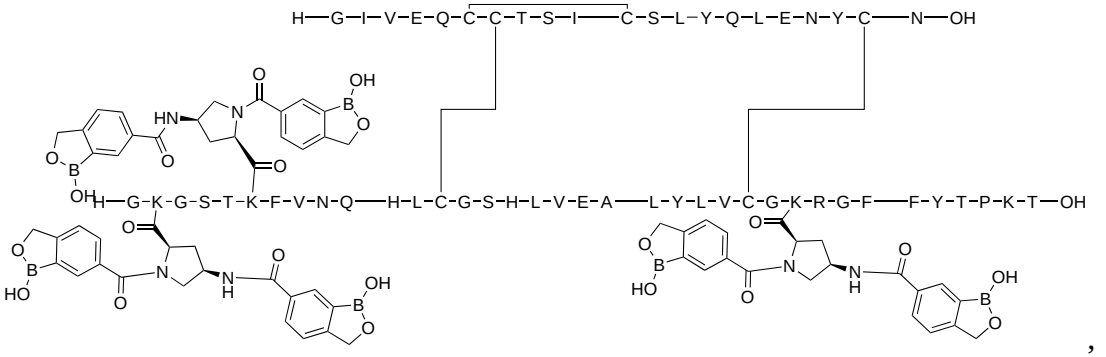
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Example 831:



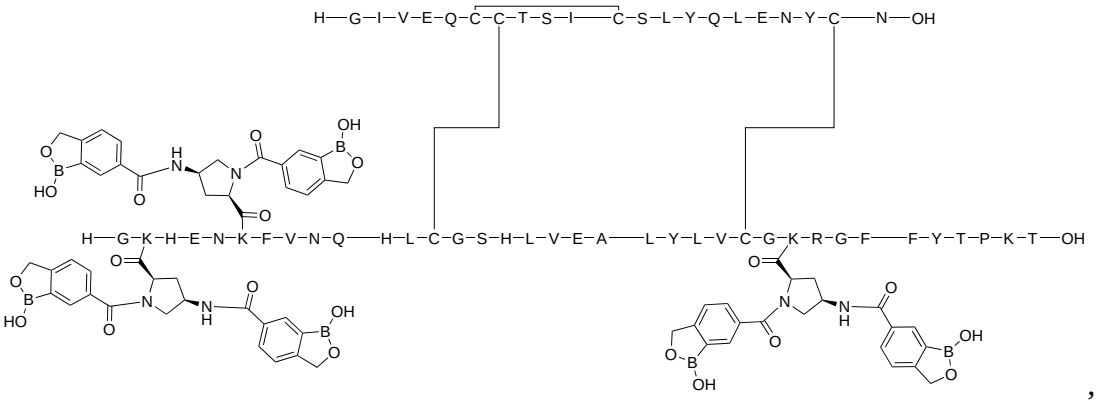
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Example 832:



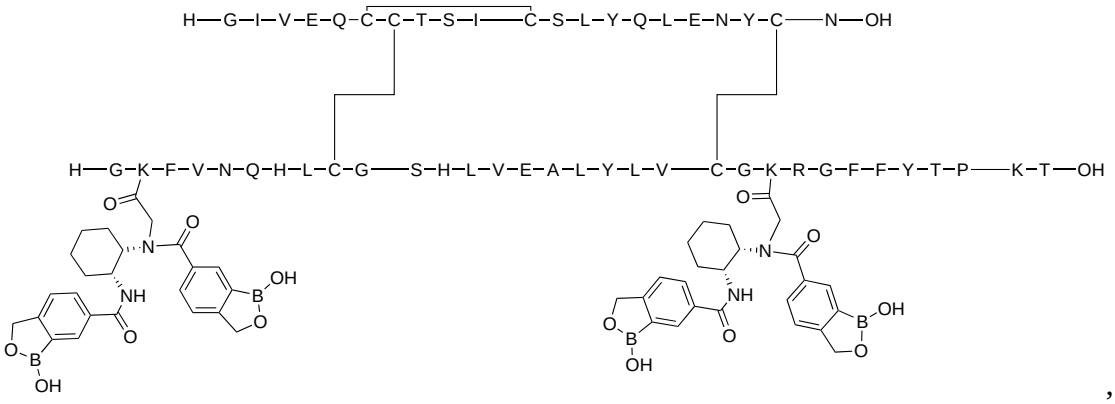
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Example 833:



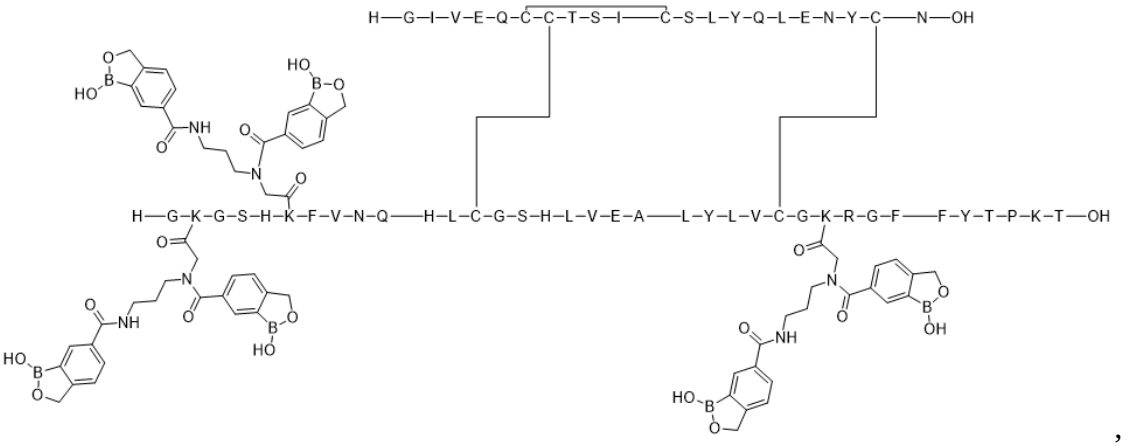
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Example 834:



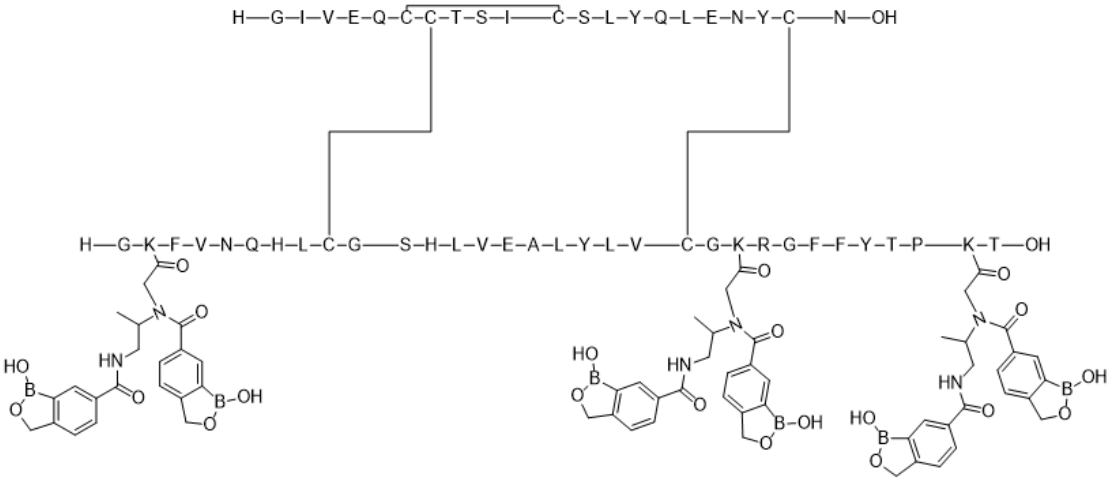
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Example 835:



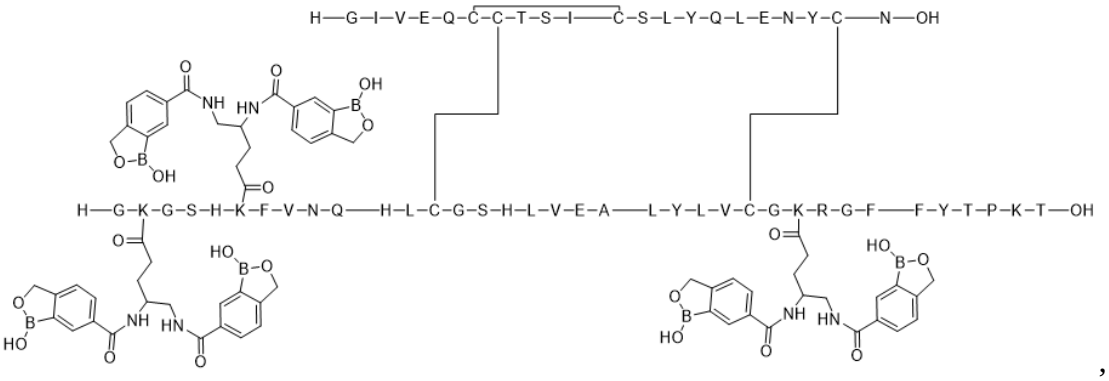
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Example 836:



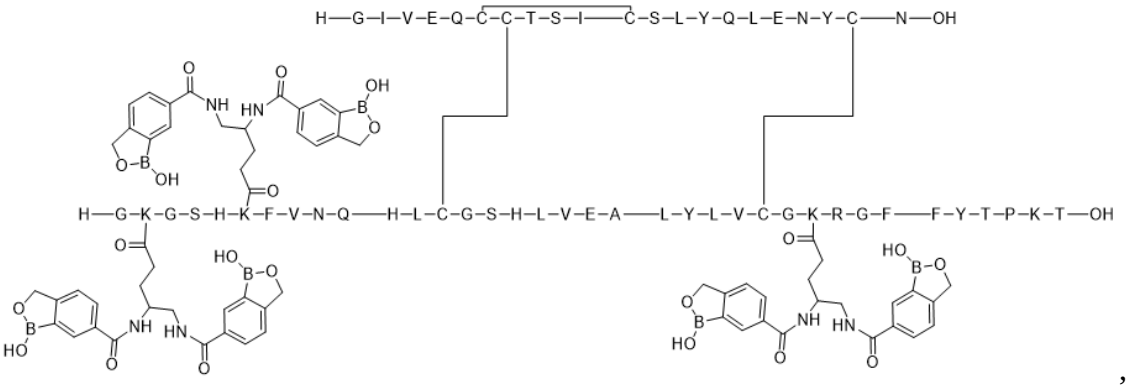
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Example 837:



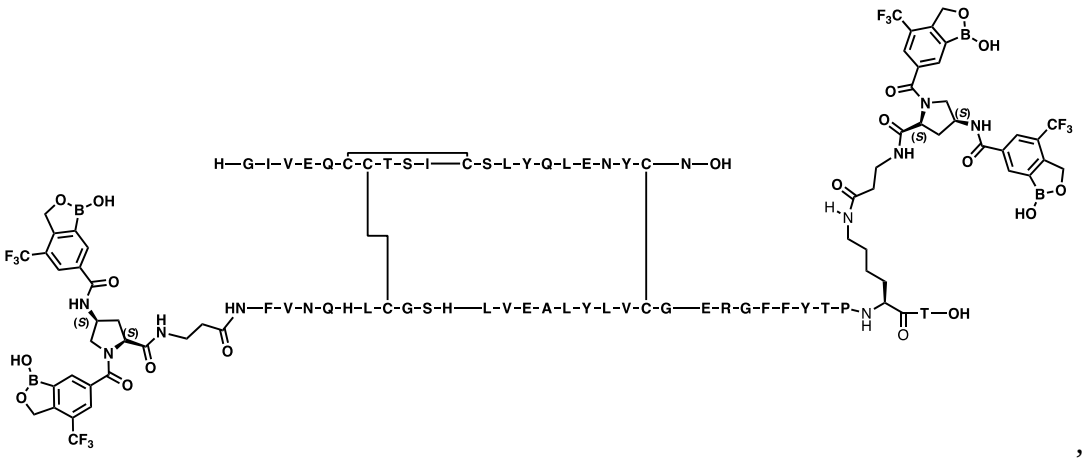
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Example 838:



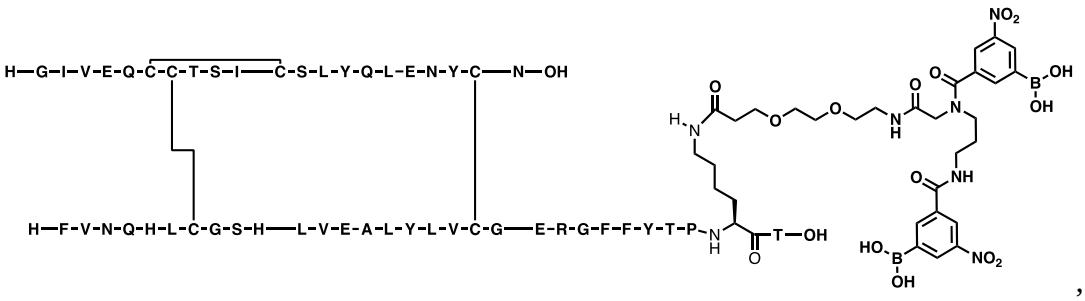
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Example 839:



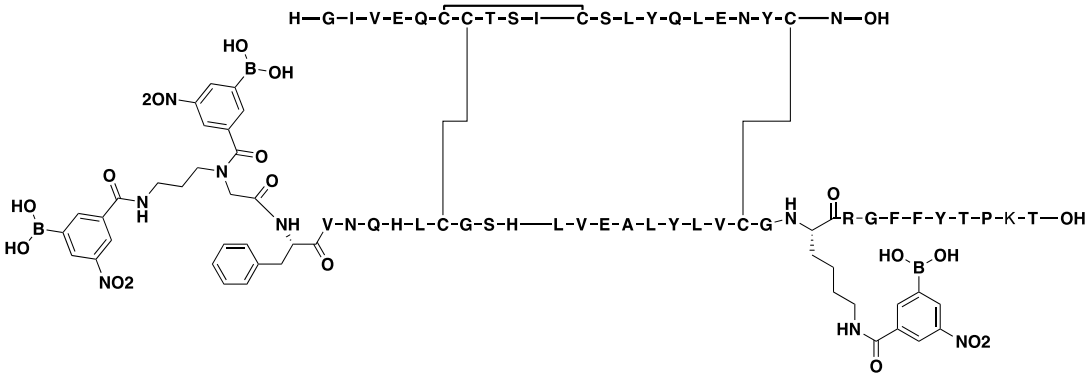
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Example 840:



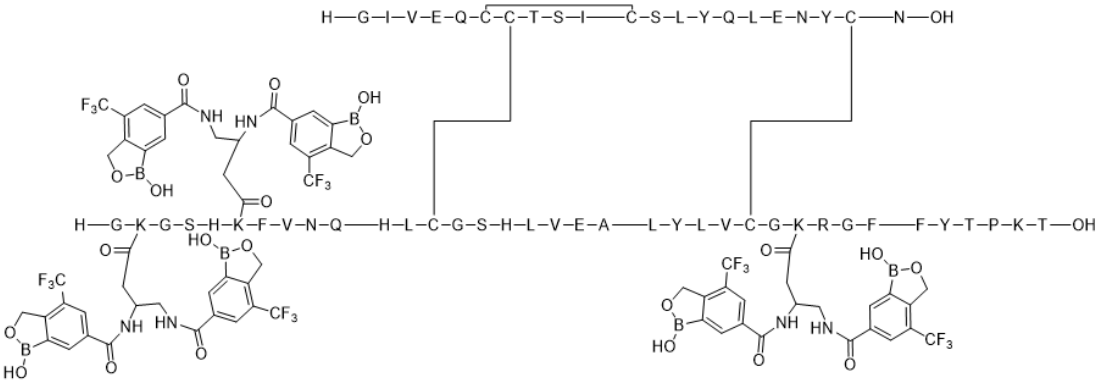
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Example 841:



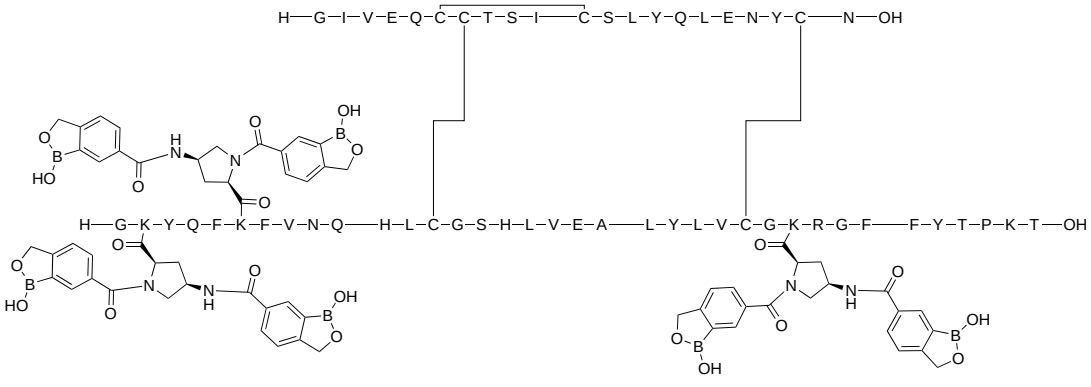
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Example 842:



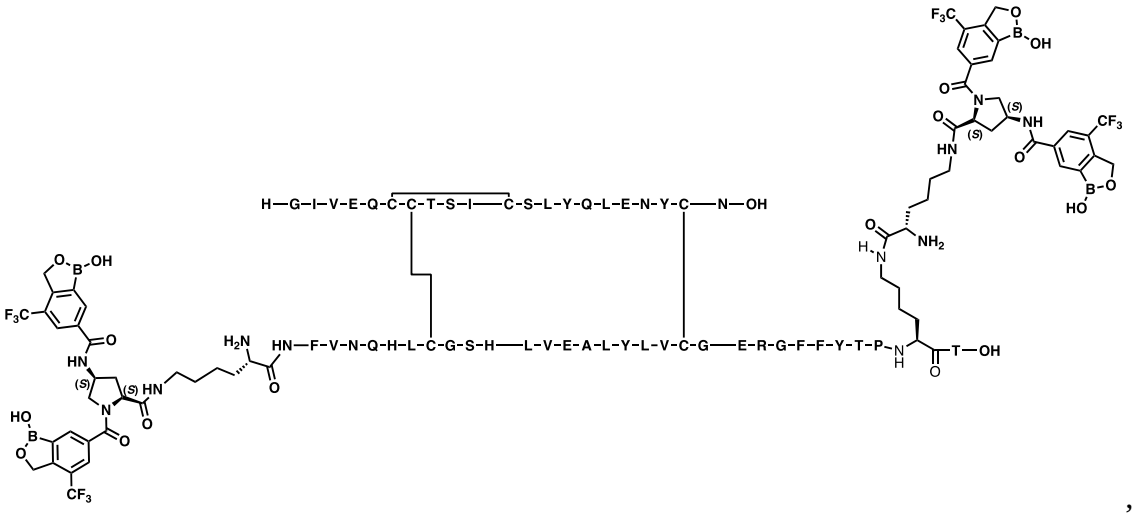
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Example 843:



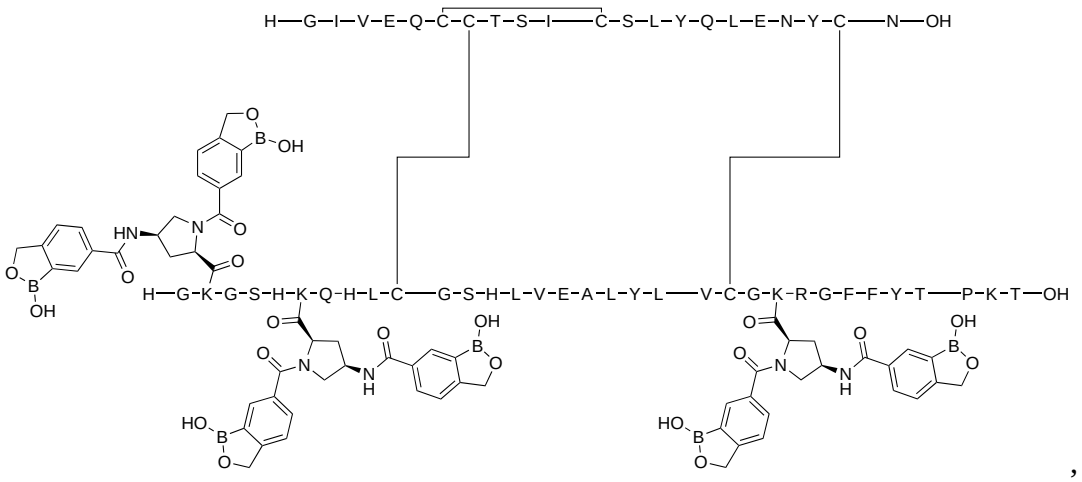
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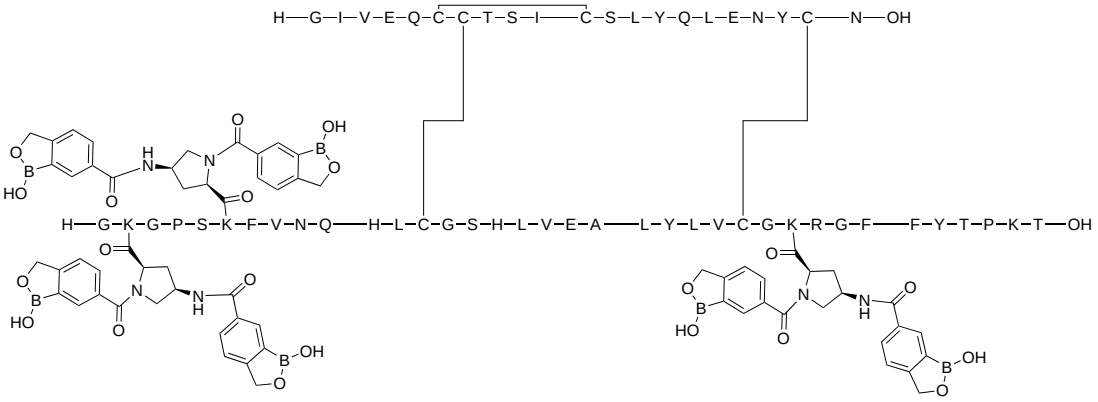
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Example 845:



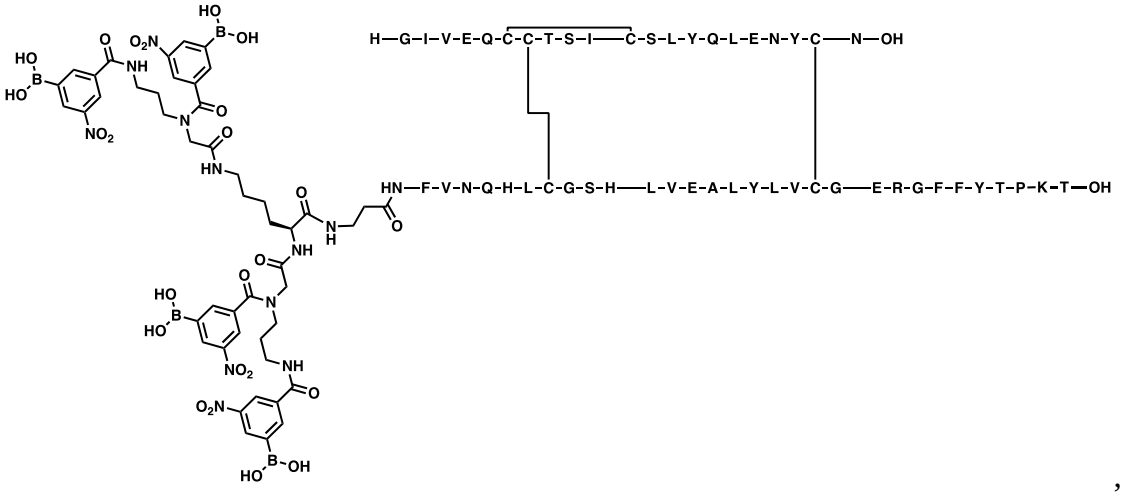
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Example 846:



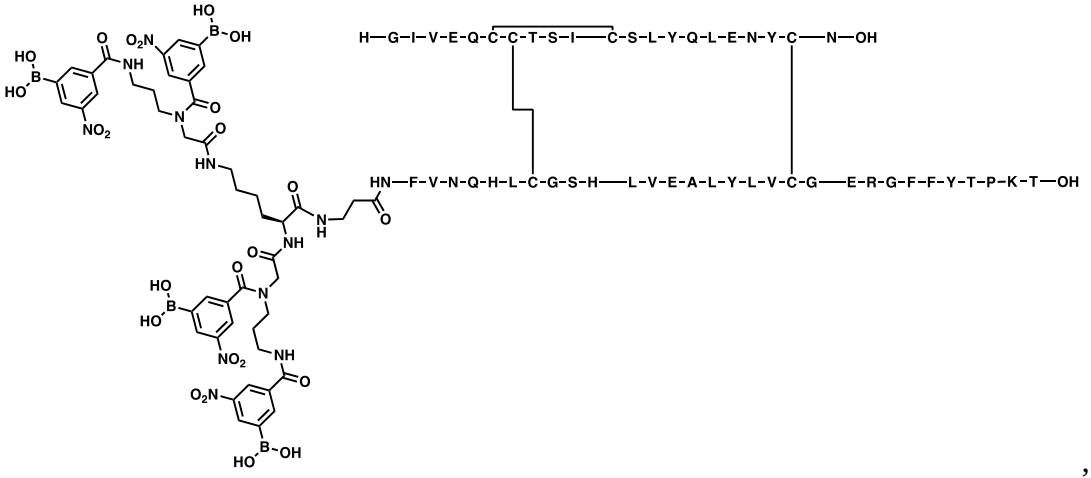
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Example 847:



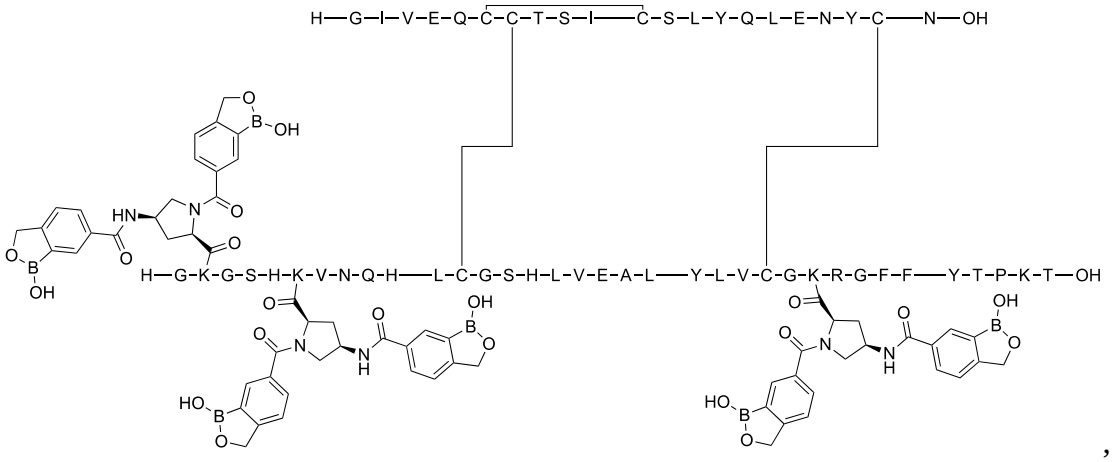
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Example 848:



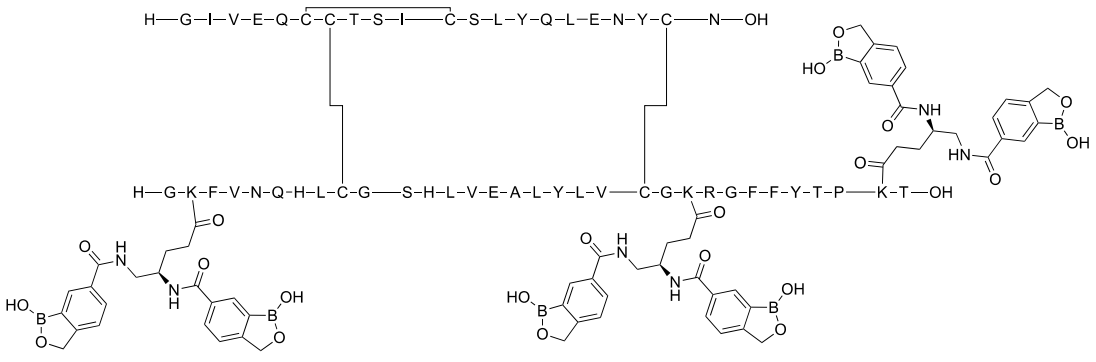
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Example 849:



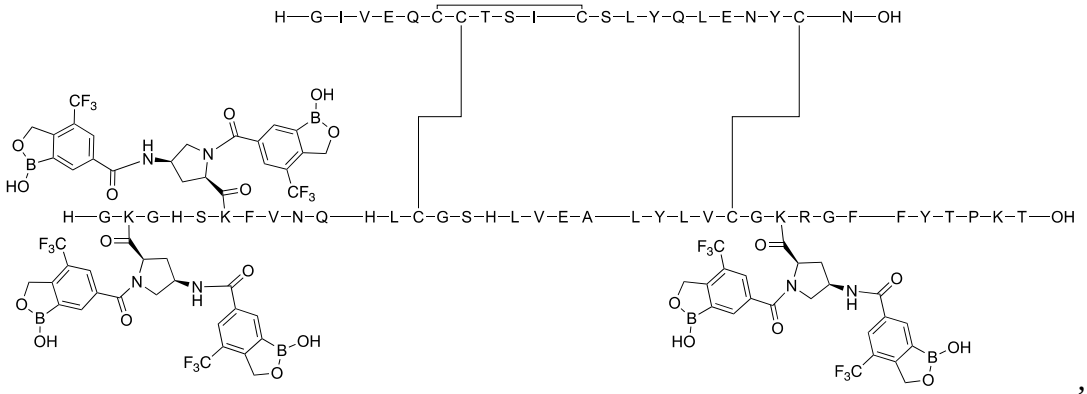
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Example 850:



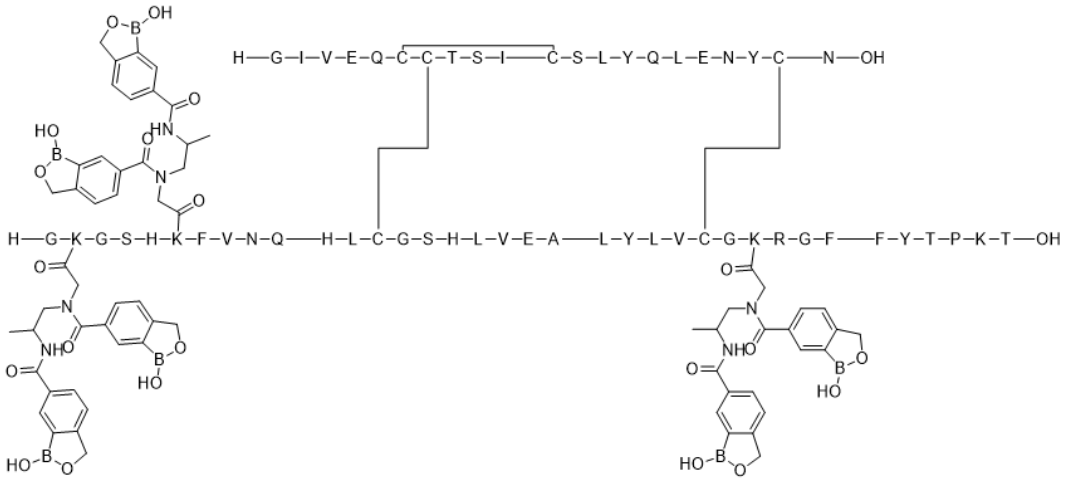
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Example 851:



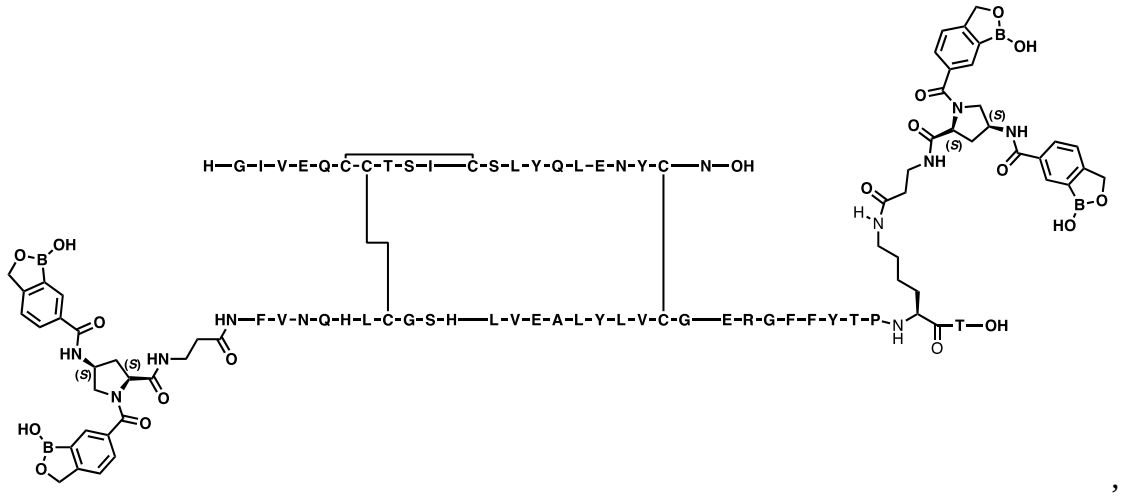
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Example 852:



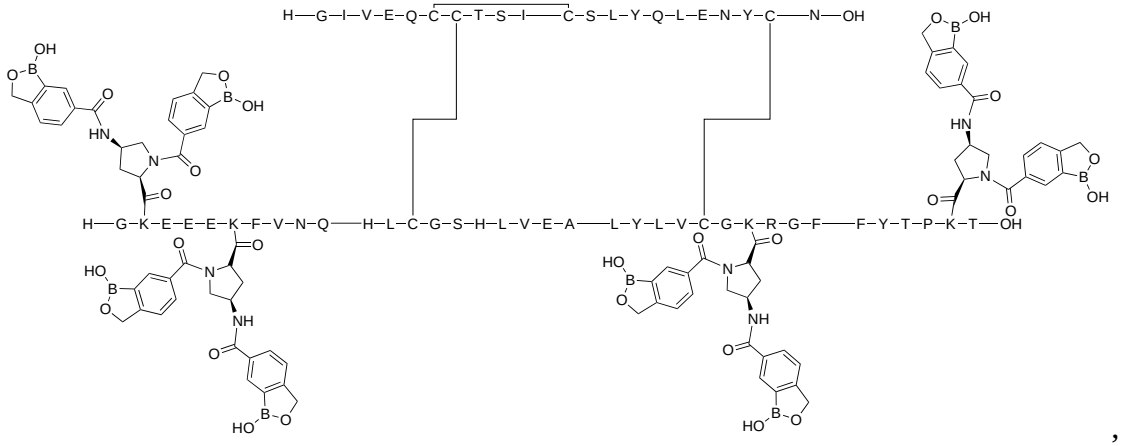
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Example 853:



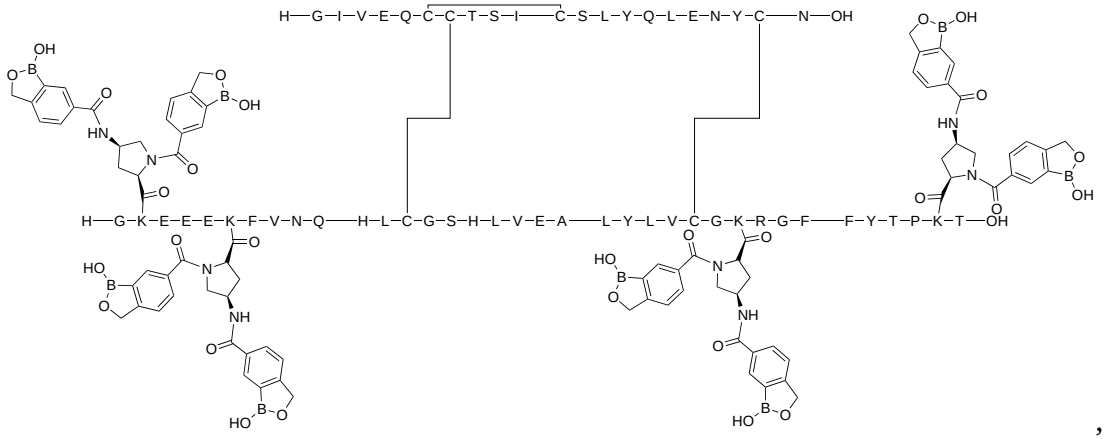
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Example 854:



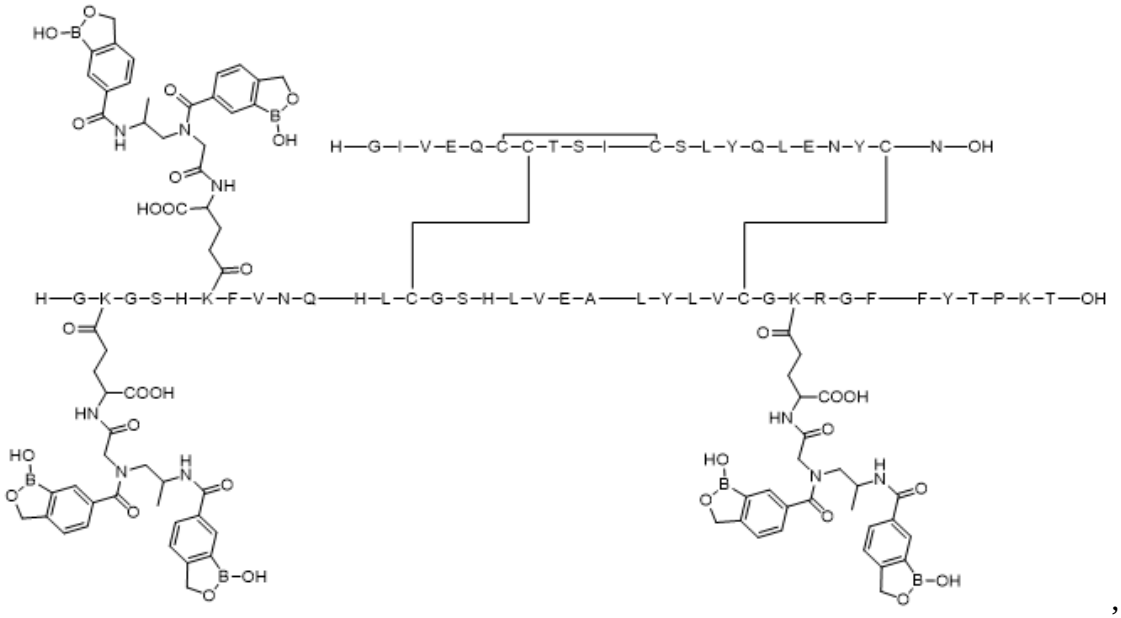
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Example 855:



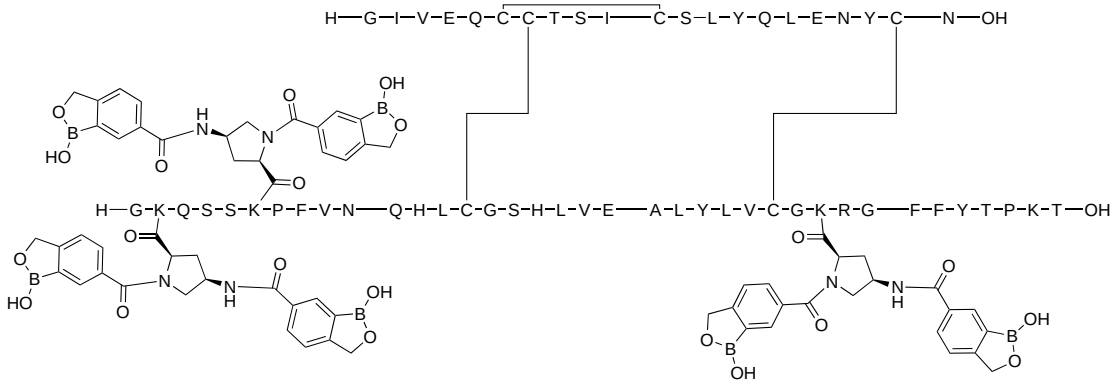
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Example 856:



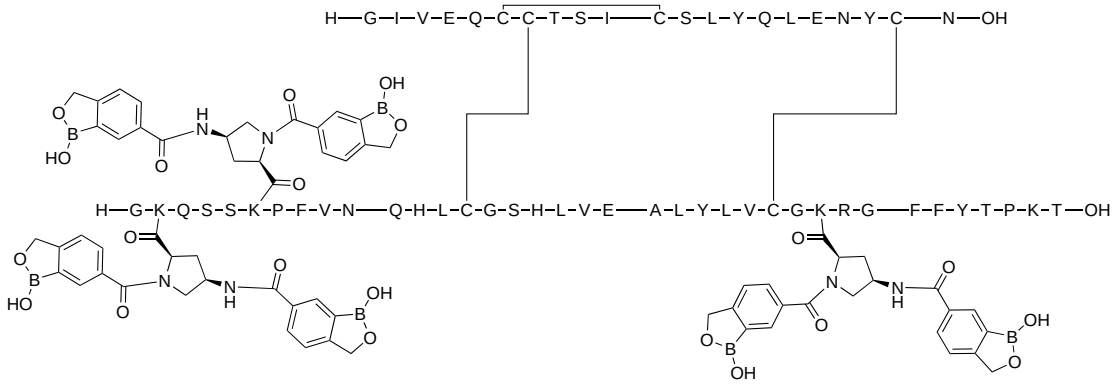
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Example 857:



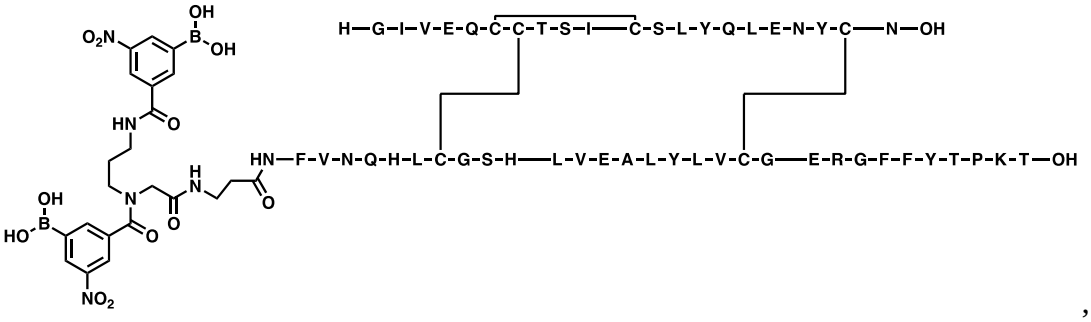
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Example 858:



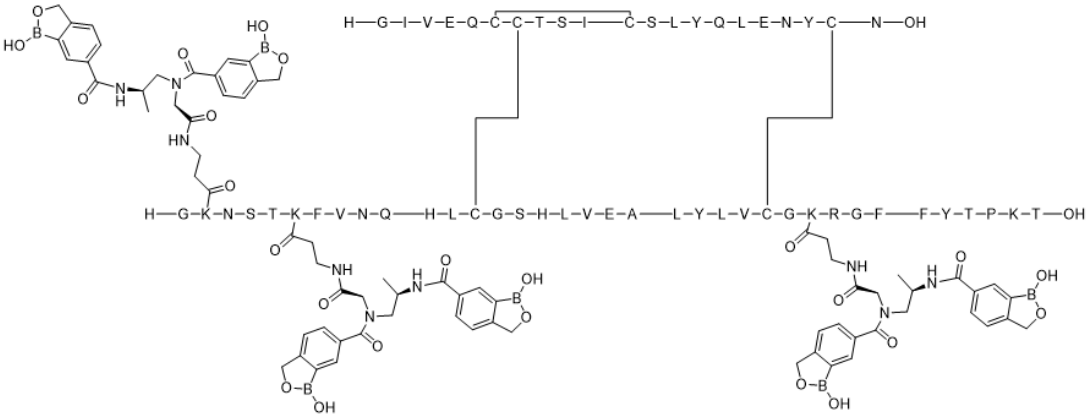
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Example 859:



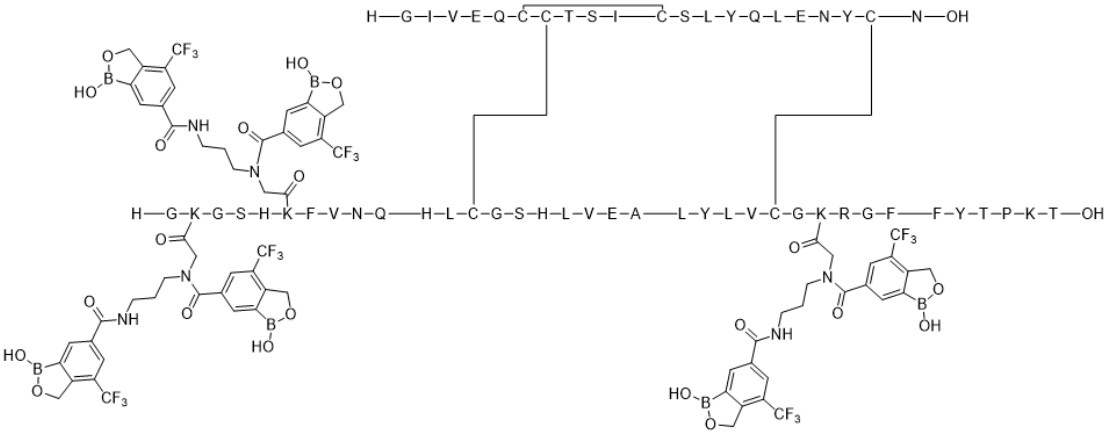
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Example 860:



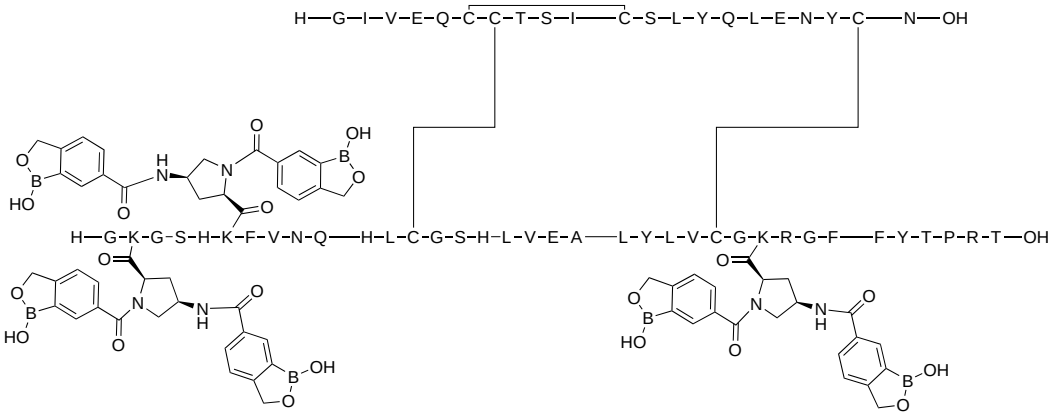
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Example 861:



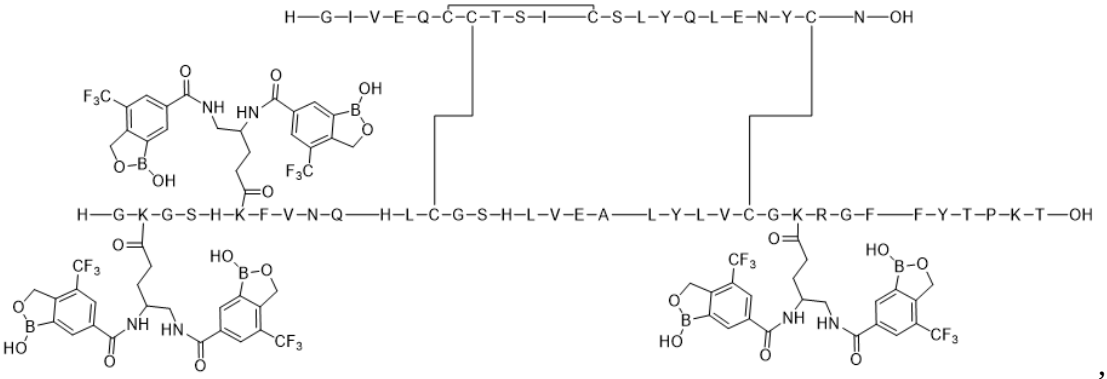
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Example 862:



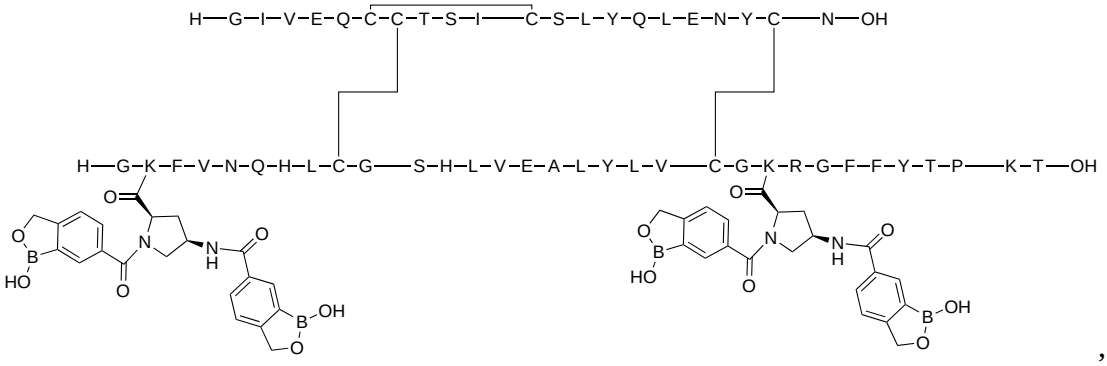
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Example 863:



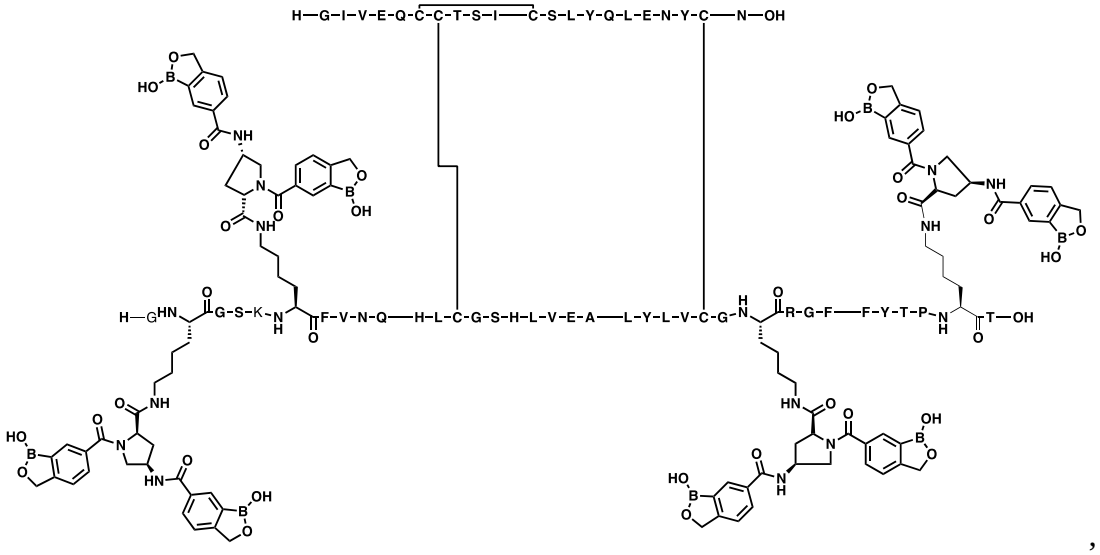
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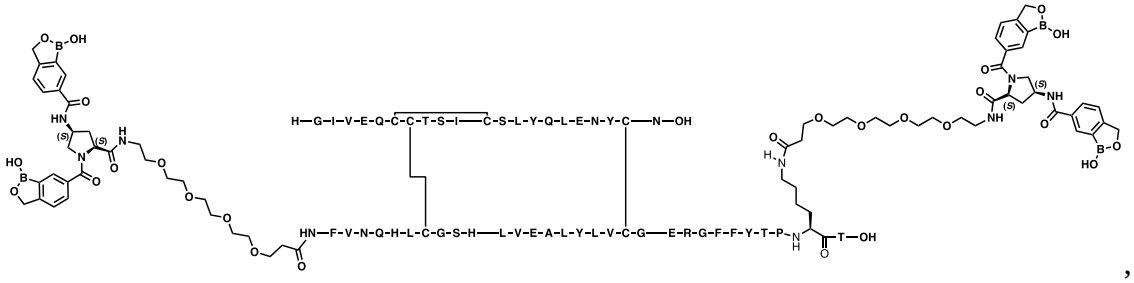
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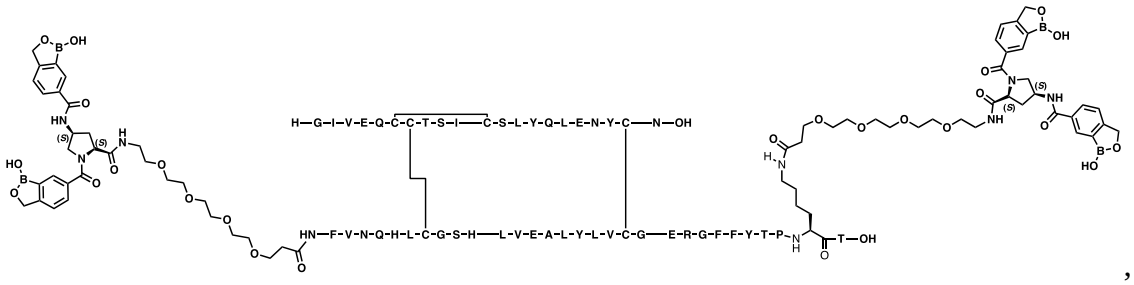
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Example 866:



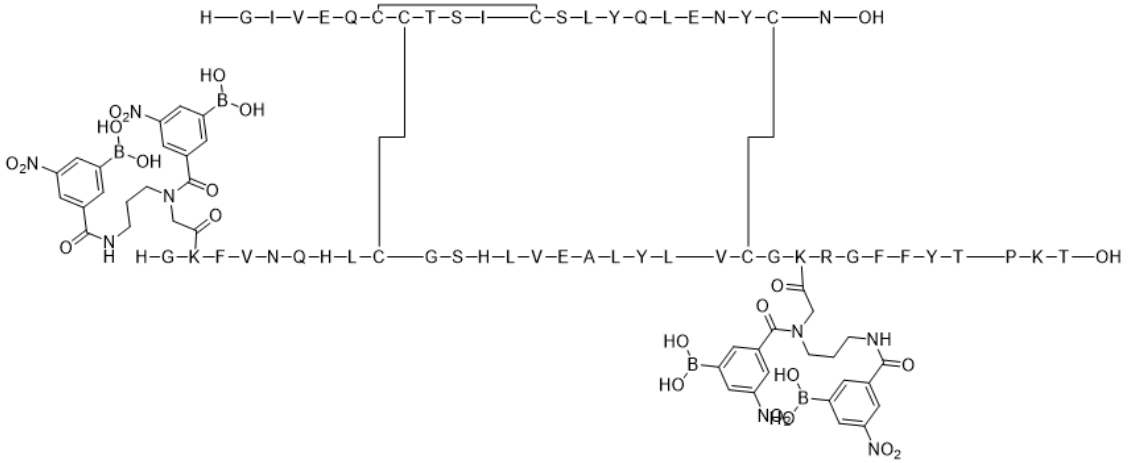
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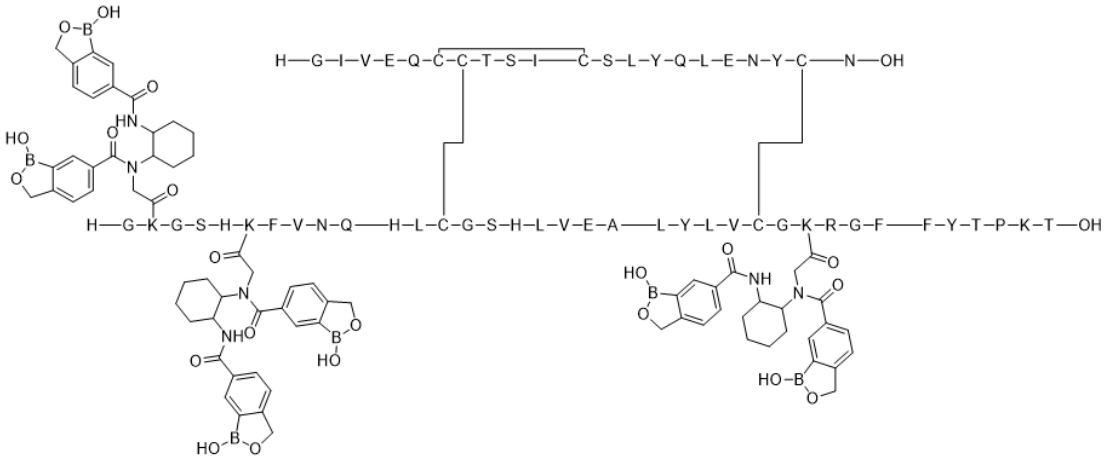
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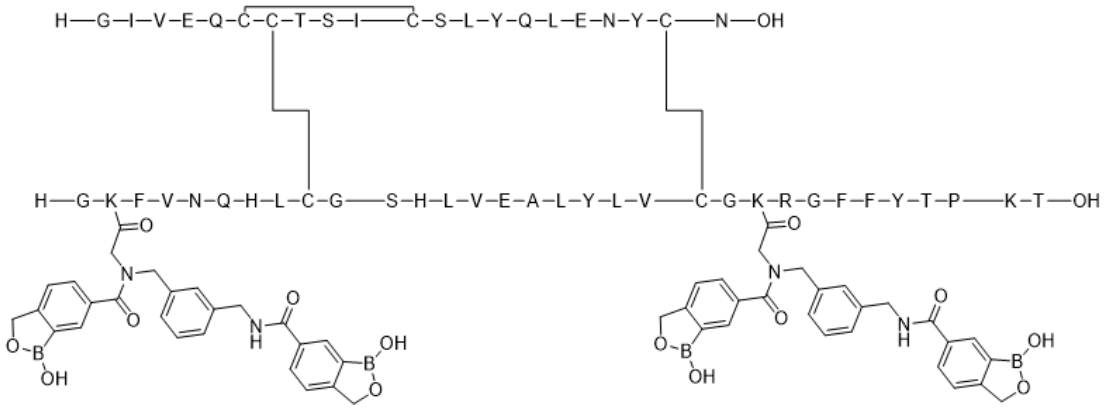
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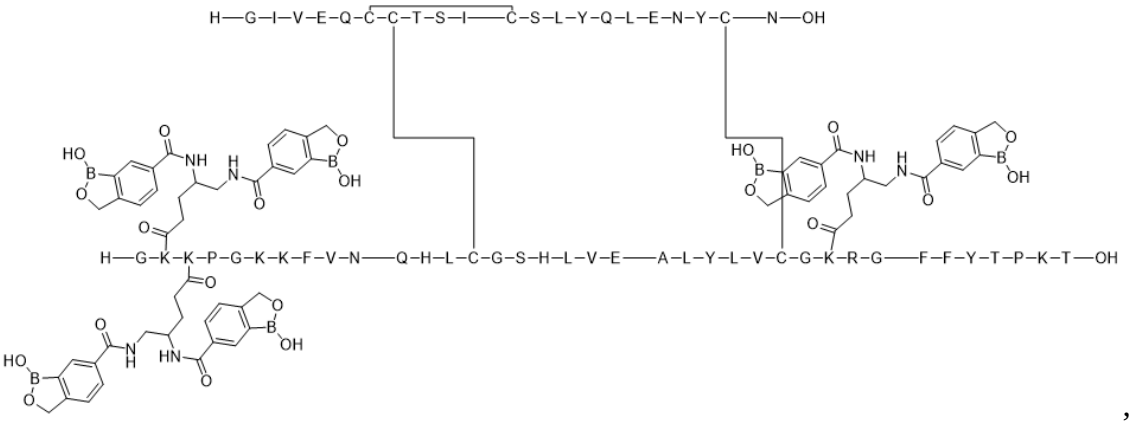
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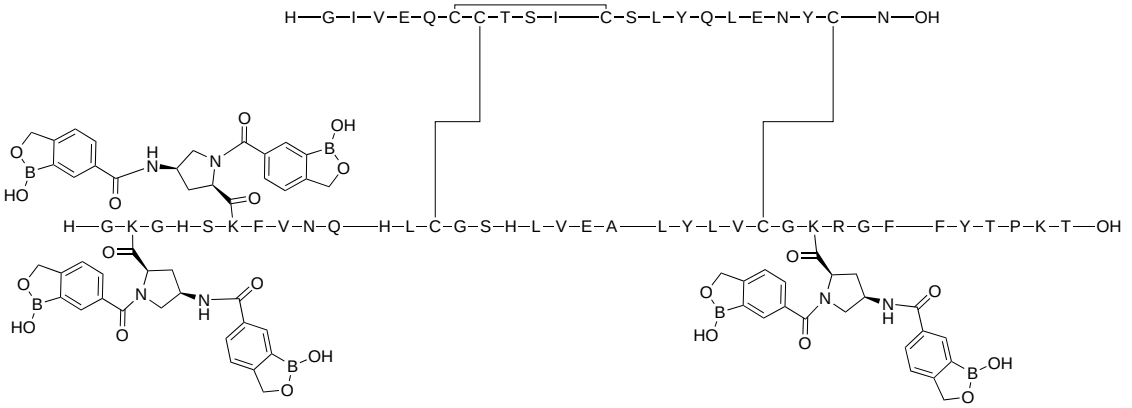
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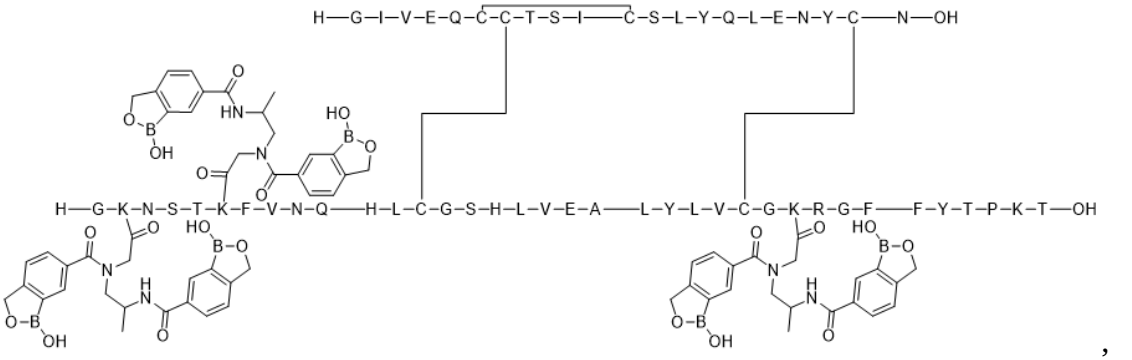
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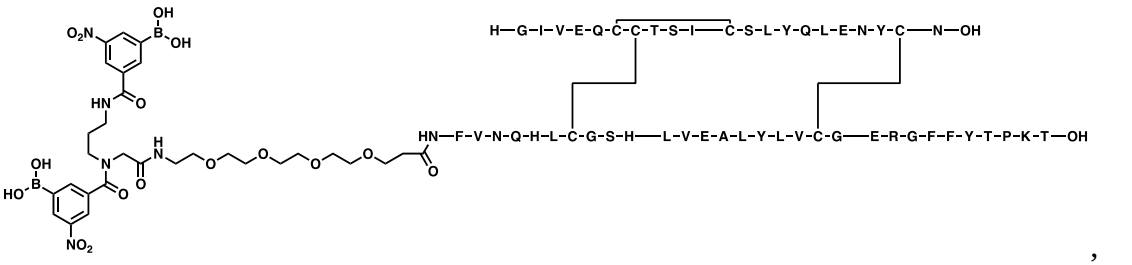
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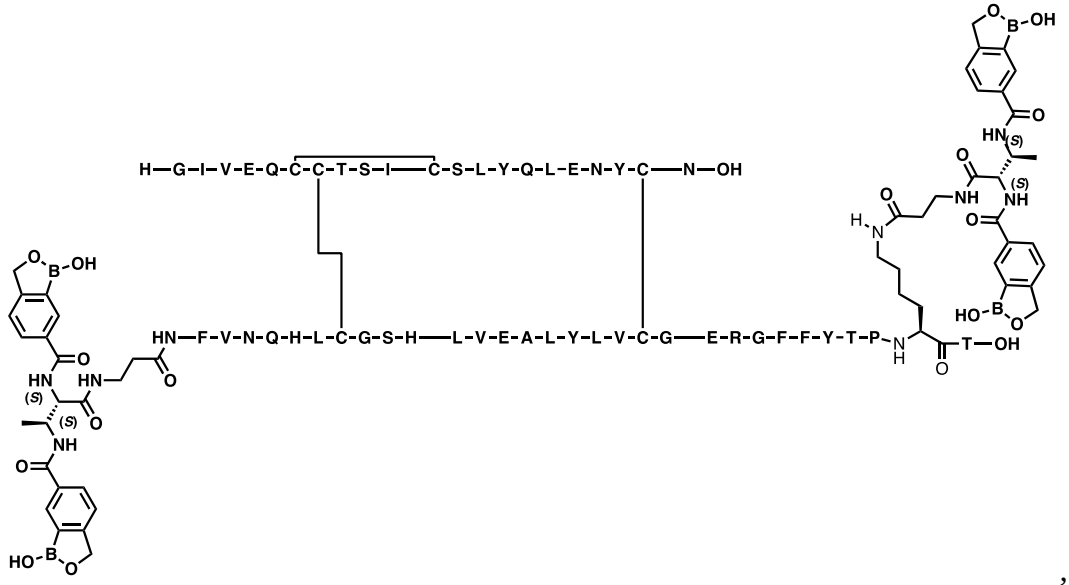
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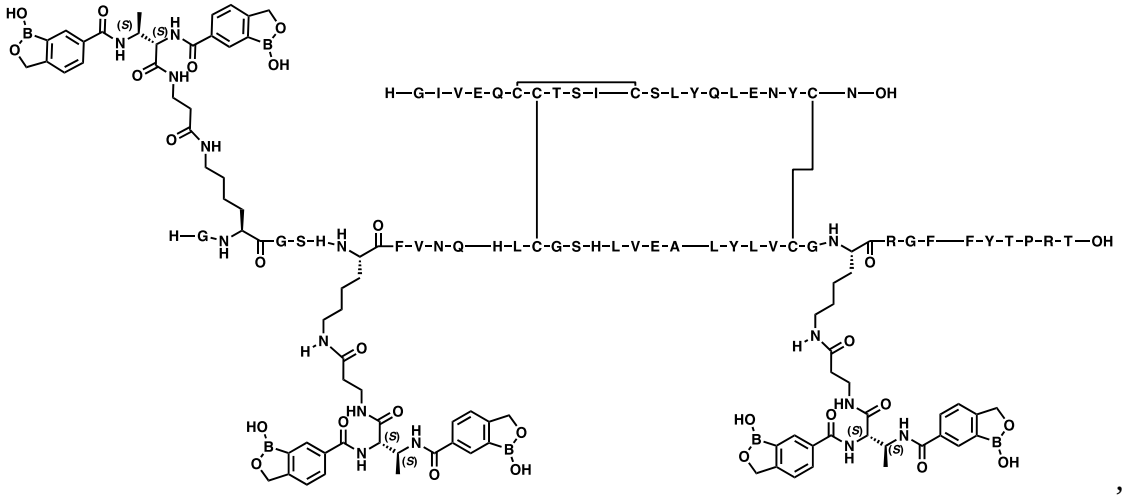
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Example 875:



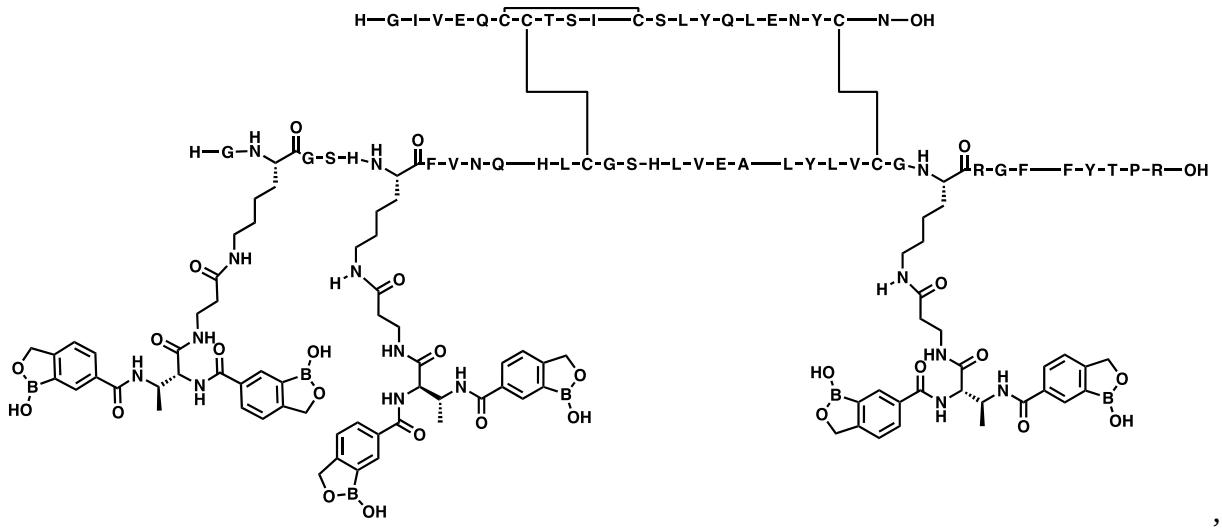
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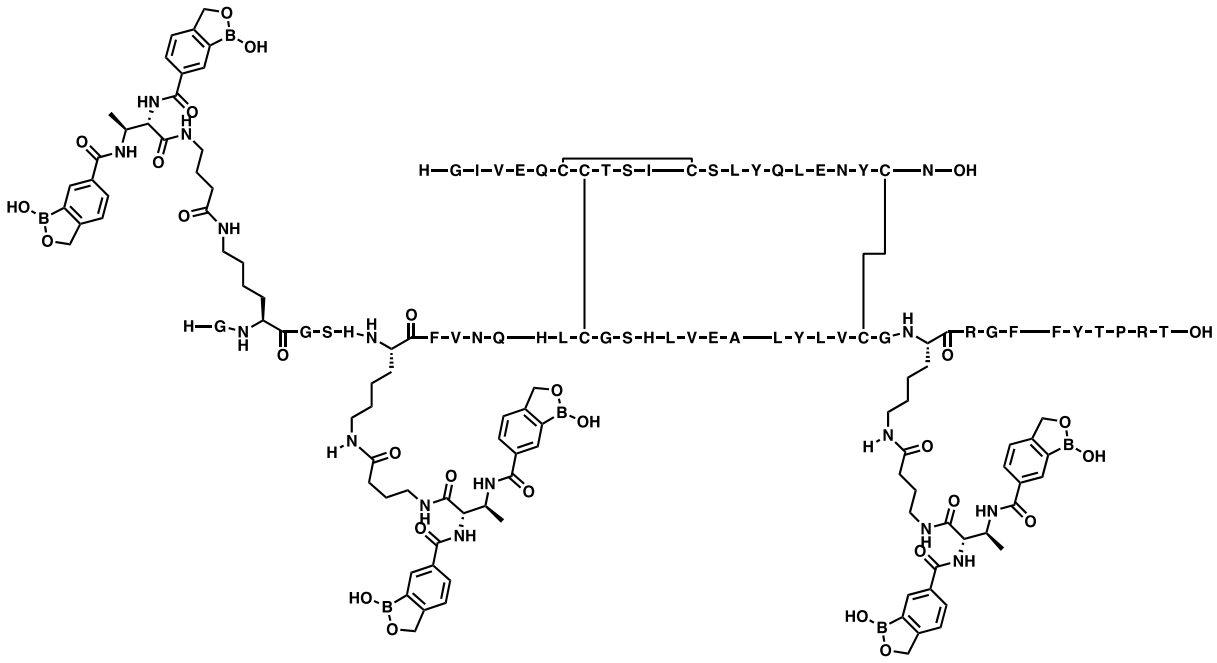
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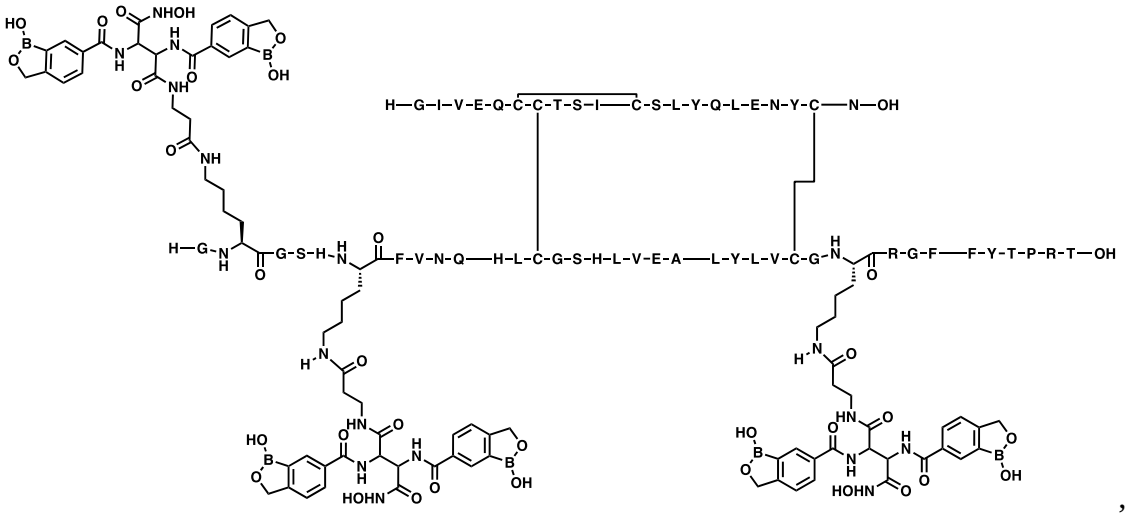
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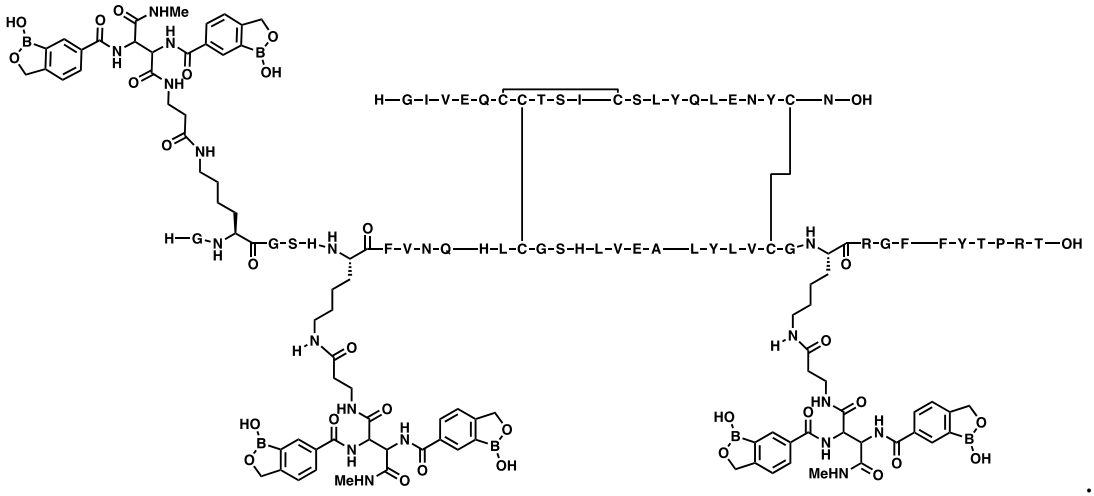
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Example 879:



, and

Example 880:



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24. The compound of claim 1 or 2, wherein X1 is a polypeptide drug substance and/or an insulin optionally having from 0 to 4 residues replaced, inserted, or mutated to lysines, and wherein the lysines are each conjugated to a Z1c.

25. The compound of claim 1 or 2, wherein one or more amines are each independently acetylated and/or independently alkylated.

26. The compound of claim 1 or 2, wherein X1 comprises a polypeptide drug substance and the covalent conjugation to X1 is to amino group(s) in one or more lysine residues and/or to the N-terminal amino groups in X1.

27. The compound of claim 1 or 2, wherein each R1 is independently selected from a C_1-C_{22} alkyl group, a C_1-C_{22} acyl group, a (C_3-C_8)cycloalkyl group, a C_1-C_{22} haloalkyl group,

an aryl group, and a heteroaryl group, each R1 optionally comprises one or more C_1-C_{22} alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, C_1-C_{22} alkyl, or aryl groups.

28. The compound of claim 1 or 2, wherein X4 is selected from -COOH, -$(CH_2)_m$COOH, a C_1-C_{22} alkyl group, a C_1-C_{22}acyl group, a (C_3-C_8)cycloalkyl group, a C_1-C_{22} haloalkyl group, an aryl group, and a heteroaryl group, each X4 optionally comprises one or more C_1-C_{22} alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, C_1-C_{22} alkyl, or aryl groups; wherein m is 1, 2, 3, 4, or 5.

29. The compound of claim 3, wherein the alkyl group of Y9 is a C_1-C_{22} alkyl.

30. The compound of claim 29, wherein Y9 is CH_3.

31. The compound of claim 1, wherein the at least one primary or secondary amine in FF1-FF223 is covalently conjugated to B6.

32. The compound of claim 1 or 2, wherein an amine in the compound is conjugated via an amide linkage to an aromatic boron-containing group.

33. The compound of claim 32, wherein the aromatic boron-containing group is selected from a phenylboronic acid, boroxole, and phenylboronate.

34. The compound of any one of claims 1-33, wherein the compound is formulated in a solution comprising one or more of a buffer, stabilizer, vasodilator, preservative, surfactant, salt, sugar, or compounds containing one or more hydroxyls, alcohols, diols, or phenols.

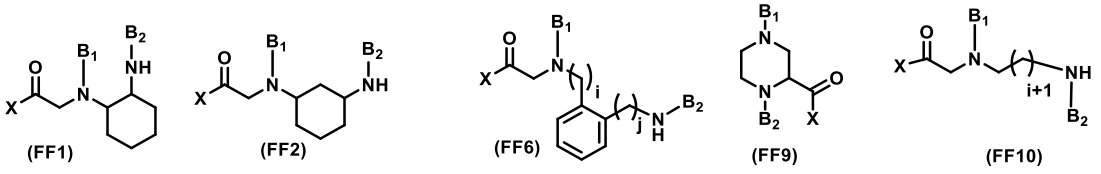
35. The compound of claim 34, wherein the solution comprises one or more of citrate, zinc, and/or cresol.

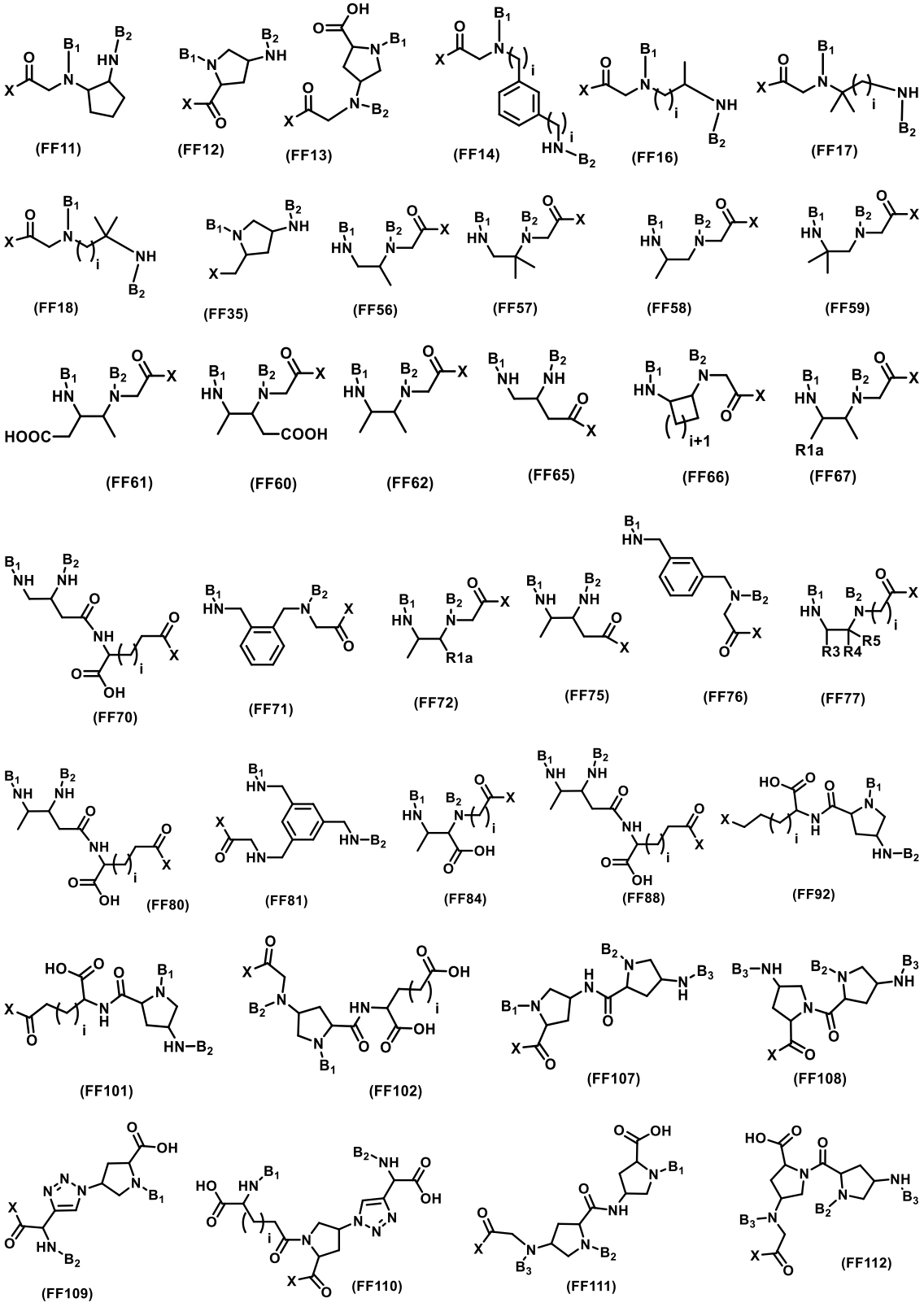
36. The compound of claim 1 or 2, wherein Z1c is conjugated to a cysteine.

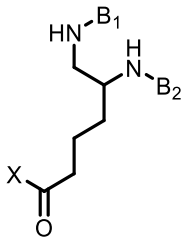
37. The compound of claim 1 or 2, wherein the compound is covalently conjugated either directly or through a linker to a diol, sugar, carbohydrate or a diol containing molecule.

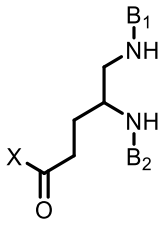
38. The compound of claim 1 or 2, wherein the compound is covalently conjugated to an antibody, albumin or a fragment thereof, or covalently conjugated either directly or through a linker to a molecule that can bind to at least one protein present in human plasma.

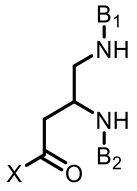
39. The compound of any one of claims 1-7, wherein the compound comprises at least one Z1c selected from:

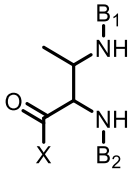


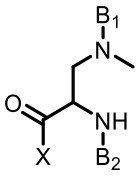

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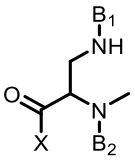

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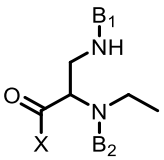

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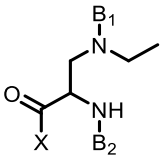

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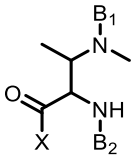

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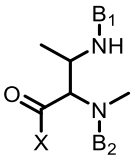

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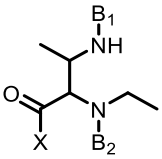

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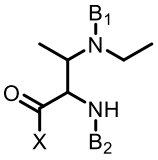

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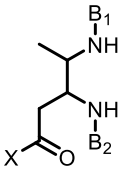

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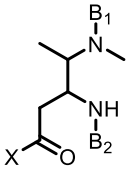

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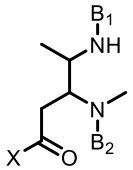

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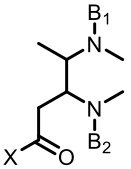

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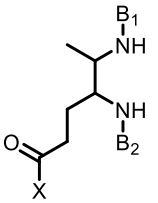

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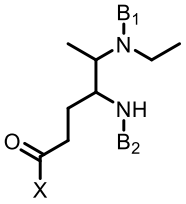

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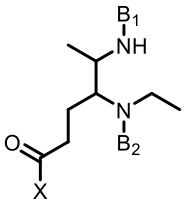

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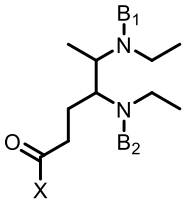

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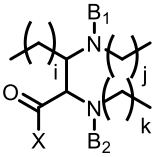

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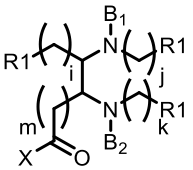

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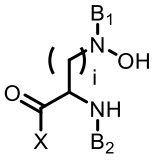

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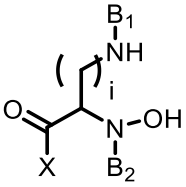

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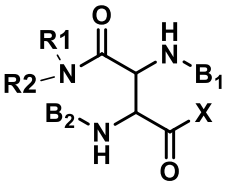

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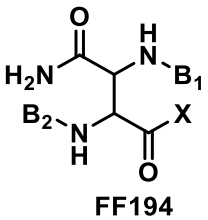

(FF133)


(FF134)

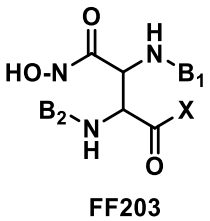

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(FF136)


FF193


FF194

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FF203

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40. The compound of claim 1 or 2, wherein the compound comprises at least one Z1c having at least one chiral center and selected from FF1, FF2, FF5, FF9, FF11-FF13, FF15-

FF24, FF27, FF31, FF34-FF36, FF38, FF39, FF43-FF58, FF60-FF70, FF72-FF75, FF77-FF80, FF82-FF84, FF86-FF212, FF216-FF220, FF222, FF223, and combinations thereof.

41. The compound of claim 40, wherein the compound comprises at least one FF12 and/or FF116; and

wherein the stereochemistry of FF12 and FF116 is independently selected from (*S*,*S*); (*S*,*R*); (*R*,*R*); and (*R*,*S*).

42. The compound of claim 1 or 2, wherein X1 comprises human insulin or a human insulin analogue comprising an A-chain and a B-chain, wherein the C-terminus of the A-chain of the human insulin analogue is optionally extended with a polypeptide of up to 20 residues, and/or the N-terminus of the B-chain of the human insulin analogue is optionally extended with a polypeptide of up to 10 residues.

43. The compound of claim 42, wherein X1 comprises at least one lysine having an amine side chain, and Z1c is covalently conjugated directly to the amine side chain.

44. The compound of claim 1 or 2, wherein X1 comprises a drug substance covalently conjugated to at least one Z1c through an acid containing linker.

45. A composition or a mixture comprising at least one compound of any one of claims 1-44, for use as a medicament for the treatment of diabetes, for control of blood sugar levels, or to control the release of a drug based on physiological levels of diol containing small molecules or sugars.

46. Use of ~~A method of administering~~ the compound of any one of claims 1-44 in the manufacture of a medicament ~~to a human subject~~ as a therapeutic or prophylactic agent.

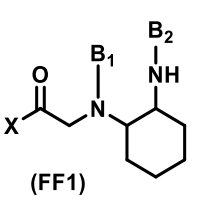
47. A method of making a compound of any one of claims 1-44, wherein the method comprises at least one alkylation and/or amidation step.

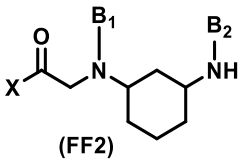
48. Use of ~~A method of treating a subject by administering~~ a device or formulation comprising a compound of any one of claims 1-44 and Examples 1-880 in the manufacture of a medicament for the treatment of a subject.

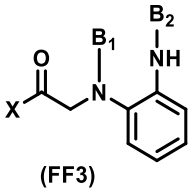
49. Use of ~~A method of treatment or prevention of diabetes, impaired glucose tolerance, hyperglycemia, or metabolic syndrome, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of~~ the compound of any one of claims 1-44 or the composition or the mixture of claim 45 in the manufacture of a medicament for the treatment or prevention of diabetes, impaired glucose tolerance, hyperglycemia, or metabolic syndrome.

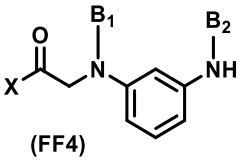
50. A compound selected from Formulae FF1-FF224:

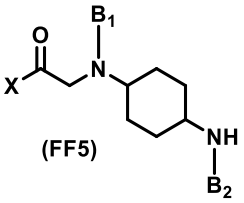
wherein Formulae FF1-FF48 are:

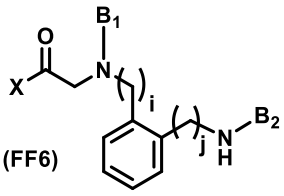

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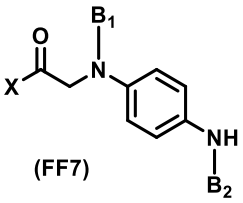

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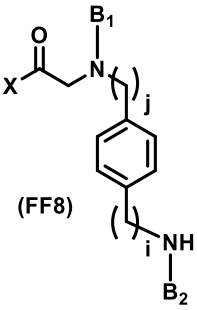

(FF3)


(FF4)

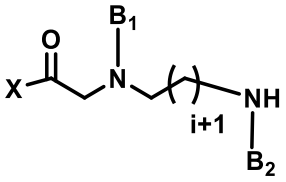

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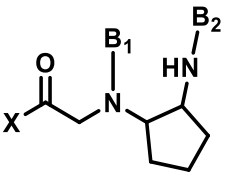

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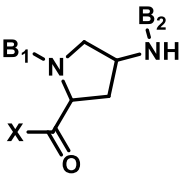

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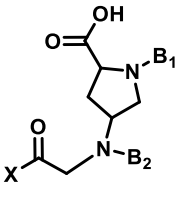

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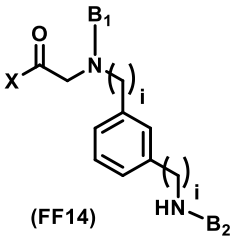

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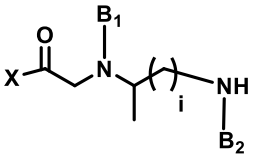

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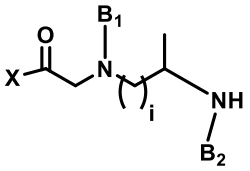

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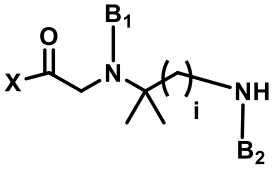

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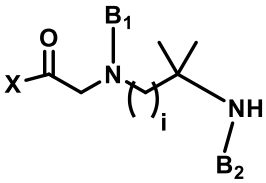

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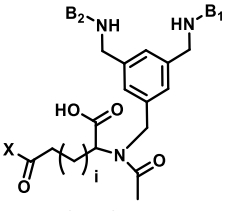

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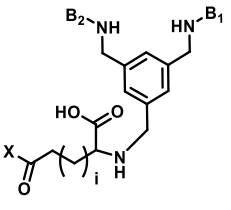

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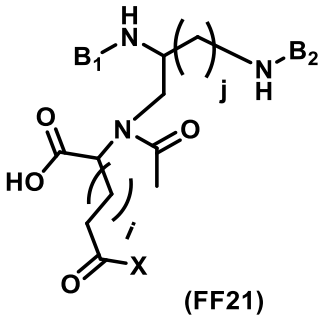

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(FF17)

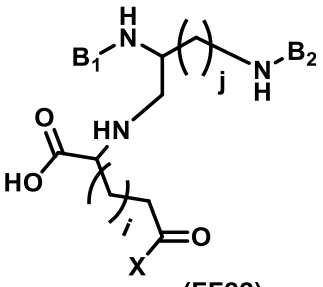

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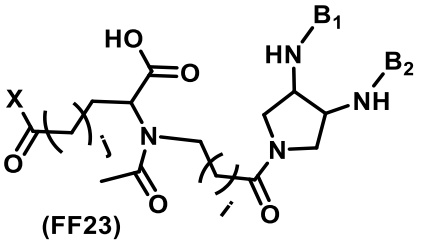

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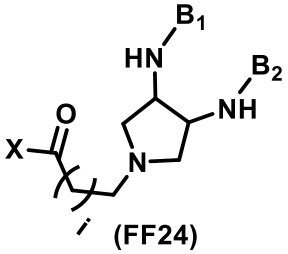
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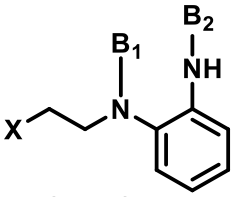
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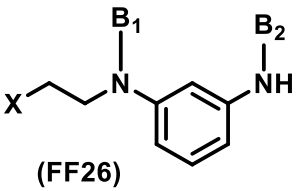
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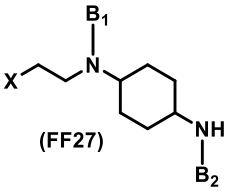
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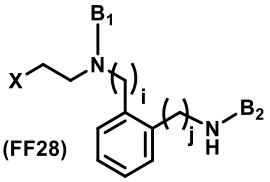
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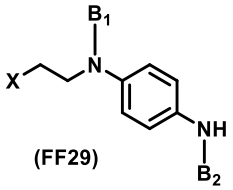
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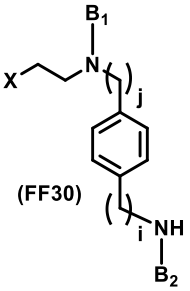
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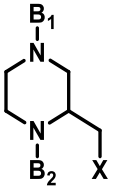
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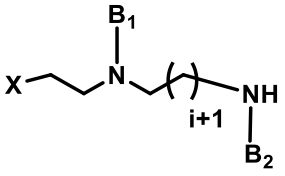
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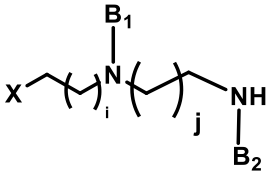
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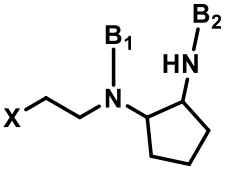
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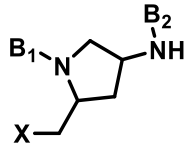
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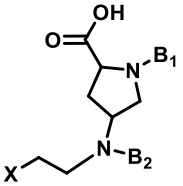
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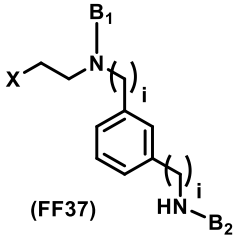
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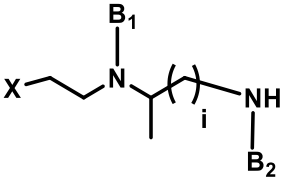
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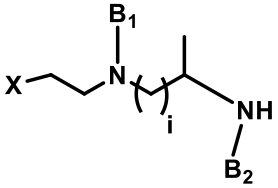
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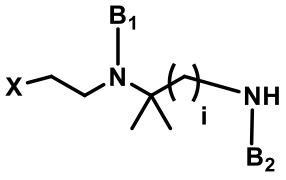
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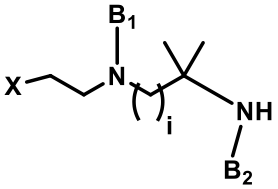
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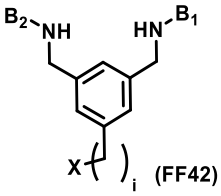
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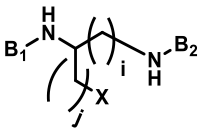


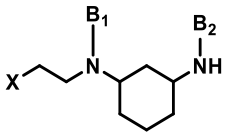
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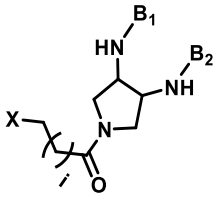


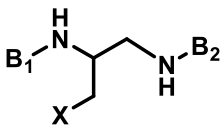
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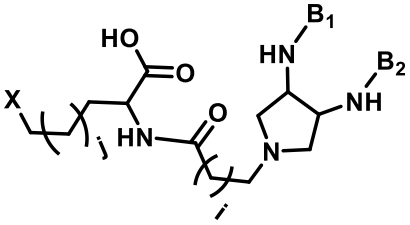

(FF42)


(FF43)

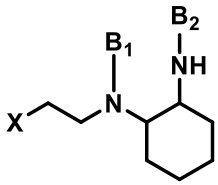

(FF44)


(FF45)


(FF46)


(FF47)

and


(FF48);

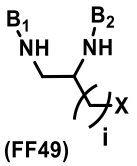
wherein X is selected from an amine, OH, and halogen; and

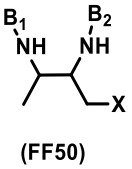
i is 1, 2, 3, 4, 5, 6, or 7;

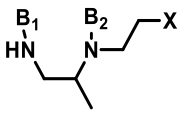
j is 1, 2, 3, 4, 5, 6, or 7; and

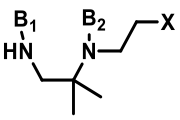
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group; and

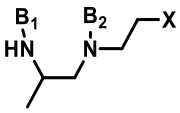
wherein Formulae FF49-FF88 are:

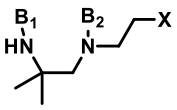

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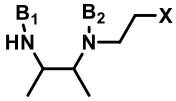

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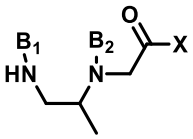

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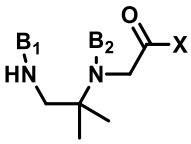

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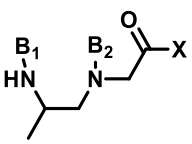

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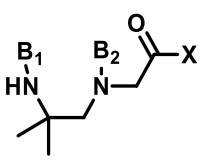

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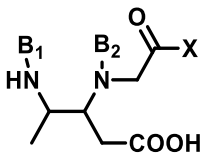

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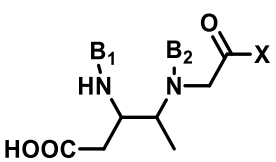

(FF56)

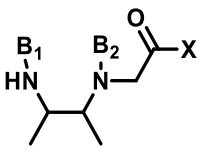

(FF57)

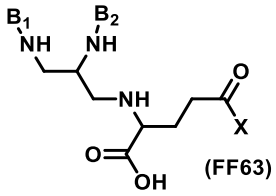

(FF58)

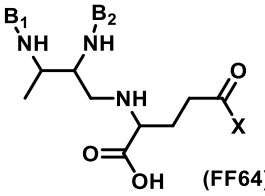

(FF59)

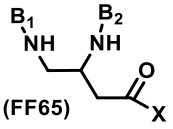

(FF60)

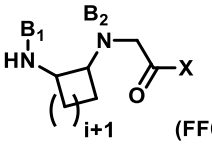

(FF61)

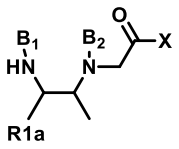

(FF62)

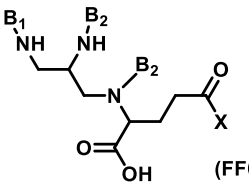

(FF63)

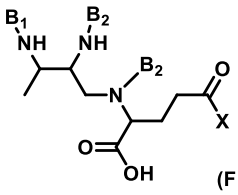

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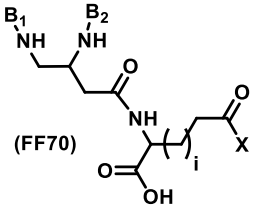

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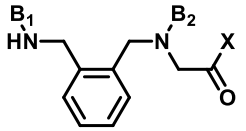

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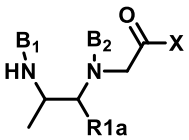

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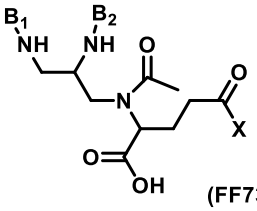

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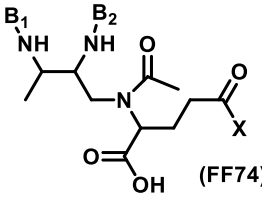

(FF69)

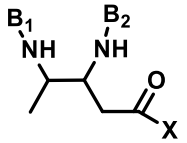

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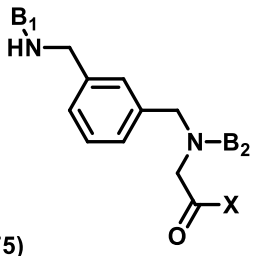

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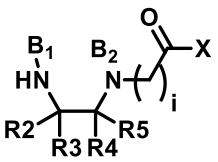

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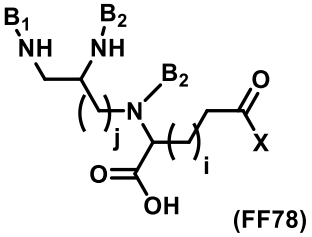

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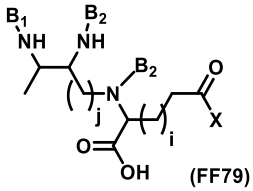

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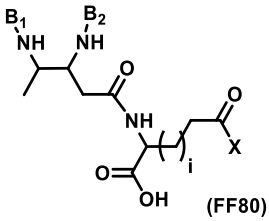

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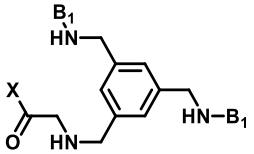

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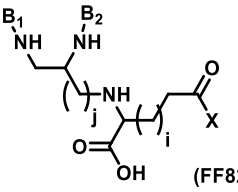

(FF77)

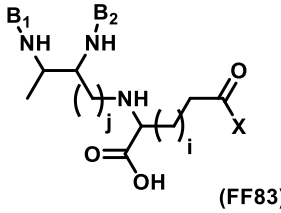

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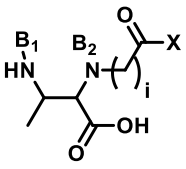

(FF79)

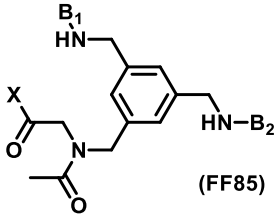

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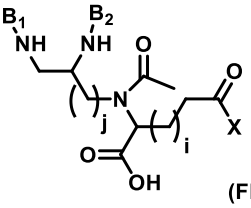

(FF81)

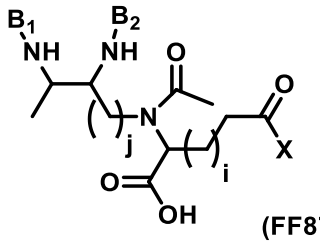

(FF82)


(FF83)

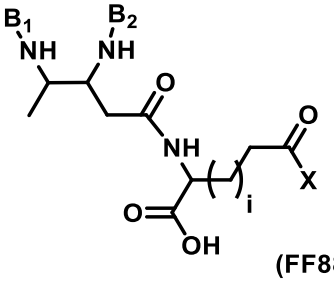

(FF84)


(FF85)


(FF86)


(FF87)

and


(FF88);

wherein X is selected from an amine, OH, and halogen;

i is 1, 2, 3, 4, 5, 6, or 7;

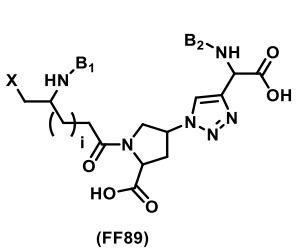
j is 1, 2, 3, 4, 5, 6, or 7;

R1a is selected from COOH, CH_3, H, and OH;

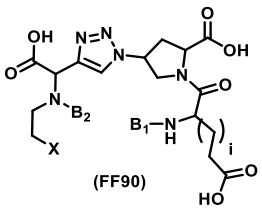
R2, R3, R4 and R5 is each independently selected from CH_3, H, OH, and COOH, and at least one of R2, R3, R4 and R5 is CH_3 or OH; and

B_1 and B_2, which may be identical or different, are each independently an aromatic boron-containing group; and

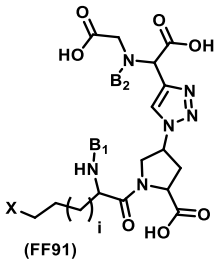
wherein Formulae FF89-FF112 are:



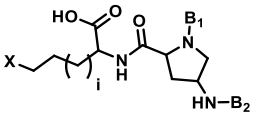
(FF89)



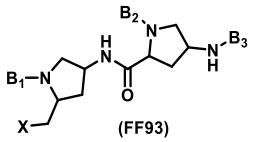
(FF90)



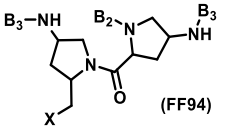
(FF91)



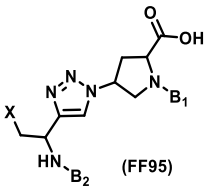
(FF92)



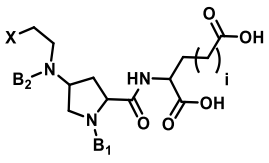
(FF93)



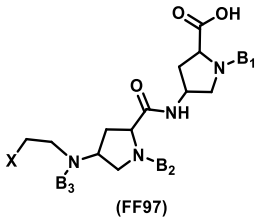
(FF94)



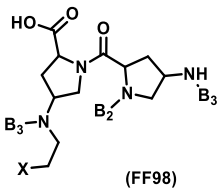
(FF95)



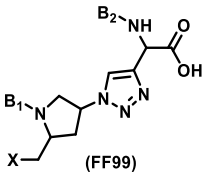
(FF96)



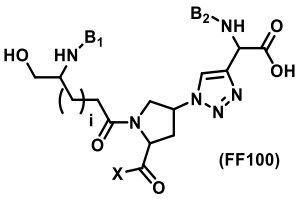
(FF97)



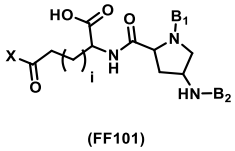
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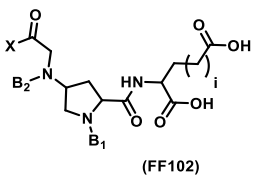
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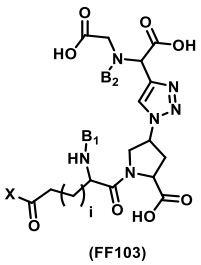
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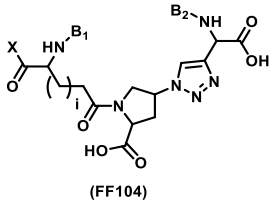
(FF101)



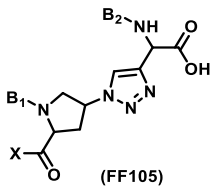
(FF102)

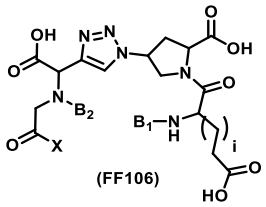


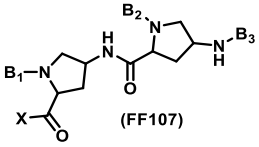
(FF103)

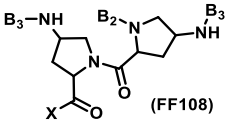


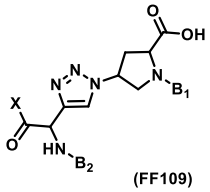
(FF104)

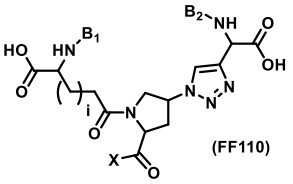

(FF105)

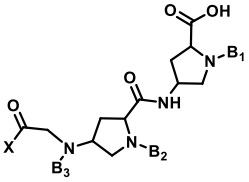

(FF106)


(FF107)

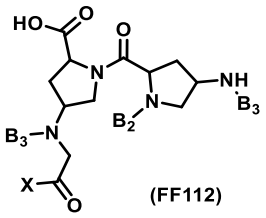

(FF108)


(FF109)


(FF110)


(FF111)

and


(FF112)

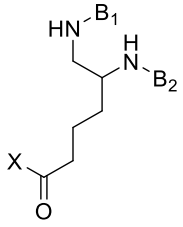
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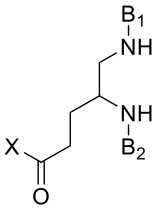
wherein X is selected from an amine, OH, and halogen;

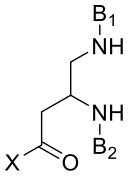
i is 1, 2, 3, 4, 5, 6, or 7; and

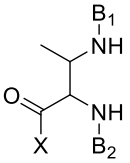
B_1, B_2 and B_3, which may be identical or different, each independently represents an aromatic boron-containing group, a carboxylic acid derivative, or a H, wherein at least two of B1, B2 and B3 in each FF structure are independently an aromatic boron-containing group; and

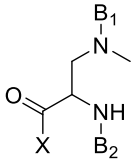
wherein Formulae FF113-FF136 are:

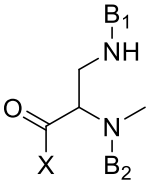

(FF113)

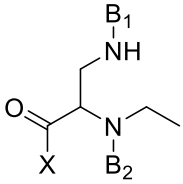

(FF114)

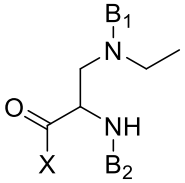

(FF115)

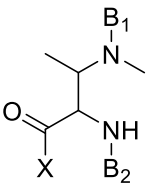

(FF116)

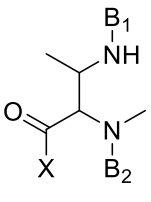

(FF117)

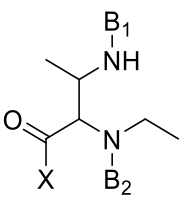

(FF118)

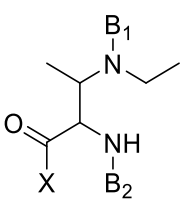

(FF119)

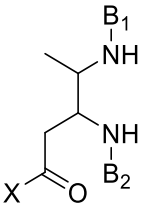

(FF120)

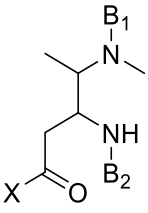

(FF121)

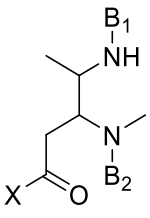

(FF122)

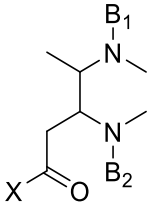

(FF123)

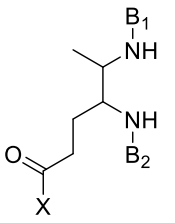

(FF124)


(FF125)

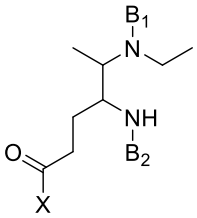

(FF126)


(FF127)

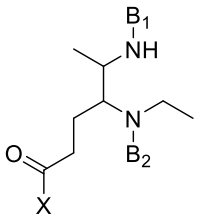

(FF128)



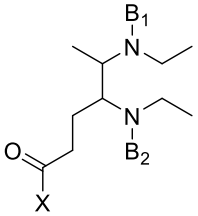
(FF129)



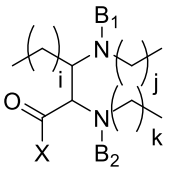
(FF130)



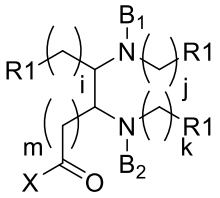
(FF131)



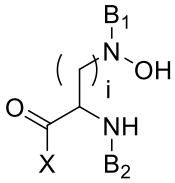
(FF132)



(FF133)

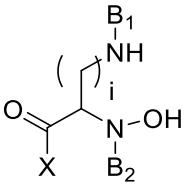


(FF134)



(FF135)

and



(FF136)

;

wherein X is selected from an amine, OH, and halogen;

i is 1, 2, 3, 4, 5, 6, or 7;

j is 1, 2, 3, 4, 5, 6, or 7;

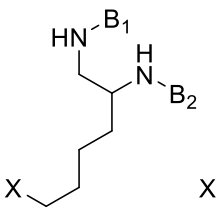
k is 1, 2, 3, 4, 5, 6, or 7;

m is 1, 2, 3, 4, 5, 6, or 7;

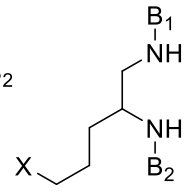
each R1 is independently selected from H, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each R1 optionally comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl or aryl groups; and

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

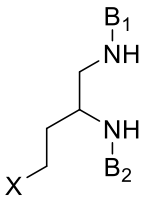
wherein Formulae FF137-FF160 are:



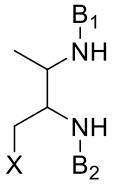
(FF137)



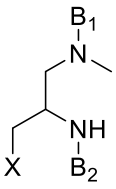
(FF138)



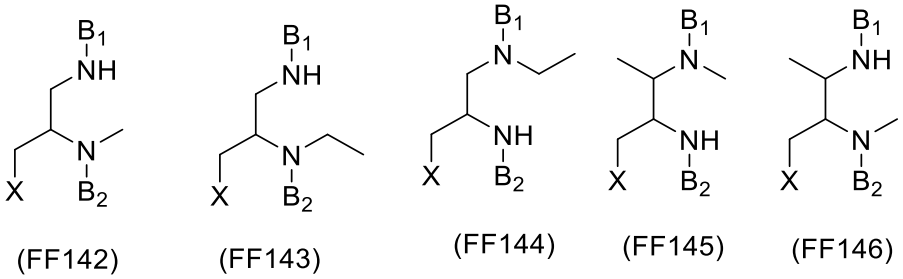
(FF139)



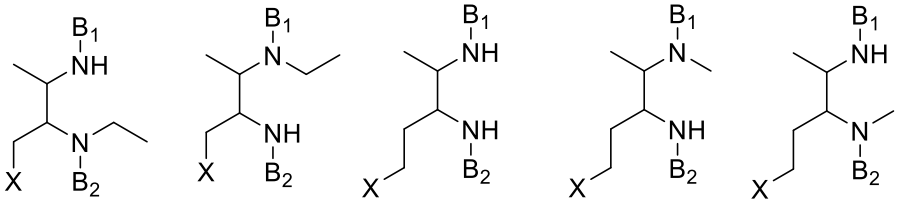
(FF140)



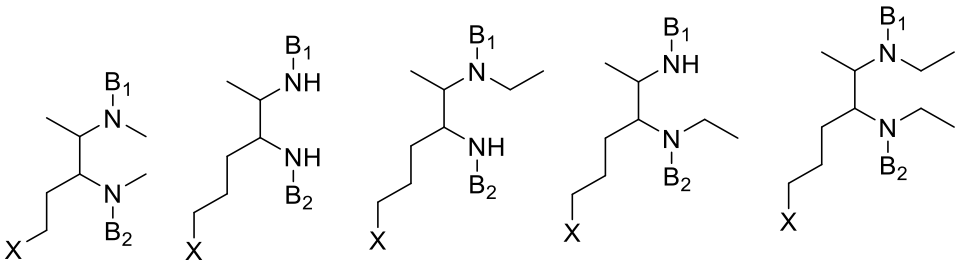
(FF141)



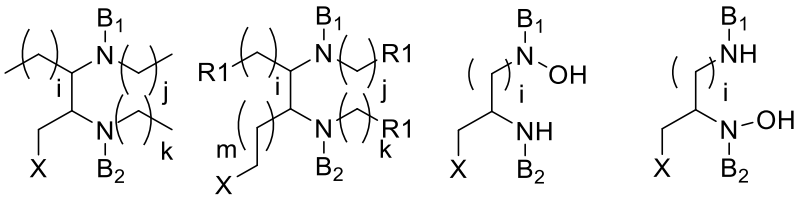
(FF142) (FF143) (FF144) (FF145) (FF146)



(FF147) (FF148) (FF149) (FF150) (FF151)



(FF152) (FF153) (FF154) (FF155) (FF156)



(FF157) (FF158) (FF159) and (FF160) ;

wherein X is selected from an amine, OH, and halogen;

i is 1, 2, 3, 4, 5, 6, or 7;

j is 1, 2, 3, 4, 5, 6, or 7;

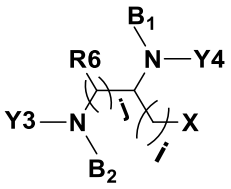
k is 1, 2, 3, 4, 5, 6, or 7;

m is 1, 2, 3, 4, 5, 6, or 7;

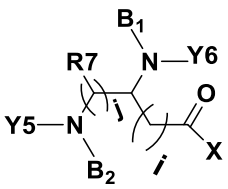
each R1 is independently selected from H, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each R1 optionally comprises one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl or aryl groups; and

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

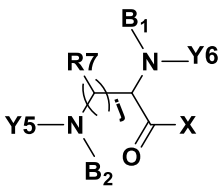
wherein Formulae FF161-FF164 are:



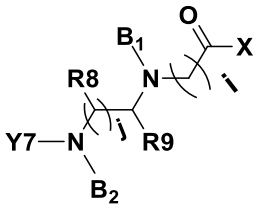
(FF161)



(FF162)



(FF163)



(FF164)

wherein X is selected from an amine, OH, and halogen;

i is 1, 2, 3, 4, or 5;

j is 1, 2, 3, 4, or 5;

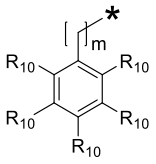
each R6, R7, R8, and R9 for different values of j is independently selected from H, CF_3, CH_3, CHF_2, and $(CH_2)_mCH_3$, wherein m is 1, 2, 3, 4, or 5;

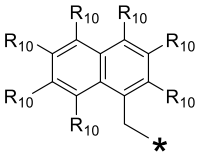
Y3, Y4, Y5, Y6 and Y7 are each independently selected from H, CH_2—X4, and Formulae IV-1 to IV-135;

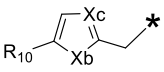
wherein X4 is selected from -COOH, -$(CH_2)_m$COOH, an alkyl group, an acyl group, a cycloalkyl group, a haloalkyl group, an aryl group, and a heteroaryl group, each optionally comprising one or more alkyl-halide, halide, sulfhydryl, aldehyde, amine, acid, hydroxyl, alkyl or aryl groups; wherein m is 1, 2, 3, 4, or 5;

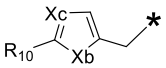
wherein at least one of Y5, Y6, and Y7 in Formulae FF162 and FF163 is not H and at least one of Y7, R8 and R9 in FF164 is not H; and

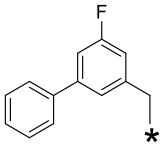
wherein Formulae IV-1 to IV-135 are:

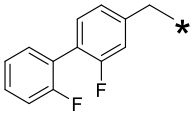

(IV-1)

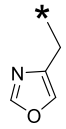

(IV-2)

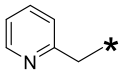

(IV-3)

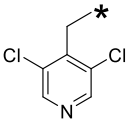

(IV-4)

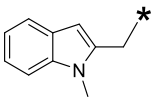

(IV-5)

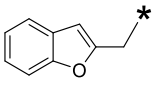

(IV-6)

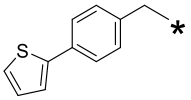

(IV-7)

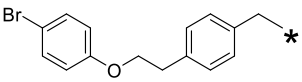

(IV-8)

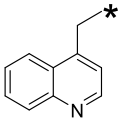

(IV-9)

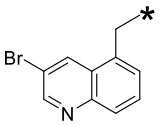

(IV-10)

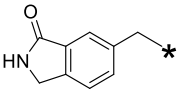

(IV-11)

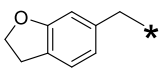

(IV-12)

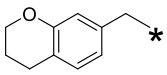

(IV-13)

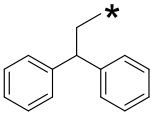

(IV-14)

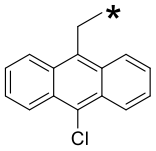

(IV-15)

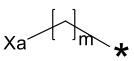

(IV-16)

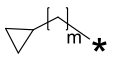

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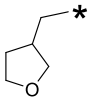

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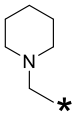

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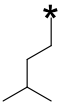

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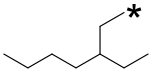

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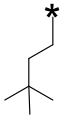

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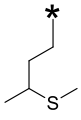

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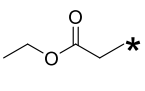

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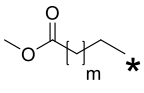

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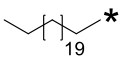

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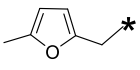

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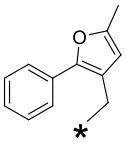
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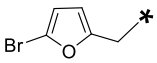

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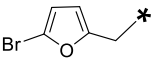

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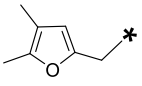

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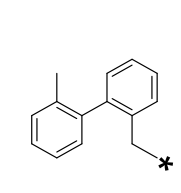
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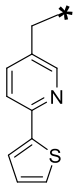
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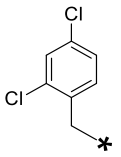
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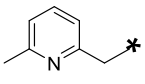
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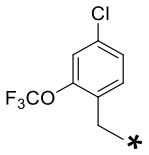
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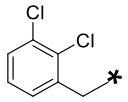
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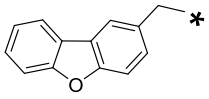
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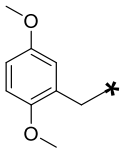
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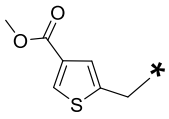
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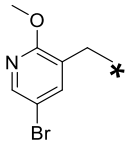
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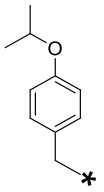
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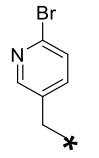
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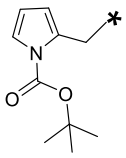
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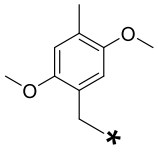
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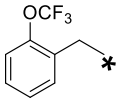
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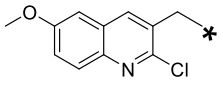
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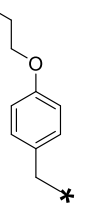
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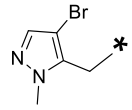
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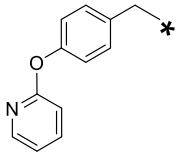
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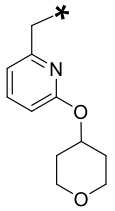
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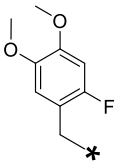
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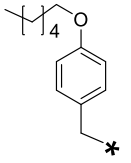
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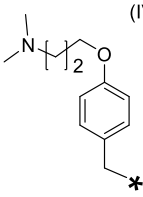
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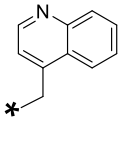
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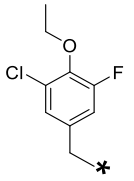
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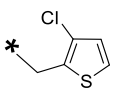
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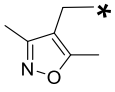
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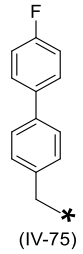
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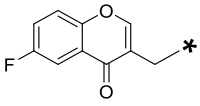
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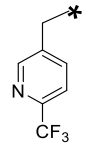
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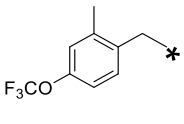
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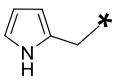
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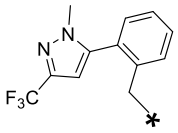
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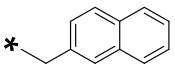
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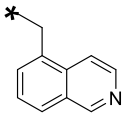
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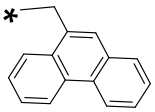
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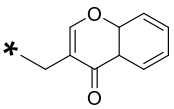
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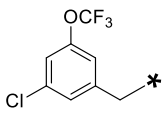
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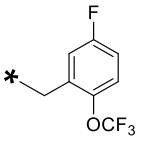
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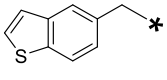
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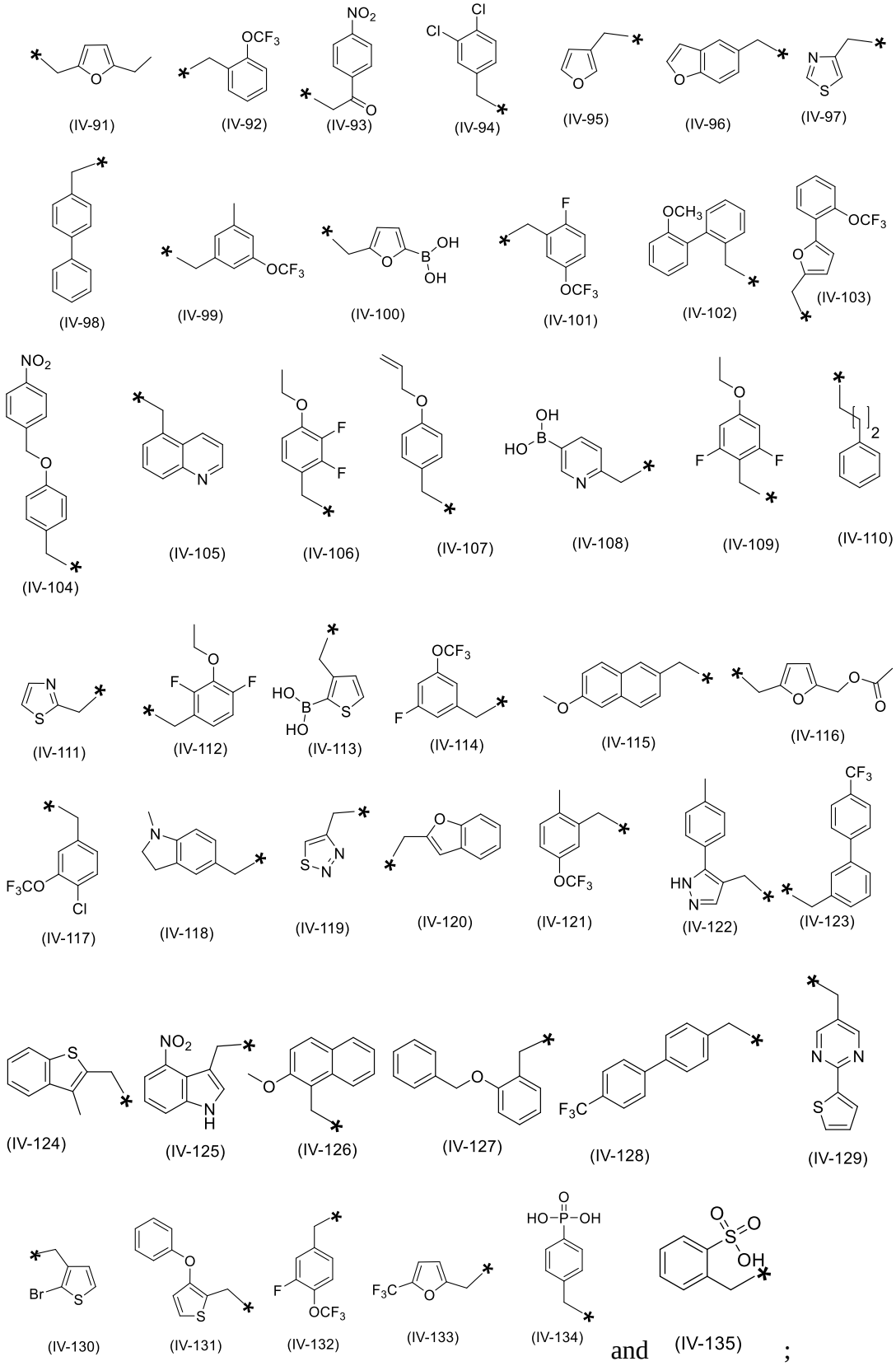


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(IV-127)
(IV-128)
(IV-129)
(IV-130)
(IV-131)
(IV-132)
(IV-133)
(IV-134)
(IV-135)

and ;

wherein:

Xa represents CH=O, CHF_2, CF_3, CH_2SH, COOH, CH_2OH, CH_2NO_2, CH_2NH_2, CH_3, $C(CH_3)_3$, $CH(CH_3)_2$, $CH((CH_2)_3\ CH_3)_2$, or $CH(CH_2\ CH_3)_2$;

Xb represents O, NH, CH_2, or S;

Xc represents CH or N;

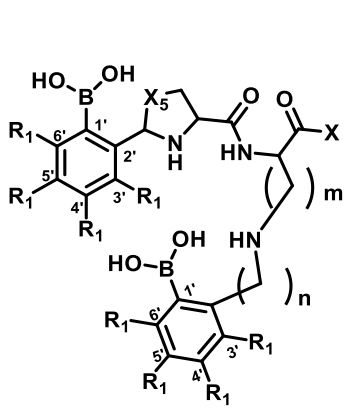
each R_{10} is independently selected from H, F, Cl, Br, CH_3, CF_3, CH=O, OH, COOH, and $(CH_2)_nCH_3$,

m is 1, 2, 3, 4, or 5; and n is 1, 2, 3, 4, or 5;

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

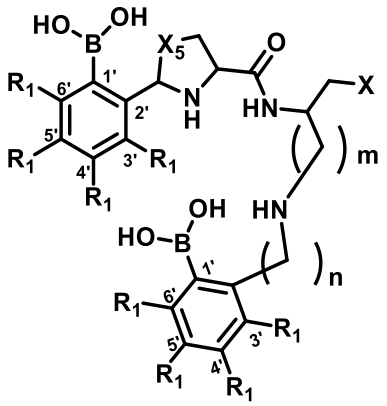
* in Formulae IV-1 to IV-135 represents the point of attachment to corresponding Formulae FF161-164; and

wherein Formulae FF165-FF166 are:



(FF165)

and



(FF166)

;

wherein X is selected from an amine, OH, and halogen;

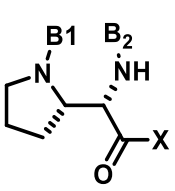
m is 1, 2, 3, 4, 5, 6, or 7;

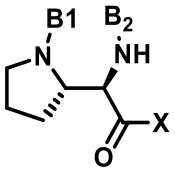
n is 1, 2, 3, 4, 5, 6, or 7;

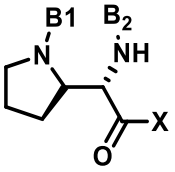
X5 is S, O, or NH; and

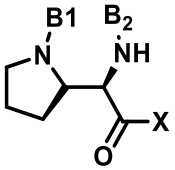
each R_1 is independently selected from H, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH\ CH_3$, —$(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3, 4, 5, 6, or 7; and

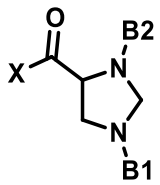
wherein Formulae FF167-FF192 are:

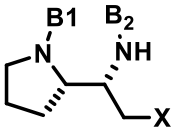

(FF167)

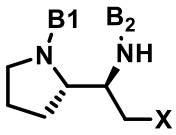

(FF168)

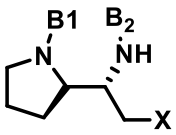

(FF169)

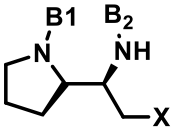

(FF170)

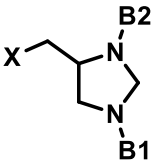

(FF171)

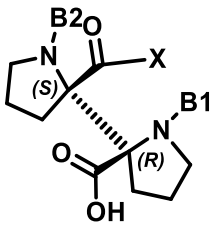

(FF172)

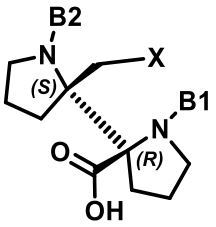

(FF173)

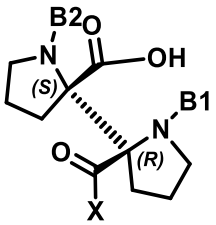

(FF174)

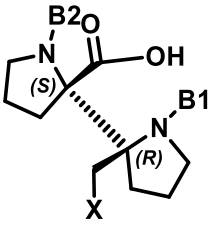

(FF175)

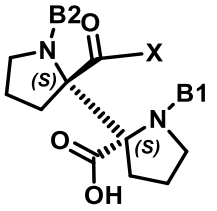

(FF176)

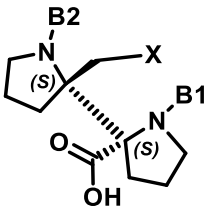

(FF177)

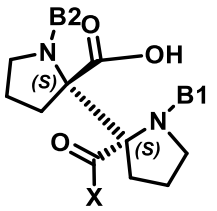

(FF178)

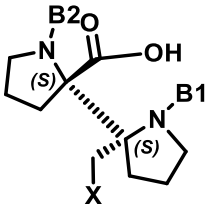

(FF179)

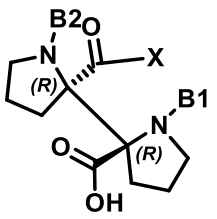

(FF180)

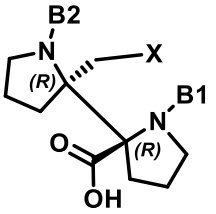

(FF181)

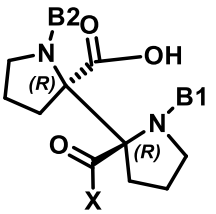

(FF182)

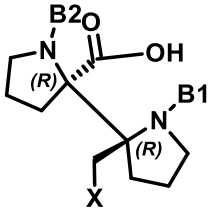

(FF183)

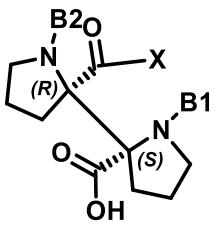

(FF184)

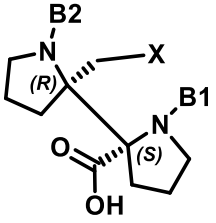

(FF185)

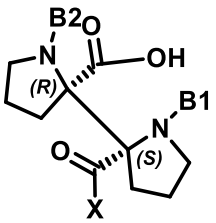

(FF186)

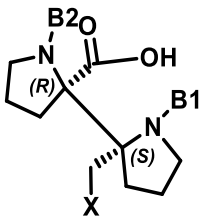

(FF187)


(FF188)


(FF189)


(FF190)


(FF191)

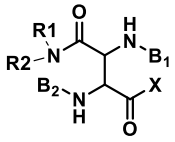

(FF192)

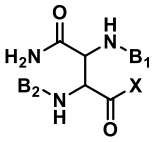
and ;

wherein X is selected from an amine, OH, and halogen;

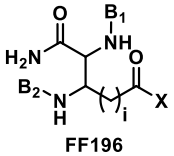
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group, and

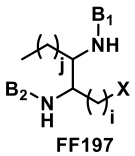
wherein Formulae FF193-FF209 are:

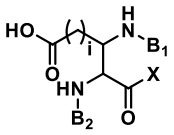

FF193

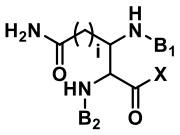

FF194

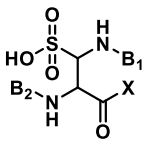

FF195

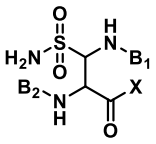

FF196

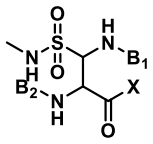

FF197

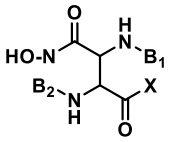

FF198

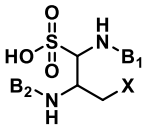

FF199

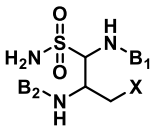

FF200

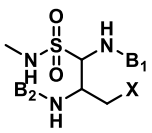

FF201

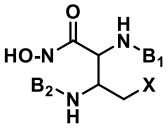

FF202

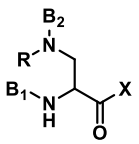

FF203

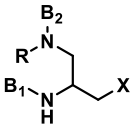

FF204


FF205


FF206


FF207


FF208


FF209

;

wherein R in FF208 and FF209 is an alkyl, aryl or halide that is covalently conjugated through at least one CH_2 group to the amino group in the side chain of FF208 or FF209;

R1 and R2 are independently selected from H, CH_3, alkyl, and formulae IV-1 to IV-135;

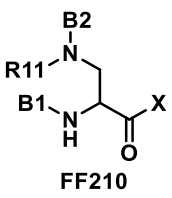
i is 1, 2, 3, 4, or 5;

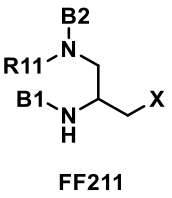
j is 1, 2, 3, 4, or 5; and

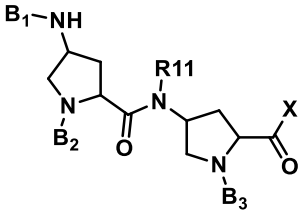
wherein X is selected from an amine, OH, and halogen; and

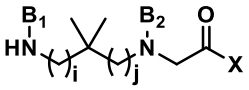
B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group; and

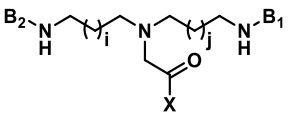
wherein Formulae FF210-FF224 are:

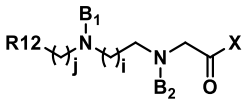

FF210

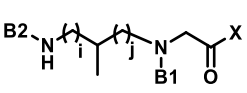

FF211

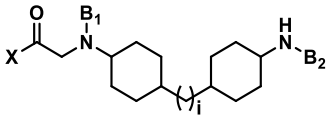

FF212

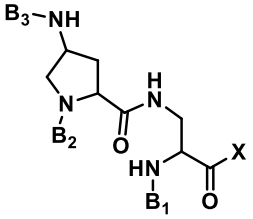

FF213

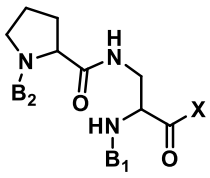

FF214

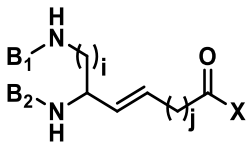

FF215

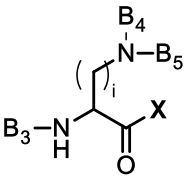

FF216

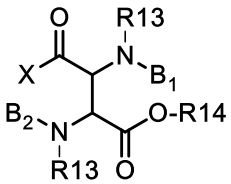

FF217

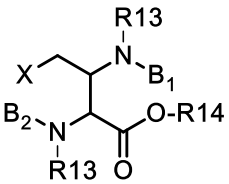

FF218


FF219


FF220


FF221


FF222


FF223



, and **FF224**;

wherein R11 in FF210 to FF212 is independently selected from Formulae IV-1 to IV-135 and R12 is selected from an amine, a hydroxyl, an alkyl, and a halide group;

wherein each R13 is independently selected from H, CH_3, alkyl, aryl, and formulae IV-1 to IV-135; R14 is selected from H, CH_3, alkyl, aryl, and heteroaryl;

wherein X is independently selected from an amine, OH, and halogen;

X'' is an amine;

i is 1, 2, 3, 4, or 5;

j is 1, 2, 3, 4, or 5; and

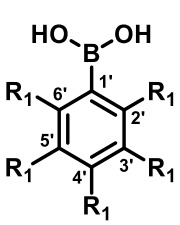
wherein at least one primary or secondary amine in FF1-FF223 is optionally covalently conjugated to B_6; and

B_1, B_2, B_3, B_4, B_5 and B_6 each independently represents an aromatic boron-containing group, wherein in each FF structure containing B1, B2 and B3 groups, at least two of the B1, B2 and B3 groups are independently an aromatic boron-containing group; and

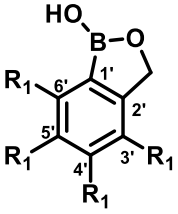
when X is an amine in any one of Formulae FF1 to FF223, X is optionally acetylated or alkylated.

51. The compound of claim 50, wherein the compound comprises at least one of B_1, B_2 and B_3 independently selected from Formulae F1-F12 or wherein the compound comprises at least one of B_4, B_5 and B_6 independently selected from Formulae F1-F10,

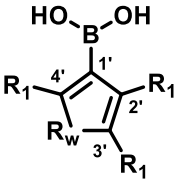
wherein Formulae F1-F10 are:



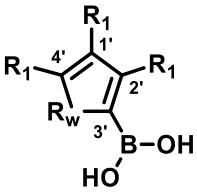
(F1)



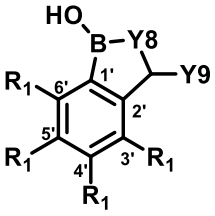
(F2)



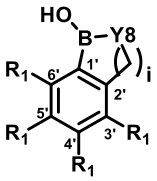
(F3)



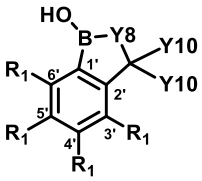
(F4)



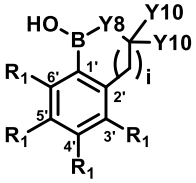
(F5)



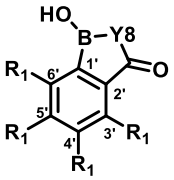
(F6)



(F7)

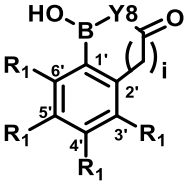


(F8)



(F9)

, and



(F10)

;

wherein for B_1, B_2, B_3:

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

each remaining R_1 is independently selected from H, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, —$(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3 ,4, 5, 6, or 7;

wherein for B_4, B_5:

one R_1 for B_4 represents $(CH_2)_m$---ø, wherein ---ø represents the attachment point (representing a covalent bond) to an amine in X1 and one R_1 for B_5 represents (C=O)---*, S(=O)(=O)---*, $(CH_2)_m$(C=O)---*, or $(CH_2)_m$---*, wherein ---* represents the attachment point to the same amine in X1, and m is 1, 2, 3, 4, 5, 6, or 7;

each remaining R_1 is independently selected from H, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, —$(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3 ,4, 5, 6, or 7;

wherein for B_6:

one R_1 for B_6 represents $(CH_2)_m$---ø, wherein ---ø represents the attachment point (representing a covalent bond) to the rest of the compound, and m is 1, 2, 3, 4, 5, 6, or 7;

each remaining R_1 is independently selected from H, F, Cl, Br, OH, CH_2-NH_2, NH_2, (C=O)-NH_2, CH=O, SO_2CH_3, SO_2CF_3, CF_3, CHF_2, NO_2, CH_3, OCH_3, $O(CH_2)_mCH_3$, —$(SO_2)NH$ CH_3, —$(SO_2)NH(CH_2)_mCH_3$, and OCF_3, wherein m is 1, 2, 3 ,4, 5, 6, or 7;

for Formulae F3-F4:

R_w is O or S;

for Formulae F5-F10:

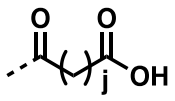
Y8 is selected from O, N, and NR, wherein R is an alkyl group or H;

Y9 is H, CH_3, or an alkyl group, provided that when Y8 is O, Y9 is a CH_3 or higher alkyl group;

each Y10 is independently selected from H, CH_3, F, CF_3, and OCH_3; and

i is 1, 2, or 3; and

wherein Formulae F11-F12 are:



(F11)



(F12),

j is 1, 2, ,3, 4, 5, 6, or 7; and

--- represents the attachment point to the rest of Z1c.

52. The compound of claim 50 or 51, wherein the compound is selected from:

N-(3-(3-borono-5-nitrobenzamido)propyl)-N-(3-borono-5-nitrobenzoyl)glycine (DS01);

N-(4-((4-(3-borono-5-nitrobenzamido)cyclohexyl)methyl)cyclohexyl)-N-(3-borono-5-nitrobenzoyl)glycine (DS02);

N-(4-((3-borono-5-nitrobenzamido)methyl)benzyl)-N-(3-borono-5-nitrobenzoyl)glycine (DS03);

N-(3-((3-borono-5-nitrobenzamido)methyl)benzyl)-N-(3-borono-5-nitrobenzoyl)glycine (DS04);

N-(4-(3-borono-5-nitrobenzamido)butyl)-N-(3-borono-5-nitrobenzoyl)glycine (DS05);

N-(3-(3-borono-5-fluorobenzamido)propyl)-N-(3-borono-5-fluorobenzoyl)glycine (DS06);

N-(3-(3-borono-5-fluorobenzamido)-2,2-dimethylpropyl)-N-(3-borono-5-fluorobenzoyl)glycine (DS07);

bis(3-(3-borono-5-fluorobenzamido)propyl)glycine (DS08);
N-(4-((3-borono-5-fluorobenzamido)methyl)benzyl)-N-(3-borono-5-fluorobenzoyl)glycine (DS09);
N-(3-((3-borono-5-fluorobenzamido)methyl)benzyl)-N-(3-borono-5-fluorobenzoyl)glycine (DS10);
N-(2-(3-borono-5-fluorobenzamido)cyclohexyl)-N-(3-borono-5-fluorobenzoyl)glycine (DS11);
N-(3-(3-borono-4-fluorobenzamido)propyl)-N-(3-borono-4-fluorobenzoyl)glycine (DS12);
N-(4-((4-(3-borono-4-fluorobenzamido)cyclohexyl)methyl)cyclohexyl)-N-(3-borono-4-fluorobenzoyl)glycine (DS13);
N-(3-(3-borono-4-fluorobenzamido)-2,2-dimethylpropyl)-N-(3-borono-4-fluorobenzoyl)glycine (DS14);
N-(4-((3-borono-4-fluorobenzamido)methyl)benzyl)-N-(3-borono-4-fluorobenzoyl)glycine (DS15);
N-(3-((3-borono-4-fluorobenzamido)methyl)benzyl)-N-(3-borono-4-fluorobenzoyl)glycine (DS16);
N-((1S,2R)-2-(3-borono-4-fluorobenzamido)cyclohexyl)-N-(3-borono-4-fluorobenzoyl)glycine (DS17);
N-((1S,2S)-2-(3-borono-4-fluorobenzamido)cyclohexyl)-N-(3-borono-4-fluorobenzoyl)glycine (DS18);
N-(3-(3-borono-5-bromobenzamido)propyl)-N-(3-borono-5-bromobenzoyl)glycine (DS19);
N-(4-((4-(3-borono-5-bromobenzamido)cyclohexyl)methyl)cyclohexyl)-N-(3-borono-5-bromobenzoyl)glycine (DS20);
bis(3-(3-borono-5-bromobenzamido)propyl)glycine (DS21);
N-(4-((3-borono-5-bromobenzamido)methyl)benzyl)-N-(3-borono-5-bromobenzoyl)glycine (DS22);
N-(3-((3-borono-5-bromobenzamido)methyl)benzyl)-N-(3-borono-5-bromobenzoyl)glycine (DS23);
N-(2-(3-borono-5-bromobenzamido)cyclohexyl)-N-(3-borono-5-bromobenzoyl)glycine (DS24);
N-(3-(4-borono-3-fluorobenzamido)propyl)-N-(4-borono-3-fluorobenzoyl)glycine (DS25);
N-(4-((4-(4-borono-3-fluorobenzamido)cyclohexyl)methyl)cyclohexyl)-N-(4-borono-3-fluorobenzoyl)glycine (DS26);

N-(3-(4-borono-3-fluorobenzamido)-2,2-dimethylpropyl)-N-(4-borono-3-fluorobenzoyl)glycine (DS27);

bis(3-(4-borono-3-fluorobenzamido)propyl)glycine (DS28);

N-(4-((4-borono-3-fluorobenzamido)methyl)benzyl)-N-(4-borono-3-fluorobenzoyl)glycine (DS29);

N-(3-((4-borono-3-fluorobenzamido)methyl)benzyl)-N-(4-borono-3-fluorobenzoyl)glycine (DS30);

N-((1S,2R)-2-(4-borono-3-fluorobenzamido)cyclohexyl)-N-(4-borono-3-fluorobenzoyl)glycine (DS31);

N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)propyl)glycine (DS32);

N-(1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborole-6-carbonyl)-*N*-(5-(1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborole-6-carboxamido)pentyl)glycine *(*DS33);

N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-2,2-dimethylpropyl)glycine (DS34);

bis(3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)propyl)glycine (DS35);

N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(3-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)methyl)benzyl)glycine (DS36);

N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-((1S,2R)-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)cyclohexyl)glycine (DS37);

N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)butyl)glycine (DS38);

N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-((1S,2S)-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)cyclohexyl)glycine (DS39);

(R)-N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)propyl)glycine (DS40);

(S)-N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)propyl)glycine (DS41);

N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)cyclohexyl)glycine (DS42);

N-(3-(4-borono-3,5-difluorobenzamido)propyl)-N-(4-borono-3,5-difluorobenzoyl)glycine (DS43);

N-(3-(4-borono-2-fluorobenzamido)propyl)-N-(4-borono-2-fluorobenzoyl)glycine (DS44);

N-(2-(N-ethyl-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)ethyl)-N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)glycine (DS45);
N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(2-(1-hydroxy-N-(2-hydroxyethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)ethyl)glycine (DS46);
N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(5-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)hexyl)glycine (DS47);
N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-N-(4-((4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)cyclohexyl)methyl)cyclohexyl)glycine (DS48);
((2S,4S)-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carbonyl)glycine (DS49);
((2S,4S)-4-(3-borono-4-fluorobenzamido)-1-(3-borono-4-fluorobenzoyl)pyrrolidine-2-carbonyl)glycine (DS50);
((2S,4S)-4-(3-borono-5-nitrobenzamido)-1-(3-borono-5-nitrobenzoyl)pyrrolidine-2-carbonyl)glycine (DS51);
((2S,4S)-4-(5-borono-2-fluorobenzamido)-1-(5-borono-2-fluorobenzoyl)pyrrolidine-2-carbonyl)glycine (DS52);
(S)-(1,4-bis(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)piperazine-2-carbonyl)glycine (DS53);
(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-N-benzyl-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS54);
(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-1-hydroxy-N-(4-(trifluoromethyl)benzyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS55);
(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-N-ethyl-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS56);
(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-1-hydroxy-N-propyl-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS57);
(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-1-hydroxy-N-isobutyl-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS58);
(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-1-hydroxy-N-((5-(thiophen-2-yl)pyridin-2-yl)methyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS59);

(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-1-hydroxy-N-isopentyl-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS60);
(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-1-hydroxy-N-(quinolin-5-ylmethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS61);
(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-1-hydroxy-N-(2-(trifluoromethoxy)benzyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS62);
(S)-N-(3-amino-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-3-oxopropyl)-1-hydroxy-N-(4-(methylsulfonyl)benzyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS63);
(3-((2S,4S)-4-(5-borono-2-(methylsulfonyl)benzamido)-2-carbamoylpyrrolidine-1-carbonyl)-4-(methylsulfonyl)phenyl)boronic acid (DS64);
(4-(((3S,5S)-1-(4-borono-2,6-difluorobenzoyl)-5-carbamoylpyrrolidin-3-yl)carbamoyl)-3,5-difluorophenyl)boronic acid (DS65);
(R,E)-4,5-bis(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pent-2-enoic acid (DS66);
(2S,4S)-1-(1-hydroxy-4-(trifluoromethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-4-(1-hydroxy-4-(trifluoromethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carboxamide (DS67);
N,N'-((2S,3S)-1-amino-1-oxobutane-2,3-diyl)bis(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide) (DS68);
(R)-3,4-bis(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)butanoic acid (DS69);
3-((2S,4S)-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carboxamido)propanoic acid (DS70);
(S)-3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-5-carboxamido)-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)butanoic acid (DS71);
(R)-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-5-carboxamido)-5-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pentanoic acid (DS72);
(2S,4R)-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carboxylic acid (DS73);

(2S,4R)-1-(1-hydroxy-4-(trifluoromethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbonyl)-4-(1-hydroxy-4-(trifluoromethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carboxylic acid (DS74);

(2S,3S)-3-(1-hydroxy-4-(trifluoromethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-2-(1-hydroxy-7-(trifluoromethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-5-carboxamido)butanoic acid (DS75);

(R)-5-(1-hydroxy-4-(trifluoromethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-4-(1-hydroxy-7-(trifluoromethyl)-1,3-dihydrobenzo[c][1,2]oxaborole-5-carboxamido)pentanoic acid (DS76);

((2S,4S)-1-(5-borono-2-nitrobenzoyl)-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carbonyl)glycine (DS77);

((2S,4S)-1-(5-borono-2-(methylsulfonyl)benzoyl)-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carbonyl)glycine (DS78);

((2S,4S)-1-(3-borono-2,6-difluorobenzoyl)-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carbonyl)glycine (DS79);

(S)-(3-((3-borono-4-fluorobenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-nitrophenyl)boronic acid (DS80);

(S)-(3-((4-borono-3,5-difluorobenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-nitrophenyl)boronic acid (DS81);

(S)-(3-((3-boronobenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-nitrophenyl)boronic acid (DS82);

(S)-(3-((4-borono-2-methoxybenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-nitrophenyl)boronic acid (DS83);

(S)-(3-((4-borono-2-(trifluoromethyl)benzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-nitrophenyl)boronic acid (DS84);

(S)-(5-((3-borono-N-(5,6-diamino-6-oxohexyl)-4-fluorobenzamido)methyl)-2-fluorophenyl)boronic acid (DS85);

(S)-(5-((4-borono-3,5-difluorobenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-2-fluorophenyl)boronic acid (DS86);

(S)-(3-((3-borono-N-(5,6-diamino-6-oxohexyl)-4-fluorobenzamido)methyl) phenyl)boronic acid (DS87);

(S)-(5-((4-borono-2-methoxybenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-2-fluorophenyl)boronic acid (DS88);

(S)-(5-((4-borono-3-(trifluoromethyl)benzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-2-fluorophenyl)boronic acid (DS89);

(S)-(4-((3-borono-4-fluorobenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-2-fluorophenyl)boronic acid (DS90);

(S)-(4-((4-borono-3,5-difluorobenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-2-fluorophenyl)boronic acid (DS91);

(S)-(4-((3-boronobenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-2-fluorophenyl)boronic acid (DS92);

(S)-(4-((4-borono-2-methoxybenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-2-fluorophenyl)boronic acid (DS93);

(S)-(4-((4-borono-2-(trifluoromethyl)benzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-2-fluorophenyl)boronic acid (DS94);

(S)-(5-((3-borono-5-bromo-N-(5,6-diamino-6-oxohexyl)benzamido)methyl)-2-fluorophenyl)boronic acid (DS95);

(S)-(3-((4-borono-3,5-difluorobenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-bromophenyl)boronic acid (DS96);

(S)-(3-((3-borono-5-bromo-N-(5,6-diamino-6-oxohexyl)benzamido)methyl) phenyl)boronic acid (DS97);

(S)-(3-((3-borono-5-bromo-N-(5,6-diamino-6-oxohexyl)benzamido)methyl)-5-methoxyphenyl)boronic acid (DS98);

(S)-(3-((4-borono-2-(trifluoromethyl)benzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-bromophenyl)boronic acid (DS99);

(S)-(3-((3-borono-4-fluorobenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-fluorophenyl)boronic acid (DS100);

(S)-(3-((4-borono-3-methoxybenzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-fluorophenyl)boronic acid (DS101);

(S)-(3-((4-borono-2-(trifluoromethyl)benzyl)(5,6-diamino-6-oxohexyl)carbamoyl)-5-fluorophenyl)boronic acid (DS102);

(S)-(4-((N-(5,6-diamino-6-oxohexyl)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)methyl)-2-fluorophenyl)boronic acid (DS103);

(S)-(4-((N-(5,6-diamino-6-oxohexyl)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)methyl)-2,6-difluorophenyl)boronic acid (DS104);

(S)-(3-((N-(5,6-diamino-6-oxohexyl)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)methyl)phenyl)boronic acid (DS105);

(S)-(4-((N-(5,6-diamino-6-oxohexyl)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)methyl)-3-methoxyphenyl)boronic acid (DS106);

(S)-N-(5,6-diamino-6-oxohexyl)-1-hydroxy-N-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS107);

(S)-N-(4-amino-3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-4-oxobutyl)-1-hydroxy-N-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS108);

(S)-N-(6-amino-5-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-6-oxohexyl)-1-hydroxy-N-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamide (DS109);

(2*S*,4*S*)-1-(1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborole-6-carbonyl)-4-(1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carboxylic acid (DS110);

(2*S*,3*S*)-2-(1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborole-5-carboxamido)-3-(1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborole-6-carboxamido)butanoic acid (DS111); and

(2*S*,4*R*)-1-(1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborole-6-carbonyl)-4-(1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborole-6-carboxamido)pyrrolidine-2-carboxylic acid (DS112).

53. The compound of any one of claims 1-44 and 50-52, wherein the compound is used as an intermediate in the manufacture of a drug substance or a therapeutic of a prophylactic compound.

54. A human insulin analog, comprising an A-chain and a B-chain,

wherein the sequence of the A-chain comprises:

$X_{aa'}X_{bb'}X_{cc'}X_{dd'}X_{ee'}X_{ff'}X_{gg'}$VEQCC$X_{hh'}X_{ii'}$ICSLYQLENYCN$X_{jj'}X_{kk'}X_{ll'}X_{mm'}X_{nn'}X_{oo'}X_{pp'}$ (SEQ ID NO:24015); and

wherein the sequence of the B-chain comprises:

(i)

$X_{aa}X_{bb}X_{cc}X_{dd}$K$X_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}$QHLCGSHLVEALYLVC$X_{oo}X_{pp}X_{qq}$GFFYT$X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24016),

wherein $X_{aa'}$, $X_{bb'}$, $X_{cc'}$, $X_{dd'}$, $X_{ee'}$, $X_{ff'}$, $X_{gg'}$, $X_{hh'}$, $X_{ii'}$, $X_{jj'}$, $X_{kk'}$, $X_{ll'}$, $X_{mm'}$, $X_{nn'}$, $X_{oo'}$, $X_{pp'}$, X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ee}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y and W,

(ii)

$X_{aa}X_{bb}X_{cc}X_{dd}KPX_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}X_{kk}X_{ll}X_{mm}X_{nn}QHLCGSHLVEALYLVCX_{oo}X_{pp}X_{qq}GFFYT$ $X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24017),

wherein $X_{aa'}$, $X_{bb'}$, $X_{cc'}$, $X_{dd'}$, $X_{ee'}$, $X_{ff'}$, $X_{gg'}$, $X_{hh'}$, $X_{ii'}$, $X_{jj'}$, $X_{kk'}$, $X_{ll'}$, $X_{mm'}$, $X_{nn'}$, $X_{oo'}$, $X_{pp'}$, X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y and W, and wherein X_{ee} is selected from amino acid residues A, E, F, H, I, K, L, N, P, Q, R, S, T, V,Y and W,

(iii)

$X_{aa}X_{bb}X_{cc}X_{dd}KX_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}QHLCGSHLVEALYLVCX_{oo}X_{pp}X_{qq}GFFYT$ $X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24018),

wherein $X_{aa'}$, $X_{bb'}$, $X_{cc'}$, $X_{dd'}$, $X_{ee'}$, $X_{ff'}$, $X_{gg'}$, $X_{hh'}$, $X_{ii'}$, $X_{jj'}$, $X_{kk'}$, $X_{ll'}$, $X_{mm'}$, $X_{nn'}$, $X_{oo'}$, $X_{pp'}$, X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ee}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y , W and at least one of $X_{ee,}X_{ff,}X_{gg,}X_{hh,}X_{ii,}X_{jj}$ is present and at least one of $X_{ee,}X_{ff,}X_{gg,}X_{hh,}X_{ii,}X_{jj}$ is G,

(iv)

$X_{aa}X_{bb}X_{cc}X_{dd}KX_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}QHLCGSHLVEALYLVCX_{oo}X_{pp}X_{qq}GFFYT$ $X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24019),

wherein $X_{aa'}$, $X_{bb'}$, $X_{cc'}$, $X_{dd'}$, $X_{ee'}$, $X_{ff'}$, $X_{gg'}$, $X_{hh'}$, $X_{ii'}$, $X_{jj'}$, $X_{kk'}$, $X_{ll'}$, $X_{mm'}$, $X_{nn'}$, $X_{oo'}$, $X_{pp'}$, X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ee}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y , W and at least one of $X_{ee,}X_{ff,}X_{gg,}X_{hh,}X_{ii,}X_{jj}$ is present and at least one of $X_{ee,}X_{ff,}X_{gg,}X_{hh,}X_{ii,}X_{jj}$ is S, or

(v)

$X_{aa}X_{bb}X_{cc}X_{dd}KX_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}QHLCGSHLVEALYLVCX_{oo}X_{pp}X_{qq}GFFYT$ $X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (SEQ ID NO:24020),

wherein $X_{aa'}$, $X_{bb'}$, $X_{cc'}$, $X_{dd'}$, $X_{ee'}$, $X_{ff'}$, $X_{gg'}$, $X_{hh'}$, $X_{ii'}$, $X_{jj'}$, $X_{kk'}$, $X_{ll'}$, $X_{mm'}$, $X_{nn'}$, $X_{oo'}$, $X_{pp'}$, X_{aa}, X_{bb}, X_{cc}, X_{dd}, X_{ee}, X_{ff}, X_{gg}, X_{hh}, X_{ii}, X_{jj}, X_{kk}, X_{ll}, X_{mm}, X_{nn}, X_{oo}, X_{pp}, X_{qq}, X_{rr}, X_{ss},X_{tt}, X_{uu}, X_{vv}, and X_{ww} are each independently either absent or selected from amino acid residues A, D, E, F, G, H, I, K, L, N, P, Q, R, S, T, V, Y , W and at least two of $X_{ee,}X_{ff,}X_{gg,}X_{hh,}X_{ii,}X_{jj}$ are present and at least one of $X_{ee,}X_{ff,}X_{gg,}X_{hh,}X_{ii,}X_{jj}$ is S, and another is G.

55. The insulin of claim 54, wherein the A-chain comprises a sequence selected from SEQ ID NOs 1 and 3 to 33, and is optionally appended at the N-terminus and/or at the C-terminus by at least one selected from KA, KD, KE, KF, KG, KH, KI, KL, KN, KP, KQ, KR, KS, KT, KY, KAA, KAD, KAE, KAF, KAG, KAH, KAI, KAL, KAN, KAQ, KAR, KAS, KAT, KAY, KDA, KDD, KDE, KDF, KDG, KDH, KDI, KDL, KDN, KDQ, KDR, KDS, KDT, KDY, KEA, KED, KEE, KEF, KEG, KEH, KEI, KEL, KEN, KEQ, KER, KES, KET, KEY, KFA, KFD, KFE, KFF, KFG, KFH, KFI, KFL, KFN, KFQ, KFR, KFS, KFT, KFY, KGA, KGD, KGE, KGF, KGG, KGH, KGI, KGL, KGN, KGQ, KGR, KGS, KGT, KGY, KHA, KHD, KHE, KHF, KHG, KHH, KHI, KHL, KHN, KHQ, KHR, KHS, KHT, KHY, KIA, KID, KIE, KIF, KIG, KIH, KII, KIL, KIN, KIQ, KIR, KIS, KIT, KIY, KLA, KLD, KLE, KLF, KLG, KLH, KLI, KLL, KLN, KLQ, KLR, KLS, KLT, KLY, KNA, KND, KNE, KNF, KNG, KNH, KNI, KNL, KNN, KNQ, KNR, KNS, KNT, KNY, KPA, KPD, KPE, KPF, KPG, KPH, KPI, KPL, KPN, KPQ, KPR, KPS, KPT, KPY, KQA, KQD, KQE, KQF, KQG, KQH, KQI, KQL, KQN, KQQ, KQR, KQS, KQT, KQY, KRA, KRD, KRE, KRF, KRG, KRH, KRI, KRL, KRN, KRQ, KRR, KRS, KRT, KRY, KSA, KSD, KSE, KSF, KSG, KSH, KSI, KSL, KSN, KSQ, KSR, KSS, KST, KSY, KTA, KTD, KTE, KTF, KTG, KTH, KTI, KTL, KTN, KTQ, KTR, KTS, KTT, KTY, KYA, KYD, KYE, KYF, KYG, KYH, KYI, KYL, KYN, KYQ, KYR, KYS, KYT, KYY, SEQ ID NOs 75 to 24014, KGSH (SEQ ID NO:24049), GKGSH (SEQ ID NO:24050), GKGSKK (SEQ ID NO:24045), GKKPGKK (SEQ ID NO:24046), GKGPSK (SEQ ID NO:24044), GKPSHKP (SEQ ID NO:24043), and GSHKGSHK (SEQ ID NO:24042); and

wherein the B-chain comprises a sequence selected from SEQ ID NOs 2 and 34 to 74, 24047, and 24048, and is optionally appended at the N-terminus and/or at the C-terminus by at least one selected from KA, KD, KE, KF, KG, KH, KI, KL, KN, KP, KQ, KR, KS, KT, KY, KAA, KAD, KAE, KAF, KAG, KAH, KAI, KAL, KAN, KAQ, KAR, KAS, KAT, KAY, KDA, KDD, KDE, KDF, KDG, KDH, KDI, KDL, KDN, KDQ, KDR, KDS, KDT, KDY, KEA, KED, KEE, KEF, KEG, KEH, KEI, KEL, KEN, KEQ, KER, KES, KET, KEY, KFA, KFD, KFE, KFF, KFG, KFH, KFI, KFL, KFN, KFQ, KFR, KFS, KFT, KFY, KGA, KGD, KGE, KGF, KGG, KGH, KGI, KGL, KGN, KGQ, KGR, KGS, KGT, KGY, KHA, KHD, KHE, KHF, KHG, KHH, KHI, KHL, KHN, KHQ, KHR, KHS, KHT, KHY, KIA, KID, KIE, KIF, KIG, KIH, KII, KIL, KIN, KIQ, KIR, KIS, KIT, KIY, KLA, KLD, KLE, KLF, KLG, KLH, KLI, KLL, KLN, KLQ, KLR, KLS, KLT, KLY, KNA, KND, KNE, KNF, KNG, KNH, KNI, KNL, KNN, KNQ, KNR, KNS, KNT, KNY, KPA,

KPD, KPE, KPF, KPG, KPH, KPI, KPL, KPN, KPQ, KPR, KPS, KPT, KPY, KQA, KQD, KQE, KQF, KQG, KQH, KQI, KQL, KQN, KQQ, KQR, KQS, KQT, KQY, KRA, KRD, KRE, KRF, KRG, KRH, KRI, KRL, KRN, KRQ, KRR, KRS, KRT, KRY, KSA, KSD, KSE, KSF, KSG, KSH, KSI, KSL, KSN, KSQ, KSR, KSS, KST, KSY, KTA, KTD, KTE, KTF, KTG, KTH, KTI, KTL, KTN, KTQ, KTR, KTS, KTT, KTY, KYA, KYD, KYE, KYF, KYG, KYH, KYI, KYL, KYN, KYQ, KYR, KYS, KYT, KYY, SEQ ID NOs 75 to 24014 , KGSH (SEQ ID NO:24049), GKGSH (SEQ ID NO:24050), GKGSKK (SEQ ID NO:24045), GKKPGKK (SEQ ID NO:24046), GKGPSK (SEQ ID NO:24044), GKPSHKP (SEQ ID NO:24043), and GSHKGSHK (SEQ ID NO:24042).

56. The insulin of claim 54, wherein no more than 4 residues are added or deleted from the A-chain and/or the B-chain.

57. The insulin of claim 54, wherein a K residue is present at the N-terminus of the A-chain and/or the B-chain, and/or

wherein no more than three K residues are present at the N-terminus of the A-chain and/or the B-chain, and/or

wherein (i) the tyrosine at A14 is replaced with glutamic acid, and/or (ii) the tyrosine at B16 is replaced with histidine, and/or (iii) the phenylalanine at B25 is replaced with a histidine, and/or

wherein one to three residues selected from residues B20, B21, and B22-B29 of the B-chain, residues A4 or A8 of the A-chain, and residues of an optionally extended polypeptide, are lysine residues, and/or

wherein only one K residue is present within 10 residues of the N-terminus of B-chain.

58. The compound of any one of claims 1-44 and 50-52, wherein X1 comprises the insulin of any one of claims 54-57.

59. The insulin of any one of claims 54-57, wherein an amino group of the side chain(s) of one to four lysine residues is each independently covalently conjugated as described by Formula I of claim 2.

60. The insulin of any one of claims 54-57, wherein the insulin is covalently conjugated as described by Formula I of claim 2,

n'=0 and the C-terminus of Z1a is directly conjugated to the N-terminus of the B-chain of insulin through a peptide bond;

Z1a comprises at least one amino acid selected from K, P, E, G, S, T, A, and R, such that the sequence comprises at least one lysine, at least one proline, and at least one amino acid selected from H, R, A and T; and

the amino group of least one lysine side chain in Z1a is covalently conjugated as described by Formula I.

61. The insulin of any one of claims 54-57, wherein the insulin is covalently conjugated as described by Formula I of claim 2,

Z1a comprises a polypeptide comprising the sequence $(XA_1A_2A_3X)_m$ (SEQ ID NO:24022), wherein:

A_1, A_2, and A_3 are each independently an L- or D-amino acid;

m is an integer in the range of 1 to 4;

each X is K or KP; and

the epsilon amine group of at least one lysine side chain in Z1a is covalently conjugated as described by Formula I.

62. The insulin of any one of claims 54-57, wherein the insulin is covalently conjugated as described by Formula I of claim 2,

Z1a comprises a polypeptide comprising a sequence selected from (XA1X)m(GGGGS)n (SEQ ID NO:24023), (XA1A2X)m (GGGGS)n (SEQ ID NO:24024), (XA1A2A3X)m(GGGGS)n (SEQ ID NO:24025), (XA1X)m(GGGGS)n (XA2X)o (SEQ ID NO:24026), and (XA1A2X)m(GGGGS)n (XA3A4X)o (SEQ ID NO:24027), wherein:

A_1, A_2, A_3, and A_4 are each independently an L- or D-amino acid;

m is an integer in the range of 1 to 4;

n is an integer in the range of 1 to 4;

o is an integer in the range of 1 to 4;

each X is K or KP; and

the epsilon amine group of each lysine side chain of at least one lysine side chain in Z1a is further covalently conjugated as described by Formula I.

63. The insulin of any one of claims 54-57, wherein the insulin is covalently conjugated as described by Formula I of claim 2,

Z1a comprises a polypeptide comprising the sequence $(GX)_m$, wherein:

X is KV;

m is an integer in the range of 1 to 4, and

the epsilon amine group of at least one lysine side chain in Z1a is further covalently conjugated as described by Formula I.

64. The insulin of any one of claims 54-57, wherein the insulin is covalently conjugated as described by Formula I of claim 2,

Z1a comprises a polypeptide comprising a sequence selected from: (GXA1KGEA2XT)m(GGSGSSS)n (GXGXA3GSSSGSSSXT)o (SEQ ID NO:24028), (GXA1ESA2LYL)m (SEQ ID NO:24029), (TXEX)m(GPGS)n (SEQ ID NO:24030), (GXESA1VA)m (KA2K)n (SEQ ID NO:24031), (GXEA1A2)m(GGS)n (TYA3XXT)o (SEQ ID NO:24032), and (TXAXYT)m(TSSS)n (SEQ ID NO:24033), wherein:

each X is KV or KP;

A_1, A_2, A_3 are each independently an L- or D-amino acid;

m is an integer in the range of 1 to 4;

n is an integer in the range of 1 to 4; and

o is an integer in the range of 1 to 4; and

the epsilon amine group of at least one lysine side chain in Z1a is further covalently conjugated as described by Formula I.

65. The insulin of any one of claims 54-57, wherein the insulin is covalently conjugated as described by Formula I of claim 2,

Z1a comprises a polypeptide comprising a sequence selected from (TKPYA1KEVETA2GSGS)m (GGGGS)n (SEQ ID NO:24034), (YTPLEA1KPYSTSYKPYSEA1L)m(GKPTSLEA2FLVEA2LYTKP)n (SEQ ID NO:24035), and (GKEALYLTPLESALYKP)m(TKPLEALYLKPEILSLKPESLA)n(GKPGSSSKPDTSSSGTPKTAAGS)o (SEQ ID NO:24036), wherein:

A_1 and A_2 are each independently an L- or D-amino acid;

m is an integer in the range of 1 to 4;

n is an integer in the range of 1 to 4; and

the epsilon amine group of at least one lysine side chain in Z1a is further covalently conjugated as described by Formula I.

66. The insulin of claim 54, wherein (i) the A- and/or B-chain sequence of the insulin is appended at the N-terminus or C-terminus by KX'K, KX', or X'K wherein X' represents a

continuous sequence of 2, 3, 4, or 5 residues selected from within wild-type A-chain (SEQ ID NO:1) and wild-type B-chain (SEQ ID NO:2), or

(ii) wherein X' is a polypeptide of up to 30 residues with amino acids independently selected from: K, G, S, E, H, E, N, Q, D, A, P, R and C, and

wherein in (i) and (ii) each K residue is optionally and independently covalently conjugated as described by Formula I of claim 2.