back toward 5 mM by the action of insulin. The hormone insulin is secreted from pancreatic beta cells, and when insulin binds to insulin receptors on cells in the body (for example muscle and fat), the cells are stimulated to absorb glucose by translocation of glucose transporters from storage vesicles to the cell surface (GLUT4) (*see, e.g.*, Huang, S.H. et al. *Cell Metabolism*, 5:237-252 (2007)).

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

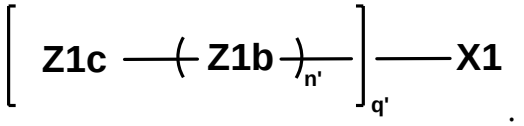
Glucose sensors and glucose sensing insulin analogs are known in the art. *See,* e.g., WO 2016/179568 A1 and WO 2021/202802 A1. However, there is a need in the art to develop glucose sensors and glucose sensing insulins that have improved properties, such as binding to the insulin receptor and being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

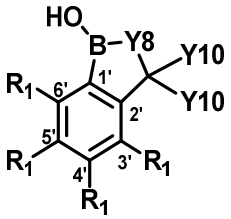
Thus, there is an unmet medical need for novel compounds, such as compounds which bind glucose and may be utilized in glucose-responsive insulin analogues/conjugates, that can control blood glucose levels.

Here, according to certain embodiments, we disclose glucose sensors and glucose sensing insulin analogs that have improved properties, such as prolonged terminal half-life and/or a decrease in clearance, improved affinity for the insulin receptor, and/or improved activation of the insulin receptor.

SUMMARY OF THE DISCLOSURE

In a first example, a compound comprises one or more diboronates of the following formula, or a stereoisomer or a mixture of stereoisomers, or pharmaceutically acceptable salt thereof:





(F7)

One R_1 of F7 represents (C=O)---*, wherein ---* represents the attachment point to the rest of Z1c. Each remaining R_1 can independently be 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. Y8 can be O or NR, wherein R is a C_1-C_6 alkyl group or H. Each Y10 is independently selected from H, CH_3, F, and CF_3, wherein for at least one F7 at least one Y10 is not H.

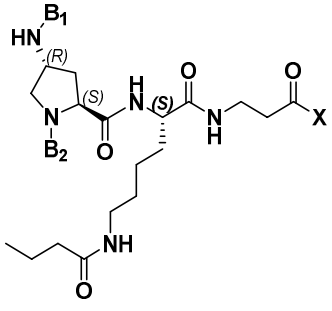
In a second example, a compound is selected from the group consisting of a polypeptide comprising an A-chain and a B-chain, wherein the A-chain comprises a sequence selected from 1, 24051, and 24052. The B-chain can comprise a sequence selected from SEQ ID NOs 24063, 25228, 25229, 25232, 25305, 25308, 25312, 25236, 25095, and 25380-25397.

In a third example, a pharmaceutical composition comprises at least one compound or a pharmaceutically acceptable salt thereof according to any one of the first and second examples.

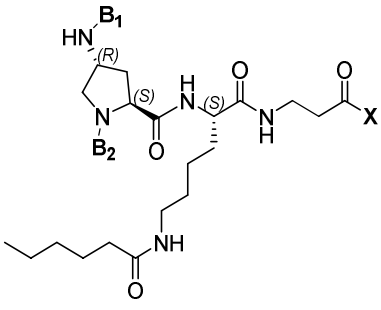
In a fourth example, the present disclosure includes a compound of the following formula, or a stereoisomer or a mixture of stereoisomers, or pharmaceutically acceptable salt thereof:

Z1c-Linker.

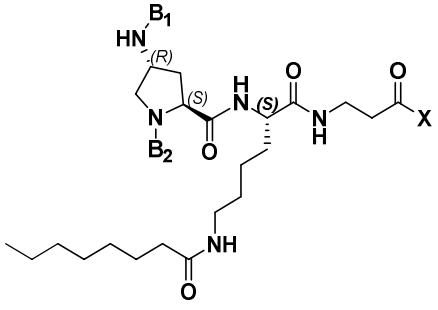
The Z1c-Linker can be selected from:



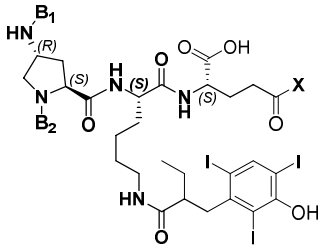
FFL-1



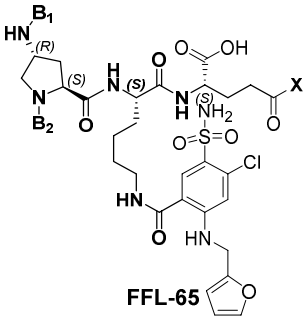
FFL-2



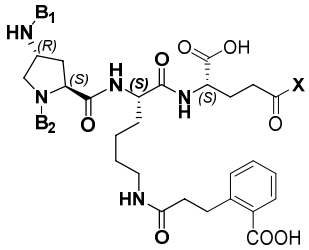
FFL-3



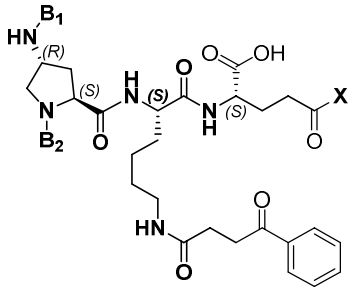
FFL-64



FFL-65

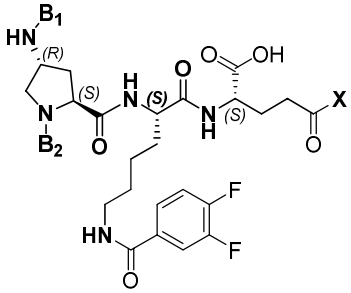


FFL-66



FFL-67

, or



FFL-68

.

The group X of the foregoing formulae can be selected from a leaving group, NH_2, and H. The groups B_1 and B_2, which may be identical or different, each independently represents an aromatic boron-containing group.

In a fifth example, the present disclosure includes a polypeptide comprising an A-chain and a B-chain, wherein the A-chain comprises a sequence selected from 1, 24051, and 24052. The B-chain can comprise a sequence selected from 25000 – 25397.

In a sixth example, the present disclosure includes a compound having agonist potency for an insulin receptor comprising at least one aromatic boron-containing group having agonist potency for an insulin receptor, or a pharmaceutically acceptable salt thereof. The compound can have a first EC50 potency for activating the insulin receptor at a first glucose concentration and a second EC50 potency for activating the insulin receptor at a second glucose concentration. When the first glucose concentration is 5.6 mM and the second glucose concentration is 16.7 mM, the compound has an insulin receptor agonist potency ratio of the first EC50 to the second EC50 of about 1.2 to about 20, such as about 1.5 to about 15, about 2 to about 14, about 2.5 to about 13, about 2.5 to about 12, about 2.5 to about 11, about 2.5 to about 10, about 2.5 to about 9, about 2.5 to about 8, about 2.5 to about 7, about 2.5 to about 6, about 2.5 to about 5, or about 2.5 to about 4.5.

In a seventh example, the present disclosure includes a compound having agonist potency for glucose comprising at least one aromatic boron-containing group having binding affinity for glucose, or a pharmaceutically acceptable salt thereof. When administered at a dose of 30 nmol/kg to a first group of rats with a first glucose infusion rate to provide a blood glucose

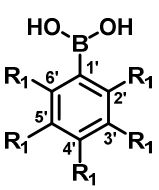
concentration of 100 mg/dL and to a second group of rats with a second glucose infusion rate to provide a blood glucose concentration of 200 mg/dL, the compound provides a relative glucose infusion rate difference (mg/kg/min.min) of about 1 to about 2500, about 1 to about 2000, about 1 to about 1500, about 100 to about 1500, and about 1000 to about 1500, and a relative glucose infusion rate ratio of about 0.1 to about 5, about 0.2 to about 4.5, about 0.5 to about 4, about 0.5 to about 3.5, about 1 to about 3.5, about 1.5 to about 3.5, or about 2 to about 3.

In an eighth example, the present disclosure includes compound according to any one of the previous examples or a pharmaceutically acceptable salt thereof, for use as a medicament.

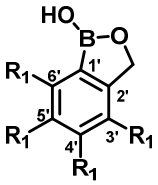
In a ninth example, the present disclosure incudes a method of treatment or prevention of diabetes, impaired glucose tolerance, hyperglycemia or metabolic syndrome. The method comprises administering to a subject in need thereof a compound of any one of the foregoing first, second or fifth through eighth example, or a pharmaceutical composition according to the third example.

In a tenth example, the present disclosure incudes a compound, a use of the compound, a method of administering the compound, or a device or formulation comprising the compound according to any one of the foregoing first, second or fifth through eighth example, or a pharmaceutical composition according to the third example. The disclosure includes the use or the method in the treatment or prevention of diabetes, impaired glucose tolerance, hyperglycemia or metabolic syndrome. The disclosure includes the manufacture of a medicament comprising such compound. The disclosure includes the use of such compound as a therapeutic agent for the treatment of diabetes or obesity, for control of blood sugar levels, or for control of release of a drug. The disclosure includes the method comprises administering to the subject the compound as a therapeutic or prophylactic agent. The disclosure includes the use of a compound according to any one of the fourth example as an intermediate in the synthesis of a drug substance or a therapeutic of a prophylactic compound.

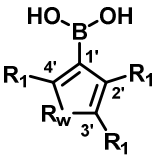
In an eleventh example, the present disclosure incudes a compound comprising at least one diboronate, wherein the diboronate comprises at least two aromatic boron-containing groups, wherein at least one aromatic boron-containing group is covalently attached to the compound and selected from F3-F11, and the other aromatic boron-containing group is covalently attached to the compound and optionally selected from F1-F11 or a boronic acid,



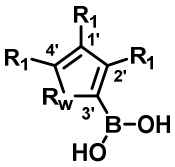
(F1)



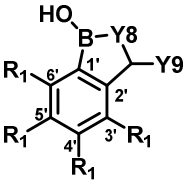
(F2)



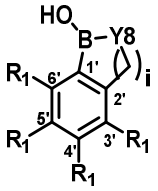
(F3)



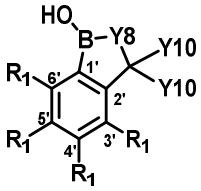
(F4)



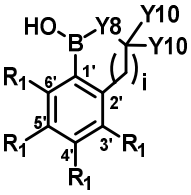
(F5)



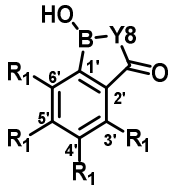
(F6)



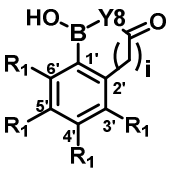
(F7)



(F8)

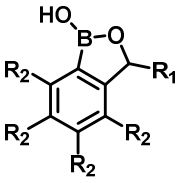


(F9)



(F10)

, and



(F11)

.

At least one R1 in each of F1-F11 is covalently attached to the compound. Each remaining R_1 and R_2 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 Formula F6, when Y8 is O, i is 1, 2, 3, 4, or 5; or i is 2, 3, 4, or 5; and none, one, or two R_1 represents F, CI, CF_2, CF_3, SF_5, OCF_3, SO_2CH_3 and/or SO_2CF_3; or when Y8 is NR, R is an alkyl group or H, and i is 1, 2, 3, 4, or 5. For Formulae F5 and F7-F10, when Y8 is O, i is 1, 2, 3, 4, or 5; or when Y8 is NR, R is an alkyl group or H, and i is 1, 2, 3, 4, or 5; Y9 is CH_3, F, CF_3, CHF_2, or OCH_3; and each Y10 is independently selected from H, CH_3, CH_2CH_3, CH_2CH_2OH, F, CF_3, CHF_2, and OCH_3, with the proviso that at least one Y10 is not H.

In a twelfth example, the present disclosure incudes a tautomer, stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt, or hydrate, or isotopic derivative thereof of the compound according to the eleventh example.

In a thirteenth example, the present disclosure incudes 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. X1 comprises:

(i) NH_2 or OH;

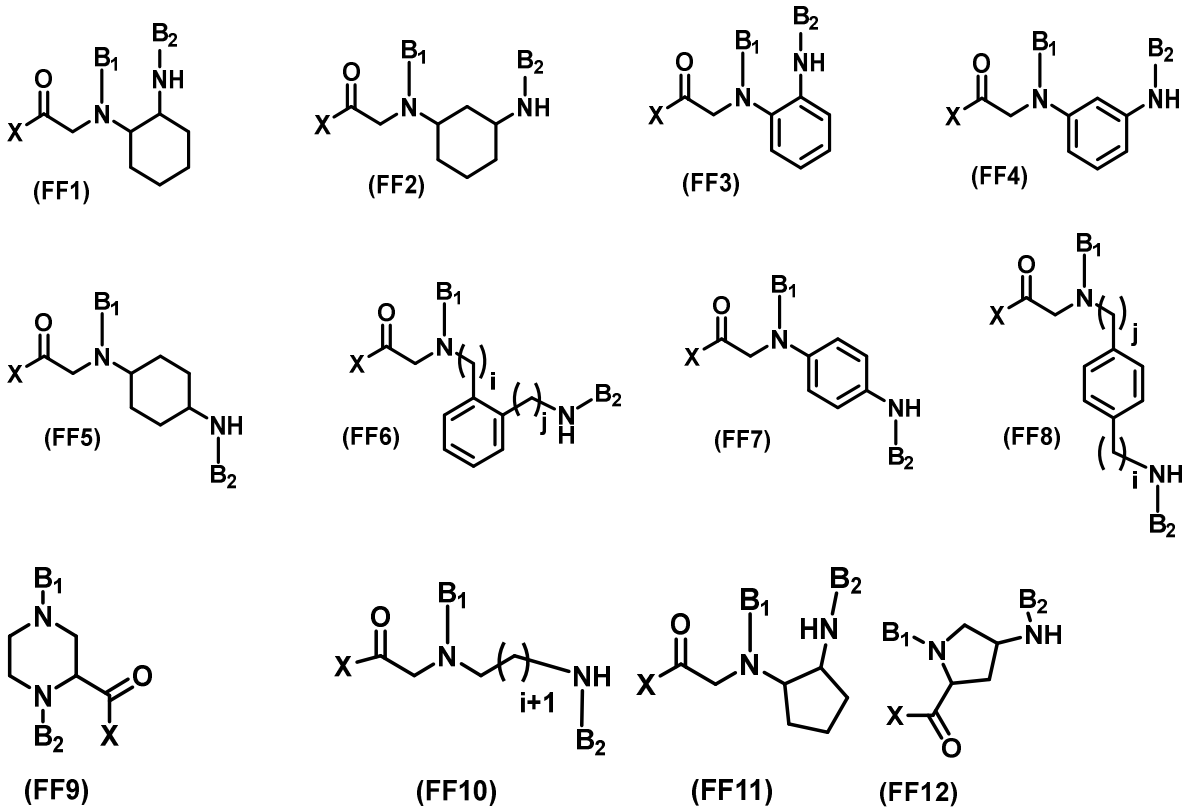
(ii) a drug substance comprising an amine;

i is 1; and

wherein at least one primary or secondary amine in FF1-FF223 and FF225-231 is optionally covalently conjugated to B_6.

In a fourteenth example, the present disclosure incudes a composition or a mixture comprising at least one compound of any one of the eleventh, twelfth, or the thirteenth example, 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. The disclosure includes a method of administering such compound to a human subject as a therapeutic or prophylactic agent. The disclosure includes a method of making such a compound, wherein the method comprises at least one alkylation and/or amidation step. The disclosure includes a method of treating a subject by administering a device or formulation comprising such a compound. The disclosure includes 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 such a compound.

In a fifteenth example, the present disclosure incudes a compound selected from Formulae FF1-FF231, wherein Formulae FF1-FF48 are:



each remaining R_1 is H;

Y8 is O; and

i is 1; and

wherein at least one primary or secondary amine in FF1-FF223 and FF225-FF231 is optionally covalently conjugated to B_6; and

when X is an amine in any one of Formulae FF1 to FF223 and FF225-FF231, X is optionally acetylated or alkylated.

In a sixteenth example, the present disclosure incudes 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)

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

$X_{aa}X_{bb}X_{cc}X_{dd}$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: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

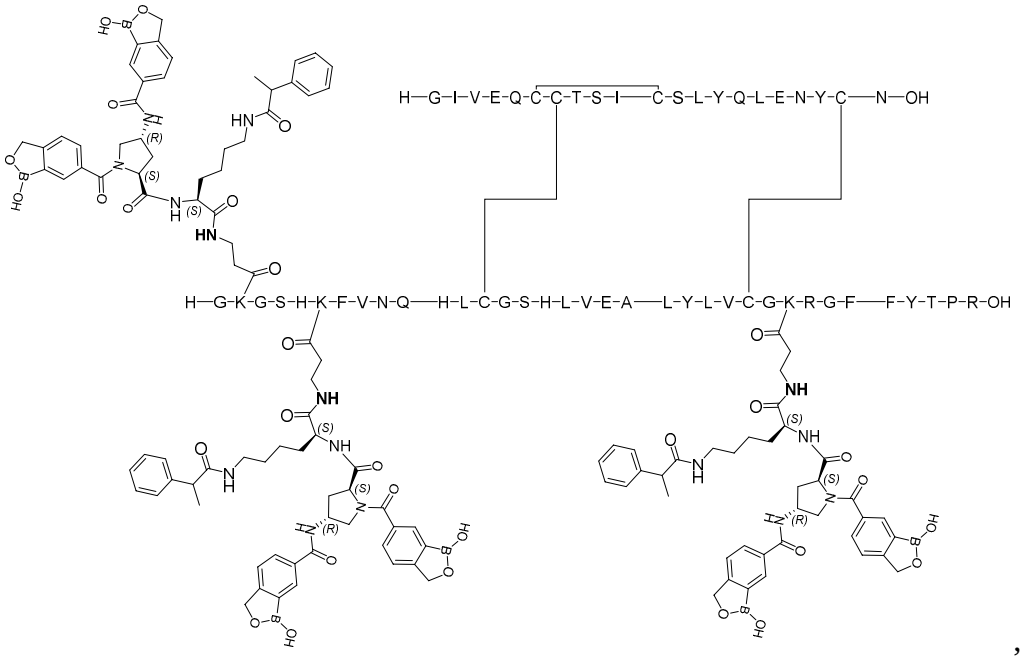
(v)

$X_{aa}X_{bb}X_{cc}X_{dd}KX_{ee}X_{ff}X_{gg}X_{hh}X_{ii}X_{jj}KX_{kk}X_{ll}X_{mm}X_{nn}QHLCGSHLVEALYLVCX_{oo}X_{pp}X_{qq}GFFYT X_{rr}X_{ss}X_{tt}X_{uu}X_{vv}X_{ww}$ (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.

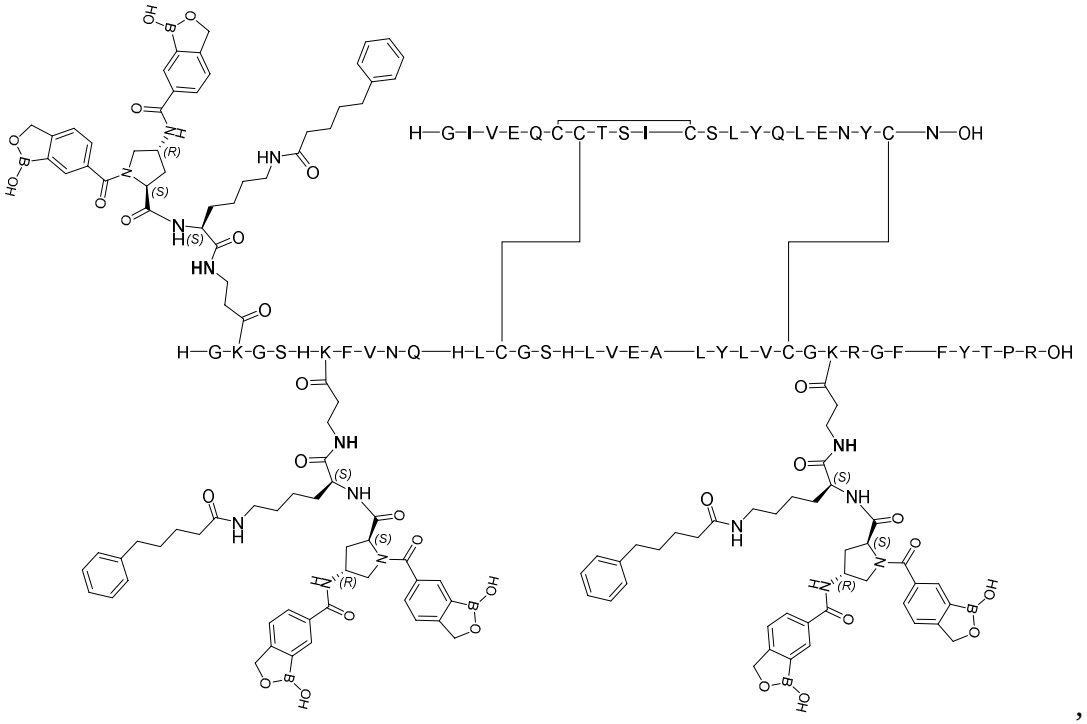
In an aspect, there is provided a compound selected from:

Example 1A:



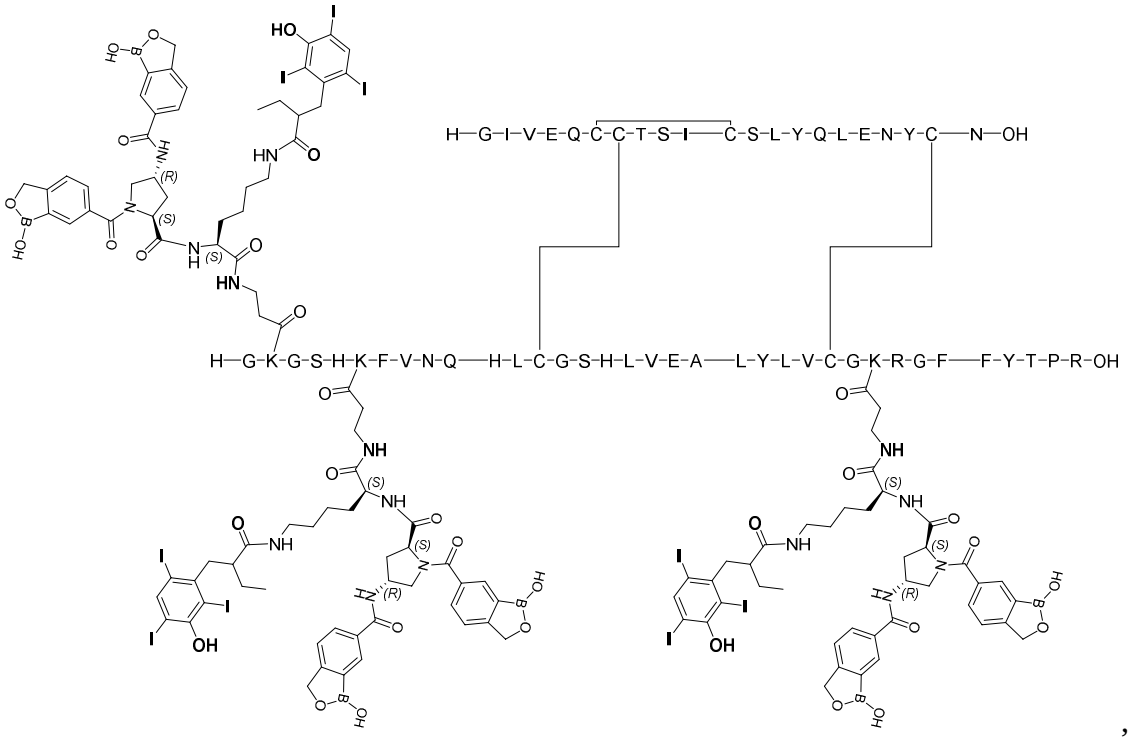
,

Example 2A:



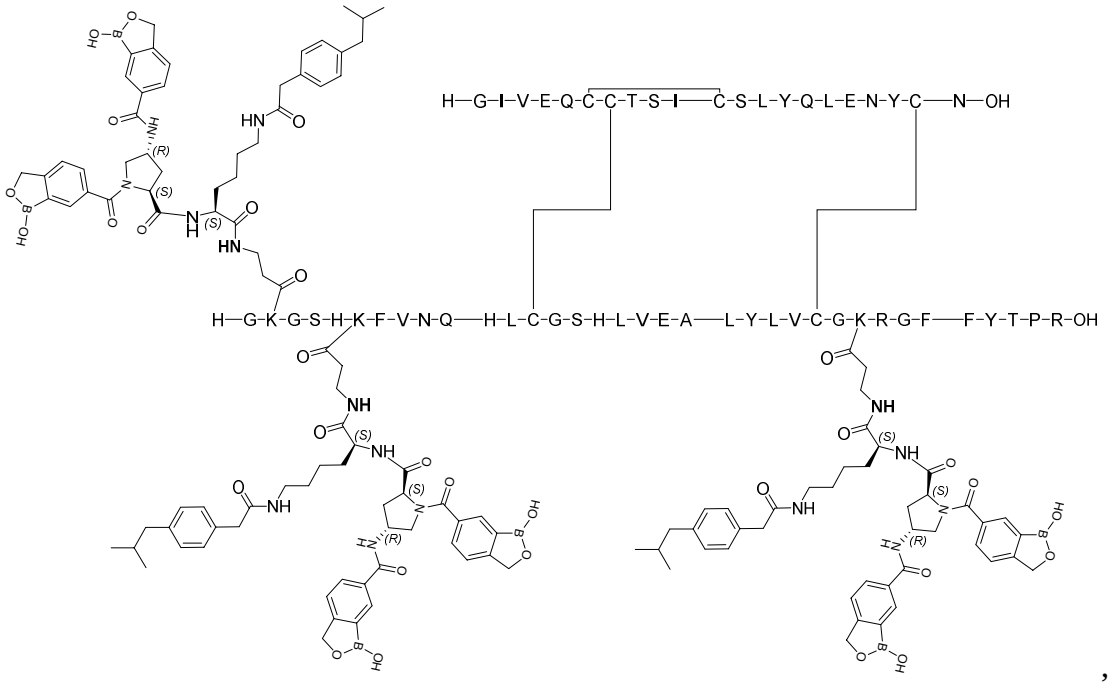
,

Example 3A:



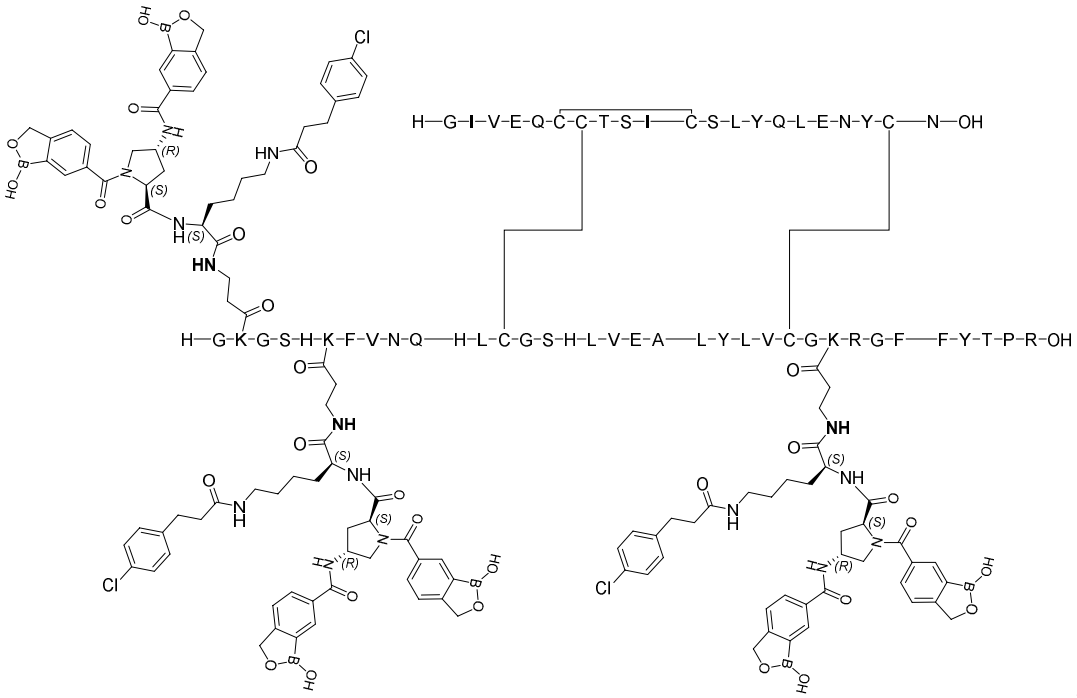
,

Example 4A:



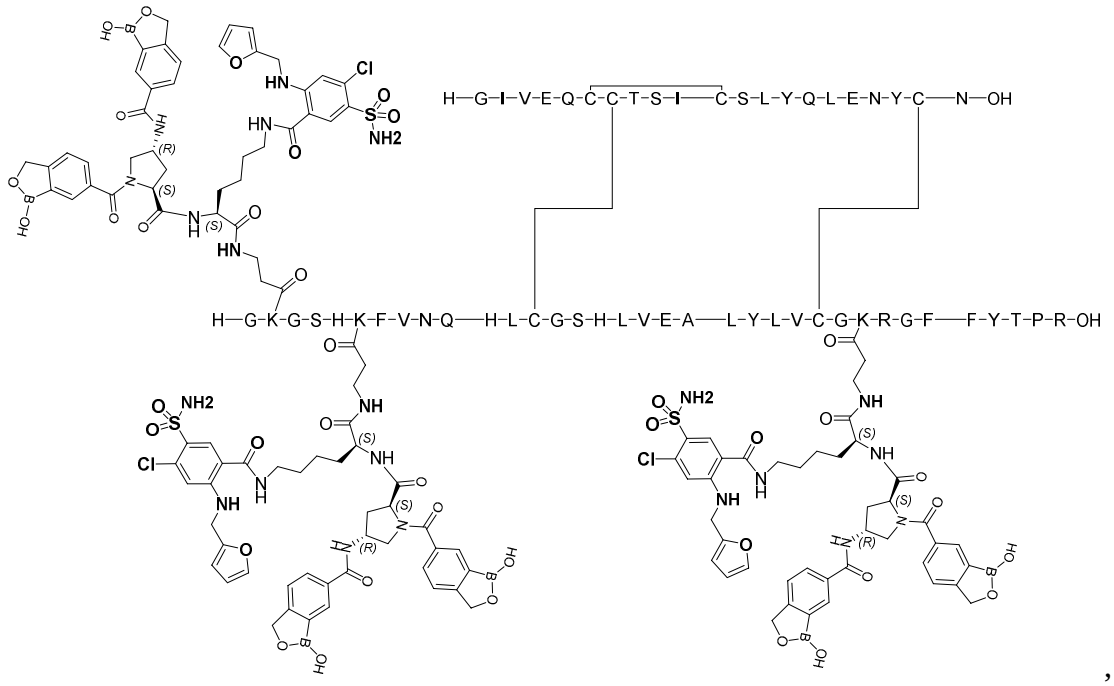
,

Example 5A:



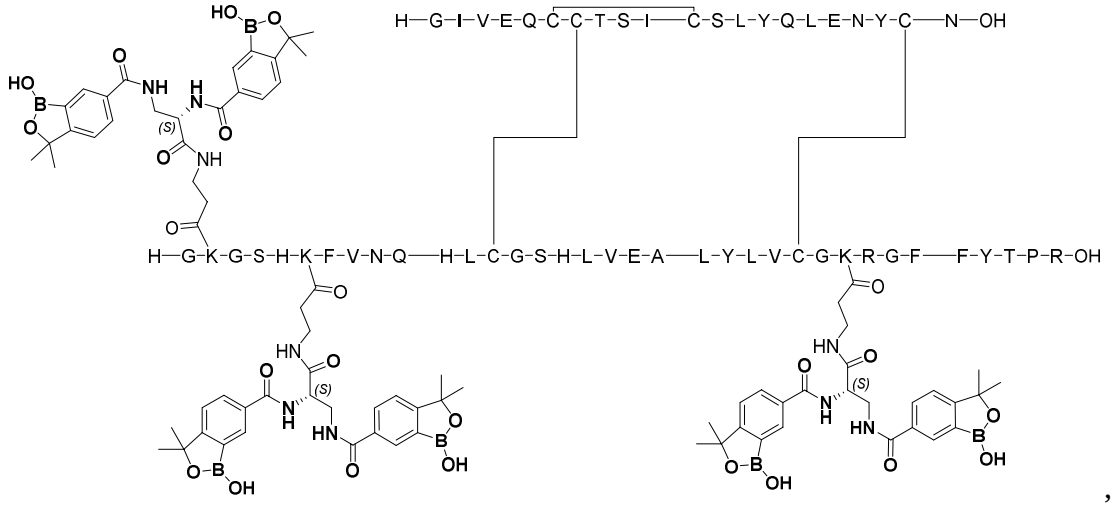
,

Example 6A:



,

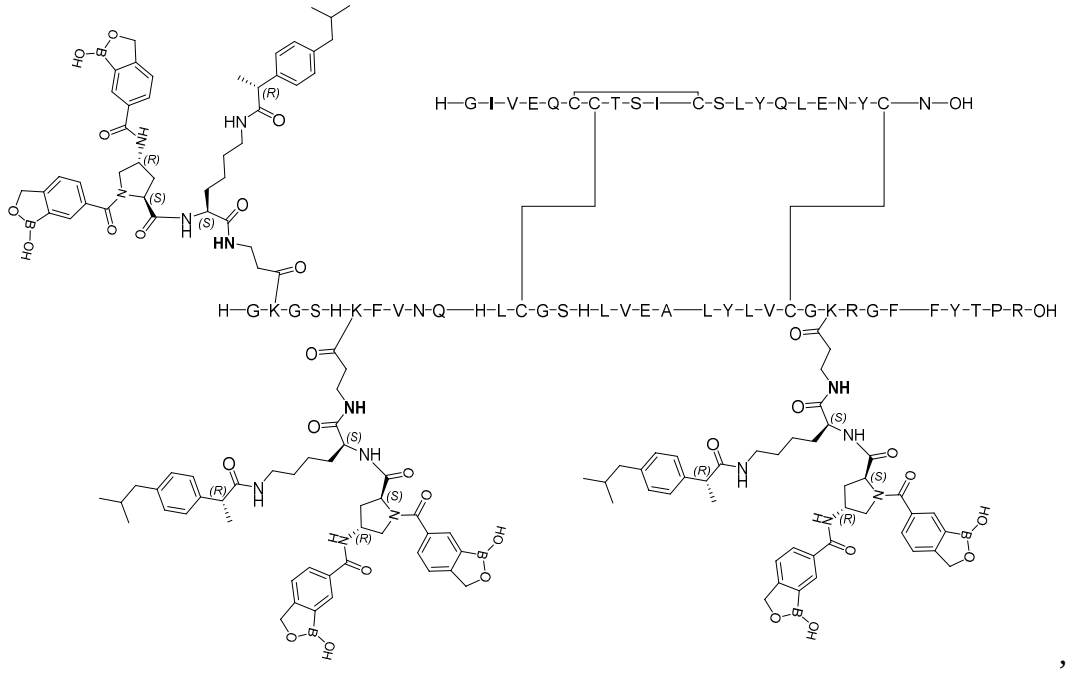
Example 7A:



,

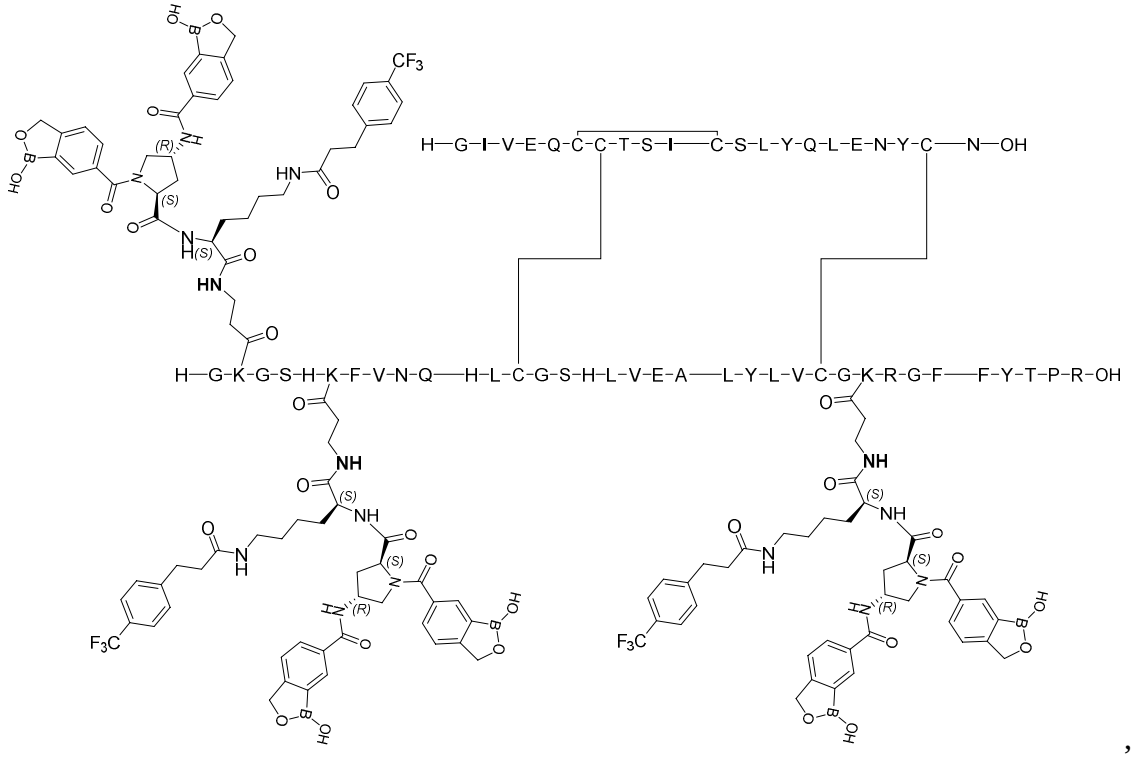
5

Example 8A:



,

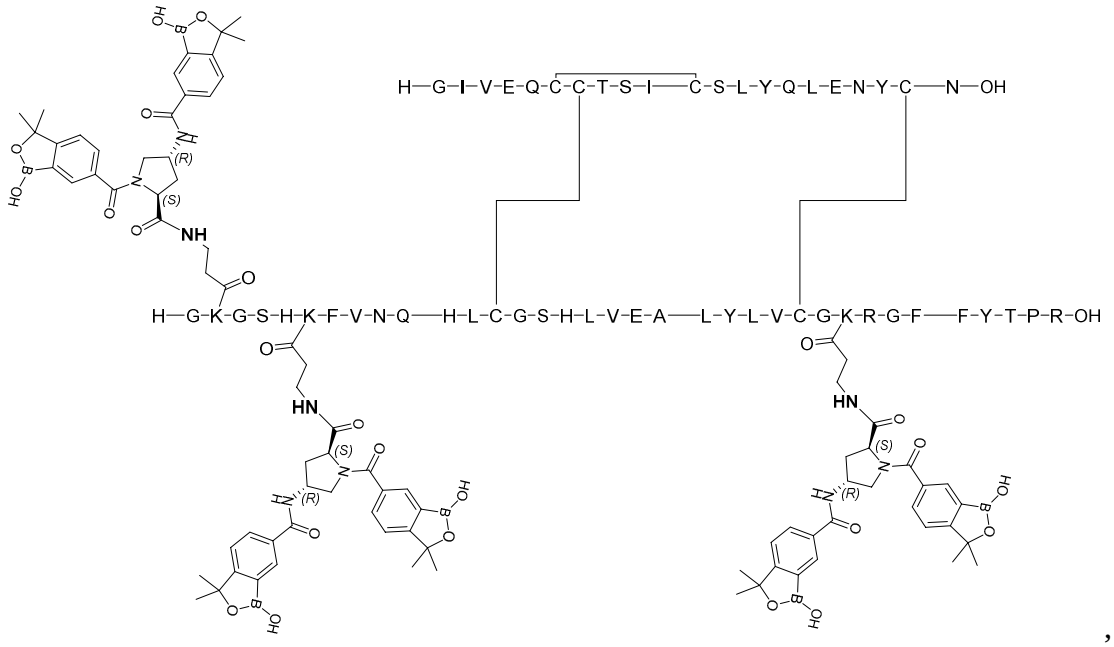
Example 9A:



,

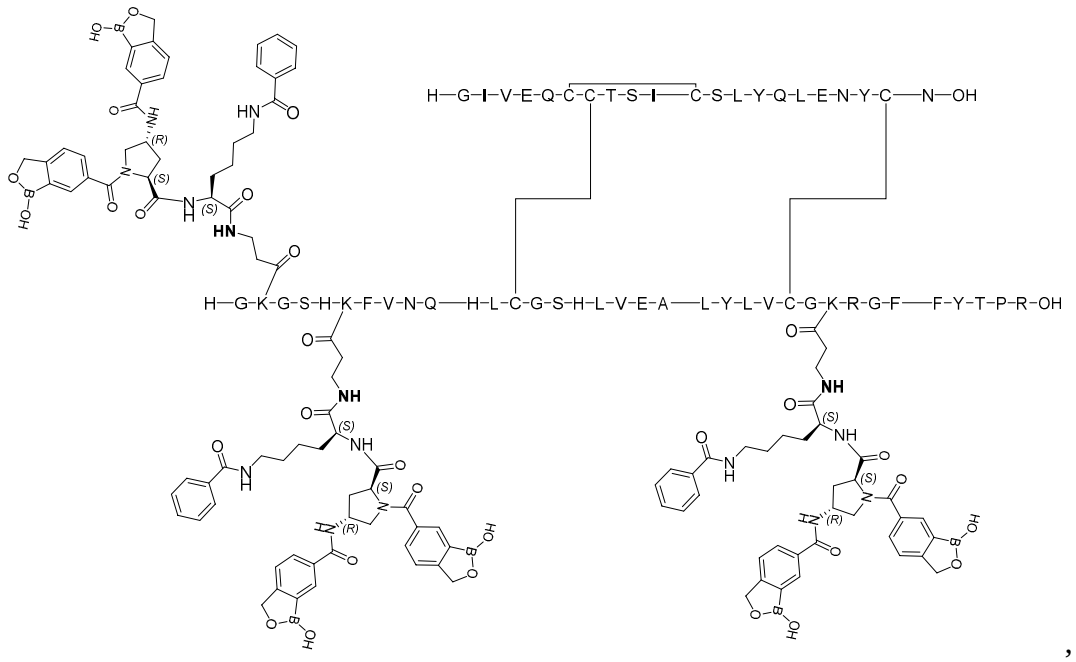
5

Example 10A:



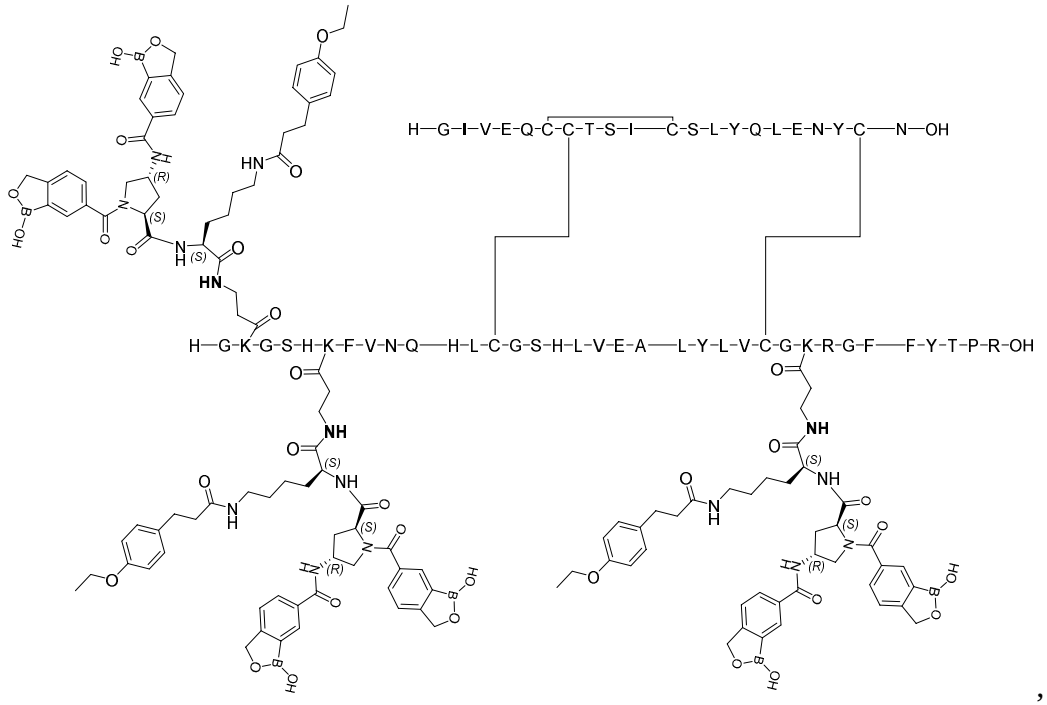
,

Example 11A:



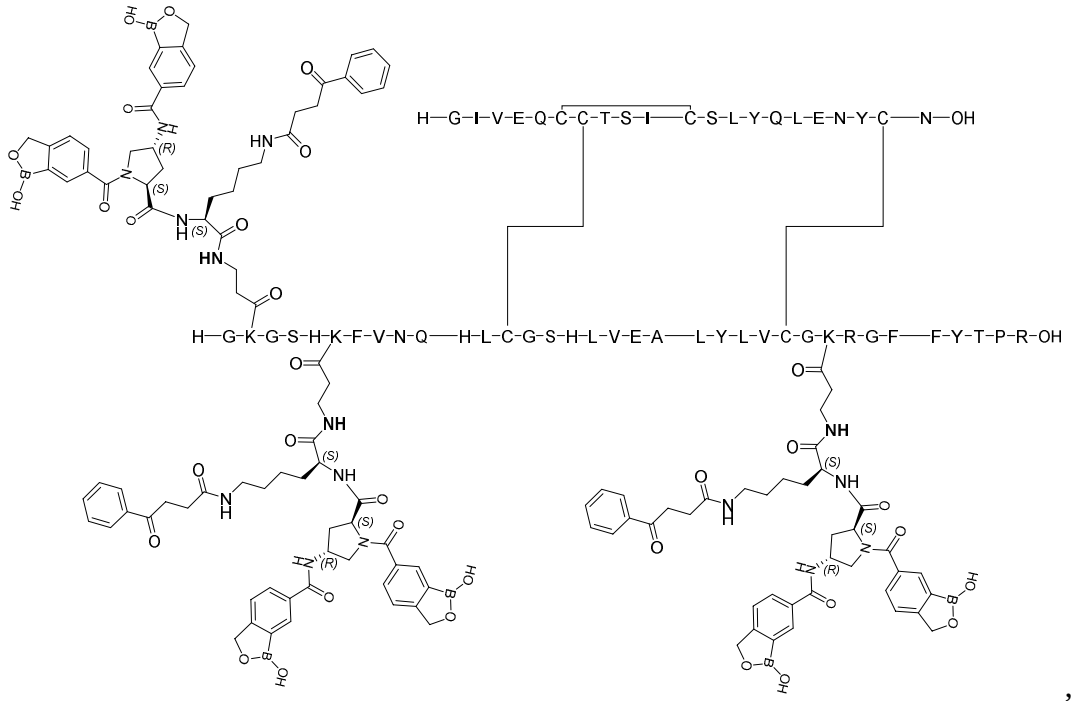
5 ,

Example 12A:



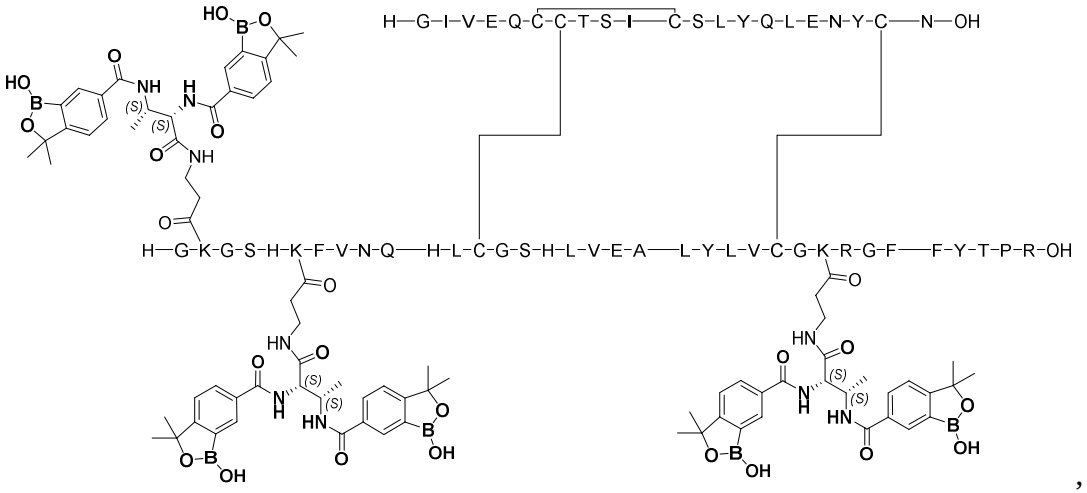
,

Example 13A:



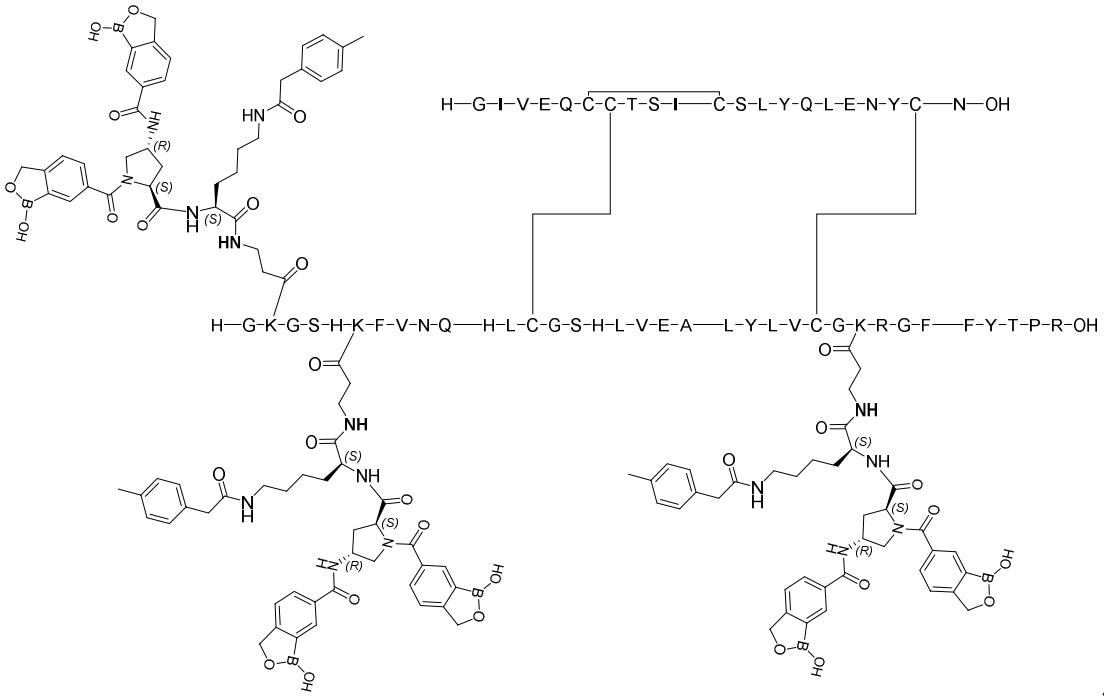
,

Example 14A:



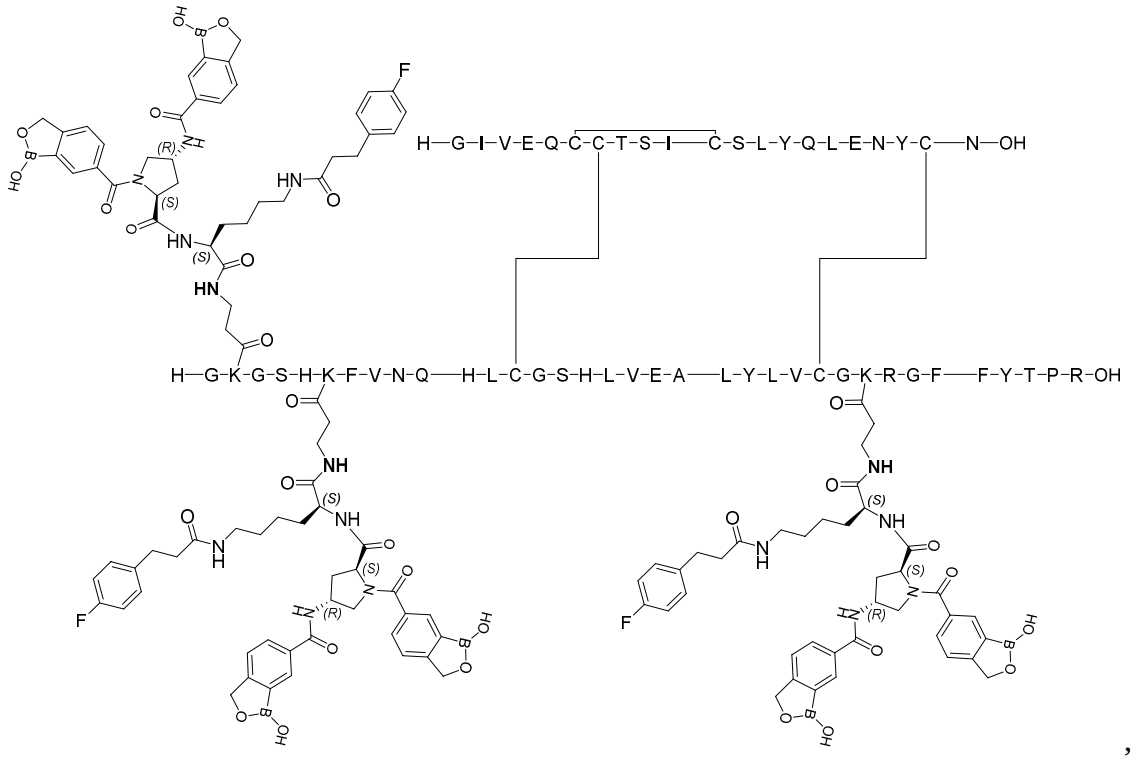
,

Example 15A:



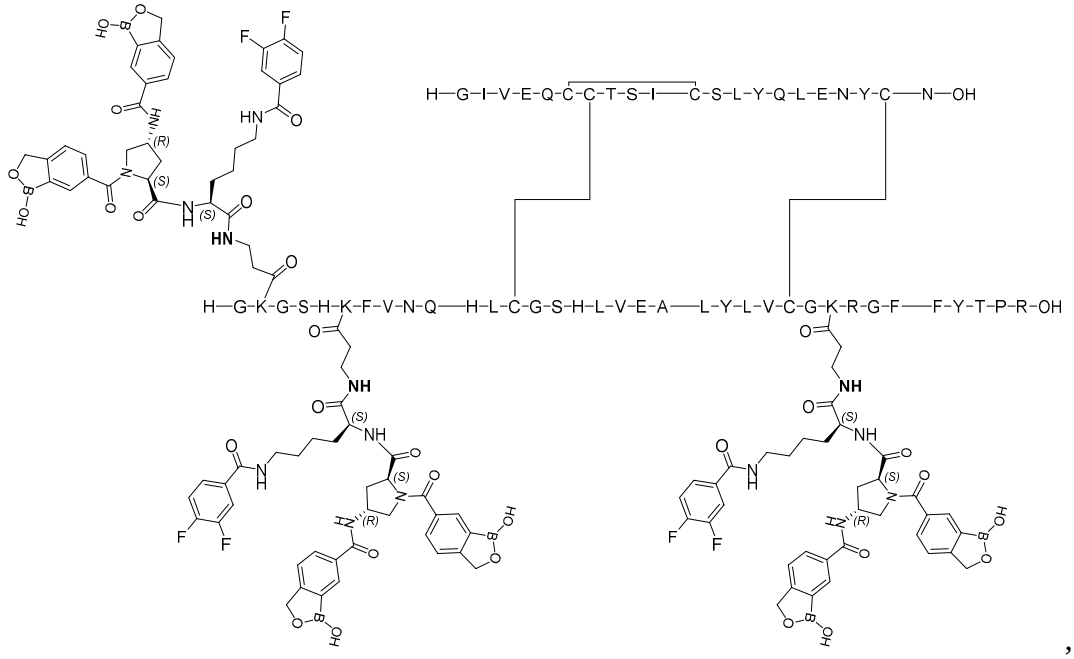
,

Example 16A:



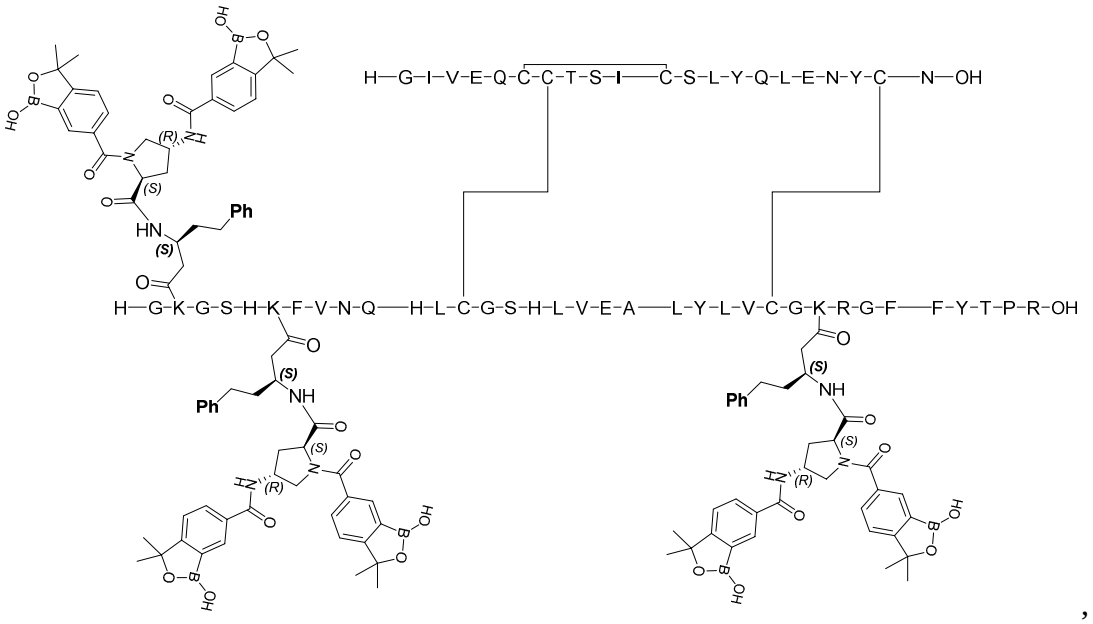
,

Example 17A:



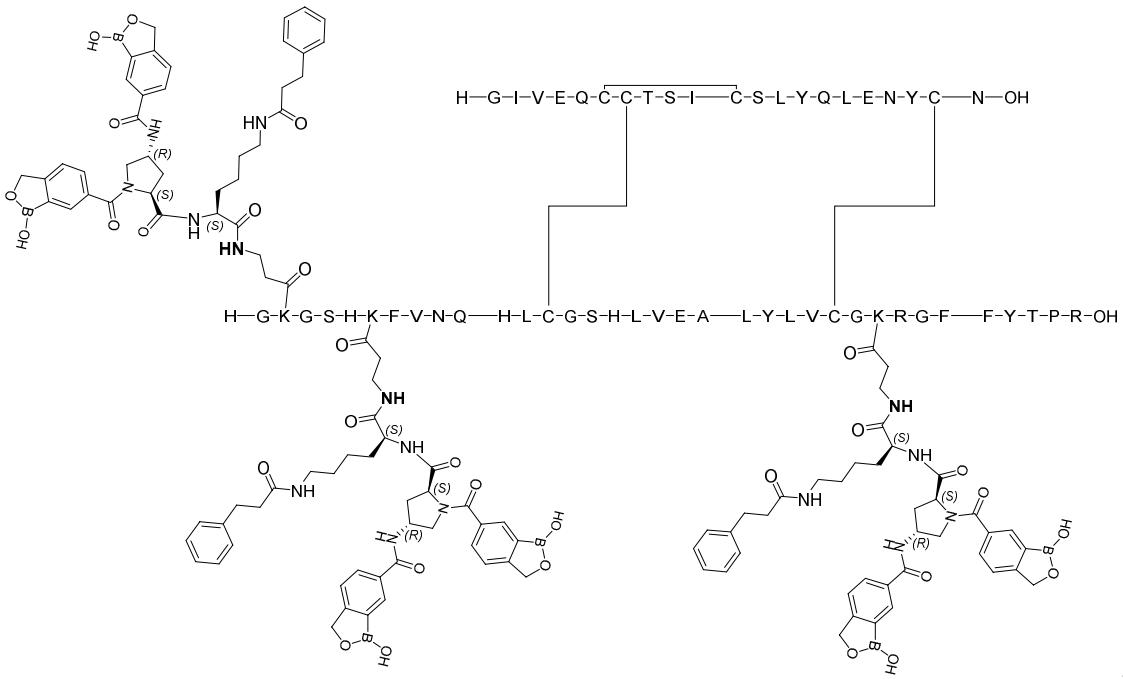
,

Example 18A:



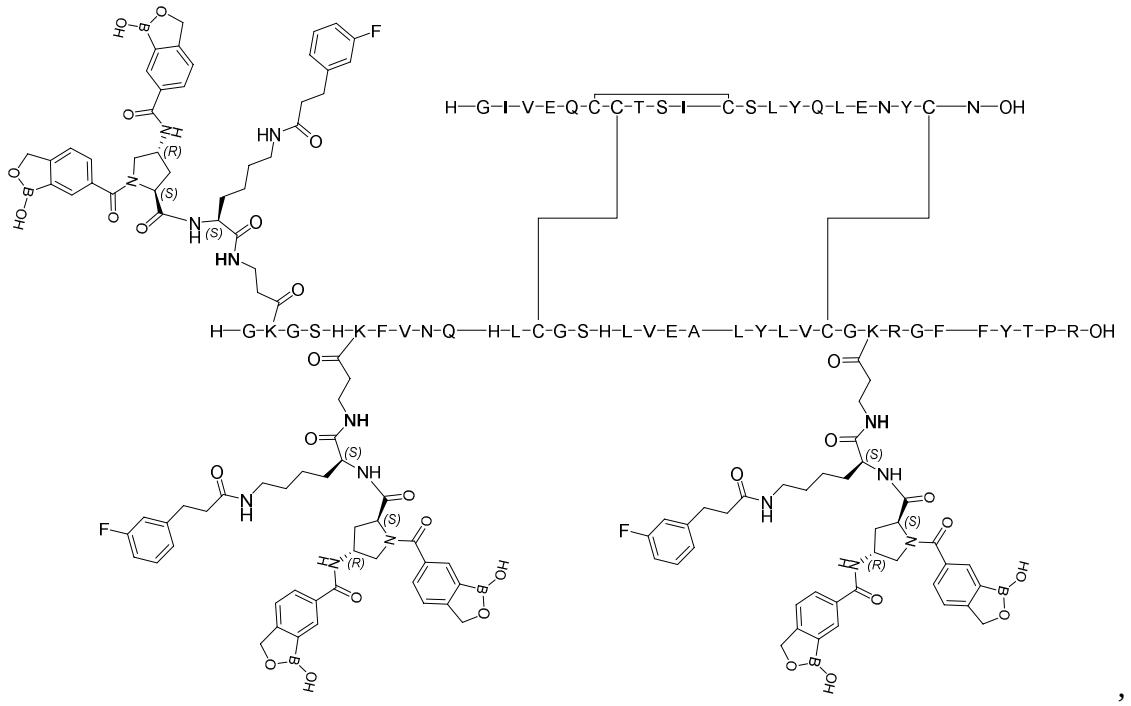
,

Example 19A:



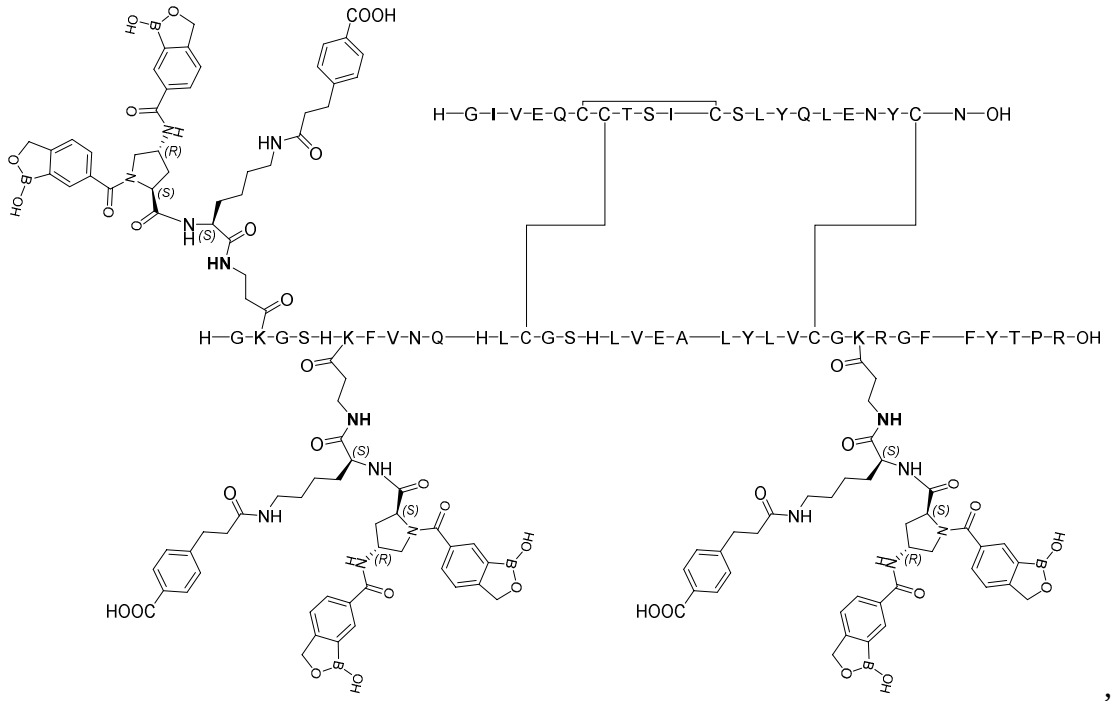
,

Example 20A:



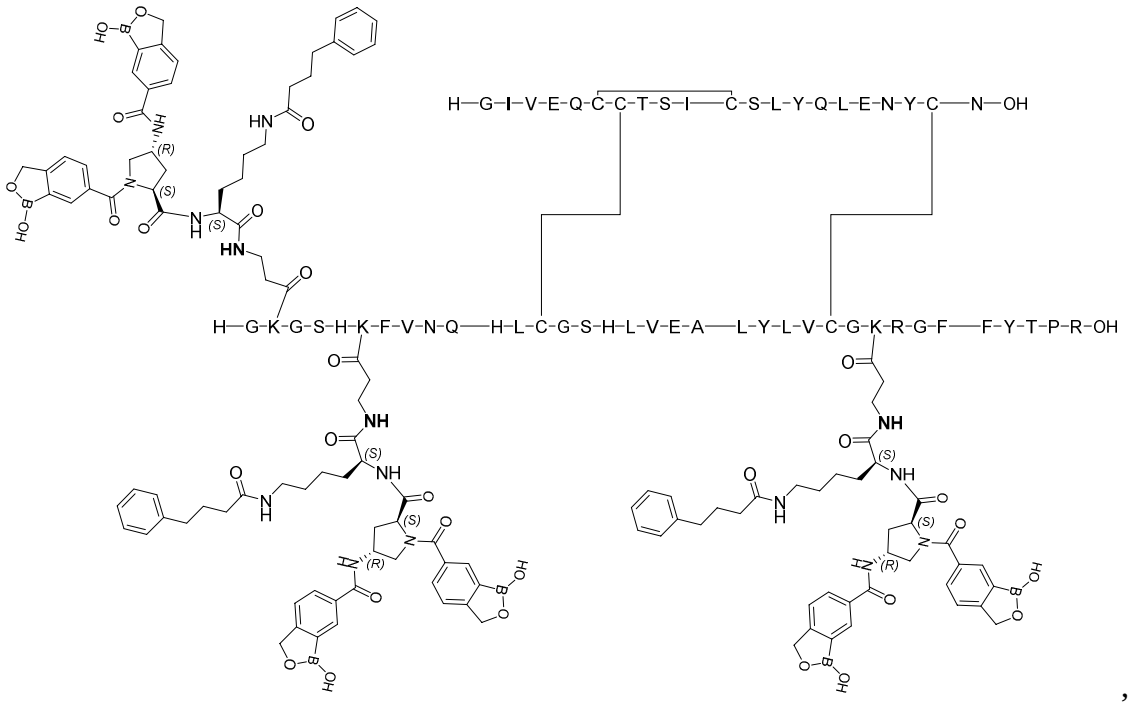
,

Example 21A:



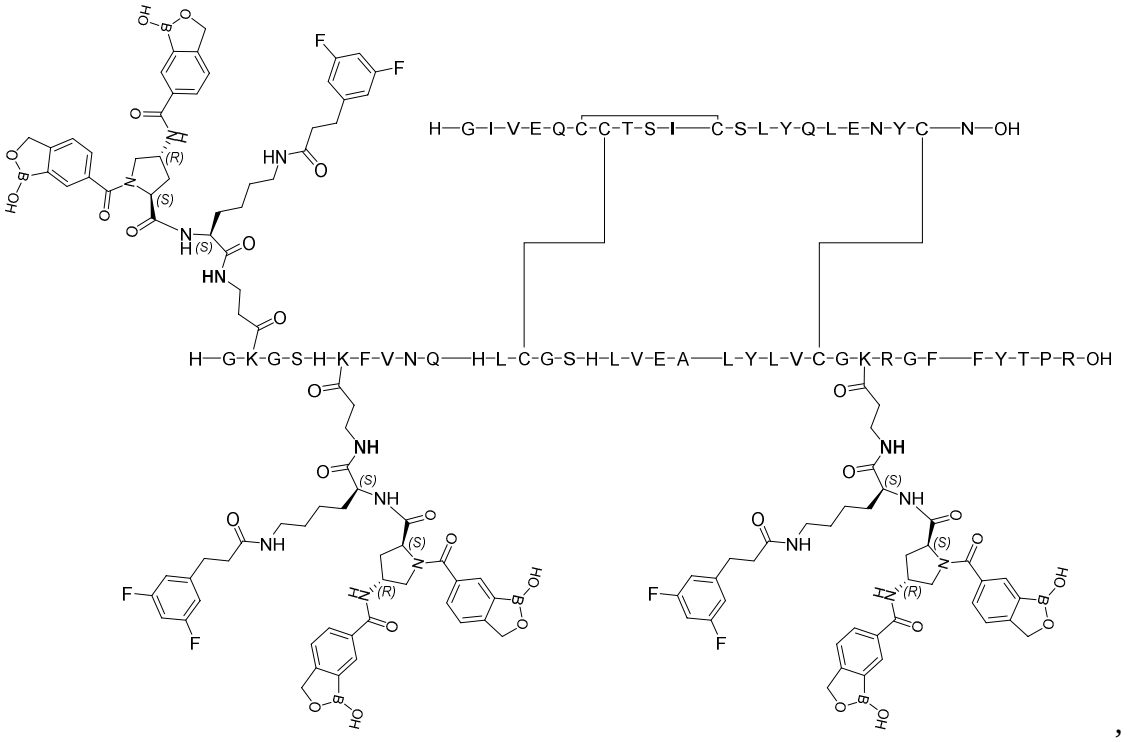
,

Example 22A:



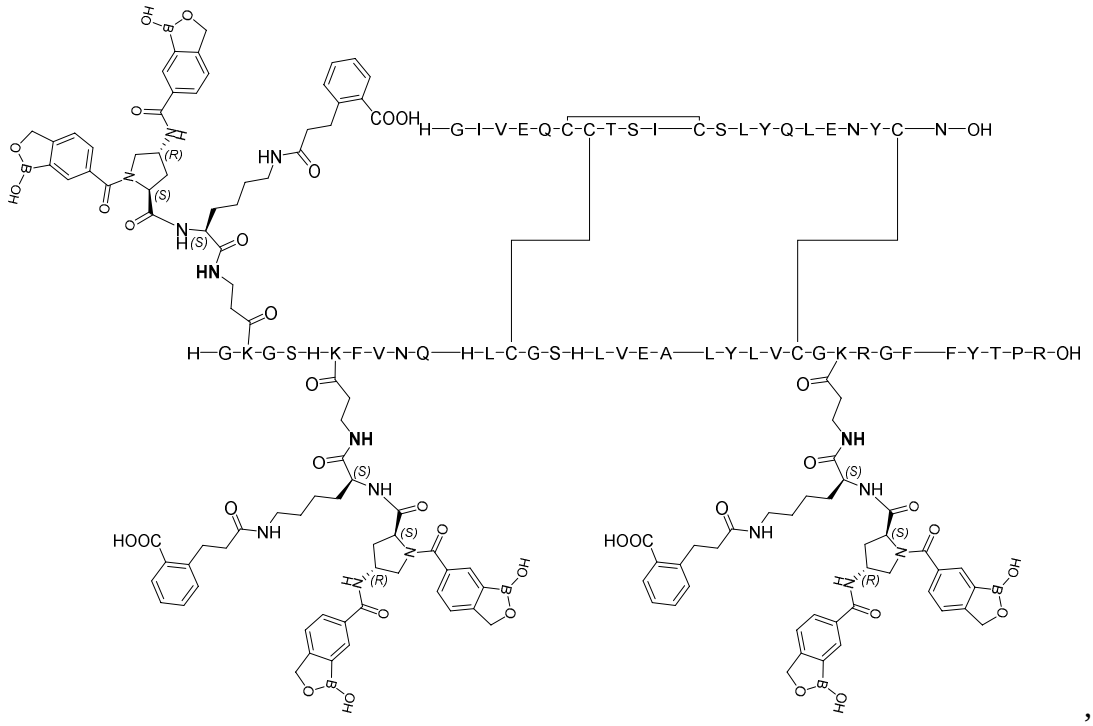
,

Example 23A:



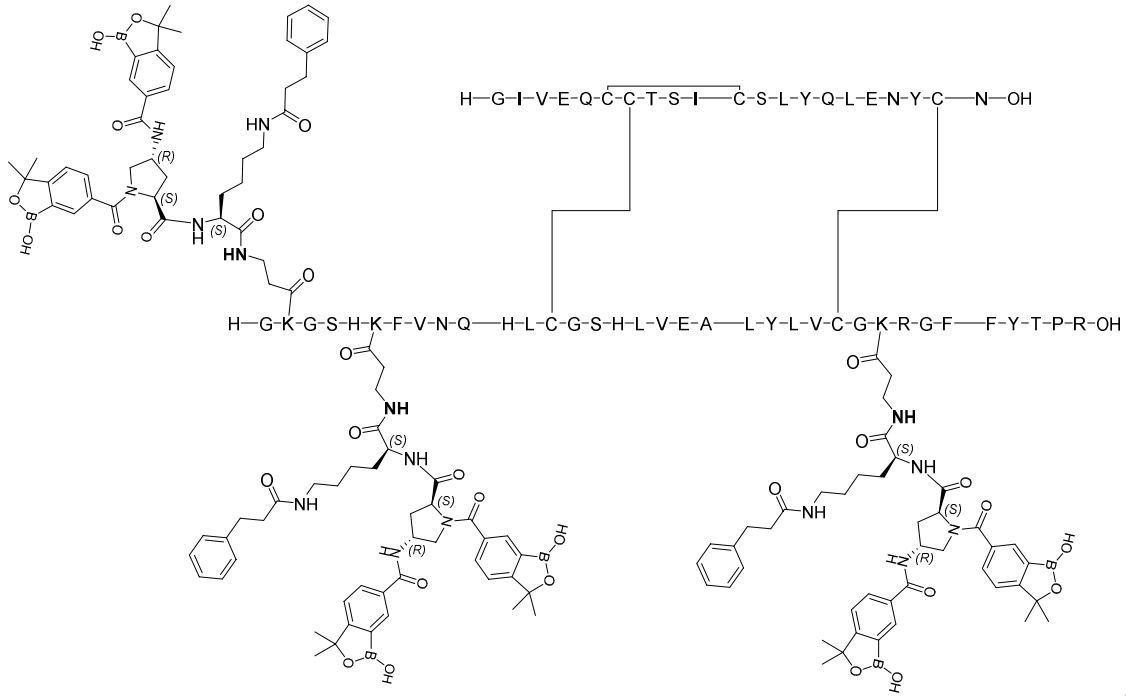
,

Example 24A:



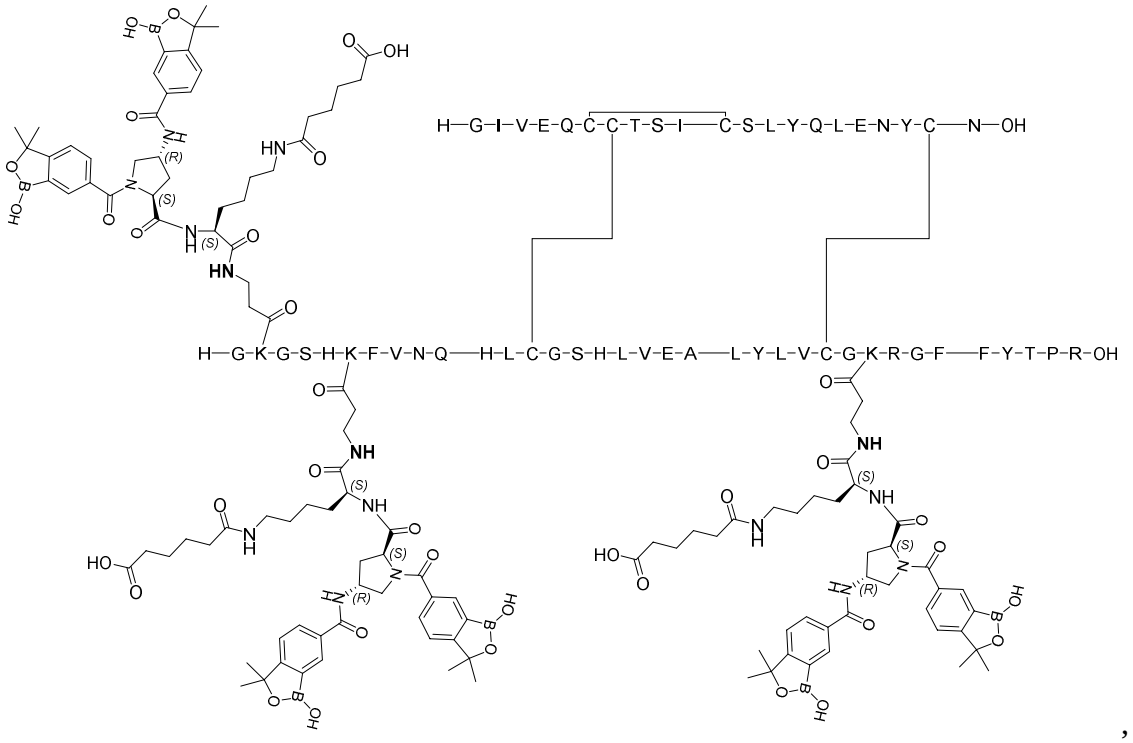
,

Example 25A:



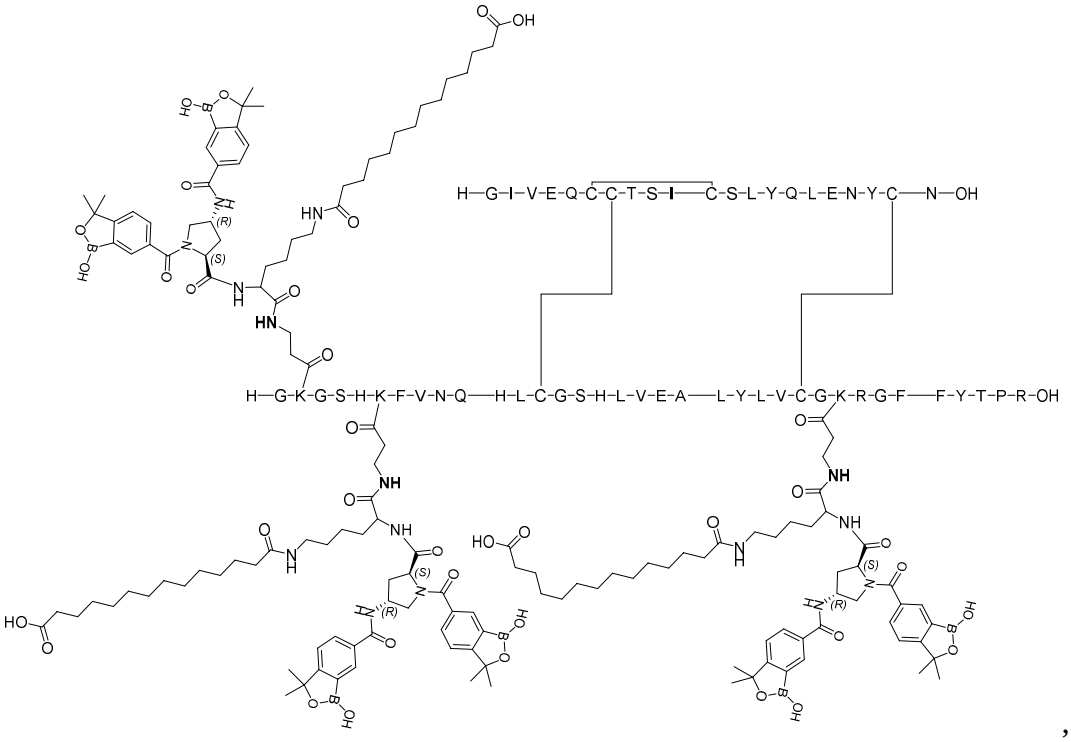
,

Example 26A:



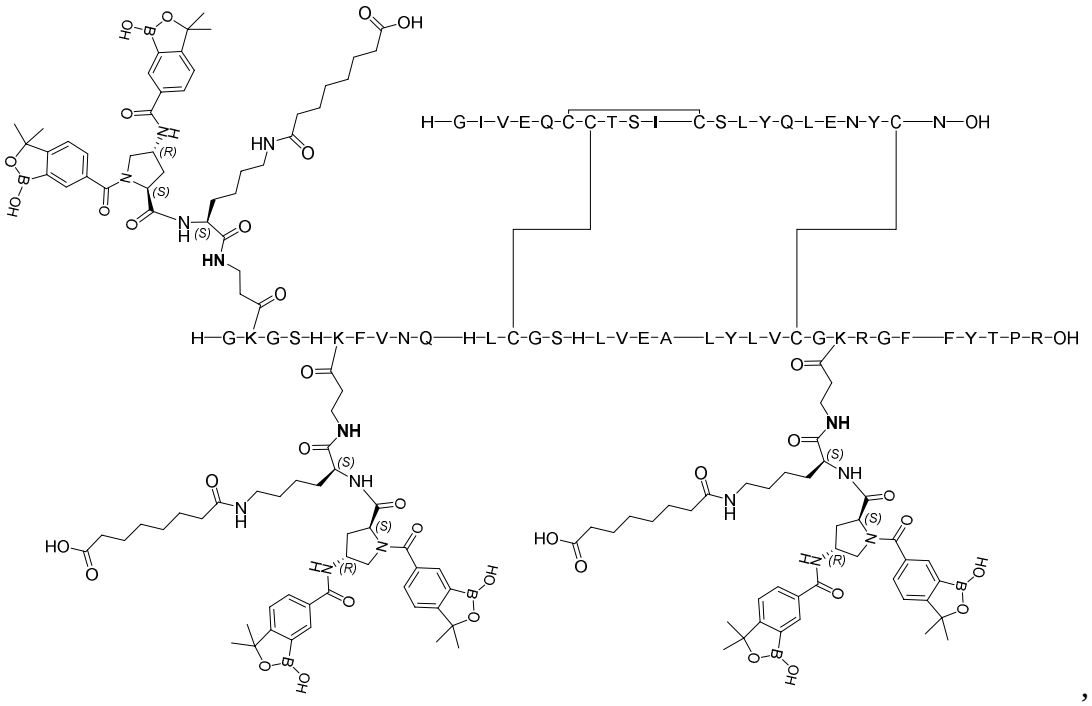
,

Example 27A:



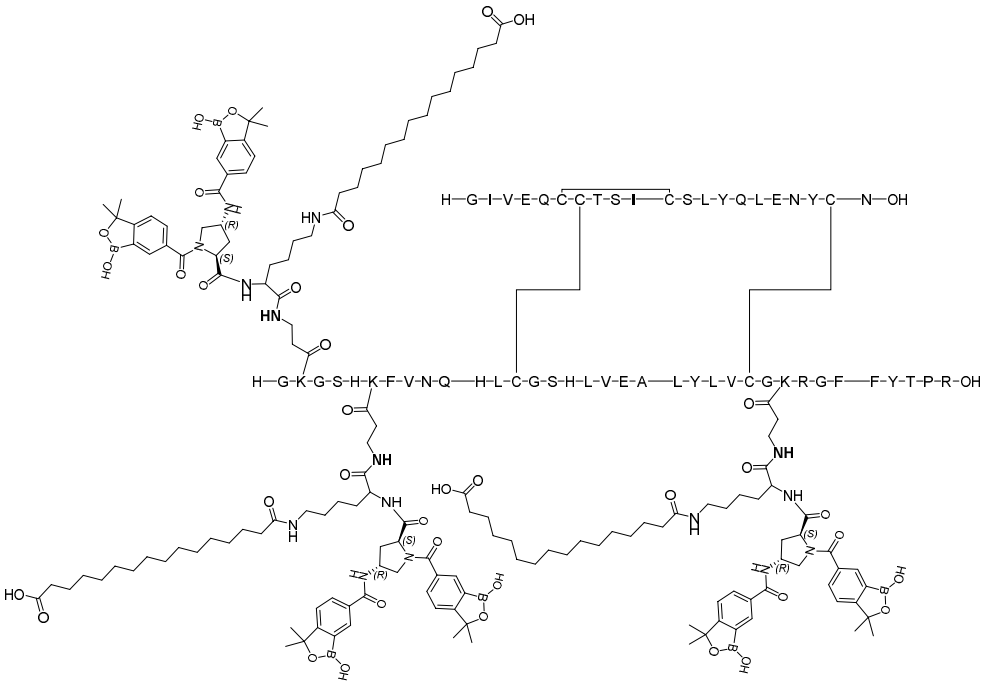
,

Example 28A:



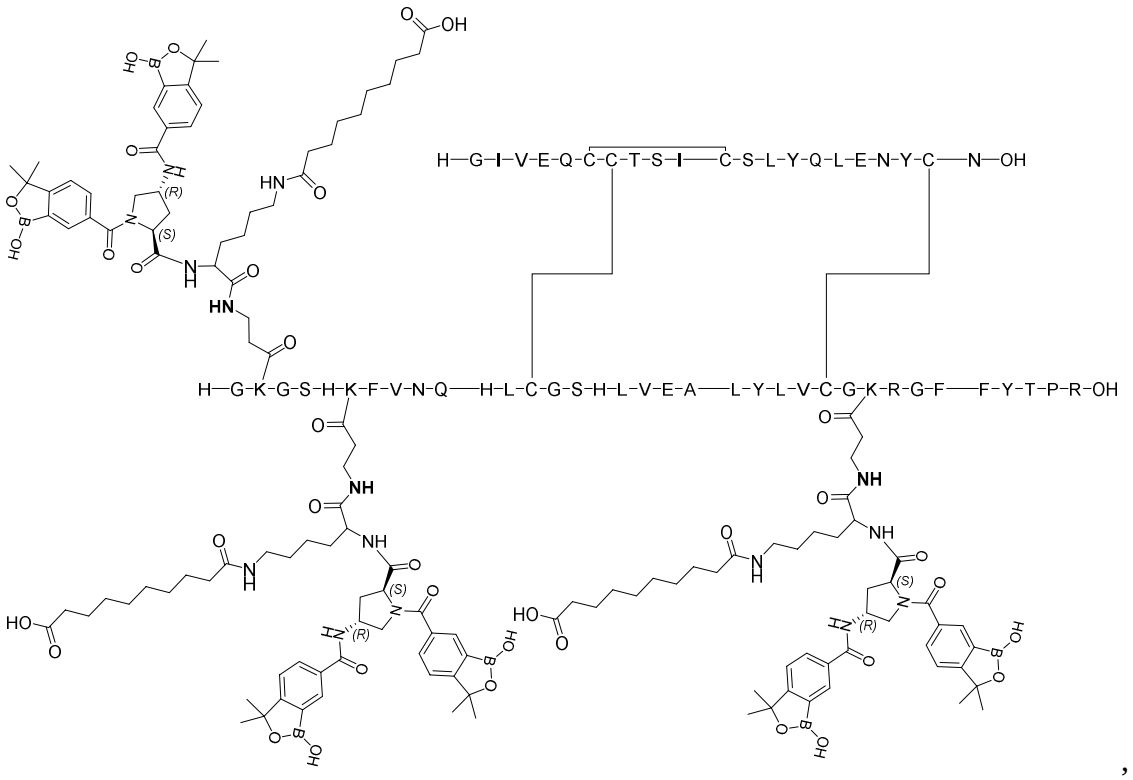
,

Example 29A:



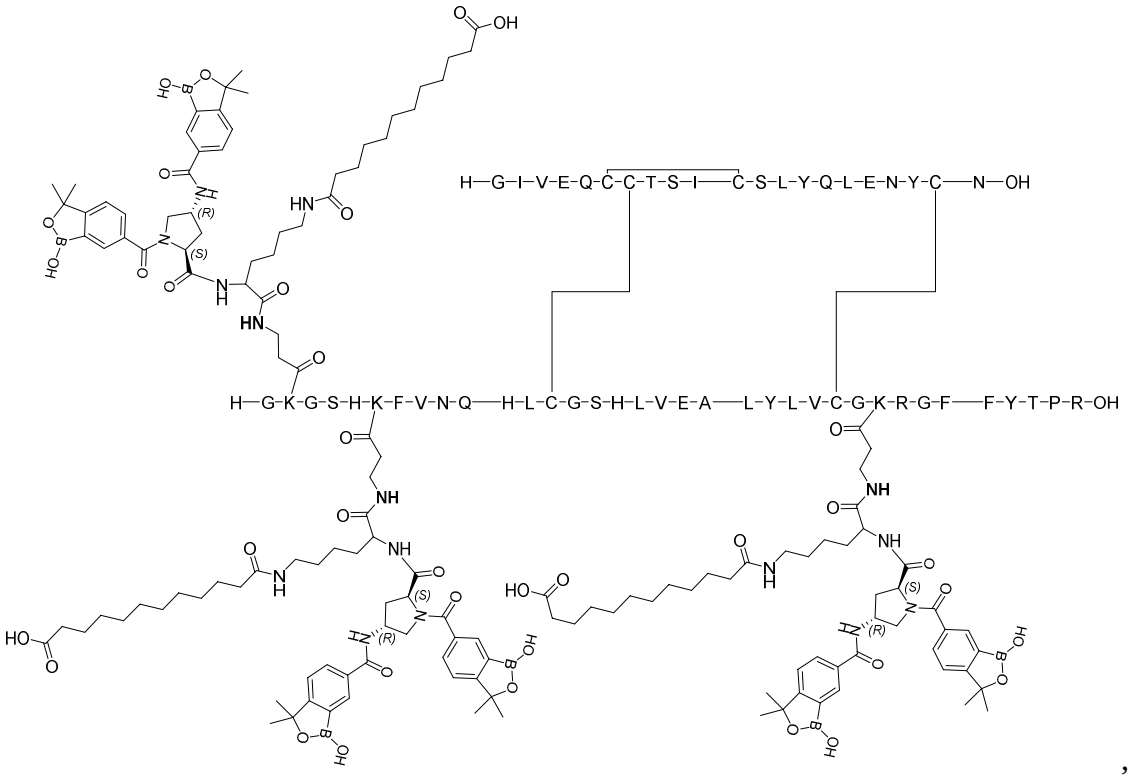
Prophetic ,

Example 30A:



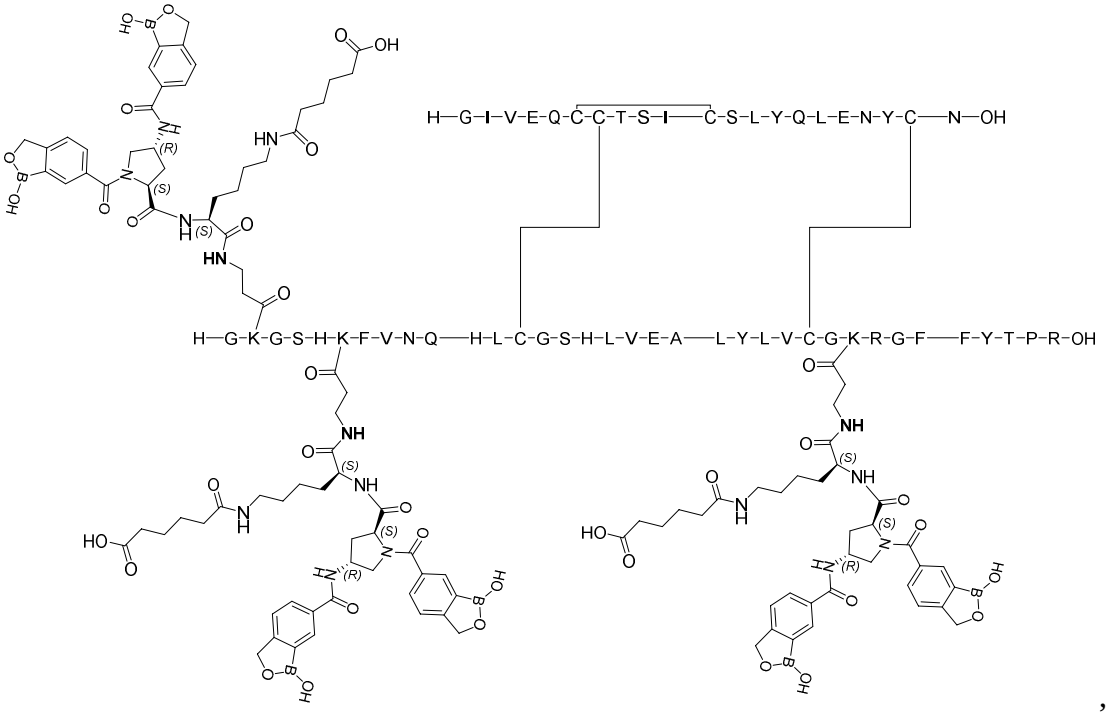
,

Example 31A:



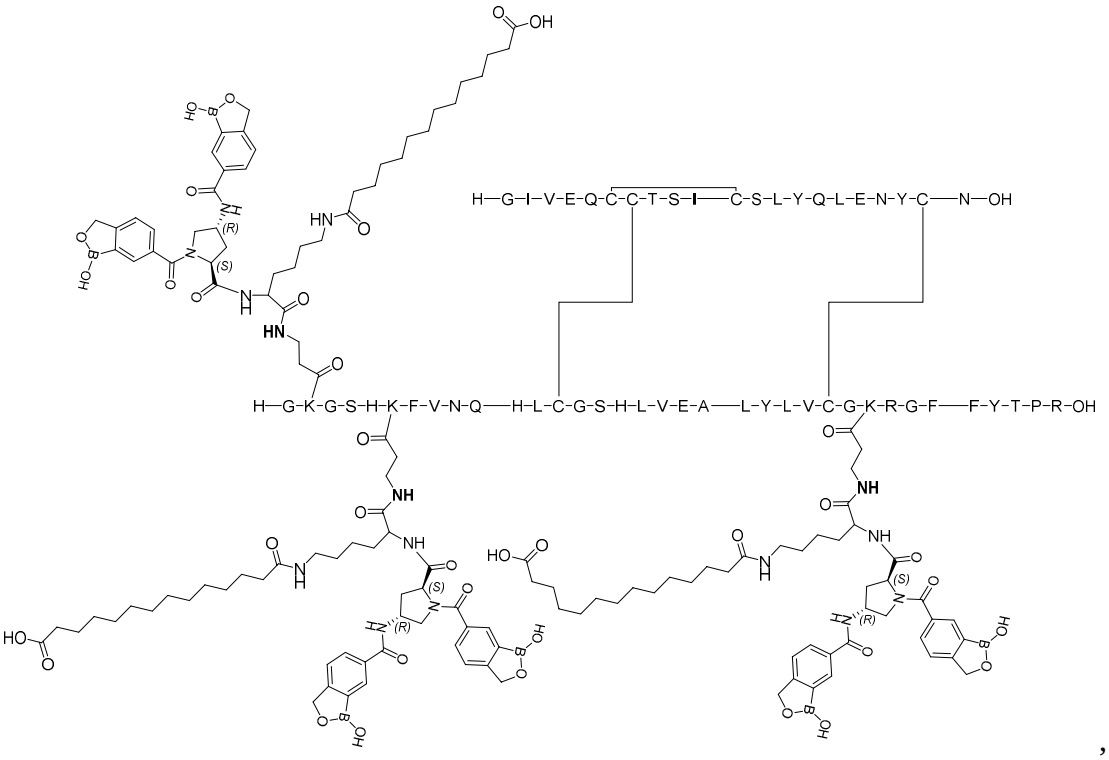
,

Example 32A:



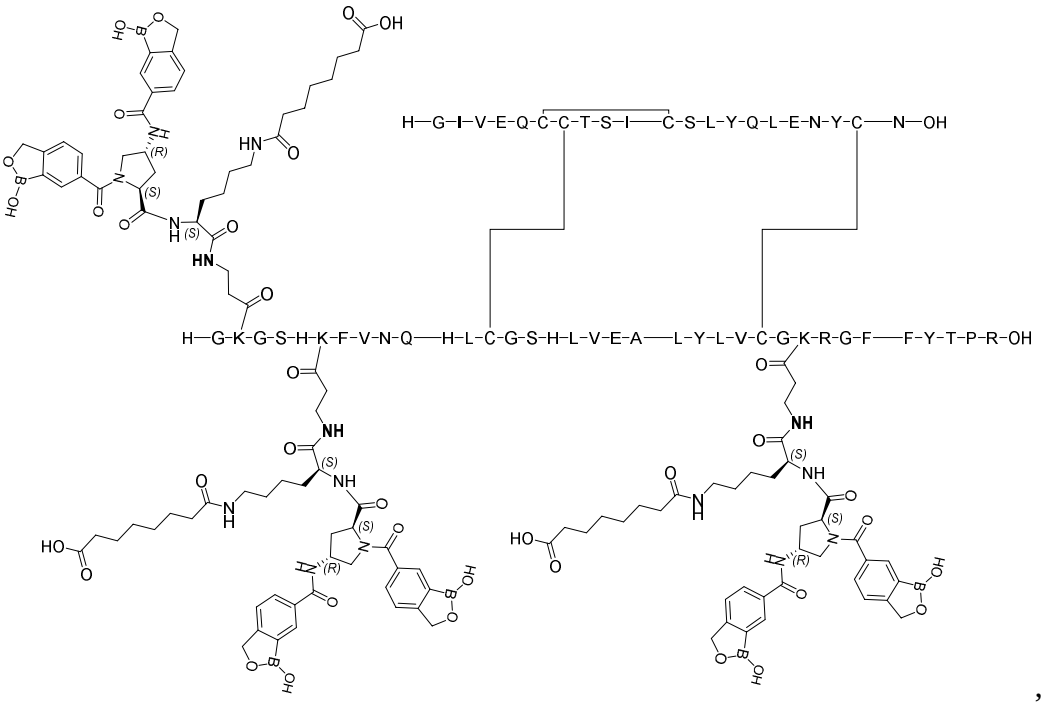
,

Example 33A:



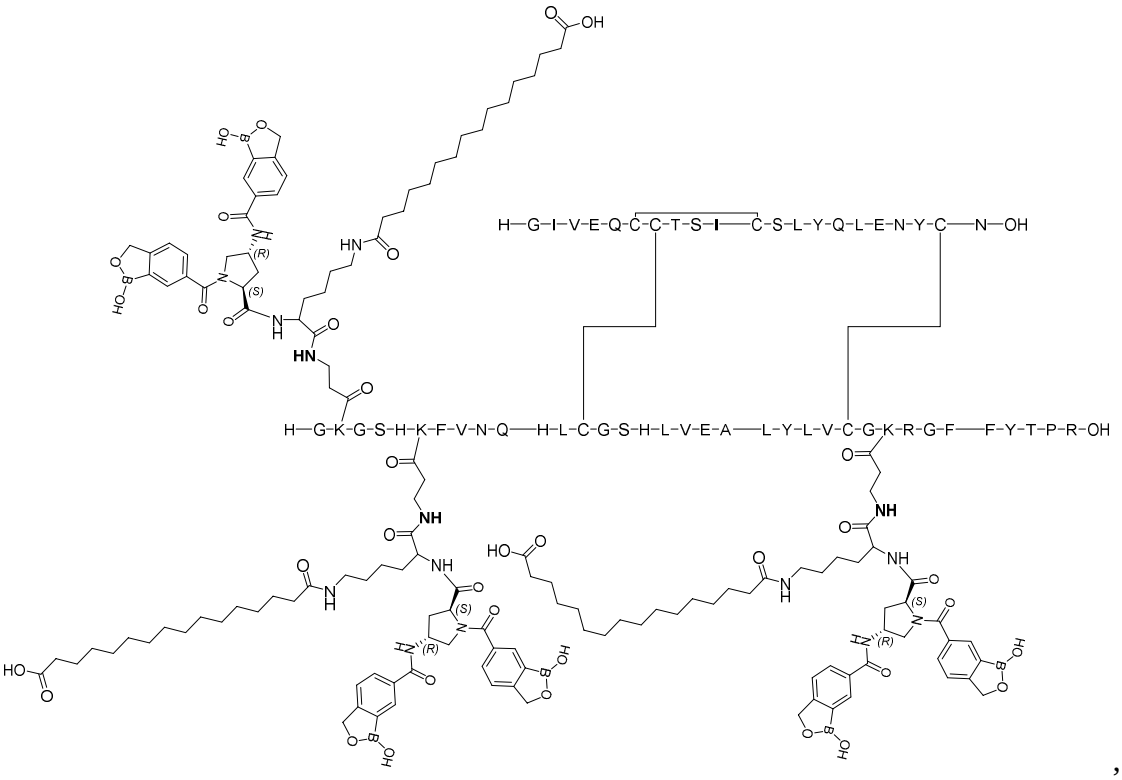
,

Example 34A:



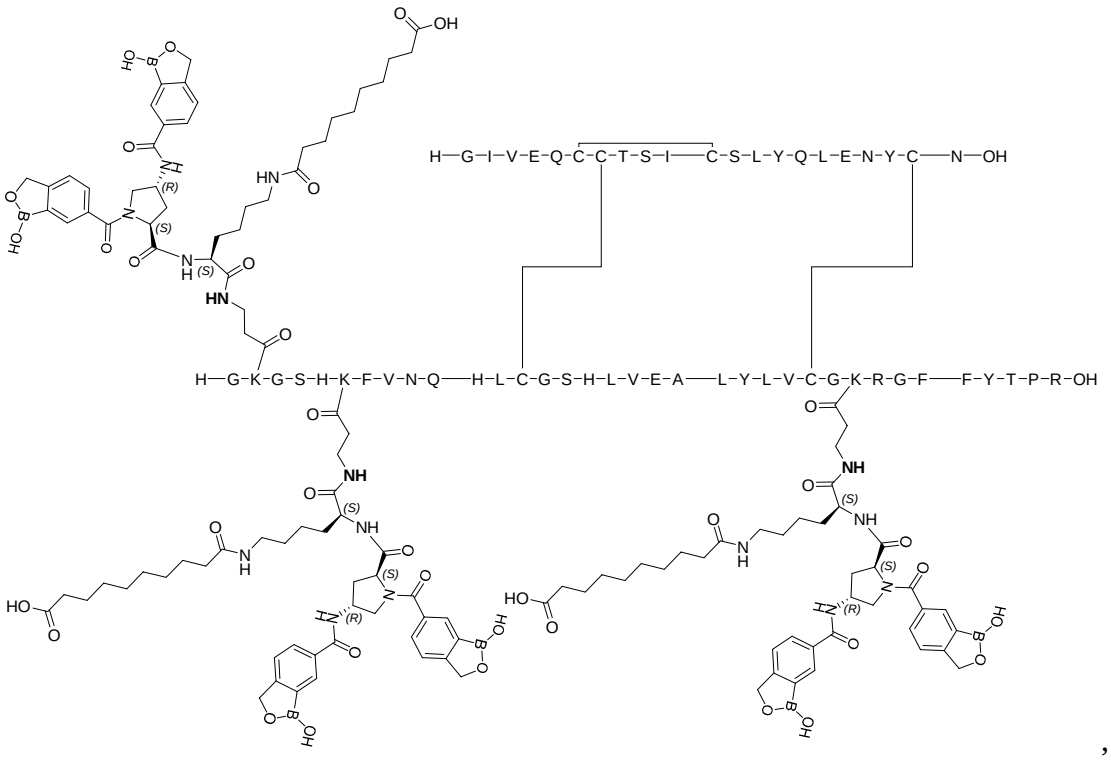
,

Example 35A:



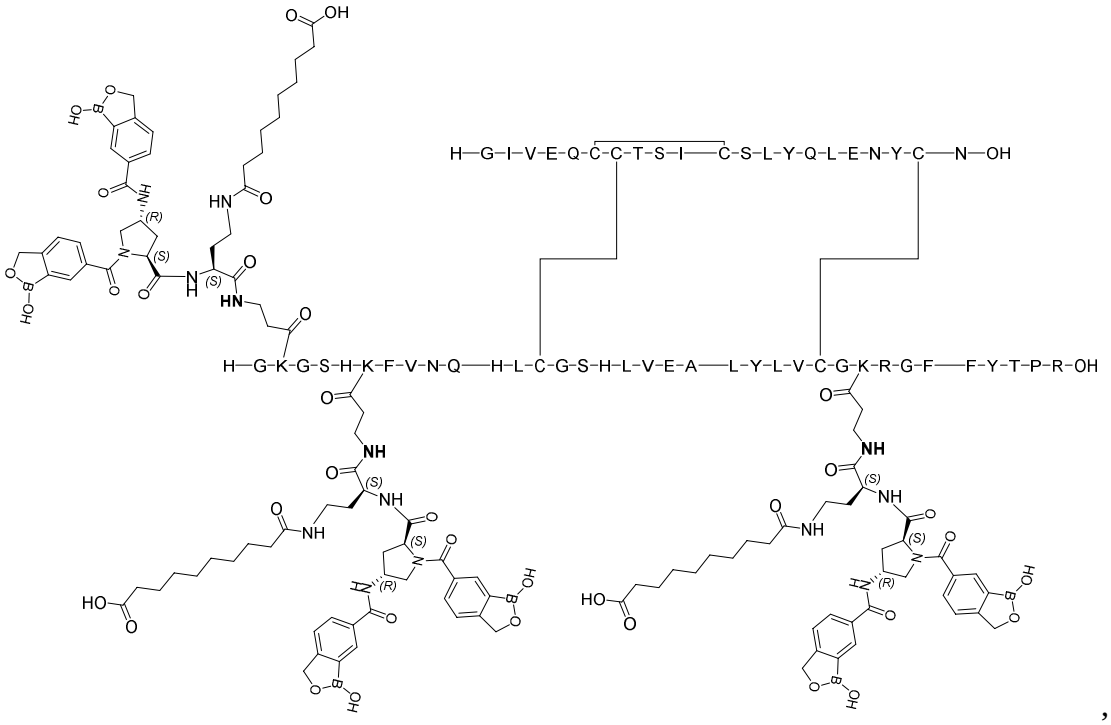
,

Example 36A:



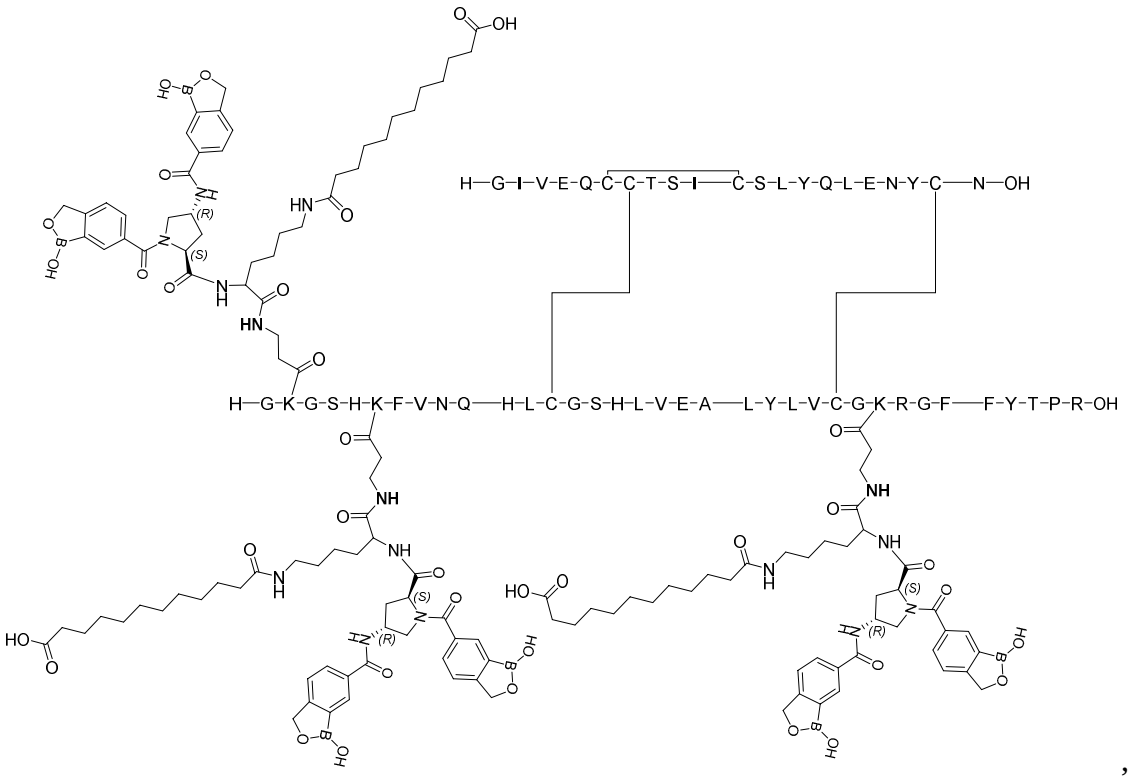
,

Example 37A:



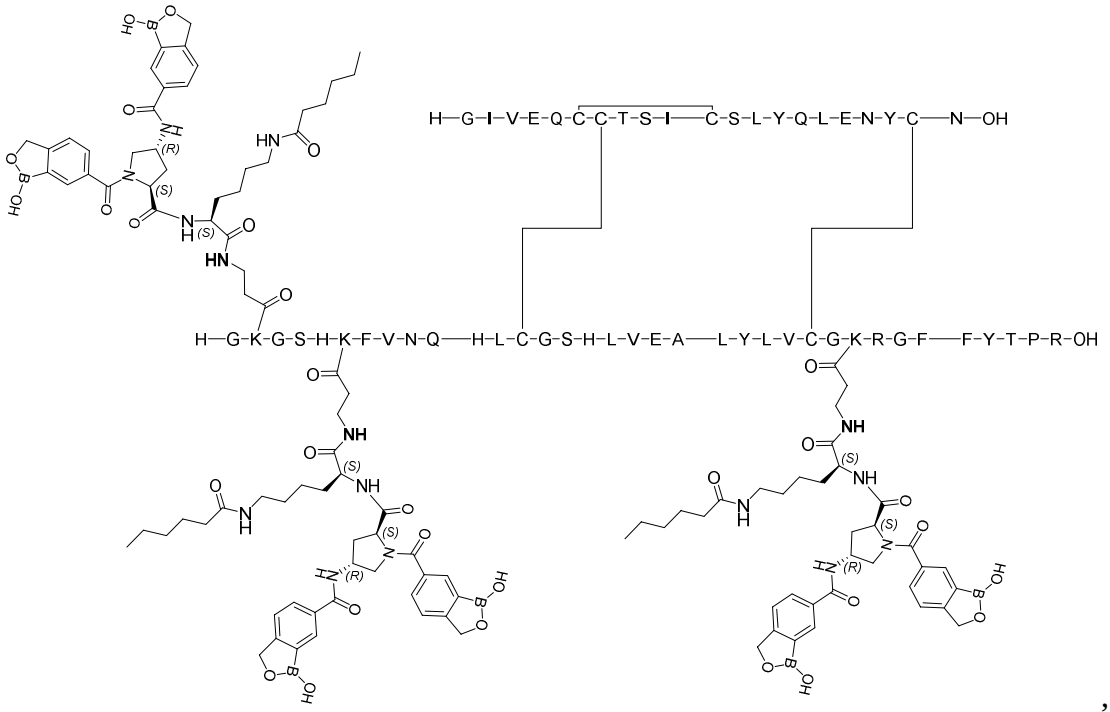
,

Example 38A:



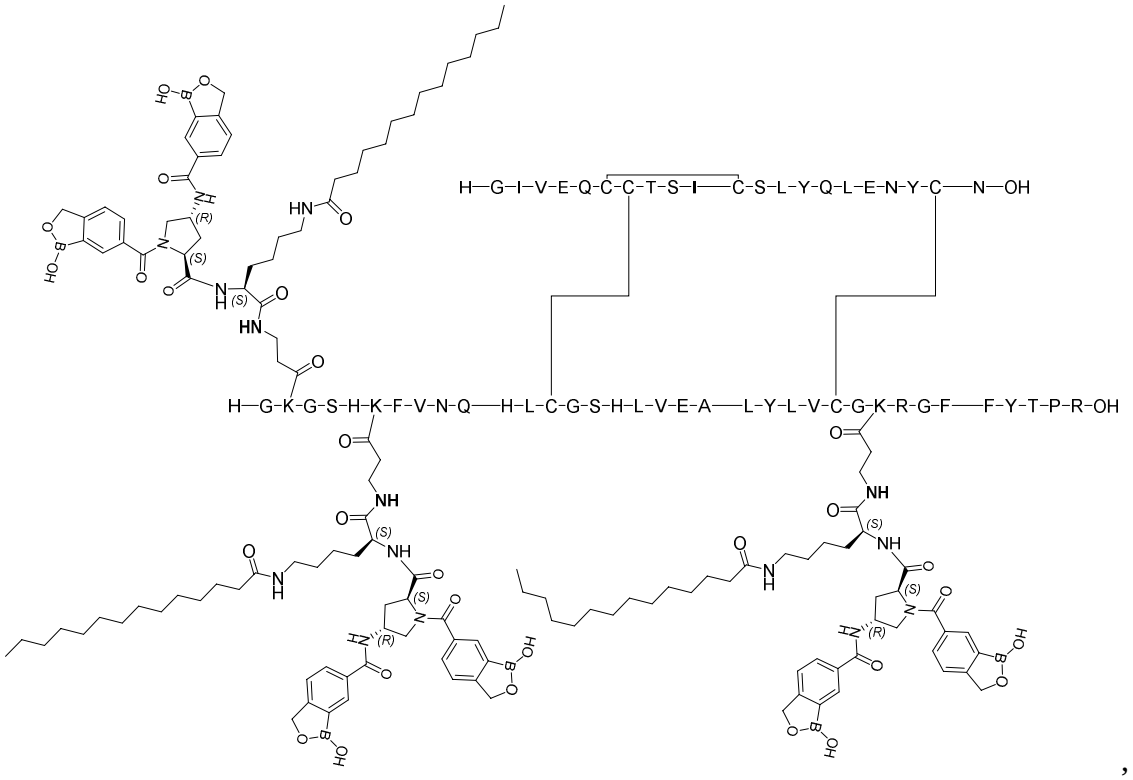
,

Example 39A:



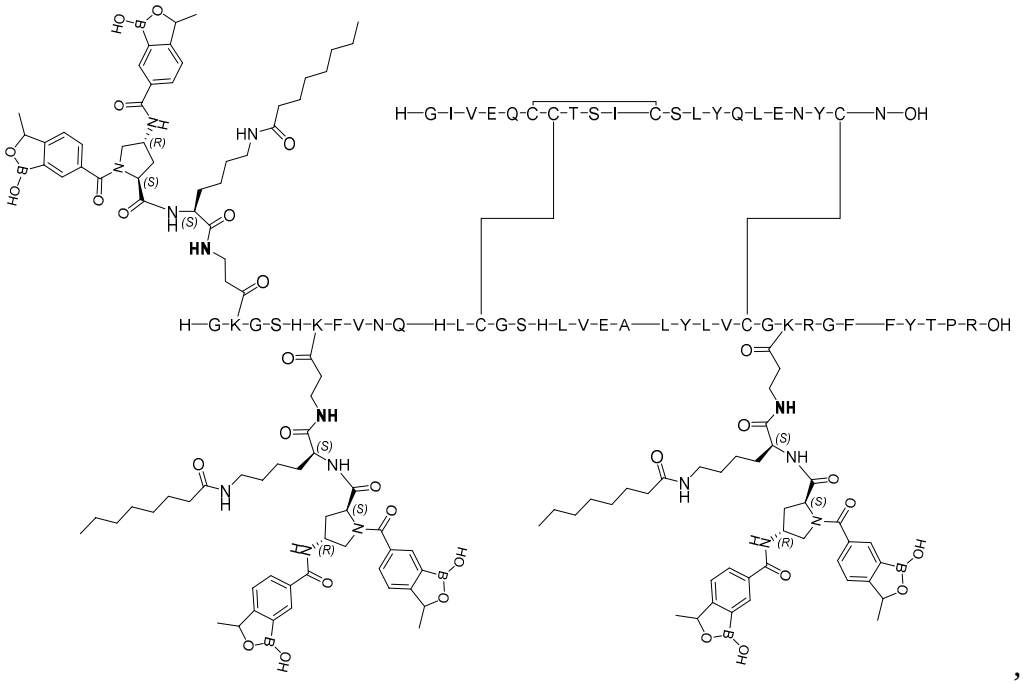
,

Example 40A:



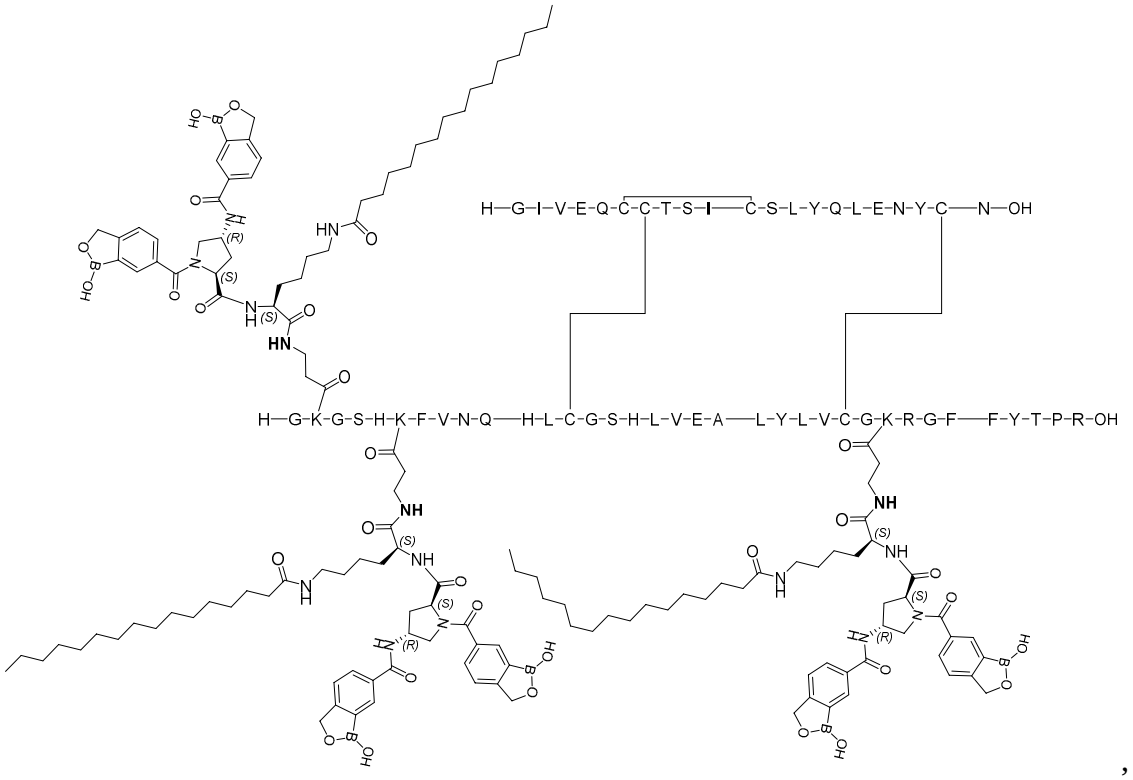
,

Example 41A:



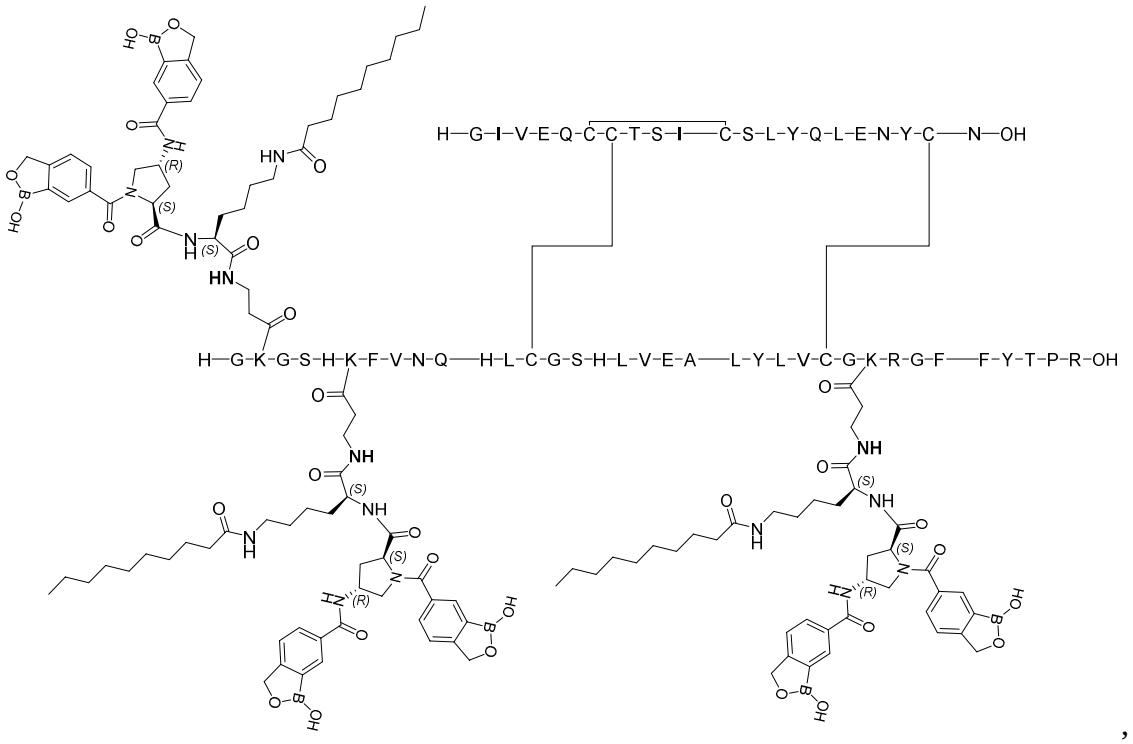
,

Example 42A:



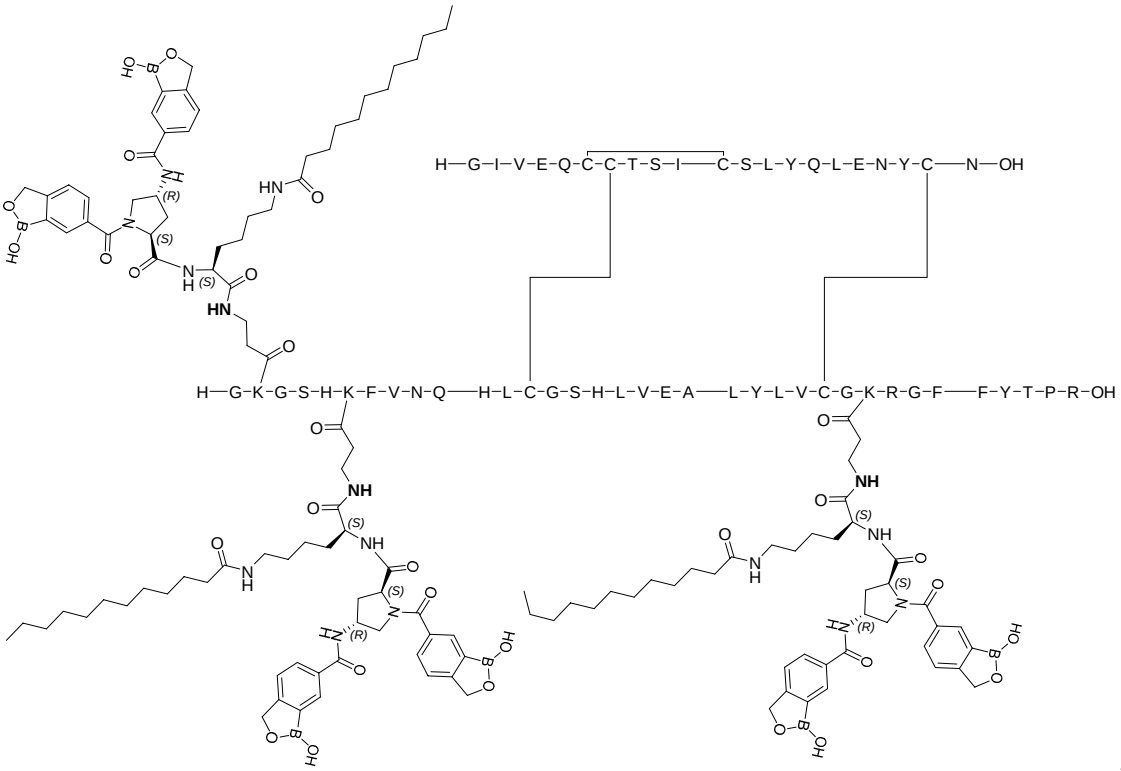
,

Example 43A:



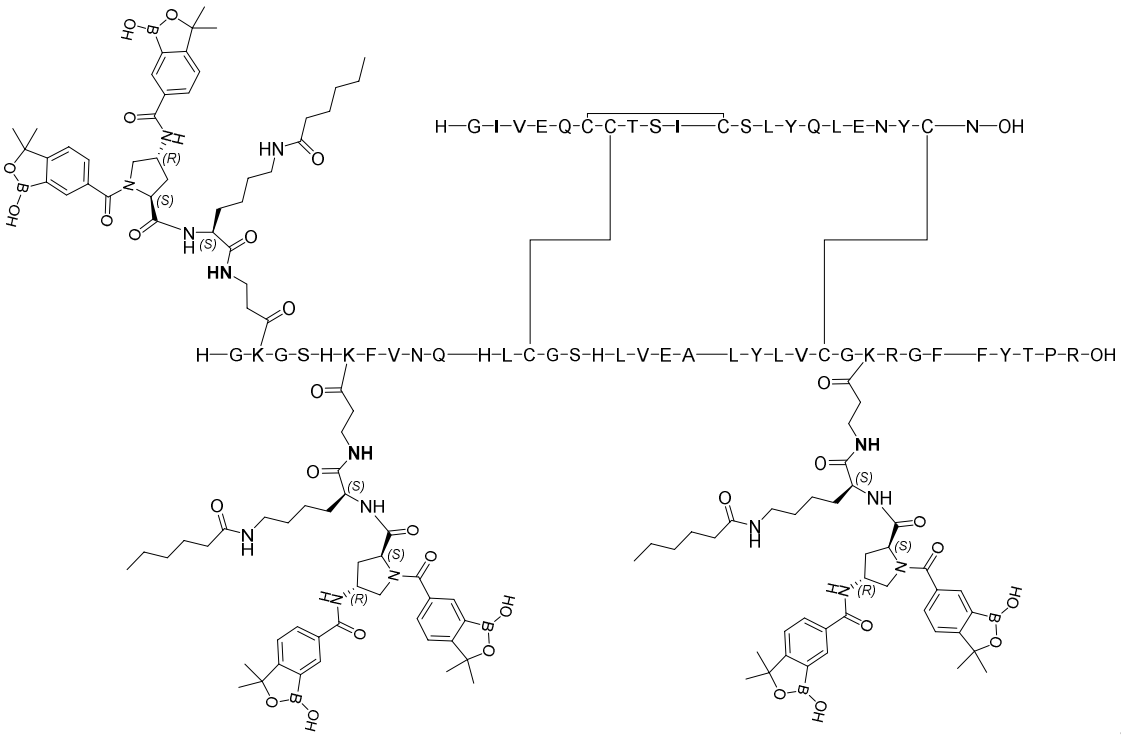
,

Example 44A:



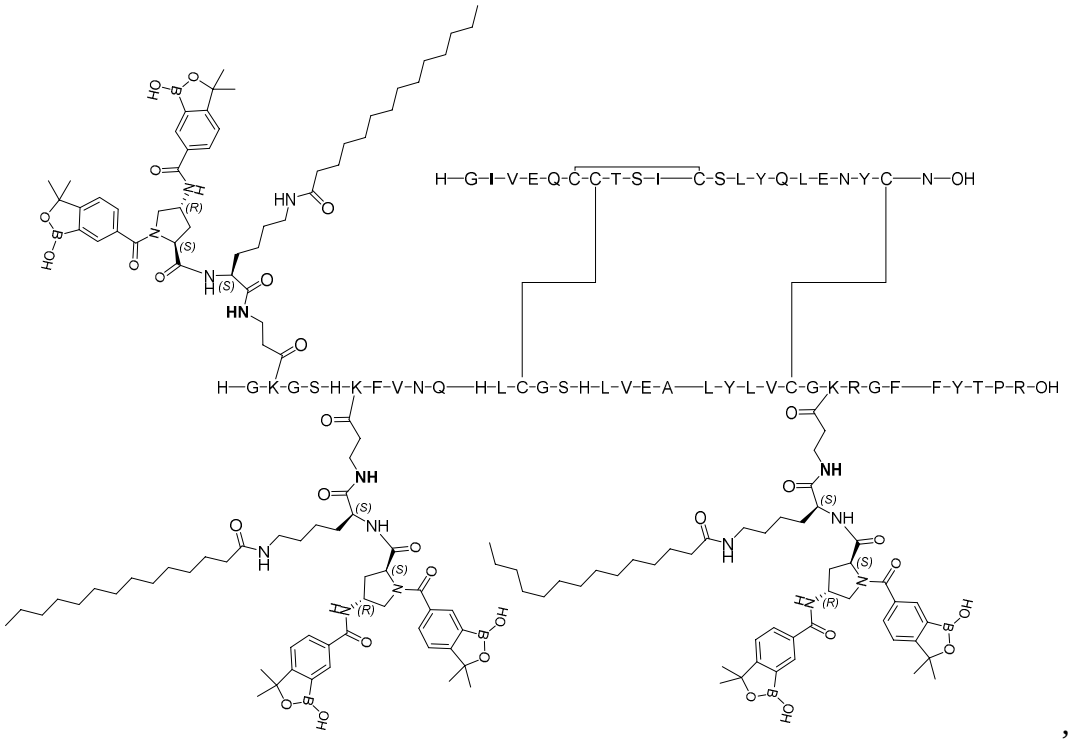
,

Example 45A:



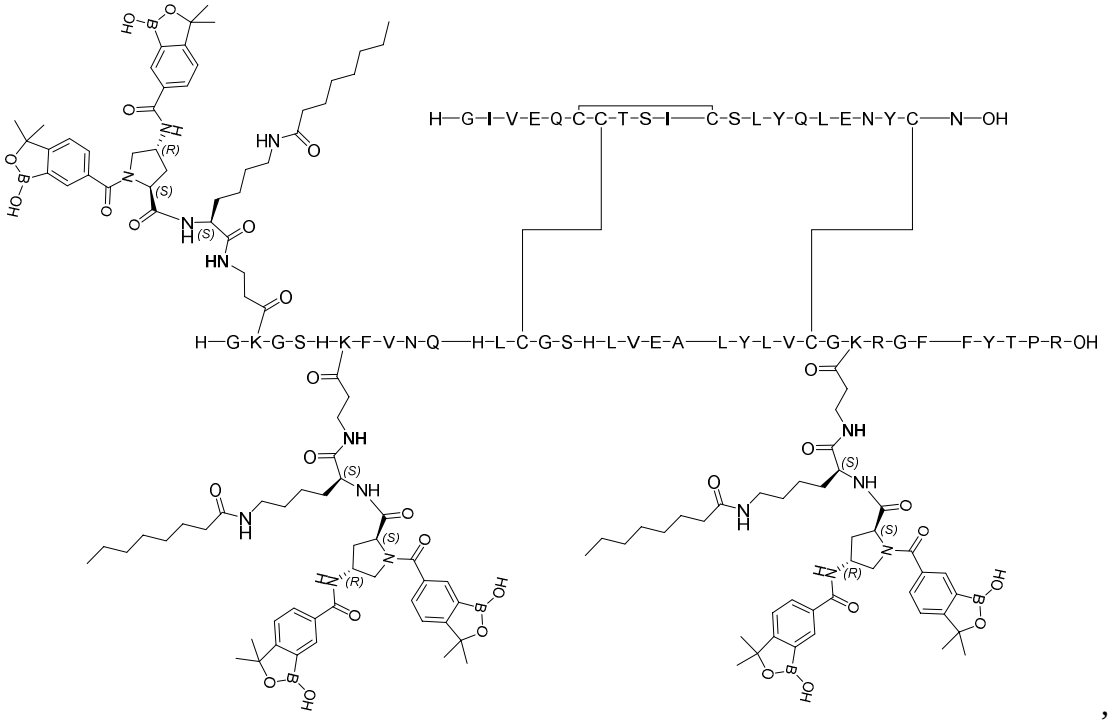
,

Example 46A:



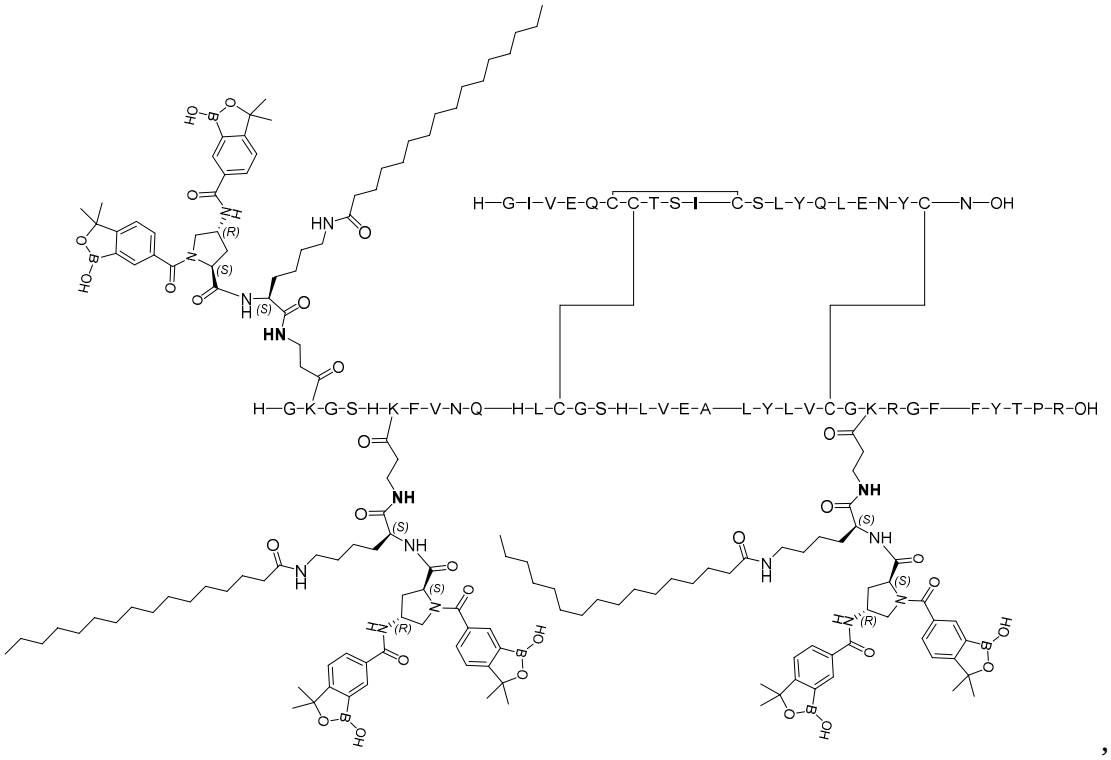
,

Example 47A:



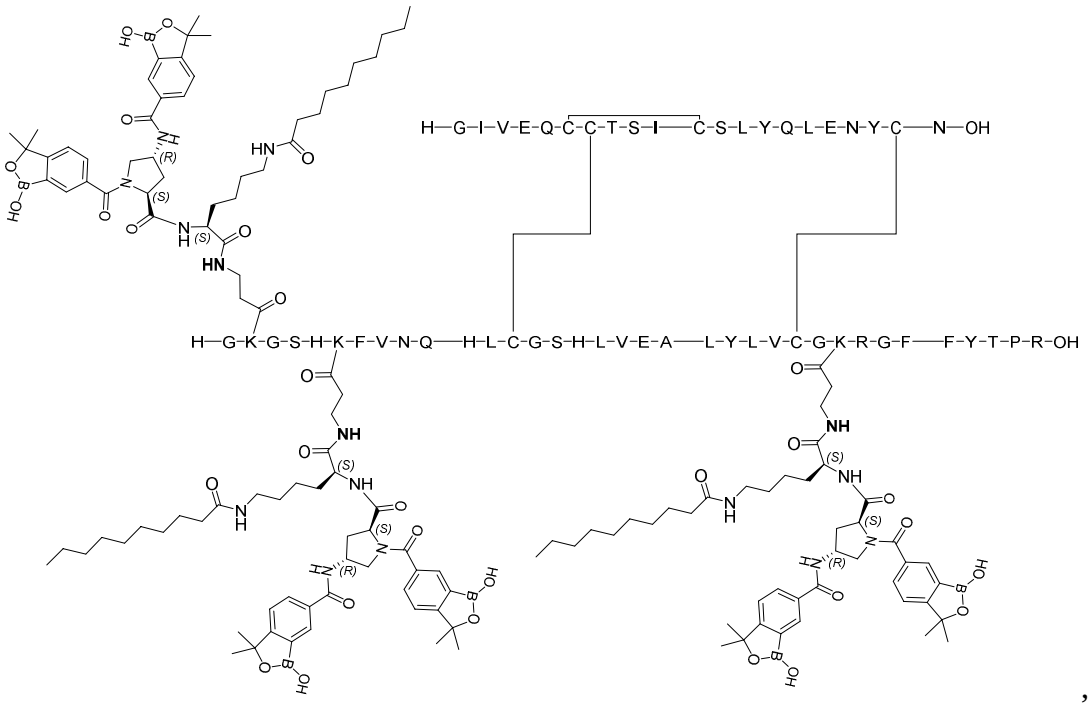
5 ,

Example 48A:



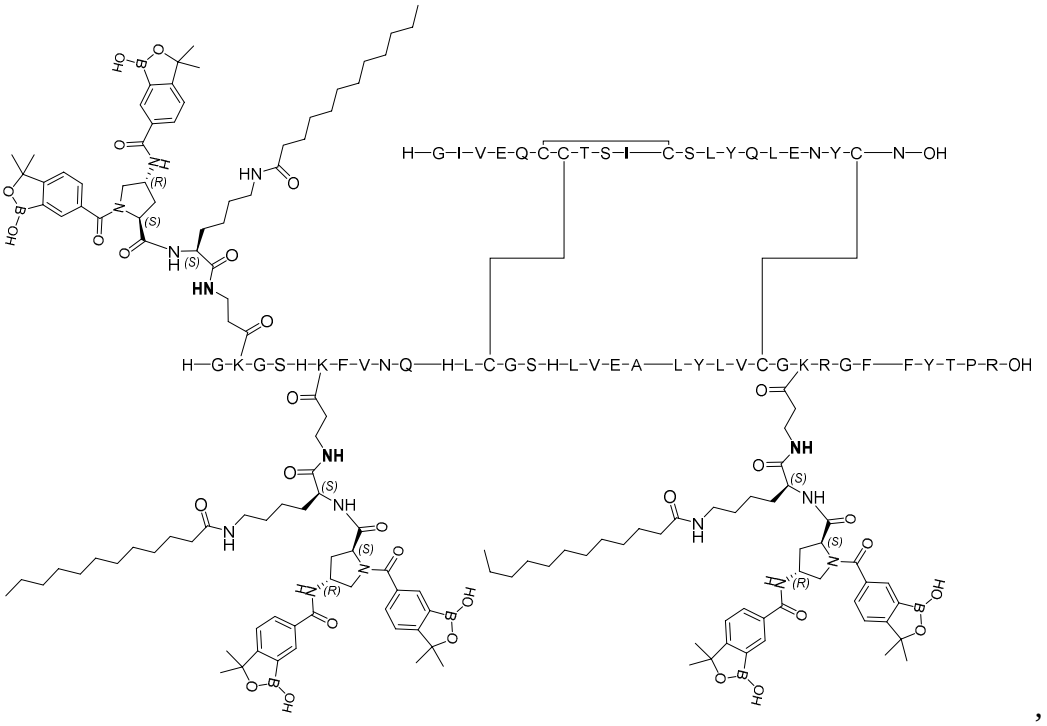
,

Example 49A:



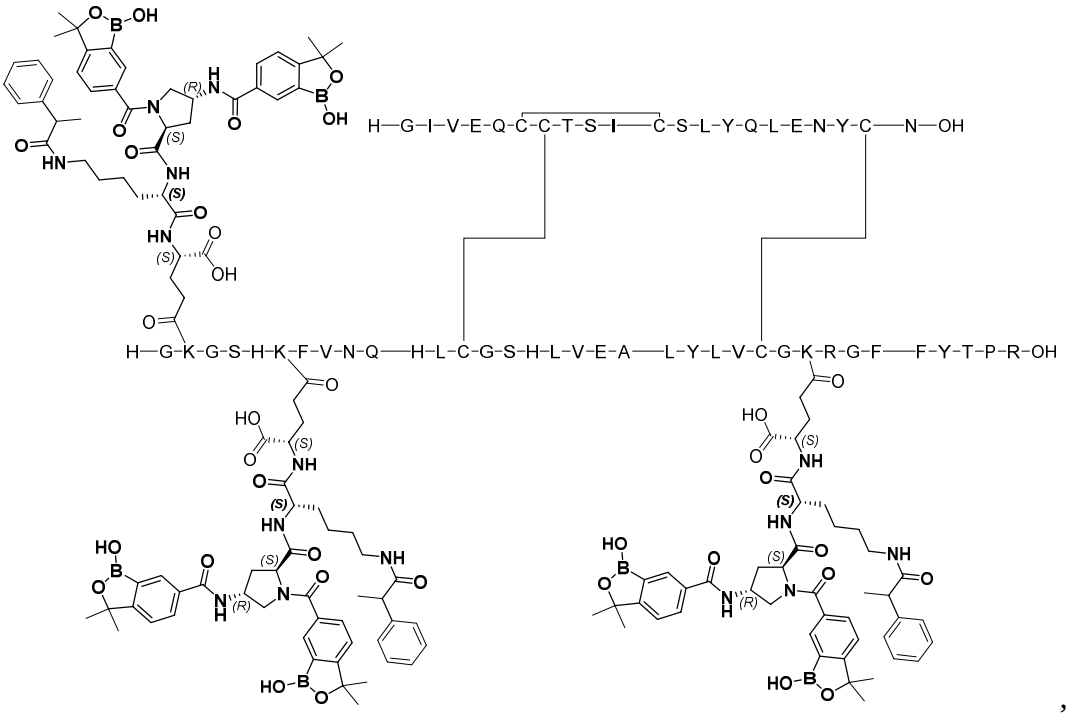
,

Example 50A:



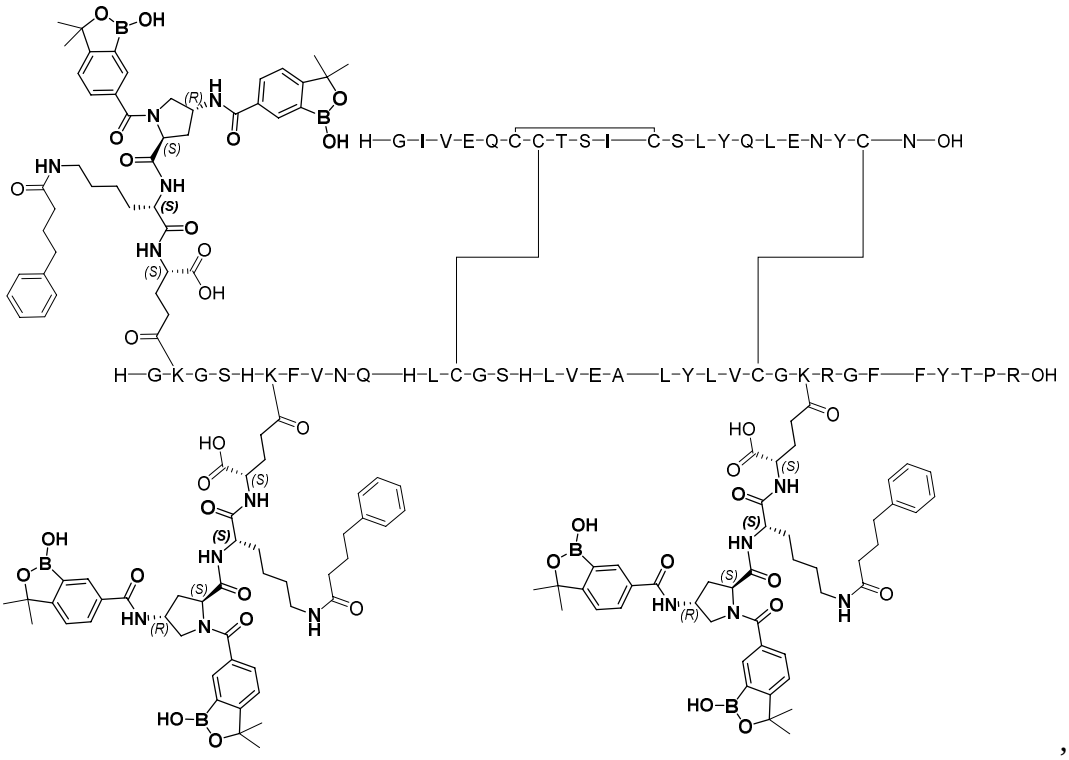
,

Example 51A:



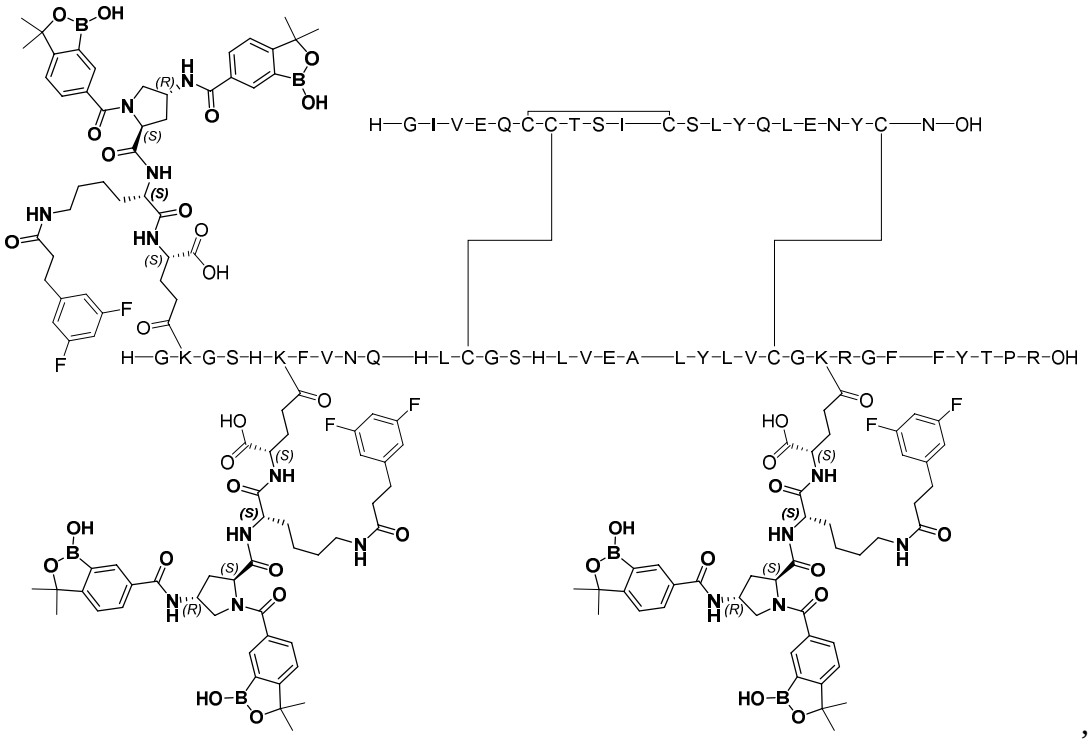
,

Example 52A:



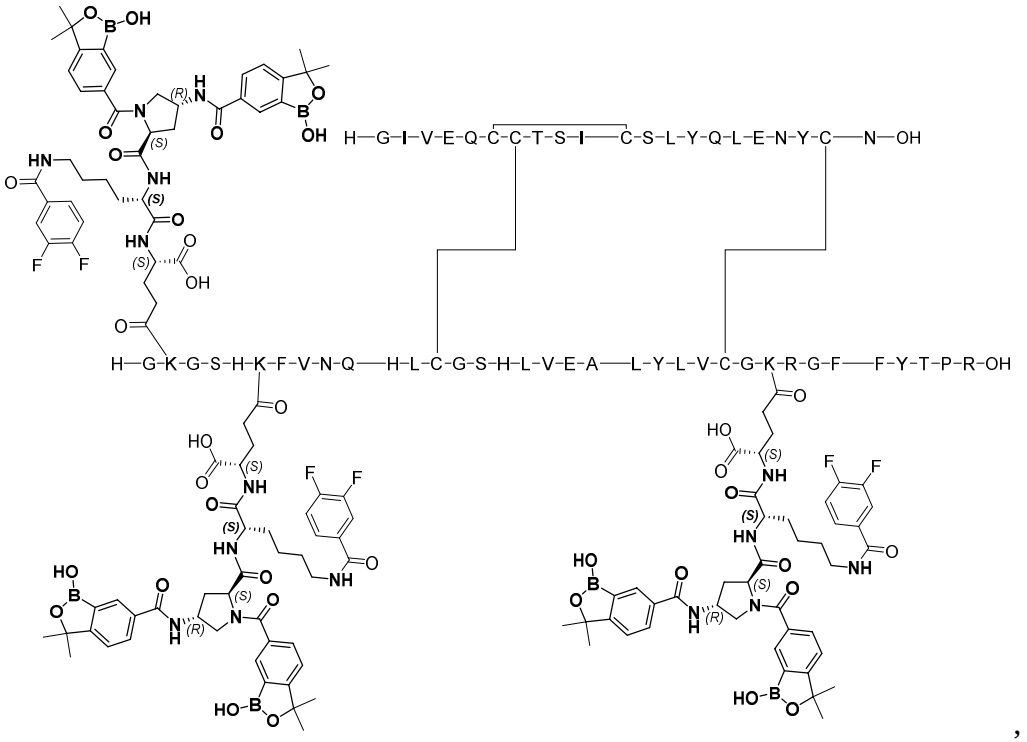
,

Example 53A:



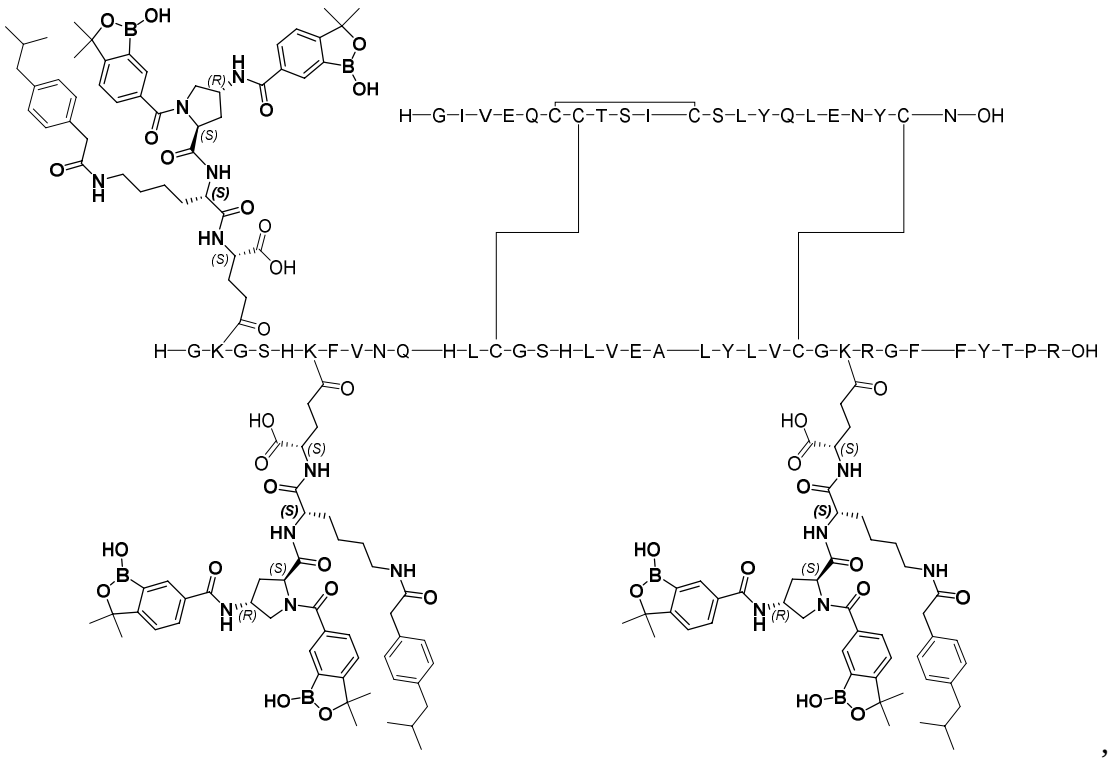
,

Example 54A:



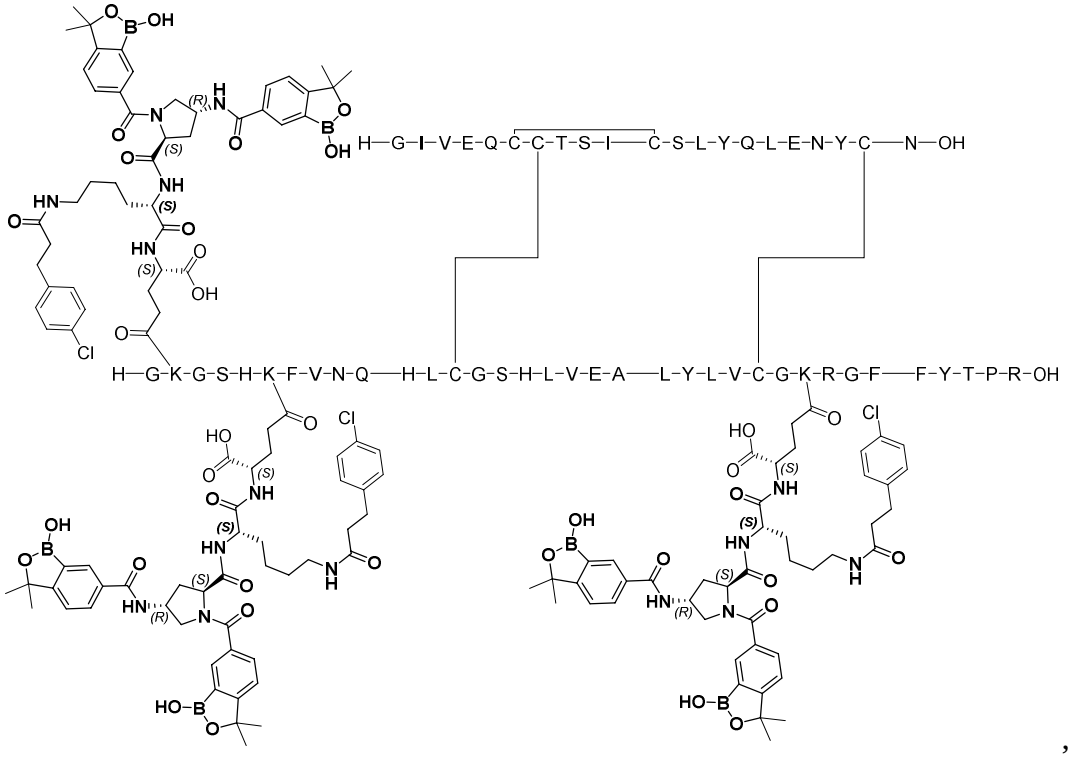
,

Example 55A:



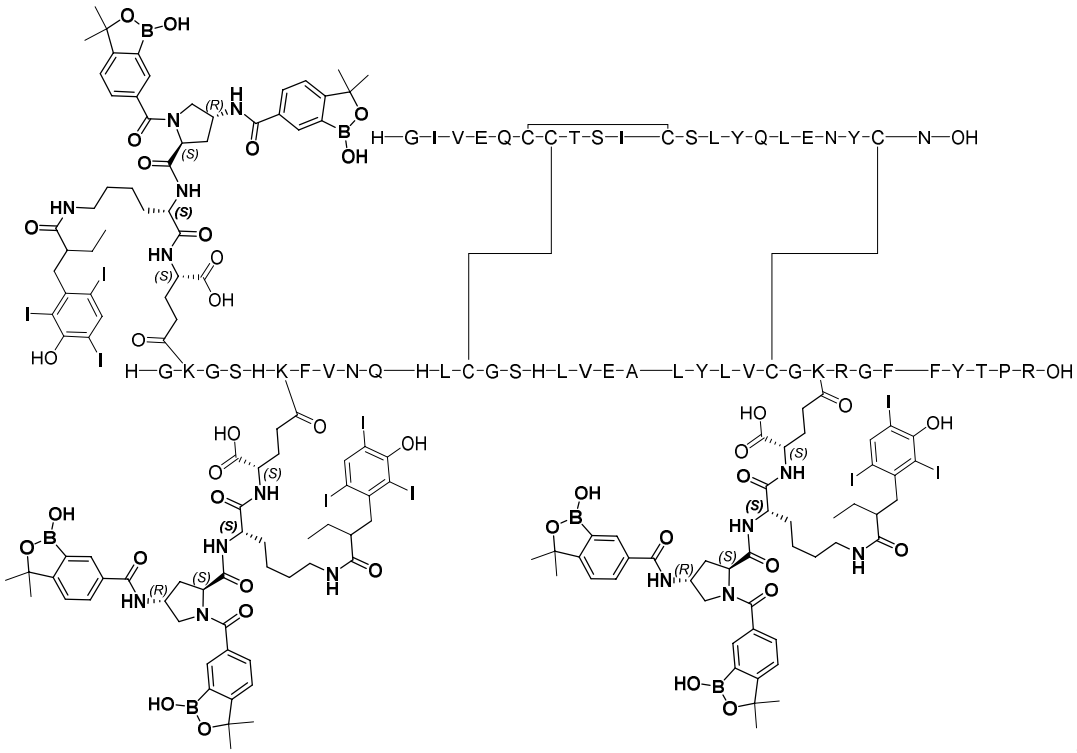
,

Example 56A:



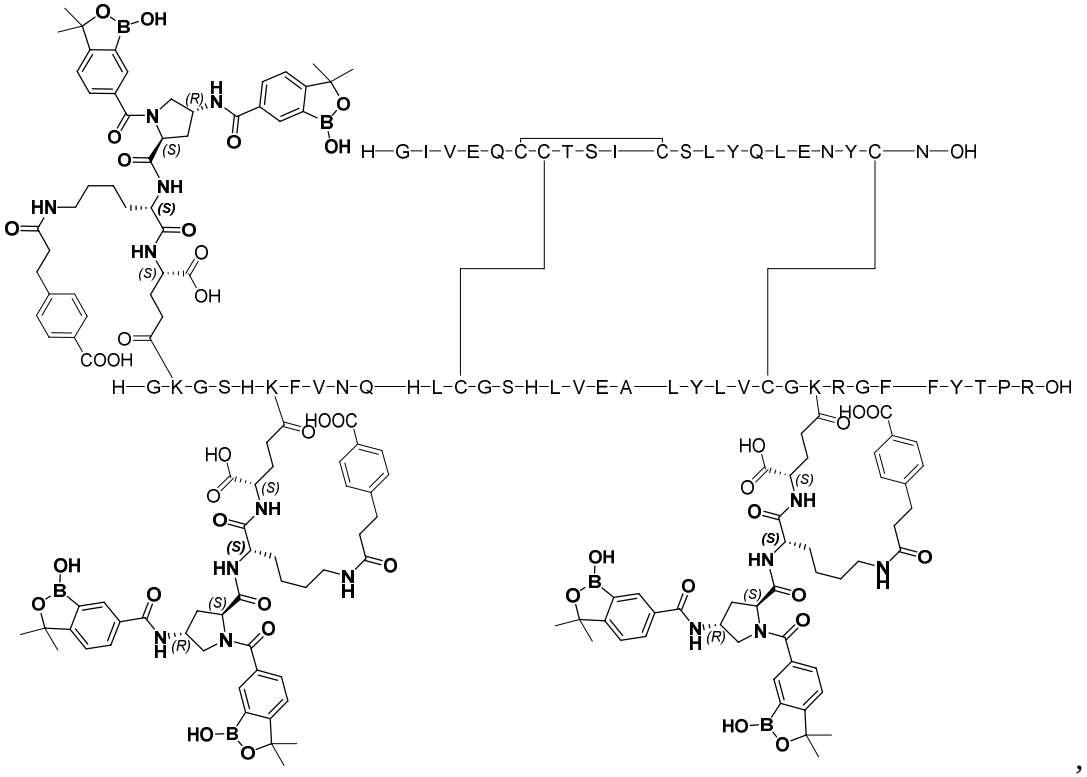
,

Example 57A:



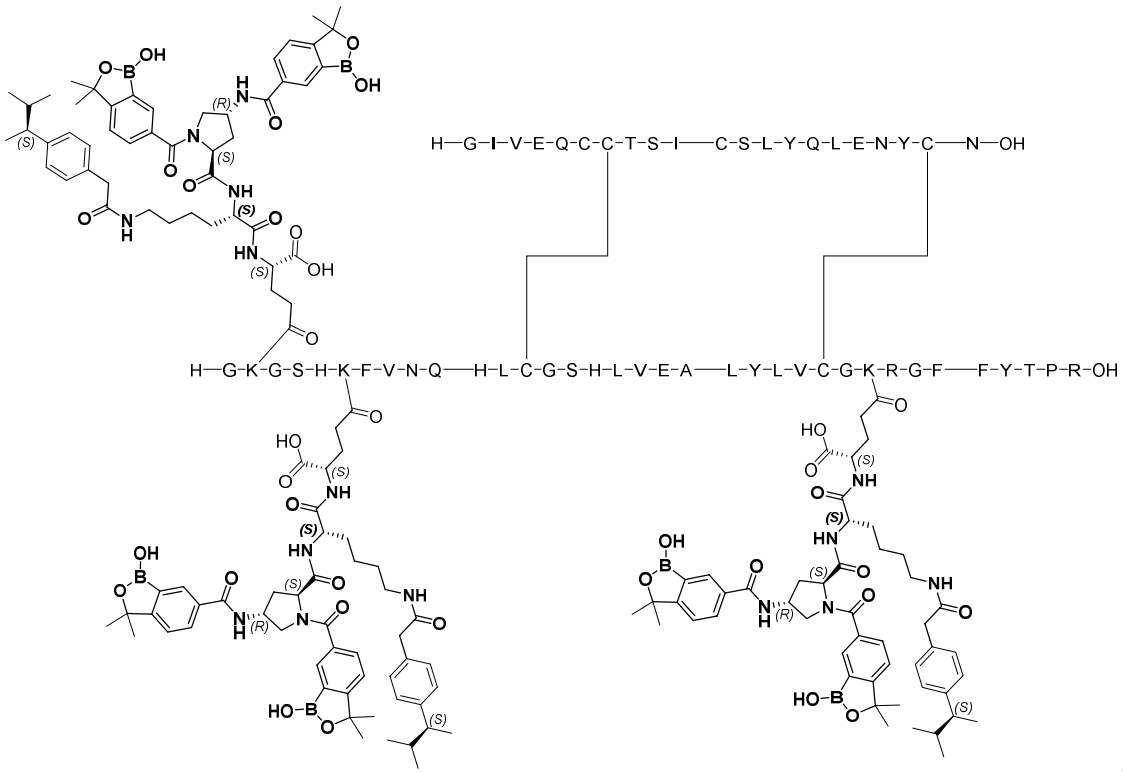
,

Example 58A:



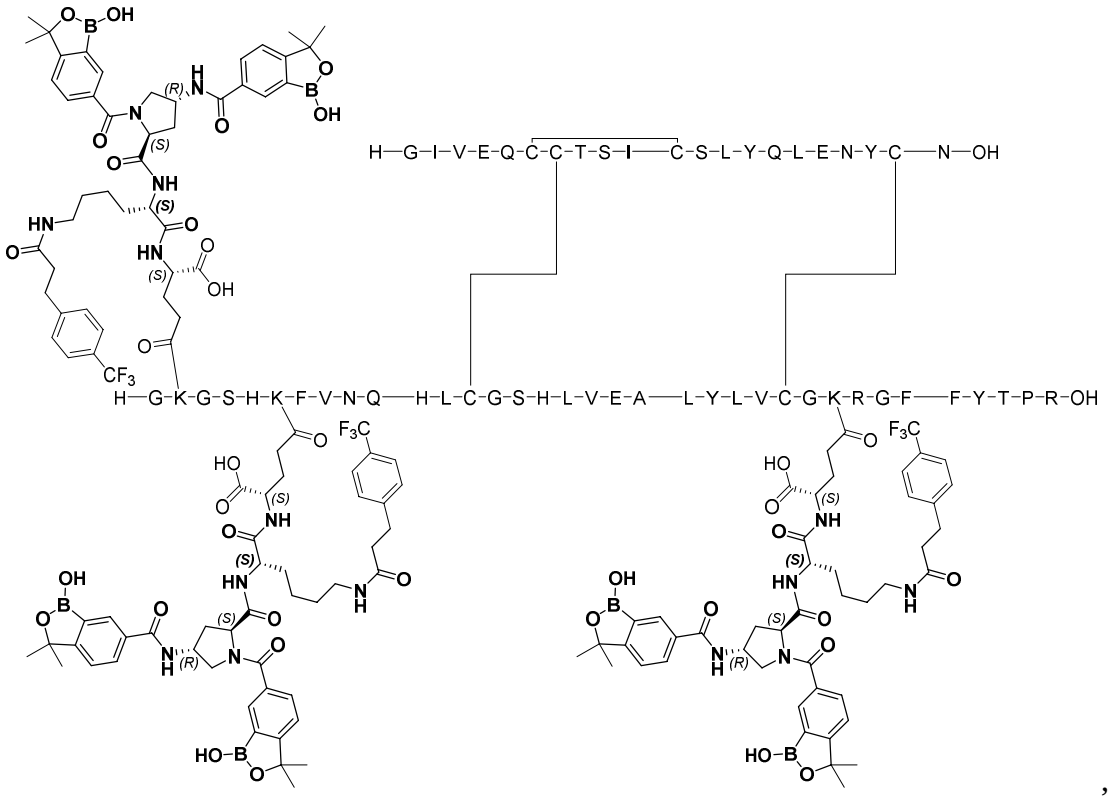
,

Example 59A:



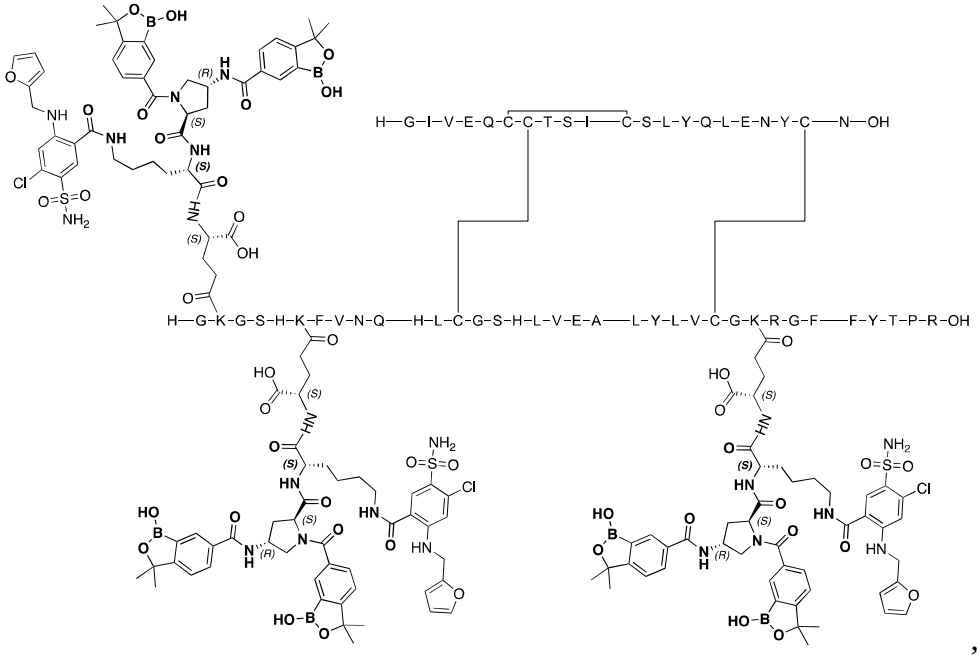
,

Example 60A:



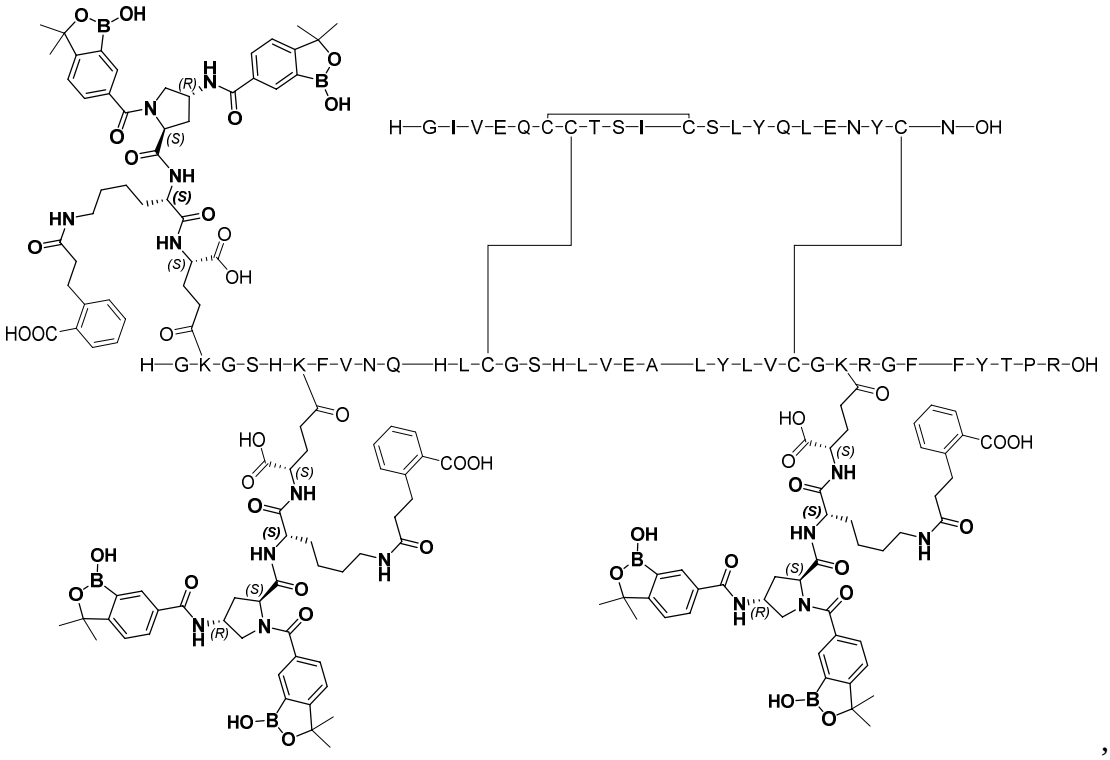
,

Example 61A:



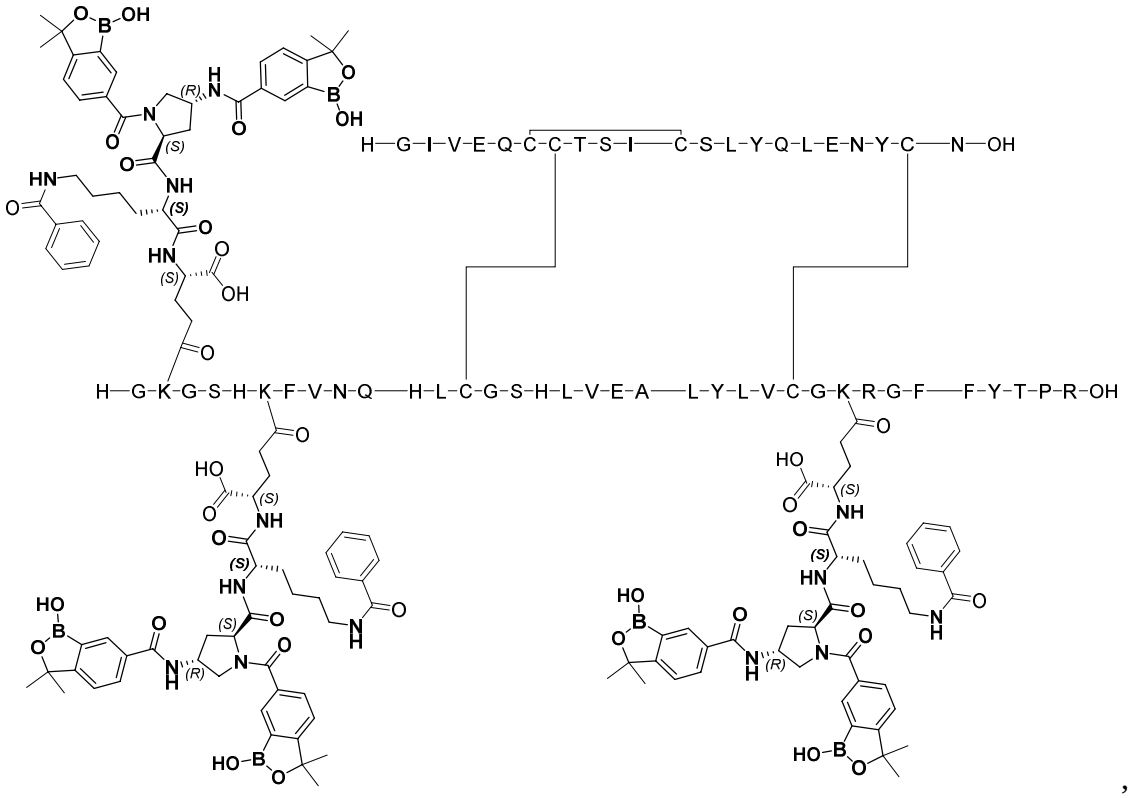
5 ,

Example 62A:



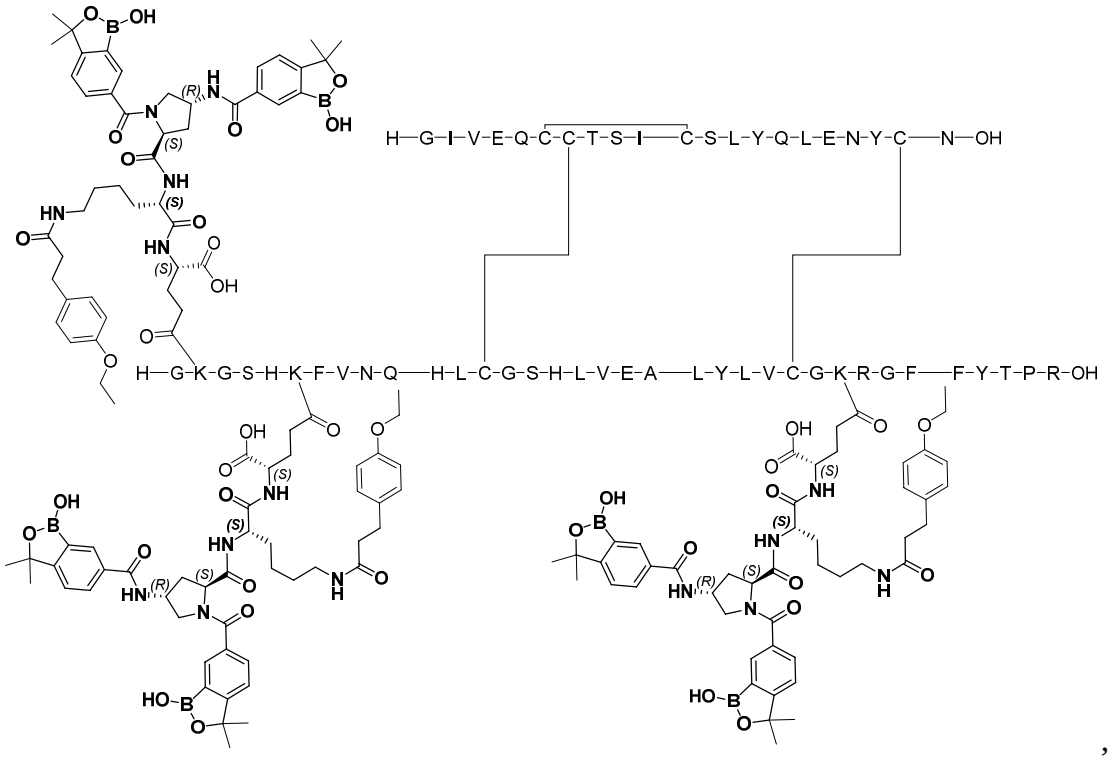
,

Example 63A:



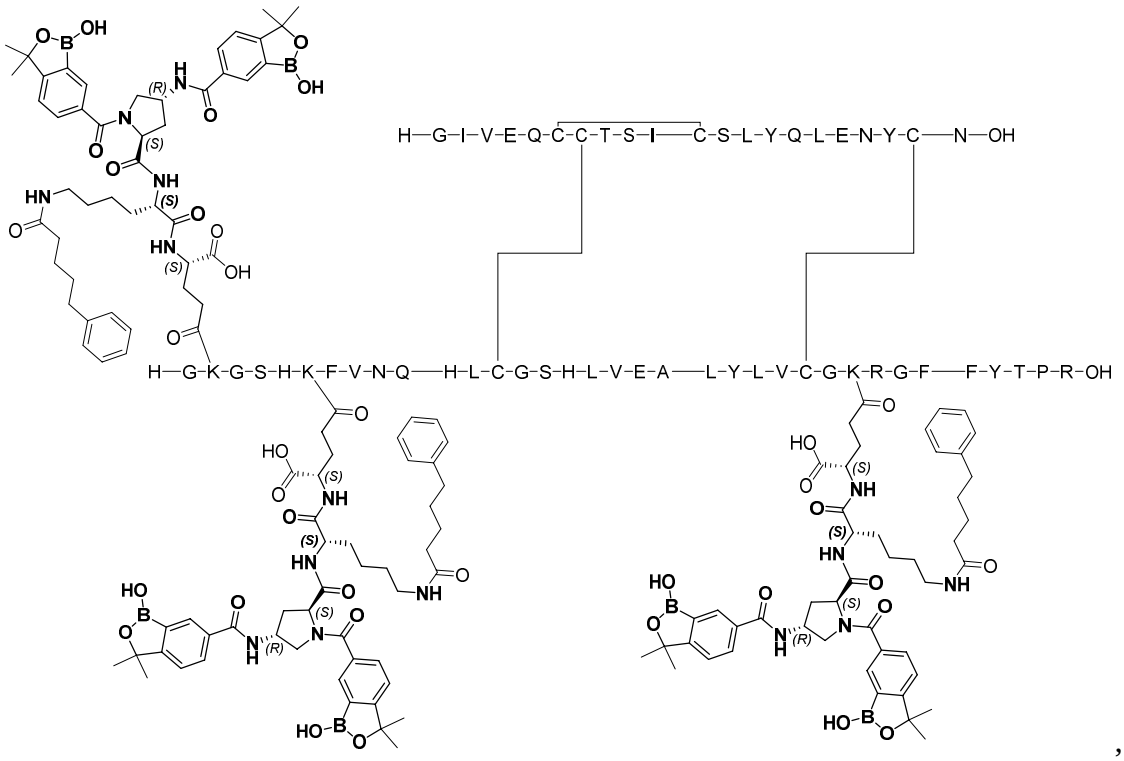
,

Example 64A:



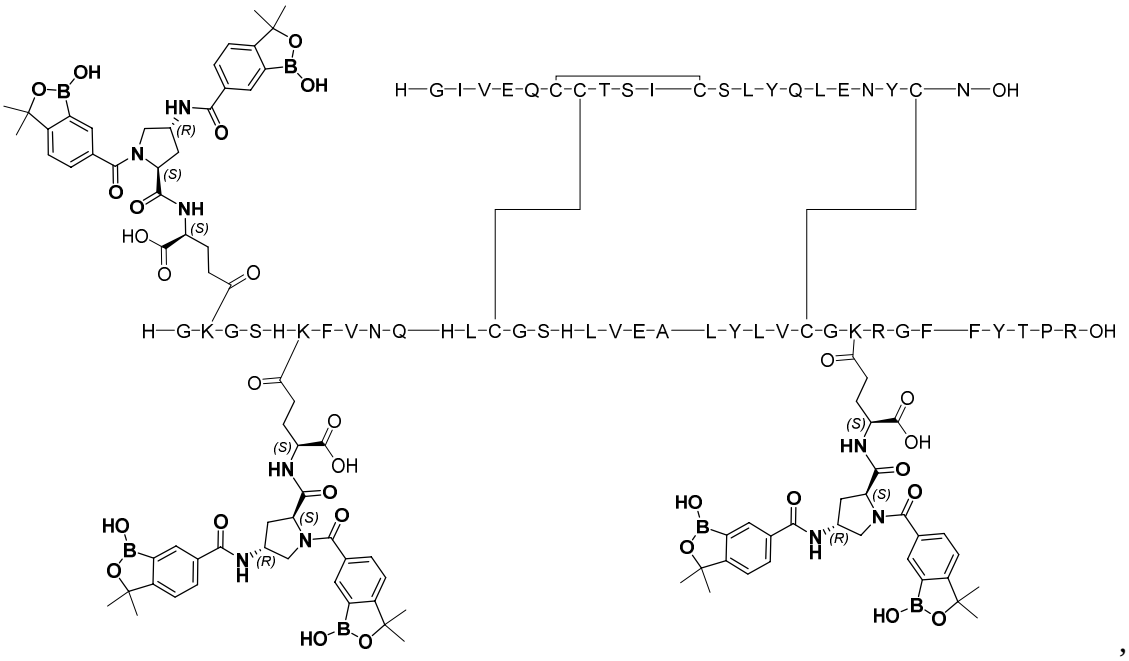
,

Example 65A:



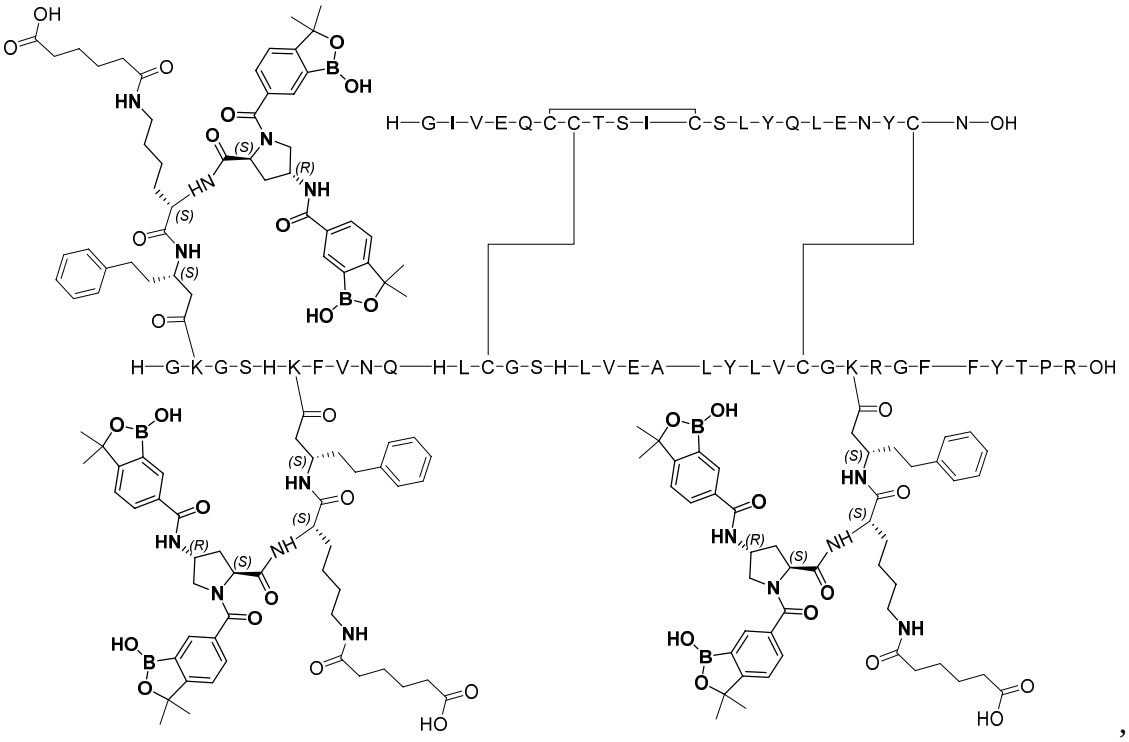
,

Example 66A:



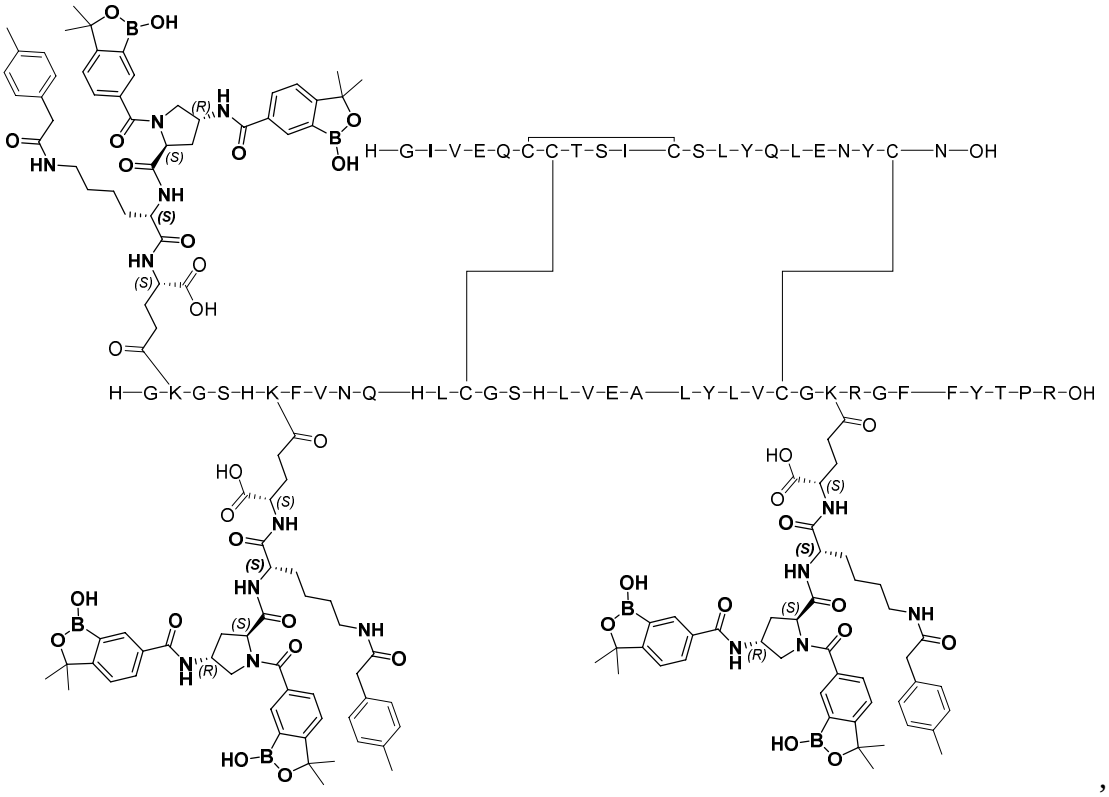
,

Example 67A:



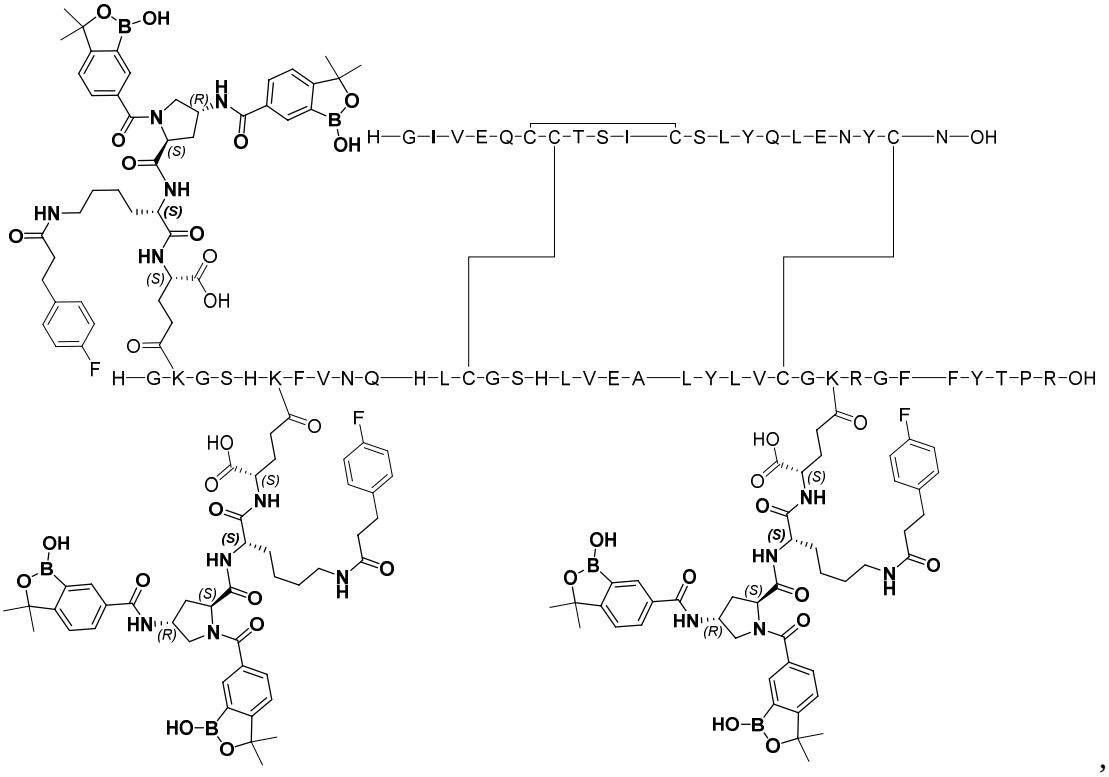
5 ,

Example 68A:



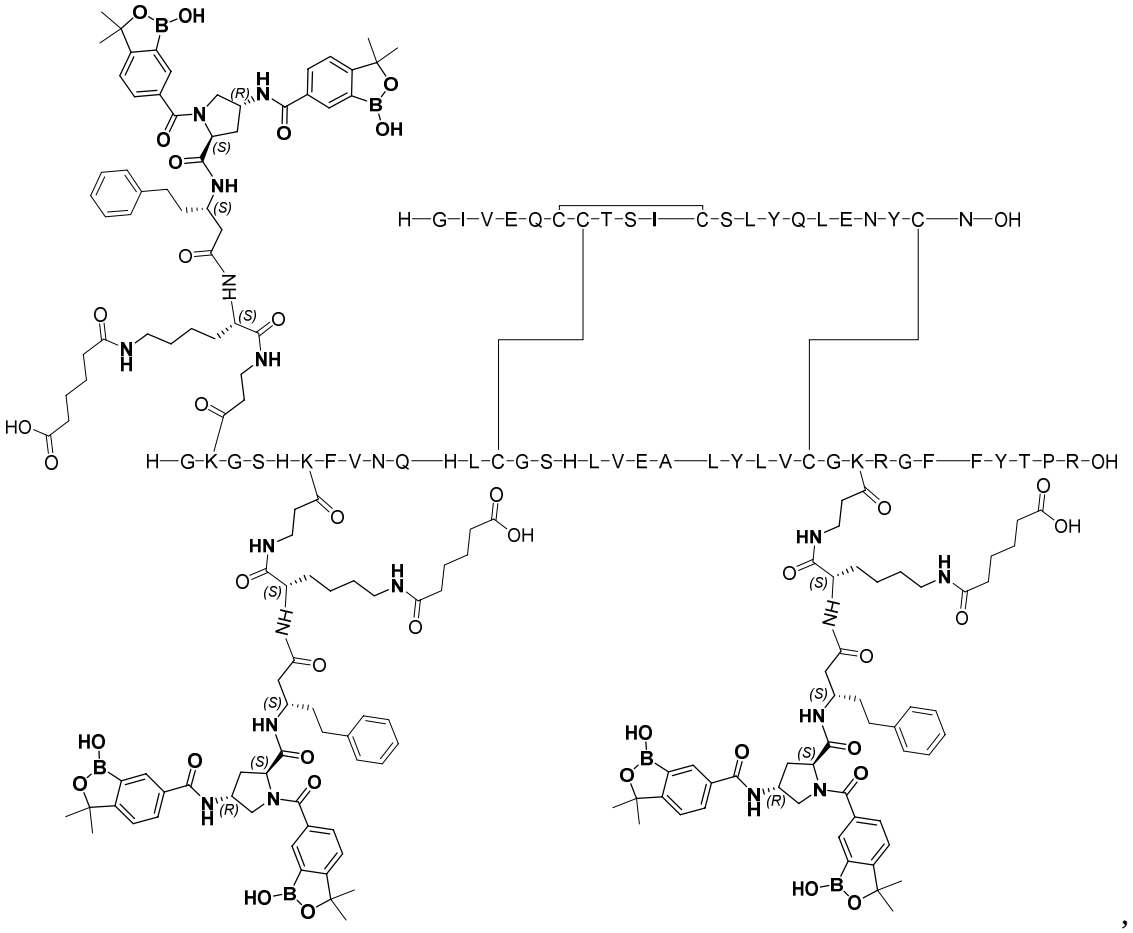
,

Example 69A:



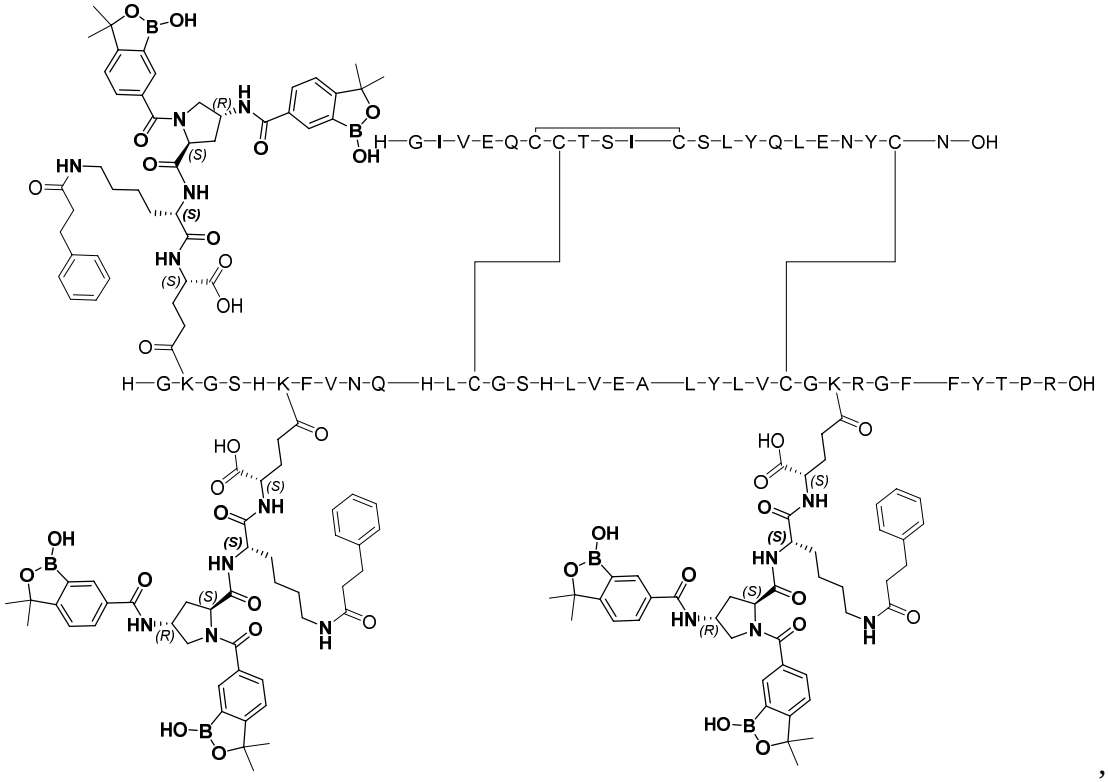
,

Example 70A:



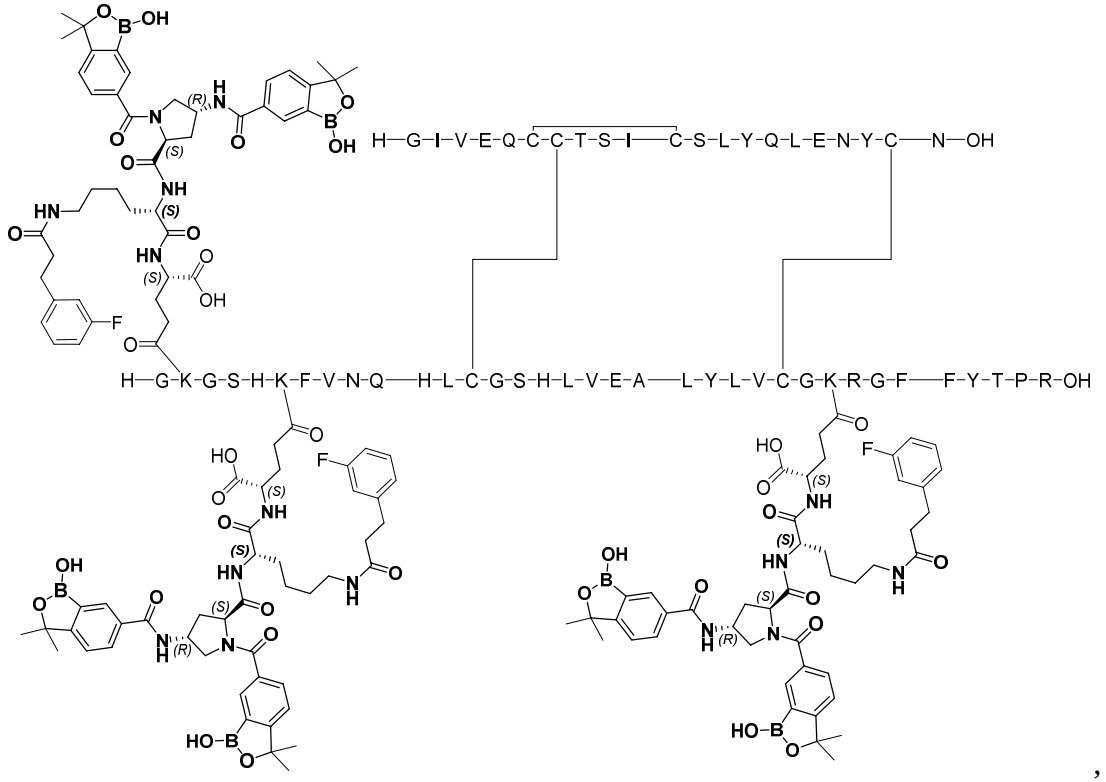
,

Example 71A:



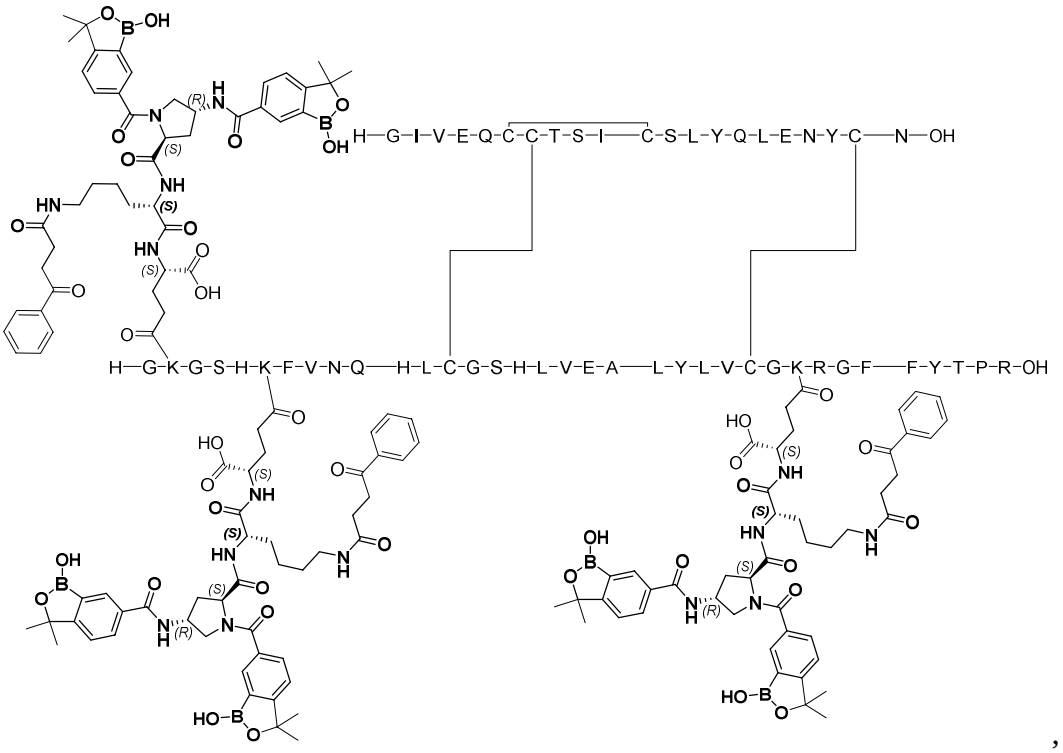
,

Example 72A:



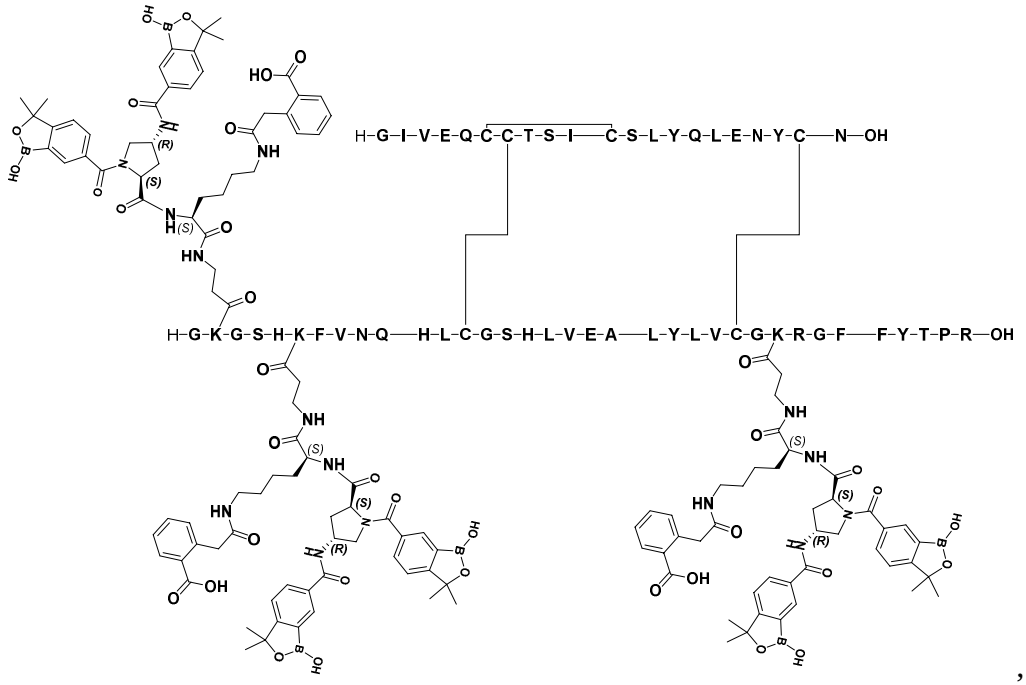
,

Example 73A:



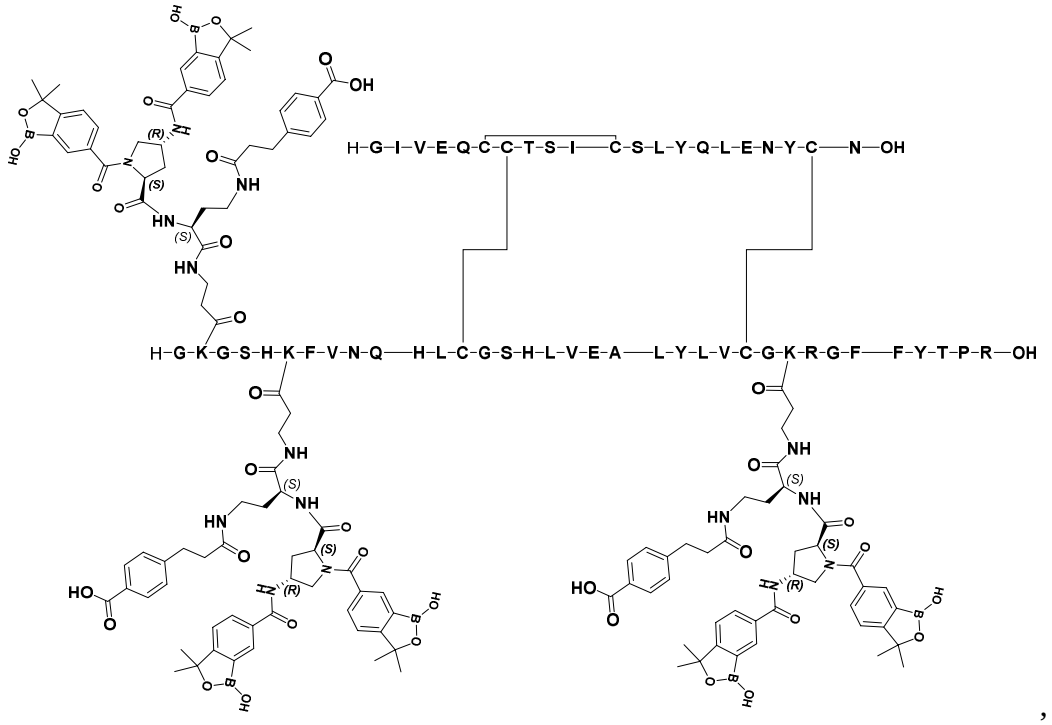
,

Example 74A:



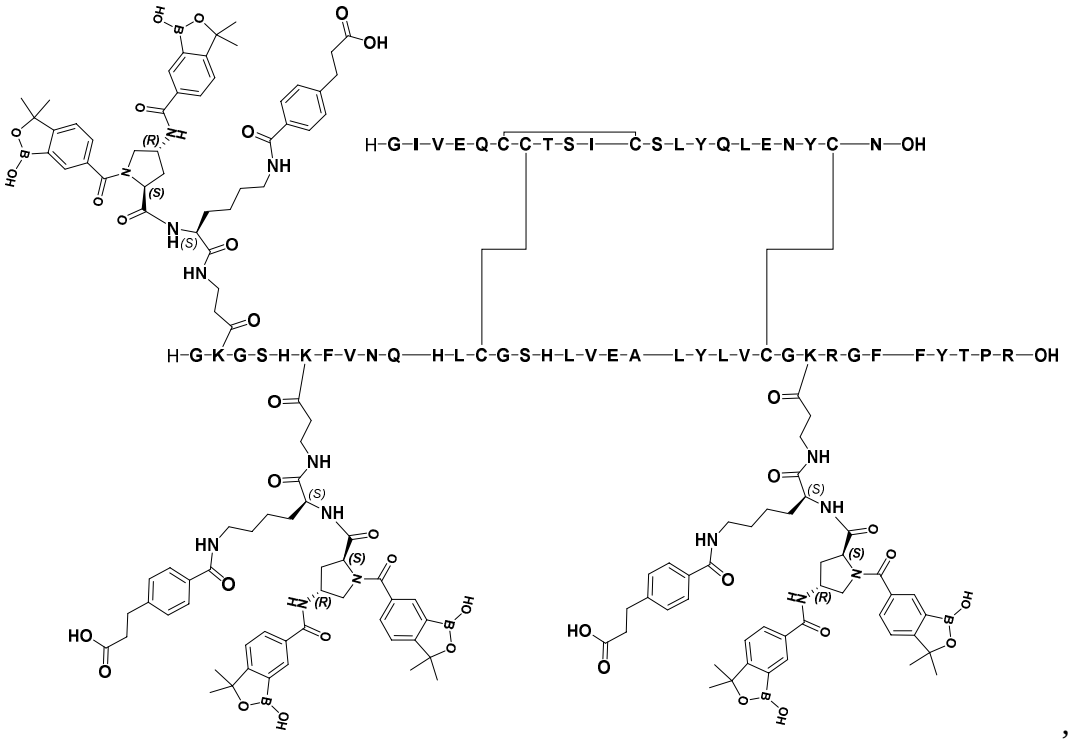
,

Example 75A:



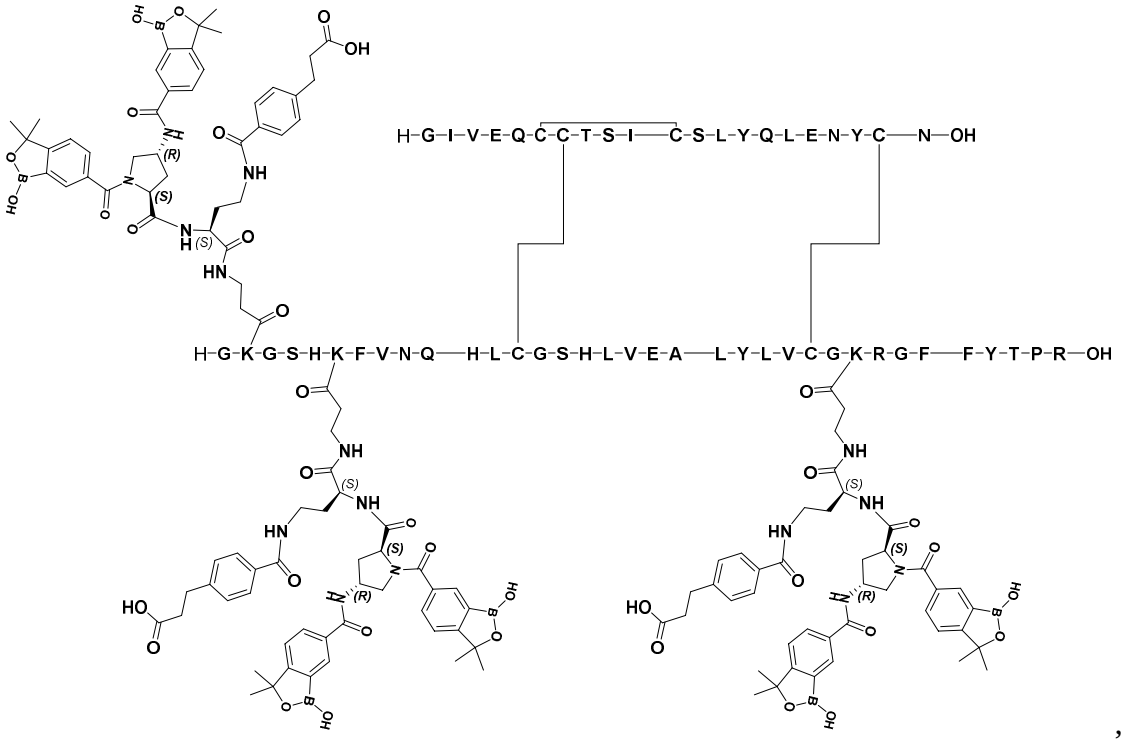
,

Example 76A:



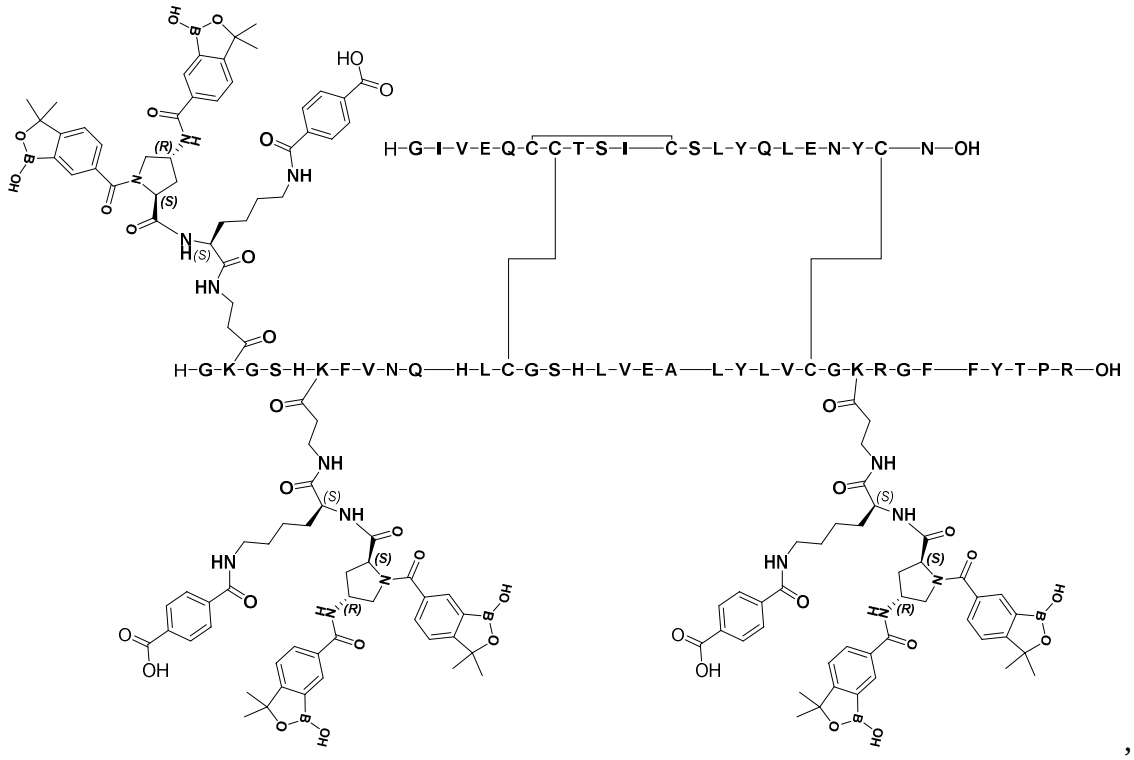
,

Example 77A:



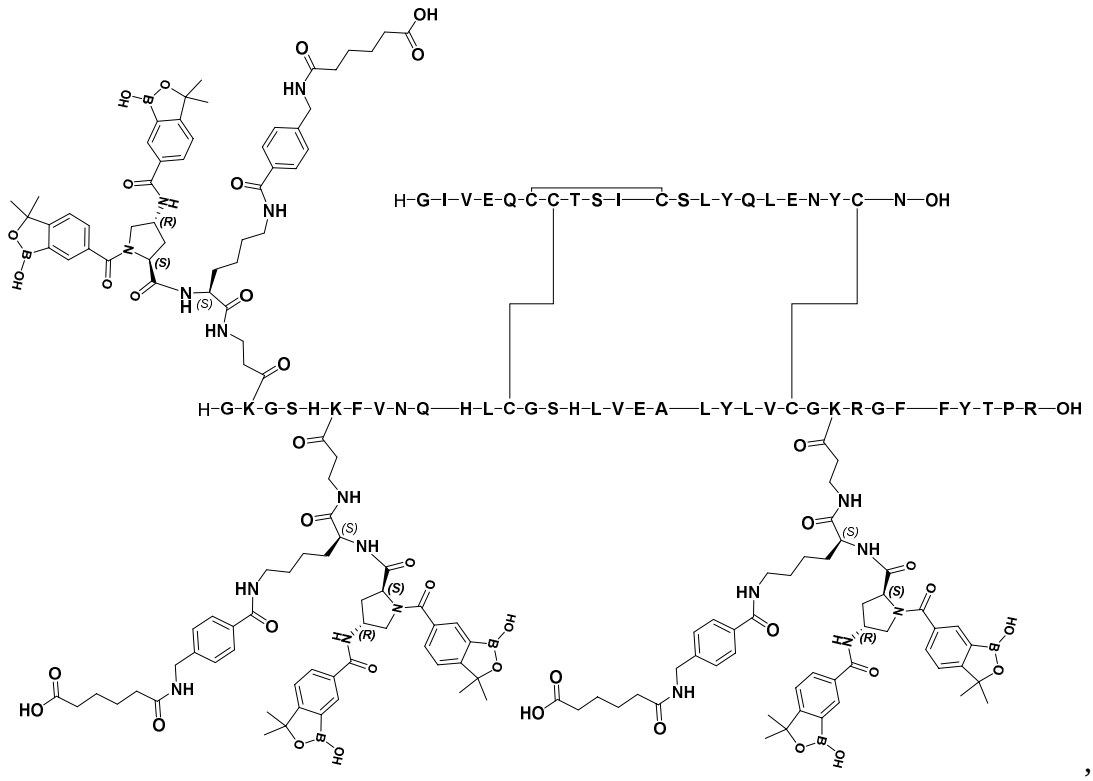
,

Example 78A:



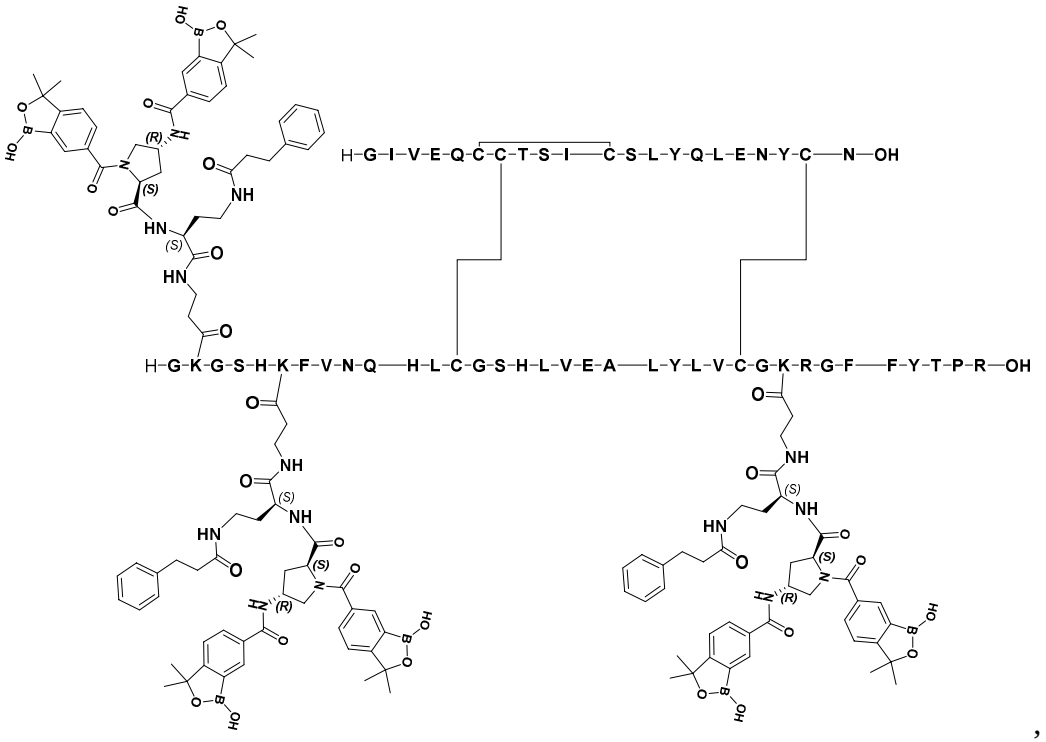
,

Example 79A:



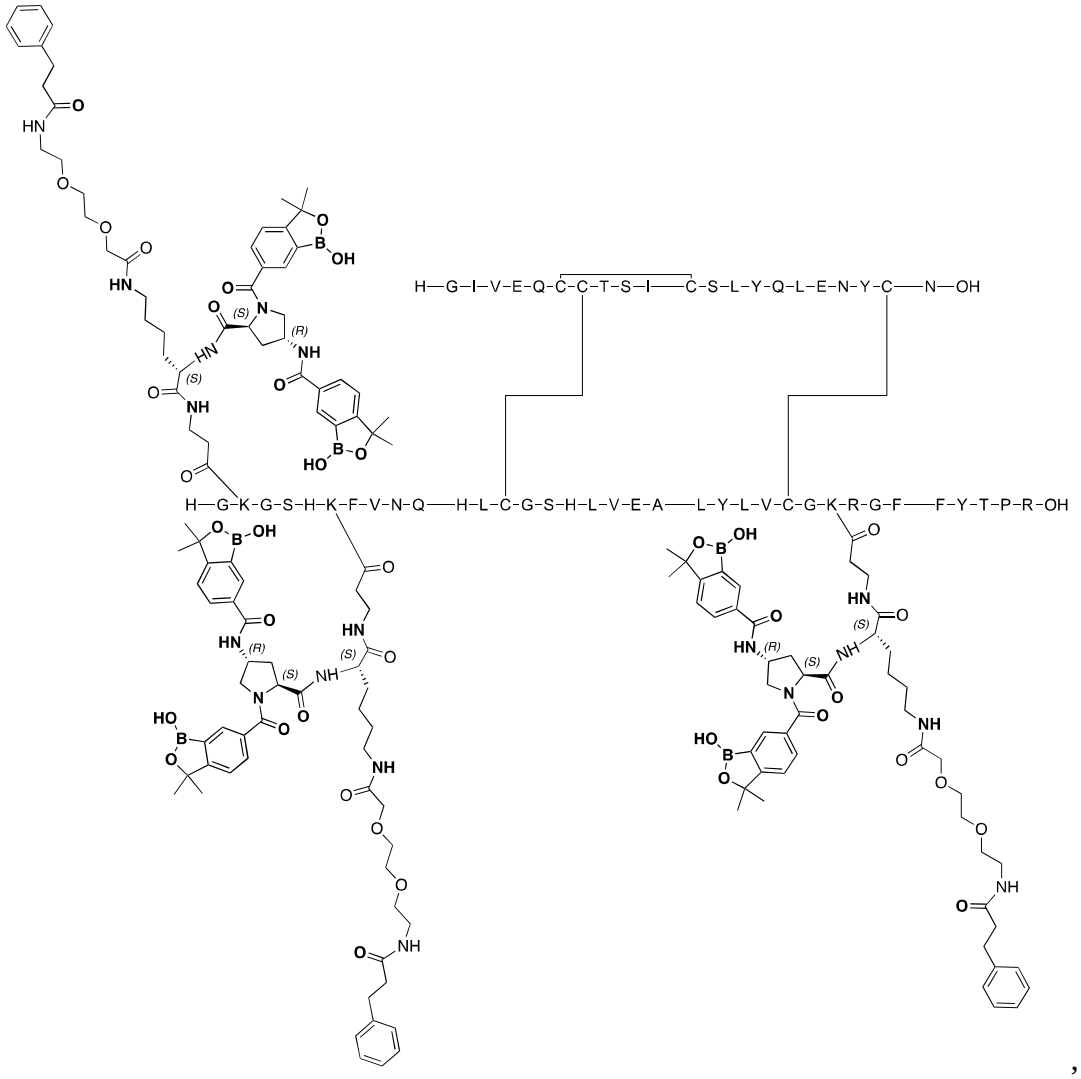
,

Example 80A:



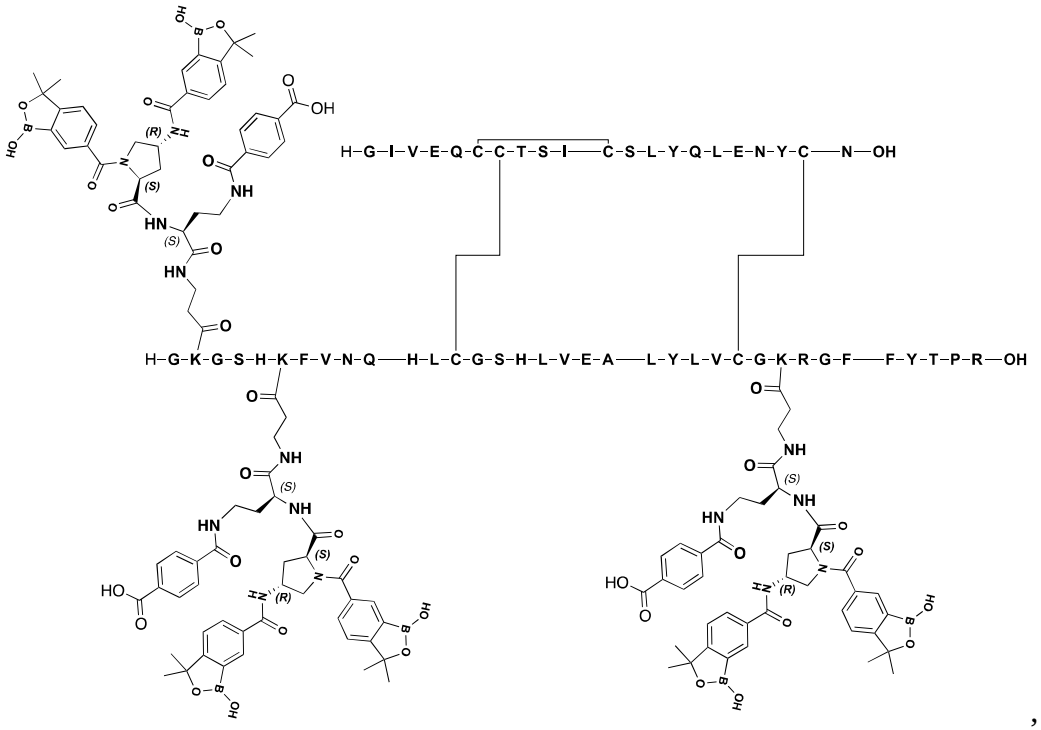
,

Example 81A:



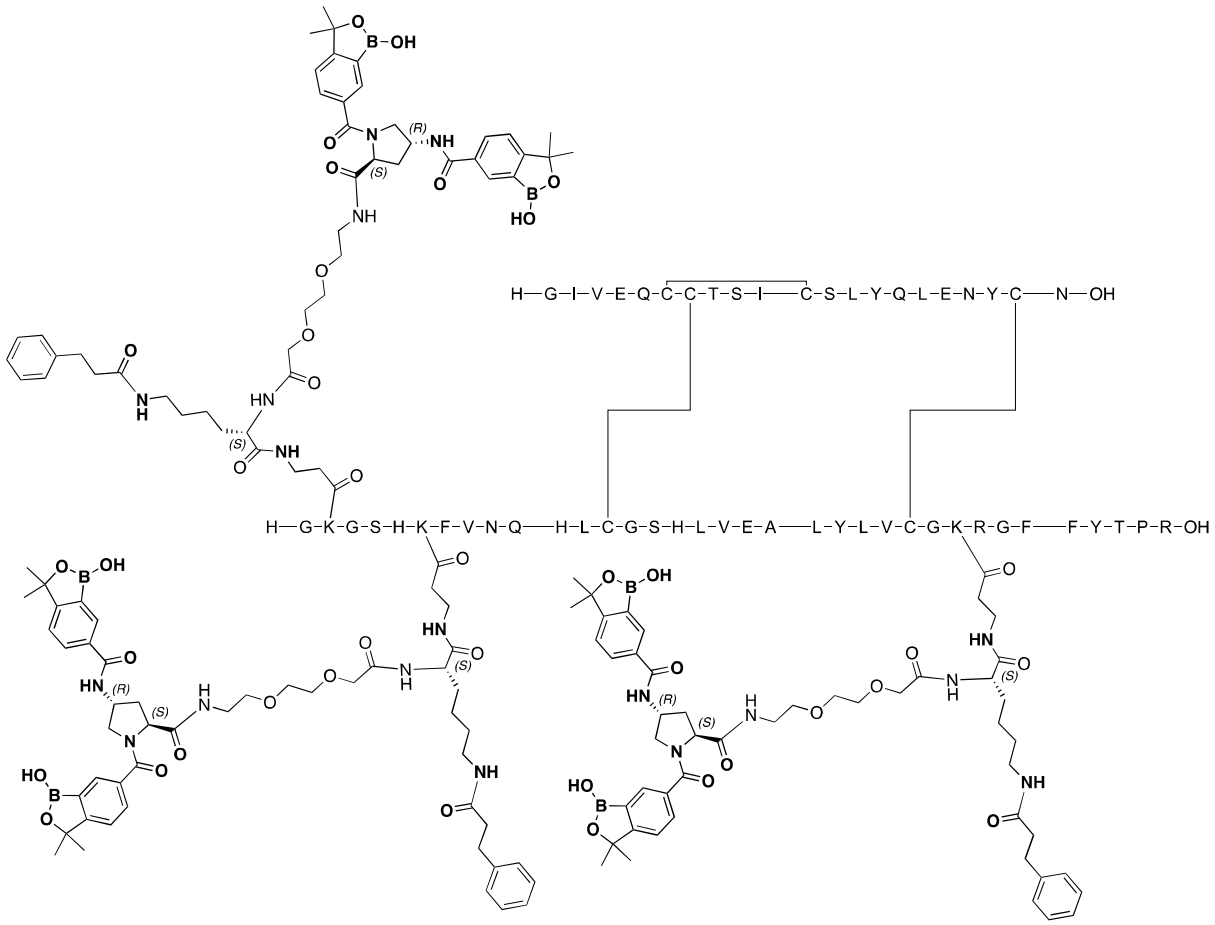
,

Example 82A:



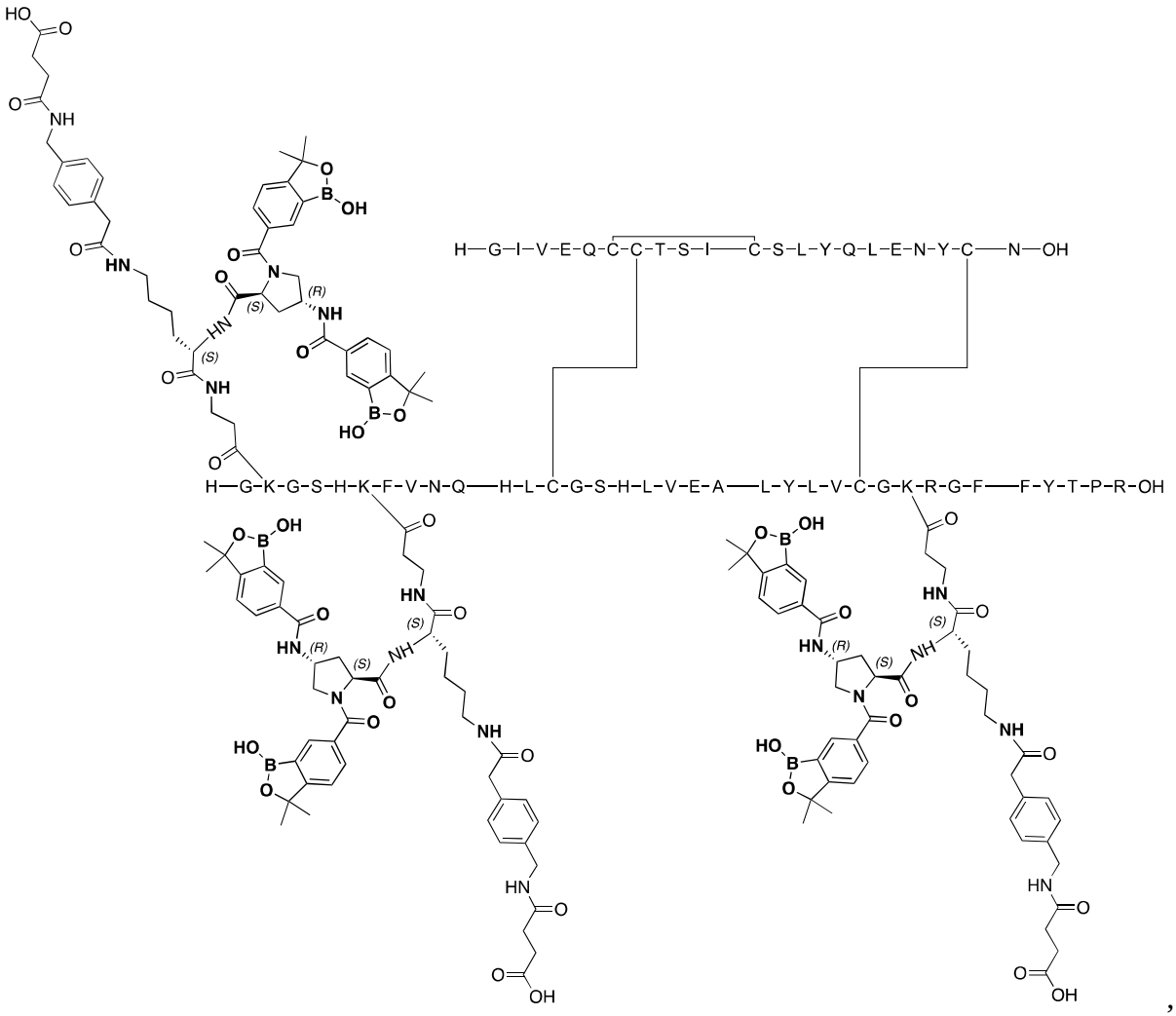
,

Example 83A:



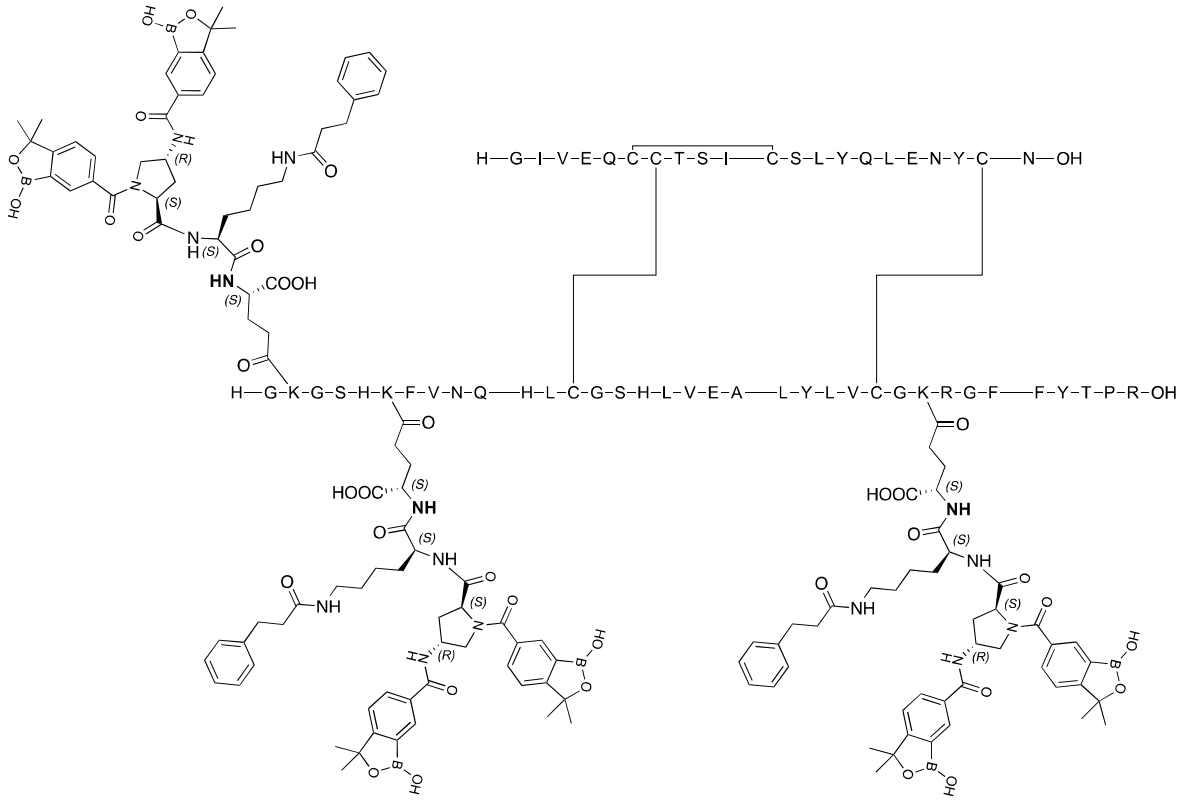
,

Example 84A:


H—G—I—V—E—Q—C—C—T—S—I—C—S—L—Y—Q—L—E—N—Y—C—N—OH
H—G—K—G—S—H—K—F—V—N—Q—H—L—C—G—S—H—L—V—E—A—L—Y—L—V—C—G—K—R—G—F—F—Y—T—P—R—OH

,

Example 85A:



; or

a pharmaceutically acceptable salt thereof, an isotope thereof, and combinations thereof.

In another aspect, there is provided a pharmaceutical composition comprising at least one compound or a pharmaceutically acceptable salt thereof as described herein and a pharmaceutically acceptable carrier.

In another aspect, there is provided a compound as described herein, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein, for use as a medicament.

In another aspect, there is provided use of a compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein, in the manufacture of a medicament for the treatment of type 2 diabetes, type 1 diabetes, diabetes during pregnancy, pre-diabetes, MODY 1 diabetes, MODY 2 diabetes, MODY 3 diabetes, impaired glucose tolerance, hyperglycemia, metabolic syndrome, obesity, control of blood sugar levels, Alzheimer's disease, mood disorders, or psychiatric disorders.

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.

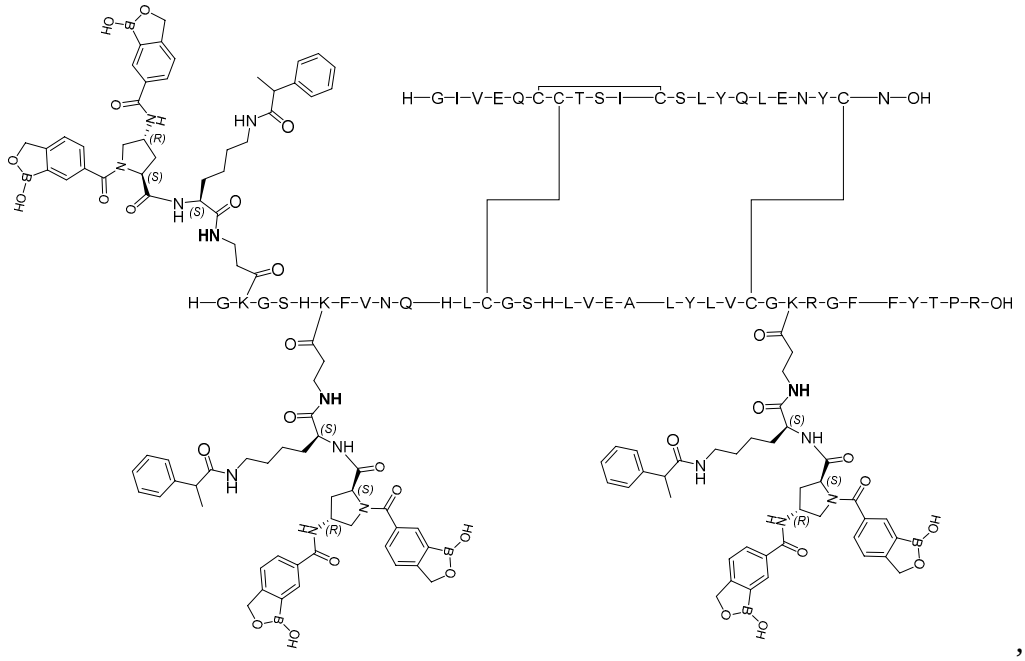
Scaffolds that position the boron functionality (*e.g.*, sensors) of the aromatic boron-containing compounds in a specific or particular ensemble of geometries can increase selectivity towards a specific vicinal diol while simultaneously maintaining affinity for the diol of interest. According to some embodiments, aromatic boron-containing compounds disclosed herein have different pendant groups on the aromatic boron-based scaffolds along with which specific scaffold geometries that impact binding to hydroxyl containing molecules.

According to some embodiments, the compounds of the present disclosure comprise aromatic boron-containing compounds that orient the boron functionalities in three dimensional space, so that the boron-containing compounds are spatially oriented to engage hexoses containing vicinal diols, such that the boron groups can appropriately engage the hydroxyls in the vicinal diol molecule and provide enhancement of selectivity. In some embodiments, the

WHAT IS CLAIMED IS:

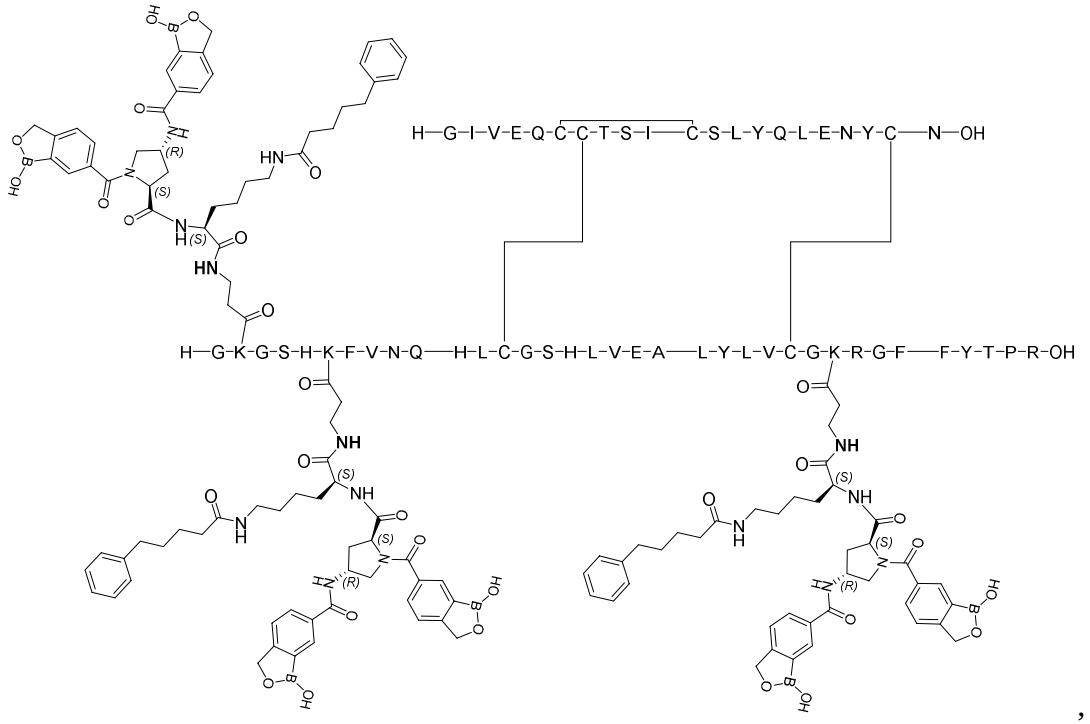
1. A compound selected from:

Example 1A:



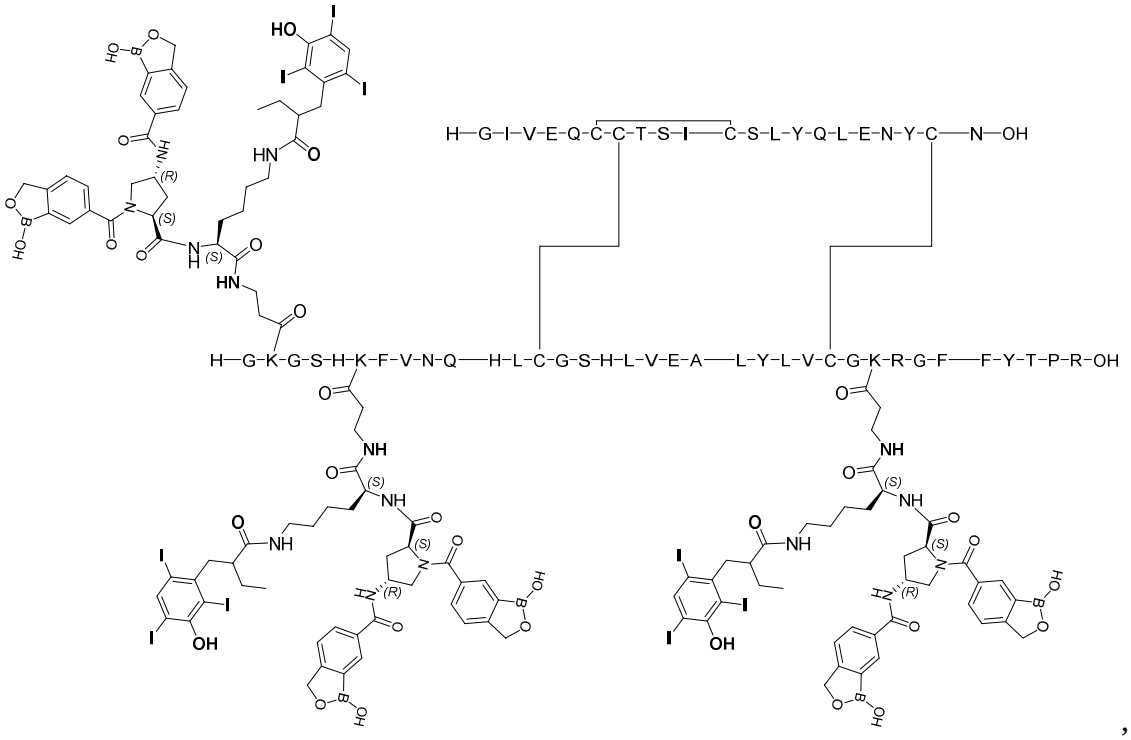
,

Example 2A:



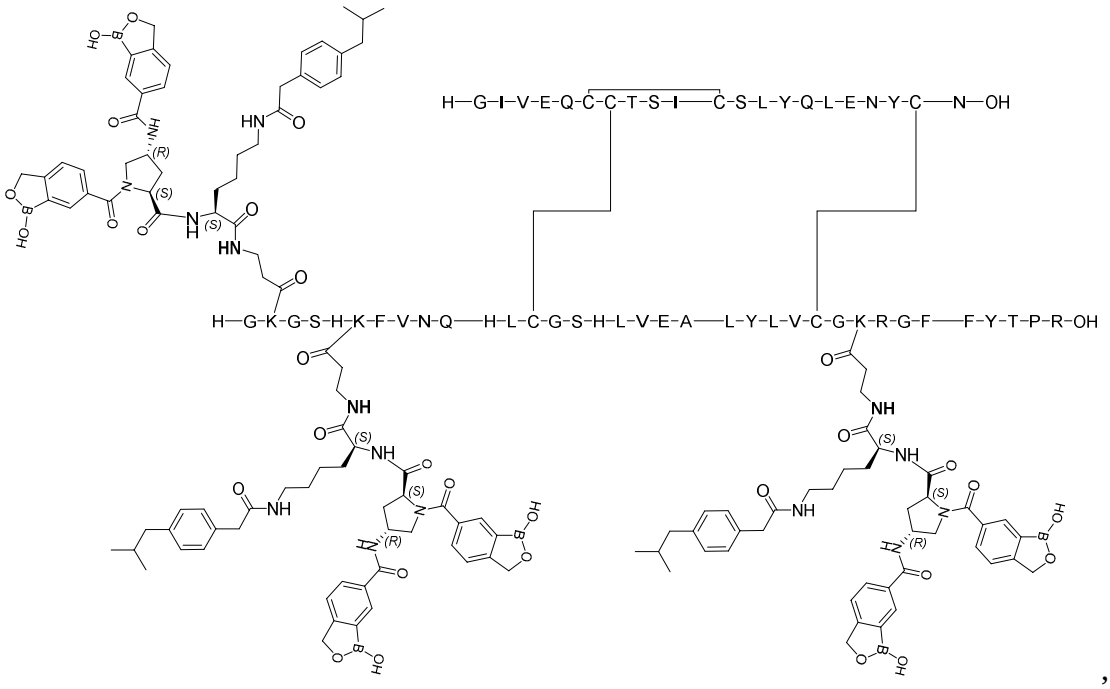
,

Example 3A:



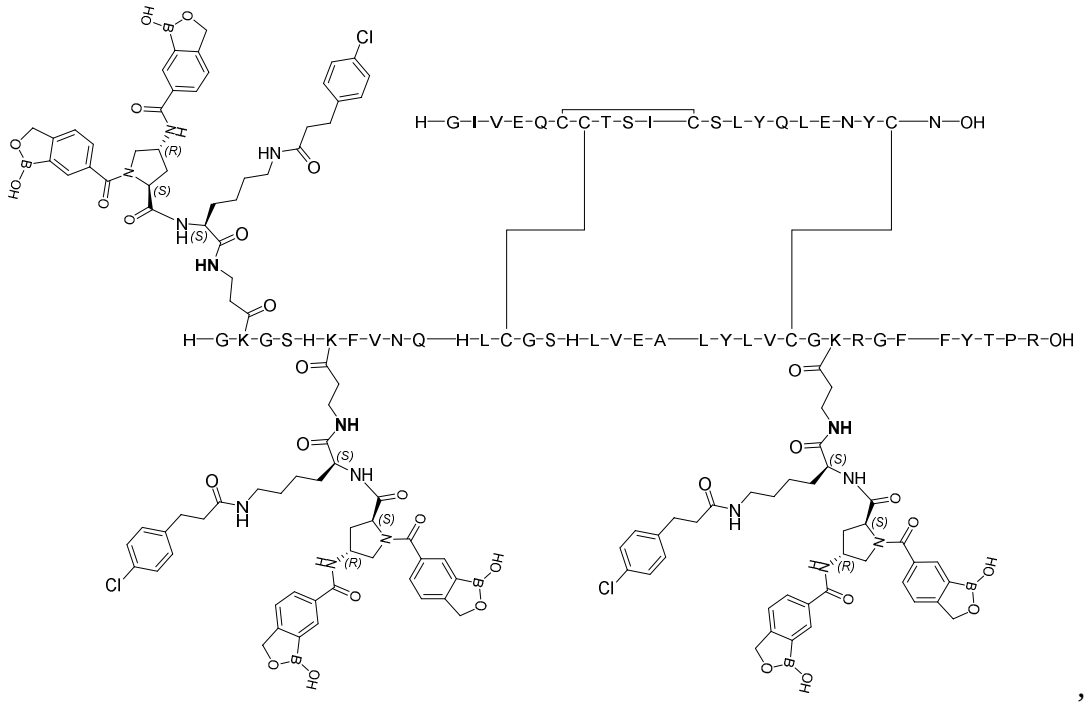
,

Example 4A:



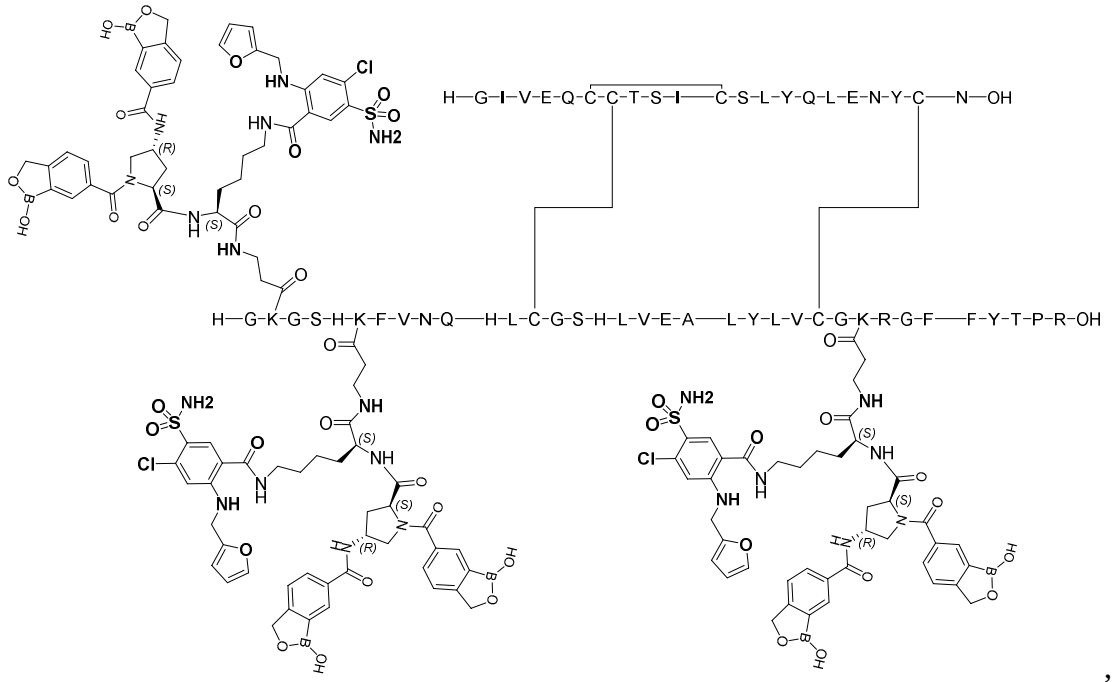
,

Example 5A:



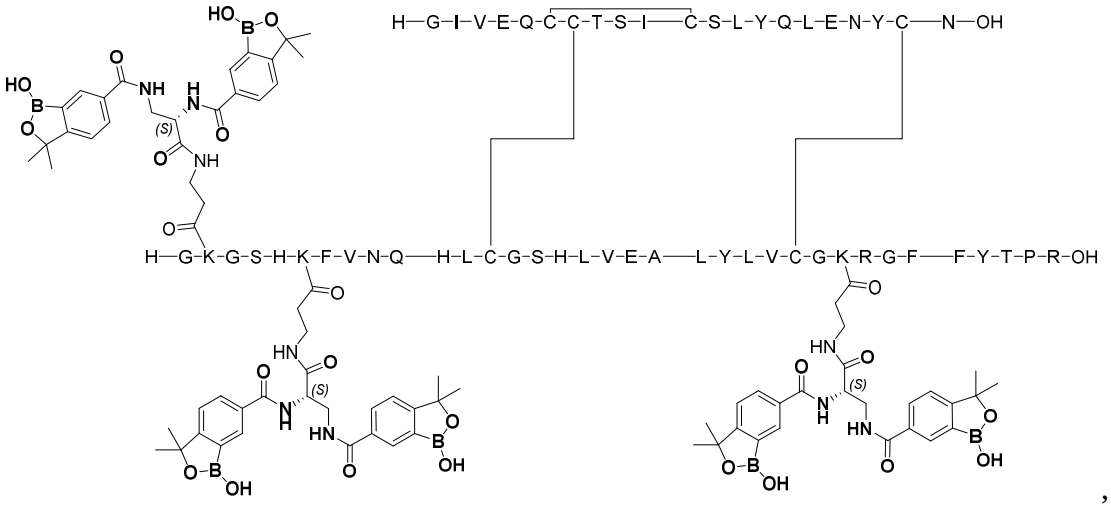
,

Example 6A:



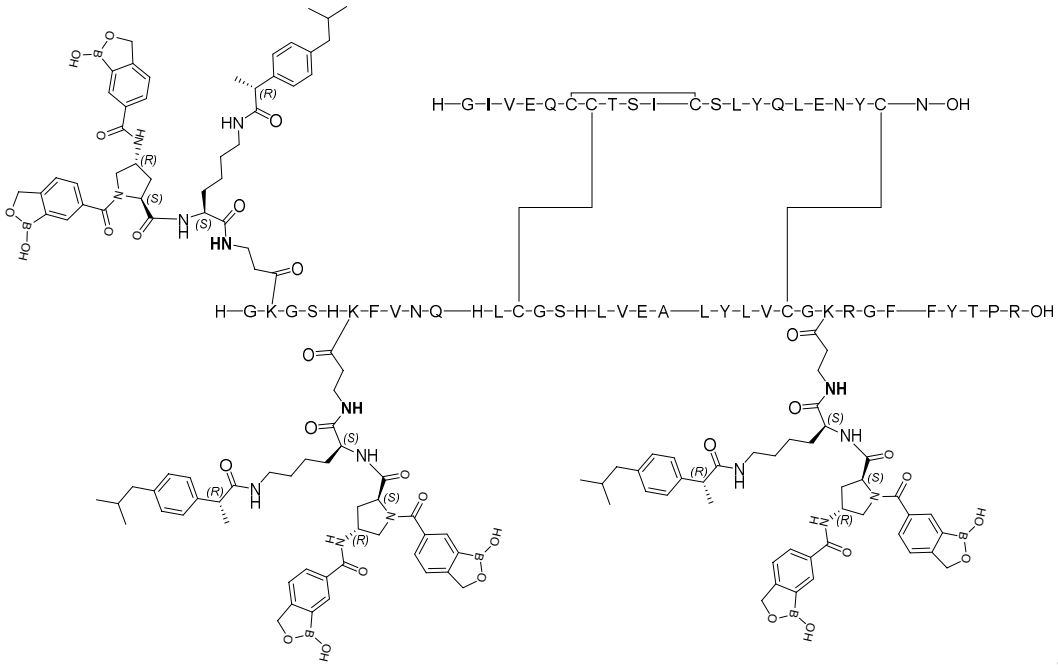
5 ,

Example 7A:



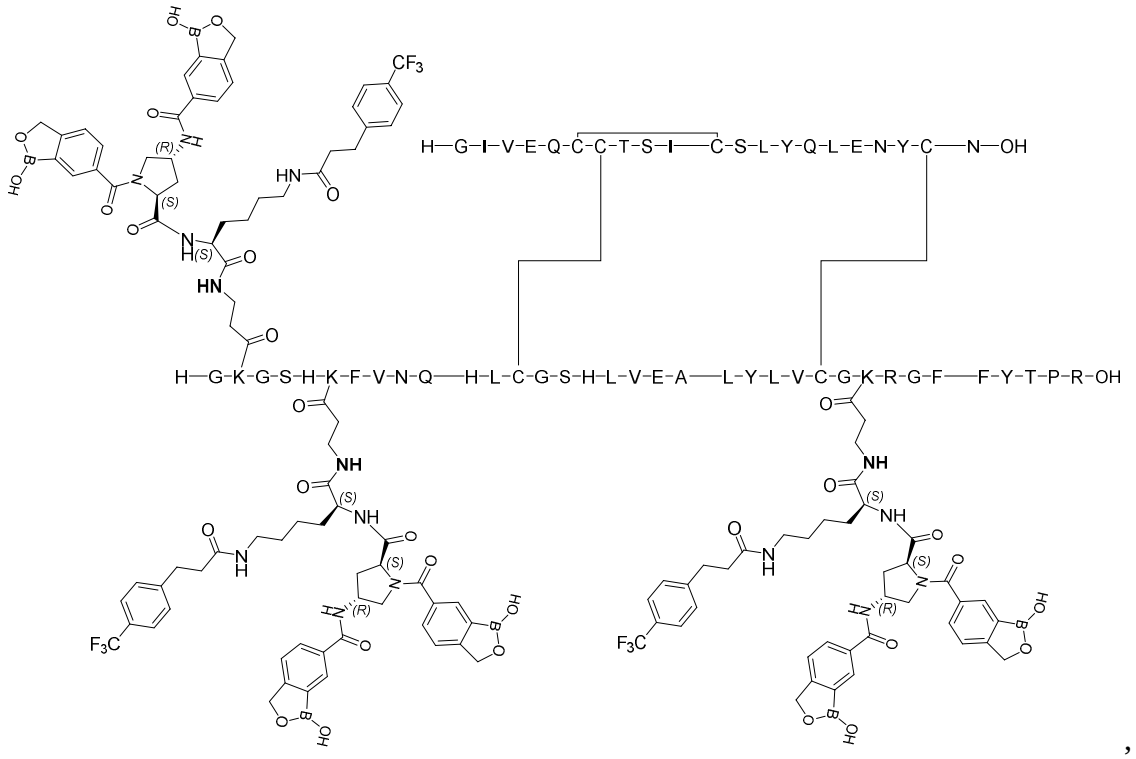
,

Example 8A:



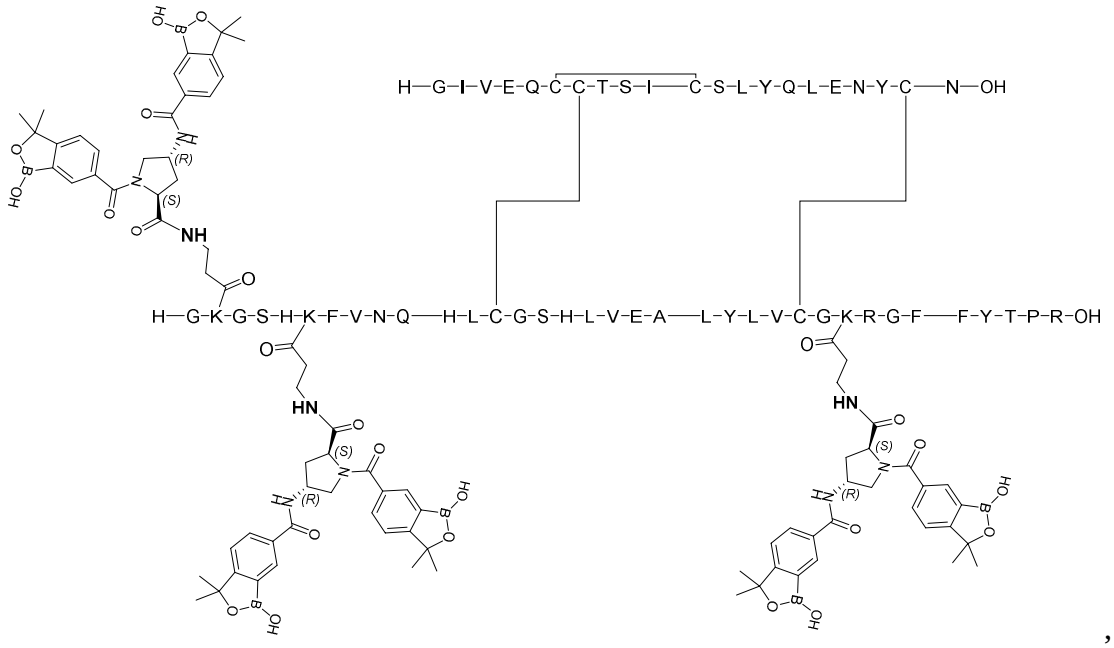
,

Example 9A:



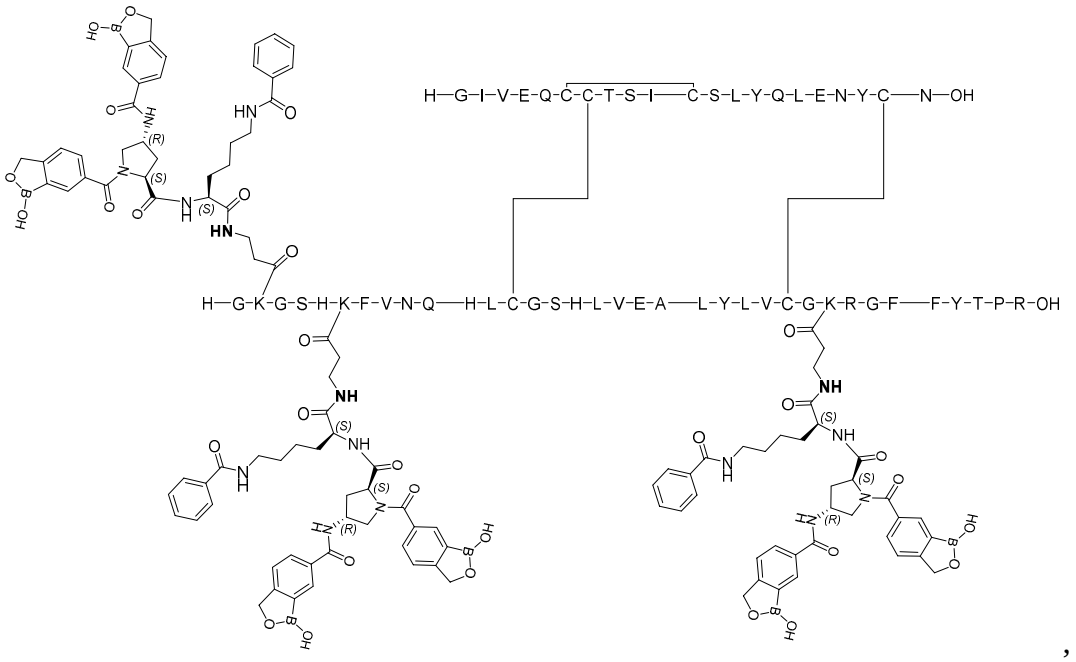
,

Example 10A:



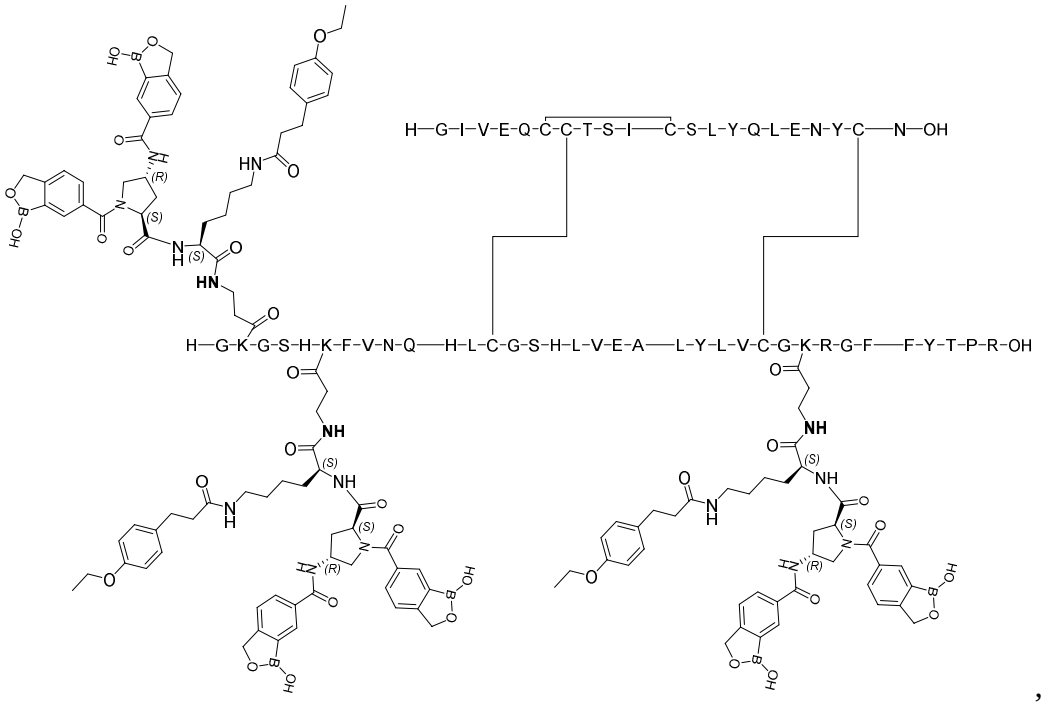
,

Example 11A:



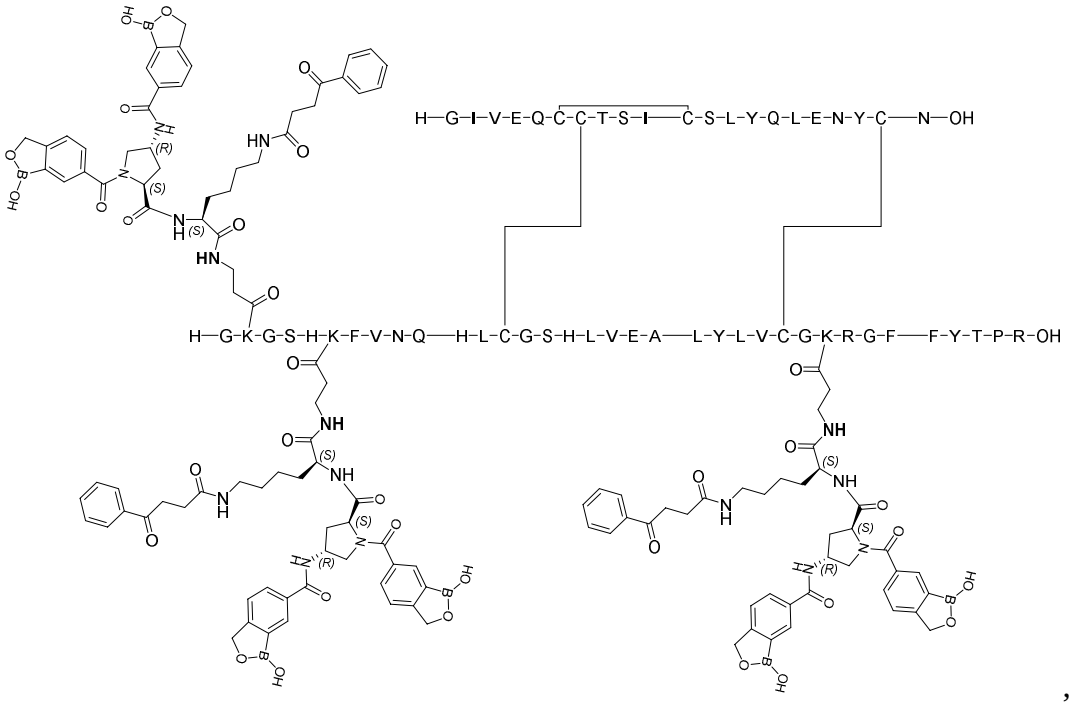
,

Example 12A:



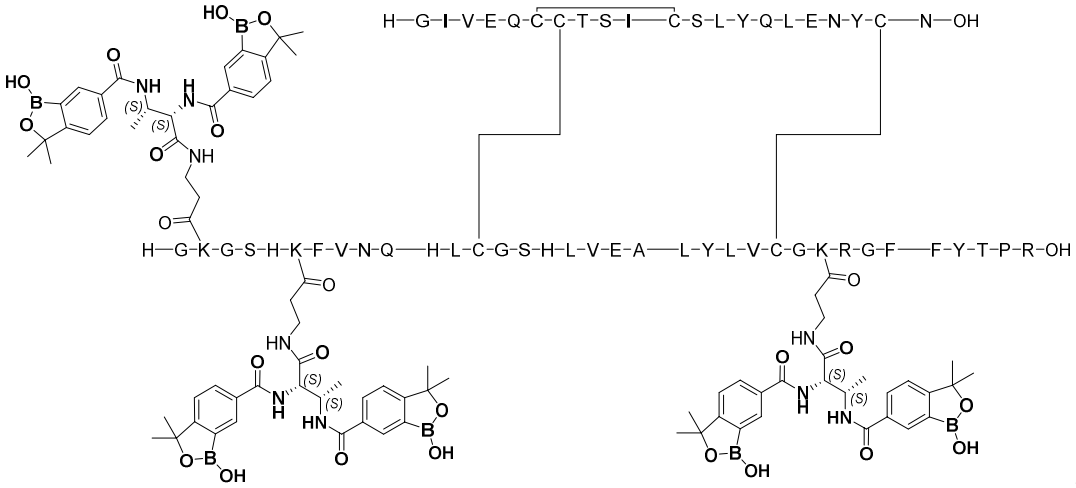
,

Example 13A:



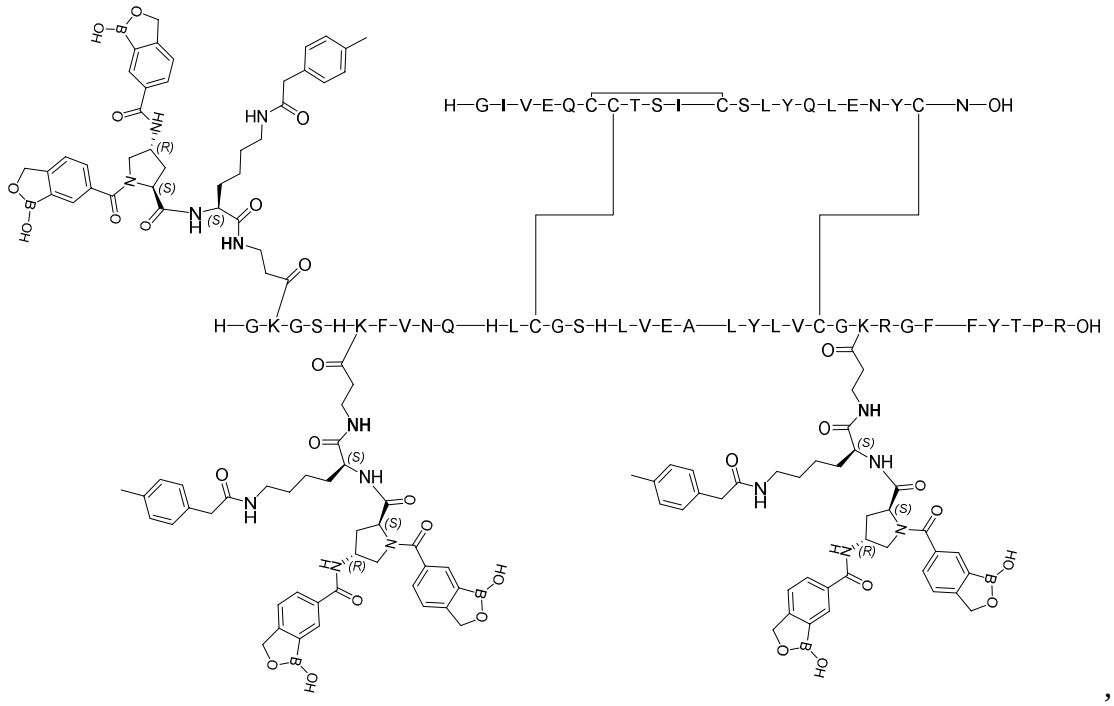
,

Example 14A:



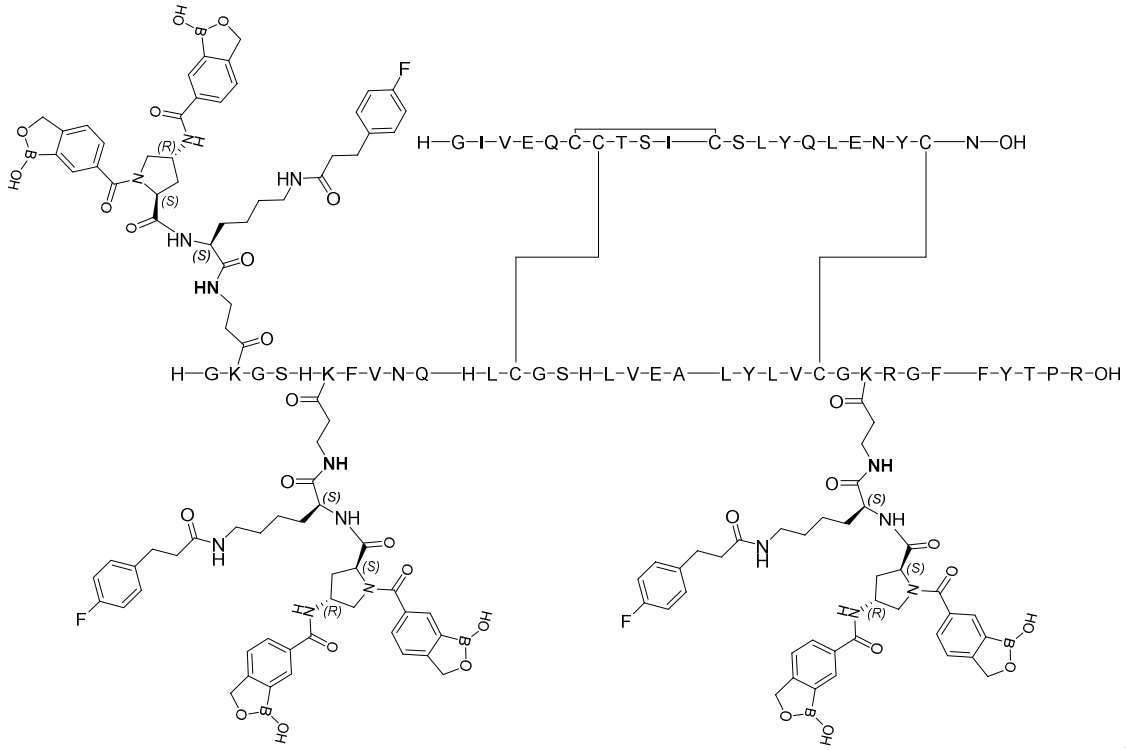
,

Example 15A:



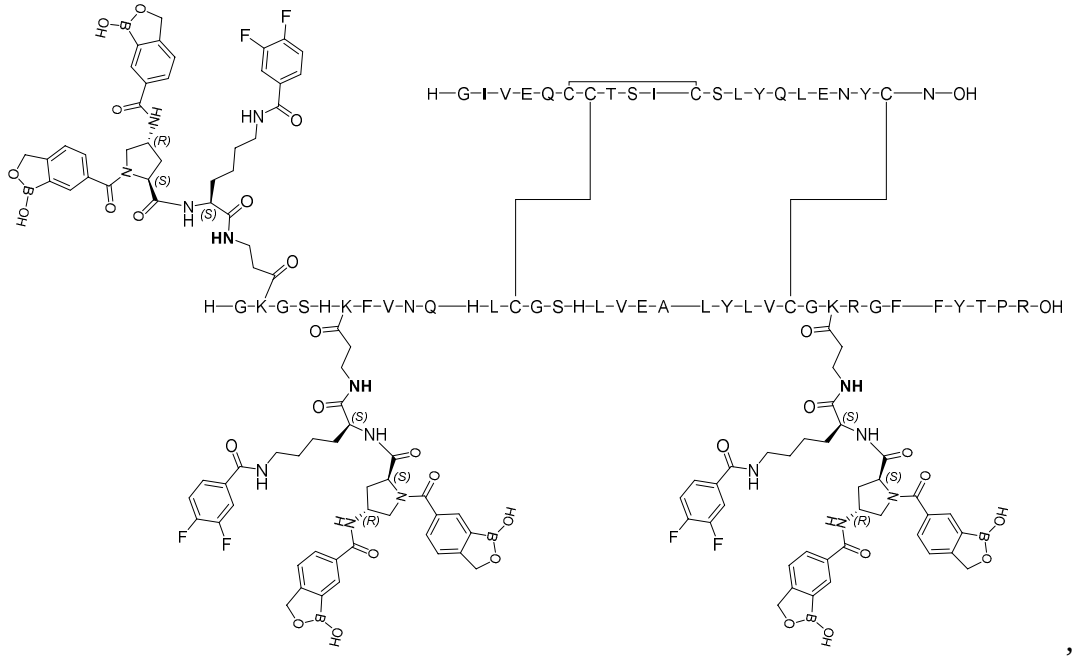
,

Example 16A:



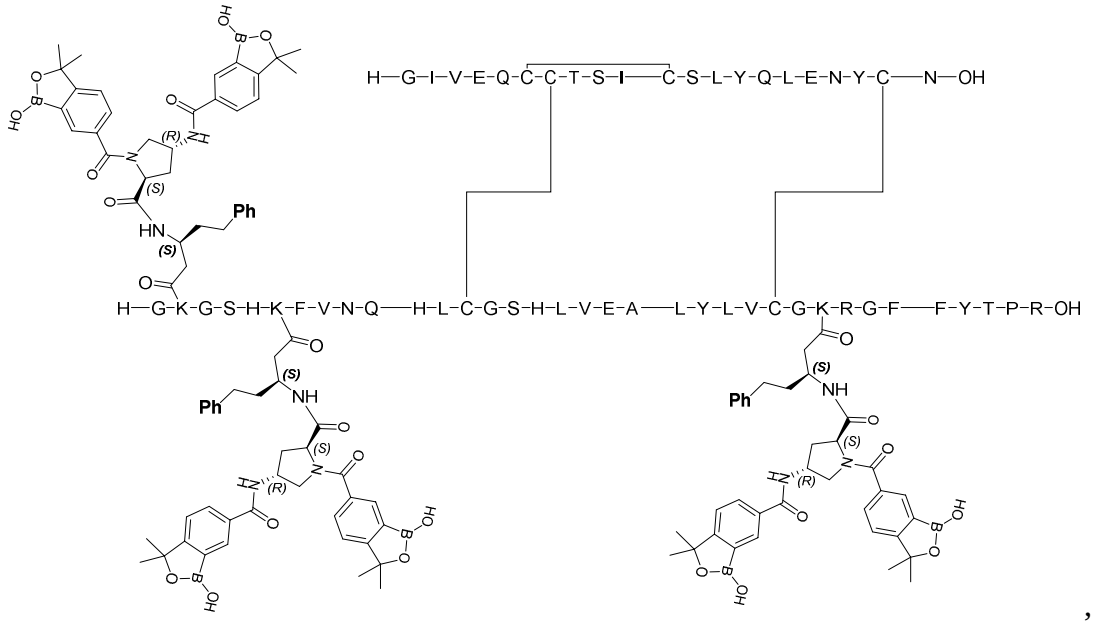
,

Example 17A:



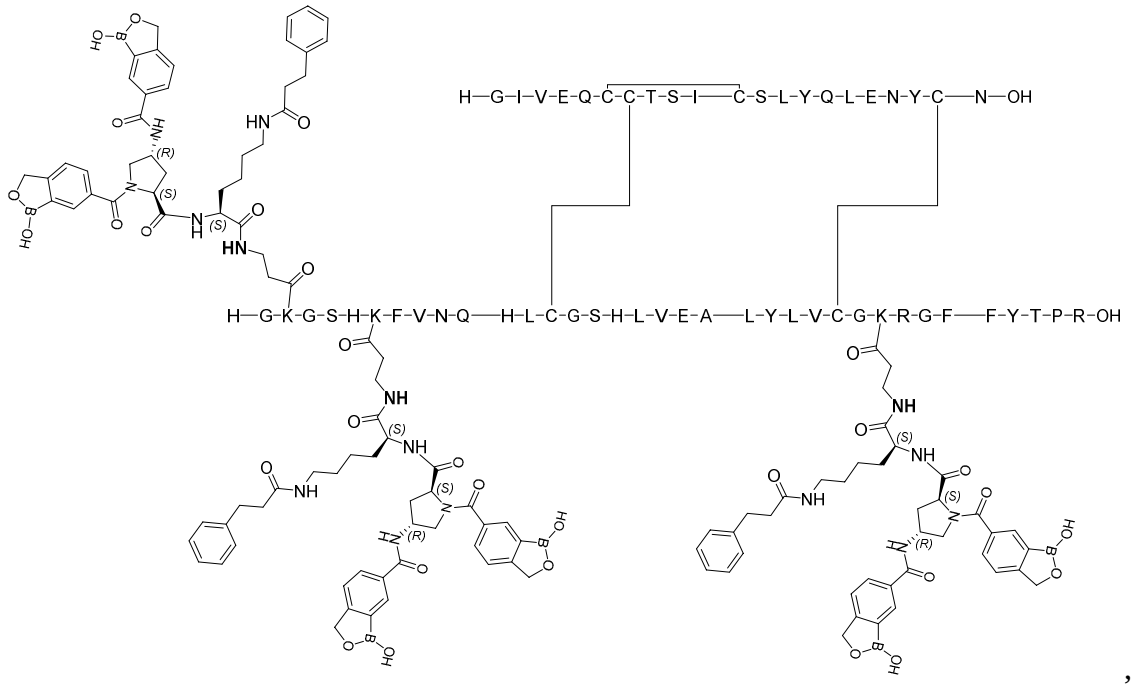
,

Example 18A:



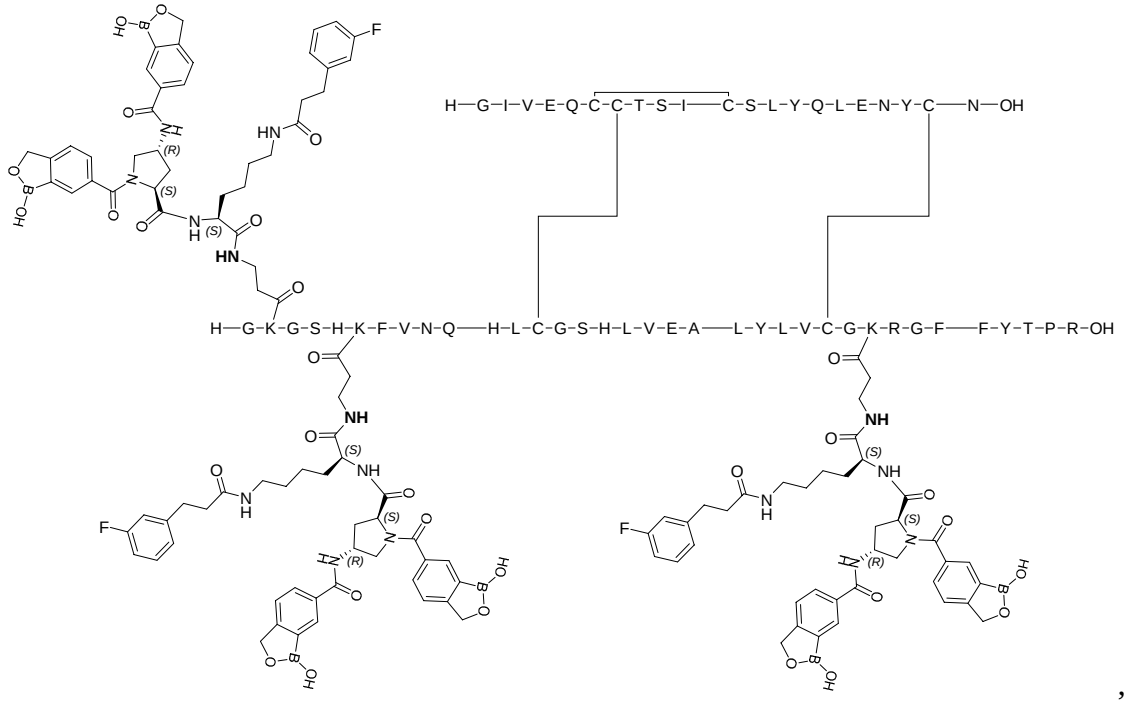
5 ,

Example 19A:



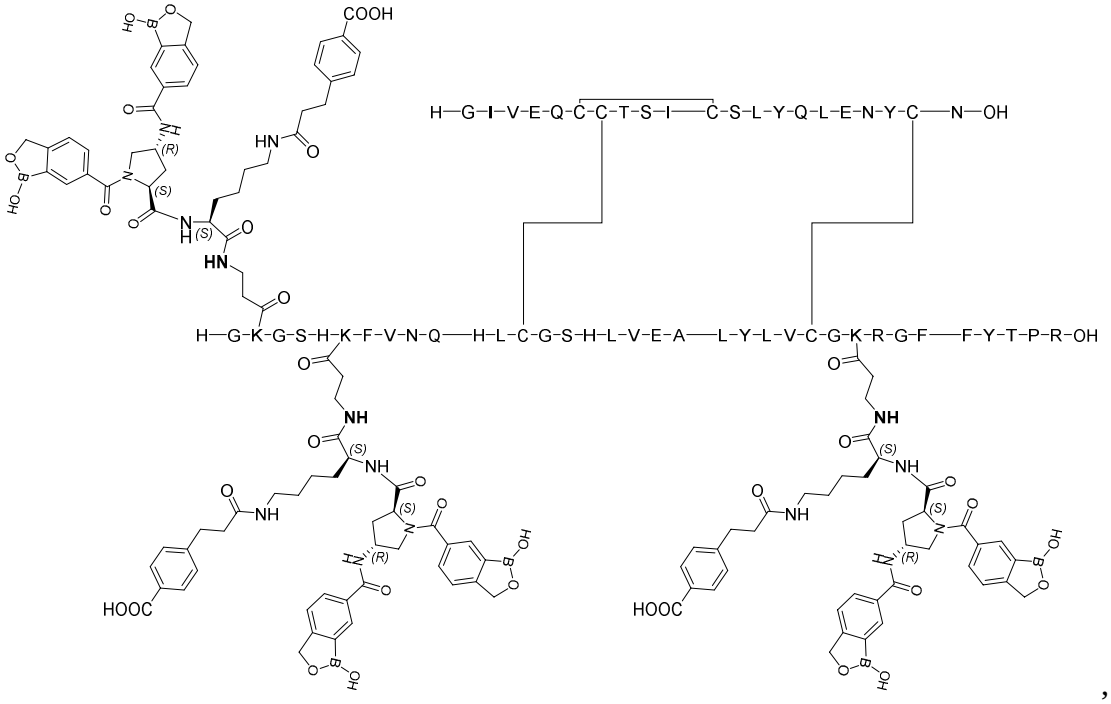
,

Example 20A:



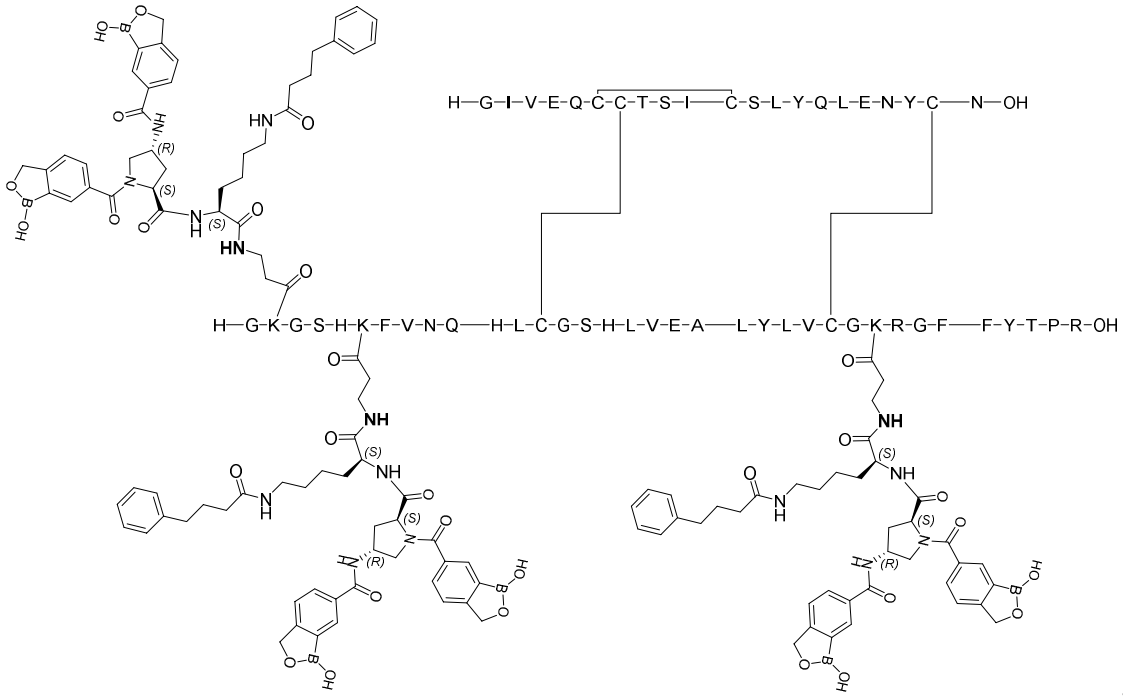
,

Example 21A:



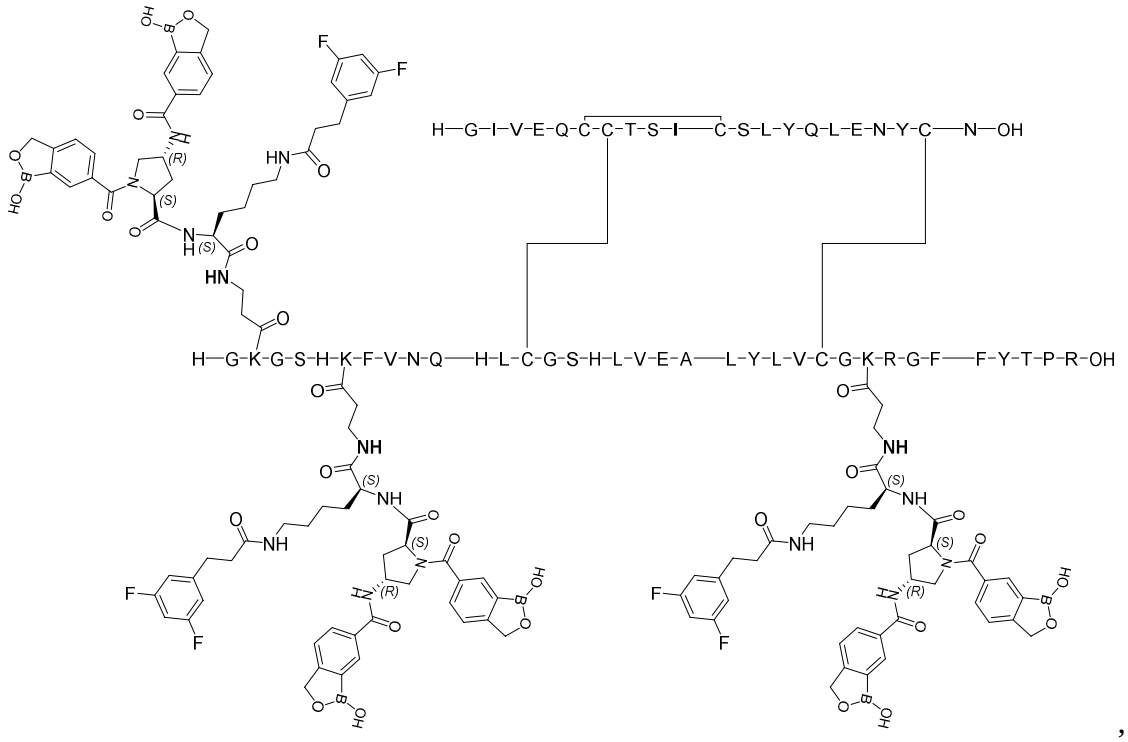
,

Example 22A:



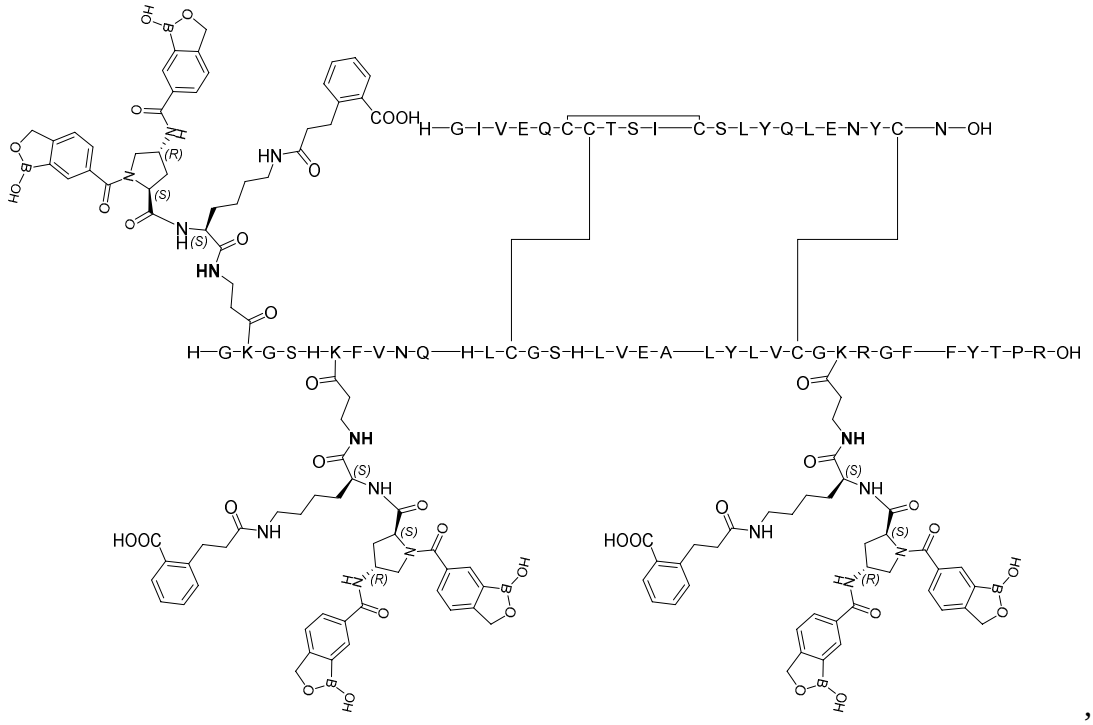
,

Example 23A:



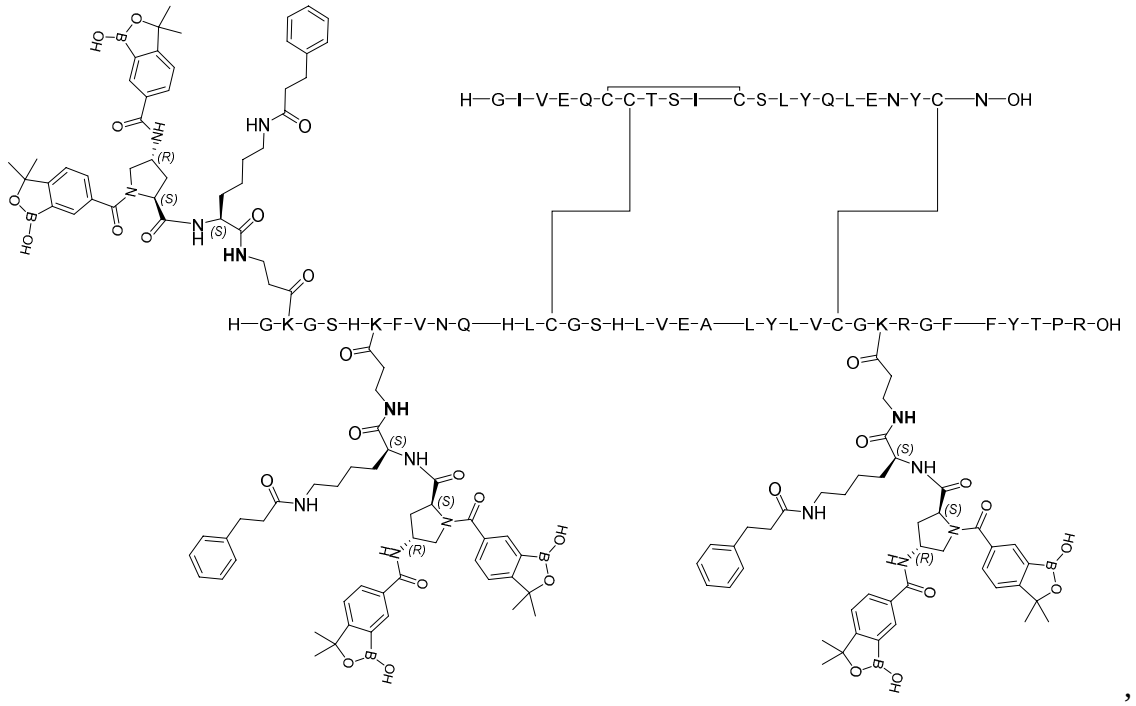
,

Example 24A:



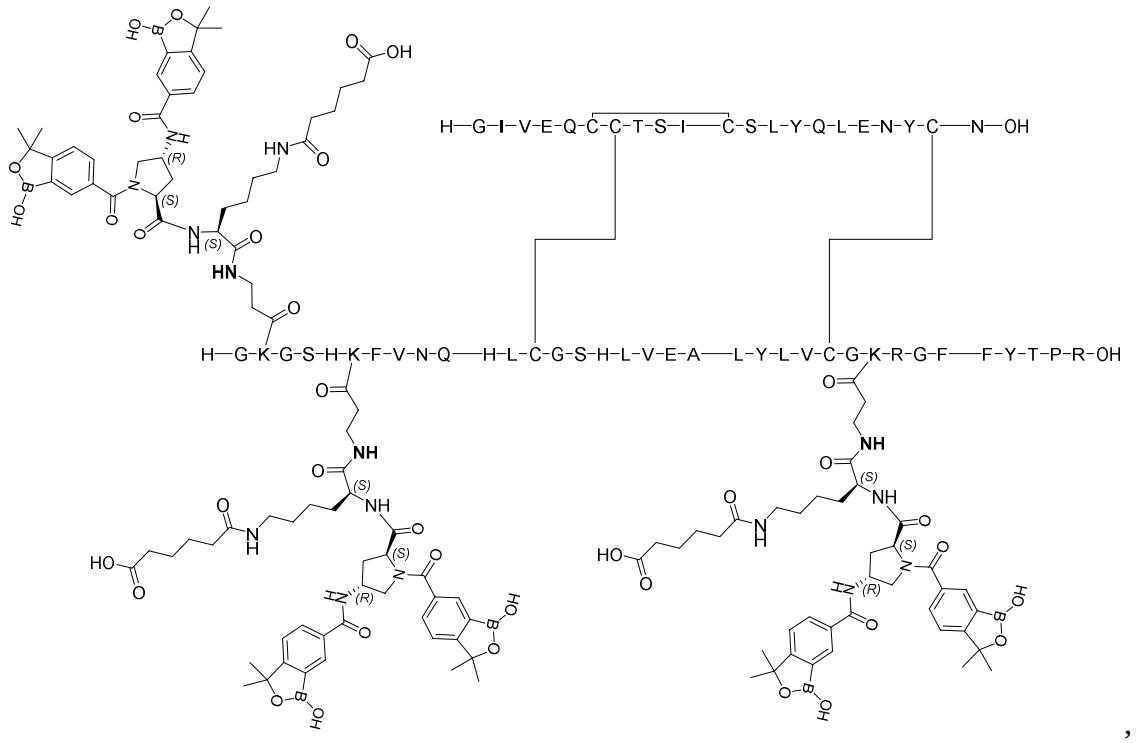
,

Example 25A:



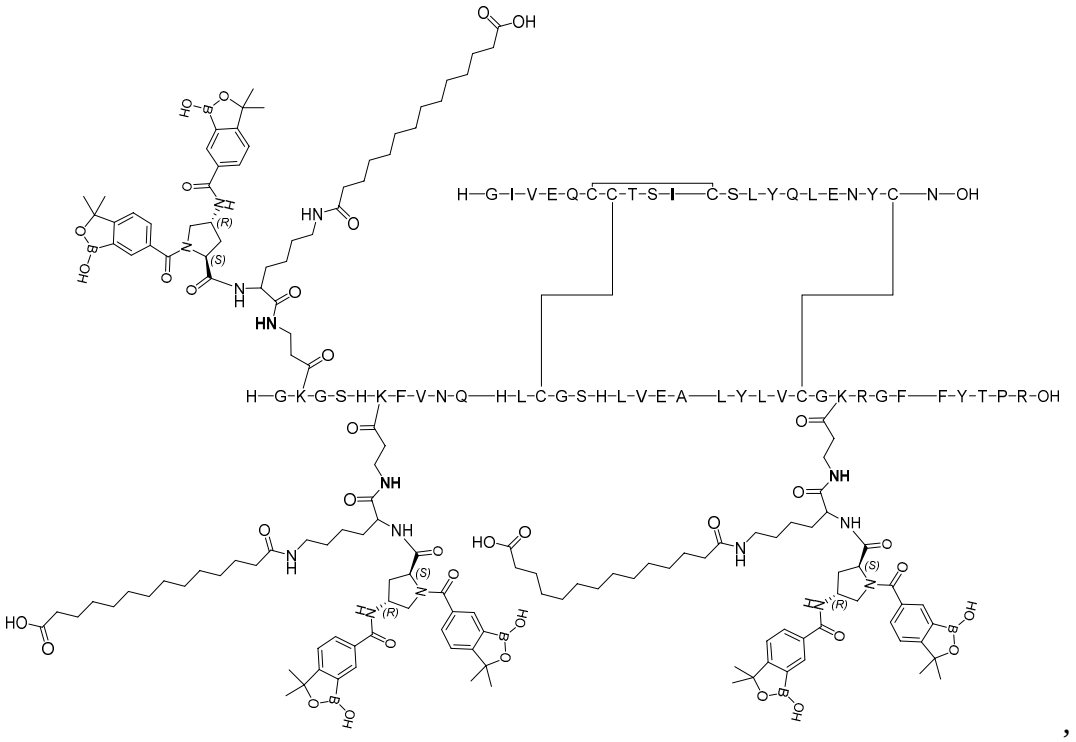
,

Example 26A:



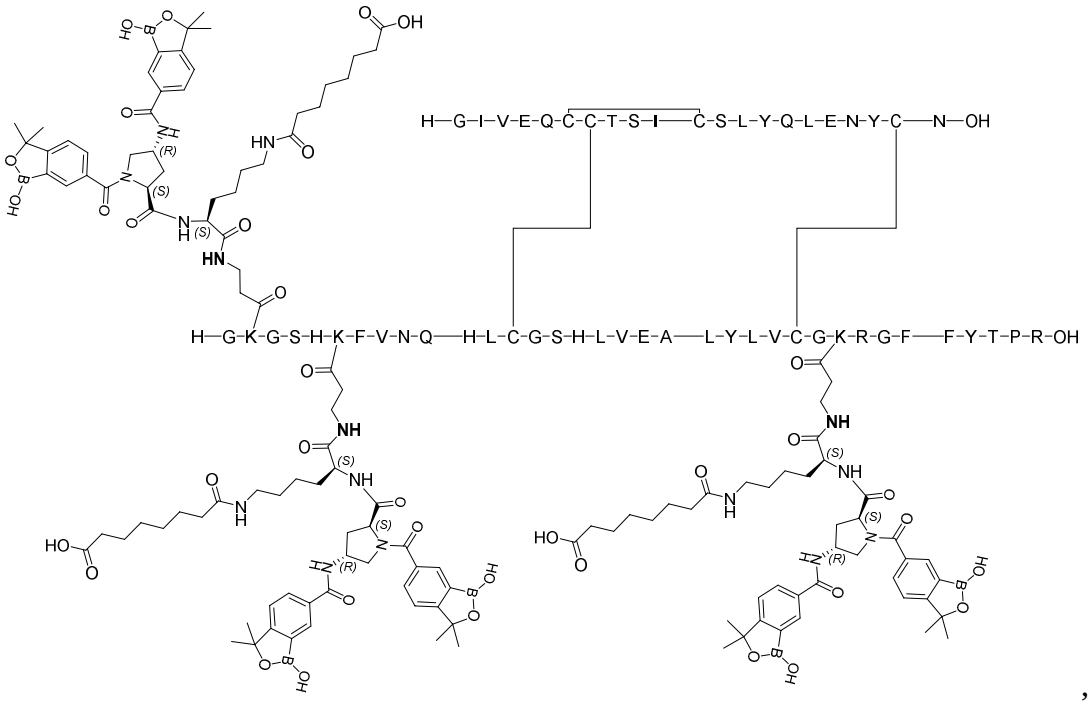
5 ,

Example 27A:



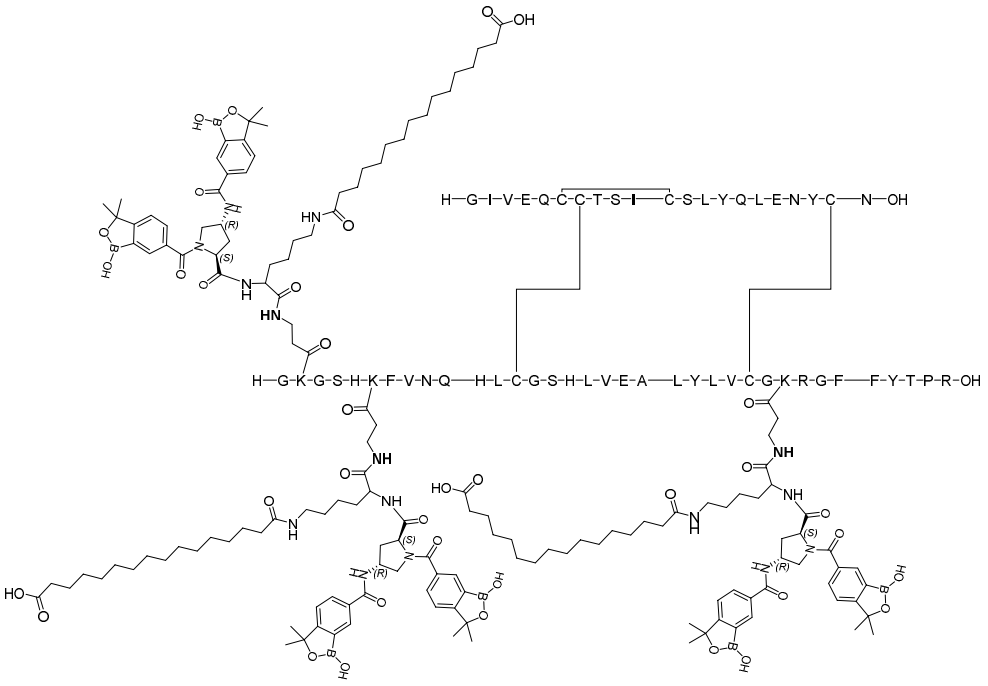
,

Example 28A:



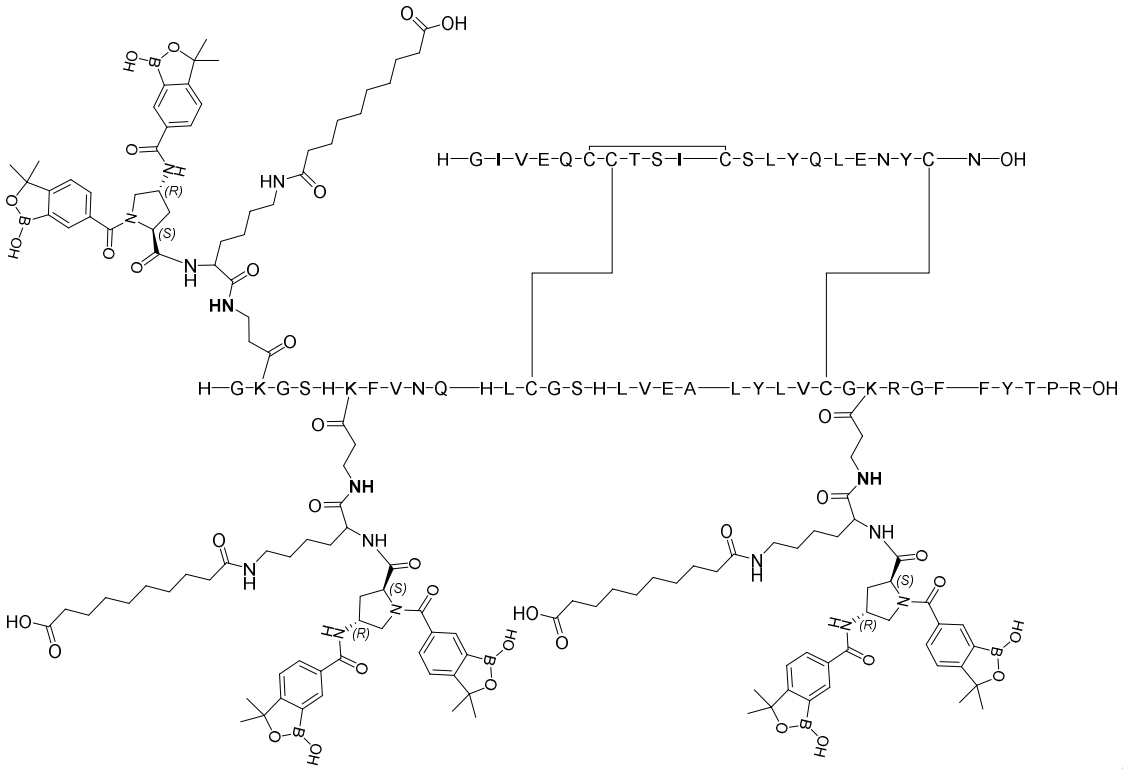
,

Example 29A:



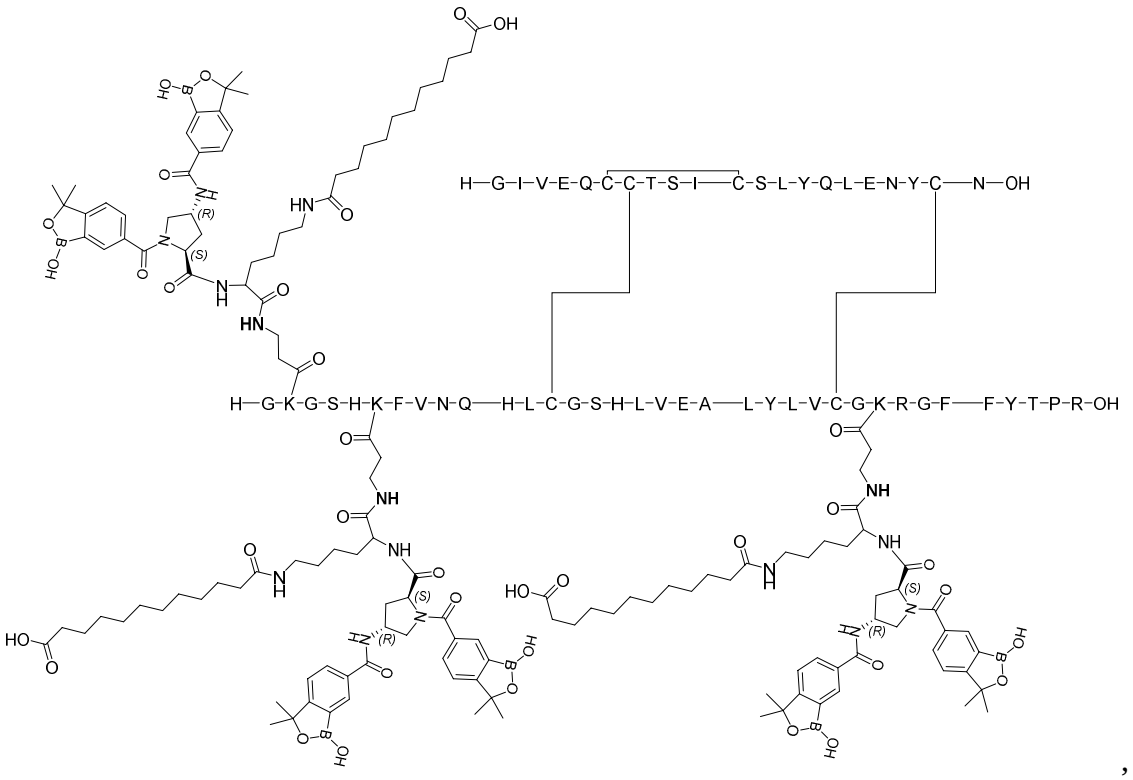
Prophetic ,

Example 30A:



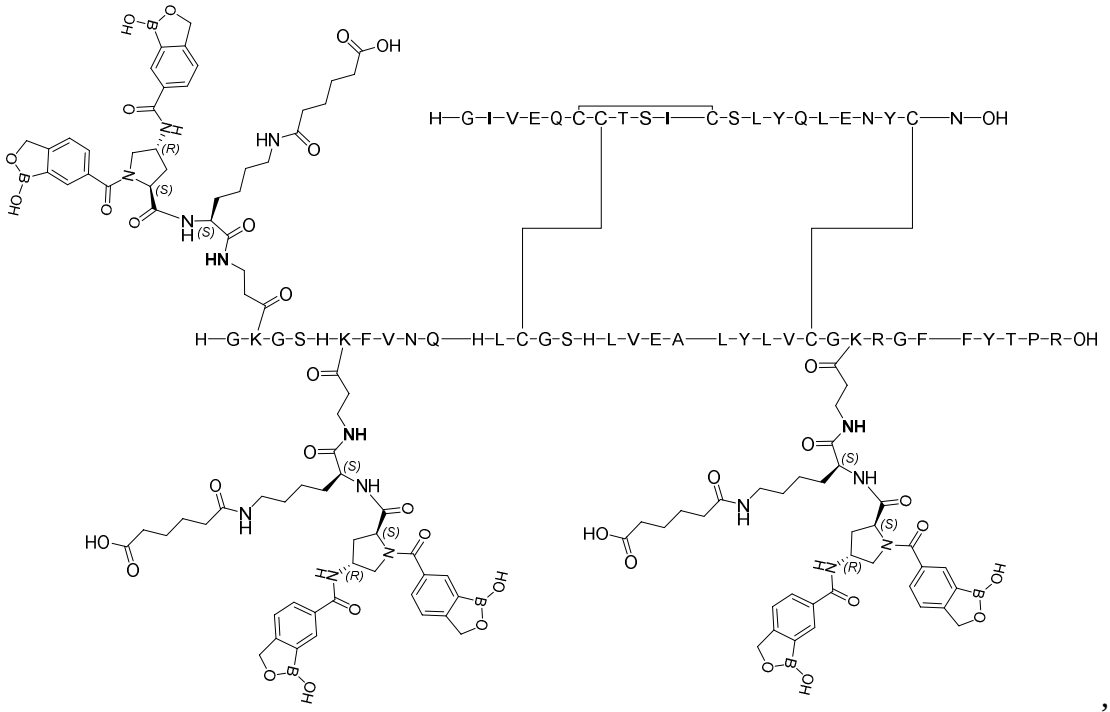
,

Example 31A:



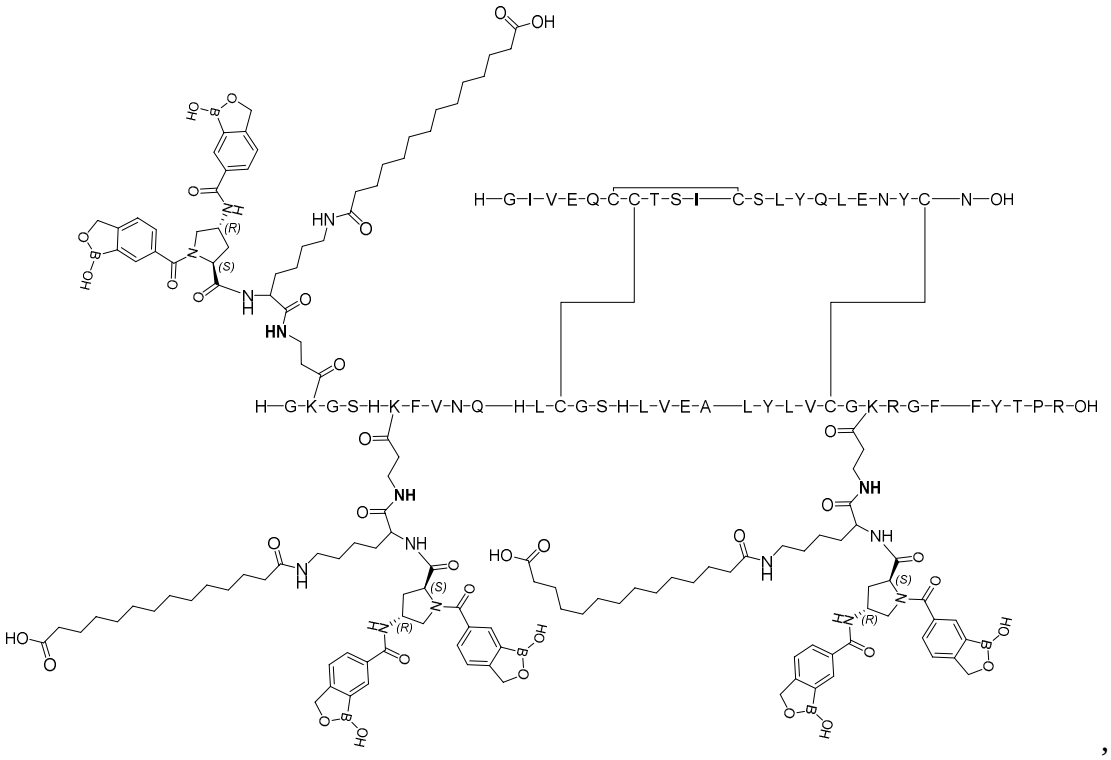
,

Example 32A:



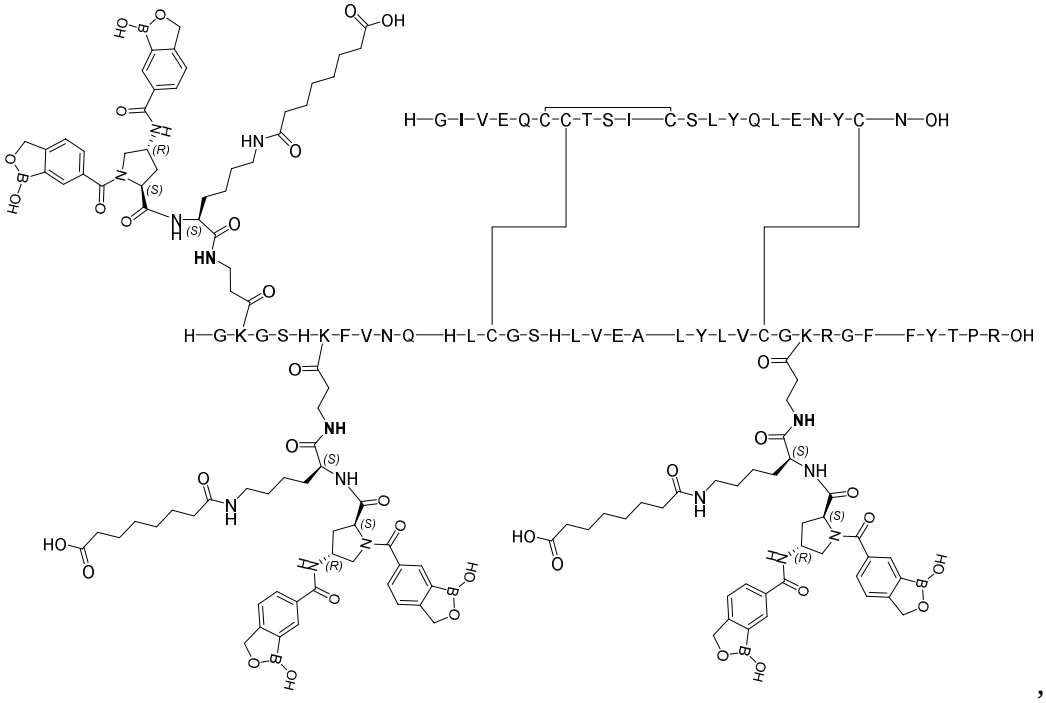
,

Example 33A:



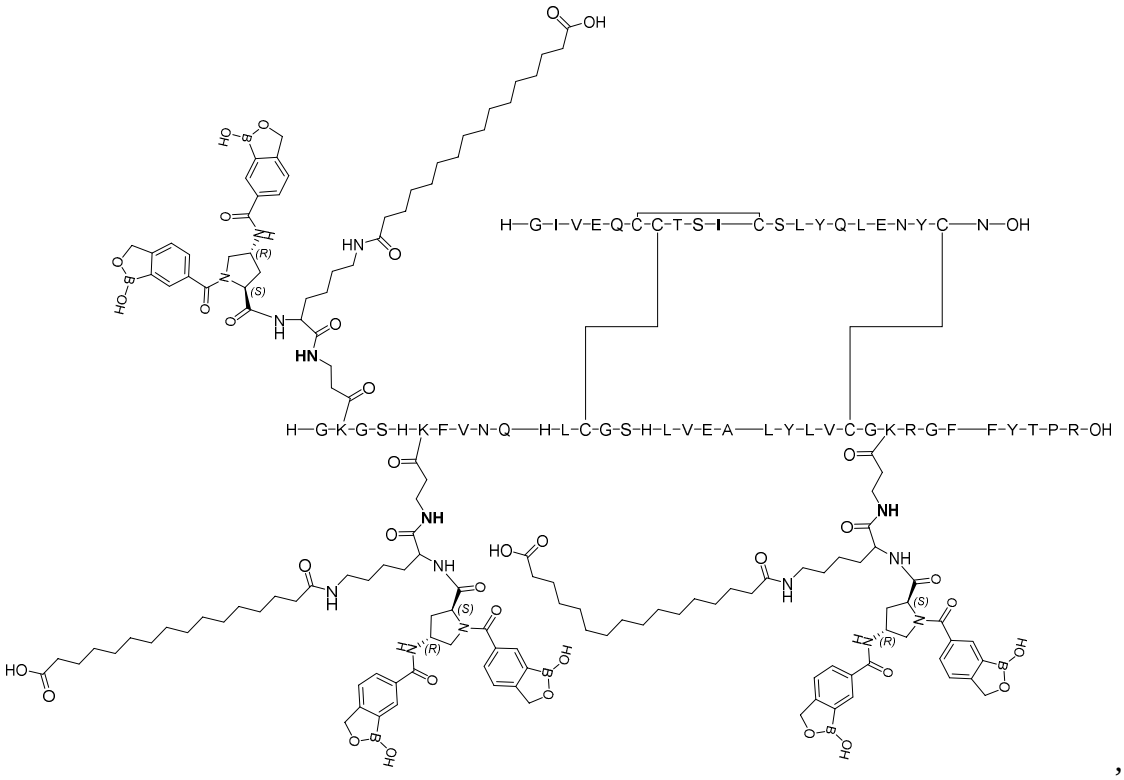
,

Example 34A:



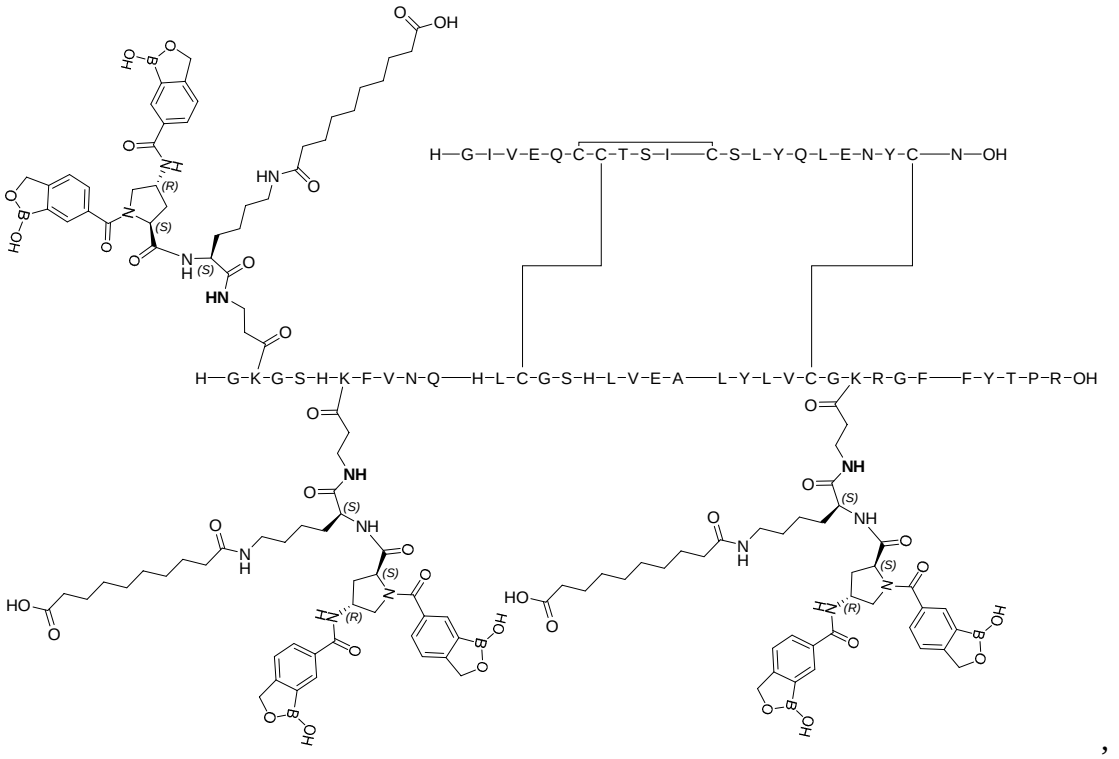
5 ,

Example 35A:



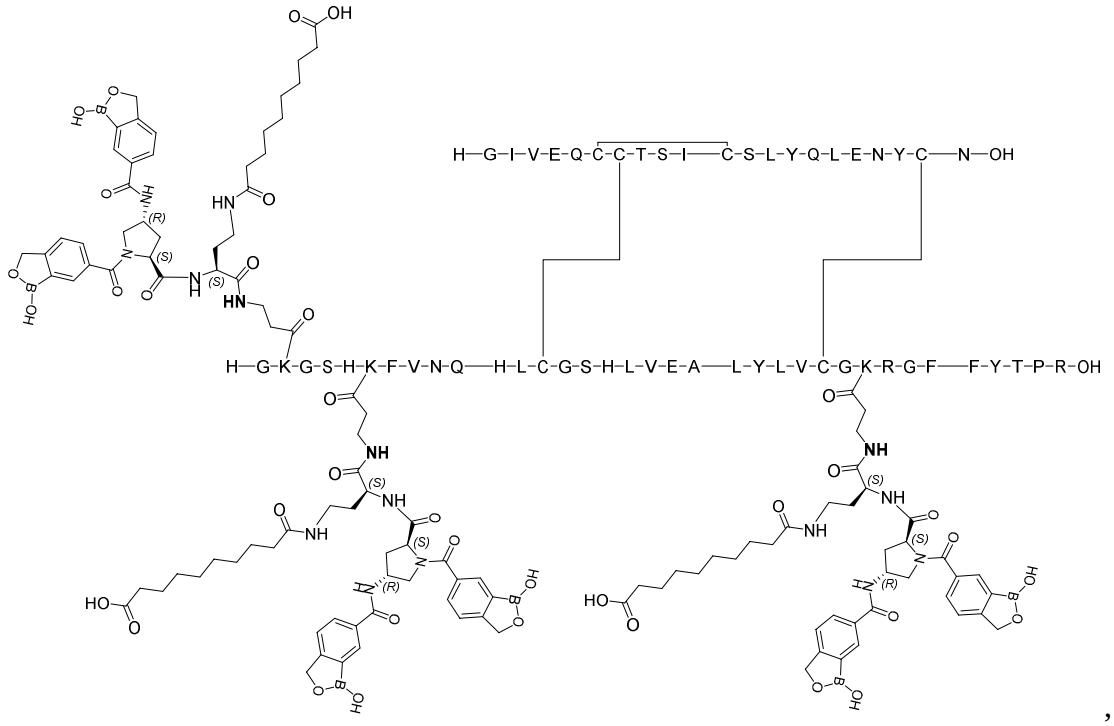
,

Example 36A:



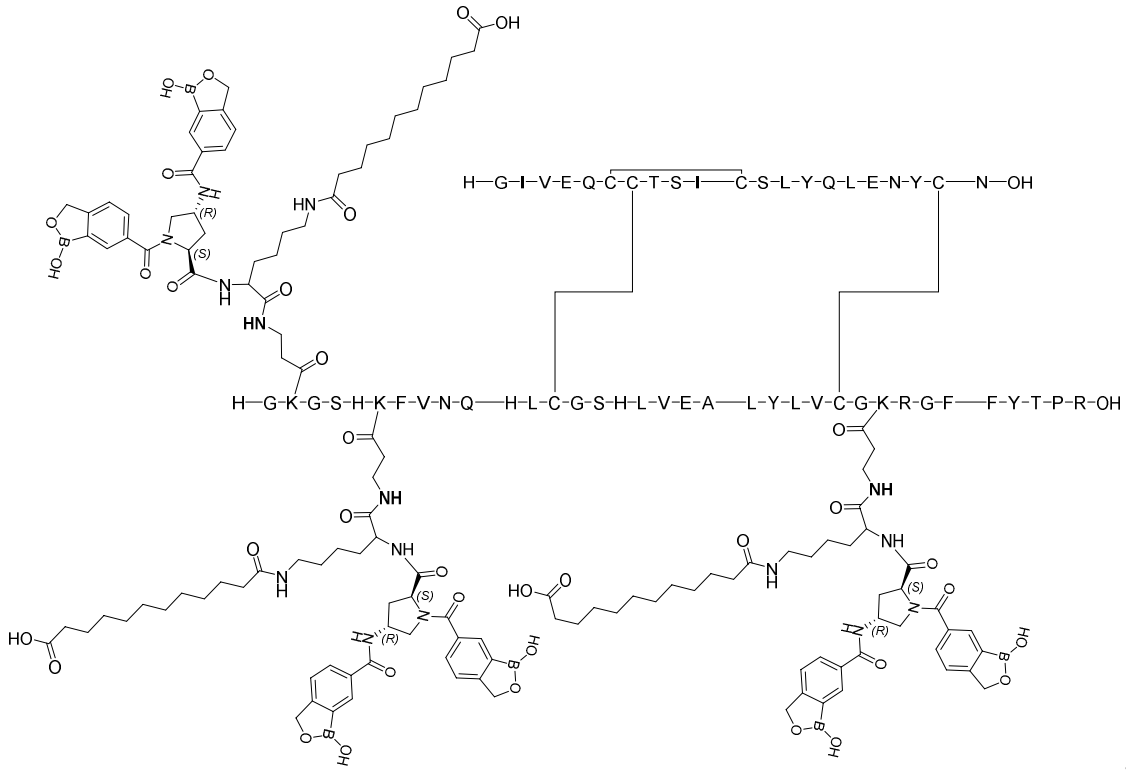
5 ,

Example 37A:



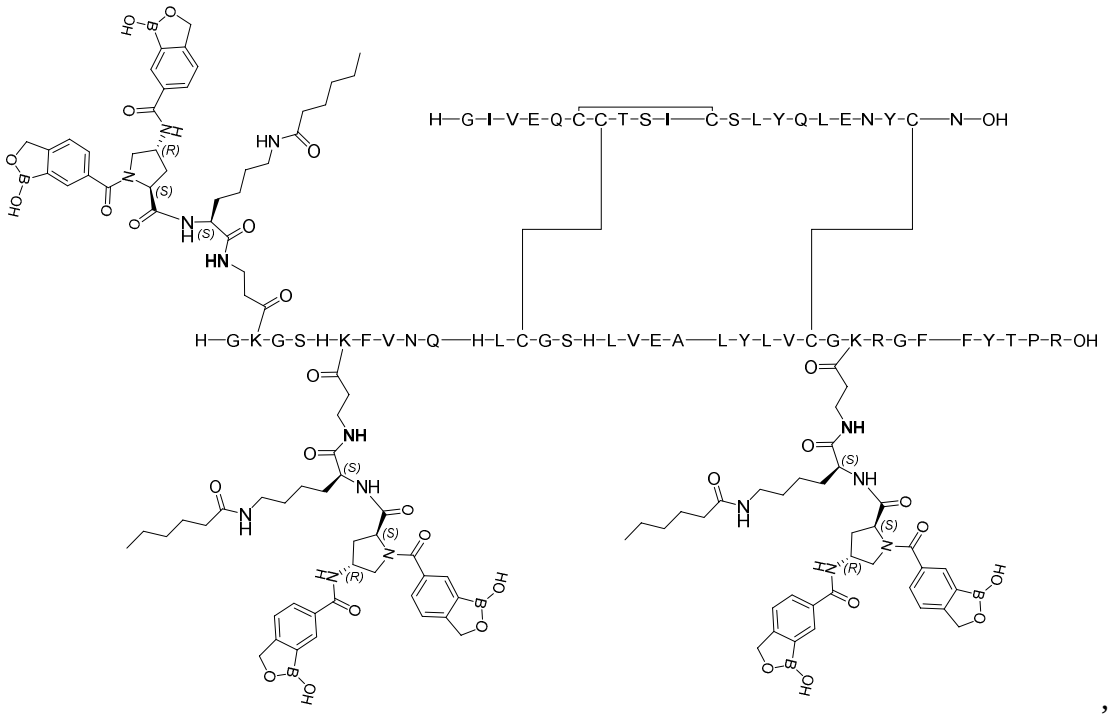
,

Example 38A:



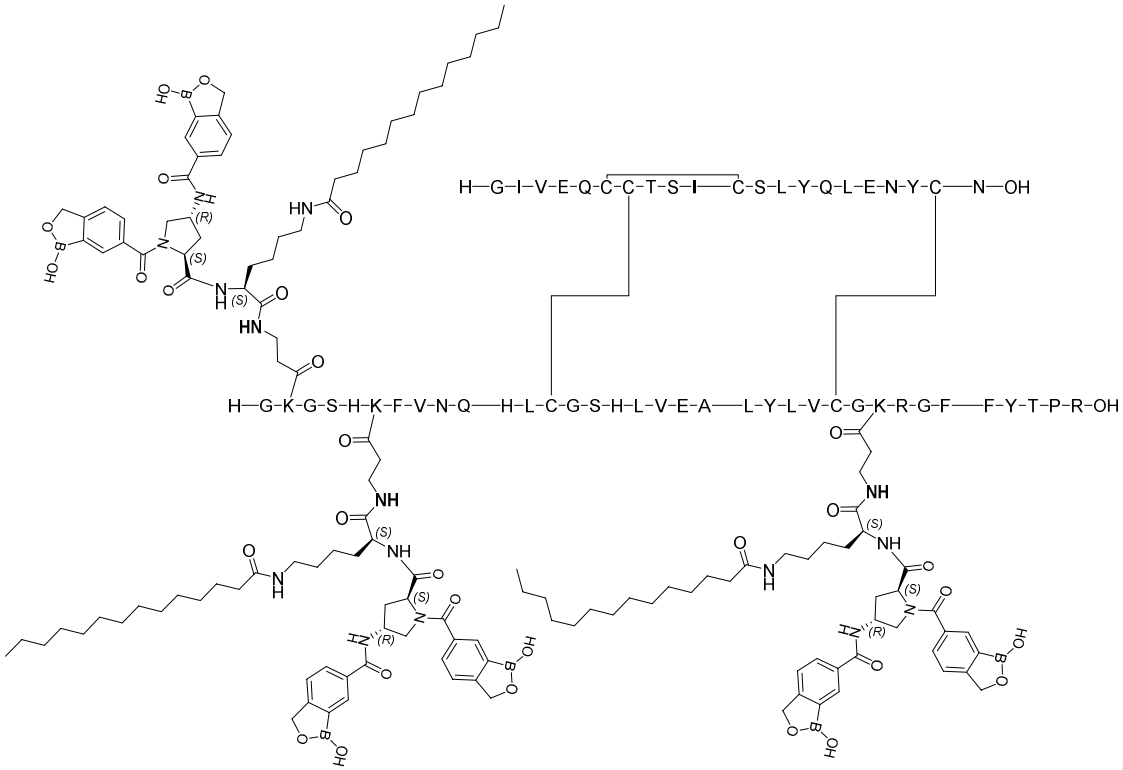
,

Example 39A:



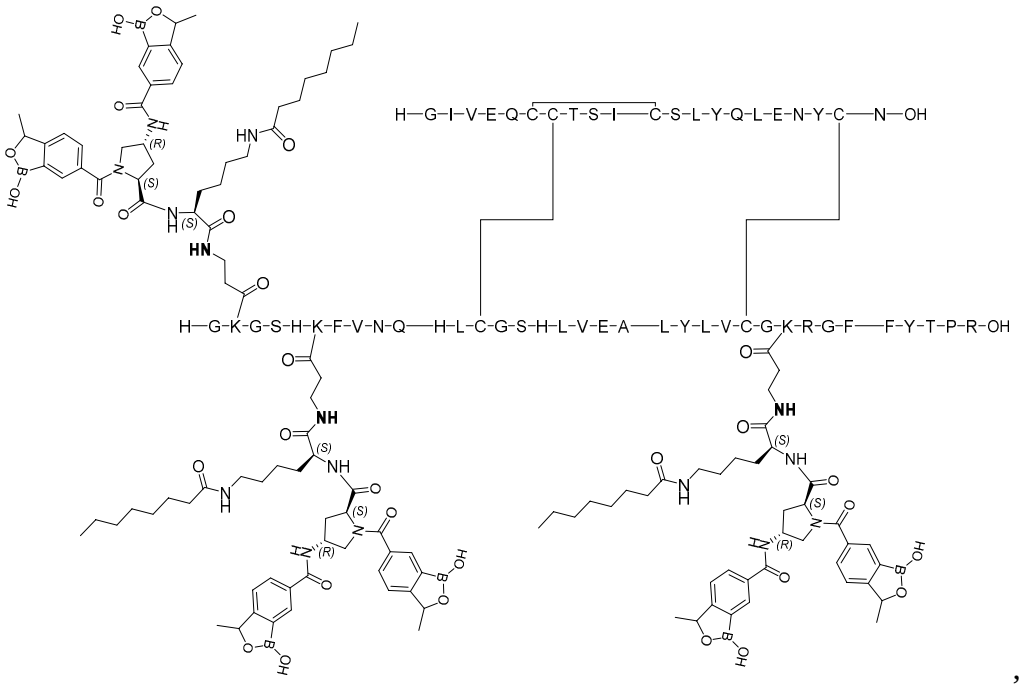
,

Example 40A:



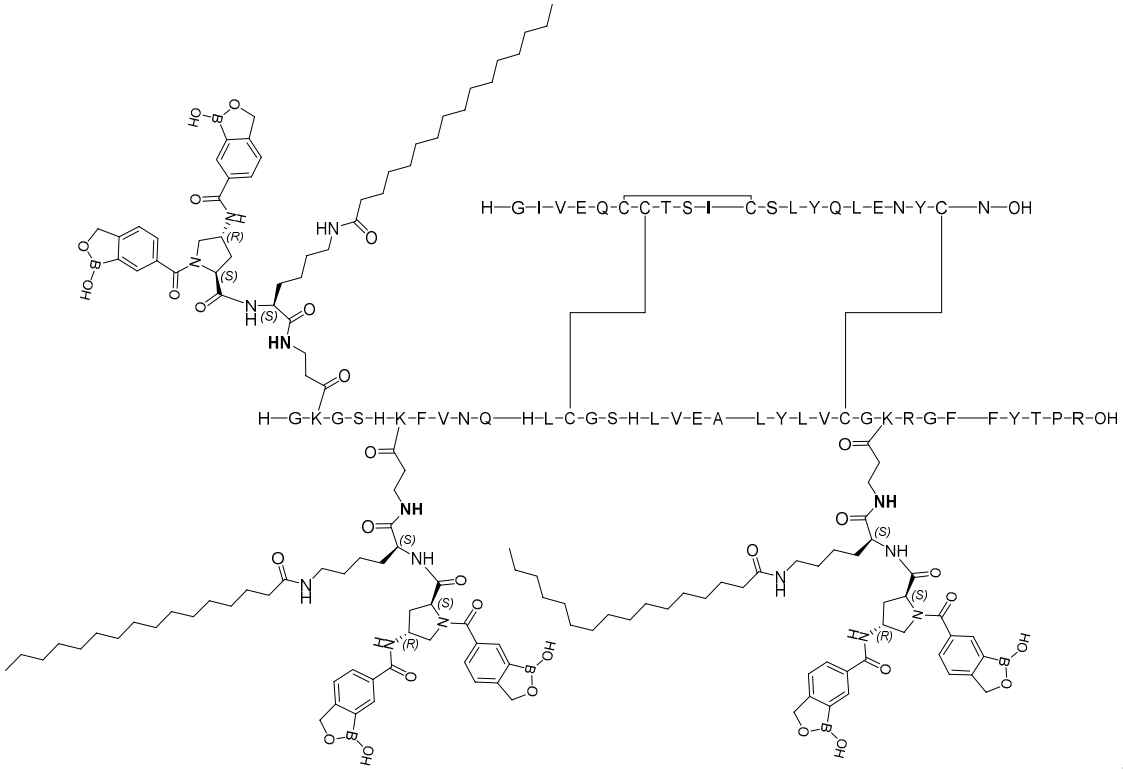
,

Example 41A:



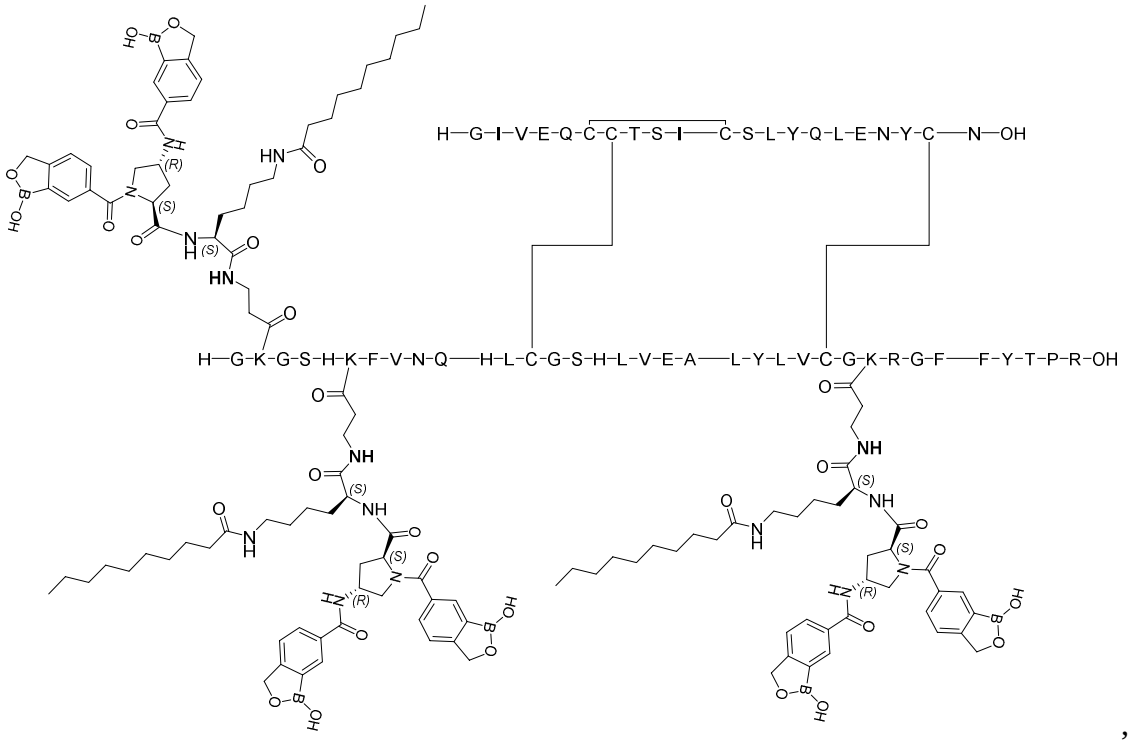
,

Example 42A:



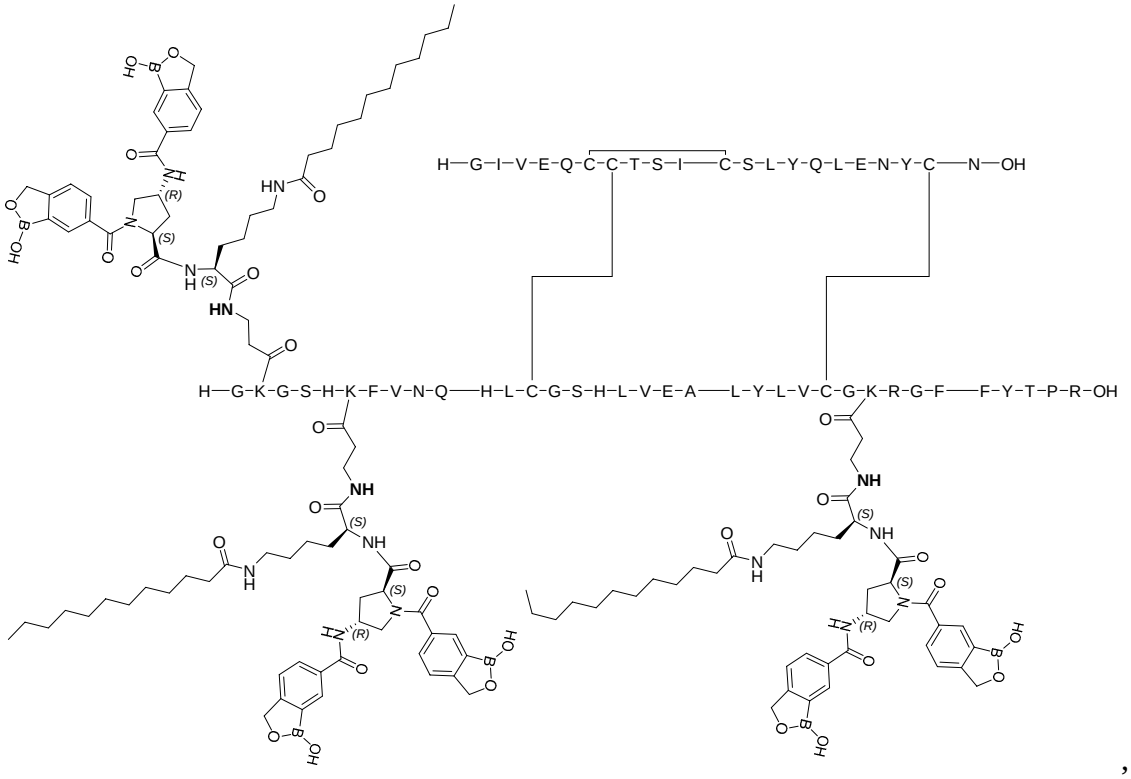
,

Example 43A:



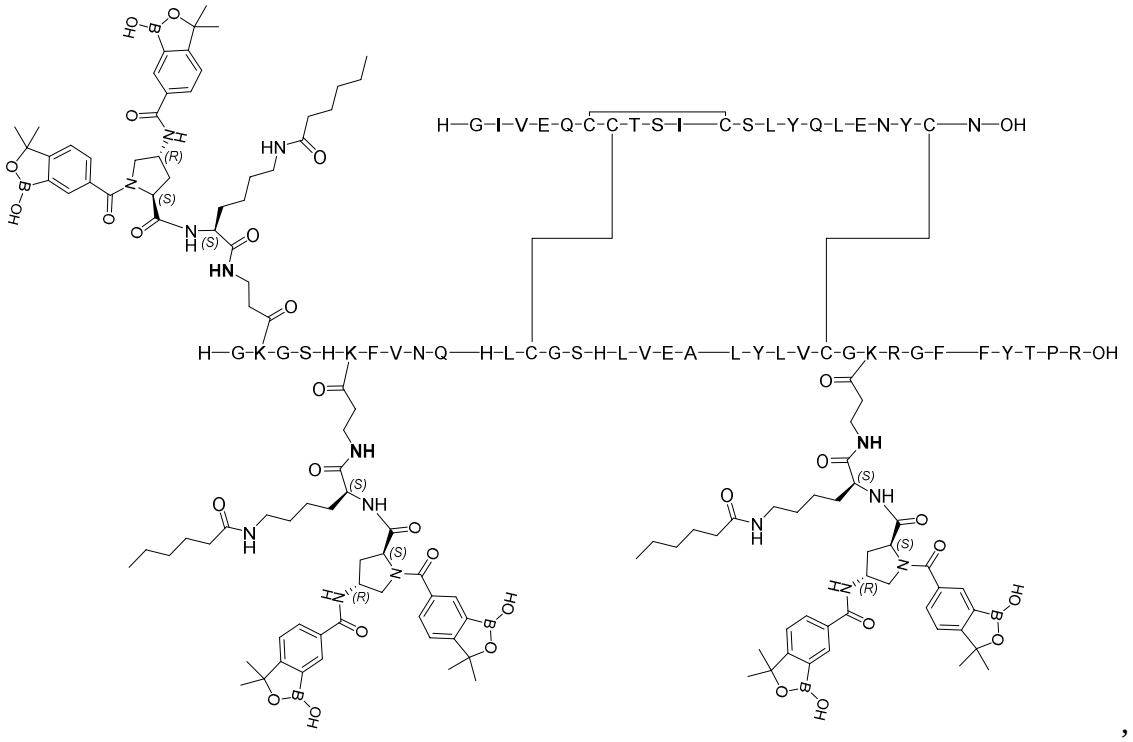
,

Example 44A:



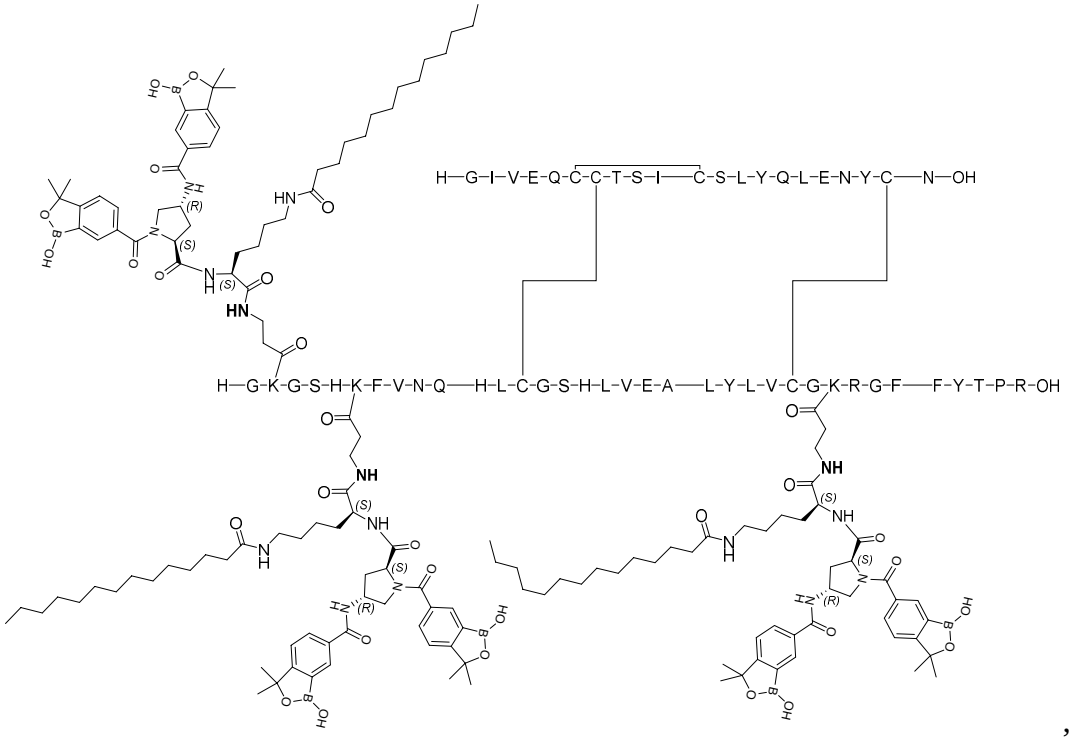
,

Example 45A:



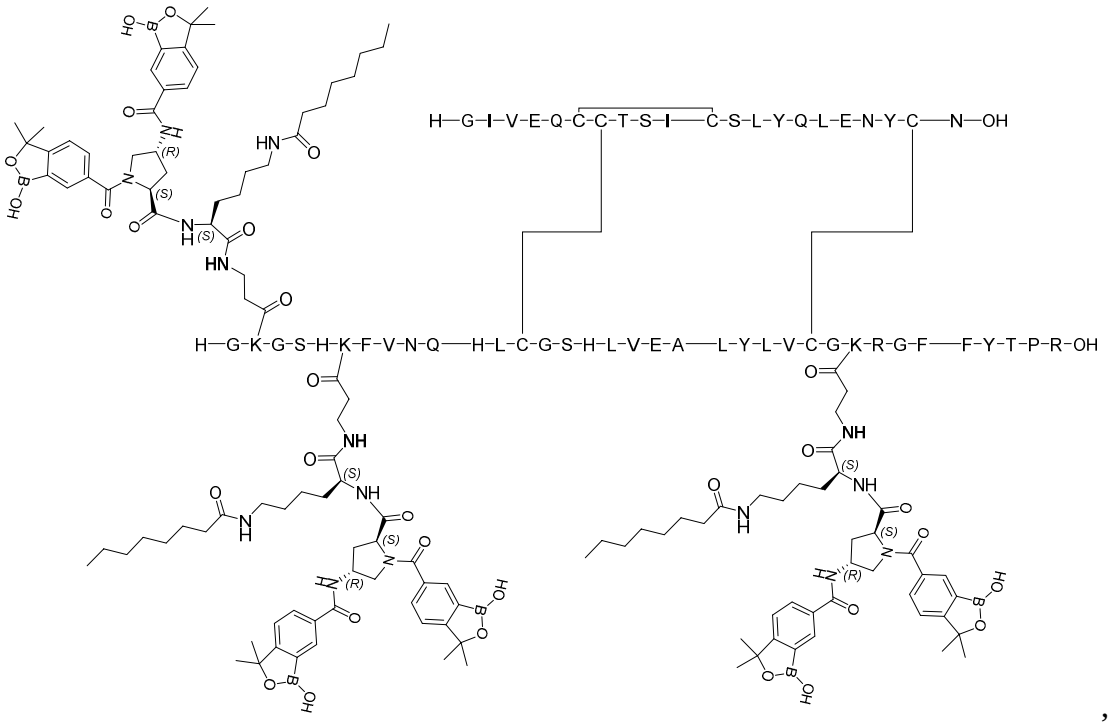
,

Example 46A:



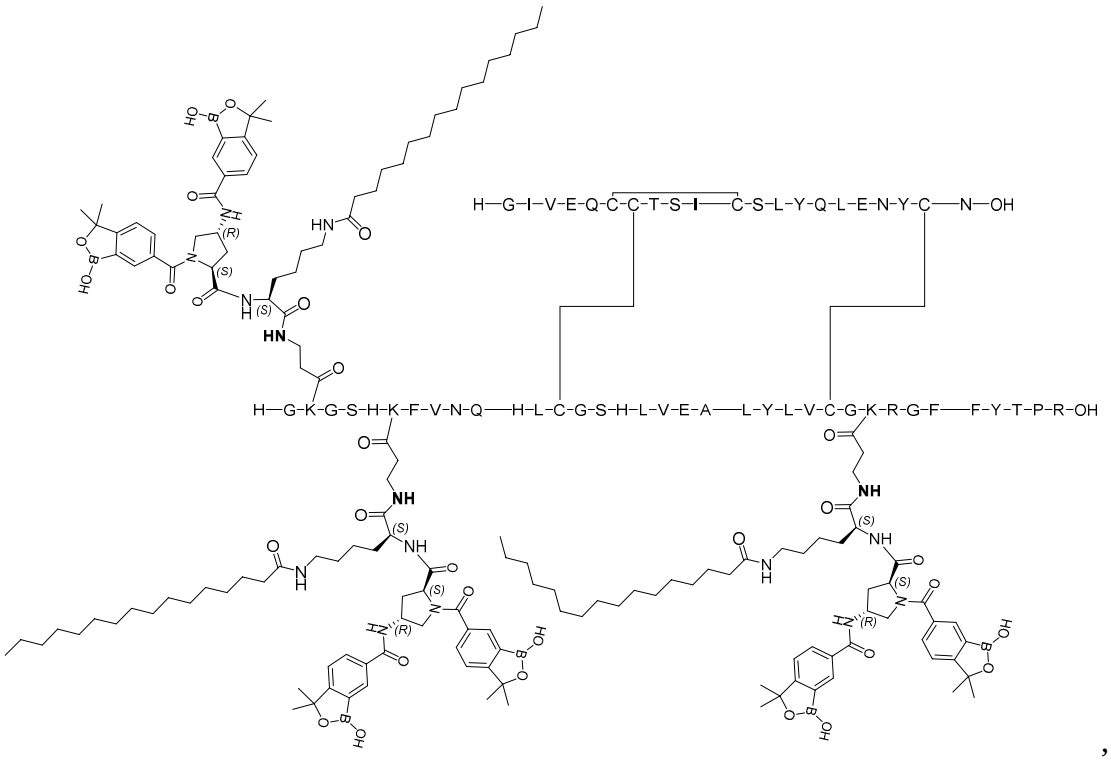
,

Example 47A:



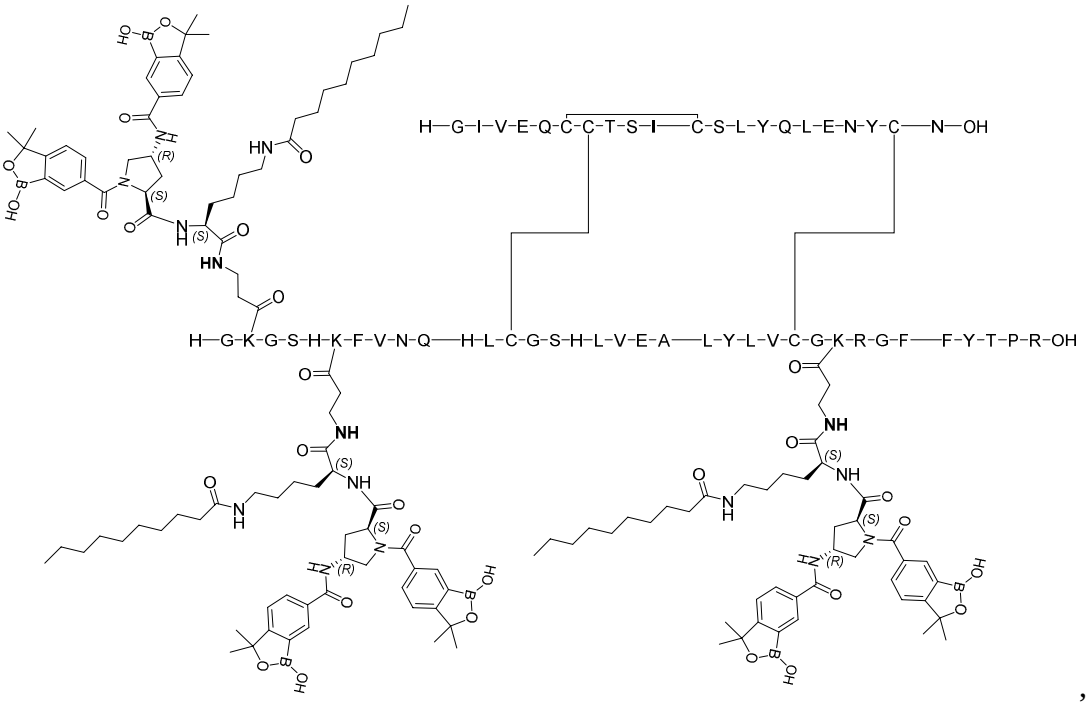
,

Example 48A:



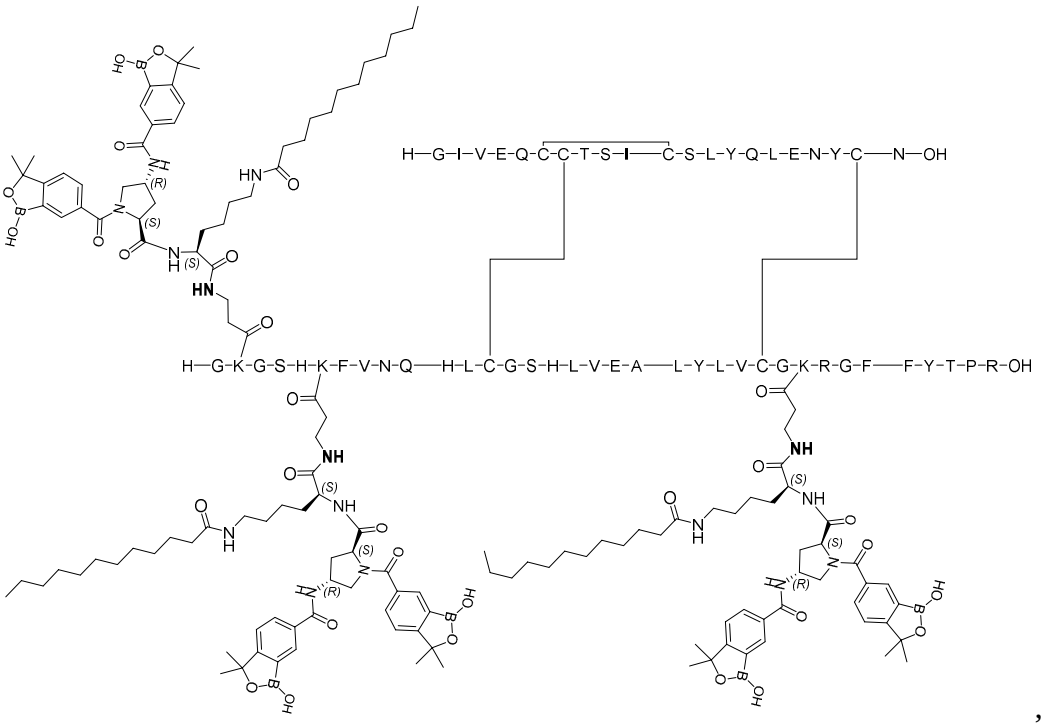
,

Example 49A:



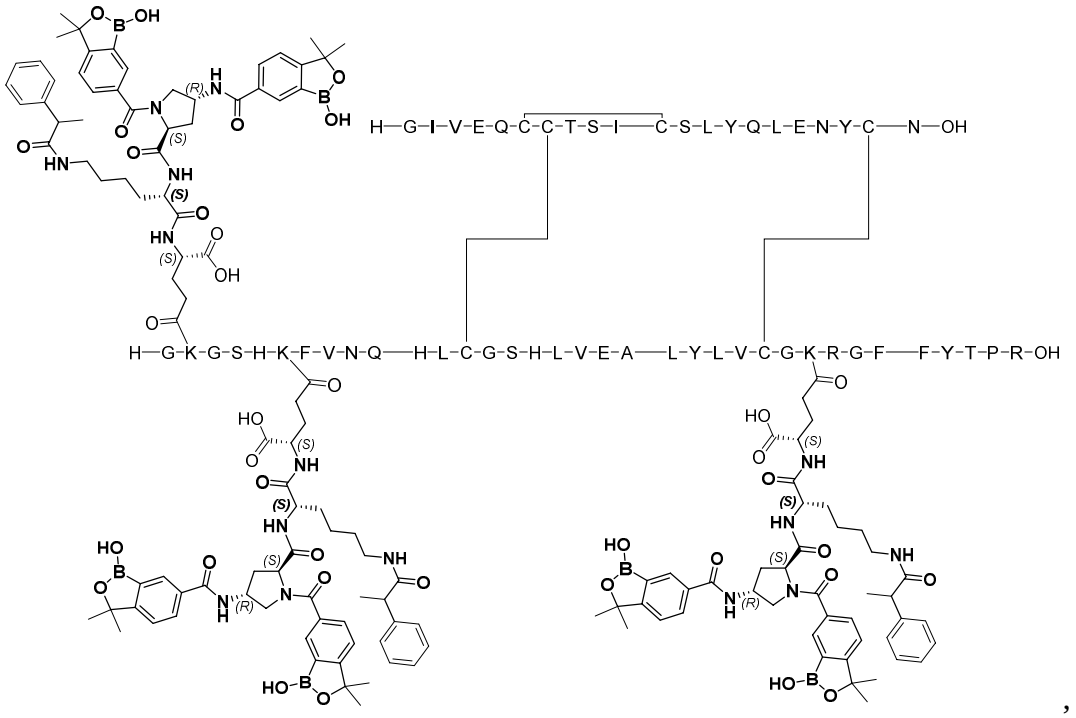
,

Example 50A:



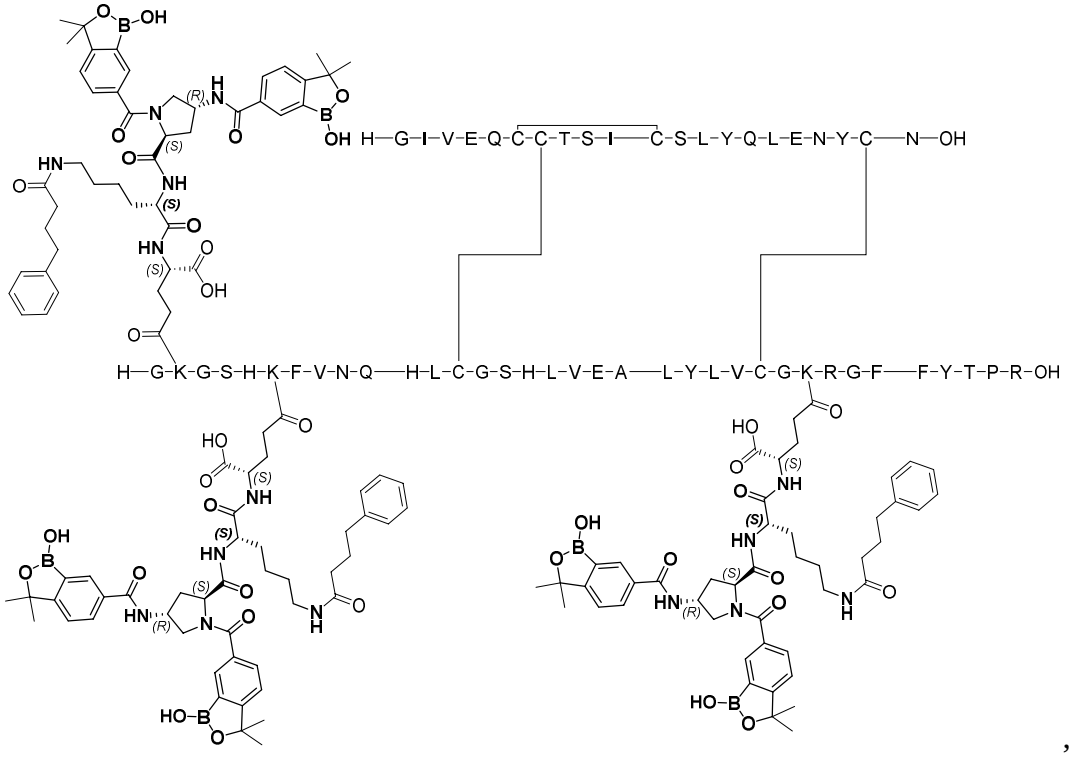
,

Example 51A:



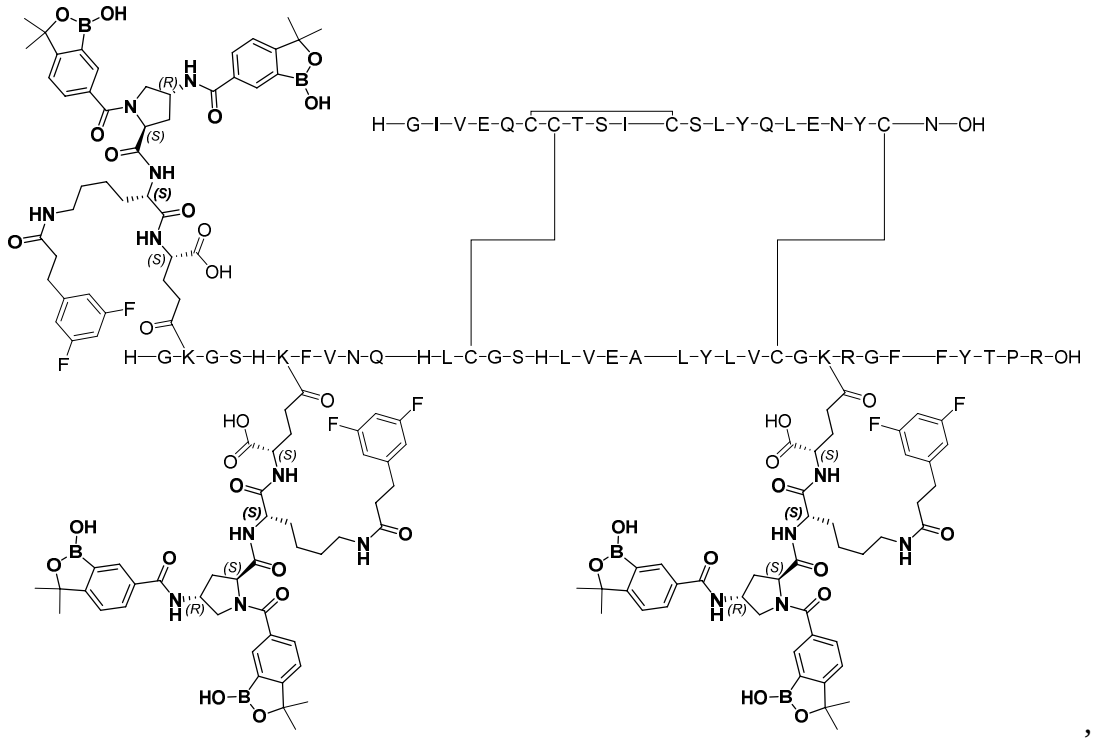
,

Example 52A:



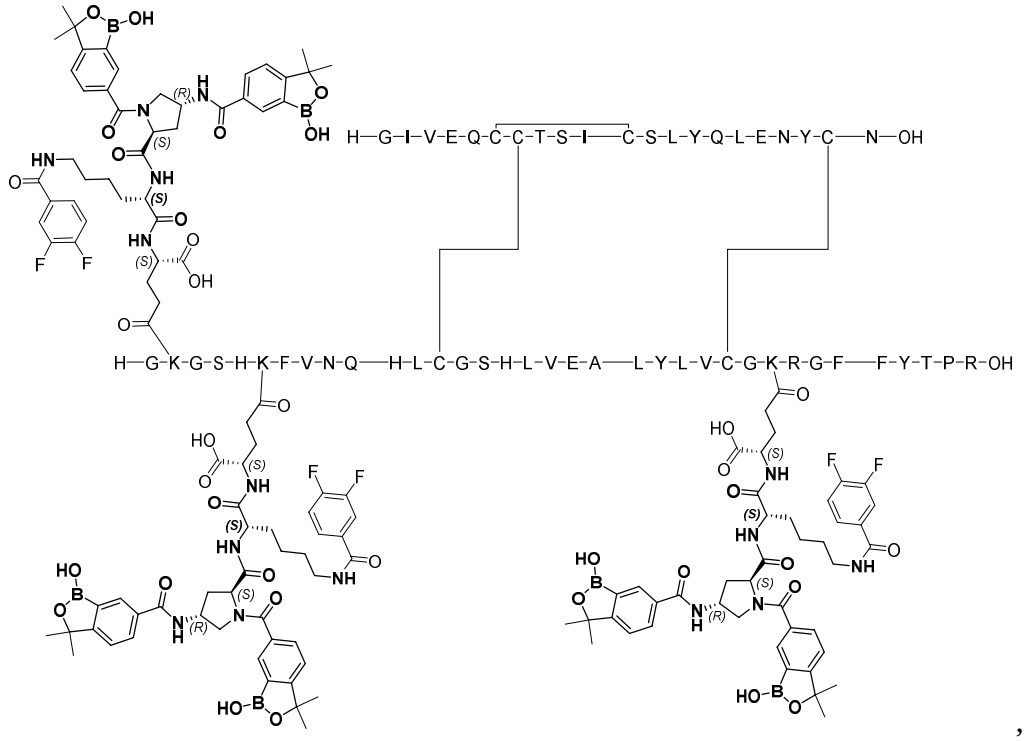
,

Example 53A:



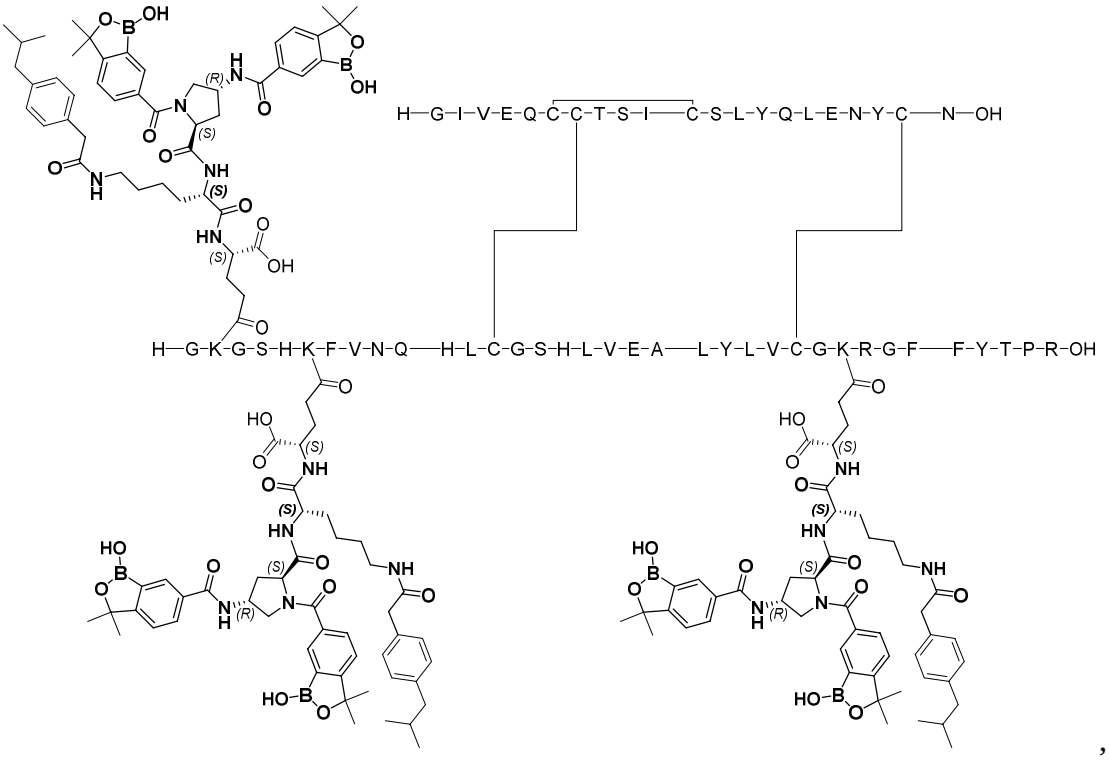
,

Example 54A:



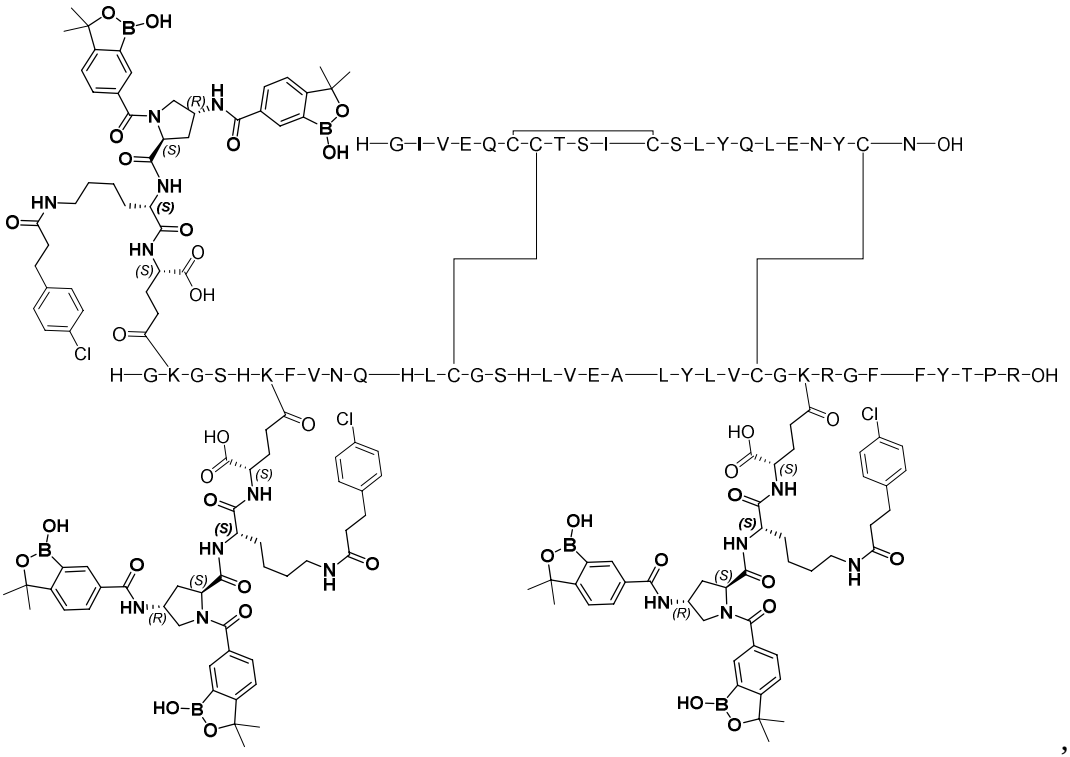
5 ,

Example 55A:



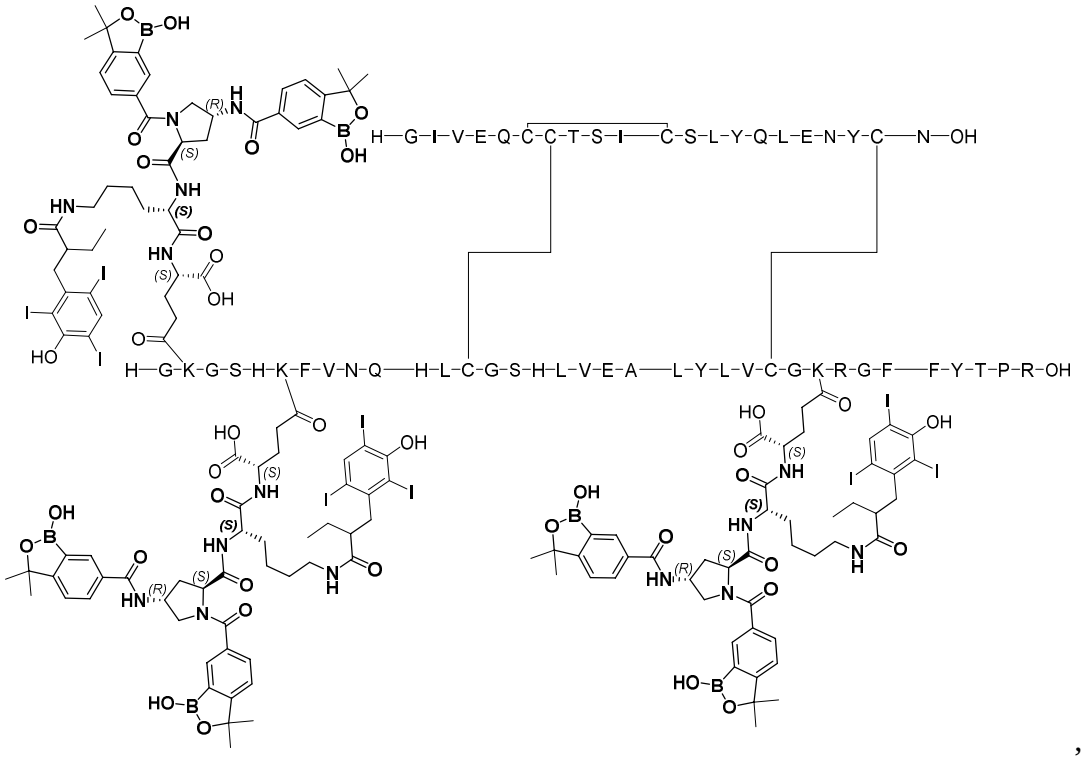
,

Example 56A:



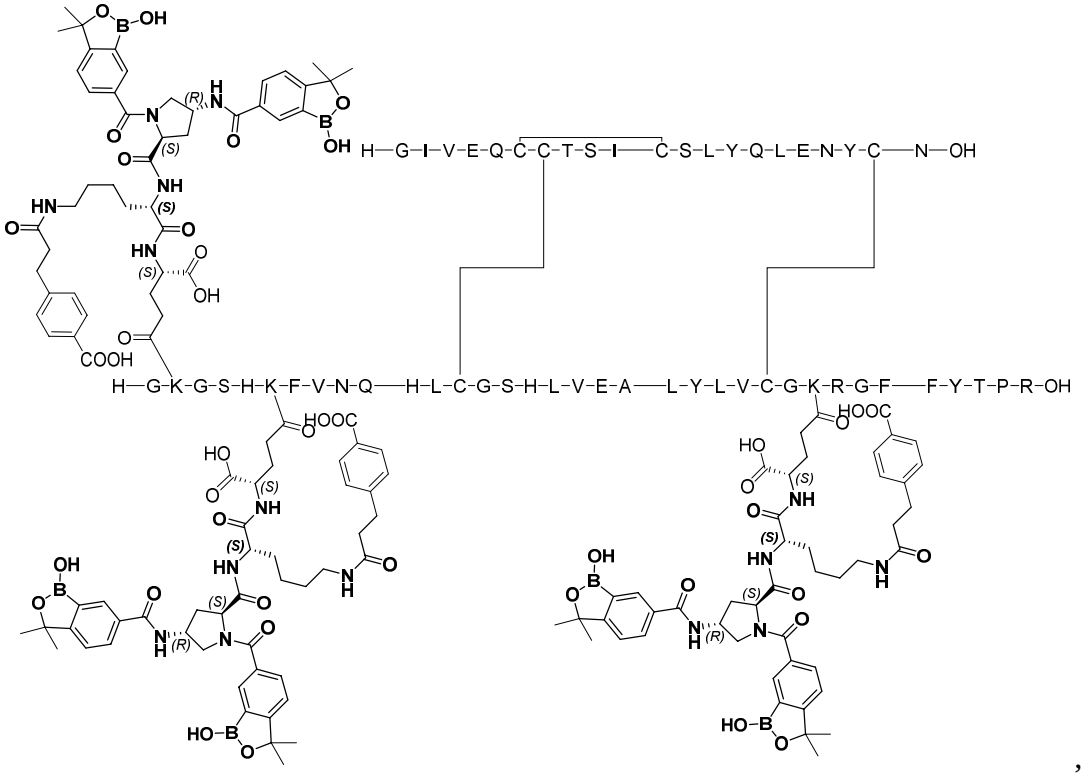
,

Example 57A:



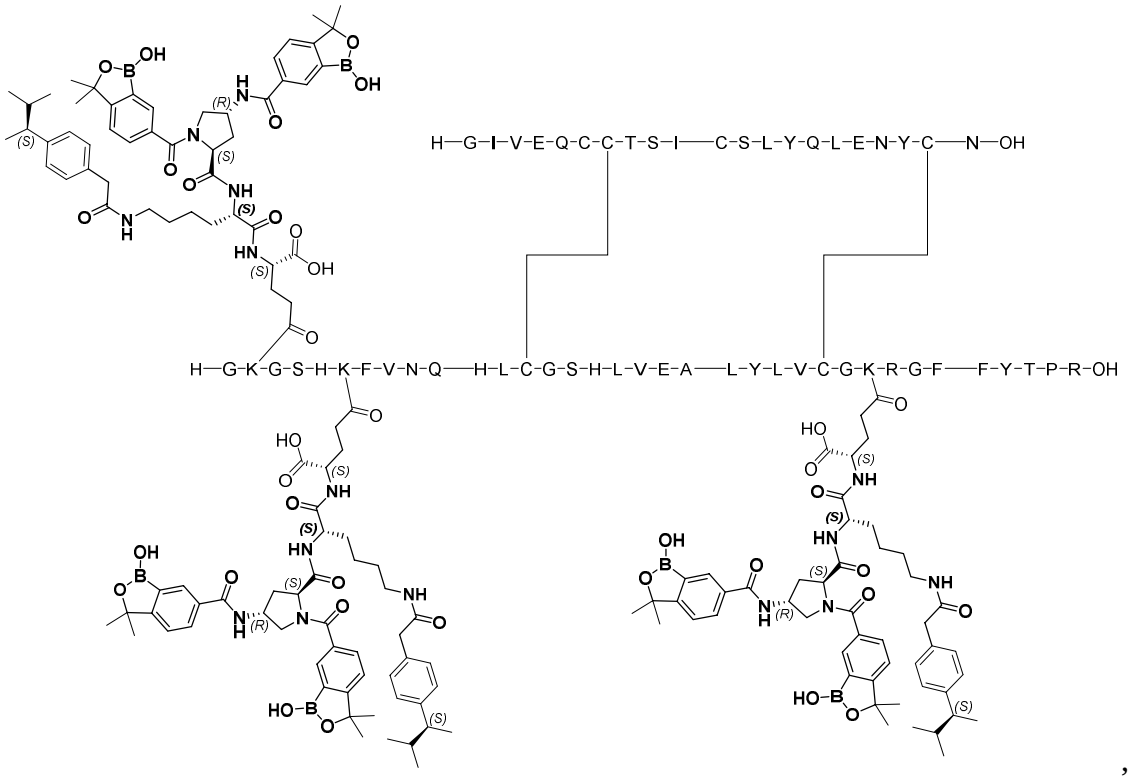
,

Example 58A:



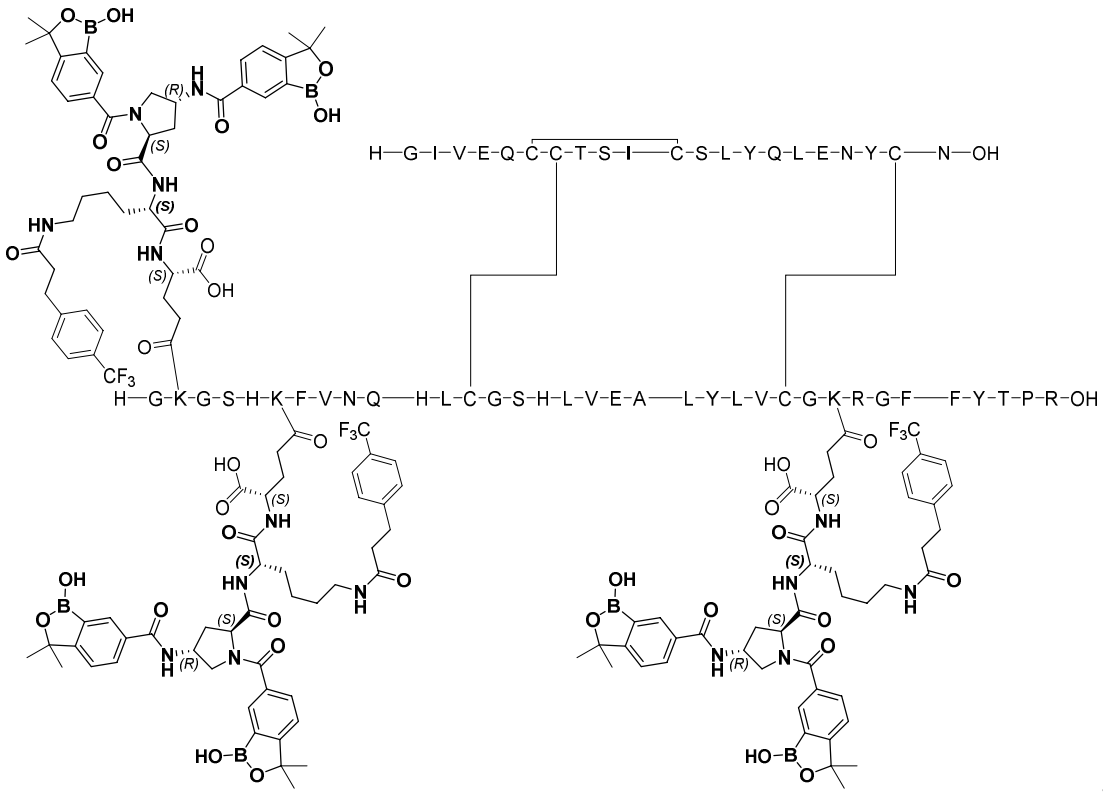
,

Example 59A:



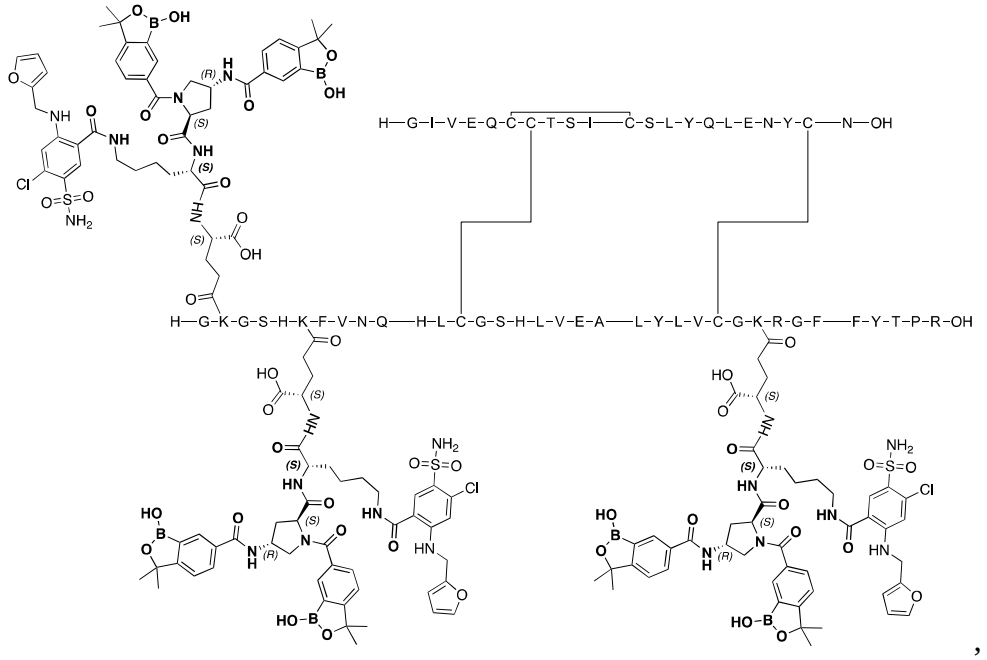
,

Example 60A:



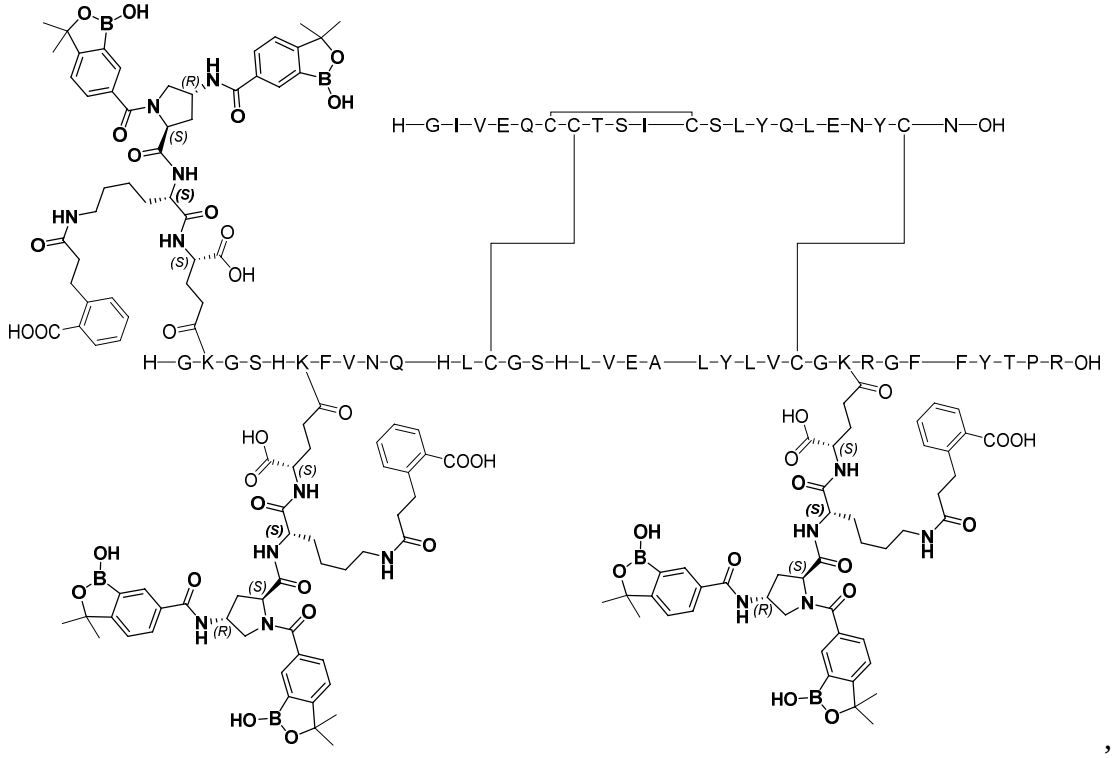
5 ,

Example 61A:



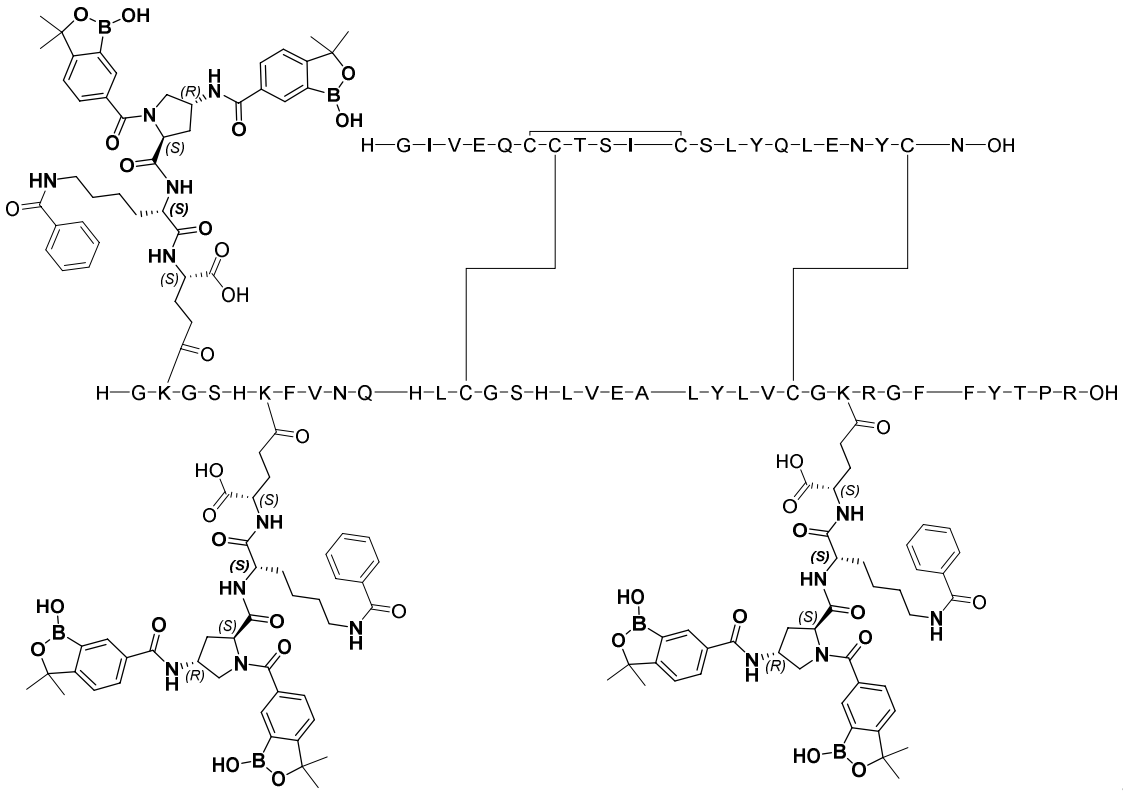
,

Example 62A:



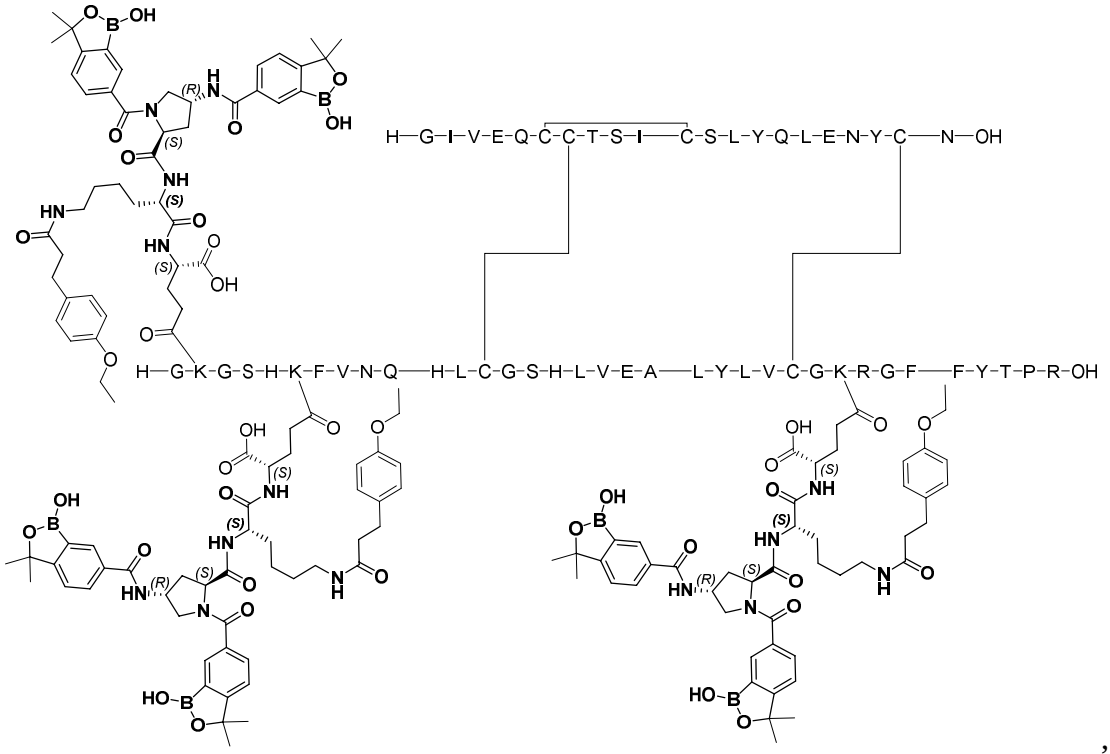
,

Example 63A:



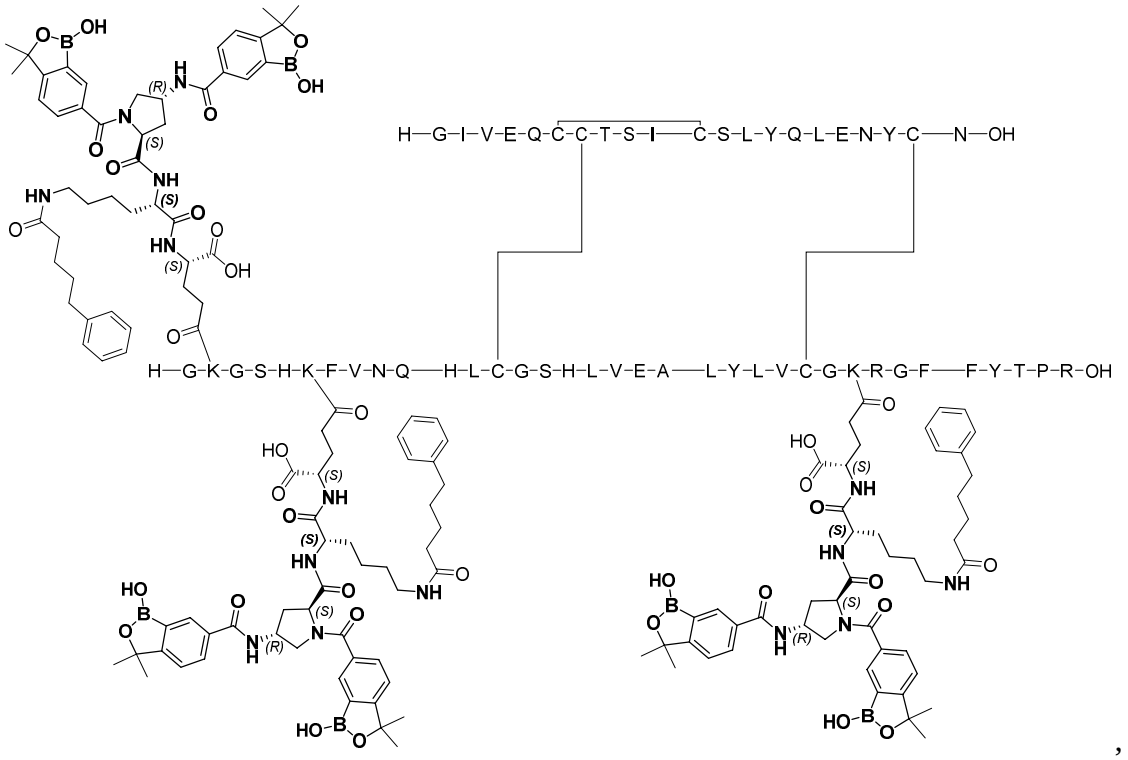
,

Example 64A:



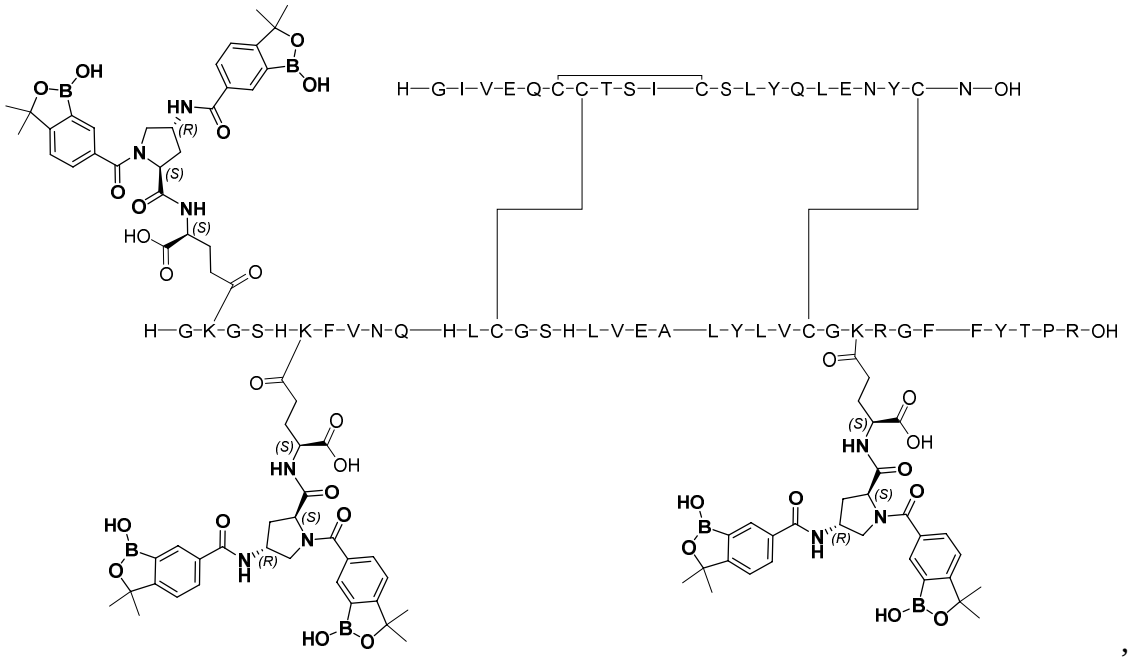
,

Example 65A:



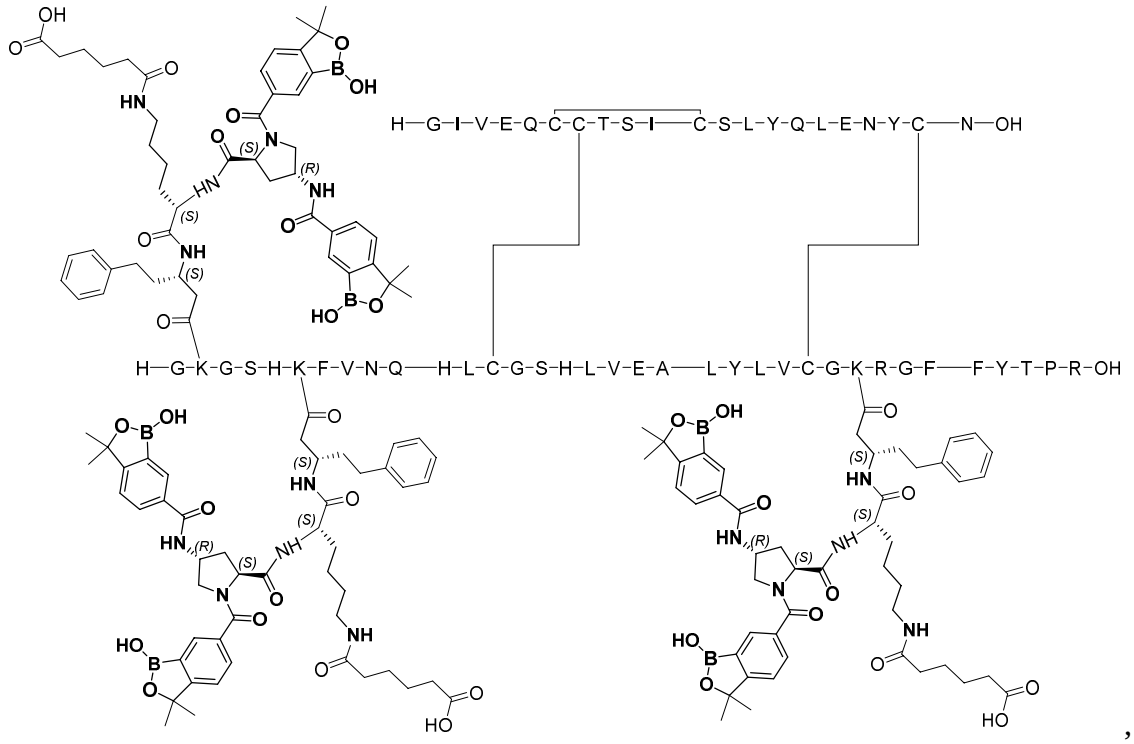
,

Example 66A:



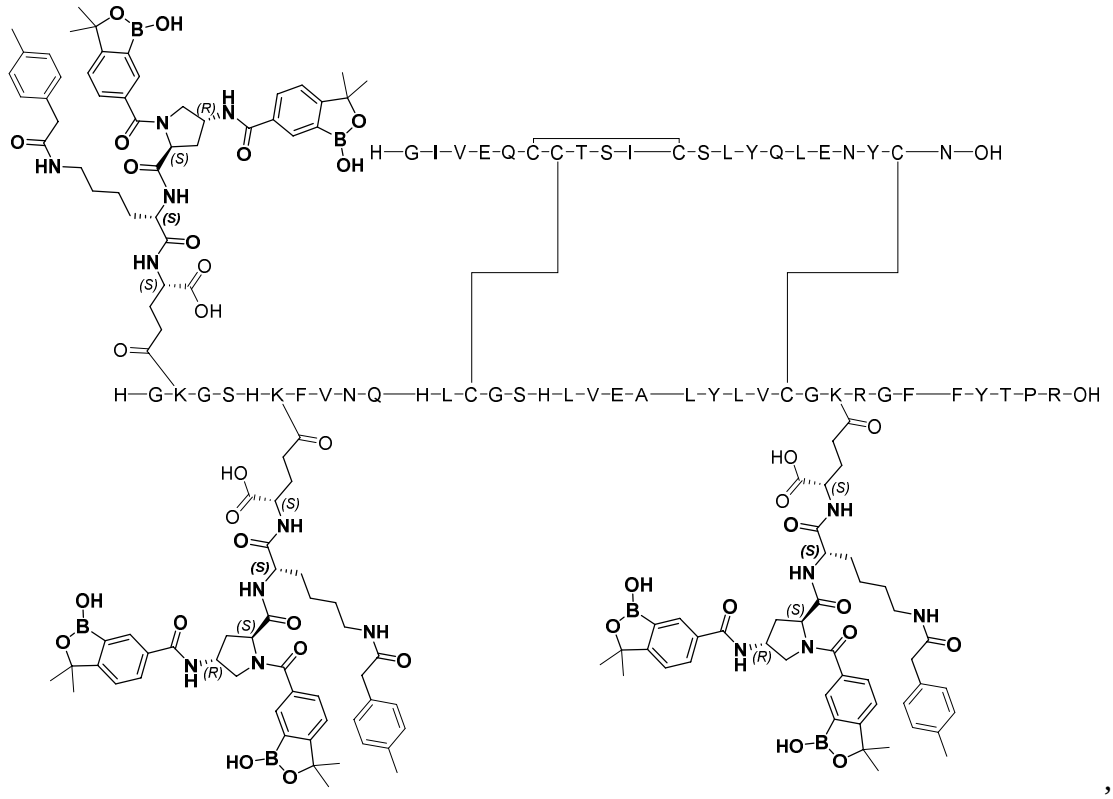
,

Example 67A:



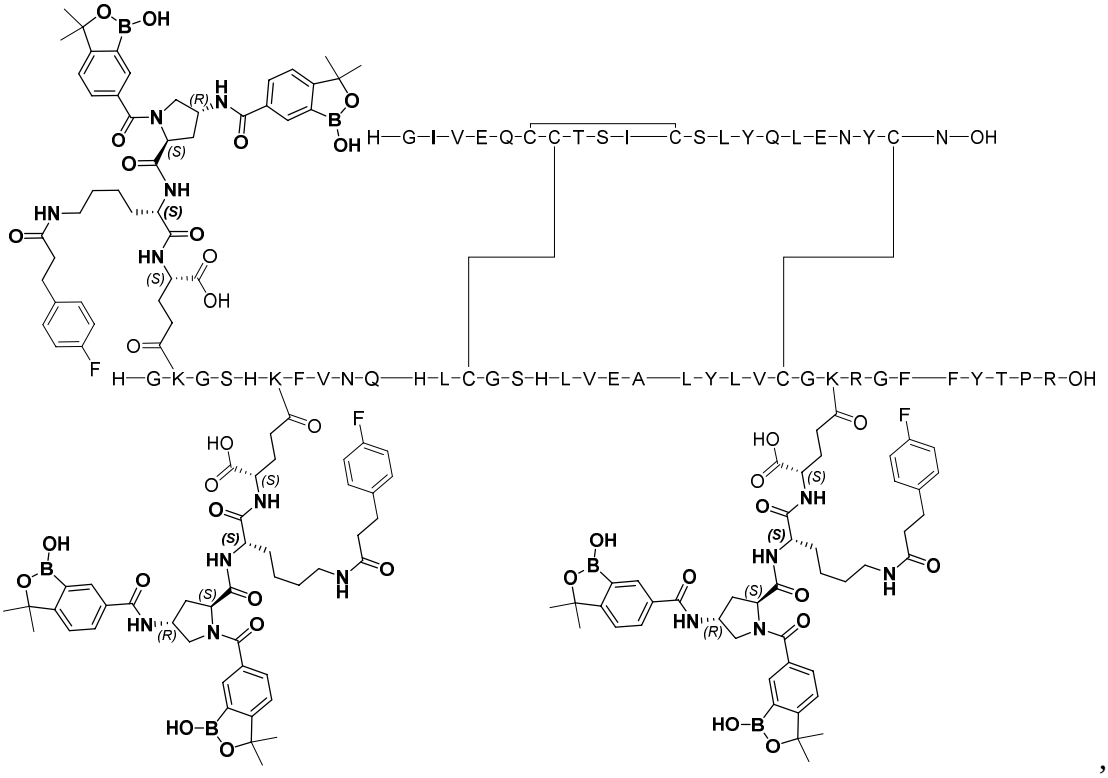
,

Example 68A:



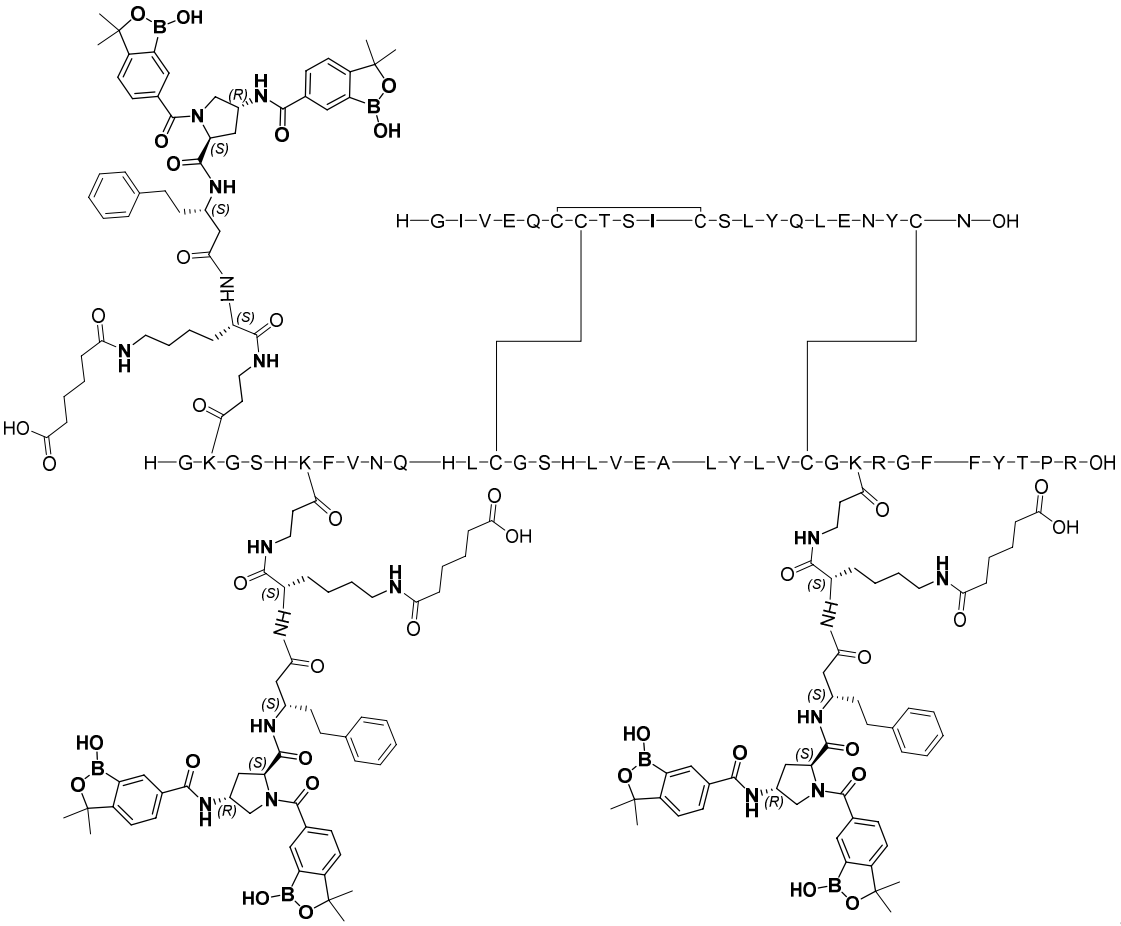
5 ,

Example 69A:



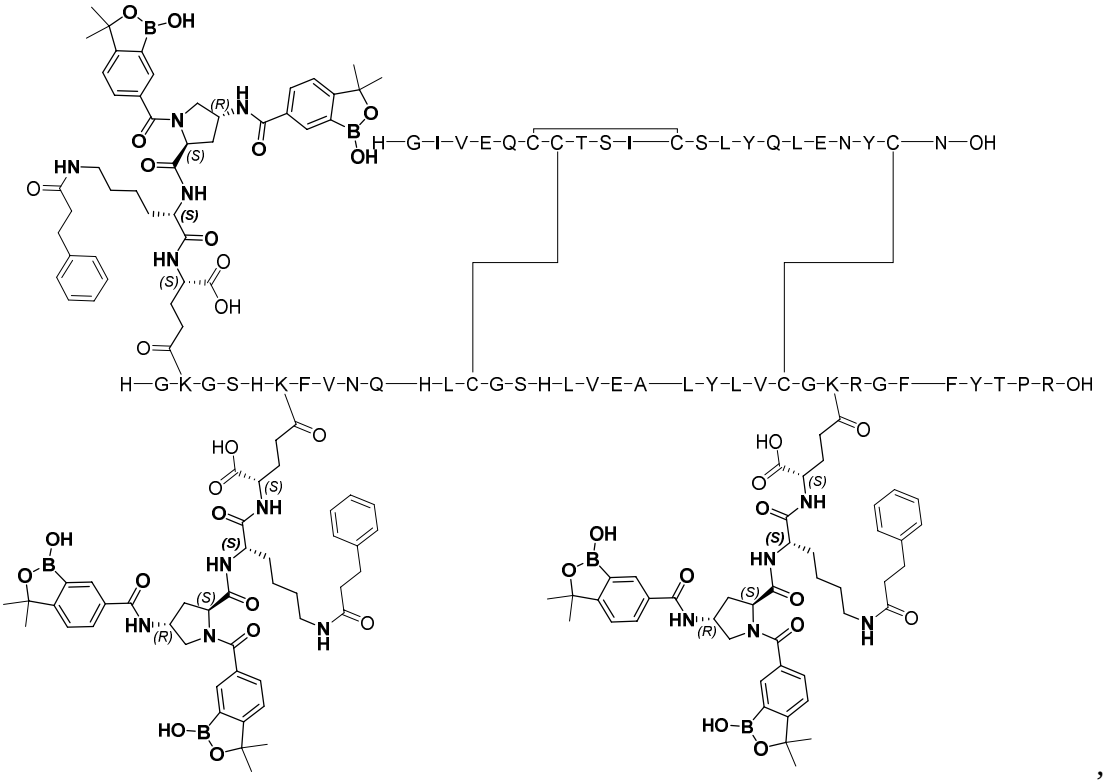
,

Example 70A:



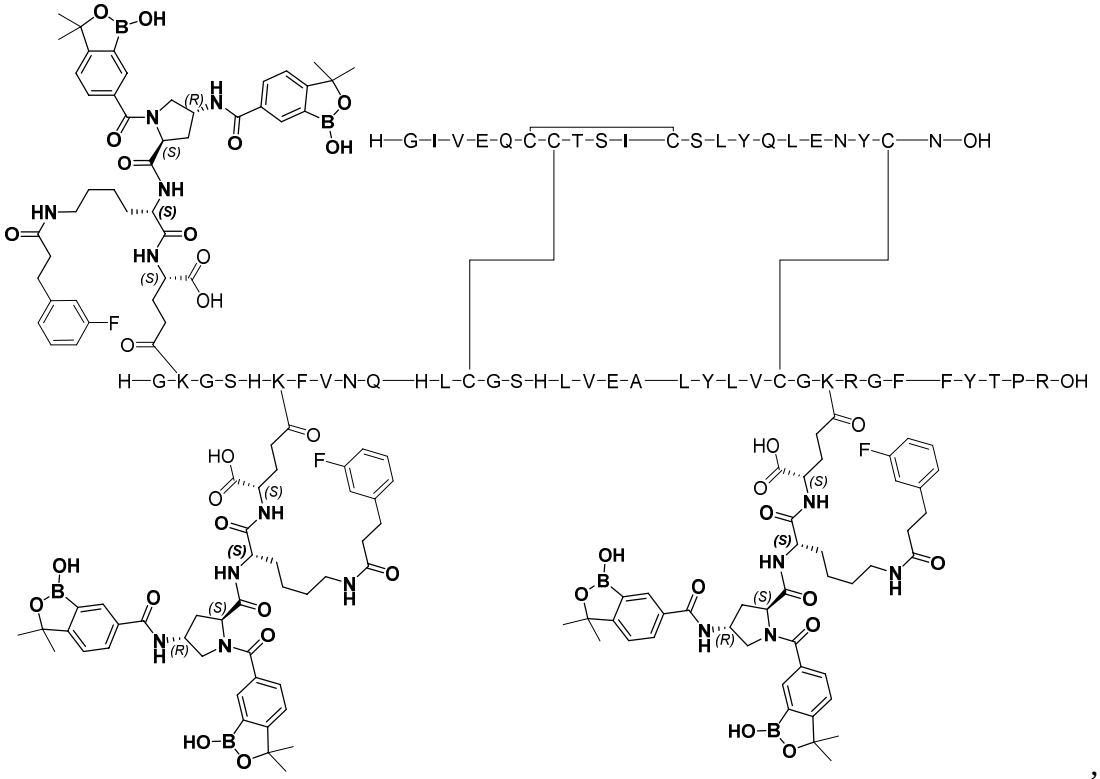
,

Example 71A:



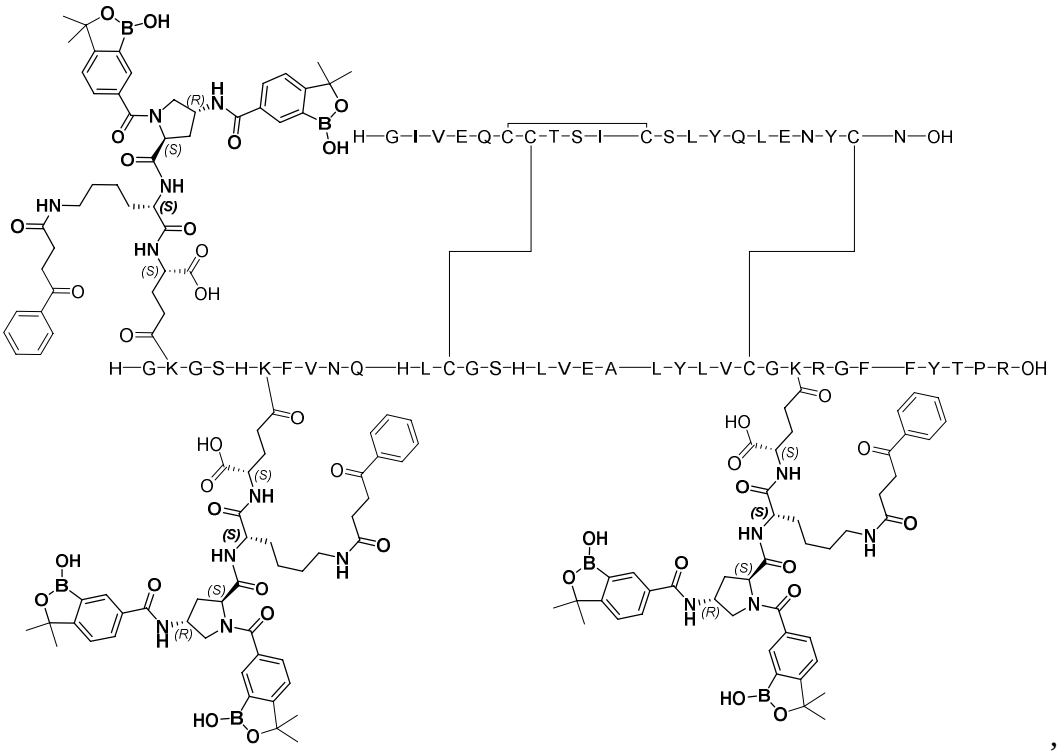
,

Example 72A:



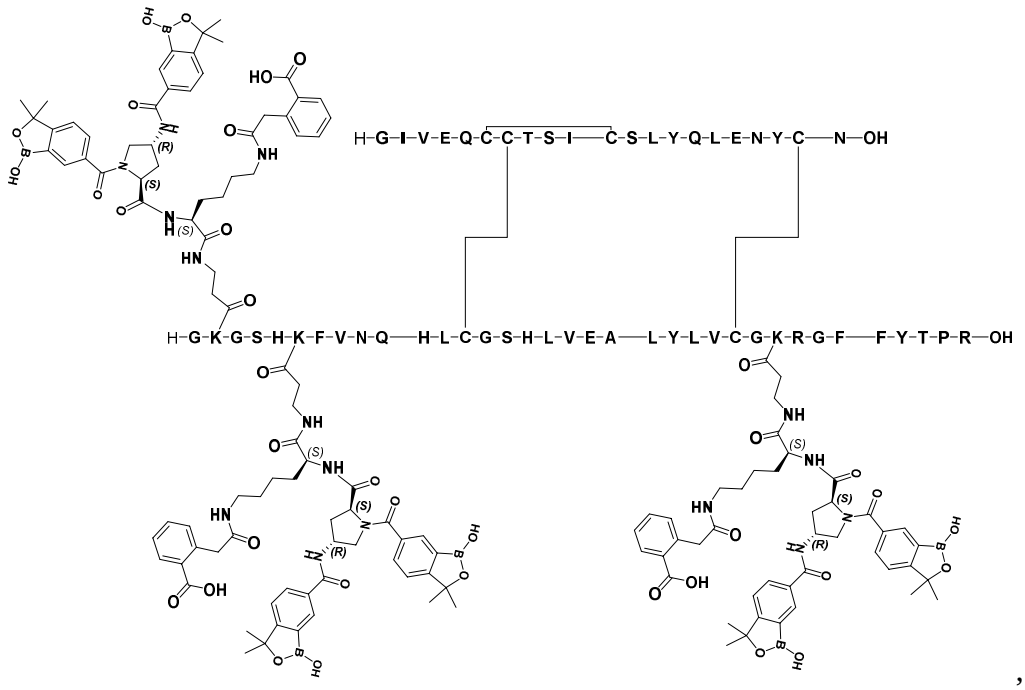
,

Example 73A:



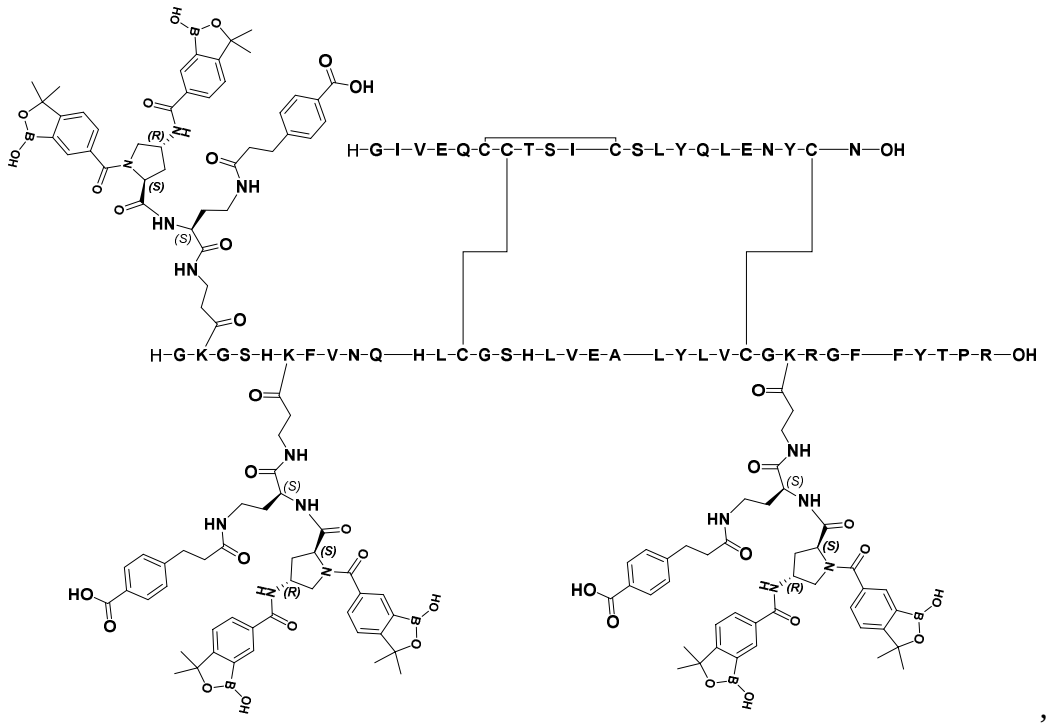
,

Example 74A:



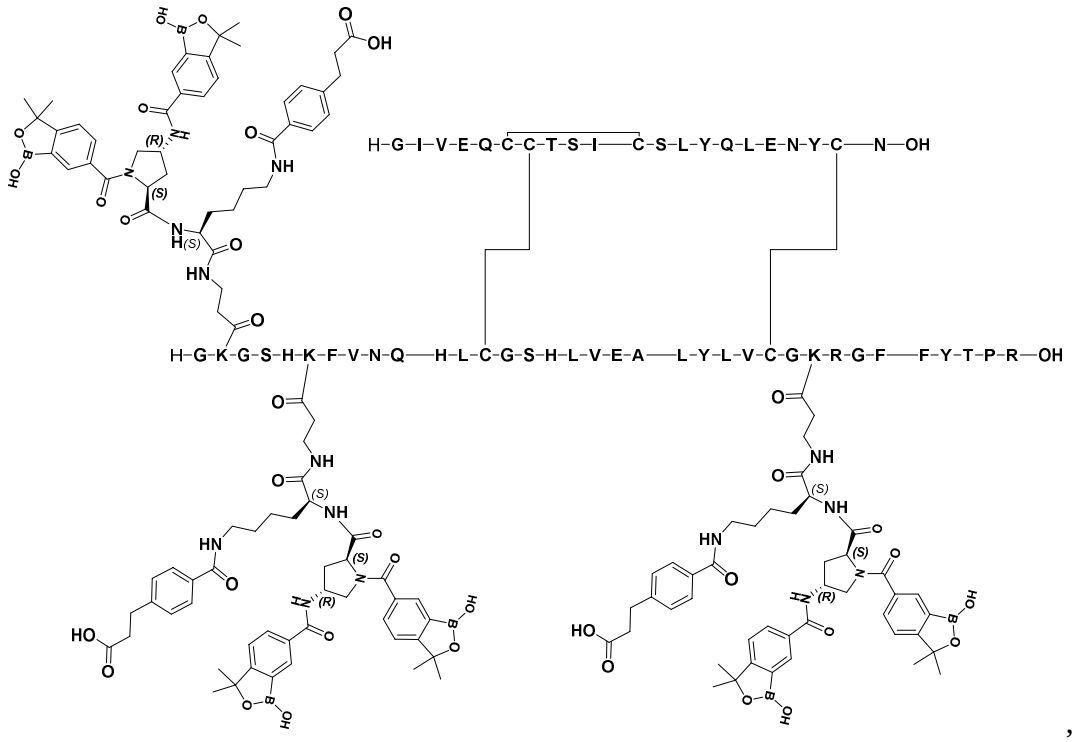
,

Example 75A:


H–G–I–V–E–Q–C–C–T–S–I––C–S–L–Y–Q–L–E–N–Y–C––N–OH
H–G–K–G–S–H–K–F–V–N–Q––H–L–C–G–S–H–L–V–E–A––L–Y–L–V–C–G–K–R–G–F––F–Y–T–P–R–OH

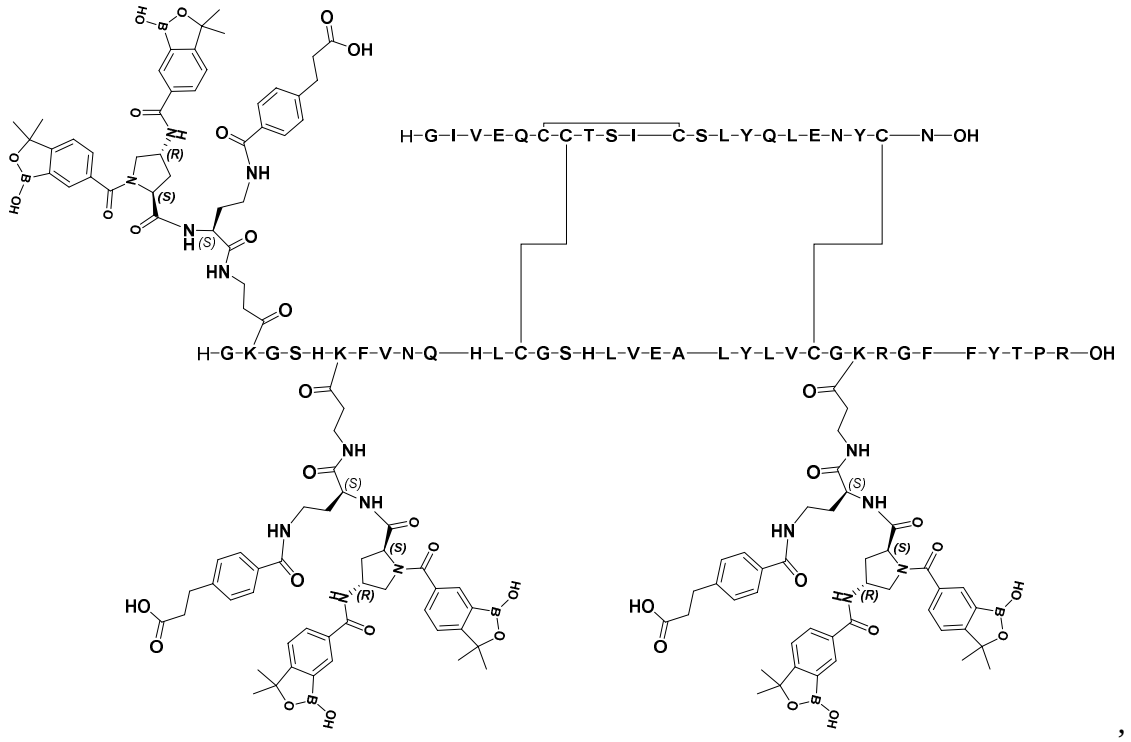
,

Example 76A:


H–G–I–V–E–Q–C–C–T–S–I––C–S–L–Y–Q–L–E–N–Y–C––N–OH
H–G–K–G–S–H–K–F–V–N–Q––H–L–C–G–S–H–L–V–E–A––L–Y–L–V–C–G–K–R–G–F––F–Y–T–P–R–OH

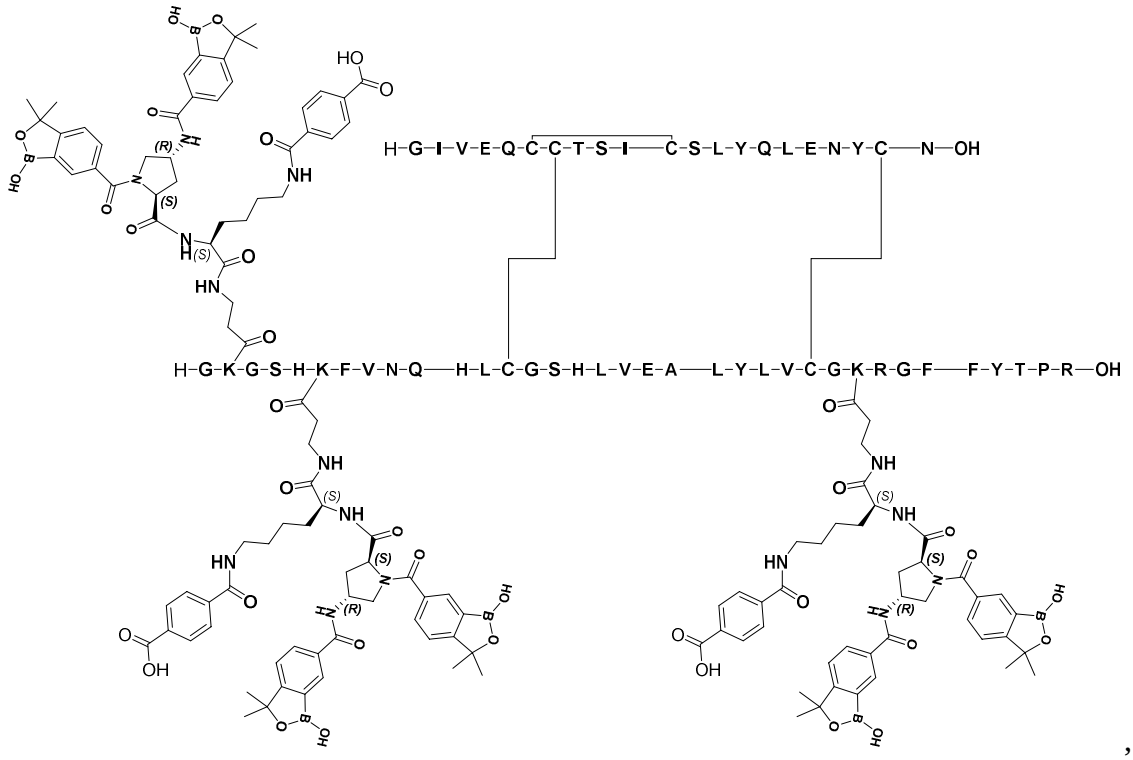
,

Example 77A:



,

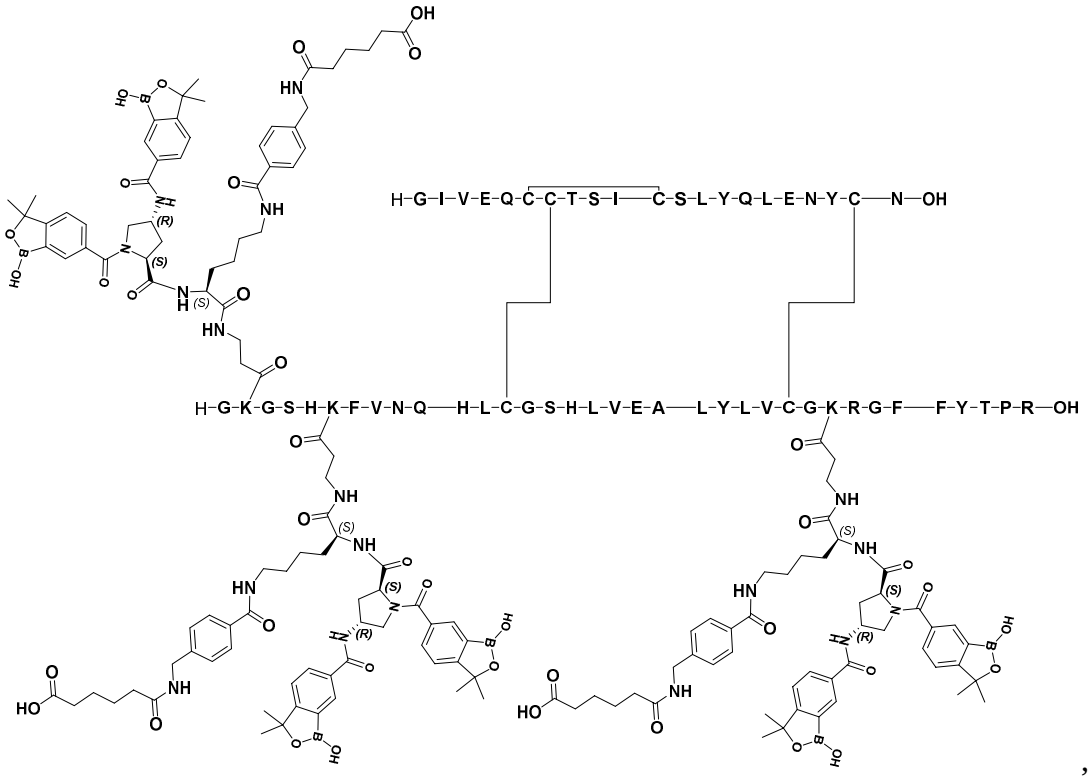
Example 78A:



,

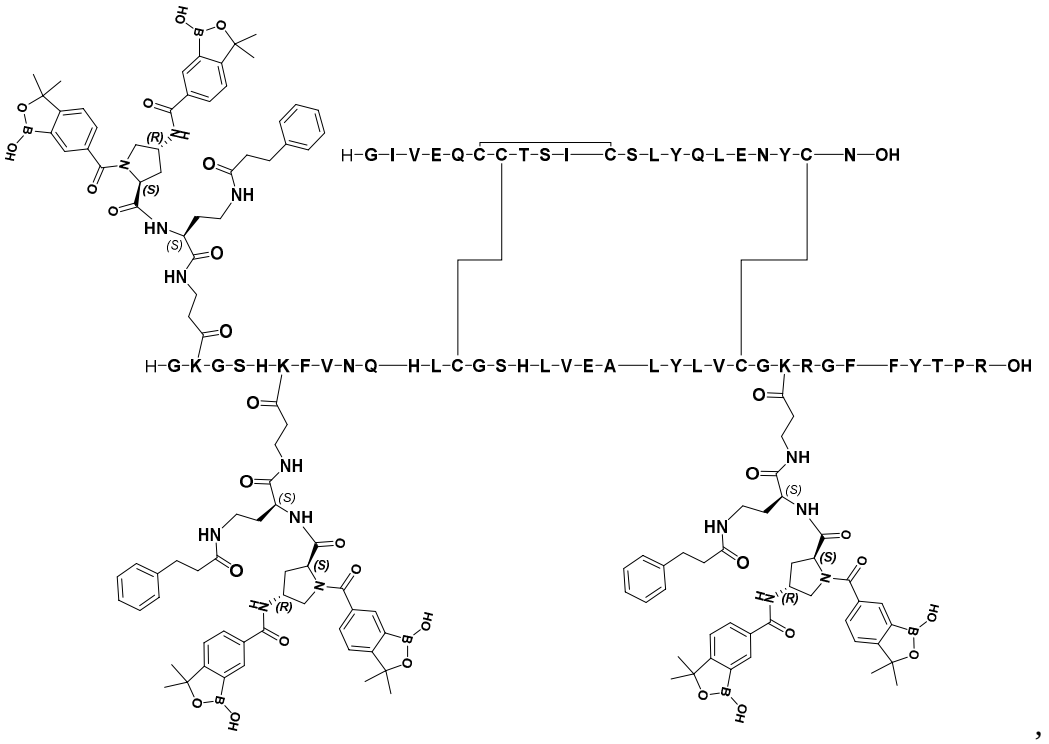
5

Example 79A:



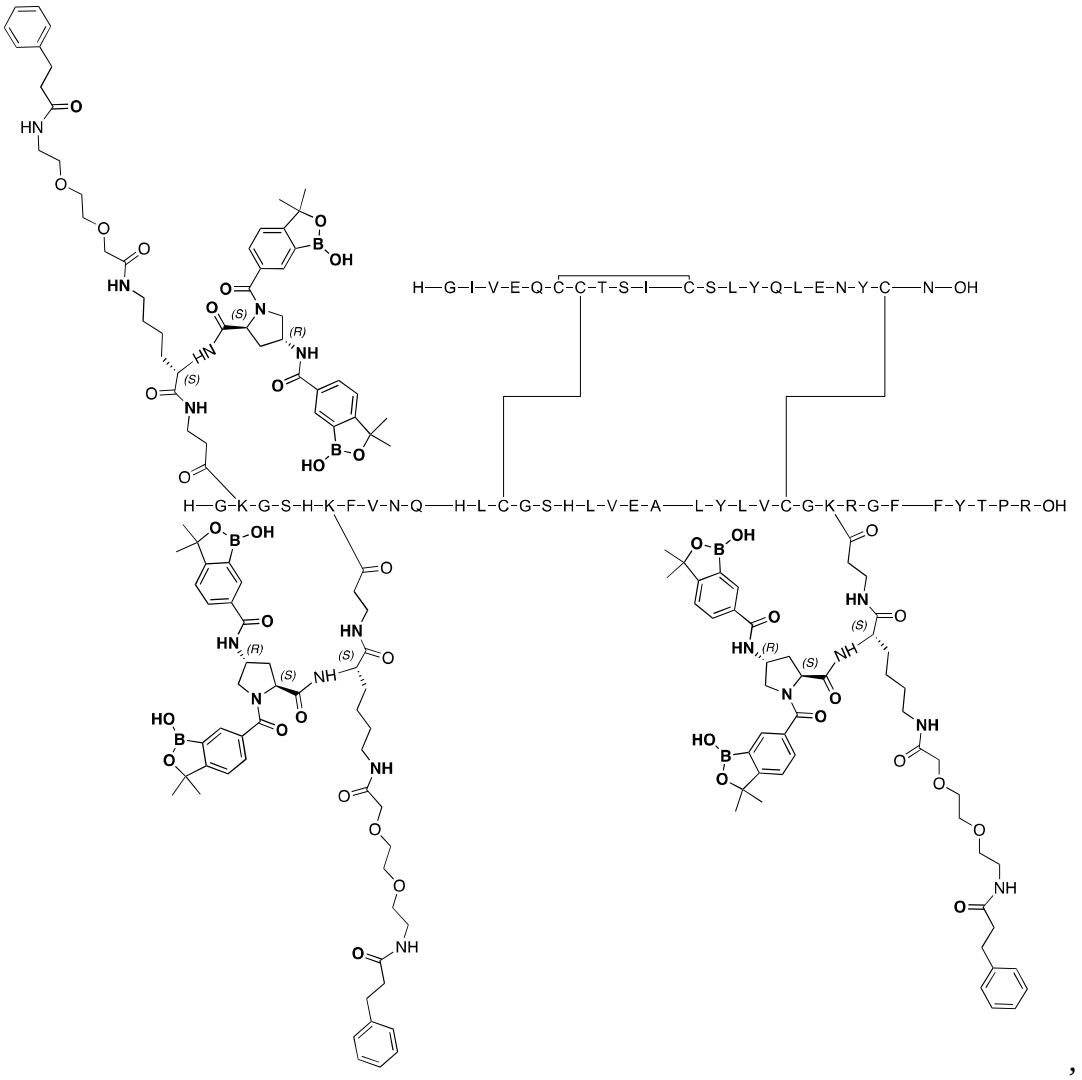
,

Example 80A:



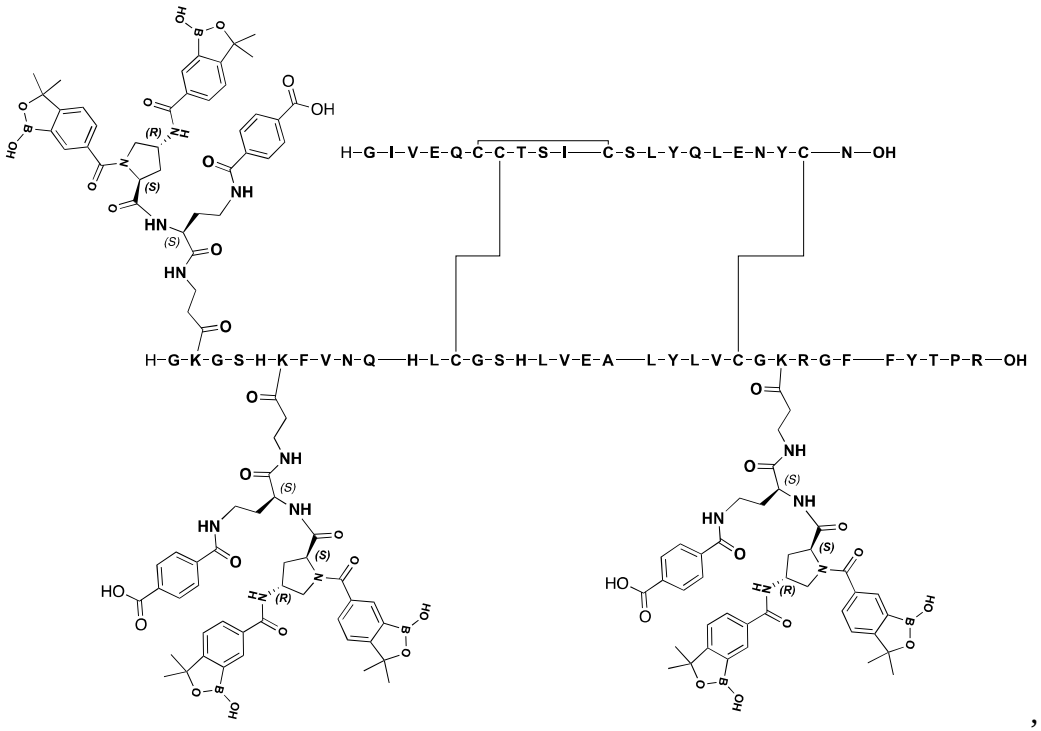
,

Example 81A:


H—G—I—V—E—Q—C—C—T—S—I—C—S—L—Y—Q—L—E—N—Y—C—N—OH
H—G—K—G—S—H—K—F—V—N—Q—H—L—C—G—S—H—L—V—E—A—L—Y—L—V—C—G—K—R—G—F—F—Y—T—P—R—OH

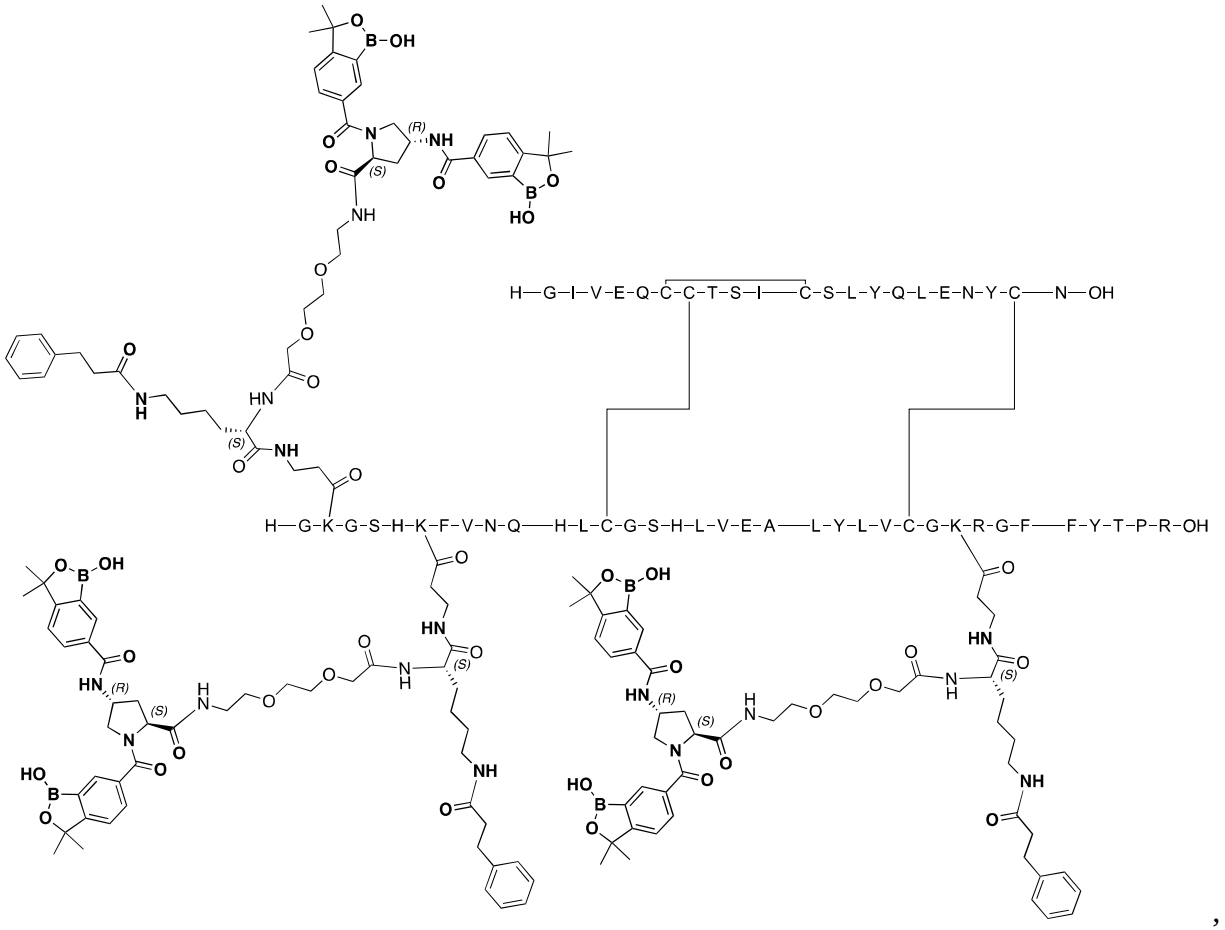
,

Example 82A:



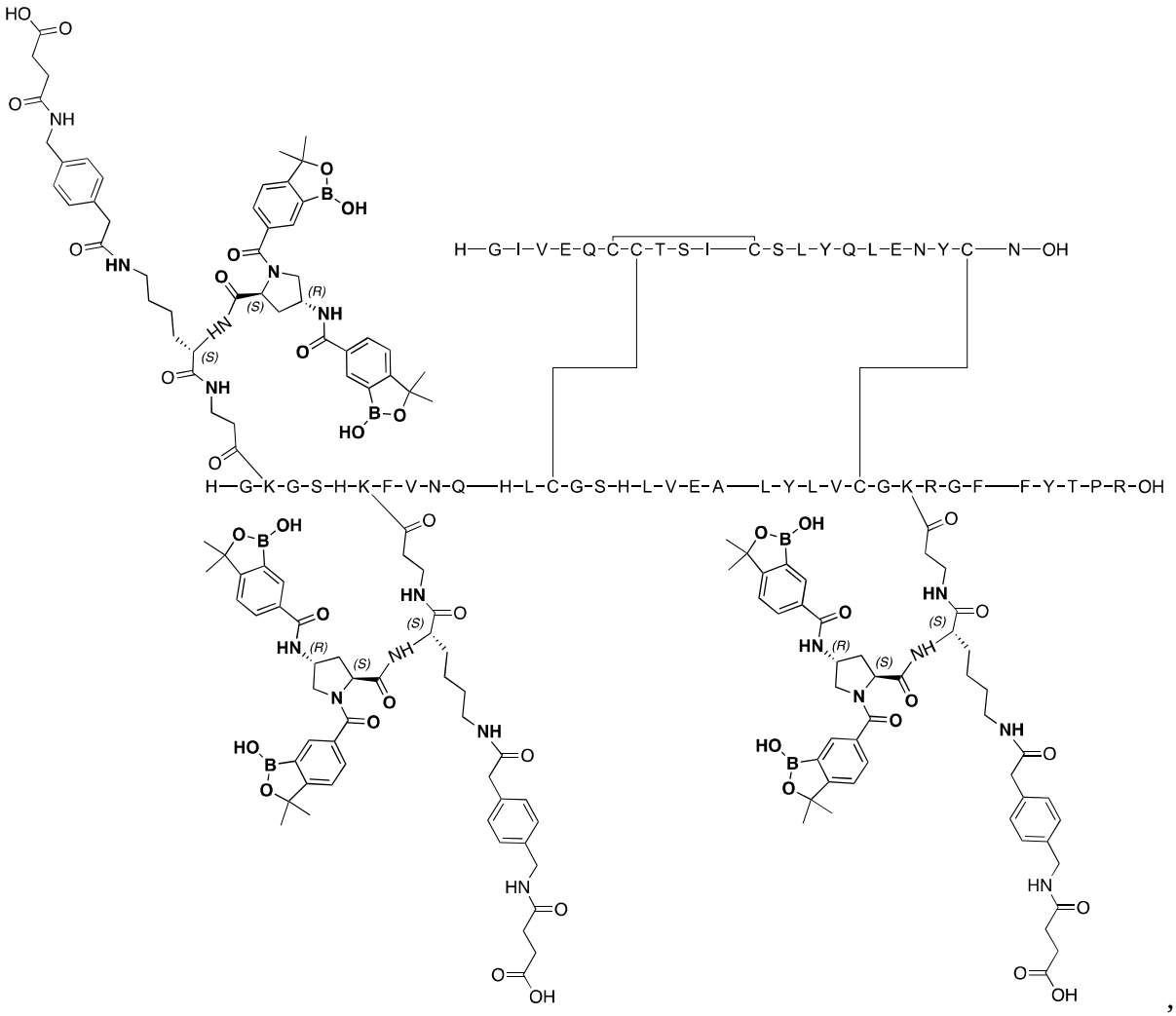
,

Example 83A:

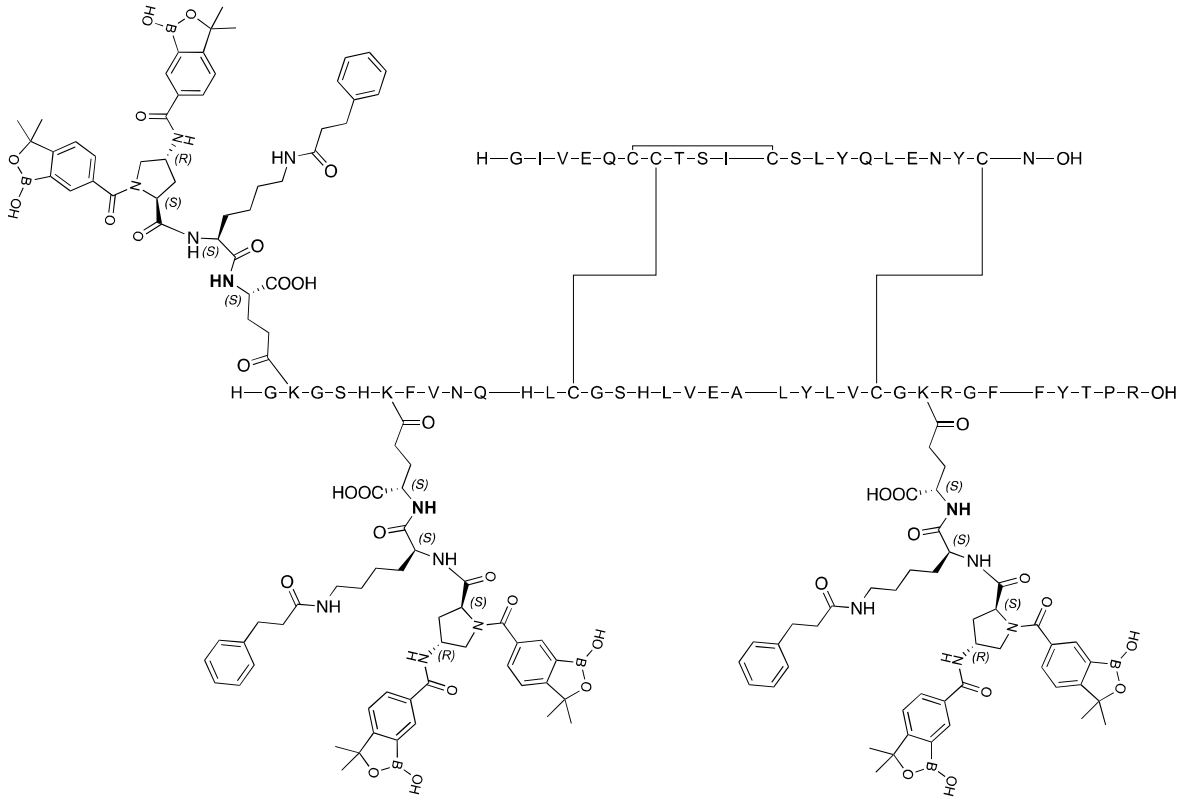


,

Example 84A:



Example 85A:



; or

a pharmaceutically acceptable salt thereof, an isotope thereof, and combinations thereof.

2. The compound according to claim 1, wherein the compound is Example 1A or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1, wherein the compound is Example 2A or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1, wherein the compound is Example 7A or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1, wherein the compound is Example 9A or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, wherein the compound is Example 14A or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, wherein the compound is Example 15A or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1, wherein the compound is Example 16A or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 1, wherein the compound is Example 18A or a pharmaceutically acceptable salt thereof.

10 The compound according to claim 1, wherein the compound is Example 19A or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 1, wherein the compound is Example 22A or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 1, wherein the compound is Example 25A or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 1, wherein the compound is Example 26A or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 1, wherein the compound is Example 27A or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1, wherein the compound is Example 28A or a pharmaceutically acceptable salt thereof.

16. The compound according to claim 1, wherein the compound is Example 30A or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 1, wherein the compound is Example 31A or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 1, wherein the compound is Example 46A or a pharmaceutically acceptable salt thereof.

19. The compound according to claim 1, wherein the compound is Example 47A or a pharmaceutically acceptable salt thereof.

20. The compound according to claim 1, wherein the compound is Example 49A or a pharmaceutically acceptable salt thereof.

21. The compound according to claim 1, wherein the compound is Example 51A or a pharmaceutically acceptable salt thereof.

22. The compound according to claim 1, wherein the compound is Example 63A or a pharmaceutically acceptable salt thereof.

23. The compound according to claim 1, wherein the compound is Example 68A or a pharmaceutically acceptable salt thereof.

24. The compound according to claim 1, wherein the compound is Example 71A or a pharmaceutically acceptable salt thereof.

25. The compound according to claim 1, wherein the compound is Example 73A or a pharmaceutically acceptable salt thereof.

26. The compound according to claim 1, wherein the compound is Example 75A or a pharmaceutically acceptable salt thereof.

27. The compound according to claim 1, wherein the compound is Example 77A or a pharmaceutically acceptable salt thereof.

28. The compound according to claim 1, wherein the compound is Example 78A or a pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition comprising at least one compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-28 and a pharmaceutically acceptable carrier.

30. A compound according to any one of claims 1-28, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 29, for use as a medicament.

31. Use of a compound according to any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 29, in the manufacture of a medicament for the treatment of type 2 diabetes, type 1 diabetes, diabetes during pregnancy, pre-diabetes, MODY 1 diabetes, MODY 2 diabetes, MODY 3 diabetes, impaired glucose tolerance, hyperglycemia, metabolic syndrome, obesity, control of blood sugar levels, Alzheimer's disease, mood disorders, or psychiatric disorders.