Bifunctional Small Molecules to Target the Selective Degradation of Circulating Proteins

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 63/498,852, filed April 28, 2023 and U.S. Provisional Patent Application No. 63/517,984, filed August 7, 2023, both of which applications are incorporated herein by reference in their entireties.

BACKGROUND

Various diseases are associated with elevated levels of certain proteins in circulation, which play a role in disease progression. For example, increased levels of multiple circulating pro-inflammatory cytokines (i.e., signaling proteins that promote inflammatory effect) contribute to a variety of systemic inflammatory conditions and autoimmune diseases, such as Rheumatoid Arthritis (RA), systemic lupus erythematosus (SLE) and atherosclerosis. Studies have also linked chronic inflammation to an increased risk of heart disease, stroke, cancer and Alzheimer's disease. In particular, increased levels of cytokines such as TNFα or MIF are associated with Rheumatoid arthritis (RA), atherosclerosis and other diseases. Taken together, the diseases and/or conditions which are associated with circulating proteins impact the lives of millions of people. There is a strong need for novel treatments to address these diseases.

Current strategies to target circulating proteins include the use of inhibiting antibodies, which possess excellent specificity and affinity for target proteins. Despite these advantages, antibody-based therapies have several drawbacks that relate primarily to their high molecular weights and/or peptidic structures the likelihood of invoking immunogenicity, their high cost, short shelf life and low oral bioavailability. The small molecule based strategy pursuant to the present invention has the potential to combine the beneficial attributes of antibody-based therapies while overcoming their most significant disadvantages.

The high prevalence of inflammatory diseases in the population presents a considerable economic burden to the healthcare system. The high demand and high cost of current antibody-based treatments is reflected in the 34.4 billion USD global sales of TNF-α antibodies. In contrast, the bifunctional small molecule according to the present invention is readily prepared by organic synthesis, and has the potential to substantially lower the cost of manufacturing, storage and treatment. Similarly, these bifunctional chemical constructs are

easier to produce in large quantity to ultimately meet high demand of treatments.

BRIEF SUMMARY OF THE INVENTION

Conceptually, the present invention is directed to bifunctional small molecules which can be used to remove circulating proteins, which mediate disease states and/or conditions in subjects. The present invention aims to establish a general small molecule strategy to target the selective degradation of disease-related circulating proteins. The bifunctional molecule construct contains a protein targeting motif derived from known small molecule ligands of the proteins of interest. The inventors refer to this moiety generically as a circulating protein binding moiety (CPBM). The other end of the bifunctional molecule is a cellular receptor binding moiety (CRBM) that binds to a cell surface receptor and leads to internalization of the circulating protein and bifunctional molecule. The two motifs are covalently linked via a linker such as a polyethylene glycol (PEG) linker with adjustable length and optionally contains one or more connector molecule which connects the linker to the CPBM and/or the CRBM.

The presently claimed bifunctional compounds selectively bind to the Immunoglobulin G ("IgG") protein of interest (which can be a pathogenic form of IgG) in circulation and form an IgG protein complex that then binds a cellular receptor and is endocytosed and degraded. As a consequence of this mechanism, the IgG protein of interest is eliminated from circulation by hepatocytes, macrophages, or another cell type, thus resulting in lowered level of the IgG protein of interest with the potential of attenuating the corresponding disease symptoms. In certain instances, the IgG protein of interest may be eliminated, resulting in substantially reduced symptoms or even a cure or elimination of the disease state or condition.

The approach pursuant to the present invention is inherently advantageous compared to the classical antibody-based strategy to target disease-related circulating proteins of the prior art. The small molecule based approach of the current invention overcomes limitations of traditional antibody-based strategies, including lack of oral bioavailability, low-temperature storage requirements, immunogenicity, and high-cost.

Furthermore, the present invention is expected to have a more lasting effect compared to the conventional inhibitory approach because the disease relevant proteins are eliminated by degradation inside hepatocytes rather than simply inhibited by reversibly blocking the protein-receptor interaction. The bifunctional molecule construct pursuant to the present invention is also versatile in the sense that different disease related proteins can be targeted

by simply switching the protein targeting motif in the construct. Thus, previously discovered non-inhibitory protein binders can be potentially therapeutically useful in these small molecules.

In one embodiment, the present invention is directed to compounds which are useful for removing IgG circulating proteins which are associated with a disease state or condition in a patient or subject according to the general chemical structure:

wherein [CPBM] is a Circulating Protein Binding Moiety which binds respectively to IgG circulating proteins as identified herein, which are related to and/or mediate a disease state and/or condition and is to be removed by the action of hepatocytes or other cells on the IgG circulating protein (the compounds preferably selectively binding to the IgG circulating protein in plasma of the subject or patient);

[CRBM] is a Cellular Receptor binding moiety, preferably an [ASGPRBM] group, which is a binding moiety which binds to hepatocytes or other cells through asialoglycoprotein receptors or other receptors as identified herein which are on the surface of hepatocytes and other degrading cells, preferably in a patient or subject;

each [CON] is an optional connector chemical moiety which, when present, connects directly to [CPBM] or to [CRBM] or connects the [LINKER] to [CPBM] or to [CRBM] and

[LINKER] is a chemical moiety having a valency from 1 to 15 which covalently attaches to one or more [CRBM] and/or [CPBM] group, optionally through a [CON], including a [MULTICON] group, wherein said [LINKER] optionally itself contains one or more [CON] or [MULTICON] group(s);

k' is an integer from 1 to 15;

j' is an integer from 1 to 15;

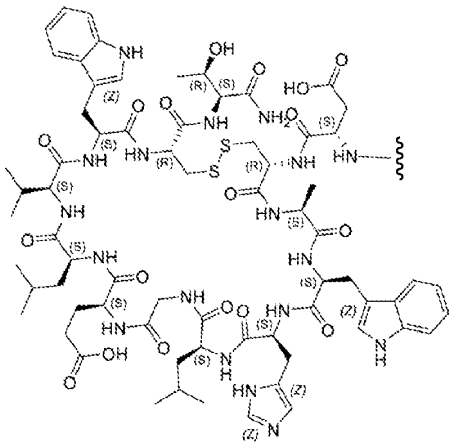
h and h' are each independently an integer from 0 to 15;

i_L is an integer from 0 to 15;

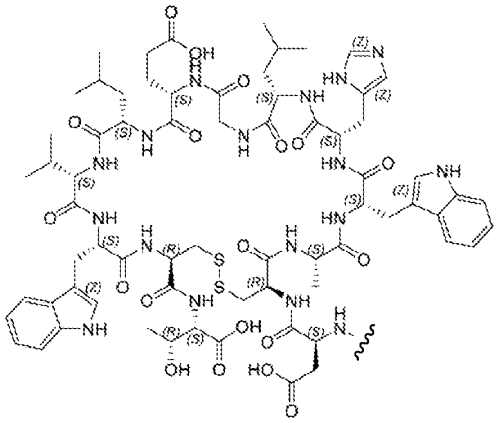
with the proviso that at least one of h, h' and i_L is at least 1, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

In various embodiments, [LINKER] has a valency of 1 to 10. In various embodiments, [LINKER] has a valency of 1 to 5. In various embodiments, [LINKER] has a valency of 1, 2 or 3. A [MULTICON] group can connect one or more of a [CRBM] or [CPBM] to one or more of a [LINKER].

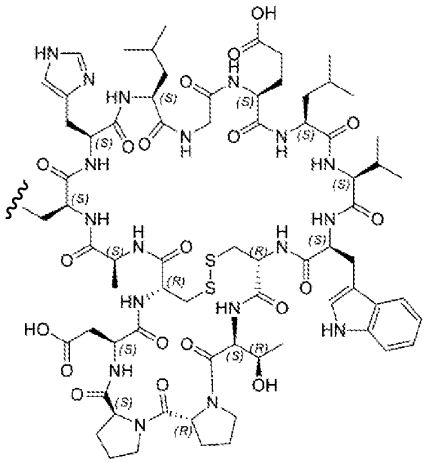
In one embodiment, [CPBM] is or includes the moiety:



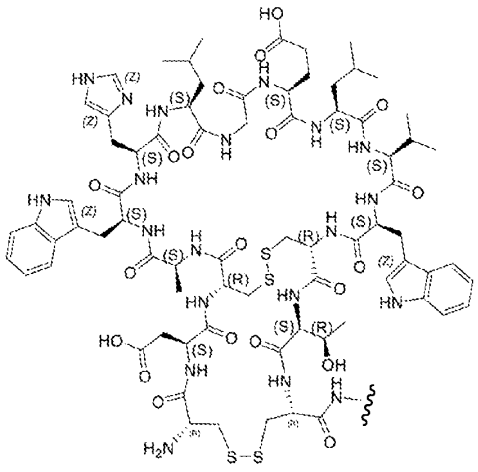
In another embodiment, [CPBM] is or includes the moiety:



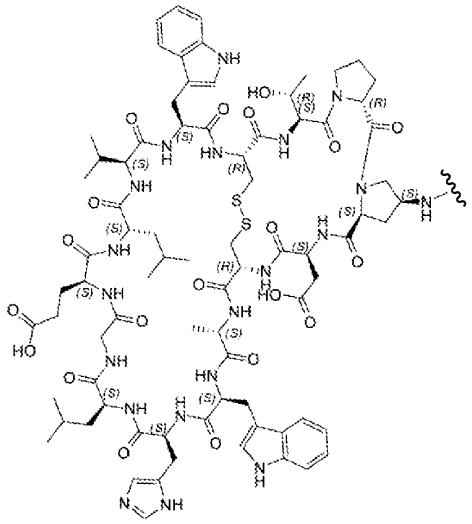
In another embodiment, [CPBM] is or includes the moiety:



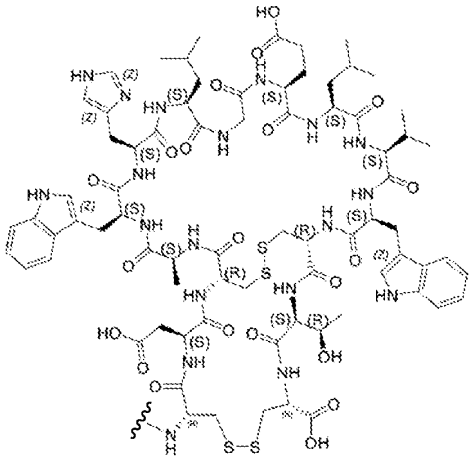
In another embodiment, [CPBM] is or includes the moiety:



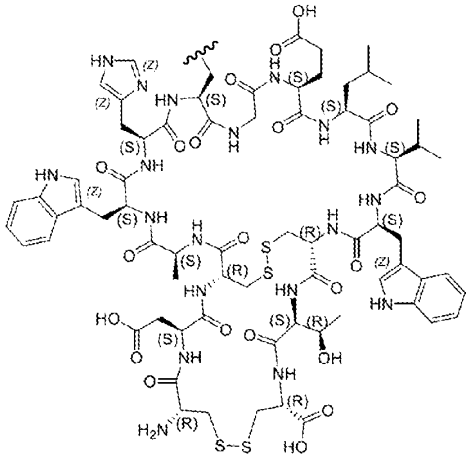
In another embodiment, [CPBM] is or includes the moiety:



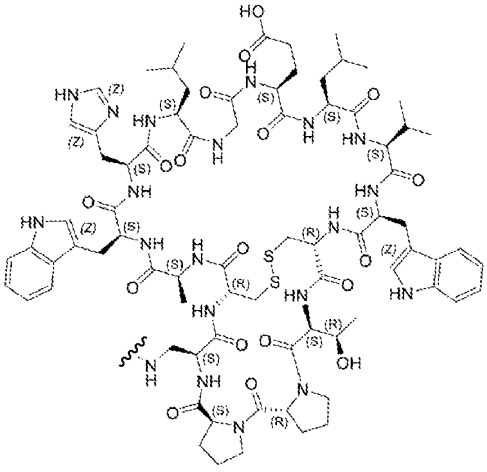
In another embodiment, [CPBM] is or includes the moiety:



In another embodiment, [CPBM] is or includes the moiety:

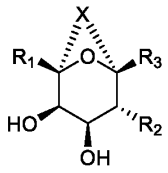


In another embodiment, [CPBM] is or includes the moiety:

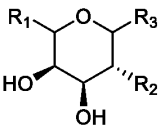


In one embodiment, [CRBM] is an [ASGPRBM] is a group according to the chemical

structure:



or



where X is 1-4 atoms in length and is at each occurrence independently selected from the group consisting of O, S, $N(R^{N1})$, and $C(R^{N1})(R^{N1})$ such that:

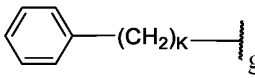
if X is 1 atom in length, X is O, S, $N(R^{N1})$, or $C(R^{N1})(R^{N1})$,

if X is 2 atoms in length, no more than 1 atom of X is O, S, or $N(R^{N1})$,

if X is 3 or 4 atoms in length, no more than 2 atoms of X are O, S or $N(R^{N1})$;

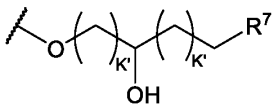
where R^{N1} is H or a C_1-C_3 alkyl group optionally substituted with from 1-3 halogen groups;

R_1 and R_3 are each independently H, $-(CH_2)_KOH$, $-(CH_2)_KOC_1$-C_4 alkyl, $-C_1$-C_4 alkyl, $-(CH_2)_K$vinyl, $-O-(CH_2)_K$vinyl, $-(CH_2)_K$alkynyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-C_1$-C_4 alkyl, --O-C(O)-C_1-C_4 alkyl, -C(O)-C_1-C_4 alkyl, in which each alkyl, vinyl, or alkynyl is optionally substituted with from 1-3 halogen groups. In various embodiments, each alkyl, vinyl, or alkynyl in R_1 and R_3 is optionally substituted with from 1-3 fluorines (F). K is independently at each occurrence an integer from 0-4.

In one embodiment, R_1 and R_3 are each independently a 

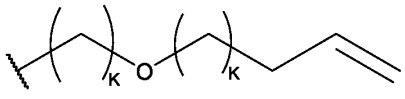
group, which is optionally substituted with 1-3 halogen groups, 1 to 3 C_1-C_4 alkyl groups, or O-C_1-C_4 alkyl groups, in which each of the alkyl groups is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, and K is independently at each occurrence and integer from 0-4; or

R_1 and R_3 are each independently a group according to the chemical structure:



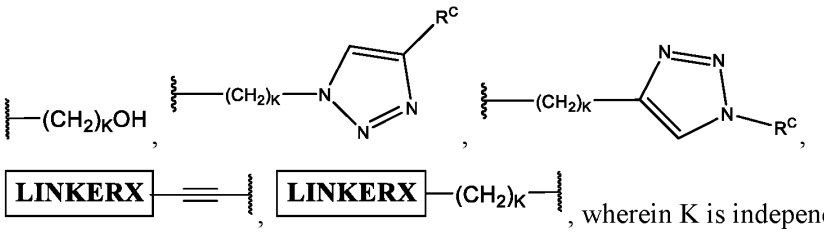
,

where R^7 is O-C_1-C_4 alkyl, which is optionally substituted with from 1 to 3 halo groups or 1 to 2 hydroxy groups, and K' is independently at each occurrence an integer from 0-4; or

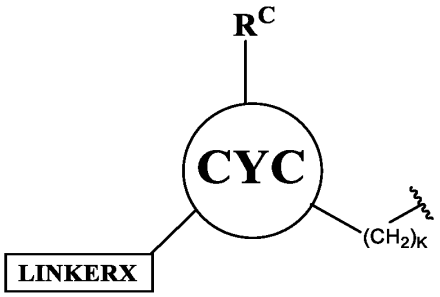
R^7 is a $-NR^{N3}R^{N4}$ group or 

, and K is independently at each occurrence an integer from 0-4; or

R_1 and R_3 are each independently a group according to the structure:

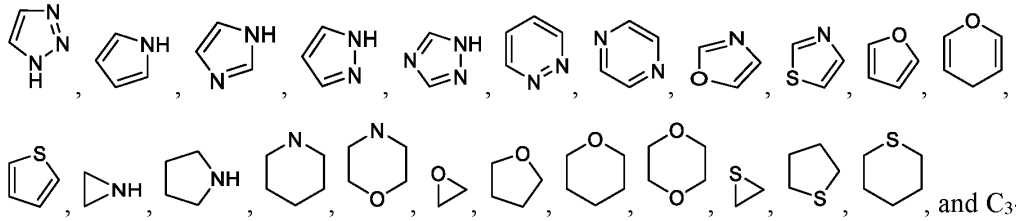


, wherein K is independently at each occurrence 0-4; or a



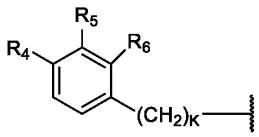
group,

wherein CYC is a ring selected from the group consisting of:



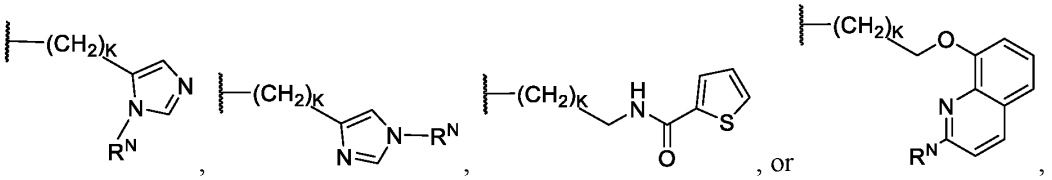
, and C_3-C_8 saturated carbocyclic, wherein each of LINKERX, R^C, and $-(CH_2)_K$- are attached to an open valence in CYC, including N-H;

R^C is absent, H, C_1-C_4 alkyl optionally substituted with from 1-3 halogen groups or 1-2 hydroxyl groups; or a group according to the structure:



where R_4, R_5 and R_6 are each independently, H, halogen, CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KOC_1$-C_4 alkyl, C_1-C_3 alkyl, -O-C_1-C_3-alkyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O$-C_1-C_4 alkyl, O-C(O)-C_1-C_4 alkyl, -C(O)-C_1-C_4 alkyl, in any of which the alkyl group is optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups; or

R^C is



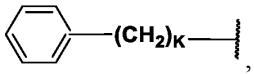
where R^N , R^{N1}, and R^{N2} are each independently H or a C_1-C_3 alkyl group optionally substituted with 1-3 halogen groups, or 1-2 hydroxyl groups;

K is independently at each occurrence an integer from 0-4;

K' is independently at each occurrence an integer from 0-4;

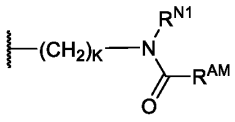
R^{N3} is H or C_1-C_3 alkyl optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups; and

R^{N4} is H or C_1-C_3 alkyl optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, or

R^{N4} is  , where K is 1;

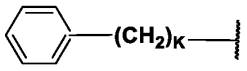
LINKERX is a linker group which includes at least one [CPBM] group and connects the [CPBM] group to the [CRBM] through one or more optional [CON] groups, or

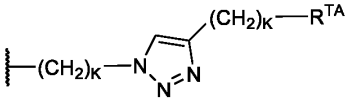
LINKERX is a linker group which includes at least one functional group that covalently bonds the linker group to at least one [CPBM] group or optional [CON] group;

R_2 is  ,where R^{N1} and K are the same as above;

R^{AM} is H, C_1-C_4 alkyl, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl, -O-C(O)-C_1-C_4 alkyl, -C(O)-C_1-C_4 alkyl, -$(CH_2)_K$-$NR^{N3}R^{N4}$ where R^{N3} is H or C_1-C_3 alkyl, in which any of the alkyl groups are optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups; and

R^{N4} is H, C_1-C_3 alkyl optionally substituted with 1-3 halo groups or 1 or 2 hydroxy groups, or

R^{N4} is  and K is 1; or

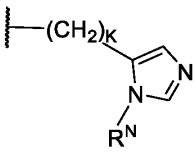
R_2 is a  ,

where R^{TA} is H, CN, $NR^{N1}R^{N2}$, -$(CH_2)_K$OH, -$(CH_2)_K$OC_1-C_4 alkyl, C_1-C_4 alkyl, -

$(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-C_1-C_4$ alkyl, $O-C(O)-C_1-C_4$ alkyl, $-C(O)-C_1-C_4$ alkyl, in which each alkyl is optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups, or

R^{TA} is a C_3-C_{10} aryl or a 3- to 10-membered heteroaryl group containing up to 5 hetero atoms, each of said aryl or heteroaryl groups being optionally substituted with 1-3 substituents selected from the group consisting of CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KOC_1-C_4$ alkyl, C_1-C_3 alkyl, $-O-C_1-C_3$-alkyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-C_1-C_4$ alkyl, $O-C(O)-C_1-C_4$ alkyl, and $-(CH_2)_KC(O)-C_1-C_4$ alkyl, in which each alkyl is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, or

R^{TA} is



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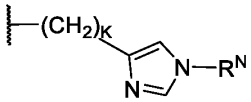

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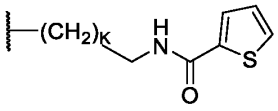
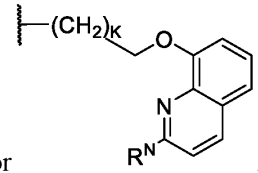
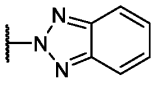
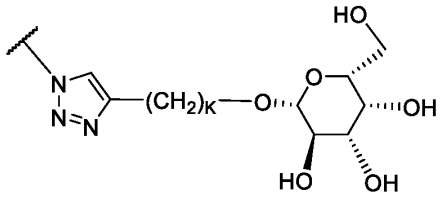


, or


,

or;

R^{TA} is  group which is optionally substituted with 1-3 C_1-C_3 alkyl groups each of which are optionally substituted with 1-3 halogen groups, or



R^{TA} is ,

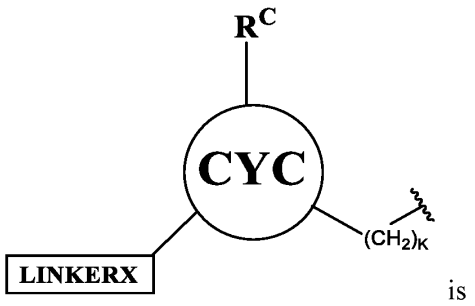
wherein R^N, R^{N1}, and R^{N2} are each independently H or a C_1-C_3 alkyl group which is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups and

wherein each $-(CH_2)_K$ group is optionally substituted with 1-4 C_1-C_3 alkyl groups which are each optionally substituted with from 1-3 fluorines or 1-2 hydroxyl groups;

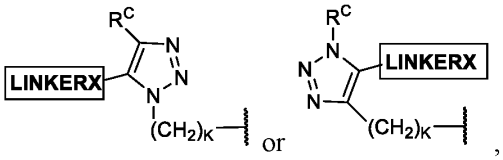
and K is independently at each occurrence 0-4.

In various embodiments, any of the alkyl groups described herein as being optionally substituted by 1-3 halogen groups, are substituted by 1, 2, or 3 fluorine (F) atoms.

In various embodiments,



is

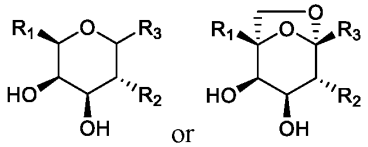


,

where R^C, LINKERX and K are the same as above.

In some embodiments of the present invention X of the [CRBM]/[ASGPRBM] group is OCH_2 or CH_2O and R^{N1} is preferably H.

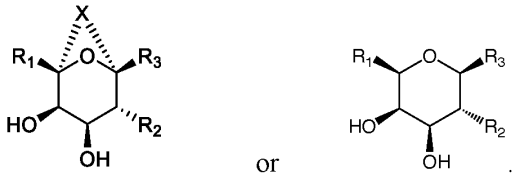
In various embodiments, the [CRBM]/[ASGPRBM] group is a group according to the chemical structure:



where R_1, R_2 and R_3 are as defined herein, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

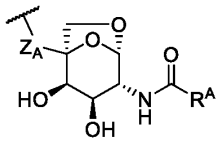
In some embodiment, the carbohydrate moiety of the [ASGPRBM] group has α-configuration at the anomeric center. In some embodiments, the carbohydrate moiety of the [ASGPRBM] group has β-configuration at the anomeric center.

In some embodiments, [CRBM] is or includes an [ASGPRBM] group according to the chemical structure:

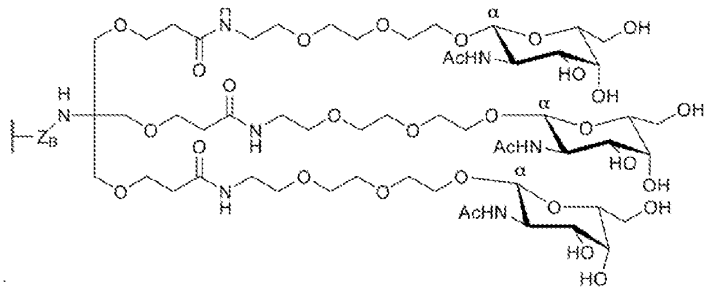


.

In some embodiments, the [CRBM]/[ASGPRBM] group is a group according to the chemical structure:



or



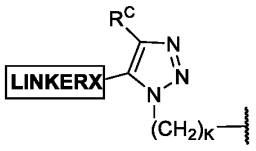
;

where R^A is C_1-C_3 alkyl optionally substituted with 1-5 halogen groups;

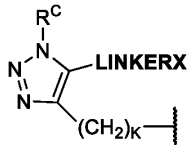
Z_A is $-(CH_2)_{IM}$, $-O-(CH_2)_{IM}$, $S-(CH_2)_{IM}$, $NR_M-(CH_2)_{IM}$, $C(O)-(CH_2)_{IM}-$, a PEG group containing 1 to 8 ethylene glycol (CH_2CH_2O or OCH_2CH_2) residues, or $-C(O)(CH_2)_{IM}NR_M$, where IM and R_M are the same as above; and

Z_B is absent, $(CH_2)_{IM}$, $C(O)-(CH_2)_{IM}-$, or $C(O)-(CH_2)_{IM}-NR_M$, where IM and R_M are the same as above.

In various embodiments, R_1 and R_3 are each independently a group according to the chemical structure:



or



, where R^C, LINKERX and K are as defined herein.

In an additional embodiment, the present invention is directed to a pharmaceutical composition comprising an effective amount of a compound according to the present invention in combination with a pharmaceutically acceptable carrier, additive or excipient, optionally in combination with at least one additional bioactive agent.

In other embodiments, the present invention is directed to a method of treating a disease state or condition where a circulating protein is related to or contributes to a disease state and or condition or the symptomology associated with the disease state or condition. These disease states and/or conditions include autoimmune diseases and numerous inflammatory diseases for example, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Alzheimer's disease, atherosclerosis, heart disease, stroke and cancer (including leukemia), among numerous others as described herein. The method of treatment according to the present invention comprises administering to a patient or subject in need of therapy an effective amount of at least one compound according to the present invention, optionally in combination with an additional bioactive agent to reduce the likelihood of, inhibit and/or treat

the disease state or condition by removing Circulating Protein associated with the disease state and/or condition from the circulation of the patient or subject.

In an additional embodiment, the present invention is directed to a pharmaceutical composition comprising an effective amount of a compound according to the present invention in combination with a pharmaceutically acceptable carrier, additive or excipient, optionally in combination with at least one additional bioactive agent.

In other embodiments, the present invention is directed to a method of treating a disease state or condition where a circulating protein is related to the symptomology associated with the disease state or condition. These disease states and/or conditions include, for example, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Alzheimer's disease, atherosclerosis, heart disease, stroke and cancer (including leukemia), among numerous others as described herein. The method comprises administering to a patient or subject in need of therapy an effective amount of at least one compound according to the present invention, optionally in combination with an additional bioactive agent to reduce the likelihood of, inhibit and/or treat the disease state or condition by removing circulating proteins associated with the disease state and/or condition.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention there may be employed conventional chemical synthetic and pharmaceutical formulation methods, as well as pharmacology, molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are well-known and are otherwise explained fully in the literature.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise (such as in the case of a group containing a number of carbon atoms), between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein

can also be used in the practice or testing of the present invention, the preferred methods and materials are now described.

It is to be noted that as used herein and in the appended claims, the singular forms "a," “an”, "and" and "the" include plural references unless the context clearly dictates otherwise.

Furthermore, the following terms shall have the definitions set out below. It is understood that in the event a specific term is not defined hereinbelow, that term shall have a meaning within its typical use within context by those of ordinary skill in the art.

The term “compound”, as used herein, unless otherwise indicated, refers to any specific chemical compound disclosed herein and includes tautomers, regioisomers, geometric isomers, stereoisomers and where applicable, optical isomers (enantiomers) thereof, as well as pharmaceutically acceptable salts and derivatives (including prodrug forms) thereof. Within its use in context, the term compound generally refers to a single compound, but also may include other compounds such as stereoisomers, regioisomers and/or optical isomers (including racemic mixtures) as well as specific enantiomers or enantiomerically enriched mixtures of disclosed compounds. The term also refers, within context, to prodrug forms of compounds which have been modified to facilitate the administration and delivery of compounds to a site of activity. It is noted that in describing the present compounds, numerous substituents, linkers and connector molecules and variables associated with same, among others, are described. The use of a bond presented as ----- signifies that a single bond is present or absent, depending on the context of the chemistry described, including the attachment of the bond to another moiety. The use of a bond presented as ------- signifies that a single bond or a double bond is intended depending on the context of the chemistry described. It is understood by those of ordinary skill that molecules which are described herein are stable compounds as generally described hereunder.

The term “patient” or “subject” is used throughout the specification within context to describe an animal, generally a mammal and preferably a human, to whom treatment, including prophylactic treatment (prophylaxis, including especially as that term is used with respect to reducing the likelihood of metastasis of an existing cancer), with the compositions according to the present invention is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human patient or a patient of a particular gender, such as a human male or female patient, the term patient refers to that specific animal. Compounds according to the present invention are useful for the treatment of numerous disease states including autoimmune disease states and/or conditions and

inflammatory disease states and/or conditions as well as cancer, including especially for use in reducing the likelihood of metastasis or recurrence of a cancer.

The term "effective" is used herein, unless otherwise indicated, to describe an amount of a compound or composition which, in context, is used to produce or effect an intended result, whether that result relates to the inhibition of the effects of a disease state (e.g. an autoimmune disease such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), among others, atherosclerosis, heart disease or stroke, among numerous others or a cancer, including leukemia) on a subject or the treatment or prophylaxis of a subject for secondary conditions, disease states or manifestations of disease states as otherwise described herein. This term subsumes all other effective amount or effective concentration terms (including the term "therapeutically effective") which are otherwise described in the present application.

The terms "treat", "treating", and "treatment", etc., as used herein, refer to any action providing a benefit to a patient at risk for a disease state or condition for which a MIF protein may be removed, such as an autoimmune disease including rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), among others, atherosclerosis, heart disease, stroke and cancer (including leukemia) including recurrence and/or metastasis of cancer, improvement in the condition through lessening or suppression of at least one symptom of the disease state or condition, inhibition of one or more manifestations of the disease state (e.g., plaque formation, heart disease, cancer growth, reduction in cancer cells or tissue), prevention, reduction in the likelihood or delay in progression of a disease state or condition or manifestation of the disease state or condition, especially including plaque formation in atheroslerosis, deterioration of tissue and inflammation in rheumatoid arthritis, further damage to cardiovascular tissue in heart disease, further damage to central nervous tissue in stroke, cancer, its recurrence or metastasis of the cancer, prevention or delay in the onset of disease states or conditions which occur secondary to the disease state or condition including cancer recurrence or metastasis, among others. Treatment, as used herein, encompasses both prophylactic and therapeutic treatment, depending on the context of the treatment. The term "prophylactic" when used, means to reduce the likelihood of an occurrence or the severity of an occurrence within the context of treatment of disease state or condition, as otherwise described hereinabove.

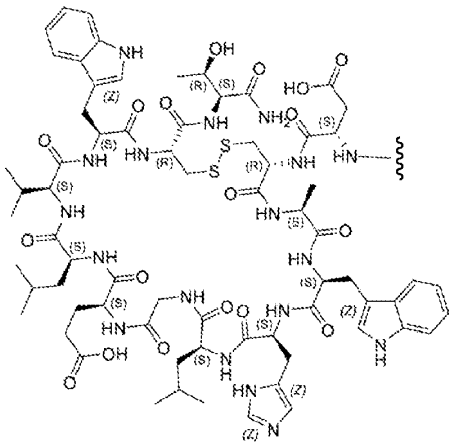
As used in this application, the terms "about" and "approximately" are used as equivalents. Any numerals used in this application with or without about/approximately are meant to cover any normal fluctuations in a value appreciated by one of ordinary skill in the

relevant.

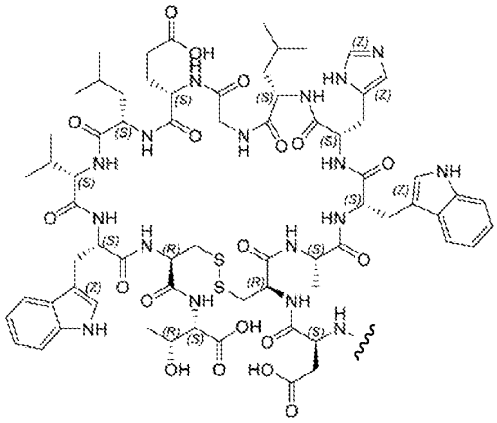
The term "circulating protein binding moiety", which term includes "immunoglobulin G binding moiety" or "IgGBM" refers to a chemical moiety on one end of the bifunctional compounds according to the present invention which is capable of binding to a circulating protein which is associated with or contribute to a disease state or condition as otherwise described herein. In the present invention, the CPBM is capable of binding to the circulating protein, forming a complex with the present compounds, and delivering the bound protein to a hepatocyte or other cell whereupon the other end of the bifunctional molecule which contains a cellular receptor binding moiety (CRBM) such an asialoglycoprotein receptor binding moiety (ASGPRBM) or as otherwise described herein can bind to the surface of a hepatocyte or other cell, respectively. Once attached to the cell, the bifunctional molecule to which is bound circulating protein is internalized by the cell through a phagocytosis/endocytosis mechanism whereupon the cell will destroy the protein via a lysosomal degradation or other degradation pathway. The term "immunoglobulin G binding moiety" or "IgGBM" is used to describe a moiety which binds to circulating IgG immunoglobulin, forming a complex with bifunctional molecules according to the present invention to be ultimately destroyed in hepatocytes. In certain instances, in describing the present invention, the terms IgGBM and other cell binding moieties are used synonymously.

CPBM groups, such as IgGBM bind to the respective circulating proteins, thus forming a complex with the bifunctional compounds according to the present invention and the bifunctional compounds complexed with the bound circulating proteins can be bound to cellular receptors on cells which can take up the complexed compounds using phagocytosis/endocytosis mechanisms of the cell and remove the proteins through a degradation process. It is noted that the CPBM which are peptides which bind to IgGBM are covalently linked to other portions of the bifunctional molecules according to the present invention through the terminal amine or carboxylic acid group of the peptide. In preferred embodiments, the carboxylic acid is amidated to form a non-reactive amide group, often with a free amine group (substituted with two H's) or an amine group which alkylated with at least one C_1-C_{10} alkyl group, more often at least one C_1-C_3 alkyl group so that the free amine on the other end of the peptide may be used to covalently link to other portions of the bifunctional molecule. In other embodiments, the amine terminus is rendered non-reactive by end-capping the amine group with a C_2-C_{10} acyl group, preferably a C_2-C_4 acyl group, so that the carboxylic acid group may be reacted, often with an amine to form an amide.

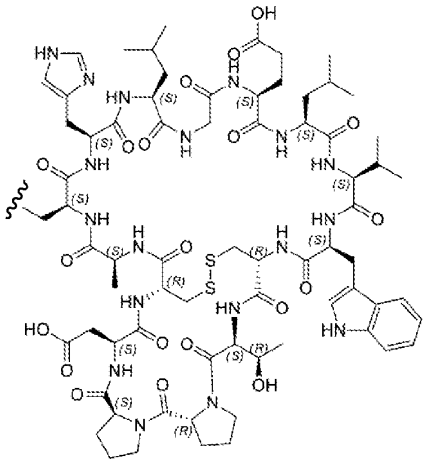
In one embodiment, [CPBM] is or includes the moiety:



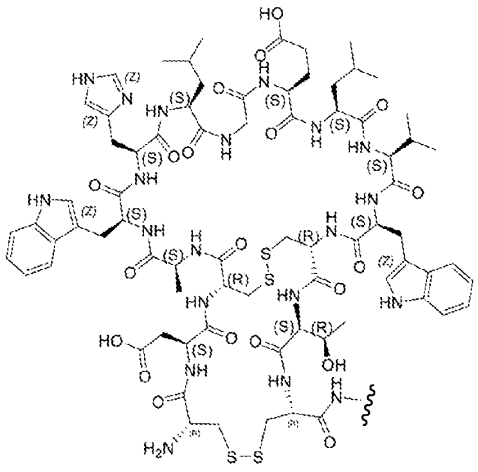
In another embodiment, [CPBM] is or includes the moiety:



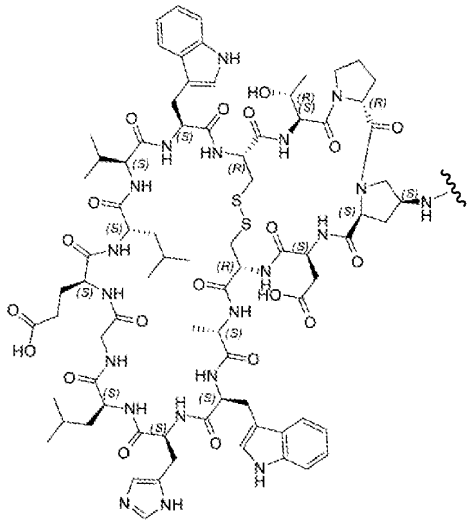
In another embodiment, [CPBM] is or includes the moiety:



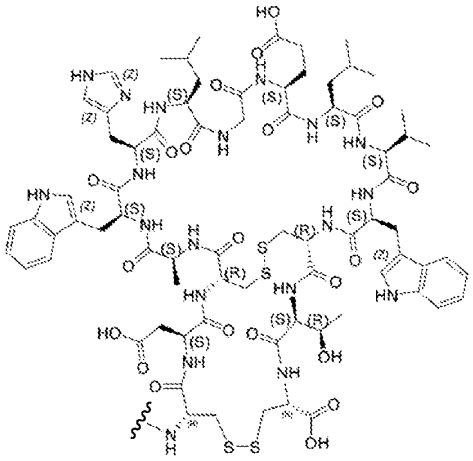
In another embodiment, [CPBM] is or includes the moiety:



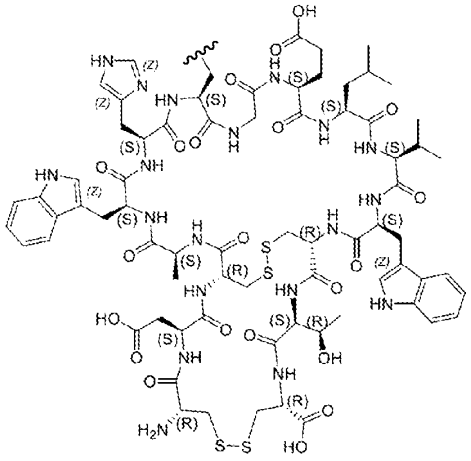
In another embodiment, [CPBM] is or includes the moiety:



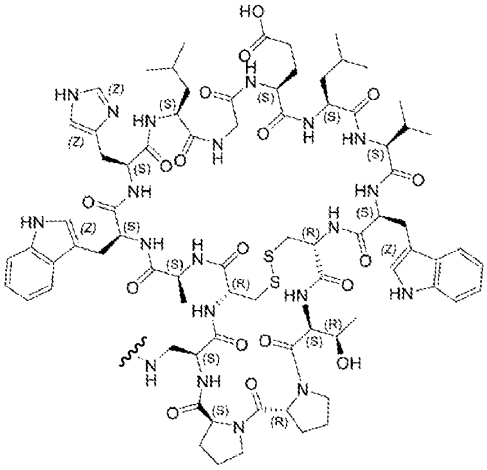
In another embodiment, [CPBM] is or includes the moiety:



In another embodiment, [CPBM] is or includes the moiety:



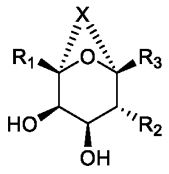
In another embodiment, [CPBM] is or includes the moiety:



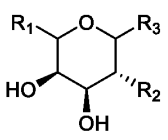
The term "cellular receptor binding moiety" refers to a moiety of the bifunctional compounds according to the present invention which is capable of binding to a receptor on a cell capable of degrading circulating proteins pursuant to the present invention herein. These are moieties which bind to asialoglycoprotein receptor, LRPR, LDLR, RcγRI, FcRN, Transferrin Receptor or Macrophage Scavenger Receptor (e.g., membrane receptors of degradation cells) as otherwise described herein. Many of these binding moieties are peptides which are covalently linked to other portions of the bifunctional compounds according to the present invention through a terminal amine or carboxylic acid group. As for the CPBM group described above, in preferred embodiments, the carboxylic acid is amidated to form a non-reactive amide group, often with a free amine group (substituted with two H's) or an amine group which alkylated with at least one C_1-C_{10} alkyl group, more often at least one C_1-C_3 alkyl group so that the free amine on the other end of the peptide may be used to covalently link to other portions of the bifunctional molecule. In other embodiments, the amine terminus is rendered non-reactive by end-capping the amine group with a C_2-C_{10} acyl group, preferably a C_2-C_4 acyl group, so that the carboxylic acid group may be reacted, often with an amine to form an amide.

The term "asialoglycoprotein receptor binding moiety" ("ASGPRBM") refers to a binding moiety which binds to hepatocyte asialoglycoprotein receptor. This binding moiety is also a component of the presently claimed bifunctional compounds as a CRBM group which is covalently bound to the CPBM group moiety through a CON group, a linker or directly. The ASGPRBM group selectively binds to hepatocyte asialoglycoprotein receptor on the surface of hepatocytes. It is through this moiety that bifunctional compounds complexed with circulating protein bind to hepatocytes. Once bound to the hepatocyte, the circulating protein is taken into the hepatocytes or other cells via a phagocytosis mechanism wherein the circulating protein is degraded through lysosomal degradation.

Exemplary ASGPRBM groups for use in compounds according to the present invention, among others, include moieties according to the chemical structures:



or



where X is 1-4 atoms in length and is at each occurrence independently selected from the group consisting of O, S, $N(R^{N1})$, and $C(R^{N1})(R^{N1})$ such that:

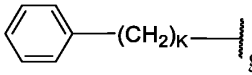
if X is 1 atom in length, X is O, S, $N(R^{N1})$, or $C(R^{N1})(R^{N1})$,

if X is 2 atoms in length, no more than 1 atom of X is O, S, or N(R^{N1}),

if X is 3 or 4 atoms in length, no more than 2 atoms of X are O, S or N(R^{N1});

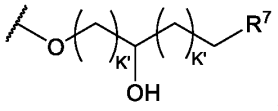
where R^{N1} is H or a C_1-C_3 alkyl group optionally substituted with from 1-3 halogen groups;

R_1 and R_3 are each independently H, -$(CH_2)_K$OH, -$(CH_2)_K$OC_1-C_4 alkyl, -C_1-C_4 alkyl, -$(CH_2)_K$vinyl, -O-$(CH_2)_K$vinyl, -$(CH_2)_K$alkynyl, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl, --O-C(O)-C_1-C_4 alkyl, -C(O)-C_1-C_4 alkyl, in which each alkyl, vinyl, or alkynyl is optionally substituted with from 1-3 halogen groups. In various embodiments, each alkyl, vinyl, or alkynyl in R_1 and R_3 is optionally substituted with from 1-3 fluorines (F). K is independently at each occurrence an integer from 0-4.

In one embodiment, R_1 and R_3 are each independently a 

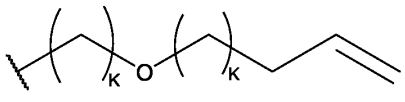
group, which is optionally substituted with 1-3 halogen groups, 1 to 3 C_1-C_4 alkyl groups, or O-C_1-C_4 alkyl groups, in which each of the alkyl groups is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, and K is independently at each occurrence and integer from 0-4; or

R_1 and R_3 are each independently a group according to the chemical structure:



,

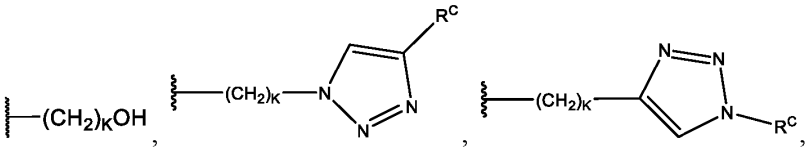
where R^7 is O-C_1-C_4 alkyl, which is optionally substituted with from 1 to 3 halo groups or 1 to 2 hydroxy groups, and K' is independently at each occurrence an integer from 0-4; or

R^7 is a -$NR^{N3}R^{N4}$ group or 

, and K is independently at each occurrence an integer from 0-4; or

R_1 and R_3 are each independently a group according to the structure:

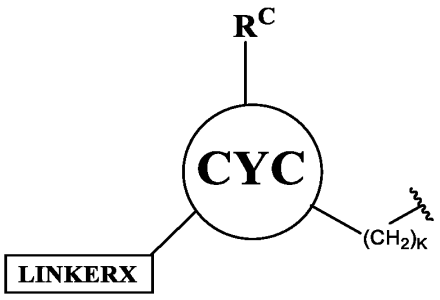
R_1 and R_3 are each independently a group according to the structure:



,

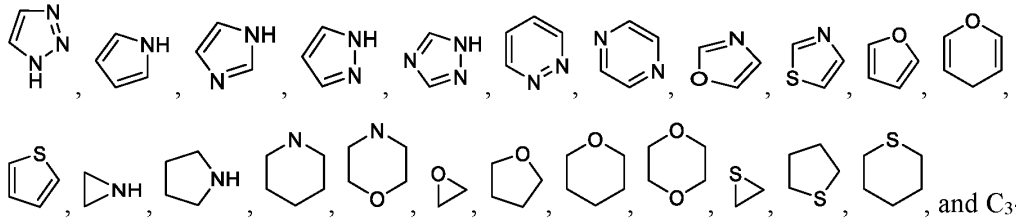
, wherein K is independently at each

occurrence 0-4; or a



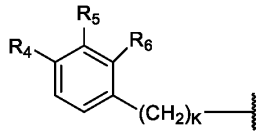
group,

wherein CYC is a ring selected from the group consisting of:



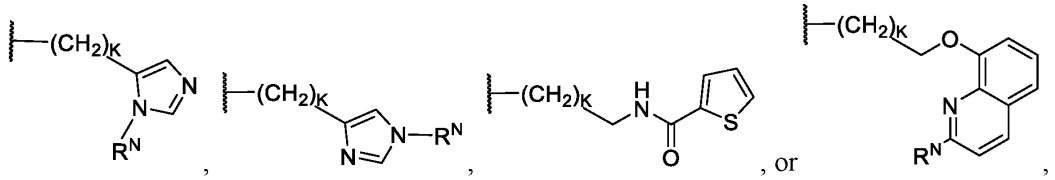
, and C_3-C_8 saturated carbocyclic, wherein each of LINKERX, R^C, and $-(CH_2)_K-$ are attached to an open valence in CYC, including N-H;

R^C is absent, H, C_1-C_4 alkyl optionally substituted with from 1-3 halogen groups or 1-2 hydroxyl groups; or a group according to the structure:



where R_4, R_5 and R_6 are each independently, H, halogen, CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KOC_1$-C_4 alkyl, C_1-C_3 alkyl, -O-C_1-C_3-alkyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O$-C_1-C_4 alkyl, O-C(O)-C_1-C_4 alkyl, -C(O)-C_1-C_4 alkyl, in any of which the alkyl group is optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups; or

R^C is



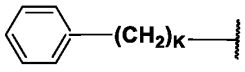
where R^N , R^{N1}, and R^{N2} are each independently H or a C_1-C_3 alkyl group optionally substituted with 1-3 halogen groups, or 1-2 hydroxyl groups;

K is independently at each occurrence an integer from 0-4;

K' is independently at each occurrence an integer from 0-4;

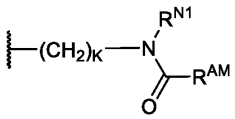
R^{N3} is H or C_1-C_3 alkyl optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups; and

R^{N4} is H or C_1-C_3 alkyl optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, or

R^{N4} is  , where K is 1;

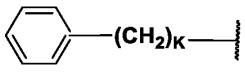
LINKERX is a linker group which includes at least one [CPBM] group and connects the [CPBM] group to the [CRBM] through one or more optional [CON] groups, or

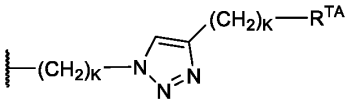
LINKERX is a linker group which includes at least one functional group that covalently bonds the linker group to at least one [CPBM] group or optional [CON] group;

R_2 is  ,where R^{N1} and K are the same as above;

R^{AM} is H, C_1-C_4 alkyl, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl, -O-C(O)-C_1-C_4 alkyl, -C(O)-C_1-C_4 alkyl, -$(CH_2)_K$-$NR^{N3}R^{N4}$ where R^{N3} is H or C_1-C_3 alkyl, in which any of the alkyl groups are optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups; and

R^{N4} is H, C_1-C_3 alkyl optionally substituted with 1-3 halo groups or 1 or 2 hydroxy groups, or

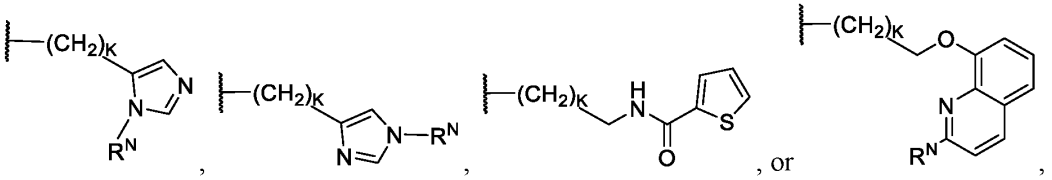
R^{N4} is  and K is 1; or

R_2 is a  ,

where R^{TA} is H, CN, $NR^{N1}R^{N2}$, -$(CH_2)_K$OH, -$(CH_2)_K$OC_1-C_4 alkyl, C_1-C_4 alkyl, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl, O-C(O)-C_1-C_4 alkyl, -C(O)-C_1-C_4 alkyl, in which each alkyl is optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups, or

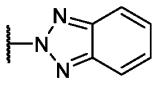
R^{TA} is a C_3-C_{10} aryl or a 3- to 10-membered heteroaryl group containing up to 5 hetero atoms, each of said aryl or heteroaryl groups being optionally substituted with 1-3 substituents selected from the group consisting of CN, $NR^{N1}R^{N2}$, -$(CH_2)_K$OH, -$(CH_2)_K$OC_1-C_4 alkyl, C_1-C_3 alkyl, -O-C_1-C_3-alkyl, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl, O-C(O)-C_1-C_4 alkyl, and -$(CH_2)_K$C(O)-C_1-C_4 alkyl, in which each alkyl is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, or

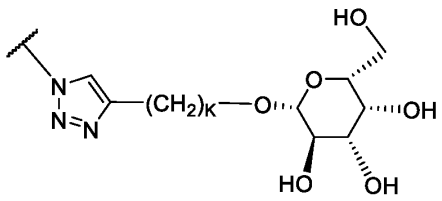
R^{TA} is



, , , or ,

or;

R^{TA} is  group which is optionally substituted with 1-3 C_1-C_3 alkyl groups each of which are optionally substituted with 1-3 halogen groups, or



R^{TA} is ,

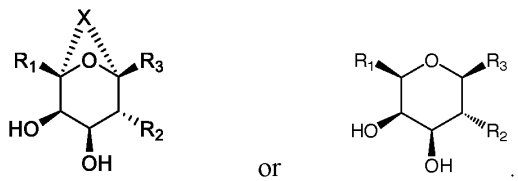
wherein R^N, R^{N1}, and R^{N2} are each independently H or a C_1-C_3 alkyl group which is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups and

wherein each $-(CH_2)_K$ group is optionally substituted with 1-4 C_1-C_3 alkyl groups which are each optionally substituted with from 1-3 fluorines or 1-2 hydroxyl groups;

and K is independently at each occurrence 0-4. In various embodiments, K is 0. In various embodiments, K is 1. In various embodiments, K is 2. In various embodiments, K is 3. In various embodiments, K is 4.

In some embodiment, the carbohydrate moiety of the [ASGPRBM] group has α-configuration at the anomeric center. In some embodiments, the carbohydrate moiety of the [ASGPRBM] group has β-configuration at the anomeric center.

In some embodiments, [CRBM] is or includes an [ASGPRBM] group according to the chemical structure:



or .

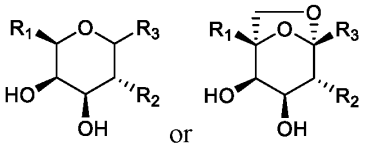
[CON] is a connector moiety (including a [MULTICON]) as otherwise described herein; and [LINKER] is a linking moiety as otherwise described herein which links [CPBM] to the [CRBM] group and optionally contains one or more connector moieties (which optionally connect(s) more than one chemical moiety to provide said linking moiety or which

connects said linking moiety to said [CPBM] group or said [CRBM] group, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

In various embodiments, X is -O-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-O-, -S-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-S-, N(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-N(R^{N1}) or C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}) when X is 2 atoms in length, X is -O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-, -O-C(R^{N1})(R^{N1})-O-, -O-C(R^{N1})(R^{N1})-S-, -O-C(R^{N1})(R^{N1})-N(R^{N1})-, -S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-S, -S-C(R^{N1})(R^{N1})-S-, -S-C(R^{N1})(R^{N1})-O-, -S-C(R^{N1})(R^{N1})-N(R^{N1})-, N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-N(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})- N(R^{N1}), N(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1}) or C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})- C(R^{N1})(R^{N1}) when X is 3 atoms in length, and X is -O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-(R^{N1})(R^{N1})-, -O-C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-, -S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, C(R^{N1})(R^{N1})-(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, -S-C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})- C(R^{N1})(R^{N1})-, C(R^{N1})(R^{N1})-N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})- N(R^{N1}), N(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1}) or C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})- C(R^{N1})(R^{N1}) when X is 4 atoms in length where R^{N1} is the same as above. Most often, R^{N1} is H.

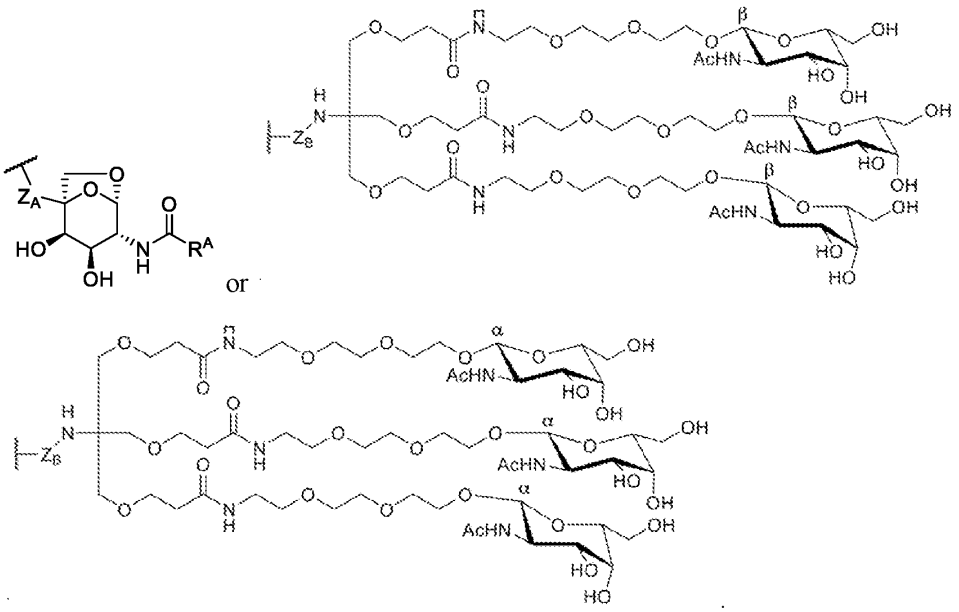
In various embodiments, X is OCH_2 or CH_2O and R^{N1} is H.

In various embodiments, the [CRBM]/[ASGPRBM] group is a group according to the chemical structure:



where R_1, R_2 and R_3 are as defined herein, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

In various embodiments, the [CRBM]/[ASGPRBM] group is a group according to the chemical structure:



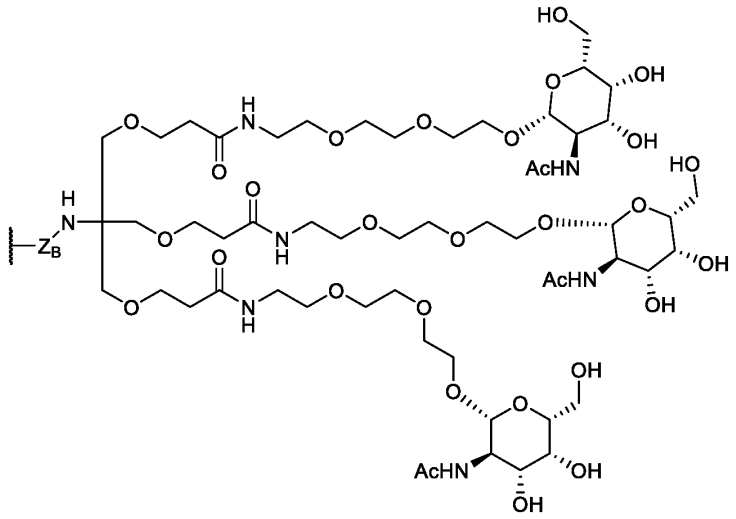
where R^A is -C_1-C_3 alkyl optionally substituted with 1-5 halogen groups;

Z_A is -$(CH_2)_{IM}$, -O-$(CH_2)_{IM}$, S-$(CH_2)_{IM}$, NR_M-$(CH_2)_{IM}$, C(O)-$(CH_2)_{IM}$-, a PEG group containing 1 to 8 ethylene glycol (CH_2CH_2O or OCH_2CH_2) units, or -C(O)$(CH_2)_{IM}NR_M$, where IM and R_M are the same as above; and

Z_B is absent, $(CH_2)_{IM}$, C(O)-$(CH_2)_{IM}$-, or C(O)-$(CH_2)_{IM}$-NR_M, where IM and R_M are the same as above.

In various embodiments, Z_A is a PEG group containing 1-4 ethylene glycol units. In various embodiments, Z_A is a PEG group containing 2-4 ethylene glycol units. In various embodiments, R^A is C_1-C_3 alkyl optionally substituted with 1-5 fluorine atoms. In various embodiments, R^A is -CH_3 optionally substituted with 1-3 fluorine atoms. In various embodiments, R^A is -CH_2CH_3 optionally substituted with 1-3 fluorine atoms;

Note that the [CRBM][ASGPRBM] group set forth above may also be represented as follows:



In the above structure, the anomeric center of the carbohydrate moieties has β-configuration. In some embodiments, the anomeric center of the carbohydrate moieties may have α-configuration.

The term "neoplasia" or "cancer" is used throughout the specification to refer to the pathological process that results in the formation and growth of a cancerous or malignant neoplasm, i.e., abnormal tissue that grows by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue and most invade surrounding tissues, metastasize to several sites, and are likely to recur after attempted removal and to cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant hematogenous, ascitic and solid tumors. Neoplasms include, without limitation, morphological irregularities in cells in tissue of a subject or host, as well as pathologic proliferation of cells in tissue of a subject, as compared with normal proliferation in the same type of tissue. Additionally, neoplasms include benign tumors and malignant tumors (e.g., colon tumors) that are either invasive or noninvasive. Malignant neoplasms (cancer) are distinguished from benign neoplasms in that the former show a greater degree of anaplasia, or loss of differentiation and orientation of cells, and have the properties of invasion and metastasis. Examples of neoplasms or neoplasias from which the target cell of the present invention may be derived include, without limitation, carcinomas (e.g., squamous-cell carcinomas, adenocarcinomas, hepatocellular carcinomas, and renal cell carcinomas),

particularly those of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, particularly Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, and synovial sarcoma; tumors of the central nervous system (e.g., gliomas, astrocytomas, oligodendrogliomas, ependymomas, glioblastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas); germ-line tumors (e.g., bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, and melanoma); mixed types of neoplasias, particularly carcinosarcoma and Hodgkin's disease; and tumors of mixed origin, such as Wilms' tumor and teratocarcinomas (Beers and Berkow (eds.), The Merck Manual of Diagnosis and Therapy, 17.sup.th ed. (Whitehouse Station, N.J.: Merck Research Laboratories, 1999) 973-74, 976, 986, 988, 991). All of these neoplasms may be treated using compounds according to the present invention.

Representative common cancers to be treated with compounds according to the present invention include, for example, prostate cancer, metastatic prostate cancer, stomach, colon, rectal, liver, pancreatic, lung, breast, cervix uteri, corpus uteri, ovary, testis, bladder, renal, brain/CNS, head and neck, throat, Hodgkin’s disease, non-Hodgkin’s lymphoma, multiple myeloma, leukemia, melanoma, non-melanoma skin cancer, acute lymphocytic leukemia, acute myelogenous leukemia, Ewing’s sarcoma, small cell lung cancer, choriocarcinoma, rhabdomyosarcoma, Wilms’ tumor, neuroblastoma, hairy cell leukemia, mouth/pharynx, oesophagus, larynx, kidney cancer and lymphoma, among others, which may be treated by one or more compounds according to the present invention. Because of the activity of the present compounds, the present invention has general applicability treating virtually any cancer in any tissue, thus the compounds, compositions and methods of the present invention are generally applicable to the treatment of cancer and in reducing the likelihood of development of cancer and/or the metastasis of an existing cancer.

In certain particular aspects of the present invention, the cancer which is treated is metastatic cancer, a recurrent cancer or a drug resistant cancer, especially including a multiple drug resistant cancer. Separately, metastatic cancer may be found in virtually all

tissues of a cancer patient in late stages of the disease, typically metastatic cancer is found in lymph system/nodes (lymphoma), in bones, in lungs, in bladder tissue, in kidney tissue, liver tissue and in virtually any tissue, including brain (brain cancer/tumor). Thus, the present invention is generally applicable and may be used to treat any cancer in any tissue, regardless of etiology.

The term “tumor” is used to describe a malignant or benign growth or tumefacent.

The term “autoimmune disease” refers to a disease or illness that occurs when the body tissues are attacked by its own immune system. The immune system is a complex organization within the body that is designed normally to "seek and destroy" invaders of the body, including infectious agents. In diseases which are described as autoimmune diseases, MIF levels are often elevated. The present invention seeks to inhibit or lower elevated MIF levels in patients with autoimmune disease (as well as inflammatory diseases and conditions and cancer) and by decreasing MIF levels, ameliorate many of the symptoms and secondary effects of these disease states and conditions. Examples of autoimmune diseases which often exhibit high expressed levels of MIF including, for example, systemic lupus erythematosus, Sjogren syndrome, Hashimoto thyroiditis, rheumatoid arthritis, juvenile (type 1) diabetes, polymyositis, scleroderma, Addison's disease, vtiligo, pernicious anemia, glomerulonephritis, and pulmonary fibrosis, among numerous others.

A more complete list of autoimmune diseases which may be treated by compounds and pharmaceutical compositions according to the present invention includes Addison's Disease, Autoimmune polyendodrine syndrome (APS) types 1, 2 and 3, autoimmune pancreatitis (AIP), diabetes mellitus type 1, autoimmune thyroiditis, Ord's thyroiditis, Grave's disease, autoimmune oophoritis, endometriosis, autoimmune orchitis, Sjogren's syndrome, autoimmune enteropathy, coeliac disease, Crohns' disease, microscopic colitis, ulcerative colitis, autophospholipid syndrome (APlS), aplastic anemia, autoimmune hemolytica anemia, autoimmune lymphoproliferative syndrome, autoimmune neutropenia, autoimmune thrombocytopenic purpura, cold agglutinin disease, essential mixed cryoglulinemia, Evans sndrome, pernicious anemia, pure red cell aplasia, thrombocytopenia, adiposis dolorosa, adult-onset Still's disease, ankylosing spondylitis, CREST syndrome, drug-induced lupus, enthesitis-related arthritis, eosinophilic fasciitis, Felty syndrome, AgG4-related disease, juvenile arthritis, Lyme disease (chronic), mixed connective tissue disease (MCTD), palindromic rheumatism, Parry Romberg syndrome, Parsonage-Turner syndrome, psoriatic arthritis, reactive arthritis, relapsing polychondritis, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schnitzler syndrome, systemic lupus erythematosus,

undifferentiated connective tissue disease (UCTD), dermatomyositis, fibromyalgia, myositis, inclusion body myositis, myasthenia gravis, neuromyotonia, paraneoplastic cerebellar degeneration, polymyositis, acute disseminated encephalomyelitis (ADEM), acute motor axonic neuropathy, anti-NMDA receptor encephalitis, Balo concentric sclerosis, Bickerstaff's encephalitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, Hashimoto's encephalopathy, idiopathic inflammatory demyelinating diseases, Lambert-Eaton myasthenic syndrome, multiple sclerosis, pattern II, Oshtoran Syndrome, Pendiatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS), progressive inflammatory neuropathy, restless leg syndrome, stiff person syndrome, Syndenham chorea, transverse myelitis, autoimmune retinopathy, autoimmune uveitis, Cogan syndrome, Graves ophthalmopathy, intermediate uveitis, ligneous conjunctivitis, Mooren's ulcer, neuromyelitis optica, opsoclonus myoclonus syndrome, optic neuritis, scleritis, Susac's syndrome, sympathetic ophthalmia, Tolosa-Hunt syndrome, autoimmune inner ear disease (AIED), Méniére's disease, Behçet's disease, Eosiniphilic granulomatosis with polyangiitis (EGPA), giant cell arteritis, granulomatosis with polyangiitis (GPA), IgA vasculitis (IgAV), Kawasaki's disease, leukocytoclastic vasculitis, lupus vasculitis, rheumatoid vasculitis, microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), polymyalgia rheumatica, urticarial vasculitis, vasculitis, primary immune deficiency, chronic fatigue syndrome, complex regional pain syndrome, eosinophilic esophagitis, gastritis, interstitial lung disease, POEMS syndrome, Raynaud's syndrome, primary immunodeficiency and pyoderma gangrenosum, among others.

The term “inflammatory disease” is used to describe a disease or illness with acute, but more often chronic inflammation as a principal manifestation of the disease or illness. Inflammatory diseases include diseases of neurodegeneration (including, for example, Alzheimer’s disease, Parkinson’s disease, Huntington’s disease; other ataxias), diseases of compromised immune response causing inflammation (e.g., dysregulation of T cell maturation, B cell and T cell homeostasis, counters damaging inflammation), chronic inflammatory diseases including, for example, inflammatory bowel disease, including Crohn’s disease, rheumatoid arthritis, lupus, multiple sclerosis, chronic obstructive pulmonary disease/COPD, pulmonary fibrosis, cystic fibrosis, Sjogren’s disease; hyperglycemic disorders, diabetes (I and II), affecting lipid metabolism islet function and/or structure, pancreatic β-cell death and related hyperglycemic disorders, including severe insulin resistance, hyperinsulinemia, insulin-resistant diabetes (e.g. Mendenhall's Syndrome, Werner Syndrome, leprechaunism, and lipoatrophic diabetes) and *dyslipidemia* (e.g.

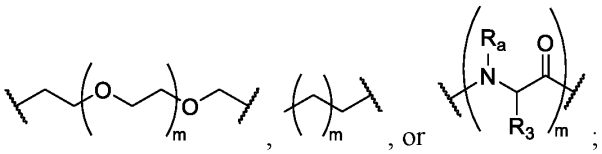
hyperlipidemia as expressed by obese subjects, elevated low-density lipoprotein (LDL), depressed high-density lipoprotein (HDL), elevated triglycerides and metabolic syndrome, liver disease, renal disease (apoptosis in plaques, glomerular disease), cardiovascular disease (especially including infarction, ischemia, stroke, pressure overload and complications during reperfusion), muscle degeneration and atrophy, low grade inflammation, gout, silicosis, atherosclerosis and associated conditions such as cardiac and neurological (both central and peripheral) manifestations including stroke, age-associated dementia and sporadic form of Alzheimer's disease, and psychiatric conditions including depression), stroke and spinal cord injury, arteriosclerosis, among others. In these diseases, elevated MIF is very often observed, making these disease states and/or conditions response to therapy using compounds and/or pharmaceutical compositions according to the present invention. It is noted that there is some overlap between certain autoimmune diseases and inflammatory diseases as described herein.

The term “linker”, refers to a chemical entity including a complex linker connecting a circulating protein binding moiety (CPBM) to the cellular receptor binding moiety (CRBM) including an asialoglycoprotein receptor binding moiety (ASGPRBM), optionally through at least one (preferably one or two) connector moiety [CON] through covalent bonds in compounds according to the present invention. The linker between the two active portions of the molecule, that is the CPBM group and the CRBM/ASGPRBM group ranges from about 5Å to about 50Å or more in length, about 6Å to about 45Å in length, about 7Å to about 40Å in length, about 8Å to about 35Å in length, about 9Å to about 30Å in length, about 10Å to about 25Å in length, about 7Å to about 20 Å in length, about 5Å to about 16Å in length, about 5Å to about 15Å in length, about 6Å to about 14Å in length, about 10Å to about 20Å in length, about 11Å to about 25Å in length, etc. Linkers which are based upon ethylene glycol units and are between 2 and 15 glycol units, 1 and 8 glycol units, 1, 2, 3, 4, 5, and 6 glycol units in length may be preferred, although the length of certain linkers may be far greater. By having a linker with a length as otherwise disclosed herein, the CPBM group and the CRBM/ASGPRBM group may be situated to advantageously take advantage of the biological activity of compounds according to the present invention which bind to receptors, including asialoglycoprotein receptors on hepatocytes and other cells resulting in the selective and targeted degradation of circulating proteins within the lysosomal degradation mechanism or other degradation mechanism of the hepatocytes. The selection of a linker component is based on its documented properties of biocompatibility, solubility in aqueous and organic media, and low immunogenicity/antigenicity. Although numerous linkers may be used as

otherwise described herein, a linker based upon polyethyleneglycol (PEG) linkages, polypropylene glycol linkages, or polyethyleneglycol-co-polypropylene oligomers (up to about 100 units, about 1 to 100, about 1 to 75, about 1 to 60, about 1 to 50, about 1 to 35, about 1 to 25, about 1 to 20, about 1 to 15, 2 to 10, about 4 to 12, about 1 to 8, 1 to 3, 1 to 4, 2 to 6, 1 to 5, etc.) may be favored as a linker because of the chemical and biological characteristics of these molecules. The use of polyethylene (PEG) linkages of between 2 and 15 ethylene glycol units is preferred. When describing linkers according to the present invention, including polyethylene glycol linkers or other linkers, one or more additional groups (e.g., methylene groups, amide groups, keto groups, amine groups, etc., with methylene groups or amide groups being preferred) may be covalently attached at either end of the linker group to attach to a CRBM/ASGPRBM group, a [CON] group, another linker group or a CPBM group.

Alternative linkers may include, for example, polyamino acid linkers of up to 100 amino acids (of any type, preferably D- or L- amino acids, preferably naturally occurring L-amino acids) in length (about 1 to 75, about 1 to 60, about 1 to 50, about 1 to 45, about 1 to 35, about 1 to 25, about 1 to 20, about 1 to 15, 2 to 10, about 4 to 12, about 5 to 10, about 4 to 6, about 1 to 8, about 1 to 6 , about 1 to 5, about 1 to 4, about 1 to 3, etc. in length), optionally including one or more connecting groups (preferably 1 or 2 connecting groups at one or both ends of the polyamino acid linker).

Preferred linkers include those according to the chemical structures:



, , or ;

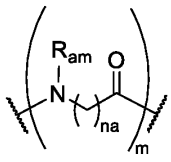
or a polypropylene glycol or polypropylene-co-polyethylene glycol linker having between 1 and 100 alkylene glycol units, preferably about 1 to 75, about 1 to 60, about 1 to 50, about 1 to 45, about 1 to 35, about 1 to 25, about 1 to 20, about 1 to 15, 2 to 10, about 4 to 12, about 5 to 10, about 4 to 6, about 1 to 8, about 1 to 6 , about 1 to 5, about 1 to 4, about 1 to 3 ;

where R_a is H, C_1-C_3 alkyl or alkanol or forms a cyclic ring with R^3 (proline) and R^3 is a side chain derived from a D- or L amino acid (preferably a naturally occurring L-amino acid) preferably selected from the group consisting of alanine (methyl), arginine (propyleneguanidine), asparagine (methylenecarboxyamide), aspartic acid (ethanoic acid), cysteine (thiol, reduced or oxidized di-thiol), glutamine (ethylcarboxyamide), glutamic acid (propanoic acid), glycine (H), histidine (methyleneimidazole), isoleucine (1-methylpropane),

leucine (2-methylpropane), lysine (butyleneamine), methionine (ethylmethylthioether), phenylalanine (benzyl), proline hydroxyproline (R^3 forms a cyclic ring with R_a and the adjacent nitrogen group to form a pyrrolidine or hydroxypyrrolidine group), serine (methanol), threonine (ethanol, 1-hydroxyethane), tryptophan (methyleneindole), tyrosine (methylene phenol) or valine (isopropyl), where the R^3 group is indicated in parentheses;

m (within the context of this use) is an integer from 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 12, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5.

In another embodiment, a linker according to the present invention comprises a polyethylene glycol linker containing from 1 to 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5 ethylene glycol units, to which is bonded a lysine group or other amino acid moiety at one or both ends of the linker (which can consist of between 1 and 10 amino acids which can bind the CPBM and/or the CRBM/ASGPRBM group. Still other linkers comprise amino acid residues (D or L) which are bonded to CPBM and/or CRBM/ASGPRBM moieties as otherwise described herein. In another embodiment, as otherwise described herein, the amino acid has anywhere from 1-15 methylene groups separating the amino group from the acid (acyl) group in providing a linker to the MIFBM and/or the ASGPRBM group, wherein the linker contains from 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5 amino acid groups linked together through peptide linkages to form the linker. This linker is represented by the chemical structure:



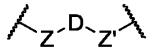
,

where R_{am} is H or a C_1-C_3 alkyl optionally substituted with one or two hydroxyl groups;

na is 1-15, 1-12, 1-10, 1-8, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11;

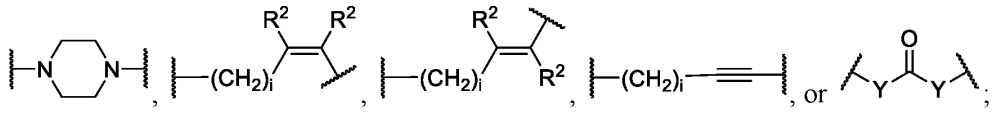
m is an integer from 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 12, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 51 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5.

In various embodiments, the linker is according to the chemical formula:



,

where Z and Z' are each independently a bond, -$(CH_2)_i$-O, -$(CH_2)_i$-S, -$(CH_2)_i$-N-R,



wherein said -$(CH_2)_i$ group, if present in Z or Z', is bonded to a connector (CON), CPBM or CRBM/ASGPRBM;

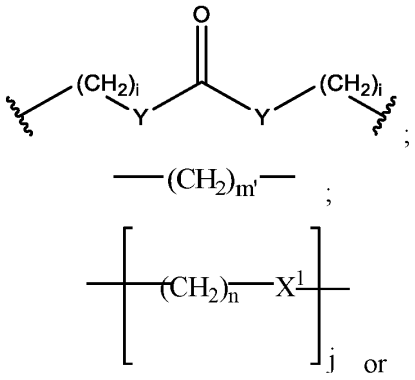
each R is H, or a C_1-C_3 alkyl or alkanol group;

each R^2 is independently H or a C_1-C_3 alkyl group;

each Y is independently a bond, O, S or N-R;

each i is independently 0 to 100, 0 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 0, 1, 2, 3, 4 or 5;

D is



a bond, with the proviso that Z, Z' and D are not each simultaneously bonds;

j is 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;

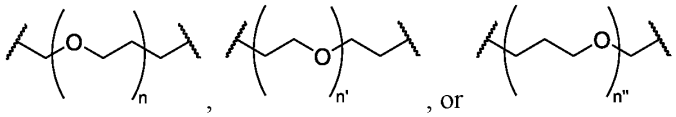
m' is 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;

n is 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5 (n is preferably 2);

X^1 is O, S or N-R; and

R is H, or a C_1-C_3 alkyl or alkanol group, or a pharmaceutical salt thereof.

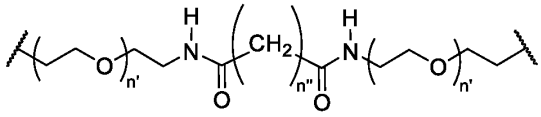
In one embodiment, other linkers which are included herein include linkers according to the chemical structure:



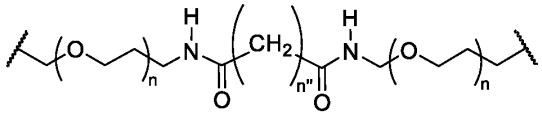
where each n and n' is independently 1 to 25, 1 to 15, 1 to 12, 2 to 11, 2 to 10, 2 to 8, 2 to 6, 2 to 5, 2 to 4 and 2 to 3 or 1, 2, 3, 4, 5, 6, 7, or 8; and

each n" is independently 0 to 8, often 1 to 7, or 1, 2, 3, 4, 5 or 6 (preferably 2, 3, 4 or 5).

Linkers also can comprise two or more linker segments (based upon the linkers described above) which are attached directly to each other or through [CON] groups forming a complex linker. Certain linkers which include a [CON] group connecting a first and second (PEG) linker group include the following structures:



or



;

where each n and n' is independently 1 to 25, 1 to 15, 1 to 12, 2 to 11, 2 to 10, 2 to 8, 2 to 6, 2 to 5, 2 to 4 and 2 to 3 or 1, 2, 3, 4, 5, 6, 7, or 8; and

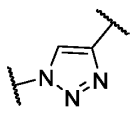
each n" is independently 0 to 8, often 1 to 7, or 1, 2, 3, 4, 5 or 6 (preferably 3).

Each of these linkers can also contain alkylene groups containing from 1 to 4 methylene groups at the distal ends of each linker group in order to facilitate connection of the linker group.

Other linkers which include a connector group [CON] include groups which are represented by the chemical formula:

PEG-[CON]-PEG,

wherein each PEG linker is independently a polyethylene glycol group containing from 1-12 ethylene glycol units and [CON] is a connector group as otherwise set forth herein. In various embodiments, [CON] is:



.

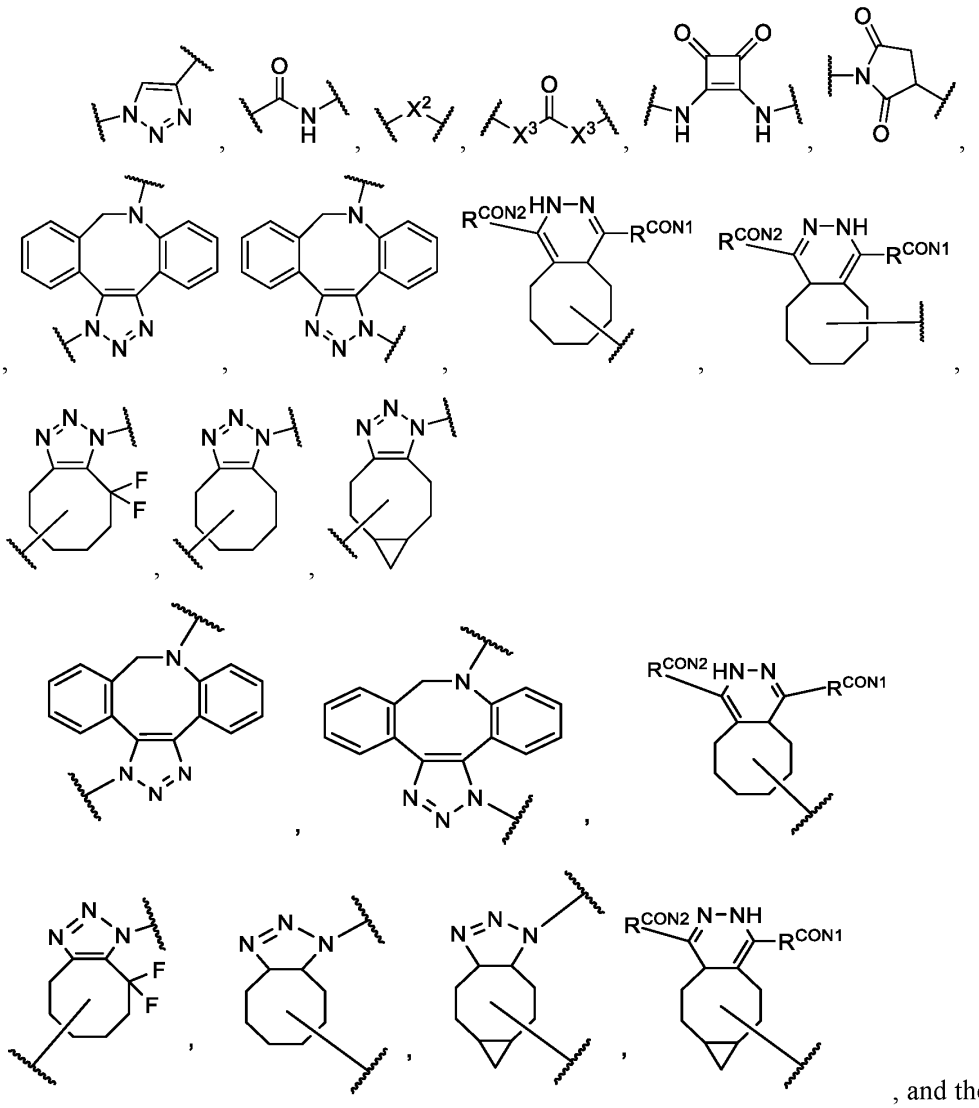
The term "connector", symbolized in the generic formulas by "CON" or [CON], is

used to describe a chemical moiety which is optionally included in bifunctional compounds according to the present invention which forms from the reaction product of an activated linker with a CPBM moiety (which also is preferably activated for covalently bonding the linker with the moiety) or a CRBM/ASGPRBM group with an activated linker. The connector group is often the resulting moiety which forms from the facile condensation of two or more separate chemical fragments which contain reactive groups which can provide connector groups as otherwise described to produce bifunctional or multifunctional compounds according to the present invention. It is noted that a connector may be distinguishable from a linker in that the connector is the result of a specific chemistry which is used to provide bifunctional compounds according to the present invention wherein the reaction product of these groups results in an identifiable connector group or part of a connector group which is distinguishable from the linker group, although in certain instances, the connector group is incorporated into and integral with the linker group as otherwise described herein.

It is noted also that a connector group may be linked to a number of linkers to provide multifunctionality (i.e., more than one CPBM moiety and/or more than one CRBM/ASGPRBM moiety) within the same molecule. It is noted that there may be some overlap between the description of the connector group and the linker group such that the connector group is actually incorporated or forms part of the linker, especially with respect to more common connector groups such as amide groups, oxygen (ether), sulfur (thioether) or amine linkages, urea or carbonate –OC(O)O- groups or as otherwise described herein. It is further noted that a connector (or linker) may be connected to CPBM, CRBM/ASGPRBM or a linker at positions which are represented as being linked to another group using the symbol:

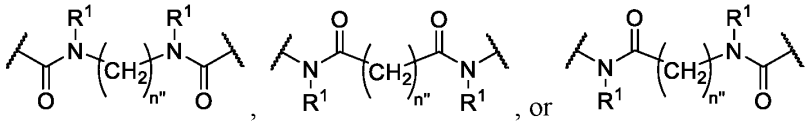
Where two or more such groups (symbols) are present in a linker or connector, any of an CRBM/ASGPRBM, a linker or a CPBM group may be bonded to such a group. Where that symbol is not used, the linker may be at one or more positions of a moiety where an open valence is present.

In various embodiments, suitable [CON] connector groups which are used in the present invention include the following chemical groups:



, and the like;

where R^{CON1} and R^{CON2} are each independently H, methyl or a bond (for attachment to another moiety); or a diamide group according to the structure:



where X^2 is CH_2, O, S, NR^4, C(O), S(O), $S(O)_2$, -$S(O)_2O$, -$OS(O)_2$, or $OS(O)_2O$;

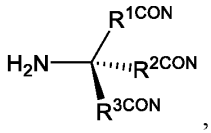
X^3 is O, S, NR^4;

R^4 is H, a C_1-C_3 alkyl or alkanol group, or a -C(O)(C_1-C_3) group;

R^1 is H or a C_1-C_3 alkyl group (preferably H); and

n" is independently 0 to 8, often 1 to 7, or 1, 2, 3, 4, 5 or 6 (preferably 3);

or the connector group [CON] is a group according to the chemical structure:



where R^{1CON}, R^{2CON}, and R^{3CON} are each independently H, $-(CH_2)_{MC1}$, $-(CH_2)_{MC1a}C(O)_{XA}(NR^4)_{XA}-(CH_2)_{MC1a}$, $-(CH_2)_{MC1a}(NR^4)_{XA}C(O)_{XA}-(CH_2)_{MC1a}$, or $-(CH_2)_{MC1a}O-(CH_2)_{MC1}-C(O)NR^4-$, with the proviso that R^{1CON}, R^{2CON}, and R^{3CON} are not simultaneously H;

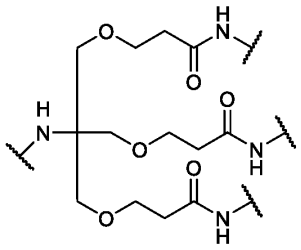
each MC1 is independently an integer from 1-4;

each MC1a is independently an integer from 0-4; and

R^4 is H, a C_1-C_3 alkyl or alkanol group, or a $-C(O)(C_1$-$C_3)$ group.

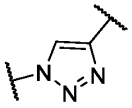
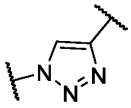
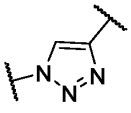
In various embodiments, MC1 is 1 or 2. In various embodiments, MC1a is 0, 1, or 2.

The triazole group, indicated above, may be a preferred connector group. An additional preferred connector group is:



which is linked to at least one CPBM and/or at least one CRBM/ASPRGBM (preferably 3 CRBM/ASPRGBM moieties). This connector group may be used to form GN_3 as otherwise described herein.

It is noted that each connector may be extended with one or more methylene groups to facilitate connection to a linker group, another CON group, a CPBM group or a CRBM/ASGPRBM group. It is noted that in certain instances, within context the diamide group may also function independently as a linker group.

In some embodiments, at least one of [CON] and [LINKER] is or includes  . In some embodiments, at least one of [CON] includes  . In some embodiments, [LINKER] is or includes  .

Additional Galactose- and Talose-based ASGPR Binding Moieties

In one embodiment, the present invention is directed to compounds which are useful for removing circulating proteins which are associated with a disease state or condition in a patient or subject according to the general chemical structure of Formula II:

Formula II

The term "Extracellular Protein Targeting Ligand" as used herein is interchangeably used with the term CPBM (cellular protein binding moiety). The term "ASGPR Ligand" as used herein is interchangeably used with an asialoglycoprotein receptor (ASGPR) binding moiety as defined herein.

In the compound of Formula II, each [CON] is an optional connector chemical moiety which, when present, connects directly to [CPBM] or to [CRBM] or connects the [LINKER-2] to [CPBM] or to [CRBM].

In the compound of Formula II:

[LINKER-2] is a chemical moiety having a valency from 1 to 15 which covalently attaches to one or more [CRBM] and/or [CPBM] group, optionally through a [CON], including a [MULTICON] group, wherein said [LINKER-2] optionally itself contains one or more [CON] or [MULTICON] group(s);

k' is an integer from 1 to 15;

j' is an integer from 1 to 15;

h and h' are each independently an integer from 0 to 15;

i_L is an integer from 0 to 15;

with the proviso that at least one of h, h' and i_L is at least 1, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

A [MULTICON] group can connect one or more of a [CRBM] or [CPBM] to one or more of a [LINKER-2]. In various embodiments, [LINKER-2] has a valency of 1 to 10. In various embodiments, [LINKER-2] has a valency of 1 to 5. In various embodiments, [LINKER-2] has a valency of 1, 2 or 3. In various embodiments, in the compound of Formula II, the [LINKER-2] includes one or more of $Linker^A$, $Linker^B$, $Linker^C$, $Linker^D$, and/or combinations thereof as defined herein.

In the compound of Formula II, xx is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25.

In the compound of Formula II, yy is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25.

In the compound of Formula II, zz is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25.

In the compound of Formula II, X^1 is 1 to 5 contiguous atoms independently selected from O, S, $N(R^b)$, and $C(R^4)(R^4)$, wherein if X^1 is 1 atom then X^1 is O, S, $N(R^6)$, or $C(R^4)(R^4)$, if X^1 is 2 atoms then no more than 1 atom of X^1 is O, S, or $N(R^6)$, if X^1 is 3, 4, or 5 atoms then no more than 2 atoms of X^1 are O, S, or $N(R^6)$;

R^3 at each occurrence is independently selected from hydrogen, alkyl, heteroalkyl, haloalkyl (including $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CH_2CH_2F$, and $-CF_2CF_3$), arylalkyl, heteroarylalkyl, alkenyl, alkynyl, and, heteroaryl, heterocycle, $-OR^8$, and $-NR^8R^9$;

R^4 is independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, $-OR^6$, $-NR^6R^7$,

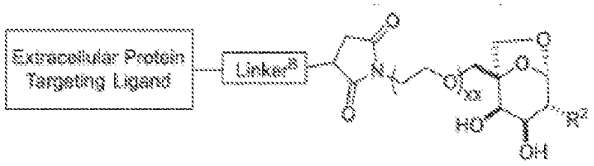
R^6 and R^7 are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroaryl alkyl, alkenyl, alkynyl, and, haloalkyl, heteroaryl, heterocycle, -alkyl-OR^8, -alkyl-NR^8R^9, $C(O)R^3$, $S(O)R^3$, $C(S)R^3$, and $S(O)_2R^3$;

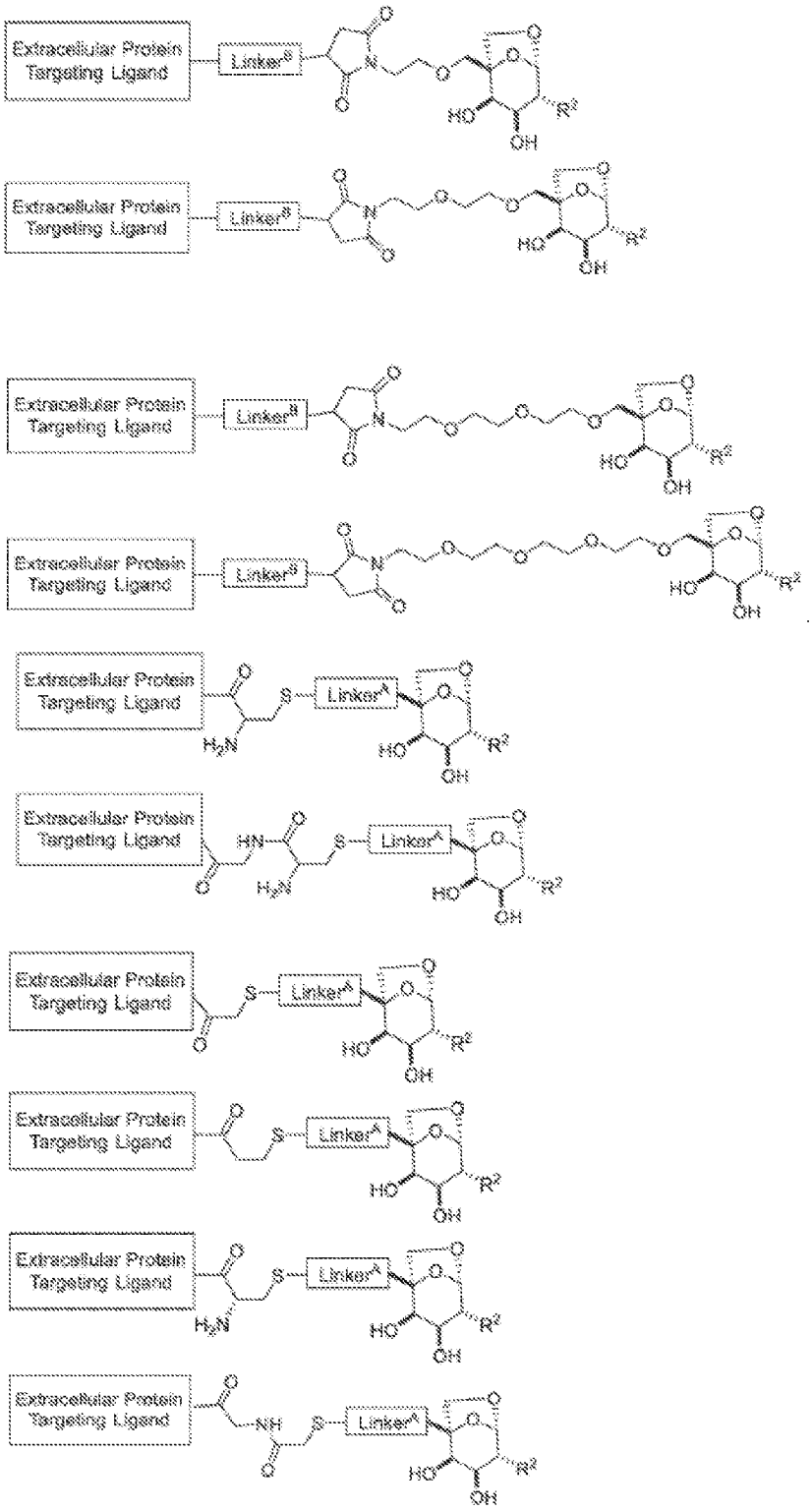
R^8 and R^9 are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle.

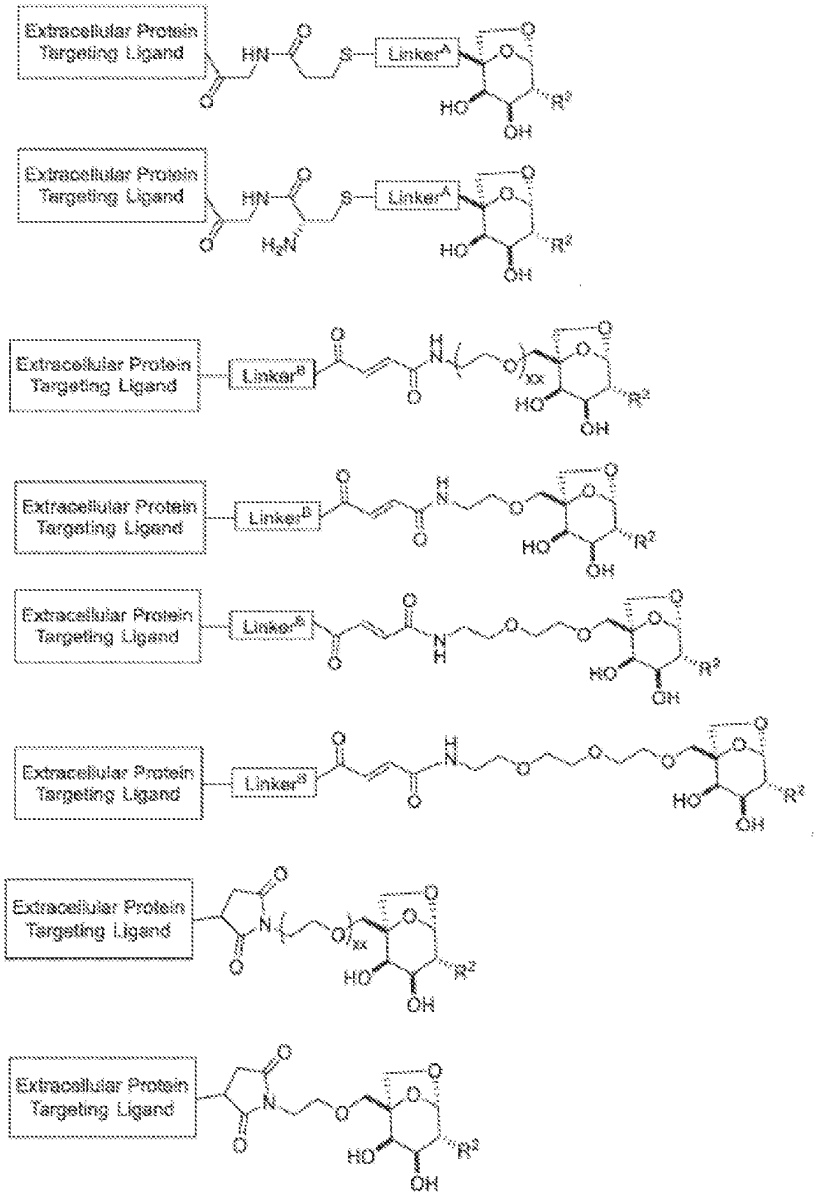
In chemical structures, throughout this application, "Extracellular Protein Targeting Ligand" corresponds to [CPBM] as described above.

A. Galactose-Based ASGPR-Binding Cellular Receptor Binding Moieties of Formula II

In certain embodiments, the compound of Formula II is selected from:




Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
R²


Extracellular Protein Targeting Ligand
HN
S
Linker^A
HO
OH
R²
Extracellular Protein Targeting Ligand
HN
S
Linker^A
H₂N
HO
OH
R²
Extracellular Protein Targeting Ligand
Linker^B
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Extracellular Protein Targeting Ligand
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Extracellular Protein Targeting Ligand
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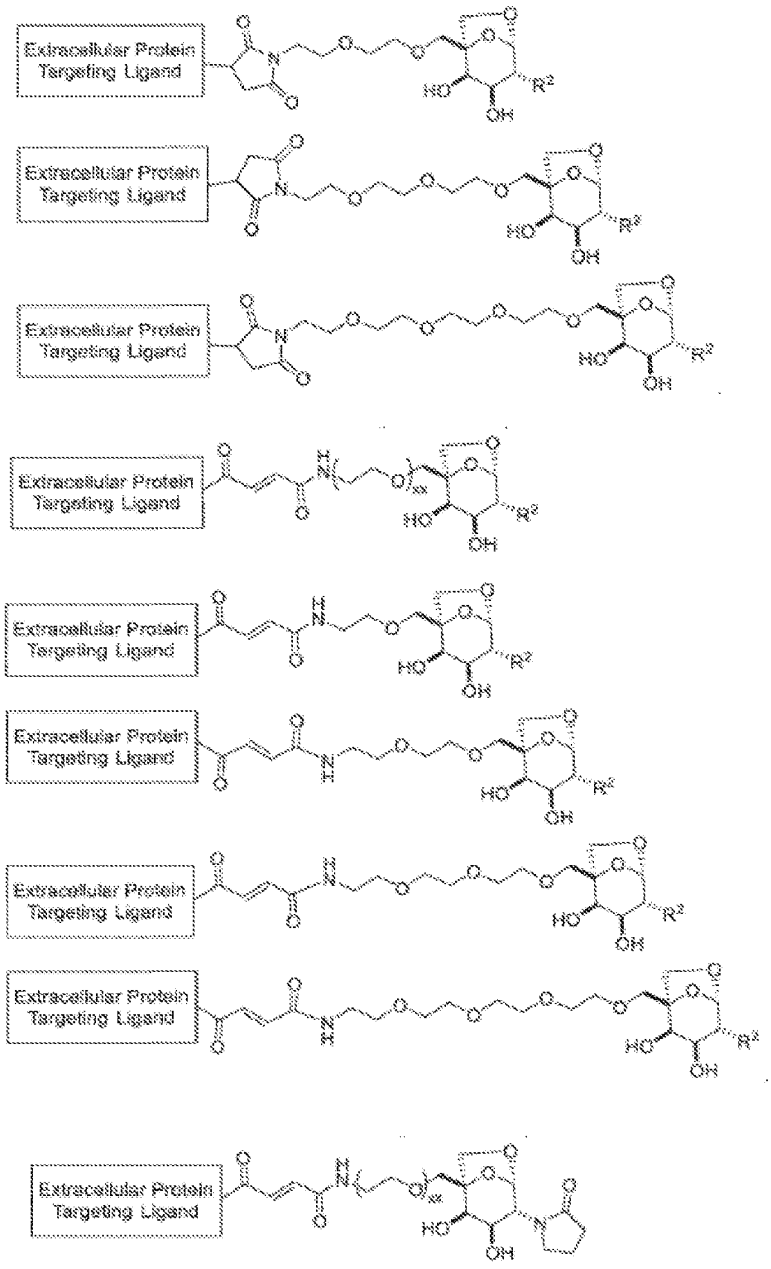
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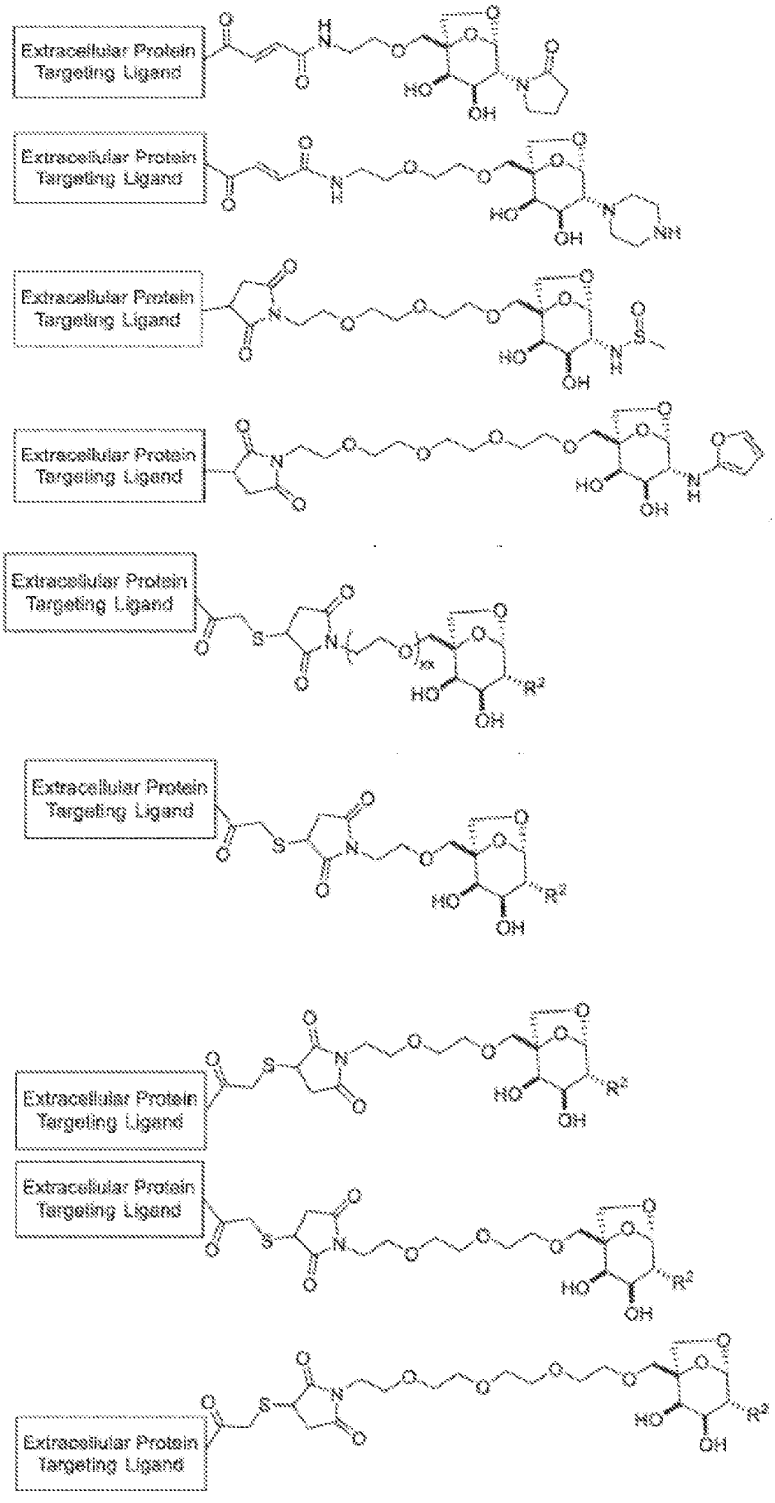
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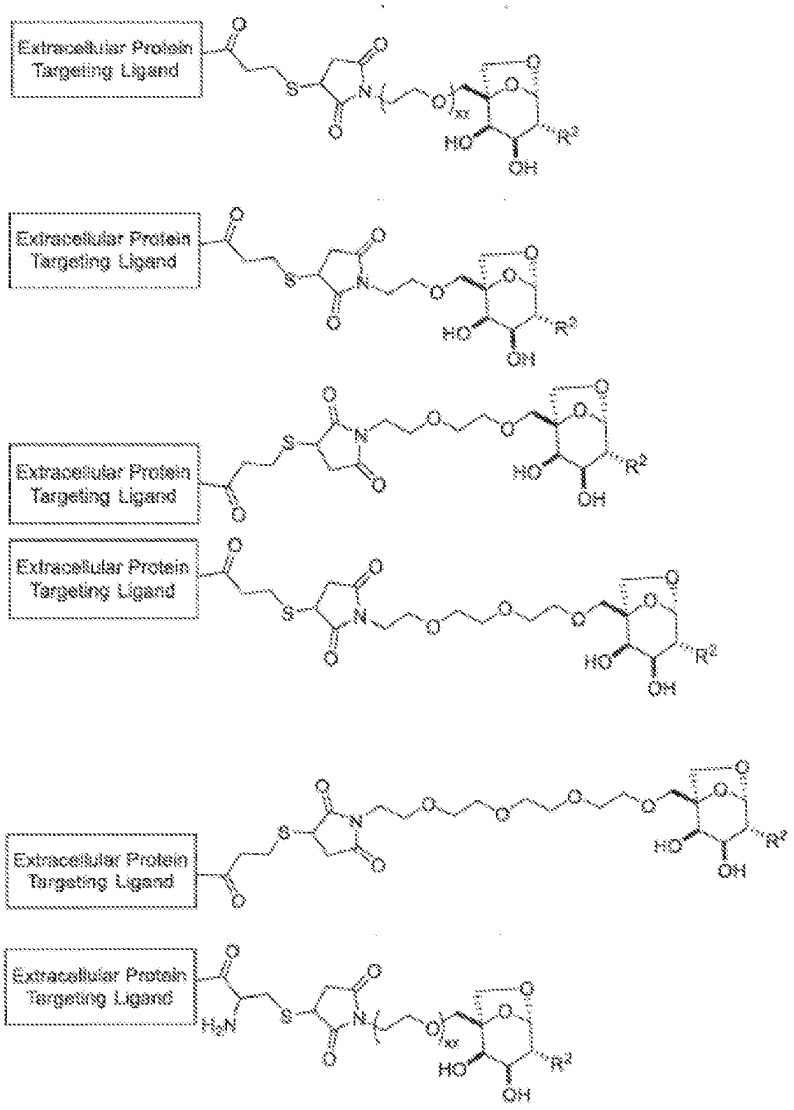
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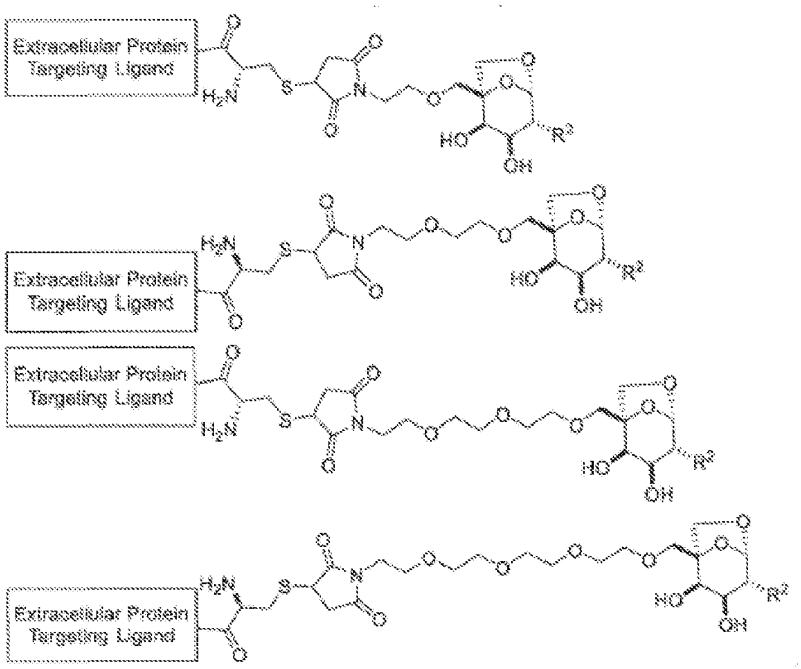
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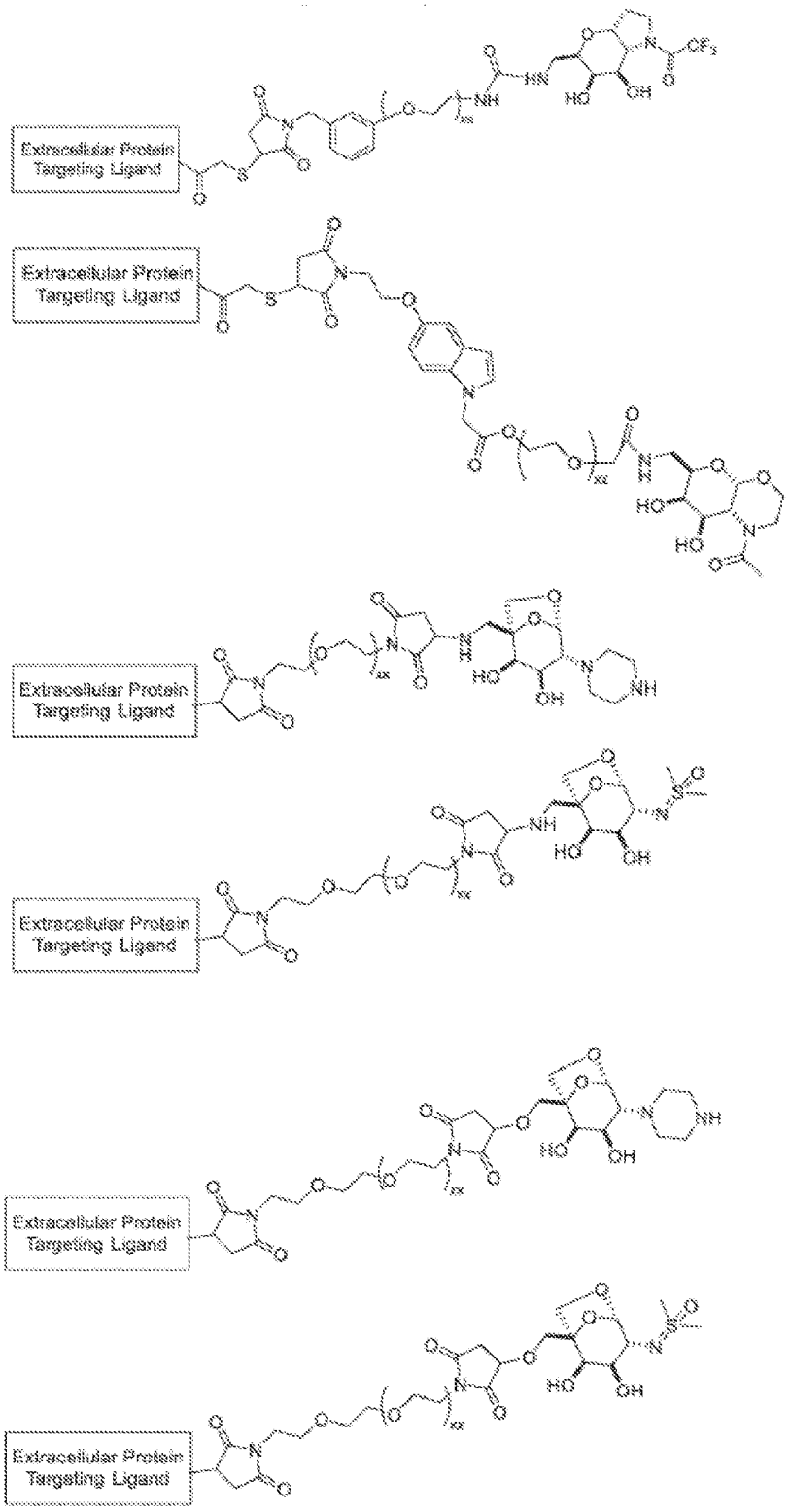
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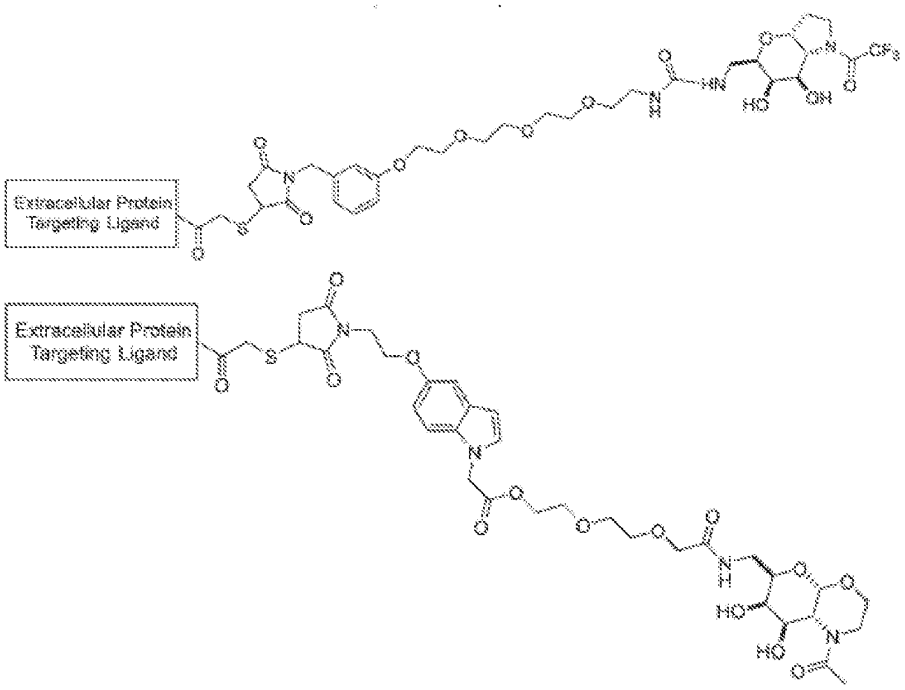
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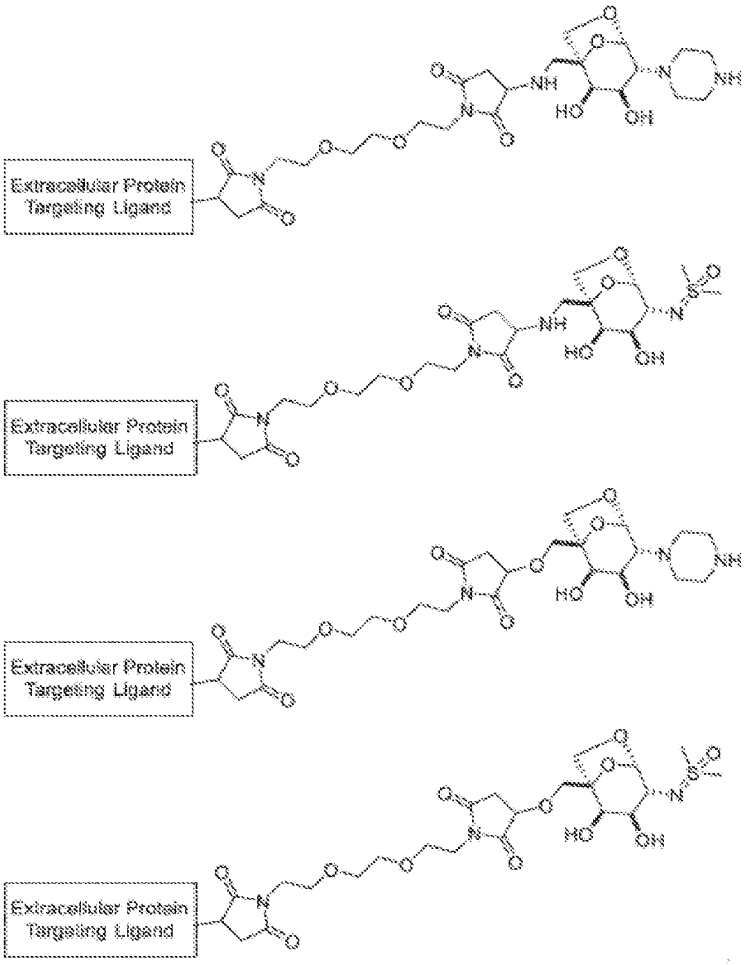
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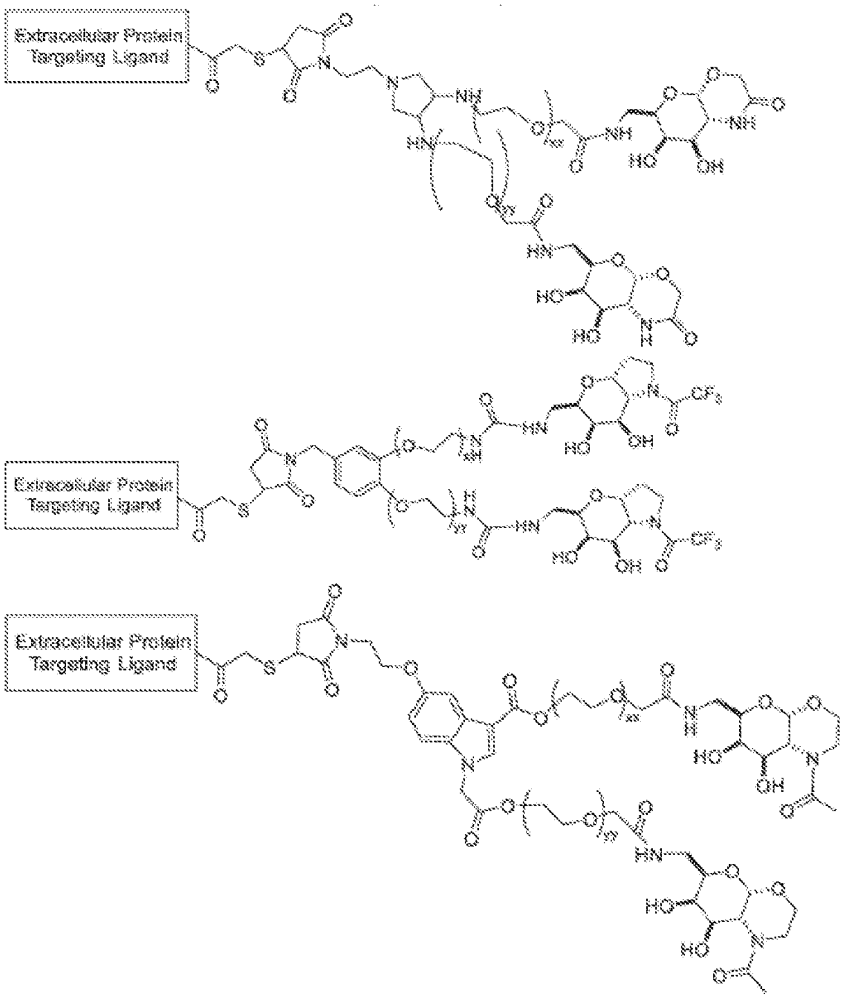
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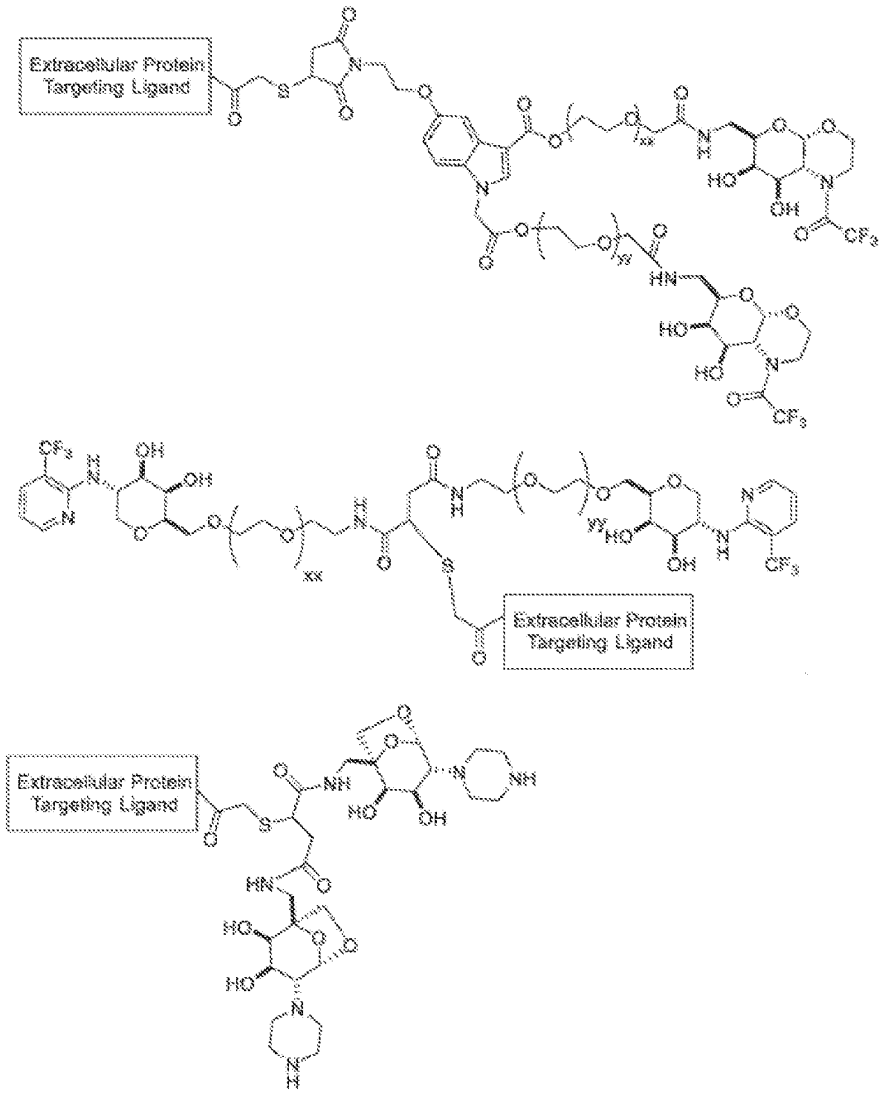
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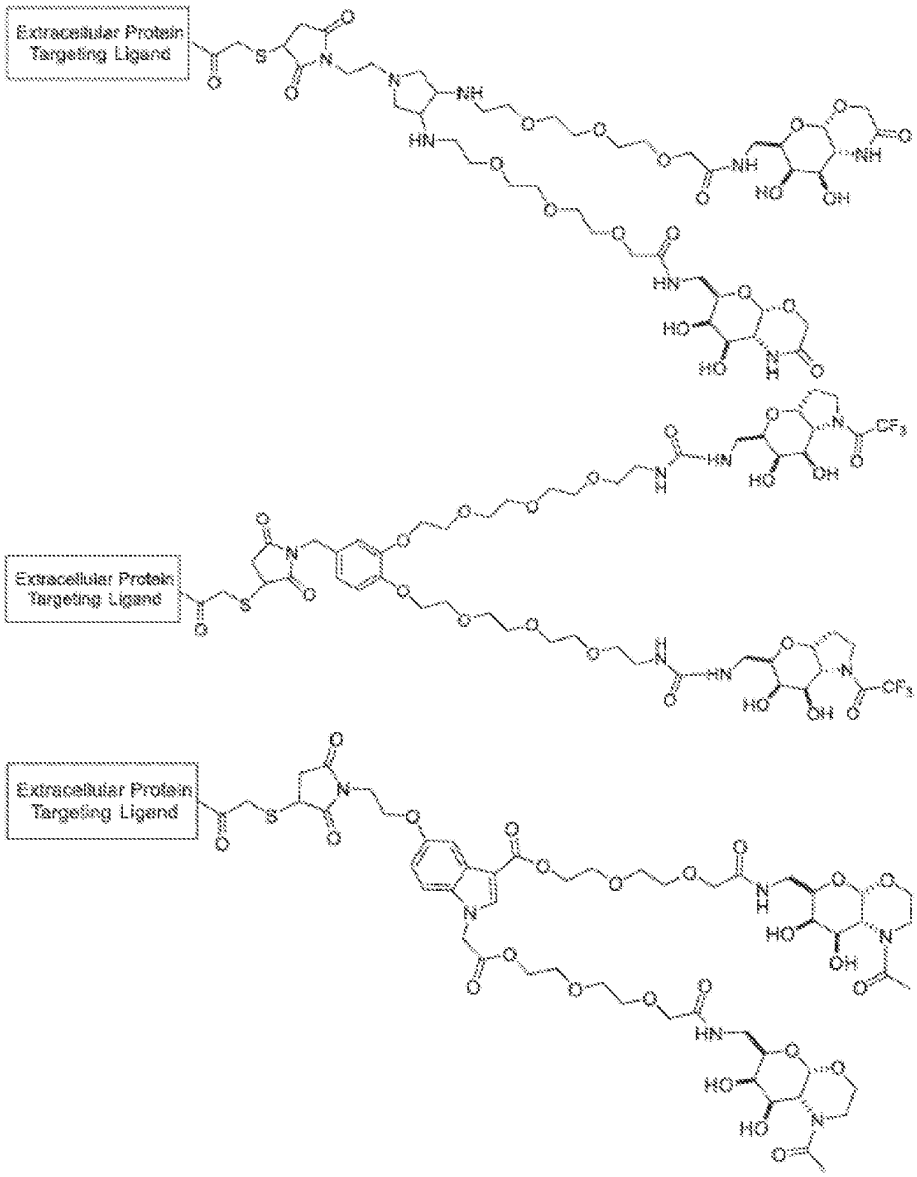
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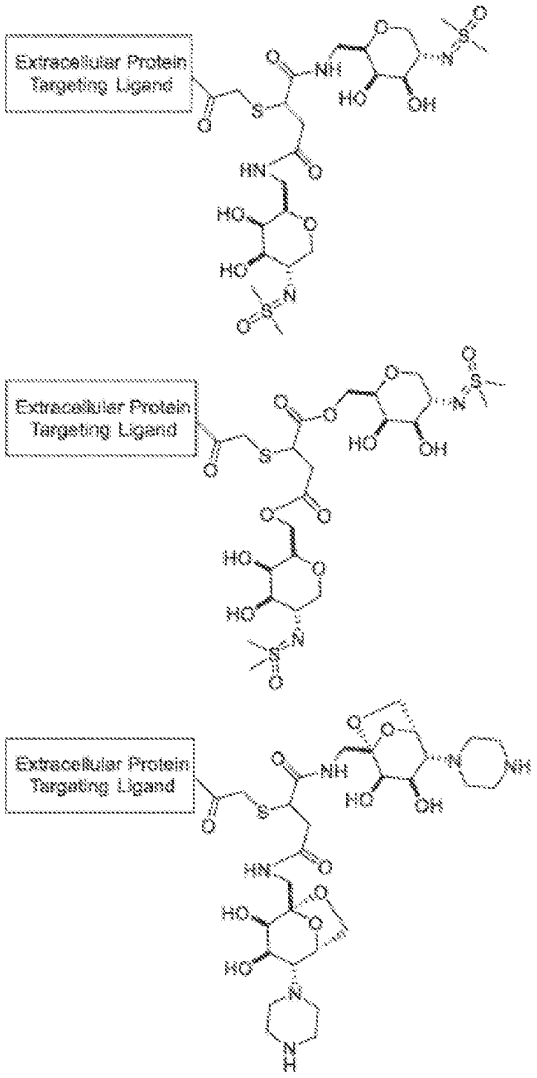
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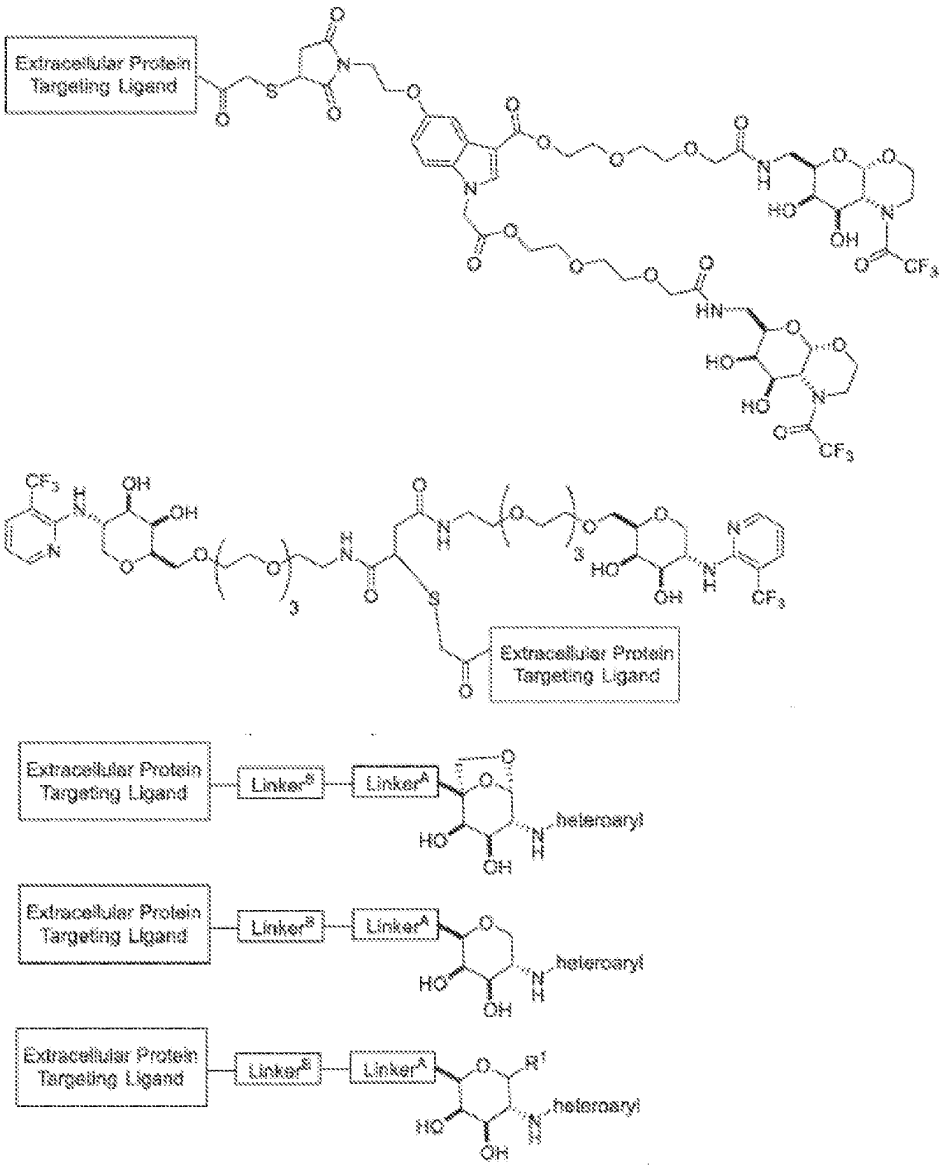
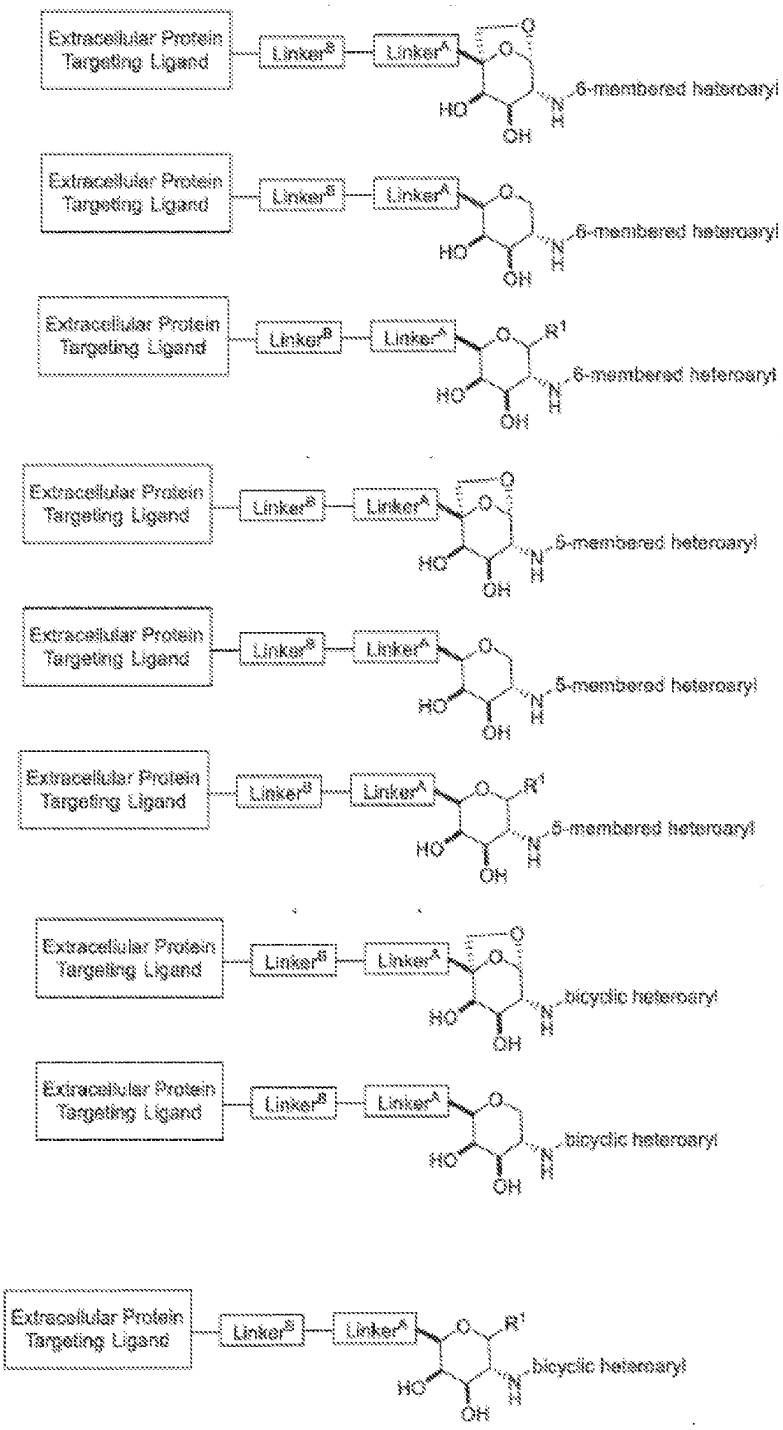
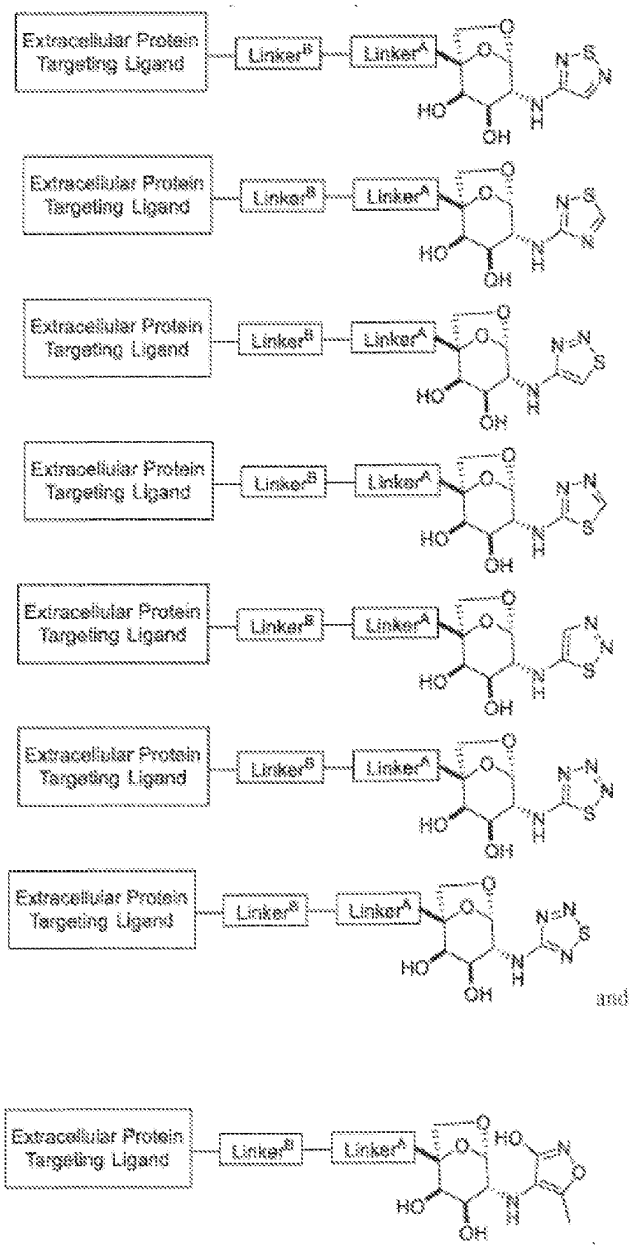
Extracellular Protein Targeting Ligand
Extracellular Protein Targeting Ligand

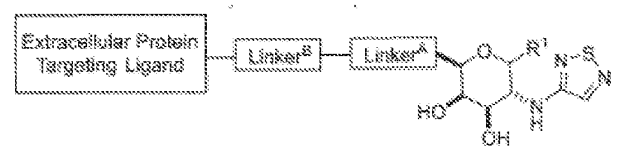

Extracellular Protein Targeting Ligand
Extracellular Protein Targeting Ligand
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
heteroaryl
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
heteroaryl
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
heteroaryl

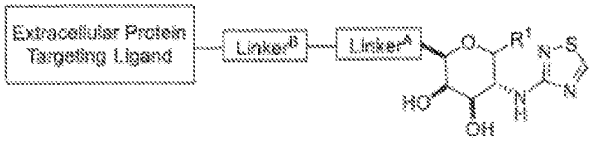

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
6-membered heteroaryl
5-membered heteroaryl
bicyclic heteroaryl

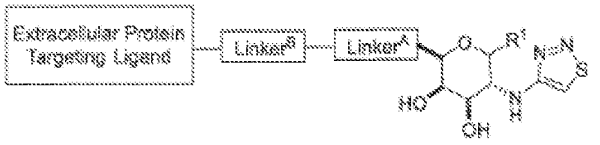

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
N
H
O
S
N

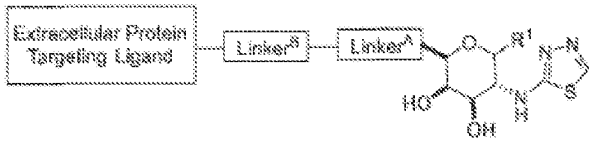
and

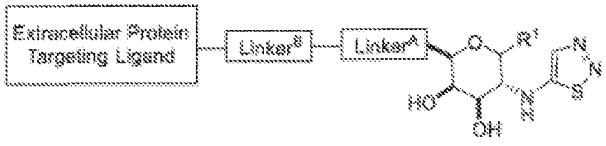
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
N
H
O
N
O

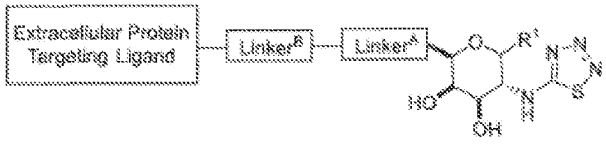

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R'
HO
OH
N
H

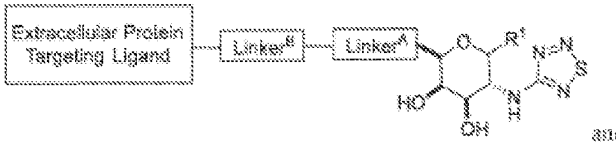

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R'
HO
OH
N
H


Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R'
HO
OH
N
H

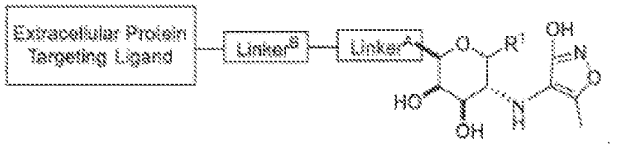

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R'
HO
OH
N
H

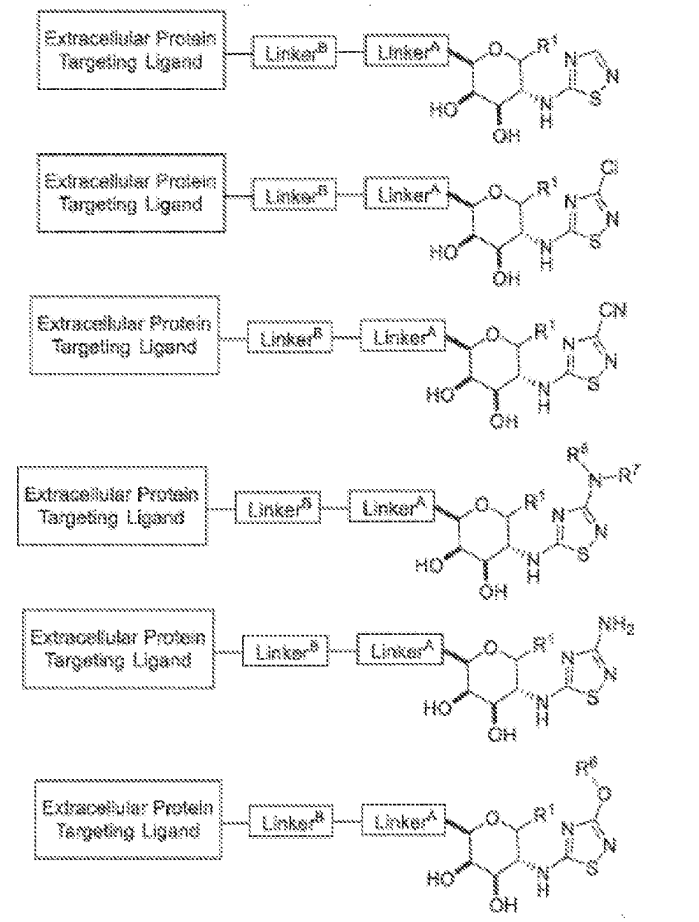

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R'
HO
OH
N
H


Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R'
HO
OH
N
H

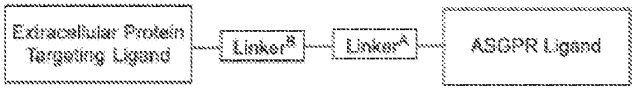

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R'
HO
OH
N
H

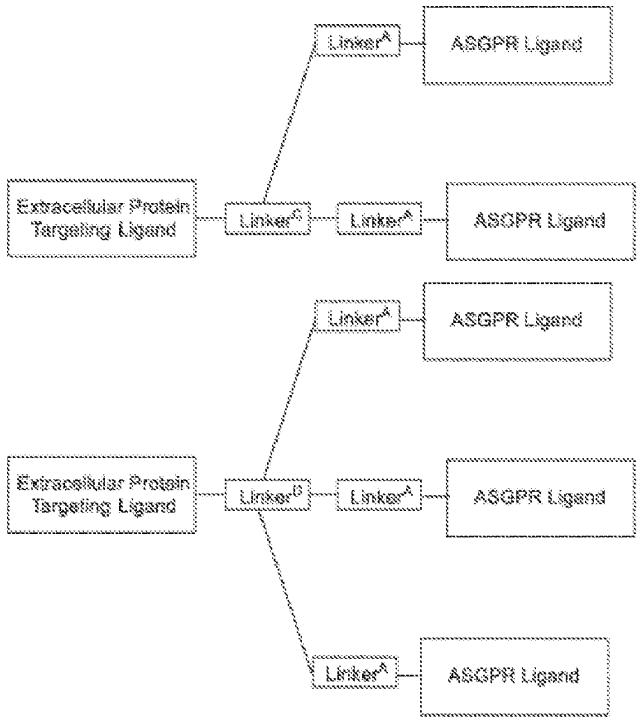
and


Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R'
HO
OH
N
H

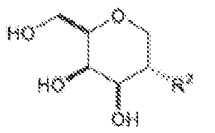


In one embodiment, the compound of Formula II has one of the following structures:



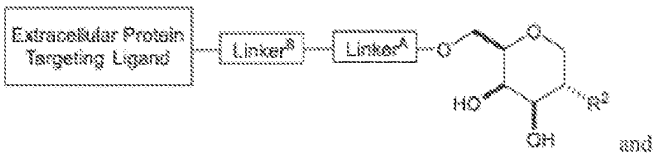


In various embodiments, the ASGPR ligand is linked at either the C^1 or C^5 (R^1 or R^5) position to form a degrading compound. In various embodiments, the ASGPR ligand is linked at C^6 position to form a degrading compound. For example, when the ASGPR ligand is

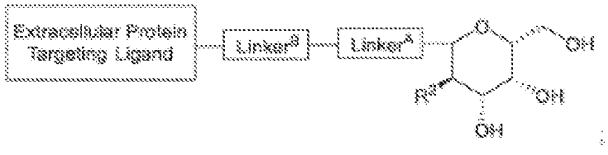


,

then non- limiting examples of ASGPR binding compounds of Formula II include:



and

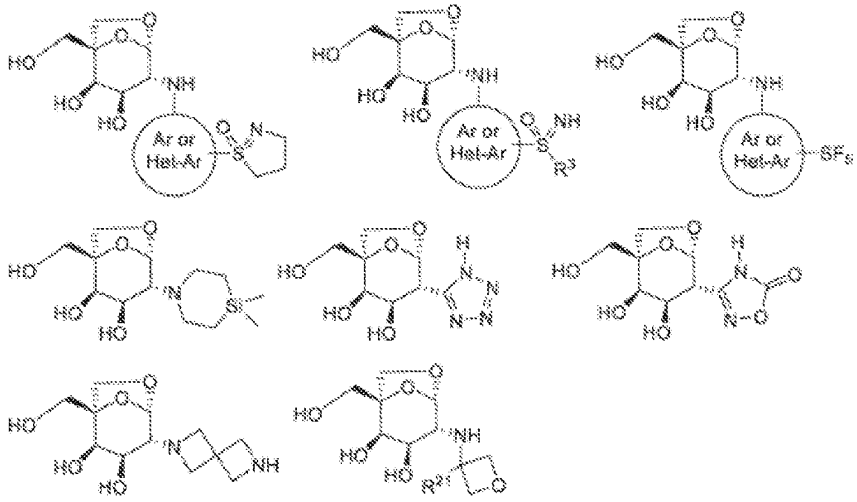


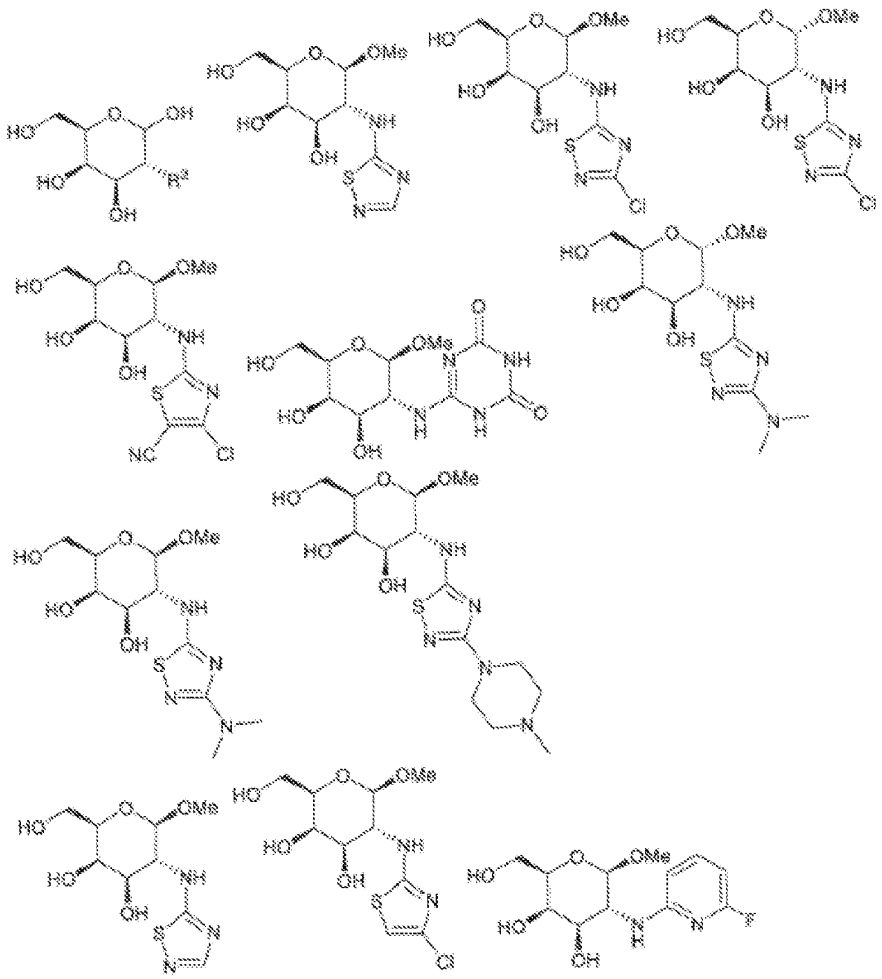
; or the bi- or tri- substituted versions thereof or pharmaceutically acceptable salts thereof, where the bi- or tri- substitution

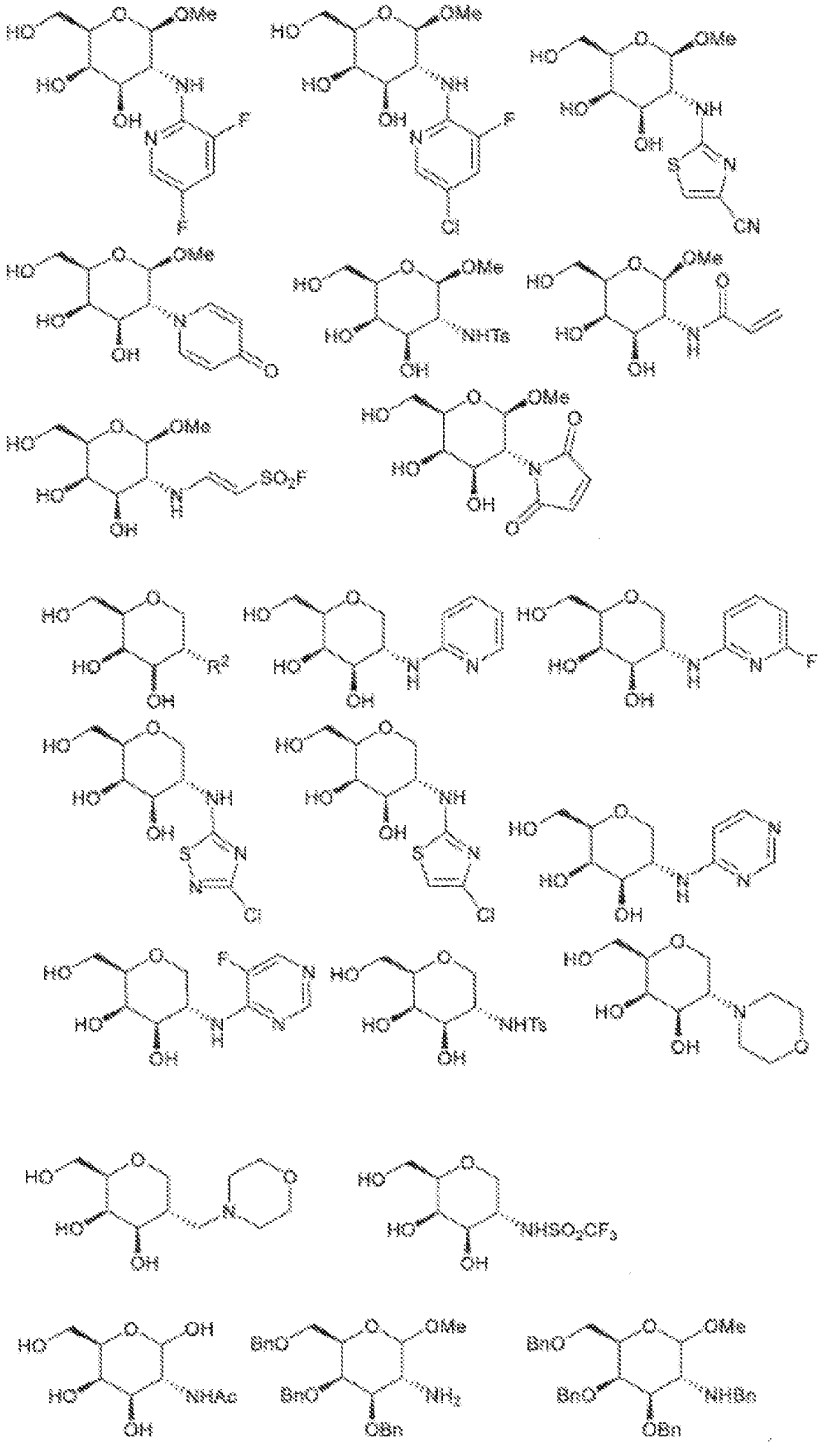
refers to the number additional galactose derivatives attached to a linker moiety.

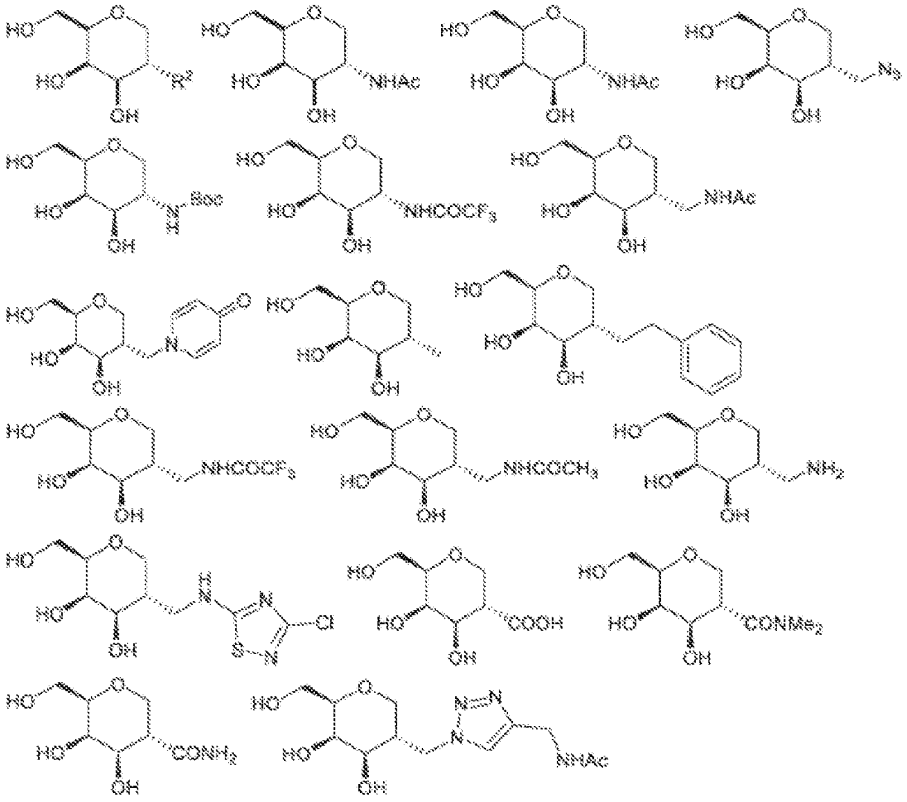
In any of the embodiments herein where an ASGPR ligand is drawn for use in a degrader the ASGPR ligand is typically linked through to the Extracellular Protein Targeting Ligand in the C^5 position (e.g., which can refer to the adjacent C^6 carbon hydroxyl or other functional moiety that can be used for linking purposes). When the linker and Extracellular Protein Targeting Ligand is connected through the C^1 position, then that carbon is appropriately functionalized for linking, for example with a hydroxyl, amino, allyl, alkyne or hydroxyl-allyl group.

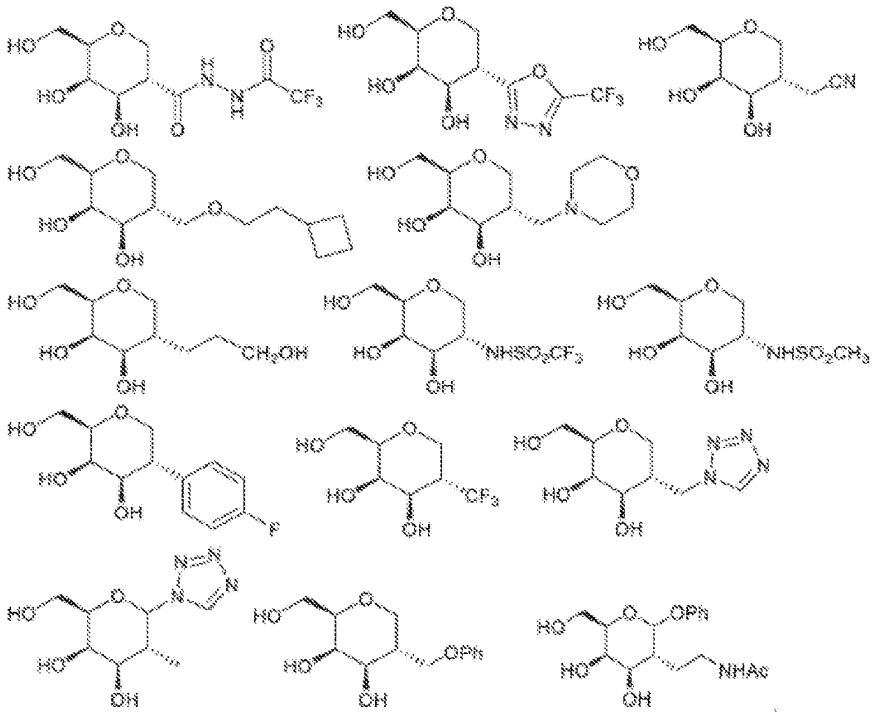
In various embodiments, the ASGPR ligand is not linked in the C^3 or C^4 position, because these positions chelate with the calcium for ASGPR binding in the liver. In certain embodiments, an ASGPR ligand useful for incorporation into a compound of Formula II is selected from:

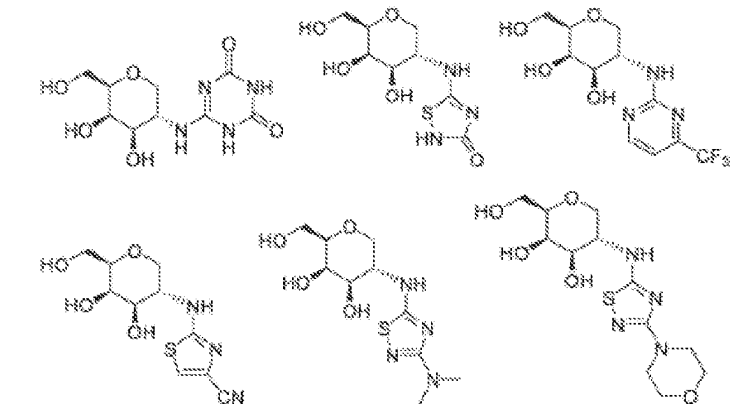


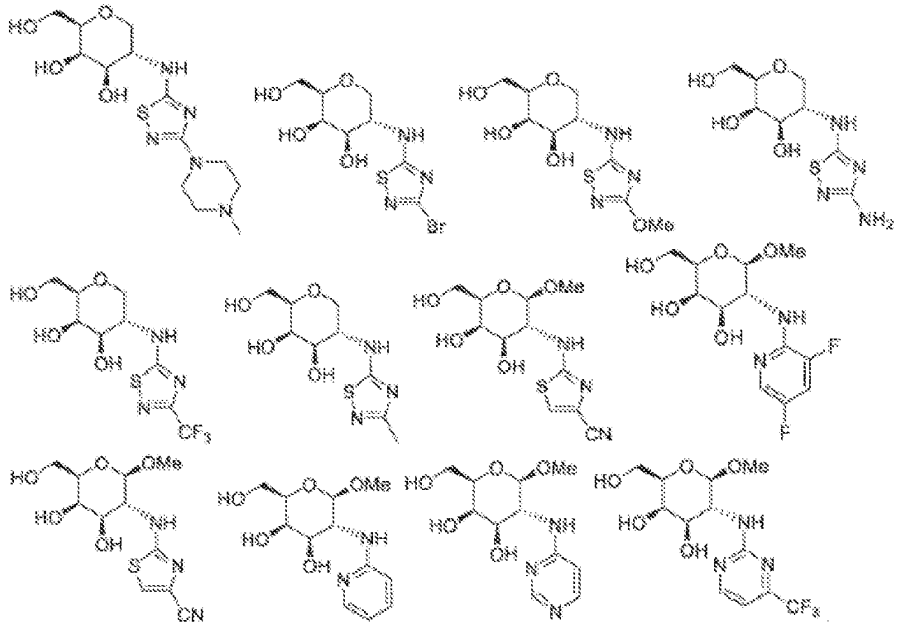


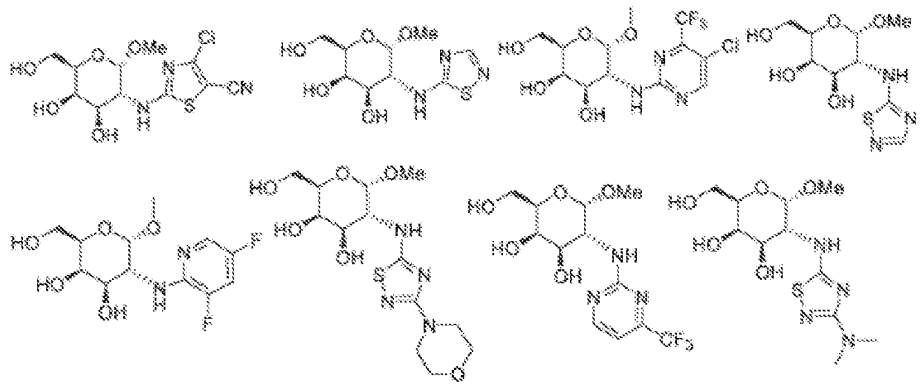


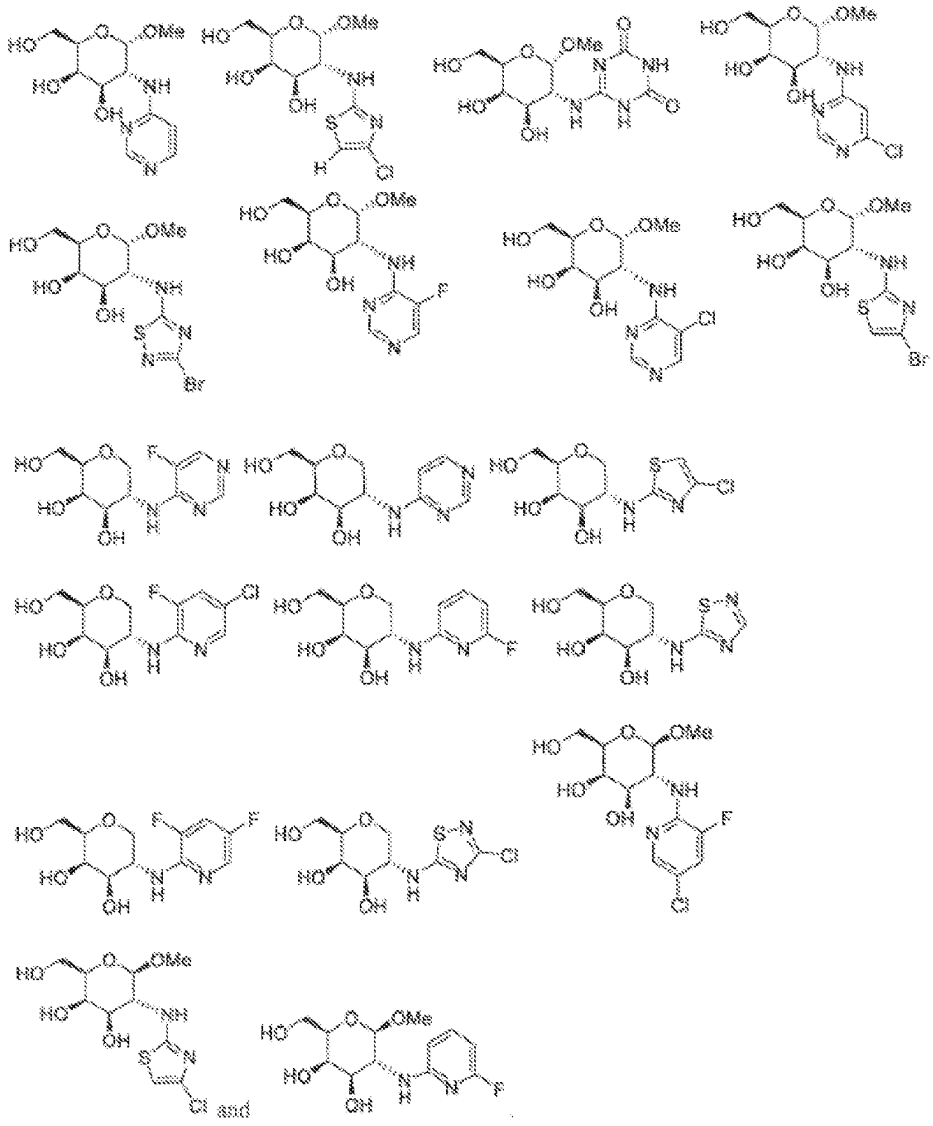












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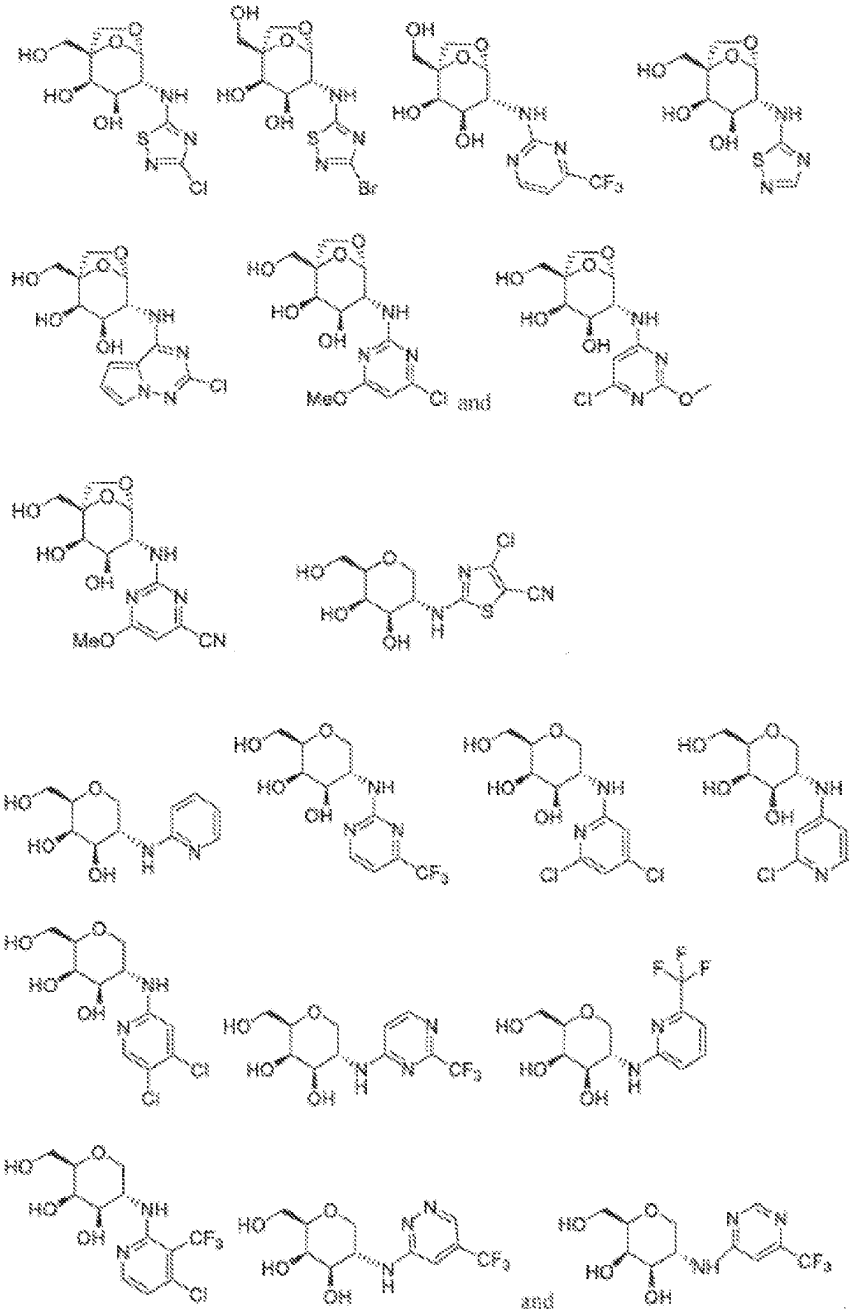
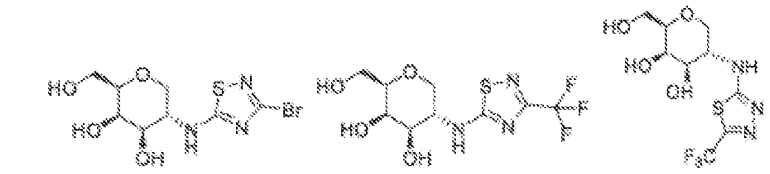
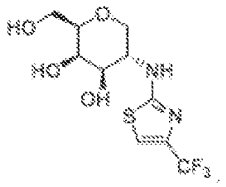
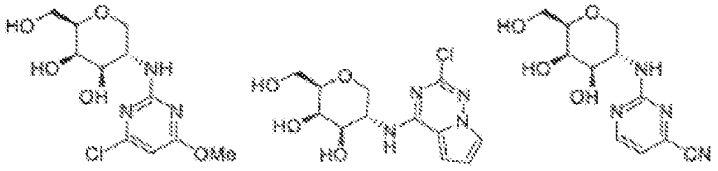
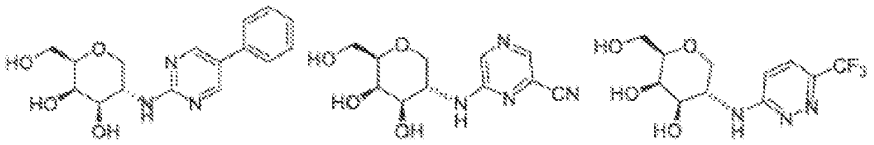
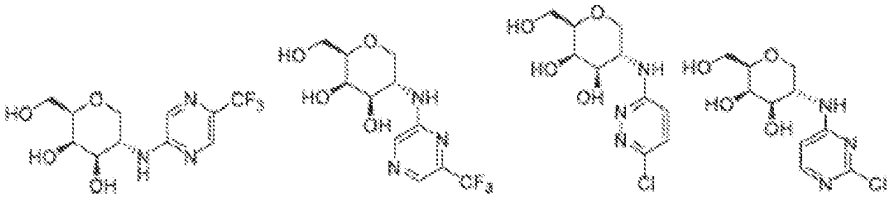


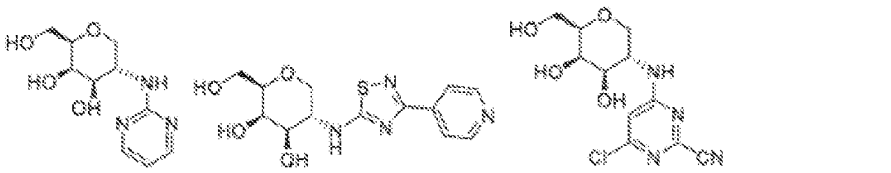


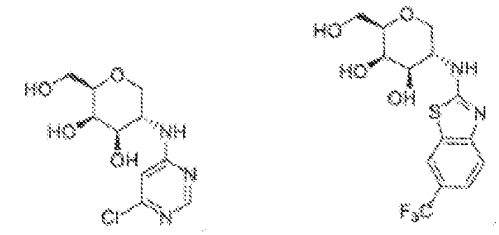


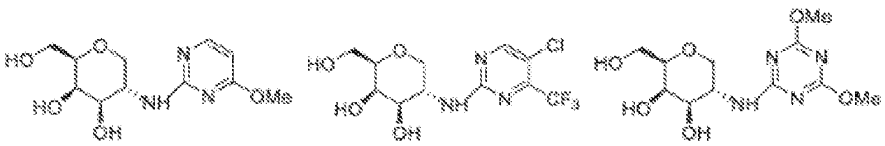


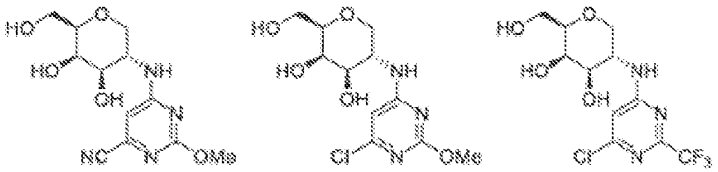


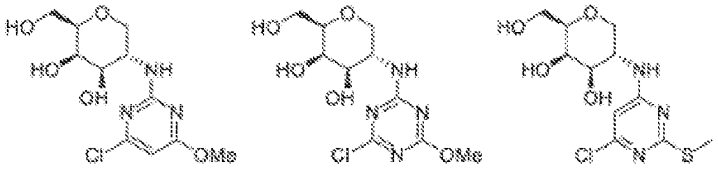


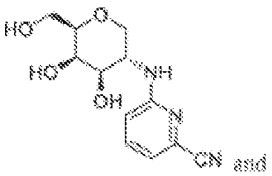
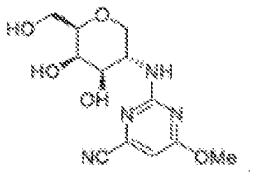


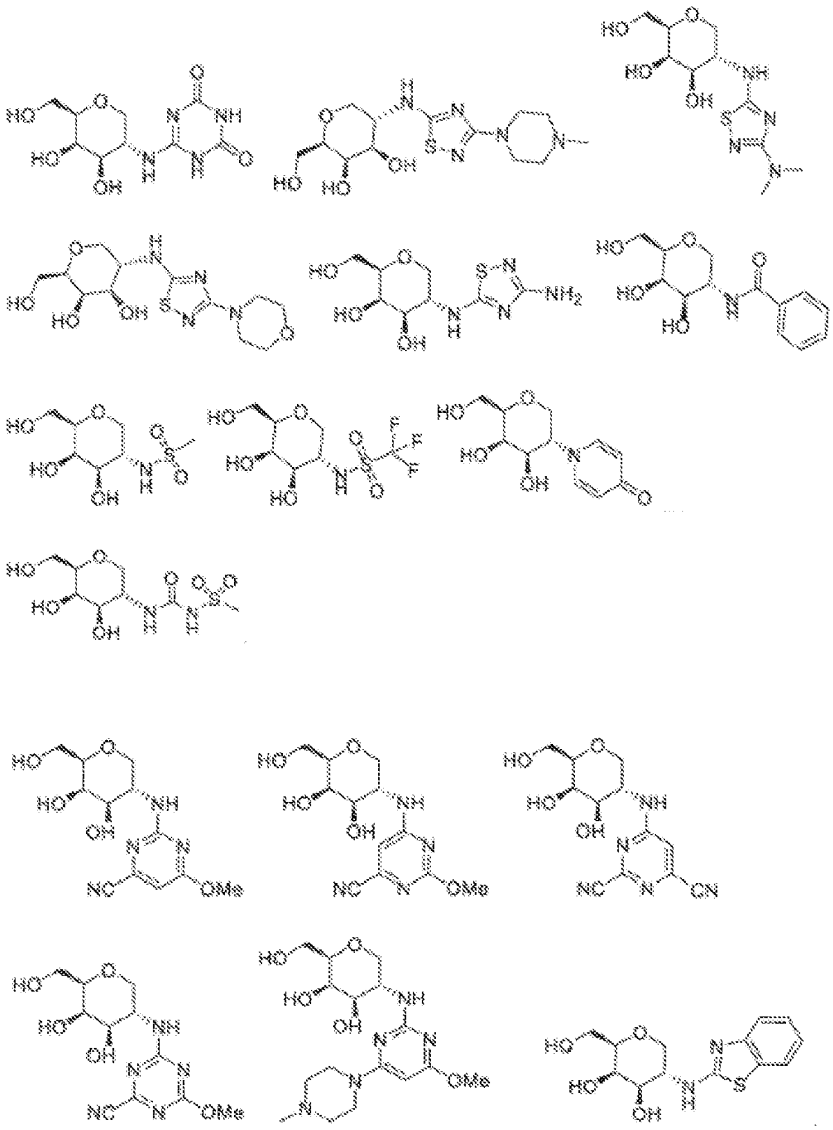


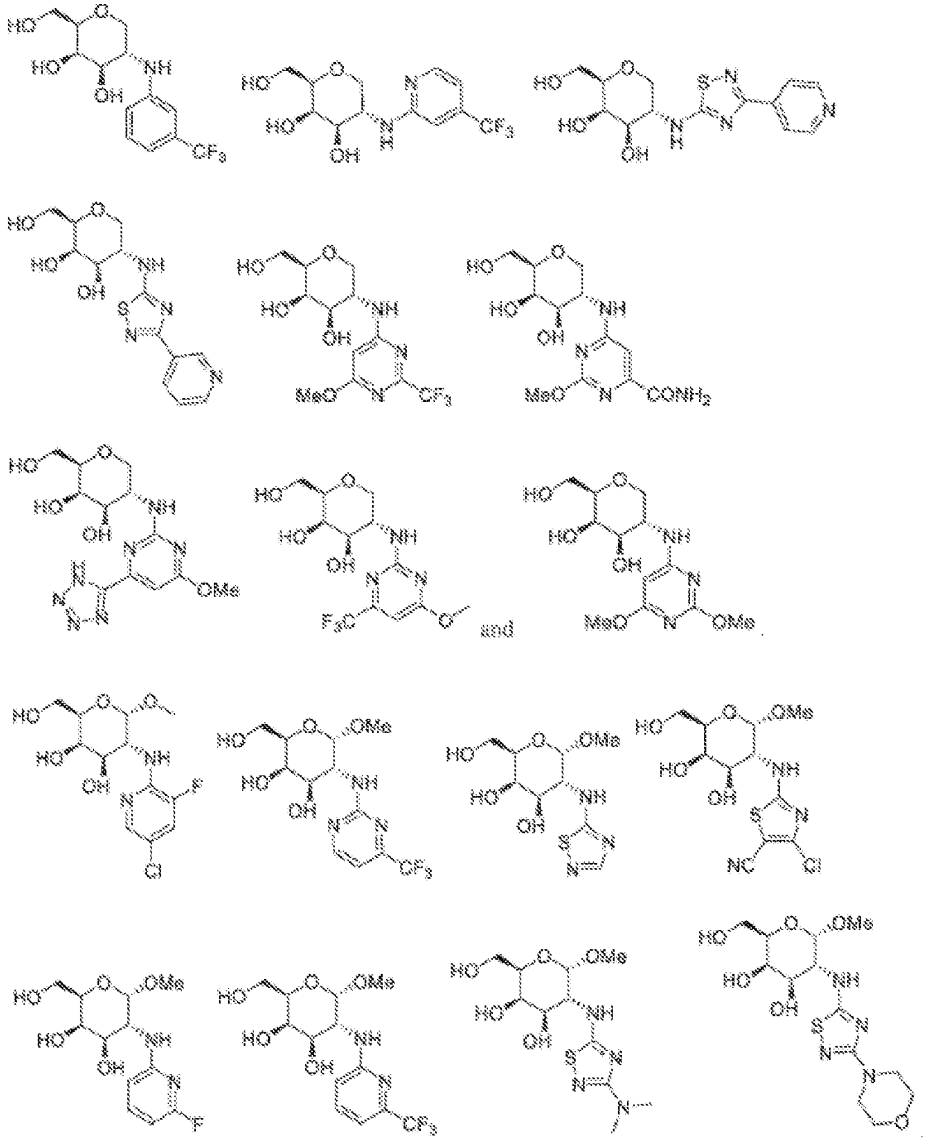


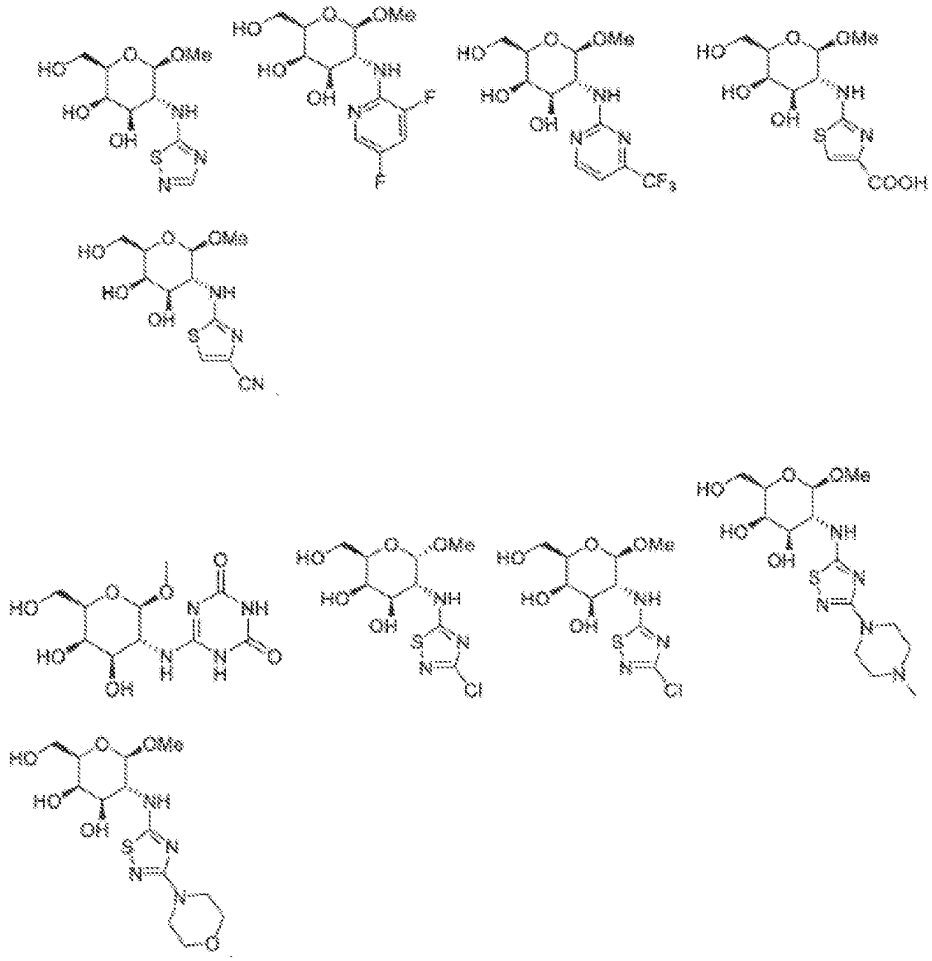




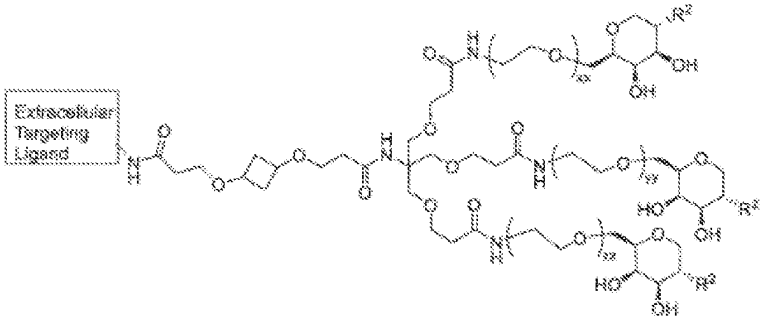

and


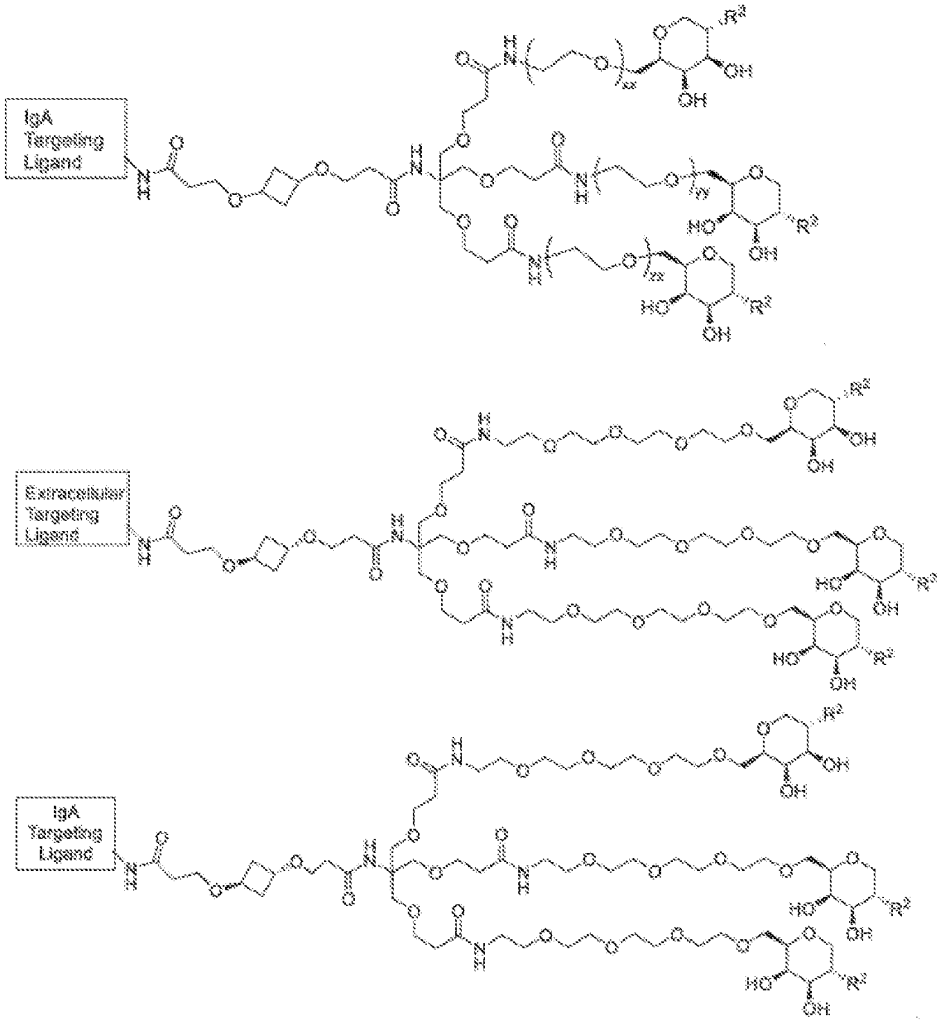


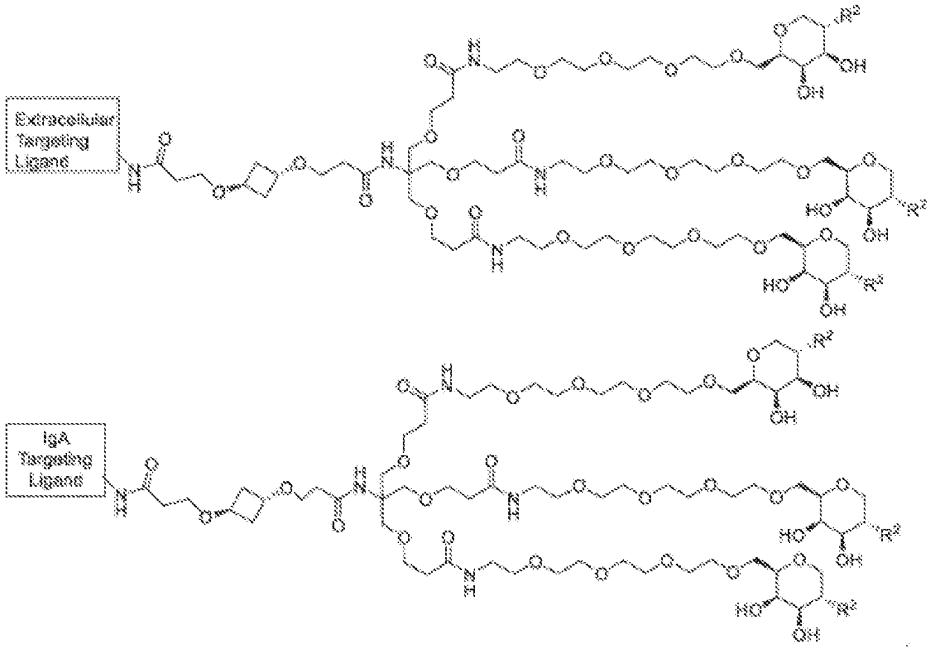


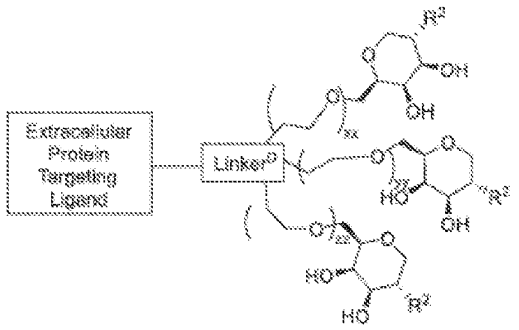


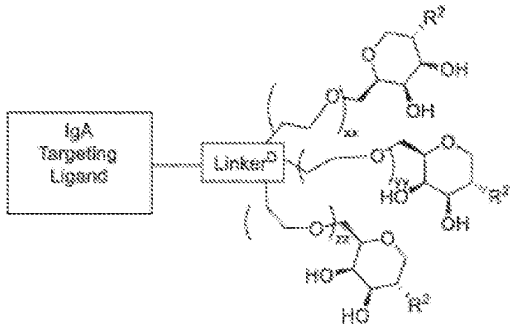
In certain embodiments, the compound of Formula II is selected from:

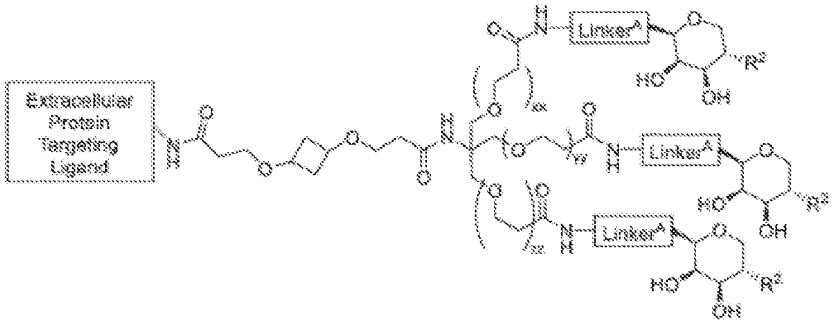


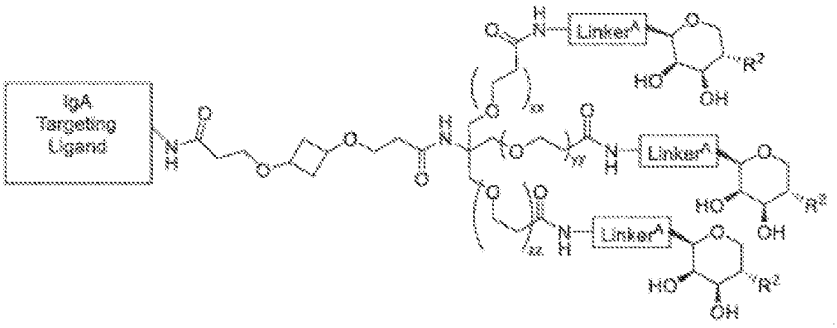

IgA Targeting Ligand
Extracellular Targeting Ligand
IgA Targeting Ligand

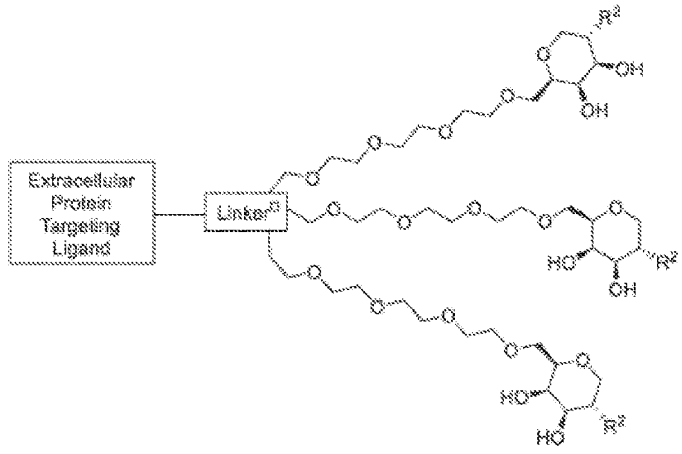

Extracellular Targeting Ligand
IgA Targeting Ligand

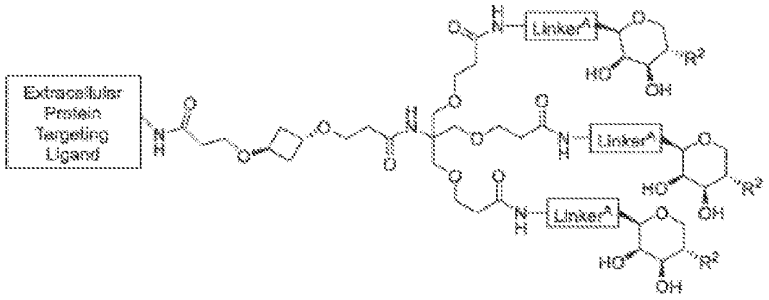

Extracellular Protein Targeting Ligand
Linker^D


IgA Targeting Ligand
Linker^D


Extracellular Protein Targeting Ligand
Linker^A

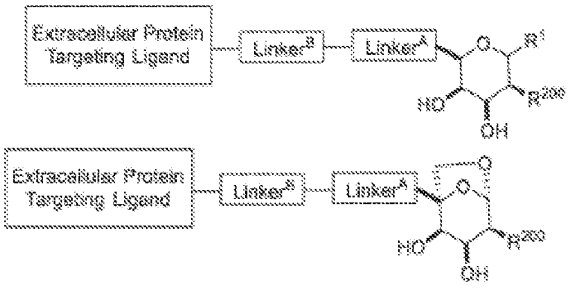

IgA Targeting Ligand
Linker^A

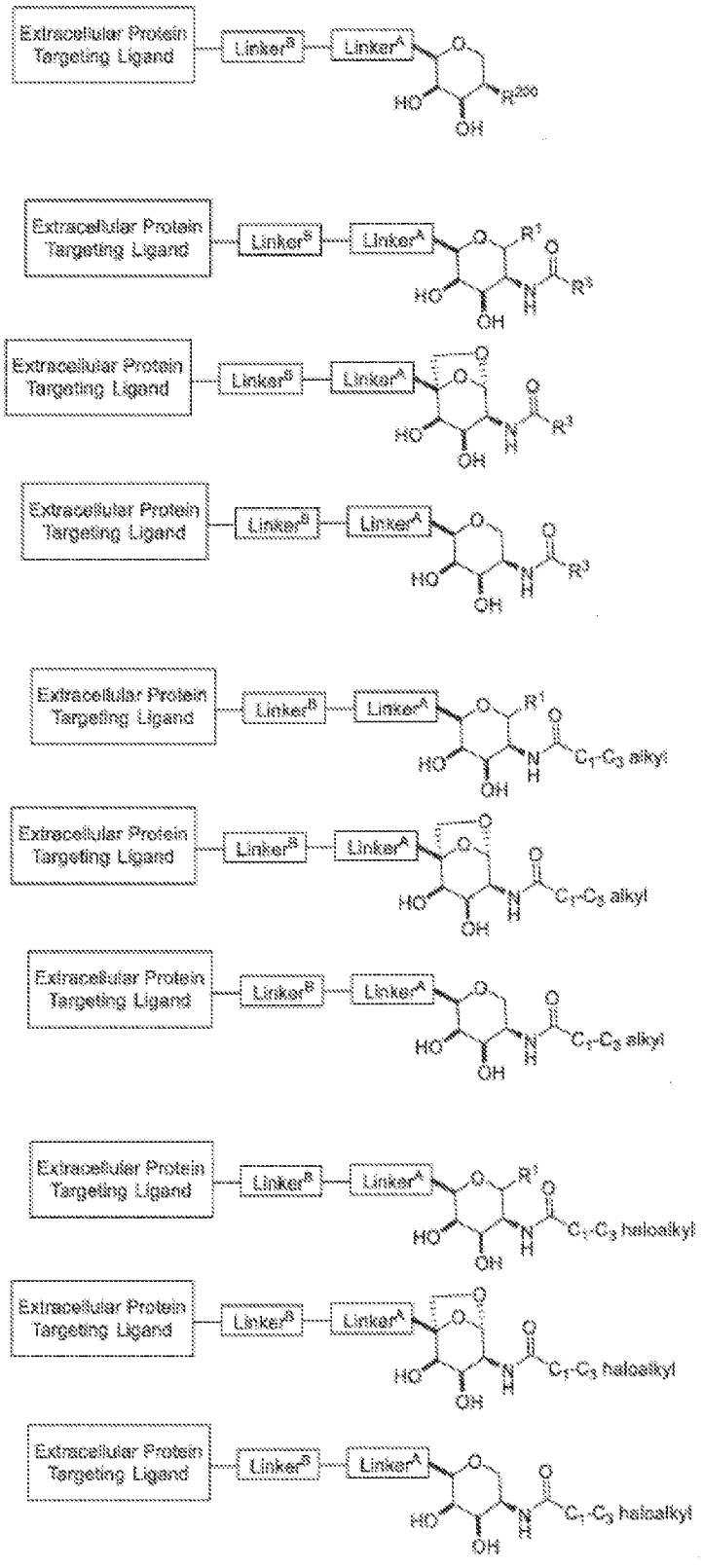


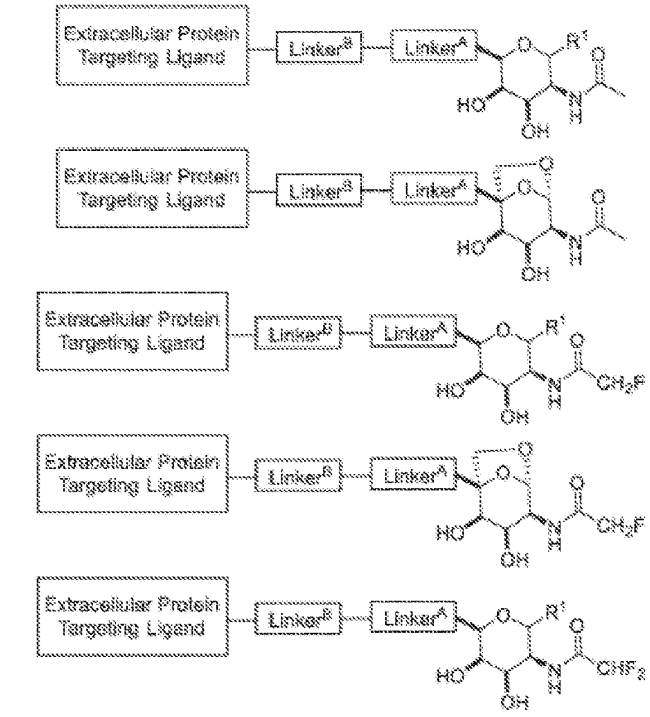


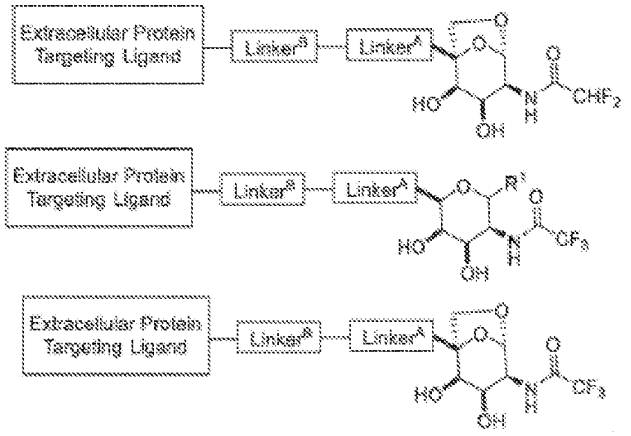
B. Talose-Based ASGPR-Binding Cellular Receptor Binding Moieties of Formula II

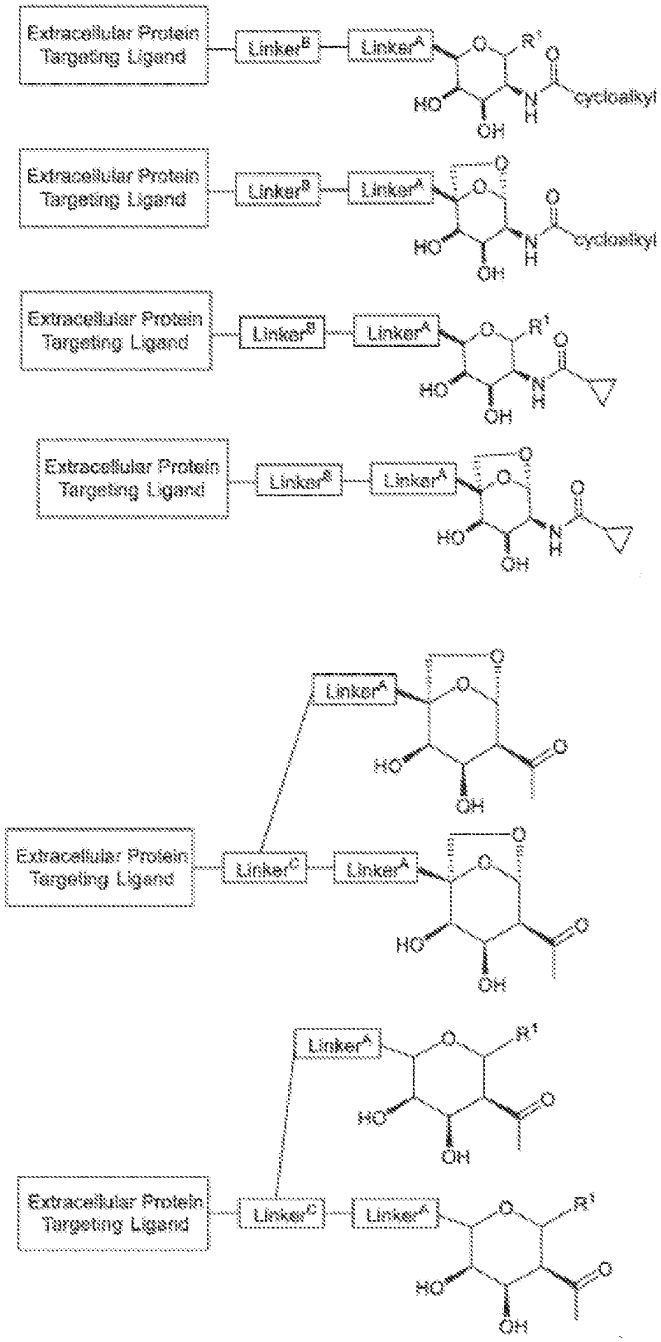
In certain embodiments, the compound of Formula II is selected from:

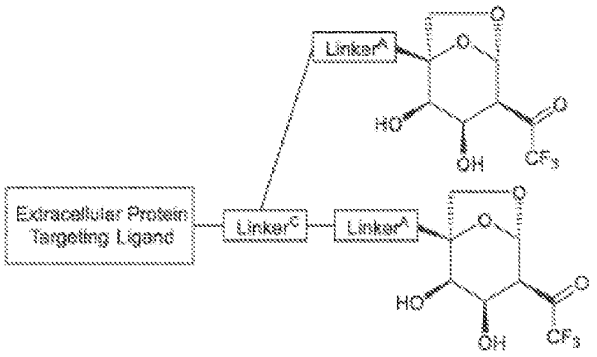


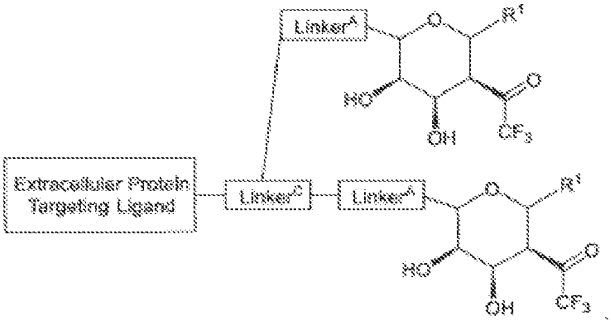

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
R^200
R^1
R^3
C1-C3 alkyl
C1-C3 haloalkyl

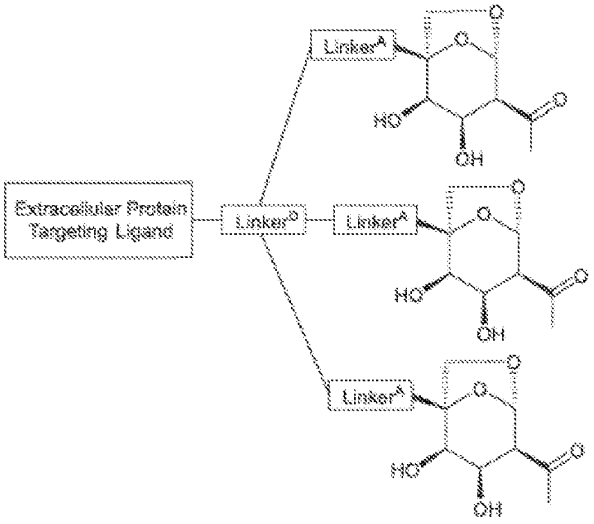

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
N
H
O
R'
CH2F
CHF2
CF3

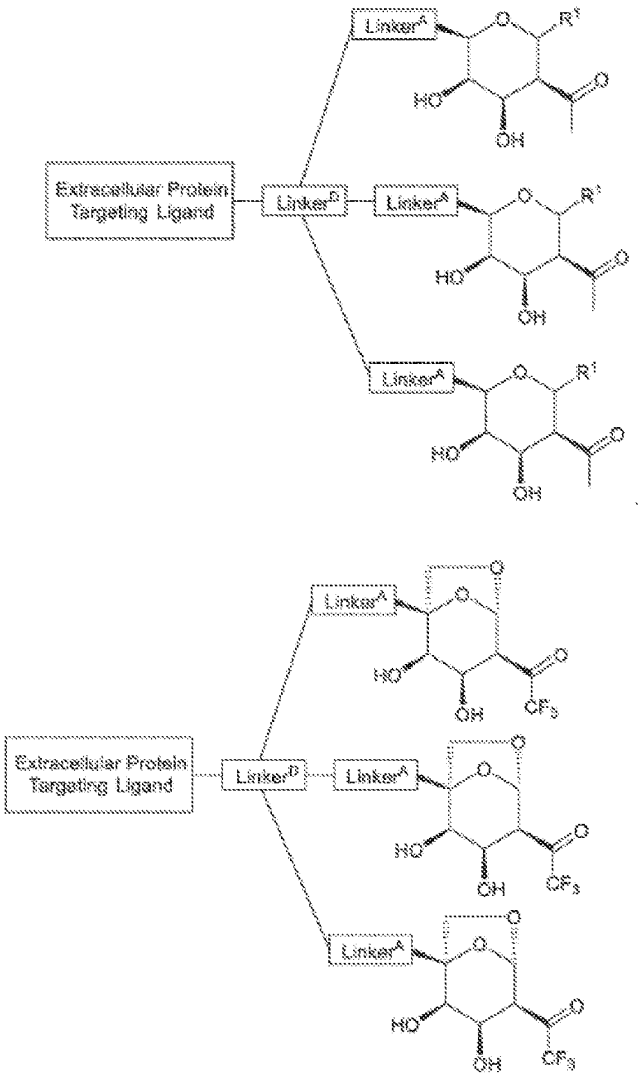

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
N
H
O
R'
CHF2
CF3

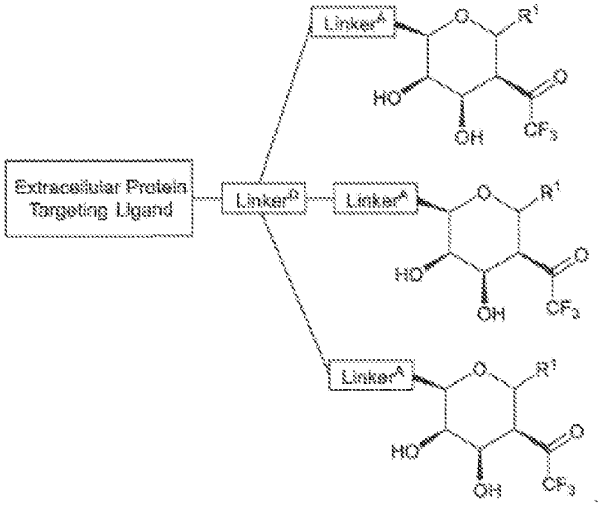

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
cycloalkyl
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
cycloalkyl
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^C
Linker^A


Linker^A
HO
OH
CF3
Extracellular Protein Targeting Ligand
Linker^C
Linker^A


Linker^A
R1
HO
OH
CF3
Extracellular Protein Targeting Ligand
Linker^C
Linker^A


Linker^A
HO
OH
Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A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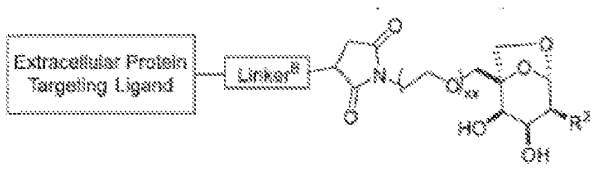
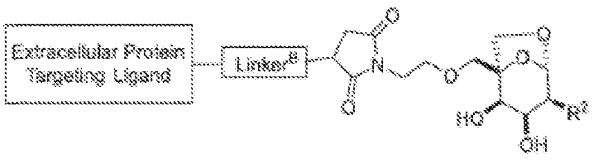
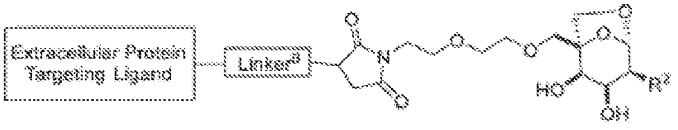
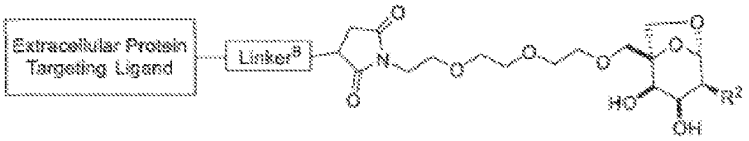
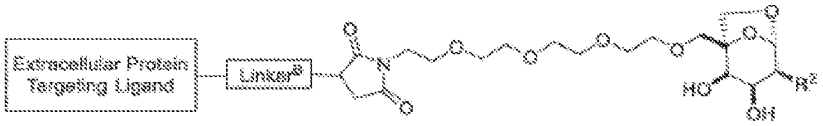
Linker^B
Linker^A
Linker^A
Linker^A
R^1
HO
OH
O
CF3

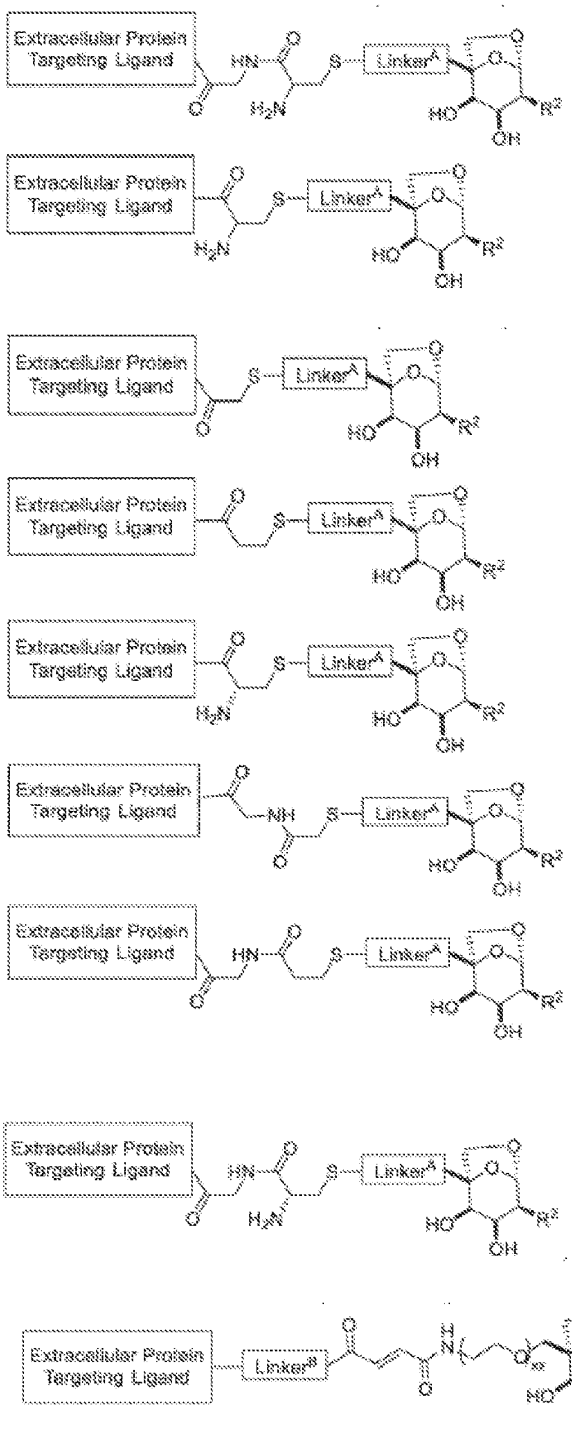

Extracellular Protein Targeting Ligand
Linker^B
HO
OH
R^2

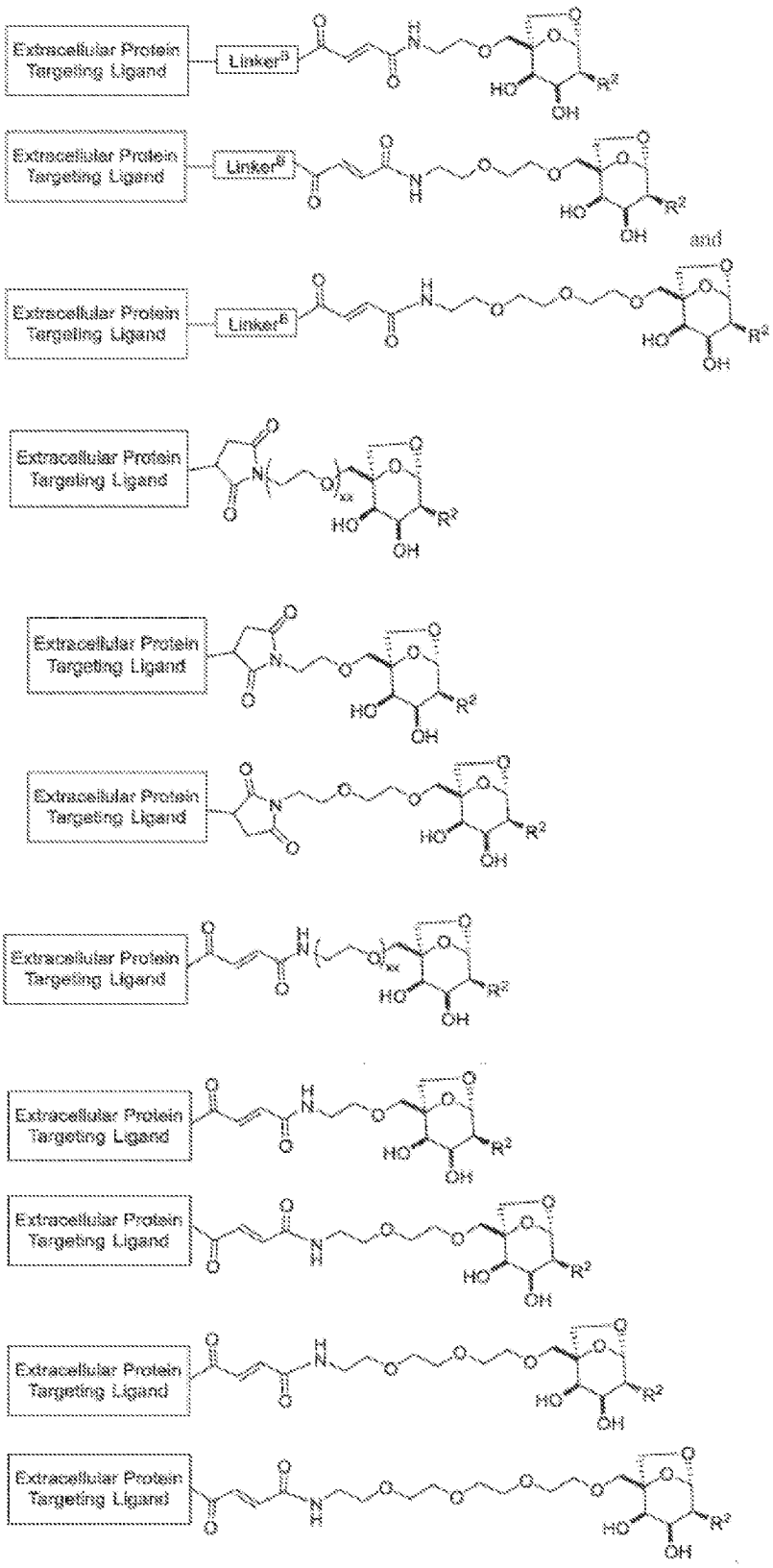

Extracellular Protein Targeting Ligand
Linker^B
HO
OH
R^2


Extracellular Protein Targeting Ligand
Linker^B
HO
OH
R^2


Extracellular Protein Targeting Ligand
Linker^B
HO
OH
R^2


Extracellular Protein Targeting Ligand
Linker^B
HO
OH
R^2


Extracellular Protein Targeting Ligand
Linker^A
Linker^B
HO
OH
R²


Extracellular Protein Targeting Ligand
Linker5
Extracellular Protein Targeting Ligand
Linker6
and
Extracellular Protein Targeting Ligand
Linker6
Extracellular Protein Targeting Ligand
Extracellular Protein Targeting Ligand
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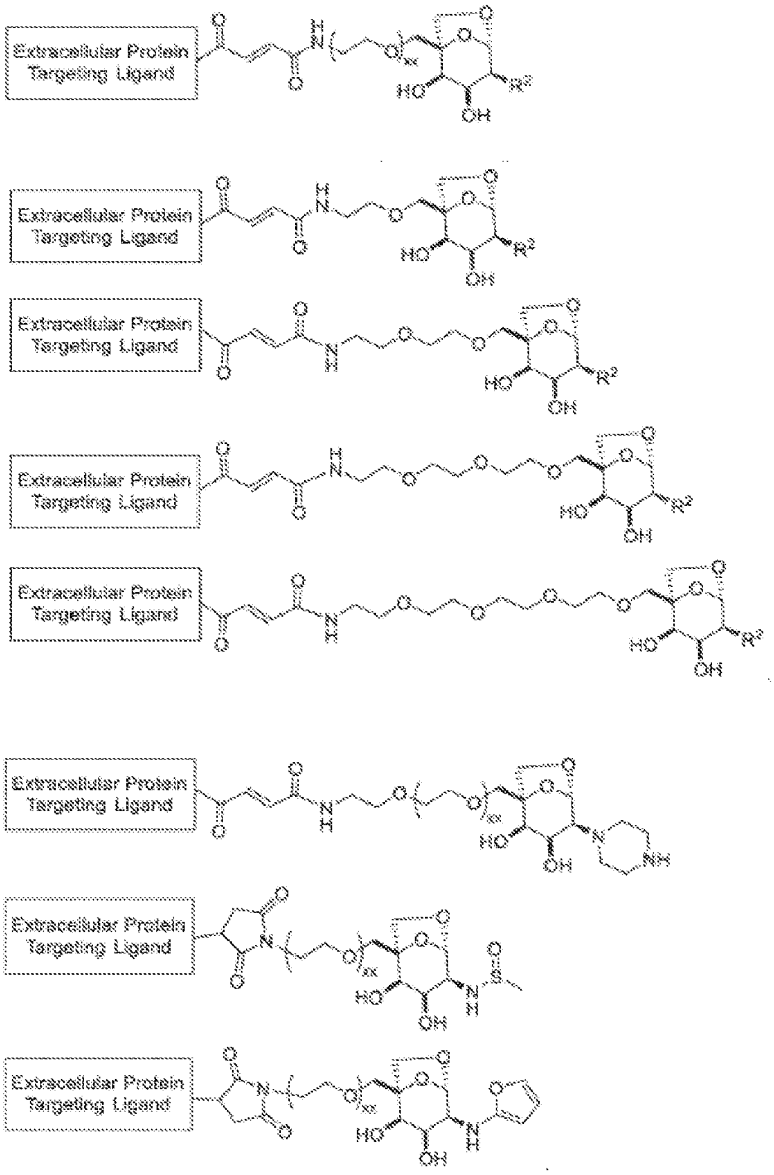
Extracellular Protein Targeting Ligand
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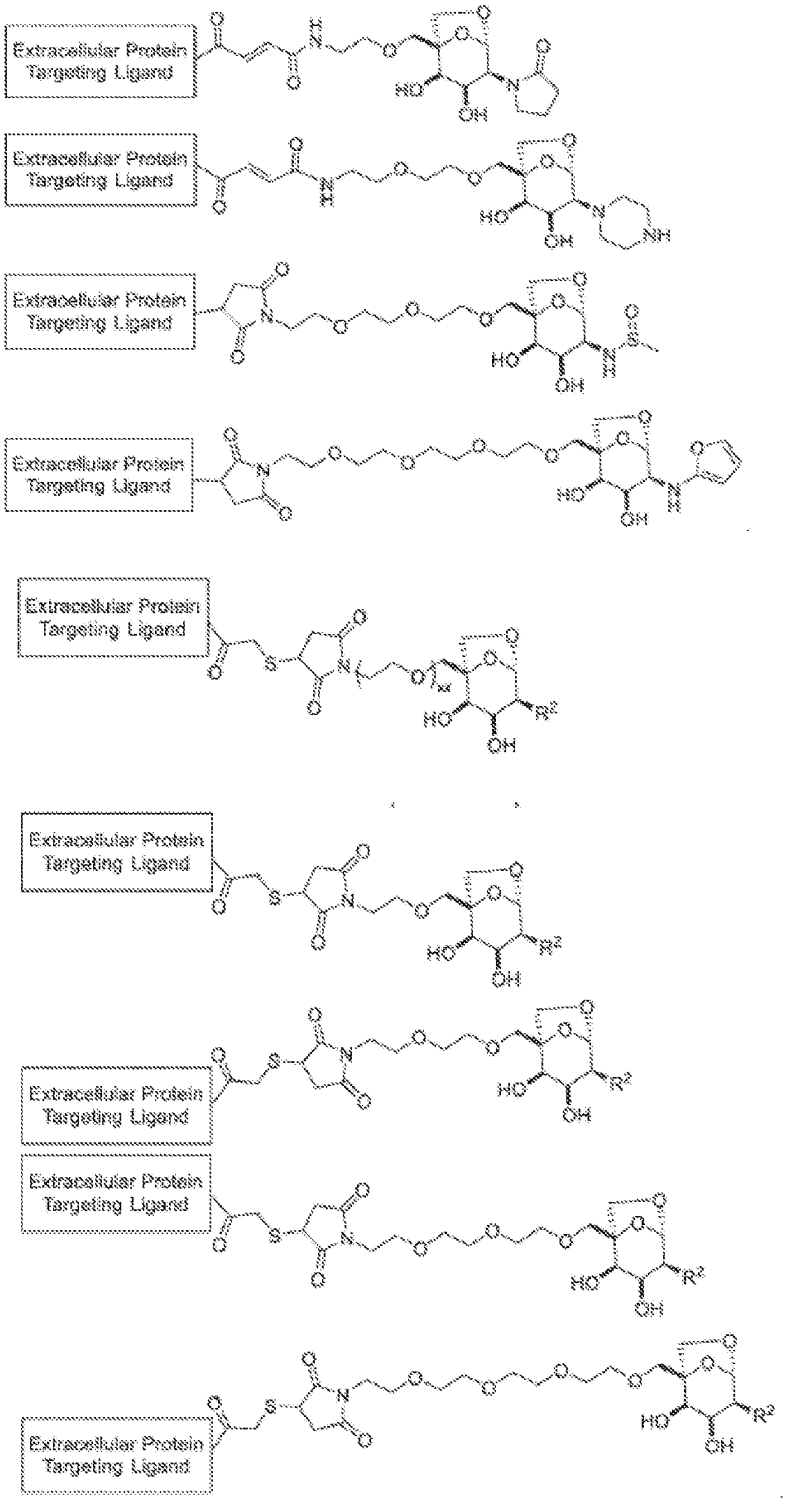
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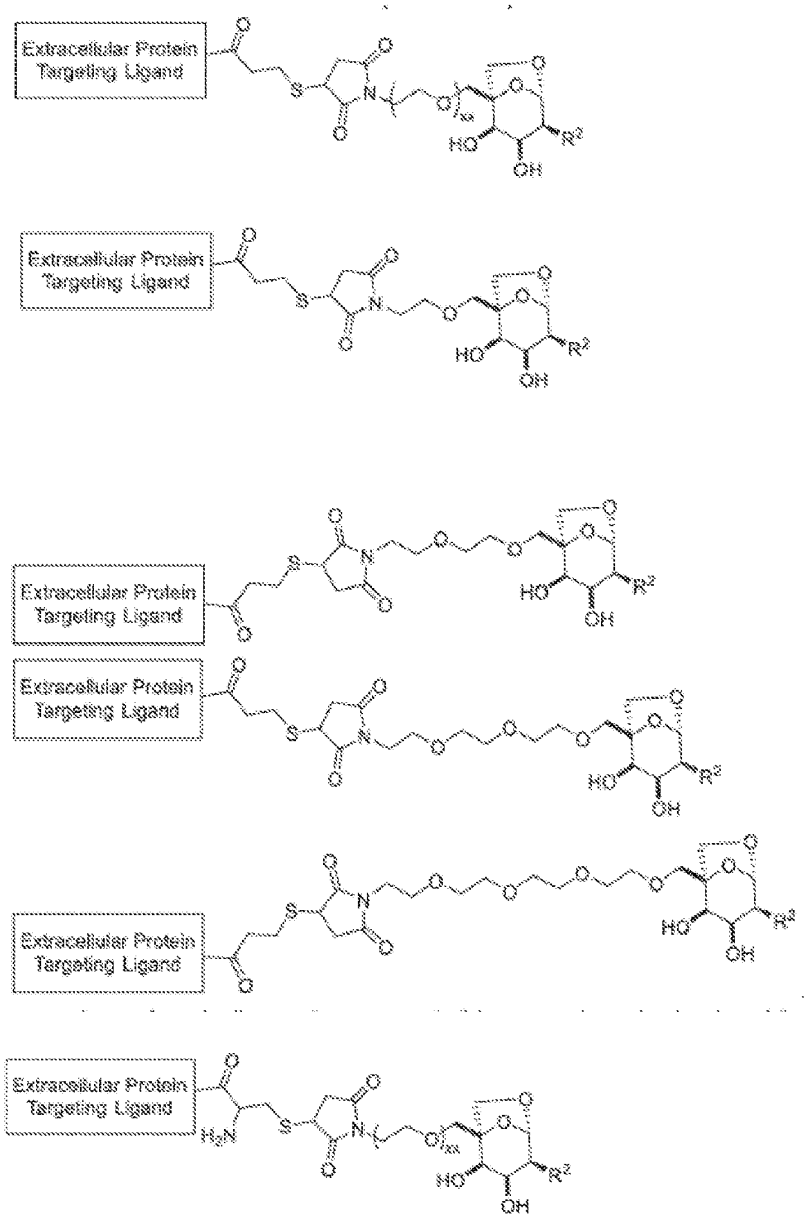
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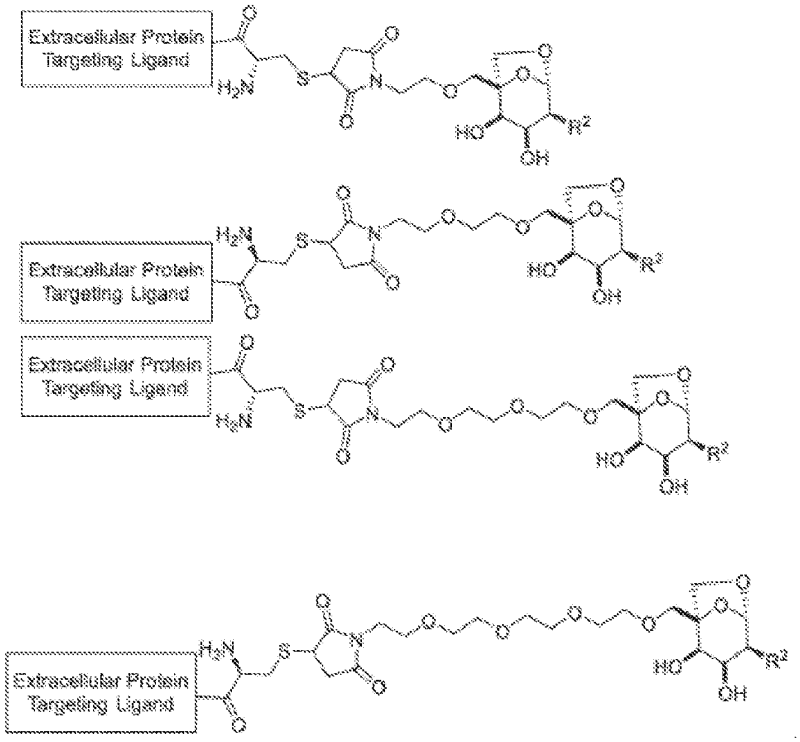
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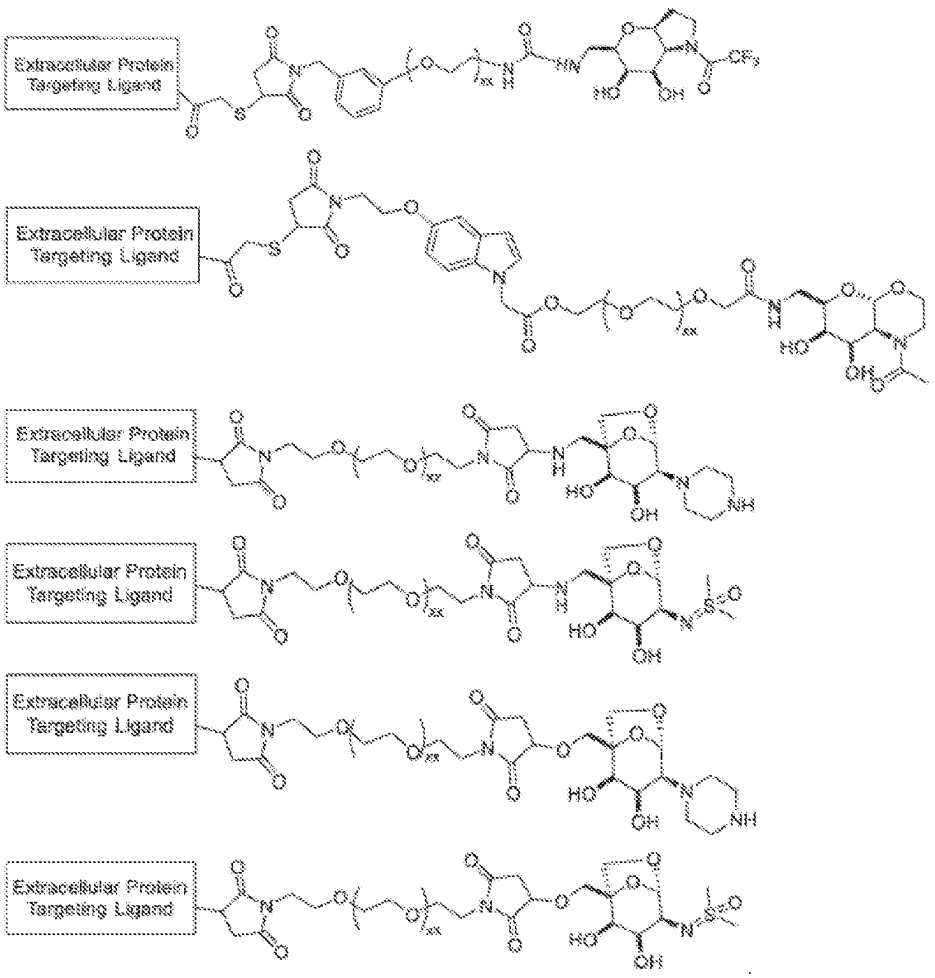
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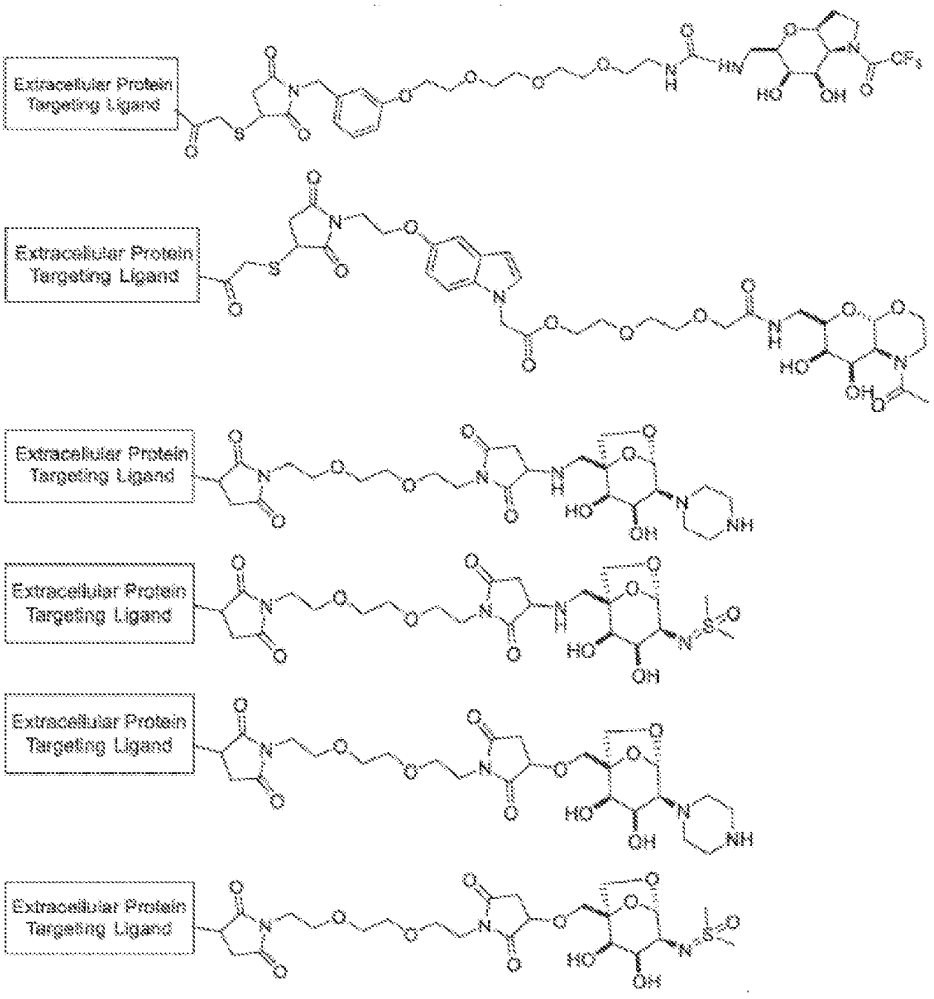
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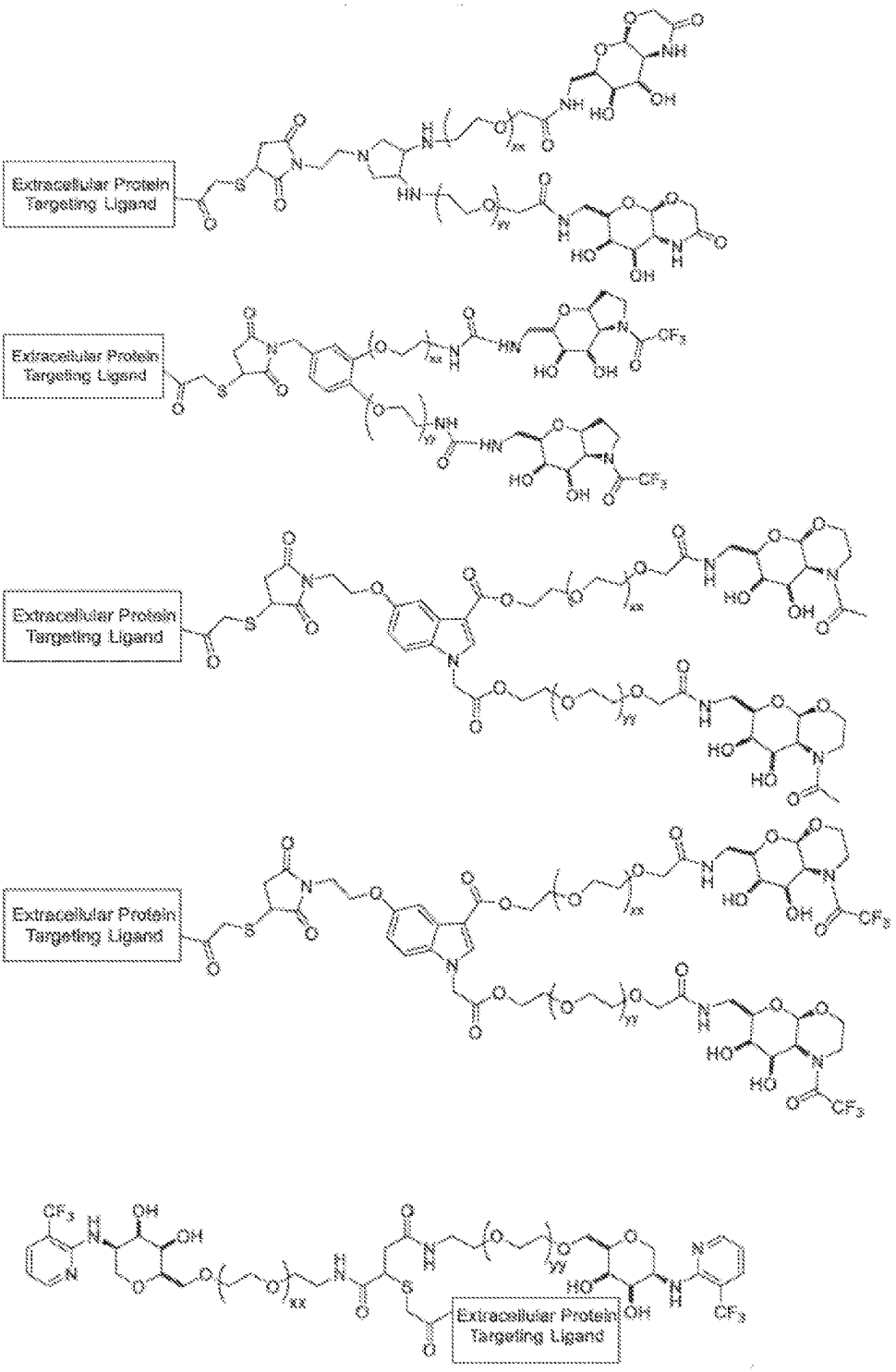
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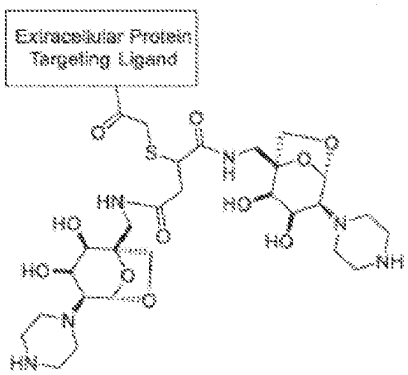
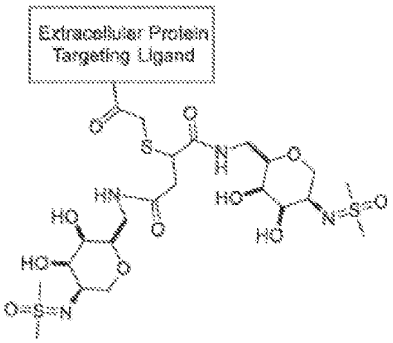

Extracellular Protein Targeting Ligand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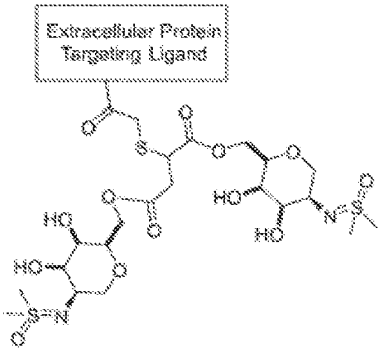
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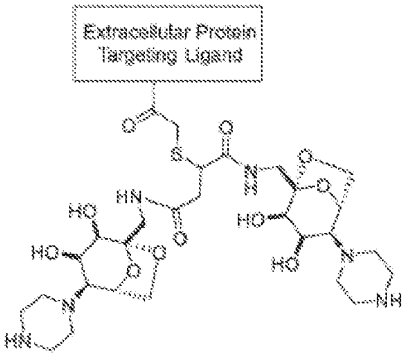
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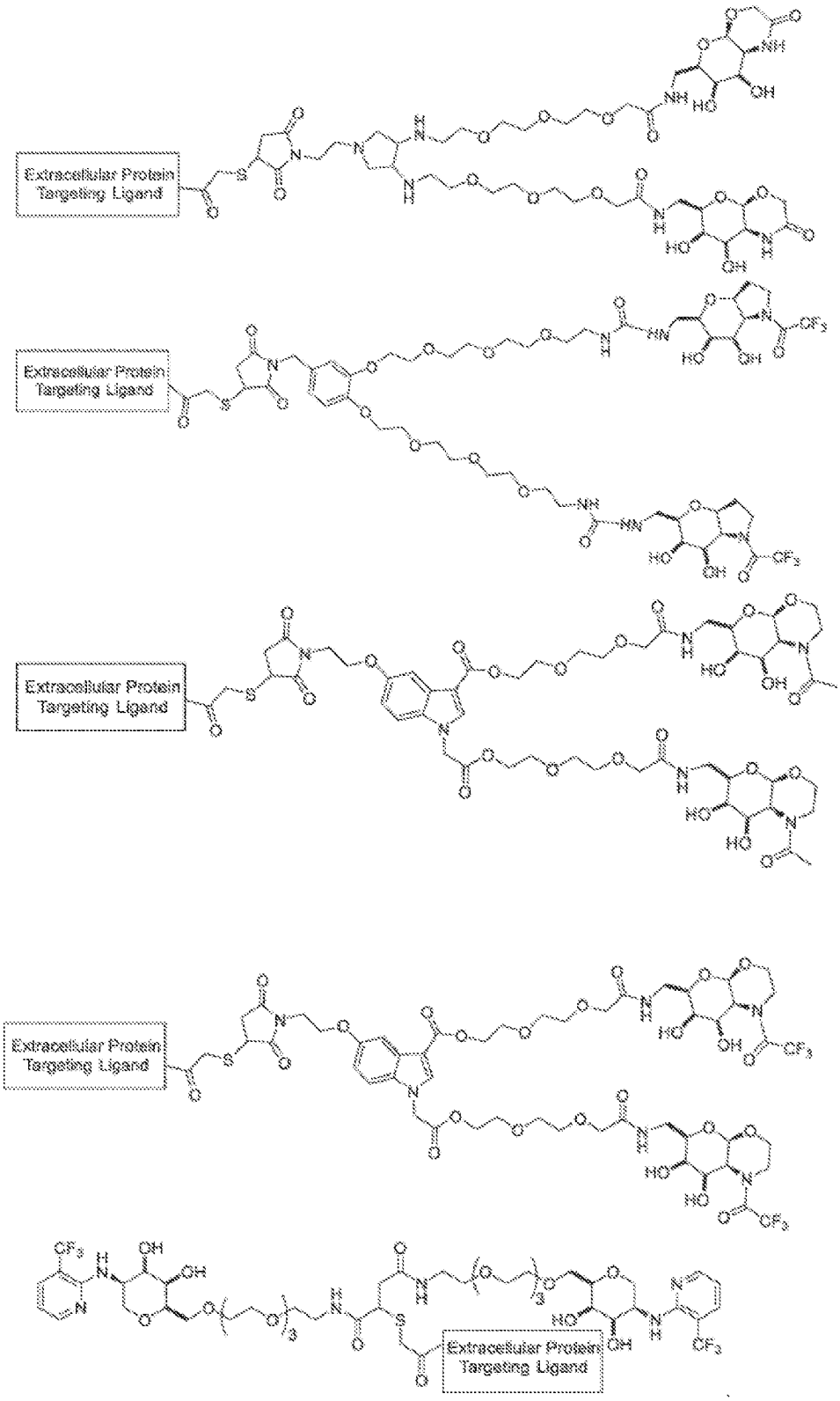
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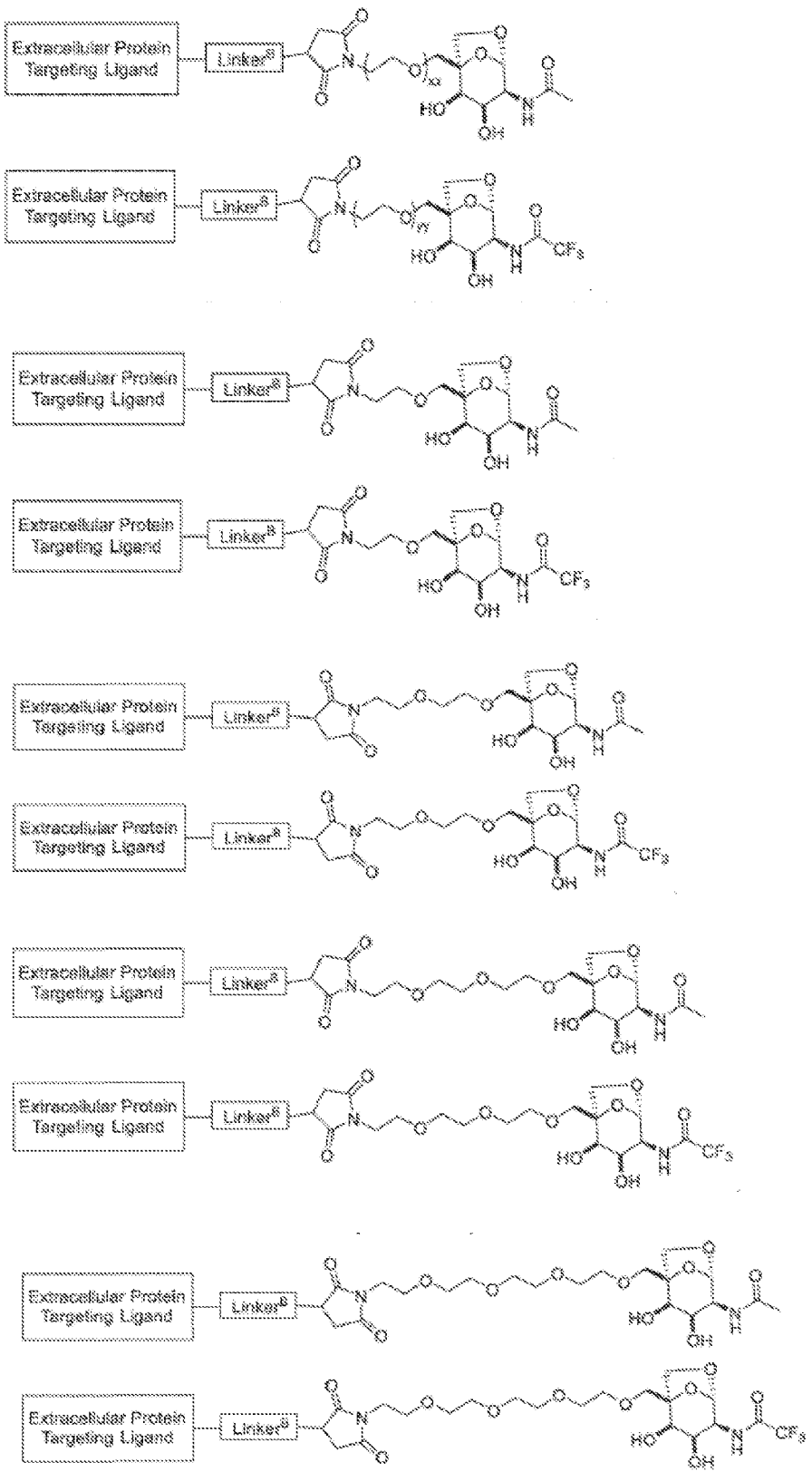
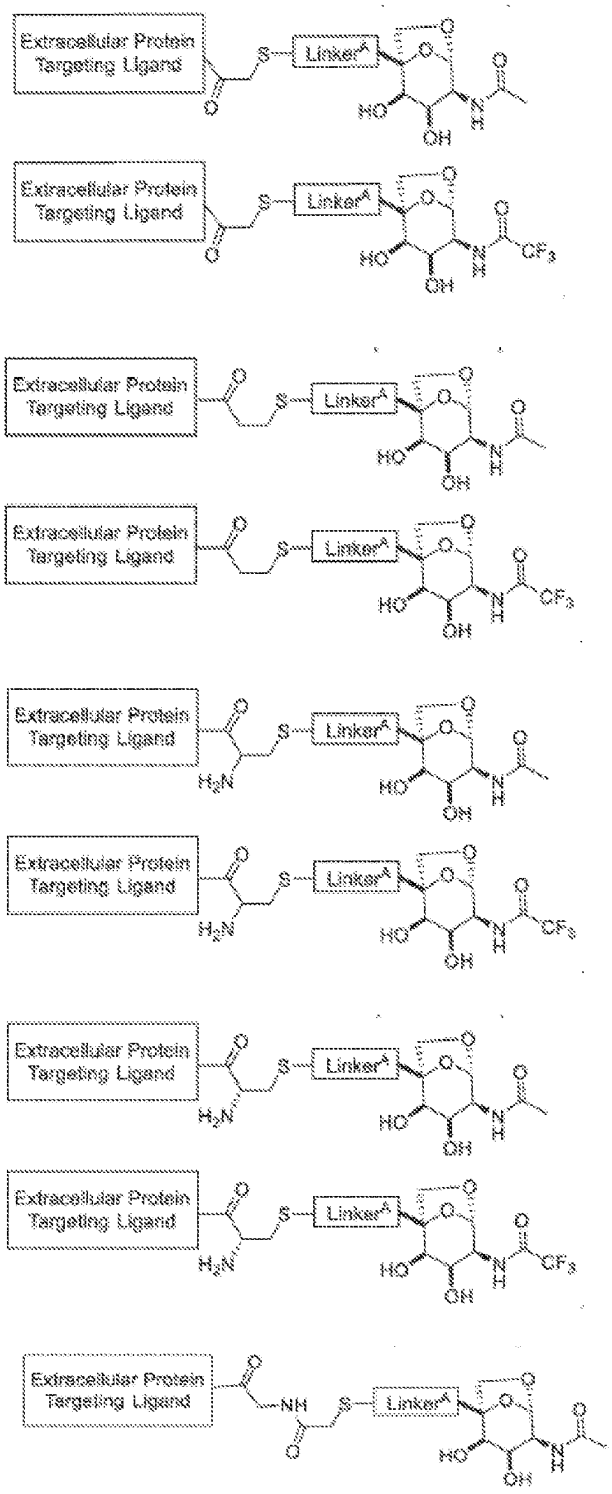
Extracellular Protein Targeting Ligand


Extracellular Protein Targeting Ligand
Linker^B
HO
OH
N
H
O
m
CF$_3$


Extracellular Protein Targeting Ligand
Linker^A
S
O
HO
OH
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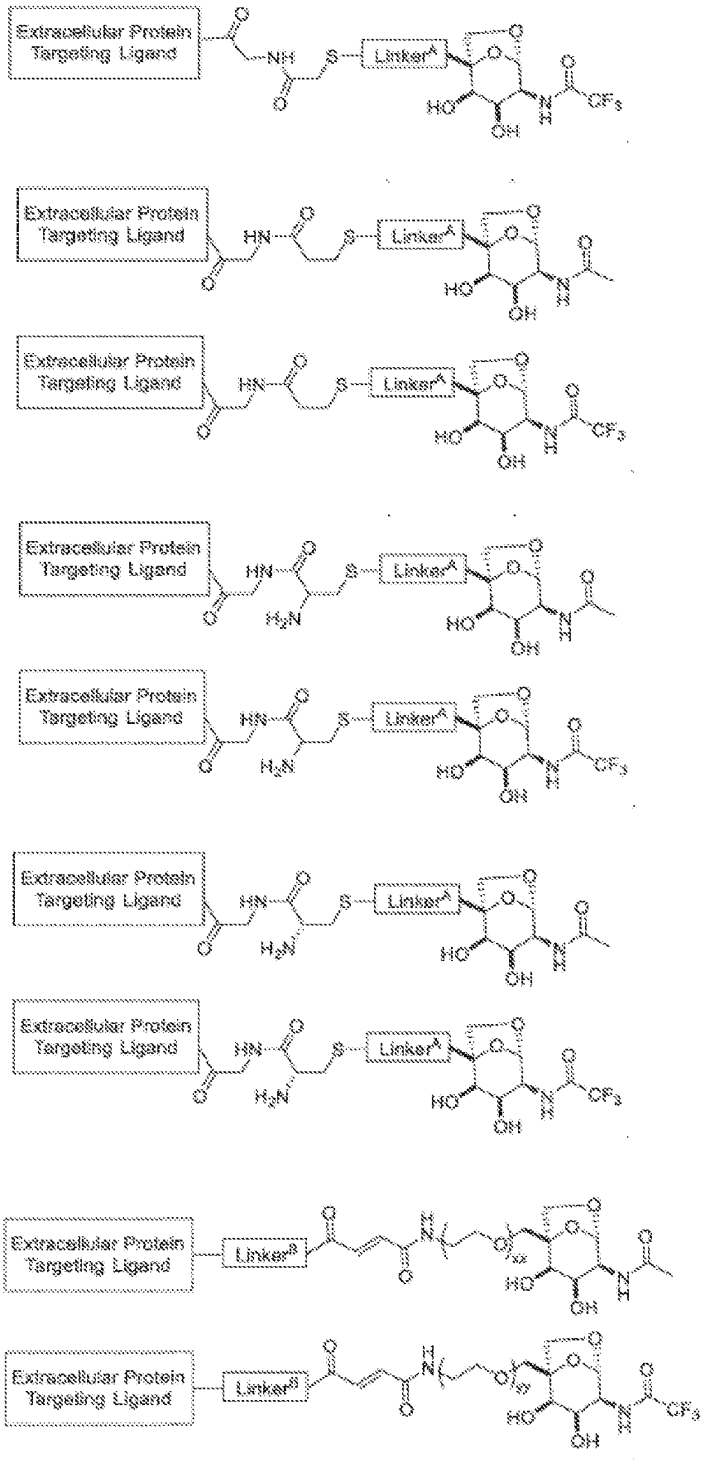
H
CF3
H2N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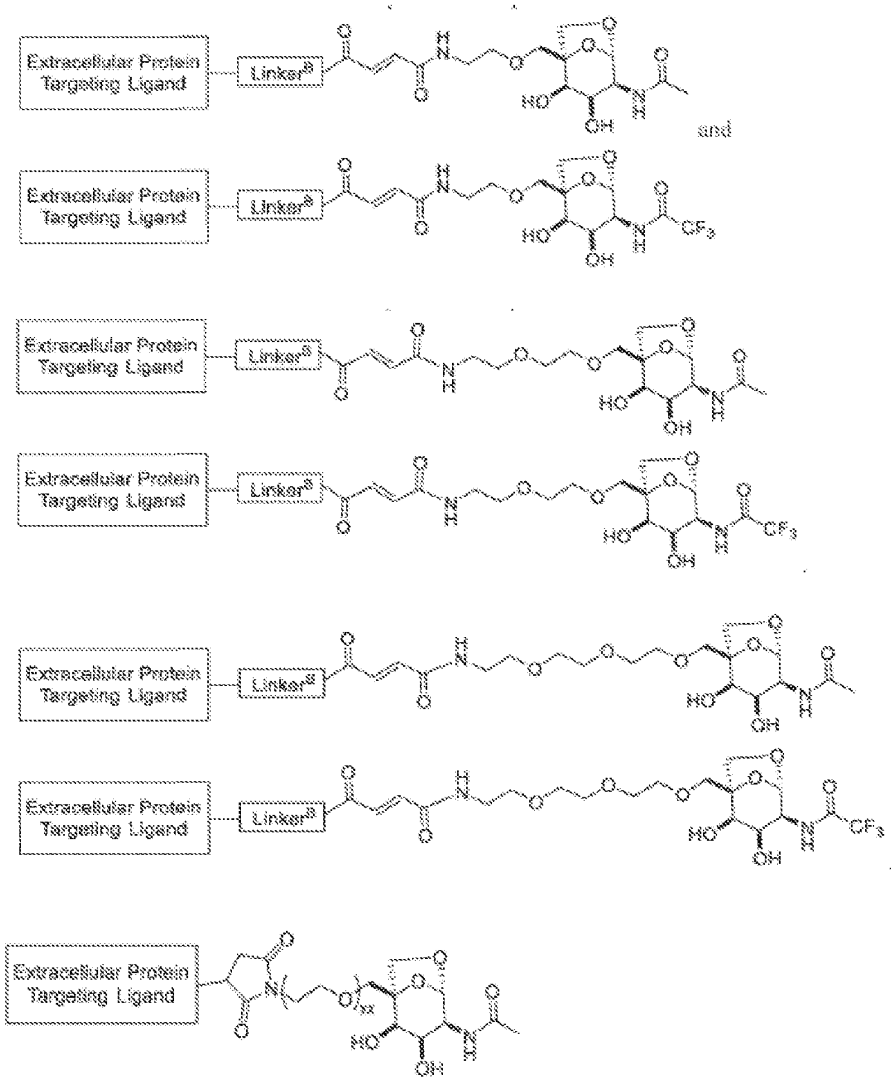
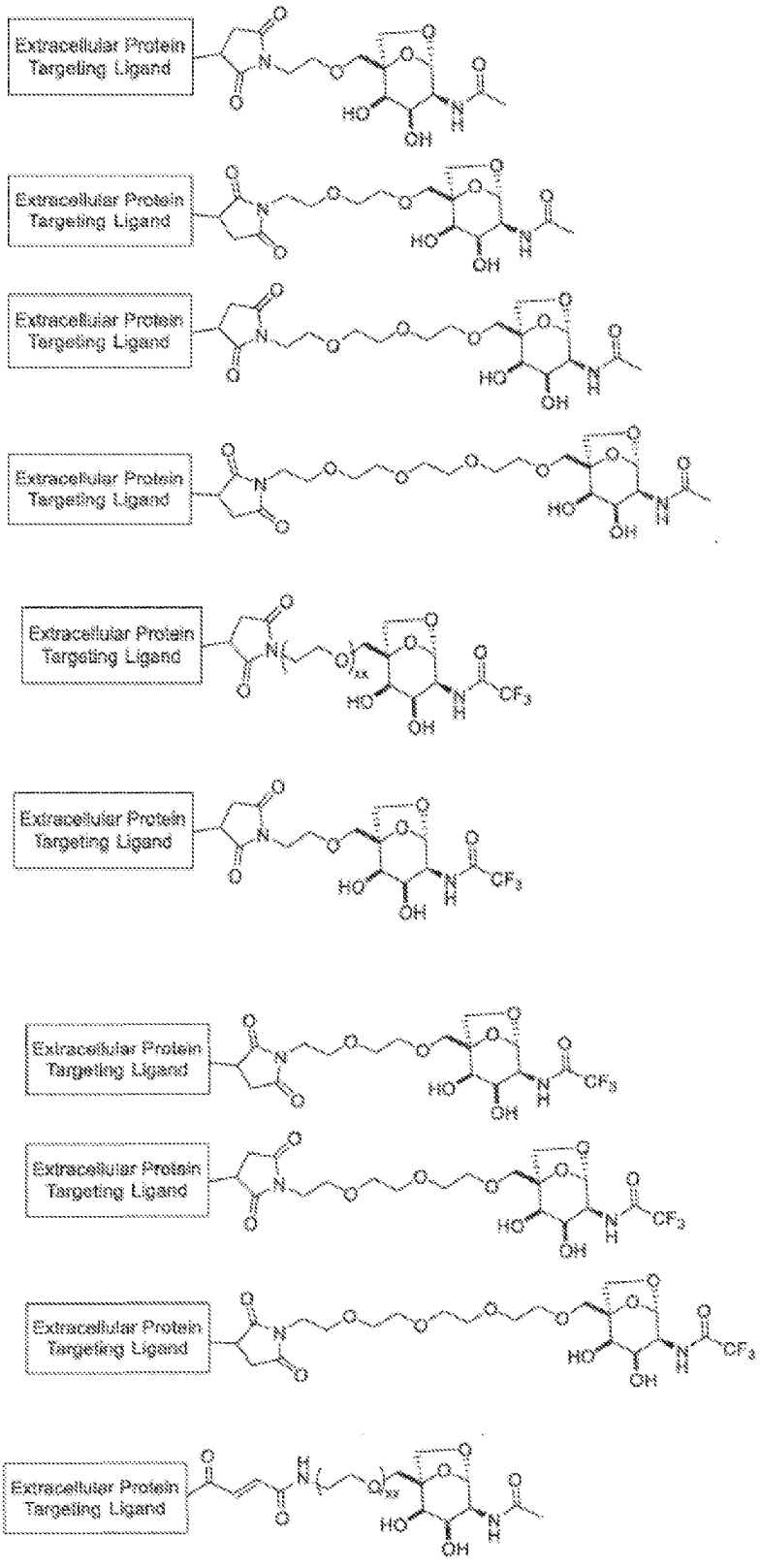
Linker^A
Linker^B


Extracellular Protein Targeting Ligand
Linker
and


Extracellular Protein Targeting Ligand
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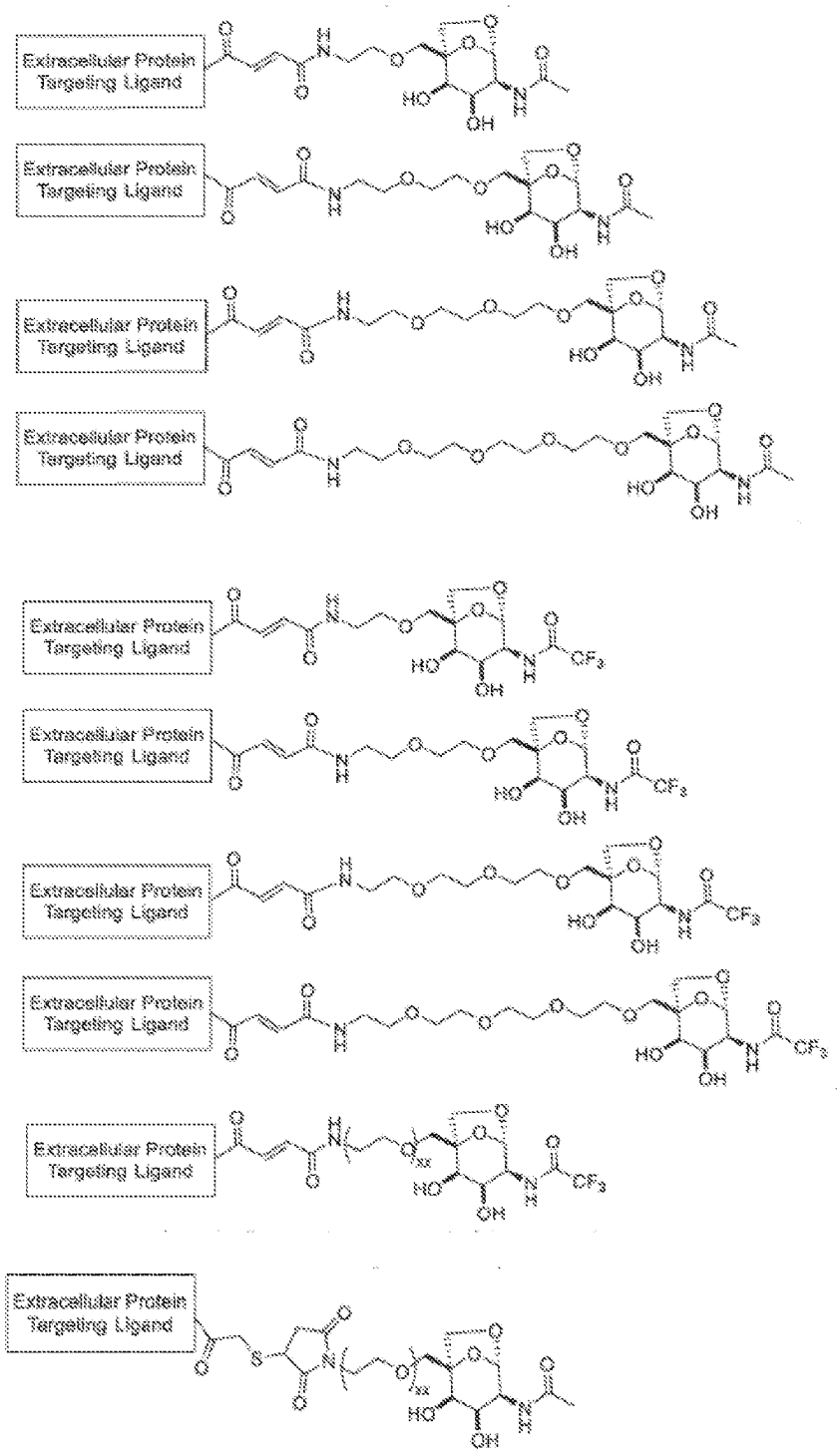
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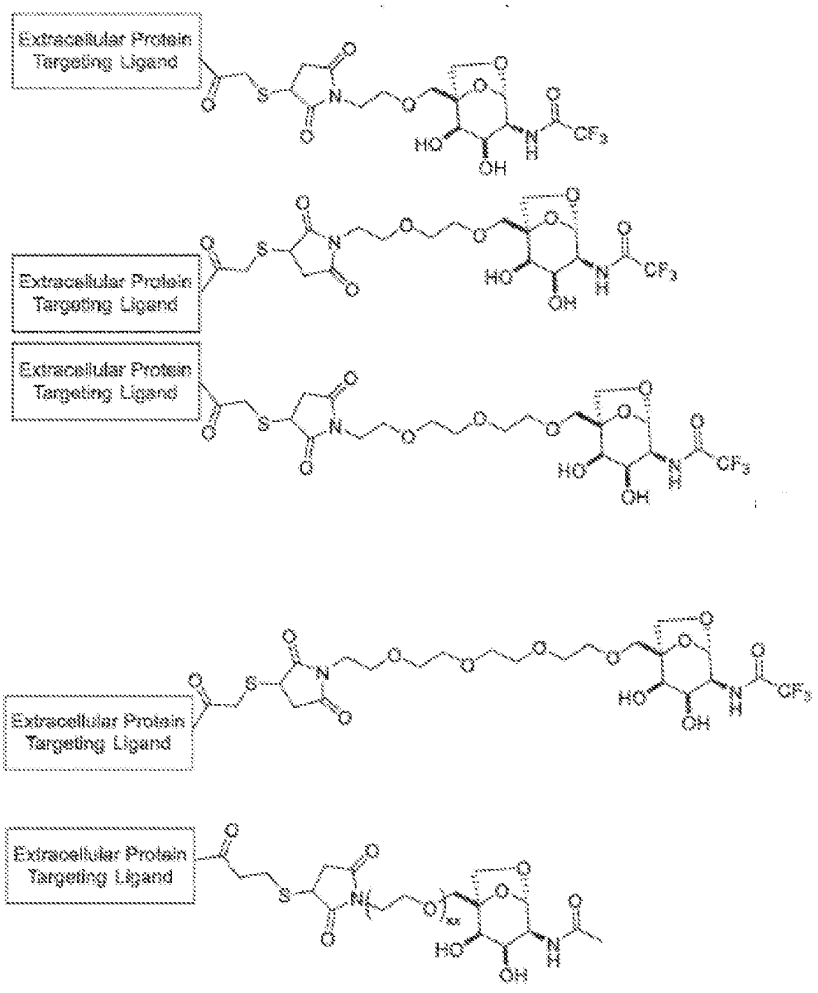
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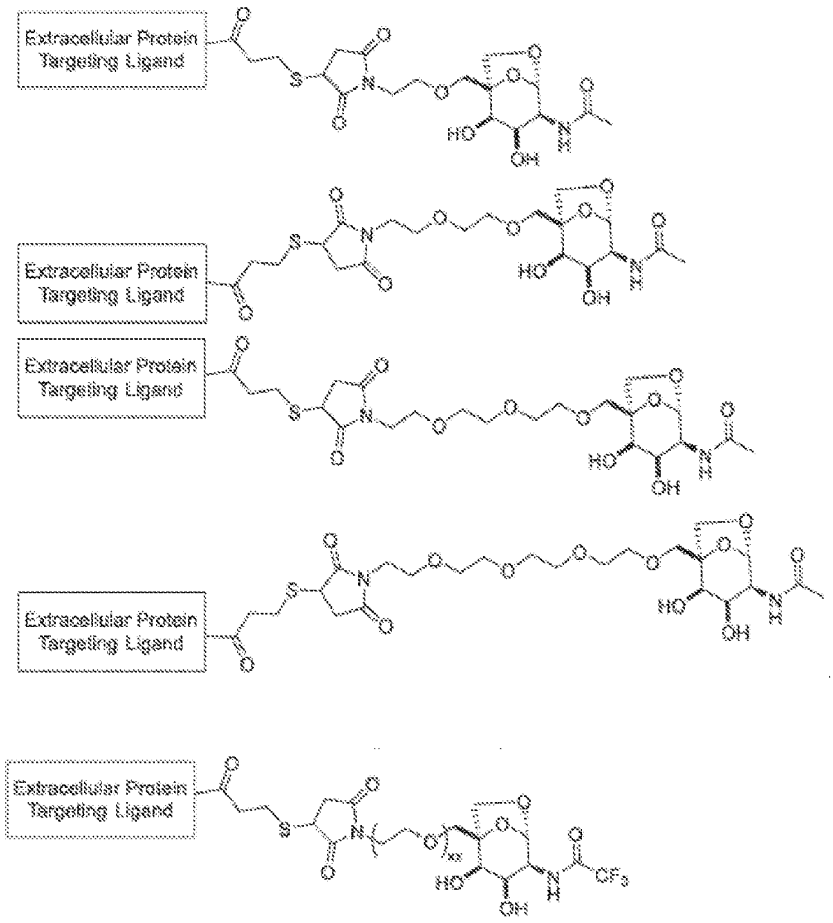
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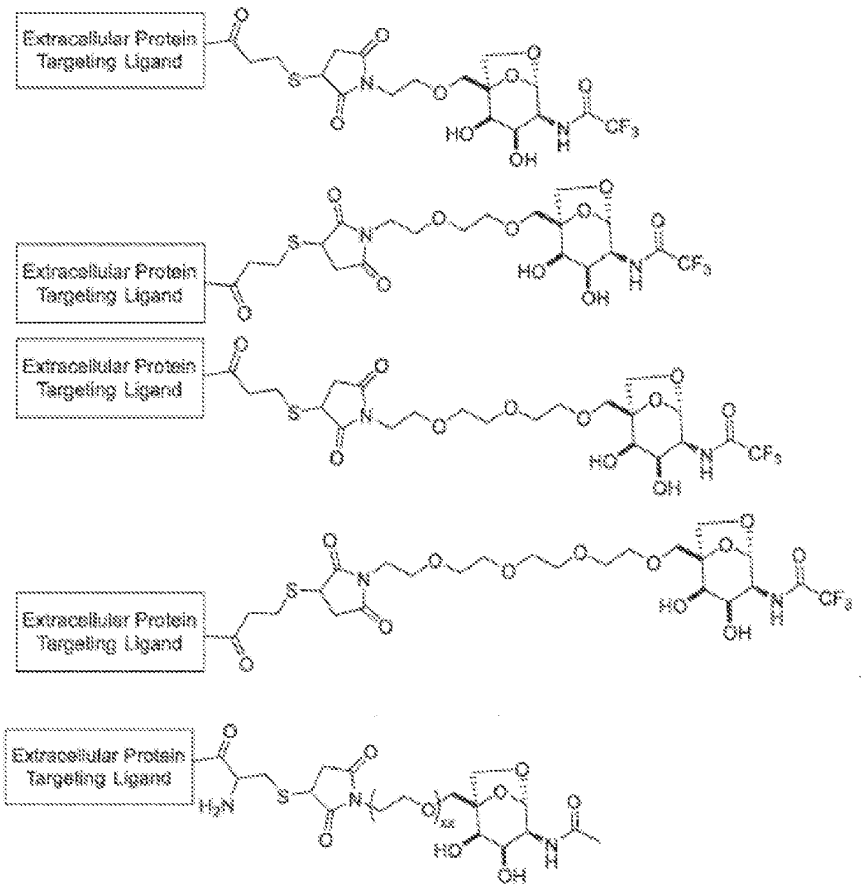
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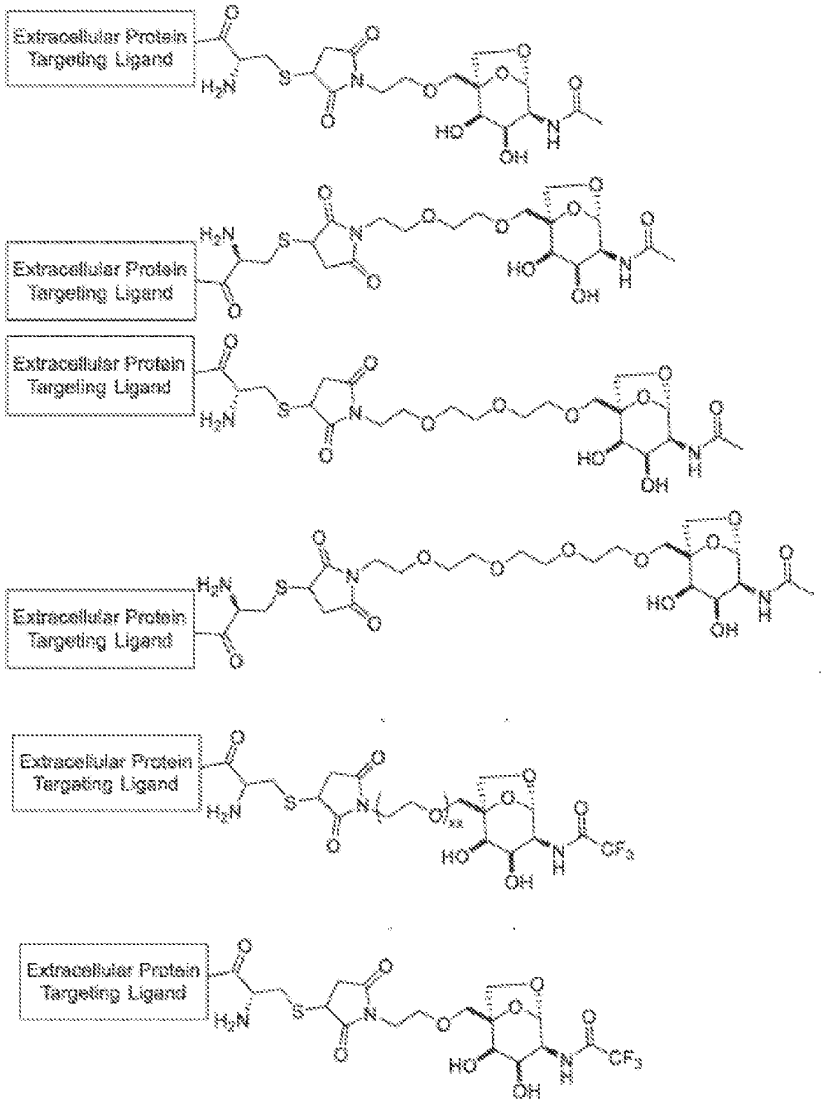
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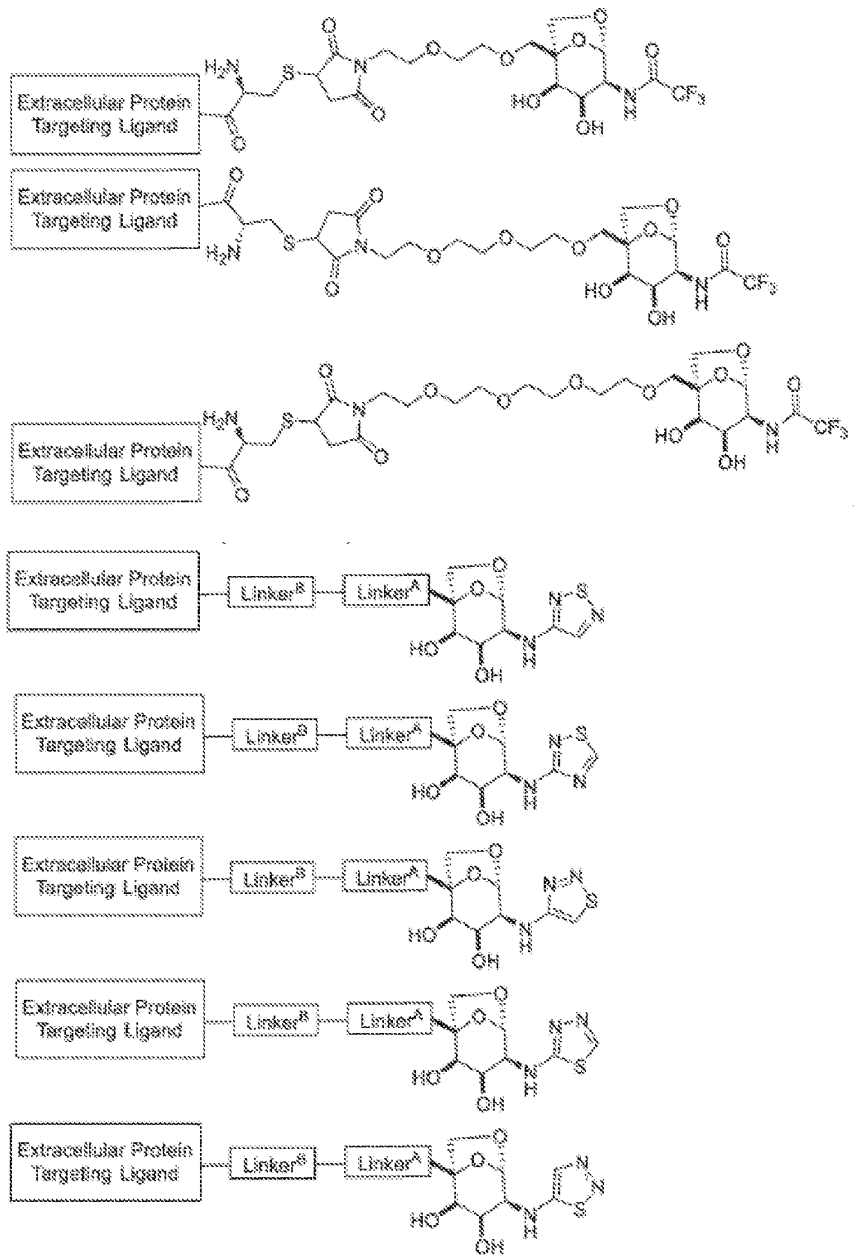
Extracellular Protein Targeting Ligand
Extracellular Protein Targeting Ligand
Extracellular Protein Targeting Ligand
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^B
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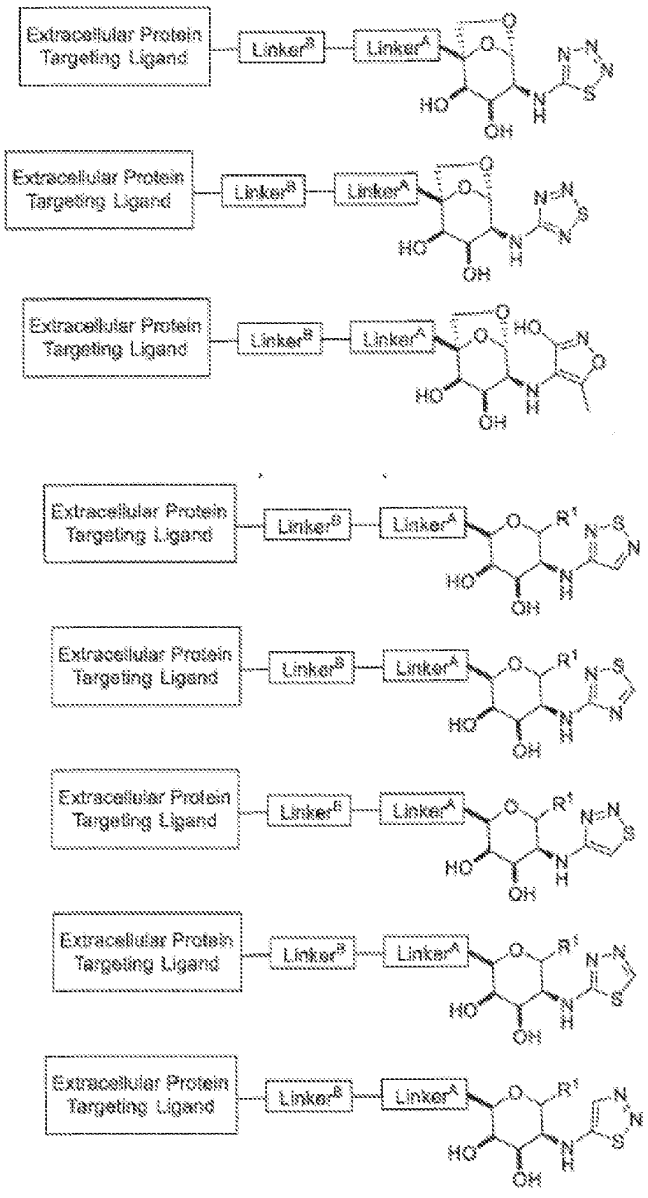
Linker^B
Linker^A


Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
N
H
O
N
S
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
N
H
O
N
S
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
HO
OH
N
H
O
N
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R^1
HO
OH
N
H
O
N
S
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R^1
HO
OH
N
H
O
N
S
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R^1
HO
OH
N
H
O
N
S
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R^1
HO
OH
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Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R^1
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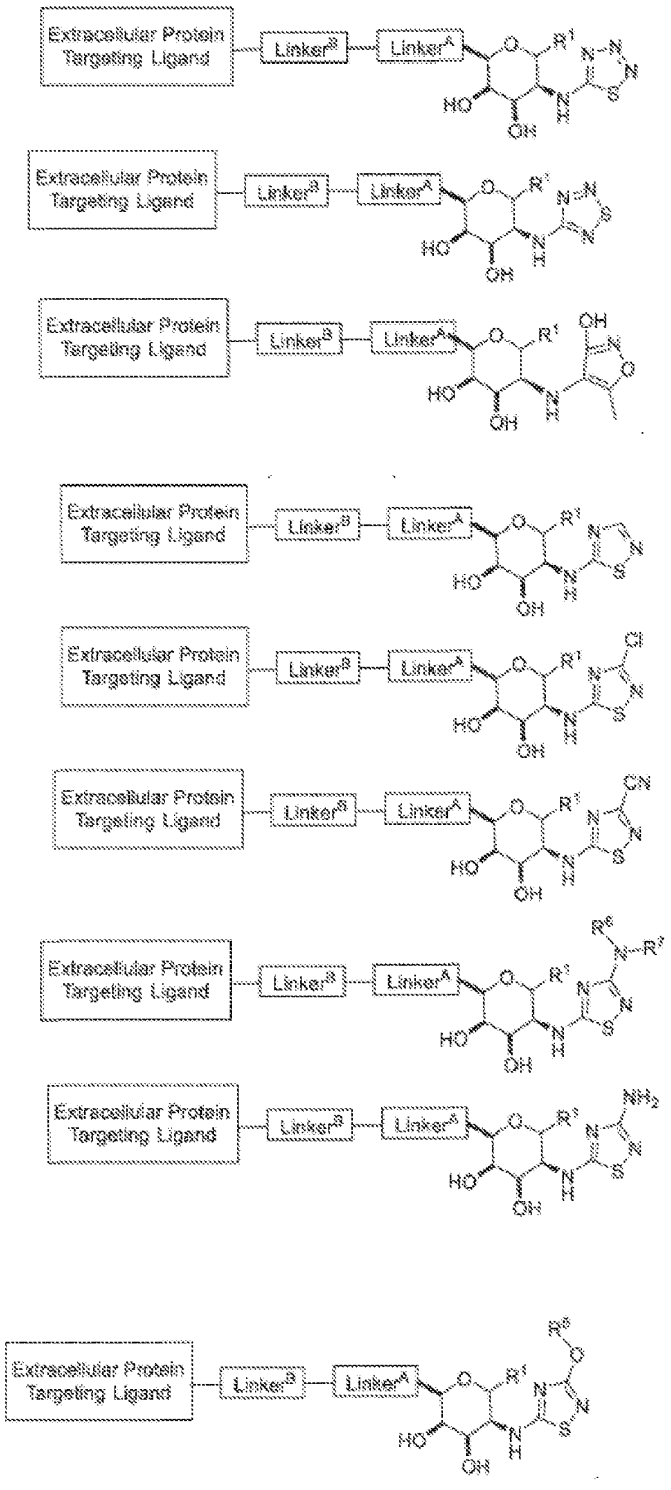
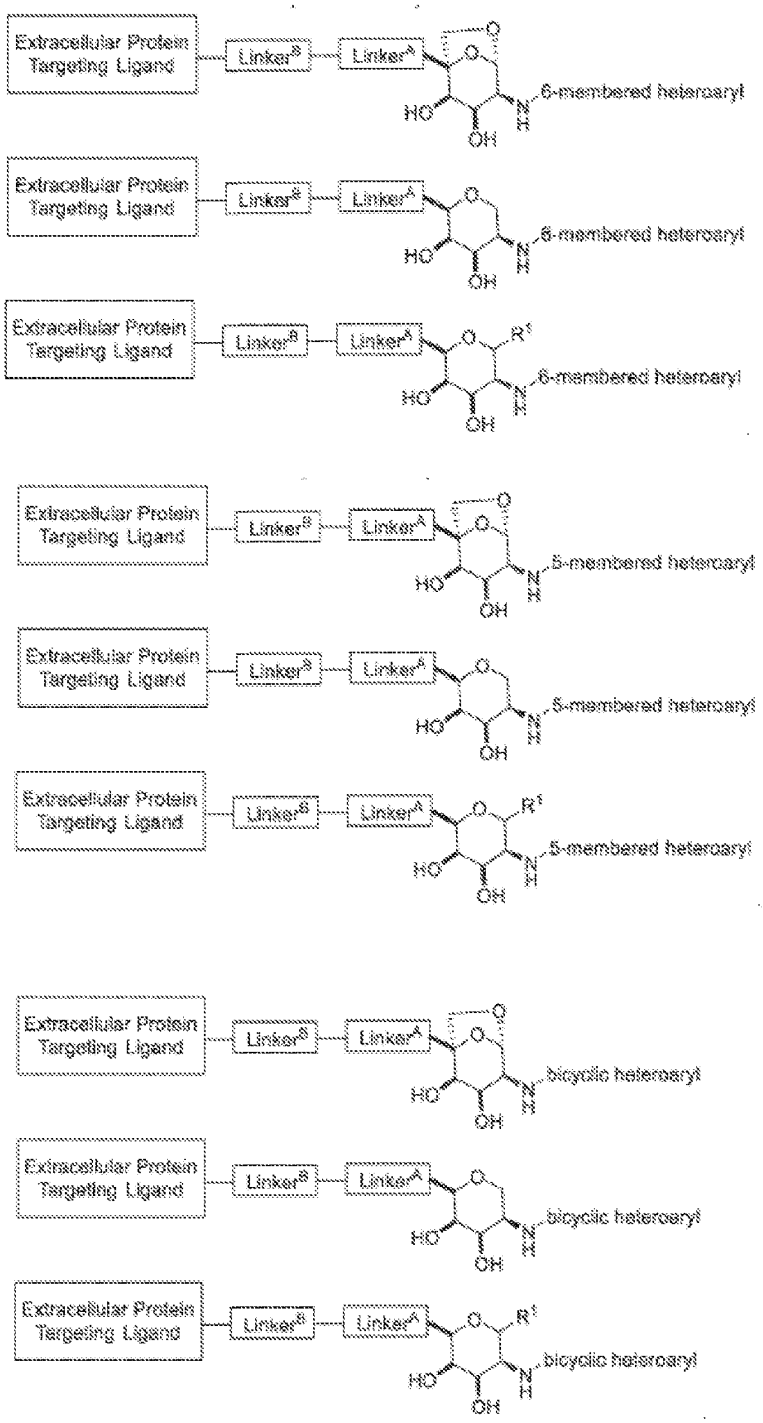
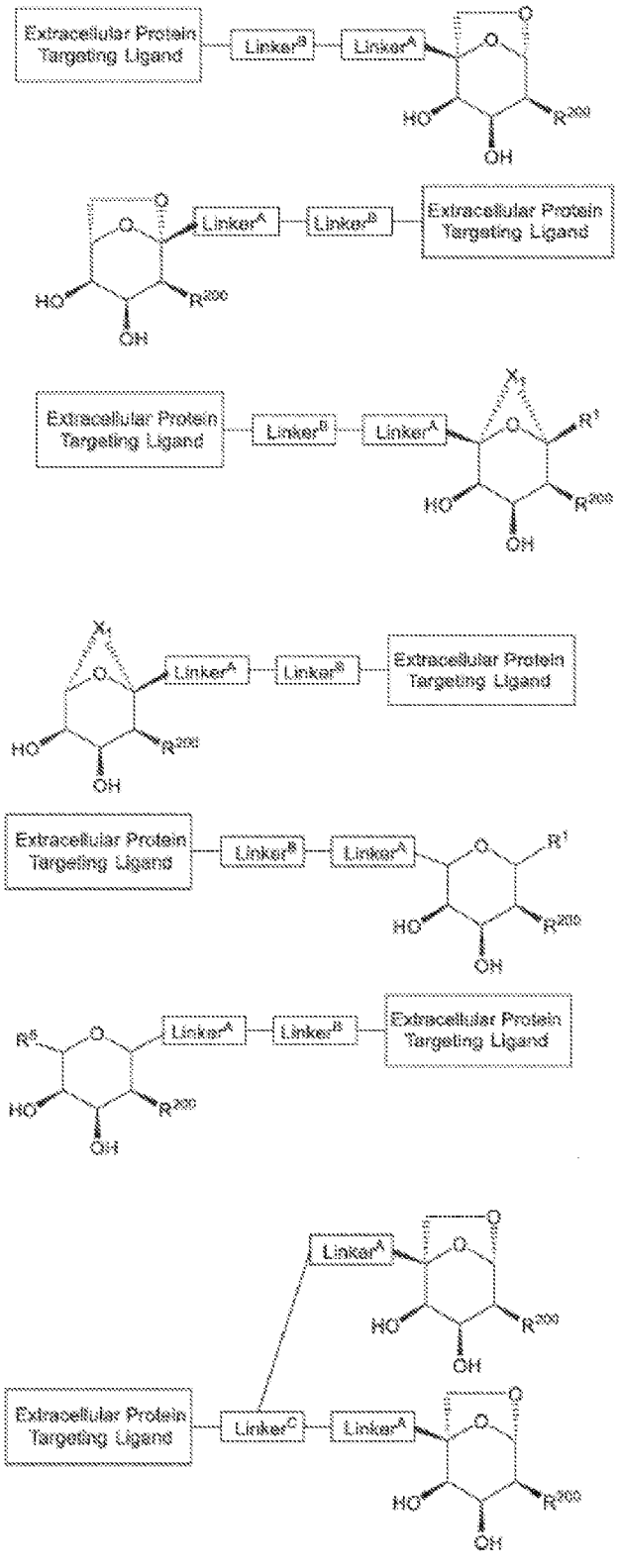
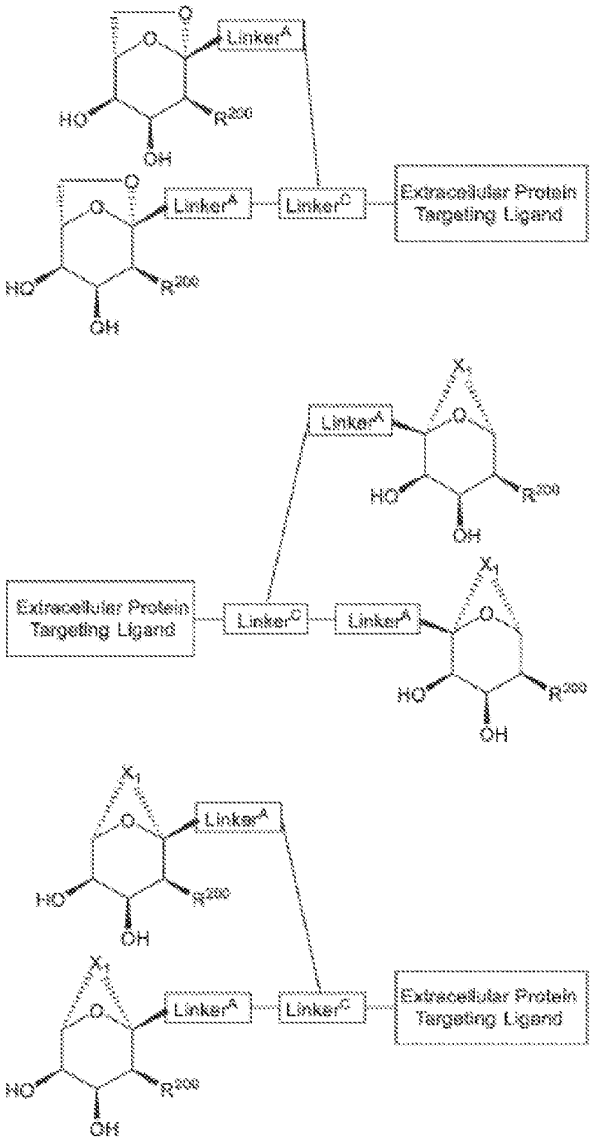
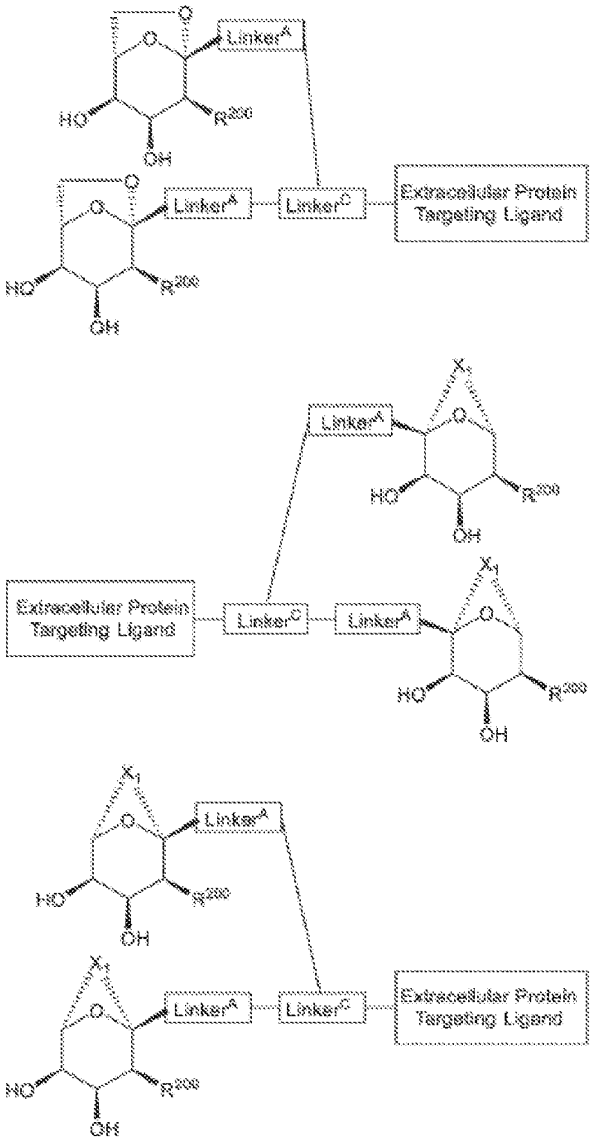
N
S

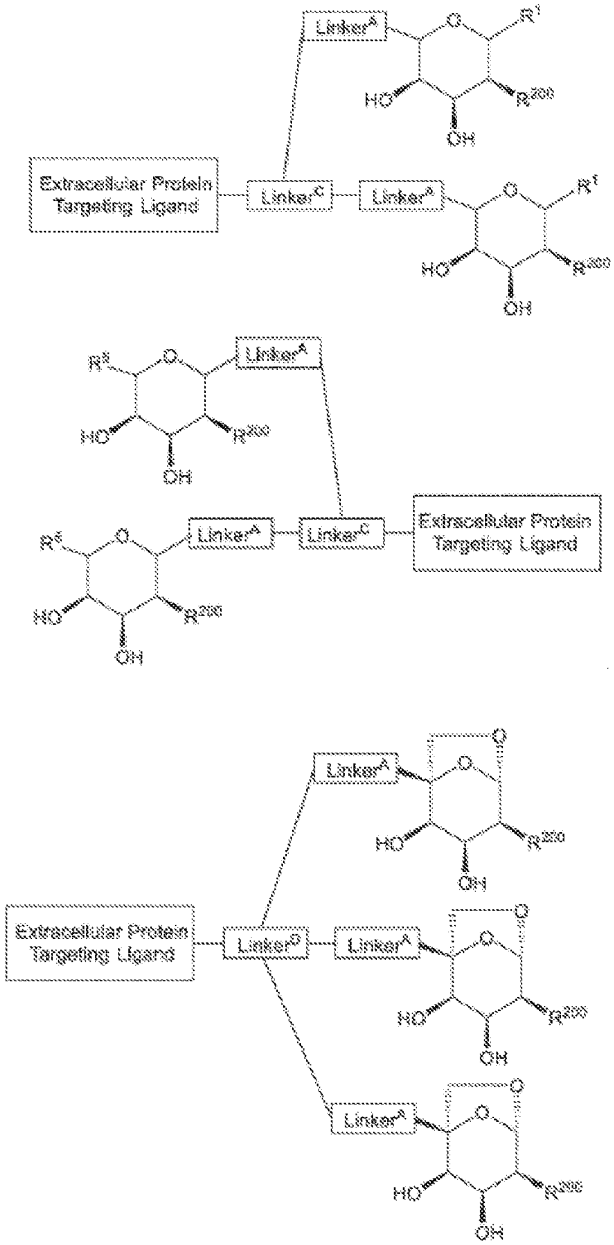

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
R^1
R^6
R^7
HO
OH
N
H
O
S
Cl
CN
NH2

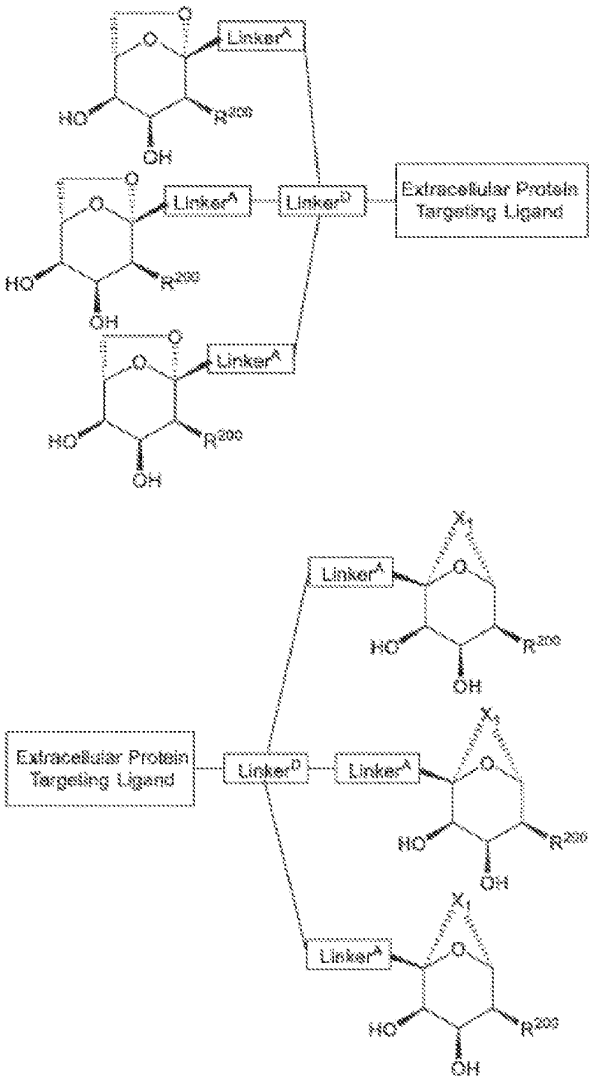

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
6-membered heteroaryl
5-membered heteroaryl
bicyclic heteroaryl

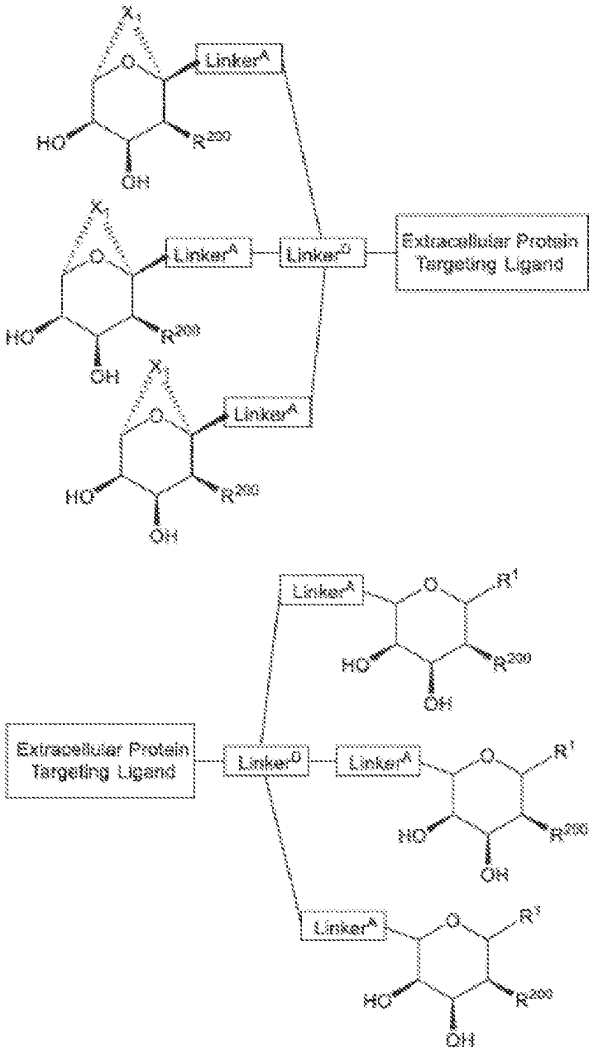

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^A
Linker^B
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^A
Linker^B
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^A
Linker^B
Extracellular Protein Targeting Ligand
Linker^A
Linker^C
Linker^A

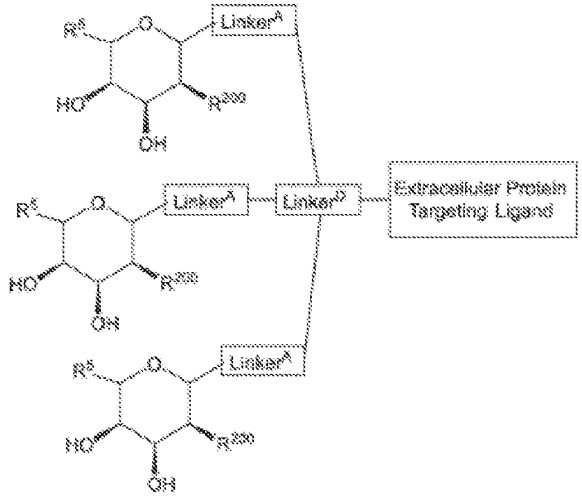

Linker^A
HO
R^200
OH
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
X1
Linker^A
HO
R^200
OH
Extracellular Protein Targeting Ligand
Linker^C
Linker^A
X1
HO
R^200
OH
X1
Linker^A
HO
R^200
OH
X1
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
HO
R^200
OH


Linker^A
HO
R^200
OH
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
X1
Linker^A
HO
R^200
OH
Extracellular Protein Targeting Ligand
Linker^C
Linker^A
X1
HO
R^200
OH
X1
Linker^A
HO
R^200
OH
X1
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
HO
R^200
OH

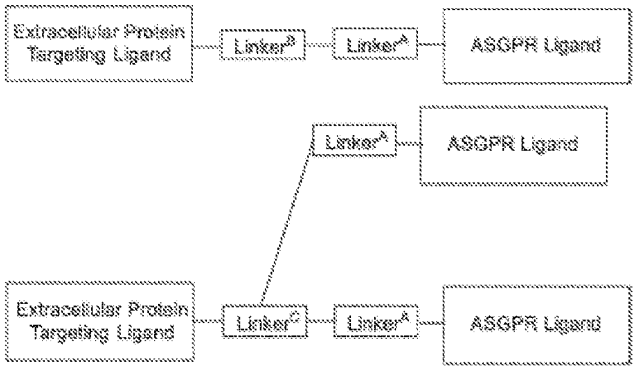

Linker^A
Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A


Linker^A
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A

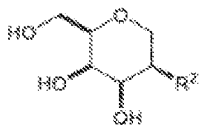

Linker^A
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A



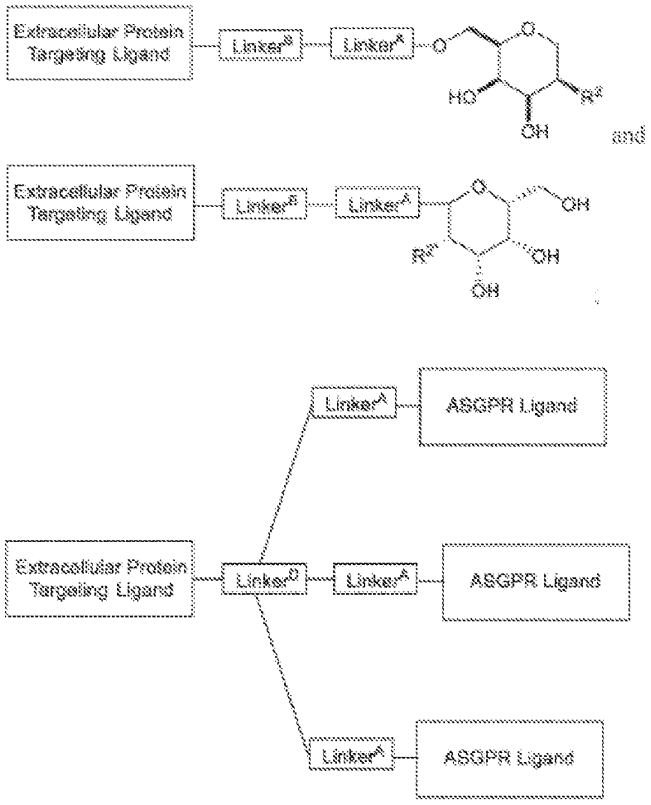
In one embodiment, the compound of Formula II is an Extracellular Protein degrading compound in which the ASGPR ligand is a ligand as described herein



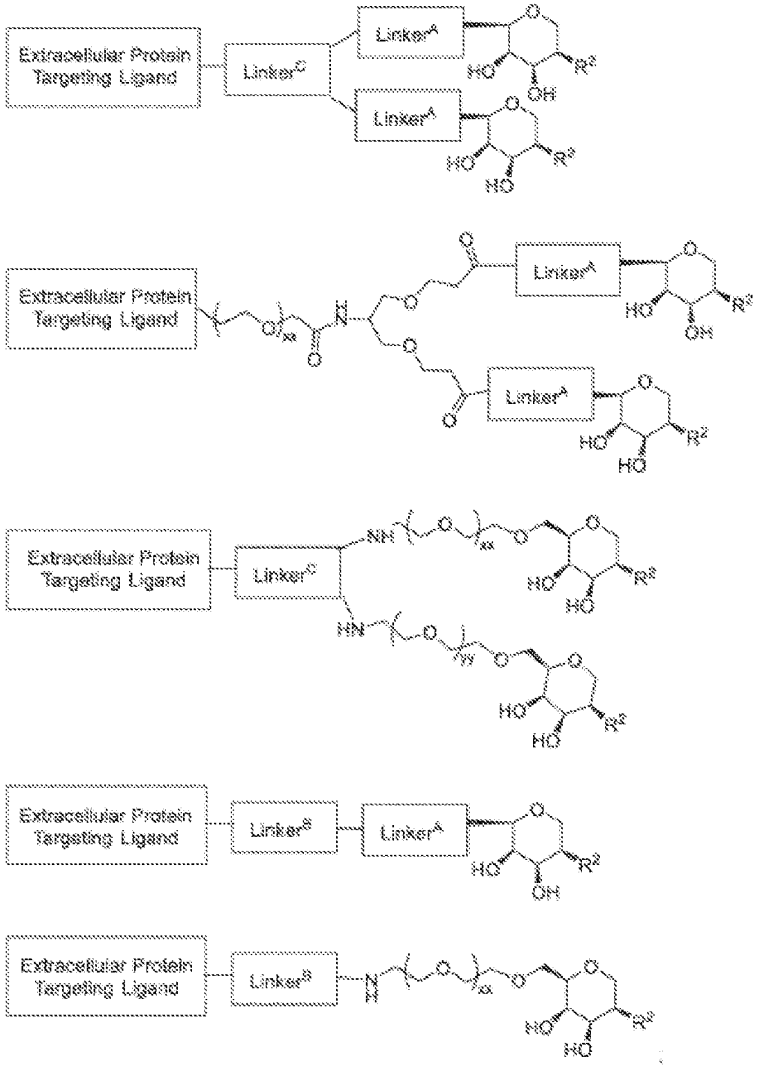
In one embodiment, in the compound of Formula II, the ASGPR ligand is linked at either the C1 or C5 (R^1 or R^5) position to form a degrading compound. In one embodiment, in the compound of Formula II, the ASGPR ligand is linked at C6. In various embodiments, when the ASGPR ligand is



then non- limiting examples of ASGPR binding compounds of Formula II include:

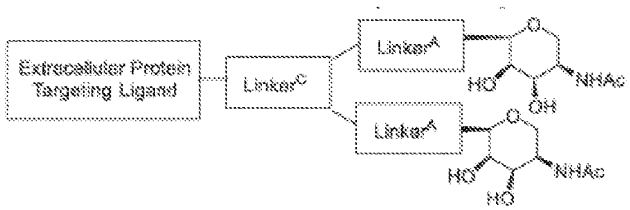


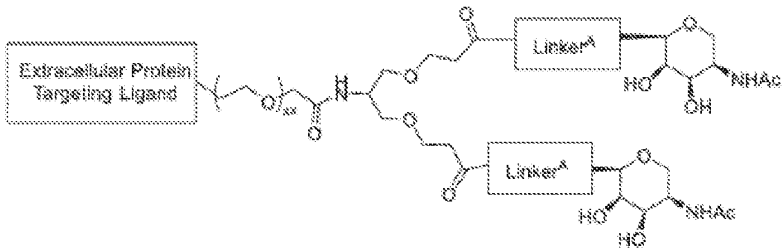
or the bi- or tri- substituted versions thereof or pharmaceutically acceptable salts thereof, where the bi- or tri- substitution refers to the number additional galactose derivatives attached to a linker moiety. In certain embodiments the compound of Formula II is selected from:

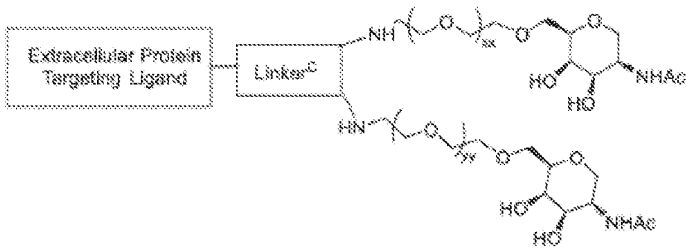


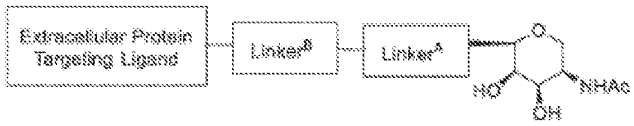
wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

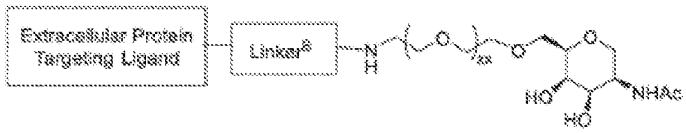
In certain embodiments, the compound of Formula II is selected from:

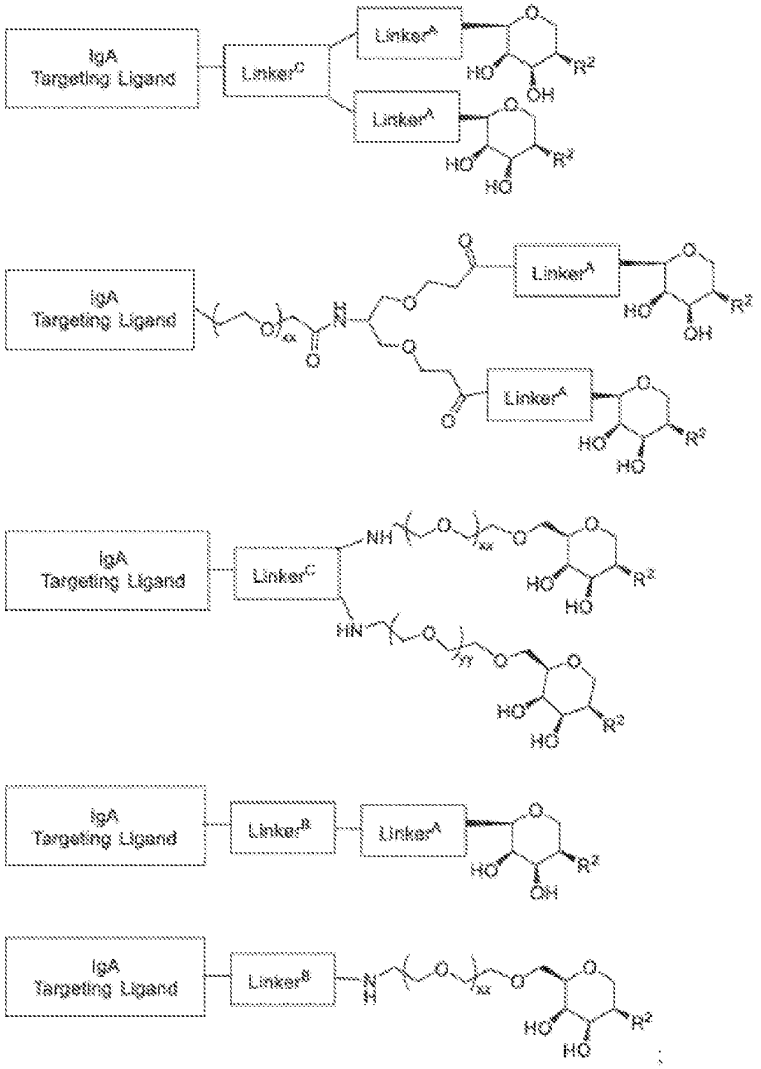

Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
HO
OH
NHAc
HO
HO
NHAc


Extracellular Protein Targeting Ligand
Linker^A
Linker^A
HO
OH
NHAc
HO
HO
NHAc


Extracellular Protein Targeting Ligand
Linker^C
NH
HN
HO
HO
NHAc
HO
HO
NHAc

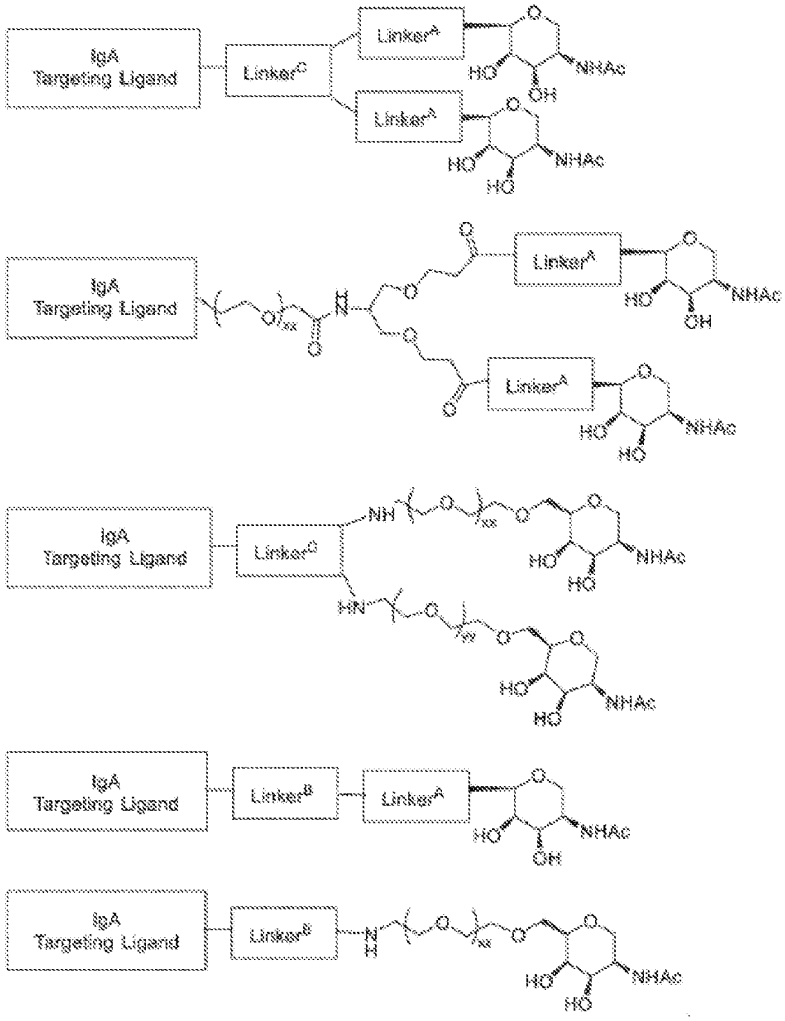

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
NHAc

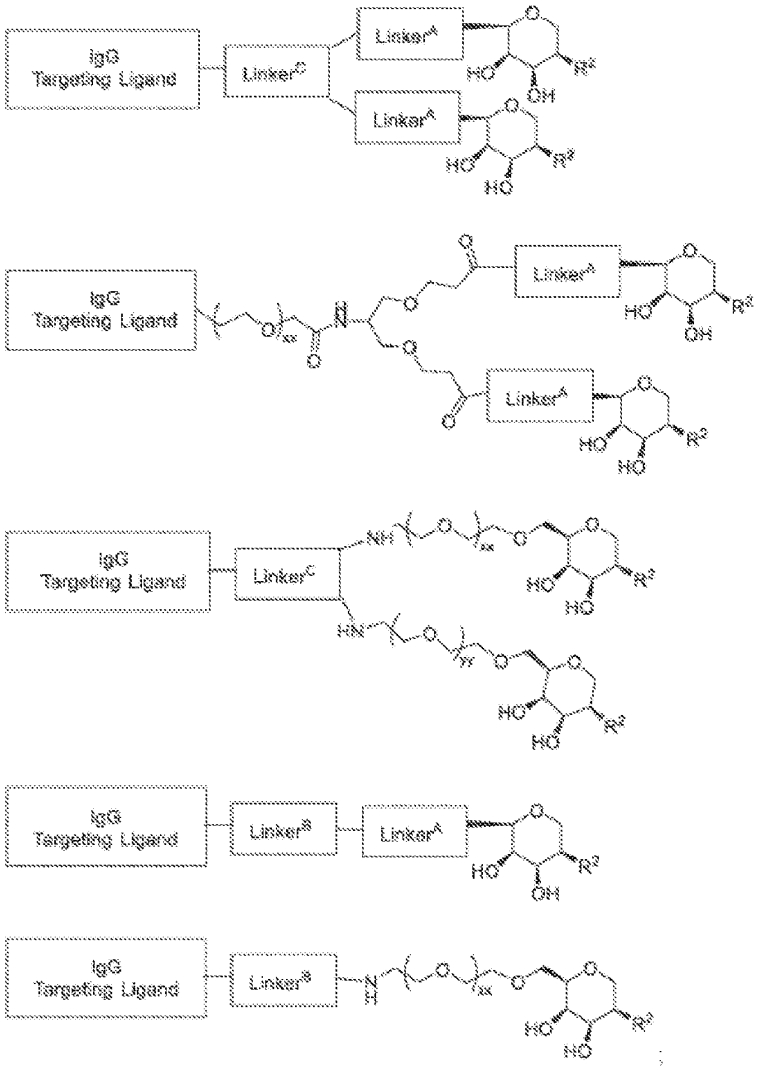

Extracellular Protein Targeting Ligand
Linker^B
N
H
HO
HO
NHAc



wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

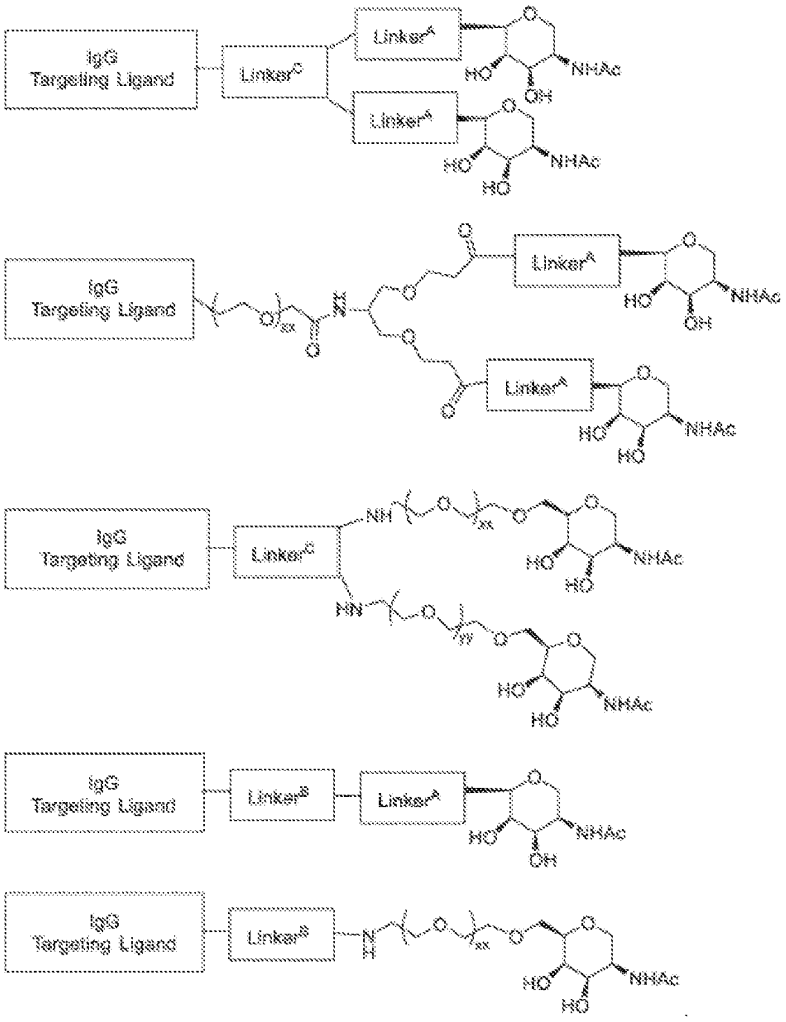
In certain embodiments, the compound of Formula II is selected from:

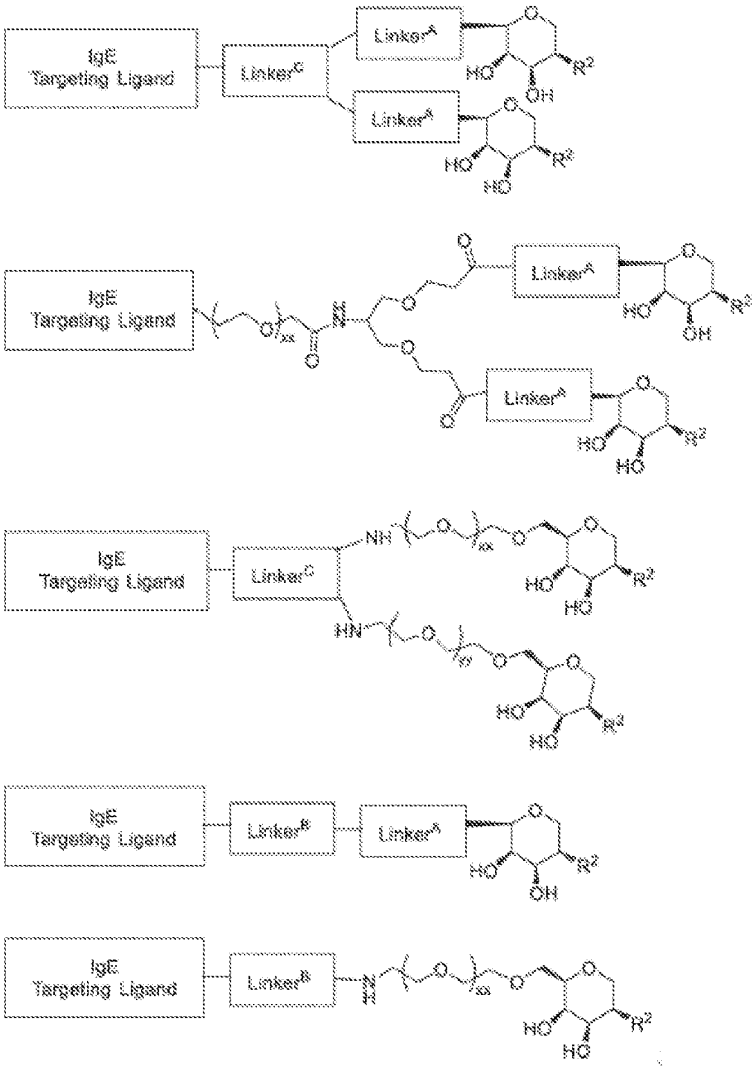

IgA Targeting Ligand
Linker^C
Linker^A
Linker^A
HO
NHAc
OH
HO
NHAc
HO
IgA Targeting Ligand
Linker^A
HO
NHAc
OH
Linker^A
HO
NHAc
HO
IgA Targeting Ligand
Linker^C
NH
HO
NHAc
HO
HN
HO
NHAc
HO
IgA Targeting Ligand
Linker^B
Linker^A
HO
NHAc
OH
IgA Targeting Ligand
Linker^B
N H
HO
NHAc
HO



wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

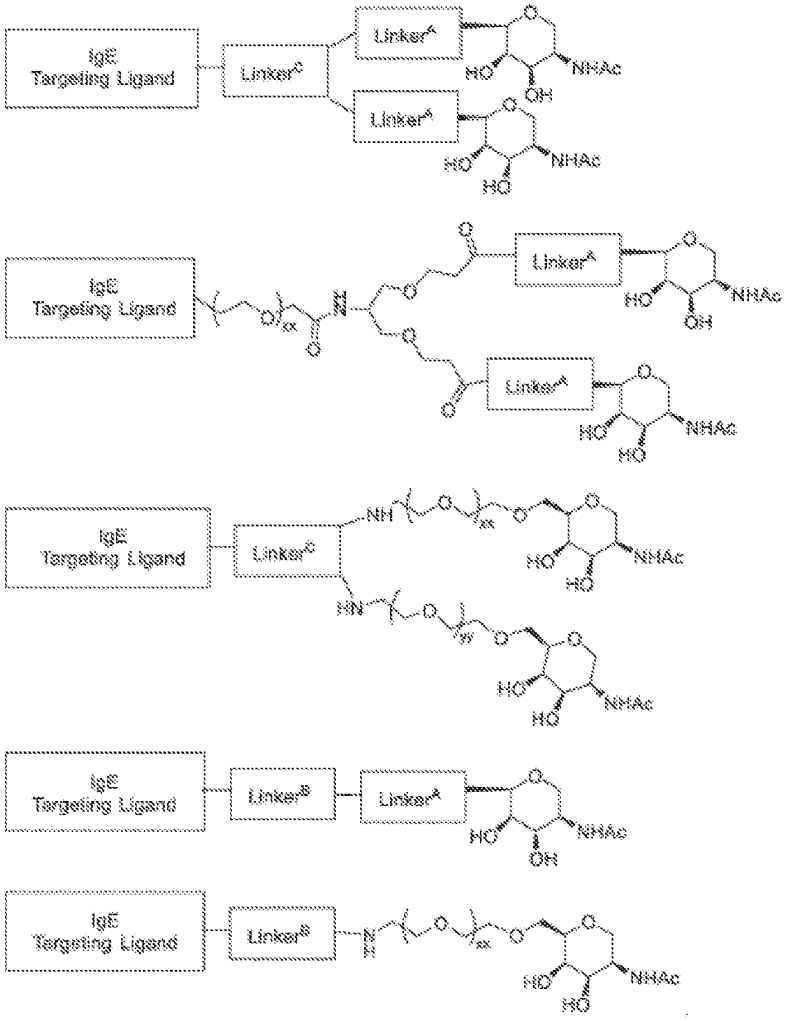
In certain embodiments, the compound of Formula II is selected from:

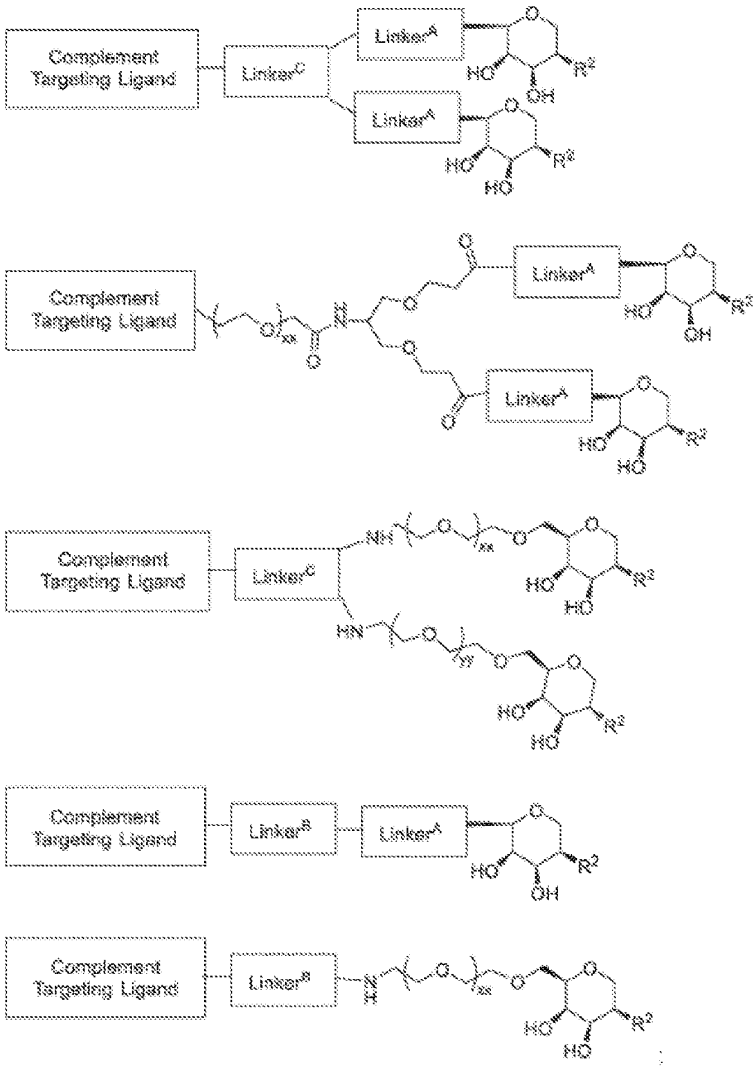

IgG Targeting Ligand
Linker^C
Linker^A
Linker^A
NHAc
NHAc
IgG Targeting Ligand
Linker^A
Linker^A
NHAc
NHAc
IgG Targeting Ligand
Linker^C
NHAc
NHAc
IgG Targeting Ligand
Linker^B
Linker^A
NHAc
IgG Targeting Ligand
Linker^B
NHAc



wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

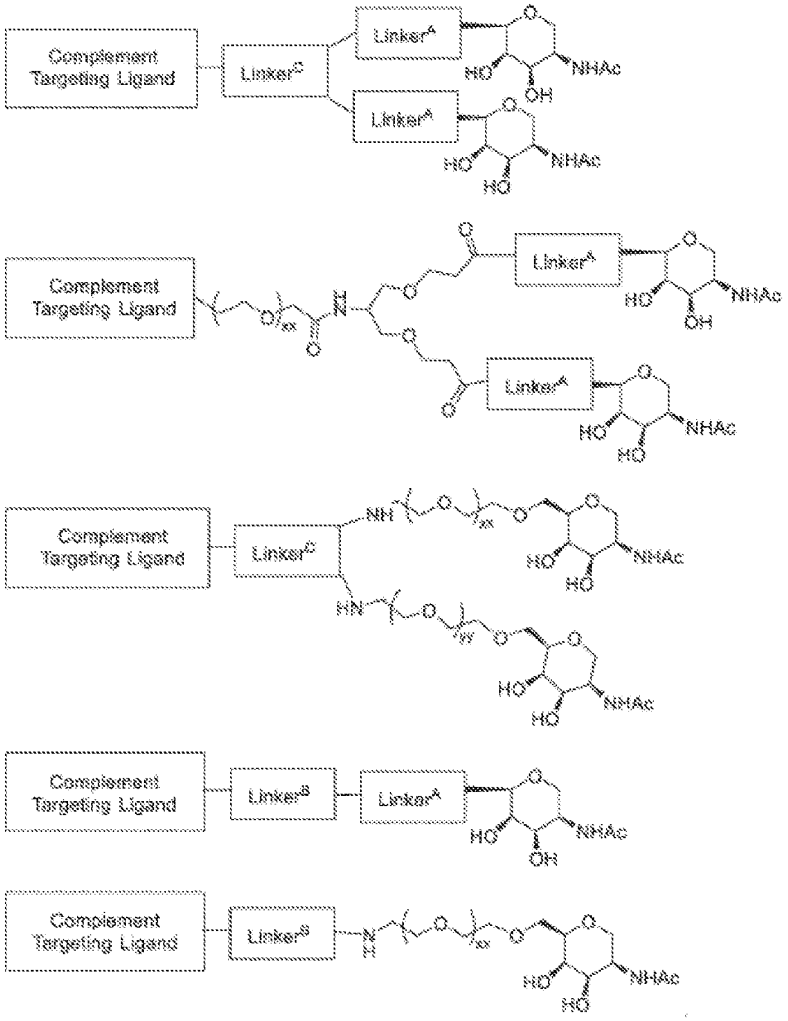
In certain embodiments, the compound of Formula II is selected from:

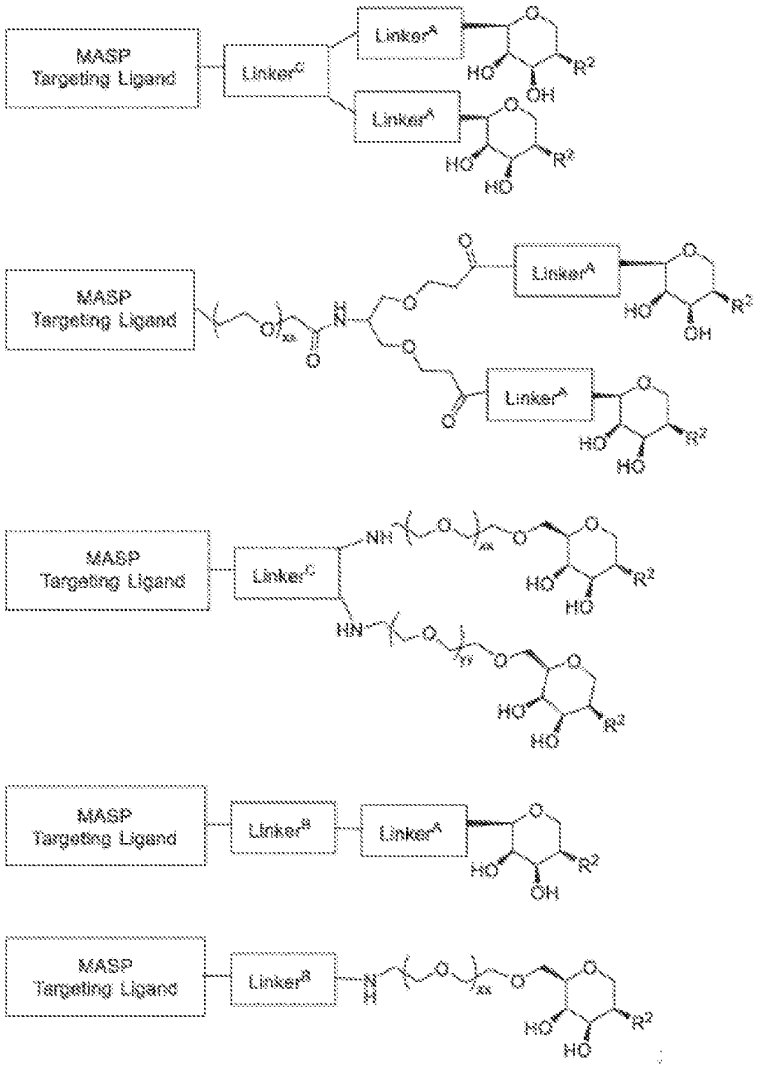

IgE Targeting Ligand
Linker^C
Linker^A
Linker^A
HO
NHAc
OH
HO
NHAc
HO
IgE Targeting Ligand
Linker^A
Linker^A
IgE Targeting Ligand
Linker^C
NH
HN
IgE Targeting Ligand
Linker^B
Linker^A
IgE Targeting Ligand
Linker^B
NHAc



wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

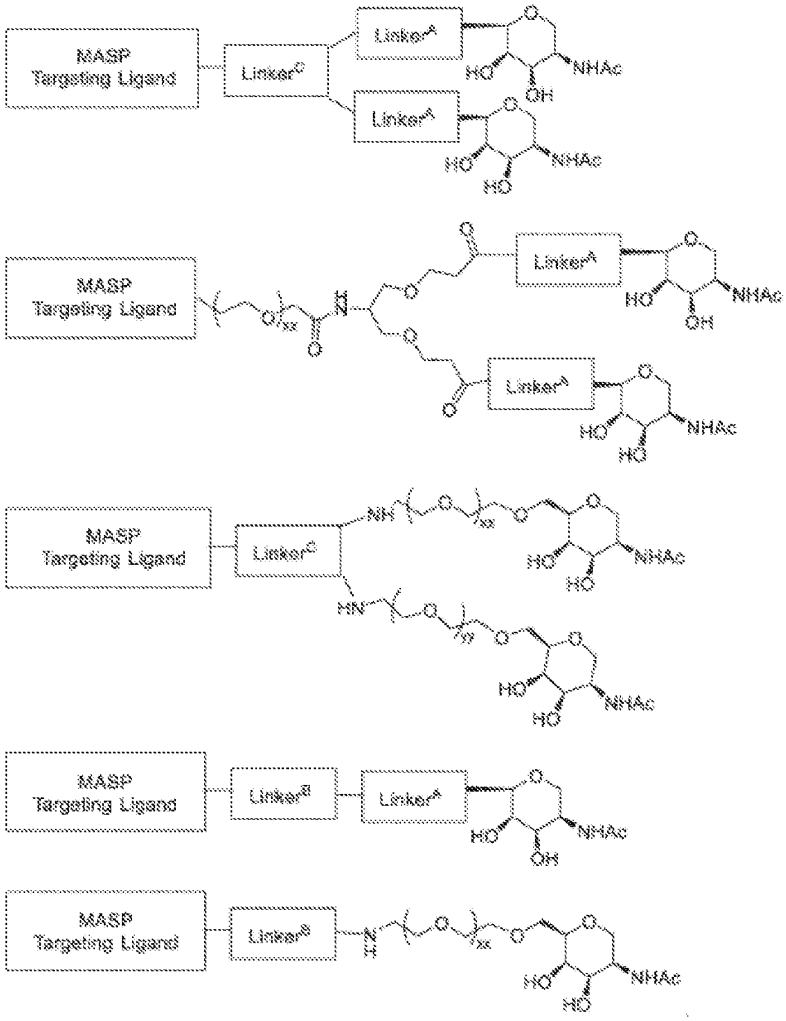
In certain embodiments, the compound of Formula II is selected from:

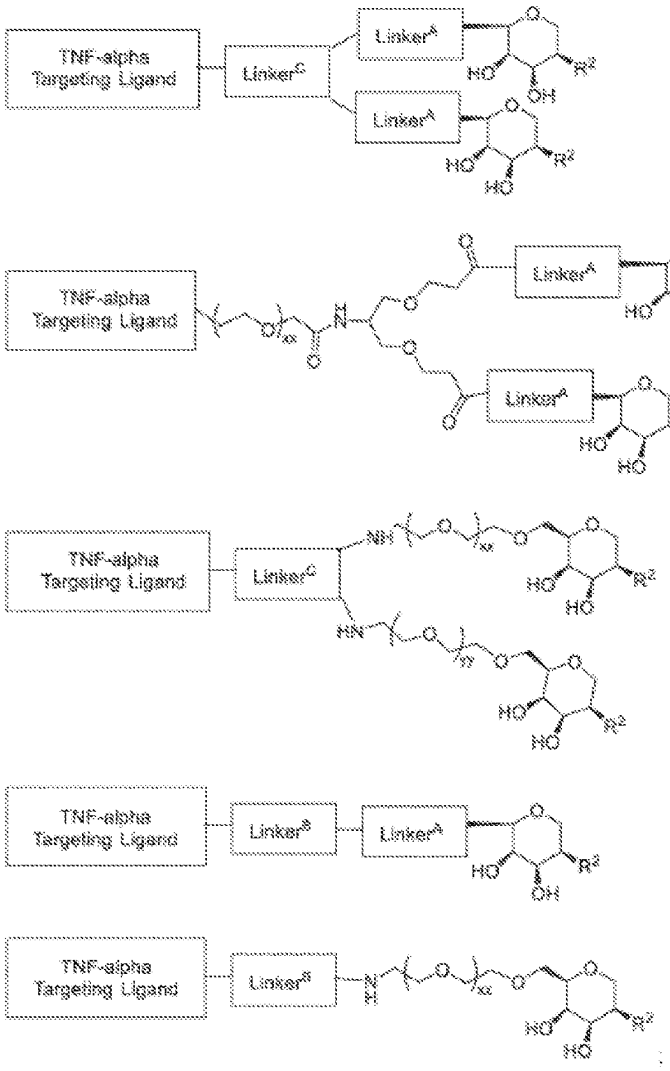

Complement Targeting Ligand
Linker^C
Linker^A
Linker^A
Complement Targeting Ligand
Linker^A
Linker^A
Complement Targeting Ligand
Linker^C
Complement Targeting Ligand
Linker^B
Linker^A
Complement Targeting Ligand
Linker^B



wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

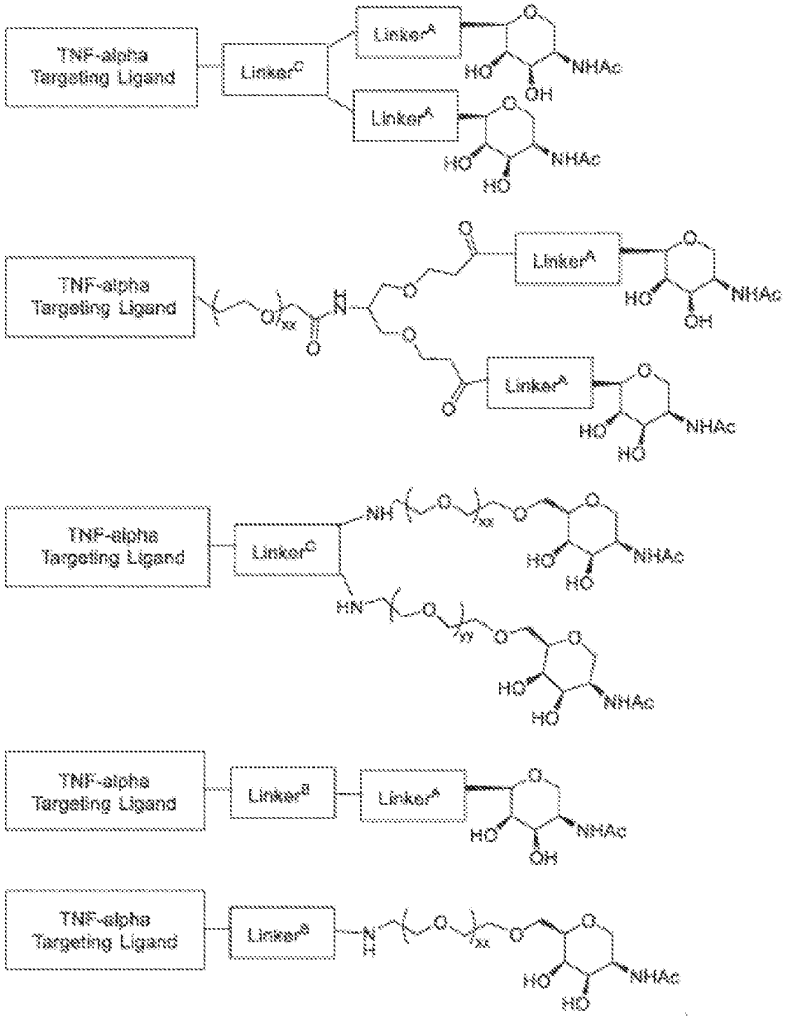
In certain embodiments, the compound of Formula II is selected from:

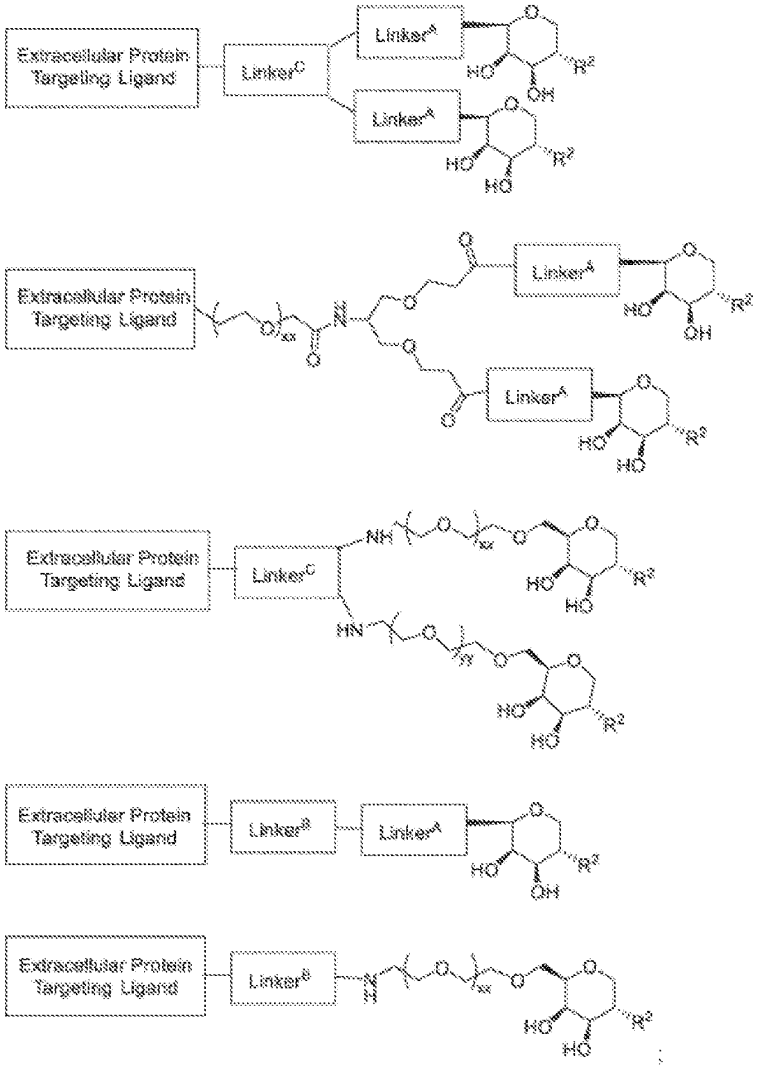

MASP
Targeting Ligand
Linker^C
Linker^A
NHAc
HO
OH
MASP
Targeting Ligand
Linker^A
NHAc
HO
OH
MASP
Targeting Ligand
Linker^C
NH
HN
NHAc
HO
MASP
Targeting Ligand
Linker^B
Linker^A
NHAc
HO
OH
MASP
Targeting Ligand
Linker^B
NHAc
HO



wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

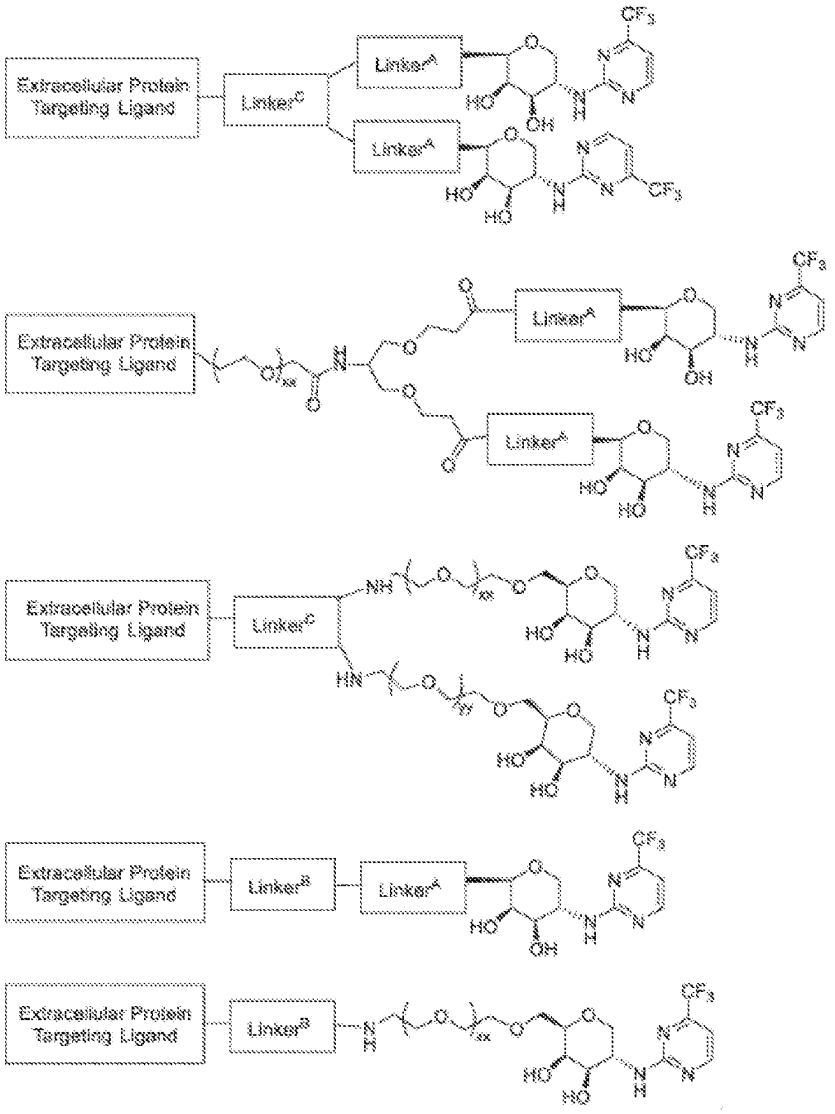
In certain embodiments, the compound of Formula II is selected from:

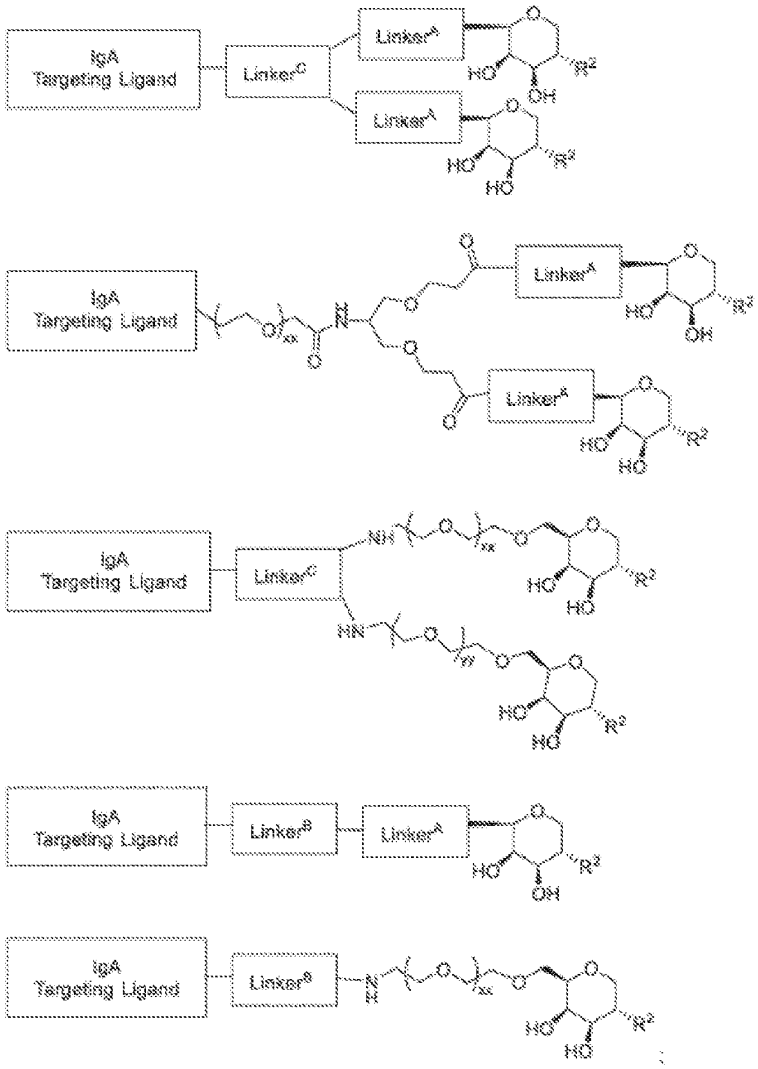

TNF-alpha Targeting Ligand
Linker^C
Linker^A
Linker^B
NHAc
HO
OH



wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

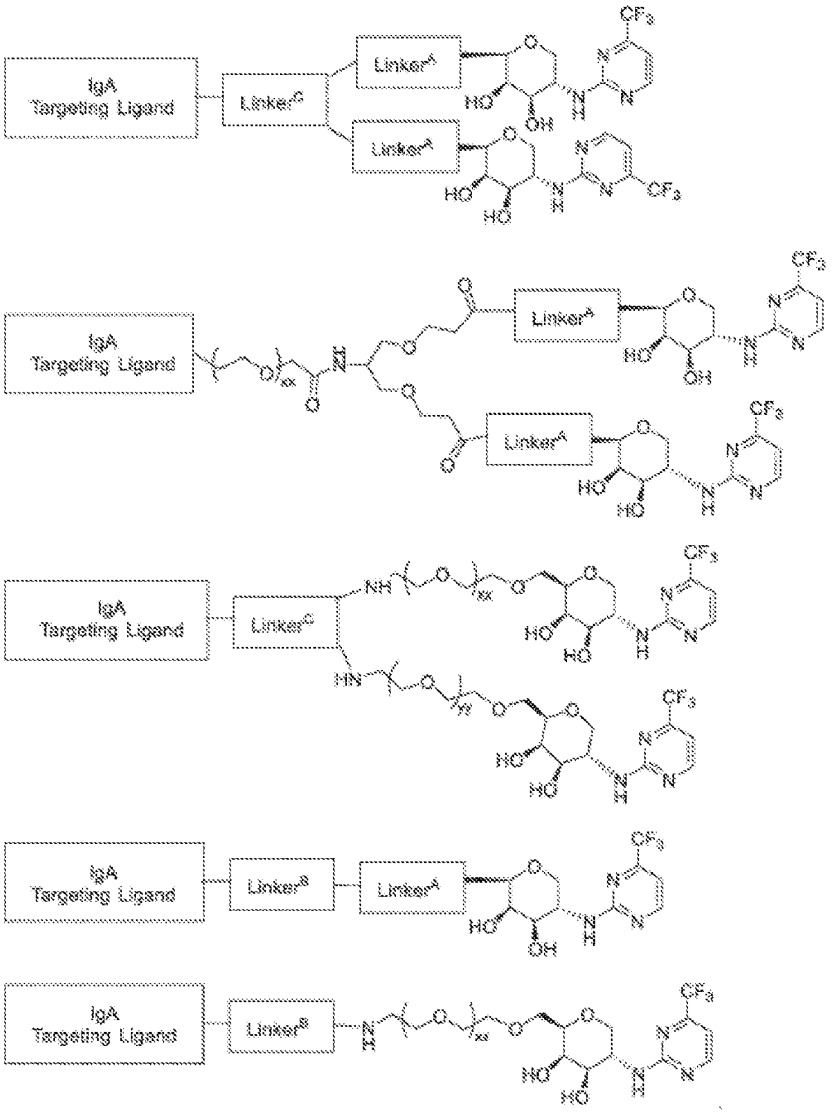
In certain embodiments, the compound of Formula II is selected from:

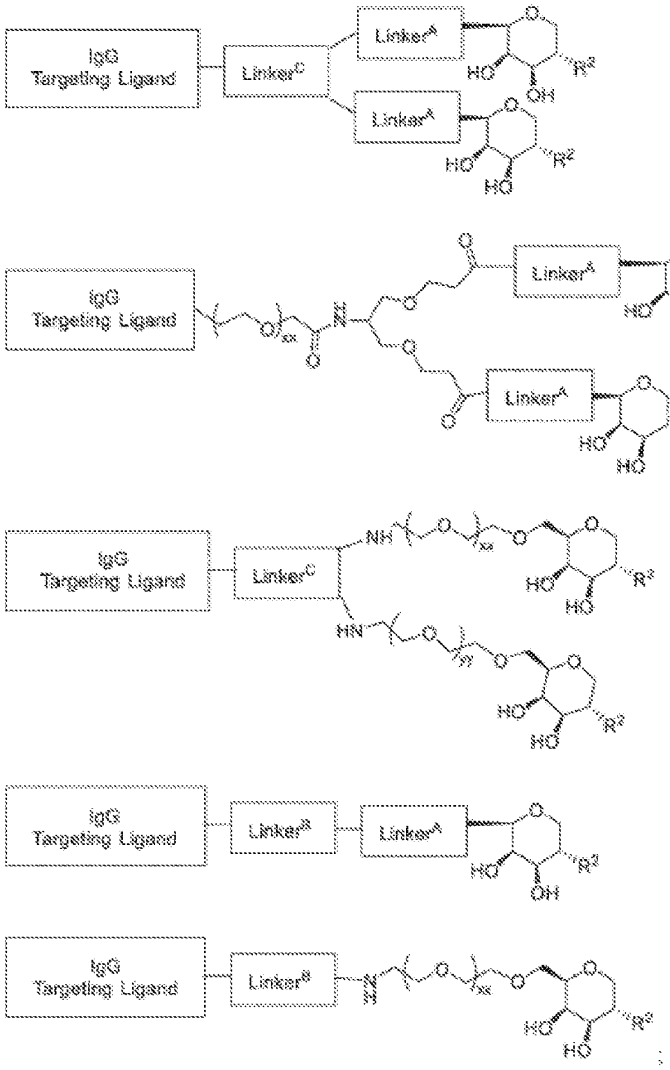

Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^C
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^B



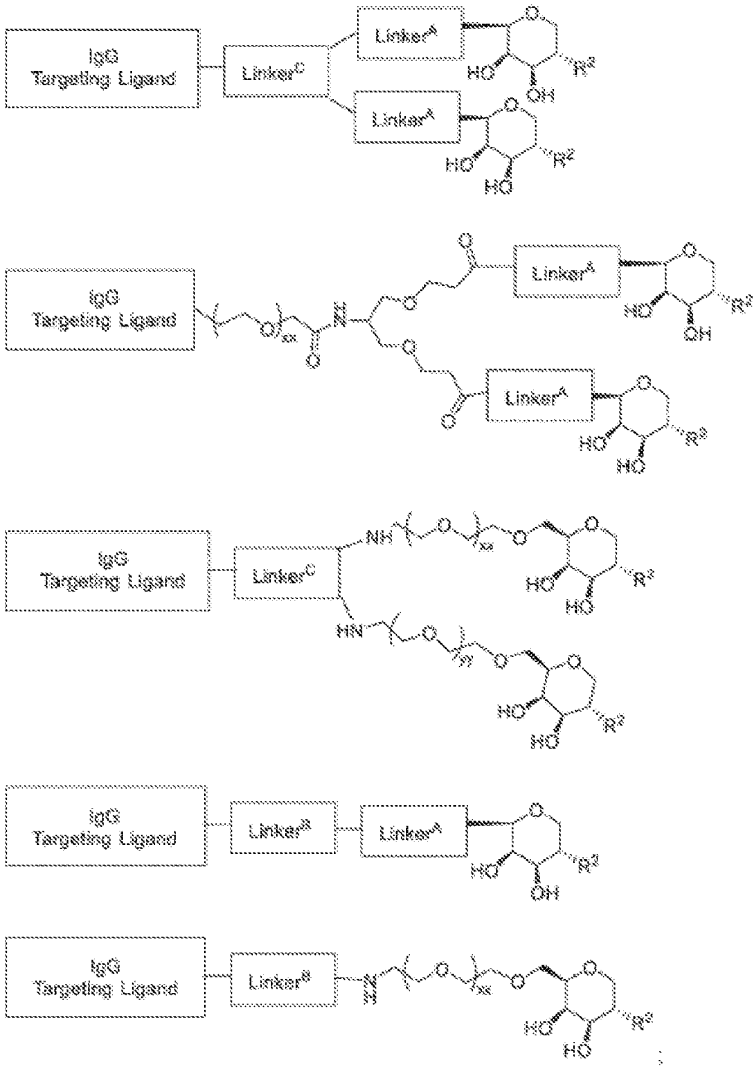
wherein in certain embodiments R^2 is selected from $-NR^bCOR^{10}$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

In certain embodiments, the compound of Formula II is selected from:


IgA Targeting Ligand
Linker^C
Linker^A
Linker^A
IgA Targeting Ligand
Linker^A
Linker^A
IgA Targeting Ligand
Linker^C
IgA Targeting Ligand
Linker^B
Linker^A
IgA Targeting Ligand
Linker^B

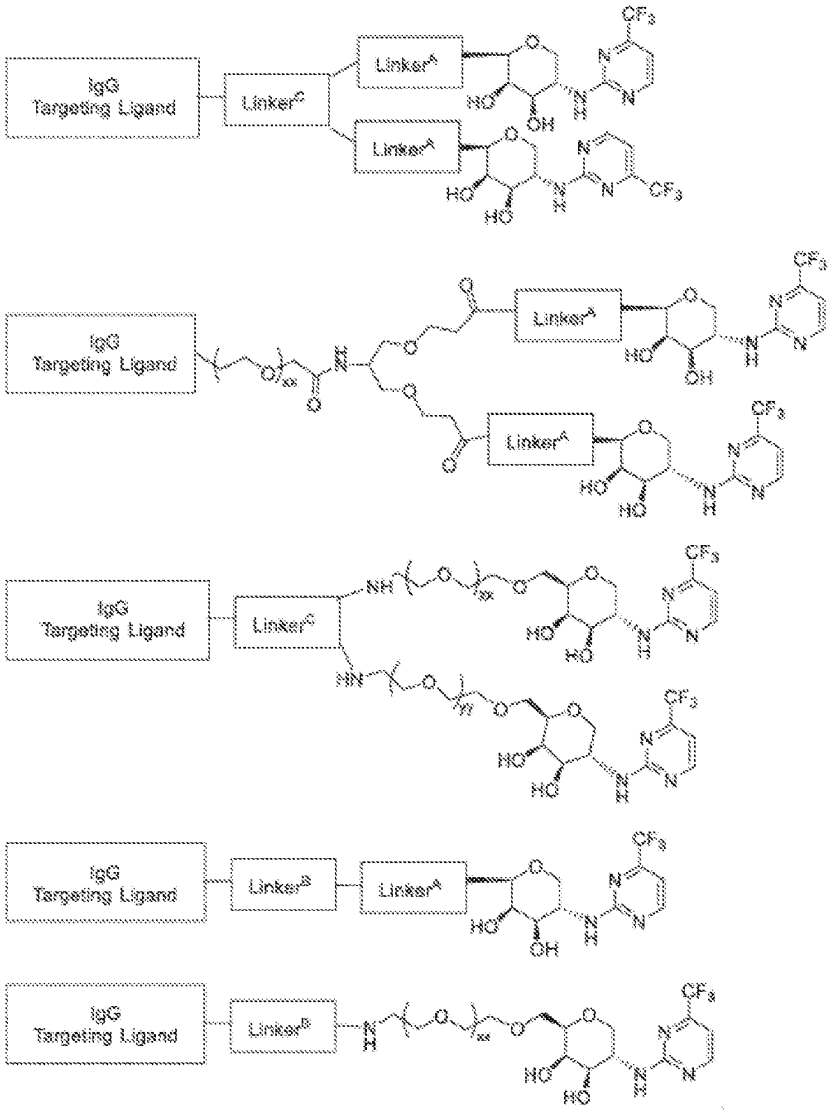

IgG Targeting Ligand
Linker^C
Linker^A
IgG Targeting Ligand
Linker^A
IgG Targeting Ligand
Linker^C
IgG Targeting Ligand
Linker^B
Linker^A
IgG Targeting Ligand
Linker^B

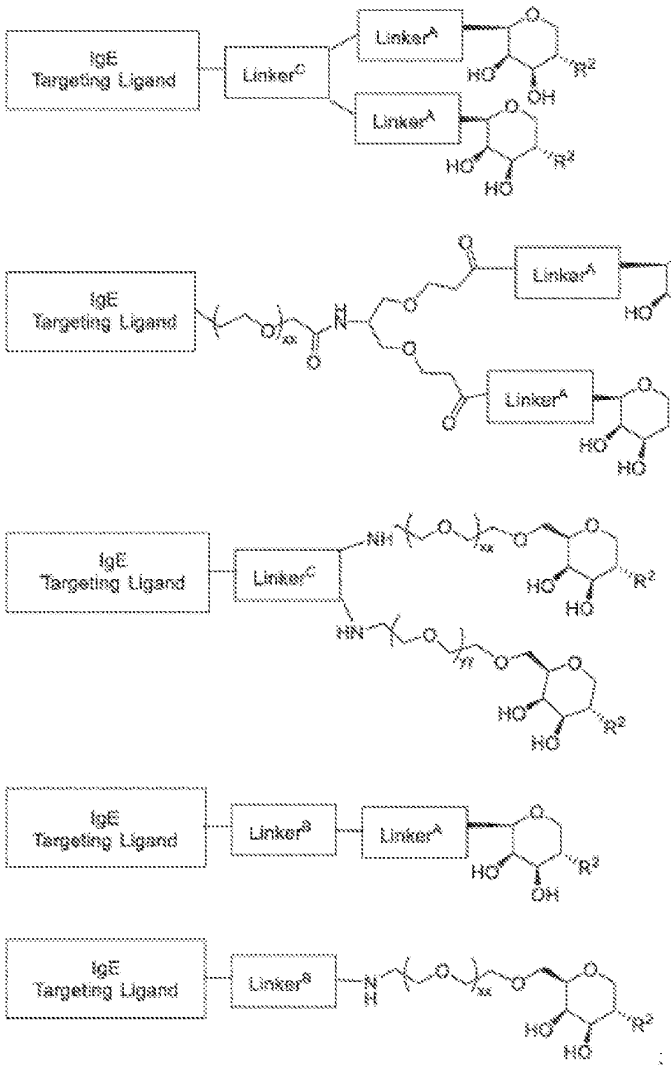
;



wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

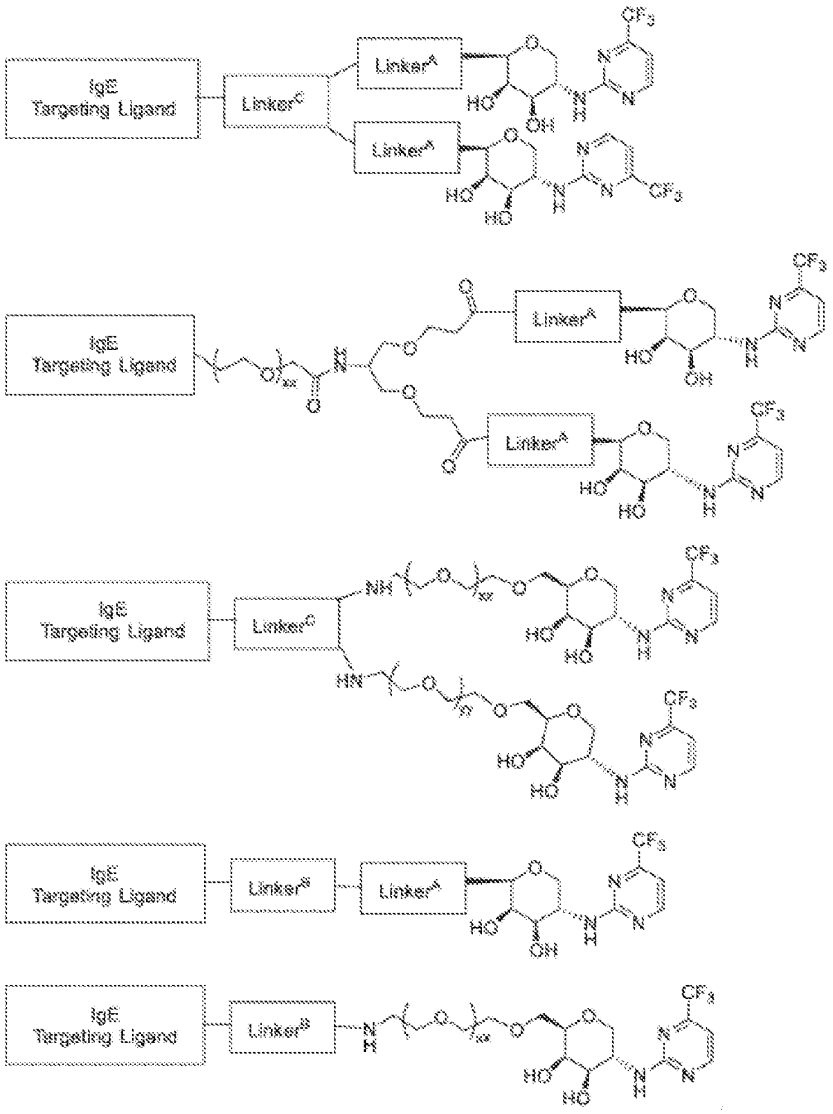
In certain embodiments, the compound of Formula II is selected from:

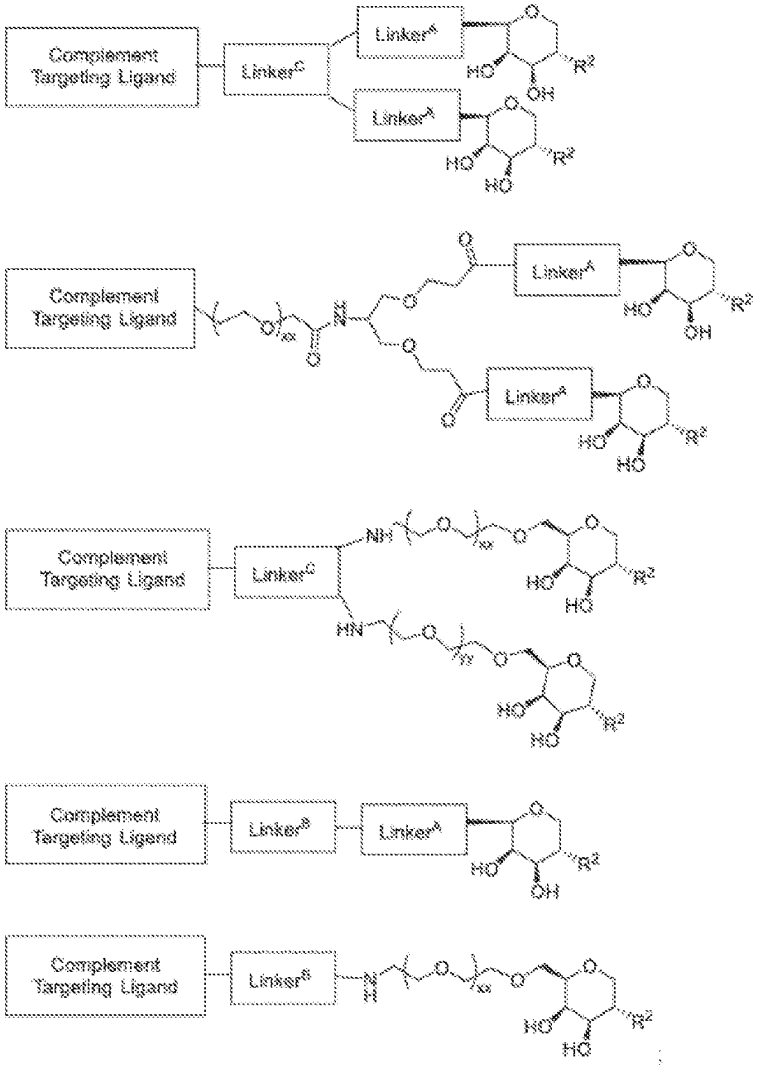

IgG
Targeting Ligand
Linker^C
Linker^A
Linker^A
IgG
Targeting Ligand
Linker^A
Linker^A
IgG
Targeting Ligand
Linker^C
IgG
Targeting Ligand
Linker^B
Linker^A
IgG
Targeting Ligand
Linker^B



wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

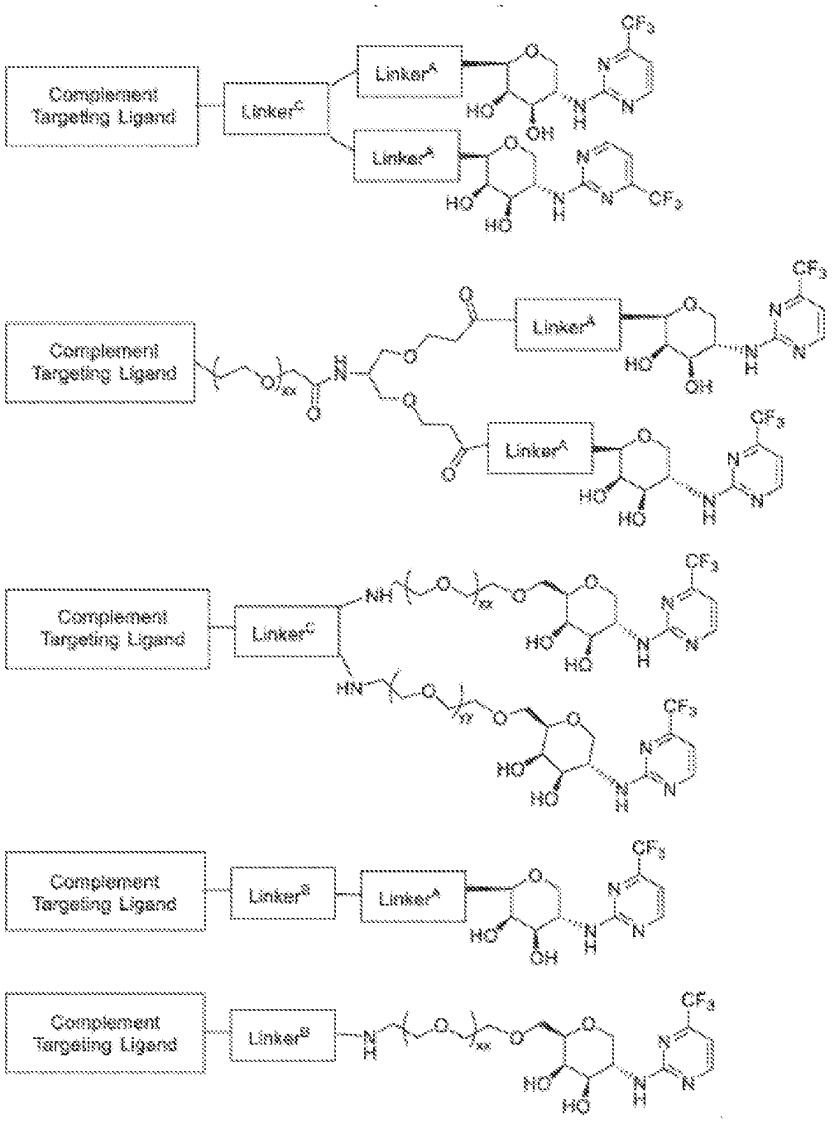
In certain embodiments, the compound of Formula II is selected from:

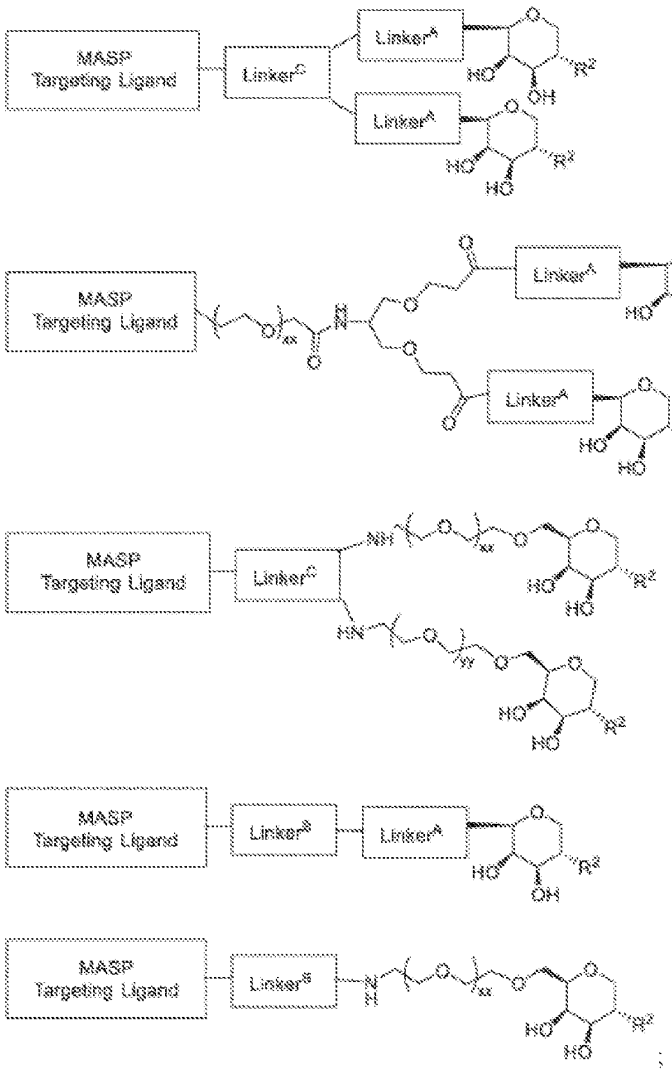

IgE Targeting Ligand
Linker^C
Linker^A
Linker^A
IgE Targeting Ligand
Linker^A
Linker^A
IgE Targeting Ligand
Linker^C
IgE Targeting Ligand
Linker^B
Linker^A
IgE Targeting Ligand
Linker^B



wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

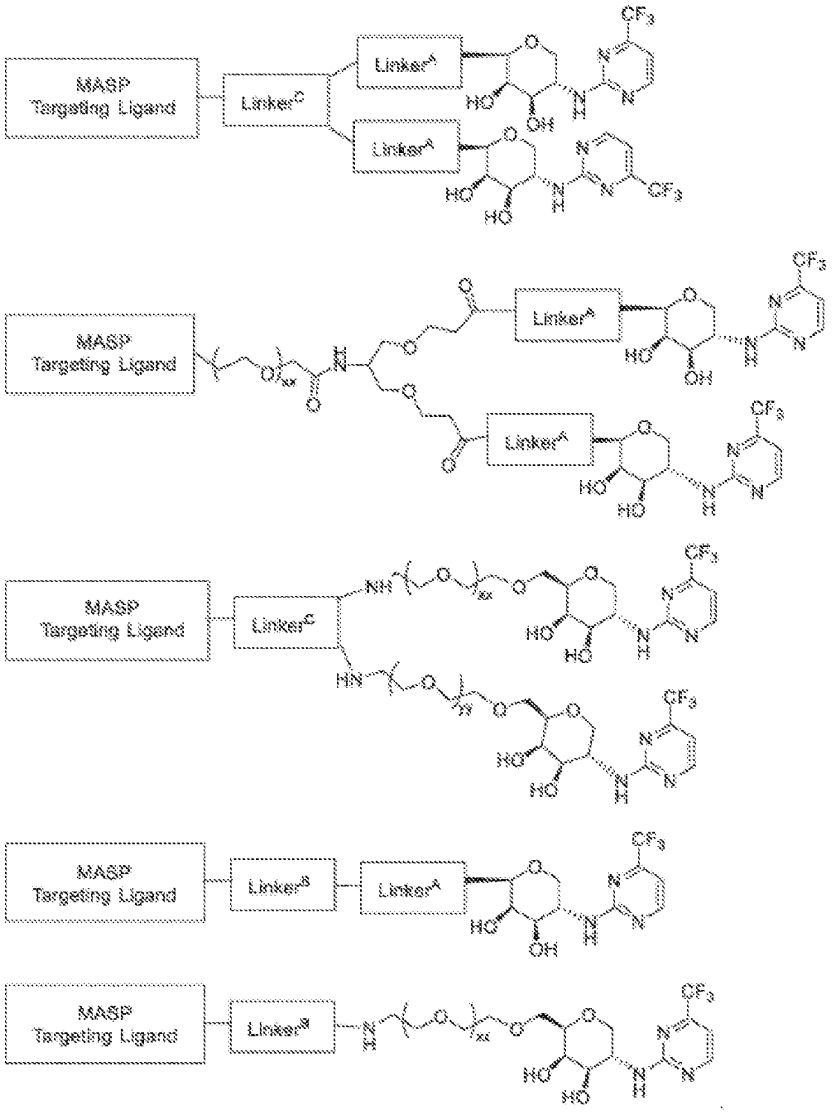
In certain embodiments, the compound of Formula II is selected from:

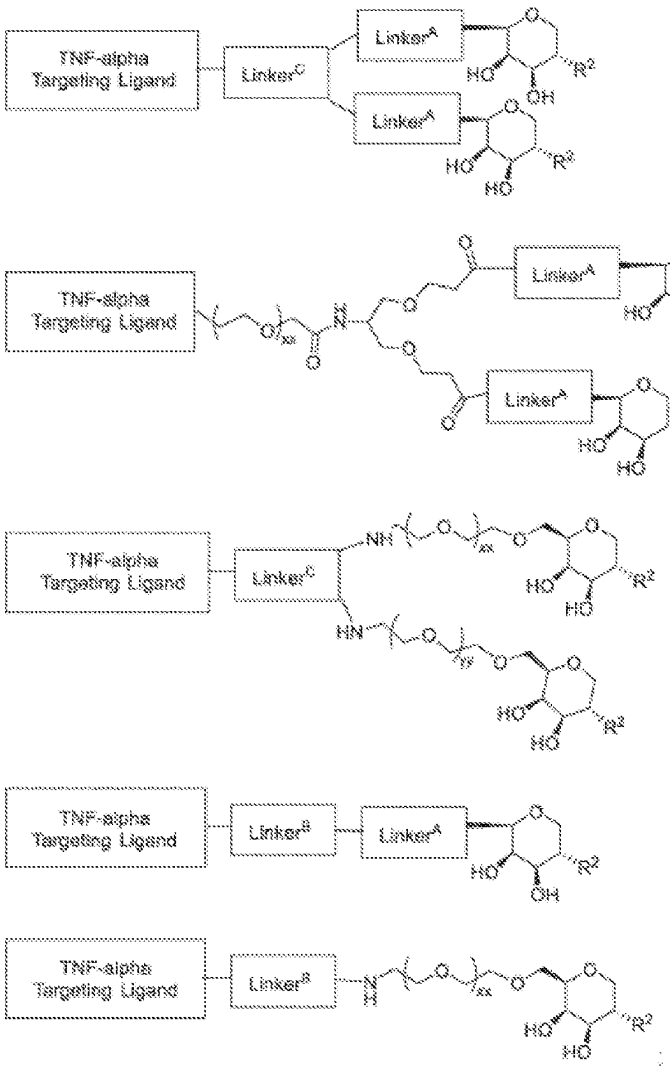

Complement Targeting Ligand
Linker^C
Linker^A
Linker^A
Complement Targeting Ligand
Linker^A
Linker^A
Complement Targeting Ligand
Linker^C
Complement Targeting Ligand
Linker^B
Linker^A
Complement Targeting Ligand
Linker^B



wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

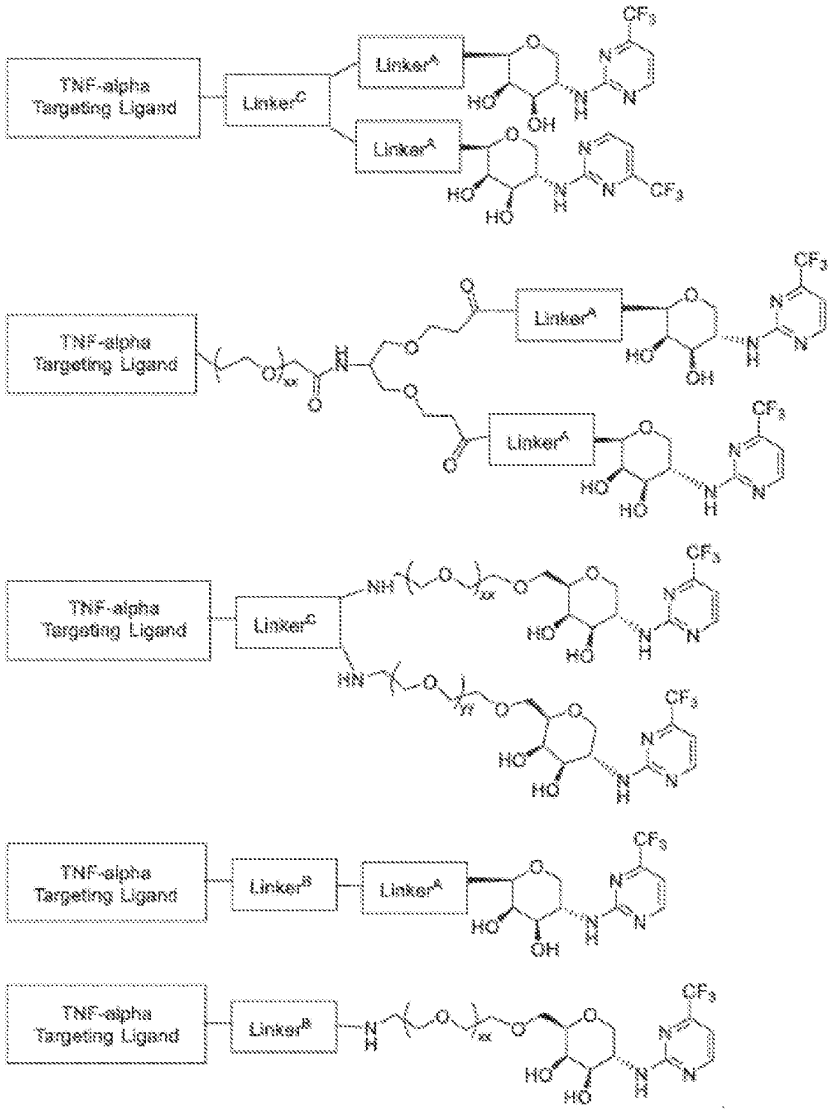
In certain embodiments, the compound of Formula II is selected from:

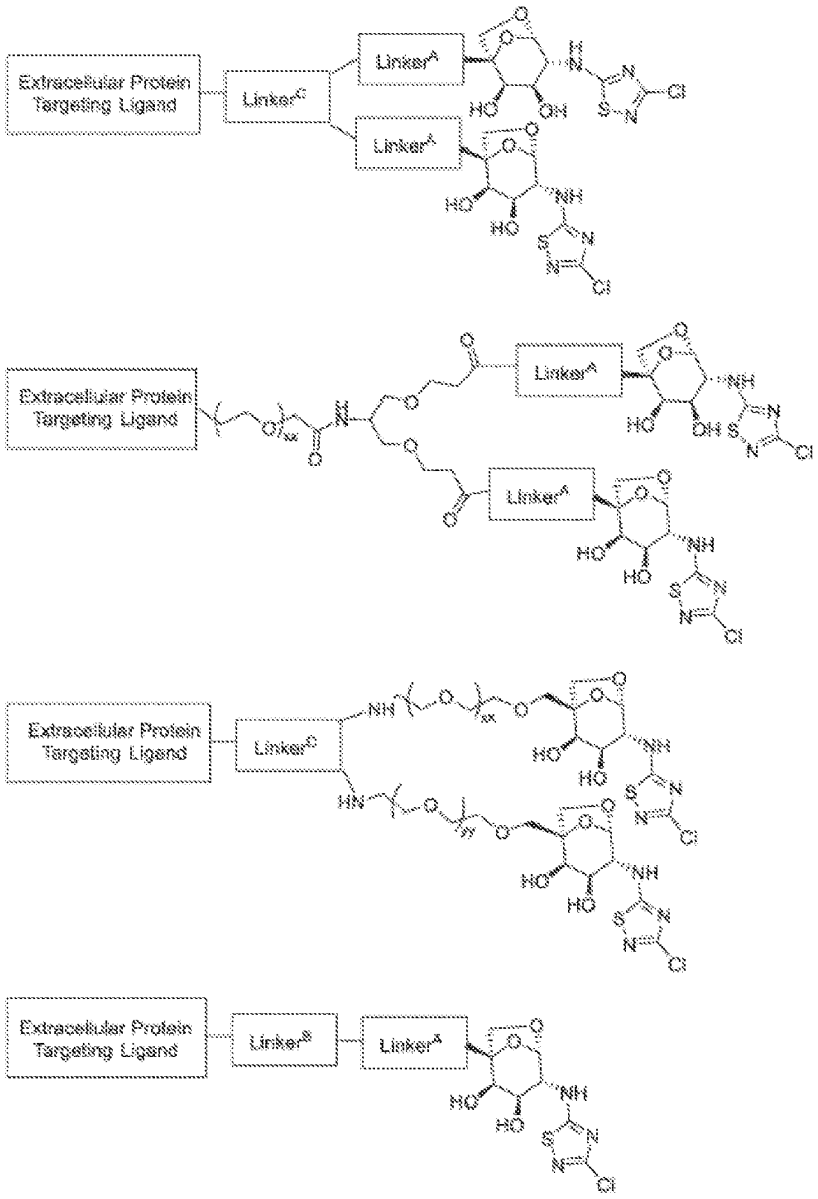

MASP Targeting Ligand
Linker^C
Linker^A
Linker^A
MASP Targeting Ligand
Linker^A
Linker^A
MASP Targeting Ligand
Linker^C
MASP Targeting Ligand
Linker^B
Linker^A
MASP Targeting Ligand
Linker^B

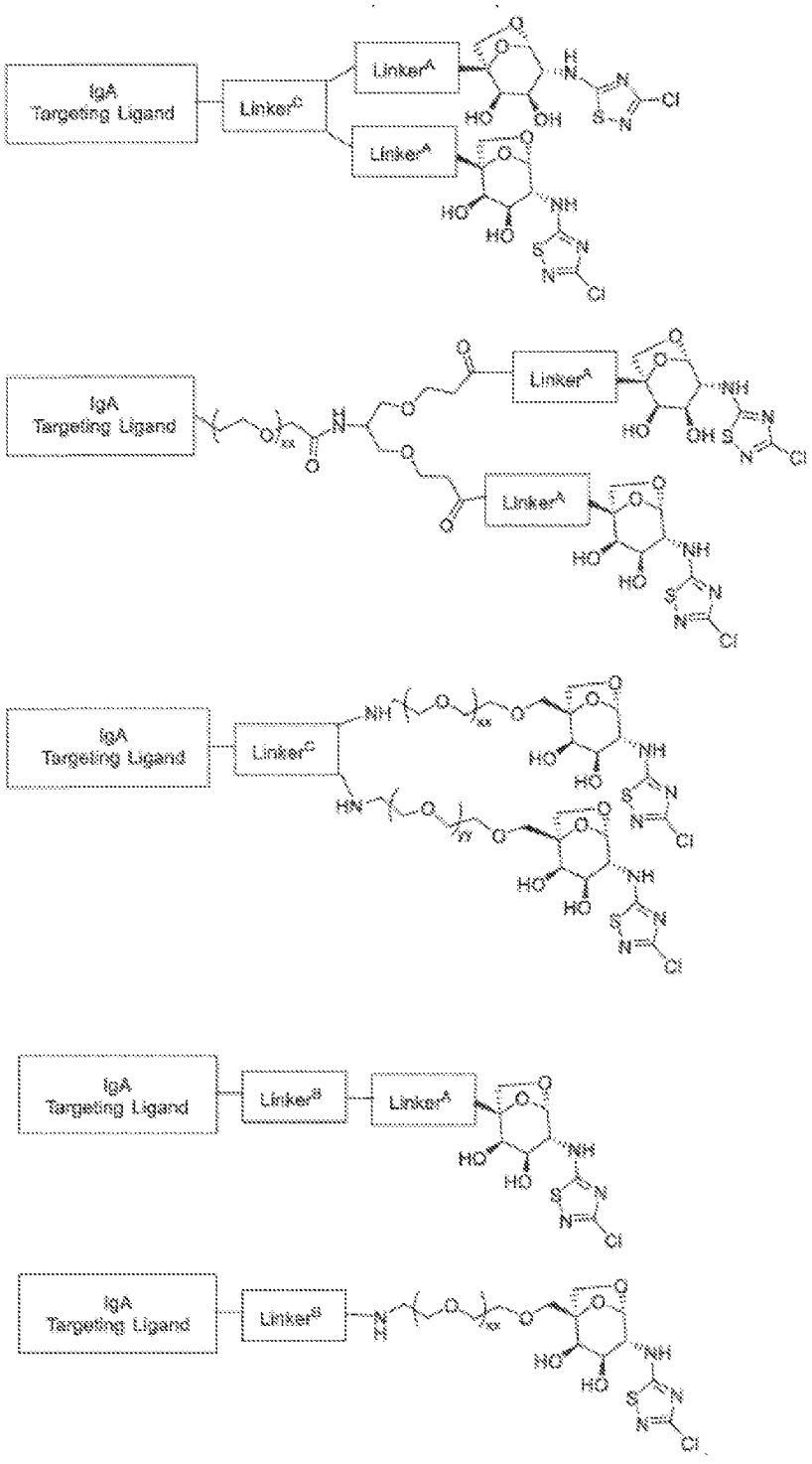


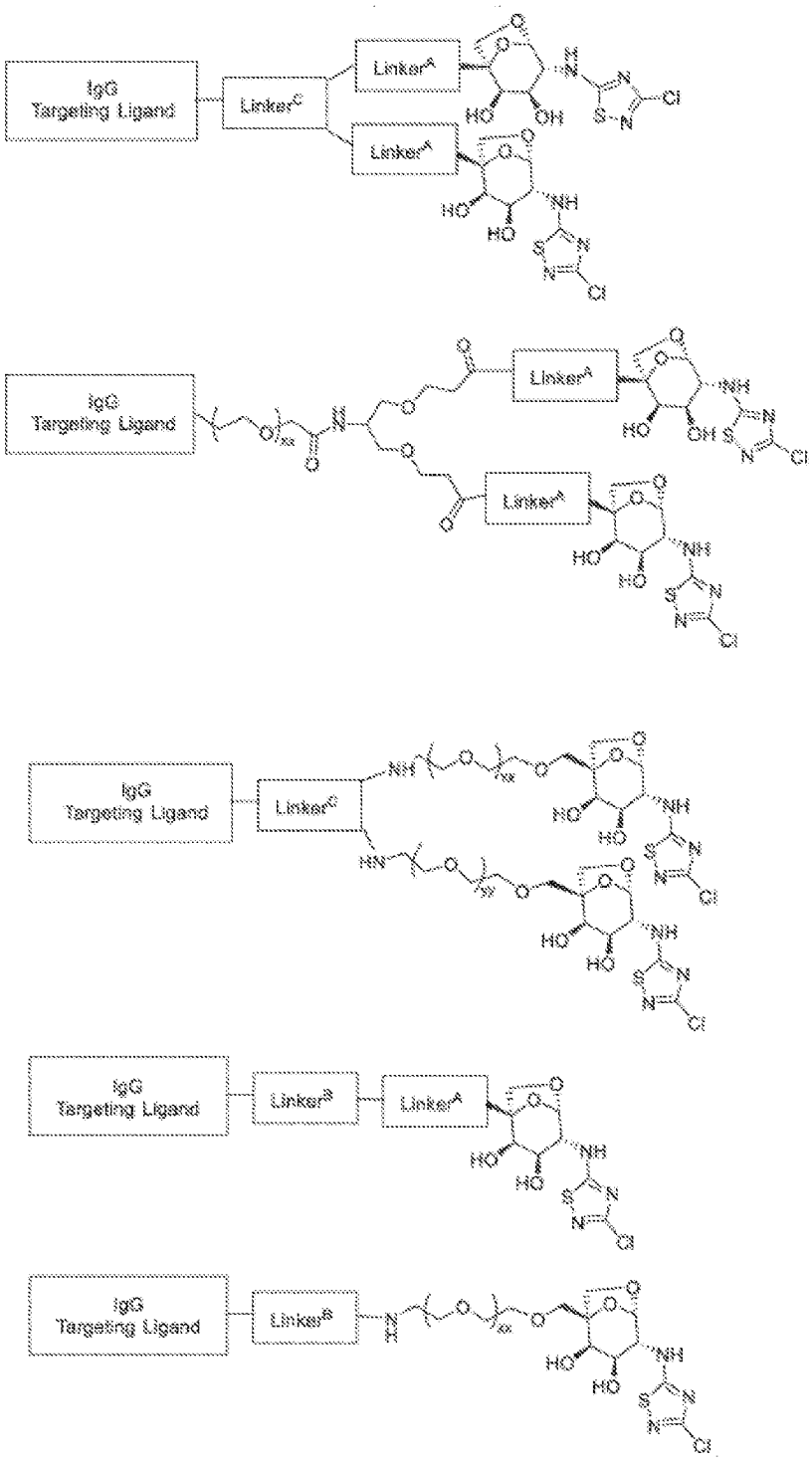
wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

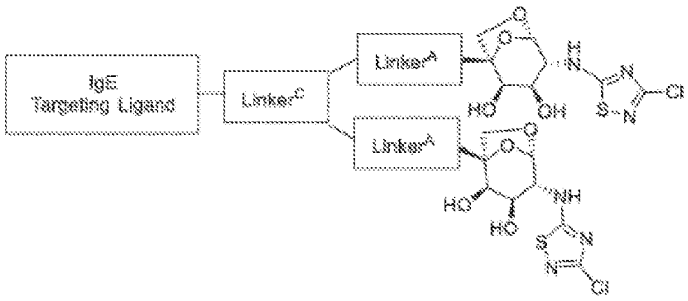
In certain embodiments, the compound of Formula II is selected from:

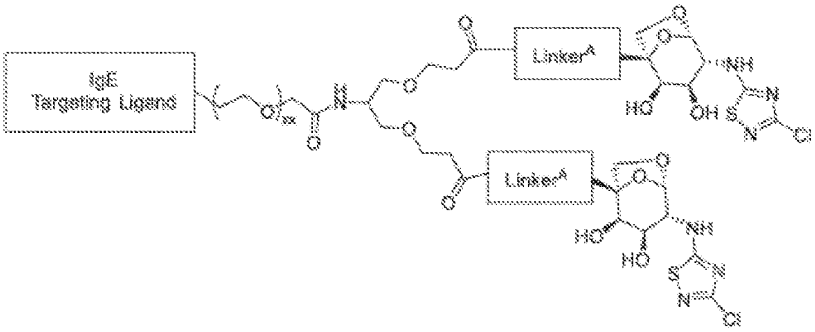

TNF-alpha Targeting Ligand
Linker^C
Linker^A
Linker^A
TNF-alpha Targeting Ligand
Linker^A
Linker^A
TNF-alpha Targeting Ligand
Linker^C
TNF-alpha Targeting Ligand
Linker^B
Linker^A
TNF-alpha Targeting Ligand
Linker^B

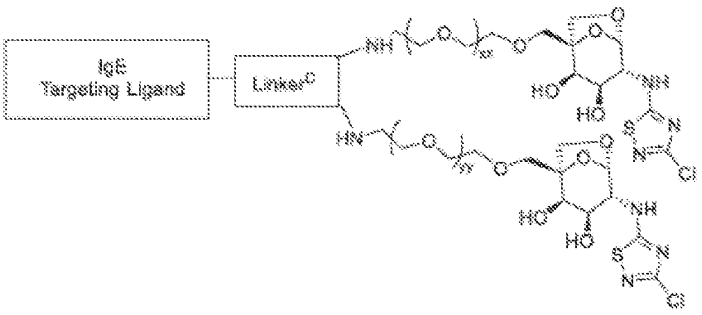

Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^C
Extracellular Protein Targeting Ligand
Linker^B
Linker^A

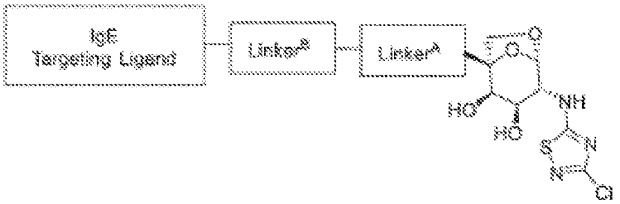

IgA Targeting Ligand
Linker^C
Linker^A
Linker^A
IgA Targeting Ligand
Linker^A
Linker^A
IgA Targeting Ligand
Linker^C
IgA Targeting Ligand
Linker^B
Linker^A
IgA Targeting Ligand
Linker^B

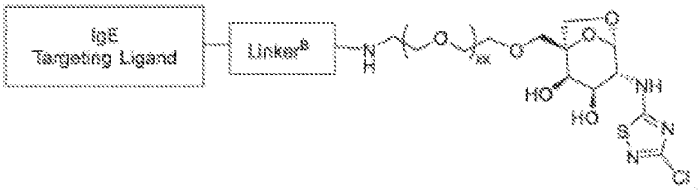

IgG Targeting Ligand
Linker^C
Linker^A
Linker^A
IgG Targeting Ligand
Linker^A
Linker^A
IgG Targeting Ligand
Linker^C
IgG Targeting Ligand
Linker^B
Linker^A
IgG Targeting Ligand
Linker^B

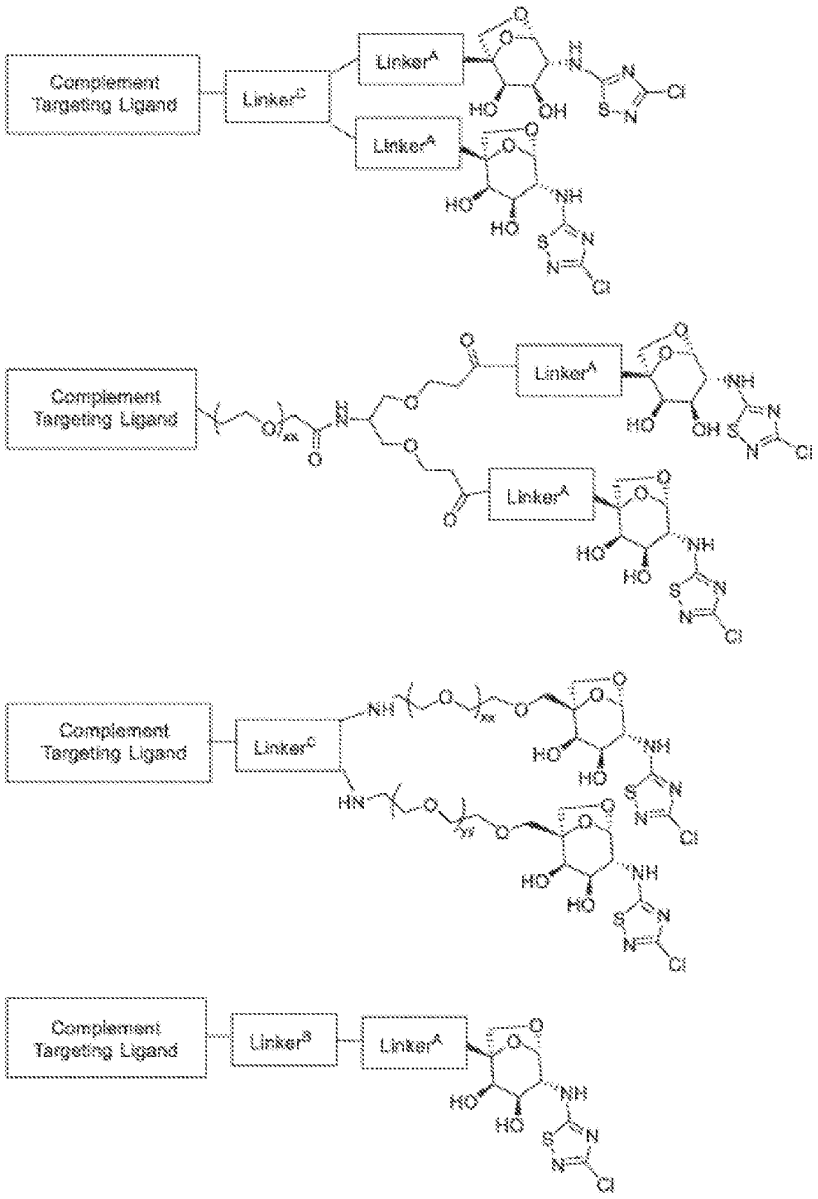

IgE
Targeting Ligand
Linker^C
Linker^A
Linker^A

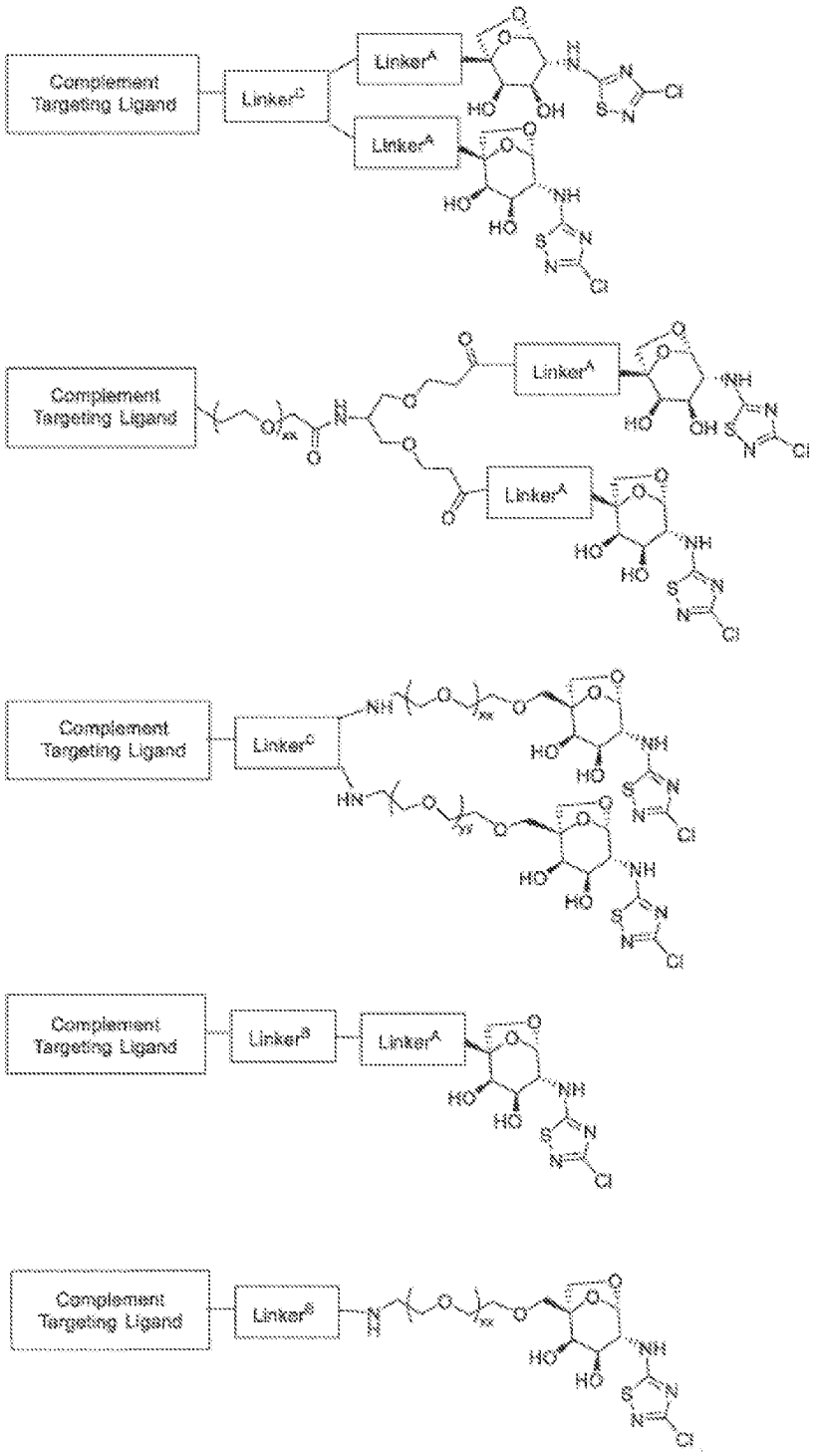

IgE
Targeting Ligand
Linker^A
Linker^A

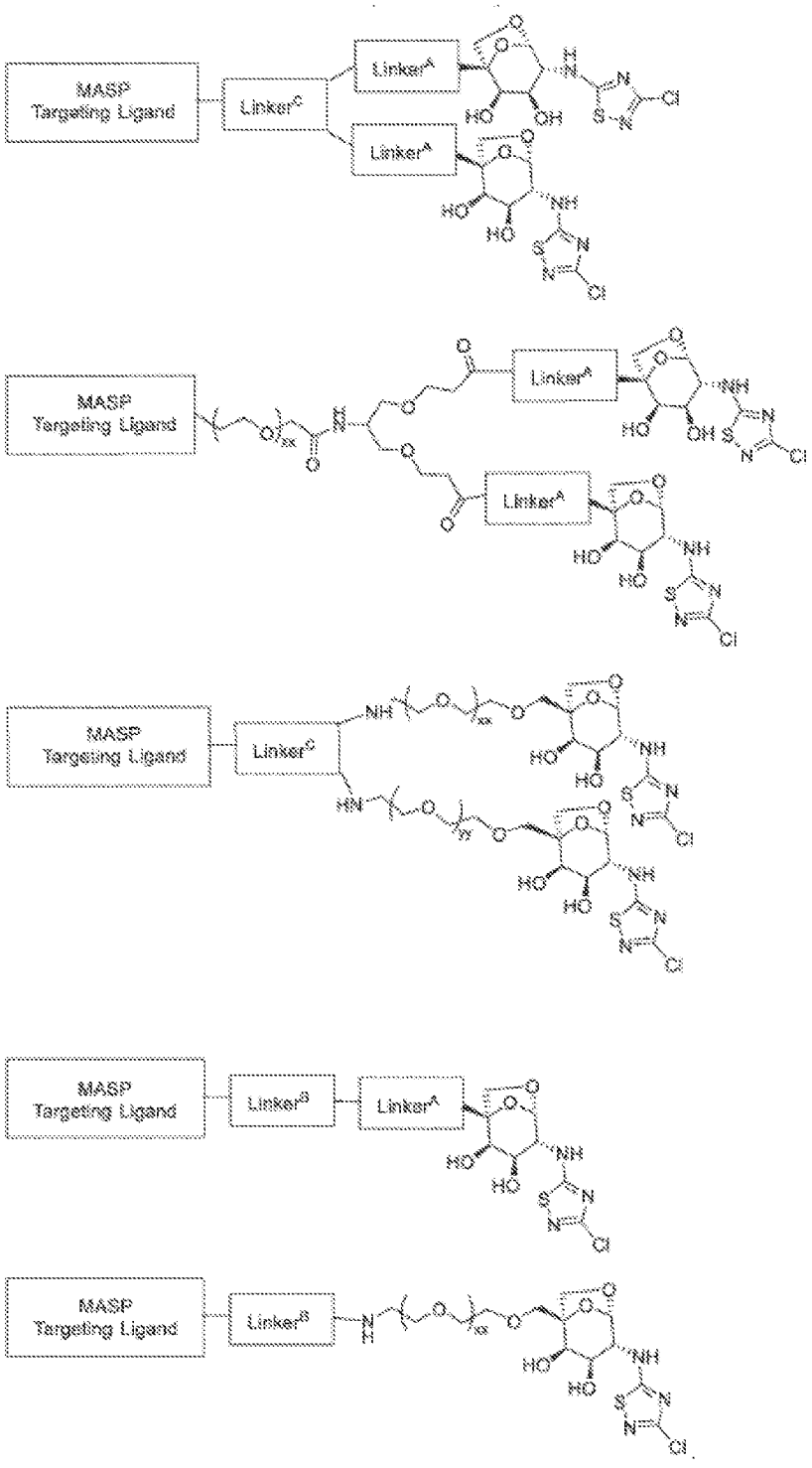

IgE
Targeting Ligand
Linker^C

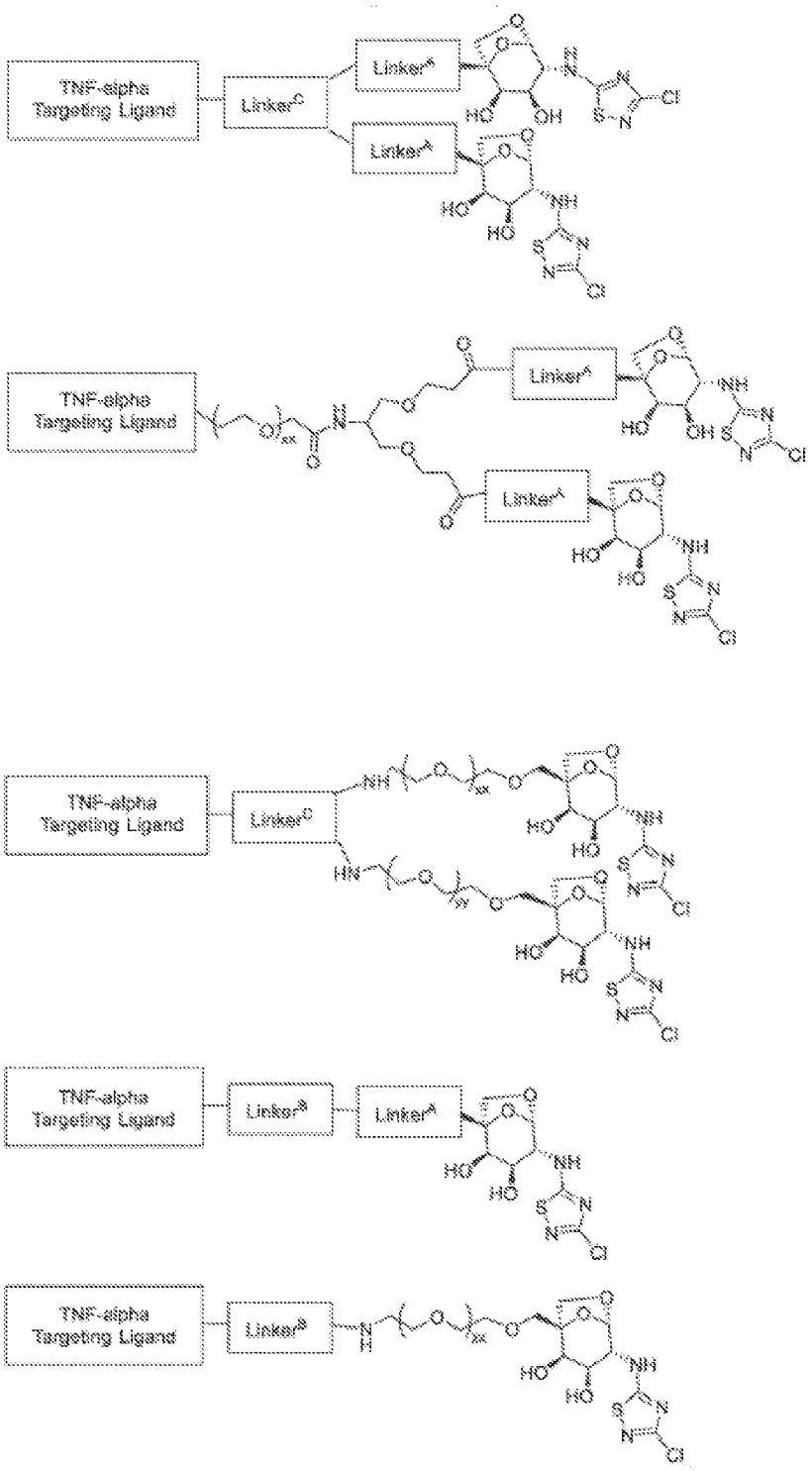

IgE
Targeting Ligand
Linker^B
Linker^A

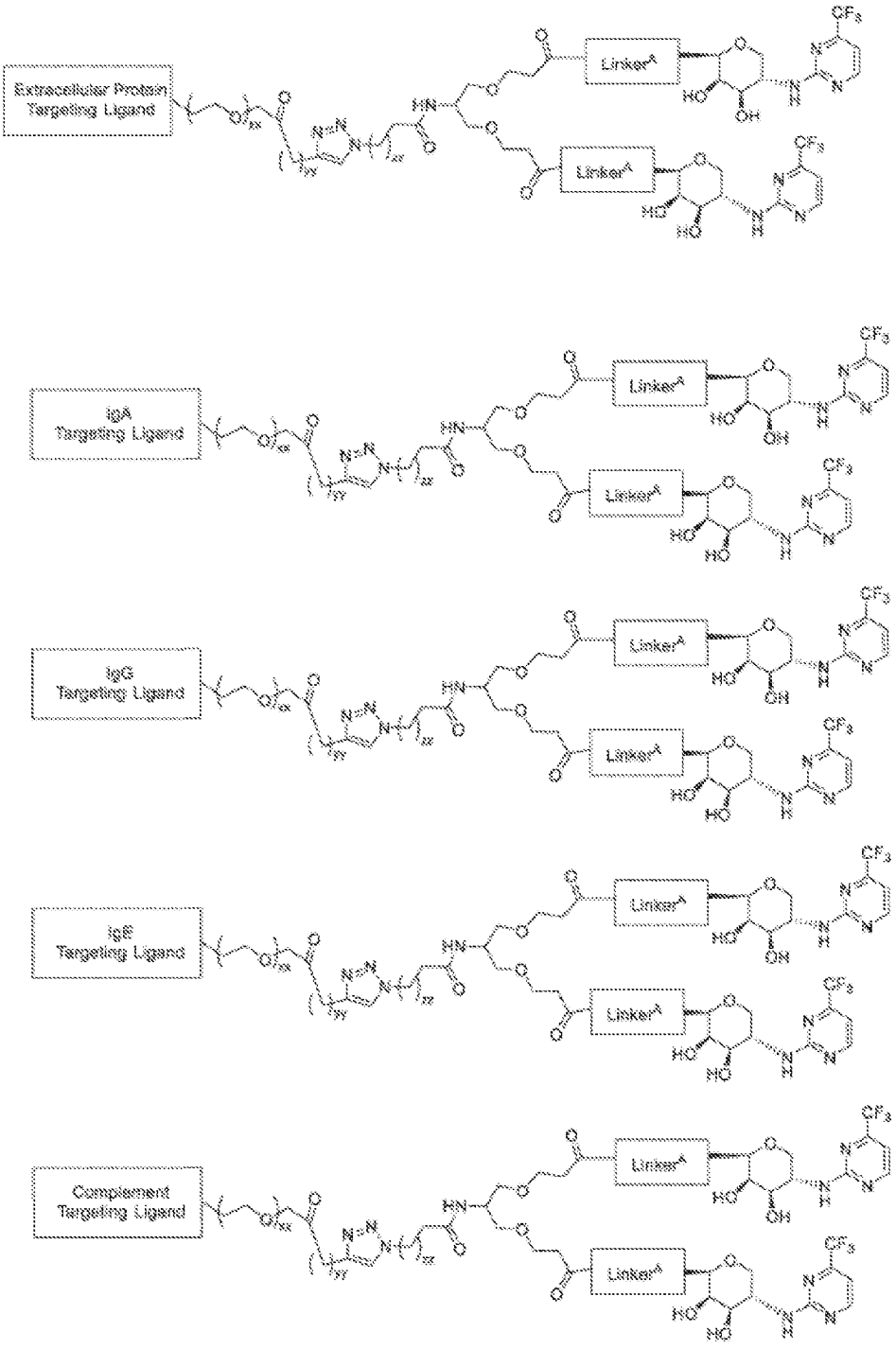

IgE
Targeting Ligand
Linker^B

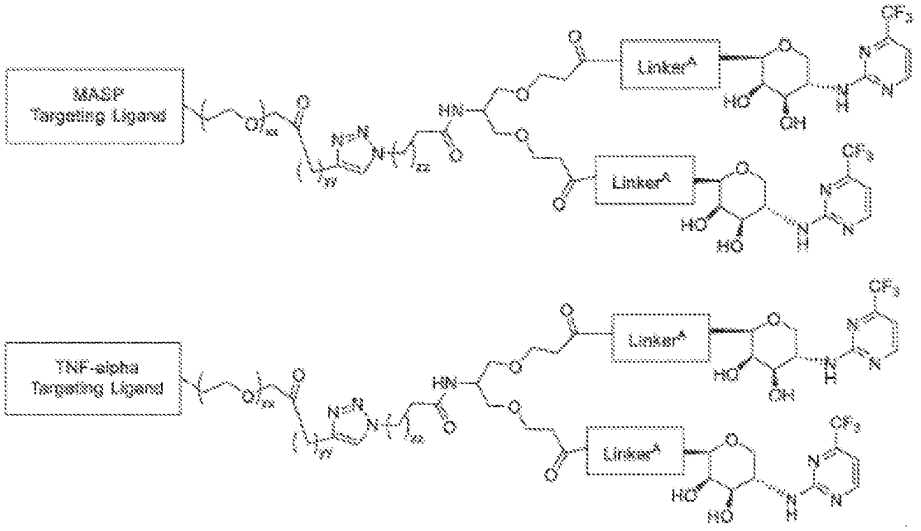

Complement Targeting Ligand
Linker^D
Linker^A
Linker^A
Complement Targeting Ligand
Linker^A
Linker^A
Complement Targeting Ligand
Linker^C
Complement Targeting Ligand
Linker^B
Linker^A


Complement Targeting Ligand
Linker^D
Linker^A
Linker^A
Complement Targeting Ligand
Linker^A
Linker^A
Complement Targeting Ligand
Linker^C
Complement Targeting Ligand
Linker^B
Linker^A
Complement Targeting Ligand
Linker^B

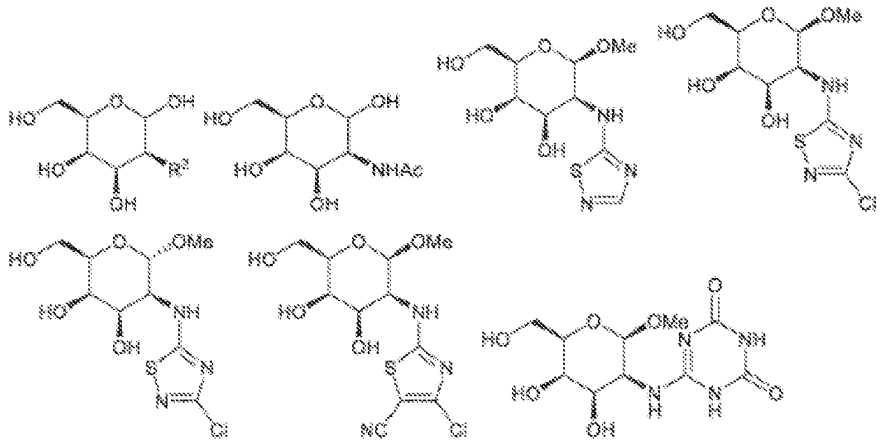

MASP Targeting Ligand
Linker^C
Linker^A
Linker^A
MASP Targeting Ligand
Linker^A
Linker^A
MASP Targeting Ligand
Linker^C
MASP Targeting Ligand
Linker^B
Linker^A
MASP Targeting Ligand
Linker^B

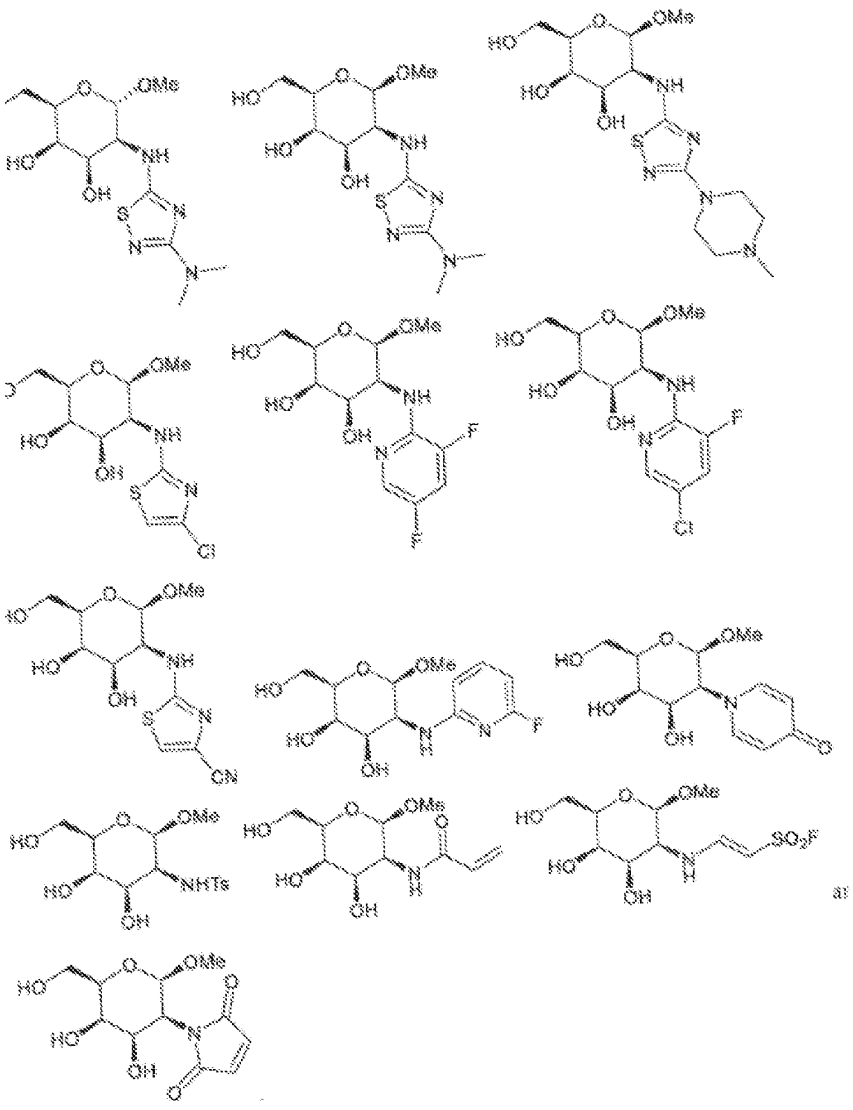

TNF-alpha Targeting Ligand
Linker^C
Linker^A
Linker^A
TNF-alpha Targeting Ligand
Linker^A
Linker^A
TNF-alpha Targeting Ligand
Linker^C
TNF-alpha Targeting Ligand
Linker^B
Linker^A
TNF-alpha Targeting Ligand
Linker^B

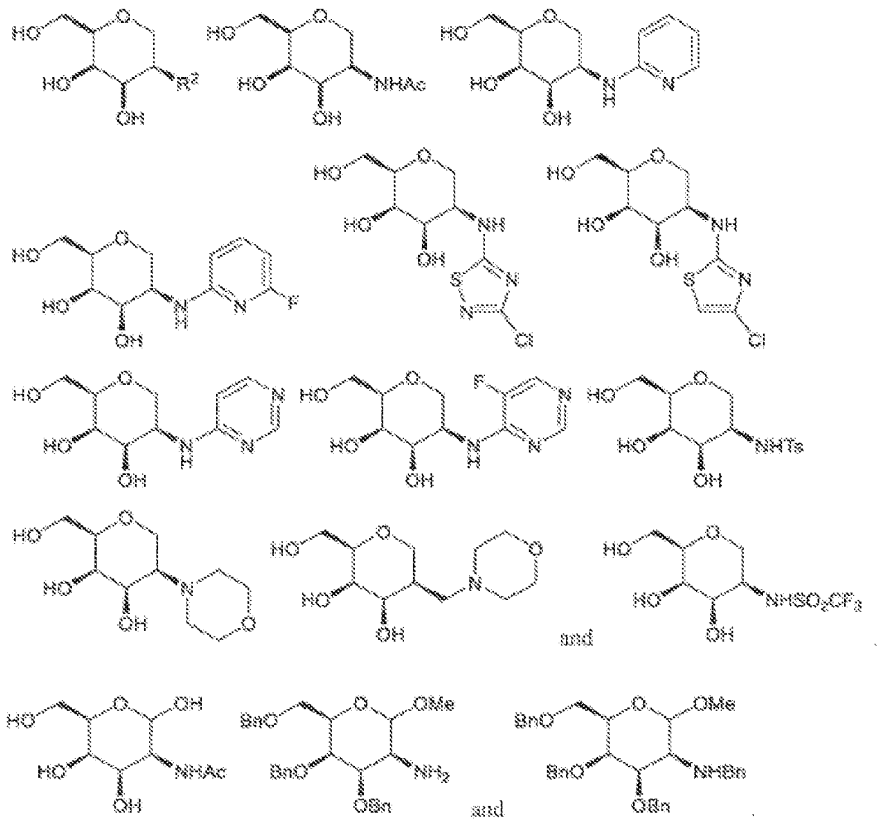

Extracellular Protein Targeting Ligand
IgA Targeting Ligand
IgG Targeting Ligand
IgE Targeting Ligand
Complement Targeting Ligand
Linker^A

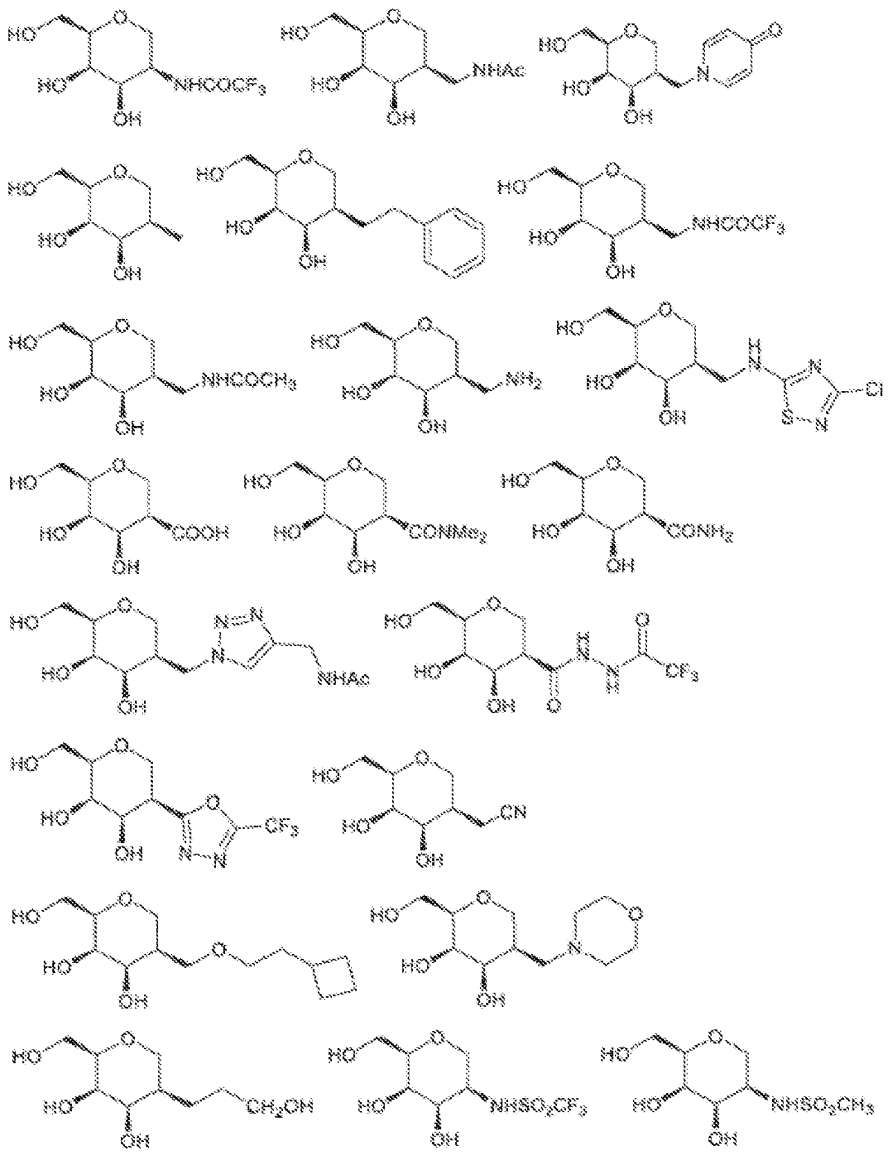


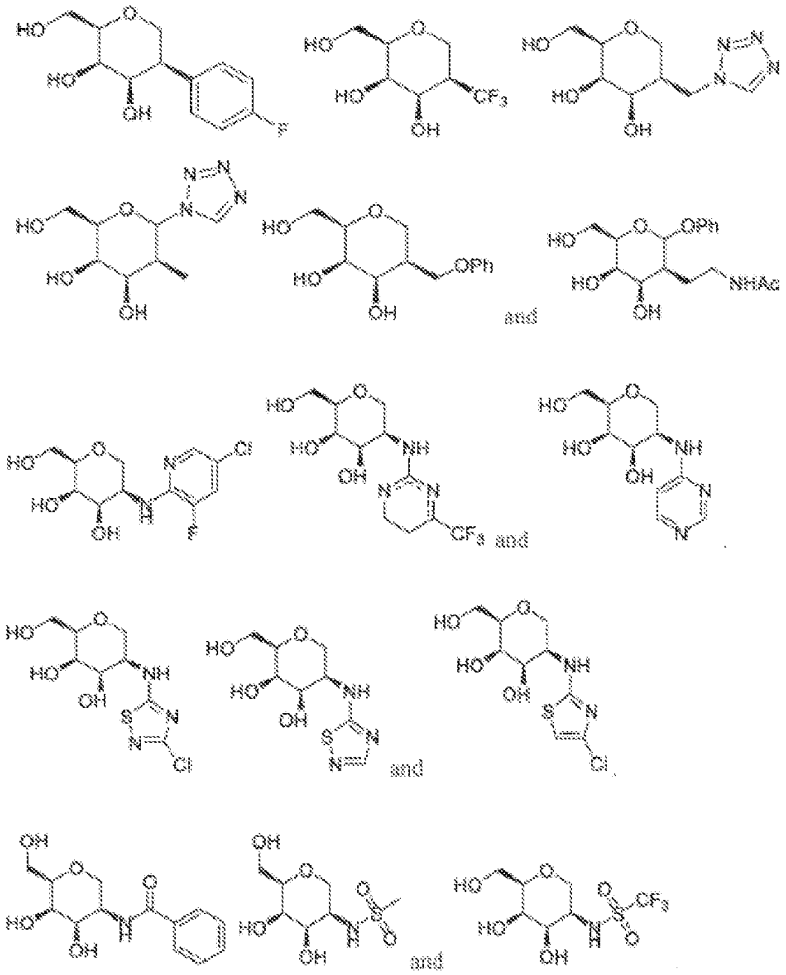
In certain embodiments, an ASGPR ligand useful for incorporation into a compound of Formula II is selected from:

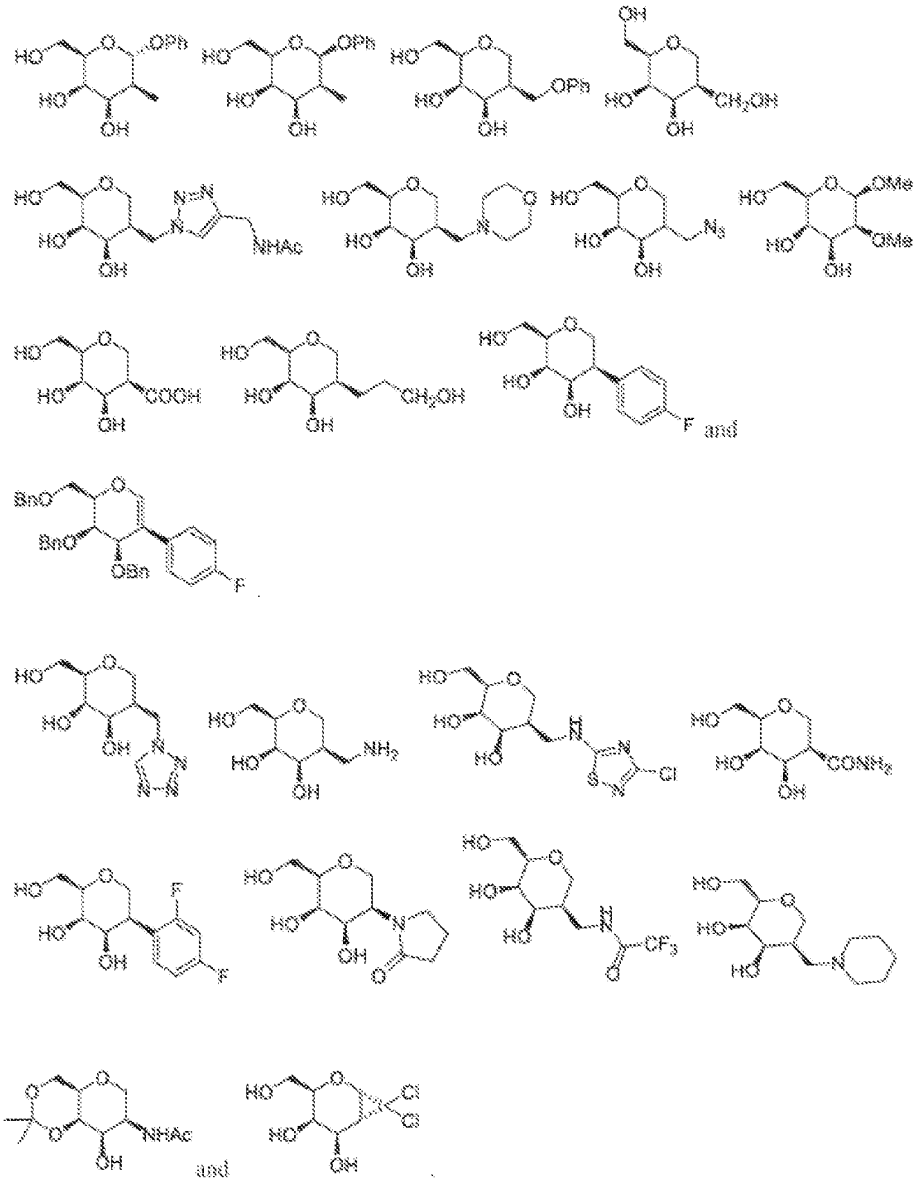




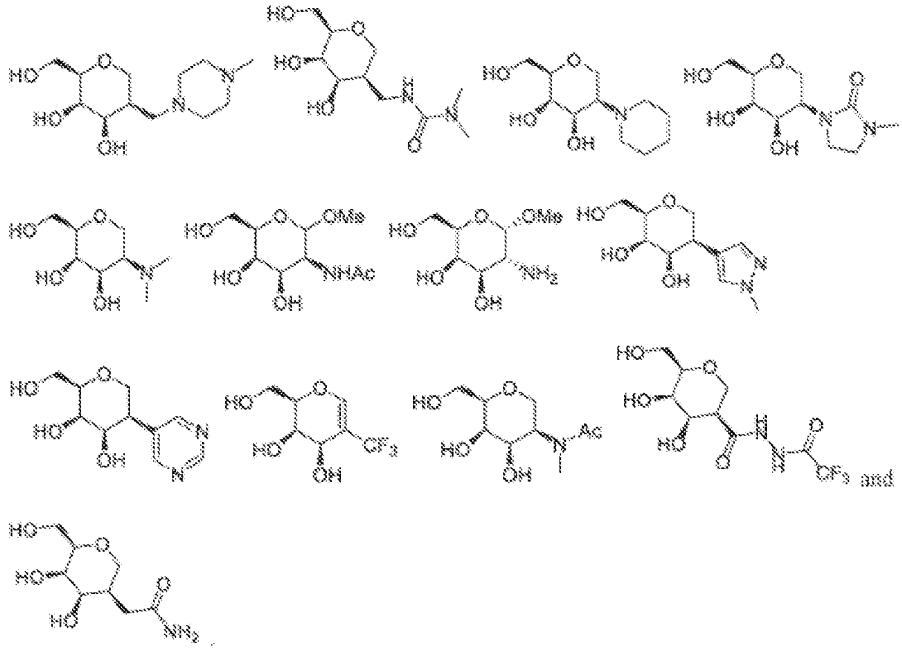

and
and



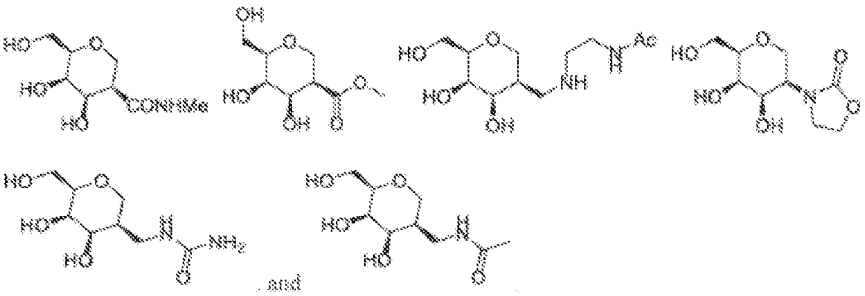




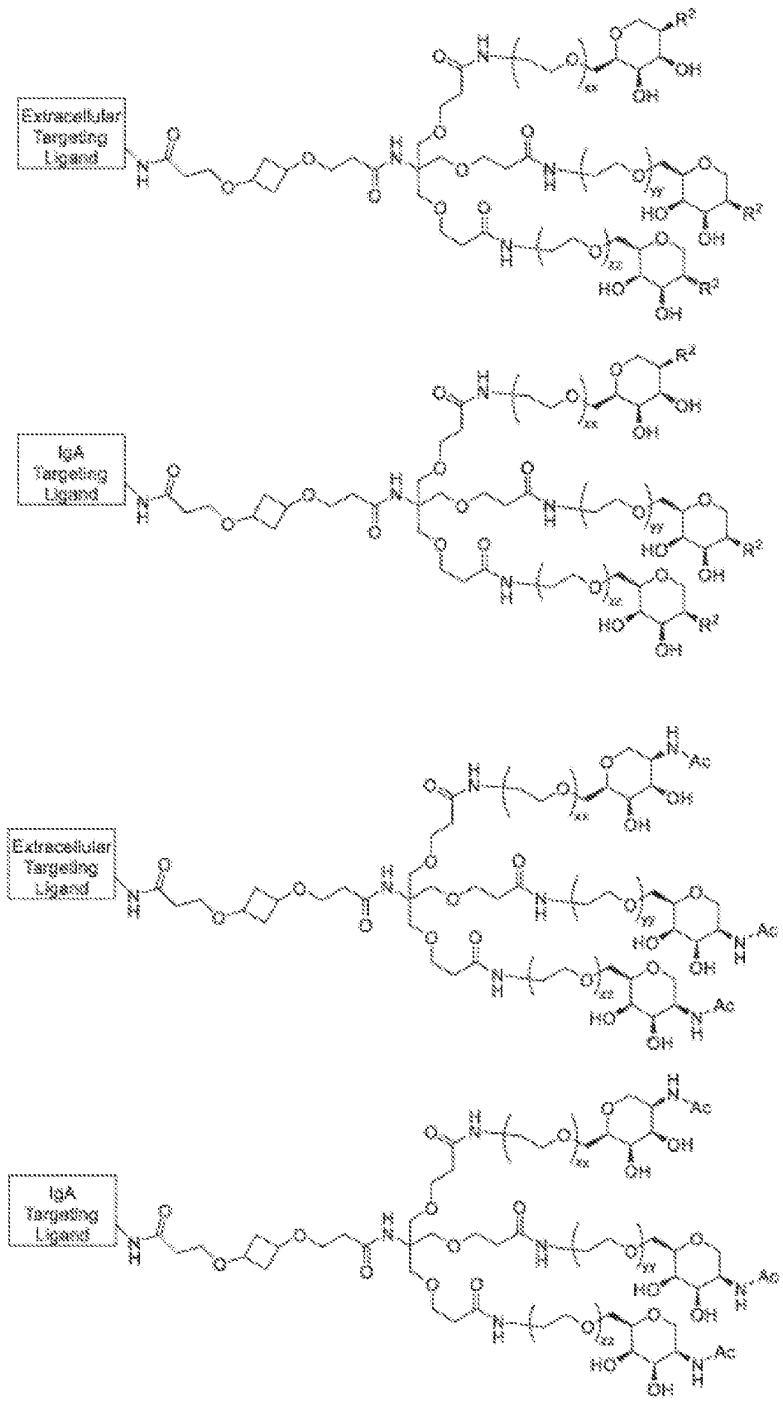
and

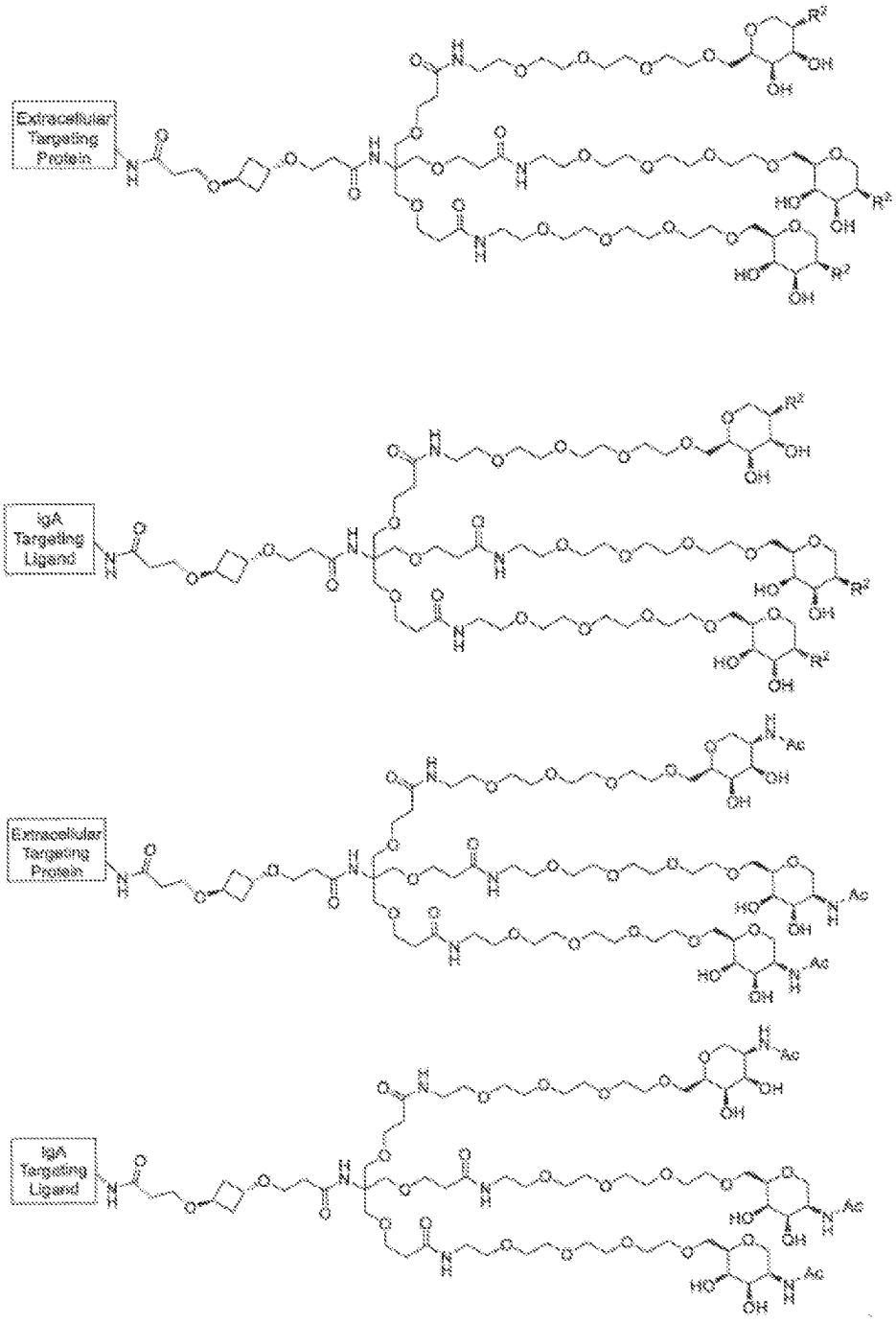


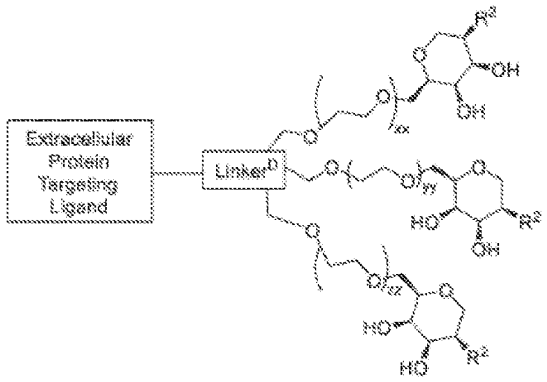
and

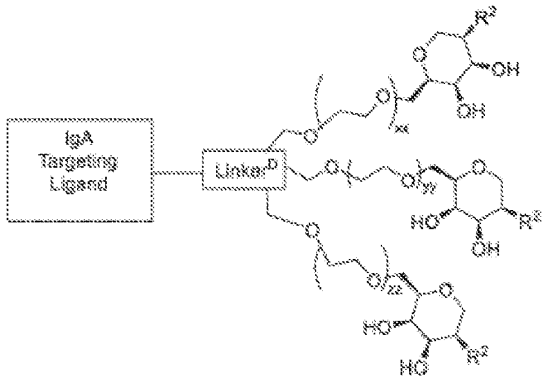


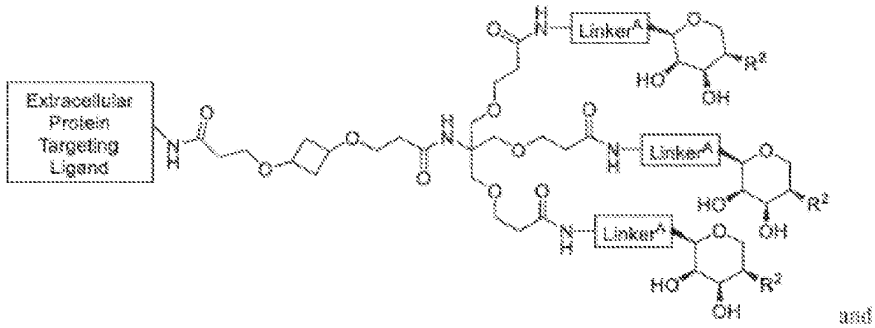
, and


Extracellular Targeting Ligand
IgA Targeting Ligand
Extracellular Targeting Ligand
IgA Targeting Ligand

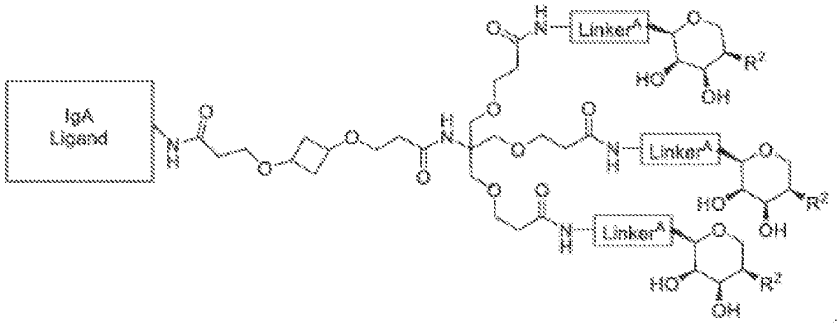

Extracellular Targeting Protein
IgA Targeting Ligand
Extracellular Targeting Protein
IgA Targeting Ligand

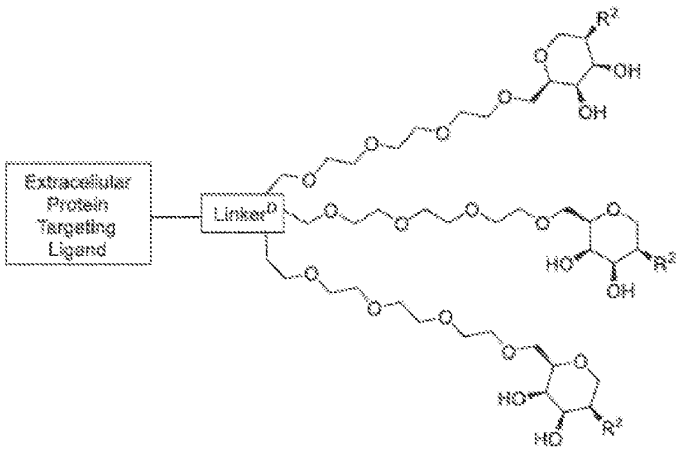

Extracellular Protein Targeting Ligand
Linker^D

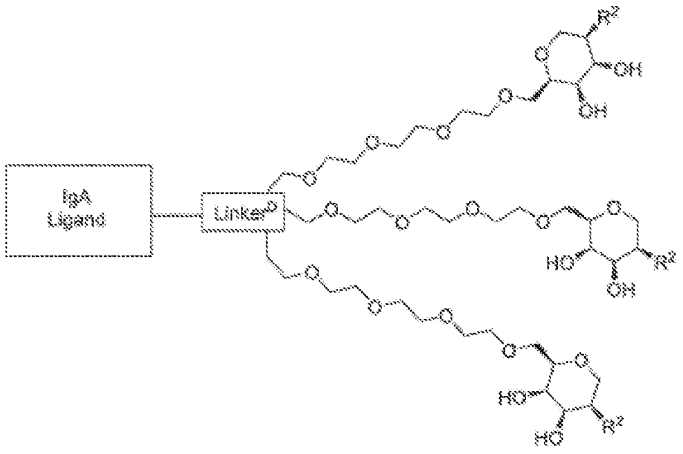

IgA Targeting Ligand
Linker^D

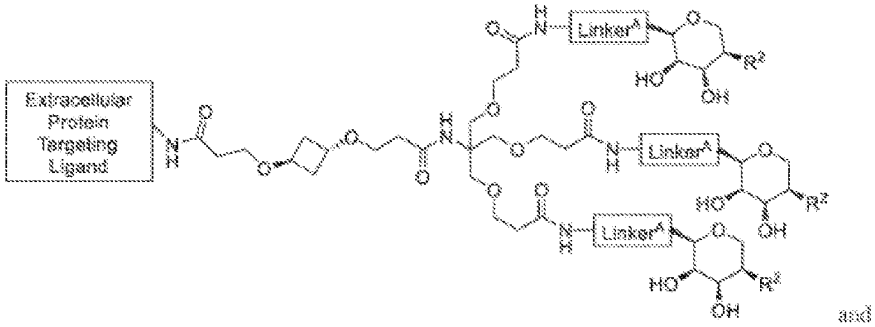

Extracellular Protein Targeting Ligand
Linker^A

and

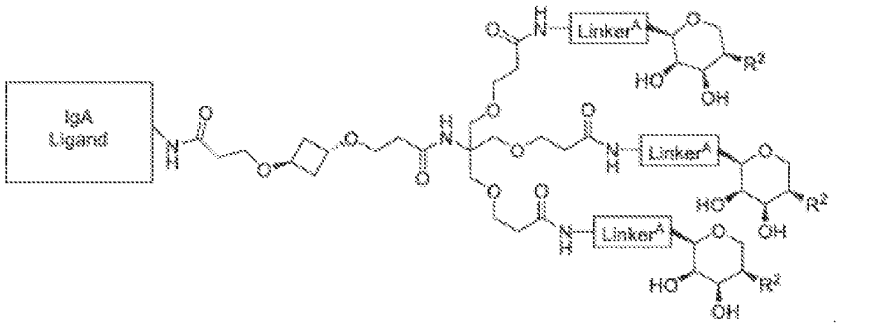

IgA Ligand
Linker^A

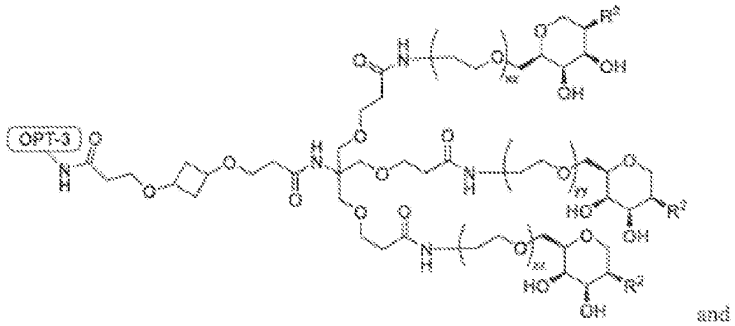

Extracellular Protein Targeting Ligand
Linker
O
R²
OH
HO

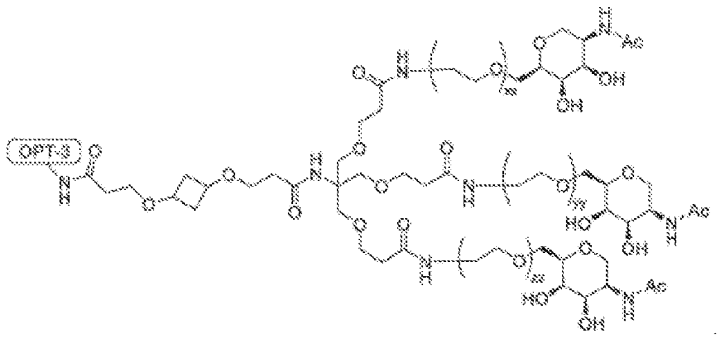

IgA Ligand
Linker^D

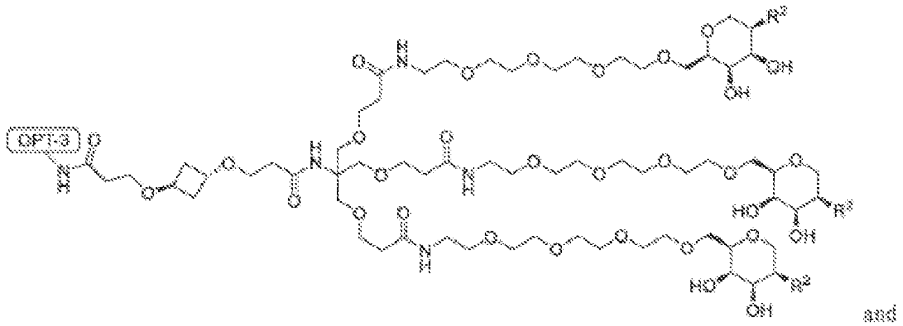

Extracellular Protein Targeting Ligand
Linker^A

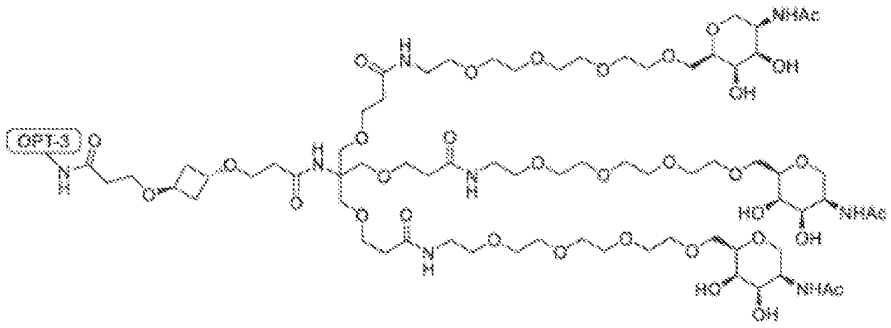
and


IgA Ligand
Linker^A









C. The ASGPR Ligand/Binding Moiety in Compounds of Formula II

In certain embodiments, in the compound of Formula II, R^1 is hydrogen.

In certain embodiments, in the compound of Formula II, R^1 is .

In certain embodiments, in the compound of Formula II, R^1 is .

In certain embodiments, in the compound of Formula II, R^1 is .

In certain embodiments, in the compound of Formula II, R^1 is .

In certain embodiments, in the compound of Formula II, R^1 is .

In certain embodiments, in the compound of Formula II, R^1 is .

In certain embodiments, in the compound of Formula II, R^1 is C_0-C_6alkyl-cyano optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^1 is alkyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^1 is alkenyl optionally substituted with 1, 2, 3, or 4 substituents. In certain embodiments, in the compound of Formula II, R^1 is alkynyl optionally substituted with 1, 2, 3, or 4 substituents. In certain embodiments, in the compound of Formula II, R^1 is haloalkyl optionally substituted with 1, 2, 3, or 4 substituents. In certain embodiments, in the compound of Formula II, R^1 is F.

In certain embodiments, in the compound of Formula II, R^1 is Cl.

In certain embodiments, in the compound of Formula II, R^1 is Br.

In certain embodiments, in the compound of Formula II, R^1 is aryl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^1 is arylalkyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^1 is heteroaryl alkyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^1 is heterocycle optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^1 is heterocycloalkyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^1 is haloalkoxy optionally substituted with 1, 2, 3, or 4 substituents.

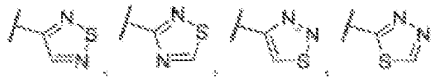
In certain embodiments, in the compound of Formula II, R^1 is -O-alkenyl, -O-alkynyl, C_0-C_6alkyl-OR^6, C_0-C_6alkyl-SR^6, C_0-C_6alkyl-NR^6R^7, C_0-C_6alkyl-$C(O)R^3$, C_0-C_6alkyl-$S(O)R^3$, C_0-C_6alkyl-$C(S)R^3$, C_0-C_6alkyl-$S(O)_2R^3$, C_0-C_6alkyl-$N(R^8)$-$C(O)R^3$, C_0-C_6alkyl-$N(R^8)$-$S(O)R^3$, C_0-C_6alkyl-$N(R^8)$-$C(S)R^3$, C_0-C_6alkyl-$N(R^8)$-$S(O)_2R^3$ C_0-C_6alkyl-O-$C(O)R^3$, C_0-C_6alkyl-O-$S(O)R^3$, C_0-C_6alkyl-O-$C(S)R^3$, -$N=S(O)(R^3)_2$, C_0-C_6alkylN_3, or C_0-C_6alkyl-O-$S(O)_2R^3$, each of which is optionally substituted with 1, 2, 3, or 4 substituents.

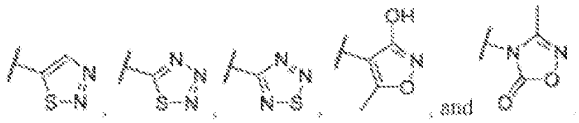
In certain embodiments, in the compound of Formula II, R^2 is aryl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is heterocycle optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is heteroaryl containing 1 or 2 heteroatoms independently selected from N, O, and S optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is selected from





In certain embodiments, in the compound of Formula II, R^2 is heterocycle optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -NR^8-$S(O)$-R^3 optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -NR^8-$C(S)$-R^3 optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -NR^8-$S(O)(NR^6)$-R^3 optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -$N=S(O)(R^3)_2$ optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -$NR^8C(O)NR^9S(O)_2R^3$

optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is $-NR^8-S(O)_2-R^{10}$ optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is $-NR^8-C(NR^6)-R^3$ optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is hydrogen.

In certain embodiments, in the compound of Formula II, R^2 is R^{10},

In certain embodiments, in the compound of Formula II, R^2 is alkyl-$C(O)-R^3$.

In certain embodiments, in the compound of Formula II, R^2 is $-C(O)-R^3$.

In certain embodiments, in the compound of Formula II, R^2 is alkyl.

In certain embodiments, in the compound of Formula II, R^2 is haloalkyl.

In certain embodiments, in the compound of Formula II, R^2 is $-OC(O)R^3$.

In certain embodiments, in the compound of Formula II, R^2 is $-NR^8-C(O)R^{10}$.

In certain embodiments, in the compound of Formula II, R^2 is alkenyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is allyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is alkynyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is $-NR^6$-alkenyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -O-alkenyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is $-NR^6$-alkynyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is $-NR^6$ -heteroaryl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is $-NR^6$-aryl optionally substituted with 1, 2, 3, or 4 substituents.

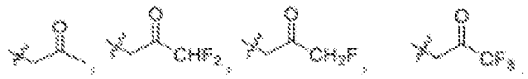
In certain embodiments, in the compound of Formula II, R^2 is -O-heteroaryl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -O-aryl optionally substituted with 1, 2, 3, or 4 substituents.

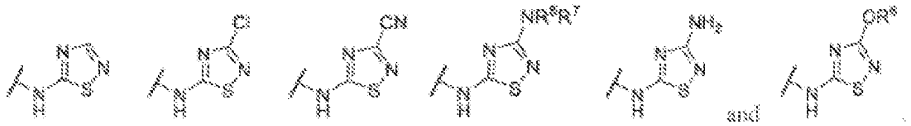
In certain embodiments, in the compound of Formula II, R^2 is -O-alkynyl optionally

substituted with 1, 2, 3, or 4 substituents.

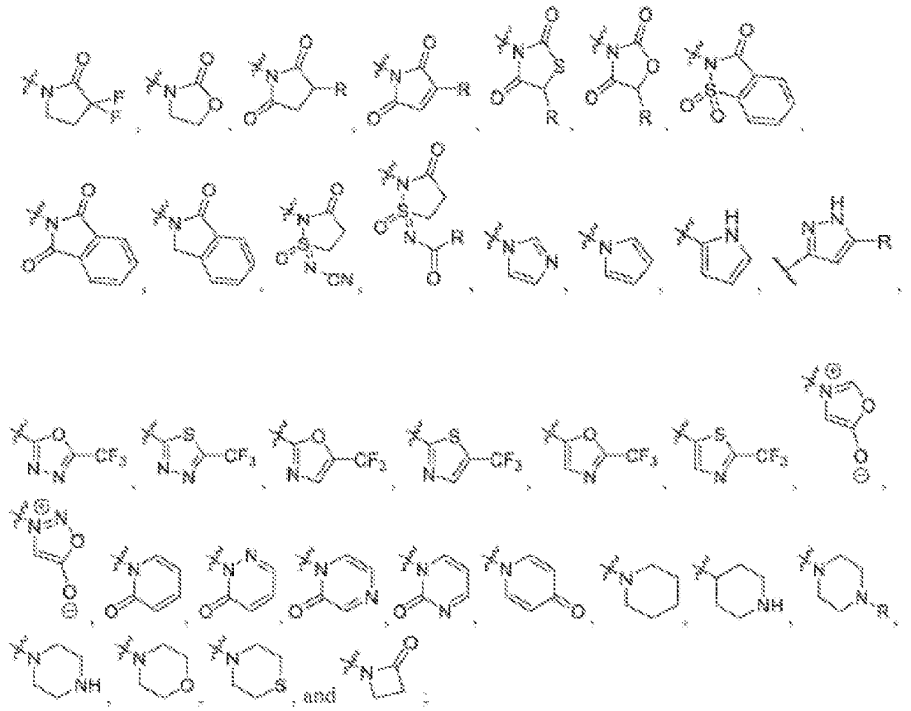
In certain embodiments, in the compound of Formula II, R^2 is selected from and



In certain embodiments, in the compound of Formula II, R^2 is selected from

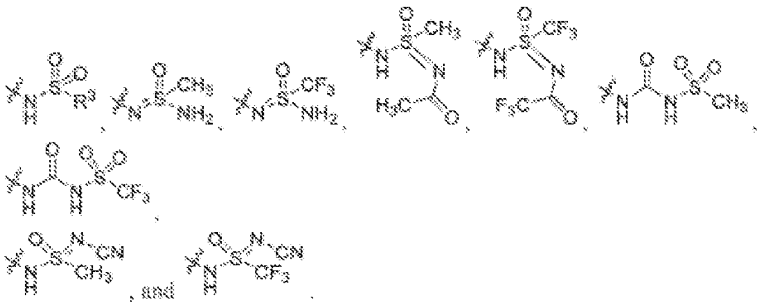


In certain embodiments, in the compound of Formula II, R^2 is selected from

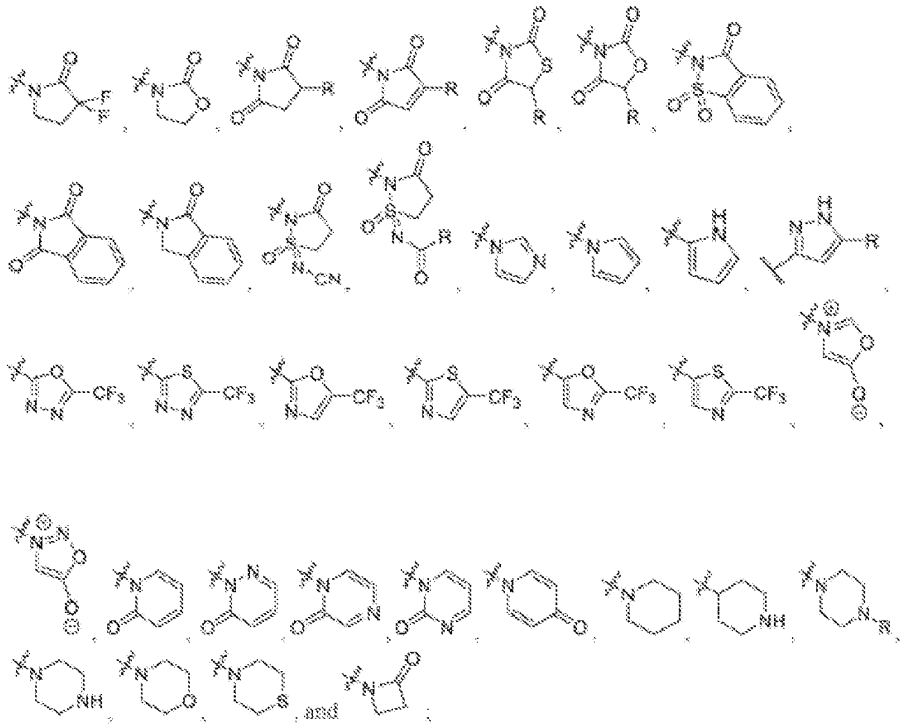


wherein R is an optional substituent as defined herein.

In certain embodiments, in the compound of Formula II, R^2 is selected from

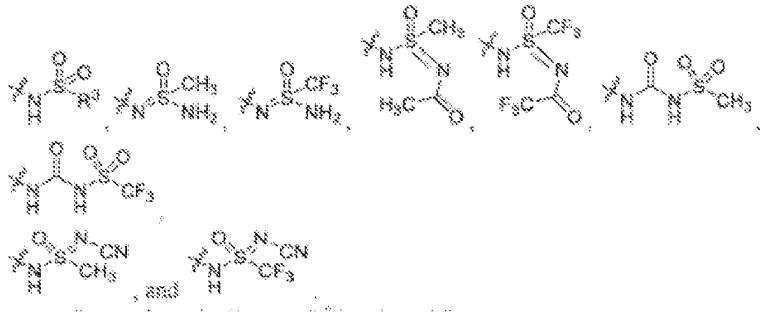


In certain embodiments, in the compound of Formula II, R^{2A} is selected from

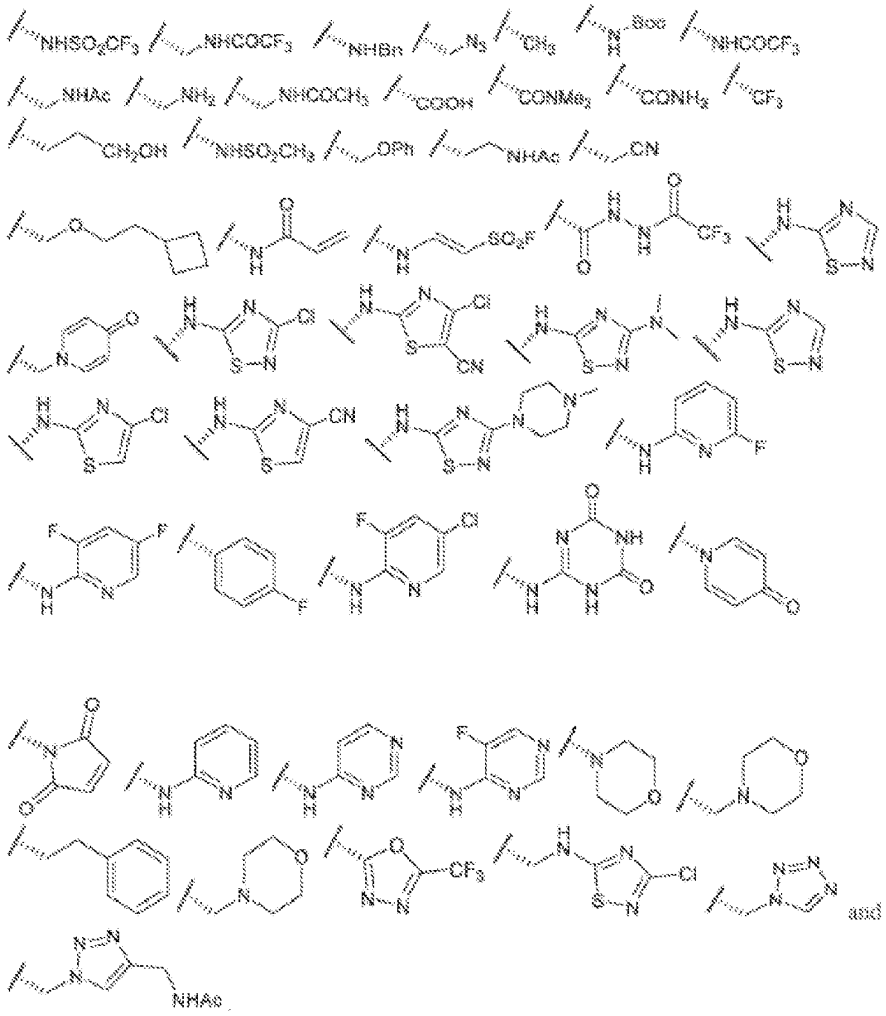


wherein R is an optional substituent as defined herein.

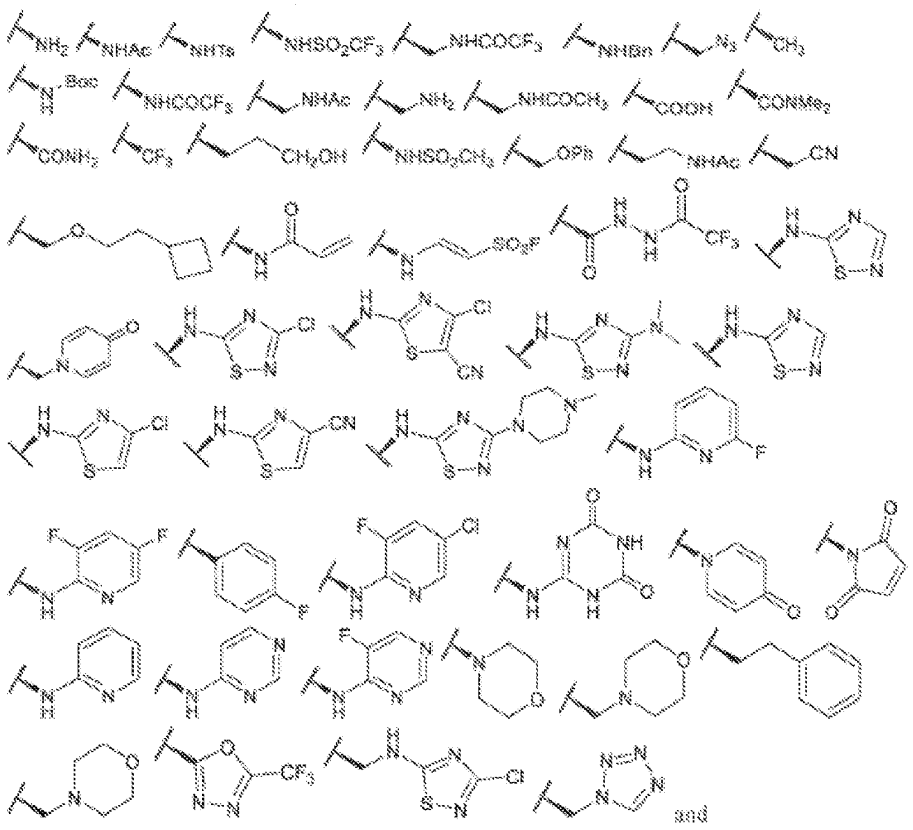
In certain embodiments, in the compound of Formula II, R^{2A} is selected from

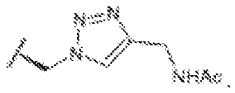


In certain embodiments, in the compound of Formula II, R^2 is selected from

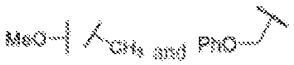


In certain embodiments, in the compound of Formula II, R^2 is selected from

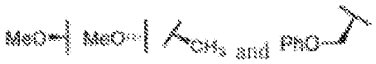




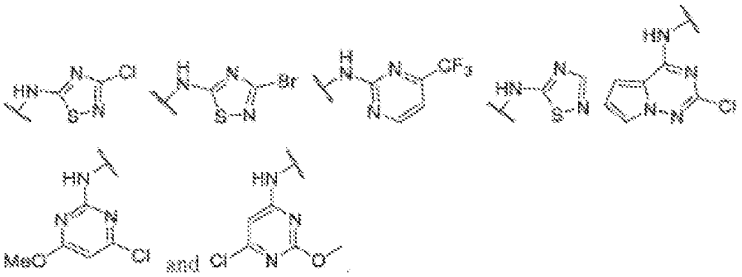
In certain embodiments, in the compound of Formula II, R^2 is selected from



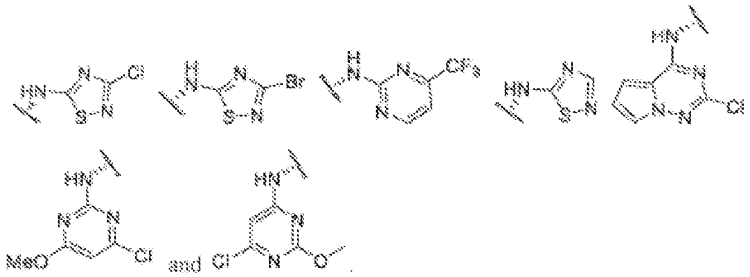
In certain embodiments, in the compound of Formula II, R^2 is selected from



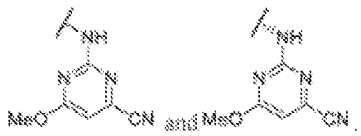
In certain embodiments, in the compound of Formula II, R^2 is selected from



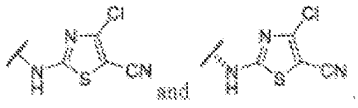
In certain embodiments, in the compound of Formula II, R^2 is selected from



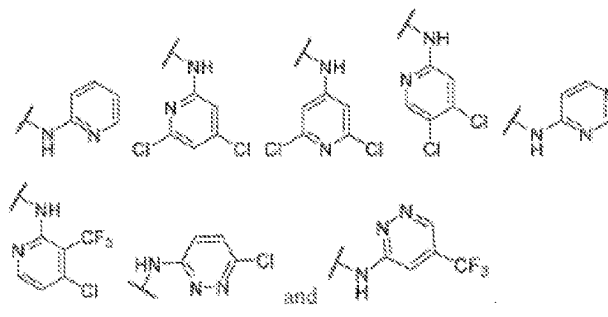
In certain embodiments, in the compound of Formula II, R^2 is selected from



In certain embodiments, in the compound of Formula II, R^2 is selected from

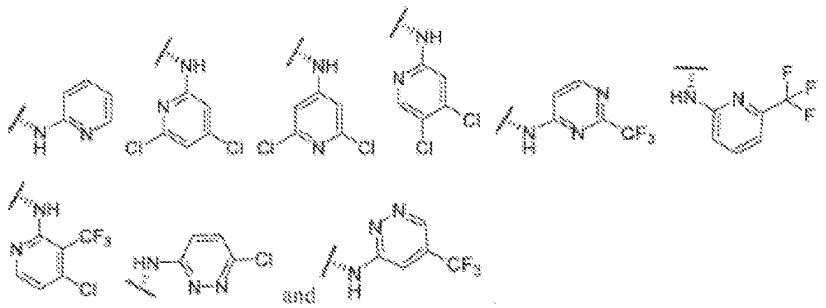


In certain embodiments, in the compound of Formula II, R^2 is selected from

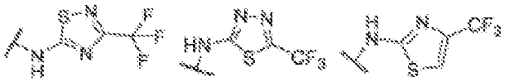


In certain embodiments, in the compound of Formula II, R^2 is selected from

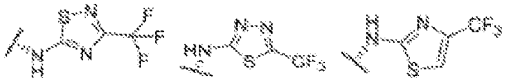
In certain embodiments, in the compound of Formula II, R^2 is selected from



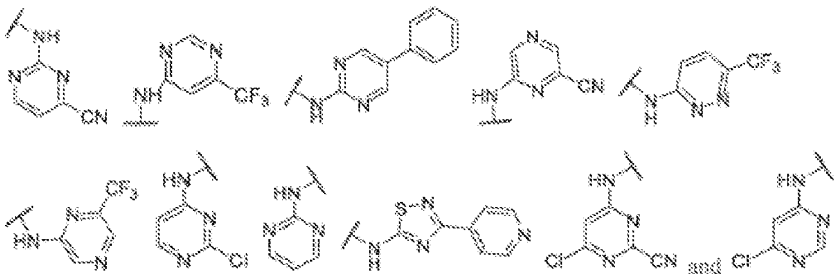
In certain embodiments, in the compound of Formula II, R^2 is selected from



In certain embodiments, in the compound of Formula II, R^2 is selected from



In certain embodiments, in the compound of Formula II, R^2 is selected from



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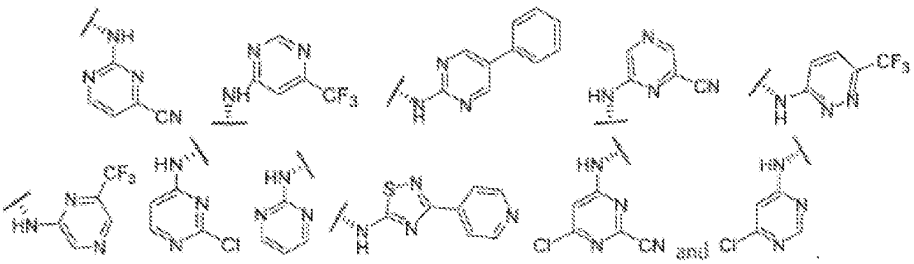
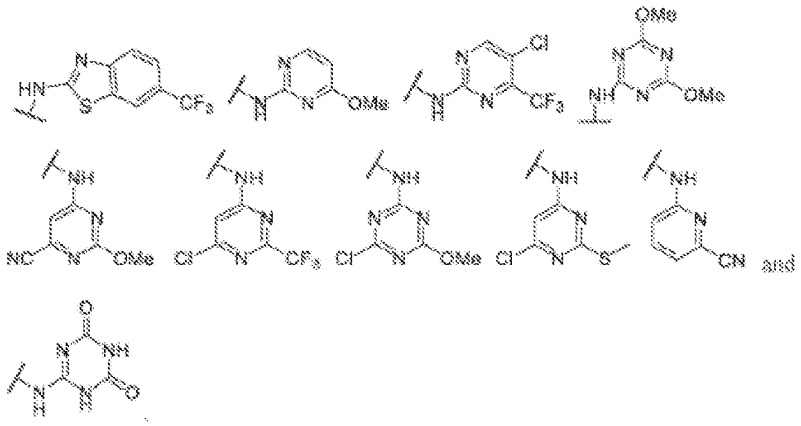
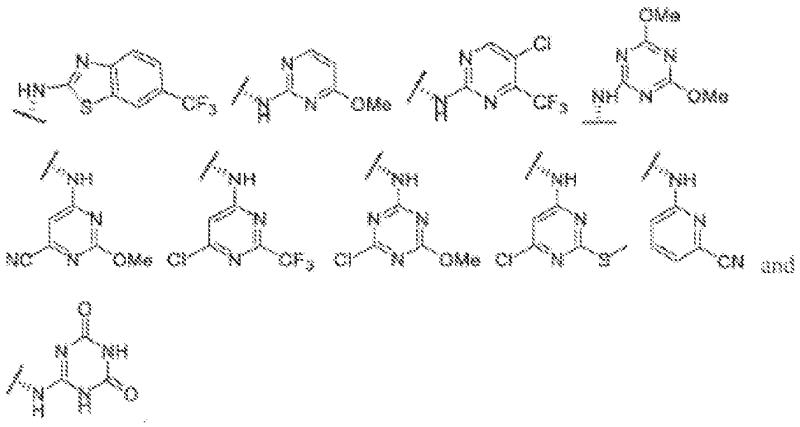


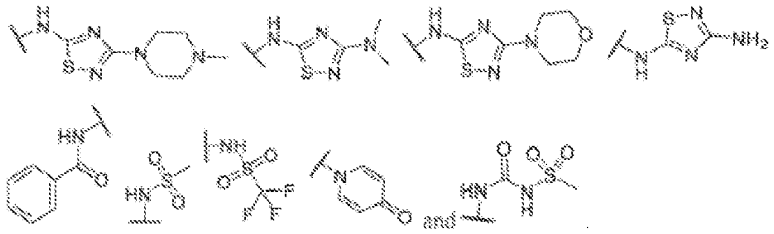
In certain embodiments, in the compound of Formula II, R^2 is selected from



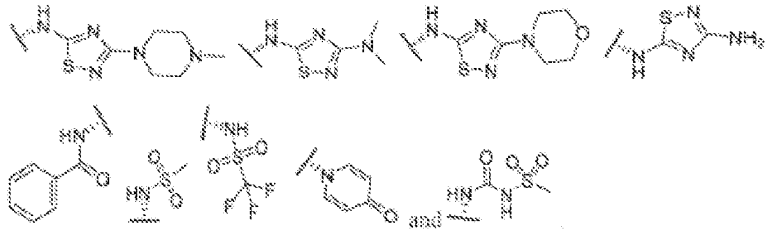
In certain embodiments, in the compound of Formula II, R^2 is selected from



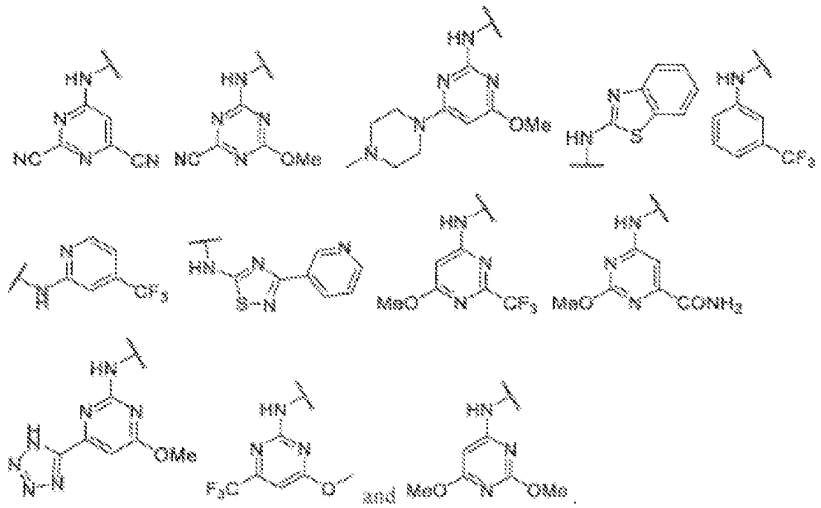
In certain embodiments, in the compound of Formula II, R^2 is selected from



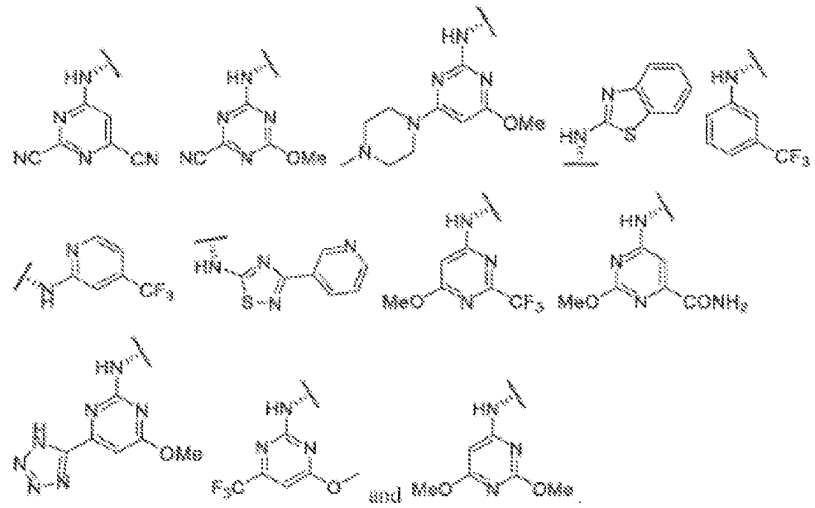
In certain embodiments, in the compound of Formula II, R^2 is selected from



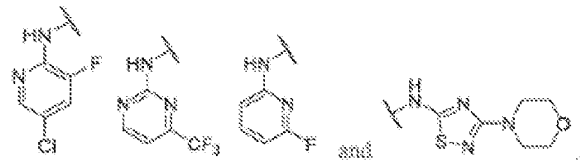
In certain embodiments, in the compound of Formula II, R^2 is selected from



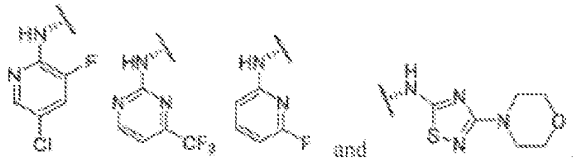
In certain embodiments, in the compound of Formula II, R^2 is selected from



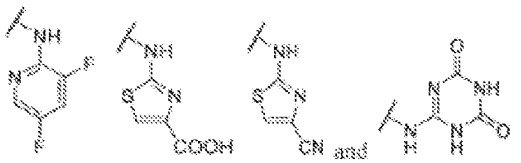
In certain embodiments, in the compound of Formula II, R^2 is selected from



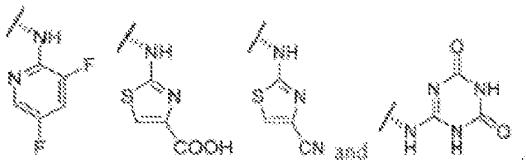
In certain embodiments, in the compound of Formula II, R^2 is selected from



In certain embodiments, in the compound of Formula II, R^2 is selected from



In certain embodiments, in the compound of Formula II, R^2 is selected from



In certain embodiments, in the compound of Formula II, R^2 is selected from

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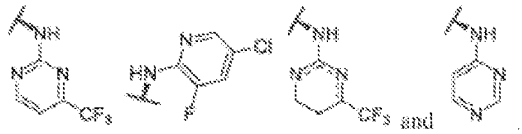

In certain embodiments, in the compound of Formula II, R^2 is selected from

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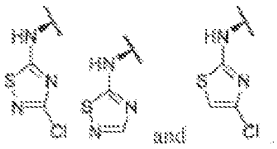
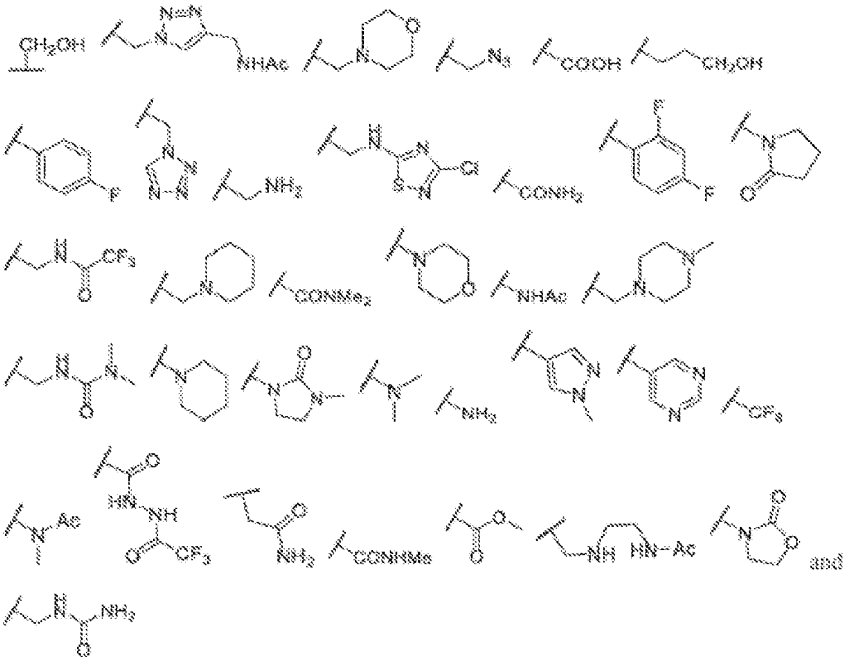
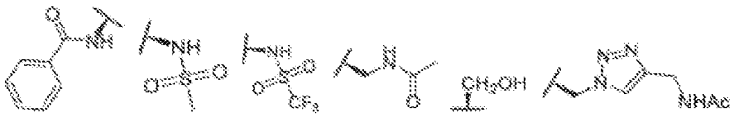
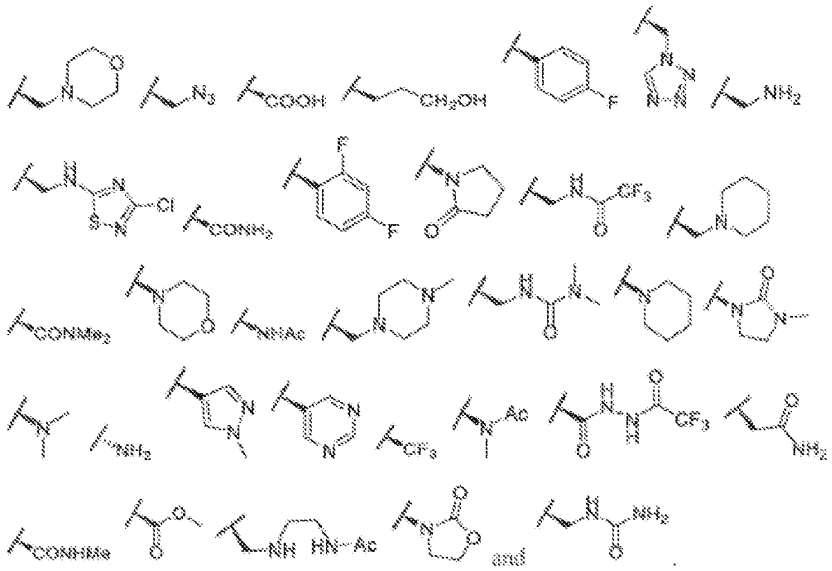


In certain embodiments, in the compound of Formula II, R^2 is selected from

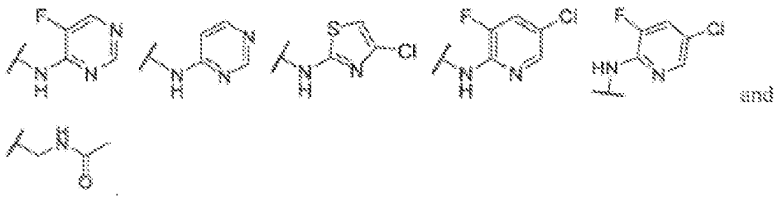


In certain embodiments, in the compound of Formula II, R^2 or R^{2A} is selected from

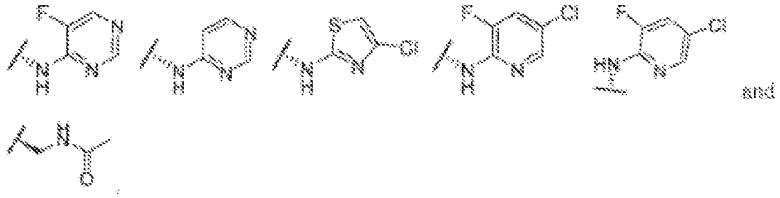




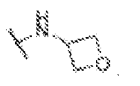
In certain embodiments, in the compound of Formula II, R^2 is selected from



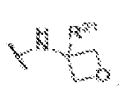
In certain embodiments, in the compound of Formula II, R^2 is selected from



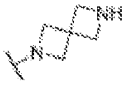
In certain embodiments, in the compound of Formula II, R^2 is selected from

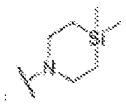


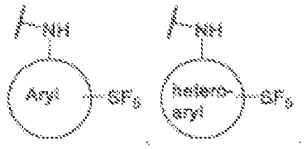
In certain embodiments, in the compound of Formula II, R^2 is selected from



In certain embodiments, in the compound of Formula II, R^2 is selected from

In certain embodiments, in the compound of Formula II, R^2 is a spirocyclic heterocycle, for example, and without limitation, 

In certain embodiments, in the compound of Formula II, R^2 is a silicon containing heterocycle, for example, and without limitation,  .

In certain embodiments, in the compound of Formula II, R^2 is substituted with SF_5, for example, and without limitation, 

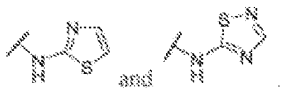
In certain embodiments, in the compound of Formula II, R^2 is substituted with a sulfoxime, for example, and without limitation,

In certain embodiments, in the compound of Formula II, R^{10} is selected from bicyclic heterocycle.

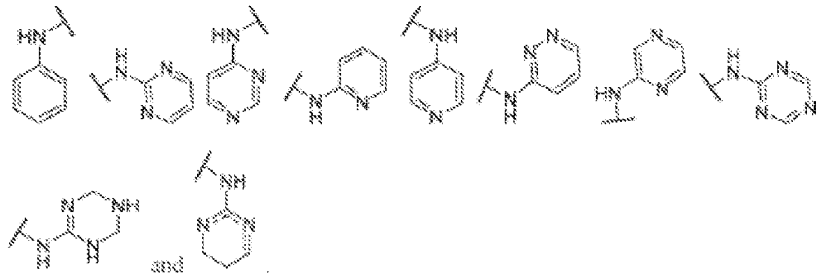
In certain embodiments, in the compound of Formula II, R^{10} is selected from spirocyclic heterocycle.

In certain embodiments, in the compound of Formula II, R^{10} is selected from -NR^6-heterocycle.

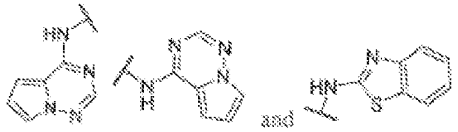
In certain embodiments, in the compound of Formula II, R^{10} is selected from



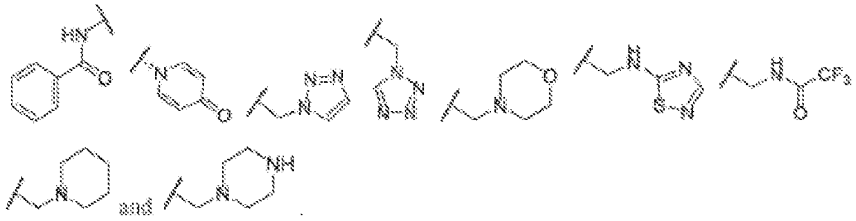
In certain embodiments, in the compound of Formula II, R^{10} is selected from



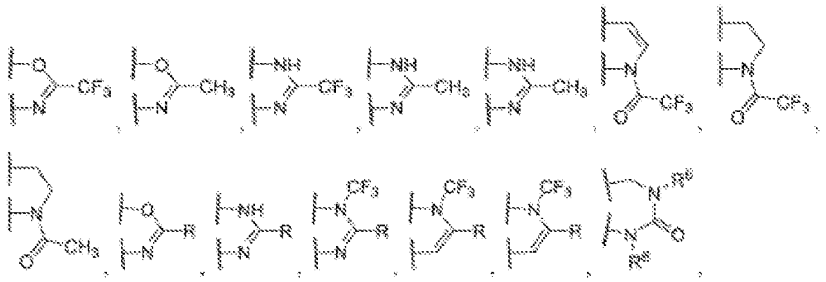
In certain embodiments, in the compound of Formula II, R^{10} is selected from

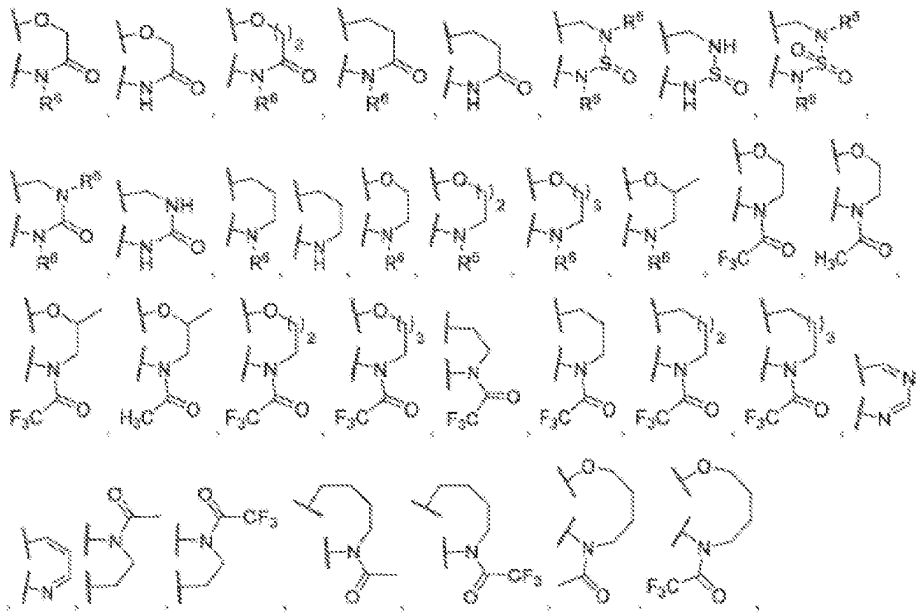


In certain embodiments, in the compound of Formula II, R^{10} is selected from

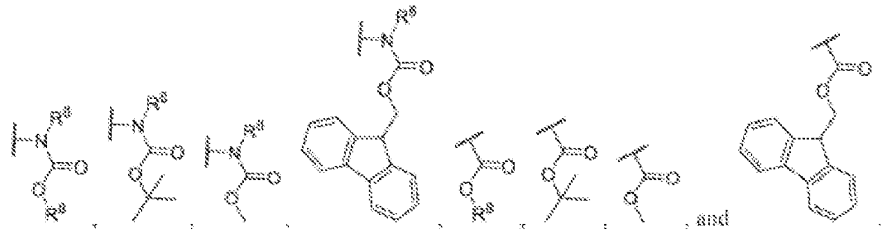


In certain embodiments, in the compound of Formula II, Cycle is selected from

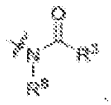


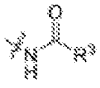


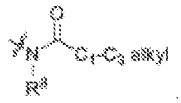
In certain embodiments, in the compound of Formula II, R^{30} is selected from:

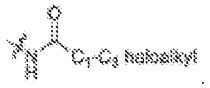


In certain embodiments, in the compound of Formula II, R^{200} is

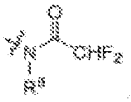


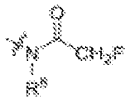
In certain embodiments, in the compound of Formula II, R^{200} is 

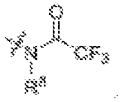
In certain embodiments, in the compound of Formula II, R^{200} is 

In certain embodiments, in the compound of Formula II, R^{200} is  .

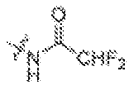
In certain embodiments, in the compound of Formula II, R^{200} is .

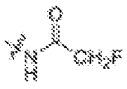
In certain embodiments, in the compound of Formula II, R^{200} is  .

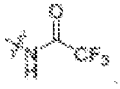
In certain embodiments, in the compound of Formula II, R^{200} is  .

In certain embodiments, in the compound of Formula II, R^{200} is  .

In certain embodiments, in the compound of Formula II, R^{200} is .

In certain embodiments, in the compound of Formula II, R^{200} is  .

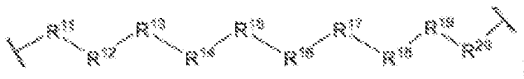
In certain embodiments, in the compound of Formula II, R^{200} is  .

In certain embodiments, in the compound of Formula II, R^{200} is  .

In certain embodiments, in the compound of Formula II, R^{200} is .

Linkers

In non-limiting embodiments, in the compound of Formula II, $Linker^A$ and $Linker^B$ are independently selected from:



wherein:

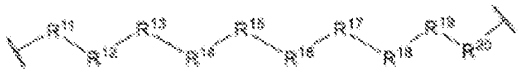
R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently at each occurrence selected from the group consisting of a bond, alkyl, -C(O)-, -C(O)O-, -OC(O)-, $-SO_2-$, -S(O)-, -C(S)-, $-C(O)NR^6-$, $-NR^6C(O)-$, -O-, -S-, $-NR^6-$, $-C(R^{21}R^{21})-$, $-P(O)(R^3)O-$, $-P(O)(R^3)-$, a

divalent residue of a natural or unnatural amino acid, alkenyl, alkynyl, haloalkyl, alkoxy, and, heterocycle, heteroaryl, $-CH_2CH_2-[O-(CH_2)_2]_n-O-$, $CH_2CH_2-[O-(CH_2)_2]_n-NR^6-$, $-CH_2CH_2-[O-(CH_2)_2]_n-$, $-[-(CH_2)_2-O-]_n-$, $-[O-(CH_2)_2]_n-$,$-[O-CH(CH_3)C(O)]_n-$, $-[C(O)-CH(CH_3)-O]_n-$, $-[O-CH_2C(O)]_n-$, $-[C(O)-CH_2-O]_n-$, a divalent residue of a fatty acid, a divalent residue of an unsaturated or saturated mono- or di-carboxylic acid; each of which is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{21};

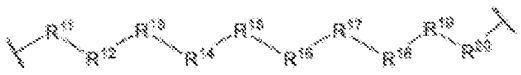
n is independently selected at each instance from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

R^{21} is independently at each occurrence selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, F, Cl, Br, I, hydroxyl, alkoxy, azide, amino, cyano, $-NR^6R^7$, $-NR^8SO_2R^3$, $-NR^8S(O)R^3$, haloalkyl, heteroalkyl, and, heteroaryl, and heterocycle; and the remaining variables are as defined herein.

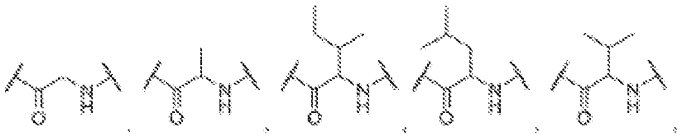
In one embodiment, in the compound of Formula II, $Linker^A$ is bond and $Linker^B$ is

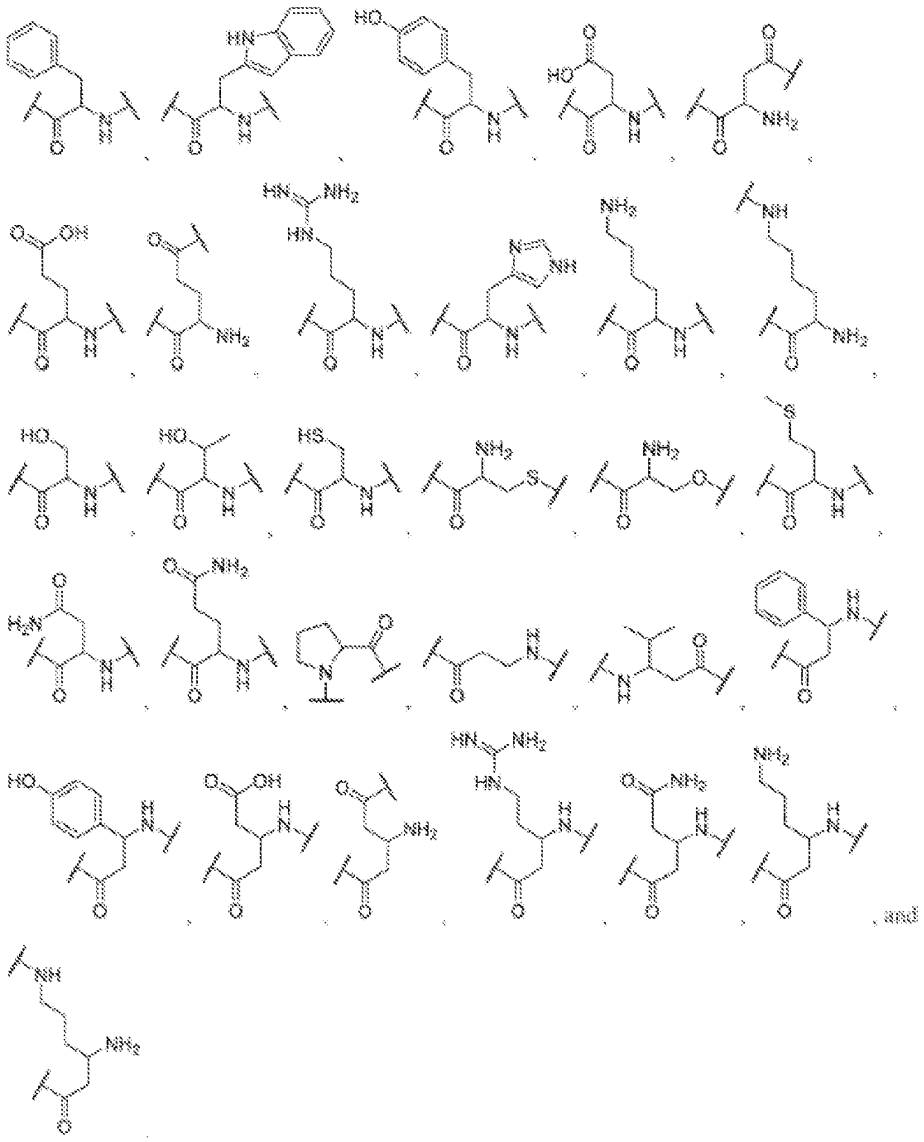


In one embodiment, in the compound of Formula II, $Linker^B$ is bond and $Linker^A$ is



In one embodiment, in the compound of Formula II, a divalent residue of an amino acid is selected from



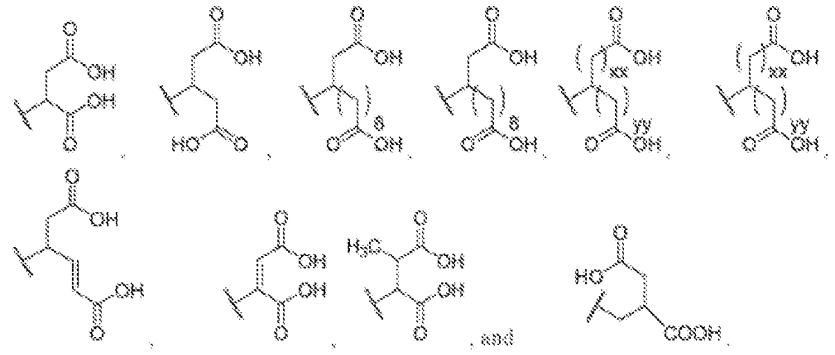


,

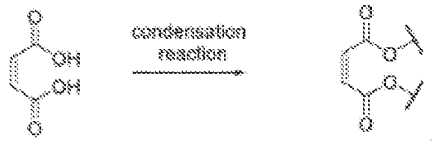
wherein the amino acid can be oriented in either direction and wherein the amino acid can be in the L- or D-form or a mixture thereof.

In one embodiment, in the compound of Formula II, a divalent residue of a dicarboxylic acid is generated from a nucleophilic addition reaction:

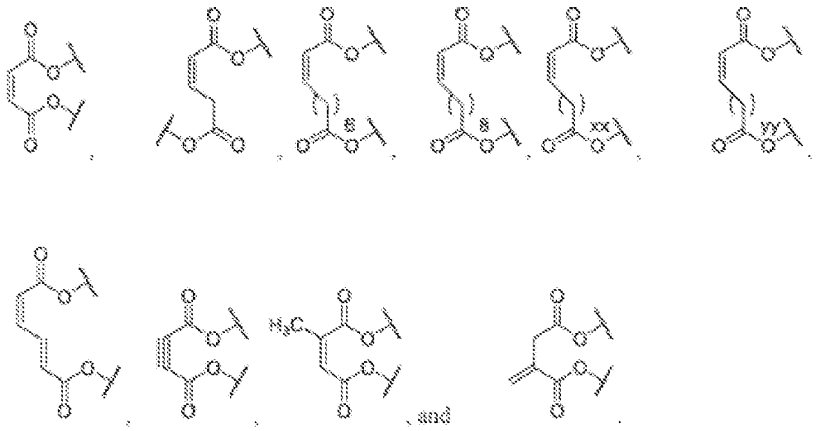
Non-limiting embodiments of a divalent residue of a dicarboxylic acid generated from a nucleophilic addition reaction include:



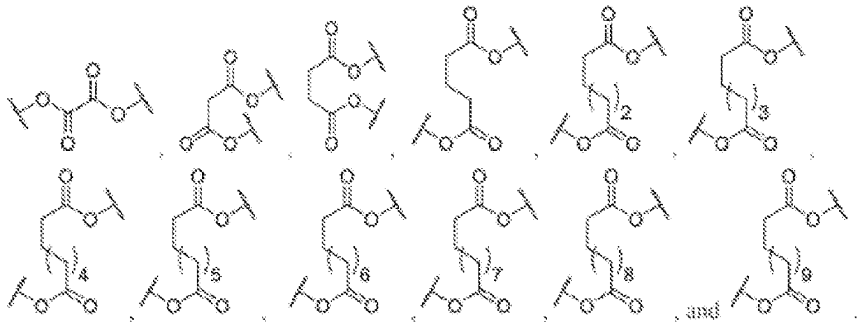
In one embodiment, in the compound of Formula II, a divalent residue of a dicarboxylic acid is generated from a condensation reaction:



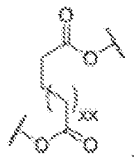
Non-limiting embodiments of a divalent residue of a dicarboxylic acid generated from a condensation include:



Non-limiting embodiments of a divalent residue of a saturated dicarboxylic acid include:

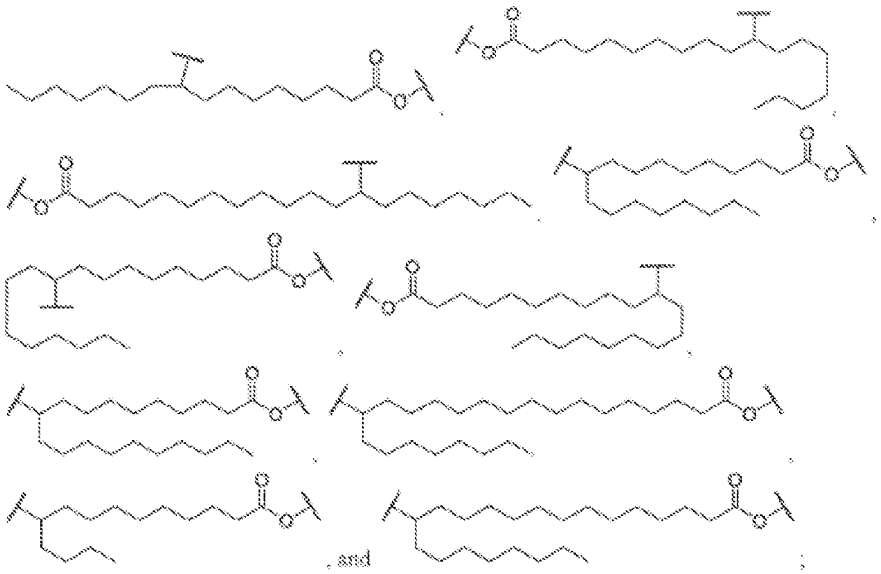


Non-limiting embodiments of a divalent residue of a saturated dicarboxylic acid include:



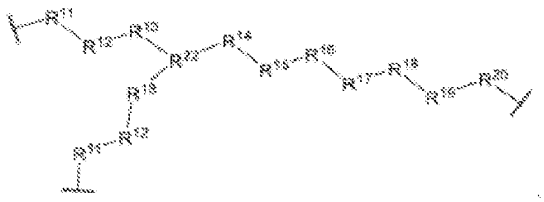
Non-limiting embodiments of a divalent residue of a saturated monocarboxylic acid is selected from butyric acid (-OC(O)$(CH_2)_2CH_2$-), caproic acid (-OC(O)$(CH_2)_4CH_2$-), caprylic acid (-OC(O)$(CH_2)_5CH_2$-), capric acid (-OC(O)$(CH_2)_8CH_2$-), lauric acid (-OC(O)$(CH_2)_{10}CH_2$-), myristic acid (-OC(O)$(CH_2)_{12}CH_2$-), pentadecanoic acid (-OC(O)$(CH_2)_{13}CH_2$-), palmitic acid (-OC(O)$(CH_2)_{14}CH_2$-), stearic acid (-OC(O)$(CH_2)_{16}CH_2$-), behenic acid (-OC(O)$(CH_2)_{20}CH_2$-), and lignoceric acid (-OC(O)$(CH_2)_{22}CH_2$-);

Non-limiting embodiments of a divalent residue of a fatty acid include residues selected from linoleic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, gadoleic acid, nervonic acid, myristoleic acid, and erucic acid:



Non-limiting embodiments of a divalent residue of a fatty acid is selected from linoleic acid (-$C(O)(CH_2)_7(CH)_2CH_2(CH)_2(CH_2)_4CH_2$-), docosahexaenoic acid (-$C(O)(CH_2)_2(CHCHCH_2)_6CH_2$-), eicosapentaenoic acid (-$C(O)(CH_2)_3(CHCHCH_2)_5CH_2$-), alpha-linolenic acid (-$C(O)(CH_2)_7(CHCHCH_2)_3CH_2$-) stearidonic acid (-$C(O)(CH_2)_4(CHCHCH_2)_4CH_2$-), y-linolenic acid (-$C(O)(CH_2)_4(CHCHCH_2)_3(CH_2)_3CH_2$-), arachidonic acid (-$C(O)(CH_2)_3,(CHCHCH_2)_4(CH_2)_4CH_2$-), docosatetraenoic acid (-$C(O)(CH_2)_5(CHCHCH_2)_4(CH_2)_4CH_2$-), palmitoleic acid (-$C(O)(CH_2)_7CHCH(CH_2)_5CH_2$-), vaccenic acid (-$C(O)(CH_2)_9CHCH(CH_2)_5CH_2$-), paullinic acid (-$C(O)(CH_2)_{11}CHCH(CH_2)_5CH_2$-), oleic acid (-$C(O)(CH_2)_7CHCH(CH_2)_7CH_2$-), elaidic acid (-$C(O)(CH_2)_7CHCH(CH_2)_7CH_2$-), gondoic acid (-$C(O)(CH_2)_9CHCH(CH_2)_7CH_2$-), gadoleic acid (-$C(O)(CH_2)_7CHCH(CH_2)_9CH_2$-), nervonic acid (-$C(O)(CH_2)_{13}CHCH(CH_2)_3CH_2$-), mead acid (-$C(O)(CH_2)_3(CHCHCH_2)_3(CH_2)_6CH_2$-), myristoleic acid (-$C(O)(CH_2)_7CHCH(CH_2)_3CH_2$-), and erucic acid (-$C(O)(CH_2)_{11}CHCH(CH_2)_7CH_2$-).

In certain embodiments, in the compound of Formula II, $Linker^C$ is selected from:

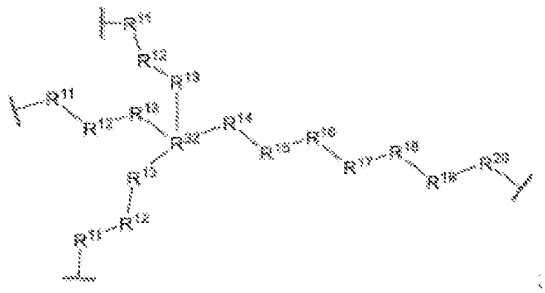


wherein:

R^{22} is independently at each occurrence selected from the group consisting of alkyl, -C(O)N-, -NC(O)-, -N-, -C(R^{21})-, -P(O)O-, -P(O)-, -P(O)(NR^6R^7)N-, alkenyl, haloalkyl, aryl, heterocycle, and heteroaryl, each of which is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{21};

and the remaining variables are as defined herein.

In certain embodiments, in the compound of Formula II, $Linker^D$ is selected from:



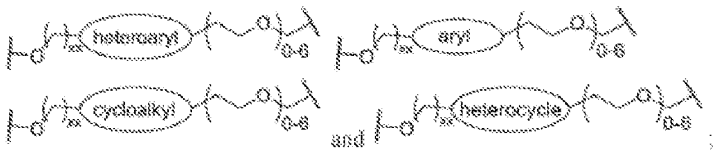
wherein:

R^{32} is independently at each occurrence selected from the group consisting of alkyl, N^+X^-, -C-, alkenyl, haloalkyl, aryl, heterocycle, and heteroaryl, each of which is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{21};

X- is an anionic group, for example Br- or Cl^-; and

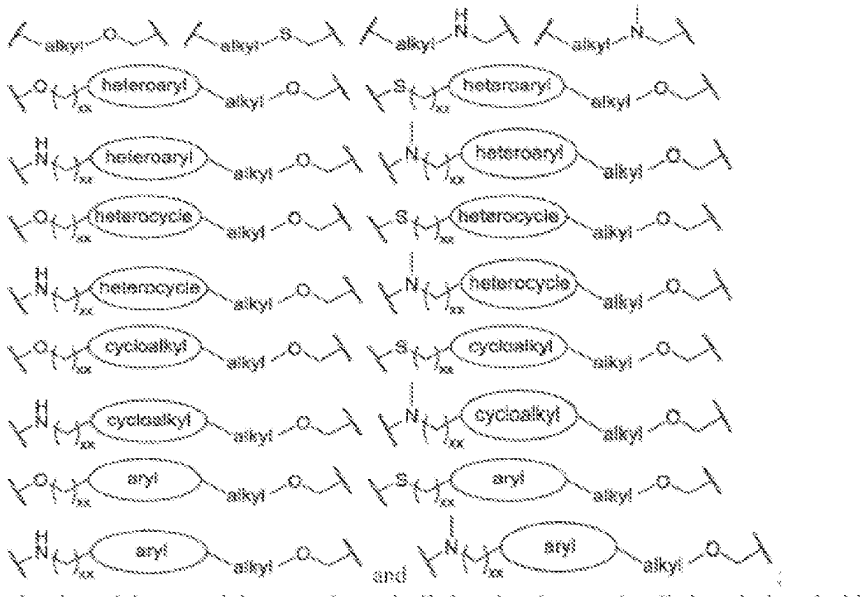
all other variables are as defined herein.

In certain embodiments, in the compound of Formula II, $Linker^A$ is selected from:



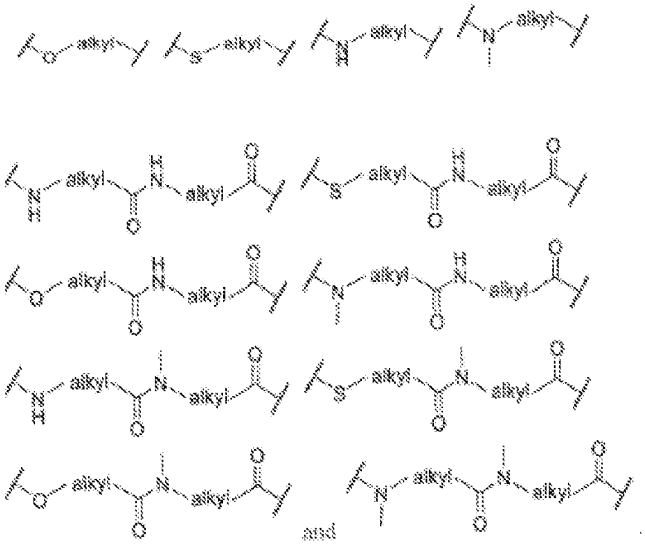
wherein each heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, and, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence.

In certain embodiments, in the compound of Formula II, $Linker^A$ is selected from:

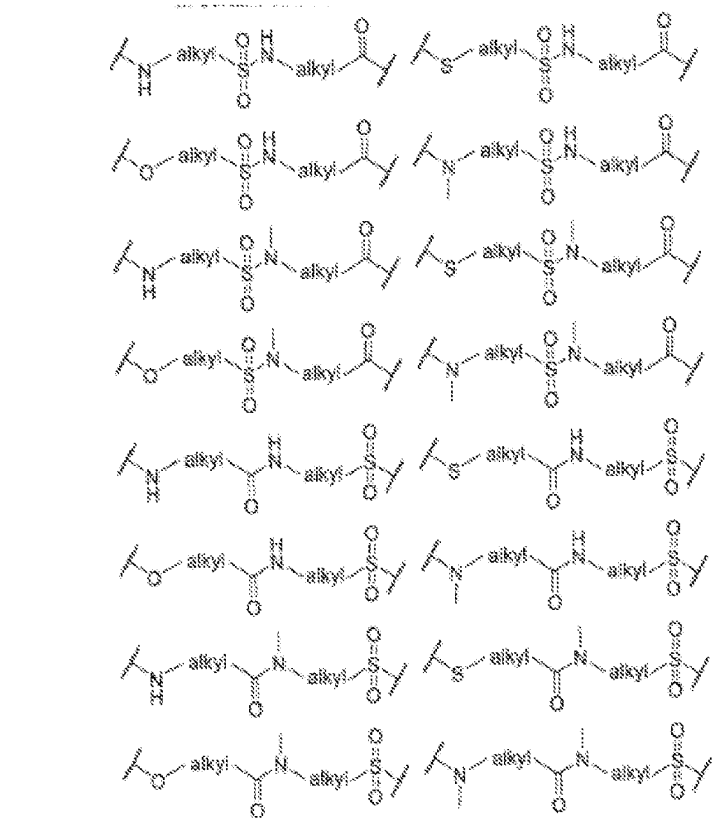


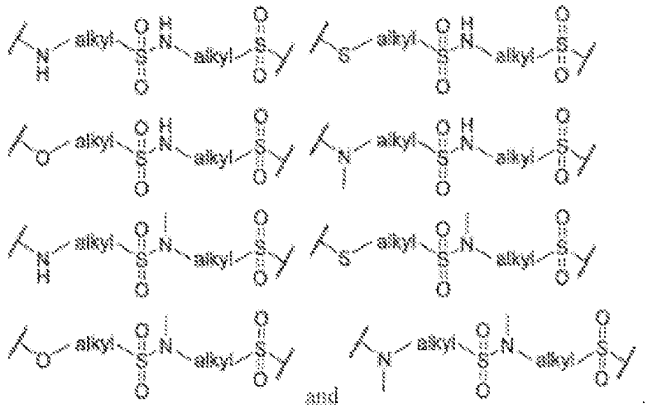
wherein each heteroaryl, heterocycle, cycloalkyl, and and can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence.

In certain embodiments, in the compound of Formula II, Linker^B is selected from:



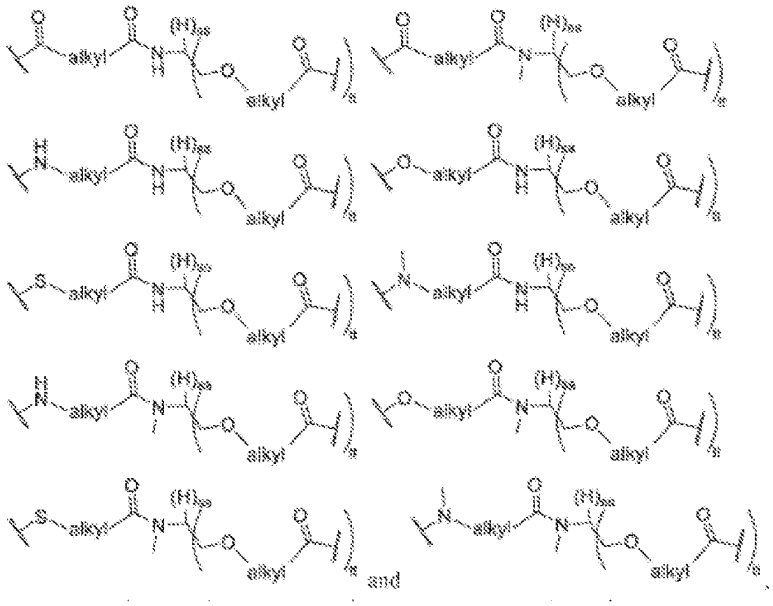
In certain embodiments, in the compound of Formula II, Linker^B is selected from:





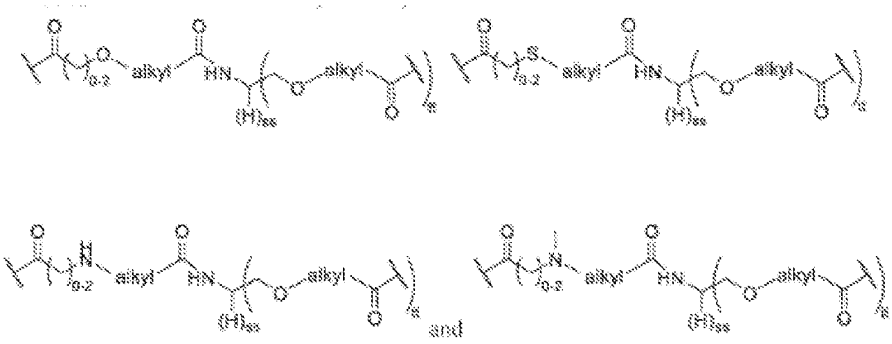
and

In certain embodiments, in the compound of Formula II, Linker^{B}, Linker^{C}, or Linker^{D} is selected from:



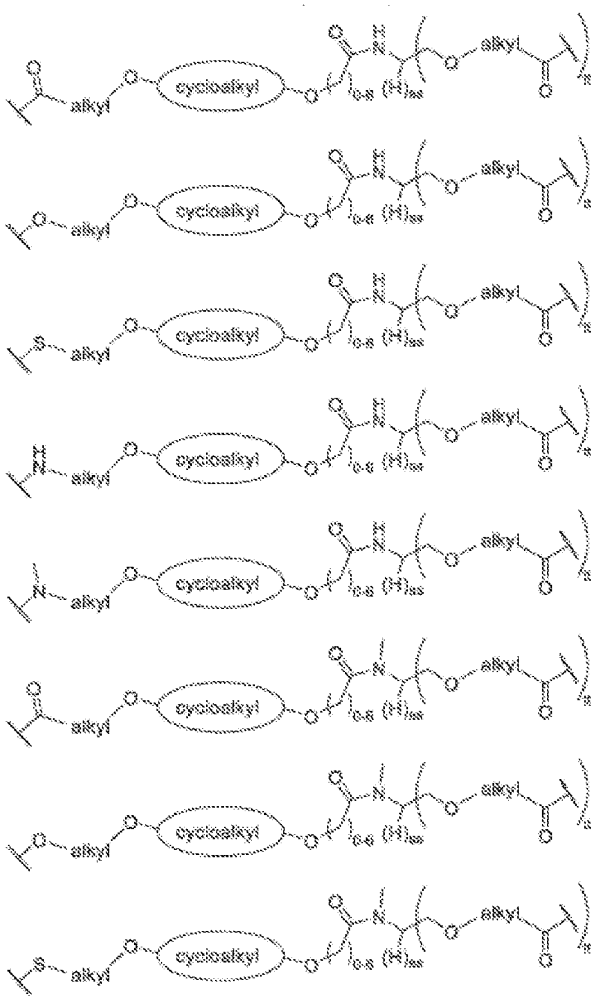
wherein tt is independently selected from 1, 2, or 3 and ss is 3 minus tt (3-tt).

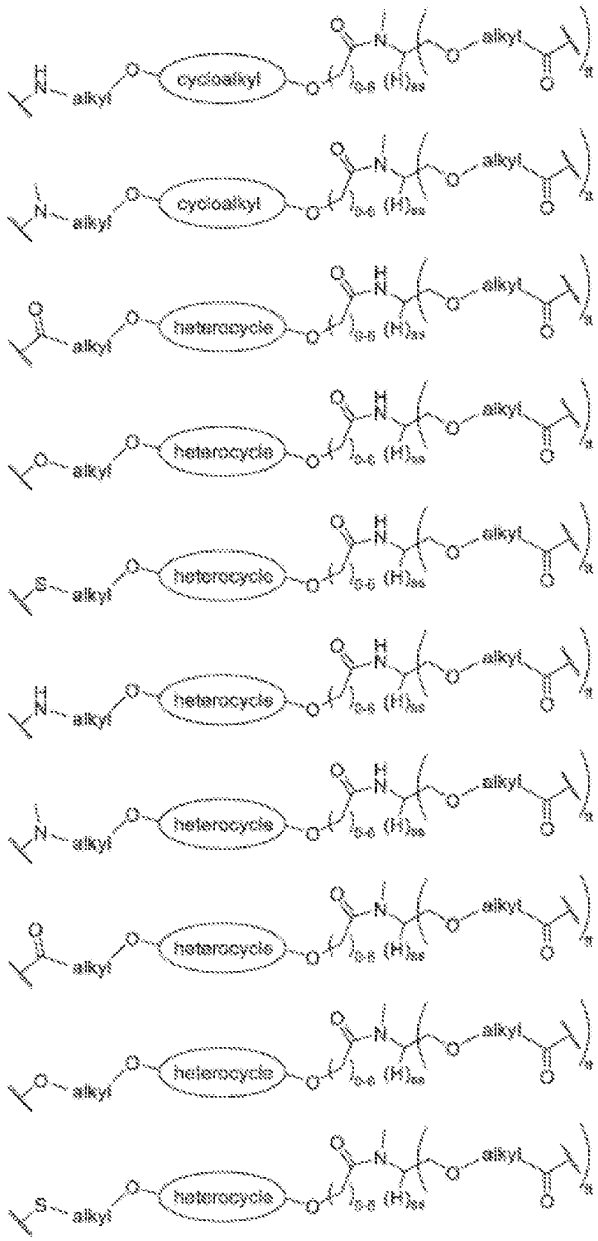
In certain embodiments, in the compound of Formula II, Linker^B, Linker^C, or Linker^D is selected from:

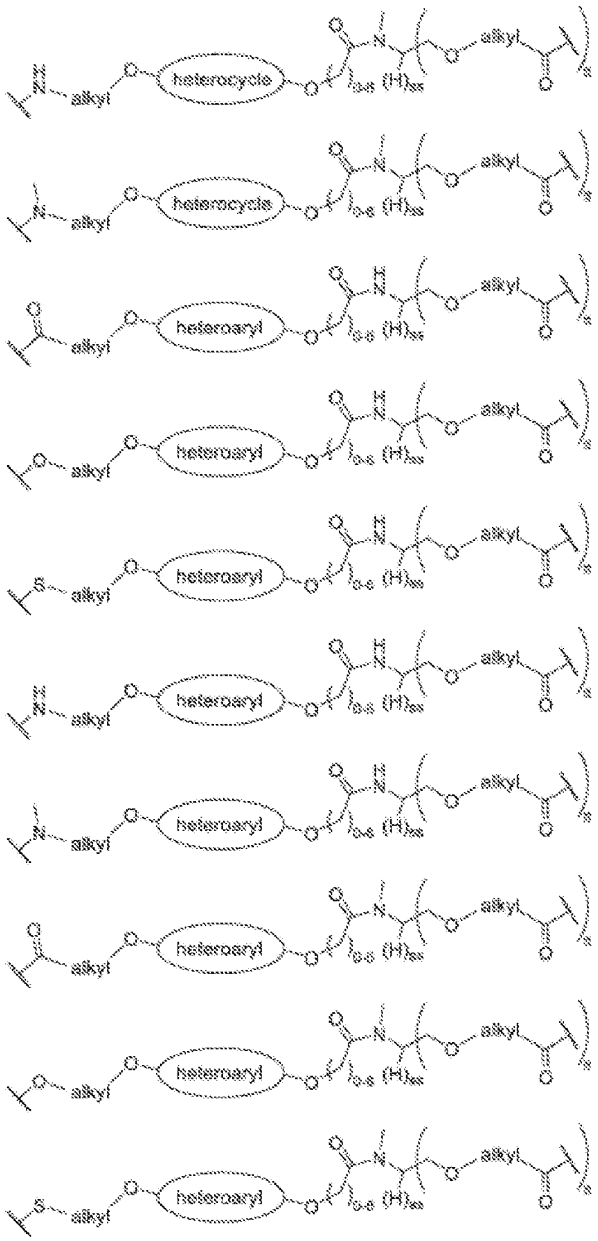


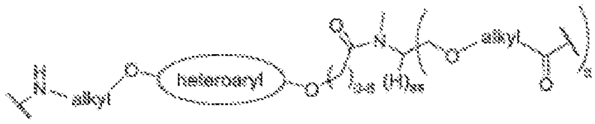
wherein tt and ss are as defined herein.

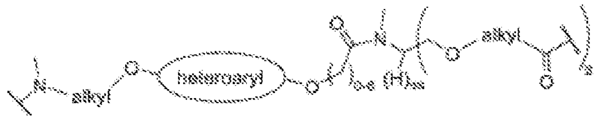
In certain embodiments, in the compound of Formula II, Linker^B, Linker^C, or Linker^D is selected from:

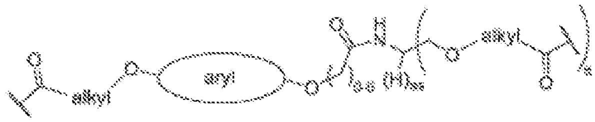

cycloalkyl
alkyl

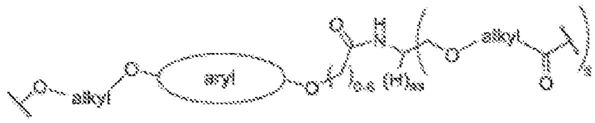

cycloalkyl
heterocycle
alkyl

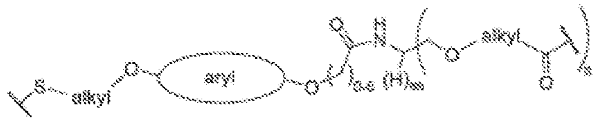

heterocycle
heteroaryl
alkyl

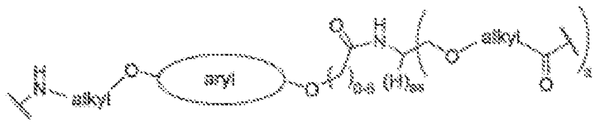


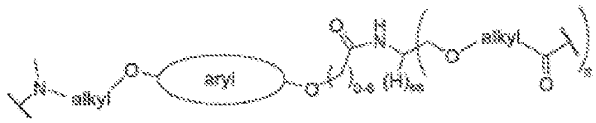


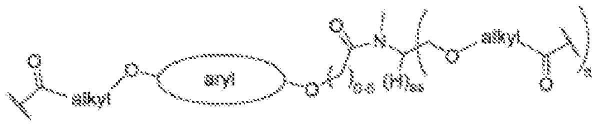


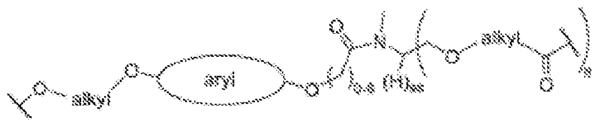


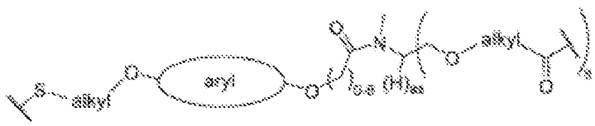


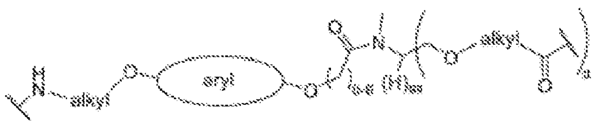




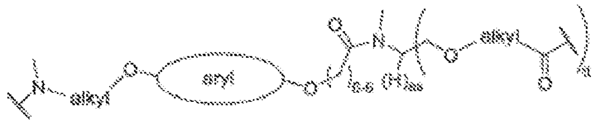








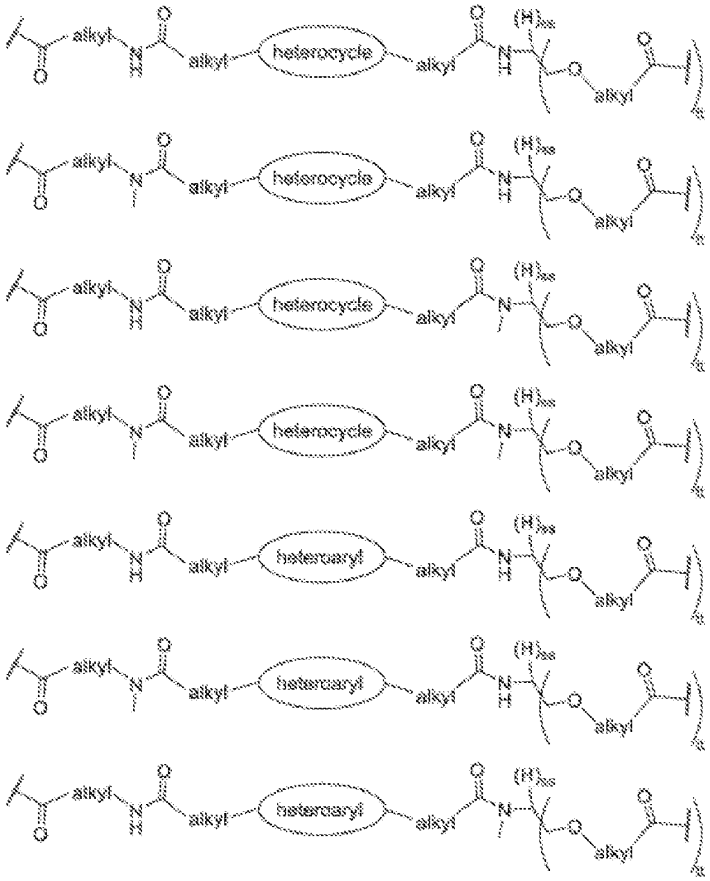
and

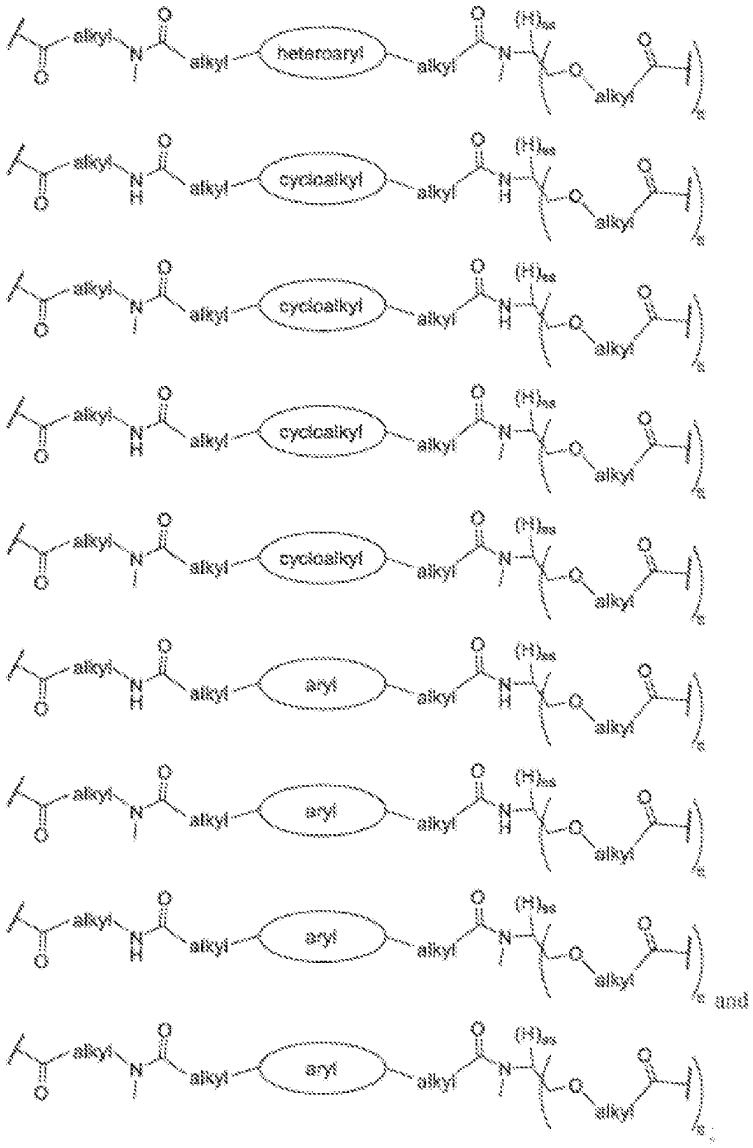


;

wherein each heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence; and tt and ss are as defined herein.

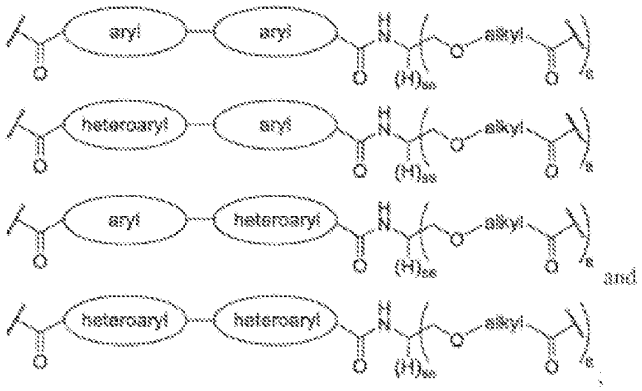
In certain embodiments, in the compound of Formula II, Linker^{B}, Linker^{C}, or Linker^{D} is selected from:





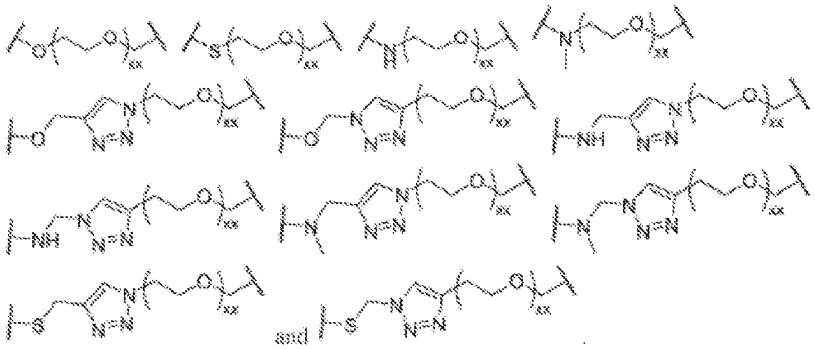
wherein each heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2 3, or 4 of any combination of halogen, alkyl, haloalkyl, and, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence: and tt and ss are as defined herein.

In certain embodiments, in the compound of Formula II, $Linker^B$, $Linker^C$, or $Linker^D$ is selected from:

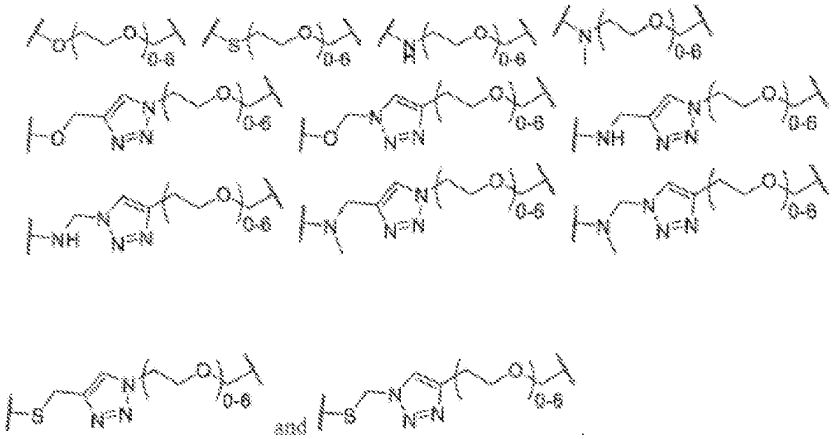


wherein each heteroaryl and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence; and tt and ss are as defined herein.

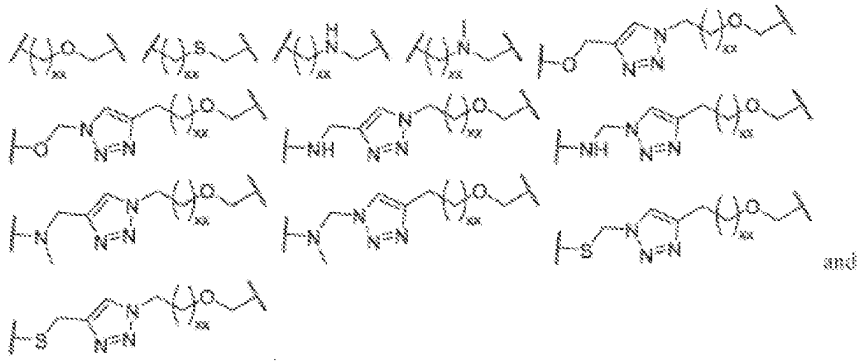
In certain embodiments, in the compound of Formula II, Linker^A is selected from:



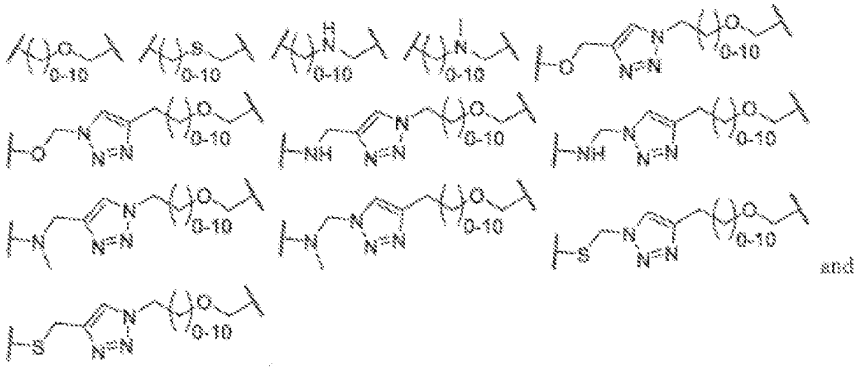
In certain embodiments, in the compound of Formula II, Linker^A is selected from:



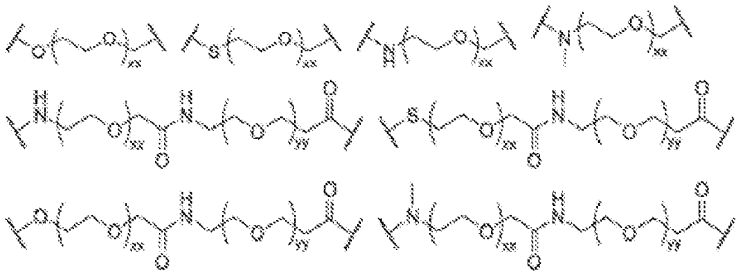
In certain embodiments, in the compound of Formula II, Linker^A is selected from:

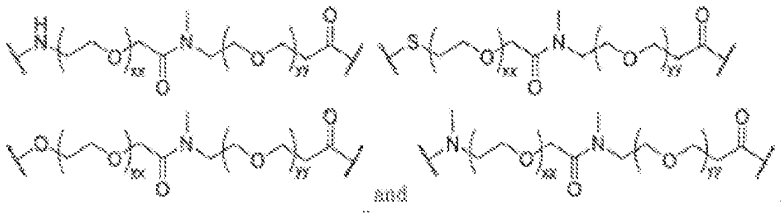


In certain embodiments, in the compound of Formula II, Linker^{A} is selected from:

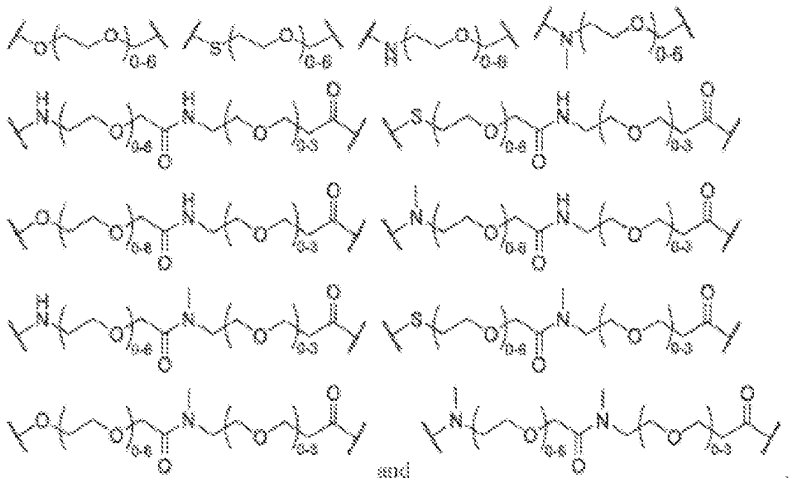


In certain embodiments, in the compound of Formula II, Linker^{B} is selected from:

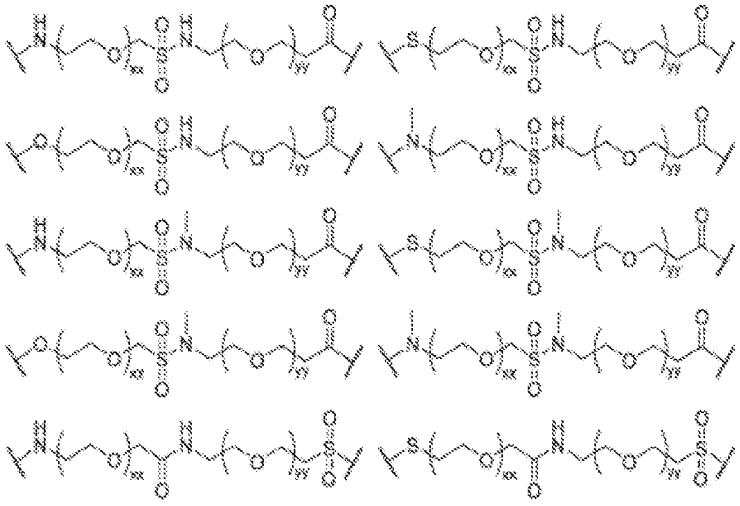


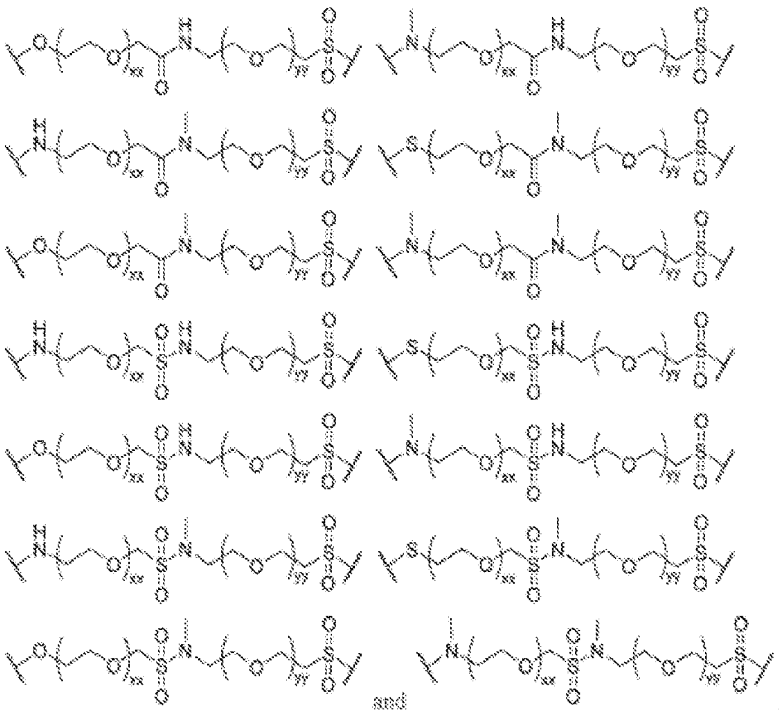


In certain embodiments, in the compound of Formula II, Linker^{B} is selected from:

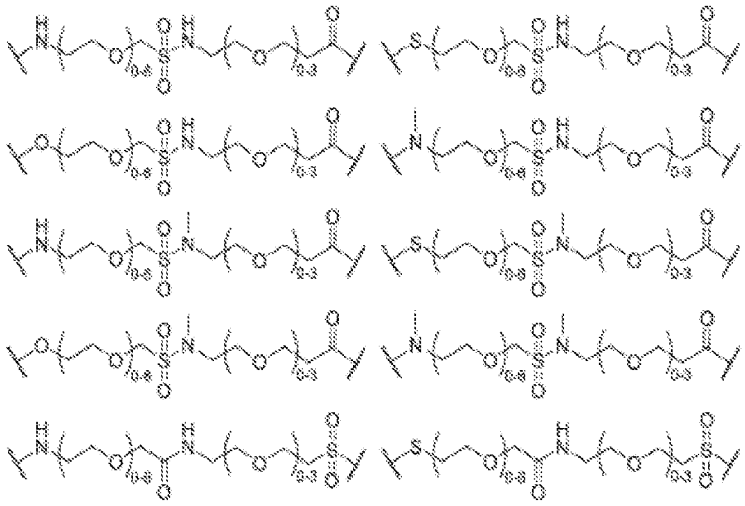


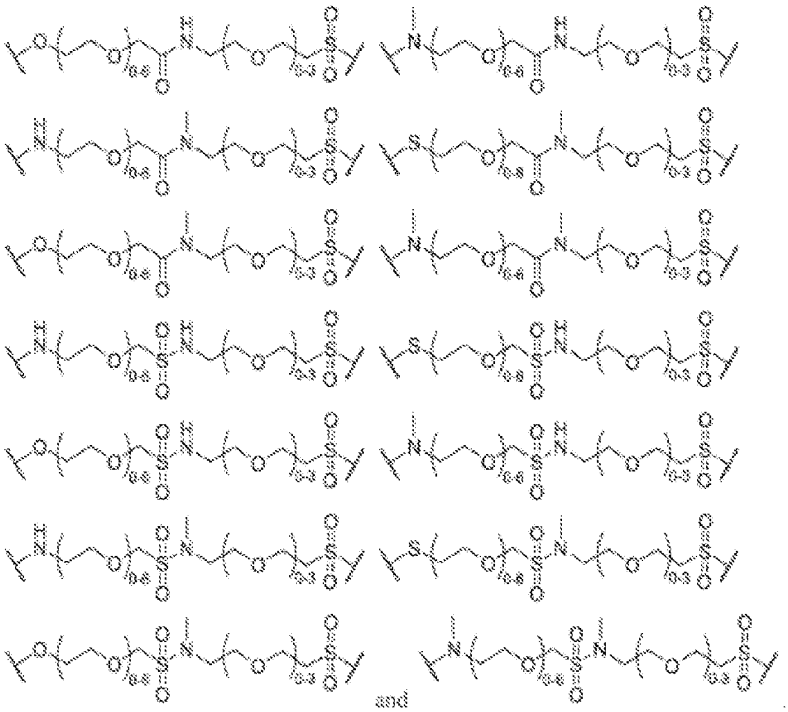
In certain embodiments, in the compound of Formula II, Linker^{B} is selected from:



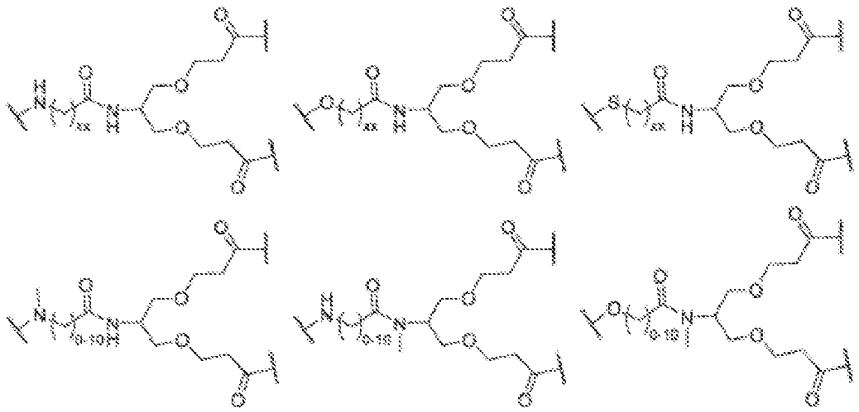


In certain embodiments, in the compound of Formula II, Linker^{B} is selected from:

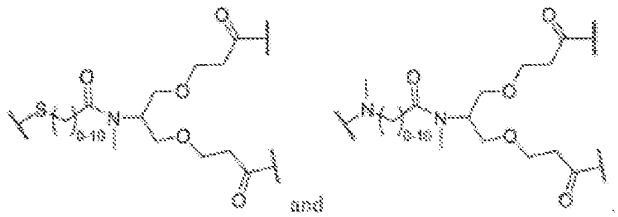




and

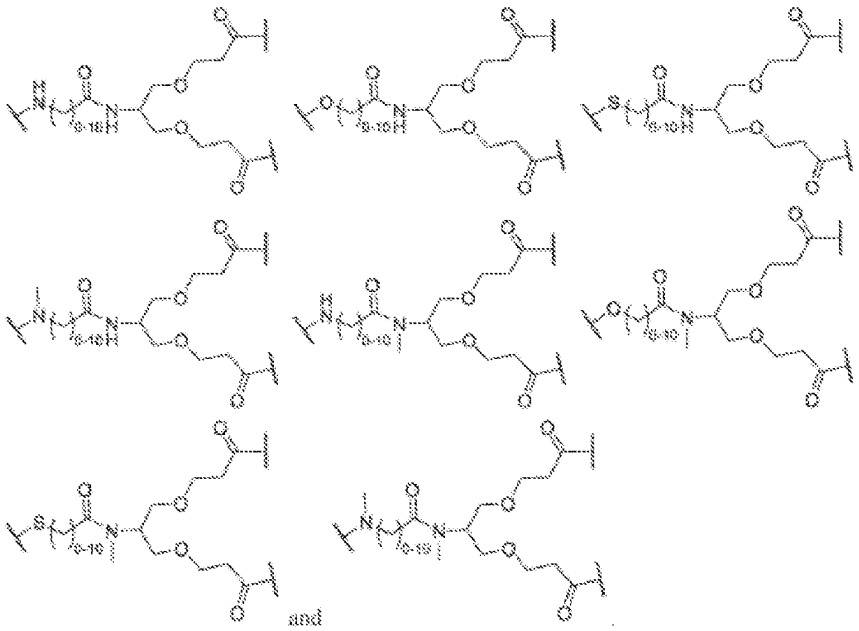


In certain embodiments, in the compound of Formula II, Linker^C is selected from:



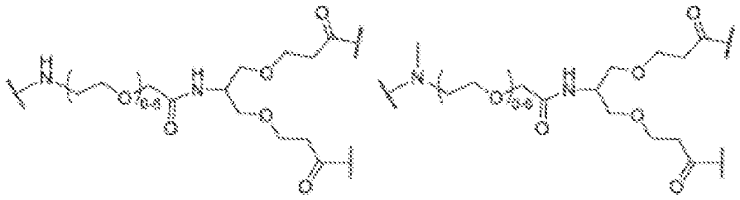
and

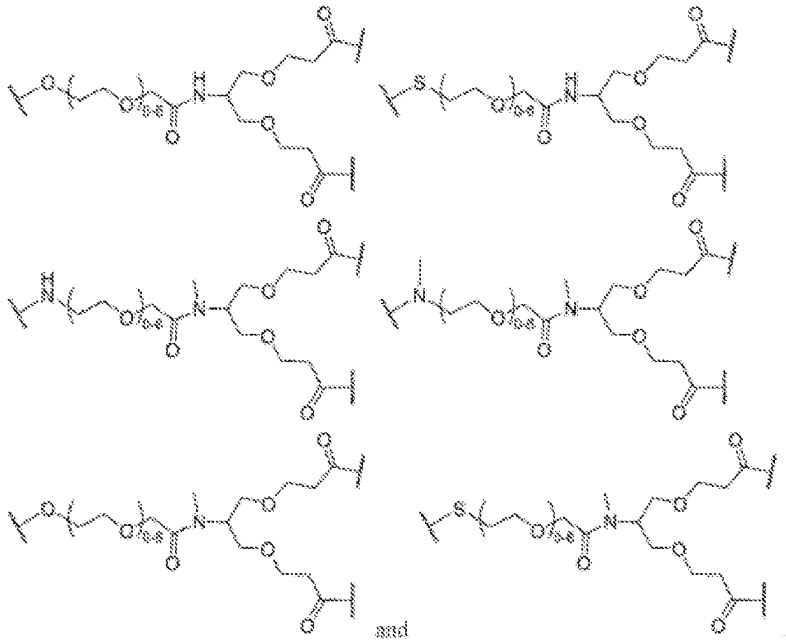
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



and

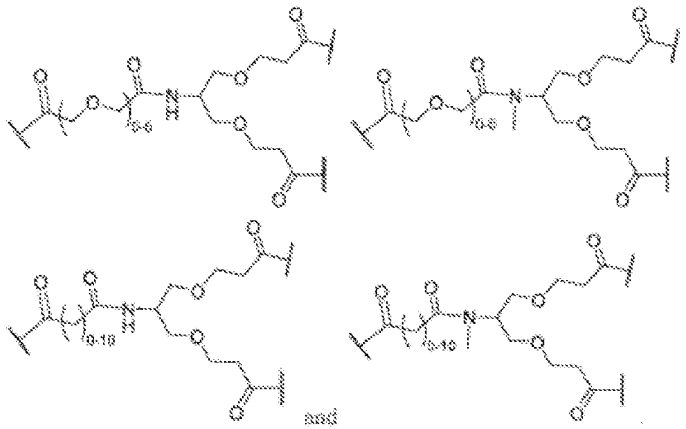
In certain embodiments, in the compound of Formula II, Linker^C is selected from:





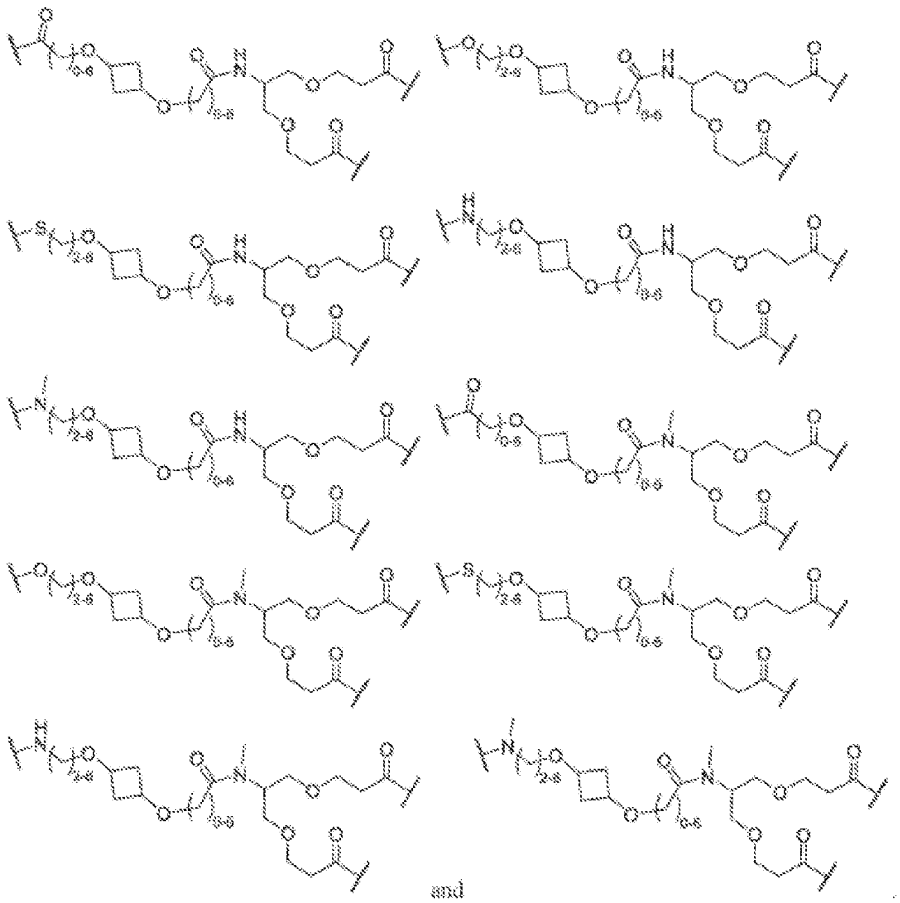
and

In certain embodiments, in the compound of Formula II, Linker^C is selected from:



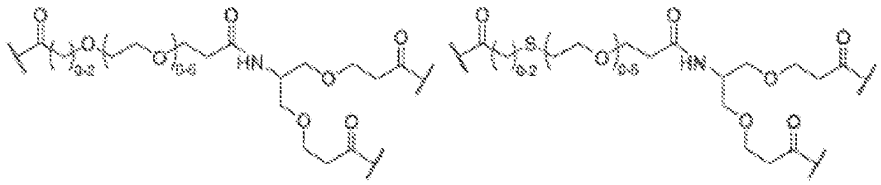
and

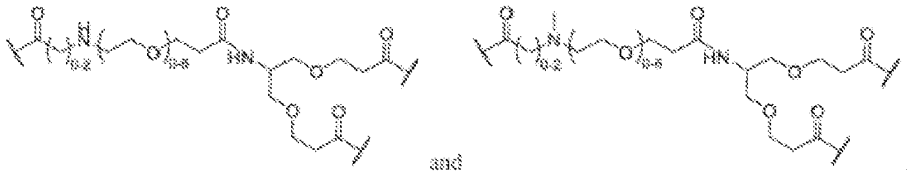
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



and

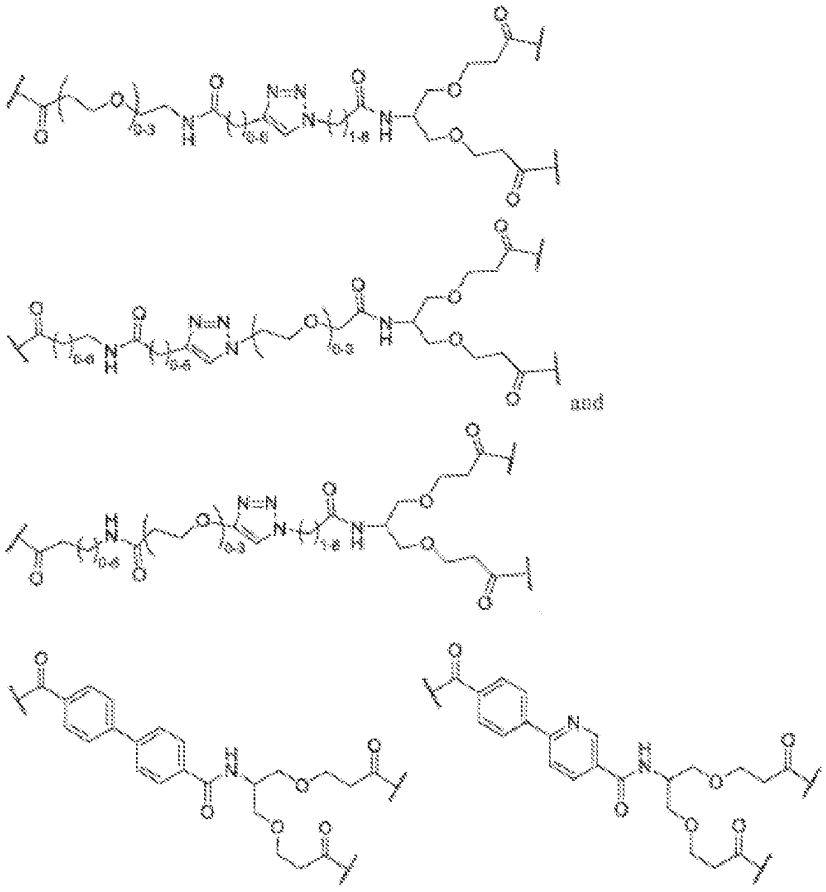
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



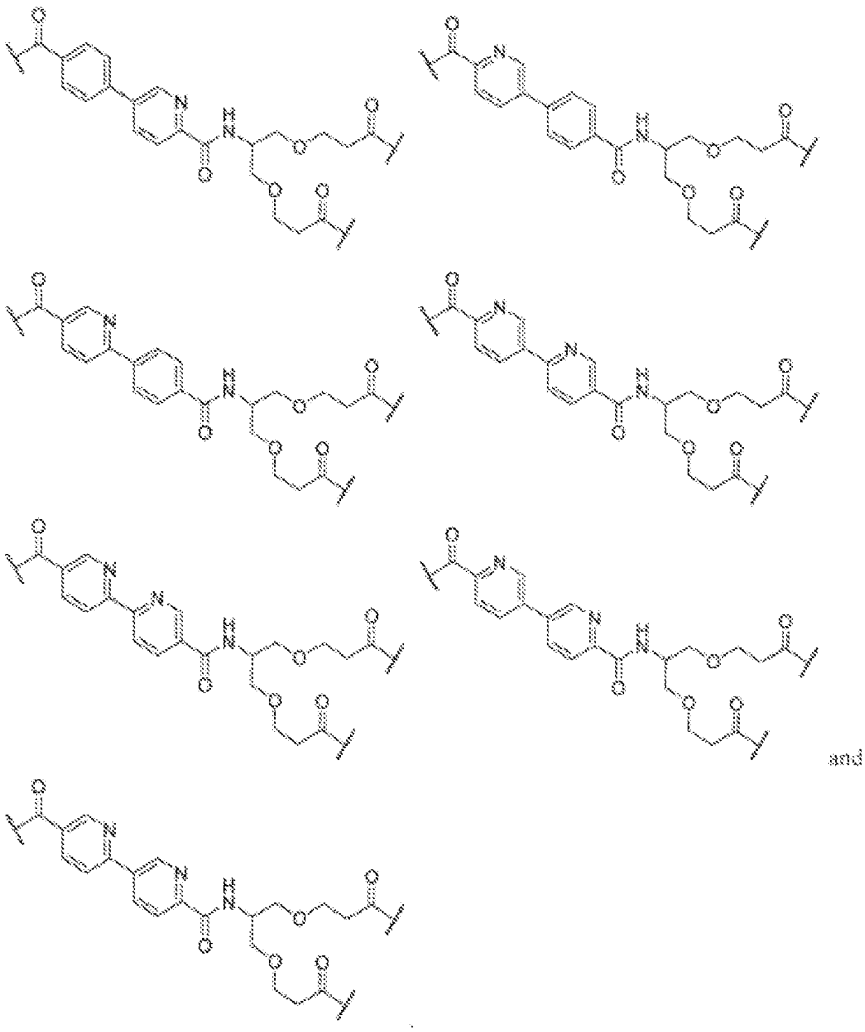


and

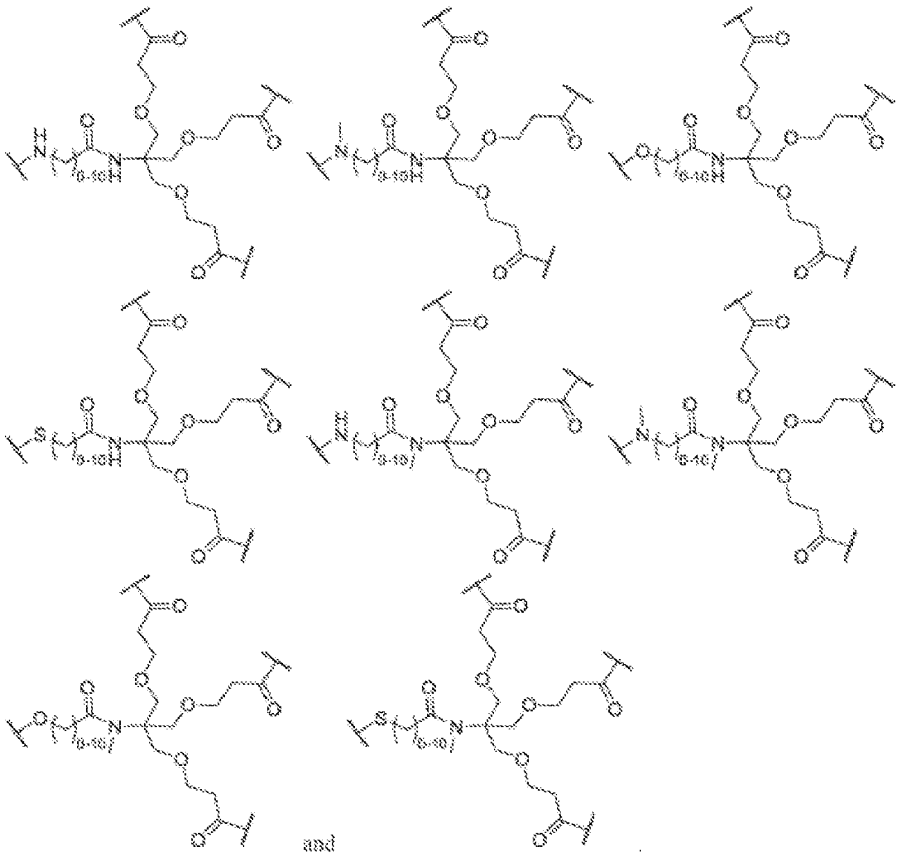
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



In certain embodiments, in the compound of Formula II, Linker^C is selected from:

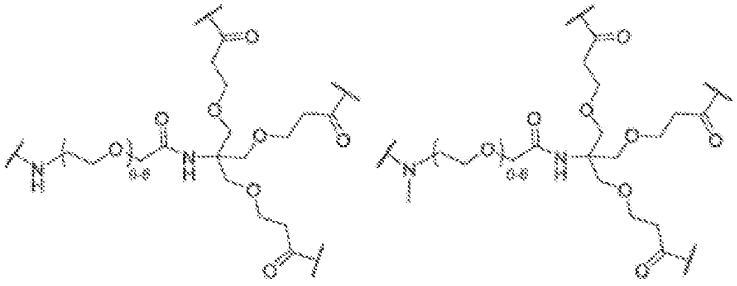


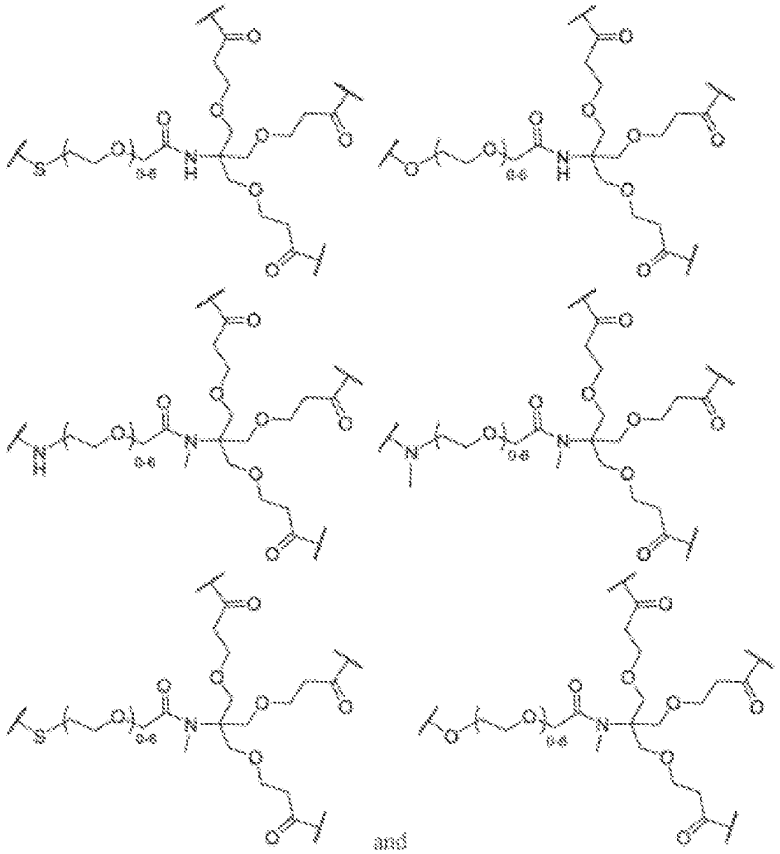
In certain embodiments, in the compound of Formula II, Linker^{D} is selected from:



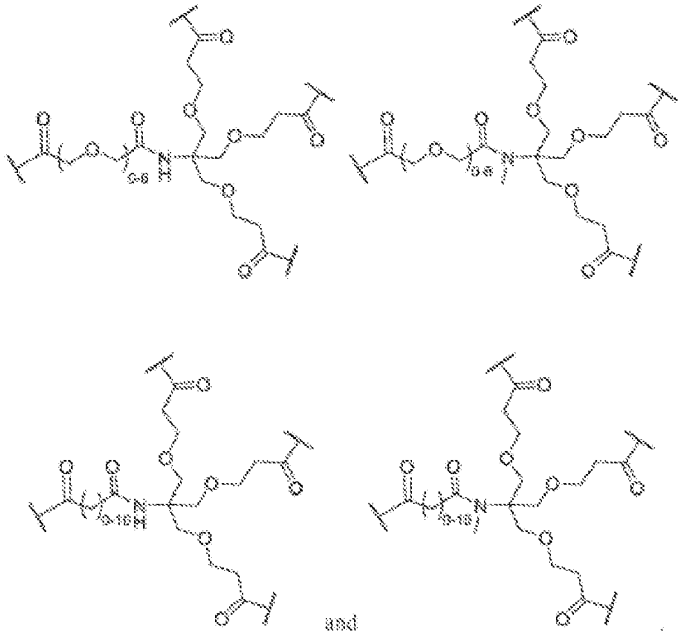
and

In certain embodiments, in the compound of Formula II, Linker^D is selected from:

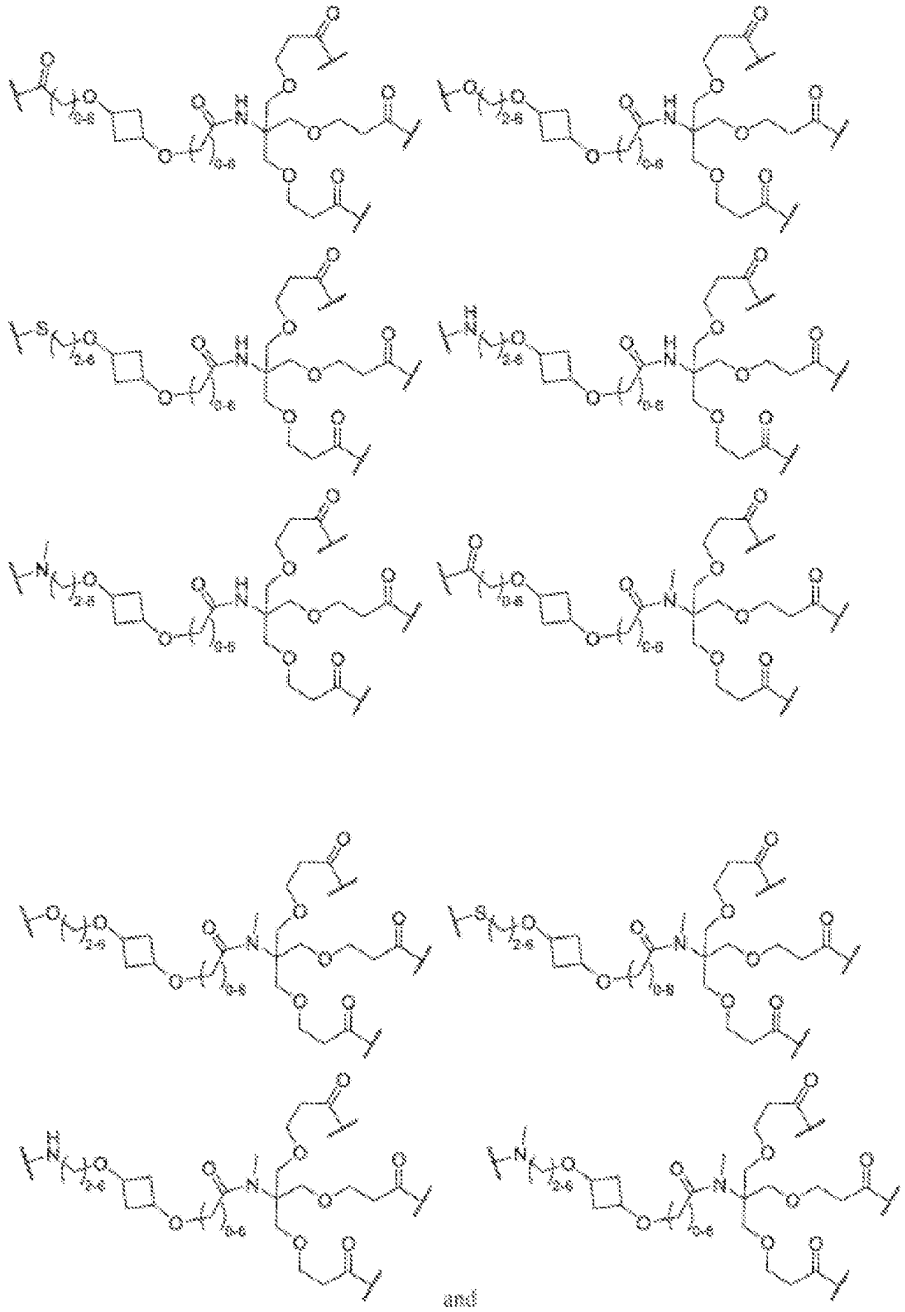




In certain embodiments, in the compound of Formula II, LinkerD is selected from:

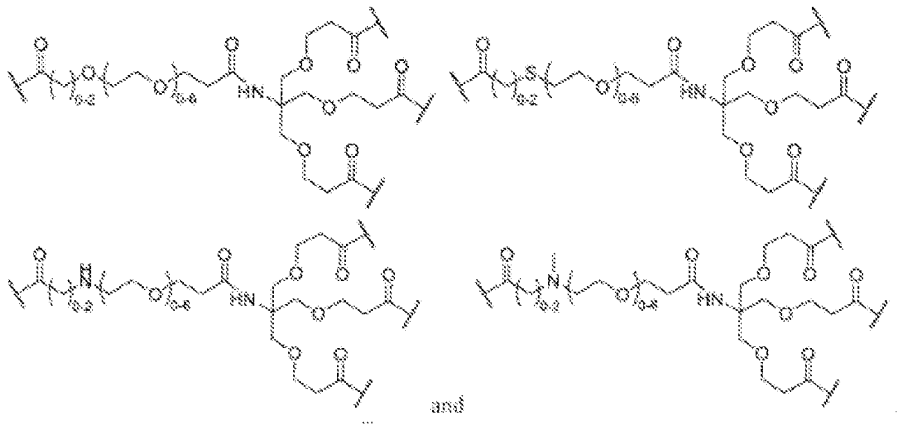


In certain embodiments, in the compound of Formula II, Linker^D is selected from:



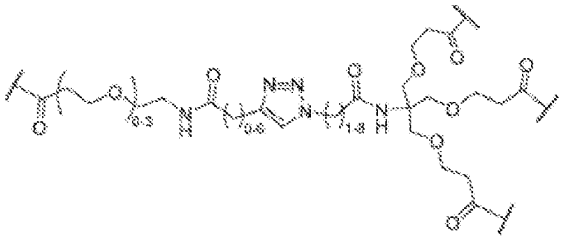
and

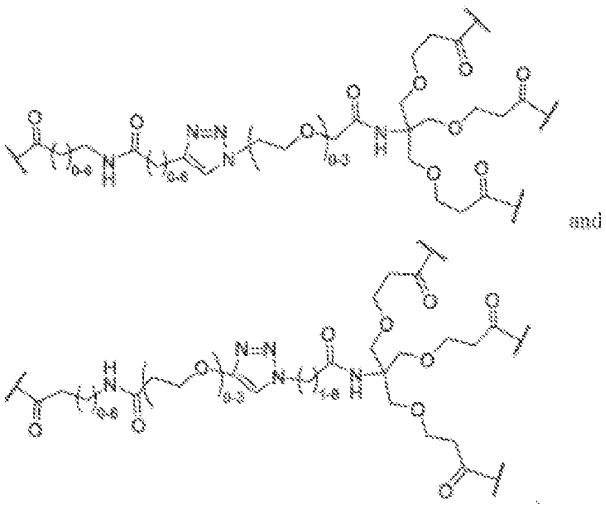
In certain embodiments, in the compound of Formula II, Linker^D is selected from:



and

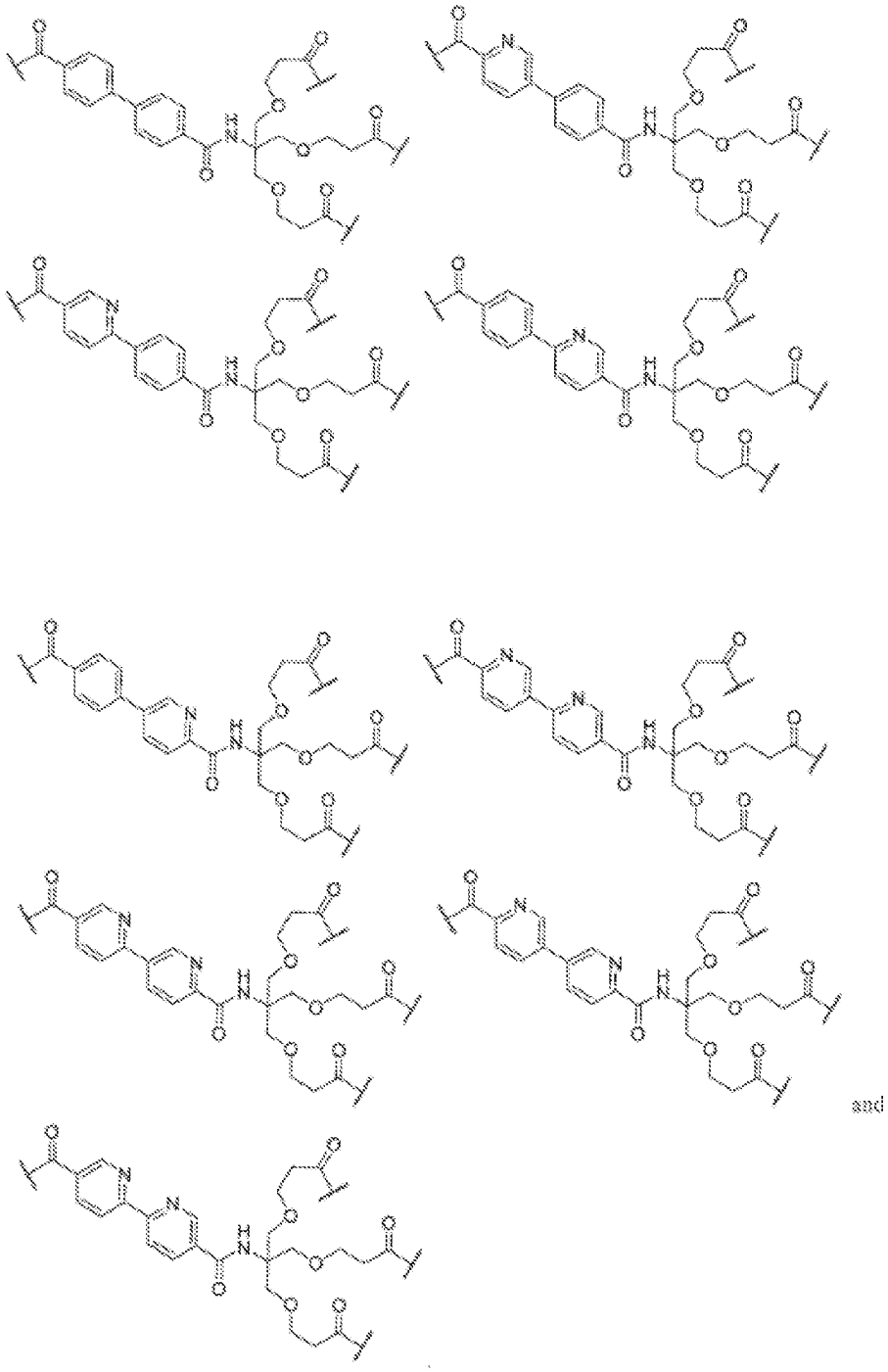
In certain embodiments, in the compound of Formula II, Linker^D is selected from:





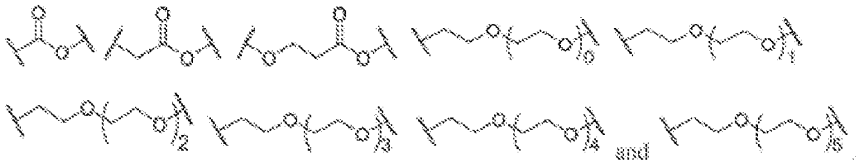
and

In certain embodiments, in the compound of Formula II, Linker^D is selected from:

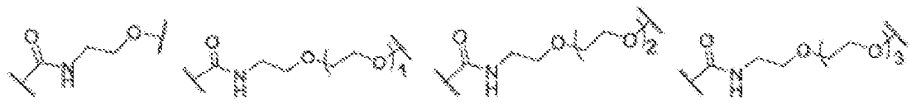


and

In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from



In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from



In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from

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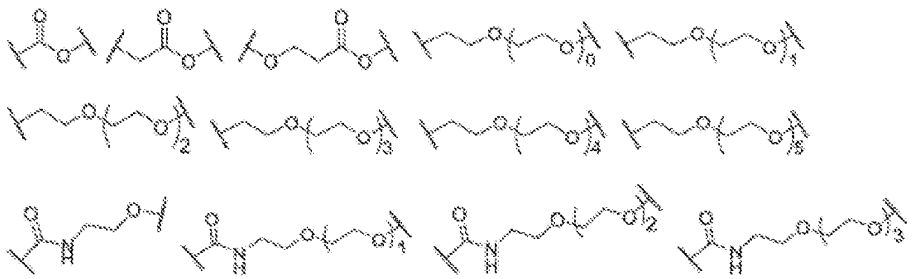
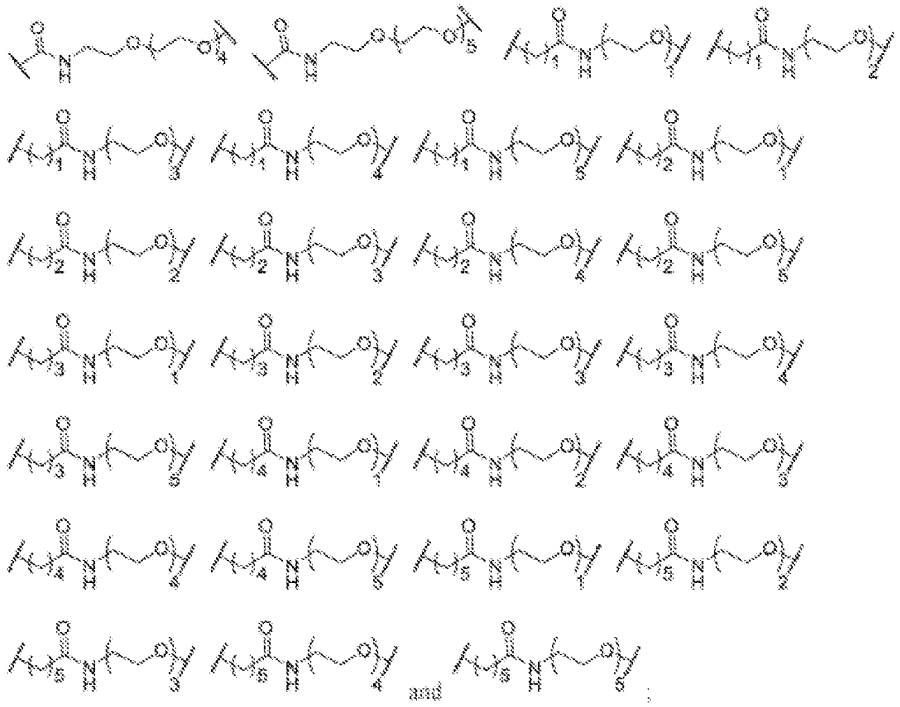
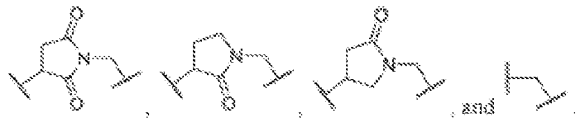


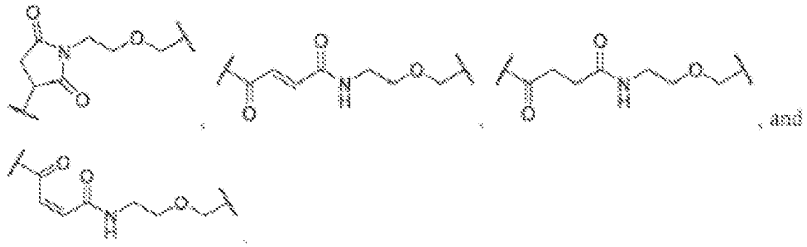


wherein each is optionally substituted with 1, 2, 3, or 4 substituents substituent selected from R^{21}.

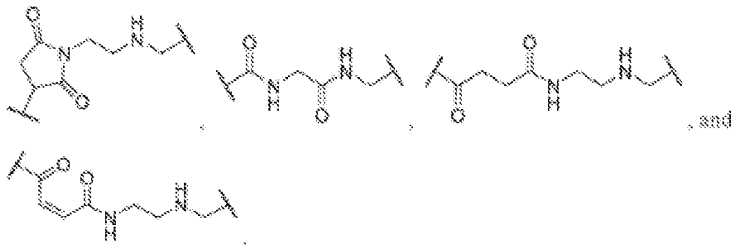
In certain embodiments, in the compound of Formula II, $Linker^A$ is selected from:



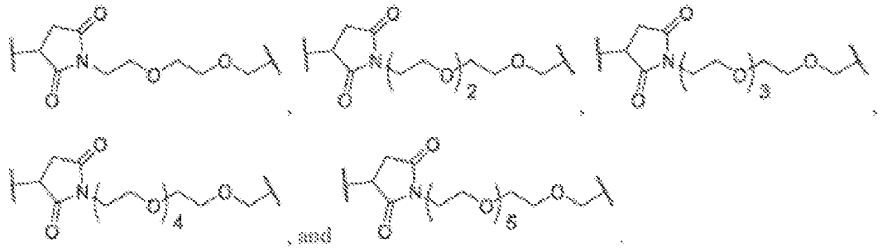
In certain embodiments, in the compound of Formula II, the $Linker^A$ is selected from



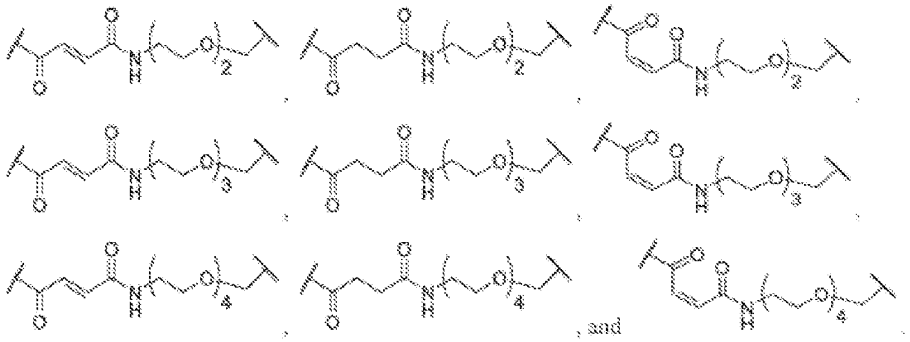
In certain embodiments, in the compound of Formula II, the $Linker^A$ is selected from



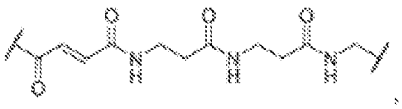
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



In certain embodiments, in the compound of Formula II, the Linker^A is selected from



In certain embodiments, in the compound of Formula II, the Linker^A is selected from



In certain embodiments, in the compound of Formula II, the Linker^A is selected from

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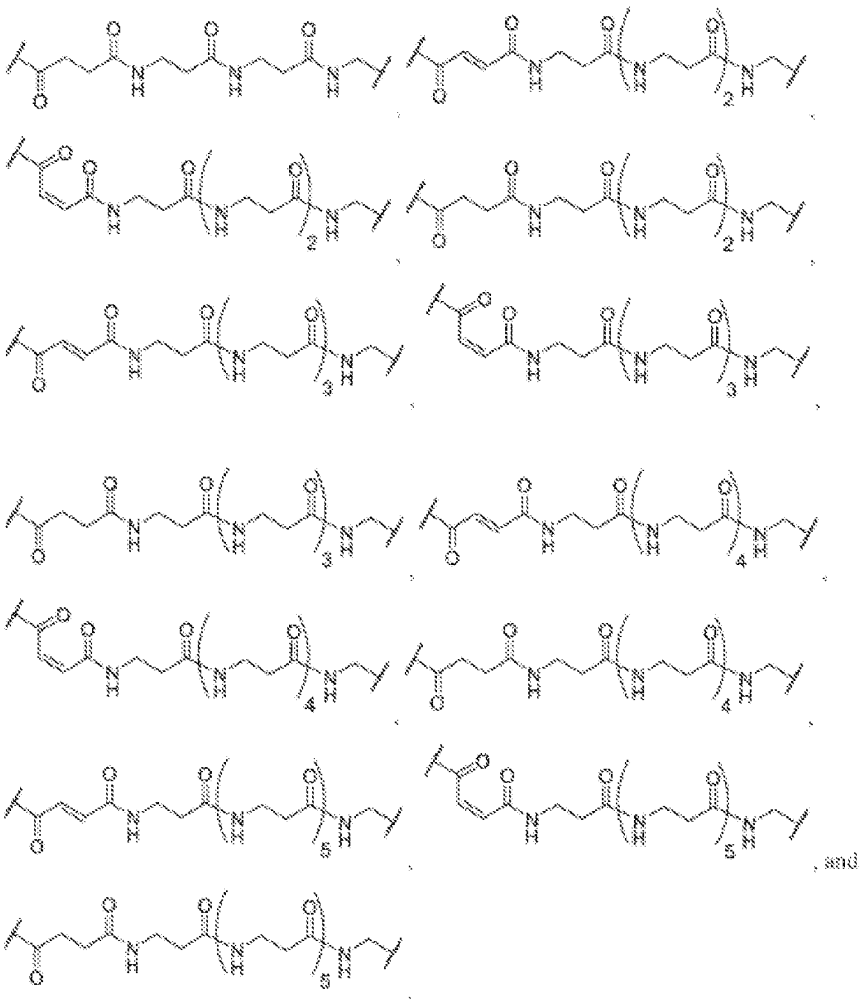
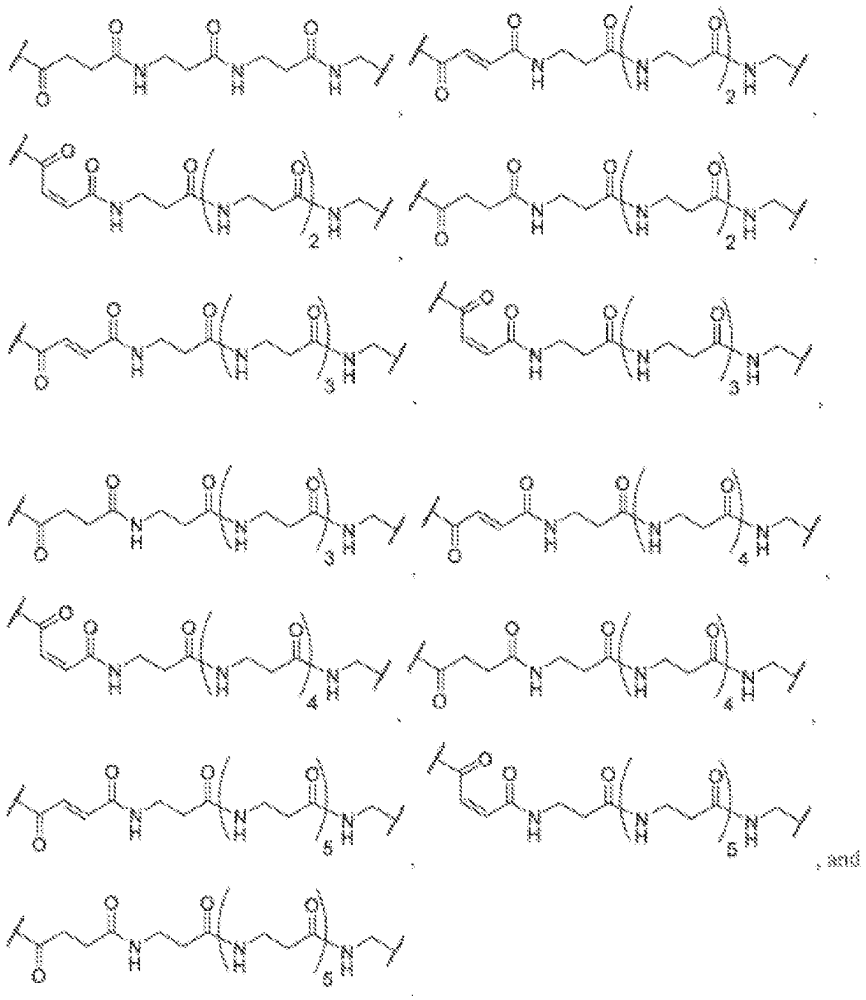
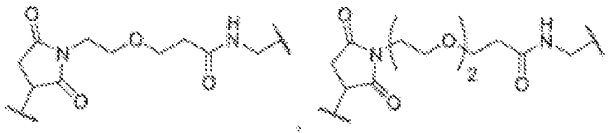
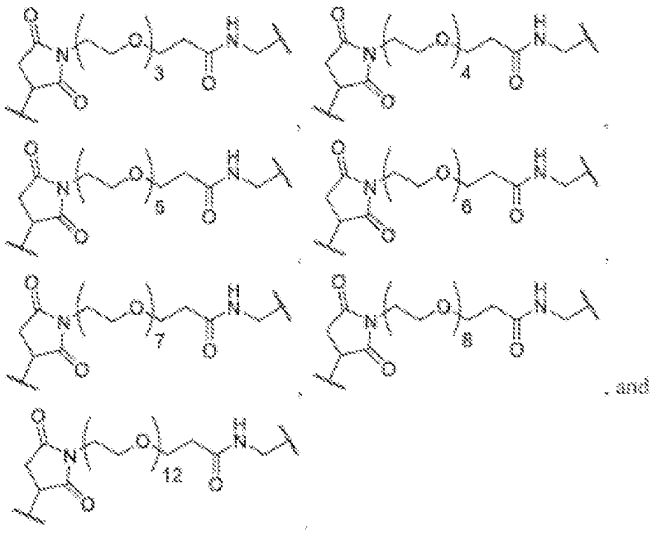


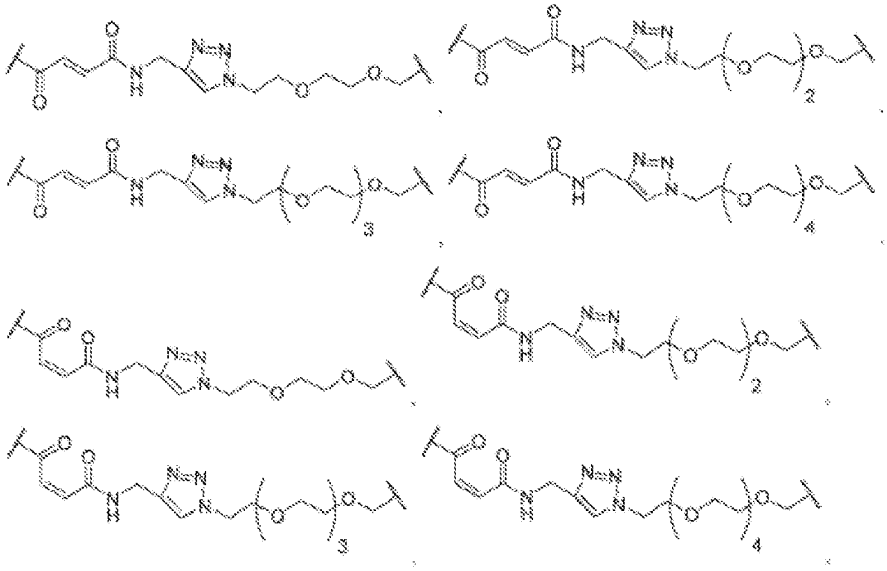


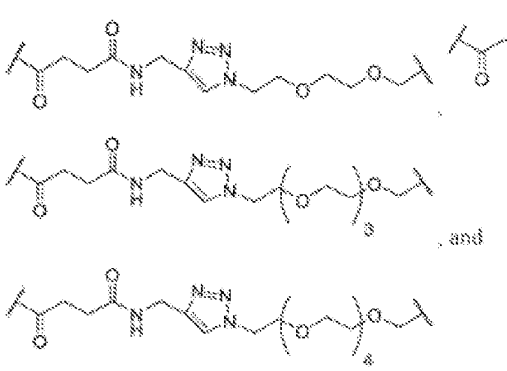
In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from



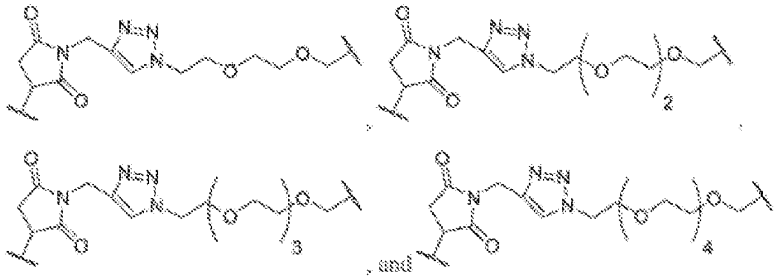


In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from

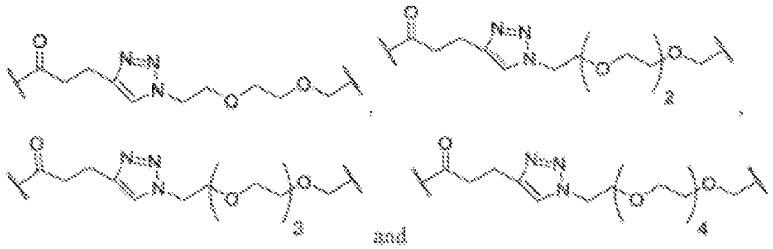




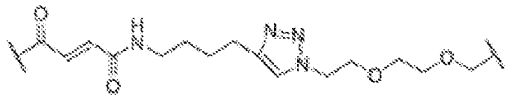
In certain embodiments, in the compound of Formula II, the Linker^A is selected from

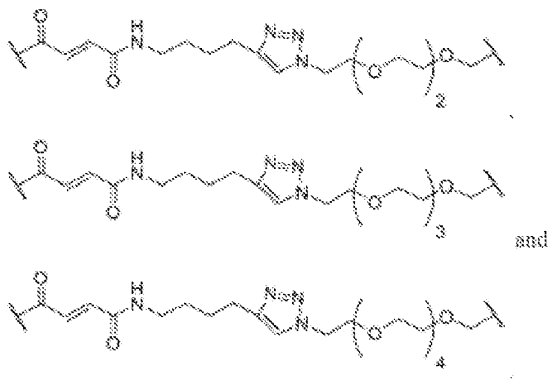


In certain embodiments, in the compound of Formula II, the Linker^A is selected from

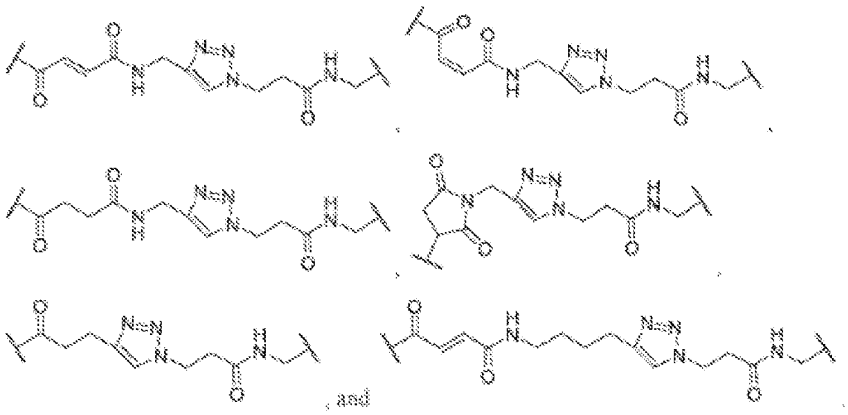


In certain embodiments, in the compound of Formula II, the Linker^A is selected from

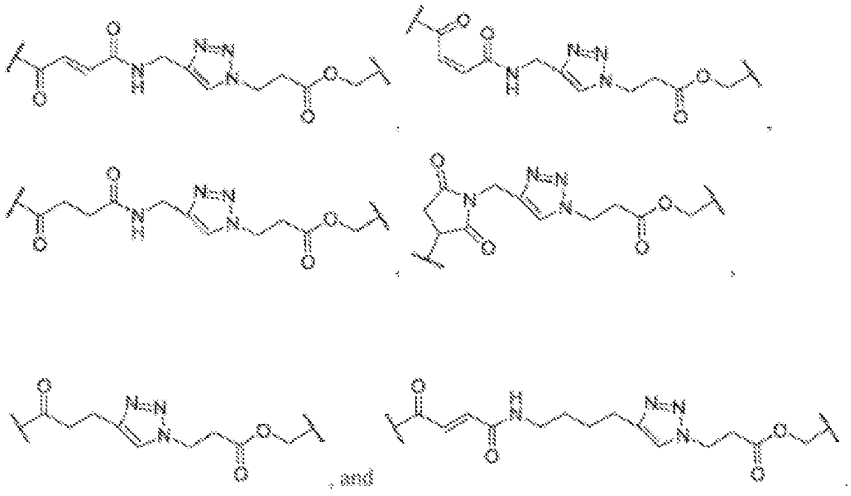




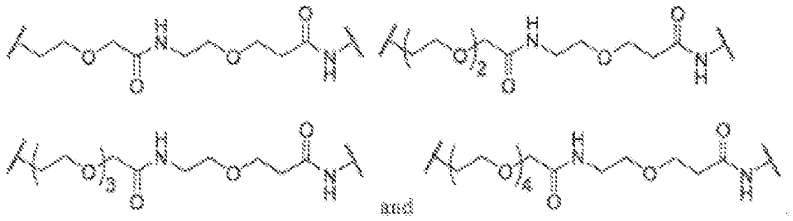
In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from



In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from

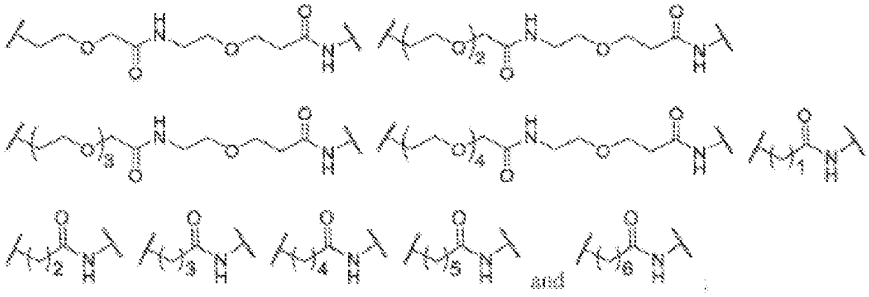


In certain embodiments, in the compound of Formula II, the Linker^{B} is selected from



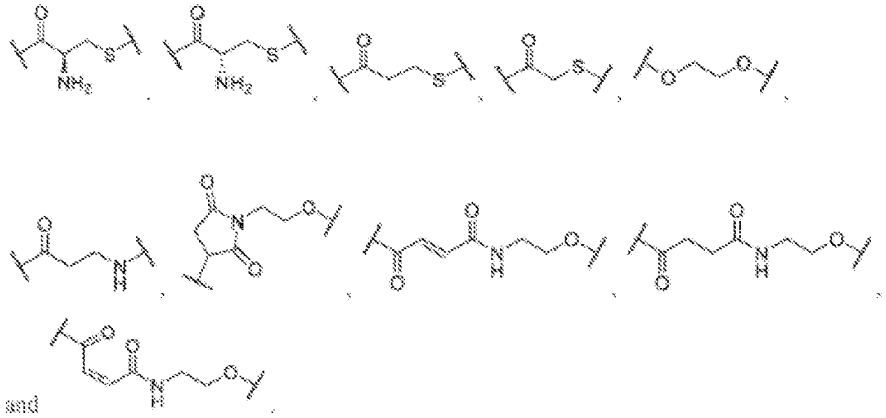
In certain embodiments, in the compound of Formula II, the Linker^B is selected from

In certain embodiments, in the compound of Formula II, the Linker^B is selected from

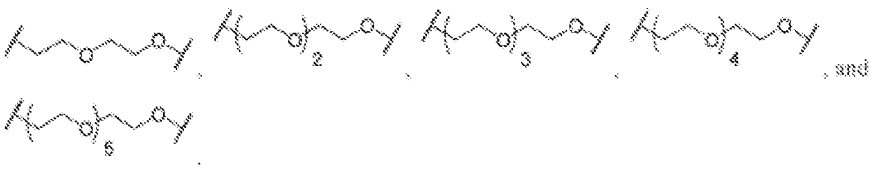


In certain embodiments, in the compound of Formula II, the Linker^B is selected from wherein each is optionally substituted with 1, 2, 3, or 4 substituents substituent selected from R^{21}.

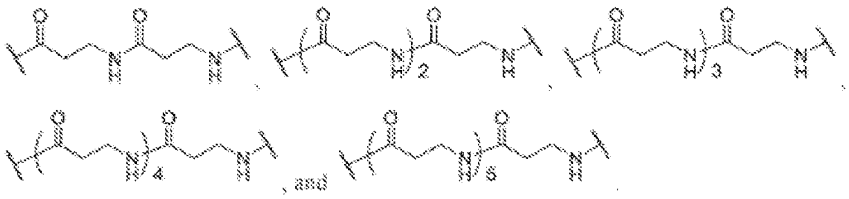
In certain embodiments, in the compound of Formula II Linker^B is selected from:



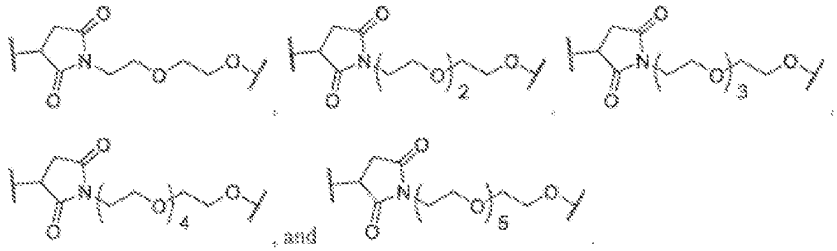
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



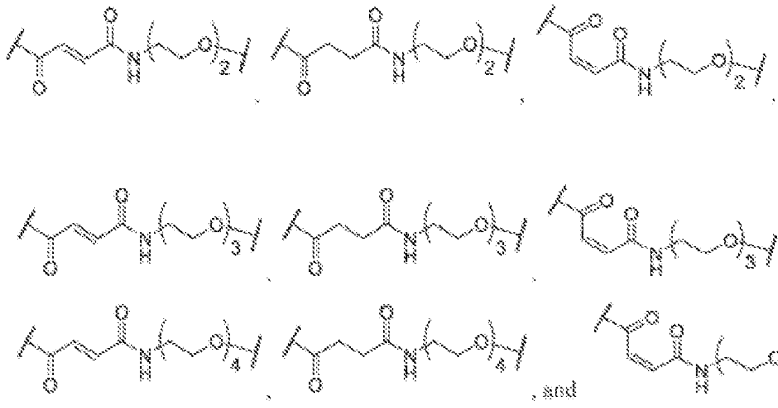
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



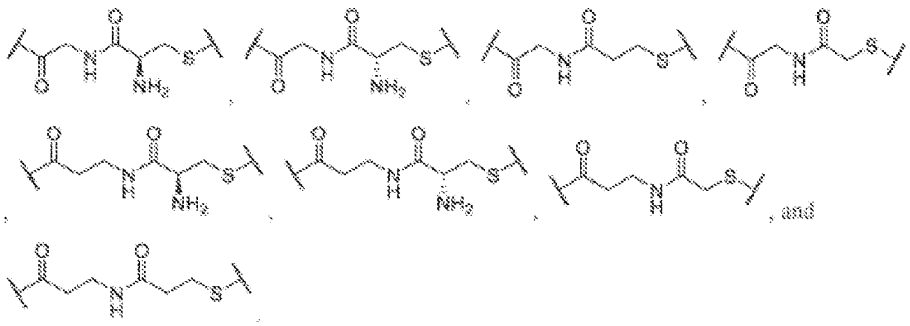
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



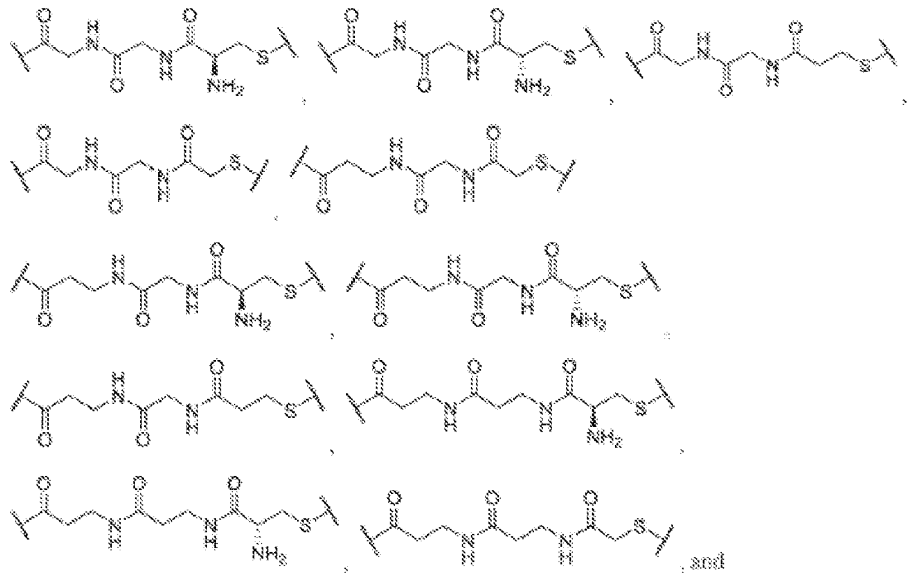
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



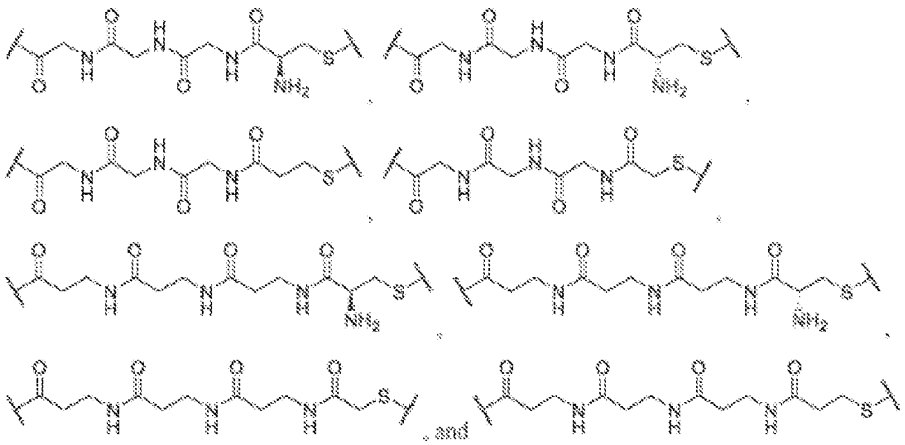
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



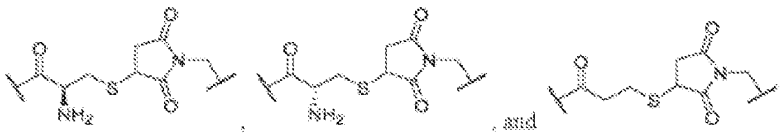
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



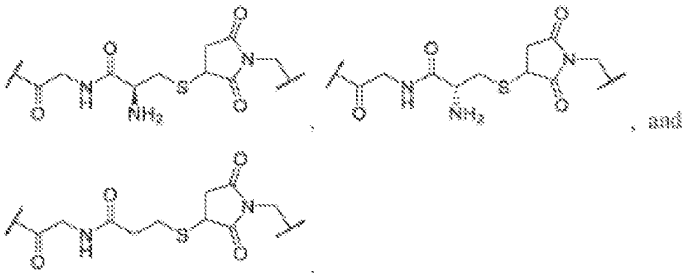
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



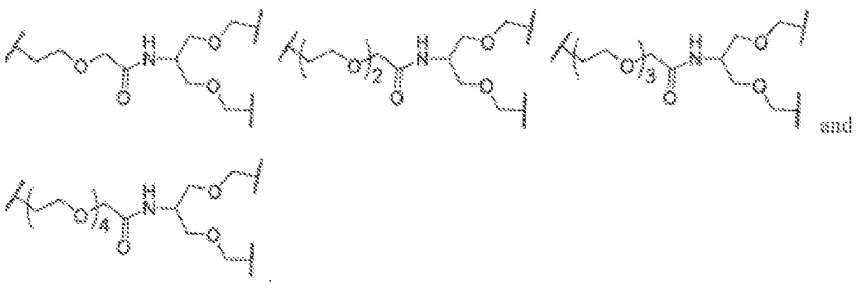
In certain embodiments, in the compound of Formula II, Linker^{B}-Linker^{A} is selected from:



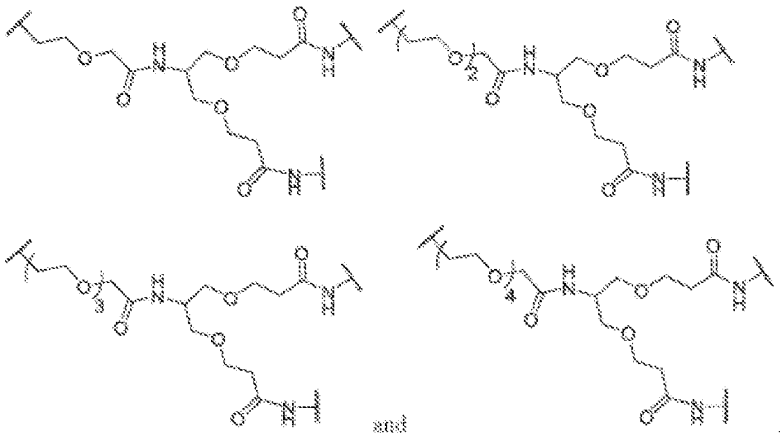
In certain embodiments, in the compound of Formula II, Linker^{B}-Linker^{A} is selected from:



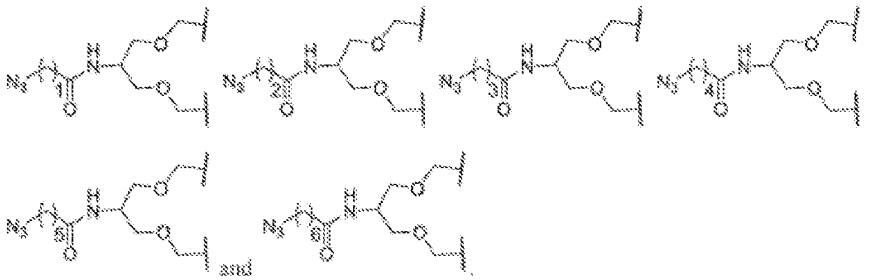
In certain embodiments, in the compound of Formula II, the Linker^{C} is selected from:



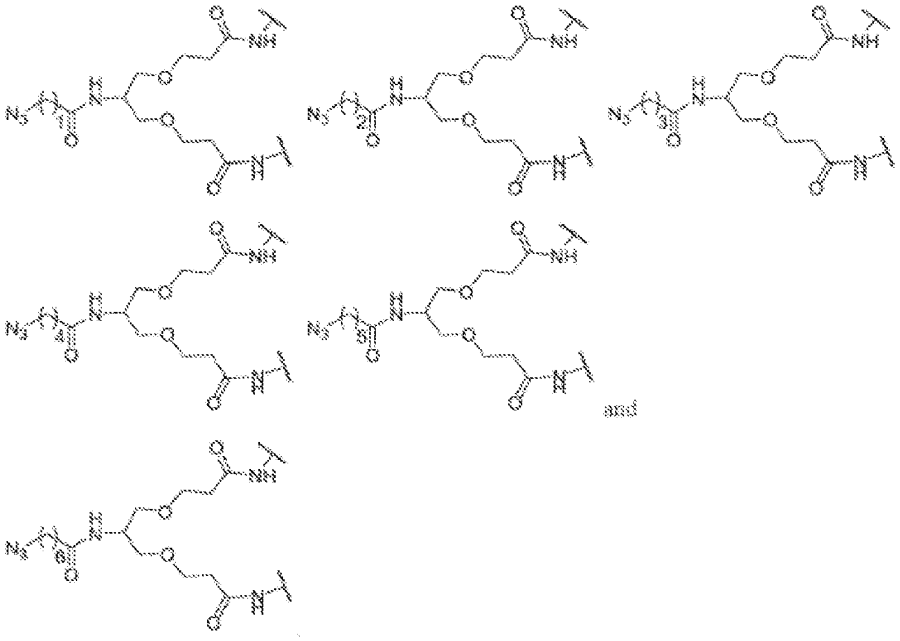
In certain embodiments, in the compound of Formula II, the Linker^{C} is selected from:



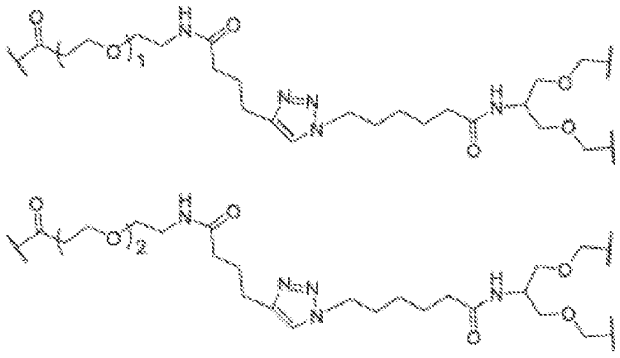
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



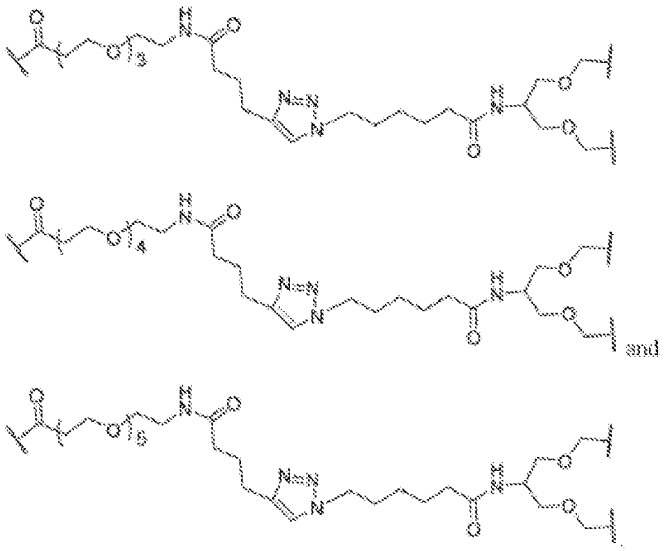
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



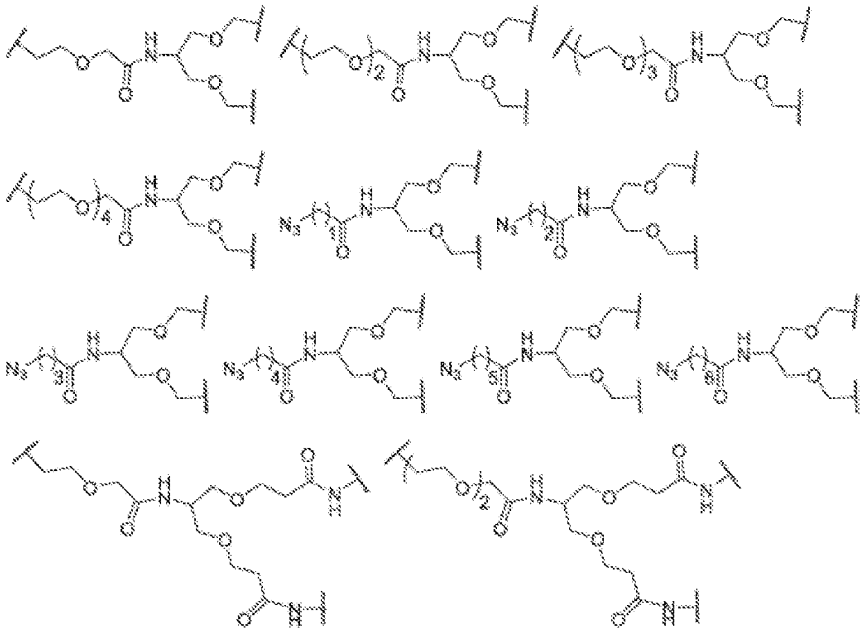
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:

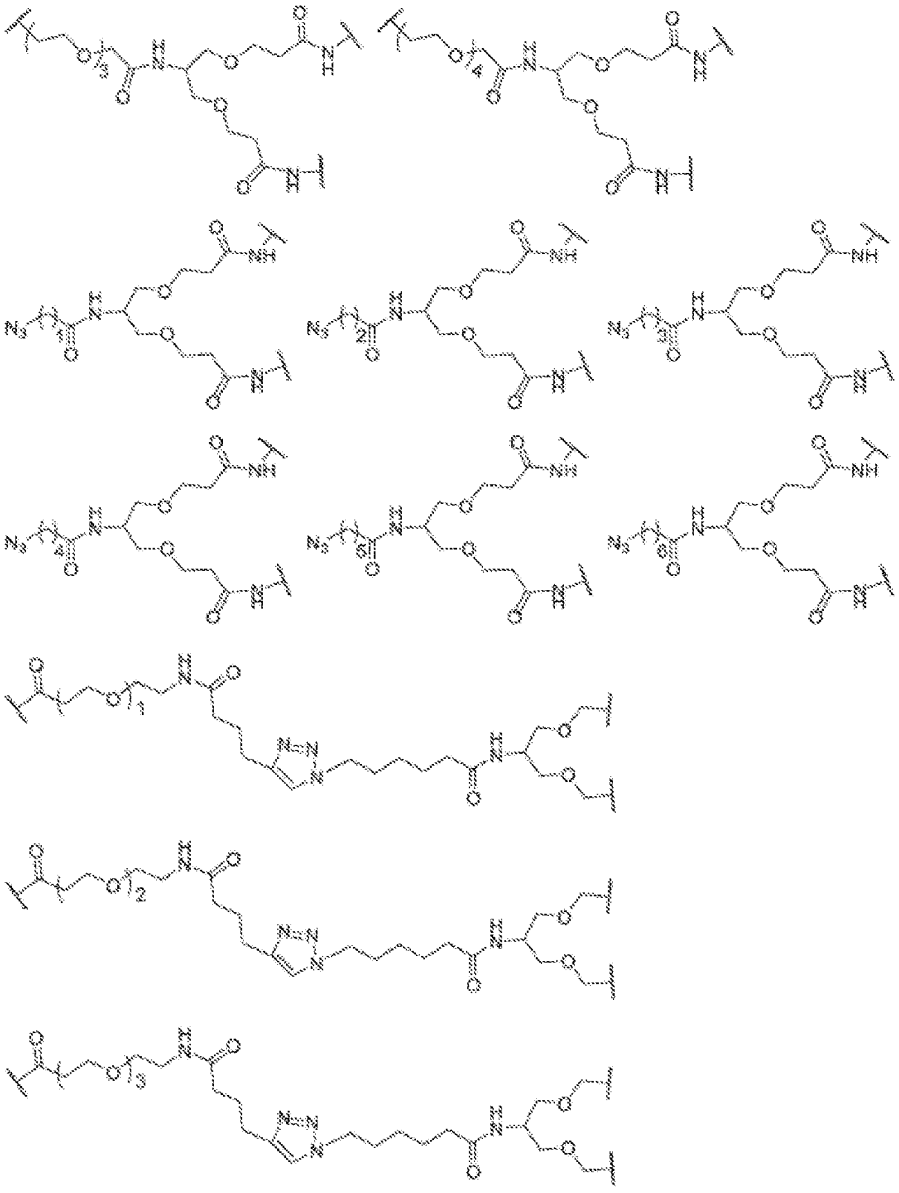


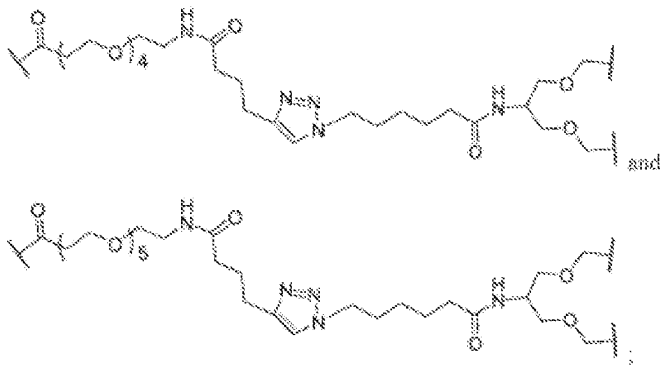
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



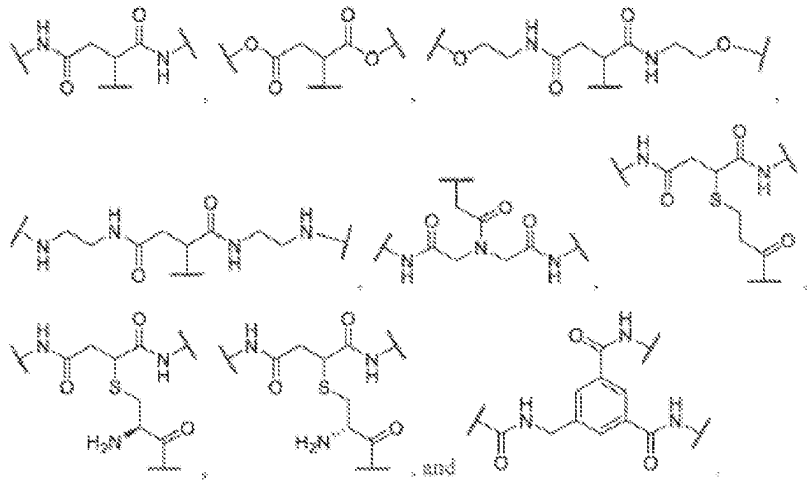




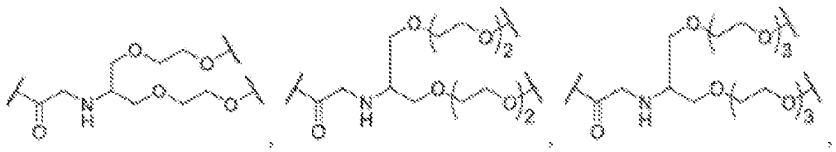
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:

wherein each is optionally substituted with 1, 2, 3, or 4 substituents substituent selected from R^{21}.

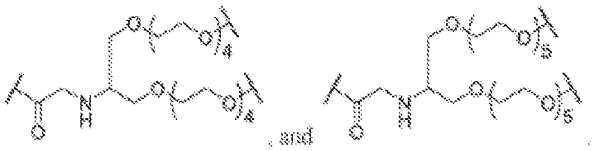
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



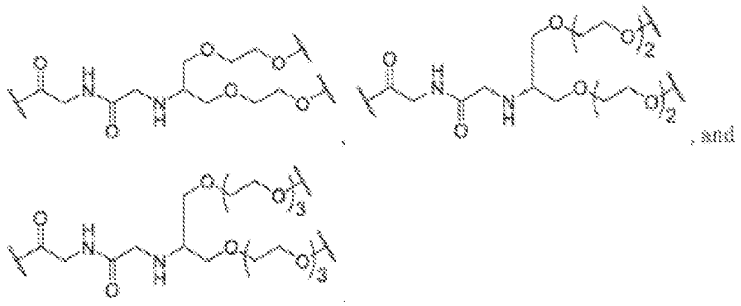
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



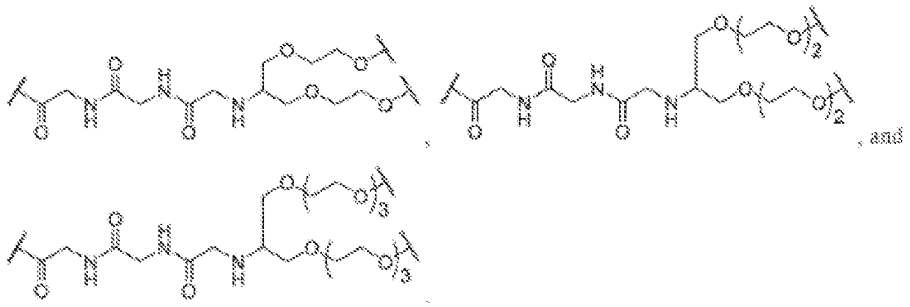
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



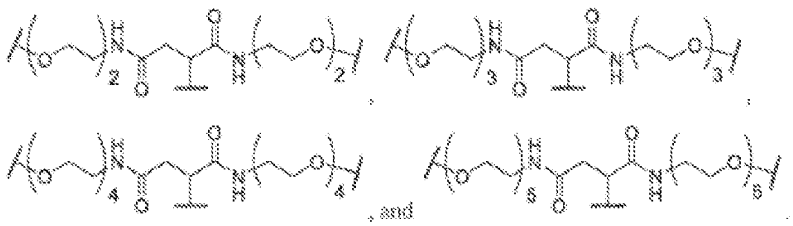
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



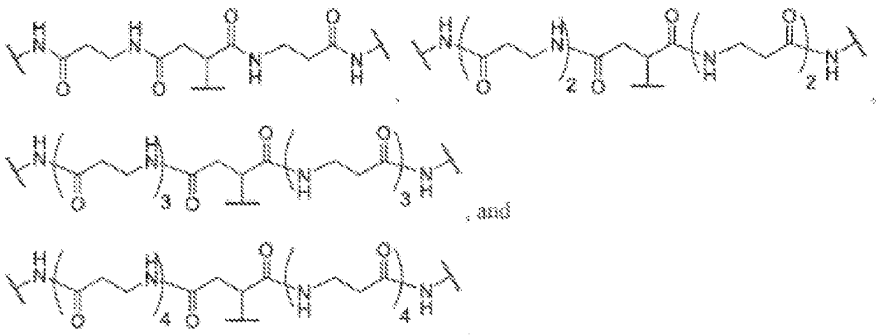
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



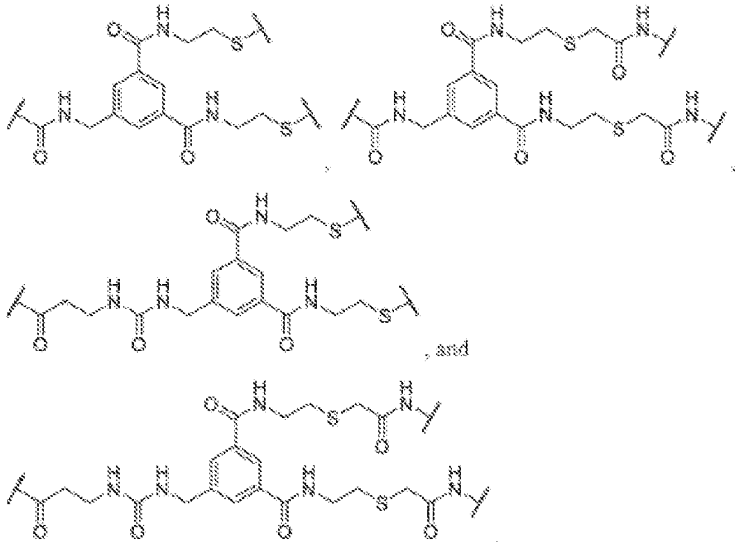
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



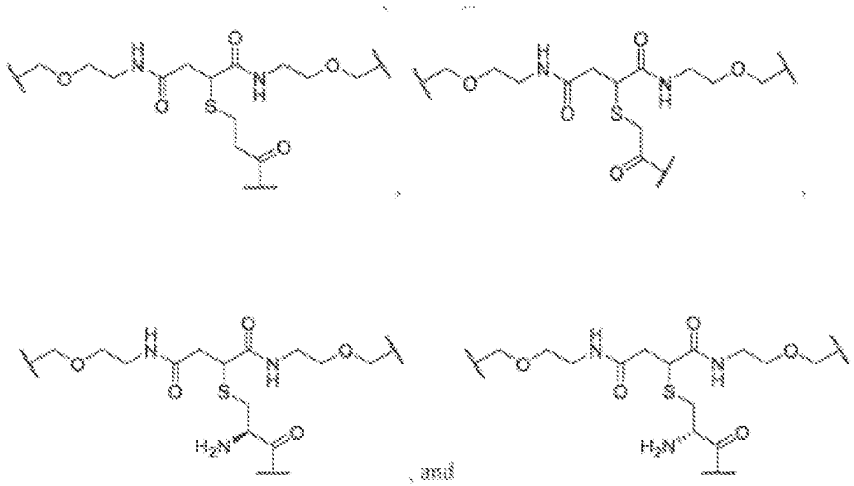
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



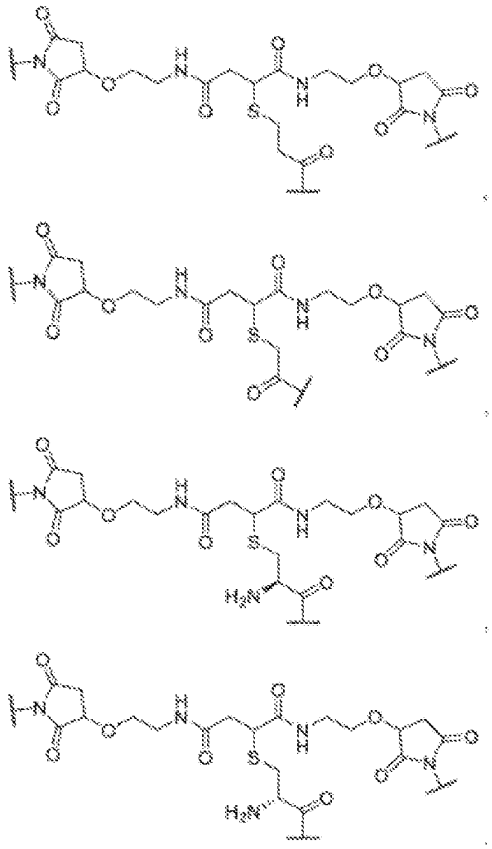
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



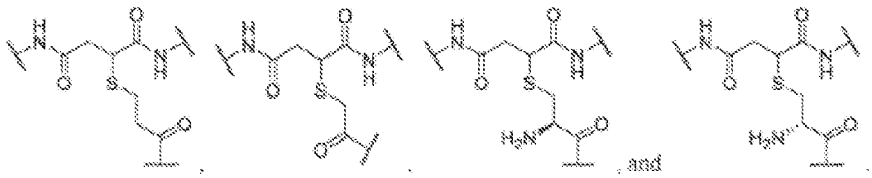
In certain embodiments, in the compound of Formula II, Linker^C -(Linker^A)$_2$ is selected from:



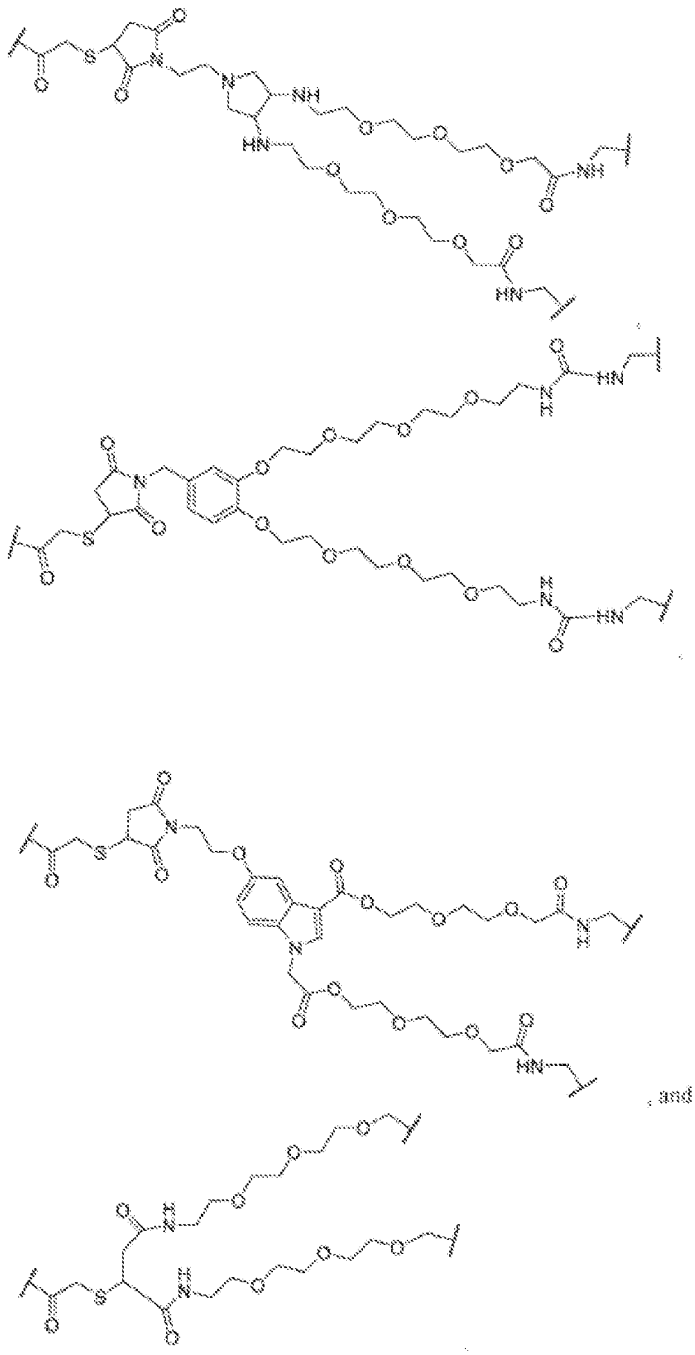
In certain embodiments, in the compound of Formula II, $Linker^C$ -$(Linker^A)_2$ is selected from:



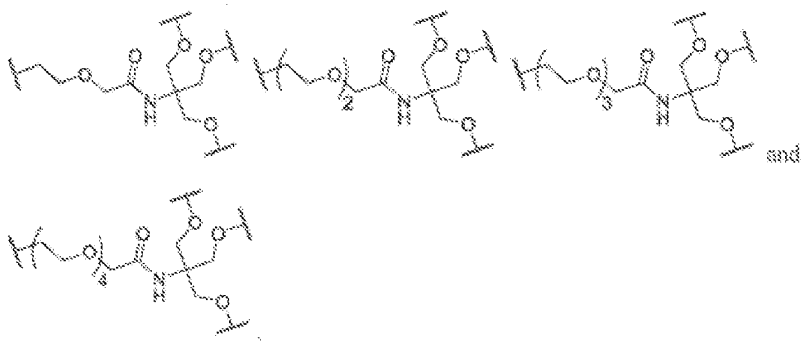
In certain embodiments, in the compound of Formula II, $Linker^C$-$(Linker^A)_2$ is selected from:



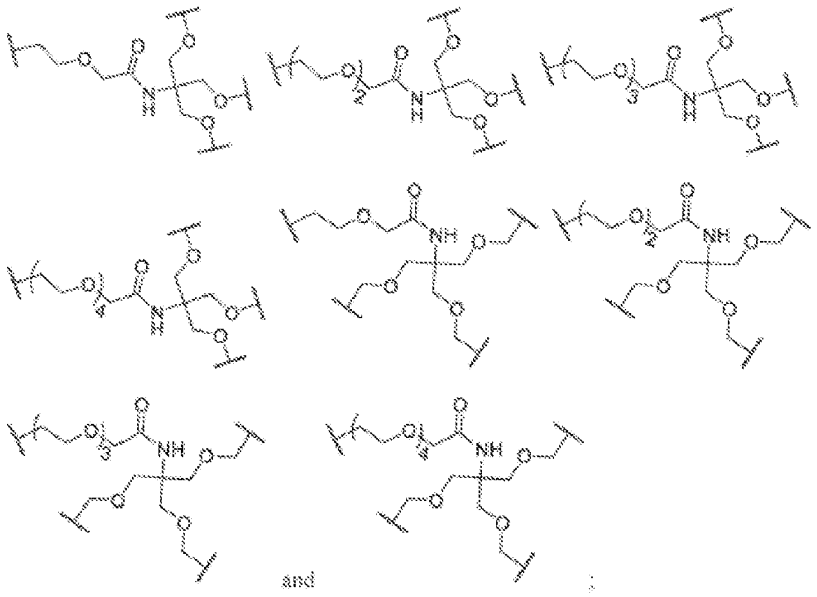
In certain embodiments, in the compound of Formula II, $Linker^C$-$(Linker^A)_2$ is selected from:



In certain embodiments, in the compound of Formula II, Linker^{D} is selected from:

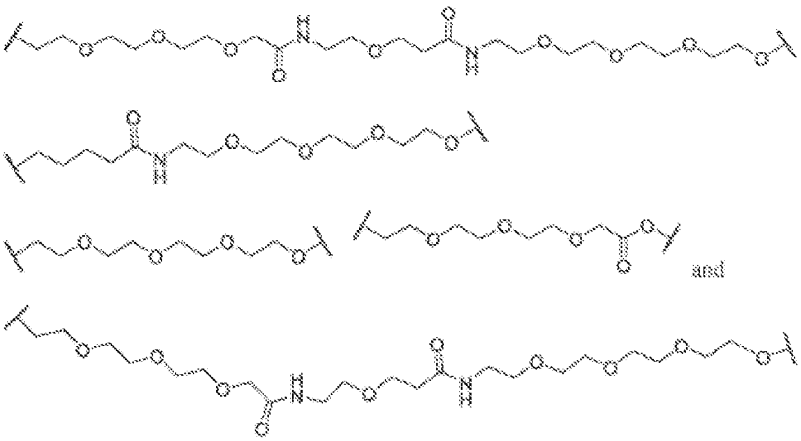


In certain embodiments, in the compound of Formula II, Linker^{D} is selected from:

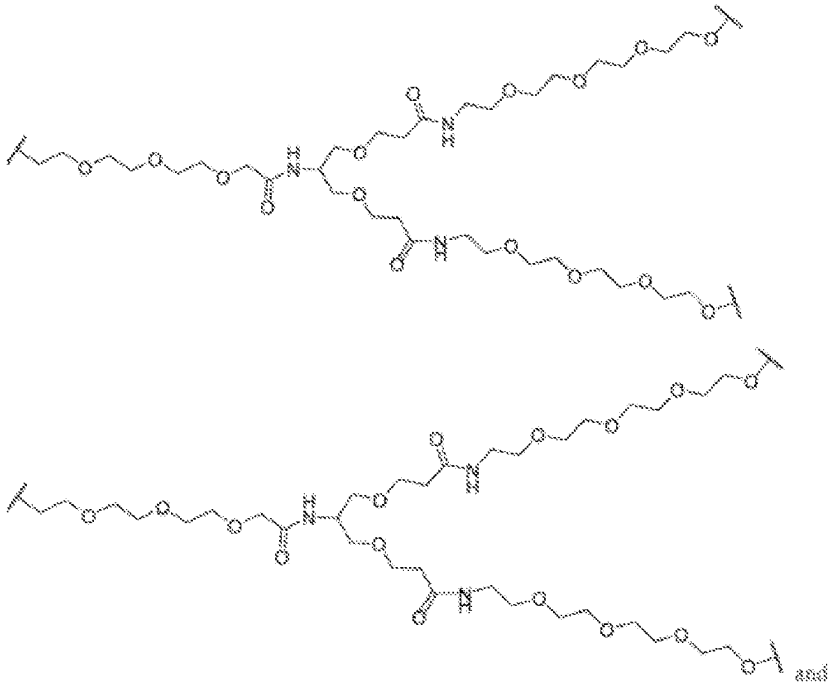


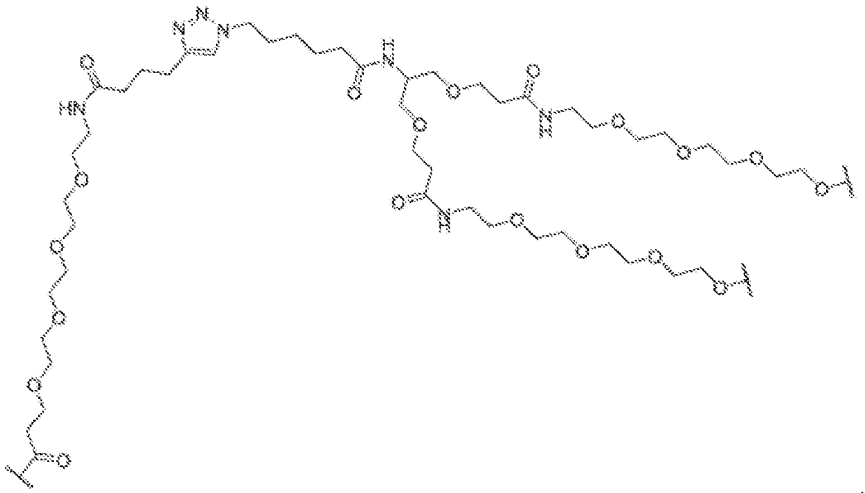
wherein each is optionally substituted with 1, 2, 3, or 4 substituents are selected from R^{21}.

In certain embodiments, in the compound of Formula II, Linker^{B} -(Linker^{A}) is selected from

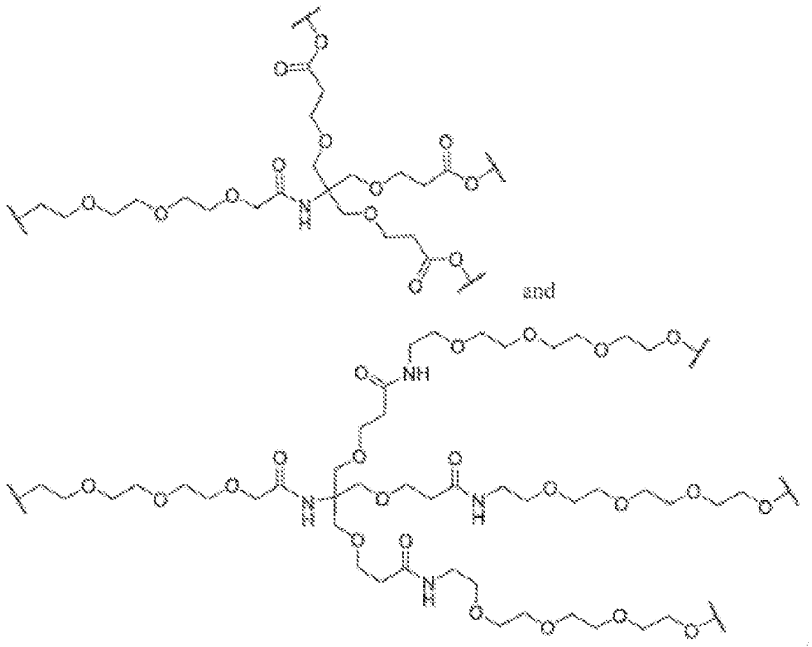


In certain embodiments, in the compound of Formula II, $Linker^{C}$-($Linker^{A}$) is selected from





In certain embodiments, in the compound of Formula II, $Linker^D$-($Linker^A$) is selected from



In various embodiments, R^4 is independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, $-OR^6$, $-NR^6R^7$, $C(O)R^3$, $S(O)R^3$, $C(S)R^3$, and $S(O)_2R^3$.

In various embodiments, in the compound of Formula II, R^5 is independently selected

from hydrogen, heteroalkyl, , C_0-C_6alkyl-cyano, alkyl, alkenyl, alkynyl, haloalkyl, F, Cl, Br, I, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocycloalkyl, haloalkoxy, -O-alkenyl, -O-alkynyl, C_0-C_6alkyl- OR^6, C_0-C_6alkyl-SR^6, C_0-C_6alkyl-NR^6R^7, C_0-C_6alkyl-$C(O)R^3$, C_0-C_6alkyl-$S(O)R^3$, C_0-C_6alkyl- $C(S)R^3$, C_0-C_6alkyl-$S(O)_2R^3$, C_0-C_6alkyl-$N(R^8)$-$C(O)R^3$, C_0-C_6alkyl-$N(R^8)$-$S(O)R^3$, C_0-C_6alkyl- $N(R^8)$-$C(S)R^3$, C_0-C_6alkyl-$N(R^8)$-$S(O)_2R^3$ C_0-C_6alkyl-O-$C(O)R^3$, C_0-C_6alkyl-O-$S(O)R^3$, C_0- C_6alkyl-O-$C(S)R^3$, -N=$S(O)(R^3)_2$, C_0-C_6alkylN_3, and C_0-C_6alkyl-O-$S(O)_2R^3$, each of which is optionally substituted with 1, 2, 3, or 4 substituents.

In various embodiments, in the compound of Formula II, R^6 and R^7 are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroaryl alkyl, alkenyl, alkynyl, and, haloalkyl, heteroaryl, heterocycle, -alkyl-OR^8, -alkyl-NR^8R^9, $C(O)R^3$, $S(O)R^3$, $C(S)R^3$, and $S(O)_2R^3$.

In various embodiments, in the compound of Formula II, R^8 and R^9 are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle.

In various embodiments, the compound of Formula II has the structure of Formula II-A.

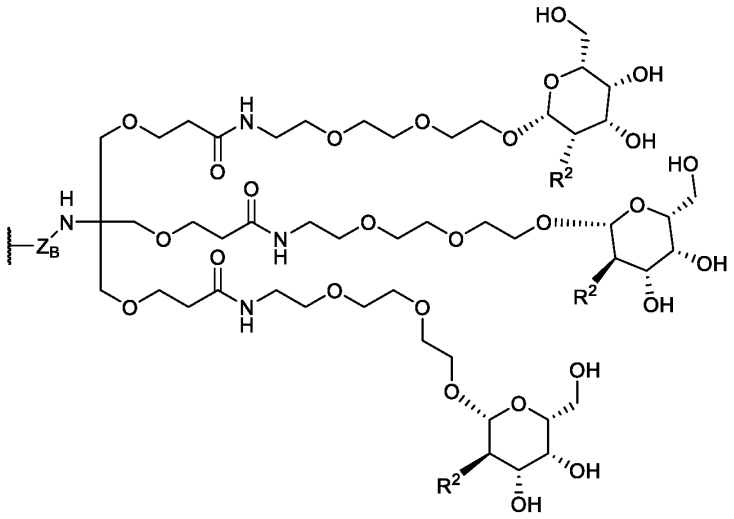
A compound of Formula II-A, having the structure:

Formula II-A

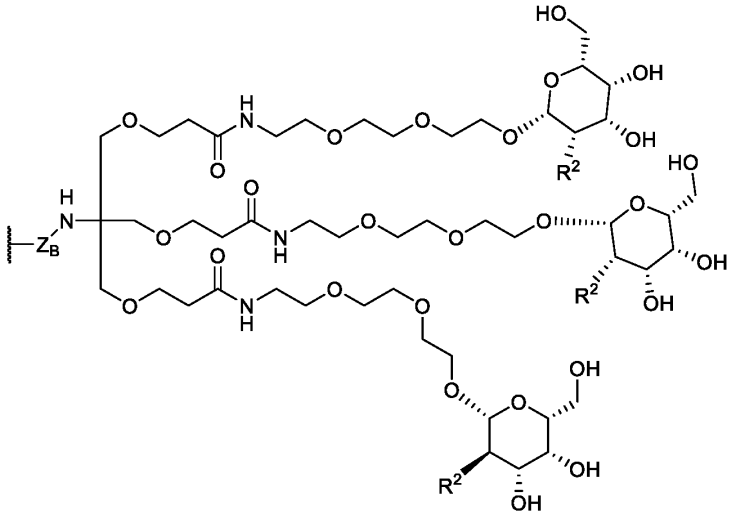
wherein:

[CPBM] is a Circulating Protein Binding Moiety which binds to a circulating protein in a subject, wherein the circulating protein mediates a disease state or condition and is to be removed by the action of hepatocytes or other cells of the subject;

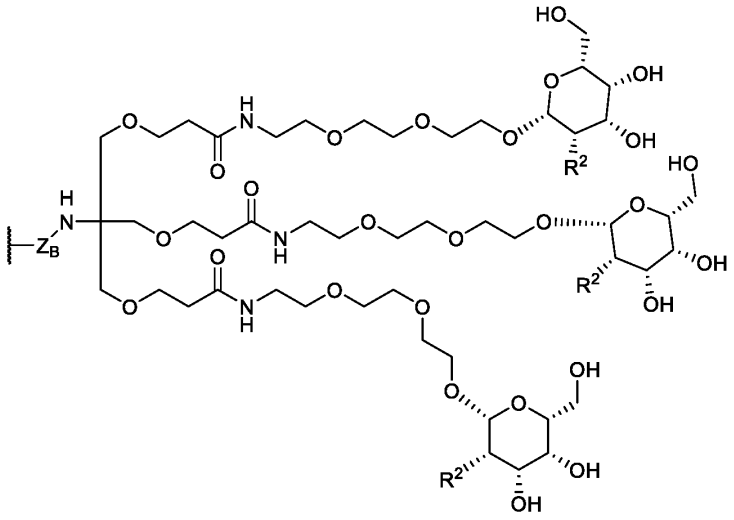
[ASGPBM] is an asialoglycoprotein receptor binding moiety having the structure selected from



,



, or



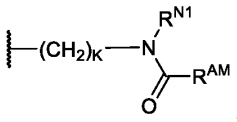
;

each [CON] is an optional connector chemical moiety which, when present, connects the [LIN] to [CPBM] or to [ASGPBM];

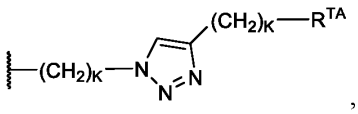
[LIN] is [LINKER] or [LINKER-2], each of which is a chemical moiety having a valency from 1 to 15, which covalently attaches to one or more [ASGPBM] or [CPBM] groups, optionally through a [CON], wherein the [LIN] optionally itself contains one or more [CON] groups;

Z_B is absent, $(CH_2)_{IM}$, $C(O)$-$(CH_2)_{IM}$-, or $C(O)$-$(CH_2)_{IM}$-NR_M;

R_M is H or a C_1-C_3 alkyl group optionally substituted with one or two hydroxyl groups;

R_2 is  ;

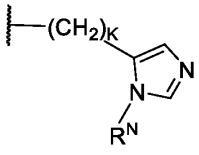
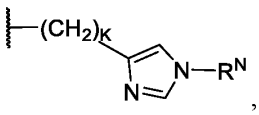
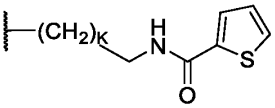
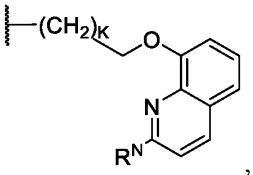
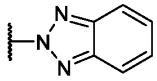
wherein R^{AM} is H, C_1-C_4 alkyl optionally substituted with up to 3 halo groups and one or two hydroxyl groups, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O$-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, -O-C(O)-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, -C(O)-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, or $-(CH_2)_K$-$NR^{N3}R^{N4}$,or

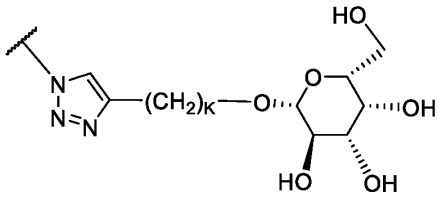
R_2 is  ,

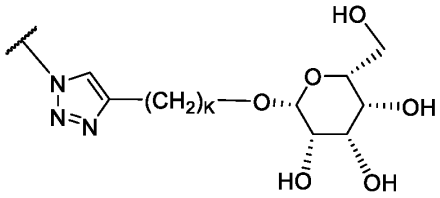
wherein

R^{TA} is H, CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KO(C_1$-C_4 alkyl) optionally substituted with 1-3 halo groups, C_1-C_4 alkyl optionally substituted with 1-3 halo groups, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O$-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, -O-C(O)-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, or -C(O)-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, or

R^{TA} is a C_3-C_{10} aryl or a three- to ten-membered heteroaryl group containing up to 5 heteroaryl atoms, each of the aryl or heteroaryl groups being optionally substituted with up to three CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KO(C_1$-C_4 alkyl) optionally substituted with 1-3 halo groups, C_1-C_3 alkyl optionally substituted with 1-3 halo groups or 1-2 hydroxy groups, -O-(C_1-C_3-alkyl) optionally substituted from 1-3 halo groups, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O$-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, O-C(O)-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, or $-(CH_2)_KC(O)$-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, or

R^{TA} is  ,  ,  ,  , or  , optionally substituted with up to three C_1-C_3 alkyl groups which are optionally substituted with up to three halo groups; or

R^{TA} is  or

 ;

R^N, R^{N1}, R^{N2}, R^{N3}, R^{N4} are each independently H or C_1-C_3 alkyl optionally substituted with one to three halo groups or one or two hydroxyl groups and each $-(CH_2)_K$ group is optionally substituted with 1-4 C_1-C_3 alkyl groups which are optionally substituted with 1-3 fluoro groups or 1-2 hydroxyl groups;

IM is independently at each occurrence an integer from 0 to 6;

K is independently at each occurrence an integer from 0 to 4;

k' is an integer ranging from 1 to 15;

j' is an integer ranging from 1 to 15;

h and h' are each independently an integer ranging from 0 to 15;

i_L is 0 to 15;

with the proviso that at least one of h, h', and i_L is at least 1,

or a salt, stereoisomer, or solvate thereof.

In various embodiments, in the compound of Formula II-A, R_2 is $-NC(=O)CH_3$.

The term "organic group" as used herein refers to any carbon-containing functional group. Examples can include an oxygen-containing group such as an alkoxy group, aryloxy group, aralkyloxy group, oxo(carbonyl) group; a carboxyl group including a carboxylic acid,

carboxylate, and a carboxylate ester; a sulfur-containing group such as an alkyl and aryl sulfide group; and other heteroatom-containing groups. Non-limiting examples of organic groups include OR, OOR, $OC(O)N(R)_2$, CN, CF_3, OCF_3, R, C(O), methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, SO_2R, $SO_2N(R)_2$, SO_3R, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}N(R)C(O)R$, $(CH_2)_{0-2}N(R)N(R)_2$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, C(=NOR)R, and substituted or unsubstituted (C_1-C_{100})hydrocarbyl, wherein R can be hydrogen (in examples that include other carbon atoms) or a carbon-based moiety, and wherein the carbon-based moiety can be substituted or unsubstituted.

The term "substituted" as used herein in conjunction with a molecule or an organic group as defined herein refers to the state in which one or more hydrogen atoms contained therein are replaced by one or more non-hydrogen atoms. The substitution can be direct substitution, whereby the hydrogen atom is replaced by a functional group or substituent, or an indirect substitution, whereby an intervening linker group replaces the hydrogen atom, and the substituent or functional group is bonded to the intervening linker group. A non-limiting example of direct substitution is: RR-H → RR-Cl, wherein RR is an organic moiety/fragment/molecule. A non-limiting example of indirect substitution is: RR-H → RR-$(LL)_{zz}$-Cl, wherein RR is an organic moiety/fragment/molecule, LL is an intervening linker group, and 'zz' is an integer from 0 to 100 inclusive. When zz is 0, LL is absent, and direct substitution results. The intervening linker group LL is at each occurrence independently selected from the group consisting of -H, -O-, -OR, -S-, $-S(=O)-$, $-S(=O)_2-$, -SR, $-N(R)-$, $-NR_2$, -CR=, -C≡, $-CH_2-$, -CHR-, $-CR_2-$, $-CH_3$, $-C(=O)-$, $-C(=NR)-$, and combinations thereof. $(LL)_{zz}$ can be linear, branched, cyclic, acyclic, and combinations thereof.

The term "functional group" or "substituent" as used herein refers to a group that can be or is substituted onto a molecule or onto an organic group. Examples of substituents or functional groups include, but are not limited to, a halogen (*e.g.*, F, Cl, Br, and I); an oxygen atom in groups such as hydroxy groups, alkoxy groups, aryloxy groups, aralkyloxy groups, oxo(carbonyl) groups, carboxyl groups including carboxylic acids, carboxylates, and carboxylate esters; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfoxide groups, sulfone groups, sulfonyl groups, and sulfonamide groups; a nitrogen atom in groups such as amines, hydroxyamines, nitriles, nitro groups, N-oxides, hydrazides, azides,

and enamines; and other heteroatoms in various other groups. Non-limiting examples of substituents that can be bonded to a substituted carbon (or other) atom include F, Cl, Br, I, OR, $OC(O)N(R)_2$, CN, NO, NO_2, ONO_2, azido, CF_3, OCF_3, R, O (oxo), S (thiono), C(O), S(O), methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, SO_2R, $SO_2N(R)_2$, SO_3R, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}N(R)C(O)R$, $(CH_2)_{0-2}N(R)N(R)_2$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, and C(=NOR)R, wherein R can be hydrogen or a carbon-based moiety; for example, R can be hydrogen, $(C_1\text{-}C_{100})$hydrocarbyl, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl; or wherein two R groups bonded to a nitrogen atom or to adjacent nitrogen atoms can together with the nitrogen atom or atoms form a heterocyclyl.

The term "alkyl" as used herein refers to straight chain and branched alkyl groups and cycloalkyl groups having from 1 to 40 carbon atoms, 1 to about 20 carbon atoms, 1 to 12 carbons or, in some embodiments, from 1 to 8 carbon atoms. Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. As used herein, the term "alkyl" encompasses n-alkyl, isoalkyl, and anteisoalkyl groups as well as other branched chain forms of alkyl. Representative substituted alkyl groups can be substituted one or more times with any of the groups listed herein, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

The term "alkenyl" as used herein refers to straight and branched chain and cyclic alkyl groups as defined herein, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to 40 carbon atoms, or 2 to about 20 carbon atoms, or 2 to 12 carbon atoms or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to vinyl, $-CH=C=CCH_2$, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others.

The term "alkynyl" as used herein refers to straight and branched chain alkyl groups, except that at least one triple bond exists between two carbon atoms. Thus, alkynyl groups have from 2 to 40 carbon atoms, 2 to about 20 carbon atoms, or from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to –

C≡CH, -C≡C(CH_3), -C≡C(CH_2CH_3), -CH_2C≡CH, -CH_2C≡C(CH_3), and -CH_2C≡C(CH_2CH_3) among others.

The term "acyl" as used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is bonded to a hydrogen forming a "formyl" group or is bonded to another carbon atom, which can be part of an alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl group or the like. An acyl group can include 0 to about 12, 0 to about 20, or 0 to about 40 additional carbon atoms bonded to the carbonyl group. An acyl group can include double or triple bonds within the meaning herein. An acryloyl group is an example of an acyl group. An acyl group can also include heteroatoms within the meaning herein. A nicotinoyl group (pyridyl-3-carbonyl) is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like. When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is termed a "haloacyl" group. An example is a trifluoroacetyl group.

The term "cycloalkyl" as used herein refers to cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined herein. Representative substituted cycloalkyl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups or mono-, di- or tri-substituted norbornyl or cycloheptyl groups, which can be substituted with, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups. The term "cycloalkenyl" alone or in combination denotes a cyclic alkenyl group.

The term "heterocycloalkyl" as used herein refers to a cycloalkyl group as defined herein in which one or more carbon atoms in the ring are replaced by a heteroatom such as O, N, S, P, and the like, each of which may be substituted as described herein if an open valence is present, and each may be in any suitable stable oxidation state.

The term "aryl" as used herein refers to cyclic aromatic hydrocarbon groups that do

not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons in the ring portions of the groups. Aryl groups can be unsubstituted or substituted, as defined herein. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, a phenyl group substituted at any one or more of 2-, 3-, 4-, 5-, or 6-positions of the phenyl ring, or a naphthyl group substituted at any one or more of 2- to 8-positions thereof.

The term "aralkyl" as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined herein. Representative aralkyl groups include benzyl and phenylethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl. Aralkenyl groups are alkenyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined herein.

The term "heterocyclyl" as used herein refers to aromatic and non-aromatic ring compounds containing three or more ring members, of which one or more is a heteroatom such as, but not limited to, N, O, and S. Thus, a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. The term heterocyclyl includes rings where a CH_2 group in the ring is replaced by one or more C=O groups, such as found in cyclic ketones, lactones, and lactams. Examples of heterocyclyl groups containing a C=O group include, but are not limited to, β-propiolactam, γ-butyrolactam, δ-valerolactam, and ε-caprolactam, as well as the corresponding lactones. A heterocyclyl group designated as a C_2-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C_4-heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms equals the total number of ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The phrase "heterocyclyl group" includes fused ring species including those that include fused aromatic and non-aromatic groups. For example, a dioxolanyl ring and a benzdioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. The phrase also includes polycyclic ring systems containing a heteroatom such as,

but not limited to, quinuclidyl. Heterocyclyl groups can be unsubstituted, or can be substituted as discussed herein. Heterocyclyl groups include, but are not limited to, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, dihydrobenzofuranyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Representative substituted heterocyclyl groups can be mono-substituted or substituted more than once, such as, but not limited to, piperidinyl or quinolinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with groups such as those listed herein.

The term "heteroaryl" as used herein refers to aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S; for instance, heteroaryl rings can have 5 to about 8-12 ring members. A heteroaryl group is a variety of a heterocyclyl group that possesses an aromatic electronic structure. A heteroaryl group designated as a C_2-heteroaryl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C_4-heteroaryl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. A heterocyclyl ring designated C_{x-y} can be any ring containing 'x' members up to 'y' members, including all intermediate integers between 'x' and 'y' and that contains one or more heteroatoms, as defined herein. In a ring designated C_{x-y}, all non-heteroatom members are carbon. Heterocyclyl rings designated C_{x-y} can also be polycyclic ring systems, such as bicyclic or tricyclic ring systems. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Heteroaryl groups can be unsubstituted, or can be substituted with groups as is discussed herein. Representative substituted heteroaryl groups can be substituted one or more times with groups such as those listed herein.

Additional examples of aryl and heteroaryl groups include but are not limited to phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-

hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl) , indolyl, oxadiazolyl, isoxazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl, (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), and the like.

The term "heterocyclylalkyl" as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group as defined herein is replaced with a bond

to a heterocyclyl group as defined herein. Representative heterocyclyl alkyl groups include, but are not limited to, furan-2-yl methyl, furan-3-yl methyl, pyridine-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

The term "arylalkyl" as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined herein.

The term "heteroarylalkyl" as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined herein.

The term "alkoxy" as used herein refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined herein. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. An alkoxy group can include about 1 to about 12, about 1 to about 20, or about 1 to about 40 carbon atoms bonded to the oxygen atom, and can further include double or triple bonds, and can also include heteroatoms. For example, an allyloxy group or a methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structure are substituted therewith.

The term "amine" as used herein refers to primary, secondary, and tertiary amines having, *e.g.*, the formula $N(group)_3$ wherein each group can independently be H or non-H, such as alkyl, aryl, and the like. Amines include but are not limited to $R\text{-}NH_2$, for example, alkylamines, arylamines, alkylarylamines; R_2NH wherein each R is independently selected, such as dialkylamines, diarylamines, aralkylamines, heterocyclylamines and the like; and R_3N wherein each R is independently selected, such as trialkylamines, dialkylarylamines, alkyldiarylamines, triarylamines, and the like. The term "amine" also includes ammonium ions as used herein.

The term "amino group" as used herein refers to a substituent of the form $-NH_2$, $-NHR$, $-NR_2$, $-NR_3^+$, wherein each R is independently selected, and protonated forms of each, except for $-NR_3^+$, which cannot be protonated. Accordingly, any compound substituted with an amino group can be viewed as an amine. An "amino group" within the meaning herein can be a primary, secondary, tertiary, or quaternary amino group. An "alkylamino" group

includes a monoalkylamino, dialkylamino, and trialkylamino group.

The terms "halo," "halogen," or "halide" group, as used herein, by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

The term "haloalkyl" group, as used herein, includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo alkyl groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkyl include trifluoromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, perfluorobutyl, and the like.

The terms "epoxy-functional" or "epoxy-substituted" as used herein refers to a functional group in which an oxygen atom, the epoxy substituent, is directly attached to two adjacent carbon atoms of a carbon chain or ring system. Examples of epoxy-substituted functional groups include, but are not limited to, 2,3-epoxypropyl, 3,4-epoxybutyl, 4,5-epoxypentyl, 2,3-epoxypropoxy, epoxypropoxypropyl, 2-glycidoxyethyl, 3-glycidoxypropyl, 4-glycidoxybutyl, 2-(glycidoxycarbonyl)propyl, 3-(3,4-epoxycylohexyl)propyl, 2-(3,4-epoxycyclohexyl)ethyl, 2-(2,3-epoxycylopentyl)ethyl, 2-(4-methyl-3,4-epoxycyclohexyl)propyl, 2-(3,4-epoxy-3-methylcylohexyl)-2-methylethyl, and 5,6-epoxyhexyl.

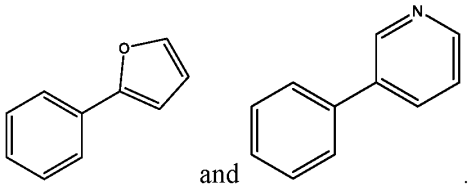
The term "monovalent" as used herein refers to a substituent connecting via a single bond to a substituted molecule. When a substituent is monovalent, such as, for example, F or Cl, it is bonded to the atom it is substituting by a single bond.

The term "hydrocarbon" or "hydrocarbyl" as used herein refers to a molecule or functional group that includes carbon and hydrogen atoms. The term can also refer to a molecule or functional group that normally includes both carbon and hydrogen atoms but wherein all the hydrogen atoms are substituted with other functional groups.

As used herein, the term "hydrocarbyl" refers to a functional group derived from a straight chain, branched, or cyclic hydrocarbon, and can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl, acyl, or any combination thereof. Hydrocarbyl groups can be shown as (C_a-C_b)hydrocarbyl, wherein a and b are integers and mean having any of a to b number of carbon atoms. For example, (C_1-C_4)hydrocarbyl means the hydrocarbyl group can be methyl (C_1), ethyl (C_2), propyl (C_3), or butyl (C_4), and (C_0-C_b)hydrocarbyl means in certain embodiments there is no hydrocarbyl group.

As used herein, the term "C_{6-10}-5-6 membered heterobiaryl" means a C_{6-10} aryl moiety covalently bonded through a single bond to a 5- or 6-membered heteroaryl moiety. The C_{6-10}

aryl moiety and the 5-6-membered heteroaryl moiety can be any of the suitable aryl and heteroaryl groups described herein. Non-limiting examples of a C_{6-10}-5-6 membered heterobiaryl include



and .

When the C_{6-10}-5-6 membered heterobiaryl is listed as a substituent (*e.g.*, as an "R" group), the C_{6-10}-5-6 membered heterobiaryl is bonded to the rest of the molecule through the C_{6-10} moiety.

As used herein, the term "5-6 membered- C_{6-10} heterobiaryl " is the same as a C_{6-10}-5-6 membered heterobiaryl, except that when the 5-6 membered- C_{6-10} heterobiaryl is listed as a substituent (*e.g.*, as an "R" group), the 5-6 membered- C_{6-10} heterobiaryl is bonded to the rest of the molecule through the 5-6-membered heteroaryl moiety.

As used herein, the term "C_{6-10}- C_{6-10} biaryl" means a C_{6-10} aryl moiety covalently bonded through a single bond to another C_{6-10} aryl moiety. The C_{6-10} aryl moiety can be any of the suitable aryl groups described herein. Non-limiting example of a C_{6-10}- C_{6-10} biaryl include biphenyl and binaphthyl.

The term “pharmaceutically acceptable salt” or “salt” is used throughout the specification to describe a salt form of one or more of the compositions herein which are presented to increase the solubility of the compound in saline for parenteral delivery or in the gastric juices of the patient’s gastrointestinal tract in order to promote dissolution and the bioavailability of the compounds. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium, magnesium and ammonium salts, among numerous other acids well known in the pharmaceutical art. Sodium and potassium salts may be preferred as neutralization salts of carboxylic acids and free acid phosphate containing compositions according to the present invention. The term “salt” shall mean any salt consistent with the use of the compounds according to the present invention. In the case where the compounds are used in pharmaceutical indications, including the treatment of prostate cancer, including metastatic prostate cancer, the term “salt” shall mean a pharmaceutically acceptable salt, consistent with

the use of the compounds as pharmaceutical agents.

The term "coadministration" shall mean that at least two compounds or compositions are administered to the patient at the same time, such that effective amounts or concentrations of each of the two or more compounds may be found in the patient at a given point in time. Although compounds according to the present invention may be co-administered to a patient at the same time, the term embraces both administration of two or more agents at the same time or at different times, provided that effective concentrations of all coadministered compounds or compositions are found in the subject at a given time. Chimeric antibody-recruiting compounds according to the present invention may be administered with one or more additional anti-cancer agents or other agents which are used to treat or ameliorate the symptoms of cancer, especially prostate cancer, including metastatic prostate cancer.

The term "anticancer agent" or "additional anticancer agent" refers to a compound other than the chimeric compounds according to the present invention which may be used in combination with a compound according to the present invention for the treatment of cancer. Exemplary anticancer agents which may be coadministered in combination with one or more chimeric compounds according to the present invention include, for example, antimetabolites, inhibitors of topoisomerase I and II, alkylating agents and microtubule inhibitors (e.g., taxol), among others. Exemplary anticancer compounds for use in the present invention may include everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab (Arzerra), zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001, IPdR$_1$ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709,

seliciclib; PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N -[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)-indolyl]-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t) 6,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH_2 acetate $[C_{59}H_{84}N_{18}Oi_4\text{-}(C_2H_4O_2)_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevac, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, irinotecan, topotecan, doxorubicin, docetaxel, vinorelbine, bevacizumab (monoclonal antibody) and erbitux, cremophor-free paclitaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684,

LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa and darbepoetin alfa, vemurafenib among others, including immunotherapy agents such as IDO inhibitors (an inhibitor of indoleamine 2,3-dioxygenase (IDO) pathway) such as Indoximod (NLG-8187), Navoximod (GDC-0919) and NLG802, PDL1 inhibitors (an inhibitor of programmed death-ligand 1) including, for example, nivolumab, durvalumab and atezolizumab, PD1 inhibitors such as pembrolizumab (Merck) and CTLA-4 inhibitors (an inhibitor of cytotoxic T-lymphocyte associated protein 4/cluster of differentiation 152), including ipilimumab and tremelimumab, among others.

In addition to anticancer agents, a number of other agents may be co-administered with chimeric compounds according to the present invention in the treatment of cancer. These include active agents, minerals, vitamins and nutritional supplements which have shown some efficacy in inhibiting cancer tissue or its growth or are otherwise useful in the treatment of cancer. For example, one or more of dietary selenium, vitamin E, lycopene, soy foods, curcumin (turmeric), vitamin D, green tea, omega-3 fatty acids and phytoestrogens, including beta-sitosterol, may be utilized in combination with the present compounds to treat cancer.

Without not being limited by way of theory, compounds according to the present invention which contain a CPBM binding moiety (CPBM) and CRBM/ASGPR binding moiety selectively bind to circulating proteins and through that binding, facilitate the introduction of the cellular protein into hepatocytes or other cells (degrading cells) which bind the CRBM/ASGPRBM selectively, where, the circulating protein, inside the hepatocyte or other degrading cell is degraded and removed from circulation. Thus, compounds

according to the present invention both bind to MIF proteins and remove the MIF proteins from circulation resulting in a dual action which is particularly effective for treating disease states and conditions.

Pharmaceutical compositions comprising combinations of an effective amount of at least one compound disclosed herein, often a bi-functional chimeric compound (containing at least one MIFBM group or antibody binding moiety and at least one ASGPRBM) according to the present invention, and one or more of the compounds as otherwise described herein, all in effective amounts, in combination with a pharmaceutically effective amount of a carrier, additive or excipient, represents a further aspect of the present invention. These may be used in combination with at least one additional, optional anticancer agent as otherwise disclosed herein.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers and may also be administered in controlled-release formulations. Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as prolamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, among others. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally (including via intubation through the mouth or nose into the stomach), intraperitoneally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1, 3-butanediol. Among

the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially to treat skin cancers, psoriasis or other diseases which occur in or on the skin. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-acceptable transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water.

Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more

pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

The amount of compound in a pharmaceutical composition of the instant invention that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host and disease treated, the particular mode of administration. Preferably, the compositions should be formulated to contain between about 0.05 mg to about 1.5 g, from 0.1 mg to 1 g, 0.5 mg to 750 mg, more often about 1 mg to about 600 mg, and even more often about 10 mg to about 500 mg of active ingredient, alone or in combination with at least one additional compound which may be used to treat cancer, prostate cancer or metastatic prostate cancer or a secondary effect or condition thereof.

Methods of treating patients or subjects in need for a particular disease state or condition as otherwise described herein, especially cancer, comprise administration of an effective amount of a pharmaceutical composition comprising therapeutic amounts of one or more of the novel compounds described herein and optionally at least one additional bioactive (e.g. anti-cancer, anti-inflammatory) agent according to the present invention. The amount of active ingredient(s) used in the methods of treatment of the instant invention that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the particular mode of administration. For example, the compositions could be formulated so that a therapeutically effective dose of between about 0.01, 0.1, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90 or 100 mg/kg of patient/day or in some embodiments, greater than 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 200 mg/kg of the novel compounds can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease or condition being treated.

A patient or subject (e.g. a human) suffering from an autoimmune disease, an inflammatory disease or cancer can be treated by administering to the patient (subject) an effective amount of a chimeric/bi-functional compound according to the present invention including pharmaceutically acceptable salts, solvates or polymorphs, thereof optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with other known pharmaceutical agents, preferably agents which can assist in treating autoimmune and/or inflammatory diseases or cancer, including metastatic cancer or recurrent cancer or ameliorating the secondary effects and/or symptoms associated with these disease states and/or conditions. This treatment can also be administered in conjunction with other conventional therapies, such as radiation treatment or surgery for cancer.

The present compounds, alone or in combination with other agents as described herein, can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid, cream, gel, or solid form, or by aerosol form.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount for the desired indication, without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the herein-mentioned conditions is in the range from about 10 ng/kg to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient/patient per day. A typical topical dosage will range from about 0.01-3% wt/wt in a suitable carrier.

The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing less than 1mg, 1 mg to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. An oral dosage of about 25-500 mg is often convenient.

The active ingredient is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30 mM, preferably about 0.1-30 μM. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active

ingredient. Oral administration is also appropriate to generate effective plasma concentrations of active agent.

The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound or its prodrug derivative can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a dispersing agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents.

The active compound or pharmaceutically acceptable salt thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active compound or pharmaceutically acceptable salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as other anticancer agents, anti-inflammatory agents,

immunosuppressants, antibiotics, antifungals, or antiviral compounds. In certain preferred aspects of the invention, one or more chimeric/bi-functional CPBM binding compound according to the present invention is co-administered with another anticancer agent and/or another bioactive agent, as otherwise described herein.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

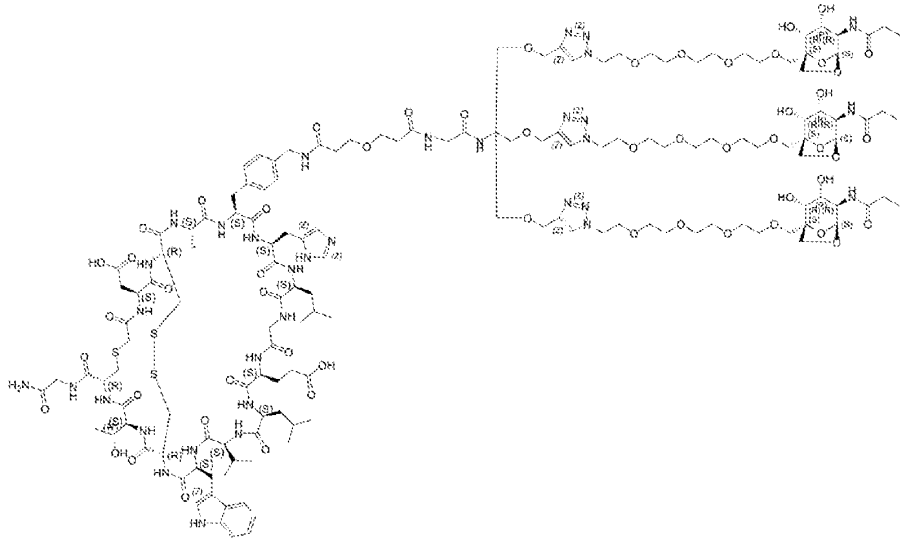
If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled and/or sustained release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

Liposomal suspensions or cholestosomes may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound are then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

The compound according to embodiments of the present invention may be a compound listed in Table 1 below:

TABLE 1



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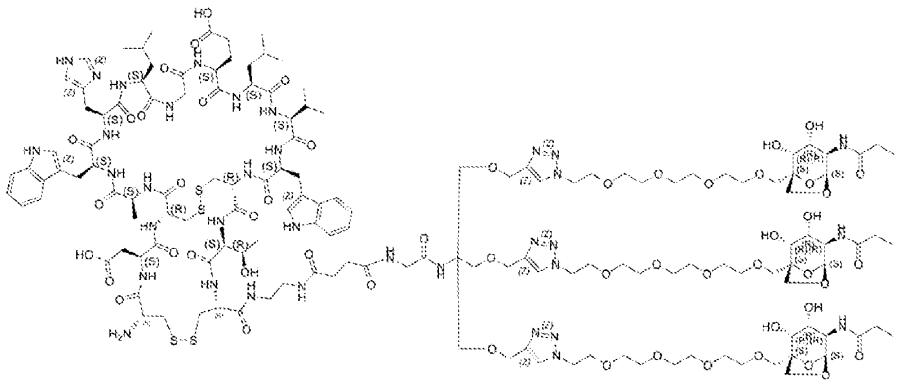

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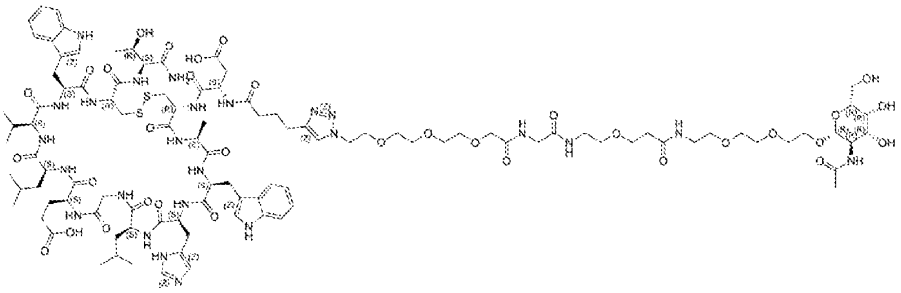

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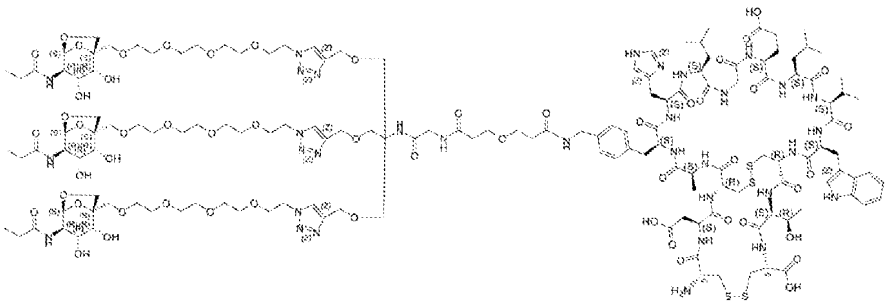

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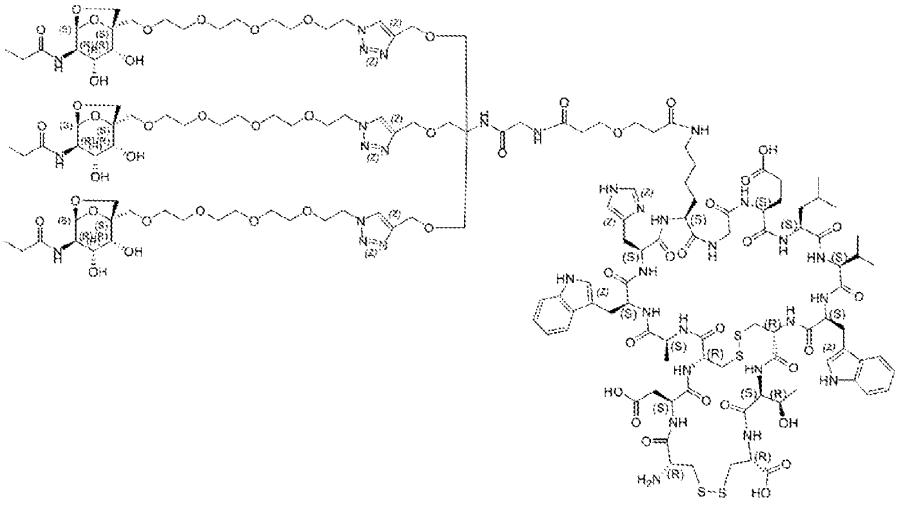

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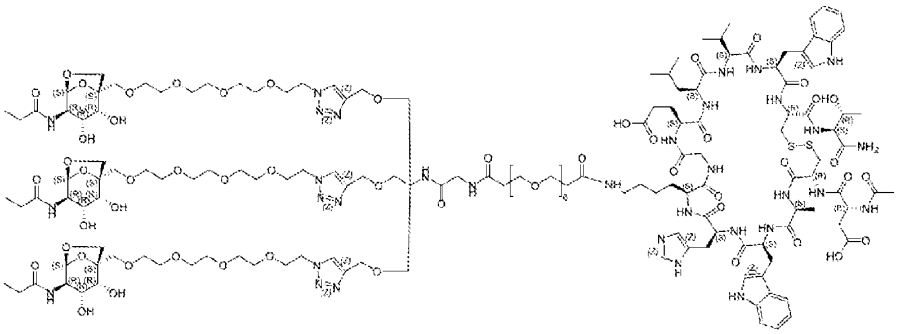

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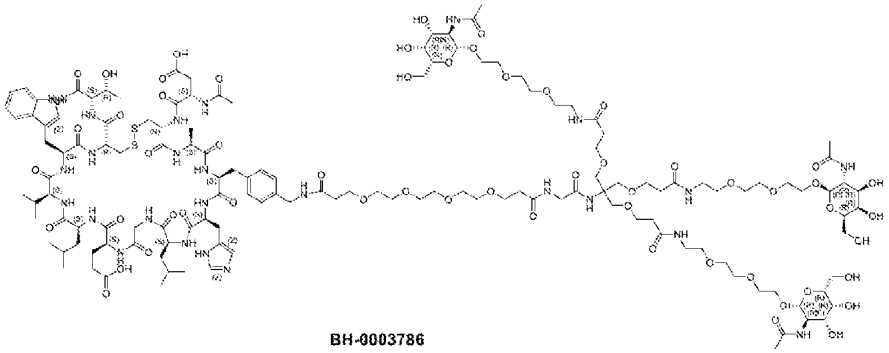

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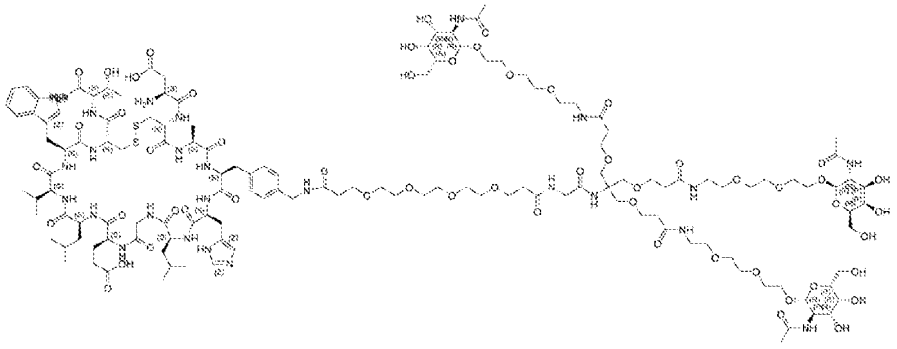

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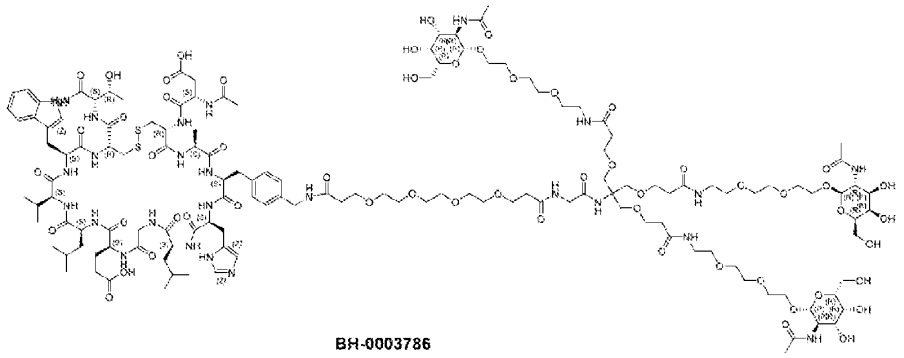

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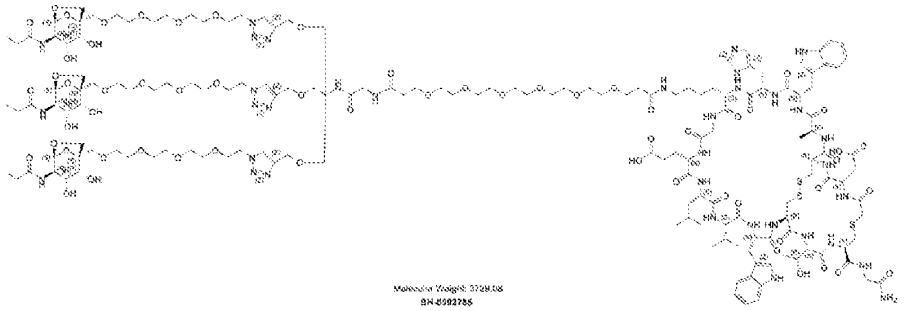

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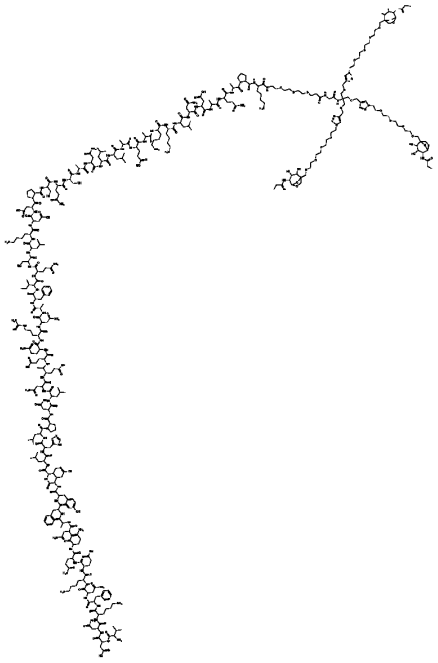

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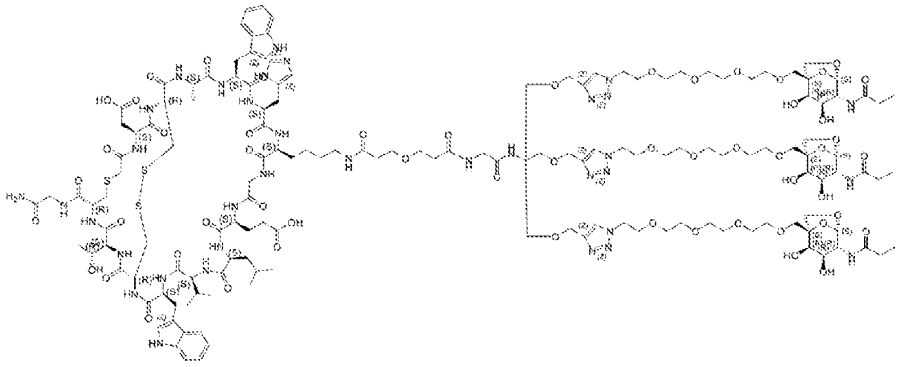

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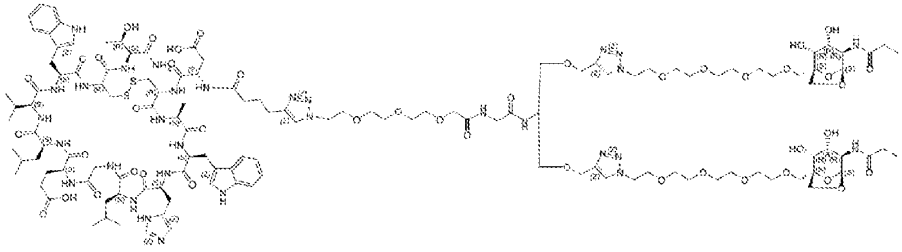

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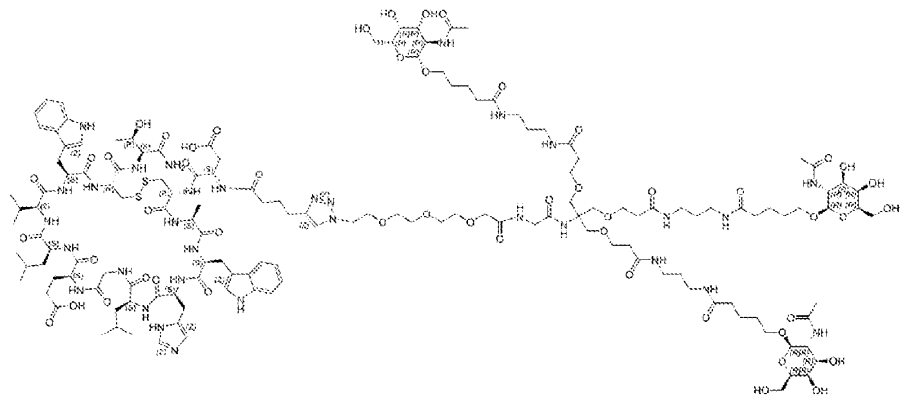

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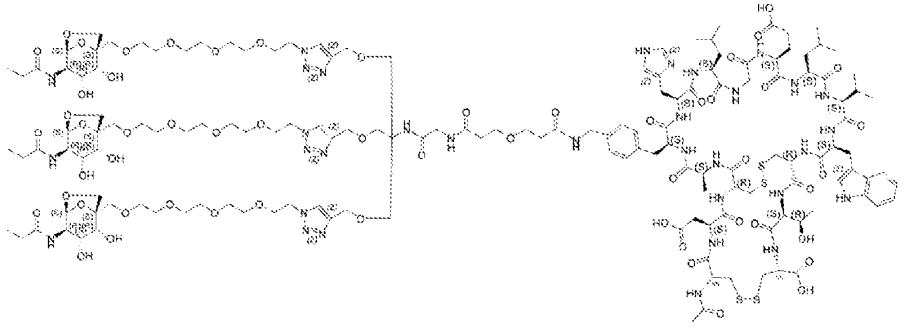

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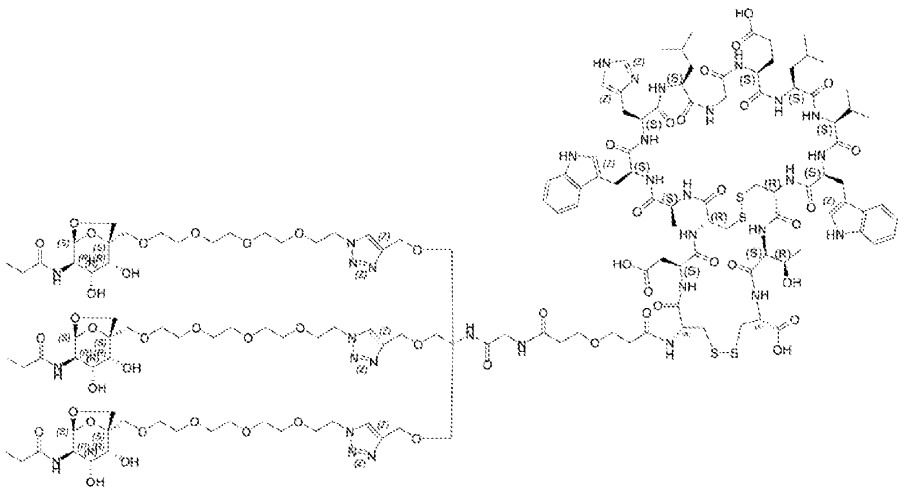

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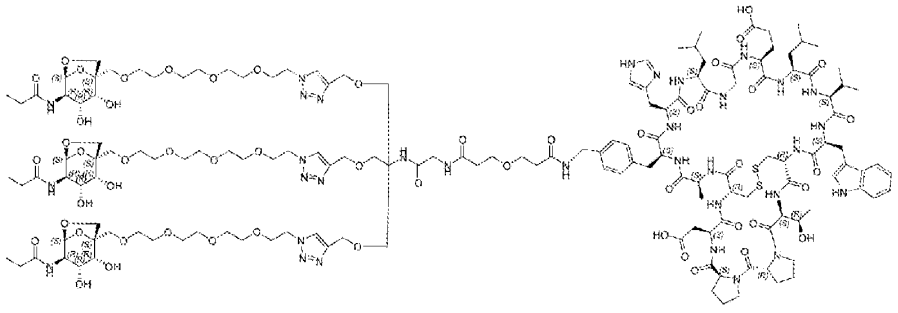

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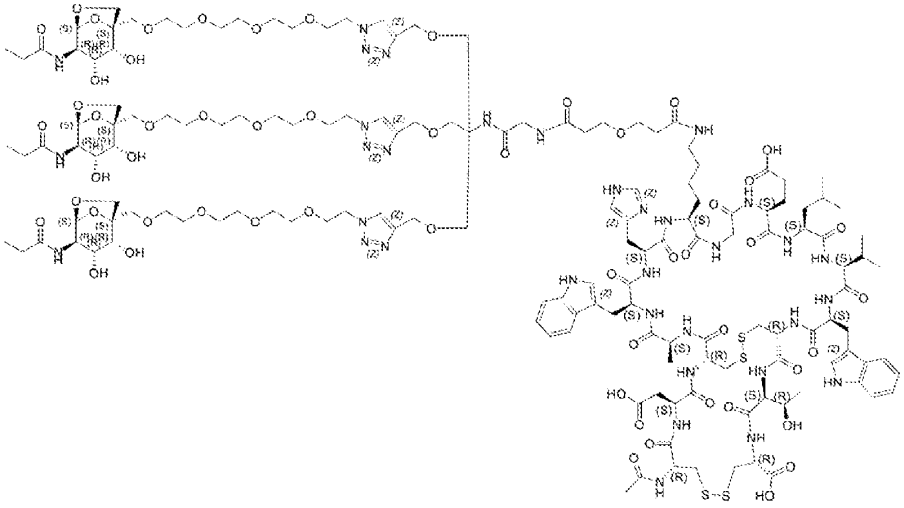

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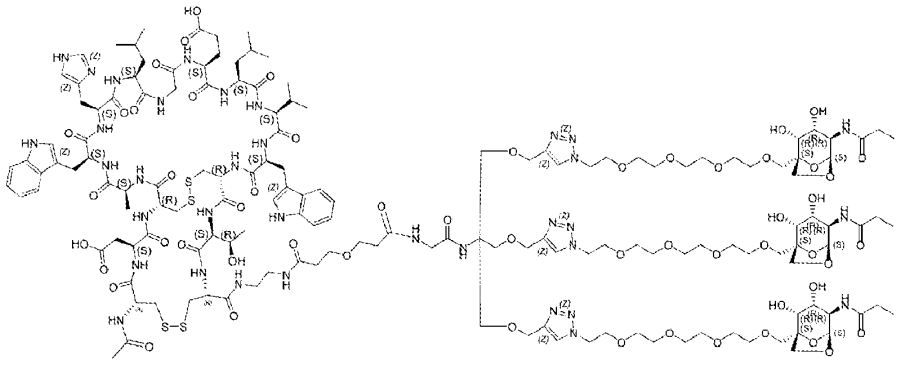

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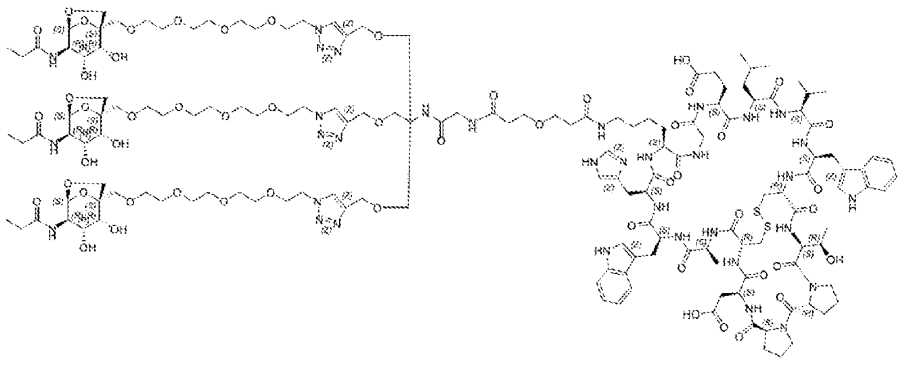

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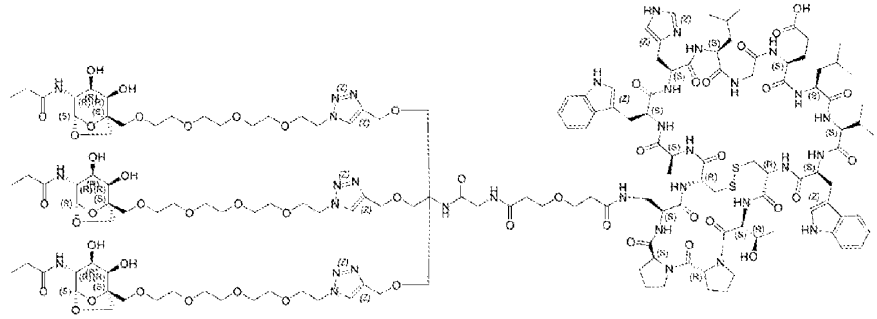

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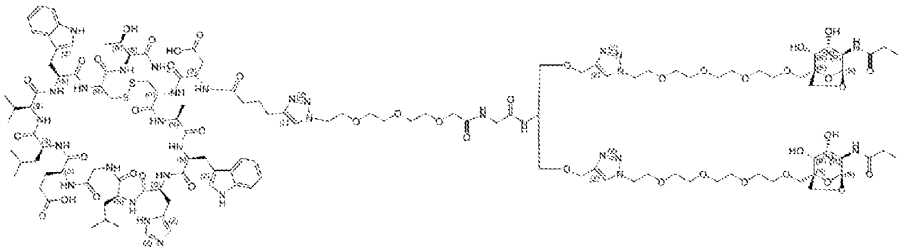

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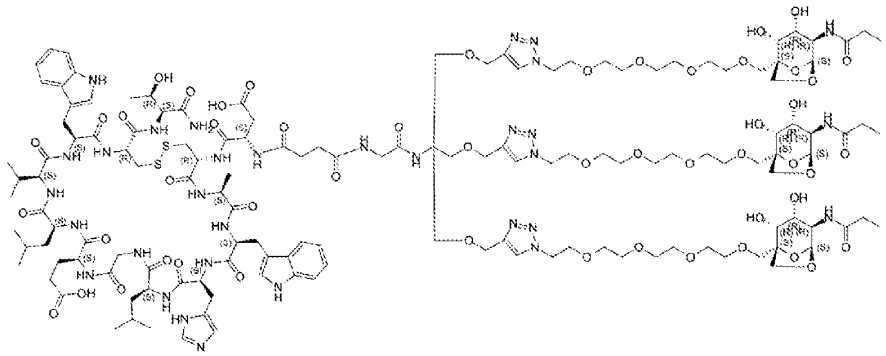

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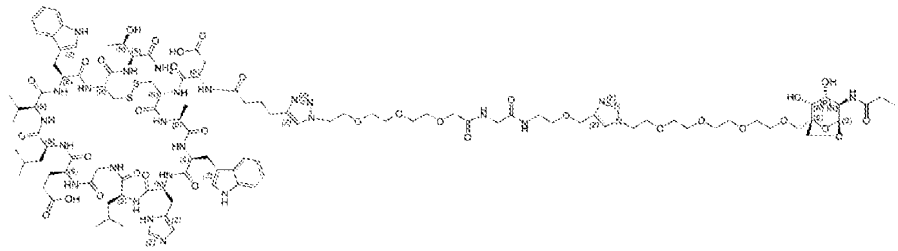

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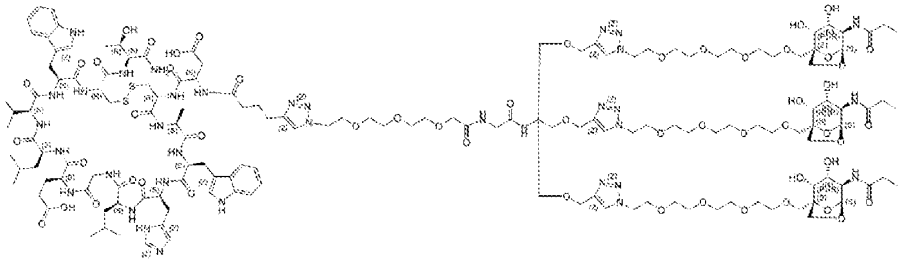

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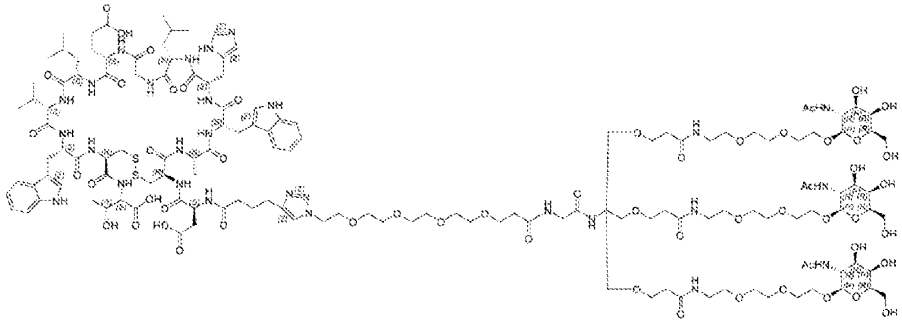

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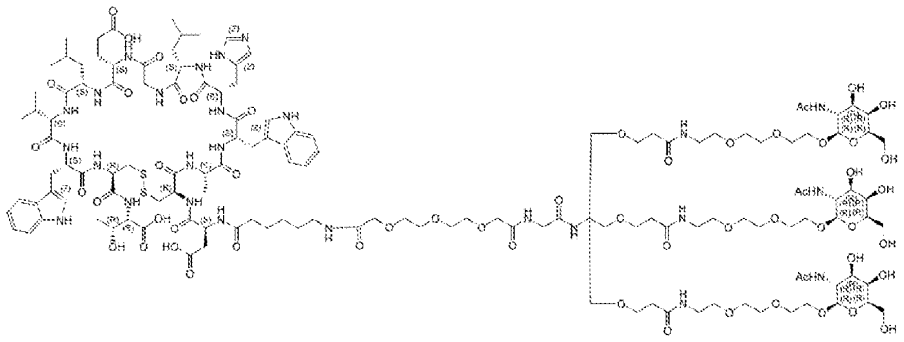

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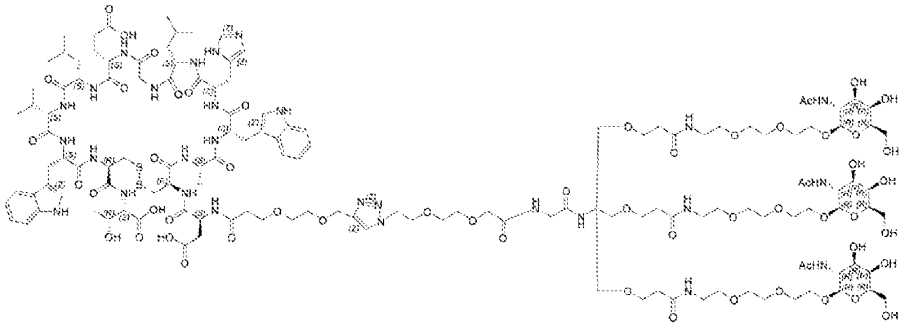

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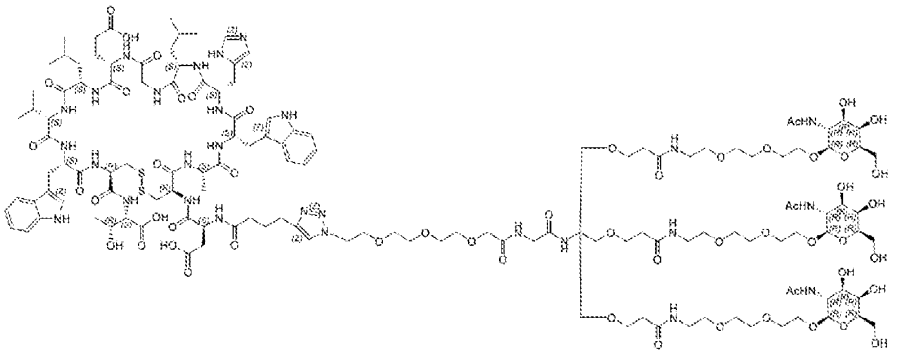

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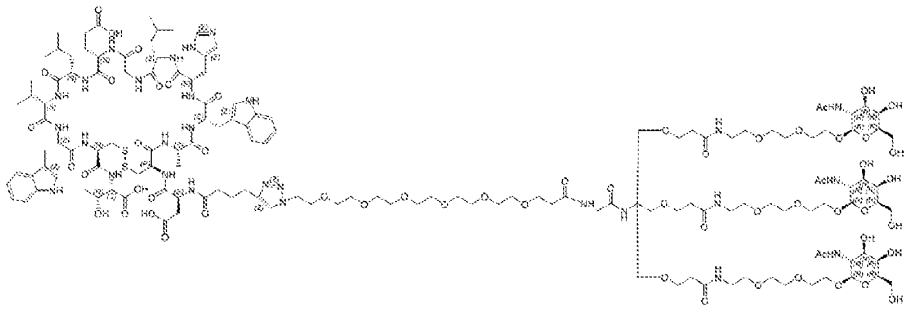

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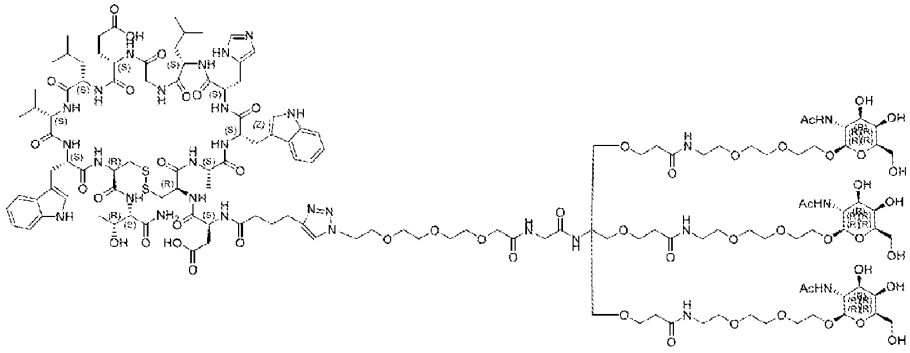

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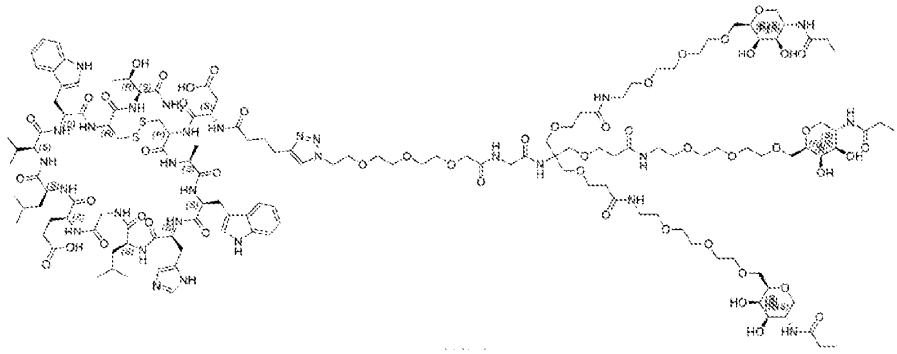

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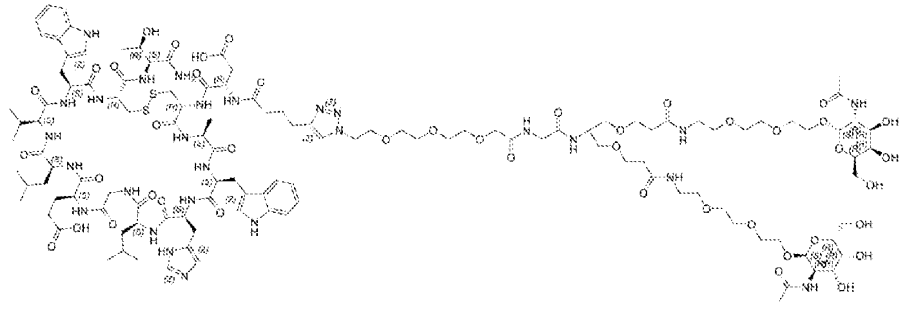

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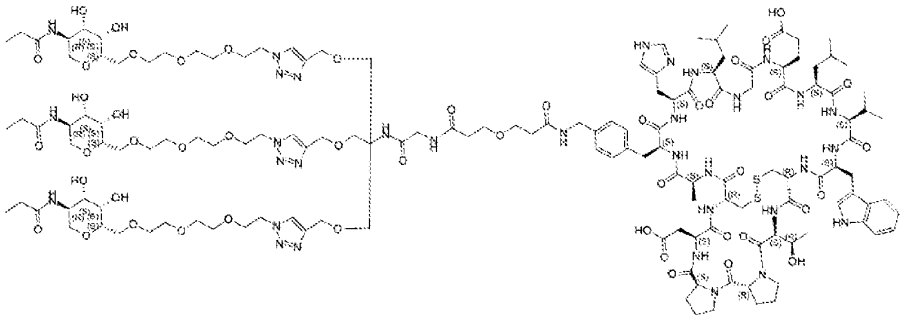

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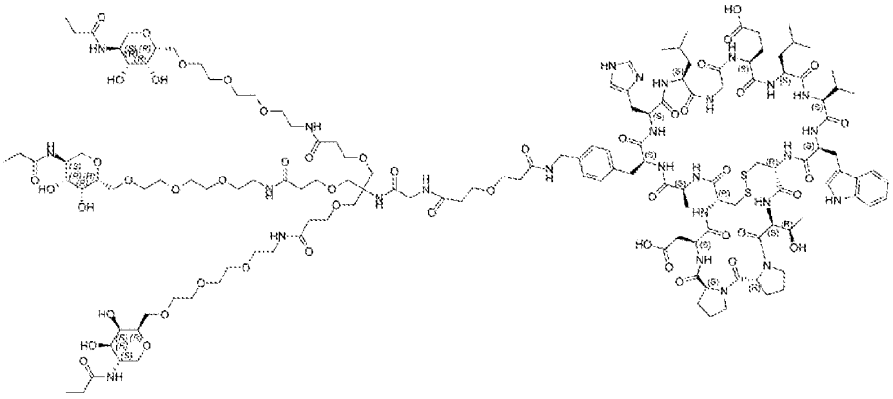

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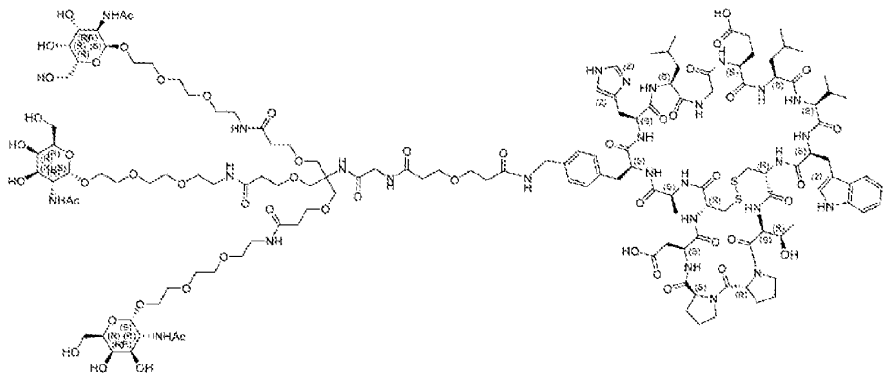

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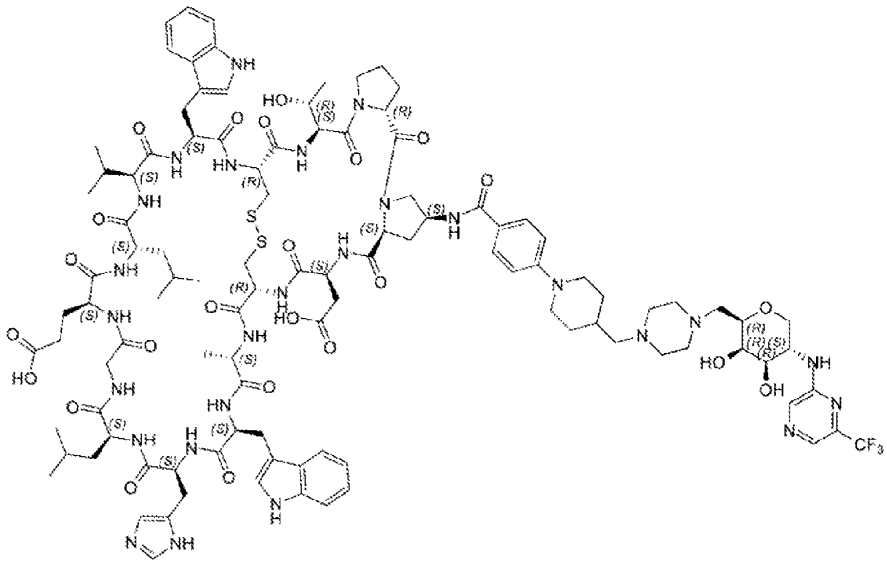

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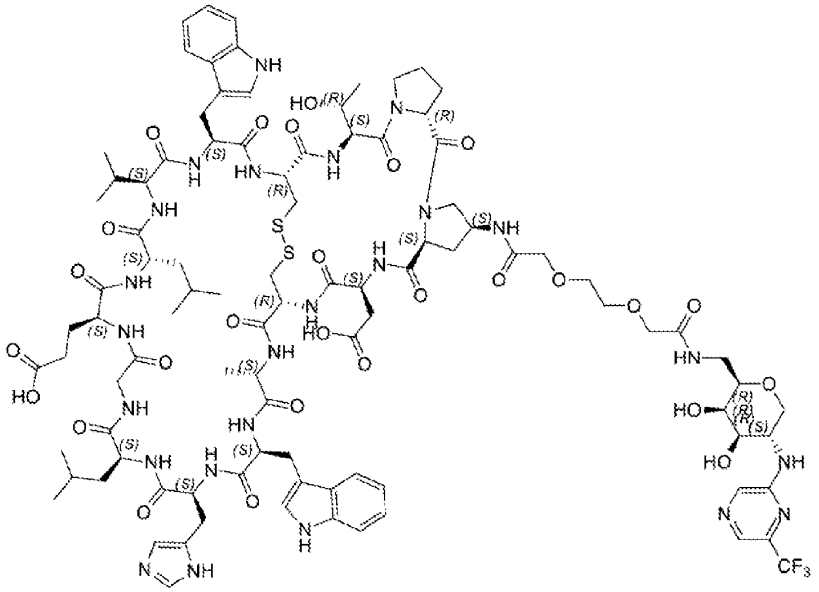

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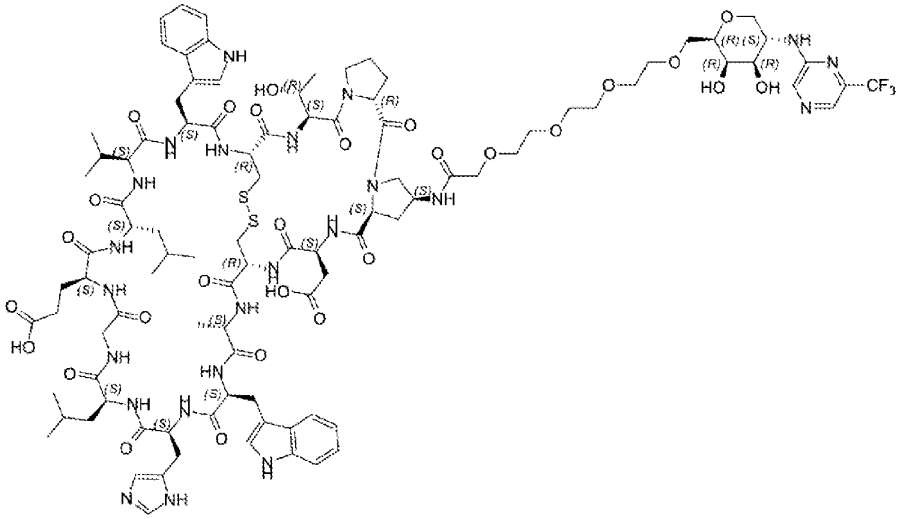

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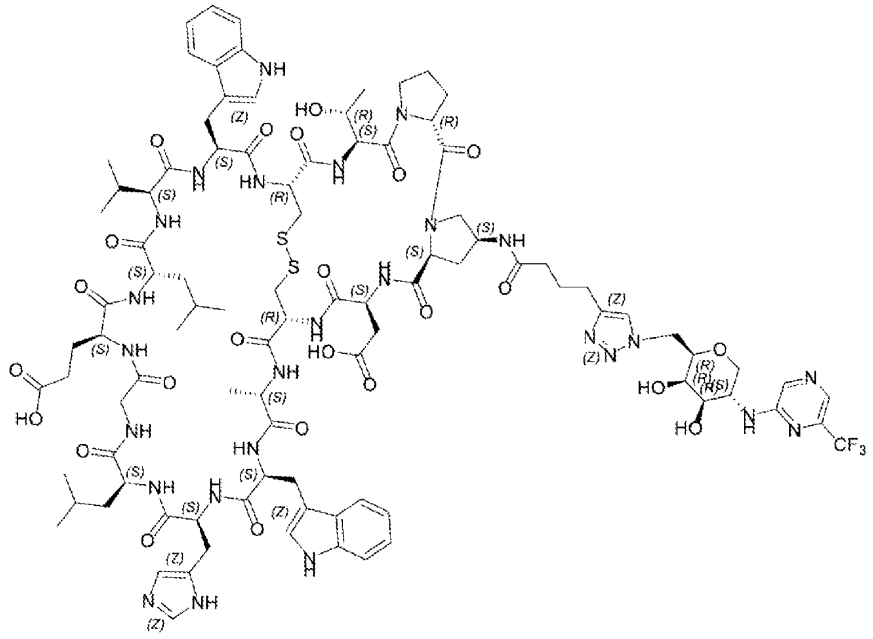

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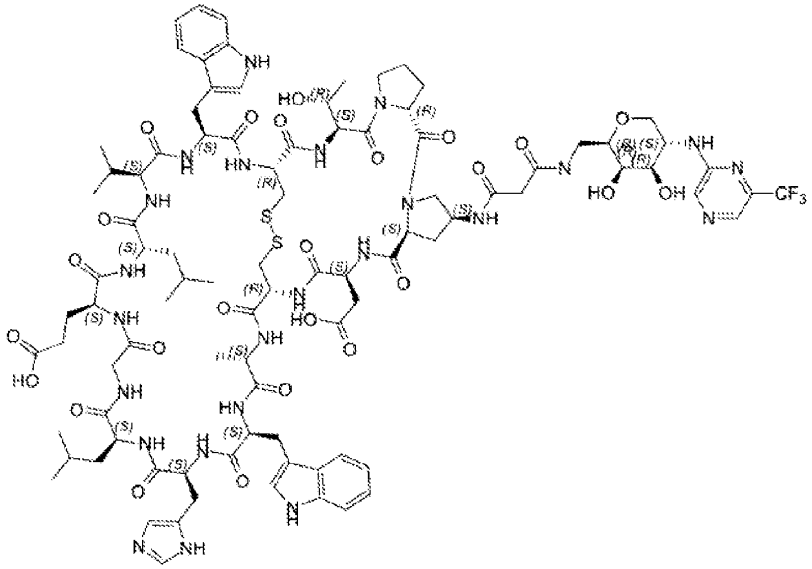

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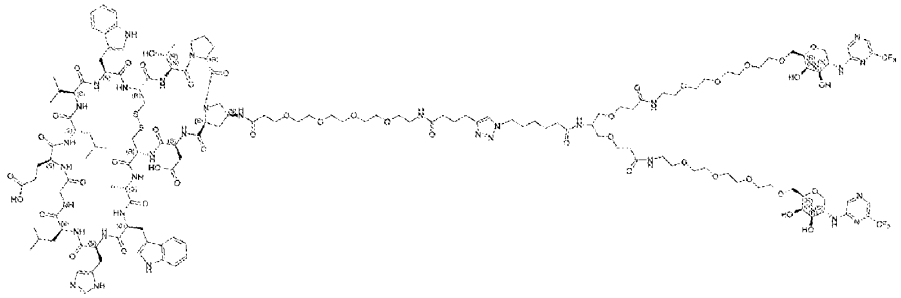

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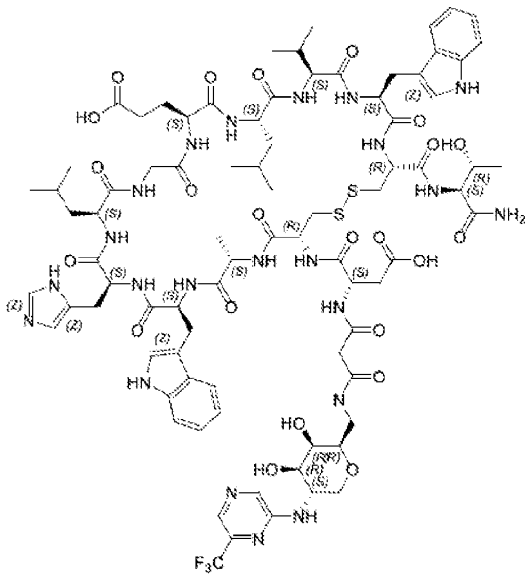

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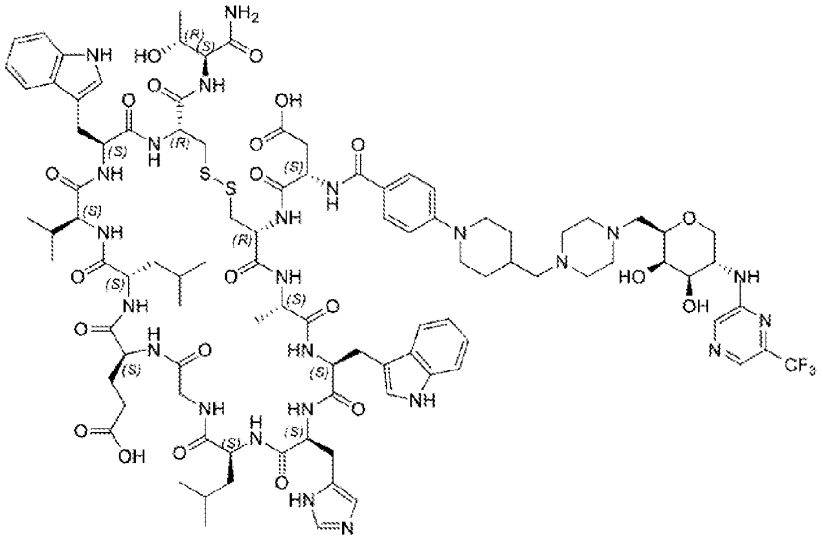

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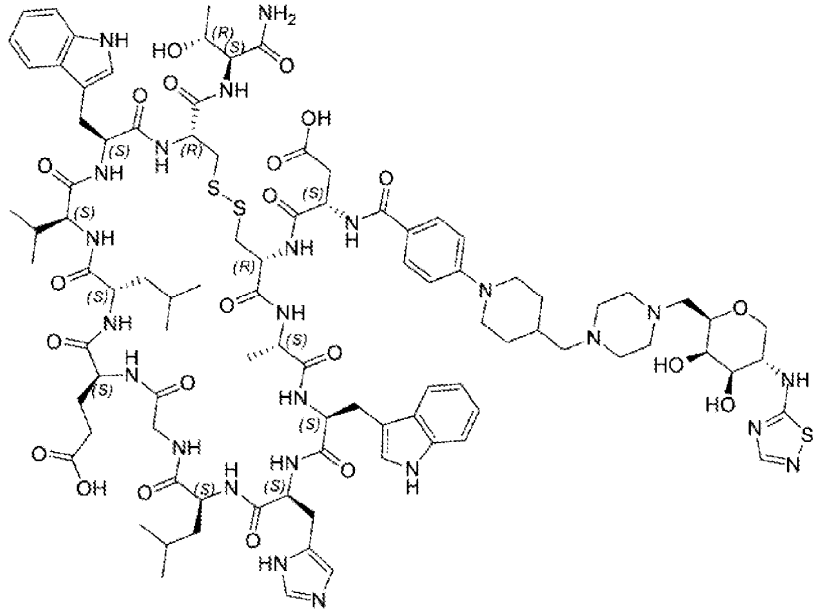

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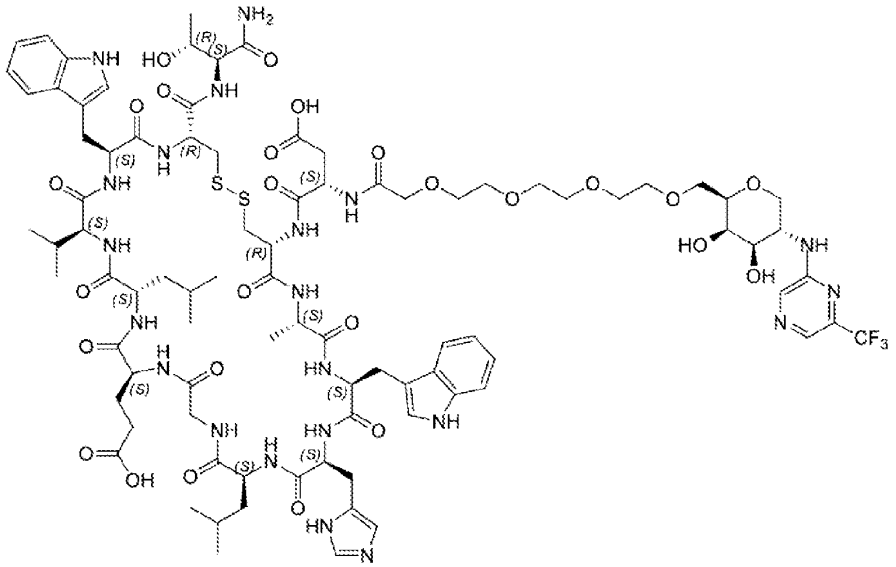

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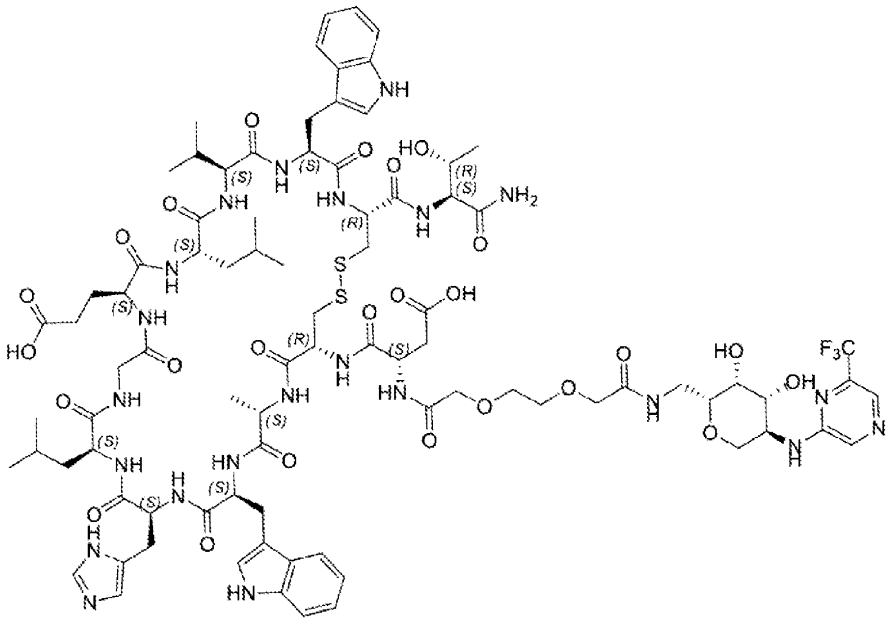

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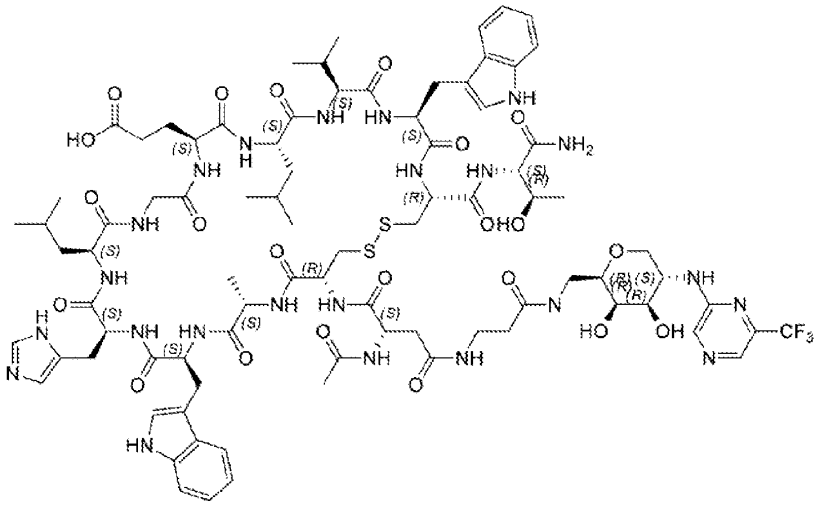

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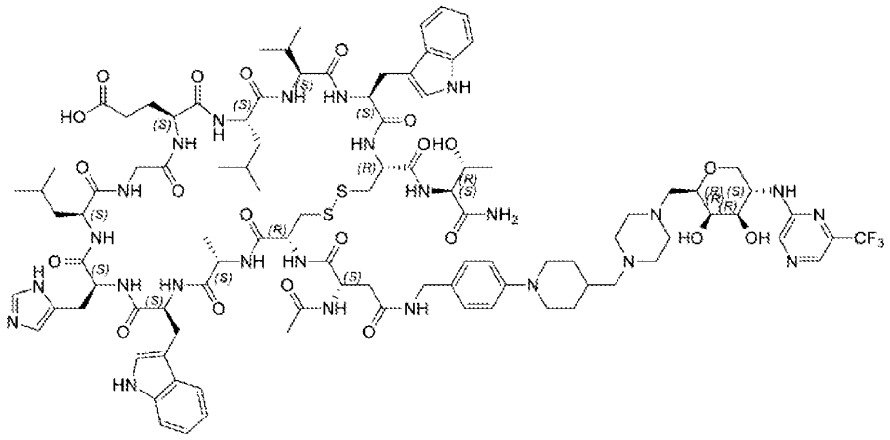

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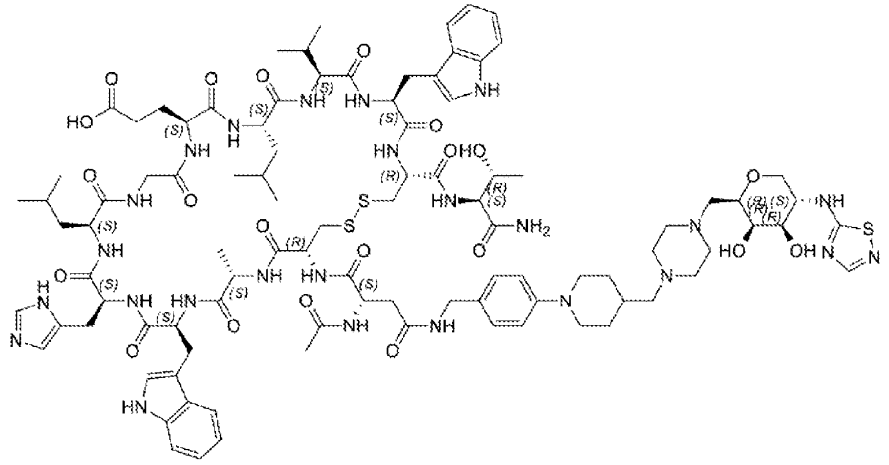

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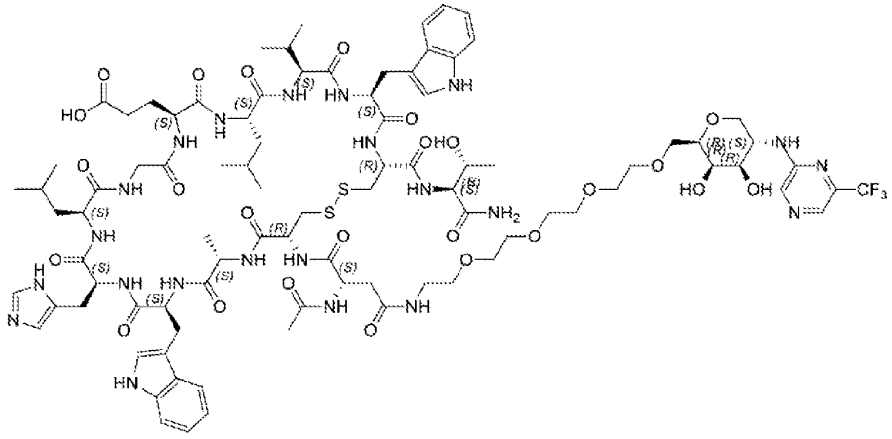

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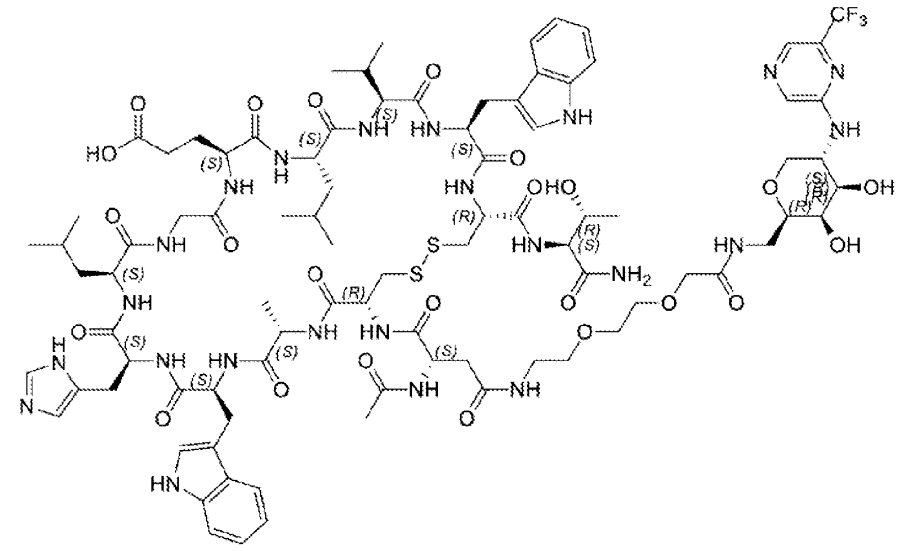

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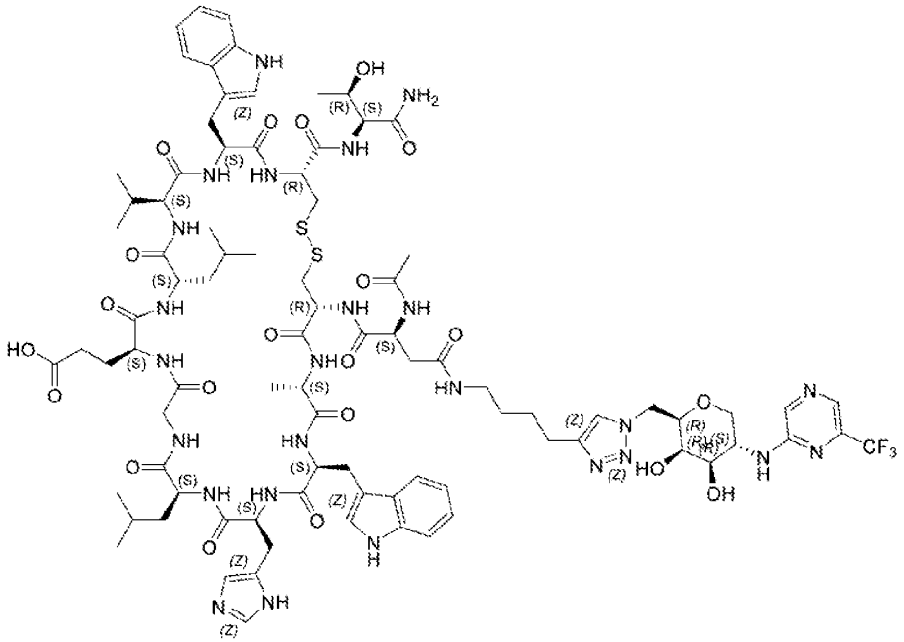

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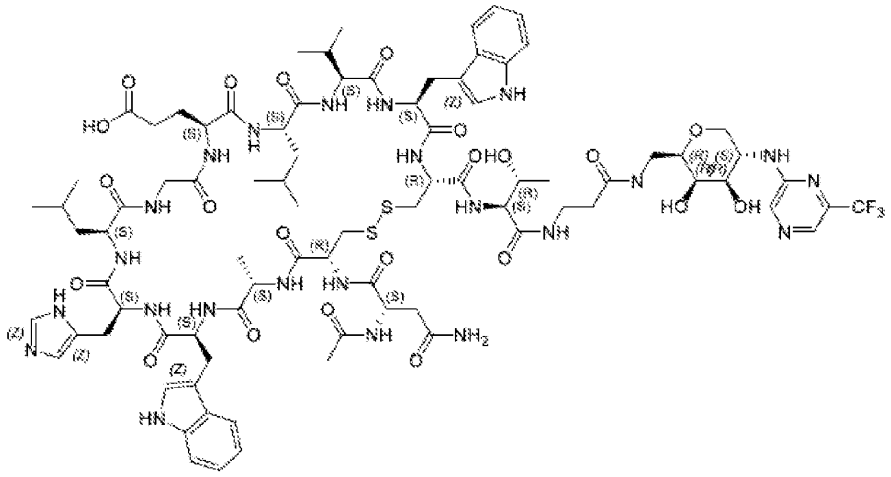

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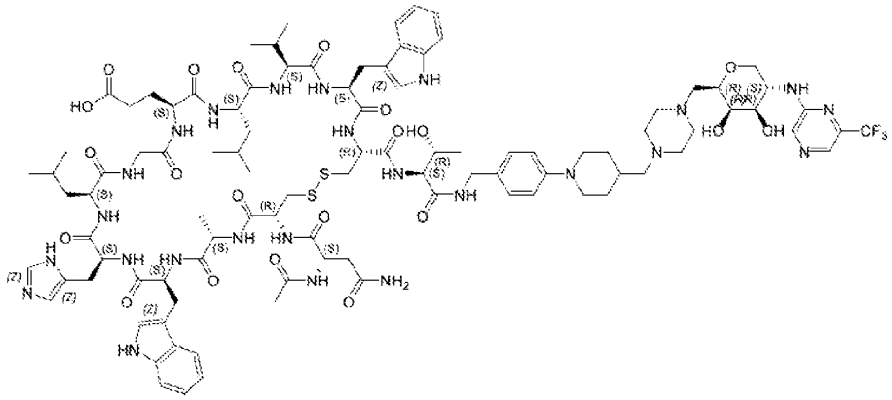

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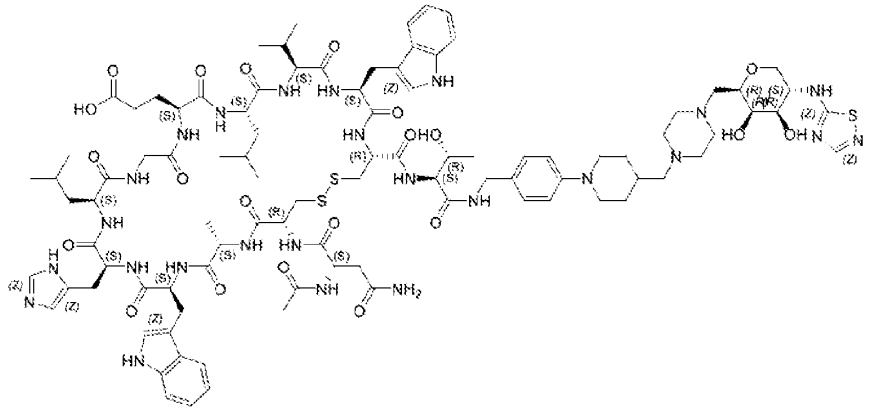

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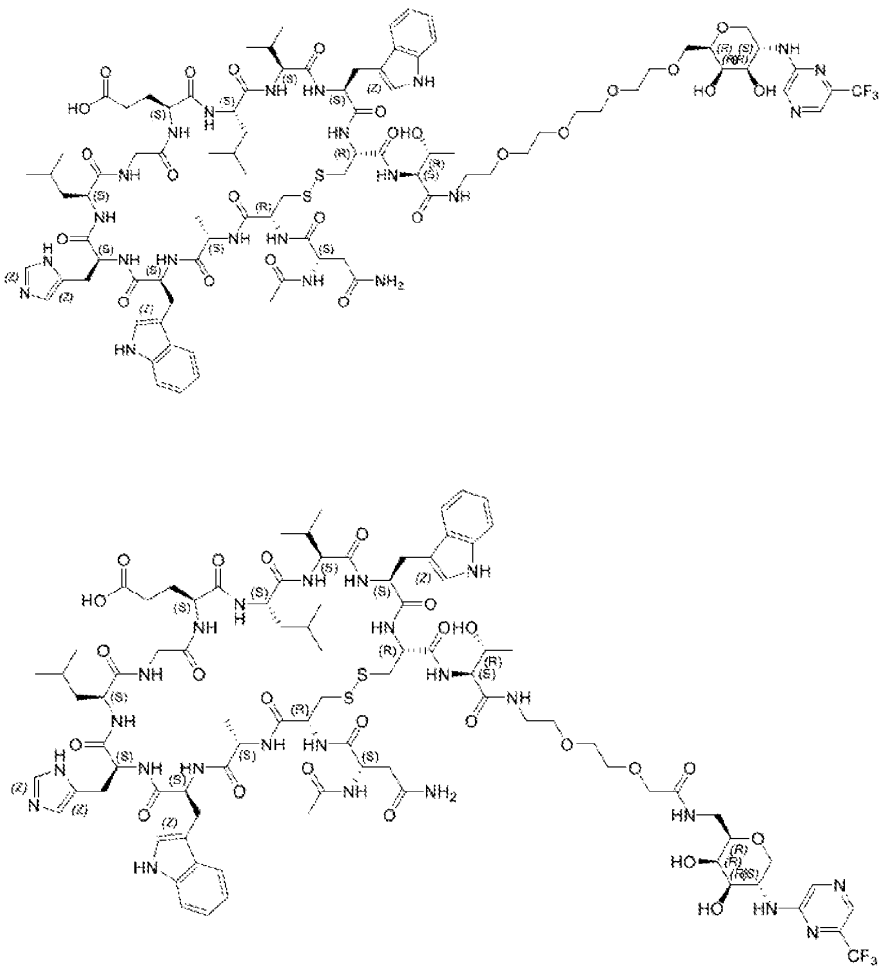

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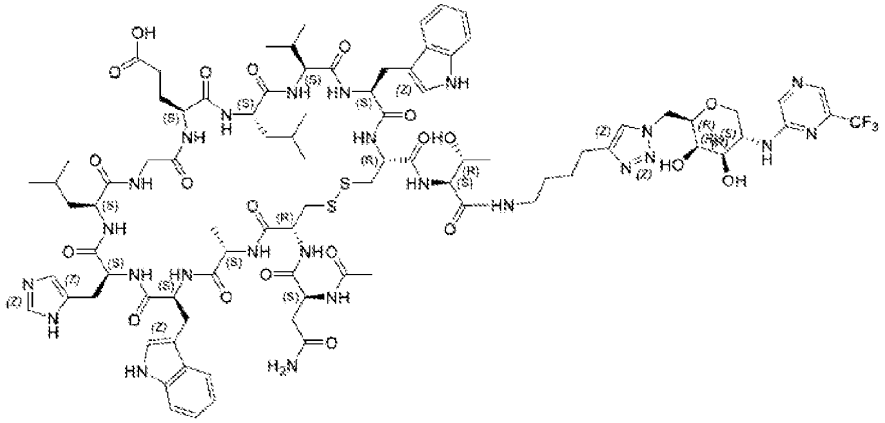

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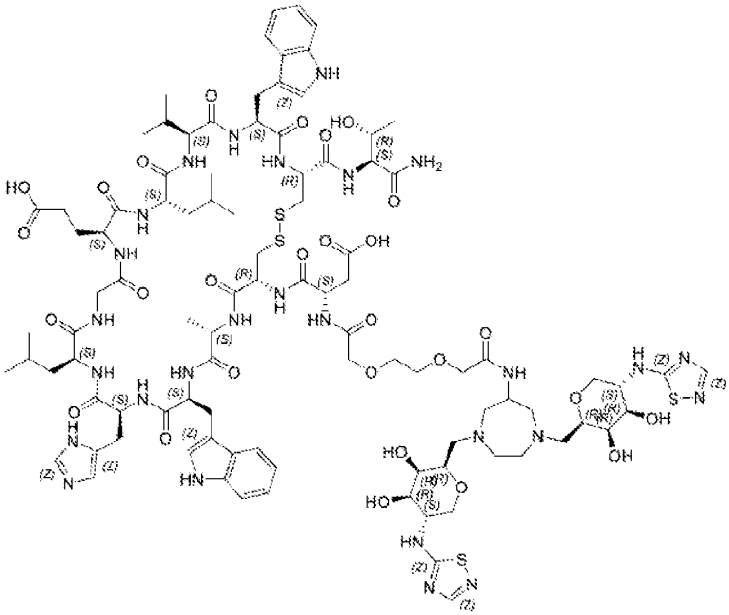

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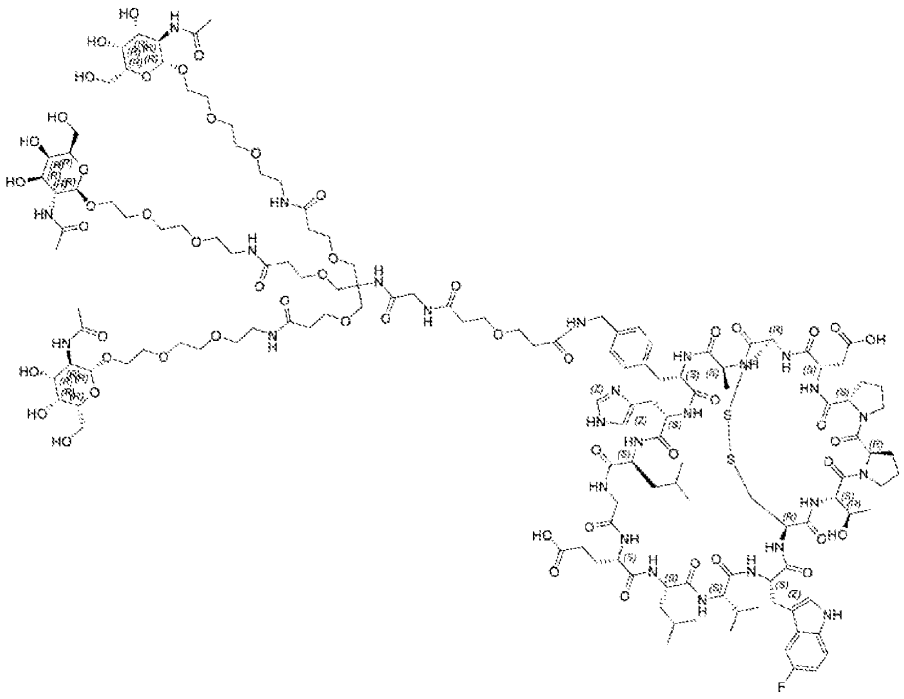

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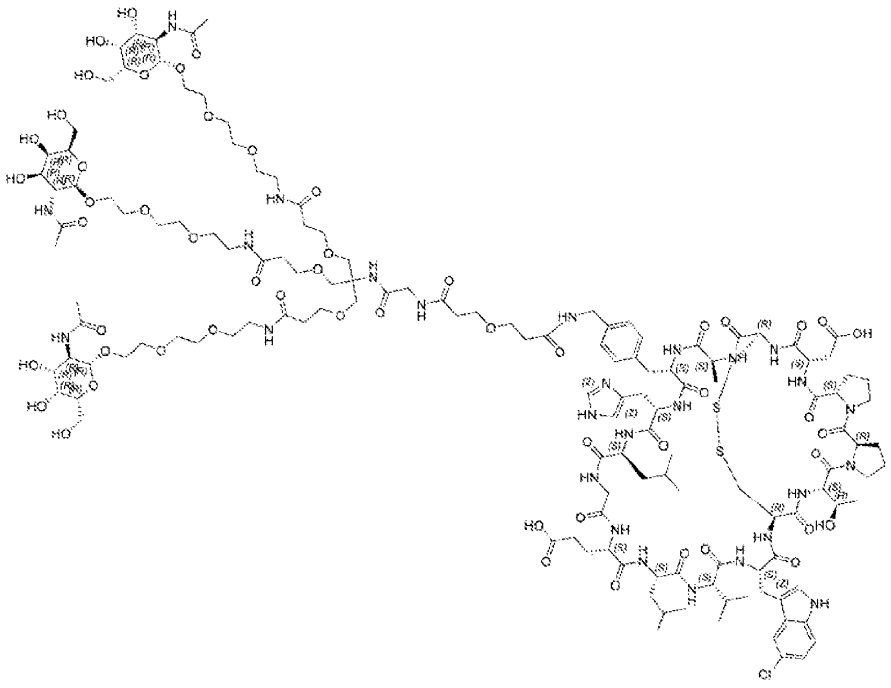

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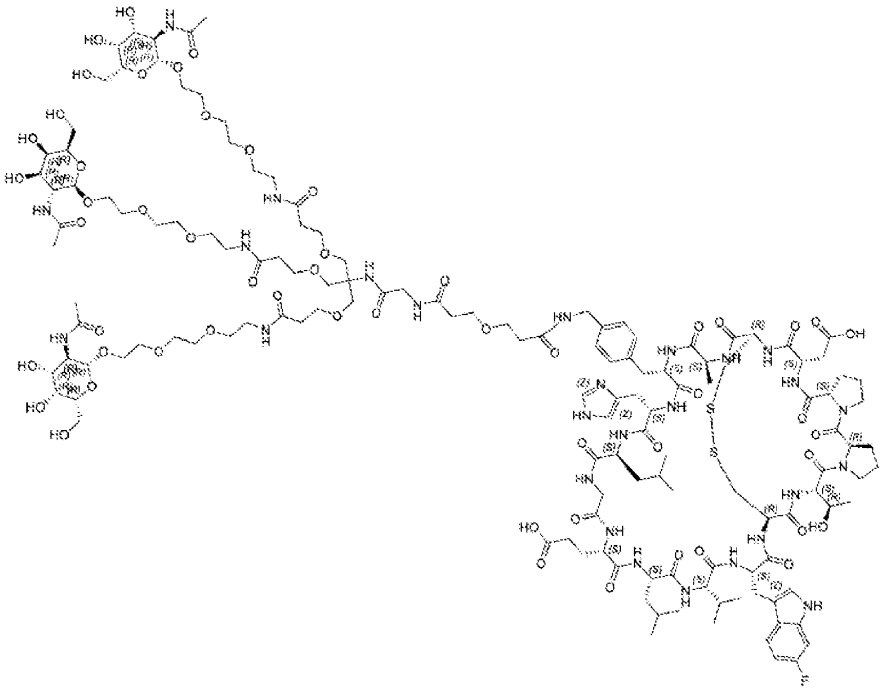

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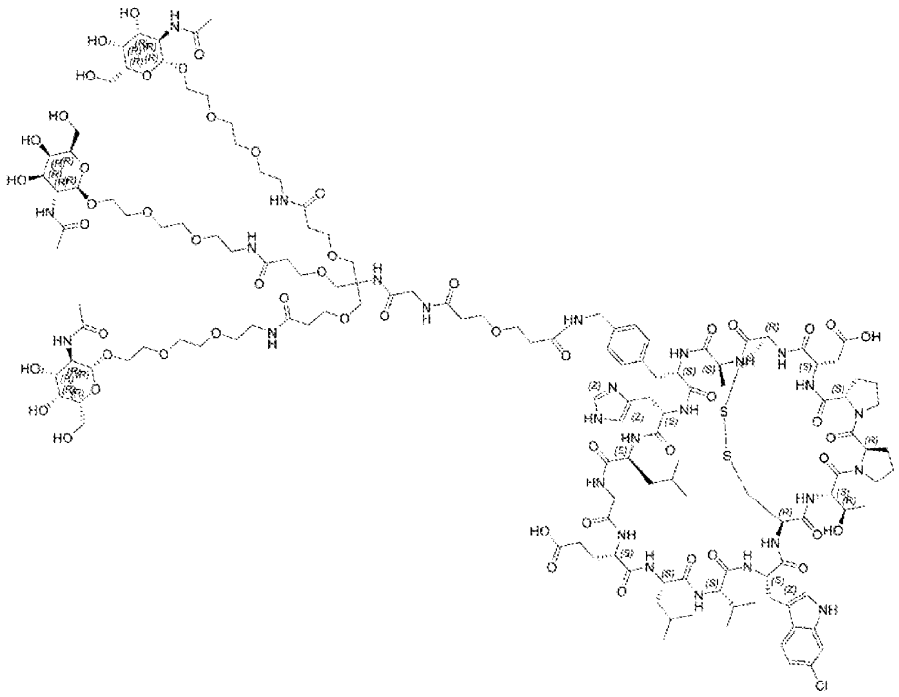

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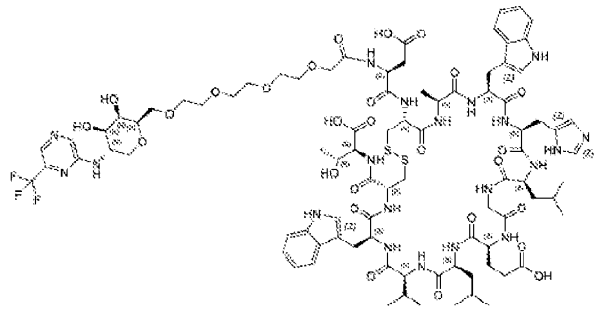

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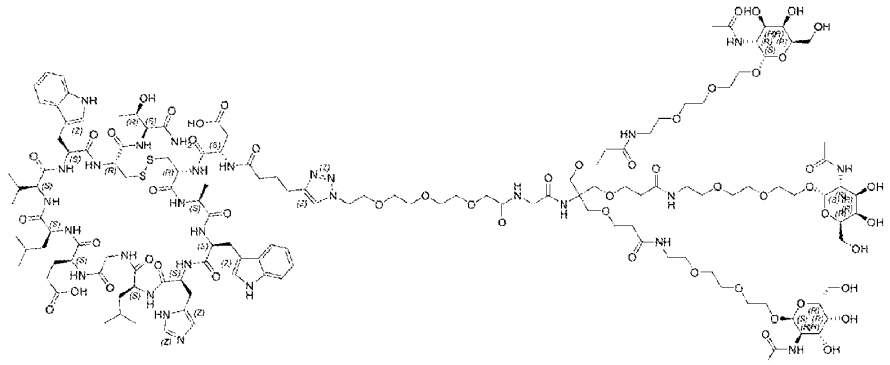

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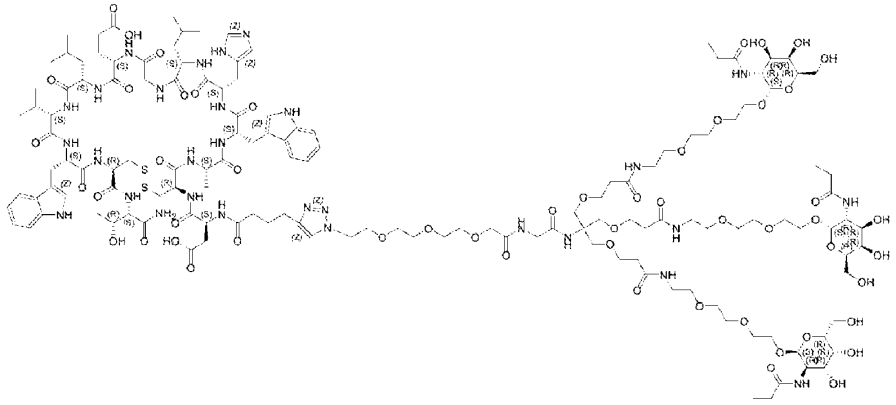

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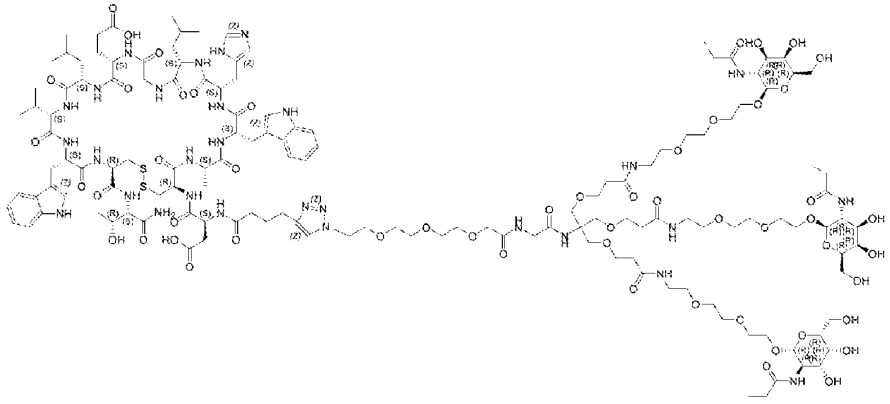

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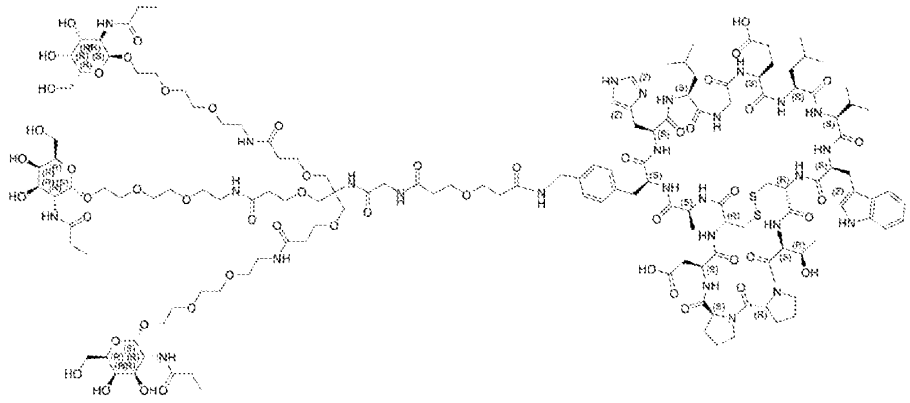

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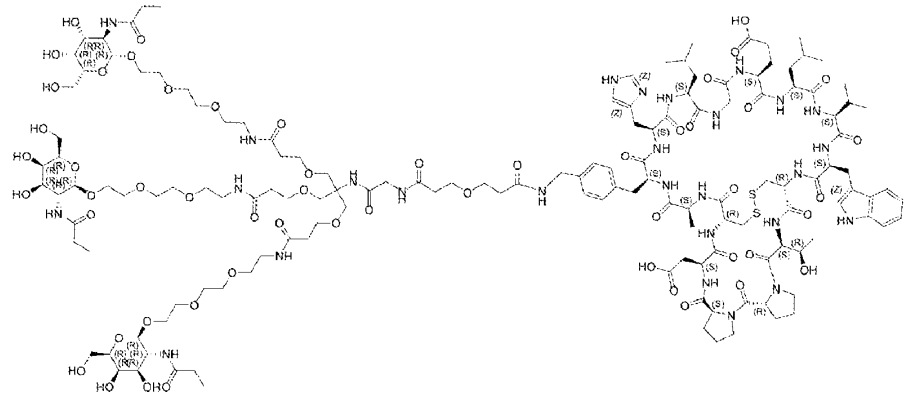
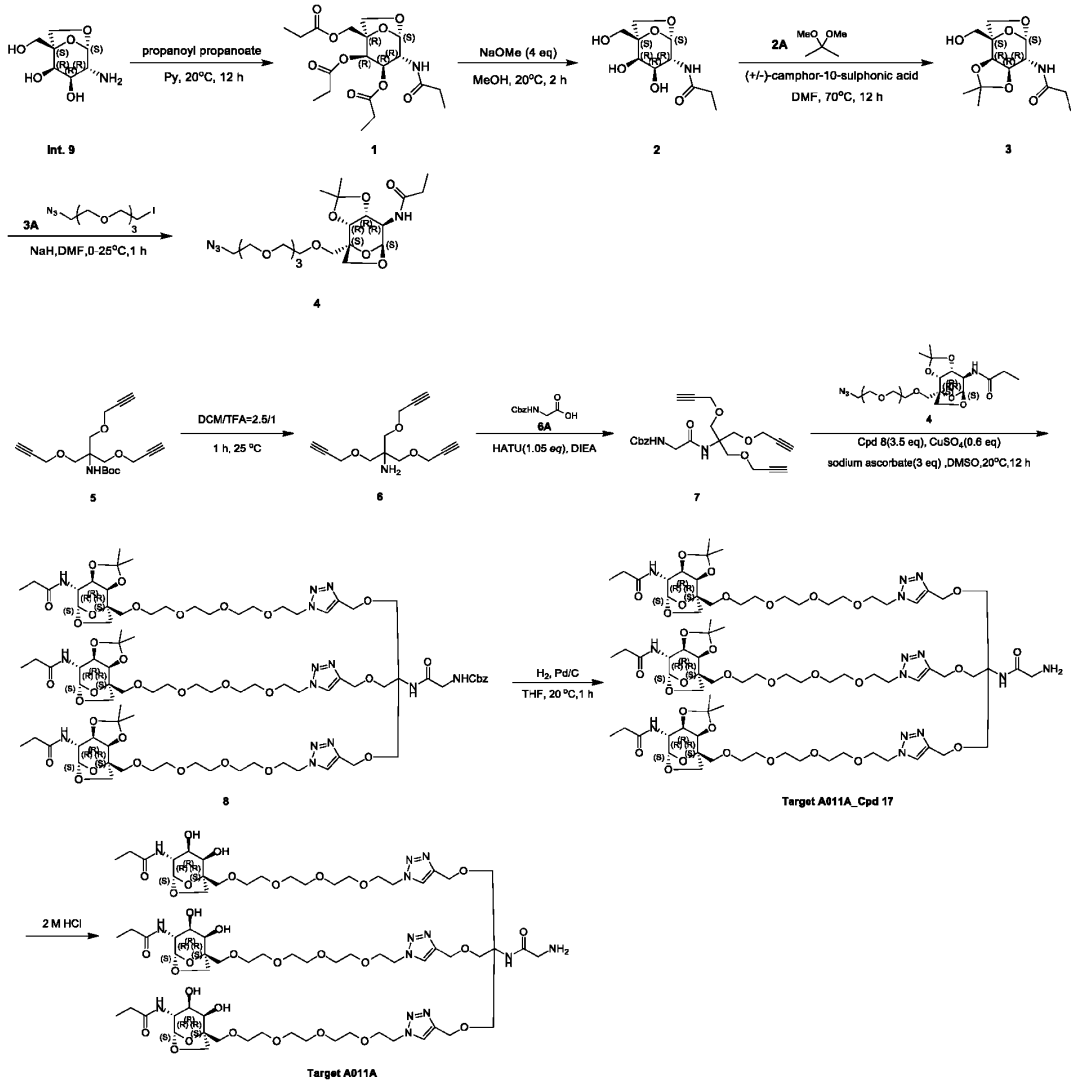


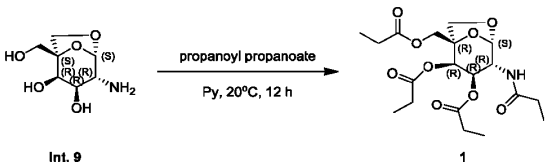
4407

The invention is further illustrated by the following non-limiting examples.

EXAMPLE 1. Procedure for Preparation of Target A011A

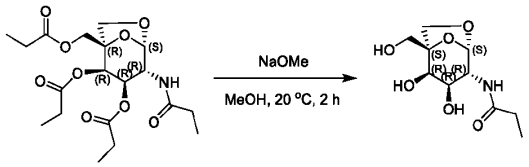


[0001] ***Preparation of Intermediate 1:***



[0002] To a solution of **Int. 9** (5.00 g, 26.15 mmol, 1.00 equiv.) in Py (100 mL) was added propanoyl propanoate (27.23 g, 209.23 mmol, 8.00 equiv.). The mixture was stirred at 20 °C for 12 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was concentrated under reduced pressure to afford **Intermediate 1** (10.86 g, crude) as yellow oil, which was used in the next step without further purification. LCMS: RT = 0.715 min, MS cal.: 415.2, found: $[M + H]^+$ = 416.2.

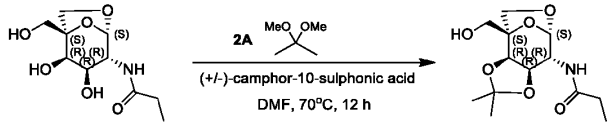
[0003] ***Preparation of Intermediate 2:***



1 2

[0004] To a solution of **Intermediate 1** (5.40 g, 13.00 mmol, 1.00 equiv.) in MeOH (50 mL) was added NaOMe (2.81 g, 51.99 mmol, 4.00 equiv.). The mixture was stirred at 20 °C for 2 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was neutralized by addition of 1M HCl. The resulting solution was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=10/1 to 5/1) to give **Intermediate 2** (4.20 g, 16.99 mmol, 65.3% yield) as a yellow solid. LCMS: RT = 0.174 min, MS cal.: 247.1, found: $[M + H]^+$ = 248.3. ^1H NMR (400 MHz, CD_3OD) δ = 5.23 (d, *J* = 1.4 Hz, 1H), 4.01 - 3.69 (m, 5H), 2.42 - 2.20 (m, 2H), 1.27 - 1.04 (m, 3H).

[0005] ***Preparation of Intermediate 3:***

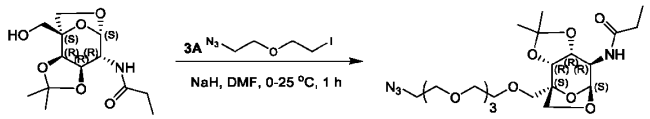


2 3

[0006] To a solution of **Intermediate 2** (2.10 g, 8.49 mmol, 1.00 equiv.) in DMF (15 mL) was added [(*1S,4R*)-7,7-dimethyl-2-oxo-norbornan-1-yl]methanesulfonic acid (1.06 g, 4.25 mmol, 0.5 equiv.) and **2A** (4.42 g, 42.47 mmol, 5.00 equiv.). The mixture was stirred at 70 °C for 12 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL * 3). The combined organic layer was washed with brine (30 mL * 3), dried over Na_2SO_4,

filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1 to 0/1) to give **Intermediate 3** (4.25 g, 14.79 mmol, 87.0% yield) as a white solid. LCMS: RT = 0.426 min, MS cal.: 287.1, found: $[M + H]^+$ = 288.2. ^1H NMR (400 MHz, CD_3OD) δ = 5.23 (s, 1H), 4.59 (s, 1H), 4.30 (d, *J* = 5.7 Hz, 1H), 4.18 (t, *J* = 6.4 Hz, 1H), 3.97 - 3.68 (m, 6H), 2.30 - 2.17 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H), 1.14 (t, *J* = 7.6 Hz, 3H).

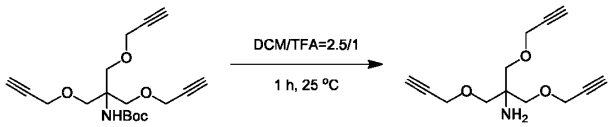
[0007] ***Preparation of Intermediate 4:***



3 4

[0008] To a solution of **intermediate 3** (2.20 g, 7.66 mmol, 1.00 equiv.) in THF (20 mL) was added NaH (3.06 g, 76.57 mmol, 60% purity, 10.00 equiv.) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, then was added **3A** (4.54 g, 13.78 mmol, 1.80 equiv.) at 0 °C, the mixture was stirred at 20 °C for 1 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was diluted with water (20 mL) and extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 2/1 to 0/1) to give **Intermediate 4** (3.70 g, 7.57 mmol, 49.4% yield) as a white solid. LCMS: RT = 1.475 min, MS cal.: 488.2, found: $[M + H]^+$ = 489.3. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.60 (br d, *J* = 8.8 Hz, 1H), 5.33 (d, *J* = 2.0 Hz, 1H), 4.21 (d, *J* = 5.9 Hz, 1H), 4.27 - 4.19 (m, 1H), 4.19 - 4.10 (m, 1H), 4.04 - 3.92 (m, 2H), 3.86 - 3.74 (m, 3H), 3.76 - 3.58 (m, 15H), 3.43 - 3.34 (m, 2H), 2.31 - 2.21(m, 2H), 1.55 (s, 3H), 1.38 - 1.32 (m, 3H), 1.20 - 1.12 (m, 3H).

[0009] ***Preparation of Intermediate 6:***

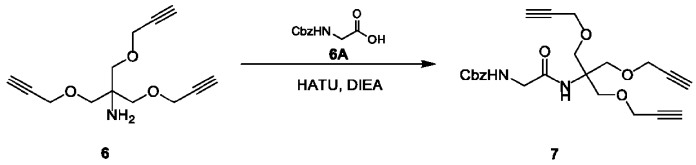


5 6

[0010] To a solution of **Intermediate 5** (2.50 g, 7.45 mmol, 1.00 equiv.) in DCM (25 mL) was added TFA (10 mL) at 0 °C. The mixture was stirred at 20 °C for 2 h. TLC (DCM: MEOH = 5:1, R_f = 0.43) showed a

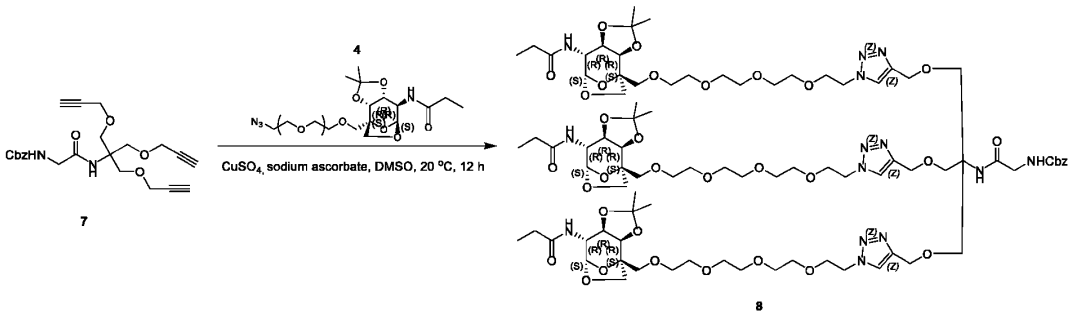
new spot and the reactant was consumed. The reaction mixture was concentrated under reduced pressure to give **Intermediate 6** (1.75 g, crude) as colorless oil, which was used in the next step directly.

[0011] ***Preparation of Intermediate 7:***



[0012] To a solution of **6A** (1.56 g, 7.44 mmol, 1.00 equiv.) in DMF (10 mL) was added HATU (2.83 g, 7.44 mmol, 1.00 equiv.) and DIEA (4.81 g, 37.19 mmol, 6.48 mL, 5.00 equiv.) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. **Intermediate 6** (1.75 g, 7.44 mmol, 1.00 equiv.) was added to the mixture. The mixture was stirred at 20 °C for 2 h. LCMS showed **6A** was consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layer was washed with brine (20 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1 to 5/1) to afford **Intermediate 7** (1.02 g, 2.39 mmol, 32.1% yield) as a white solid. LCMS: RT = 2.188 min, MS cal.: 426.2, found: $[M + H]^+$ = 427.3. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40 - 7.29 (m, 5H), 6.08 (s, 1H), 5.40 (br s, 1H), 5.13 (s, 2H), 4.13 (d, *J* = 1.7 Hz, 6H), 3.84 (s, 6H), 2.44 (t, *J* = 2.3 Hz, 3H).

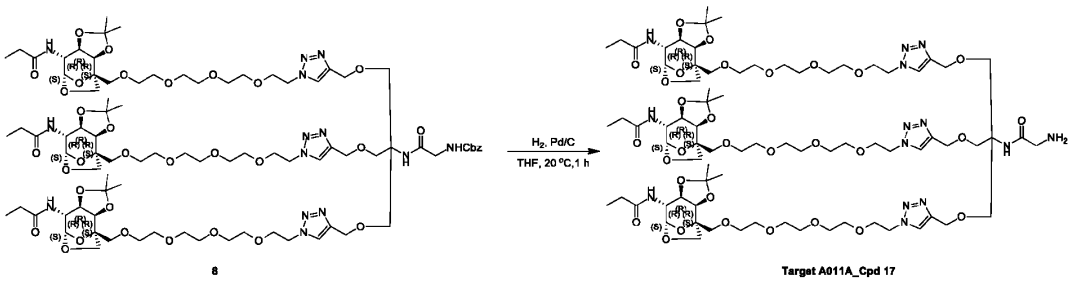
[0013] ***Preparation of Intermediate 8:***



[0014] To a solution of **Intermediate 7** (552.0 mg, 1.28 mmol, 99.0% purity, 1.00 equiv.), **Intermediate 4** (1.88 g, 3.84 mmol, 3.00 equiv.) in DMSO (8 mL) was added sodium ascorbate (634.6 mg, 3.20 mmol, 2.50 equiv.) and $CuSO_4.5H_2O$ (320.0 mg, 1.28 mmol, 1.00 equiv.). The mixture was stirred at 25 °C for 2 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was diluted with water (20 mL) and extracted with DCM (10 mL * 3). The combined organic layer was washed

with brine (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 µm; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 30%-60%, 8 min) to give **Intermediate 8** (1.25 g, 660.66 µmol, 51.6% yield) as yellow oil. LCMS: RT = 2.065 min, MS cal.: 1891.9, found: $[M + 2H]^{2+}$ = 947.2. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm = 8.06 - 7.99 (m, 6H), 7.40 - 7.27 (m, 6H), 5.15 (d, *J* = 1.9 Hz, 3H), 5.03 (s, 2H), 4.55 - 4.43 (m, 12H), 4.24 (d, J = 5.9 Hz, 3H), 4.17 - 4.11 (m, 3H), 3.84 - 3.78 (m, 12H), 3.76 - 3.69 (m, 6H), 3.67 - 3.62 (m, 9H), 3.62 - 3.55 (m, 7H), 3.54 - 3.43 (m, 32H), 2.13 (q, *J* = 7.6 Hz, 6H), 1.39 (s, 9H), 1.30 - 1.22 (m, 9H), 0.99 (t, *J* = 7.6 Hz, 9H).

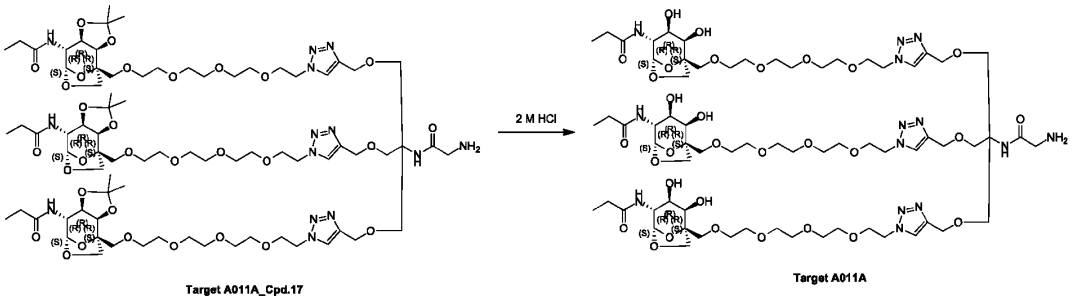
[0015] ***Preparation of Target A011A_Cpd.17:***



8 Target A011A_Cpd 17

[0016] To a solution of **Intermediate 8** (400.0 mg, 211.41 µmol, 1.00 equiv.) in THF (1.0 mL) was added Pd/C (5.00 mg, 21.14 µmol, 10% purity). The mixture was stirred at 20 °C for 2 h under H_2 (15 Psi). LCMS showed the desired mass and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to afford **Target A011A_Cpd.17** (330.3 mg, 187.89 µmol, 88.8% yield) as yellow oil. LCMS: RT = 1.810 min, MS cal.: 1757.9, found: $[M+2H]^{2+}$ = 880.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ= 8.05 - 7.99 (m, 6H), 5.16 (d, *J* = 2.0 Hz, 3H), 4.55 - 4.45 (m, 13H), 4.25 (d, *J* = 5.9 Hz, 3H), 4.15 - 4.10 (m, 3H), 3.84 - 3.56 (m, 35H), 3.53 - 3.46 (m, 32H), 2.13 (q, *J* = 7.5 Hz, 6H), 1.40 (s, 9H), 1.27 (s, 9H), 0.99 (t, *J* = 7.6 Hz, 9H).

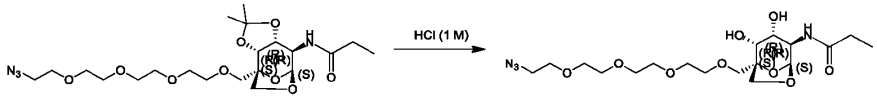
[0017] ***Preparation of Target A011A:***



Target A011A_Cpd.17 Target A011A

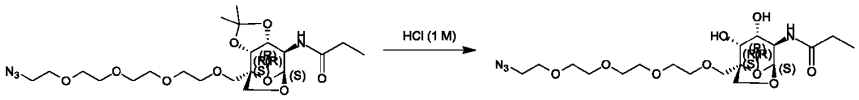
[0018] A mixture of **Target A011A_Cpd.17** (90.0 mg, 51.20 µmol, 1.00 equiv.) in HCl/H_2O (2.0 M, 1.0 mL) and MeCN (0.5 mL) was stirred at 20 °C for 1 h. The mixture was lyophilized to afford **Target A011A** (85.0 mg, 45.69 µmol, 90.0% purity, 89.3% yield, HCl salt) as a colorless solid. LCMS: RT = 0.705 min, MS cal.: 1637.73, found: $[M + 2H]^{2+}$ = 819.600.

EXAMPLE 2. Procedure for Preparation of Target A093.



4 Target A093

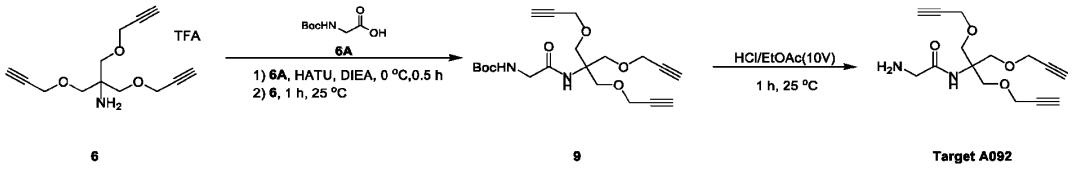
[0019] ***Preparation of Target A093:***



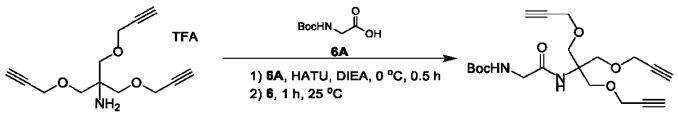
4 Target A093

[0020] **Intermediate 4** (500.0 mg, 1.02 mmol, 1.00 equiv.) was dissolved in HCl (1 M, 5 mL, 10.05 equiv.). The mixture was stirred at 20 °C for 1 h. LCMS showed the starting material was consumed and the desired mass of product was detected. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 µm; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 5%-35%, 8 min) to give **Target A093** (305.0 mg, 680.09 umol, 66.4% yield) as colorless oil. LCMS: RT = 1.810 min, MS cal.: 448.5, mass observed: $[M + H]^+$ = 449.3. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 5.21 (d, *J* = 1.4 Hz, 1H), 3.98 (d, *J* = 9.5 Hz, 1H), 3.95 (dd, *J* = 1.4, 10.0 Hz, 1H), 3.91 - 3.87 (m, 1H), 3.78 (d, *J* = 8.0 Hz, 1H), 3.75 - 3.57 (m, 17H), 3.41 - 3.35 (m, 2H), 2.27 (q, *J* = 7.6 Hz, 2H), 1.14 (t, *J* = 7.6 Hz, 3H).

EXAMPLE 3. Procedure for Preparation of Target A092.

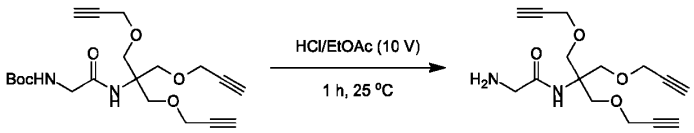


[0021] ***Preparation of Intermediate 9:***



[0022] To a solution of **6A** (4.00 g, 22.83 mmol, 1.05 equiv.) in DMF (50 mL) was added HATU (9.12 g, 23.98 mmol, 1.05 equiv.) and DIEA (8.85 g, 68.50 mmol, 11.93 mL, 3.00 equiv.) at 0 °C and the mixture was stirred at 0 °C for 0.5 h. Then **Intermediate 6** (9.17 g, 22.83 mmol, 87.0% purity, 1.00 equiv., TFA) was added and the mixture was stirred at 20 °C for 1 h. LCMS showed **6A** was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with water 50 mL and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 1/1) to give **Intermediate 9** (6.50 g, 16.56 mmol, 72.5% yield) as colorless oil. LCMS: RT = 2.143 min, MS cal.: 392.2, $[M + H]^+$ = 393.3.

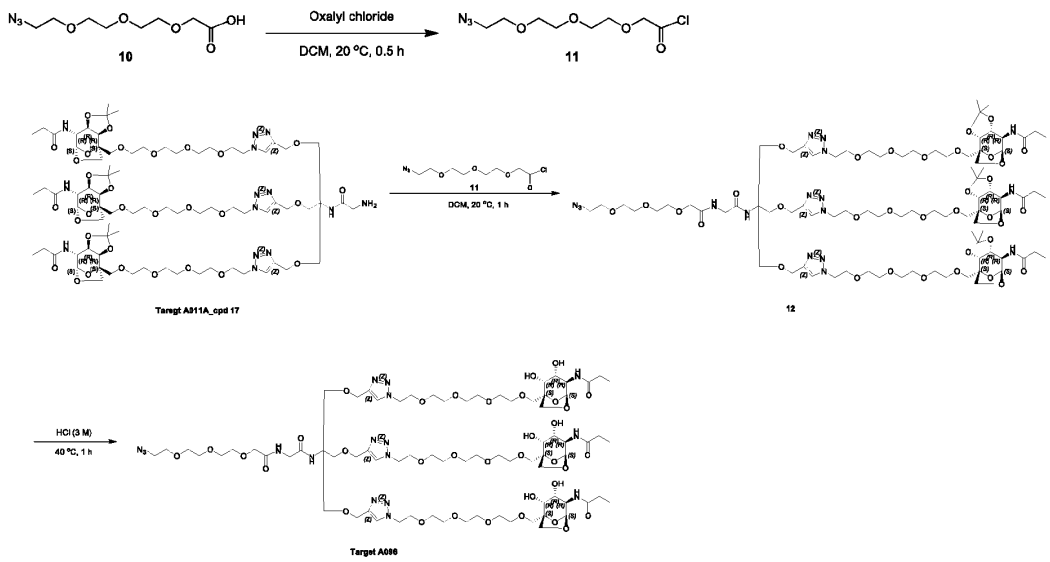
[0023] ***Preparation of Target A092:***



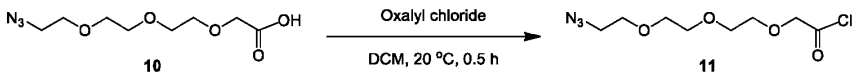
[0024] A solution of **Intermediate 9** (5.00 g, 12.74 mmol, 1.00 equiv.) in HCl/EtOAc (4 M, 50 mL) was stirred at 20 °C for 3 h. LCMS showed **Intermediate 9** was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Agela DuraShell C18 250 * 70 mm * 10 μm; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 15%-45%,8 min) to afford **Target A092** (2.10 g, 7.18 mmol, 56.4% yield, 100.0% purity) as yellow oil. LCMS: RT

= 1.519 min, MS cal.: 292.3, $[M + H]^+$ = 293.2. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 4.15 (d, J =2.38 Hz, 6 H), 3.82 (s, 6 H), 3.23 (s, 2 H), 2.84 (t, J =2.44 Hz, 3 H).

EXAMPLE 4. Procedure for Preparation of Target A096.

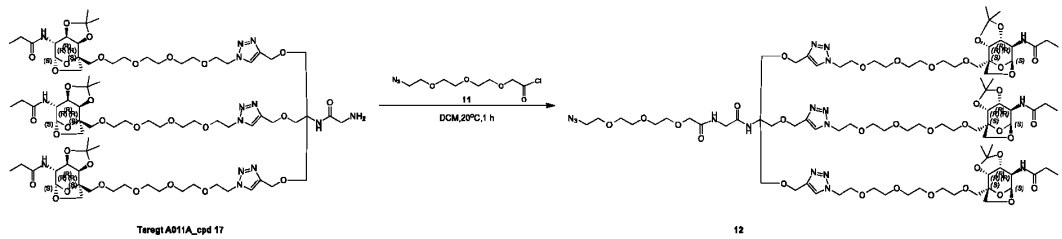


[0025] ***Preparation of Intermediate 11:***



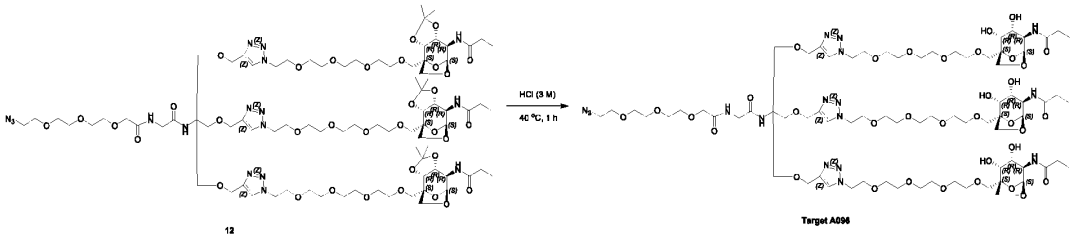
[0026] To a solution of **10** (40.0 mg, 171.51 μmol, 1.00 equiv.) in DCM (1 mL) was added oxalyl chloride (25.2 mg, 205.8 μmol, 18.9 μL, 1.20 equiv.) and DMF (1.25 mg, 17.15 μmol, 1.32 μL, 0.10 equiv.). The mixture was stirred at 0 °C for 0.5 h. TLC (DCM: MeOH =10:1, R_f = 0.6) showed the reactant was consumed and one main spot was formed. **Intermediate 11** (43.0 mg, 170.86 μmol, crude) was used to next step directly.

[0027] ***Preparation of Intermediate 12:***



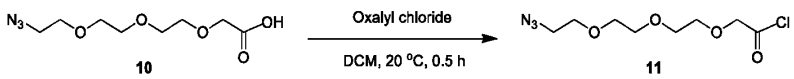
[0028] To a solution of **Target A011A_cpd 17** (210.0 mg, 119.46 µmol, 1.00 equiv.) in DCM (1 mL) was added DIEA (46.3 mg, 358.38 µmol, 62.42 µL, 3.00 equiv.), then **Intermediate 11** (30.0 mg, 119.46 µmol, 1.00 equiv.) was added to the mixture. The mixture was stirred at 20 °C for 1 h. LCMS showed the desired mass and the reactant was consumed. **Intermediate 12** (230.0 mg, crude) was obtained as yellow oil and used into the next step without further purification. LCMS: RT=1.990 min, MS cal.: 1971.9, $[M + 2H]^{2+}$ = 987.6.

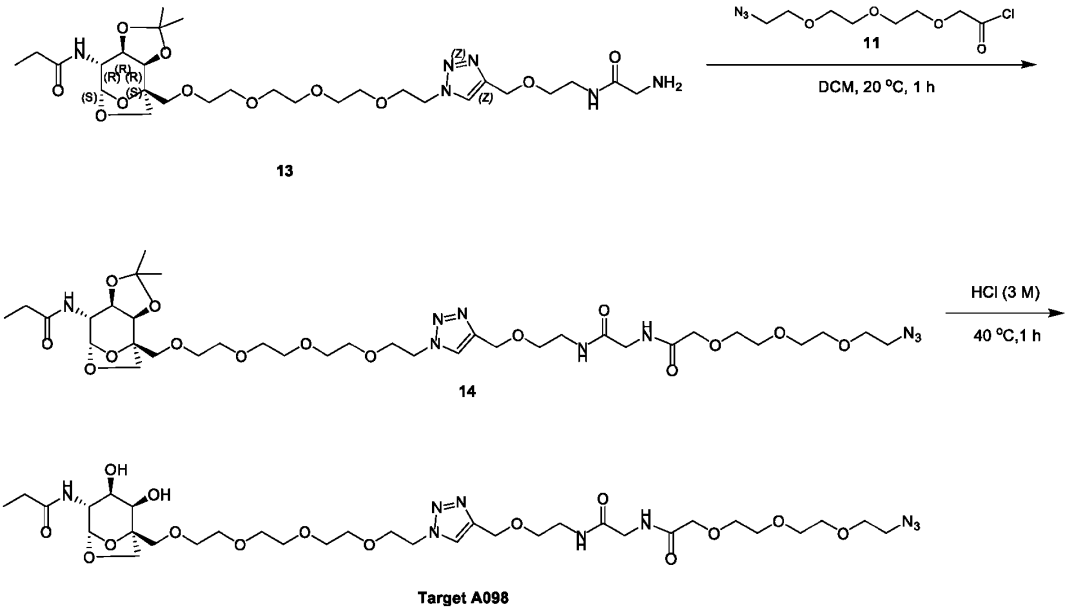
[0029] ***Preparation of Target A096:***



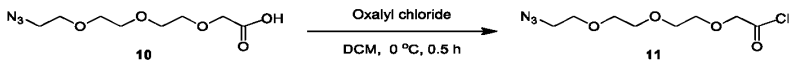
[0030] A solution of **Intermediate 12** (230.0 mg, 116.57 µmol, 1.00 equiv.) in HCl (3 M, 1 mL) was stirred at 40 °C for 1 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 µm; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 10%-40%, 8 min) to afford **Target A096** (72.0 mg, 38.86 µmol, 33.3% yield) as a white solid. LCMS: RT = 1.521 min, MS cal.: 1851.8, $[M + 2H]^{2+}$ = 927.7. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.01 (s, 3H), 7.80 - 7.75 (m, 3H), 7.35 (br s, 1H), 6.11 - 5.97 (m, 1H), 6.04 (br s, 1H), 5.08 (s, 3H), 4.55 - 4.43 (m, 13H), 3.92 (s, 2H), 3.85 - 3.77 (m, 9H), 3.72 (br d, J = 6.4 Hz, 5H), 3.66 - 3.62 (m, 9H), 3.60 - 3.54 (m, 17H), 3.66 - 3.45 (m, 1H), 3.41 - 3.36 (m, 5H), 2.12 (q, J = 7.6 Hz, 6H), 1.02 - 0.92 (m, 9H).

EXAMPLE 5. Procedure for Preparation of Target A098.



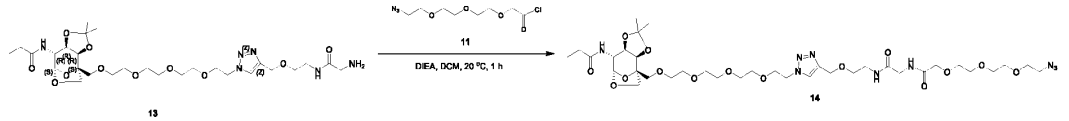


[0031] ***Preparation of Intermediate 11:***



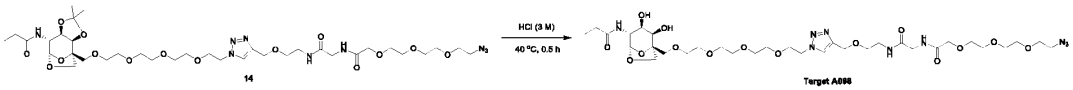
[0032] To a solution of **Intermediate 10** (400.0 mg, 1.72 mmol, 1.00 equiv.) in DCM (5 mL) was added oxalyl chloride (252.1 mg, 2.06 mmol, 189.58 µL, 1.20 equiv.) and DMF (12.5 mg, 171.51 µmol, 13.20 µL, 0.10 equiv.). The mixture was stirred at 0 °C for 0.5 h. TLC (DCM: MeOH =10:1, R_f=0.43) showed the reactant was consumed and one main spot was formed. **Intermediate 11** (420.0 mg, 1.67 mmol, crude) was used to next step directly.

[0033] ***Preparation of Intermediate 14:***



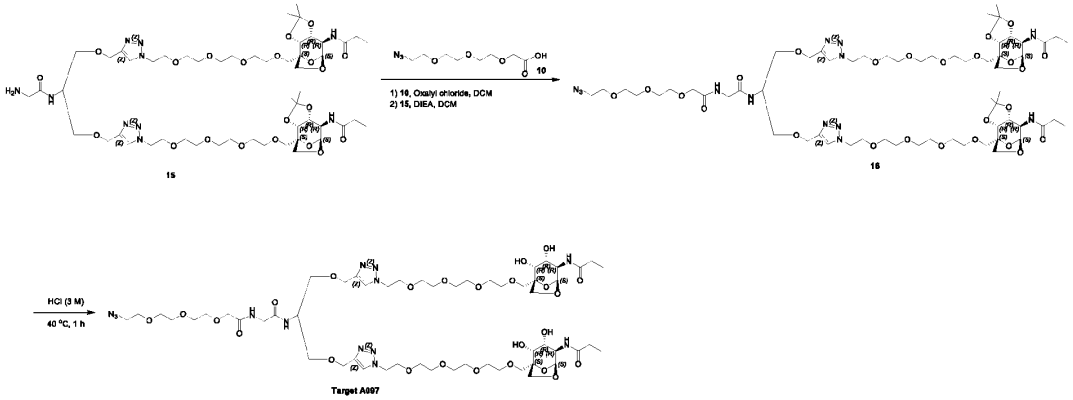
[0034] To a solution of **Intermediate 13** (950.0 mg, 1.47 mmol, 1.00 equiv.) in DCM (20 mL) was added DIEA (952.1 mg, 7.37 mmol, 1.28 mL, 5.00 equiv.), followed by the addition of **Intermediate 11** (370.8 mg, 1.47 mmol, 1.00 equiv.). The mixture was stirred at 20 °C for 1 h. LCMS showed the desired mass and the reactant was consumed. **Intermediate 14** (1.20 g, crude) was obtained as yellow oil and used into the next step without further purification. LCMS: RT=1.645 min, MS cal.: 859.4, $[M + H]^+$ = 860.4.

[0035] ***Preparation of Target A098:***

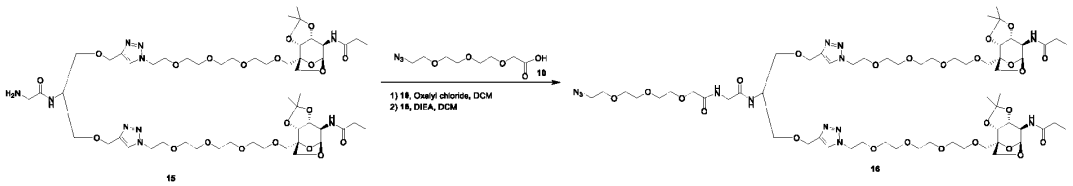


[0036] To a solution of **Intermediate 14** (1.20 g, 1.40 mmol, 1.00 equiv.) in HCl (3 M, 1 mL). The mixture was stirred at 40 °C for 0.5 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 μm; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 5%-35%, 8 min) to afford **Target A098** (350.0 mg, 426.90 μmol, 30.6% yield) as a white solid. LCMS: RT = 1.283 min, MS cal.: 819.4, $[M + H]^+$ = 820.3. ^1H NMR (400MHz, DMSO-d_6) δ = 8.05 (s, 1H), 7.96 (br d, J = 5.1 Hz, 1H), 7.88 - 7.72 (m, 2H), 5.07 (s, 1H), 4.51 (br s, 4H), 3.92 (s, 2H), 3.86 - 3.77 (m, 3H), 3.71 (br d, J = 6.0 Hz, 3H), 3.66 - 3.35 (m, 31H), 3.30 - 3.20 (m, 4H), 2.11 (q, J = 7.5 Hz, 2H), 1.07 - 0.88 (m, 3H).

EXAMPLE 6. Procedure for Preparation of Target A097.



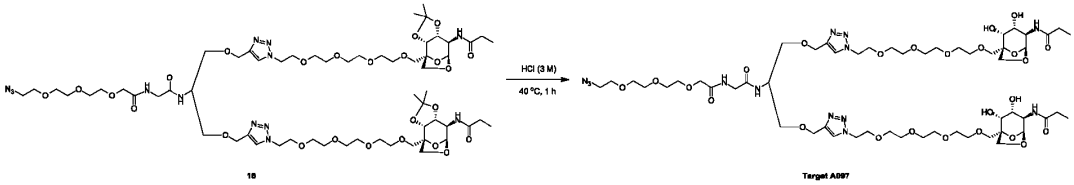
[0037] ***Preparation of Intermediate 16:***



[0038] To a solution of **Intermediate 10** (40.0 mg, 171.51 μmol, 1.00 equiv.) in DCM (1 mL) was added oxalyl dichloride (26.12 mg, 205.81 μmol, 18.02 μL, 1.20 equiv.) and DMF (12.5 mg, 171.51 μmol,

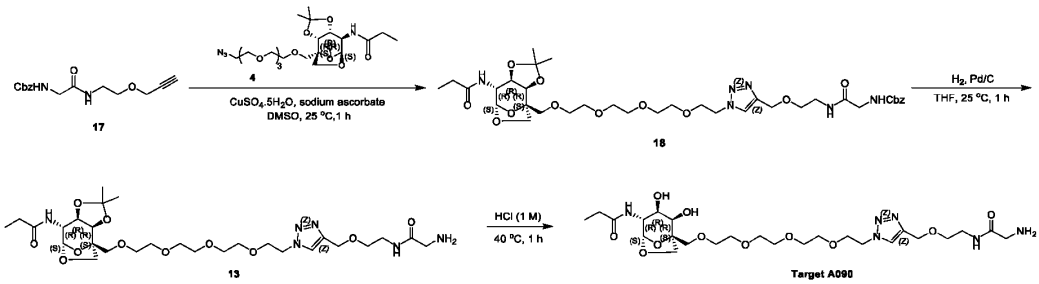
13.20 µL, 1.00 equiv.) at 0 °C. The mixture was stirred at 25 °C for 0.5 h. Then **Intermediate 15** (140.0 mg, 116.54 µmol, 1.00 equiv.), DIEA (45.1 mg, 349.62 µmol, 60.90 µL, 3.00 equiv.) were dissolved in the mixture. The mixture was stirred at 25 °C for 0.5 h. LCMS showed **Intermediate 15** was consumed completely and one main peak with desired mass was detected. After filtration, **Intermediate 16** was afforded as colorless liquid and used into the next step directly. LCMS: RT = 1.818 min, MS cal.:1415.7, $[M + 2H]^{2+}$=709.3.

[0039] ***Preparation of Target A097:***

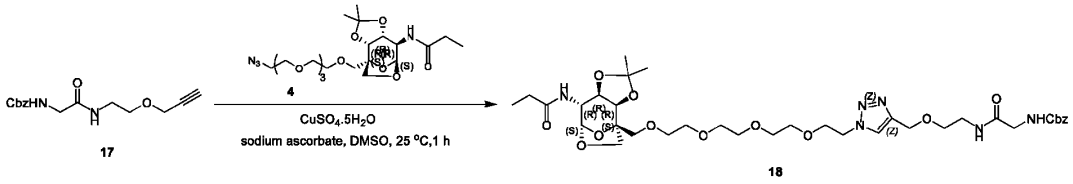


[0040] HCl (3 M, 376.51 uL, 10.00 equiv.) was added to the solution of **Intermediate 16**. The mixture was stirred at 40 °C for 1 h. LC-MS showed **Intermediate 16** was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30 mm * 10 µm; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 25%-45%, 8 min) to afford **Target A097** (64.0 mg, 47.89 µmol, 42.4% yield, 100.0% purity) as colorless oil. LCMS: RT = 1.459 min, MS cal.: 1335.6, $[M + 2H]^{2+}$ = 669.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.05 (s, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 7.4 Hz, 2H), 5.08 (d, J = 1.1 Hz, 2H), 4.83 (d, J = 5.4 Hz, 2H), 4.56 - 4.49 (m, 10H), 4.07 - 3.99 (m, 1H), 3.92 (s, 2H), 3.85 - 3.79 (m, 6H), 3.77 - 3.71 (m, 4H), 3.67 - 3.44 (m, 49H), 3.41 - 3.37 (m, 2H), 2.12 (q, J = 7.6 Hz, 4H), 0.99 (t, J = 7.6 Hz, 6H).

EXAMPLE 7. Procedure for Preparation of Target A090.

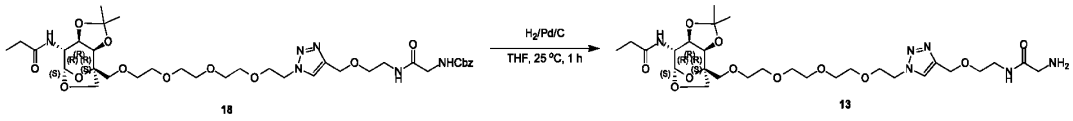


[0041] ***Preparation of intermediate 18:***



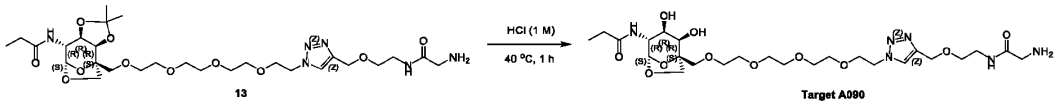
[0042] To a solution of **Intermediate 17** (420.0 mg, 773.75 μmol, 90.0% purity, 1.00 equiv.) and **Intermediate 4** (269.5 mg, 928.50 μmol, 1.20 equiv.) in DMSO (4 mL) was added sodium ascorbate (168.6 mg, 851.12 μmol, 1.10 *equiv.*) and $CuSO_4.5H_2O$ (193.1 mg, 773.75 μmol, 1.00 equiv.) at 25 °C. Then the reaction was stirred for 1 h at 25 °C. LCMS showed the reaction was completed. The reaction was concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex C18 80 * 40 mm * 3 μm; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 20%-50%, 8 min) to afford **Intermediate 18** (300.0 mg, 385.19 μmol, 49.8% yield) as yellow oil. LCMS: RT = 1.793 min, MS cal.: 778.4, $[M+H]^+$ = 779.6. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.74 (s, 1H), 7.41 - 7.29 (m, 5H), 6.58 (br s, 1H), 5.76 (br d, *J* = 8.1 Hz, 1H), 5.63 (br s, 1H), 5.33 (d, *J* = 1.9 Hz, 1H), 5.13 (s, 2H), 4.64 (s, 2H), 4.53 (t, *J* = 4.9 Hz, 2H), 4.19 (d, *J* = 5.9 Hz, 1H), 4.13 (ddd, *J* = 2.0, 6.8, 8.8 Hz, 1H), 4.05 - 3.98 (m, 1H), 3.94 (d, *J* = 10.1 Hz, 1H), 3.90 - 3.84 (m, 4H), 3.83 - 3.72 (m, 2H), 3.66 (br s, 3H), 3.65 - 3.55 (m, 12H), 2.25 (dq, *J* = 2.8, 7.6 Hz, 2H), 1.63 (s, 2H), 1.56 (s, 3H), 1.35 (s, 3H), 1.16 (t, *J* = 7.6 Hz, 3H).

[0043] ***Preparation of Intermediate 13:***



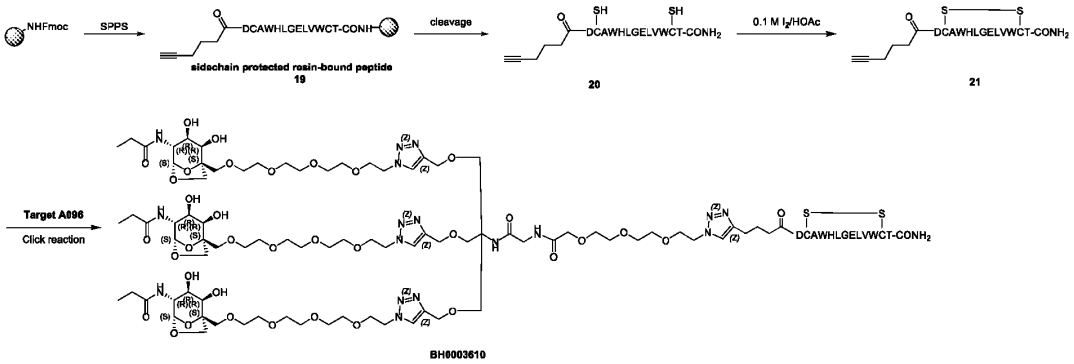
[0044] To a solution of **Intermediate 18** (400.0 mg, 513.58 μmol, 1.00 equiv.) in THF (1 mL) was added Pd/C (100 mg, 10 % purity) at 25 °C. Then the reaction was stirred for 1 h at 25 °C. LCMS showed the reaction was completed. The reaction was filtered and the filtrate was concentrated under reduced pressure to afford **Intermediate 13** (200.0 mg, 310.22 μmol, 60.4% yield) as yellow oil. LCMS: RT = 1.218 min, MS cal.: 644.3, $[M+H]^+$ = 645.4. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.92 (br s, 1H), 7.80 (s, 1H), 6.02 (br d, *J* = 8.6 Hz, 1H), 5.33 (d, *J* = 1.5 Hz, 1H), 4.69 - 4.59 (m, 3H), 4.55 (br t, *J* = 4.9 Hz, 2H), 4.17 (br d, *J* = 5.8 Hz, 2H), 4.14 - 4.01 (m, 3H), 3.96 - 3.54 (m, 30H), 3.50 - 3.39 (m, 3H), 2.25 (dq, *J* = 2.3, 7.6 Hz, 2H), 1.55 (s, 3H), 1.34 (s, 3H), 1.14 (t, *J* = 7.5 Hz, 3H).

[0045] ***Preparation of Target A090:***

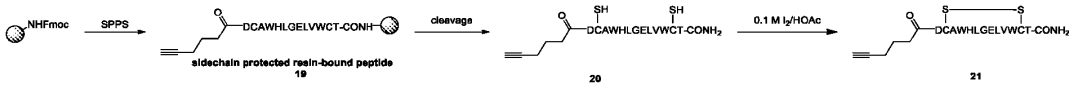


[0046] A mixture of **Intermediate 13** (70.0 mg, 108.58 μmol, 1.00 equiv.) in HCl (1 M, 2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 40 °C for 1 h under N_2 atmosphere. LCMS showed the reaction was completed. The reaction was concentrated under reduced pressure to afford **Target A090** (60.0 mg, 99.23 μmol, 91.3% yield) as colorless oil. LCMS: RT = 1.471 min, MS cal.: 604.3, $[M+H]^+$ = 605.2. ^1H NMR (400 MHz, MeOH-d_4) δ = 8.51 (s, 1H), 5.20 (s, 1H), 4.82 - 4.75 (m, 4H), 4.00 - 3.95 (m, 2H), 3.94 - 3.86 (m, 3H), 3.79 - 3.74 (m, 3H), 3.73 - 3.69 (m, 3H), 3.68 - 3.57 (m, 14H), 3.52 - 3.47 (m, 2H), 2.29 (q, J = 7.6 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).

EXAMPLE 8. Procedure for preparation of BH0003610, BH0003665, BH0003611, BH0003782 and BH0003795.



[0047] ***Preparation of Intermediate 21:***



[0048] Peptide was synthesized using standard Fmoc chemistry (Rink AM resin).

1) Resin preparation: To the vessel containing Rink Amide AM resin (15.62 g, 5.00 mmol, 0.32 mmol/g) and DMF (100 mL) was bubbled with N_2 for 2 h at 25 °C. Then 20% piperidine in DMF (200 mL) was added and the mixture was bubbled with N_2 for 30 min at 25 °C. The mixture was filtered and washed with DMF (100 mL) * 5 before proceeding to next step.

2) Coupling: A solution of Fmoc-Thr(tBu)-OH (5.95 g, 15.00 mmol, 3.00 equiv.), HBTU (5.48 g, 14.25 mmol, 2.85 equiv.), DIEA (3.87 g, 30.00 mmol, 6.00 equiv.) in DMF (100 mL) was added to the resin with

N_2 bubbling for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test. The resin was then washed with DMF (200 mL) * 5.

3) Deprotection: 20% piperidine in DMF (200 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The deprotection reaction was monitored by ninhydrin test. The resin was then washed with DMF (200 mL) * 5.

4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 2-14, Table 1.

5) After all the steps were completed, the resin was washed with DMF (100 mL) * 5, MeOH (100 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 19** (Rink AM resin, 12.3 g, 5.00 mmol).

Table 1: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	2-Oxohept-6-ynoic acid (2.00 equiv.)	HATU (1.90 equiv.) and DIEA (4.00 equiv.)

[0049] Peptide cleavage and cyclization.

1) Cleavage solution (TFA/TIS/H_2O, 95/2.5/2.5, v/v/v, 250 mL) was added to the flask containing the side-chain protected resin-bound peptide **Intermediate 19** (Rink AM resin, 12.3 g, 5.00 mmol) at 25 °C and stirred for 2 h.

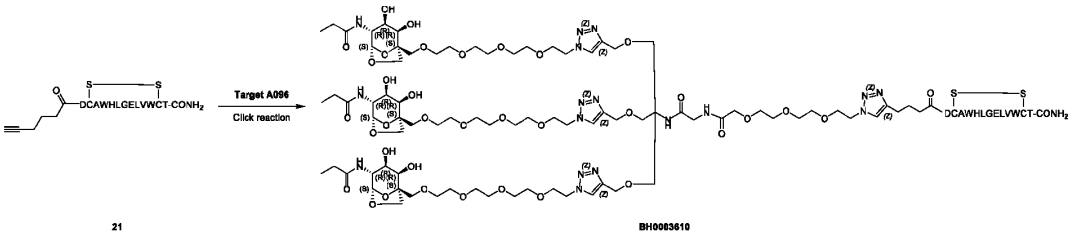
2) After filtration, the filtrate was collected.

3) The filtrate was precipitated with cold isopropyl ether (3.0 L). After filtration, the solid was washed with isopropyl ether (1.5 L) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 20** (10.1 g, crude) as a white solid.

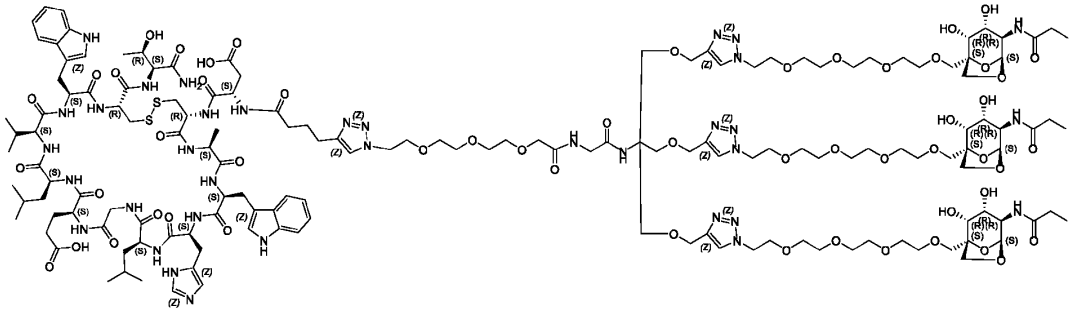
4) To a mixture of **Intermediate 20** (10.1 g, crude) in HOAc/MeCN/H_2O (4/3/3, v/v/v, 3.0 L) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5

min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 21** (2.00 g, 92.1% purity, 24.6% yield) as a white solid. LCMS: RT = 1.764 min, MS calcd.: M_{av} = 1623.85, mass observed: $[M + H]^+$ = 1625.0, $[M + 2H]^{2+}$ = 813.1.

[0050] ***Preparation of BH0003610 (click reaction):***

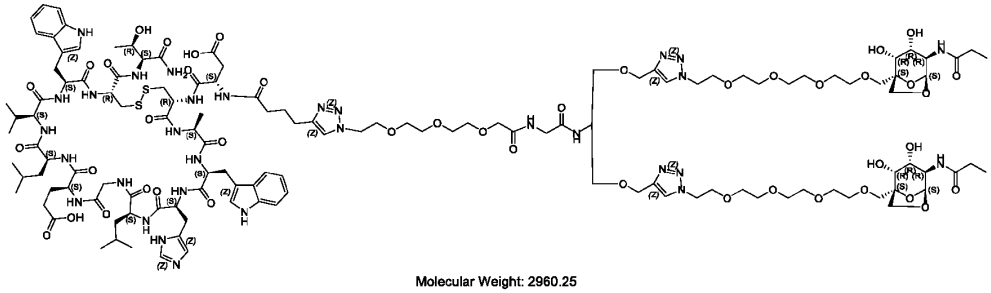


[0051] To a solution of **Intermediate 21** (65.7 mg, 40.5 μmol, 1.00 equiv.) and **Target A096** (75.0 mg, 40.5 μmol, 1.00 equiv.) in DMF (5 mL) was added $CuSO_4$ (0.4 M, 101.25 μL, 40.5 μmol, 1.00 equiv.), sodium ascorbate (0.4 M, 405.0 μL, 162.0 μmol, 4.00 equiv.) and THPTA (tris-hydroxypropyltriazolylmethylamine, 17.6 mg, 40.5 μmol, 1.00 equiv.) under nitrogen atmosphere at 0 °C, and the resulting mixture was stirred for 3 h at 0 °C. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **BH0003610** (30.5 mg, 91.8% purity, 21.7% yield) as a white solid. LCMS: RT = 9.0 min, MS calcd.: M_{av} = 3476.79, mass observed: $[M + 2H]^{2+}$ = 1738.80, $[M + 3H]^{3+}$ = 1159.53, $[M + 4H]^{4+}$ = 869.90, $[M + 5H]^{5+}$ = 696.12.



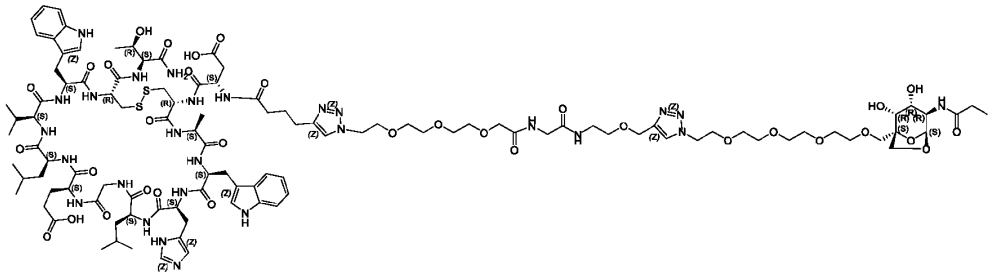
[0052] **BH0003665, BH0003611, BH0003782, BH0003781, BH0003795** were synthesized using the same procedure as **BH0003610,** which was performed by following the procedure mentioned in **[0050] – [0051]**,

[0053] 58.0 mg of **Target A097** afforded **BH0003665** (17.9 mg, 95.6% purity, 13.9% yield) as a white solid. LCMS: RT = 9.1 min, MS calcd.: M_{av} = 2960.25, mass observed: $[2M + 3H]^{3+}$ = 1974.23, $[M + 2H]^{2+}$ = 1480.67, $[M + 3H]^{3+}$ = 987.79, $[M + 4H]^{4+}$ = 740.84.



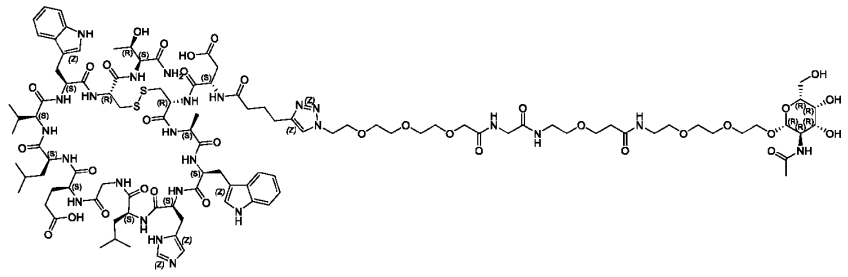
Molecular Weight: 2960.25
BH0003665

[0054] 57.9 mg of **Target A098** afforded **BH0003611** (29.2 mg, 95.7% purity, 16.9% yield) as a white solid. LCMS: RT = 9.0 min, MS calcd.: M_{av} = 2443.71, mass observed: $[2M + 3H]^{3+}$ = 1629.74, $[M + 2H]^{2+}$ = 1223.06, $[M + 3H]^{3+}$ = 815.04, $[M + 4H]^{4+}$ = 611.53.



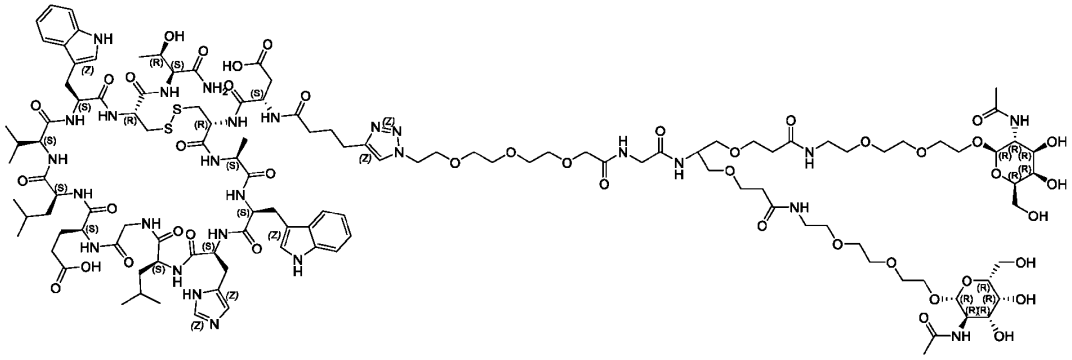
Molecular Weight: 2443.71
BH0003611

[0055] 130 mg of **Target A100** afforded **BH0003795** (98 mg, 94.5% purity, 22.3% yield) as a white solid. LCMS: RT = 1.34 min, MS calcd.: M_{av} = 2363.62, mass observed: $[2M + 3H]^{3+}$ = 1576.5, $[M + Na]^{2+}$ = 1193.8, $[M + 2H]^{2+}$ = 1182.8, $[M\text{-Sugar} + 2H]^{2+}$ = 1080.8 $[M + 3H]^{3+}$ = 788.8.



Molecular Weight: 2363.62
BH0003795

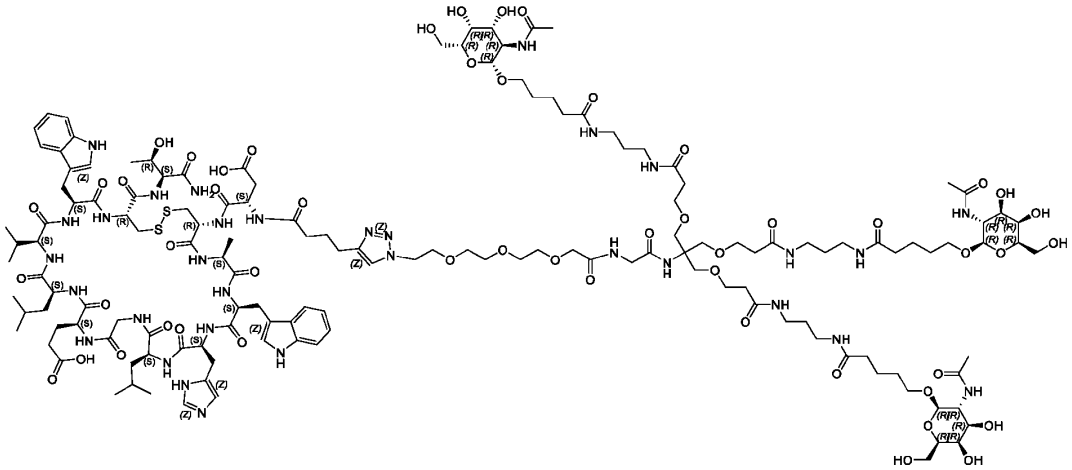
[0056] 110 mg of **Target A099** afforded **BH0003782** (149 mg, 96.0% purity, 54.6% yield) as a white solid. LCMS: RT = 1.34 min, MS calcd.: M_{av} = 2800.07, mass observed: $[2M + 3H]^{3+}$ = 1867.3, $[M + Na]^{2+}$ = 1411.5, $[M + 2H]^{2+}$ = 1400.9, $[M\text{-Sugar} + 2H]^{2+}$ = 1299.4 $[M + 3H]^{3+}$ = 934.4.



Molecular Weight: 2800.07

BH0003782

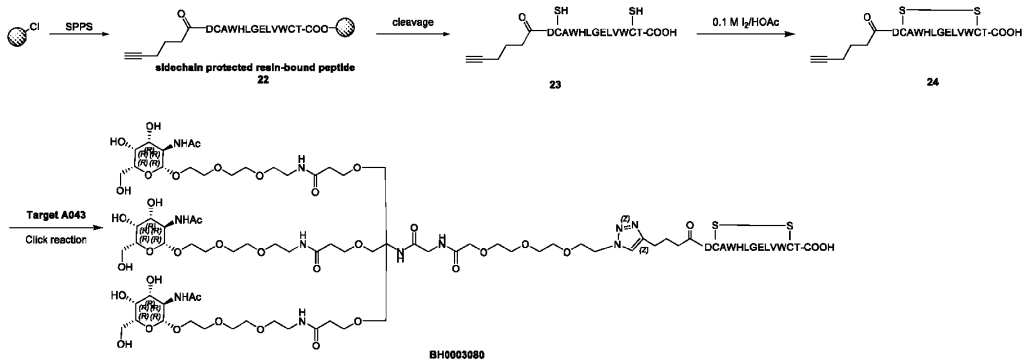
[0057] 26 mg of **Target A094** afforded **BH0003781** (19 mg, 95.5% purity, 35.9% yield) as a white solid. LCMS: RT = 1.32 min, MS calcd.: M_{av} = 3311.69, mass observed: $[M + 2H]^{2+}$ = 1656.3, $[M\text{-}203 + 2H]^{2+}$ = 1554.7, $[M + 3H]^{3+}$ = 1104.7.



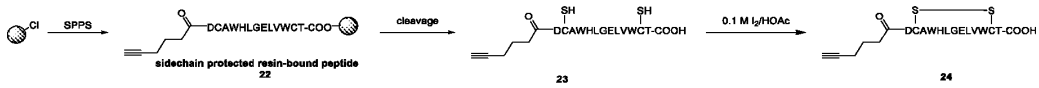
Molecular Weight: 3311.69

BH0003781

EXAMPLE 9. Procedure for preparation of BH0003080, BH0003081, BH0003083 and BH0003050.



[0058] ***Preparation of Intermediate 24:***



[0059] Peptide was synthesized using standard Fmoc chemistry (CTC resin).

1) Resin preparation: To the vessel containing CTC resin (0.50 g, 0.50 mmol, 1.00 mmol/g) and Fmoc-Thr(*t*BU)-OH (198.5 mg, 0.5 mmol, 1.00 equiv.) in DCM (10 mL) was added DIEA (4.00 equiv.) dropwise and mixed for 2 h with N_2 bubbling at 25 °C. Then MeOH (2.0 mL) was added and bubbled with N_2 for another 30 min. The resin was washed with DMF (10 mL) * 5, followed by the addition of 20% piperidine in DMF (10 mL) and bubbled with N_2 for 30 min at 25 °C for Fmoc deprotection. The mixture was filtered and the resin was washed with DMF (10 mL) * 5 before proceeding to next step.

2) Coupling: A solution of Fmoc-Leu-OH (0.53 g, 1.5 mmol, 3.00 equiv.), HBTU (0.41 g, 1.43 mmol, 2.85 equiv.) in DMF (10 mL) was added to the resin with N_2 bubbling. Then DIEA (6.00 equiv.) was added to the mixture dropwise and bubbled with N_2 for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test, if it showed colorless, the coupling was completed. The resin was then washed with DMF (10 mL) * 5.

3) Deprotection: 20% piperidine in DMF (10 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The resin was then washed with DMF (10 mL) * 5.

4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 2-14, Table 2.

5) After all the steps were completed, the resin was washed with DMF (100 mL) * 5, MeOH (100 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 22** (CTC resin, 1.10 g, 0.50 mmol).

Table 2: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	2-Oxohept-6-ynoic acid (2.00 equiv.)	HATU (1.90 equiv.) and DIEA (4.00 equiv.)

[0060] Peptide cleavage and cyclization.

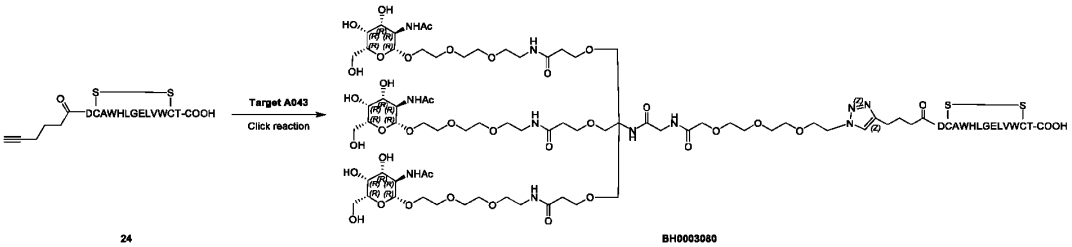
1) Cleavage solution (TFA/TIS/H2O, 95/2.5/2.5, v/v/v, 20 mL) was added to the flask containing the side-chain protected resin-bound peptide Intermediate 22, 1.23 g, 0.50 mmol at 25 ºC and stirred for 2 h.

2) After filtration, the filtrate was collected.

3) The filtrate was precipitated with cold isopropyl ether (100 mL). After filtration, the solid was washed with isopropyl ether (100 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 23** (768 mg, crude) as a white solid.

4) To a mixture of **Intermediate 23** (768 mg, crude) in MeCN/H_2O (4/6, v/v, 500 mL) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 24** (56.2 mg, 90.0% purity) as a white solid.

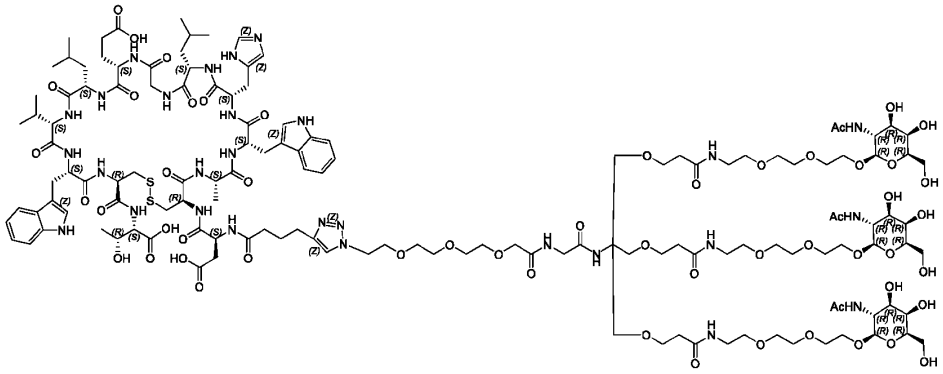
[0061] ***Preparation of BH0003080***



24 BH0003080

[0062] Click reaction: **BH0003080** was synthesized using the same procedure as **BH0003610,** which was performed by following the procedure mentioned in **[0050]** – **[0051]**.

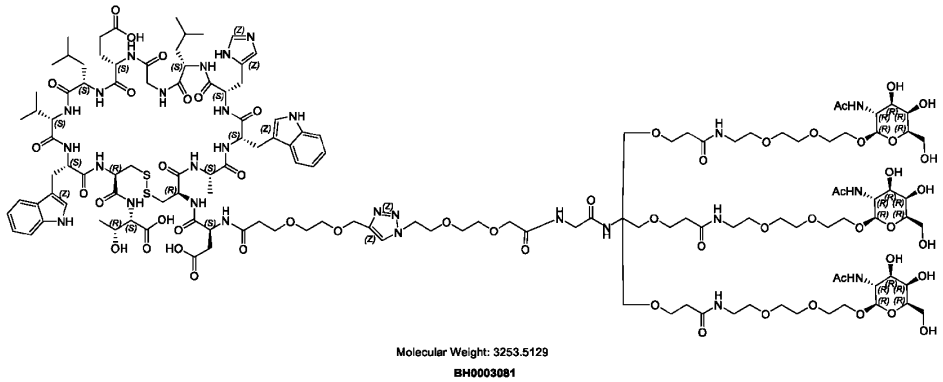
[0063] 50.0 mg of **Target A043** afforded **BH0003080** (28 mg, 95.4% purity, 50.1% yield) as a white solid. LCMS: RT = 1.44 min, MS calcd.: M_{av} = 3237.51, mass observed: $[M + 2H]^{2+}$ = 1620.10, $[M – 203 + 2H]^{2+}$ = 1519.10, $[M – 2 \times 203 + 2H]^{2+}$ = 1417.10, $[M + 3H]^{3+}$ = 1080.50.



Molecular Weight: 3237.51
BH0003080

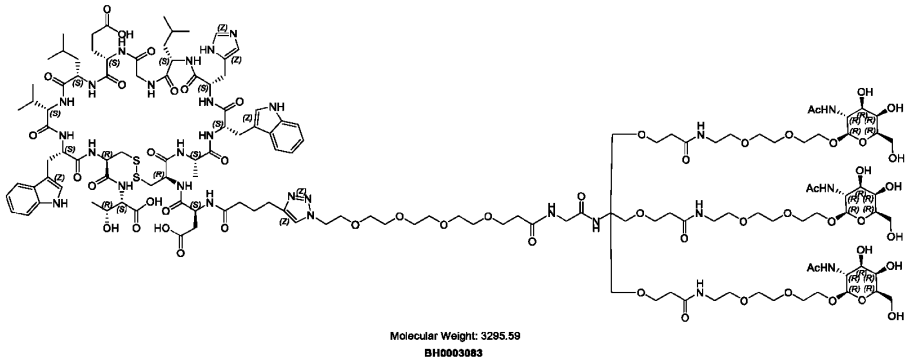
[0064] **BH0003081, BH0003083, BH0003050** were synthesized using the same procedure as **BH0003080**, which were performed by following the procedure mentioned in **[0059]** – **[0063]**.

[0065] 50.0 mg of **Target A044** afforded **BH0003081** (53.0 mg, 95.8% purity, 49.2% yield) as a white solid. LCMS: RT = 1.44 min, MS calcd.: M_{av} = 3253.51, mass observed: $[M + 2H]^{2+}$ = 1628.70, $[M – 203 + 2H]^{2+}$ = 1526.50, $[M – 2 \times 203 + 2H]^{2+}$ = 1424.50, $[M + 3H]^{3+}$ = 1085.80.

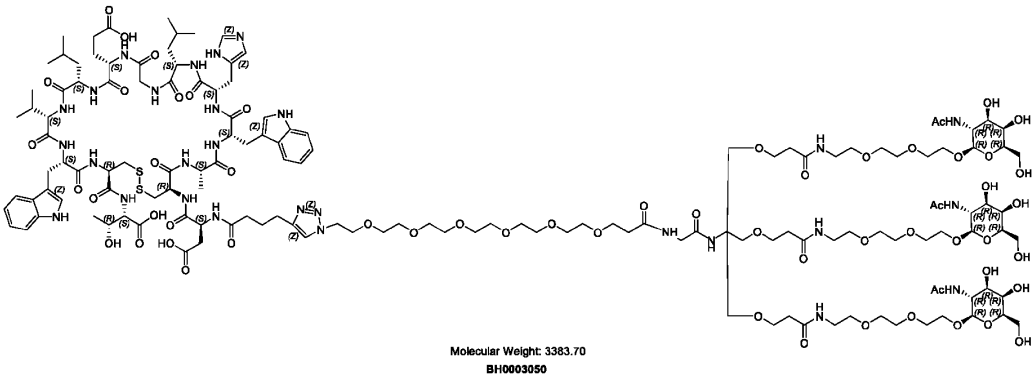


Molecular Weight: 3253.5129
BH0003081

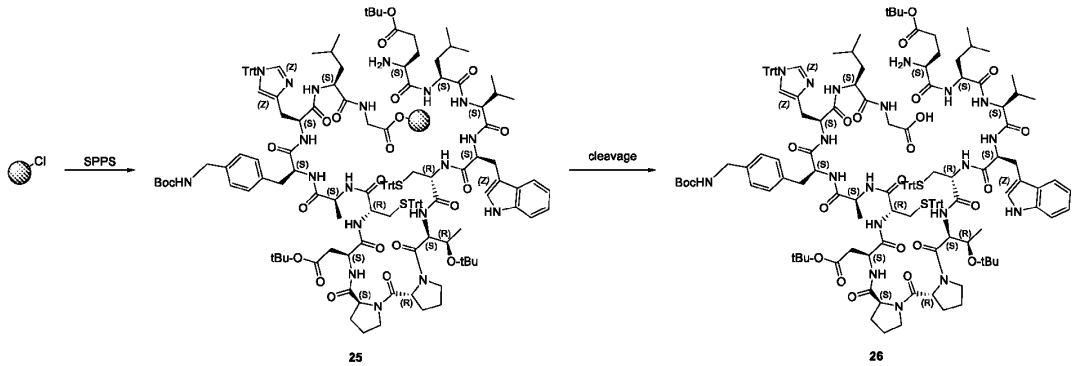
[0066] 50.0 mg of **Target A042** afforded **BH0003083** (45.0 mg, 95.8% purity, 43.7% yield) as a white solid. LCMS: RT = 1.45 min, MS calcd.: M_{av} = 3295.59, mass observed: $[M + 2H]^{2+}$ = 1649.10, $[M - 203 + 2H]^{2+}$ = 1547.50, $[M - 2 \times 203 + 2H]^{2+}$ =1446.00, $[M + 3H]^{3+}$ = 1099.80.

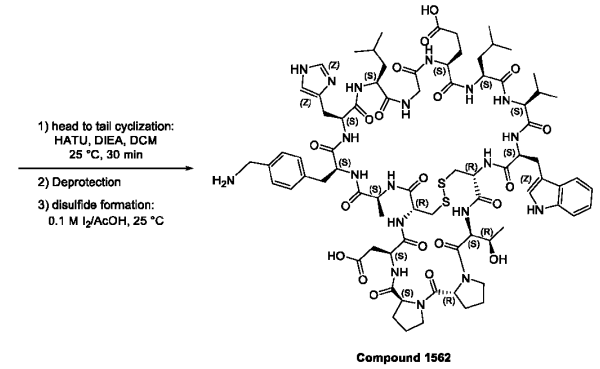


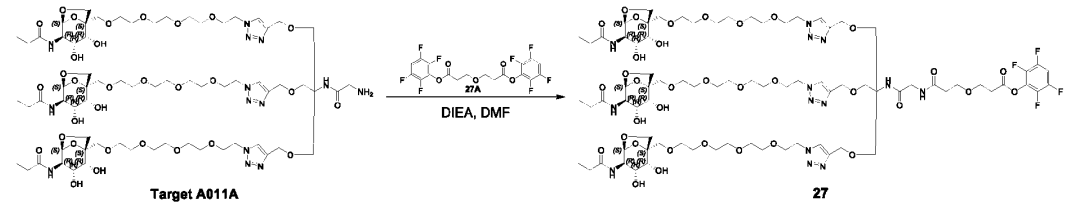
[0067] 20 mg of **Target A041** afforded **BH0003050** (19.8 mg, 97.2% purity, 37.7% yield) as a white solid. LCMS: RT = 0.84 min, MS calcd.: M_{av} = 3383.70, mass observed: $[M + 2H]^{2+}$ = 1692.40, $[M - \text{sugar} + 2H]^{2+}$ = 1590.90, $[M + 3H]^{3+}$ = 1128.50.

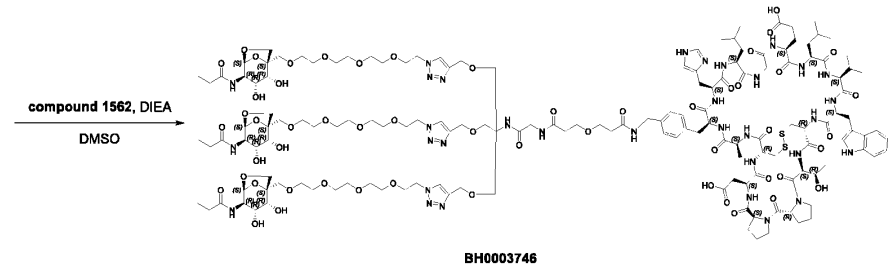


EXAMPLE 10. Procedure for Preparation of BH0003746 and BH-0003602.

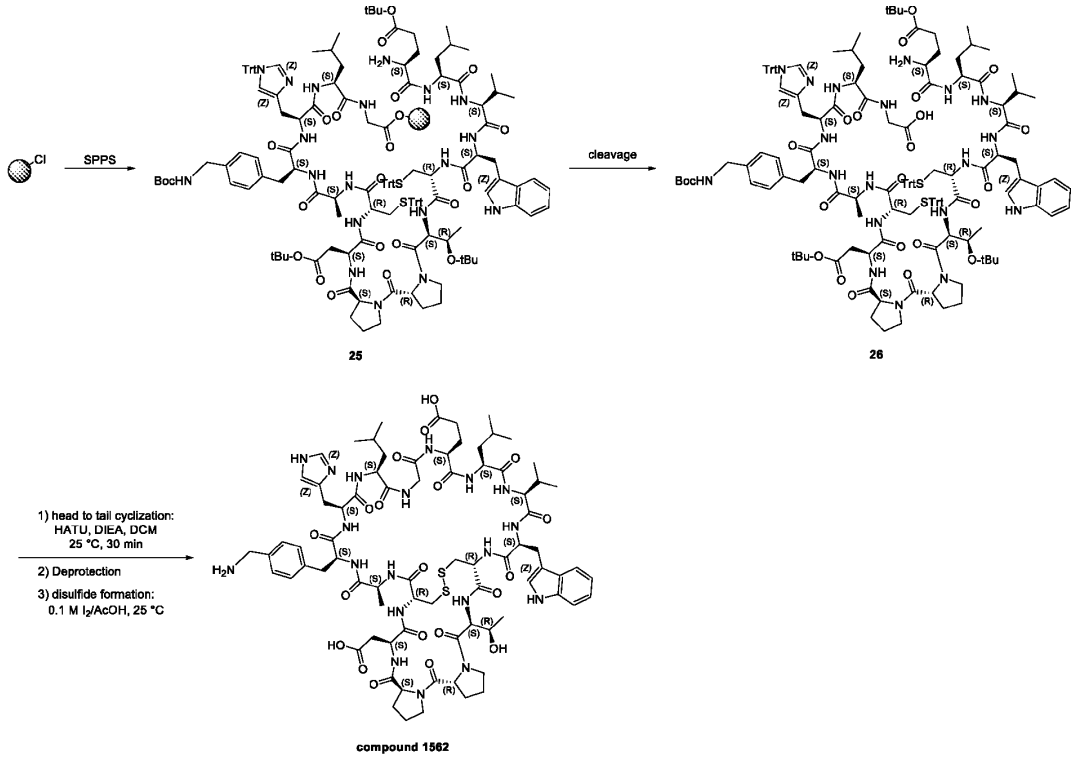








[0068] ***Preparation of Compound 1562:***



[0069] Peptide was synthesized using standard Fmoc chemistry (CTC resin).

1) Resin preparation: To the vessel containing CTC resin (0.50 g, 0.50 mmol, 1.00 mmol/g) and Fmoc-Gly-OH (148.8 mg, 0.5 mmol, 1.00 equiv.) in DCM (10 mL) was added DIEA (4.00 equiv.) dropwise and mixed for 2 h with N2 bubbling at 25 °C. Then MeOH (2.0 mL) was added and bubbled with N2 for another 30 min. The resin was washed with DMF (10 mL) * 5, followed by the addition of 20% piperidine in DMF (10 mL) and bubbled with N2 for 30 min at 25 °C for Fmoc deprotection. The mixture was filtered and the resin was washed with DMF (10 mL) * 5 before proceeding to next step.

2) Coupling: A solution of Fmoc-Leu-OH (0.53 g, 1.5 mmol, 3.00 equiv.), HBTU (0.41 g, 1.43 mmol, 2.85 equiv.) in DMF (10 mL) was added to the resin with N_2 bubbling. Then DIEA (6.00 equiv.) was added to the mixture dropwise and bubbled with N_2 for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test, if it showed colorless, the coupling was completed. The resin was then washed with DMF (10 mL) * 5.

3) Deprotection: 20% piperidine in DMF (10 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The resin was then washed with DMF (10 mL) * 5.

4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 3-15, Table 3.

5) After all the steps were completed, the resin was washed with DMF (100 mL) * 5, MeOH (100 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 25** (CTC resin, 1.10 g, 0.5 mmol).

Table 3: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Gly-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-4-(Boc-aminomethyl)-*L*-phenylalanine (2.00 equiv.)	HBTU (1.90 equiv.) and DIEA (4.00 equiv.)
5	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-D-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

[0070] Peptide cleavage and cyclization, TFA de-protection and disulfide formation:

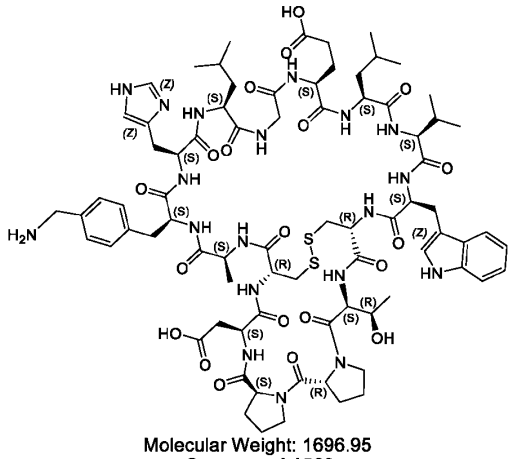
1) Cleavage: A solution of 1% TFA/DCM (20 mL) was added to the resin above at room temperature and stirred for 2 h. After filtration, the filtrate was collected (which contained **Intermediate 26**).

2) Head to tail cyclization: The filtrate was diluted with DCM to 500 mL (1 mM), then HATU (380.2 mg, 1.0 mmol, 2.00 equiv.) was added, followed by the addition of DIEA (348.6 µL, 2.0 mmol, 4.00 equiv.), and the resulting mixture was stirred for 30 min at 25 °C. After completion monitored by LC-MS, the reaction was washed with 1 M HCl (300 mL), then washed with H_2O (300 mL). The organic layer was collected and concentrated under reduced pressure to give a residue.

3) Deprotection: To the residue from step 2 was added a solution of TFA/TIS/H_2O/3-mercaptopropanoic acid (v/v/v/v, 92.5/2.5/2.5/2.5, 50 mL), and the resulting mixture was stirred for 1 h at 25 °C. The mixture was precipitated with cold isopropyl ether (cold, 300 mL). After filtration, the solid was washed with isopropyl ether (100 mL) twice, and the crude peptide was dried under reduced pressure.

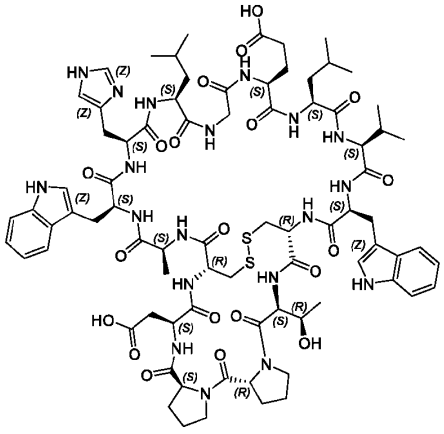
4) Disulfide formation: To the crude peptide from step 3 in MeCN/H_2O (1/1, v/v, 500 mL) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The

mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Compound 1562** (164.8 mg, 96.6% purity, 19.4% yield) as a white solid. LCMS: RT = 7.9 min, MS calcd.: M_{av} = 1696.95, mass observed: $[M + H]^+$ = 1696.76, $[2M + 3H]^{3+}$ = 1132.18, $[M + 2H]^{2+}$ = 848.88, $[M + 3H]^{3+}$ = 566.26.



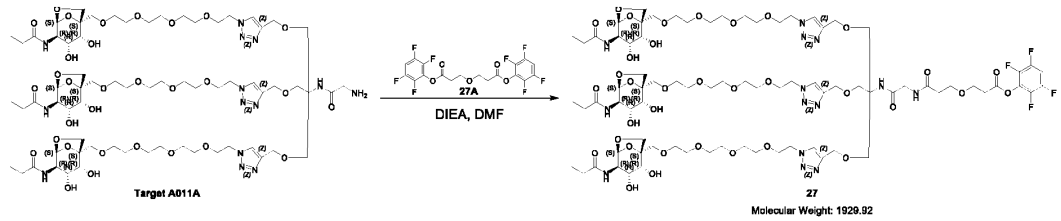
Molecular Weight: 1696.95
Compound 1562

[0071] **BH-0003602** was synthesized using the same procedure as **Compound 1562** which was performed by following the procedure mentioned in **[0069]** – **[0070]**. 0.50 mmol resin afforded **BH-0003602** (110.4mg, 95.0% purity, 12.9% yield) as a white solid. LCMS: RT = 1.78 min, MS calcd.: M_{av} = 1706.94, mass observed: $[M + H]^+$ = 1707.1, $[M + 2H]^{2+}$ = 854.1.



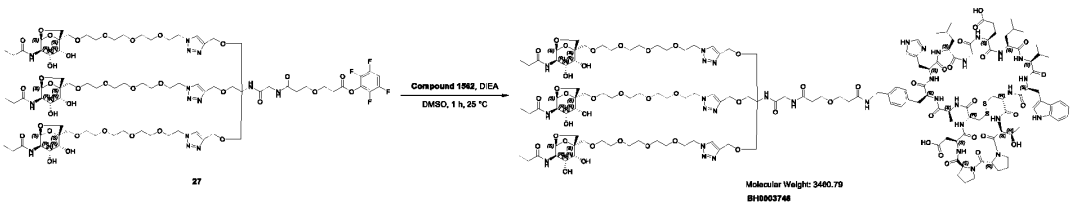
Molecular Weight: 1706.94
BH-0003602

[0072] ***Preparation of Intermediate 27:***



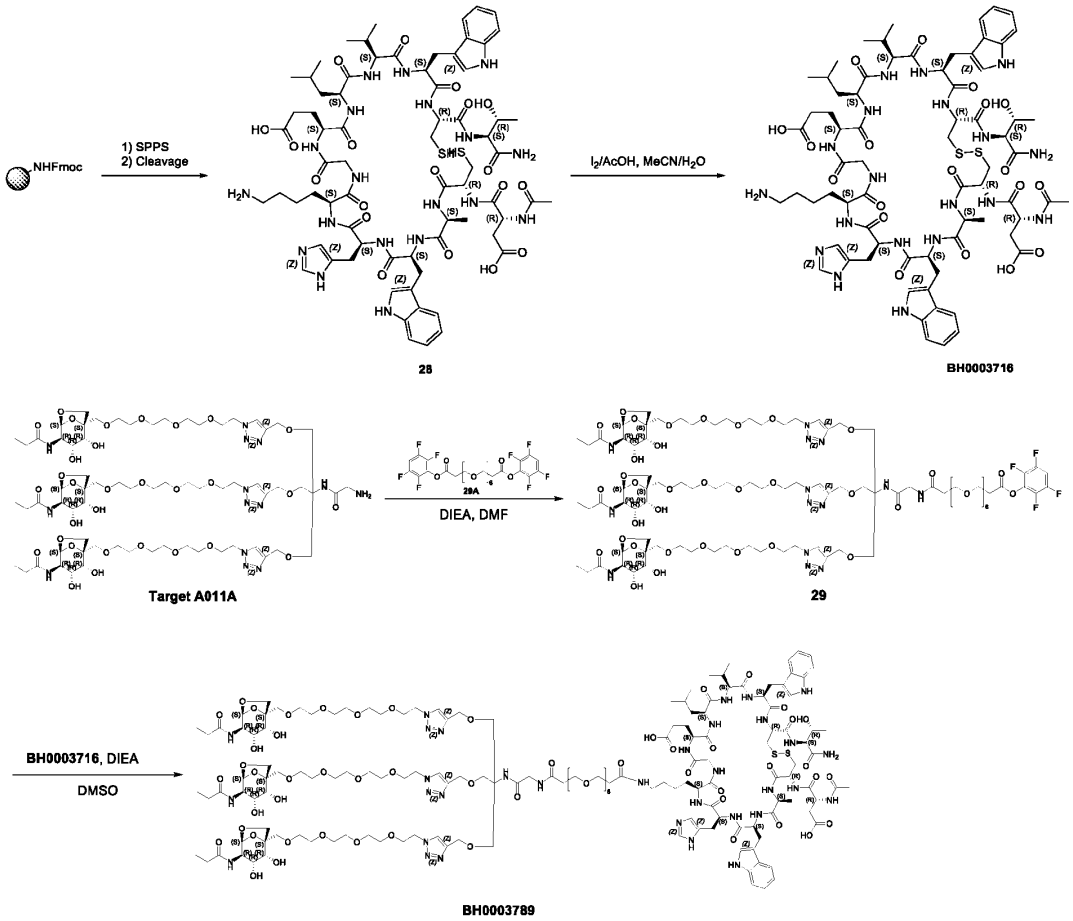
[0073] To a mixture of **27A** (151.1 mg, 329.7 µmol, 3.00 equiv.) in DMF (0.5 mL) was added a mixture of **Target A011A** (180.0 mg, 109.9 µmol, 1.00 equiv.) and DIEA (76.6 uL, 439.63 µmol, 4.00 equiv.) in DMF (0.5 mL) at 0 °C, and the resulting reaction was stirred for 5 min at 0 °C. After completion monitored by LC-MS. The mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **Intermediate 27** (160.0 mg, 75.4% yield) as colorless oil. LCMS: RT = 0.828 min, MS calcd.: M_{av} = 1929.92, mass observed: $[M + 2H]^{2+}$ = 965.7.

[0074] ***Preparation of BH0003746:***

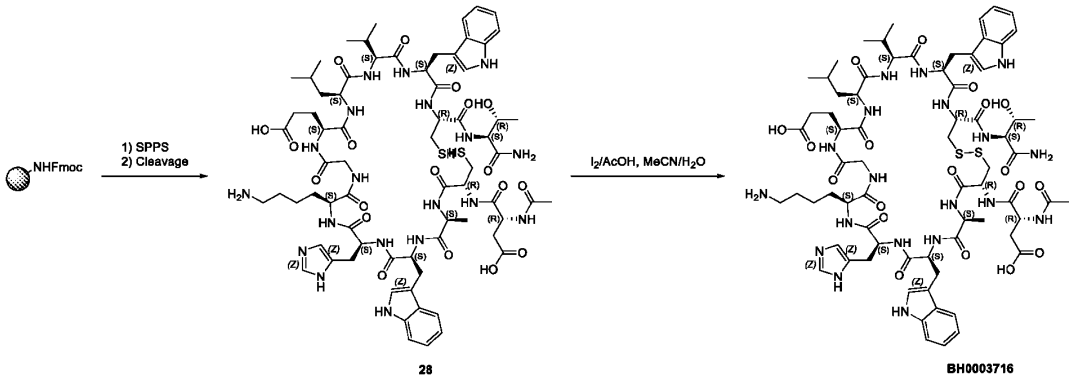


[0075] To a mixture of **Intermediate 27** (24.9 mg, 12.9 µmol, 1.00 equiv.) and **Compound 1562** (21.9 mg, 12.9 µmol, 1.00 equiv.) in DMF (0.2 mL) was added DIEA (22.0 µL, 129 µmol, 10.0 equiv.) at 25 °C. The mixture was stirred at 25 °C for 2 h. After completion monitored by LC-MS, the mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **BH0003746** (8.1 mg, 92.5% purity, 18.1% yield) as a white solid. LCMS: RT = 9.3 min, MS calcd.: M_{av} = 3460.79, mass observed: $[M + 2H]^{2+}$ = 1730.80, $[M + 3H]^{3+}$ = 1154.54, $[M + 4H]^{4+}$ = 865.90.

EXAMPLE 11. Procedure for Preparation of BH0003716, BH0003789 and BH0003082.



[0076] ***Preparation of BH0003716:***



[0077] SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 4 by following the procedure mentioned in section **[0048]**.

[0078] Acetylation: A solution of Ac_2O/NMM/DMF (2/1/17, v/v/v, 40 mL) was added to the resin, the mixture was bubbled with N_2 for 20 min. The acetylation reaction was monitored by ninhydrin test. The resin was then washed with DMF (20 mL) * 5, MeOH (20 mL) * 3, then dried under reduced pressure to afford **Intermediate 28** (peptide resin, 0.50 mmol).

Table 4: The list of amino acids and the corresponding reagents used on SPPS.

Materials	Coupling reagents
Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Lys(Boc)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Acetylation	Ac2O/NMM/DMF(10/5/85, V/V/V, 50 mL)

[0079] Peptide cleavage and disulfide formation:

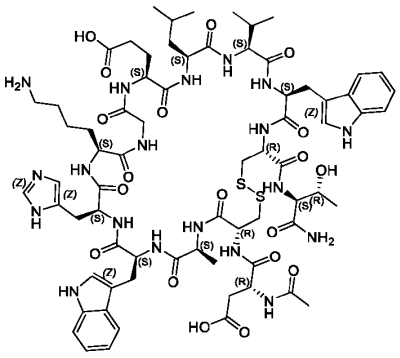
5) Cleavage solution (TFA/TIS/H_2O, 95/2.5/2.5, v/v/v, 30 mL) was added to the flask containing the side-chain protected resin-bound peptide (Rink AM resin, 1.84 g, 0.50 mmol) at 25 °C and stirred for 2 h.

6) After filtration, the filtrate was collected.

7) The filtrate was precipitated with cold isopropyl ether (150 mL). After filtration, the solid was washed with isopropyl ether (150 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 28** (785 mg, crude) as a white solid.

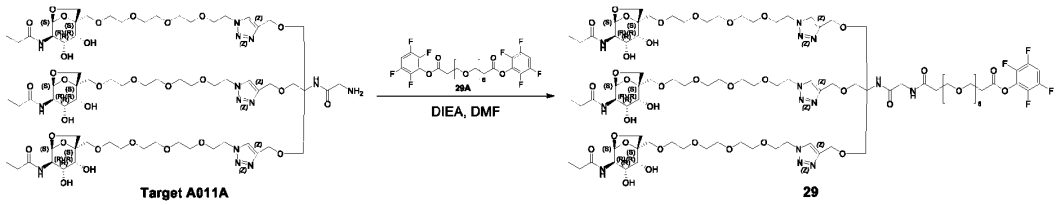
5) Disulfide formation: To the **Intermediate 28** in MeCN/H_2O (1/1, v/v, 500 mL) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization

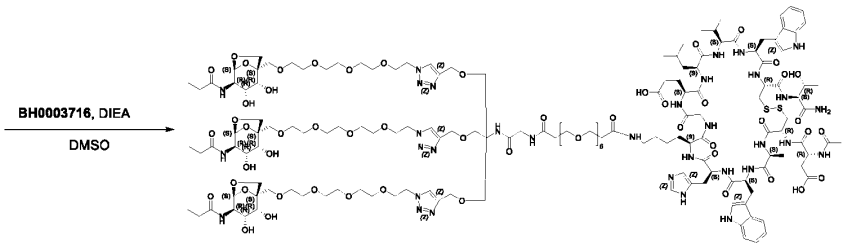
to afford **BH0003716** (59.7 mg, 95.2% purity, 7.2% yield) as a white solid. LCMS: RT = 1.23 min, MS calcd.: M_{av} = 1586.79, mass observed: $[M + H]^+$ = 1586.79, $[M + 2H]^{2+}$ = 794.1.



Molecular Weight: 1586.79
BH0003716

[0080] ***Preparation of BH0003789:***

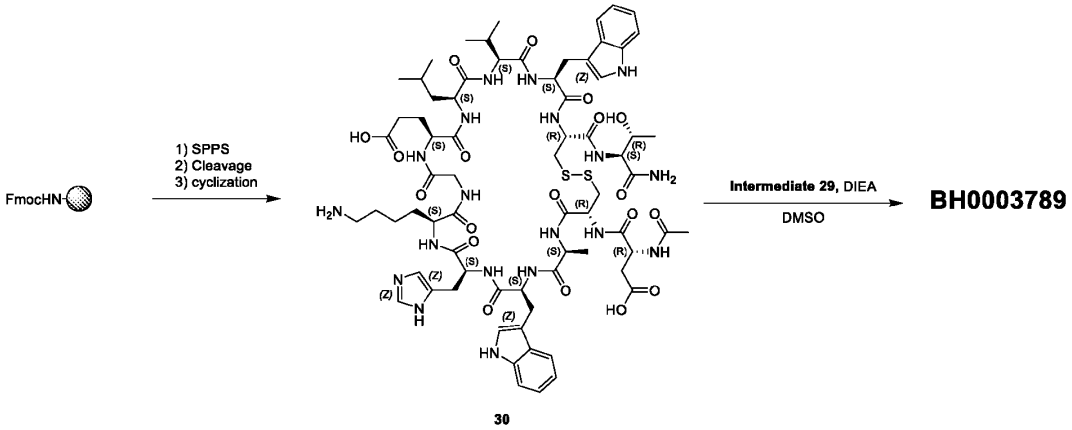




BH0003789

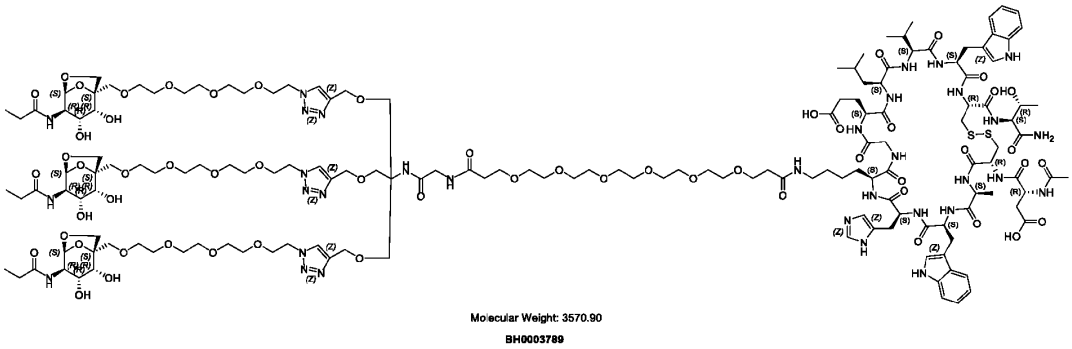
[0081] **BH0003789, BH-0003082** were synthesized using the same procedure as **BH0003746**, which was performed by following the procedure mentioned in **[0072]** – **[0075]**.

[0082] ***Preparation of BH0003789:***

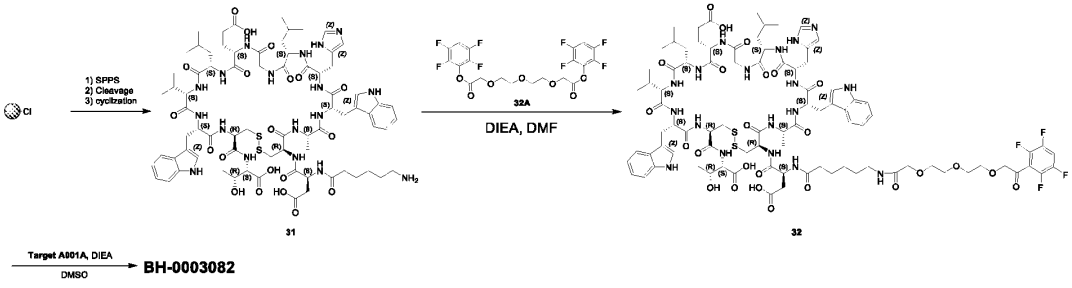


[0083] **Intermediate 30** were synthesized using the same procedure which was performed by following the procedure mentioned in **[0048]- [0049]**.

[0084] 50.0 mg of **Intermediate 29** afforded **BH0003789** (20.3 mg, 93.2% purity, 22.8% yield) as a white solid. LCMS: RT = 1.31 min, MS calcd.: M_{av} = 3570.90, mass observed: $[M + 2H]^{2+}$ = 1786.7, $[M + 3H]^{3+}$ = 1191.1, $[M + 4H]^{4+}$ = 893.7, $[M + 5H]^{5+}$ = 715.3.



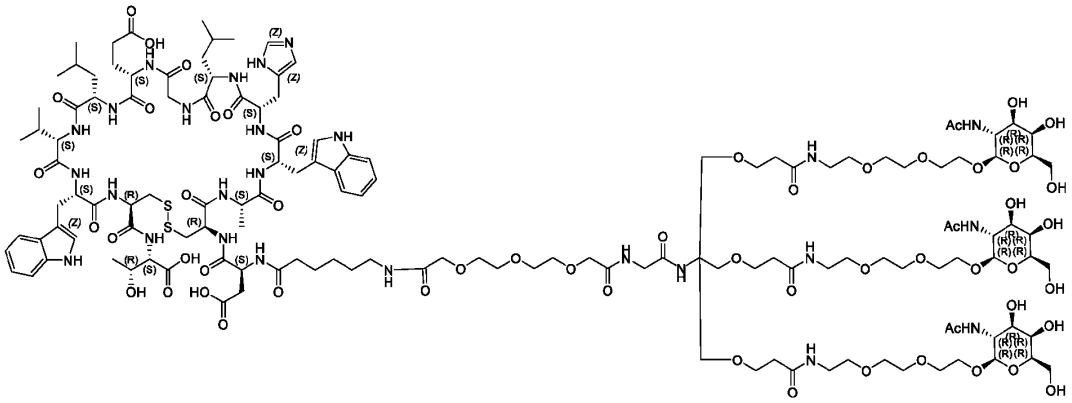
[0085] ***Preparation of BH0003082:***



[0086] **Intermediate 31** were synthesized using the same procedure which was performed by following the procedure mentioned in **[0059]-[0060]**.

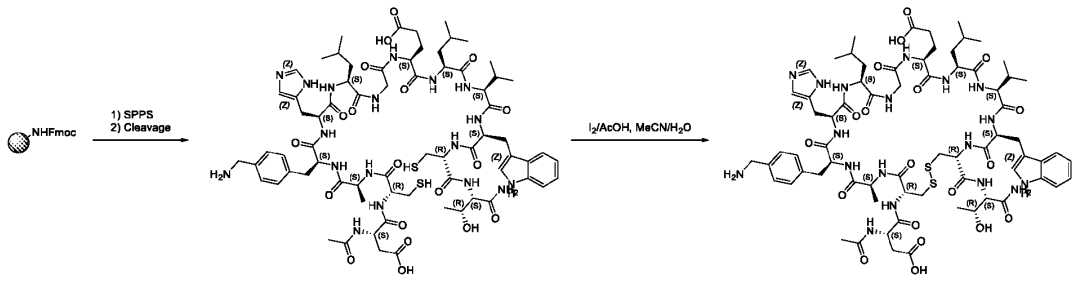
[0087] **Intermediate 32** were synthesized using the same procedure as **Intermediate 27**, which was performed by following the procedure mentioned in **[0072]**.

[0088] 8 mg of **Target A001A** afforded **BH-0003082** (5 mg, 94.6% purity, 32.2% yield) as a white solid. LCMS: RT = 0.83 min, MS calcd.: M_{av} = 3227.52, mass observed: $[M + 2H]^{2+}$ = 1614.17, $[M – sugar + 4H]^{4+}$ = 1076.40, $[M + 3H]^{3+}$ = 1076.40.

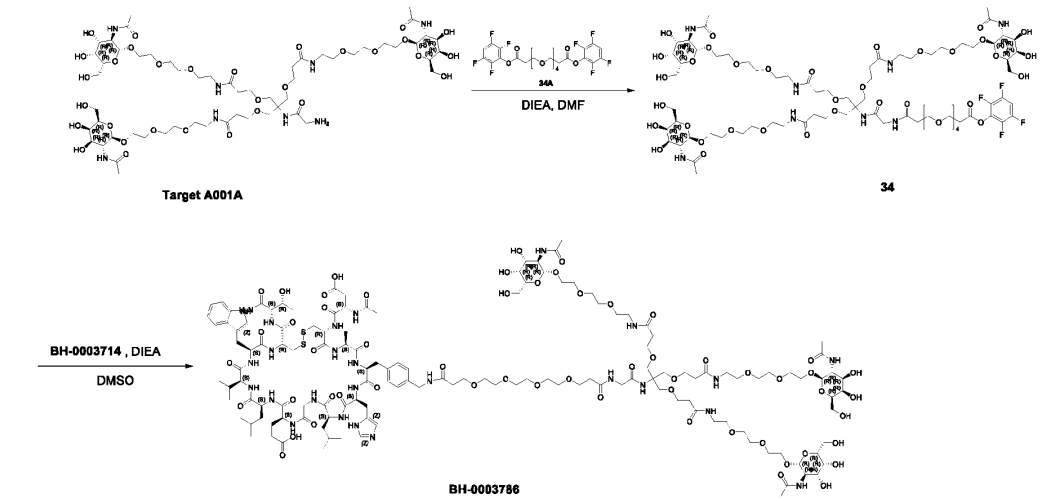


Molecular Weight: 3227.52
BH-0003082

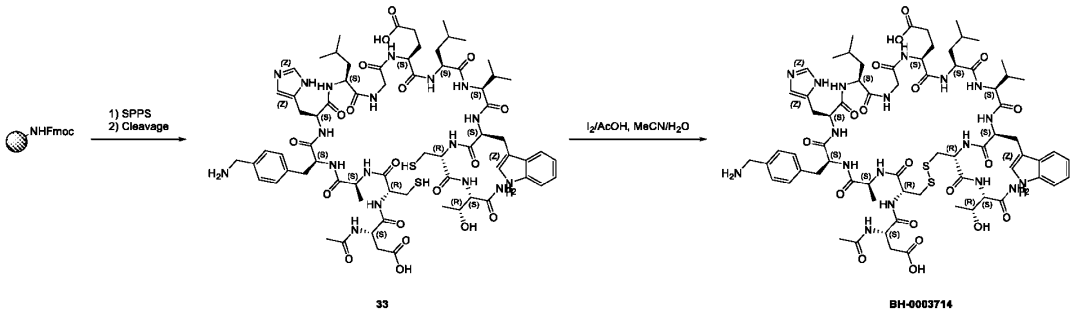
EXAMPLE12. Procedure for Preparation of BH-0003714, BH-0003715 and BH-0003786



33 **BH-0003714**



[0089] **Preparation of *BH-0003714*:**



[0090] **BH-0003714** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0048]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 5.

Table 5: The list of amino acids and the corresponding reagents used on SPPS.

Materials	Coupling reagents
Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

Fmoc-4-(Boc-aminomethyl)-*L*-phenylalanine (2.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Acetylation	Ac2O/NMM/DMF(10/5/85, V/V/V, 50 mL)

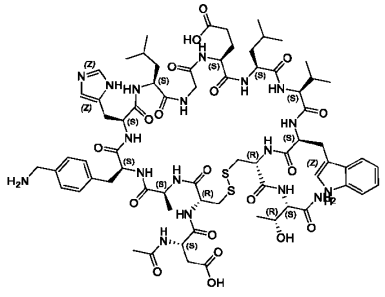
[0091] Peptide cleavage and disulfide formation:

1) Cleavage solution (TFA/TIS/H2O, 95/2.5/2.5, v/v/v, 30 mL) was added to the flask containing the side-chain protected resin-bound peptide Rink AM resin, 1.84 g, 0.50 mmolat 25 ºC and stirred for 2 h.

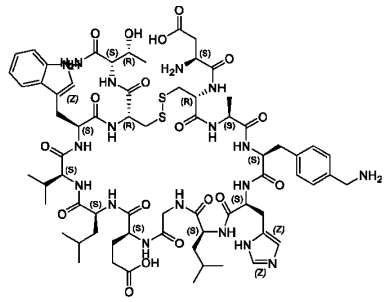
2) After filtration, the filtrate was collected.

3) The filtrate was precipitated with cold isopropyl ether (150 mL). After filtration, the solid was washed with isopropyl ether (150 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 33** (785 mg, crude) as a white solid.

4) Disulfide formation: To the Intermediate 30 in MeCN/H2O (1/1, v/v, 500 mL) was added 0.1 M I2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H2O, B: MeCN), followed by lyophilization to afford **BH-0003714** (156 mg, 96.5% purity, 19.3% yield) as a white solid. LCMS: RT = 1.26 min, MS calcd.: Mav =1561.78, mass observed: [M + H]+ = 1561.9, $[M + 2H]^{2+}$ = 781.6.



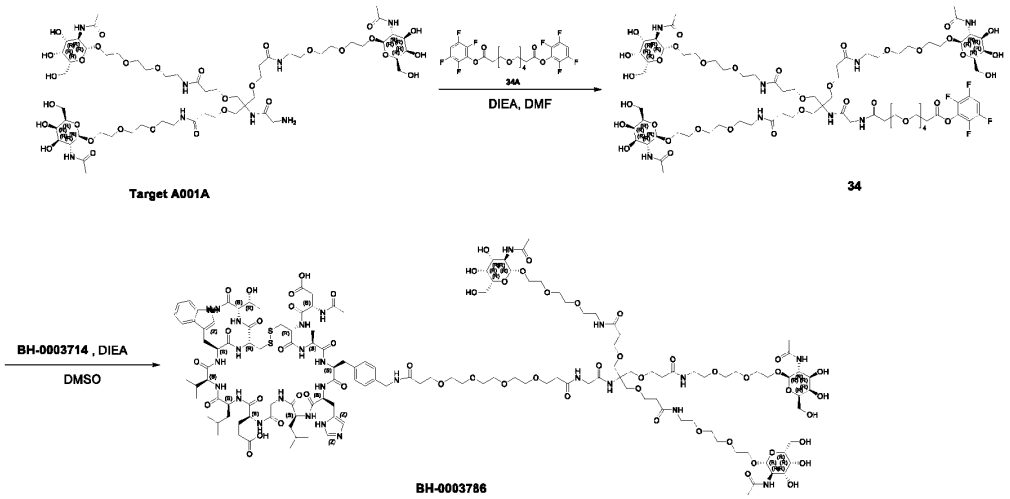
[0092] **BH-0003715** was synthesized using the same procedure as **BH-0003714** which was performed by following the procedure mentioned in **[0089]** – **[0091]**. 1.00 mmol resin to afford **BH-0003715** (495.2 mg, 95.8% purity, 31.2% yield) as a white solid. LCMS: RT = 1.25, MS calcd.: M_{av} = 1519.75, mass observed: $[M + H]^+$ = 1519.75, $[M + 2H]^{2+}$ = 760.5.



Molecular Weight: 1519.75

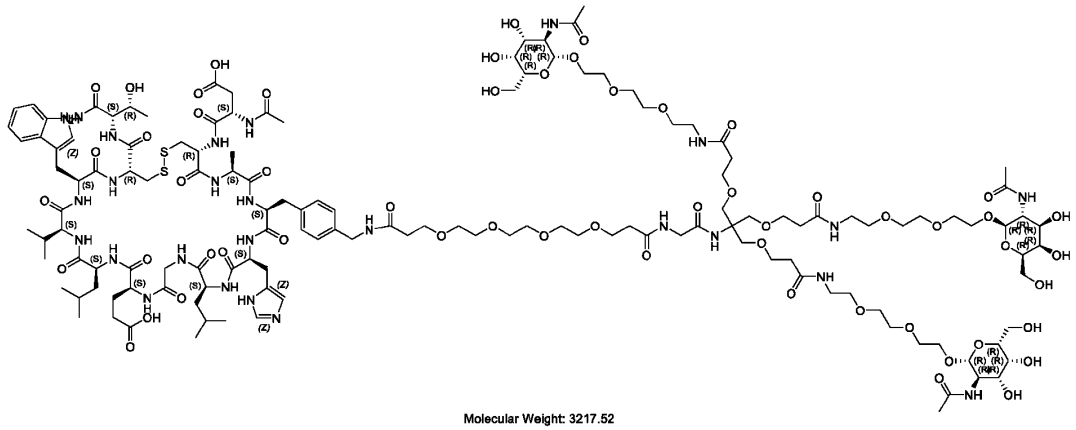
BH-0003715

[0093] ***Preparation of BH0003786***



[0094] **BH0003786** were synthesized using the same procedure as **BH0003746** which was performed by following the procedure mentioned in **[0072]** – **[0075]**.

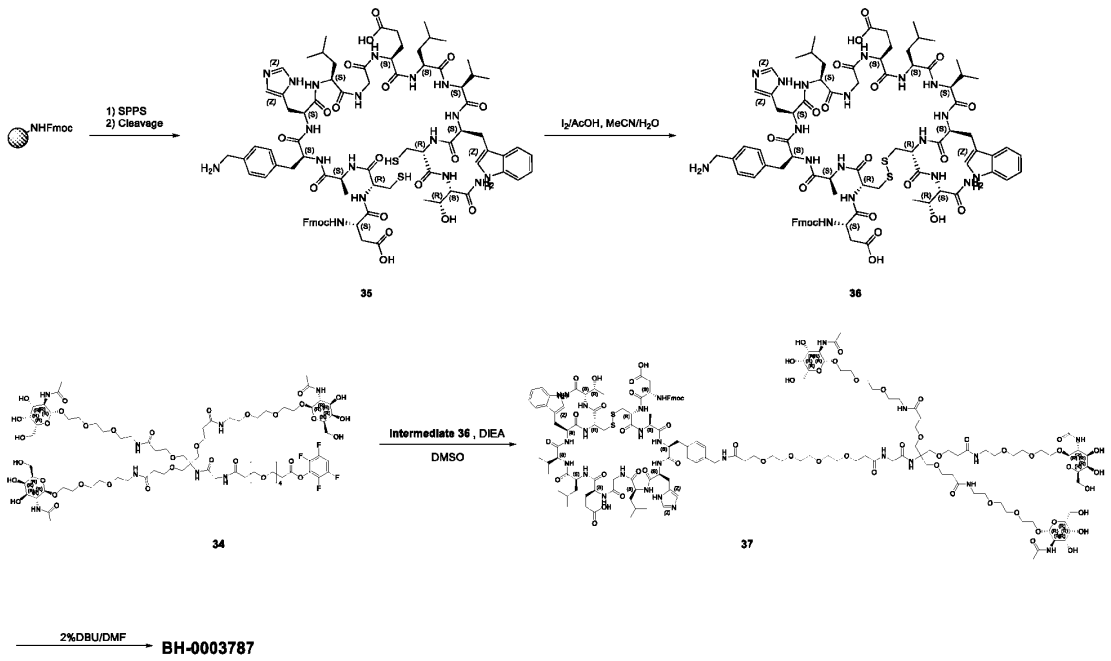
[0095] 54.0 mg of **Intermediate 34** afforded **BH-0003786** (28.3 mg, 96.7% purity, 28.7% yield) as a white solid. LCMS: RT = 1.31 min, MS calcd.: M_{av} = 3217.52, mass observed: $[M + 2H]^{2+}$ = 1609.5, $[M\text{-sugar} + 2H]^{2+}$ = 1508.0, $[M\text{- 2 x sugar } +2H]^{2+}$ = 1406.4, $[M\text{- 3 x sugar} + 2H]^{2+}$ = 1304.6, $[M + 3H]^{3+}$ = 1073.



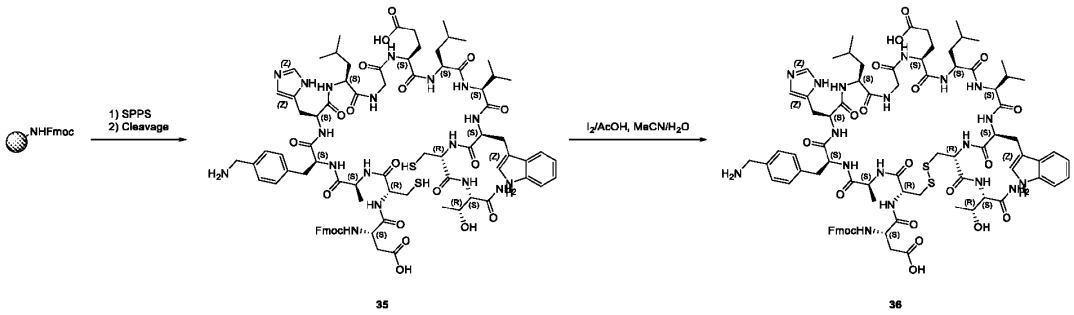
Molecular Weight: 3217.52

BH-0003786

EXAMPLE13. Procedure for Preparation of BH-0003787



5 **[0096] Preparation of Intermediate 36:**



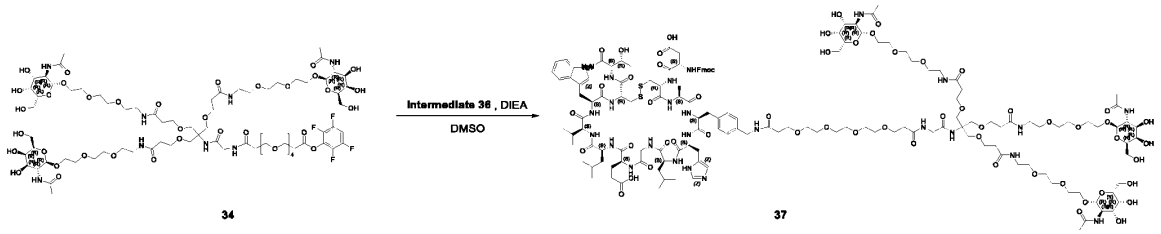
[0097] **Intermediate 35** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0048]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 6.

Table 6: The list of amino acids and the corresponding reagents used on SPPS.

Materials	Coupling reagents
Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-4-(Boc-aminomethyl)-*L*-phenylalanine (2.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

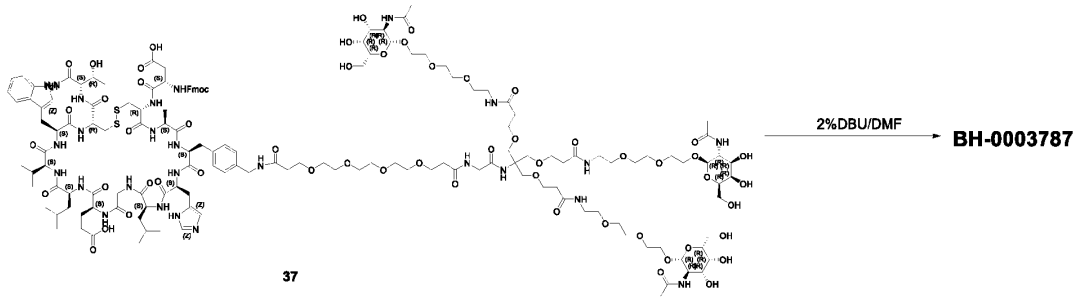
[0098] **Intermediate 36** was synthesized using the same procedure as **BH-0003714** which was performed by following the procedure mentioned in **[0086]** – **[0088]**. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 36** (156 mg, 90% purity, 15.7% yield) as a white solid.

[0099] **Preparation of Intermediate 37:**

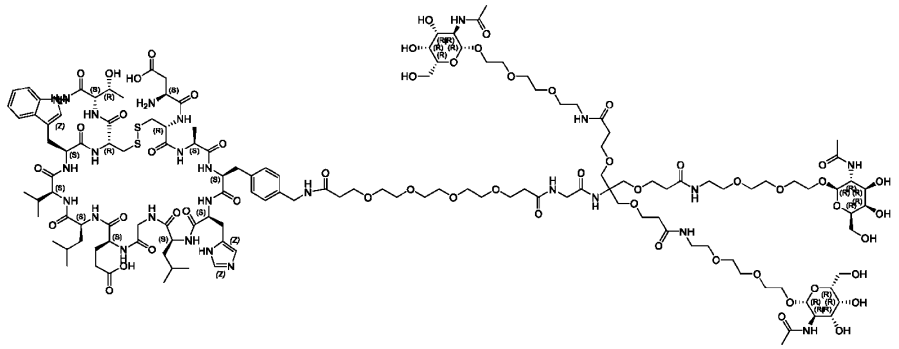


[0100] **Intermediate 37** was synthesized using the same procedure as **BH0003746** which was performed by following the procedure mentioned in **[0074]- [0075]**. 92.0 mg of **Intermediate 34** afforded **Intermediate 37** (80 mg, 51.27% yield) as a white solid.

[0101] **Preparation of BH-0003787:**

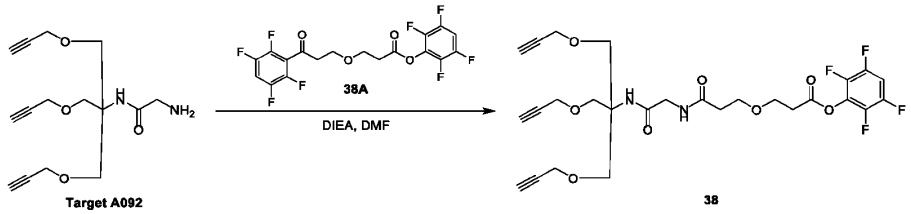


[0102] To a mixture of **Intermediate 37** (80 mg, 23.55 µmol, 1.00 equiv.) in 2%DBU/DMF (1.0 mL). The mixture was stirred at 25 °C for 15 min. After completion monitored by LC-MS, the mixture was then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afforded **BH-0003787** (35.7 mg, 97.1% purity, 35.5% yield) as a white solid. LCMS: RT = 1.24 min, MS calcd.: M_{av} = 3175.48, mass observed: $[M + 2H]^{2+}$ = 1588.6, $[M- sugar + 2H]^{2+}$ =1487.1, $[M- 2 x sugar +2H]^{2+}$ = 1385.4, $[M + 3H]^{3+}$ = 1059.1.



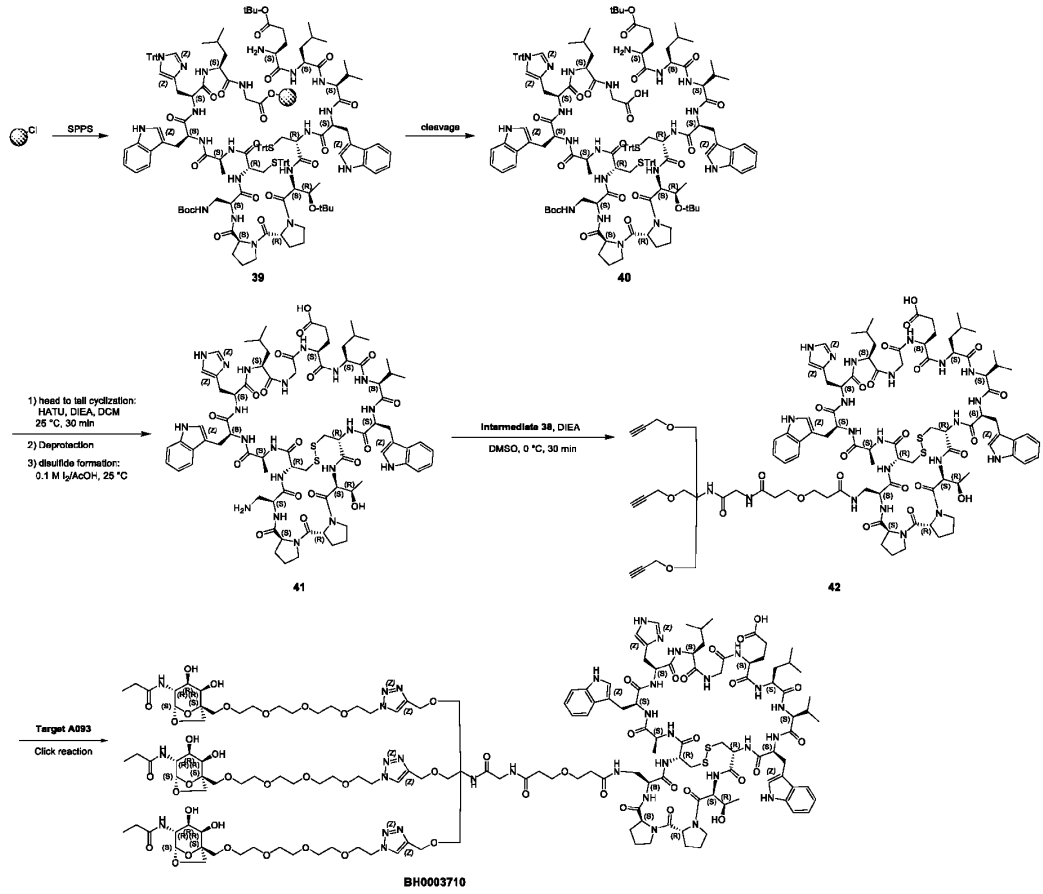
Molecular Weight: 3175.48
BH-0003787

EXAMPLE 14. Procedure for Preparation of BH0003710 and BH0003711.

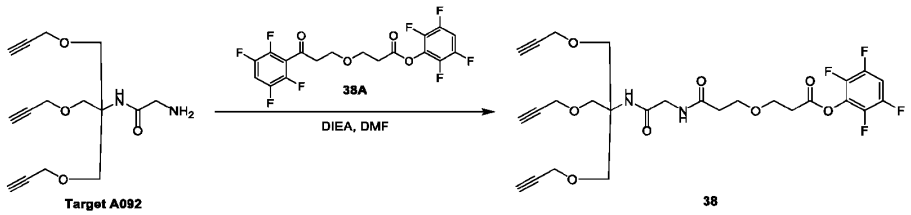


Target A092

38



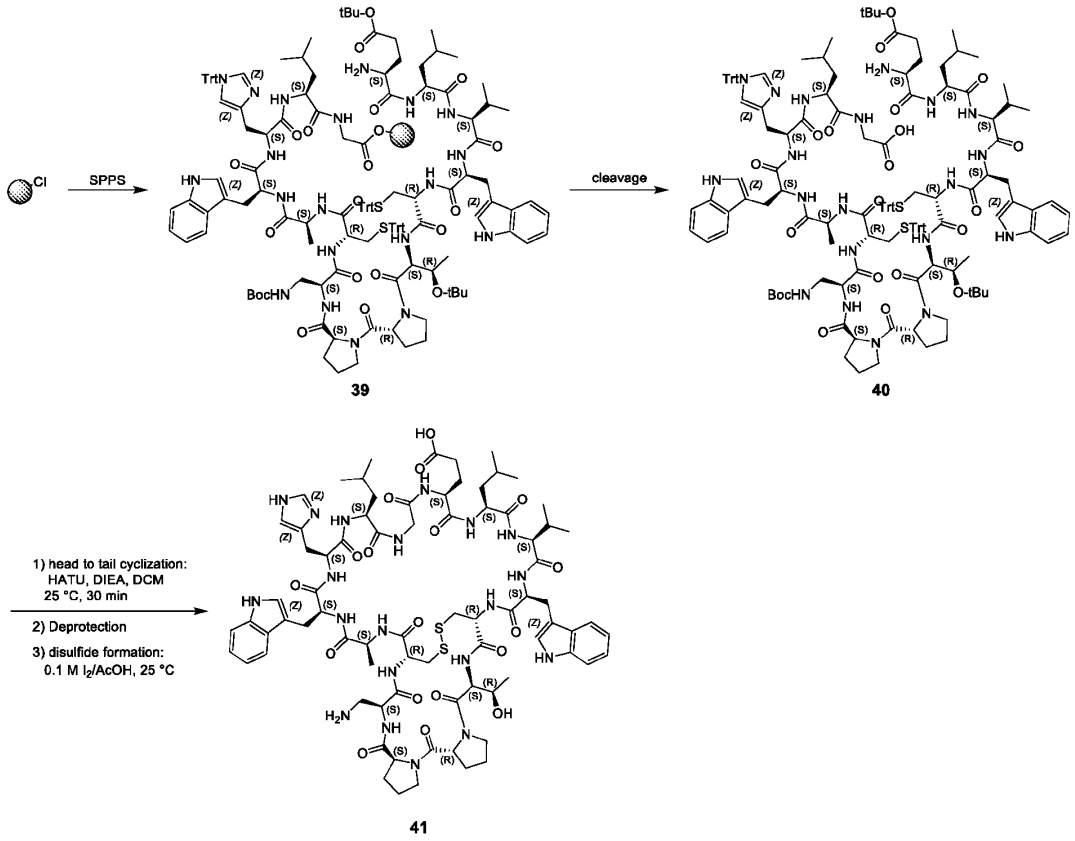
[0103] ***Preparation of Intermediate 38:***



[0104] To a mixture of **Intermediate 38A** (2.35 g, 5.13 mmol, 3.0 equiv.) in DMF (5 mL) was added a mixture of **Target A092** (0.50 g, 1.71 mmol, 1.0 equiv.) and DIEA (582.3 uL, 3.42 mmol, 2.0 equiv.) in DMF (2 mL), and the resulting reaction was stirred for 5 min at 0 °C. After completion monitored by LC-MS. The mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **Intermediate 38** (750.0 mg,

75.1% yield) as a white solid. LCMS: RT = 1.11 min, MS calcd.: M_{av} = 584.51, mass observed: $[M + H]^+$ = 585.28.

[0105] ***Preparation of Intermediate 41:***



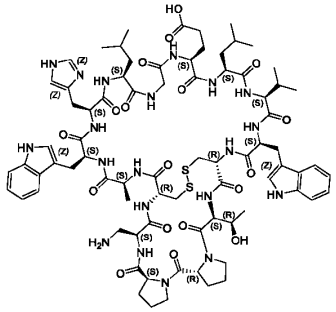
[0106] **Intermediate 39** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0069]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 7.

Table 7: The list of amino acids and the corresponding reagents used on SPPS.

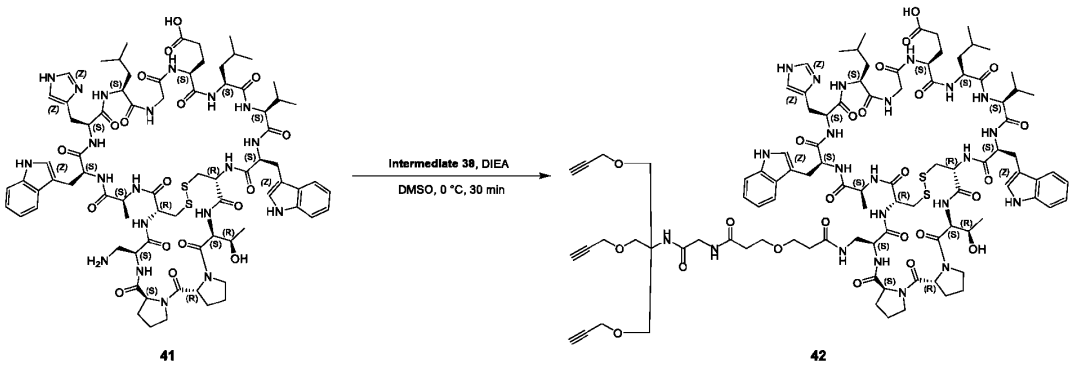
#	Materials	Coupling reagents
1	Fmoc-Gly-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

7	Fmoc-Dap(Boc)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-*D*-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Glu(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

[0107] **Intermediate 41** (peptide cleavage, cyclization, TFA deprotection, disulfide formation) was synthesized by following the procedure mentioned in section **[0070]**. 0.50 mmol resin afforded **Intermediate 41** (200.0 mg, 95.4% purity, 23.8% yield) was obtained as a white solid after lyophilization. LCMS: RT = 0.863 min, MS calcd.: M_{av} = 1677.94, mass observed: $[M + H]^+$ = 1678.7, $[M + 2H]^{2+}$ = 839.6.



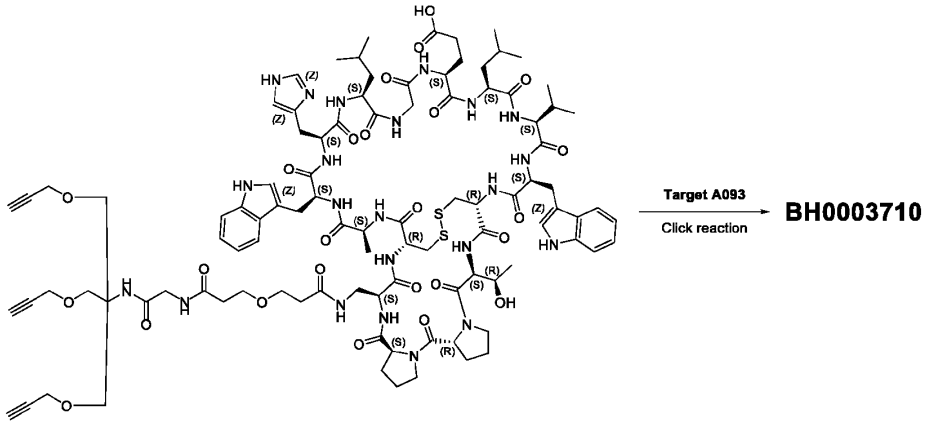
[0108] ***preparation of Intermediate 42:***



[0109] To a mixture of **Intermediate 41** (103.2 mg, 61.5 µmol, 1.00 equiv.) in DMSO (0.5 mL) was added a mixture of **Intermediate 38** (35.9 g, 61.5 µmol, 1.00 equiv.) and DIEA (20.9 uL, 123.0 µmol, 2.00 equiv.) in DMSO (0.2 mL), and the resulting reaction was stirred for 30 min at 0 °C. After completion

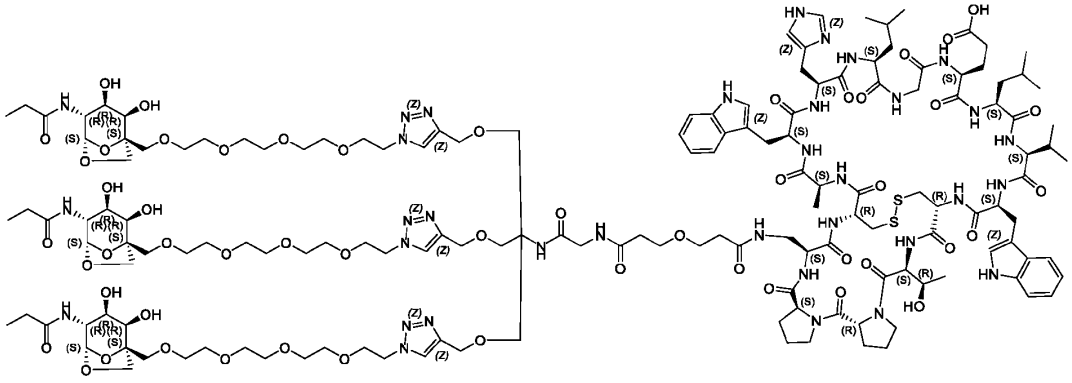
monitored by LC-MS, the mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **Intermediate 42** (44.7 mg, 34.7% yield) as a white solid. LCMS: RT = 1.76 min, MS calcd.: M_{av} = 2096.39, mass observed: $[M + 2H]^{2+}$ = 1048.96.

[0110] ***Preparation of BH0003710:***



42

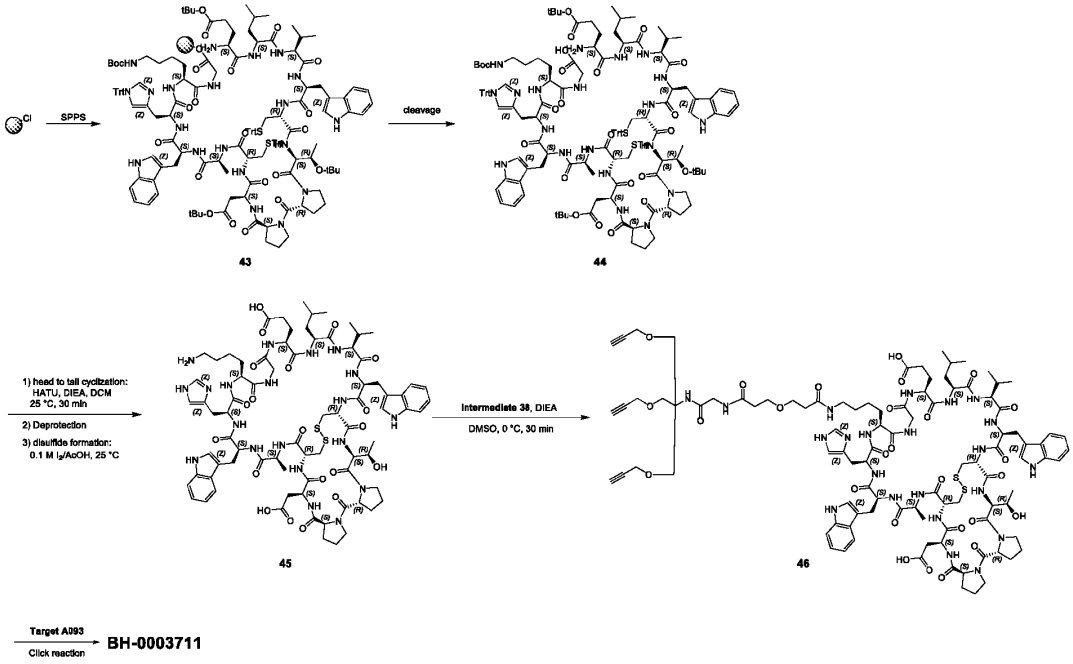
[0111] To a solution of **Intermediate 42** (45.0 mg, 21.5 μmol, 1.00 equiv.) and **Target A093** (30.8 mg, 68.7 μmol, 3.20 equiv.) in DMF (0.5 mL) was added $CuSO_4$ (10.2 mg, 64.5 μmol, 3.00 equiv.), Na ascorbate (51.0 mg, 258.0 μmol, 12.00 equiv.) and THPTA (27.9 mg, 64.5 μmol, 3.00 equiv.) under nitrogen atmosphere at 0 °C, and the resulting mixture was stirred for 1 h at 0 ºC. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **BH0003710** (22.1 mg, 96.7% purity, 28.9% yield) as a white solid. LCMS: RT = 1.437 min, MS calcd.: M_{av} = 3441.79, mass observed: $[M + 2H]^{2+}$ = 1721.80, $[M + 3H]^{3+}$ = 1148.20, $[M + 4H]^{4+}$ = 861.40.



Molecular Weight: 3441.79

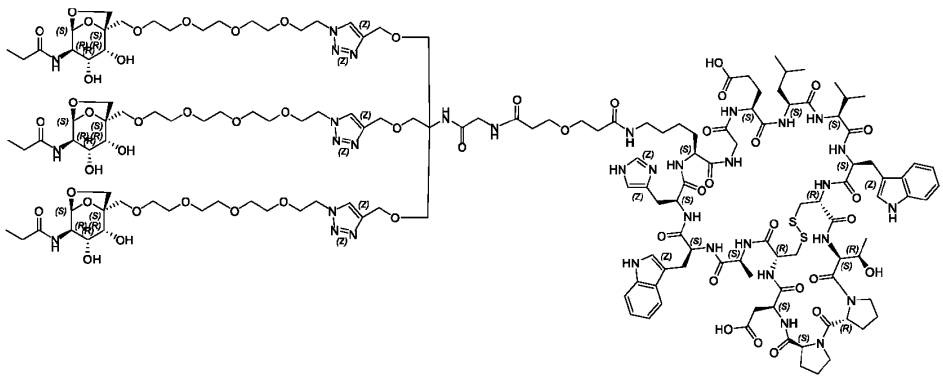
BH0003710

[0112] ***Preparation of BH0003711:***



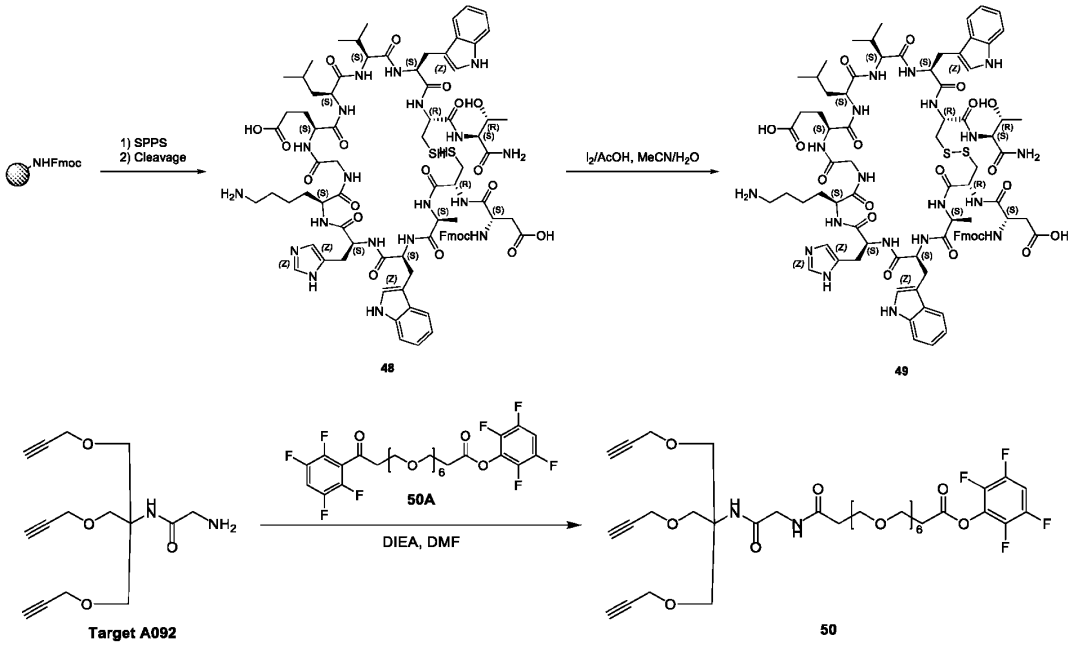
[0113] **BH-0003711** was synthesized using the same procedure as **BH0003710** which was performed by following the procedure mentioned in **[0103]** – **[0111]**.

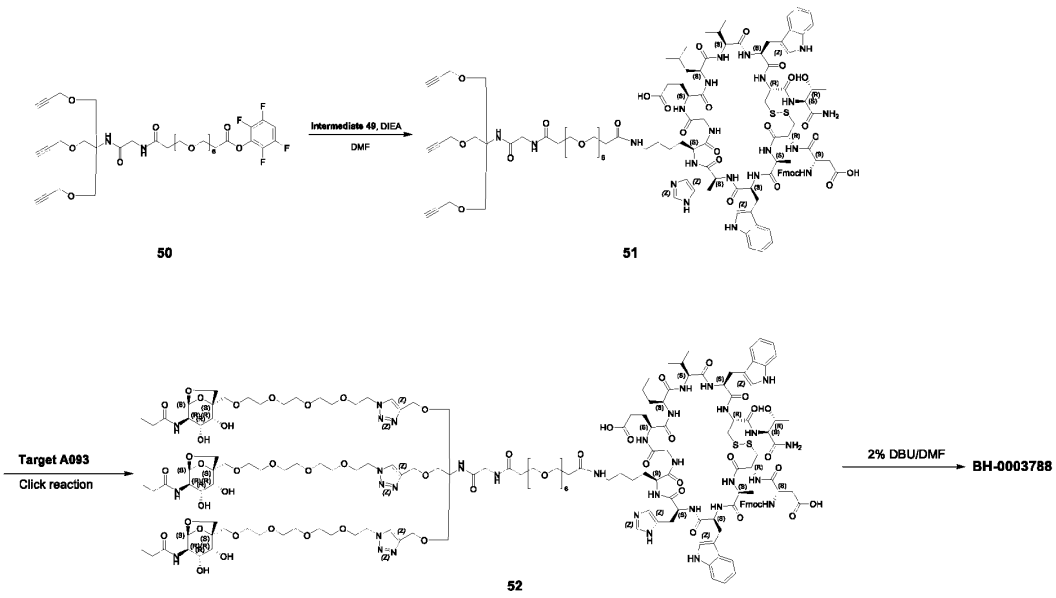
[0114] 16.8 mg of **Target A093** with **Intermediate 46** afforded **BH-0003711** (23.7 mg, 93.7% purity, 59.3% yield) as a white solid. LCMS: RT = 1.37 min, MS calcd.: M_{av} = 3485.80, mass observed: $[M + 2H]^{2+}$ = 1743.6, $[M + 3H]^{3+}$ = 1162.8, $[M + 4H]^{4+}$ =872.5.



Molecular Weight: 3485.80
BH-0003711

EXAMPLE15. Procedure for Preparation of BH-0003788 and BH-0003787.





[0115] ***Preparation of Intermediate 49:***

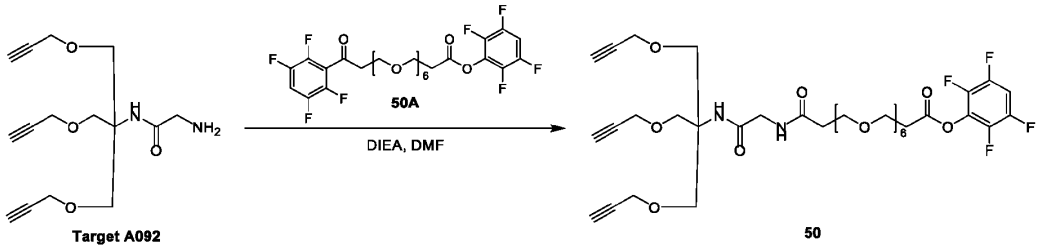
[0116] **Intermediate 48** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0048]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 8.

Table 8: The list of amino acids and the corresponding reagents used on SPPS.

Materials	Coupling reagents
Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Lys(Boc)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

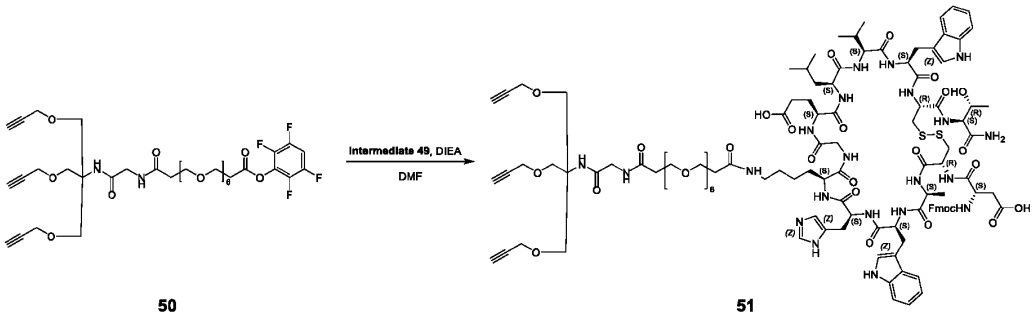
[0117] **Intermediate 49** was synthesized using the same procedure as **Intermediate 21** which was performed by following the procedure mentioned in **[0049]**. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H2O, B: MeCN), followed by lyophilization to afford **Intermediate 49** (162 mg, 90% purity, 16.5% yield) as a white solid.

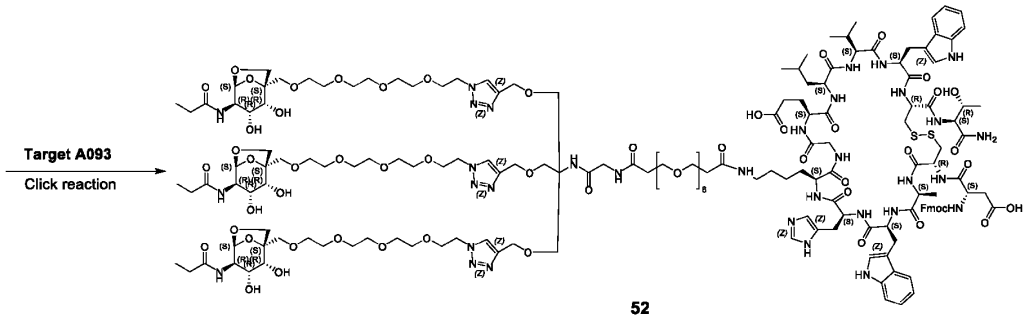
[0118] **Preparation of Intermediate 50:**



[0119] **Intermediate 50** was synthesized using the same procedure as **Intermediate 38** which was performed by following the procedure mentioned in **[0104].** The mixture was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **Intermediate 50** (380 mg, 75.1% yield) as colorless oil.

[0120] **Preparation of Intermediate 52:**

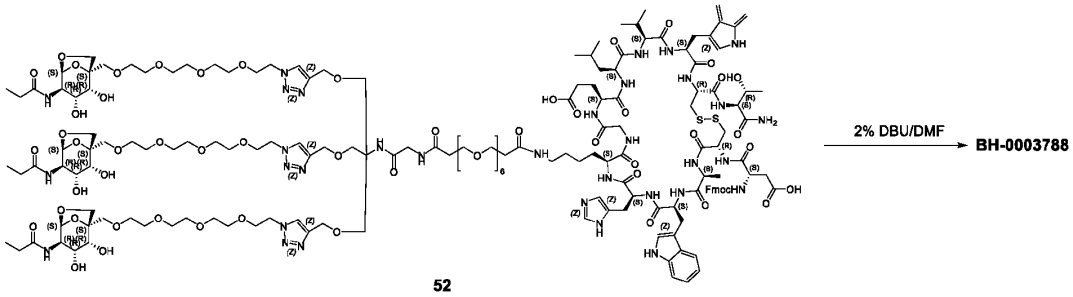




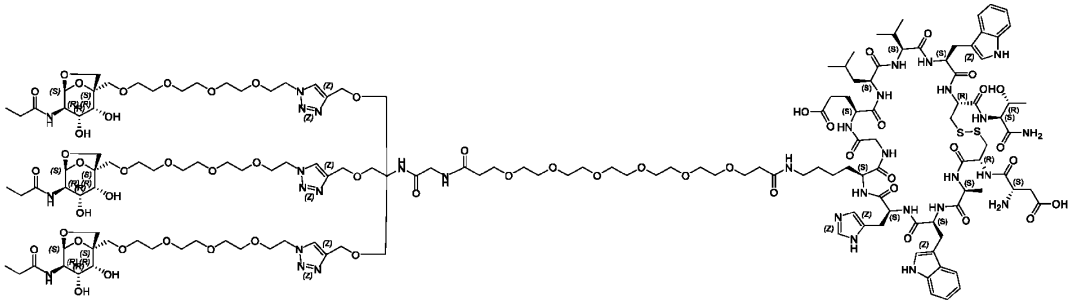
[0121] **Intermediate 52** was synthesized using the same procedure as **BH0003710** which was performed by following the procedure mentioned in **[0108]- [0111].** The reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **Intermediate 52** (36 mg, 38.89% yield).

[0122] ***Preparation of BH0003788:***

[0123] **BH0003788** was synthesized using the same procedure as **BH-0003787** which was performed by following the procedure mentioned in **[0101]- [0102].**



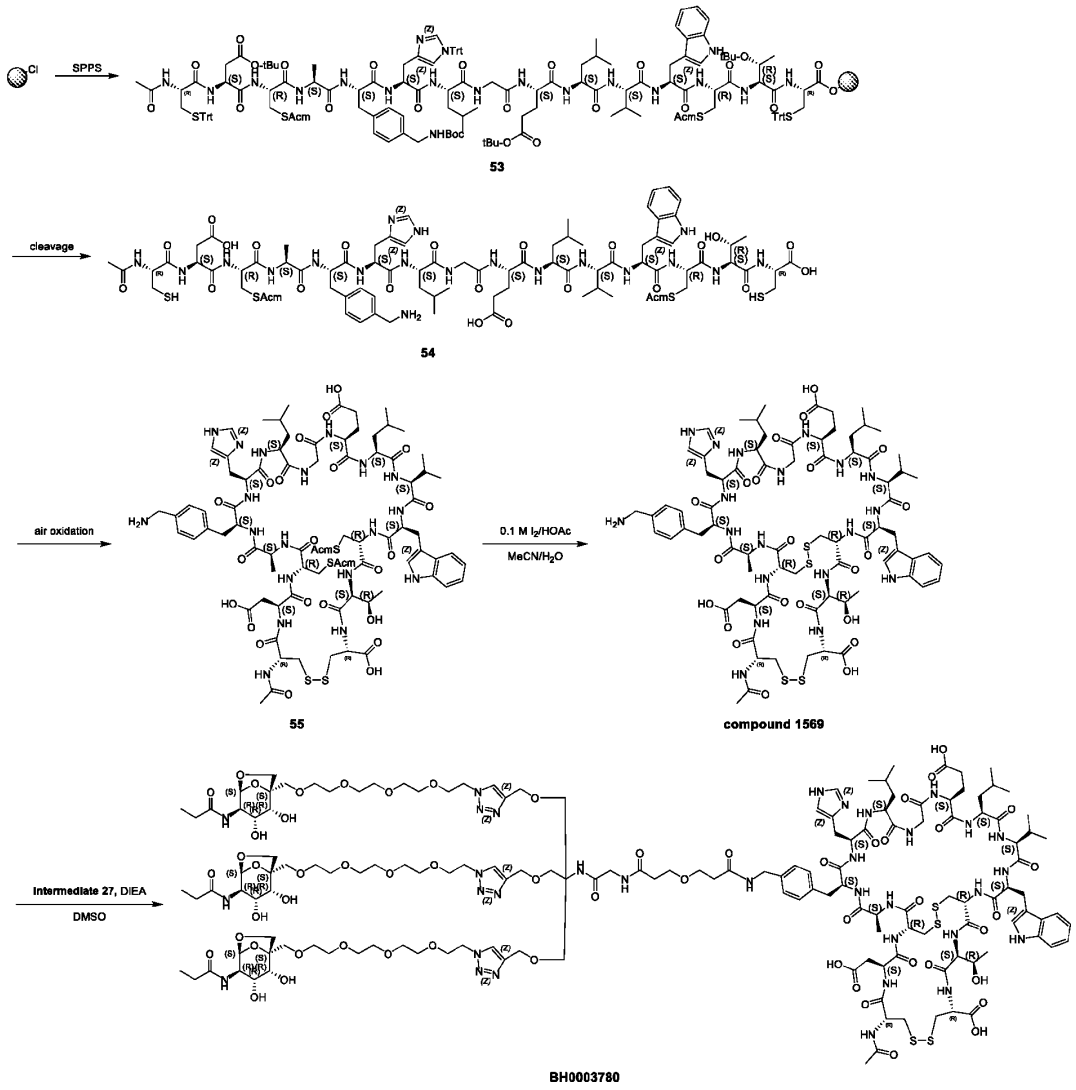
[0124] 38.89 mg of **Intermediate 52** afforded **BH0003788** (11.8 mg, 92.9% purity, 30.0% yield) as a white solid. LCMS: RT = 1.88 min, MS calcd.: M_{av} = 3528.86, mass observed: $[M + 2H]^{2+}$ = 1765.2, $[M + 3H]^{3+}$ = 1177.5, $[M + 4H]^{4+}$ = 883.1, $[M + 5H]^{5+}$ = 706.8.



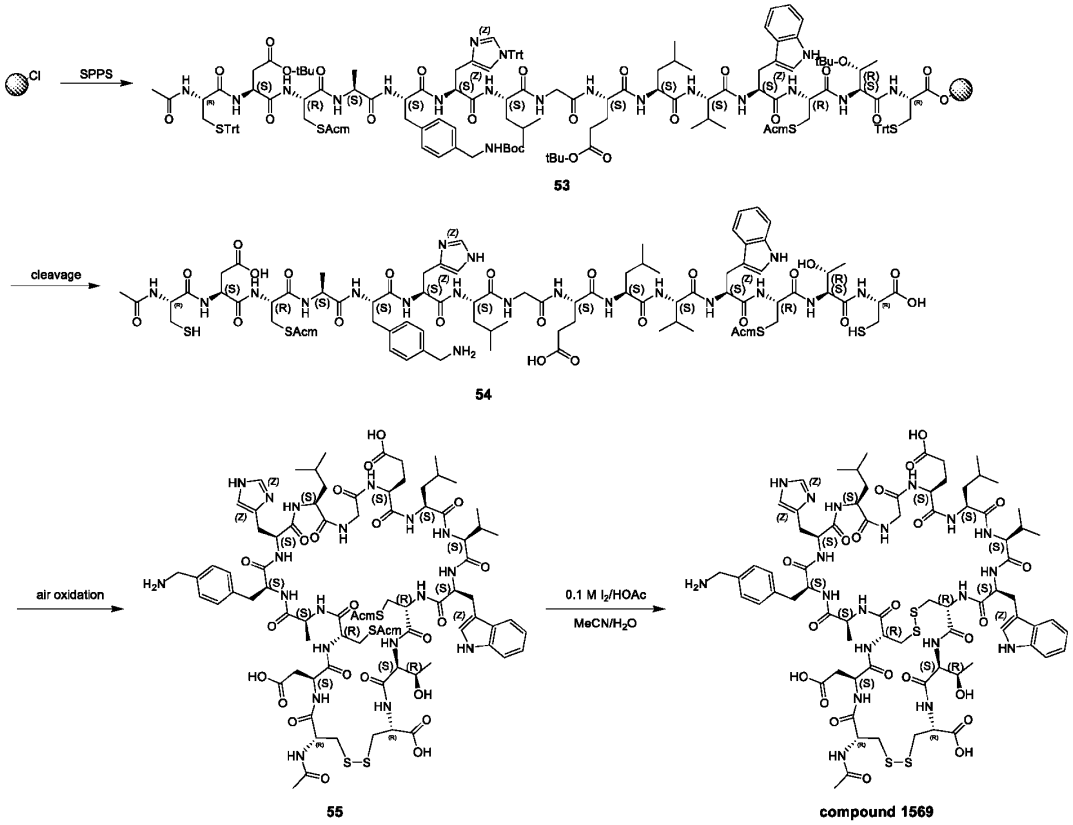
Molecular Weight: 3528.86

BH-0003788

EXAMPLE 16. Procedure for Preparation of BH0003780.



[0125] ***Preparation of Compound 1569:***



[0126] **Intermediate 53** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0059]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 9.

[0127] Acetylation: A solution of Ac_2O/NMM/DMF (2/1/17, v/v/v, 40 mL) was added to the resin, the mixture was bubbled with N_2 for 20 min. The acetylation reaction was monitored by ninhydrin test. The resin was then washed with DMF (20 mL) * 5, MeOH (20 mL) * 3, then dried under reduced pressure to afford **Intermediate 53** (peptide resin, 0.50 mmol).

Table 9: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Cys(Trt)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

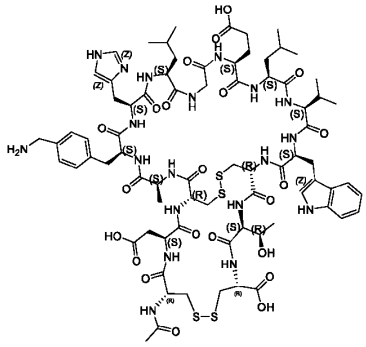
6	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-4-(Boc-aminomethyl)-L-phenylalanine (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
16	Acetylation	Ac_2O/NMM/DMF (2/1/17, v/v/v)

[0128] Peptide cleavage and double disulfide formation:

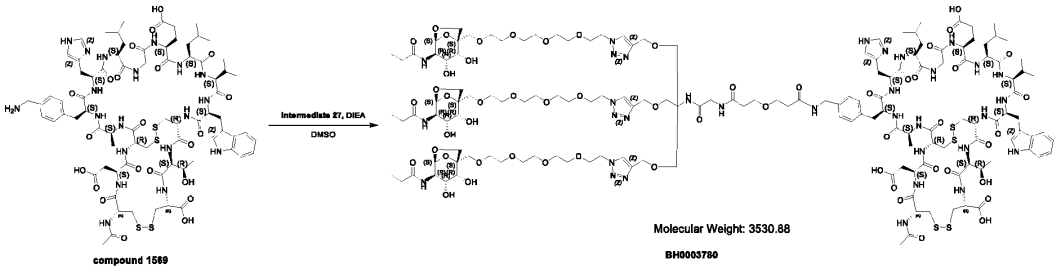
1) Cleavage: A solution of TFA/TIS/H_2O (95/2.5/2.5, v/v/v, 40 mL) was added to the flask containing the side-chain protected resin-bound peptide (**Intermediate 53**), and the resulting mixture was stirred for 2 h at 25 °C. After filtration, the filtrate was collected and precipitated with cold isopropyl ether (200 mL), then filtered off, and the solid was washed with isopropyl ether (100 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 54** (0.50 mmol, crude) as a white solid.

2) First disulfide formation: To a mixture of **Intermediate 54** (0.50 mmol, crude) in MeCN/H_2O (4/6, v/v, 500 mL) was added $NaHCO_3$ to pH = 8 at 25 °C. Then the mixture was open to the air and stirred at 25 °C for 24 h. After filtration, the mixture was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) to afford **Intermediate 55** (355.4 mg, 20.1% yield) as a white solid.

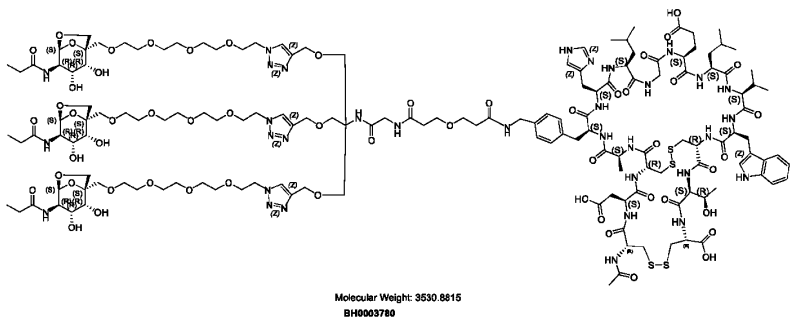
3) Second disulfide formation: To a mixture of **Intermediate 55** (355.4 mg, 0.20 mmol) in MeCN/H_2O (4/6, v/v, 200 mL) was added 1 M aq. HCl (1.5 mL), AcOH (3.0 mL) to pH = 1. The mixture was added 0.1 M I_2/AcOH dropwise until the yellow color persisted, then the mixture was stirred at 25 °C for 5 h. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified directly by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Compound 1569** (245.4 mg, 91.7% purity, 69.0% yield) as a white solid. LCMS: RT = 1.294 min, MS calcd.: M_{av} = 1767.04, mass observed: $[M + H]^+$ = 1767.7, $[M + 2H]^{2+}$ = 884.6.



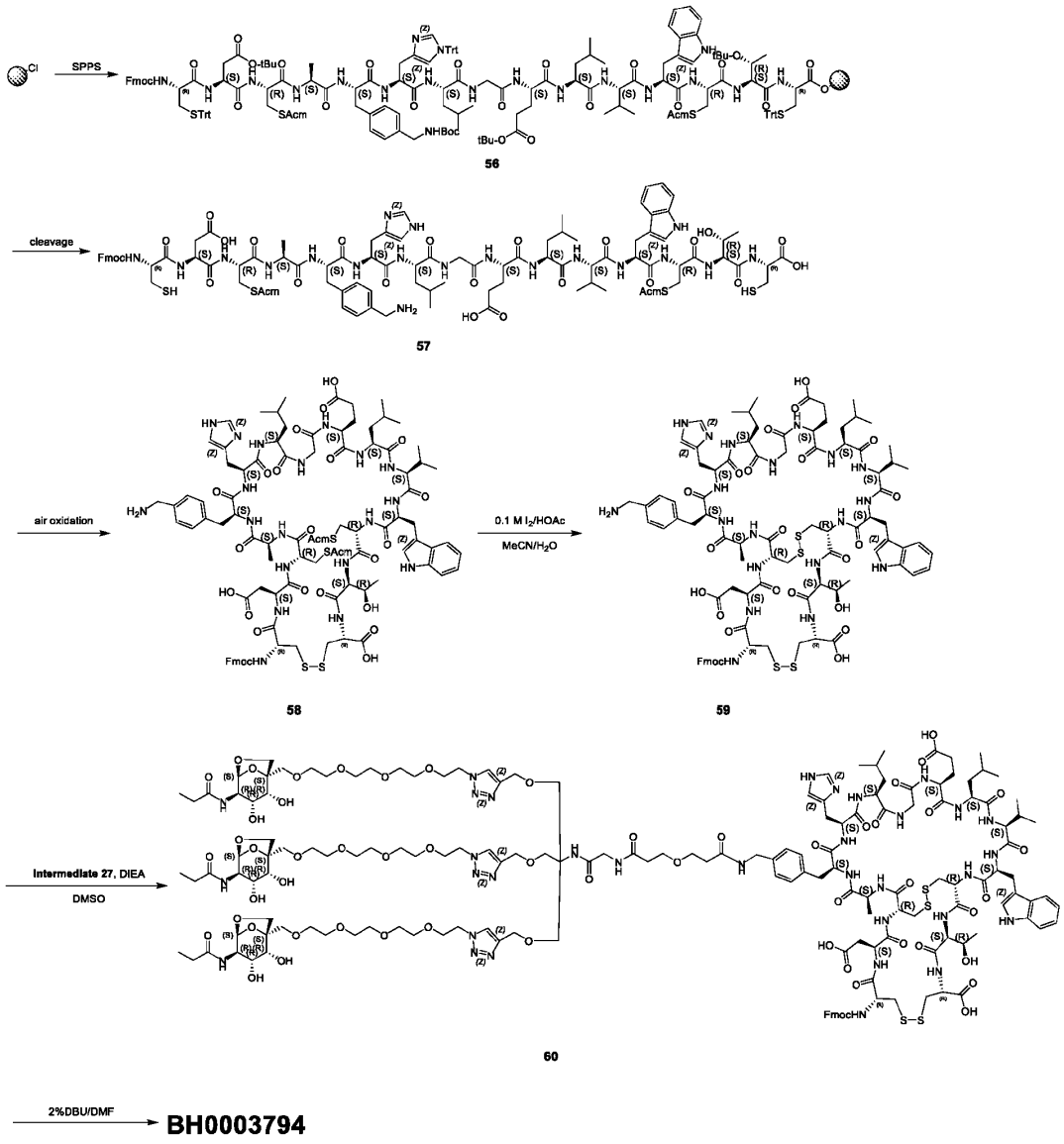
[0129] ***Preparation of BH0003780***



[0130] To a mixture of **Compound 1569** (98.4 mg, 51.0 μmol, 1.00 equiv.) and **Intermediate 27** (90.1 mg, 51.0 μmol, 1.00 equiv.) in DMSO (0.5 mL) was added DIEA (87.0 μL, 510 μmol, 10.0 equiv.) at 25 °C. The mixture was stirred at 25 °C for 2 h. After completion monitored by LC-MS, the mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **BH0003780** (36.2 mg, 96.9% purity, 20.1% yield) as a white solid. LCMS: RT = 1.346 min, MS calcd.: M_{av} = 3530.88, mass observed: $[M + 2H]^{2+}$ = 1766.1, $[M + 3H]^{3+}$ = 1177.7, $[M + 4H]^{4+}$ = 883.7.



EXAMPLE 17. Procedure for Preparation of BH0003794 and BH-0003793.



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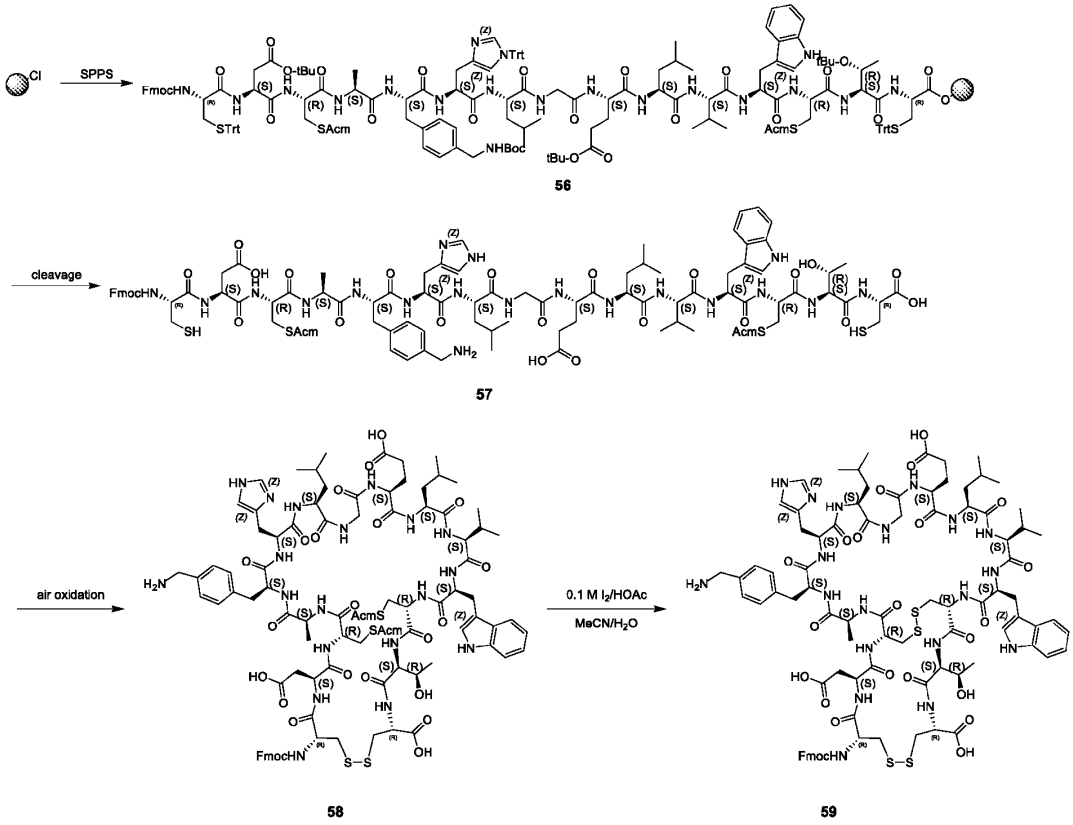
[0131] *Preparation of* Intermediate *59:*



[0132] **Intermediate 56** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0059]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 10, Number # 1-15.

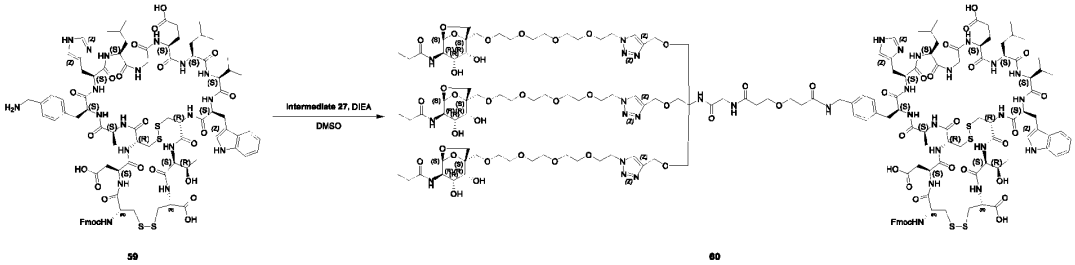
Table 10: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Cys(Trt)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

11	Fmoc-4-(Boc-aminomethyl)-L-phenylalanine (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

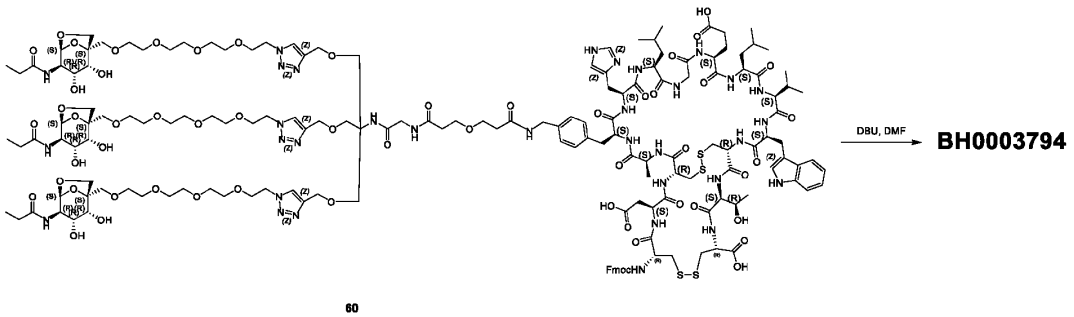
[0133] **Intermediate 59** were synthesized using the same procedure as **Compound 1569** which was performed by following the procedure mentioned in **[0128]**.

[0134] **Preparation of Intermediate 60:**

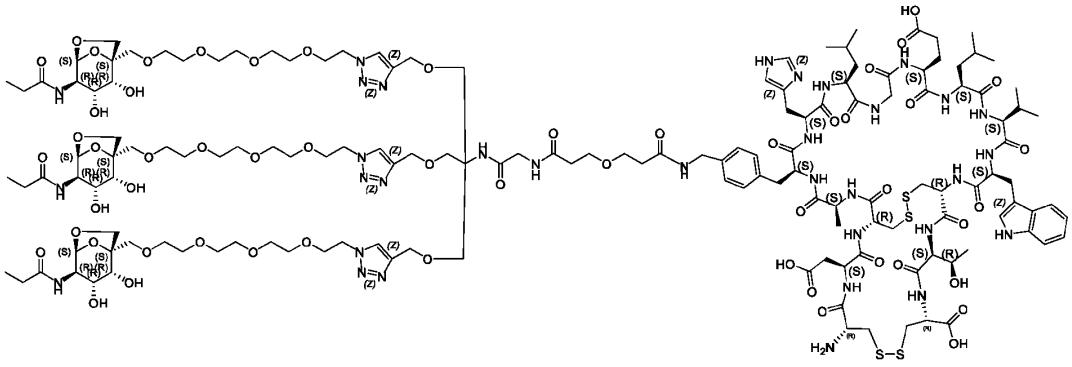


[0135] **Intermediate 60** was synthesized using the same procedure as **BH0003780** which was performed by following the procedure mentioned in **[0129]- [0130]**.

[0136] ***Preparation of*** **BH-0003794*:***



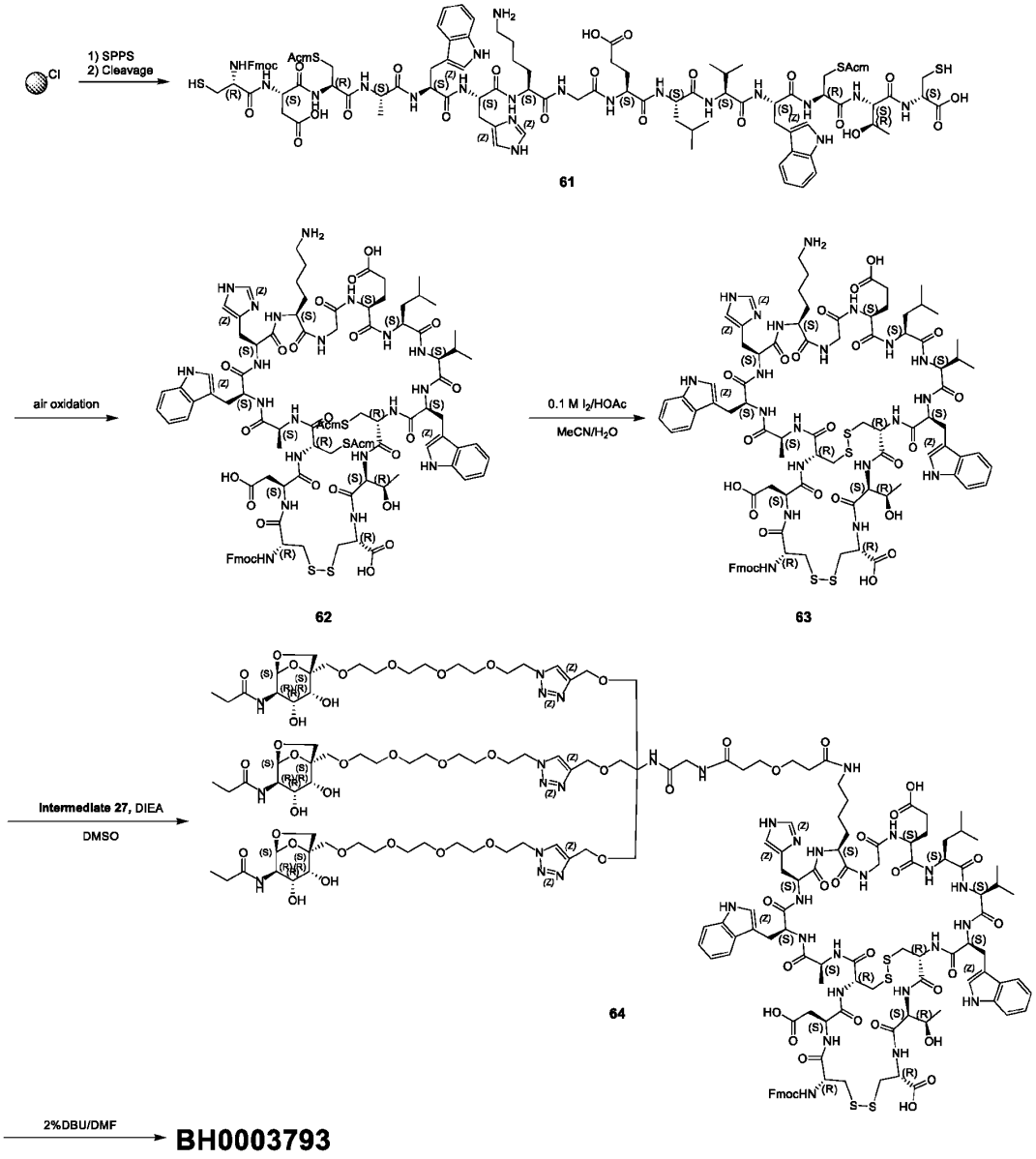
[0137] To a mixture of **Intermediate 60** (29 mg, 7.76 µmol, 1.00 equiv.) in 2%DBU/DMF (0.5 mL). The mixture was stirred at 25 °C for 15 min. After completion monitored by LC-MS, the mixture was then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **BH0003794** (16.2 mg, 97.0% purity, 58.0% yield) as a white solid. LCMS: RT = 1.32 min, MS calcd.: M_{av} = 3488.84, mass observed: $[M + 2H]^{2+}$ = 1745.1, $[M + 3H]^{3+}$ = 1164.1, $[M + 4H]^{4+}$ = 873.2, $[M + 5H]^{5+}$ = 698.7.



Molecular Weight: 3488.84

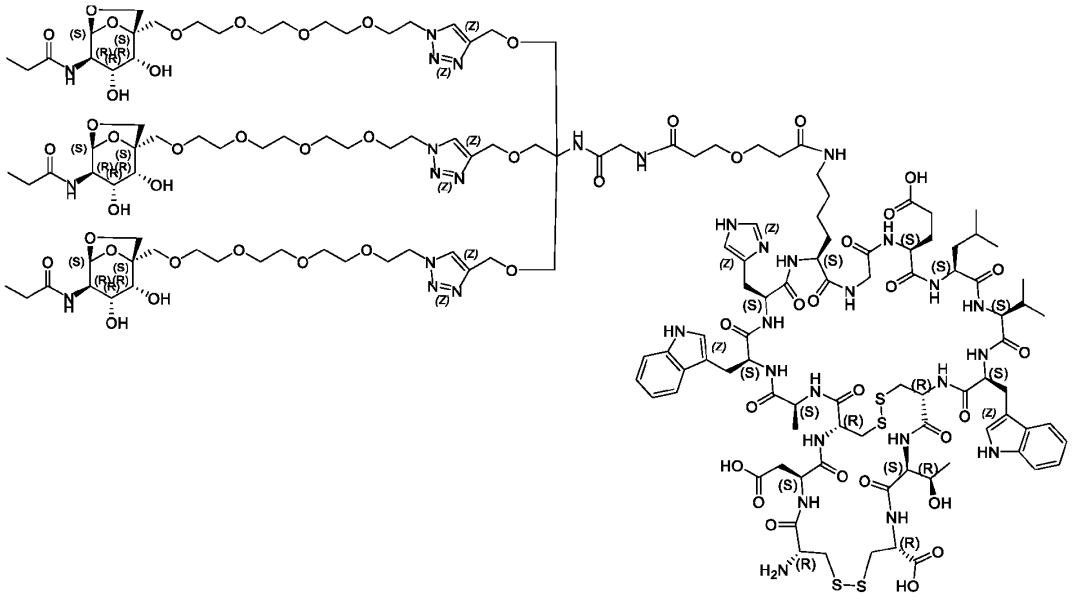
BH-0003794

[0138] ***Preparation of BH-0003793:***



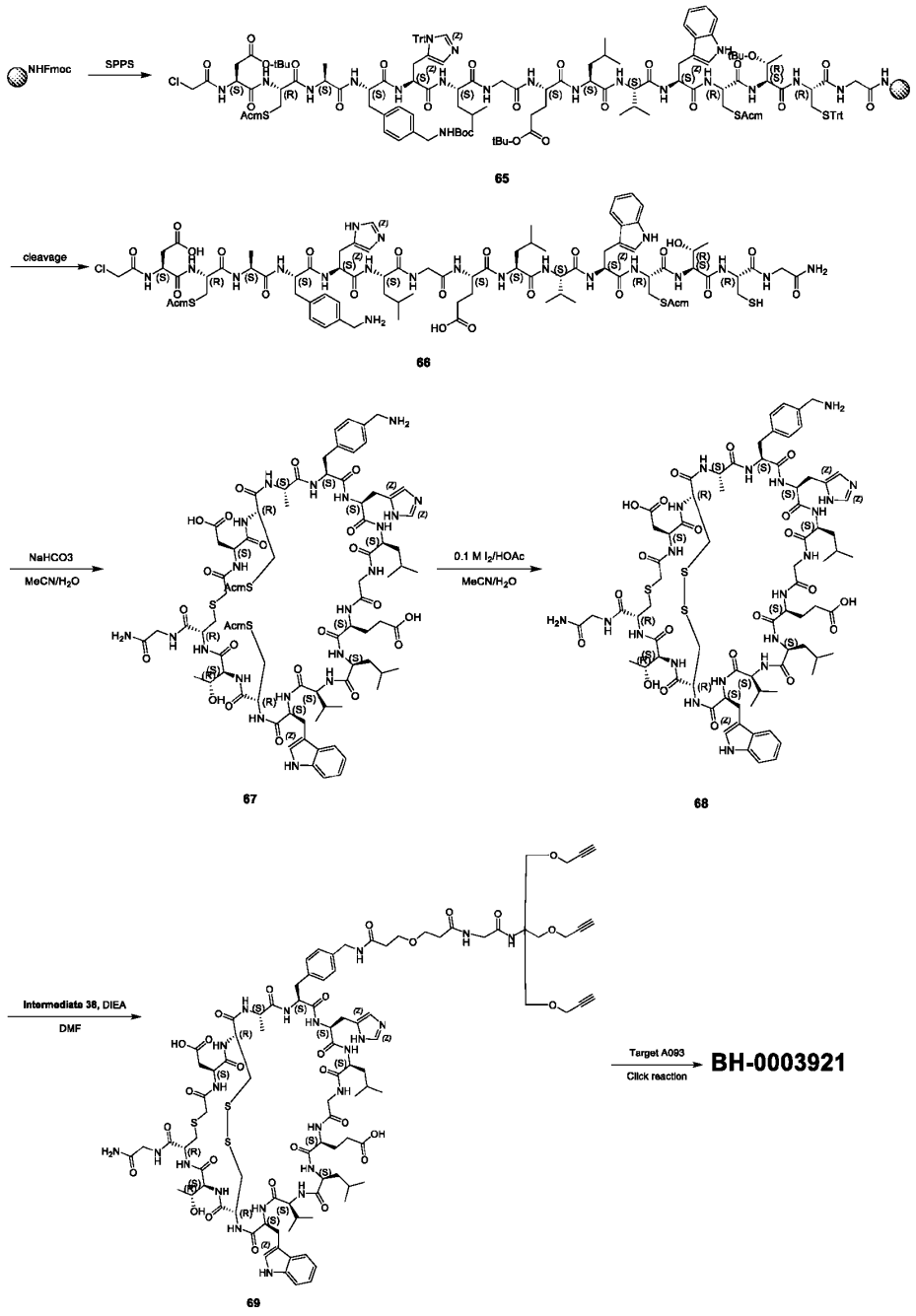
[0139] **BH-0003793** was synthesized using the same procedure as **BH0003794** which was performed by following the procedure mentioned in **[0131]** – **[0137]**.

[0140] **Intermediate 64** afforded **BH-0003793** (13.4 mg, 97.3% purity, 47.8% yield) as a white solid. LCMS: RT = 1.32 min, MS calcd.: M_{av} = 3513.85, mass observed: $[M + 2H]^{2+}$ = 1757.7, $[M + 3H]^{3+}$ = 1172.3, $[M + 4H]^{4+}$ = 879.4, $[M + 5H]^{5+}$ = 703.6.

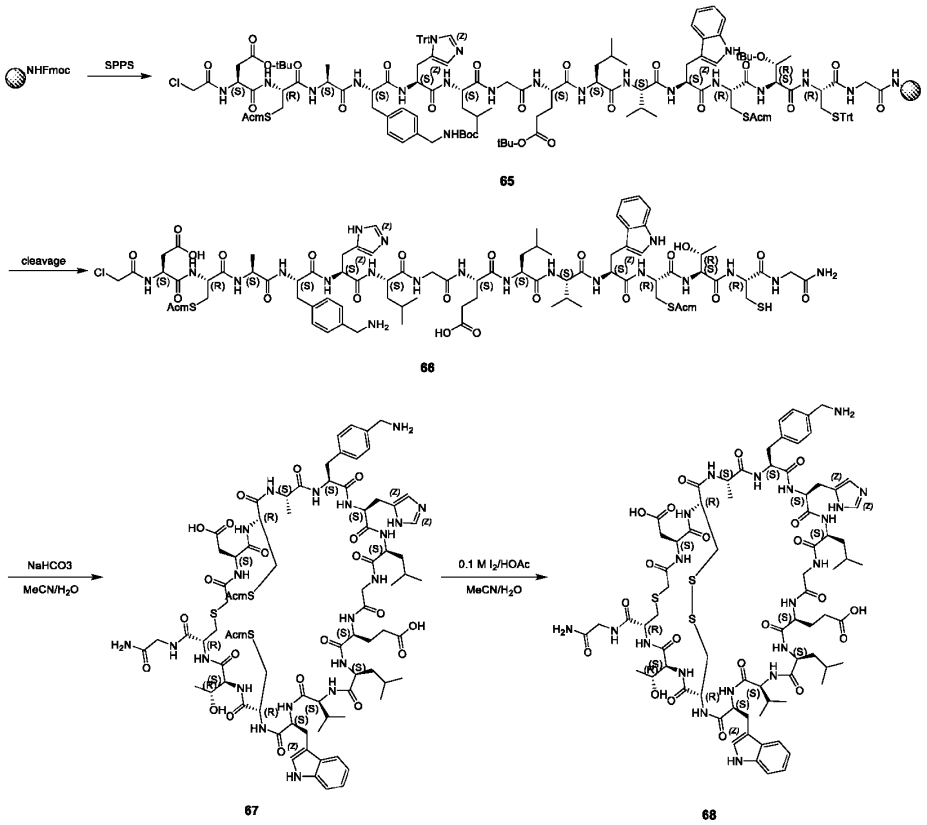


Molecular Weight: 3513.85
BH-0003793

EXAMPLE 18. Procedure for Preparation of BH-0003921, BH-0001685, BH-0003783 and BH-0003785.



[0141] ***Preparation of Intermediate 68:***



[0142] **Intermediate 65** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0048]**. SPPS (0.30 mmol loading resin) was performed with amino acids elongation shown in Table 11, Number # 1-15.

Table 11: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Gly-OH (1.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

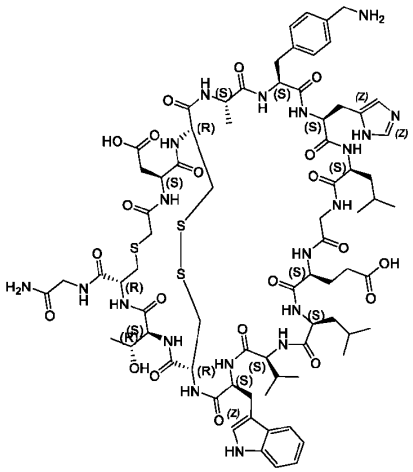
10	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-4-(Boc-aminomethyl)-L-phenylalanine (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	2,5-dioxopyrrolidin-1-yl 2-chloroacetate (3.00 equiv.)	DIEA (6.00 equiv.)

[0143] **Peptide cleavage and cyclization:**

1) Cleavage: A solution of TFA/TIS/H2O (95/2.5/2.5, v/v/v, 40 mL) was added to the flask containing the side-chain protected resin-bound peptide (Intermediate 50), and the resulting mixture was stirred for 2 h at 25 oC. After filtration, the filtrate was collected and precipitated with cold isopropyl ether (200 mL), then filtered off, and the solid was washed with isopropyl ether (100 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford Intermediate 51 (0.30 mmol, crude) as a white solid.

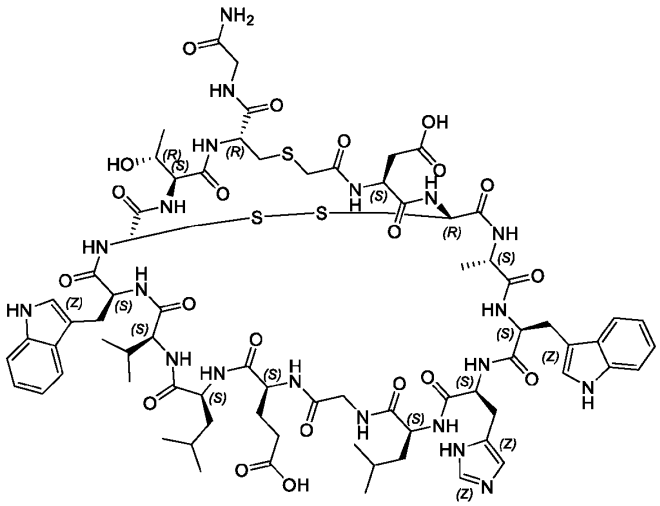
2) Thioether ring formation: To a mixture of **Intermediate 66** (0.30 mmol, crude) in MeCN/H_2O (4/6, v/v, 300 mL) was added $NaHCO_3$ to pH = 8 at 25 °C. Then the mixture was stirred at 25 °C for 24 h under N_2 atmosphere. After filtration, the mixture was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) to afford **Intermediate 67** (240 mg, 90 purity, 38.6% yield) as a white solid.

3) Disulfide formation: To a mixture of **Intermediate 67** (240 mg, 0.13 mmol) in MeCN/H_2O (4/6, v/v, 130 mL) was added 1 M aq. HCl (1.5 mL), AcOH (3.0 mL) to pH = 1. The mixture was added 0.1 M I_2/AcOH dropwise until the yellow color persisted, then the mixture was stirred at 25 °C for 5 h. After filtration, the filtrate was purified directly by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 68** (173 mg, 95% purity, 76.5% yield) as a white solid. LCMS: RT = 0.82 min, MS calcd.: M_{av} = 1719.91, mass observed: $[M + 2H]^{2+}$ = 860.



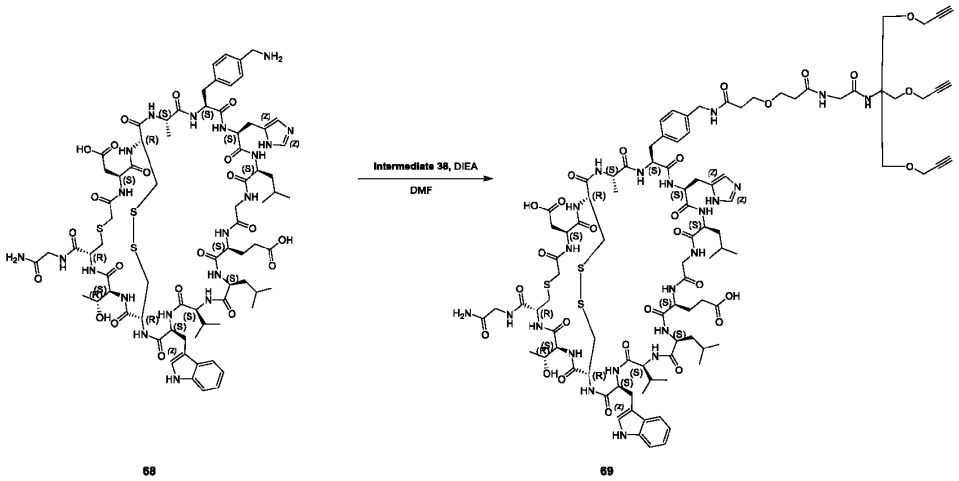
Molecular Weight: 1719.97
Intermediate 68

[0144] **BH-0001685** was synthesized using the same procedure as **Intermediate 68** which was performed by following the procedure mentioned in **[0141]** – **[0143]**. 0.3 mmol resin afforded **BH-0001685** (8.6 mg, 91.1% purity, 1.51% yield) as a white solid. LCMS: RT = 1.41 min, MS calcd.: M_{av} = 1729.96, mass observed: $[M + H]^+$ = 1729.9, $[M + 2H]^{2+}$ = 865.6.



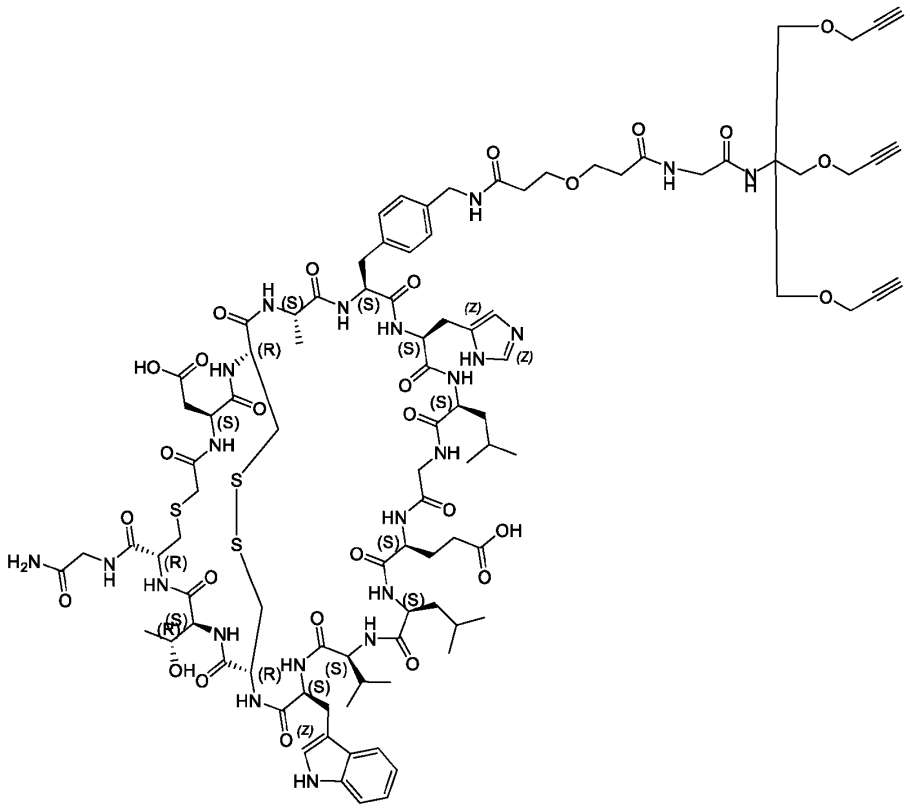
Molecular Weight: 1729.96
BH-0001685

[0145] ***Preparation of Intermediate 69:***



68 69

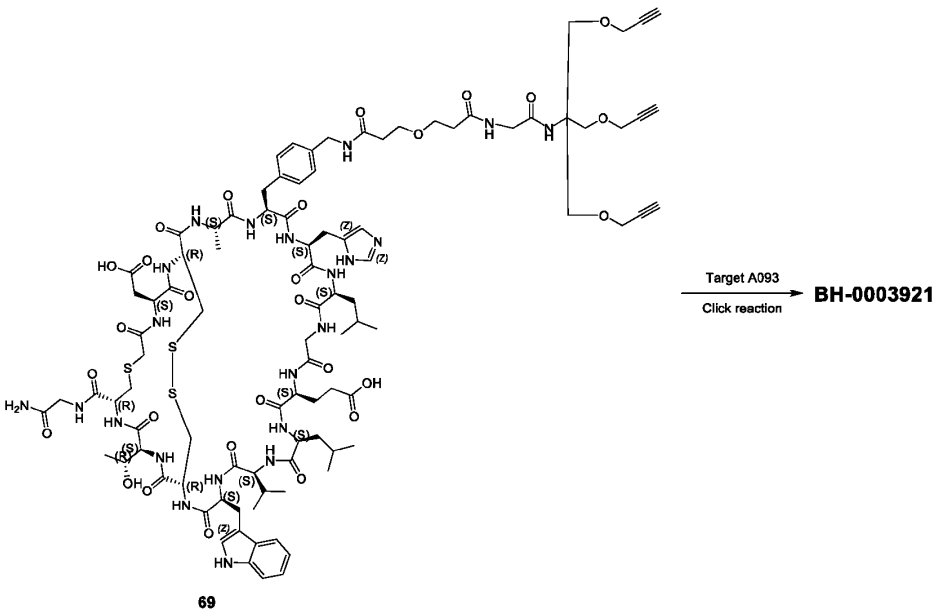
[0146] To a mixture of **Intermediate 68** (173 mg, 100.0 µmol, 1.00 equiv.) and **Intermediate 38** (59 mg, 100.0 µmol, 1.00 equiv.) in DMF (0.5 mL) was added DIEA (70.0 µL, 402 µmol, 4.00 equiv.) at 25 °C. The mixture was stirred at 25 °C for 0.5 h. After completion monitored by LC-MS, the mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **Intermediate 69** (95 mg, 95% purity, 44.1% yield) as a white solid. LCMS: RT = 0.96 min, MS calcd.: M_{av} = 2138.42, mass observed: $[M + 2H]^{2+}$ = 1069.7, $[M + 3H]^{3+}$ = 713.9.



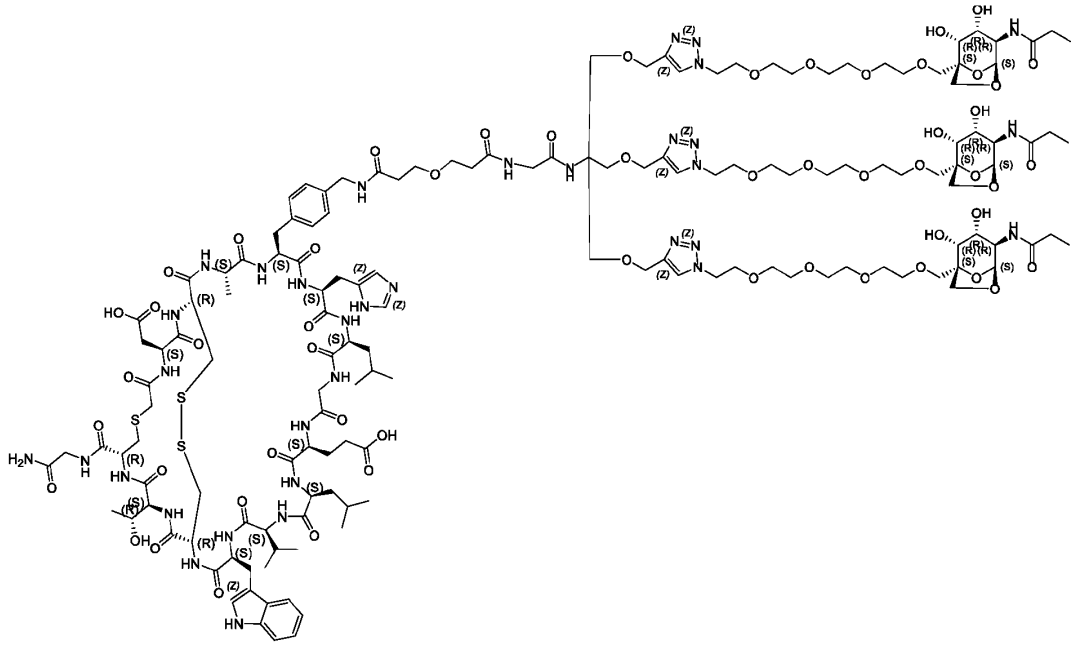
Molecular Weight: 2138.42

Intermediate 69

[0147] ***Preparation of BH-0003921*:**



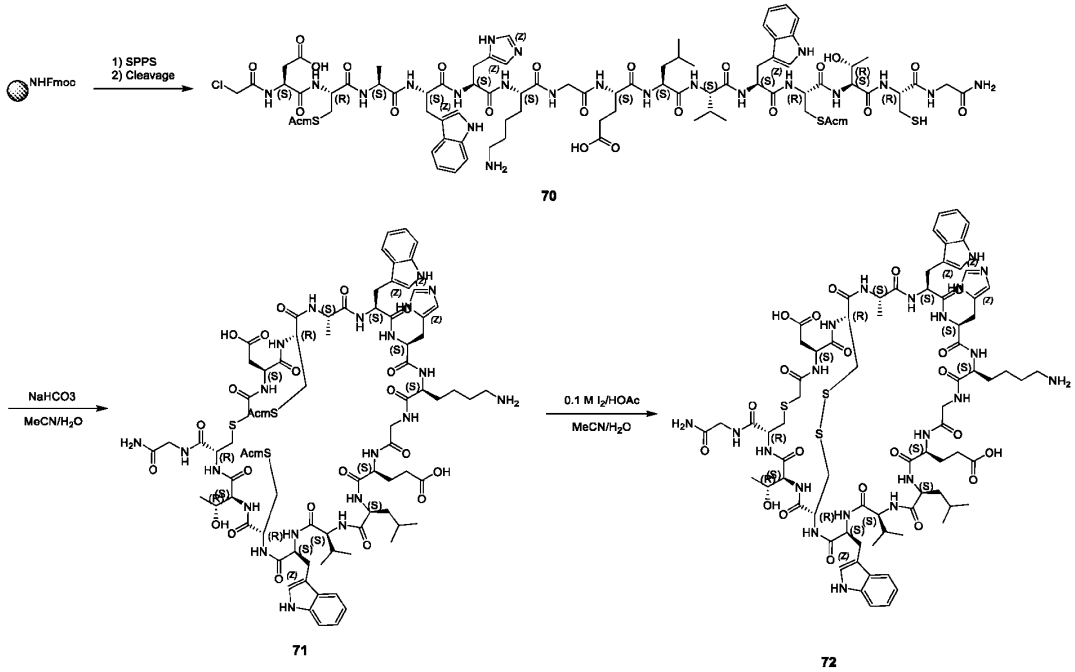
[0148] To a mixture of **Intermediate 69** (30.0 mg, 14.3 μmol, 1.00 equiv.) and **Target A093** (25.2 mg, 56.1 μmol, 4.00 equiv.) in DMF (0.5 mL) was added $CuSO_4.5H_2O$ (0.4 M, 105.2 μL, 3.00 equiv.) and sodium ascorbate (0.5 M, 252.5 μL, 9.00 equiv.) and THPTA (18.6 mg, 42.1 μmol, 3.00 equiv.). The resulting reaction was degassed and purged with N_2 for three times. Then the mixture was stirred at 25 °C for 2 h under N_2 atmosphere. LC-MS showed **Intermediate 69** was consumed completely, one main peak was shown on LC-MS and desired compound was detected. The resulting reaction mixture was purified by prep-HPLC (A: 0.075% HOAc in H_2O, B: MeCN) to afford **BH-0003921** (20.1 mg, 92.4% purity, 38.0% as a white solid. LCMS: RT = 1.305 min, MS calcd.: M_{av} = 3483.84, mass observed: $[M + 2H]^{2+}$ = 1742.6, $[M + 3H]^{3+}$ = 1162.2, $[M + 4H]^{4+}$ = 872.0.

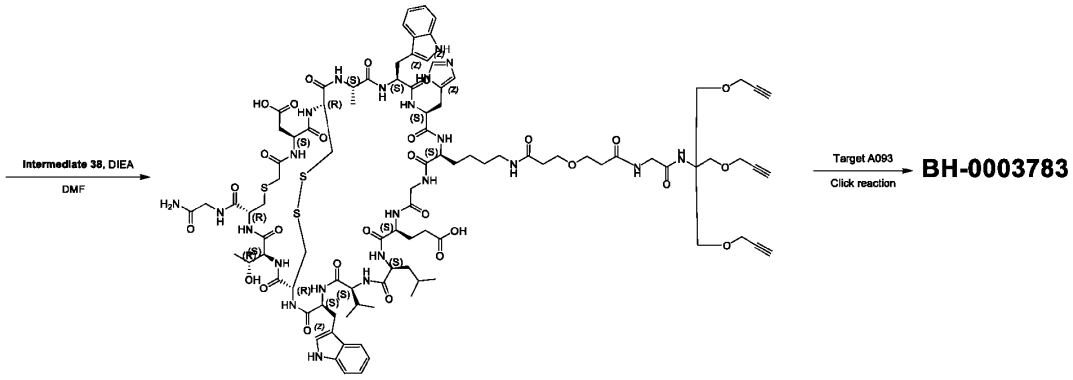


Molecular Weight: 3483.84

BH-0003921

[0149] **Preparation of *BH-0003783*:**

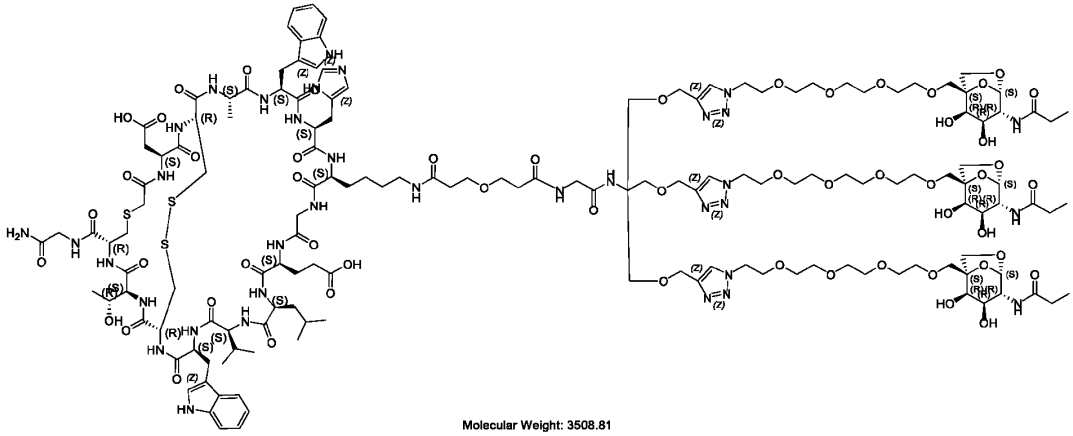




73

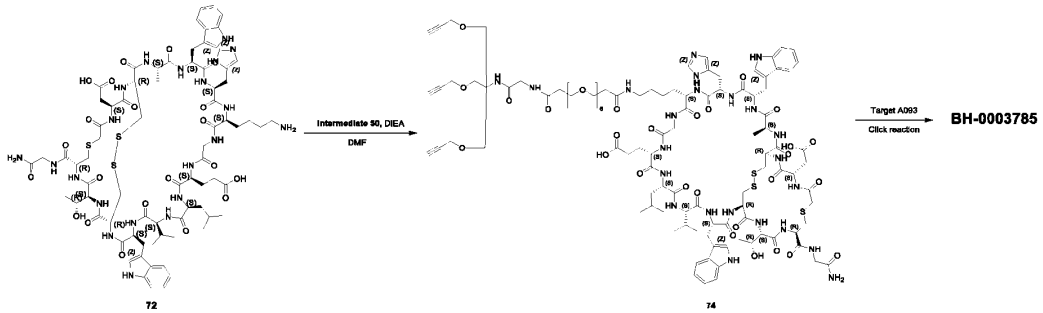
[0150] **BH-0003783** was synthesized using the same procedure as ***BH0003921*** which was performed by following the procedure mentioned in **[0141]** – **[0148]**.

[0151] 33.1 mg of **Target A093** with **Intermediate 73** afforded **BH-0003783** (18.1 mg, 93.7% purity, 26.1% yield) as a white solid. LCMS: RT = 1.30 min, MS calcd.: M_{av} = 3508.81, mass observed: $[M + 2H]^{2+}$ = 1755.2, $[M + 3H]^{3+}$ = 1170.5, $[M + 4H]^{4+}$ = 878.0.

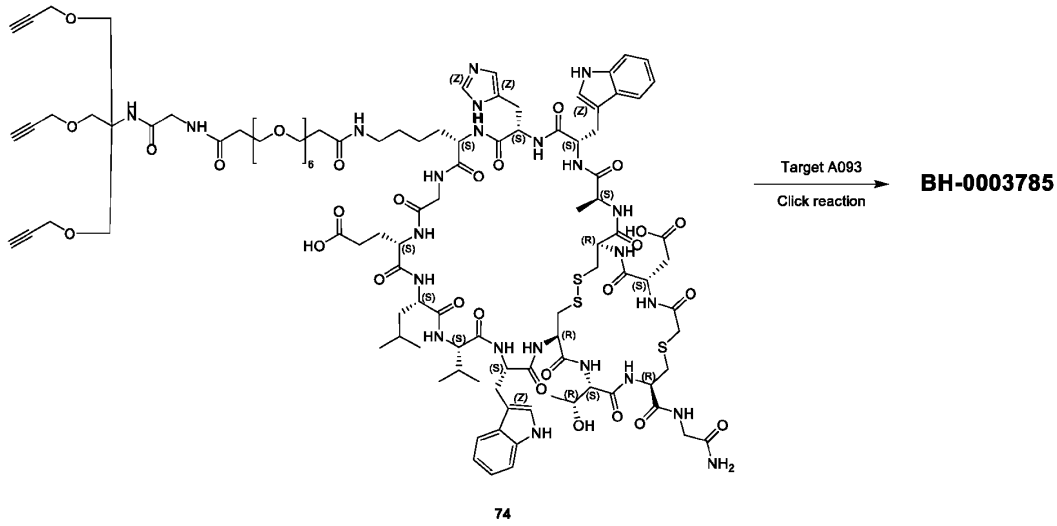


Molecular Weight: 3508.81
BH-0003783

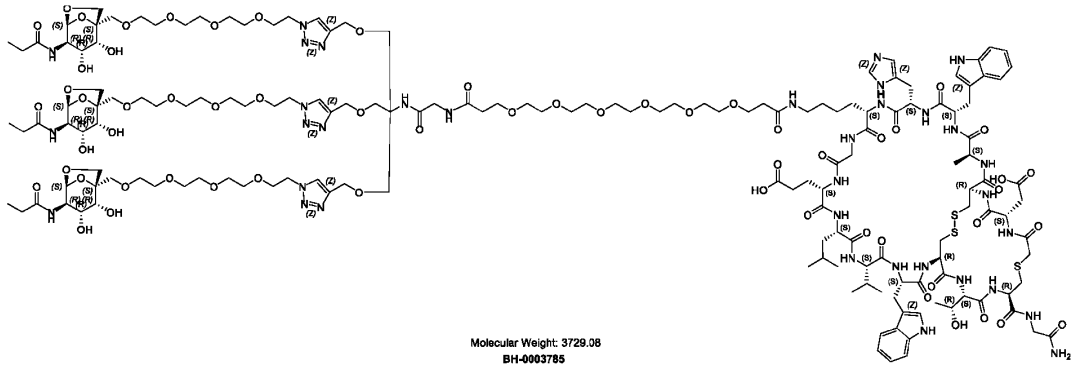
[0152] ***Preparation* of *BH-0003785*:**



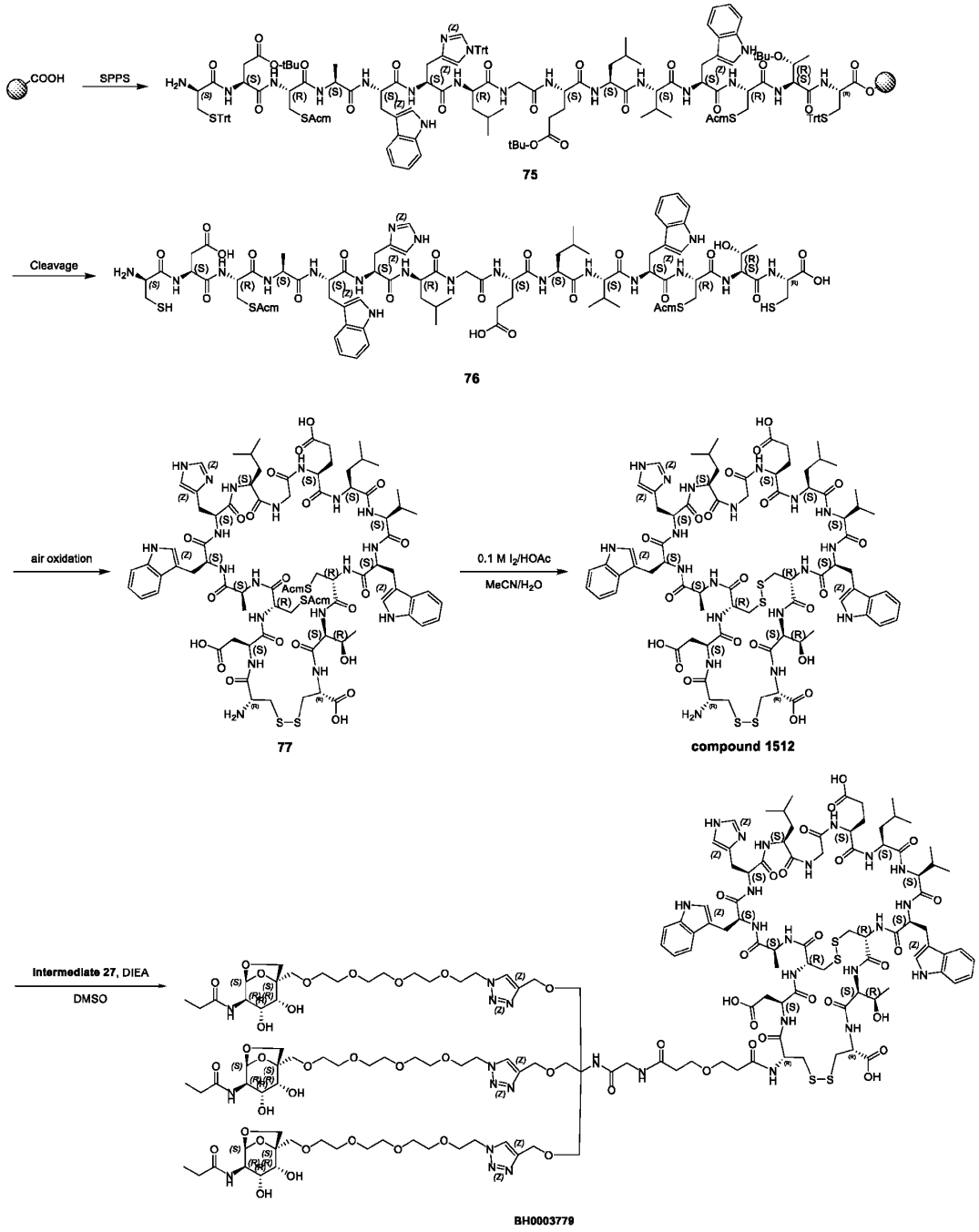
[0153] **BH-0003785** was synthesized using the same procedure as ***BH0003921*** which was performed by following the procedure mentioned in **[0141]** – **[0148]**.



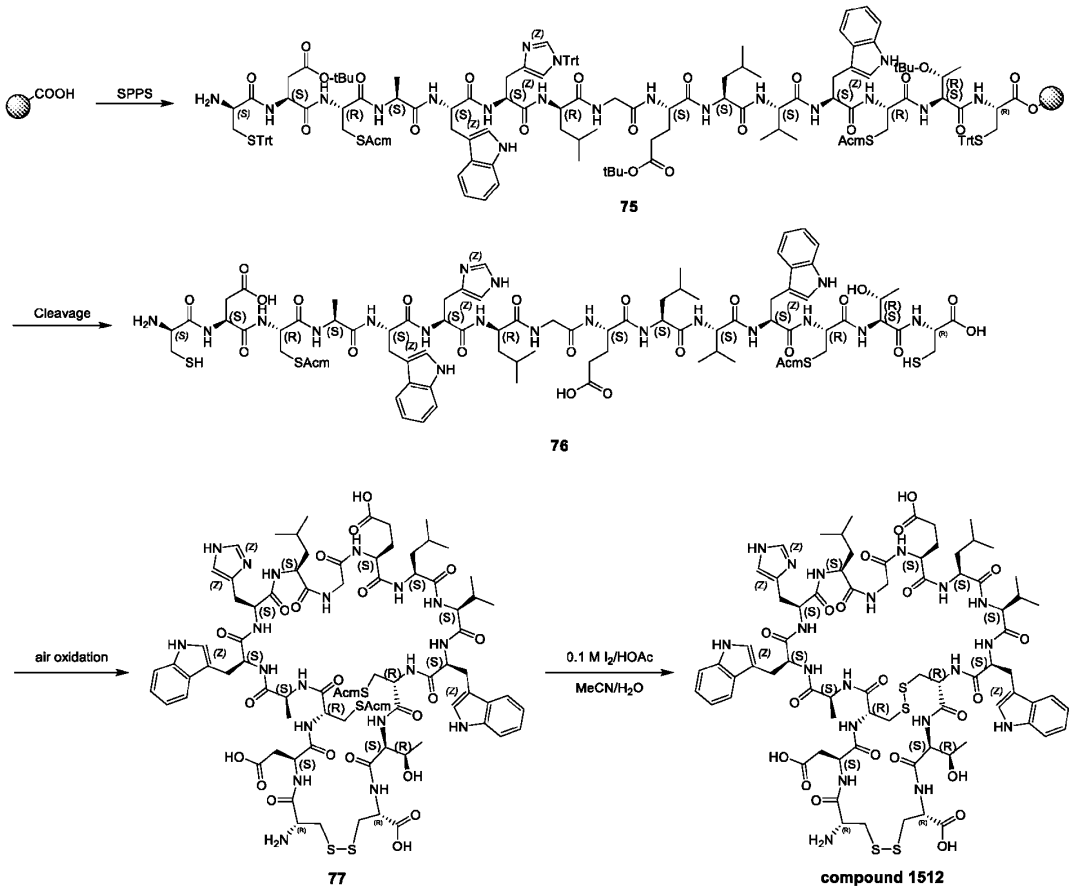
[0154] 34.6 mg of **Target A093** with **Intermediate 74** afforded **BH-0003785** (39.5 mg, 97.3% purity, 53.3% yield) as a white solid. LCMS: RT = 1.31 min, MS calcd.: M_{av} = 3279.08, mass observed: $[M + 2H]^{2+}$ = 1864.9, $[M + 3H]^{3+}$ = 1244.0, $[M + 4H]^{4+}$ = 933.2, $[M + 5H]^{5+}$ = 746.9.



EXAMPLE 19. Procedure for Preparation of BH003779 and BH-0003713.



[0155] ***Preparation of Compound 1512:***



[0156] **Intermediate 75** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0059]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 12, Number # 1-15.

Table 12: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Cys(Trt)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

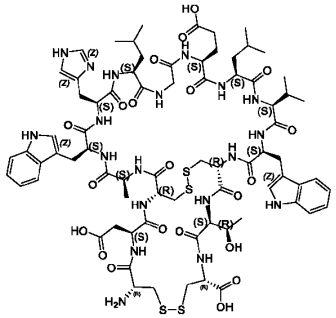
10	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

[0157] Peptide cleavage and double disulfide formation:

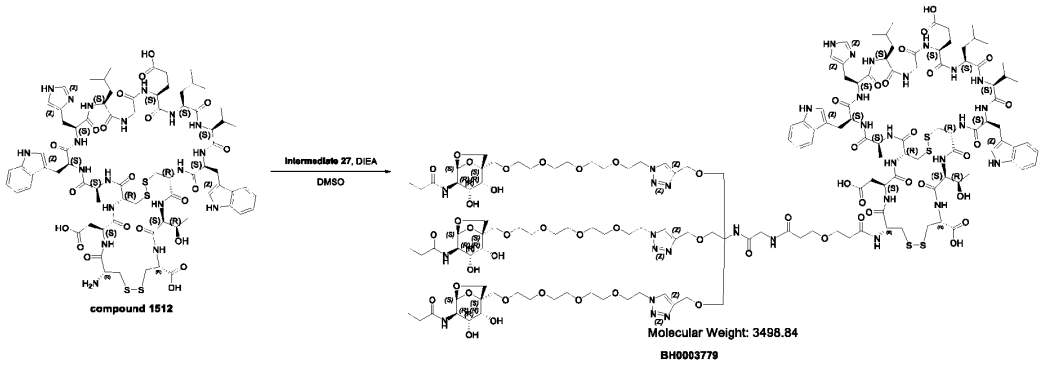
1) Cleavage: A solution of TFA/TIS/H_2O (95/2.5/2.5, v/v/v, 40 mL) was added to the flask containing the side-chain protected resin-bound peptide (**Intermediate 75**), and the resulting mixture was stirred for 2 h at 25 °C. After filtration, the filtrate was collected and precipitated with cold isopropyl ether (200 mL), then filtered off, and the solid was washed with isopropyl ether (100 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 76** (0.50 mmol, crude) as a white solid.

2) First disulfide formation: To a mixture of **Intermediate 76** (0.50 mmol, crude) in MeCN/H_2O (4/6, v/v, 500 mL) was added $NaHCO_3$ to pH = 8 at 25 °C. Then the mixture was open to the air and stirred at 25 °C for 24 h. After filtration, the mixture was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) to afford **Intermediate 77** (439.5 mg, 25.3% yield) as a white solid.

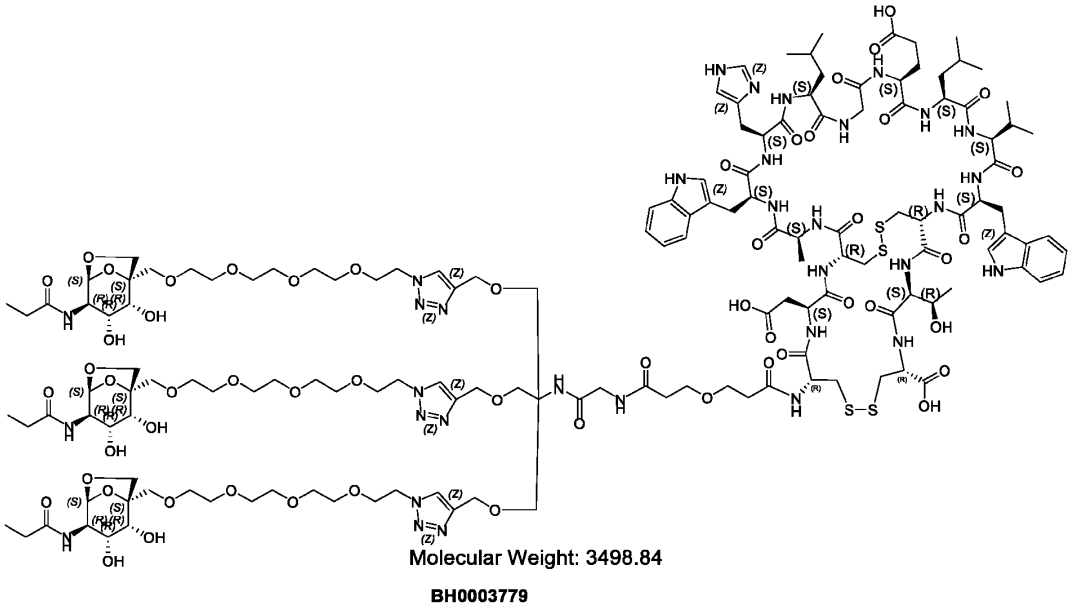
3) Second disulfide formation: To a mixture of **Intermediate 77** (439.5 mg, 25.3% yield) in MeCN/H_2O (4/6, v/v, 300 mL) was added 1 M aq. HCl (1.5 mL), AcOH (3.0 mL) to pH = 1. The mixture was added 0.1 M I_2/AcOH dropwise until the yellow color persisted, then the mixture was stirred at 25 °C for 5 h. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified directly by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Compound 1512** (160.5 mg, 95.8% purity, 36.5% yield) as a white solid. LCMS: RT = 1.355 min, MS calcd.: M_{av} = 1735.00, mass observed: $[M + H]^+$ = 1735.8, $[M + 2H]^{2+}$ = 868.6.



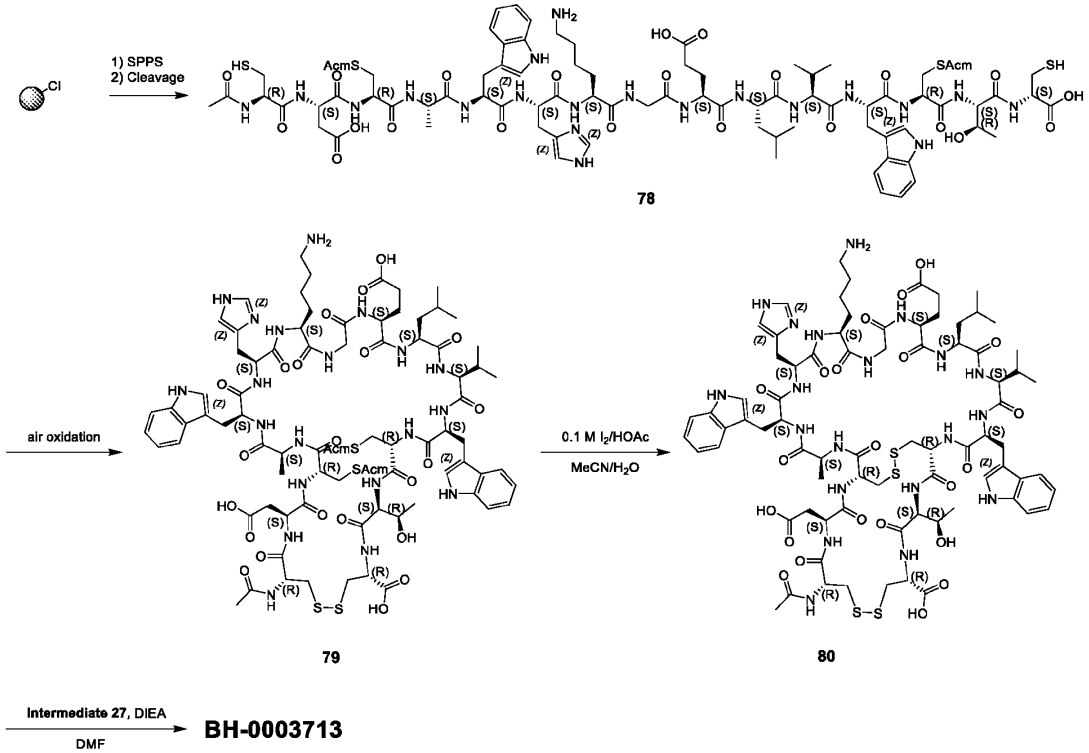
[0158] ***Preparation of BH0003779:***



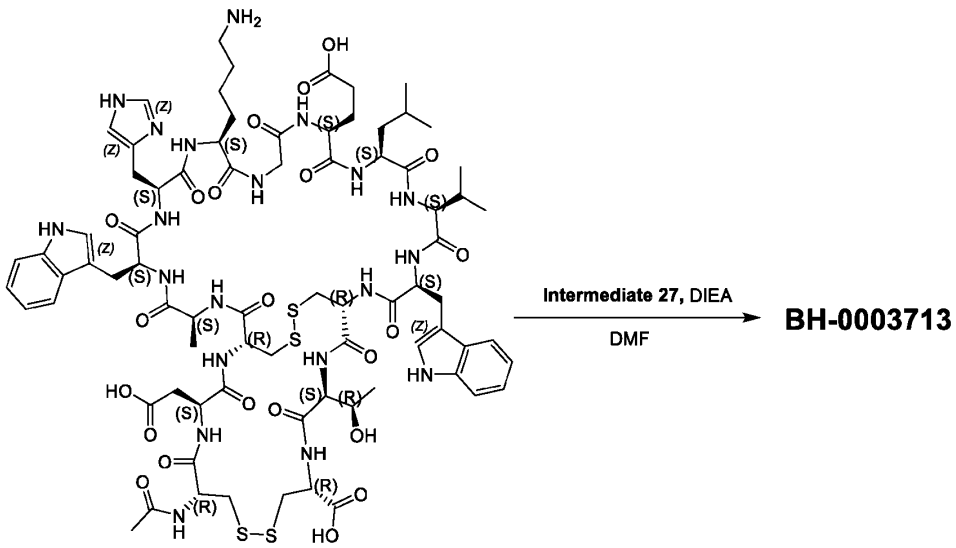
[0159] To a mixture of **Compound 1512** (49.2 mg, 25.5 μmol, 1.00 equiv.) and **Intermediate 27** (44.2 mg, 25.5 μmol, 1.00 equiv.) in DMSO (0.5 mL) was added DIEA (43.5 μL, 255 μmol, 10.0 equiv.) at 25 °C. The mixture was stirred at 25 °C for 2 h. After completion monitored by LC-MS, the mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **BH0003779** (9.0 mg, 95.0% purity, 10.1% yield) as a white solid. LCMS: RT = 1.407 min, MS calcd.: M_{av} = 3498.84, mass observed: $[M + 2H]^{2+}$ = 1750.6, $[M + 3H]^{3+}$ = 1167.1, $[M + 4H]^{4+}$ = 876.1.



[0160] ***Preparation of BH0003713:***

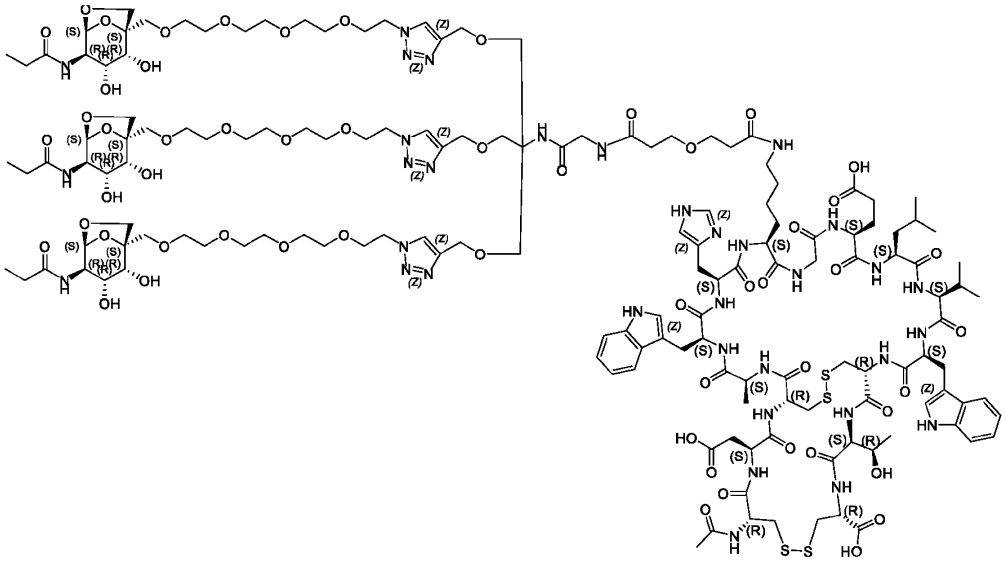


[0161] **BH-0003713** was synthesized using the same procedure as ***BH0003779*** which was performed by following the procedure mentioned in **[0156]** – **[0159]**.



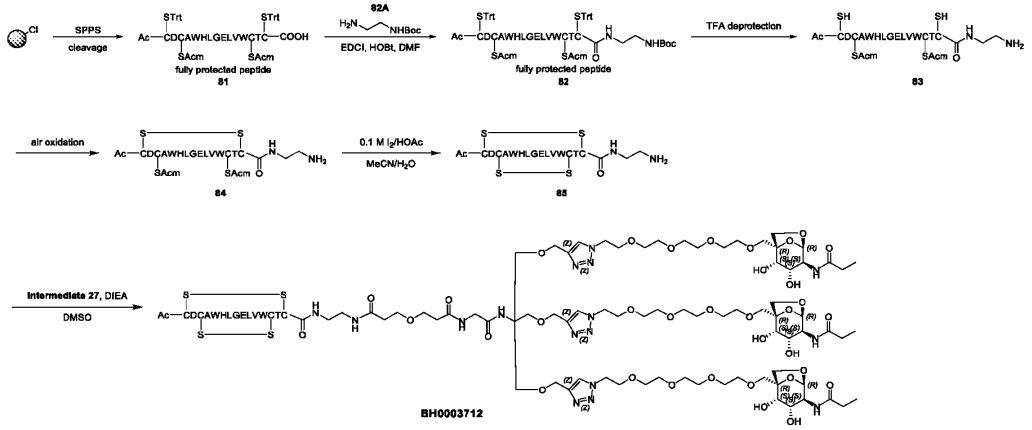
80

[0162] 30 mg of **Intermediate 27** with **Intermediate 80** afforded **BH-0003713** (27.7 mg, 88.4% purity, 44.3% yield) as a white solid. LCMS: RT = 1.32 min, MS calcd.: M_{av} = 3555.89, mass observed: $[M + 2H]^{2+}$ = 1778.7, $[M + 3H]^{3+}$ = 1186.1, $[M + 4H]^{4+}$ =889.7.

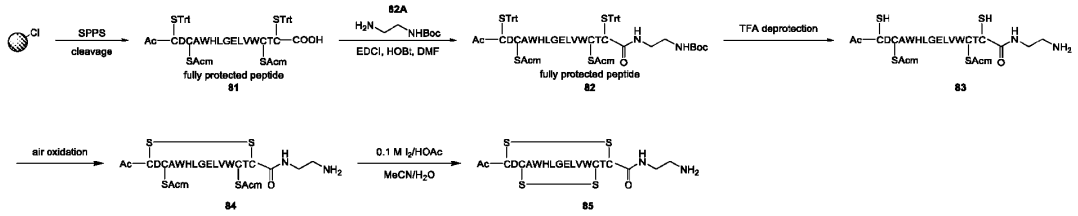


Molecular Weight: 3555.89
BH0003713

EXAMPLE 20. Procedure for Preparation of BH0003712.



[0163] ***Preparation of Intermediate 85:***



[0164] **Intermediate 81** was synthesized by following the procedure mentioned in section **[0059]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 13, Number # 1-15.

[0165] Acetylation: A solution of Ac_2O/NMM/DMF (2/1/17, v/v/v, 40 mL) was added to the resin, the mixture was bubbled with N_2 for 20 min. The acetylation reaction was monitored by ninhydrin test. The resin was then washed with DMF (20 mL) * 5, MeOH (20 mL) * 3, then dried under reduced pressure to afford peptide resin (0.50 mmol).

Table 13: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Cys(Trt)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

6	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
16	Acetylation	Ac_2O/NMM/DMF (2/1/17, v/v/v)

[0166] Peptide cleavage and fragments coupling, TFA deprotection and double disulfide formation:

1) Cleavage from resin: A solution of 20% HFIP/DCM (50 mL) was added to the resin above at room temperature and stirred for 1 h. After filtration, the filtrate was collected and concentrated under reduced pressure to afford fully protected peptide **Intermediate 81** (1.40 g, crude) as a white solid.

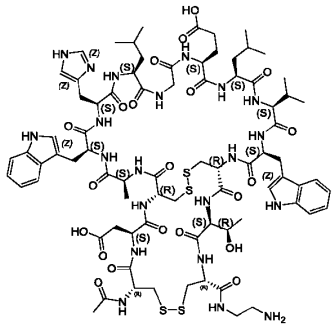
2) Fragments coupling: To the mixture of **Intermediate 81** (1.40 g, crude, 496.72 μmol, 1.00 equiv.), **59A** (238.7 mg, 1.49 mmol, 3.00 equiv.), HOBt (201.2 mg, 1.49 mmol, 3.00 equiv.) in DMF (2.0 mL) was added EDCI (285.6 mg, 1.49 mmol, 3.00 equiv.) at 0 °C. The resulting reaction was stirred for 2 h at 0 °C. After completion monitored by LC-MS, the reaction was added into flask with cold 0.1 M HCl (30 mL), and the precipitate was filtered off to afford the crude as **Intermediate 82**.

3) Deprotection: A solution of TFA/TIS/H_2O/3-mercaptopropanoic acid (v/v/v/v, 92.5/2.5/2.5/2.5, 20 mL) was added to the flask containing **Intermediate 82** (crude) in step 2, and the resulting mixture was stirred for 1 h at 25 °C. The mixture was precipitated with cold isopropyl ether (100 mL), then filtered off, and the solid was washed with isopropyl ether (50 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 83** (858.3 mg, crude) as a white solid.

4) First disulfide formation: A solution of **Intermediate 83** (858.3 mg, crude) in MeCN/H2O (4/6, v/v, 500 mL) based by $NaHCO_3$ to pH = 8. The mixture was open to the air and stirred at 25 °C for 24 h. After filtration, the mixture was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) to afford **Intermediate 84** (260.9 mg, 30.4% yield) as a white solid.

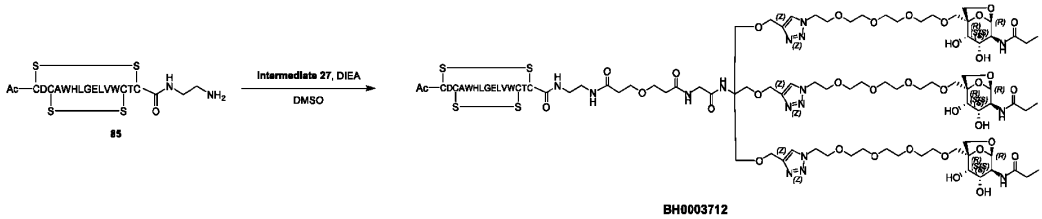
5) Second disulfide formation: To a mixture of **Intermediate 84** (260.9 mg, 133.0 μmol) in MeCN/H_2O (4/6, v/v, 130 mL) was added 1 M aq. HCl (1.5 mL), AcOH (3.0 mL) to pH = 1. The mixture was added 0.1 M I_2/AcOH dropwise until the yellow color persisted, then the mixture was stirred at 25 °C for 5 h. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After

filtration, the filtrate was purified directly by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 85** (86.1 mg, 33.0% yield) as a white solid. UPLC: RT = 0.845 min, MS calcd.: M_{av} = 1819.11, mass observed: $[M + H]^+$ = 1819.69, $[M + 2H]^{2+}$ = 910.04.

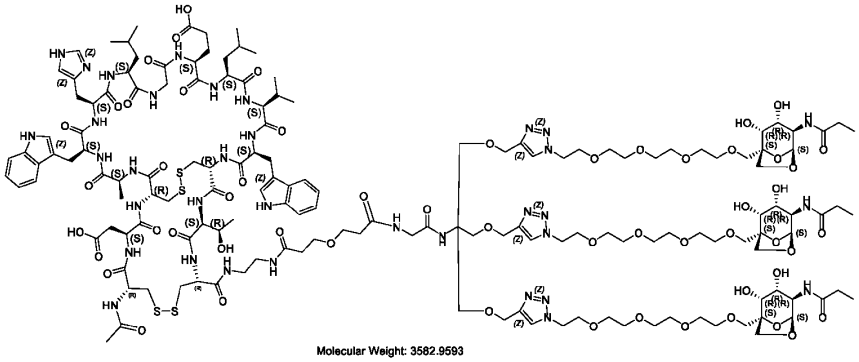


Molecular Weight: 1819.11
Intermediate 85

[0167] ***Preparation of BH0003712:***

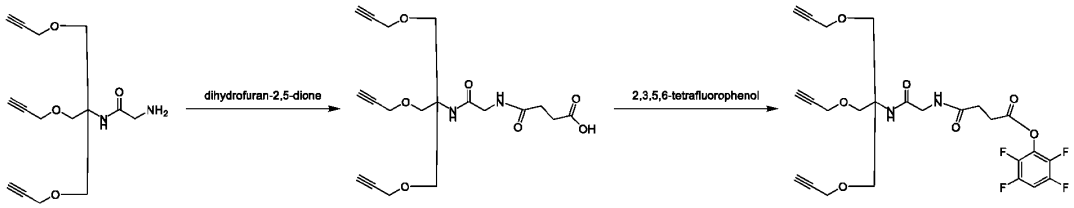


[0168] To a mixture of **Intermediate 85** (36.7 mg, 20.21 umol, 1.30 equiv.) and **Intermediate 27** (30.0 mg, 15.54 µmol, 1.00 equiv.) in DMSO (0.5 mL) was added DIEA (6.03 mg, 46.63 µmol, 8.12 µL, 3.00 equiv.) at 25 °C. The mixture was stirred at 25 °C for 2 h. After completion monitored by LC-MS, the mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **BH0003712** (13.5 mg, 92.2% purity, 22.3% yield) as a white solid. LCMS: RT = 1.401 min, MS calcd.: M_{av} = 3582.96, mass observed: $[M + 2H]^{2+}$ = 1792.7, $[M + 3H]^{3+}$ = 1195.1, $[M + 4H]^{4+}$ = 896.7.

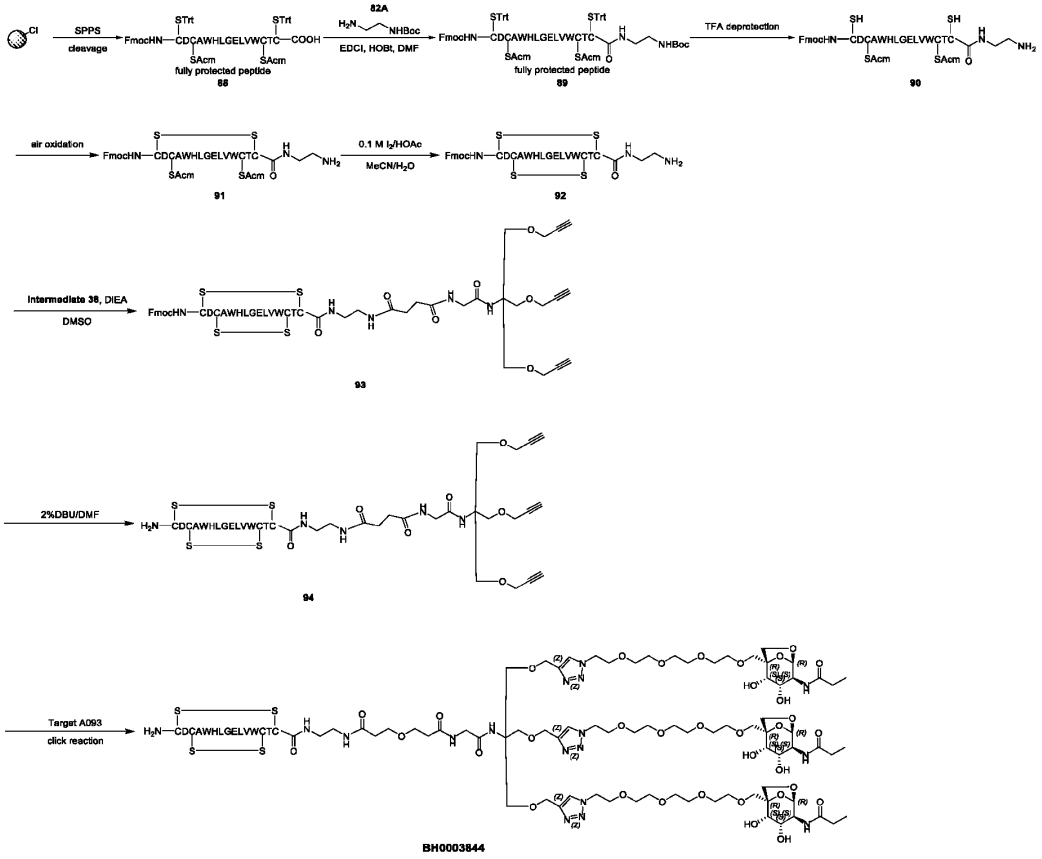


Molecular Weight: 3582.9593
BH0003712

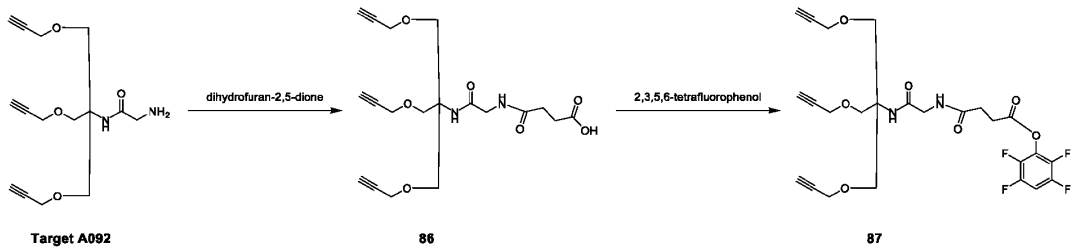
EXAMPLE 21. Procedure for Preparation of BH0003844.



Target A092 86 87



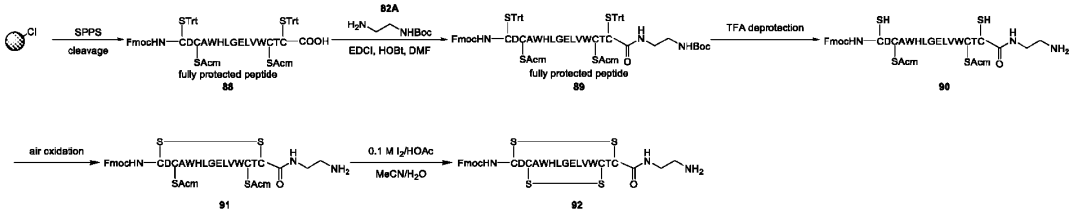
[0169] ***Preparation of Intermediate 87:***



[0170] To a mixture of **Target A092** (200 mg, 684.1 umol, 1.00 equiv.) and **dihydrofuran-2,5-dione** (68.47 mg, 684.1 µmol, 1.00 equiv.) in DMF (2 mL) was added DIEA (176.8 mg, 1.37 mmol, 238.3 µL, 2.00 equiv.) at 25 °C. The mixture was stirred at 15 °C for 1 h. After completion monitored by LC-MS, the mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford ***Intermediate* 86** (250 mg, 93. 12% yield) as a colorless oil. To

a mixture of ***Intermediate* 86** (250 mg, 637.1 umol, 1.00 equiv.) and **2,3,5,6-tetrafluorophenol** (423.2 mg, 2.55 mmol, 4.00 equiv.) in DMF (3 mL) was added EDCI (244.2 mg, 1.27 mmol, 2.00 equiv.) at 25 °C. The mixture was stirred at 25 °C for 2 h. After completion monitored by LC-MS, the mixture was then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford ***Intermediate* 87** (160 mg, 46.4% yield) as a colorless oil.

[0171] ***Preparation of Intermediate 92:***

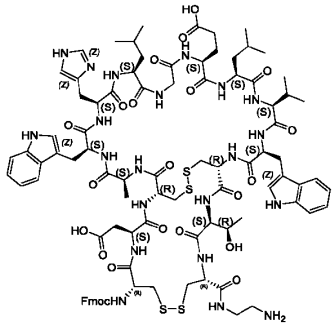


[0172] **Intermediate 88** was synthesized by following the procedure mentioned in section **[0059]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 14, Number # 1-15.

Table 14: The list of amino acids and the corresponding reagents used on SPPS.

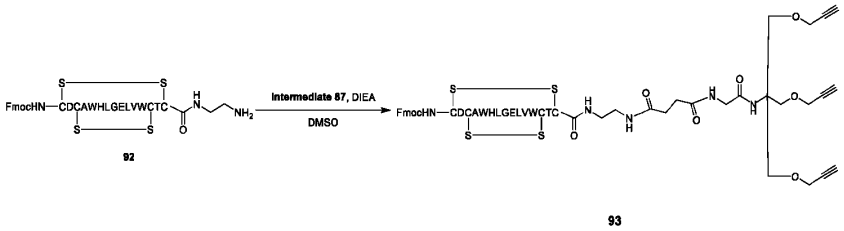
#	Materials	Coupling reagents
1	Fmoc-Cys(Trt)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Cys(Acm)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

[0173] **Intermediate 92** was synthesized using the same procedure as **Intermediate 85** which was performed by following the procedure mentioned in **[0166]** to afford **Intermediate 92** (86.1 mg, 33.0% yield).



Intermediate 92

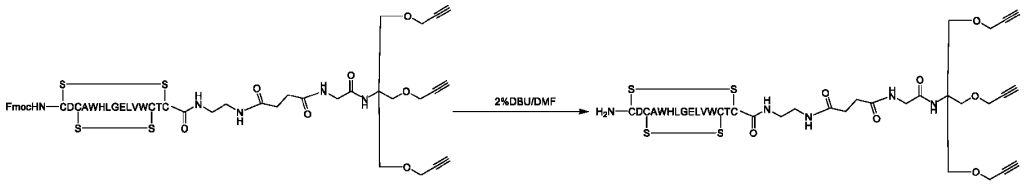
[0174] ***Preparation of*** **Intermediate 93*:***



92 93

[0175] To a mixture of **Intermediate 92** (73.9 mg, 37.0 umol, 1.00 equiv.) and **Intermediate 87** (20.0 mg, 37.0 μmol, 1.00 equiv.) in DMSO (1.0 mL) was added DIEA (19.1 mg, 148.0 μmol, 25.8 μL, 4.00 equiv.) at 25 °C. The mixture was stirred at 25 °C for 2 h. After completion monitored by LC-MS, the mixture was acidified by 1 M HCl to pH = 5, then purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **Intermediate 93** (26 mg, 90% purity,26.6% yield) as a white solid.

[0176] ***Preparation of*** **Intermediate 94*:***

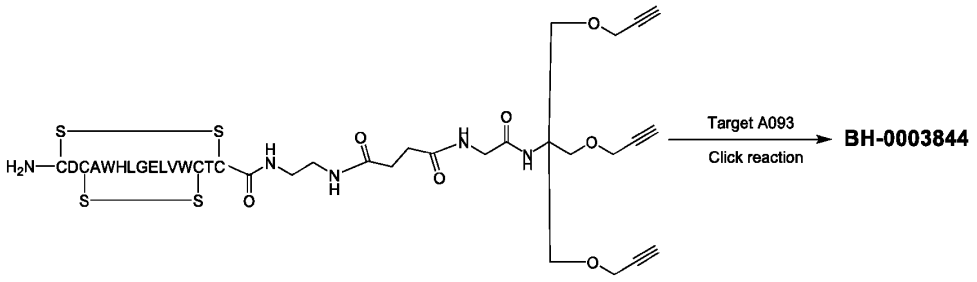


93 94

[0177] To a mixture of **Intermediate 93** (26 mg, 10.9 μmol, 1.00 equiv.) in 2%DBU/DMF (1.0 mL). The mixture was stirred at 25 °C for 15 min. After completion monitored by LC-MS, the mixture was then

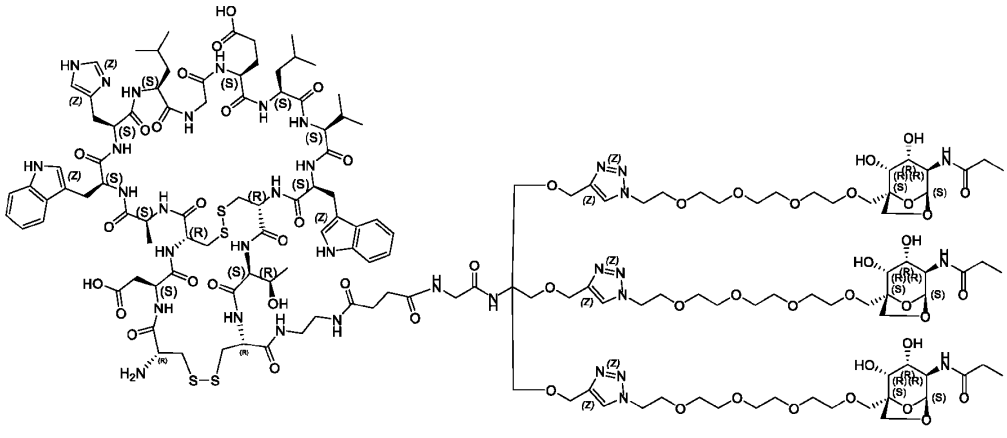
purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afforded **Intermediate 94** (15 mg, 90% purity, 57.3% yield) as a white solid.

[0178] ***Preparation of* BH-0003844*:***



94

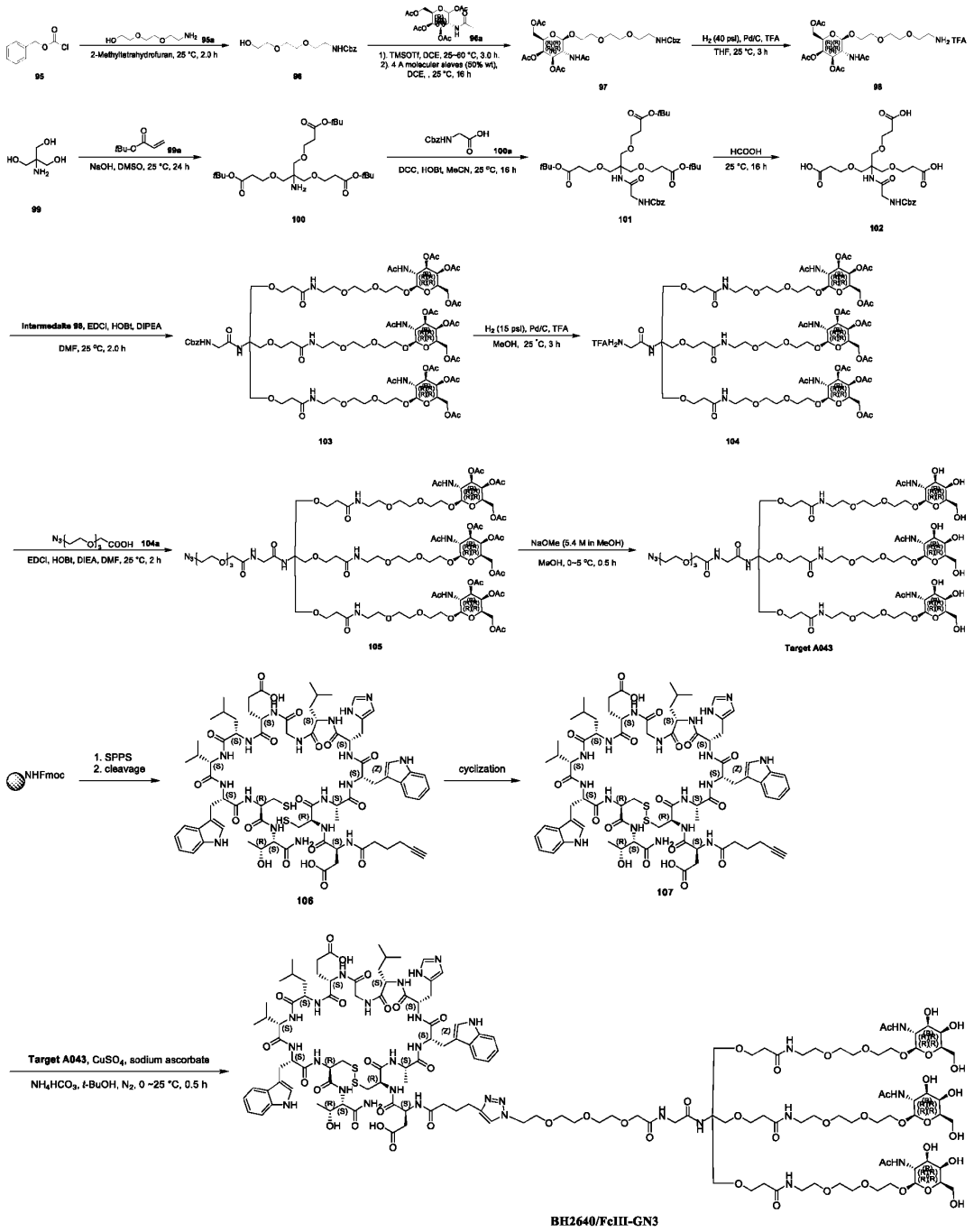
[0179] To a solution of **Intermediate 94** (15 mg, 6.97 μmol, 1.00 equiv.) and **Target A093** (11.8 mg, 27.9 μmol, 4.00 equiv.) in DMF (1 mL) was added $CuSO_4$ (0.4 M, 52.3 μL, 20.9 μmol, 3.00 equiv.), sodium ascorbate (0.4 M, 156.8 μL, 62.7 μmol, 9.0 equiv.) and THPTA (tris-hydroxypropyltriazolylmethylamine (9.09 mg, 20.9 μmol, 3.00 equiv.) under nitrogen atmosphere at 0 °C, and the resulting mixture was stirred for 3 h at 0 °C. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **BH0003844** (7.1 mg, 93.2% purity, 27.1% yield) as a white solid. LCMS: RT = 0.82 min, MS calcd.: M_{av} = 3496.87, mass observed: $[M + 2H]^{2+}$ = 1748.40, $[M + 3H]^{3+}$ = 1166.17, $[M + 4H]^{4+}$ = 874.88.



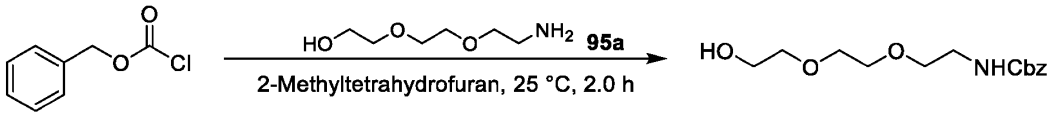
Molecular Weight: 3496.87

BH-0003844

EXAMPLE 22. Procedure for Preparation of BH2640 (FcIII-GN3).



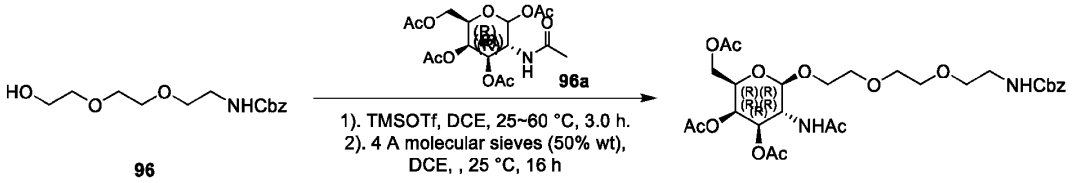
[0180] ***Preparation of Intermediate 96:***



95 96

[0181] To a solution of **95a** (60.0 g, 400 mmol, 2.00 equiv.) in 2-Methyltetrahydrofuran (450 mL) was added **95** (34.2 g, 200 mmol, 1.00 equiv.) in 2-Methyltetrahydrofuran (160 mL) at 0 °C. The mixture was stirred at 25 °C for 2 h. TLC (DCM: MeOH = 20: 1, R_f = 0.70) showed the reaction was completed, one major new spot with lower polarity was detected. The reaction mixture was added HCl/EA (1 N, 27.0 mL) and stirred for 30 min, and the white precipitate was removed by filtration, the filtrate was concentrated under reduced pressure to afford **Intermediate 96** (crude, 105.0 g, 370.6 mmol) as yellow oil. LCMS: RT = 0.797 min, MS cal.: 283.14, mass observed: $[M + Na]^+$ = 306.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.23 - 7.41 (m, 5 H), 5.01 (s, 2 H), 4.60 (br s, 1 H), 3.45 - 3.52 (m, 6 H), 3.38 - 3.43 (m, 5 H), 3.14 (q, J = 5.94 Hz, 2 H), 2.53 - 2.55 (m, 1 H).

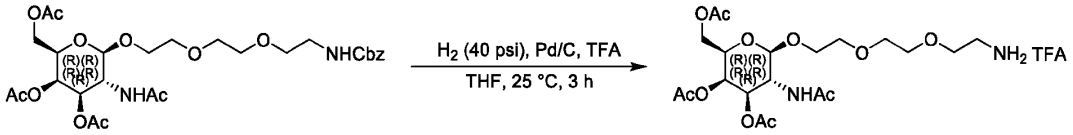
[0182] ***Preparation of Intermediate 97:***



[0183] To a solution of **96a** (100.0 g, 257 mmol, 1.00 equiv.) in DCE (500 mL) was added TMSOTf (85.6 g, 385 mmol, 1.50 equiv.) and stirred at 60 °C for 2 h. The reaction was then cooled to room temperature (25 °C) and stirred for another 1 h. A mixture of **Intermediate 96** (80.0 g, 282 mmol, 1.10 equiv.) and 4 Å powder molecular sieves (50.0 g) in DCE (500 mL) was added to the reaction. The resulting mixture was stirred for 30 min under N_2 atmosphere. Then a solution of **Intermediate 96a** (100.0 g, 257 mmol, 1.00 equiv.) in DCE was added dropwise to the mixture at 0 °C. The mixture was stirred for 16 h at 25 °C under N_2 atmosphere. TLC (DCM: MeOH = 10: 1, R_f = 0.42) indicated **Intermediate 96a** was consumed completely, and one major new spot with larger polarity was detected. The reaction mixture was filtered and washed with sat. $NaHCO_3$ (500 mL), water (500 mL) and brine (500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, PE: EA = 3: 1 to 1: 6, then DCM: MeOH = 20: 1) to afford **Intermediate 97** (90.0 g, 146.9 mmol, 91.6% purity, 57.2% yield) as yellow oil. LCMS: RT = 0.860 min, MS

cal.: 612.25, mass observed: $[M + H]^+$ = 613.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.80 (d, J = 9.03 Hz, 1 H), 7.24 - 7.39 (m, 6 H), 5.22 (d, J = 3.51 Hz, 1 H), 4.95 - 5.05 (m, 3 H), 4.53 - 4.59 (m, 1 H), 3.99 - 4.06 (m, 3 H), 3.84 - 3.92 (m, 1 H), 3.73 - 3.82 (m, 1 H), 3.55 - 3.61 (m, 1 H), 3.45 - 3.53 (m, 7 H), 3.41 (t, J = 5.90 Hz, 2 H), 3.11 - 3.18 (m, 3 H), 2.10 (s, 3 H), 1.99 (s, 3 H), 1.89 (s, 3 H), 1.77 (s, 3 H).

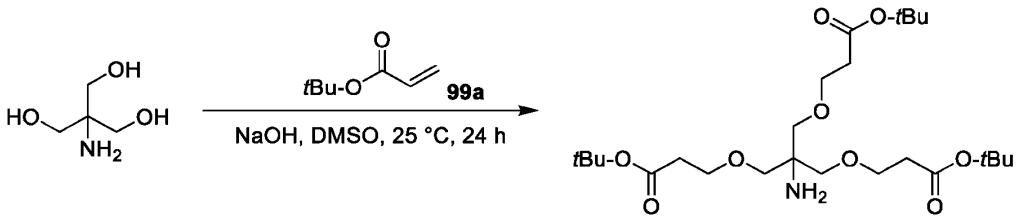
[0184] ***Preparation of Intermediate 98:***



97 **98**

[0185] Pd/C (9.00 g, 10% purity) in reaction bottle (purged with Ar for three times) was added THF (180 mL) slowly, then a solution of TFA (16.7 g, 147 mmol, 1.00 equiv.) and **Intermediate 97** (90.0 g, 147.0 mmol, 1.00 equiv.) in THF (720 mL) was added to the reaction slowly under N_2. The reaction was degassed and purged with N_2 and H_2 for three times, then stirred at 25 °C for 3 h under H_2 atmosphere (40 psi). TLC (DCM: MeOH = 10: 1, R_f = 0.20) indicated **Intermediate 97** was consumed completely, and one major new spot with larger polarity was detected. The reaction mixture was dissolved in THF (100 mL), filtered carefully through siliceous earth under N_2 atmosphere, the cake was washed with THF (100 mL * 2), and the filtrate was concentrated under reduced pressure to get the residue. The residue was diluted with water (1000 mL), washed with DCM (300 mL * 3), the aqueous layer was lyophilized to afford **Intermediate 98** (80.0 g, 139.0 mmol, 95.1% purity, 91.8% yield, TFA salt) as a white solid. LCMS: RT = 0.484 min, MS cal.: 478.22, mass observed: $[M + H]^+$ = 478.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.91 (br t, J = 9.03 Hz, 4 H), 5.21 (d, J = 3.26 Hz, 1 H), 4.96 (dd, J = 11.17, 3.39 Hz, 1 H), 4.54 (d, J = 8.53 Hz, 1 H), 3.98 - 4.08 (m, 3 H), 3.85 - 3.93 (m, 1 H), 3.75 - 3.84 (m, 1 H), 3.59 (br t, J = 5.14 Hz, 3 H), 3.50 - 3.56 (m, 6 H), 2.98 (br s, 2 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.89 (s, 3 H), 1.78 (s, 3 H).

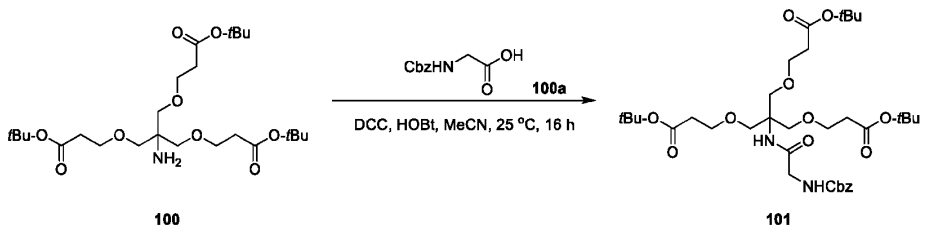
[0186] ***Preparation of Intermediate 100:***



99 **100**

[0187] To a mixture of **99** (60.0 g, 495.0 mmol, 1.00 equiv.) in DMSO (166 mL) was added aqueous NaOH (5.0 M, 9.91 mL, 0.10 equiv.) dropwise at 0-15 °C for over 5 min. After addition, the mixture was stirred at 0-15 °C for 5 min, then 99**a** (254.0 g, 1.98 mol, 287 mL, 4.00 equiv.) was added to the reaction mixture dropwise at 20 °C. The resulting mixture was stirred at 25 °C for 16 h. TLC (DCM: MeOH = 10: 1, R_f = 0.7) indicated **Intermediate 99** was consumed completely, and one major new spot with lower polarity was detected. The resulting reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in EtOAc (400 mL), quenched by addition of water (400 mL), and extracted with EtOAc (400 mL * 3). The combined organic layers were washed with brine (300 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **Intermediate 100** (100.0 g, 197.8 mmol, 96.0% purity, 40.0% yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.51 - 3.61 (m, 7 H), 3.17 (s, 5 H), 2.39 (t, J = 6.02 Hz, 6 H), 1.40 (s, 27 H).

[0188] ***Preparation of Intermediate 101:***

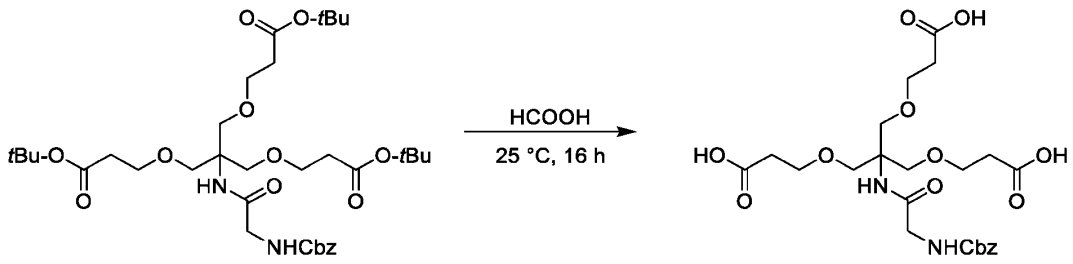


100 **101**

[0189] To a solution of **Intermediate 100** (40.0 g, 79.1 mmol, 1.00 equiv.) in MeCN (400 mL) was added HOBt (10.7 g, 79.1 mmol, 1.00 equiv.). Then **100a** (16.5 g, 79.1 mmol, 1.00 equiv.) and DCC (16.3 g, 79.1 mmol, 1.00 equiv.) were added. The reaction was stirred at 25 °C for 16 h. TLC (PE: EA = 1: 1, R_f = 0.80) indicated **Intermediate 100** was consumed completely, and one major new spot with lower polarity was detected. MeCN was evaporated to get the residue. The residue was purified by column chromatography (SiO_2, PE: EA = 10: 1 to 1: 1) to afford **Intermediate 101** (40.0 g, 57.4 mmol, 82.9% purity, 72.5% yield) as a white solid. LCMS: RT = 1.151 min, MS cal.: 696.38, mass observed: $[M + H]^+$ = 697.3, [M

+ Na]$^+$ = 719.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.26 - 7.40 (m, 6 H), 7.06 (s, 1 H), 5.03 (s, 2 H), 3.49 - 3.61 (m, 14 H), 2.39 (br t, J = 6.02 Hz, 6 H), 1.40 (s, 27 H).

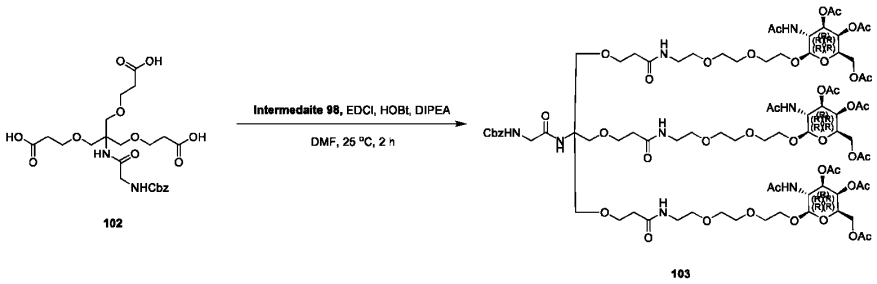
[0190] ***Preparation of Intermediate 102:***



101 **102**

[0191] A solution of **Intermediate 101** (30.0 g, 43.0 mmol, 1.00 equiv.) in HCOOH (300 mL) was stirred at 25 °C for 16 h. TLC (PE: EA = 1: 1, R_f = 0.04) indicated **Intermediate 101** was consumed completely, and one major new spot with larger polarity was detected. Solvent was evaporated under reduced pressure, then co-evaporated with toluene (50 mL * 3) under reduced pressure, and dried under reduced pressure to get the residue. The residue was purified by prep-HPLC (A: 0.1% FA condition/H_2O, B: MeCN) to afford **Intermediate 102** (20.0 g, 37.8 mmol, 98.2% purity, 87.9% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.17 (br s, 3 H), 7.26 - 7.43 (m, 6 H), 7.06 (s, 1 H), 5.02 (s, 2 H), 3.49 - 3.65 (m, 14 H), 2.42 (br t, J = 6.27 Hz, 6 H). LCMS: RT = 0.790 min, MS cal.: 528.20, mass observed: [M + H]$^+$ = 529.2.

[0192] ***Preparation of Intermediate 103:***

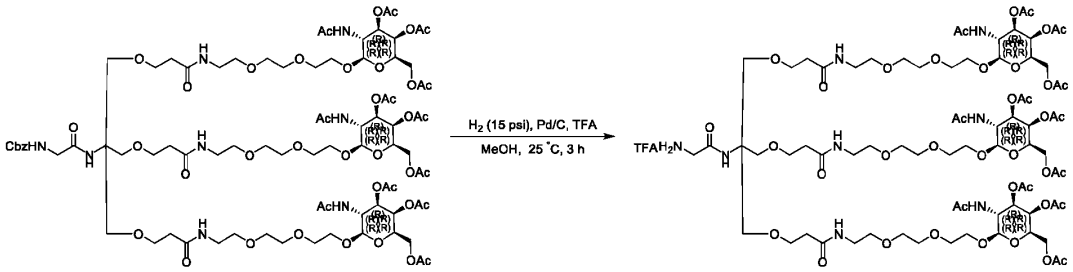


102 **103**

[0193] To a stirring solution of **Intermediate 102** (20.0 g, 37.8 mmol, 1.00 equiv.) and **Intermediate 98** (78.5 g, 132 mmol, 3.50 equiv., TFA salt) in DMF (400 mL) was added HOBT (20.4 g, 151 mmol, 4.00 equiv.), EDCI (29.0 g, 151 mmol, 4.00 equiv.) and DIEA (22.0 g, 170 mmol, 4.50 equiv.) successively. The reaction was stirred at 25 °C for 2 h. TLC (DCM: MeOH = 10: 1, R_f = 0.4) indicated

Intermediate 102 was consumed completely, and one major new spot with larger polarity was detected. The reaction mixture was slowly poured into a stirring cold 0.5 mol/L HCl solution (900 mL), and stirred for 10 min. White precipitate was formed and filtered, the aqueous phase was extracted with DCM (600 mL* 2) twice. The combined organic layers were washed with 5% $NaHCO_3$ (450 mL), dried over Na_2SO_4, and concentrated under reduced pressure to get a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 100: 1 to 5: 1) to afford **Intermediate 103** (58.0 g, 30.4 mmol, 82.7% purity, 80.3% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.92 (br t, J = 5.14 Hz, 3 H), 7.81 (d, J = 9.03 Hz, 3 H), 7.28 - 7.39 (m, 6 H), 7.13 (s, 1 H), 5.21 (d, J = 3.26 Hz, 3 H), 5.02 (s, 2 H), 4.97 (dd, J = 11.17, 3.39 Hz, 3 H), 4.54 (d, J = 8.53 Hz, 3 H), 4.03 (s, 9 H), 3.84 - 3.92 (m, 3 H), 3.75 - 3.81 (m, 3 H), 3.45 - 3.61 (m, 37 H), 3.39 (br s, 3 H), 3.18 - 3.23 (m, 6 H), 2.30 (br t, J=6.15 Hz, 6 H), 2.10 (s, 9 H), 2.00 (s, 9 H), 1.89 (s, 9 H), 1.77 (s, 9 H). LCMS: RT = 3.455 min, MS cal.: 1908.81, mass observed: $[M + 2H]^{2+}$ = 955.7.

[0194] ***Preparation of Intermediate 104:***

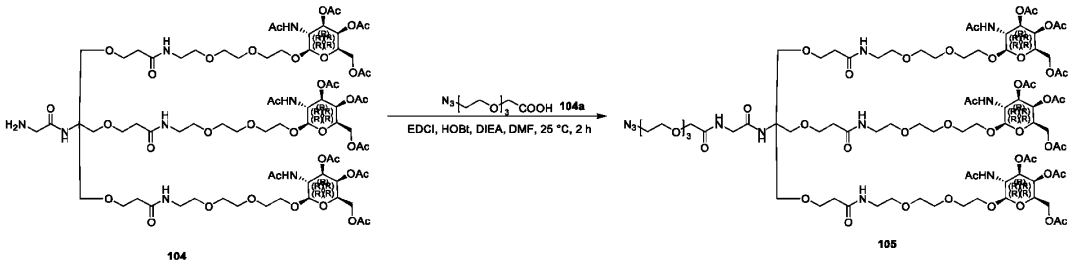


103 104

[0195] Pd/C (4.6 g, 25.13 mmol, 10% purity, 1.00 equiv.) in reaction bottle (purged with N_2 for three times) was added MeOH (230 mL) slowly, then a solution of TFA (2.75 g, 24.1 mmol, 1.00 equiv.) and **Intermediate 103** (46.0 g, 24.1 mmol, 1.00 equiv.) in MeOH (230 mL) was added to the reaction slowly under N_2 atmosphere. The reaction was degassed and purged with N_2 and H_2 for three times, stirred at 25 °C for 2 h under H_2 atmosphere (15 psi). TLC (DCM: MeOH = 10: 1, R_f = 0.3) indicated **Intermediate 103** was consumed completely, and one major new spot with larger polarity was detected. The reaction mixture was dissolved in MeOH (250 mL), filtered carefully through siliceous earth under N_2 atmosphere, the cake was washed with MeOH (250 mL * 2), and the filtrate was concentrated under reduced pressure to afford **Intermediate 104** (crude, 42.0 g, 22.4 mmol, 94.1% purity, 92.2% yield, TFA salt) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.97 (br t, J = 5.44 Hz, 6 H), 7.81 - 7.88 (m, 3 H), 7.73 - 7.77 (m, 1 H), 5.19 - 5.26 (m, 3 H), 4.97 (dd, J = 11.13, 3.38 Hz, 3 H), 4.52 - 4.61 (m, 3 H), 3.99 - 4.06 (m, 10 H), 3.84 - 3.93 (m, 4 H), 3.74 - 3.82 (m, 4 H), 3.46 - 3.61 (m, 42 H), 3.38 - 3.42 (m, 8 H), 3.19 - 3.24 (m, 6 H), 2.28 - 2.34 (m,

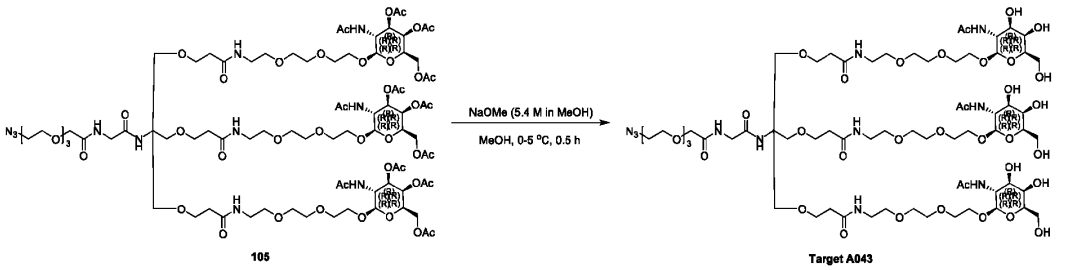
6 H), 2.08 - 2.12 (m, 9 H), 1.98 - 2.02 (m, 9 H), 1.87 - 1.90 (m, 9 H), 1.75 - 1.80 (m, 9 H). LCMS: RT = 1.585 min, MS cal.: 1774.78, mass observed: $[M + H]^+$ = 1775.7, $[M + 2H]^{2+}$ = 888.7.

[0196] ***Preparation of Intermediate 105:***



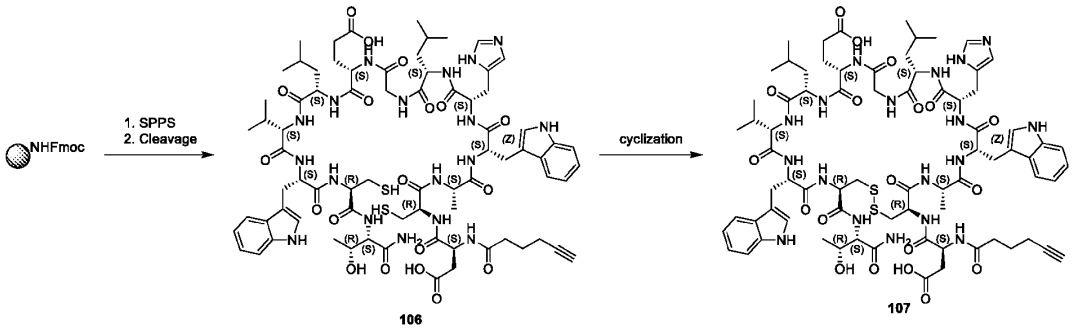
[0197] DIEA (8.62 g, 66.6 mmol, 3.00 equiv.), EDCI (6.69 g, 33.3 mmol, 1.50 equiv.) and HOBt (6.38 g, 33.3 mmol, 1.50 equiv.) were added to the solution of **Intermediate 104** (42.0 g, 22.2 mmol, 1.00 equiv., TFA salt) and **104a** (7.77 g, 33.3 mmol, 1.50 equiv.) in DMF (420 mL). The mixture was stirred at 25 °C for 2.0 h. LCMS indicated **Intermediate 104** was consumed completely, several new peaks were shown on LC-MS and desired compound was detected. The reaction mixture was slowly poured into a stirring 0.5 mol/L HCl solution (cold, 500 mL). The aqueous phase was extracted with DCM (500 mL * 3). The combined organic layers were washed with 5% $NaHCO_3$ (500 mL), dried over Na_2SO_4, then concentrated under reduced pressure to get a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 100: 1 to 5: 1) to afford **Intermediate 105** (34.0 g, 17.1 mmol, 93.3% purity, 77.0% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.88 - 7.94 (m, 3 H), 7.78 - 7.83 (m, 3 H), 7.71 - 7.76 (m, 1 H), 7.21 - 7.26 (m, 1 H), 5.19 - 5.23 (m, 3 H), 4.94 - 5.02 (m, 3 H), 4.51 - 4.59 (m, 3 H), 4.00 - 4.06 (m, 9 H), 3.91 - 3.93 (m, 2 H), 3.84 - 3.90 (m, 3 H), 3.72 - 3.81 (m, 5 H), 3.46 - 3.63 (m, 46 H), 3.37 - 3.43 (m, 9 H), 3.18 - 3.23 (m, 6 H), 2.27 - 2.34 (m, 6 H), 2.09 - 2.12 (m, 9 H), 1.98 - 2.01 (m, 9 H), 1.88 - 1.90 (m, 9 H), 1.75 - 1.79 (m, 9 H). LCMS: RT = 0.501 min, MS cal.: 1989.87, mass observed: $[M + 2H]^{2+}$ = 996.3.

[0198] ***Preparation of Target A043:***



[0199] To a solution of **Intermediate 105** (34.0 g, 12.6 mmol, 1.00 equiv.) in MeOH (400 mL) was added NaOMe (5.4 M in MeOH, 9.91 mL, 4.26 equiv.) at 0 °C. Then the solution was stirred at 0 °C for 0.5 h. LCMS indicated **Intermediate 105** was consumed completely, several new peaks were shown on LC-MS and desired compound was detected. The reaction mixture was adjusted pH to 6 with 1.0 M HCl solution at 0 °C, and washed with DCM (250 mL * 3) for three times, the aqueous layer was lyophilized to afford **Target A043** (crude, containing NaCl, 20.0 g, 12.4 mmol, 96.3% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.92 - 7.98 (m, 3 H), 7.73 - 7.77 (m, 1 H), 7.61 - 7.65 (m, 3 H), 7.22 - 7.27 (m, 1 H), 4.59 - 4.64 (m, 3 H), 4.55 - 4.58 (m, 3 H), 4.49 - 4.52 (m, 3 H), 4.25 - 4.31 (m, 3 H), 3.90 - 3.94 (m, 2 H), 3.68 - 3.81 (m, 9 H), 3.63 - 3.67 (m, 4 H), 3.59 - 3.62 (m, 6 H), 3.58 - 3.62 (m, 7 H), 3.38 - 3.41 (m, 13 H), 3.17 - 3.24 (m, 7 H), 2.28 - 2.34 (m, 7 H), 1.78 - 1.82 (m, 9 H). LCMS: RT = 0.501 min, MS cal.: 1611.77, mass observed: $[M + H]^+$ = 1612.8, $[M + 2H]^{2+}$ = 807.2.

[0200] ***Preparation of Intermediate 107:***



[0201] Peptide was synthesized using standard Fmoc chemistry (Rink AM resin).

1) Resin preparation: To the vessel containing Rink Amide AM resin (624.80 g, 200.00 mmol, 0.32 mmol/g) and DMF (2 L) was bubbled with N_2 for 2 h at 25 °C. Then 20% piperidine in DMF (4 L) was added and the mixture was bubbled with N_2 for 30 min at 25 °C. The mixture was filtered and washed with DMF (4 L) * 5 before proceeding to next step.

2) Coupling: A solution of Fmoc-Thr(*t*Bu)-OH (238.00 g, 600.00 mmol, 3.00 equiv.), DIC (75.60 g, 600.00 mmol, 3.00 equiv.), HOBt (81.20 g, 600.00 mmol, 3.00 equiv.) in DMF (2 L) was added to the resin with N_2 bubbling for 1 h at 25 °C. The coupling reaction was monitored by ninhydrin test. The resin was then washed with DMF (4 L) * 5.

3) Deprotection: 20% piperidine in DMF (2 L) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The resin was then washed with DMF (4 L) * 5.

4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 2-14, Table 15.

5) After all the steps were completed, the resin was washed with DMF (4 L) * 5, MeOH (4 L) * 5, then dried under reduced pressure to afford resin-bound peptide (Rink AM resin, 450.5 g, 200 mmol).

Table 15: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
13	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
14	2-Oxohept-6-ynoic acid (2.00 equiv.)	HATU (1.90 equiv.) and DIEA (4.00 equiv.)

[0202] Peptide cleavage and cyclization.

1) Cleavage solution (TFA/TIS/H_2O, 95/2.5/2.5, v/v/v, 5 L) was added to the flask containing the side-chain protected resin-bound peptide (Rink AM resin, 450.5 g, 200 mmol) at 25 °C and stirred for 2 h.

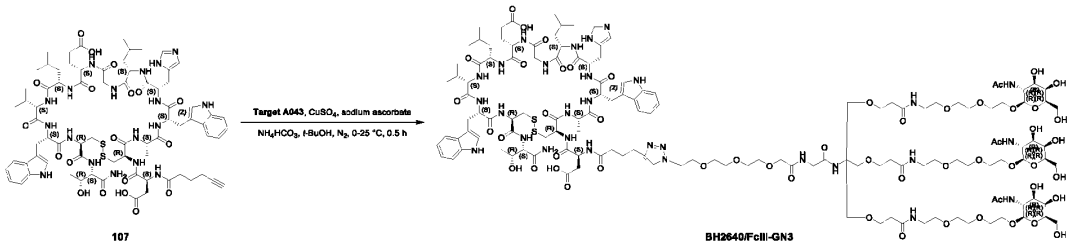
2) After filtration, the filtrate was collected.

3) The filtrate was precipitated with cold isopropyl ether (30 L). After filtration, the solid was washed with isopropyl ether (5 L) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 106** (320.0 g, crude) as a white solid.

4) To the mixture of **Intermediate 106** (320.0 g, crude) in HOAc/MeCN/H_2O (4/3/3, v/v/v, 70 L) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 107** (109.0 g, 90.7% purity, 30.4% yield) as a white solid. LCMS: RT = 10.492 min, MS calcd.: M_{av} = 1623.85, mass observed: $[M + H]^+$ = 1625.57, $[M + 2H]^{2+}$ = 813.02.

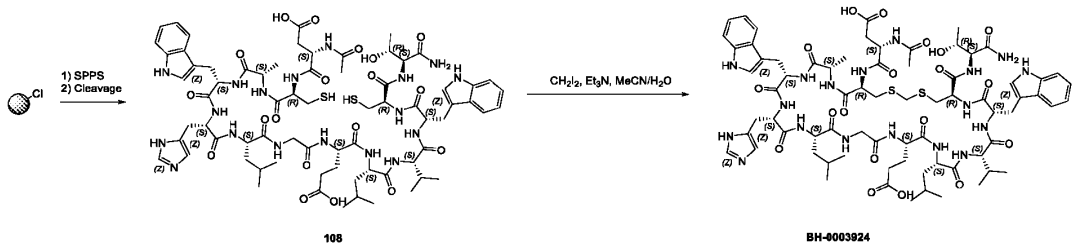
5) Another 200 mmol resin was performed to afford **Intermediate 107** as 107.8 g.

[0203] ***Preparation of BH0002640 (FcII-GN3):***



[0204] A mixture of **Target A043** (15.0 g, crude, 9.30 mmol, 1.00 equiv.) and **Intermediate 107** (8.86 g, 5.46 mmol, 1.00 equiv.) in NH_4HCO_3 (0.2 M, 100 mL, 3.67 equiv.) and *t*-BuOH (100 mL) was added $CuSO_4.5H_2O$ (0.4 M, 13.64 mL, 1.00 equiv.) and sodium ascorbate (4.32 g, 21.8 mmol, 4.00 equiv.). The resulting reaction was degassed and purged with N_2 for three times. Then the mixture was stirred at 25 °C for 0.5 h under N_2 atmosphere. LC-MS showed **Target A043** was consumed completely, several new peaks were shown on LC-MS and desired compound was detected. The resulting reaction mixture was lyophilized to get a residue. The residue was purified by prep-HPLC (A: 0.075% HOAc in H_2O, B: MeCN) to afford **BH0002640** (7.0 g, 2.16 mmol, 98.4% purity, 23.2% yield, 0.42% TFA content, < 0.05% HOAc content, 2.00% water content) as a white solid. LCMS: RT = 1.554 min, MS cal.: 3234.47, mass observed: $[M + H]^+$ = 3235.44, $[M + 2H]^{2+}$ = 1618.72. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.71 (br s, 2 H), 8.66 (br s, 2 H), 8.19 - 8.39 (m, 5 H), 8.15 (br d, *J* = 7.28 Hz, 1 H), 8.05 (br s, 2 H), 7.95 (br t, *J* = 5.65 Hz, 3 H), 7.70 - 7.87 (m, 6 H), 7.62 (d, *J* = 9.03 Hz, 3 H), 7.52 (br d, *J* = 8.03 Hz, 1 H), 7.42 (br d, *J* = 7.53 Hz, 1 H), 7.22 - 7.29 (m, 4 H), 7.18 (br s, 1 H), 7.11 (br s, 1 H), 7.07 (br s, 1 H), 7.01 (q, *J* = 7.45 Hz, 2 H), 6.88 - 6.94 (m, 3 H), 4.87 (br s, 2 H), 4.61 - 4.82 (m, 7 H), 4.52 (br s, 5 H), 4.45 (br t, *J* = 5.14 Hz, 3 H), 4.31 - 4.41 (m, 3 H), 4.28 (d, *J* = 8.53 Hz, 5 H), 4.09 - 4.18 (m, 2 H), 3.94 - 4.09 (m, 3 H), 3.91 (s, 3 H), 3.75 - 3.82 (m, 6 H), 3.73 (br d, *J* = 8.53 Hz, 4 H), 3.67 - 3.70 (m, 2 H), 3.64 (br d, *J* = 2.76 Hz, 4 H), 3.51 - 3.59 (m, 27 H), 3.43 (br d, *J* = 3.01 Hz, 3 H), 3.39 (br t, *J* = 5.77 Hz, 10 H), 3.30 (br t, *J* = 6.15 Hz, 6 H), 3.20 (q, *J* = 5.94 Hz, 9 H), 3.09 (br d, *J* = 14.31 Hz, 4 H), 2.92 (br s, 10 H), 2.73 (br s, 1 H), 2.58 (br t, *J* = 7.53 Hz, 3 H), 2.30 (br t, *J* = 6.27 Hz, 6 H), 2.18 (br s, 4 H), 1.90 - 1.98 (m, 1 H), 1.86 (s, 1 H), 1.80 (s, 12 H), 1.26 - 1.58 (m, 6 H), 1.15 (br d, *J* = 6.78 Hz, 3 H), 1.03 (br d, *J*=6.27 Hz, 3 H), 0.81 (br d, *J* = 6.27 Hz, 3 H), 0.77 (br d, *J* = 6.02 Hz, 6 H), 0.66 - 0.74 (m, 6 H), 0.63 (br d, *J* = 6.53 Hz, 3 H).

EXAMPLE 23. Procedure for Preparation of BH-0003924.



[0205] **Intermediate 108** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0048]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 16.

Table 16: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Acetylation	Ac2O/NMM/DMF(10/5/85, V/V/V, 50 mL)

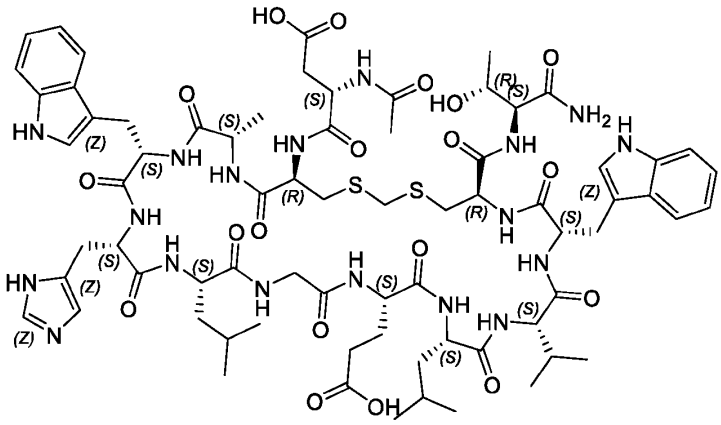
[0206] Cleavage and Cyclizaiton.

1) Cleavage solution (TFA/TIS/H2O, 95/2.5/2.5, v/v/v, 30 mL) was added to the flask containing the side-chain protected resin-bound peptide Intermediate 108 (Rink AM resin, 1.87 g, 0.50 mmol) at 25 ºC and stirred for 2 h.

2) After filtration, the filtrate was collected.

3) The filtrate was precipitated with cold isopropyl ether (150 mL). After filtration, the solid was washed with isopropyl ether (150 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 108** (793 mg, crude) as a white solid.

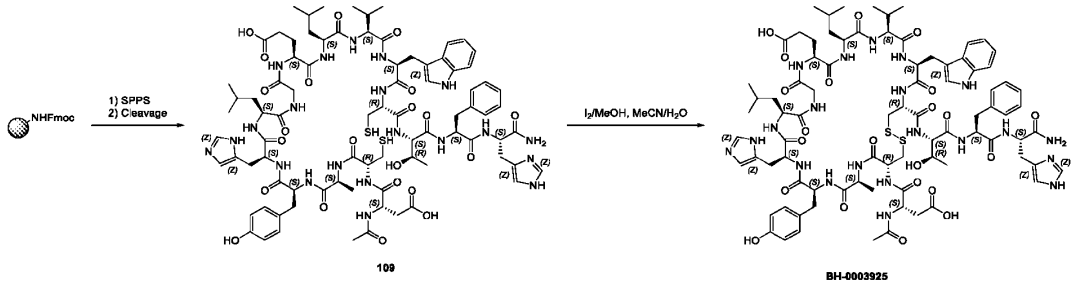
[0207] To a mixture of **Intermediate 108** (793 mg, crude) in MeCN/H_2O (4/6, v/v/, 500 mL) was added CH_2I_2 (15.0 equiv.) and Et_3N (6.00 equiv.), then the mixture was stirred at 25 °C for 8 h under N_2. The mixture was quenched by addition of 1 M HCl. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **BH-0003924** (94.0 mg, 96.4% purity, 11.4% yield) was obtained as a white solid after lyophilization. LCMS: RT = 1.41 min, MS calcd.: M_{av} = 1585.80, mass observed: $[M + H]^+$ = 1586.80, $[M + 2H]^{2+}$ = 793.6.



Molecular Weight: 1585.80

BH-0003924

EXAMPLE 24. Procedure for Preparation of BH-0003925.

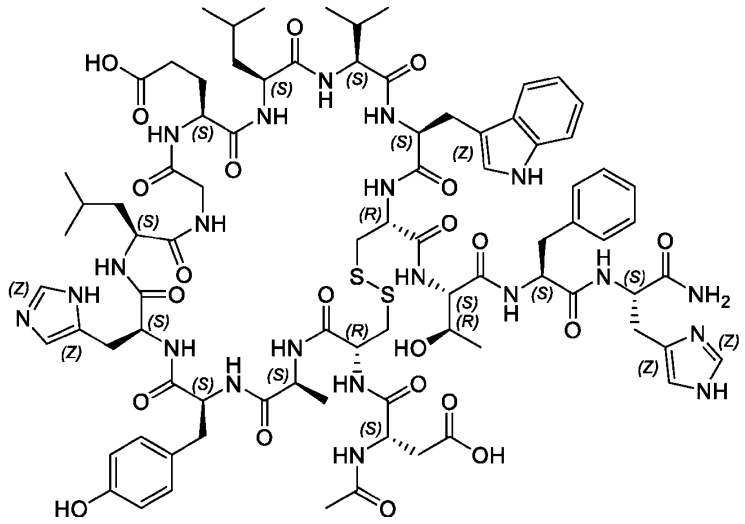


[0208] **Intermediate 109** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0048]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 17.

Table 17: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
2	Fmoc-Phe-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Tyr-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
16	Acetylation	Ac2O/NMM/DMF(10/5/85, V/V/V, 50 mL)

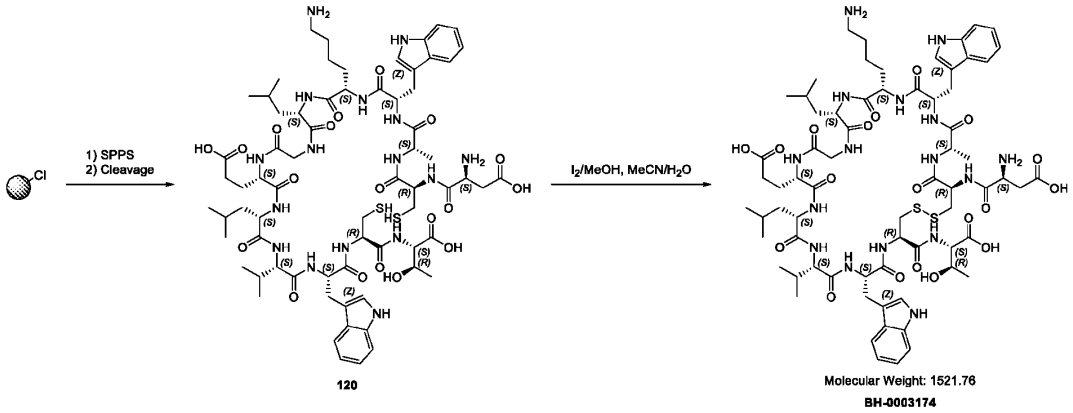
[0209] **BH-0003925** (peptide cleavage, disulfide formation) was synthesized by following the procedure mentioned in section **[0049]**. 0.50 mmol resin afforded **BH-0003925** (80.6 mg, 97.8% purity, 8.60% yield) was obtained as a white solid after lyophilization. LCMS: RT = 1.38 min, MS calcd.: M_{av} = 1833.05, mass observed: $[M + H]^+$ = 1834.0, $[M + 2H]^{2+}$ = 917.2.



Molecular Weight: 1833.05

BH-0003925

EXAMPLE 25. Procedure for Preparation of BH-0003174.

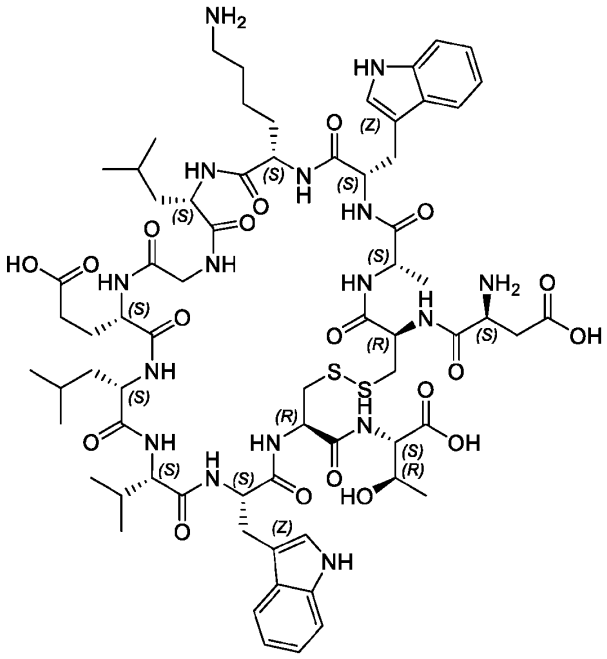


[0210] **Intermediate 120** (resin-bound peptide) was synthesized by following the procedure mentioned in section **[0059]**. SPPS (0.50 mmol loading resin) was performed with amino acids elongation shown in Table 18.

Table 18: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

[0211] **BH-0003174** (peptide cleavage, disulfide formation) was synthesized by following the procedure mentioned in section **[0060]**. 0.5 mmol resin afforded **BH-0003174** (93 mg, 94.6% purity, 11.6% yield) as a white solid. LCMS: RT = 0.81 min, MS calcd.: M_{av} = 1521.76, mass observed: $[M + H]^+$ = 1521.76, $[M + 2H]^{2+}$ = 761.50



Molecular Weight: 1521.76

BH-0003174

EXAMPLE 26. Procedure for Preparation of BH-0003747.

BH-0003747

[0212] **BH-0003747** was synthesized by following the procedure mentioned in section **[0059]**.

SPPS (1.00 mmol resin) was performed with amino acids elongation shown in Table 19, Number # 1-58.

Table 19: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Lys(Boc)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

9	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
16	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
17	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
18	Fmoc-Ser(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
19	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
20	Fmoc-Ser(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
21	Fmoc-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
22	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
23	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
24	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
25	Fmoc-Leu-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
26	Fmoc-Ser(*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
27	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
28	Fmoc-Ile-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
29	Fmoc-Phe-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
30	Fmoc-Ala-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
31	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
32	Fmoc-Arg(Pbf)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
33	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
34	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
35	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
36	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
37	Fmoc-Leu-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
38	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
39	Fmoc-Pro-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
40	Fmoc-Leu-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
41	Fmoc-His(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
42	Fmoc-Leu-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
43	Fmoc-Ile-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
44	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
45	Fmoc-Tyr(tBu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
46	Fmoc-Phe-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
47	Fmoc-Ala-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
48	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
49	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
50	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)

51	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
52	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
53	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
54	Fmoc-Phe-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
55	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
56	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
57	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
58	Fmoc-Val-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)

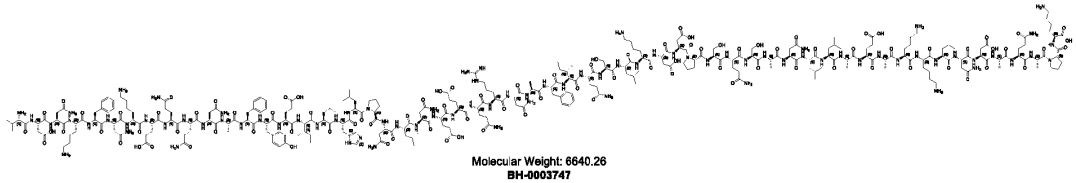
[0213] Peptide cleavage.

1) Cleavage solution (TFA/TIS/H2O, 95/2.5/2.5, v/v/v, 250 mL) was added to the flask containing the side-chain protected resin-bound peptide, 7.89 g, 1.00 mmol) at 25 ºC and stirred for 2 h.

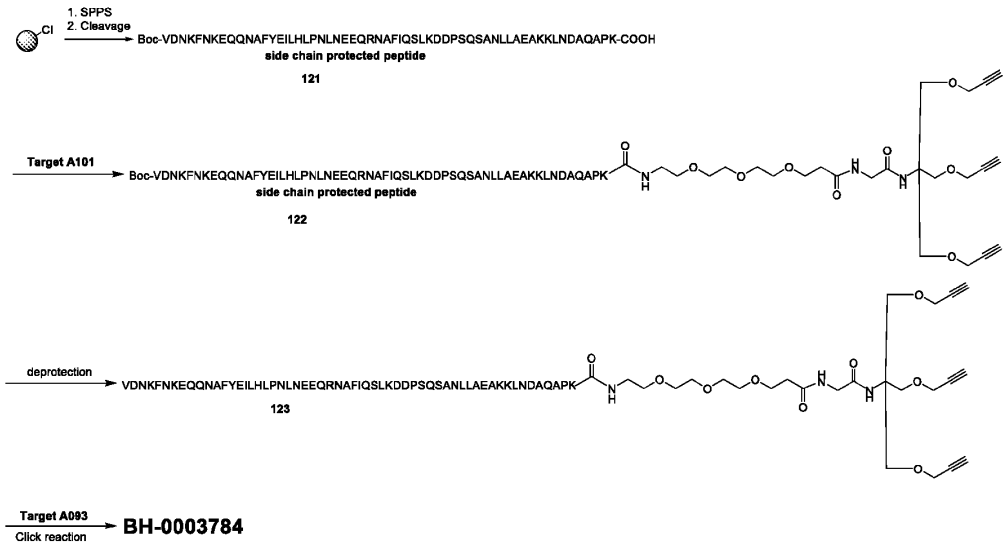
2) After filtration, the filtrate was collected.

3) The filtrate was precipitated with cold isopropyl ether (600 mL). After filtration, the solid was washed with isopropyl ether (600 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **BH-0003747** (6.53 g, crude) as a white solid.

4) The crude **BH-0003747** was purified by prep-HPLC (A: 0.075% TFA/H2O, B: MeCN), followed by lyophilization to afford BH-0003747 (547.1 mg, 97.8% purity, 8.05% yield) as a white solid. LCMS: RT = 0.72 min, MS calcd.: Mav = 6640.26, mass observed: $[M + 4H]^{4+}$ = 1660.80, $[M + 5H]^{5+}$ = 1328.90, $[M + 6H]^{6+}$ = 1107.70, $[M + 7H]^{7+}$ = 949.52, $[M + 8H]^{8+}$ = 830.90, $[M + 9H]^{9+}$ = 738.80, $[M + 11H]^{11+}$ = 604.61, $[M + 12H]^{12+}$ =554.30.



EXAMPLE 27. Procedure for Preparation of BH-0003784.



[0214] **Intermediate 121** was synthesized by following the procedure mentioned in section **[0059]** SPPS (1.00 mmol resin) was performed with amino acids elongation shown in Table 20, Number # 1-59.

Table 20: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Lys(Boc)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
16	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
17	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
18	Fmoc-Ser(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
19	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
20	Fmoc-Ser(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

21	Fmoc-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
22	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
23	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
24	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
25	Fmoc-Leu-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
26	Fmoc-Ser(*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
27	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
28	Fmoc-Ile-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
29	Fmoc-Phe-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
30	Fmoc-Ala-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
31	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
32	Fmoc-Arg(Pbf)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
33	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
34	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
35	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
36	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
37	Fmoc-Leu-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
38	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
39	Fmoc-Pro-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
40	Fmoc-Leu-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
41	Fmoc-His(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
42	Fmoc-Leu-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
43	Fmoc-Ile-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
44	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
45	Fmoc-Tyr(tBu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
46	Fmoc-Phe-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
47	Fmoc-Ala-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
48	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
49	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
50	Fmoc-Gln(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
51	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
52	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
53	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
54	Fmoc-Phe-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
55	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
56	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
57	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
58	Fmoc-Val-OH (3.00 equiv.)	HATU (2.85 equiv.) and DIEA (6.00 equiv.)
59	Boc_2O (6.00 equiv.)	DIEA (12.0 equiv.)

[0215] Peptide cleavage and fragment coupling.

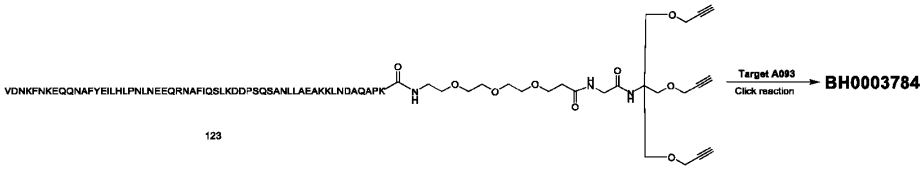
1) Cleavage from resin: A solution of 20% HFIP/DCM (50 mL) was added to the resin above at room temperature and stirred for 1 h. After filtration, the filtrate was collected and concentrated under reduced pressure to afford fully protected peptide **Intermediate 121** (6.51 g, crude) as a white solid.

2) Fragments coupling: To the mixture of **Intermediate 121** (1.40 g, crude, 122.0 μmol, 1.00 equiv.), **Target A101** (120.9 mg, 244.0 mmol, 2.00 equiv.), HOBt (49.4 mg, 366.0 mmol, 3.00 equiv.) in DMF (2.0 mL) was added EDCI (69.9 mg, 366.0 mmol, 3.00 equiv.) at 0 °C. The resulting reaction was stirred for 8 h at 25 °C. The reaction was added into flask with cold 0.1 M HCl (30 mL), and the precipitate was filtered off to afford the crude as **Intermediate 122**.

3) Deprotection: A solution of TFA/TIS/H_2O/3-mercaptopropanoic acid (v/v/v/v, 92.5/2.5/2.5/2.5, 20 mL) was added to the flask containing **Intermediate 122** (crude) in step 2, and the resulting mixture was stirred for 1 h at 25 °C. The mixture was precipitated with cold isopropyl ether (100 mL), then filtered off, and the solid was washed with isopropyl ether (50 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 123** (845 mg, crude) as a white solid.

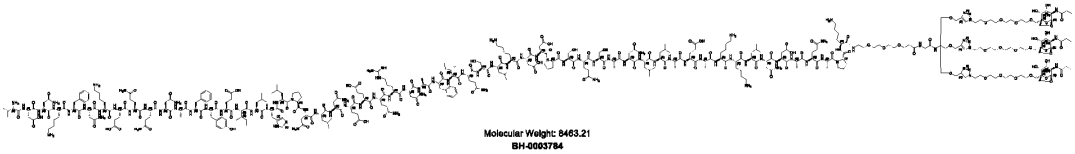
5) The crude **Intermediate 123** was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 123** (120 mg, 13.8% yield) as a white solid.

[0216] ***Preparation of BH0003784 (click reaction):***

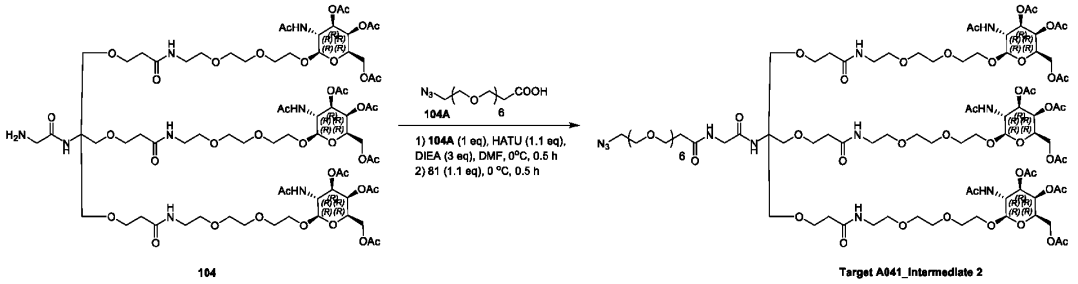


[0217] Click reaction **BH0003784** was synthesized using the same procedure as **BH0003610,** which was performed by following the procedure mentioned in **[0050]- [0051]**.

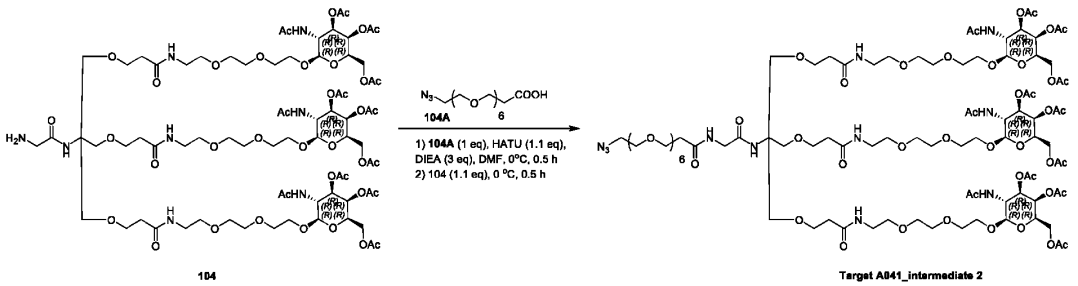
[0218] 30.2 mg of **Target A093** afforded **BH0003784** (92 mg, 90.7% purity, 58.5% yield) as a white solid. LCMS: RT =1.26 min, MS calcd.: M_{av} = 8463.21, mass observed: $[M + 5H]^{5+}$ = 1693.6, $[M + 6H]^{6+}$ = 1411.6, $[M + 7H]^{7+}$ = 1210.1, $[M + 8H]^{8+}$ = 1058.9, $[M + 9H]^{9+}$ = 941.5, $[M + 10H]^{10+}$ =847.3, $[M + 11H]^{11+}$ = 770.5, $[M + 12H]^{12+}$ =706.2, $[M + 13H]^{13+}$ = 652.1, $[M + 14H]^{14+}$ = 605.5.



EXAMPLE 28. Procedure for Preparation of Target A041_Intermediate 2.

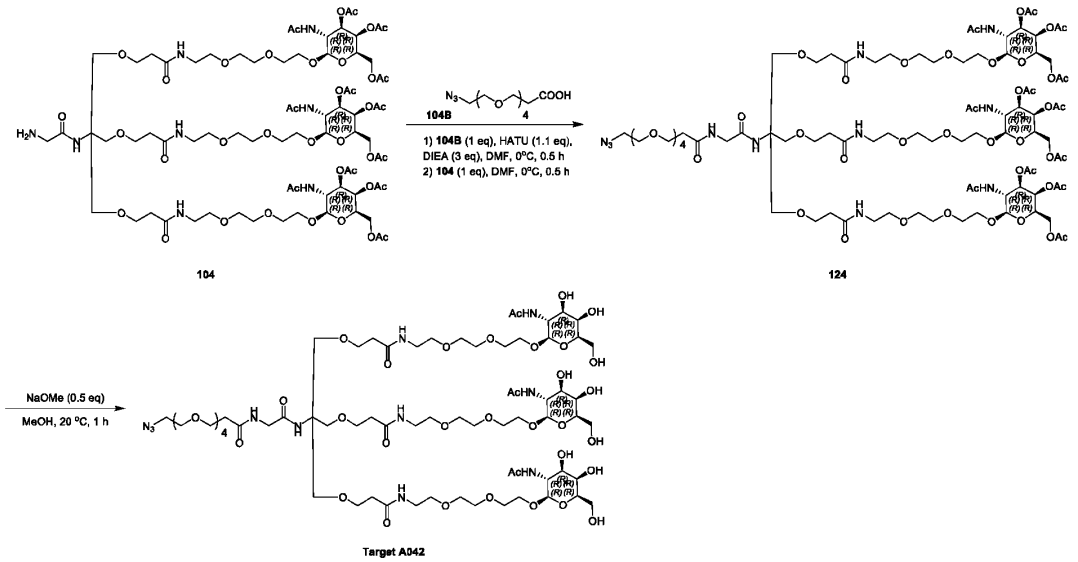


[0219] ***Preparation of*** **Target A041_Intermediate 2*:***

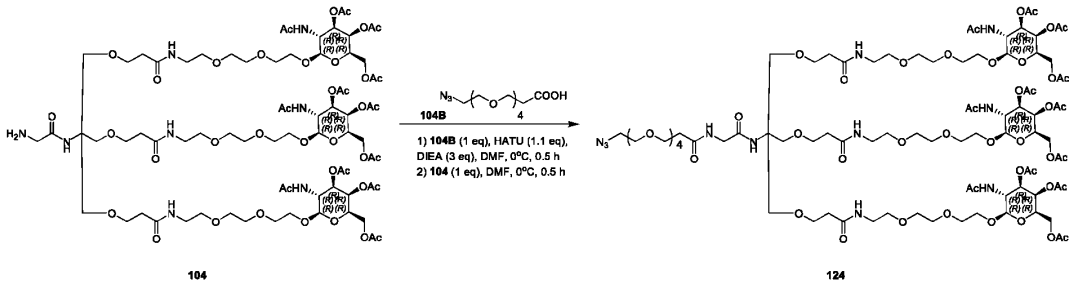


[0220] To a solution of **Intermediate 104A** (100 mg, 263.57 umol, 1 equiv.) in DMF (2 mL) was added HATU (110.24 mg, 289.93 umol, 1.1 equiv.) and DIEA (102.19 mg, 790.71 umol, 137.73 uL, 3 equiv.) at 0°C and the reaction was stirred for 0.5 h at 0°C. Then **Intermediate 104** (514.85 mg, 289.93 umol, 1.1 equiv.) was added at 0 °C and the reaction was stirred 0.5 h at 0 °C. TLC showed the reaction was completed. The reaction was poured into H_2O (20 mL) and extracted with DCM (10 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (SiO_2, dichloromethane: methanol = 100: 1 to 10: 1) to give **Target 041_Intermediate 2** (310 mg, 145.05 umol, 55.03% yield, 100% purity) as yellow solid. LCMS: RT = 2.596 min, MS cal.: 2135.9, found: $[M/3 + H]^+$ = 713.2. ^{1}H NMR (400 MHz, MeOH-*d4*) δ ppm = 5.34 (d, *J* =3.07 Hz, 3 H), 5.07 (dd, *J* =11.18, 3.07 Hz, 3 H), 4.65 (d, *J* =8.55 Hz, 3 H), 4.00 - 4.20 (m, 12 H), 3.91 - 3.99 (m, 3 H), 3.86 (s, 2 H), 3.60 - 3.79 (m, 59 H), 3.54 - 3.59 (m, 6 H), 3.39 (br t, *J* =4.93 Hz, 8 H), 2.42 - 2.48 (m, 6 H), 2.15 (s, 9 H), 2.03 (s, 9 H), 1.95 (d, *J* =5.92 Hz, 18 H). Theoretical number of H: 149, found: 141, exchangeable H: 8.

EXAMPLE 29 Procedure for Preparation of Target A042.



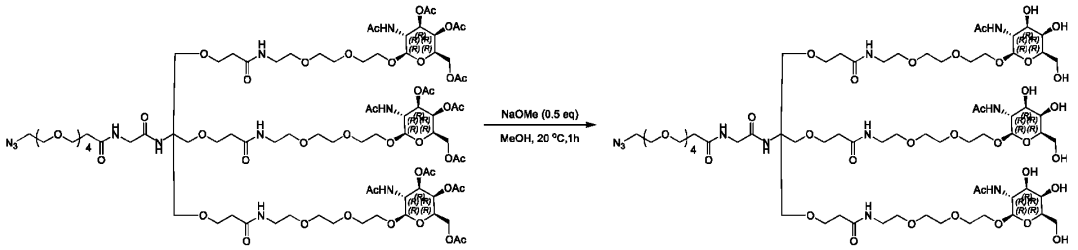
[0221] **Preparation of Intermediate *124*:**



[0222] To a solution of **Intermediate 104B** (100 mg, 343.29 umol, 1 equiv.) in DMF (20 mL) was added HATU (143.58 mg, 377.62 umol, 1.1 equiv.) and DIEA (133.10 mg, 1.03 mmol, 179.38 uL, 3 equiv.) at 0 °C and the reaction was stirred for 0.5 h at 0 °C. Then **Intermediate 104** (609.61 mg, 343.29 umol, 1 equiv.) was added at 0 °C and the reaction was stirred for 0.5 h at 0 °C. TLC showed the reaction was completed. The reaction was poured into H_2O (50 mL) and extracted with DCM (30 mL x 2). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (SiO_2, dichloromethane: methanol = 100: 1 to 10: 1) to give **Intermediate 124** (200 mg, 97.60 umol, 28.43% yield) as white solid. LCMS: RT = 1.821 min, MS cal.: 2049.1, found: $[M/2 + H]^+$ = 1025.6. ^{1}H NMR (400 MHz, MeOH-*d4*) δ = 5.34 (d, *J* = 3.1 Hz, 3H), 5.07 (dd, *J* = 3.3, 11.2 Hz, 3H), 4.65 (d, *J* = 8.5 Hz, 3H), 4.17 - 4.00 (m, 13H), 3.97 - 3.91 (m, 3H), 3.77 - 3.60 (m, 52H), 3.58 - 3.53 (m, 6H), 3.39 (br t,

J = 5.0 Hz, 8H), 2.45 (t, *J* = 6.0 Hz, 6H), 2.15 (s, 9H), 2.03 (s, 9H), 1.95 (d, *J* = 5.8 Hz, 18H). Theoretical number of H: 141, found: 133, exchangeable H: 8.

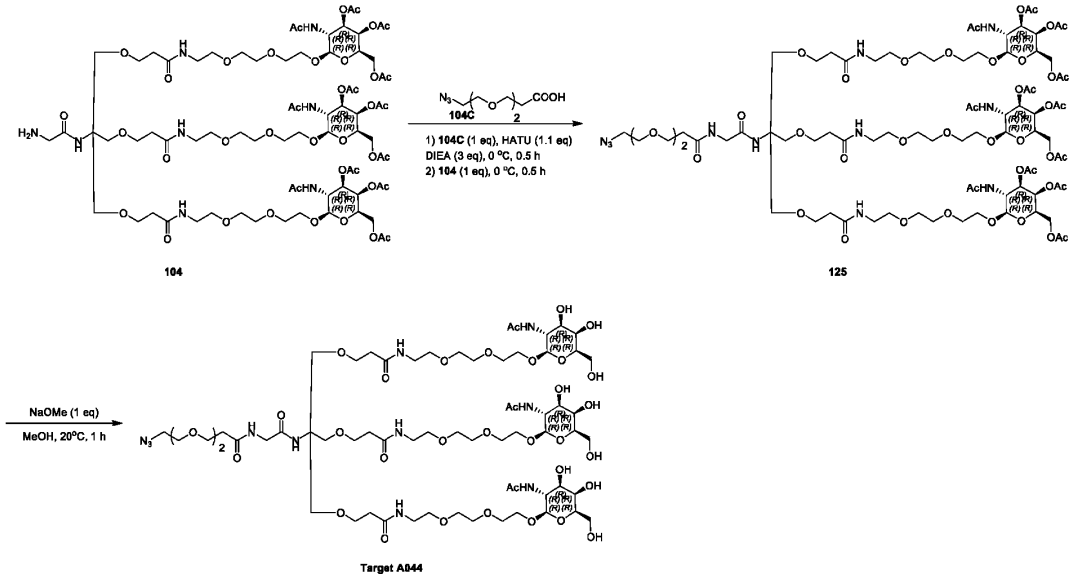
[0223] ***Preparation of Target A042***



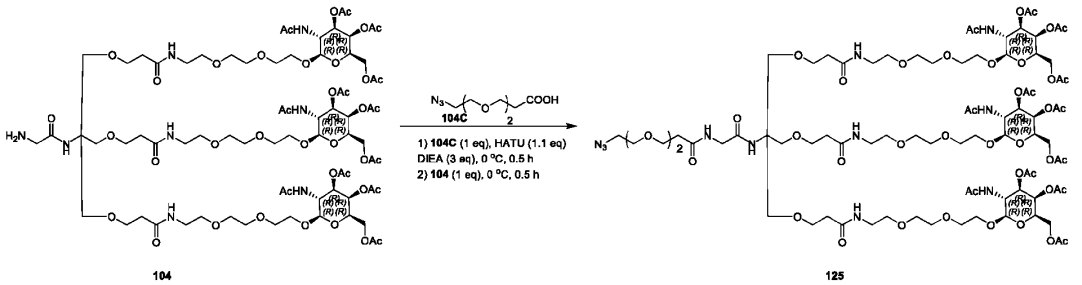
124 Target A042

[0224] To a solution of **Intermediate 124** (230 mg, 112.25 umol, 1 equiv.) in MeOH (3 mL) was added NaOMe (3.03 mg, 56.12 umol, 0.5 equiv.). The mixture was stirred at 20 °C for 1 h. LCMS showed Reactant 1 was consumed and one new peak of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give **Target A042** (183.04 mg, 109.56 umol, 97.60% yield) as yellow oil. LCMS: RT = 0.553 min, MS cal.: 1669.81, $[M/2+H]^+$ = 836.3. ^{1}H NMR (400MHz, MeOD) δ = 4.44 (d, *J* = 8.4 Hz, 3H), 4.00 - 3.91 (m, 6H), 3.88 (s, 2H), 3.84 (d, *J* = 2.9 Hz, 3H), 3.76 (t, *J* = 6.4 Hz, 7H), 3.70 - 3.67 (m, 14H), 3.61 - 3.61 (m, 1H), 3.67 - 3.60 (m, 33H), 3.59 - 3.54 (m, 8H), 3.51 (t, *J* = 6.1 Hz, 4H), 3.42 - 3.36 (m, 8H), 2.55 (t, *J* = 6.2 Hz, 2H), 2.45 (t, *J* = 6.0 Hz, 6H), 1.99 (s, 9H). Theoretical number of H: 123, found: 106, exchangeable H: 17.

EXAMPLE 30 Procedure for Preparation of Target A044



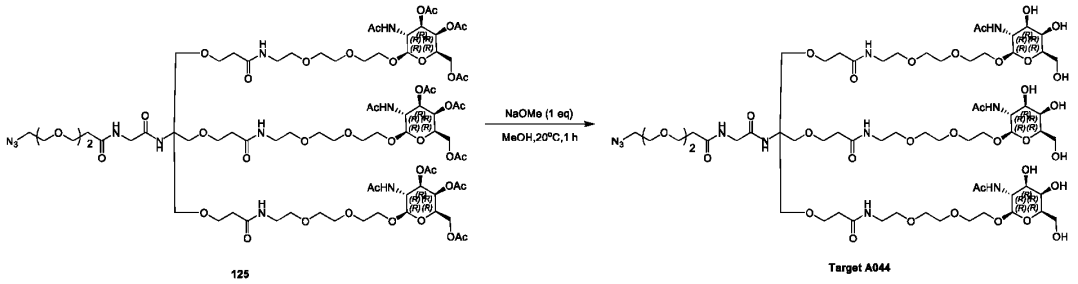
[0225] **Preparation of Intermediate *91*:**



[0226] To a solution of **Intermediate 104C** (80 mg, 422.90 umol, 1.0 equiv.) in DMF (10 mL) was added HATU (176.88 mg, 465.19 umol, 1.1 equiv.) and DIEA (163.97 mg, 1.27 mmol, 220.98 uL, 3.0 equiv.) at 0°C and the reaction was stirred for 0.5 h at 0°C. **Intermediate 104** (750.99 mg, 422.90 umol, 1.0 equiv.) was added to the reaction mixture at 0°C and the reaction was stirred for 0.5 h at 0°C. TLC showed the reaction was completed. The reaction was poured into H_2O (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layer was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (SiO_2, DCM: MeOH = 100/1 to 10/1) to give **Intermediate 125** (270 mg, 32.79% yield) as colorless oil. LCMS: RT = 1.750 min, MS cal.: 1946.9, $[M/2+H]^+$ = 974.5. ^1H NMR (400 MHz, MeOH-d_4) δ = 5.32 (d, *J* = 3.1 Hz, 3H), 5.06 (dd, *J* = 3.5, 11.2 Hz, 3H), 4.63 (d, *J* = 8.3 Hz, 3H), 4.16 - 4.00 (m, 14H), 3.95 - 3.95 (m, 1H), 3.95 - 3.90 (m, 5H), 3.73 - 3.60 (m, 39H), 3.56 - 3.52 (m, 6H), 3.42 - 3.36 (m, 8H),

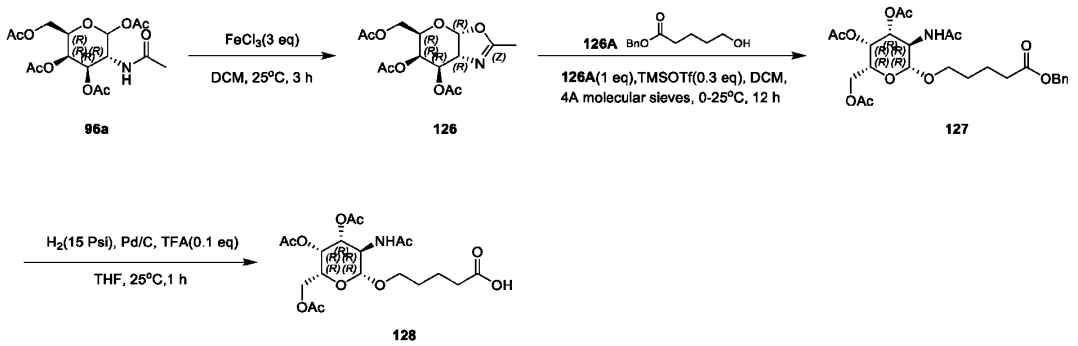
2.43 (t, *J* = 6.0 Hz, 6H), 2.13 (s, 9H), 2.01 (s, 9H), 1.93 (d, *J* = 6.1 Hz, 18H) Theoretical number of H:133, found: 125, exchangeable H: 8.

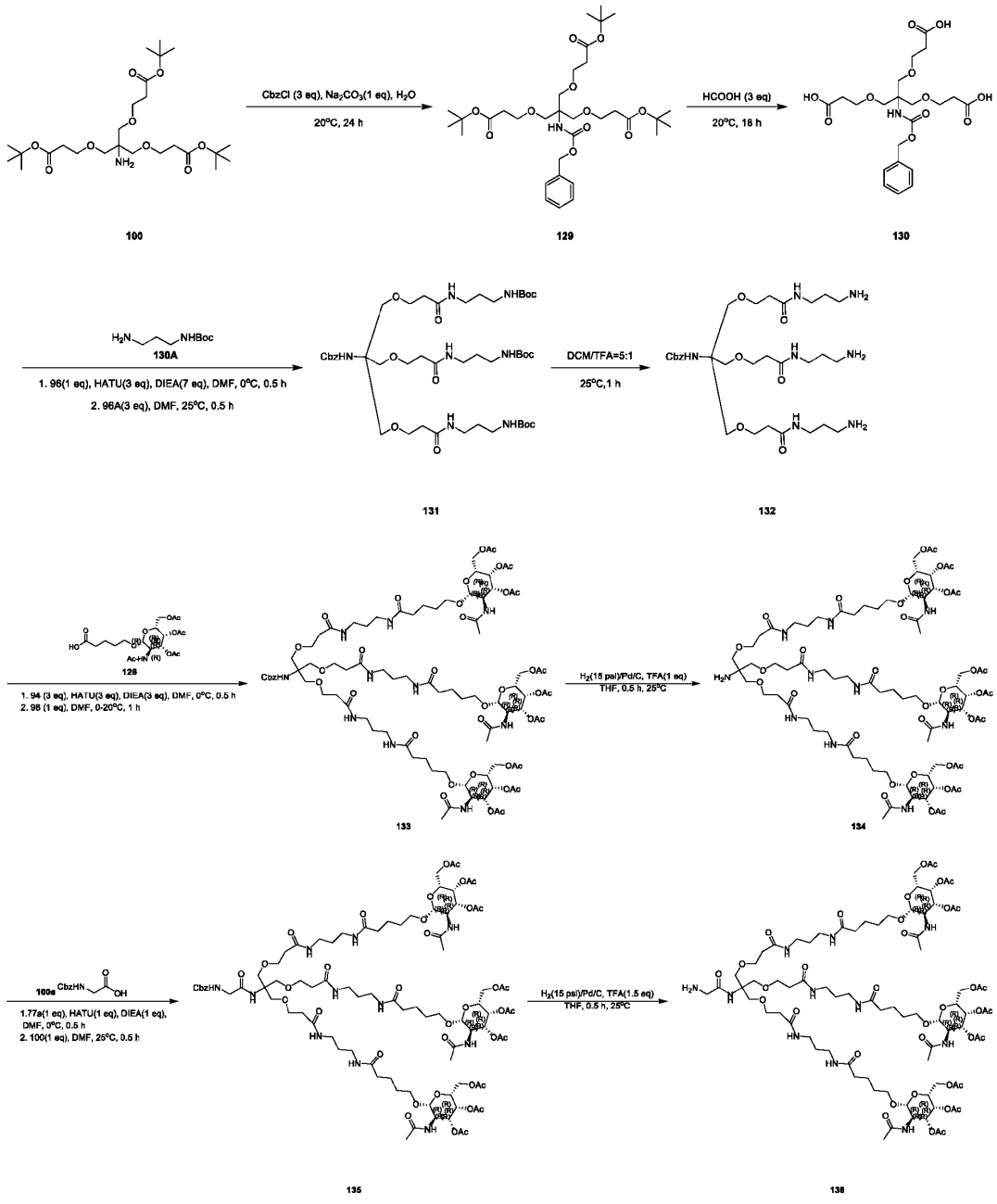
[0227] ***Preparation of Target A044***

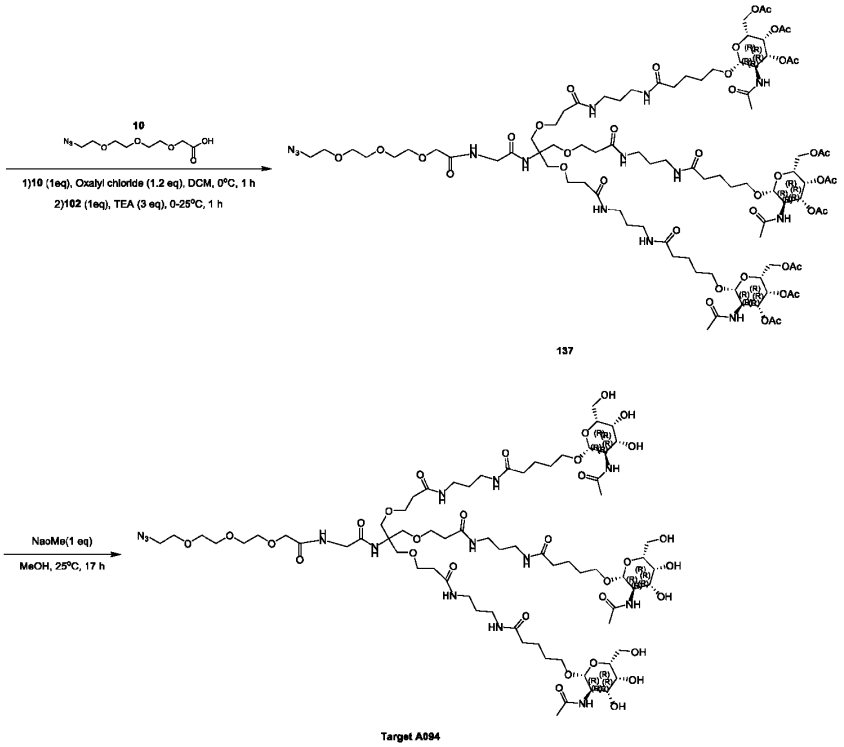


[0228] To a solution of **Intermediate 125** (270.00 mg, 138.68 umol, 1.0 *equiv.*) in MeOH (3 mL) was added NaOMe (7.49 mg, 138.68 umol, 1.0 *equiv.*). The mixture was stirred at 20 °C for 1 h. LCMS showed Reactant 1 was consumed, and one new peak of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give **Target A044** (205.41 mg, 130.95 umol, 94.43% yield) as a white solid. LCMS: RT = 1.833 min, MS cal.: 1567.75, $[M/2+H]^+$ = 785.0. ^{1}H NMR (400MHz, MeOD) δ = 4.44 (d, *J* =8.4 Hz, 3H), 4.08 (s, 2H), 4.00 - 3.91 (m, 8H), 3.84 (d, J =3.1 Hz, 3H), 3.79 - 3.73 (m, 8H), 3.73 - 3.68 (m, 18H), 3.66 - 3.60 (m, 20H), 3.59 - 3.53 (m, 8H), 3.52 - 3.48 (m, 3H), 3.44 - 3.38 (m, 8H), 2.45 (t, *J* =6.0 Hz, 6H), 1.99 (s, 9H). Theoretical number of H: 113, found: 96, exchangeable H: 17.

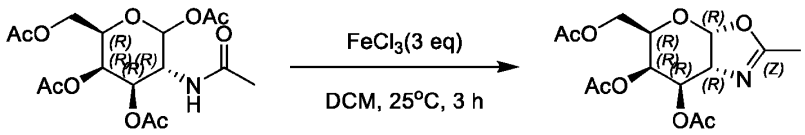
EXAMPLE 31. Procedure for Preparation of Target A094




CbzCl (3 eq), Na2CO3(1 eq), H2O
20°C, 24 h
HCOOH (3 eq)
20°C, 16 h
100
129
130
130A
1. 96(1 eq), HATU(3 eq), DIEA(7 eq), DMF, 0°C, 0.5 h
2. 96A(3 eq), DMF, 25°C, 0.5 h
DCM/TFA=5:1
25°C,1 h
131
132
128
1. 94 (3 eq), HATU(3 eq), DIEA(3 eq), DMF, 0°C, 0.5 h
2. 98 (1 eq), DMF, 0-20°C, 1 h
H2(15 psi)/Pd/C, TFA(1 eq)
THF, 0.5 h, 25°C
133
134
100a
1.77a(1 eq), HATU(1 eq), DIEA(1 eq),
DMF, 0°C, 0.5 h
2. 100(1 eq), DMF, 25°C, 0.5 h
H2(15 psi)/Pd/C, TFA(1.5 eq)
THF, 0.5 h, 25°C
135
136



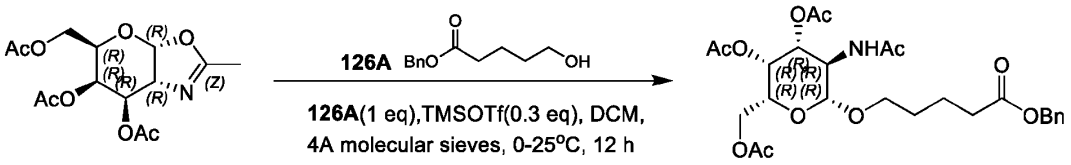
[0229] ***Preparation of Intermediate 126:***



96a **126**

[0230] To a solution of **Intermediate 96a** (5.00 g, 12.84 mmol, 1.00 equiv.) in DCM (500 mL) was added $FeCl_3$ (6.25 g, 38.53 mmol, 2.23 mL, 3.00 equiv.). The mixture was stirred at 25 °C for 3 h. TLC (DCM: MeOH = 10:1, Starting material R_f = 0.6, product R_f = 0.7) showed the one new point was detected and the reactant was consumed. The reaction mixture was diluted with DCM (100 mL) and extracted with H_2O (500 mL * 5). The combined organic layers were washed with brine (200 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **Intermediate 126** (4.10 g, crude) as white solid, which was used in the next step without further purification.

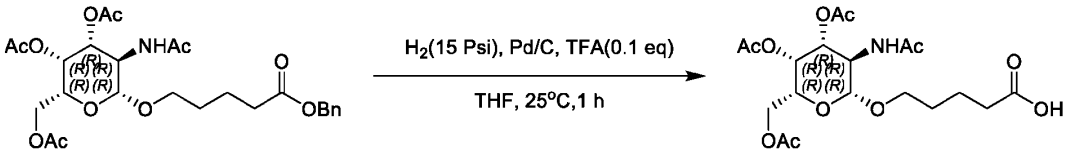
[0231] ***Preparation of Intermediate 127:***



126 127

[0232] To a solution of **Intermediate 126** (4.10 g, 12.45 mmol, 1.00 equiv.) and **Intermediate 126A** (2.59 g, 12.45 mmol, 1.00 equiv.) in DCM (80 mL) was added TMSOTf (830.17 mg, 3.74 mmol, 674.94 uL, 0.30 equiv.) and 4A molecular sieves (4.10 g) at 0 °C. The mixture was stirred at 25 °C for 12 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was diluted with H_2O (200 mL) and extracted with DCM (200 mL *3). The combined organic layers were washed with brine (200 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 100/1 to 30/1) to give **Intermediate 127** (3.60 g, 6.70 mmol, 53.79% yield) as a yellow solid. LCMS: RT = 1.970 min, MS cal.: 537.2, found: [M - H] $^+$ = 536.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.810-7.787 (d, J = 9.2 Hz, 1H), 7.373 – 7.322 (m, 6H), 5.212(s, 1H), 5.203(s, 1H), 5.078 – 4.934 (m, 1H), 4.490 - 4.469 (d, J = 8.4 Hz, 1H), 3.722 - 3.697(m, 5H), 3.431 - 3.406 (m, 1H), 2.373 – 2.337 (m, 2H), 2.097 (s, 3H), 1.990 (s, 3H), 1.888 (s, 3H), 1.738 (s, 3H), 1.574 – 1.488 (m, 4H). Theoretical number of H: 35, found: 35.

[0233] ***Preparation of Intermediate 128:***

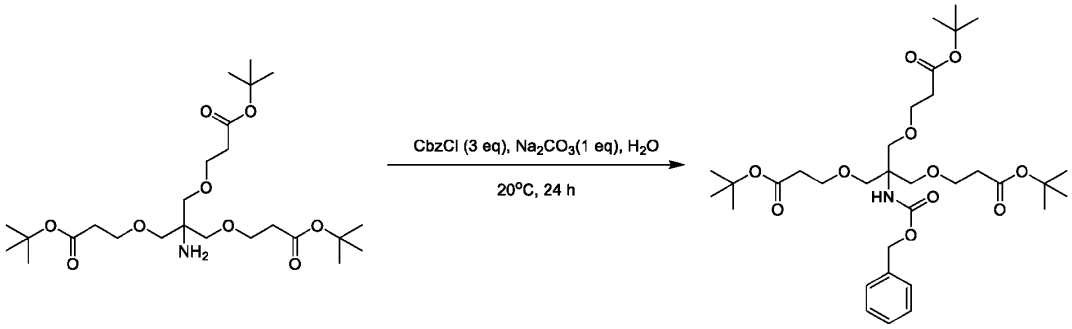


127 128

[0234] To a solution of **Intermediate 127** (3.00 g, 5.58 mmol, 1.00 equiv.) in THF (90 mL) was added Pd/C (1.00 g, 10% purity) and TFA (63.63 mg, 558.08 umol, 41.32 uL, 0.10 equiv.). The solution was degassed and purged with H_2 for 3 times, and stirred at 25 °C for 1 h under H_2 atmosphere. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to afford **Intermediate 128** (2.40 g, 5.36 mmol, 96.11% yield) as yellow oil, which was used in the next step without further purification. LCMS: RT = 0.926 min, MS cal.: 447.17, found: [M + H] $^+$ = 448.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.974 (*s*, 1H), 7.814 – 7.791 (d, J = 9.2 Hz, 1H), 7.245 – 7.159 (m, 1H), 5.210(s, 1H), 4.972 – 4.936 (m, 1H), 4.490 – 4.470 (d, J = 8 Hz, 1H), 4.019 (s, 3H), 3.689 -

3.580 (m, 7H), 2.097 (s, 3H), 1.770 (s, 3H), 1.763 (s, 3H), 1.493 – 1.486 (m, 4H). Theoretical number of H: 29, found: 29.

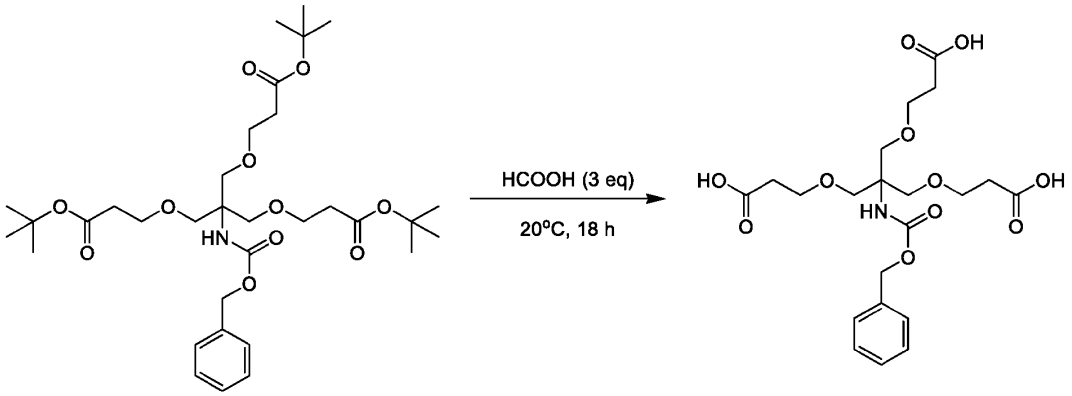
[0235] ***Preparation of Intermediate 129:***



100 **129**

[0236] To a solution of **Intermediate 100** (38.00 g, 75.15 mmol, 1.00 equiv.) in CH_2Cl_2 (323 mL) was added Na_2CO_3 (31.86 g, 75.15 mmol, 25% purity, 1.00 equiv.) while stirring. Then CbzCl (39.74 g, 232.97 mmol, 3.00 equiv.) was added dropwise and the reaction mixture was stirred for 24 h at 20 °C. TLC (Petrolum ether: ethyl acetate = 5:1, the starting material R_f = 0.5, product R_f = 0.3) showed the reaction was completed. The reaction was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: ethyl acetate = 100/1 to 10:/1) to give **Intermediate 129** (104.71 g, 163.67 mmol, 72.59% yield) as colouless oil.

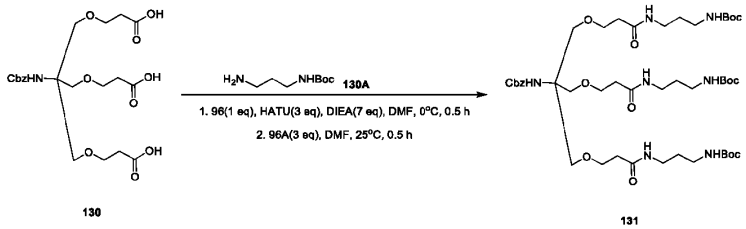
[0237] ***Preparation of Intermediate 130:***



129 **130**

[0238] To a solution of **Intermediate 129** (25.7 g, 40.17 mmol, 1.00 equiv.) in HCOOH (400 mL) was added formic acid (5.55 g, 120.51 mmol, 4.55 mL, 3.00 equiv.), then the reaction was stirred for 18 h at 20 °C. After completed, four parallel reactions were combined for work up. The reaction solution was concentrated under reduced pressure to give **Intermediate 130** (17.00 g, 89.76% yield) as colorless oil, which was used into next step directly without further purification.

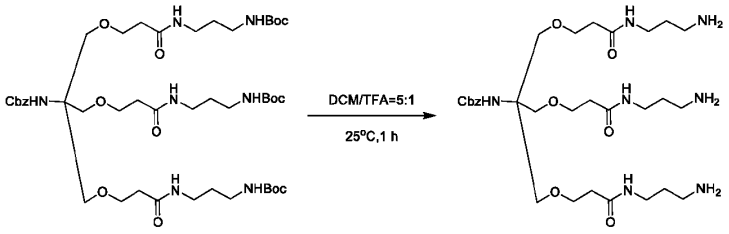
[0239] ***Preparation of Intermediate 131:***



130 131

[0240] To a solution of **Intermediate 130** (1.00 g, 2.12 mmol, 1.00 equiv.) in DMF (10 mL) was added HATU (2.42 g, 6.36 mmol, 3.00 equiv.) and DIEA (1.92 g, 14.85 mmol, 2.59 mL, 7.00 equiv.) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. Then **Intermediate 130A** (1.11 g, 6.36 mmol, 1.11 mL, 3.00 equiv.) was added and the mixture was stirred at 25 °C for 0.5 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine 10 mL (5 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 100/1 to 10/1) to afford **Intermediate 131** (1.9 g, 2.02 mmol, 95.28% yield) as a yellow solid. LCMS: RT = 2.264 min, MS cal.: 939.55, found: $[M + H]^+$ = 940.8.

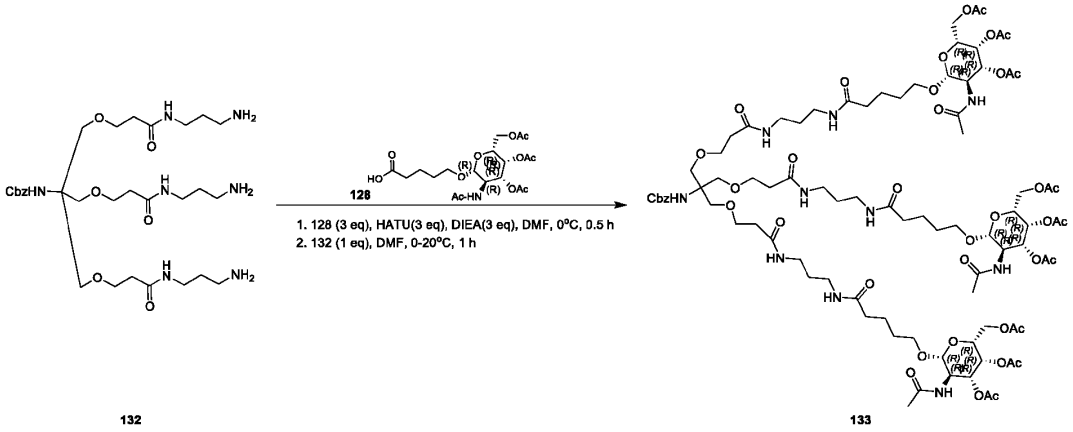
[0241] ***Preparation of Intermediate 132:***



131 132

[0242] To a solution of **intermediate 131** (2.00 g, 2.13 mmol, 1.00 equiv.) in DCM (20 mL) and TFA (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 h under N_2 atmosphere. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give **Intermediate 132** (1.30 g, 2.03 mmol, 95.51% yield) as yellow oil. LCMS: RT = 1.170 min, MS cal.: 639.4, found: $[M + H]^+$ = 640.5. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.052-8.024 (m, 3H), 7.854 - 7.757 (m, 9H), 7.384 - 7.306 (m, 5H), 6.546 (*s*, 1H), 4.984 (*s*, 2H), 3.652 – 3.483 (m, 9H), 3.130 – 3.082 (m, 6H), 2.791 – 2.742 (m, 6H), 2.321 – 2.290 (m, 6H), 1.697 – 1.627 (m, 6H). Theoretical number of H: 53, found: 53.

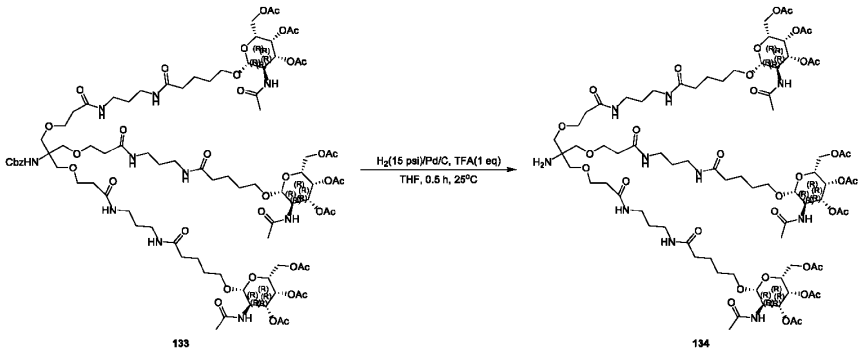
[0243] ***Preparation of Intermediate 133:***



132 133

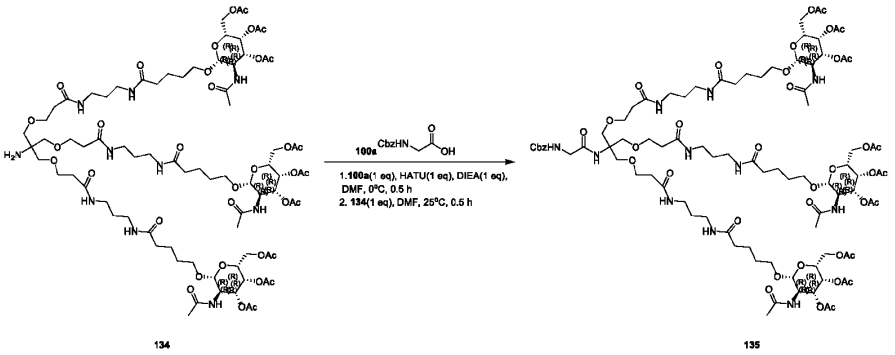
[0244] To a solution of **Intermediate 128** (2.00 g, 4.47 mmol, 3.00 equiv.) in DMF (10 mL) was added HATU (1.70 g, 4.47 mmol, 3.00 equiv.) and DIEA (577.71 mg, 4.47 mmol, 778.58 uL, 3.00 equiv) at 0 °C for 0.5 h. Then **Intermediate 132** was added at 0 °C. The mixture was stirred at 20 °C for 1 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was diluted with H_2O (200 mL) and extracted with DCM (200 mL *3). The combined organic layers were washed with brine (200 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 100/1 to 30/1) to give **Intermediate 133** (1.20 g, 622.40 umol, 41.77% yield) as yellow solid. LCMS: RT = 1.900 min, MS cal.: 1928.06, found: $[M/2+ H]^+$ = 965.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.829 - 7.807 (m, 6H), 7.739 - 7.711 (m, 3H), 7.354 - 7.314 (m, 6H), 5.214 - 4.982 (m, 3H), 4.973 - 4.945 (m, 5H), 4.492 - 4.471 (d, *J* = 8.4 Hz, 3H), 4.021 -3.011 (m, 46H), 2.287 - 2.272 (t, *J* = 3 Hz, 7H), 2.035 (*s*, 9H), 1.888 (*s*, 9H), 1.777 (*s*, 9H), 1.769 (*s*, 9H), 1.514 - 1.461 (m, 19H). Theoretical number of H: 134, found: 134.

[0245] ***Preparation of Intermediate 134:***



[0246] To a solution of **Intermediate 133** (1.00 g, 518.66 umol, 1.00 equiv.), Pd/C (500 mg, 518.66 umol, 10% purity, 1.00 equiv.) and TFA (59.14 mg, 518.66 umol, 38.40 uL, 1.00 equiv.) in THF (30 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25 °C for 0.5 h under H_2 atmosphere. LCMS showed reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to afford **Intermediate 134** (760.00 mg, 423.66 umol, 81.68% yield) as yellow oil, which was used in the next step without further purification. LCMS: RT = 1.673 min, MS cal.: 1792.85, found: $[M/2 + H]^+ = 898.2$.

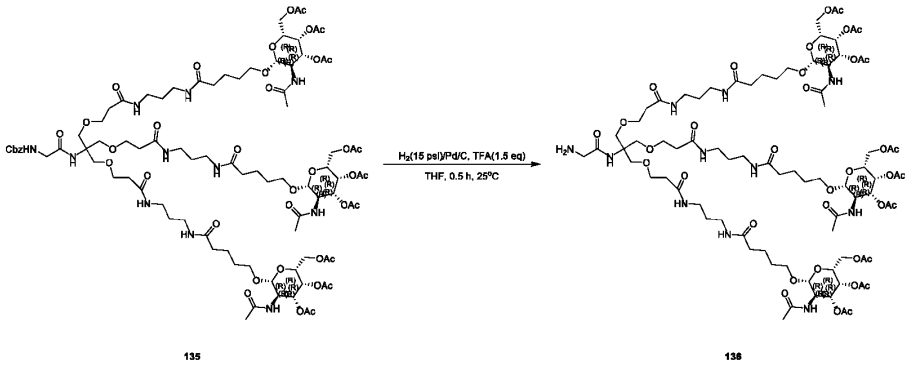
[0247] ***Preparation of Intermediate 135:***



[0248] To a solution of **Intermediate 100a** (93.29 mg, 445.96 umol, 1.00 equiv.) in DMF (8 mL) was added HATU (169.57 mg, 445.96 umol, 1.00 equiv.) and DIEA (57.64 mg, 445.96 umol, 77.68 uL, 1.00 equiv.) at 0 °C for 0.5 h. Then **Intermediate 134** (800.00 mg, 445.96 umol, 1.00 equiv.) was added, and the mixture was stirred at 25°C for 0.5 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase:

[water(TFA)-ACN];B%: 30%-50%,8min) to afford **Intermediate 135** (200.00 mg, 100.75 umol, 22.59% yield) as yellow solid. LCMS: RT = 1.982 min, MS cal.: 1983.9, found: $[M/2 + H]^+$ = 993.5. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.855 - 7.812 (m, 6H), 7.751 - 7.723 (m, 3H), 7.364 - 7.328 (m, 6H), 5.212 – 5.021 (m, 3H), 4.978 - 4.942 (m, 6H), 4.487 – 4.466 (d, *J* = 8.4 Hz, 3H), 4.020 -3.854 (m, 9H), 3.685 -3.522 (m, 26H), 3.045 – 3.015 (t, *J* = 6 Hz, 13H), 2.292 – 2.260 (t, *J* = 6.4 Hz, 7H), 2.035 (*s*, 9H), 1.888 (*s*, 9H), 1.777 (*s*, 9H), 1.769 (*s*, 9H), 1.514 – 1.461 (m, 19H). Theoretical number of H: 137, found: 137.

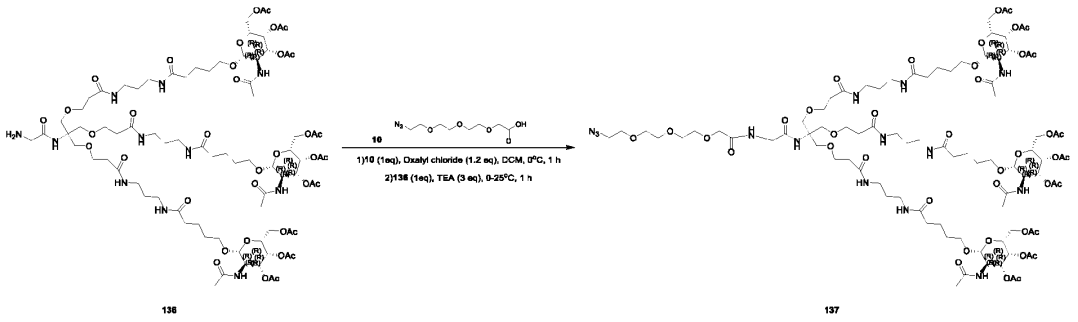
[0249] ***Preparation of Intermediate 136:***



135 136

[0250] To a solution of **Intermediate 135** (180.00 mg, 90.68 umol, 1.00 equiv.) in THF (3 mL) was added Pd/C (150 mg, 90.68 umol, 10% purity, 1.00 equiv.) and TFA (15.51 mg, 136.01 umol, 10.07 uL, 1.50 equiv.) at 25 °C and the reaction was stirred for 0.5 h at 25 °C. LCMS showed the reaction was completed. The reaction was filtered and the filtrate was concentrated under reduced pressure to give **Intermediate 136** (80.00 mg, 43.22 umol, 47.67% yield) as white solid. LCMS: RT = 1.685 min, MS cal.: 1849.8, $[M/2+H]^+$ = 926.6.

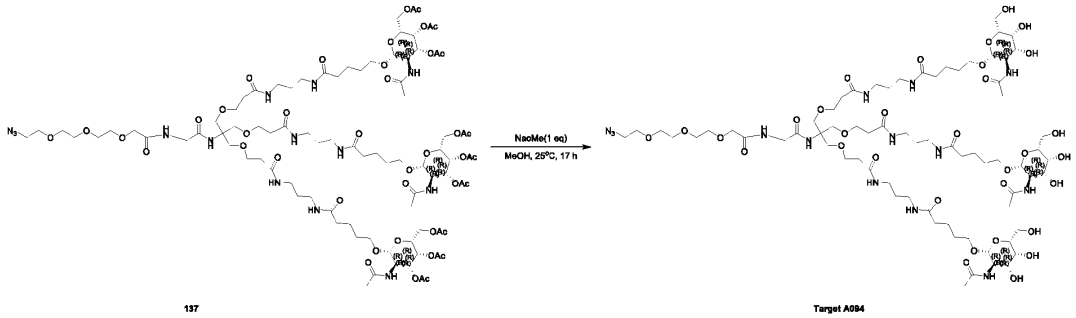
[0251] ***Preparation of Intermediate 137:***



136 137

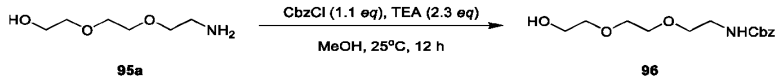
[0252] To a solution of oxalyl dichloride (13.06 mg, 102.91 umol, 9.01 uL, 1.20 equiv.) in DCM (0.30 mL) was added **Intermediate 10** (20.00 mg, 85.76 umol, 1.00 eq) and DMF (0.10 mL), and the reaction mixture was stirred at 0 °C for 1 h. TLC (DCM: MeOH = 10:1, Starting material R_f = 0.3，product R_f = 0.4) showed the reaction was completed. Then TEA (19.68 mg, 194.49 umol, 27.07 uL, 3.00 equiv.) and **Intermediate 136** (120.00 mg, 64.83 umol, 1.00 equiv.) in DCM (2 mL) was added dropwise to the above solution at 0 °C, then the mixture was stirred at 25 °C for 1 h. LCMS showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to afford **Intermediate 137** (125 mg, crude) as yellow oil. LCMS: RT = 1.724 min, MS cal.: 2064.96, found: $[M/2 + H]^+$ = 1034.3.

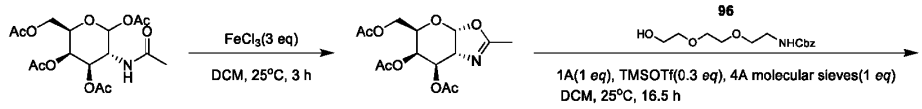
[0253] ***Preparation of Target A094:***



[0254] To a solution of **Intermediate 137** (119.80 mg, 57.98 umol, 1.00 equiv.) in MeOH (2 mL) was added NaOMe (3.13 mg, 57.98 umol, 1.00 equiv.). The mixture was stirred at 25 °C for 17 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: C18-1 150*30mm*5um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 5%-35%,10min) to afford **Target A094** (26 mg, 15.40 umol, 26.57% yield) as white solid. LCMS: RT = 1.078 min, MS cal.: 1686.87, found: $[M/2+H]^+$ = 845.1. ^{1}H NMR (400 MHz, CD_3OD) δ = 4.37 (m, 2H), 4.36 - 4.33 (m, 2H), 3.97 - 3.87 (m, 8H), 3.84 (br s, 3H), 3.80 - 3.64 (m, 28H), 3.60 (br s, 2H), 3.58 (br s, 2H), 3.49 (br s, 8H), 3.26 - 3.20 (m, 12H), 2.43 (br s, 6H), 2.21 (br t, *J* = 6.3 Hz, 6H), 2.04 - 1.95 (m, 9H), 1.75 - 1.63 (m, 12H), 1.58 (br d, *J* = 6.0 Hz, 6H). Theoretical number of H: 126, found: 106, exchangeable H: 20.

EXAMPLE 32. Procedure for Preparation of *Target A099*

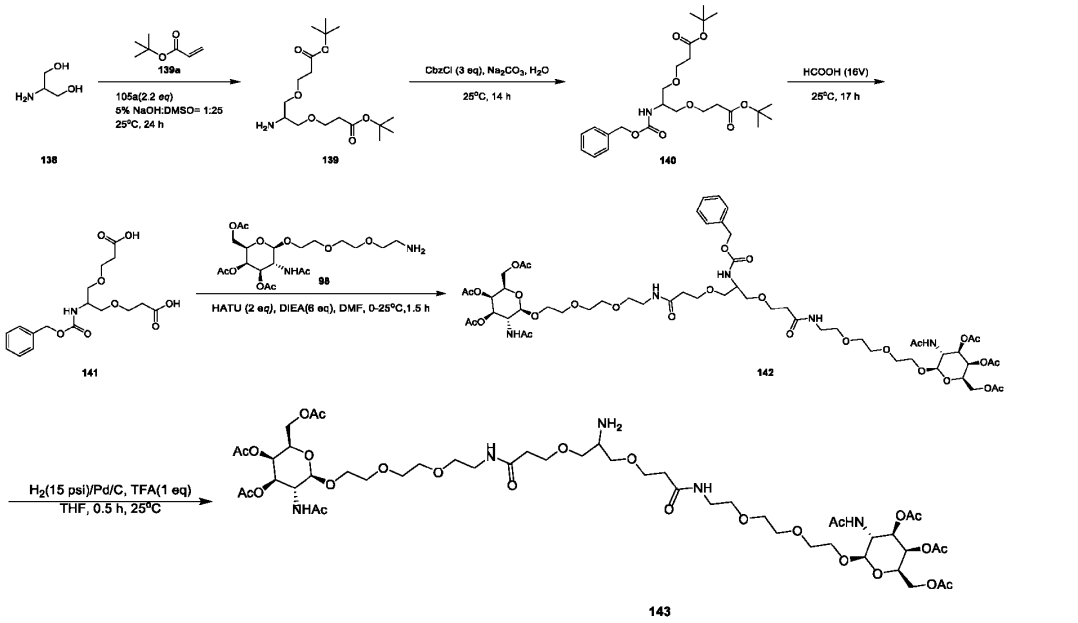


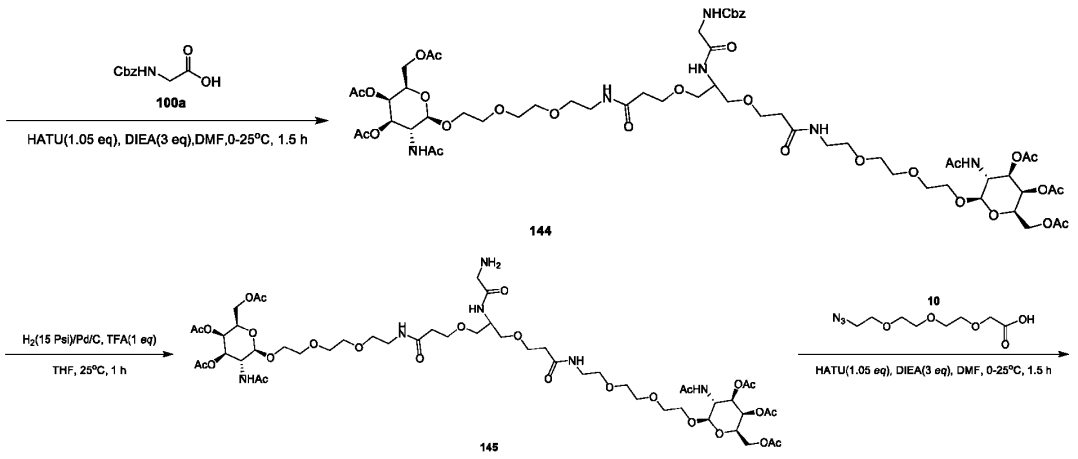

AcO
OAc
AcO
N
H
OAc
FeCl3(3 eq)
DCM, 25°C, 3 h
AcO
O
AcO
N
OAc
96
HO
O
O
NHCbz
1A(1 eq), TMSOTf(0.3 eq), 4A molecular sieves(1 eq)
DCM, 25°C, 16.5 h

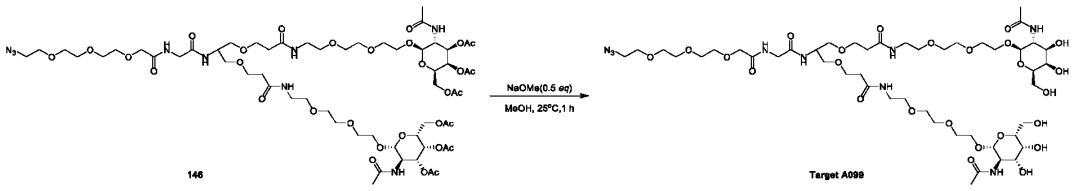
96a 126

OAc
O
O
O
NHCbz
AcO
NHAc
OAc
H2/Pd/C
EtOAc
OAc
O
O
O
NH2 TFA
AcO
NHAc
OAc

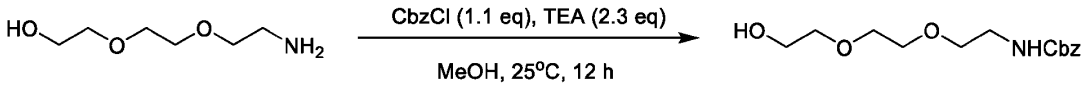
97 98


139a
105a(2.2 eq)
5% NaOH:DMSO= 1:25
25°C, 24 h
CbzCl (3 eq), Na2CO3, H2O
25°C, 14 h
HCOOH (16V)
25°C, 17 h
138
139
140
141
98
HATU (2 eq), DIEA(6 eq), DMF, 0-25°C,1.5 h
142
H2(15 psi)/Pd/C, TFA(1 eq)
THF, 0.5 h, 25°C
143


100a
HATU(1.05 eq), DIEA(3 eq),DMF,0-25°C, 1.5 h
144
H2(15 Psi)/Pd/C, TFA(1 eq)
THF, 25°C, 1 h
145
10
HATU(1.05 eq), DIEA(3 eq), DMF, 0-25°C, 1.5 h


NaOMe(0.5 eq)
MeOH, 25°C,1 h
146
Target A099

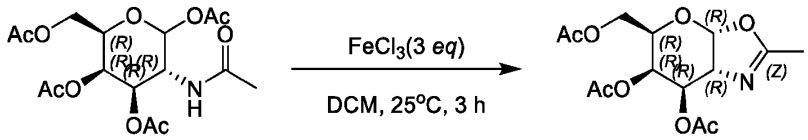
[0255] **Preparation of Intermediate 96**



95a **96**

[0256] To a solution of ***Intermediate* 95a** (50 g, 335.15 mmol, 1 *eq*) in MeOH (500 mL) was added CbzCl (62.89 g, 368.66 mmol, 52.41 mL, 1.1 *eq*) and TEA (78.00 g, 770.84 mmol, 107.29 mL, 2.3 *eq*). The mixture was stirred at 25 °C for 12 hr. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. TLC (Dichloromethane: Methanol = 10:1 R_f = 0.7) indicated Reactant 1 was consumed completely and one new spot formed. The reaction mixture was diluted with H_2O (500 mL) and extracted with EtOAc (300 mL * 2). The combined organic layers were washed with brine (300 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 1/0 to 10/1) to give ***Intermediate* 96** (52 g, 183.54 mmol, 54.76% yield) as colorless oil. LCMS: RT = 1.522 min, MS cal.: 283.14, found: $[M+H]^+$ = 284.2. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.22 - 7.33 (m, 5 H), 5.34 (br s, 1 H), 5.03 (s, 2 H), 3.62 - 3.68 (m, 2 H), 3.56 (s, 4 H), 3.49 - 3.53 (m, 4 H), 3.33 (q, *J* = 5.04 Hz, 2 H), 2.18 - 2.57 (m, 1 H). Theoretical number of H: 21, found: 21.

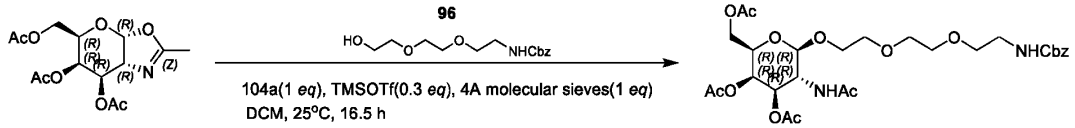
[0257] **Preparation of Intermediate 126**



96a **126**

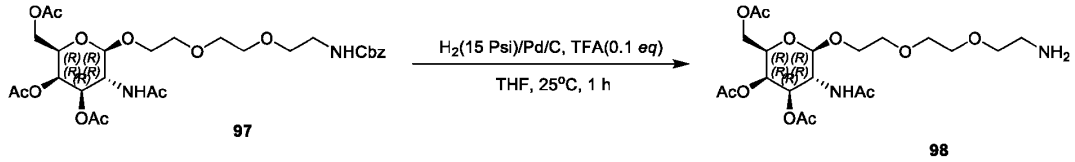
[0258] To a solution of ***Intermediate* 96a** (20 g, 51.37 mmol, 1 *eq*) in DCM (2000 mL) was added $FeCl_3$ (25.00 g, 154.10 mmol, 8.93 mL, 3 *eq*). The mixture was stirred at 25°C for 3 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was diluted with water (2000 mL) and extracted with water (2000 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue ***Intermediate* 126** (14 g, 42.51 mmol, 82.77% yield) as white oil. LCMS: RT = 1.421 min, MS cal.: 329.11, found: $[M+H]^+$ = 330.2. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 6.00 (d, *J* = 6.8 Hz, 1H), 5.47 (t, *J* = 3.0 Hz, 1H), 4.92 (dd, *J* = 3.3, 7.4 Hz, 1H), 4.28 - 4.22 (m, 1H), 4.21 - 4.17 (m, 1H), 4.14 - 4.08 (m, 1H), 4.04 - 3.98 (m, 1H), 2.13 (s, 3H), 2.09 - 2.04 (m, 9H). Theoretical number of H: 19, found: 19.

[0259] ***Preparation of*** **Intermediate 97:**



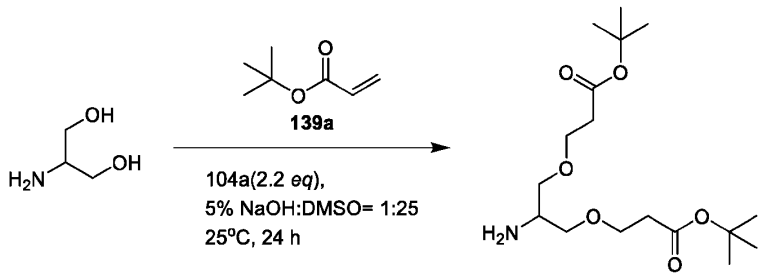
[0260] To a solution of ***Intermediate*** **126** (13.5 g, 41.00 mmol, 1 *eq*), ***Intermediate*** **96** (11.61 g, 41.00 mmol, 1 *eq*) in DCM (280 mL) was added TMSOTf (2.73 g, 12.30 mmol, 2.22 mL, 0.3 *eq*) and 4A molecular sieves (14 g, 41.00 mmol, 1 *eq*) at 0°C. The mixture was stirred at 25°C for 16.5 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was diluted with water (300 mL) and extracted with DCM (300 mL * 3). The combined organic layers were washed with brine (300 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 0/1) to give ***Intermediate*** **97** (22 g, 35.91 mmol, 87.60% yield) as a white solid. LCMS: RT = 1.857 min, MS cal.: 612.3, found: $[M+H]^+$ = 613.4. ^1H NMR (400MHz, MeOD-d_4) δ = 7.41 - 7.27 (m, 5H), 5.32 (d, *J* = 2.9 Hz, 1H), 5.11 - 5.03 (m, 3H), 4.85 (s, 4H), 4.89 - 4.81 (m, 1H), 4.64 (d, *J* = 8.5 Hz, 1H), 4.18 - 4.05 (m, 4H), 4.00 (d, *J* = 6.6 Hz, 1H), 3.91 (td, *J* = 4.0, 11.4 Hz, 1H), 3.72 (ddd, *J* = 4.0, 6.6, 11.0 Hz, 1H), 3.65 - 3.62 (m, 2H), 3.55 (t, *J* = 5.5 Hz, 2H), 2.13 (s, 3H), 2.02 (s, 3H), 1.94 (s, 3H), 1.92 (s, 3H). Theoretical number of H: 40, found: 38, exchangeable H: 2.

[0261] ***Preparation of*** **Intermediate 98:**



[0262] To a solution of ***Intermediate*** **97** (2 g, 3.26 mmol, 1 *eq*) in THF (20 mL) was added TFA (37.22 mg, 326.47 umol, 24.17 uL, 0.1 *eq*) and Pd/C (500 mg, 3.26 mmol, 10% purity, 1 *eq*). The mixture was stirred at 25 °C for 1 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give ***Intermediate*** **98** (1.5 g, 3.13 mmol, 96.02% yield) as yellow oil. LCMS: RT = 0.369 min, MS cal.: 478.2, found: $[M+H]^+$ = 479.4. ^1H NMR (400MHz, MeOD-d_4) δ = 5.34 (d, *J* = 2.8 Hz, 1H), 5.10 - 5.00 (m, 1H), 4.64 - 4.56 (m, 1H), 4.16 - 4.00 (m, 4H), 3.95 (td, *J* = 4.2, 11.2 Hz, 1H), 3.75 - 3.69 (m, 3H), 3.65 - 3.61 (m, 6H), 3.01 - 2.90 (m, 2H), 2.14 (s, 3H), 2.02 (s, 3H), 1.95 - 1.92 (m, 6H). Theoretical number of H: 34, found: 31, exchangeable H: 3.

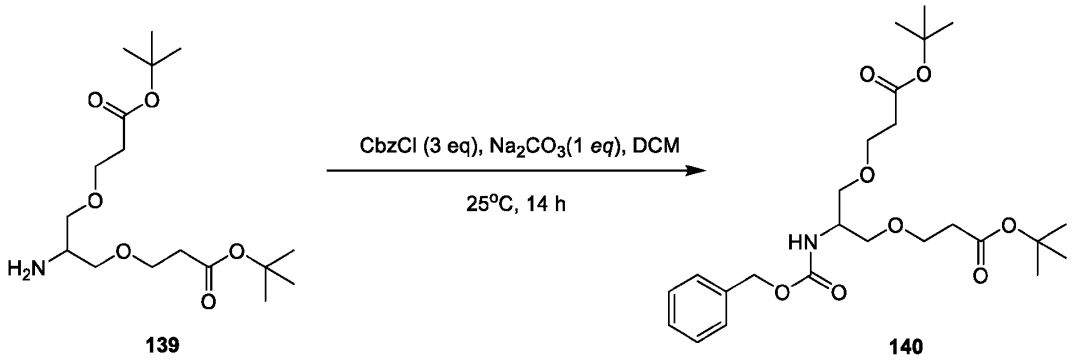
[0263] ***Preparation of*** **Intermediate 139:**



138 139

[0264] To a solution of ***Intermediate 138*** (50 g, 548.80 mmol, 1 *eq*), ***Intermediate* 139a** (154.74 g, 1.21 mol, 175.25 mL, 2.2 *eq*) in DMSO (500 mL) was added NaOH (439.00 g, 548.80 mmol, 5% purity, 1 *eq*). The mixture was stirred at 25 °C for 24 hr. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. TLC (Petroleum ether: Ethyl acetate = 1: 1 R_f = 0.67) indicated Reactant 1 was consumed completely and one new spot formed. The reaction mixture was diluted with H_2O (500 mL) and extracted with EtOAc (300 mL * 2). The combined organic layers were washed with brine (300 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1/0 to 1/1) to give ***Intermediate 139*** (37.6 g, 108.22 mmol, 19.72% yield) as a colorless oil. LCMS: RT=2.826 min, MS cal.: 333.22, found: $[M+CH_3]^+$ = 348.3. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.30 (s, 1H), 3.73 - 3.61 (m, 4H), 3.52 - 3.39 (m, 2H), 3.36 - 3.29 (m, 1H), 3.16 - 3.09 (m, 1H), 2.96 - 2.76 (m, 1H), 2.47 (t, *J* = 6.4 Hz, 3H), 1.45 (s, 18H) Theoretical number of H: 34, found: 31, exchangeable H: 3.

[0265] Preparation of ***Intermediate 140***:

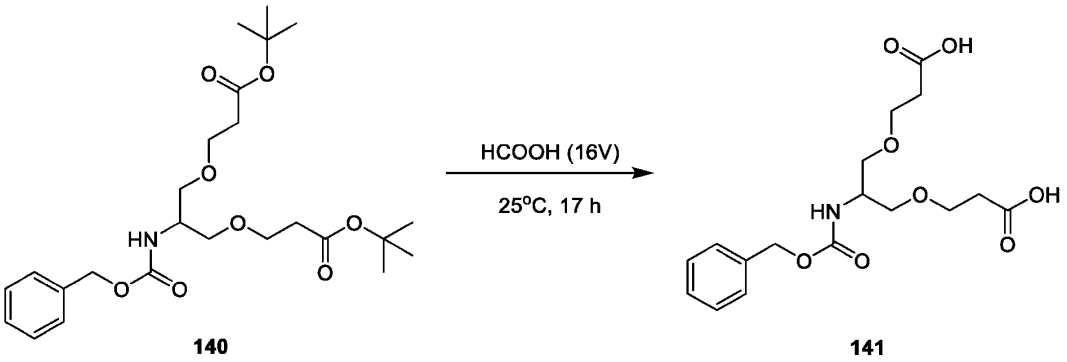


139 140

[0266] To a solution of ***Intermediate 139***(30 g, 86.34 mmol, 1 *eq*) in DCM (500 mL) was added Na_2CO_3 (36.61 g, 86.34 mmol, 315 mL, 25% purity, 1 *eq*) and CbzCl (44.19 g, 259.03 mmol, 36.82 mL, 3 *eq*). The mixture was stirred at 25°C for 14 hr. LCMS showed the desired mass of product was detected and

the reactant was consumed completely. TLC (PE: EA = 2: 1, R_f = 0.6) indicated Reactant 1 was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was diluted with water 200 mL and extracted with DCM 200 mL * 3. The combined organic layers were washed with brine 200 mL dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=4/1 to 3/1) to obtained ***Intermediate 140*** (28 g, 58.14 mmol, 67.34% yield) as a white solid. LCMS: RT = 2.826 min, MS cal.: 481.27, found: $[M+H]^+$ = 482.4. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.37 - 7.28 (m, 5H), 5.30 (br d, *J* = 7.9 Hz, 1H), 5.09 (s, 2H), 4.12 (d, *J* = 7.2 Hz, 1H), 3.94 - 3.86 (m, 1H), 3.60 - 3.52 (m, 2H), 3.48 - 3.42 (m, 2H), 2.45 (t, *J* = 6.3 Hz, 4H), 2.05 (s, 1H), 1.63 - 1.52 (m, 1H), 1.43 (s, 17H), 1.26 (t, *J* = 7.2 Hz, 1H). Theoretical number of H: 39, found: 38, exchangeable H: 1.

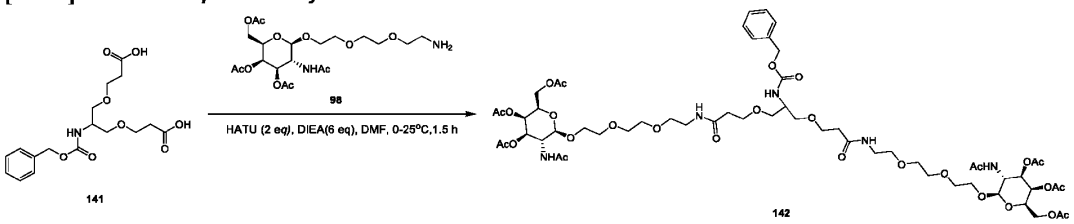
[0267] Preparation of ***Intermediate 141***:



140 **141**

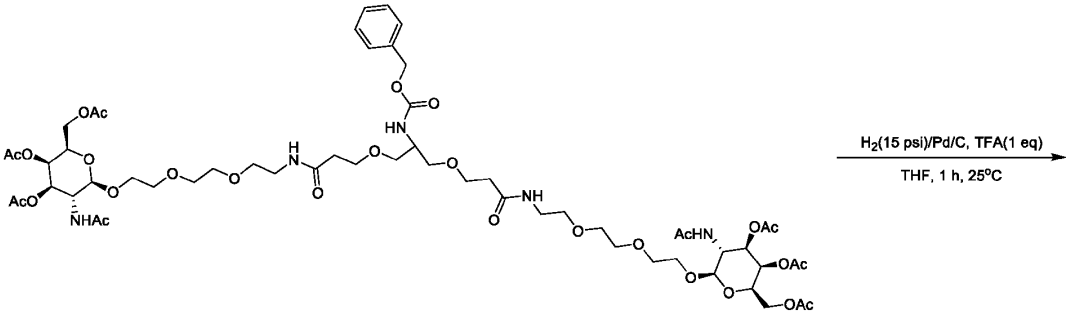
[0268] A mixture of ***Intermediate 140*** (28 g, 58.14 mmol, 1 *eq*) in HCOOH (500 mL) was stirred at 25°C for 17 hr. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was dried over and concentrated under reduced pressure to give ***Intermediate 141*** (21.24 g, 57.50 mmol, 98.90% yield) as yellow oil. LCMS: RT = 0.514 min, MS cal.: 369.14, found: $[M+H]^+$ = 370.3. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.15 (s, 1H), 7.42 - 7.27 (m, 5H), 5.32 - 5.19 (m, 1H), 5.09 (s, 2H), 4.02 - 3.85 (m, 1H), 3.77 - 3.62 (m, 3H), 3.61 - 3.41 (m, 3H), 2.58 (t, *J* = 6.1 Hz, 3H). Theoretical number of H: 23, found: 19, exchangeable H: 4.

[0269] ***Preparation of Intermediate 142:***

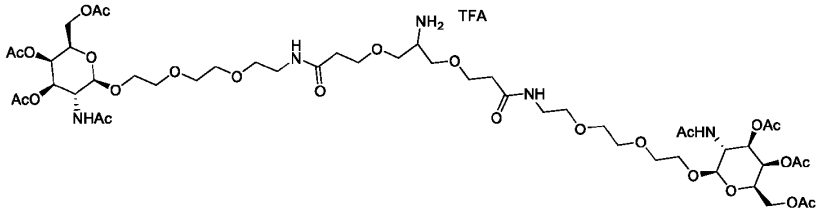


[0270] To a solution of ***Intermediate 141*** (1.4 g, 3.79 mmol, 1 *eq*) in DMF (25 mL) was added HATU (2.88 g, 7.58 mmol, 2 *eq*) and DIEA (2.94 g, 22.74 mmol, 3.96 mL, 6 *eq*) at 0°C. The mixture was stirred at 0°C for 0.5 h, then was added ***Intermediate 98*** (3.63 g, 7.58 mmol, 2 *eq*) at 0°C, then was stirred at 25°C for 1 h. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with water (20 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 250*70mm#10um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 20%-50%,20min) to give ***Intermediate 142*** (1.7 g, 1.32 mmol, 34.76% yield) as yellow oil. LCMS: RT = 1.862 min, MS cal.: 1289.55, found: $[M+H]^+$ = 1290.9. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.39 - 7.33 (m, 5H), 5.36 - 5.30 (m, 2H), 5.20 - 5.20 (m, 1H), 5.20 - 5.13 (m, 2H), 5.10 (br s, 2H), 4.79 (br d, *J* = 8.5 Hz, 2H), 4.20 - 4.04 (m, 7H), 3.98 - 3.82 (m, 7H), 3.66 - 3.52 (m, 22H), 3.51 - 3.47 (m, 5H), 2.50 - 2.39 (m, 5H), 2.17 (br s, 2H), 2.15 (s, 5H), 2.04 (s, 7H), 1.99 (s, 7H), 1.95 - 1.95 (m, 1H). Theoretical number of H: 87, found: 82, exchangeable H: 5.

[0271] ***Preparation of*** **Intermediate 143*:***



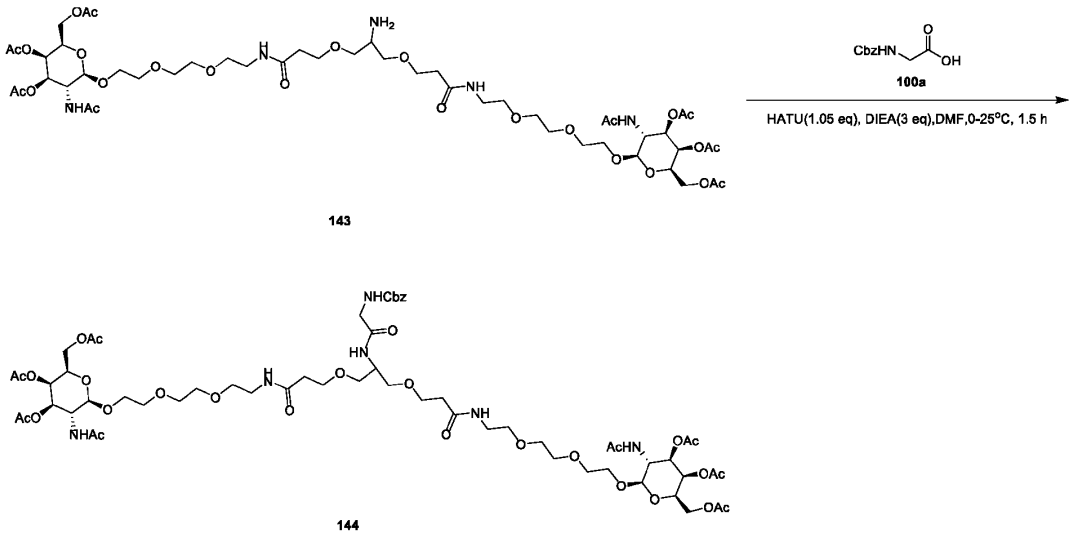
142



143

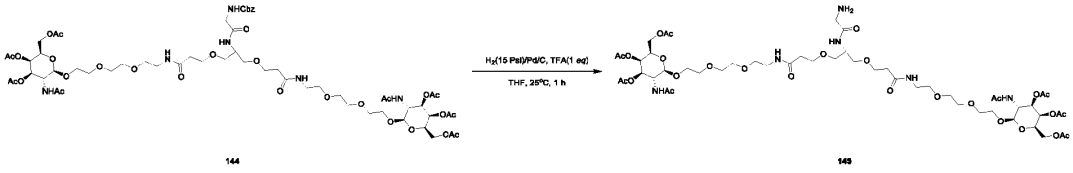
[0272] To a solution of ***Intermediate 142*** (1 g, 775.01 umol, 1 *eq*) in THF (40 mL) was added TFA (88.37 mg, 775.01 umol, 57.38 uL, 1 *eq*). The mixture was stirred at 25°C for 1 hr under 15 psi. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. TLC (DCM: MEOH = 10:1, R_f = 0.6) indicated Reactant 1 was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give ***Intermediate 143*** (896 mg, 774.96 umol, 99.99% yield) as yellow oil. LCMS: RT = 1.499 min, MS cal.: 1155.52, found: $[M+H]^+$ = 1156.8. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 5.37 - 5.31 (m, 2H), 5.10 - 5.02 (m, 2H), 4.67 - 4.57 (m, 2H), 4.18 - 3.91 (m, 10H), 3.86 - 3.46 (m, 32H), 3.42 - 3.35 (m, 4H), 2.53 - 2.47 (m, 4H), 2.18 - 2.12 (m, 6H), 2.07 - 2.00 (m, 6H), 1.97 - 1.91 (m, 12H). Theoretical number of H: 81, found: 80, exchangeable H: 1.

[0273] ***Preparation of Intermediate 144:***



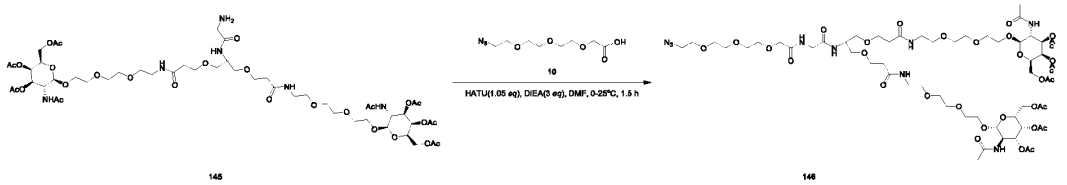
[0274] To a solution of ***Intermediate 100a*** (452.35 mg, 2.16 mmol, 1 *eq*) in DMF (10 mL) was added HATU (863.28 mg, 2.27 mmol, 1.05 *eq*) and DIEA (838.38 mg, 6.49 mmol, 1.13 mL, 3 *eq*). The mixture was stirred at 0°C for 0.5 h. ***Intermediate 143*** (2.5 g, 2.16 mmol, 1 *eq*) was added at 0°C, and the mixture was stirred at 25°C for 1h. TLC (PE/EA = 0: 1, R_f = 0.6) indicated Reactant 1 was consumed completely and one new spot formed. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was dried by N_2. The residue was purified by column chromatography (SiO_2, DCM/MEOH = 100/1 to 5/1) to give ***Intermediate 144*** (1.2 g, 890.63 umol, 41.19% yield) as faint yellow solid. LCMS: RT = 1.793 min, MS cal.: 1346.58, found: $[M+H]^+$ = 1347.9. ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.36 (br d, *J* = 6.3 Hz, 5H), 5.33 (br d, *J* = 2.8 Hz, 2H), 5.16 - 5.04 (m, 4H), 4.64 (d, *J* = 8.5 Hz, 2H), 4.14 (br t, *J* = 6.0 Hz, 7H), 3.97 - 3.89 (m, 2H), 3.81 (s, 2H), 3.74 - 3.58 (m, 19H), 3.41 - 3.37 (m, 3H), 2.44 (br t, *J* = 5.6 Hz, 4H), 2.14 (s, 6H), 2.02 (s, 6H), 1.94 (d, *J* = 6.6 Hz, 12H), 1.41 - 1.34 (m, 10H). Theoretical number of H: 90, found: 84, exchangeable H: 6.

[0275] ***Preparation of Intermediate 145:***



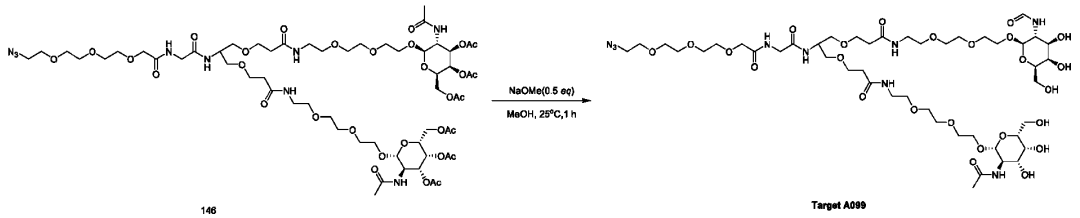
[0276] To a solution of ***Intermediate 144*** (1.4 g, 1.04 mmol, 1 *eq*) in THF (2 mL) was added Pd/C (700 mg, 1.04 mmol, 10% purity, 1 *eq*) and TFA (118.48 mg, 1.04 mmol, 76.93 uL, 1 *eq*). The mixture was stirred at 20°C for 1 hr under 15 psi. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give ***Intermediate 145*** (1.24 g, 1.02 mmol, 98.36% yield) as yellow oil. LCMS: RT = 1.449 min, MS cal.: 1212.54, found: $[M+H]^+$ = 1213.9. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 5.35 (d, *J* = 3.1 Hz, 2H), 5.09 - 5.04 (m, 3H), 4.64 - 4.57 (m, 2H), 4.15 (br d, *J* = 6.6 Hz, 10H), 3.99 - 3.93 (m, 2H), 3.75 - 3.69 (m, 10H), 3.67 - 3.62 (m, 10H), 3.56 (br d, *J* = 5.3 Hz, 5H), 3.39 (br t, *J* = 5.4 Hz, 5H), 2.46 (br t, *J* = 5.9 Hz, 4H), 2.15 (s, 6H), 2.03 (s, 6H), 1.95 (d, *J* = 5.4 Hz, 12H) Theoretical number of H: 84, found: 77, exchangeable H: 7.

[0277] ***Preparation of Intermediate 146:***



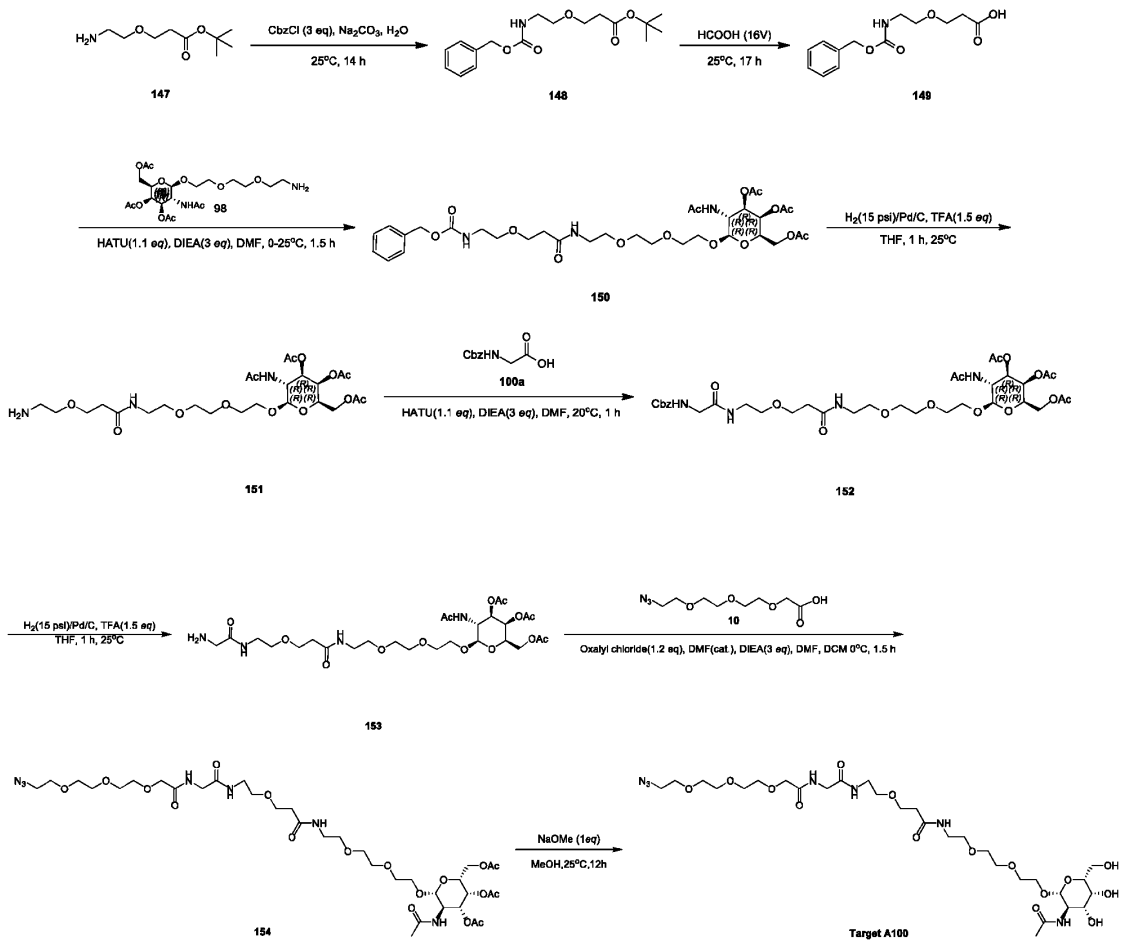
[0278] To a solution of ***Intermediate 10*** (1.2 g, 820.95 umol, 83% purity, 1 *eq*) in DMF (5 mL) was added HATU (327.76 mg, 861.99 umol, 1.05 *eq*) and DIEA (318.30 mg, 2.46 mmol, 428.98 uL, 3 *eq*). The mixture was stirred at 0°C for 0.5 h. ***Intermediate 145*** (201.04 mg, 861.99 umol, 1.05 *eq*) was added at 0°C, and the mixture was stirred at 25°C for 1h. TLC (PE/EA =0: 1, R_f = 0.6) indicated Reactant 1 was consumed completely and one new spot formed. LC-MS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was dried by N_2 and purified by column chromatography (SiO_2, DCM/MEOH = 100/1 to 5/1) to give ***Intermediate 146*** (1.11 g, 777.07 umol, 94.66% yield) as faint yellow solid. LCMS: RT = 1.800 min, MS cal.: 1427.63, found: $[M/2+H]^+$ = 715.0. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 5.50 (s, 2H), 5.34 (d, *J* = 2.9 Hz, 2H), 5.10 - 5.04 (m, 2H), 4.64 (d, *J* = 8.3 Hz, 2H), 4.20 - 4.01 (m, 11H), 3.95 (s, 4H), 3.74 - 3.62 (m, 26H), 3.55 (br d, *J* = 5.5 Hz, 7H), 3.42 - 3.34 (m, 6H), 3.27 - 3.19 (m, 1H), 2.46 (t, *J* = 6.0 Hz, 4H), 2.15 (s, 6H), 2.03 (s, 6H), 2.00 - 1.90 (m, 12H). Theoretical number of H: 97, found: 91, exchangeable H: 6.

[0279] ***Preparation of Target A099:***

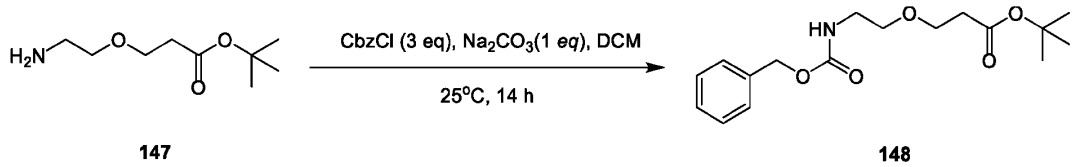


[0280] To a solution of ***Intermediate 146*** (500 mg, 350.03 umol, 1 *eq*) in MeOH (2 mL) was added NaOMe (9.46 mg, 175.02 umol, 0.5 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was adjust pH to 7-8 and filtered. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(TFA)-ACN];B%: 5%-30%,8min) to give ***Target A099*** (145 mg, 123.28 umol, 35.22% yield) as a white solid. LCMS: RT = 1.589 min, MS cal.: 1175.57, found: $[M/2+H]^+$ = 589.0. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 4.44 (d, *J* = 8.4 Hz, 2H), 4.13 (s, 1H), 4.06 (s, 2H), 3.95 (s, 6H), 3.83 (d, *J* = 3.0 Hz, 2H), 3.75 - 3.60 (m, 34H), 3.55 (s, 10H), 3.38 (t, *J* = 5.4 Hz, 6H), 2.45 (t, *J* = 6.1 Hz, 4H), 1.98 (s, 6H). Theoretical number of H: 85, found: 73, exchangeable H: 12.

EXAMPLE 33. Procedure for Preparation of *Target A100*



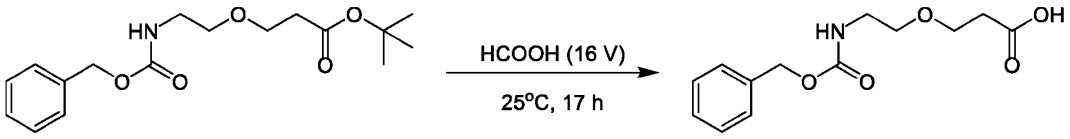
[0281] **Preparation of Intermediate 148:**



[0282] To a solution of ***intermediate* 147** (9 g, 47.56 mmol, 1 *eq*) in DCM (135 mL) was added Na_2CO_3 (20.16 g, 47.56 mmol, 63 mL, 25% purity, 1 *eq*) and CbzCl (24.34 g, 142.67 mmol, 20.28 mL, 3 *eq*).

The mixture was stirred at 25°C for 14 hr. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was diluted with H_2O 10 mL and extracted with DCM 90 mL (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 1/1) to give ***intermediate* 148** (11.03 g, 34.11 mmol, 71.72% yield) as a colorless oil. LCMS: RT = 2.208 min, MS cal.: 323.17, found: $[M+H]^+$ = 268.2. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.39 - 7.34 (m, 5H), 5.33 - 5.27 (m, 1H), 5.13 - 5.08 (m, 2H), 3.67 (s, 2H), 3.57 - 3.48 (m, 2H), 3.44 - 3.31 (m, 2H), 2.47 (t, *J* = 6.2 Hz, 2H), 1.45 (s, 9H). Theoretical number of H: 25, found: 25.

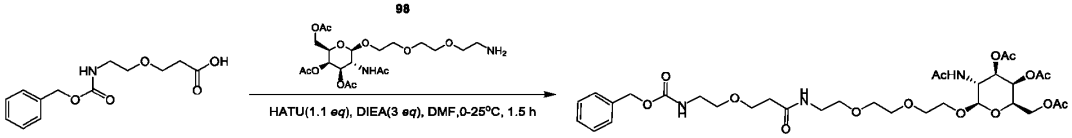
[0283] ***Preparation of Intermediate* 149*:***



148 **149**

[0284] A mixture of ***intermediate* 148** (11 g, 34.02 mmol, 1 *eq*) and HCOOH (171 mL) was stirred at 25°C for 17 hr. LCMS showed Reactant 1 was consumed completely and one peak with the desired Ms were detected. The reaction mixture was concentrated under reduced pressure to give ***intermediate* 149** (8.9 g, 33.30 mmol, 97.89% yield, 100% purity) as a yellow oil. LCMS: RT = 1.1.138 min, MS cal.: 267.11, found: $[M+H]^+$ = 268.2. ^{1}H NMR (400MHz, ACN-d_4) δ = 7.41-7.32 (m, 5H), 5.21 (s, 1H), 5.08 (s, 1H), 3.72 – 3.69 (t, *J* = 6.4 Hz, 2H), 3.54 – 3.51 (t, *J* = 6.0 Hz, 2H), 3.33 – 3.30 (t, *J* = 5.6 Hz, 2H), 2.57 – 2.54 (t, *J* = 6.0 Hz, 2H). Theoretical number of H: 17, found: 15, exchangeable H: 2.

[0285] **Preparation of *Intermediate* 150:**

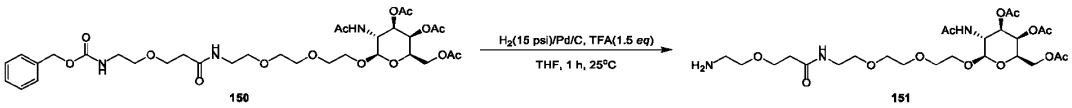


148 150

[0286] To a solution of ***intermediate* 149** (2.5 g, 9.35 mmol, 1 *eq*) in DMF (25 mL) was added HATU (3.91 g, 10.29 mmol, 1.1 *eq*) and DIEA (3.63 g, 28.06 mmol, 4.89 mL, 3 *eq*) at 0°C for 0.5 hr. Then the solution of ***intermediate* 98** (4.92 g, 10.29 mmol, 1.1 *eq*) in DMF (50 mL) was added at 0°C and the reaction was stirred for 1 hr at 25°C. LCMS showed the reaction was completed. The reaction mixture

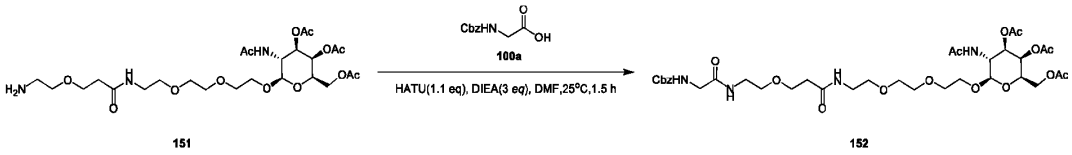
was poured into H_2O (50 mL) and extracted with DCM (100 mL x3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give crude product. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 100/1 to 1/1) to give ***intermediate* 150** (3.36 g, 4.62 mmol, 49.36% yield) as yellow oil. LCMS: RT = 1.762 min, MS cal.: 727.3, found: $[M+H]^+$ = 728.5. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.38 - 7.30 (m, 3H), 6.83 - 6.69 (m, 1H), 6.39 - 6.31 (m, 1H), 5.60 (br s, 1H), 5.37 - 5.27 (m, 2H), 5.19 - 5.07 (m, 2H), 4.78 (d, *J* = 8.5 Hz, 1H), 4.21 - 4.04 (m, 2H), 3.97 - 3.33 (m, 15H), 3.22 - 3.13 (m, 1H), 2.96 (s, 1H), 2.88 (s, 1H), 2.80 (s, 1H), 2.45 (br t, *J* = 5.6 Hz, 1H), 2.21 - 1.92 (m, 8H), 1.52 - 1.39 (m, 3H). Theoretical number of H: 49, found: 44, exchangeable H: 5.

[0287] ***Preparation of Intermediate* 151*:***



[0288] To a solution of ***intermediate* 150** (1.2 g, 1.65 mmol, 1 *eq*) in THF (10 mL) was added TFA (282.02 mg, 2.47 mmol, 183.13 uL, 1.5 *eq*) and Pd/C (0.6 g, 1.65 mmol, 10% purity, 1 *eq*). The mixture was stirred at 25°C for 1 hr. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give ***intermediate* 151** (1.12 g, 1.58 mmol, 95.99% yield, TFA) as yellow oil. LCMS: RT = 0.783 min, MS cal.: 593.28, found: $[M+H]^+$ = 594.2. ^1H NMR (400 MHz, METHANOL-d_4) δ = 4.62 - 4.56 (m, 1H), 4.19 - 3.94 (m, 5H), 3.80 - 3.63 (m, 14H), 3.60 - 3.56 (m, 2H), 3.43 - 3.36 (m, 2H), 3.19 - 3.14 (m, 2H), 2.54 - 2.49 (m, 2H), 2.14 (s, 3H), 2.03 (s, 3H), 1.95 (d, *J* = 2.9 Hz, 6H). Theoretical number of H: 43, found: 40, exchangeable H: 3.

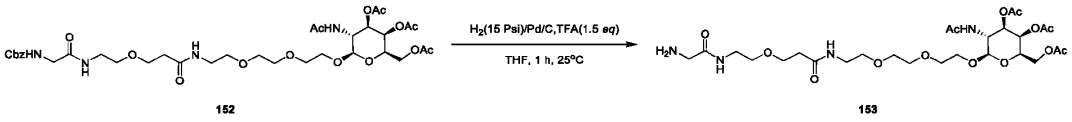
[0289] **Preparation of *Intermediate 152:***



[0290] To a solution of ***intermediate* 100a** (271.36 mg, 1.30 mmol, 1.1 *eq*) in DMF (5 mL) was added DIEA (457.20 mg, 3.54 mmol, 616.18 uL, 3 *eq*) and HATU (493.21 mg, 1.30 mmol, 1.1 *eq*) at 0°C. The mixture was stirred at 0°C for 0.5 hr, then ***intermediate* 151** (0.7 g, 1.18 mmol, 1 *eq*) was added at

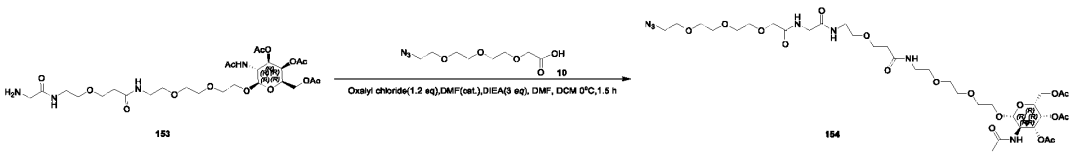
0°C. The mixture was stirred at 25°C for 1 hr. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250*70mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 15%-45%,18min) to give ***intermediate* 152** (0.7 g, 891.94 umol, 75.64% yield) as a yellow solid. LCMS: RT = 1.546 min, MS cal.: 784.34, found: $[M+H]^+$ = 785.5. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.42 - 7.26 (m, 5H), 5.37 - 5.31 (m, 1H), 5.11 (s, 3H), 4.67 - 4.59 (m, 1H), 4.20 - 3.88 (m, 5H), 3.82 - 3.75 (m, 2H), 3.74 - 3.58 (m, 9H), 3.55 - 3.45 (m, 4H), 3.41 - 3.35 (m, 4H), 2.49 - 2.40 (m, 2H), 2.13 (s, 3H), 2.02 (s, 3H), 1.94 (d, *J* = 7.3 Hz, 6H). Theoretical number of H: 52, found: 48, exchangeable H: 4.

[0291] **Preparation of *Intermediate 153:***



[0292] To a solution of ***intermediate* 152** (150 mg, 191.13 umol, 1 *eq*) in MeOH (2 mL) was added Pd/C (75 mg, 191.13 umol, 10% purity, 1 *eq*) and TFA (32.69 mg, 286.70 umol, 21.23 uL, 1.5 *eq*). The mixture was stirred at 25°C for 1 hr. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give ***intermediate* 153** (146 mg, 190.93 umol, 99.89% yield, TFA) was obtained as a yellow oil. LCMS: RT = 1.145 min, MS cal.: 650.3, found: $[M+H]^+$ = 651.5. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 5.35 (d, *J* = 3.0 Hz, 1H), 5.09 - 5.03 (m, 1H), 4.61 (d, *J* = 8.5 Hz, 1H), 4.15 (d, *J* = 6.5 Hz, 5H), 3.72 (s, 3H), 3.68 (s, 7H), 3.59 - 3.53 (m, 4H), 3.45 - 3.37 (m, 4H), 2.47 (t, *J* = 5.9 Hz, 2H), 2.15 (s, 3H), 2.03 (s, 3H), 1.94 (d, *J* = 4.9 Hz, 6H). Theoretical number of H: 46, found: 40, exchangeable H: 6.

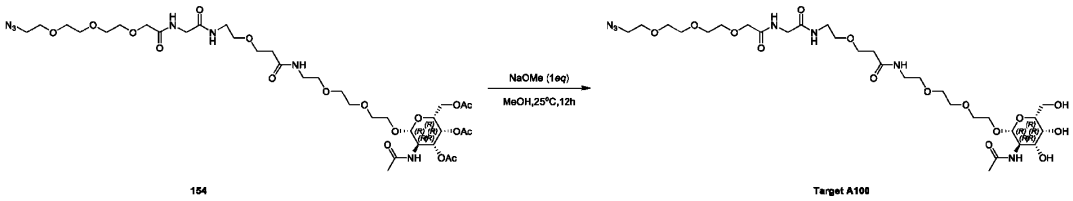
[0293] ***Preparation of Intermediate 154:***



[0294] To a solution of ***intermediate* 10** (128 mg, 548.84 umol, 1.1 *eq*) in DCM (1 mL) was added Oxalyl chloride (80.68 mg, 658.60 umol, 60.66 uL, 1.2 *eq*) and DMF (4.01 mg, 54.88 umol, 4.22 uL, 0.1 *eq*). The mixture was stirred at 0°C for 1 h. TLC showed ***intermediate* 10** was consumed and one new spot was formed. The ***intermediate* 153** (306 mg, 470.28 umol, 1 *eq*) and DIEA (182.34 mg, 1.41 mmol, 245.74 uL,

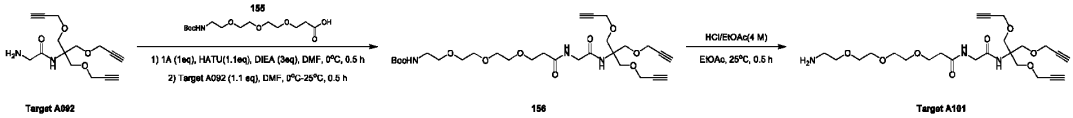
3 *eq*) was dissolved in the mixture at 0°C. The mixture was stirred at 0°C for 0.5 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was concentrated under reduced pressure to remove solvent to give ***intermediate* 154** (400 mg, 461.96 umol, 98.23% yield) as yellow oil. LCMS: RT = 1.492 min, MS cal.: 865.4, found: $[M+H]^+$ = 866.6.

[0295] ***Preparation of Target A100:***

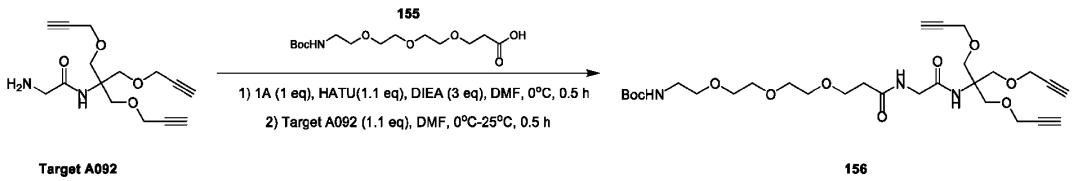


[0296] To a solution of ***intermediate* 154** (300 mg, 346.47 umol, 1 *eq*) in MeOH (3 mL) was added NaOMe (18.72 mg, 346.47 umol, 1 *eq*). The mixture was stirred at 25°C for 12 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by *prep*-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(TFA)-ACN];B%: 15%-30%,8min) to give **Target A100** (145 mg, 196.01 umol, 84.86% yield) as yellow oil. LCMS: RT = 1.571 min, MS cal.: 739.36, found: [M-GalNaC]$^+$ = 537.2. ^{1}H NMR (400MHz, MeOD-d_4) δ = 4.44 (d, = 8.5 Hz, 1H), 4.07 (s, 2H), 3.95 - 3.90 (m, 3H), 3.83 (d, *J* = 3.1 Hz, 1H), 3.75 - 3.70 (m, 8H), 3.69 - 3.61 (m, 14H), 3.58 - 3.48 (m, 6H), 3.38 (br t, *J* = 4.8 Hz, 6H), 2.49 - 2.44 (m, 2H), 2.01 - 1.97 (m, 3H). Theoretical number of H: 53, found: 46, exchangeable H: 7.

EXAMPLE 34. Procedure for Preparation of Target A101

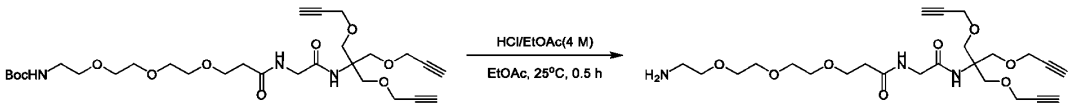


[0297] ***Preparation of Intermediate 122:***



[0298] To a solution of **Intermediate 155** (500.00 mg, 1.56 mmol, 1.00 equiv.) in DMF (5 mL) was added HATU (650.74 mg, 1.71 mmol, 1.10 equiv.) and DIEA (603.25 mg, 4.67 mmol, 813.01 uL, 3.00 equiv.) at 0 °C and the reaction was stirred at 0 °C for 0.5 h. Then **Target A092** (500.31 mg, 1.71 mmol, 1.10 equiv.) in DMF (5 mL) was added at 0°C. The mixture was stirred at 25°C for 0.5 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was poured into H_2O (10 mL) and extracted with DCM (10 mL x 5). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to afford **Intermediate 156** (658.13 mg, 1.10 mmol, 71.01% yield) as yellow oil. LCMS: RT = 0.478 min, MS cal.: 595.7, found: $[M + H-100]^+$ = 496.4. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.07 (br d, *J* = 1.5 Hz, 1H), 6.19 (br s, 1H), 5.14 (br t, *J* = 9.0 Hz, 1H), 4.15 (d, *J* = 2.3 Hz, 4H), 3.89 (d, *J* = 5.4 Hz, 2H), 3.84 (s, 5H), 3.77 (t, *J* = 5.8 Hz, 2H), 3.69 - 3.59 (m, 7H), 3.54 (t, *J* = 5.2 Hz, 2H), 3.31 (br d, *J* = 4.4 Hz, 2H), 3.23 - 3.13 (m, 1H), 2.54 (t, *J* = 5.8 Hz, 2H), 2.45 (t, *J* = 2.3 Hz, 2H), 1.50 - 1.40 (m, 12H). Theoretical number of H: 45, found: 44, exchangeable H: 1.

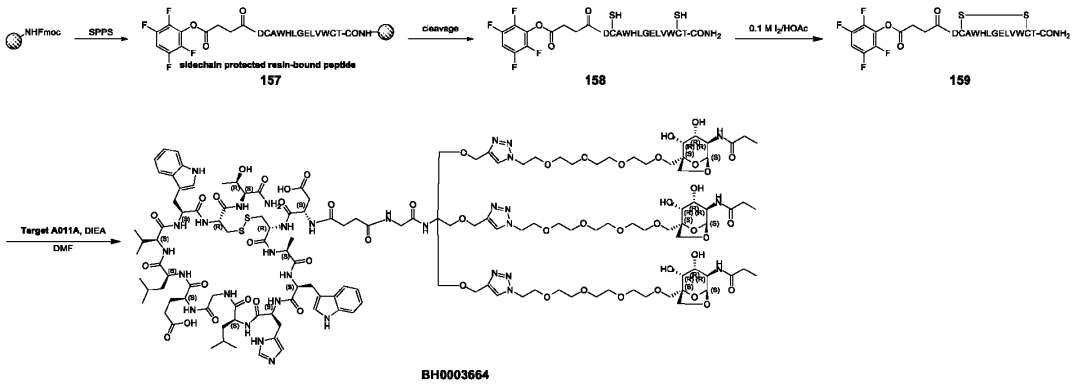
[0299] ***Preparation of Target A101:***



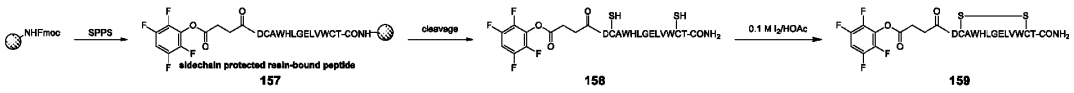
156 Target A101

[0300] To a solution of **Intermediate 122** (900.00 mg, 1.51 mmol, 1.00 equiv.) in EtOAc (2 mL) was added HCl/EtOAc (4 M, 10.00 mL, 26.47 equiv.), and the mixture was stirred 0.5 h at 25 °C. LCMS showed the desired mass and the reactant was consumed. The reaction solution was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: C18-1 150*30mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 15%-45%,10min) to afford **Target A101** (360 mg, 726.44 umol, 48.08% yield) as yellow oil. LCMS: RT = 1.46 min, MS cal.: 495.6, found: $[M + H]^+$ = 496.4. ^1H NMR (400 MHz, CD_3OD) δ = 4.16 (d, *J* = 2.1 Hz, 6H), 3.84 (s, 2H), 3.80 (s, 6H), 3.76 (t, *J* = 6.1 Hz, 2H), 3.69 - 3.57 (m, 11H), 2.91 (br s, 2H), 2.86 (t, *J* = 2.3 Hz, 2H), 2.53 (t, *J* = 6.1 Hz, 2H). Theoretical number of H: 37, found: 33, exchangeable H: 4.

EXAMPLE 35. Procedure for preparation of BH0003664.



[0301] ***Preparation of Intermediate 159:***



[0302] Peptide was synthesized using standard Fmoc chemistry (Rink AM resin).

1) Resin preparation: To the vessel containing Rink Amide AM resin (1.56 g, 0.50 mmol, 0.32 mmol/g) and DMF (20 mL) was bubbled with N_2 for 2 h at 25 °C. Then 20% piperidine in DMF (40 mL) was added and the mixture was bubbled with N_2 for 30 min at 25 °C. The mixture was filtered and washed with DMF (20 mL) * 5 before proceeding to next step.

2) Coupling: A solution of Fmoc-Thr(*t*Bu)-OH (0.60 g, 1.50 mmol, 3.00 equiv.), HBTU (0.558 g, 1.43 mmol, 2.85 equiv.), DIEA (0.39 g, 3.00 mmol, 6.00 equiv.) in DMF (20 mL) was added to the resin with N_2 bubbling for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test. The resin was then washed with DMF (40 mL) * 5.

3) Deprotection: 20% piperidine in DMF (40 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The deprotection reaction was monitored by ninhydrin test. The resin was then washed with DMF (40 mL) * 5.

4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 2-13, Table 21.

5) Coupling succinic anhydride: A solution of succinic anhydride (3.00 equiv.), DIEA (0.39 g, 3.00 mmol, 6.00 equiv.) in DMF (20 mL) was added to the resin with N_2 bubbling for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test. The resin was then washed with DMF (40 mL) * 5.

6) Coupling 2,3,5,6-tetrafluorophenol: A solution of 2,3,5,6-tetrafluorophenol (10.00 equiv.), DIC 10.00 equiv.) in DMF (20 mL) was added to the resin with N_2 bubbling for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test. The resin was then washed with DMF (40 mL) * 5, isopropyl

ether (40 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 157** (Rink AM resin, 1.30 g, 0.50 mmol).

Table 21: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Succinic anhydride (3.00 equiv.)	DIEA (6.00 equiv.)
15	2,3,5,6-tetrafluorophenol (10.00 equiv.)	DIC (10.00 equiv.)

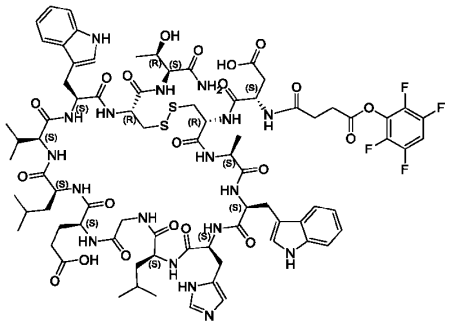
[0303] Peptide cleavage and cyclization.

1) Cleavage solution (TFA/TIS/H_2O, 95/2.5/2.5, v/v/v, 20 mL) was added to the flask containing the side-chain protected resin-bound peptide **Intermediate 157** (Rink AM resin, 1.30 g, 0.50 mmol) at 25 °C and stirred for 2 h.

2) After filtration, the filtrate was collected.

3) The filtrate was precipitated with cold isopropyl ether (100 mL). After filtration, the solid was washed with isopropyl ether (100 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 158** (1.10 g, crude) as a white solid.

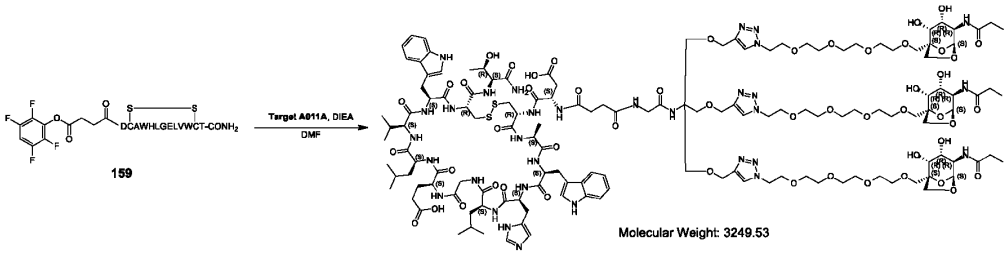
4) To a mixture of **Intermediate 158** (1.10 g, crude) in HOAc/MeCN/H_2O (4/3/3, v/v/v, 500 mL) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 159** (40.0 mg, 98.5% purity, 4.5% yield) as a white solid. LCMS: RT = 1.835 min, MS calcd.: M_{av} = 1777.87, mass observed: $[M + H]^+$ = 1778.65, $[M + 2H]^{2+}$ = 889.32.



Molecular Weight: 1777.87

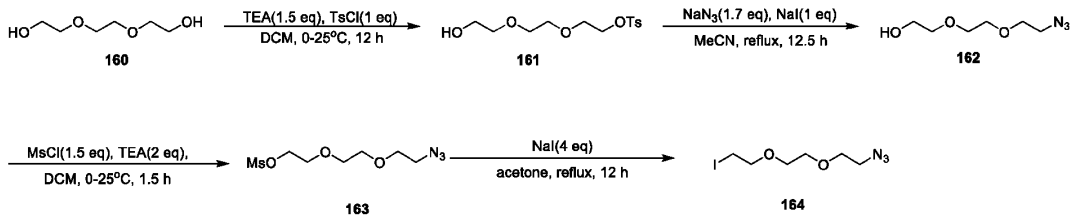
Intermediate 159

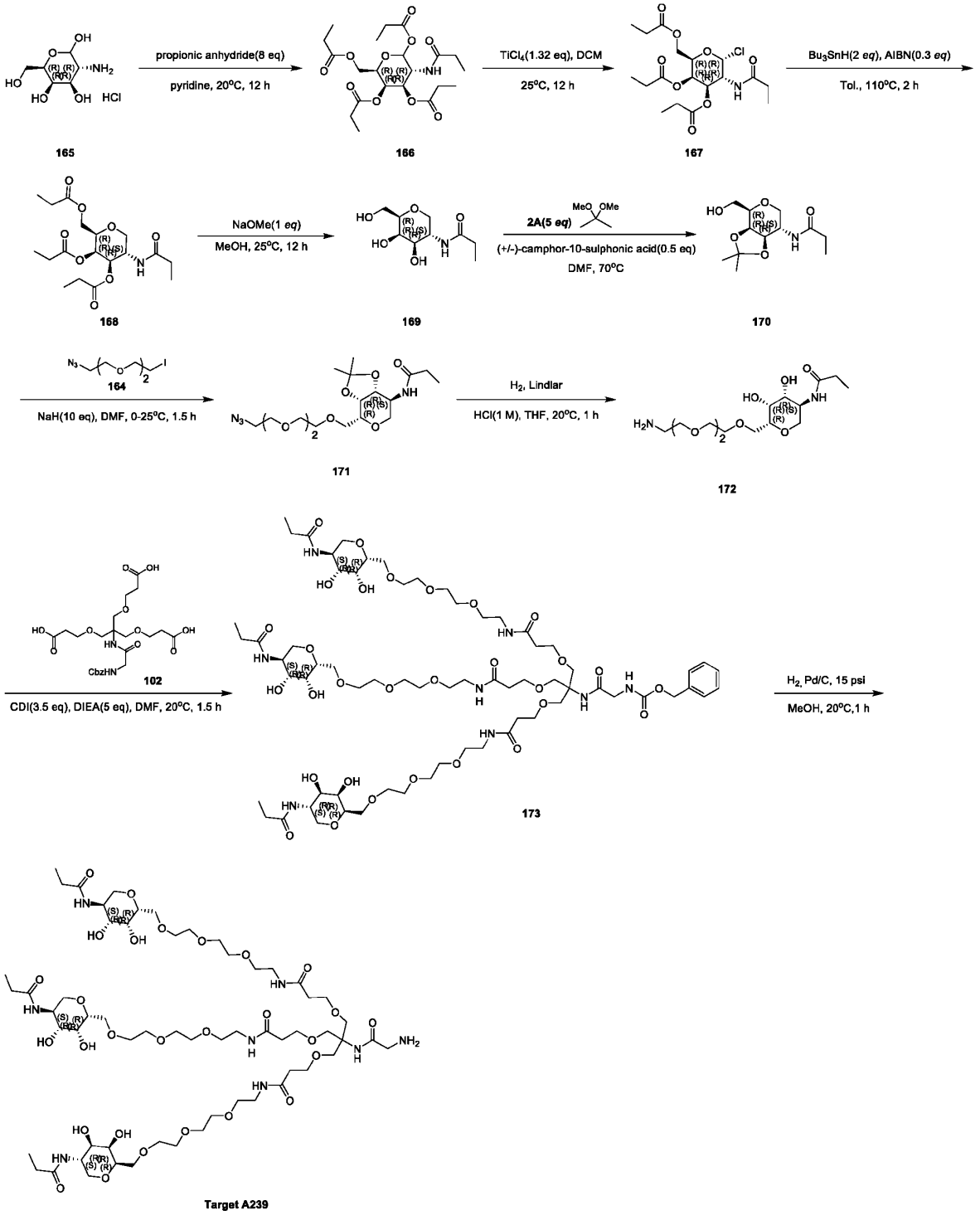
[0304] ***Preparation of BH0003664:***



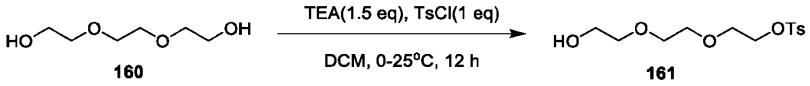
[0305] A mixture of **Intermediate 159** (40.0 mg, 21.98 µmol, 1.20 equiv.) and **Target A011A** (30.0 mg, 18.32 µmol, 1.00 equiv.), DIEA (4.73 mg, 36.64 µmol, 6.38 µL, 2 equiv.) in DMF (1 mL) was stirred at 25 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **BH0003664** (16.9 mg, 94.9% purity, 28.3% yield) as a white solid. LCMS: RT = 1.379 min, MS calcd.: M_{av} = 3249.53, mass observed: $[M + 2H]^{2+}$ = 1625.6, $[M + 3H]^{3+}$ = 1084.1, $[M + 4H]^{4+}$ = 813.0.

EXAMPLE 36. Procedure for Preparation of Target A239




propionic anhydride(8 eq)
pyridine, 20°C, 12 h
TiCl4(1.32 eq), DCM
25°C, 12 h
Bu3SnH(2 eq), AIBN(0.3 eq)
Tol., 110°C, 2 h
NaOMe(1 eq)
MeOH, 25°C, 12 h
2A(5 eq)
(+/-)-camphor-10-sulphonic acid(0.5 eq)
DMF, 70°C
NaH(10 eq), DMF, 0-25°C, 1.5 h
H2, Lindlar
HCl(1 M), THF, 20°C, 1 h
CDI(3.5 eq), DIEA(5 eq), DMF, 20°C, 1.5 h
H2, Pd/C, 15 psi
MeOH, 20°C,1 h
165
166
167
168
169
170
164
171
172
102
173
Target A239

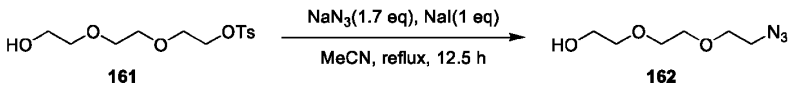
[0306] ***Preparation of Intermediate 161***



160 161

[0307] To a mixture of intermediate 160 (100 g, 665.90 mmol, 89.29 mL, 3.00 equiv.) and TsCl (42.32 g, 221.97 mmol, 1.00 equiv.) in DCM (400 mL) was added TEA (33.69 g, 332.95 mmol, 46.34 mL, 1.50 equiv.) in DCM (100 mL) in one portion at 0°C under N_2. The mixture was stirred at 25°C for 12 hours. TLC indicated TsCl was consumed completely and one new spot formed. The reaction was clean according to TLC. The residue was poured into water (w/w = 1/1) (1000 mL) and stirred for 5 min. The aqueous phase was extracted with DCM (500 mL * 2). The combined organic phase was washed with brine (300 mL * 1), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 2/1 to 1/2) to afford **Intermediate 161** (105 g, 344.99 mmol, 31.08% yield) as a yellow oil. LCMS: RT =0.646 min, MS cal.: 304.36, $[M+H]^+$ = 305.0. ^{1}H NMR (400 MHz, CDCl3) δ = 7.82 - 7.8 (d, *J* = 8.0 Hz, 2H), 7.36 - 7.34 (d, *J* = 8.0 Hz 2H), 4.18 - 4.16 (t, *J* = 4.8 Hz, 2H), 3.73 - 3.70 (m, 4H), 3.62 - 3.58 (m, 6H), 3.33 - 3.25 (m, 3H), 2.11 (s, 1H). Theoretical number of H: 20, found: 20.

[0308] ***Preparation of Intermediate 162***

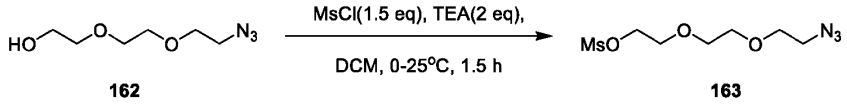


161 162

[0309] Equip a 1000 mL three-necked round bottom flask, addition funnel and thermometer, N_2 balloon etc. MeCN (600 mL) was charged to the 1000 mL three-necked round bottom flask, then **intermediate 161** (50 g, 164.28 mmol, 1.00 equiv.) and NaI (24.62 g, 164.28 mmol, 1.00 equiv.) was added at 25°C. At 25°C (inner temperature), NaN_3 (18.16 g, 279.28 mmol, 1.70 equiv.) was slowly added to the reaction mixture at 25°C within 0.5 hours. After the addition, the mixture was stirred at 80°C for 12 hours. LCMS showed **intermediate 161** was consumed completely and one main peak with desired desired mass was detected. The reaction mixture was added H_2O (50 mL), then was added sat. Na_2CO_3 adjust to pH > 9. The aqueous phase was extracted with EtOAc (100 mL * 5), the combined organic layers were dried over Na_2SO_4, and the solvent was concentrated at 45°C under reduce pressure. H_2O (2.5 L) was added to the aqueous phase then NaOH (2 M) was added to it until pH > 12, then NaClO (50 mL) was added slowly to the aqueous phase at 0°C, it was quenched at 25°C for 18 h. When the pH > 12, it was discarded to a special bucket. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate

= 2/1 to 1/2) to afford intermediate 162 (28 g, 159.83 mmol, 97.29% yield) as a yellow oil. LCMS: RT =0.447 min, MS cal.: 175.19, $[M+H]^+$ = 176.1. ^{1}H NMR (400 MHz, CDCl3) δ = 3.74 - 3.69 (m, 4H), 3.62 - 3.60 (m, 4H), 3.40 - 3.38 (m, 3H), 2.45 - 2.42 (t, J = 6.0, 2H). Theoretical number of H: 13, found H: 13.

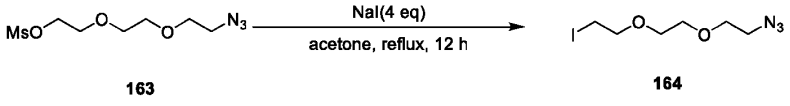
[0310] ***Preparation of Intermediate 163***



162 **163**

[0311] Equip a 2000 mL three-necked round bottom flask, addition funnel and thermometer, N_2 balloon etc. DCM (500 mL) was charged to the 2000 mL three-necked round bottom flask, then **intermediate 162** (60 g, 342.49 mmol, 1.00 equiv.) and TEA (69.31 g, 684.99 mmol, 95.34 mL, 2.00 equiv.) was added at 25°C. At 0°C (inner temperature), MsCl (58.85 g, 513.74 mmol, 39.76 mL, 1.50 *equiv.*) in DCM (100 mL) was added dropwise to the reaction mixture at 0°C within 0.5 h. After the addition, the mixture was stirred at 0°C for 1 hr. LCMS showed **intermediate 162** was consumed completely and one main peak with desired mass was detected. The reaction mixture was washed with 3% HCl (50 mL) and extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **intermediate 163** (86 g, 339.55 mmol, crude, yellow oil), used for next step without further purification. LCMS: RT =0.661 min, MS cal.: 253.28, $[M+NH_4]^+$ = 271.0.

[0312] ***Preparation of Intermediate 164***

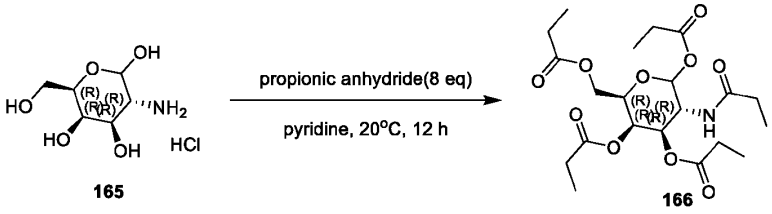


163 **164**

[0313] To a mixture of **intermediate 163** (86 g, 339.55 mmol, 1.00 equiv.) and NaI (203.59 g, 1.36 mol, 4.00 equiv.) in acetone (600 mL) in one portion at 25°C under N_2. The mixture was stirred for 12 hours. LCMS showed **intermediate 163** was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure. The residue was poured into water (100 mL). The aqueous phase was extracted with DCM (50 mL * 3). The combined organic phase was washed with brine (50 mL * 1), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1 to 0/1) to afford **intermediate 164** (83 g, 291.14 mmol, 85.74% yield) as a yellow oil. LCMS: RT =0.742 min, MS

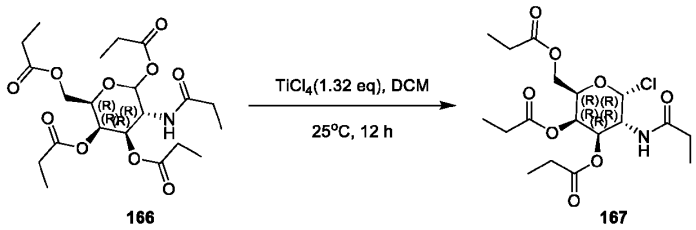
cal.: 285.08, $[M + NH_4]^+$ = 303.0. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.79 - 3.60 (m, J = 6.0, 2H), 3.71 - 3.69 (m, 6H), 3.41 - 3.4 (m, 2H), 2.29 - 2.25 (m, 2H). Theoretical number of H: 12, found H : 12.

[0314] *Preparation of* ***Intermediate 166***



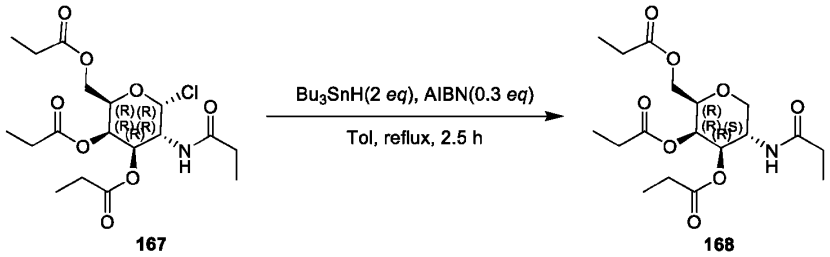
[0315] To a solution of **Intermediate 165** (40 g, 185.50 mmol, 1.00 equiv., HCl) in Py (200 mL) was added propionic anhydride (193.13 g, 1.48 mol, 191.22 mL, 8.00 equiv.). The mixture was stirred at 20°C for 12 h. LCMS showed the desired compound was detected and the reactant was consumed. The mixture was diluted with 1M HCl (100 mL) and extracted with EtOAc (100 mL*3), the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 1/1) to give **Intermediate 166** (19.7 g, 42.87 mmol, 23.11% yield) as colorless oil. LCMS: RT=0.815 min, MS cal.: 459.2, found: MS= 386.4.

[0316] *Preparation of* ***Intermediate 167.***



[0317] To a solution of **Intermediate 166** (5 g, 10.88 mmol, 1.00 equiv.) in DCM (50 mL) was added $TiCl_4$ (2.72 g, 14.36 mmol, 1.32 equiv.). The mixture was stirred at 25°C for 12 h. TLC (PE: EA = 2:1, R_f = 0.5) showed the reactant was consumed and one main spot was formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/9 to 0/1) to give **Intermediate 167** (4.5 g, crude) as a yellow solid.

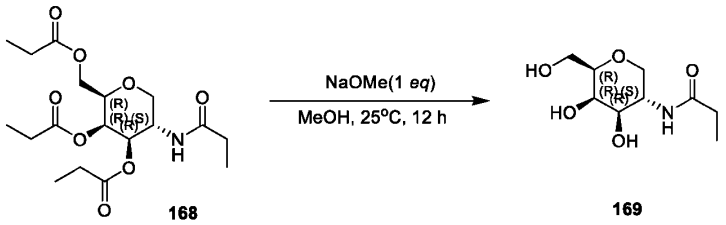
[0318] *Preparation of* ***Intermediate 168***



167 168

[0319] To a solution of **Intermediate 167** (4 g, 9.48 mmol, 1.00 equiv.) in Tol. (100 mL) was added AIBN (467.09 mg, 2.84 mmol, 0.30 equiv.) and Bu_3SnH (5.52 g, 18.96 mmol, 5.02 mL, 2.00 equiv.) at 20°C. The mixture was refluxed for 2 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was added to saturated solution of KF (50 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (50 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/1) to give **Intermediate 168** (1.28 g, 3.31 mmol, 35.2 % yield) as a white solid. LCMS: RT=1.804 min, MS cal.: 387.2, $[M+H]^+$ = 388.3. ^1H NMR (400MHz, MeOD-d_4) δ = 5.43 (d, J = 2.4 Hz, 1H), 4.99 (dd, J = 3.2, 11.1 Hz, 1H), 4.34 (dt, J = 5.2, 11.1 Hz, 1H), 4.12 - 4.08 (m, 1H), 4.02 - 3.88 (m, 2H), 3.31 (s, 2H), 2.45 (q, J = 7.6 Hz, 2H), 2.35 - 2.29 (m, 2H), 2.28 - 2.12 (m, 4H), 1.16 (t, J = 7.6 Hz, 3H), 1.13 - 1.03 (m, 9H). Theoretical number of H: 29, found H : 28, exchangeable: 1.

[0320] *Preparation of **Intermediate 169.***

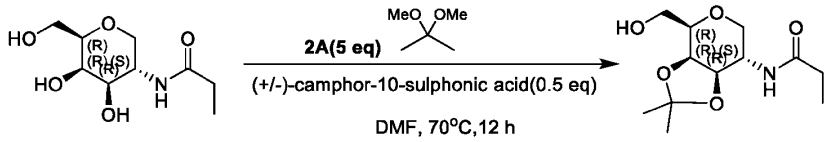


168 169

[0321] To a solution of **Intermediate 168** (3.5 g, 9.03 mmol, 1.00 equiv.) in MeOH (30 mL) was added NaOMe (488.05 mg, 9.03 mmol, 1.00 equiv.). The mixture was stirred at 25°C for 12 h. TLC (DCM: MeOH =10: 1, R_f = 0.3) showed the reactant was consumed and one new spot was formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 20/1 to 5/1) to give **Intermediate 169** (1.6 g, 7.30 mmol, 80.78% yield) as a white solid. ^1H NMR (400MHz, MeOD-d_4) δ = 4.17 (dt, J = 5.2, 10.7 Hz, 1H), 3.96 (dd, J

= 5.2, 10.9 Hz, 1H), 3.88 (d, *J* = 2.8 Hz, 1H), 3.80 - 3.73 (m, 1H), 3.72 - 3.66 (m, 1H), 3.54 (dd, *J* = 3.2, 10.6 Hz, 1H), 3.46 - 3.39 (m, 1H), 3.10 (t, *J* = 10.8 Hz, 1H), 2.31 - 2.20 (m, 2H), 1.19 - 1.12 (m, 3H). Theoretical number of H: 17, found H: 13, exchangeable: 4.

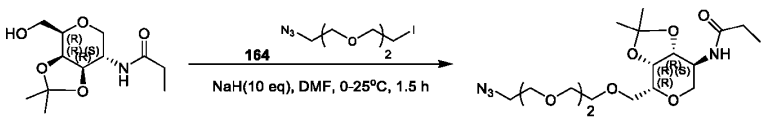
[0322] *Preparation of* ***Intermediate 170.***



169 **170**

[0323] To a solution of **Intermediate 169** (440 mg, 2.01 mmol, 1.00 equiv.) in DMF (10 mL) was added [(1S, 4R)-7, 7-dimethyl-2-oxo-norbornan-1-yl]methanesulfonic acid; hydrate (251.19 mg, 1.00 mmol, 0.50 equiv.) and **2A** (1.05 g, 10.03 mmol, 1.23 mL, 5.00 equiv.). The mixture was stirred at 70°C for 12 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was diluted with $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (5 mL *3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 30/1 to 10/1) to give **Intermediate 170** (450 mg, 1.74 mmol, 86.47% yield) as a yellow solid. LCMS: RT=0.522 min, MS cal.: 259.1, $[M+H]^+$ = 260.3. ^1H NMR (400MHz, MeOD-d_4) δ = 4.24 (d, *J* = 4.8 Hz, 1H), 4.13 - 3.98 (m, 2H), 3.90 - 3.69 (m, 4H), 3.08 (t, *J* = 10.8 Hz, 1H), 2.31 - 2.20 (m, 2H), 1.52 (s, 3H), 1.35 (s, 3H), 1.15 (t, *J* = 7.6 Hz, 3H). Theoretical number of H: 21, found H: 19, exchangeable: 2.

[0324] ***Preparation of Intermediate 171:***

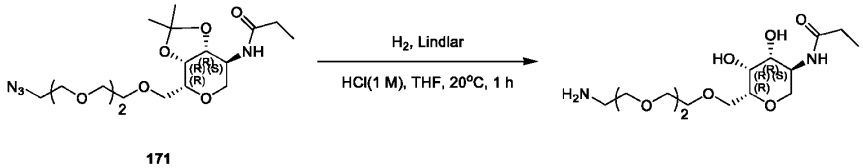


170 **171**

[0325] To a solution of **Intermediate 170** (9 g, 34.71 mmol, 1.00 equiv.) in DMF (90 mL) was added NaH (13.88 g, 347.09 mmol, 60% purity, 10 equiv.) at 0°C within 10 min. The mixture was stirred at 0°C for 0.5 h, then **intermediate 164** (19.79 g, 69.42 mmol, 2.00 equiv.) was added at 0°C, and the mixture was stirred at 25°C for 1 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was poured into ice H_2O (100 ml) slowly within 10 min, and extracted with DCM (100 mL * 3). The combined organic layers were washed with brine (100 mL * 3), dried over Na_2SO_4, filtered and

concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 10: 1) to give **Intermediate 171** (9 g, 21.61 mmol, 62.26% yield) as yellow oil. LCMS: RT = 1.155 min, MS cal.: 416.2, found: $[M + H]^+$ = 417.2. ^1H NMR (400MHz, $CDCl_3$) δ = 5.39 - 5.29 (m, 1H), 4.20 - 4.14 (m, 1H), 4.08 - 4.02 (m, 2H), 3.99 - 3.93 (m, 1H), 3.87 (ddd, *J* = 2.0, 4.8, 6.8 Hz, 1H), 3.80 - 3.73 (m, 3H), 3.70 - 3.67 (m, 9H), 3.42 - 3.38 (m, 2H), 3.18 (t, *J* = 10.8 Hz, 1H), 2.27 - 2.19 (m, 2H), 1.55 (s, 3H), 1.35 (s, 3H), 1.15 (t, *J* = 7.6 Hz, 3H). Theoretical number of H: 32, found H: 32.

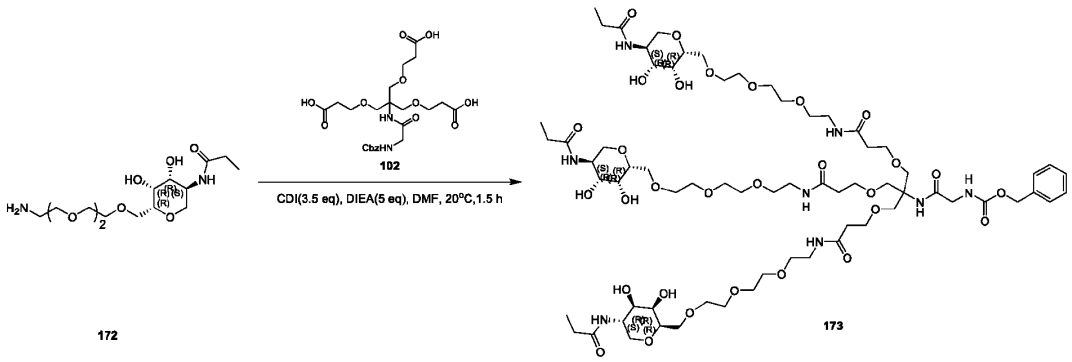
[0326] ***Preparation of Intermediate 172:***



171 172

[0327] To a solution of **Intermediate 171** (9.8 g, 23.53 mmol, 1.00 equiv.) in THF (200 mL) was added HCl (1 M, 117.66 mL, 5.00 equiv.) and calcium; palladium; carbonate (4.86 g, 2.35 mmol, 4.86 mL, 10% purity, 0.10 equiv.). The mixture was stirred at 20°C for 1 h under H_2(15 psi). LCMS showed the Reactant was consumed and desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [water (HCl)-ACN]; gradient: 1%-12% B over 10 min) to give **Intermediate 172** (6.8 g, 19.41 mmol, 82.47% yield) as yellow oil. LCMS: RT = 0.300 min, MS cal.: 350.2, found: $[M + H]^+$ = 351.2.

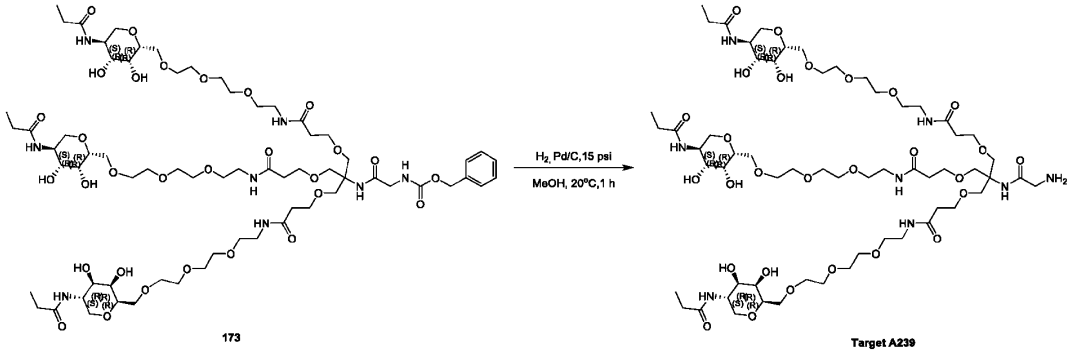
[0328] ***Preparation of Intermediate 173:***



172 173

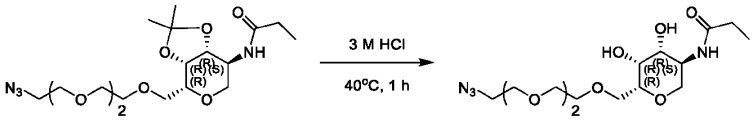
[0329] To a solution of **Intermediate 102** (0.65 g, 1.23 mmol, 1.00 equiv.) in THF (25 mL) was added CDI (697.99 mg, 4.30 mmol, 3.50 equiv.), the mixture was stirred at 20°C for 0.5 h, then **intermediate 172** (1.51 g, 4.30 mmol, 3.50 equiv.) and DIEA (794.77 mg, 6.15 mmol, 1.07 mL, 5.00 equiv.) was added at 20°C. The mixture was stirred at 20°C for 1 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex C18 250*70mm 10u; mobile phase: [water(NH_4HCO_3)-ACN]; B%: 10%-40%,15min) to give **Intermediate 173** (1 g, 655.45 µmol, 53.29% yield) as a white solid. LCMS: RT =1.410 min, MS cal.: 1524.7, found: $[M/2 + H]^+$= 763.8.

[0330] ***Preparation of Target 239:***



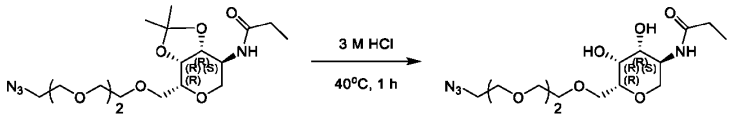
[0331] To a solution of **Intermediate 173** (1.7 g, 1.11 mmol, 1.00 equiv.) in MeOH (20 mL) was added Pd/C (500 mg, 111.43 µmol, 10% purity, 0.10 equiv.). The mixture was stirred at 20 °C for 1 h under H_2 (15 psi). LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 250*70mm 10u; mobile phase: [water(NH_4HCO_3)-ACN]; B%: 10%-40%,15min) to give **Target A239** (1.15 g, 826.42 µmol, 74.17% yield) as yellow oil. LCMS: RT = 1.710 min, MS cal.: 1390.7, found: $[M/2 + H]^+$ = 696.5. ^{1}H NMR (400MHz, MeOD-d_4) δ = 4.13 (dt, J = 5.2, 10.8 Hz, 3H), 3.93 (dd, J = 5.2, 10.8 Hz, 3H), 3.87 (d, J = 3.2 Hz, 3H), 3.76 - 3.72 (m, 3H), 3.71 - 3.67 (m, 16H), 3.66 - 3.63 (m, 24H), 3.60 - 3.51 (m, 13H), 3.42 - 3.38 (m, 6H), 3.09 (t, J = 10.8 Hz, 3H), 2.46 (t, J = 5.8 Hz, 6H), 2.24 (dq, J = 1.6, 7.6 Hz, 6H), 1.13 (t, J = 7.6 Hz, 9H). Theoretical number of H: 110, found H: 95, exchangeable: 15.

EXAMPLE 37. Procedure for Preparation of Target A247



171 Target A247

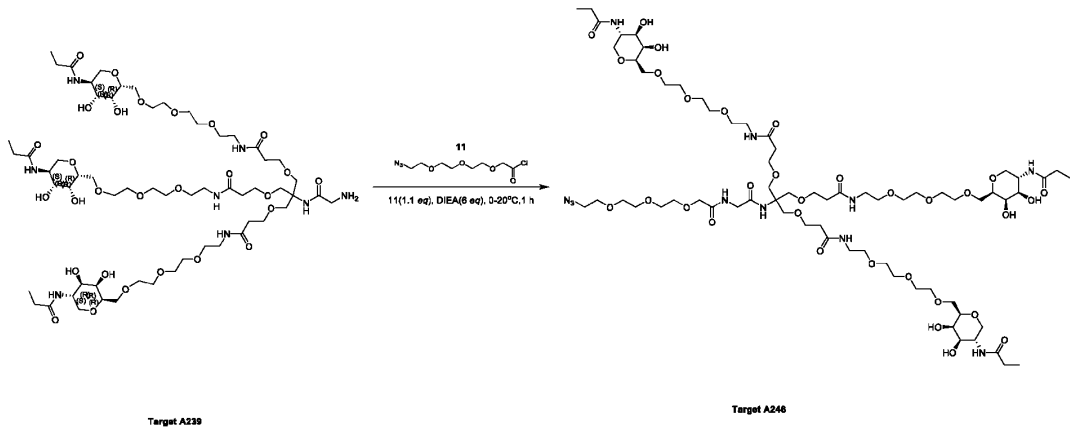
[0332] ***Preparation of Intermediate 171:***



171 Target A247

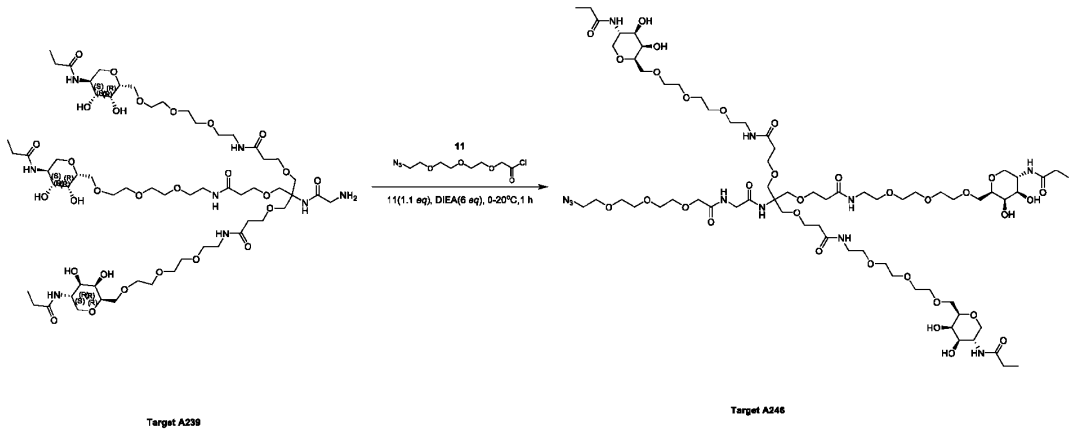
[0333] A solution of **Intermediate 171** (0.75 g, 1.80 mmol, 1.00 equiv.) in HCl (3 M, 30.00 mL, 49.98 equiv.) was stirred at 40°C for 1 h. LCMS showed the desired mass and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna 80*30mm*3um; mobile phase: [water (HCl) -ACN]; B%: 1%-25%, 8min) to give **Target A247** (350 mg, 929.85 μmol, 51.63% yield) as white oil. LCMS: RT = 8.334 min, MS cal.: 376.2, found: $[M + H]^+$ = 377.2. ^{1}H NMR (400MHz, MeOD-d_4) δ = 4.13 (dt, J = 5.2, 10.8 Hz, 1H), 3.91 (dd, J = 5.2, 11.0 Hz, 1H), 3.85 (d, J = 2.7 Hz, 1H), 3.70 - 3.63 (m, 12H), 3.55 - 3.48 (m, 2H), 3.38 (t, J = 5.0 Hz, 2H), 3.07 (t, J = 10.9 Hz, 1H), 2.23 (dq, J = 1.5, 7.6 Hz, 2H), 1.12 (t, J = 7.6 Hz, 3H). Theoretical number of H: 28, found H : 25, exchangeable: 3.

EXAMPLE 38. Procedure for Preparation of Target A246



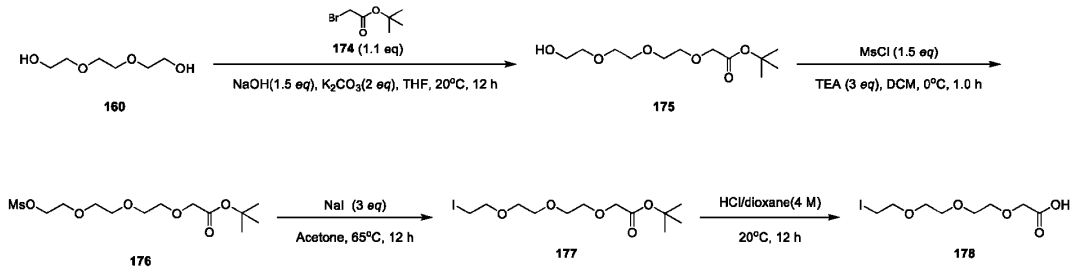
Target A239 Target A246

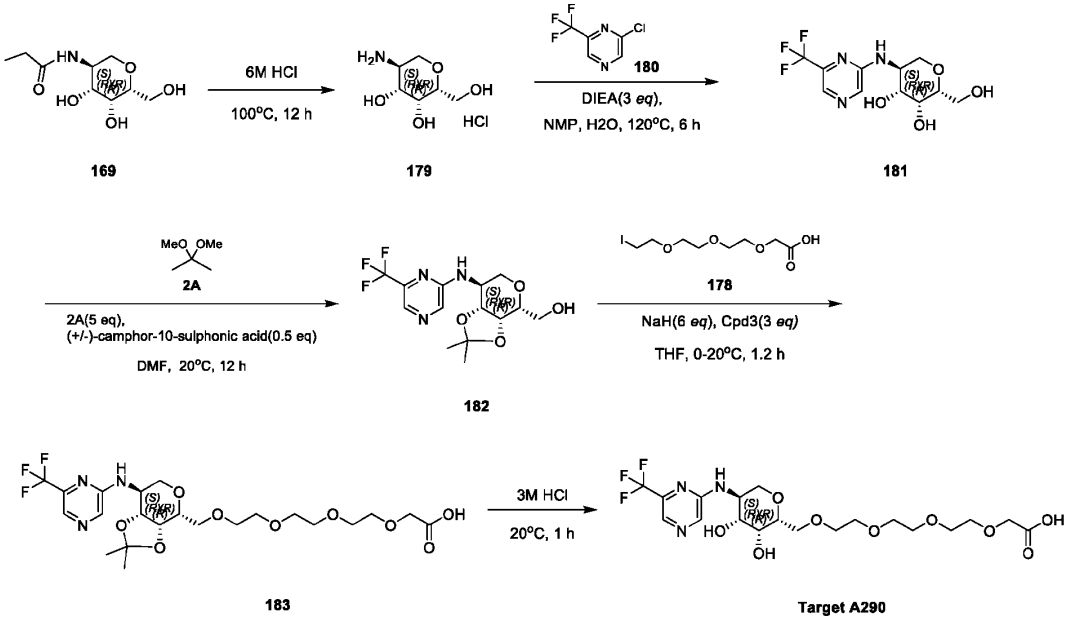
[0334] ***Preparation of Target A246:***



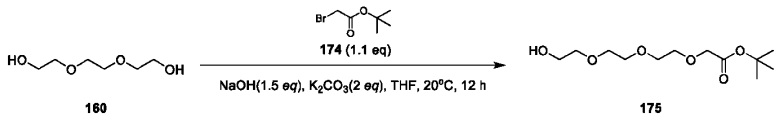
[0335] To a solution of **Target A239** (350 mg, 251.52 μmol, 1.00 equiv.) in DMF (3 mL) was added DIEA (195.04 mg, 1.51 mmol, 262.86 μL, 6.00 equiv.) and **Intermediate 11** (69.63 mg, 276.67 μmol, 1.10 equiv.) at 0°C. The mixture was stirred at 20°C for 1 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(HCl)-ACN];B%: 1%-25%,10min) to give **Target A246** (258 mg, 160.57 μmol, 63.84% yield) as a white solid. LCMS: RT = 0.884 min, MS cal.: 1606.8, found: $[M + H]^+$ = 1606.7. ^{1}H NMR (400MHz, MeOD-d_4) δ = 4.18 - 4.11 (m, 3H), 4.08 (s, 2H), 3.93 (t, *J* = 2.4 Hz, 3H), 3.90 (d, *J* = 5.2 Hz, 2H), 3.87 (d, *J* = 2.8 Hz, 3H), 3.73 - 3.70 (m, 5H), 3.70 - 3.67 (m, 19H), 3.66 - 3.62 (m, 28H), 3.59 - 3.52 (m, 12H), 3.44 - 3.38 (m, 8H), 3.09 (t, *J* = 10.8 Hz, 3H), 2.50 (t, *J* = 6.0 Hz, 6H), 2.27 (dq, *J* = 1.2, 7.6 Hz, 6H), 1.14 (t, *J* = 7.6 Hz, 9H). Theoretical number of H: 123, found H : 109, exchangeable: 14.

EXAMPLE 39. Procedure for Preparation of Target A290



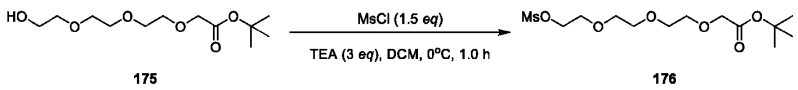


[0336] Preparation of Intermediate 175:



[0337] To a solution of **Intermediate 160** (40.00 g, 266.36 mmol, 35.62 mL, 1.00 equiv.) and **Intermediate 174** (57.15 g, 293.00 mmol, 43.26 mL, 1.10 equiv.) in THF (1000 mL) was added NaOH (15.98 g, 399.54 mmol, 1.50 equiv.) and K_2CO_3 (73.62 g, 532.72 mmol, 2.00 equiv.) at 20°C, and the reaction was stirred at 20°C for 12 h. LCMS showed the reaction was completed and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with water (100 mL) and extracted with EtOAc 300 mL (100 mL x 3). The combined organic layers were washed with brine 100 mL (100 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100: 1 – 1 : 1) to afford **Intermediate 175** (13.00 g, 49.18 mmol, 18.47% yield) as yellow oil. LCMS: RT = 1.070 min, MS cal.: 264.3, found: $[M + Na]^+$ = 287.2. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.03 (s, 2H), 3.76 - 3.70 (m, 6H), 3.69 - 3.67 (m, 4H), 3.64 - 3.60 (m, 2H), 1.48 (s, 9H). Theoretical number of H: 24, found: 23. Exchangeable H: 1.

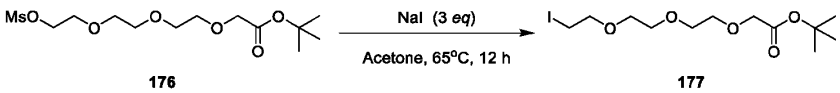
[0338] ***Preparation of Intermediate 176:***



175 176

[0339] Equipped a 1000 mL three-necked round bottom flask, addition funnel and thermometer, N_2 balloon etc. DCM (400 mL) was charged to the three-necked round bottom flask, then **Intermediate 175** (40.00 g, 151.33 mmol, 1.00 equiv.) and TEA (45.94 g, 454.00 mmol, 63.19 mL, 3.00 equiv.) was added to the mixture at 20°C for 1 min, then cooled to 0°C (inert atmosphere). At 0°C, MsCl (26.00 g, 227.00 mmol, 17.57 mL, 1.50 equiv.) in DCM (20 mL) was added dropwise within 5 min to the reaction mixture. After the addition, the mixture was stirred at 0°C for 1 h. TLC (Petroleum: ether ethyl ester = 0: 1, R_f = 0.6) showed the reaction was completed and one major new spot with lower polarity was detected. The reaction mixture was poured into H_2O (100 mL) and HCl (1 M, 100 mL) slowly at 0°C within 10 min. The aqueous phase was extracted with DCM 300 mL (100 mL x 3) at 0°C. The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The mixture was concentrated at 45°C under reduced pressure to afford **Intermediate 176** (50.00 g, 146.03 mmol, 96.49% yield) as yellow oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.41 - 4.37 (m, 2H), 4.01 (s, 2H), 3.80 - 3.76 (m, 2H), 3.73 - 3.65 (m, 8H), 3.09 (s, 3H), 1.48 (s, 9H). Theoretical number of H: 26, found: 26.

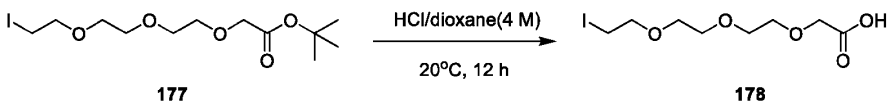
[0340] ***Preparation of Intermediate 177:***



176 177

[0341] To a solution of **Intermediate 176** (25.00 g, 73.01 mmol, 1.00 equiv.) in acetone (375 mL) was added NaI (32.83 g, 219.04 mmol, 3.00 equiv.) and the reaction was stirred at 65°C for 12 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction solution was concentrated under reduced pressure to remove acetone. The mixture was quenched by H_2O (300 mL) at 20°C, and extracted with EtOAc 1500 mL (500 mL * 3). The combined organic layers were washed with brine (300 mL), dried overNa_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 0/1) to afford **Intermediate 177** (45.00 g, 120.25 mmol, 82.35% yield) as a white solid. LCMS: RT = 1.631 min, MS cal.: 374.2, found: $[M + Na]^+$ = 397.1.

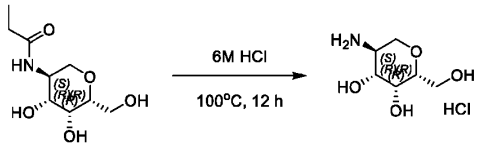
[0342] ***Preparation of Intermediate 178:***



177 178

[0343] To a solution of **Intermediate 177** (25.00 g, 66.81 mmol, 1.00 equiv.) was added HCl/dioxane (4 M, 60 mL, 3.59 equiv.), and the reaction solution was stirred at 20°C for 12 h. LCMS showed the reactant was consumed and the desired mass was detected. The reaction solution was concentrated under reduced pressure to afford **Intermediate 178** (21 g, 66.02 mmol, 98.82% yield) as yellow oil. LCMS: RT = 0.891 min, MS cal.: 318.1, found: $[M + H]^+$ = 319.0. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.18 (s, 2H), 3.79 - 3.69 (m, 10H), 3.28 (t, *J* = 6.8 Hz, 2H). Theoretical number of H: 15, found: 14, Exchangeable H: 1.

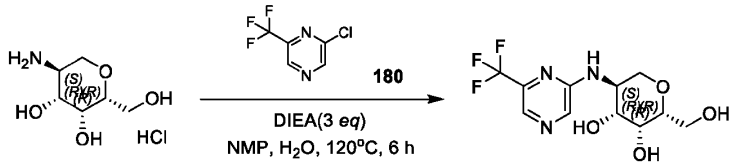
[0344] ***Preparation of Intermediate 169:***



169 179

[0345] To a solution of **Intermediate 169** (7.5 g, 34.21 mmol, 1.00 equiv.) in HCl (6 M, 150.00 mL, 26.31 equiv.). The mixture was stirred at 100°C for 12 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was triturated with MTBE at 20°C for 30 min to give **Intermediate 179** (6.8 g, 34.06 mmol, 99.57% yield, HCl) as a brown solid. LCMS: RT = 0.245 min, MS cal.: 163.1, found: $[M + H]^+$ = 164.2. ^1H NMR (400MHz, MeOD-d_4) δ = 4.12 - 4.08 (m, 1H), 3.90 (d, *J* = 2.4 Hz, 1H), 3.76 - 3.71 (m, 1H), 3.70 - 3.64 (m, 1H), 3.62 - 3.57 (m, 1H), 3.48 - 3.43 (m, 1H), 3.40 - 3.33 (m, 2H). Theoretical number of H: 13, found: 8.Exchangeable H: 5.

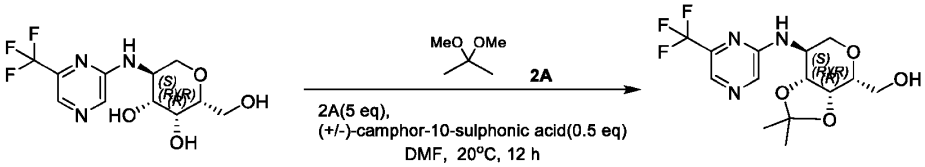
[0346] ***Preparation of Intermediate 181:***



179 181

[0347] To a solution of **Intermediate 180** (5 g, 30.64 mmol, 1.00 equiv.) in NMP (50 mL) and H_2O (25 mL) was added **Intermediate 179** (5.59 g, 30.64 mmol, 1.00 equiv.) and DIEA (11.88 g, 91.93 mmol, 16.01 mL, 3.00 equiv.). The mixture was stirred at 120°C for 6 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 (250*70mm,15 um); mobile phase: [H_2O(0.04%HCl)-ACN]; gradient:1%-32% B over 18.0 min) to give **Intermediate 181** (4 g, 24.32 mmol, 39.68% yield) as a yellow solid. LCMS: RT = 0.792 min, MS cal.: 309.1, found: $[M + H]^+$ = 310.0. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.11 (s, 1H), 8.00 (s, 1H), 4.35 (dt, *J* = 5.2, 10.6 Hz, 1H), 4.21 - 4.09 (m, 1H), 3.92 (d, *J* = 2.8 Hz, 1H), 3.80 - 3.73 (m, 1H), 3.73 - 3.63 (m, 2H), 3.52 - 3.42 (m, 1H), 3.13 (t, *J* = 10.8 Hz, 1H). Theoretical number of H: 14, found: 10.Exchangeable H: 4.

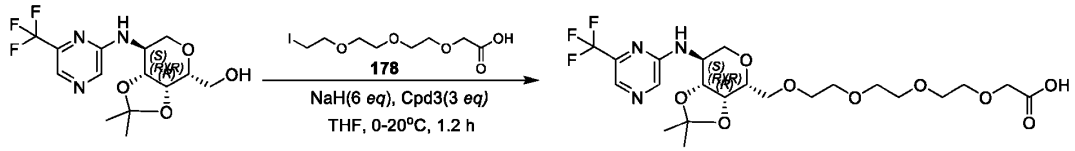
[0348] ***Preparation of Intermediate 182:***



181 **182**

[0349] To a solution of **Intermediate 181** (8.6 g, 27.81 mmol, 1.00 equiv.) in DMF (90 mL) was added [(1S, 4R)-7, 7-dimethyl-2-oxo-norbornan-1-yl]methanesulfonic acid; hydrate (3.48 g, 13.91 mmol, 0.50 equiv.) and ***2A*** (14.48 g, 139.05 mmol, 17.04 mL, 5.00 equiv.). The mixture was stirred at 20 °C for 12 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was diluted with 1M Na_2CO_3 (100 mL) and extracted with EtOAc (80 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by *pre*-HPLC (column: Welch Xtimate C18 250*100mm#10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 15%-45% B over 20.0 min) to give **Intermediate 182** (5 g, 14.31 mmol, 51.47% yield) as yellow oil. LCMS: RT = 1.206 min, MS cal.: 349.1, found: $[M + H]^+$ = 350.1. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.20 (s, 1H), 8.11 (s, 1H), 7.80 (br d, *J* = 7.5 Hz, 1H), 4.81 (t, *J* = 5.6 Hz, 1H), 4.20 (br d, *J* = 2.4 Hz, 1H), 4.15 - 4.06 (m, 2H), 3.80 (dd, *J* = 4.2, 11.1 Hz, 1H), 3.74 - 3.68 (m, 1H), 3.60 - 3.52 (m, 2H), 3.11 - 2.96 (m, 1H), 1.40 (s, 3H), 1.26 (s, 3H). Theoretical number of H: 18, found: 18.

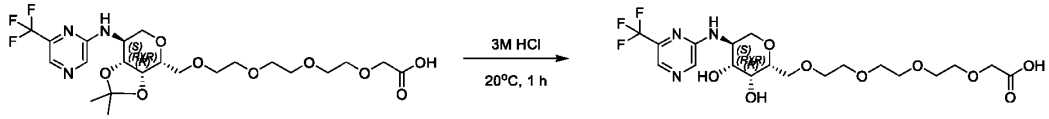
[0350] ***Preparation of Intermediate 183:***



182 183

[0351] Equipped a 100 mL three-necked round bottom flask, addition funnel and thermometer, N_2 balloon. THF (20 mL) was charged to the three-necked round bottom flask, then **Intermediate 182** (1.5 g, 4.29 mmol, 1.00 equiv.) was added to the mixture at 20°C. At 0°C (inner temperature), NaH (1.03 g, 25.77 mmol, 60% purity, 6.00 equiv.) was added in portions to the reaction mixture at 0°C within 0.1 h. After the addition, the mixture was stirred at 0°C for 0.5 h. At 0°C (inner temperature), **Intermediate 178** (2.05 g, 6.44 mmol, 1.50 equiv.) was added dropwise to the reaction mixture at 0°C within 0.1 h. After the addition, the mixture was stirred at 20°C for 0.5 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was added to ice H_2O (30 mL) at 0°C within 5 min. The mixture was extracted by EtOAc (30 mL*3). Then organic phase was combined, washed with brine (30 mL), dried with Na_2SO_4 and filtered. The organic phase was concentrated under reduced pressure at 45°C to give **Intermediate 183** (2.3 g, crude) as yellow oil. LCMS: RT = 1.346 min, MS cal.: 539.2, found: $[M + H]^+$ = 540.2.

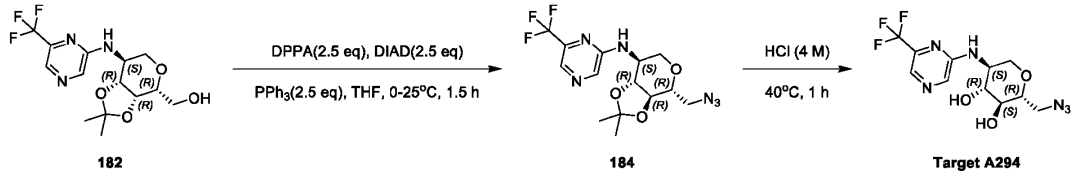
[0352] ***Preparation of Target A290:***



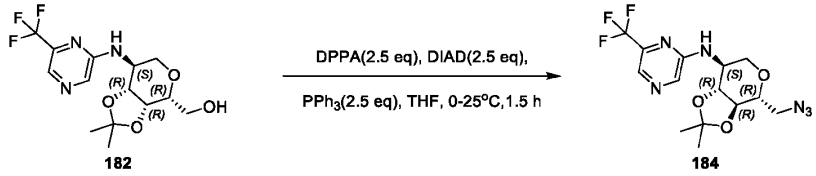
183 Target A290

[0353] To a solution of **Intermediate 183** (2.3 g, 4.26 mmol, 1.00 equiv.) in HCl (3 M, 5 mL, 3.52 equiv.). The mixture was stirred at 20°C for 1 h. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 (250*70mm, 10 um); mobile phase: [H_2O (0.04%HCl)-ACN]; gradient: 5%-50% B over 18.0 min) to give **Target A290** (603 mg, 1.21 mmol, 28.32% yield) as a yellow solid. LCMS: RT = 9.662 min, MS cal.: 499.2, found: $[M + H]^+$ = 500.4. ^{1}H NMR (400MHz, MeOD-d_4) δ = 8.12 (s, 1H), 8.01 (s, 1H), 4.34 (dt, J = 5.2, 10.8 Hz, 1H), 4.14 (s, 2H), 4.12 - 4.08 (m, 1H), 3.93 (d, J = 3.0 Hz, 1H), 3.73 - 3.64 (m, 15H), 3.63 - 3.59 (m, 1H), 3.19 - 3.10 (m, 1H). Theoretical number of H: 28, found: 24.Exchangeable H: 4.

EXAMPLE 40. Procedure for Preparation of *Target A294*

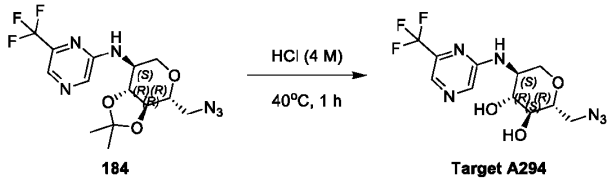


[0354] **Preparation of *Intermediate 184*:**



[0355] To a solution of **Intermediate 182** (0.50 g, 1.43 mmol, 1.00 *equiv.*) and DIAD (723.61 mg, 3.58 mmol, 693.77 µL, 2.50 *equiv.*) in THF (12 mL) was added PPh_3 (938.60 mg, 3.58 mmol, 2.50 *equiv.*) at 0°C and the mixture was stirred at 0°C for 30 min. Then DPPA (984.81 mg, 3.58 mmol, 772.40 µL, 2.50 *equiv.*) was added to the solution and the mixture was stirred at 25°C for 1 hr. LCMS showed **Intermediate 182** was consumed completely and desired mass was detected. The reaction mixture was diluted with H_2O (12 mL) and extracted with EtOAc (8 mL * 3). The combined organic layers were washed with brine (6 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 1/1) to give **Intermediate 184** (1.38 g, crude) as yellow oil. LCMS: RT = 1.773 min, MS cal.: 374.1, found: $[M+H]^+$ = 375.2. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.09 (s, 1H), 8.02 (s, 1H), 4.30 (ddd, *J* = 4.8, 8.8, 10.8 Hz, 1H), 4.24 (dd, *J* = 2.2, 5.1 Hz, 1H), 4.18 - 4.06 (m, 2H), 4.00 - 3.89 (m, 2H), 3.59 (dd, *J* = 8.2, 12.8 Hz, 1H), 3.43 (dd, *J* = 4.4, 12.8 Hz, 1H), 3.16 (t, *J* = 11.2 Hz, 1H), 1.51 (s, 3H), 1.33 (s, 3H). Theoretical number of H: 17, found: 17.

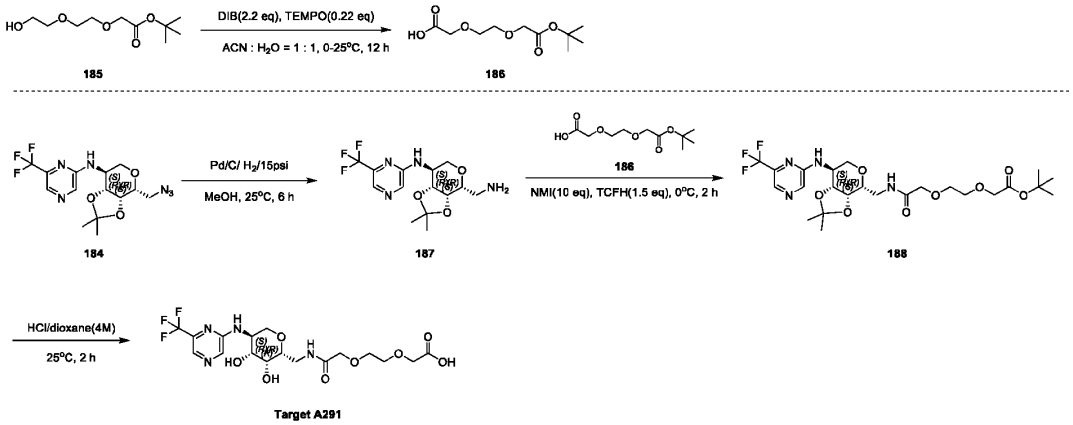
[0356] ***Preparation of Target A294:***



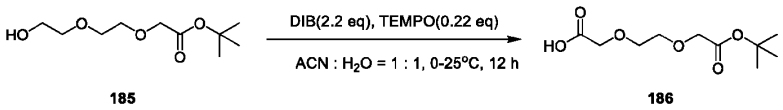
[0357] A solution of **Intermediate 184** (0.37 g, 988.47 µmol, 1.00 *equiv.*) in HCl (4 M, 4 mL) was

stirred at 40°C for 1 hr. LCMS showed the reaction was completed. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.2% FA)-ACN]; gradient: 10%-55% B over 8.0 min) to afford **Target A294** (247 mg, 731.57 µmol, 74.01% yield, 99% purity) as a white solid. LCMS: RT = 1.975 min, MS cal.: 334.1, found: $[M+H]^+$ = 335.1. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.22 (s, 1H), 8.07 (s, 1H), 7.63 (br d, *J* = 7.6 Hz, 1H), 4.91 (t, *J* = 5.8 Hz, 2H), 4.13 - 4.03 (m, 1H), 3.93 (dd, *J* = 4.8, 10.8 Hz, 1H), 3.73 - 3.67 (m, 1H), 3.59 - 3.48 (m, 3H), 3.29 (d, *J* = 9.2 Hz, 1H), 3.02 (t, *J* = 10.8 Hz, 1H). Theoretical number of H: 13, found: 13.

EXAMPLE 41. Procedure for Preparation of *Target A291*



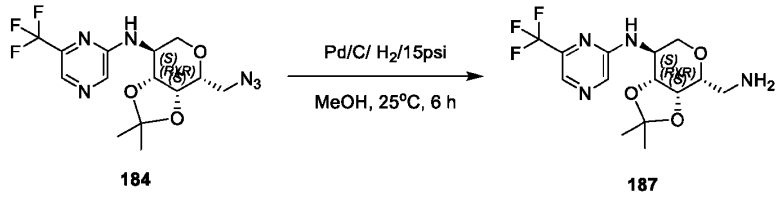
[0358] Preparation of ***Intermediate 186***:



[0359] To a solution of **Intermediate 185** (2.00 g, 9.08 mmol, 1.00 *equiv.*) in ACN (5 mL) and H_2O (5 mL) was added TEMPO (314.13 mg, 2.00 mmol, 0.22 *equiv.*) and (diacetoxyiodo)benzene (6.43 g, 19.98 mmol, 2.20 *equiv.*) at 0°C. The mixture was stirred at 25°C for 12 hr. LCMS showed **Intermediate 185** was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O (2 mL) and extracted with DCM (2 mL * 3). The combined organic layers were washed with brine (2 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 10%-40% B over 9.0 min) to give **Intermediate 186** (1.88 g, 7.87 mmol, 86.62% yield, 98% purity) as yellow oil. LCMS: RT = 0.974 min, MS cal.: 234.1, found:

[M+Na] $^{+}$ = 257.2. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 4.02 (s, 2H), 3.98 (s, 2H), 3.68 (s, 4H), 3.49 (s, 1H), 1.47 (s, 9H). Theoretical number of H: 18, found: 18.

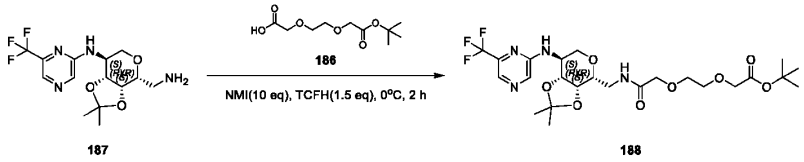
[0360] ***Preparation of intermediate 187:***



184 187

[0361] To a solution of **Intermediate 184** (3.40 g, 9.08 mmol, 1.00 *equiv.*) in MeOH (5 mL) was added Pd/C (966.63 mg, 908.32 μmol, 10% purity, 0.10 *equiv.*), and the mixture was stirred at 25°C for 6 hr under H_2 atmosphere. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give **Intermediate 187** (3.1 g, 6.94 mmol, 76.43% yield, 78.0% purity) as yellow oil. LCMS: RT = 1.009 min, MS cal.: 348.1, found: [M+H] $^{+}$ = 349.1.

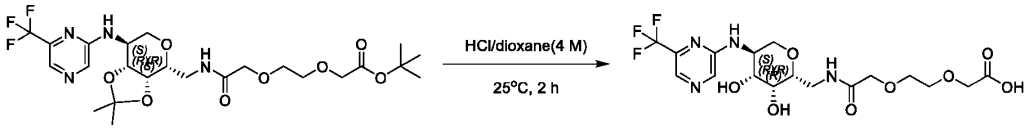
[0362] ***Preparation of Intermediate 188:***



187 188

[0363] To a solution of **Intermediate 186** (807.00 mg, 3.45 mmol, 1.20 *equiv.*) in DMF (5 mL) was added NMI (2.36 g, 28.71 mmol, 2.29 mL, 10.00 *equiv.*) and **Intermediate 187** (1.00 g, 2.87 mmol, 1.00 *equiv.*). Then TCFH (1.21 g, 4.31 mmol, 1.50 *equiv.*) in DMF (5 mL) was added to the solution. The mixture was stirred at 0°C for 2 hr. LCMS showed **Intermediate 187** was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O (5 mL) and extracted with DCM (5 mL* 3). The combined organic layers were washed with brine (5 mL* 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 50/1 to 25/1). **Intermediate 188** (460 mg, 782.22 μmol, 27.25% yield, 96% purity) was obtained as colourless oil. LCMS: RT = 1.657 min, MS cal.: 564.2, found: [M+H]$^{+}$ = 565.3. ^{1}H NMR (400 MHz, MeOD-d_4) δ = 8.08 (s, 1H), 8.02 (s, 1H), 4.34 - 4.24 (m, 2H), 4.13 (dd, *J* = 4.8, 8.8 Hz, 1H), 4.06 (s, 2H), 4.03 (s, 2H), 3.94 (dd, *J* = 4.8, 11.2 Hz, 1H), 3.91 - 3.86 (m, 1H), 3.77 - 3.66 (m, 5H), 3.50 (dd, *J* = 8.4, 13.9 Hz, 1H), 3.10 (t, *J* = 11.2 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 9H), 1.35 (s, 3H). Theoretical number of H: 35, found: 33. Exchange H: 2.

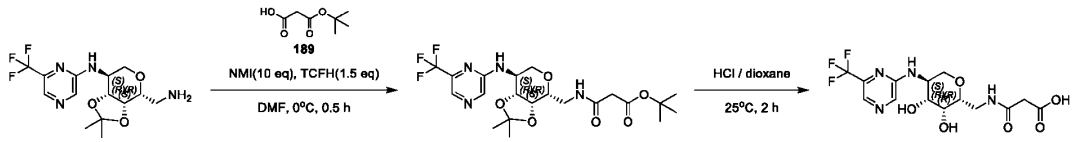
[0364] ***Preparation of Target A291:***



188 Target A291

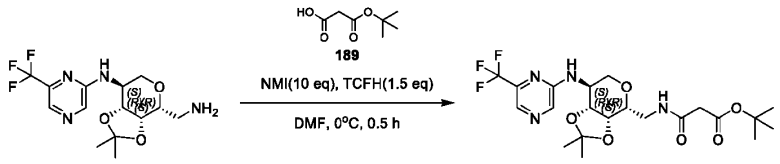
[0365] A solution of **Intermediate 188** (0.20 g, 354.26 µmol, 1.00 *equiv.*) in HCl/dioxane (4 M, 6.67 mL, 75.27 *equiv.*) was stirred at 25°C for 2 hr. LCMS showed **Intermediate 188** was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 1%-35% B over 8.0 min) to give **Target A291** (73.40 mg, 153.11 µmol, 43.22% yield, 97.7% purity) as a white solid. LCMS: RT = 11.002 min, MS cal.:468.1, found: $[M+H]^+$ = 469.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.21 (s, 1H), 8.06 (s, 1H), 7.75 - 7.67 (m, 1H), 7.64 (br d, *J* = 7.2 Hz, 1H), 4.96 - 4.73 (m, 1H), 4.04 (s, 3H), 3.92 - 3.86 (m, 3H), 3.68 (d, *J* = 2.8 Hz, 1H), 3.64 - 3.58 (m, 4H), 3.51 (dd, *J* = 3.2, 10.4 Hz, 1H), 3.44 - 3.37 (m, 2H), 3.30 - 3.24 (m, 3H), 2.94 (t, *J* = 10.8 Hz, 1H). Theoretical number of H: 23, found: 23.

EXAMPLE 42. Procedure for Preparation of *Target A295*



187 190 Target A295

[0366] **Preparation of Intermediate 190*:***

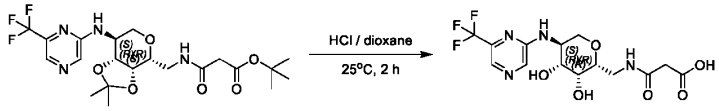


187 190

[0367] To a solution of **Intermediate 187** (1.00 g, 2.87 mmol, 1.00 equiv.) in DMF (8 mL) was added NMI (2.36 g, 28.71 mmol, 2.29 mL 10.00 equiv.) and **Intermediate 189** (551.79 mg, 3.45 mmol, 530.57 µL, 1.20 equiv.) and TCFH (1.21 g, 4.31 mmol, 1.50 equiv.). The reaction was stirred at 0°C for 0.5 h. LCMS showed **Intermediate 187** was consumed completely and desired mass was detected. The

reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (8 mL x 3). The combined organic layers were washed with brine (8 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1 to 1/3) to afford **Intermediate 190** (1.20 g, 2.45 mmol, 85.22% yield) as a white solid. LCMS: RT = 1.599 min, MS cal.: 490.2, found: $[M+H-56]^+$ = 435.2.

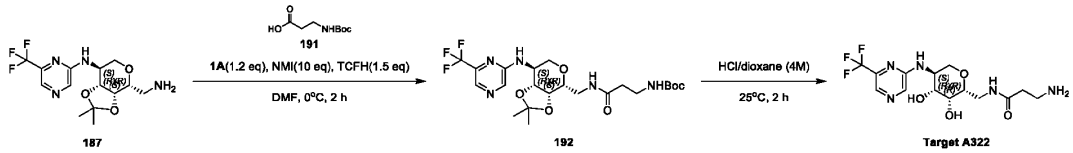
[0368] ***Preparation of Intermediate Target A295:***



190 Target A295

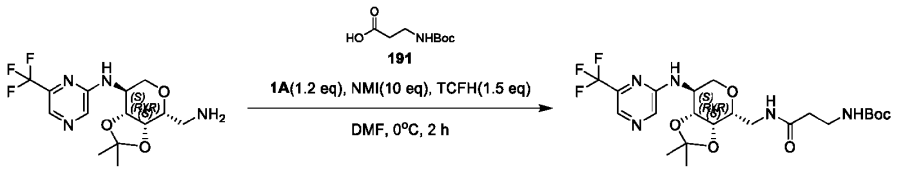
[0369] A solution of **Intermediate 190** (600.00 mg, 1.22 mmol, 1.00 equiv.) in HCl/dioxane (6 ml) was stirred at 25°C for 2 h. LCMS showed the reaction was consumed completely and desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100 * 40mm * 5 um; mobile phase: [H_2O (0.04% HCl)-ACN]; gradient: 1%-40% B over 8.0 min) to give **Target A295** (202 mg, 512.30 µmol, 41.88% yield) as a yellow solid. LCMS: RT = 0.783 min, MS cal.: 394.1, $[M+H]^+$ = 395.1. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.13 (s, 1H), 8.02 (s, 1H), 4.33 (dt, *J* = 5.2, 10.8 Hz, 1H), 4.12 (dd, *J* = 5.2, 11.0 Hz, 1H), 3.90 - 3.86 (m, 1H), 3.65 (dd, *J* = 3.2, 10.5 Hz, 1H), 3.61 - 3.46 (m, 3H), 3.40 - 3.32 (m, 2H), 3.11 (t, *J* = 10.8 Hz, 1H). Theoretical number of H: 17, found: 12, exchanged H: 5.

EXAMPLE 43. Procedure for Preparation of *Target A322*



187 192 Target A322

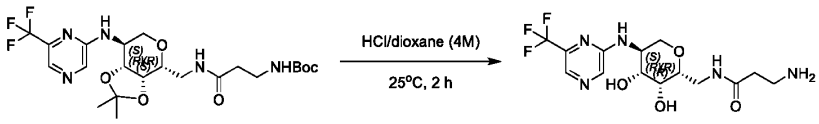
[0370] Preparation of ***Intermediate 192***:



187 192

[0371] To a solution of **Intermediate 191** (423.70 mg, 2.24 mmol, 1.20 *equiv.*) in DMF (6 mL) was added NMI (1.53 g, 18.66 mmol, 1.49 mL, 10.00 *equiv.*) and **Intermediate 187** (650 mg, 1.87 mmol, 1.00 *equiv.*). Then TCFH (785.38 mg, 2.80 mmol, 1.50 *equiv.*) was added to the solution and the mixture was stirred at 0°C for 2 hr. LCMS showed **Intermediate 187** was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol=50/1 to 10/1) to give **Intermediate 192** (350 mg, 592.86 µmol, 31.77% yield, 88% purity) as colourless oil. LCMS: RT = 1.523 min, MS cal.: 519.2, found: $[M+H-100]^+$ = 420.2. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.09 (s, 1H), 8.02 (s, 1H), 4.33 - 4.20 (m, 2H), 4.12 (dd, *J* = 5.0, 8.8 Hz, 1H), 4.00 - 3.89 (m, 1H), 3.84 (ddd, *J* = 2.0, 4.1, 8.5 Hz, 1H), 3.57 (dd, *J* = 4.0, 13.9 Hz, 1H), 3.41 (dd, *J* = 8.4, 13.9 Hz, 1H), 3.35 (s, 2H), 3.16 - 3.05 (m, 1H), 2.39 (t, *J* = 6.8 Hz, 2H), 1.51 (s, 3H), 1.42 (s, 9H), 1.35 (s, 3H). Theoretical number of H: 32, found: 29. Exchange H: 3.

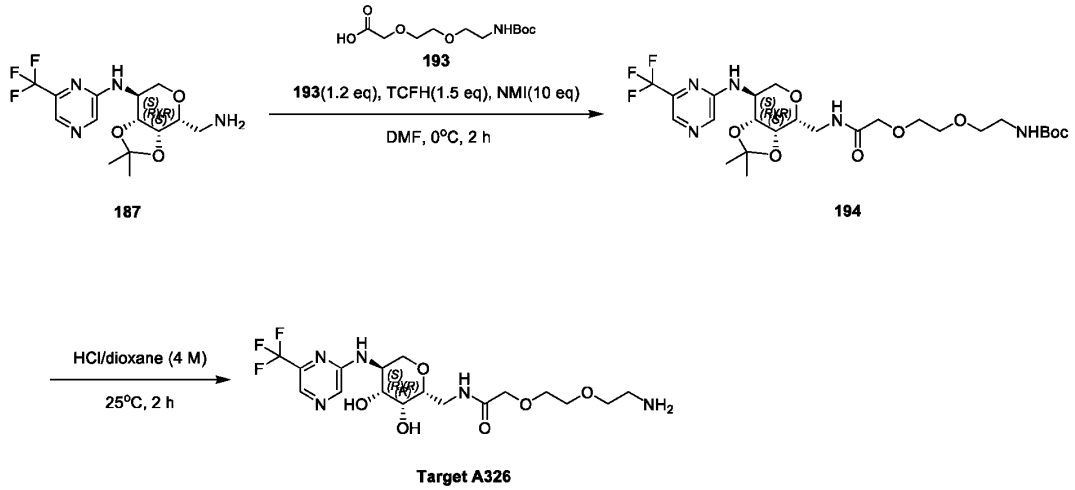
[0372] ***Preparation of <u>Target A322</u>:***



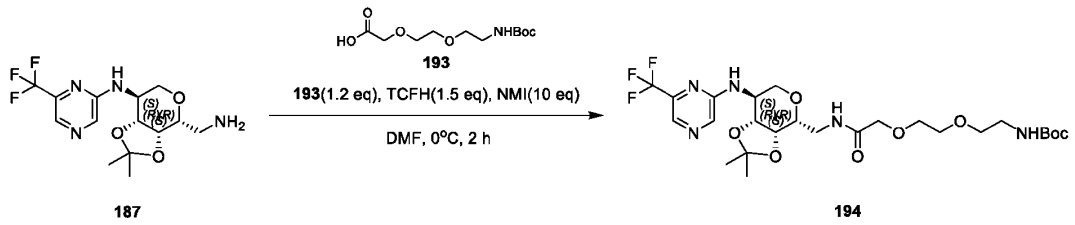
192 Target A322

[0373] **Intermediate 192** (300.00 mg, 577.46 µmol, 1.00 *equiv.*) in HCl/dioxane (4 M, 5 mL, 34.63 *equiv.*) was stirred at 25°C for 2 hr. LCMS showed the reaction was completed. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 1%-30% B over 8.0 min) to give **Target A322** (128.1 mg, 333.64 µmol, 57.78% yield, 98.8% purity) as a white solid. LCMS: RT = 0.615 min, MS cal.: 379.2, found: $[M+H]^+$ = 380.2. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.21 (s, 1H), 8.06 (s, 1H), 8.02 - 7.93 (m, 1H), 7.64 (br d, *J* = 7.5 Hz, 1H), 4.92 - 4.68 (m, 1H), 4.11 - 4.00 (m, 1H), 3.89 (dd, *J* = 5.2, 10.8 Hz, 1H), 3.67 (d, *J* = 2.8 Hz, 1H), 3.50 (dd, *J* = 3.2, 10.4 Hz, 1H), 3.37 (br s, 1H), 3.33 (br s, 1H), 3.32 - 3.22 (m, 3H), 3.20 - 3.09 (m, 2H), 2.94 (t, *J* = 10.8 Hz, 1H), 2.73 (t, *J* = 6.8 Hz, 1H), 2.24 (br t, *J* = 7.2 Hz, 1H), 2.18 (t, *J* = 6.8 Hz, 1H). Theoretical number of H: 20, found: 20.

EXAMPLE 44. Procedure for Preparation of <u>*Target A326*</u>

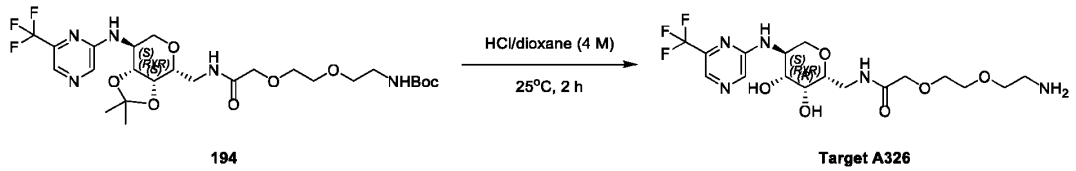


[0374] Preparation of ***Intermediate 194***:



[0375] To a solution of **Intermediate 193** (589.58 mg, 2.24 mmol, 1.20 *equiv.*) in DMF (6 mL) was added NMI (1.53 g, 18.66 mmol, 1.49 mL, 10.00 *equiv.*) and **Intermediate 187** (650 mg, 1.87 mmol, 1.00 *equiv.*) at 0°C. Then TCFH (785.38 mg, 2.80 mmol, 1.50 *equiv.*) was added to the solution and the mixture was stirred at 0°C for 2 hr. LCMS showed **Intermediate 187** was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O 10 mL and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol=50/1 to 10/1) to give **Intermediate 194** (420 mg, 438.69 µmol, 23.51% yield, 62% purity) as colourless oil. LCMS: RT = 1.583 min, MS cal.: 593.3, found: $[M-100+H]^+$ = 494.2. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.09 (s, 1H), 8.02 (s, 1H), 4.35 - 4.21 (m, 2H), 4.14 (dd, *J* = 5.2, 8.8 Hz, 1H), 4.03 (s, 2H), 3.96 (dd, *J* = 5.2, 11.3 Hz, 1H), 3.91 - 3.86 (m, 1H), 3.76 - 3.62 (m, 5H), 3.60 - 3.46 (m, 3H), 3.25 (t, *J* = 5.6 Hz, 2H), 3.17 - 3.08 (m, 1H), 1.52 (s, 3H), 1.46 - 1.39 (m, 9H), 1.35 (s, 3H). Theoretical number of H: 38, found: 35. Exchange H: 3.

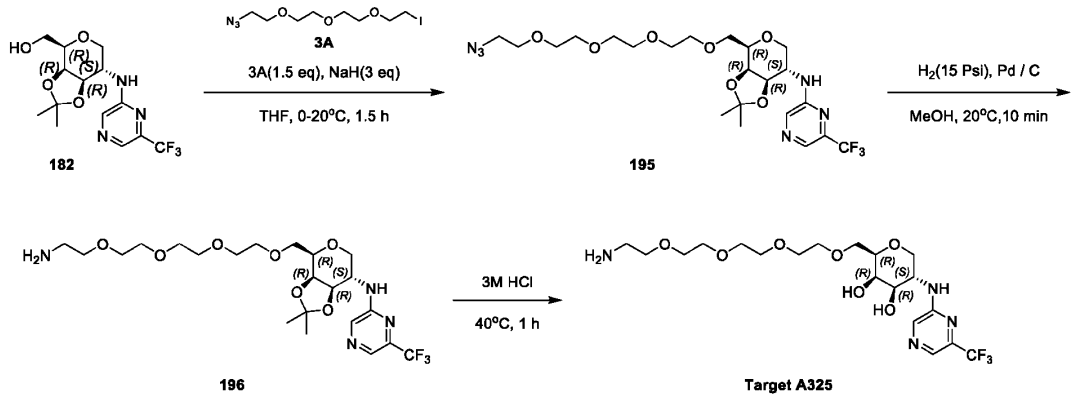
[0376] ***Preparation of Target A326:***



194 Target A326

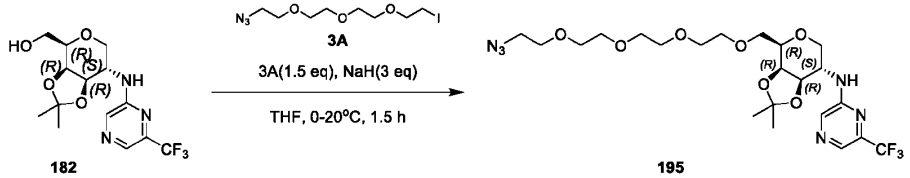
[0377] **Intermediate 194** (300.00 mg, 577.46 µmol, 1.00 *equiv.*) in HCl/dioxane (4 M, 5 mL, 34.63 *equiv.*) was stirred at 25°C for 2 hr. LCMS showed the reaction was completed. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 5%-35% B over 8.0 min) to give **Target A326** (121.6 mg, 268.19 µmol, 39.80% yield) as a white soild. LCMS: RT = 0.897 min, MS cal.: 453.2, found: $[M+H]^+$ = 454.2. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.21 (s, 1H), 8.06 (s, 1H), 7.76 - 7.58 (m, 2H), 4.05 (br dd, *J* = 5.2, 7.3 Hz, 1H), 3.92 - 3.86 (m, 3H), 3.68 (d, *J* = 2.8 Hz, 1H), 3.62 - 3.48 (m, 6H), 3.44 - 3.37 (m, 4H), 3.33 - 3.26 (m, 3H), 3.13 - 3.05 (m, 1H), 2.94 (t, *J* = 10.8 Hz, 1H), 2.69 (t, *J* = 5.6 Hz, 2H).

EXAMPLE 45. Procedure for Preparation of Target A325



182 195 196 Target A325

[0378] ***Preparation of Intermediate 195:***

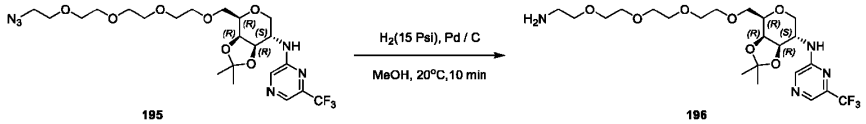


182 195

[0379] To a solution of **Intermediate 182** (300 mg, 858.85 µmol, 1 *equiv.*) in THF (3 mL) was added NaH (103.05 mg, 2.58 mmol, 60% purity, 3 *equiv.*) in portions at 0°C within 10 min. After the

addition, the mixture was stirred at 0°C for 0.5 hr. Then **Intermediate 3A** (424.01 mg, 1.29 mmol, 1.5 *equiv.*) was added in portions to the reaction mixture at 0°C within 10 min. After the addition, the mixture was stirred at 20°C for 1 hr. LCMS showed **Intermediate 182** was consumed completely and one main peak with desired mass was detected. After 1.5 hr, the reaction mixture was added to H_2O (10 mL) at 0°C within 10 min and extracted by EtOAc (20 mL * 2). Then organic phase was washed by H_2O (10 mL * 3), aq. NaCl (20 mL * 1). The organic were dried over Na_2SO_4, and concentrated under reduced pressure at 45°C to obtain **Intermediate 195** (345 mg, 626.67 µmol, 72.97% yield) as colorless oil. LCMS: RT = 1.732 min, MS cal.: 550.2, found: $[M + H]^+$ = 551.2. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.21 - 8.14 (s, 1H), 8.10 (s, 1H), 4.80 - 4.70 (m, 1H), 4.24 - 4.15 (m, 3H), 4.11 - 4.06 (m, 1H), 3.97 - 3.92 (m, 1H), 3.81 - 3.71 (m, 4H), 3.70 - 3.67 (m, 12H), 3.43 - 3.38 (m, 2H), 3.22 - 3.14 (m, 1H), 1.57 (m, 3H), 1.36 (s, 3H). Theoretical number of H: 33, found: 33.

[0380] ***Preparation of Intermediate 196:***



195 196

[0381] To a solution of ***Intermediate 195*** (350 mg, 635.75 µmol, 1.00 *equiv.*) in MeOH (3 mL) was added Pd/C (175.00 mg, 10% purity) in portions at 20°C within 5 min. After the addition, the mixture was stirred at 20°C for 10 min under H_2(15 Psi). LCMS showed ***Intermediate 195*** was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to get ***Intermediate 196*** (300 mg, 571.94 µmol, 89.96% yield) as a white solid. LCMS: RT = 1.252 min, MS cal.: 524.2, found: $[M + H]^+$ = 525.3. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.12 - 8.06 (s, 1H), 8.04 - 7.99 (s, 1H), 4.34 - 4.24 (m, 2H), 4.18 - 4.09 (m, 1H), 4.00 - 3.91 (m, 2H), 3.75 (d, *J* = 6 Hz, 2H), 3.72 - 3.56 (m, 13H), 3.53 (m, 2H), 3.13 (t, *J* = 11.2 Hz, 1H), 2.80 (t, *J* = 5.2 Hz, 1H), 1.50 (s, 3H), 1.33 (s, 3H). Theoretical number of H: 35, found: 32, exchangeable: 3.

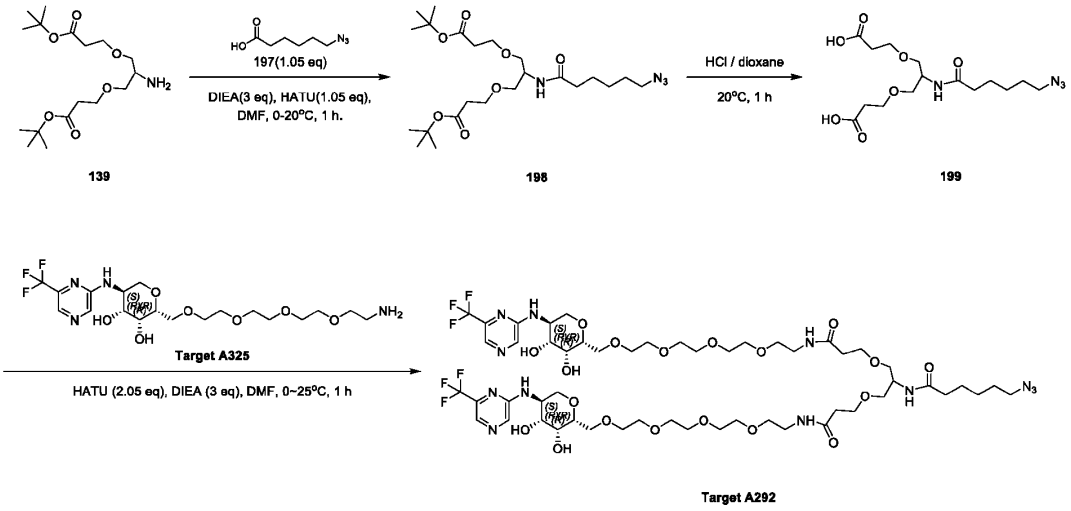
[0382] ***Preparation of Target A325:***

196 Target A325

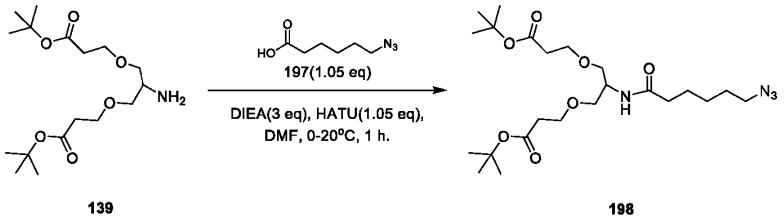
[0383] A mixture of ***Intermediate 196*** (240 mg, 457.55 µmol, 1 *equiv.*) and HCl (3 M, 7.50 mL, 49.17 *equiv.*) was degassed and purged with N_2 for 3 times at 20°C, and then the mixture was stirred at

40°C for 1 h under N_2 atmosphere. LCMS showed ***Intermediate 196*** was consumed completely and one main peak with desired mass was detected. The residue was filtered and purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [H_2O(0.04% HCl)-ACN]; gradient:1%-30% B over 8.0 min)to get ***Target A325*** (78 mg, 161.00 µmol, 35.19% yield) as a yellow solid. LCMS: RT = 0.894 min, MS cal.: 484.2, found: $[M + H]^+$ = 485.2. ^{1}H NMR (400 MHz, DEUTERIUM OXIDE) δ = 8.12 - 8.02 (m, 2H), 4.36 - 4.25 (m, 1H), 4.09 - 4.02 (m, 1H), 3.98 - 3.95 (m, 1H), 3.80 - 3.65 (m, 18H), 3.23 (s, 1H), 3.17 (br t, *J* = 4.8 Hz, 2H). Theoretical number of H: 31, found: 26, exchangeable: 5.

EXAMPLE 46. Procedure for Preparation of Target A292



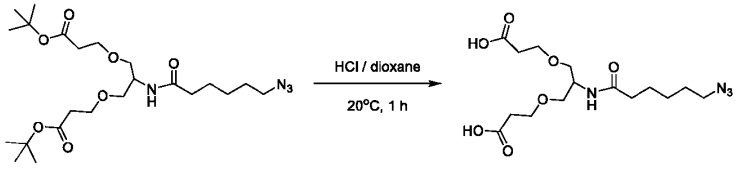
[0384] ***Preparation of Intermediate 198:***



[0385] To a solution of **Intermediate 197** (2.37 g, 15.11 mmol, 1.05 equiv.) in DMF (30 mL) was added DIEA (5.58 g, 43.17 mmol, 7.52 mL, 3.00 equiv.) followed by HATU (5.75 g, 15.11 mmol, 1.05 equiv.) at 0°C. The mixture was stirred at 0°C for 0.5 h, then **Intermediate 139** (5 g, 14.39 mmol, 1.00 equiv.) was added at 0°C. The mixture was stirred at 20°C for 0.5 h. LCMS showed the desired mass was detected.

The reaction mixture was concentrated under reduced pressure to remove DMF. The residue was diluted with water (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether / Ethyl acetate = 10 / 1 to 3 / 1) to obtained **Intermediate 198** (4 g, 8.22 mmol, 57.12% yield) as yellow oil. LCMS: RT = 2.067 min, MS cal.: 486.3, found: $[M + H]^+$ = 487.3. ^1H NMR (400 MHz, METHANOL-d_4) δ = 4.69 - 4.63 (m, 1H), 3.98 - 3.87 (m, 1H), 3.49 (s, 4H), 3.36 - 3.26 (m, 4H), 3.16 - 3.09 (m, 3H), 2.64 (s, 1H), 2.29 (s, 4H), 2.08 - 2.01 (m, 2H), 1.54 - 1.39 (m, 4H), 1.28 (s, 18H). Theoretical number of H: 42, found: 42.

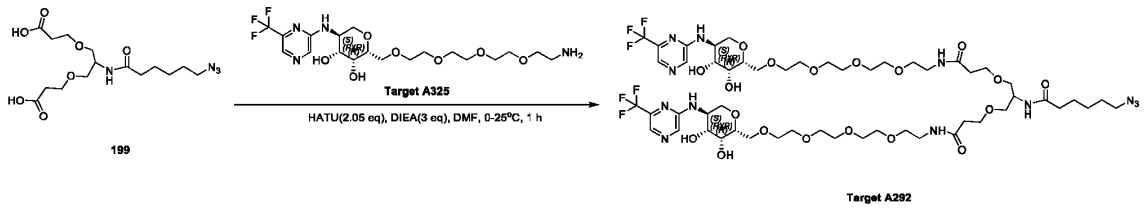
[0386] ***Preparation of Intermediate 199:***



198 199

[0387] A mixture of **Intermediate 198** (1.4 g, 2.88 mmol, 1.00 equiv.) and HCl/dioxane (4 M, 719.28 µL, 1.00 equiv.) was stirred at 20°C for 1 h under N_2 atmosphere. LCMS showed **Intermediate 198** was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure and purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 15 um); mobile phase: [H_2O (0.04%HCl)-ACN]; gradient: 10%-55% B over 20.0 min) to obtained **Intermediate 199** (0.8 g, 2.14 mmol, 74.27% yield) as a white solid. LCMS: RT = 1.032 min, MS cal.: 374.2, found: $[M + H]^+$ = 375.2. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.68 (br d, *J* = 8.4 Hz, 1H), 4.00 - 3.91 (m, 1H), 3.57 (t, *J* = 6.4 Hz, 4H), 3.37 - 3.31 (m, 5H), 3.28 (br s, 1H), 2.43 (t, *J* = 6.4 Hz, 4H), 2.07 (br t, *J* = 7.2 Hz, 2H), 1.56 - 1.45 (m, 4H), 1.27 (br s, 2H). Theoretical number of H: 26, found: 24.

[0388] ***Preparation of Target A292:***

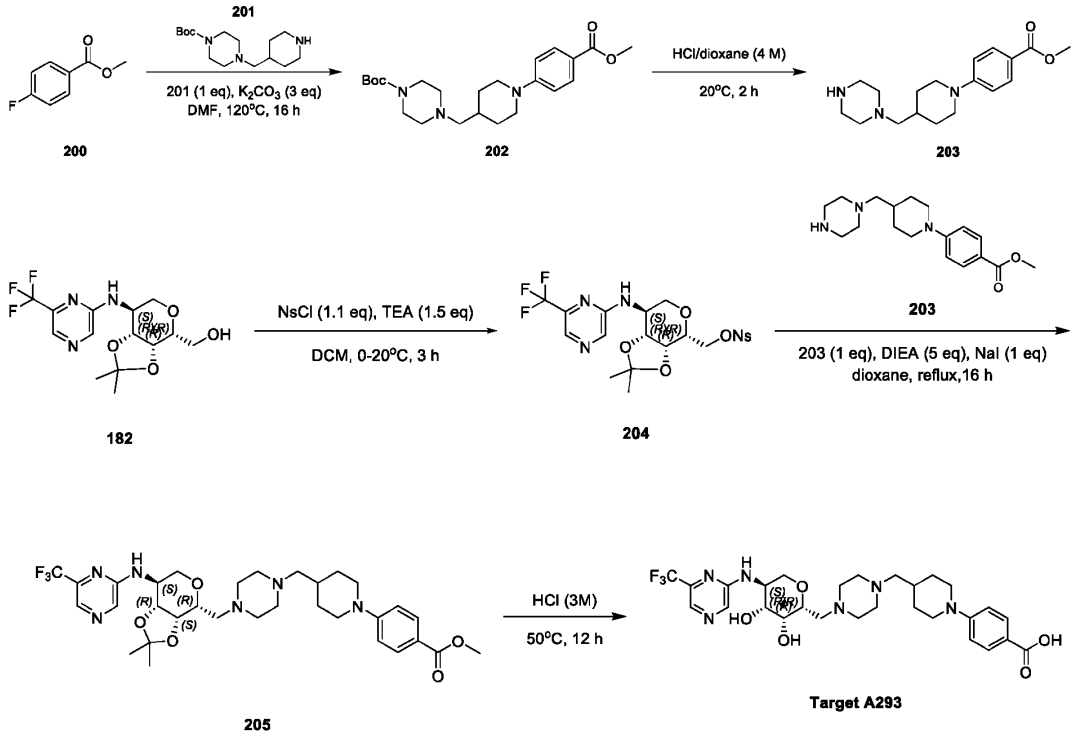


199 Target A292

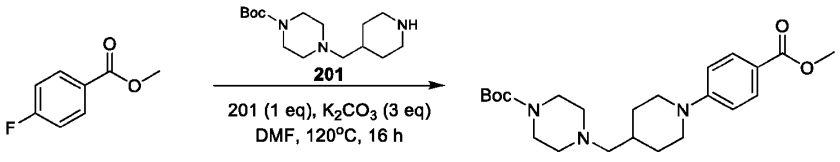
[0389] To a solution of **Intermediate 199** (80 mg, 213.68 µmol, 1.00 equiv.) in DMF (1 mL) was added HATU (166.56 mg, 438.05 µmol, 2.05 equiv.) and DIEA (82.85 mg, 641.05 µmol, 111.66 µL, 3.00

equiv.) at 0°C and the reaction solution was stirred for 0.5 h at 0°C. Then **Target A325** (217.40 mg, 448.73 µmol, 2.10 equiv.) in DMF (1 mL) was added and the reaction mixture was stirred for 0.5 h at 25°C. LCMS showed the reaction was completed. The reaction solution was concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 25%-55% B over 8.0 min) to give **Target A292** (52.17 mg, 39.91 µmol, 18.68% yield) as yellow solid. LCMS: RT = 1.512 min, MS cal.: 1306.6, found: $[M/2 + H]^+$ = 654.6. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.12 (s, 2H), 8.00 (s, 2H), 4.34 (dt, *J* = 5.2, 10.6 Hz, 2H), 4.12 (dd, *J* = 5.2, 10.8 Hz, 3H), 3.93 (d, *J* = 2.8 Hz, 2H), 3.73 - 3.58 (m, 36H), 3.57 - 3.53 (m, 4H), 3.53 - 3.43 (m, 5H), 3.40 - 3.36 (m, 4H), 3.28 (s, 1H), 3.12 (t, J = 10.8 Hz, 2H), 2.45 (t, J = 6.8 Hz, 4H), 2.23 (t, J = 8.4 Hz, 2H), 1.68 - 1.55 (m, 4H), 1.45 - 1.36 (m, 2H). Theoretical number of H: 84, found: 75. exchangeable: 9.

EXAMPLE 47. Procedure for Preparation of *Target A293*



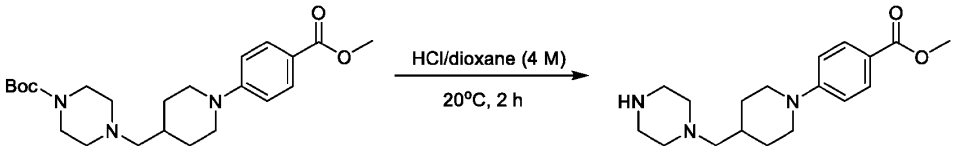
[0390] ***Preparation of Intermediate 202:***



200 202

[0391] A mixture of **Intermediate 200** (2.12 g, 13.76 mmol, 1.78 mL, 1.50 equiv.), **Intermediate 201** (2.60 g, 9.17 mmol, 1.00 equiv.), K_2CO_3 (3.80 g, 27.52 mmol, 3.00 equiv.) in DMF (20 mL) was degassed and purged with Ar for 3 times, and then the mixture was stirred at 120°C for 16 h under Ar atmosphere. LCMS showed **Intermediate 200** was consumed and the reaction was complete. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. The crude product was purified column chromatography (SiO_2, petroleum ether: ethyl acetate = 5: 1 to 0: 1) to afford **Intermediate 202** (6.00 g, 14.37 mmol, 52.21% yield) as a white solid. LCMS: RT = 1.149 min, MS cal.: 417.3, found: $[M + H]^+$ =418.3.

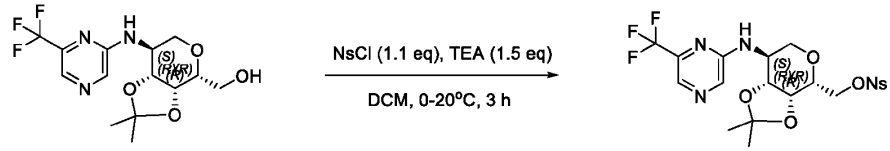
[0392] ***Preparation of Intermediate 203:***



202 203

[0393] To a solution of **Intermediate 202** (3.25 g, 7.78 mmol, 1.00 equiv.) in HCl/dioxane (30 mL). The mixture was stirred at 20°C for 2 h. LCMS showed **Intermediate 202** was consumed and the reaction was completed. The reaction was filtered and the filtrate was concentrated under reduced pressure to afford **Intermediate 203** (4.70 g, 14.81 mmol, 95.11% yield) as yellow solid, which was used to next step without further purification. LCMS: RT = 0.683 min, MS cal.: 317.2, found: $[M + H]^+$ =318.2. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.75 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 3.89 (br d, *J* = 12.8 Hz, 2H), 3.76 (s, 3H), 3.32 (s, 3H), 2.85 - 2.76 (m, 2H), 2.68 (t, *J* = 4.8 Hz, 4H), 2.25 (brs, 3H), 2.09 (d, *J* = 6.8 Hz, 1H), 1.76 (brd, *J* = 10.4 Hz, 2H), 1.18 - 1.05 (m, 2H). Theoretical number of H: 27, found: 27.

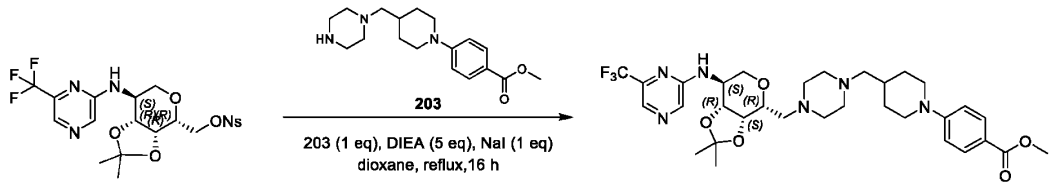
[0394] ***Preparation of Intermediate 204:***



182 204

[0395] To a solution of **Intermediate 182** (1.50 g, 2.15 mmol, 1.00 equiv.) and TEA (325.90 mg, 3.22 mmol, 448.28 µL, 1.50 equiv.) in DCM (5 mL) was added 4-nitrobenzenesulfonyl chloride (523.43 mg, 2.36 mmol, 1.10 equiv.) in DCM (5 mL) at 0°C. Then the mixture was stirred at 20°C for 3 h. LCMS showed reactant was consumed and the reaction was completed. The reaction mixture was poured into H_2O (10 mL) and extracted with DCM (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. The crude product was purified column chromatography (SiO_2, Dichloromethane: Methanol = 100: 1 to 80: 1) to afford **Intermediate 204** (1.90 g, 3.55 mmol, 82.78% yield) as yellow solid. LCMS: RT = 1.861 min, MS cal.: 534.1, found: $[M + H]^+$ =535.1. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.45 - 8.41 (m, 2H), 8.19 (s, 1H), 8.18 - 8.14 (m, 2H), 8.09 (s, 1H), 4.72 (brd, *J* = 6.0 Hz, 1H), 4.41 - 4.38 (m, 1H), 4.37 - 4.35 (m, 1H), 4.21 - 4.18 (m, 1H), 4.15 - 4.13 (m, 1H), 4.10 (s, 1H), 4.06 (d, *J* = 4.4 Hz, 1H), 4.03 (ddd, *J* = 2.4, 4.2, 7.5 Hz, 1H), 3.18 - 3.11 (m, 1H), 1.51 (s, 3H), 1.32 (s, 3H). Theoretical number of H: 21, found: 21.

[0396] ***Preparation of Intermediate 205:***

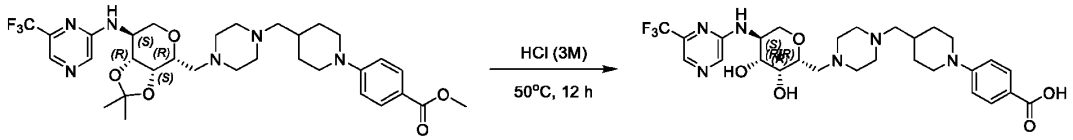


204 205

[0397] To a solution of **Intermediate 204** (600.00 mg, 1.12 mmol, 1.00 equiv.) and **Intermediate 203** (391.98 mg, 1.23 mmol, 1.10 equiv.) in dioxane (4 mL) was added DIEA (725.46 mg, 5.61 mmol, 977.70 µL, 5.00 equiv.) and NaI (168.27 mg, 1.12 mmol, 1.00 equiv.). The mixture was refluxed for 16 h. LCMS showed **Intermediate 204** was consumed and the reaction was completed. The reaction was poured into H_2O (5 mL) and extracted with DCM (5 mL x 2). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (SiO_2, Dichloromethane: Ethyl acetate = 20: 1

to 10: 1) to afford **Intermediate 205** (1.2 g, 1.85 mmol, 82.39% yield) as yellow solid. LCMS: RT = 1.311 min, MS cal.: 648.3, found: $[M + H]^+$ = 649.4. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.17 (s, 1H), 8.12 (s, 1H), 7.90 (d, *J* = 9.2 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 2H), 4.24 - 4.16 (m, 3H), 4.11 (br d, *J* = 5.6 Hz, 1H), 3.91 - 3.85 (m, 5H), 3.25 - 3.06 (m, 2H), 3.04 - 2.90 (m, 1H), 2.84 (br t, *J* = 11.4 Hz, 3H), 2.78 - 2.49 (m, 7H), 2.26 (br d, *J* = 2.4 Hz, 2H), 1.87 (br d, *J* = 12.8 Hz, 2H), 1.78 - 1.68 (m, 1H), 1.57 (s, 3H), 1.49 - 1.44 (m, 1H), 1.37 (s, 3H), 1.33 - 1.23 (m, 2H). Theoretical number of H: 43, found: 42, exchangeable H: 1.

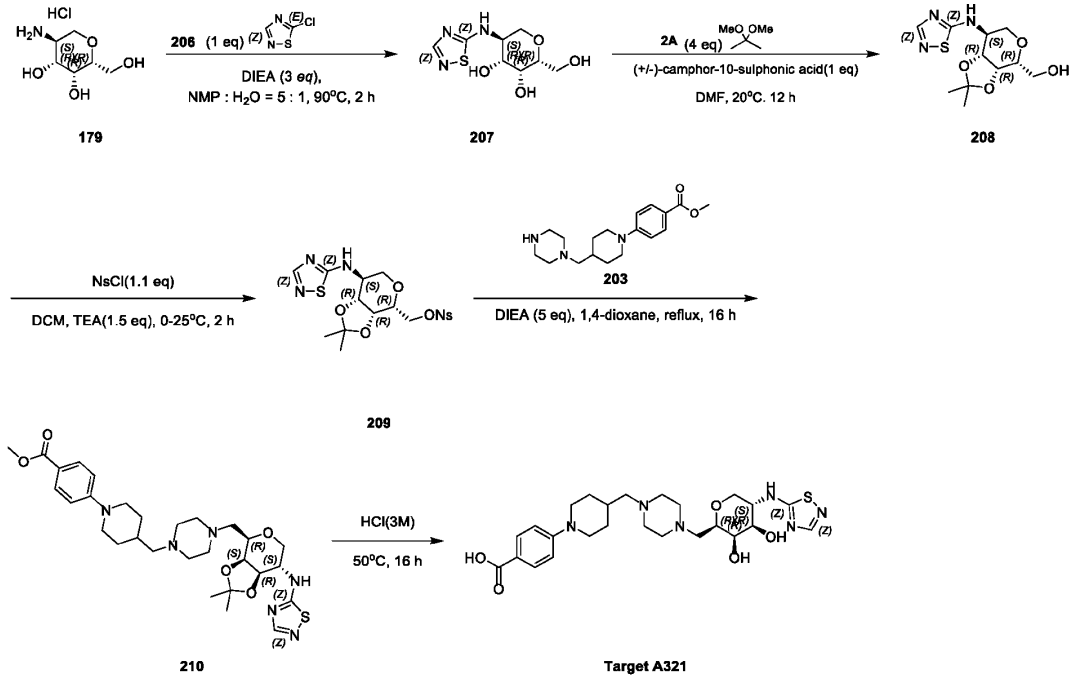
[0398] ***Preparation of Target A293:***



205 **Target A293**

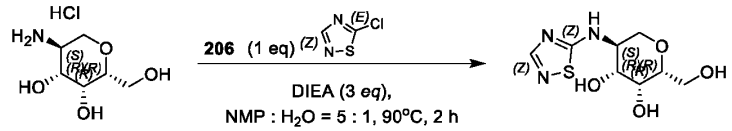
[0399] A mixture of **Intermediate 205** (333.00 mg, 513.32 µmol, 1.00 equiv.) in HCl (3 mL, 3M) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 50°C for 12 h under N_2 atmosphere. LCMS showed **Intermediate 205** was consumed and the reaction was complete. The reaction was filtered and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (column: Phenomenex Luna C18 75 * 30mm * 3um; mobile phase: [water (0.04% HCl) - ACN]; gradient: 20% - 50% B over 8.0 min) to afford **Target A293** (501.71 mg, 843.74 µmol, 54.79% yield) as yellow solid. LCMS: RT = 11.854 min, MS cal.: 594.3, found: $[M + H]^+$ =595.3. ^1H NMR (400 MHz, D_2O) δ = 8.10 (br d, *J* = 10.4 Hz, 2H), 8.01 (br d, *J* = 8.8 Hz, 2H), 7.34 (br d, *J* = 8.4 Hz, 2H), 4.33 (dt, *J* = 5.6, 10.2 Hz, 1H), 4.11 (br dd, *J* = 4.8, 11.3 Hz, 1H), 3.96 (br s, 2H), 3.89 - 3.77 (m, 4H), 3.47 (br d, *J* = 10.4 Hz, 7H), 3.30 - 3.18 (m, 5H), 3.07 (br d, *J* = 6.4 Hz, 2H), 2.26 - 2.18 (m, 1H), 2.01 (br d, *J* = 13.6 Hz, 2H), 1.61 - 1.51 (m, 2H). Theoretical number of H: 37, found: 33, exchangeable H: 4.

EXAMPLE 48. Procedure for Preparation of *Target A321*



179 207 208 209 210 Target A321

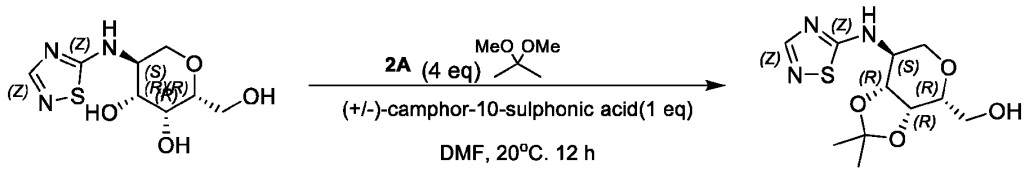
[0400] **Preparation of Intermediate *207***



179 207

[0401] To a solution of **Intermediate 179** (1.50 g, 9.19 mmol, 1.00 *equiv.*) in NMP (15 mL) and H_2O (3 mL) was added DIEA (3.56 g, 27.58 mmol, 3.00 *equiv.*) and **Intermediate *206*** (1.33 g, 11.03 mmol, 1.00 *equiv.*). The mixture was stirred at 90°C for 2 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 (250*70mm, 15 um); mobile phase: [H_2O (0.04%HCl)-ACN]; gradient: 1%-10% B over 20.0 min) to give **Intermediate *207*** (1 g, 4.04 mmol, 43.99% yield) as yellow oil. LCMS: RT = 0.355 min, MS cal.: 247.3, found: $[M+H]^+$ = 248.1. ^1H NMR (400 MHz, DEUTERIUM OXIDE) δ = 7.99 (s, 1H), 4.14 - 4.08 (m, 1H), 3.97 (s, 1H), 3.79 (br s, 2H), 3.73 - 3.67 (m, 2H), 3.61 - 3.56 (m, 1H), 3.35 - 3.28 (m, 1H). Theoretical number of H: 13, found: 9, exchangeable H: 4.

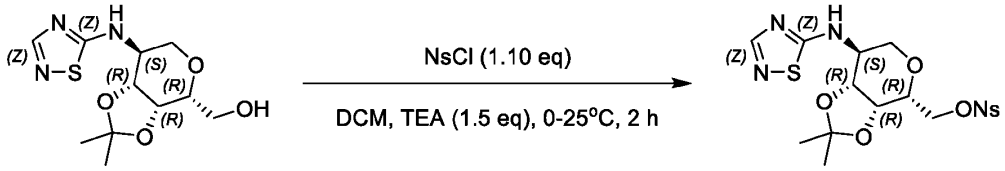
[0402] ***Preparation of Intermediate 208:***



207 **208**

[0403] To a solution of **Intermediate 207** (1.00 g, 4.04 mmol, 1.00 *equiv.*) in DMF (10 mL) was added [(1S, 4R)-7, 7-dimethyl-2-oxo-norbornan-1-yl] methanesulfonic acid; hydrate (1.01 g, 4.04 mmol, 1.00 *equiv.*) and **2A** (1.68 g, 16.18 mmol, 1.98 mL, 4.00 *equiv.*). The mixture was stirred at 20°C for 12 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 1%-15% B over 8.0 min) to give **Intermediate 208** (550 mg, 1.91 mmol, 47.33% yield) as a white solid. LCMS: RT = 1.392 min, MS cal.: 287.3, found: $[M+H]^+$ = 288.1. 1H NMR (400 MHz, DMSO-d_6) δ = 8.68 - 8.46 (m, 1H), 7.97 - 7.90 (m, 1H), 4.80 (t, *J* = 5.6 Hz, 1H), 4.20 (dd, *J* = 2.0, 5.1 Hz, 1H), 4.11 (dd, *J* = 5.2, 8.4 Hz, 1H), 3.89 (dd, *J* = 4.8, 11.1 Hz, 1H), 3.69 (dt, *J* = 2.0, 6.1 Hz, 2H), 3.59 - 3.53 (m, 2H), 3.07 (t, *J* = 11.2 Hz, 1H), 1.42 (s, 3H), 1.27 (s, 3H). Theoretical number of H: 17, found: 17.

[0404] ***Preparation of Intermediate 209:***

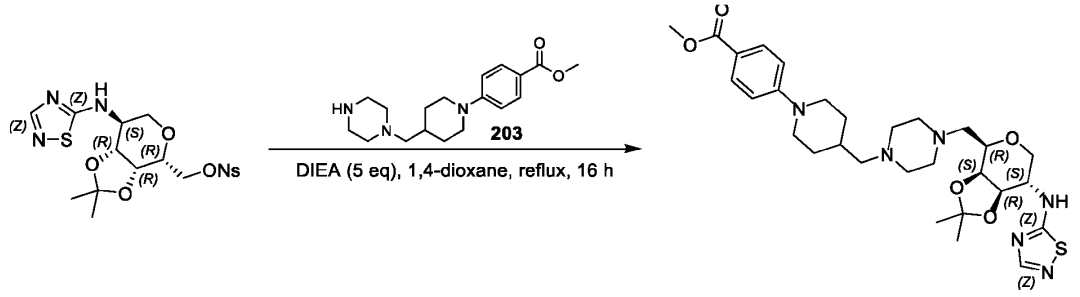


208 **209**

[0405] To a solution of **Intermediate 208** (0.98 g, 3.41 mmol, 1.00 *equiv.*) in DCM (10 mL) was added TEA (517.69 mg, 5.12 mmol, 1.50 *equiv.*), 4-nitrobenzenesulfonyl chloride (831.45 mg, 3.75 mmol, 1.10 *equiv.*) at 0°C. The mixture was stirred at 25°C for 2 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O (5 mL) and extracted with DCM (15 mL*3). The combined organic layers were washed with brine (5 mL * 2), dried over Na_2SO_4, filtered and concentrated under pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/0 to 40/60) to give **Intermediate 209** (1.15 g, 2.43 mmol, 71.36% yield) as a yellow solid. LCMS: RT = 1.623 min, MS cal.: 472.5,

found: $[M+H]^+$ = 473.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.57 (br d, *J* = 7.6 Hz, 1H), 8.51 - 8.44 (m, 2H), 8.23 - 8.19 (m, 2H), 7.91 (s, 1H), 4.42 (dd, *J* = 2.8, 10.5 Hz, 1H), 4.22 - 4.16 (m, 2H), 4.16 - 4.11 (m, 1H), 4.10 - 3.98 (m, 1H), 3.83 (dd, *J* = 4.8, 11.3 Hz, 1H), 3.70 - 3.56 (m, 1H), 3.07 (t, *J* = 11.2 Hz, 1H), 1.43 - 1.36 (m, 3H), 1.22 (s, 3H). Theoretical number of H: 20, found: 20.

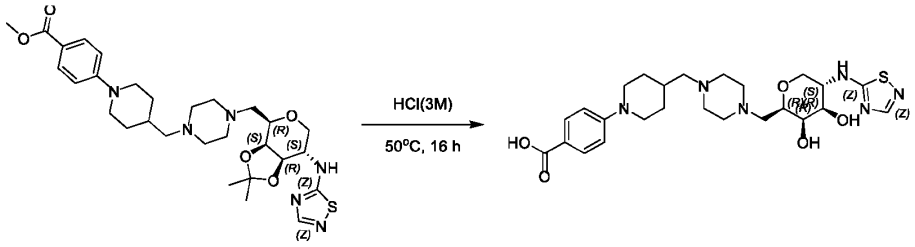
[0406] ***Preparation of Intermediate 210:***



209 **210**

[0407] To a solution of ***Intermediate 203*** (295.60 mg, 931.23 µmol, 1.10 *equiv.*) in 1, 4-dioxane (4 mL) was added DIEA (547.06 mg, 4.23 mmol, 737.27 µL, 5.00 *equiv.*). Then ***Intermediate 209*** (400 mg, 846.58 µmol, 1.00 *equiv.*) was added and the mixture was refluxed for 16 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O (15 mL) and extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (15 mL * 2), dried over Na_2SO_4, filtered and concentrated under pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 100/1 to 20/1) to give **Intermediate 210** (350 mg, 596.51 µmol, 70.46% yield) as a yellow solid. LCMS: RT = 1.820 min, MS cal.: 586.8, found: $[M+H]^+$ = 587.3. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.34 - 8.27 (m, 1H), 8.07 - 8.00 (m, 1H), 7.86 (s, 1H), 7.84 (d, *J* = 9.2 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 4.21 (dd, *J* = 2.0, 5.1 Hz, 1H), 4.17 - 4.12 (m, 1H), 4.06 - 4.00 (m, 1H), 3.99 - 3.90 (m, 3H), 3.83 (s, 3H), 3.77 - 3.68 (m, 1H), 3.26 - 3.14 (m, 2H), 2.90 - 2.81 (m, 3H), 2.73 - 2.54 (m, 6H), 2.35 - 2.23 (m, 2H), 1.91 - 1.81 (m, 3H), 1.52 (s, 3H), 1.34 (s, 3H), 1.31 - 1.24 (m, 2H). Theoretical number of H: 42, found: 41, exchangeable H: 1.

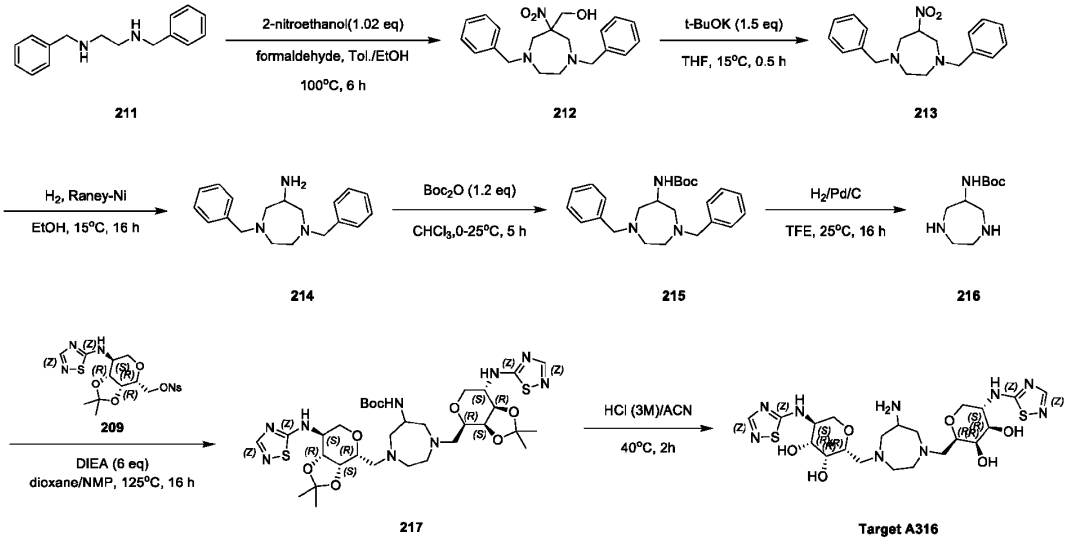
[0408] ***Preparation of Intermediate Target A321:***



210 Target A321

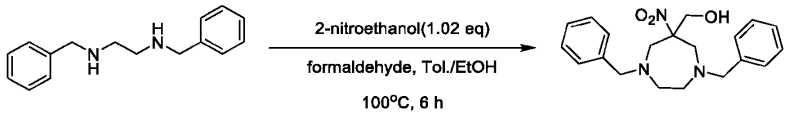
[0409] A solution of ***Intermediate 210*** (250 mg, 426.08 μmol, 1.00 *equiv.*) in HCl (3 M, 2.50 mL, 17.60 *equiv.*) was stirred at 50°C for 16 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.04% HCl)-ACN]; gradient: 1%-25% B over 8.0 min) to give ***Target A321*** (170 mg, 310.97 μmol, 72.98% yield) as a white solid. LCMS: RT = 0.97 min, MS cal.: 532.7, found: $[M+H]^+$ = 533.3. ^{1}H NMR (400 MHz, DEUTERIUM OXIDE) δ = 8.11 - 8.02 (m, 2H), 7.91 (s, 1H), 7.45 (d, *J* = 9.2 Hz, 2H), 4.16 (dd, *J* = 4.8, 11.4 Hz, 1H), 4.03 - 3.94 (m, 2H), 3.93 - 3.49 (m, 13H), 3.43 - 3.27 (m, 4H), 3.18 (d, *J* = 7.2 Hz, 2H), 2.37 - 2.23 (m, 1H), 2.08 (br d, *J* = 13.2 Hz, 2H), 1.74 - 1.57 (m, 2H). Theoretical number of H: 36, found: 32, exchangeable H: 4.

EXAMPLE 49. Procedure for Preparation of *Target A316*



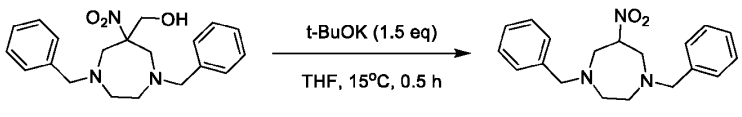
211 212 213 214 215 216 209 217 Target A316

[0410] **Preparation of *Intermediate 212***



[0411] To a solution of **Intermediate 211** (5.00 g, 20.80 mmol, 1.00 *equiv.*) and 2-nitroethanol (1.94 g, 21.29 mmol, 1.02 *equiv.*) in Tol. (200 mL) and EtOH (200 mL) was added paraformaldehyde (2.25 g). The mixture was stirred at 100°C for 6h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (100 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over Na_2SO_4, filtered and concentrated under pressure to give a residue. Two batches of residue were combined and purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 5/1) to give **Intermediate 212** (9.4 g, 63.56% yield) as yellow oil. LCMS: RT = 0.368 min, MS cal.: 355.2, found: $[M+H]^+$ = 356.3. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.36 - 7.28 (m, 10H), 3.74 - 3.61 (m, 6H), 3.51 (d, *J* = 14.4 Hz, 2H), 3.03 (d, *J* = 14.0 Hz, 2H), 2.71 - 2.60 (m, 4H). Theoretical number of H: 25, found: 24, exchangeable H: 1.

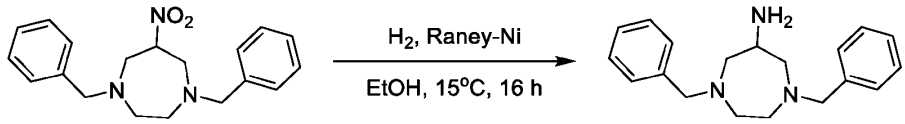
[0412] ***Preparation of Intermediate 213:***



[0413] To a solution of **Intermediate 212** (8.40 g, 23.63 mmol, 1.00 *equiv.*) in THF (84 mL) was added t-BuOK (3.98 g, 35.45 mmol, 1.50 *equiv.*). The mixture was stirred at 15°C for 0.5 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was adjusted to pH = 5 by Hydroxylamine Hydrochloride, then the reaction mixture diluted with H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine 10 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, then the reaction mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 85/15) to give **Intermediate 213** (5.76 g, 74.90% yield) as yellow oil. LCMS: RT = 1.184 min, MS cal.: 325.4, found: $[M+H]^+$ = 326.2. ^1H NMR (400 MHz, CHLOROFORM-d) δ

= 7.35 - 7.30 (m, 10H), 4.61 - 4.55 (m, 1H), 3.75 (d, *J* = 11.2 Hz, 4H), 3.46 (dd, *J* = 6.4, 14.0 Hz, 2H), 3.30 - 3.25 (m, 2H), 2.71 - 2.64 (m, 4H). Theoretical number of H: 23, found: 23.

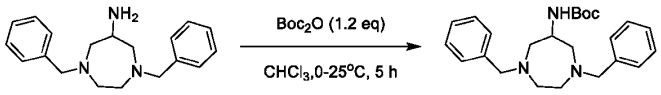
[0414] ***Preparation of Intermediate 214:***



213 **214**

[0415] A mixture of ***Intermediate 213*** (3.70 g, 11.37 mmol, 1.00 *equiv.*), Raney-Ni (1.00 *equiv.*) in EtOH (5 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 15°C for 16 h under H_2 atmosphere (15 Psi). LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The suspension was filtered through a pad of Celite and the filter cake was washed with EtOH, then the reaction mixture was concentrated in vacuum to give ***Intermediate 214*** (3 g, crude) as yellow oil. The crude product used for next step without purification. LCMS: RT = 0.303 min, MS cal.: 295.4, found: $[M+H]^+$ = 296.3. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.37 - 7.23 (m, 10H), 3.74 - 3.62 (m, 4H), 3.07 - 2.86 (m, 3H), 2.71 - 2.61 (m, 4H), 2.50 (dd, *J* = 6.0, 12.8 Hz, 2H). Theoretical number of H: 25, found: 23, exchangeable H: 2.

[0416] ***Preparation of Intermediate 215:***

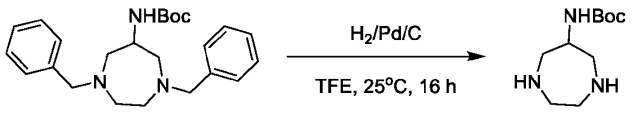


214 **215**

[0417] To a solution of ***Intermediate 214*** (2.74 g, 9.27 mmol, 1.00 *equiv.*) in $CHCl_3$ (27 mL) was added tert-butoxycarbonyl tert-butyl carbonate (2.43 g, 11.13 mmol, 1.20 *equiv.*) at 0°C for 10 min, then the mixture was stirred at 25°C for 5 h. TLC (Petroleum ether: Ethyl acetate = 3:1, R_f = 0.54) indicated reactant was consumed, and one major new spot with larger polarity was detected. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (20 mL * 2), dried over Na_2SO_4, filtered and concentrated under pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/0 to 75/15) to give ***Intermediate 215*** (2.88 g, 78.50% yield) as yellow oil. ^{1}H NMR (400 MHz,

CHLOROFORM-d) δ = 7.27 (s, 10H), 5.42 - 5.24 (m, 1H), 3.83 - 3.50 (m, 5H), 2.99 - 2.84 (m, 2H), 2.77 - 2.60 (m, 4H), 2.59 - 2.49 (m, 2H), 1.52 - 1.30 (m, 9H). Theoretical number of H: 33, found: 33.

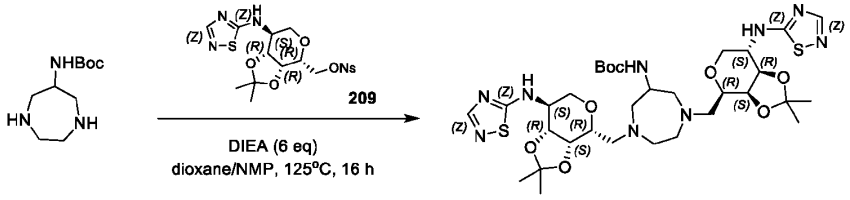
[0418] ***Preparation of Intermediate 216:***



215 **216**

[0419] A mixture of **Intermediate 215** (1.20 g, 3.03 mmol, 1.00 *equiv.*), Pd/C (10% purity) in 2,2,2-trifluoroethanol (12 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25°C for 16 h under H_2 atmosphere. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The suspension was filtered through a pad of Celite and the filter cake was washed with MeOH, then the reaction mixture was concentrated in vacuum to give **Intermediate 216** (1.38 g, crude) as a white solid, the crude product used for next step directly without purification. LCMS: RT = 0.516 min, MS cal.: 215.3, found: $[M+H]^+$ = 216.4. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.53 - 3.44 (m, 1H), 3.41 - 3.27 (m, 1H), 2.92 - 2.83 (m, 2H), 2.68 - 2.62 (m, 3H), 2.61 - 2.52 (m, 3H), 2.15 - 1.95 (m, 2H), 1.43 - 1.33 (m, 9H). Theoretical number of H: 21, found: 21.

[0420] ***Preparation of Intermediate 217:***

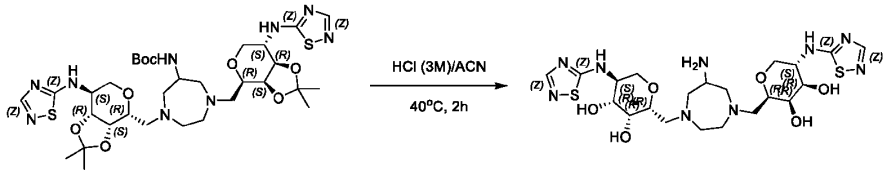


216 **217**

[0421] To a solution of **Intermediate 216** (88.00 mg, 347.44 μmol, 1.00 *equiv.*) in NMP (0.5 mL) and dioxane (1 mL) was added DIEA (269.42 mg, 2.08 mmol, 6.00 *equiv.*), then **Intermediate 209** (328.32 mg, 694.87 μmol, 2.00 *equiv.*) was added and the mixture was stirred at 125°C for 16 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated to give residue, which was then purified by column chromatography (SiO_2, DCM/MeOH = 100/0 to 85/15) to give crude product, and then further purified by pre-HPLC to give **Intermediate 217** (200 mg, 76.35% yield) as a brown solid. LCMS: RT = 0.383 min, MS cal.: 753.3, found:

$[M+H]^+$ = 754.3. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.86 (d, *J* = 1.2 Hz, 2H), 4.26 (dd, *J* = 2.4, 4.8 Hz, 2H), 4.19 - 4.01 (m, 4H), 3.85 (br dd, *J* = 5.6, 11.4 Hz, 4H), 3.63 (br s, 1H), 3.24 - 3.11 (m, 2H), 3.02 - 2.87 (m, 7H), 2.87 - 2.64 (m, 5H), 1.53 (s, 6H), 1.42 (s, 9H), 1.36 (s, 6H). Theoretical number of H: 51, found: 48, exchangeable H: 3.

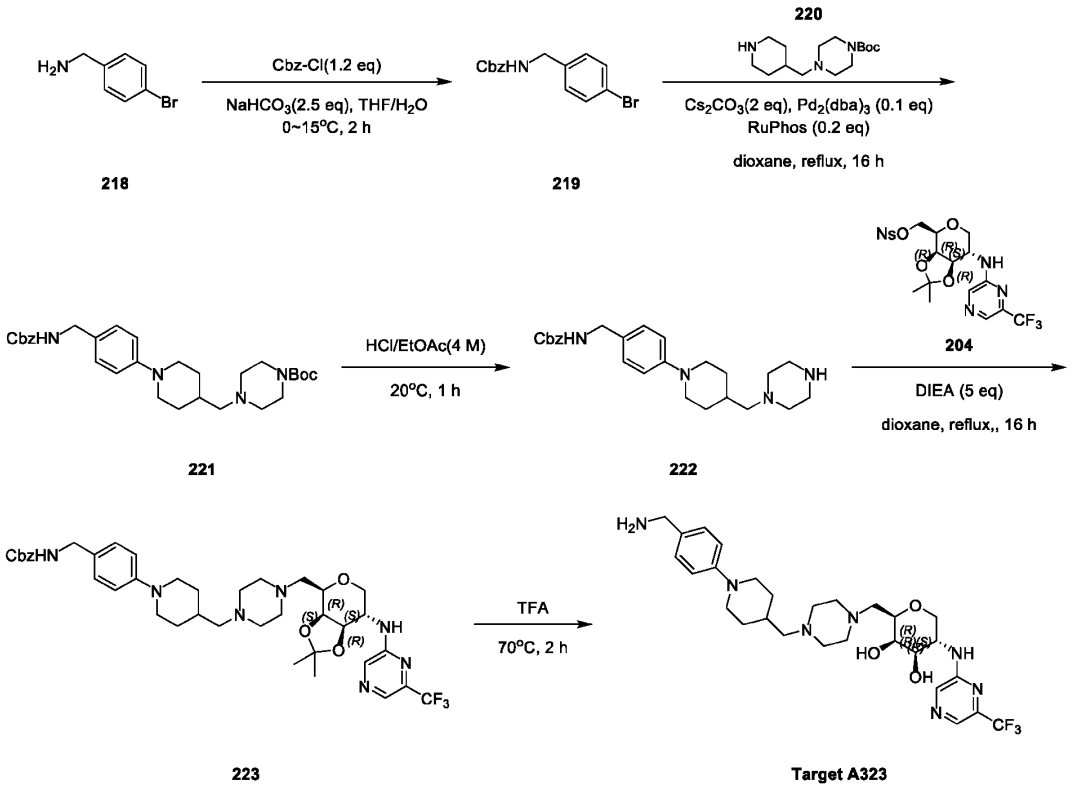
[0422] ***Preparation of Target A316***



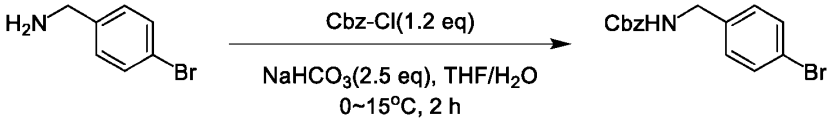
217 **Target A316**

[0423] To a solution of **Intermediate 217** (180 mg, 238.75 µmol, 1.00 *equiv.*) in ACN (0.2 mL) was added HCl (3 M, 0.5 mL). The mixture was stirred at 40°C for 2 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was purified by pre-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.04% HCl)-ACN]; gradient: 1%-20% B over 8.0 min) to give **Target A316** (110.8 mg, 76.06% yield, HCl) as a white solid. LCMS: RT = 0.694 min, MS cal.: 573.2, found: $[M+H]^+$ = 574.2. ^{1}H NMR (400 MHz, DEUTERIUM OXIDE) δ = 7.87 (d, *J* = 6.8 Hz, 2H), 4.20 - 4.08 (m, 2H), 3.97 - 3.72 (m, 9H), 3.56 (dd, *J* = 3.2, 14.4 Hz, 2H), 3.48 - 3.13 (m, 12H). Theoretical number of H: 35, found: 27. exchangeable H: 8.

EXAMPLE 50. Procedure for Preparation of Target A323



[0424] ***Preparation of Intermediate 219:***

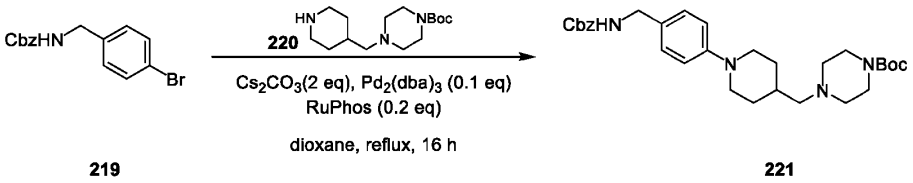


218 **219**

[0425] To a solution of **Intermediate 218** (10.00 g, 53.75 mmol, 1.00 *equiv.*) and $NaHCO_3$ (11.29 g, 134.37 mmol, 2.50 *equiv.*) in THF (70 mL) and H_2O (70 mL) was slowly added benzyl carbonochloridate (11.00 g, 64.50 mmol, 1.20 *equiv.*) at 0°C. The mixture was stirred at 15°C for 2 h. TLC (Petroleum ether: Ethyl acetate = 3: 1, R_f = 0.51) indicated reactant was consumed completely and one new spot formed. The reaction was diluted with H_2O (50 mL), the aqueous phase was extracted with EtOAc (30 mL * 3). The combined organic phase was washed with brine (40 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 30/1 ~ 5/1) to afford **Intermediate 219** (15 g, 87.16% yield) as a white solid. ^1H NMR (400 MHz,

CHLOROFORM-d) δ = 7.69 - 7.29 (m, 7H), 7.16 (br d, *J* = 7.6 Hz, 2H), 5.14 (s, 3H), 4.33 (br d, *J* = 5.6 Hz, 2H). Theoretical number of H: 14, found: 14.

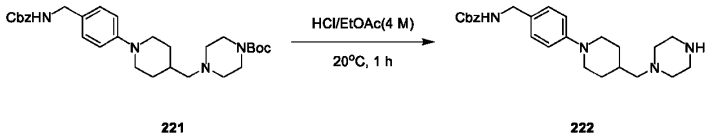
[0426] ***Preparation of Intermediate 221:***



219 **221**

[0427] To a solution of **Intermediate 219** (5.00 g, 15.62 mmol, 1.00 *equiv.*), **Intermediate 220** (4.43 g, 15.62 mmol, 1.00 *equiv.*), Cs_2CO_3 (10.18 g, 31.23 mmol, 2.00 *equiv.*), RuPhos (1.46 g, 3.12 mmol, 0.2 *equiv.*) in dioxane (250 mL) was added $Pd_2(dba)_3$ (1.43 g, 1.56 mmol, 0.10 *equiv.*). The mixture was stirred at 110°C for 16 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was cooled to 15°C, filtered and the filterate was diluted with water (100 mL) and extracted with ethyl acetate (50 mL * 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 10/1, 0/1) to afford **Intermediate 221** (3.4 g, 41.66% yield) as a brown solid. LCMS: RT = 0.582 min, MS cal.: 522.3, found: $[M+H]^+$ = 523.4. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.40 - 7.29 (m, 5H), 7.18 (br d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.13 (s, 2H), 4.97 (br s, 1H), 4.30 (br d, *J* = 5.6 Hz, 2H), 3.67 (br d, *J* = 12.4 Hz, 2H), 3.50 - 3.35 (m, 4H), 2.75 - 2.61 (m, 2H), 2.36 (br s, 4H), 2.22 (d, *J* = 7.2 Hz, 2H), 1.86 (br d, *J* = 12.4 Hz, 2H), 1.72 - 1.62 (m, 1H), 1.47 (s, 9H), 1.33 (dq, *J* = 3.2, 12.4 Hz, 2H). Theoretical number of H: 42, found: 42.

[0428] ***Preparation of Intermediate 222:***

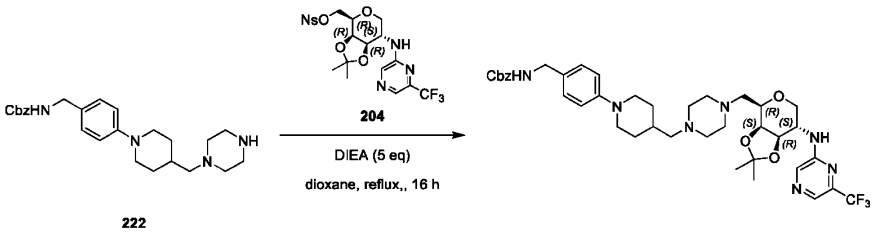


221 **222**

[0429] A solution of **Intermediate 221** (2.30 g, 4.40 mmol, 1.00 *equiv.*) in HCl/EtOAc (4 M, 50.00 mL) was stirred at 20°C for 1 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The solvent was removed under reduced pressure to give residue. The crude product was triturated with MTBE (20 mL) at 15°C for 10 min and filtered. The filter cake was diluted with H_2O (10 mL), then adjusted to pH = 8 ~ 9 with sat. Na_2CO_3, then extracted with ethyl acetate (10 mL * 6).

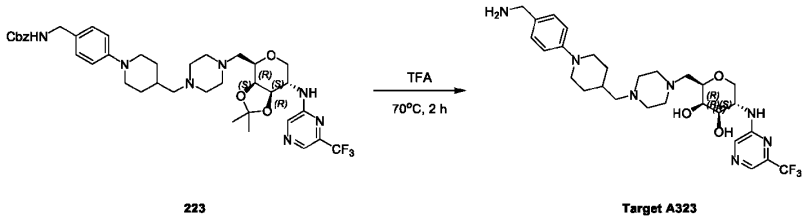
The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give **Intermediate 222** (1.5 g, 74.26% yield, HCl) as a brown solid. LCMS: RT = 0.312 min, MS cal.: 422.3, found: $[M+H]^+$ = 423.4. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.41 - 7.25 (m, 5H), 7.16 (br d, *J* = 8.4 Hz, 2H), 6.94 (br d, *J* = 8.4 Hz, 2H), 5.09 (s, 2H), 4.20 (s, 2H), 3.63 (br d, *J* = 12.4 Hz, 2H), 2.86 (t, *J* = 4.8 Hz, 3H), 2.72 - 2.59 (m, 2H), 2.44 (br s, 4H), 2.23 (d, *J* = 7.2 Hz, 2H), 1.87 (br d, *J* = 12.4 Hz, 2H), 1.77 - 1.60 (m, 2H), 1.33 (dq, *J* = 3.6, 12.2 Hz, 2H). Theoretical number of H: 34, found: 32. exchangeable H: 2.

[0430] ***Preparation of Intermediate 223:***



[0431] To a mixture of **Intermediate 204** (500 mg, 935.52 µmol, 1.00 *equiv.*) and **Intermediate 222** (474.38 mg, 1.12 mmol, 1.20 *equiv.*) in 1, 4-dioxane (10 mL) was added DIEA (604.53 mg, 4.68 mmol, 5.00 *equiv.*) in one portion at 15°C under N_2. The mixture was refluxed for 16 hours. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was poured into water (10 mL) and extracted with ethyl acetate (5 mL * 5). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Dichloromethane: Methanol = 20/1 to 10/1) to afford **Intermediate 223** (400 mg, 56.72% yield) as a brown solid. LCMS: RT = 0.385 min, MS cal.: 753.4, found: $[M+H]^+$ = 754.4. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.24 - 8.17 (m, 1H), 8.10 (s, 1H), 7.86 - 7.75 (m, 1H), 7.68 (br t, *J* = 6.0 Hz, 1H), 7.40 - 7.23 (m, 5H), 7.12 - 7.03 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.02 (s, 2H), 4.20 - 3.99 (m, 5H), 3.88 (br d, *J* = 2.0 Hz, 1H), 3.82 - 3.71 (m, 1H), 3.62 (br d, *J* = 11.5 Hz, 2H), 3.07 - 2.96 (m, 1H), 2.69 - 2.51 (m, 6H), 2.48 - 2.26 (m, 6H), 2.13 (br d, *J* = 6.4 Hz, 2H), 1.75 (br d, *J* = 11.6 Hz, 2H), 1.68 - 1.52 (m, 1H), 1.40 (s, 3H), 1.26 (s, 3H), 1.22 - 1.14 (m, 2H). Theoretical number of H: 50, found: 50.

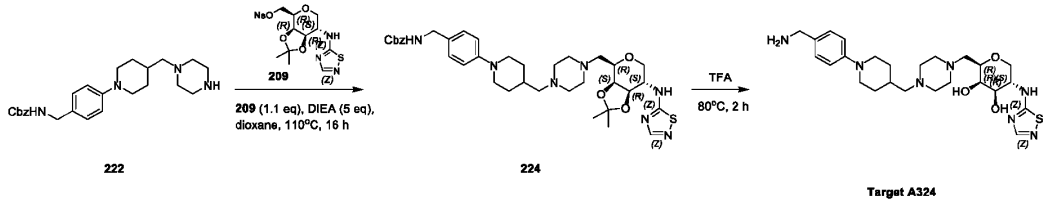
[0432] ***Preparation of Intermediate Target A323:***



223 Target A323

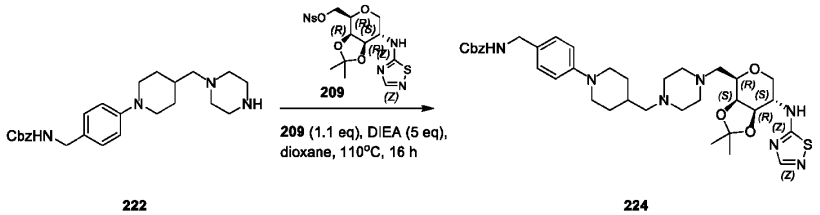
[0433] A solution of **Intermediate 223** (280 mg, 371.43 μmol, 1.00 *equiv.*) in TFA (2 mL) and DCM (0.5 mL) was stirred at 70°C for 2 h. LCMS showed one main peak with desired MS. The mixture was concentrated to give residue, diluted with 2 mL MeOH, adjusted with 1M NaOH aq. to pH = 5~6. The mixture was purified by pre-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 10% - 60% B over 8.0 min) to give crude product. Then further purified by pre-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.04% HCl)-ACN]; gradient: 1% - 25% B over 8.0 min) to give **Target A323** (150 mg, 69.67% yield) as a white solid. LCMS: RT = 1.162 min, MS cal.: 579.3, found: $[M+H]^+$ = 580.4. ^{1}H NMR (400 MHz, DEUTERIUM OXIDE) δ = 8.08 (d, *J* = 12.4 Hz, 2H), 7.60 (s, 4H), 4.31 (dt, *J* = 5.2, 10.7 Hz, 1H), 4.20 (s, 2H), 4.10 (dd, *J* = 5.2, 11.4 Hz, 1H), 4.01 - 3.91 (m, 2H), 3.85 - 3.69 (m, 3H), 3.67 - 3.20 (m, 13H), 3.09 (br d, *J* = 6.8 Hz, 2H), 2.40 - 2.25 (m, 1H), 2.17 (br d, *J* = 13.6 Hz, 2H), 1.85 - 1.66 (m, 2H). Theoretical number of H: 40, found: 35. exchangeable H: 5.

EXAMPLE 51. Procedure for Preparation of Target A324



222 224 Target A324

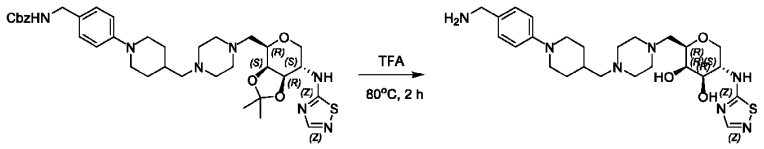
[0434] ***Preparation of Intermediate 224:***



222 224

[0435] To a solution of **Intermediate 209** (400 mg, 846.58 µmol, 1.00 equiv.) and **Intermediate 222** (393.50 mg, 931.23 µmol, 1.10 equiv.) in dioxane (10 mL) was added DIEA (547.07 mg, 4.23 mmol, 737.29 µL, 5.00 equiv.). The mixture was stirred at 110°C for 16 h. LCMS showed the reaction was completed. The reaction solution was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (SiO_2, dichloromethane: methanol =100: 1 to 10: 1) to give **Intermediate 224** (300 mg, 433.60 µmol, 51.22% yield) as yellow solid. LCMS: RT = 0.348 min, MS cal.: 691.4, found: $[M + H]^+$ =692.4. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.92 (s, 1H), 7.40 - 7.31 (m, 5H), 7.21 - 7.13 (m, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.10 - 5.98 (m, 1H), 5.13 (s, 2H), 4.97 (br s, 1H), 4.30 (br d, J = 6 Hz, 2H), 4.21 - 4.08 (m, 3H), 4.06 - 3.90 (m, 1H), 3.70 - 3.55 (m, 3H), 3.24 (br t, J = 10.4 Hz, 1H), 2.95 - 2.87 (m, 1H), 2.83 - 2.47 (m, 10H), 2.28 (s, 2H), 1.86 (br d, J = 11.2 Hz, 2H), 1.72 - 1.61 (m, 2H), 1.58 (s, 3H), 1.37 (s, 3H), 1.35 - 1.26 (m, 2H). Theoretical number of H: 49, found: 49.

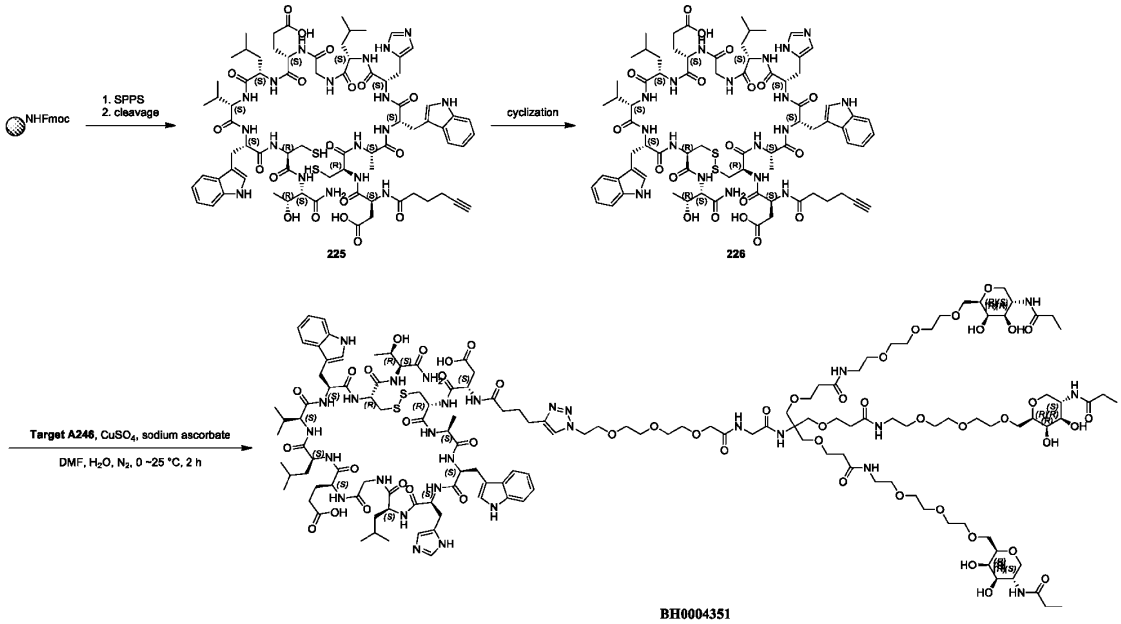
[0436] ***Preparation of Target A324:***



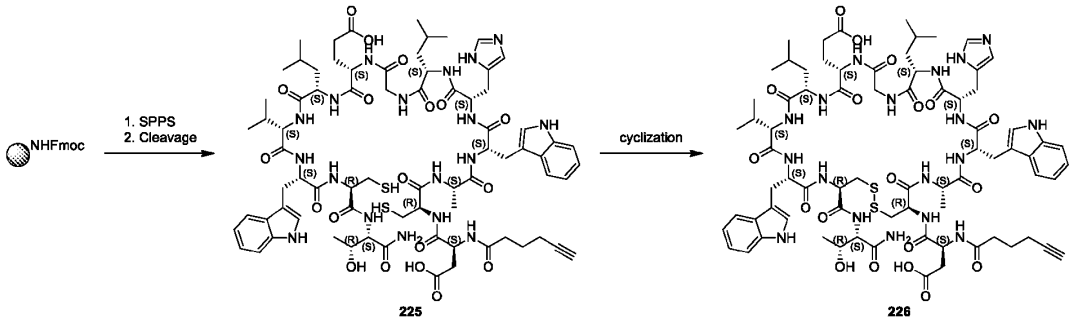
224 **Target A324**

[0437] A mixture of **Intermediate 224** (300 mg, 433.60 µmol, 1.00 equiv.) in TFA (6 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 2 hr under N_2 atmosphere. LCMS showed the reaction was completed. The reaction was concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 5%-35% B over 8.0 min) to give **Target A324** (108 mg, 208.62 µmol, 48.11% yield) as white solid. LCMS: RT = 0.863 min, MS cal.: 517.3, found: $[M + H]^+$ =518.3. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.85 (s, 1H), 7.22 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.11 (dd, J = 5.2, 11.0 Hz, 1H), 4.00 - 3.90 (m, 1H), 3.86 (d, J = 2.8 Hz, 1H), 3.76 (s, 2H), 3.69 - 3.61 (m, 3H), 3.60 - 3.55 (m, 2H), 3.17 (t, J = 10.8 Hz, 1H), 2.79 - 2.59 (m, 8H), 2.50 (br d, J = 2.4 Hz, 3H), 2.25 (d, J = 6.8 Hz, 2H), 1.87 (br d, J = 12 Hz, 2H), 1.76 - 1.64 (m, 1H), 1.40 - 1.27 (m, 2H). . Theoretical number of H: 39, found: 34, exchangeable: 5.

EXAMPLE 52. Procedure for preparation of BH0004351, BH0004689



[0438] ***Preparation of Intermediate 225:***



[0439] Peptide was synthesized using standard Fmoc chemistry (Rink AM resin).

1) Resin preparation: To the vessel containing Rink Amide AM resin (624.80 g, 200.00 mmol, 0.32 mmol/g) and DMF (2 L) was bubbled with N_2 for 2 h at 25 °C. Then 20% piperidine in DMF (4 L) was added and the mixture was bubbled with N_2 for 30 min at 25 °C. The mixture was filtered and washed with DMF (4 L) * 5 before proceeding to next step.

2) Coupling: A solution of Fmoc-Thr(*t*Bu)-OH (238.00 g, 600.00 mmol, 3.00 equiv.), DIC (75.60 g, 600.00 mmol, 3.00 equiv.), HOBt (81.20 g, 600.00 mmol, 3.00 equiv.) in DMF (2 L) was added to the resin with N_2 bubbling for 1 h at 25 °C. The coupling reaction was monitored by ninhydrin test. The resin was then washed with DMF (4 L) * 5.

3) Deprotection: 20% piperidine in DMF (2 L) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The resin was then washed with DMF (4 L) * 5.

4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 2-14, Table 15.

5) After all the steps were completed, the resin was washed with DMF (4 L) * 5, MeOH (4 L) * 5, then dried under reduced pressure to afford resin-bound peptide (Rink AM resin, 450.5 g, 200 mmol).

Table 22: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
13	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOBt (3.00 equiv.)
14	2-Oxohept-6-ynoic acid (2.00 equiv.)	HATU (1.90 equiv.) and DIEA (4.00 equiv.)

[0440] Peptide cleavage and cyclization.

1) Cleavage solution (TFA/TIS/H_2O, 95/2.5/2.5, v/v/v, 5 L) was added to the flask containing the side-chain protected resin-bound peptide (Rink AM resin, 450.5 g, 200 mmol) at 25 °C and stirred for 2 h.

2) After filtration, the filtrate was collected.

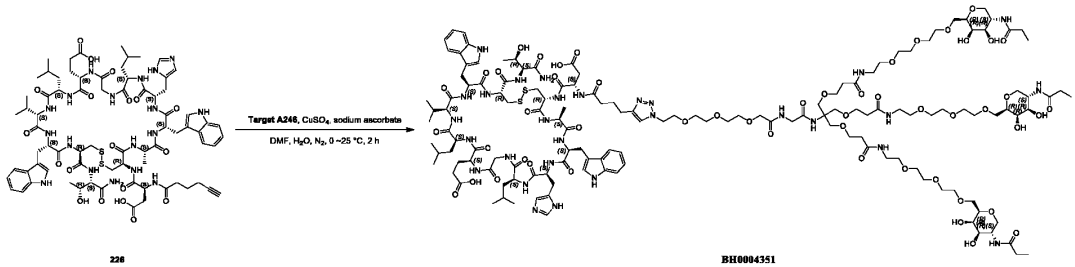
3) The filtrate was precipitated with cold isopropyl ether (30 L). After filtration, the solid was washed with isopropyl ether (5 L) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 225** (320.0 g, crude) as a white solid.

4) To the mixture of **Intermediate 225** (320.0 g, crude) in HOAc/MeCN/H_2O (4/3/3, v/v/v, 70 L) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color

disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 226** (109.0 g, 90.7% purity, 30.4% yield) as a white solid. LCMS: RT = 10.492 min, MS calcd: M_{av} = 1623.85, mass observed: $[M + H]^+$ = 1625.57, $[M + 2H]^{2+}$ = 813.02.

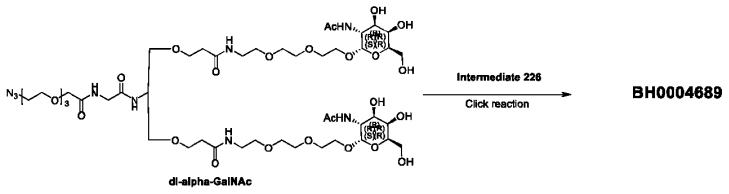
Another 200 mmol resin was performed to afford **Intermediate 226** as 107.8 g.

[0441] Preparation of ***BH0004351***:

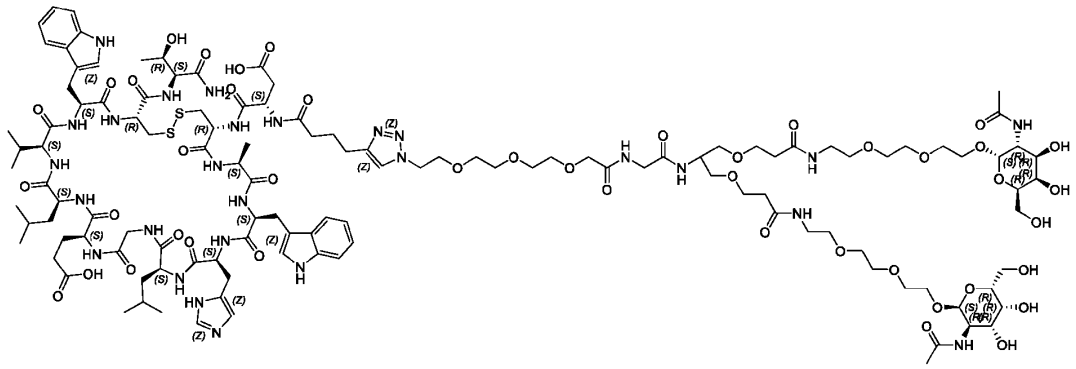


[0442] To a solution of **Intermediate 226** (121.28 mg, 74.68 μmol, 1.00 equiv.) and **Target A246** (120.0 mg, 74.68 μmol, 1.00 equiv.) in DMF (2 mL), H2O (2 mL)was added $CuSO_4$ (0.4 M, 186.71 μL, 74.6 μmol, 1.00 equiv.), sodium ascorbate (0.4 M, 560.14 μL, 224.0 μmol, 3.00 equiv.) and THPTA (tris-hydroxypropyltriazolylmethylamine, 32.45 mg, 74.68 μmol, 1.00 equiv.) under nitrogen atmosphere at 0 °C, and the resulting mixture was stirred for 2 h at 0 °C. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **BH0004351** (125.7 mg, 97.0% purity 52.10% yield) as a white solid. LCMS: RT = 1.396 min, MS calcd: M_{av} = 3230.61, mass observed: $[M + 3H]^{3+}$ = 1077.80, $[M + 4H]^{4+}$ = 808.40.

[0443] **BH0004689** was synthesized using the same procedure as ***BH0004351*** which was performed by following the procedure mentioned in **[0438]** – **[0442]**.

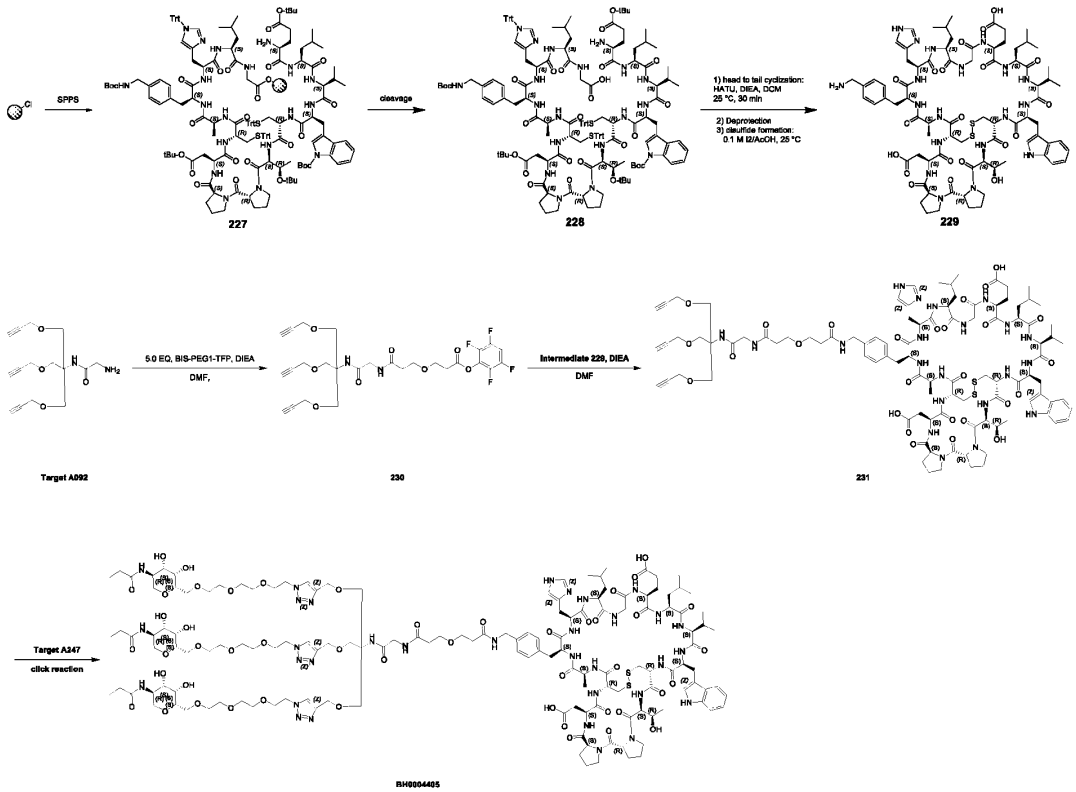


[0444] 108.65 mg of **di-alpha-GalNAc** with **Intermediate 226** afforded **BH0004689** (44.5 mg, 98.2% purity, 25.3% yield) as a white solid. LCMS: RT = 0.845-0.951 min, MS calcd: Mav = 2800.07, mass observed: [M + 2H]2+ = 1400.80, [M + 3H]3+ = 934.36, [M + 4H]4+ = 700.98.



BH0004689

EXAMPLE 53. Procedure for preparation of BH0004405, BH0004408, BH0004586



[0445] ***Preparation of Intermediate 229:***

Peptide was synthesized using standard Fmoc chemistry (CTC resin).

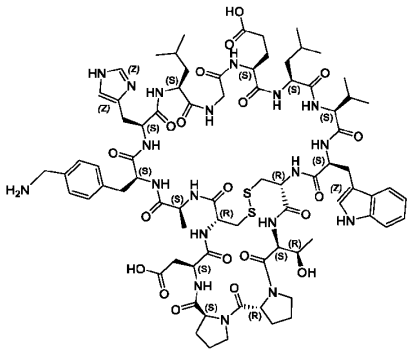
1) Resin preparation: To the vessel containing CTC resin (50 g, 50 mmol, 1.00 mmol/g) and Fmoc-Gly-OH (14.9 g, 50 mmol, 1.00 equiv.) in DCM (500 mL) was added DIEA (4.00 equiv.) dropwise and mixed for 2 h with N2 bubbling at 25 °C. Then MeOH (50 mL) was added and bubbled with N2 for another 30 min. The resin was washed with DMF (1000 mL) * 5, followed by the addition of 20% piperidine in DMF (1000 mL) and bubbled with N2 for 30 min at 25 °C for Fmoc deprotection. The mixture was filtered and the resin was washed with DMF (1000 mL) * 5 before proceeding to next step.
2) Coupling: A solution of Fmoc-Leu-OH (53 g, 150 mmol, 3.00 equiv.), HBTU (41 g, 143 mmol, 2.85 equiv.) in DMF (500 mL) was added to the resin with N_2 bubbling. Then DIEA (6.00 equiv.) was added to the mixture dropwise and bubbled with N_2 for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test, if it showed colorless, the coupling was completed. The resin was then washed with DMF (1000 mL) * 5.
3) Deprotection: 20% piperidine in DMF (1000 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The resin was then washed with DMF (1000 mL) * 5.
4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 3-15, Table 23.
5) After all the steps were completed, the resin was washed with DMF (1000 mL) * 5, MeOH (1000 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 227** (CTC resin, 50 mmol).

Table 23: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Gly-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-4-(Boc-aminomethyl)-*L*-phenylalanine (2.00 equiv.)	HATU (1.90 equiv.) and DIEA (4.00 equiv.)
5	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-D-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

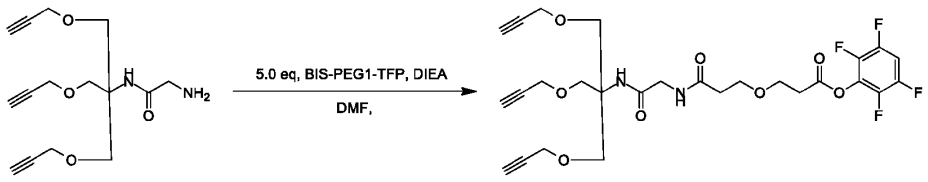
[0446] Peptide cleavage and cyclization, TFA de-protection and disulfide formation:

1) Cleavage: A solution of 1% TFA/DCM (1g/20mL) was added to the resin above at room temperature and stirred for 30mis. After filtration, the filtrate was collected (which contained **Intermediate 228**).
2) Head to tail cyclization: The filtrate was diluted with DCM to give us peptide solution with conc. 1mM, then HATU (2.00 equiv.) was added, followed by the addition of DIEA (4.00 equiv.), and the resulting mixture was stirred for 30 min at 25 °C. After completion monitored by LC-MS, the reaction was washed with 1 M HCl (2500 mL), then washed with H_2O (2500 mL). The organic layer was collected and concentrated under reduced pressure to give a residue.
3) Deprotection: To the residue from step 2 was added a solution of TFA/TIS/H_2O/3-mercaptopropanoic acid (v/v/v/v, 92.5/2.5/2.5/2.5, 1g/20ml, 20V), and the resulting mixture was stirred for 2 h at 25 °C. The mixture was precipitated with cold isopropyl ether (cold, 5V). After filtration, the solid was washed with isopropyl ether (5000 mL) twice, and the crude peptide was dried under reduced pressure.
4) Disulfide formation: To the crude peptide from step 3 in MeCN/H_2O (1/1, v/v, 1mM peptide solution) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 229** (31.0g, 90.0% purity, 19.4% yield) as a white solid. LCMS: RT = 7.9 min, MS calcd: M_{av} = 1696.95, mass observed: $[M + H]^+$ = 1696.76, $[2M + 3H]^{3+}$ = 1132.18, $[M + 2H]^{2+}$ = 848.88, $[M + 3H]^{3+}$ = 566.26.



Intermediate 229

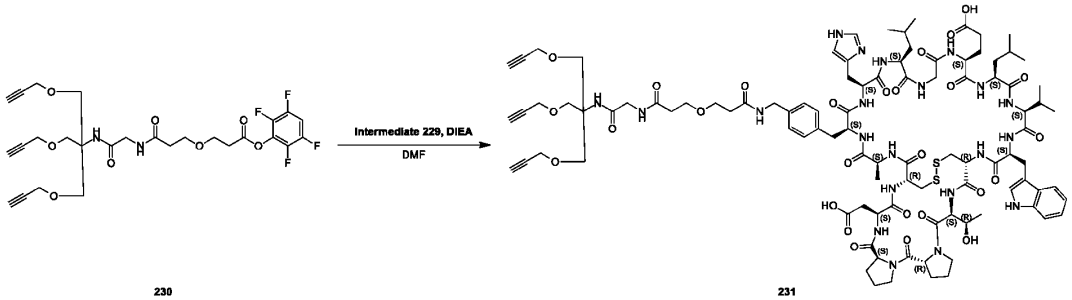
[0447] ***Preparation of Intermediate 230:***



Target A092 230

[0448] To a solution of **Bis-PEG1-TFP** (2.35 g, 5.13 mmol, 5.00 equiv) in DMF (10 mL) was added a mixture of **Target A092** (300 mg, 1.03 mmol, 1.00 equiv) and DIEA (397.9 mg, 3.08 mmol, 536.26 µL, 3 equiv) in 3mL DMF at 0 °C. The resulting reaction was stirred for 5 min at 0 °C. After completion monitored by LC-MS, the mixture was directly injected into the reverse column, purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 230** (137.9 mg, 90.0% purity, 22.99% yield) as colorless oil. LCMS: RT = 0.645 min, MS calcd: M_{av} = 584.51, mass observed: $[M + H]^+$ = 585.28.

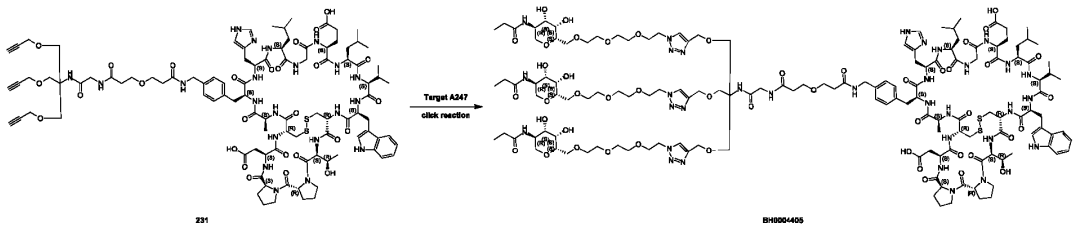
[0449] ***Preparation of Intermediate 231:***



230 231

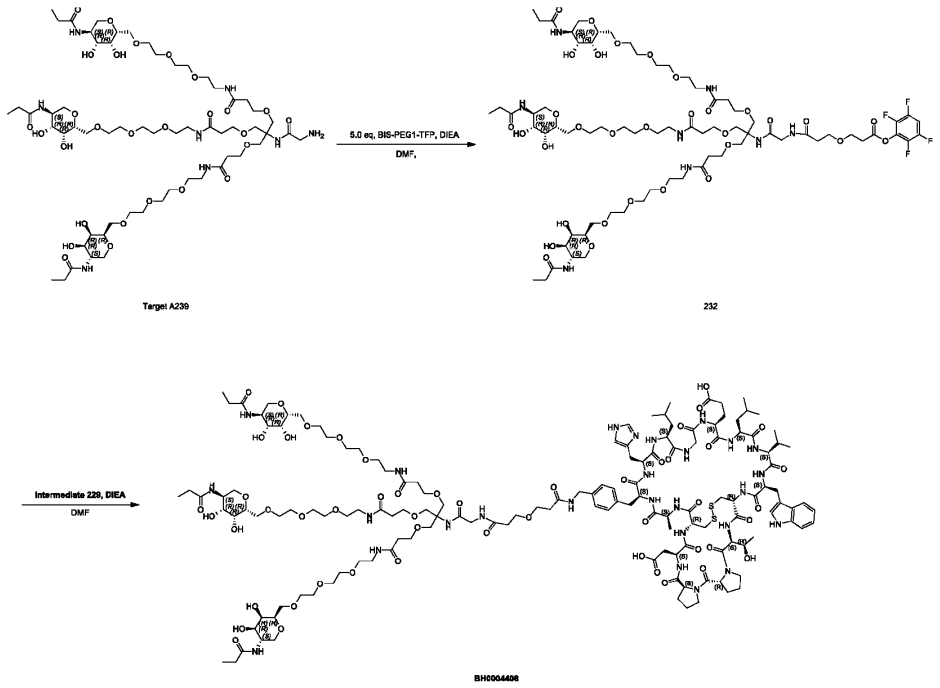
[0450] To a solution of **Intermediate 230** (137.9 mg, 235.92 µmol, 1.1 equiv) and **Intermediate 229** (363.95 mg, 214.48 µmol, 1.00 equiv) in DMF (5 mL) was added DIEA (83.16 mg, 643.43 µmol, 112.07 µL, 3.00 equiv). The mixture was stirred at 20 °C for 1 hr. After completion monitored by LC-MS, the mixture was acidified by 1 M HCl to pH = 5. The mixture was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN) directly, followed by lyophilization to afford **Intermediate 231** (208.8 mg, 92.0% purity, 42.34% yield.) as a white solid. LCMS: RT = 0.654 min, MS calcd: M_{av} = 2115.39, mass observed: $[M + 2H]^{2+}$ =1058.70.

[0451] Preparation of **BH0004405**:



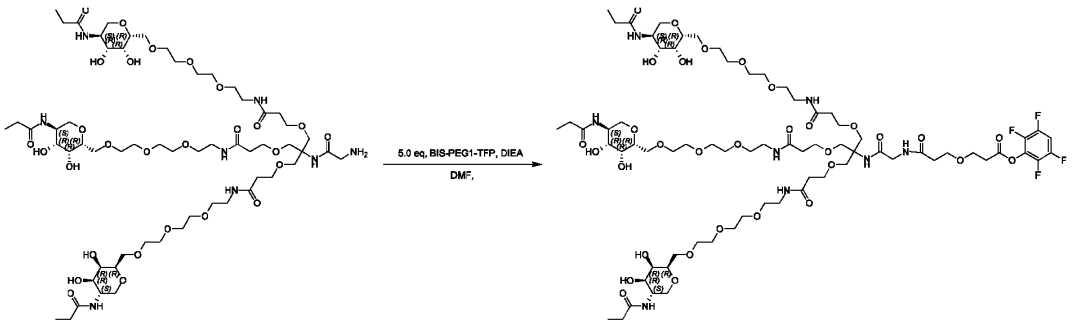
[0452] To a solution of **Target A247** (92.53 mg, 245.82 µmol, 4.00 equiv) and **Intermediate 231** (130 mg, 61.45 µmol, 1.00 equiv) in DMF (1 mL) and H2O (1 mL) was added CuSO4 (0.4 M, 460.91 µL, 3 .00 equiv), sodium ascorbate (0.4 M, 1.38 mL, 9.00 equiv) and THPTA (80.11 mg, 184.36 µmol, 3.00 equiv) under nitrogen atmosphere at 0 °C, and the resulting mixture was stirred for 2 h at 0 ºC. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H2O; B: MeCN), followed by lyophilization to afford **BH0004405** (140.3 mg, 97.11% purity, 68.33% yield) as a white LCMS: RT = 1.534 min, MS cal.: 3244.60, mass observed: $[M + 3H]^{3+}$ =1082.30, $[M + 4H]^{4+}$ =812.20.

[0453] Preparation of ***BH0004408:***



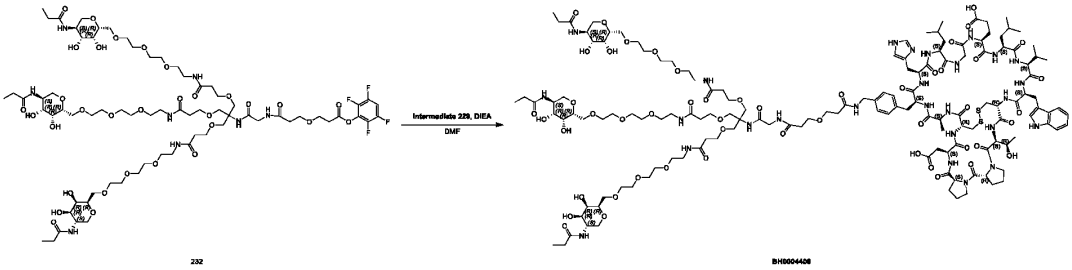
[0454] **Intermediate 229** was synthesized using the same procedure as **BH0004405** which was performed by following the procedure mentioned in **[0445]** – **[0446]**.

[0455] ***Preparation of Intermediate 232:***



[0456] To a solution of **Bis-PEG1-TFP** (230.52 mg, 503.04 µmol, 5.00 equiv) in DMF (1 mL) was added a mixture of **Target A239** (140 mg, 100.61 µmol, 1.00 equiv) and DIEA (39.01 mg, 301.82 µmol, 52.57 µL, 3.00 equiv) in 1mL DMF at 0 °C. The resulting reaction was stirred for 5 min at 0 °C. After completion monitored by LC-MS, the mixture was directly injected into the reverse column, purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 232** (127.5 mg, 90% purity, 75.27% yield) as colorless oil. LCMS: RT = 0.583 min, MS calcd: M_{av} = 1683.74, mass observed: $[M + 2H]^{2+}$ = 842.60.

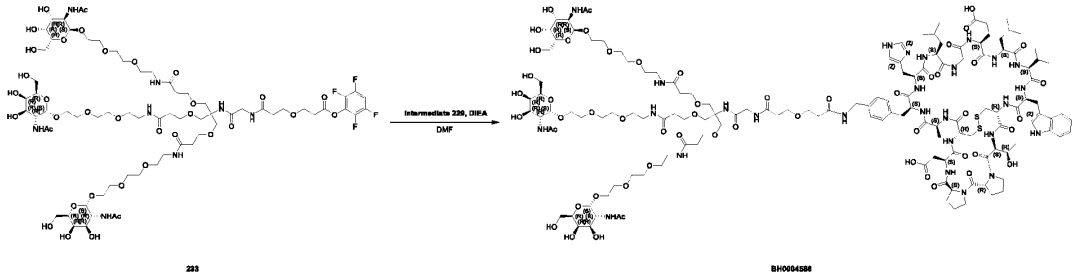
[0457] Preparation of **BH0004408**:



[0458] A mixture of **Intermediate 232** (113.5 mg, 67.41 µmol, 1.10 equiv.) and **Intermediate 229** (103.99 mg, 61.28 µmol, 1.00 equiv.), DIEA (23.76 mg, 183.85 µmol, 32.02 µL, 3.00 equiv.) in DMF (2 mL) was stirred at 25 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **BH0004408**

(101 mg, 97.5% purity, 49.9% yield) as a white solid. LCMS: RT = 1.381 min, MS calcd: M_{av} = 3214.61, mass observed: $[M + 3H]^{3+}$ = 1072.50, $[M + 4H]^{4+}$ = 804.60.

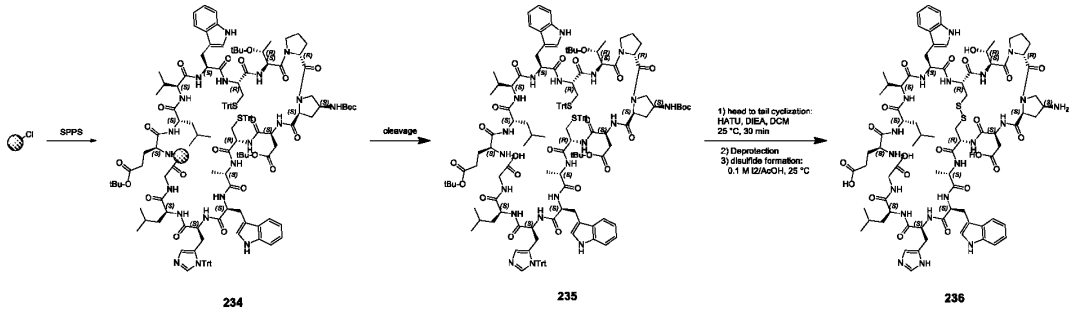
[0459] **BH0004586** was synthesized using the same procedure as **BH0004408** which was performed by following the procedure mentioned in **[0454]** – **[0458]**.



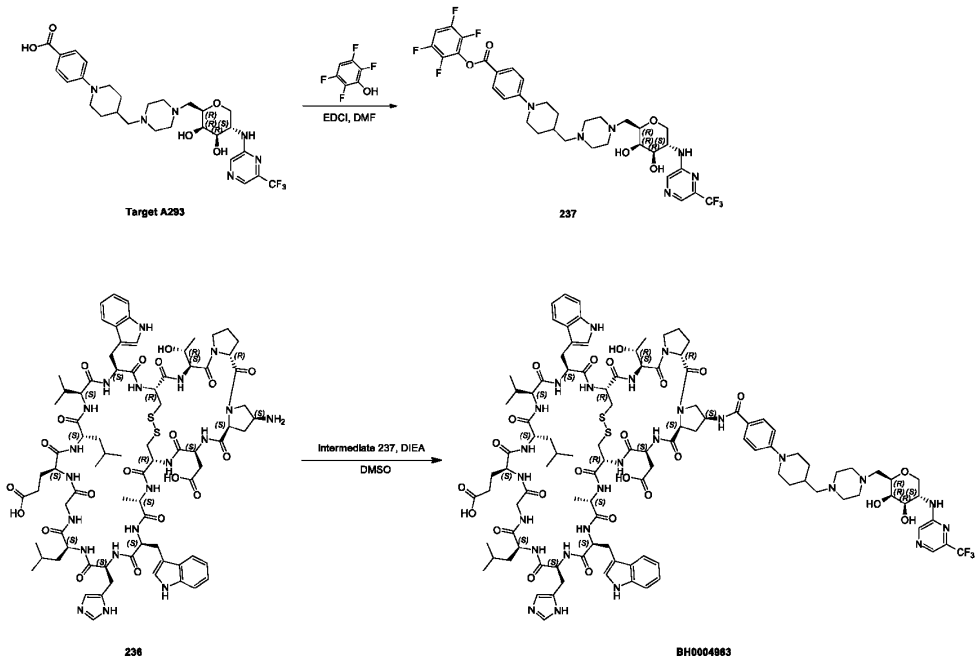
233 BH0004586

[0460] 2.3 g of **Intermediate 233** with **Intermediate 229** afforded **BH0004586** (2.11 g, 95.0% purity, 54.8 % yield) as a white solid. LCMS: RT = 1.324min, MS calcd: Mav = 3220.53, mass observed: [M + 2H]2+ = 1611.10, [M + 3H]3+ = 1074.60.

EXAMPLE 53. Procedure for preparation of BH0004963, BH0004964, BH0004925, BH0004888, BH0004980, BH0005130



234 235 236



[0461] ***Preparation of Intermediate 236:***

Peptide was synthesized using standard Fmoc chemistry (CTC resin).

1) Resin preparation: To the vessel containing CTC resin (10 g, 10 mmol, 1.00 mmol/g) and Fmoc-Gly-OH (2.9 g, 10 mmol, 1.00 equiv.) in DCM (100 mL) was added DIEA (4.00 equiv.) dropwise and mixed for 2 h with N2 bubbling at 25 °C. Then MeOH (20 mL) was added and bubbled with N2 for another 30 min. The resin was washed with DMF (200 mL) * 5, followed by the addition of 20% piperidine in DMF (200 mL) and bubbled with N2 for 30 min at 25 °C for Fmoc deprotection. The mixture was filtered and the resin was washed with DMF (200 mL) * 5 before proceeding to next step.
2) Coupling: A solution of Fmoc-Leu-OH (10.6 g, 30 mmol, 3.00 equiv.), HBTU (10.8 g, 28.5 mmol, 2.85 equiv.) in DMF (100 mL) was added to the resin with N_2 bubbling. Then DIEA (6.00 equiv.) was added to the mixture dropwise and bubbled with N_2 for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test, if it showed colorless, the coupling was completed. The resin was then washed with DMF (200 mL) * 5.
3) Deprotection: 20% piperidine in DMF (200 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The resin was then washed with DMF (200 mL) * 5.
4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 3-15, Table 24.

5) After all the steps were completed, the resin was washed with DMF (200 mL) * 5, MeOH (200 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 234** (CTC resin, 10 mmol).

Table 24: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Gly-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	(2S,4S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-((tert-butoxycarbonyl)amino)pyrrolidine-2-carboxylic acid (2.00 equiv.)	HATU (1.90 equiv.) and DIEA (4.00 equiv.)
9	Fmoc-D-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

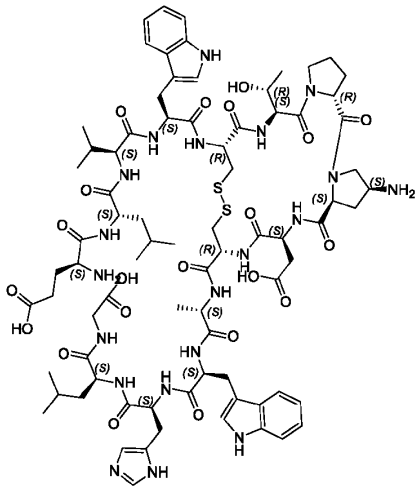
[0462] Peptide cleavage and cyclization, TFA de-protection and disulfide formation:

1) Cleavage: A solution of 1% TFA/DCM (1g/20mL) was added to the resin above at room temperature and stirred for 30mis. After filtration, the filtrate was collected (which contained **Intermediate 235**).

2) Head to tail cyclization: The filtrate was diluted with DCM to give us peptide solution with conc. 1mM, then HATU (2.00 equiv.) was added, followed by the addition of DIEA (4.00 equiv.), and the resulting mixture was stirred for 30 min at 25 °C. After completion monitored by LC-MS, the reaction was washed with 1 M HCl (500 mL), then washed with H_2O (500 mL). The organic layer was collected and concentrated under reduced pressure to give a residue.

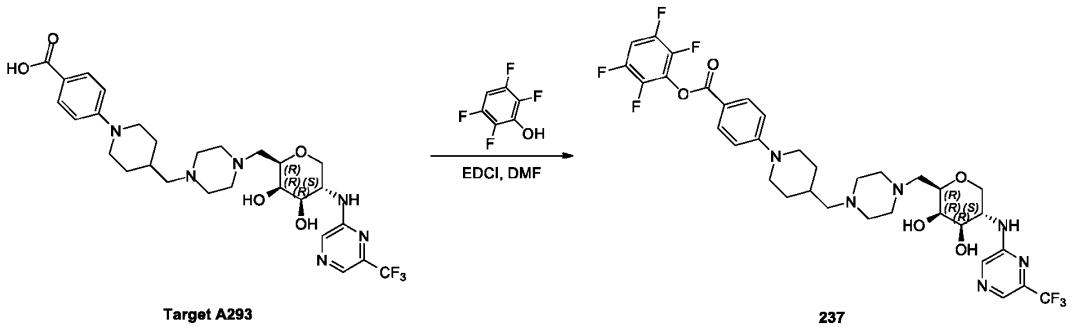
3) Deprotection: To the residue from step 2 was added a solution of TFA/TIS/H_2O/3-mercaptopropanoic acid (v/v/v/v, 92.5/2.5/2.5/2.5, 1g/20ml, 20V), and the resulting mixture was stirred for 2 h at 25 °C. The mixture was precipitated with cold isopropyl ether (cold, 5V). After filtration, the solid was washed with isopropyl ether (5000 mL) twice, and the crude peptide was dried under reduced pressure.

4) Disulfide formation: To the crude peptide from step 3 in MeCN/H_2O (1/1, v/v, 1mM peptide solution) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 236**(2.5 g, 98.0% purity, 16.0% yield) as a white solid. LCMS: RT = 0.881-0.942 min, MS calcd: M_{av} = 1721.95, mass observed: $[M + 2H]^{2+}$ = 861.40.



236

[0463] ***Preparation of Intermediate 237:***

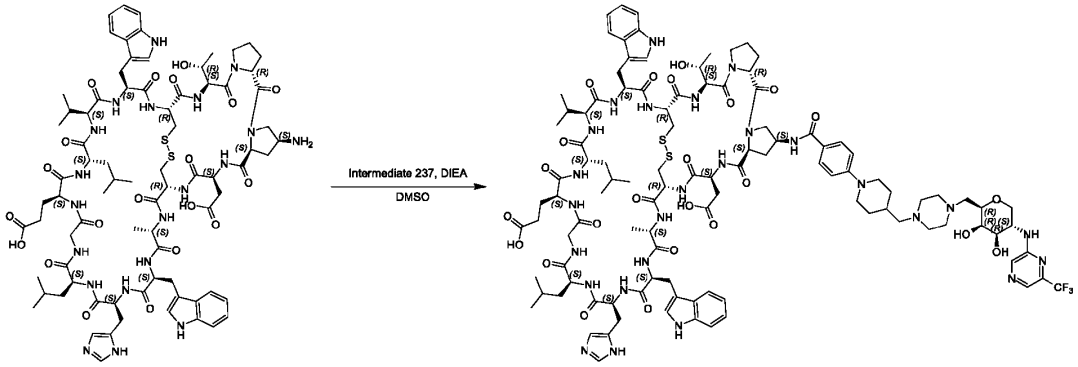


Target A293 **237**

[0464] To a solution of **Target A293** (150 mg, 252.26 μmol, 1.00 equiv) and **2,3,5,6-tetrafluorophenol** (251.36 mg, 1.51 mmol, 6.00 equiv) in DMF (2 mL) was added EDCI (145.08 mg, 756.78

μmol, 3.00 equiv). The mixture was stirred at 0 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **Intermediate 237** (110 mg, 90.0% purity, 58.7% yield) as a white solid. LCMS: RT = 0.691 min, MS calcd: M_{av} = 742.68, mass observed: $[M + 2H]^{2+}$ = 372.20.

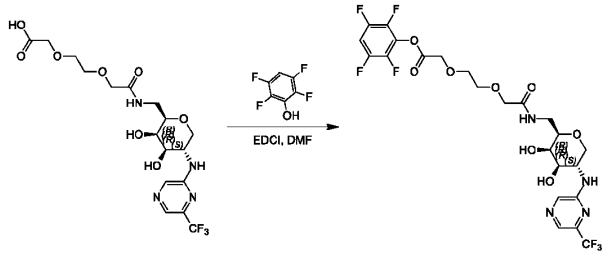
[0465] Preparation of **BH0004963**:



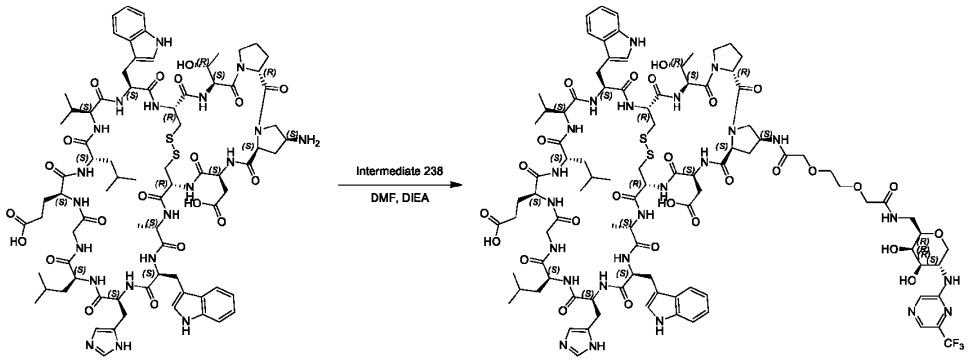
236 BH0004963

[0466] A mixture of **Intermediate 236** (173.43 mg, 100.72 μmol, 1.10 equiv.) and **Intermediate 237** (68.0 mg, 91.56 μmol, 1.00 equiv), DIEA (59.17 mg, 457.80 μmol, 79.74 μL, 5.00 equiv.) in DMSO (2 mL) was stirred at 40 ºC for 16 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 10Mm NH_4HCO_3 /H_2O; B: MeCN), followed by lyophilization to afford **BH0004963** (100.0 mg, 98.9% purity, 46.99% yield) as a white solid. LCMS: RT = 1.492 min, MS calcd: M_{av} = 2298.57, mass observed: $[M + 2H]^{2+}$ = 1149.90, $[M + 3H]^{3+}$ = 767.30.

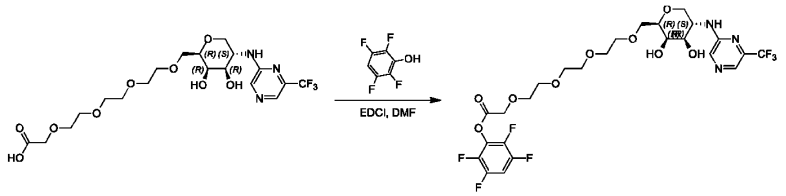
[0467] Preparation of **BH0004964, BH0004925:**



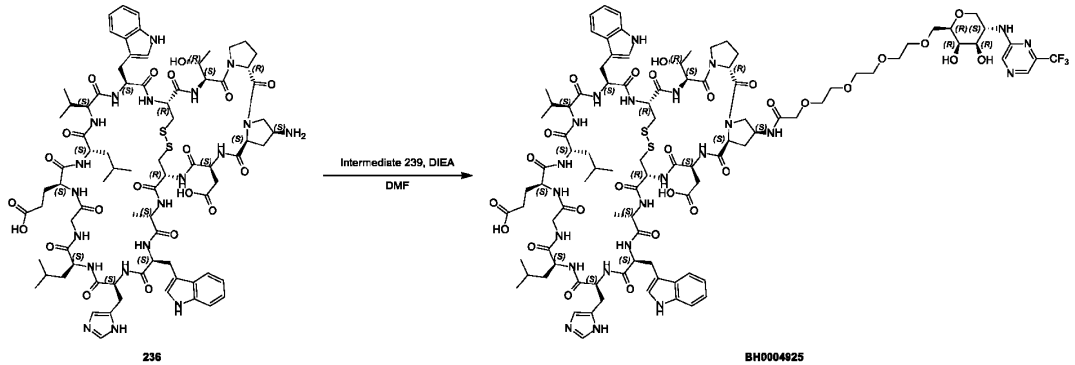
Target A291 238



236 BH0004964

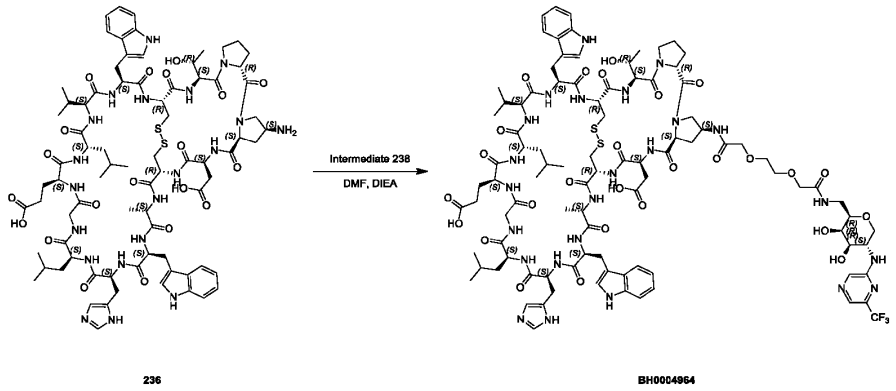


Target A290 239

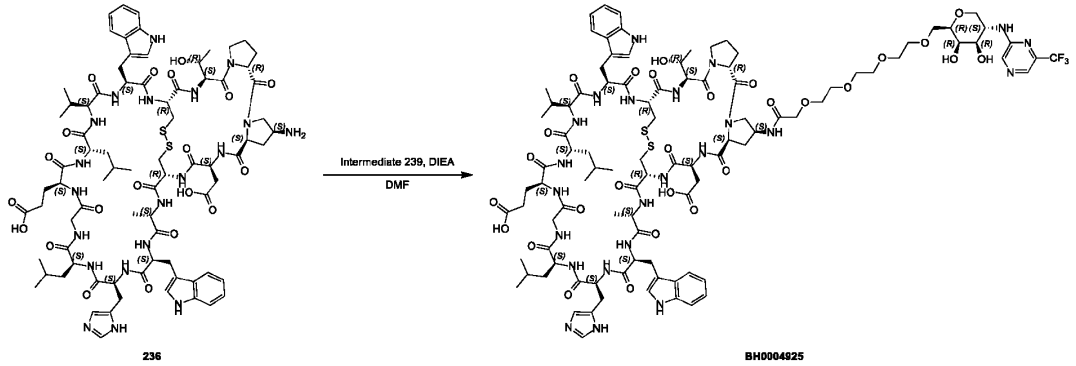


236 BH0004925

[0468] **BH0004964**，**BH004925** was synthesized using the same procedure as **BH0004963** which was performed by following the procedure mentioned in **[0461]** – **[0464]**.

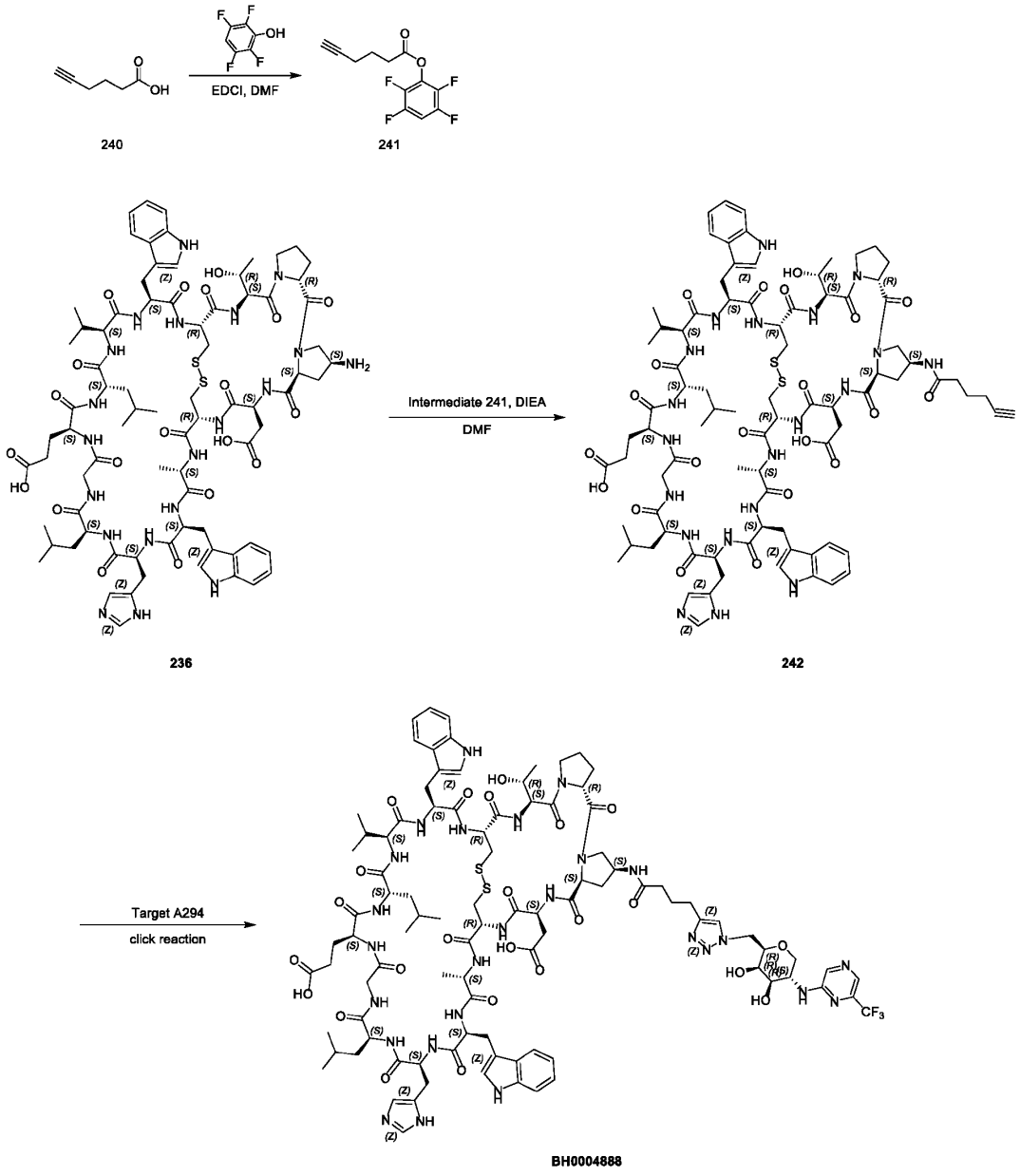


[0469] A mixture of **Intermediate 236** (150.0 mg, 87.11 µmol, 1.00 equiv.) and **Intermediate 238** (59.07 mg, 95.82 µmol, 1.10 equiv), DIEA (22.52 mg, 174.22 µmol, 30.35 µL, 2.00 equiv.) in DMF (2 mL) was stirred at 20 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H2O; B: MeCN), followed by lyophilization to afford **BH0004964** (110 mg, 99.3% purity, 57.7% yield) as a white solid. LCMS: RT = 1.475 min, MS calcd: Mav = 2172.32, mass observed: $[M + 2H]^{2+}$ = 1086.80, $[M + 3H]^{3+}$ = 725.00.



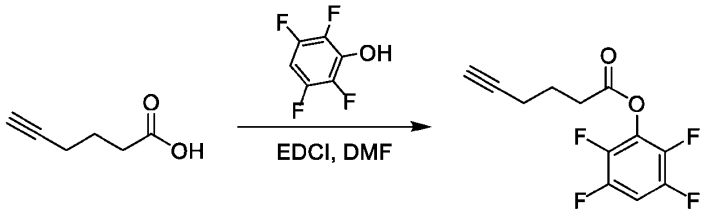
[0470] 200 mg of **Intermediate 236** with **Intermediate 239** afforded **BH0004925** (150.0 mg, 98.9% purity, 57.9 % yield) as a white solid. LCMS: RT = 1.510min, MS calcd: Mav = 2203.38, mass observed: $[M + 2H]^{2+}$ = 1102.30, $[M + 3H]^{3+}$ = 735.30.

[0471] Preparation of **BH0004888**:



[0472] **BH0004888** was synthesized using the same procedure as **BH0004963** which was performed by following the procedure mentioned in **[0461]** – **[0462]**.

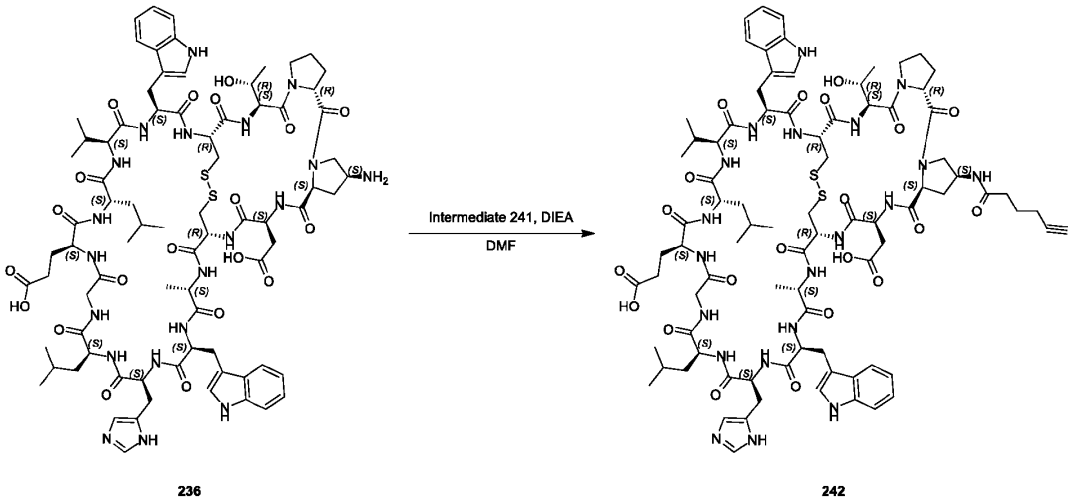
[0473] ***Preparation of Intermediate 241:***



240 241

[0474] To a solution of **Intermediate 240** (500.0 mg, 4.46 mmol, 1.00 equiv) and **2,3,5,6-tetrafluorophenol** (2.22 g, 13.38 mmol, 3.00 equiv) in DMF (5 mL) was added EDCI (1.71 g, 8.92 mmol, 2.00 equiv). The mixture was stirred at 20 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **Intermediate 241** (703.0 mg, 99.0% purity, 59.9% yield) as a colourless oil. LCMS: RT = 1.226-1.328 min, MS calcd: M_{av} = 260.18, mass observed: $[M + 2H]^{2+}$ = 130.10.

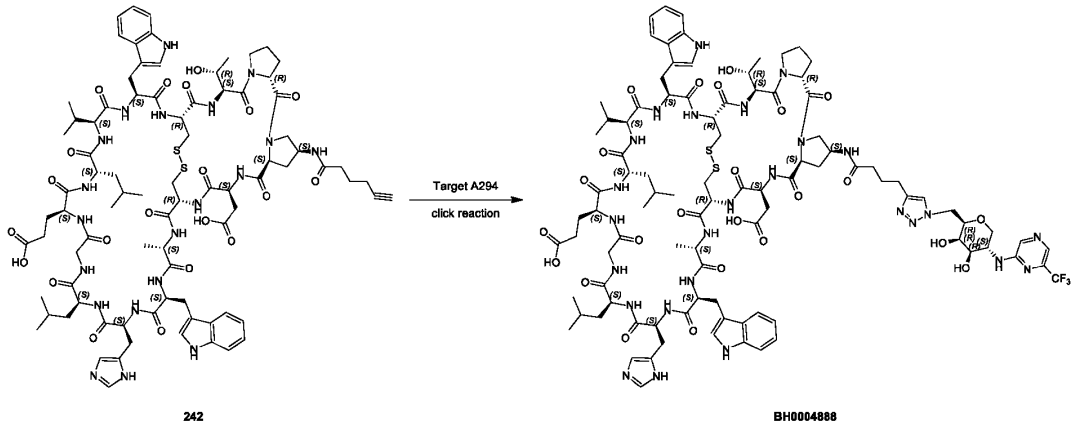
[0475] ***Preparation of Intermediate 242:***



236 242

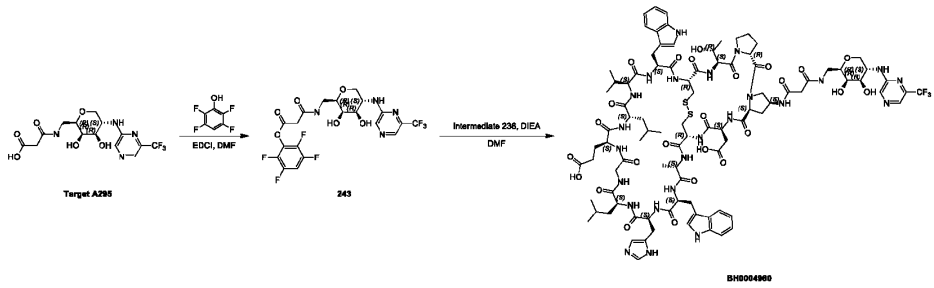
[0476] To a solution of **Intermediate 236** (200.0 mg, 116.15 µmol, 1.00 equiv) and **Intermediate 241** (105.77 mg, 406.52 µmol, 3.50 equiv) in DMF (3 mL) was added DIEA (15.01 mg, 116.15 µmol, 20.23 µL 1.00 equiv). The mixture was stirred at 20 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **Intermediate 242** (150.0 mg, 98.0% purity, 69.6% yield) as a white solid. LCMS: RT = 0.986-1.092 min, MS calcd: M_{av} = 1816.07, mass observed: $[M + 2H]^{2+}$ = 908.70.

[0477] Preparation of **BH0004888**:



[0478] To a solution of **Target A294** (28.71 mg, 85.90 μmol, 1.20 equiv) and **Intermediate 242** (130 mg, 71.58 μmol, 1.00 equiv) in DMF (1 mL) and H2O (1 mL) was added CuSO4 (0.4 M, 178.96 μL, 1.00 equiv), sodium ascorbate (0.4 M, 536.88 μL, 3.00 equiv) and THPTA (31.10 mg, 71.58 μmol, 1.00 equiv) under nitrogen atmosphere at 0 °C, and the resulting mixture was stirred for 2 h at 0 ºC. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H2O; B: MeCN), followed by lyophilization to afford **BH0004888** (108.0 mg, 98.5% purity, 69.1% yield) as a white solid. LCMS: RT = 1.525 min, MS cal.: 2150.32, mass observed: $[M + 2H]^{2+}$ =1075.80, $[M + 3H]^{3+}$ =717.60.

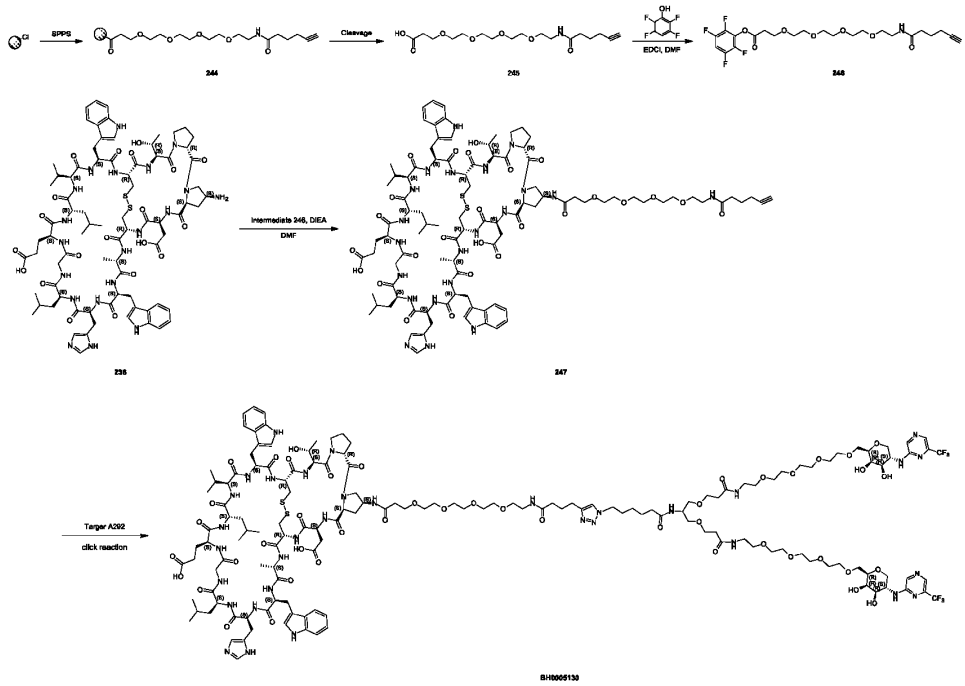
[0479] Preparation of **BH0004980**:



[0480] To a solution of **Target A295** (50.0 mg, 1.00 equiv) and **2,3,5,6-tetrafluorophenol** (126.3 mg, 6.00 equiv) in DMF (0.5 mL) was added EDCI (29.1 mg, 1.20 equiv). The mixture was stirred at 0 ºC for 1 h. After completion monitored by LC-MS, the mixture was added **Intermediate 236 (**174.62 mg, 101.41 μmol, 1.10 equiv), DIEA (35.74 mg, 276.57 μmol, 48.17 μL, 3.00 equiv) at 20 ºC for 0.5 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 10Mm NH_4HCO_3 /H_2O; B:

MeCN), followed by lyophilization to afford **BH0004980** (25.2 mg, 99.4% purity, 12.9% yield) as a white solid. LCMS: RT = 1.501 min, MS calcd: M_{av} = 2098.24, mass observed: $[M + 2H]^{2+}$ = 1049.70, $[M + 3H]^{3+}$ =700.30.

[0481] Preparation of **BH0005130**:



[0482] **BH0005130** was synthesized using the same procedure as **BH0004963** which was performed by following the procedure mentioned in **[0461]** – **[0462]**.

[0483] ***Preparation of Intermediate 245:***

Peptide was synthesized using standard Fmoc chemistry (CTC resin).

1) Resin preparation: To the vessel containing CTC resin (2.0 g, 2 mmol, 1.00 mmol/g) and Fmoc-PEG4-CH_3CH_2OH (975.0mg, 2 mmol, 1.00 equiv.) in DCM (20 mL) was added DIEA (4.00 equiv.) dropwise and mixed for 2 h with N2 bubbling at 25 °C. Then MeOH (2.0 mL) was added and bubbled with N2 for another 30 min. The resin was washed with DMF (50 mL) * 5, followed by the addition of 20% piperidine in DMF (50 mL) and bubbled with N2 for 30 min at 25 °C for Fmoc deprotection. The mixture was filtered and the resin was washed with DMF (50 mL) * 5 before proceeding to next step.

2) Coupling: A solution of Hex-5-ynoic acid (672.7 mg, 6.0 mmol, 3.00 equiv.), HBTU (2.16 g, 5.7 mmol, 2.85 equiv.) in DMF (20 mL) was added to the resin with N_2 bubbling. Then DIEA (6.00 equiv.) was added to the mixture dropwise and bubbled with N_2 for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test, if it showed colorless, the coupling was completed. The resin was then washed with DMF (50 mL) * 5.

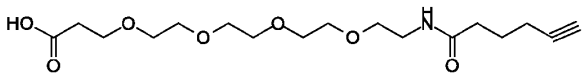
3) After all the steps were completed, the resin was washed with DMF (50 mL) * 5, MeOH (50 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 244** (CTC resin, 2.0 mmol).

Table 25: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-PEG4-CH_3CH_2OH-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Hex-5-ynoic acid (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

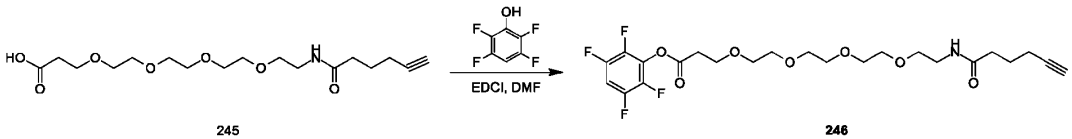
[0484] Peptide cleavage and cyclization, TFA de-protection and disulfide formation:

Cleavage: A solution of 20% HFIP/DCM (1g/20mL) was added to the resin above at room temperature and stirred for 30mis twice. After filtration, the filtrate was collected followed by lyophilization to afford **Intermediate 245** (564 mg, crude) as a white solid. LCMS: RT = 0.553 min, MS calcd: M_{av} = 359.41, mass observed: [M + H]+ = 360.20



245

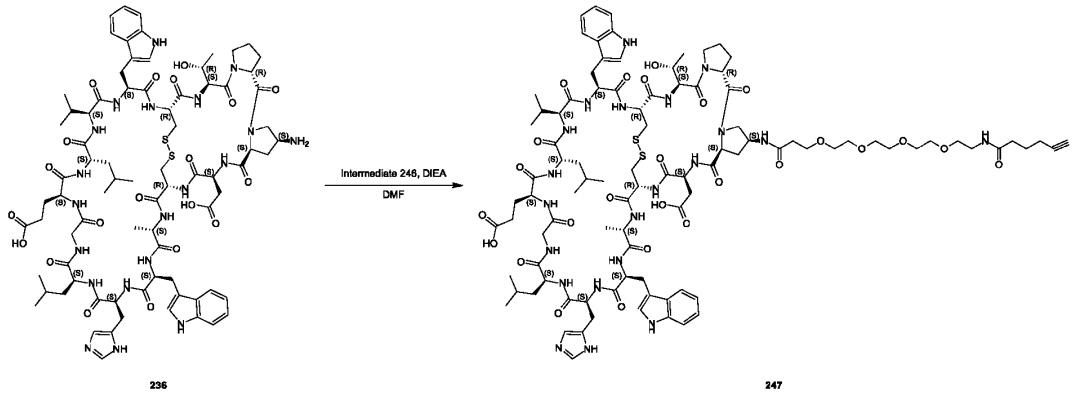
[0485] ***Preparation of Intermediate 246:***



245 **246**

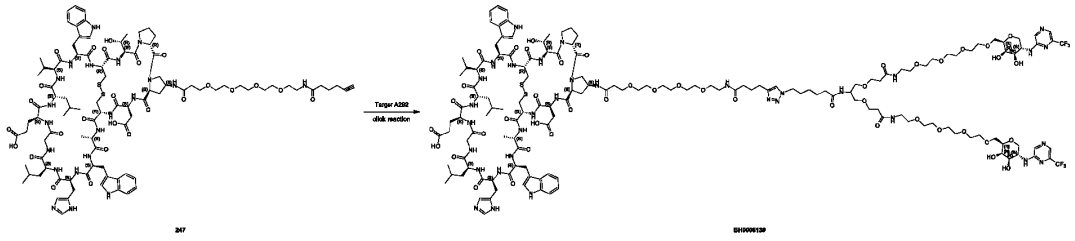
[0486] To a solution of **Intermediate 245** (550.0 mg, 1.53 mmol, 1.00 equiv) and **2,3,5,6-tetrafluorophenol** (762.41 mg, 4.59 mmol, 3.00 equiv) in DMF (6 mL) was added EDCI (586.71 mg, 3.06 mmol, 2.00 equiv). The mixture was stirred at 20 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **Intermediate 246** (689 mg, 90.0% purity, 88.7% yield) as a colourless oil. LCMS: RT = 1.066-1.162 min, MS calcd: M_{av} = 507.47, mass observed: $[M + H]^+$ = 508.39.

[0487] ***Preparation of Intermediate 247:***



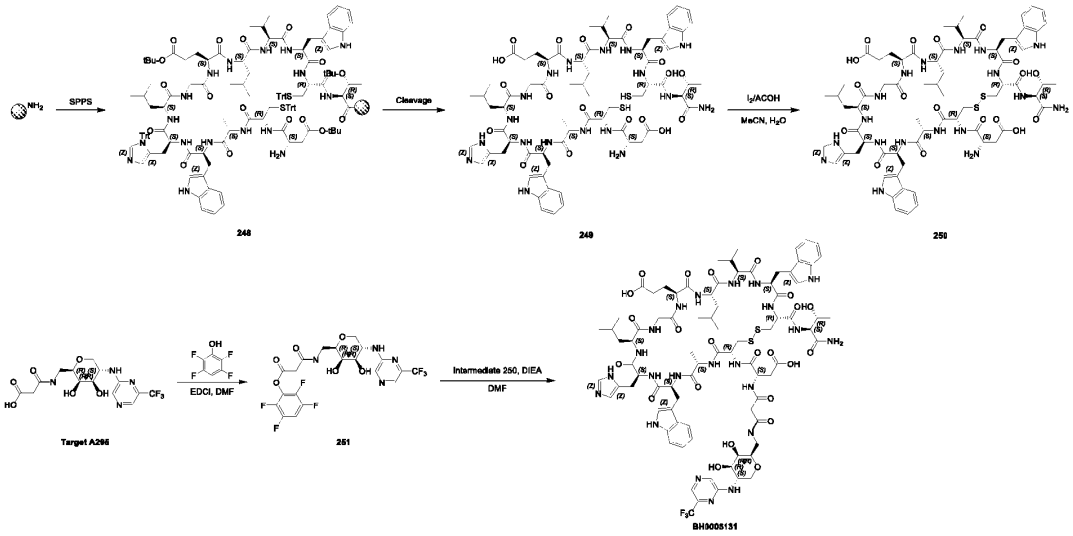
[0488] To a solution of **Intermediate 236** (250.0 mg, 145.18 µmol, 1.00 equiv) and **Intermediate 246** (110.52 mg, 217.78 µmol, 1.50 equiv) in DMF (3 mL) was added DIEA (37.53 mg, 290.37 µmol, 50.58 µL, 2.00 equiv). The mixture was stirred at 20 °C for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **Intermediate 247** (220.0 mg, 98.0% purity, 71.9% yield) as a white solid. LCMS: RT = 0.651 min, MS calcd: M_{av} = 2063.35, mass observed: $[M + 2H]^{2+}$ = 1032.40, $[M + 3H]^{3+}$ =688.50.

[0489] Preparation of **BH0005130**



[0490] To a solution of **Target A292** (55.75 mg, 42.65 µmol, 1.10 equiv) and **Intermediate 247** (80 mg, 38.77 µmol, 1.00 equiv) in DMF (1 mL) and H2O (1 mL) was added CuSO4 (0.4 M, 96.93 µL, 1 .00 equiv), sodium ascorbate (0.4 M, 290.79 µL, 3.00 equiv) and THPTA (16.85 mg, 38.77 µmol, 1.00 equiv) under nitrogen atmosphere at 0 °C, and the resulting mixture was stirred for 2 h at 0 ºC. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H_2O; B: MeCN), followed by lyophilization to afford **BH0005130** (60.7 mg, 98.5% purity, 45.7% yield) as a white solid. LCMS: RT = 1.515 min, MS cal.: 3370.65, mass observed: $[M + 2H]^{2+}$ =1686.30, $[M + 3H]^{3+}$ =1124.30, $[M + 4H]^{4+}$ =843.50.

EXAMPLE 54. Procedure for preparation of BH0005131, BH0004965, BH0004966, BH0004967, BH0004968, BH0004868.



[0491] ***Preparation of Intermediate 250:***

Peptide was synthesized using standard Fmoc chemistry (Rink AM resin).

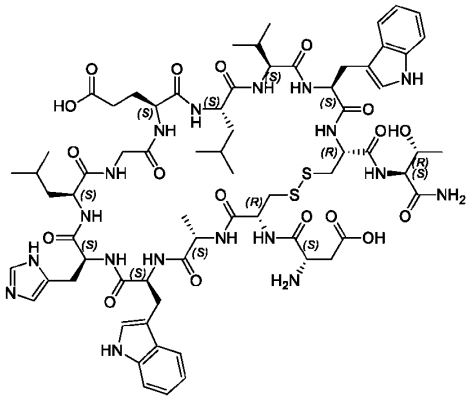
1) Resin preparation: To the vessel containing Rink Amide AM resin (14.28 g, 5.00 mmol, 0.35 mmol/g) and DMF (500 mL) was bubbled with N_2 for 2 h at 25 °C. Then 20% piperidine in DMF (1000 mL) was added and the mixture was bubbled with N_2 for 30 min at 25 °C. The mixture was filtered and washed with DMF (1000 mL) * 5 before proceeding to next step.
2) Coupling: A solution of Fmoc-Thr(*t*Bu)-OH (5.96 g, 15.00 mmol, 3.00 equiv.), HBTU (5.41 g, 14.2 mmol, 2.85 equiv.), DIEA (30.00 mmol, 6.00 equiv.) in DMF (500 mL) was added to the resin with N_2 bubbling for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test. The resin was then washed with DMF (1000 mL) * 5.
3) Deprotection: 20% piperidine in DMF (1000 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The deprotection reaction was monitored by ninhydrin test. The resin was then washed with DMF (1000 mL) * 5.
4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 2-13, Table 26.
5) After all the steps were completed, the resin was washed with DMF (1000 mL) * 5, MeOH (1000 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 248** (Rink AM resin, 5.00 mmol).

Table 26: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

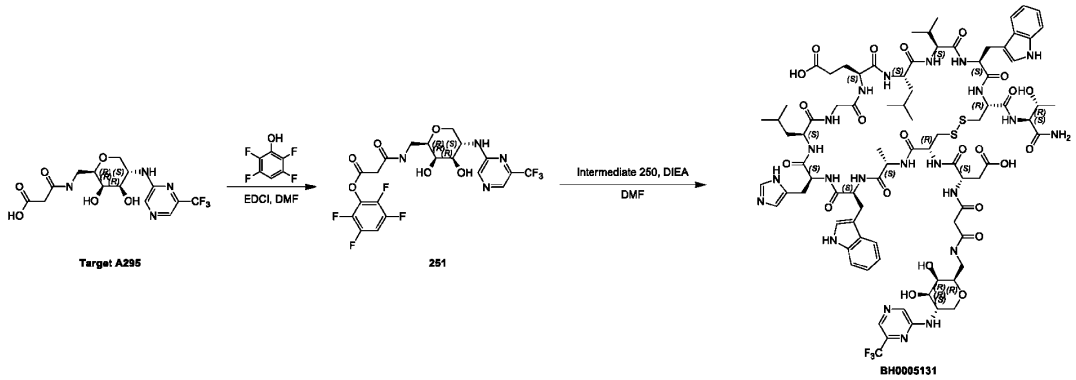
[0492] Peptide cleavage and cyclization.

1) Cleavage solution (TFA/TIS/H_2O, 95/2.5/2.5, v/v/v, 250 mL) was added to the flask containing the side-chain protected resin-bound peptide **Intermediate 248** (Rink AM resin, 20.5 g, 5.00 mmol) at 25 °C and stirred for 2 h.
2) After filtration, the filtrate was collected.
3) The filtrate was precipitated with cold isopropyl ether (1.0 L). After filtration, the solid was washed with isopropyl ether (1.0 L) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 249** (10.5 g, crude) as a white solid.
4) To a mixture of **Intermediate 249** (10.5 g, crude) in HOAc/MeCN/H_2O (4/3/3, v/v/v, 5.0 L) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 250** (1.05 g, 90.0% purity, 13.7% yield) as a white solid. LCMS: RT = 0.872-0.969 min, MS calcd: M_{av} = 1529.74, mass observed: $[M + 2H]^{2+}$ = 765.50.



250

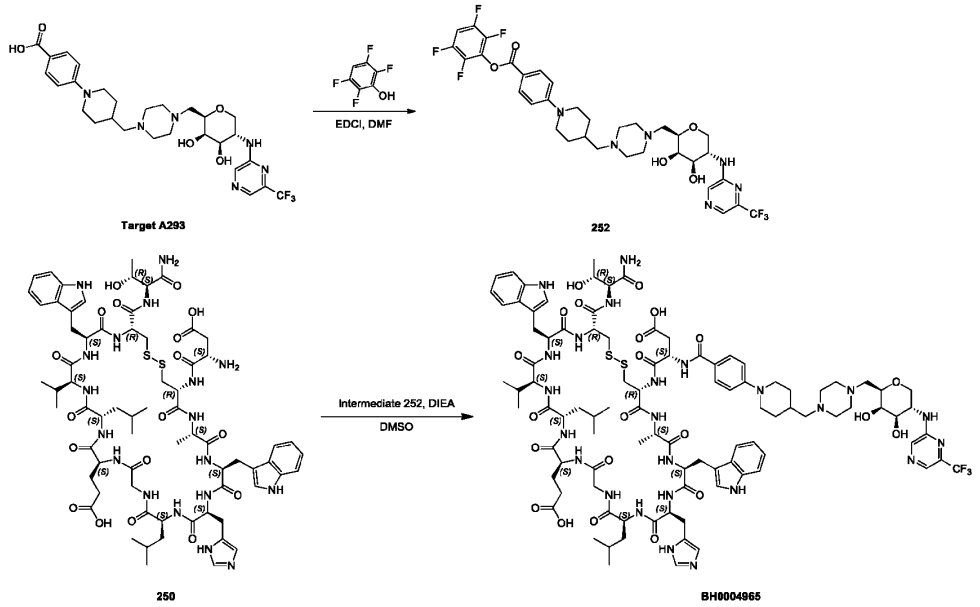
[0493] **BH0005131** was synthesized using the same procedure as **BH0004980** which was performed by following the procedure mentioned in **[0479]** – **[0480]**.



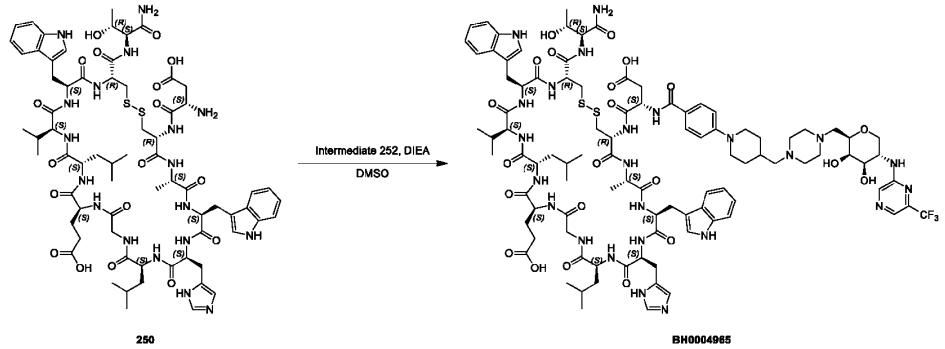
Target A295 251 BH0005131

[0494] 50 mg of **Target A295** with **Intermediate 250** afforded **BH0005131** (3.7 mg, 90.3% purity, 19.8 % yield) as a white solid. LCMS: RT = 1.473 min, MS calcd: Mav = 1906.03, mass observed: [M + 2H]2+ = 953.60.

[0495] Preparation of **BH0004965**

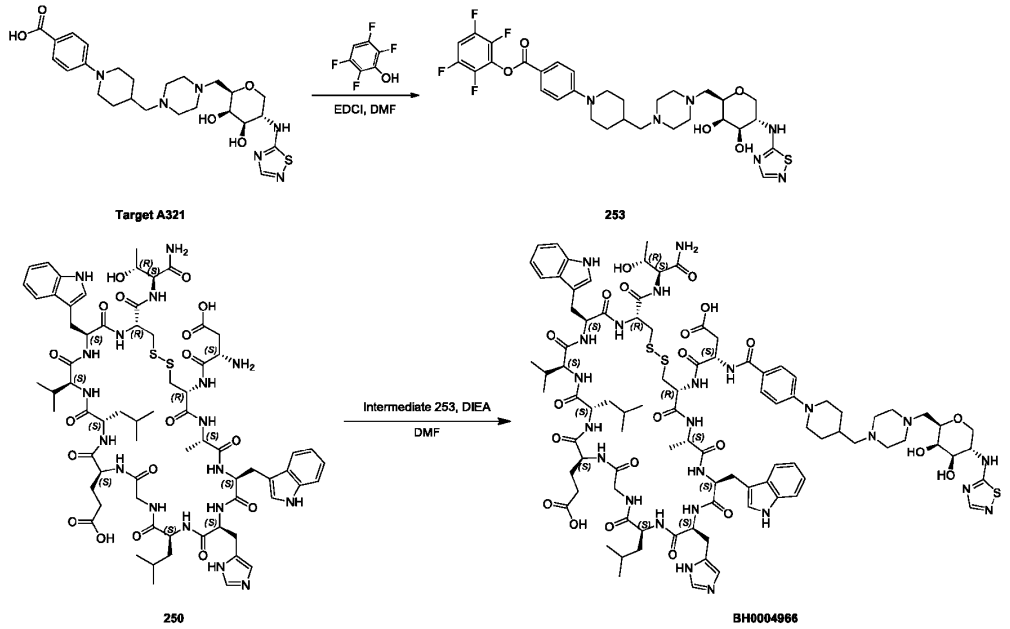


[0496] **BH0004965** was synthesized using the same procedure as **BH0005135, BH0004963** which was performed by following the procedure mentioned in **[0481]** – **[0482]**, **[0463]** – **[0466]**.

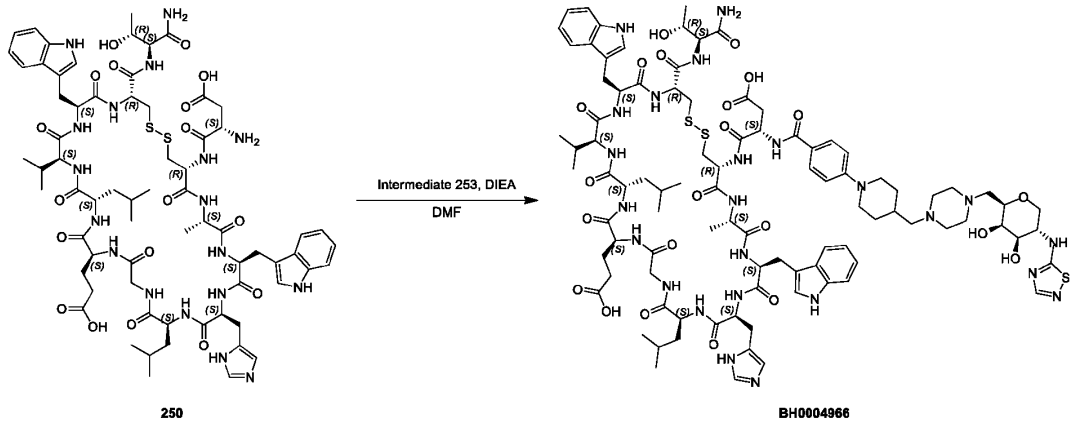


[0497] 36 mg of **Intermediate 252** with **Intermediate 250** afforded **BH0004965** (17 mg, 98.2% purity, 16.3% yield) as a white solid. LCMS: RT = 1.430 min, MS calcd: M_{av} = 2106.35, mass observed: $[M + 2H]^{2+}$ = 1053.70, $[M + 3H]^{3+}$ = 702.70.

[0498] Preparation of **BH0004966**



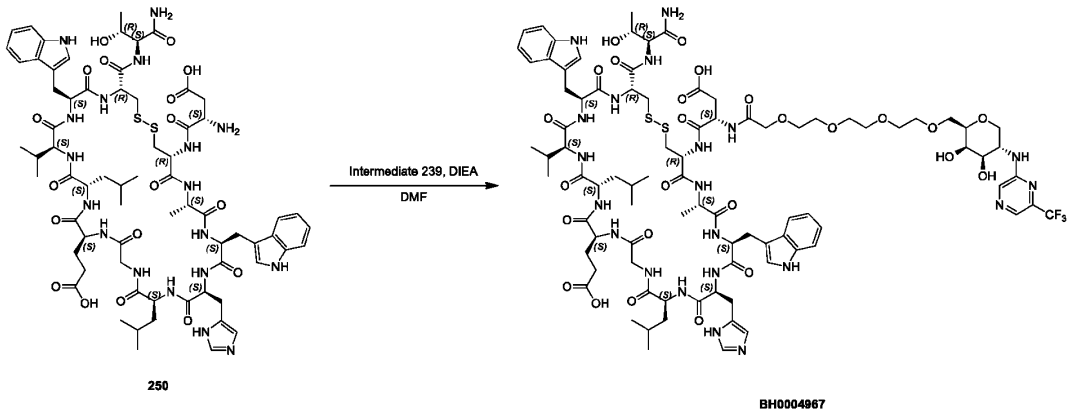
[0499] **BH0004966** was synthesized using the same procedure as **BH0005135, BH0004963** which was performed by following the procedure mentioned in **[0481]** – **[0482]**, **[0463]** – **[0466]**.



[0500] A mixture of **Intermediate 250** (110.50 mg, 72.23 µmol, 1.10 equiv.) and **Intermediate 253** (44.7 mg, 65.67 µmol, 1.00 equiv), DIEA (42.43 mg, 328.33 µmol, 57.19 µL, 5.00 equiv.) in DMF (2 mL) was stirred at 20 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H2O; B: MeCN), followed by lyophilization to afford **BH0004966** (42.3 mg, 98.6% purity, 31.1% yield) as a white solid. LCMS: RT = 1.358 min, MS calcd: Mav = 2044.38, mass observed: $[M + 2H]^{2+}$ = 1022.80, $[M + 3H]^{3+}$ = 682.30.

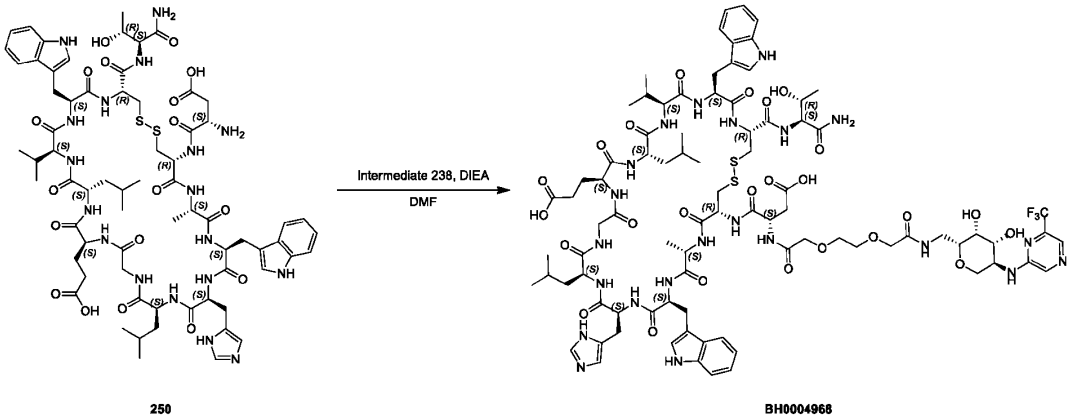
[0501] **BH0004967, BH0004968** were synthesized using the same procedure as **BH0004966,** which was performed by following the procedure mentioned in **[0498]** – **[0500].**

[0502] Preparation of **BH0004967**



[0503] 42.3 mg of **Intermediate 239** with **Intermediate 250** afforded **BH0004967** (64 mg, 98.6% purity, 48.0% yield) as a white solid. LCMS: RT = 1.477 min, MS calcd: M_{av} = 2011.16, mass observed: $[M + 2H]^{2+}$ = 1006.20.

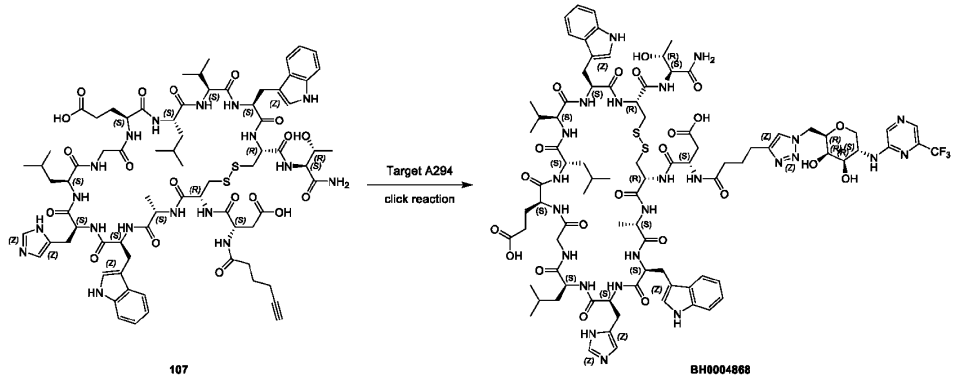
[0504] Preparation of **BH0004968**



[0505] 44.3 mg of **Intermediate 238** with **Intermediate 250** afforded **BH0004968** (47.6 mg, 97.4% purity, 35.8% yield) as a white solid. LCMS: RT = 1.473 min, MS calcd: M_{av} = 1980.11, mass observed: $[M + H]^{+}$ = 1980.20, $[M + 2H]^{2+}$ = 990.70.

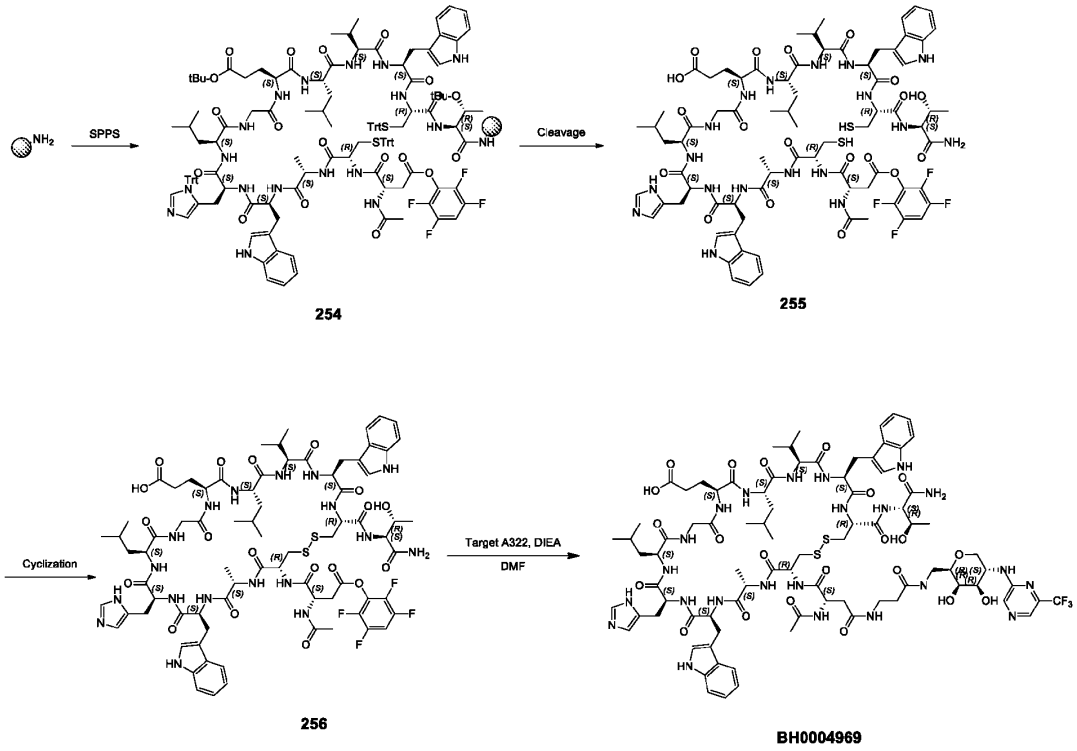
[0506] Preparation of **BH0004868**

[0507] **BH0004868** was synthesized using the same procedure as **BH0002640,** which was performed by following the procedure mentioned in **[0200]** – **[0204]**.



[0508] 18.11 mg of **Target A294** with **Intermediate 107** afforded **BH0004868** (37.5 mg, 97.0% purity, 37.7% yield) as a white solid. LCMS: RT = 1.474 min, MS calcd: M_{av} = 1958.11, mass observed: $[M + H]^+$ = 1958.20, $[M + 2H]^{2+}$ = 979.70.

EXAMPLE 55. Procedure for preparation of BH0004969, BH0004926, BH0004927, BH0004928, BH0004970, BH0004869.



[0509] ***Preparation of Intermediate 256:***

Peptide was synthesized using standard Fmoc chemistry (Rink AM resin).

1) Resin preparation: To the vessel containing Rink Amide AM resin (14.28 g, 5.00 mmol, 0.35 mmol/g) and DMF (500 mL) was bubbled with N_2 for 2 h at 25 °C. Then 20% piperidine in DMF (1000 mL) was added and the mixture was bubbled with N_2 for 30 min at 25 °C. The mixture was filtered and washed with DMF (1000 mL) * 5 before proceeding to next step.

2) Coupling: A solution of Fmoc-Thr(*t*Bu)-OH (5.96 g, 15.00 mmol, 3.00 equiv.), HBTU (5.41 g, 14.2 mmol, 2.85 equiv.), DIEA (30.00 mmol, 6.00 equiv.) in DMF (500 mL) was added to the resin with N_2 bubbling for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test. The resin was then washed with DMF (1000 mL) * 5.

3) Deprotection: 20% piperidine in DMF (1000 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The deprotection reaction was monitored by ninhydrin test. The resin was then washed with DMF (1000 mL) * 5.

4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 2-16, Table 27.

5) After all the steps were completed, the resin was washed with DMF (1000 mL) * 5, MeOH (1000 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 254** (Rink AM resin, 5.00 mmol).

Table 27: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Asp(OAll)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	AC	AC2O:NMM:DMF=10;5;85
15	De-OAll	$PhSiH_3$, $Pd(PPh_3)_4$
16	2,3,5,6-tetrafluorophenol (20.00 equiv.)	DIC (18.00 equiv.)

[0510] Peptide cleavage and cyclization.

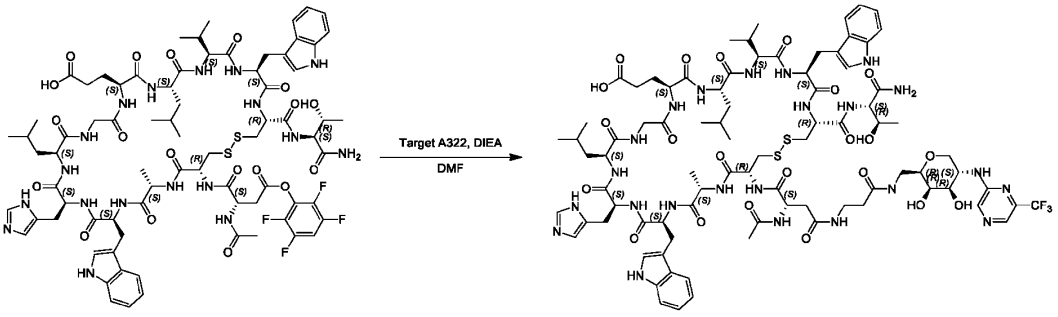
1) Cleavage solution (TFA/TIS/H_2O, 95/2.5/2.5, v/v/v, 250 mL) was added to the flask containing the side-chain protected resin-bound peptide **Intermediate 254** (Rink AM resin, 20.5 g, 5.00 mmol) at 25 °C and stirred for 2 h.

2) After filtration, the filtrate was collected.

3) The filtrate was precipitated with cold isopropyl ether (1.0 L). After filtration, the solid was washed with isopropyl ether (1.0 L) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 255** (10.5 g, crude) as a white solid.

4) To a mixture of **Intermediate 255** (10.5 g, crude) in HOAc/MeCN/H_2O (4/3/3, v/v/v, 5.0 L) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 256** (630 mg, 90.0% purity, 7.33% yield) as a white solid. LCMS: RT = 0.653 min, MS calcd: M_{av} = 1719.83, mass observed: $[M + 2H]^{2+}$ = 860.91.

[0511] Preparation of **BH0004969**

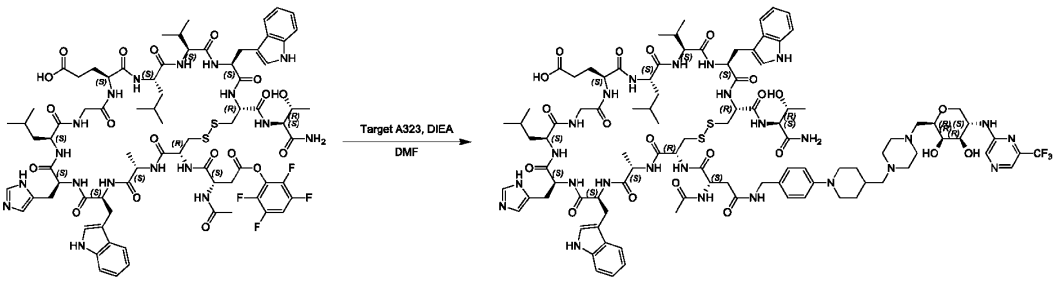


256 **BH0004969**

[0512] A mixture of **Intermediate 256** (70 mg, 40.70 µmol, 1.00 equiv.) and **Target A322** (15.44 mg, 40.70 µmol, 1.00 equiv), DIEA (5.26 mg, 40.70 µmol, 7.09 µL, 1.00 equiv.) in DMF (1 mL) was stirred at 20 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H2O; B: MeCN), followed by lyophilization to afford **BH0004969** (36.0 mg, 93.6% purity, 42.8% yield) as a white solid. LCMS: RT = 1.488 min, MS calcd: Mav = 1933.10, mass observed: $[M + H]^+$ = 1933.30, [M + 2H]2+ = 967.00, [M + 3H]3+ = 645.30.

[0513] **BH0004926, BH0004927, BH0004928, BH0004970** was synthesized using the same procedure as **BH0004969,** which was performed by following the procedure mentioned in **[0509]** – **[0512]**

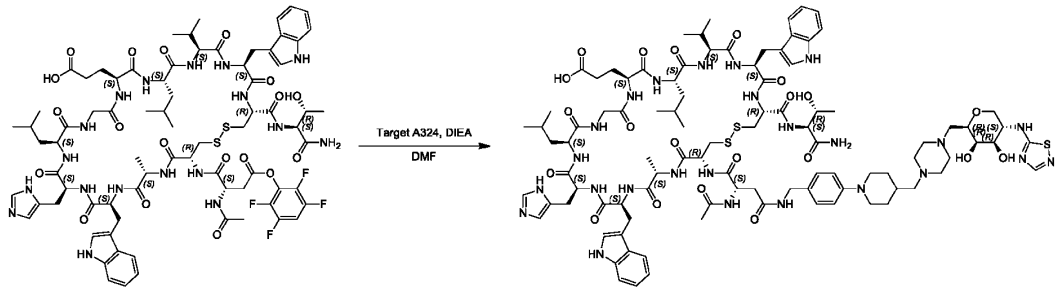
[0514] Preparation of **BH0004926**



256 **BH0004926**

[0515] 46.4 mg of **Target A323** with **Intermediate 256** afforded **BH0004926** (60 mg, 95.6% purity, 46.2% yield) as a white solid. LCMS: RT = 1.384 min, MS calcd: M_{av} = 2133.42, mass observed: $[M + 2H]^{2+}$ = 1067.30, $[M + 3H]^{3+}$ = 712.00.

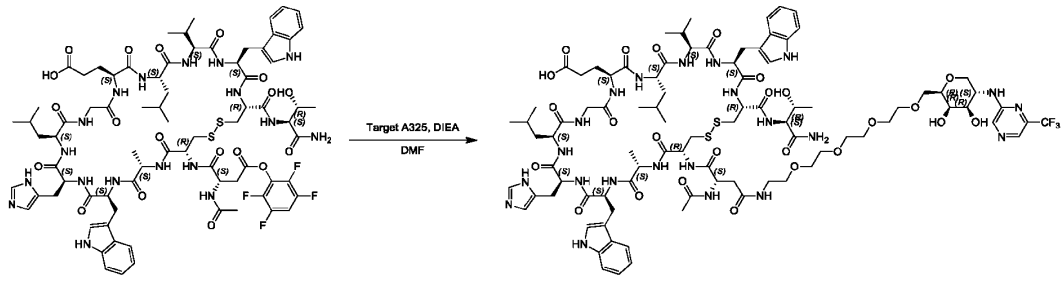
[0516] Preparation of **BH0004927**



256 BH0004927

[0517] 33.1 mg of **Target A324** with **Intermediate 256** afforded **BH0004927** (35.1 mg, 98.0% purity, 28.5% yield) as a white solid. LCMS: RT = 1.342 min, MS calcd: M_{av} = 2071.45, mass observed: $[M + 2H]^{2+}$ = 1036.60, $[M + 3H]^{3+}$ = 691.20.

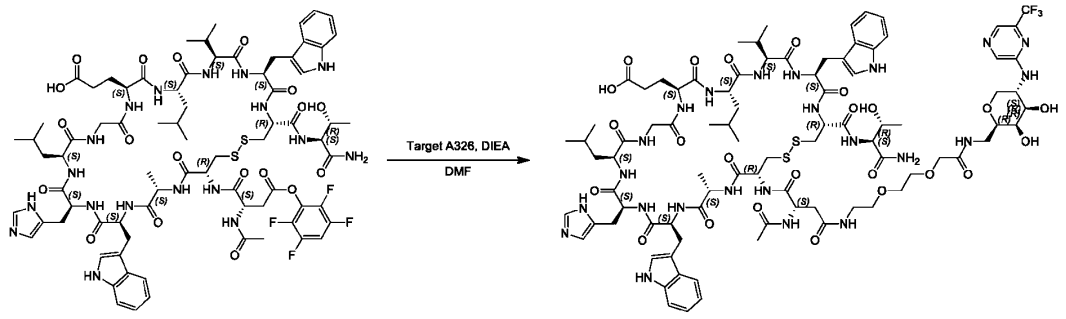
[0518] Preparation of **BH0004928**



256 BH0004928

[0519] 35.6 mg of **Target A325** with **Intermediate 256** afforded **BH0004928** (47.0 mg, 97.8% purity, 38.7% yield) as a white solid. LCMS: RT = 1.465 min, MS calcd: M_{av} = 2038.23, mass observed: $[M + 2H]^{2+}$ = 1019.80.

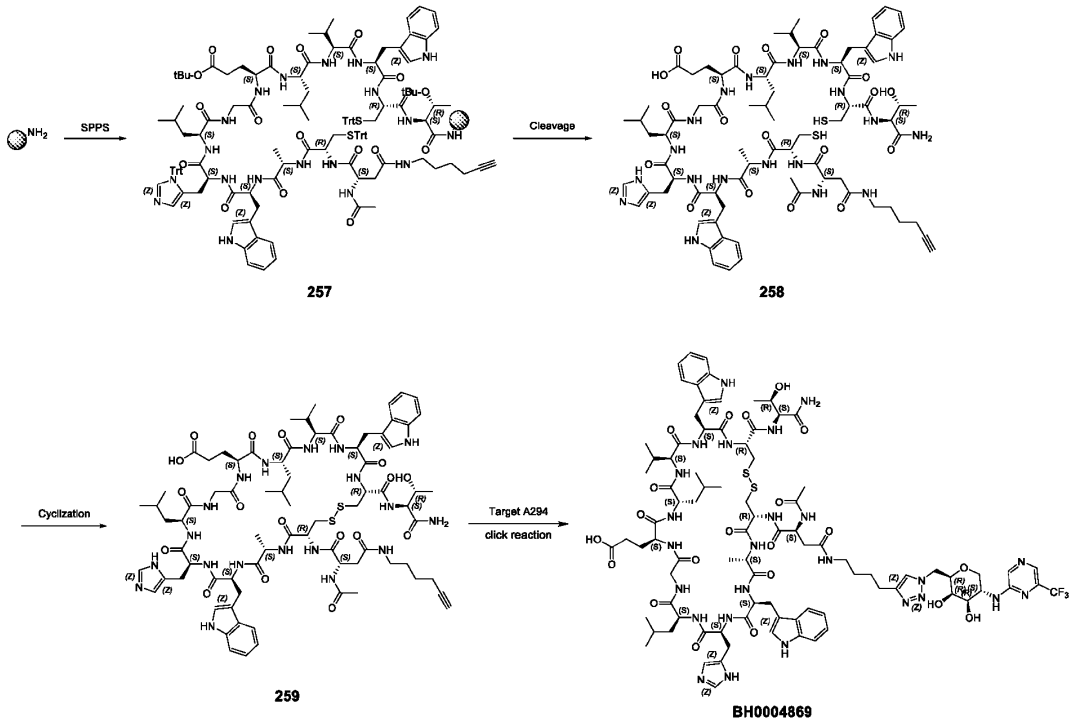
[0520] Preparation of **BH0004970**



256 BH0004970

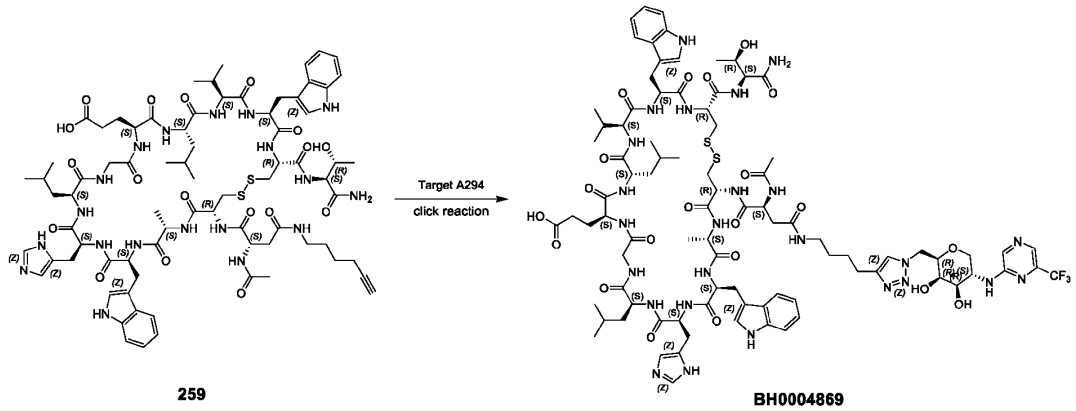
[0521] 15.0 mg of **Target A326** with **Intermediate 256** afforded **BH0004970** (26.0 mg, 95.0% purity, 37.1% yield) as a white solid. LCMS: RT = 1.461 min, MS calcd: M_{av} = 2007.18, mass observed: $[M + 2H]^{2+}$ = 1004.20.

[0522] Preparation of **BH0004869**



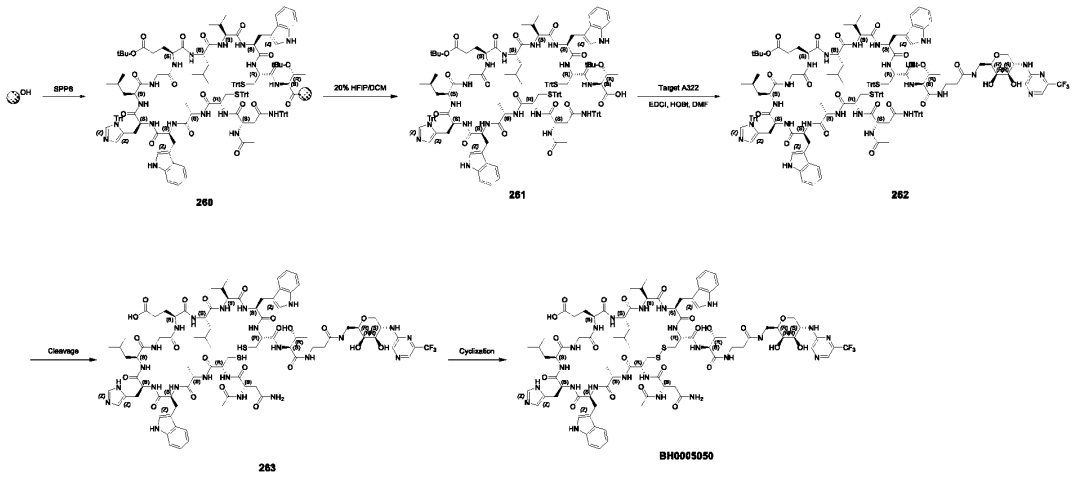
257 258 259 BH0004869

[0523] **Intermediate 259** was synthesized using the same procedure as **Intermediate 256,** which was performed by following the procedure mentioned in **[0509]** – **[0510]** but reacting with alkyne amine after Alloc deprotection instead of reacting with TFP-OH.



[0524] To a solution of **Target A294** (10.84 mg, 32.42 µmol, 1.20 equiv) and **Intermediate 259** (44.6 mg, 27.02 µmol, 1.00 equiv) in DMF (1 mL) and H2O (1 mL) was added $CuSO_4$ (0.4 M, 67.54 µL, 1 .00 equiv), sodium ascorbate (0.4 M, 202.61 µL, 3.00 equiv) and THPTA (11.74 mg, 27.02 µmol, 1.00 equiv) under nitrogen atmosphere at 0 °C, and the resulting mixture was stirred for 2 h at 0 ºC. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.075% TFA/H2O; B: MeCN), followed by lyophilization to afford **BH0004869** (26.7 mg, 95.1% purity, 47.3% yield) as a white solid. LCMS: RT = 1.487 min, MS cal.: 1985.17, mass observed: $[M + H]^+$ =1986.20. $[M + 2H]^{2+}$ =993.20, $[M + 3H]^{3+}$ =662.60, $[M + 4H]^{4+}$ =843.50.

EXAMPLE 56. Procedure for preparation of BH0005050, BH0004971, BH0005051, BH0004929, BH0005052, BH0004930.



[0525] ***Preparation of Intermediate 261:***

Peptide was synthesized using standard Fmoc chemistry (CTC resin).

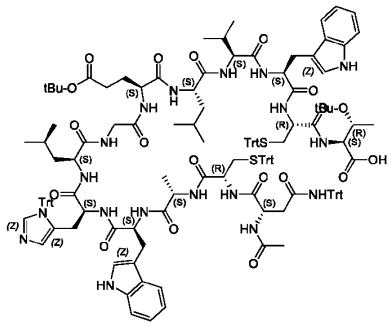
1) Resin preparation: To the vessel containing CTC resin (5.0 g, 5.0 mmol, 1.00 mmol/g) and Fmoc-Thr(tBu)-OH (1.98 g, 5 mmol, 1.00 equiv.) in DCM (100 mL) was added DIEA (4.00 equiv.) dropwise and mixed for 2 h with N2 bubbling at 25 °C. Then MeOH (5 mL) was added and bubbled with N2 for another 30 min. The resin was washed with DMF (200 mL) * 5, followed by the addition of 20% piperidine in DMF (200 mL) and bubbled with N2 for 30 min at 25 °C for Fmoc deprotection. The mixture was filtered and the resin was washed with DMF (200 mL) * 5 before proceeding to next step.
2) Coupling: A solution of Fmoc-Cys(Trt)-OH (8.78 g, 15.0 mmol, 3.00 equiv.), HBTU (5.4 g, 14.2 mmol, 2.85 equiv.) in DMF (100 mL) was added to the resin with N_2 bubbling. Then DIEA (6.00 equiv.) was added to the mixture dropwise and bubbled with N_2 for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test, if it showed colorless, the coupling was completed. The resin was then washed with DMF (200 mL) * 5.
3) Deprotection: 20% piperidine in DMF (200 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The resin was then washed with DMF (200 mL) * 5.
4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 3-14, Table 28.
5) After all the steps were completed, the resin was washed with DMF (200 mL) * 5, MeOH (200 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 261** (CTC resin, 5 mmol).

Table 28: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	AC	AC2O:NMM:DMF=10;5;85

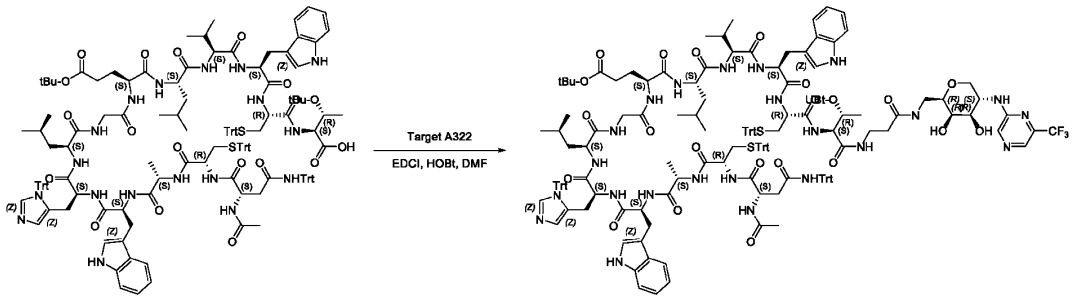
[0526] Peptide cleavage and cyclization, TFA de-protection and disulfide formation:

1) Cleavage: A solution of 20% HFIP/DCM (1g/20mL) was added to the resin above at room temperature and stirred for 30min twice. After filtration, the filtrate was followed by lyophilization to afford **Intermediate 261**(9.0 g, crude) as a white solid. LCMS: RT = 2.246-2.369 min, MS calcd: M_{av} = 2655.26 mass observed: $[M + 22 + 2H]^{2+}$ = 1339.48.



261

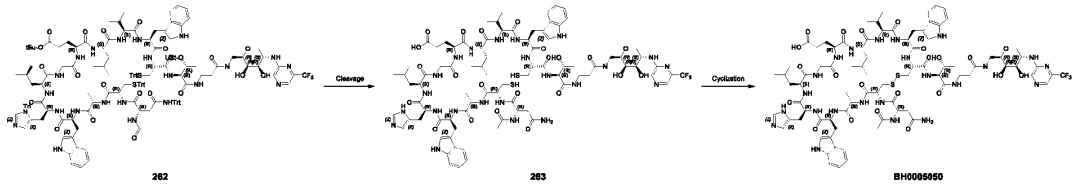
[0527] ***Preparation of Intermediate 262:***



261 **262**

[0528] To a solution of **Intermediate 261** (200 mg, 75.32 μmol, 1.10 equiv), **Target A322** (25.97 mg, 68.47 μmol, 1.00 equiv), HOBt (18.51 mg, 136.95 μmol, 2.00 equiv) in DMF (2 mL) was added EDCI (26.25 mg, 136.95 μmol, 2.00 equiv). The mixture was stirred at 20 ºC for 1 h. After completion monitored by LC-MS, the mixture was added to 0.5 M HCl (cold, 30 mL), there appeared lots of white solid. After filtered, the solid was dried in lyophilization to afford **Intermediate 262** (200 mg, crude) as a white solid.

[0529] Preparation of **BH0005050**

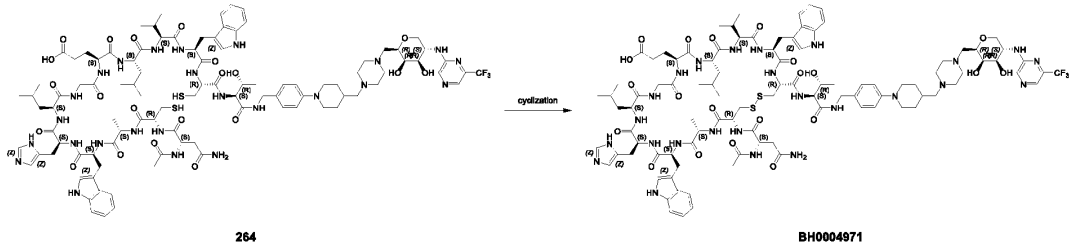


[0530] A mixture of **Intermediate 262** (200 mg, crude) in 95% TFA/2.5% TIS/2.5% H_2O (10 mL) was stirred at 20 ºC for 1 h. After filtration, the filtrate was collected, the filtrate was precipitated with cold isopropyl ether (50 mL). After filtration, the solid was washed with isopropyl ether (50 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 263** (100 mg, crude) as a white solid

[0531] To a mixture of **Intermediate 263** (100 mg, crude) in MeCN/H_2O (3/7, v/v, 60 mL) was added 1 M NH4HCO3 to pH=8.0, then the mixture was stirred at 25 °C for 16 h. The mixture was added 1 M HCl to Ph=6.0. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **BH0005050** (32.2 mg, 95.1% purity, 27.6% yield) as a white solid. LCMS: RT = 1.456 min, MS calcd: M_{av} = 1933.10, mass observed: $[M + H]^+$ = 1934.20. $[M + 2H]^{2+}$ = 967.70, $[M + 3H]^{3+}$ = 645.30.

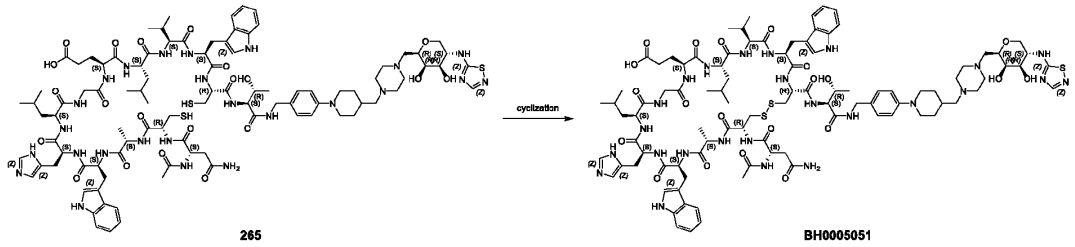
[0532] **BH0004971, BH0005051, BH0004929, BH0005052** was synthesized using the same procedure as **BH0005050,** which was performed by following the procedure mentioned in **[0525]** – **[0531]**.

[0533] Preparation of **BH0004971**



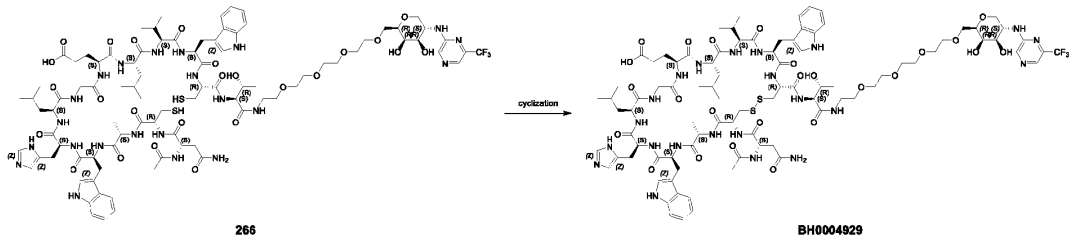
[0534] 80 mg of **Intermediate 264** afforded **BH0004971** (20.0 mg, 99.6% purity, 25.0% yield) as a white solid. LCMS: RT = 1.401 min, MS calcd: M_{av} = 2133.42, mass observed: $[M + 2H]^{2+}$ = 1067.30, $[M + 3H]^{3+}$ = 712.10.

[0535] Preparation of **BH0005051**



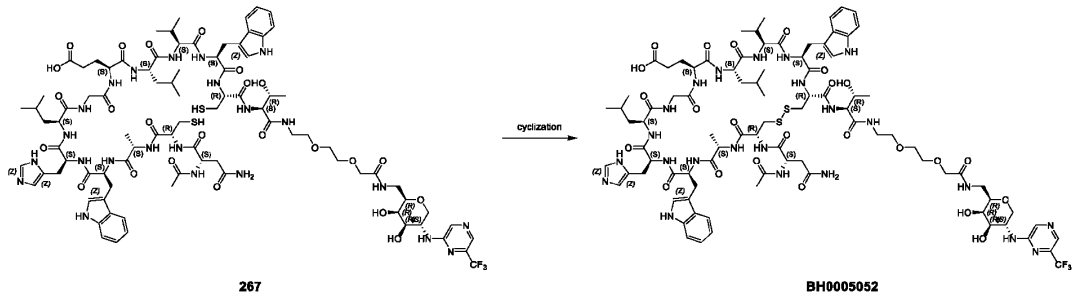
[0536] 60 mg of **Intermediate 265** afforded **BH0005051** (Q1: 10 mg, Q2: 2 mg, Q1: 98.7% Q2: 99.2% purity, 20.3% yield) as a white solid. LCMS: RT = 1.342 min, MS calcd: M_{av} = 2071.45, mass observed: $[M + 2H]^{2+}$ = 1036.30, $[M + 3H]^{3+}$ = 691.40.

[0537] Preparation of **BH0004929**



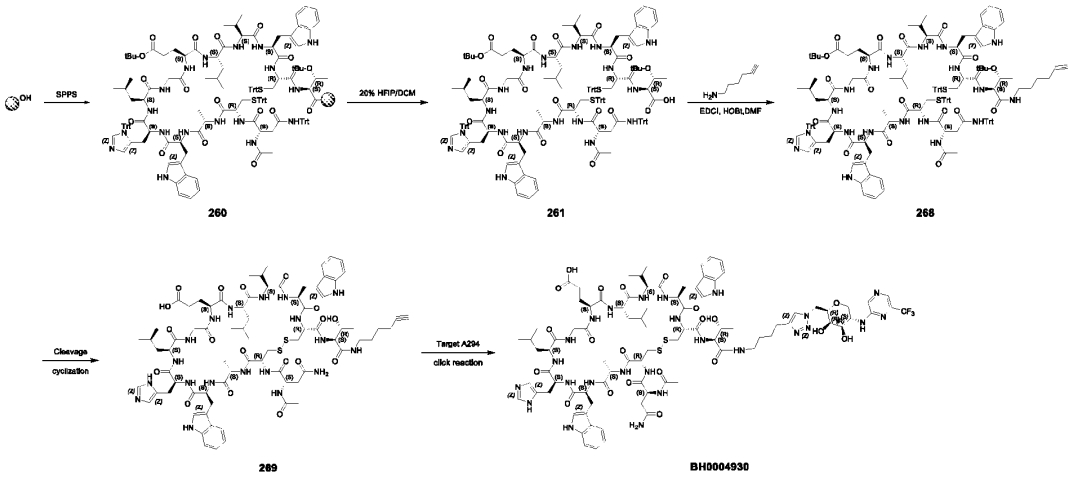
[0538] 100 mg of **Intermediate 266** afforded **BH0004929** (32 mg, 96.8% purity, 32.3% yield) as a white solid. LCMS: RT = 1.496 min, MS calcd: M_{av} = 2038.23, mass observed: $[M + 2H]^{2+}$ = 1019.80, $[M + 3H]^{3+}$ = 680.40.

[0539] Preparation of **BH0005052**

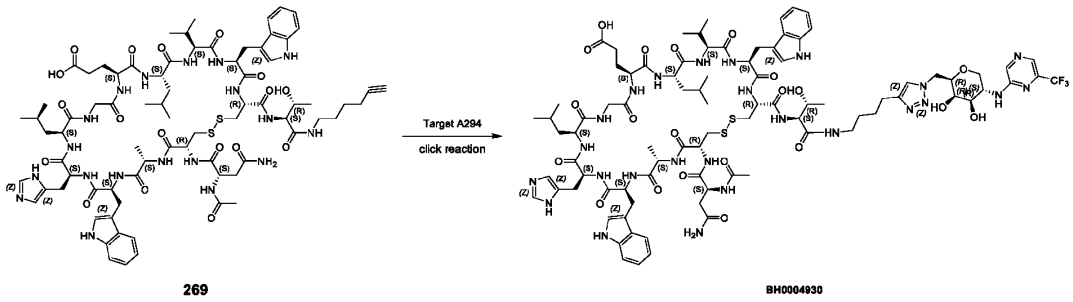


[0540] 120 mg of **Intermediate 267** afforded **BH0005052** (51 mg, 98.2% purity, 32.3% yield) as a white solid. LCMS: RT = 1.468 min, MS calcd: M_{av} = 2007.18, mass observed: $[M + 2H]^{2+}$ = 1004.20, $[M + 3H]^{3+}$ = 670.00.

[0541] Preparation of **BH0004930**

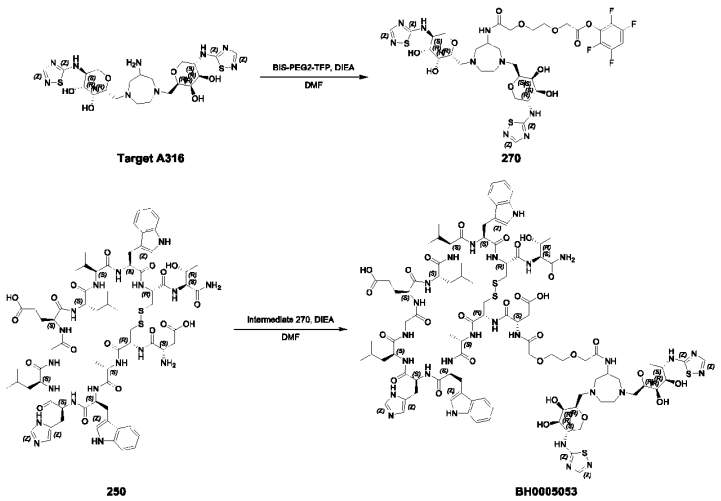


[0542] **BH0004930** was synthesized using the same procedure as **BH0005050, BH0004869** which was performed by following the procedure mentioned in **[0525]** – **[0531], [0524]**.

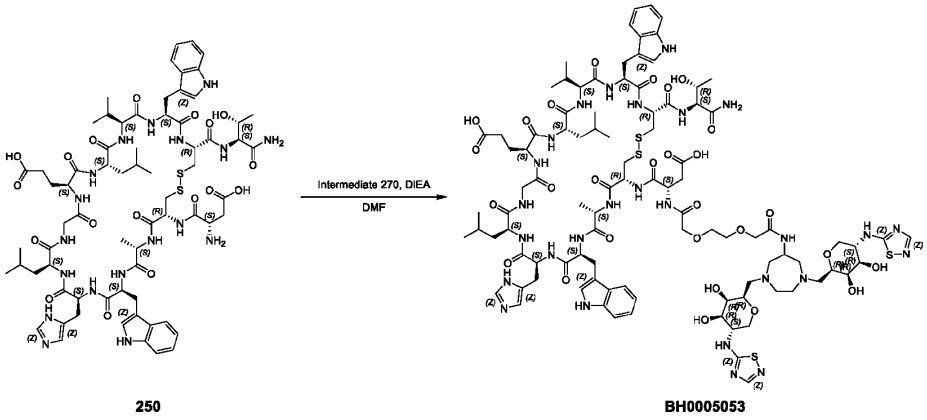


[0543] 22.2 mg of **Target A294** with **Intermediate 269** afforded **BH0004930** (24.0 mg, 91.5% purity, 18.2% yield) as a white solid. LCMS: RT = 1.504 min, MS calcd: M_{av} = 1985.17, mass observed: $[M + H]^+$ = 1986.20, $[M + 2H]^{2+}$ = 993.20, $[M + 3H]^{3+}$ = 662.80.

EXAMPLE 57. Procedure for preparation of BH0005053

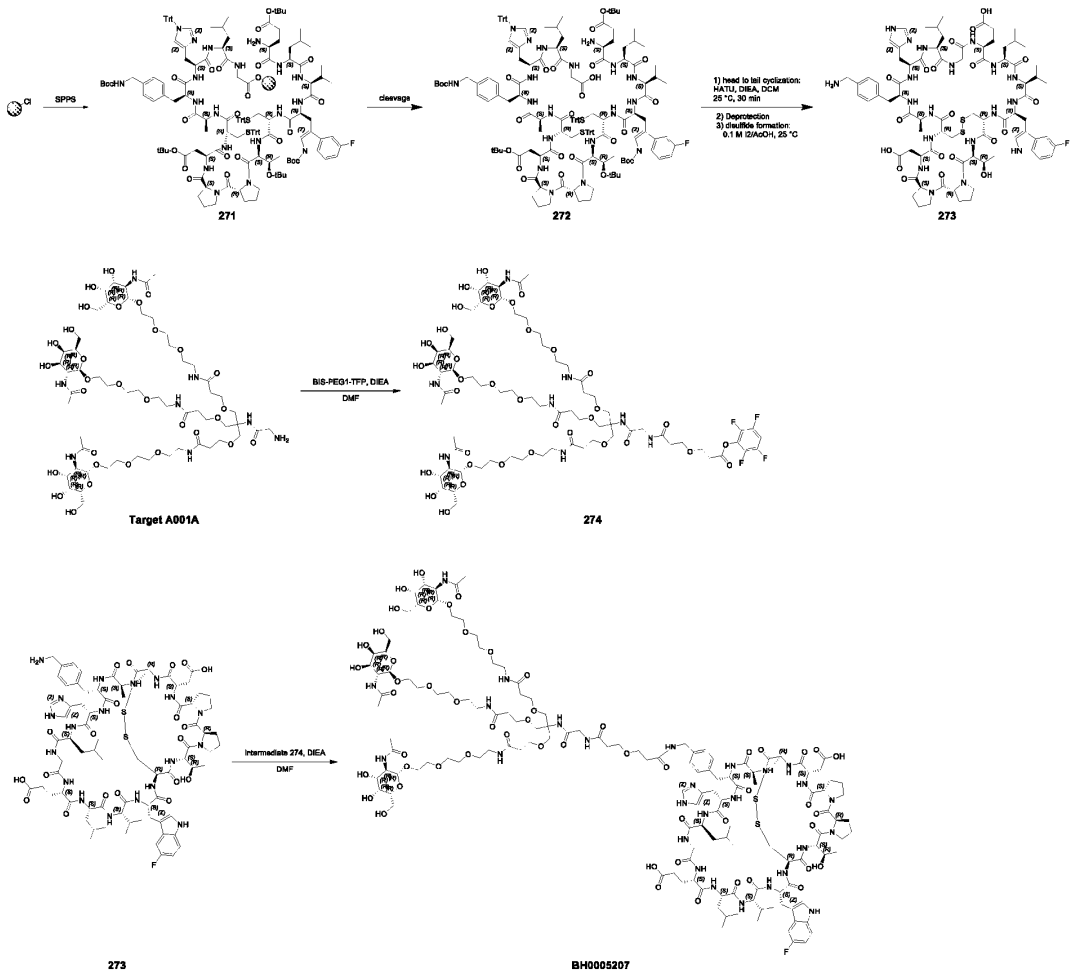


[0544] **BH0005053** was synthesized using the same procedure as **BH0005131, BH0004408** which was performed by following the procedure mentioned in **[0491]** – **[0492], [0453]** – **[0458]**.



[0545] 50.0 mg of **Intermediate 270** with **Intermediate 250** afforded **BH0005053** (50.0 mg, 98.2% purity, 42.4% yield) as a white solid. LCMS: RT = 1.359 min, MS calcd: M_{av} = 2245.54, mass observed: $[M + 2H]^{2+}$ = 1123.30, $[M + 3H]^{3+}$ = 749.40

EXAMPLE 58. Procedure for preparation of BH0005207, BH0005208, BH0005209, BH0005210



[0546] ***Preparation of Intermediate 273:***

Peptide was synthesized using standard Fmoc chemistry (CTC resin).

1) Resin preparation: To the vessel containing CTC resin (0.5 g, 0.5 mmol, 1.00 mmol/g) and Fmoc-Gly-OH (0.14 g, 0.5 mmol, 1.00 equiv.) in DCM (50 mL) was added DIEA (4.00 equiv.) dropwise and mixed for 2 h with N2 bubbling at 25 °C. Then MeOH (0.5 mL) was added and bubbled with N2 for another 30 min. The resin was washed with DMF (100 mL) * 5, followed by the addition of 20% piperidine in DMF (100 mL) and bubbled with N2 for 30 min at 25 °C for Fmoc deprotection. The mixture was filtered and the resin was washed with DMF (100 mL) * 5 before proceeding to next step.
2) Coupling: A solution of Fmoc-Leu-OH (0.53 g, 1.5 mmol, 3.00 equiv.), HBTU (0.54 g, 1.43 mmol, 2.85 equiv.) in DMF (50 mL) was added to the resin with N_2 bubbling. Then DIEA (6.00 equiv.) was added

to the mixture dropwise and bubbled with N_2 for 30 min at 25 °C. The coupling reaction was monitored by ninhydrin test, if it showed colorless, the coupling was completed. The resin was then washed with DMF (100 mL) * 5.

3) Deprotection: 20% piperidine in DMF (100 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The resin was then washed with DMF (100 mL) * 5.

4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 3-15, Table 29.

5) After all the steps were completed, the resin was washed with DMF (100 mL) * 5, MeOH (100 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 271** (CTC resin, 0.5 mmol).

Table 29: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Gly-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-4-(Boc-aminomethyl)-*L*-phenylalanine (2.00 equiv.)	HATU (1.90 equiv.) and DIEA (4.00 equiv.)
5	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Asp(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-D-Pro-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Thr(*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-5-F-Trp-OH (2.00 equiv.)	HATU (1.90 equiv.) and DIEA (4.00 equiv.)
13	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
15	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

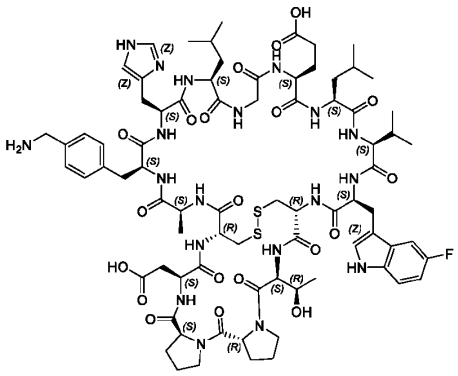
[0547] Peptide cleavage and cyclization, TFA de-protection and disulfide formation:

1) Cleavage: A solution of 1% TFA/DCM (1g/20mL) was added to the resin above at room temperature and stirred for 30mis. After filtration, the filtrate was collected (which contained **Intermediate 272**).

2) Head to tail cyclization: The filtrate was diluted with DCM to give us peptide solution with conc. 1mM, then HATU (2.00 equiv.) was added, followed by the addition of DIEA (4.00 equiv.), and the resulting mixture was stirred for 30 min at 25 °C. After completion monitored by LC-MS, the reaction was washed with 1 M HCl (200 mL), then washed with H_2O (200 mL). The organic layer was collected and concentrated under reduced pressure to give a residue.

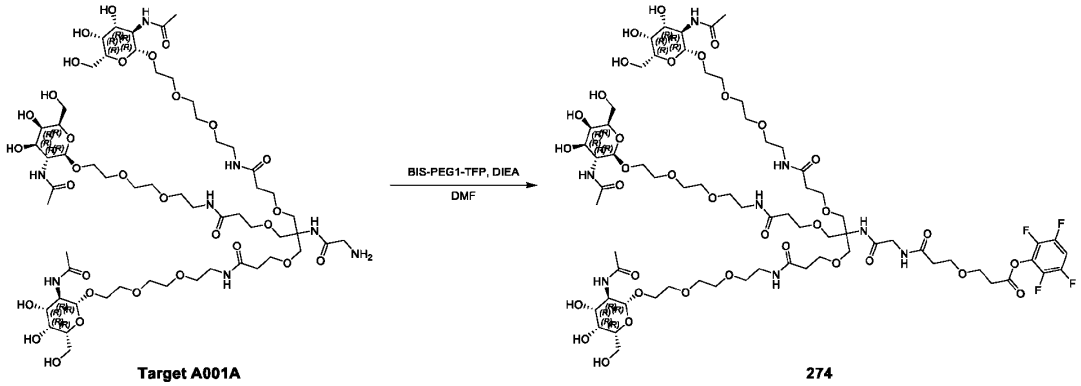
3) Deprotection: To the residue from step 2 was added a solution of TFA/TIS/H_2O/3-mercaptopropanoic acid (v/v/v/v, 92.5/2.5/2.5/2.5, 1g/20ml, 20V), and the resulting mixture was stirred for 2 h at 25 °C. The mixture was precipitated with cold isopropyl ether (cold, 5V). After filtration, the solid was washed with isopropyl ether (100 mL) twice, and the crude peptide was dried under reduced pressure.

4) Disulfide formation: To the crude peptide from step 3 in MeCN/H_2O (1/1, v/v, 1mM peptide solution) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 273** (116.7 mg, 97.9% purity, 13.6% yield) as a white solid. LCMS: RT = 1.372 min, MS calcd: M_{av} = 1714.94, mass observed: $[M + H]^+$ = 1716.00, $[M + 2H]^{2+}$ = 858.20.



273

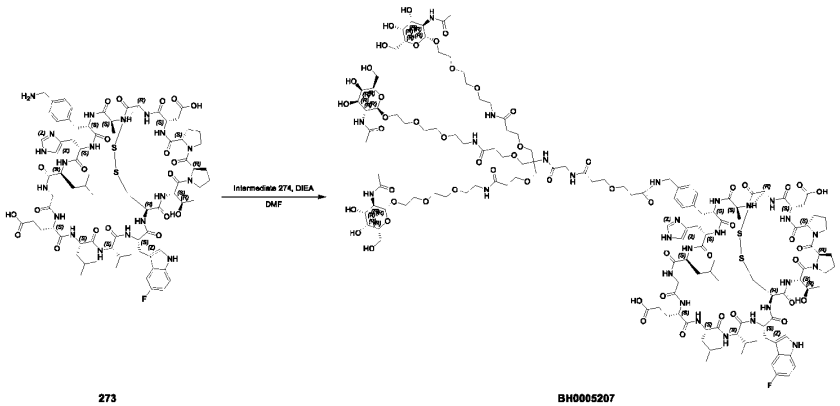
[0548] ***Preparation of Intermediate 274:***



Target A001A **274**

[0549] To a solution of **Bis-PEG1-TFP** (1.18 g, 2.58 mmol, 3.00 equiv) in DMF (10 mL) was added a mixture of **Target A001A** (1.2 g, 858.70 µmol, 1.00 equiv) and DIEA (332.94 mg, 2.58 mmol, 448.71 µL, 3 equiv) in 10 mL DMF at 0 °C. The resulting reaction was stirred for 5 min at 0 °C. After completion monitored by LC-MS, the mixture was directly injected into the reverse column, purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **Intermediate 274** (791.69 mg, 95.0% purity, 51.8% yield) as colorless oil. LCMS: RT = 0.757-0.837 min, MS calcd: M_{av} = 1689.65, mass observed: $[M + 2H]^{2+}$ = 845.60.

[0550] Preparation of **BH0005207**

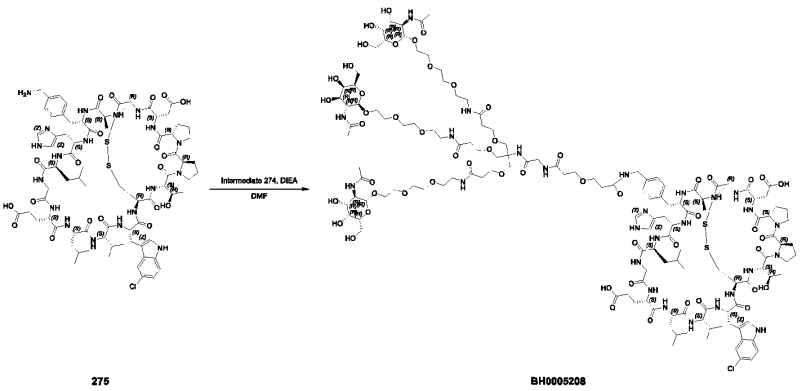


273 BH0005207

[0551] A mixture of **Intermediate 273** (65 mg, 37.90 µmol, 1.00 equiv.) and **Intermediate 274** (76.85 mg, 45.48 µmol, 1.20 equiv), DIEA (14.70 mg, 113.71 µmol, 19.81 µL, 3.00 equiv.) in DMF (2 mL) was stirred at 20 ºC for 1 h. After completion monitored by LC-MS, the reaction was filtered off and purified by prep-HPLC (A: 0.5% Acetic Acid/H2O; B: MeCN), followed by lyophilization to afford **BH0005207** (52.2 mg, 98.4% purity, 41.8% yield) as a white solid. LCMS: RT = 1.344 min, MS calcd: Mav = 3238.52, mass observed: $[M + 2H]^{2+}$ = 1620.23, $[M + 3H]^{3+}$ = 1080.49, $[M + 4H]^{4+}$ = 810.62.

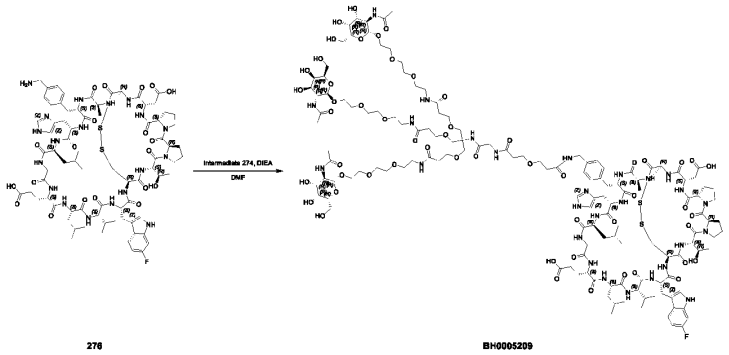
[0552] **BH0005208, BH0005209, BH0005210** was synthesized using the same procedure as **BH0005207** which was performed by following the procedure mentioned in **[0491]** – **[0492]**.

[0553] Preparation of **BH0005208**



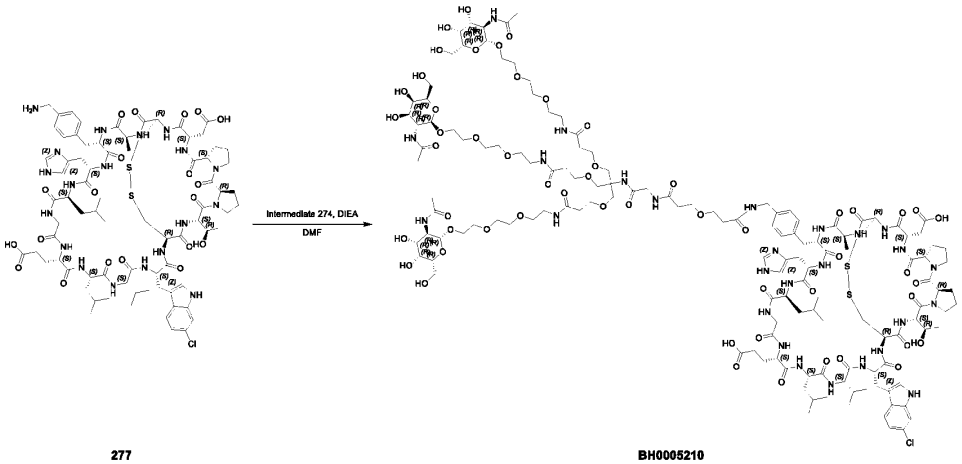
[0554] 76.1 mg of **Intermediate 274** with **Intermediate 275** afforded **BH0005208** (61.0 mg, 96.5% purity, 48.1% yield) as a white solid. LCMS: RT = 1.366 min, MS calcd: M_{av} = 3254.97, mass observed: $[M + 2H]^{2+}$ = 1628.21, $[M + 3H]^{3+}$ = 1085.80, [M + 4H]4+ = 814.61.

[0555] Preparation of **BH0005209**



[0556] 76.8 mg of **Intermediate 274** with **Intermediate 276** afforded **BH0005209** (54.5 mg, 98.3% purity, 43.6% yield) as a white solid. LCMS: RT = 1.331 min, MS calcd: M_{av} = 3238.52, mass observed: $[M + 2H]^{2+}$ = 1620.23, $[M + 3H]^{3+}$ = 1080.49, $[M + 4H]^{4+}$ = 810.62.

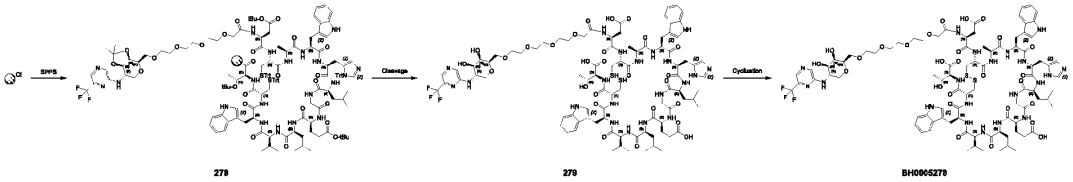
[0557] Preparation of **BH0005210**



277 BH0005210

[0558] 76.1 mg of **Intermediate 274** with **Intermediate 277** afforded **BH0005210** (48.0 mg, 95.6% purity, 37.5% yield) as a white solid. LCMS: RT = 1.369 min, MS calcd: M_{av} = 3254.97, mass observed: $[M + 2H]^{2+}$ = 1628.21, $[M + 3H]^{3+}$ = 1085.80, [M + 4H]4+ = 814.61.

EXAMPLE 59. Procedure for preparation of BH0005278



278 279 BH0005278

[0559] Preparation of **BH0005278**

Peptide was synthesized using standard Fmoc chemistry (CTC resin).

1) Resin preparation: To the vessel containing CTC resin (0.15 g, 0.15 mmol, 1.00 mmol/g) and Fmoc-Thr(*t*Bu)-OH (59.6 mg, 0.15 mmol, 1.00 equiv.) in DCM (10 mL) was added DIEA (4.00 equiv.) dropwise and mixed for 2 h with N2 bubbling at 25 °C. Then MeOH (0.15 mL) was added and bubbled with N2 for another 30 min. The resin was washed with DMF (20 mL) * 5, followed by the addition of 20% piperidine in DMF (20 mL) and bubbled with N2 for 30 min at 25 °C for Fmoc deprotection. The mixture was filtered and the resin was washed with DMF (20 mL) * 5 before proceeding to next step.
2) Coupling: A solution of Fmoc-Cys(Trt)-OH (263.5 mg, 0.45 mmol, 3.00 equiv.), HBTU (162.4 mg, 0.42 mmol, 2.85 equiv.) in DMF (10 mL) was added to the resin with N_2 bubbling. Then DIEA (6.00 equiv.) was added to the mixture dropwise and bubbled with N_2 for 30 min at 25 °C. The coupling reaction

was monitored by ninhydrin test, if it showed colorless, the coupling was completed. The resin was then washed with DMF (20 mL) * 5.

3) Deprotection: 20% piperidine in DMF (20 mL) was added to the resin and the mixture was bubbled with N_2 for 30 min at 25 °C. The resin was then washed with DMF (20 mL) * 5.

4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 3-14, Table 30.

5) After all the steps were completed, the resin was washed with DMF (20 mL) * 5, MeOH (20 mL) * 5, then dried under reduced pressure to afford resin-bound peptide **Intermediate 278** (CTC resin, 0.15 mmol).

Table 30: The list of amino acids and the corresponding reagents used on SPPS.

#	Materials	Coupling reagents
1	Fmoc-Thr(*t*Bu)-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Val-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
5	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Glu(O*t*Bu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Gly-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Leu-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
9	Fmoc-His(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Trp-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Ala-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
12	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
13	Fmoc-Asp(OtBu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
14	Target A293_Int6 (1.50 equiv.)	HATU (1.42 equiv.) and DIEA (3.00 equiv.)

[0560] Peptide cleavage and cyclization.

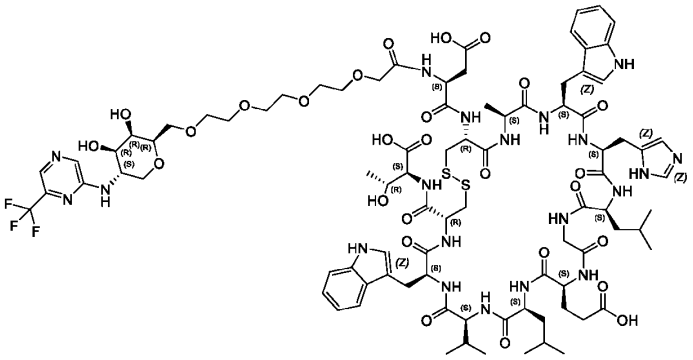
1) Cleavage solution (TFA/TIS/H_2O/3-MPA, 92.5/2.5/2.5/2.5, v/v/v/v, 10 mL) was added to the flask containing the side-chain protected resin-bound peptide **Intermediate 278** (CTC resin, 1.05 g, 0.15 mmol) at 25 °C and stirred for 2 h.

After filtration, the filtrate was collected.

2) The filtrate was precipitated with cold isopropyl ether (50 mL). After filtration, the solid was washed with isopropyl ether (50 mL) twice, and the crude peptide was dried under reduced pressure for 2 h to afford **Intermediate 279** (300 mg, crude) as a white solid.

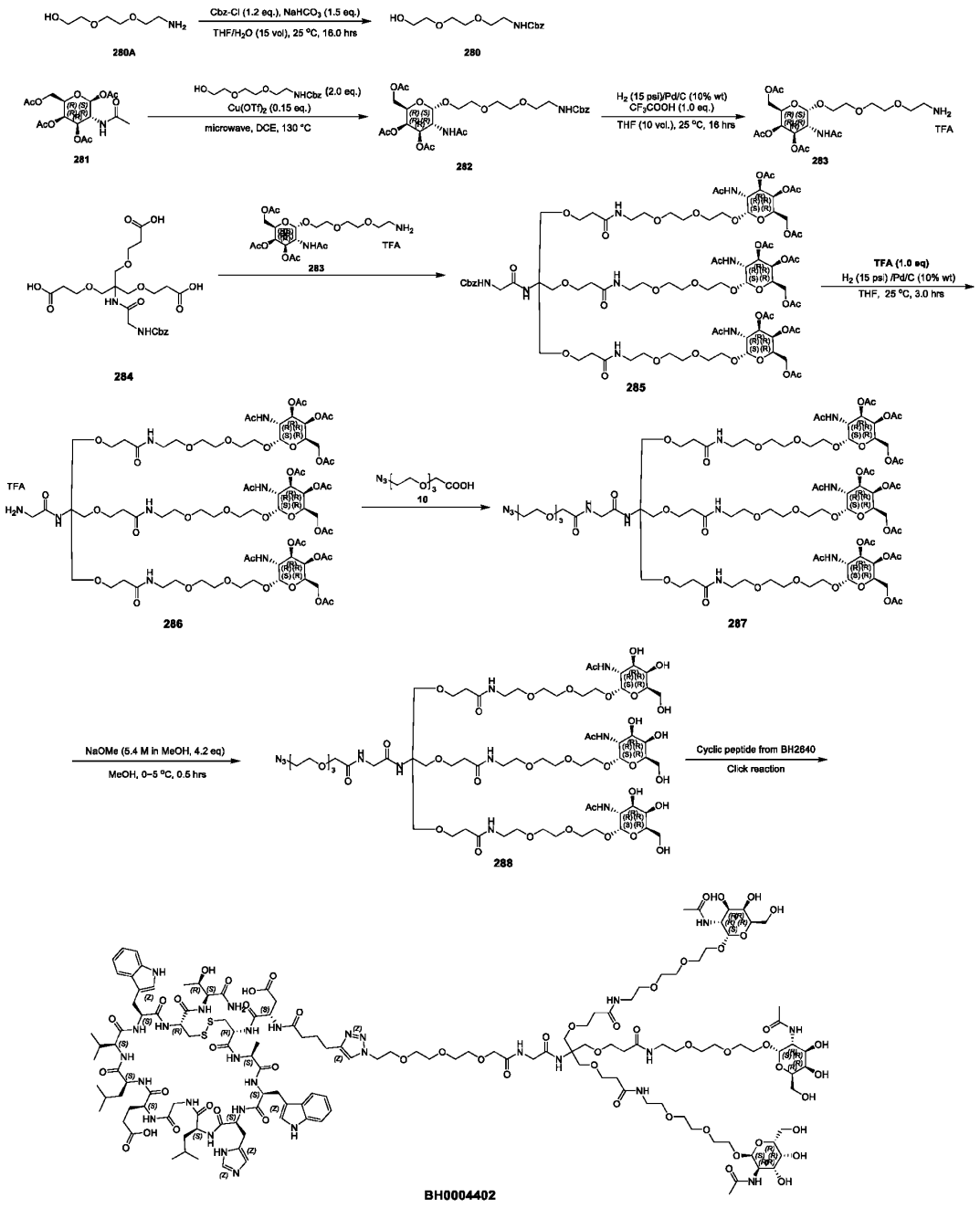
3) To a mixture of **Intermediate 279** (300 mg, crude) in MeCN/H_2O (3/7, v/v, 150 mL) was added 0.1 M I_2/AcOH dropwise until a yellow color persisted, then the mixture was stirred at 25 °C for 5 min. The mixture was quenched by addition of 0.1 M aq. $Na_2S_2O_3$ dropwise until the yellow color disappeared.

After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H_2O, B: MeCN), followed by lyophilization to afford **BH0005278** (58.0 mg, 99.1% purity, 19.2% yield) as a white solid. LCMS: RT = 0.954-1.052 min, MS calcd: M_{av} = 2012.15, mass observed: $[M + 2H]^{2+}$ = 1006.80, $[M + 3H]^{3+}$ = 671.80.

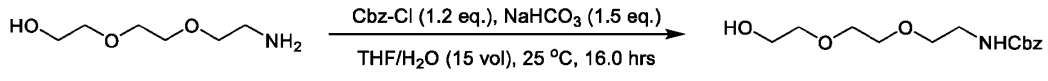


BH0005278

EXAMPLE 59. Procedure for preparation of BH0004587



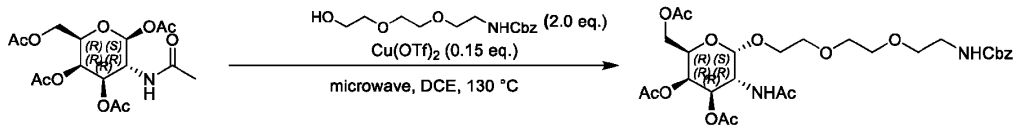
[0561] ***Preparation of Intermediate 280:***



280A **280**

[0562] A mixture of **280A** (50.0 g, 335 mmol, 1.0 equiv.), CbzCl (68.6 g, 402 mmol, 57.4 mL, 1.2 equiv.), $NaHCO_3$ (42.2 g, 503 mmol, 19.6 mL, 1.5 equiv.) in THF (400 mL) and H_2O (100 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 16 hrs under N_2 atmosphere. TLC showed **280A** was consumed completely and one main peak with desired m/z or desired mass was detected. The reaction mixture was quenched by addition H_2O (100 mL) at 25 °C, and then extracted with EtOAc 300 mL (100 mL * 3). The combined organic layers were washed with sat. NaCl (30.0 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1) to give **Intermediate 280** (62.0 g, 218 mmol, 65.3% yield) as a colorless oil. LCMS: RT =0.279 min, MS cal.: 283.32, found: $[M + H]^+$ = 283.9. ^1H NMR (400 MHz, DMSO-d6) δ = 7.40 - 7.29 (m, 5 H), 5.02 (s, 2 H), 4.61 - 4.53 (m, 1 H), 3.55 - 3.48 (m, 6 H), 3.42 (br s, 4 H), 3.39 - 3.36 (m, 1 H), 3.17 (br d, J = 5.13 Hz, 2 H).

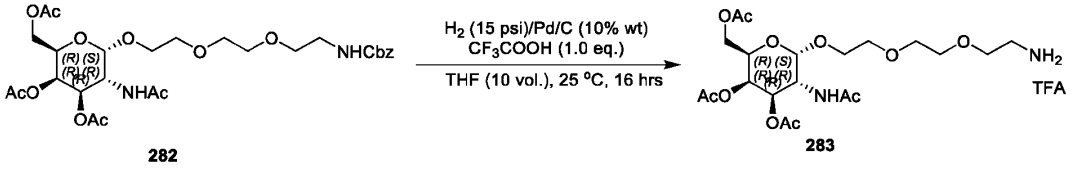
[0563] ***Preparation of Intermediate 282:***



281 **282**

[0564] Two parallel batches were performed. To a solution of **Intermediate 281** (2.00 g, 5.14 mmol, 1.0 equiv.), **Intermediate 280** (2.91 g, 10.3 mmol, 2.0 equiv.) and bis (trifluoromethylsulfonyloxy) copper (278 mg, 2.31 mmol, 0.15 equiv.) were taken up into a microwave tube in DCE (15.0 mL). The sealed tube was heated at 130 °C for 2 hrs under microwave. LCMS showed the desired mass and the reactant was consumed. The two batches were treated together after work-up. After cooling to 25 °C, DCM (200mL) and 5% $NaHCO_3$ (200 mL) were added. The aqueous layer was extracted with DCM (100 mL*2). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/4) , and then purified by reversed-phase HPLC (0.1% FA condition) to give **Intermediate 282** (2.80 g, 4.57 mmol, 44.5% yield) as a yellow oil. LCMS: RT =0.377 min, MS cal.: 612.25, found: $[M + H]^+$ = 613.6.

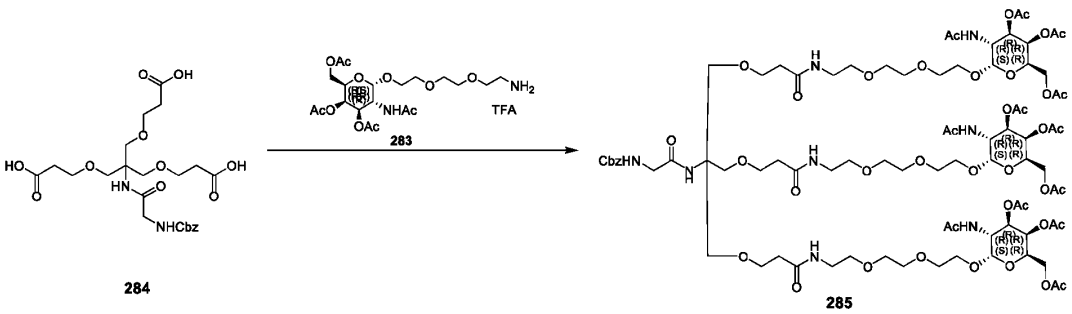
[0565] ***Preparation of intermediate 283:***



282 283

[0566] To a solution of **Intermediate 282** (2.00 g, 3.26 mmol, 1.0 equiv.) in THF (15.0 mL) was added TFA (372 mg, 3.26 mmol, 242 µL, 1.0 equiv.). The 50 mL round-bottom flask was purged with Ar for 3 times and added Pd/C (0.20 g, 10% purity) (dry) carefully. Then THF (5.0 mL) was added to infiltrate the Pd/C completely, followed by the mixture. The resulting mixture was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25 °C for 16 hrs under H_2 atmosphere. LC-MS showed **Intermediate 282** was consumed completely and one main peak with desired m/z or desired mass was detected. The reaction mixture was filtered under reduced pressure carefully under N_2 atmosphere. Then, the filter cake was added water immediately. The organic layer concentrated under reduced pressure to give a crude compound. The crude product was diluted with water (40 ml), washed by EtOAc 60 mL (20.0 mL * 3). The water layers was lyophilized to give **Intermediate 283** (1.70 g, 2.87 mmol, 87.9% yield, TFA salt) as a colorless oil. LCMS: RT = 0.313 min, MS cal.:478.2, found: $[M + H]^+$ = 479.4. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.13 (br d, J = 8.25 Hz, 1 H), 5.43 - 5.34 (m, 1 H), 5.17 - 5.02 (m, 1 H), 5.02 – 4.85 (m, 1 H), 4.36 - 4.22 (m, 2 H), 4.19 – 3.97 (m, 2 H), 3.83 - 3.71 (m, 1 H), 3.49 - 3.47 (m, 10 H), 2.80 - 2.47 (m, 7 H), 2.25 (s, 3 H), 2.00 – 1.92 (S, 3 H), 1.92 - 1.86(S, 3 H), 1.85 - 1.81 (S, 3 H), 1.79 - 1.76 (m, 2 H).

[0567] ***Preparation of Intermediate 285:***

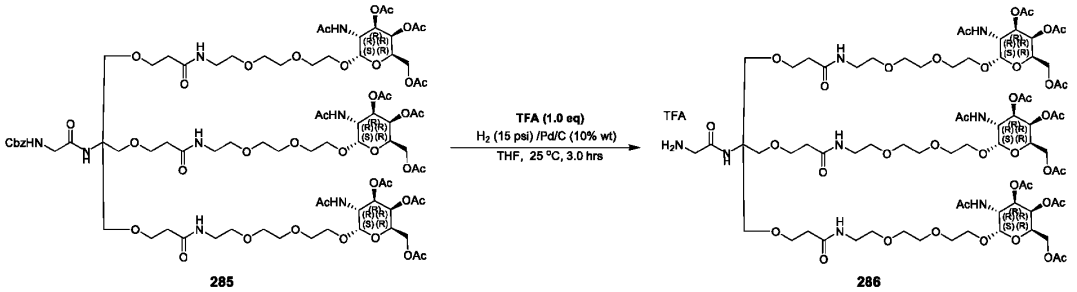


284 285

[0568] To a solution of **Intermediate 284** (250 mg, 473 µmol, 1.0 equiv.) and **Intermediate 283** (1.40 g, 2.37 mmol, 5.0 equiv, TFA) in DMF (14.0 mL) was added HOBt (255 mg, 1.89 mmol, 4.0 equiv.) and DIPEA (275 mg, 2.13 mmol, 370 µL, 4.5 equiv.) and EDCI (362 mg, 1.89 mmol, 4.0 equiv.) successively at 0-5 °C, the mixture was warmed up and stirred at 25 °C for 2.0 hrs. The reaction was monitored by LCMS. The reaction mixture was slowly poured into a stirred cold 0.5 mol/L HCl solution (50.0 mL), stirred

for 10 min, white solid was formed and filtered, the aqueous phase extracted with DCM (60.0 mL* 2) for two times. The combined organic layers were washed with 5% $NaHCO_3$ (50.0 mL) before being dried (Na_2SO_4) then concentrated by evaporating under vacuum to get the residue. The crude product was purified by column chromatography on silica gel (100-200 mesh size) using DCM/MeOH (10/1) as eluent to give **Intermediate 285** (600 mg, 253 µmol, 66.4% yield, 80.7% purity) as a yellow solid. HNMR confirmed the desired product and LCMS showed the purity was 80.7%. LCMS: RT =1.935min, MS cal.: 1909.93, found: $[M + 2H]^{2+}$ = 955.8. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.00 (s, 6 H), 7.36 (s, 5 H), 5.32 (d, *J* = 2.50 Hz, 3 H), 5.03 (s, 5 H), 4.91 (d, *J* = 3.38 Hz, 3 H), 4.28 - 4.17 (m, 5 H), 4.11 – 3.98 (m, 6 H), 3.76 - 3.67 (m, 3 H), 3.65 - 3.45 (m, 35 H), 3.45 - 3.36 (m, 10 H), 3.21 (br d, *J* = 5.63 Hz, 6 H), 2.31 (br s, 6 H), 2.10 (s, 9 H), 2.00 (s, 9 H), 1.90 (s, 9 H), 1.85 - 1.77 (m, 9 H).

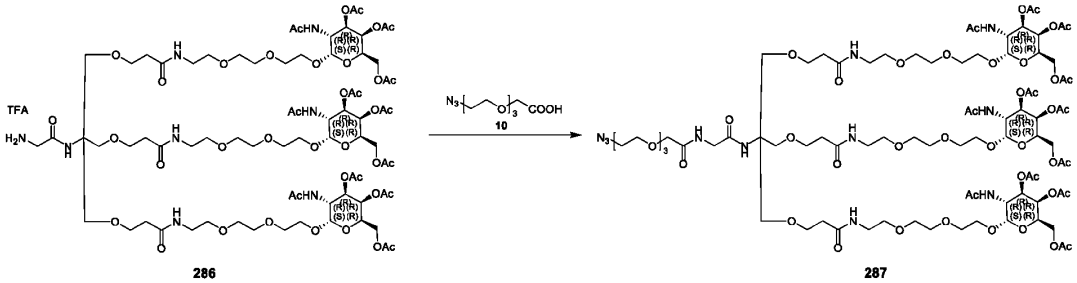
[0569] ***Preparation of Intermediate 286:***



285 286

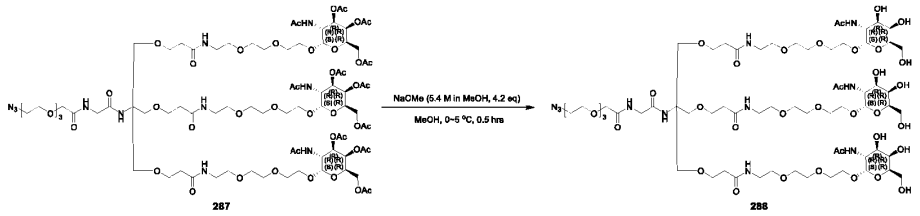
[0570] The 50 mL round-bottom flask was purged with Ar for 3 times and added Pd/C (0.06 g, 10% purity) (dry) carefully. Then THF (5.0 mL) was added to infiltrate the Pd/C completely, followed by the **intermediate 285** (600 mg, 314 µmol, 1.0 equiv.) and TFA (35.8 mg, 314 µmol, 23.3 µL, 1.0 equiv.) in THF (6.0 mL) slowly under Ar atmoshpere. The resulting mixture was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25 °C for 3 hrs under H_2 atmosphere. The reaction was monitored by LCMS. The reaction mixture was filtered under reduced pressure carefully under N_2 atmosphere. Then, the filter cake was added water immediately. The organic layer concentrated under reduced pressure to give **Intermediate 286** (500 mg, 261 µmol, 84.3% yield, 98.7% purity, TFA) as a colorless oil. LCMS: RT = 1.137 min, MS cal.: 1774.78, found: $[M + 2H]^{2+}$ = 888.7. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.10 - 7.99 (m, 3 H), 7.94 (s, 3 H), 7.63 - 7.51 (m, 1 H), 6.69 (s, 1 H), 5.08 (dd, *J* = 11.82, 3.19 Hz, 3 H), 4.96 (d, *J* = 3.50 Hz, 3 H), 4.34 - 4.19 (m, 6 H), 4.18 - 3.99 (m, 6 H), 3.76 (br s, 3 H), 3.68 - 3.55 (m, 33 H), 3.51 - 3.45 (m, 9 H), 3.33 - 3.20 (m, 6 H), 2.36 (br t, *J* = 6.38 Hz, 6 H), 2.16 (s, 9 H), 2.05 (s, 9 H), 2.00 (S, 9 H), 1.91 (S, 9 H).

[0571] ***Preparation of Intermediate 287:***



[0572] A mixture of **Intermediate 286** (500 mg, 281 µmol, 1.0 equiv.), **10** (98.5 mg, 422 µmol, 1.5 equiv.), DIEA (109 mg, 844 µmol, 147 µL, 3.0 equiv.), HOBt (57.0 mg, 422 µmol, 1.5 equiv.) and EDCI (80.9 mg, 422 µmol, 1.5 equiv.) in DMF (5.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 2 hrs under N_2 atmosphere. The reaction was monitored by LCMS. The reaction mixture was slowly poured into a stirred cold 0.5 mol/L HCl solution (20.0 mL), stirred for 10 min, white solid was formed and filtered, the aqueous phase extracted with DCM (20.0 mL* 2) for two times. The combined organic layers were washed with 5% $NaHCO_3$ (30.0 mL) before being dried (Na_2SO_4) then concentrated by evaporating under vacuum to get the residue. The crude product was purified by column chromatography on silica gel (100-200 mesh size) using DCM/MeOH (10/1) as eluent to give **Intermediate 287** (400 mg, 178 µmol, 71.4% yield, 89.0% purity) as yellow oil. LCMS: RT = 1.437 min, MS cal.:1989.87, found: $[M + 2H]^{2+}$ =996.0. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.02 - 7.92(m, 6 H), 7.76 - 7.71 (m, 1 H), 7.23 (s, 1 H), 5.32 (d, *J* = 2.38 Hz, 3 H), 5.03 (dd, *J* = 11.76, 2.88 Hz, 3 H), 4.91 (d, *J* = 3.13 Hz, 3 H), 4.27 - 4.20 (m, 6 H), 4.09 - 4.01 (m, 6 H), 3.93 (s, 2 H), 3.73 (dd, *J* = 11.13, 6.75 Hz, 6 H), 3.63 - 3.54 (m, 41H), 3.44 - 3.40 (m, 9 H), 3.21 (br d, *J*=5.75 Hz, 6 H), 2.31 (br t, *J* = 6.19 Hz, 6 H), 2.11 (s, 9 H), 2.00 (s, 9 H), 1.90 (s, 9 H),1.82 (s, 9 H).

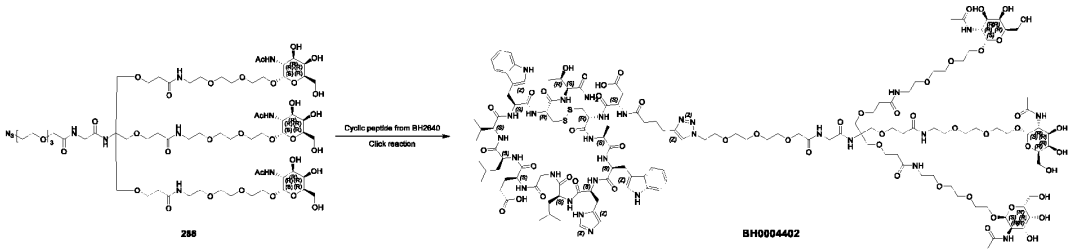
[0573] ***Preparation of Intermediate 288:***



[0574] To a solution of **Intermediate 287** (400 mg, 200 µmol, 1.0 equiv) in MeOH (4.0 mL) was added NaOMe (5.4 M, 158 µL, 4.26 equiv) at 0 °C, then the solution was stirred at 0 °C for 0.5 hrs. The

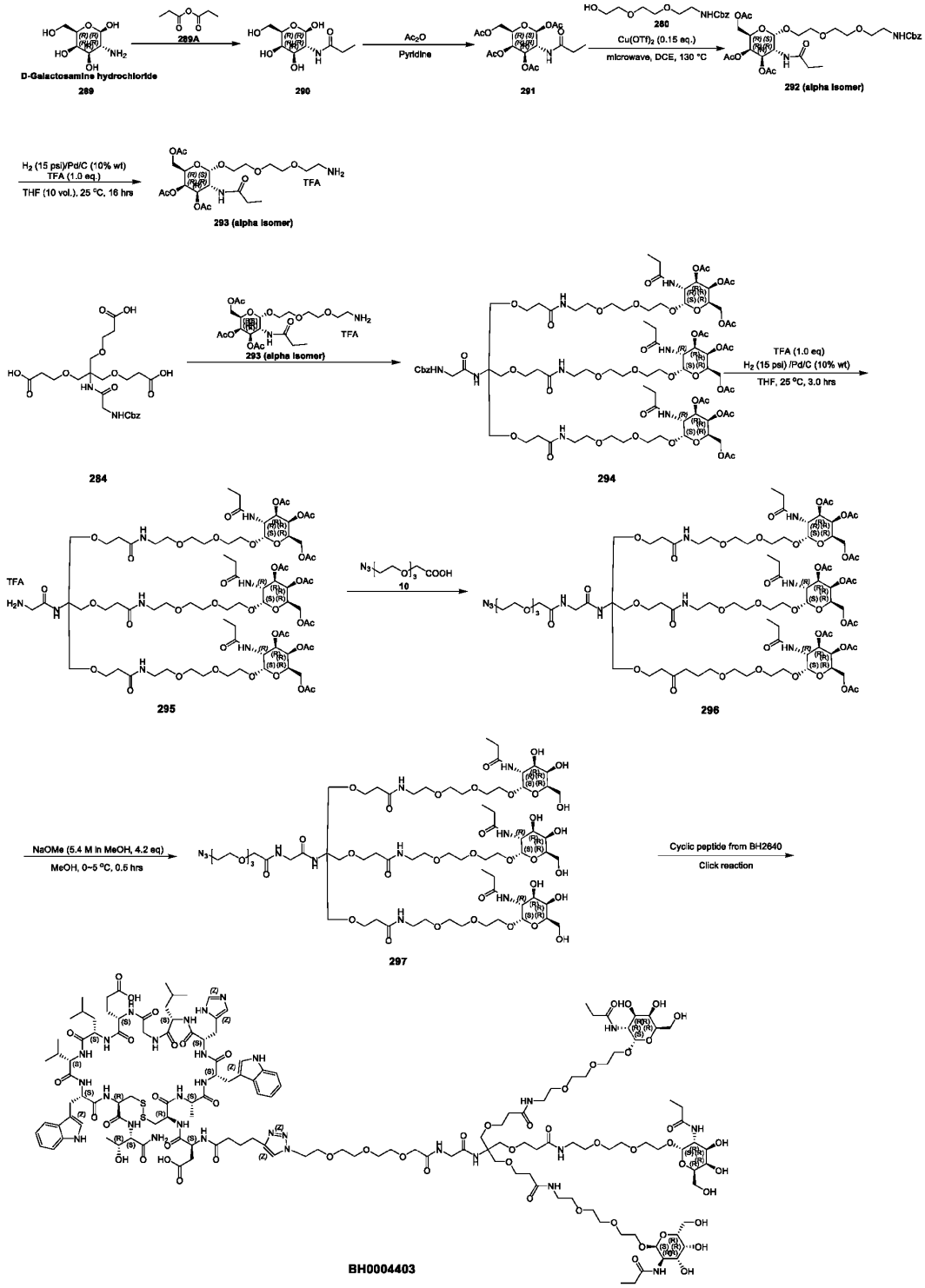
reaction was monitored by LCMS, the reaction mixture was adjusted pH to about 6 with 1.0 M HCl solution at 0 °C, and extracted with DCM (250 mL * 3) for three times, the aqueous layer was lyophilized to afford **Intermediate 288** (380 mg, crude) as a white solid. LCMS: RT = 0.833 min, MS cal.: 1611.77, found: $[M + 2H]^{2+}$ =807.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.01 (s, 3 H), 7.78 (br t, *J* = 5.69 Hz, 1 H), 7.65 - 7.59 (m, 3 H), 7.26 (s, 1 H), 4.72 (d, *J* = 3.50 Hz, 3 H), 4.68 - 4.61 (m, 6 H), 4.56 (d, *J* = 6.88 Hz, 3 H), 4.00-3.96 (m, 3 H), 3.93 (s, 2 H), 3.74 (br d, *J* = 4.00 Hz, 6 H), 3.65 - 3.49 (m, 57 H), 3.45 - 3.41 (m, 9 H), 3.24 - 3.18 (m, 6 H), 2.32 (br t, *J* = 6.38 Hz, 6 H), 1.83 (S, 9 H),

[0575] ***Preparation of BH0004402:***

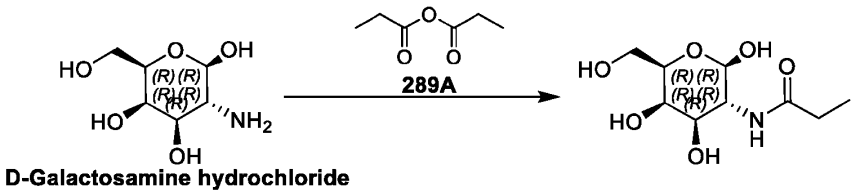


[0576] A mixture of **107** from BH2640 (342 mg, 211 µmol, 1.0 equiv.), **Intermediate 288** (340 mg, 210 µmol, 1.0 equiv.), $CuSO_4.5H_2O$ (0.4 M, 527 µL, 1.0 equiv.), sodium; (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (167 mg, 843 µmol, 4.0 equiv.) and NH_4HCO_3 (0.2 M, 3.87 mL, 3.67 equiv.) in t-BuOH (3.80 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 0-25 °C for 2 hrs under N_2 atmosphere. The reaction was monitored by LCMS, The resulting reaction mixture was lyophilized to get a residue. The residue was purified by prep-HPLC (A: 0.5% HOAc in H_2O, B: MeCN.) to give **BH0004402** (80.0 mg, 23.7 µmol, 12.3% yield over two steps, 95.0% purity) as a white solid. LCMS: RT = 0.89min, MS cal.:3234.47, found: $[M + 3H]^{3+}$ =1079.51.

EXAMPLE 60. Procedure for preparation of BH0004403


D-Galactosamine hydrochloride
289
289A
290
Ac2O
Pyridine
291
280
Cu(OTf)2 (0.15 eq.)
microwave, DCE, 130 °C
292 (alpha isomer)
H2 (15 psi)/Pd/C (10% wt)
TFA (1.0 eq.)
THF (10 vol.), 25 °C, 16 hrs
293 (alpha isomer)
284
293 (alpha isomer)
294
TFA (1.0 eq)
H2 (15 psi) /Pd/C (10% wt)
THF, 25 °C, 3.0 hrs
295
10
296
NaOMe (5.4 M in MeOH, 4.2 eq)
MeOH, 0~5 °C, 0.5 hrs
297
Cyclic peptide from BH2640
Click reaction
BH0004403

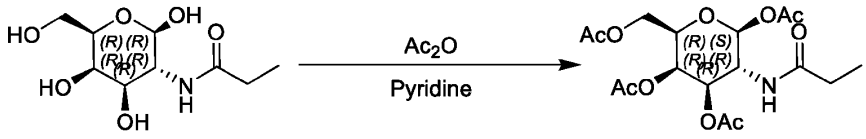
[0577] ***Preparation of Intermediate 290:***



289 **290**

[0578] A mixture of **289** (25.0 g, 116 mmol, 1.0 equiv., HCl.), **289A** (18.1 g, 139 mmol, 17.9 mL, 1.2 equiv.), NaOMe (20.9 g, 116 mmol, 30% purity, 1.0 equiv.) in MeOH (200 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 16 hrs under N_2 atmosphere. The solution was evaporated under reduced pressure to leave a solid. Which was stirred in dry EtOAc (molecular sieve) for 1 hr at 25°C. The solid was filtered off to give **Intermediate 290** (25.0 g, 106 mmol, 76.2% yield.) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.46 (br d, J = 8.38 Hz, 1 H), 6.39 - 6.26 (m, 1 H), 4.97 - 4.92 (m, 1 H), 3.82 - 3.73 (m, 2 H), 3.70 - 3.48 (m, 4 H), 2.19 - 2.05 (m, 3 H).

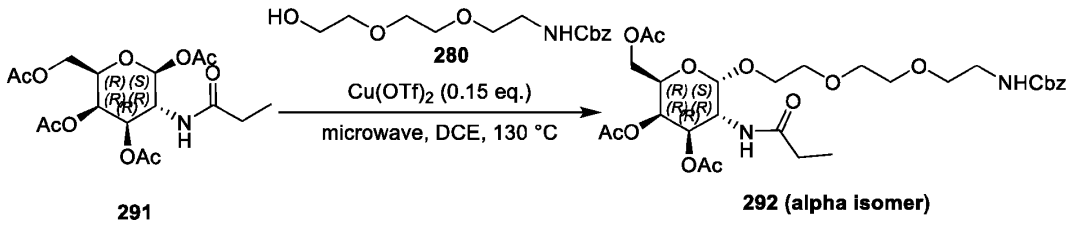
[0579] ***Preparation of Intermediate 291:***



290 **291**

[0580] A mixture of **Intermediate 290** (25.0 g, 106 mmol, 1.0 equiv.), Ac_2O (358 g, 3.51 mol, 329 mL, 33 equiv.), Py (563 g, 7.12 mol, 574 mL, 67 equiv.) and DMAP (129 mg, 1.06 mmol, 0.01 equiv.) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 16 hrs under N_2 atmosphere. The reaction was monitored by LCMS. The reaction mixture was diluted with DCM (30.0 mL) and extracted with 1M HCl (300 mL *3). The combined organic layers were washed with $NaHCO_3$ (300 mL * 3), dried over NaCl, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with EtOAc at 25 °C for 30 min to give **Intermediate 291** (21.0 g, 52.1 mmol, 49.0% yield.) as a white solid. LCMS: RT = 2.690 min, MS cal.:403.15, found: $[M + Na]^+$ = 426.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.04 (d, J = 8.00 Hz, 1 H), 6.04 (d, J = 3.50 Hz, 1 H), 5.40 (d, J = 2.13 Hz, 1 H), 5.11 (dd, J = 11.82, 3.19 Hz, 1 H), 4.40 - 4.32 (m, 2 H), 4.08 - 3.98 (m, 2 H), 2.14 (d, J = 6.13 Hz, 6 H), 2.09 - 2.02 (m, 2 H), 2.01 – 1.98 (m, 3 H), 1.93 (s, 3 H), 0.99 - 0.93 (m, 3 H).

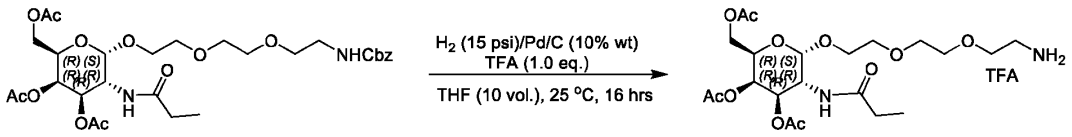
[0581] ***Preparation of Intermediate 292:***



291 **292 (alpha isomer)**

[0582] Five parallel batches were performed. A mixture of **Intermediate 291** (2.0 g, 4.96 mmol, 1.0 equiv.), **280** (2.81 g, 9.92 mmol, 2.0 equiv.) and bis(trifluoromethylsulfonyloxy)copper (269 mg, 744 µmol, 0.15 equiv.) were taken up into a microwave tube in DCE (45.0 mL) .The sealed tube was heated at 130 °C for 2 hrs under microwave. The reaction was monitored by LCMS. The five batches were treated together after work-up. After cooling to 25°C, ethyl acetate (500mL) and 5% $NaHCO_3$ (300 mL) were added. The aqueous layer was extracted with ethyl acetate (100 mL*3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/4), and then the product was purified by HPLC (0.1% FA condition) again to give **Intermediate 292** (5.5 g, 8.78 mmol, 35.40% yield) was obtained as a white solid. LCMS: RT =0.415 min, MS cal.: 626.27, found: $[M + H]^+$ =627.4. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.87 (br d, *J* = 8.25 Hz, 1 H), 7.38 - 7.22 (m, 6 H), 5.76 (s, 1 H), 5.38 - 5.27 (m, 1 H), 5.02 (s, 3 H), 4.98 - 4.83 (m, 1 H), 4.29 - 4.16 (m, 2 H), 4.14 - 3.93 (m, 2 H), 3.76 - 3.63 (m, 1 H), 3.62 - 3.56 (m, 3 H), 3.52 (br d, *J* = 2.50 Hz, 3 H), 3.42 (t, *J* = 5.94 Hz, 2 H), 3.21 - 3.10 (m, 2 H), 2.11 (s, 3 H), 2.10 - 2.04 (m, 2 H), 1.99 (s, 3 H), 1.89 (s, 3 H), 0.97 (t, *J* = 7.57 Hz, 3 H).

[0583] ***Preparation of Intermediate 293:***

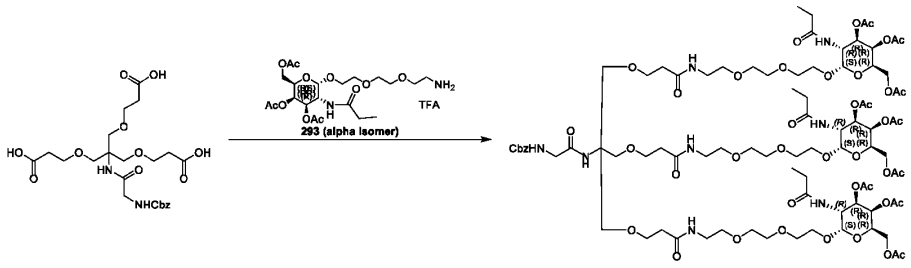


292 (alpha isomer) **293 (alpha isomer)**

[0584] The 50 mL round-bottom flask was purged with Ar for 3 times and added Pd/C (0.55 g, 10.0% purity, 1.0 equiv.) (dry) carefully. Then THF (2.0 mL) was added to infiltrate the Pd/C completely, followed by the **Intermediate 292** (5.5 g, 8.78 mmol, 1.0 equiv.) and TFA (1.0 g, 8.78 mmol, 652 µL, 1.0 equiv.) in THF (60.0 mL) slowly under Ar atmosphere. The resulting mixture was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25 °C for 16 hrs under H_2 atmosphere. The reaction

was monitored by LCMS, the reaction mixture was filtered under reduced pressure carefully under N_2 atmosphere. Then, the filter cake was added water immediately. The organic layer concentrated under reduced pressure to give a crude compound. The residue was diluted with water (100 mL), extracted with DCM (100 mL *3), the aqueous layer was to lyophilized to give **Intermediate 293** (5.00 g, 8.24 mmol, 93.9% yield, TFA) as colorless oil. LCMS: RT = 0.326 min, MS cal.: 492.23, found: $[M + H]^+$ = 493.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.05 - 7.78 (m, 4 H), 5.37 (d, *J* = 2.75 Hz, 1 H), 5.08 (dd, *J* = 11.82, 3.19 Hz, 1 H), 4.99 (d, *J* = 3.50 Hz, 1 H), 4.33 - 4.23 (m, 2 H), 4.15 - 4.04 (m, 2 H), 3.79 - 3.73 (m, 1 H), 3.70 - 3.59 (m, 10 H), 3.08 - 3.01 (m, 2 H), 2.20 - 2.10 (m, 5 H), 2.06 (s, 3 H), 1.94 (s, 3 H), 1.03 (t, *J* = 7.57 Hz, 3 H).

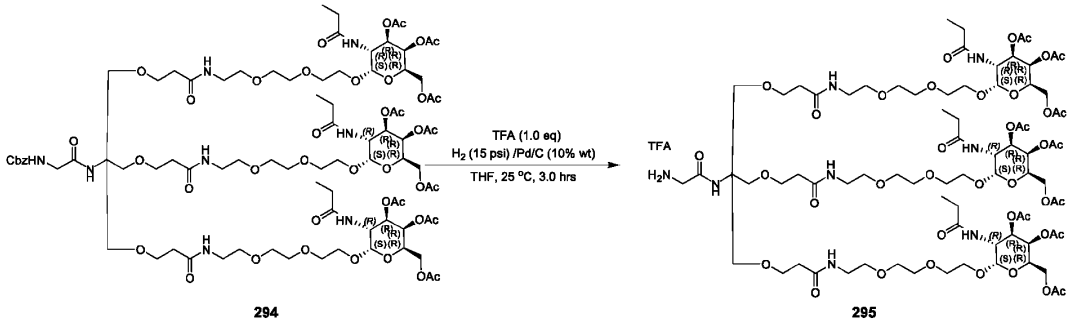
[0585] ***Preparation of Intermediate 294:***



284 294

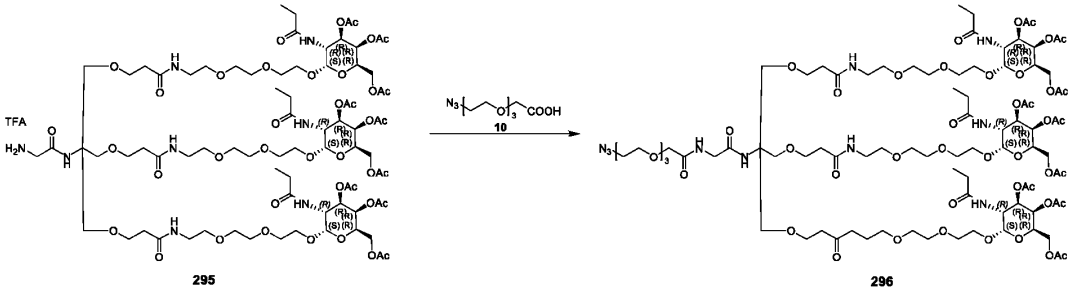
[0586] To a solution of **Intermediate 284** (871 mg, 1.65 mmol, 1.0 equiv.) and **Intermediate 293** (5 g, 8.24 mmol, 5.0 equiv, TFA) in DMF (50.0 mL) was added HOBt (891 mg, 6.59 mmol, 4.0 equiv.) and DIPEA (959 mg, 7.42 mmol, 1.29 mL, 4.5 equiv.) and EDCI (1.26 g, 6.59 mmol, 4.0 equiv.) successively at 0-5 °C, the mixture was warmed up and stirred at 25 °C for 2.0 hrs. The reaction was monitored by LCMS, the reaction was monitored by TLC, TLC (Dichloromethane: Methanol = 10:1, product R_f = 0.33). The reaction mixture was slowly poured into a stirred cold 0.5 mol/L HCl solution (100 mL), stirred for 10 min, white solid was formed and filtered, the aqueous phase extracted with DCM (100 mL* 2) for two times. The combined organic layers were washed with 5% $NaHCO_3$ (100 mL) before being dried (Na_2SO_4) then concentrated by evaporating under vacuum to get the residue. The crude product was purified by column chromatography on silica gel (100-200 mesh size) using DCM/MeOH (10:1) as eluent to give **Intermediate 294** (3.10 g, 1.41 mmol, 96.5% yield, 88.9% purity) as yellow solid. LCMS: RT = 0.573 min, MS cal.: 1950.86, found: $[M + 2H]^{2+}$ =976.8. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.95 - 7.79 (m, 6 H), 7.41 - 7.31 (m, 5 H), 5.37 - 5.28 (m, 3 H), 5.08 - 4.98 (m, 5 H), 4.94 - 4.86 (m, 3 H), 4.31 - 4.18 (m, 6 H), 4.10 - 3.98 (m, 6 H), 3.76 - 3.67 (m, 3 H), 3.63 - 3.49 (m, 36 H), 3.44 - 3.36 (m, 7 H), 3.25 - 3.14 (m, 6 H), 2.35 - 2.27 (m, 6 H), 2.15 - 2.05 (m, 15 H), 2.04 - 1.99 (m, 9 H), 1.89 (s, 9 H), 0.97 (t, *J* = 7.57 Hz, 9 H).

[0587] ***Preparation of Intermediate 295:***



[0588] The 50 mL round-bottom flask was purged with Ar for 3 times and added Pd/C (0.30 g, 10% purity) (dry) carefully. Then THF (5 mL) was added to infiltrate the Pd/C completely, followed by the **Intermediate 294** (3.10 g, 1.59 mmol, 1.0 equiv.) and TFA (181 mg, 1.59 mmol, 118 µL, 1.0 equiv.) in THF (2.0 mL) slowly under Ar atmosphere. The resulting mixture was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25 °C for 3 hrs under H_2 atmosphere. The reaction was monitored by LCMS. The reaction mixture was filtered under reduced pressure carefully under N_2 atmosphere. Then, the filter cake was added water immediately. The organic layer concentrated under reduced pressure to give a crude compound. The crude product was diluted with water 40 ml, washed by EtOAc (20.0 mL * 3). The water layers were lyophilization to give **Intermediate 295** (3.0 g, 1.47 mmol, 97.7% yield, TFA) as a colorless oil. LCMS: RT = 1.611 min, MS cal.: 1816.82, found: $[M+2H]^{2+}$ =909.8.

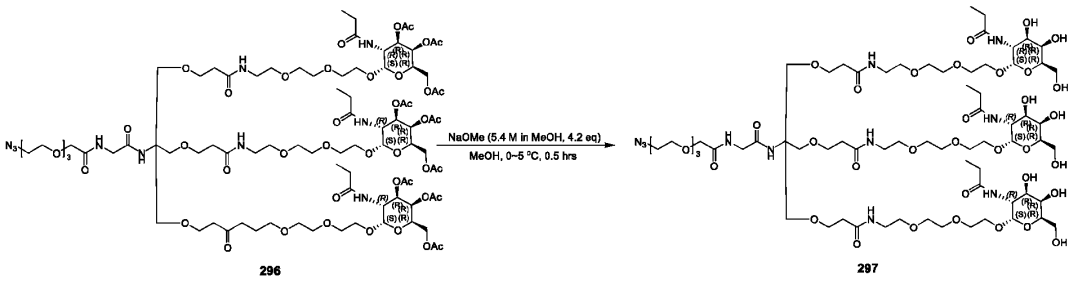
[0589] ***Preparation of Intermediate 296:***



[0590] A mixture of **Intermediate 295** (1.00 g, 517 µmol, 1.0 equiv., TFA), **10** (181 mg, 776 µmol, 1.5 equiv.), DIEA (200 mg, 1.55 mmol, 270 µL, 3.0 equiv.), HOBt (104 mg, 776 µmol, 1.5 equiv.) and EDCI (149 mg, 776 µmol, 1.5 equiv.) in DMF (10.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 2 hrs under N_2 atmosphere. The reaction was monitored by LCMS, The

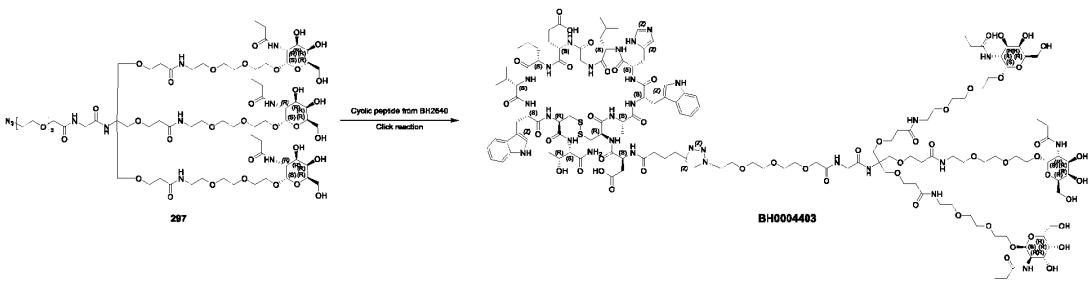
reaction was monitored by TLC, TLC (Dichloromethane: Methanol = 10:1, product R_f = 0.36). The reaction mixture was slowly poured into a stirred cold 0.5 mol/L HCl solution (30.0 mL), stirred for 10 mins, white solid was formed and filtered, the aqueous phase extracted with DCM (50.0 mL* 2) for two times. The combined organic layers were washed with 5% $NaHCO_3$ (50.0 mL) before being dried (Na_2SO_4) then concentrated by evaporating under vacuum to get the residue. The crude product was purified by column chromatography on silica gel (100-200 mesh size) using DCM/MeOH (10:1) as eluent to give **Intermediate 296** (820 mg, 382 µmol, 78.0% yield, 94.7% purity) as a yellow solid. LCMS: RT = 1.976min, MS cal.:2030.09, found: $[M + 3H]^{3+}$ = 678.4.

[0591] ***Preparation of Intermediate 297:***



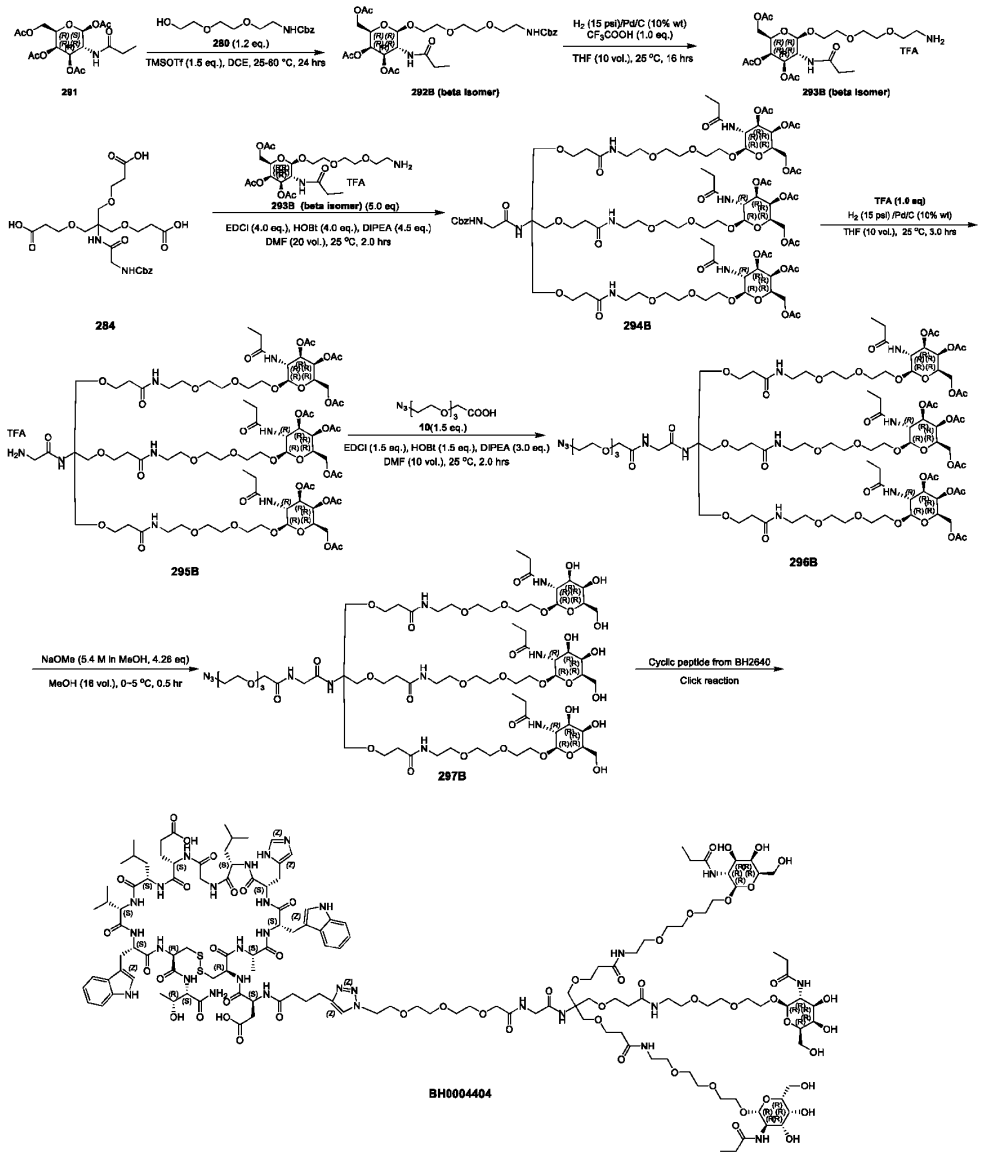
[0592] To a solution of **Intermediate 296** (820 mg, 402 µmol, 1.0 equiv.) in MeOH (8.0 mL) was added NaOMe (5.4 M, 317 µL, 4.26 equiv.) at 0 °C, then the solution was stirred at 0 °C for 0.5 hrs. The reaction was monitored by LCMS. The reaction mixture was adjusted pH to about 6 with 1.0 M HCl solution at 0 °C, and extracted with DCM (250 mL * 3) for three times, the aqueous layer was lyophilized to afford the residue to give **Intermediate 297** (840 mg, crude) as a white solid. LCMS: RT = 0.912 min, MS cal.: 1653.82, found: $[M+2H]^{2+}$ = 828.2.

[0593] ***Preparation of BH0004403:***

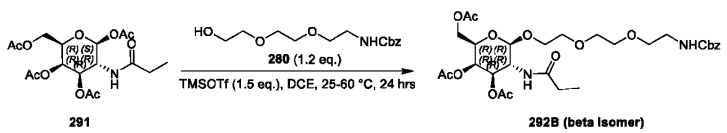


[0594] A mixture of **Cyclic peptide 107** (392 mg, 241 μmol, 1.0 equiv.), **Intermediate 297** (400 mg, 241 μmol, 1.0 equiv.), $CuSO_4.5H_2O$ (0.4 M, 604 μL, 1.0 equiv.), sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (191 mg, 967 μmol, 4.0 equiv.) and NH_4HCO_3 (0.2 M, 4.44 mL, 3.67 equiv.) in t-BuOH (4.44 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. The reaction was monitored by LCMS and HPLC. The resulting reaction mixture was lyophilized to get a residue. The residue was purified by prep-HPLC (A: 0.5% HOAc in H2O, B: MeCN) to give **BH0004403** (64.0 mg, 19.0 μmol, 10.1% yield over two steps, 96.8% purity) as a white solid. LCMS: RT = 0.90 min, MS cal.: 3276.52, found: $[M + 3H]^{3+}$ =1093.64.

EXAMPLE 61. Procedure for preparation of BH0004404



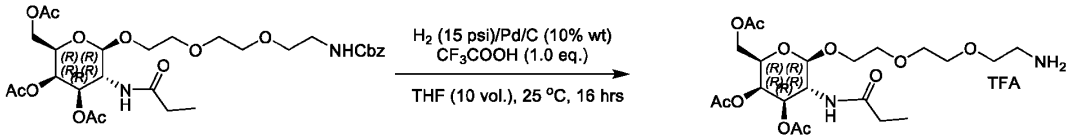
[0595] ***Preparation of Intermediate 292B:***



[0596] A mixture of **Intermediate 291** (10.0 g, 24.8 mmol, 1.0 equiv.), **280** (8.43 g, 29.8 mmol, 1.2 equiv.) and TMSOTf (8.26 g, 37.2 mmol, 6.72 mL, 1.5 equiv.) in DCE (100 mL) was degassed and purged

with N_2 for 3 times, and then the mixture was stirred at 60 °C for 24 hrs under N_2 atmosphere. LCMS showed the desired mass was detected and the reactant was consumed. After cooling to 25°C, ethyl acetate (200 mL) and 5% $NaHCO_3$ (100 mL) were added, the aqueous layer was extracted with ethyl acetate (100 mL*3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/4), and then purified by prep-HPLC (0.1% FA condition) to afford **Intermediate 292B** (7.00 g, 10.9 mmol, 43.9% yield, 97.4% purity) as a white solid. LCMS: RT = 0.401 min, MS cal.: 626.27, found: $[M + H]^+$ = 627.4. ^{1}H NMR (400 MHz, DMSO-d_6) ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.70 (d, *J* = 9.13 Hz, 1 H), 7.39 - 7.28 (m, 5 H), 5.22 (d, *J* = 3.38 Hz, 1 H), 5.04 - 4.96 (m, 3 H), 4.56 (d, *J* = 8.50 Hz, 1 H), 4.08 - 3.99 (m, 4 H), 3.90 (dt, *J* = 10.98, 8.96 Hz, 1 H), 3.81 - 3.73 (m, 1 H), 3.60 - 3.55 (m, 1 H), 3.53 - 3.46 (m, 6 H), 3.41 (t, *J* = 5.94 Hz, 2 H), 3.15 (q, *J* = 5.84 Hz, 2 H), 2.10 (s, 3 H), 2.04 - 1.98 (m, 6 H), 1.88 (s, 3 H), 0.96 (t, *J* = 7.57 Hz, 3 H).

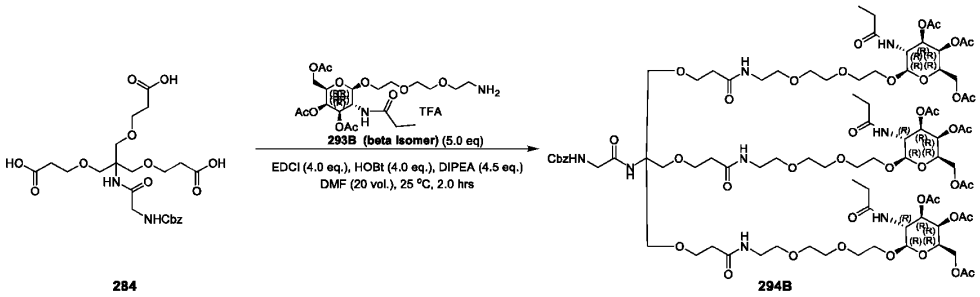
[0597] ***Preparation of Intermediate 293B:***



292B (beta isomer) **293B (beta isomer)**

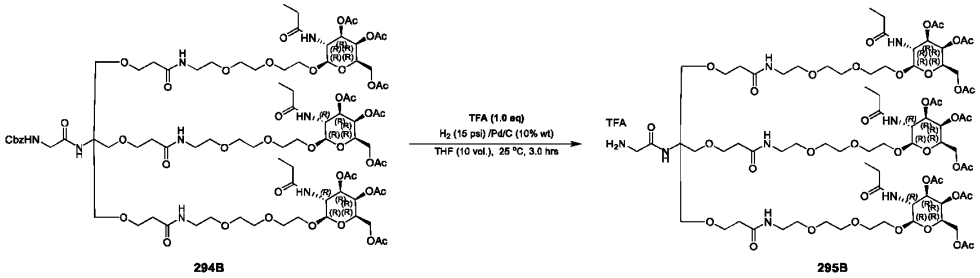
[0598] The 250 mL round-bottom flask was purged with Ar for 3 times and added Pd/C (0.70 g, 10% purity) (dry) carefully. Then THF (5.0 mL) was added to infiltrate the Pd/C completely, followed by the solution **Intermediate 292B** (7.00 g, 11.2 mmol, 1.0 equiv.) and CF_3COOH (1.27 g, 11.2 mmol, 830 µL, 1.0 equiv.) in THF (70.0 mL) slowly under Ar atmosphere. The resulting mixture was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25 °C for 16 hrs under H_2 atmosphere. TLC (DCM: MeOH = 10: 1, R_f = 0.33) indicated **Intermediate 292B** was consumed completely, and one major new spot with larger polarity was detected. The reaction mixture was filtered under reduced pressure carefully under N_2 atmosphere and the organic layer concentrated under reduced pressure to give **Intermediate 293B** (7.00 g, crude, TFA salt) as a yellow oil. LCMS: RT = 0.128 min, MS cal.: 492.23, found: $[M + H]^+$ = 493.7. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.95 - 7.68 (m, 4 H). 5.22 (d, *J* = 3.00 Hz, 1 H). 4.99 (dd, *J* = 11.13, 3.25 Hz, 1 H), 4.55 (d, *J* = 8.50 Hz, 1 H), 4.03 (br s, 2 H), 3.90 (br d, *J* = 10.76 Hz, 1 H), 3.79 (br dd, *J* = 10.44, 5.07 Hz, 1 H), 3.61 - 3.47 (m, 10 H), 3.02 - 2.92 (m, 2 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.88 (s, 3 H), 0.97 (t, *J* = 7.57 Hz, 3 H)

[0599] ***Preparation of Intermediate 294B:***



[0600] To a solution of **Intermediate 284** (1.05 g, 1.98 mmol, 1.0 equiv.) and **293B** (6.00 g, 9.89 mmol, 5.0 equiv., TFA) in DMF (60.0 mL) was added DIPEA (1.15 g, 8.90 mmol, 1.55 mL, 4.5 equiv.), HOBt (1.07 g, 7.91 mmol, 4.0 equiv.) and EDCI (1.52 g, 7.91 mmol, 4.0 equiv.) successively, the mixture was stirred at 25 °C for 2 hrs. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was slowly poured into a stirring cold 0.5 mol/L HCl solution (50.0 mL), then extracted with DCM (70.0 mL* 3). The combined organic layers were washed with 5% $NaHCO_3$ (140 mL), dried over Na_2SO_4, and concentrated under reduced pressure to get a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 100:1 to 5:1) to afford **Intermediate 294B** (2.80 g, 1.36 mmol, 68.5% yield) as a gray solid. LCMS: RT = 1.460 min, MS cal.: 1950.86, found: $[M + 2H]^{2+}$ = 976.8. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.90 (br t, *J* = 5.50 Hz, 3 H), 7.72 (d, *J* = 9.26 Hz, 3 H), 7.38 - 7.30 (m, 5 H), 7.11 (s, 1 H), 5.21 (d, *J* = 3.38 Hz, 3 H), 5.05 - 4.94 (m, 5 H), 4.56 (d, *J* = 8.51 Hz, 3 H), 4.07 - 3.98 (m, 9 H), 3.94 - 3.84 (m, 3 H), 3.81 - 3.74 (m, 3 H), 3.62 - 3.45 (m, 36 H), 3.41 - 3.36 (m, 7 H), 3.22 - 3.15 (m, 7 H), 2.34 - 2.26 (m, 6 H), 2.10 (s, 9 H), 2.05 - 1.97 (m, 15 H), 1.88 (s, 9 H), 0.96 (t, *J* = 7.57 Hz, 9 H).

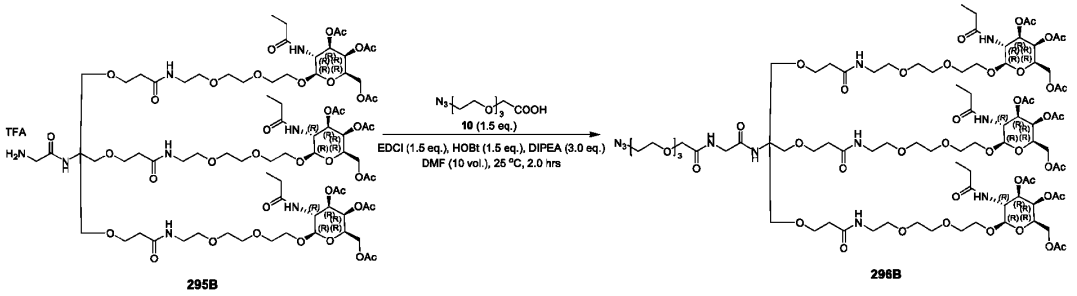
[0601] ***Preparation of Intermediate 295B:***



[0602] The 100 mL round-bottom flask was purged with Ar for 3 times and added Pd/C (0.26 g, 10 % purity) (dry) carefully. Then THF (5.0 mL) was added to infiltrate the Pd/C completely, followed by the solution of **Intermediate 294B** (2.60 g, 1.33 mmol, 1.0 equiv.) and TFA (152 mg, 1.33 mmol, 98.9 µL, 1.0 equiv.) in THF (20.0 mL) slowly under Ar atmosphere. The resulting mixture was degassed and purged

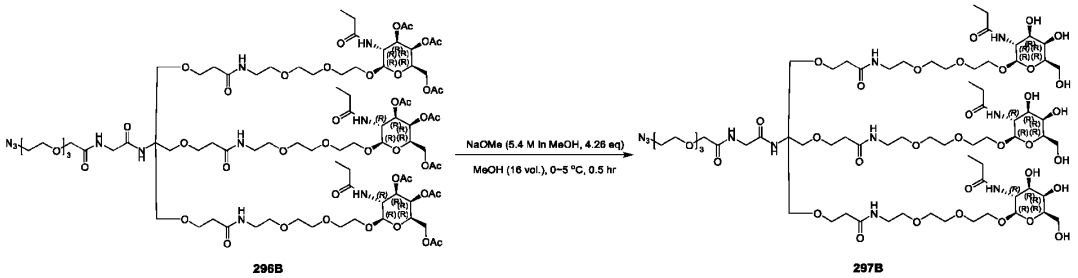
with H_2 for 3 times, and then the mixture was stirred at 25 °C for 3 hrs under H_2 atmosphere. TLC (DCM: MeOH = 10: 1, R_f = 0.34) indicated **Intermediate 294B** was consumed completely, and one major new spot with larger polarity was detected. The reaction mixture was filtered under reduced pressure carefully under N_2 atmosphere and the organic layer concentrated under reduced pressure to afford **Intermediate 295B** (2.60 g, crude, TFA salt) as a gray solid. LCMS: RT = 1.136 min, MS cal.: 1816.82, found: $[M + 2H]^{2+}$ = 909.7. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.97 - 7.88 (m, 5 H), 7.77 - 7.68 (m, 4 H), 5.22 (d, *J* = 3.25 Hz, 3 H), 4.99 (dd, *J* = 11.13, 3.38 Hz, 3 H), 4.55 (d, *J* = 8.50 Hz, 3 H), 4.07 - 3.99 (m, 9 H), 3.94 - 3.86 (m, 3 H), 3.82 - 3.75 (m, 3 H), 3.59- 3.47 (m, 35 H), 3.21 (q, *J* = 5.50 Hz, 6 H), 2.31 (br t, *J* = 6.25 Hz, 6 H), 2.11 (s, 9 H), 2.05 - 1.98 (m, 15 H), 1.88 (s, 9 H), 1.27 - 1.21 (m, 3 H), 0.96 (t, *J* = 7.63 Hz, 9 H).

[0603] ***Preparation of Intermediate 296B:***



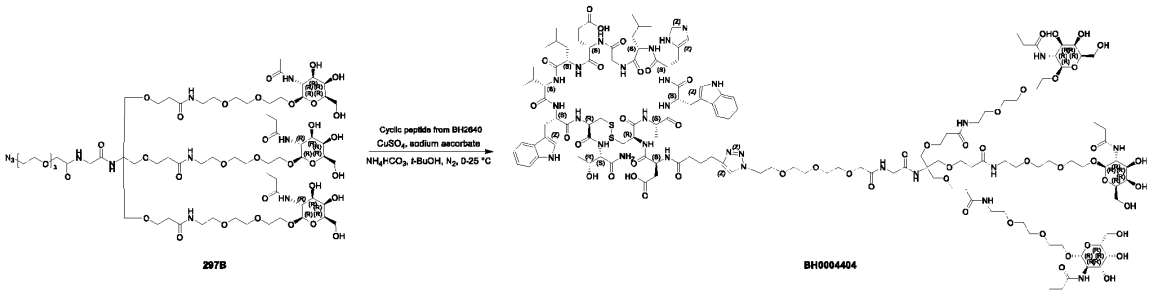
[0604] To a solution of **Intermediate 295B** (500 mg, 258 µmol, 1.0 equiv., TFA) in DMF (5.0 mL) was added **10A** (90.5 mg, 388 µmol, 1.5 equiv.), DIPEA (100 mg, 776 µmol, 135 µL, 3.0 equiv.) and HOBt (52.4 mg, 388 µmol, 1.5 equiv.), EDCI (74.4 mg, 388 µmol, 1.5 equiv.). The mixture was stirred at 25 °C for 2 hrs. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was slowly poured into a stirring cold 0.5 mol/L HCl solution (10.0 mL), then extracted with DCM (20.0 mL* 3). The combined organic layers were washed with 5% $NaHCO_3$ (50.0 mL), dried over Na_2SO_4, and concentrated under reduced pressure to get a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 100:1 to 5:1) to afford **Intermediate 296B** (370 mg, 173 µmol, 66.8% yield, 95.0% purity) as a gray solid. LCMS: RT = 1.394 min, MS cal.: 2031.91, found: $[M + 3H]^{3+}$ = 678.7.

[0605] ***Preparation of Intermediate 297B:***



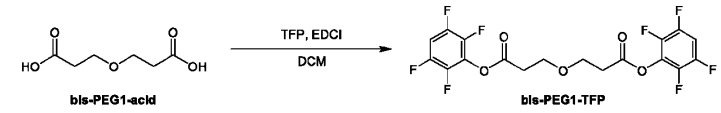
[0606] To a solution of **Intermediate 296B** (370 mg, 182 μmol, 1.0 equiv.) in MeOH (4.50 mL) was added NaOMe (5.4 M, 143 μL, 4.26 equiv.) at 0 °C, then the solution was stirred at 0 °C for 0.5 hrs. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was adjusted pH to 6 with 1.0 M HCl solution at 0 °C, and washed with DCM (15.0 mL * 3) for three times, the aqueous layer was lyophilized to afford **Intermediate 297B** (300 mg, crude) as a white solid. LCMS: RT = 0.871 min, MS cal.: 1653.82, found: $[M + 2H]^{2+}$ = 828.0.

[0607] ***Preparation of BH0004404:***

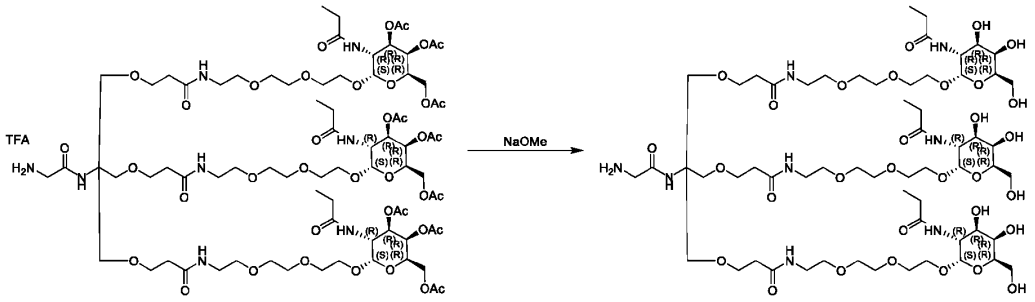


[0608] A mixture of **Cyclic peptide 107** (294 mg, 181 μmol, 1.0 equiv.) and **Intermediate 297B** (300 mg, 181 μmol, 1.0 equiv.) in t-BuOH (3.33 mL) and NH_4HCO_3 (0.2 M, 3.33 mL, 3.67 equiv.) was added $CuSO_4.5H_2O$ (0.4 M, 453 μL, 1.0 equiv.) and sodium ascorbate (143 mg, 725 μmol, 4.0 equiv.), the resulting reaction was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 2 hrs under N_2 atmosphere. LCMS showed the desired mass was detected and the reactant was consumed. The resulting reaction mixture was lyophilized to get a residue. The residue was purified by prep-HPLC (A: 0.5% HOAc in H_2O, B: MeCN) to afford **BH0004404** (130 mg, 38.5 μmol, 21.3% yield, 96.2% purity) as a white solid. LCMS: RT = 0.89 min, MS cal.: 3276.52, found: $[M + 3H]^{3+}$ = 1093.59.

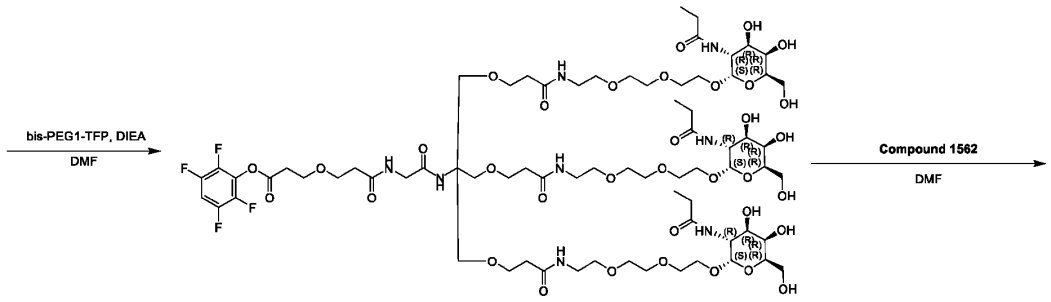
EXAMPLE 62. Procedure for preparation of BH0004406



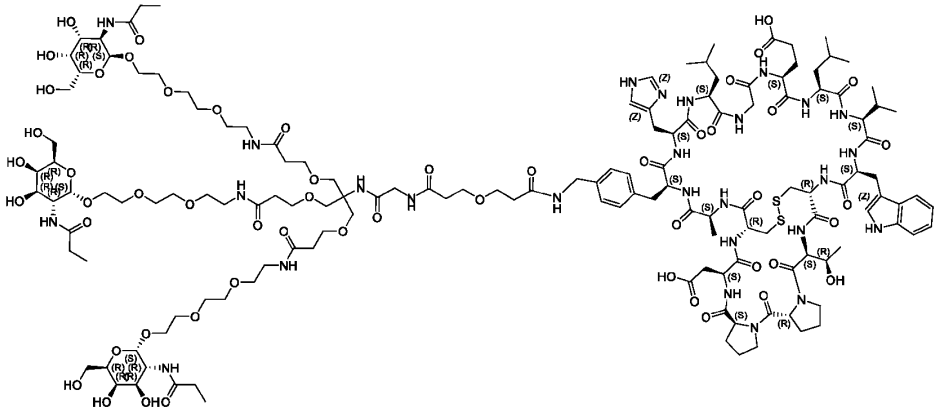
bis-PEG1-acid bis-PEG1-TFP



295 298

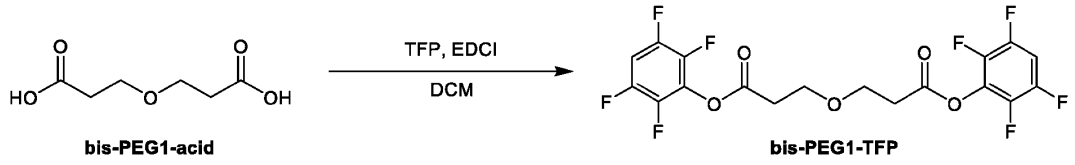


299



BH0004406

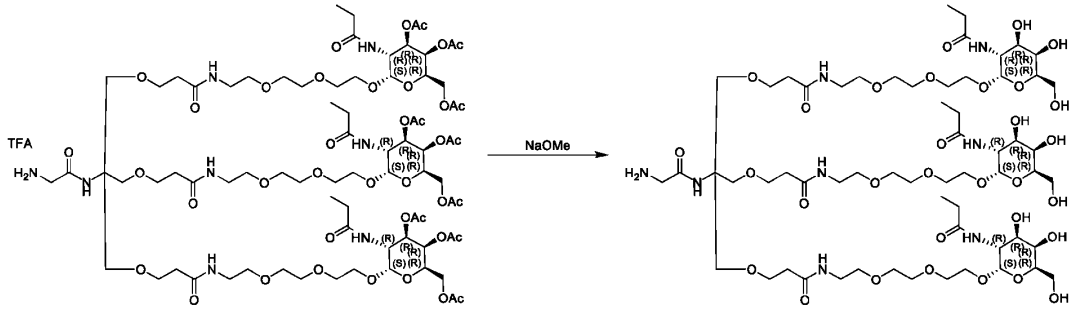
[0609] *Preparation of bis-PEG1-TFP:*



bis-PEG1-acid **bis-PEG1-TFP**

[0610] A mixture of **bis-PEG1-acid** (1.0 g, 6.17 mmol, 1.0 equiv.) and TFP (6.15 g, 37.0 mmol, 6.0 equiv.) was dissolved in DCM (10.0 mL). The solution was cooled to 0 ℃ in ice bath and EDCI (4.73 g, 24.6 mmol, 4.0 equiv.) was added. The solution was allowed to warm to 25 °C and stirred for 6 hrs. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was diluted with H_2O (50.0 mL) and extracted with DCM (20.0 mL * 3). The combined organic layers were washed with $NaHCO_3$ (10.0 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (A: 0.1% TFA in H_2O, B: MeCN) to afford **bis-PEG1-TFP** (2.65 g, 5.70 mmol, 92.3% yield) as a yellow solid. LCMS: RT = 2.505 min, MS cal.: 458.04, found: $[M + Na]^+$ = 480.9. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.99 - 7.86 (m, 2 H), 3.80 (t, *J* = 5.75 Hz, 4 H), 3.02 (t, *J* = 5.75 Hz, 4 H).

[0611] ***Preparation of Intermediate 298:***

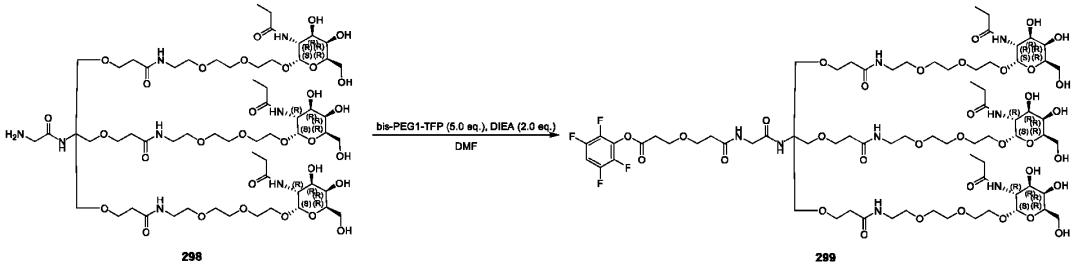


295 **298**

[0612] To a solution of **Intermediate 295** (500 mg, 258 μmol, 1.0 equiv., TFA) in MeOH (7.00 mL) was added NaOMe (5.4 M, 204 μL, 4.26 equiv.) at 0 °C, then the solution was stirred at 0 °C for 0.5 hrs. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was adjusted pH to 6 with 1.0 M HCl solution at 0 °C, and washed with DCM (15.0 mL * 3) for three times, the aqueous layer was lyophilized to afford **Intermediate 298** (400 mg, crude) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.97 (br t, *J* = 5.44 Hz, 3 H), 7.68 - 7.63 (m, 1 H), 7.44 (br d, *J* = 8.13 Hz, 3 H), 4.72 (d, *J* = 3.50 Hz, 3 H), 4.60 - 4.41 (m, 8 H), 4.11 (d, *J* = 5.25 Hz, 1 H), 4.01 (ddd, *J* = 11.01, 7.94, 3.56 Hz, 3 H), 3.64

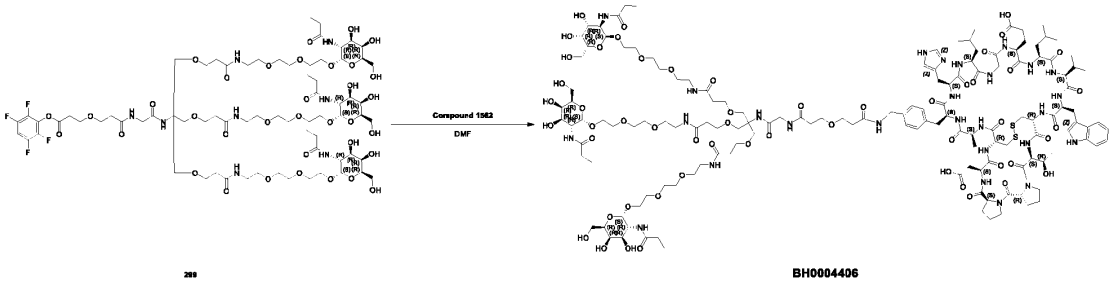
- 3.47 (m, 51 H), 3.42 - 3.37 (m, 8 H), 3.16 (d, *J* = 5.13 Hz, 6 H), 2.31 (br t, *J* = 6.19 Hz, 6 H), 2.16 - 2.07 (m, 6 H), 0.98 (t, *J* = 7.57 Hz, 9 H).

[0613] ***Preparation of Intermediate 299:***



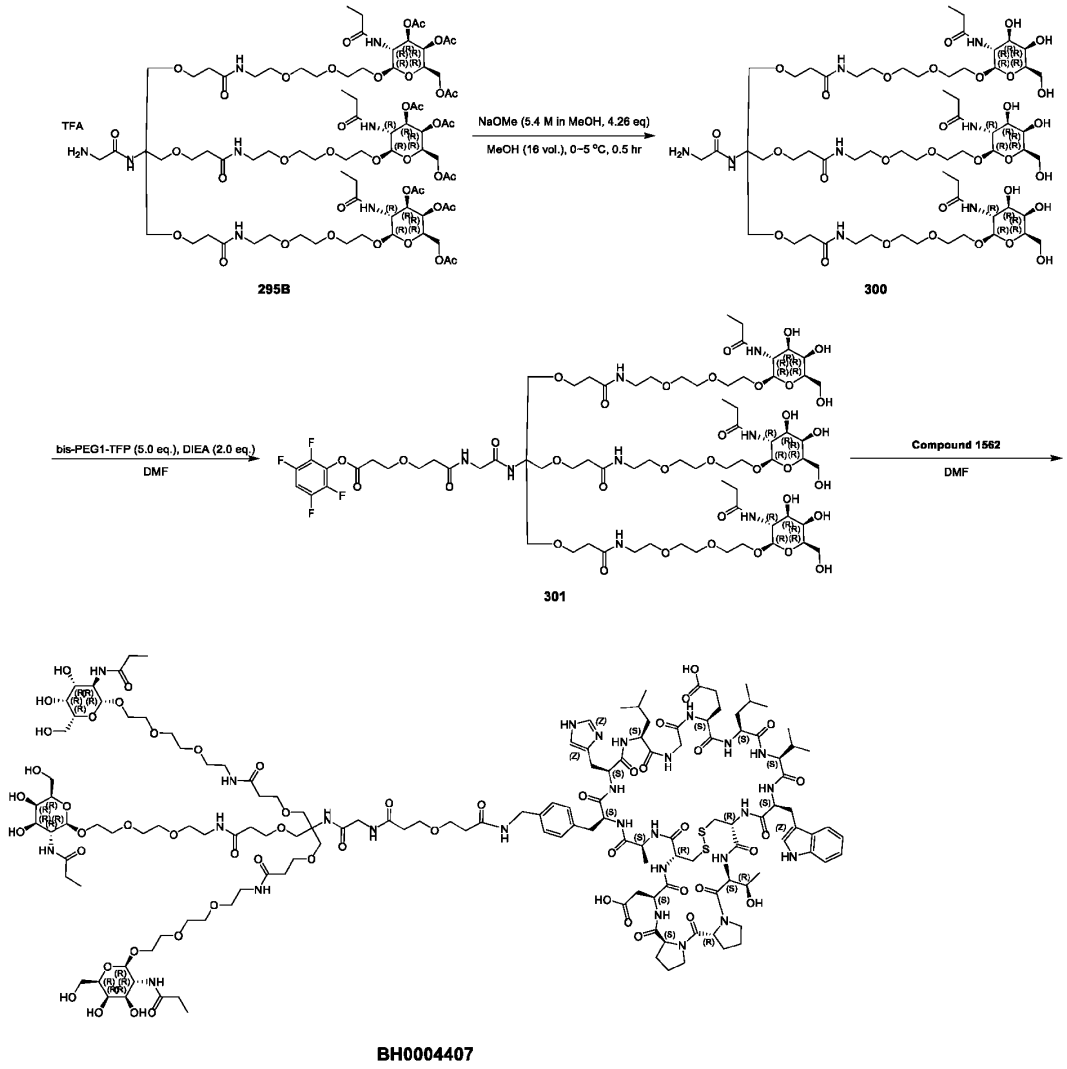
[0614] To a solution of **bis-PEG1-TFP** (636 mg, 1.39 mmol, 5.0 equiv.) in DMF (2.0 mL) was added **Intermediate 298** (400 mg, 277 µmol, 1.0 equiv.) and DIEA (71.8 mg, 555 µmol, 96.8 µL, 2.0 equiv.) in DMF (2.0 mL) at 0 °C, then the solution was stirred at 0 °C for 0.5 hrs. LCMS showed the desired mass was detected and the reactant was consumed. The reaction was purified by prep-HPLC (A: 0.1% TFA in H_2O, B: MeCN) to afford **Intermediate 299** (190 mg, 103 µmol, 37.0% yield, 93.7% purity) as a white solid. LCMS: RT = 0.341 min, MS cal.: 1730.76, found: $[M + 2H]^{2+}$ = 866.7.

[0615] ***Preparation of BH0004406:***



[0616] To a mixture of **Compound 1562** (223 mg, 131 µmol, 1.2 equiv.) and DIEA (42.5 mg, 329 µmol, 57.3 µL, 3.0 equiv.) in DMF (1.0 mL) was added **Intermediate 299** (190 mg, 109 µmol, 1.0 equiv.) in DMF (1.0 mL), and then the mixture was stirred at 0 °C for 1 hr. LCMS showed the desired mass was detected and the reactant was consumed. The reaction was purified by prep-HPLC (A: 0.5% HOAc in H_2O, B: MeCN) to afford **BH0004406** (162 mg, 47.6 µmol, 43.4% yield, 97.5% purity) as a white solid. LCMS: RT = 0.90 min, MS cal.: 3260.51, found: $[M + 3H]^{3+}$ = 1088.3.

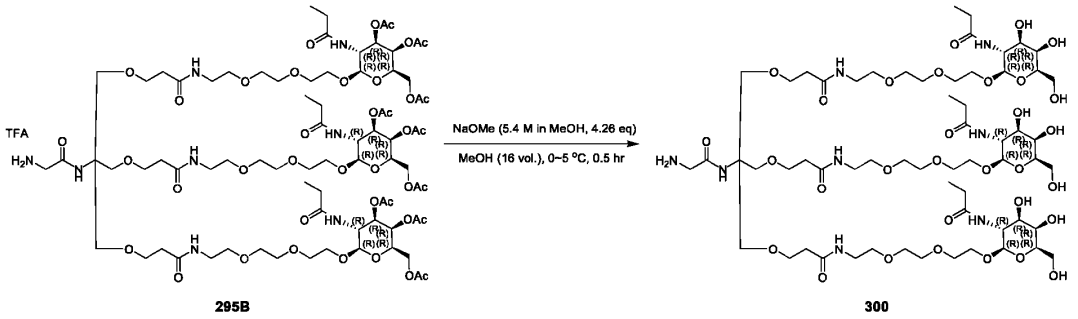
EXAMPLE 63. Procedure for preparation of BH0004407



295B 300 301

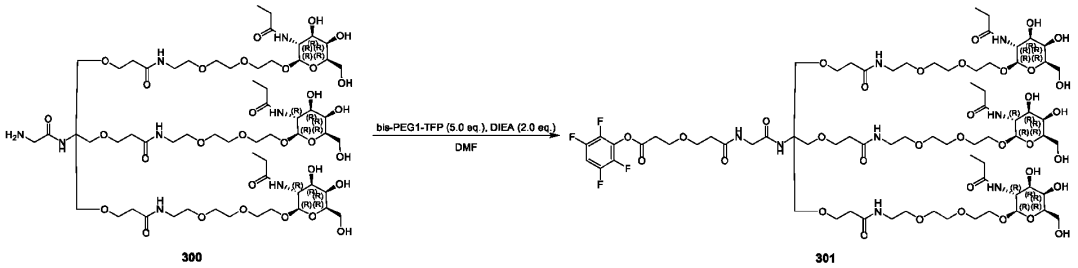
BH0004407

[0617] ***Preparation of Intermediate 300:***



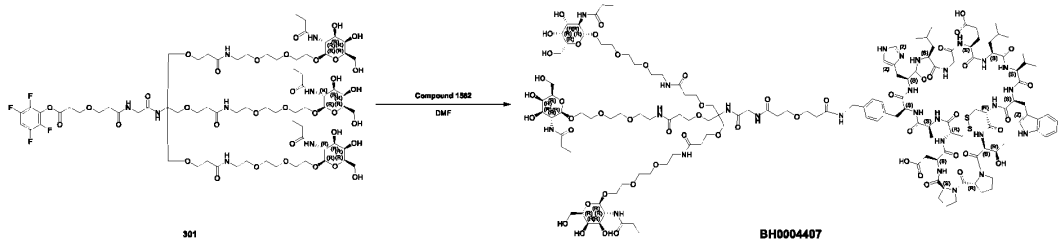
[0618] To a solution of **295B** (500 mg, 258 μmol, 1.00 equiv., TFA) in MeOH (7.00 mL) was added NaOMe (5.4 M, 204 μL, 4.26 equiv.) at 0 °C, then the solution was stirred at 0 °C for 0.5 hr. LCMS showed the desired mass was detected and the reactant was consumed. The reaction mixture was adjusted pH to 6 with 1.0 M HCl solution at 0 °C, and washed with DCM (15.0 mL * 3) for three times, the aqueous layer was lyophilized to afford **Intermediate 300** (400 mg, crude) as a white solid. LCMS: RT = 0.866 min, MS cal.: 1438.73, found: $[M + 2H]^{2+}$ = 720.5. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.01 (br t, *J* = 5.32 Hz, 3 H), 7.67 - 7.50 (m, 4 H), 4.71 - 4.43 (m, 7 H), 4.29 (d, *J* = 8.51 Hz, 3 H), 3.80 - 3.64 (m, 11 H), 3.44 - 3.58 (m, 46 H), 3.32 - 3.27(m, 7 H), 3.19 (br d, *J* = 5.88 Hz, 8 H), 2.31 (br t, *J* = 6.19 Hz, 6 H), 2.07 (q, *J* = 7.59 Hz, 6 H), 0.99 (t, *J* = 7.57 Hz, 9 H).

[0619] ***Preparation of Intermediate 301:***



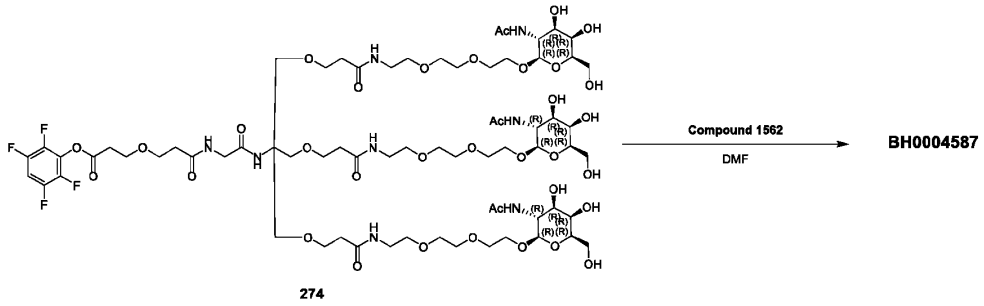
[0620] To a solution of **bis-PEG1-TFP** (636 mg, 1.39 mmol, 5.00 equiv.) in DMF (2.00 mL) was added **Intermediate 300** (400 mg, 277 μmol, 1.0 0equiv.) and DIEA (71.8 mg, 555 μmol, 96.8 μL, 2.00 equiv.) in DMF (2.00 mL) at 0 °C, then the solution was stirred at 0 °C for 0.5 hr. LCMS showed the desired mass was detected and the reactant was consumed. The reaction was purified by prep-HPLC (A: 0.1% TFA in H_2O, B: MeCN) to afford **Intermediate 301** (180 mg, 89.6 μmol, 32.2% yield, 86.2% purity) as a white solid. LCMS: RT = 0.328 min, MS cal.: 1730.76, found: $[M + 2H]^{2+}$ = 866.8.

[0621] ***Preparation of BH0004407:***



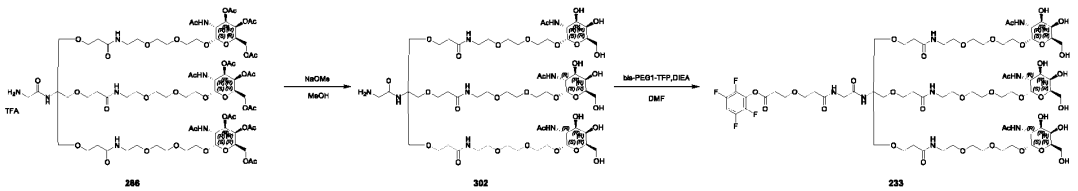
[0622] To a mixture of **Compound 1562** (211 mg, 124 µmol, 1.20 equiv.), DIEA (40.3 mg, 311 µmol, 54.3 µL, 3.00 equiv.) in DMF (1.00 mL) was added **Intermediate 301** (180 mg, 103 µmol, 1.00 equiv.) in DMF (1.00 mL), and then the mixture was stirred at 0 °C for 1 hr. LCMS showed the desired mass was detected and the reactant was consumed. The reaction was purified by prep-HPLC (A: 0.5% HOAc in H_2O, B: MeCN) to afford **BH0004407** (126 mg, 37.8 µmol, 36.4% yield, 98.7% purity) as a white solid. LCMS: RT = 0.90 min, MS cal.: 3260.51, found: $[M + 3H]^{3+}$ = 1088.3.

[0623] **BH0004587** was synthesized using the same procedure as **BH0004407** which was performed by following the procedure mentioned in **[0622]**.

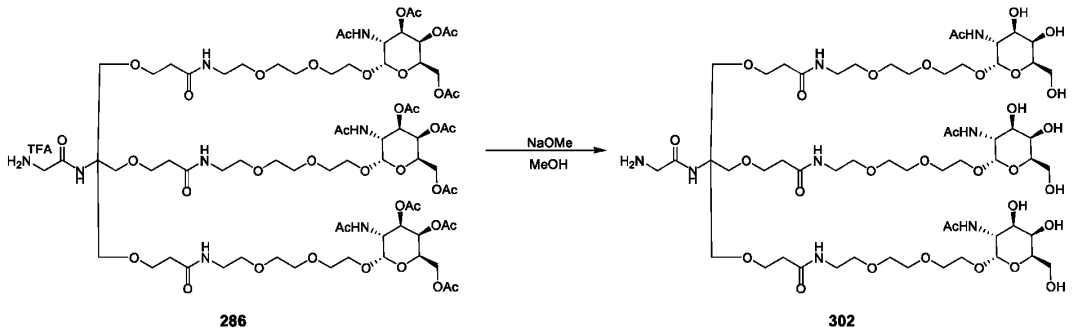


[0624] 150 mg of **Intermediate 274** with **Compound 1562** afforded **BH0004587** (129 mg, 38.7 µmol, 43.6% yield, 96.8% purity) as a white solid. LCMS: RT =0.350 min, MS cal.:3218.47, found: $[M + 3H]^{3+}$ =1074.2.

EXAMPLE 64. Procedure for preparation of *Intermediate 233:*

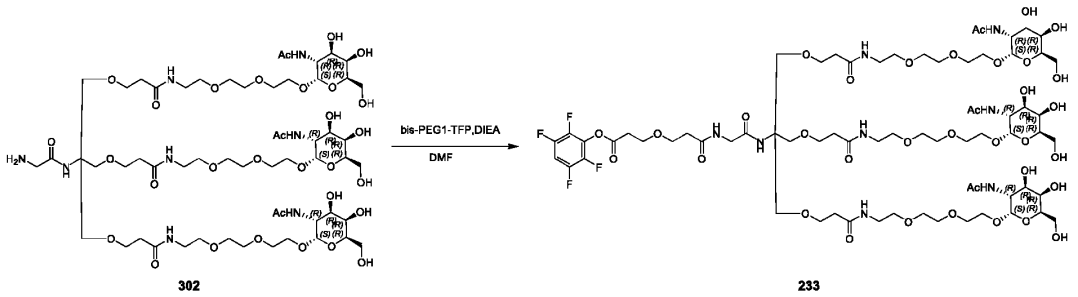


[0625] ***Preparation of Intermediate 302:***



[0626] A mixture of **Intermediate 286** (1.9 g, 1.01 mmol, 1.0 equiv, TFA) in MeOH (19 mL) was added NaOMe (5.4 M, 793 µL, 4.2 equiv.). The mixture was stirred at 0 °C for 0.5 hr. The reaction was monitored by LCMS, LCMS showed one main peak with desired m/z was detected. The reaction mixture was adjusted pH to 6 with 1.0 M HCl solution at 0 °C, and washed with DCM (10 mL * 3) for three times, the aqueous layer was lyophilized. **Intermediate 302** (1.5 g, 847 µmol, 84.2% yield, 78.9% purity) as yellow oil. LCMS: RT = 0.577 min, MS cal.:1396.68, found: $[M + 2H^{2+}]$ =699.4.

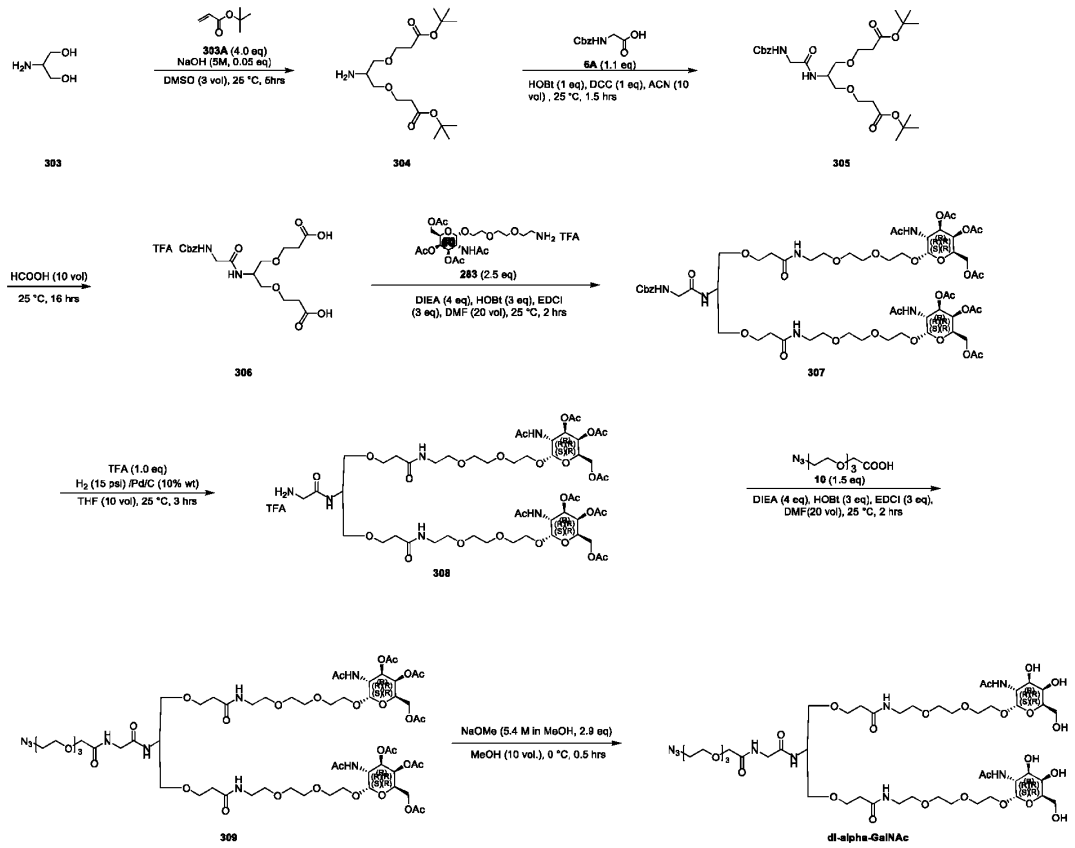
[0627] ***Preparation of Intermediate 233:***



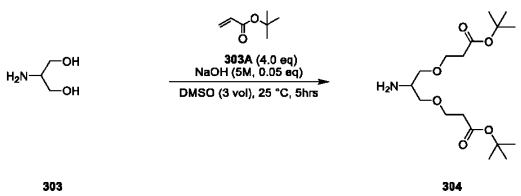
[0628] To a solution of **bis-PEG1-TFP** (1.39 g, 3.04 mmol, 5.0 equiv.) in DMF (9 mL) was added **Intermediate 302** (850 mg, 608 µmol, 1.0 equiv.) and DIEA (157 mg, 1.22 mmol, 211 µL, 2.0 equiv.) in DMF (9 mL) at 0 °C The mixture was stirred at 0 °C for 0.5 hr. The reaction was monitored by LCMS, LCMS

showed one main peak with desired m/z was detected. The reaction mixture was filtrated. The combined was purified by prep-HPLC (TFA condition). **Intermediate 233** (170 mg, 80.5 μmol, 18.4% yield, 80% purity) as a white solid. LCMS: RT = 1.012 min, MS cal.: 1688.72, found: $[M + 2H]^{2+}$ =845.6.

EXAMPLE 65. Procedure for preparation of di-alpha-GalNAc*:*

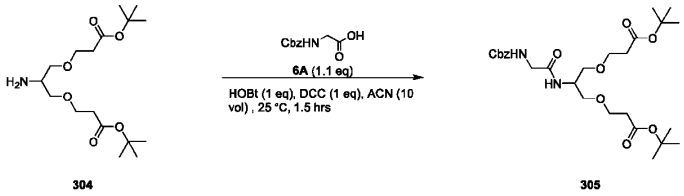


[0629] ***Preparation of Intermediate 304:***



[0630] To a mixture of ***Intermediate* 303** (5.20 g, 57.0 mmol, 1.0 equiv.) in DMSO (16.0 mL) was added aqueous NaOH (5.0 M, 570 µL, 0.05 equiv.) dropwise at 0 - 15 °C for over 5 min. After addition, the mixture was stirred at 0 - 15 °C for 5 min, then ***Intermediate* 303A** (29.2 g, 228 mmol, 33.1 mL, 4.0 equiv.) was added to the reaction mixture dropwise at 20 °C. The resulting mixture was stirred at 25 °C for 5 hrs. The reaction was monitored by LCMS, LCMS showed the desired mass (one main peak with desired was detected.). The resulting reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in EtOAc (20.0 mL), quenched by addition of water (20.0 mL), and extracted with EtOAc (20.0 mL *3). The combined organic layers were washed with brine (60.0 mL *2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **Intermediate 304** (19.6 g, crude) as colorless oil. LCMS: RT = 1.336 min, MS cal.: 347.23, found: $[M + H]^+$ = 348.2. ^{1}H NMR (400 MHz, CHLOROFORM) δ =3.75 - 3.59 (m, 4 H), 3.56 - 3.26 (m, 4 H), 2.96 - 2.77 (m, 1 H), 2.48 (br t, *J* = 6.32 Hz, 3 H), 2.46 - 2.29 (m, 1 H), 1.48 - 1.43 (m, 18 H).

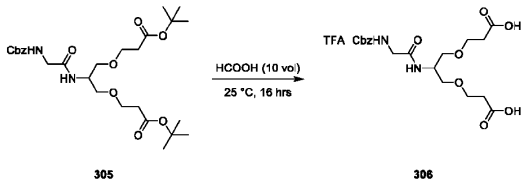
[0631] ***Preparation of Intermediate 305:***



304 305

[0632] To a solution of **Intermediate 304** (4.40 g, 9.30 mmol, 1.0 equiv.) in ACN (44.0 mL) was added HOBt (1.26 g, 9.30 mmol, 1.0 equiv.), **Intermediate 6A** (2.14 g, 10.2 mmol, 1.1 equiv.) and DCC (1.92 g, 9.30 mmol, 1.88 mL, 1.0 equiv.). The mixture was stirred at 25 °C for 1.5 hrs. The reaction was monitored by LCMS, LCMS showed the desired mass (one main peak with desired was detected.). The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel (100-200 mesh size) using DCM/MeOH (10:1) as eluent. **Intermediate 305** (4.18 g, 7.37 mmol, 79.2% yield, >95% purity) was obtained as a yellow oil. LCMS: RT = 1.653 min, MS cal.: 538.29, found: [M –Two tert-butyl groups$^+$]$^+$ = 427.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ =7.69 (br d, *J* = 8.13 Hz, 1 H), 7.41 - 7.30 (m, 6 H), 5.02 (s, 2 H), 3.92 - 3.99 (m, 1 H), 3.61 - 3.54 (m, 6 H), 3.35 (br d, *J* = 5.00 Hz, 4 H), 2.41 (br t, *J* = 6.07 Hz, 4 H), 1.40 (s, 18 H).

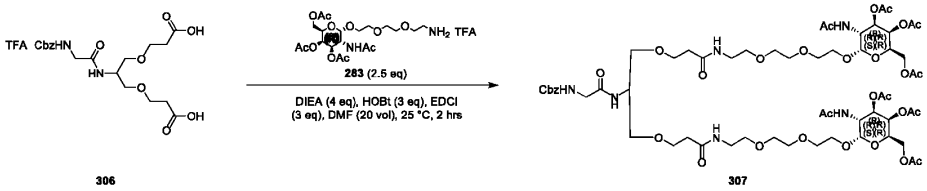
[0633] ***Preparation of Intermediate 306:***



305 306

[0634] To a solution of **Intermediate 305** (2.00 g, 3.53 mmol, 1.0 equiv.) in HCOOH (20.0 mL) was stirred at 25 °C for 16 hrs. The reaction was monitored by LCMS, LCMS showed the desired mass (one main peak with desired was detected.). The reaction mixture was concentrated under reduced pressure to remove solvent. The crude was precipitated by petroleum ether (200 mL) at 25°C to afford **Intermediate 306** (1.69 g, crude) as a yellow oil. LCMS: RT = 0.938 min, MS cal.: 426.16, found: $[M + H]^+$ = 427.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.42 - 11.85 (m, 2 H), 7.69 (br d, J = 8.13 Hz, 1 H), 7.53 - 7.04 (m, 6 H), 5.03 (s, 2 H), 3.99 - 3.91 (m, 1 H), 3.64 - 3.55 (m, 6 H), 3.40 - 3.32 (m, 4 H), 2.44 (br t, J = 6.32 Hz, 4 H).

[0635] ***Preparation of Intermediate 307:***

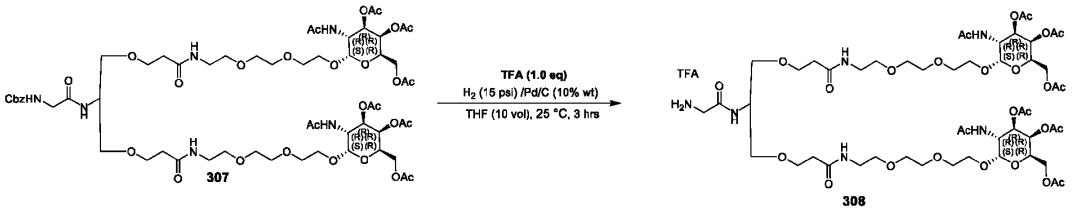


306 307

[0636] To a solution of **Intermediate 306** (0.79 g, 1.85 mmol, 1.0 equiv.) and **Intermediate 283** (2.22 g, 4.63 mmol, 2.5 equiv.) in DMF (15 mL) was added DIEA (958 mg, 7.41 mmol, 1.29 mL, 4.0 equiv.), HOBt (751 mg, 5.56 mmol, 3.0 equiv.) and EDCI (1.07 g, 5.56 mmol, 3.0 equiv.). The mixture was stirred at 25 °C for 2 hrs. The reaction was monitored by LCMS, LCMS showed the desired mass (one main peak with desired was detected.). The reaction mixture was slowly poured into a stirring cold 0.5 mol/L HCl solution (20.0 mL), and stirred for 10 min. White precipitate was formed and filtered, the aqueous phase was extracted with DCM (20.0 mL* 2). The combined organic layers were washed with Sat. $NaHCO_3$ (60.0 mL), dried over Na_2SO_4, and concentrated under reduced pressure to get a residue. The crude product was purified by column chromatography on silica gel (100-200 mesh size) using DCM/MeOH (10:1) as eluent. **Intermediate 307** (1.85 g, 1.30 mmol, 70.3% yield, >95% purity) was obtained as a pink oil. LCMS: RT = 1.267 min, MS cal.: 1346.58, found: $[M + 2H]^{2+}$ = 674.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.03 - 7.89 (m, 5 H), 7.72 (br d, J = 8.00 Hz, 1 H), 7.39 - 7.31 (m, 5 H), 5.31 (br d, J = 2.38 Hz, 2 H), 5.10 - 4.99 (m, 4 H), 4.90 (br d, J = 3.13 Hz, 2 H), 4.27 - 4.16 (m, 4 H), 4.05 - 3.91 (m, 4 H), 3.69 (br dd, J = 11.63, 7.88 Hz, 2 H), 3.66 -

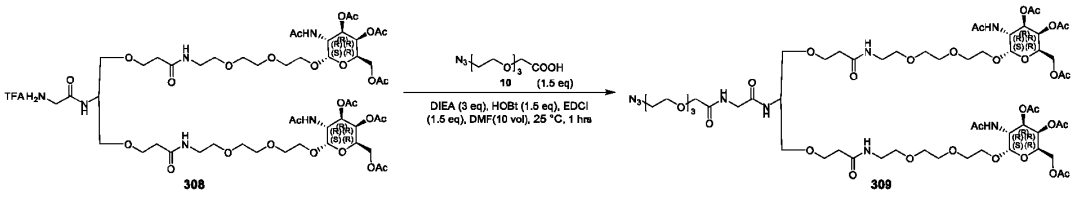
3.46 (m, 22 H), 3.40 (br t, *J* = 5.82 Hz, 6 H), 3.23 – 3.16 (m, 4 H), 2.31 (br t, *J* = 6.13 Hz, 4 H), 1.99 (s, 6 H), 2.10 (s, 6 H), 1.89 (s, 6 H), 1.81 (s, 6 H).

[0637] ***Preparation of Intermediate 308:***



[0638] The 50 mL round-bottom flask was purged with Ar for 3 times and added Pd/C (0.18 g, 1.37 mmol, 10% purity, 1.0 equiv.) carefully. Then THF (18.0 mL) was added to infiltrate the Pd/C completely, followed by the solution **Intermediate 307** (1.84 g, 1.37 mmol, 1.0 equiv.) and TFA (156 mg, 1.37 mmol, 101 µL, 1.0 equiv.) in THF slowly under Ar atmosphere. The resulting mixture was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25 °C for 3hrs under H_2 atmosphere (15 psi). The reaction was monitored by LCMS, LCMS showed the desired mass (one main peak with desired was detected.). The reaction mixture was filtered carefully through siliceous earth under N_2 atmosphere, the cake was washed with THF (20.0 mL*2). Then, the filter cake was added water immediately. The organic layer concentrated under reduced pressure to afford **Intermediate 308** (1.82 g, crude, TFA) as a yellow oil. LCMS: RT = 0.962 min, MS cal.: 1213.25, found: $[M + 2H]^{2+}$ = 607.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.30 (br d, *J* = 8.13 Hz, 1 H), 8.06 - 7.95 (m, 6 H), 5.31 (d, *J* = 2.50 Hz, 2 H), 5.02 (dd, *J* = 11.76, 3.25 Hz, 2 H), 4.91 (d, *J* = 3.38 Hz, 2 H), 4.25 - 4.18 (m, 4 H), 4.08 - 3.98 (m, 5 H), 3.72 - 3.67 (m, 2 H), 3.62 - 3.50 (m, 22 H), 3.43 - 3.38 (m, 6 H), 3.20 (q, *J* = 5.84 Hz, 4 H), 2.32 (t, *J* = 6.44 Hz, 4 H), 2.10 (s, 6 H), 1.99 (s, 6 H), 1.91 - 1.88 (m, 6 H), 1.81 (s, 6 H).

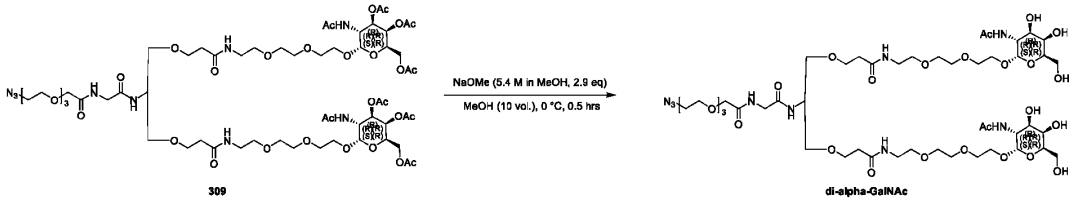
[0639] ***Preparation of Intermediate 309:***



[0640] To a solution of **Intermediate 308** (1.80 g, 1.36 mmol, TFA, 1.0 equiv.) and **Intermediate 10** (474 mg, 2.03 mmol, 1.5 equiv.) in DMF (18.0 mL) was added DIEA (526 mg, 4.07 mmol, 709 µL, 3.0 equiv.). HOBt (275 mg, 2.03 mmol, 1.5 equiv.) and EDCI (390 mg, 2.03 mmol, 1.5 equiv.). The mixture was

stirred at 25 °C for 1 hr. The reaction was monitored by LCMS, LCMS showed the desired mass (one main peak with desired was detected.). The reaction mixture was slowly poured into a stirring cold 0.5 mol/L HCl solution (20.0 mL), and stirred for 10 min. White precipitate was formed and filtered, the aqueous phase was extracted with DCM (20.0 mL* 2). The combined organic layers were washed with Sat.$NaHCO_3$ (60.0 mL), dried over Na_2SO_4, and concentrated under reduced pressure to get a residue. The crude product was purified by column chromatography on silica gel (100-200 mesh size) using DCM/MeOH (10:1) as eluent. **Intermediate 309** (1.21 g, 841 µmol, 62.0% yield, 99% purity) was obtained as a pink oil. LCMS: RT = 1.188 min, MS cal.: 1427.63, found: $[M + 2H]^{2+}$ = 714.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.99 (d, *J* = 8.13 Hz, 2 H), 7.90 (br t, *J* = 5.44 Hz, 2 H), 7.83 - 7.75 (m, 2 H), 5.31 (d, *J* = 2.63 Hz, 2 H), 5.02 (dd, *J* = 11.82, 3.19 Hz, 2 H), 4.90 (d, *J* = 3.38 Hz, 2 H), 4.25 - 4.17 (m, 4 H), 4.09 - 3.95 (m, 5 H), 3.77 - 3.68 (m, 4 H), 3.92 (s, 2 H), 3.63 - 3.52 (m, 28 H), 3.44 - 3.36 (m, 8 H), 3.34 (br d, *J* = 5.63 Hz, 2 H), 3.20 (br d, *J* = 5.75 Hz, 4 H), 2.31 (br t, *J* = 6.38 Hz, 4 H), 2.10 (s, 6 H), 1.99 (s, 6 H), 1.89 (s, 6 H), 1.81 (s, 6 H).

[0641] ***Preparation of Intermediate di-alpha-GalNAc***:



[0642] To a solution of **Intermediate 309** (1.21 g, 894 µmol, 1.0 equiv.) in MeOH (12.0 mL) was added NaOMe (5.4 M, 480 µL, 2.9 equiv.) at 0 °C. The mixture was stirred at 0 °C for 0.5 hrs. The reaction was monitored by LCMS, LCMS showed the desired mass (one main peak with desired was detected.). The reaction mixture was added with 1.0 M HCl solution (2.50 mL) till the pH=6. The mixture was diluted with H_2O (7.50 mL) and extracted with DCM (120 mL * 3). The mixture was freeze-dried to afford ***di-alpha-GalNAc*** (1.18 g, crude) as a white solid. LCMS: RT = 0.828 min, MS cal.: 1175.57, found: $[M + 2H]^{2+}$ = 589.0 ^{1}H NMR (400 MHz, DMSO-d_6) δ= 8.02 (br t, *J* = 5.50 Hz, 2 H), 7.90 (br d, *J* = 8.13 Hz, 1 H), 7.80 (t, *J* = 5.69 Hz, 1 H), 7.62 (d, *J* = 8.00 Hz, 2 H), 4.70 (d, *J* = 3.63 Hz, 2 H), 3.99 - 3.90 (m, 6 H), 3.76 - 3.71 (m, 5 H), 3.63 - 3.44 (m, 44 H), 3.40 - 3.35 (m, 8 H), 3.21 - 3.17 (m, 4 H), 2.31 (br t, *J* = 6.50 Hz, 4 H), 1.82 (s, 6 H).

Throughout this application, various publications are referenced by author name and date, or by patent number or patent publication number. The disclosures of these publications are hereby incorporated in their entireties by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein. However, the citation of a reference herein should not be construed as an acknowledgement that such reference is prior art to the present invention.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims. For example, pharmaceutically acceptable salts other than those specifically disclosed in the description and Examples herein can be employed. Furthermore, it is intended that specific items within lists of items, or subset groups of items within larger groups of items, can be combined with other specific items, subset groups of items or larger groups of items whether or not there is a specific disclosure herein identifying such a combination.

CLAIMS

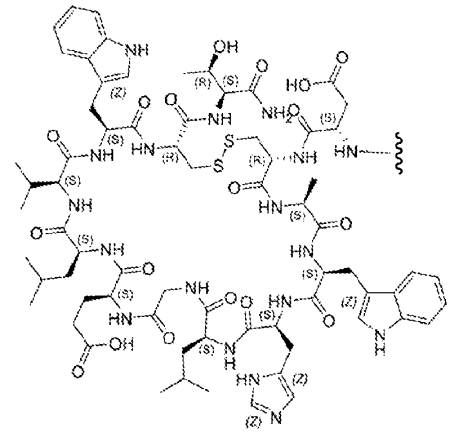
What is claimed is:

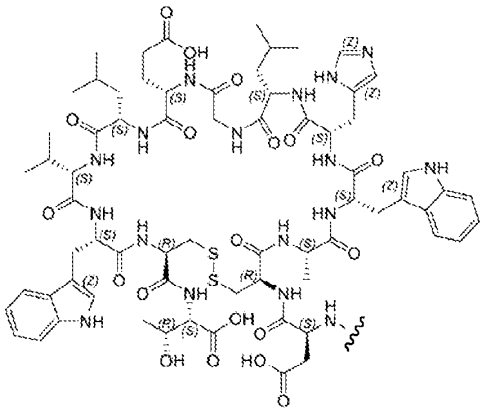
1. A bifunctional compound according to the chemical structure:

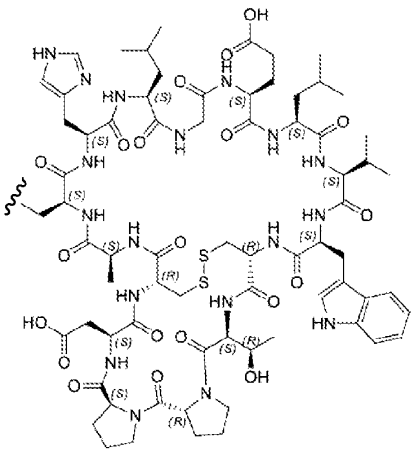
,

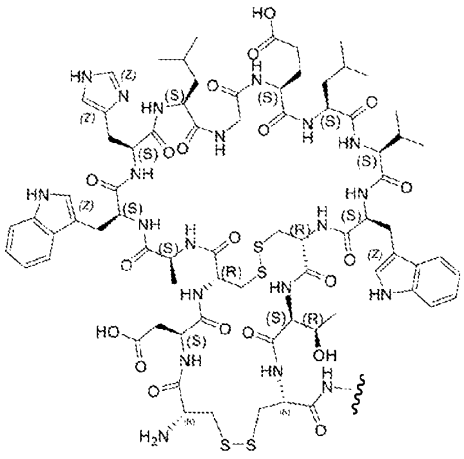
wherein:

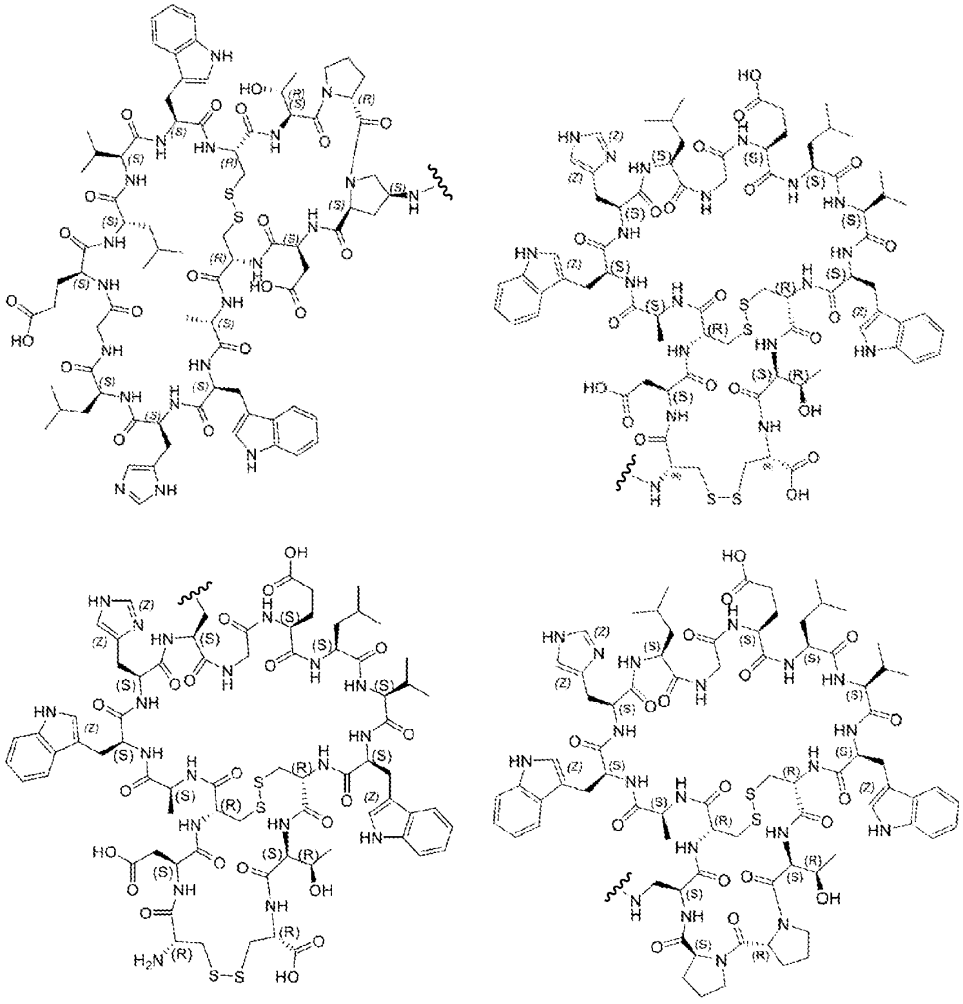
[CPBM] is a Circulating Protein Binding Moiety which binds to Immunoglobulin G (IgG) in a subject, wherein IgG mediates a disease state or condition and is to be removed by the action of hepatocytes or other cells of the subject, wherein [CPBM] is or comprises a moiety selected from:





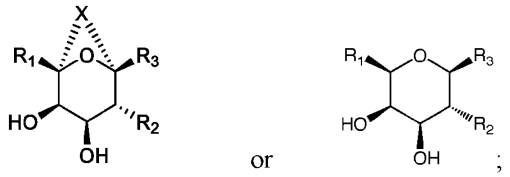






;

[CRBM] is a Cellular Receptor Binding Moiety which binds to asialoglycoprotein receptors of hepatocytes or other cell receptors in the subject, wherein [CRBM] is or comprises an [ASGPRBM] group according to the chemical structure:



or ;

each [CON] is an optional connector chemical moiety which, when present, connects the [LINKER] to [CPBM] or to [CRBM];

[LINKER] is a chemical moiety having a valency from 1 to 15, which covalently attaches to one or more [CRBM] or [CPBM] groups, optionally through a [CON], wherein the [LINKER] optionally itself contains one or more [CON] groups;

k' is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

j' is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

h and h' are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

i_L is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

with the proviso that at least one of h, h', and i_L is at least 1,

or a salt, stereoisomer, or solvate thereof.

2. The compound of claim 1, wherein k', j', h, h', and i_L are each independently 1, 2, or 3.

3. The compound of claim 1, wherein:

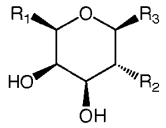
X in [ASGPRBM] is -O-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-O-, -S-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-S-, -N(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-N(R^{N1})-, or -C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, when X is 2 atoms in length,

X in [ASGPRBM] is -O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-, -O-C(R^{N1})(R^{N1})-O-, -O-C(R^{N1})(R^{N1})-S-, -O-C(R^{N1})(R^{N1})-N(R^{N1})-, -S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-S, -S-C(R^{N1})(R^{N1})-S-, -S-C(R^{N1})(R^{N1})-O-, -S-C(R^{N1})(R^{N1})-N(R^{N1})-, -N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-N(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1})-, -N(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1})-, or -C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})- C(R^{N1})(R^{N1}), when X is 3 atoms in length, and

X in [ASGPRBM] is -O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -O-C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-, -S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, -S-C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, -N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, or -C(R^{N1})(R^{N1})-N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, when X is 4 atoms in length.

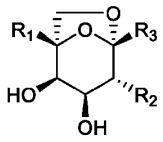
4. The compound of claim 1, wherein X is OCH_2 or CH_2O and wherein R^{N1} is H.

5. The compound of claim 1, wherein the [CRBM]/[ASGPRBM] group is a group according to the chemical structure:



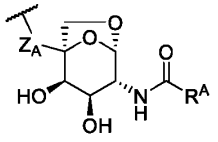
or a salt, stereoisomer, or solvate thereof.

6. The compound of claim 1, wherein the [CRBM]/[ASGPRBM] group is a group according to the chemical structure:

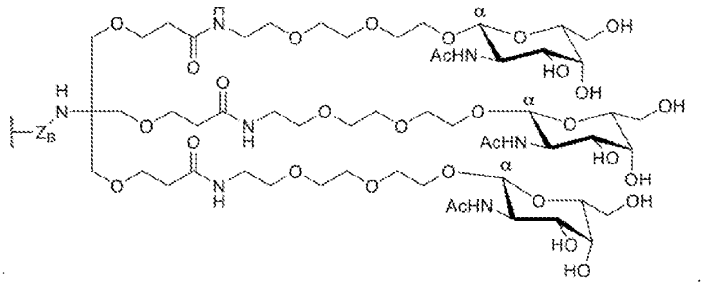


or a salt, stereoisomer, or solvate thereof.

7. The compound of claim 1, wherein the [ASGPRBM] group is a group according to the chemical structure:



or



;

wherein:

R^A is C_1-C_3 alkyl optionally substituted with 1-5 halo groups;

Z_A is -$(CH_2)_{IM}$-, -O-$(CH_2)_{IM}$-, -S-$(CH_2)_{IM}$-, -NR_M-$(CH_2)_{IM}$-, -C(O)-$(CH_2)_{IM}$-, a PEG group containing from 1 to 8 ethylene glycol residues, or -C(O)$(CH_2)_{IM}NR_M$-; and

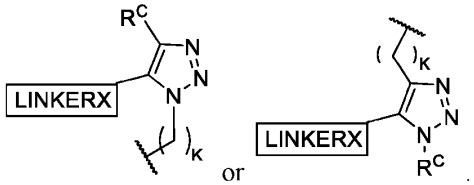
Z_B is absent, -$(CH_2)_{IM}$-, -C(O)-$(CH_2)_{IM}$-, or -C(O)-$(CH_2)_{IM}$-NR_M-.

8. The compound of claim 7, wherein at least one applies:

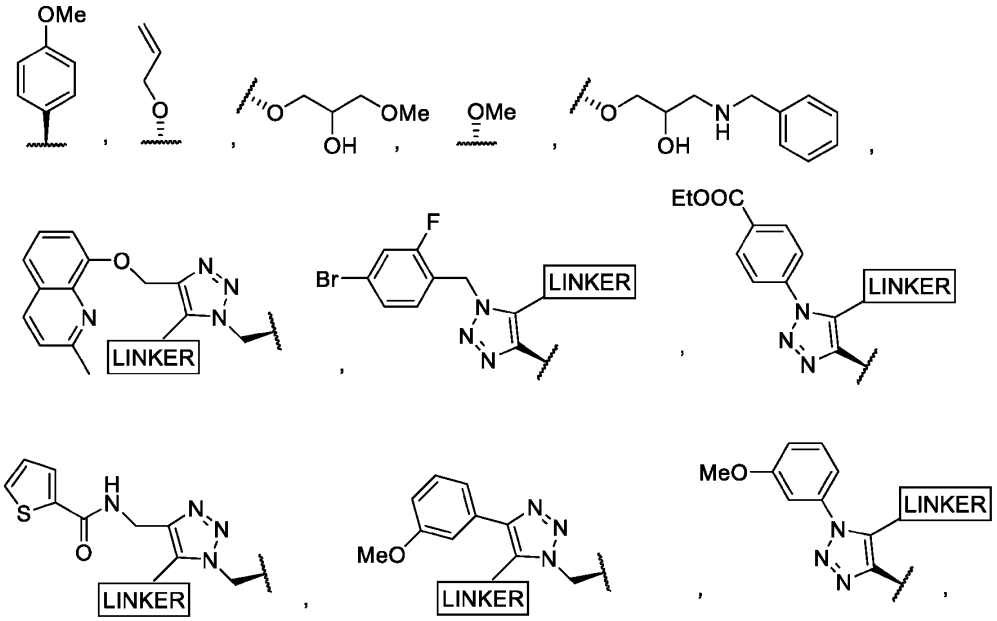
R^A is a methyl or ethyl group which is optionally substituted with 1-3 fluoro groups, or

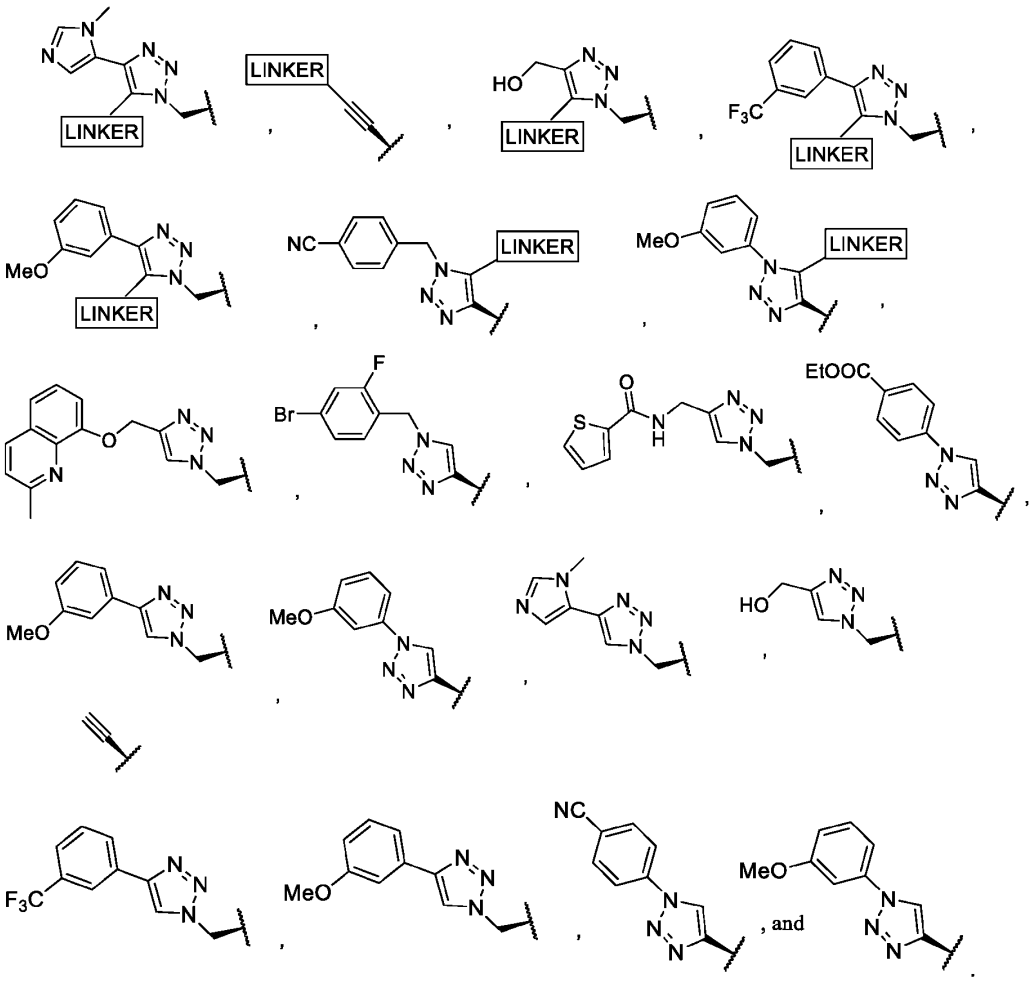
Z_A is a PEG group containing from 1 to 4 ethylene glycol residues.

9. The compound of claim 1, wherein R_1 and R_3 are each independently a group according to the chemical structure:

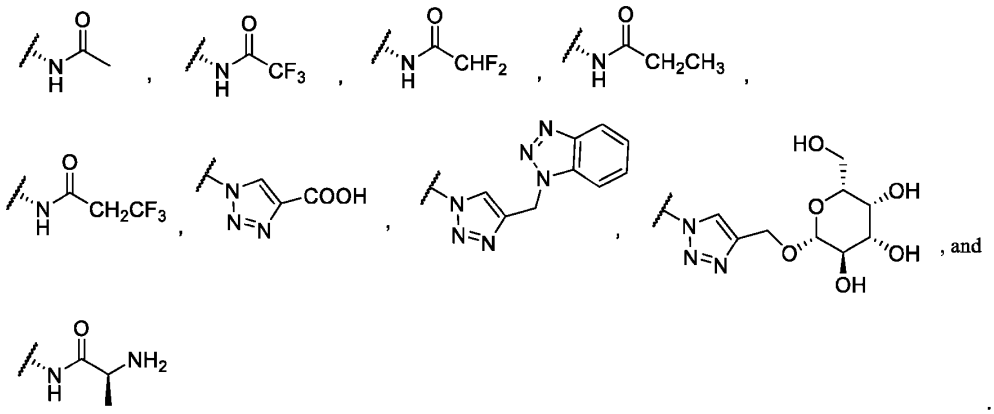


10. The compound of claim 1, wherein R_1 and R_3 of the [CRBM]/[ASGPRBM] group are each independently a moiety selected from the group consisting of

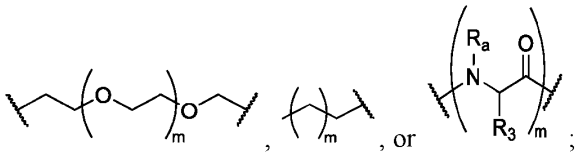




11. The compound of claim 1, where R_2 of the [CRBM]/[ASGPRBM] group is a moiety selected from the group consisting of



12. The compound of claim 1, wherein the linker is according to the chemical structure:



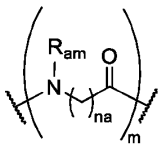
or a polypropylene glycol or polypropylene-co-polyethylene glycol linker containing between 1 and 100 alkylene glycol units;

wherein R_a is H, C_1-C_3 alkyl or alkanol or forms a cyclic ring with R^3 to form a pyrrolidine or hydroxypyrroline group and R^3 is a side chain derived from a D- or L amino acid selected from the group consisting of alanine (methyl), arginine (propyleneguanidine), asparagine (methylenecarboxyamide), aspartic acid (ethanoic acid), cysteine (thiol, reduced or oxidized di-thiol), glutamine (ethylcarboxyamide), glutamic acid (propanoic acid), glycine (H), histidine (methyleneimidazole), isoleucine (1-methylpropane), leucine (2-methylpropane), lysine (butyleneamine), methionine (ethylmethylthioether), phenylalanine (benzyl), proline, hydroxyproline (R^3 forms a cyclic ring with R_a and the adjacent nitrogen group to form a pyrrolidine or hydroxypyrrolidine group), serine (methanol), threonine (ethanol, 1-hydroxyethane), tryptophan (methyleneindole), tyrosine (methylene phenol) or valine (isopropyl); and

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15.

13. The compound of claim 1,

wherein the linker is a group according to the chemical formula:



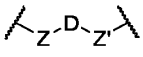
wherein:

R_{am} is H or C_1-C_3 alkyl optionally substituted with one or two hydroxyl groups;

na is 1-15; and

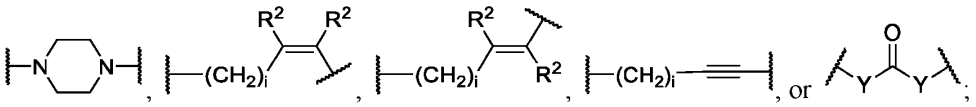
m is an integer ranging from 1 to 100; or

wherein the linker is a group according to the chemical formula:



wherein:

Z and Z' are each independently a bond, $-(CH_2)_i$-O-, $-(CH_2)_i$-S-, $-(CH_2)_i$-N(R)-,



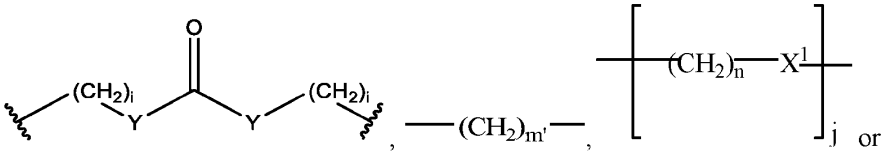
wherein the $-(CH_2)_i$ group, if present in Z or Z', is bonded to a connector group [CON], [MIFBM]/[IgGBM] or [ASGPRBM];

each R is H, or C_1-C_3 alkyl or alkanol;

each R^2 is independently H or C_1-C_3 alkyl;

each Y is independently a bond, O, S, or N-R;

each i is independently 0 to 100;

D is  or a bond, with the proviso that Z, Z' and D are not each simultaneously bonds;

j is an integer ranging from 1 to 100;

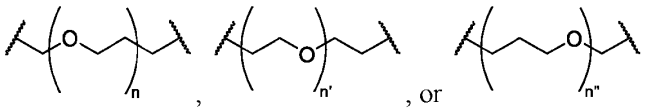
m' is an integer ranging from 1 to 100;

n is an integer ranging from 1 to 100;

X^1 is O, S, or N-R; and

R is H, or C_1-C_3 alkyl or alkanol.

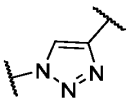
14. The compound of claim 1, wherein the linker is or comprises a group according to the chemical structure:



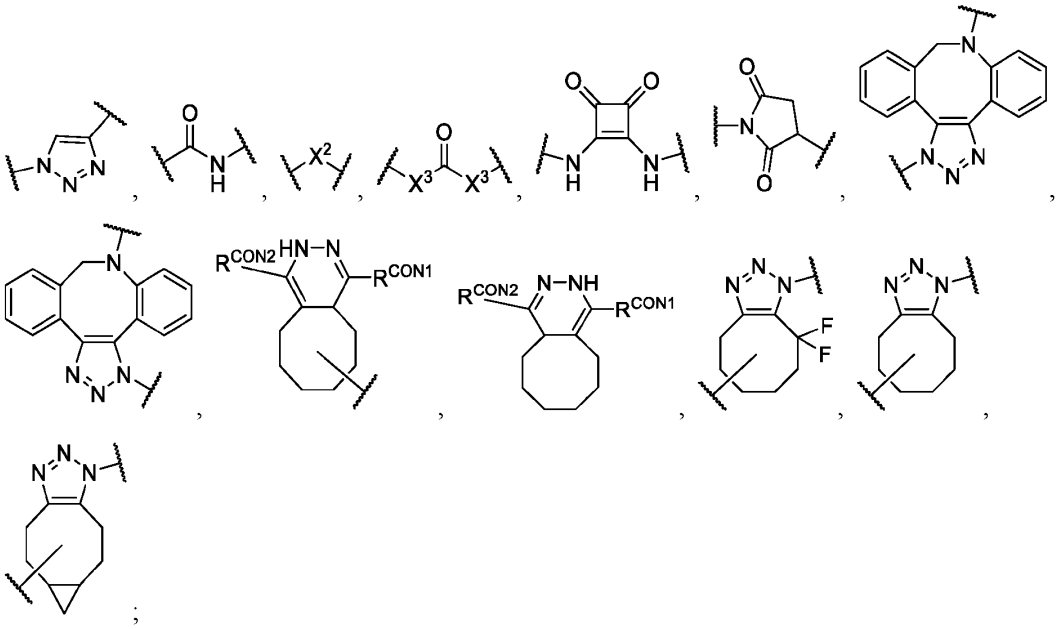
wherein each n and n' is independently 1 to 25; and each n" is independently 0, 1, 2, 3, 4, 5, 6, 7, or 8; or

wherein the linker is a group represented by the chemical formula:

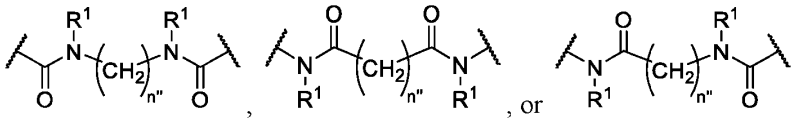
PEG-[CON]-PEG

wherein each PEG is independently a polyethylene glycol group containing from 1-12 ethylene glycol residues and [CON] is a triazole group  .

15. The compound of claim 1, wherein the [CON] is a group according to the structure:



wherein R^{CON1} and R^{CON2} are each independently H, methyl, a bond (for attachment to another moiety); or a diamide group according to the structure:



wherein:

X^2 is CH_2, O, S, NR^4, C(O), S(O), $S(O)_2$, $-S(O)_2O$, $-OS(O)_2$, or $OS(O)_2O$;

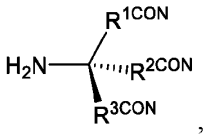
X^3 is O, S, or NR^4;

R^4 is H, C_1-C_3 alkyl or alkanol, or $-C(O)(C_1$-C_3 alkyl);

R^1 is H or C_1-C_3 alkyl; and

n" is independently 0, 1, 2, 3, 4, 5, 6, 7, or 8; or

the [CON] is a group according to the chemical structure:



wherein R^{1CON}, R^{2CON}, and R^{3CON} are each independently H, $-(CH_2)_{MC1}$-, $-(CH_2)_{MC1a}C(O)_{XA}(NR^4)_{XA}-(CH_2)_{MC1a}$-, $-(CH_2)_{MC1a}(NR^4)_{XA}C(O)_{XA}-(CH_2)_{MC1a}$-, or $-(CH_2)_{MC1a}O-(CH_2)_{MC1}-C(O)NR^4$-, with the proviso that R^{1CON}, R^{2CON} and R^{3CON} are not simultaneously H;

each MC1 is independently 1, 2, 3, or 4;

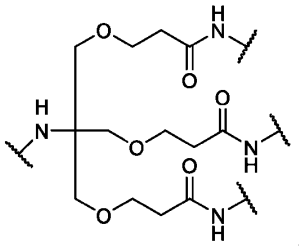
each MC1a is independently 0, 1, 2, 3, or 4;

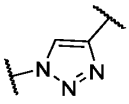
each XA is 0 or 1; and

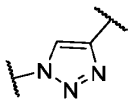
R^4 is H, C_1-C_3 alkyl or alkanol, or $-C(O)(C_1$-C_3 alkyl),

with the proviso that MC1a and XA in a moiety are not all simultaneously 0.

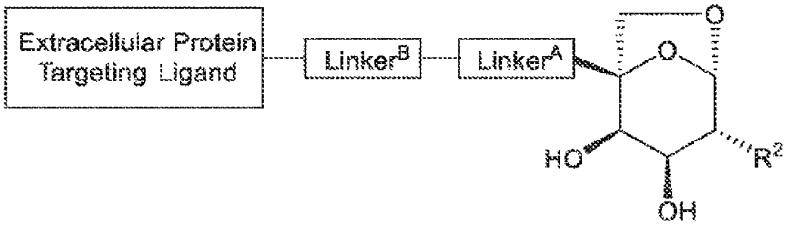
16. The compound of claim 1, wherein the [CON] is a group according to the chemical structure:



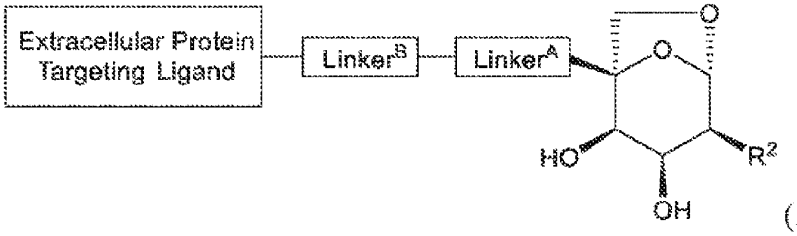
17, The compound of claim 1, wherein at least one [CON] is or comprises  .

18. The compound of claim 1, wherein [LINKER] is or comprises  .

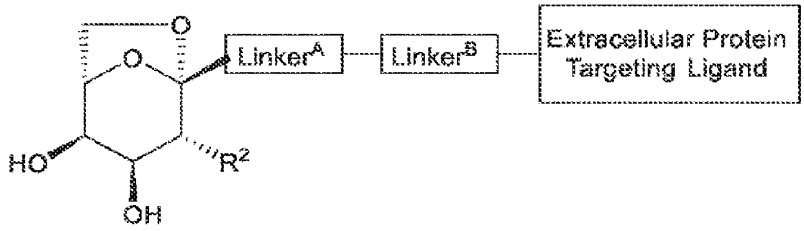
19. A bifunctional compound according to the chemical structure:



(I),



(I-d),



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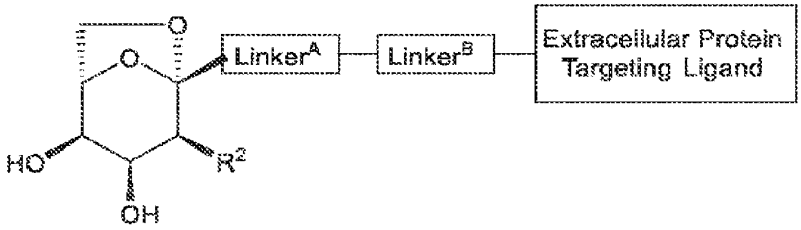

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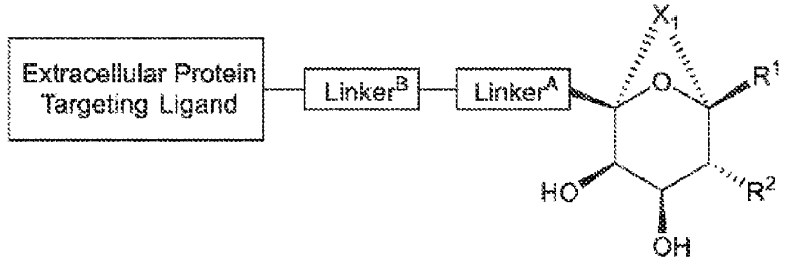

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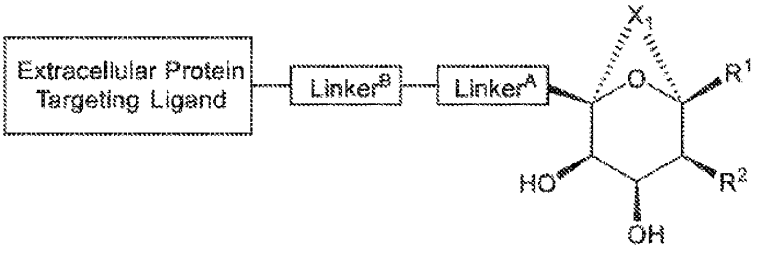

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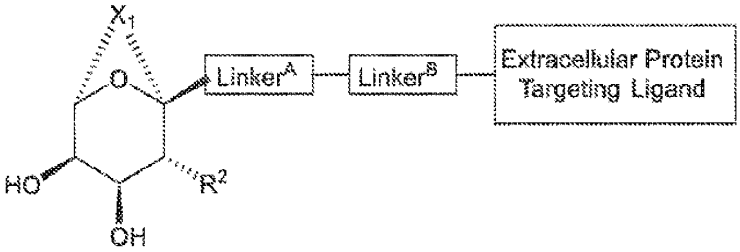

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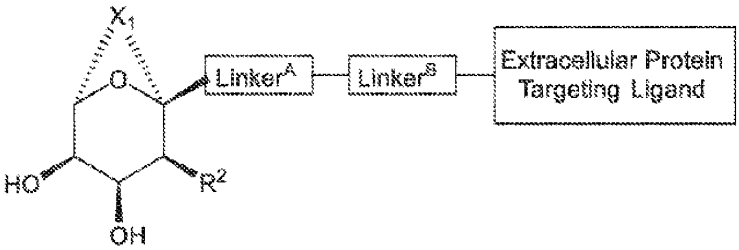

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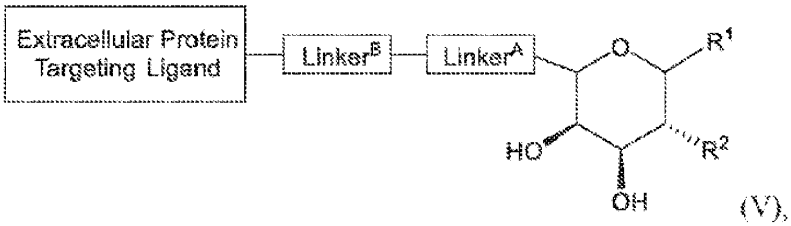

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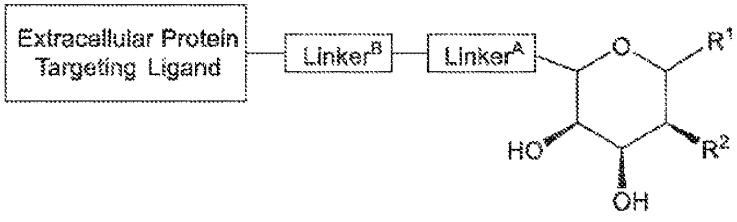

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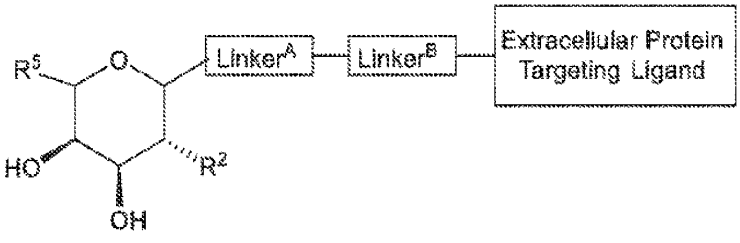

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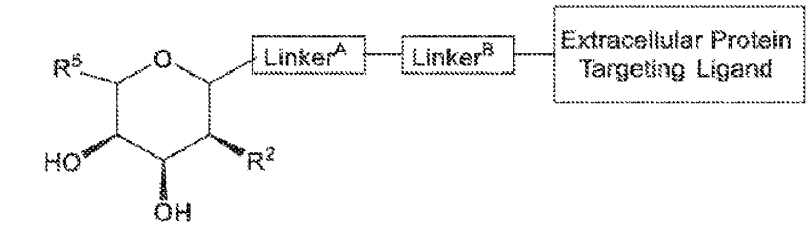

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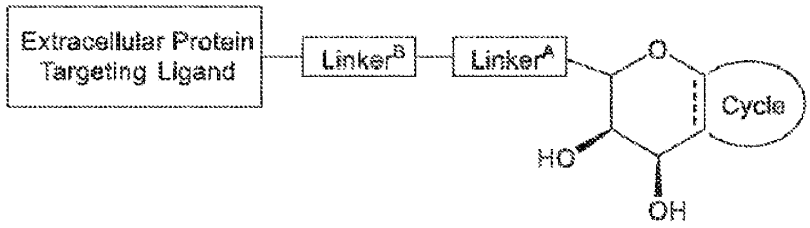

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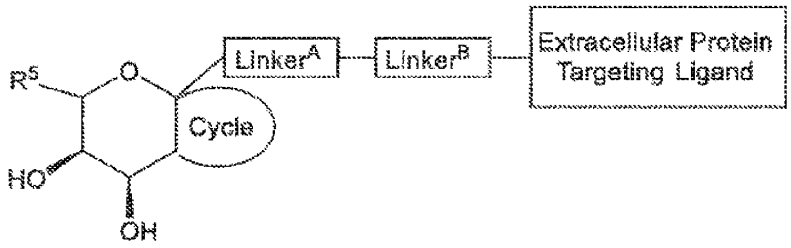

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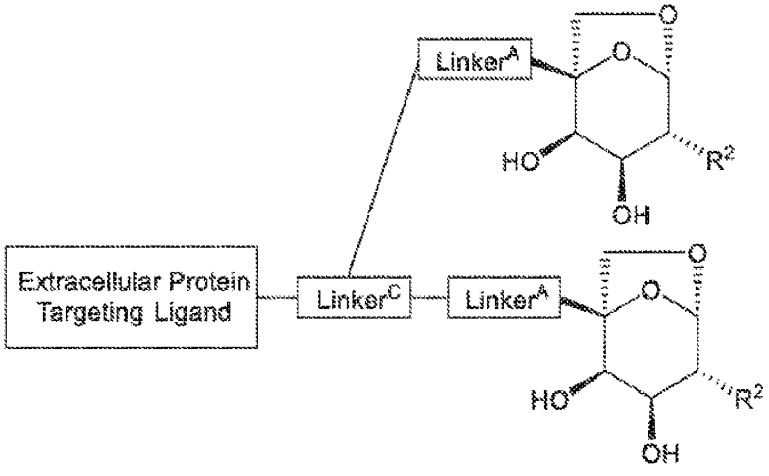

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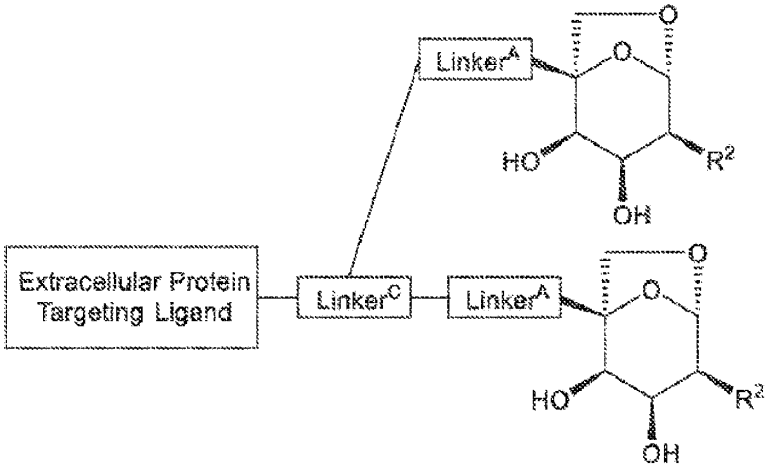

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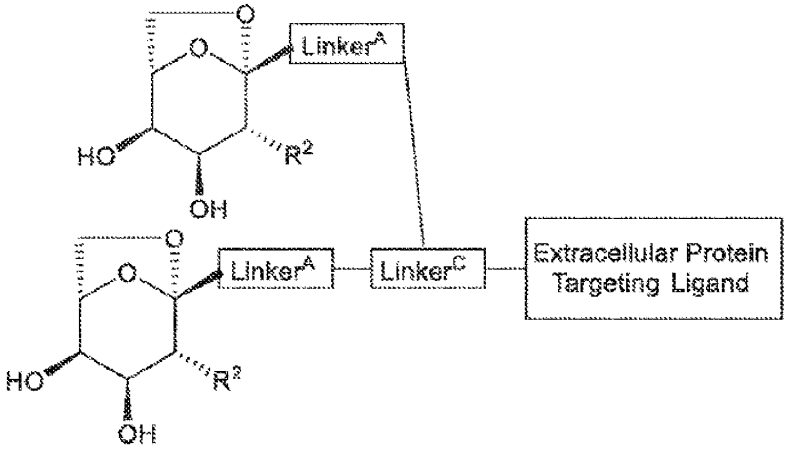

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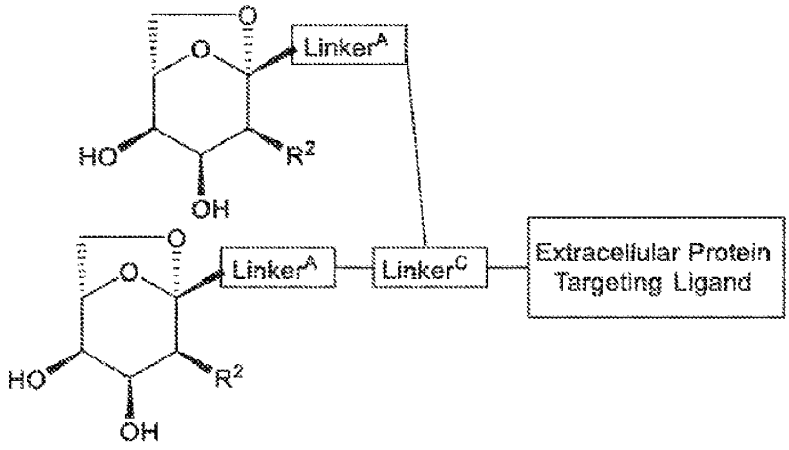

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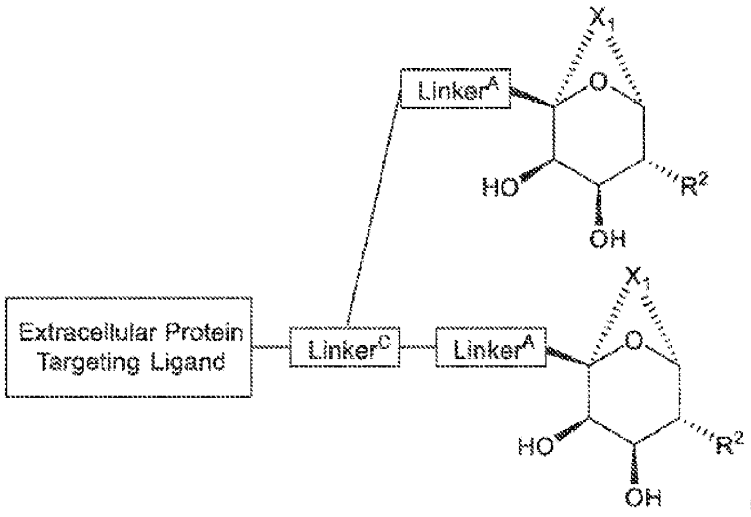

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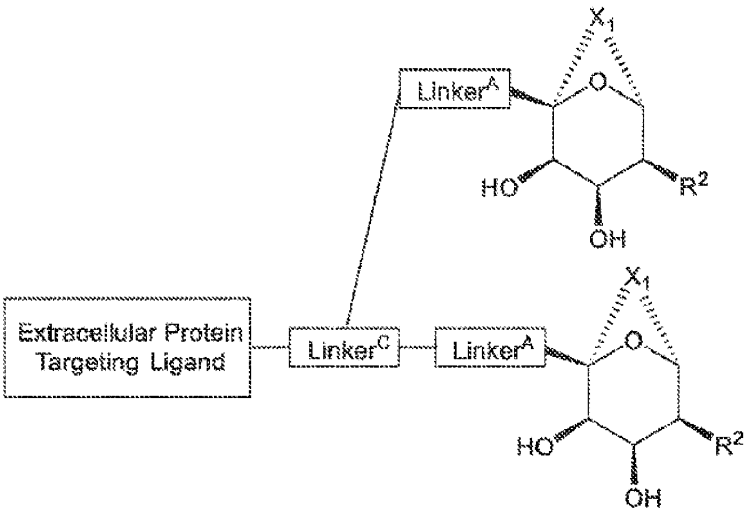

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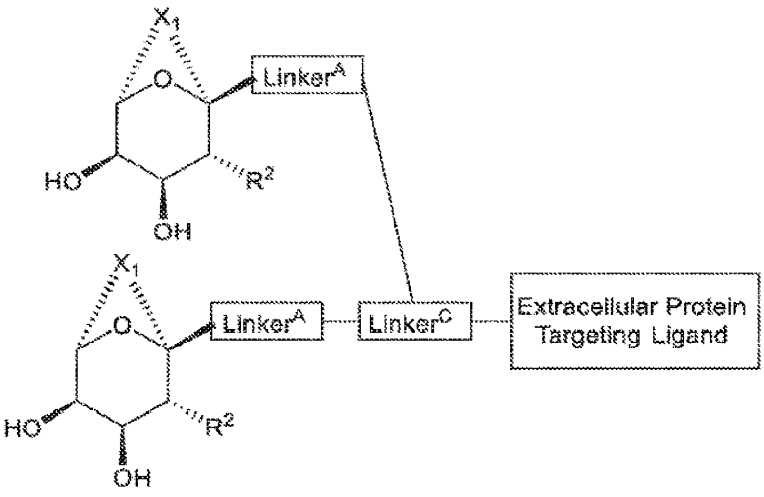

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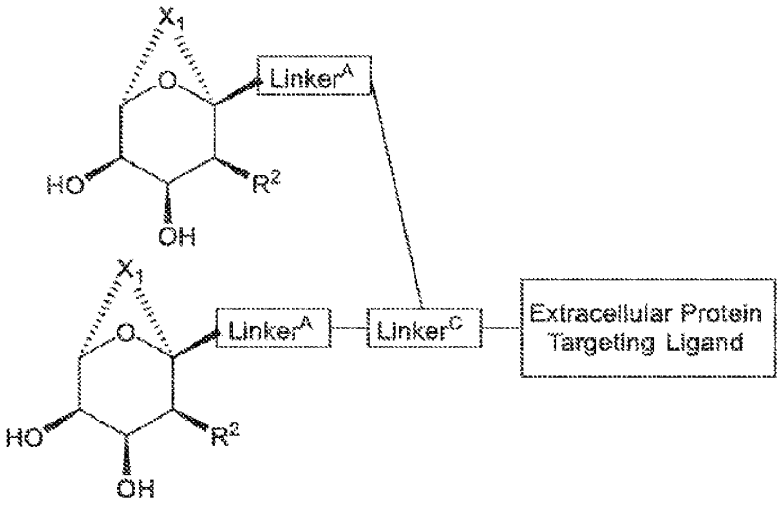

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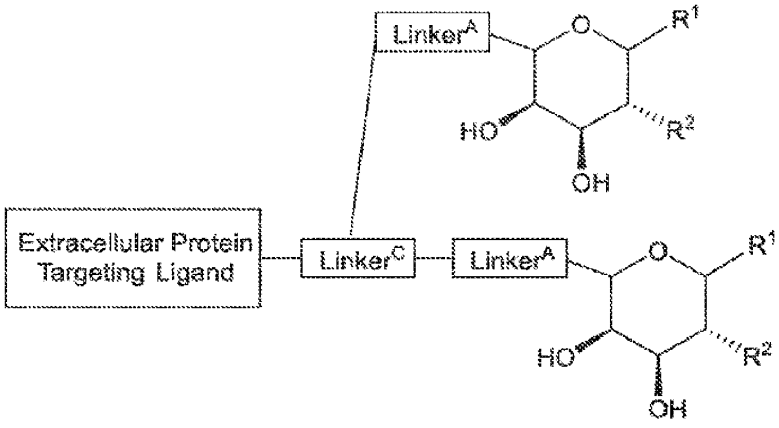

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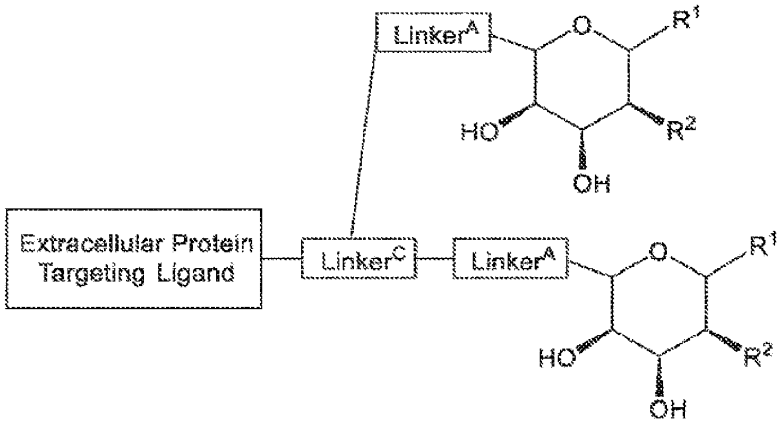

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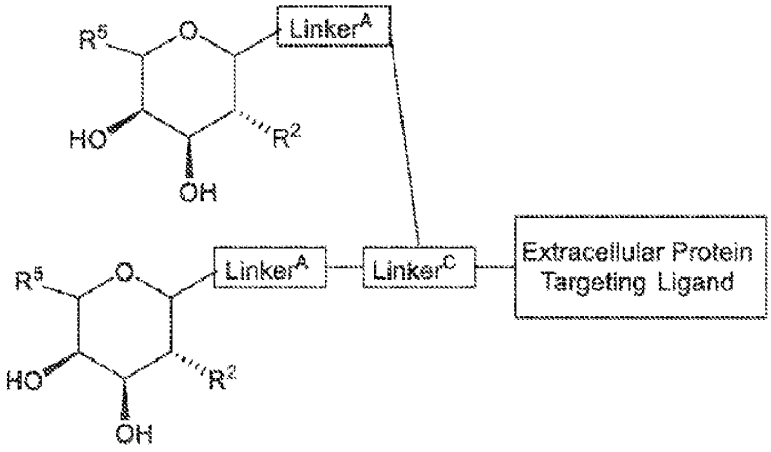

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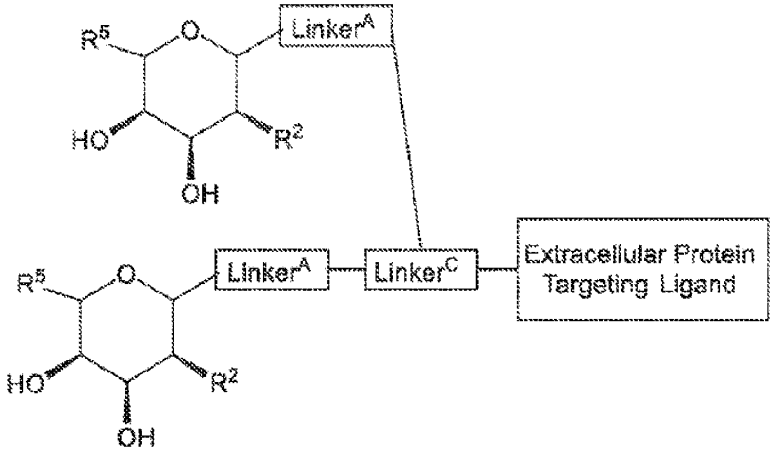

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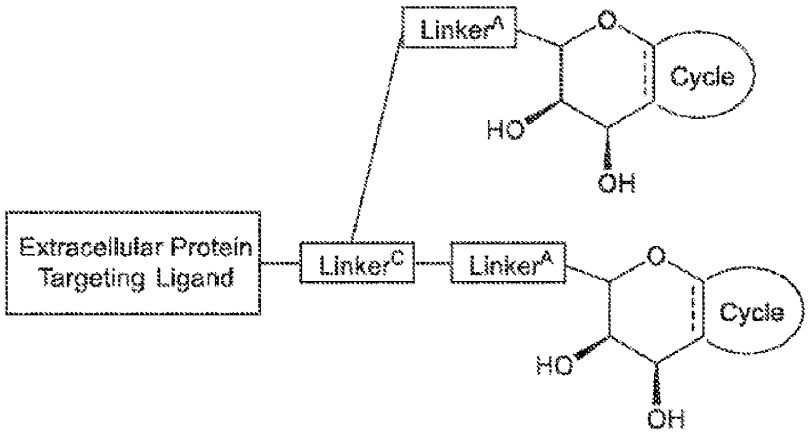

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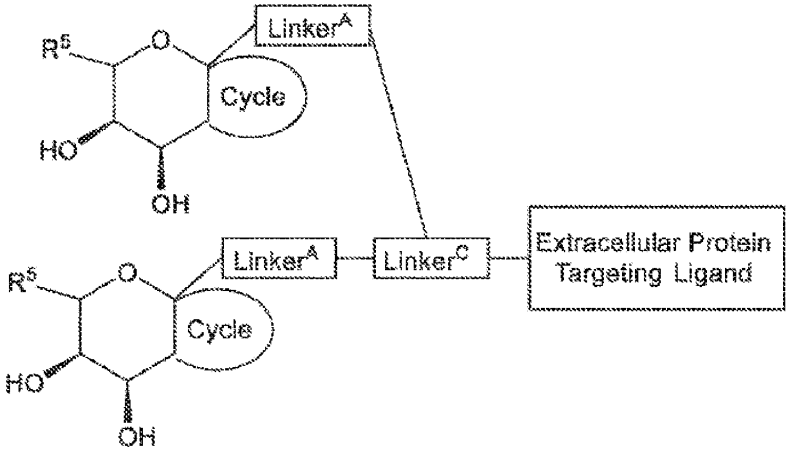
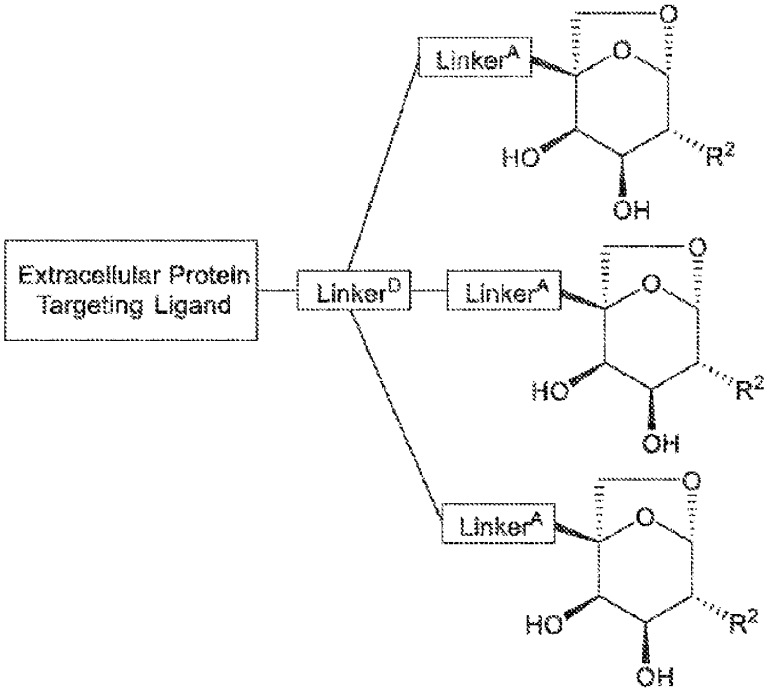
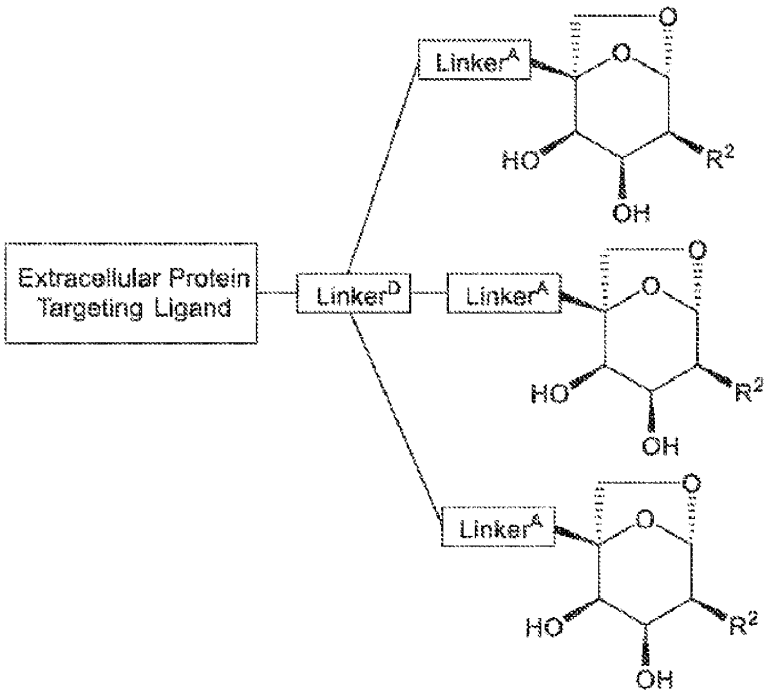

R5
O
Linker^A
Cycle
HO
OH
R5
O
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
Cycle
HO
OH

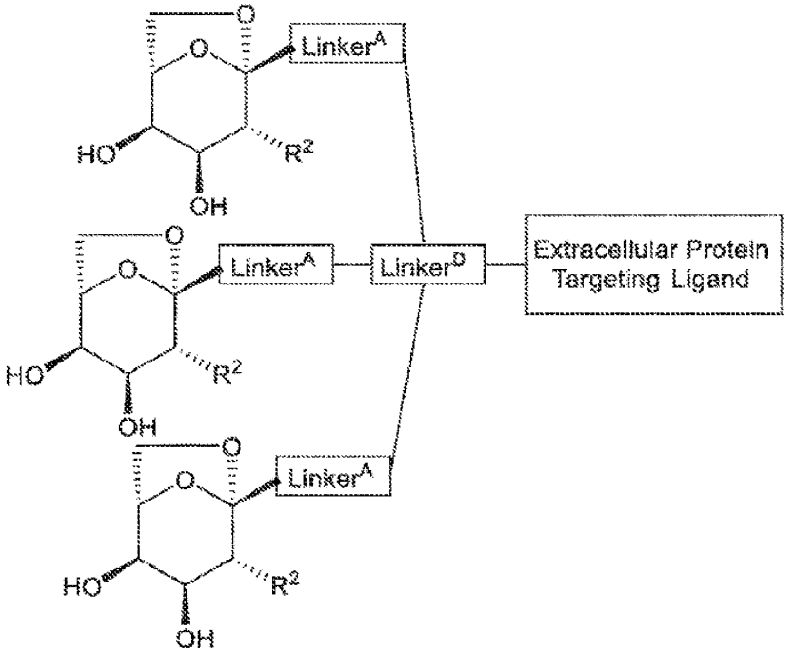
(VIII-Bi),


Linker^A
O
O
HO
R2
OH
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
O
O
HO
R2
OH
Linker^A
O
O
HO
R2
OH

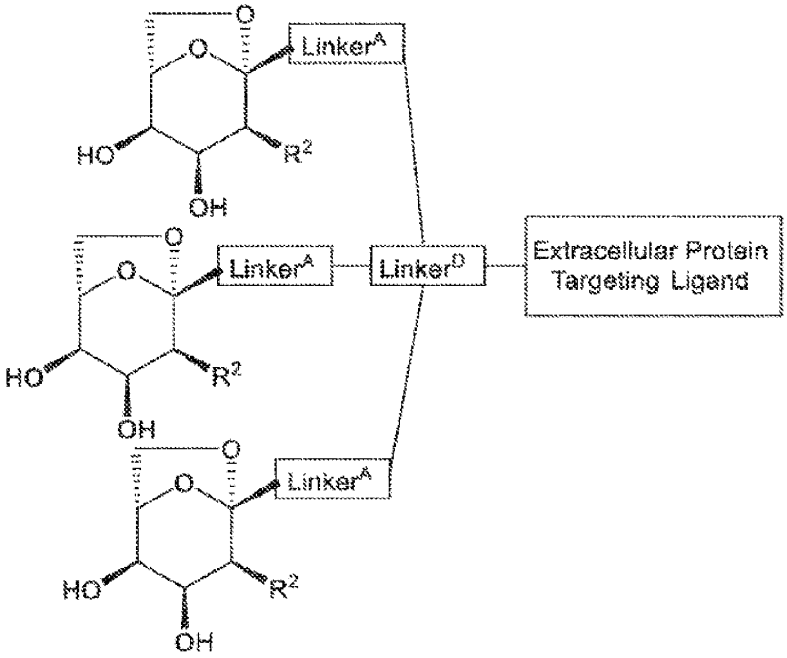
(I-Tri),


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A
HO
R^2
OH

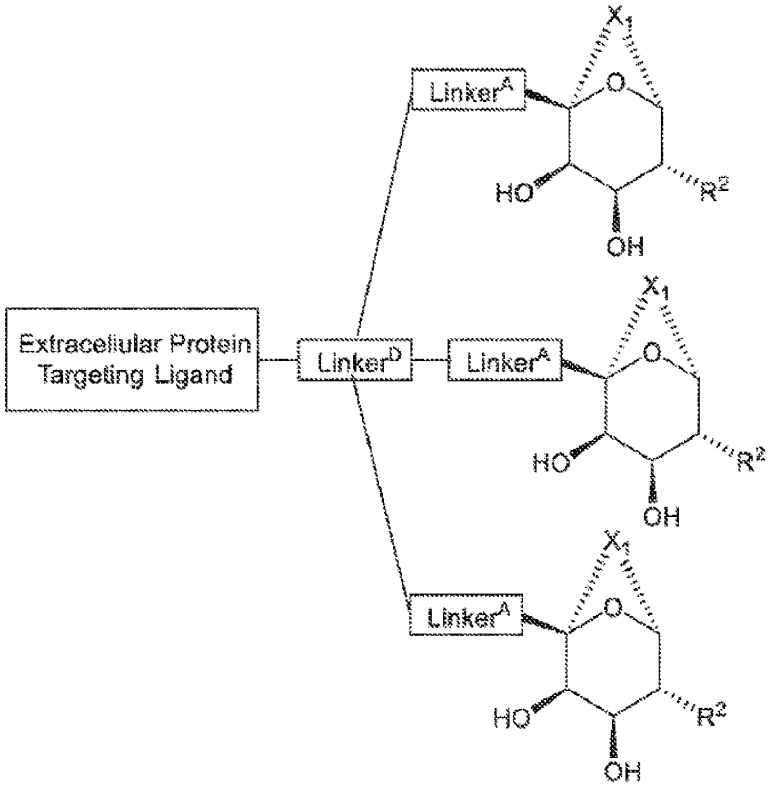
(I-d-Tri),


Linker^A
Linker^A
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
HO
R^2
OH

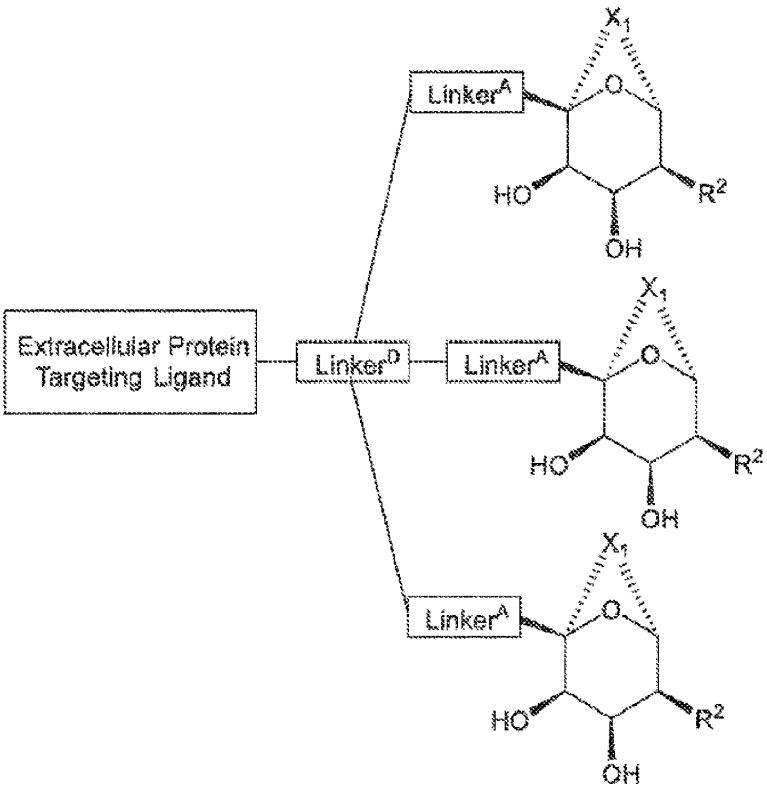
(II-Tri),



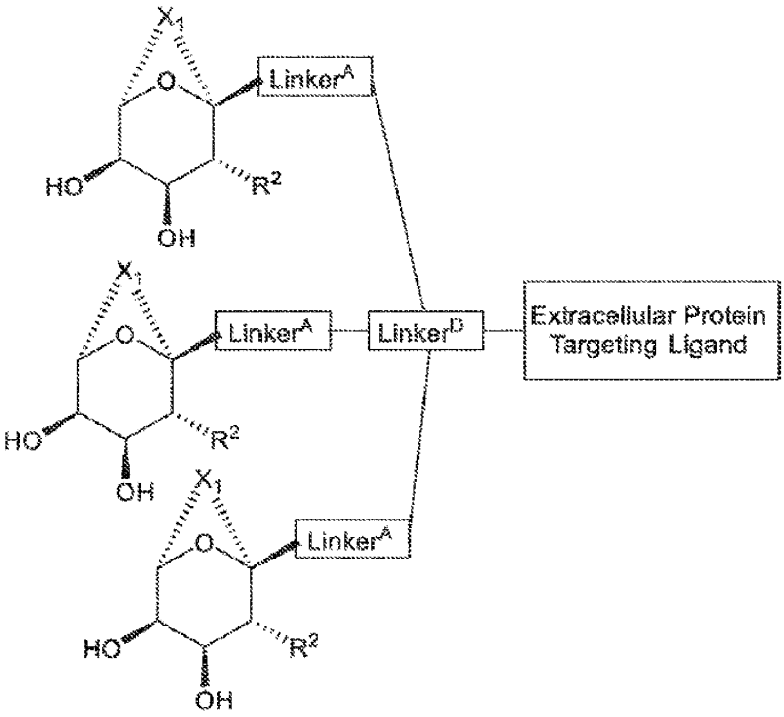
(II-d-Tri),



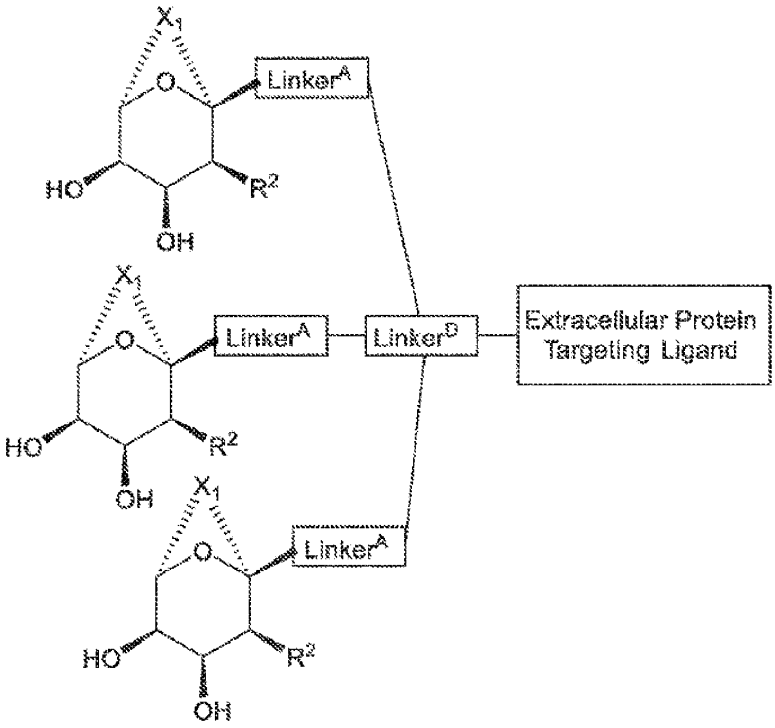
(III-Tri).



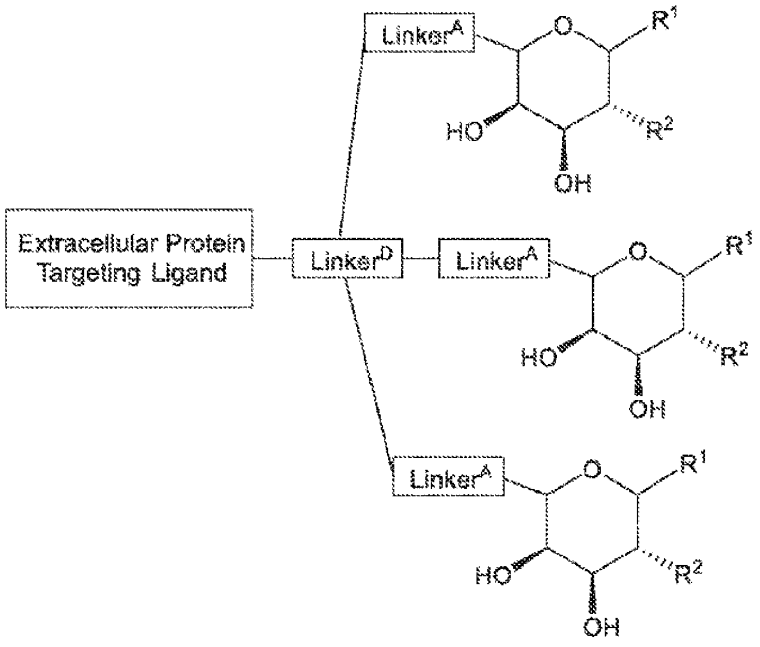
(III-d-Tri),



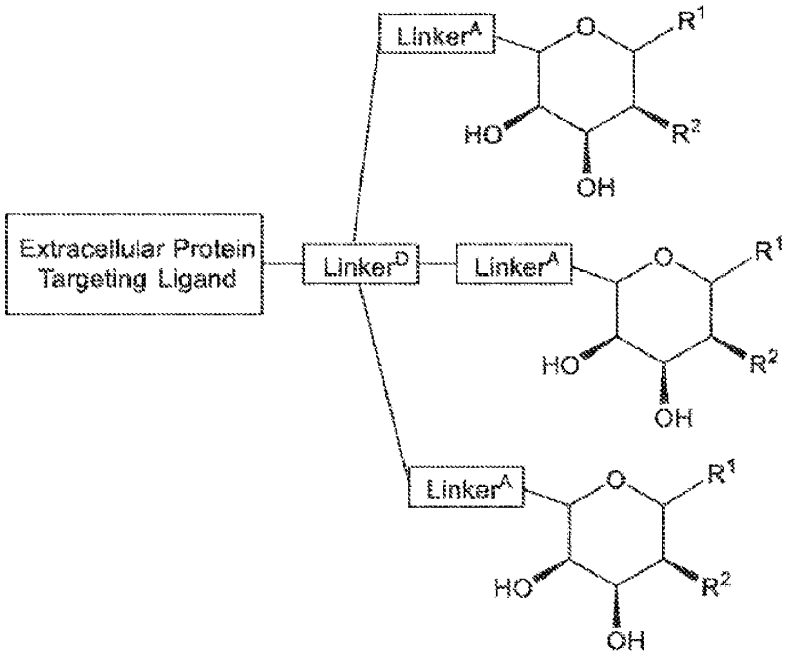
(IV-Tri),


X1
O
Linker^A
HO
R2
OH
X1
O
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
HO
R2
OH
X1
O
Linker^A
HO
R2
OH

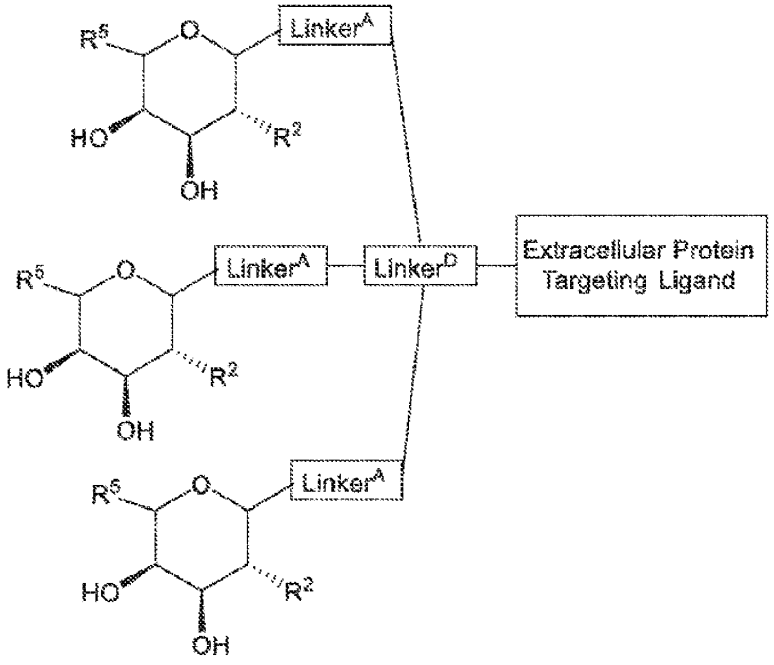
(IV-d-Tri),


Linker^A
O
R1
HO
R2
OH
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
O
R1
HO
R2
OH
Linker^A
O
R1
HO
R2
OH

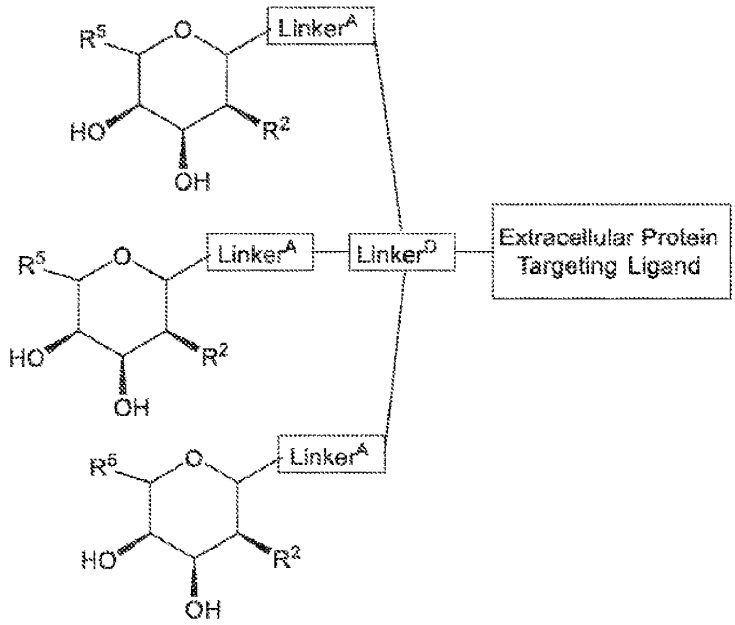
(V-Tri),


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A
R^1
R^2
HO
OH

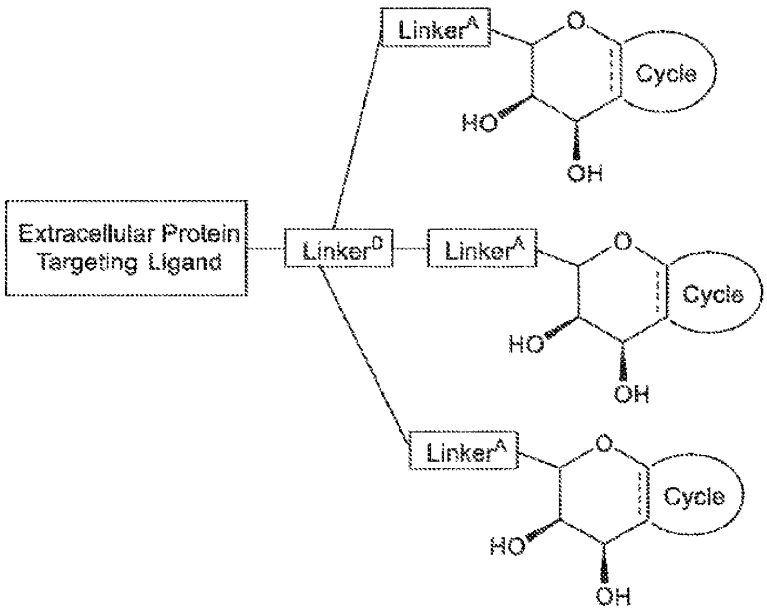
(V-d-Tri),


Linker^A
Linker^A
Linker^D
Linker^A
Extracellular Protein Targeting Ligand
R^5
R^2
HO
OH

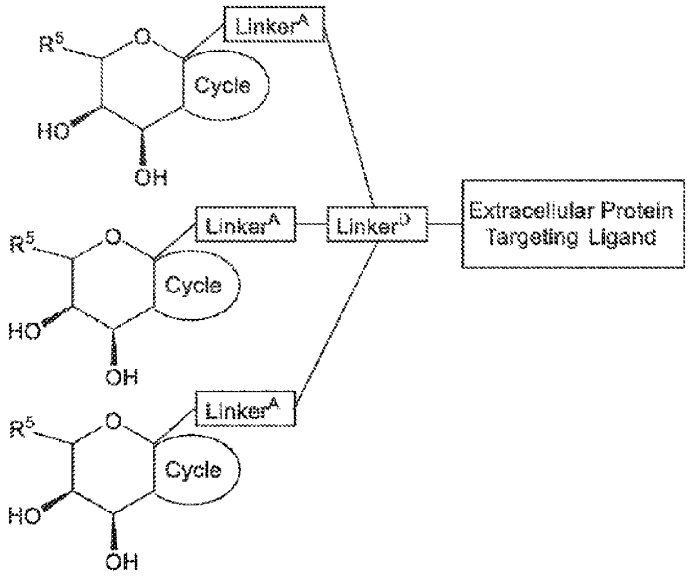
(VI-Tri),



(VI-d-Tri),



(VII-Tri), or

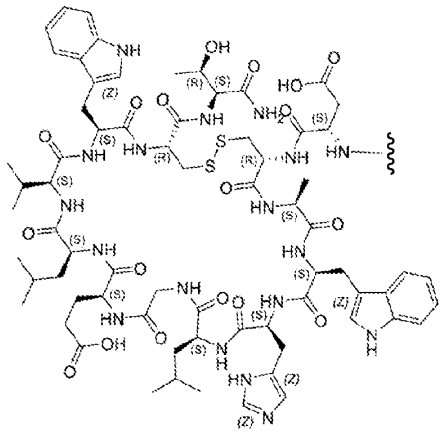


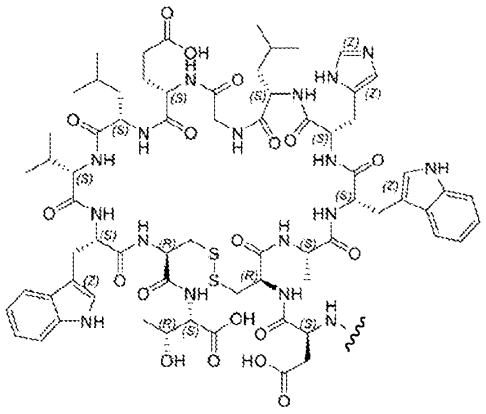
(VIII-Tri),

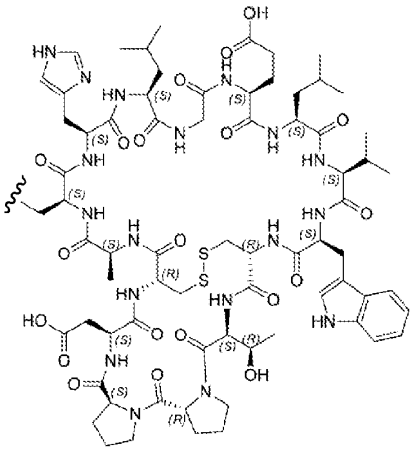
of a pharmaceutically acceptable salt thereof,

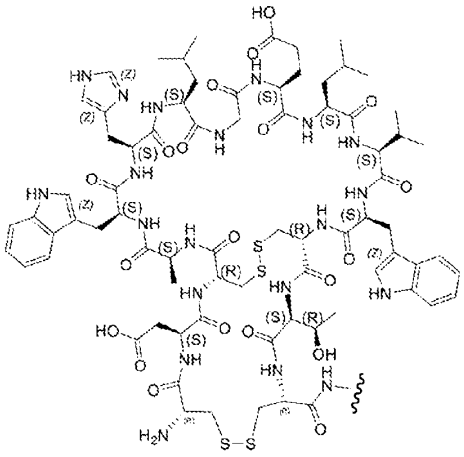
wherein:

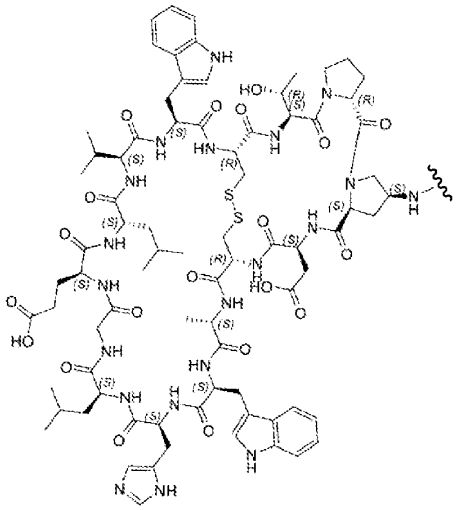
Extracellular Protein Targeting Ligand is a moiety which binds to Immunoglobulin G (IgG) in a subject, wherein IgG mediates a disease state or condition and is to be removed by the action of hepatocytes or other cells of the subject, wherein Extracellular Protein Targeting Ligand is or comprises a moiety selected from:

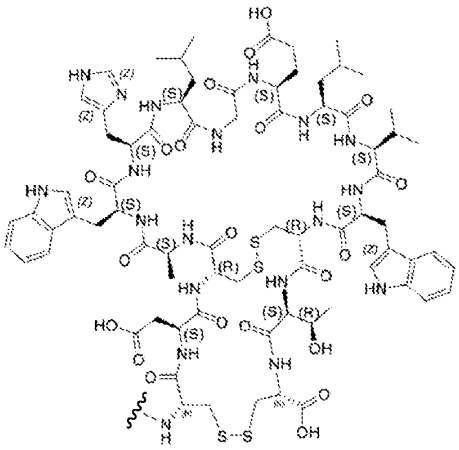


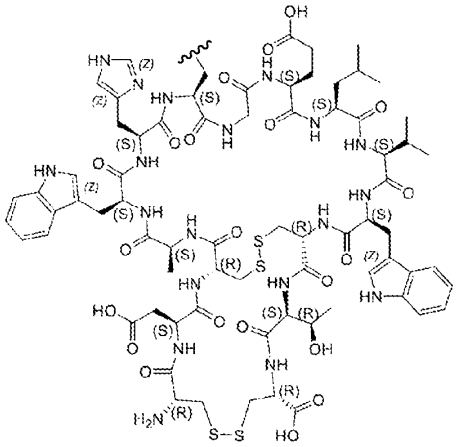
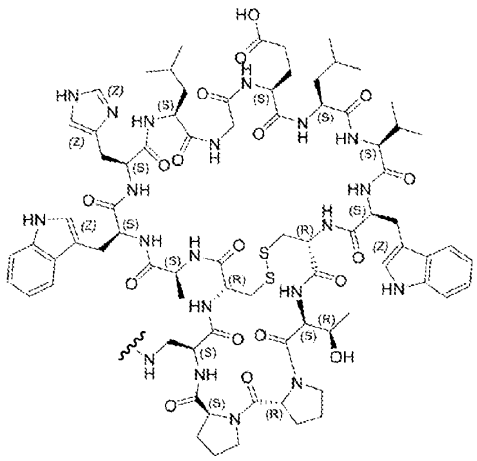








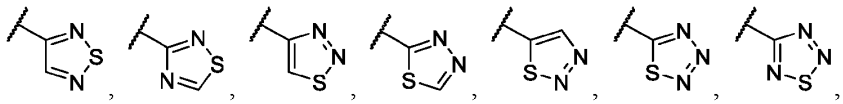
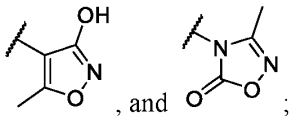




;

X_1 is 1 to 5 groups independently selected from the group consisting of O, S, $N(R^6)$, and $C(R^4)(R^4)$, wherein if X_1 is 1 atom then X_1 is O, S, $N(R^6)$, or $C(R^4)(R^4)$, if X_1 is 2 atoms then no more than 1 atom of X_1 is O, S, or $N(R^6)$, if X_1 is 3, 4, or 5 atoms then no more than 2 atoms of X_1 are O, S, or $N(R^6)$;

R^2 is selected from the group consisting of:

(i) aryl, heterocycle, and heteroaryl containing 1 or 2 heteroatoms independently selected from the group consisting of N, O, and S, each of which aryl, heterocycle, and heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents;

(ii) 

, and
;

(iii) $-NR^8-S(O)-R^3$, $-NR^8-C(S)-R^3$, $-NR^8-S(O)(NR^6)-R^3$, $-N=S(O)(R^3)_2$, $-NR^8C(O)NR^9S(O)_2R^3$, $-NR^8-S(O)_2-R^{10}$, and $-NR^8-C(NR^6)-R^3$ each of which is optionally substituted with 1, 2, 3, or 4 substituents; and

(iv) hydrogen, R^{10}, alkyl-$C(O)-R^3$, $-C(O)-R^3$, alkyl, haloalkyl, $-OC(O)R^3$, and $-NR^8-C(O)R^{10}$;

R^{10} is selected from the group consisting of aryl, alkyl-$NR^8-C(O)-R^3$, alkyl-aryl, alkyl-heteroaryl with 1, 2, or 4 heteroatoms, alkyl-cyano, alkyl-OR^6, alkyl-NR^6R^8, $NR^8-NR^6-C(O)R^3$,

NR^8-$S(O)_2$-R^3, alkenyl, allyl, alkynyl, -NR^6-alkenyl, -O-alkenyl, -NR^6-alkynyl, -O-alkynyl, -NR^6-heteroaryl, -NR^6-aryl, -O-heteroaryl, -O-aryl, and -O-alkynyl, each of which R^{10} is optionally substituted with 1, 2, 3, or 4 substituents;

R^1 and R^5 are independently selected from the group consisting of hydrogen, heteroalkyl, C_0-C_6alkyl-cyano, alkyl, alkenyl, alkynyl, haloalkyl, F, Cl, Br, I, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocycloalkyl, haloalkoxy, -O-alkenyl, -O-alkynyl, C_0-C_6alkyl-OR^6, C_0-C_6alkyl-SR^6, C_0-C_6alkyl-NR^6R^7, C_0-C_6alkyl-$C(O)R^3$, C_0-C_6alkyl-$S(O)R^3$, C_0-C_6alkyl-$C(S)R^3$, C_0-C_6alkyl-$S(O)_2R^3$, C_0-C_6alkyl-$N(R^8)$-$C(O)R^3$, C_0-C_6alkyl-$N(R^8)$-$S(O)R^3$, C_0-C_6alkyl-$N(R^8)$-$C(S)R^3$, C_0-C_6alkyl-$N(R^8)$-$S(O)_2R^3$ C_0-C_6alkyl-0-$C(O)R^3$, C_0-C_6alkyl-0-$S(O)R^3$, C_0-C_6alkyl-O-$C(S)R^3$, -$N{=}S(O)(R^3)_2$, C_0-C_6alkyN_3, and C_0-C_6alkyl-O-$S(O)_2R^3$, each of which is optionally substituted with 1, 2, 3, or 4 substituents;

R^3 at each occurrence is independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, -OR^8, and -NR^8R^9;

R^4 is independently selected at each occurrence from the group consisting of hydrogen, heteroalkyl, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, -OR^6, -NR^6R^7, $C(O)R^3$, $S(O)R^3$, $C(S)R^3$, and $S(O)_2R^3$;

R^6 and R^7 are independently selected at each occurrence from the group consisting of hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, haloalkyl, heteroaryl, heterocycle, -alkyl-OR^8, -alkyl-NR^8R^9, $C(O)R^3$, $S(O)R^3$, $C(S)R^3$, and $S(O)_2R^3$;

R^8 and R^9 are independently selected at each occurrence from the group consisting of hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle;

Cycle is a 3-8 membered fused cyclic group optionally substituted with 1, 2, 3, or 4 substituents;

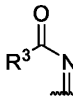
each $Linker^A$ is a bond or moiety that covalently links the [ASGPRBM] group to $Linker^B$,

$Linker^B$ is a bond or moiety that covalently links $Linker^A$ group to the Extracellular Protein Targeting Ligand;

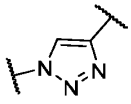
$Linker^C$ is a chemical group that links each $Linker^A$ group to the Extracellular Protein Targeting Ligand;

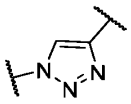
Linker^{D} is a chemical group that links each Linker^{A} group to the Extracellular Protein Targeting Ligand;

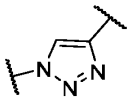
wherein, when R^2 is -NR^6-alkenyl, -NR^6-alkynyl, -NR^8-C(O)R^{10}, -NR^8-$S(O)_2$-alkenyl, -NR^8-$S(O)_2$-alkynyl, -NR^6-heteroaryl, or -NR^6-aryl, then Extracellular Protein Targeting Ligand does not comprise an oligonucleotide; and

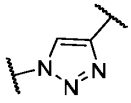
the optional substituents are selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, -OR^6, F, Cl, Br, I, -NR^6R^7, heteroalkyl, cyano, nitro, C(O)R^3, , , ,  , and , as allowed by valence such that a stable compound results;

or a salt, stereoisomer, or solvate thereof.

20. The compound of Claim 19, wherein Linker^{A} is or comprises  .

21. The compound of Claim 19, wherein Linker^{B} is or comprises  .

22. The compound of Claim 19, wherein Linker^{C} is or comprises  .

23. The compound of Claim 19, wherein Linker^{D} is or comprises  .

24. A compound selected from the compounds listed in Table 1 of the specification, or a salt, stereoisomer, or solvate thereof.

25. A pharmaceutical composition comprising an effective amount of a compound of any one of preceding claims and a pharmaceutically acceptable carrier, additive, or excipient, optionally further comprising an additional bioactive agent that is effective to treat cancer, autoimmune disease, or inflammatory disease in a patient or that is associated with the upregulation of a circulating protein in the patient.

26. The composition of claim 25, wherein the composition comprises an additional anticancer agent selected from the group consisting of: everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101 , pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab (Arzerra), zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601 , ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001 , IPdR$_1$ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311 , romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N -[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11 , CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)- indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t) 6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH $_2$ acetate [$C_{59}H_{84}N_{18}Oi_4$ -$(C_2H_4O_2)_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate,

hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, lonafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, amsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevec, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, irinotecan, topotecan, doxorubicin, docetaxel, vinorelbine, bevacizumab, erbitux, cremophor-free paclitaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11 , dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine,

hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa and darbepoetin alfa, vemurafenib, immunotherapy agents PDL1 inhibitors, PD1 inhibitors, and CTLA-4 inhibitors.