

Title

Molecular Degradars of Anti- β_1 EC_{II} Auto-Antibodies

Description**Introduction**

The present invention the invention concerns bifunctional compounds of Formula (I) A-T-L¹-AG, Formula (II) A-T-L¹-Con(L²-AG)_n or Formula (III) A_{k'}-T_h-L³_{ii}-AG_{j'} wherein A is an anti- β_1 adrenergic receptor antibody binding moiety and AG is an asialoglycoprotein receptor binding moiety (ASGPR binding moiety). L¹, Con and L² are part of a linker and T connects A to L¹. The anti- β_1 adrenergic receptor antibody binding moiety has the ability to bind to anti- β_1 EC_{II} autoantibodies and the asialoglycoprotein receptor binding moiety binds to hepatic cells thereby initiating endocytosis and removal of the anti- β_1 EC_{II} autoantibodies from the blood stream.

Background of the invention

Dilated cardiomyopathy (DCM) is a heart disease where the heart cannot pump blood effectively. It affects approximately 1 in 2500 people and is a leading cause for heart failure and heart transplantation in younger adults. The five-year survival rate is about 50%. Causes include genetics, alcohol, cocaine, some toxins and certain infections. It is also well known that certain autoantibodies cause dilated cardiomyopathy and other heart diseases (see e.g. Caforio et al, "Clinical implications of anti-heart autoantibodies in myocarditis and dilated cardiomyopathy", *Autoimmunity*, 2008 Feb;41(1):35-45). These antibodies are pathogenic anti- β_1 EC_{II} autoantibodies, i.e. antibodies to the second extracellular loop of the β_1 adrenergic receptor. The β_1 adrenergic receptor is in the present technical field and in the following also addressed as "Anti-B1AR", "beta-1 adrenergic receptor", "ADRB1", " β_1 -AR" or "B1AR". Presently used treatments for DCM, such as β_1 -AR (AR = adrenoreceptor) blockers and whole IgG depletion, are associated with significant undesirable side effects such as fatigue and dizziness, poor circulation, gastrointestinal symptoms and sexual dysfunction. Existing literature has suggested that neutralization or removal of these antibodies can alleviate DCM and related heart diseases.

The present inventors have shown that proteins including antibodies may be removed from the blood stream by use of bifunctional molecules (see WO 2019/199621 A1, WO 2023/028590 A1 and WO 2023/028597). These bifunctional molecules comprise a first moiety that binds to the protein to be removed and a second moiety that binds to the

hepatocyte asialoglycoprotein receptor (in the following also "ASGPR"). The ASGPR is presented at the surface of liver cells and binds sugars, aminosugars and molecules that have a partial structure thereof or a similar structure. Once bound to the ASGPR the molecules are endocytosed and digested in the hepatocyte. Therefore, the bifunctional molecules are introduced into the blood stream, bind to the protein or other molecule to be removed with the first moiety and bind to the ASPGR by means of the second moiety. These complexes are then endocytosed and the molecules to be removed from the blood stream are digested by the hepatocytes. These bifunctional molecules therefore utilize the endolysosomal machinery in the liver to eliminate unwanted molecules as for example autoantibodies from the blood stream.

The documents WO 2023/028590 A1 and WO 2023/028597 A1, disclose bifunctional molecules in which the first moiety binds to anti- β_1 EC_{II} autoantibodies (also "anti- β_1 AR" or "anti-B1AR") and the second moiety to ASGPR. The first moiety binding to the anti- β_1 EC_{II} autoantibodies is in the following also designated "anti- β_1 adrenergic receptor antibody binding moiety" or "anti- β_1 AR antibody binding moiety." It is shown in these documents that these bifunctional molecules are able to remove anti- β_1 EC_{II} autoantibodies from the blood stream and can therefore ameliorate DCM. The compound disclosed in these two documents serves as a proof of concept. However, further improvements are necessary. The compound is obtained as a mixture of regioisomers. The use of mixtures of compounds always carries the risk of increased side effects. The efficacy of the compound requires improvement. Pharmacokinetic and pharmacodynamic properties also require improvement.

Molecular structures that bind to ASGPR, i.e. asialoglycoprotein receptor binding moieties also named "ASGPR binding moieties" or "ASGPR targeting agents" are well known. Sugars such as galactose, n-acetyl galactosamine and other galactose derivatives are often used as ASGPR binding moieties. Such derivatives and other structural parts suitable for the aforementioned bifunctional molecules are for example disclosed in WO 2023/028590 A1, WO 2023/028597 A1, WO 2021/155317 A1, WO 2022/235699 A1 and WO 2019/199621 A1, M.G. Finn and V. Mascitti et al. in the *Journal of the American Chemical Society*, 134, 1978 (2012). EP 3 145 934 B1 discloses bicyclic sugar derivatives for this purpose and the literature cited therein and the literature cited during the examination thereof discloses further asialoglycoprotein receptor binding moieties.

Objective of the invention

There remains a need to solve the aforementioned problems and to improve the effect of the bifunctional molecules, to improve their pharmacological properties and to improve

their synthesis. It is one object of the present invention to provide improved bifunctional molecules.

Detailed description

In one aspect of the present invention, the invention concerns a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof, having the structure

A-T-L¹-AG Formula (I)

A-T-L¹-Con(L²-AG)_n Formula (II),

wherein

A is an anti-β₁ adrenergic receptor antibody binding moiety that has the structure

-L^{B1AR}-Pep, wherein

Pep is a peptide comprising AA,

wherein AA is an amino acid sequence at least 80% homologous to SEQ ID NO: 1 or an amino acid sequence at least 80% homologous to SEQ ID NO: 2 and

m is an integer in the range of 1 to 10;

T is selected from the group consisting of (1) a single cycle aromatic 5- or 6-membered heterocycle selected from the group consisting of pyrroles, furans, thiophenes, pyrazoles, oxazoles, isoxazoles, thiazoles, isothiazoles, triazoles, furazans, oxadiazoles, thiadiazoles, tetrazoles, pyridines, diazines and triazines and (2) -C(=O)-NR-, wherein R is hydrogen or C1 to C4 alkyl;

in which heterocycles a first ring atom is covalently bonded to the -(CH₂)_m- group of A and a second ring atom is covalently bonded to an open valence in L¹ and the remainder of the ring atoms may be substituted or unsubstituted;

L¹, L² and L^{B1AR} are linker and all linker L¹, L² and L^{B1AR} may be the same or different and all occurrences of L² in Formula (II) may be the same or different and

L¹, L² and L^{B1AR} may also be a direct bond and

L^{B1AR} is bound to T and to Pep;

Con is a connector that is covalently bonded to an open valence of linker L¹ and of each linker L²;

n is an integer of 2 or 3 and

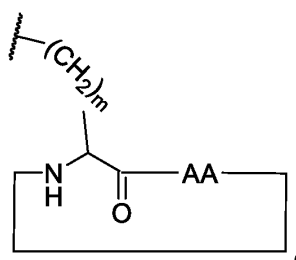
AG is an asialoglycoprotein receptor binding moiety and each occurrence of AG in Formula (II) may be the same or different.

In another aspect of the present invention, the invention concerns a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof, having the structure



wherein

A is an anti- β_1 adrenergic receptor antibody binding moiety that has the structure



AA is an amino acid sequence at least 80% homologous to SEQ ID NO: 1 and

m is an integer in the range of 1 to 10;

T is selected from the group consisting of a single cycle aromatic 5- or 6-membered heterocycle selected from the group consisting of pyrroles, furans, thiophenes, pyrazoles, oxazoles, isoxazoles, thiazoles, isothiazoles, triazoles, furazans, oxadiazoles, thiadiazoles and tetrazoles, pyridines, diazines and triazines;

in which heterocycles a first ring atom is covalently bonded to the $-(CH_2)_m-$ group of A and a second ring atom is covalently bonded to an open valence in L^1 and the remainder of the ring atoms may be substituted or unsubstituted;

L^1 and L^2 are linker and all linker L^1 and L^2 may be the same or different and all occurrences of L^2 in Formula (II) may be the same or different and

L^1 and L^2 may also be a direct bond;

Con is a connector that is covalently bonded to an open valence of linker L^1 and of each linker L^2 ;

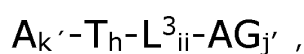
n is an integer of 2 or 3 and

AG is an asialoglycoprotein receptor binding moiety (ASGPR binding moiety) and each occurrence of AG in Formula (II) may be the same or different.

The compounds of the present invention, and especially the compounds of Formulae (I) and (II), are pharmaceutically acceptable compounds. Compounds of the present invention are molecular degraders of anti- β_1EC_{II} auto-antibodies. The moiety A binds to pathogenic anti- β_1EC_{II} autoantibodies and the moiety AG binds to the hepatocyte

asialoglycoprotein receptor. The complexes of the compounds of the present invention and the pathogenic anti- $\beta_1\text{EC}_{\text{II}}$ autoantibodies are then endocytosed and digested by the hepatocytes, thereby eliminating the pathogenic anti- $\beta_1\text{EC}_{\text{II}}$ autoantibodies from the blood stream. In various aspects, compounds of the present invention are useful in methods of preventing, treating, and/or ameliorating heart failure in a subject when administered in therapeutically effective amounts. The compounds of the present invention are therefore suitable for the treatment or prevention of dilated cardiomyopathy (DCM).

In a further embodiment of the present invention, the present disclosure is directed to compounds of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof. These compounds of the present invention are also useful for removing circulating proteins which are associated with a disease state or condition in a patient or subject as described herein. In the compound of Formula (III), A and T are as defined herein and L^3 is a linker.

In the compound of Formula (III):

L^3 is a chemical moiety having a valency from 1 to 15 which covalently attaches to one or more T and/or AG group;

k' is an integer from 1 to 15;

h is an integer from 1 to 15;

ii is an integer from 0 to 15;

j' is an integer from 1 to 15.

In various embodiments, L^3 has a valency of 1 to 10. In various embodiments, L^3 has a valency of 1 to 5. In various embodiments, L^3 has a valency of 2, 3 or 4. In various embodiments, T has a valency of 1 to 5. In various embodiments, T has a valency of 1 to 3. In preferred embodiments T has a valency of 1. In various embodiments, in the compound of Formula (III), L^3 is selected from the group consisting of L^1 and $-\text{L}^1-\text{Con}(\text{L}^2-)_{\text{n}}$. In various embodiments, in the compound of Formula (III), L^3 comprises a partial structure selected from the group consisting of L^1 , L^2 , $-\text{Con}(-)_{\text{n}}$, $-\text{L}^1-\text{Con}(-)_{\text{n}}$, $-\text{Con}(\text{L}^2-)_{\text{n}}$, $-\text{L}^1-\text{Con}(\text{L}^2-)_{\text{n}}$, Linker^{A} , Linker^{B} , Linker^{C} , Linker^{D} , and/or combinations thereof as described herein.

L^3 may comprise one or more of each L^1 , L^2 or $-\text{L}^1-\text{Con}(\text{L}^2-)_{\text{n}}$ of Formulae (I) or (II). L^1 and/or L^2 may also consist of a combination of one or more Linker^{A} and one or

more Linker^B as described hereunder. The group $-L^1\text{-Con}(L^2\text{-})_n$ of Formula (II) may be identical to Linker^C and/or Linker^D as described hereunder. The group $-L^1\text{-Con}(L^2\text{-})_n$ of Formula (II) may be identical to a combination of one or more of Linker^A and/or Linker^B with one or more of either Linker^C or Linker^D. $-L^1\text{-Con}(L^2\text{-})_n$ of Formula (II) may also include Linker^A, Linker^B, Linker^C and/or Linker^D as described hereunder.

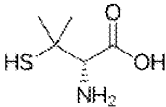
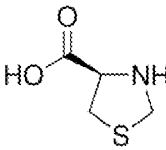
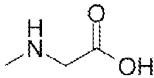
In the following formula the designations "Extracellular Targeting Ligand" and "Extracellular Protein Targeting Ligand" refers to the group A-T- of Formulae (I) and/or (II) and to the group A_k'-T_h- of Formula (III).

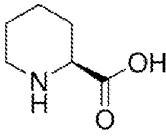
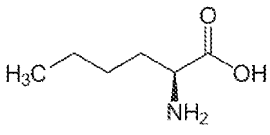
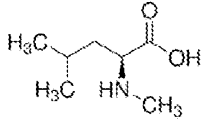
Anti-β₁AR antibody binding moiety A (peptide)

The amino acid sequence AA is the part of A that provides the binding properties in regard to the anti-β₁AR antibodies to the compounds of the present invention. AA is an amino acid sequence at least 80% homologous to SEQ ID NO: 1:

DEARRCYNDPKCSDFVQ (SEQ ID NO: 1)

SEQ ID NO: 1 is known to bind to anti-β₁AR antibodies. Amino acid sequences AA that are 80% homologous to SEQ ID NO: 1, includes amino acid sequences that contain more residues, including synthetically modified residues, than SEQ ID NO: 1. AA may therefore also comprise non-standard amino acids, preferably non-standard amino acids selected from the group consisting of

Non-standard Amino Acid	Structure	Name
Pen		penicillamine
Thz		L-thiazolidine-4-carboxylic acid
Sar		sarcosine

Pip		L-pipecolic acid
Nleu		norleucine
NMeLeu		N-methyl leucine

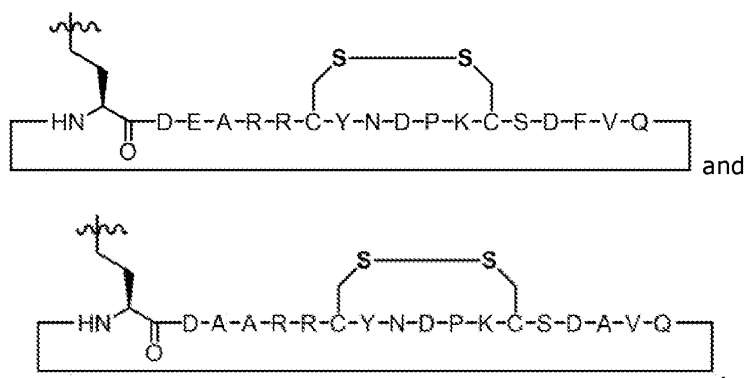
In a preferred embodiment of the present invention, AA is a (6,12) cyclic peptide. This is known to improve the binding between AA and the anti- β_1 adrenergic receptor antibodies. It is also preferred that AA is at least 95% homologous to SEQ ID NO: 1. In even more preferred embodiments AA is an amino acid of sequence of SEQ ID NO: 1.

In one embodiment AA is an amino acid sequence of SEQ ID NO: 2:

DAARRCYNDPKCSDAVQ (SEQ ID NO: 2)

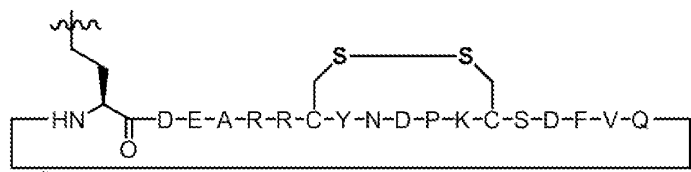
m is preferably an integer in the range of 1 to 5, more preferably in the range of 1 to 3 and most preferably m is 2.

In preferred embodiments of the present invention, A has a structure selected from the group consisting of



wherein the wavy line marks the bond that bonds -A to the remainder of the molecule.

In most preferred embodiments of the present invention, A has the structure



wherein the wavy line marks the bond that bonds –A to the remainder of the molecule.

xx% homologous means that sequences are comprised, which have a nucleic acid sequence which differs due to at least one substitution, deletion, insertion and/or addition from the indicated sequence. The term "at least one", as used herein means one, or more than one, such as "at least two", "at least three", etc. ..

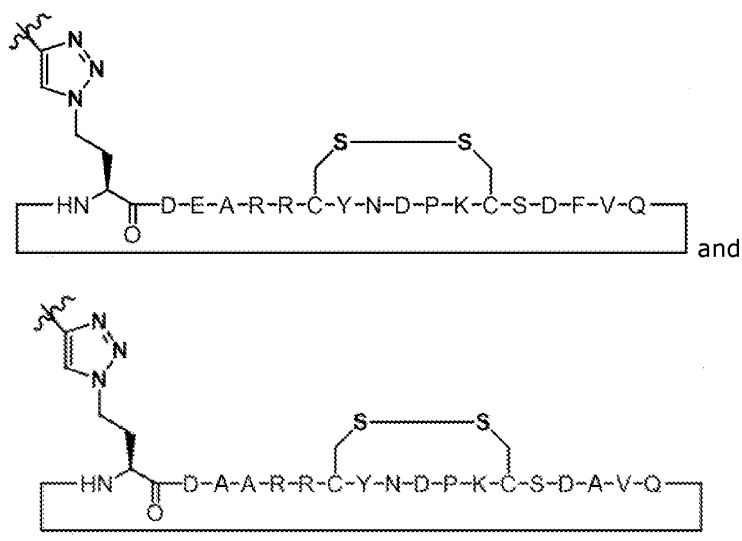
The degree of homology expressed as "% homologous" between two biological sequences, preferably proteins in the context of the present invention, can be determined by algorithms well known in the art. Preferably, the degree of homology is determined by comparing two optimally aligned sequences over a comparison window, where the fragment of sequence in the comparison window may comprise additions or deletions (e.g., gaps or overhangs) as compared to the sequence it is compared to for optimal alignment. The percentage is calculated by determining, preferably over the whole length of the polypeptide, the number of positions at which the identical residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence homology. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman (1981), by the homology alignment algorithm of Needleman and Wunsch (1970), by the search for similarity method of Pearson and Lipman (1988), by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, PASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by visual inspection. Given that two sequences have been identified for comparison, GAP and BESTFIT are preferably employed to determine their optimal alignment and, thus, the degree of homology. Preferably, the default values of 5.00 for gap weight and 0.30 for gap weight length are used.

T and A-T-

The structure of T may have an influence on bioavailability, pharmacokinetic and/or pharmacodynamics. T is preferably selected from the group consisting of pyrroles, furans, thiophenes, pyrazoles, oxazoles, isoxazoles, thiazoles, isothiazoles, triazoles, furazans, oxadiazoles, thiadiazoles and tetrazoles. T is preferably a nitrogen containing heterocycle. T is preferably a 5-membered heterocycle. More preferably T is a nitrogen containing 5-membered heterocycle. Even more preferably T is triazole or and –C(=O)–

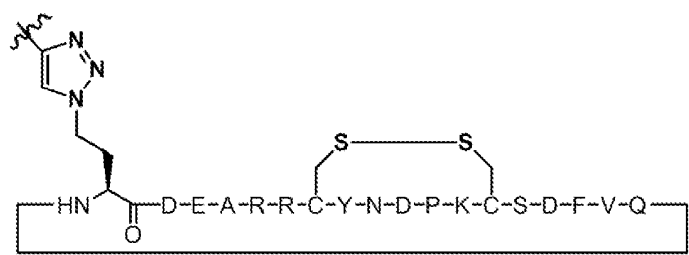
NR- group. Among the triazoles 1,2,3-triazoles are preferred and 1*H*-1,2,3-triazoles are even more preferred. Most preferably T is a 1*H*-1,2,3-triazole, wherein A is bound to the triazole in 1-position and L¹ is bound to the triazole in 4-position.

In preferred embodiments of the present invention, A-T- has a structure selected from the group consisting of



wherein the wavy line marks the bond to the remainder of the molecule.

A-T- most preferably has the structure



wherein the wavy line marks the bond to the remainder of the molecule.

Groups AG

In principle the asialoglycoprotein receptors (ASGPR) bind asialoglycoprotein and glycoproteins from which a sialic acid has been removed to expose galactose. The asialoglycoprotein receptors of the liver are however not very specific and bind a wide variety of molecules that comprise structures or partial structures of sugars and related

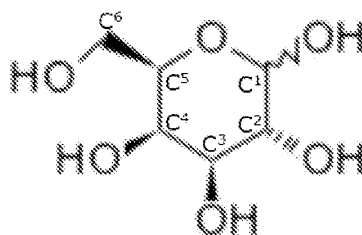
molecules. The asialoglycoprotein receptor binding moiety AG of the compounds of the present invention may therefore be chosen from a wide variety of compounds.

Asialoglycoprotein receptor binding moiety have been intensively researched and disclosed. Some examples are described in: WO 2023/028590 A1, WO 2023/028597 A1, WO 2021/155317 A1, WO 2022/235699 A1, WO 2019/199621 A1, EP 3 145 934 B1, Reshitko, G. S., et al., "Synthesis and Evaluation of New Trivalent Ligands for Hepatocyte Targeting via the Asialoglycoprotein Receptor," *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00202; Majouga, A. G., et al., "Identification of Novel Small-Molecule ASGP-R Ligands," *Current Drug Delivery*, **2016**, 13, 1303-1312, doi: 10.2174/1567201813666160719144651; Olshanova, A. S., et al., "Synthesis of a new betulinic acid glycoconjugate with N-acetyl-D-galactosamine for the targeted delivery to hepatocellular carcinoma cells," *Russian Chemical Bulletin, International Edition*, Vol. 69, No. 1, pp. 158–163, January 2020; Yamansarov, E. Yu., et al., "New ASGPR-targeted ligands based on glycoconjugated natural triterpenoids," *Russian Chemical Bulletin, International Edition*, Vol. 68, No. 12, pp. 2331–2338, December 2019; Congdon, M. D., et al., "Enhanced Binding and Reduced Immunogenicity of Glycoconjugates Prepared via Solid-State Photoactivation of Aliphatic Diazirine Carbohydrates," *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00555; and Dhawan, V., et al., "Polysaccharide conjugates surpass monosaccharide ligands in hepatospecific targeting – Synthesis and comparative in silico and in vitro assessment," *Carbohydrate Research* 509 (2021) 108417, doi: 10.1016/j.carres.2021.108417. AG of the present invention may be any known asialoglycoprotein receptor binding moiety and may especially be any asialoglycoprotein receptor binding moiety disclosed in the aforementioned publications.

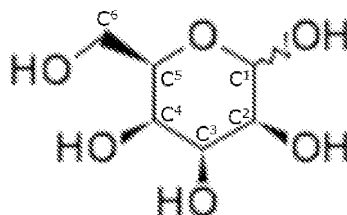
The following ASGPR binding moieties are illustrative and not intended to be limiting.

Preferably AG is selected from the group consisting of monosaccharides, disaccharides, oligosaccharides of up to 20 monosaccharides and derivatives thereof. The monosaccharides are preferably selected from the group consisting of aldoses, aldotetroses, aldopentoses, aldohexoses, ketotrioses, ketotetroses, ketopentose, ketohexoses, aminosugars, sulfosugars, sedoheptulose and sedoheptulose anhydride. The disaccharides are preferably selected from the group consisting of sucrose, lactose, maltose, trehalose, cellobiose, kojibiose, nigerose, isomaltose, β,β -trehalose, sophorose, laminaribiose, gentiobiose, turanose, maltulose, palatinose, gentiobulose, mannobiose, melibiose, melibiulose, rutinose, rutinulose and xylobiose.

Even more preferred, the group AG of the compounds of the present invention is selected from the group consisting of galactose, talose and their derivatives. In a most preferred embodiment AG is galactose or a derivative thereof. Galactose has the structure



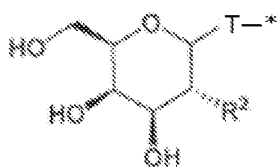
and talose has the structure



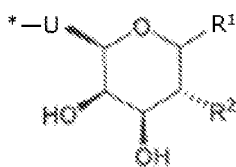
As can be seen talose is the C² epimer of galactose and therefore only differs in the stereochemistry at C². Galactose and talose chelate with the asialoglycoprotein receptors of the liver by means of the oxygen atoms bonded to the C³ and/or C⁴ atom. It is therefore preferred that these groups are not altered in the asialoglycoprotein receptor binding moiety AG of the compounds of the present invention. All other parts of the structures may be altered to adjust the properties of the compounds of the present invention. Alteration may have an effect on the affinity of the groups to the asialoglycoprotein receptors of the liver or may influence the pharmacokinetic and/or pharmacodynamics of the compounds of the present invention. Further considerations in the choice of the structure of AG are ease of production, stability under physiological conditions, stability in hepatocytes and other factors.

The simplest suitable derivatives of galactose and talose that are useful in the present invention are 1-deoxygalactose, 2-deoxygalactose, 1,2-deoxygalactose, 1-deoxytalose, 2-deoxytalose and 1,2-deoxytalose. In preferred embodiments AG is selected from the following formulae:

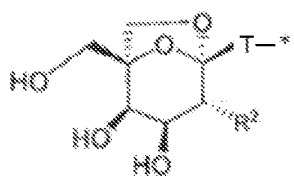
(Galactose-based derivatives)



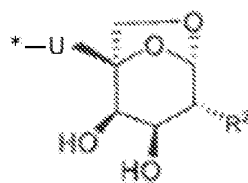
Formula AG-1,



Formula AG-2,

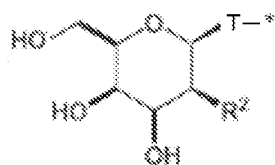


Formula AG-3

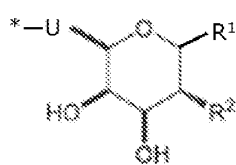


Formula AG-4,

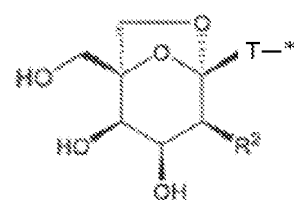
(Talose based derivatives)



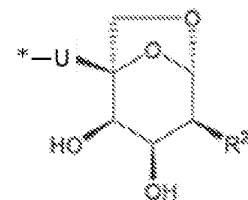
Formula AG-5



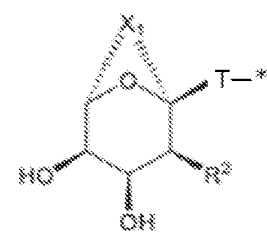
Formula AG-6,



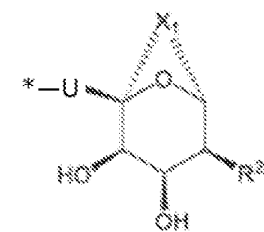
Formula AG-7,



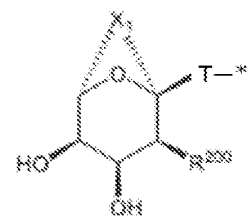
Formula AG-8,



Formula AG-9

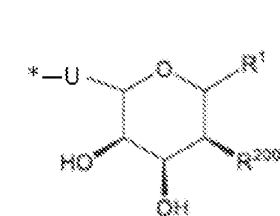


Formula AG-10



Formula AG-11

and



Formula AG-12

wherein T is selected from the group consisting of a direct bond and O (an oxygen atom) and U is selected from the group consisting of a direct bond, O (an oxygen atom) and O-CH₂, wherein if U is O-CH₂, the carbon atom of O-CH₂ is bound to the C5-atom of the sugar ring moiety and * marks the bond that bonds AG to the remainder of the compounds of the present invention, e.g. L¹, L², L³ or Con, with the proviso that no oxygen-oxygen bond is formed between AG and the remainder of the compounds of the present invention. That means that T and U are not O (an oxygen atom), when AG is bound to an oxygen atom of the remainder of the compounds of the present invention, e.g. L¹, L², L³ or Con. Some of the embodiments of L¹, L², L³ and Con enclosed herein have terminal oxygen atoms or their definitions allow for terminal oxygen atoms. If an oxygen atom of AG is bound to an oxygen atom of the remainder of the compounds of the present invention a peroxide partial structure results, which is a potentially unstable. The compounds of the present invention preferably do not comprise an oxygen-oxygen bond and an oxygen atom of AG may not be bound to an oxygen atom of the remainder of the compounds of the present invention. Preferably, AG is bound to the remainder of the compounds of the present invention by an (a single) oxygen atom.

More preferably, AG is of Formula AG-1 or of Formula AG-5 and even more preferably of Formula AG-1. Most preferably, AG is of Formula AG-1, wherein T is O (an oxygen atom) and AG is not bound to an oxygen atom of the remainder of the compounds of the present invention or AG is of Formula AG-1, wherein T is a direct bond and AG is bound to an oxygen atom of the remainder of the compounds of the present invention.

Definition of variables:

Hereunder further variables used in Formulae AG-1 to AG-12 and variables used in other formulae described herein are defined. Further variables are defined in other parts of the present text.

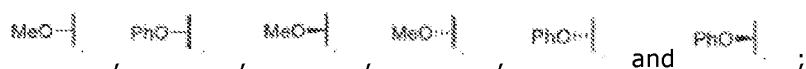
X¹ is 1 to 5 contiguous atoms independently selected from O, S, N(R⁶), and C(R⁴)(R⁴), wherein if X¹ is 1 atom then X¹ is O, S, N(R⁶), or C(R⁴)(R⁴), if X¹ is 2 atoms then no more than 1 atom of X¹ is O, S, or N(R⁶), if X¹ is 3, 4, or 5 atoms then no more than 2 atoms of X¹ are O, S, or N(R⁶), wherein preferably no two oxygen atoms are adjacent to each other;

Unless R is defined otherwise for other embodiments herein, R is selected from the group consisting of H, or C₁-C₃ alkyl optionally substituted with 1-3 hydroxyl groups;

R¹ is selected from the group consisting of hydrogen, hydroxyl, F, Cl, Br, I, -CN, -N₃, alkyl optionally substituted with 1, 2, 3, or 4 substituents, C₁-C₆-alkyl-CN optionally substituted with 1, 2, 3, or 4 substituents, alkenyl optionally substituted with 1, 2, 3, or 4 substituents, alkynyl optionally substituted with 1, 2, 3, or 4 substituents, haloalkyl optionally substituted with 1, 2, 3, or 4 substituents, aryl optionally substituted with 1, 2,

3, or 4 substituents, arylalkyl optionally substituted with 1, 2, 3, or 4 substituents, heteroaryl optionally substituted with 1, 2, 3, or 4 substituents, heteroaryl alkyl optionally substituted with 1, 2, 3, or 4 substituents, heterocycle optionally substituted with 1, 2, 3, or 4 substituents, heterocycloalkyl optionally substituted with 1, 2, 3, or 4 substituents, alkoxy optionally substituted with 1, 2, 3, or 4 substituents, haloalkoxy optionally substituted with 1, 2, 3, or 4 substituents, -O-alkenyl, -O-alkynyl, -OR⁶, C₁-C₆-alkyl-OR⁶, -SR⁶, C₁-C₆-alkyl-SR⁶, -NR⁶R⁷, C₀-C₆-alkyl-NR⁶R⁷, -C(O)R³, C₀-C₆-alkyl-C(O)R³, -S(O)R³, C₁-C₆-alkyl-S(O)R³, -C(S)R³, C₁-C₆-alkyl-C(S)R³, -S(O)₂R³, C₁-C₆-alkyl-S(O)₂R³, -N(R⁸)-C(O)R³, C₁-C₆-alkyl-N(R⁸)-C(O)R³, -N(R⁸)-S(O)R³, C₁-C₆-alkyl-N(R⁸)-S(O)R³, -N(R⁸)-C(S)R³, C₁-C₆-alkyl-N(R⁸)-C(S)R³, -N(R⁸)-S(O)₂R³, C₁-C₆-alkyl-N(R⁸)-S(O)₂R³, -O-C(O)R³, C₁-C₆-alkyl-O-C(O)R³, -O-S(O)R³, C₁-C₆-alkyl-O-S(O)R³, -O-C(S)R³, C₁-C₆-alkyl-O-C(S)R³, -N=S(O)(R³)₂, C₁-C₆-alkyl-N₃, -O-S(O)₂R³, or C₀-C₆-alkyl-O-S(O)₂R³, each of which is optionally substituted with 1, 2, 3, or 4 substituents;

In preferred embodiments R¹ is selected from the groups consisting from H,



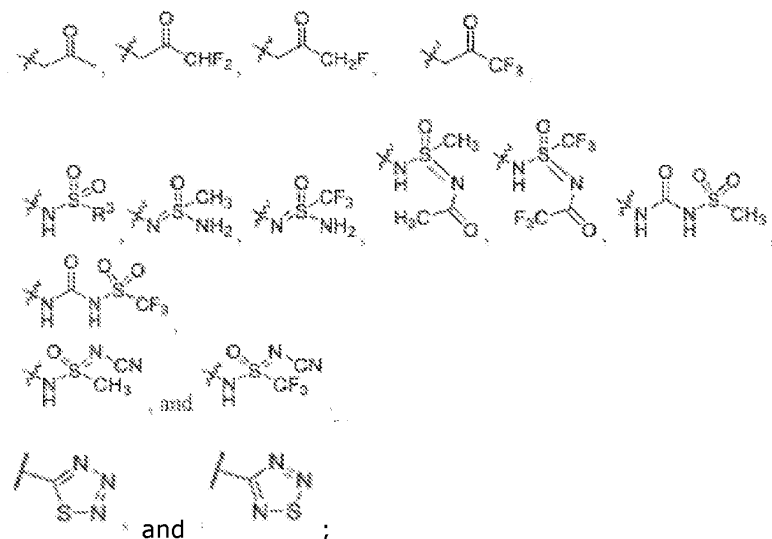
wherein or the wavy line respectively mark the bond with which R² is bonded to the remainder of the compound of the present invention.

In certain embodiments R¹ is C₀-C₆-alkyl-cyano optionally substituted with 1, 2, 3, or 4 substituents.

Most preferred R¹ is hydrogen.

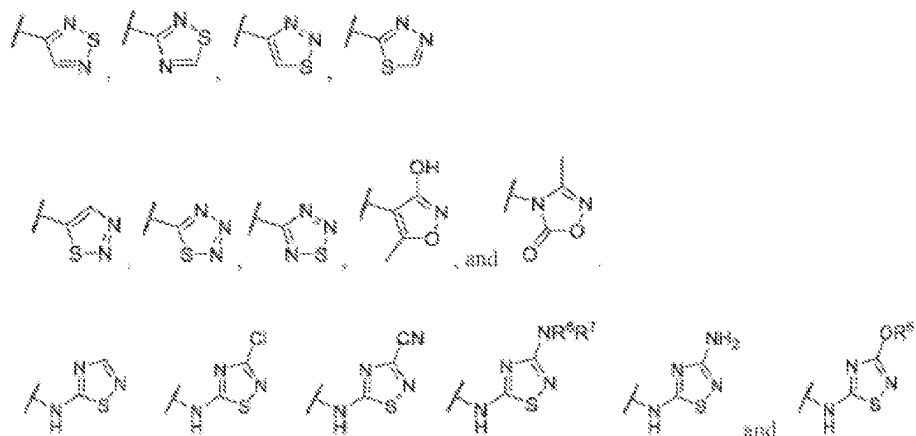
R² is selected from the group consisting of hydrogen, optionally substituted amino, alkyl optionally substituted with 1, 2, 3, or 4 substituents, alkenyl optionally substituted with 1, 2, 3, or 4 substituents, allyl optionally substituted with 1, 2, 3, or 4 substituents, alkynyl optionally substituted with 1, 2, 3, or 4 substituents, aryl optionally substituted with 1, 2, 3, or 4 substituents, a heterocycle optionally substituted with 1, 2, 3, or 4 substituents, heteroaryl containing 1, 2 or 3 heteroatoms in the ring which are independently selected from N, O, and S and wherein the heteroaryl groups are optionally substituted with 1, 2, 3, or 4 substituents, R¹⁰, alkoxy optionally substituted with 1, 2, 3, or 4 substituents, -O-alkenyl optionally substituted with 1, 2, 3, or 4 substituents, -O-alkynyl optionally substituted with 1, 2, 3, or 4 substituents, -O-aryl optionally substituted with 1, 2, 3, or 4 substituents, -O-heteroaryl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-alkyl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-alkenyl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-alkynyl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-heteroaryl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-aryl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-C(O)R¹⁰, -NR⁸-S(O)-R³ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-C(S)-R³ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-

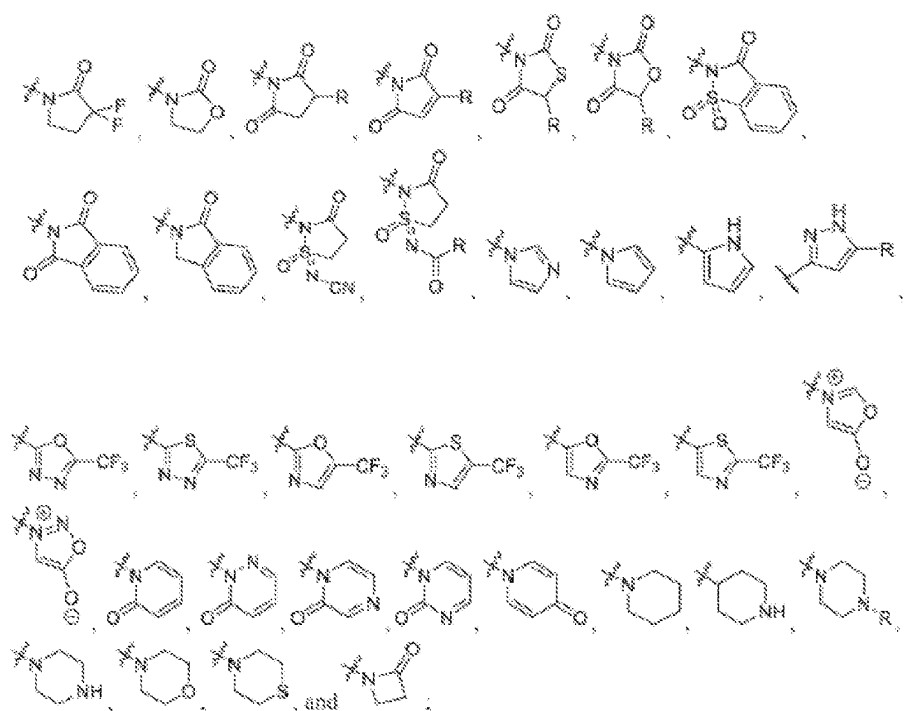
S(O)(NR⁶)-R³ optionally substituted with 1, 2, 3, or 4 substituents, -N=S(O)(R³)₂ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸C(O)NR⁹S(O)₂R³ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-S(O)₂-R¹⁰ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-C(NR⁶)-R³ optionally substituted with 1, 2, 3, or 4 substituents, alkyl-C(O)-R³, -C(O)-R³, haloalkyl, -OC(O)R³,



wherein and the wavy line, respectively, mark the bond with which R² is bonded to the remainder of the compound of the present invention.

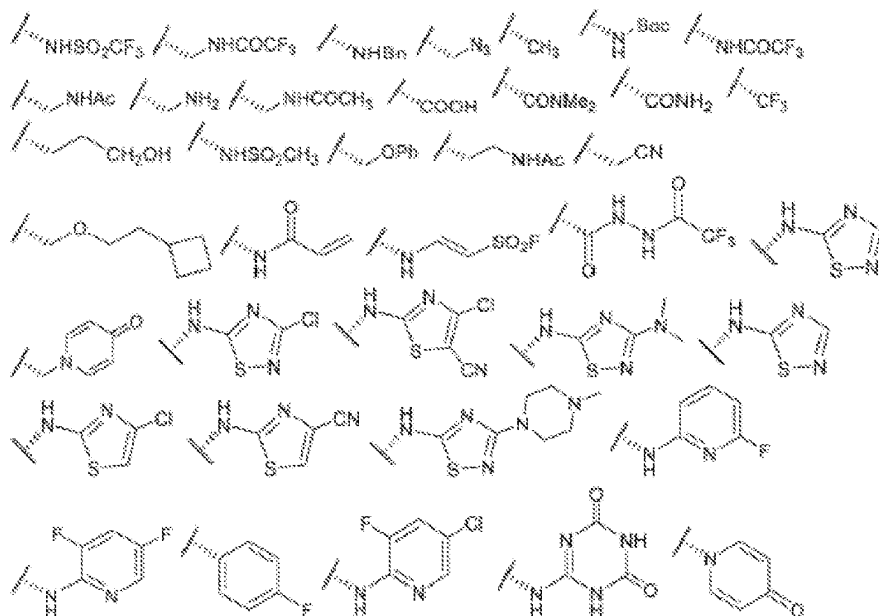
R^2 is preferably selected from the group consisting of

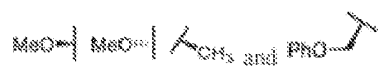
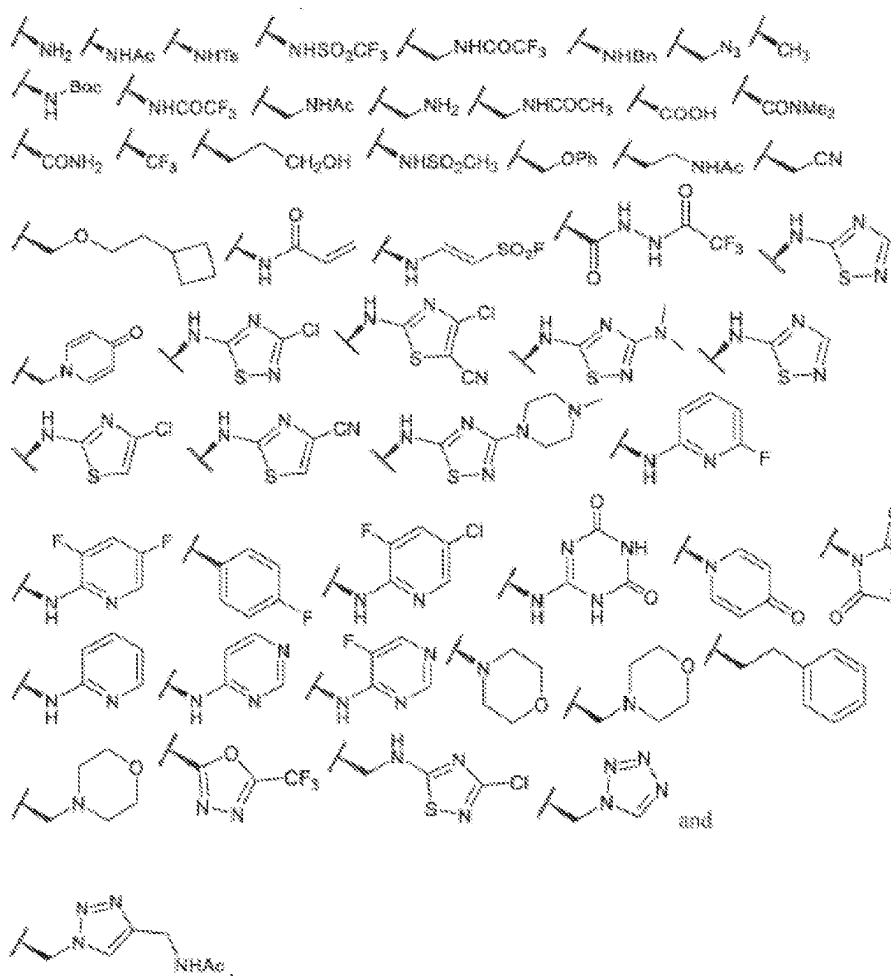
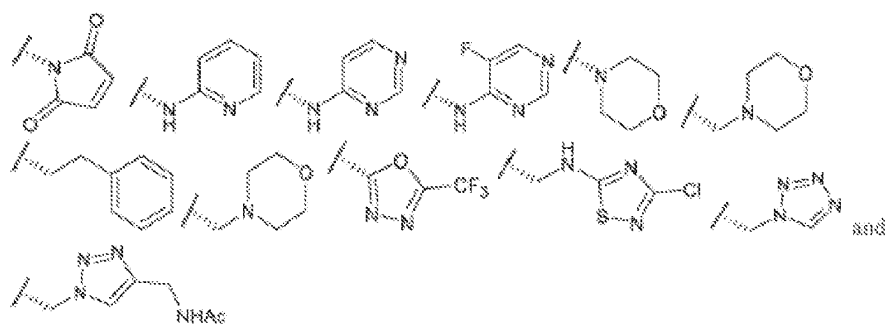


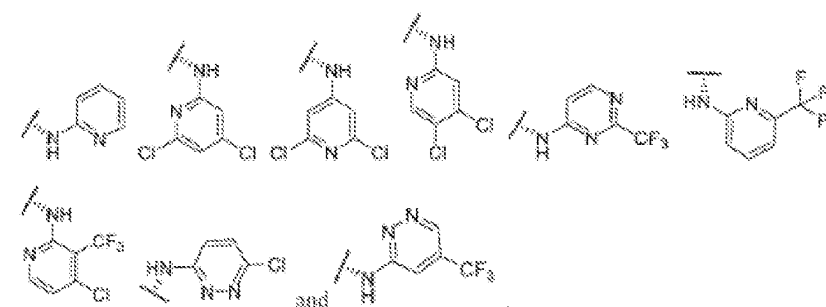
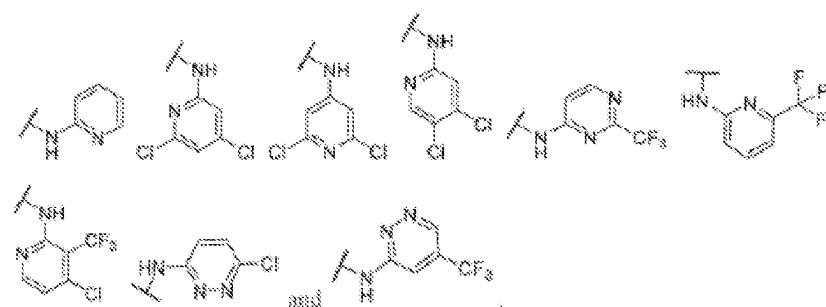
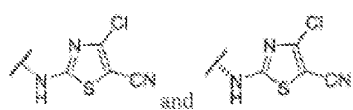
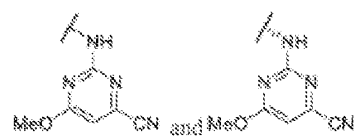
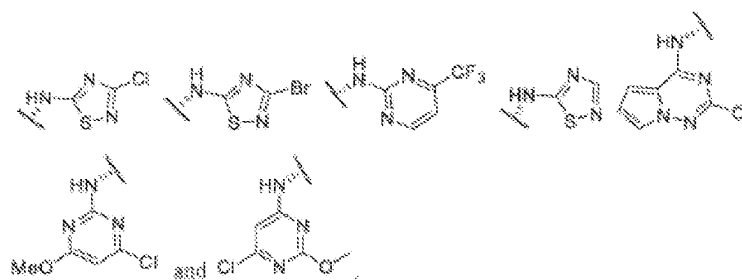
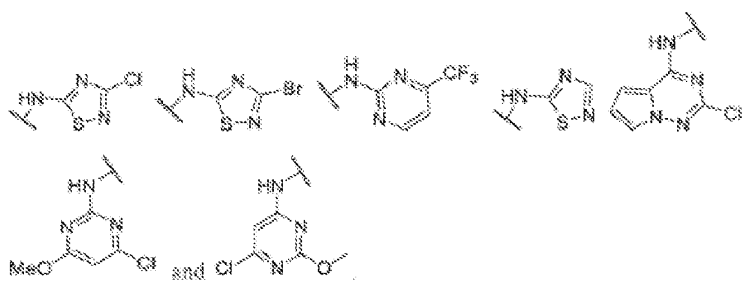


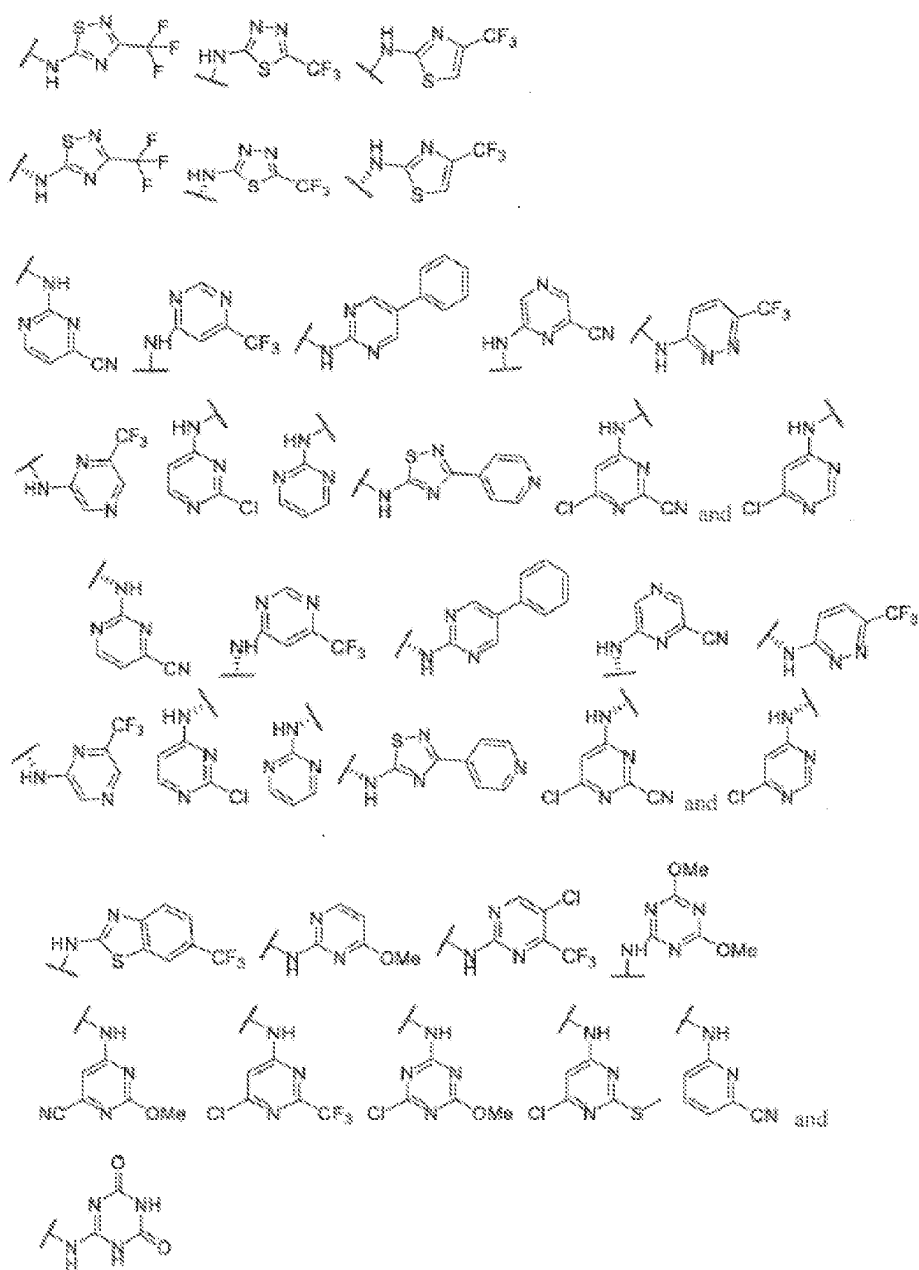
wherein R is an optional substituent selected from the group consisting of H, or C₁-C₃ alkyl optionally substituted with 1-3 hydroxyl groups.

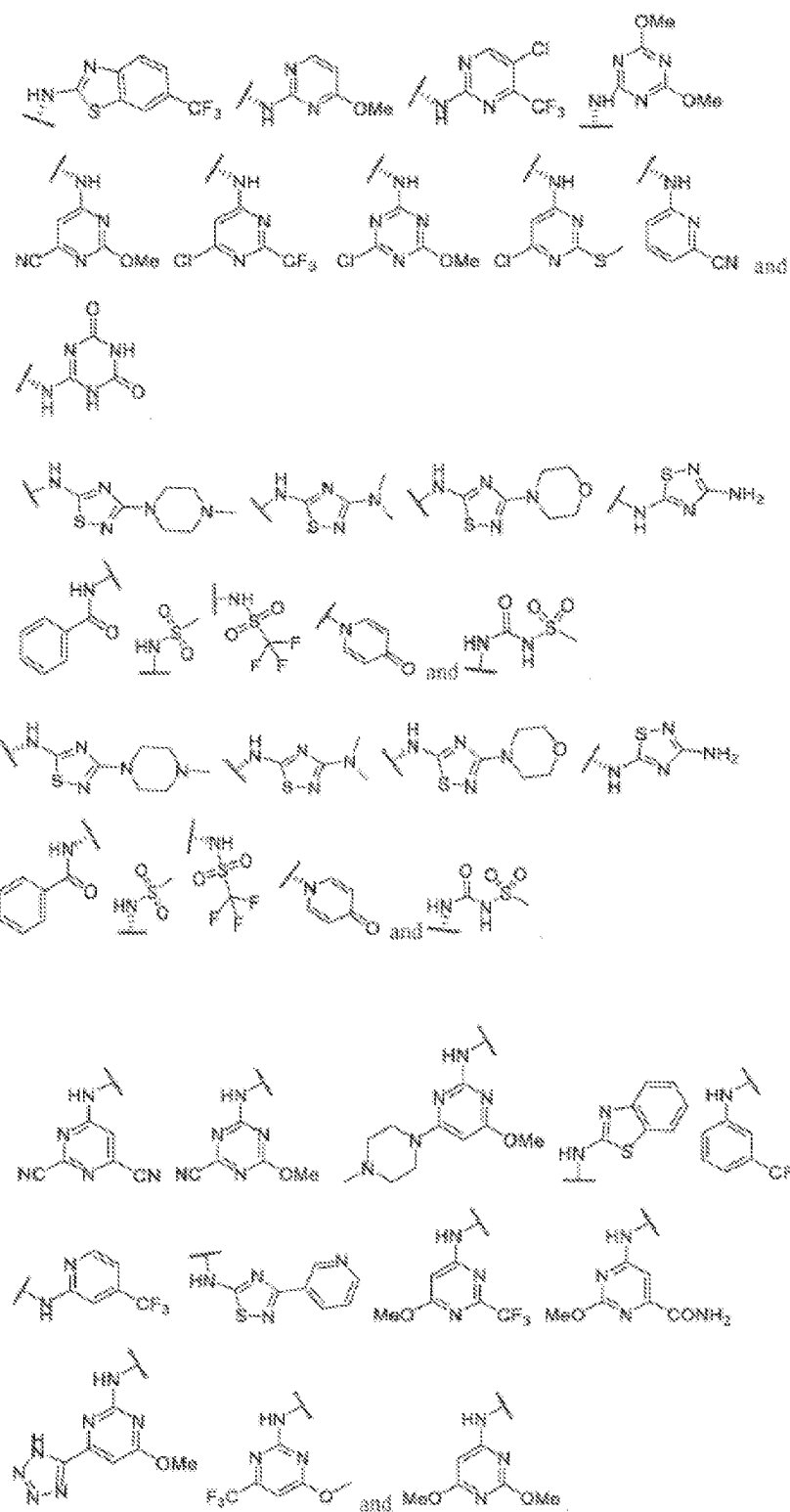
Additionally, R^2 is preferably selected from the group consisting of

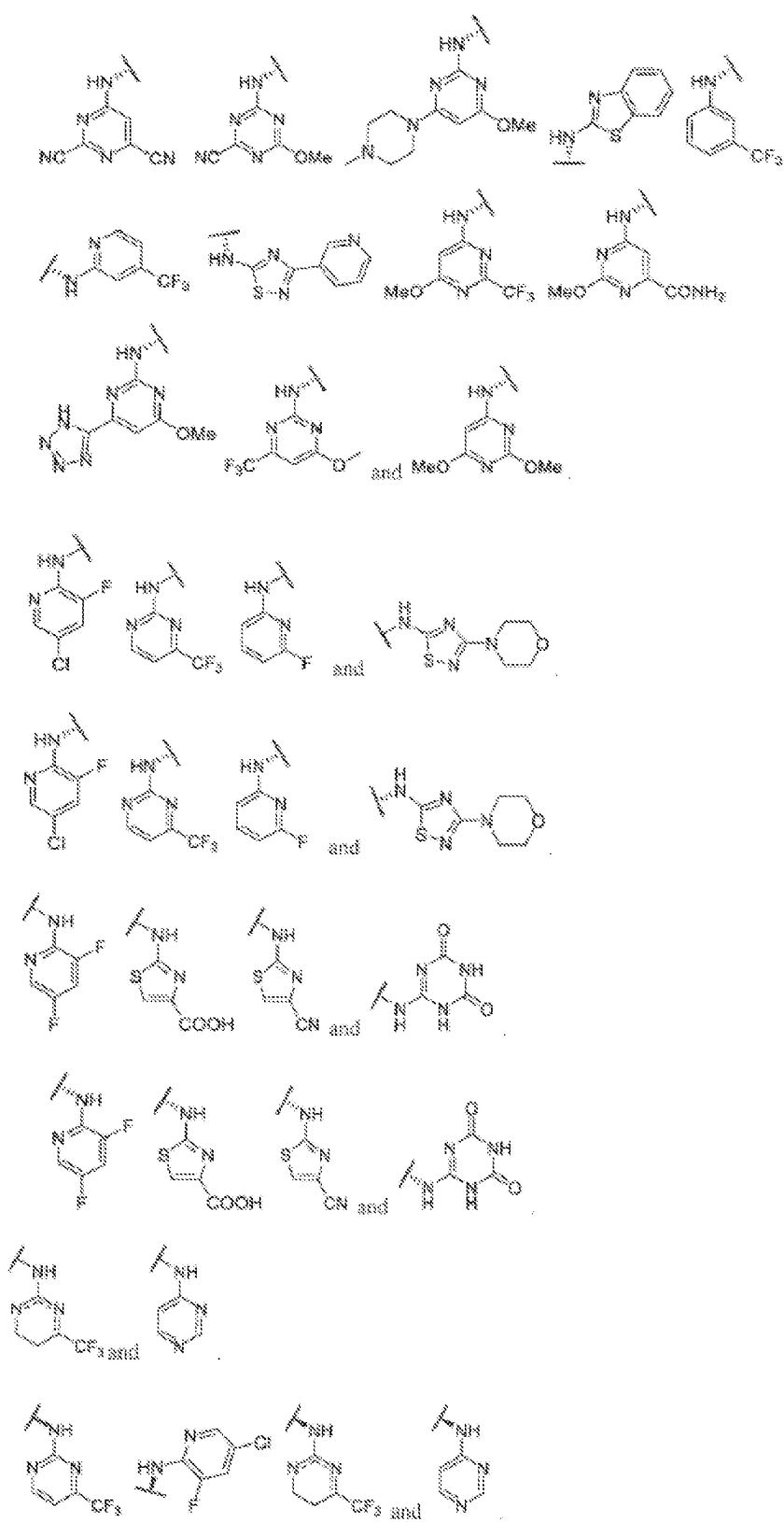


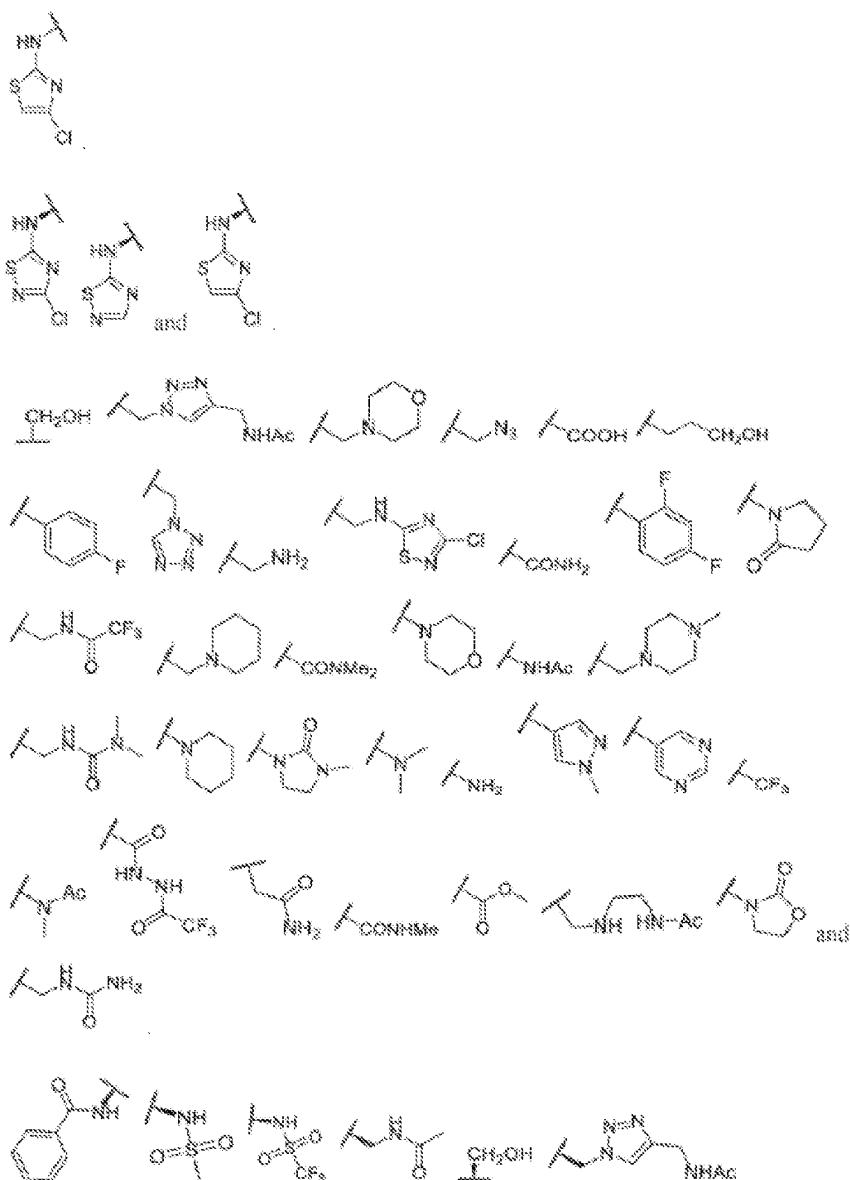


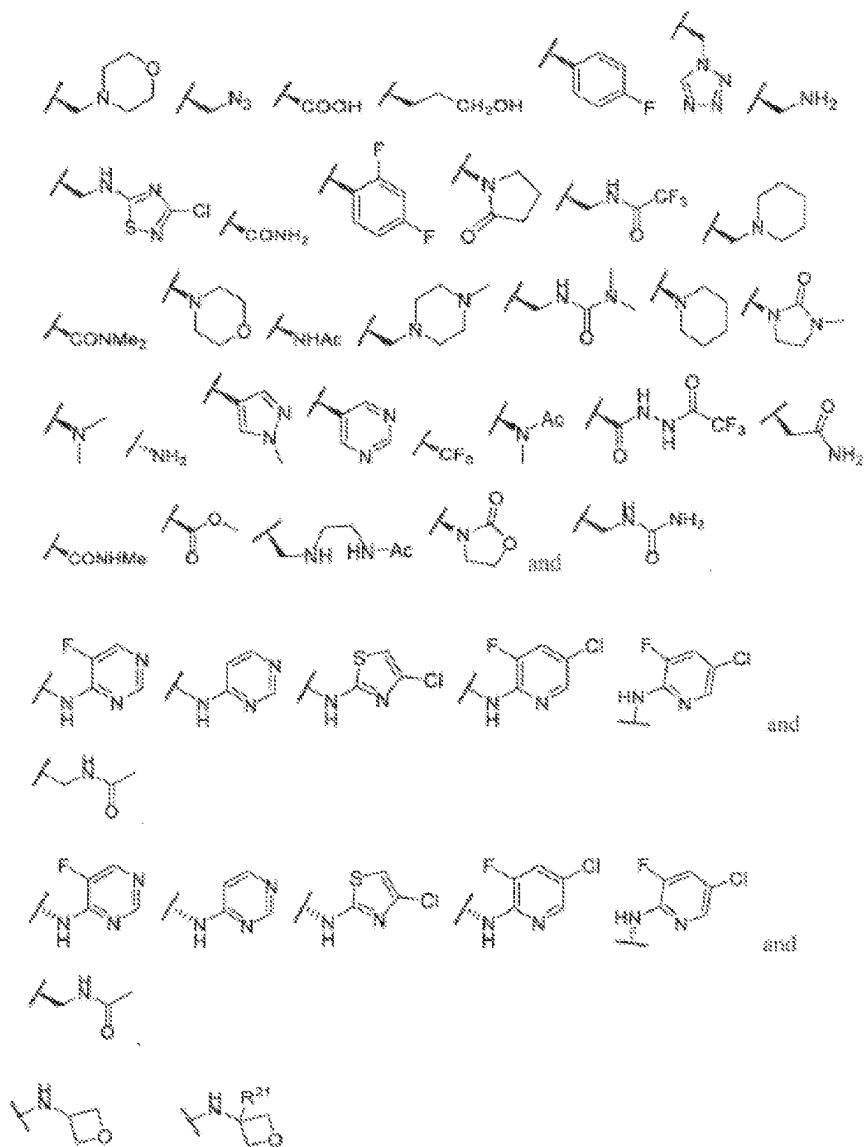












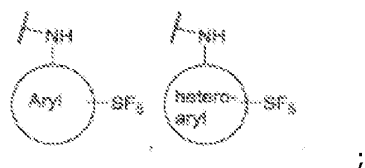
bicyclic heterocycle, a spirocyclic heterocycle, for example, and without limitation,



a silicon containing heterocycle, for example, and without limitation,

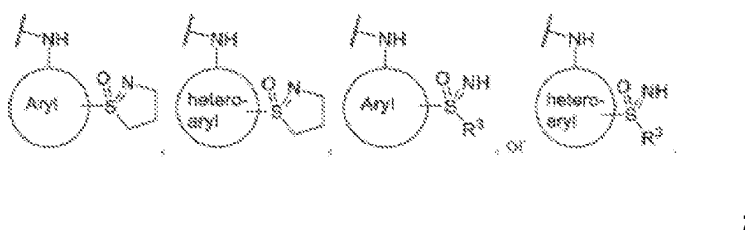
wherein --- marks the bond with which R^2 is bonded to the remainder of the compound of the present invention.

In certain embodiments, R^2 is substituted with SF_5 , for example, and without limitation,



wherein — marks the bond with which R^2 is bonded to the remainder of the compound of the present invention

In certain embodiments R^2 is substituted with a sulfoxime, for example, and without limitation,



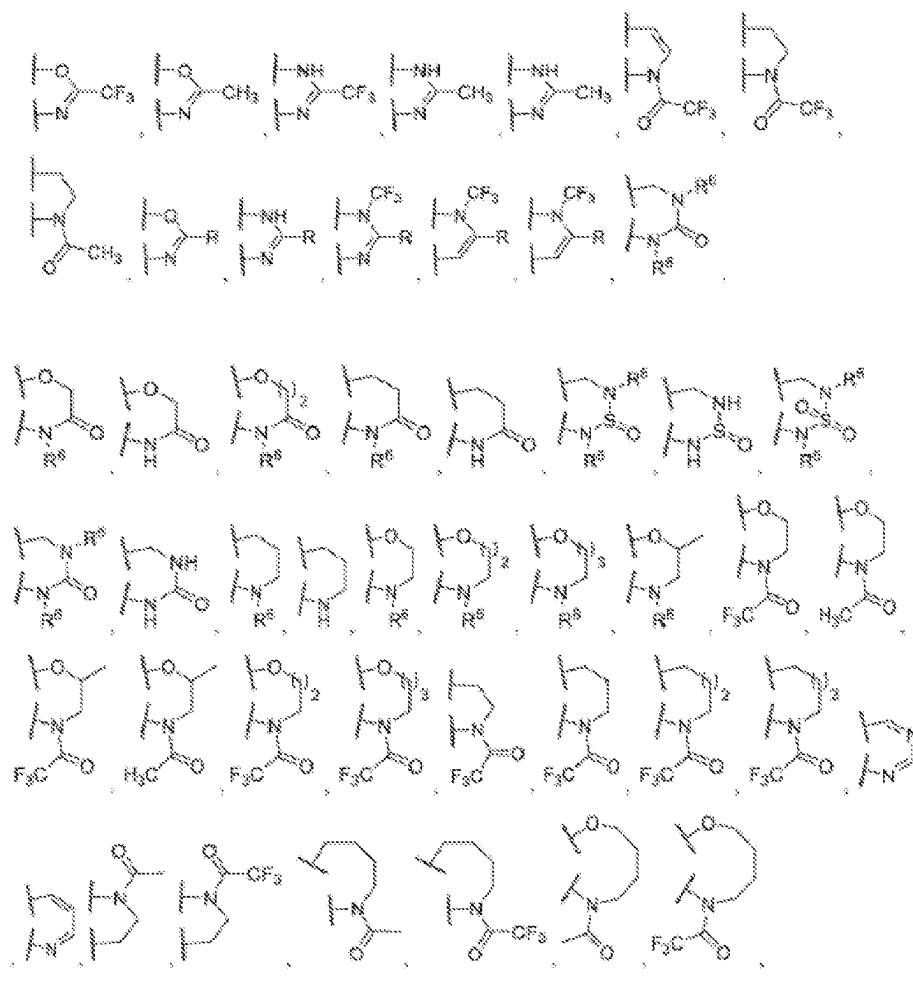
wherein — marks the bond with which R^2 is bonded to the remainder of the compound of the present invention.

In certain embodiments R^1 and R^2 form a 5 to 7 membered saturated heterocycle that comprises up to 3 heteroatoms selected from the group consisting of N, S and O and preferably the heterocycle is a 5 or 6-membered heterocycle;

In certain embodiments R^1 and R^2 form a 3 to 7 membered saturated optionally substituted carbocycle. Preferably the carbocycle is a 3 to 6-membered carbocycle optionally substituted by at least one halogen atom and more preferably the carbocycle is a 3-membered carbocycle substituted by two fluorine atoms;

In a certain embodiments the C^4 and C^5 atoms of Formula AG-1 to Formula AG-12 are connected to form a 5 to 7 membered saturated optionally substituted heterocycle that comprises up to 3 heteroatoms selected from the group consisting of N, S and O and preferably the heterocycle is a 5 or 6-membered heterocycle, the C^6 carbon atom and the oxygen atom of the sugar bonded to the $C6$ carbon atom of the sugar may or may not be part of that heterocycle;

When R^1 and R^2 form a cycle, R^1 and R^2 are preferably selected from



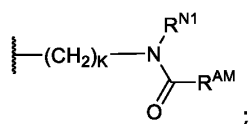
;

wherein f marks the bond with which R^{10} is bonded to the remainder of the compound of the present invention.

In various embodiments, R^2 is $-\text{NH}-\text{C}(=\text{O})-\text{CH}_3$. These embodiments are very much preferred.

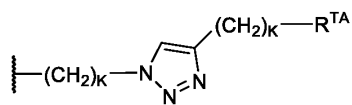
In a preferred embodiment R^2 is RR .

RR is



wherein R^{AM} is H, $\text{C}_1\text{-C}_4$ alkyl optionally substituted with up to 3 halo groups and one or two hydroxyl groups, $-(\text{CH}_2)_k\text{COOH}$, $-(\text{CH}_2)_k\text{C}(\text{O})\text{O}-(\text{C}_1\text{-C}_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, $-\text{O}-\text{C}(\text{O})-(\text{C}_1\text{-C}_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, $-\text{C}(\text{O})-(\text{C}_1\text{-C}_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, or $-(\text{CH}_2)_k\text{-NR}^{\text{N3}}\text{R}^{\text{N4}}$, or

RR is

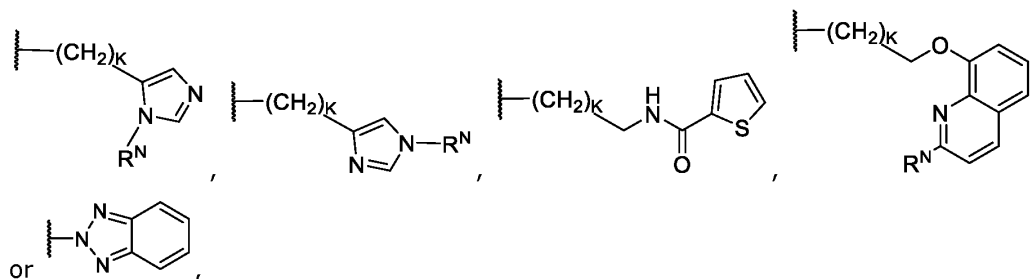


wherein

R^{TA} is H, CN, $NR^{N1}R^{N2}$, $-(CH_2)_kOH$, $-(CH_2)_kO(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, C_1-C_4 alkyl optionally substituted with 1-3 halo groups, $-(CH_2)_kCOOH$, $-(CH_2)_kC(O)O-(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, $-O-C(O)-(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, or $-C(O)-(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, or

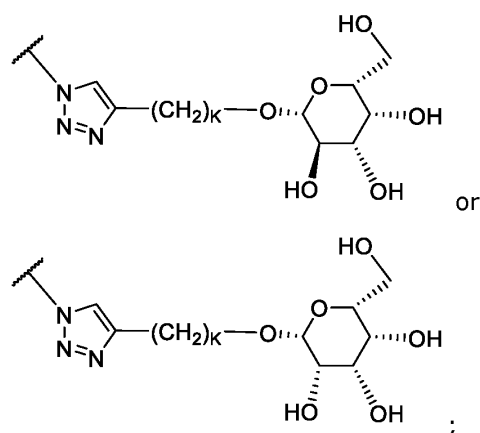
R^{TA} is a C_3-C_{10} aryl or a three- to ten-membered heteroaryl group containing up to 5 hetero atoms in the rings, each of the aryl or heteroaryl groups being optionally substituted with up to three CN, $NR^{N1}R^{N2}$, $-(CH_2)_kOH$, $-(CH_2)_kO(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, C_1-C_3 alkyl optionally substituted with 1-3 halo groups or 1-2 hydroxy groups, $-O-(C_1-C_3\text{-alkyl})$ optionally substituted with 1-3 halo groups, $-(CH_2)_kCOOH$, $-(CH_2)_kC(O)O-(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, $O-C(O)-(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, or $-(CH_2)_kC(O)-(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, or

R^{TA} is



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



wherein the wavy line marks the bond with which R^{TA} is bonded to the remainder of the compound of the present invention.

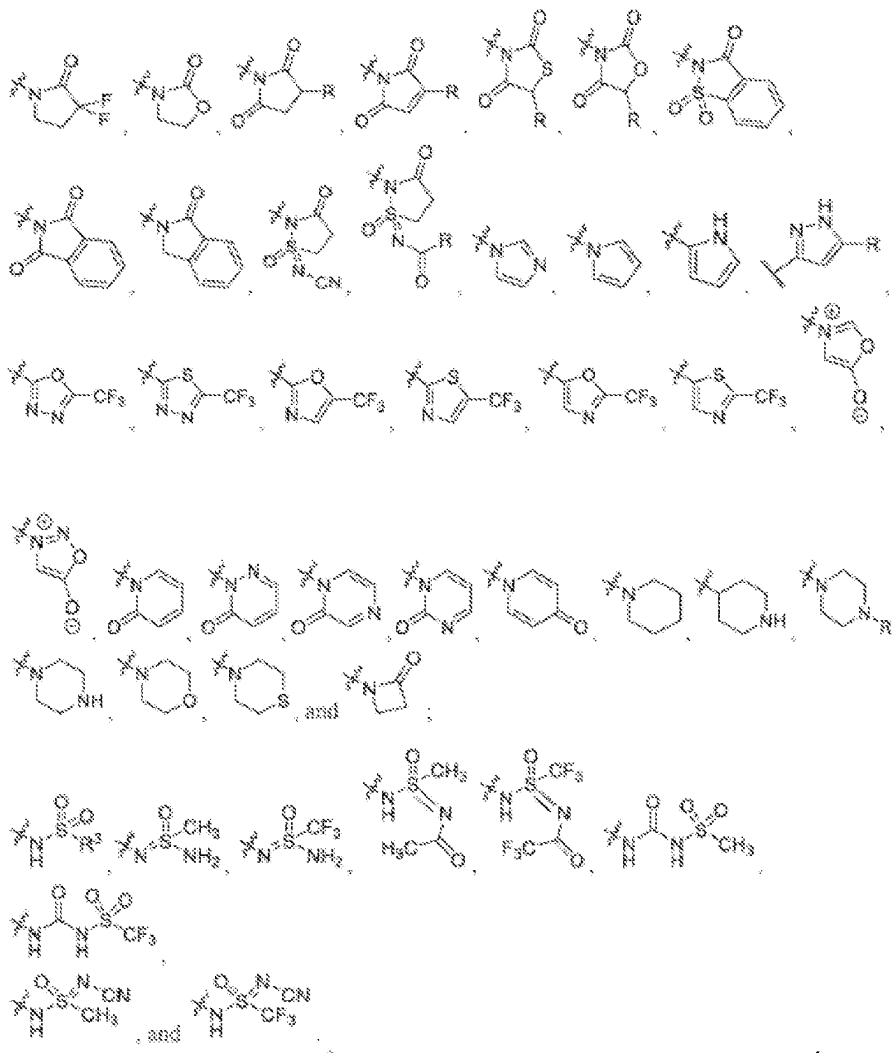
R^N, R^{N1}, R^{N2}, R^{N3}, R^{N4} are each independently H or C₁-C₃ alkyl optionally substituted with one to three halo groups or one or two hydroxyl groups and each - (CH₂)_k group is optionally substituted with 1-4 C₁-C₃ alkyl groups which are optionally substituted with 1-3 fluoro groups or 1-2 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.

In one preferred embodiment R² is selected from -NR⁶COR³, -NR⁶-(5-membered heteroaryl) and -NR⁶-(6-membered heteroaryl), each of which R² 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.

R² is preferably selected from



wherein R is an optional substituent as defined herein and wherein the wavy line marks the bond with which R² is bonded to the remainder of the compound of the present invention.

R³ at each occurrence is independently selected from hydrogen, alkyl, heteroalkyl, haloalkyl (including -CF₃, -CHF₂, -CH₂F, -CH₂CF₃, -CH₂CH₂F, and -CF₂CF₃), arylalkyl, heteroarylalkyl, alkenyl, alkynyl, and, heteroaryl, heterocycle, -OR⁸, and -NR⁸R⁹;

R⁴ is independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, -OR⁶, -NR⁶R⁷, C(O)R³, S(O)R³, C(S)R³, and S(O)₂R³;

R⁵ is independently selected from hydrogen, heteroalkyl,



C₀-C₆alkyl-cyano, alkyl, alkenyl, alkynyl, haloalkyl, F, Cl, Br, I, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocycloalkyl, haloalkoxy, -O-alkenyl, -O-alkynyl, C₀-C₆alkyl-OR⁶, C₀-C₆alkyl-SR⁶, C₀-C₆alkyl-NR⁶R⁷, C₀-C₆alkyl-C(O)R³, C₀-C₆alkyl-S(O)R³, C₀-C₆alkyl-C(S)R³, C₀-C₆alkyl-S(O)₂R³, C₀-C₆alkyl-N(R⁸)-C(O)R³, C₀-C₆alkyl-N(R⁸)-S(O)R³, C₀-C₆alkyl-N(R⁸)-C(S)R³, C₀-C₆alkyl-N(R⁸)-S(O)₂R³, C₀-C₆alkyl-O-C(O)R³, C₀-C₆alkyl-O-S(O)R³, C₀-C₆alkyl-O-C(S)R³, -N=S(O)(R³)₂, C₀-C₆alkylN₃, and C₀-C₆alkyl-O-S(O)₂R³, each of which is optionally substituted with 1, 2, 3, or 4 substituents. R⁶ and R⁷ are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroaryl alkyl, alkenyl, alkynyl, and, haloalkyl, heteroaryl, heterocycle, -alkyl-OR⁸, -alkyl-NR⁸R⁹, C(O)R³, S(O)R³, C(S)R³, and S(O)₂R³;

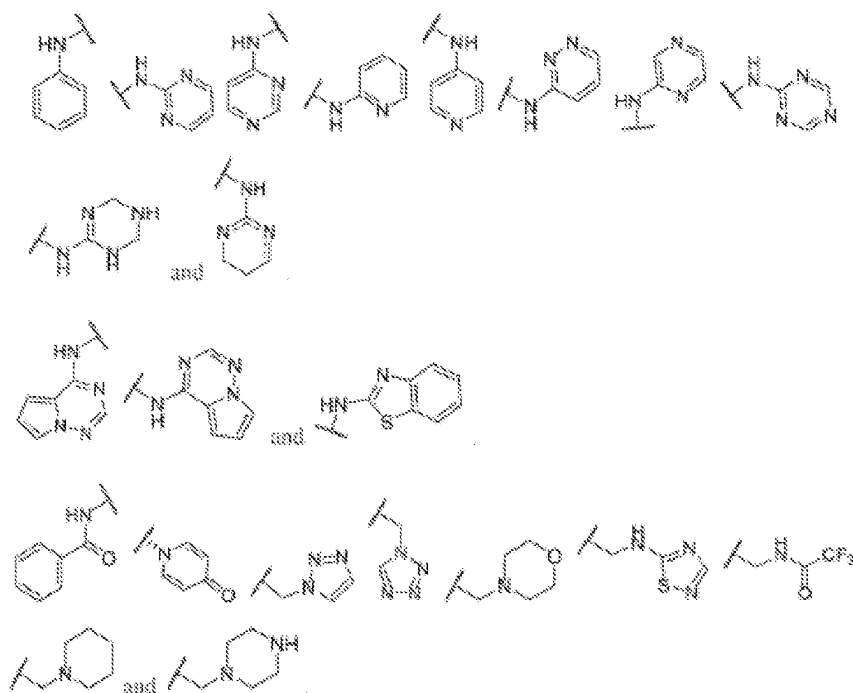
R⁶ and R⁷ are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroaryl alkyl, alkenyl, alkynyl, and, haloalkyl, heteroaryl, heterocycle, -alkyl-OR⁸, -alkyl-NR⁸R⁹, C(O)R³, S(O)R³, C(S)R³, and S(O)₂R³.

R⁸ and R⁹ are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle.

R¹⁰ is preferably selected from C⁵ or C⁶ heterocycles, bicyclic heterocycles, spirocyclic heterocycle, -NR⁶-heterocycle and more preferably from C⁵ or C⁶ heterocycles comprising 1 to 3 heteroatoms selected from N, O and S as ring atoms.

In even more preferred embodiments R¹⁰ is selected from

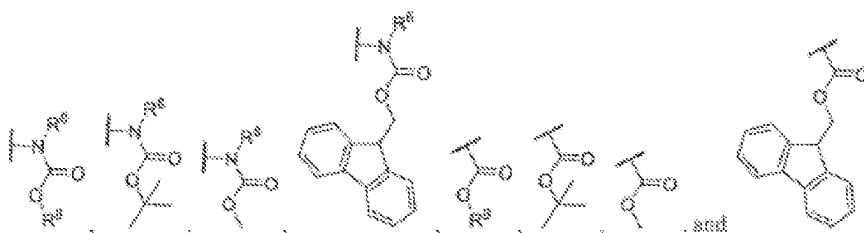




wherein  marks the bond with which R¹⁰ is bonded to the remainder of the compound of the present invention.

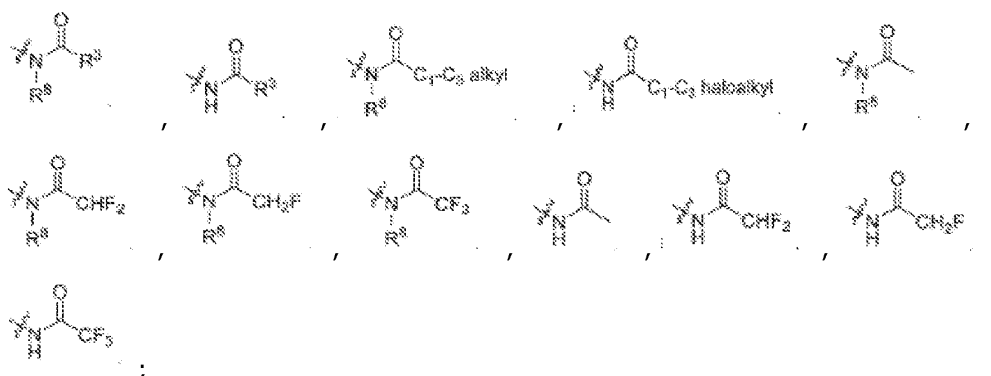
R²¹ is independently at each occurrence selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, F, Cl, Br, I, hydroxyl, alkoxy, azide, amino, cyano, -NR⁶R⁷, -NR⁸SO₂R³, -NR⁸S(O)R³, haloalkyl, heteroalkyl, and, heteroaryl, and heterocycle;

R³⁰ is preferably selected from:



wherein marks the bond with which R³⁰ is bonded to the remainder of the compound of the present invention.

R^{200} is selected from



wherein the wavy line marks the bond with which R^{200} is bonded to the remainder of the compound of the present invention.

Boc is *tert*-butoxycarbonyl.

In the compounds of the present invention, tt is independently selected from 1, 2, or 3.

In the compounds of the present invention, ss is 3 minus tt (3-tt).

In the compounds of the present invention, 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 unless stated otherwise.

In the compounds of the present invention, 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 unless stated otherwise.

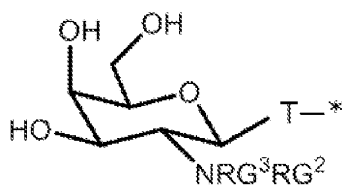
In the compounds of the present invention, zz is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 unless stated otherwise.

Aminosugars

Among the derivatives of monosaccharides, disaccharides and oligosaccharides aminosugars are preferred. In a preferred embodiment AG is a monosaccharide, disaccharide, or oligosaccharide, wherein one or more of the hydroxy (OH) groups in the particular sugar is (are) replaced (independently of each other) with a -NRG₂RG₃ group, wherein RG₂ and RG₃ are each independently selected from the group consisting of hydrogen and -C(=O)R and an optionally substituted 5- or 6-membered aromatic heterocycle, wherein R is C1-10 alkyl and wherein the heterocycle or R, respectively, are optionally substituted by 1-5 groups selected from the group consisting of halogen, C1-10 alkoxy, C1-10 aminoalkyl, and combinations thereof, or RG₂ and RG₃ taken together with the nitrogen atom to which they are attached, form a 5- or 6-membered heterocycle that is optionally substituted by 1-5 substituents selected from the group consisting of optionally substituted C1-10 alkyl, optionally substituted C1-10 alkoxy, optionally substituted C1-10 aminoalkyl, optionally substituted C6-10 aryl, optionally substituted

C5-10 heteroaryl, halogen, and combinations thereof. The 5- or 6-membered aromatic heterocycles of this embodiment preferably comprise one or more heteroatom as ring atom that is selected from the group consisting of N, O and S. The 5- or 6-membered aromatic heterocycles of this embodiment may be aromatic or non-aromatic and they may be saturated or unsaturated. In a preferred embodiment -NRG²RG³ is -NH-C(=O)-CH₃.

In a more preferred embodiment of the compounds of the present invention that comprise partial structures of aminosugars, AG has the structure



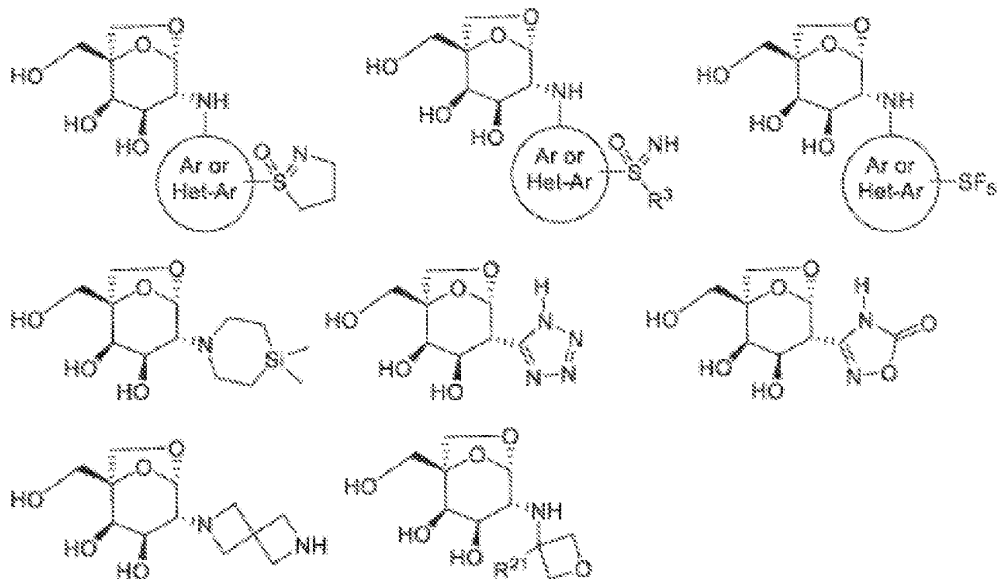
wherein T is a direct bond or O (an oxygen atom) and * marks the bond to the remainder of the compounds of the present invention with the proviso that not oxygen-oxygen bond is formed between AG and the remainder of the compounds of the present invention. In a more preferred embodiment RG² is hydrogen and RG³ is an aromatic heterocycle selected from the group consisting of 1H-pyrrole, pyrazole, imidazole, furan, thiophene, oxazole, isoxazole, isothiazole, thiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine. In an even more preferred embodiment RG² is hydrogen and RG³ is -C(=O)-CH₃. Accordingly, in a very preferred embodiment AG is n-acetylgalactosamine (GalNAc), which is bound by an oxygen atom bound to the C1 atom to the remainder of the compounds of the present invention.

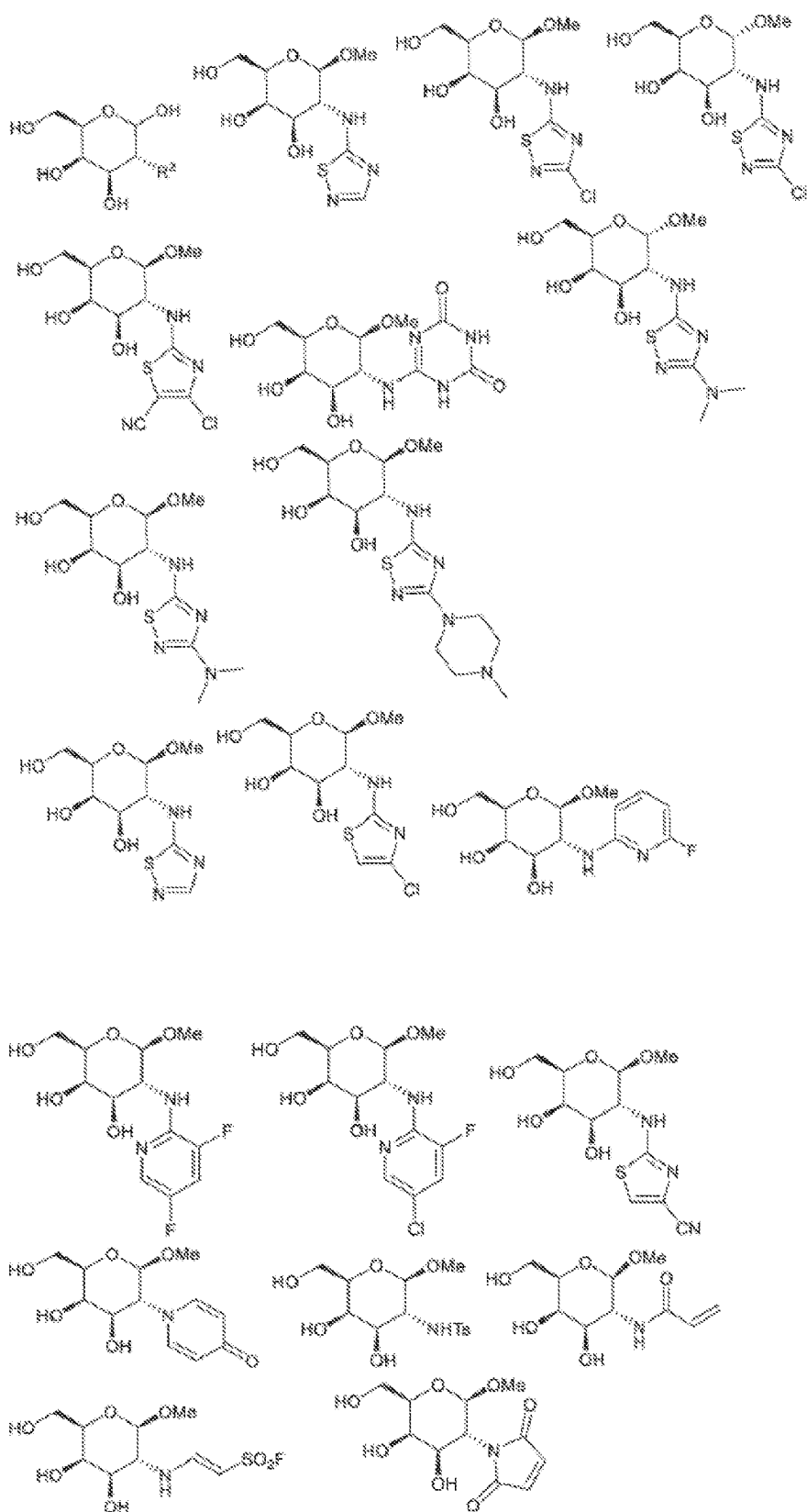
For the purposes of this invention the sugar molecule or its derivative may be bonded to the remainder of the compounds of the present invention by any part of their structure. They can for example be bonded by a carbon atom or an oxygen atom of the sugar to the remainder of the compounds of the present invention. Galactose, talose and their derivatives are preferably bound by means of C¹, C⁵ or C⁶ or by means of the oxygen atoms of the hydroxyl group of the C¹ or C⁶ carbon atom thereof. The C⁵ and C⁶ positions are preferred. Usually the bond to the remainder of the molecule is formed by substituting one hydrogen atom or a hydroxyl group for the bond to the remainder of the molecule. When the sugar or the derivative thereof is connected through the C¹ position, then that carbon may be appropriately functionalized for linking, for example by substituting a hydrogen atom or the hydroxyl group for a group selected from the groups consisting of amino, allyl, alkyne or hydroxyl-allyl group. When the sugar or the derivative thereof is connected through the C⁵ carbon atom the C⁶ carbon atom, i.e. the HO-C⁶H₂- group may be substituted for the bond to the remainder of the molecule. The bond between the sugar or the derivative thereof and the remainder of the compound of

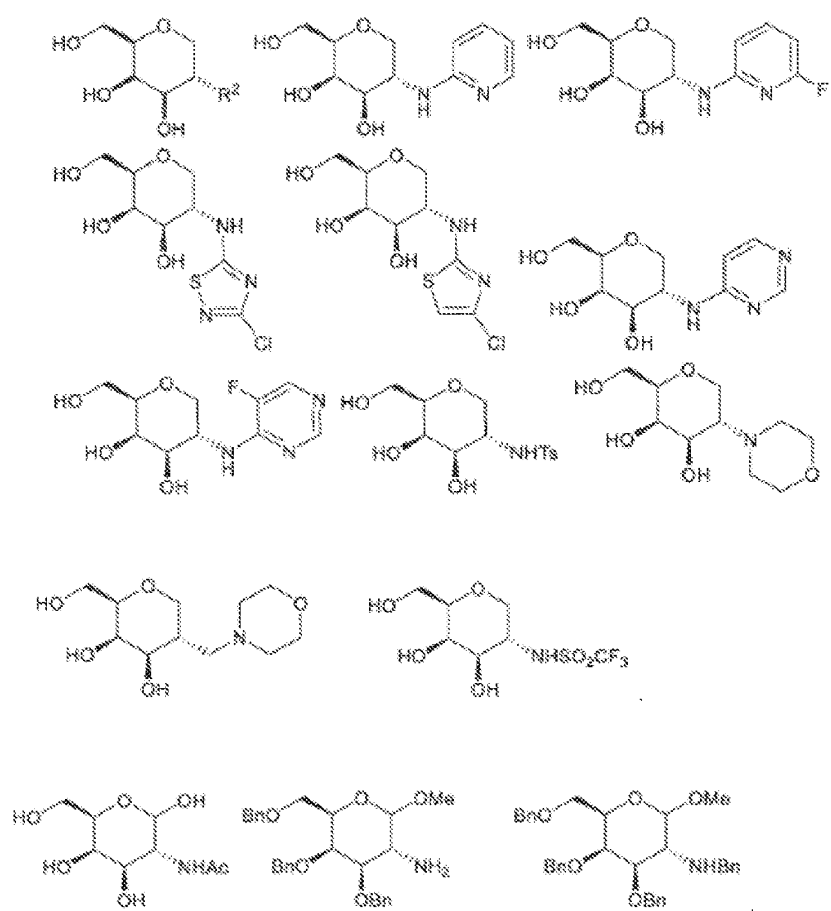
the present invention may be formed by substituting the remainder of the molecule for a hydrogen atom or an OH group of the sugar.

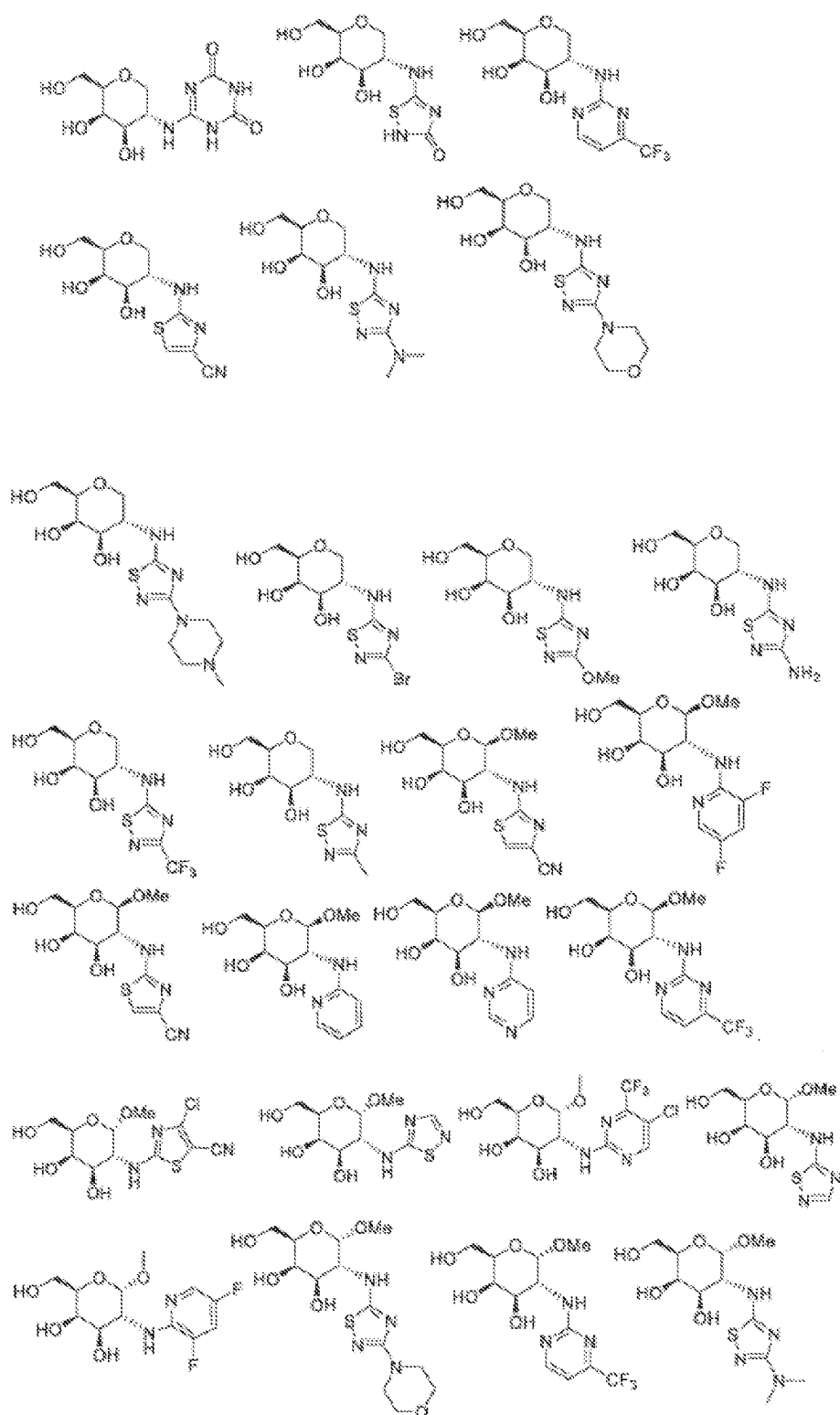
Formulae of sugar derivatives

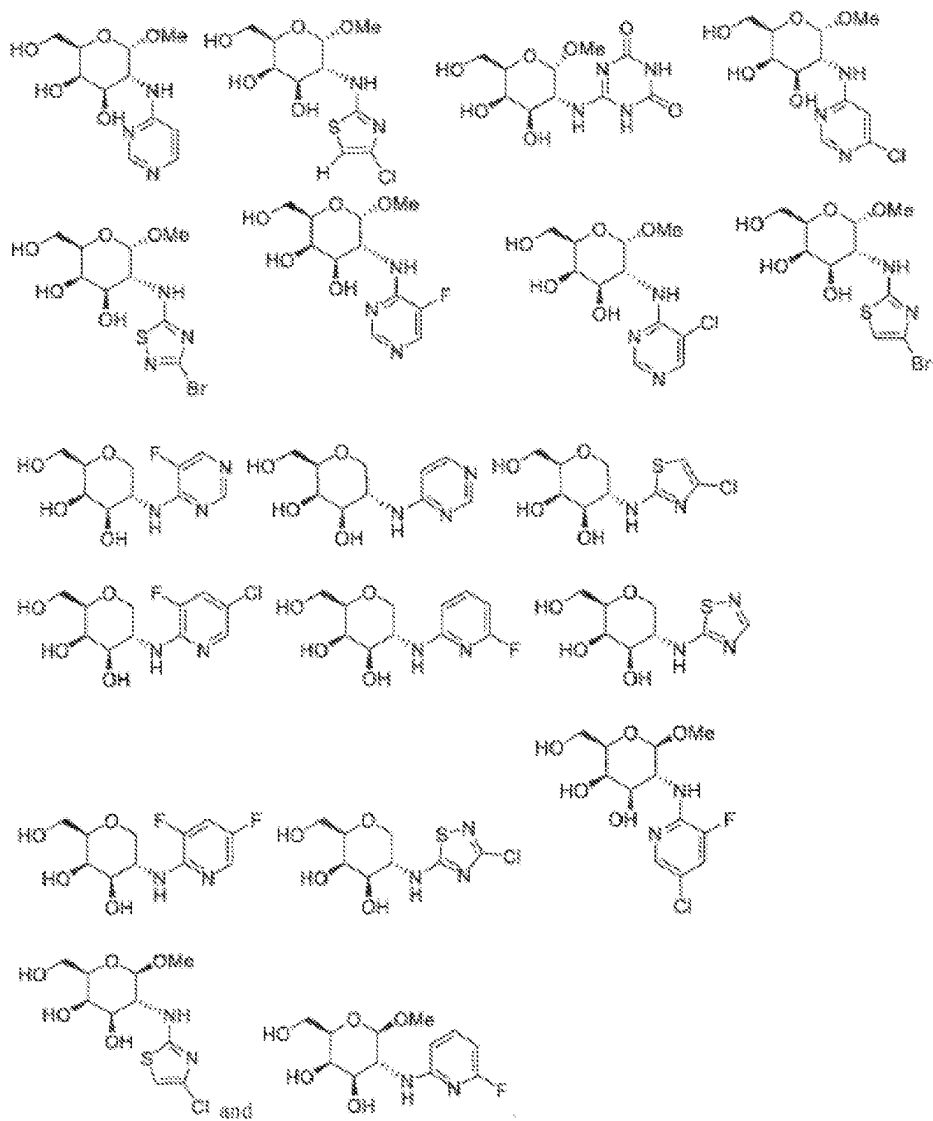
Further sugar derivatives that are useful as group AG in the present invention that are derivatives of galactose may be selected from the group consisting of:

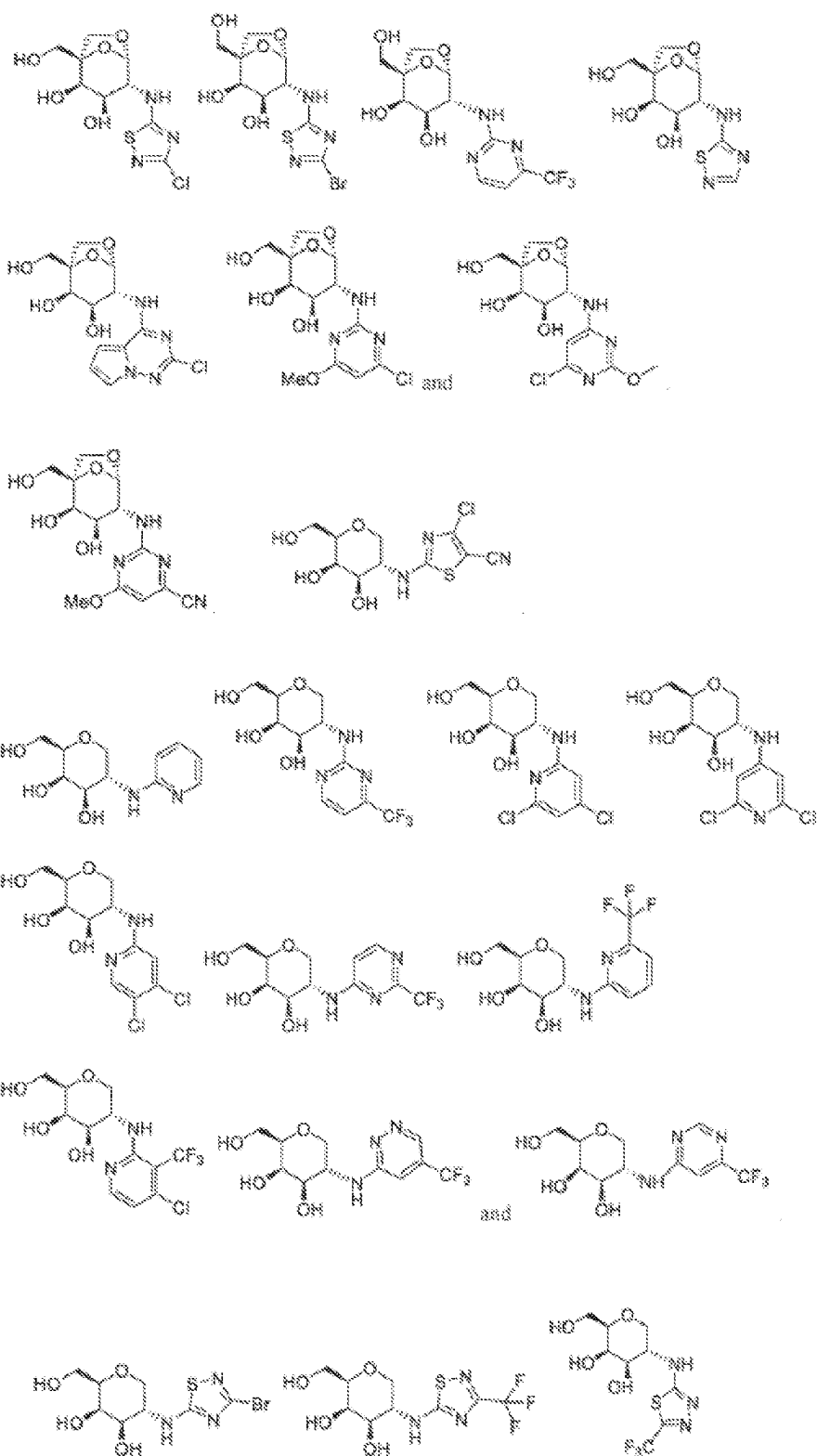


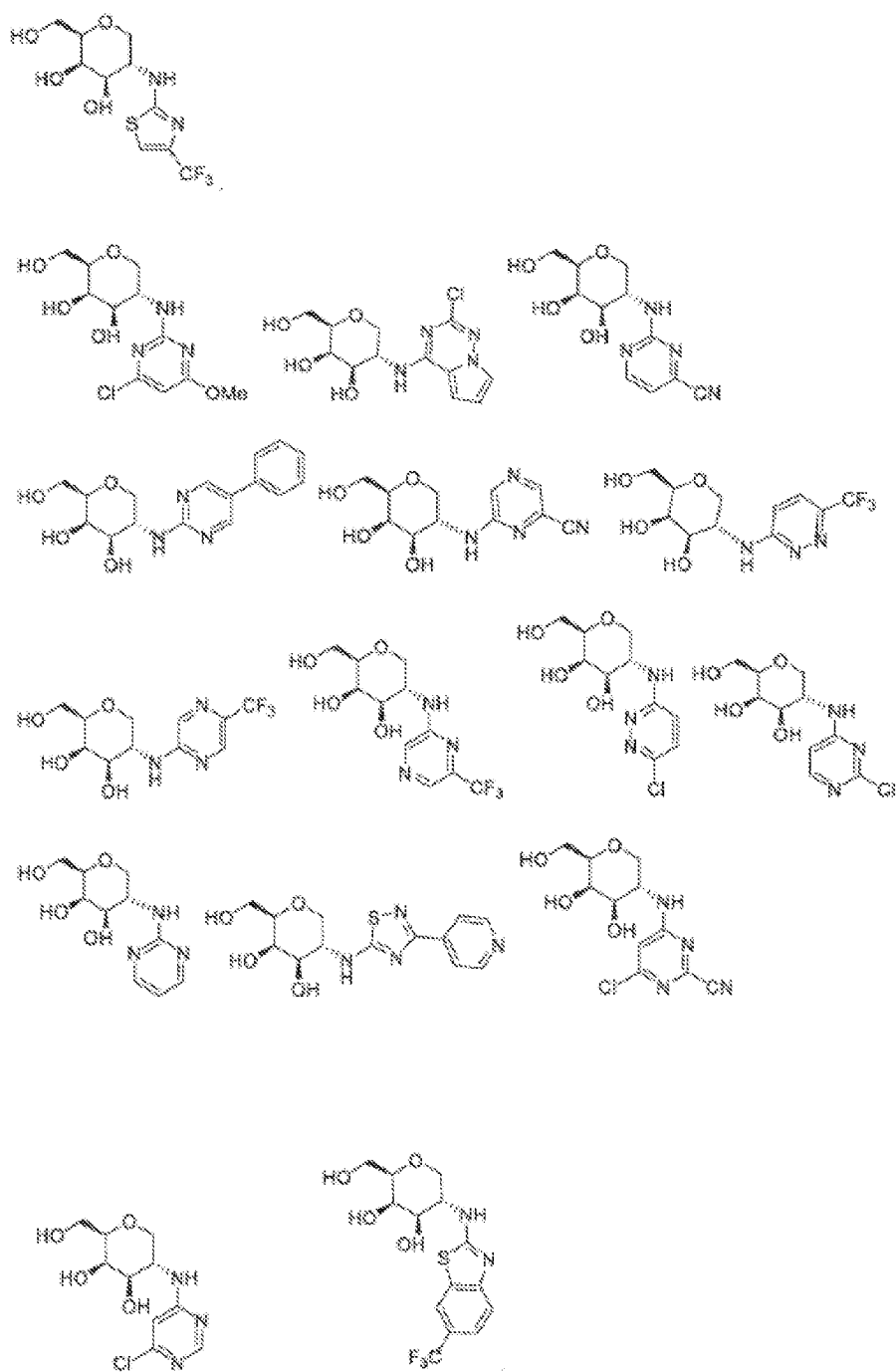


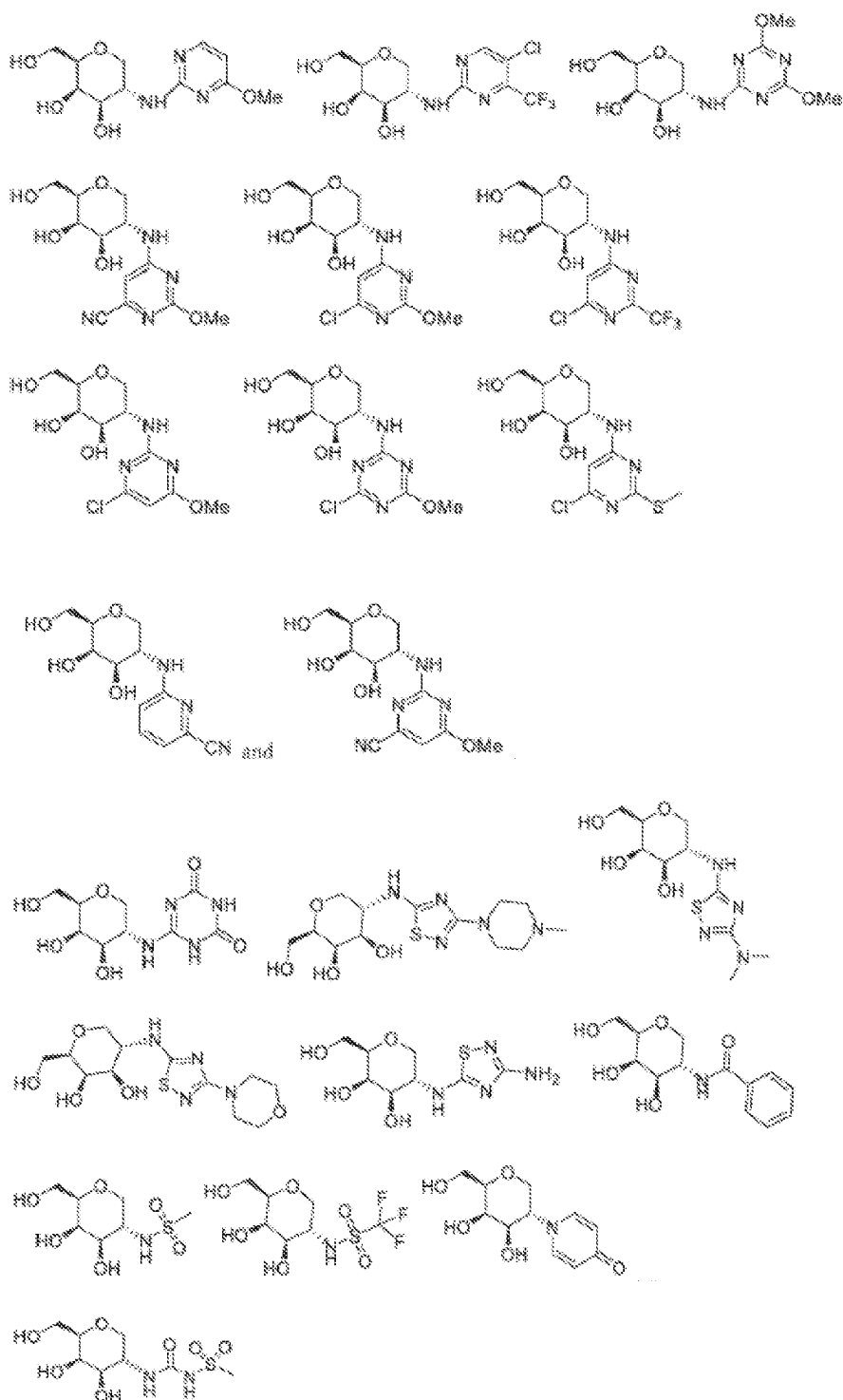


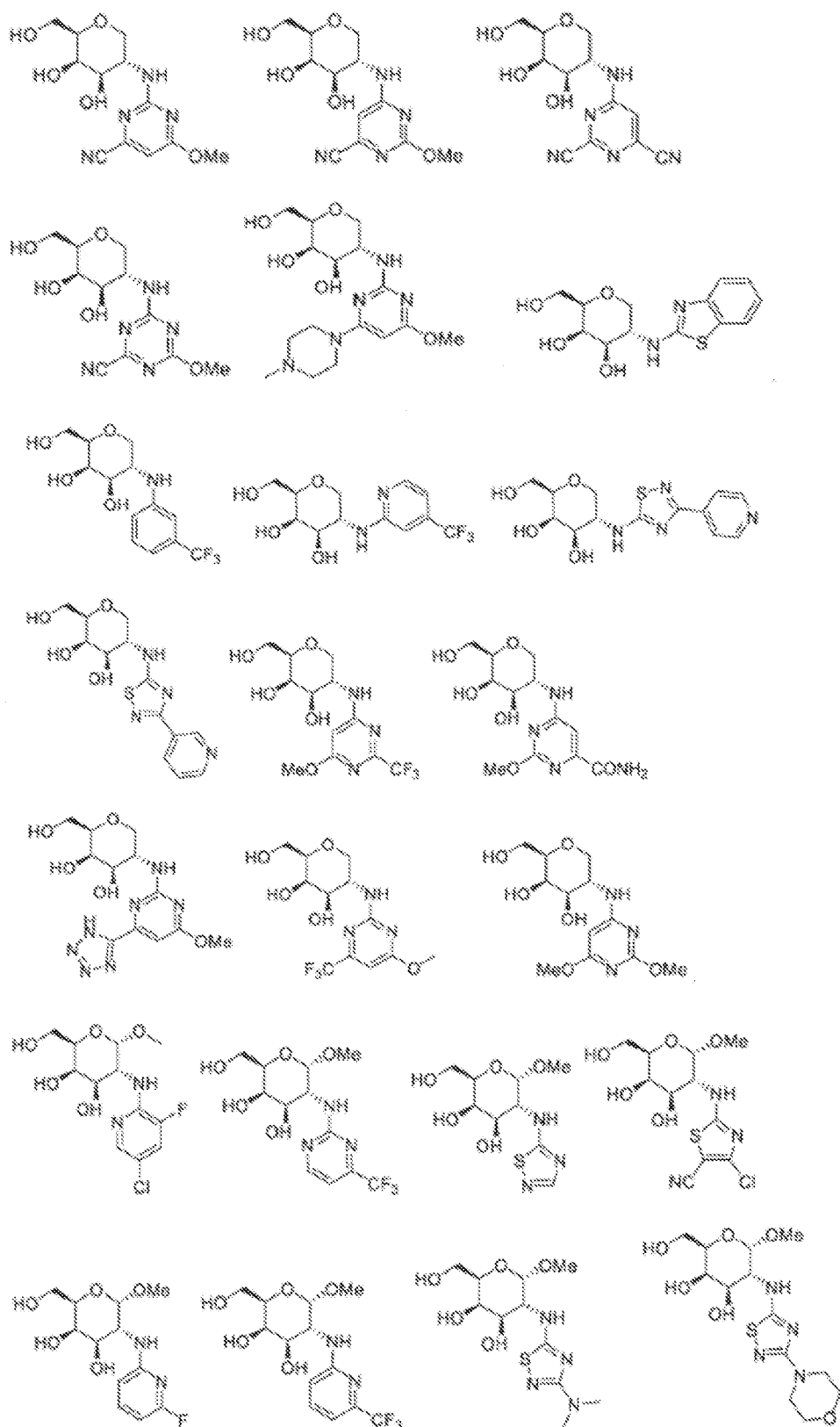


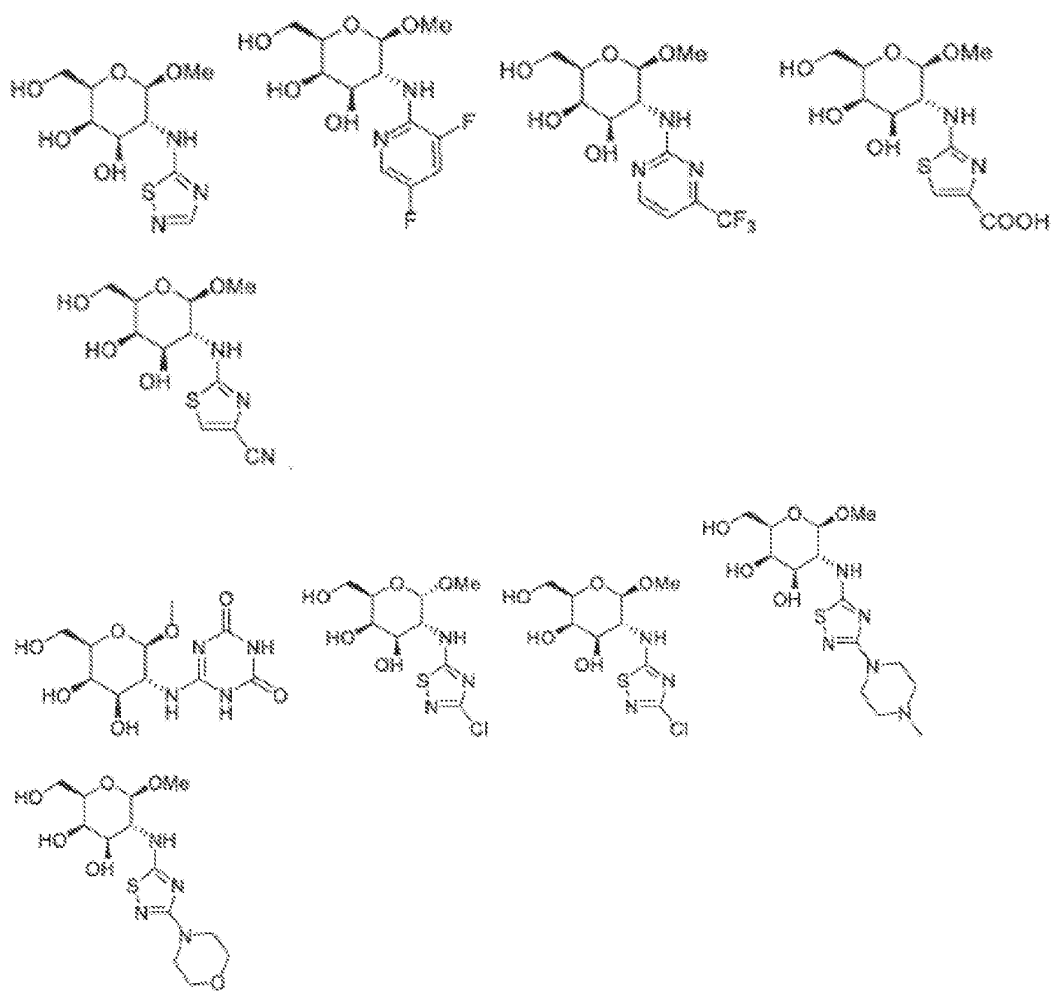






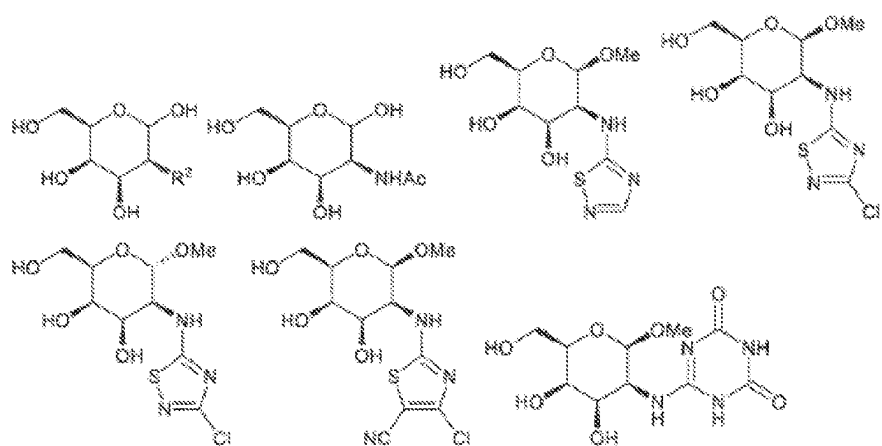


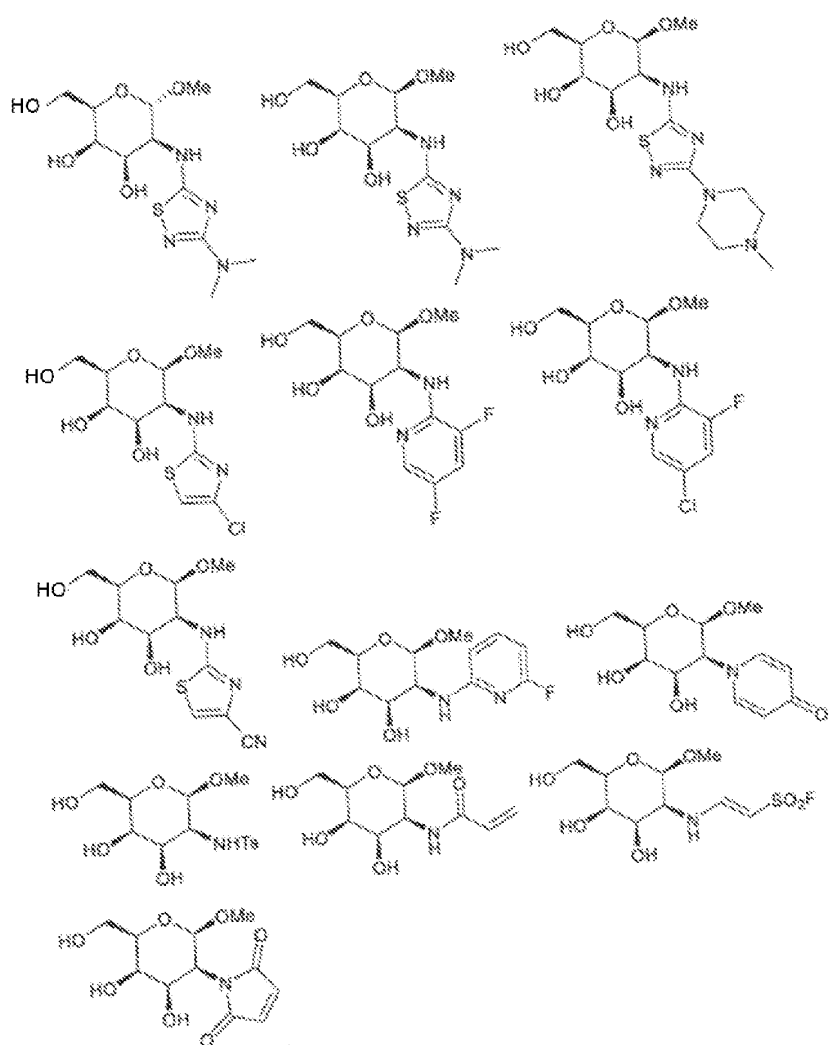


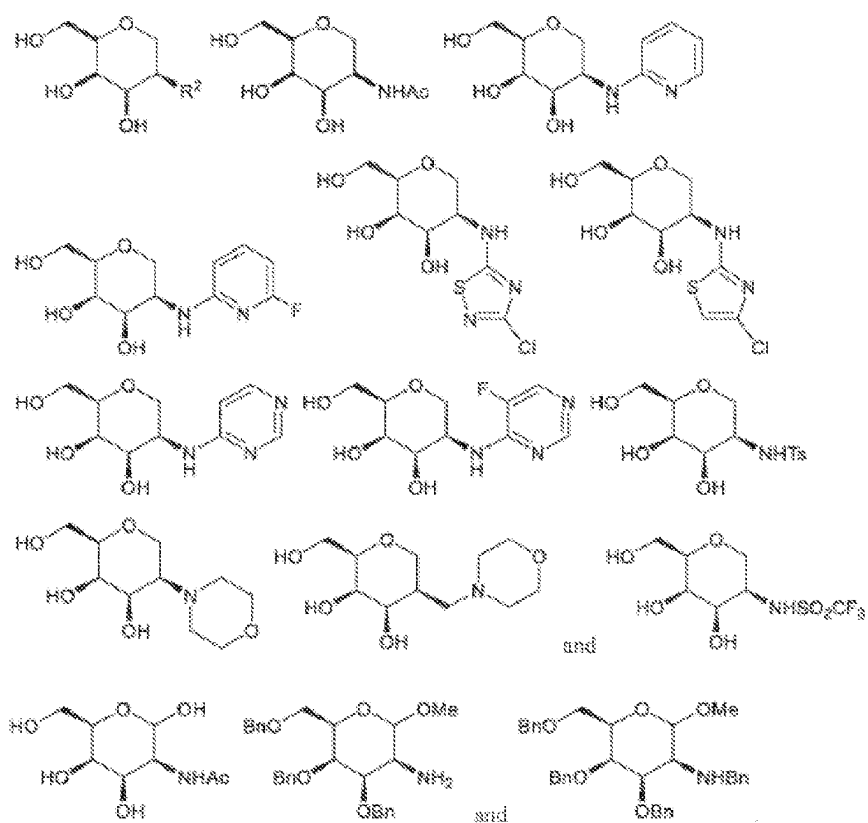


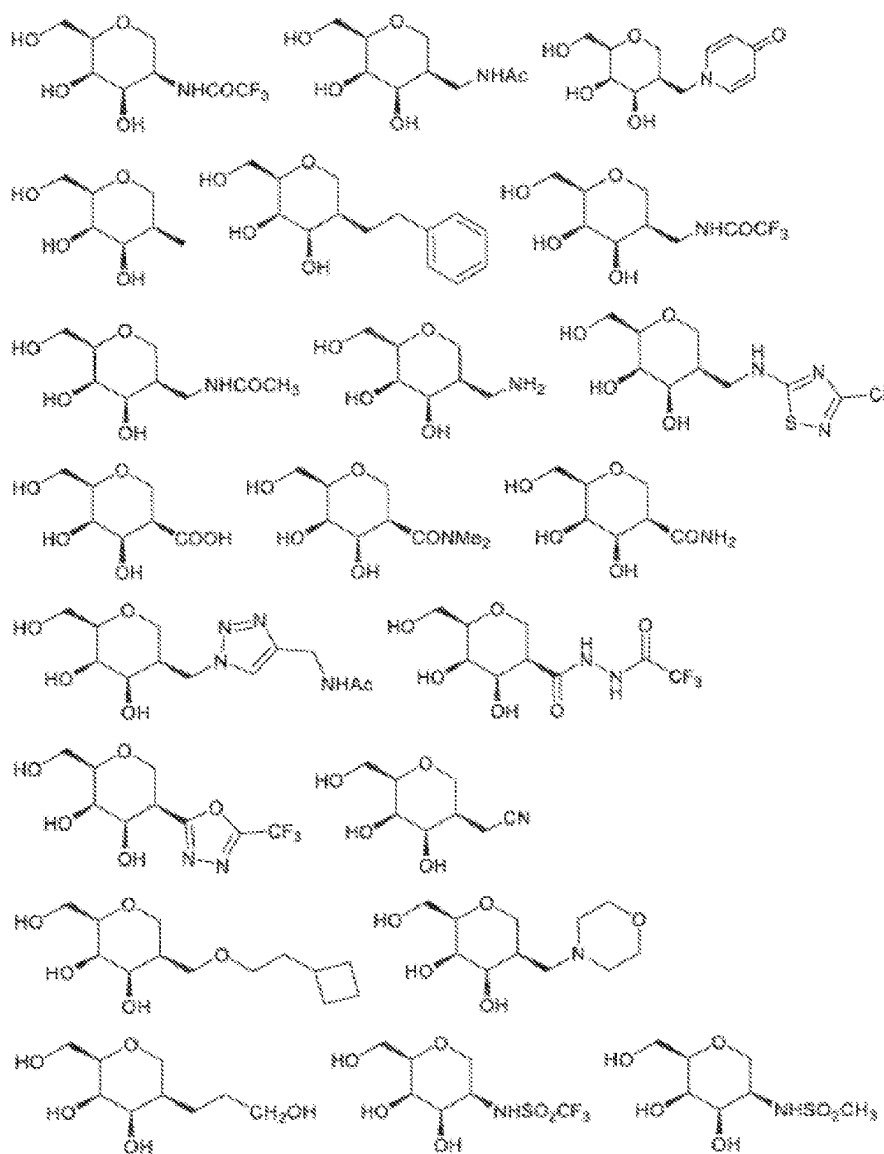
wherein these compounds are preferably bonded to the remainder of the compounds of the present invention by the C¹, C⁵ or C⁶ carbon atom or an oxygen atom of a hydroxyl group attached thereto, by substituting the hydrogen atom of the hydroxyl group for a bond to the remainder of the compounds of the present invention, as described above. More preferably these compounds are bonded by the C5 or C6 atom or a hydroxyl group attached thereto, as described above.

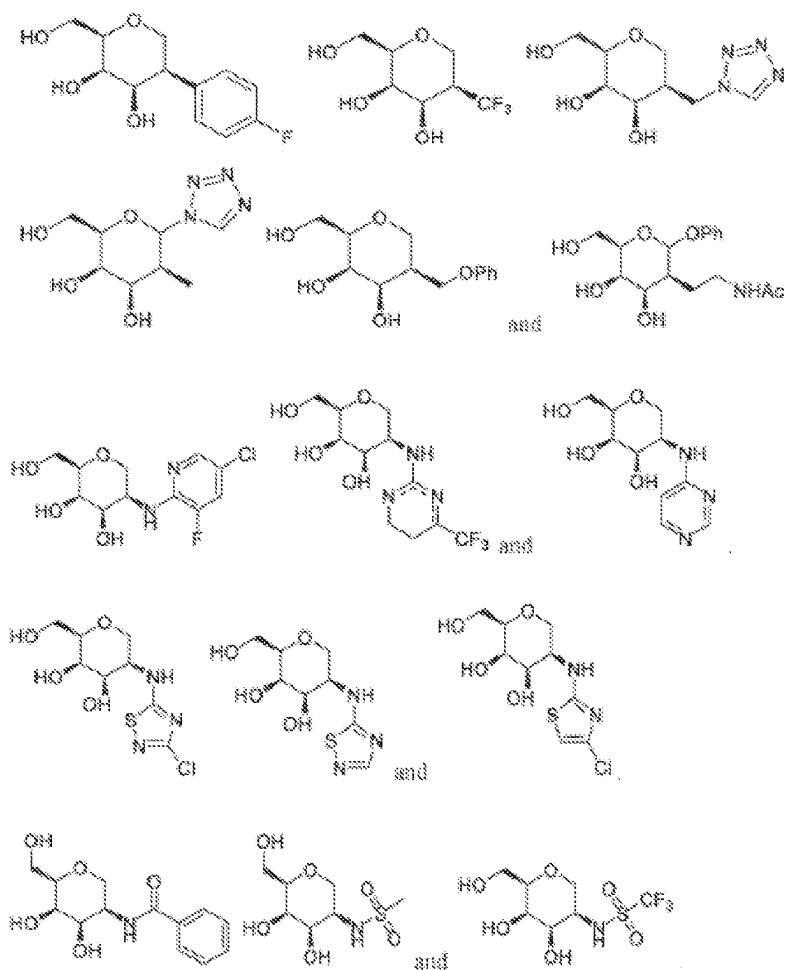
Further sugar derivatives that are useful as group AG in the present invention that are derivatives of talose may be selected from the group consisting of:

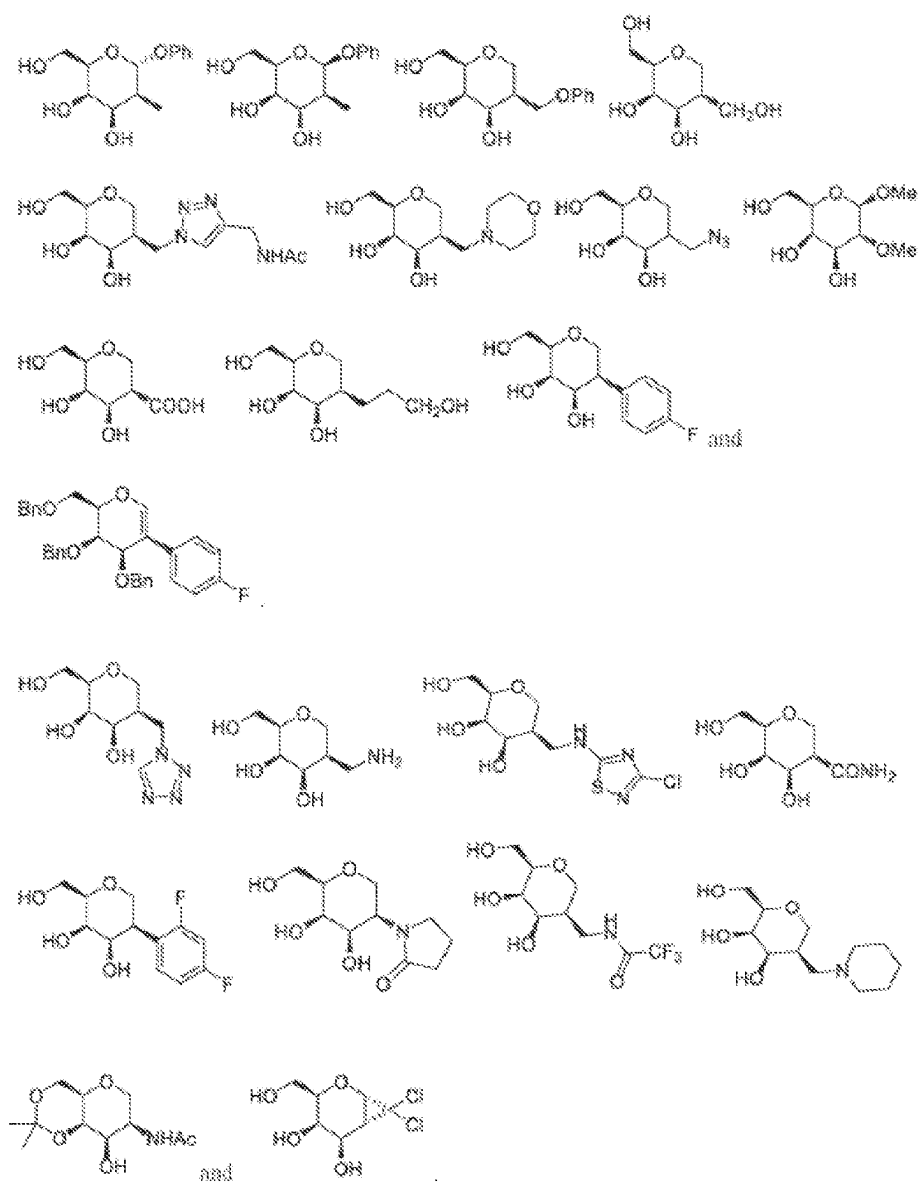


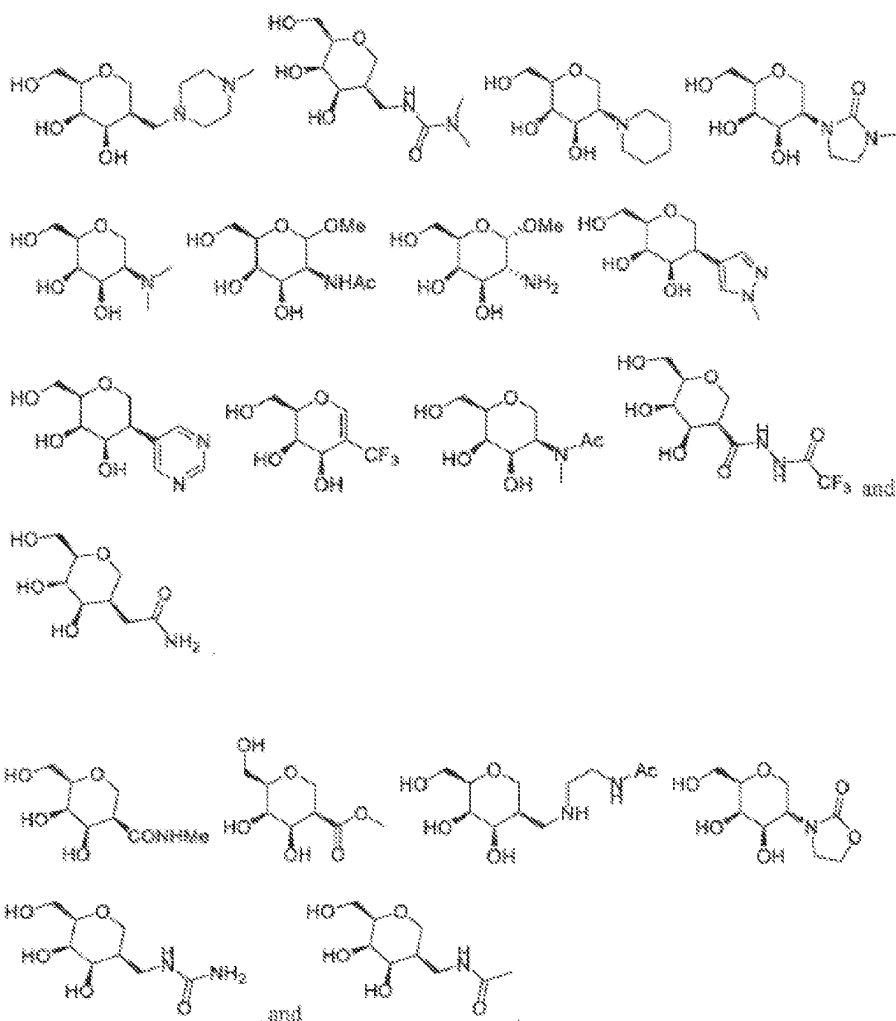












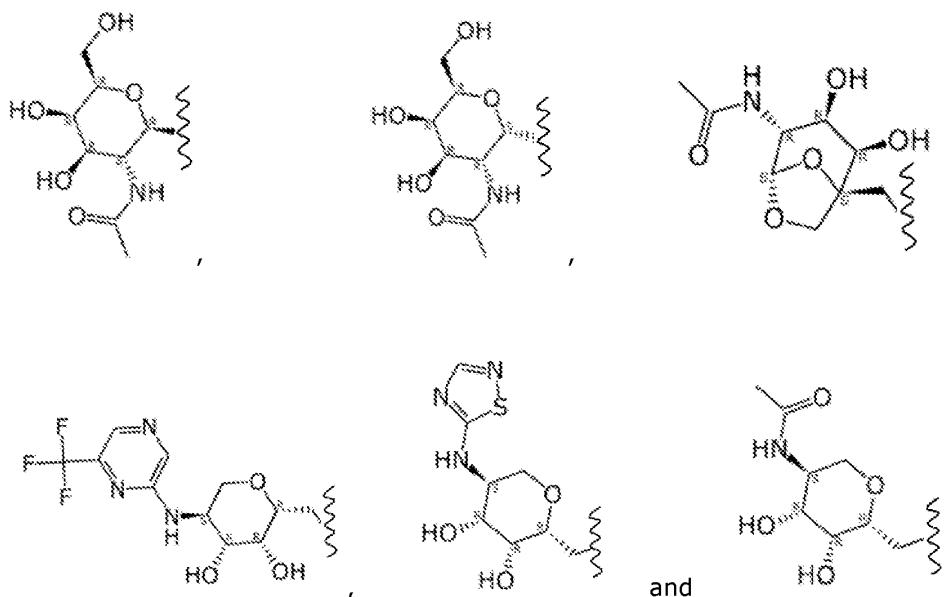
wherein these compounds are preferably bonded to the remainder of the compounds of the present invention by the C¹, C⁵ or C⁶ carbon atom or an oxygen atom of a hydroxyl group attached thereto, by substituting the hydrogen atom of the hydroxyl group for a bond to the remainder of the compounds of the present invention, as described above. More preferably these compounds are bonded by the C5 or C6 atom or a hydroxyl group attached thereto, as described above.

These compounds can be attached to the remainder of the compounds of the present invention through any suitable reactive group contained therein. Without limitation, they can be attached to a linker or Con as described herein through or by reaction with at least one OH, NH, vinyl, alkynyl, amide, acid, ester, ketone, or aromatic halogen contained therein. Suitable reaction modes for attaching these compounds to a linker or Con as described herein include, but are not limited to, substitution (e.g. alkylation of OH or NH groups), esterification (forming an ester), amidation (forming an

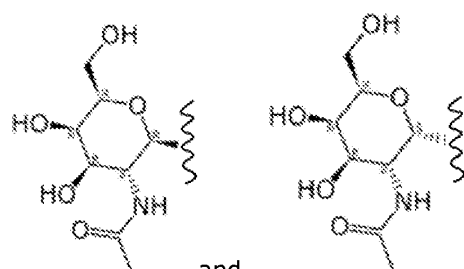
amide), transesterification (exchanging one ester for another), transamidation (exchanging one amide for another), azide-alkyne cycloaddition, and other reactions capable of forming C-C, N-C, or O-C bonds with vinyl and alkynyl groups such as cycloadditions, aminations, oxidations, alkylations, rearrangement reactions (e.g. Claisen, Cope, etc.), and the like.

In a more preferred embodiment R^1 is H and R^2 is -NH-R, wherein R is selected from the group consisting of acetyl which may be substituted with a group selected from the group consisting of up to three fluorine atoms; and a 5 or 6-membered single cycle aromatic heterocycle with up to three heteroatoms in the ring, that may be unsubstituted or substituted with at least one group selected from halogen and C1-C3 alkyl, which may be substituted with one or more halogen atoms, preferably fluorine. In an even more preferred embodiment R^1 is H and R^2 is selected from the group consisting of acetyl, 1,2,4-thiadiazole which is substituted by a $-CF_3$ group and 1,4-diazine. Herein, preferably the 1,2,4-thiadiazole group is connected to the -NH- of R^2 in 5-position of the 1,2,4-thiadiazole group. Preferably the 1,4-diazine group is connected to the -NH- of R^2 in 2-position of the 1,4-diazine and the $-CF_3$ group is located in 6-position of the 1,4-diazine.

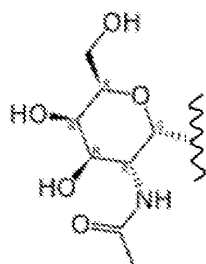
In an even more preferred embodiment AG is selected from the group consisting of



wherein the wavy lines mark the bond by which the sugar moiety is bonded to the remainder of the compounds of the present invention. Among these



and , are preferred and



is most preferred.

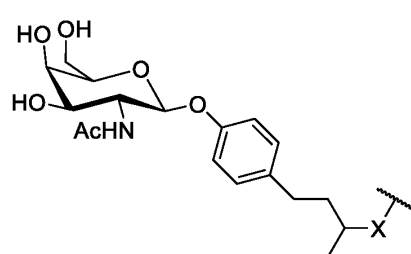
Other-Based groups AG

In some embodiments, the asialoglycoprotein binding moieties can be any of the moieties described in: Reshitko, G. S., et al., "Synthesis and Evaluation of New Trivalent Ligands for Hepatocyte Targeting via the Asialoglycoprotein Receptor," *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00202; Majouga, A. G., et al., "Identification of Novel Small-Molecule ASGP-R Ligands," *Current Drug Delivery*, **2016**, 13, 1303-1312, doi: 10.2174/1567201813666160719144651; Olshanova, A. S., et al., "Synthesis of a new betulinic acid glycoconjugate with N-acetyl-D-galactosamine for the targeted delivery to hepatocellular carcinoma cells," *Russian Chemical Bulletin, International Edition*, Vol. 69, No. 1, pp. 158—163, January 2020; Yamansarov, E. Yu., et al., "New ASGPR-targeted ligands based on glycoconjugated natural triterpenoids," *Russian Chemical Bulletin, International Edition*, Vol. 68, No. 12, pp. 2331—2338, December 2019; Congdon, M. D., et al., "Enhanced Binding and Reduced Immunogenicity of Glycoconjugates Prepared via Solid-State Photoactivation of Aliphatic Diazirine Carbohydrates," *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00555; and Dhawan, V., et al., "Polysaccharide conjugates surpass monosaccharide ligands in hepatospecific targeting – Synthesis and comparative in silico and in vitro assessment," *Carbohydrate Research* 509 (2021) 108417, doi: 10.1016/j.carres.2021.108417. The following ASGPR binding moieties are illustrative and not intended to be limiting.

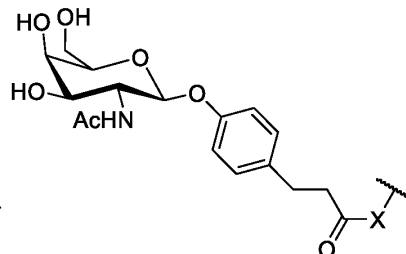
1. GalNAc-Tyrosine Based Moieties

In some embodiments, the AG can be a moiety having the structure of M1, M2, M3, or

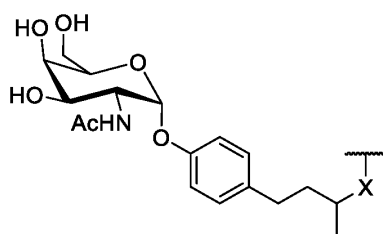
M4, or a combination thereof. In the structures of M1, M2, M3, and M4, X is independently at each occurrence O, NH, or S. In various embodiments, compounds of Formula I or Formula II can have one, two, or three groups AG with the structure of M1, M2, M3, or M4.



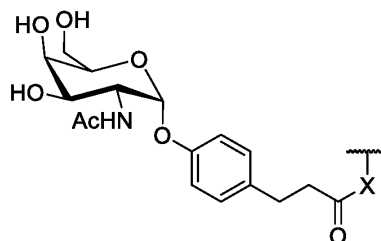
M1



M2



M3

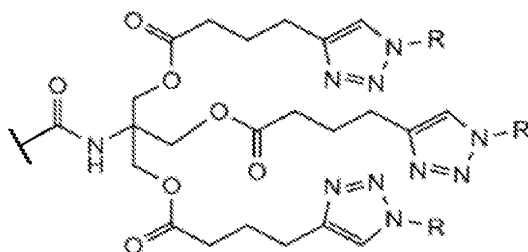


M4.

In various embodiments, AG of formulae M1 to M4 can be conjugated to any suitable Linker L¹, L², Linker^A, Linker^B, Linker^C or Linker^D as described herein and in Congdon, M. D., et al., "Enhanced Binding and Reduced Immunogenicity of Glycoconjugates Prepared via Solid-State Photoactivation of Aliphatic Diazirine Carbohydrates," *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00555.

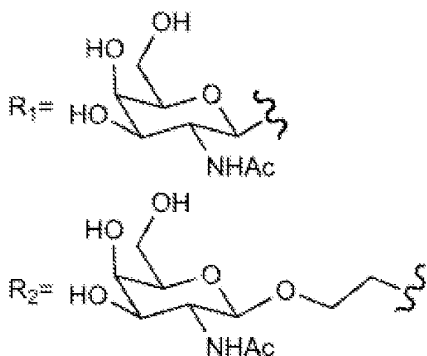
2. Trivalent Triazole-Based Moieties

In some embodiments, comprise a moiety having the structure of M5:



, M5.

In the structures M5, each R is independently at each occurrence R₁ or R₂,

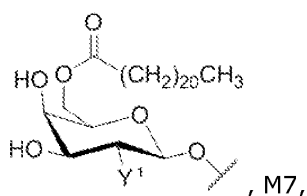


In the compounds of the present invention M5 the partial structure – C(=O)-NH- of M5 preferably is part of a linker L^1 , L^2 , Linker^A or Linker^B as described herein with which M5 is bound to the group A-T- of the present invention. In various embodiments, compounds of the present invention can contain a group with the structure of M5. In various embodiments, each R in M5 is R_1 . In various embodiments, each R in M5 is R_2 .

In various embodiments, M5 can be conjugated/bonded to any suitable linker as described herein and in Reshitko, G. S., et al., "Synthesis and Evaluation of New Trivalent Ligands for Hepatocyte Targeting via the Asialoglycoprotein Receptor," *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00202.

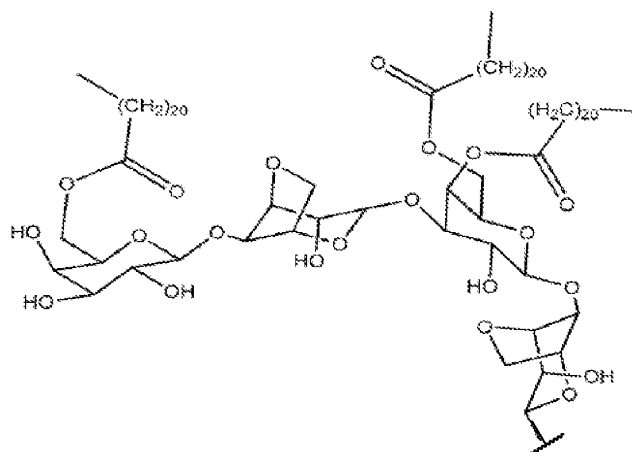
3. Galactose- and Agarose-derived Behenic Acid Ester Moieties

In various embodiments, the AG can be the galactose behenic acid ester-derived moiety M7:



wherein Y^1 is OH or NHAc.

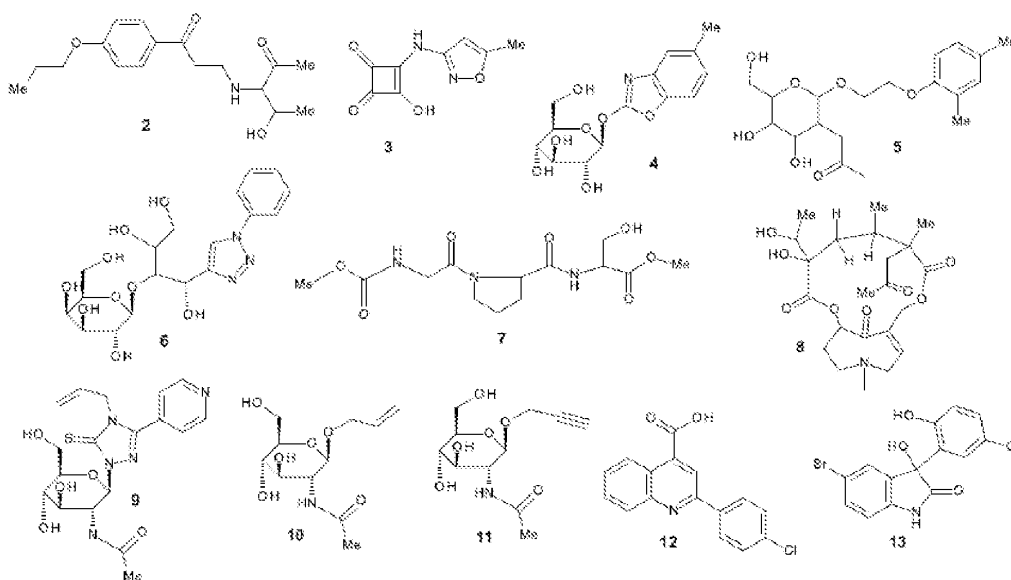
In various embodiments, the AG can be the agarose behenic acid ester-derived moiety M8:

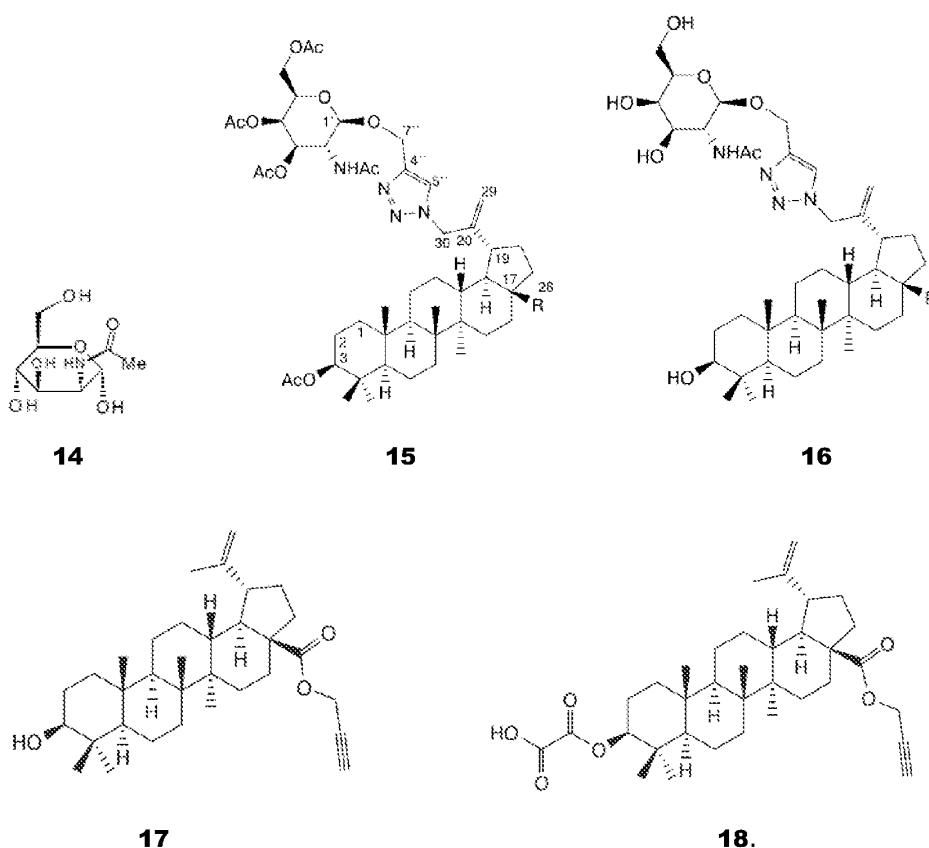


In various embodiments, M7 and M8 can be conjugated to any suitable linker or Con as described herein and in Dhawan, V., et al., "Polysaccharide conjugates surpass monosaccharide ligands in hepatospecific targeting – Synthesis and comparative *in silico* and *in vitro* assessment," Carbohydrate Research 509 (2021) 108417, doi: 10.1016/j.carres.2021.108417.

4. Other Small Molecule Asialoglycoprotein Binding Moieties

A large variety of groups that bind to the asialoglycoprotein are known. Some of them are useful in the present invention. In various embodiments, the AG can be any of the compounds **2-18** below:





In various embodiments, in compounds **15** and **16**, R is CH₂OAc, COOH, or CH₂OH. Compounds **2-18** can be conjugated/bonded to any suitable linker or Con as described herein and in Majouga, A. G., et al., "Identification of Novel Small-Molecule ASGP-R Ligands," *Current Drug Delivery*, **2016**, *13*, 1303-1312, doi: 10.2174/1567201813666160719144651; Olshanova, A. S., et al., "Synthesis of a new betulinic acid glycoconjugate with N-acetyl-D-galactosamine for the targeted delivery to hepatocellular carcinoma cells," *Russian Chemical Bulletin, International Edition*, Vol. 69, No. 1, pp. 158—163, January 2020; Yamansarov, E. Yu., et al., "New ASGPR-targeted ligands based on glycoconjugated natural triterpenoids," *Russian Chemical Bulletin, International Edition*, Vol. 68, No. 12, pp. 2331—2338, December 2019.

Compounds **2-18** can be attached through any suitable reactive group contained therein. Without limitation, compounds 2-13 can be attached to a linker or Con as described herein through or by reaction with at least one OH, NH, vinyl, alkynyl, amide, acid, ester, ketone, or aromatic halogen contained in compounds **2-18**. Suitable reaction modes for attaching compounds **2-18** to a linker or Con as described herein include, but are not limited to, substitution (e.g. alkylation of OH or NH groups), esterification

(forming an ester), amidation (forming an amide), transesterification (exchanging one ester for another), transamidation (exchanging one amide for another), azide-alkyne cycloaddition, and other reactions capable of forming C-C, N-C, or O-C bonds with vinyl and alkynyl groups such as cycloadditions, aminations, oxidations, alkylations, rearrangement reactions (e.g. Claisen, Cope, etc.), and the like.

In preferred embodiments AG does not comprise 6-ring aromatic rings. In preferred embodiments the compounds of the present invention do not comprise 6-ring aromatic rings.

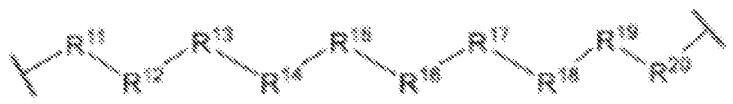
Linkers L¹ and L²

The principal function of Linkers L¹ and L² and Con is to connect the two functional parts A and AG of the inventive compounds with each other. In principle any group that bonds A and AG covalently with each other and which is generally stable under physiological conditions is suitable for L¹, L² and Con. Therefore, a wide variety of structures is possible for L¹ and L². Suitable linkers that may be used in the present invention as for example L¹, L², L³, Linker^A, Linker^B, Linker^C and/or Linker^D are disclosed in WO 2023/028590 A1, WO 2023/028597 A1, WO 2021/155317 A1, WO 2022/235699 A1, WO 2019/199621 A1, M.G. Finn and V. Mascitti et al. in the *Journal of the American Chemical Society*, 134, 1978 (2012) and EP 3 145 934 B1.

In a preferred embodiment of the present invention, L¹ has the structure $-(XG)_n-$, wherein n is an integer from 1 to 105 and L² has the structure $-(XG)_p-$, wherein p is an integer from 1 to 50; wherein each occurrence of XG is independently selected from the group consisting of $-CH_2-$, $-CH(CH_2-OCH_3)-$, $-CH(CH_2-OCH_2CH_3)-$, $-C(=O)-$, $-NH-$, $-O-$, $-S(=O)_2-$ and $-P(=O)_2-$ with the proviso that in linker L¹ and L² no two oxygen atoms are adjacent to each other and L² may also be a direct bond between Con and AG. Preferably no two heteroatoms selected from the group consisting of N and O are adjacent to each other. In some embodiments of the present invention, the linker L¹ and L² do not comprise carboxyl ester groups. In an more preferred embodiment the compound of the present invention, L¹ and L² are copolymers with a chain length of 3 to 50 atoms, comprising one or more of $-(CH_2)_r-$, wherein r is an integer in the range of 1 to 5, and one of the hydrogen atoms in each $-CH_2-$ residue may be substituted by a residue selected from the group consisting of a halogen atom or a residue $-CH_2-O-CH_3$ or $-CH_2-O-CH_2-CH_3$, and wherein a plurality of $-(CH_2)_r-$ moieties may be bonded to each other by a residue selected from the group consisting of $-O-$, $-CONH-$, $-NHCONH-$, $-SO_2-NH-$ and $-PO_2-NH-$. r is preferably an integer in the range of 1 to 4 and more preferably 1 to 3. Even more preferred are embodiments wherein L¹ and L² are copolymers comprising repeating units selected from the group consisting of $-CH_2-$, $-NH-$, $-CH_2-O-$, $-(CH_2CH_2-$

O)-, -(CH₂-NH)-, -(CH₂CH₂-NH)-, -CH₂C(=O)-, -CH₂CH₂C(=O)-, -CH₂CH₂CH₂C(=O)- and -C(=O)CH₂CH₂C(=O)-. L¹ and L² preferably consist of the repeating units.

In preferred non-limiting embodiments L¹, L² Linker^A and/or Linker^B are independently selected from:



wherein:

R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are independently at each occurrence selected from the group consisting of a bond, alkylene, -C(O)-, -C(O)O-, -OC(O)-, -SO₂-, -S(O)-, -C(S)-, -C(O)NR⁶-, -NR⁶C(O)-, -O-, -S-, -NR⁶-, -C(R²¹R²¹)-, -P(O)(R³)O-, -P(O)(R³)-, a divalent residue of a natural or unnatural amino acid, alkenylene, alkynylene, haloalkylene, alkoxyalkylene, heterocycle, heteroaryl, -[(CR³⁰⁰)_{aa}-O]_{aa}-, -CH₂CH₂-[O-(CH₂)₂]_{aa}-O-, -CH₂CH₂-[O-(CH₂)₂]_{aa}-NR⁶-, -CH₂CH₂-[O-(CH₂)₂]_{aa}-, -[-(CH₂)₂-O-]_{aa}-, -[O-(CH₂)₂]_{aa}-, -[CH₂CH(CH₂-OCH₃)]_{aa}-, -[CH₂CH(CH₂-OCH₂CH₃)]_{aa}-, -[O-CH(CH₃)C(O)]_{aa}-, -[C(O)-CH(CH₃)-O]_{aa}-, -[O-CH₂C(O)]_{aa}-, -[C(O)-CH₂-O]_{aa}-, 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 R²¹;

R³⁰⁰ are independently of each other selected from the groups consisting of H and C1-C3 alkyl;

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

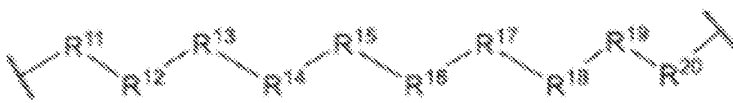
and the remaining variables are as defined herein.

In the formulae of the present invention,



marks an open valence for bonding to the remainder of the compounds of the present invention.

In one embodiment L¹ is a direct bond and L² is



In one embodiment L^2 is a direct bond and L^1 is



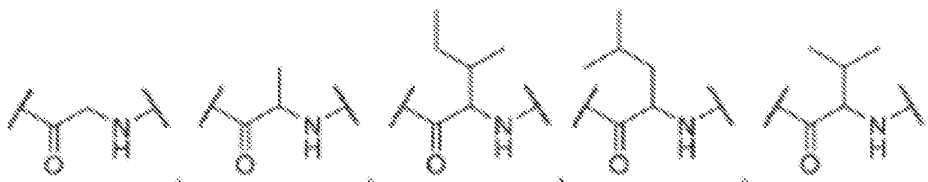
In preferred embodiments R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are independently at each occurrence selected from the group consisting of a bond, alkylene, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-SO_2-$, $-S(O)-$, $-C(S)-$, $-C(O)NR^6-$, $-NR^6C(O)-$, $-O-$, $-S-$, $-NR^6-$, $-P(O)(R^3)O-$, $-P(O)(R^3)-$, a divalent residue of a natural or unnatural amino acid, alkenylene, alkynylene, haloalkylene, alkoxyalkylene, heterocycle, heteroaryl, $-[(CR^{300})_{aa}O]_{aa}-$, $-CH_2CH_2-[O-(CH_2)_2]_{aa}O-$, $-CH_2CH_2-[O-(CH_2)_2]_{aa}NR^6-$, $-CH_2CH_2-[O-(CH_2)_2]_{aa}-$, $-[-(CH_2)_2-O]_{aa}-$, $-[O-(CH_2)_2]_{aa}-$, $-[CH_2CH(CH_2OCH_3)]_{aa}-$, $-[CH_2CH(CH_2OCH_2CH_3)]_{aa}-$, $-[O-CH(CH_3)C(O)]_{aa}-$, $-[C(O)-CH(CH_3)-O]_{aa}-$, $-[O-CH_2C(O)]_{aa}-$, $-[C(O)-CH_2-O]_{aa}-$, a divalent residue of a fatty acid, a divalent residue of an unsaturated or saturated mono- or di-carboxylic acid;

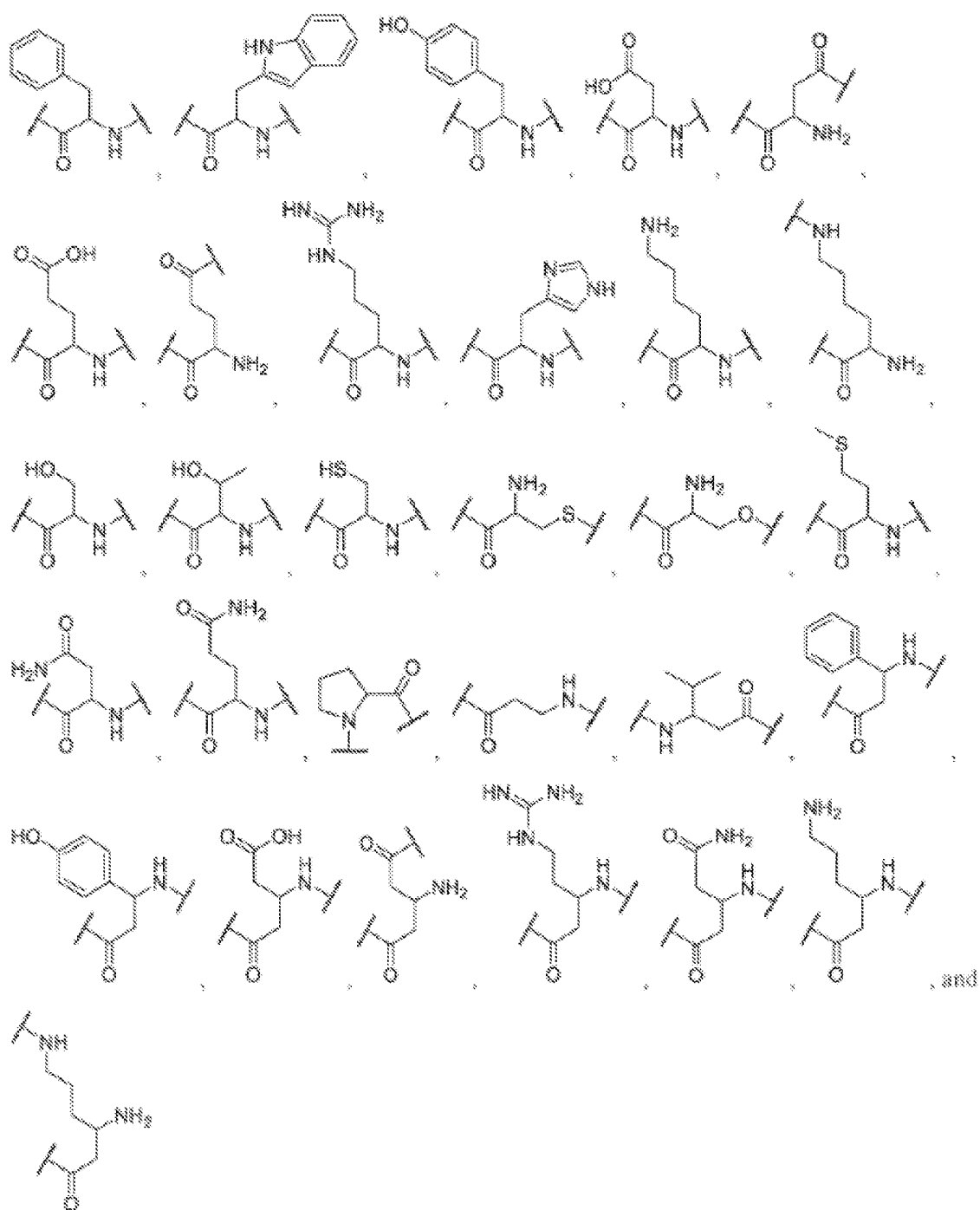
R^{300} and aa are as defined above and the remaining variables are as defined herein.

In more preferred embodiments 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, alkylene, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-C(O)NR^{300}-$, $-NR^{300}C(O)-$, $-O-$, $-S-$, $-NR^{300}-$, $-P(O)(R^{300})O-$, $-P(O)(R^{300})-$, a divalent residue of a natural or unnatural amino acid, alkenylene, alkynylene, haloalkylene, alkoxyalkylene, $-[(CR^{300})_{aa}O]_{aa}-$, $-CH_2CH_2-[O-(CH_2)_2]_{aa}O-$, $-CH_2CH_2-[O-(CH_2)_2]_{aa}NR^6-$, $-CH_2CH_2-[O-(CH_2)_2]_{aa}-$, $-[-(CH_2)_2-O]_{aa}-$, $-[O-(CH_2)_2]_{aa}-$, $-[CH_2CH(CH_2OCH_3)]_{aa}-$, $-[CH_2CH(CH_2OCH_2CH_3)]_{aa}-$, $-[O-CH(CH_3)C(O)]_{aa}-$, $-[C(O)-CH(CH_3)-O]_{aa}-$, $-[O-CH_2C(O)]_{aa}-$, $-[C(O)-CH_2-O]_{aa}-$, a divalent residue of a fatty acid, a divalent residue of an unsaturated or saturated mono- or di-carboxylic acid;

R^{300} and aa are as defined above and the remaining variables are as defined herein.

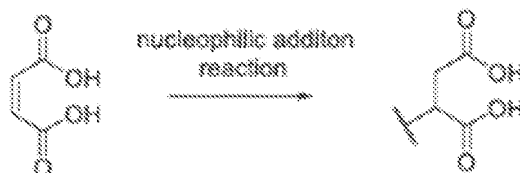
In one embodiment a divalent residue of an amino acid is selected from



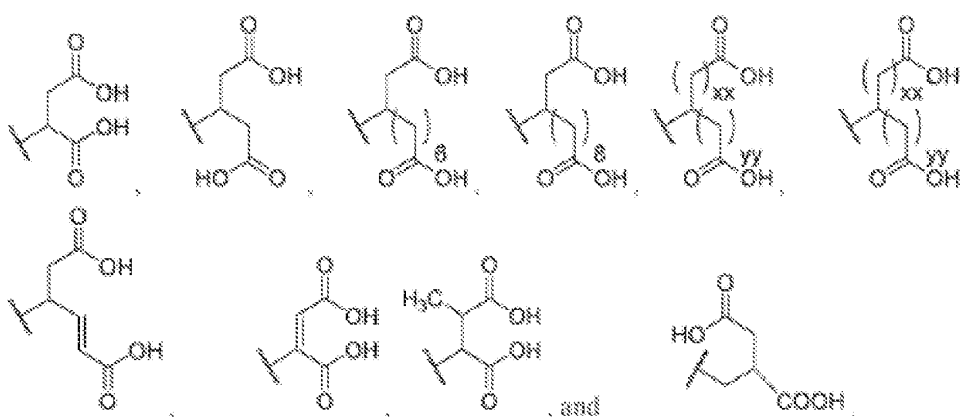


wherein the amino acid can be oriented in either direction and wherein the amino acid can be in the L- or D-form or a mixture thereof.

In one embodiment a divalent residue of a dicarboxylic acid is generated from a nucleophilic addition reaction:

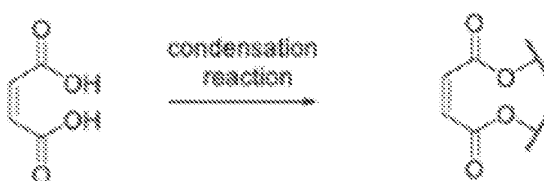


Non-limiting embodiments of a divalent residue of a dicarboxylic acid generated from a nucleophilic addition reaction include:

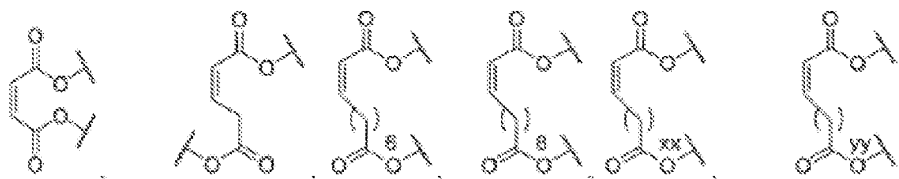


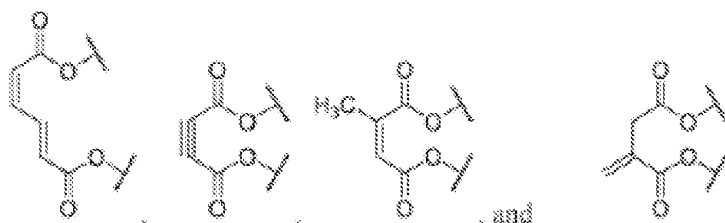
wherein yy is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25.

In one embodiment a divalent residue of a dicarboxylic acid is generated from a condensation reaction:



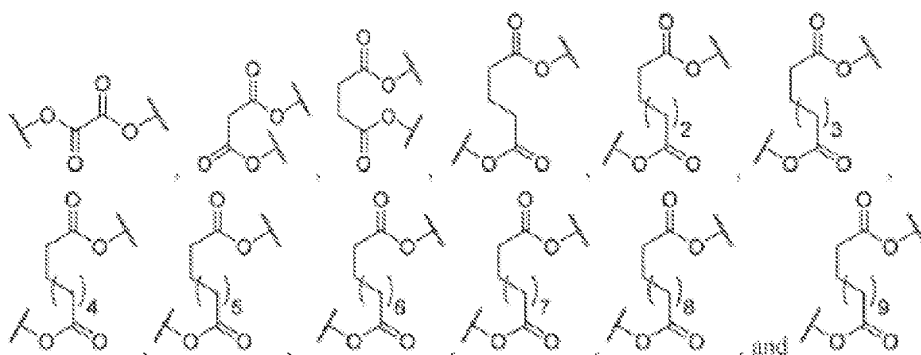
Non-limiting embodiments of a divalent residue of a dicarboxylic acid generated from a condensation include:





wherein xx and yy are independently of each other 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.

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



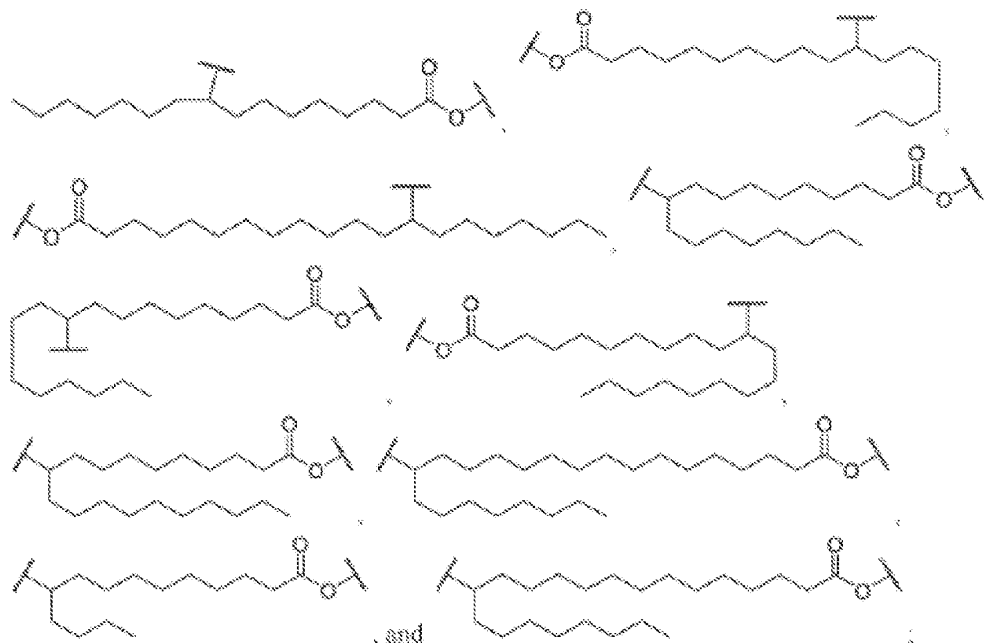
Non-limiting embodiments of a divalent residue of a saturated dicarboxylic acid include:



wherein xx is selected from 0, 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25.

Non-limiting embodiments of a divalent residue of a saturated monocarboxylic acid is selected from butyric acid ($-\text{OC}(\text{O})(\text{CH}_2)_2\text{CH}_2-$), caproic acid ($-\text{OC}(\text{O})(\text{CH}_2)_4\text{CH}_2-$), caprylic acid ($-\text{OC}(\text{O})(\text{CH}_2)_5\text{CH}_2-$), capric acid ($-\text{OC}(\text{O})(\text{CH}_2)_8\text{CH}_2-$), lauric acid ($-\text{OC}(\text{O})(\text{CH}_2)_{10}\text{CH}_2-$), myristic acid ($-\text{OC}(\text{O})(\text{CH}_2)_{12}\text{CH}_2-$), pentadecanoic acid ($-\text{OC}(\text{O})(\text{CH}_2)_{13}\text{CH}_2-$), palmitic acid ($-\text{OC}(\text{O})(\text{CH}_2)_{14}\text{CH}_2-$), stearic acid ($-\text{OC}(\text{O})(\text{CH}_2)_{16}\text{CH}_2-$), behenic acid ($-\text{OC}(\text{O})(\text{CH}_2)_{20}\text{CH}_2-$), and lignoceric acid ($-\text{OC}(\text{O})(\text{CH}_2)_{22}\text{CH}_2-$);

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 $(-C(O)(CH_2)_4(CHCHCH_2)_4CH_2-)$,

gamma-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 $(-C(O)(CH_2)_9CHCH(CH_2)_7CH_2-)$,

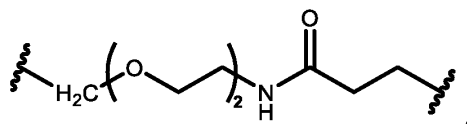
gadoleic acid $(-C(O)(CH_2)_7CHCH(CH_2)_9CH_2-)$,

nervonic acid $(-C(O)(CH_2)_{13}CHCH(CH_2)_3CH_2-)$,

mead acid $(-C(O)(CH_2)_3(CHCHCH_2)_3(CH_2)_6CH_2-)$,

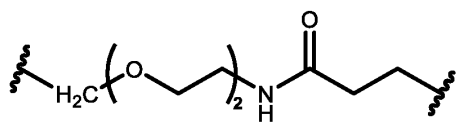
myristoleic acid ($-\text{C}(\text{O})(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_3\text{CH}_2-$), and
erucic acid ($-\text{C}(\text{O})(\text{CH}_2)_{11}\text{CHCH}(\text{CH}_2)_7\text{CH}_2-$).

In preferred embodiments L^1 , L^2 , Linker^{A} and/or Linker^{B} are independently selected from the group consisting of



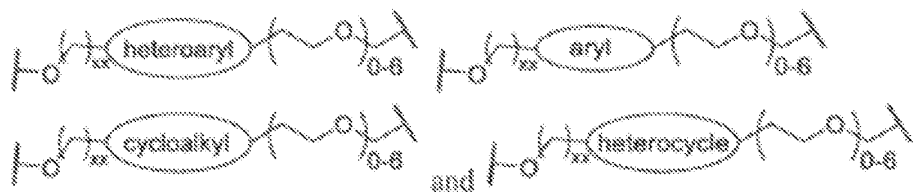
$-\text{O}-(\text{CH}_2)_3-$, $-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_3-\text{CH}_2-$, and $=\text{N}^*(\text{C}=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})\text{NHCH}_2\text{CH}_2-(\text{OCH}_2\text{CH}_2)_4-$,
wherein $=\text{N}^*$ is a ring nitrogen in a heterocyclic ring system.

In a more preferred embodiment L^2 are independently selected from the group consisting of:



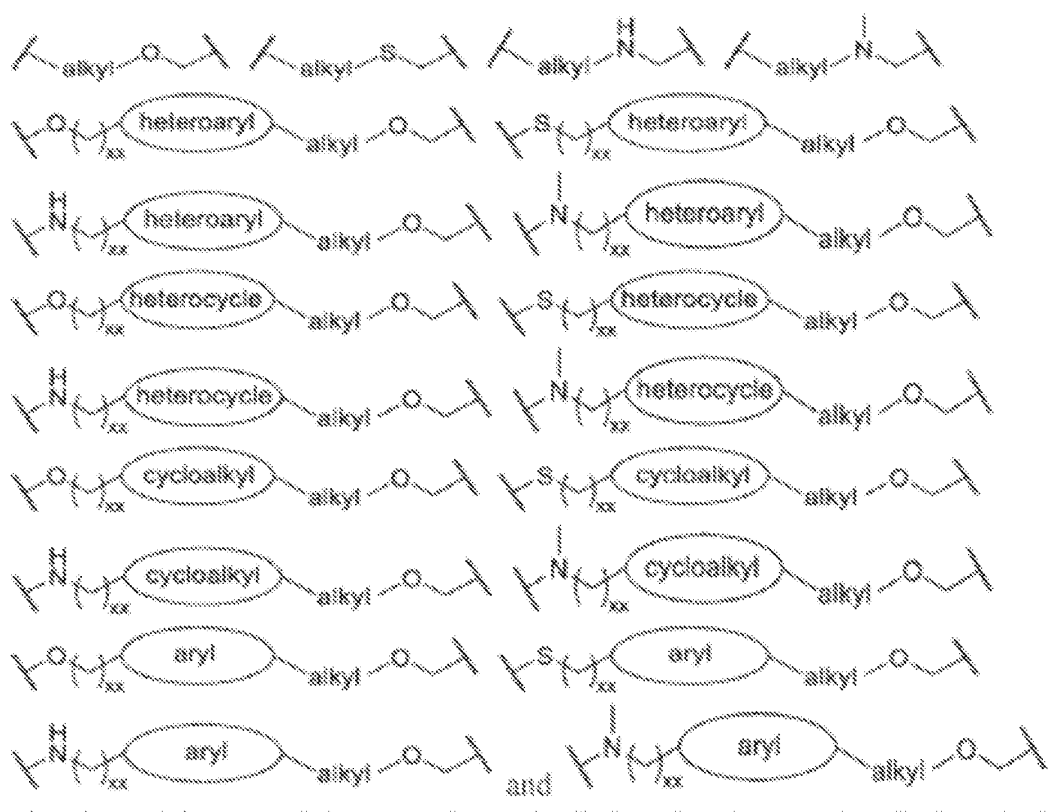
$-\text{O}-(\text{CH}_2)_3-$, $-\text{NH}-(\text{CH}_2\text{CH}_2\text{O})_3-\text{CH}_2-$, and $=\text{N}^*(\text{C}=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})\text{NHCH}_2\text{CH}_2-(\text{OCH}_2\text{CH}_2)_4-$,
wherein $=\text{N}^*$ is a ring nitrogen in a heterocyclic ring system. In this embodiment AG is preferably an aminosugar.

In certain embodiments L^1 , L^2 , Linker^{A} and/or Linker^{B} are independently of each other selected from:



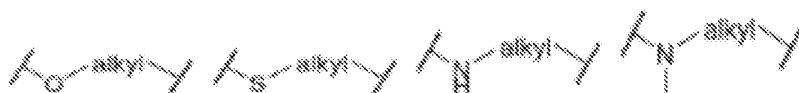
wherein each heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, and, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence.

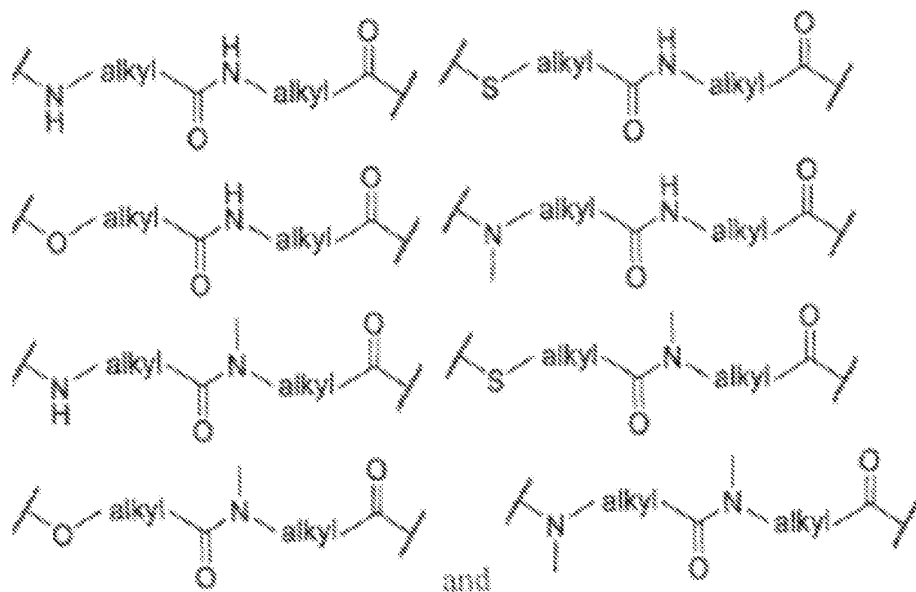
In certain embodiments L^1 , L^2 , Linker^{A} and/or Linker^{B} are independently of each other selected from:



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

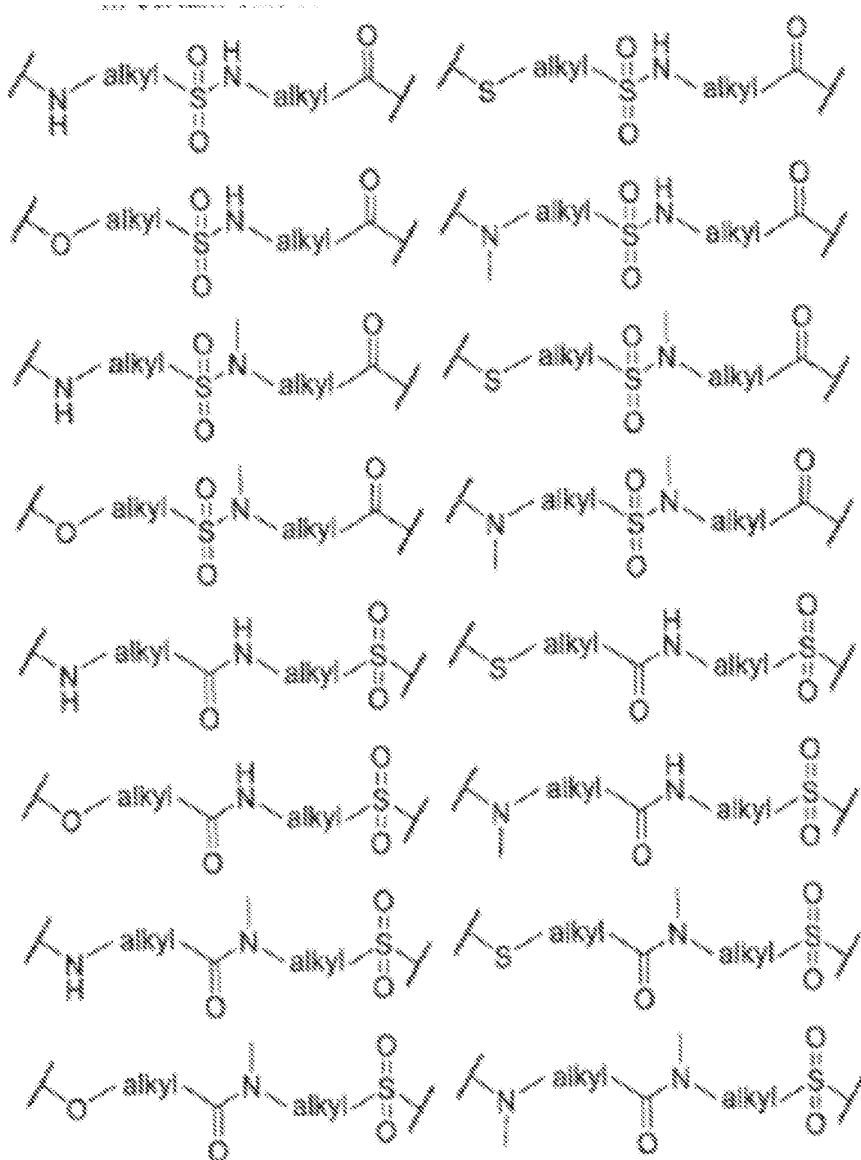
In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from:

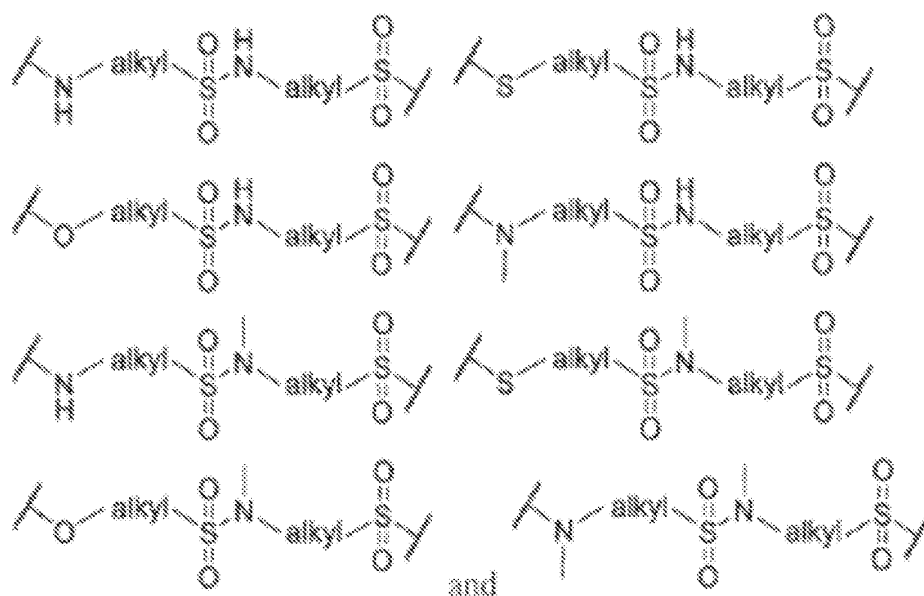




wherein each alkyl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence.

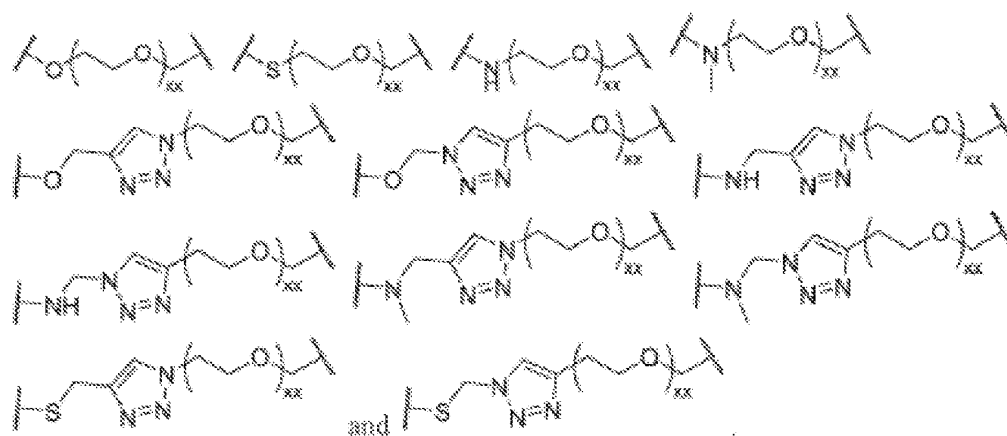
In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from:



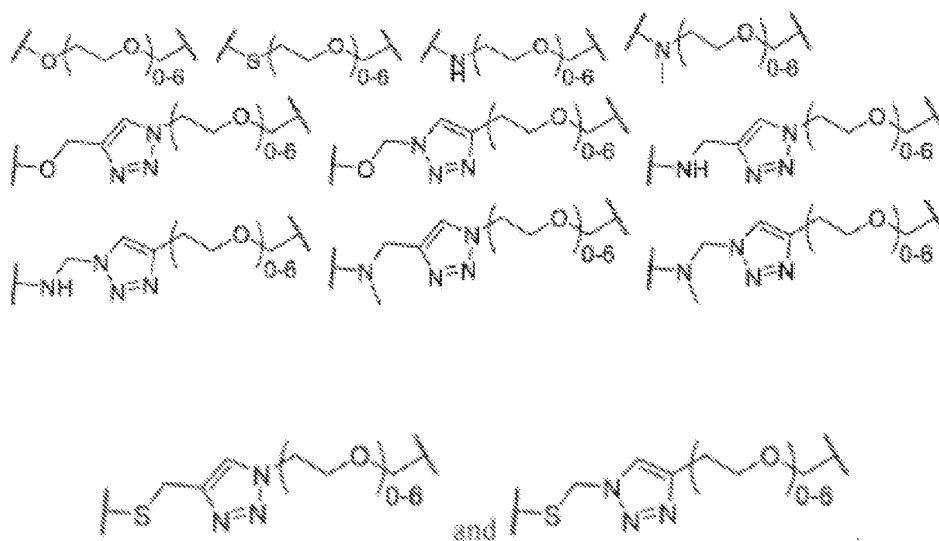


wherein each alkyl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence.

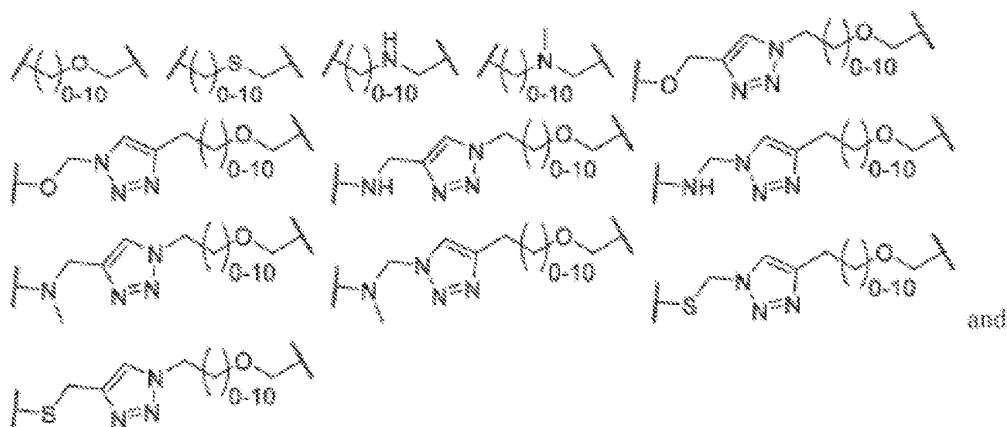
In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from:



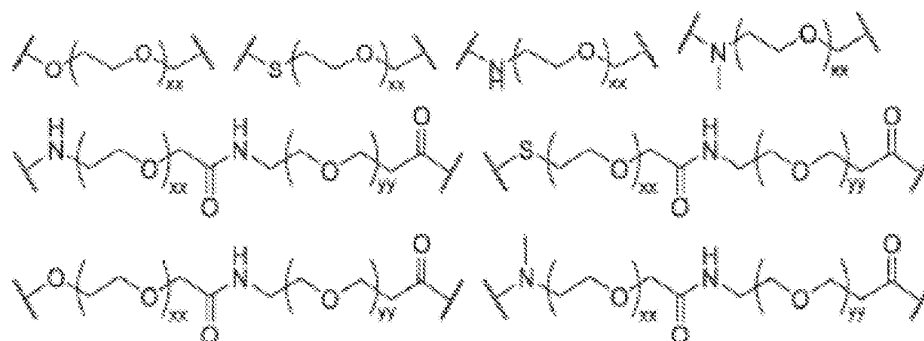
In certain embodiments of the present invention, L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from:

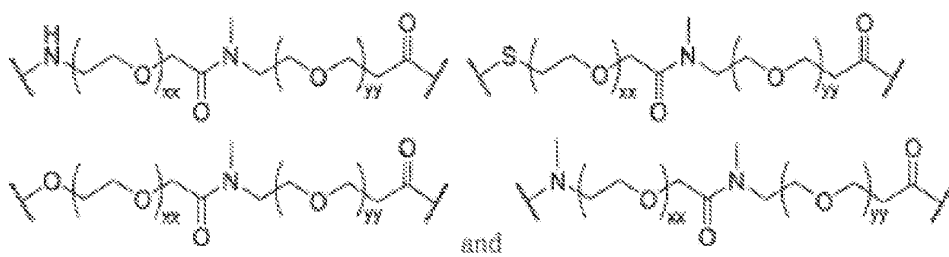


In certain embodiments of the present invention, L¹ and/or L² are independently of each other is selected from:

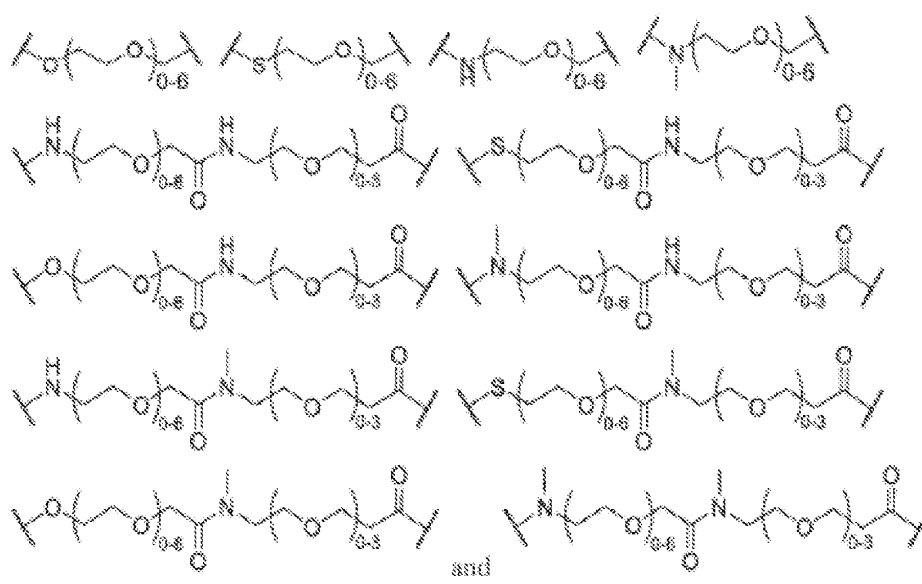


In certain embodiments of the present invention, L¹ and/or L² are independently of each other selected from:

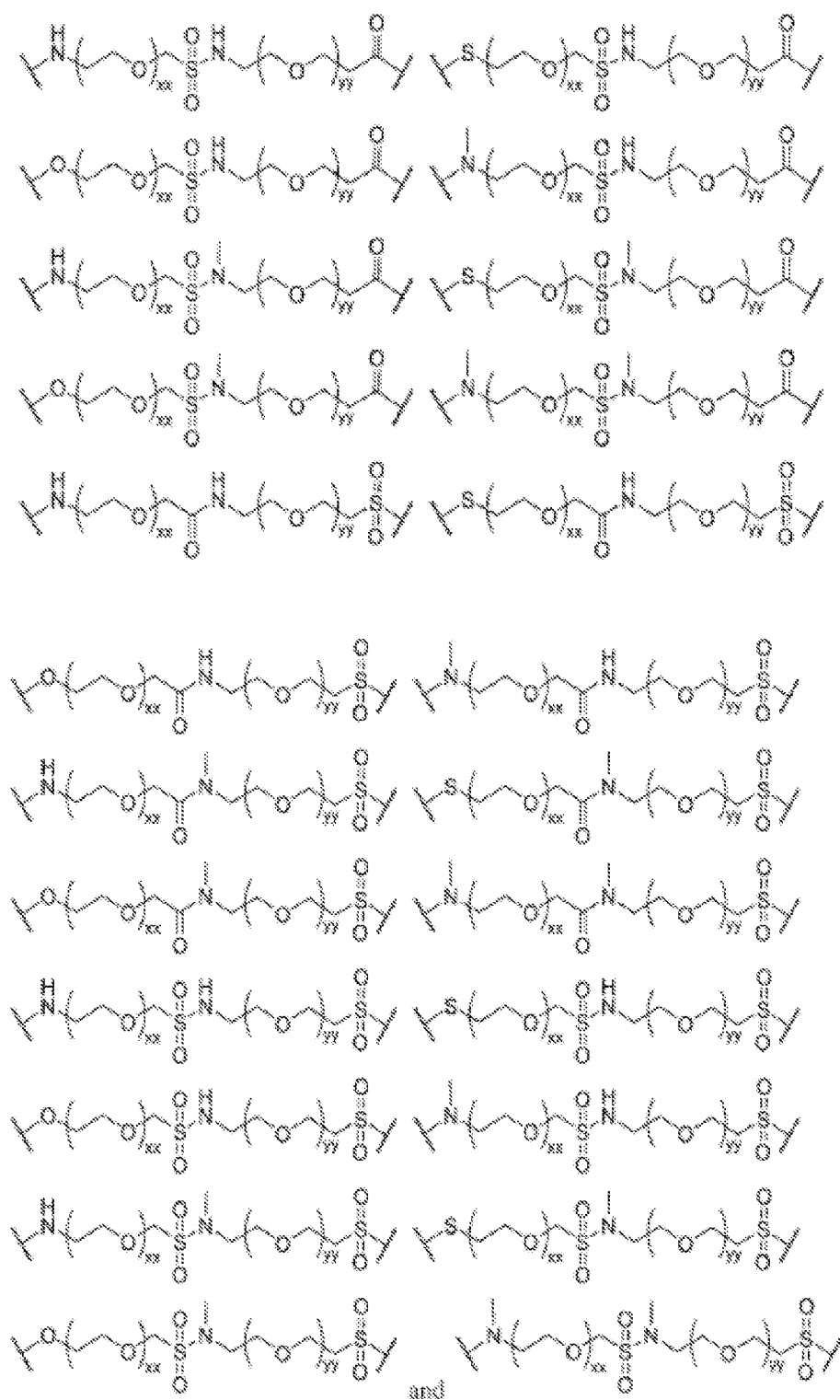




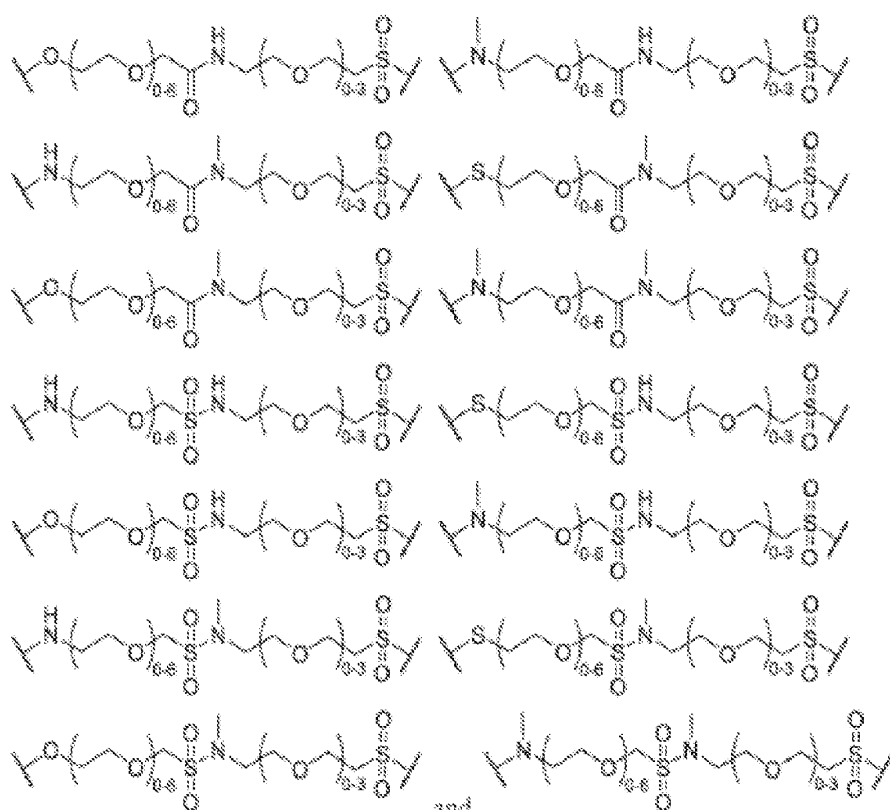
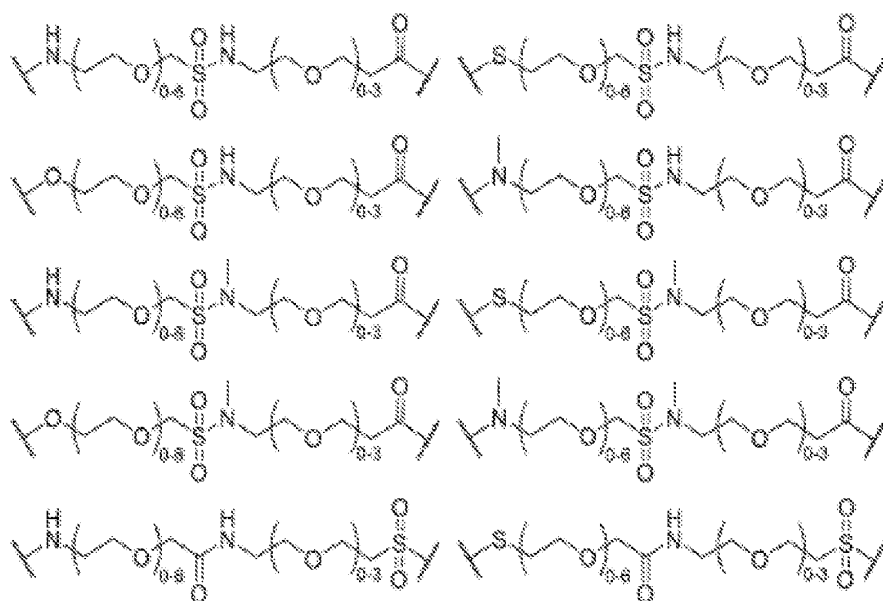
In certain embodiments of the present invention, L^1 , L^2 , Linker^A and/or Linker^B are independently of each other is selected from:



In certain embodiments of the present invention, L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from:

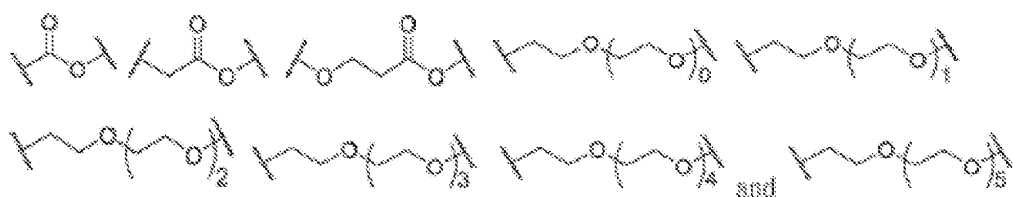


In certain embodiments L¹ and/or L² are independently of each other selected from:



and

In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from



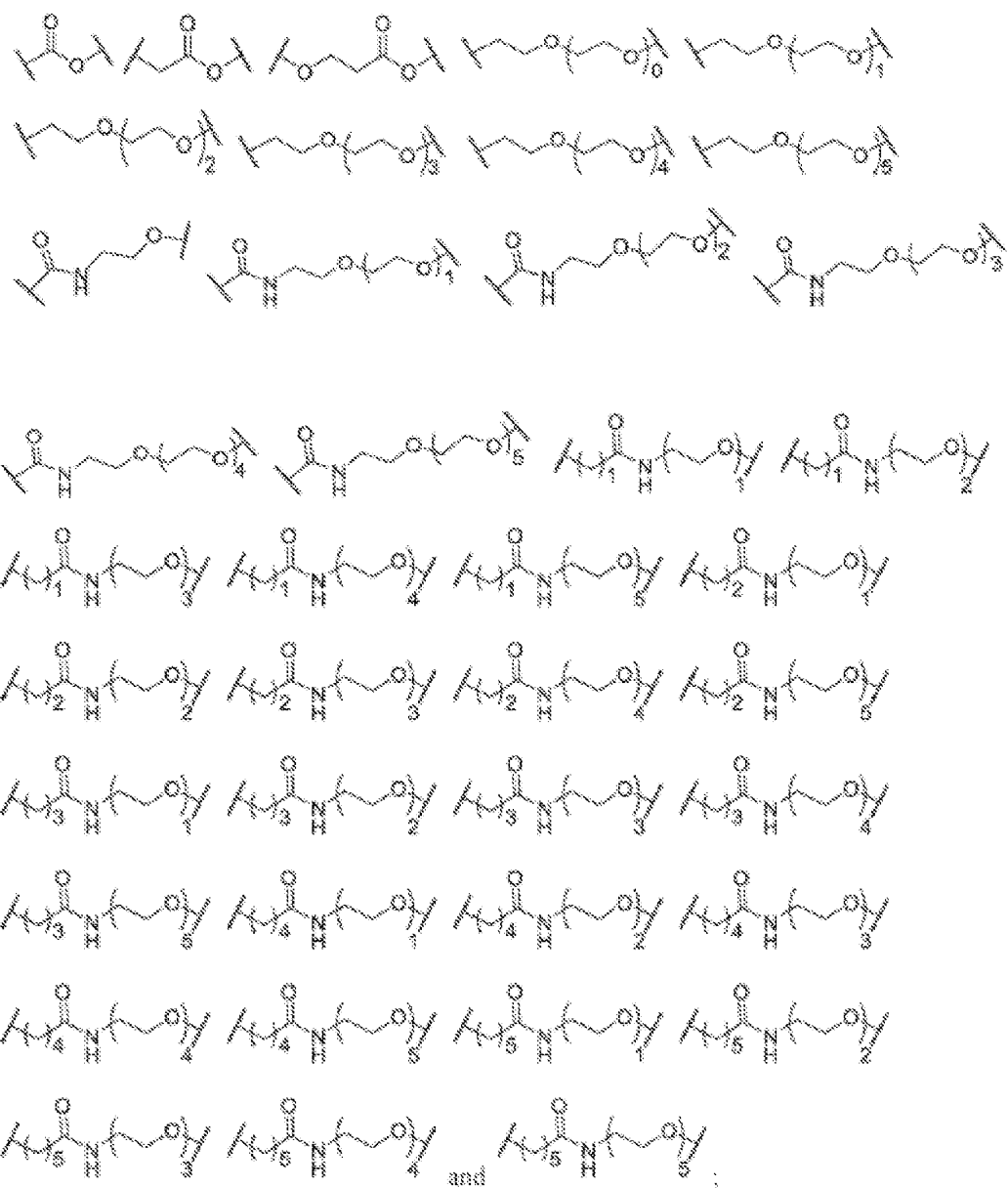
In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from



In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from

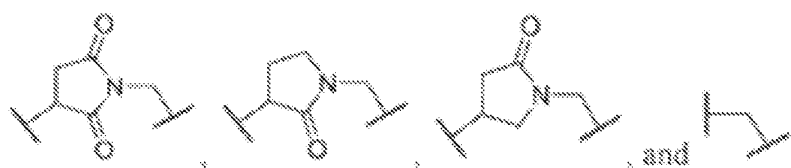


In certain embodiments, L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from

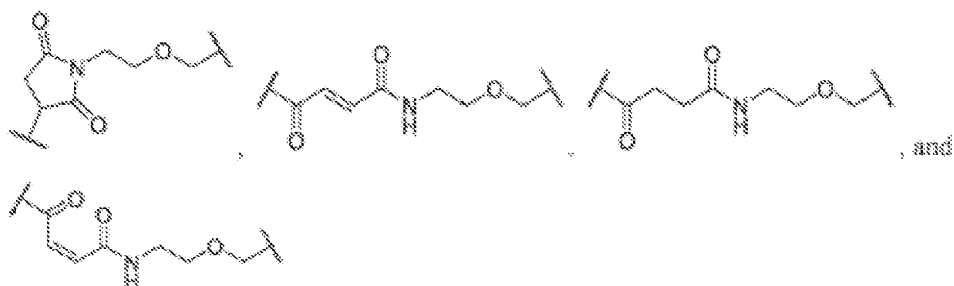


wherein each is optionally substituted with 1, 2, 3, or 4 substituents selected from R^{21} .

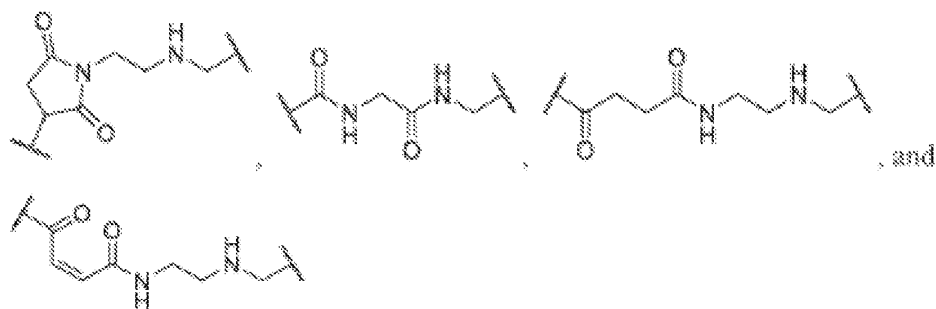
In certain embodiments, L¹, L², Linker^A and/or Linker^B are independently of each other selected from:



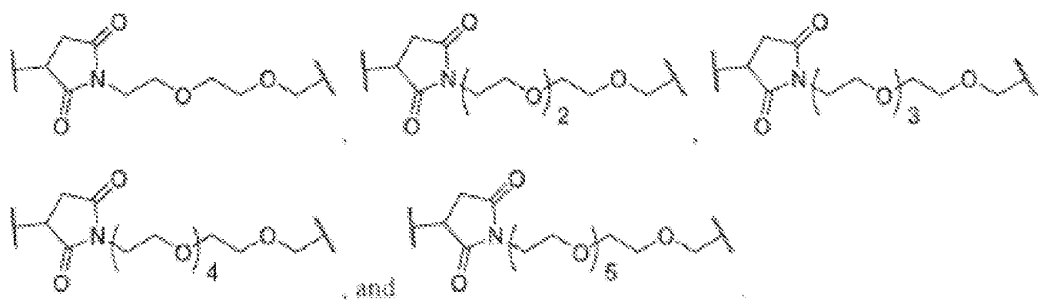
In certain embodiments, L¹, L², Linker^A and/or Linker^B are independently of each other selected from



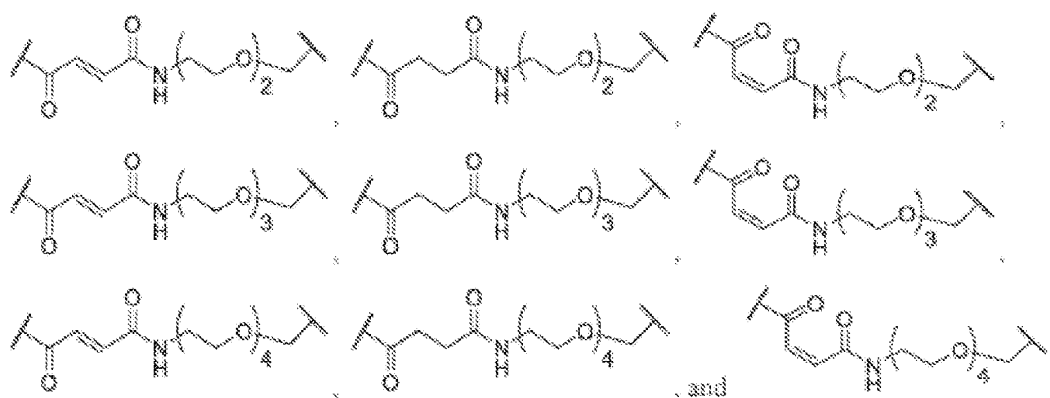
In certain embodiments, L¹, L², Linker^A and/or Linker^B are independently of each other selected from



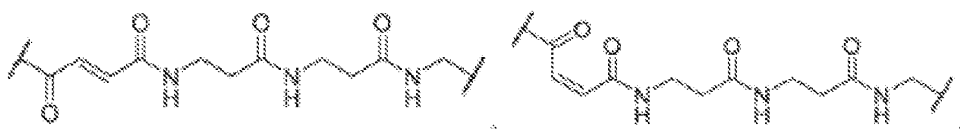
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from



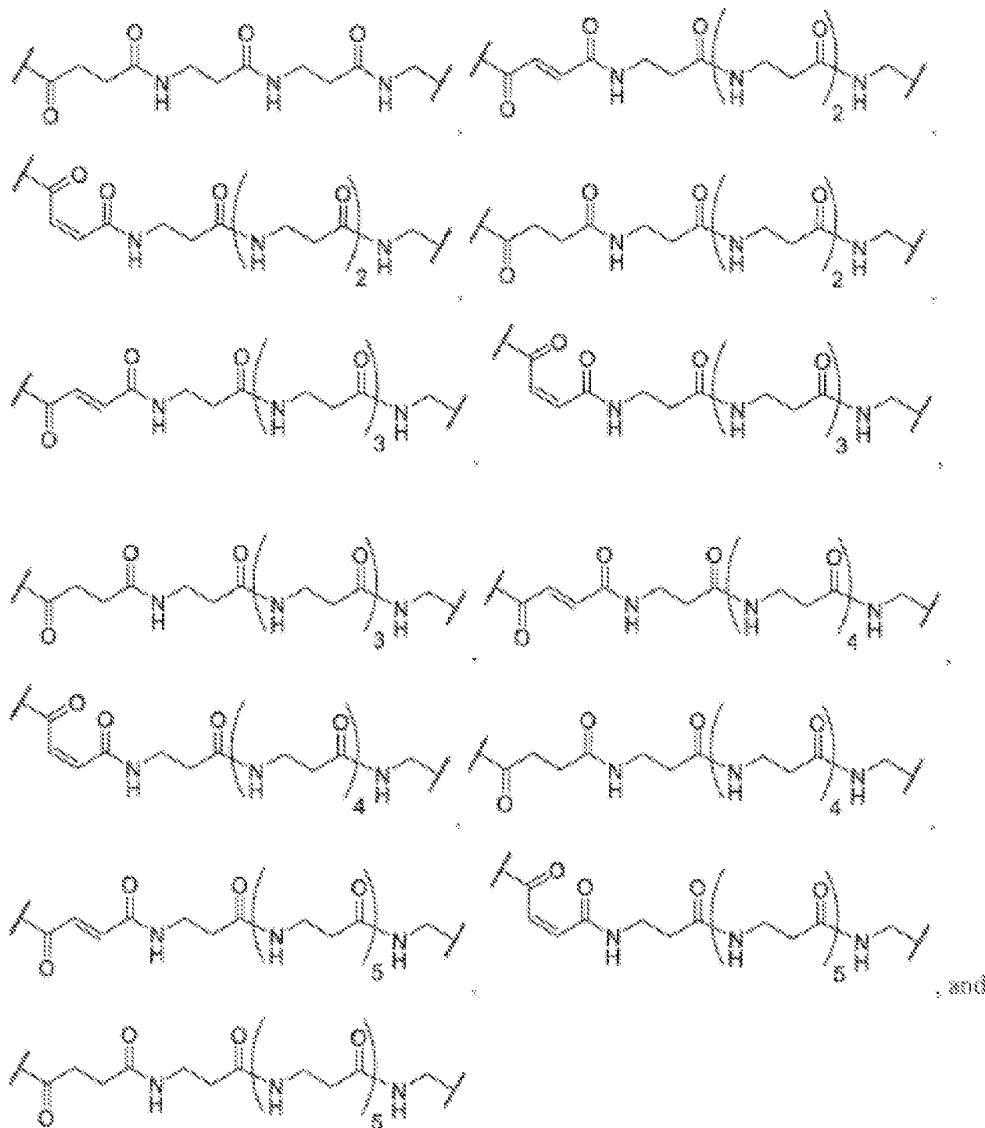
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from

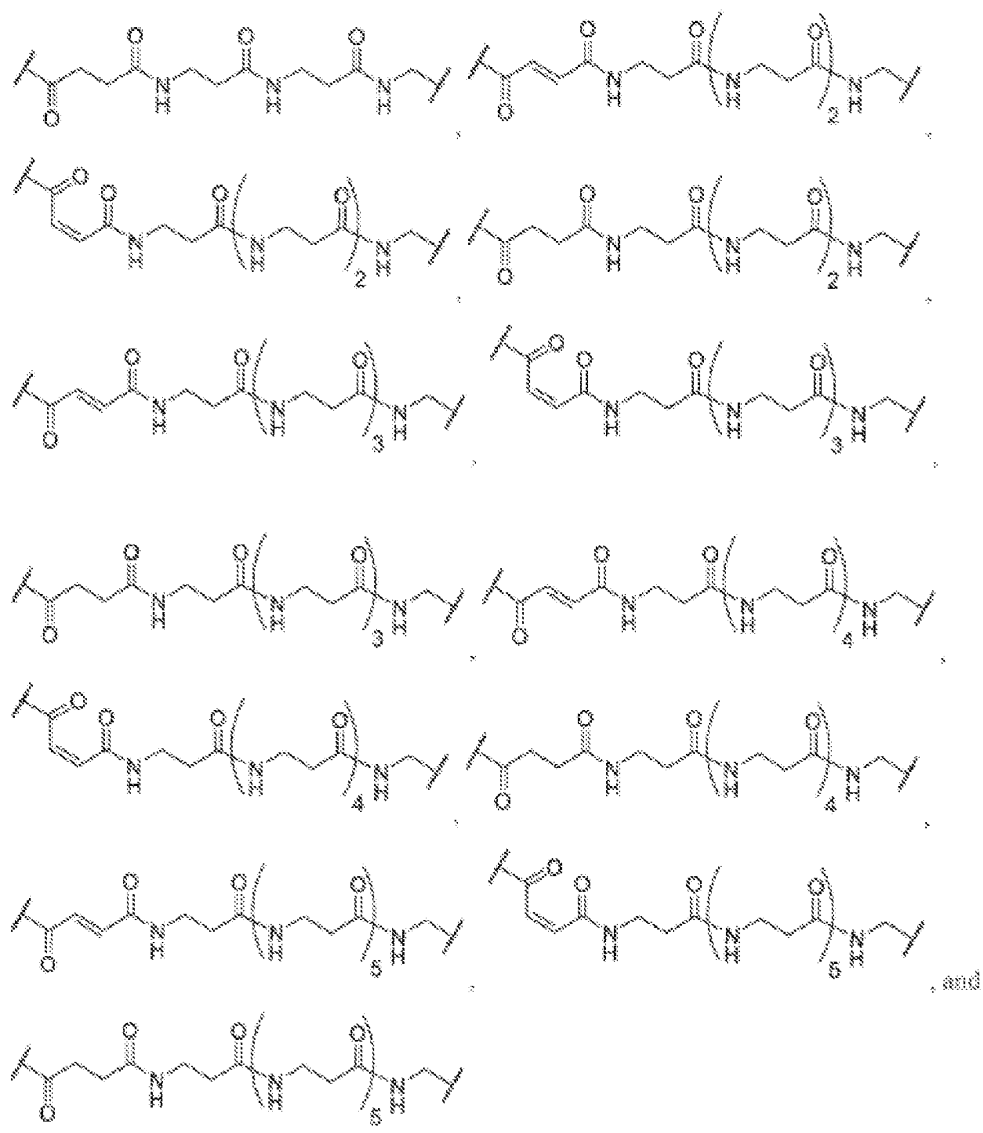


In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from

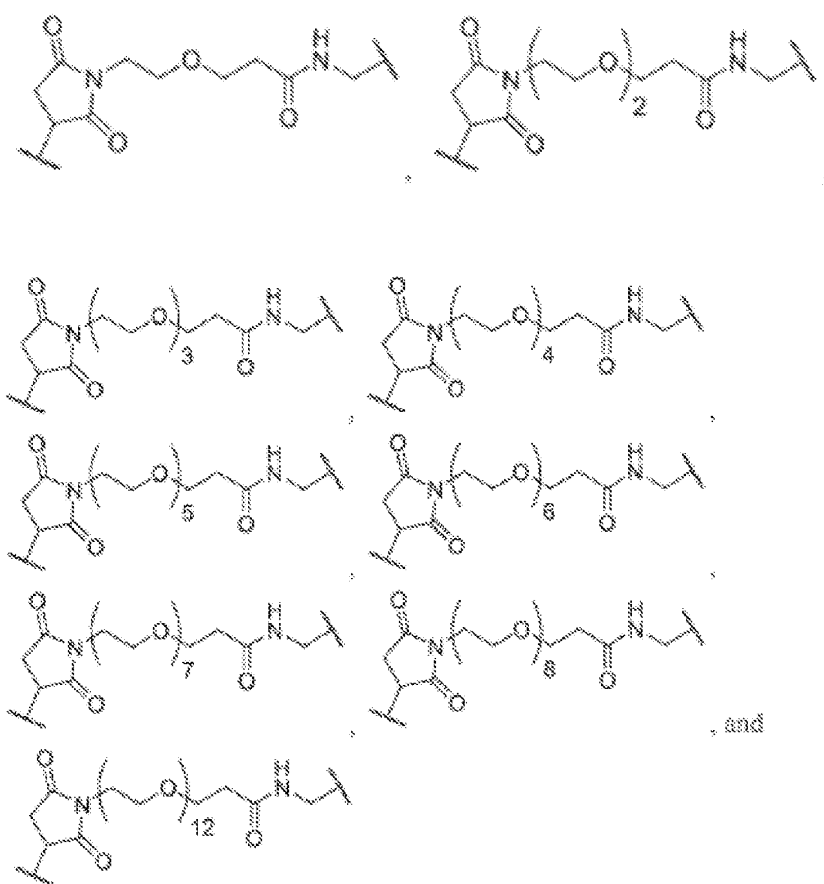


In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from

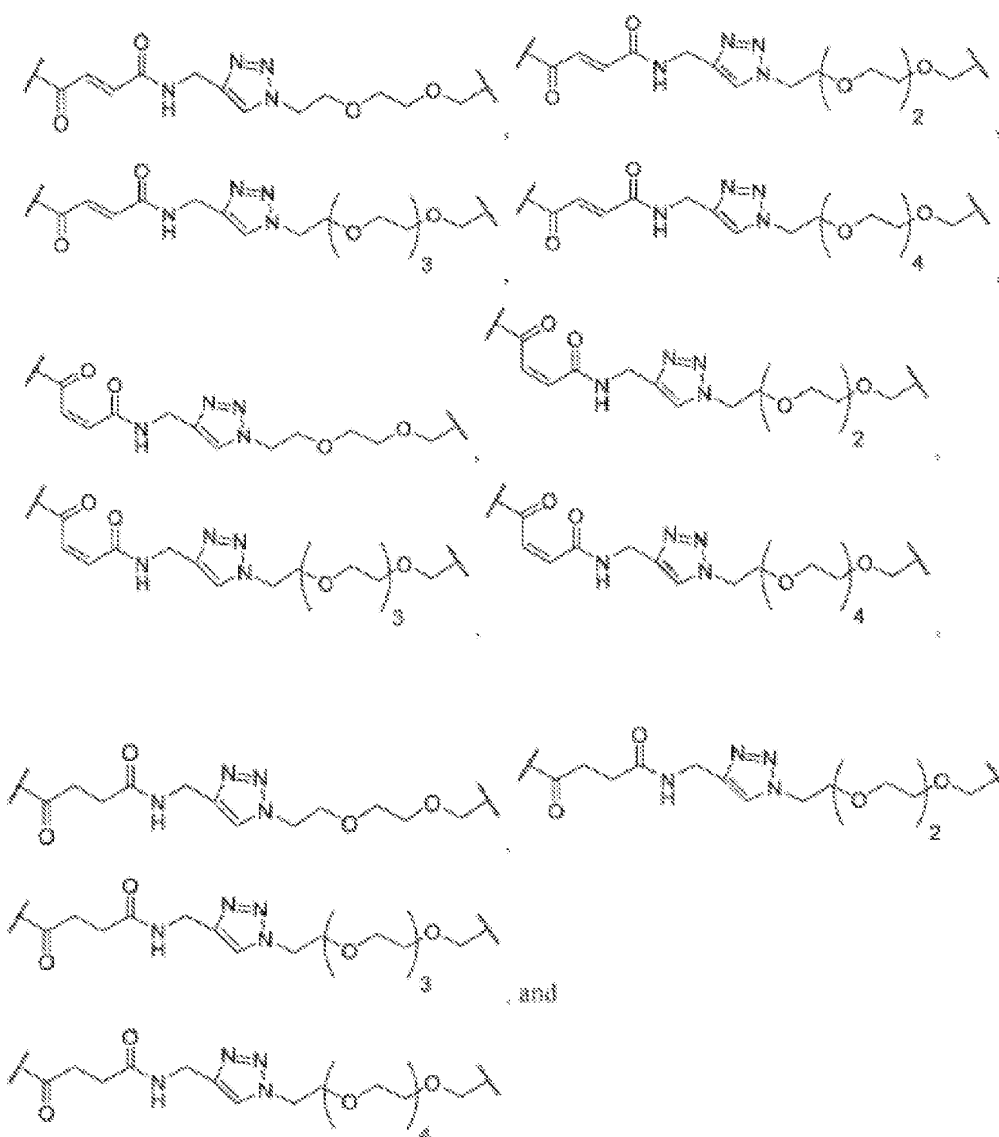




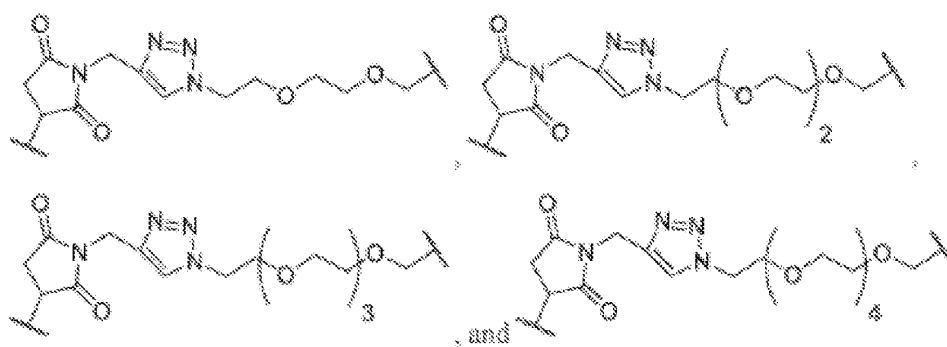
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from



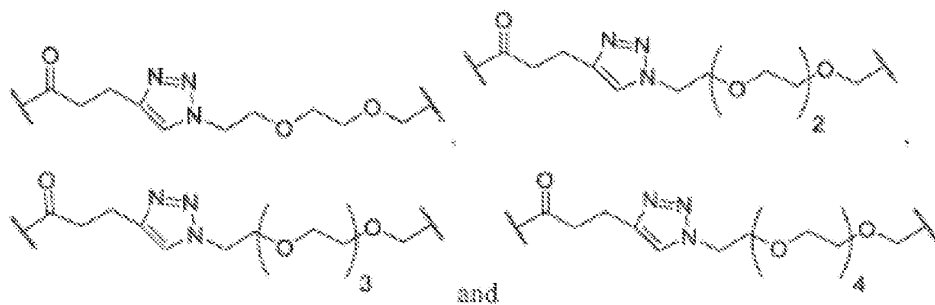
In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from



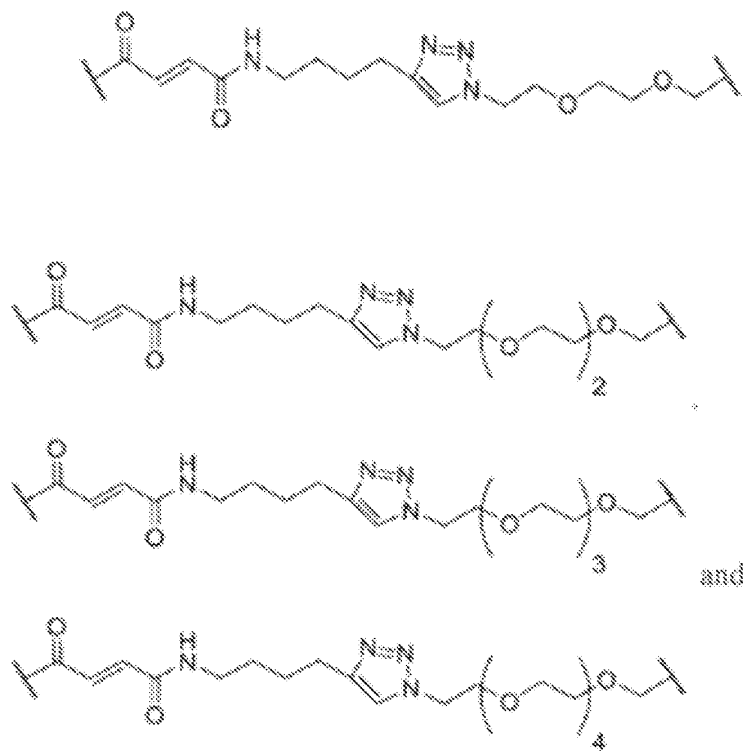
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from



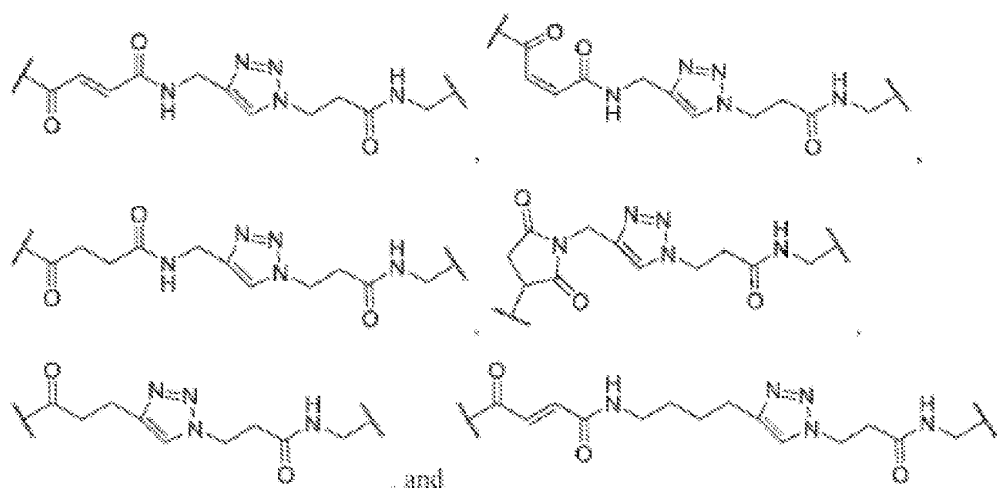
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from



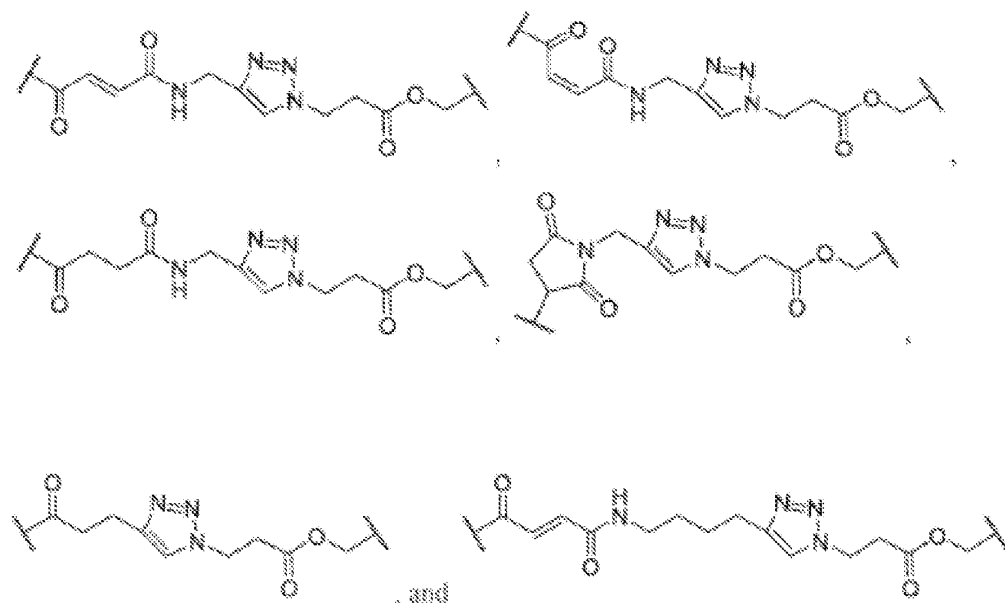
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from



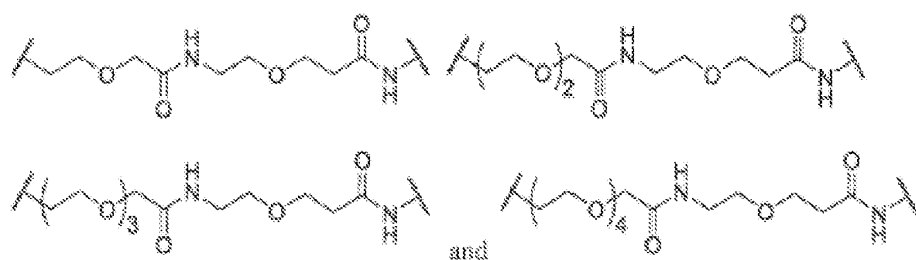
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from



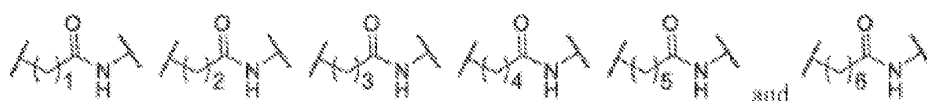
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from



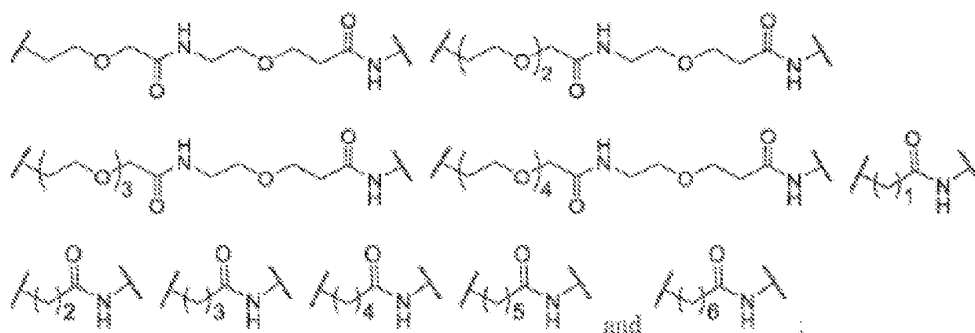
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from



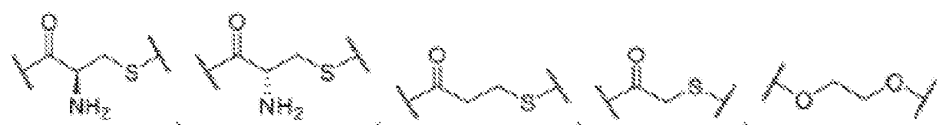
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from

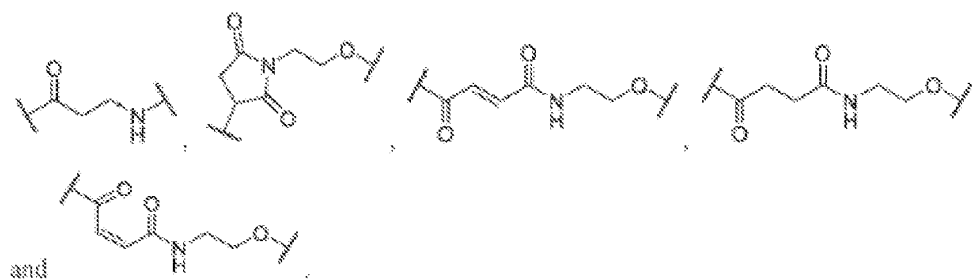


In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from

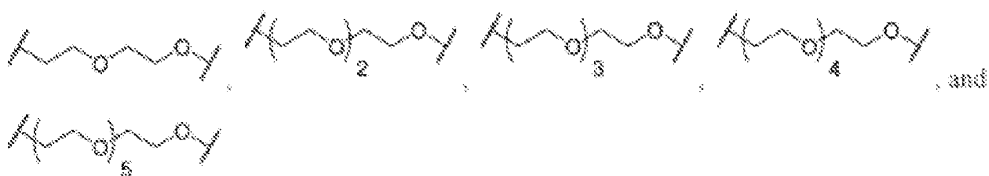


In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from:

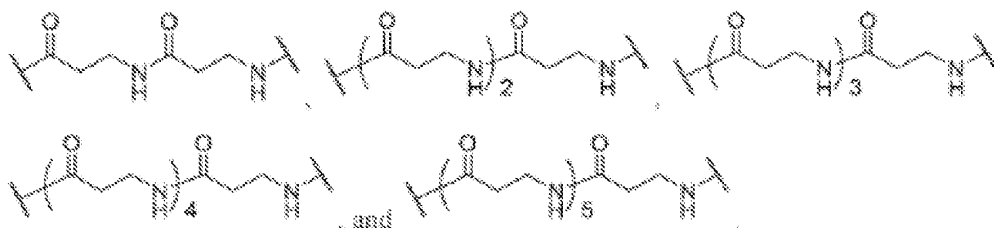




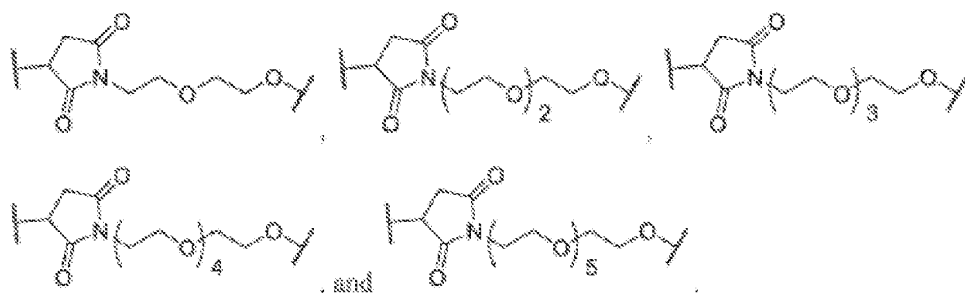
In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from:



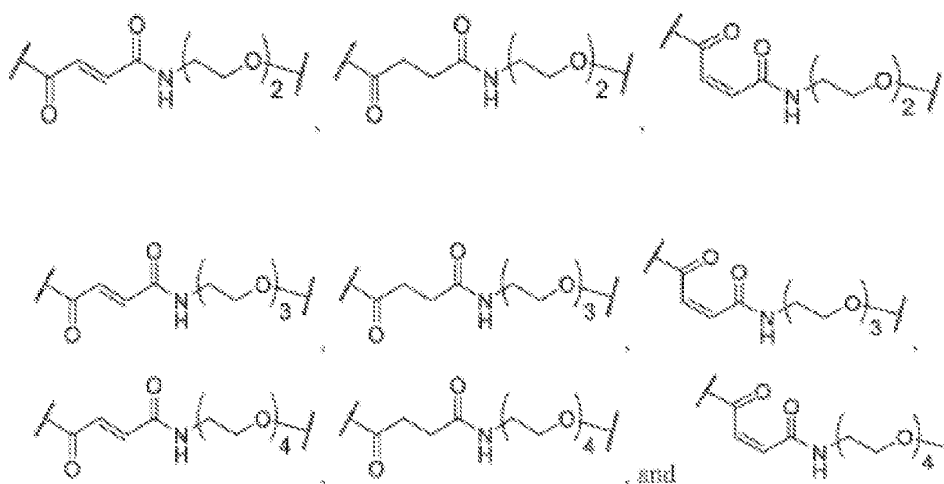
In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from:



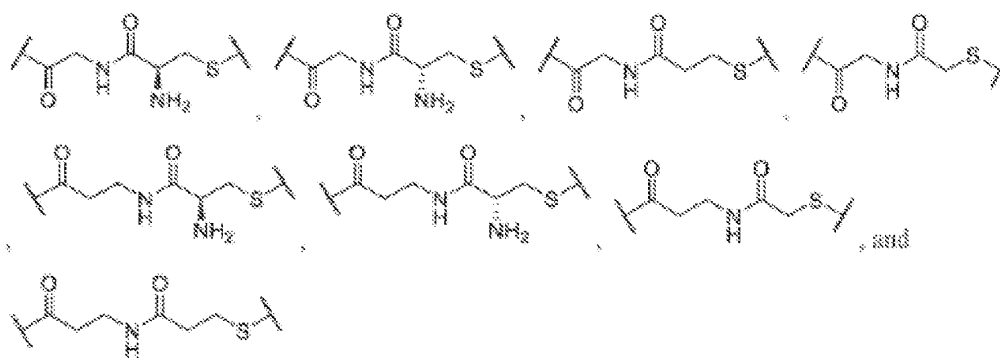
In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from:



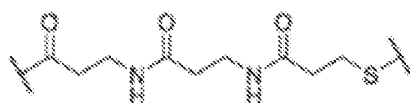
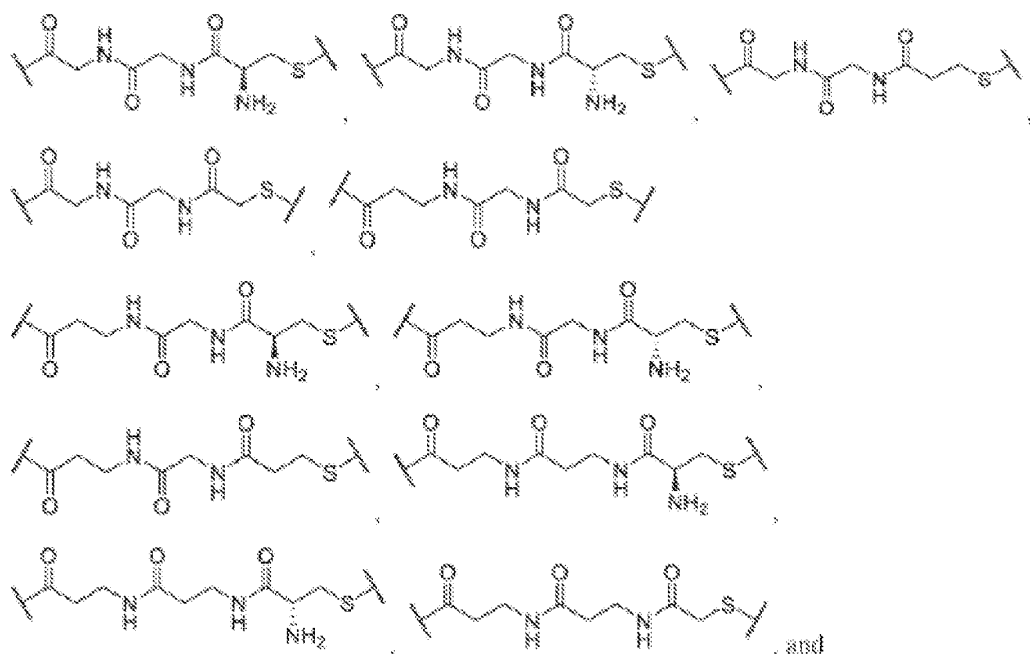
In certain embodiments L^1 , L^2 , Linker^A and/or Linker^B are independently of each other selected from:



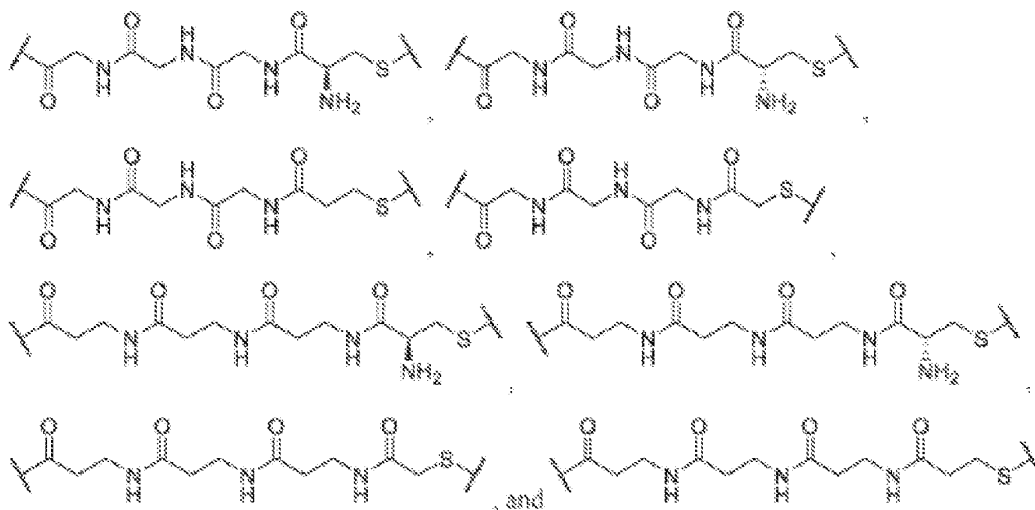
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from:



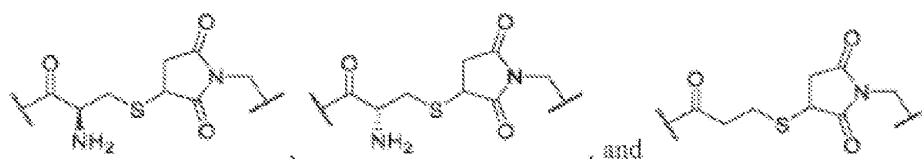
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from:



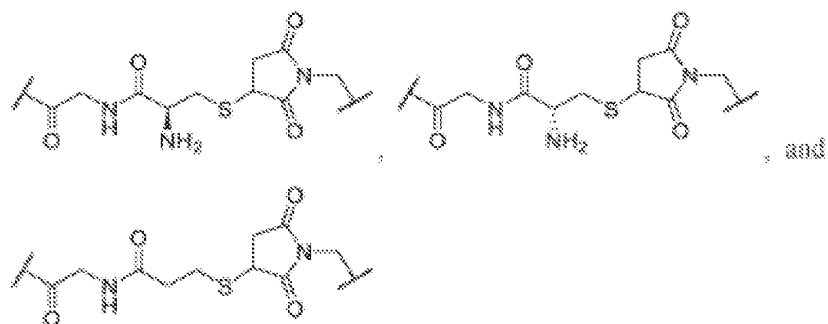
In certain embodiments L¹, L², Linker^A and/or Linker^B are independently of each other selected from:



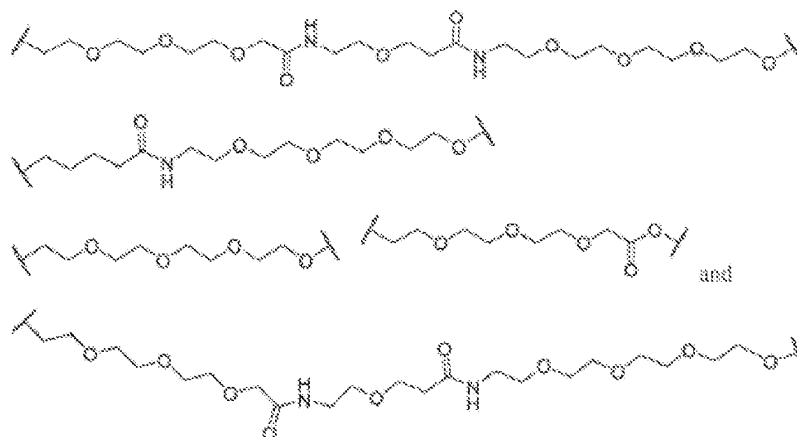
In certain embodiments L¹, L², Linker^A, Linker^B and/or Linker^B-Linker^A are independently of each other selected from:



In certain embodiments L^1 , L^2 , Linker^A , Linker^B and/or $\text{Linker}^B\text{-Linker}^A$ are independently of each other selected from:

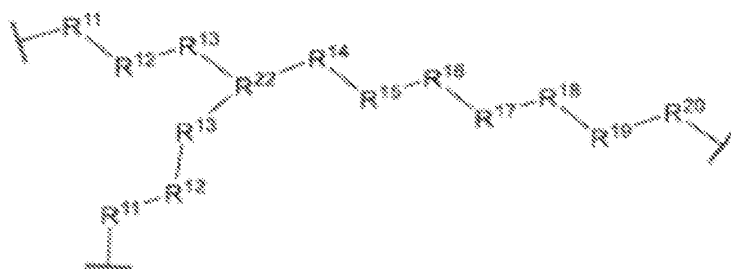


In certain embodiments L^1 , L^2 , Linker^A , Linker^B and/or $\text{Linker}^B\text{-Linker}^A$ are independently of each other selected from:



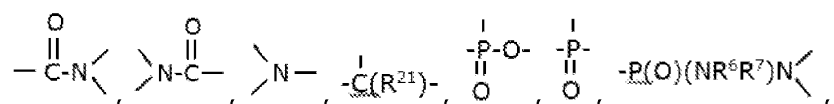
Linker - $L^1\text{-Con}(L^2\text{-})_n$

In certain embodiments $-L^1\text{-Con}(L^2\text{-})_n$ is selected from:



wherein:

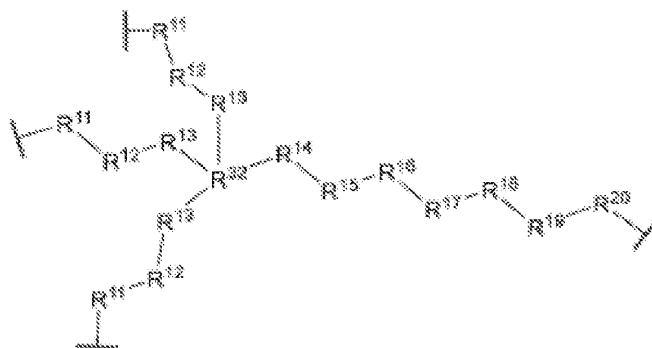
R^{22} is independently at each occurrence selected from the group consisting of alkyl, heteroalkyl,



alkenyl, haloalkyl, aryl, heterocycle, and heteroaryl, each of which has three valences bonded to R^{13} and R^{14} , respectively, and is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{21} ;

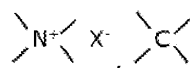
and the remaining variables are as defined herein.

In certain embodiments $-L^1-Con(L^2)_n$ is selected from:



wherein:

R^{32} is independently at each occurrence selected from the group consisting of alkyl, heteroalkyl,

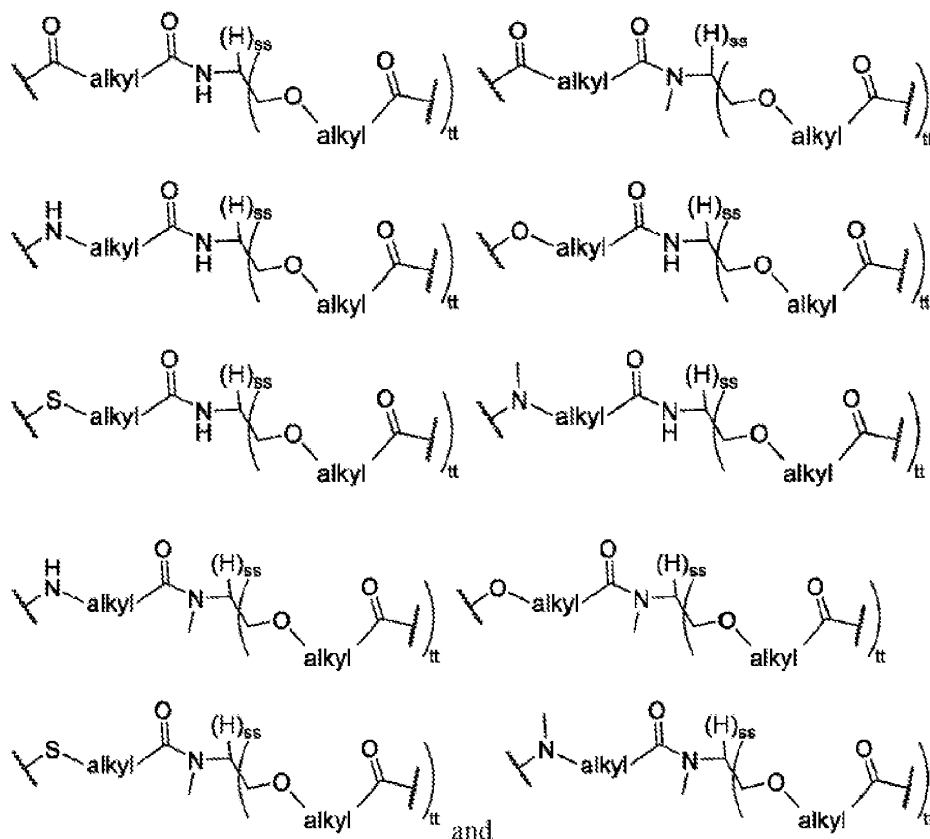


alkenyl, haloalkyl, aryl, heterocycle, and heteroaryl, each of which has three valences bonded to R^{13} and R^{14} , respectively, and is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{21} ;

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

all other variables are as defined herein.

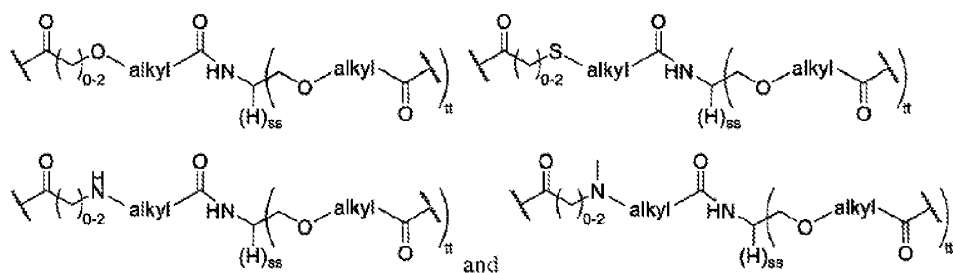
In certain embodiments L^1 , L^2 , Linker^A , Linker^B , Linker^C , Linker^D and/or $-L^1-\text{Con}(L^2-)_n$, respectively, are selected from:



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

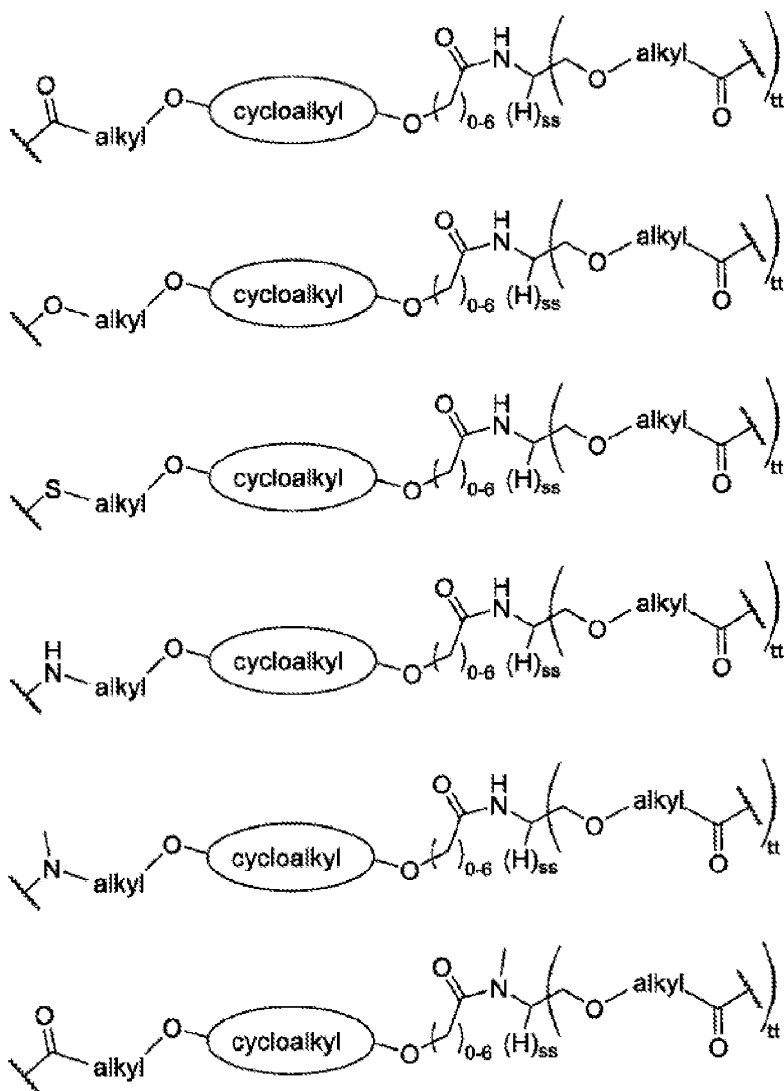
When tt is 1, the structures are embodiments of L^1 and L^2 , Linker^A or Linker^B . Otherwise they are embodiments of Linker^C , Linker^D or $-L^1-\text{Con}(L^2-)_n$. The same is applicable to the following embodiments.

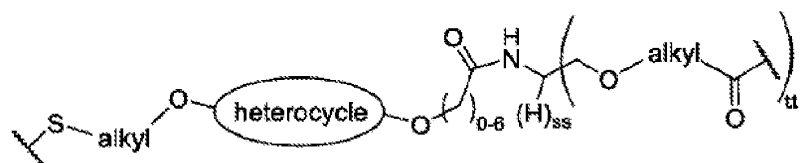
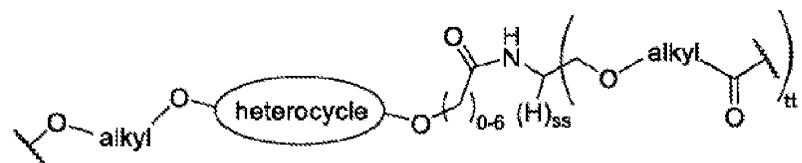
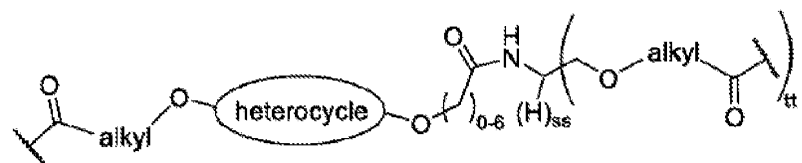
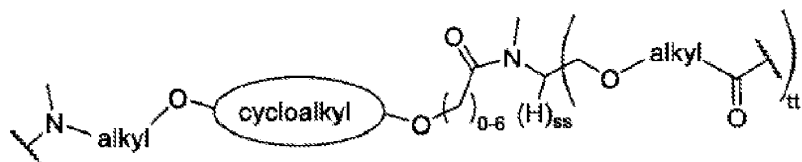
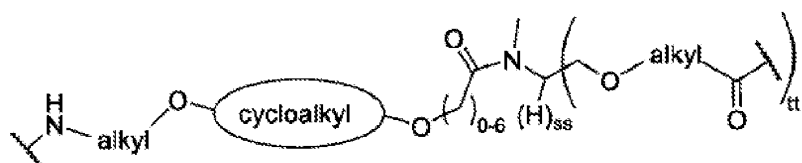
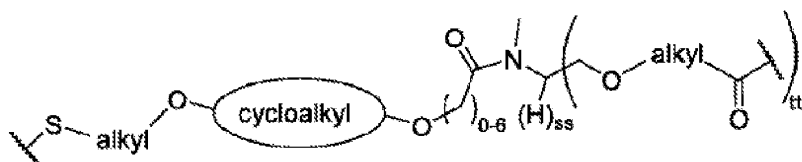
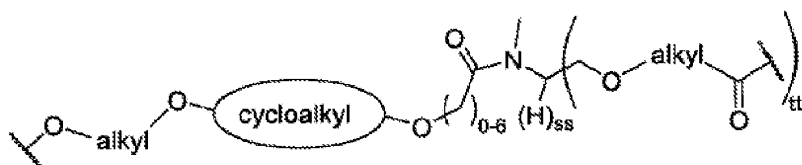
In certain embodiments L^1 , L^2 , Linker^A , Linker^B , Linker^C , Linker^D and/or $-L^1-\text{Con}(L^2-)_n$, respectively, are selected from:

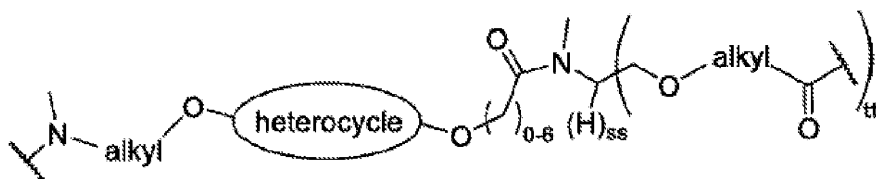
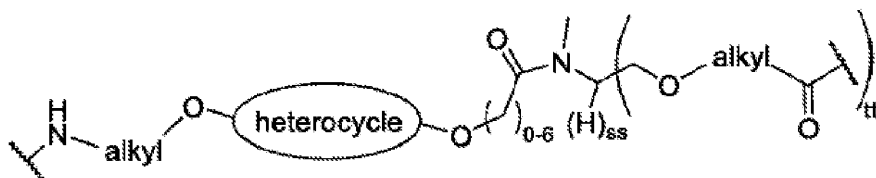
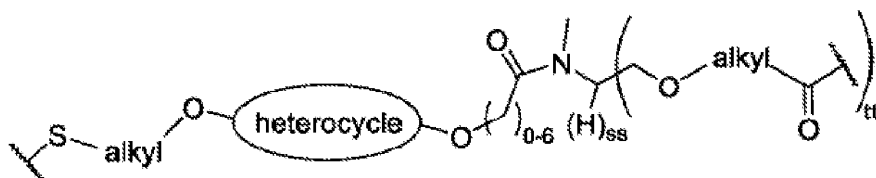
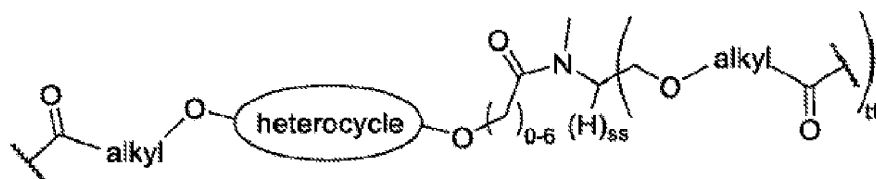
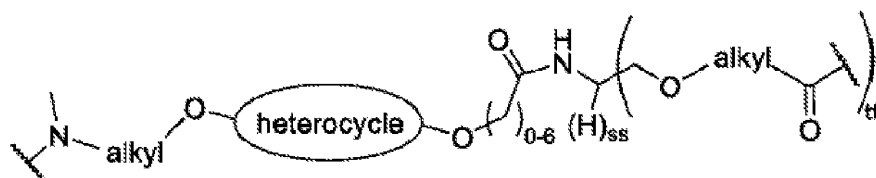
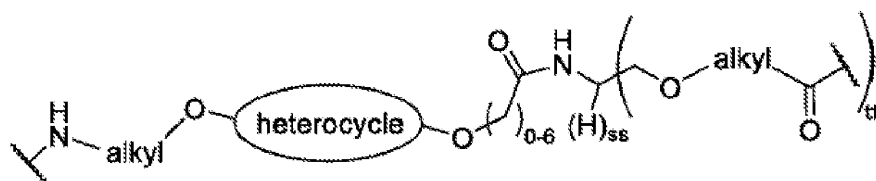


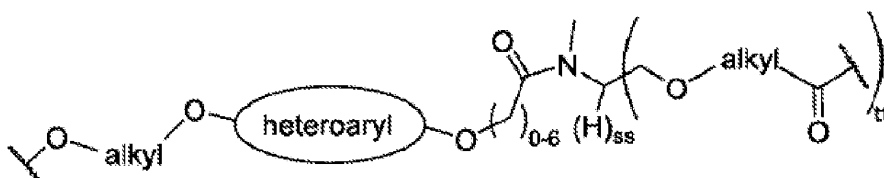
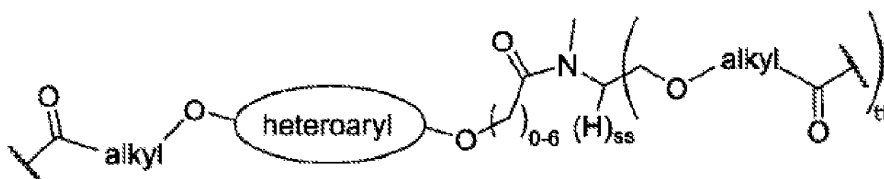
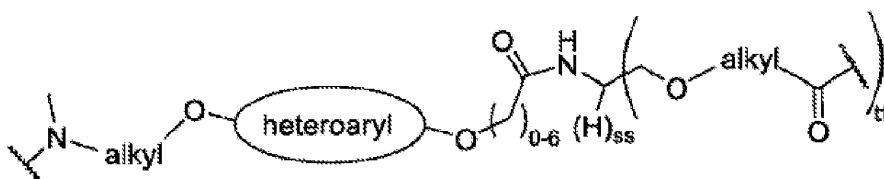
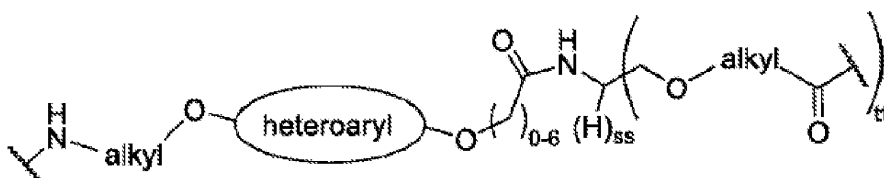
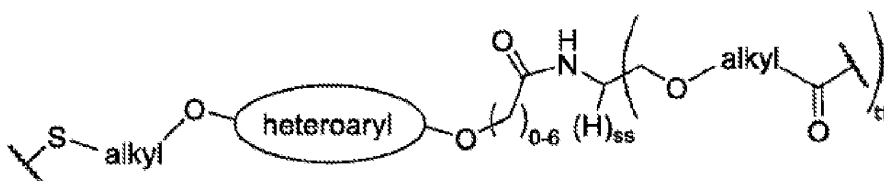
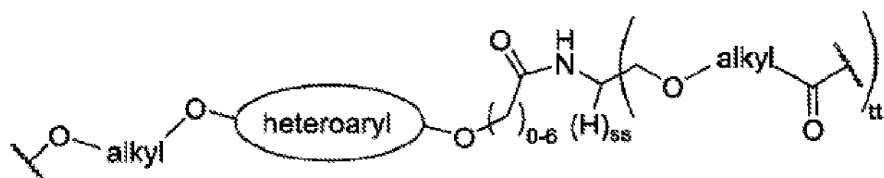
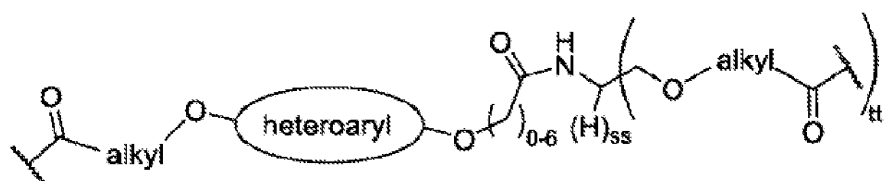
wherein tt and ss are as defined herein.

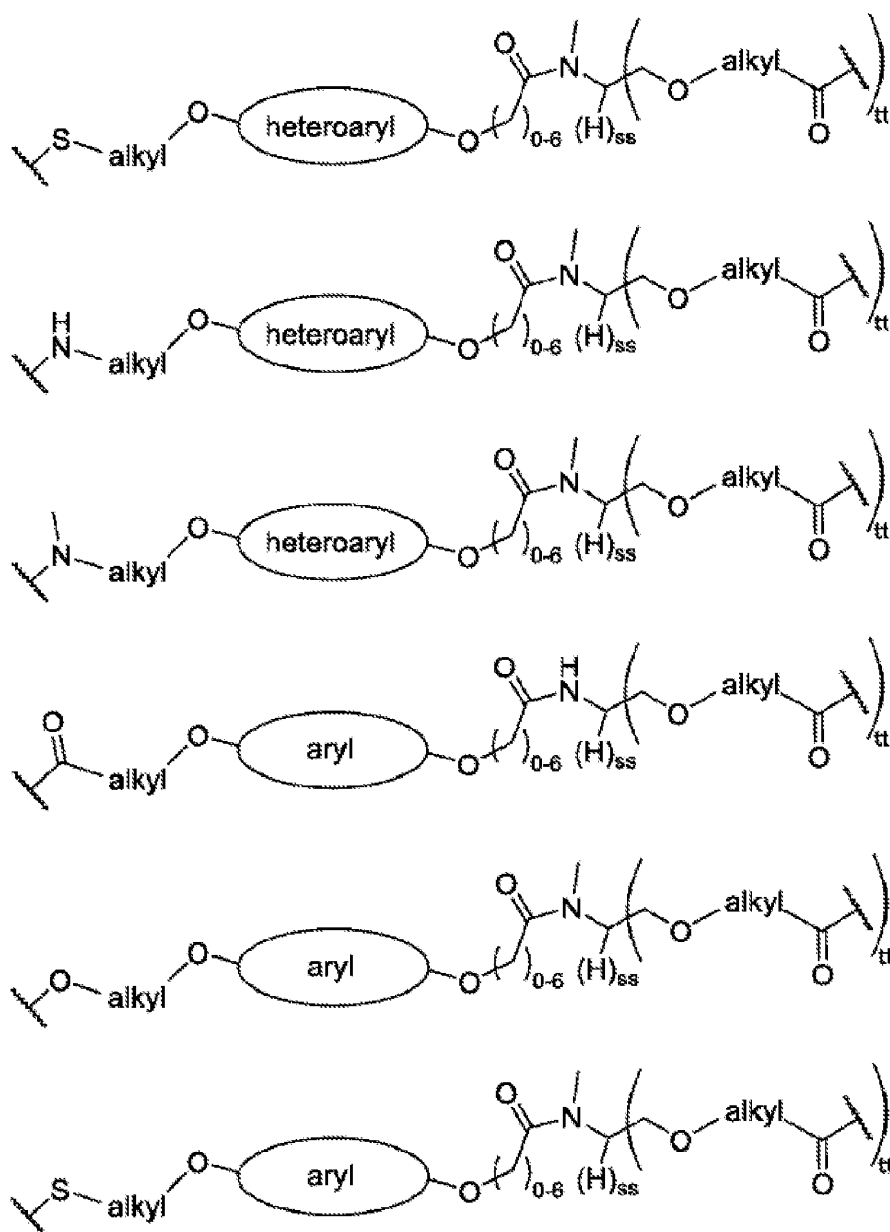
In certain embodiments L^1 , L^2 , $Linker^A$, $Linker^B$, $Linker^C$, $Linker^D$ and/or $-L^1-Con(L^2-)_n$, respectively, are selected from:

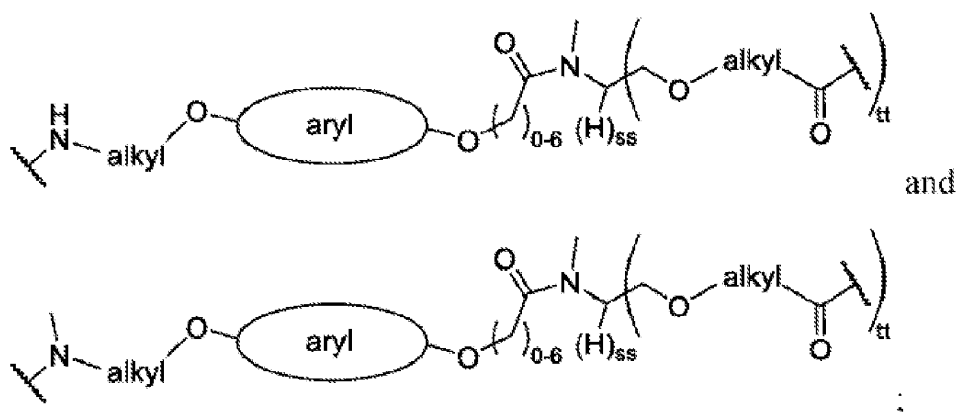






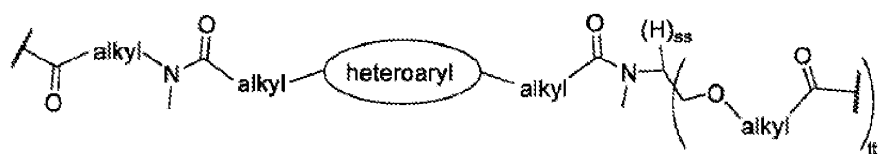
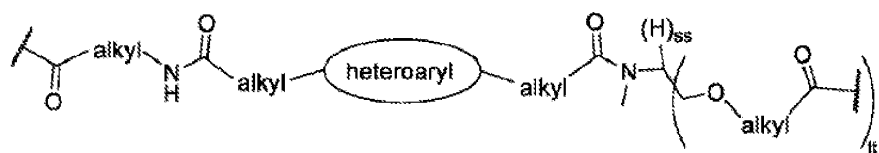
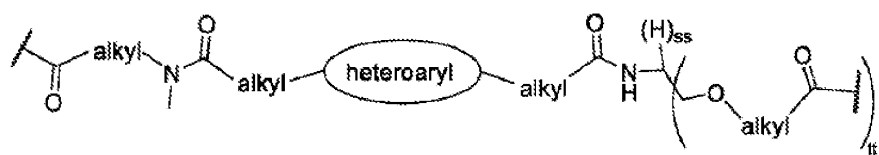
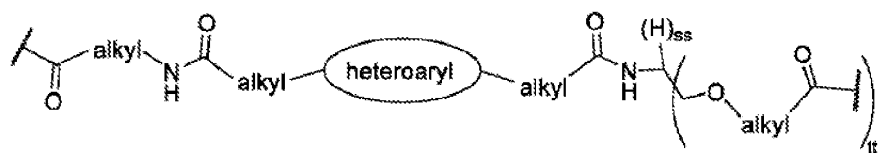
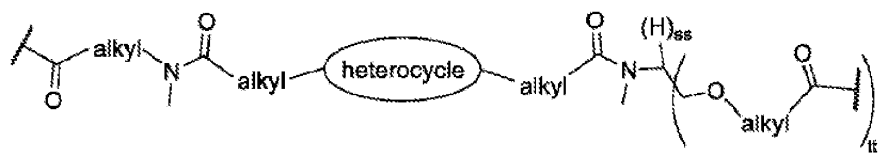
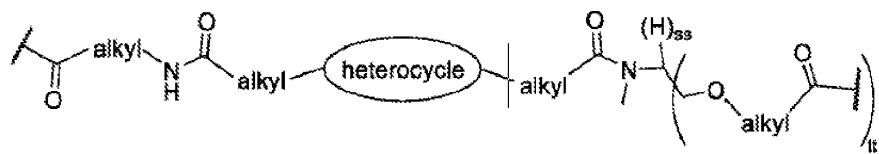
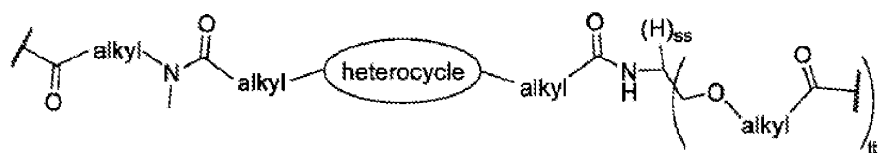
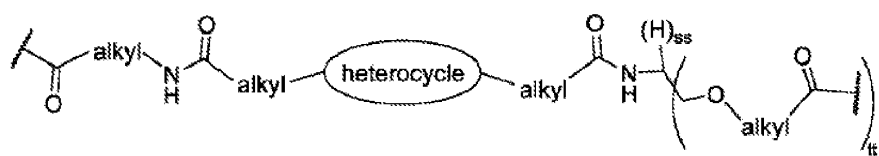


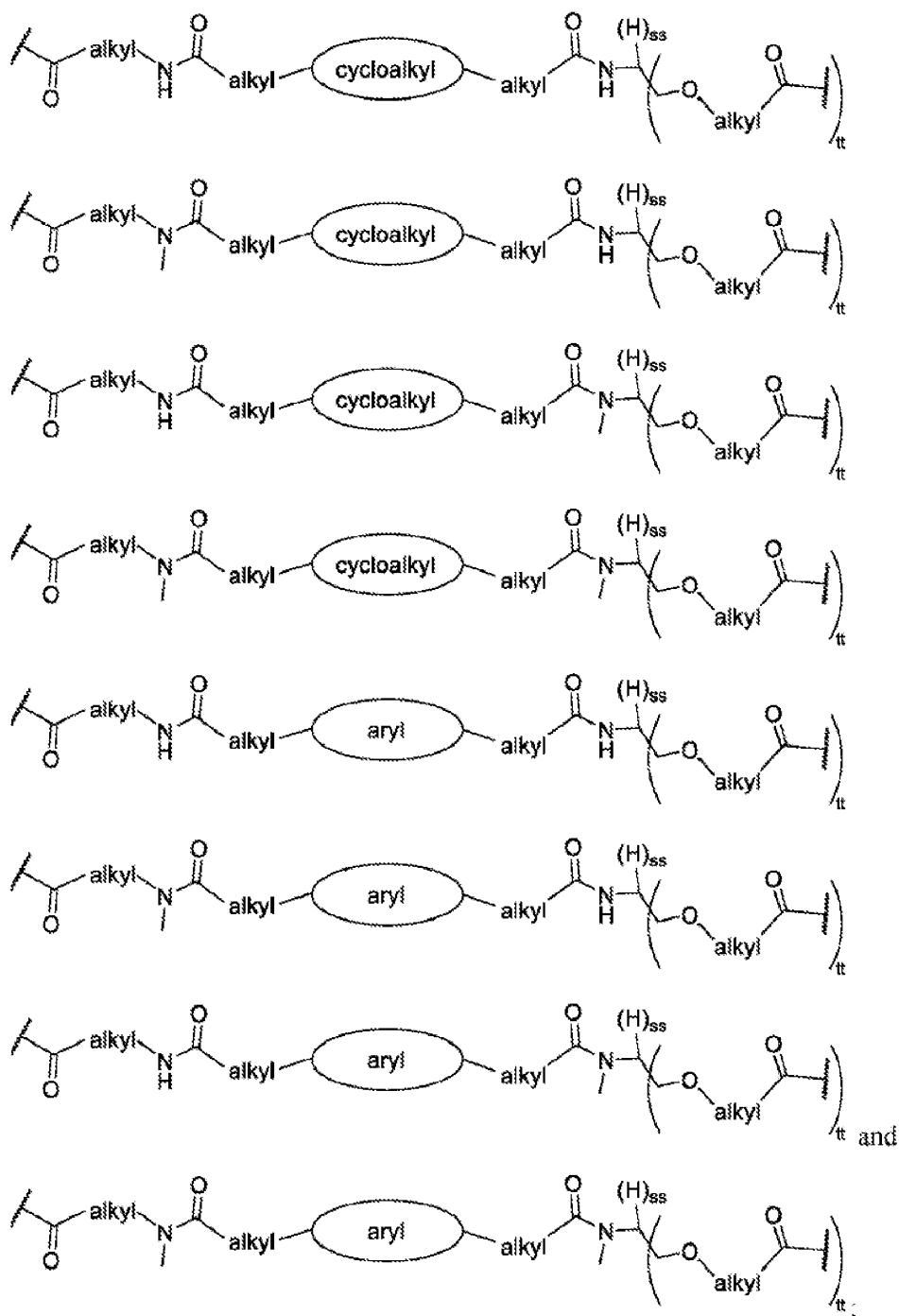




wherein each heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence and the alkyl substituents of the heteroaryl, heterocycle, cycloalkyl, and aryl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

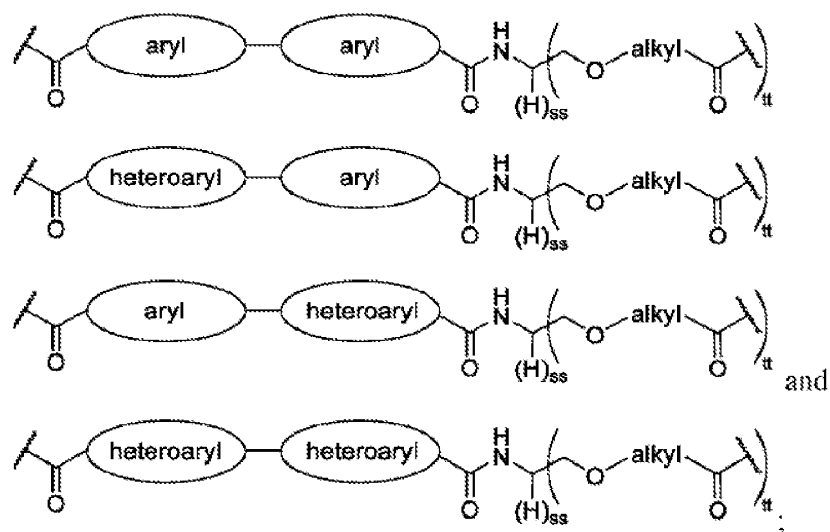
In certain embodiments L^1 , L^2 , Linker^A, Linker^B, Linker^C, Linker^D and/or $-L^1-$ Con(L^2-)_n, respectively, are selected from:





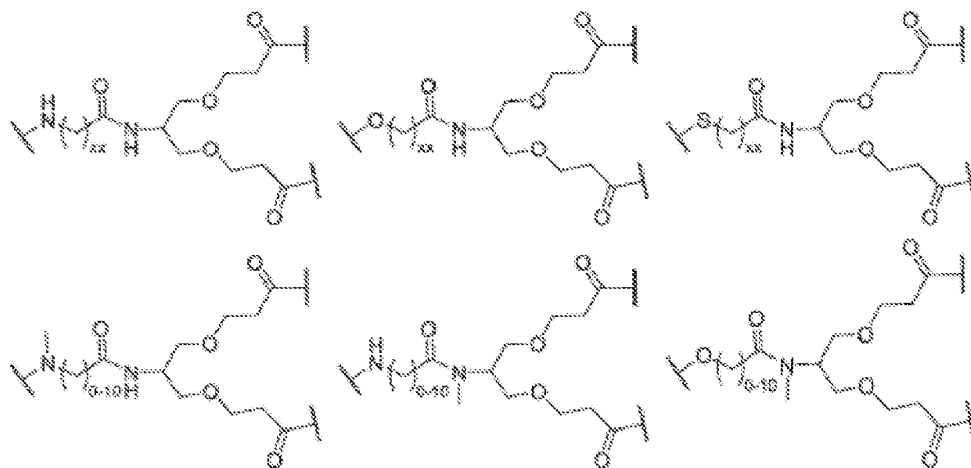
wherein each alkyl, heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, and, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence and the alkyl substituents of the heteroaryl, heterocycle, cycloalkyl,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

In certain embodiments L^1 , L^2 , Linker^A , Linker^B , Linker^C , Linker^D and/or $-L^1-\text{Con}(L^2-)_n$, respectively, are selected from:

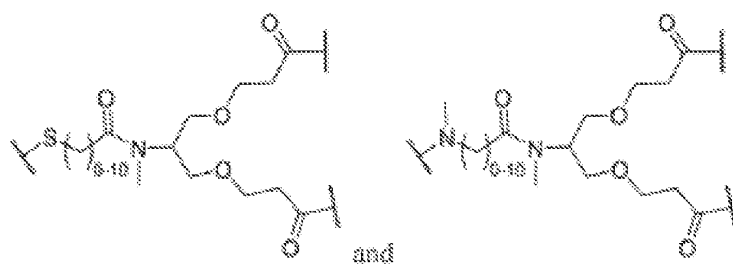


wherein each alkyl, heteroaryl and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence; and tt and ss are as defined herein.

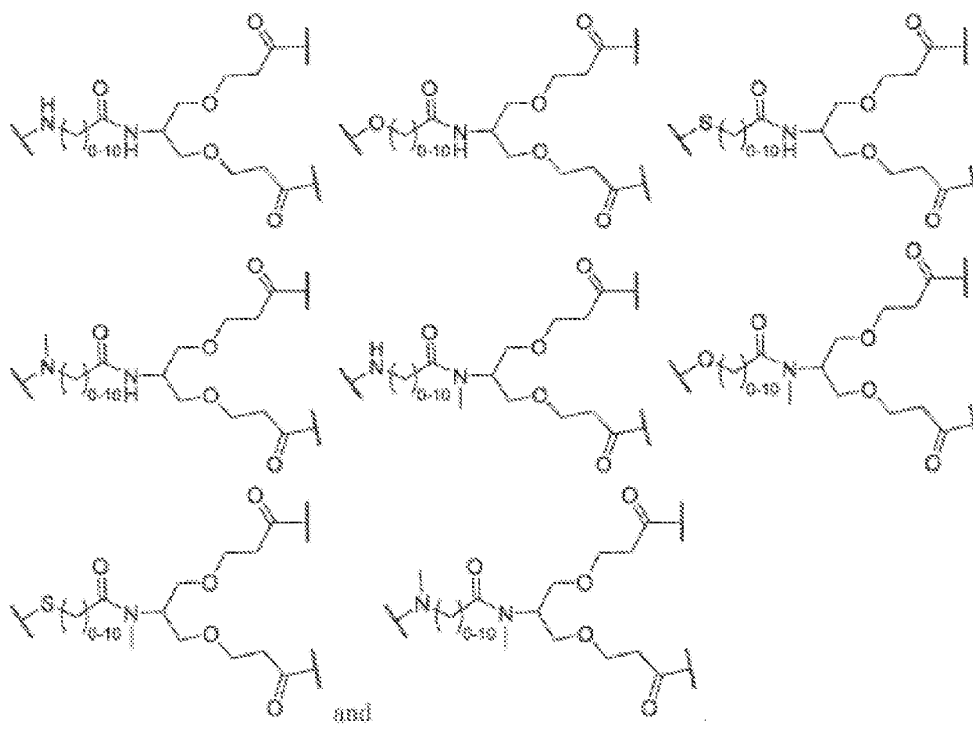
In certain embodiments Linker^C , Linker^D and/or $-L^1-\text{Con}(L^2-)_n$, respectively, are selected from:



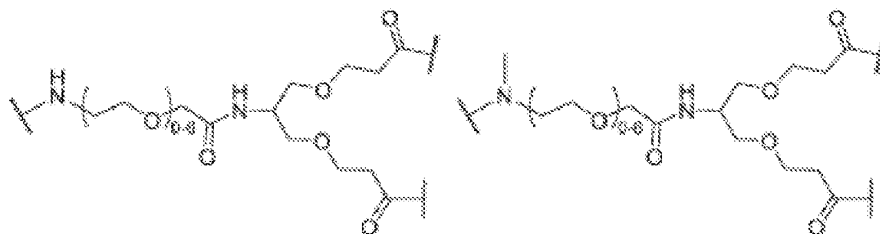
In certain embodiments Linker^C , Linker^D and/or $-L^1-\text{Con}(L^2-)_n$, respectively, are selected from:

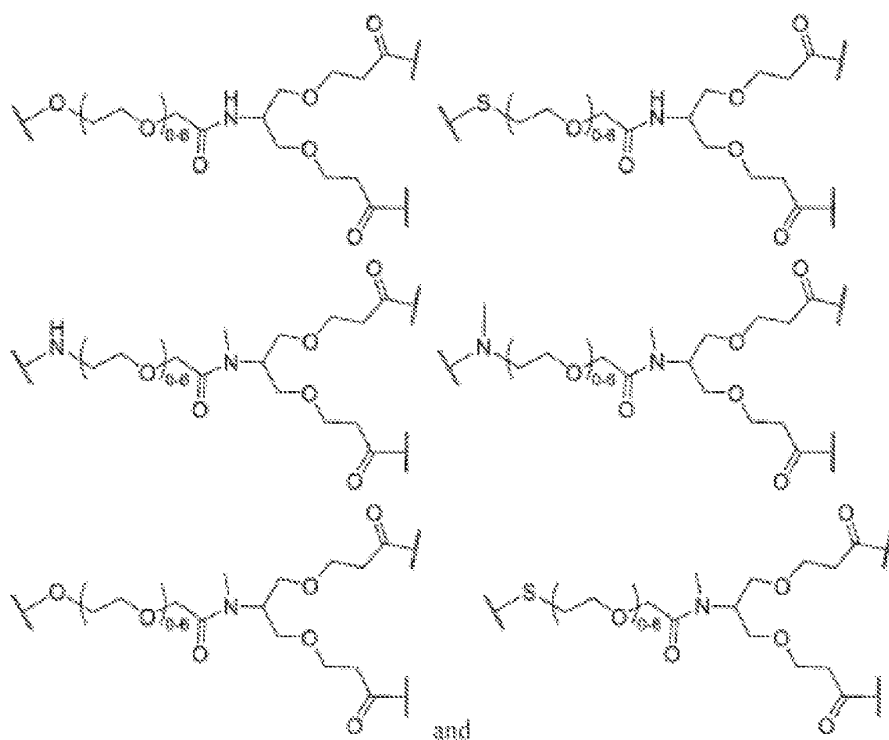


In certain embodiments Linker^C, Linker^D and/or $-\text{L}^1\text{-Con}(\text{L}^2-)_n$, respectively, are selected from:

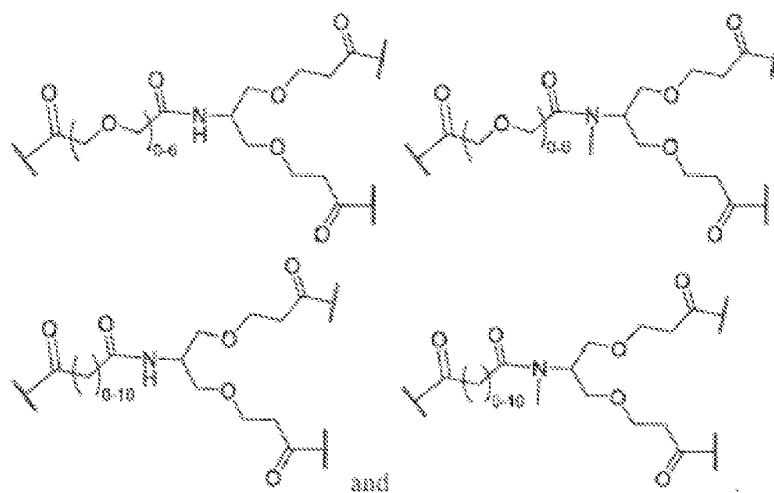


In certain embodiments Linker^C, Linker^D and/or $-\text{L}^1\text{-Con}(\text{L}^2-)_n$, respectively, are selected from:

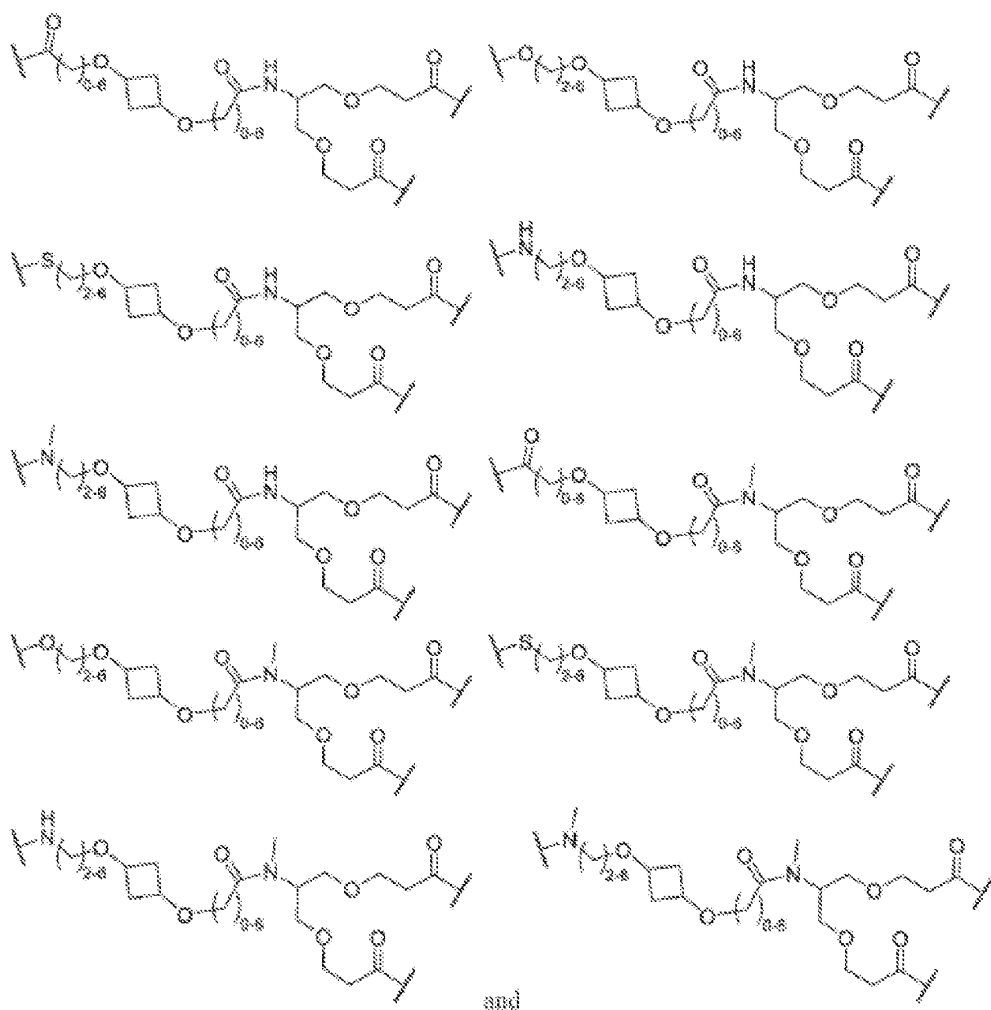




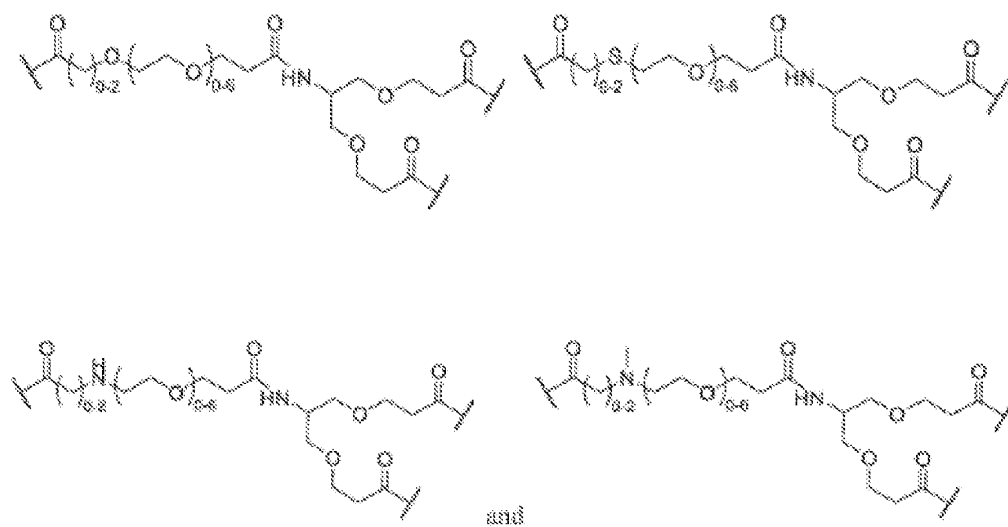
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



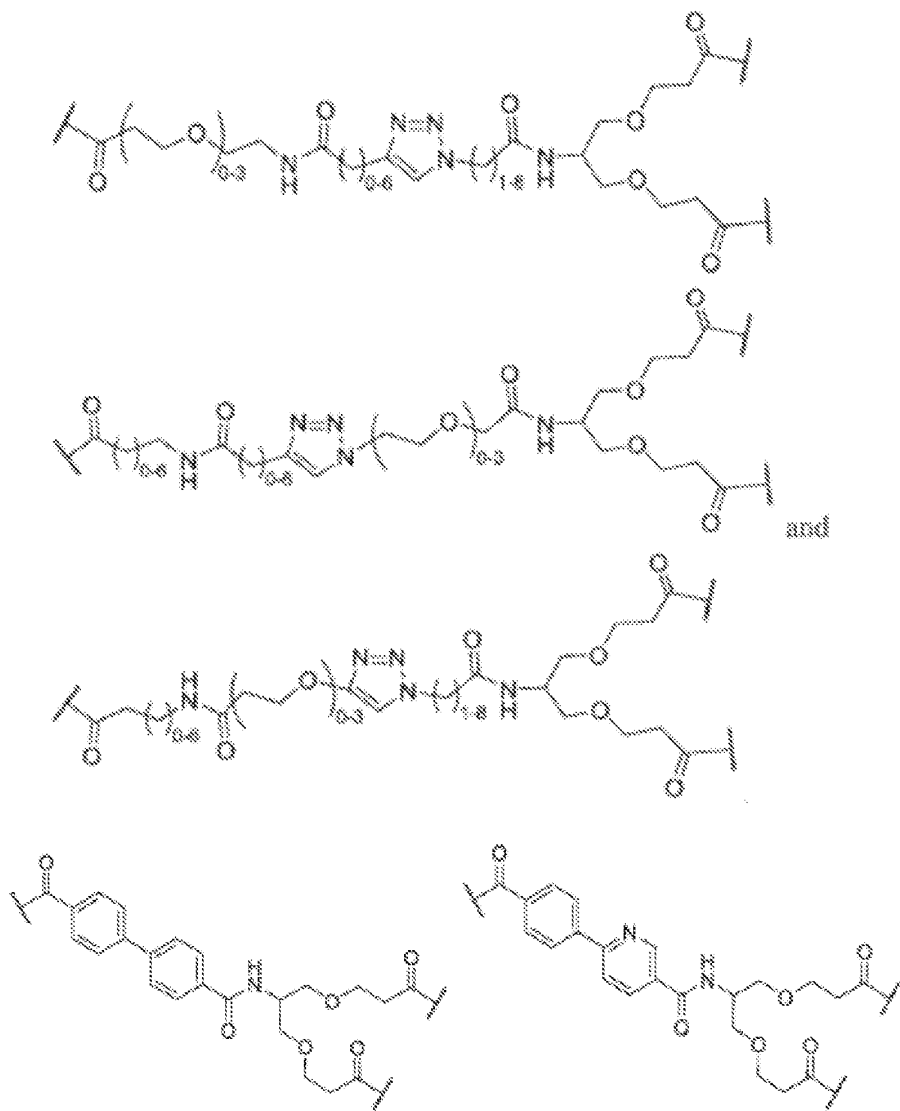
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



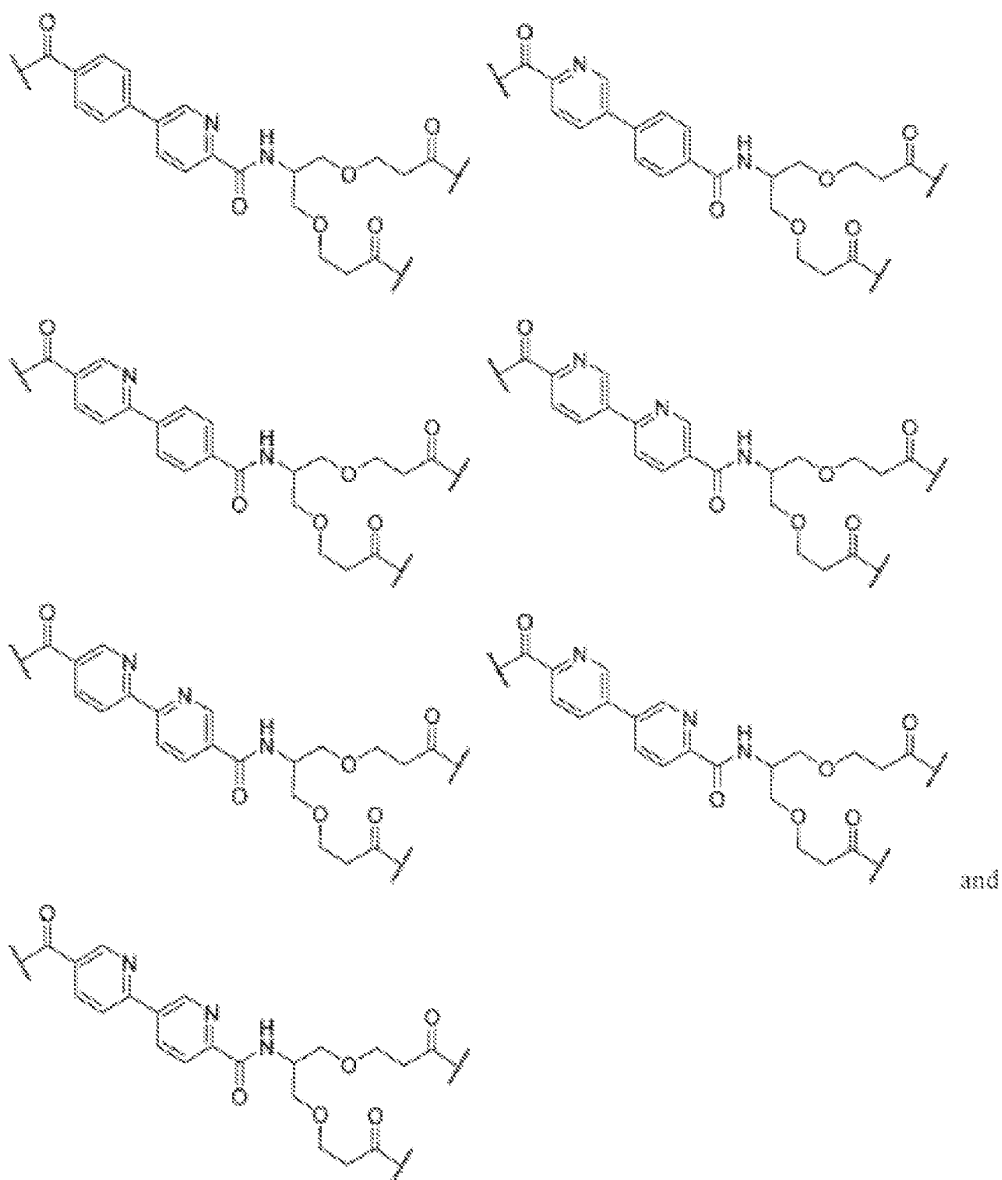
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



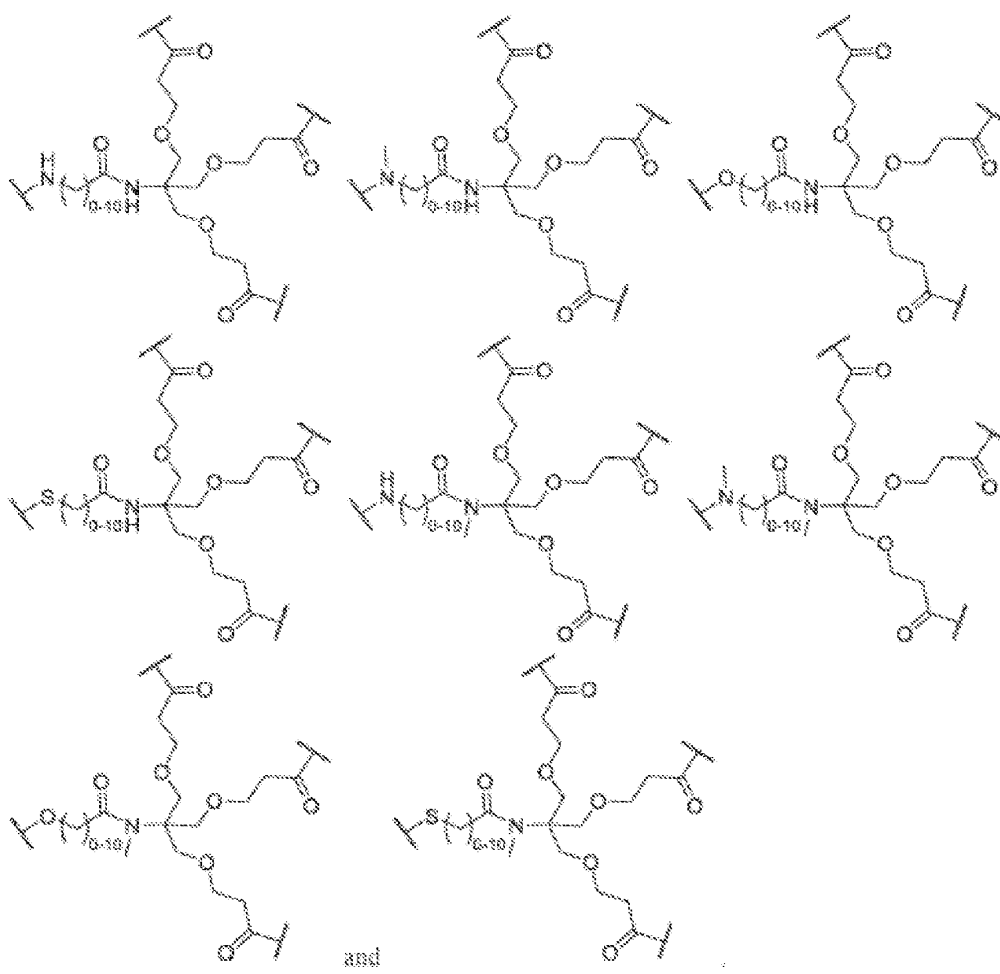
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



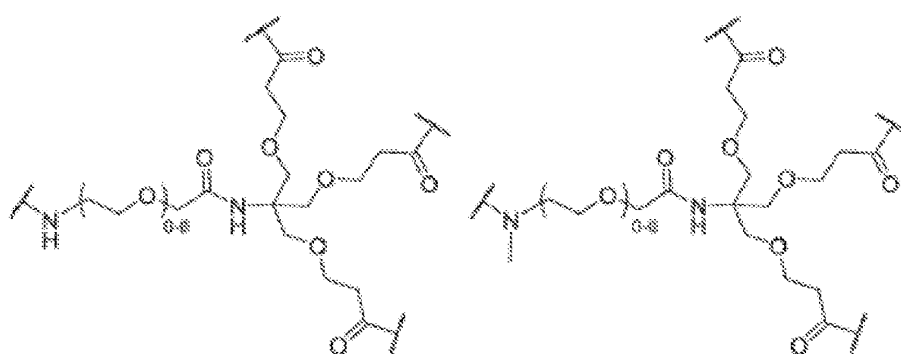
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:

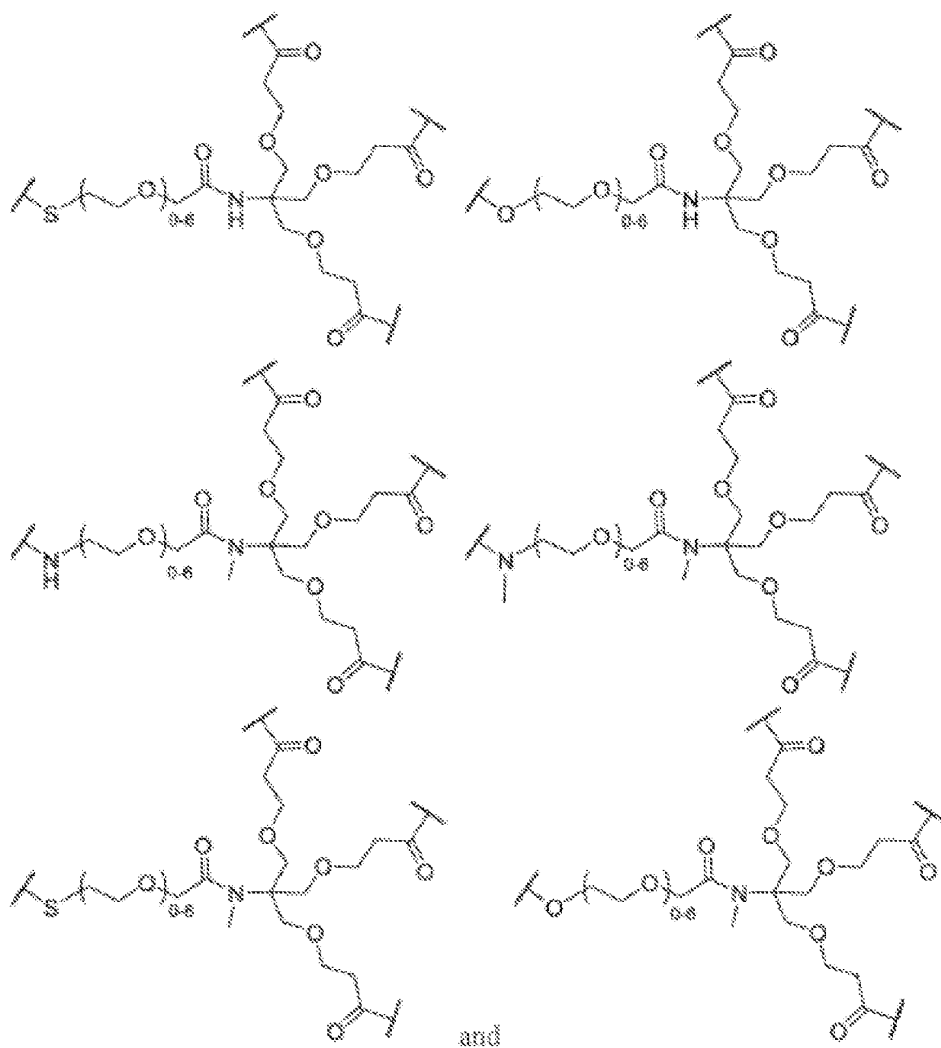


In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:

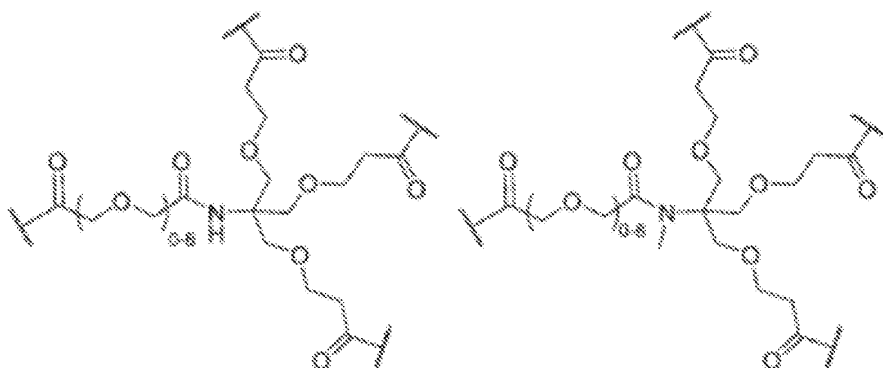


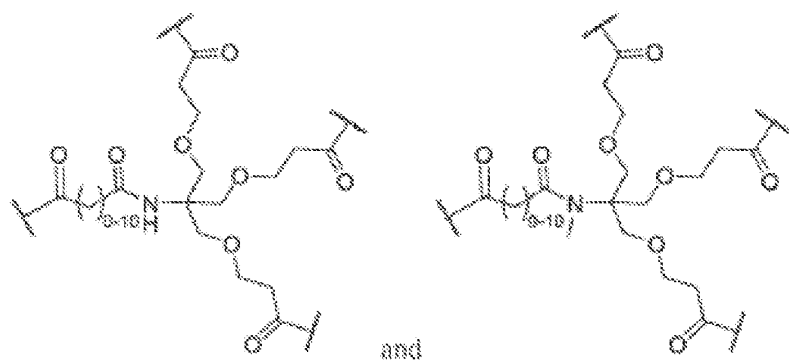
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



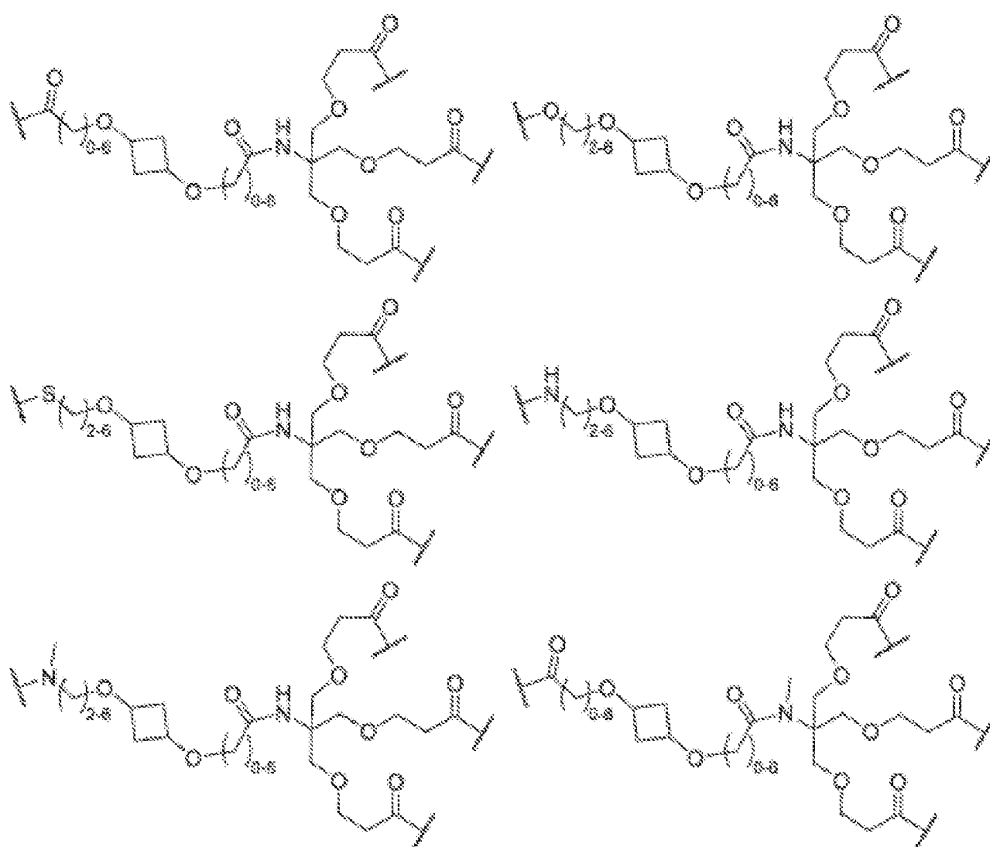


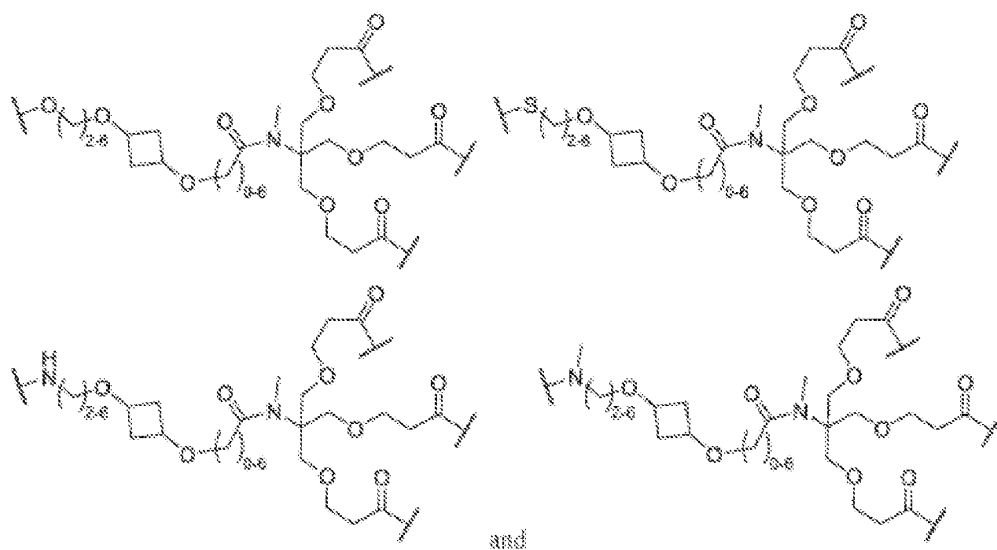
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



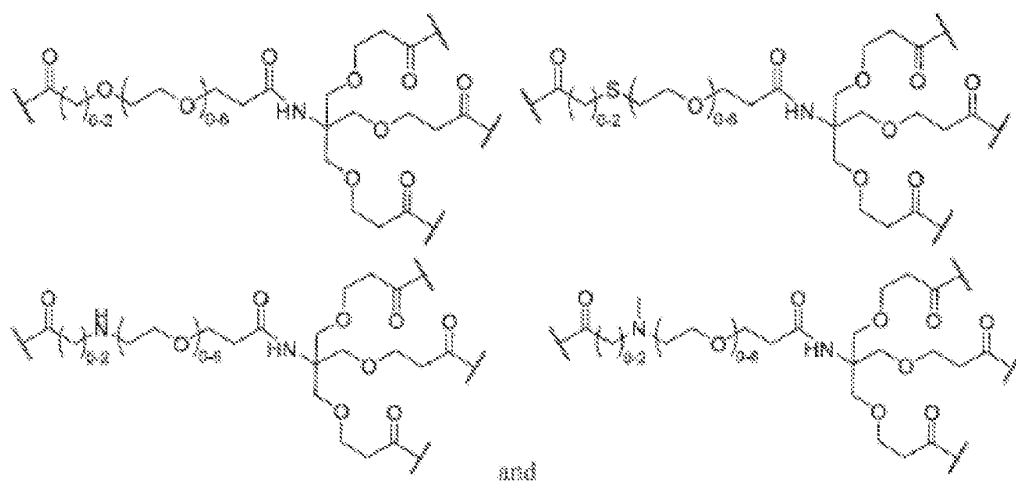


In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:

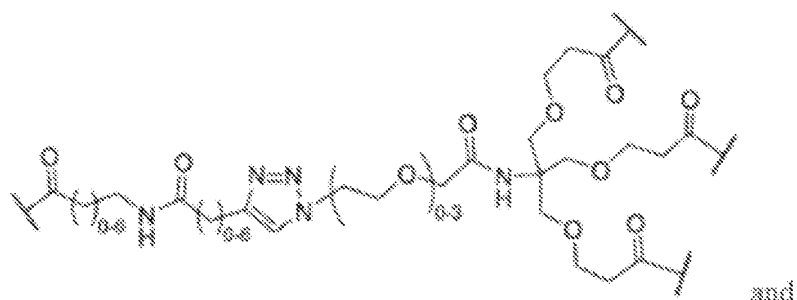
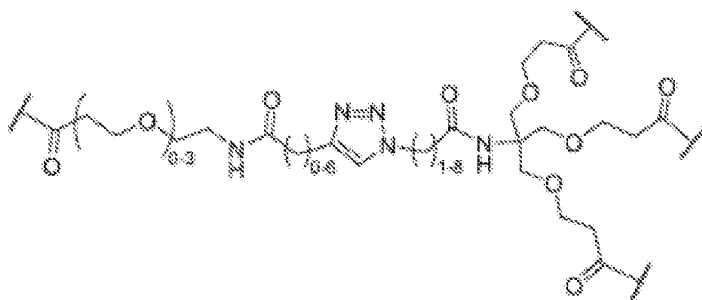




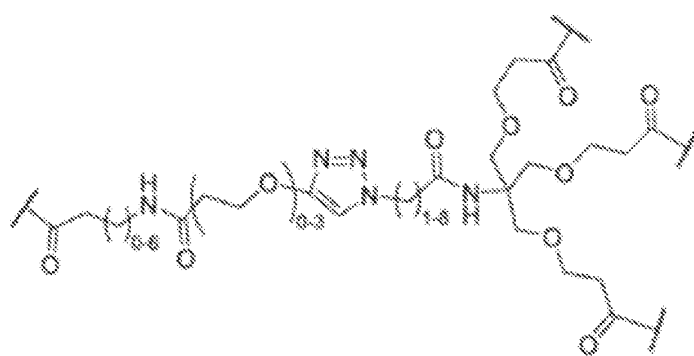
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



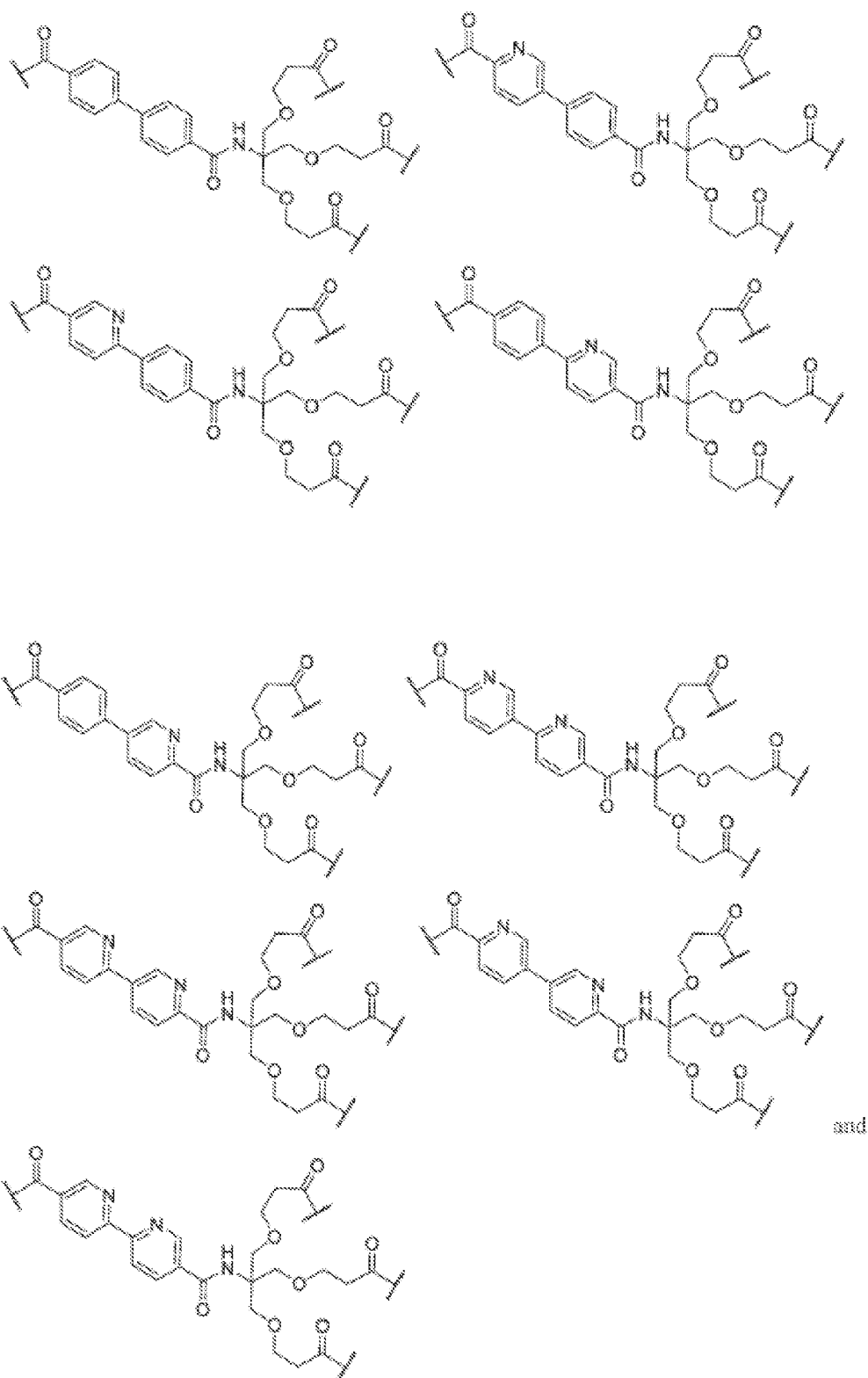
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



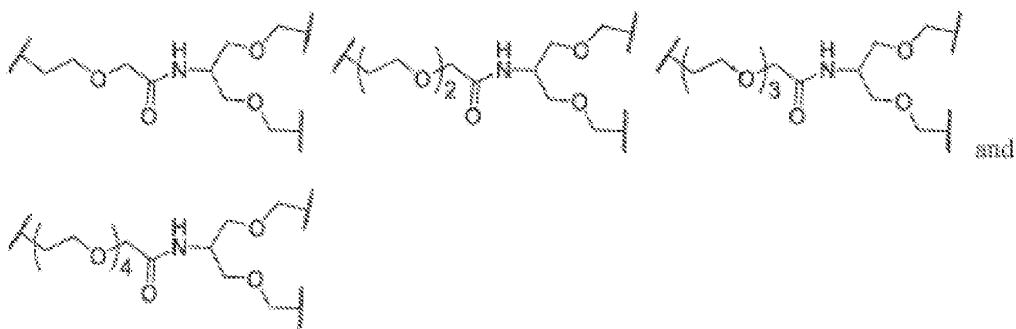
and



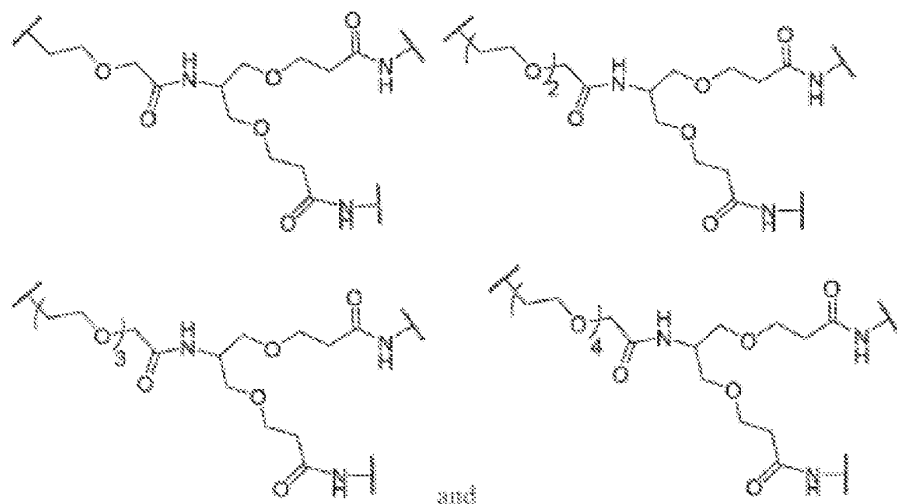
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



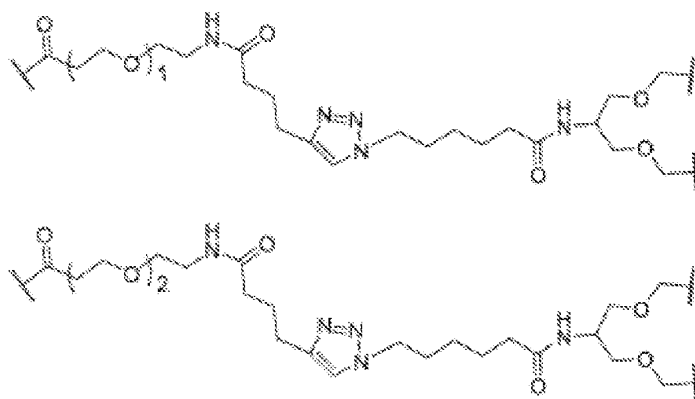
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



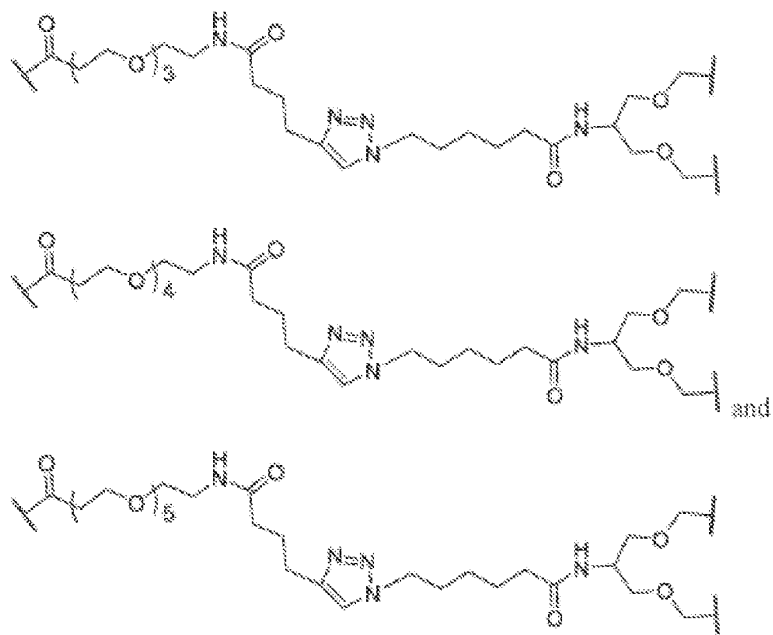
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:

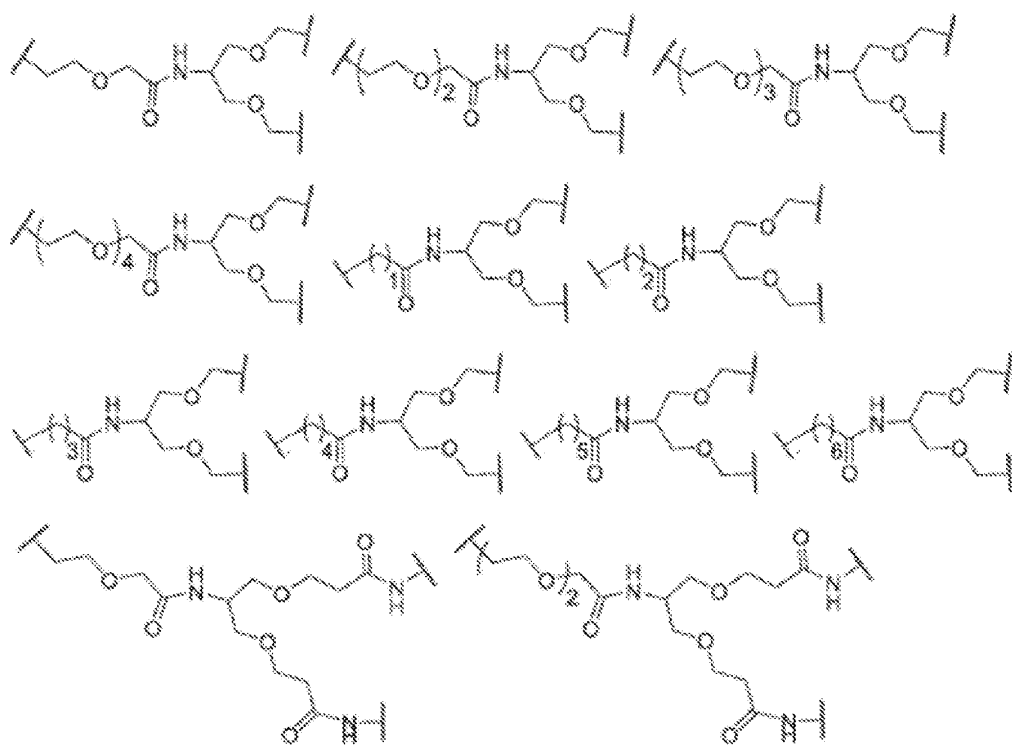


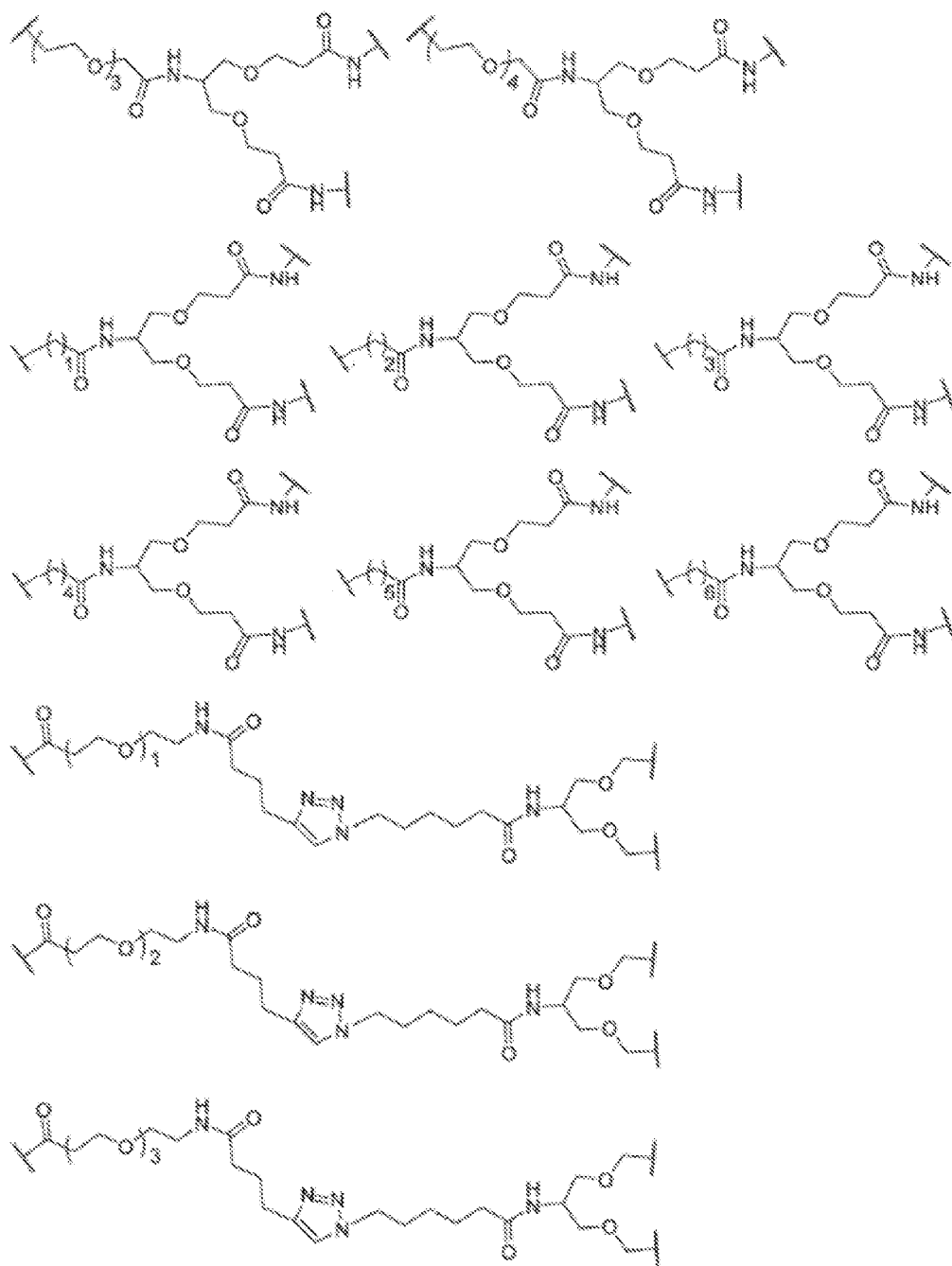
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are

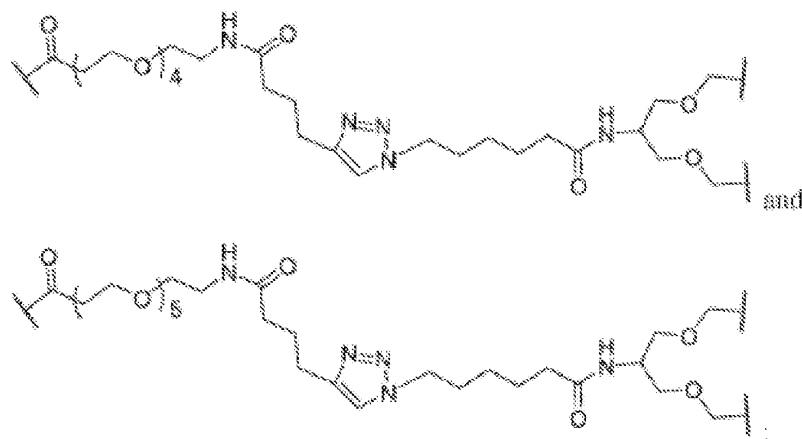


selected from:

In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:

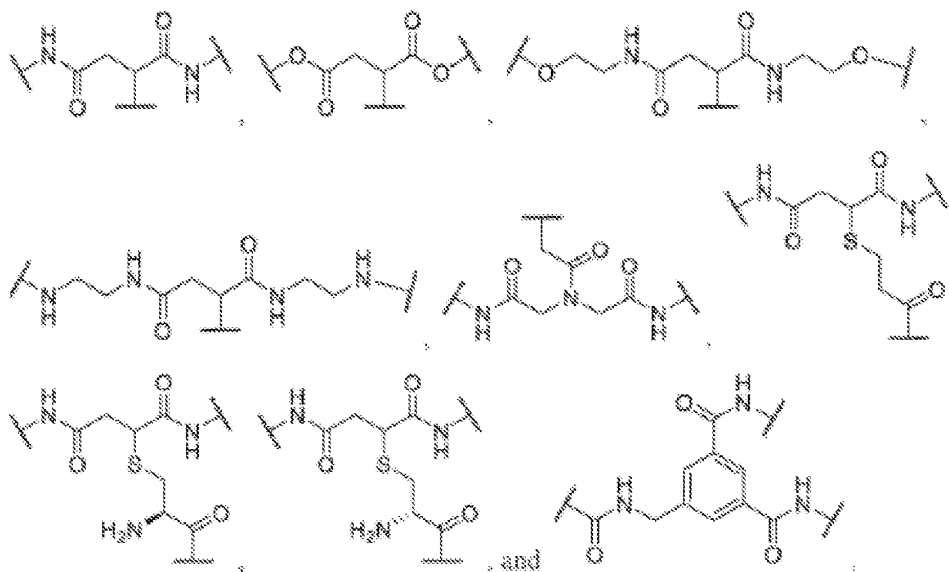




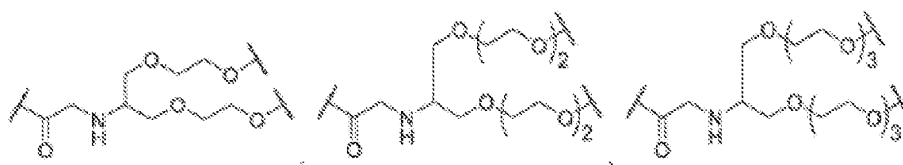


In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from: wherein each is optionally substituted with 1, 2, 3, or 4 substituents substituent selected from R²¹.

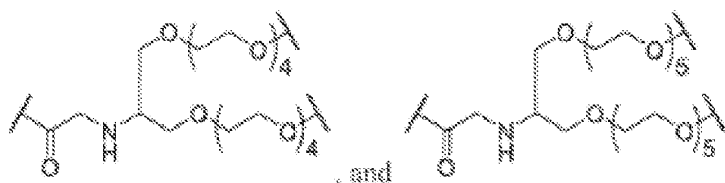
In certain embodiments -L¹-Con(L²-)_n is selected from:



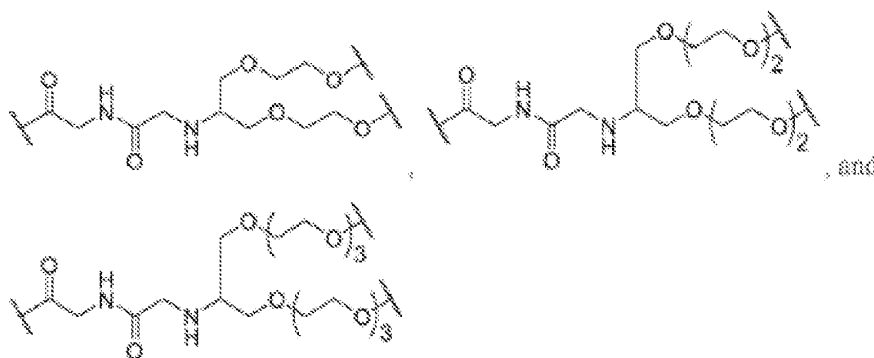
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



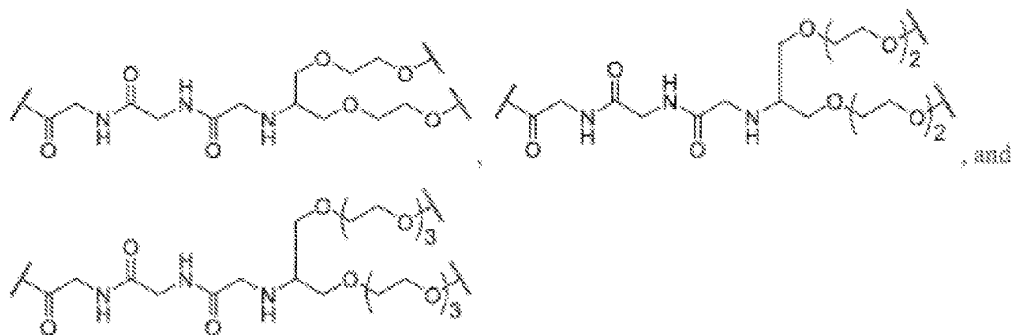
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



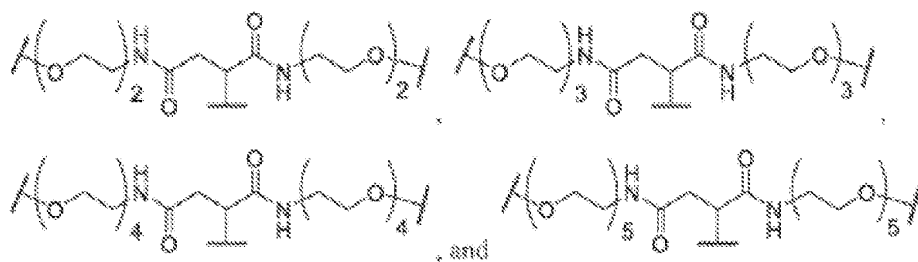
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



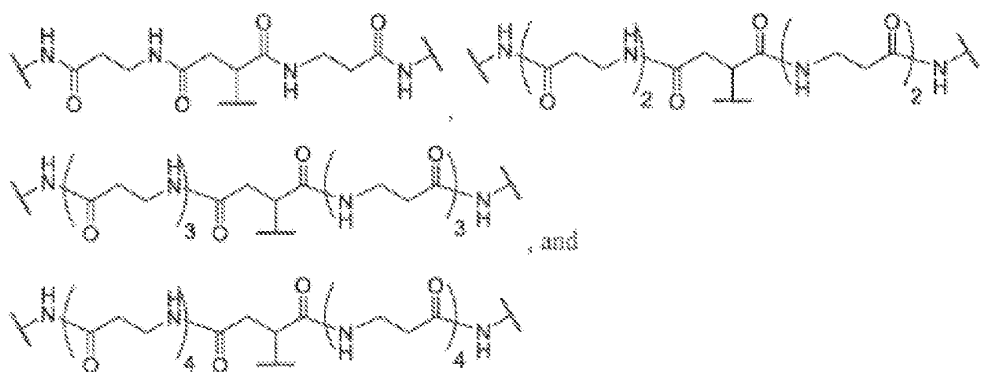
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



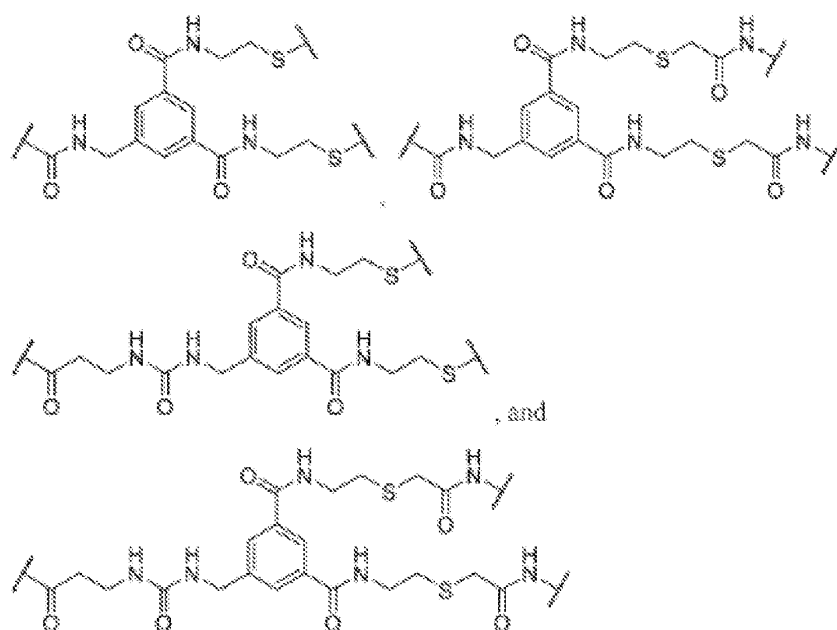
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



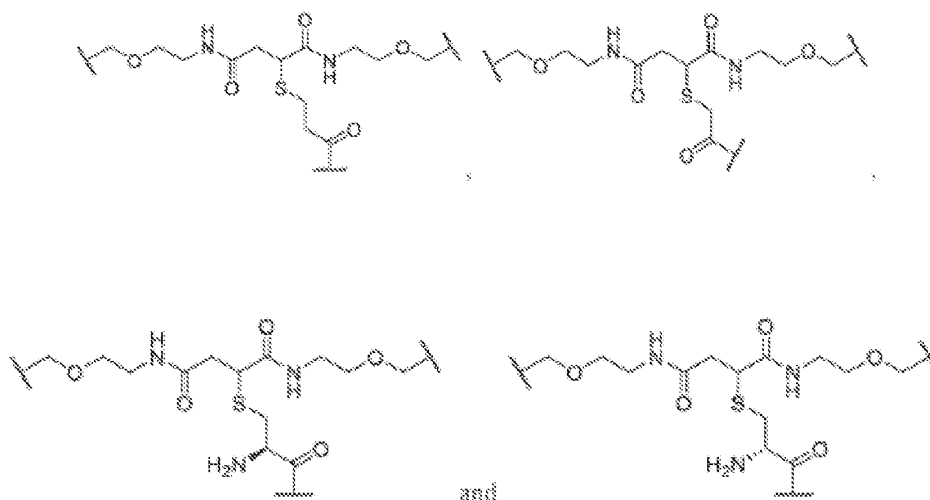
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



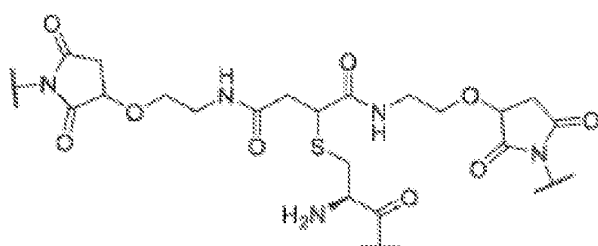
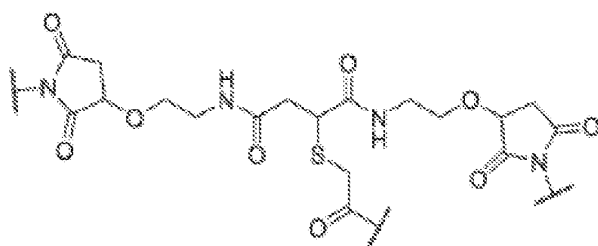
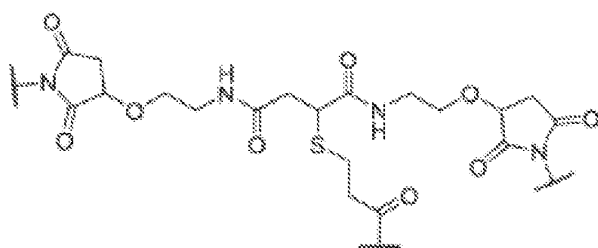
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



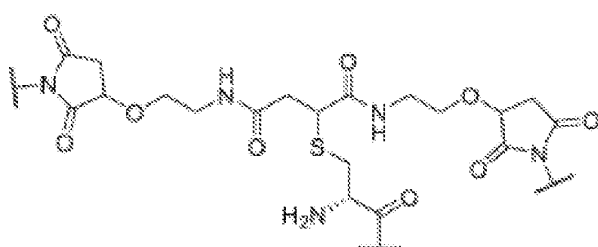
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



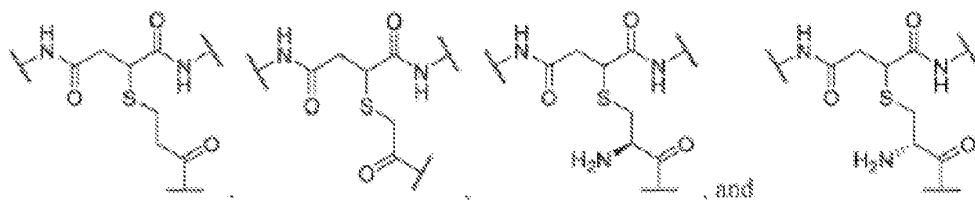
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



, and

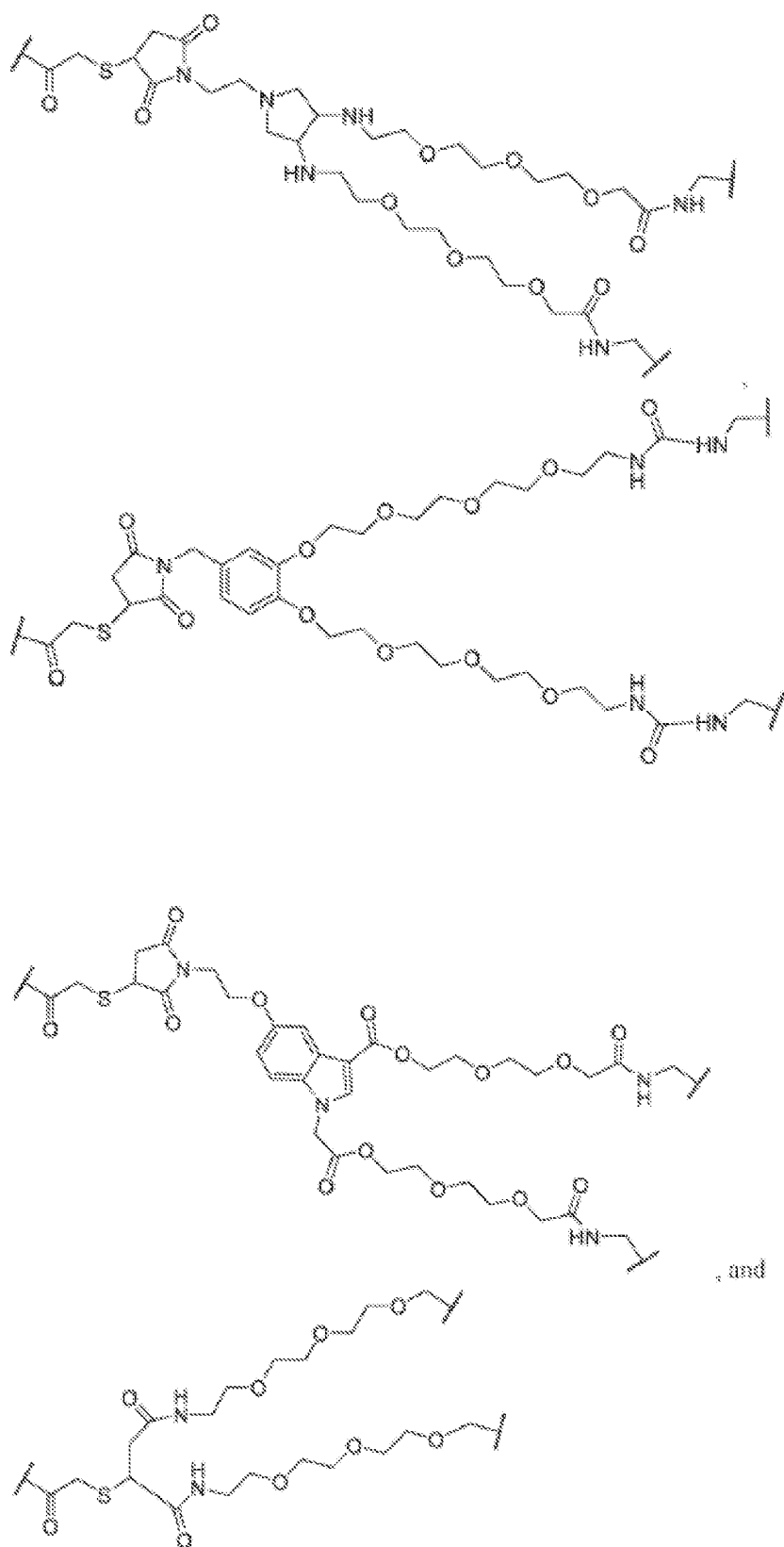


In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:

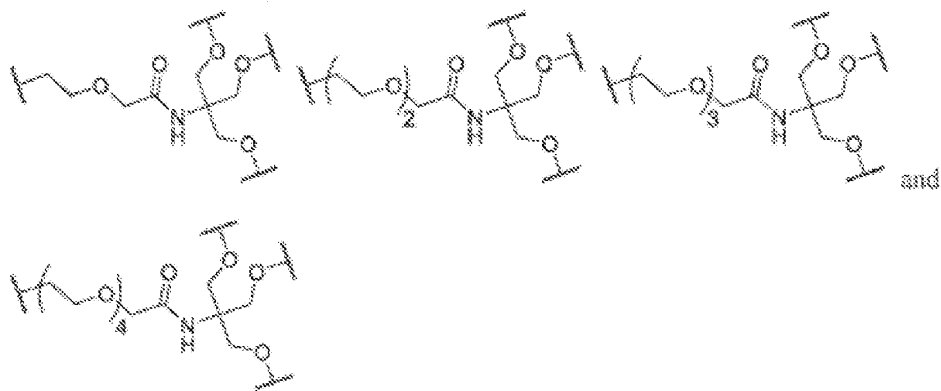


, and

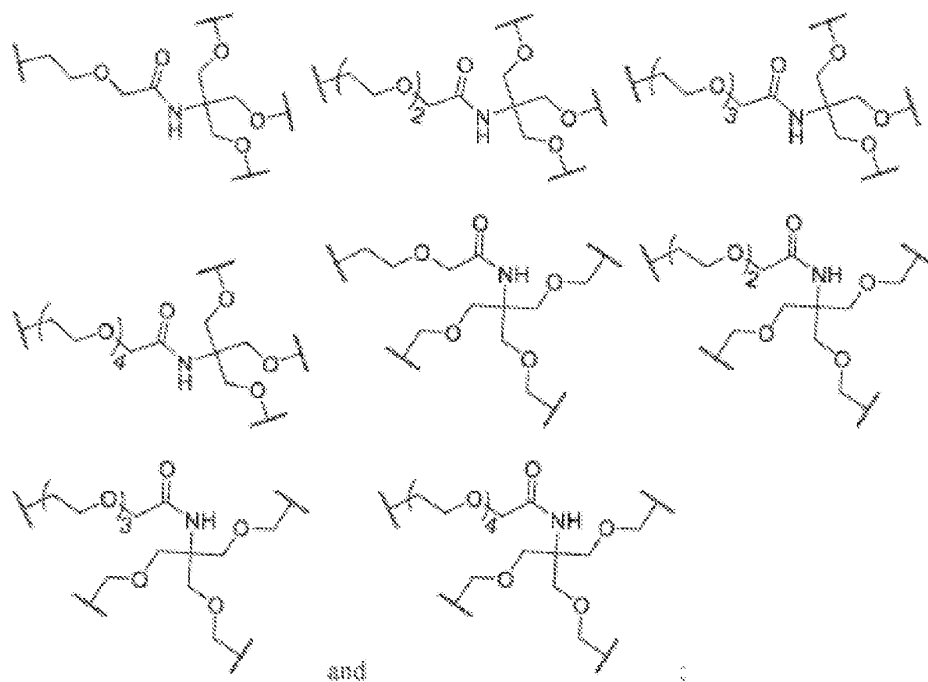
In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:



In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:

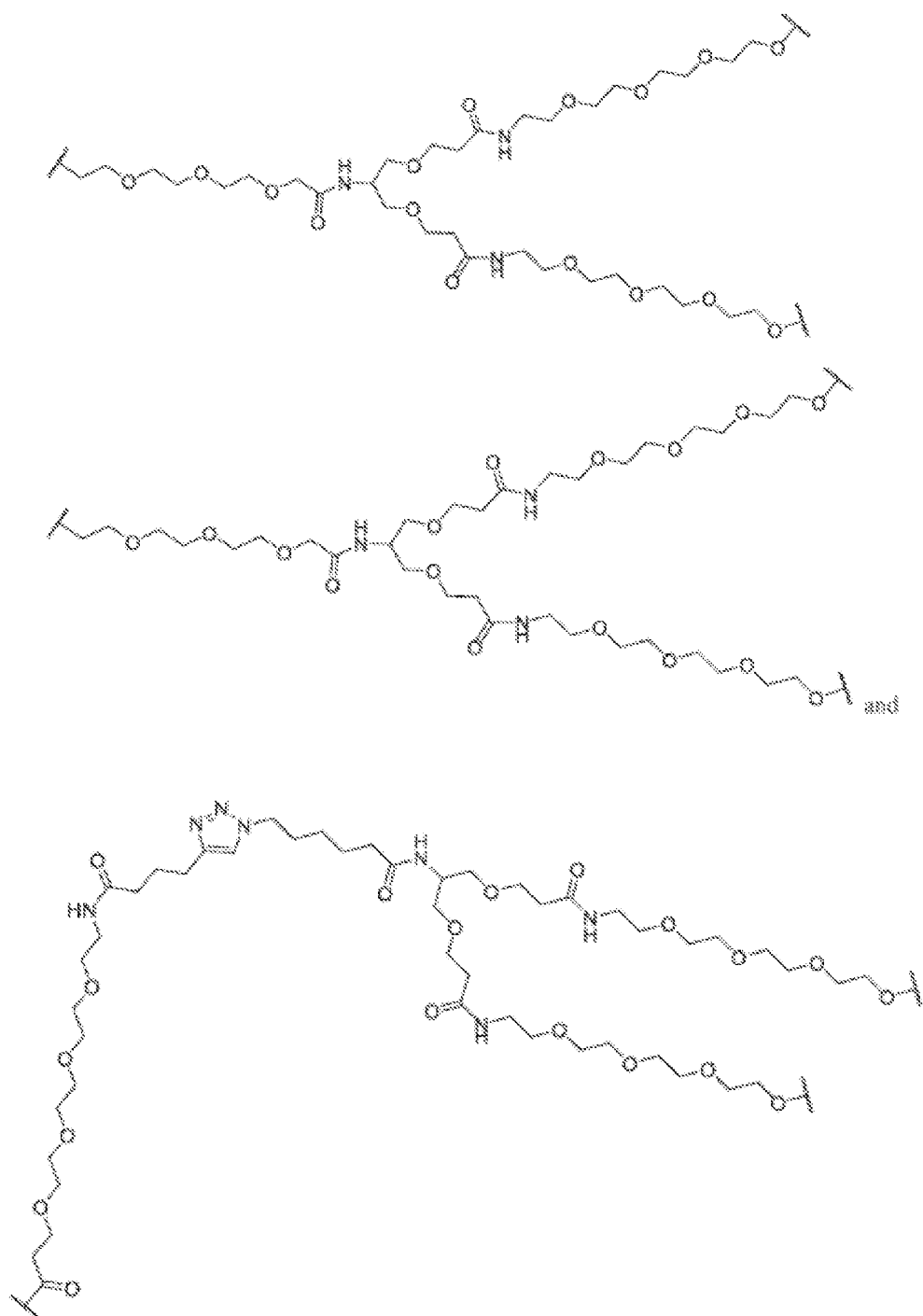


In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from:

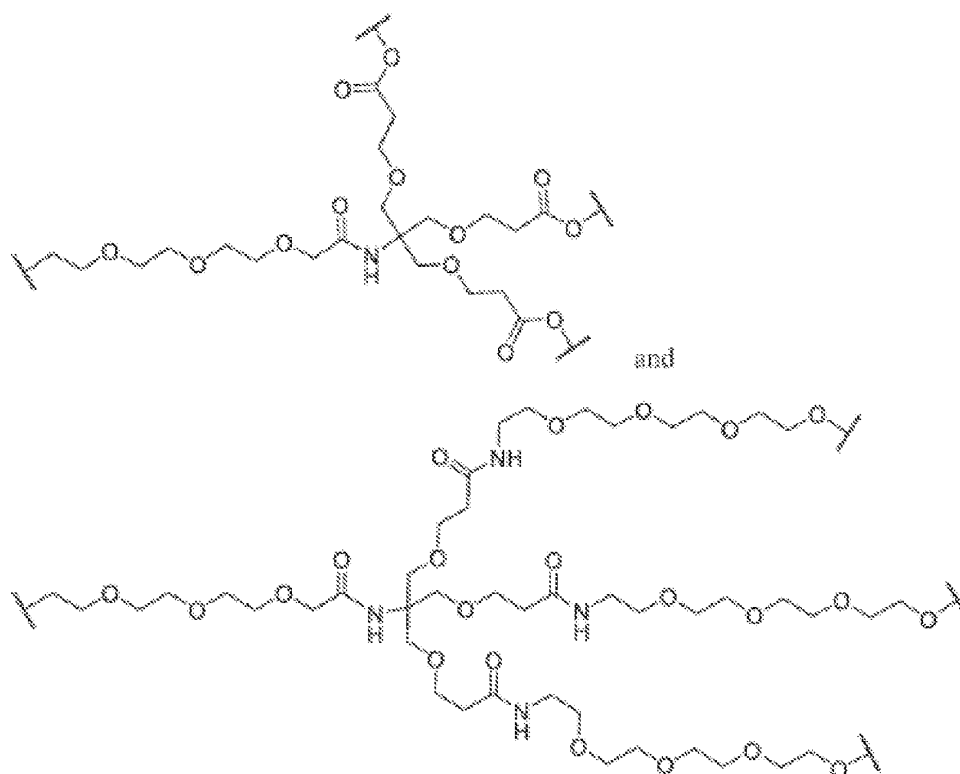


wherein each is optionally substituted with 1, 2, 3, or 4 substituents are selected from R²¹.

In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from

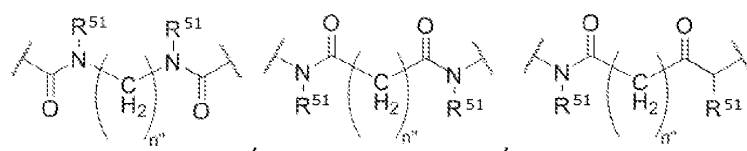


In certain embodiments Linker^C, Linker^D and/or -L¹-Con(L²-)_n, respectively, are selected from



In various embodiments, L^1 , L^2 , Linker^A , Linker^B , Linker^C and/or Linker^D are cyclic or acyclic moieties, and may be selected from the group consisting of:

a)

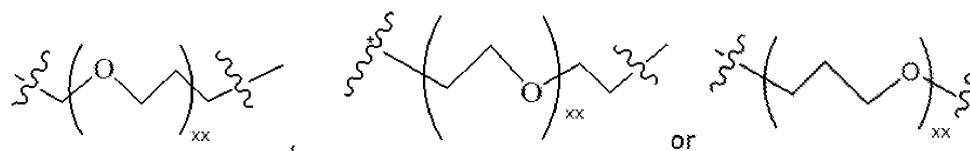


wherein:

R^{51} is H or C_1 - C_3 alkyl; and

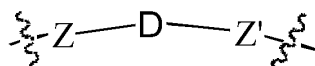
n'' is independently an integer ranging from 0 to 20; or

b)

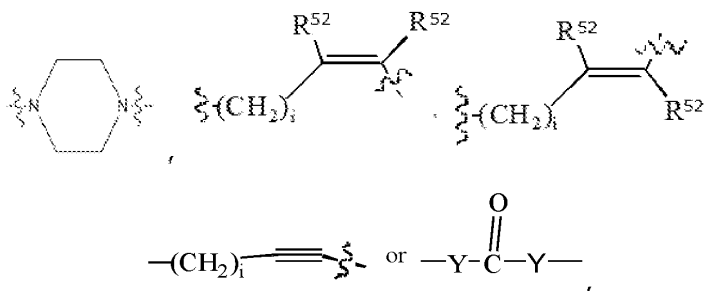


wherein xx is as defined herein; or

c)

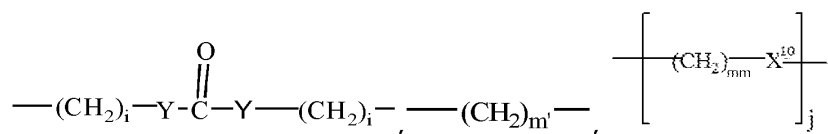


wherein:

Z and Z' are each independently a bond, $-(\text{CH}_2)_i\text{-O-}$, $-(\text{CH}_2)_i\text{-S-}$, $-(\text{CH}_2)_i\text{-N(R)-}$,each R^{52} is independently H or $\text{C}_1\text{-C}_3$ alkyl;each Y is independently a bond, O, S, or N-R; wherein R is H, or $\text{C}_1\text{-C}_3$ alkyl optionally substituted with 1-3 hydroxyl groups

each i is independently an integer from 0 to 100;

D is



or a bond,

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

i is as defined above

j is an integer from 1 to 100;

 m' is an integer from 1 to 100; mm is an integer from 1 to 100; X^{10} is O, S, or N-R;

y is as defined above;

R is H, or $\text{C}_1\text{-C}_3$ alkyl optionally substituted with 1-3 hydroxyl groups; or

d) $\text{C}_6\text{-18}$ aryl, $\text{C}_3\text{-18}$ heterocyclyl, $\text{C}_6\text{-18}$ biaryl, or $\text{C}_6\text{-18}$ heterobiaryl, each of which is optionally substituted by 1-6 substituents selected from the group consisting of F, Cl, Br, I, -ORG, -OC(O)N(RG)₂, -CN, -NO, -NO₂, -ONO₂, -CF₃, -OCF₃, -RG, -N(RG)₂, -SRG, -SORG, -SO₂RG, -SO₂N(RG)₂, and -SO₃RG, wherein each occurrence of RG is

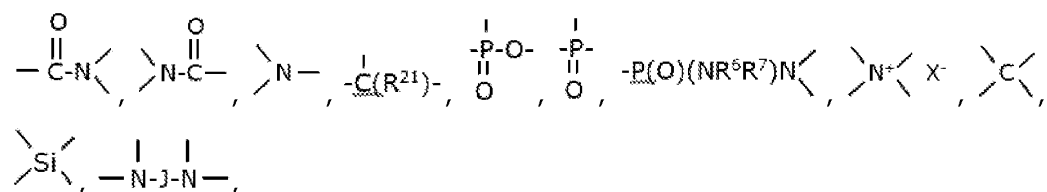
independently H, optionally substituted C1-10 alkyl, optionally substituted C3-10 cycloalkyl, optionally substituted C6-18 aryl, or optionally substituted C5-18 heteroaryl.

L¹, L², Linker^A, Linker^B, Linker^C and/or Linker^D may also be combinations of the groups a) through d).

Con

The structural element Con of the compounds of the present invention serves as a branching point to connect one anti-β₁ adrenergic receptor antibody binding moiety A with two or three asialoglycoprotein receptor binding moieties. The requirements for Con are therefore that it can form 1 covalent bond with L¹ or A and two or three covalent bonds with L² or AG wherein the covalent bonds are stable under physiological conditions.

Con is preferably selected from the group consisting of alkyl, heteroalkyl



alkenyl, haloalkyl, aryl, heterocycle, and heteroaryl, each of which has three or more, preferably three or four valences bonded to L¹, L², A and/or AG, respectively, and is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

wherein X⁻ is a pharmaceutically acceptable anionic group, for example Br⁻ or Cl⁻;

J is a direct bond or a hydrocarbon with 1 to 10 carbon atoms, preferably –(CH₂)_e–, wherein e is 1 to 10, more preferably 2 to 5 and

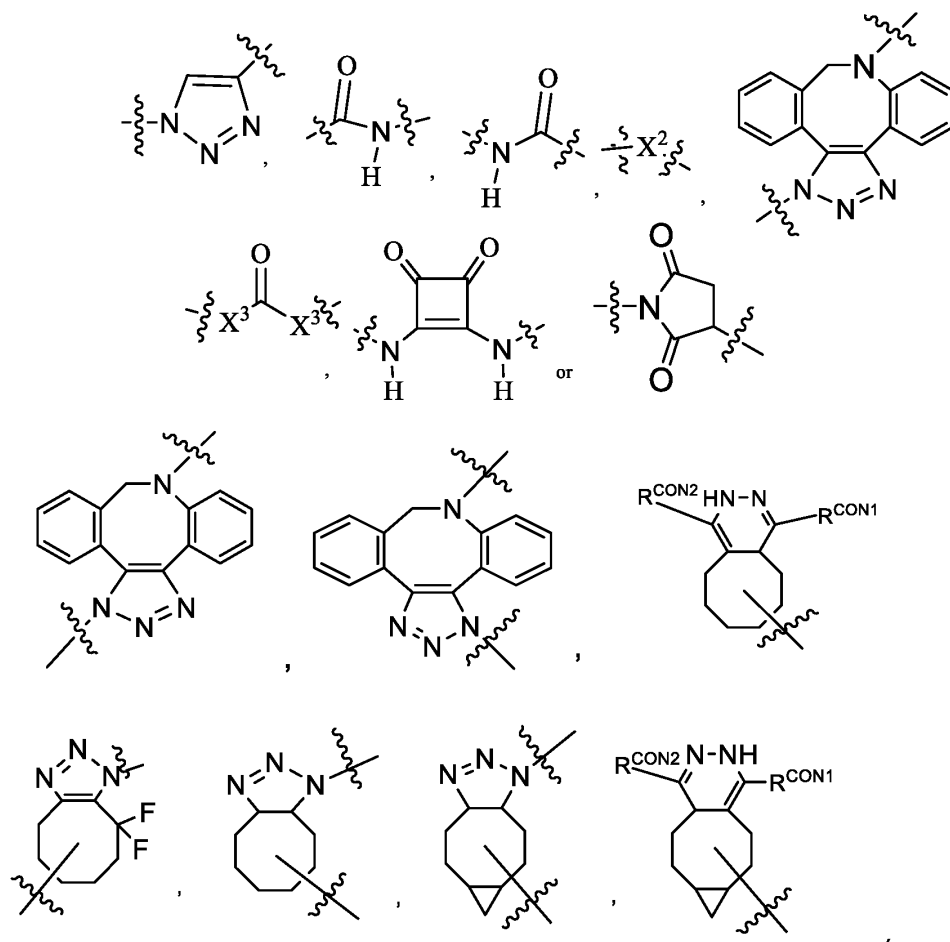
all other variables are as defined herein.

Preferably, R⁶, R⁷ and R²¹ of Con are hydrogen or C1-C3 alkyl.

In a preferred embodiment Con is a hydrocarbon with 1 to 10 carbon atoms or a heterocycle with 4 to 8 ring members, wherein the heterocycle may be saturated or unsaturated, aromatic or aliphatic and comprise up to 4 heteroatoms as ring atoms, wherein the heteroatoms are selected from the group consisting of nitrogen, oxygen and sulfur and wherein in the hydrocarbon or the heterocycle one hydrogen atom is substituted by linker L¹ or by the group A-T- and n hydrogen atoms are substituted by linker L² or by the group AG. The heterocycle may further be substituted as permissible by valence with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl. Preferably Con is a hydrocarbon with 1 to 10 carbon atoms or a heterocycle with 5 to 7 ring members, wherein the heterocycle may be

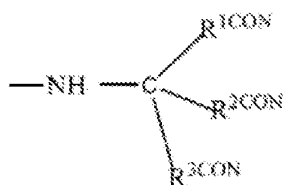
saturated or unsaturated, aromatic or aliphatic and comprise up to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur.

In one embodiment Con is selected from the group consisting of



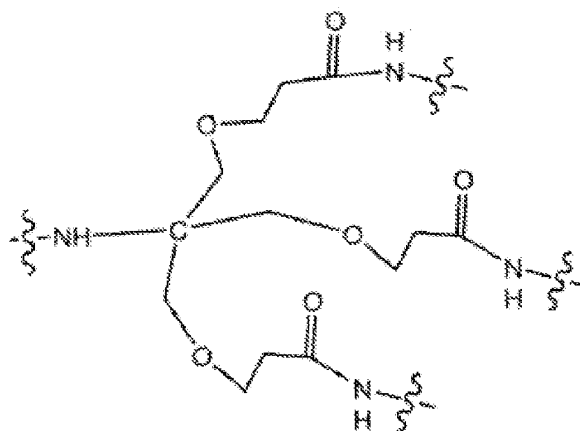
wherein R^{CON1} and R^{CON2} are each independently H, methyl or a bond (for attachment to another moiety) and one or more further linkers, A or AG may be bonded to these groups Con by substituting one or more hydrogen atoms.

In another preferred embodiment Con is



wherein 1CON, 2CON and 3CON are selected from the groups consisting of H and $-(CH_2)_f-$, with f is an integer from 1 to 10, preferably one to 5 and most preferably 1 to 3, with the proviso that at least two of 1CON, 2CON and 3CON are not hydrogen

In one embodiment Con is



In an even more preferred embodiments Con is selected from the group consisting of $-\text{CH}_{(3-n)}(\text{CH}_2-)_{n-}$, wherein n is 2 or 3 and diazacycloheptane. It is most preferred that Con is $-\text{CH}_{(3-n)}(\text{CH}_2-)_{n-}$.

In a preferred embodiment of the present invention one terminal end of L^1 is a $-\text{NH}-$ residue, by which it is connected to Con and the one terminal end of the $n L^2$ linker are $-\text{O}-$ residues, by which the linkers L^2 are connected to Con.

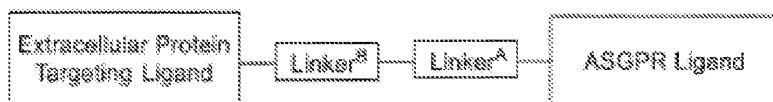
It is further noted that any connector or linker described herein may be connected to the remainder of the molecule of the compounds of the present invention at positions which are represented as being linked to another group using the symbol $*$ or the symbol

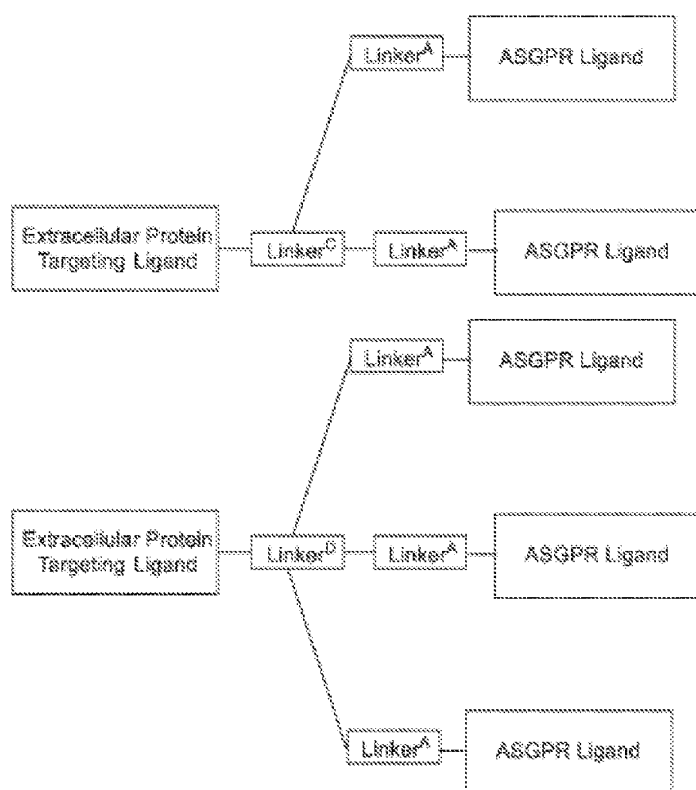


Where that symbol is not used, the linker may be at one or more positions of a moiety where a hydrogen atom is located and can be substituted for a bond.

General structures of Formulae (I), (II) and (III)

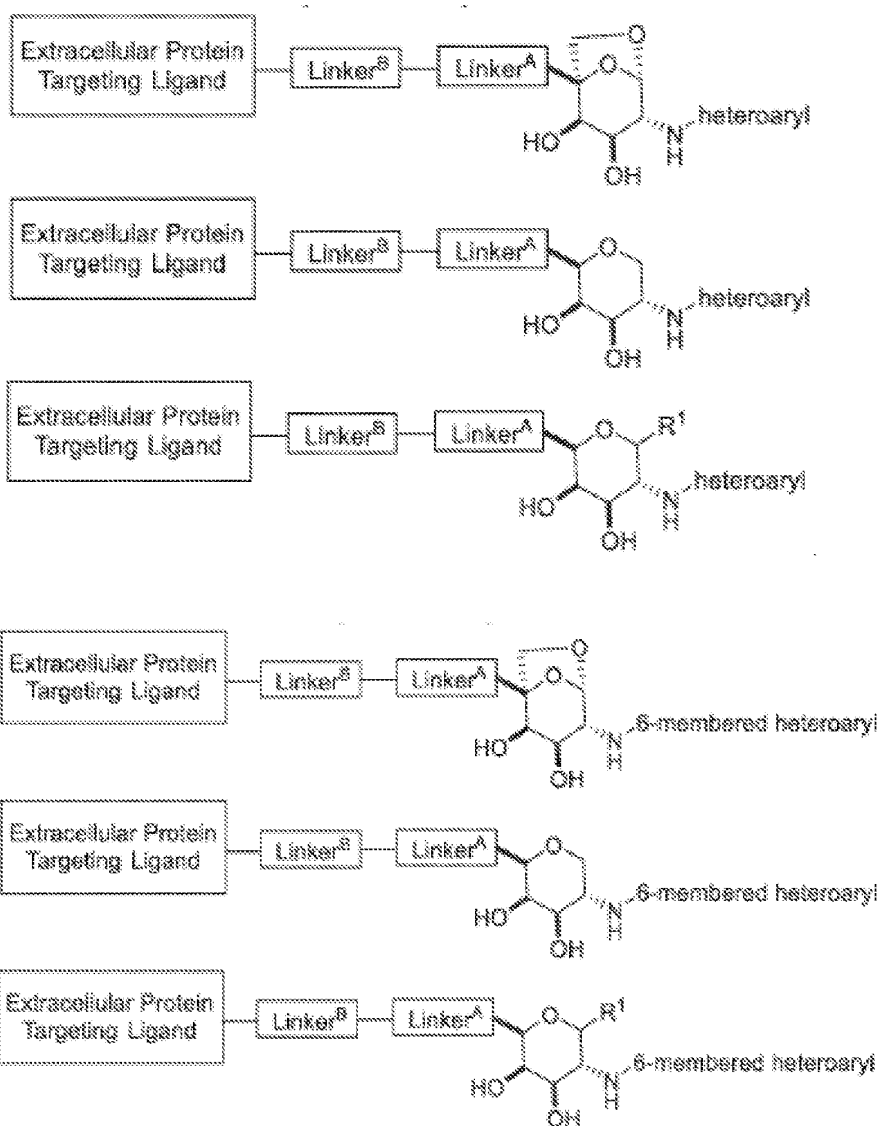
In one embodiment, the compounds of Formulae (I), (II) or (III) have one of the following structures, wherein the designation "ASGPR Ligand" refers to the group AG and the designation "Extracellular Protein Targeting Ligand" refers to the partial structure "A-T-" of Formulae (I), (II) and (III) and Linker^A, Linker^B, Linker^C and Linker^D are as defined herein:

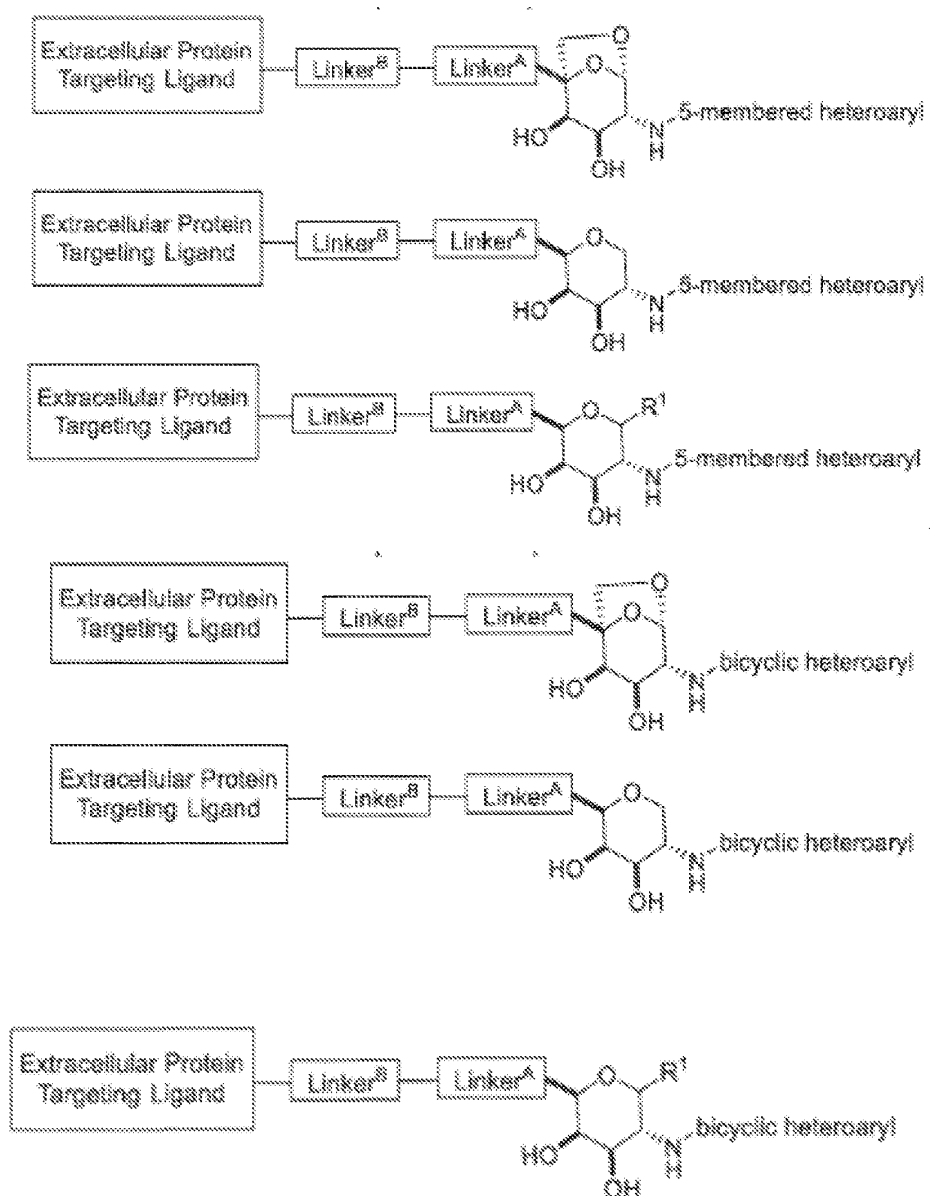


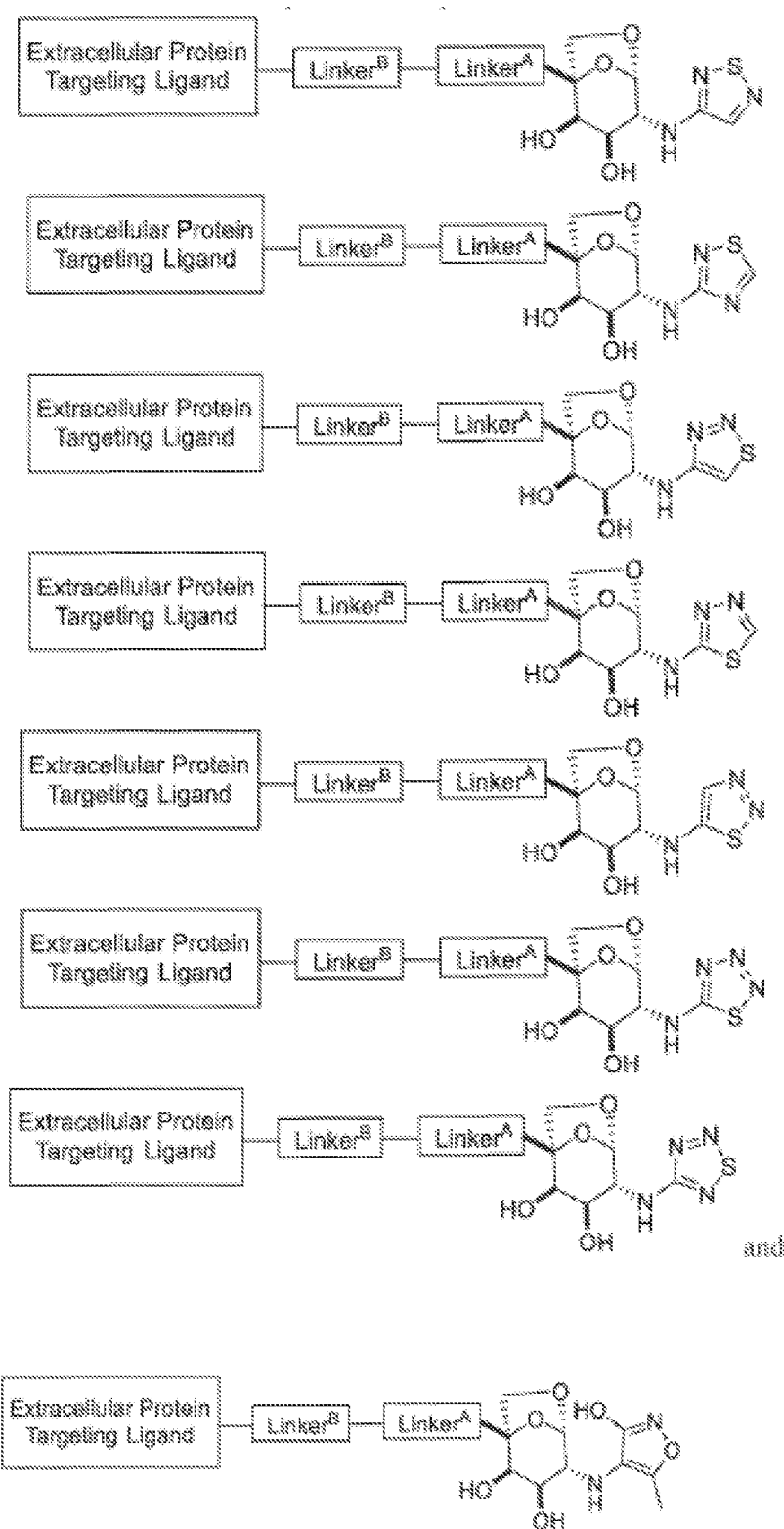


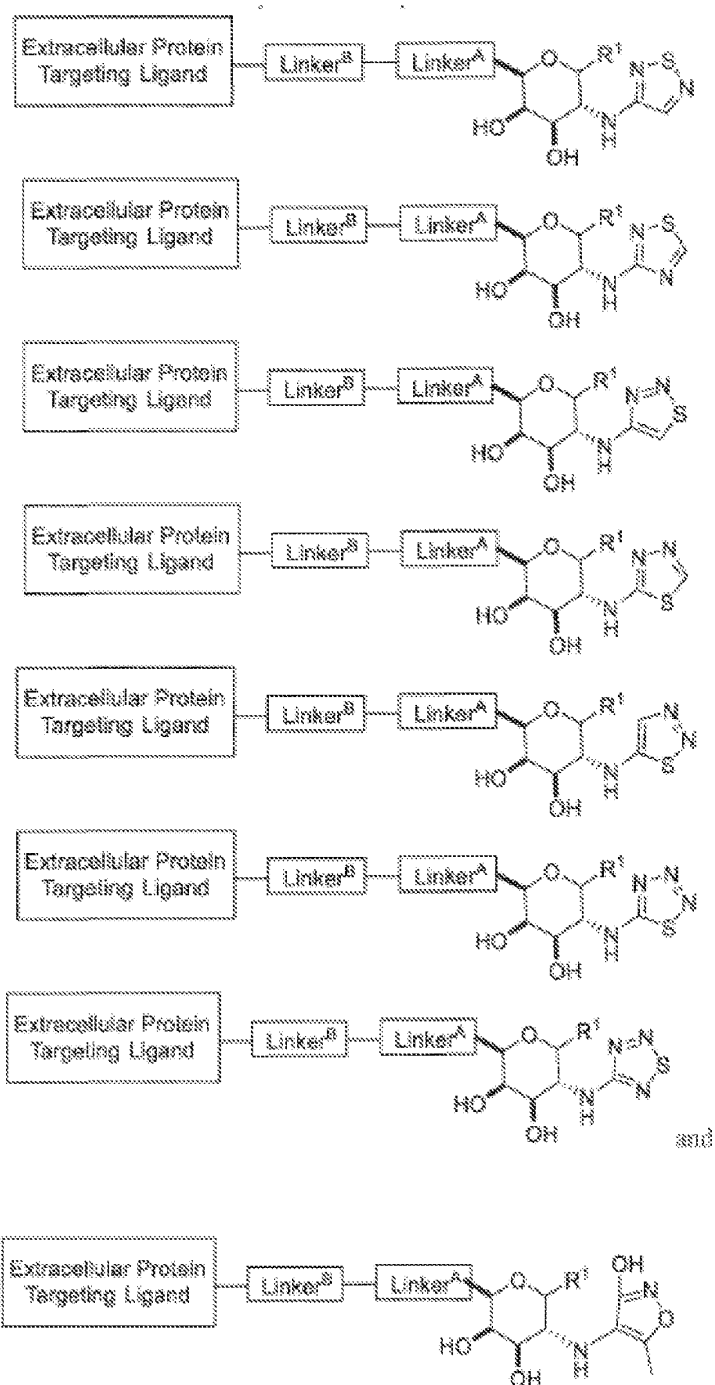
A. Galactose-Based ASGPR-Binding Cellular Receptor Binding Moieties AG

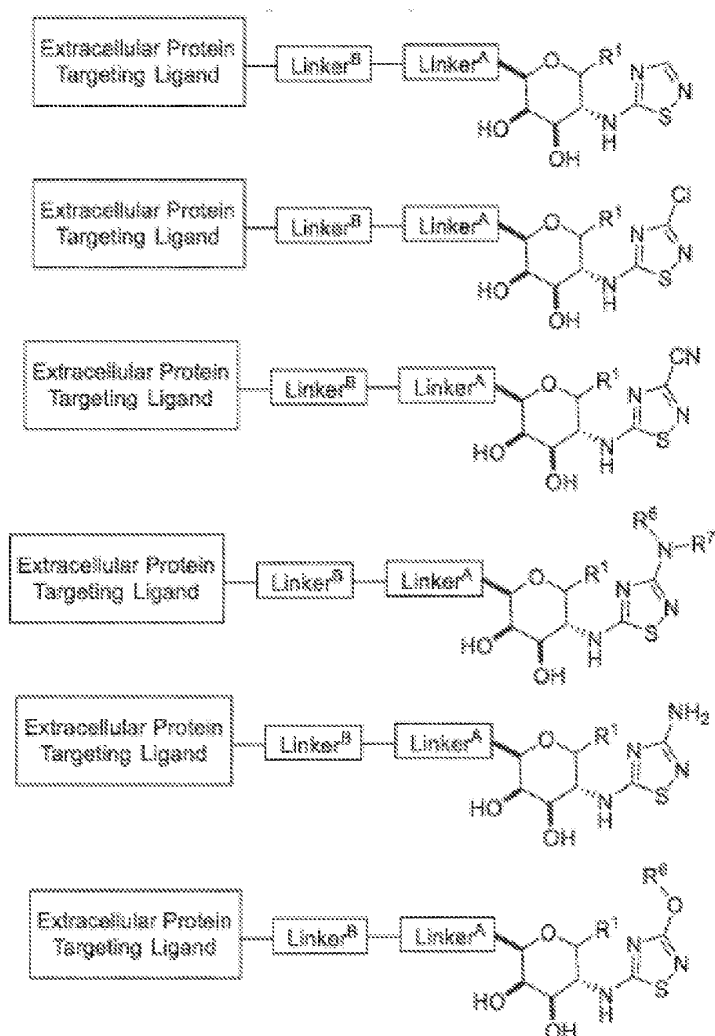
In the following formulae examples of the structures of Formulae (I), (II) and (III) are disclosed in which AG is a galactose derivative. The partial structures of galactose and its derivatives in these formulae may be used as group AG in any of Formulae (I), (II) and (III). The partial structure marked as "Extracellular Protein Targeting Ligand" is as defined above. Linker^A, Linker^B, Linker^C and Linker^D are as defined herein. In certain embodiments, the compounds of Formulae (I) or (III) are selected from:



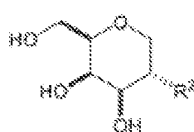




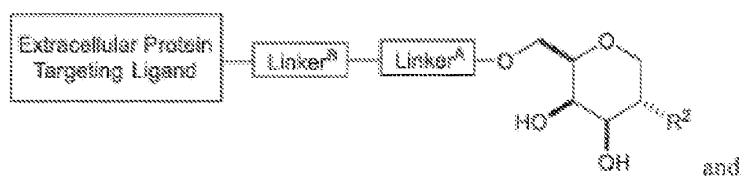


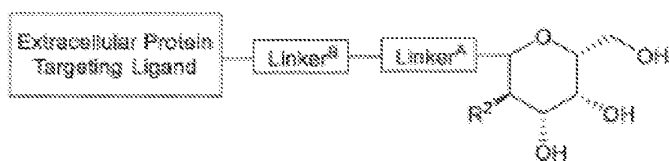


In various embodiments, AG is derived from the partial structure



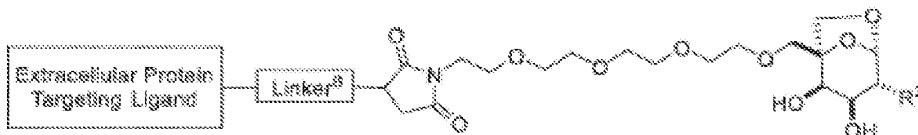
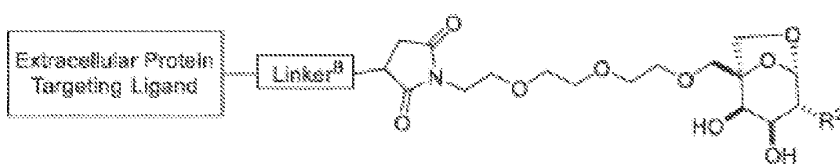
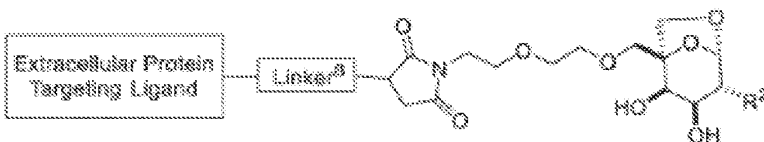
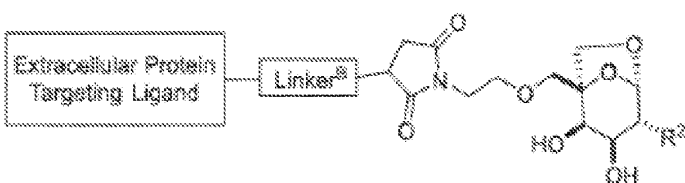
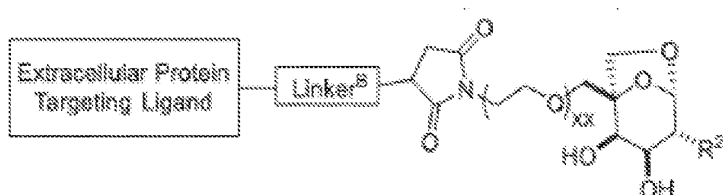
then non-limiting examples compounds of Formulae (I) and (III) include:

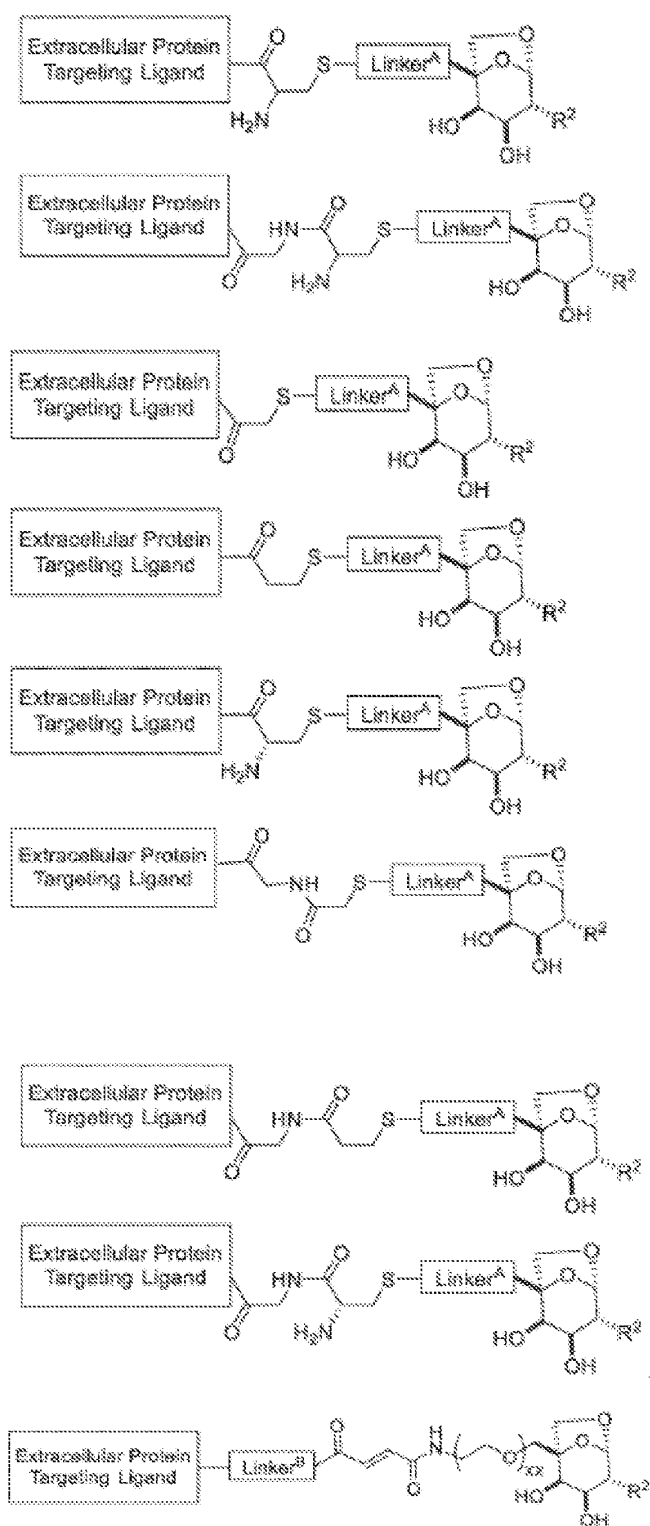


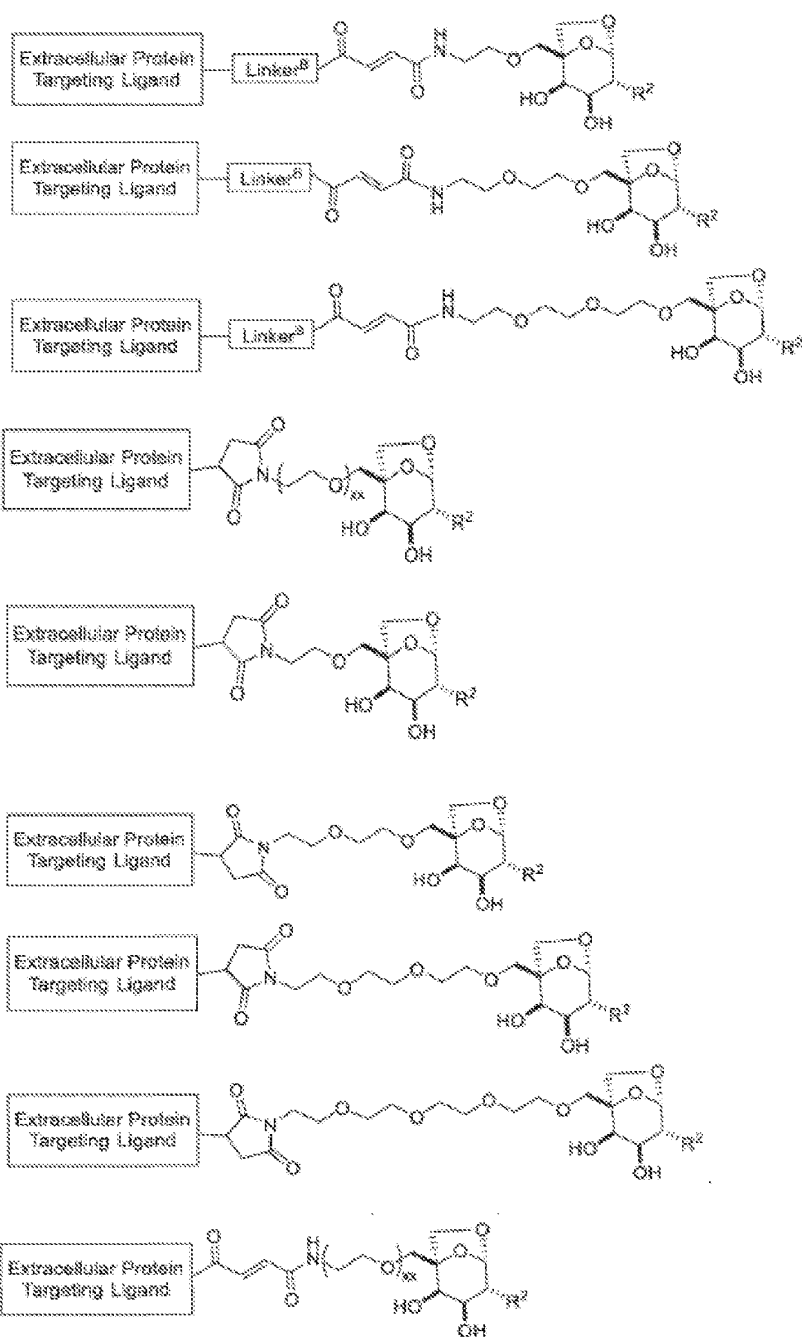


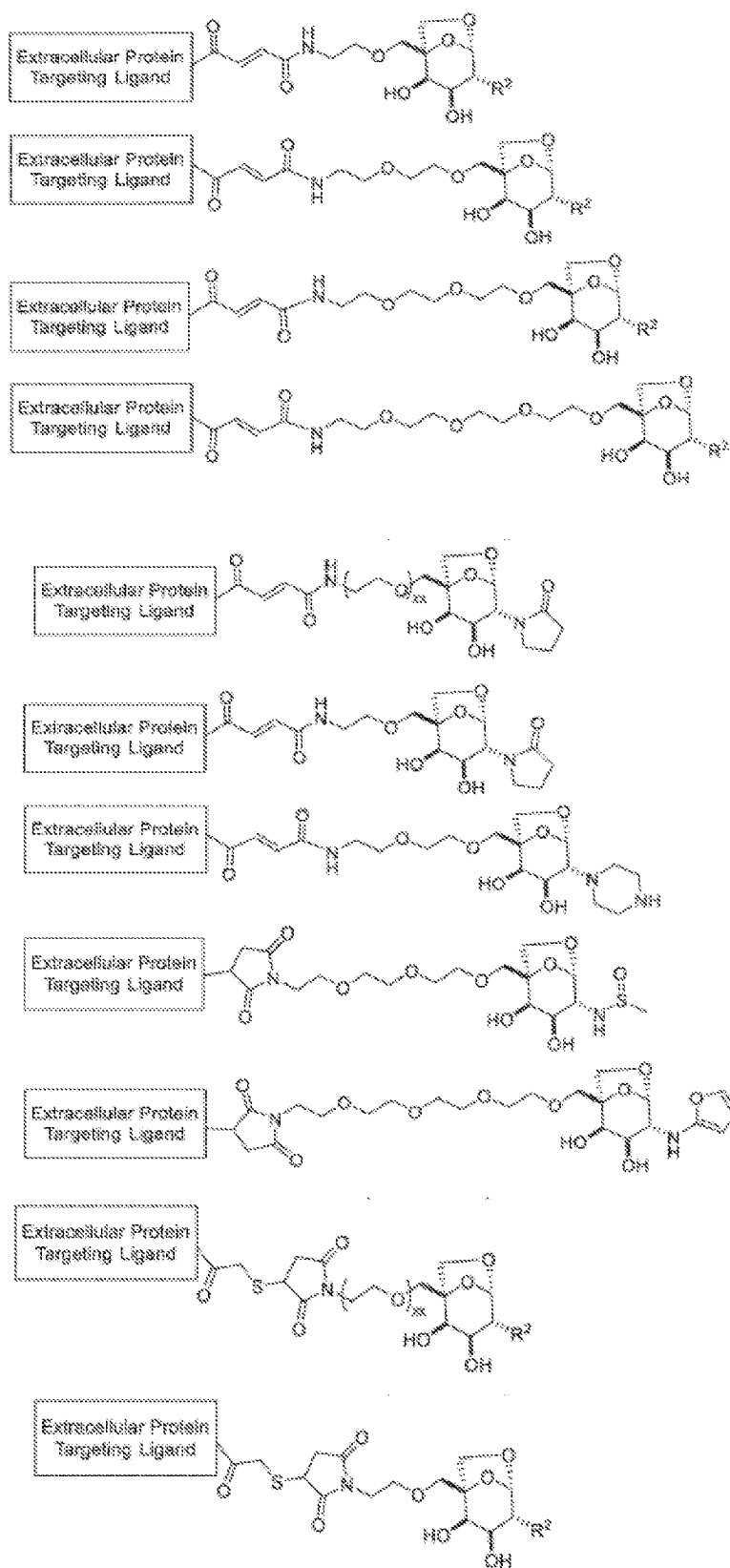
or the bi- or tri- substituted versions thereof or pharmaceutically acceptable salts thereof, where the bi- or tri- substitution refers to the number additional galactose derivatives attached to a linker moiety, i.e. n in Formula (II).

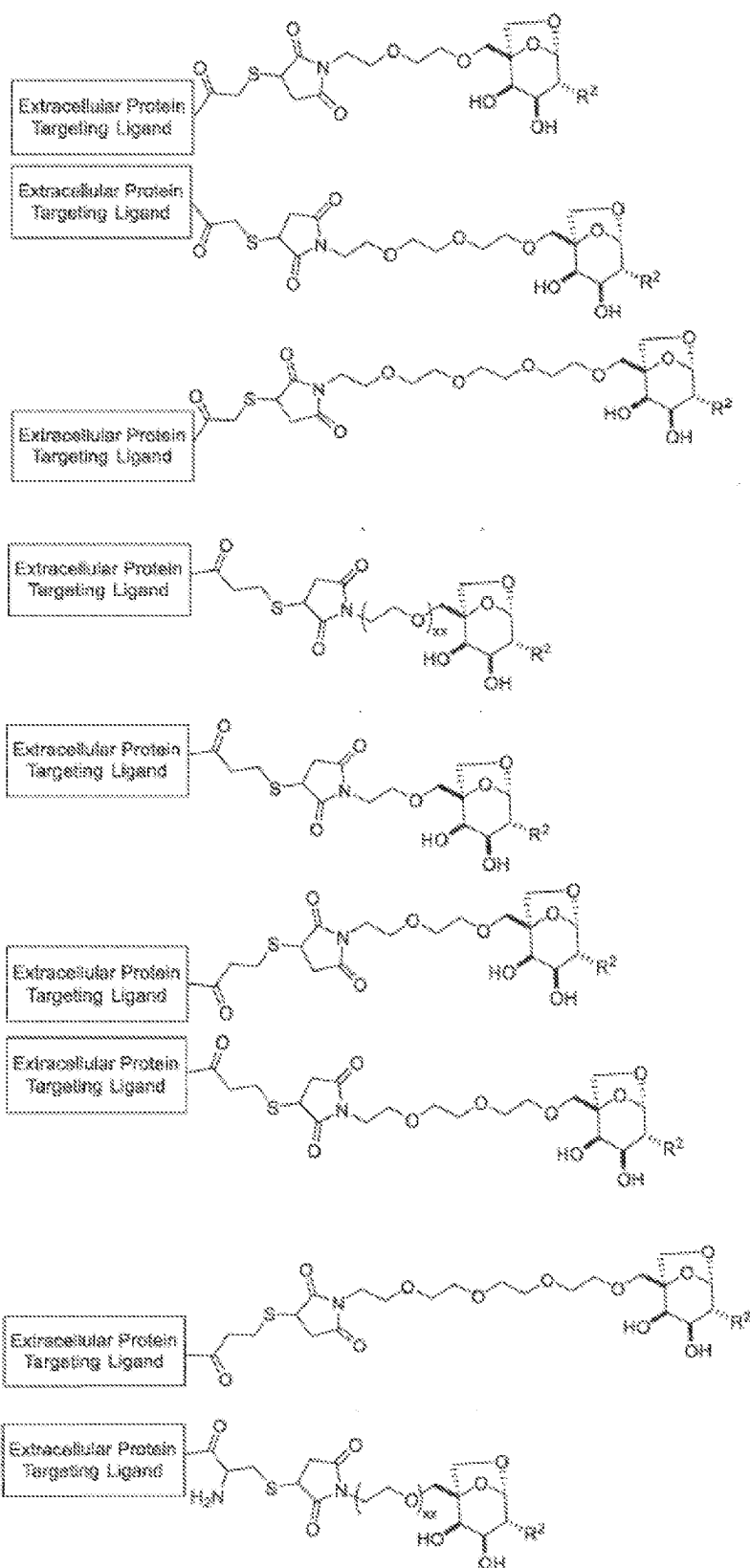
In certain embodiments, the compounds of Formulae (I) or (III) are selected from:

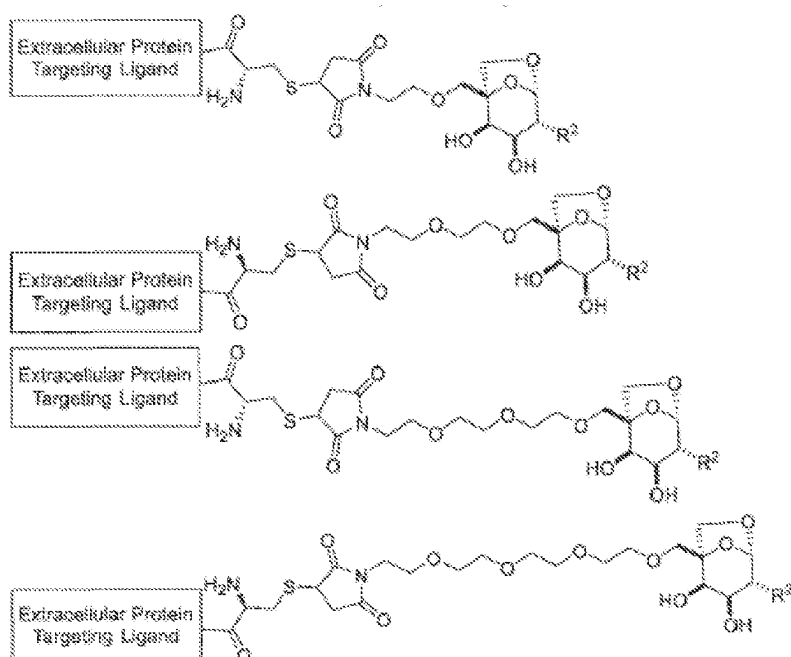


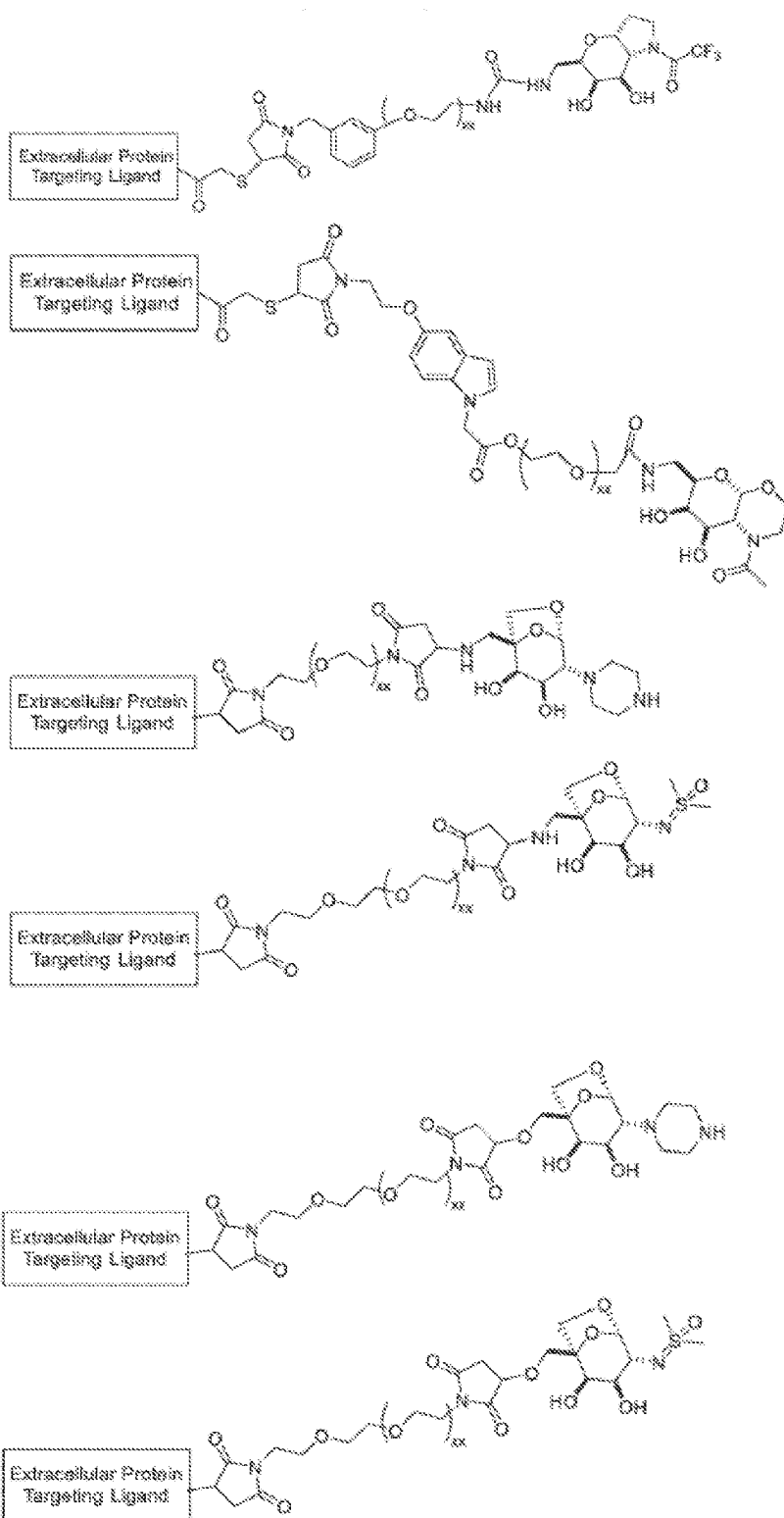


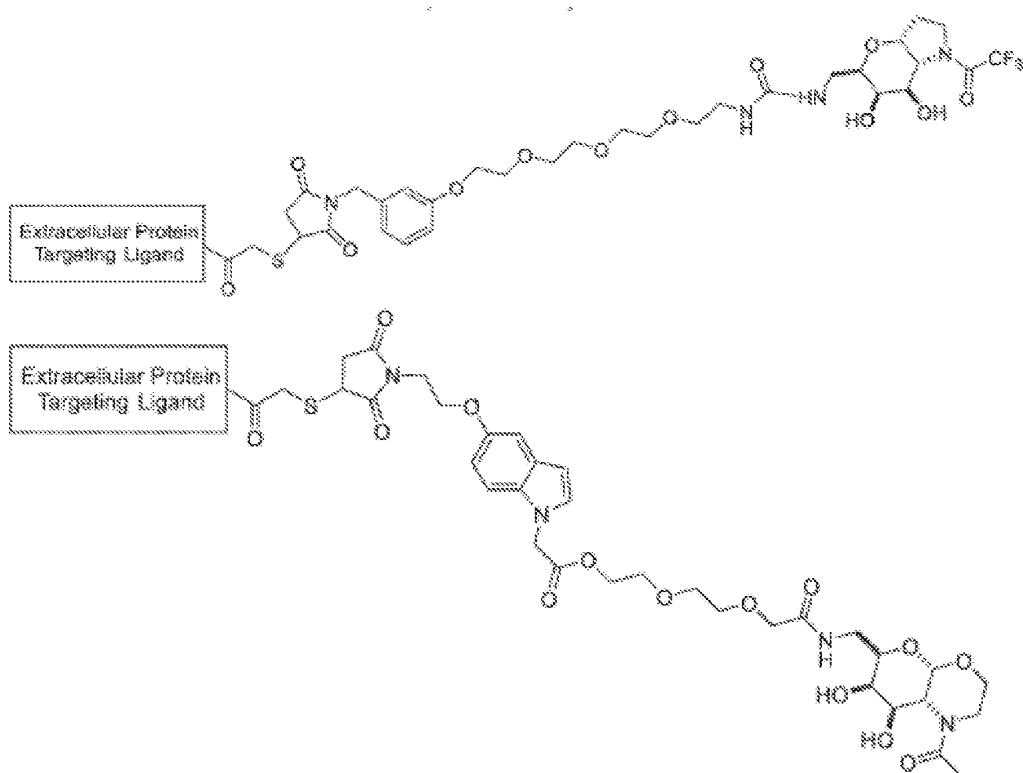


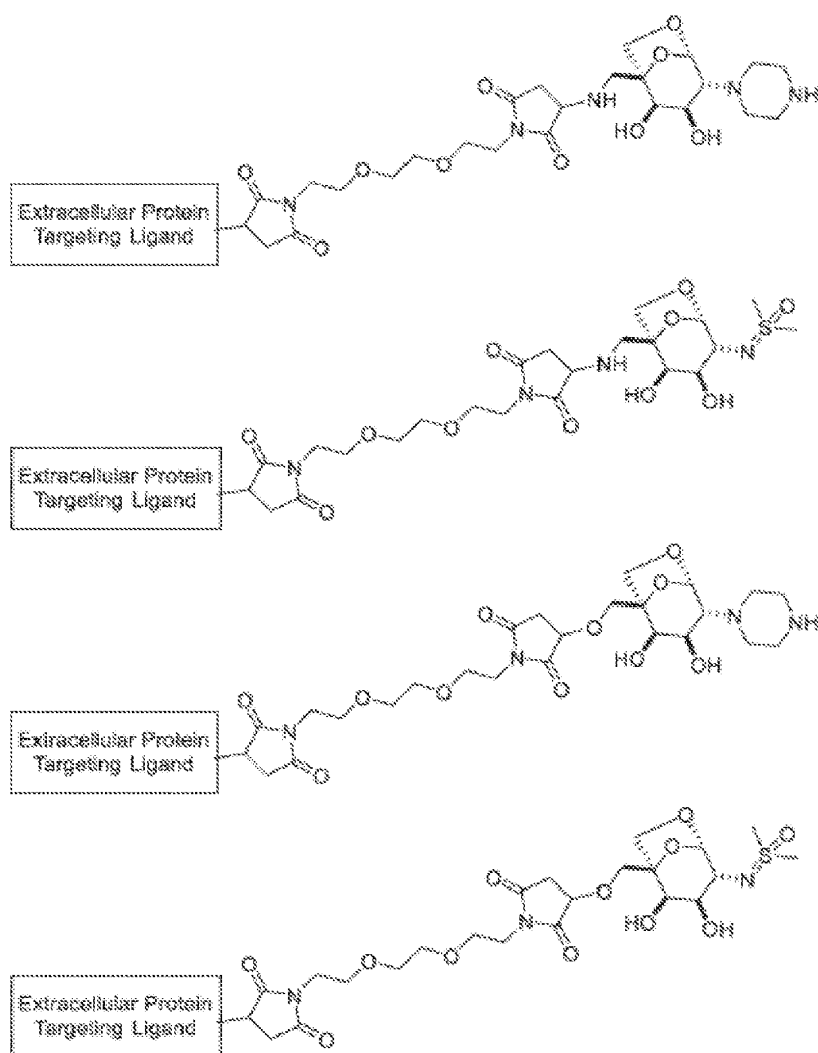




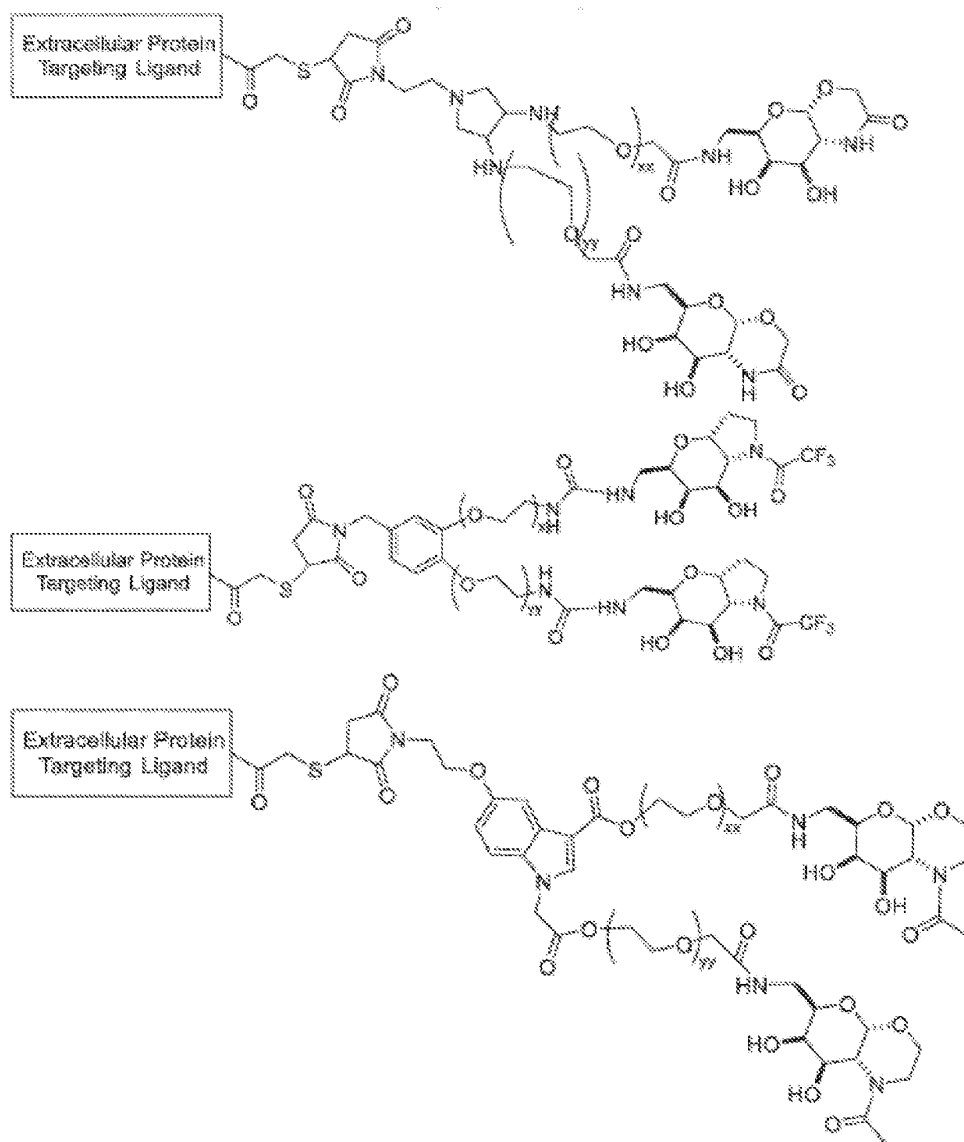


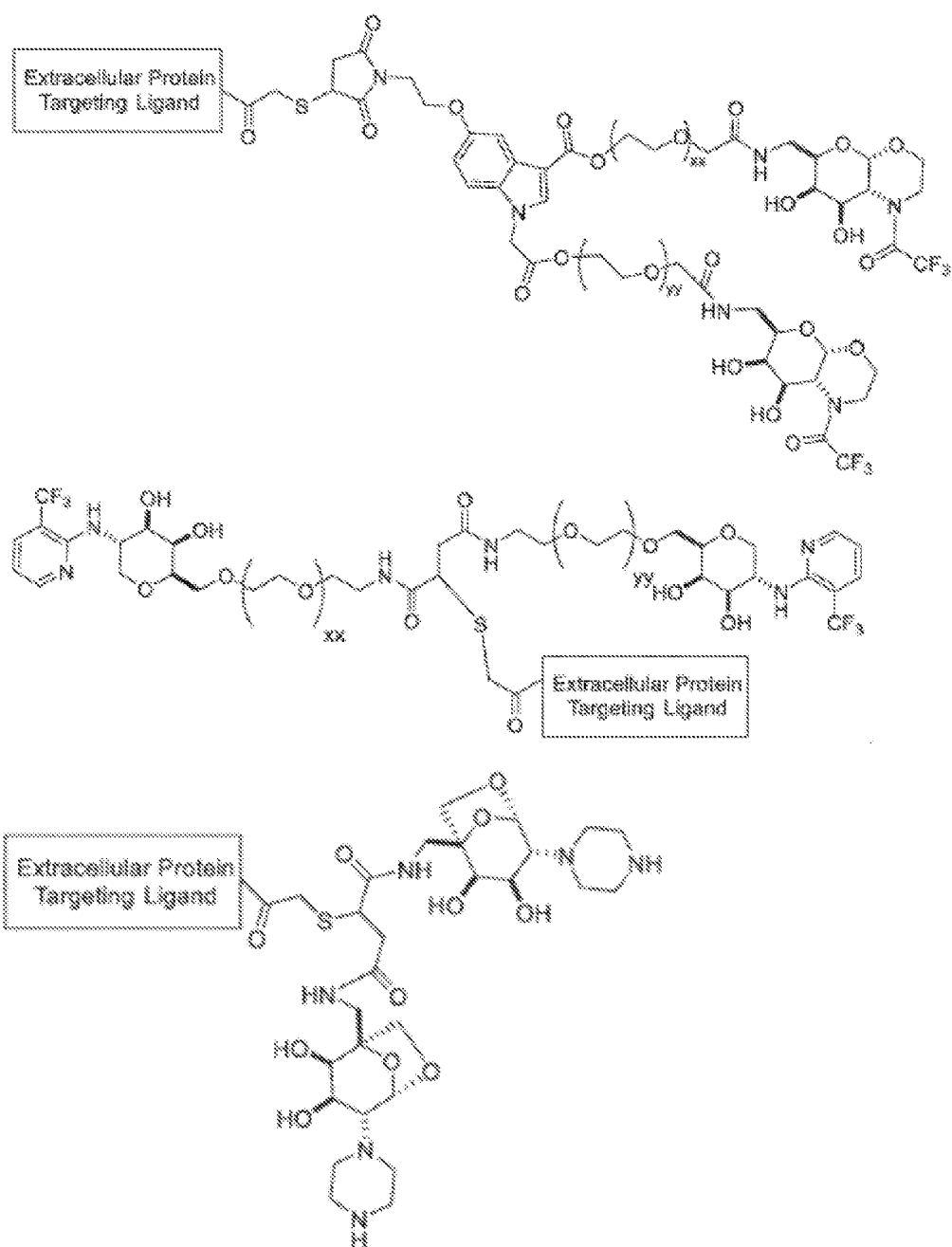


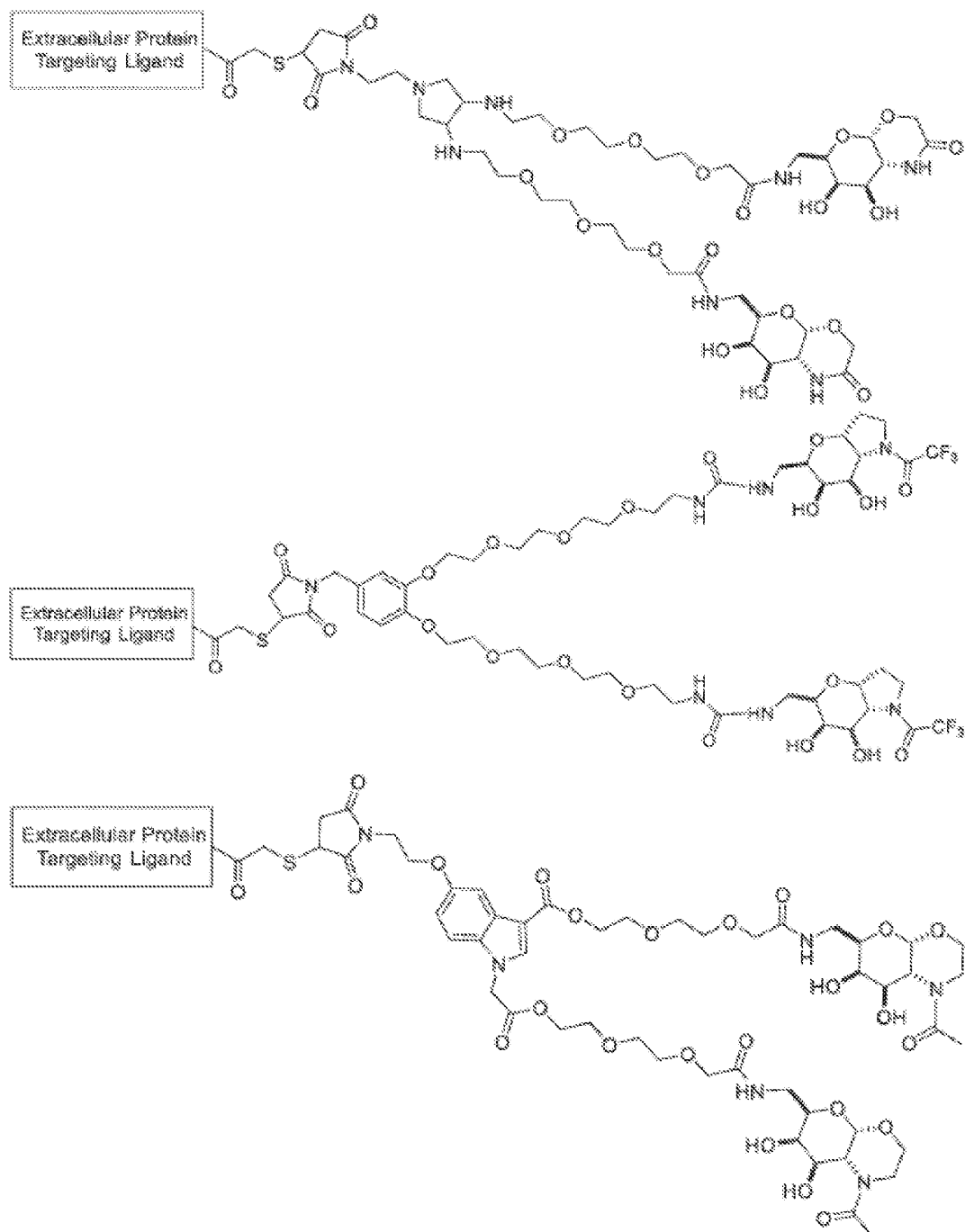


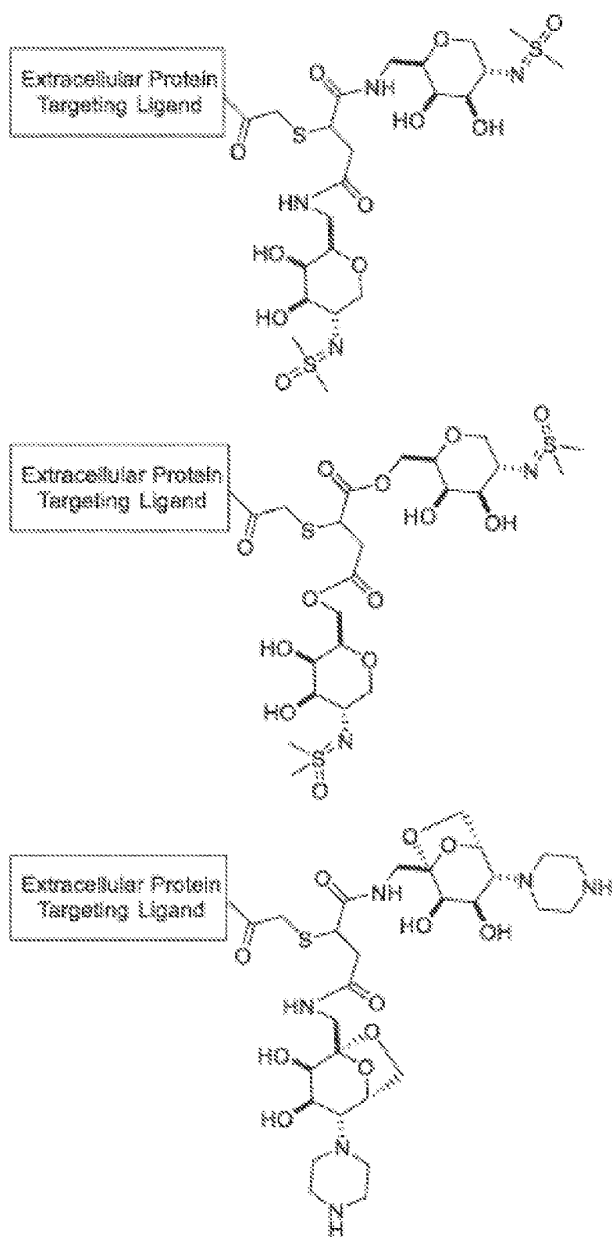


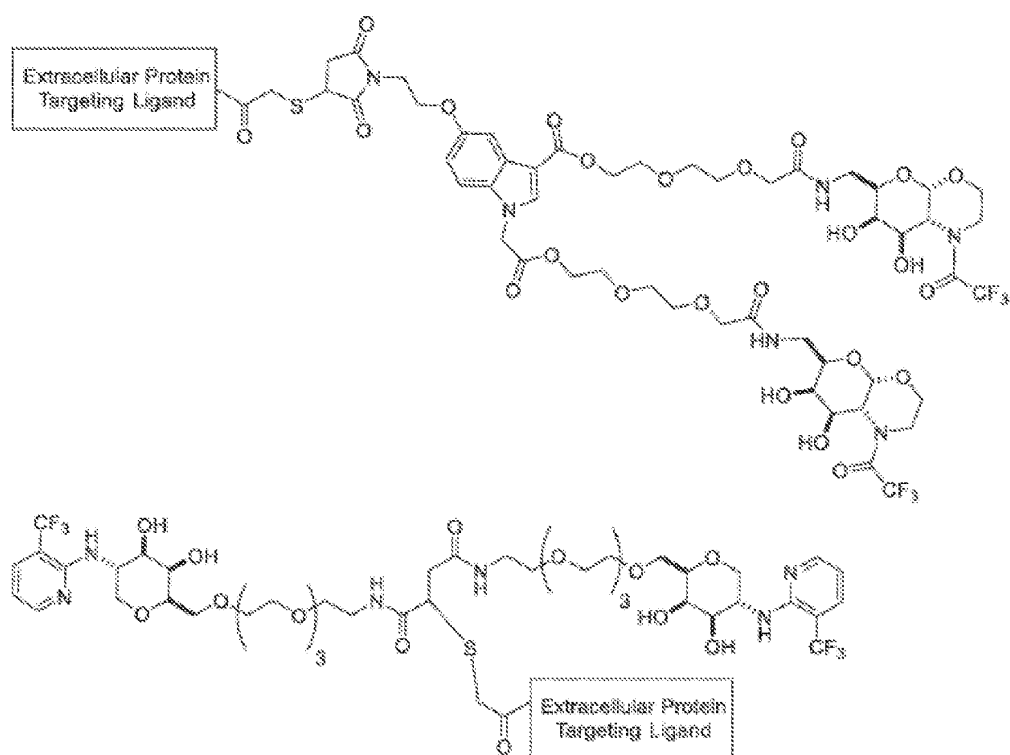
In certain embodiments, the compounds of Formulae (II) or (III) are selected from:



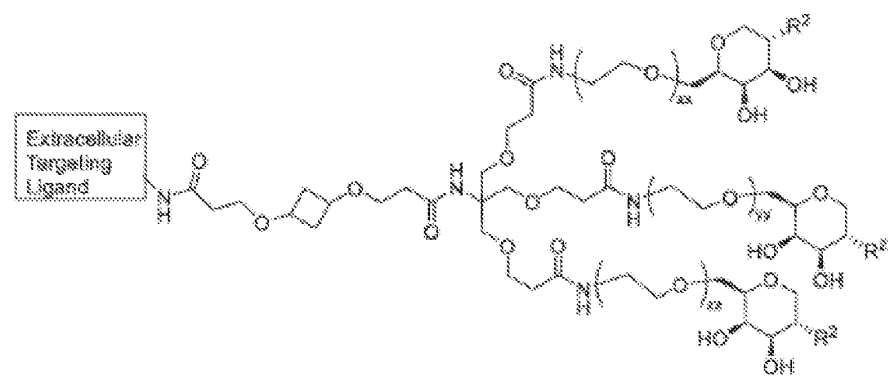


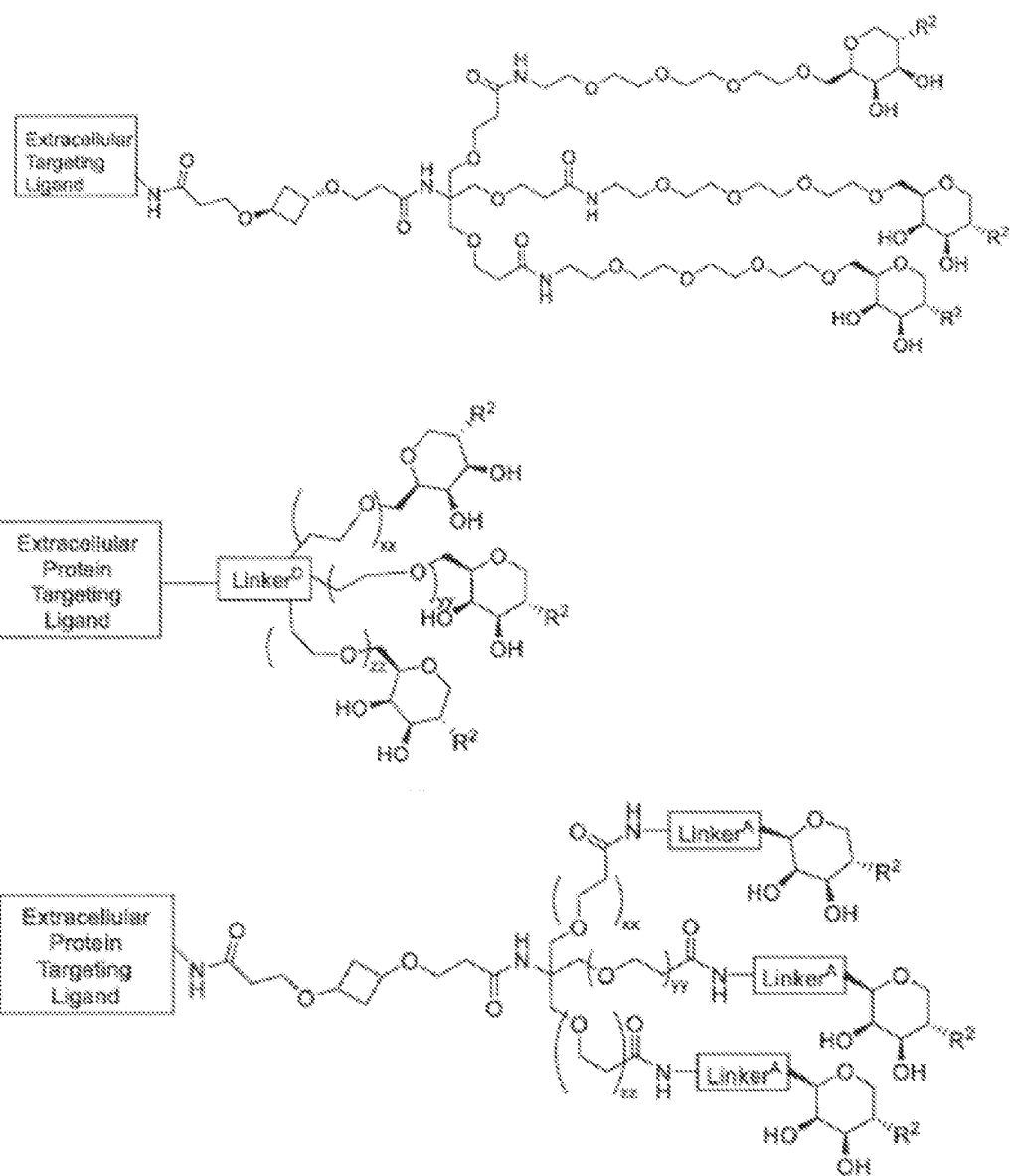


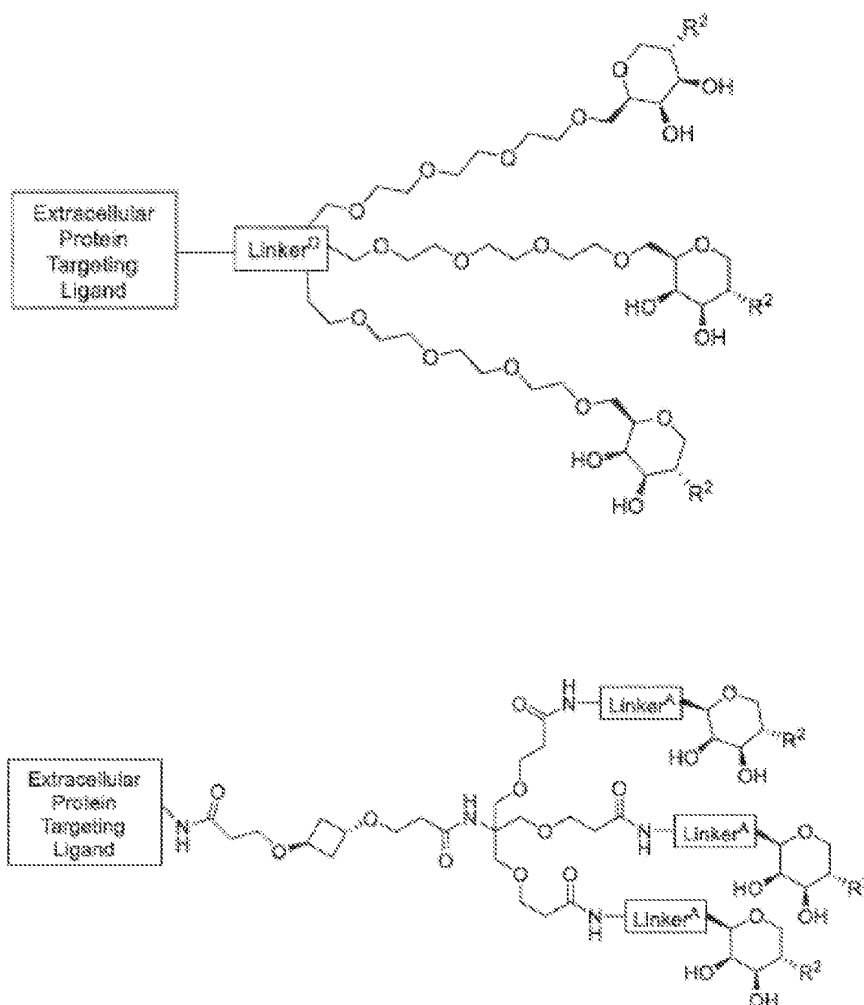




In certain embodiments, the compounds of Formulae (II) or (III) are selected from:



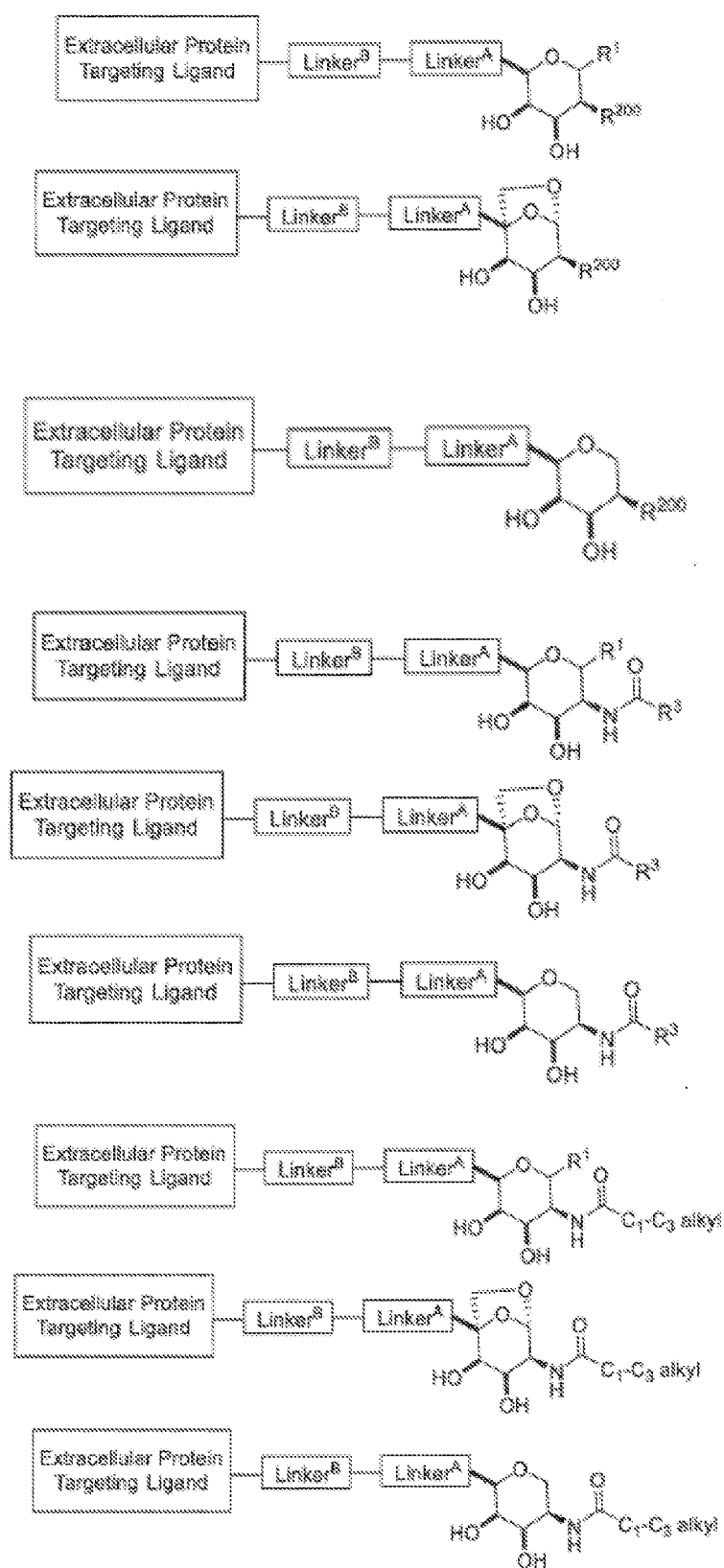


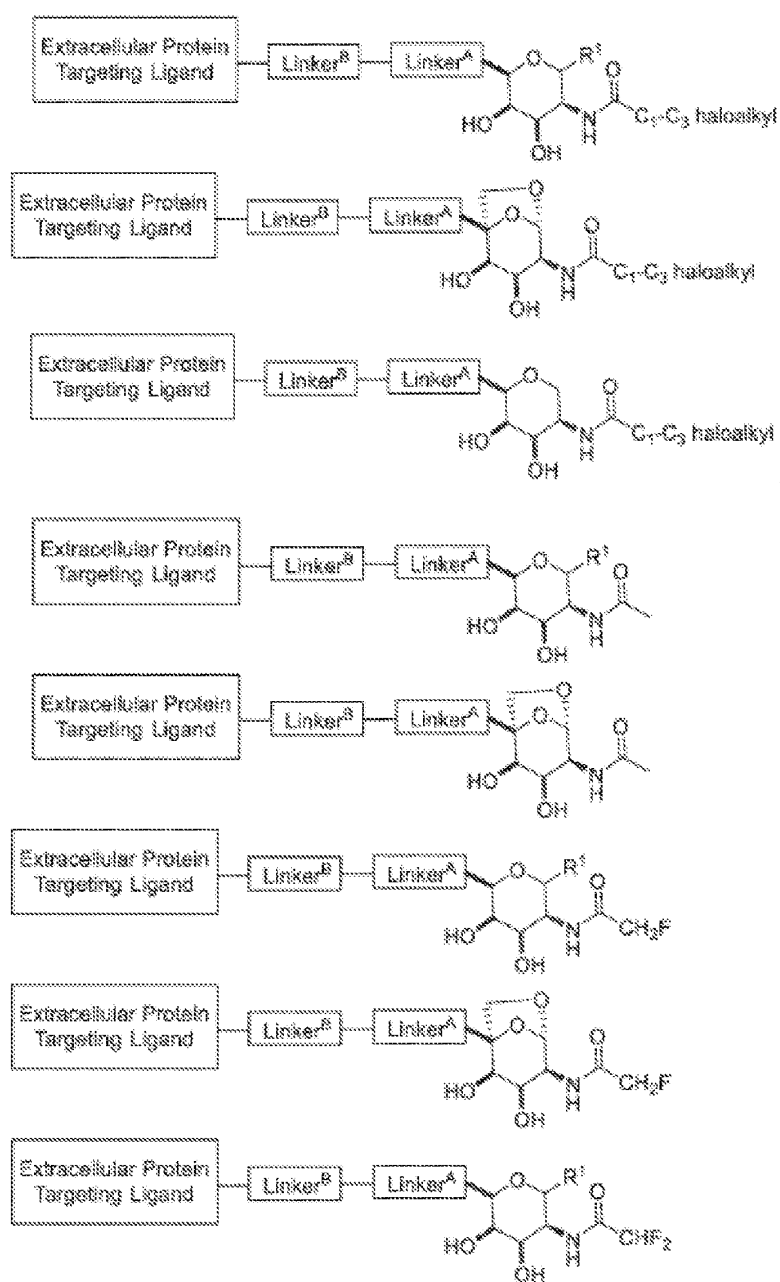


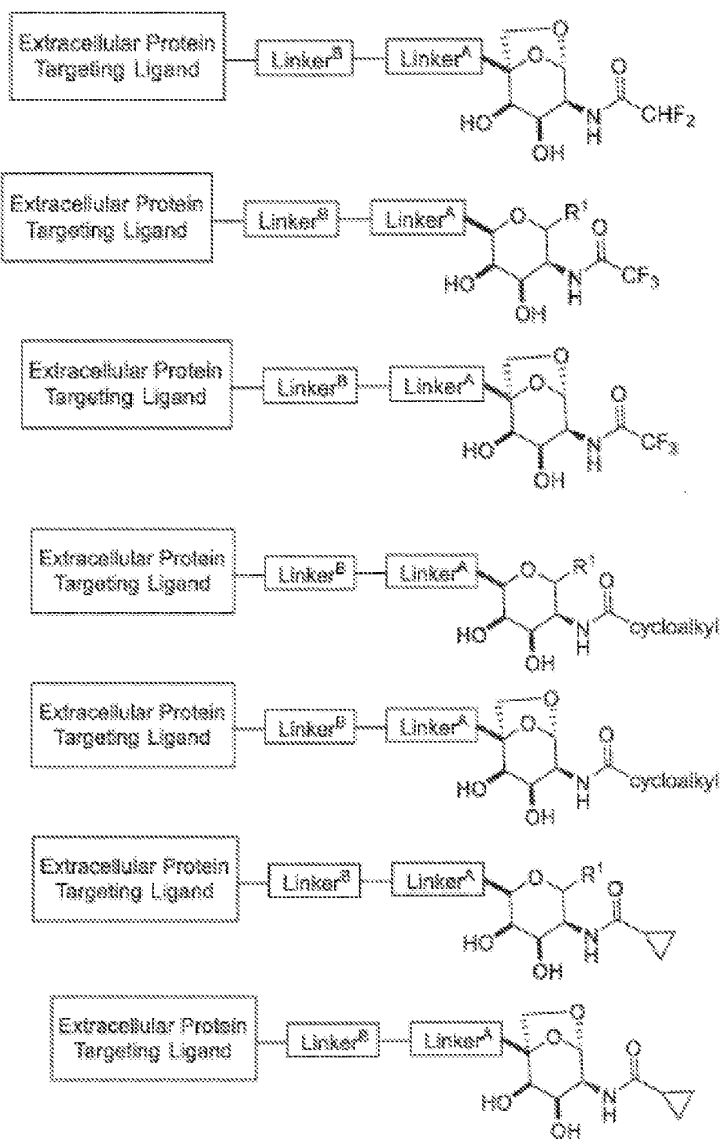
B. Talose-Based ASGPR-Binding Cellular Receptor Binding Moieties AG

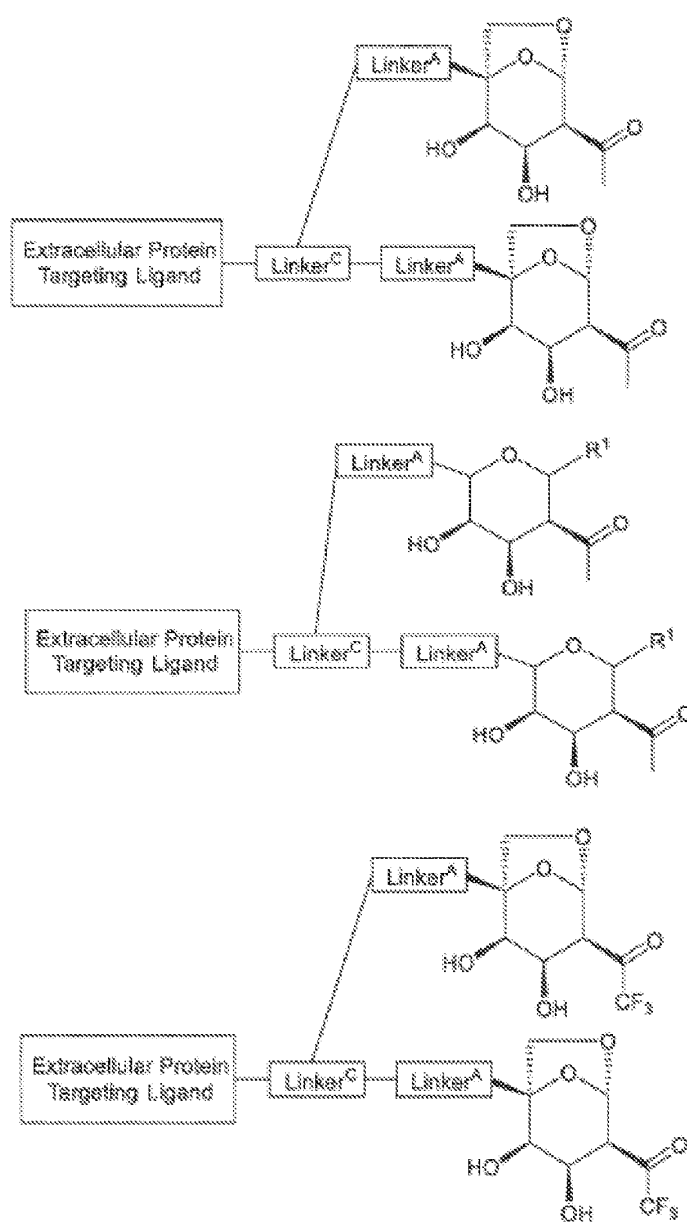
In the following formulae examples of the structures of Formulae (I), (II) and (III) are disclosed in which AG is a talose derivative. The partial structures of talose and its derivatives in these formulae may be used as group AG in any of Formulae (I), (II) and (III). The definitions of variables are as described herein and especially as described above for the galactose based embodiments.

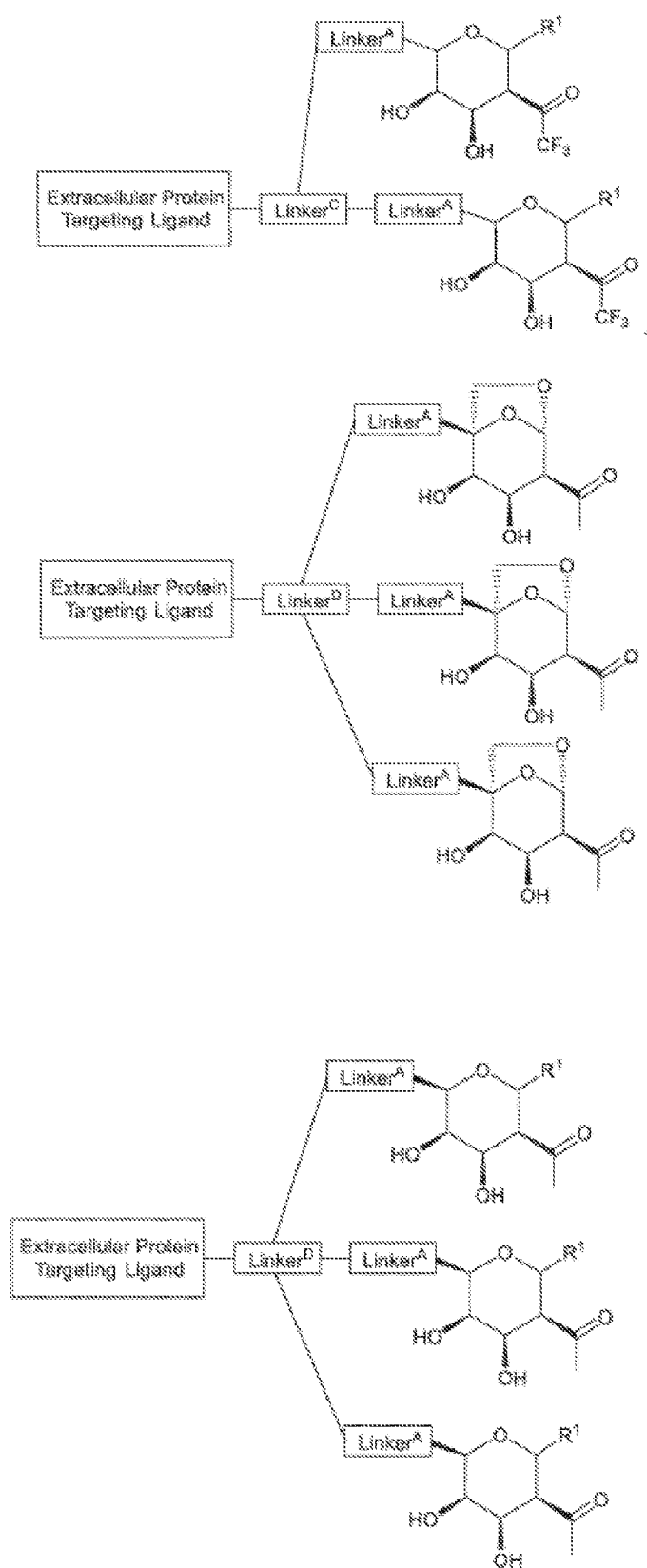
In certain embodiments, the compounds of Formulae (I), (II) or (III) are selected from:

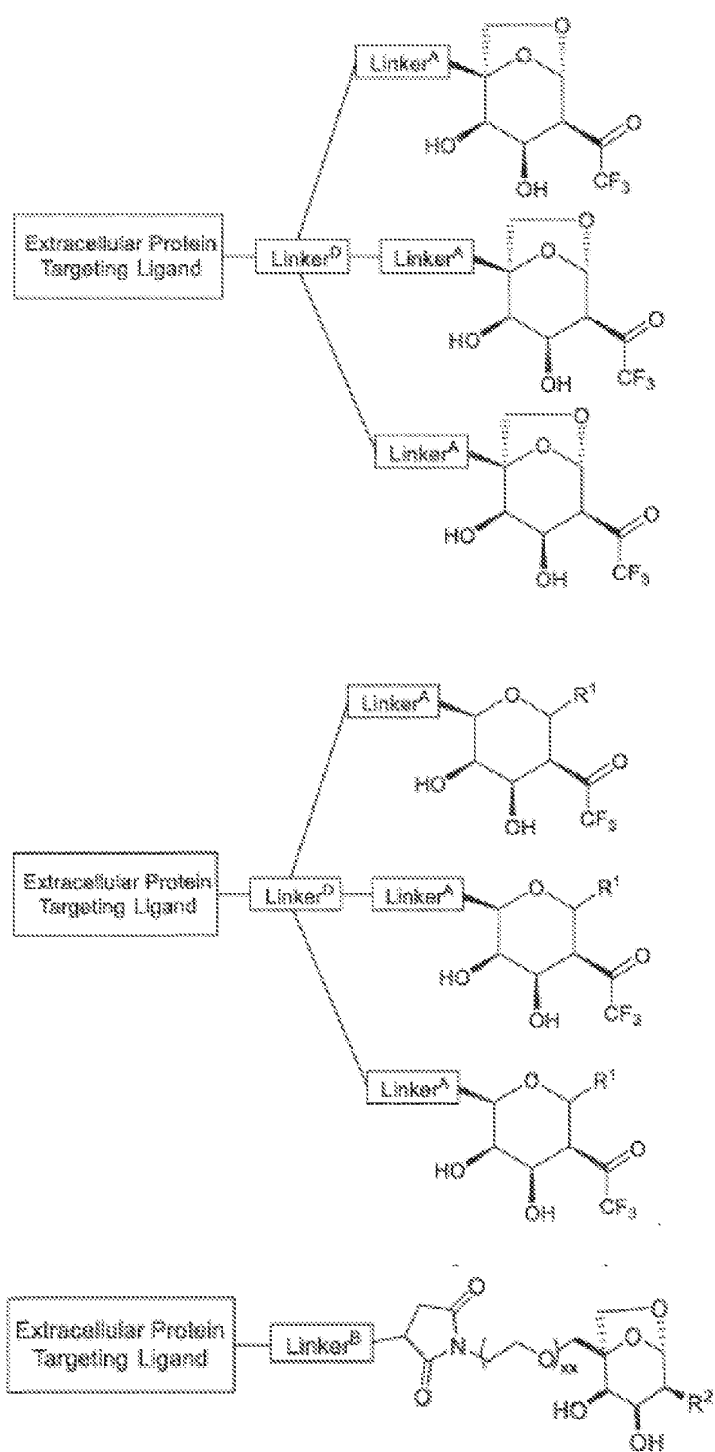


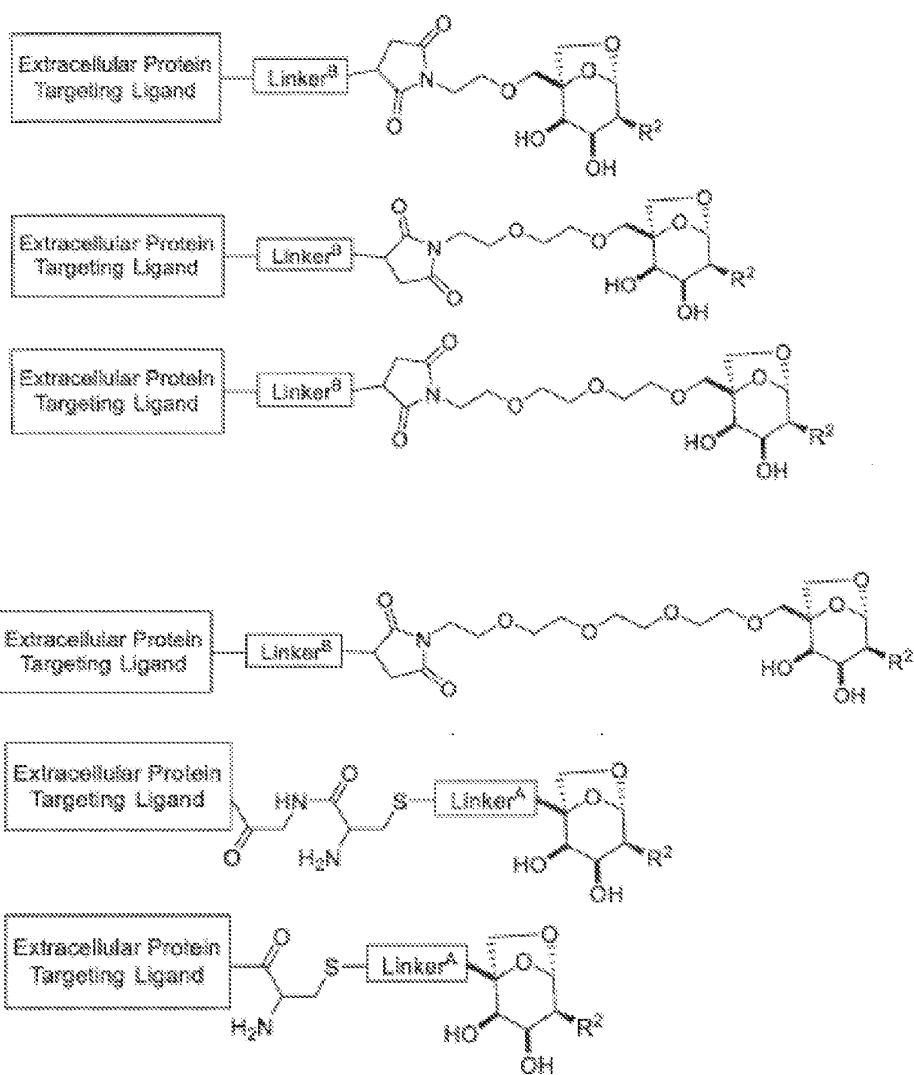


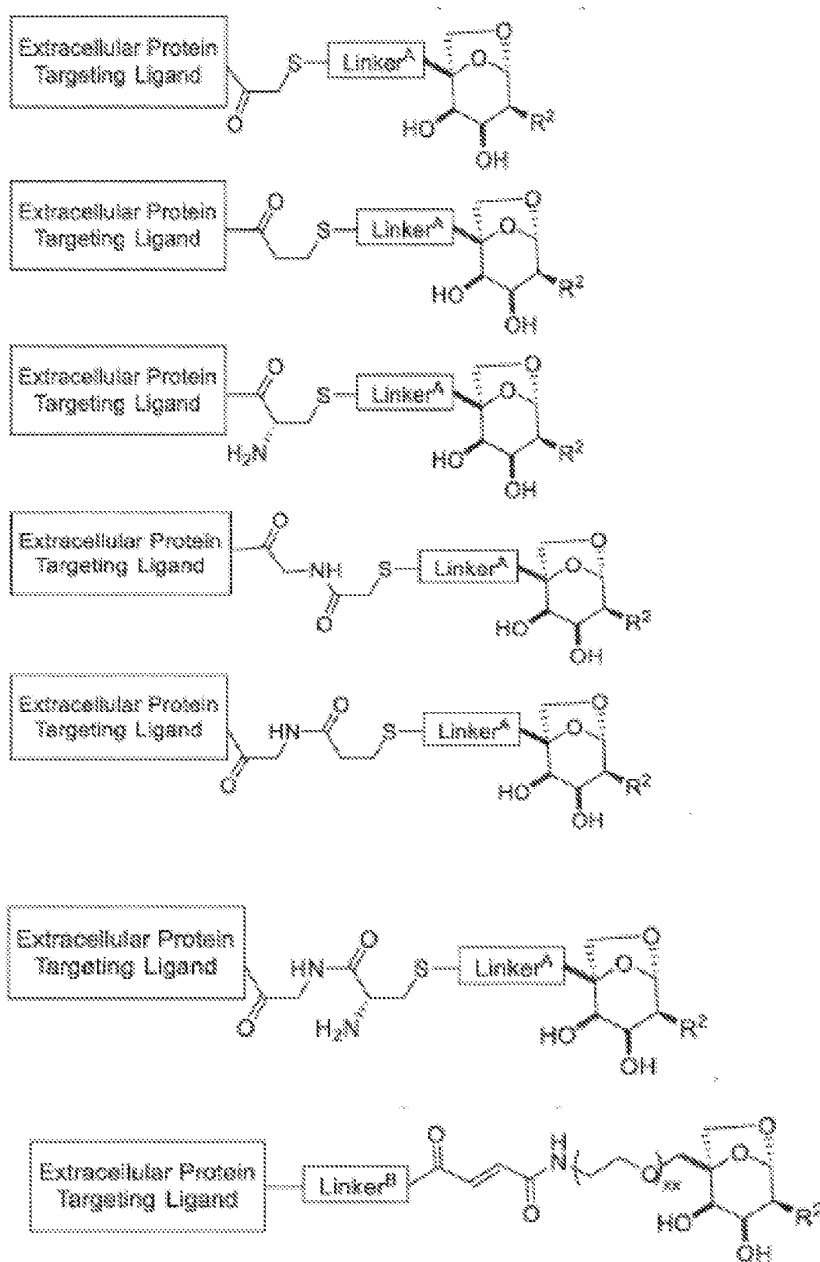


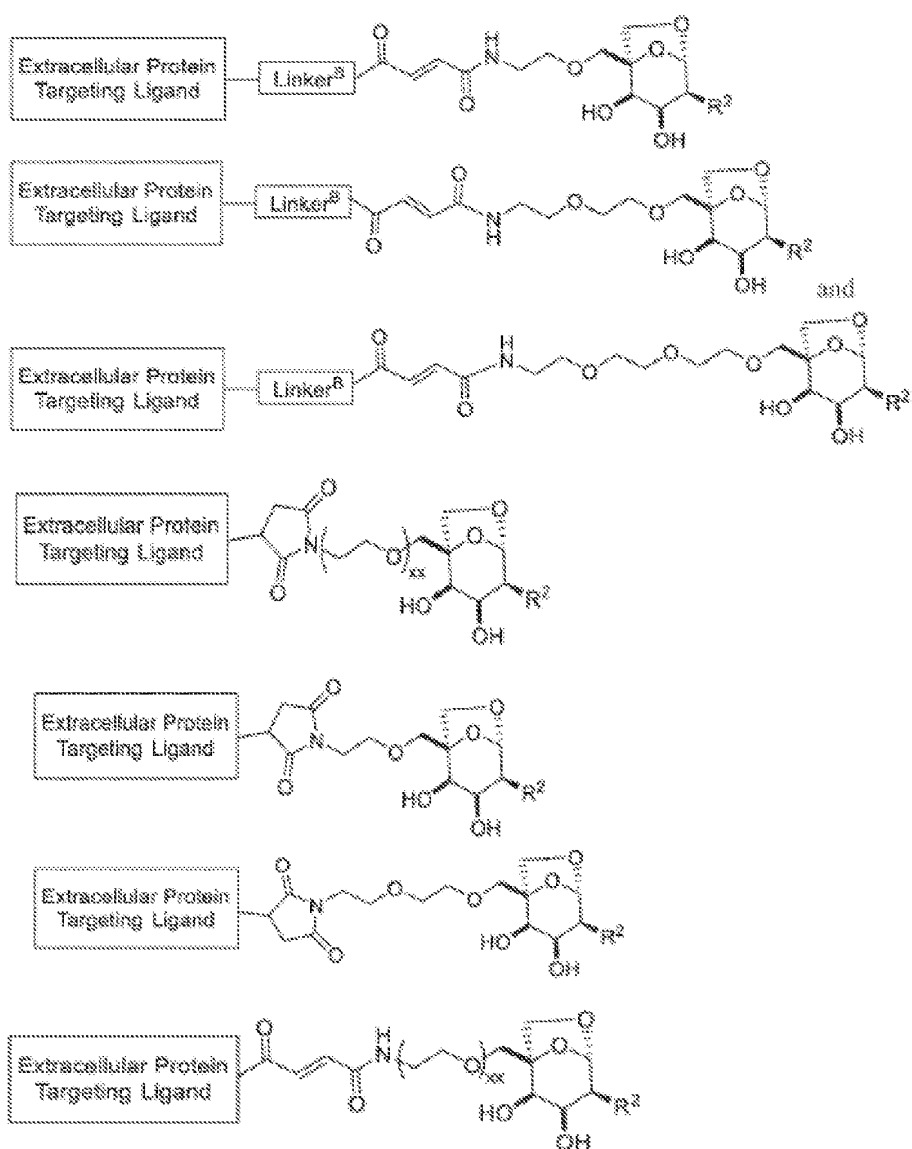


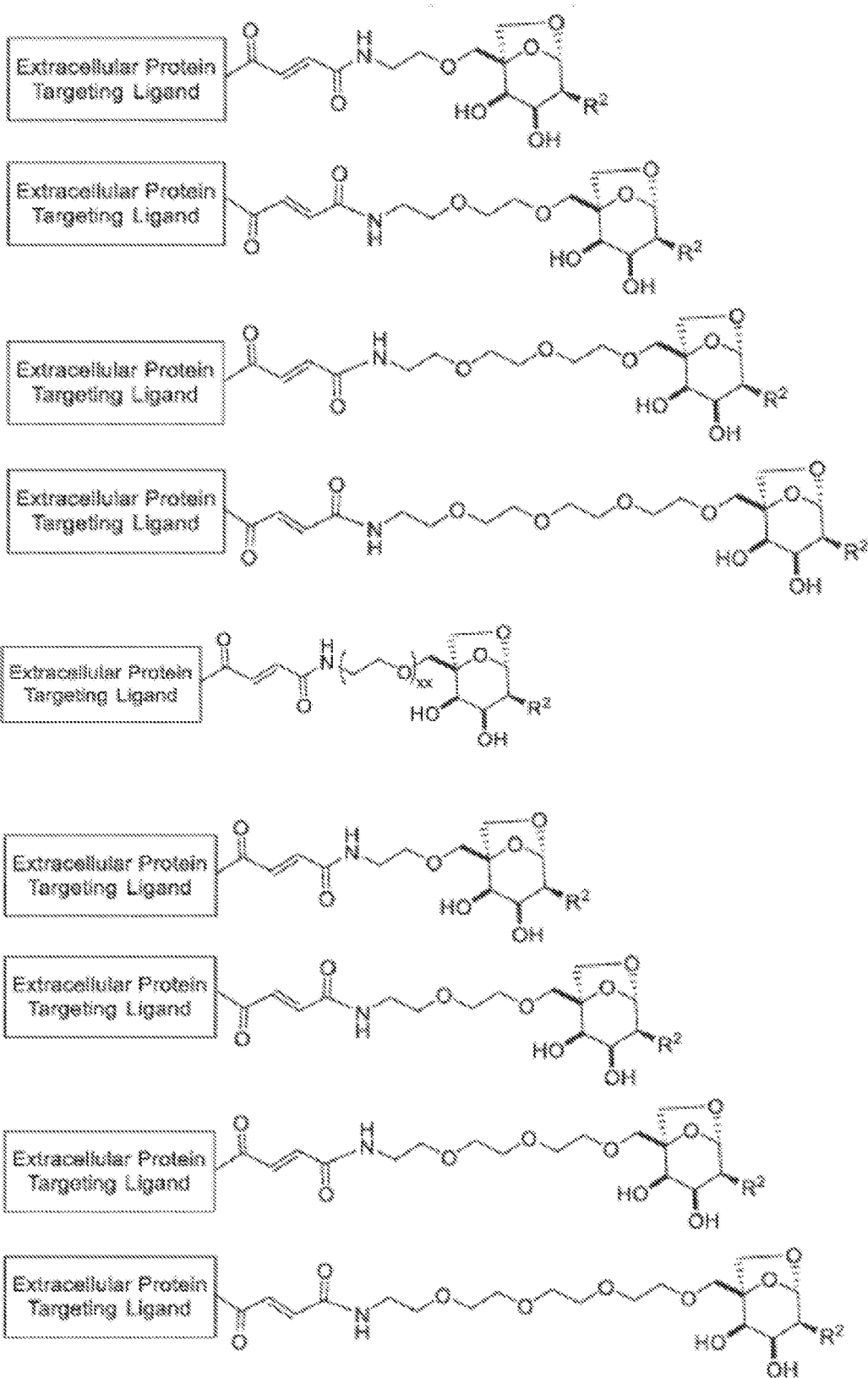


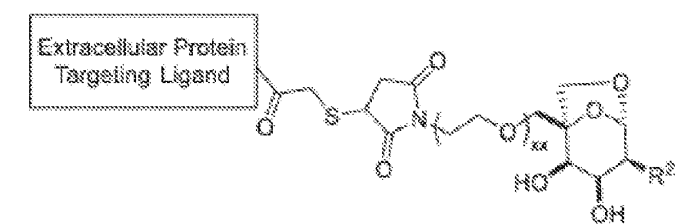
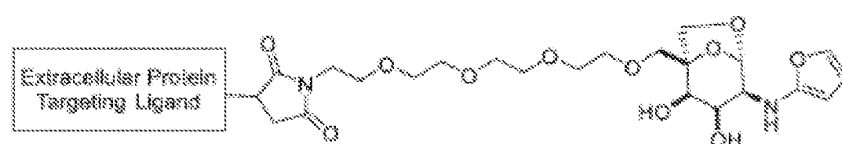
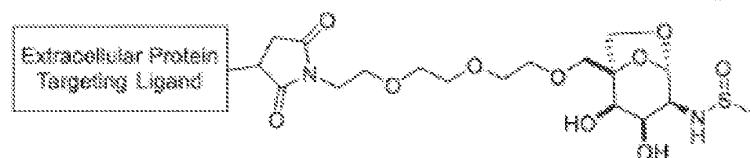
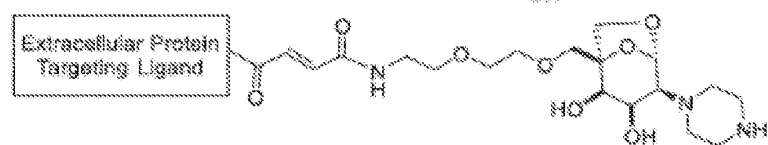
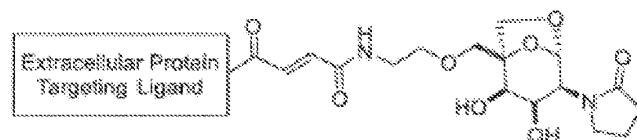
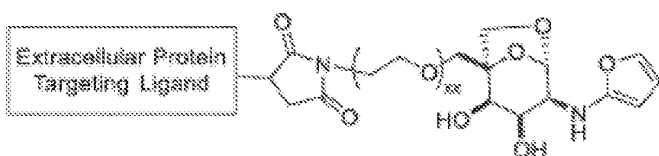
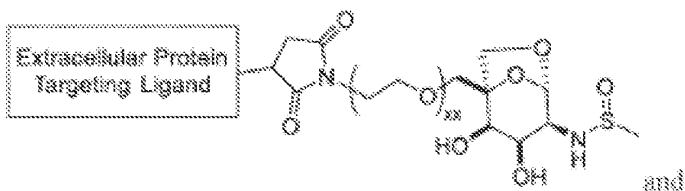
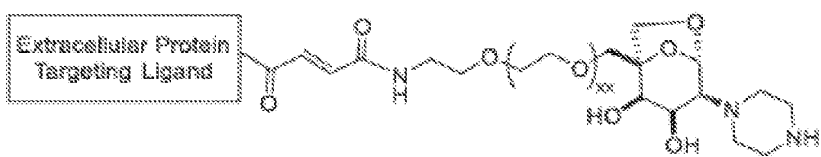


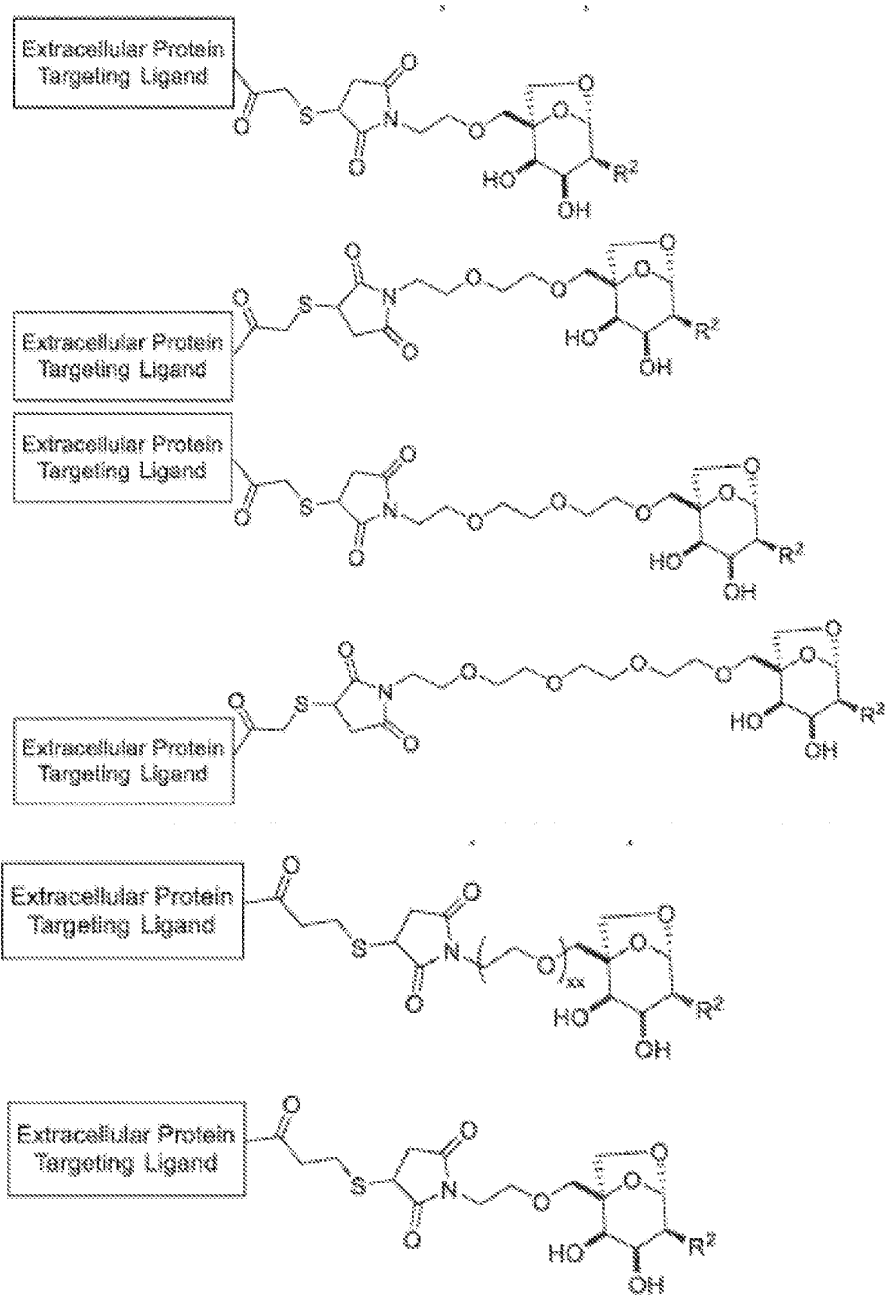


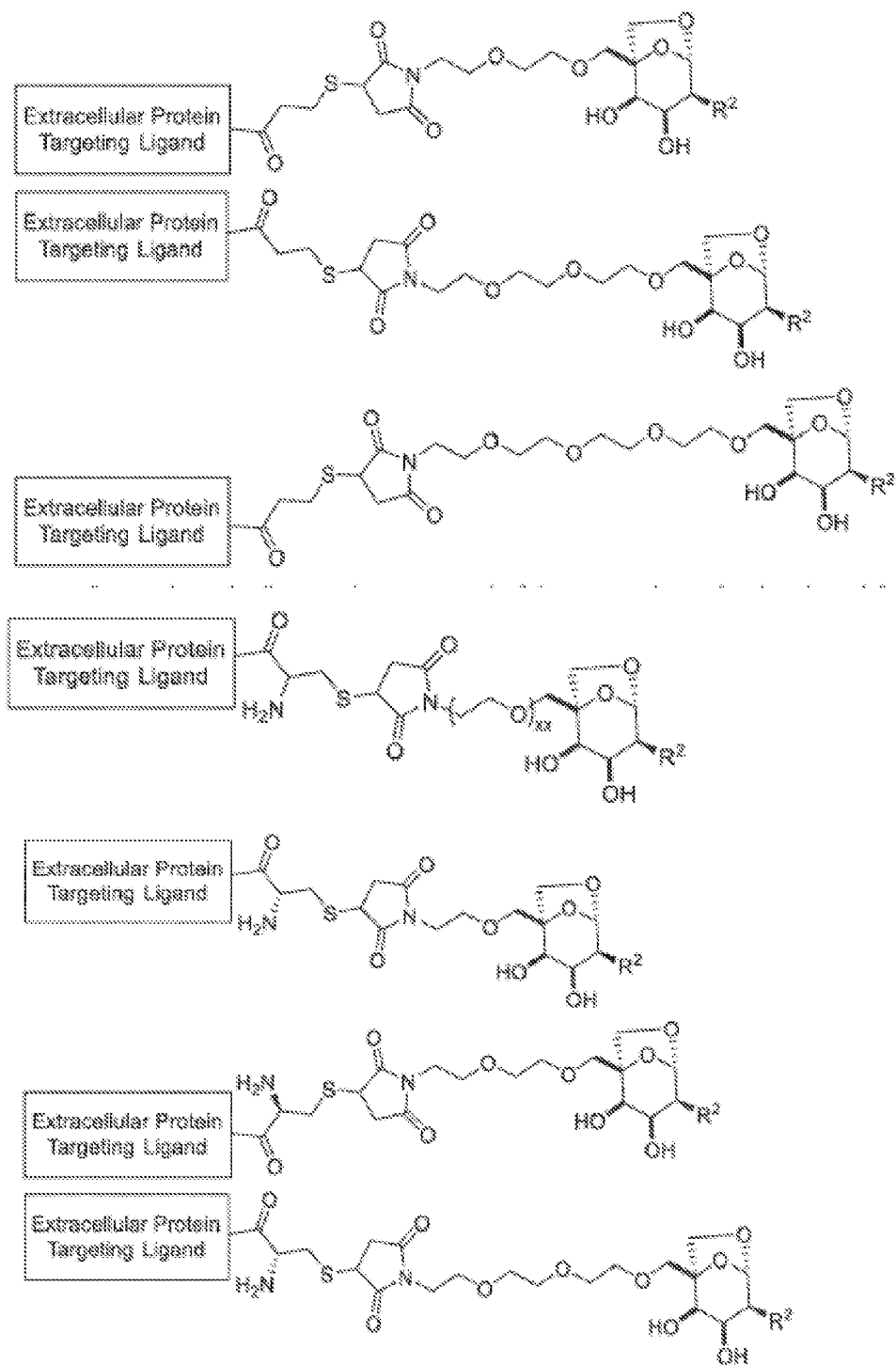


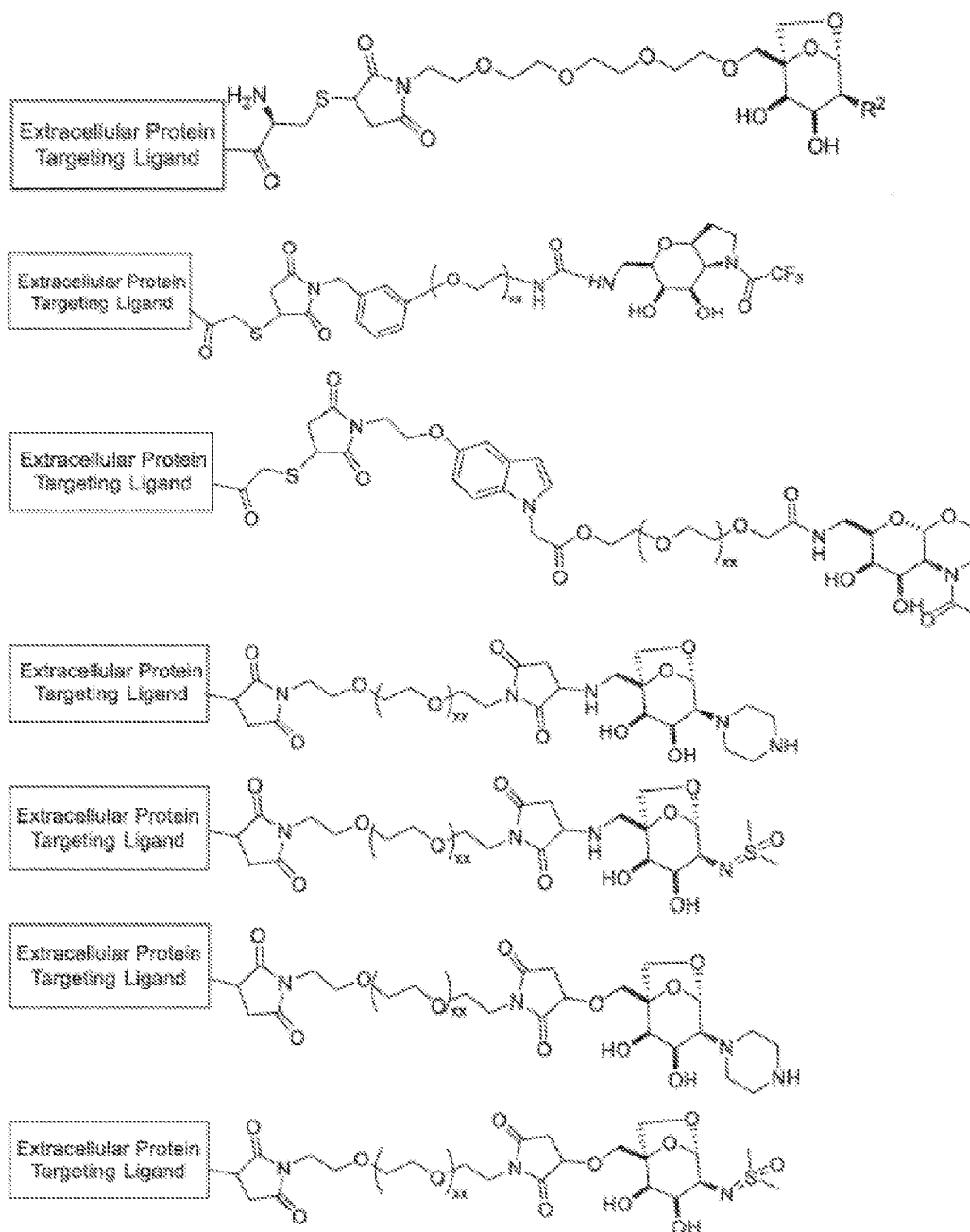


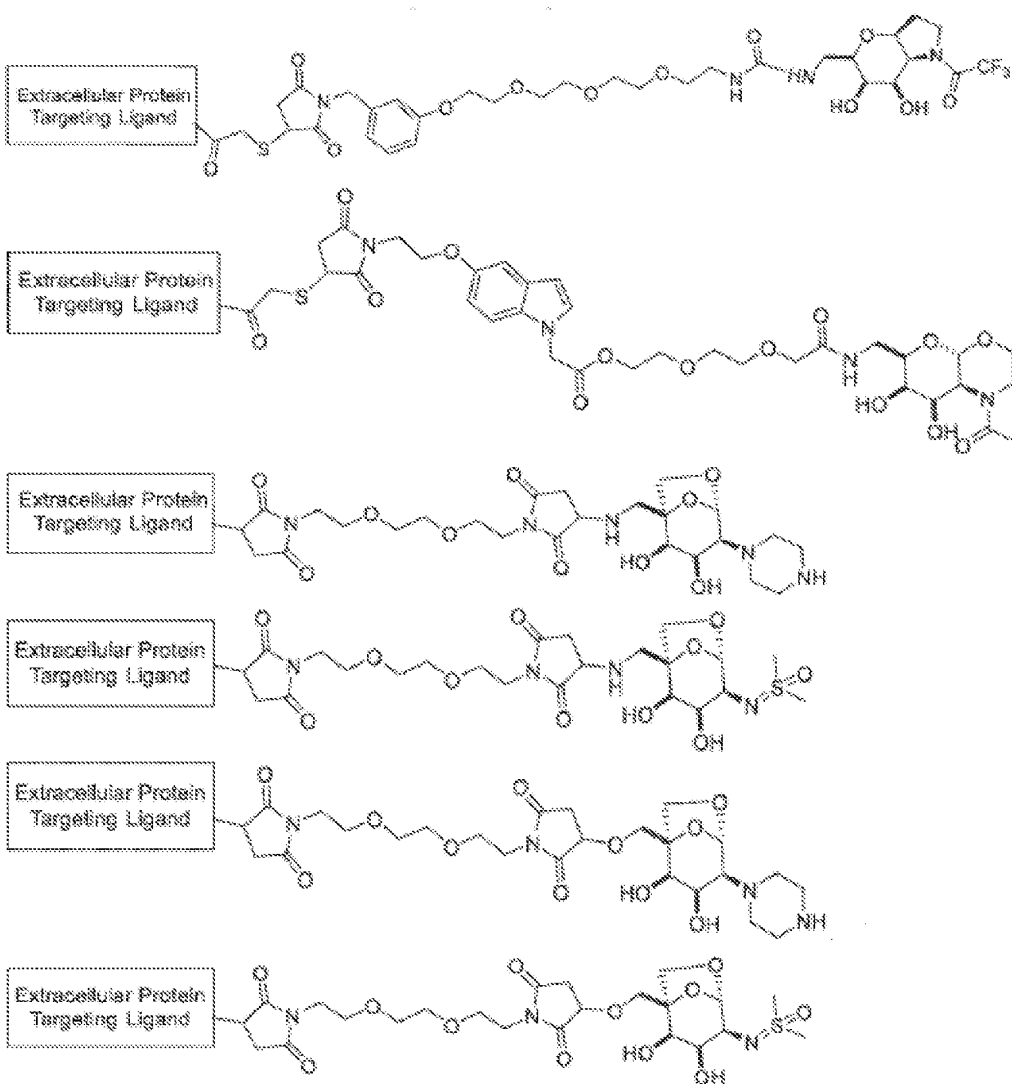


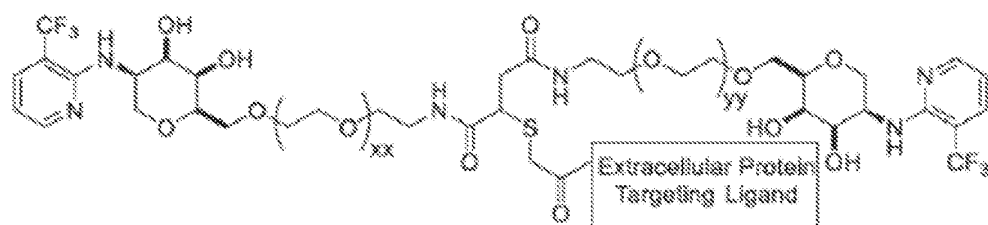
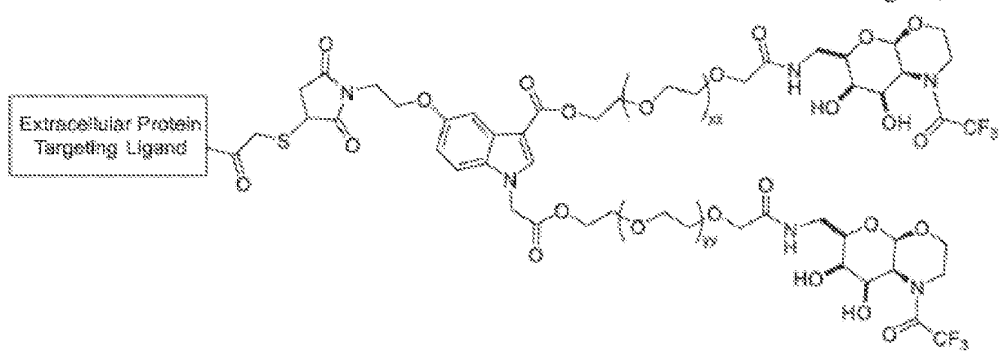
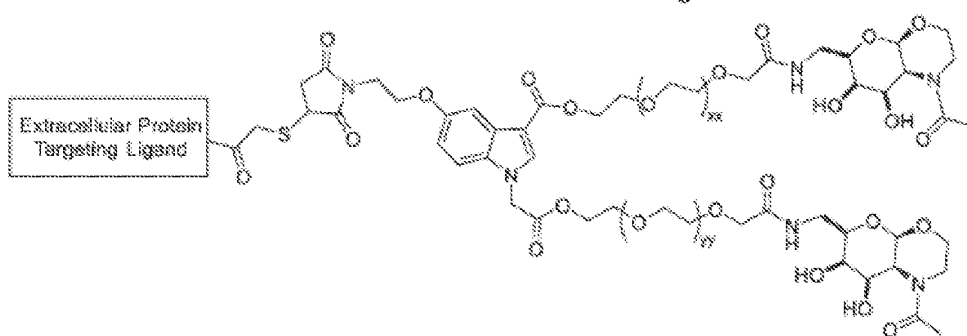
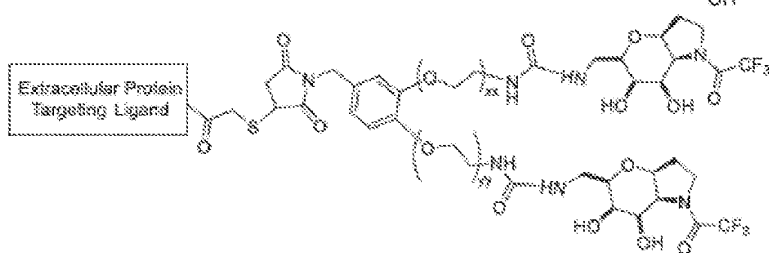
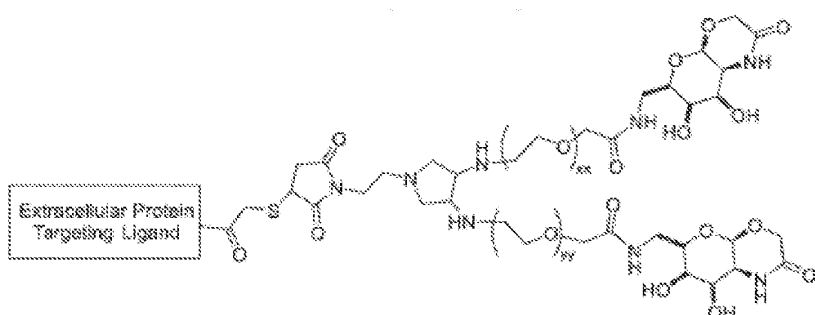


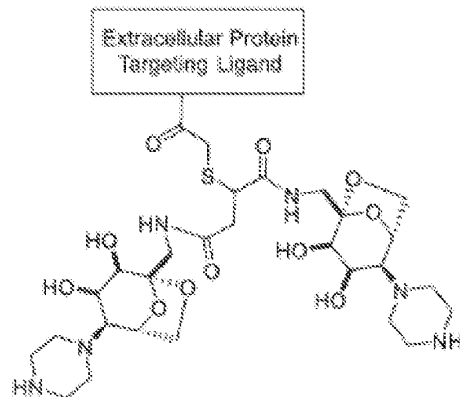
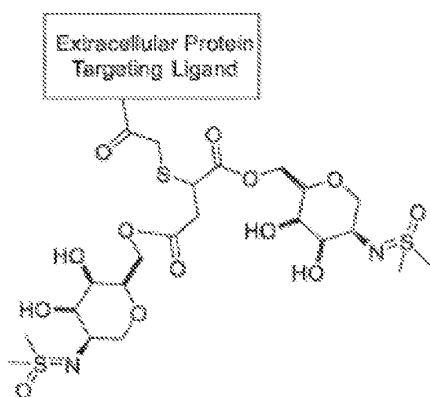
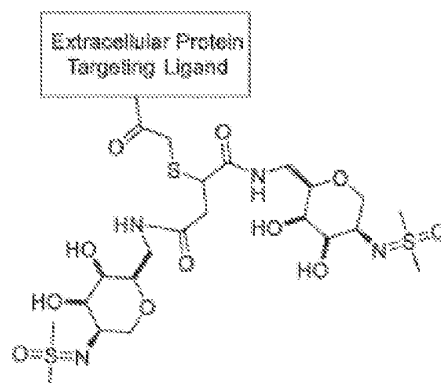
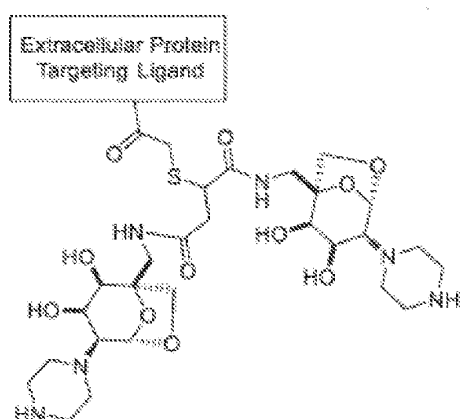


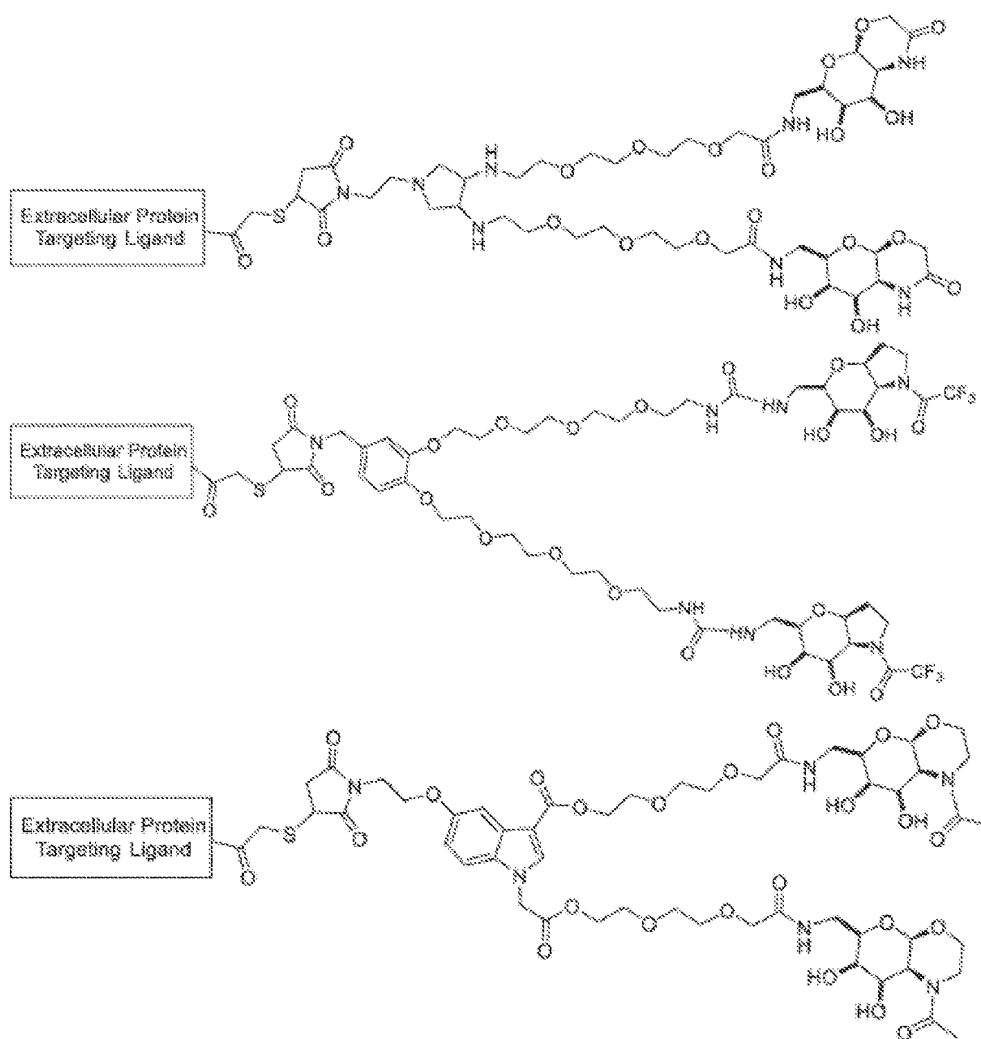


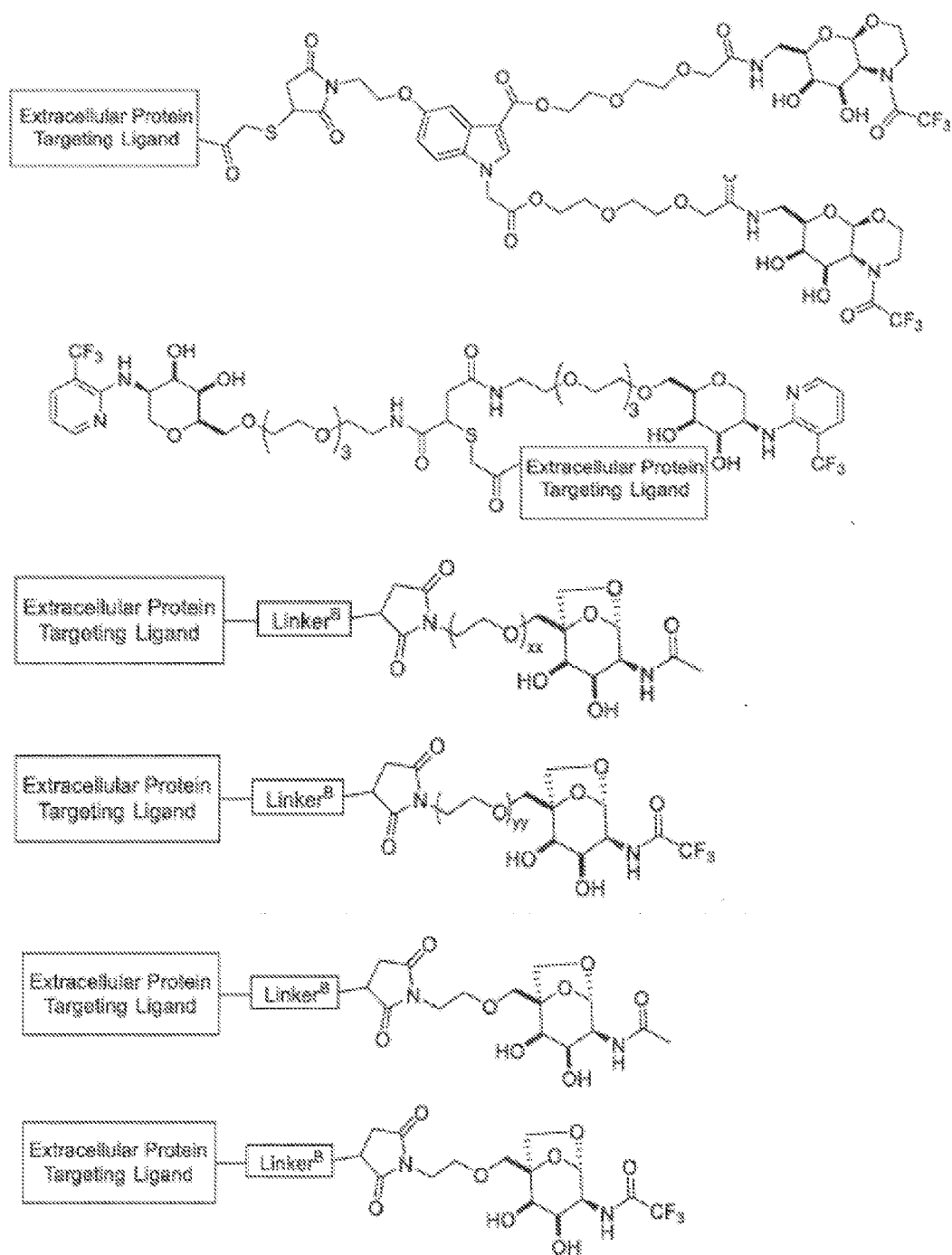


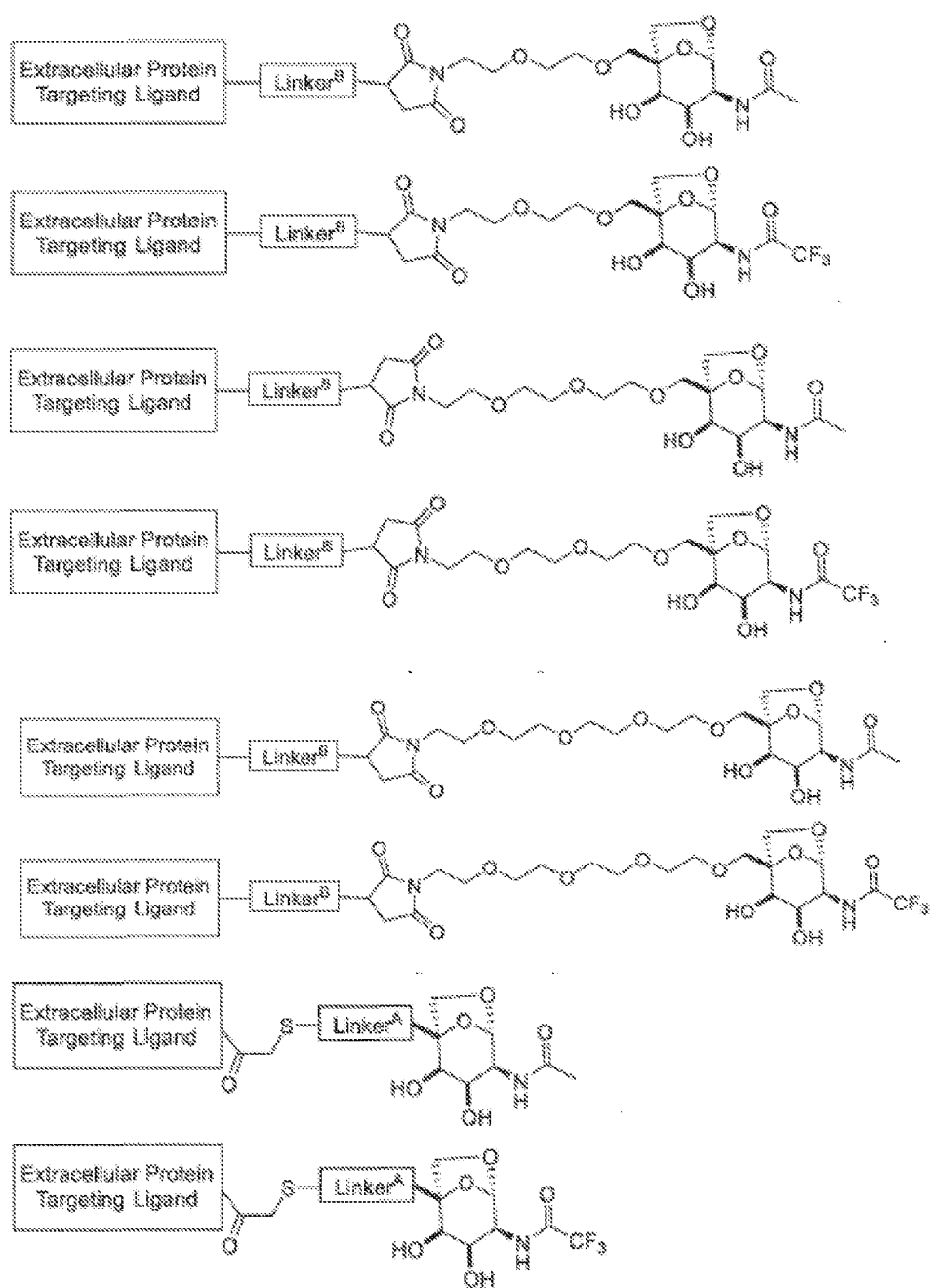


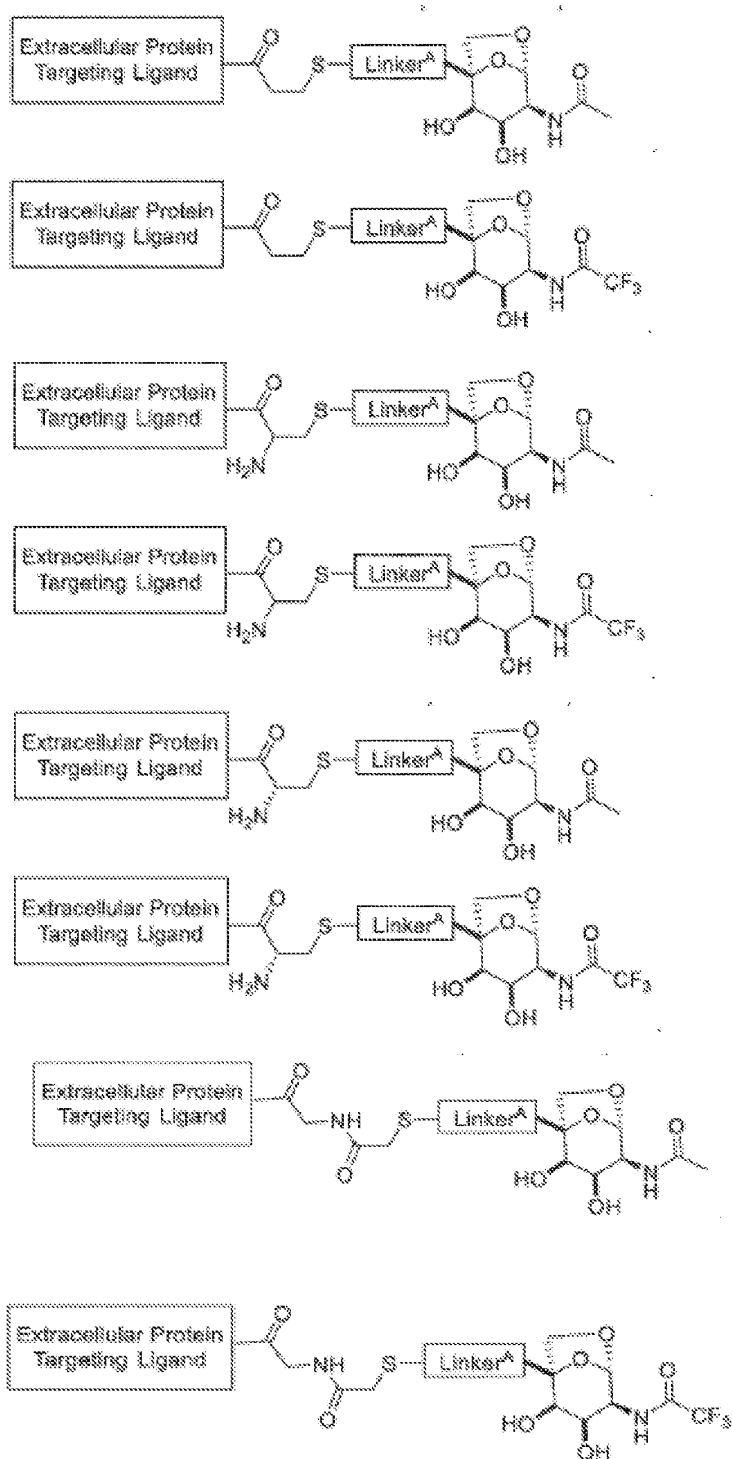


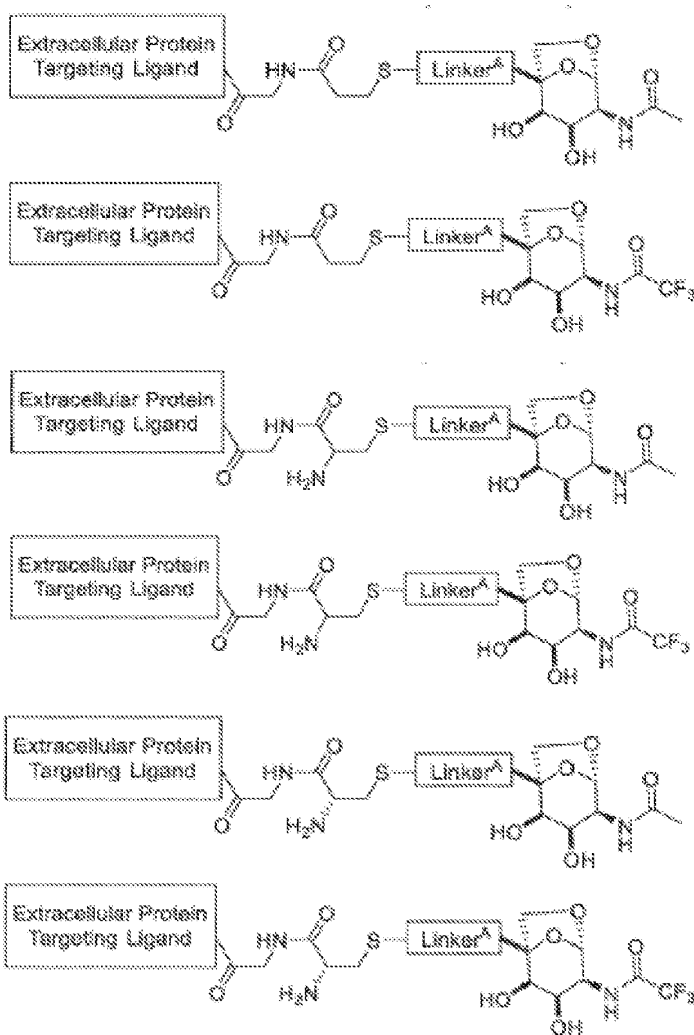


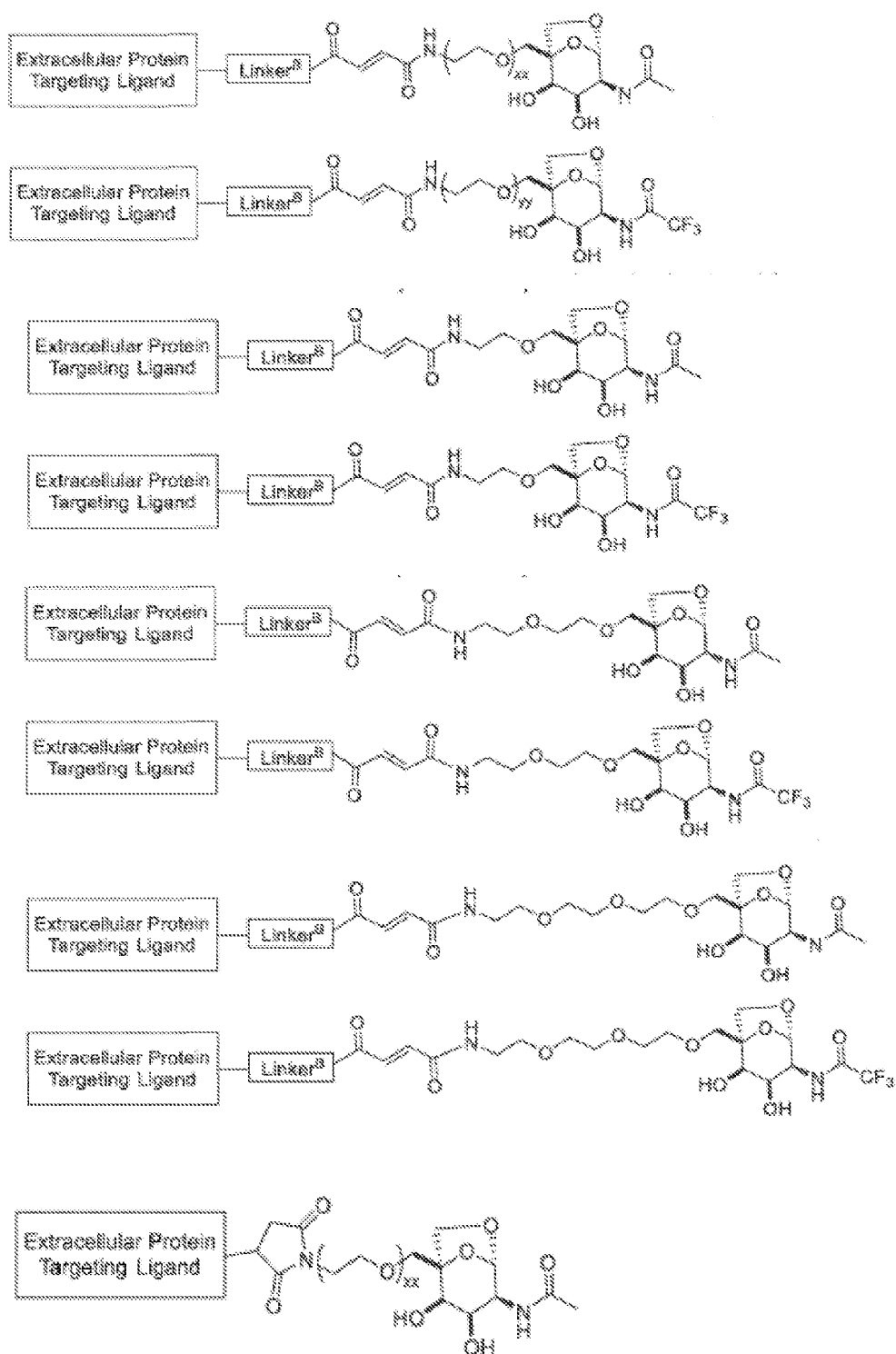


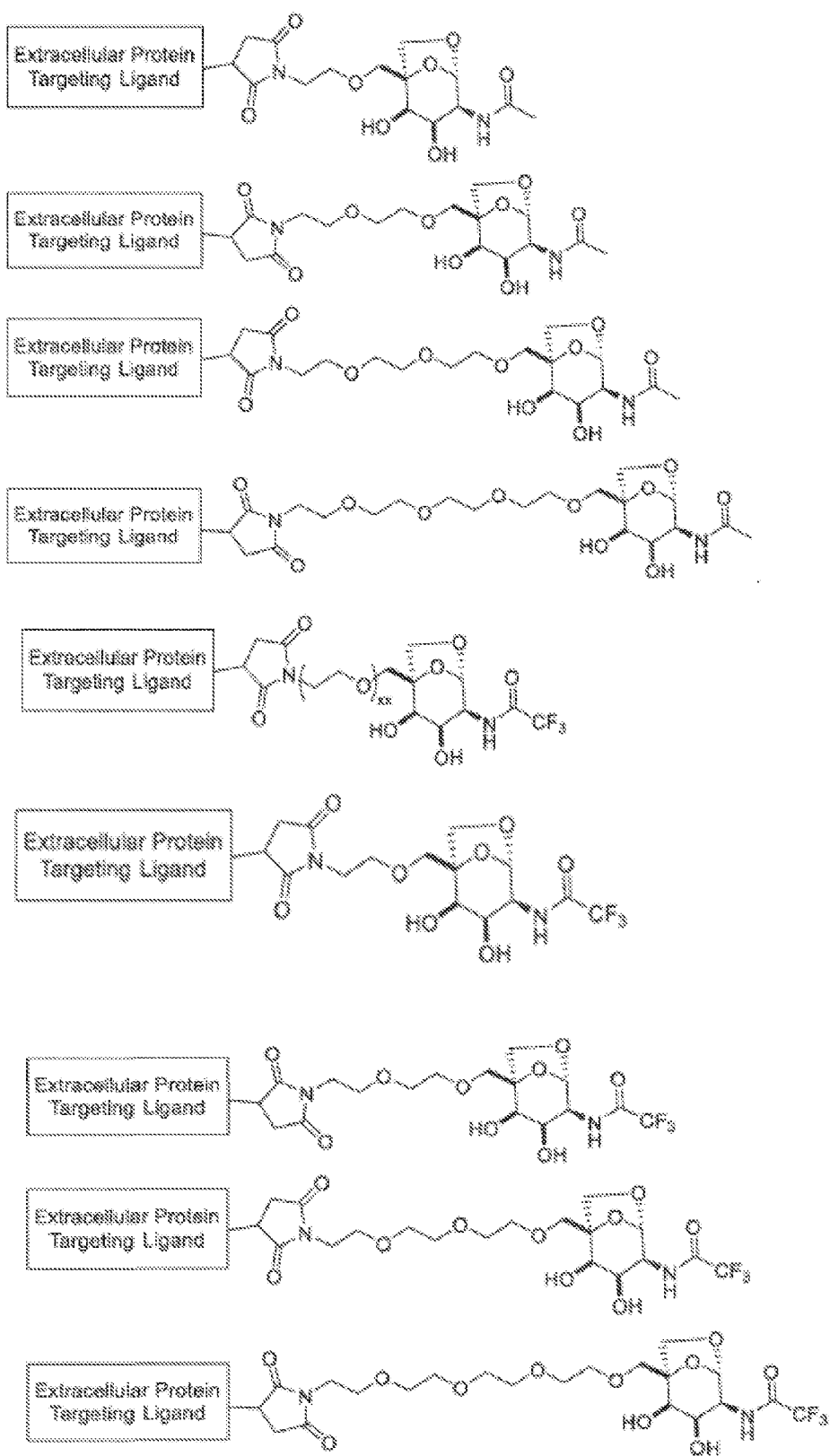


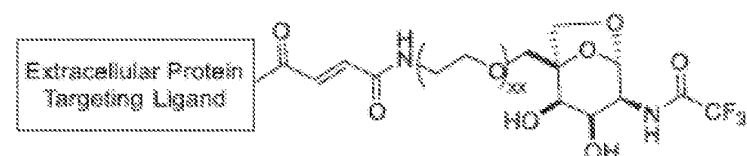
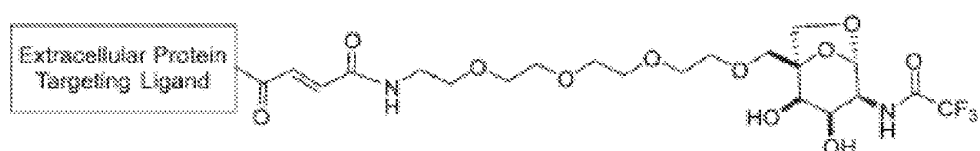
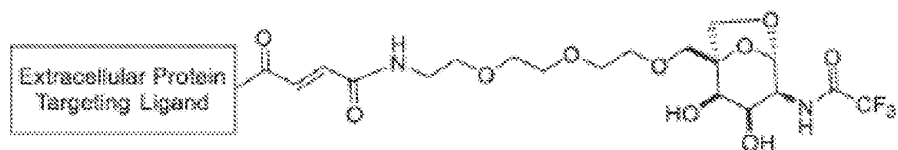
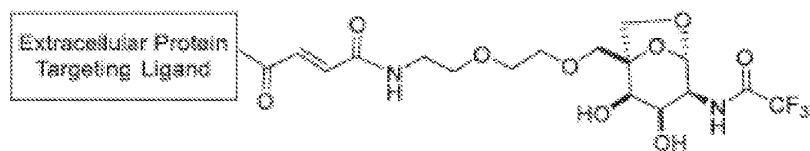
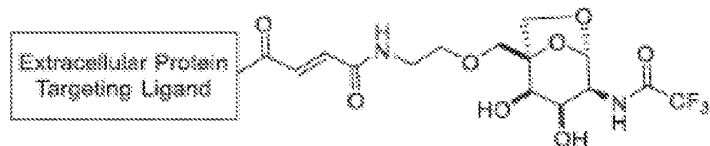
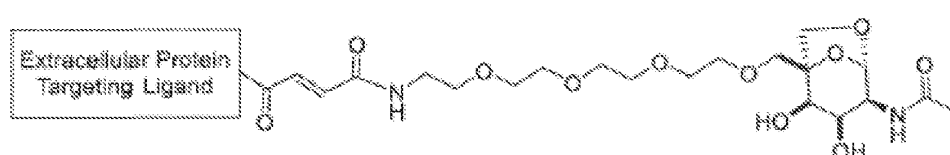
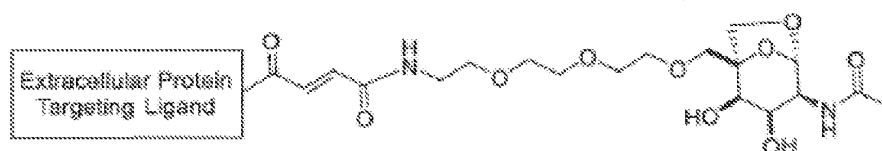
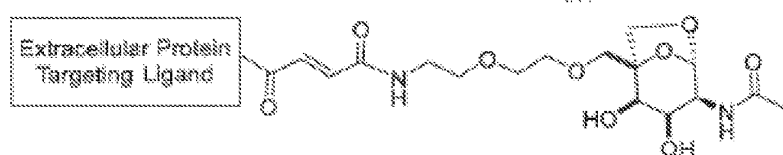
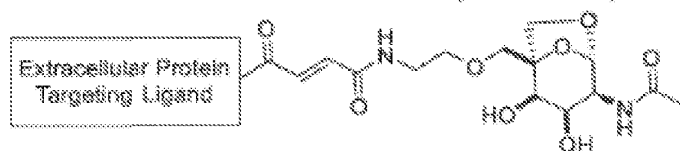
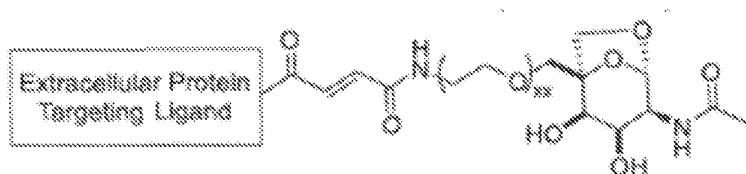


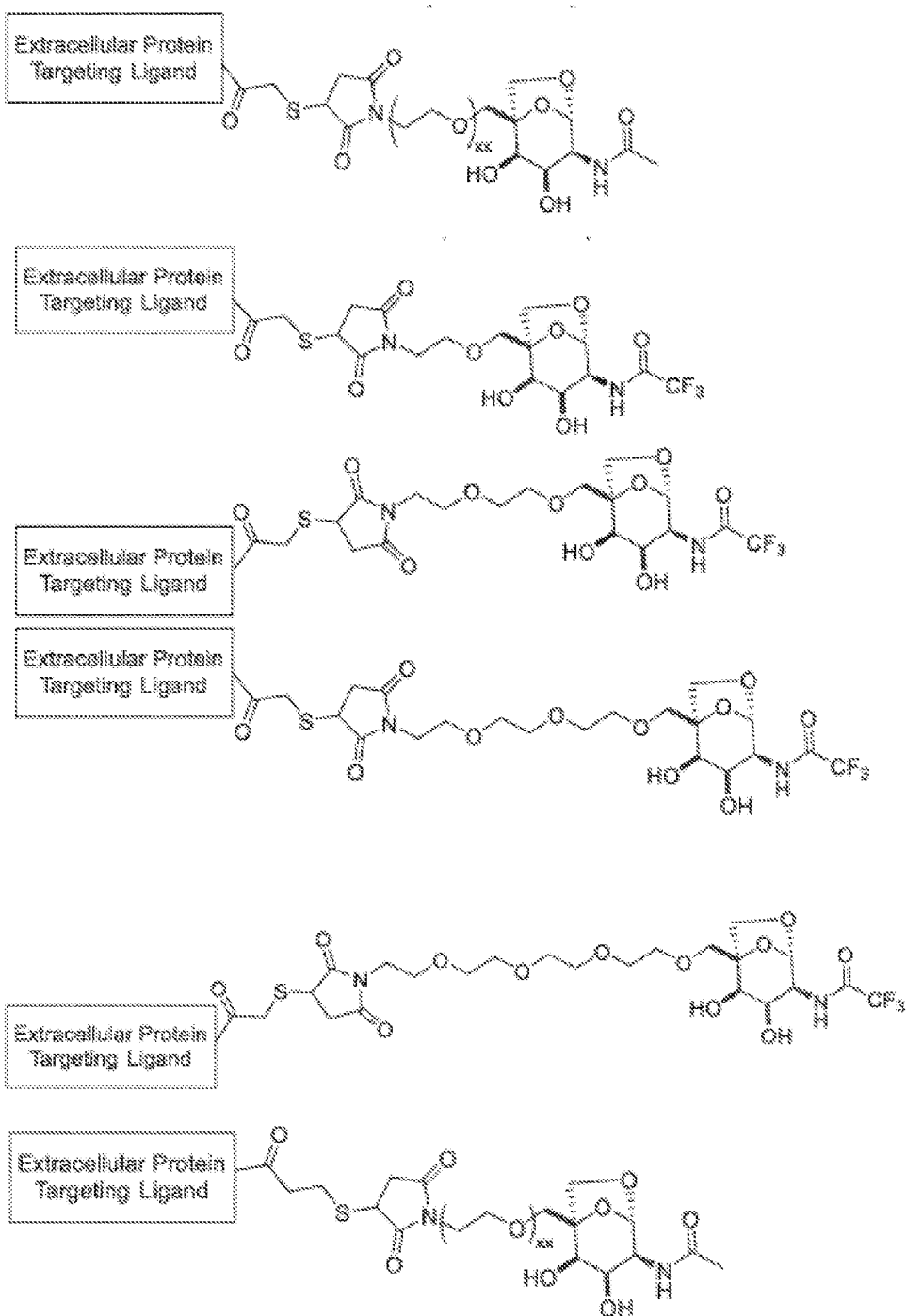


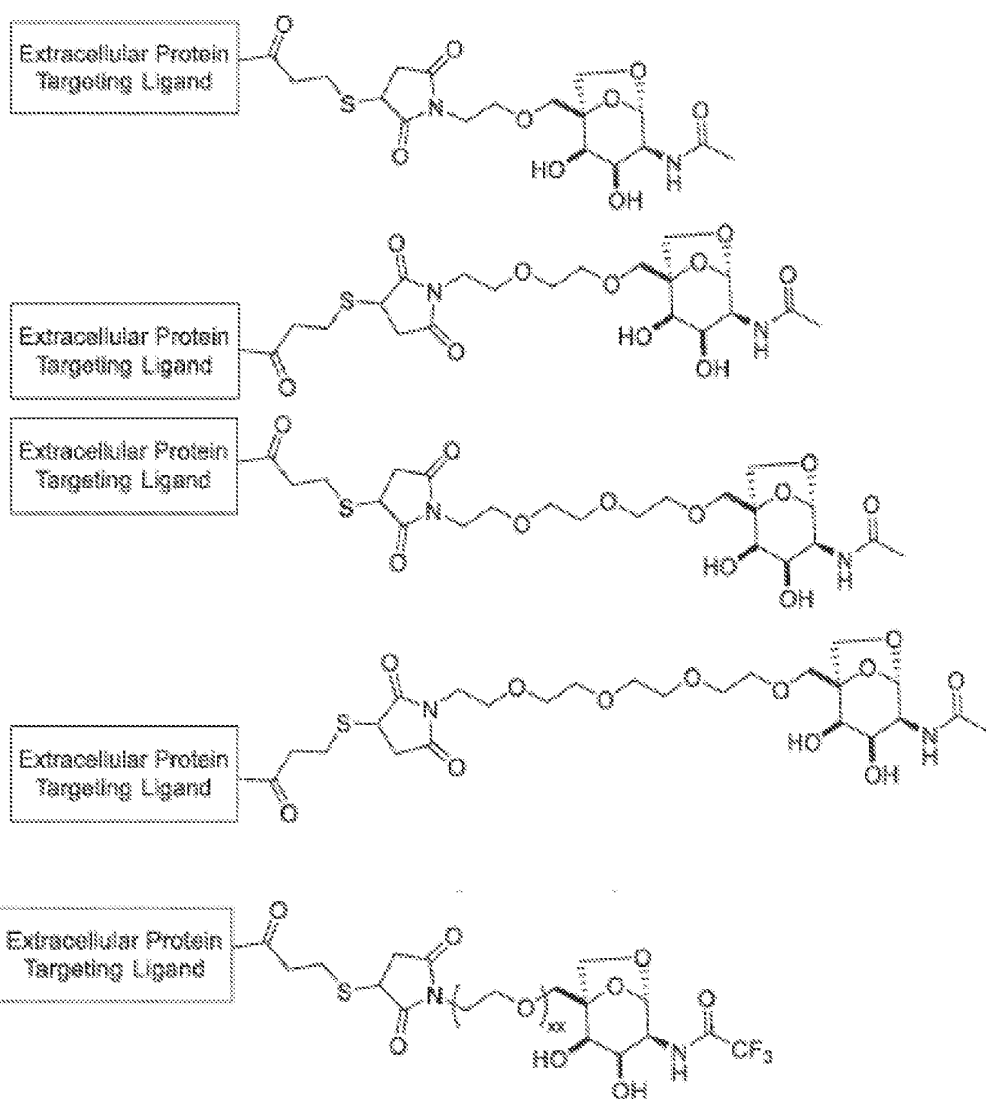


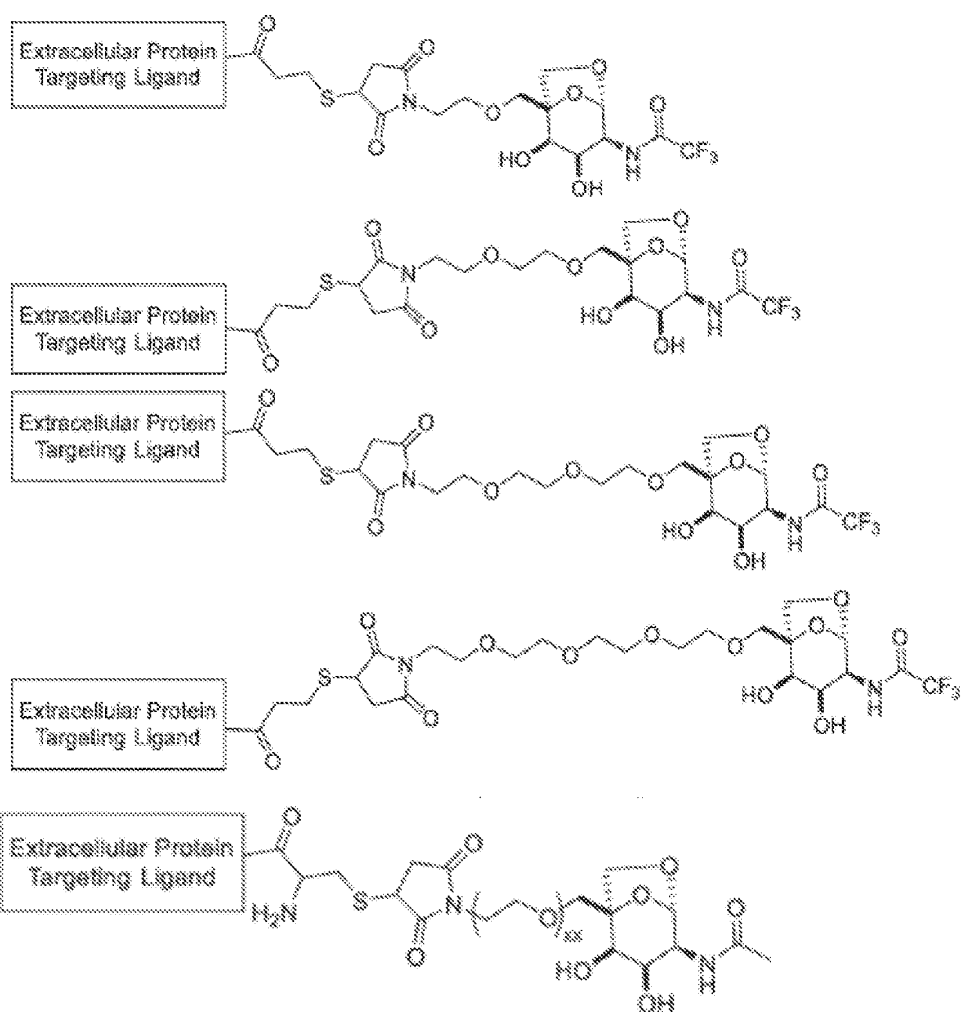


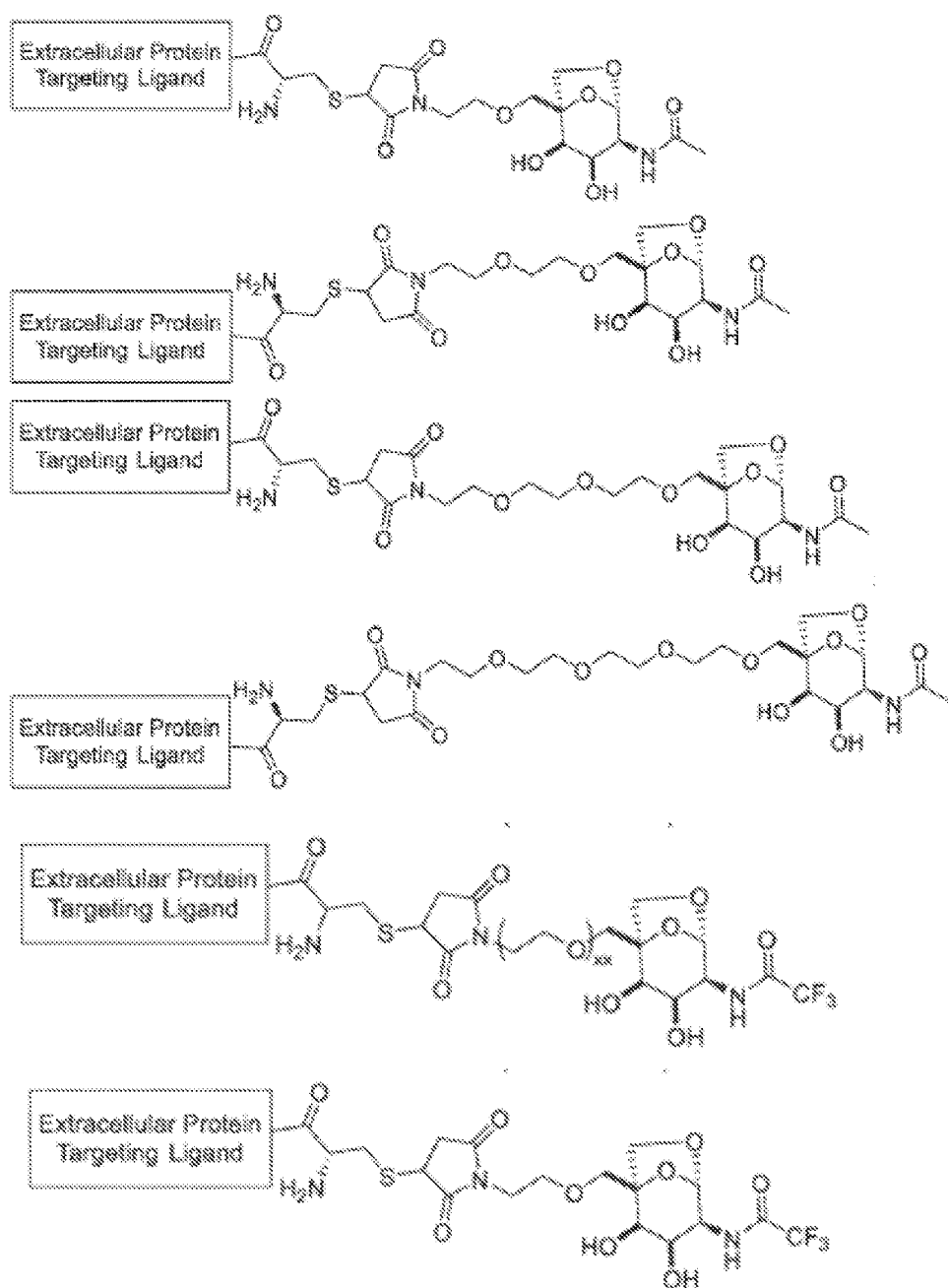


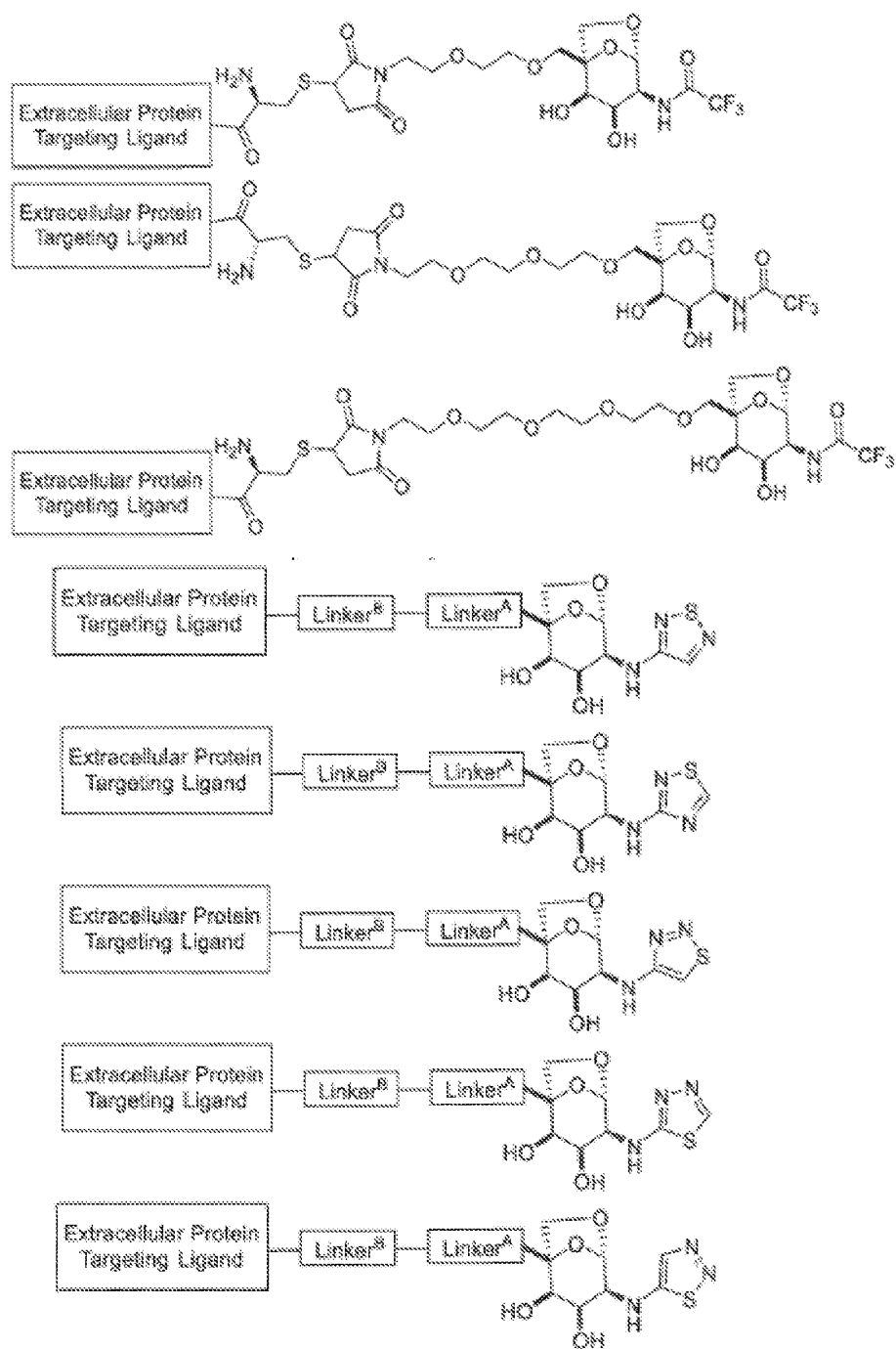


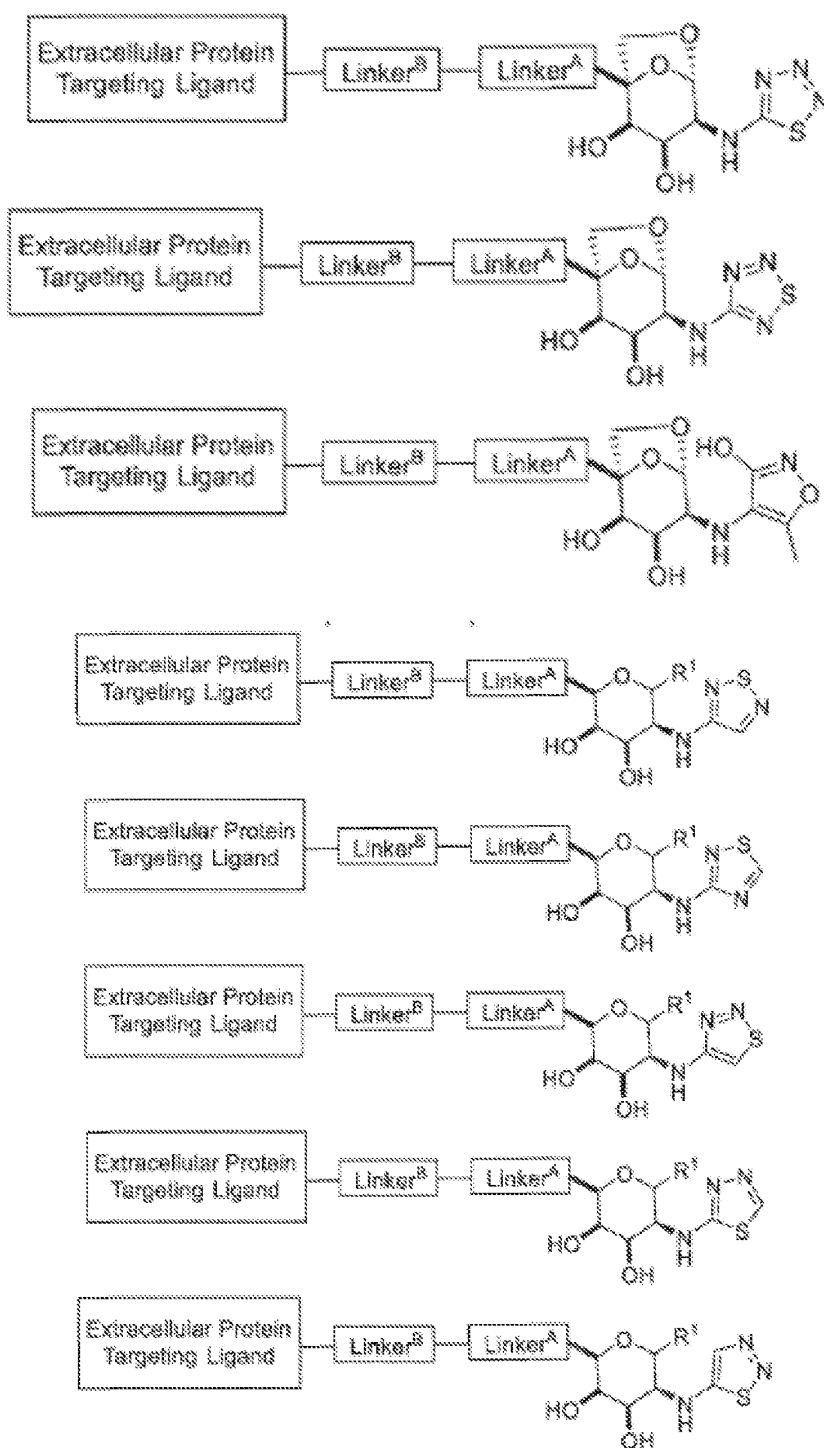


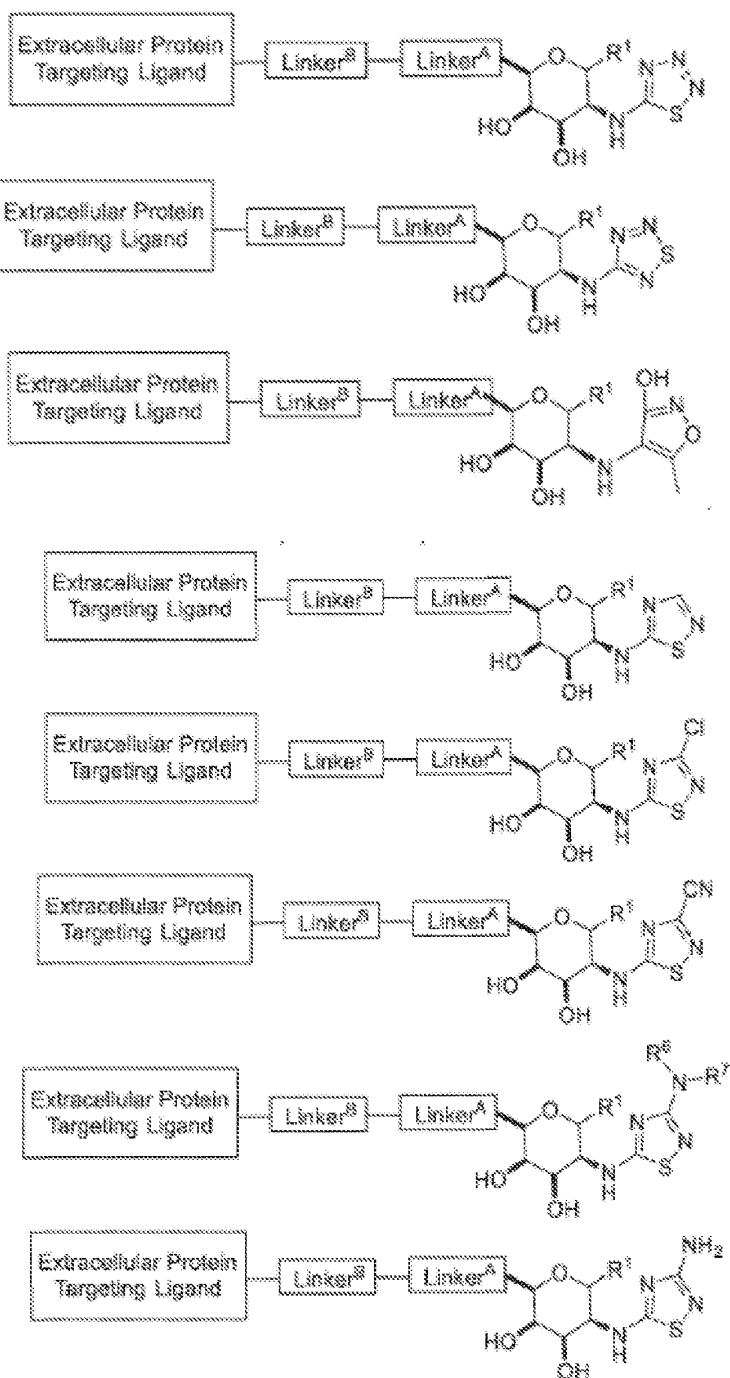


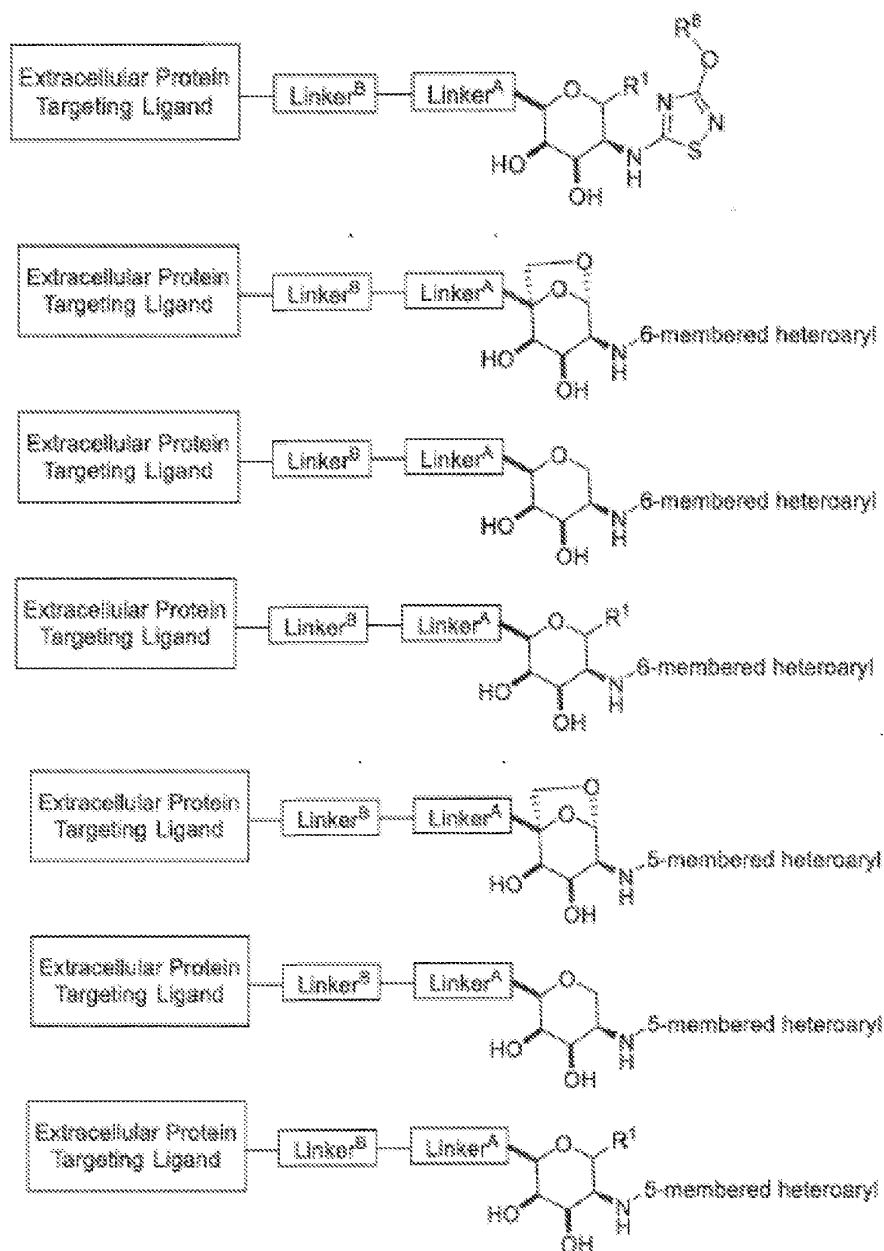


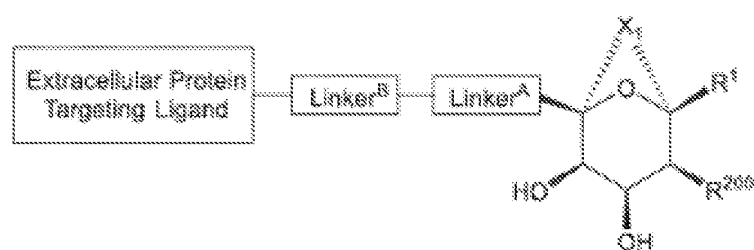
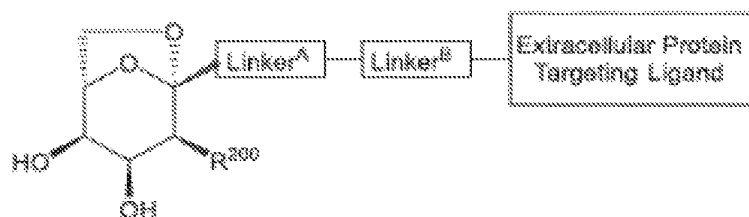
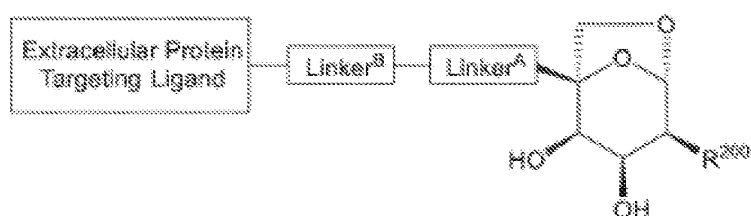
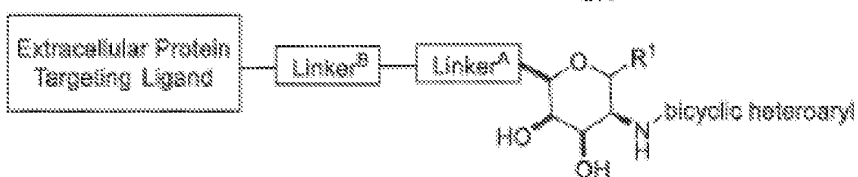
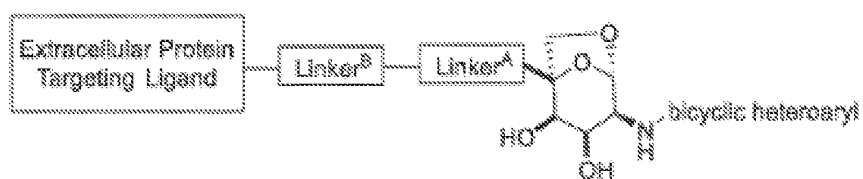


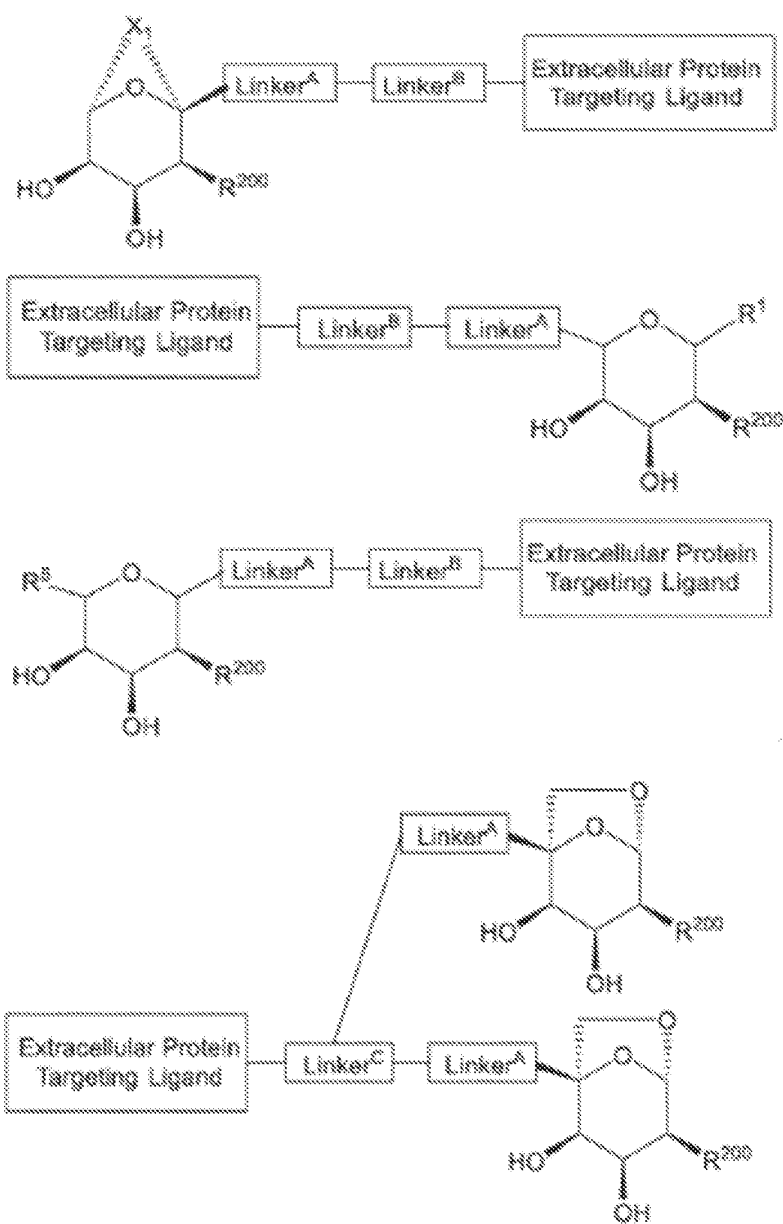


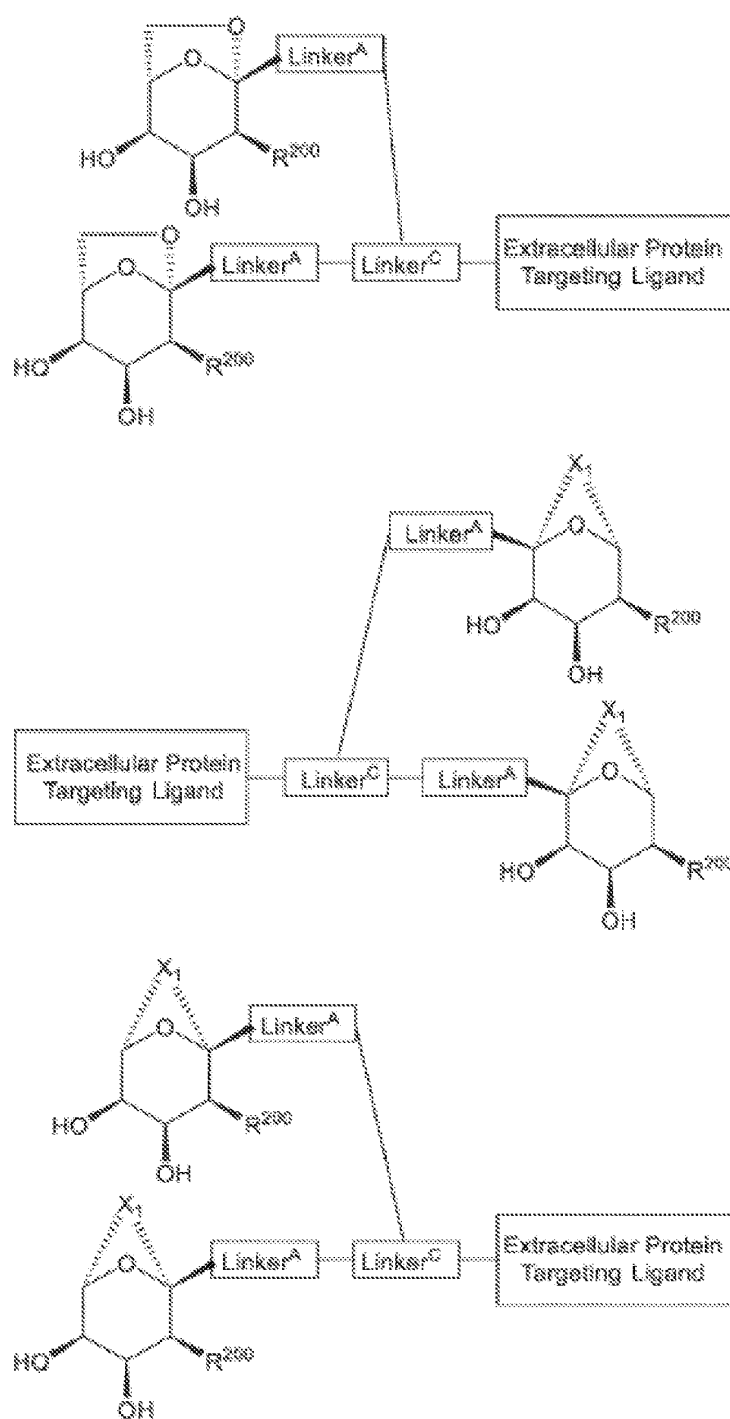


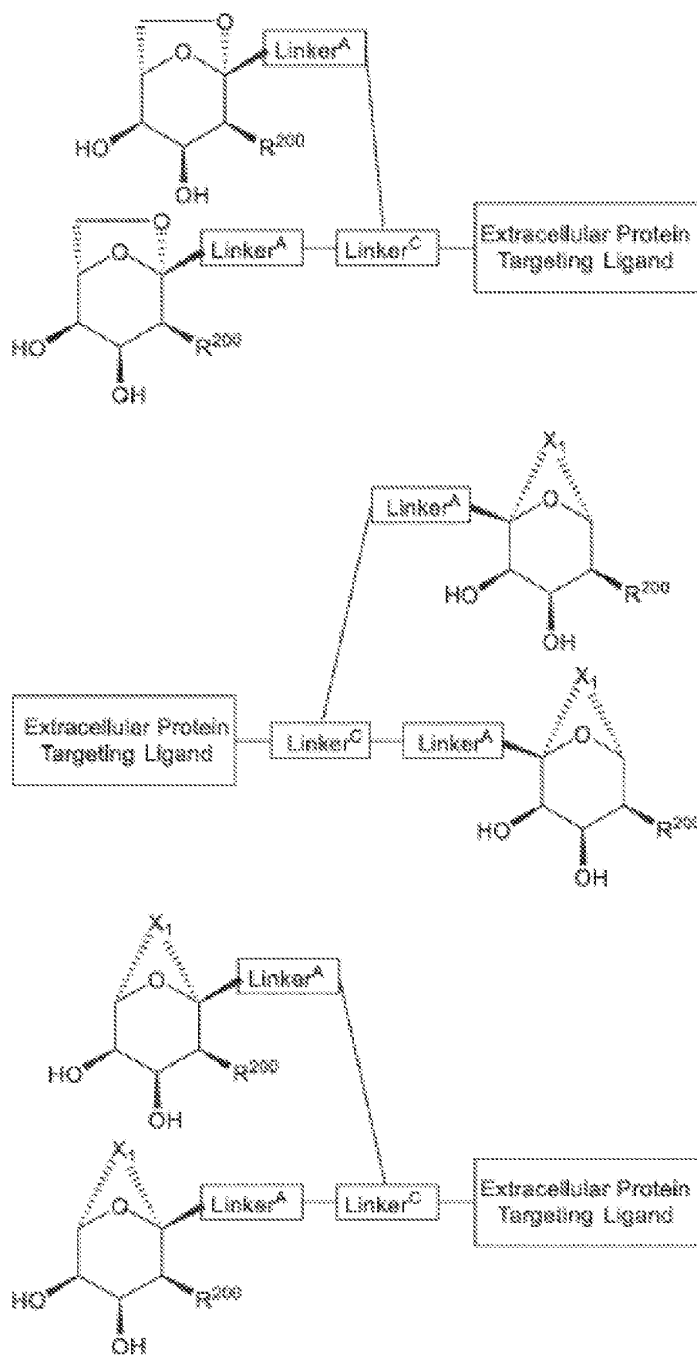


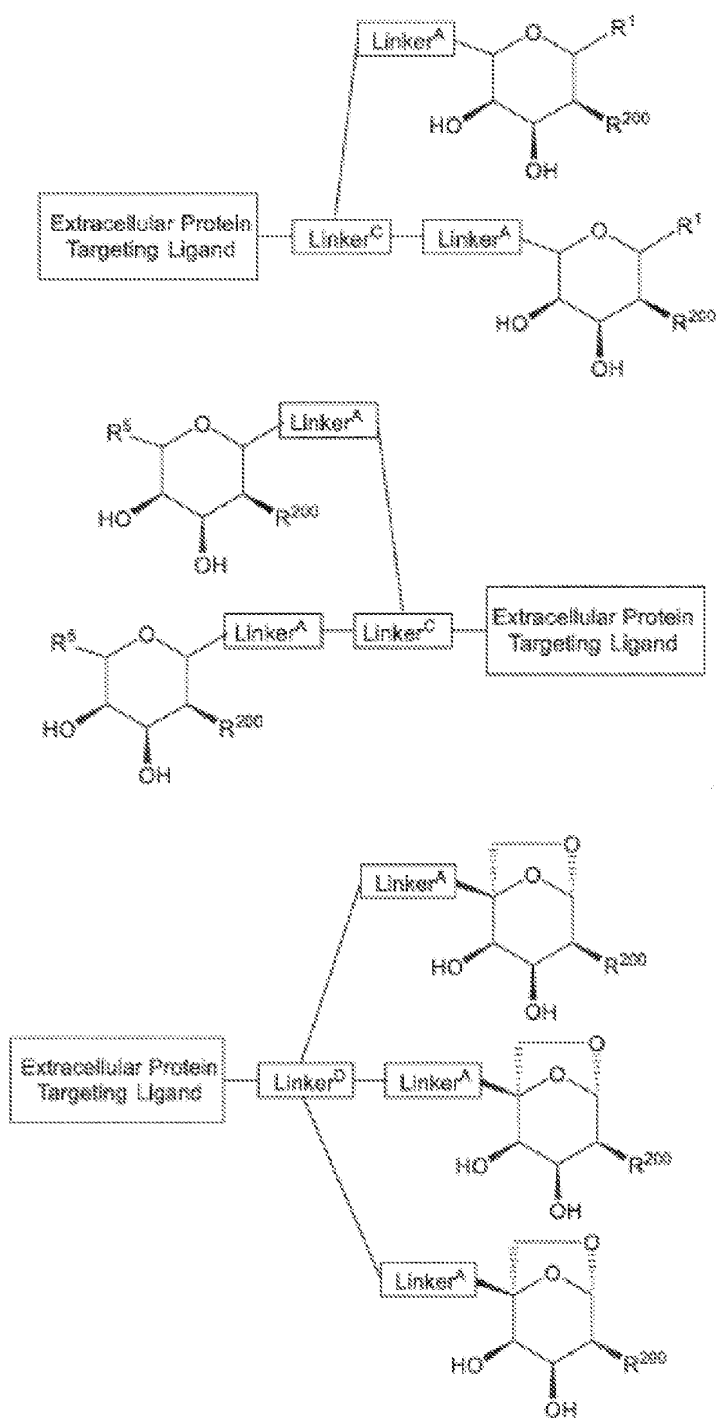


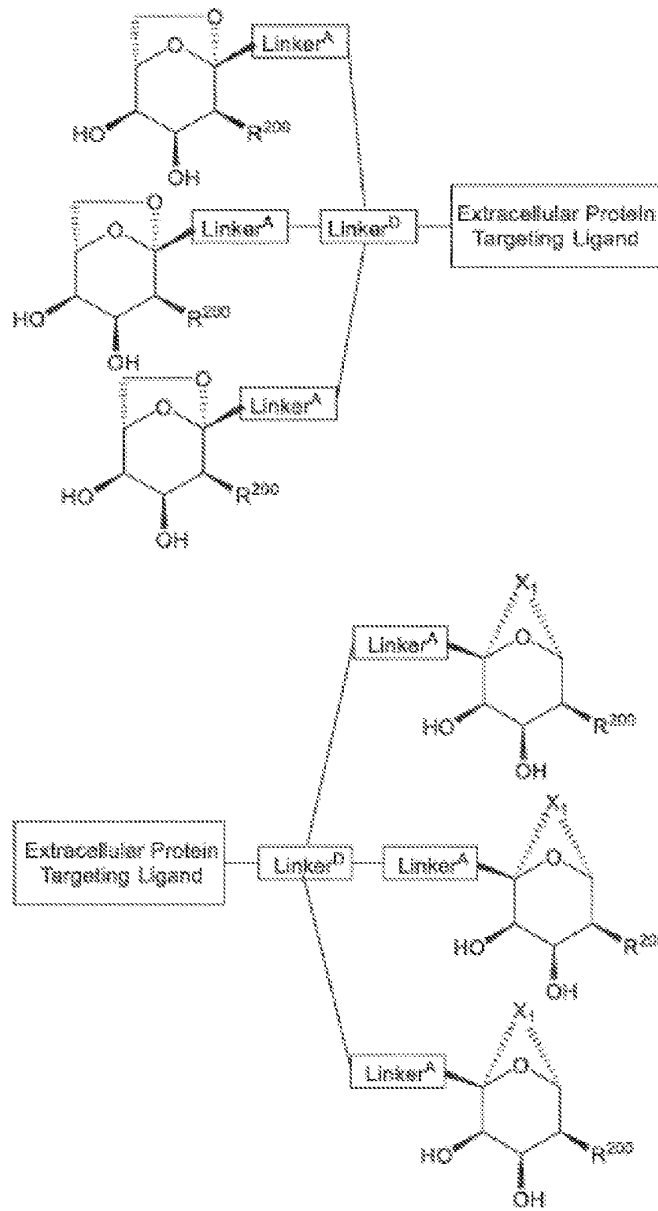


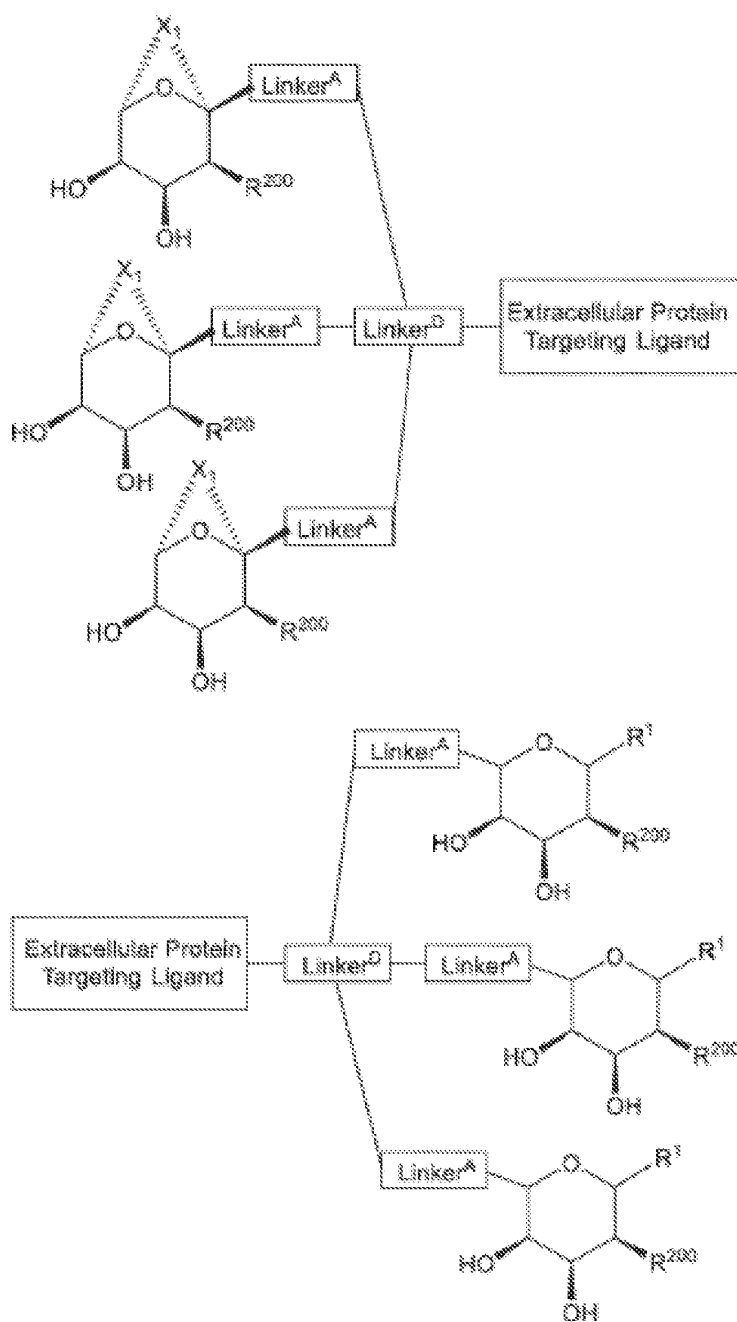


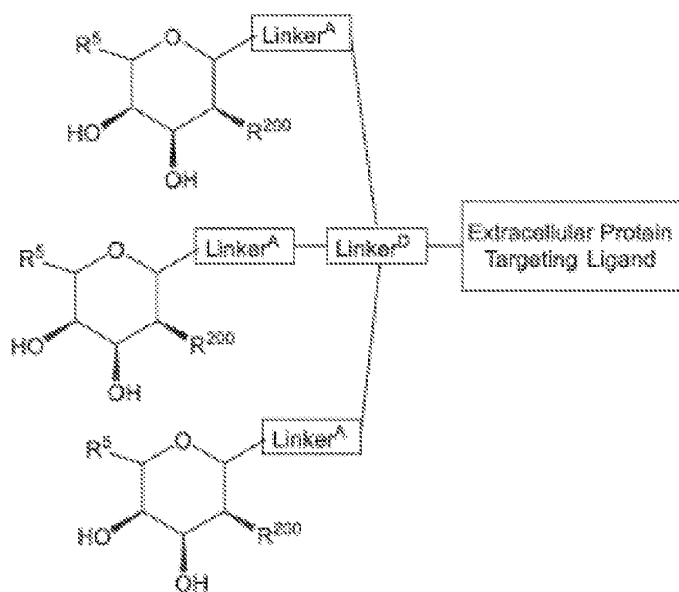




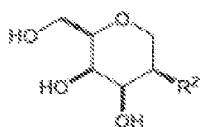




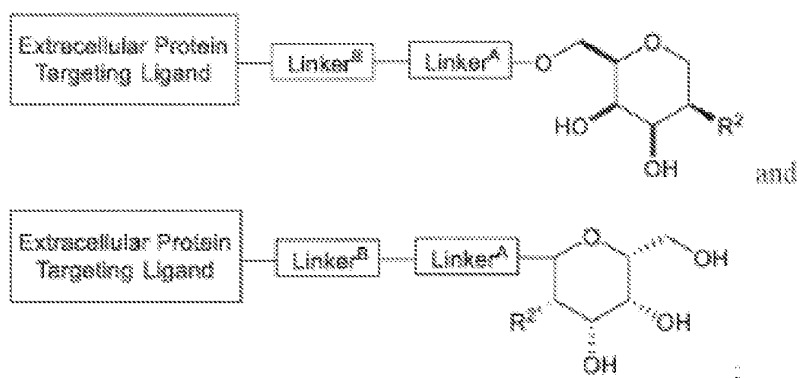




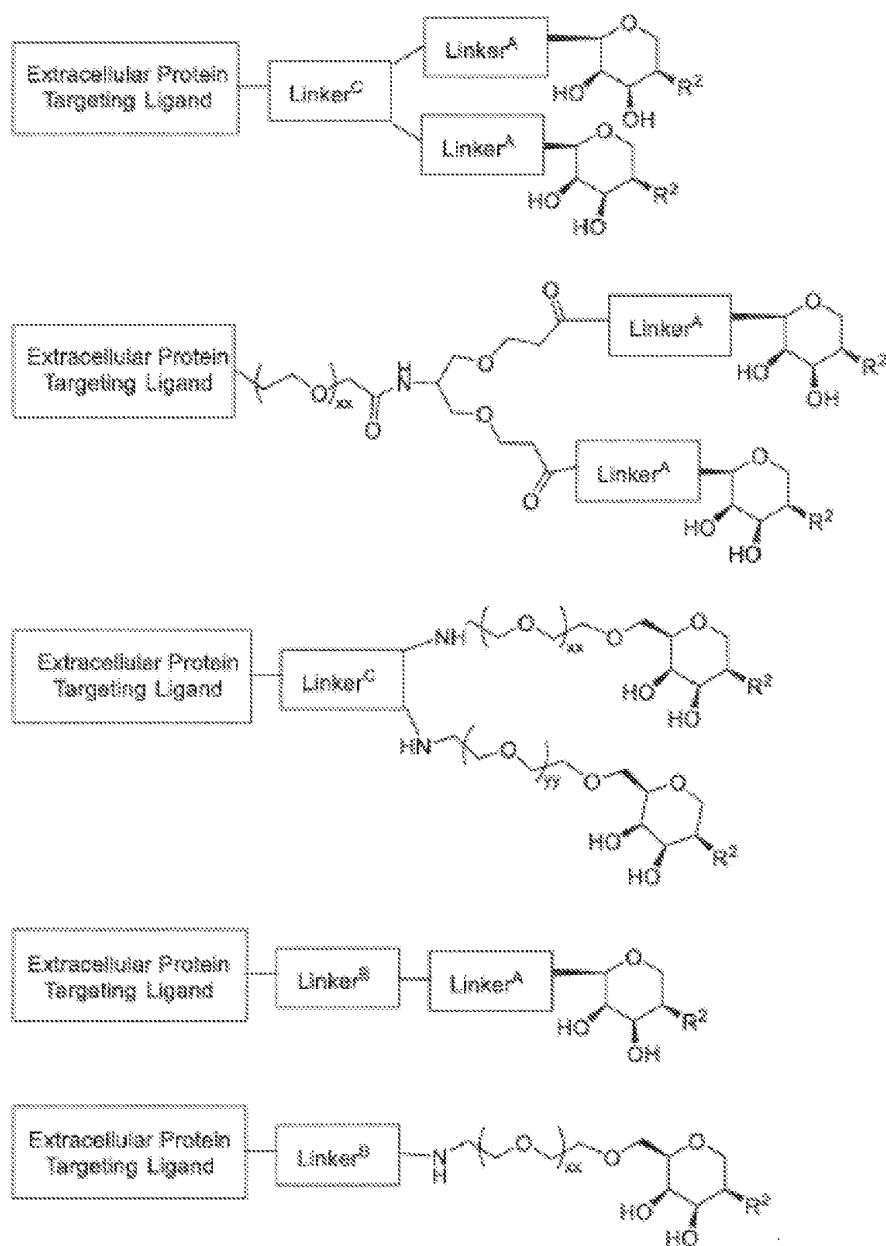
In various embodiments, AG is derived from the partial structure



Then non-limiting examples of AG of compounds of Formulae (I), (II) or (III) include:

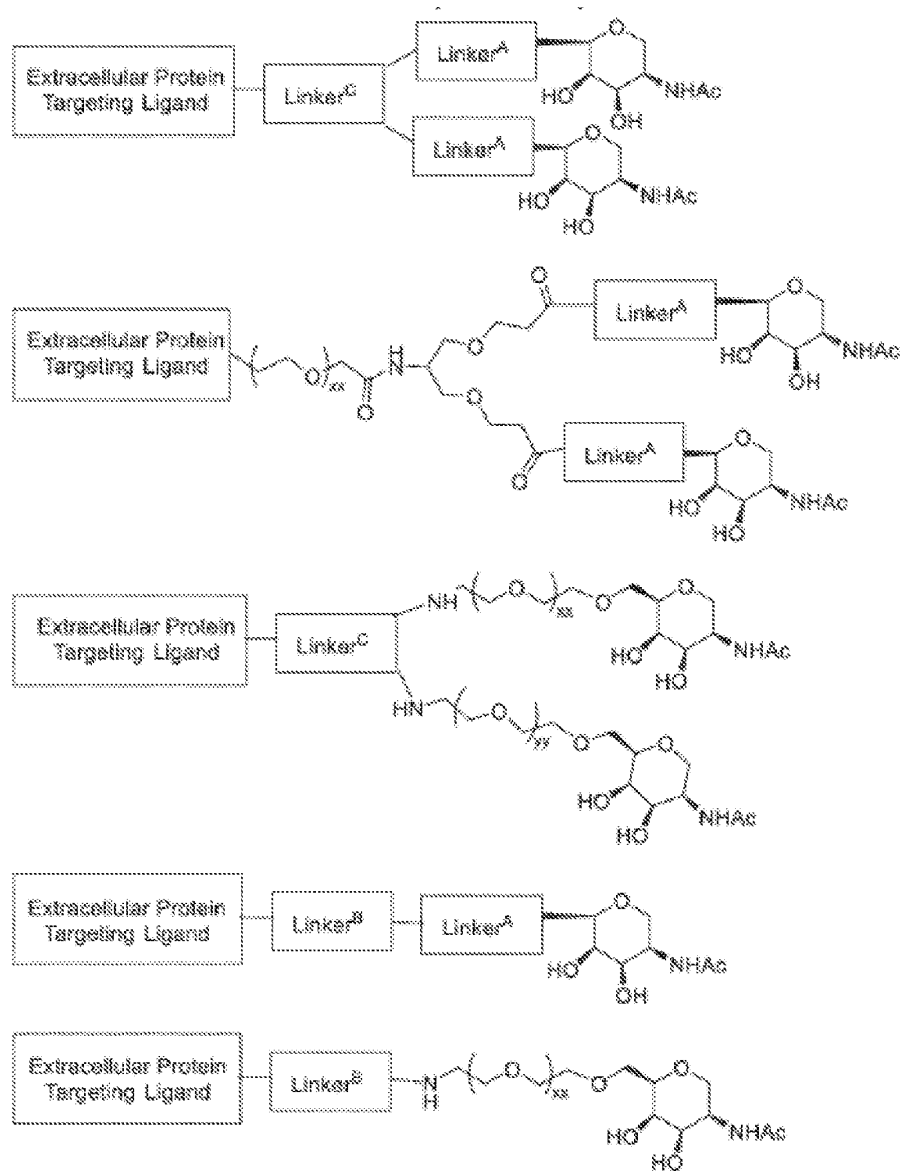


In some embodiments, the compounds of the present invention are selected from:

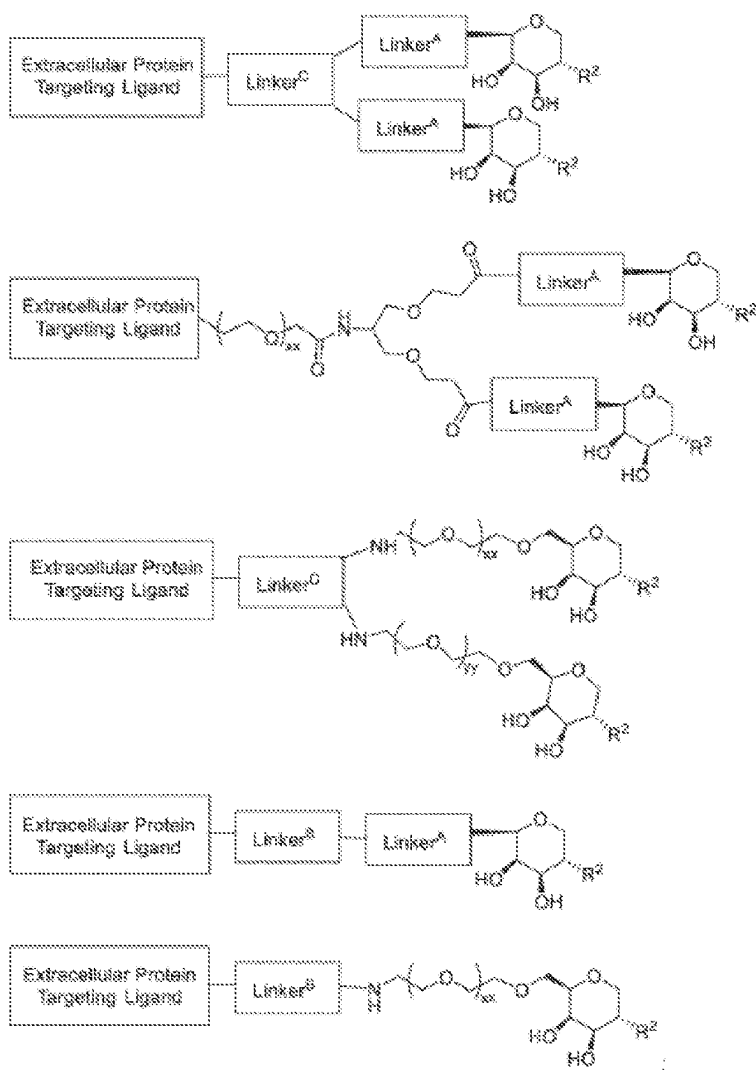


wherein in certain embodiments R² is selected from -NR⁶COR³, -NR⁶-(5-membered heteroaryl), and -NR⁶-(6-membered heteroaryl), each of which R² groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

In certain embodiments, the compounds of Formulae (II) or (III) are selected from:

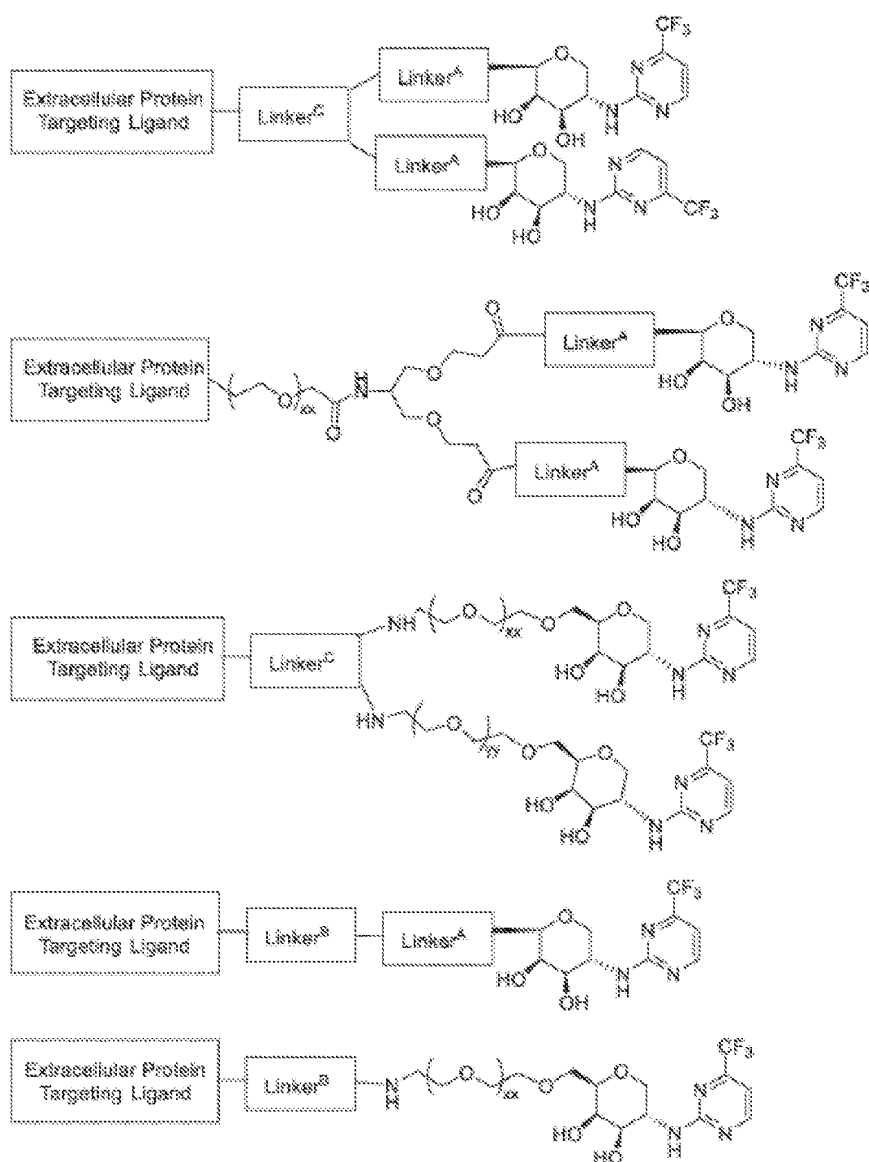


In certain embodiments, the compounds of Formulae (I), (II) or (III) are selected from:

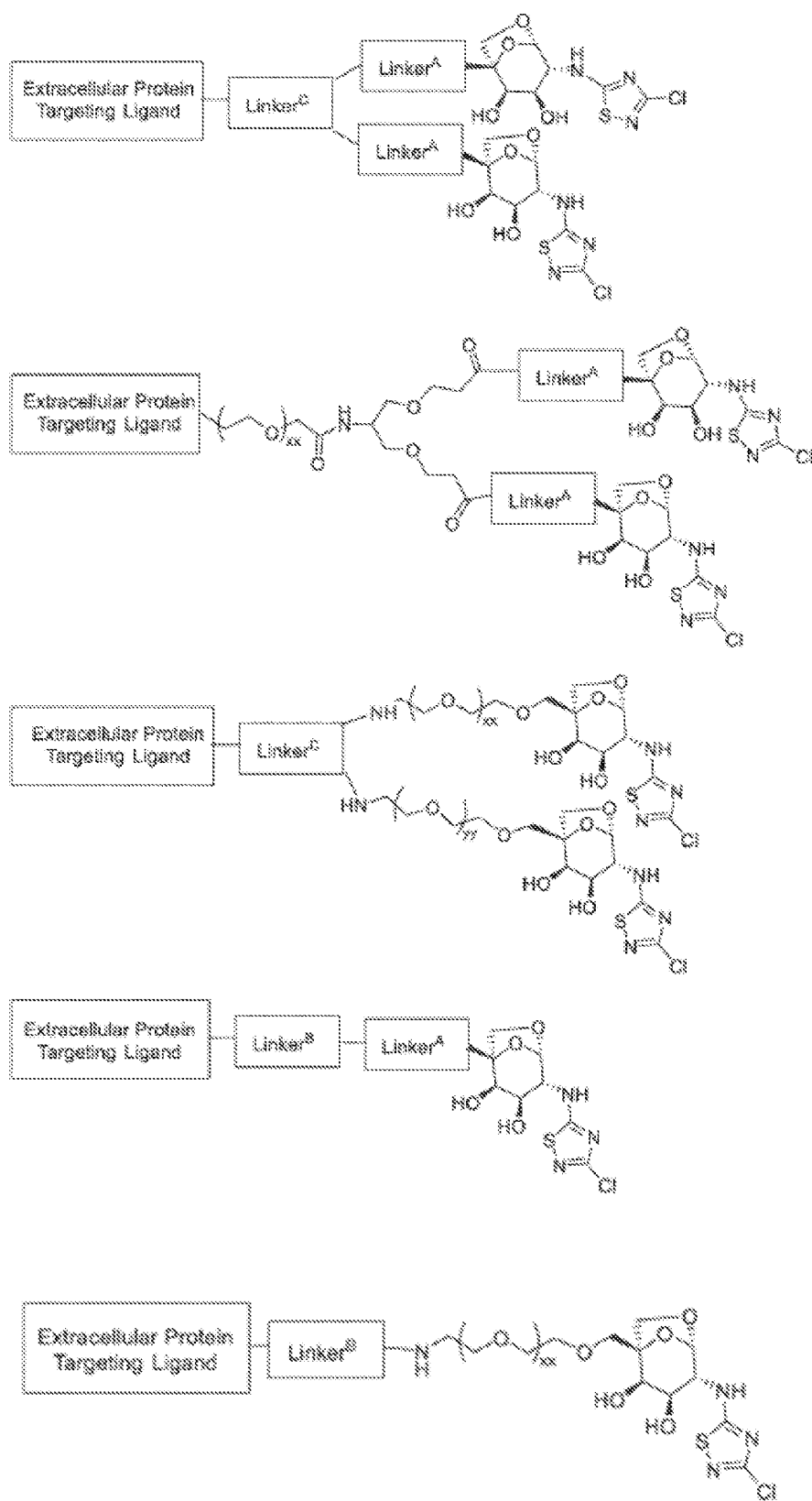


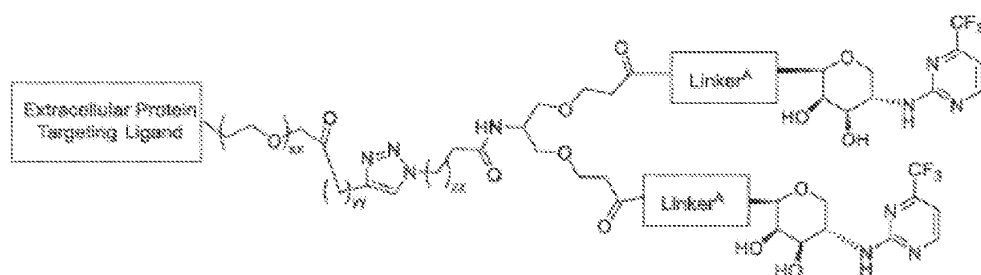
wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$ -(5-membered heteroaryl), and $-NR^6$ -(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

In certain embodiments, the compounds of Formulae (I), (II) or (III) are selected from:

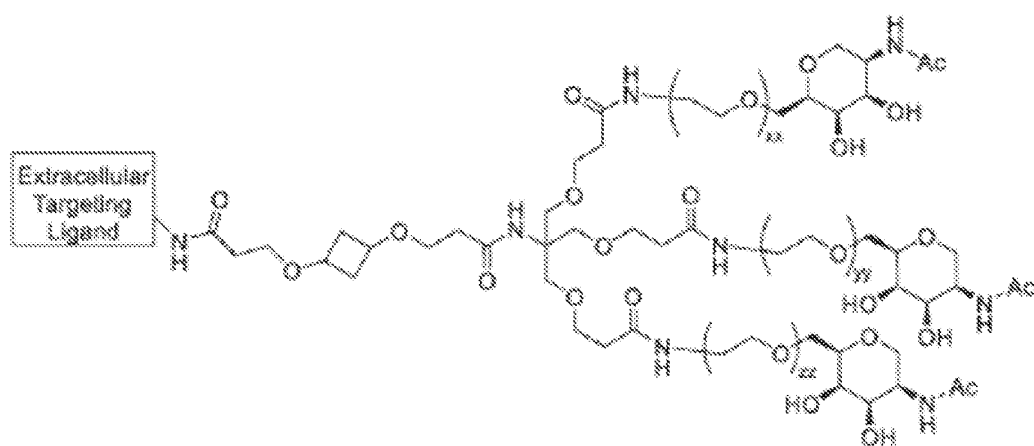
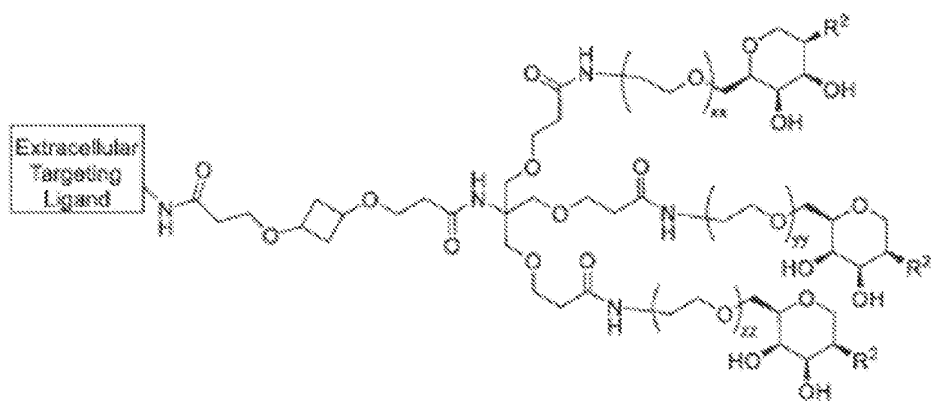


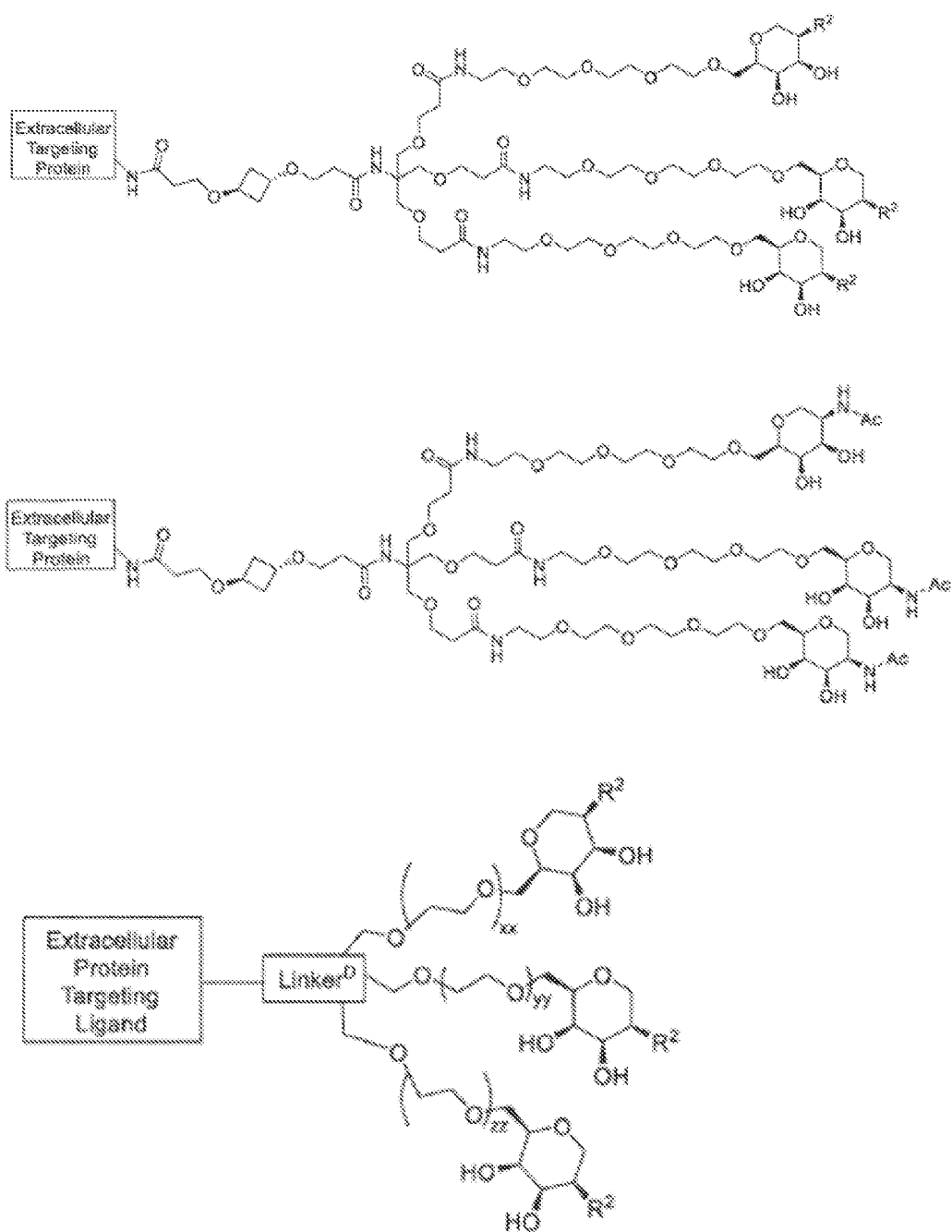
In certain embodiments, the compounds of Formulae (I), (II) or (III) are selected from:

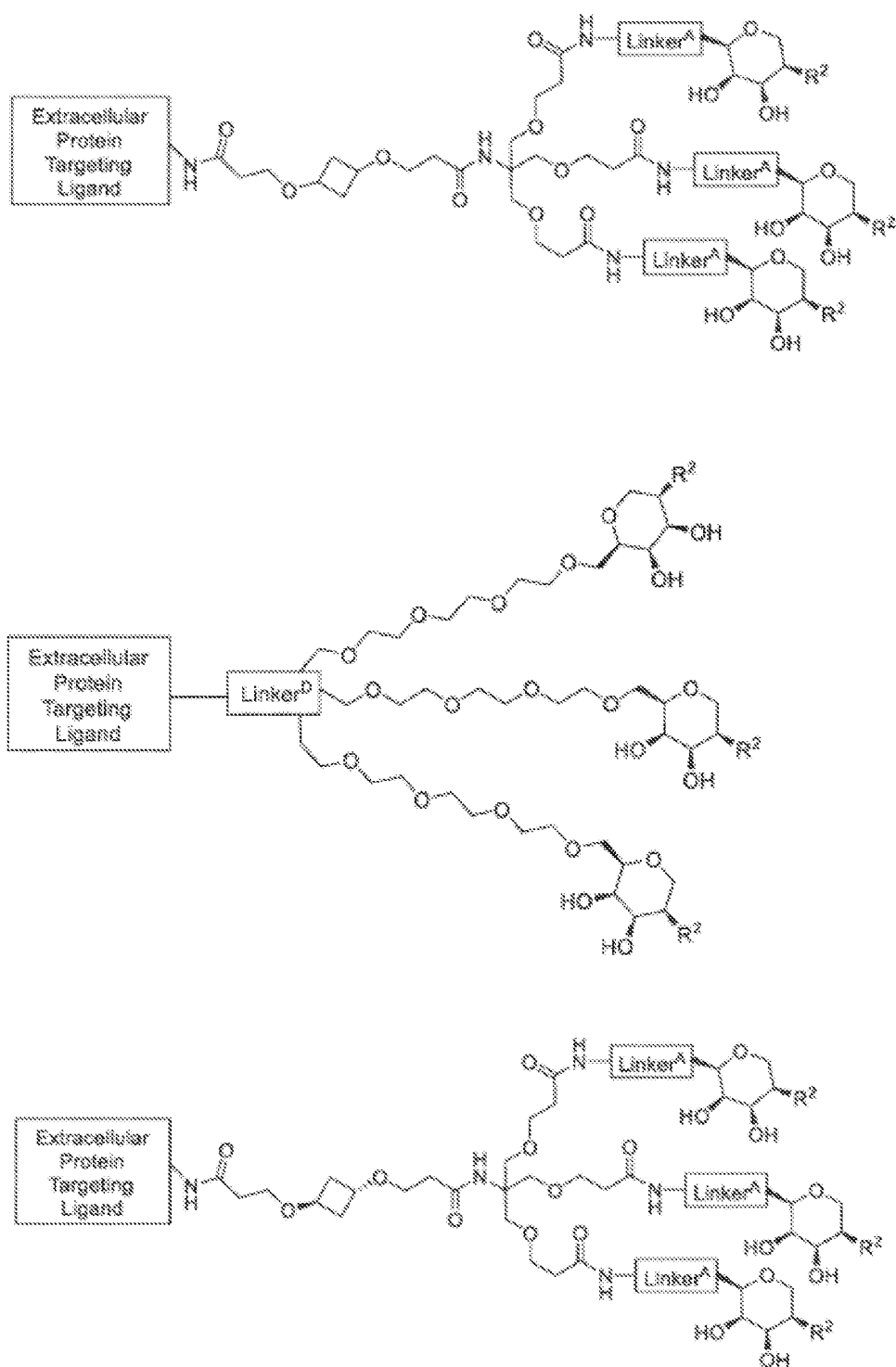




In certain embodiments, the compounds of Formulae (II) or (III) are selected from:

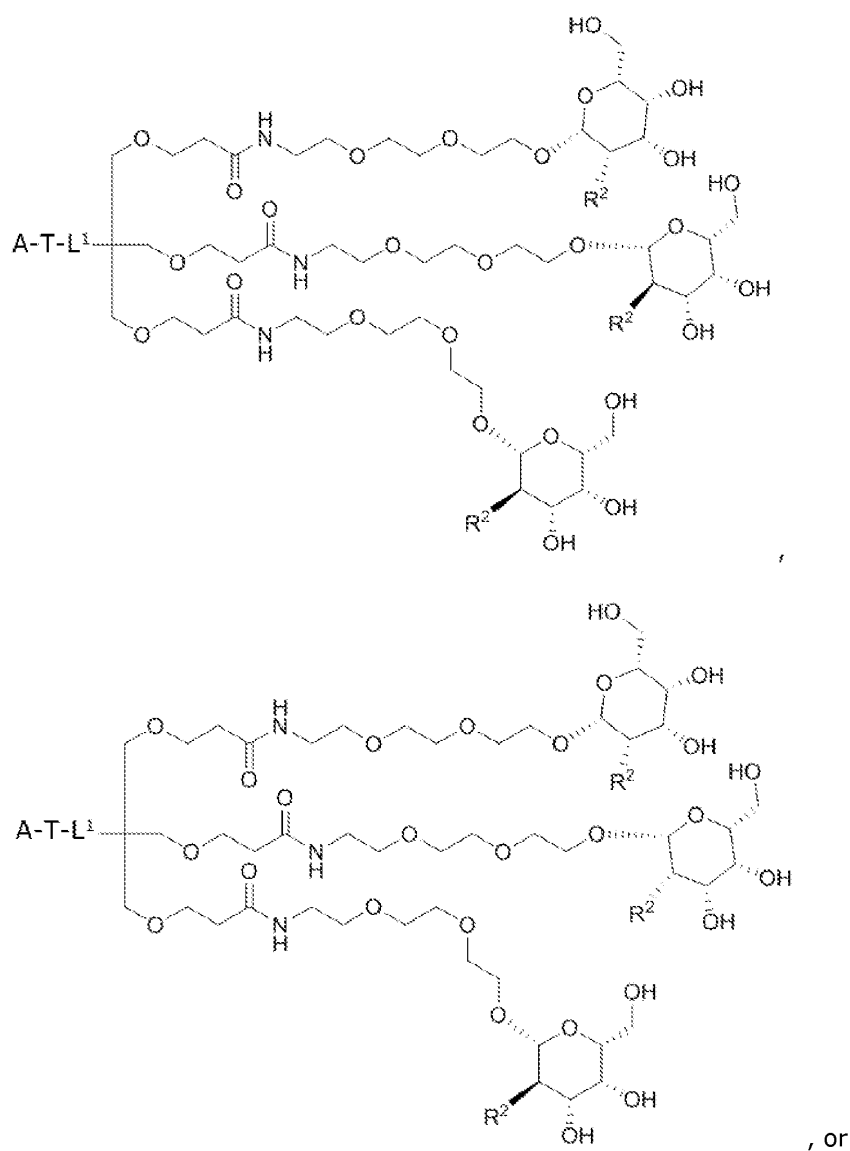


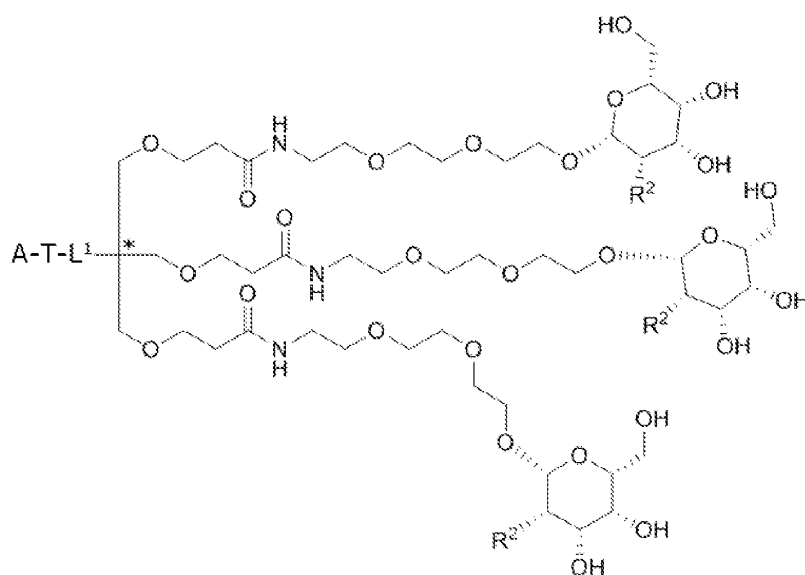




C. The ASGPR Ligand/Binding Moiety in Compounds of Formula II

In a preferred embodiment, the compounds of the present invention have a structure selected from the group consisting of:





wherein L1 comprises or consists of a group -Z_B-NH-, wherein the NH group is bonded to the tertiary carbon atom marked with * and R² is RR;

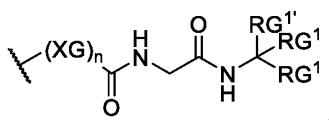
Z_B is absent, $(CH_2)_{IM}$, $C(O)-(CH_2)_{IM}-$, or $C(O)-(CH_2)_{IM}-NR_M-$;

IM is as defined above;

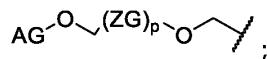
R_M is H or a C₁-C₃ alkyl group optionally substituted with one or two hydroxyl groups.

Further groups -T-L1-Con(L2-AG)n

In a preferred embodiment the compounds of Formula (II) or (III) are of Formula (II), wherein -L¹-Con(L²-AG)_n has the structure:



wherein $RG^{1'}$ is



AG is an aminosaccharide;

each occurrence of XG is independently selected from the group consisting of -CH₂-, -C(=O)-, -NH-, and -O-;

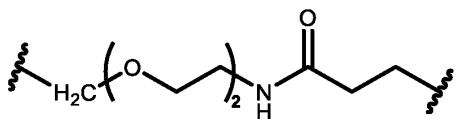
each occurrence of ZG is independently selected from the group consisting of -CH₂-, -C(=O)-, -NH-, and -O-;

m is an integer from 2 to 10;

n is an integer from 1 to 100; and

p is an integer from 1 to 50.

In a more preferred embodiment (ZG)_p has the structure:



Definition L1 and L2

In a further preferred embodiments L¹ or L² or both comprise one or more units selected from the group consisting of $-(\text{CH}_2\text{CH}_2\text{-O})_q-$, $-(\text{CH}_2\text{CH}(\text{CH}_2\text{OCH}_3)\text{-O})_q-$ and $-(\text{CH}_2\text{CH}(\text{CH}_2\text{OCH}_2\text{CH}_3)\text{-O})_q-$, wherein the values of q are independently of each other selected from an integer in the range of 1 to 10, preferably 1 to 4.

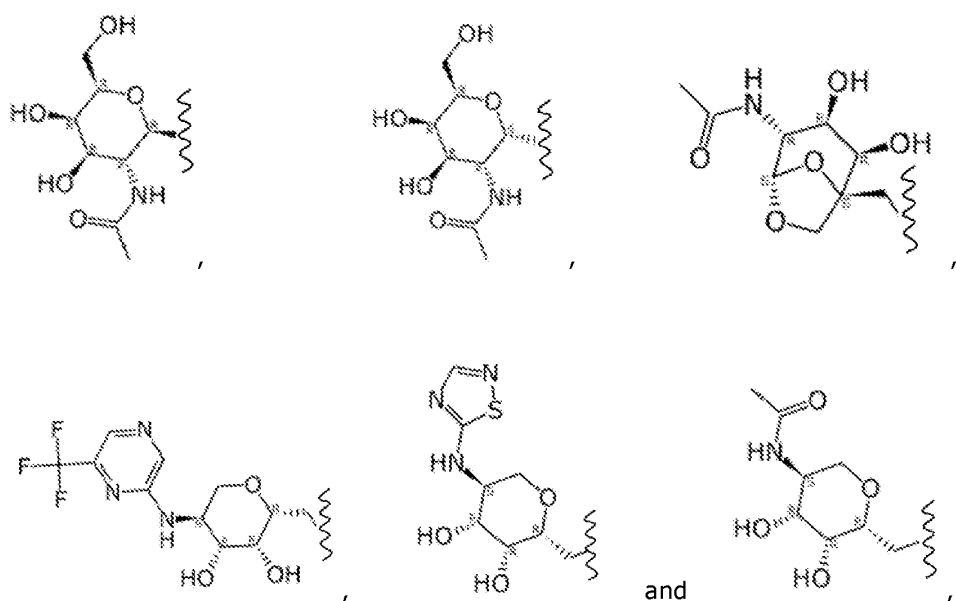
In even more preferred embodiments of the present invention, at least one of L¹ and L² is selected from the group consisting of

- (a) $-\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{-NH-}(\text{CH}_2\text{CH}_2\text{-O})_3\text{-CH}_2\text{CH}_2\text{C}(=\text{O})\text{-NH-CH}_2\text{C}(=\text{O})\text{-NH-}$,
- (b) $-\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{C}(=\text{O})\text{-NH-CH}_2\text{C}(=\text{O})\text{-NH-}$,
- (c) $-\text{CH}_2\text{-O-}(\text{CH}_2\text{CH}_2\text{-O})_3\text{-CH}_2\text{CH}_2\text{C}(=\text{O})\text{-NH-CH}_2\text{C}(=\text{O})\text{-NH-}$,
- (d) $-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{-NHCH}_2\text{C}(=\text{O})\text{-NH-}$,
- (e) $-\text{CH}_2\text{-O-}(\text{CH}_2\text{CH}_2\text{-O})_3-$,
- (f) $-\text{NH-C}(=\text{O})\text{-CH}_2\text{-O-CH}_2\text{CH}_2\text{-O-CH}_2\text{C}(=\text{O})\text{-NH-}$ and
- (g) $-\text{O-CH}_2\text{CH}_2\text{C}(=\text{O})\text{-NH-}(\text{CH}_2\text{CH}_2\text{-O})_3-$

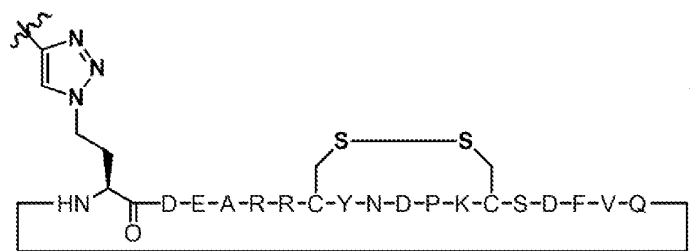
or L² is a direct bond. In even more preferred embodiments L¹ is selected from the group consisting of items (a) to (f). In these embodiments the linker is preferably bonded to T by the terminal carbon atom. Embodiments of the present invention in which L¹ is selected from the group consisting of items (a) to (f) and wherein L² is selected from the group consisting of item (g) and a direct bond are most preferred. The linker of items (a) to (f) are preferably bonded to T by the terminal carbon atom and the linker of item (g) is preferably bonded to AG by the terminal trimethylene oxide group.

Combinations of L1 and L2 with A and AG

In a most preferred embodiment L¹ is selected from the group consisting of items (a) to (f), L², if present, is selected from the group consisting of item (g) and a direct bond, Con if present is selected from $-\text{CH}_{(3-n)}(\text{CH}_2)_n-$, wherein n is 2 or 3, AG is selected from the group consisting of



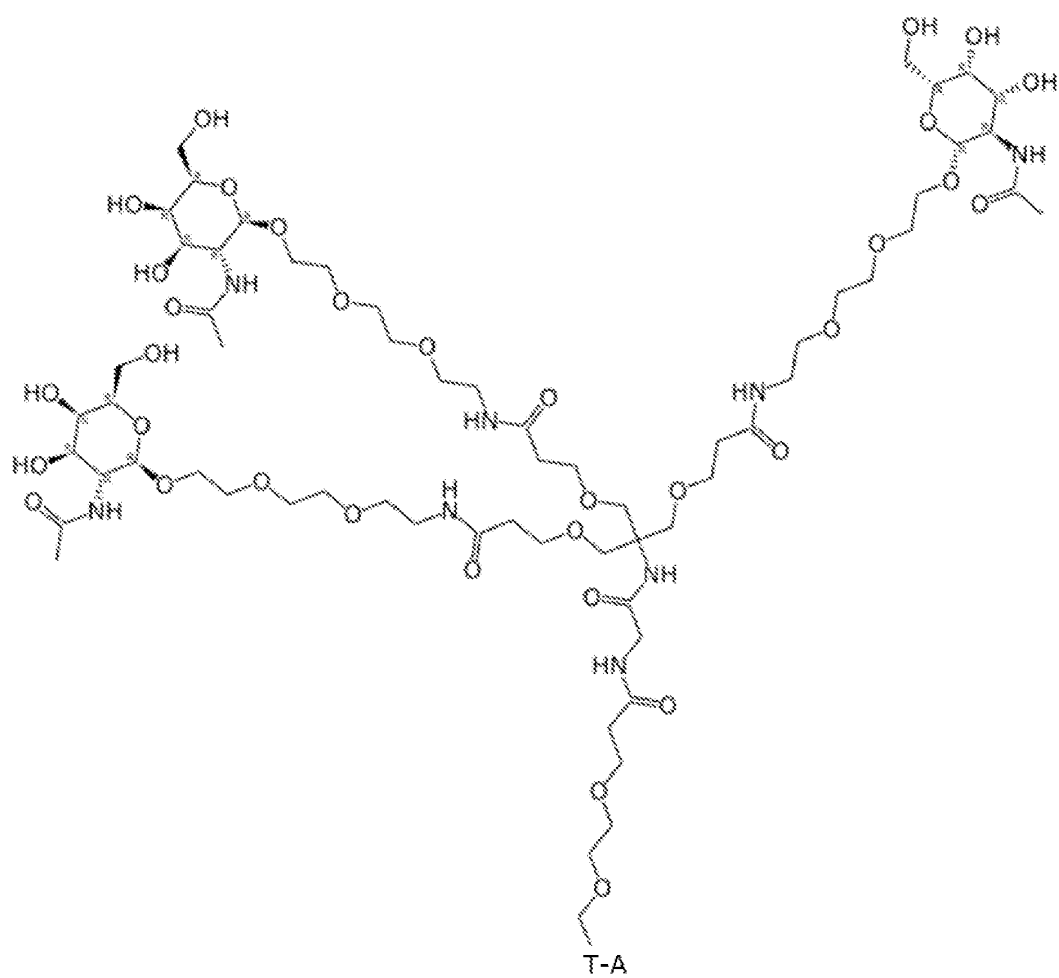
wherein the wavy lines mark the bond by which the sugar moiety is bonded to the remainder of the compounds of the present invention and A-T-is



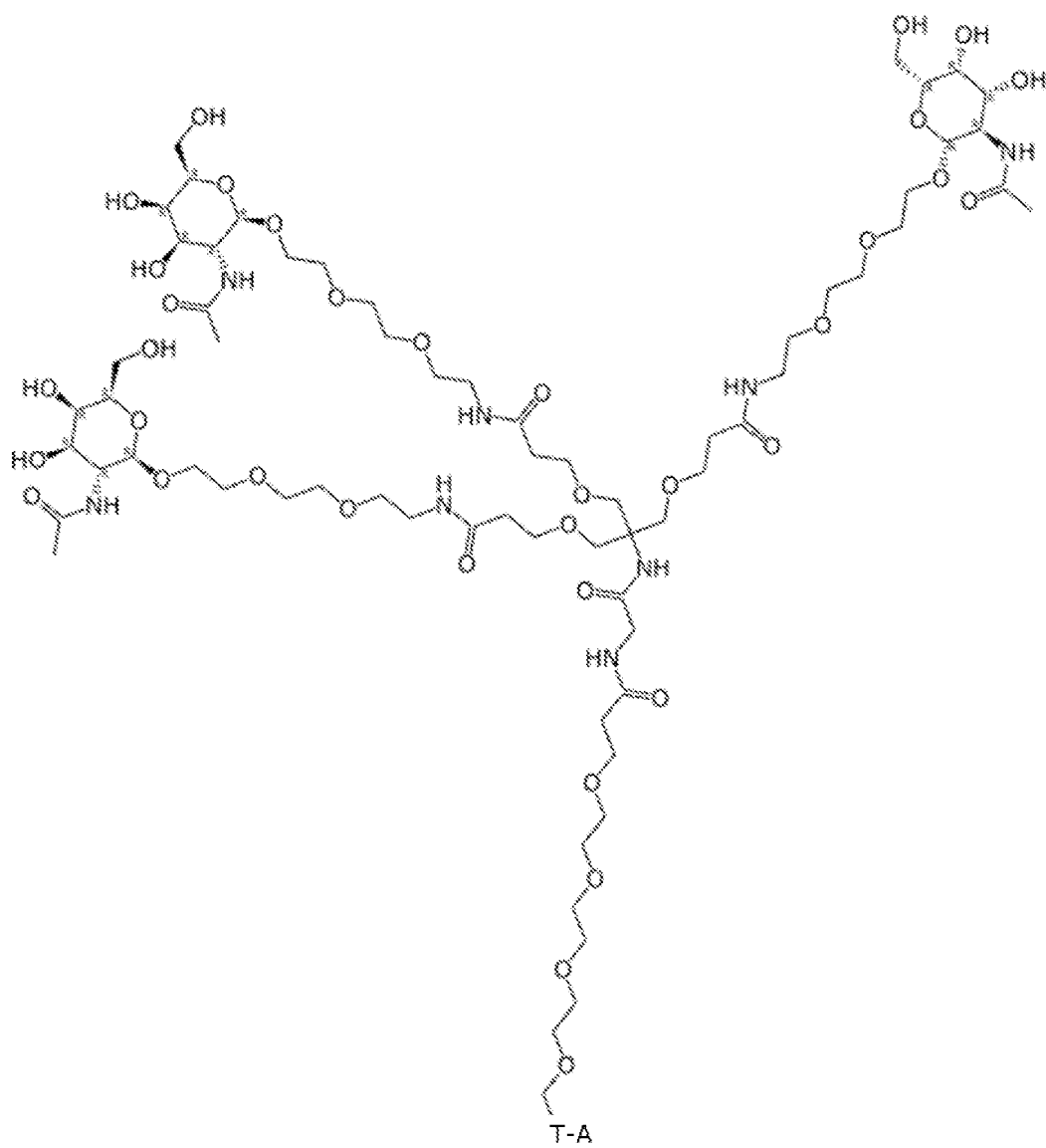
In this embodiment the linker of items (a) to (f) are preferably bonded to T by the terminal carbon atom and the linker of item (g) is preferably bonded to AG by the terminal trimethylene oxide group.

Single compounds

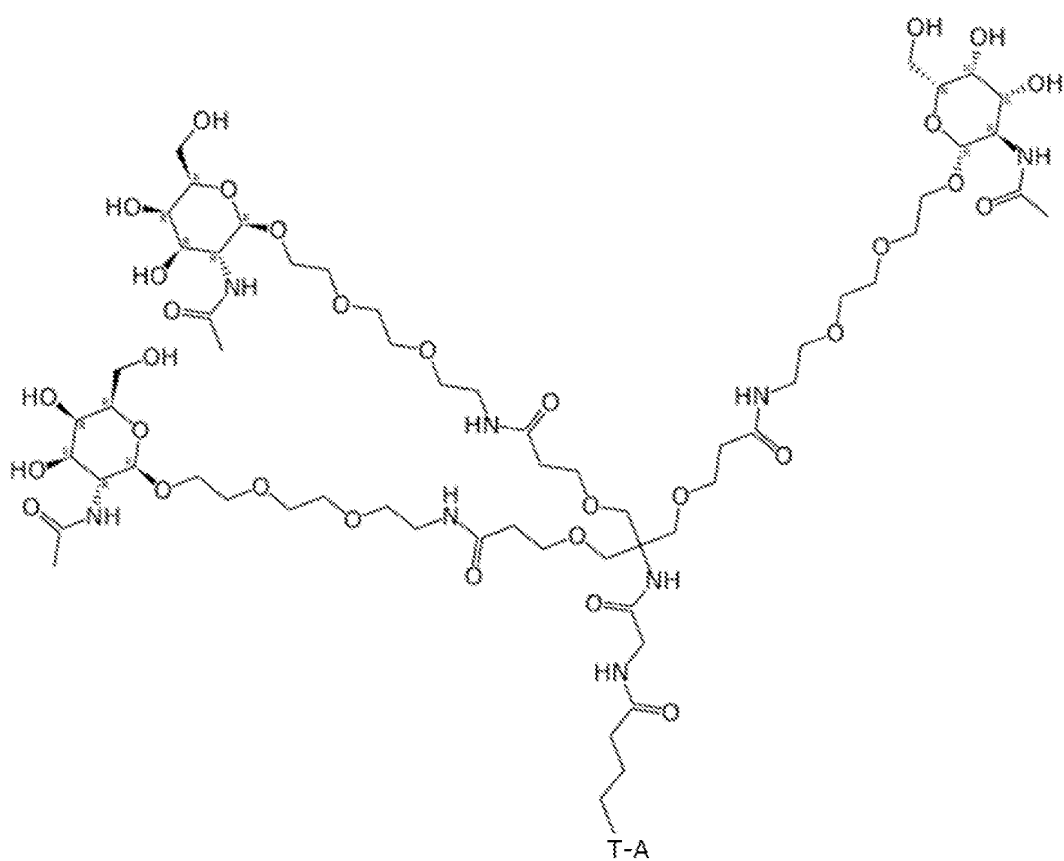
In a preferred embodiment, the compounds of the present invention are selected from the group consisting of:



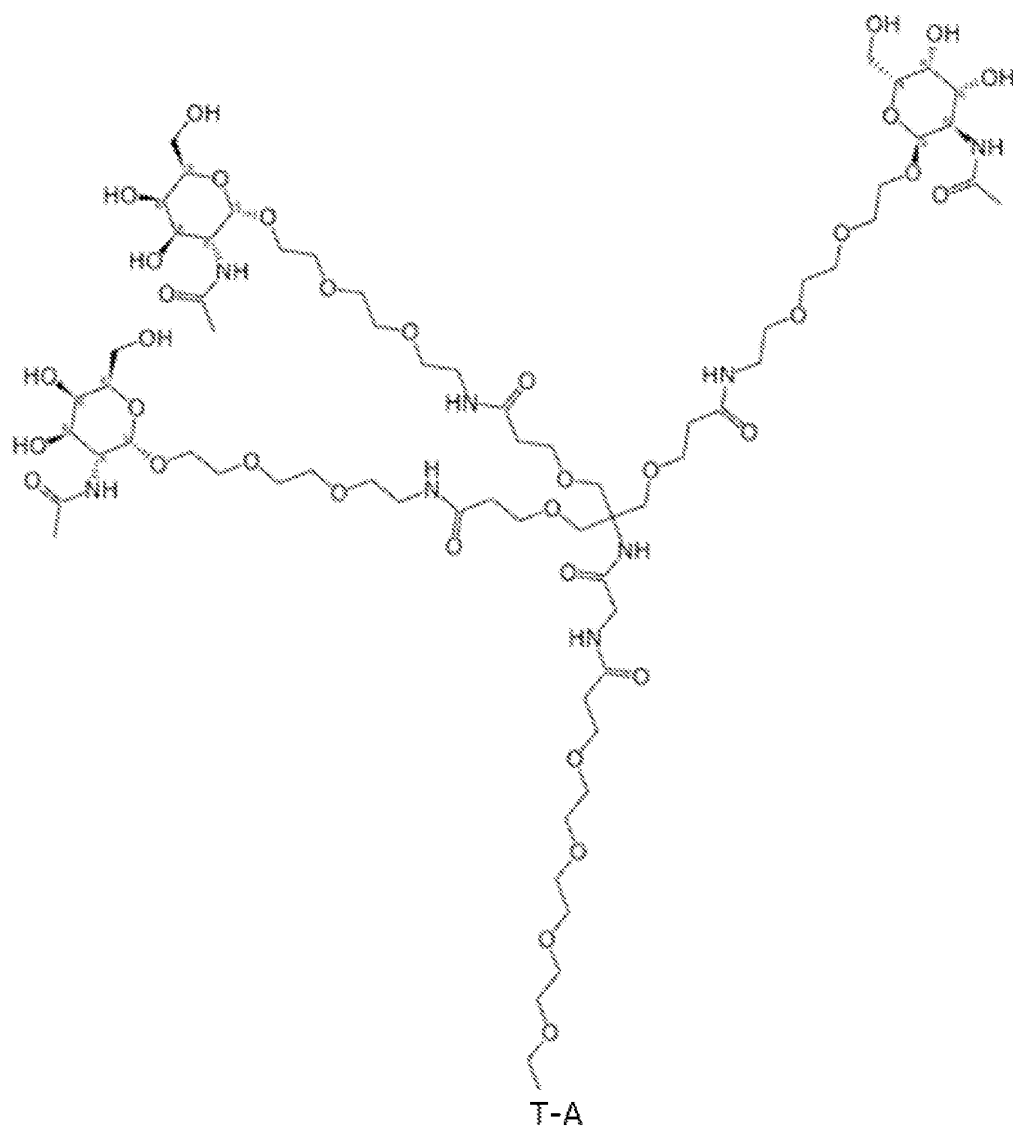
(BH5271),



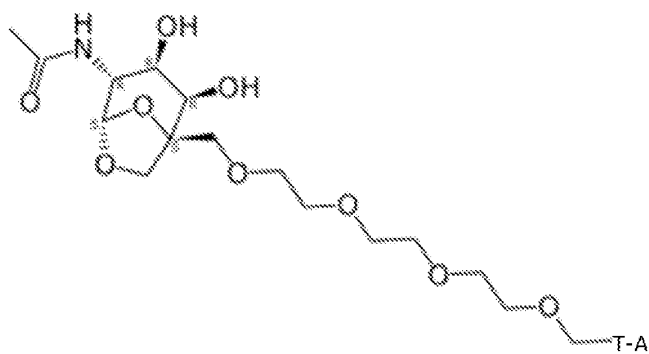
(BH5272),



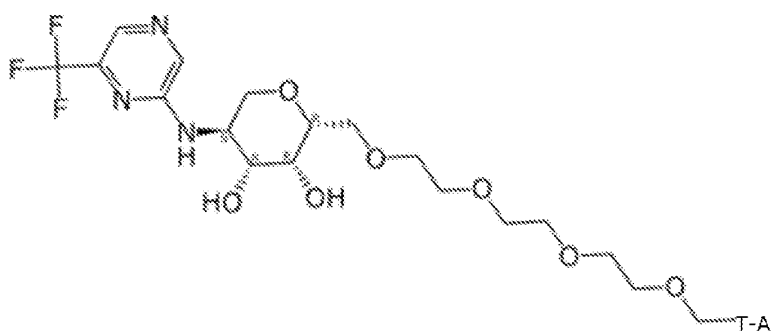
(BH5273)



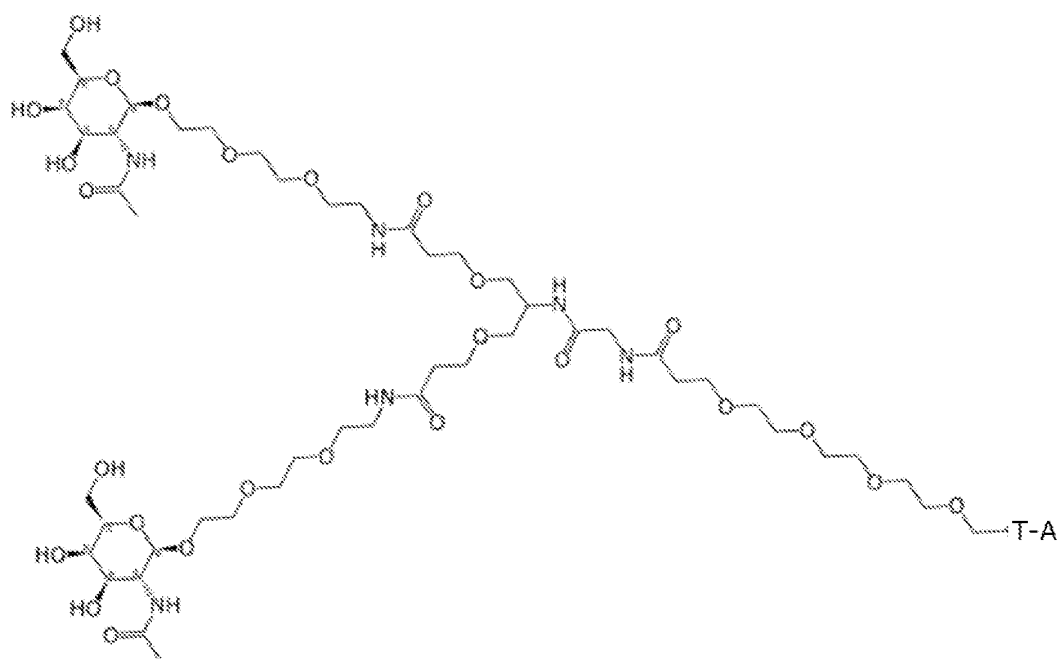
(BH5339),



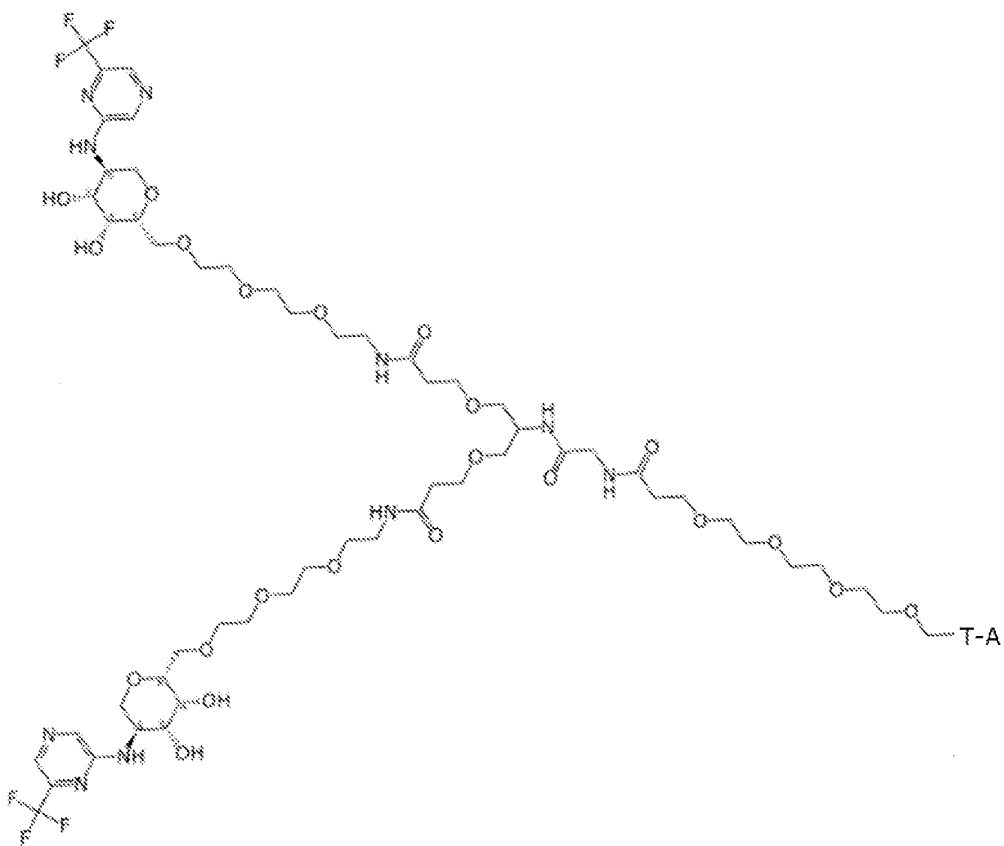
(BH5274),



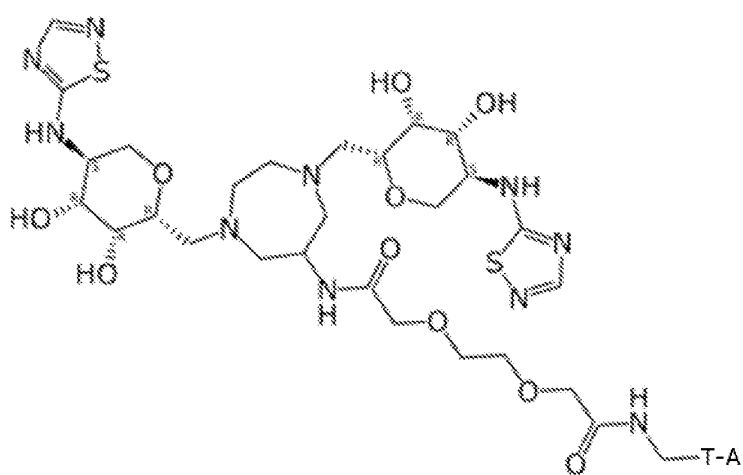
(BH5463),



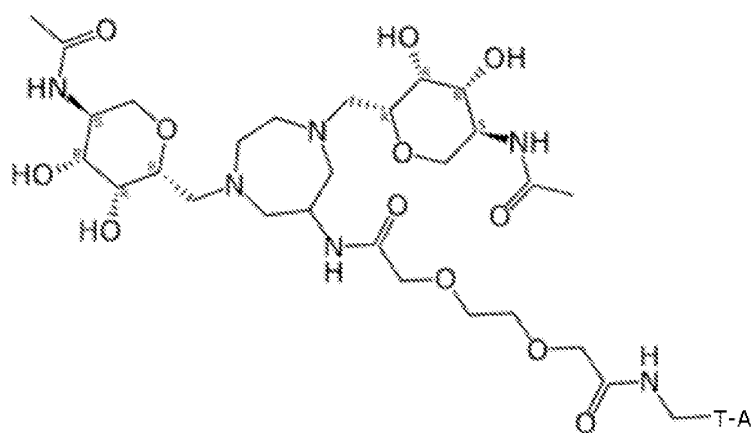
(BH5552),



(BH5775),

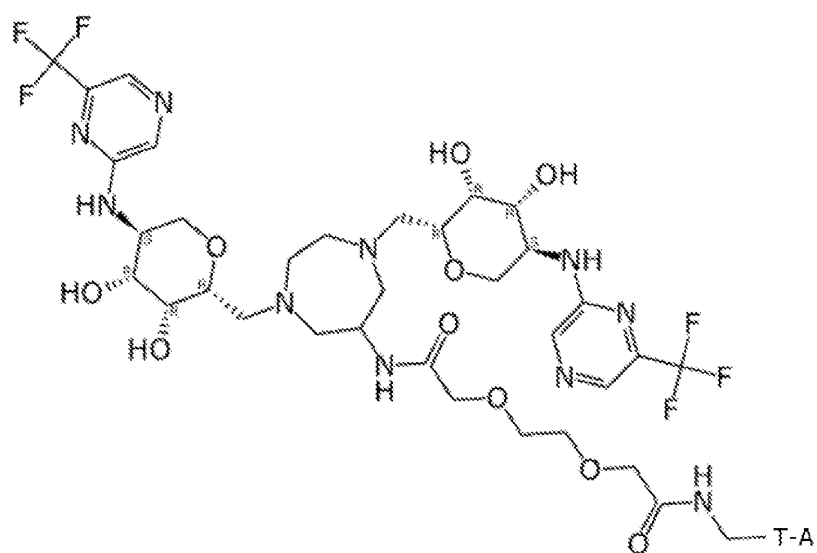


(BH5633),



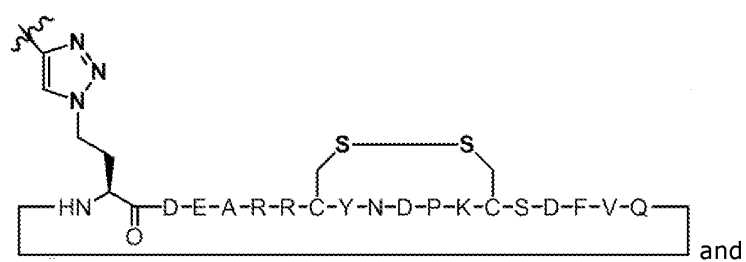
(BH5634),

and



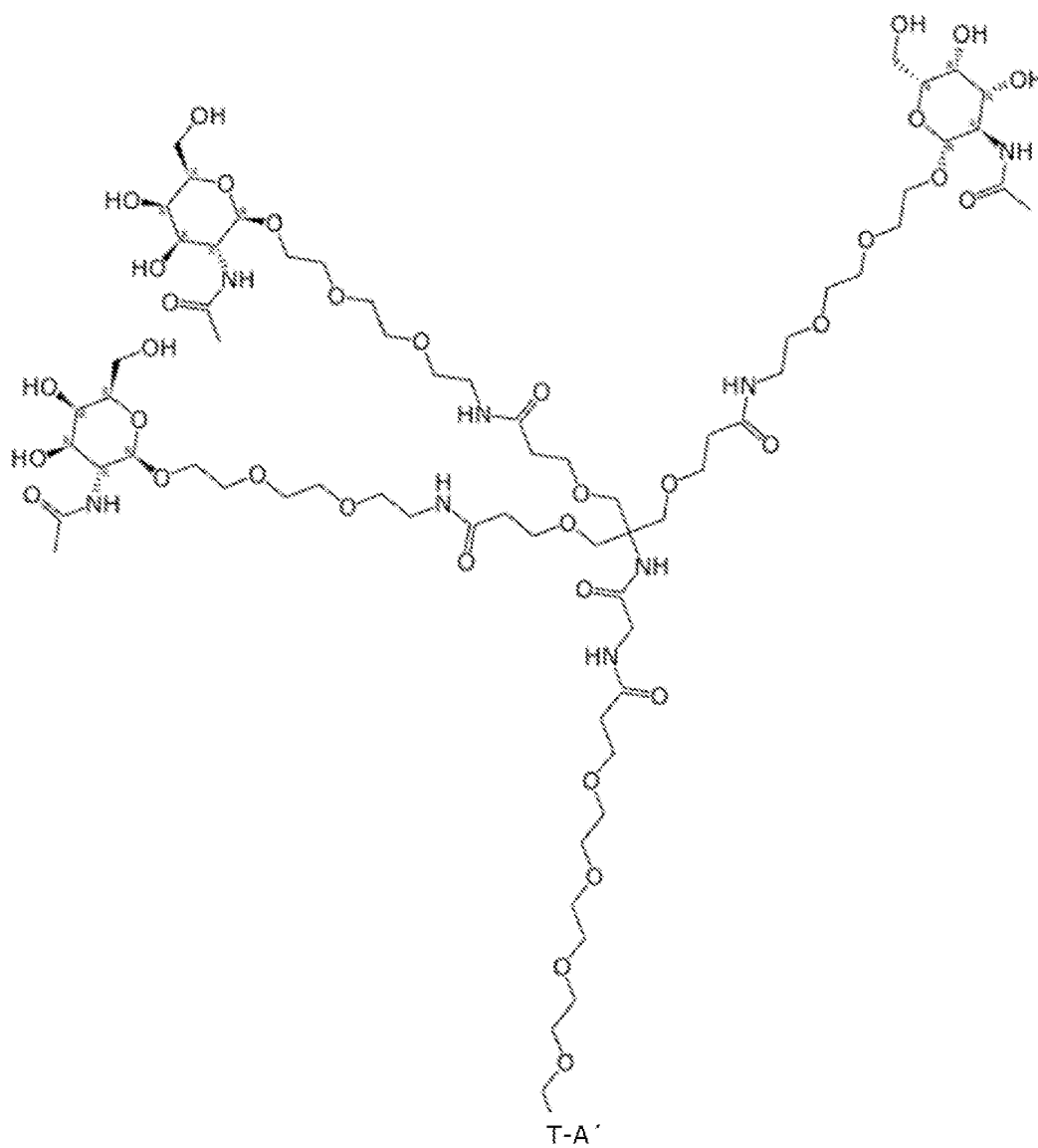
(BH5637)

wherein -T-A is



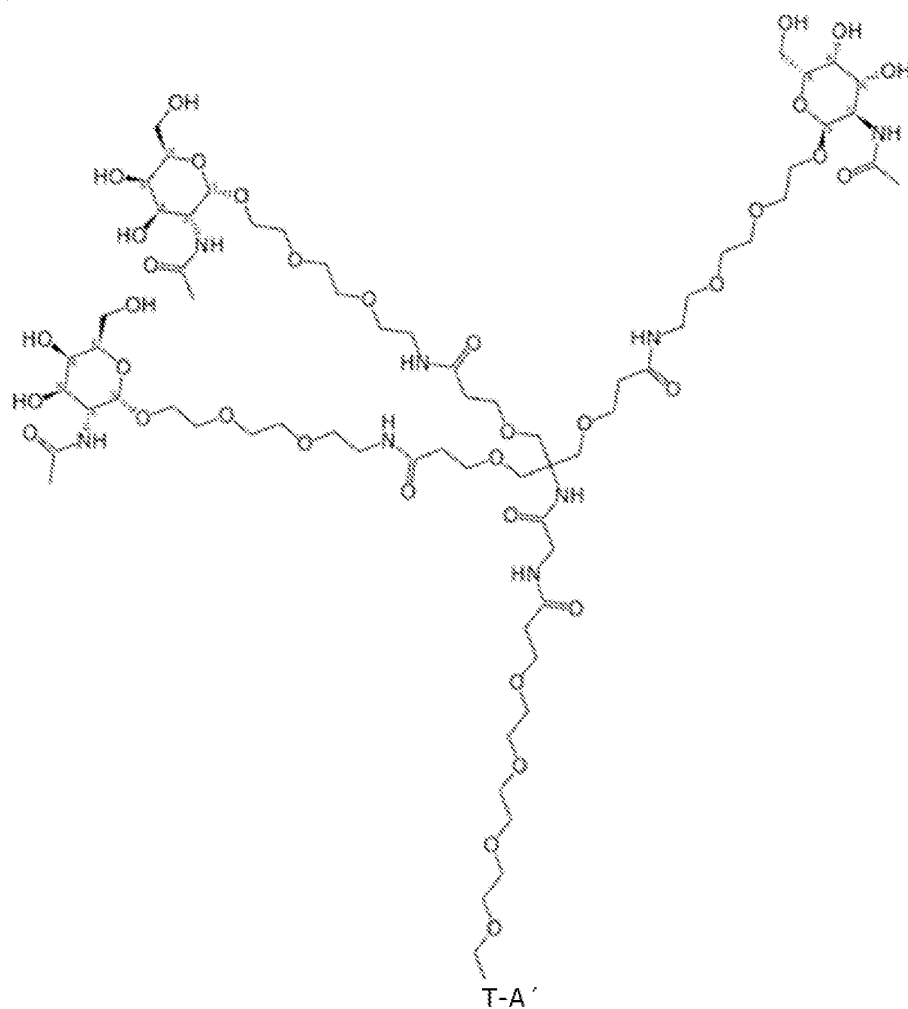
wherein the wavy line marks the bond that bonds -T-A to the remainder of the molecule.

Or in the aforementioned preferred embodiment, the compounds of the present invention are selected from the group consisting of:



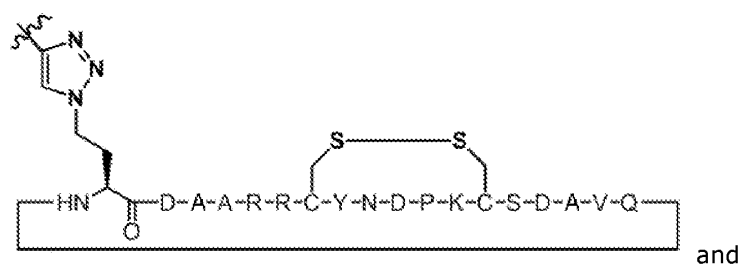
(BH7033),

and



(BH7034),

wherein -T-A' is



wherein the wavy line marks the bond that bonds -T-A' to the remainder of the molecule.

Various other properties of the compounds

The compounds described herein can possess one or more stereocenters, and each stereocenter can exist independently in either the (*R*) or (*S*) configuration. In certain embodiments, compounds described herein are present in optically active or racemic forms. It is to be understood that the compounds described herein encompass racemic, optically-active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful properties described herein. Preparation of optically active forms is achieved in any suitable manner, including by way of non-limiting example, by resolution of the racemic form with recrystallization techniques, synthesis from optically-active starting materials, chiral synthesis, or chromatographic separation using a chiral stationary phase. In certain embodiments, a mixture of one or more isomer is utilized as the therapeutic compound described herein. In other embodiments, compounds described herein contain one or more chiral centers. These compounds are prepared by any means, including stereoselective synthesis, enantioselective synthesis and/or separation of a mixture of enantiomers and/or diastereomers. Resolution of compounds and isomers thereof is achieved by any means including, by way of non-limiting example, chemical processes, enzymatic processes, fractional crystallization, distillation, and chromatography.

The methods and formulations described herein include the use of N-oxides (if appropriate), crystalline forms (also known as polymorphs), solvates, amorphous phases, and/or pharmaceutically acceptable salts of compounds having the structure of any compound(s) described herein, as well as metabolites and active metabolites of these compounds having the same type of activity. Solvates include water, ether (e.g., tetrahydrofuran, methyl tert-butyl ether) or alcohol (e.g., ethanol) solvates, acetates and the like. In certain embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, and ethanol. In other embodiments, the compounds described herein exist in unsolvated form.

In certain embodiments, the compound(s) described herein can exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

In certain embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In other embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

In certain embodiments, sites on, for example, the aromatic ring portion of compound(s) described herein are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the aromatic ring structures may reduce,

minimize or eliminate this metabolic pathway. In certain embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a deuterium, a halogen, or an alkyl group. Compounds described herein also include isotopically-labeled compounds wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds described herein include and are not limited to ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{36}Cl , ^{18}F , ^{123}I , ^{125}I , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , and ^{35}S . In certain embodiments, isotopically-labeled compounds are useful in drug and/or substrate tissue distribution studies. In other embodiments, substitution with heavier isotopes such as deuterium affords greater metabolic stability (for example, increased *in vivo* half-life or reduced dosage requirements). In yet other embodiments, substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , is useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds are prepared by any suitable method or by processes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

In certain embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

The compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein and as described, for example, in Fieser & Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, Advanced Organic Chemistry 4th Ed., (Wiley 1992); Carey & Sundberg, Advanced Organic Chemistry 4th Ed., Vols. A and B (Plenum 2000,2001), and Green & Wuts, Protective Groups in Organic Synthesis 3rd Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure). General methods for the preparation of compound as described herein are modified by the use of appropriate reagents and conditions, for the introduction of the various moieties found in the formula as provided herein.

Compounds described herein are synthesized using any suitable procedures starting from compounds that are available from commercial sources, or are prepared using procedures described herein.

In certain embodiments, reactive functional groups, such as hydroxyl, amino, imino, thio or carboxy groups, are protected in order to avoid their unwanted participation in reactions. Protecting groups are used to block some or all of the reactive

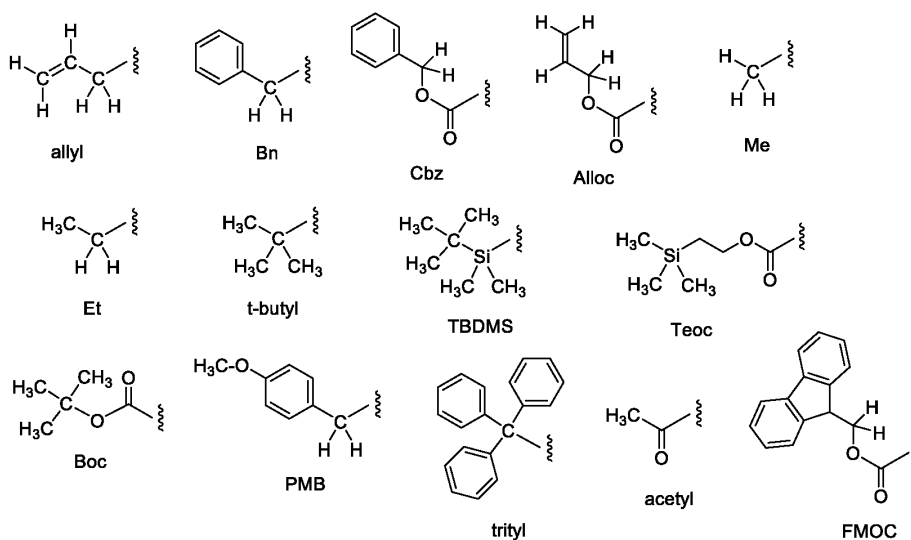
moieties and prevent such groups from participating in chemical reactions until the protective group is removed. In other embodiments, each protective group is removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal.

In certain embodiments, protective groups are removed by acid, base, reducing conditions (such as, for example, hydrogenolysis), and/or oxidative conditions. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and are used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties are blocked with base labile groups such as, but not limited to, methyl, ethyl, and acetyl, in the presence of amines that are blocked with acid labile groups, such as t-butyl carbamate, or with carbamates that are both acid and base stable but hydrolytically removable.

In certain embodiments, carboxylic acid and hydroxy reactive moieties are blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids are blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties are protected by conversion to simple ester compounds as exemplified herein, which include conversion to alkyl esters, or are blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups are blocked with fluoride labile silyl carbamates.

Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and are subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid is deprotected with a palladium-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate is attached. As long as the residue is attached to the resin, that functional group is blocked and does not react. Once released from the resin, the functional group is available to react.

Typically blocking/protecting groups may be selected from:



Other protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene & Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, *Protective Groups*, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure.

Preferably, the compounds of the present invention do not comprise two oxygen atoms that are adjacent to each other.

Definitions

Throughout this document, values expressed in a range format should be interpreted in a flexible manner to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. For example, a range of "about 0.1% to about 5%" or "about 0.1% to 5%" should be interpreted to include not just about 0.1% to about 5%, but also the individual values (*e.g.*, 1%, 2%, 3%, and 4%) and the sub-ranges (*e.g.*, 0.1% to 0.5%, 1.1% to 2.2%, 3.3% to 4.4%) within the indicated range. The statement "about X to Y" has the same meaning as "about X to about Y," unless indicated otherwise. Likewise, the statement "about X, Y, or about Z" has the same meaning as "about X, about Y, or about Z," unless indicated otherwise.

In this document, the terms "a," "an," or "the" are used to include one or more than one unless the context clearly dictates otherwise. The term "or" is used to refer to a nonexclusive "or" unless otherwise indicated. The statement "at least one of A and B" or "at least one of A or B" has the same meaning as "A, B, or A and B." In addition, it is to be understood that the phraseology or terminology employed herein, and not otherwise defined, is for the purpose of description only and not of limitation. Any use of

section headings is intended to aid reading of the document and is not to be interpreted as limiting; information that is relevant to a section heading may occur within or outside of that particular section. All publications, patents, and patent documents referred to in this document are incorporated by reference herein in their entirety, as though individually incorporated by reference.

In the methods described herein, the acts can be carried out in any order, except when a temporal or operational sequence is explicitly recited. Furthermore, specified acts can be carried out concurrently unless explicit claim language recites that they be carried out separately. For example, a claimed act of doing X and a claimed act of doing Y can be conducted simultaneously within a single operation, and the resulting process will fall within the literal scope of the claimed process.

The term "about" as used herein can allow for a degree of variability in a value or range, for example, within 10%, within 5%, or within 1% of a stated value or of a stated limit of a range, and includes the exact stated value or range.

The term "substantially" as used herein refers to a majority of, or mostly, as in at least about 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, 99.99%, or at least about 99.999% or more, or 100%. The term "substantially free of" as used herein can mean having none or having a trivial amount of, such that the amount of material present does not affect the material properties of the composition including the material, such that the composition is about 0 wt% to about 5 wt% of the material, or about 0 wt% to about 1 wt%, or about 5 wt% or less, or less than, equal to, or greater than about 4.5 wt%, 4, 3.5, 3, 2.5, 2, 1.5, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.01, or about 0.001 wt% or less. The term "substantially free of" can mean having a trivial amount of, such that a composition is about 0 wt% to about 5 wt% of the material, or about 0 wt% to about 1 wt%, or about 5 wt% or less, or less than, equal to, or greater than about 4.5 wt%, 4, 3.5, 3, 2.5, 2, 1.5, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.01, or about 0.001 wt% or less, or about 0 wt%.

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, CF₃, OCF₃, R, C(O), methylenedioxy, ethylenedioxy, N(R)₂, SR, SOR, SO₂R, SO₂N(R)₂, SO₃R, C(O)R, C(O)C(O)R, C(O)CH₂C(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, (CH₂)₀₋₂N(R)C(O)R, (CH₂)₀₋₂N(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)SO₂R, N(R)SO₂N(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 (C₁-C₁₀₀)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 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, NO₂, ONO₂, azido, CF₃, OCF₃, R, O (oxo), S (thiono), C(O), S(O), methylenedioxy, ethylenedioxy, N(R)₂, SR, SOR, SO₂R, SO₂N(R)₂, SO₃R, C(O)R, C(O)C(O)R, C(O)CH₂C(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, (CH₂)₀₋₂N(R)C(O)R, (CH₂)₀₋₂N(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)SO₂R, N(R)SO₂N(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, (C₁-C₁₀₀)hydrocarbonyl, 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 "aminoalkyl" as used herein refers to an alkyl group as defined herein wherein at least one hydrogen atom in the alkyl group is replaced by nitrogen, forming a

primary, secondary, or tertiary amine, depending upon the substitution of the nitrogen. Additionally, an aminoalkyl can have one or more nitrogen atoms between any two carbons in the alkyl chain, forming a secondary or tertiary amine, depending upon the substitution of the nitrogen.

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, $-\text{CH}=\text{C}=\text{CH}_2$, $-\text{CH}=\text{CH}(\text{CH}_3)$, $-\text{CH}=\text{C}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{C}(\text{CH}_3)=\text{CH}(\text{CH}_3)$, $-\text{C}(\text{CH}_2\text{CH}_3)=\text{CH}_2$, 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 $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{C}(\text{CH}_3)$, $-\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{C}\equiv\text{C}(\text{CH}_3)$, and $-\text{CH}_2\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$ 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 "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 CH₂ 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 C₂-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 C₄-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 benzodioxolanyl 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 C₂-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 C₄-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, quinazolyl, 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 "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 a heteroaryl 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 $N(\text{group})_3$ wherein each group can independently be H or non-H, such as alkyl, aryl, and the like. Amines include but are not limited to $R-NH_2$, 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, alkylarylamines, 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-halogen alkyl groups, poly-halogen alkyl groups wherein all halogen atoms can be the same or different, and per-halogen 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-epoxycyclohexyl)propyl, 2-(3,4-epoxycyclohexyl)ethyl, 2-(2,3-epoxycyclopentyl)ethyl, 2-(4-methyl-3,4-epoxycyclohexyl)propyl, 2-(3,4-epoxy-3-methylcyclohexyl)-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, (C₁-C₄)hydrocarbyl means the hydrocarbyl group can be methyl (C₁), ethyl (C₂), propyl (C₃), or butyl (C₄), and (C₀-C_b)hydrocarbyl means in certain embodiments there is no hydrocarbyl group.

The term "solvent" as used herein refers to a liquid that can dissolve a solid, liquid, or gas. Non-limiting examples of solvents are silicones, organic compounds, water, alcohols, ionic liquids, and supercritical fluids.

The term "independently selected from" as used herein refers to referenced groups being the same, different, or a mixture thereof, unless the context clearly indicates otherwise. Thus, under this definition, the phrase "X¹, X², and X³ are independently selected from noble gases" would include the scenario where, for example, X¹, X², and X³ are all the same, where X¹, X², and X³ are all different, where X¹ and X² are the same but X³ is different, and other analogous permutations.

The term "room temperature" as used herein refers to a temperature of about 15 °C to 28 °C.

The term "standard temperature and pressure" as used herein refers to 20 °C and 101 kPa.

As used herein, the term "composition" or "pharmaceutical composition" refers to a mixture of at least one compound described herein with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration.

A "disease" is a state of health of an animal wherein the animal cannot maintain homeostasis, and wherein if the disease is not ameliorated then the animal's health continues to deteriorate.

In contrast, a "disorder" in an animal is a state of health in which the animal is able to maintain homeostasis, but in which the animal's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the animal's state of health.

As used herein, the terms "effective amount," "pharmaceutically effective amount" and "therapeutically effective amount" refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the term "efficacy" refers to the maximal effect ($E_{\max}$) achieved within an assay.

As used herein, the term "pharmaceutically acceptable" refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, *i.e.*, the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the language "pharmaceutically acceptable salt" refers to a salt of the administered compounds prepared from pharmaceutically acceptable non-toxic acids or bases, including inorganic acids or bases, organic acids or bases, solvates, hydrates, or clathrates thereof.

Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric (including sulfate and hydrogen sulfate), and phosphoric acids (including hydrogen phosphate and dihydrogen phosphate). Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, malonic, saccharin, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid.

Suitable pharmaceutically acceptable base addition salts of compounds described herein include, for example, ammonium salts, metallic salts including alkali metal,

alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, N,N'-dibenzylethylene-diamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

As used herein, the term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound described herein within or to the patient such that it may perform its intended function. Typically, such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation, including the compound(s) described herein, and not injurious to the patient. Some examples of materials that may serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations. As used herein, "pharmaceutically acceptable carrier" also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound(s) described herein, and are physiologically acceptable to the patient. Supplementary active compounds may also be incorporated into the compositions. The "pharmaceutically acceptable carrier" may further include a pharmaceutically acceptable salt of the compound(s) described herein. Other additional ingredients that may be included in the pharmaceutical compositions used with the methods or compounds described herein are known in the art and described, for example in Remington's Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

The terms "patient," "subject," or "individual" are used interchangeably herein,

and refer to any animal, or cells thereof whether in vitro or in situ, amenable to the methods described herein. In a non-limiting embodiment, the patient, subject or individual is a human.

As used herein, the term "potency" refers to the dose needed to produce half the maximal response (ED_{50}).

A "therapeutic" treatment is a treatment administered to a subject who exhibits signs of pathology, for the purpose of diminishing or eliminating those signs.

As used herein, the term "treatment" or "treating" is defined as the application or administration of a therapeutic agent, *i.e.*, a compound or compounds as described herein (alone or in combination with another pharmaceutical agent), to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient (*e.g.*, for diagnosis or *ex vivo* applications), who has a condition contemplated herein or a symptom of a condition contemplated herein, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect a condition contemplated herein, or the symptoms of a condition contemplated herein. Such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

If in the present disclosure a structural element is defined that is intended to be part of a formulae disclosed herein and the definition of that structural element does not comprise sufficient free valences to allow the bonding of the remainder of the structural elements of the formula, it is to be assumed that for the purposes of this invention a corresponding structural element is meant in which one or more hydrogen atoms, as needed to fulfil the requirements of the formula, are substituted by a bond to the remainder of the structural elements in this formula. If for example the structural element A in the formula A-B is defined to be a 1*H*-1,2,3-Triazole, then for the purposes of the present invention it is to be assumed that A is a 1*H*-1,2,3-Triazo-yl rest, *i.e.* that one of the hydrogen atoms is substituted by the bond to B. This rule applies unless specified otherwise for certain embodiments.

In the formulae of the present disclosure  or a wavy line, respectively mark the bond that binds the shown partial structure to the remainder of the molecule. In the present disclosure amino acid sequences are stated in the one-letter notation of the IUPAC-IUB as published in the article "IUPAC-IUB Commission of Biochemical Nomenclature A One-Letter Notation for Amino Acid Sequences," *Journal of Biological Chemistry*, **243** (13): 3557–3559. 10 July 1968. doi:10.1016/S0021-9258(19)34176-6 ([https://www.jbc.org/article/S0021-9258\(19\)34176-6/pdf](https://www.jbc.org/article/S0021-9258(19)34176-6/pdf)).

In the present disclosure compounds are in some cases addressed by a designation "BHXXXX", wherein BH indicates that the addressed molecule is a target compound of the present invention and "XXXX" are four digits that identify the specific compound (*e.g.* BH5272).

Compositions

The compositions containing the compound(s) described herein include a pharmaceutical composition comprising at least one compound as described herein and at least one pharmaceutically acceptable carrier. In certain embodiments, the composition is formulated for an administration route such as oral or parenteral, for example, transdermal, transmucosal (*e.g.*, sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (*e.g.*, trans- and perivaginally), (intra)nasal and (trans)rectal, intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration.

Methods of Treatment

The presence of auto-antibodies against the beta-1 adrenergic receptor can be used to identify populations of patients that are particularly at risk after heart failure. In certain embodiments, chronic activation of the beta-1 adrenergic receptor can result in reduced cardiac function and weakening of the cardiac structure. Autoantibodies that remain functionally active and are directed against (and stimulate) cardiac beta-1 adrenergic receptors are often present in patients suffering from DCM, and the continued presence of these anti beta-1 adrenergic receptor antibodies is frequently associated with cardiac disorders such as ventricular arrhythmias, sudden cardiac death, and increased cardiovascular mortality. In various embodiments, and without wishing to be bound by theory, compounds of the present invention can bind to these anti beta-1 adrenergic receptor antibodies through the A moiety in the compound of the present invention. In various embodiments, and without being bound by theory, by bringing the AG moiety of the compounds of the present invention into proximity of these antibodies through binding of the AG moiety to the hepatocyte asialoglycoprotein receptor, endocytosis and/or degradation of these harmful antibodies can be achieved.

The disclosure includes a method of preventing, treating, and/or ameliorating heart failure in a subject, the method comprising administering to the subject a compound of the present invention or administering to the subject a composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of the present invention. Non-limiting examples of heart failure include dilated cardiomyopathy, hypertrophic cardiomyopathy, and/or restrictive cardiomyopathy. Cardiomyopathy can be the result of a variety of conditions including, long-term high blood pressure, heart tissue damage due to heart attack, heart valve malfunction, COVID-19 infection, hemochromatosis, amyloidosis, sarcoidosis, and/or chemotherapy drugs, and the like. The method includes administering a

composition comprising a therapeutically effective amount of a compound of the present invention, and at least one pharmaceutically acceptable carrier. In preferred embodiments, the heart failure is dilated cardiomyopathy (DCM).

In various embodiments, the compound of the present invention or the composition is administered by a route selected from the group consisting of oral and parenteral, e.g. transdermal, transmucosal (e.g., sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (e.g., trans- and perivaginally), (intra)nasal, and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration. In a preferred embodiment, the compound of the present invention or the composition is administered intravenously.

In various embodiments, the subject is a mammal. In a preferred embodiment, the subject is human.

The methods described herein include administering to the subject a therapeutically effective amount of at least one compound described herein, which is optionally formulated in a pharmaceutical composition. In various embodiments, a therapeutically effective amount of at least one compound described herein present in a pharmaceutical composition is the only therapeutically active compound in a pharmaceutical composition. In certain embodiments, the method further comprises administering to the subject an additional therapeutic agent that treats heart failure.

In certain embodiments, administering the compound(s) described herein to the subject allows for administering a lower dose of the additional therapeutic agent as compared to the dose of the additional therapeutic agent alone that is required to achieve similar results in treating a heart failure in the subject. For example, in certain embodiments, the compound(s) described herein enhance(s) the activity of the additional therapeutic compound, thereby allowing for a lower dose of the additional therapeutic compound to provide the same effect.

In certain embodiments, the compound(s) described herein and the therapeutic agent are co-administered to the subject. In other embodiments, the compound(s) described herein and the therapeutic agent are co-formulated and co-administered to the subject.

In certain embodiments, the subject is a mammal. In preferred embodiments, the mammal is a human.

Combination Therapies

The compounds useful within the methods described herein can be used in combination with one or more additional therapeutic agents useful for treating heart failure. These additional therapeutic agents may comprise compounds that are

commercially available or synthetically accessible to those skilled in the art. These additional therapeutic agents are known to treat or reduce the symptoms of heart failure.

In various embodiments, compounds of the present invention can be administered either sequentially or concurrently with β_1 -AR blockers, such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol, and/or carvedilol, and the like. In some embodiments, when β_1 -AR blockers are co-administered with compounds of the present invention, they can be administered at a lowered dose than if the β_1 -AR blocker was administered as a monotherapy. In various embodiments, the β_1 -AR blocker is administered at 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, or 5% of the minimum approved therapeutic dose for the particular β_1 -AR blocker used in therapy in combination with a compound of the present invention. In various embodiments, co-administration of β_1 -AR blockers and the compound of the present invention results in fewer, less severe, or no side effects associated with the use of β_1 -AR blockers.

In certain embodiments, the compounds described herein can be used in combination with radiation therapy. In other embodiments, the combination of administration of the compounds described herein and application of radiation therapy is more effective in treating, ameliorating, or preventing heart failure than application of radiation therapy by itself. In yet other embodiments, the combination of administration of the compounds described herein and application of radiation therapy allows for use of lower amount of radiation therapy in treating the subject.

In various embodiments, a synergistic effect is observed when a compound as described herein is administered with one or more additional therapeutic agents or compounds. A synergistic effect may be calculated, for example, using suitable methods such as, for example, the Sigmoid- E_{max} equation (Holford & Scheiner, 1981, Clin. Pharmacokinet. 6:429-453), the equation of Loewe additivity (Loewe & Muischnek, 1926, Arch. Exp. Pathol Pharmacol. 114:313-326) and the median-effect equation (Chou & Talalay, 1984, Adv. Enzyme Regul. 22:27-55). Each equation referred to above may be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

Administration/Dosage/Formulations

The regimen of administration may affect what constitutes an effective amount. The therapeutic formulations may be administered to the subject either prior to or after the onset of a heart failure. Further, several divided dosages, as well as staggered dosages may be administered daily or sequentially, or the dose may be continuously infused, or may be a bolus injection. Further, the dosages of the therapeutic formulations may be proportionally increased or decreased as indicated by the exigencies

of the therapeutic or prophylactic situation.

Administration of the compositions described herein to a patient, preferably a mammal, more preferably a human, may be carried out using known procedures, at dosages and for periods of time effective to treat heart failure in the patient. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the state of the disease or disorder in the patient; the age, sex, and weight of the patient; and the ability of the therapeutic compound to treat heart failure in the patient. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A non-limiting example of an effective dose range for a therapeutic compound described herein is from about 1 and 5,000 mg/kg of body weight/per day. One of ordinary skill in the art would be able to study the relevant factors and make the determination regarding the effective amount of the therapeutic compound without undue experimentation.

Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

In particular, the selected dosage level depends upon a variety of factors including the activity of the particular compound employed, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds or materials used in combination with the compound, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well, known in the medical arts.

A medical doctor, *e.g.*, physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds described herein employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In particular embodiments, it is especially advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms of the compound(s) described herein are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b)

the limitations inherent in the art of compounding/formulating such a therapeutic compound.

In certain embodiments, the compositions described herein are formulated using one or more pharmaceutically acceptable excipients or carriers. In certain embodiments, the pharmaceutical compositions described herein comprise a therapeutically effective amount of a compound described herein and a pharmaceutically acceptable carrier.

The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it is preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions may be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

In certain embodiments, the compounds and/or compositions described herein are administered to the patient in dosages that range from one to five times per day or more. In other embodiments, the compounds and/or compositions described herein are administered to the patient in range of dosages that include, but are not limited to, once every day, every two, days, every three days to once a week, and once every two weeks. It is readily apparent to one skilled in the art that the frequency of administration of the compounds and/or various combination compositions described herein varies from individual to individual depending on many factors including, but not limited to, age, disease or disorder to be treated, gender, overall health, and other factors. Thus, administration of the compounds and compositions described herein should not be construed to be limited to any particular dosage regime and the precise dosage and composition to be administered to any patient is determined by the attending physician taking all other factors about the patient into account.

The compound(s) described herein for administration may be in the range of from about 1 µg to about 10,000 mg, about 20 µg to about 9,500 mg, about 40 µg to about 9,000 mg, about 75 µg to about 8,500 mg, about 150 µg to about 7,500 mg, about 200 µg to about 7,000 mg, about 350 µg to about 6,000 mg, about 500 µg to about 5,000 mg, about 750 µg to about 4,000 mg, about 1 mg to about 3,000 mg, about 10 mg to about 2,500 mg, about 20 mg to about 2,000 mg, about 25 mg to about 1,500 mg, about 30 mg to about 1,000 mg, about 40 mg to about 900 mg, about 50 mg to about 800 mg, about 60 mg to about 750 mg, about 70 mg to about 600 mg, about 80 mg to

about 500 mg, and any and all whole or partial increments therebetween. In various embodiments, compounds of the present invention are administered at a dose of 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg.

In some embodiments, the dose of a compound described herein is from about 1 mg and about 2,500 mg. In some embodiments, a dose of a compound described herein used in compositions described herein is less than about 10,000 mg, or less than about 8,000 mg, or less than about 6,000 mg, or less than about 5,000 mg, or less than about 3,000 mg, or less than about 2,000 mg, or less than about 1,000 mg, or less than about 500 mg, or less than about 200 mg, or less than about 50 mg. Similarly, in some embodiments, a dose of a second compound as described herein is less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 400 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than about 40 mg, or less than about 30 mg, or less than about 25 mg, or less than about 20 mg, or less than about 15 mg, or less than about 10 mg, or less than about 5 mg, or less than about 2 mg, or less than about 1 mg, or less than about 0.5 mg, and any and all whole or partial increments thereof. In a preferred embodiment, the compound of the present invention is administered in a dose of 0.01 mg/kg to 20 mg/kg. In a preferred embodiment, the composition of the present invention is administered in a dose of 0.01 mg/kg to 20 mg/kg.

In certain embodiments, a composition as described herein is a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a compound described herein, alone or in combination with a second pharmaceutical agent; and instructions for using the compound to treat, prevent, or reduce one or more symptoms of heart failure in a patient.

Formulations may be employed in admixtures with conventional excipients, *i.e.*, pharmaceutically acceptable organic or inorganic carrier substances suitable for oral, parenteral, nasal, intravenous, subcutaneous, enteral, or any other suitable mode of administration, known to the art. The pharmaceutical preparations may be sterilized and if desired mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like. They may also be combined where desired with other active agents, *e.g.*, other analgesic agents.

Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry

powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and compositions described herein are not limited to the particular formulations and compositions that are described herein.

Oral Administration

For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gelcaps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

For oral administration, the compound(s) described herein can be in the form of tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, polyvinylpyrrolidone, hydroxypropylcellulose or hydroxypropyl methylcellulose); fillers (*e.g.*, cornstarch, lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.*, magnesium stearate, talc, or silica); disintegrates (*e.g.*, sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). If desired, the tablets may be coated using suitable methods and coating materials such as OPADRY™ film coating systems available from Colorcon, West Point, Pa. (*e.g.*, OPADRY™ OY Type, OYC Type, Organic Enteric OY-P Type, Aqueous Enteric OY-A Type, OY-PM Type and OPADRY™ White, 32K18400). Liquid preparation for oral administration may be in the form of solutions, syrups or suspensions. The liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.*, methyl or propyl p-hydroxy benzoates or sorbic acid).

Compositions as described herein can be prepared, packaged, or sold in a formulation suitable for oral or buccal administration. A tablet that includes a compound as described herein can, for example, be made by compressing or molding the active ingredient, optionally with one or more additional ingredients. Compressed tablets may be prepared by compressing, in a suitable device, the active ingredient in a free-flowing form such as a powder or granular preparation, optionally mixed with one or more of a binder, a lubricant, an excipient, a surface active agent, and a dispersing agent. Molded

tablets may be made by molding, in a suitable device, a mixture of the active ingredient, a pharmaceutically acceptable carrier, and at least sufficient liquid to moisten the mixture. Pharmaceutically acceptable excipients used in the manufacture of tablets include, but are not limited to, inert diluents, granulating and disintegrating agents, dispersing agents, surface-active agents, disintegrating agents, binding agents, and lubricating agents.

Suitable dispersing agents include, but are not limited to, potato starch, sodium starch glycolate, poloxamer 407, or poloxamer 188. One or more dispersing agents can each be individually present in the composition in an amount of about 0.01% w/w to about 90% w/w relative to weight of the dosage form. One or more dispersing agents can each be individually present in the composition in an amount of at least, greater than, or less than about 0.01%, 0.05%, 0.1%, 0.5%, 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% w/w relative to weight of the dosage form.

Surface-active agents (surfactants) include cationic, anionic, or non-ionic surfactants, or combinations thereof. Suitable surfactants include, but are not limited to, behentrimonium chloride, benzalkonium chloride, benzethonium chloride, benzododecinium bromide, carbethopendecinium bromide, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cetylpyridine chloride, didecyldimethylammonium chloride, dimethyldioctadecylammonium bromide, dimethyldioctadecylammonium chloride, domiphen bromide, lauryl methyl gluceth-10 hydroxypropyl dimonium chloride, tetramethylammonium hydroxide, thonzonium bromide, stearalkonium chloride, octenidine dihydrochloride, olaflur, N-oleyl-1,3-propanediamine, 2-acrylamido-2-methylpropane sulfonic acid, alkylbenzene sulfonates, ammonium lauryl sulfate, ammonium perfluorononanoate, docusate, disodium cocoamphodiacetate, magnesium laureth sulfate, perfluorobutanesulfonic acid, perfluorononanoic acid, perfluorooctanesulfonic acid, perfluorooctanoic acid, potassium lauryl sulfate, sodium alkyl sulfate, sodium dodecyl sulfate, sodium laurate, sodium laureth sulfate, sodium lauroyl sarcosinate, sodium myreth sulfate, sodium nonanoyloxybenzenesulfonate, sodium pareth sulfate, sodium stearate, sodium sulfosuccinate esters, cetomacrogol 1000, cetostearyl alcohol, cetyl alcohol, cocamide diethanolamine, cocamide monoethanolamine, decyl glucoside, decyl polyglucose, glycerol monostearate, octylphenoxypolyethoxyethanol CA-630, isoceteth-20, lauryl glucoside, octylphenoxypolyethoxyethanol P-40, Nonoxynol-9, Nonoxynols, nonyl phenoxypolyethoxyethanol (NP-40), octaethylene glycol monododecyl ether, N-octyl beta-D-thioglucopyranoside, octyl glucoside, oleyl alcohol, PEG-10 sunflower glycerides, pentaethylene glycol monododecyl ether, polidocanol, poloxamer, poloxamer 407, polyethoxylated tallow amine, polyglycerol polyricinoleate, polysorbate, polysorbate 20, polysorbate 80, sorbitan, sorbitan monolaurate, sorbitan monostearate, sorbitan

tristearate, stearyl alcohol, surfactin, Triton X-100, and Tween 80. One or more surfactants can each be individually present in the composition in an amount of about 0.01% w/w to about 90% w/w relative to weight of the dosage form. One or more surfactants can each be individually present in the composition in an amount of at least, greater than, or less than about 0.01%, 0.05%, 0.1%, 0.5%, 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% w/w relative to weight of the dosage form.

Suitable diluents include, but are not limited to, calcium carbonate, magnesium carbonate, magnesium oxide, sodium carbonate, lactose, microcrystalline cellulose, calcium phosphate, calcium hydrogen phosphate, and sodium phosphate, Cellactose® 80 (75 % α -lactose monohydrate and 25 % cellulose powder), mannitol, pre-gelatinized starch, starch, sucrose, sodium chloride, talc, anhydrous lactose, and granulated lactose. One or more diluents can each be individually present in the composition in an amount of about 0.01% w/w to about 90% w/w relative to weight of the dosage form. One or more diluents can each be individually present in the composition in an amount of at least, greater than, or less than about 0.01%, 0.05%, 0.1%, 0.5%, 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% w/w relative to weight of the dosage form.

Suitable granulating and disintegrating agents include, but are not limited to, sucrose, copovidone, corn starch, microcrystalline cellulose, methyl cellulose, sodium starch glycolate, pregelatinized starch, povidone, sodium carboxy methyl cellulose, sodium alginate, citric acid, croscarmellose sodium, cellulose, carboxymethylcellulose calcium, colloidal silicone dioxide, crosspovidone and alginic acid. One or more granulating or disintegrating agents can each be individually present in the composition in an amount of about 0.01% w/w to about 90% w/w relative to weight of the dosage form. One or more granulating or disintegrating agents can each be individually present in the composition in an amount of at least, greater than, or less than about 0.01%, 0.05%, 0.1%, 0.5%, 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% w/w relative to weight of the dosage form.

Suitable binding agents include, but are not limited to, gelatin, acacia, pre-gelatinized maize starch, polyvinylpyrrolidone, anhydrous lactose, lactose monohydrate, hydroxypropyl methylcellulose, methylcellulose, povidone, polyacrylamides, sucrose, dextrose, maltose, gelatin, polyethylene glycol. One or more binding agents can each be individually present in the composition in an amount of about 0.01% w/w to about 90% w/w relative to weight of the dosage form. One or more binding agents can each be individually present in the composition in an amount of at least, greater than, or less than about 0.01%, 0.05%, 0.1%, 0.5%, 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% w/w

relative to weight of the dosage form.

Suitable lubricating agents include, but are not limited to, magnesium stearate, calcium stearate, hydrogenated castor oil, glyceryl monostearate, glyceryl behenate, mineral oil, polyethylene glycol, poloxamer 407, poloxamer 188, sodium laureth sulfate, sodium benzoate, stearic acid, sodium stearyl fumarate, silica, and talc. One or more lubricating agents can each be individually present in the composition in an amount of about 0.01% w/w to about 90% w/w relative to weight of the dosage form. One or more lubricating agents can each be individually present in the composition in an amount of at least, greater than, or less than about 0.01%, 0.05%, 0.1%, 0.5%, 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% w/w relative to weight of the dosage form.

Tablets can be non-coated or they may be coated using known methods to achieve delayed disintegration in the gastrointestinal tract of a subject, thereby providing sustained release and absorption of the active ingredient. By way of example, a material such as glyceryl monostearate or glyceryl distearate may be used to coat tablets. Further by way of example, tablets may be coated using methods described in U.S. Patent Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotically controlled release tablets. Tablets may further comprise a sweetening agent, a flavoring agent, a coloring agent, a preservative, or some combination of these in order to provide for pharmaceutically elegant and palatable preparation.

Tablets can also be enterically coated such that the coating begins to dissolve at a certain pH, such as at about pH 5.0 to about pH 7.5, thereby releasing a compound as described herein. The coating can contain, for example, EUDRAGIT® L, S, FS, and/or E polymers with acidic or alkaline groups to allow release of a compound as described herein in a particular location, including in any desired section(s) of the intestine. The coating can also contain, for example, EUDRAGIT® RL and/or RS polymers with cationic or neutral groups to allow for time controlled release of a compound as described herein by pH-independent swelling.

Parenteral Administration

For parenteral administration, the compounds as described herein may be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose and/or continuous infusion. Suspensions, solutions or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing and/or dispersing agents may be used.

Sterile injectable forms of the compositions described herein 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. 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 lauryl, stearyl, or oleyl alcohols, or similar alcohol.

Additional Administration Forms

Additional dosage forms suitable for use with the compound(s) and compositions described herein include dosage forms as described in U.S. Patents Nos. 6,340,475; 6,488,962; 6,451,808; 5,972,389; 5,582,837; and 5,007,790. Additional dosage forms suitable for use with the compound(s) and compositions described herein also include dosage forms as described in U.S. Patent Applications Nos. 20030147952; 20030104062; 20030104053; 20030044466; 20030039688; and 20020051820. Additional dosage forms suitable for use with the compound(s) and compositions described herein also include dosage forms as described in PCT Applications Nos. WO 03/35041; WO 03/35040; WO 03/35029; WO 03/35177; WO 03/35039; WO 02/96404; WO 02/32416; WO 01/97783; WO 01/56544; WO 01/32217; WO 98/55107; WO 98/11879; WO 97/47285; WO 93/18755; and WO 90/11757.

Controlled Release Formulations and Drug Delivery Systems

In certain embodiments, the formulations described herein can be, but are not limited to, short-term, rapid-offset, as well as controlled, for example, sustained release, delayed release and pulsatile release formulations.

The term sustained release is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that may, although not necessarily, result in substantially constant blood levels of a drug over an extended time period. The period of time may be as long as a month or more and should be a release which is longer than the same amount of agent administered in bolus form.

For sustained release, the compounds may be formulated with a suitable polymer or hydrophobic material which provides sustained release properties to the compounds. As such, the compounds for use with the method(s) described herein may be administered in the form of microparticles, for example, by injection or in the form of wafers or discs by implantation.

In some cases, the dosage forms to be used can be provided as slow or controlled-

release of one or more active ingredients therein using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the pharmaceutical compositions described herein. Thus, single unit dosage forms suitable for oral administration, such as tablets, capsules, gelcaps, and caplets that are adapted for controlled-release are encompassed by the compositions and dosage forms described herein.

Most controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood level of the drug, and thus can affect the occurrence of side effects.

Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body.

Controlled-release of an active ingredient can be stimulated by various inducers, for example pH, temperature, enzymes, water, or other physiological conditions or compounds. The term "controlled-release component" is defined herein as a compound or compounds, including, but not limited to, polymers, polymer matrices, gels, permeable membranes, liposomes, or microspheres or a combination thereof that facilitates the controlled-release of the active ingredient. In one embodiment, the compound(s) described herein are administered to a patient, alone or in combination with another pharmaceutical agent, using a sustained release formulation. In one embodiment, the compound(s) described herein are administered to a patient, alone or in combination with another pharmaceutical agent, using a sustained release formulation.

The term delayed release is used herein in its conventional sense to refer to a drug formulation that provides for an initial release of the drug after some delay following drug administration and that mat, although not necessarily, includes a delay of from about 10 minutes up to about 12 hours.

The term pulsatile release is used herein in its conventional sense to refer to a drug

formulation that provides release of the drug in such a way as to produce pulsed plasma profiles of the drug after drug administration.

The term immediate release is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration.

As used herein, short-term refers to any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes and any or all whole or partial increments thereof after drug administration after drug administration.

As used herein, rapid-offset refers to any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes, and any and all whole or partial increments thereof after drug administration.

Dosing

The therapeutically effective amount or dose of a compound described herein depends on the age, sex and weight of the patient, the current medical condition of the patient and the progression of heart failure in the patient being treated. The skilled artisan is able to determine appropriate dosages depending on these and other factors.

A suitable dose of a compound described herein can be in the range of from about 0.01 mg to about 5,000 mg per day, such as from about 0.1 mg to about 1,000 mg, for example, from about 1 mg to about 500 mg, such as about 5 mg to about 250 mg per day. The dose may be administered in a single dosage or in multiple dosages, for example from 1 to 4 or more times per day. When multiple dosages are used, the amount of each dosage may be the same or different. For example, a dose of 1 mg per day may be administered as two 0.5 mg doses, with about a 12-hour interval between doses.

It is understood that the amount of compound dosed per day may be administered, in non-limiting examples, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days. For example, with every other day administration, a 5 mg per day dose may be initiated on Monday with a first subsequent 5 mg per day dose administered on Wednesday, a second subsequent 5 mg per day dose administered on Friday, and so on.

In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compound(s) described herein is optionally given continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). The length of the drug holiday optionally varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days,

20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday includes from 10%-100%, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is reduced to a level at which the improved disease is retained. In certain embodiments, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms and/or infection.

The compounds described herein can be formulated in unit dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosage for patients undergoing treatment, with each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form may be for a single daily dose or one of multiple daily doses (*e.g.*, about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form may be the same or different for each dose.

Toxicity and therapeutic efficacy of such therapeutic regimens are optionally determined in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD₅₀ and ED₅₀. The data obtained from cell culture assays and animal studies are optionally used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage optionally varies within this range depending upon the dosage form employed and the route of administration utilized.

Brief description of the figures

The drawings illustrate generally, by way of example, but not by way of limitation, various embodiments of the present application.

- Figure 1: Figure 1 shows the result of surface plasmon resonance (SPR) measurements of **BH5272**. The figure shows the interaction of **BH5272** with anti- β_1 EC_{II} autoantibodies.
- Figure 2: Figure 2 shows the result of surface plasmon resonance (SPR) measurements of **BH5272**. The figure shows the interaction of **BH5272** with the asialoglycoprotein receptor ("ASGPR").
- Figure 3: Figure 3 shows the stability over time of **BH5272** in blood plasma of mice, rats and humans.
- Figure 4: Figure 4 shows the plasma protein binding of **BH5272** in blood plasma of mice, rats and humans.
- Figure 5: Figure 5 shows the development over time of the blood level of anti- β_1 EC_{II} autoantibodies *in vivo* in mice after an IV dosage of BH5270 and **BH5272**, respectively. The lines from top to bottom show dosage of phosphate-buffered saline (PBS) without **BH5272**; "Peptide Alone" is an anti- β_1 adrenergic receptor antibody binding moiety A (see Figure 8) in PBS; **BH5272** in a dosage of 0.2 mg/kg body weight in PBS and **BH5270** in a dosage of 1.0 mg/kg body weight in PBS. BH5270 is a compound of the prior art.
- Figure 6: Figure 6 shows the area under the curve (AUC) for the anti- β_1 EC_{II} autoantibodies in the experiment of Figure 5.
- Figure 7: Figure 7 shows the pharmacokinetics of **BH5272** in the experiment of Figure 5.
- Figure 8: Figure 8 shows the structure of the peptide used for comparison in the experiments shown in Figures 5 and 6 in two different presentations. This peptide is an anti- β_1 adrenergic receptor antibody binding moiety A with sequence ID NO: 1. It is identical in structure with **Int-00001**, but for the azido group bearing amino acid which is exchanged for alanine.
- Figure 9: Figure 9 shows a comparison of the binding of BH5270 and BH5272 to plasma protein in mice, rat and human plasma. BH5270 is a compound of the prior art.

Examples

Various embodiments of the present application can be better understood by reference to the following examples which are offered by way of illustration. The scope of the present application is not limited to the examples given herein.

Materials and Methods

Data analysis

Data was analyzed and visualized using GraphPad Prism 7.0a software. All statistical tests were two-sided and significance was assessed at $p < 0.05$.

Method 1: *In vitro* stability in blood plasma of mice, rats and humans

2 μ M solutions of test compound (e.g. **BH5272** prepared as described below) and somatostatin acetate in DMSO and a 2 μ M solution of propantheline bromide in water were prepared. Somatostatin acetate and propantheline bromide are used for calibration and comparison. Mouse plasma of the strain "CD-1 Mouse Plasma" of the vendor "Beijing Vital River Laboratory Animal Technology" with the batch number "MICE-ICR-PPL-HS-B20220523-M" was used. The plasma used was a mixture of plasma from a minimum number of 20 male mouse. Rat plasma of the strain "SD Rat Plasma" of the vendor "Beijing Vital River Laboratory Animal Technology" with the lot number "VR-Rat-PL-HS-20211026" was used. The plasma used was a mixture of plasma from a minimum number of 10 male rats. As human plasma the "Human Plasma" of the vendor "BioreclamationIVT" with the catalog number "HUMANPLNHP2N" and the lot number "HMN551176" was used. The plasma used was a mixture of plasma from a minimum number of 6 humans, male and female. Heparin was used as anticoagulant for all three species of plasma. The pooled frozen plasma was thawed in a water bath at 37°C prior to experiment. Plasma was centrifuged at 4000 rpm for 5 min and the clots were removed if any. Using an Apricot automation workstation, 98 μ L/well of blank plasma were added to all 96-well reaction plates (Blank; i.e. no test compound, e.g. **BH5272**), T=0, T=10 min, T=30 min, T=60 min and T=120 min). An Apricot automation workstation was used to add 2 μ L/well of working solution (100 μ M) to all reaction plates except the blank. All reaction plates containing mixtures of compound and plasma were incubated at 37°C in water bath for the stated amounts of time. At the end of incubation 800 μ L of stop solution (200 ng/mL tolbutamide and 200 ng/mL labetalol in MeOH) were added to precipitate protein in the case of mouse plasma and 500 μ L were of the same solution was added to rat and human plasma. Subsequently the solution was mixed thoroughly. Each plate was sealed and shaken for 20 minutes. After shaking, each plate was centrifuged at 4000 rpm and 4°C for 20 minutes. After centrifugation, an Apricot automation workstation was used to transfer 150 μ L of supernatant from each reaction

plate to its corresponding bioanalysis plate. Each bioanalysis plate was sealed and shaken for 10 minutes prior to LC-MS/MS analysis. The % remaining of the test compound (e.g. **BH5272**) after incubation in plasma was calculated using following equation: % Remaining = $100 \times (\text{PAR at appointed incubation time} / \text{PAR at } T_0 \text{ time})$, where PAR is the peak area ratio of analyte versus internal standard (IS). The appointed incubation time points were T_0 (0 min), T_n ($n=0, 10, 30, 60, 120$ min). The results are shown in Figure 3.

Method 2: Plasma protein binding in blood plasma of mice, rats and humans

1. Materials:

Plasma protein binding was performed with the same plasma as described above for the stability measurements. As anticoagulant, ethylenediaminetetraacetic acid dipotassium salt (EDTA- K_2) was used for mouse and rat plasma and citrate was used for human plasma. For separation an ultracentrifuge (Beckman Coulter. Optima XPN-90) combined with Rotor (Beckman 42.2Ti) and Ultracentrifuge tube (Beckman, Polycarbonate, 7×20 mm) were used. The buffer was prepared as follows: BupHTM Phosphate Buffered Saline Pack supplied by Thermo Fisher Scientific, product number 28372, lot number XE353076 comprising 0.1 M sodium phosphate and 0.15 M sodium chloride. The pouch contents were dissolved in a final volume of 500 ml deionized water for a pH of 7.2. Before use, the pH value will be adjusted to pH 7.4 ± 0.1 using 1% phosphoric acid or 1 N sodium hydroxide. Titrated solution will be stored at 4°C for up to 1 month. Stop solution A for the test compound (e.g. **BH5272**) is MeOH containing tolbutamide at 200 ng/mL and labetalol at 200 ng/mL. Stop solution B for the control, for which Warfarin is used is Acetonitrile containing tolbutamide at 200 ng/mL and labetalol at 200 ng/mL.

2. Method:

On the day of experiment, the plasma was thawed by running under cold tap water and centrifuged at 3220 ×g for 5 minutes to remove any clots. The pH value of the resulting plasma was measured and adjusted to pH 7.4 ± 0.1 using 1% phosphoric acid or 1 N sodium hydroxide, if required. Test compound and control compound were dissolved in DMSO to achieve 10 mM stock solutions. Working solutions (400 μM) of test compound and control compound in DMSO were prepared. Loading matrix solutions (2 μM) of test compound and control compound were prepared by diluting 4 μL of working solutions with 796 μL of blank matrix. The concentration of organic solvent in the final solutions was 0.5% DMSO. The samples were mixed thoroughly before the next step. To prepare the time zero (T_0) samples to be used for the determination of the amount of the remaining, aliquots of 30 μL loading matrix were transferred ($n=2$) to sample collection plate. The samples were immediately matched with opposite blank buffer to obtain a final volume of 60 μL with a volume ratio of plasma:buffer (1:1, v:v) in each well. 300 μL stop solution for control compound sample and 480 μL stop solution for test compound sample

were added to these T0 samples. They were then stored at 2-8°C pending further processes along with other samples. The rest of loading plasma samples were pre-incubated in a carbon dioxide incubator at $37 \pm 1^\circ\text{C}$ for 30 min. To prepare the protein-free samples to be used for unbound determination, an aliquot of 230 μL of the pre-incubated matrix containing test compound or control compound was transferred to ultracentrifuge tubes ($n=2$) and subjected to ultracentrifugation at 37°C , $155000 \times g$ (35000 rpm) for 4 hr to generate the protein-free samples. At the end of the ultracentrifugation or incubation, aliquots of 30 μL samples were taken from the second layer (beneath top layer) of the supernatant to generate the F samples. To prepare the T_{4.5} samples to be used for unbound and remaining measurement, at the same time of ultracentrifugation, the residual aliquot of pre-incubated spiked plasma was placed into the same incubator ($n=1$) and continued to be incubated at $37 \pm 1^\circ\text{C}$ for 4 hr to get the T_{4.5} samples. These samples were transferred into new 96 well plates. Each sample was added with equal volume of opposite blank matrix (buffer or plasma) to reach a final volume of 60 μL with volume ratio of plasma:buffer at 1:1 (v:v) in each well. 300 μL stop solution for control compound sample and 480 μL stop solution for test compound sample. The mixture was vortexed and centrifuged at 4000 rpm for about 20 minutes. An aliquot of 100 μL of supernatant of all the samples was then removed for LC-MS/MS analysis. The %Unbound, %Bound and %Remaining were calculated by the following equations: % Unbound = $100 * F / \text{Mean of } T_{4.5}$; % Bound = $100 - \% \text{ Unbound}$; % Remaining = $100 * \text{Mean of } T_{4.5} / \text{Mean of } T_0$, wherein F is the measured value for the protein-free samples. The results are shown in Figure 4.

Method 3: *In vivo* pharmacokinetic

1. Procedures

Animals (mice) are fed a standard laboratory rodent diet and housed in individual cages on a 12-hour light and 12-hour dark cycle with room temperature maintained at $22 \pm 3^\circ\text{C}$ and relative humidity at $50 \pm 20\%$. Animals are fasted overnight before dosing, with food returned after the 6 hour blood samples are obtained. Water is provided *ad libitum* throughout the study. The dosing solution of each test compound is prepared in a desired formulation. Three animals are dosed via tail vein injection for intravenous administration with anti- $\beta_1\text{EC}_{II}$ autoantibody (2 mg/kg) injected first and then each peptide injected at a desired dose level (5 mL/kg) an hour later. All blood samples (50-60 μL per sample) are taken via appropriate vein (saphenous vein) at 0 (predose of each peptide), 5, 15, 30 min, and 2, 4, 8 and 24 h. Blood samples are collected in Greiner MiniCollect K2EDTA tubes, placed on ice, and within 30 minutes, centrifuged at $15,000g$ for 5 min to obtain plasma samples. All plasma samples are stored at -70°C until analysis.

2. Bioanalysis of pharmacokinetic samples

Plasma samples are prepared as follows. Three volumes of acetonitrile containing internal standard is added to one volume of plasma to precipitate proteins. Samples are centrifuged (3000 g for 10 min) and supernatant removed for analysis by LC-MS/MS. Calibration standards and quality controls are made by preparation of a 1 mg/mL stock solution and subsequently a series of working solutions in methanol:water (1:1, v/v) which are spiked into blank plasma to yield a series of calibration standard samples in the range of 1 ng/mL to 10 µg/mL and quality control samples at three concentration levels (low, middle and high). All incurred pharmacokinetic plasma samples are treated identically to the calibration standards and quality control samples. LC-MS/MS analysis is performed utilizing multiple reaction monitoring for detection of characteristic ions for each drug candidate, additional related analytes and internal standard.

3. Pharmacokinetic data analysis

Plasma concentrations are measured as described above to determine a concentration vs. time profile. The area under the plasma concentration vs time curve (AUC) is calculated using the linear trapezoidal method. Fitting of the data to obtain pharmacokinetic parameters is generally carried out using non-compartmental analysis.

Method 4: Endocytosis assays

HEK293 cells (ATCC) were transfected with full-length ASGPR1 cDNA in a pcDNA3.1(+) plasmid containing a Neomycin resistance cassette, using Lipofectamine 3000, according to the vendor's recommendations. Transfected cells were kept under constant selection for ASGPR1 expression using G418 Sulfate Solution at 200 µg/mL in DMEM supplemented with 10% FBS and 1% Penicillin/Streptomycin (DMEM growth media). HEK293-ASGPR1 cells were grown in adherent conditions at 37°C and 5% CO₂, using cell culture flasks and maintaining a density at or below 90% confluency. Cells were harvested using Accutase and resuspended in DMEM growth media. Viable cell density was measured by trypan blue exclusion using a Countess II cell counter. Viable cells were prepared in DMEM growth media supplemented with 2 µg/mL Poly-D-Lysine (to facilitate monolayer attachment to assay well) to a concentration of 0.4E6 cell/mL and 40E3 viable cells were plated in each well of an assay plate. Assay plates were incubated overnight at 37 °C and 5% CO₂ to allow for cell attachment and monolayer establishment.

The next day, compounds were serially diluted in a 96-well plate starting at a concentration of 250 µM and 1 µL of each serial dilution was transferred to a new well and diluted 100-fold in 99 µL OptiMEM. A solution of 110 nM mouse anti-β1-AR antibody, and 37.5 nM anti-mouse IgG-AF488 was prepared in OptiMEM. The assay plate

containing cells was removed from the incubator and media was gently removed by aspiration. 90 μ L of the solution containing 110 nM mouse anti- β 1-AR antibody and 37.5 nM anti-mouse IgG-AF488 was added to all wells except for media-only control wells, which received OptiMEM instead. 10 μ L of the compound dilution series prepared in OptiMEM was added to select wells in duplicate, omitting antibody-complex-only and media-only control wells. 10 μ L of media only was added to control wells in place of a compound dilution. Final anti- β 1-AR antibody concentration in the assay plate was constant 100 nM, and the final compound concentration in the assay plate ranged from 250 nM to 0 nM. Cells were incubated at 37 °C and 5% CO₂, and phase and green fluorescence images were captured using an Incucyte SX5 Live-Cell Analysis Instrument, 4 h following sample preparation. Incucyte Analysis Software v. 2023A was used to process individual images and subtract fluorescent background signal. Mean fluorescent intensity (MFI) was calculated from two replicate wells and concentration-response curves were analyzed in GraphPad Prism 10. EC₅₀ values were determined by fitting the data to a four-parameter non-linear regression model.

Method 5; *In vivo* assay

In vivo experiments were conducted at Touchstone Biosciences, 5217 Militia Hill Rd, Suite 200, Plymouth Meeting, PA 19462. Experiments were performed in male CD-1 mice. Antibody was administered i.v. in a volume of 100 μ L PBS 15 minutes prior to compound administration. Compounds were administered i.v. in a volume of 100 μ L PBS. Approximately 50 μ L of blood was collected at each time point by saphenous bleed. For data analysis, antibody levels were normalized to the recorded concentration of antibody observed just prior to compound administration.

Biological Reagents

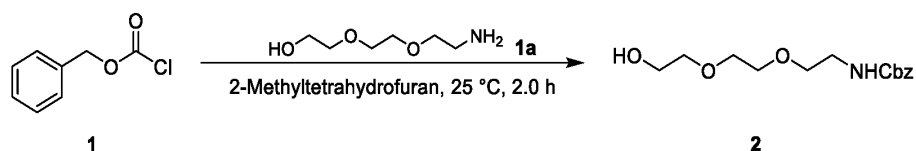
HEK293T cells (ATCC CRL-1573), transfected with ASGPR1_1-291 pcDNA3.1(+) plasmid (GenScript, custom order) are cultured in Dulbecco's Modified Eagle Medium, high glucose (Gibco 11965092) supplemented with heat inactivated Fetal Bovine Serum (ThermoFisher 10082-147) and Penicillin-Streptomycin (ThermoFisher 15070063). Cells are washed with PBS (ThermoFisher 10010023) and dissociated using ACCUTASE Cell detachment solution (STEMCELL Technologies 07920). Plated cells are supplemented with Poly-D-Lysine (ThermoFisher A3890401). All dilutions of degrader and the antibody complex are performed in OptiMEM I Reduced Serum Medium (ThermoFisher 31985062). The antibodies used in the assay are mouse anti-ADRB1 recombinant antibody (CreativeBiolabs HPAB-0273-YC) and Alexa Fluor 488 AffiniPure F(ab')₂ Fragment Goat anti-Mouse IgG, Fcy fragment specific (Jackson ImmunoResearch 115-546-071).

Further methods and procedures

Further methods and procedures have been performed as disclosed in WO 2023/028590 A1, especially from page 47 to page 52.

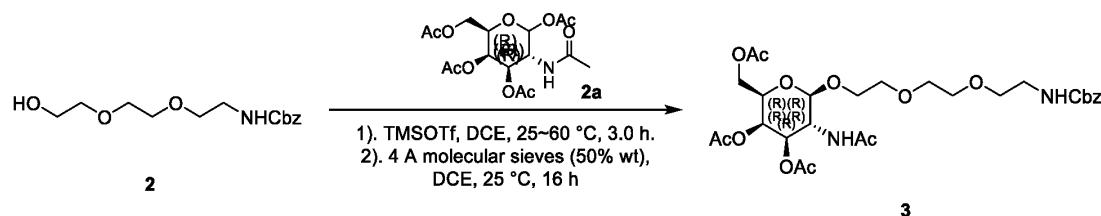
Synthetic ExamplesSynthetic MethodsGeneral Chemistry Methods

Flash chromatography was performed on a CombiFlash NEXTGEN 300+ system by Teledyne ISCO running software version 5.0.62. Separation was accomplished on RediSep Rf High performance gold C18 columns (reverse phase) and RediSep Rf flash columns (normal phase). HPLC purification of compounds was performed using a Shimadzu chromatography system using a Waters SunFire C18 OBD Prep Column (10 mm x 150 mm) and the LabSolutions Software Version 5.92. NMR analysis was performed on Agilent DD2 400 MHz and Agilent DD2 600 MHz NMR spectrometers. The 600 MHz instrument was equipped with a C[H] cold probe. HRMS analysis was performed on a Shimadzu 9030 Quadrupole Time-of-Flight LC-MS system following separation on a Shim-pack Scepter C18-120 1.9 μm (2.1 x 50 mm) reverse phase chromatography column. Separation was performed using a gradient of water to acetonitrile with the addition of 0.1% formic acid. Infrared (IR) spectra were collected using neat samples and recorded using a Thermo Nicolet 6700 equipped with a diamond ATR cell. Select ν_{ma} are reported in cm^{-1} . Optical rotation was recorded on a Rudolph Autopol IV polarimeter. Chemicals were purchased from Sigma Aldrich, Fisher, and Carbosynth. Solvents were purchased from Fisher and Macron.

Synthetic examples*Example 1: Preparation of compound BH5272:***[001] Preparation of Intermediate 2:**

[002] To a solution of 2-(2-(2-aminoethoxy)ethoxy)ethan-1-ol **1a** (60.0 g, 400 mmol, 2.00 equiv.) in 2-Methyltetrahydrofuran (450 mL) was added benzyl chloroformate **1** (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. thin layer chromatography (TLC, dichloromethane (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/ethyl acetate (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 2**, i.e. **N-benzyloxycarbonyl (Cbz) derivative of 1a** (crude, 105.0 g, 370.6 mmol) as yellow oil. LCMS: RT = 0.797 min, MS cal.: 283.14, mass observed: $[M + Na]^+ = 306.1$. 1H 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).

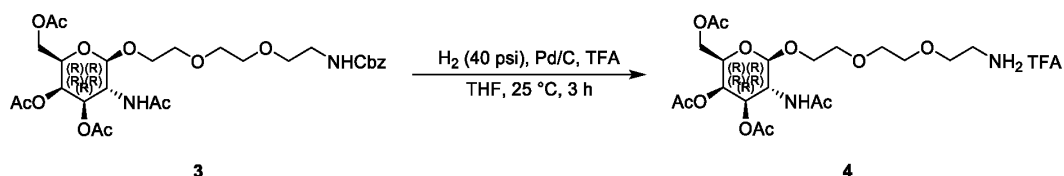
[003] Preparation of Intermediate 3:



[004] To a solution of D-Galactosamine **2a** (100.0 g, 257 mmol, 1.00 equiv.) in dichloroethane (DCE, 500 mL) was added trimethylsilyl trifluoromethanesulfonate (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 2** (80.0 g, 282 mmol, 1.10 equiv.) and 4 Å powder molecular sieves (50.0 g) in 1,2-dichloroethane (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 2a** (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 D-Galactosamine **2a** 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 , petroleum ether (PE): ethyl acetate (EA) = 3: 1 to 1: 6, then DCM: MeOH = 20: 1) to afford **Intermediate 3** (90.0 g, 146.9 mmol, 91.6% purity, 57.2% yield) as yellow oil. **Intermediate 3** has (R) configuration at all at all chiral carbon atoms. LCMS: RT = 0.860 min, MS cal.: 612.25, mass observed: $[M + H]^+ = 613.2$. 1H 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 -

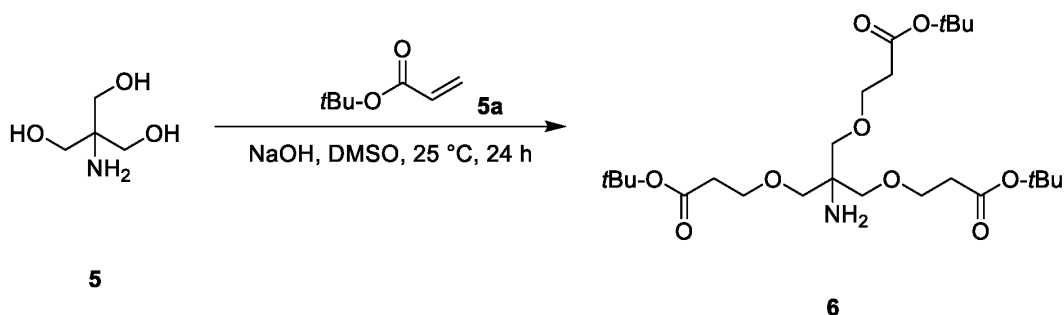
4.59 (m, 1 H), 3.99 - 4.06 (m, 3 H), 3.84 - 3.92 (m, 1 H), 3.73 - 3.82 (m, 1 H), 3.55 - 3.61 (m, 1 H), 3.45 - 3.53 (m, 7 H), 3.41 (t, $J = 5.90$ Hz, 2 H), 3.11 - 3.18 (m, 3 H), 2.10 (s, 3 H), 1.99 (s, 3 H), 1.89 (s, 3 H), 1.77 (s, 3 H).

[005] Preparation of Intermediate 4:



[006] 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 trifluoroacetic acid (TFA, 16.7 g, 147 mmol, 1.00 equiv.) and **Intermediate 3** (90.0 g, 147.0 mmol, 1.00 equiv.) in tetrahydrofuran (THF; 720 mL) was added to the reaction slowly under N₂. The reaction was degassed and purged with N₂ and H₂ for three times, then stirred at 25 °C for 3 h under H₂ atmosphere (40 psi). TLC (DCM: MeOH = 10: 1, $R_f = 0.20$) indicated **Intermediate 3** 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 N₂ 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 4** (80.0 g, 139.0 mmol, 95.1% purity, 91.8% yield, TFA salt) as a white solid. **Intermediate 4** has (R) configuration at all at all chiral carbon atoms. LCMS: RT = 0.484 min, MS cal.: 478.22, mass observed: $[M + H]^+ = 478.9$. ¹H 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).

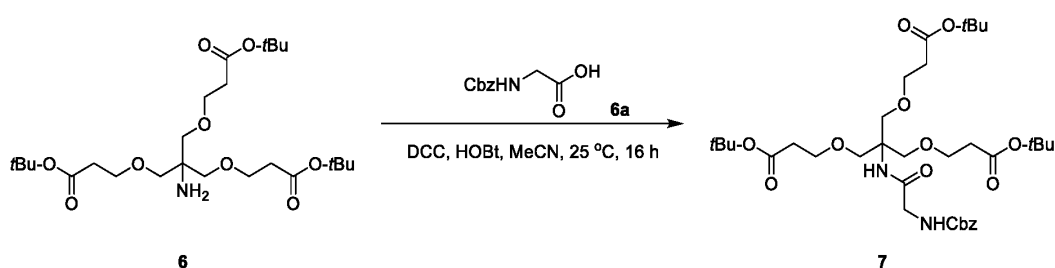
[007] Preparation of Intermediate 6:



[008] To a mixture of **5** (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.

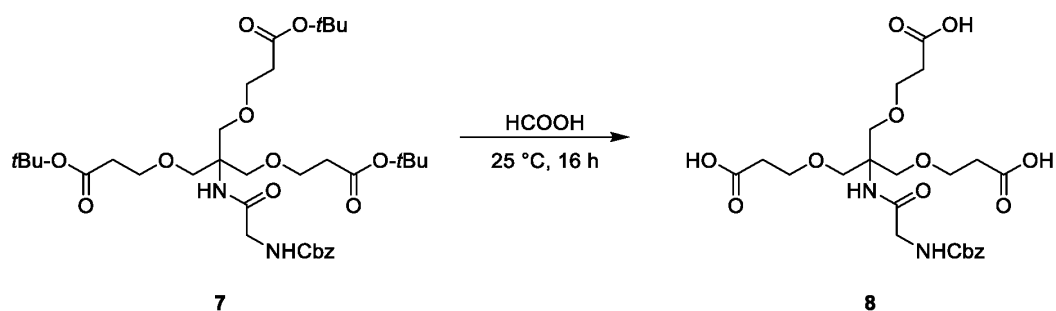
After addition, the mixture was stirred at 0-15 °C for 5 min, then tert-butyl acrylate (**5a**, 254.0 g, 1.98 mol, 287 mL, 4.00 equiv.) was added to the reaction mixture dropwise at 20 °C. The resulting mixture was stirred at 25 °C for 16 h. TLC (DCM: MeOH = 10: 1, R_f = 0.7) indicated **Intermediate 5** 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 Na₂SO₄, filtered and concentrated under reduced pressure to afford **Intermediate 6** (100.0 g, 197.8 mmol, 96.0% purity, 40.0% yield) as colorless oil. ¹H 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).

[009] Preparation of Intermediate 7:



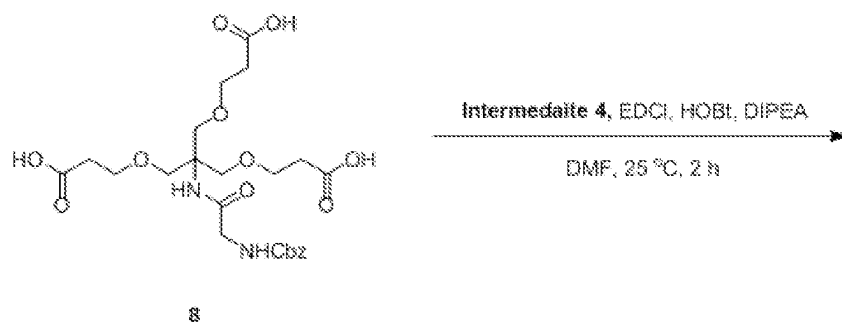
[0010] To a solution of **Intermediate 6** (40.0 g, 79.1 mmol, 1.00 equiv.) in MeCN (400 mL) was added 1*H*-1,2,3-benzotriazole-1-ol (HOBT; 10.7 g, 79.1 mmol, 1.00 equiv.). Then **6a** (16.5 g, 79.1 mmol, 1.00 equiv.) and *N,N'*-dicyclohexylcarbodiimide (DCC, 16.3 g, 79.1 mmol, 1.00 equiv.) were added. The reaction was stirred at 25 °C for 16 h. TLC (PE: EA = 1: 1, R_f = 0.80) indicated **Intermediate 6** 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 (SiO₂, PE: EA = 10: 1 to 1: 1) to afford **Intermediate 7** (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. ¹H 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).

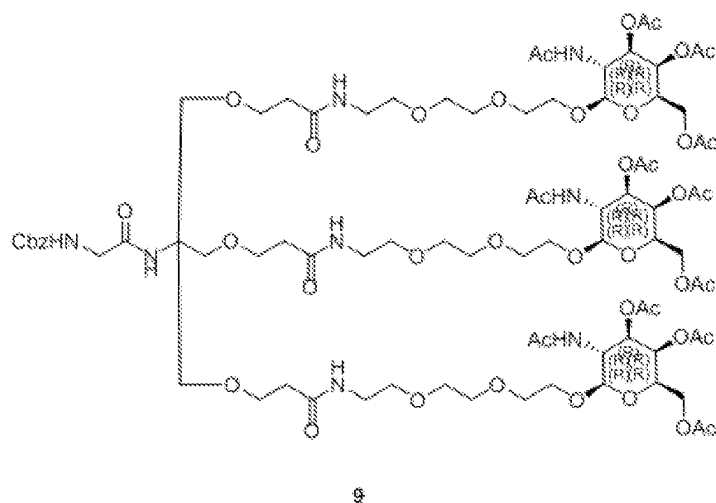
[0011] Preparation of Intermediate 8:



[0012] A solution of **Intermediate 7** (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 7** 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% formic acid (FA) condition/H₂O, B: MeCN) to afford **Intermediate 8** (20.0 g, 37.8 mmol, 98.2% purity, 87.9% yield). ¹H 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.

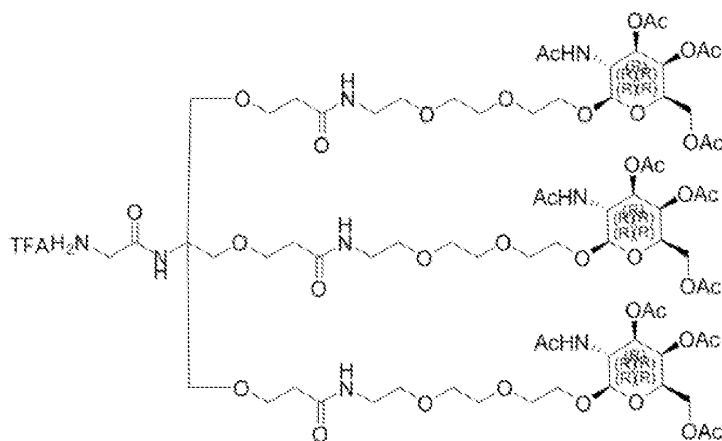
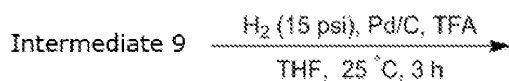
[0013] **Preparation of Intermediate 9:**





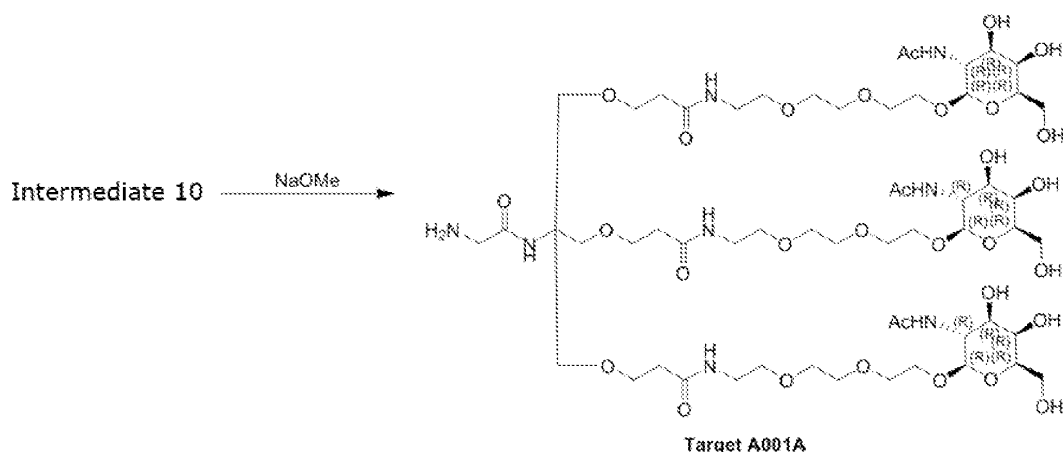
[0014] To a stirring solution of Intermediate 8 (20.0 g, 37.8 mmol, 1.00 equiv.) and **Intermediate 4** (78.5 g, 132 mmol, 3.50 equiv., TFA salt) in DMF (400 mL) was added HOBT (20.4 g, 151 mmol, 4.00 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 29.0 g, 151 mmol, 4.00 equiv.) and N,N-diisopropylethylamine (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 8** 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% NaHCO₃ (450 mL), dried over Na₂SO₄, and concentrated under reduced pressure to get a residue. The residue was purified by column chromatography (SiO₂, DCM: MeOH = 100: 1 to 5: 1) to afford **Intermediate 9** (58.0 g, 30.4 mmol, 82.7% purity, 80.3% yield) as a white solid. **Intermediate 9** has (R) configuration at all at all chiral carbon atoms. ¹H 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.

[0015] **Preparation of Intermediate 10:**

**10**

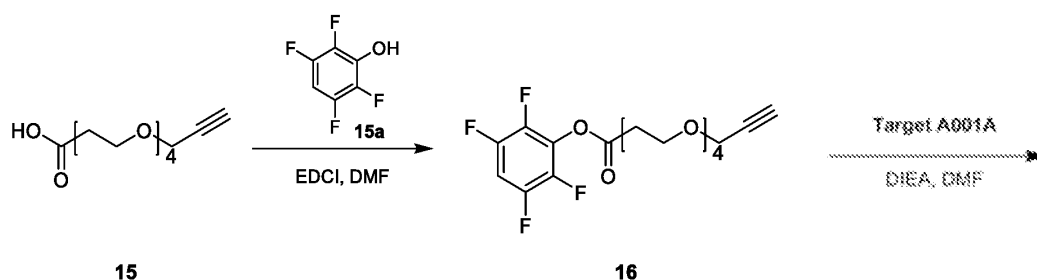
[0016] The 500 mL round-bottom flask was purged with Ar gas for 3 times and added dry Pd/C (1.50 g, 1.41 mmol, 10% purity, 1.00 equiv.) carefully. Then THF (150.0 mL) was added to infiltrate the Pd/C completely, followed by the solution of **Intermediate 9** (15.0 g, 7.85 mmol, 1.00 equiv.) and TFA (895 mg, 7.85 mmol, 583 μL , 1.00 equiv.) in THF (75 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 $^\circ\text{C}$ for 3 h under H_2 atmosphere (15 psi). The reaction was monitored by liquid chromatography-mass spectrometry (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 (100 mL*2). Then, the filter cake was added water immediately. The organic layer concentrated under reduced pressure to afford **Intermediate 10** (13.0 g, 6.54 mmol, 83.2% yield, 99.7% purity, TFA salt) as a white solid. **Intermediate 10** has (R) configuration at all at all chiral carbon atoms. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.89 - 7.99 (m, 5 H), 7.82 (d, J = 9.3 Hz, 3 H), 7.74 (s, 1 H), 7.14 - 7.28 (m, 1 H), 5.22 (d, J = 3.3 Hz, 3 H), 4.97 (dd, J = 11.3, 3.4 Hz, 3 H), 4.54 (d, J = 8.5 Hz, 3 H), 3.84 - 3.93 (m, 3 H), 3.76 - 3.82 (m, 3 H), 3.47 - 3.61 (m, 43 H), 3.21 (q, J = 5.8 Hz, 6 H), 2.29 - 2.34 (m, 6 H), 2.10 (s, 9 H), 2.00 (s, 9 H), 1.89 (s, 8 H), 1.77 (s, 9 H). LCMS: RT = 1.333 min, MS cal.: 1774.7, found: $[\text{M} + 2\text{H}]^{2+}$ = 888.6.

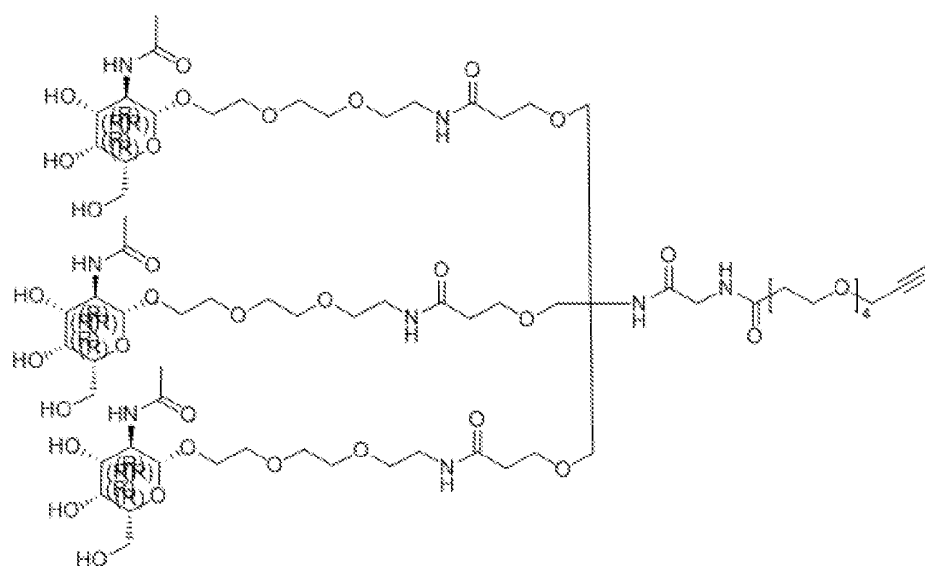
[0017] **Preparation of Intermediate Target A001A:**



[0018] To a solution of **Intermediate 10** (12.0 g, 6.35 mmol, 1.00 equiv., TFA) in MeOH (120.0 mL) was added NaOMe (5.4 M, 5.01 mL, 4.26 equiv.) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. 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 (10.0 mL) till the pH = 6. The mixture was diluted with H₂O (75.0 mL) and extracted with DCM (120 mL * 3). The mixture was freeze-dried to afford **Target A001A** (9.0 g, 5.96 mmol, 93.9% yield, >95% purity, HCl) as a white solid. **Target A001A** has (R) configuration at all chiral carbon atoms. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.96 (br t, *J* = 5.4 Hz, 3 H), 7.67 (d, *J* = 8.9 Hz, 3 H), 7.51 (s, 1 H), 4.27 (d, *J* = 8.4 Hz, 3 H), 3.75 - 3.80 (m, 6 H), 3.70 (br d, *J* = 10.0 Hz, 6 H), 3.49 (br d, *J* = 4.0 Hz, 31 H), 3.37 - 3.42 (m, 12 H), 3.30 (br d, *J* = 6.1 Hz, 4 H), 3.20 (br d, *J* = 5.8 Hz, 6 H), 2.99 (s, 2 H), 2.30 (br t, *J* = 6.4 Hz, 6 H), 1.80 (s, 9 H). LCMS: RT = 0.966 min, MS cal.: 1396.6, found: [M + 2H]²⁺ = 699.1.

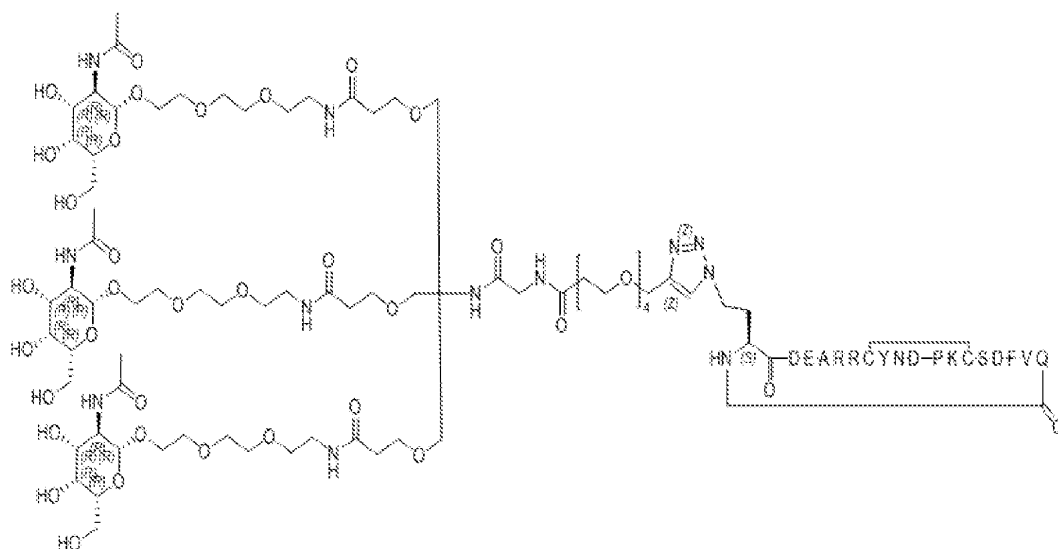
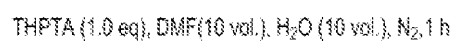
Procedure for Preparation of BH5272 :





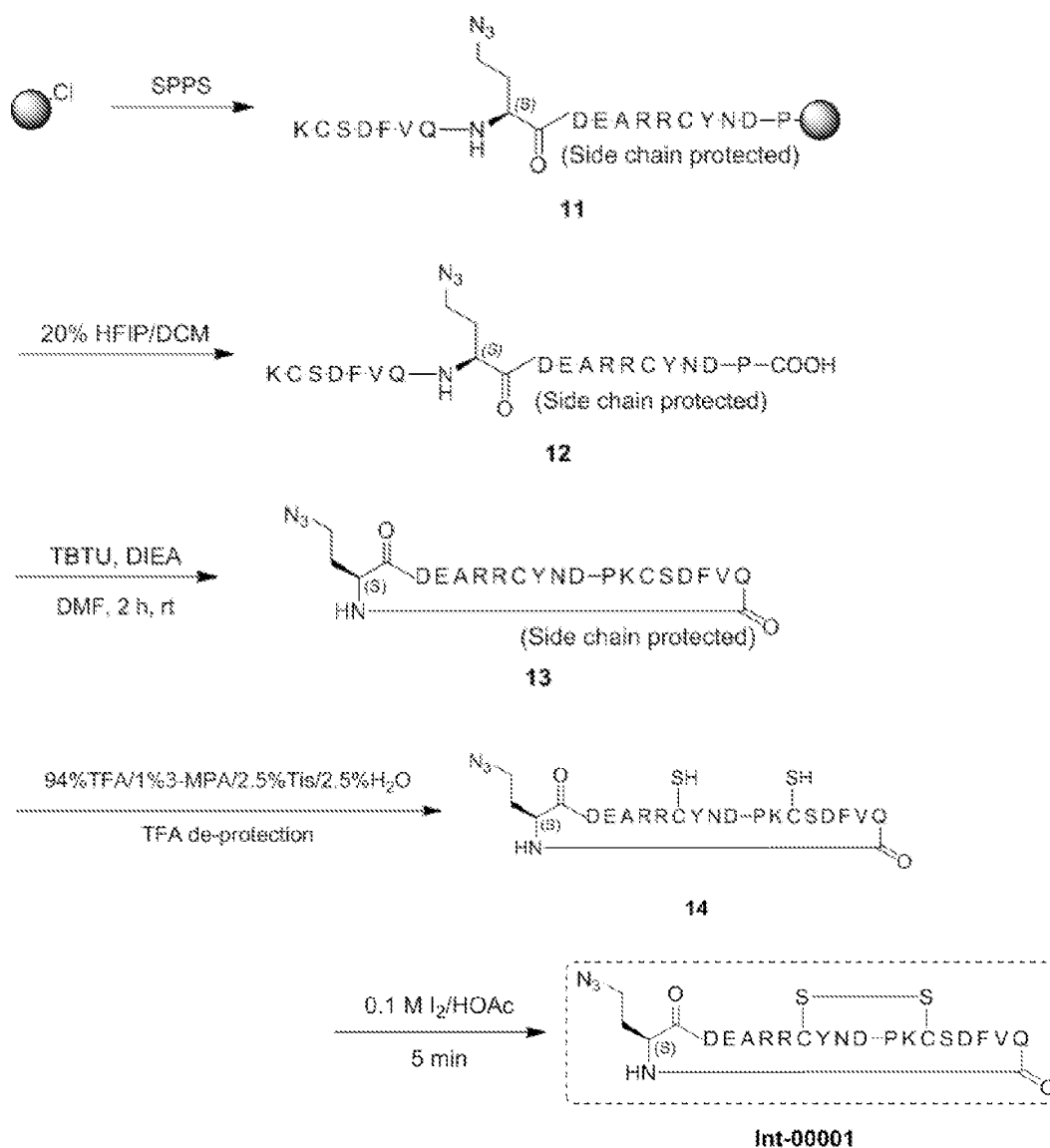
Target A001A-PEG4-Alkyne

Int-00001 CuSO4 (0.4 M, 1.0 eq), sodium L-ascorbate (4.0 eq)



BH-0005272

[0019] Preparation of Int-00001:



[0020] Peptide was synthesized using standard fluorenylmethoxycarbonyl (Fmoc) chemistry (CTC resin).

1) Resin preparation: To the vessel containing chlorotrityl polystyrene resin (CTC Resin, 20.0 mmol, 40.0 g, 1.00 mmol/g) and Fmoc-Pro-OH (6.74 g, 20.0 mmol, 1.00 equiv.) in DCM (300 mL) was added DIEA (4.00 equiv.) dropwise and mix for 2 h with N₂ bubbling at 25 °C. Then added MeOH (40 mL) and bubbled with N₂ for another 30 min. The resin was washed with dimethylformamide (DMF, 600 mL) * 5. Then 20% piperidine in DMF (600 mL) was added and the mixture was bubbled with N₂ for 30 min at 25 °C. Then the mixture was filtered to obtain the resin. The resin was washed with DMF (600 mL) * 5 before proceeding to next step.

- 2) Coupling: A solution of Fmoc-Asp(OtBu)-OH (24.7 g, 60.0 mmol, 3.00 equiv.), HBTU (21.7 g, 2.85 equiv.) in DMF (300 mL) was added to the resin with N₂ bubbling. Then DIEA (6.00 equiv.) was added to the mixture dropwise and bubbled with N₂ 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 (600 mL) * 5.
- 3) Deprotection: 20% piperidine in DMF (600 mL) was added to the resin and the mixture was bubbled with N₂ for 30 mins at 25 °C. The resin was then washed with DMF (600 mL) * 5. The De-protection reaction was monitored by ninhydrin test, if it showed blue or brownish red, the reaction was completed.
- 4) Steps 2 and 3 were repeated for the following amino acids elongation: Number # 3-18, Table 1.
- 5) After the last position completed, the resin was then washed with DMF (200 mL) * 5, MeOH (200 mL) * 5, and dried under reduced pressure to afford **Intermediate 11** (peptide-bound-resin, 20.0 mmol).

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

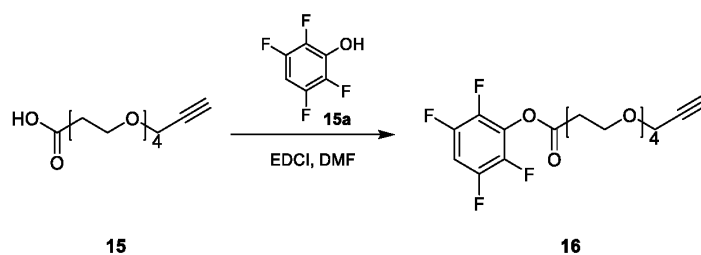
#	Materials	Coupling reagents
1	Fmoc-Pro-OH (1.00 equiv.)	DIEA (4.00 equiv.)
2	Fmoc-Asp(OtBu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
3	Fmoc-Asn(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
4	Fmoc-Tyr(tBu)-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOAt (3.00 equiv.)
5	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
6	Fmoc-Arg(Pbf)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
7	Fmoc-Arg(Pbf)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
8	Fmoc-Ala-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOAt (3.00 equiv.)
9	Fmoc-Glu(OtBu)-OH (2.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
10	Fmoc-Asp(OtBu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
11	Fmoc-Dab(N ₃)-OH (1.50 equiv.)	DIC (1.50 equiv.) and HOAt (1.50 equiv.)
12	Fmoc-Gln(Trt)-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-Phe-OH (3.00 equiv.)	DIC (3.00 equiv.) and HOAt (3.00 equiv.)
15	Fmoc-Asp(OtBu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
16	Fmoc-Ser(tBu)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
17	Fmoc-Cys(Trt)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)

18	Fmoc-Lys(Boc)-OH (3.00 equiv.)	HBTU (2.85 equiv.) and DIEA (6.00 equiv.)
----	--------------------------------	---

[0021] Peptide Cleavage, head to tail cyclization, TFA de-protection and disulfide formation:

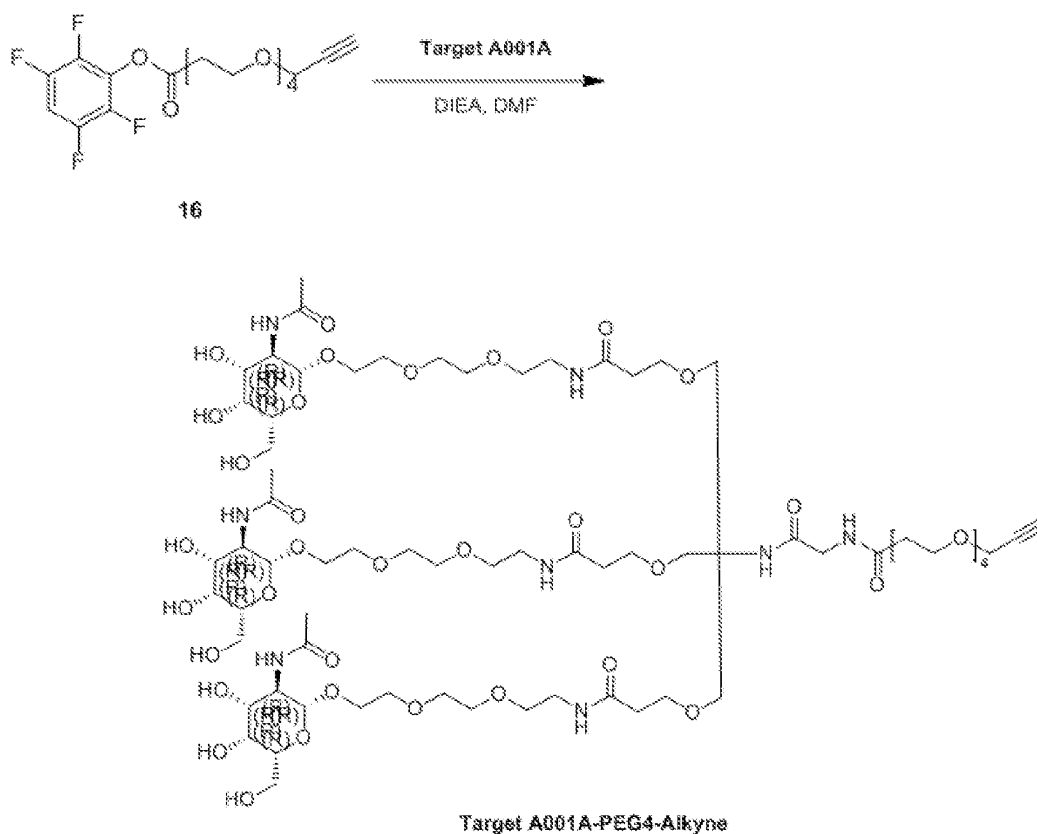
- 1) Cleavage: Cleavage cocktail (20% hexafluoroisopropanol (HFIP)/DCM, 1 L) was added to the flask containing the side chain protected peptide at room temperature and the mixture was bubbled with N₂ for 10 min * 3. After filtration, the filtrate was collected and concentrated under pressure. The residue was dried by lyophilization to afford **Intermediate 12** (71.5 g, crude).
- 2) Head to tail cyclization: Intermediate 12 (26.5 g, crude) was dissolved in DMF (7 L). Then 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU) (2.00 equiv.) and HOBT (2.00 equiv.) and DIEA (4.00 equiv.) was added to the mixture. The mixture was stirred at 25 °C for 2 h. The reaction was concentrated under pressure. The residue was dissolved in DMC (2 L), washed with 1 M HCl (200 mL * 2), concentrated under reduced pressure to give the Intermediate 13 (30.0 g, crude) as a white solid.
- 3) TFA De-protection: Intermediate 13 (30.0 g, crude) was stirred in a solution of TFA/3-mercaptopropionic acid (3-MPA)/triisopropylsilane (Tis)/H₂O (94/1/2.5/2.5, v/v/v/v, 900 mL) at 25 °C for 1 h. The mixture was precipitated with isopropyl ether (cold, 4 L). After filtration, the solid was washed with isopropyl ether (cold, 4 L) for two additional times, and dried under reduced pressure for 2 h to afford Intermediate 14 (21.0 g, crude) as a white solid.
- 4) Disulfide formation: Intermediate 14 (21.0 g, crude) was dissolved in H₂O (4 L) and MeCN (4 L) at 25 °C. Then the mixture 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 anhydrous Na₂S₂O₃ dropwise until the yellow color disappeared. After filtration, the filtrate was purified by prep-HPLC (A: 0.075% TFA/H₂O, B: MeCN) directly to afford Int-00001 (4.10 g, 23.6% yield, 92.9% purity) as a white solid. LCMS: RT = 1.437 min, MS calcd.: Mav = 2152.28, mass observed: [M + 2H]²⁺ = 1076.4, [M + 3H]³⁺ = 718.2.

[0022] *Preparation of Intermediate 6:*



[0023] To a solution of **Intermediate 15** (600 mg, 2.31 mmol, 1.00 equiv.), **2,3,5,6-tetrafluorophenol 15a** (2.30 g, 13.8 mmol, 6.00 equiv.) in DMF (6 mL) was added EDCI (1.33 g, 6.92 mmol, 3.00 equiv.) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was purified by prep-HPLC (TFA condition) directly to afford **Intermediate 16** (800 mg, 1.92 mmol, 83.4% yield, 98.2 % purity) as yellow oil. LCMS: RT = 1.430 min, MS calcd.: $M_{av} = 408.34$, mass observed: $[M + Na]^+ = 431.0$.

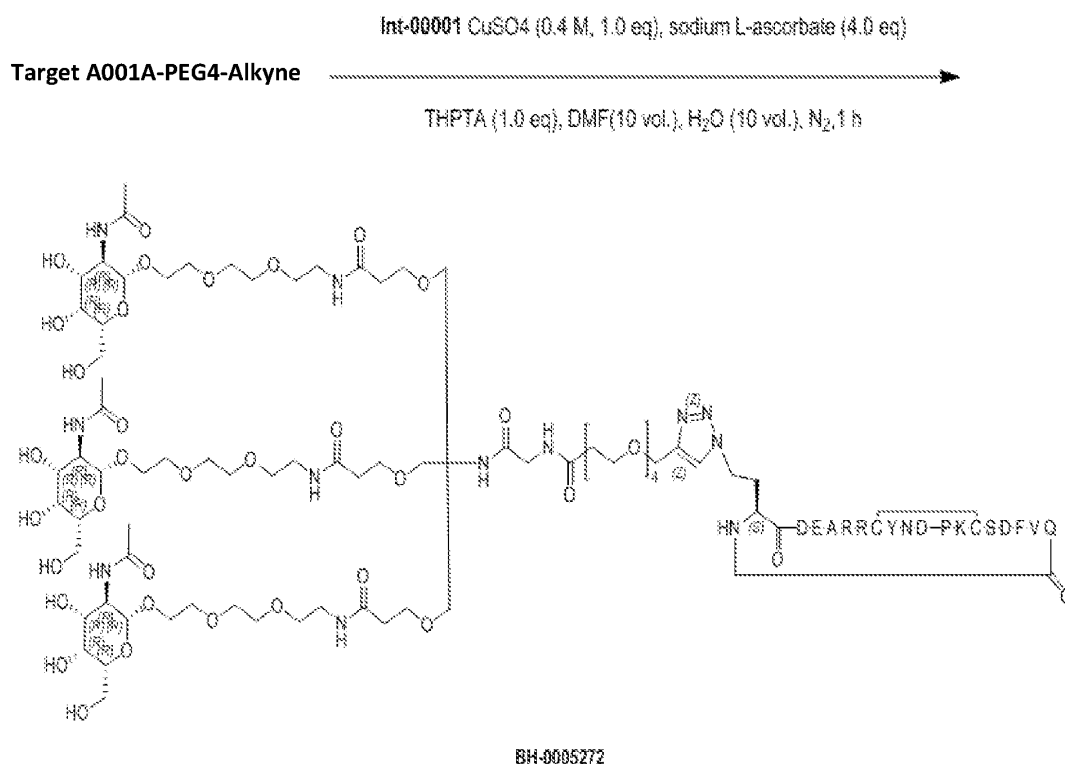
[0024] Preparation of Target A001A-PEG4-Alkyne:



[0025] To a solution of **Intermediate 16** (276 mg, 676 μ mol, 1.05 equiv.) and **Target A001A** (1.00 g, 644 μ mol, 1.00 equiv.) in DMF (0.25 mL) was added DIEA (166

mg, 230 μ L, 2.00 equiv.). The mixture was stirred at 0 °C for 12 h. DMF was removed by lyophilization. The residue was purified by prep-HPLC (AcOH condition) directly to afford **Target A001A-PEG4-Alkyne** (0.60 g, 93.5% purity, 56.8% yield) as colorless oil. **Target A001A-PEG4-Alkyne** has (R) configuration at all chiral carbon atoms. LCMS: RT = 0.368 min, MS calcd.: M_{av} = 1639.74, mass observed: $[M + H]^+$ = 1639.8, $[M - \text{sugar} + H]^+$ = 1426.6, $[M - 2*\text{sugar} + H]^+$ = 1233.6, $[M - 3*\text{sugar} + H]^+$ = 1030.3, $[M + 2H]^{2+}$ = 820.6.

[0026] Preparation of BH-0005272 (=BH5272):



[0027] To a solution of **Int-00001** (250 mg, 116 μ mol, 1.10 equiv.) and **Target A001A-PEG4-Alkyne** (173 mg, 105 μ mol, 1.00 equiv.) in DMF (2.5 mL) was added a solution of CuSO₄ (0.4 M, 263 μ L, 1.00 equiv.), sodium L-ascorbate (0.4 M, 1.06 mL, 4.00 equiv.) and tris-hydroxypropyltriazolylmethylamine (THPTA, 45.8 mg, 105 μ mol, 1.00 equiv.) at 20 °C. The mixture was stirred at 25 °C for 1 h under N₂ atmosphere. The residue was purified by prep-HPLC (AcOH condition) directly to afford **BH5272** (288 mg, 73.1 μ mol, 69.2% yield, 96.2% purity) as a white solid. **BH5272** has (R) configuration at all chiral carbon atoms of the sugar moieties. LCMS: RT = 1.384 min, MS calcd.: M_{av} = 3792.02, $[M + 2H]^{2+}$ = 1896.4, $[M + 3H]^{3+}$ = 1264.9, $[M + 4H]^{4+}$ = 948.6.

[0028] Figures 1 to 7 show the properties of **BH5272** as discussed above.

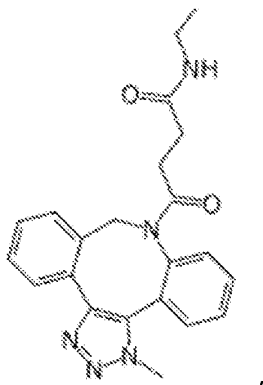
Example 2: Preparation of further compounds

Compounds BH5271, BH 5273, BH5274, BH5339, BH5463, BH5552, BH5633, BH5634, BH5637, BH5775, BH7033 and BH7034 have been prepared *mutatis mutandis* according to the procedure disclosed in Example 1. The structures of these compounds are disclosed above. All compounds prepared show sufficient *in vitro* activity against anti- β 1ECII autoantibodies.

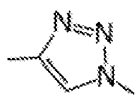
Discussion of Results

Effect

Figure 5 shows a comparison between the efficacy of BH5272 and BH5270. The latter is the compound of the prior art as described in the examples of WO 2023/028590 A1 and WO 2023/028597 A1. BH5270 and BH5272 differ only in that BH5270 comprises the partial structure



wherein BH5270 is a 1 to 1 mixture of regioisomers in respect to the position of the bond with which the 5-membered ring is bonded to the remainder of the molecule. The bond may be at the 1-N atom or the 3-N atom, i.e. the N-C(=O)- group may be at the same side of the bond with which the 5-membered ring is bonded to the remainder of the molecule or at the opposite side. This partial structure is substituted in BH5272 by the partial structure of T, i.e.



As can be seen from Figure 5, this difference in structure results in a much better *in vivo* efficacy of BH5272 over BH5270. BH5272 depletes anti- β_1 ECII autoantibodies faster and to a lower concentration, even though the dosage is only one fifth (0.2 mg/kg of body weight of BH5272 instead of 1 mg/kg of body weight of BH5270). Significantly more anti-B1AR antibody depletion is observed 5 to 30 minutes post-dose with BH5272 compared to BH5270. The AUC values of the anti- β_1 ECII autoantibodies in Figure 6 show the amount of anti- β_1 ECII autoantibodies in plasma is also lowered to a larger extend by 0.2 mg/kg of body weight of BH5272 than by 2 mg/kg of body weight of BH5270 over two hours.

The following Table 2 shows some of the properties of some of the prepared compounds next to compound BH5270 as described in the examples of WO 2023/028590 A1 and WO 2023/028597 A1.

Table 2:

Compound ID	PPB; Unbound [%]*	K _D ASGPR [nM]	Endocytosis
BH5270	41.0	1.0	21.5
BH5271	65.6		17.0
BH5272	72.4	2.5	16.3
BH5273	75.1		16.4
BH5274	74.9		3.4
BH5339	62.2	1.2	18.2
BH5463	75.6	198	35.9
BH5552	99.0	2800	3.5
BH5633	57.9	76	28.9
BH5634	59.7	420	26.8
BH5775	43.6		22.8

Unbound compound of the present invention in percent according to the method for the measurement of plasma protein binding described above.

All compounds listed in Table 2 show sufficient *in vitro* activity against anti- β_1 ECII autoantibodies. All have a half-life time in human blood-plasma of more than 289 minutes, which is more than sufficient. BH5272 has more unbound active substance *in vitro* in human blood plasma than BH5270. The same can be observed in mice and rat plasma (see Figure 9). This may contribute to improved effect shown in Figures 5 and 6. However, binding to ASGPR is stronger for BH5270 than for BH5272. Usually it would be

expected that a lower value here would contribute to a higher efficacy. Also endocytosis for BH5272 is lower than for BH5270, which in theory may also result in a lower efficacy. It could be considered that either the influence of the percentage of the active substance that is not plasma protein bound has a stronger influence on efficacy than the binding to ASGPR and endocytosis or that a well-balance relationship of these properties leads to a high efficacy. It must also be considered that pharmacokinetics of these compounds is unusual and difficult to predict, as the mechanism of action of these compounds relies on their clearance from circulation. Once the compounds have entered steady-state, they are no longer active, i.e. the compounds of the present invention are only active when their clearance is rapid.

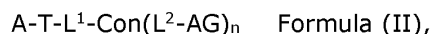
BH5271, BH5272 and BH5274 differ only in the structure of L¹. BH5272 has three ethylene oxide units (-CH₂-CH₂-O-) in L¹ while BH5271 has one of these units and BH5273 has none. However, all three compounds show about the same efficacy. Also, as can be seen from Table 2, the influence of the length of the spacer on the percent of the active substance not bound to plasma protein and on endocytosis is negligible. The length of spacer L¹ may therefore not have a strong influence on the properties of the inventive substances.

BH5339 differs from BH5272 only in the stereochemistry at the C-1 atom of the sugar moiety. There seems to be some influence of this parameter on the unbound percentage of the substance and on the binding to the ASGPR receptor. The influence of this parameter on endocytosis seems weak.

It is further interesting that the number of sugar moieties seems to have only a small influence on endocytosis (see the last 7 entries of Table 2).

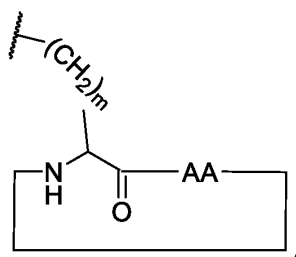
What is claimed is:

1. A compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof, having the structure



wherein

A is an anti- β_1 adrenergic receptor antibody binding moiety that has the structure



AA is an amino acid sequence at least 80% homologous to SEQ ID NO: 1 and

m is an integer in the range of 1 to 10;

T is selected from the group consisting of (1) a single cycle aromatic 5- or 6-membered heterocycle selected from the group consisting of pyrroles, furans, thiophenes, pyrazoles, oxazoles, isoxazoles, thiazoles, isothiazoles, triazoles, furazans, oxadiazoles, thiadiazoles, tetrazoles, pyridines, diazines and triazines and (2) $-\text{C}(=\text{O})-\text{NR}-$, wherein R is hydrogen or C1 to C4 alkyl;

in which heterocycles a first ring atom is covalently bonded to the $-(\text{CH}_2)_m-$ group of A and a second ring atom is covalently bonded to an open valence in L^1 and the remainder of the ring atoms may be substituted or unsubstituted;

L^1 and L^2 are linker and all linker L^1 and L^2 may be the same or different and all occurrences of L^2 in Formula (II) may be the same or different and

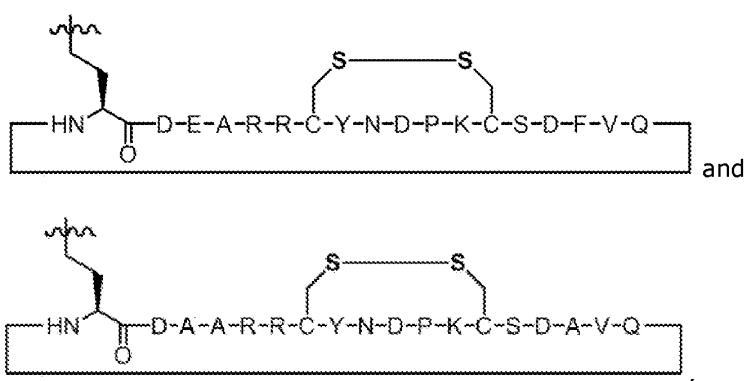
L^1 and L^2 may also be a direct bond;

Con is a connector that is covalently bonded to an open valence of linker L^1 and of each linker L^2 ;

n is an integer of 2 or 3 and

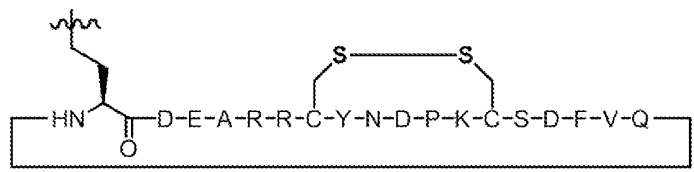
AG is an asialoglycoprotein receptor binding moiety and each occurrence of AG in Formula (II) may be the same or different.

2. The compound of any of the preceding claims, wherein AA is at least 95% homologous to SEQ ID NO:1.
3. The compound of any of the preceding claims, wherein AA is an amino acid of sequence of SEQ ID NO: 1.
4. The compound of any of the preceding claims, wherein A is selected from the group consisting of



wherein the wavy line marks the bond that bonds A to the remainder of the molecule.

5. The compound of any of the preceding claims, wherein A has the structure

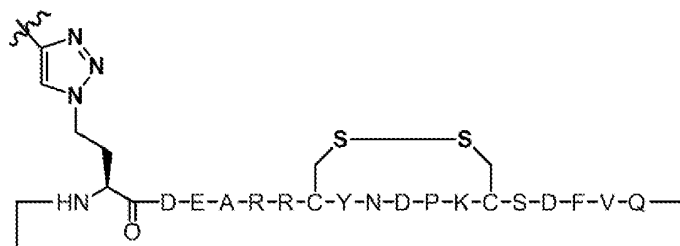


wherein the wavy line marks the bond that bonds -A to the remainder of the molecule.

6. The compound of any of the preceding claims, wherein T is a triazole ring.
7. The compound of any of the preceding claims, wherein T is a 1,2,3-triazole.
8. The compound of any of the preceding claims, wherein T is a 1H-1,2,3-triazole.

9. The compound of claim 8, wherein A is bound to the triazole in 1 position and L¹ is bound to the triazole in 4-position.

10. The compound of any of the preceding claims, wherein A-T- has the structure



11. The compound of any of the preceding claims, wherein

L¹ has the structure $-(XG)_n-$, wherein n is an integer from 1 to 105;

L² has the structure $-(XG)_p-$, wherein p is an integer from 1 to 50;

wherein each occurrence of XG is independently selected from the group consisting of $-CH_2-$, $-CH(CH_2-OCH_3)-$, $-CH(CH_2-OCH_2CH_3)-$, $-C(=O)-$, $-NH-$, $-O-$, $-S(=O)_2-$ and $-P(=O)_2-$ with the proviso that in linker L¹ and L² no two oxygen atoms are adjacent to each other and L² may also be a direct bond between Con and AG.

12. The compound of any of the preceding claims, wherein the linker L¹ and L² do not comprise carboxyl ester groups.

13. The compound of any of the preceding claims, wherein L¹ and L² are copolymers with a chain length of 3 to 50 atoms, comprising one or more of $-(CH_2)_Y-$, wherein Y is an integer in the range of 1 to 5, and one of the hydrogen atoms in each $-CH_2-$ residue may be substituted by a residue selected from the group consisting of a halogen atom or a residue $-CH_2-O-CH_3$ or $-CH_2-O-CH_2-CH_3$, and

wherein a plurality of $-(CH_2)_Y-$ moieties are bonded to each other by a residue selected from the group consisting of $-O-$, $-CONH-$, $-NHCONH-$, $-SO_2-NH-$ and $-PO_2-NH-$.

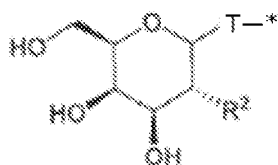
14. The compound of claim 13, wherein Y is an integer in the range of 1 to 4, preferably 1 to 3.
15. The compound of any of the preceding claims, wherein L^1 and L^2 are copolymers comprising repeating units selected from the group consisting of $-\text{CH}_2-$, $-\text{NH}-$, $-\text{CH}_2-\text{O}-$, $-(\text{CH}_2\text{CH}_2-\text{O})-$, $-(\text{CH}_2-\text{NH})-$, $-(\text{CH}_2\text{CH}_2-\text{NH})-$, $-\text{CH}_2\text{C}(=\text{O})-$, $-\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$ and $-\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$.
16. The compound of claim 13, wherein L^1 and L^2 consist of the repeating units.
17. The compound of any of the preceding claims, wherein L^1 or L^2 or both comprise one or more units selected from the group consisting of $-(\text{CH}_2\text{CH}_2-\text{O})_q-$, $-(\text{CH}_2\text{CH}(\text{CH}_2\text{OCH}_3)-\text{O})_q-$ and $-(\text{CH}_2\text{CH}(\text{CH}_2\text{OCH}_2\text{CH}_3)-\text{O})_q-$, wherein the values of q are independently of each other selected from an integer in the range of 1 to 10, preferably 1 to 4.
18. The compound of any of the preceding claims, wherein at least one of L^1 and L^2 is selected from the group consisting of
- (a) $-\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{C}(=\text{O})-\text{NH}-(\text{CH}_2\text{CH}_2-\text{O})_3-\text{CH}_2\text{CH}_2\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{C}(=\text{O})-\text{NH}-$,
 - (b) $-\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{C}(=\text{O})-\text{NH}-$,
 - (c) $-\text{CH}_2-\text{O}-(\text{CH}_2\text{CH}_2-\text{O})_3-\text{CH}_2\text{CH}_2\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{C}(=\text{O})-\text{NH}-$,
 - (d) $-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-\text{NHCH}_2\text{C}(=\text{O})-\text{NH}-$,
 - (e) $-\text{CH}_2-\text{O}-(\text{CH}_2\text{CH}_2-\text{O})_3-$,
 - (f) $-\text{NH}-\text{C}(=\text{O})-\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{C}(=\text{O})-\text{NH}-$ and
 - (g) $-\text{O}-\text{CH}_2\text{CH}_2\text{C}(=\text{O})-\text{NH}-(\text{CH}_2\text{CH}_2-\text{O})_3-$
- or wherein L^2 is a direct bond.
19. The compound of claim 18, wherein L^1 is selected from the group consisting of items (a) to (f).
20. The compound of any of claims 18 or 19, wherein L^2 is selected from the group consisting of item (g) and a direct bond.
21. The compound of any of the preceding claims, wherein AG is selected from the

group consisting of monosaccharides, disaccharides, oligosaccharides of up to 20 monosaccharides and derivatives thereof.

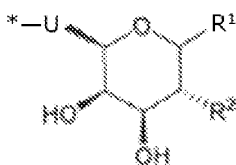
22. The compound of any of the preceding claims, wherein AG is a monosaccharide selected from the group consisting of aldoses, aldotetroses, aldopentoses, aldohexoses, ketotrioses, ketotetroses, ketopentose, ketohexoses, aminosugars, sulfosugars, sedoheptulose and sedoheptulose anhydride.

23. The compound of any of the preceding claims, wherein AG is a disaccharide selected from the group consisting of sucrose, lactose, maltose, trehalose, cellobiose, kojibiose, nigerose, isomaltose, β,β -trehalose, sophorose, laminaribiose, gentiobiose, turanose, maltulose, palatinose, gentiobulose, mannobiose, melibiose, melibiulose, rutinose, rutinulose and xylobiose.

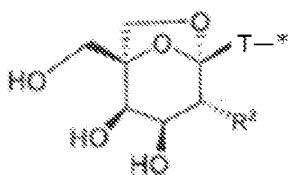
24. The compound of any of the preceding claims, wherein AG is selected from the group consisting of



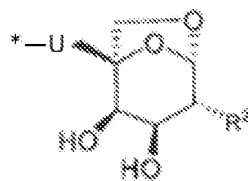
Formula AG-1,



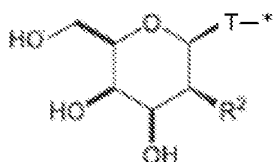
Formula AG-2,



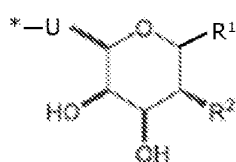
Formula AG-3



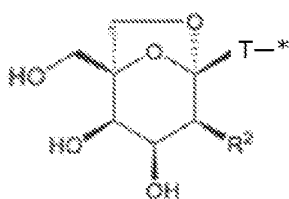
Formula AG-4,



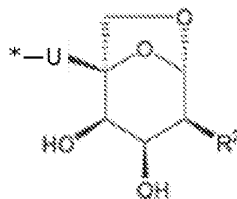
Formula AG-5



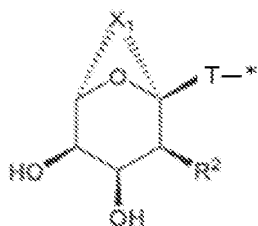
Formula AG-6,



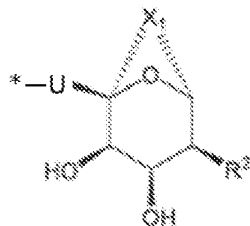
Formula AG-7,



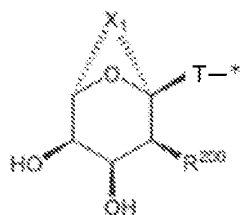
Formula AG-8,



Formula AG-9

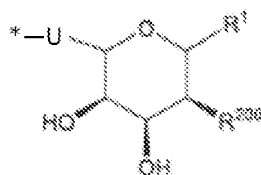


Formula AG-10



Formula AG-11

and



Formula AG-12

wherein T is selected from the group consisting of a direct bond and O and U is selected from the group consisting of a direct bond, O and O-CH₂, wherein if U is O-CH₂, the carbon atom of O-CH₂ is bound to the C5-atom of the sugar ring moiety and wherein * marks the bond that bonds AG to the remainder of the compounds, with the proviso that no oxygen-oxygen bond is formed between AG and the remainder of the compounds of the present invention;

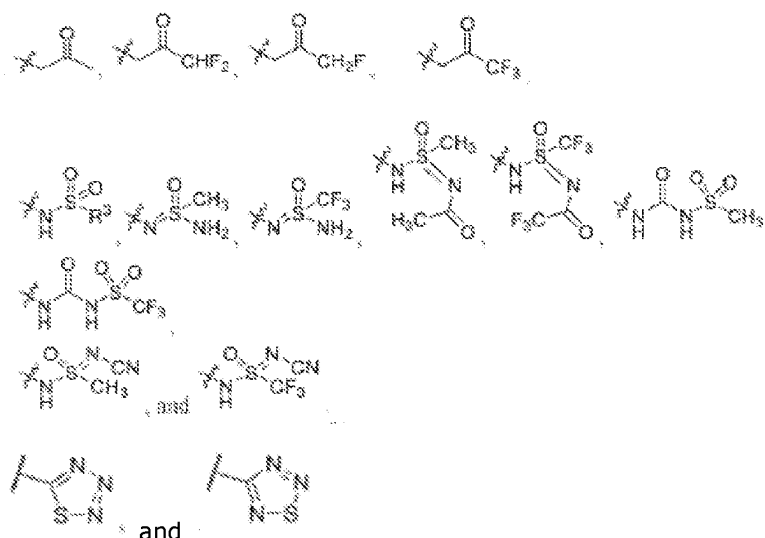
X¹ is 1 to 5 contiguous atoms independently selected from O, S, N(R⁶), and C(R⁴)(R⁴), wherein if X¹ is 1 atom then X¹ is O, S, N(R⁶), or C(R⁴)(R⁴), if X¹ is 2 atoms then no more than 1 atom of X¹ is O, S, or N(R⁶), if X¹ is 3, 4, or 5 atoms then no more than 2 atoms of X¹ are O, S, or N(R⁶), wherein preferably no two oxygen atoms are adjacent to each other;

R is selected from the group consisting of H, or C₁-C₃ alkyl optionally substituted with 1-3 hydroxyl groups;

R¹ is selected from the group consisting of hydrogen, hydroxyl, F, Cl, Br, I, -CN, -N₃, alkyl optionally substituted with 1, 2, 3, or 4 substituents, C₁-C₆-alkyl-CN optionally

substituted with 1, 2, 3, or 4 substituents, alkenyl optionally substituted with 1, 2, 3, or 4 substituents, alkynyl optionally substituted with 1, 2, 3, or 4 substituents, haloalkyl optionally substituted with 1, 2, 3, or 4 substituents, aryl optionally substituted with 1, 2, 3, or 4 substituents, arylalkyl optionally substituted with 1, 2, 3, or 4 substituents, heteroaryl optionally substituted with 1, 2, 3, or 4 substituents, heteroaryl alkyl optionally substituted with 1, 2, 3, or 4 substituents, heterocycle optionally substituted with 1, 2, 3, or 4 substituents, heterocycloalkyl optionally substituted with 1, 2, 3, or 4 substituents, alkoxy optionally substituted with 1, 2, 3, or 4 substituents, haloalkoxy optionally substituted with 1, 2, 3, or 4 substituents, -O-alkenyl, -O-alkynyl, -OR⁶, C₁-C₆-alkyl-OR⁶, -SR⁶, C₁-C₆-alkyl-SR⁶, -NR⁶R⁷, C₀-C₆-alkyl-NR⁶R⁷, -C(O)R³, C₀-C₆-alkyl-C(O)R³, -S(O)R³, C₁-C₆-alkyl-S(O)R³, -C(S)R³, C₁-C₆-alkyl-C(S)R³, -S(O)₂R³, C₁-C₆-alkyl-S(O)₂R³, -N(R⁸)-C(O)R³, C₁-C₆-alkyl-N(R⁸)-C(O)R³, -N(R⁸)-S(O)R³, C₁-C₆-alkyl-N(R⁸)-S(O)R³, -N(R⁸)-C(S)R³, C₁-C₆-alkyl-N(R⁸)-C(S)R³, -N(R⁸)-S(O)₂R³, C₁-C₆-alkyl-N(R⁸)-S(O)₂R³, -O-C(O)R³, C₁-C₆-alkyl-O-C(O)R³, -O-S(O)R³, C₁-C₆-alkyl-O-S(O)R³, -O-C(S)R³, C₁-C₆-alkyl-O-C(S)R³, -N=S(O)(R³)₂, C₁-C₆-alkyl-N₃, -O-S(O)₂R³, or C₀-C₆-alkyl-O-S(O)₂R³, each of which is optionally substituted with 1, 2, 3, or 4 substituents;

R² is selected from the group consisting of hydrogen, optionally substituted amino, alkyl optionally substituted with 1, 2, 3, or 4 substituents, alkenyl optionally substituted with 1, 2, 3, or 4 substituents, allyl optionally substituted with 1, 2, 3, or 4 substituents, alkynyl optionally substituted with 1, 2, 3, or 4 substituents, aryl optionally substituted with 1, 2, 3, or 4 substituents, a heterocycle optionally substituted with 1, 2, 3, or 4 substituents, heteroaryl containing 1, 2 or 3 heteroatoms in the ring which are independently selected from N, O, and S and wherein the heteroaryl groups are optionally substituted with 1, 2, 3, or 4 substituents, R¹⁰, alkoxy optionally substituted with 1, 2, 3, or 4 substituents, -O-alkenyl optionally substituted with 1, 2, 3, or 4 substituents, -O-alkynyl optionally substituted with 1, 2, 3, or 4 substituents, -O-aryl optionally substituted with 1, 2, 3, or 4 substituents, -O-heteroaryl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-alkyl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-alkenyl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-alkynyl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-heteroaryl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁶-aryl optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-C(O)R¹⁰, -NR⁸-S(O)-R³ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-C(S)-R³ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-S(O)(NR⁶)-R³ optionally substituted with 1, 2, 3, or 4 substituents, -N=S(O)(R³)₂ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸C(O)NR⁹S(O)₂R³ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-S(O)₂-R¹⁰ optionally substituted with 1, 2, 3, or 4 substituents, -NR⁸-C(NR⁶)-R³ optionally substituted with 1, 2, 3, or 4 substituents, alkyl-C(O)-R³, -C(O)-R³, haloalkyl, -OC(O)R³,



R¹ and R² may also form a 5 to 7 membered saturated heterocycle that comprises up to 3 heteroatoms selected from the group consisting of N, S and O and preferably the heterocycle is a 5 or 6-membered heterocycle;

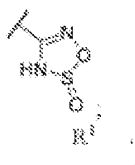
R¹ and R² may also form a 3 to 7 membered saturated optionally substituted carbocycle;

the C⁴ and C⁵ atoms of Formula AG-1 to Formula AG-12 may be connected to form a 5 to 7 membered saturated optionally substituted heterocycle that comprises up to 3 heteroatoms selected from the group consisting of N, S and O;

R³ at each occurrence is independently selected from hydrogen, alkyl, heteroalkyl, haloalkyl (including -CF₃, -CHF₂, -CH₂F, -CH₂CF₃, -CH₂CH₂F, and -CF₂CF₃), arylalkyl, heteroarylalkyl, alkenyl, alkynyl, and, heteroaryl, heterocycle, -OR⁸, and -NR⁸R⁹;

R⁴ is independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, -OR⁶, -NR⁶R⁷, C(O)R³, S(O)R³, C(S)R³, and S(O)₂R³;

R⁵ is independently selected from hydrogen, heteroalkyl,



C₀-C₆alkyl-cyano, alkyl, alkenyl, alkynyl, haloalkyl, F, Cl, Br, I, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocycloalkyl, haloalkoxy, -O-alkenyl, -O-alkynyl, C₀-C₆alkyl-OR⁶, C₀-C₆alkyl-SR⁶, C₀-C₆alkyl-NR⁶R⁷, C₀-C₆alkyl-C(O)R³, C₀-C₆alkyl-S(O)R³, C₀-C₆alkyl-C(S)R³, C₀-C₆alkyl-S(O)₂R³, C₀-C₆alkyl-N(R⁸)-C(O)R³, C₀-C₆alkyl-N(R⁸)-S(O)R³, C₀-C₆alkyl-N(R⁸)-C(S)R³, C₀-C₆alkyl-N(R⁸)-S(O)₂R³, C₀-C₆alkyl-O-C(O)R³, C₀-C₆alkyl-O-S(O)R³, C₀-C₆alkyl-O-C(S)R³, -N=S(O)(R³)₂, C₀-C₆alkylN₃, and C₀-C₆alkyl-O-S(O)₂R³, each of which is optionally substituted with 1, 2, 3, or 4 substituents. R⁶ and R⁷ are

independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroaryl alkyl, alkenyl, alkynyl, and, haloalkyl, heteroaryl, heterocycle, -alkyl-OR⁸, -alkyl-NR⁸R⁹, C(O)R³, S(O)R³, C(S)R³, and S(O)₂R³;

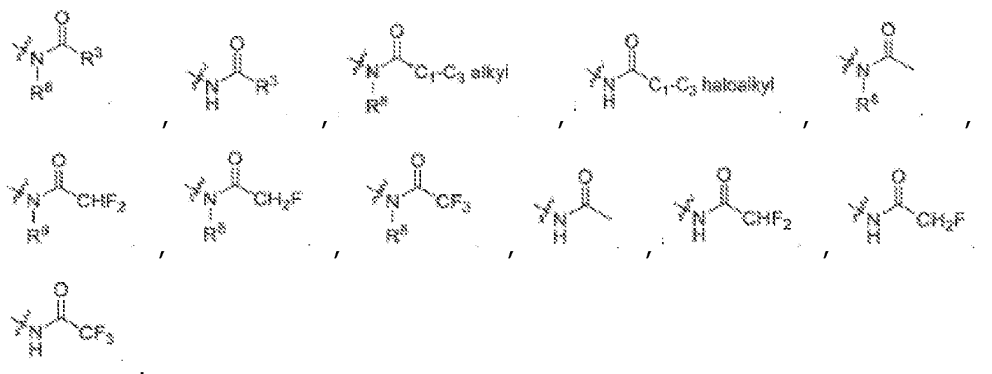
R⁶ and R⁷ are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroaryl alkyl, alkenyl, alkynyl, and, haloalkyl, heteroaryl, heterocycle, -alkyl-OR⁸, -alkyl-NR⁸R⁹, C(O)R³, S(O)R³, C(S)R³, and S(O)₂R³.

R⁸ and R⁹ are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle.

R¹⁰ is preferably selected from C⁵ or C⁶ heterocycles, bicyclic heterocycles, spirocyclic heterocycle, -NR⁶-heterocycle and more preferably from C⁵ or C⁶ heterocycles comprising 1 to 3 heteroatoms selected from N, O and S as ring atoms.

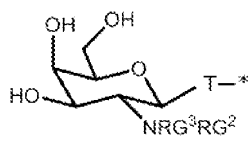
R²¹ is independently at each occurrence selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, F, Cl, Br, I, hydroxyl, alkoxy, azide, amino, cyano, -NR⁶R⁷, -NR⁸SO₂R³, -NR⁸S(O)R³, haloalkyl, heteroalkyl, and, heteroaryl, and heterocycle;

R²⁰⁰ is selected from



25. The compound of claim 21, wherein AG is a monosaccharide, disaccharide, or oligosaccharide, wherein one or more of the hydroxy (OH) groups in the particular sugar is be replaced with a -NRG²RG³ group, wherein RG² and RG³ are each independently selected from the group consisting of hydrogen and -C(=O)R and an optionally substituted C5 or C6 aromatic heterocycle, wherein R is C₁₋₁₀ alkyl, which is optionally substituted by 1-5 groups selected from the group consisting of halogen, C₁₋₁₀ alkoxy, C₁₋₁₀ aminoalkyl, and combinations thereof, or RG² and RG³ taken together with the nitrogen atom to which they are attached, form a C5 heterocycle that is optionally substituted by 1-5 substituents selected from the group consisting of optionally substituted C₁₋₁₀ alkyl, optionally substituted C₁₋₁₀ alkoxy, optionally substituted C₁₋₁₀ aminoalkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₅₋₁₀ heteroaryl, halogen, and combinations thereof.

26. The compound of any of the preceding claims, wherein AG has the structure

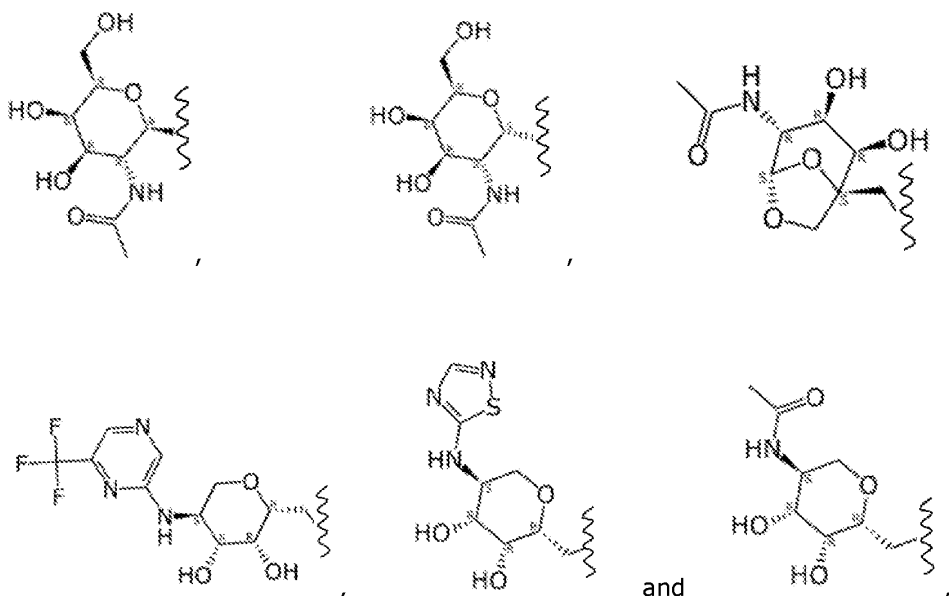


wherein T is selected from the group consisting of a direct bond and O and wherein * marks the bond that bonds AG to the remainder of the compounds, with the proviso that no oxygen-oxygen bond is formed between AG and the remainder of the compounds of the present invention.

27. The compound of any of claims 25 and 26, wherein RG^2 is hydrogen and RG^3 is -C(=O)CH₃.

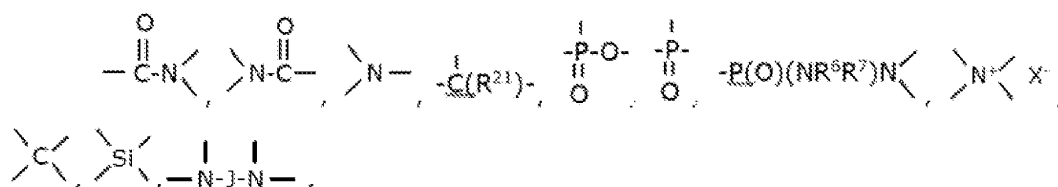
28. The compound of any of claims 25 or 26, wherein RG^2 is hydrogen and RG^3 is an aromatic heterocycle selected from the group consisting of 1H-pyrrole, pyrazole, imidazole, furan, thiophene, oxazole, isoxazole, isothiazole, thiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine.

29. The compound of any of claims 1 to 20, wherein AG is selected from the group consisting of



wherein the wavy lines mark the bond that bonds AG to the remainder of the compounds.

30. The compound of any of the preceding claims, wherein Con is selected from the group consisting of alkyl, heteroalkyl,



alkenyl, haloalkyl, aryl, heterocycle, and heteroaryl, each of which has three or four valences bonded to L¹, L², A and/or AG, respectively, and is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

wherein X⁻ is a pharmaceutically acceptable anionic group, for example Br⁻ or Cl⁻;

J is a direct bond or a hydrocarbon with 1 to 10 carbon atoms and

R₆, R₇ and R₂₁ are as defined as in Claim 24.

31. The compound of any of the preceding claims, wherein Con is a hydrocarbon with 1 to 10 carbon atoms or a heterocycle with 5 to 8 ring members, wherein the hydrocarbon may be saturated or unsaturated and in which the heterocycle may be saturated or unsaturated, aromatic or aliphatic and comprise up to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and wherein in the hydrocarbon or the heterocycle one hydrogen atom is substituted by linker L¹ and n hydrogen atoms are substituted by linker L².

32. The compound of any of the preceding claims, wherein Con is selected from the group consisting of -CH_(3-n)(CH₂-)_n, wherein n is 2 or 3 and diazacycloheptane, wherein one hydrogen atom is substituted by linker L¹ and n hydrogen atoms are substituted by linker L².

33. The compound of Formula (II) of any of the preceding claims, wherein Con is



34. The compound of Formula (II) of any of the preceding claims, wherein one terminal end of L^1 is a $-NH-$ residue, by which L^1 is bonded to Con and one terminal end of each of the n L^2 linkers are $-O-$ residues, by which the linker L^2 are bonded to Con.
35. The compound of claims 1, 10, 19, 20 and 29 of Formula (I).
36. The compound of claims 1, 10, 19, 20, 29 and 31 of Formula (II).
37. A method of preventing, treating, and/or ameliorating heart failure in a subject, the method comprising administering to the subject a composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of any of claims 1-31.
38. The method of claim 32, wherein the heart failure is dilated cardiomyopathy.
39. The method of any of claims 37 or 38, wherein the composition is administered by a route selected from the group consisting of oral, transdermal, transmucosal, (intra)nasal, (trans)rectal, intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical.
40. The method of any of claims 37 to 39, wherein the composition is administered intravenously.
41. The method of any of claims 37 to 40, wherein the composition is administered in a dose of 0.01 mg/kg to 20 mg/kg.
42. The method of any of claims 37 to 41, wherein the subject is a mammal.
43. The method of any of claims 37 to 42, wherein the subject is human.