

TITLE

Bifunctional Small Molecules to Target the Selective Degradation
of Circulating Proteins

5 CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Application No. 17/695,645, filed
March 15, 2022, which application is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

10 This invention was made with government support under GM067543 awarded by
National Institutes of Health and under W81XWH-13-1-0062 awarded by the United States
Army Medical Research and Material Command. The government has certain rights in the
invention.

SEQUENCE LISTING

15 The instant application contains a Sequence Listing which has been submitted in
ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said
ASCII copy, created on March 14, 2023, is named
"047162-7239WO2_sequence_listing.xml" and is 156.6 kilobytes in size.

20 BACKGROUND

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

Current strategies to target circulating proteins include the use of inhibiting
antibodies, which possess excellent specificity and affinity for target proteins. Despite these
advantages, antibody-based therapies have several drawbacks that relate primarily to their

high molecular weights and/or peptidic structures the likelihood of invoking immunogenicity, their high cost, short shelf life and low oral bioavailability. The small molecule based strategy pursuant to the present disclosure has the potential to combine the beneficial attributes of antibody-based therapies while overcoming their most significant disadvantages.

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

BRIEF SUMMARY

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

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

The approach pursuant to the present disclosure is inherently advantageous compared

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

Furthermore, the present disclosure is expected to have a more lasting effect compared to the conventional inhibitory approach because the disease relevant proteins are eliminated by degradation inside hepatocytes rather than simply inhibited by reversibly blocking the protein-receptor interaction. The bifunctional molecule construct pursuant to the present disclosure is also versatile in the sense that different disease related proteins can be targeted by simply switching the protein targeting motif in the construct. Thus, previously discovered non-inhibitory protein binders can be potentially therapeutically useful in these small molecules.

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



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

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

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

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

k' is an integer from 1 to 15;

j' is an integer from 1 to 15;

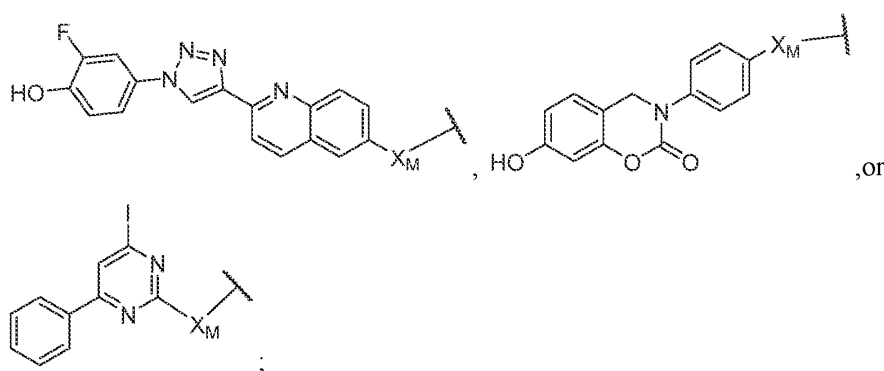
h and h' are each independently an integer from 0 to 15;

i_L is an integer from 0 to 15;

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

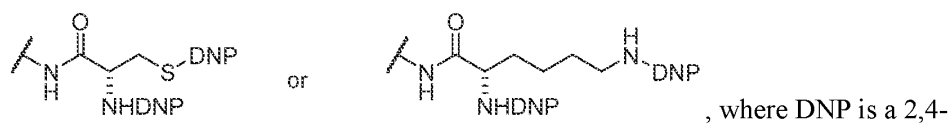
- 5 In various embodiments, [LINKER] has a valency of 1 to 10. In various embodiments, [LINKER] has a valency of 1 to 5. In various embodiments, [LINKER] has a valency of 1, 2 or 3. A [MULTICON] group can connect one or more of a [CRBM] or [CPBM] to one or more of a [LINKER].

- 10 In an embodiment, [CPBM] is a [MIFBM] moiety according to the chemical structure:

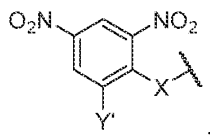


- wherein X_M is -(CH₂)_{IM}, -O-(CH₂)_{IM}, S-(CH₂)_{IM}, NR_M-(CH₂)_{IM}, C(O)-(CH₂)_{IM}-, a PEG (polyethylene glycol) group containing from 1 to 8 ethylene glycol residues or a -C(O)(CH₂)_{IM}NR_M group; R_M is H or a C₁-C₃ alkyl group which is optionally substituted with one or two hydroxyl groups; IM is an integer ranging from 0-6.

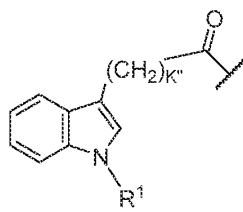
- 15 In various embodiments, [CPBM] is a [IgGMB] group according to the chemical structure:



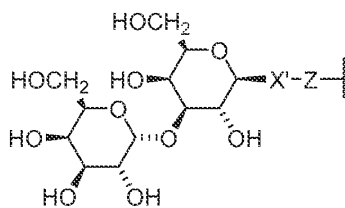
- 20 dinitrophenyl group; or a group according to the chemical structure:



where Y' is H or NO₂; X is O, CH₂, NR¹, S(O), S(O)₂, -S(O)₂O, -OS(O)₂, or OS(O)₂O; and R¹ is H, a C₁-C₃ alkyl group, or a -C(O)(C₁-C₃) group; or a group according to the chemical structure:



where R¹ is the same as above; and K'' is 1-5, or a group represented by the chemical formula:



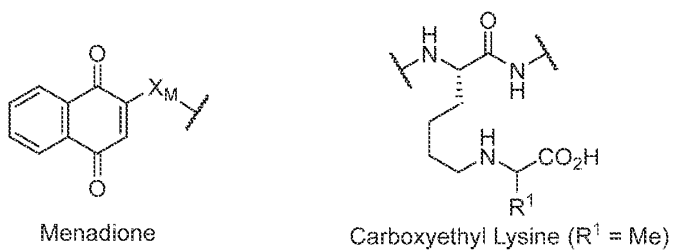
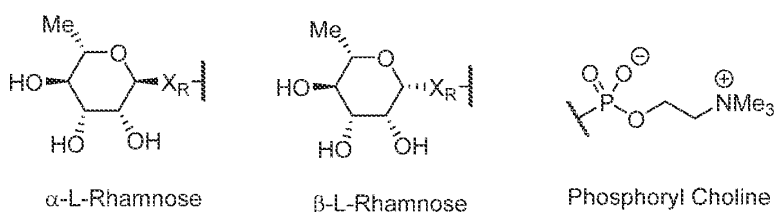
- 5 where X' is CH₂, O, N-R^{1'}, or S; R^{1'} is H or C₁-C₃ alkyl; and Z is a bond, a monosaccharide, disaccharide, oligosaccharide, more preferably a sugar group selected from the monosaccharides, including aldoses and ketoses, and disaccharides, including those disaccharides described herein.

- Monosaccharide aldoses include monosaccharides such as aldotriose (D-
 10 glyceraldehyde, among others), aldotetroses (D-erythrose and D-Threose, among others), aldopentoses, (D-ribose, D-arabinose, D-xylose, D-lyxose, among others), aldohexoses (D-allose, D-altrose, D-Glucose, D-Mannose, D-gulose, D-idose, D-galactose and D-Talose, among others), and the monosaccharide ketoses include monosaccharides such as ketotriose (dihydroxyacetone, among others), ketotetrose (D-erythrulose, among others), ketopentose
 15 (D-ribulose and D-xylulose, among others), ketohexoses (D-Psicone, D-Fructose, D-Sorbose, D-Tagatose, among others), aminosugars, including galactoseamine, sialic acid, N-acetylglucosamine, among others and sulfosugars, including sulfoquinovose, among others.

- Exemplary disaccharides which find use in the present disclosure include sucrose (which may have the glucose optionally N-acetylated), lactose (which may have the galactose
 20 and/or the glucose optionally N-acetylated), maltose (which may have one or both of the glucose residues optionally N-acetylated), trehalose (which may have one or both of the glucose residues optionally N-acetylated), cellobiose (which may have one or both of the glucose residues optionally N-acetylated), kojibiose (which may have one or both of the glucose residues optionally N-acetylated), nigerose (which may have one or both of the
 25 glucose residues optionally N-acetylated), isomaltose (which may have one or both of the glucose residues optionally N-acetylated), β,β-trehalose (which may have one or both of the

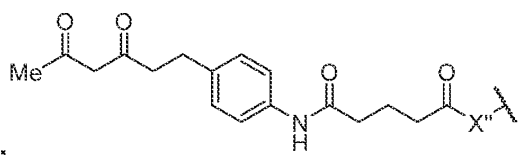
glucose residues optionally N-acetylated), sophorose (which may have one or both of the glucose residues optionally N-acetylated), laminaribiose (which may have one or both of the glucose residues optionally N-acetylated), gentiobiose (which may have one or both of the glucose residues optionally N-acetylated), turanose (which may have the glucose residue optionally N-acetylated), maltulose (which may have the glucose residue optionally N-acetylated), palatinose (which may have the glucose residue optionally N-acetylated), gentiobulose (which may have the glucose residue optionally N-acetylated), mannobiose, melibiose (which may have the glucose residue and/or the galactose residue optionally N-acetylated), melibiulose (which may have the galactose residue optionally N-acetylated), rutinose, (which may have the glucose residue optionally N-acetylated), rutinulose and xylobiose, among others; or

[CPBM] is a [IgGBM] group according to the chemical structure:

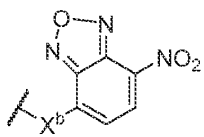


where X_R is O, S or NR¹; and X_M is O, NR¹ or S, and R¹ is H or a C₁-C₃ alkyl group; or

[CPBM] is a [IgGBM] group according to the chemical structure:

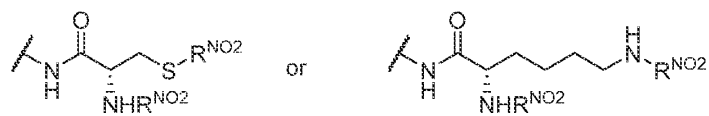


where X'' is O, CH₂, NR¹, S; and R¹ is H, a C₁-C₃ alkyl group or a -C(O)(C₁-C₃) group; or

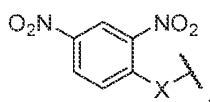


where X^b is a bond, O, CH₂ or NR¹ or S; and R¹ is H, C₁-C₃ alkyl, or a -C(O)(C₁-C₃) group;

or a group according to the chemical structure:

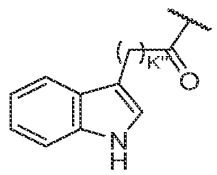


where R^{NO2} is a dinitrophenyl group optionally linked through CH_2 , $S(O)$, $S(O)_2$, $-S(O)_2O$, $-OS(O)_2$, or $OS(O)_2O$; or a dinitrophenyl group according to the chemical structure:

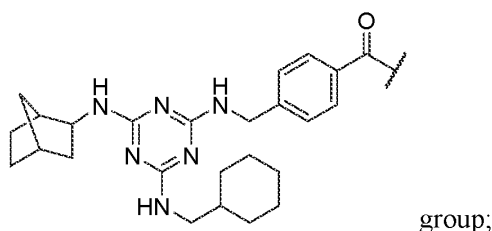


where X is O, CH_2 , NR^1 , $S(O)$, $S(O)_2$, $-S(O)_2O$, $-OS(O)_2$, or $OS(O)_2O$; and R^1 is H, a C_1 - C_3 alkyl group, or a $-C(O)(C_1-C_3)$ group, or

[CPBM] is a [IgGBM] group which is a 3-indoleacetic acid group according to the chemical structure:



where K''' is 1-4; or a



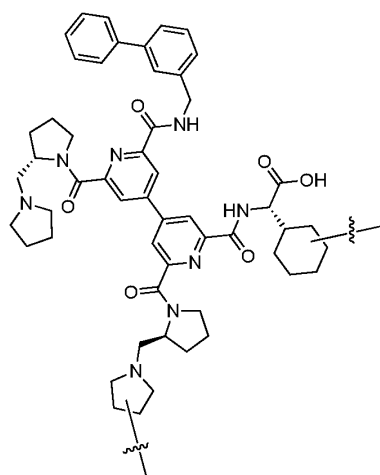
or a group according to a chemical structure which is set forth in FIGURE 67 hereof which is covalently attached to a [CON] group, a [LINKER] group or a [CRBM] group which includes an [ASGPRBM] group through an amine group, preferably a primary or secondary alkyl amine group which is optionally substituted on the amine group with a C_1 - C_3 alkyl group.

In various embodiments, [CPBM] is a [IgGBM] group which is a peptide according to the sequence (all references cited are incorporated by reference herein):

- 20 PAM (Fassina, et al., *J. Mol. Recognit.* 1996, 9, 564–569);
 D-PAM (Verdoliva, et al., *J. Immunol. Methods*, 2002, 271, 77–88);
 D-PAM- Φ (Dinon, et al. *J. Mol. Recognit.* 2011, 24, 1087–1094);
 TWKTSRISIF (Krook, et al., *J. Immunol. Methods* 1998, 221, 151–157) SEQ ID NO:1;

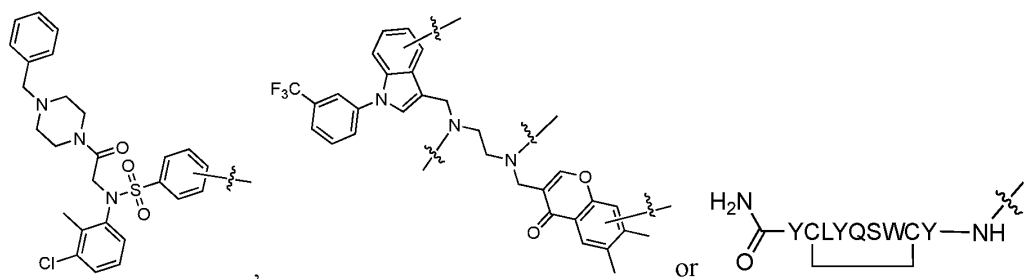
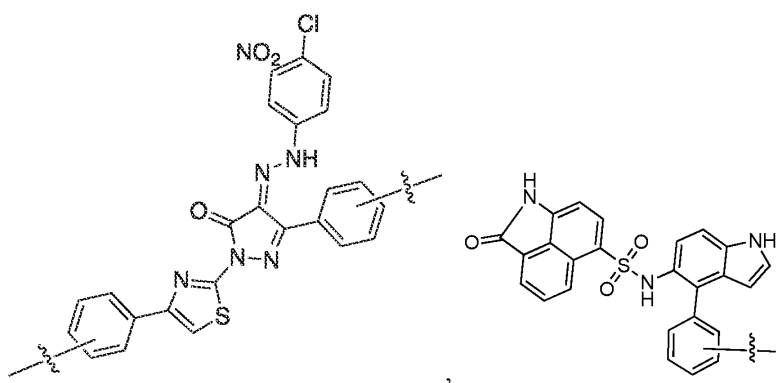
- FGRLVSSIRY (Krook, et al., *J. Immunol. Methods* 1998, 221, 151–157) SEQ ID NO:2;
Fc-III (DeLano, et al., *Science* 2000, 287, 1279–1283);
FcBP-1 (Kang, et al., *J. Chromatogr. A* 2016, 1466, 105–112);
FcBP-2 (Dias, et al., *J. Am. Chem. Soc.* 2006, 128, 2726–2732);
5 Fc-III-4c (Gong, et al., *Bioconjug. Chem.* 2016, 27, 1569–1573);
EPIHRSTLTALL (Ehrlich, et al., *J. Biochem. Biophys. Method* 2001, 49, 443–454)
SEQ ID NO:3;
APAR (Camperi, et al., *Biotechnol. Lett.* 2003, 25, 1545–1548) SEQ ID NO:4;
FcRM (Fc Receptor Mimetic, Verdoliva, et al., *ChemBioChem* 2005, 6, 1242–1253);
10 HWRGWV (Yang, et al., *J. Peptide Res.* 2006, 66, 110–137) SEQ ID NO:5;
HYFKFD (Yang, et al., *J. Chromatogr. A* 2009, 1216, 910–918) SEQ ID NO:6;
HFRRL (Menegatti, et al., *J. Chromatogr. A* 2016, 1445, 93–104) SEQ ID NO:7;
HWCitGWV (Menegatti, et al., *J. Chromatogr. A* 2016, 1445, 93–104) SEQ ID NO:8;
D2AAG (Small Synthetic peptide ligand, Lund, et al., *J. Chromatogr. A* 2012, 1225, 158–
15 167);
DAAG (Small Synthetic peptide ligand, Lund, et al., *J. Chromatogr. A* 2012, 1225, 158–
167);
cyclo[(N-Ac)S(A)-RWHYFK-Lact-E] (Menegatti, et al., *Anal. Chem.* 2013, 85, 9229–9237)
(SEQ ID NO:9-Lact-E);
20 cyclo[(N-Ac)-Dap(A)-RWHYFK-Lact-E] (Menegatti, et al., *Anal. Chem.* 2013, 85, 9229–
9237) (SEQ ID NO:10-Lact-E);
cyclo[Link-M-WFRHYK] (Menegatti, et al., *Biotechnol. Bioeng.* 2013, 110, 857–870)
SEQ ID NO:11;
NKFRGKYK (Sugita, et al., *Biochem. Eng. J.* 2013, 79, 33–40) SEQ ID NO:12;
25 NARKFYKG (Sugita, et al., *Biochem. Eng. J.* 2013, 79, 33–40) SEQ ID NO:13;
FYWHCLDE (Zhao, et al., *Biochem. Eng. J.* 2014, 88, 1–11) SEQ ID NO:14;
FYCHWALE (Zhao, et al., *J. Chromatogr. A* 2014, 1355, 107–114) SEQ ID NO:15;
FYCHTIDE (Zhao, et al., *J. Chromatogr. A* 2014, 1359, 100–111) SEQ ID NO:16;
Dual 1/3 (Zhao, et al., *J. Chromatogr. A* 2014, 1369, 64–72);
30 RRGW (Tsai, et al., *Anal. Chem.* 2014, 86, 2931–2938) SEQ ID NO:17; or
KHRFNKD (Yoo and Choi, *BioChip J.* 2015, 10, 88–94) SEQ ID NO:18.

In some embodiments, [CPBM] is a CD40L-targeting motif according to the chemical structure:



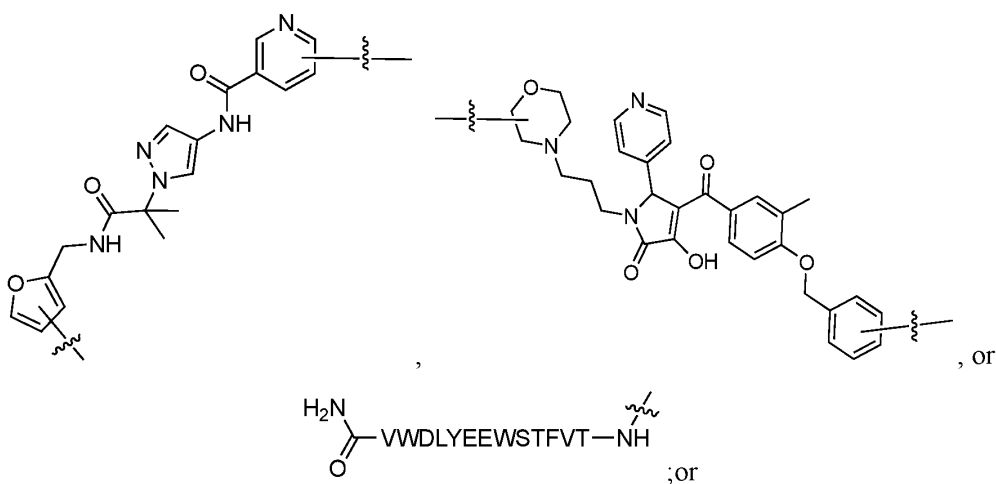
; or

[CPBM] is a TNF alpha-targeting motif according to chemical structure:

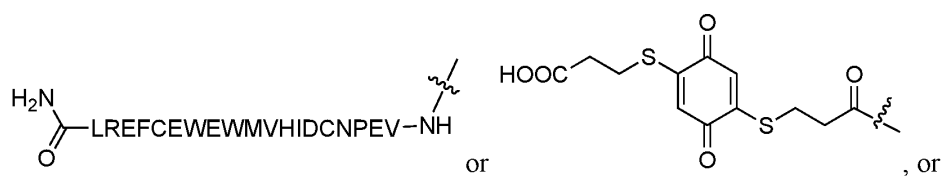


5 or

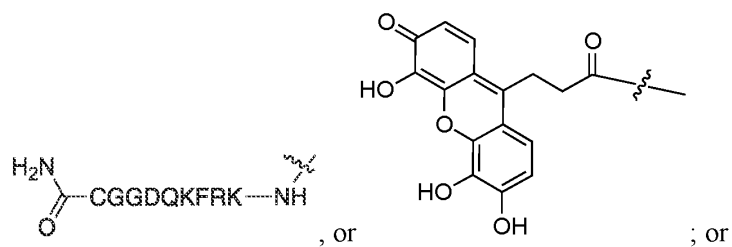
[CPBM] is a PCSK9-targeting motif according to the chemical structure:



[CPBM] is a VEGF-targeting motif according to the chemical structure:



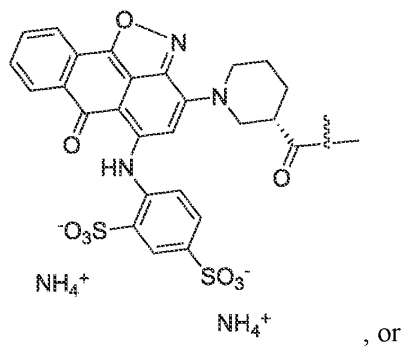
- 5 [CPBM] is a TGF beta-targeting motif according to the chemical structure:



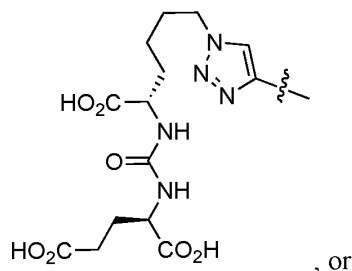
[CPBM] is a TSP-1 targeting motif according to the chemical structure:



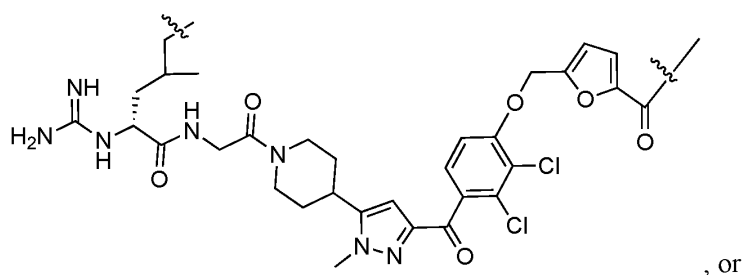
[CPBM] is a soluble uPAR targeting motif according to the chemical structure:



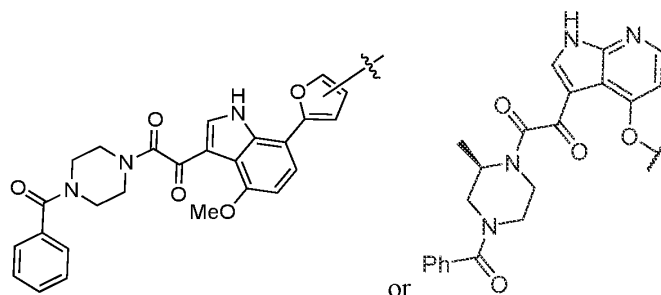
[CPBM] is a soluble PSMA targeting motif according to the chemical structure:



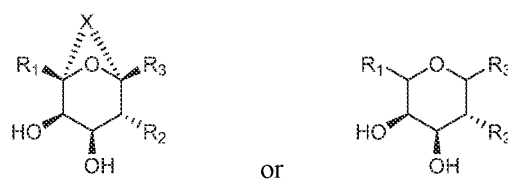
[CPBM] is a IL-2 targeting motif according to the chemical structure:



- 5 [CPBM] is a GP120-targeting motif according to the chemical structure:



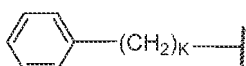
In certain embodiments, [CRBM] is an [ASGPRBM] is a group according to the chemical structure:



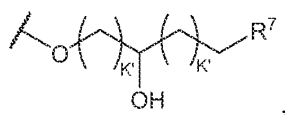
- 10 where X is 1-4 atoms in length and is at each occurrence independently selected from the group consisting of O, S, N(R^{N1}), and C(R^{N1})(R^{N1}) such that:
- if X is 1 atom in length, X is O, S, N(R^{N1}), or C(R^{N1})(R^{N1}),
- if X is 2 atoms in length, no more than 1 atom of X is O, S, or N(R^{N1}),
- if X is 3 or 4 atoms in length, no more than 2 atoms of X are O, S or N(R^{N1});
- 15 where R^{N1} is H or a C₁-C₃ alkyl group optionally substituted with from 1-3 halogen

groups;

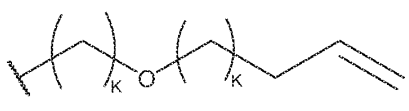
- 5 R₁ and R₃ are each independently H, -(CH₂)_KOH, -(CH₂)_KOC₁-C₄ alkyl, -C₁-C₄ alkyl, -(CH₂)_Kvinyl, -O-(CH₂)_Kvinyl, -(CH₂)_Kalkynyl, -(CH₂)_KCOOH, -(CH₂)_KC(O)O-C₁-C₄ alkyl, -O-C(O)-C₁-C₄ alkyl, -C(O)-C₁-C₄ alkyl, in which each alkyl, vinyl, or alkynyl is optionally substituted with from 1-3 halogen groups. In various embodiments, each alkyl, vinyl, or alkynyl in R₁ and R₃ is optionally substituted with from 1-3 fluorines (F). K is independently at each occurrence an integer from 0-4.

- 10 In certain embodiments, R₁ and R₃ are each independently a  group, which is optionally substituted with 1-3 halogen groups, 1 to 3 C₁-C₄ alkyl groups, or O-C₁-C₄ alkyl groups, in which each of the alkyl groups is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, and K is independently at each occurrence an integer from 0-4; or

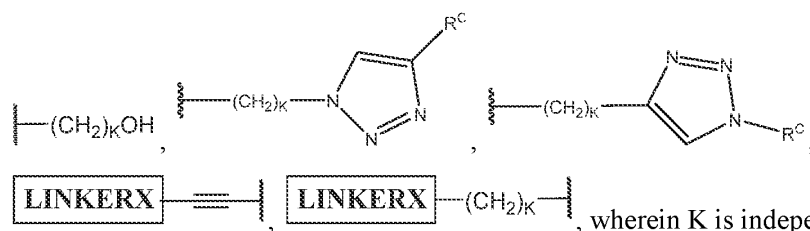
R₁ and R₃ are each independently a group according to the chemical structure:



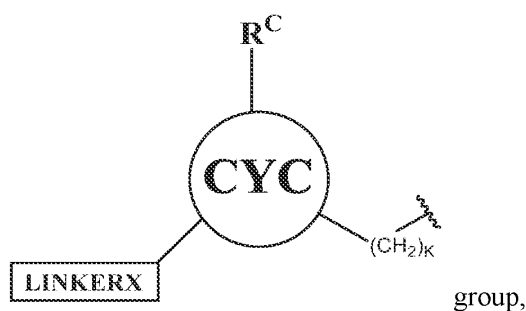
- 15 where R⁷ is O-C₁-C₄ alkyl, which is optionally substituted with from 1 to 3 halo groups or 1 to 2 hydroxy groups, and K' is independently at each occurrence an integer from 0-4; or

R⁷ is a -NR^{N3}R^{N4} group or , and K is independently at each occurrence an integer from 0-4; or

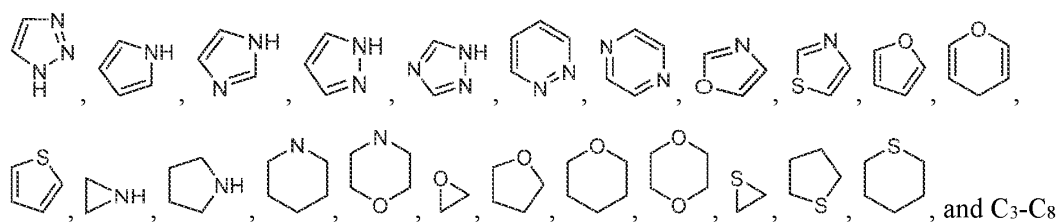
- 20 R₁ and R₃ are each independently a group according to the structure:



occurrence 0-4; or a

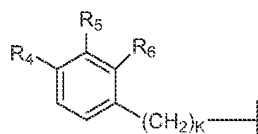


wherein CYC is a ring selected from the group consisting of:

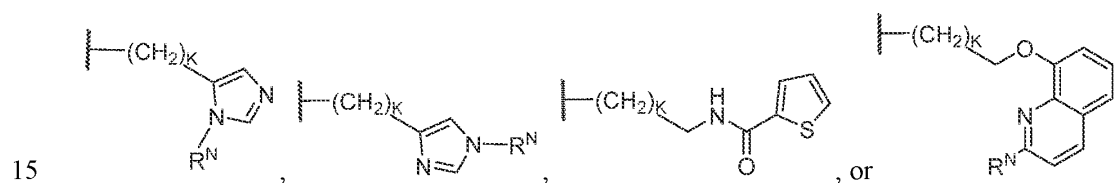


5 saturated carbocyclic, wherein each of LINKERX, R^C, and -(CH₂)_K- are attached to an open valence in CYC, including N-H;

R^C is absent, H, C₁-C₄ alkyl optionally substituted with from 1-3 halogen groups or 1-2 hydroxyl groups; or a group according to the structure:



10 where R₄, R₅ and R₆ are each independently, H, halogen, CN, NR^{N1}R^{N2},
-(CH₂)_KOH, -(CH₂)_KOC₁₋₄ alkyl, C₁₋₃ alkyl, -O-C₁₋₃-alkyl, -(CH₂)_KCOOH, -
(CH₂)_KC(O)O-C₁₋₄ alkyl, O-C(O)-C₁₋₄ alkyl, -C(O)-C₁₋₄ alkyl, in any of which the alkyl
group is optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups; or

 R^C is

where R^N, R^{N1}, and R^{N2} are each independently H or a C₁-C₃ alkyl group optionally substituted with 1-3 halogen groups, or 1-2 hydroxyl groups;

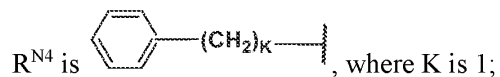
K is independently at each occurrence an integer from 0-4;

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

20 R^{N3} is H or C₁-C₃ alkyl optionally substituted with 1-3 halogen groups or 1-2

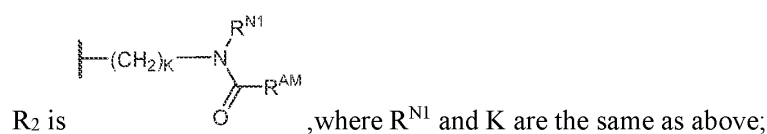
hydroxyl groups; and

R^{N4} is H or C₁-C₃ alkyl optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, or



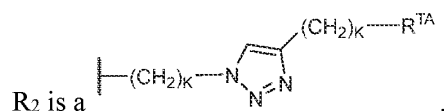
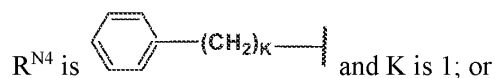
5 **LINKERX** is a linker group which includes at least one [CPBM] group and connects the [CPBM] group to the [CRBM] through one or more optional [CON] groups, or

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



10 R^{AM} is H, C₁-C₄ alkyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-C_1-C_4$ alkyl, $-O-C(O)-C_1-C_4$ alkyl, $-C(O)-C_1-C_4$ alkyl, $-(CH_2)_K-NR^{N3}R^{N4}$ where R^{N3} is H or C₁-C₃ alkyl, in which any of the alkyl groups are optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups; and

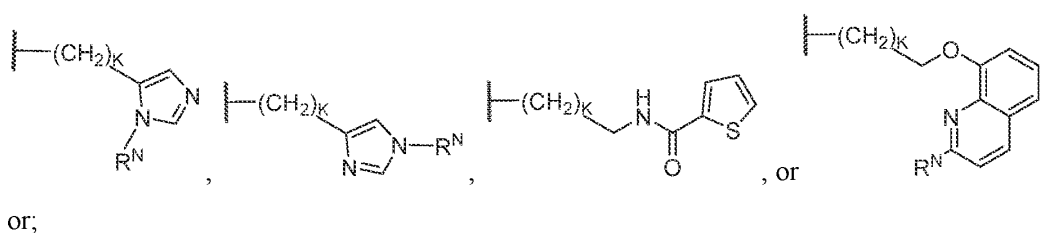
15 R^{N4} is H, C₁-C₃ alkyl optionally substituted with 1-3 halo groups or 1 or 2 hydroxy groups, or

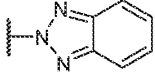


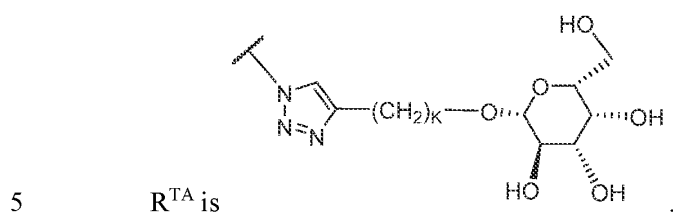
20 where R^{TA} is H, CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KOC_1-C_4$ alkyl, C₁-C₄ alkyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-C_1-C_4$ alkyl, $O-C(O)-C_1-C_4$ alkyl, $-C(O)-C_1-C_4$ alkyl, in which each alkyl is optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups, or

R^{TA} is a C₃-C₁₀ aryl or a 3- to 10-membered heteroaryl group containing up to 5 hetero atoms, each of said aryl or heteroaryl groups being optionally substituted with 1-3 substituents selected from the group consisting of CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KOC_1-C_4$ alkyl, C₁-C₃ alkyl, $-O-C_1-C_3$ -alkyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-C_1-C_4$ alkyl, $O-C(O)-C_1-$
25 C₄ alkyl, and $-(CH_2)_KC(O)-C_1-C_4$ alkyl, in which each alkyl is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, or

R^{TA} is



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



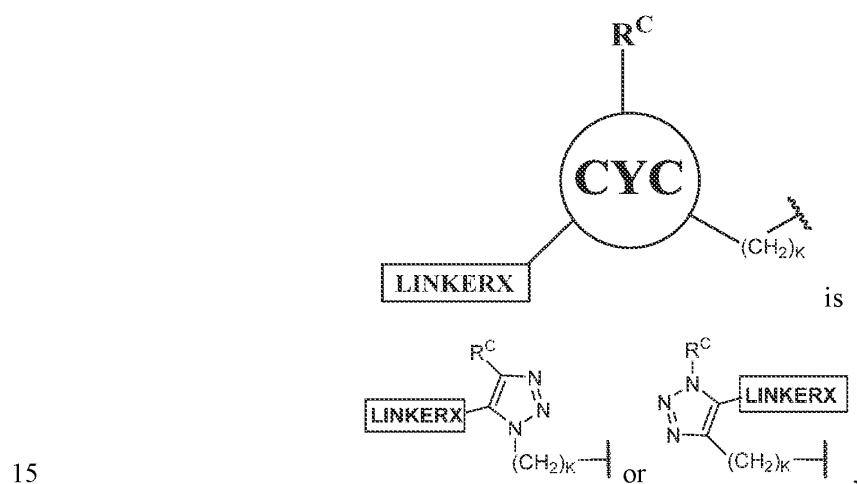
wherein R^N , R^{N1} , and R^{N2} are each independently H or a C_1 - C_3 alkyl group which is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups and

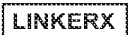
wherein each $-(CH_2)_K$ group is optionally substituted with 1-4 C_1 - C_3 alkyl groups which are each optionally substituted with from 1-3 fluorines or 1-2 hydroxyl groups;

10 and K is independently at each occurrence 0-4.

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

In various embodiments,



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

In certain embodiments, [CRBM] is a LRP1 (Low density lipoprotein receptor-related

protein 1 or alpha-2-macroglobulin receptor) peptide binding group according to the peptide sequence (it is noted that in each case where a peptide is used, the amino end or the carboxylic acid end of the peptide is preferably linked, and more preferably the carboxylic acid terminus of the peptide is a non-reactive carboxamide group and the amine terminus is covalently linked to a CON, LINKER or CPBM group):

Ac-VKFNKPFVFLNleIEQNTK-NH₂ SEQ ID NO: 19 (See, Toldo, Stefano, et al. *JACC: Basic to Translational Science* 2.5 (2017): 561-574) where Nle is neorleucine,

VKFNKPFVFLMIEQNTK SEQ ID NO:20 (See, Toldo, Stefano, et al. *JACC: Basic to Translational Science* 2.5 (2017): 561-574.),

TWPKHFDKHTFYSLKLGKH-OH SEQ ID NO: 21 (See, Sakamoto, Kotaro, et al. *Biochemistry and biophysics reports* 12 (2017): 135-139.),

Angiopep-2: TFFYGGSRGKRNNFKTEEY-OH SEQ ID NO:22 (See, Sakamoto, Kotaro, et al. *Biochemistry and biophysics reports* 12 (2017): 135-139.),

LRKLRKRLLRDADDLLRKLRKRLLRDADDL SEQ ID NO:23 (See, Croy, Johnny E., Theodore Brandon, and Elizabeth A. Komives. *Biochemistry* 43.23 (2004): 7328-7335.)

TEELRVLASHLRKLRKRL SEQ ID NO:24 (Croy, Johnny E., Theodore Brandon, and Elizabeth A. Komives. *Biochemistry* 43.23 (2004): 7328-7335.)

Rap12: EAKIEKHNYQK (Ruan, Huitong, et al. "A novel peptide ligand RAP12 of LRP1 for glioma targeted drug delivery." *Journal of Controlled Release* 279 (2018): 306-315.)

Rap22: EAKIEKHNYQKQLEIAHEKLR SEQ ID NO: 25 (Ruan, Huitong, et al. "A novel peptide ligand RAP12 of LRP1 for glioma targeted drug delivery." *Journal of Controlled Release* 279 (2018): 306-315.)

ANG: TFFYGGSRGKRNNFKTEEY SEQ ID NO:26 (Kim, Jong Ah, et al. *Scientific reports* 6 (2016): 34297), or

[CRBM] is a LDLR (low density lipoprotein receptor) binding group according to the peptide sequence:

VH4127: cM"Thz"RLRG"Pen" (cyclized c-Pen) SEQ ID NO:27 (See, Molino, Yves, et al. *The FASEB Journal* 31.5 (2017): 1807-1827) where Pen is Penicillamine and Thz is thiazolidine-4-carboxylic acid,

VH434: CMPRLRGC (cyclized C-C) SEQ ID NO:28 (Molino, Yves, et al. *The FASEB Journal* 31.5 (2017): 1807-1827),

- VH101: HLDCMPRGCFRN (cyclized C-C) SEQ ID NO:29 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- VH202: CQVKSMPPRC (cyclized C-C) SEQ ID NO:30 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- 5 VH203: CTPMPRLC (cyclized C-C) SEQ ID NO:31 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- VH204: CKAPQMPPRC (cyclized C-C) SEQ ID NO:32 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- VH205: CLNPSMPPRC (cyclized C-C) SEQ ID NO:33 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- 10 VH306: CLVSSMPPRC (cyclized C-C) SEQ ID NO:34 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- VH307: CLQPMRLC (cyclized C-C) SEQ ID NO:35 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- 15 VH308: CPVSSMPPRC (cyclized C-C) SEQ ID NO:36 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- VH309: CQSPMRLC (cyclized C-C) SEQ ID NO:37 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- VH310: CLTPMRLC (cyclized C-C) SEQ ID NO:38 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- 20 VH411: DSGLCMPRLRGCDPR (cyclized C-C) SEQ ID NO:39 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- VH549: TPSAHAMALQSLSVG SEQ ID NO:40 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- 25 AcVH411: Ac-DSGLCMPRLRGCDPR-NH₂ (cyclized C-C) SEQ ID NO:41 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- Pr VH434: Pr-CMPRLRGC-NH₂ (cyclized C-C) SEQ ID NO:42 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- VH445: Pr-cMPRLRGC-NH₂ (cyclized C-C) SEQ ID NO:43 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052),
- 30 VH4127: Pr-cMThzRLRG"Pen"-NH₂ (cyclized C-Pen) SEQ ID NO:44 (David, Marion, et al. *PloS one* 13.2 (2018): e0191052), where Pen is penacillamine,
- Ac VH434: Ac-CMPRLRGC-NH₂ (cyclized C-C) SEQ ID NO:45 (Jacquot, Guillaume, et al. *Molecular pharmaceuticals* 13.12 (2016): 4094-4105),

- Ac VH445: Ac-cMPRLRGC-NH₂ (cyclized C-C) SEQ ID NO:46 (Jacquot, Guillaume, et al. *Molecular pharmaceuticals* 13.12 (2016): 4094-4105),
- VH4106: Ac-D-“Pen”M”Thz”RLRGC-NH₂ (cyclized Pen-C) SEQ ID NO:47 (Jacquot, Guillaume, et al. *Molecular pharmaceuticals* 13.12 (2016): 4094-4105),
- 5 where Pen is penacillamine and Thz is thiazolidine-4-carboxylic acid,
- VH4127: Pr-cM”Thz”RLRG”Pen-NH₂ (cyclized c-Pen) SEQ ID NO:48 (Jacquot, Guillaume, et al. *Molecular pharmaceuticals* 13.12 (2016): 4094-4105) where Pen is penacillamine and Thz is thiazolidine-4-carboxylic acid,
- VH4128: Pr-cM”Thz”RLR”Sar””Pen”-NH₂ (cyclized C-Pen) SEQ ID NO:49 (Jacquot, Guillaume, et al. *Molecular pharmaceuticals* 13.12 (2016): 4094-4105),
- 10 where Pen is Penicillamine, Thz is thiazolidine-4-carboxylic acid, and Sar is Sarcosine,
- VH4129: Pr-cM”Pip”RLR”Sar”C-NH₂ (cyclized C-C) SEQ ID NO:50 (Jacquot, Guillaume, et al. *Molecular pharmaceuticals* 13.12 (2016): 4094-4105), where Pip
- 15 is a Pipecolic group and Sar is a sarcosine group,
- VH4130: Pr-cM”Pip”RLRG”Pen”-NH₂ (cyclized c-Pen) SEQ ID NO:51 (Jacquot, Guillaume, et al. *Molecular pharmaceuticals* 13.12 (2016): 4094-4105), or
- VH4131: Pr-[cM”Pip”RLR”Sar””Pen”-NH₂ (cyclized c-Pen) SEQ ID NO:52 (Jacquot, Guillaume, et al. *Molecular pharmaceuticals* 13.12 (2016): 4094-4105),
- 20 where Pen is Penicillamine, Thz is thiazolidine-4-carboxylic acid, Pip is pipecolic acid and Sar is sarcosine, or
- [CRBM] is a FcγRI binding group according to the peptide sequence:
- Cp22: TDT C LMLPLLLG C DEE (cyclized C-C) SEQ ID NO:53, Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- 25 Cp21: DPI C WYFPRLLG C TTL (cyclized C-C) SEQ ID NO:54, Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- Cp23: WYP C YIYPRLLG C DGD (cyclized C-C) SEQ ID NO:55, Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- Cp24: GNI C MLIPGLLG C SYE (cyclized C-C) SEQ ID NO:56 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- 30 Cp33: VNS C LLLPNLLG C GDD (cyclized C-C) SEQ ID NO:57 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- Cp25: TPV C ILLPSLLG C DTQ (cyclized C-C) SEQ ID NO:58 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,

- Cp26: TVL C SLWPELLG C PPE (cyclized C-C) SEQ ID NO:59 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- Cp27: TFS C LMWPWLLG C ESL (cyclized C-C) SEQ ID NO:60 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- 5 Cp32: FGT C YTWPWLLG C EGF (cyclized C-C) SEQ ID NO:61 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- Cp34: SLF C RLLLTTPVG C VSQ (cyclized C-C) SEQ ID NO:62 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- 10 P35: HLL V LPRGLLG C TTLA (cyclized C-C) SEQ ID NO:63 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- Cp28: TSL C SMFPDLLG C FNL (cyclized C-C) SEQ ID NO:64 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- Cp29: SHP C GRPLMLLG C AES (cyclized C-C) SEQ ID NO:65 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- 15 P37: TST C SMVPGPLGAV STW (cyclized C-C) SEQ ID NO:66 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- Cp30: KDP C TRWAMLLG C DGE (cyclized C-C) SEQ ID NO:67 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585,
- Cp31: IMT C SVYPFLLG C VDK (cyclized C-C) SEQ ID NO:68 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585, or
- 20 Cp36: IHS C AHVMRLLG C WSR (cyclized C-C) SEQ ID NO:69 Bonetto, Stephane, et al. *The FASEB Journal*23.2 (2009): 575-585, or
- [CRBM] is a FcRN binding moiety according to the peptide sequence:
- SYN746: Ac-NH-QRFCTGHFGGLYPCNGP-CONH₂ (cyclized C-C) SEQ ID NO:70 (Mezo, Adam R., et al. *Proceedings of the National Academy of Sciences* 105.7 (2008): 2337-2342.),
- 25 SYN1327: Ac-NH-RF-Pen-TGHFG-Sar-NMeLeu-YPC-CONH₂ (cyclized C-C) SEQ ID NO:71 (Mezo, Adam R., et al. *Proceedings of the National Academy of Sciences* 105.7 (2008): 2337-2342), where Pen is Penicillamine, Sar is a sarcosine and NMeLeu is N-methyleucine, or
- 30 SYN1436: succinic anhydride N-N dimerized SYN1327 (each cyclized C-C) (Mezo, Adam R., et al. *Proceedings of the National Academy of Sciences* 105.7 (2008): 2337-2342.), or

[CRBM] is a Transferrin Receptor binding group according to the peptide sequence:

- Tf1: CGGGPFWWWP SEQ ID NO:72 (Santi, Melissa, et al. "Rational design of a transferrin-binding peptide sequence tailored to targeted nanoparticle internalization." *Bioconjugate chemistry* 28.2 (2016): 471-480),
- 5 Tf2: CGGGHKYLRW SEQ ID NO:73 (Santi, Melissa, et al. "Rational design of a transferrin-binding peptide sequence tailored to targeted nanoparticle internalization." *Bioconjugate chemistry* 28.2 (2016): 471-480),
- Tf3: CGGGKRIFMV SEQ ID NO:74 (Santi, Melissa, et al. "Rational design of a transferrin-binding peptide sequence tailored to targeted nanoparticle internalization." *Bioconjugate chemistry* 28.2 (2016): 471-480),
- 10 Tf2-scr: CGGGKWHYLR SEQ ID NO:75 (Santi, Melissa, et al. "Rational design of a transferrin-binding peptide sequence tailored to targeted nanoparticle internalization." *Bioconjugate chemistry* 28.2 (2016): 471-480),
- TfR-T12: THRPPMWSPVWP SEQ ID NO:76 (Mu, Li-Min, et al. *Scientific reports* 7.1 (2017): 3487),
- 15 HAIYPRH SEQ ID NO:77 (Lee, Jae H., et al. *European journal of biochemistry* 268.7 (2001): 2004-2012),
- THRPPMWSPVWP SEQ ID NO:78 (Lee, Jae H., et al. *European journal of biochemistry* 268.7 (2001): 2004-2012),
- THRPPMWSPVWP SEQ ID NO:79 (Wängler, Carmen, et al. *Molecular Imaging and Biology* 13.2 (2011): 332-341), or
- 20 [CRBM] is a Macrophage Scavenger Receptor Binding Moiety according to the peptide sequence:
- PP1: LSLERFLRCWSDAPA SEQ ID NO:80 (Segers, Filip ME, et al. *Arteriosclerosis, thrombosis, and vascular biology* 32.4 (2012): 971-978),
- 25 PP1-13: LERFLRCWSDAPA SEQ ID NO:81 (Segers, Filip ME, et al. *Arteriosclerosis, thrombosis, and vascular biology* 32.4 (2012): 971-978),
- PP1-11: RFLRCWSDAPA SEQ ID NO:82 (Segers, Filip ME, et al. *Arteriosclerosis, thrombosis, and vascular biology* 32.4 (2012): 971-978),
- PP1-9: LRCWSDAPA SEQ ID NO:83 (Segers, Filip ME, et al. *Arteriosclerosis, thrombosis, and vascular biology* 32.4 (2012): 971-978.)
- 30 PP1-7: CWSAPA SEQ ID NO:84 (Segers, Filip ME, et al. *Arteriosclerosis, thrombosis, and vascular biology* 32.4 (2012): 971-978.)
- 4F: DWFKAFYDKVAEKFEAF SEQ ID NO:85 (Neyen, Claudine, et al. *Biochemistry* 48.50 (2009): 11858-11871);

[CON] is a connector moiety (including a [MULTICON]) as otherwise described herein; and [LINKER] is a linking moiety as otherwise described herein which links [CPBM] to the [CRBM] group and optionally contains one or more connector moieties (which optionally connect(s) more than one chemical moiety to provide said linking moiety or which connects said linking moiety to said [CPBM] group or said [CRBM] group, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

In certain embodiments of the present disclosure X of the [CRBM]/[ASGPRBM]

group is often -O-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-O-, -S-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-S-, N(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-N(R^{N1}) or C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}) when X is

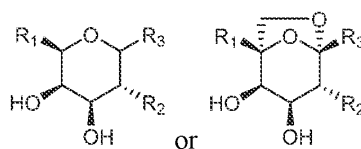
2 atoms in length,

X is -O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-, -O-C(R^{N1})(R^{N1})-O-, -O-C(R^{N1})(R^{N1})-S-, -O-C(R^{N1})(R^{N1})-N(R^{N1})-, -S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-S-, -S-C(R^{N1})(R^{N1})-S-, -S-C(R^{N1})(R^{N1})-O-, -S-C(R^{N1})(R^{N1})-N(R^{N1})-, N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-N(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1}), N(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1}) or C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}) when X is 3 atoms in length, and

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

In certain embodiments of the present disclosure X of the [CRBM]/[ASGPRBM] group is OCH₂ or CH₂O and R^{N1} is preferably H.

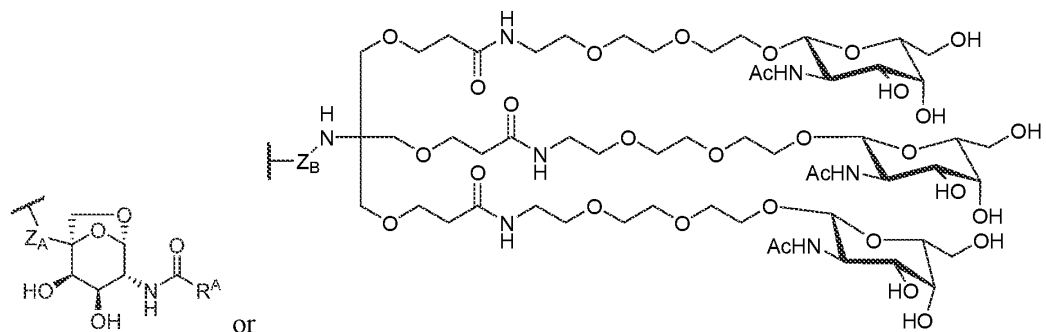
In various embodiments, the [CRBM]/[ASGPRBM] group is a group according to the chemical structure:



where R₁, R₂ and R₃ are as defined herein, or a pharmaceutically acceptable salt,

stereoisomer, solvate or polymorph thereof.

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

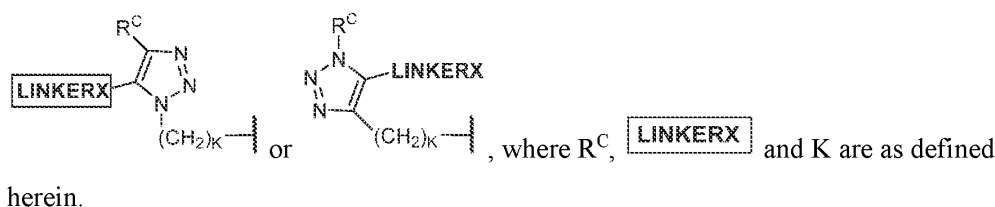


5 where R^A is C_1 - C_3 alkyl optionally substituted with 1-5 halogen groups;

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

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

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



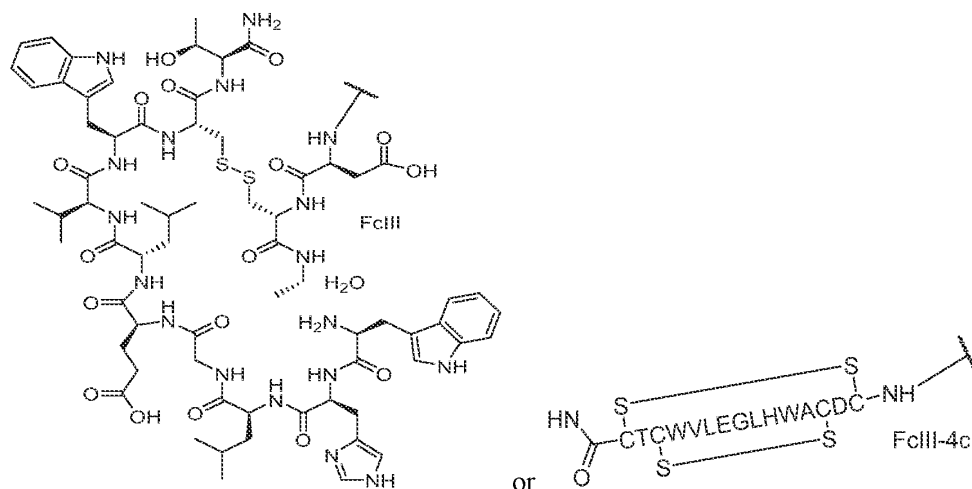
15

In certain embodiments, preferred compounds include the compounds which are presented in FIGURES 1, 7 and 13, as well as FIGURES 29-88. In certain embodiments, additional compounds are presented in FIGURES 16-66 and include final compounds set forth therein and intermediates which are used to make final compounds pursuant to the present disclosure.

20 In certain embodiments, R_1 and R_3 of the [CRBM]/[ASGPRBM] group include those moieties which are presented in FIGURE 68 hereof. In certain embodiments, R_2 of the [CRBM]/[ASGPRBM] group include those moieties which are presented in FIGURE 69 hereof.

25 In certain embodiments, the [CPBM]/[IgGBM] group is a peptide moiety according to

the chemical structure for FcIII or FcIII-4c:



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

In other embodiments, the present disclosure is directed to a method of treating a disease state or condition where a circulating protein is related to or contributes to a disease state and or condition or the symptomology associated with the disease state or condition. These disease states and/or conditions include, autoimmune diseases and numerous inflammatory diseases for example, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Alzheimer's disease, atherosclerosis, heart disease, stroke and cancer (including leukemia), among numerous others as described herein including as set forth in FIGURE 89 hereof. The method of treatment according to the present disclosure comprises administering to a patient or subject in need of therapy an effective amount of at least one compound according to the present disclosure, optionally in combination with an additional bioactive agent to reduce the likelihood of, inhibit and/or treat the disease state or condition by removing Circulating Protein associated with the disease state and/or condition from the circulation of the patient or subject.

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

In other embodiments, the present disclosure is directed to a method of treating a

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

10

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows representative compounds according to the present disclosure. Note that the figure discloses compound 3w (negative control for MIF inhibition), MIF-NVS-PEGnGN3, MIFGN3, MIF-PEGnGN3, MIF-AcF3-1, MIF-AcF3-2 and MIF-AcF3-3. Note that n in the PEG linker preferably ranges from 1-12, 1 to 10, 2 to 8, 2 to 6, 2 to 5 or 1, 2, 3 or 4.

FIG. 2 shows fluorescence polarization data of MIF-FITC binding to human MIF, indicating that our MIF-binding moiety binds MIF. Bifunctional molecules WJ-PEG4-GN3, WJ-PEG2-GN3, and NVS-PEG3-GN3 bound competitively with MIF-FITC, indicating that the bifunctional molecules maintain the ability to bind human MIF.

FIG. 3 shows that bifunctional molecules are able to deplete human MIF from the supernatant of culture HepG2 cells.

FIG. 4 shows that MIF internalized by HepG2 cells is trafficked to lysosomes.

FIG. 5 shows that MIF-GN3 mediates the depletion of injected human MIF from mice.

FIG. 6 shows that MIF-GN3 is able to delay tumor growth in a mouse model of prostate cancer.

FIG. 7 shows molecules DNP-GN3 and DNP-AcF3-3, which are bifunctional molecules that bind to anti-DNP IgG and ASGPR.

FIG. 8 shows that DNP-GN3 and DNP-AcF3-3 mediate the formation of a ternary complex between HepG2 cells and anti-DNP.

FIG. 9 shows that DNP-GN3 and DNP-AcF3-3 mediate the uptake of alexa 488-labeled anti-DNP by HepG2 cells.

FIG. 10 shows that DNP-GN3 and DNP-AcF3-3 mediate the localization of alexa

568 labeled anti-DNP to late endosomes and lysosomes.

FIG. 11 shows that DNP-AcF3-3 mediates the degradation of alexa 488-labeled anti-DNP in HepG2 cells.

FIG. 12 shows that DNP-GN3 mediates the depletion of anti-DNP from mouse
5 serum.

FIG. 13 shows the structures of IgG-degrading molecules IBA-GN3, Triazine-GN3, FcIII-GN3, and FcIII-4c-GN3.

FIG. 14 shows that FcIII-GN3 mediates the uptake of human IgG into HepG2 cells. Experiment performed as described above.

10 **FIG. 15** shows that FcIII-GN3 mediates the localization of IgG to late endosomes in HepG2 cells. Experiment performed as described above.

FIGs. 16-18 show the synthesis of PEG linkers used in several molecules outlined in this disclosure.

FIGs. 19-21 show the synthesis of ASGPR-binding precursors and ligands used in
15 several molecules in this disclosure.

FIGs. 22-26 show the synthesis of valency linkers used in several molecules in this disclosure.

FIGs. 27-28 show the synthesis of MIF ligands used in several bifunctional molecules.

20 **FIG. 29** describes the synthesis of the bifunctional molecule MIF-NVS-PEGn-GN3.

FIG. 30 describes the synthesis of bifunctional molecules MIF-GN3 and MIF-PEGn-GN3.

FIG. 31 describes the synthesis of the bifunctional molecule targeting MIF and ASGPR, containing one bicyclic ASGPR AcF3 ligands.

25 **FIG. 32** describes the synthesis of the bifunctional molecule targeting MIF and ASGPR, containing two bicyclic ASGPr AcF3 ligands.

FIG. 33 describes the synthesis of the bifunctional molecule targeting MIF and ASGPR, containing three bicyclic ASGPr ligands.

FIG. 34 shows the synthesis of DNP-GN3.

30 **FIG. 35** shows the synthesis of DNP-AcF3-3.

FIG. 36 shows the synthetic scheme used to obtain IBA-GN3.

FIG. 37 shows the synthesis of triazine-GN3.

FIG. 38 shows the synthetic scheme used to access FcIII-GN3.

FIG. 39 shows the synthetic scheme used to access FcIII-4c-GN3.

FIGs. 40-43 describe the synthesis of bifunctional molecules targeting MIF and ASGPr, containing three bicyclic ASGPR ligands with different substitutions on the 2-amine of the sugar.

FIG. 44 shows the synthesis of compound MIF-18-3.

5 **FIG. 45** shows the synthesis of compound MIF-31-3.

FIG. 46 shows the synthesis of compound MIF-15-3.

FIG. 47 shows the synthesis of compound MIF-19-3.

FIG. 48 shows the synthesis of compound MIF-16-3

FIG. 49 shows the synthesis of compound MIF-20-3

10 **FIG. 50** shows the synthesis of compound MIF-14-3

FIG. 51 shows the synthesis of compound MIF-21-3

FIGs. 52-66 show the synthesis of a number of MIF-binding compounds with various ASGPRBM moieties.

15 **FIG. 67** shows exemplary IgGBM groups each of which is covalently attached to a [CON] group, a [LINKER] group or a [ASGPRBM] group through an amine group, preferably a primary or secondary alkyl amine group which is optionally substituted on the amine group with a C₁-C₃ alkyl group.

FIG. 68 shows exemplary R₁ and R₃ substituents on ASGPRBM groups as otherwise described herein.

20 **FIG. 69** shows exemplary R₂ substituents on ASGPRBM groups as otherwise described herein.

FIG. 70 shows the synthesis of CD40L-binding bifunctional molecule BIO8898-GN3.

FIG. 71 shows the synthesis of TNF-alpha binding bifunctional molecule c87-GN3.

25 **FIG. 72** shows the synthesis of TNF-alpha binding bifunctional molecule 4e-GN3.

FIG. 73 shows the synthesis of TNF-alpha binding bifunctional molecule Cpd1-GN3.

FIG. 74 shows the synthesis of TNF-alpha binding bifunctional molecule SP307-GN3.

30 **FIG. 75** shows the synthesis of TNF-alpha binding bifunctional molecule YCWSQYLCY-GN3.

FIG. 76 shows the synthesis of PCSK9 binding bifunctional molecule SBC110424-GN3.

FIG. 77 shows the synthesis of PCSK9 binding bifunctional molecule SBC110076-GN3.

FIG. 78 shows the synthesis of PSCK9 binding bifunctional molecule TVFTSWEEYLDWV-GN3.

FIG. 79 shows the synthesis of VEGF binding bifunctional molecule VEPNCDIHVMWEWECFERL-GN3.

5 **FIG. 80** shows the synthesis of VEGF binding bifunctional molecule VEGFSM-GN3.

FIG. 81 shows the synthesis of TGF-beta binding bifunctional molecule KRFK-GN3.

FIG. 82 shows the synthesis of TGF-beta binding bifunctional molecule TGFBSM-GN3.

FIG. 83 shows the synthesis of TSP-1 binding bifunctional molecule LSKL-GN3.

10 **FIG. 84** shows the synthesis of soluble uPAR binding bifunctional molecule uPAR-GN3.

FIG. 85 shows the synthesis of soluble PSMA binding bifunctional molecule PSMA-GN3.

FIG. 86 shows the synthesis of IL-2 binding bifunctional molecule IL2-GN3.

15 **FIG. 87** shows the synthesis of GP120 binding bifunctional molecule BMS378806-GN3.

FIG. 88 shows the synthesis of GP120 binding bifunctional molecule CPD7-GN3.

FIG. 89 lists a table of possible target proteins with their indications, examples of *in vitro* assays, and known binding molecules.

20 **FIG. 90** includes proposed derivatization sites for several ligands that bind target circulating proteins.

DETAILED DESCRIPTION

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

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

the limits, ranges excluding either both of those included limits are also included in the disclosure.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure
5 belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described.

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

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

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

The term "patient" or "subject" is used throughout the specification within context to describe an animal, generally a mammal and preferably a human, to whom treatment, including prophylactic treatment (prophylaxis, including especially as that term is used with respect to reducing the likelihood of metastasis of an existing cancer), with the compositions

according to the present disclosure is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human patient or a patient of a particular gender, such as a human male or female patient, the term patient refers to that specific animal. Compounds according to the present disclosure are useful for the treatment
5 of numerous disease states including autoimmune disease states and/or conditions and inflammatory disease states and/or conditions as well as cancer, including especially for use in reducing the likelihood of metastasis or recurrence of a cancer.

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

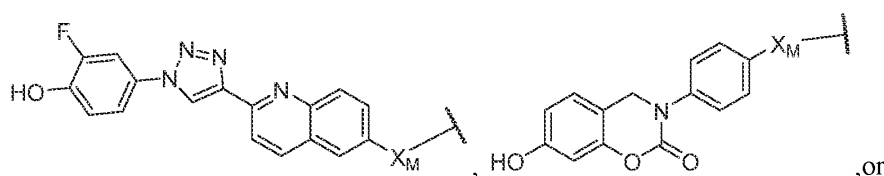
The terms “treat”, “treating”, and “treatment”, etc., as used herein, refer to any action providing a benefit to a patient at risk for a disease state or condition for which a MIF protein
20 may be removed, such as an autoimmune disease including rheumatoid arthritis (RA) or systemic lupus erythematosus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

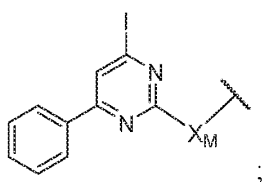
an occurrence within the context of treatment of disease state or condition, as otherwise described hereinabove.

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

The term “circulating protein binding moiety”, which term includes “macrophage migration inhibitory factor binding moiety” or “MIFBM”, “immunoglobulin G binding moiety” or “IgGBM” refers to a chemical moiety on one end of the bifunctional compounds according to the present disclosure which is capable of binding to a circulating protein (such as MIF, IgG, CD40L, TNFalpha, PCSK9, VEGf, TGFbeta, TSP-1, uPAR, PSMA and IL-2 which are associated with or contribute to a disease state or condition as otherwise described herein. In the present disclosure, the CPBM is capable of binding to the circulating protein, forming a complex with the present compounds, and delivering the bound protein to a hepatocyte or other cell whereupon the other end of the bifunctional molecule which contains a cellular receptor binding moiety (CRBM) such as an asialoglycoprotein receptor binding moiety (ASGPRBM) or as otherwise described herein can bind to the surface of a hepatocyte or other cell, respectively. Once attached to the cell, the bifunctional molecule to which is bound circulating protein is internalized by the cell through a phagocytosis/endocytosis mechanism whereupon the cell will destroy the protein via a lysosomal degradation or other degradation pathway. The term “immunoglobulin G binding moiety” or “IgGBM” is used to describe a moiety which binds to circulating IgG immunoglobulin, forming a complex with bifunctional molecules according to the present disclosure to be ultimately destroyed in hepatocytes. In certain instances in describing the present disclosure, the terms MIFBM and IgGBM and other cell binding moieties are used synonymously.

Exemplary MIFBMs for inclusion in bifunctional compounds according to the present disclosure include moieties found in bifunctional chemical structures which appear in Figure 1, attached hereto. MIFBMs according to the present disclosure include moieties according to the chemical structures:





wherein X_M is $-(CH_2)_{IM}$, $-O-(CH_2)_{IM}$, $S-(CH_2)_{IM}$, $NR_M-(CH_2)_{IM}$, $C(O)-(CH_2)_{IM}-$, a PEG (polyethylene glycol) group containing from 1 to 8 ethylene glycol residues or a $-C(O)(CH_2)_{IM}NR_M$ group; R_M is H or a C_1 - C_3 alkyl group which is optionally substituted with one or two hydroxyl groups; IM is an integer from 0-6. In various embodiments, IM is 1.

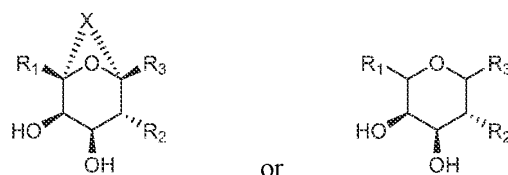
Other CPBM groups, such as IgGBM and various previously described moieties which bind to CD40L, TNF α , PCSK9, VEGf, TGF β , TSP-1, uPAR, PSMA and IL-2 are set forth hereinabove. These bind to the respective circulating proteins, thus forming a complex with the bifunctional compounds according to the present disclosure and the bifunctional compounds complexed with the bound circulating proteins can be bound to cellular receptors on cells which can take up the complexed compounds using phagocytosis/endocytosis mechanisms of the cell and remove the proteins through a degradation process. It is noted that the CPBM which are peptides which bind to IgGBM, CD40L, TNF α , PCSK9, VEGf, TGF β , TSP-1, uPAR, PSMA and IL-2 are covalently linked to other portions of the bifunctional molecules according to the present disclosure through the terminal amine or carboxylic acid group of the peptide. In preferred embodiments, the carboxylic acid is amidated to form a non-reactive amide group, often with a free amine group (substituted with two H's) or an amine group which alkylated with at least one C_1 - C_{10} alkyl group, more often at least one C_1 - C_3 alkyl group so that the free amine on the other end of the peptide may be used to covalently link to other portions of the bifunctional molecule. In other embodiments, the amine terminus is rendered non-reactive by end-capping the amine group with a C_2 - C_{10} acyl group, preferably a C_2 - C_4 acyl group, so that the carboxylic acid group may be reacted, often with an amine to form an amide.

The term "cellular receptor binding moiety" refers to a moiety of the bifunctional compounds according to the present disclosure which is capable of binding to a receptor on a cell capable of degrading circulating proteins pursuant to the present disclosure herein. These are moieties which bind to asialoglycoprotein receptor, LRPR, LDLR, R γ RI, FcRN, Transferrin Receptor or Macrophage Scavenger Receptor (e.g., membrane receptors of degradation cells) as otherwise described herein. Many of these binding moieties are peptides which are covalently linked to other portions of the bifunctional compounds according to the present disclosure through a terminal amine or carboxylic acid group. As for

the CPBM group described above, in preferred embodiments, the carboxylic acid is amidated to form a non-reactive amide group, often with a free amine group (substituted with two H's) or an amine group which alkylated with at least one C₁-C₁₀ alkyl group, more often at least one C₁-C₃ alkyl group so that the free amine on the other end of the peptide may be used to covalently link to other portions of the bifunctional molecule. In other embodiments, the amine terminus is rendered non-reactive by end-capping the amine group with a C₂-C₁₀ acyl group, preferably a C₂-C₄ acyl group, so that the carboxylic acid group may be reacted, often with an amine to form an amide.

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

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



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

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

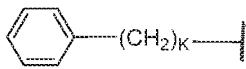
if X is 2 atoms in length, no more than 1 atom of X is O, S, or N(R^{N1}),

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

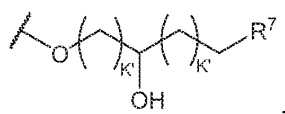
where R^{N1} is H or a C₁-C₃ alkyl group optionally substituted with from 1-3 halogen groups;

R₁ and R₃ are each independently H, -(CH₂)_KOH, -(CH₂)_KOC₁-C₄ alkyl, -C₁-C₄ alkyl, -(CH₂)_Kvinyl, -O-(CH₂)_Kvinyl, -(CH₂)_Kalkynyl, -(CH₂)_KCOOH, -(CH₂)_KC(O)O-C₁-C₄ alkyl, -O-C(O)-C₁-C₄ alkyl, -C(O)-C₁-C₄ alkyl, in which each alkyl, vinyl, or alkynyl is optionally substituted with from 1-3 halogen groups. In various embodiments, each alkyl, vinyl, or

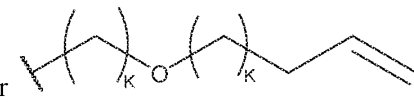
alkynyl in R₁ and R₃ is optionally substituted with from 1-3 fluorines (F). K is independently at each occurrence an integer from 0-4.

- In certain embodiments, R₁ and R₃ are each independently a  group, which is optionally substituted with 1-3 halogen groups, 1 to 3 C₁-C₄ alkyl groups, or
 5 O-C₁-C₄ alkyl groups, in which each of the alkyl groups is optionally substituted with 1-3 halogen groups or 1-2 hydroxyl groups, and K is independently at each occurrence and integer from 0-4; or

R₁ and R₃ are each independently a group according to the chemical structure:

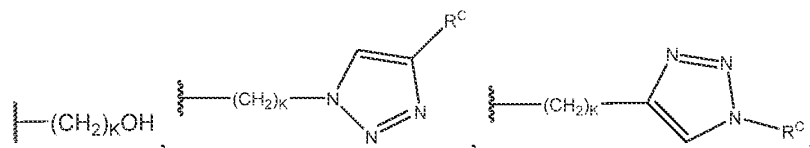


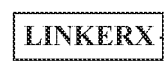
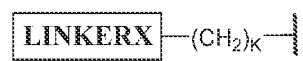
- 10 where R⁷ is O-C₁-C₄ alkyl, which is optionally substituted with from 1 to 3 halo groups or 1 to 2 hydroxy groups, and K' is independently at each occurrence an integer from 0-4; or

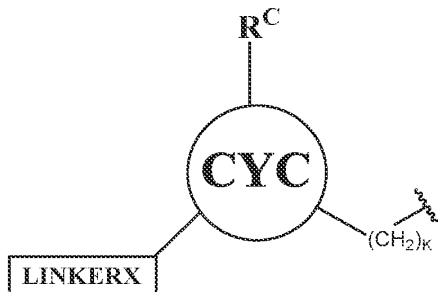
R⁷ is a -NR^{N3}R^{N4} group or , and K is independently at each occurrence an integer from 0-4; or

- 15 R₁ and R₃ are each independently a group according to the structure:

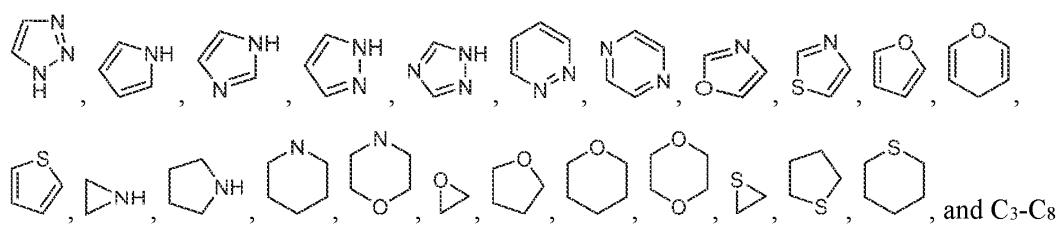
R₁ and R₃ are each independently a group according to the structure:



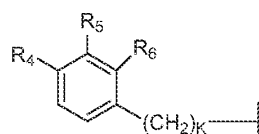
, , wherein K is independently at each occurrence 0-4; or a

- 20  group,

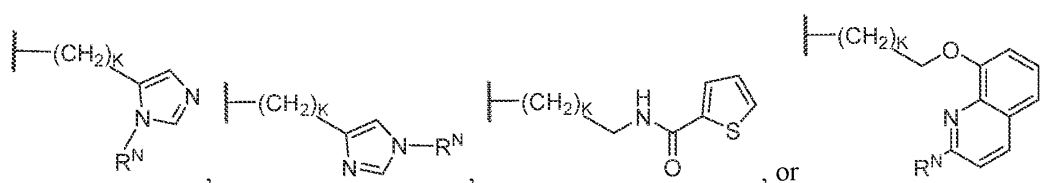
wherein CYC is a ring selected from the group consisting of:


 saturated carbocyclic, wherein each of LINKERX, R^C, and -(CH₂)_K- are attached to an open valence in CYC, including N-H;

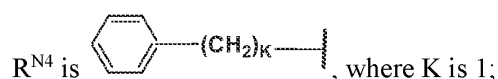
- 5 R^C is absent, H, C₁-C₄ alkyl optionally substituted with from 1-3 halogen groups or 1-2 hydroxyl groups; or a group according to the structure:



- where R₄, R₅ and R₆ are each independently, H, halogen, CN, NR^{N1}R^{N2},
 -(CH₂)_KOH, -(CH₂)_KOC₁-C₄ alkyl, C₁-C₃ alkyl, -O-C₁-C₃-alkyl, -(CH₂)_KCOOH, -
 10 (CH₂)_KC(O)O-C₁-C₄ alkyl, O-C(O)-C₁-C₄ alkyl, -C(O)-C₁-C₄ alkyl, in any of which the alkyl
 group is optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups; or
 R^C is

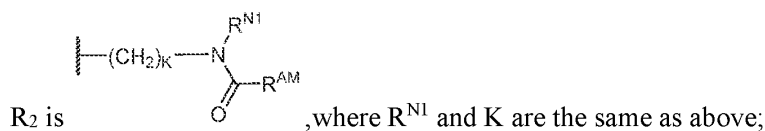


- where R^N, R^{N1}, and R^{N2} are each independently H or a C₁-C₃ alkyl group optionally
 15 substituted with 1-3 halogen groups, or 1-2 hydroxyl groups;
 K is independently at each occurrence an integer from 0-4;
 K' is independently at each occurrence an integer from 0-4;
 R^{N3} is H or C₁-C₃ alkyl optionally substituted with 1-3 halogen groups or 1-2
 hydroxyl groups; and
 20 R^{N4} is H or C₁-C₃ alkyl optionally substituted with 1-3 halogen groups or 1-2
 hydroxyl groups, or



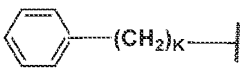
LINKERX is a linker group which includes at least one [CPBM] group and connects
 the [CPBM] group to the [CRBM] through one or more optional [CON] groups, or

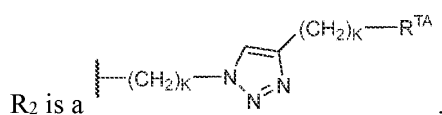
LINKERX is a linker group which includes at least one functional group that covalently bonds the linker group to at least one [CPBM] group or optional [CON] group;



- R^{AM} is H, C₁-C₄ alkyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-C_1-C_4$ alkyl, $-O-C(O)-C_1-C_4$ alkyl, $-C(O)-C_1-C_4$ alkyl, $-(CH_2)_K-NR^{N3}R^{N4}$ where R^{N3} is H or C₁-C₃ alkyl, in which any of the alkyl groups are optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups; and

R^{N4} is H, C₁-C₃ alkyl optionally substituted with 1-3 halo groups or 1 or 2 hydroxy groups, or

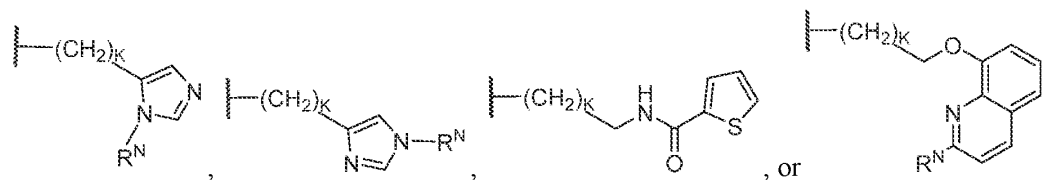
- 10 R^{N4} is  and K is 1; or



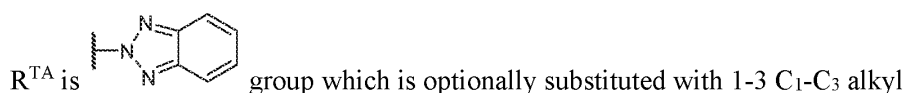
where R^{TA} is H, CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KOC_1-C_4$ alkyl, C₁-C₄ alkyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-C_1-C_4$ alkyl, $O-C(O)-C_1-C_4$ alkyl, $-C(O)-C_1-C_4$ alkyl, in which each alkyl is optionally substituted by 1-3 halogen groups or 1-2 hydroxyl groups, or

- 15 R^{TA} is a C₃-C₁₀ aryl or a 3- to 10-membered heteroaryl group containing up to 5 hetero atoms, each of said aryl or heteroaryl groups being optionally substituted with 1-3 substituents selected from the group consisting of CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KOC_1-C_4$ alkyl, C₁-C₃ alkyl, $-O-C_1-C_3$ -alkyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-C_1-C_4$ alkyl, $O-C(O)-C_1-C_4$ alkyl, and $-(CH_2)_KC(O)-C_1-C_4$ alkyl, in which each alkyl is optionally substituted with 1-3
- 20 halogen groups or 1-2 hydroxyl groups, or

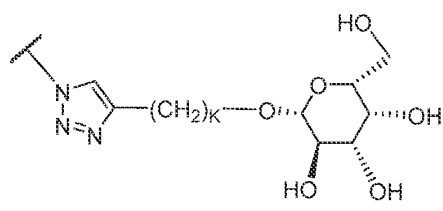
R^{TA} is



or;



- 25 groups each of which are optionally substituted with 1-3 halogen groups, or



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

wherein each $-(CH_2)_K$ group is optionally substituted with 1-4 C_1 - C_3 alkyl groups

5 which are each optionally substituted with from 1-3 fluorines or 1-2 hydroxyl groups;

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

[CON] is a connector moiety (including a [MULTICON]) as otherwise described
10 herein; and [LINKER] is a linking moiety as otherwise described herein which links [CPBM] to the [CRBM] group and optionally contains one or more connector moieties (which optionally connect(s) more than one chemical moiety to provide said linking moiety or which connects said linking moiety to said [CPBM] group or said [CRBM] group, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

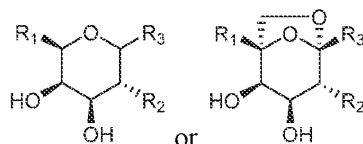
15 In various embodiments, X is $-O-C(R^{N1})(R^{N1})$,
 $C(R^{N1})(R^{N1})-O-$, $-S-C(R^{N1})(R^{N1})$, $C(R^{N1})(R^{N1})-S-$, $N(R^{N1})-C(R^{N1})(R^{N1})$,
 $C(R^{N1})(R^{N1})-N(R^{N1})$ or $C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})$ when X is 2 atoms in length,
X is $-O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})$, $C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-$, $-O-C(R^{N1})(R^{N1})-O-$,
 $-O-C(R^{N1})(R^{N1})-S-$, $-O-C(R^{N1})(R^{N1})-N(R^{N1})-$, $-S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})$,
20 $C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-$, $C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-S$, $-S-C(R^{N1})(R^{N1})-S-$,
 $-S-C(R^{N1})(R^{N1})-O-$, $-S-C(R^{N1})(R^{N1})-N(R^{N1})-$, $N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})$,
 $C(R^{N1})(R^{N1})-N(R^{N1})-C(R^{N1})(R^{N1})$, $C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1})$,
 $N(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1})$ or $C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})$ when X is
3 atoms in length, and

25 X is $-O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})$, $C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-$
 $(R^{N1})(R^{N1})-$, $-O-C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-$, $-S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-$
 $C(R^{N1})(R^{N1})-$, $C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-$, $C(R^{N1})(R^{N1})-(R^{N1})(R^{N1})-$
 $S-C(R^{N1})(R^{N1})-$, $-S-C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-$, $N(R^{N1})-C(R^{N1})(R^{N1})-$
 $C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-$, $C(R^{N1})(R^{N1})-N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})$,
30 $C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1})$, $N(R^{N1})-C(R^{N1})(R^{N1})-N(R^{N1})$ or $C(R^{N1})(R^{N1})-$

$C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})$ when X is 4 atoms in length where R^{N1} is the same as above. Most often, R^{N1} is H.

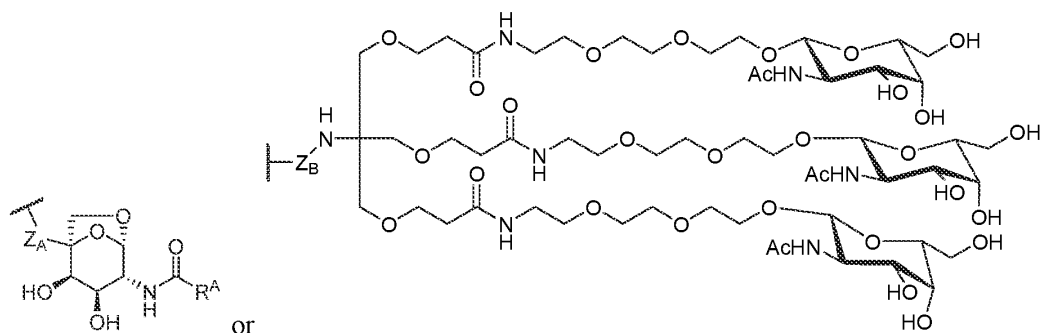
In various embodiments, X is OCH_2 or CH_2O and R^{N1} is H.

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



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

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



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

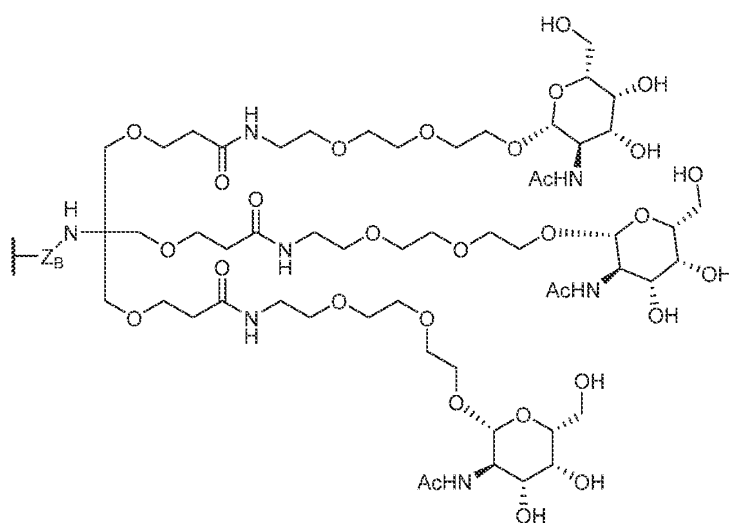
Z_A is $-(CH_2)_{IM}$, $-O-(CH_2)_{IM}$, $S-(CH_2)_{IM}$, $NR_M-(CH_2)_{IM}$, $C(O)-(CH_2)_{IM}-$, a PEG group containing 1 to 8 ethylene glycol (CH_2CH_2O or OCH_2CH_2) units, or $-C(O)(CH_2)_{IM}NR_M$,

15 where IM and R_M are the same as above; and

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

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

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



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

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

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

In certain particular aspects of the present disclosure, the cancer which is treated is metastatic cancer, a recurrent cancer or a drug resistant cancer, especially including a multiple drug resistant cancer. Separately, metastatic cancer may be found in virtually all tissues of a cancer patient in late stages of the disease, typically metastatic cancer is found in lymph system/nodes (lymphoma), in bones, in lungs, in bladder tissue, in kidney tissue, liver tissue and in virtually any tissue, including brain (brain cancer/tumor). Thus, the present disclosure is generally applicable and may be used to treat any cancer in any tissue, regardless of etiology.

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

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

A more complete list of autoimmune diseases which may be treated by compounds and pharmaceutical compositions according to the present disclosure includes Addison's Disease, Autoimmune polyendocrine syndrome (APS) types 1, 2 and 3, autoimmune pancreatitis (AIP), diabetes mellitus type 1, autoimmune thyroiditis, Ord's thyroiditis, Grave's disease, autoimmune oophoritis, endometriosis, autoimmune orchitis, Sjogren's syndrome, autoimmune enteropathy, coeliac disease, Crohn's disease, microscopic colitis, ulcerative colitis, autophospholipid syndrome (APIS), aplastic anemia, autoimmune hemolytic anemia, autoimmune lymphoproliferative syndrome, autoimmune neutropenia, autoimmune thrombocytopenic purpura, cold agglutinin disease, essential mixed cryoglobulinemia, Evans syndrome, pernicious anemia, pure red cell aplasia, thrombocytopenia, adiposis dolorosa, adult-onset Still's disease, ankylosing spondylitis, CREST syndrome, drug-induced lupus, enthesitis-related arthritis, eosinophilic fasciitis, Felty syndrome, AgG4-related disease, juvenile arthritis, Lyme disease (chronic), mixed connective tissue disease (MCTD), palindromic rheumatism, Parry Romberg syndrome, Parsonage-Turner syndrome, psoriatic arthritis, reactive arthritis, relapsing polychondritis, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schnitzler syndrome, systemic lupus erythematosus, undifferentiated connective tissue disease (UCTD), dermatomyositis, fibromyalgia, myositis, inclusion body myositis, myasthenia gravis, neuromyotonia, paraneoplastic cerebellar degeneration, polymyositis, acute disseminated encephalomyelitis (ADEM), acute motor axonic neuropathy, anti-NMDA receptor encephalitis, Balo concentric sclerosis, Bickerstaff's encephalitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome,

Hashimoto's encephalopathy, idiopathic inflammatory demyelinating diseases, Lambert-Eaton myasthenic syndrome, multiple sclerosis, pattern II, Oshtoran Syndrome, Pendiatic Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS), progressive inflammatory neuropathy, restless leg syndrome, stiff person syndrome,

5 Sydenham chorea, transverse myelitis, autoimmune retinopathy, autoimmune uveitis, Cogan syndrome, Graves ophthalmopathy, intermediate uveitis, ligneous conjunctivitis, Mooren's ulcer, neuromyelitis optica, opsoclonus myoclonus syndrome, optic neuritis, scleritis, Susac's syndrome, sympathetic ophthalmia, Tolosa-Hunt syndrome, autoimmune inner ear disease (AIED), Ménière's disease, Behçet's disease, Eosinophilic granulomatosis with polyangiitis (EGPA), giant cell arteritis, granulomatosis with polyangiitis (GPA), IgA vasculitis (IgAV),

10 Kawasaki's disease, leukocytoclastic vasculitis, lupus vasculitis, rheumatoid vasculitis, microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), polymyalgia rheumatica, urticarial vasculitis, vasculitis, primary immune deficiency, chronic fatigue syndrome, complex regional pain syndrome, eosinophilic esophagitis, gastritis, interstitial lung disease,

15 POEMS syndrome, Raynaud's syndrome, primary immunodeficiency and pyoderma gangrenosum, among others.

The term “inflammatory disease” is used to describe a disease or illness with acute, but more often chronic inflammation as a principal manifestation of the disease or illness. Inflammatory diseases include diseases of neurodegeneration (including, for example,

20 Alzheimer's disease, Parkinson's disease, Huntington's disease; other ataxias), diseases of compromised immune response causing inflammation (e.g., dysregulation of T cell maturation, B cell and T cell homeostasis, counters damaging inflammation), chronic inflammatory diseases including, for example, inflammatory bowel disease, including Crohn's disease, rheumatoid arthritis, lupus, multiple sclerosis, chronic obstructive

25 pulmonary disease/COPD, pulmonary fibrosis, cystic fibrosis, Sjogren's disease; hyperglycemic disorders, diabetes (I and II), affecting lipid metabolism islet function and/or structure, pancreatic β -cell death and related hyperglycemic disorders, including severe insulin resistance, hyperinsulinemia, insulin-resistant diabetes (e.g. Mendenhall's Syndrome, Werner Syndrome, leprechaunism, and lipoatrophic diabetes) and *dyslipidemia* (e.g.

30 hyperlipidemia as expressed by obese subjects, elevated low-density lipoprotein (LDL), depressed high-density lipoprotein (HDL), elevated triglycerides and metabolic syndrome, liver disease, renal disease (apoptosis in plaques, glomerular disease), cardiovascular disease (especially including infarction, ischemia, stroke, pressure overload and complications during reperfusion), muscle degeneration and atrophy, low grade inflammation, gout, silicosis,

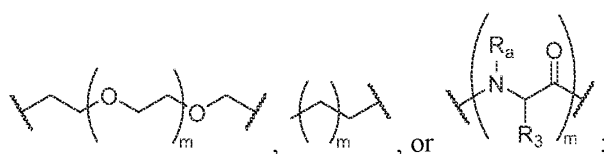
atherosclerosis and associated conditions such as cardiac and neurological (both central and peripheral) manifestations including stroke, age-associated dementia and sporadic form of Alzheimer's disease, and psychiatric conditions including depression), stroke and spinal cord injury, arteriosclerosis, among others. In these diseases, elevated MIF is very often
5 observed, making these disease states and/or conditions response to therapy using compounds and/or pharmaceutical compositions according to the present disclosure. It is noted that there is some overlap between certain autoimmune diseases and inflammatory diseases as described herein.

The term "linker", refers to a chemical entity including a complex linker connecting a
10 circulating protein binding moiety (CPBM) to the cellular receptor binding moiety (CRBM) including an asialoglycoprotein receptor binding moiety (ASGPRBM), optionally through at least one (preferably one or two) connector moiety [CON] through covalent bonds in compounds according to the present disclosure. The linker between the two active portions of the molecule, that is the CPBM group and the CRBM/ASGPRBM group ranges from
15 about 5 Å to about 50 Å or more in length, about 6 Å to about 45 Å in length, about 7 Å to about 40 Å in length, about 8 Å to about 35 Å in length, about 9 Å to about 30 Å in length, about 10 Å to about 25 Å in length, about 7 Å to about 20 Å in length, about 5 Å to about 16 Å in length, about 5 Å to about 15 Å in length, about 6 Å to about 14 Å in length, about 10 Å to about 20 Å in length, about 11 Å to about 25 Å in length, etc. Linkers which are based upon ethylene glycol
20 units and are between 2 and 15 glycol units, 1 and 8 glycol units, 1, 2, 3, 4, 5, and 6 glycol units in length may be preferred, although the length of certain linkers may be far greater. By having a linker with a length as otherwise disclosed herein, the CPBM group and the CRBM/ASGPRBM group may be situated to advantageously take advantage of the biological activity of compounds according to the present disclosure which bind to receptors, including
25 asialoglycoprotein receptors on hepatocytes and other cells resulting in the selective and targeted degradation of circulating proteins within the lysosomal degradation mechanism or other degradation mechanism of the hepatocytes. The selection of a linker component is based on its documented properties of biocompatibility, solubility in aqueous and organic media, and low immunogenicity/antigenicity. Although numerous linkers may be used as
30 otherwise described herein, a linker based upon polyethyleneglycol (PEG) linkages, polypropylene glycol linkages, or polyethyleneglycol-co-polypropylene oligomers (up to about 100 units, about 1 to 100, about 1 to 75, about 1 to 60, about 1 to 50, about 1 to 35, about 1 to 25, about 1 to 20, about 1 to 15, 2 to 10, about 4 to 12, about 1 to 8, 1 to 3, 1 to 4, 2 to 6, 1 to 5, etc.) may be favored as a linker because of the chemical and biological

characteristics of these molecules. The use of polyethylene (PEG) linkages of between 2 and 15 ethylene glycol units is preferred. When describing linkers according to the present disclosure, including polyethylene glycol linkers or other linkers, one or more additional groups (e.g., methylene groups, amide groups, keto groups, amine groups, etc., with methylene groups or amide groups being preferred) may be covalently attached at either end of the linker group to attach to a CRBM/ASGPRBM group, a [CON] group, another linker group or a CPBM group.

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

Preferred linkers include those according to the chemical structures:

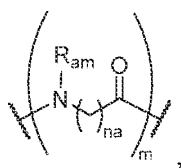


or a polypropylene glycol or polypropylene-co-polyethylene glycol linker having between 1 and 100 alkylene glycol units, preferably about 1 to 75, about 1 to 60, about 1 to 50, about 1 to 45, about 1 to 35, about 1 to 25, about 1 to 20, about 1 to 15, 2 to 10, about 4 to 12, about 5 to 10, about 4 to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

where R_a is H, C₁-C₃ alkyl or alkanol or forms a cyclic ring with R^3 (proline) and R^3 is a side chain derived from a D- or L amino acid (preferably a naturally occurring L-amino acid) preferably selected from the group consisting of alanine (methyl), arginine (propyleneguanidine), asparagine (methylenecarboxamide), aspartic acid (ethanoic acid), cysteine (thiol, reduced or oxidized di-thiol), glutamine (ethylcarboxamide), glutamic acid (propanoic acid), glycine (H), histidine (methyleneimidazole), isoleucine (1-methylpropane), leucine (2-methylpropane), lysine (butyleneamine), methionine (ethylmethylthioether), phenylalanine (benzyl), proline hydroxyproline (R^3 forms a cyclic ring with R_a and the adjacent nitrogen group to form a pyrrolidine or hydroxypyrrolidine group), serine (methanol), threonine (ethanol, 1-hydroxyethane), tryptophan (methyleneindole), tyrosine (methylene phenol) or valine (isopropyl), where the R^3 group is indicated in parentheses;

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

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

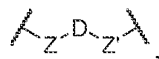


where R_{am} is H or a C_1 - C_3 alkyl optionally substituted with one or two hydroxyl groups;

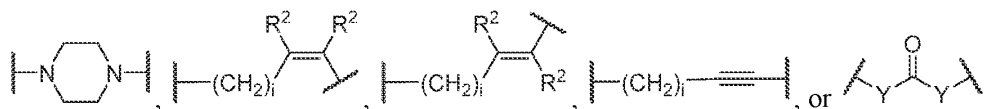
n_a is 1-15, 1-12, 1-10, 1-8, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11;

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

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



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



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

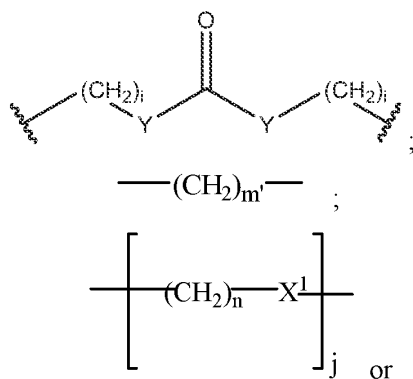
each R is H, or a C_1 - C_3 alkyl or alkanol group;

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

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

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

5 D is



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

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

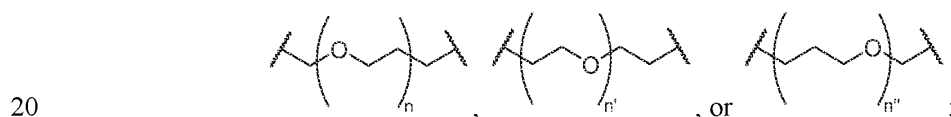
m' is 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;

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

X¹ is O, S or N-R; and

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

In certain embodiments, other linkers which are included herein include linkers according to the chemical structure:



20

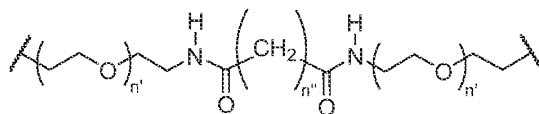
where each n and n' is independently 1 to 25, 1 to 15, 1 to 12, 2 to 11, 2 to 10, 2 to 8, 2 to 6, 2 to 5, 2 to 4 and 2 to 3 or 1, 2, 3, 4, 5, 6, 7, or 8; and

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

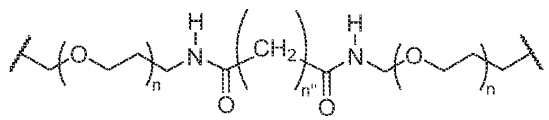
25

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

(PEG) linker group include the following structures:



or



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

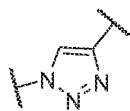
each n'' is independently 0 to 8, often 1 to 7, or 1, 2, 3, 4, 5 or 6 (preferably 3).

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

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



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



The term “connector”, symbolized in the generic formulas by “CON” or [CON], is used to describe a chemical moiety which is optionally included in bifunctional compounds
20 according to the present disclosure which forms from the reaction product of an activated linker with a CPBM moiety (which also is preferably activated for covalently bonding the linker with the moiety) or a CRBM/ASGPRBM group with an activated linker. The connector group is often the resulting moiety which forms from the facile condensation of two or more separate chemical fragments which contain reactive groups which can provide
25 connector groups as otherwise described to produce bifunctional or multifunctional compounds according to the present disclosure. It is noted that a connector may be distinguishable from a linker in that the connector is the result of a specific chemistry which is used to provide bifunctional compounds according to the present disclosure wherein the

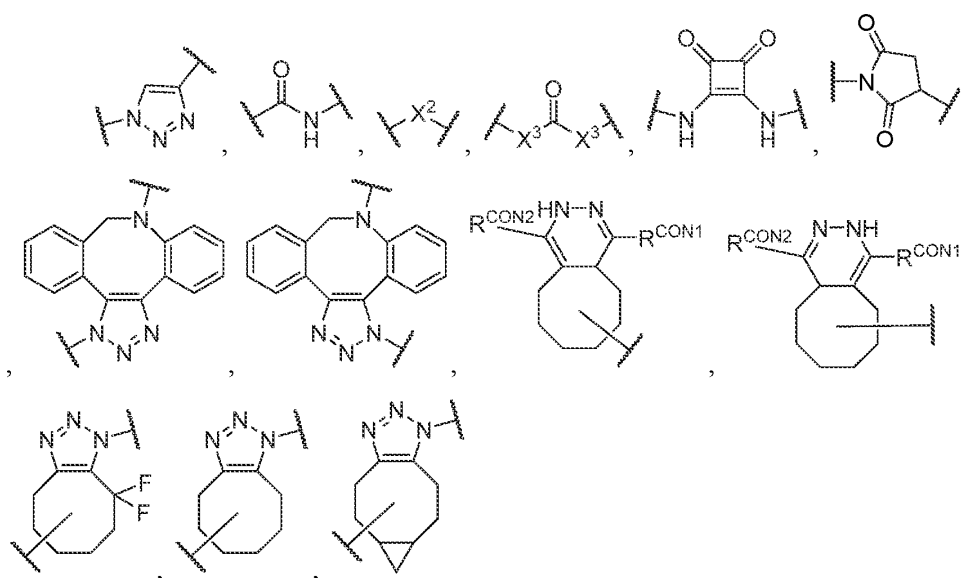
reaction product of these groups results in an identifiable connector group or part of a connector group which is distinguishable from the linker group, although in certain instances, the connector group is incorporated into and integral with the linker group as otherwise described herein.

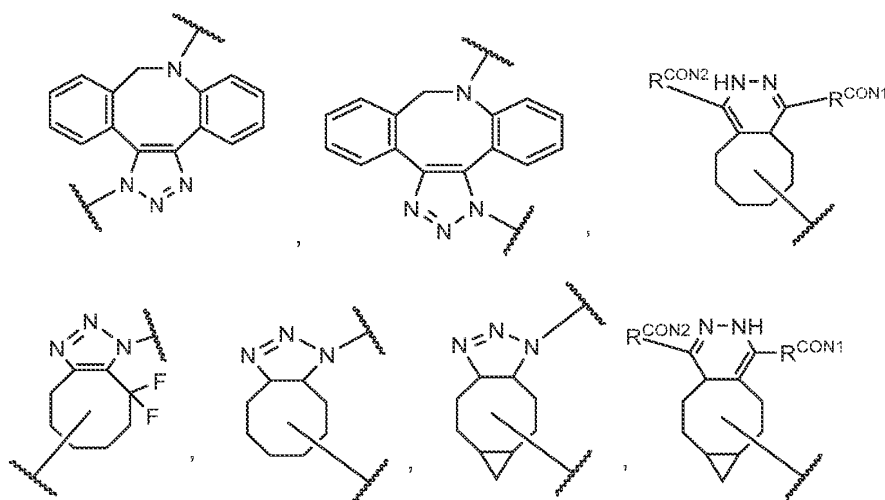
- 5 It is noted also that a connector group may be linked to a number of linkers to provide multifunctionality (i.e., more than one CPBM moiety and/or more than one CRBM/ASGPRBM moiety) within the same molecule. It is noted that there may be some overlap between the description of the connector group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



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

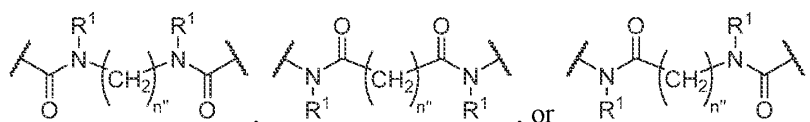
- 20 In various embodiments, suitable [CON] connector groups which are used in the present disclosure include the following chemical groups:





, and the like;

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



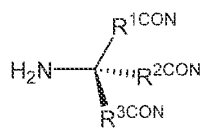
- 5 where X^2 is CH_2 , O, S, NR^4 , $C(O)$, $S(O)$, $S(O)_2$, $-S(O)_2O$, $-OS(O)_2$, or $OS(O)_2O$;
 X^3 is O, S, NR^4 ;

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

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

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

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



where R^{1CON} , R^{2CON} , and R^{3CON} are each independently H, $-(CH_2)_{MC1}$, -

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

- 15 H;

each $MC1$ is independently an integer from 1-4;

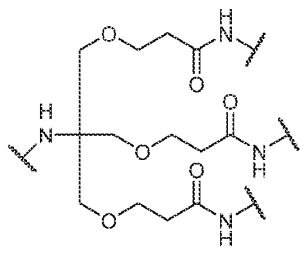
each $MC1a$ is independently an integer from 0-4; and

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

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

- 20 The triazole group, indicated above, may be a preferred connector group. An

additional preferred connector group is:



which is linked to at least one CPBM and/or at least one CRBM/ASPRGBM (preferably 3 CRBM/ASPRGBM moieties). This connector group may be used to form GN₃ as otherwise described herein.

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

Additional Galactose- and Talose-based ASGPR Binding Moieties

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



Formula II

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

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

In the compound of Formula II:

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

k' is an integer from 1 to 15;

j' is an integer from 1 to 15;

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

i_L is an integer from 0 to 15;

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

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

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

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

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

In the compound of Formula II, X¹ is 1 to 5 contiguous atoms independently selected
 20 from O, S, N(R^b), 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);

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

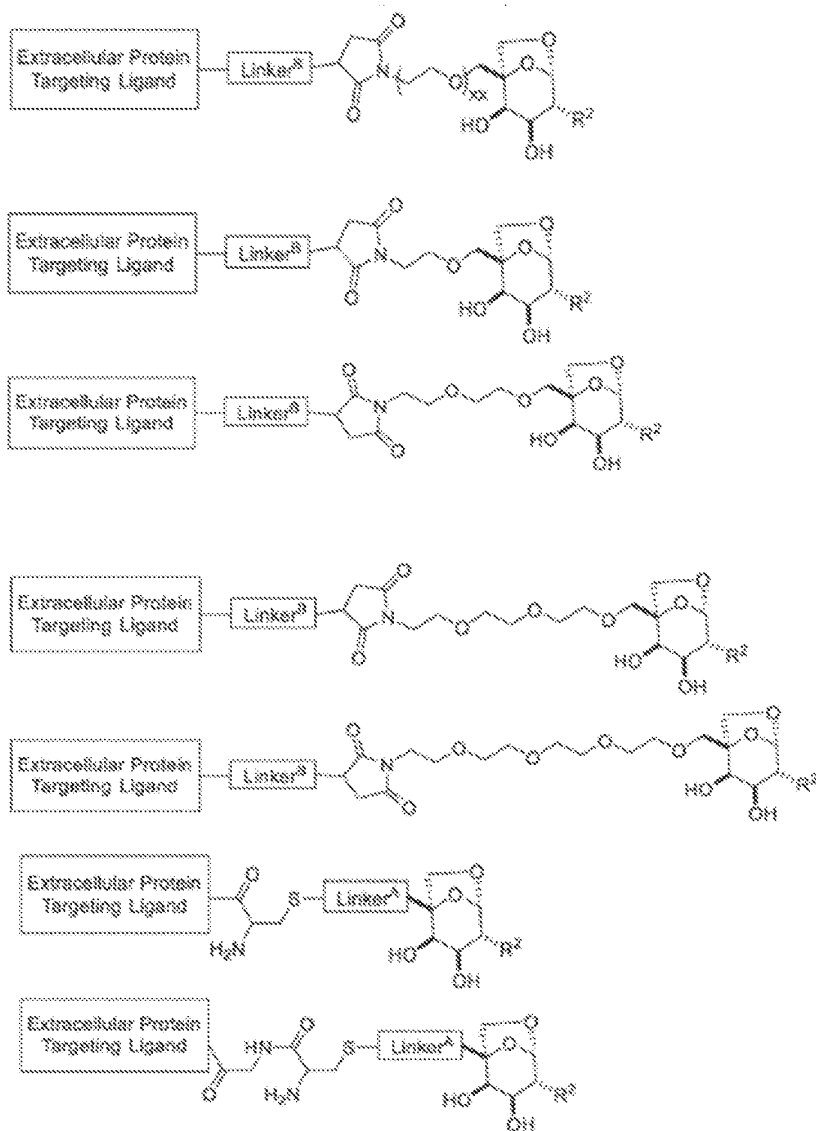
R⁴ is independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, -OR⁶, -NR⁶R⁷,

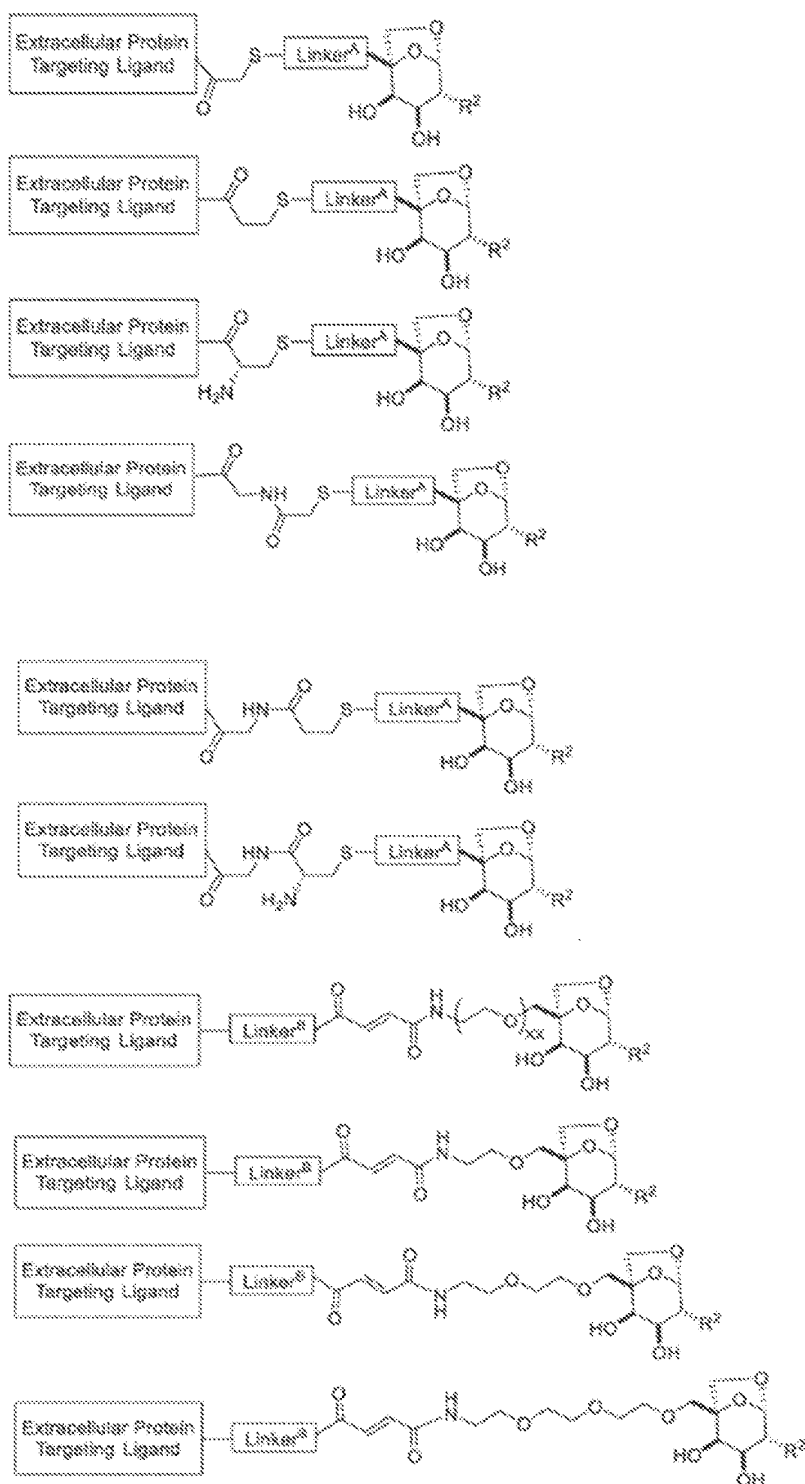
R⁶ and R⁷ are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroaryl alkyl, alkenyl, alkynyl, and, haloalkyl, heteroaryl, heterocycle, -alkyl-OR⁸, -alkyl-NR⁸R⁹, C(O)R³, S(O)R³, C(S)R³, and S(O)₂R³;
 30

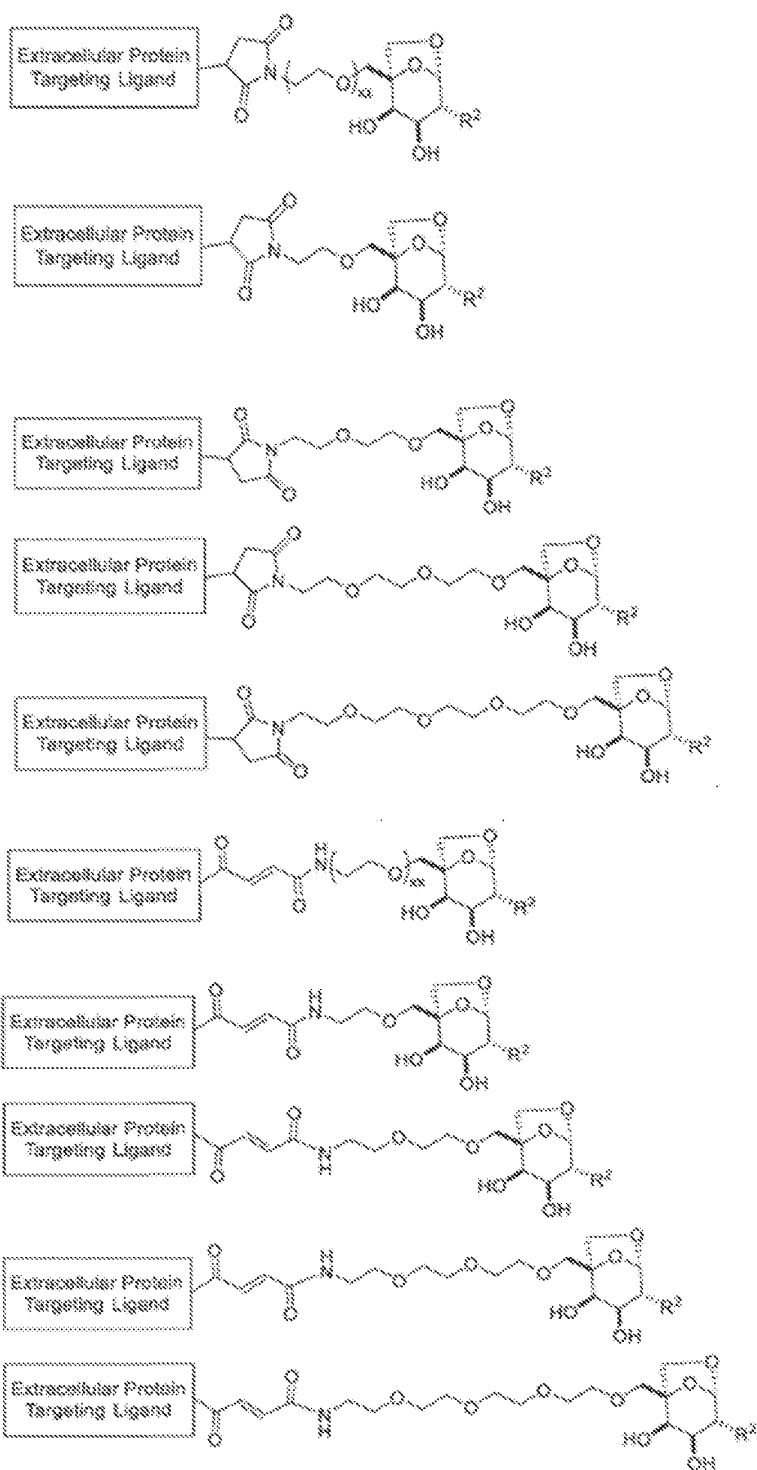
R⁸ and R⁹ are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle.

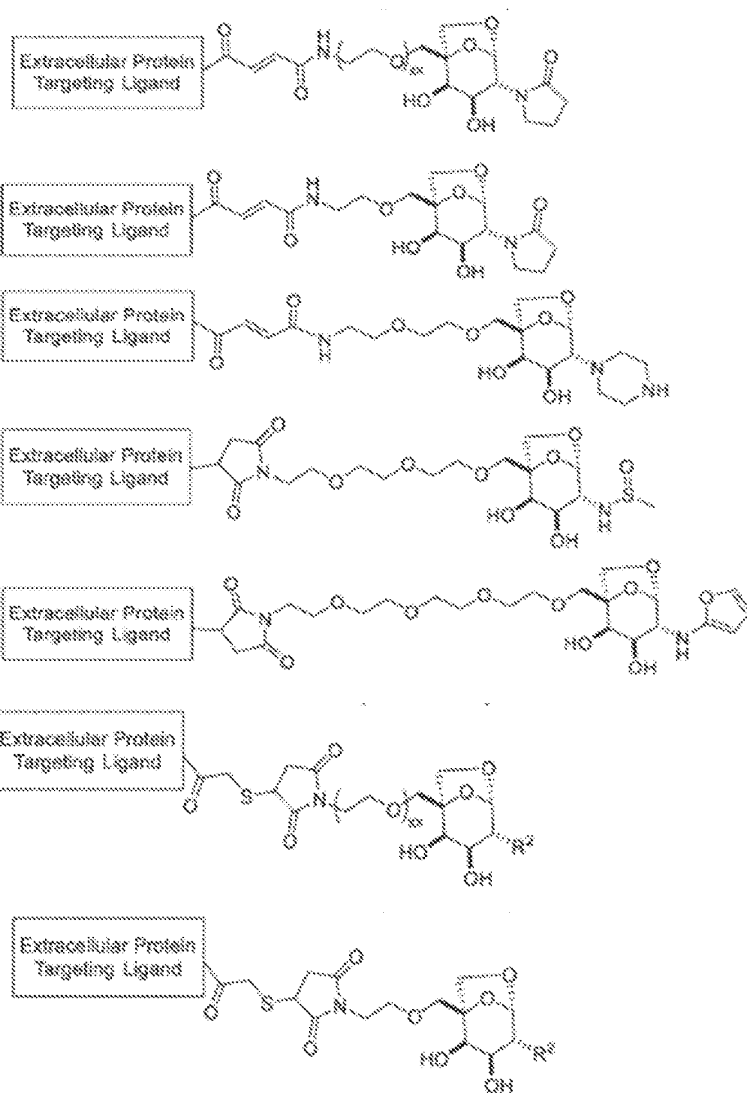
A. Galactose-Based ASGPR-Binding Cellular Receptor Binding Moieties of Formula II

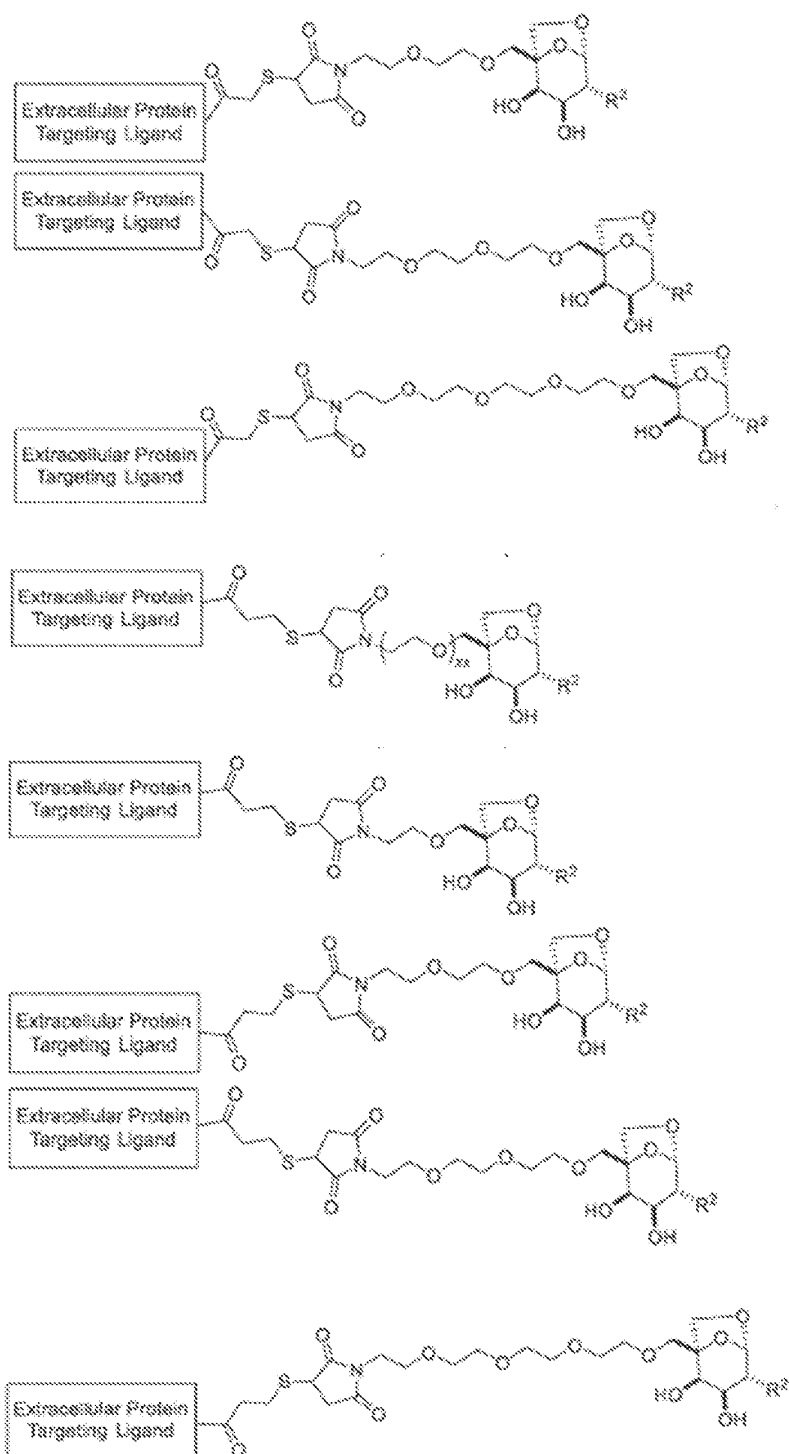
In certain embodiments, the compound of Formula II is selected from:

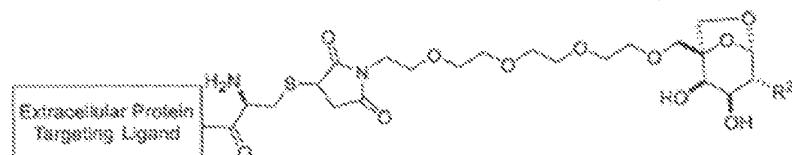
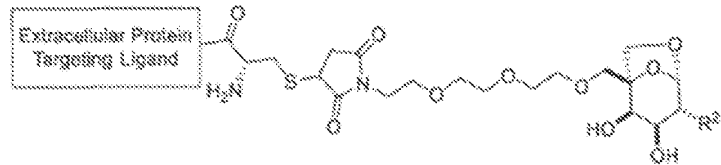
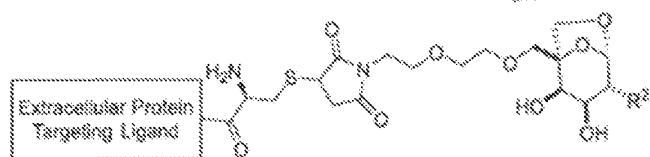
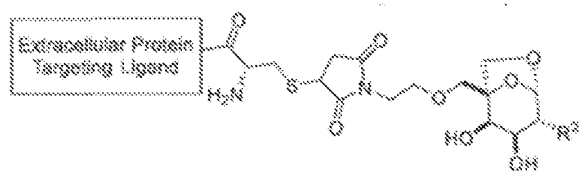
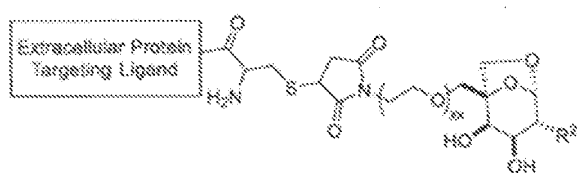


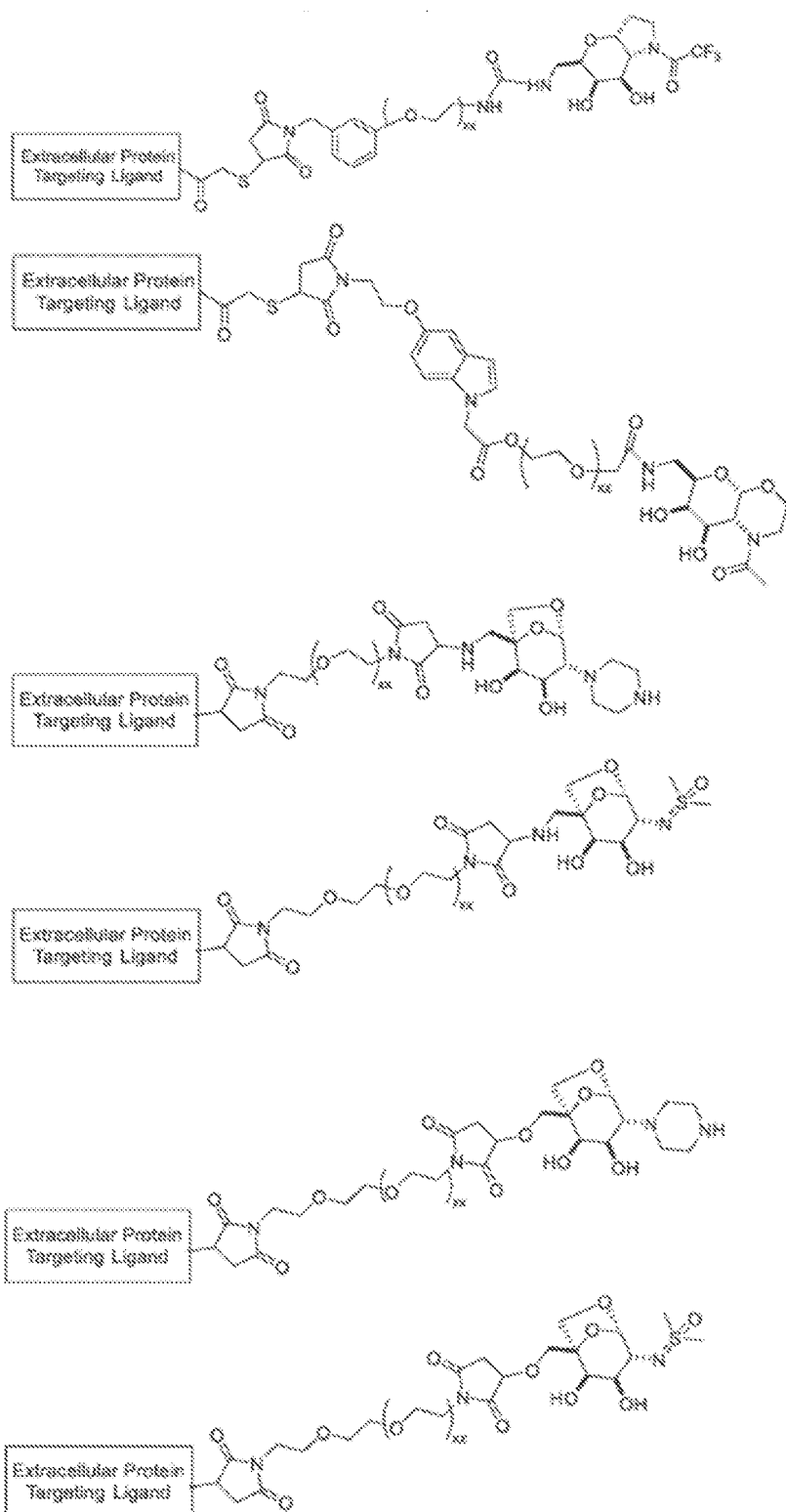


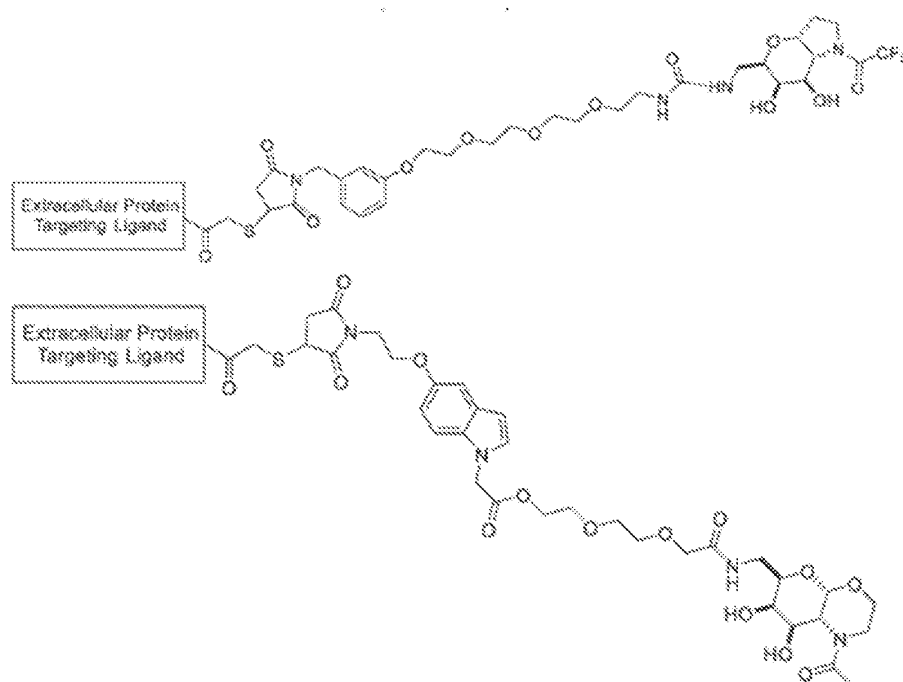


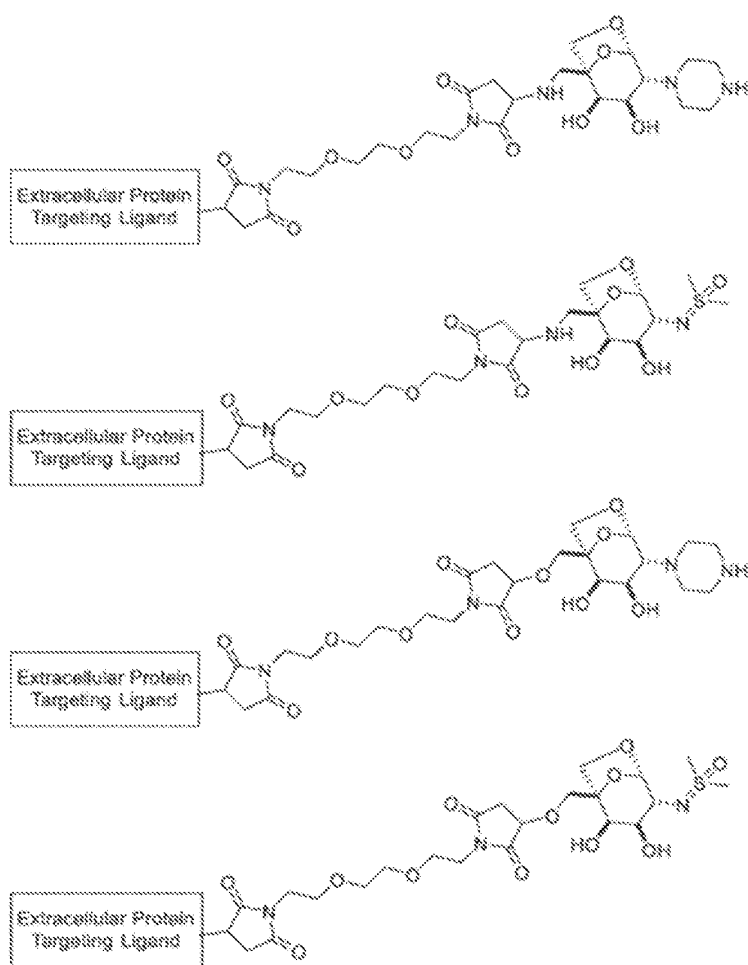


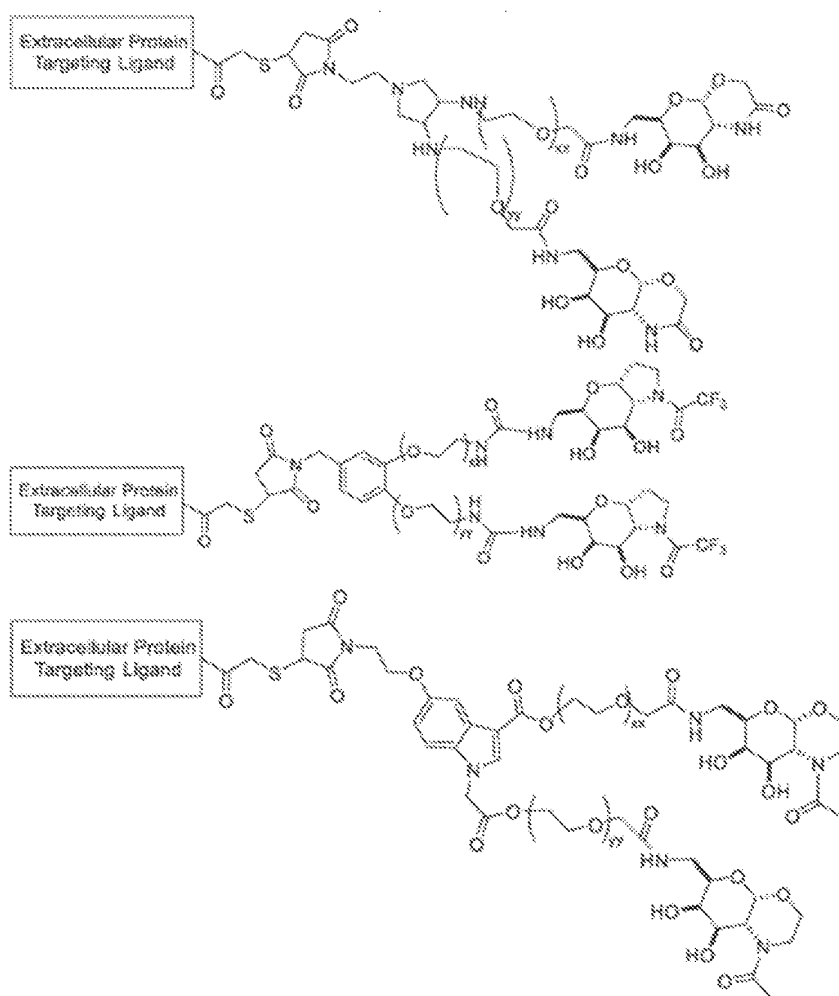


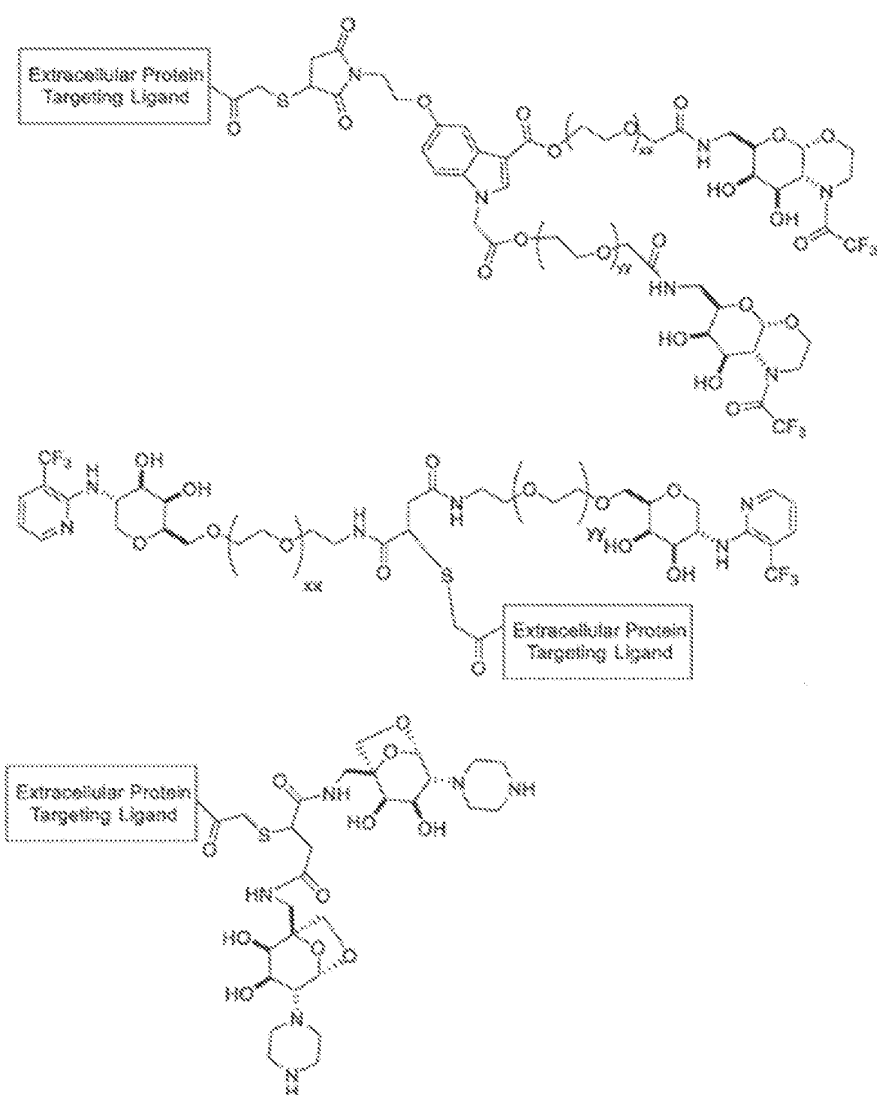


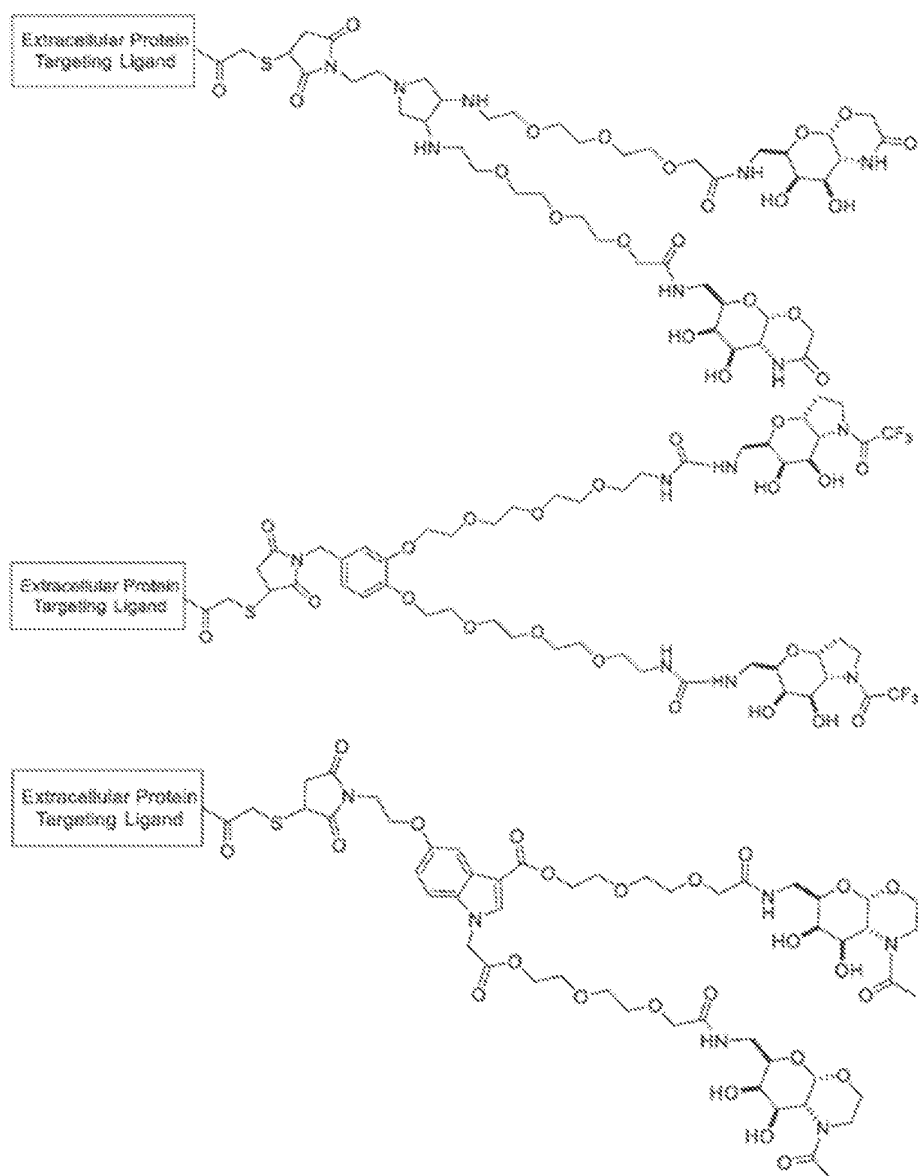


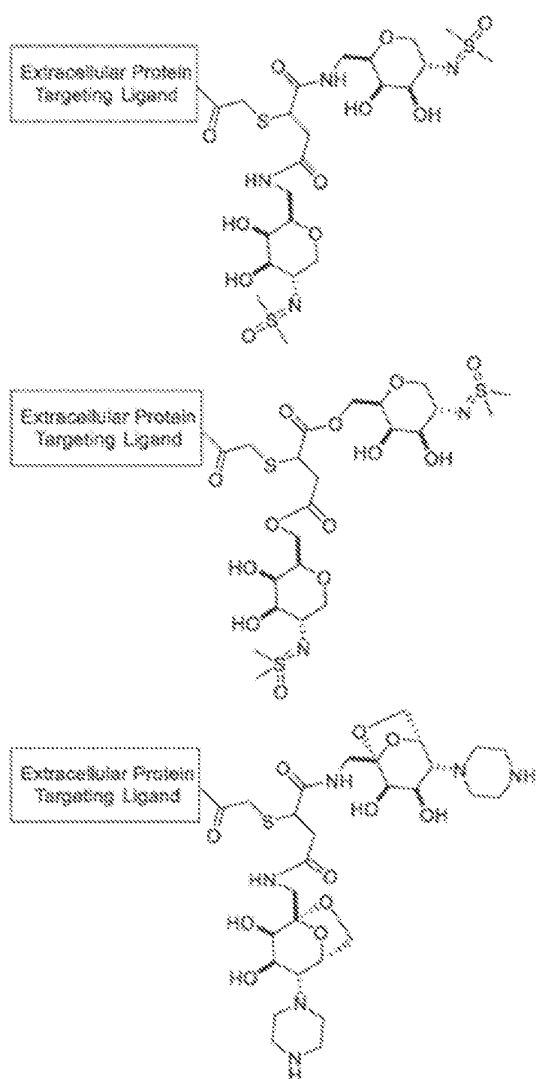


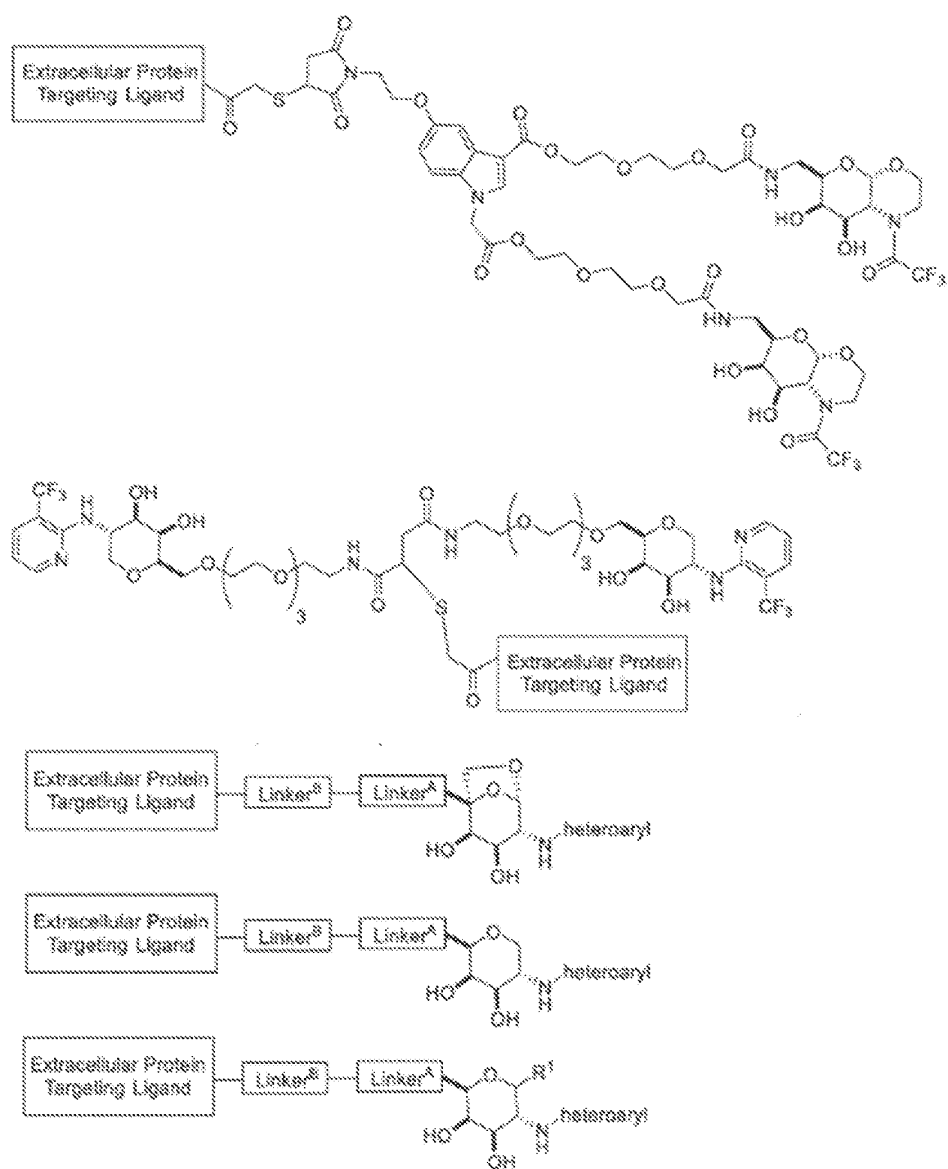


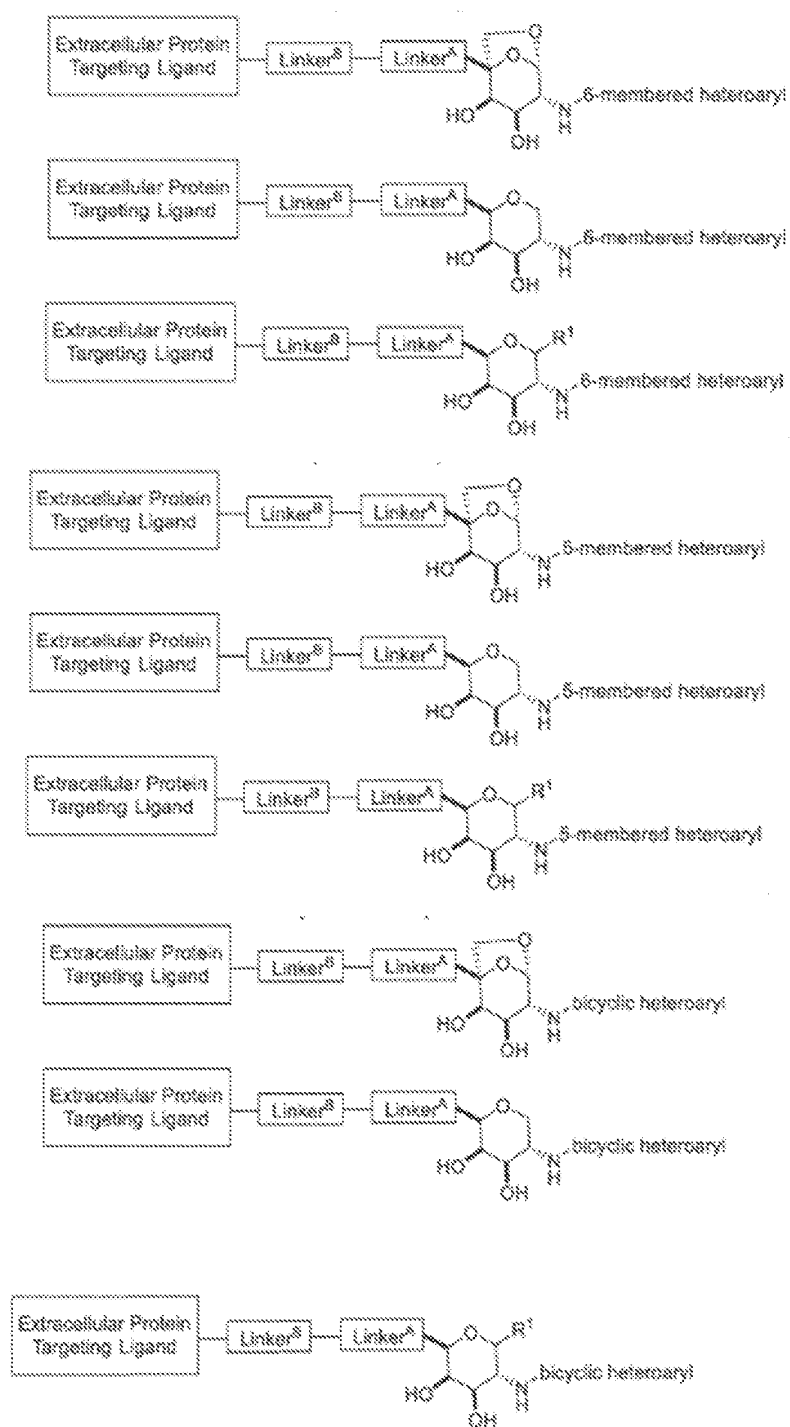


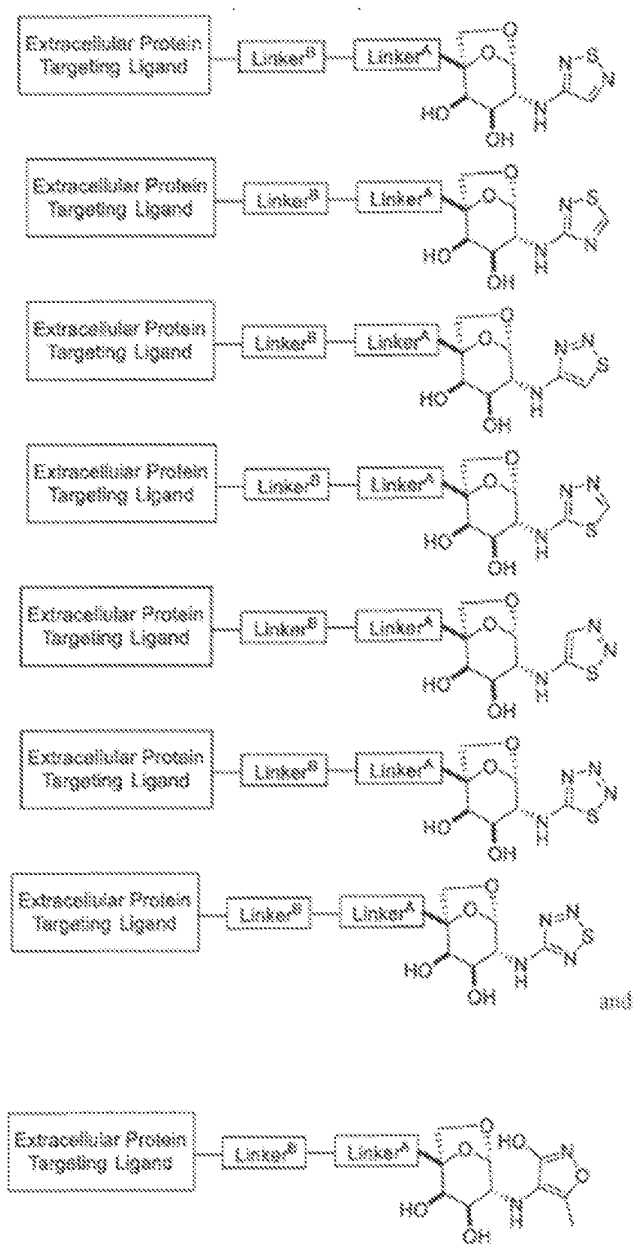


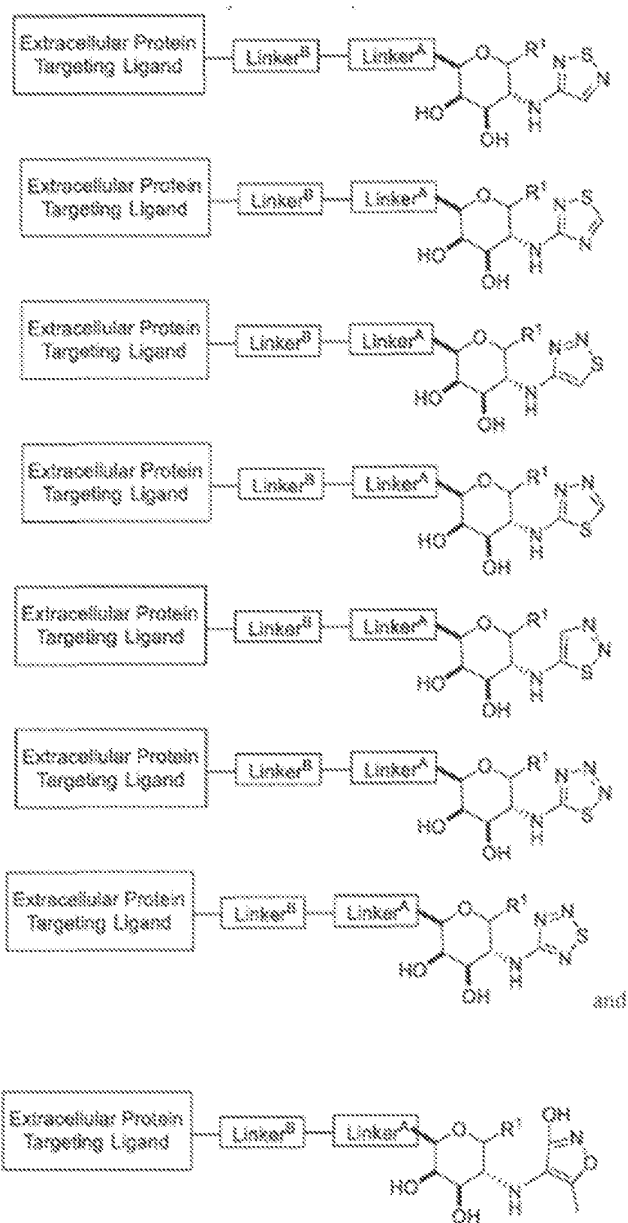


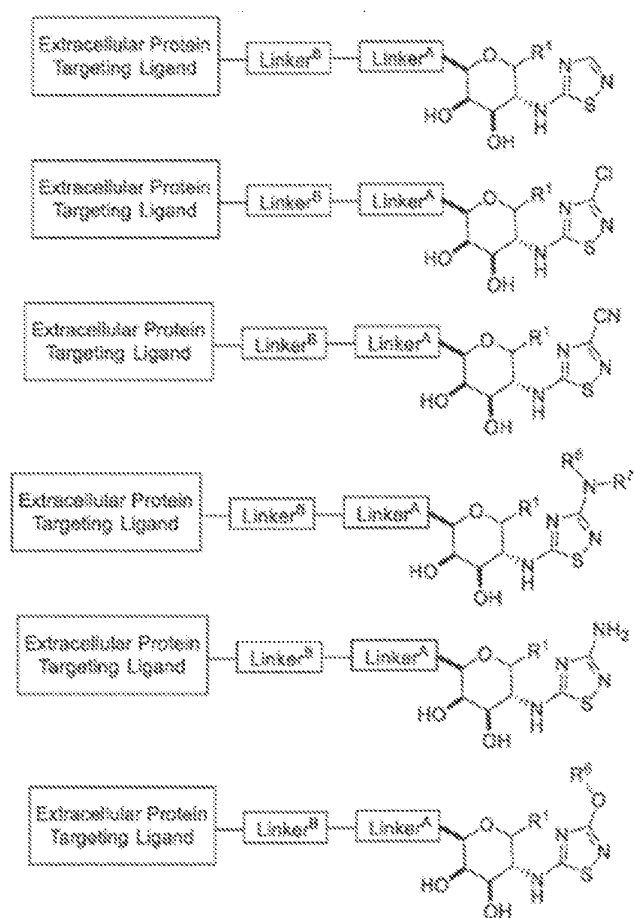




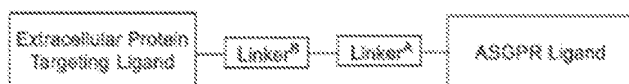


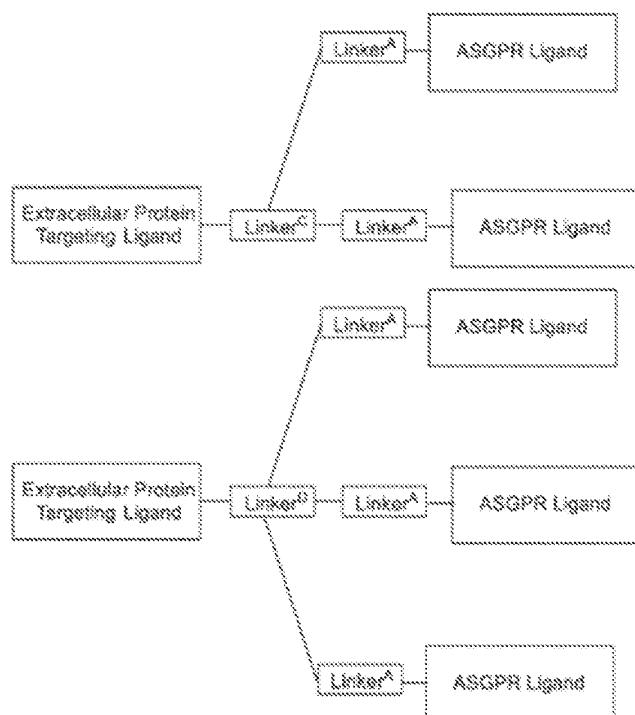






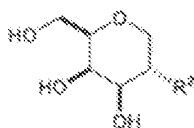
In certain embodiments, the compound of Formula II has one of the following structures:



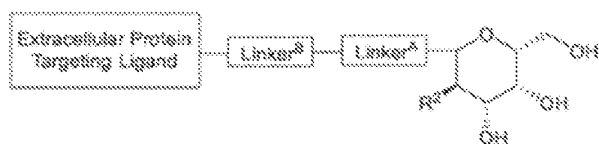
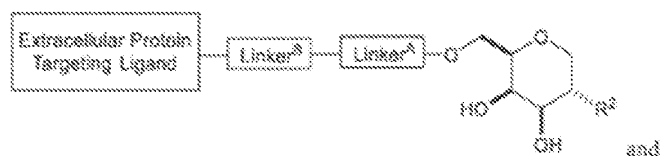


In various embodiments, the ASGPR ligand is linked at either the C¹ or C⁵ (R¹ or R⁵) position to form a degrading compound. In various embodiments, the ASGPR ligand is linked at C⁶ position to form a degrading compound. For example, when the ASGPR ligand

5 is



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



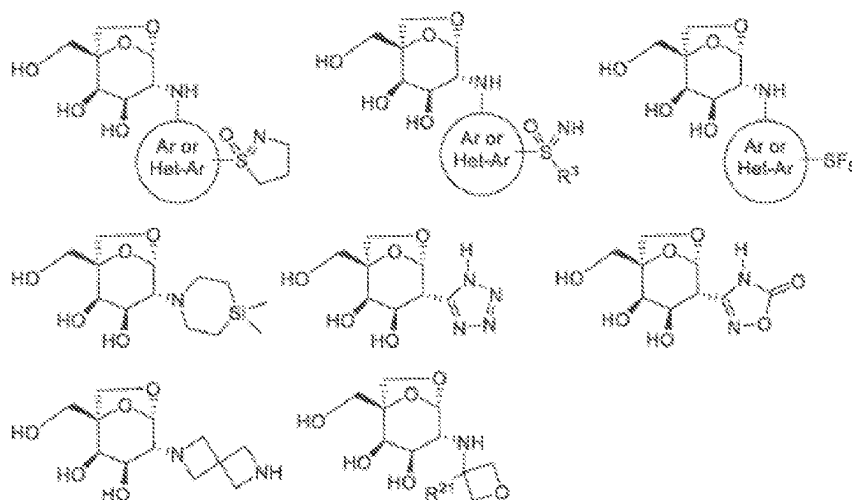
or the bi- or tri- substituted

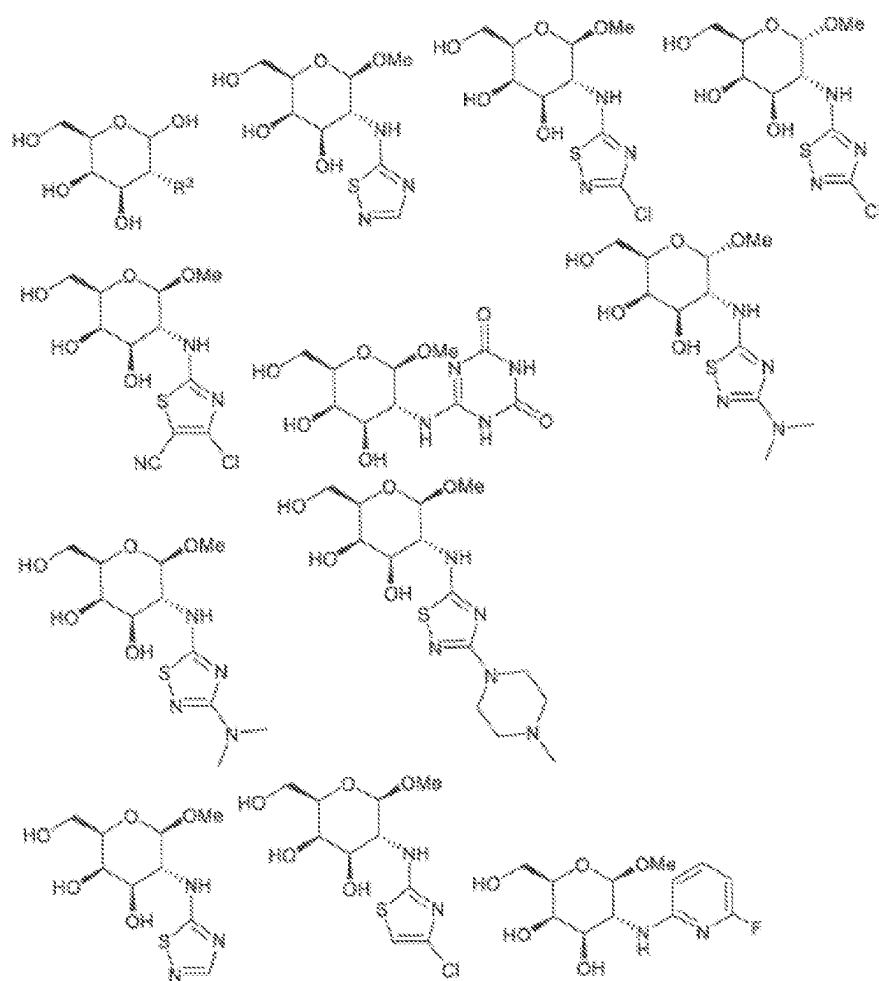
10 versions thereof or pharmaceutically acceptable salts thereof, where the bi- or tri- substitution

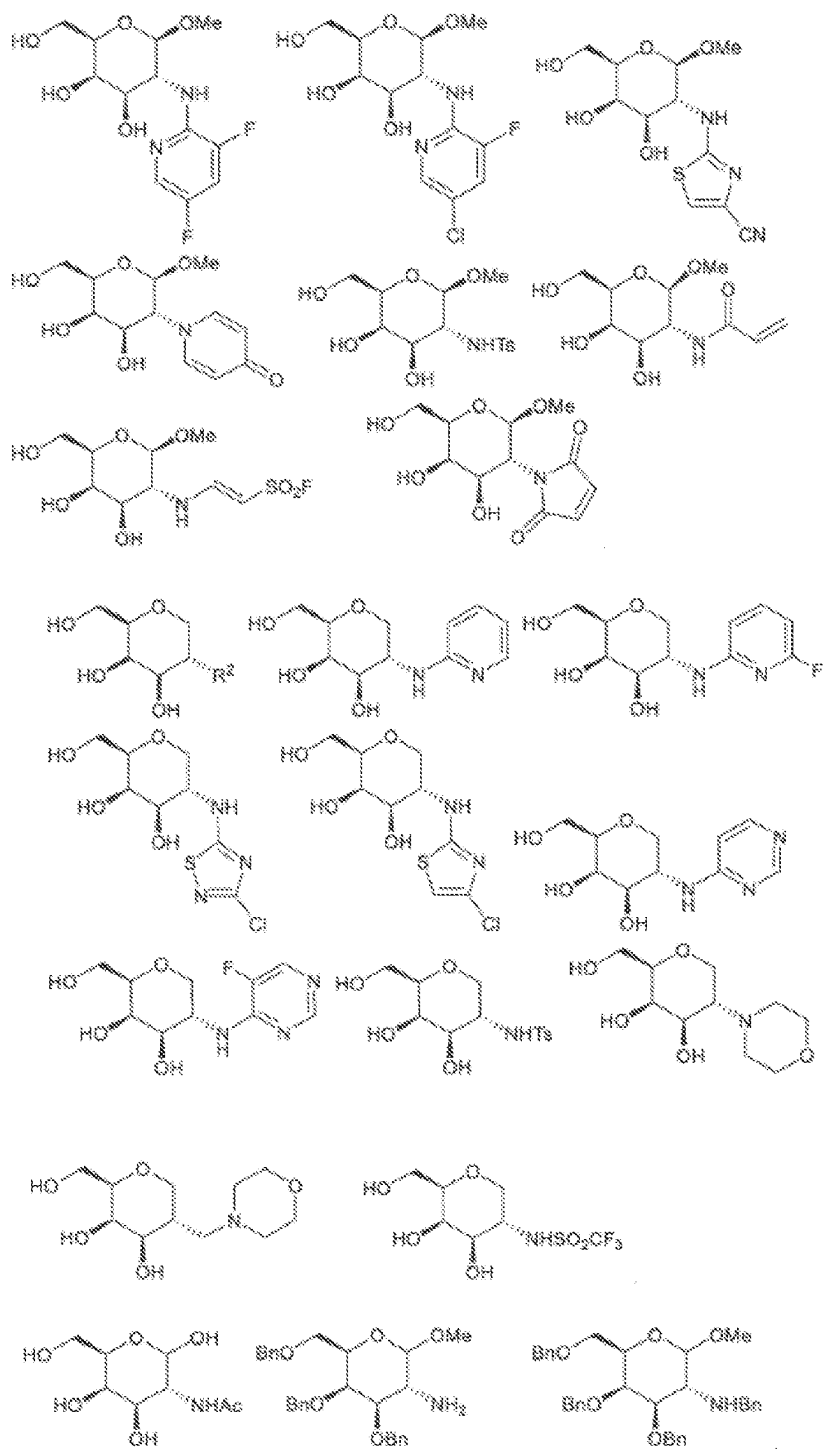
refers to the number additional galactose derivatives attached to a linker moiety.

In any of the embodiments herein where an ASGPR ligand is drawn for use in a degrader the ASGPR ligand is typically linked through to the Extracellular Protein Targeting Ligand in the C⁵ position (e.g., which can refer to the adjacent C⁶ carbon hydroxyl or other functional moiety that can be used for linking purposes). When the linker and Extracellular Protein Targeting Ligand is connected through the C¹ position, then that carbon is appropriately functionalized for linking, for example with a hydroxyl, amino, allyl, alkyne or hydroxyl-allyl group.

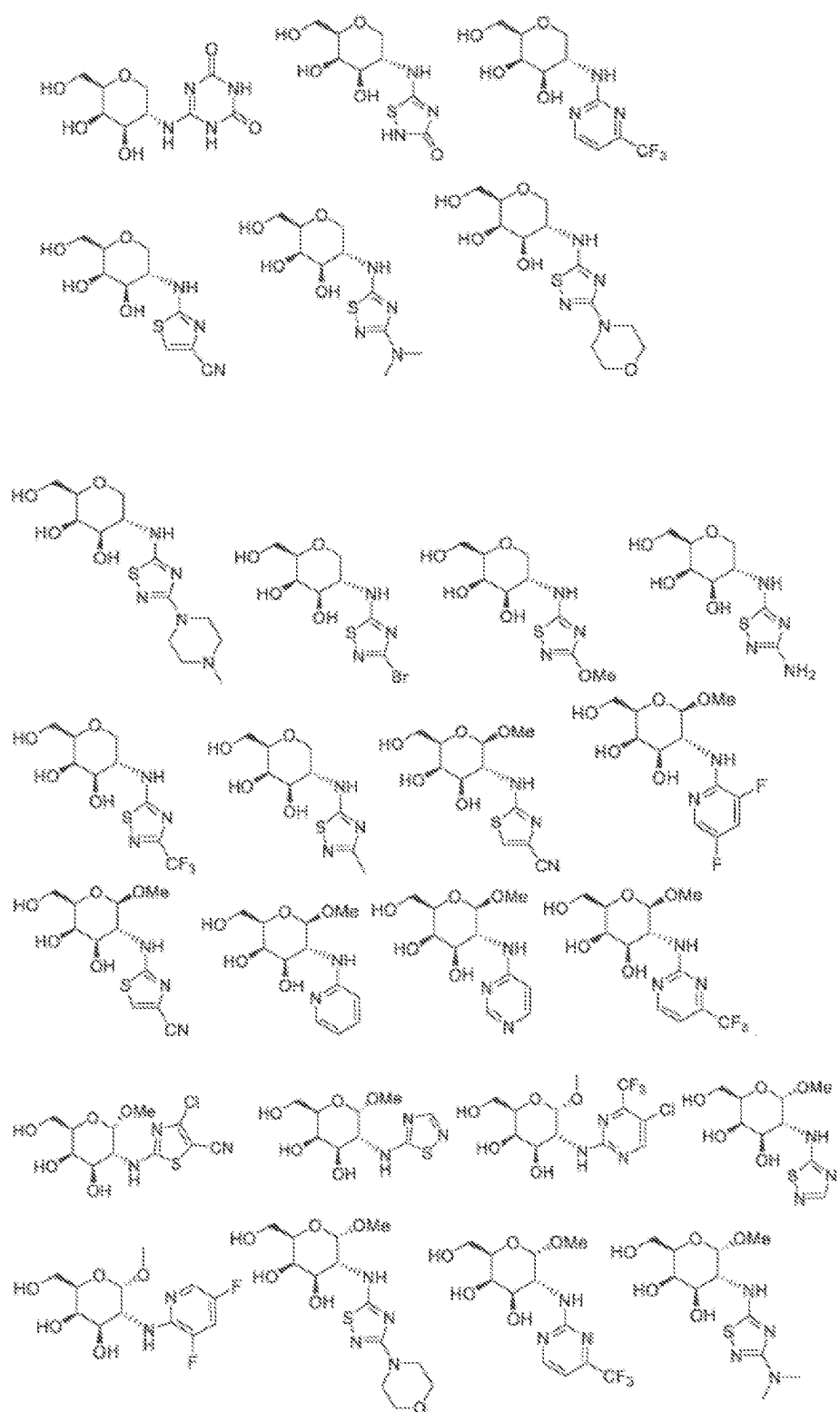
In various embodiments, the ASGPR ligand is not linked in the C³ or C⁴ position, because these positions chelate with the calcium for ASGPR binding in the liver. In certain embodiments, an ASGPR ligand useful for incorporation into a compound of Formula II is selected from:

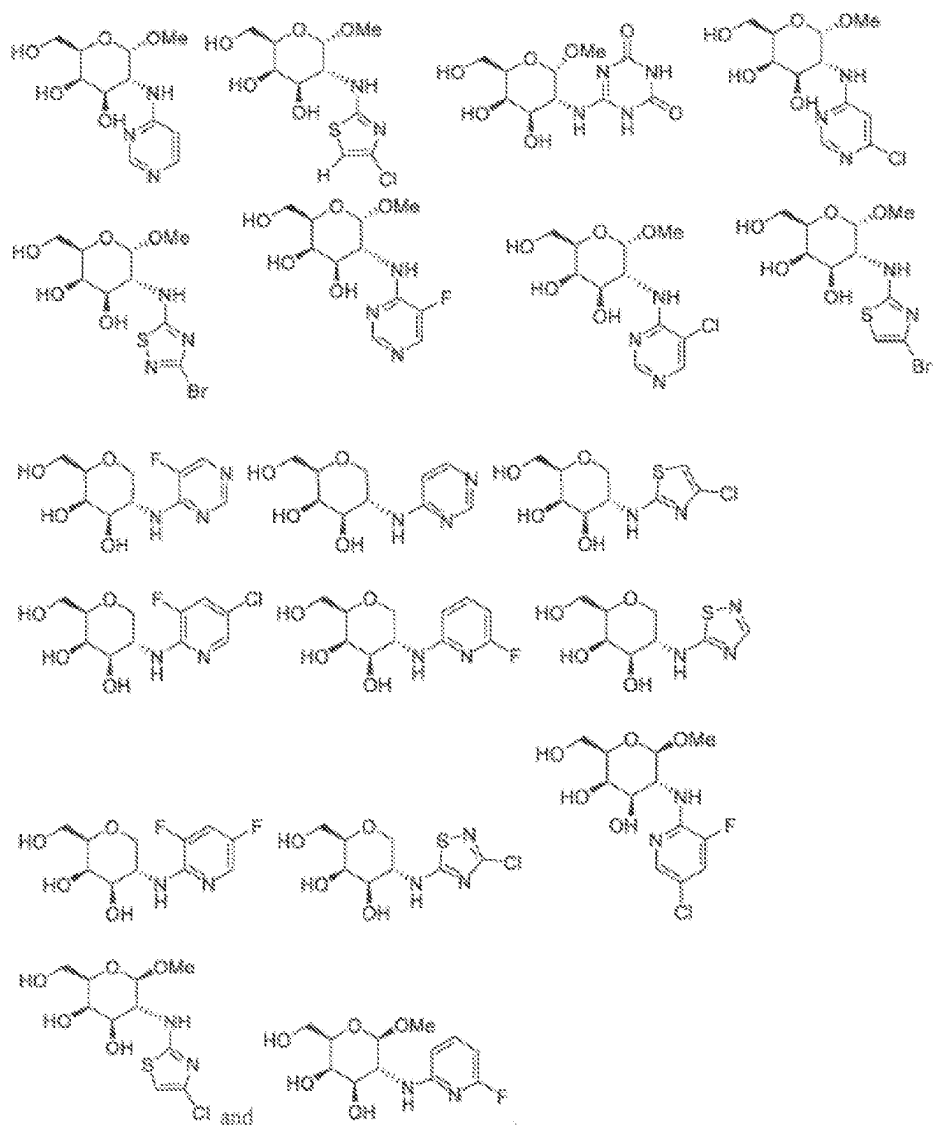


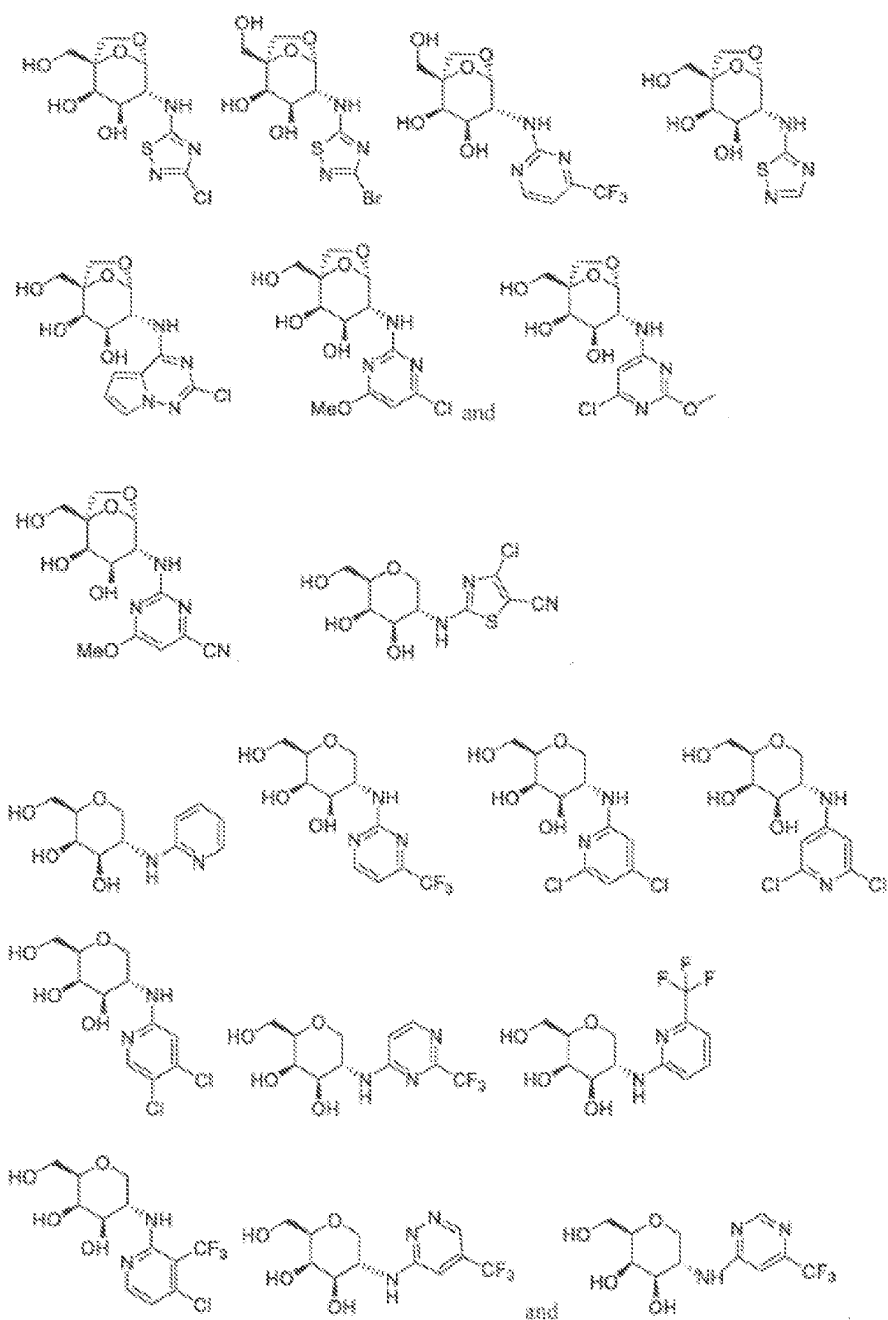


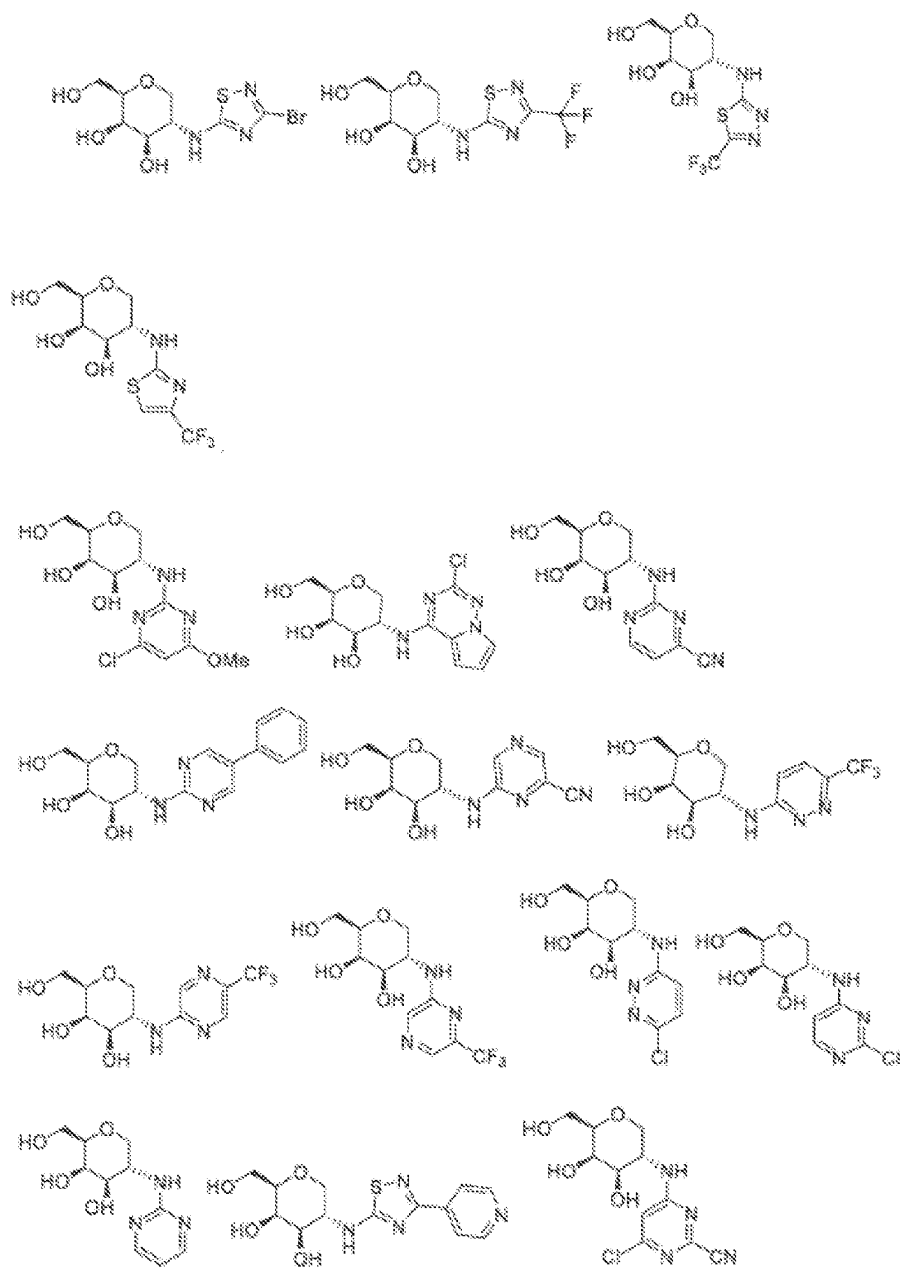


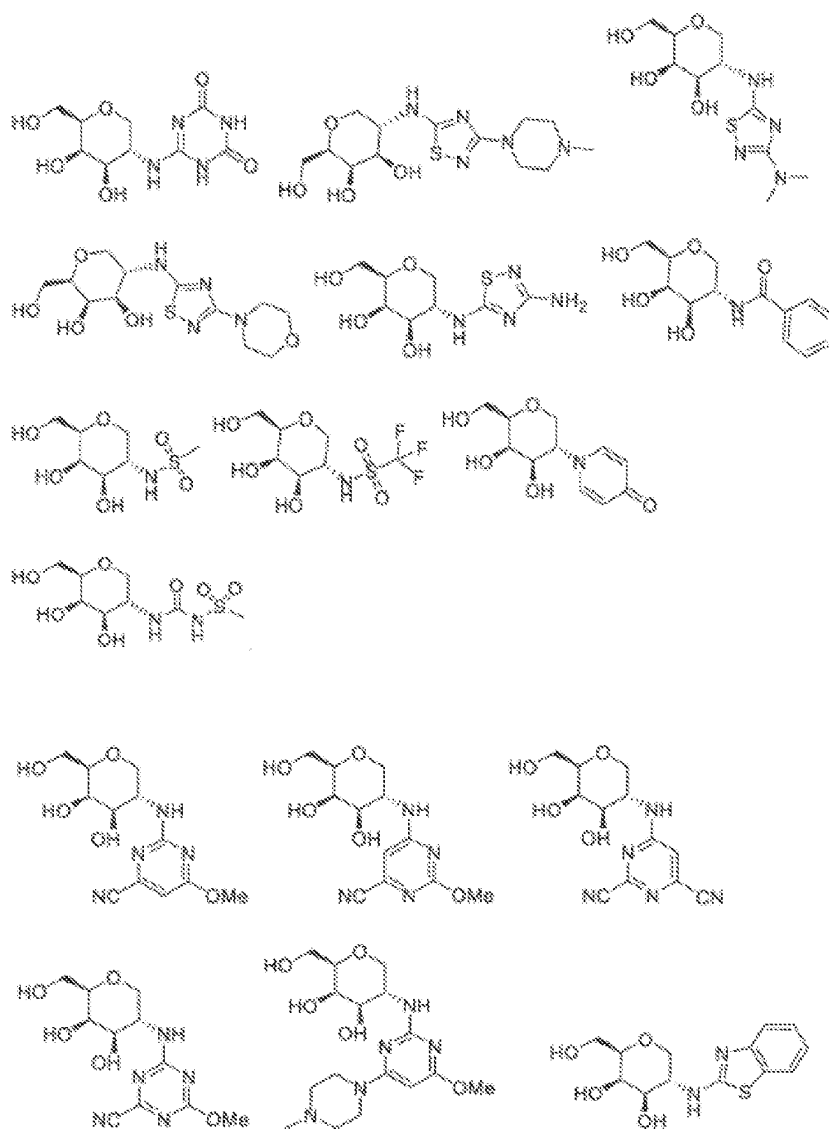


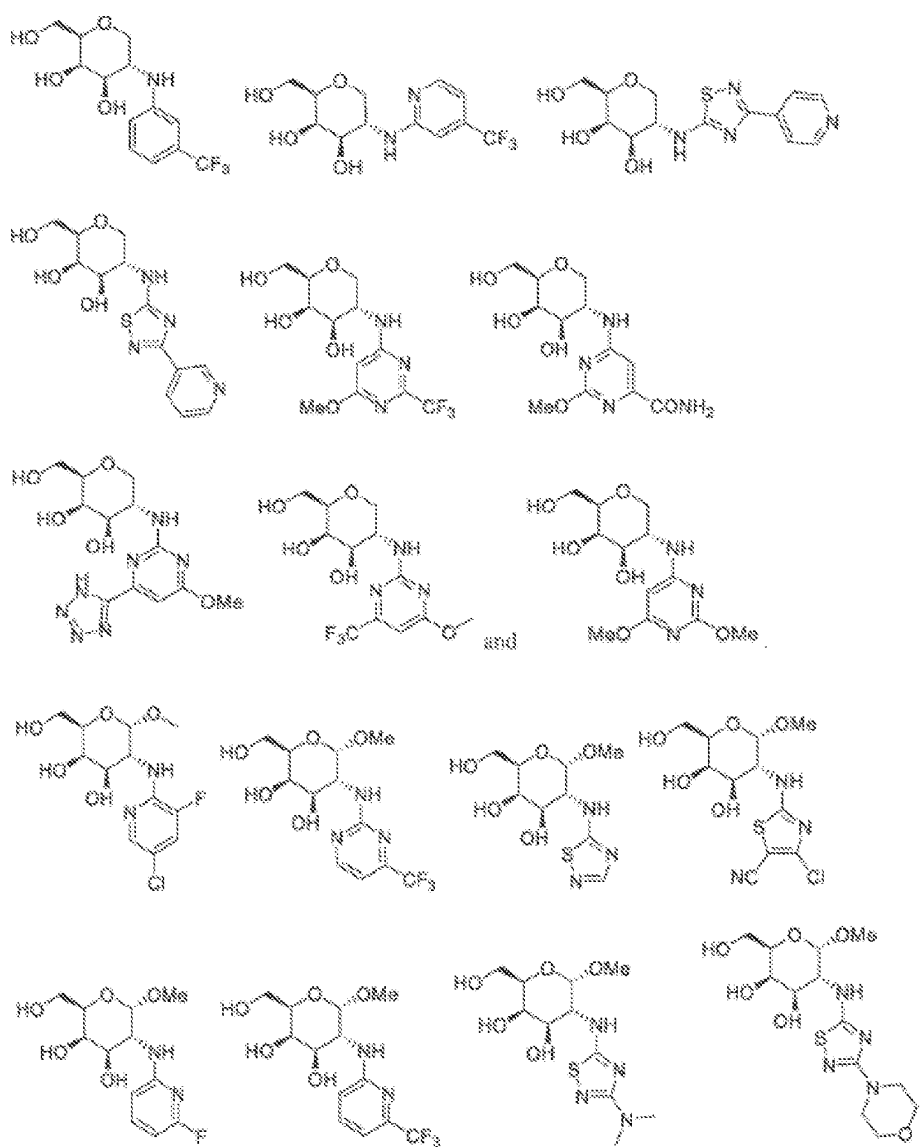


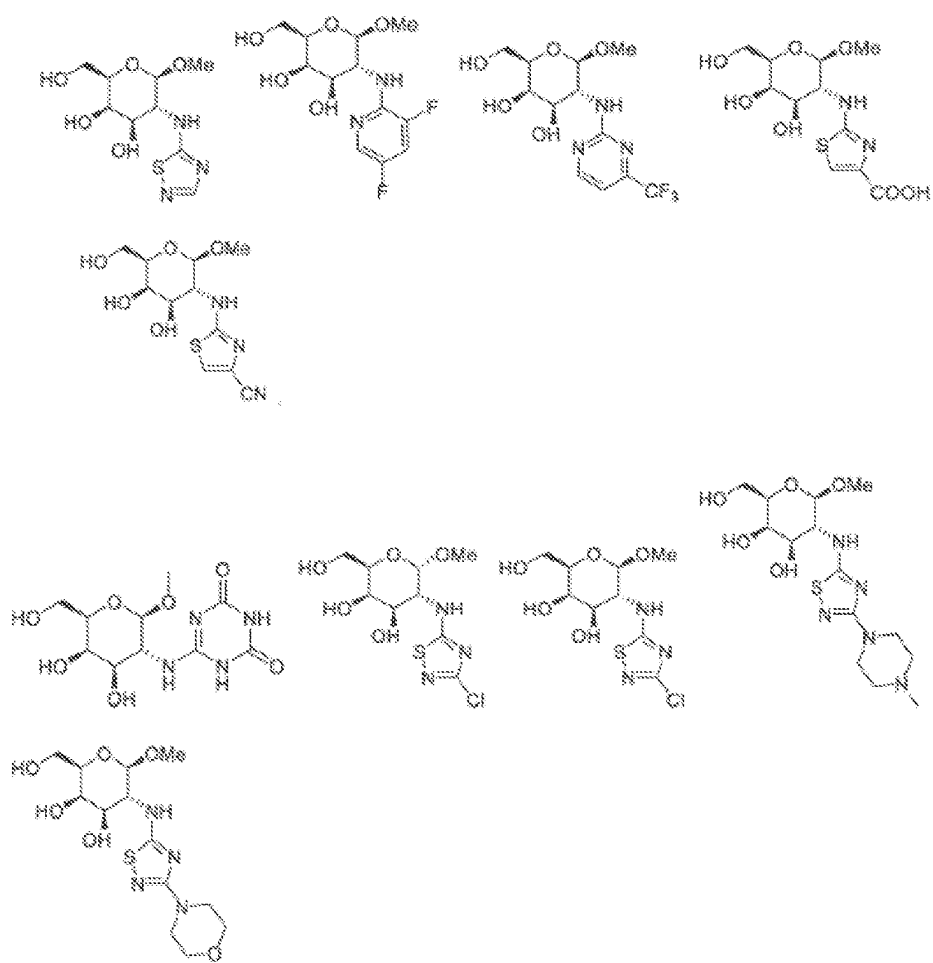




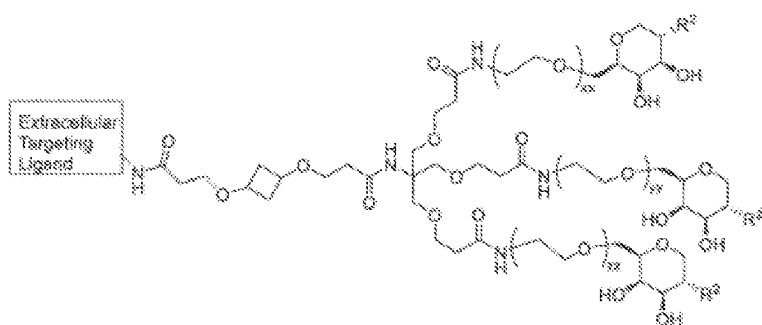


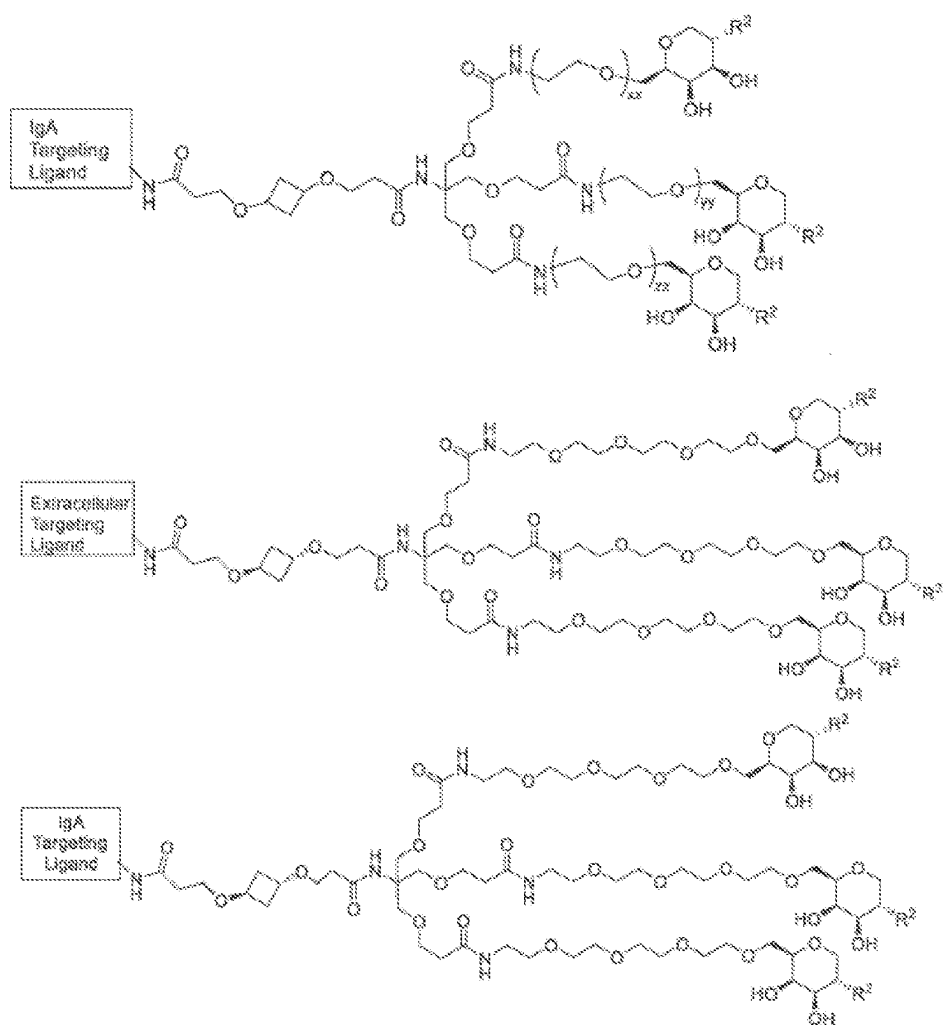


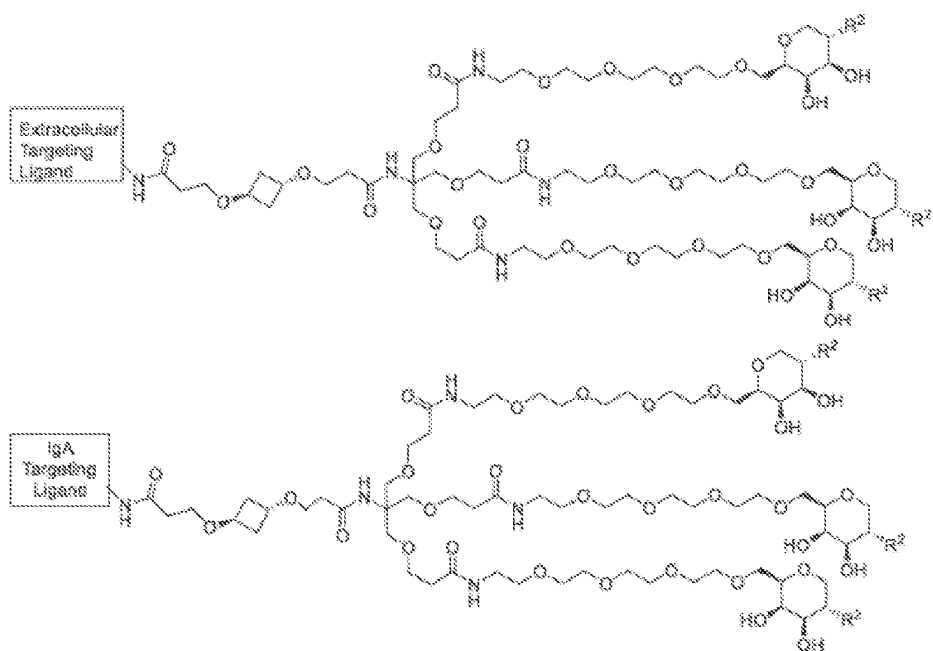


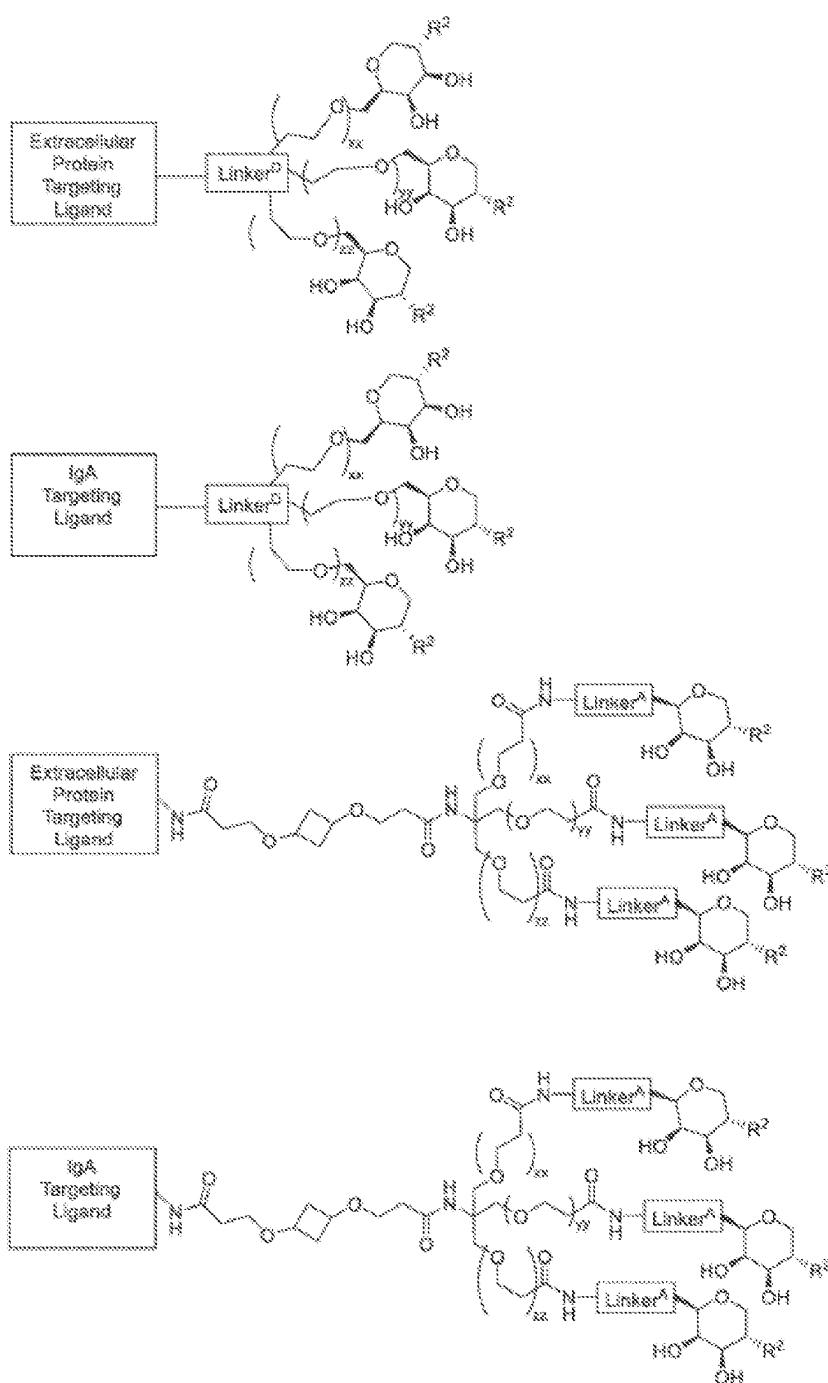


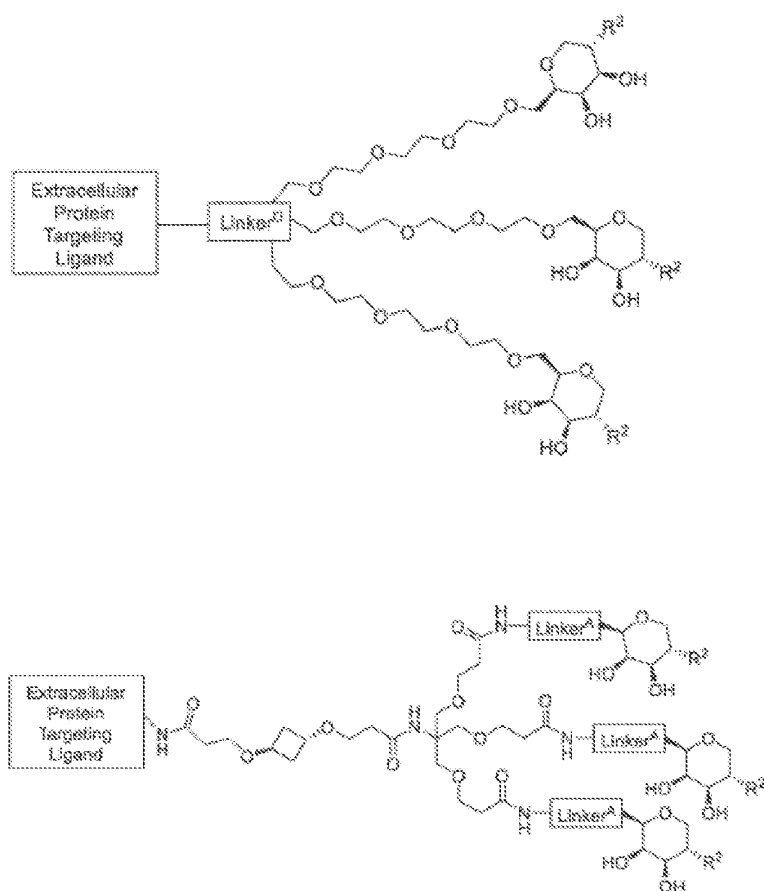
In certain embodiments, the compound of Formula II is selected from:





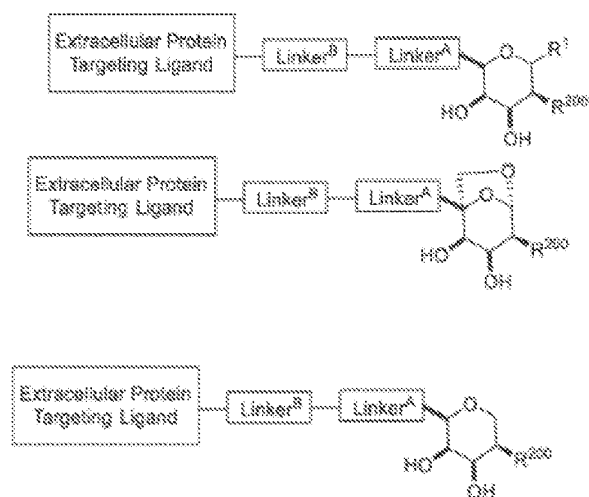


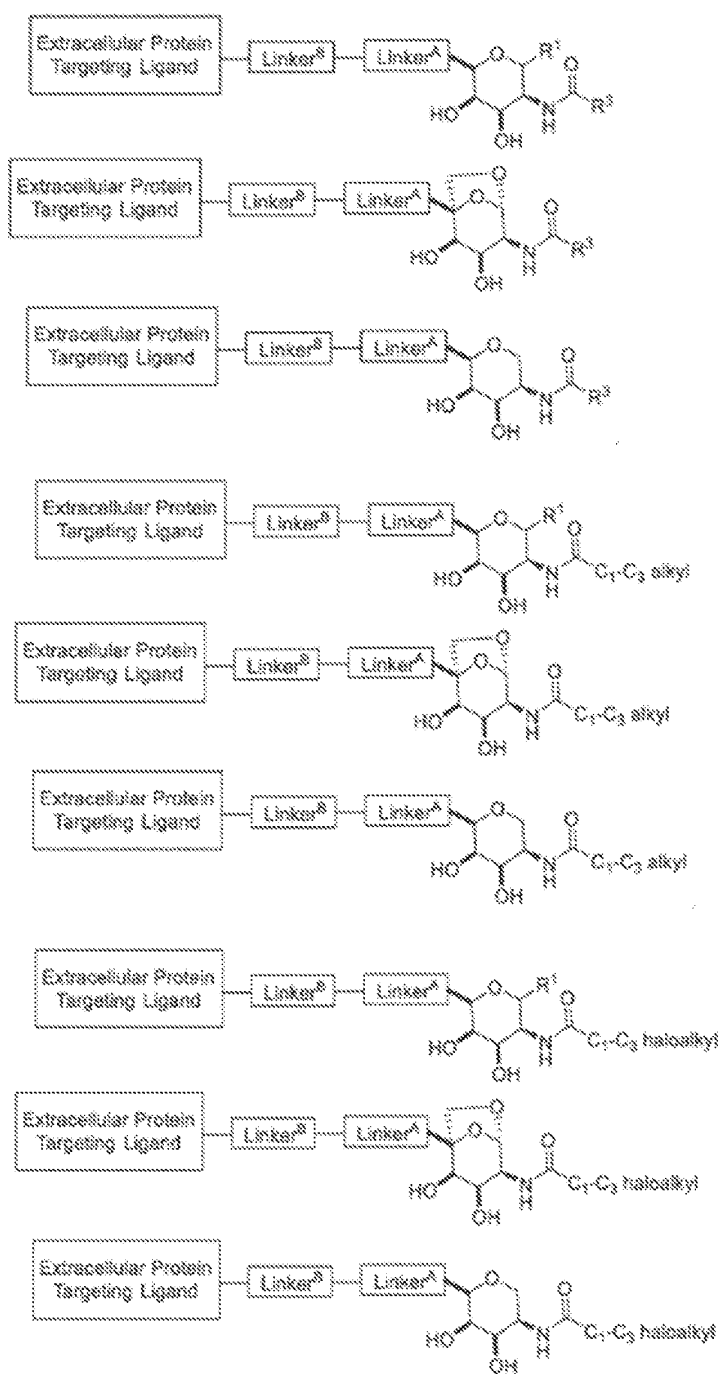


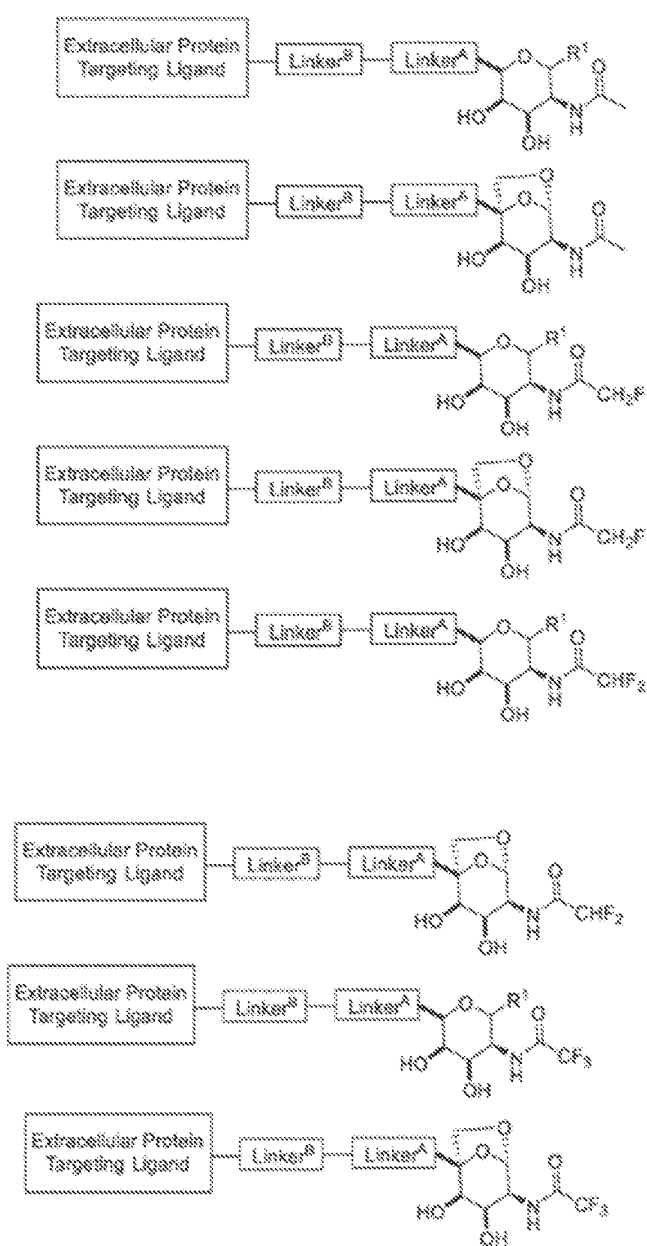


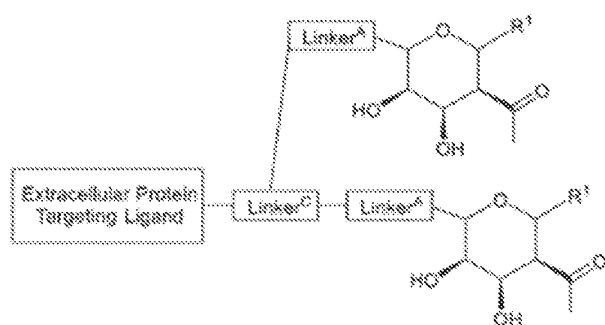
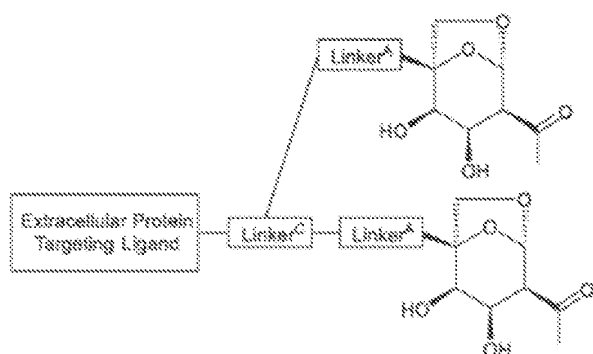
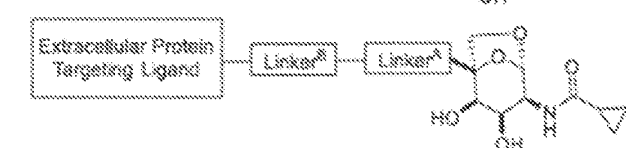
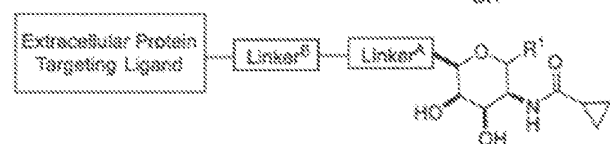
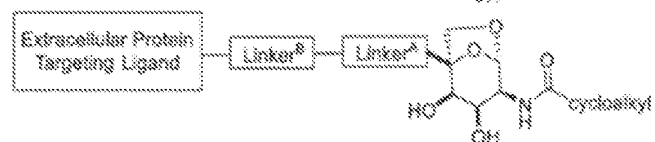
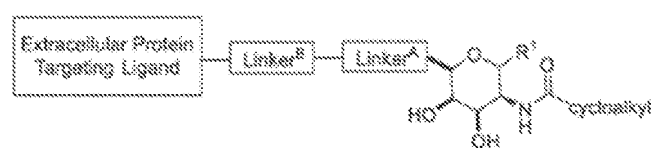
B. Talose-Based ASGPR-Binding Cellular Receptor Binding Moieties of Formula II

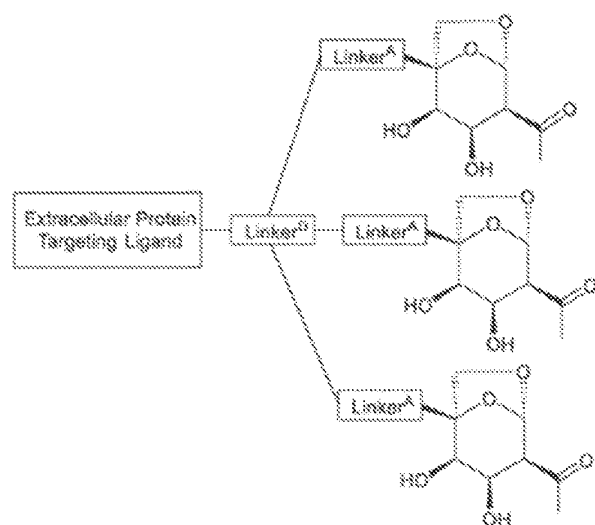
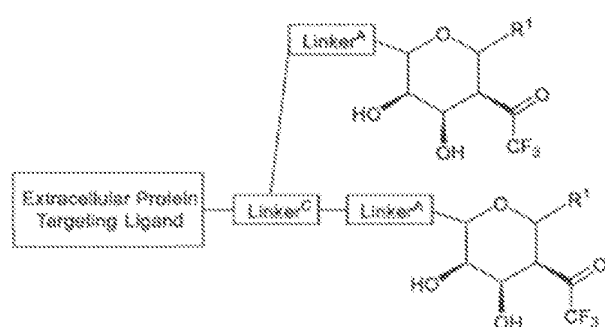
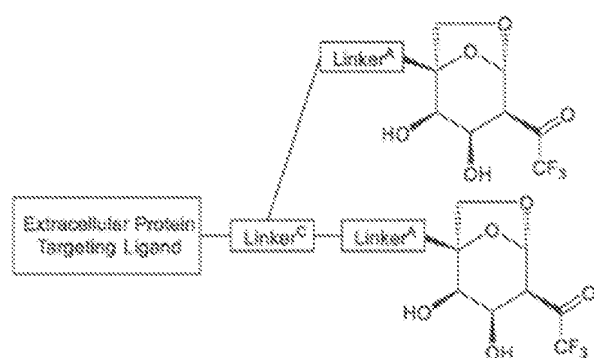
5 In certain embodiments, the compound of Formula II is selected from:

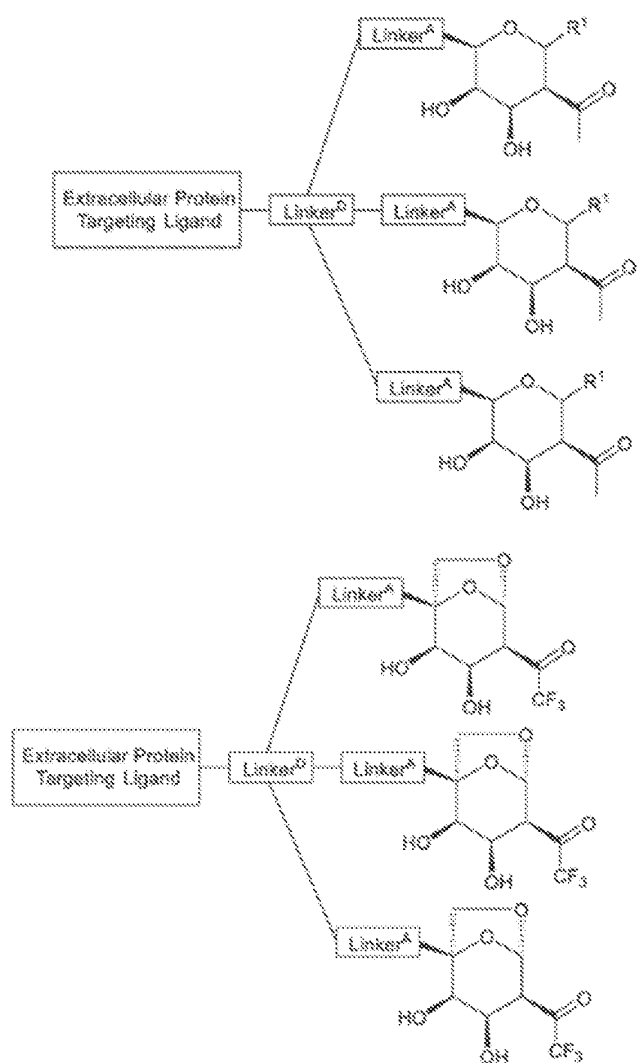


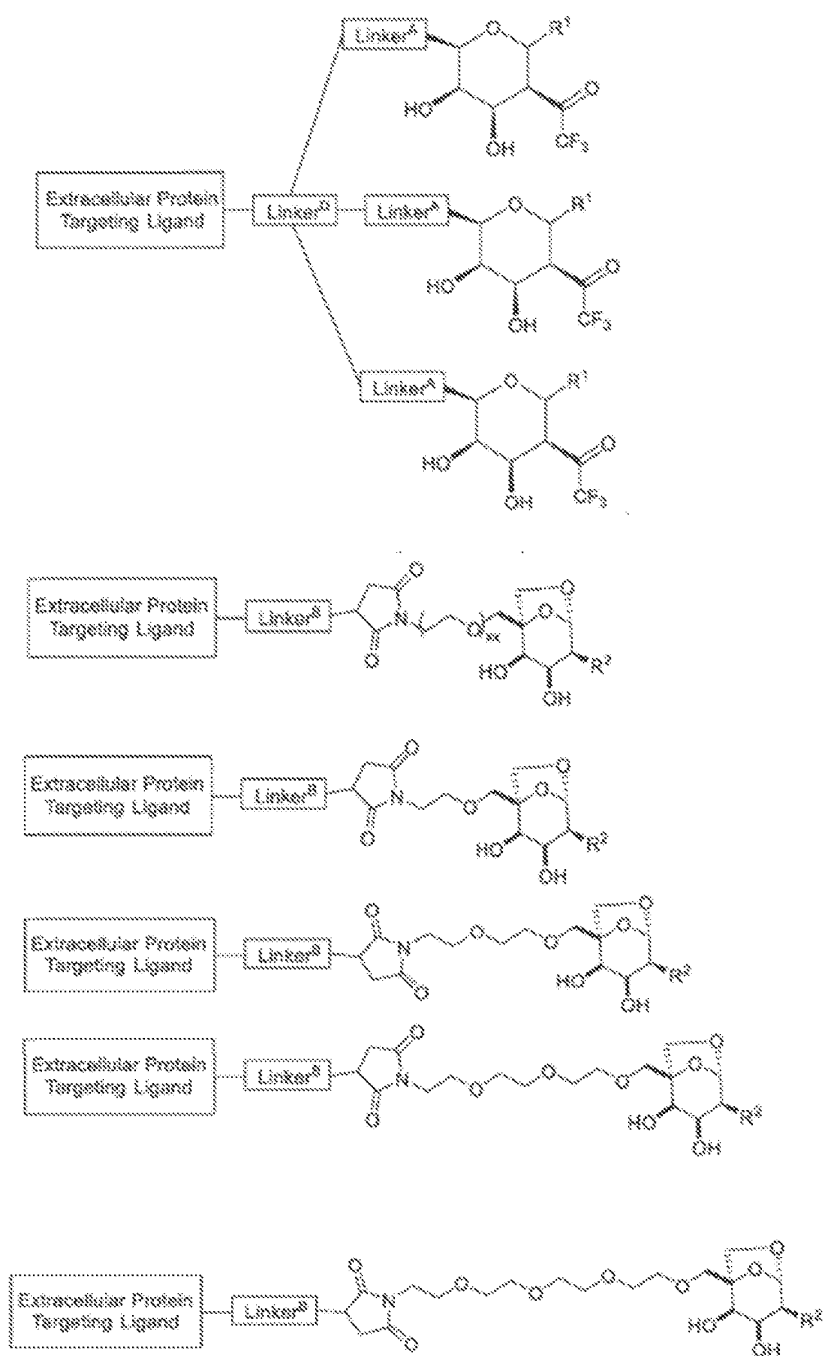


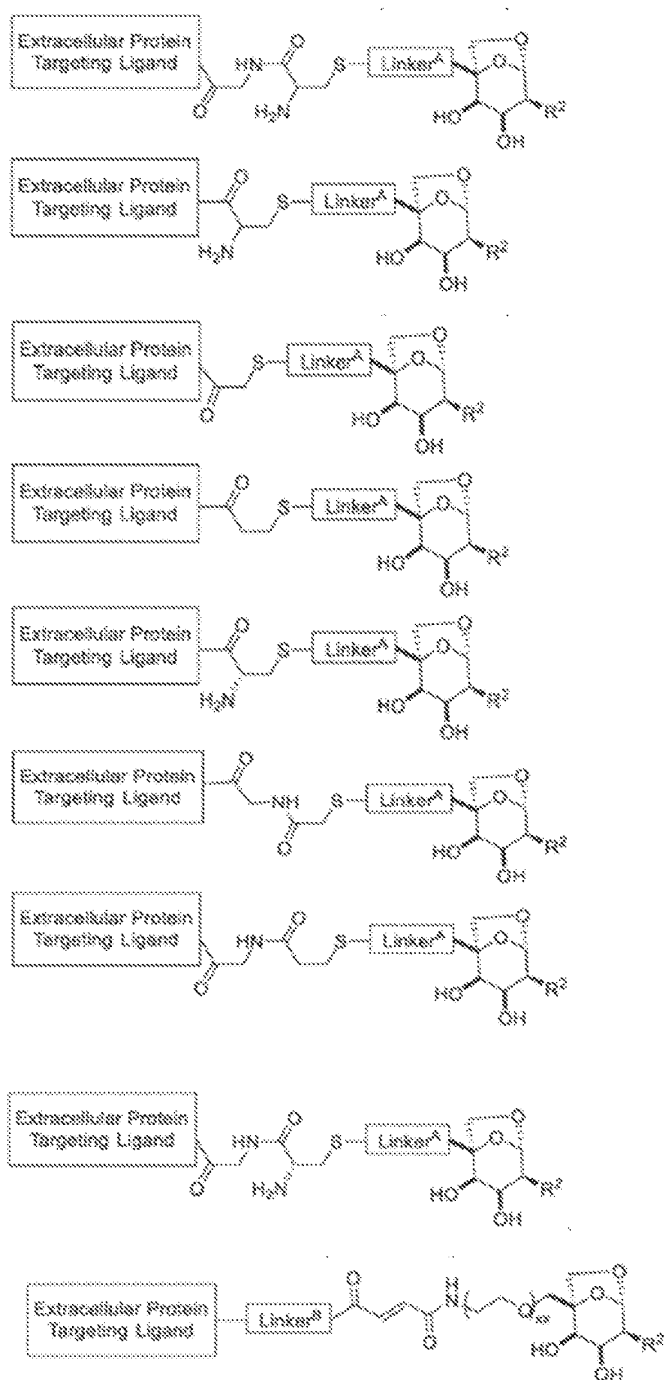


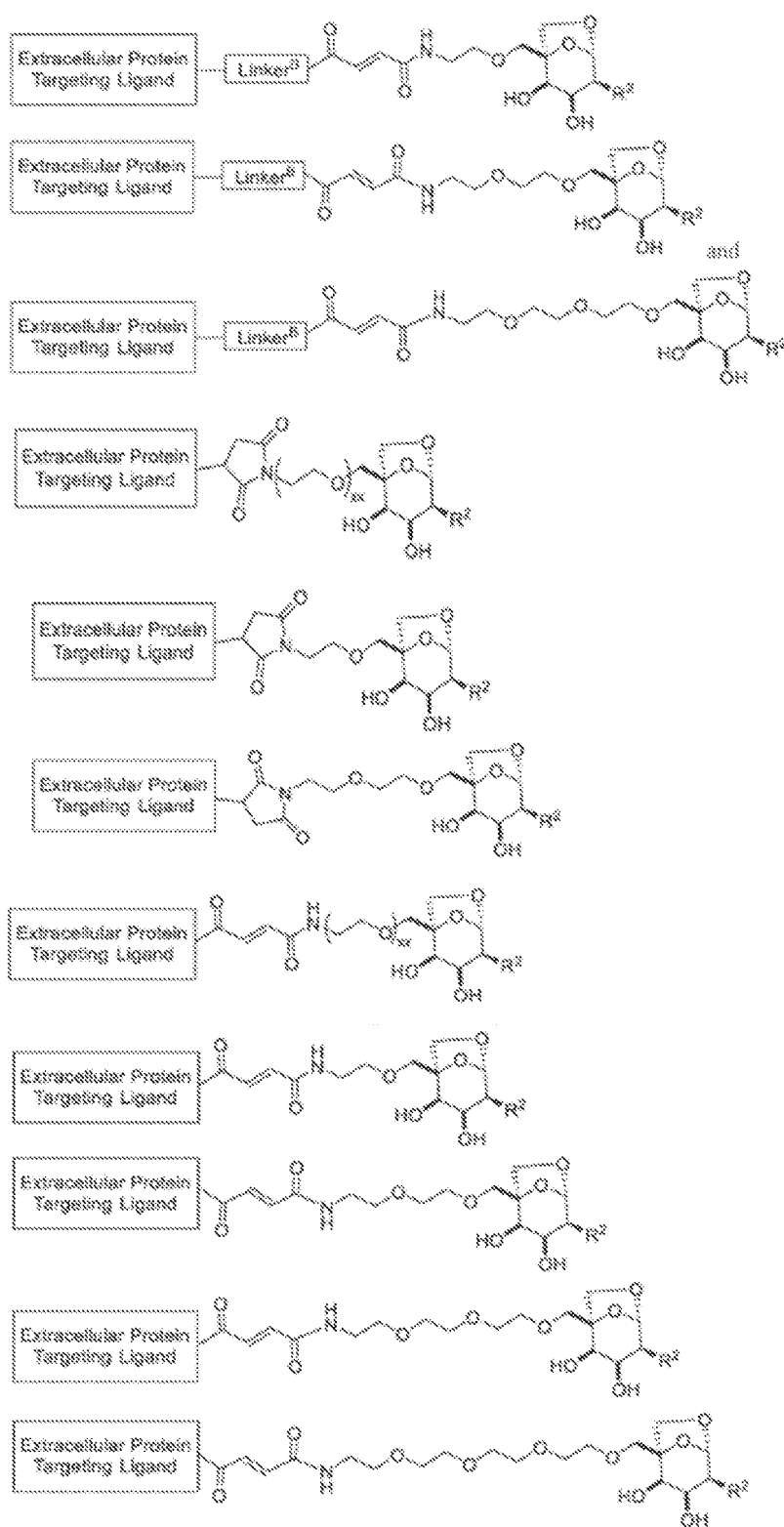


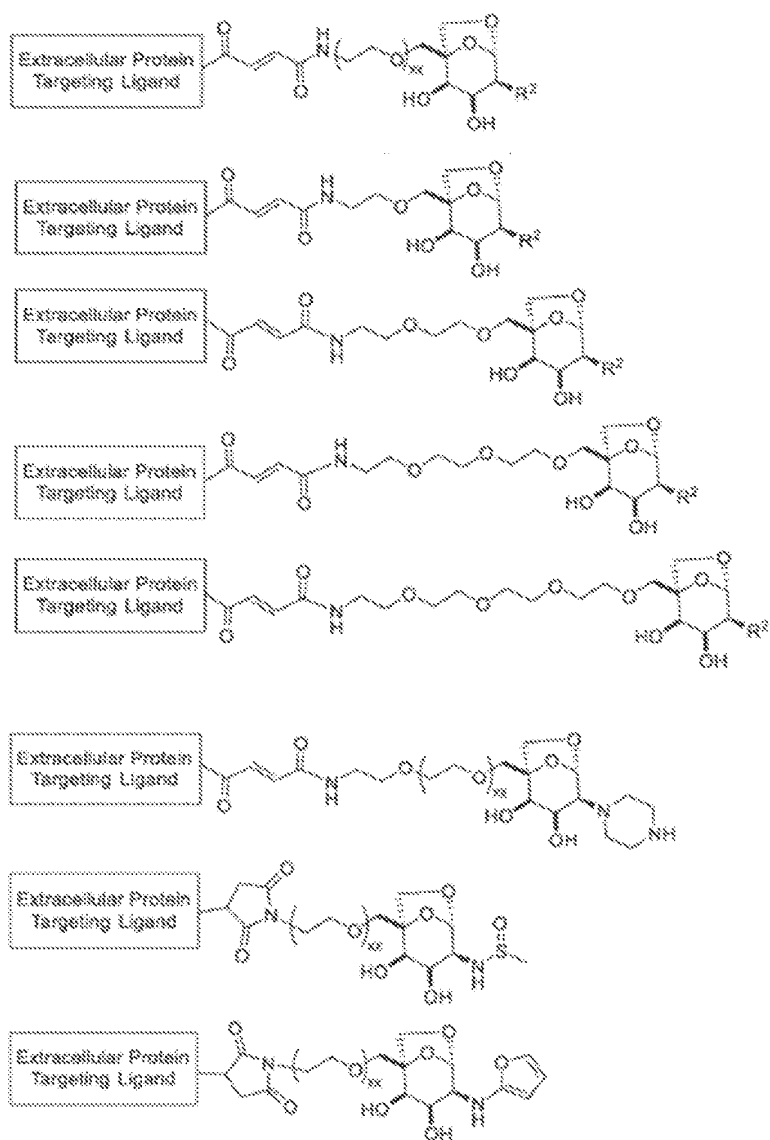


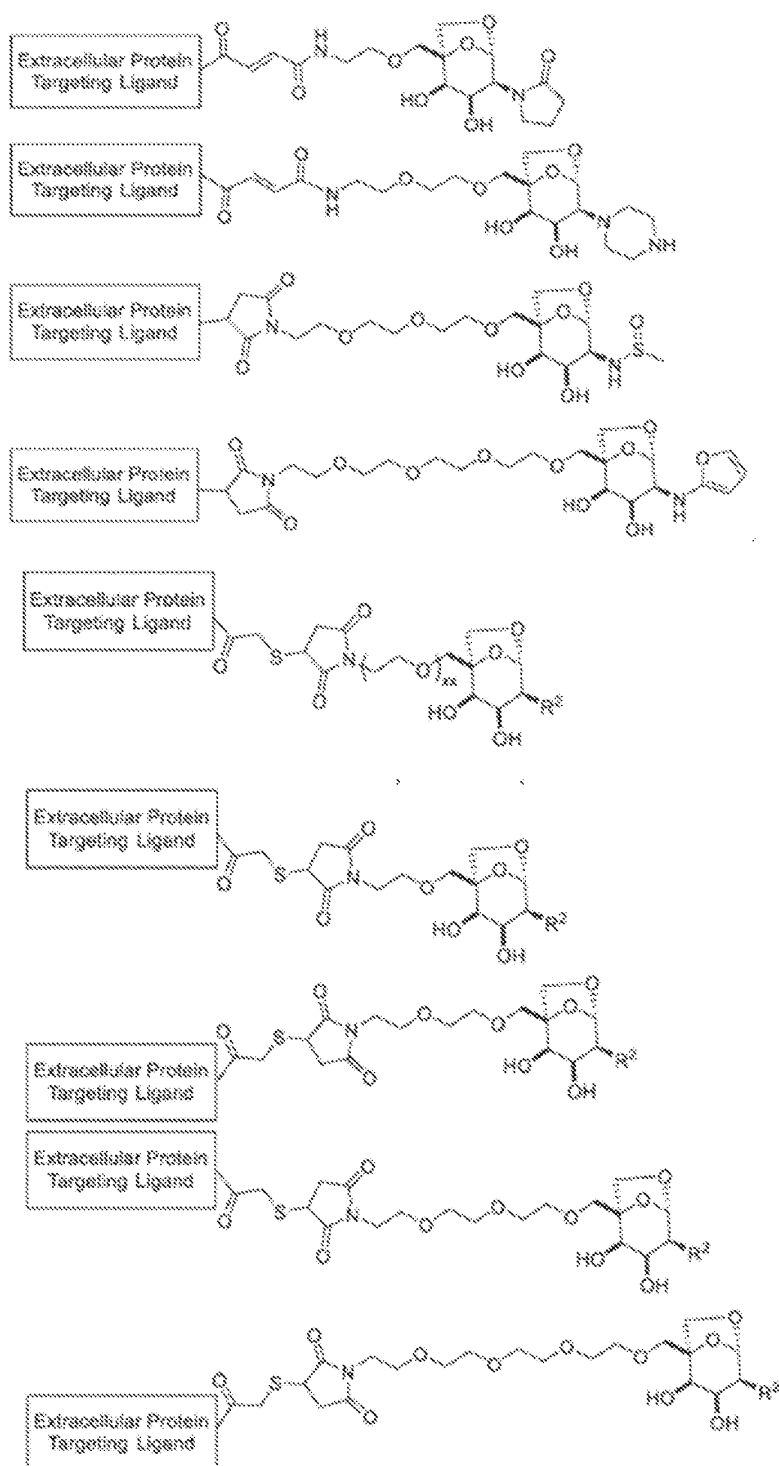


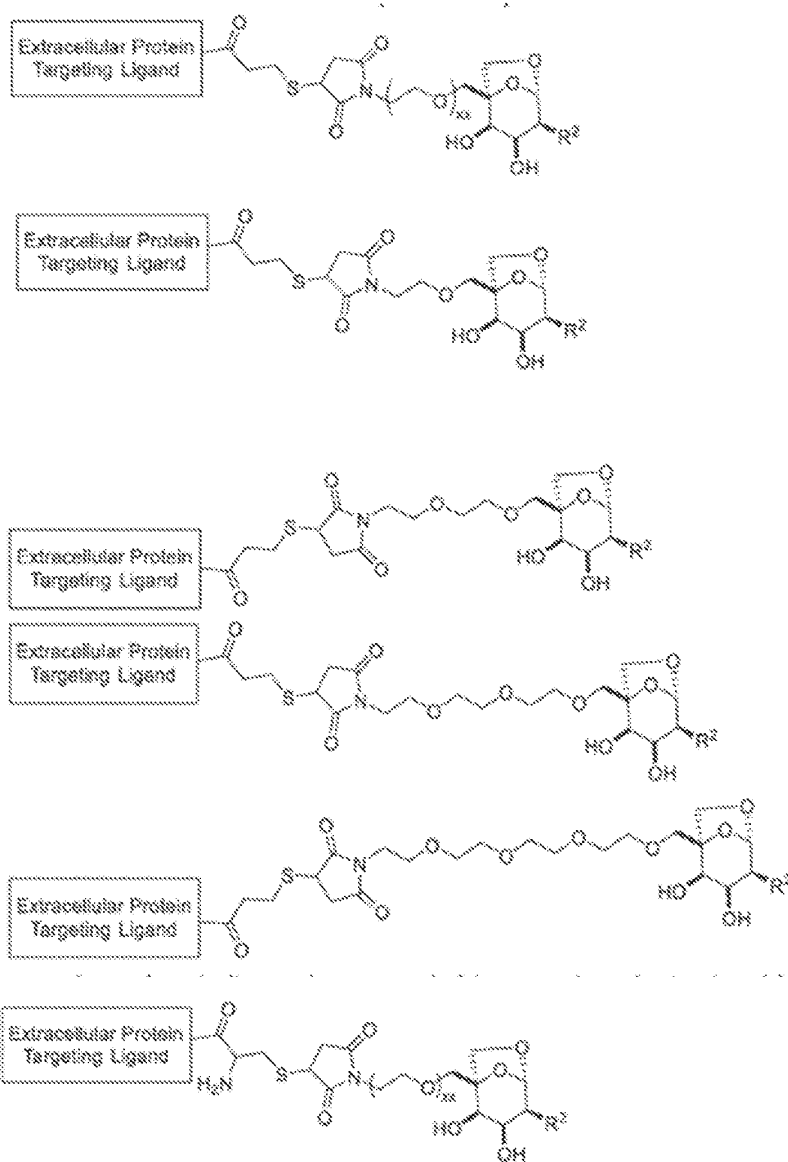


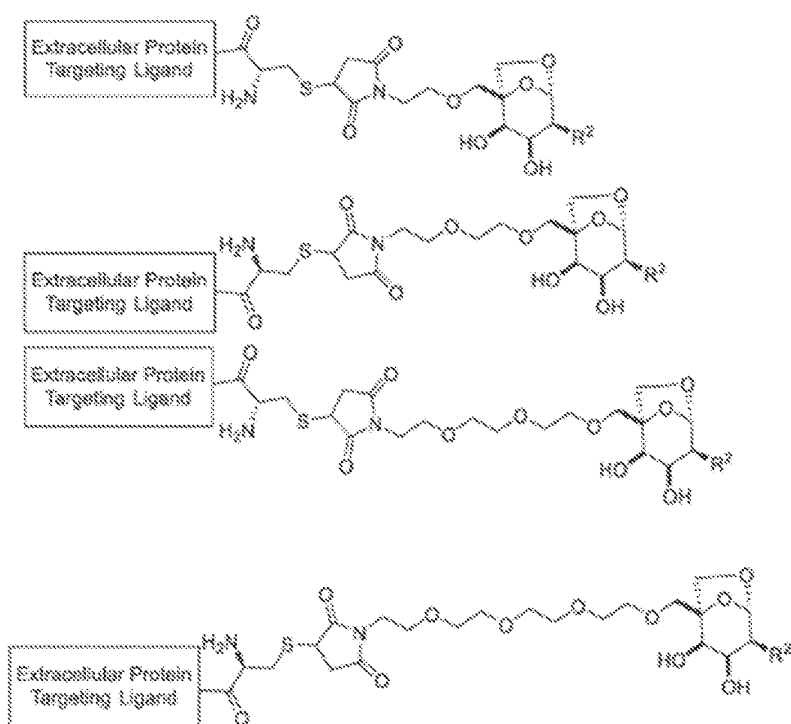


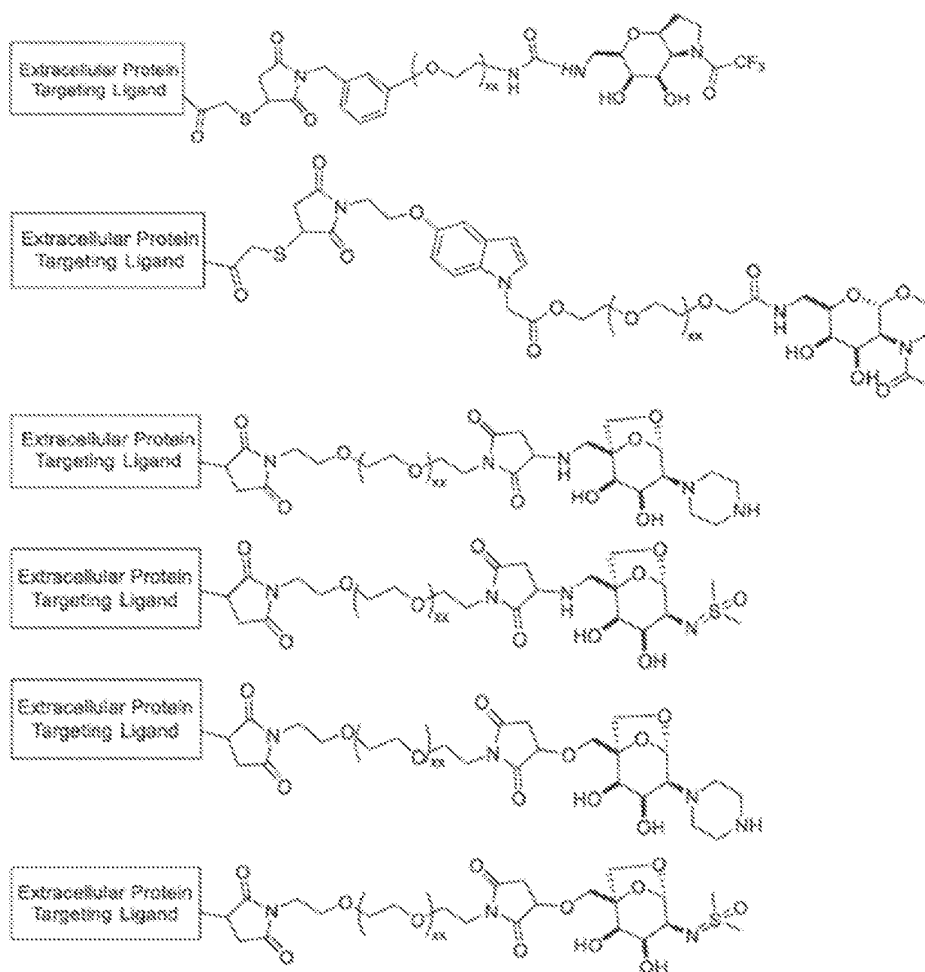


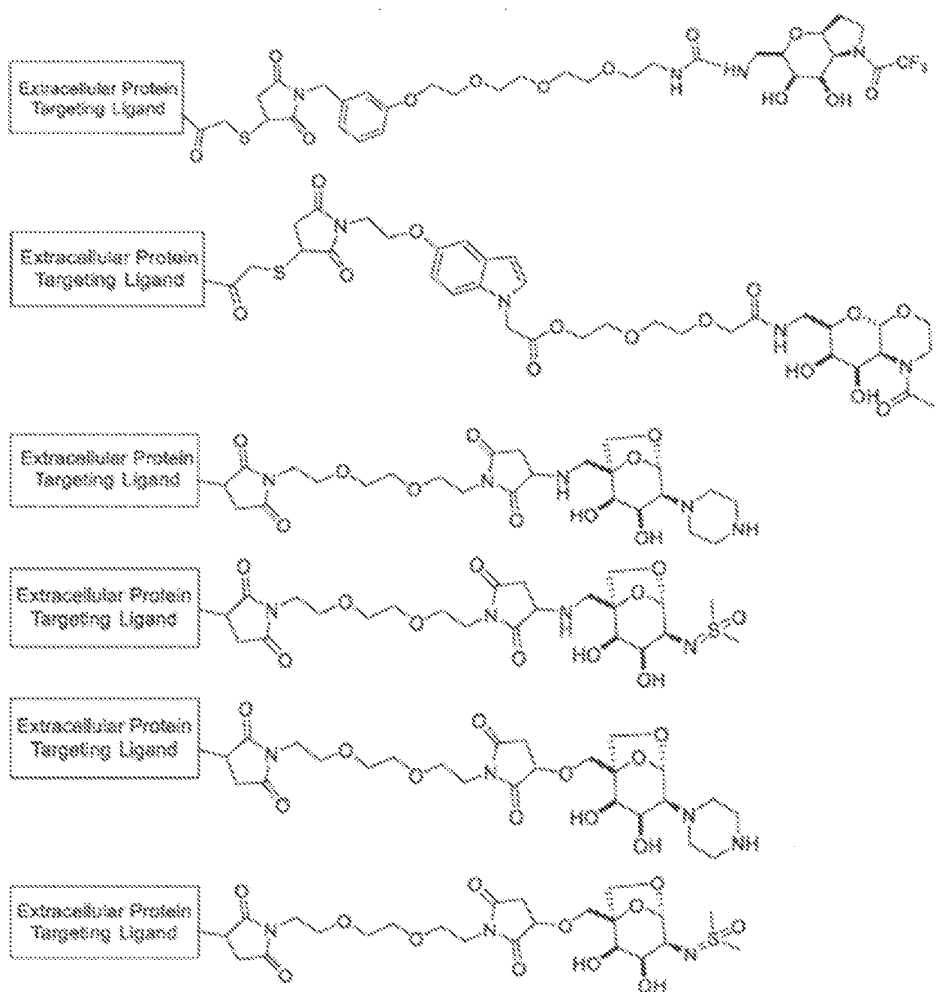


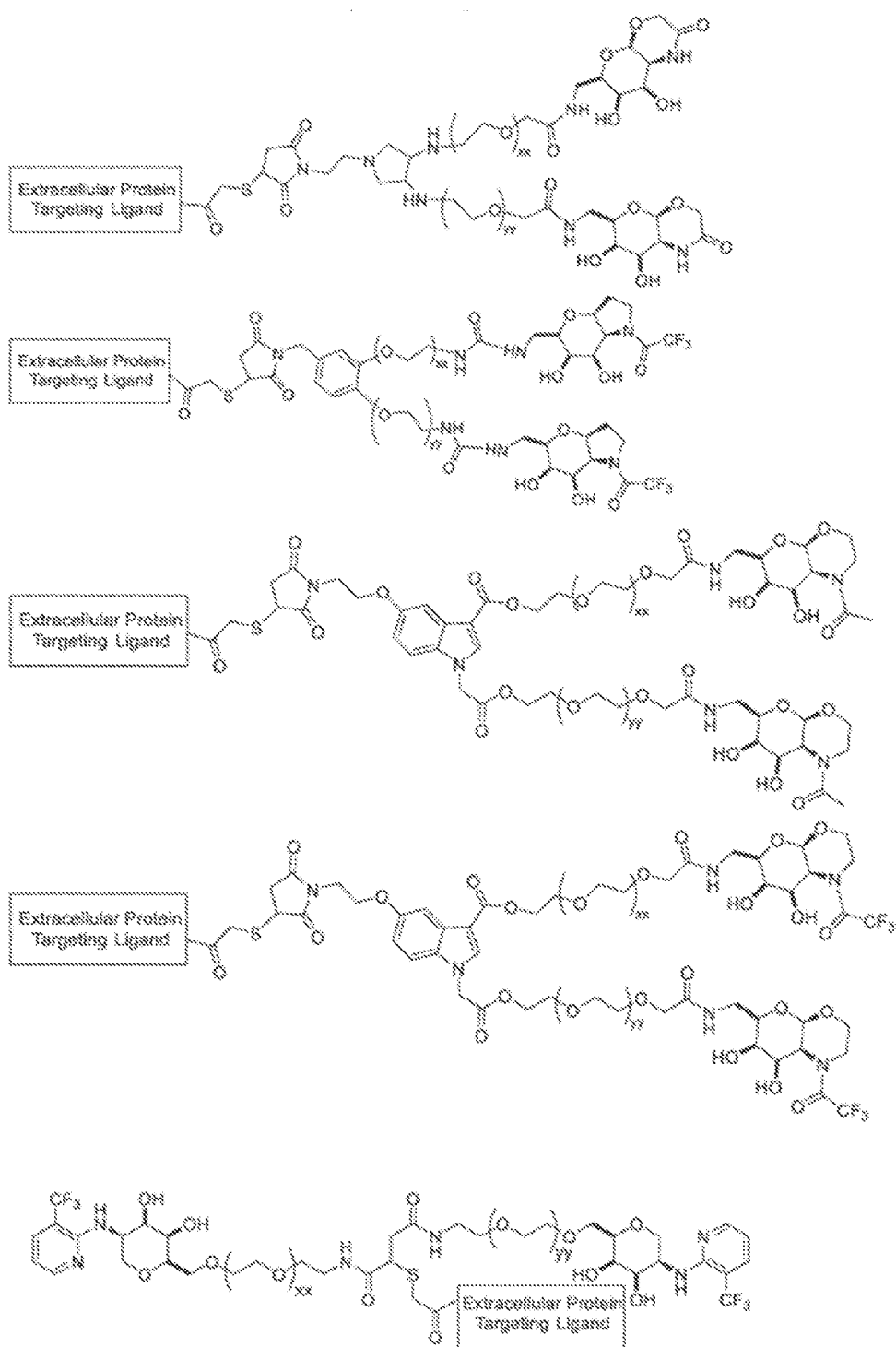


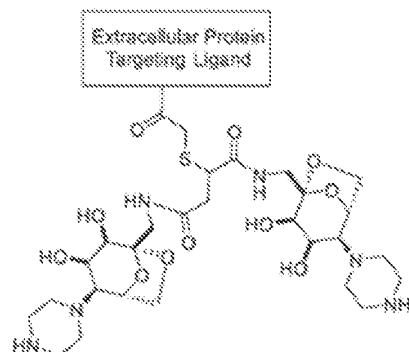
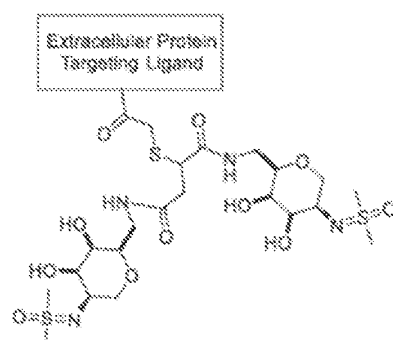
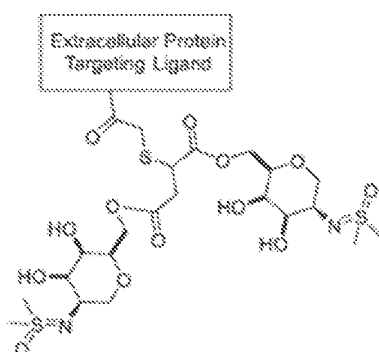
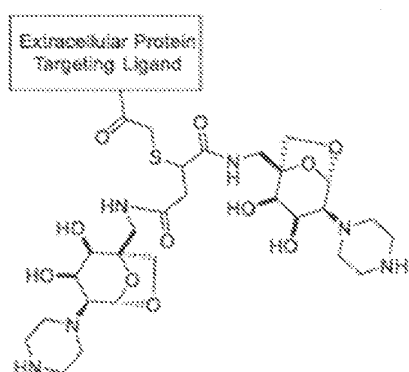


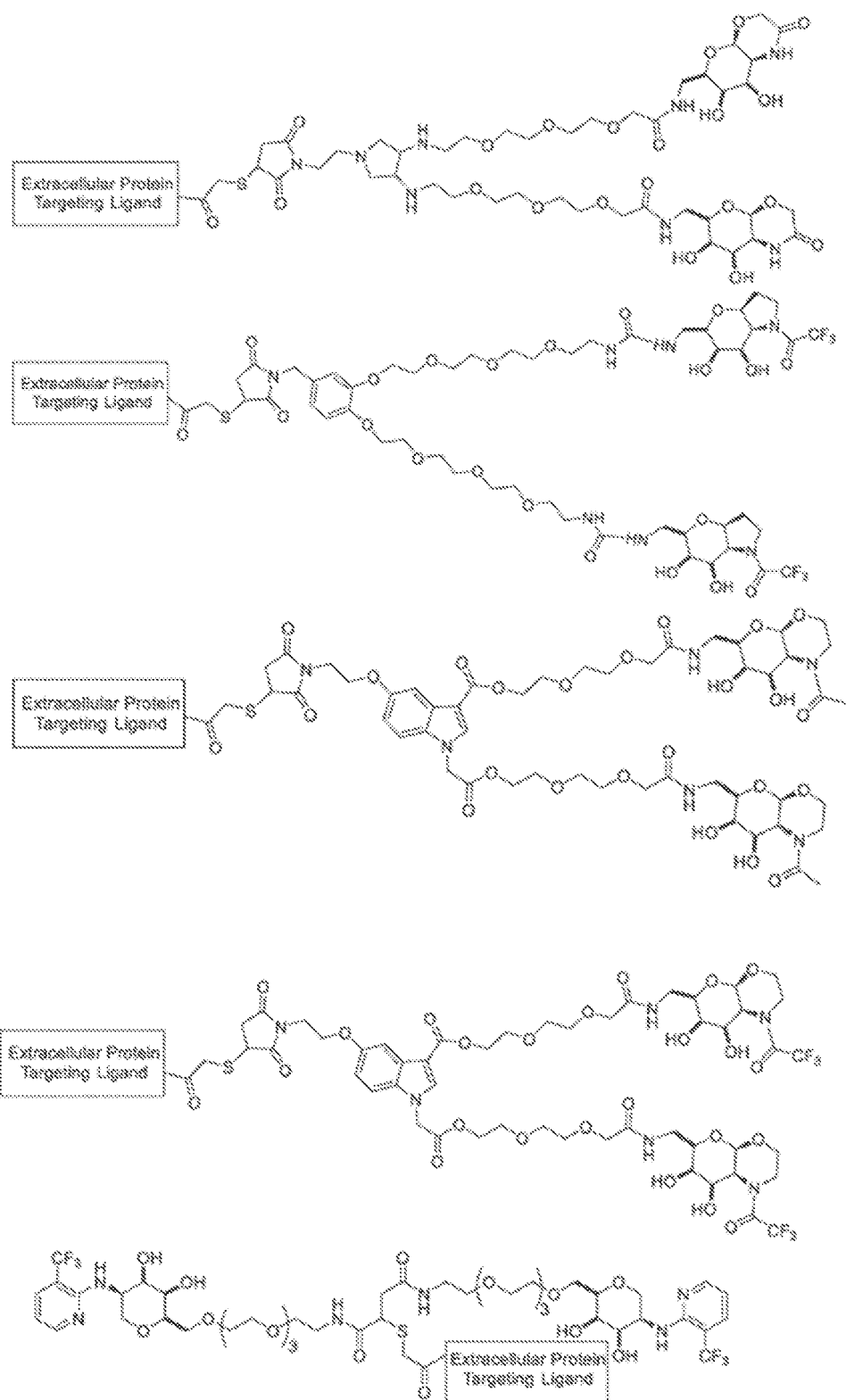


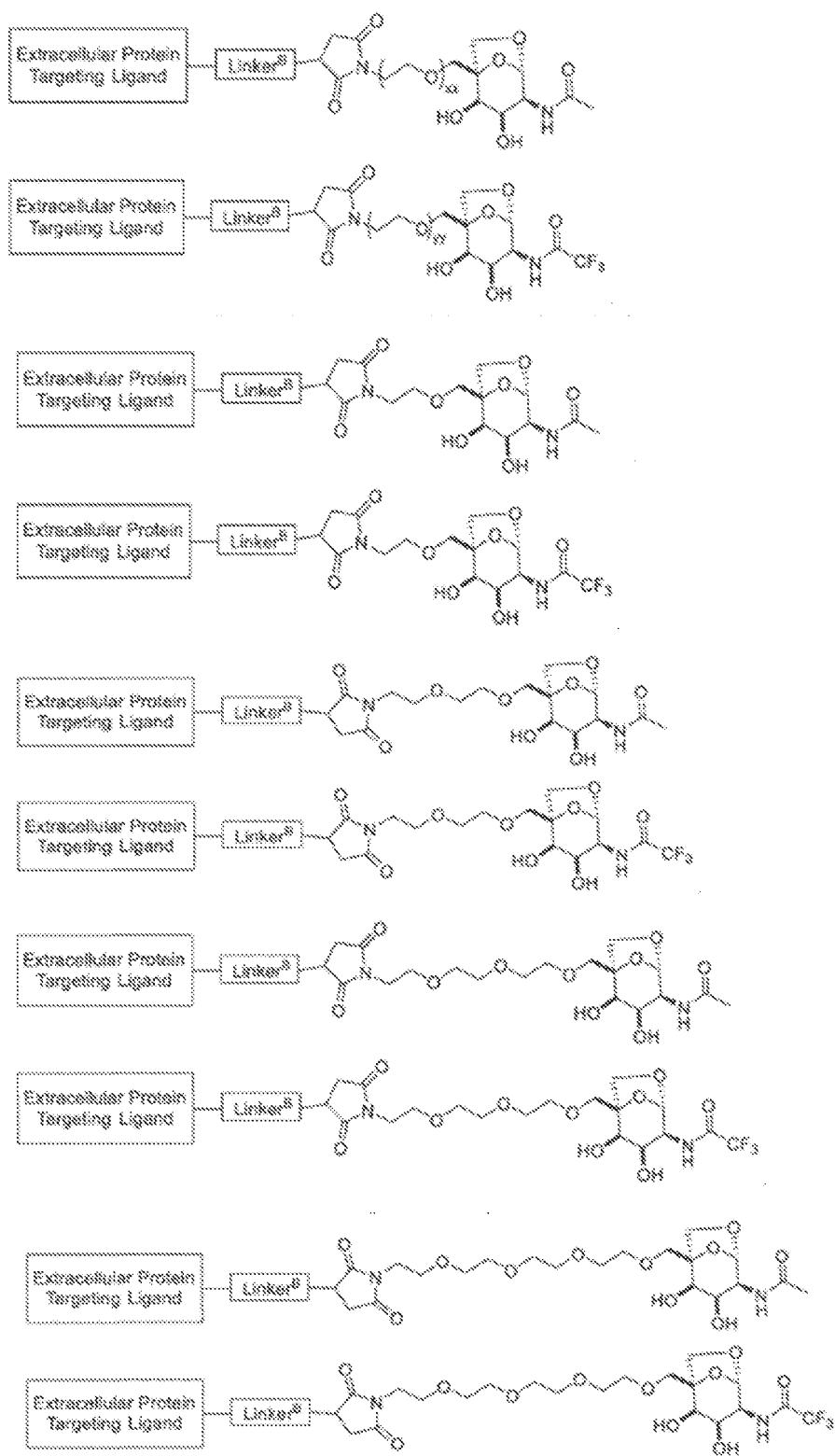


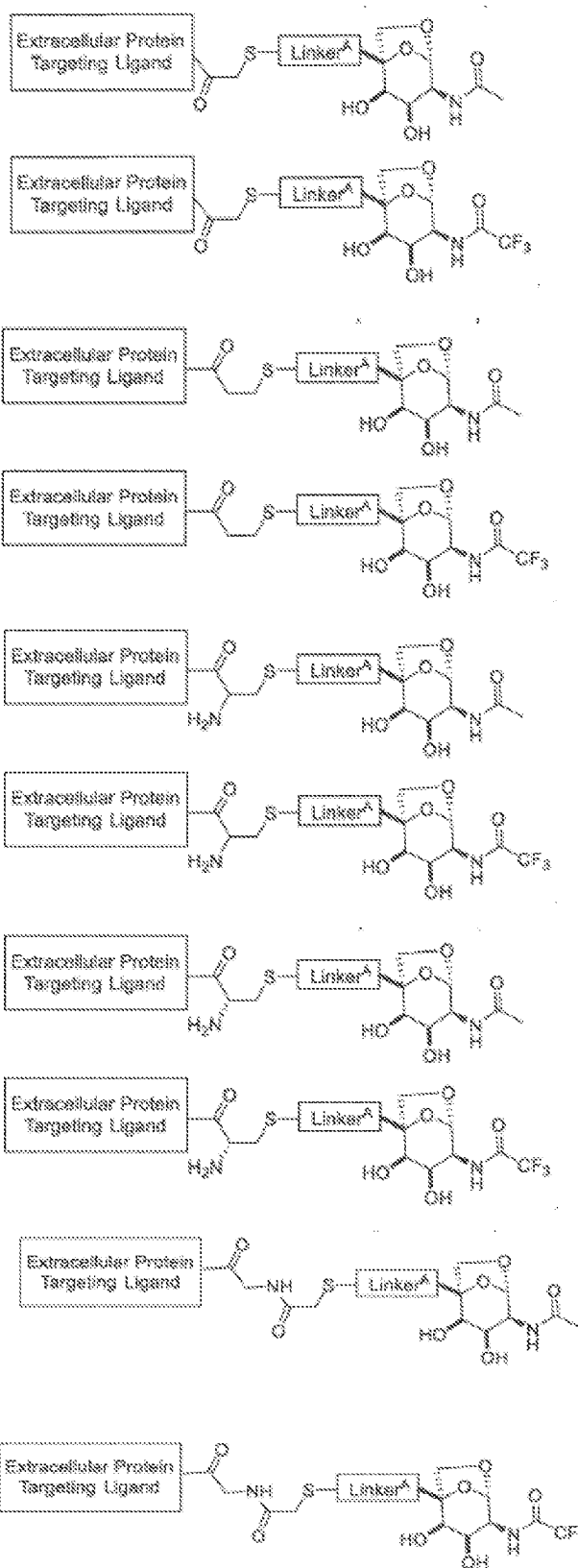


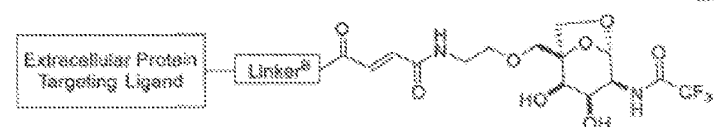
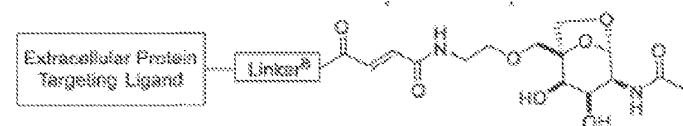
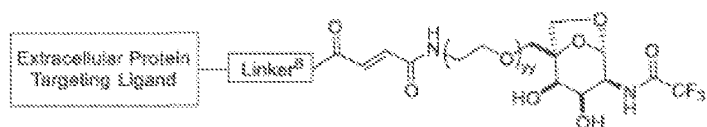
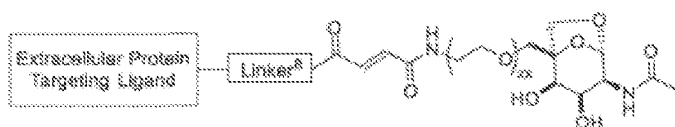
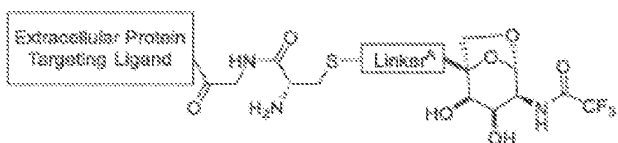
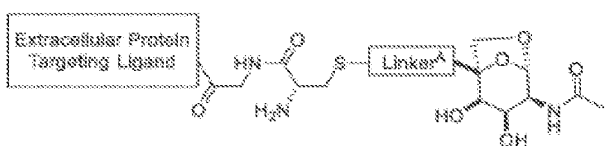
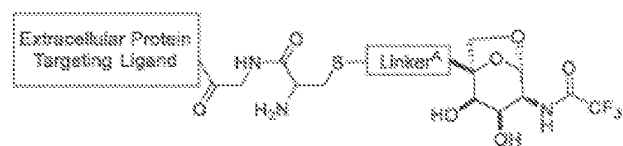
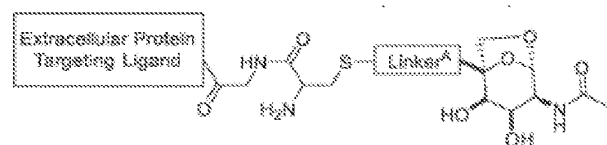
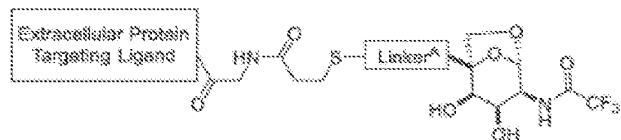
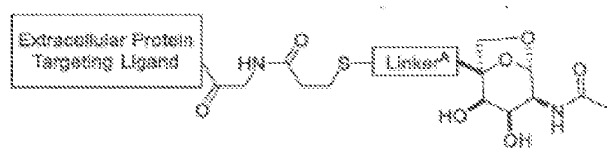


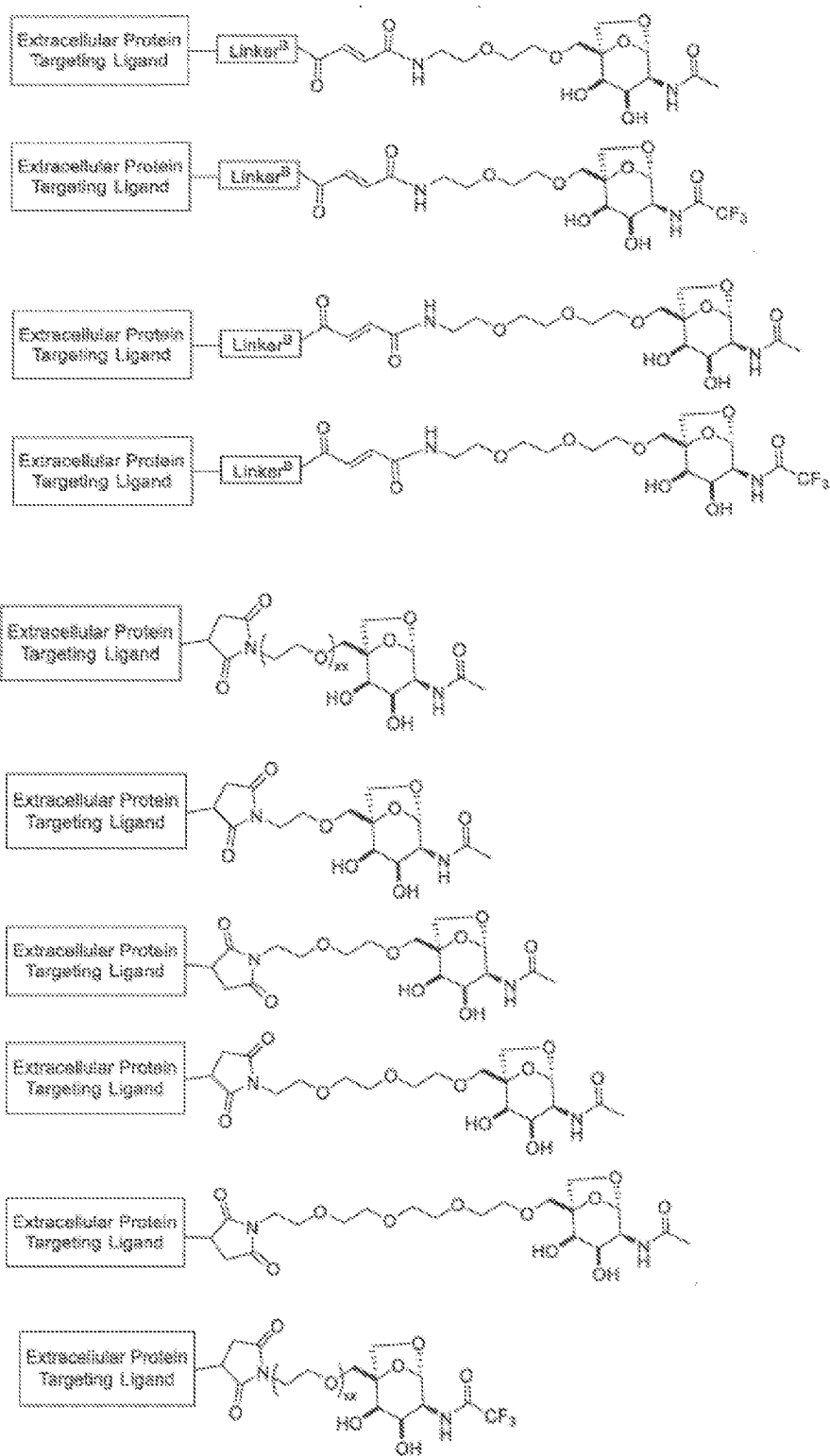


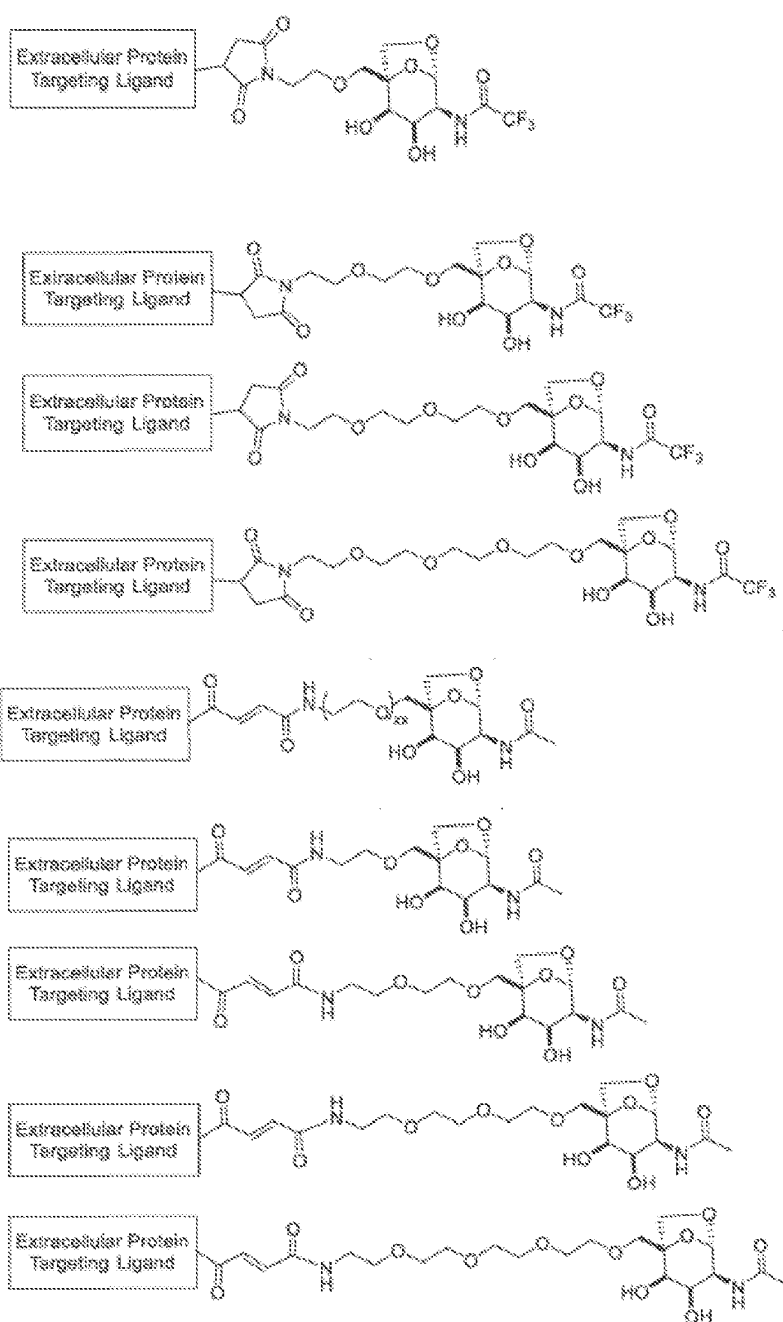


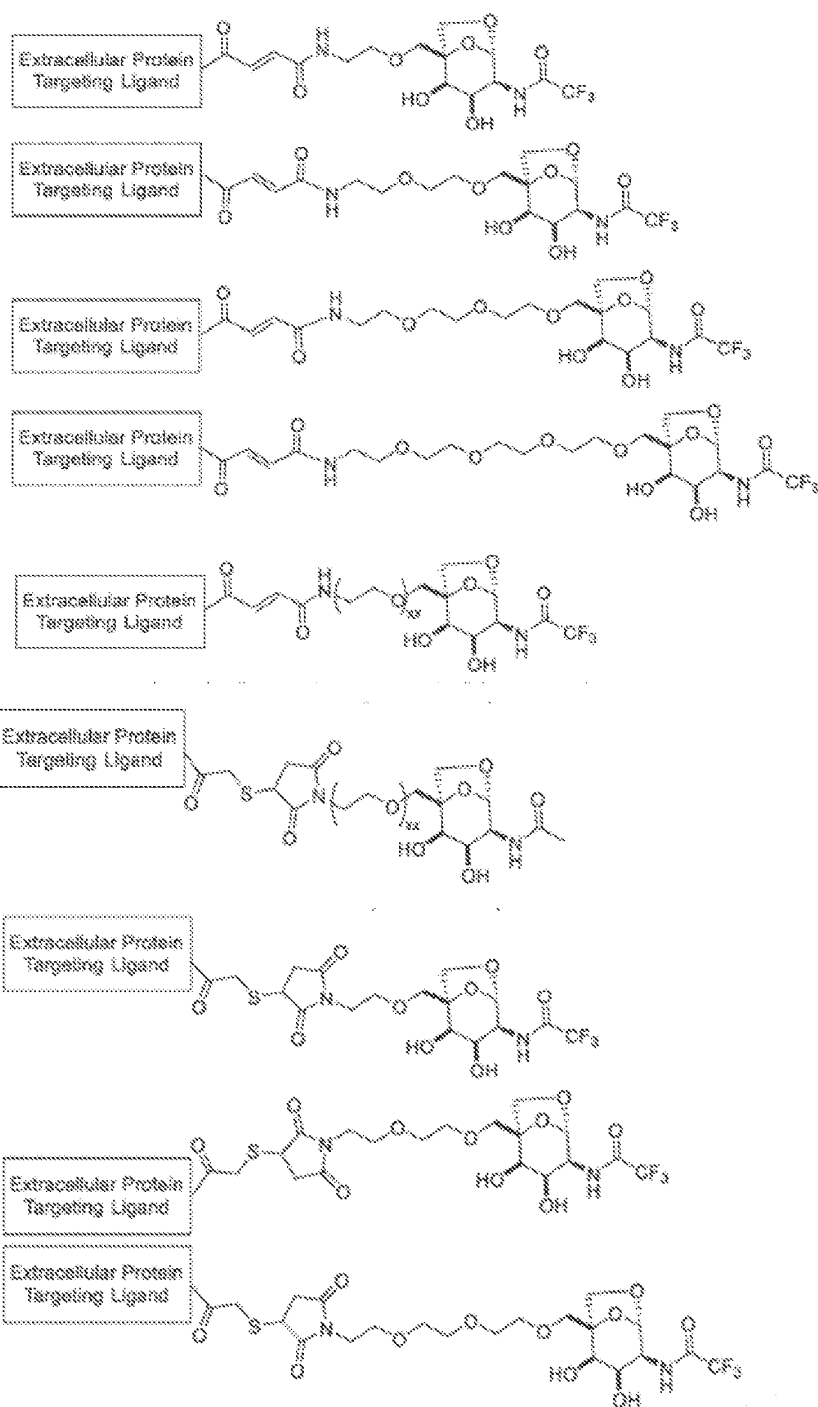


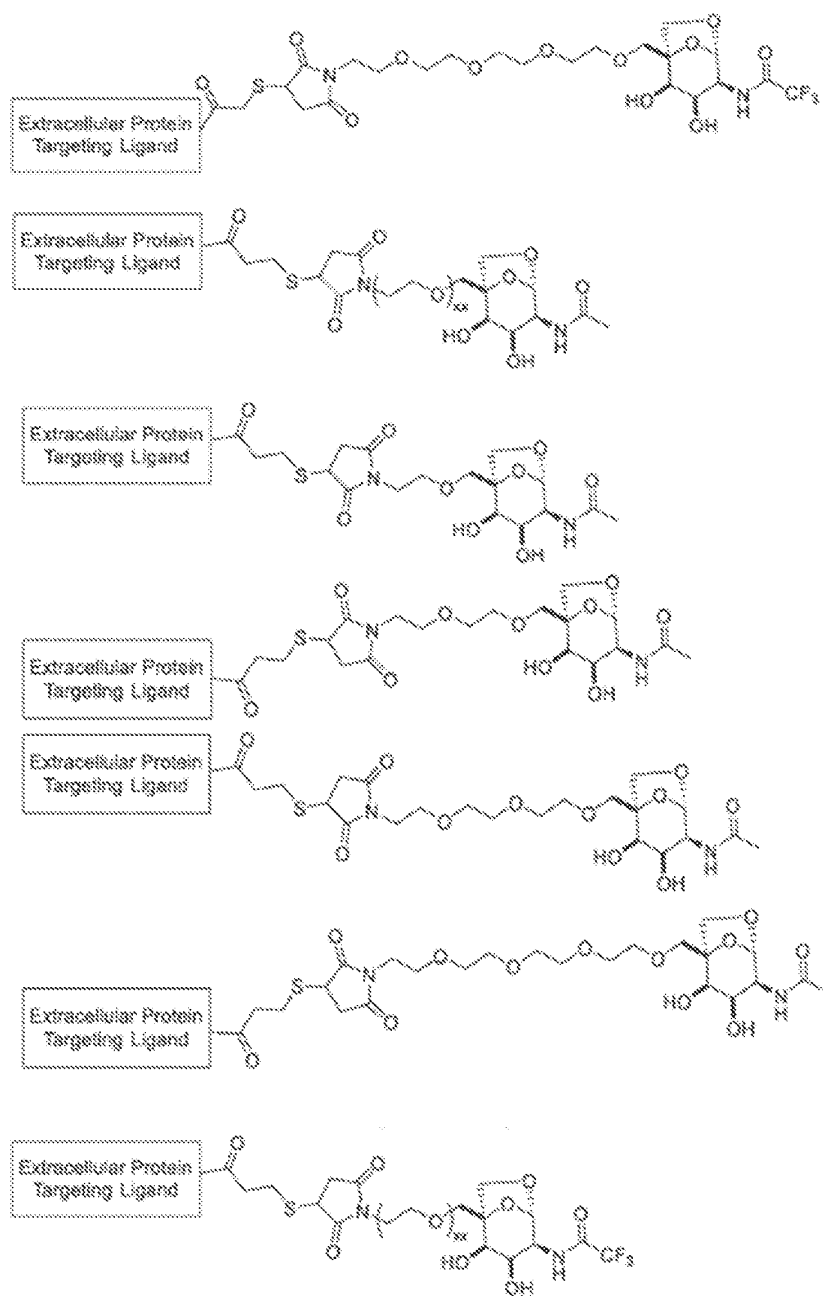


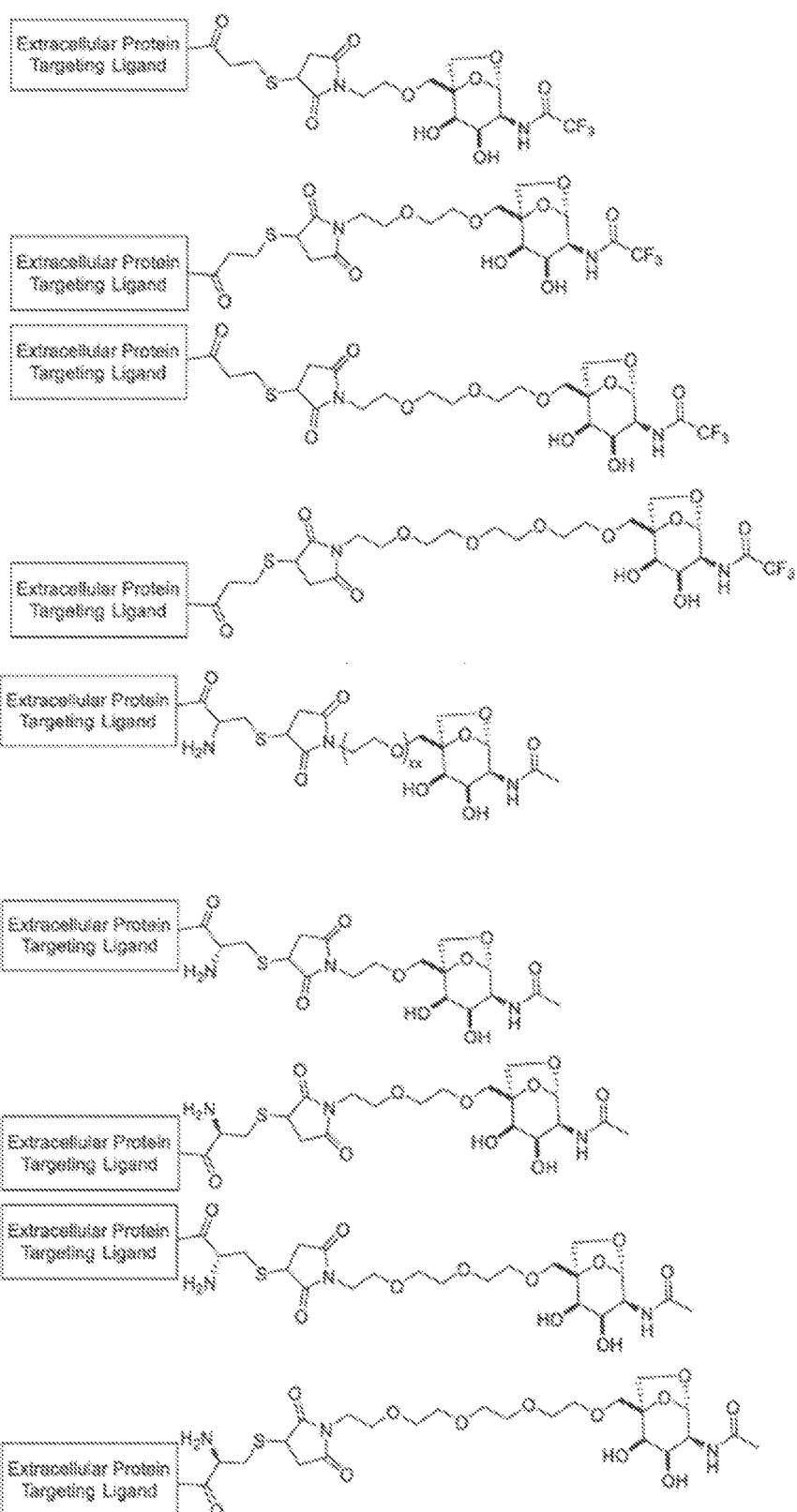


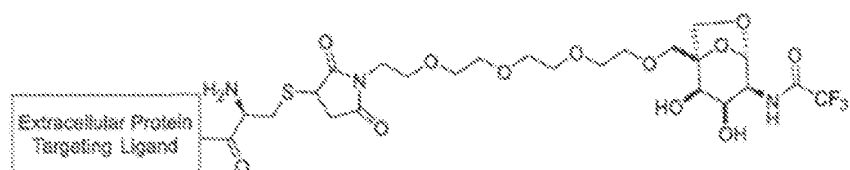
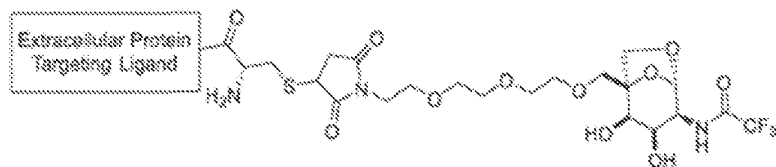
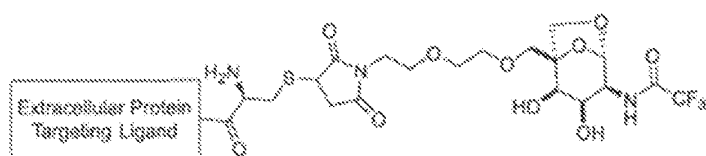
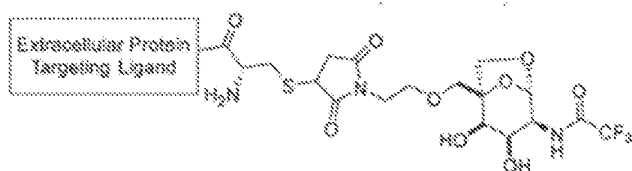
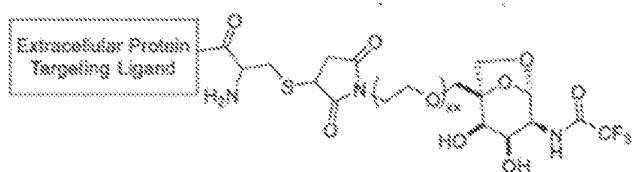


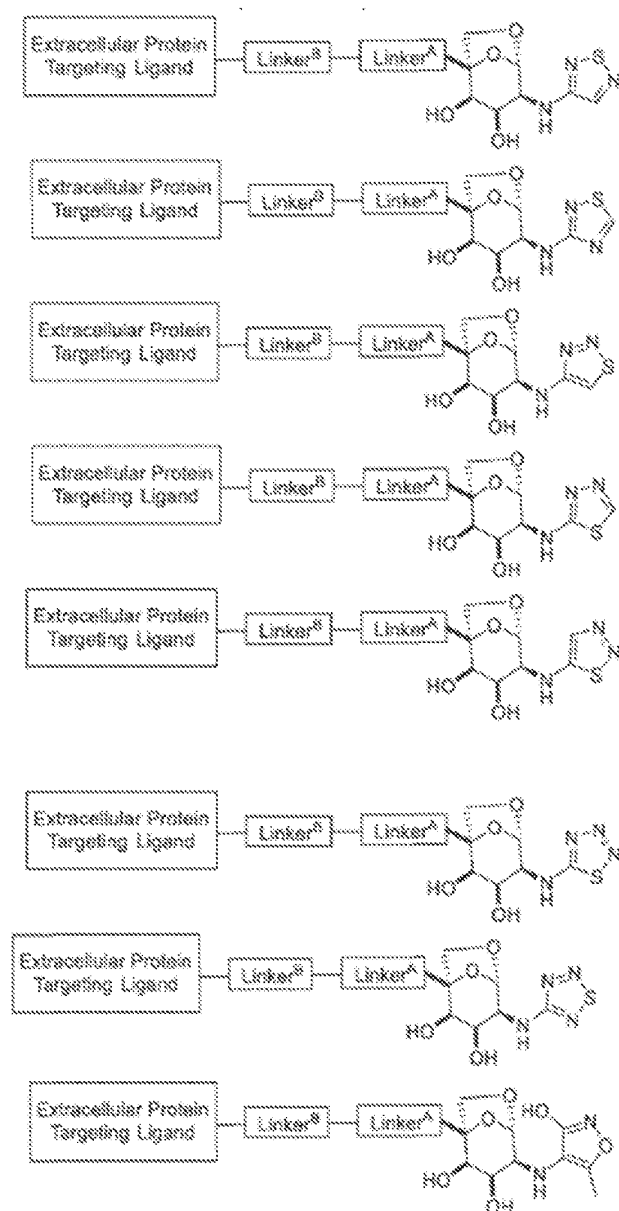


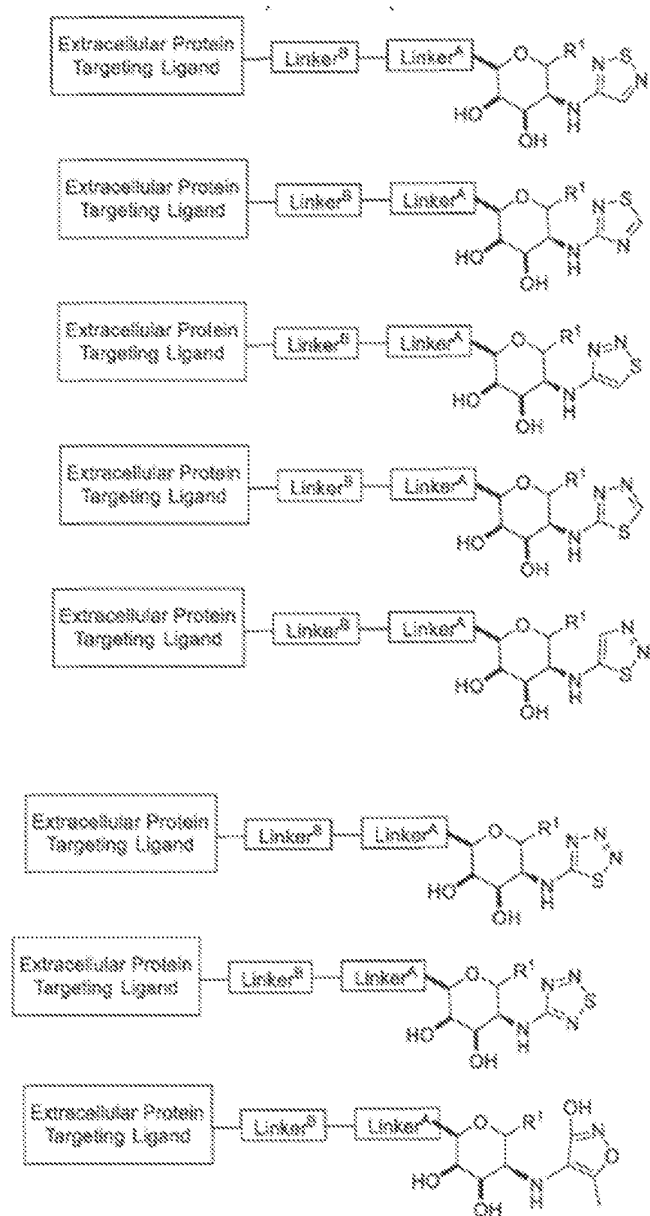


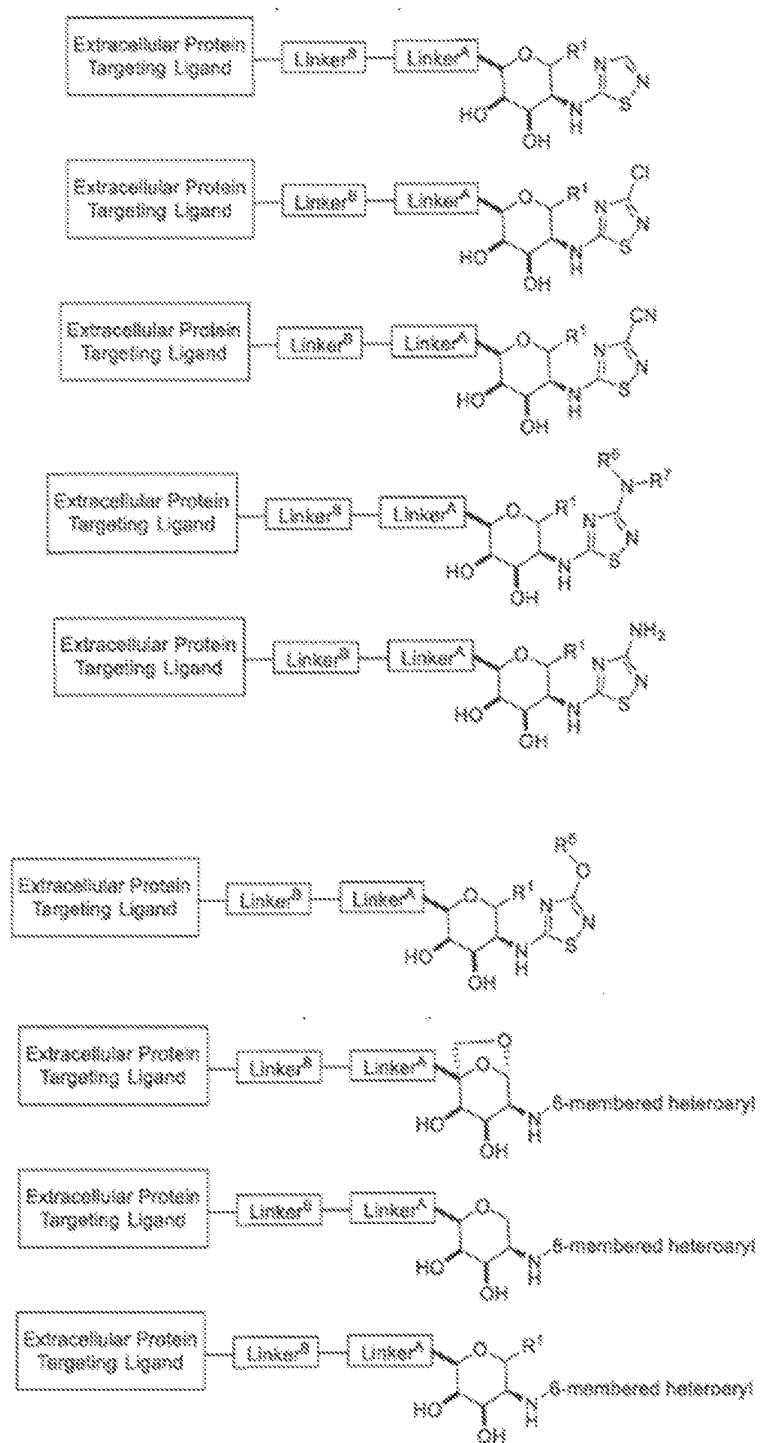


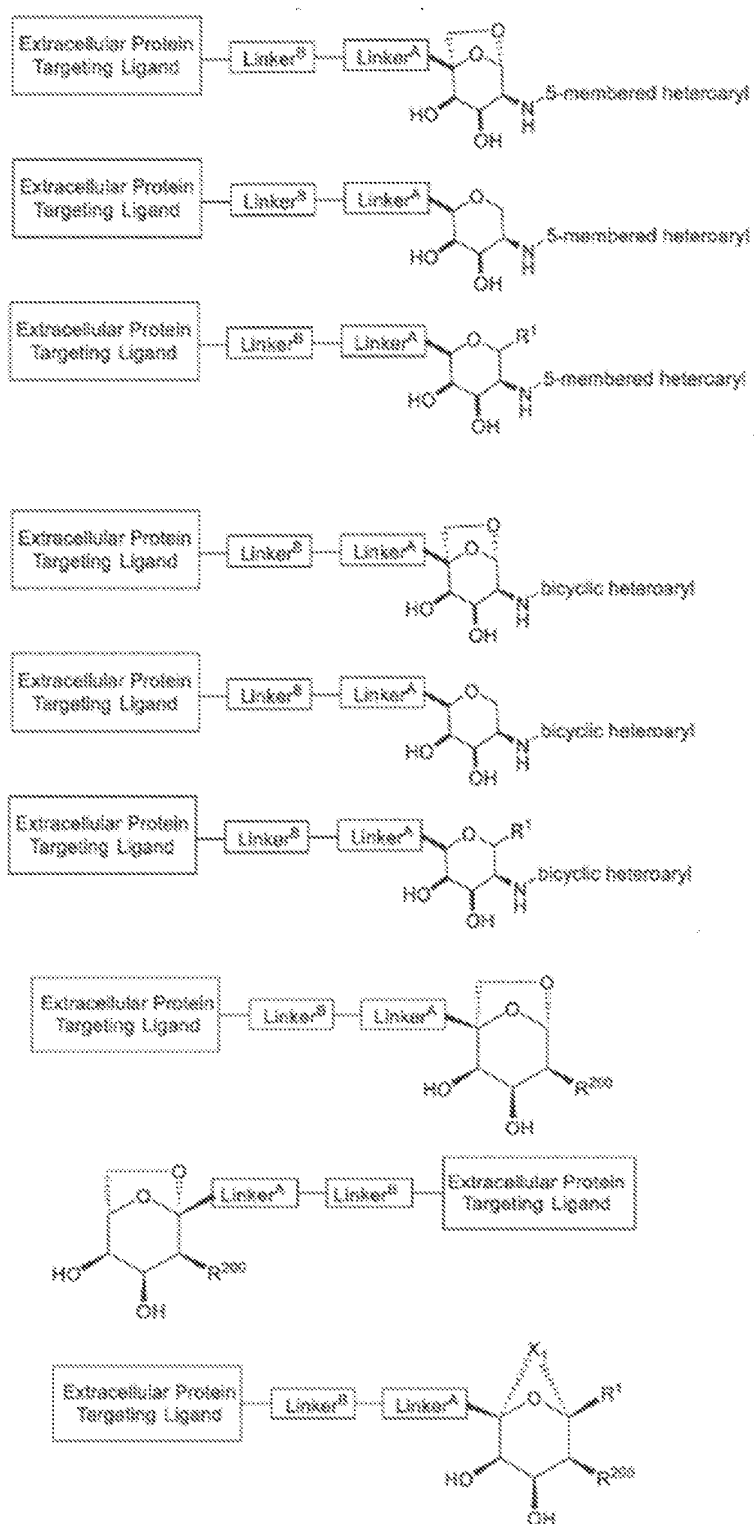


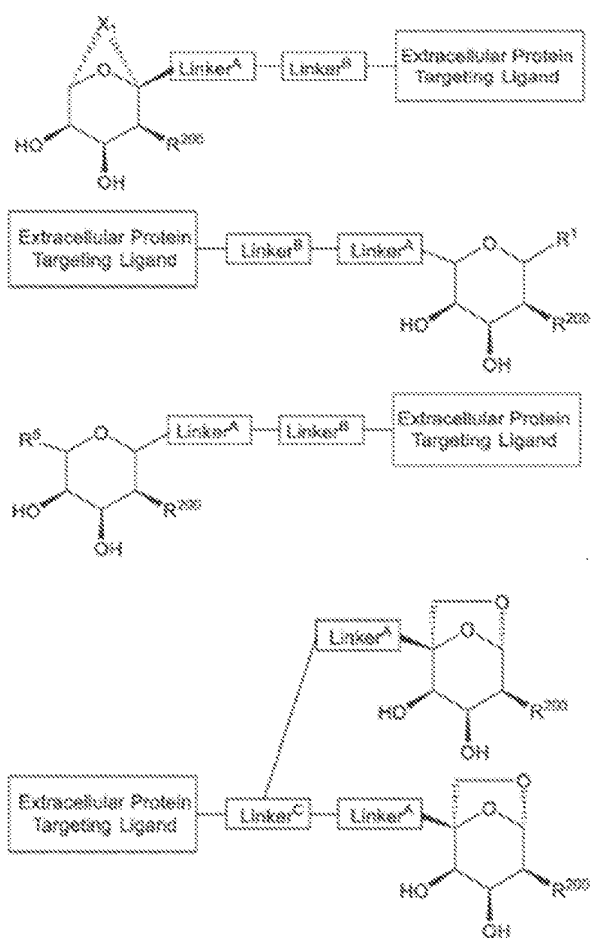


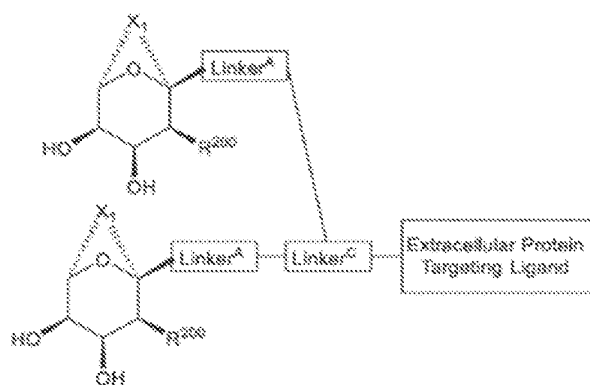
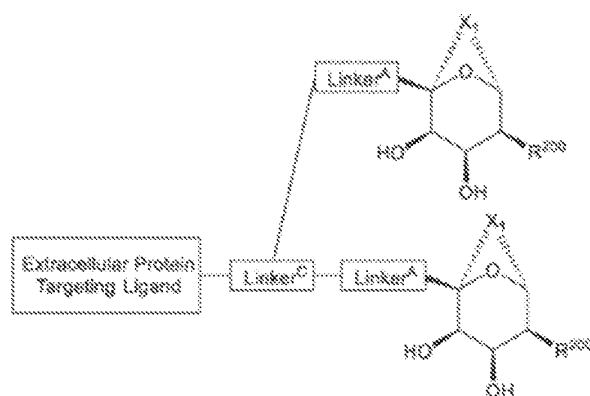
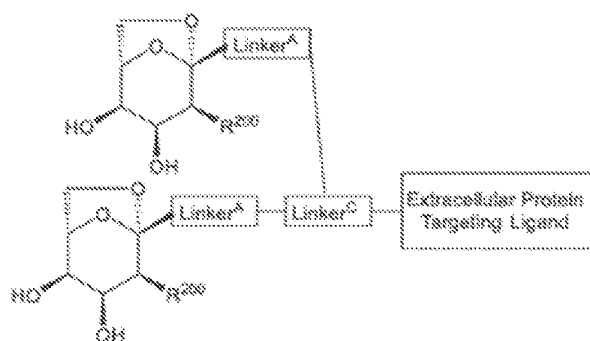


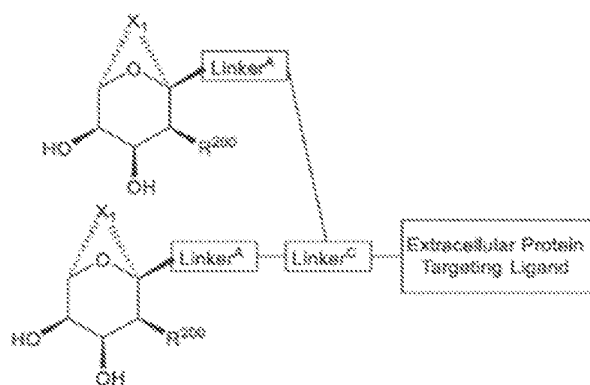
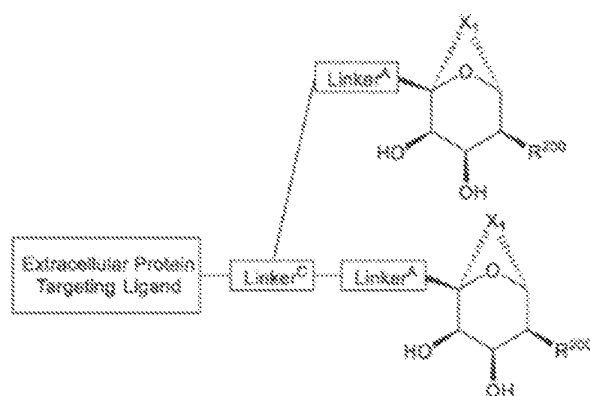
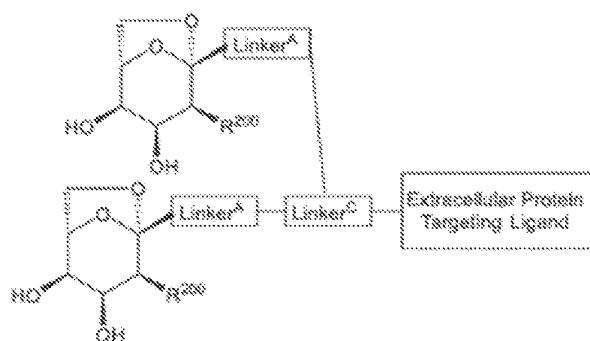


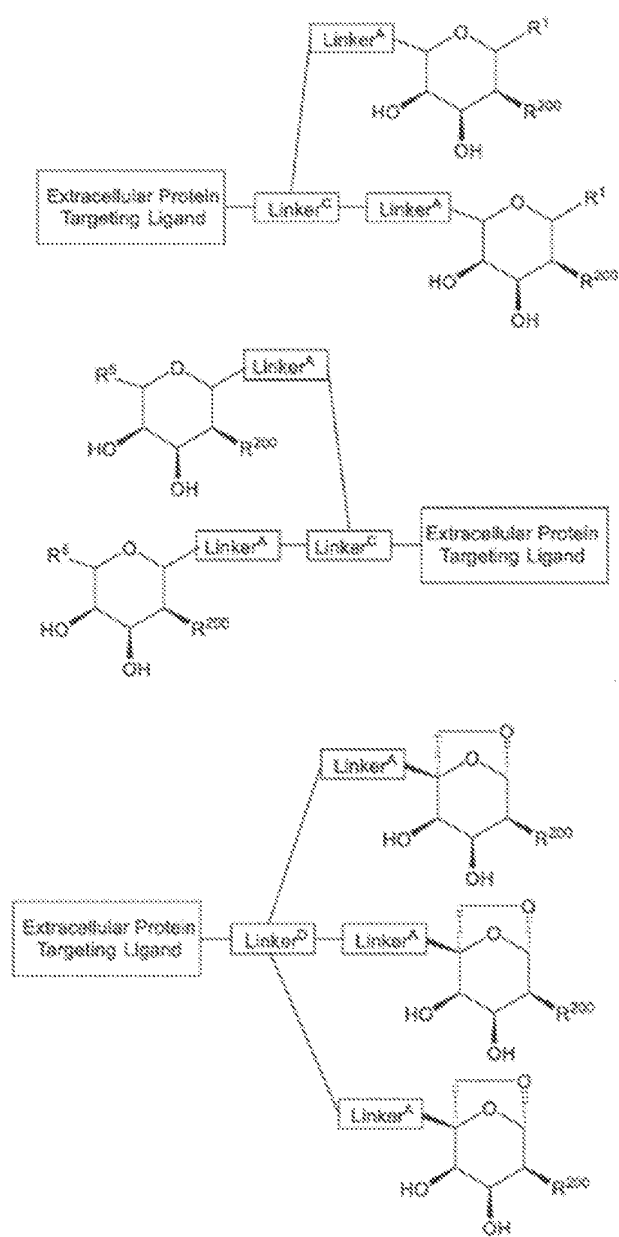


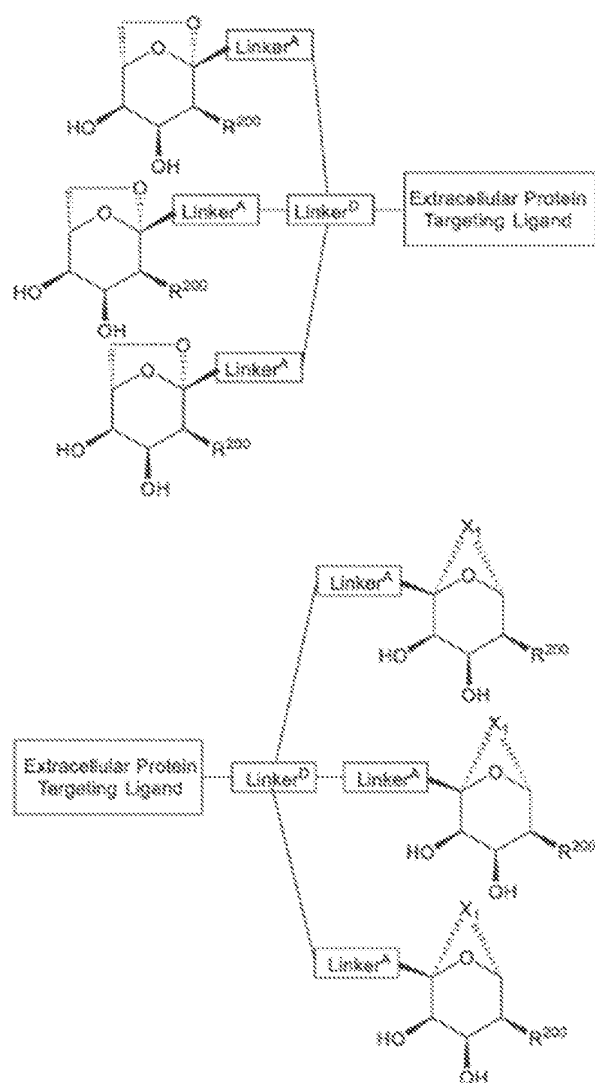


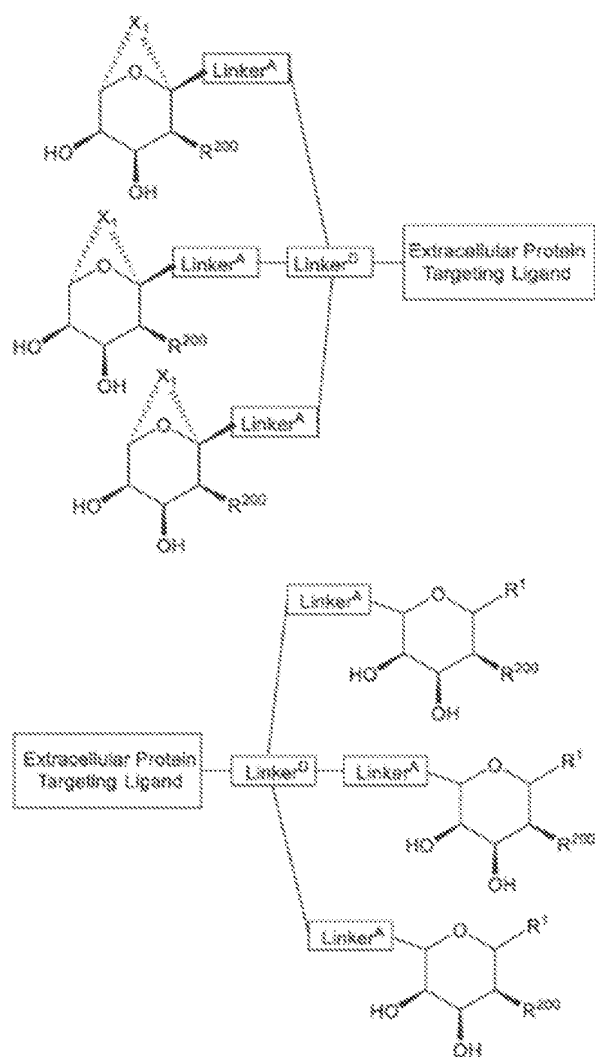


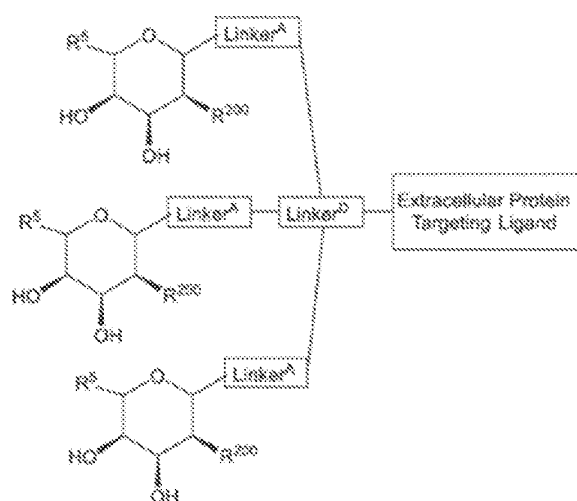




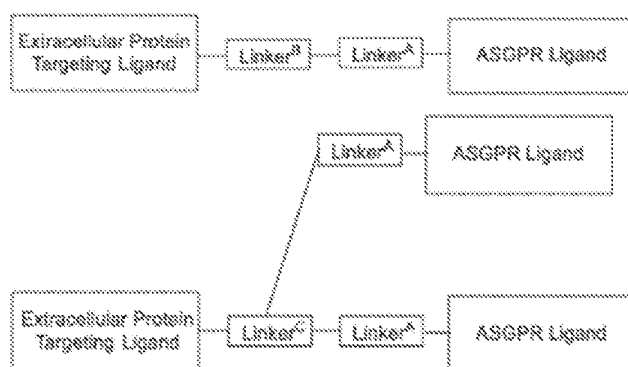






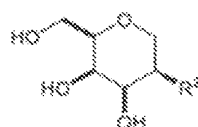


In certain embodiments, the compound of Formula II is an Extracellular Protein degrading compound in which the ASGPR ligand is a ligand as described herein



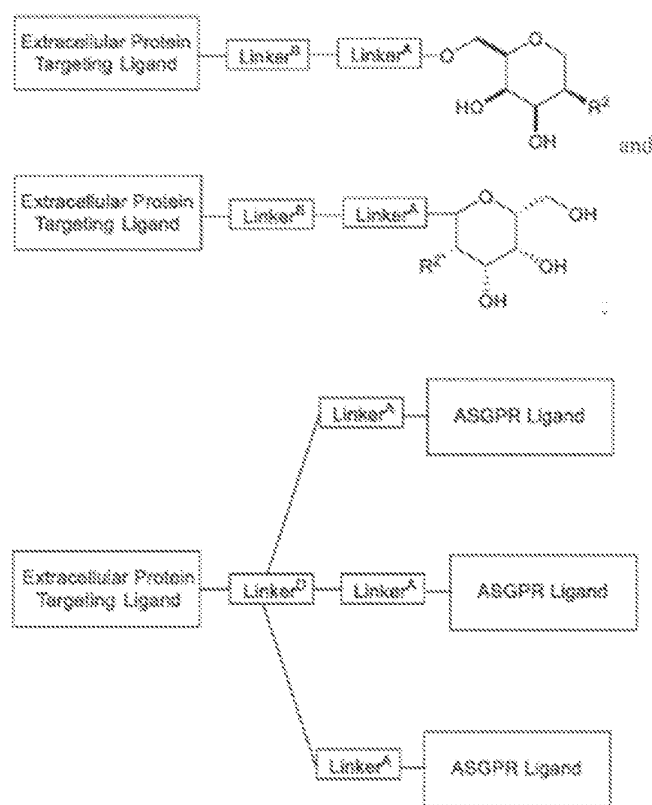
5

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

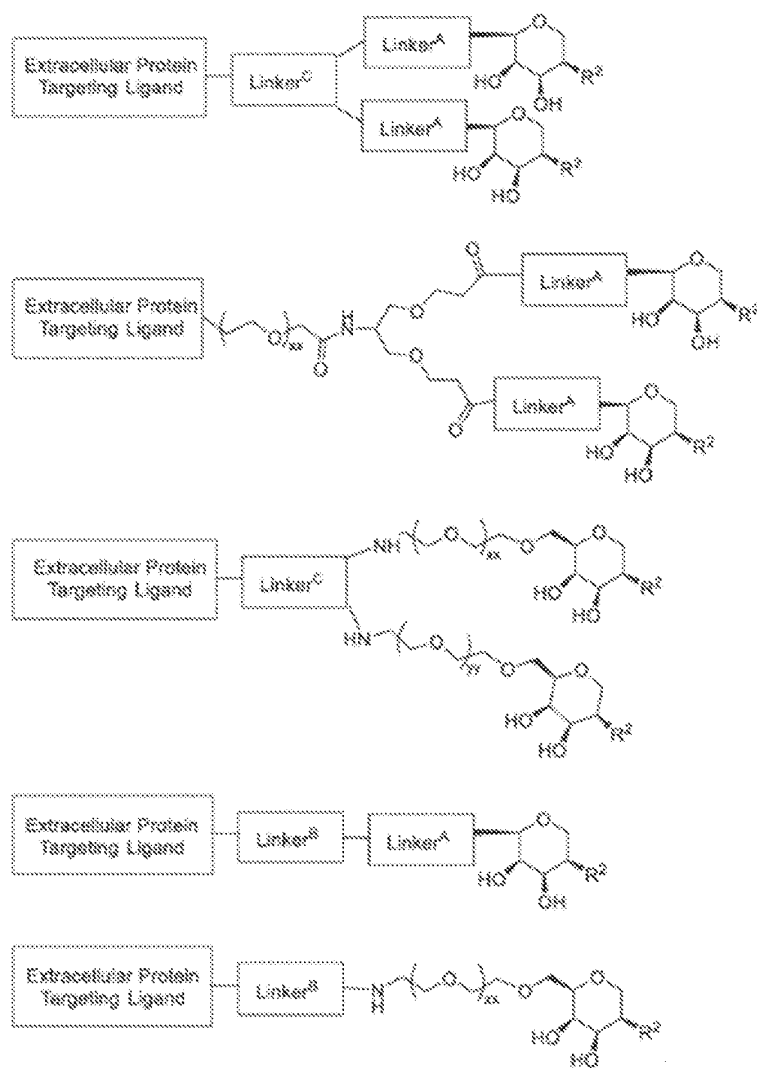


10

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

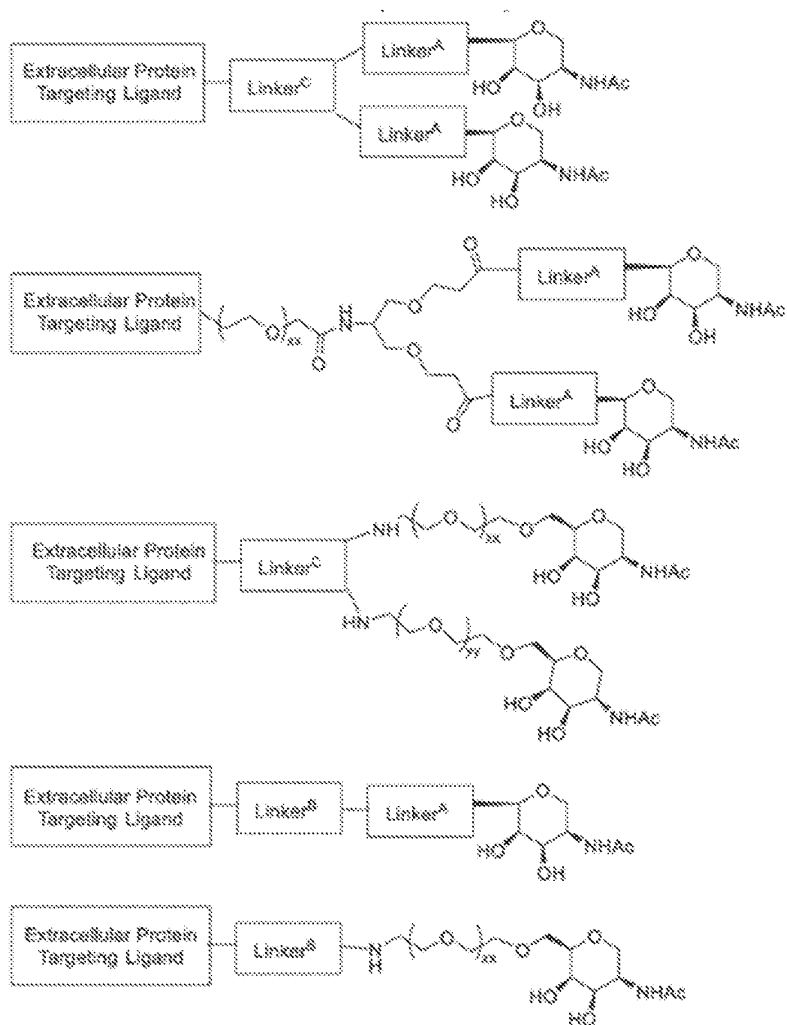


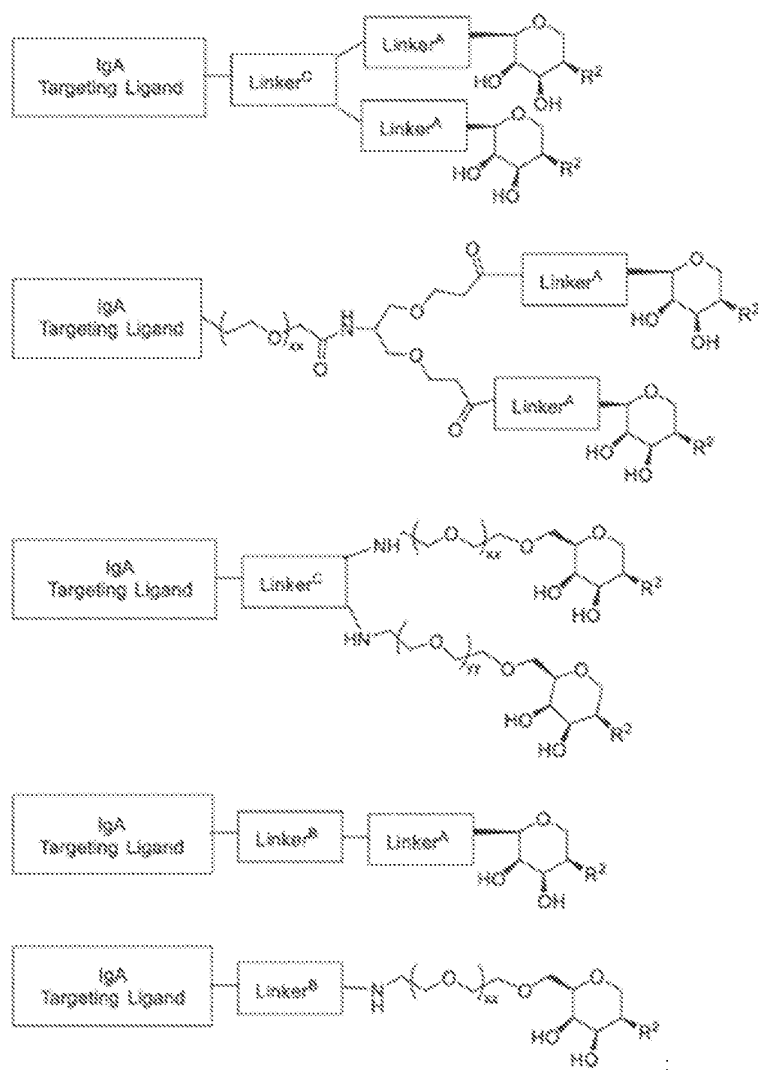
or the bi- or tri- substituted versions thereof or pharmaceutically acceptable salts thereof, where the bi- or tri- substitution refers to the number additional galactose derivatives
 5 attached to a linker moiety. In certain embodiments the compound of Formula II is selected from:



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

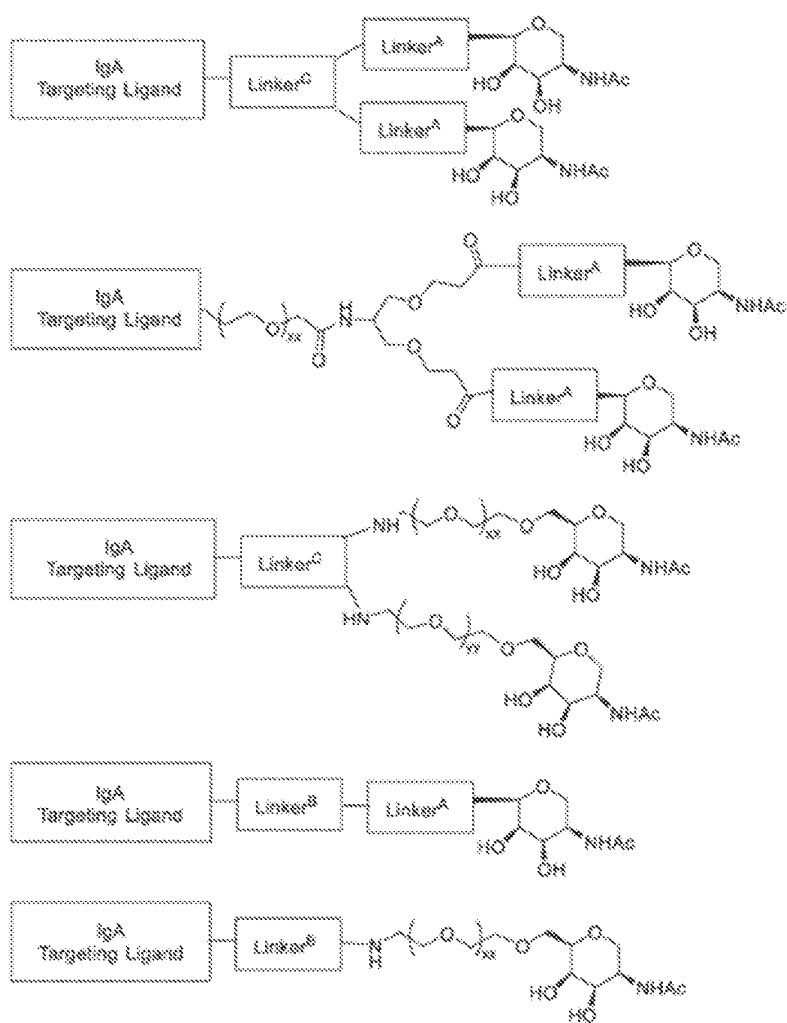
In certain embodiments, the compound of Formula II is selected from:

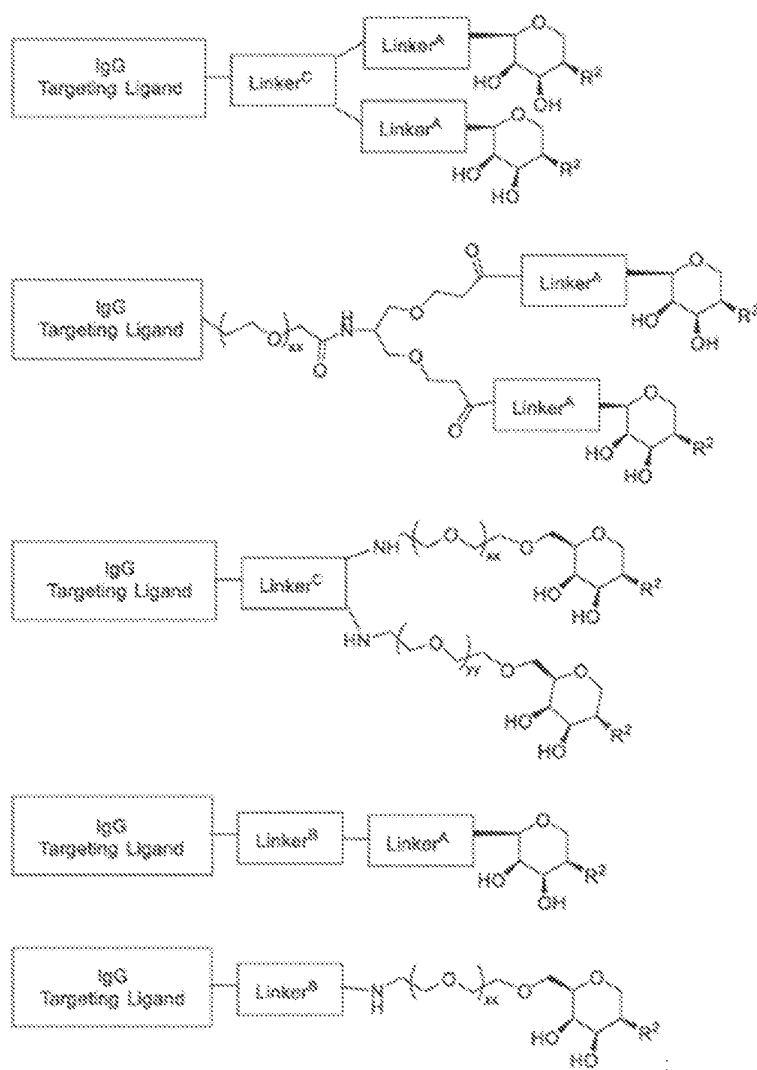




wherein in certain embodiments R² is selected from -NR⁶COR³, -NR⁶-(5-membered heteroaryl), and -NR⁶-(6-membered heteroaryl), each of which R² groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected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

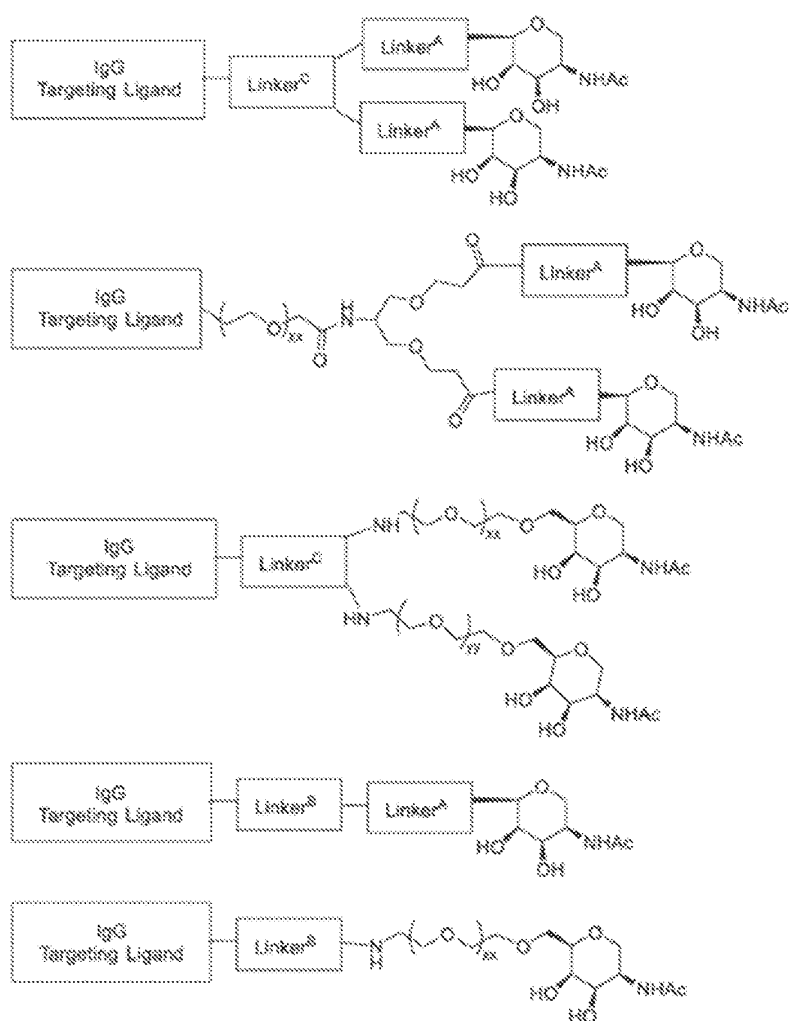
In certain embodiments, the compound of Formula II is selected from:

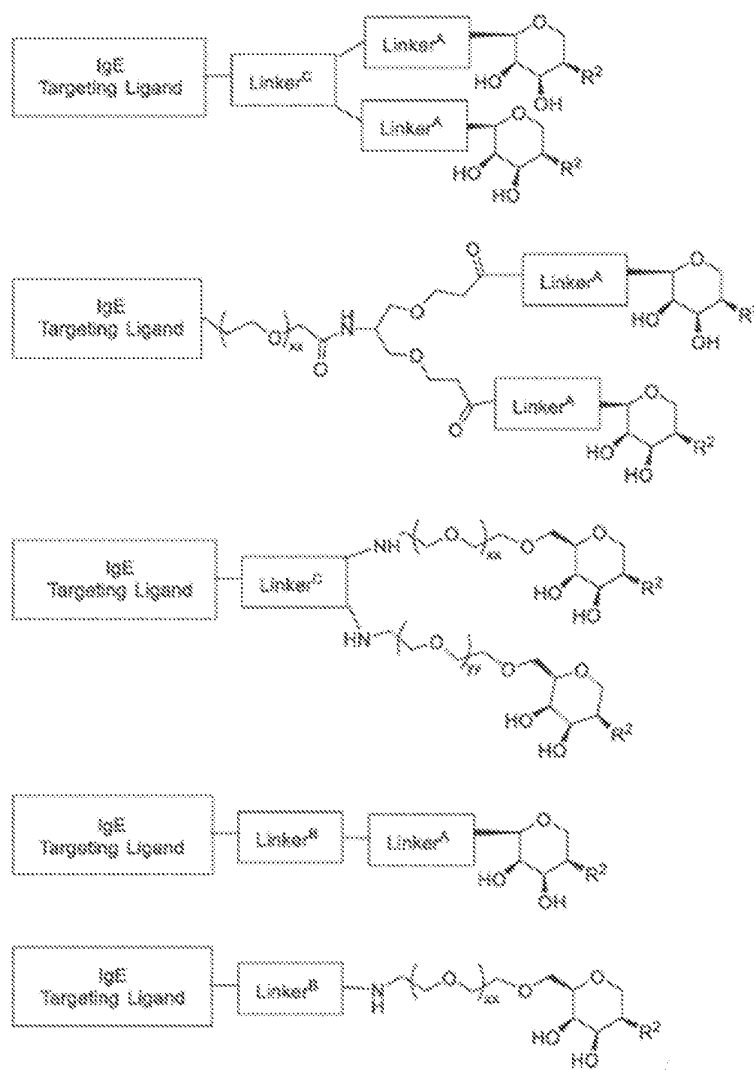




wherein in certain embodiments R² is selected from -NR⁶COR³, -NR⁶-(5-membered heteroaryl), and -NR⁶-(6-membered heteroaryl), each of which R² groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected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

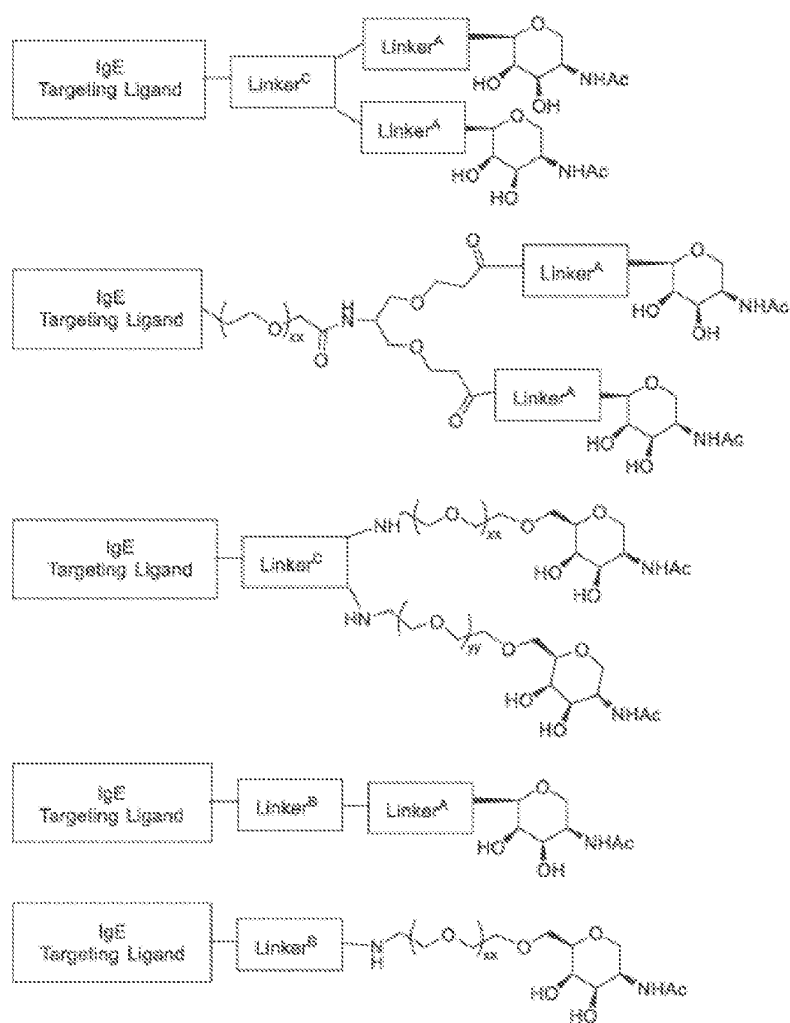
In certain embodiments, the compound of Formula II is selected from:

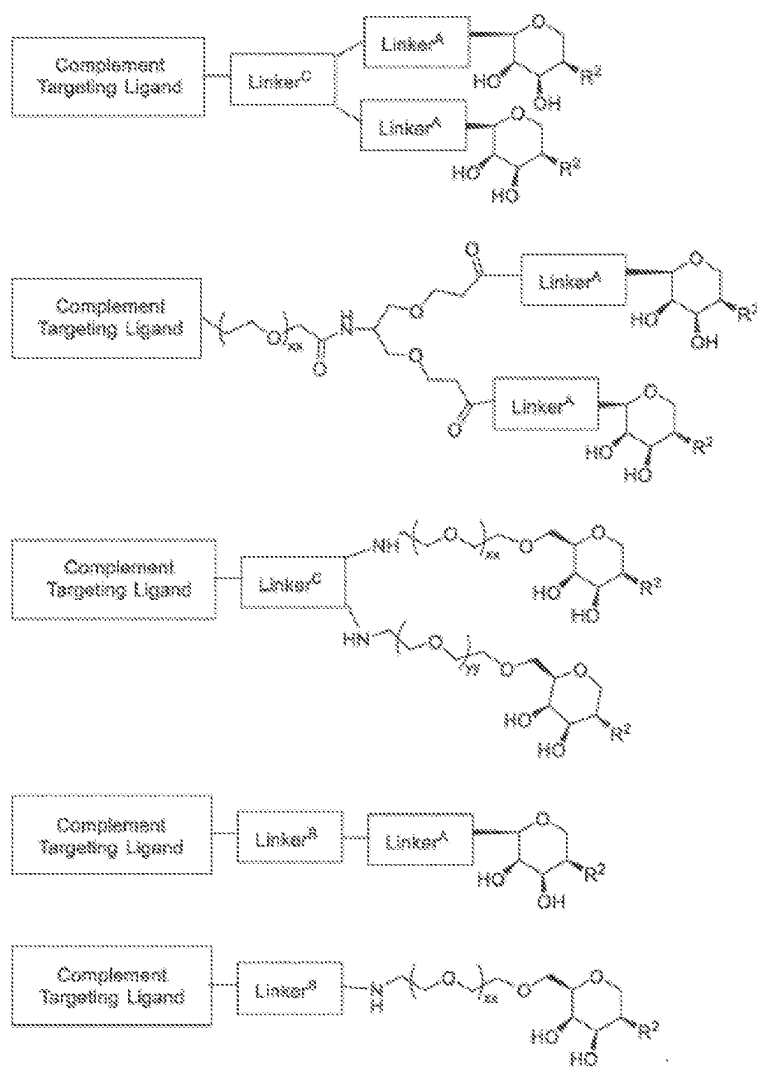




wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$ -(5-membered heteroaryl), and $-NR^6$ -(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

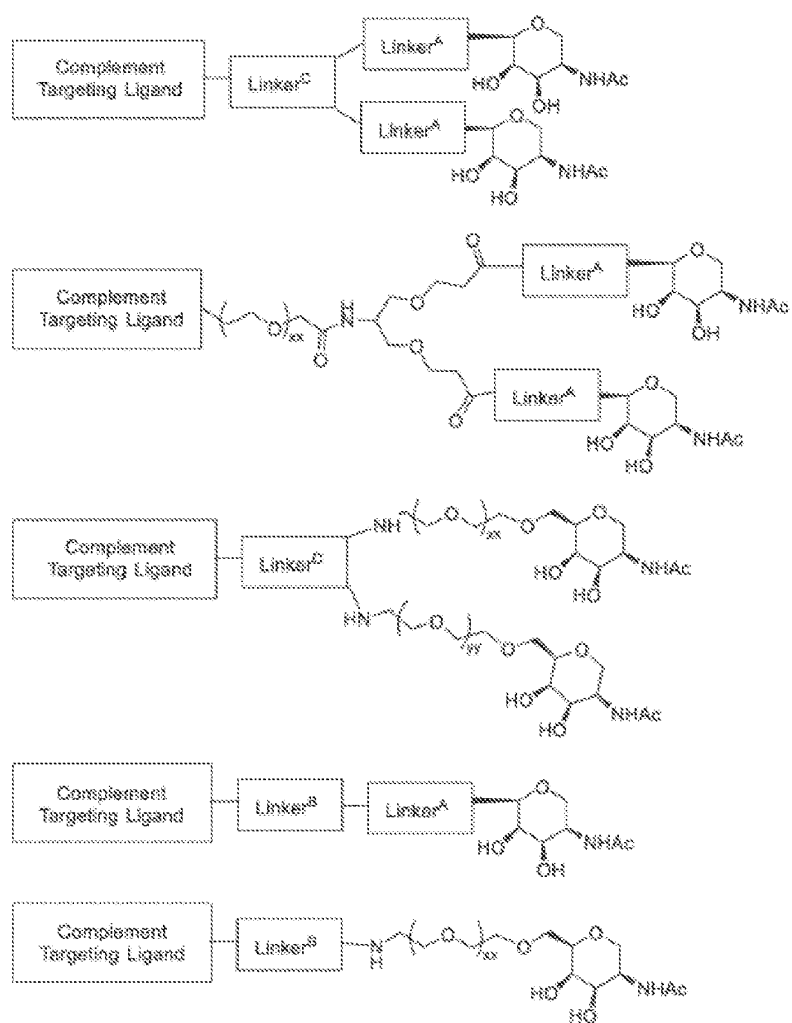
In certain embodiments, the compound of Formula II is selected from:

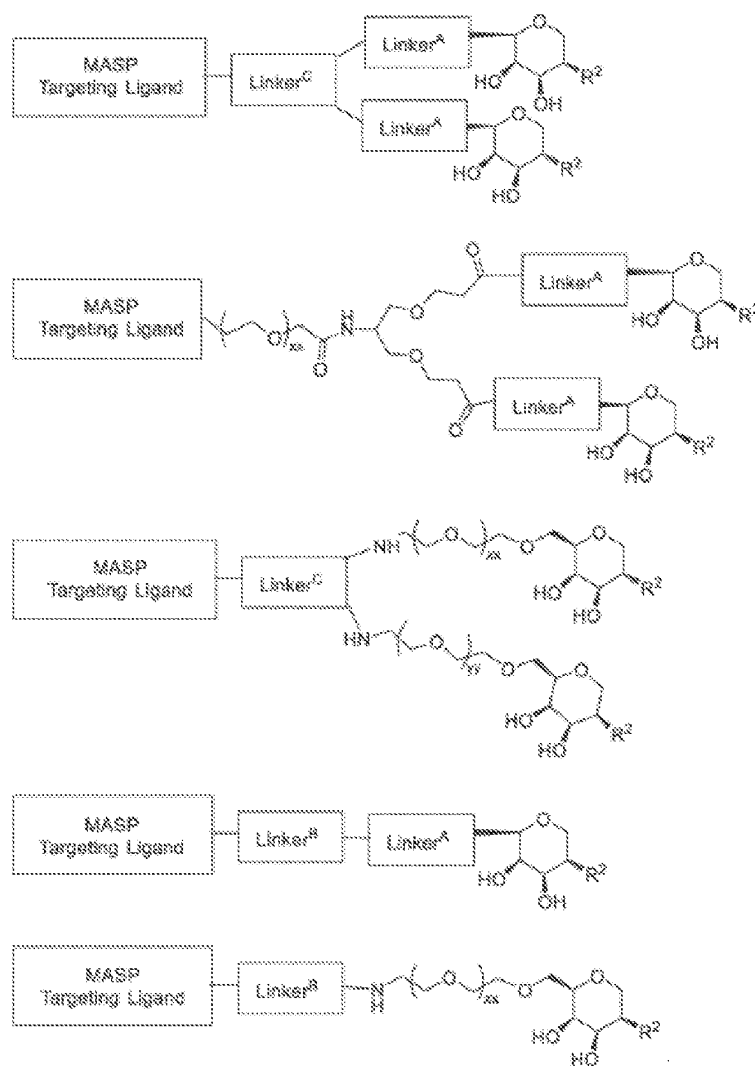




wherein in certain embodiments R² is selected from -NR⁶COR³, -NR⁶-(5-membered heteroaryl), and -NR⁶-(6-membered heteroaryl), each of which R² groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected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

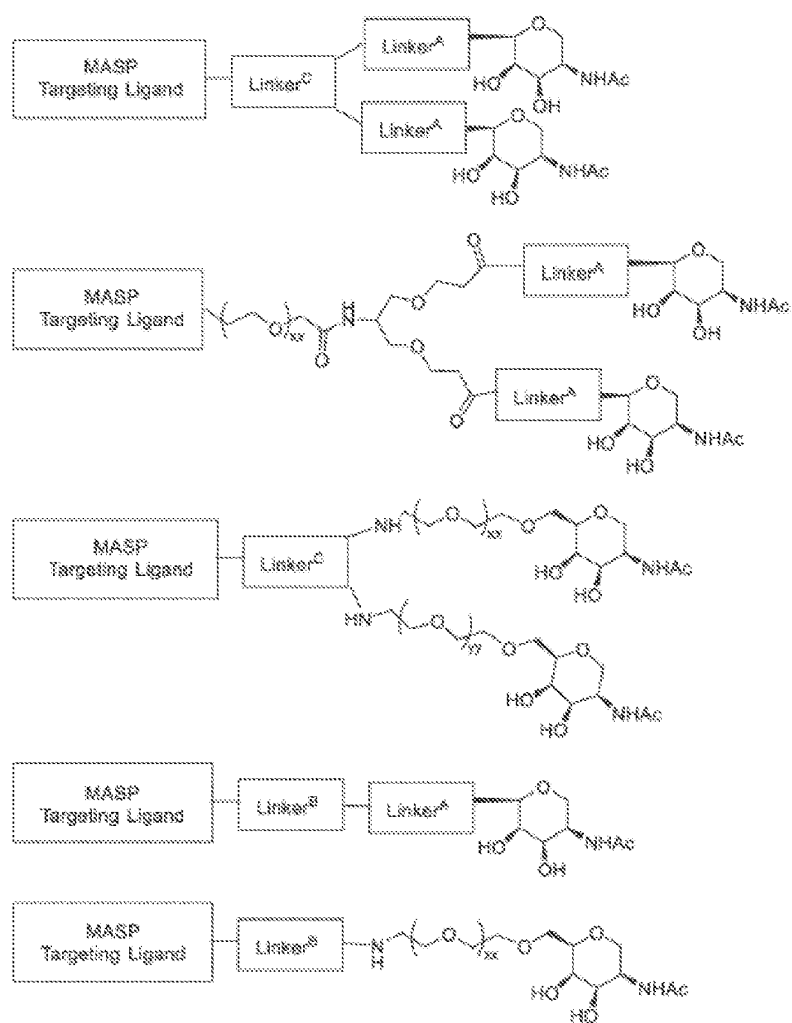
In certain embodiments, the compound of Formula II is selected from:

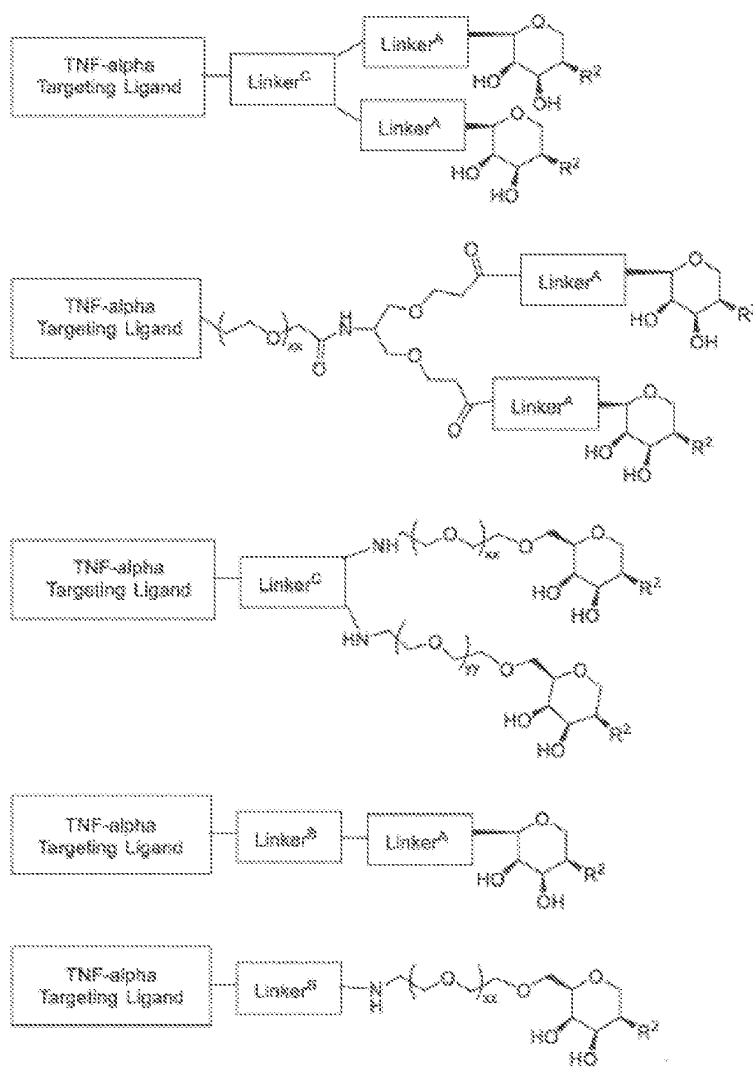




wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$ -(5-membered heteroaryl), and $-NR^6$ -(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

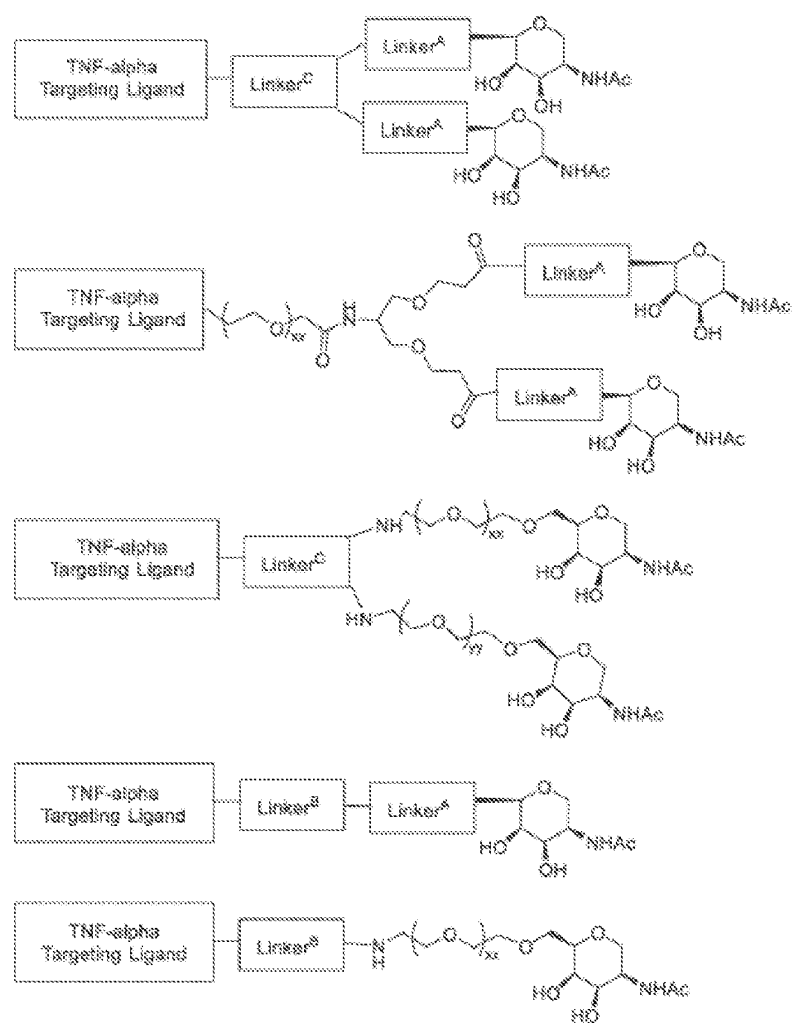
In certain embodiments, the compound of Formula II is selected from:

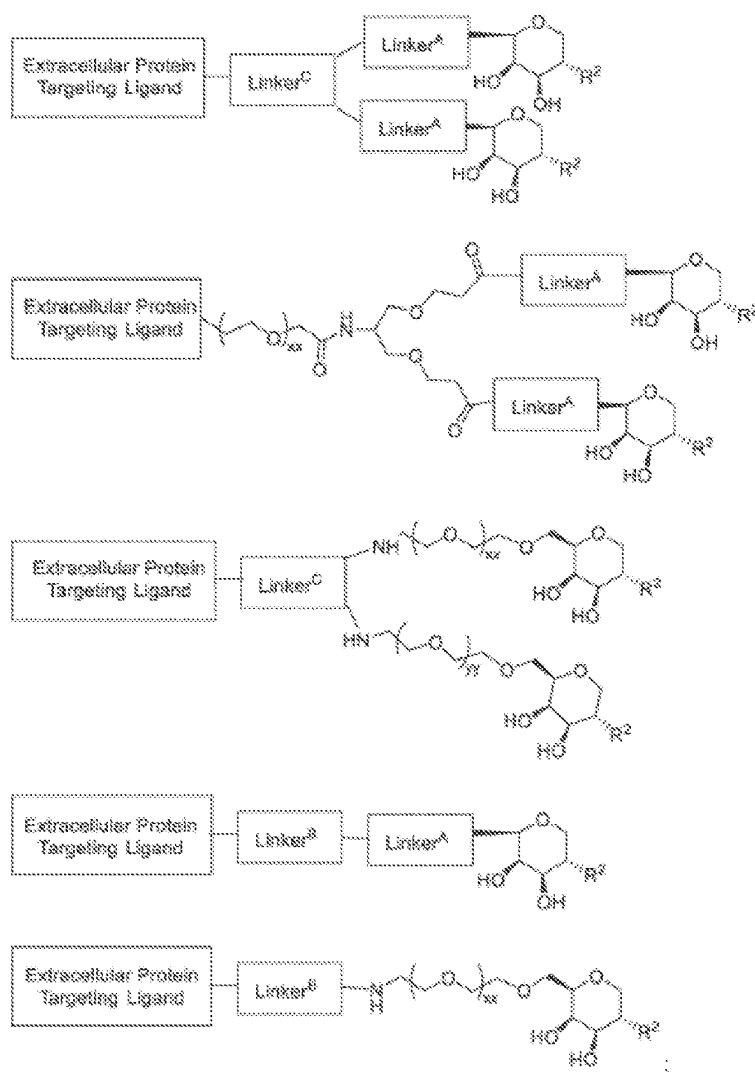




wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$ -(5-membered heteroaryl), and $-NR^6$ -(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

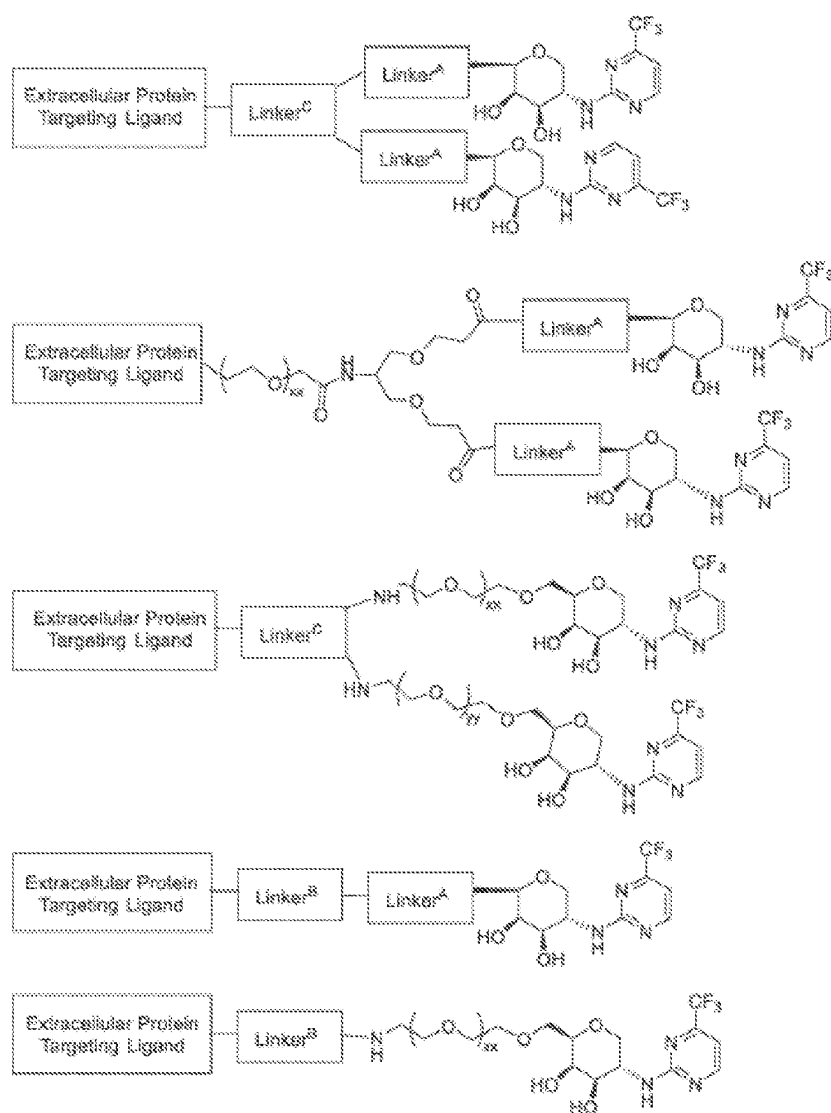
In certain embodiments, the compound of Formula II is selected from:

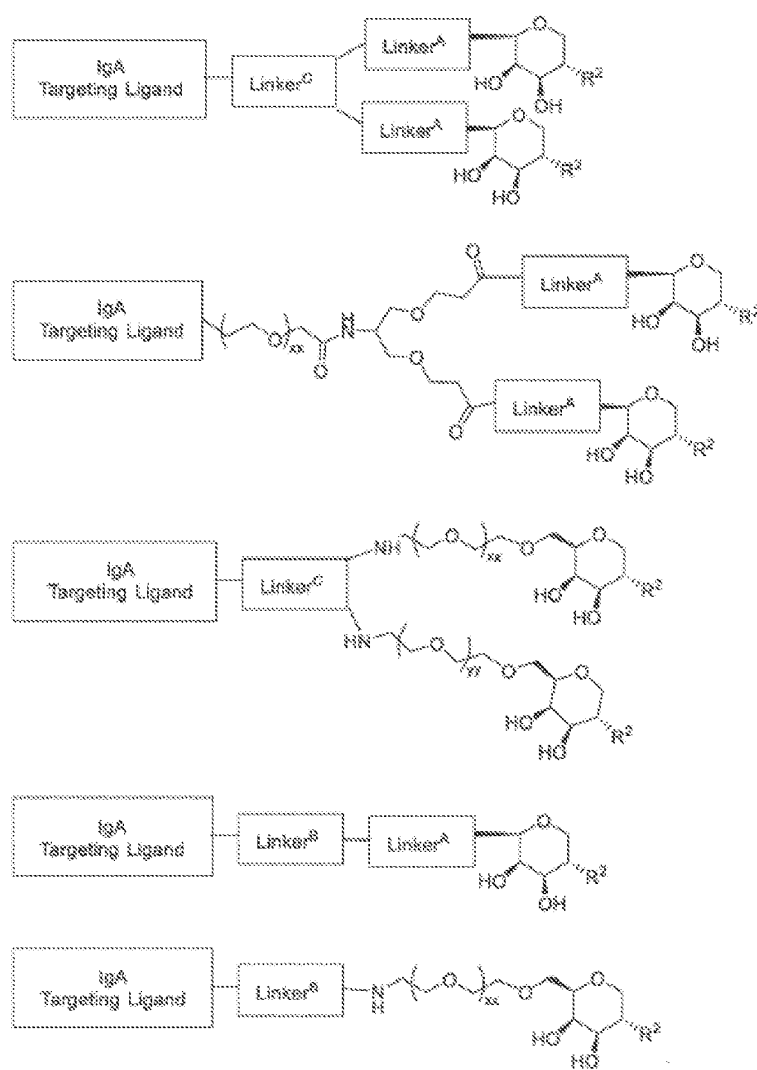




wherein in certain embodiments R² is selected from -NR⁶COR¹⁰, -NR⁶-(5-membered heteroaryl), and -NR⁶-(6-membered heteroaryl), each of which R² groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

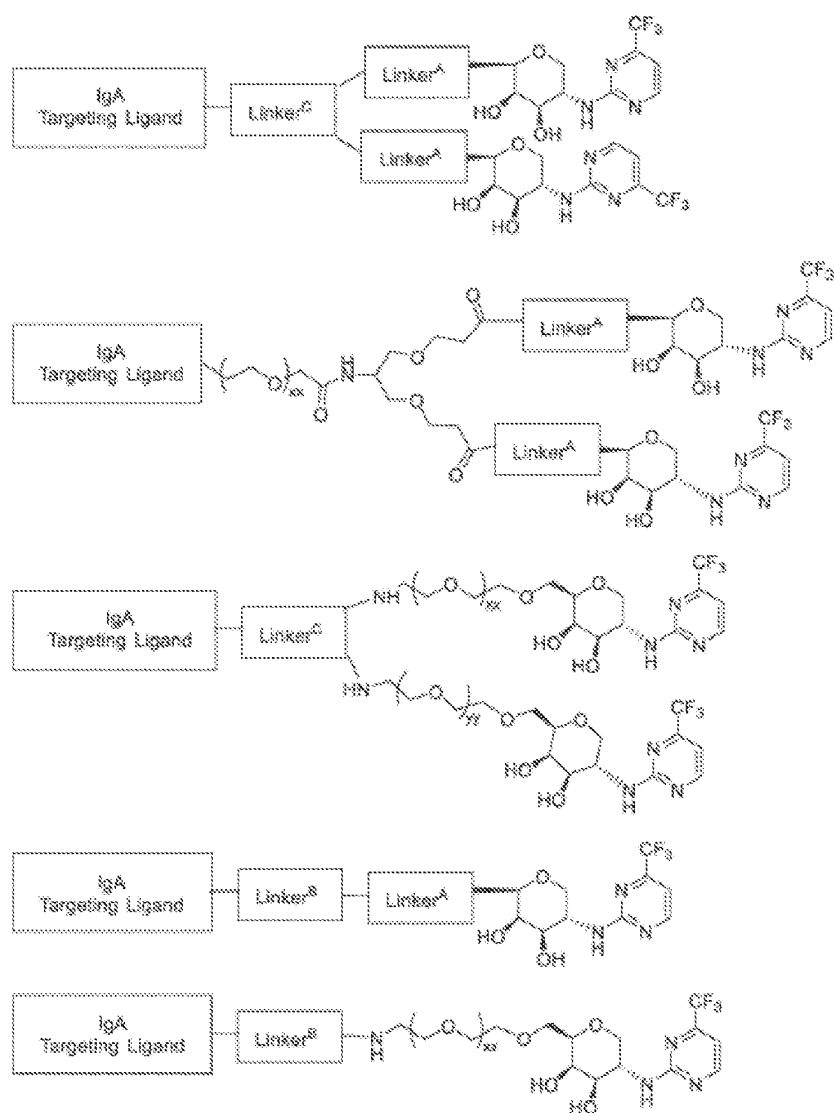
In certain embodiments, the compound of Formula II is selected from:

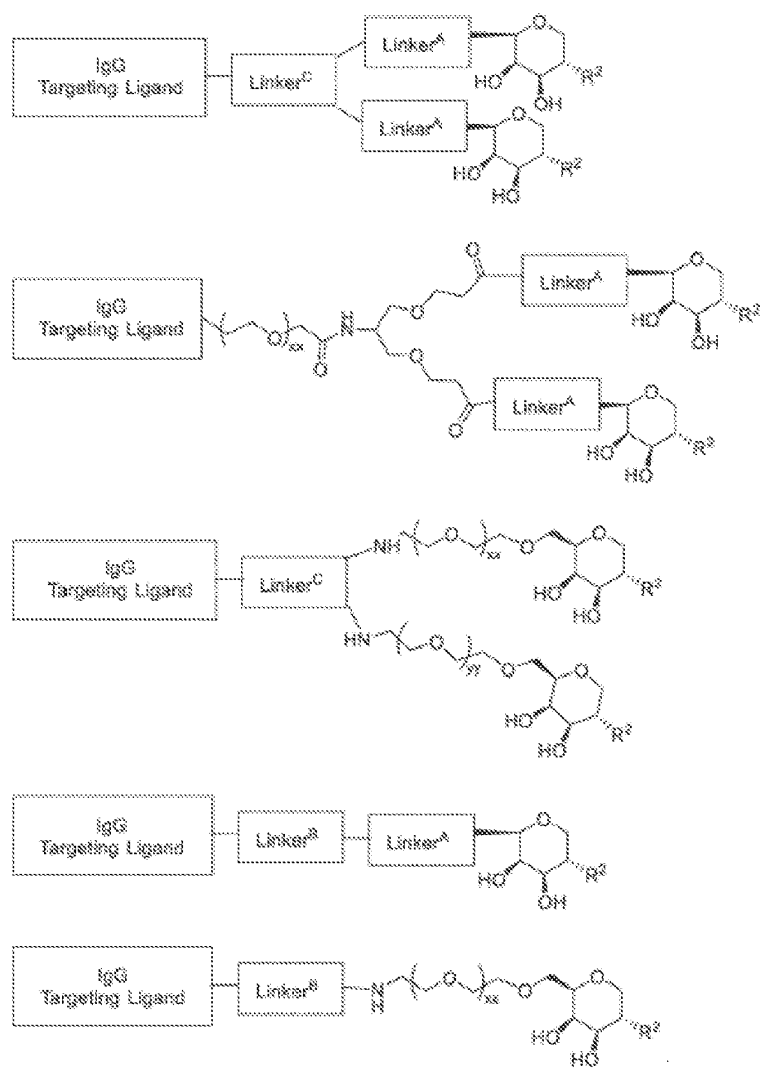


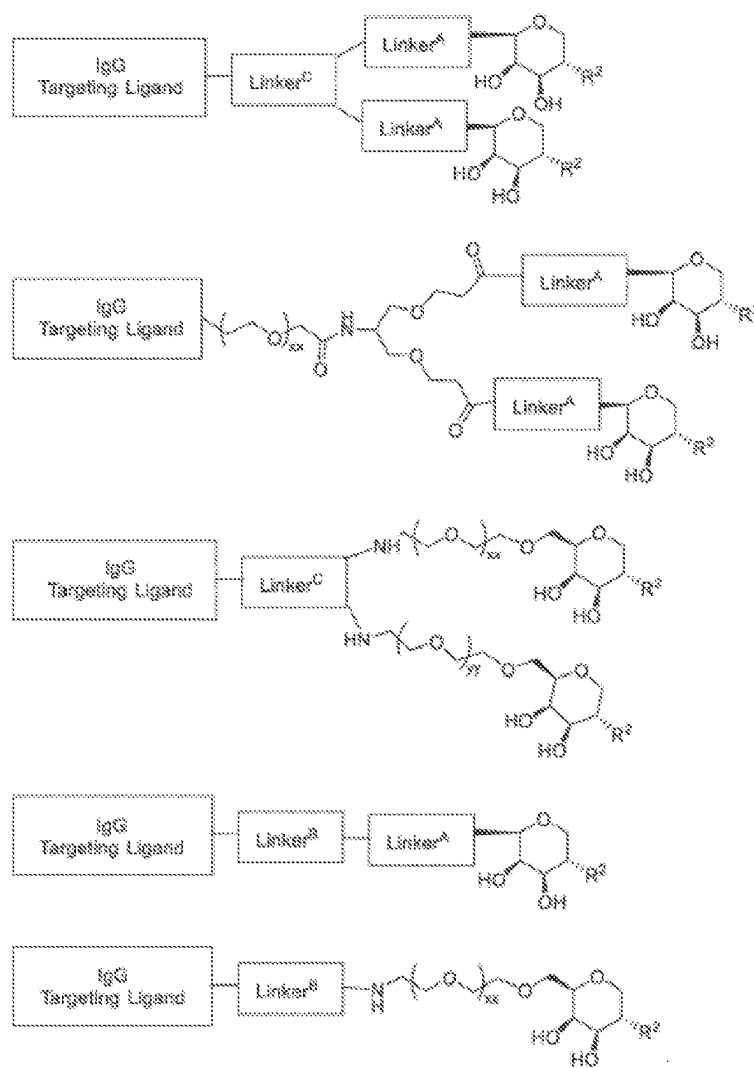


wherein in certain embodiments R^2 is selected from $-NR^bCOR^{10}$, $-NR^6$ -(5-membered heteroaryl), and $-NR^6$ -(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

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

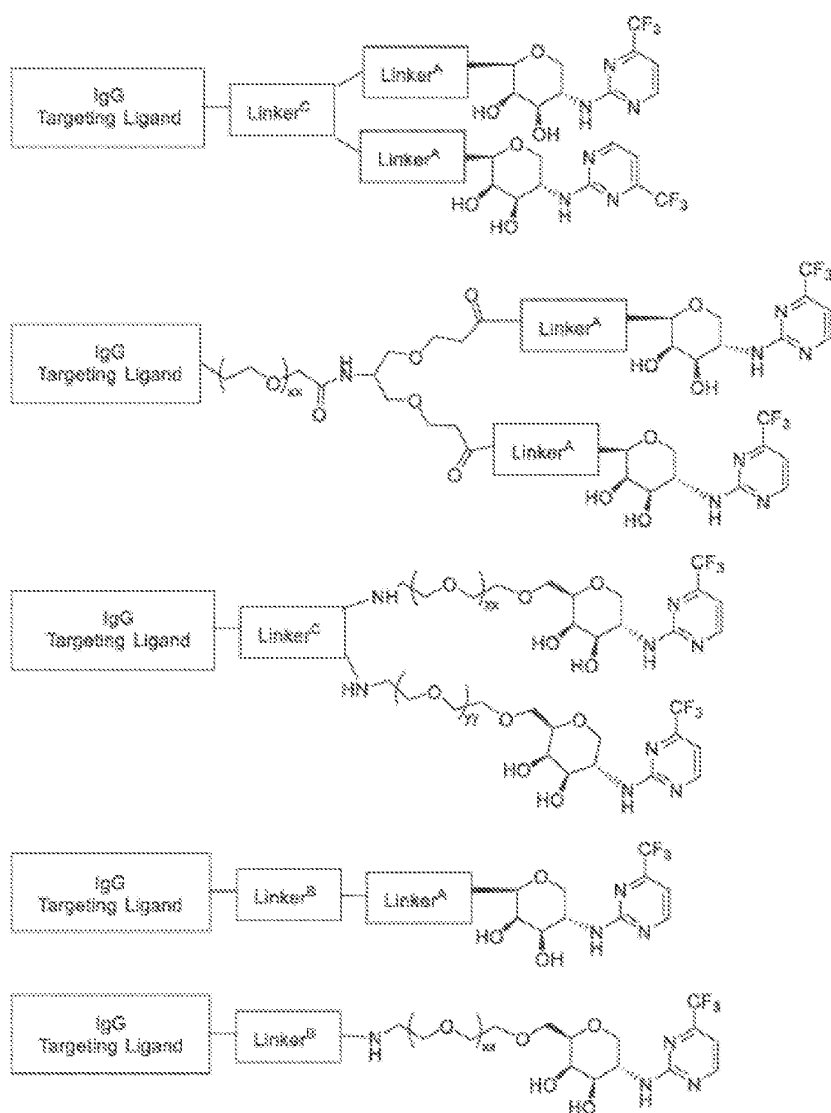


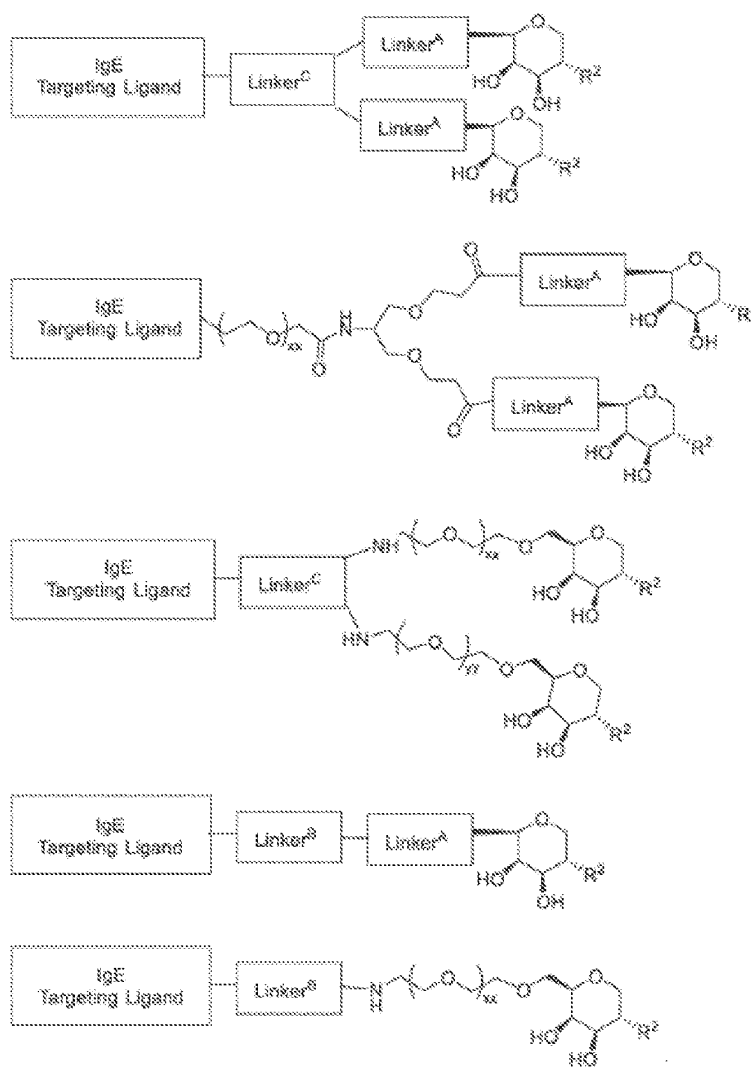




wherein in certain embodiments R² is selected from -NR⁶COR¹⁰, -NR⁶-(5-membered heteroaryl), and -NR⁶-(6-membered heteroaryl), each of which R² groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

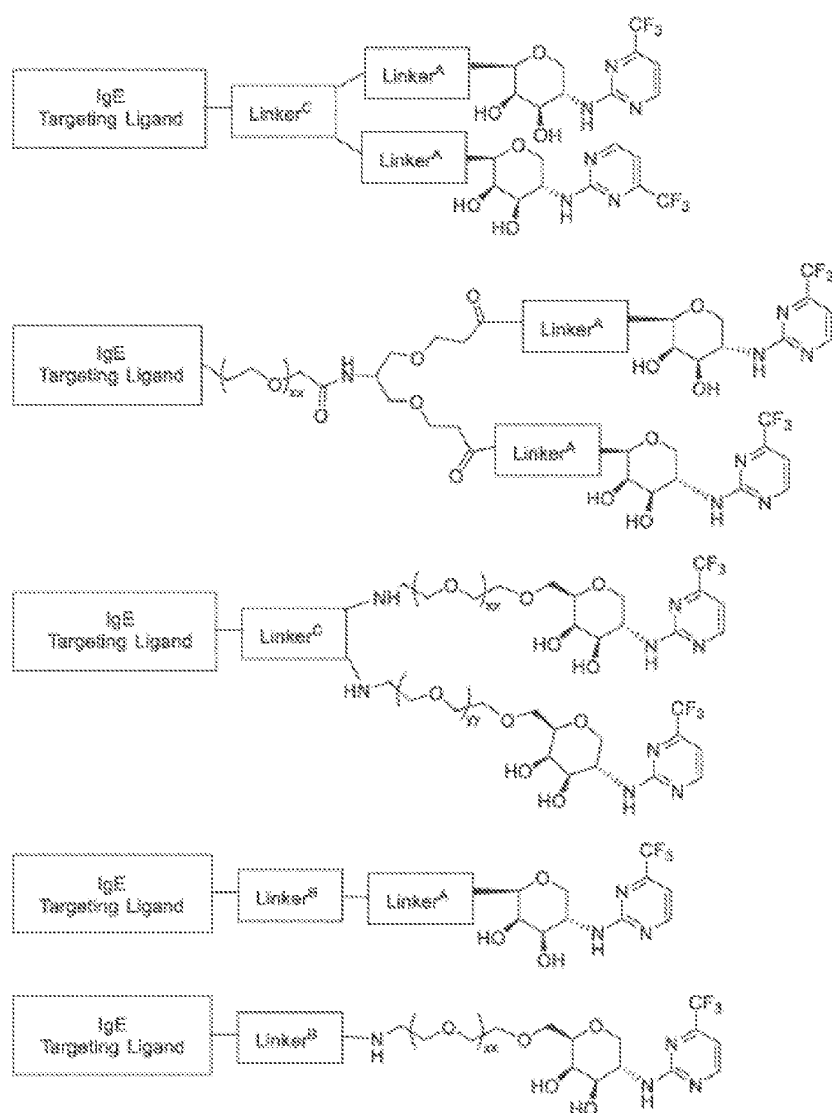
In certain embodiments, the compound of Formula II is selected from:

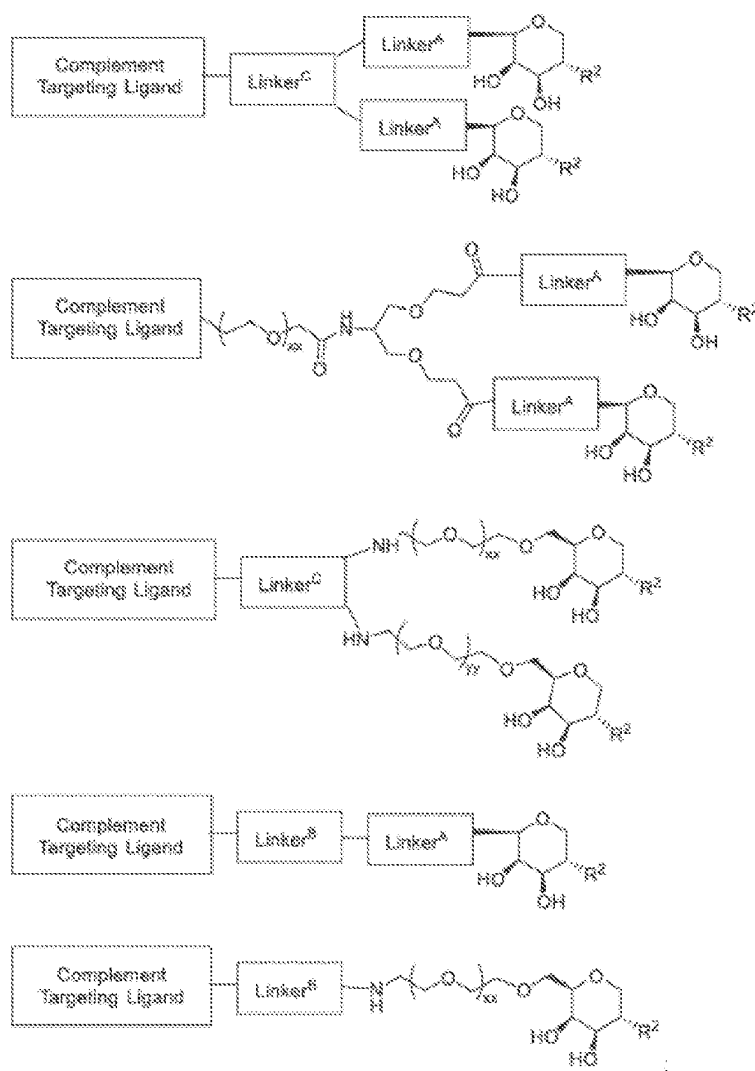




wherein in certain embodiments R² is selected from -NR⁶COR¹⁰, -NR⁶-(5-membered heteroaryl), and -NR⁶-(6-membered heteroaryl), each of which R² group is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2,
 5 3, or 4 substituents independently selected from F, Cl, Br, haloalkyl, or alkyl.

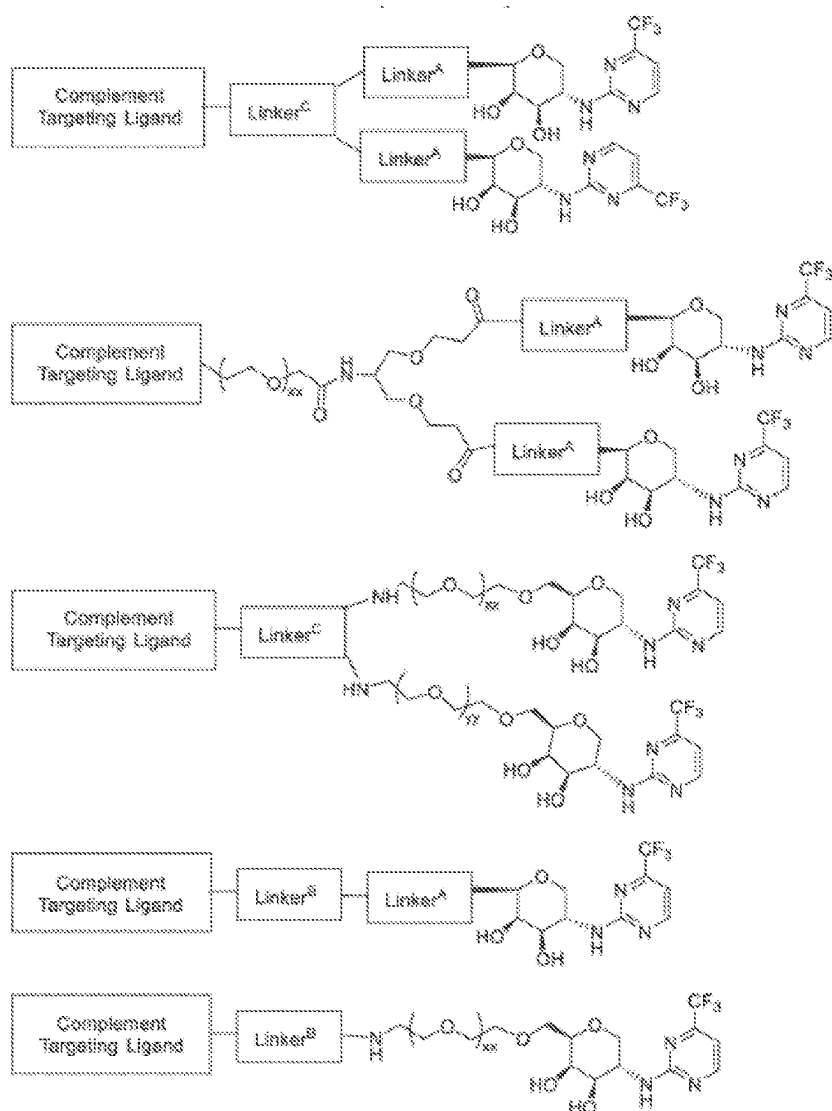
In certain embodiments, the compound of Formula II is selected from:

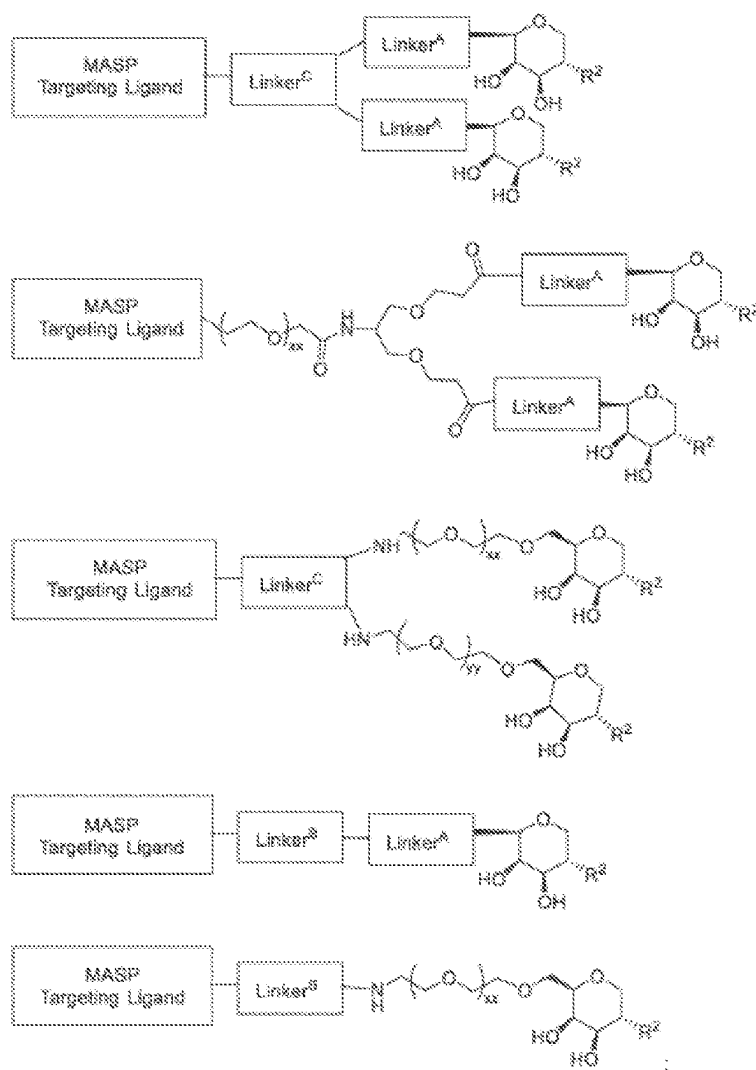




wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$ -(5-membered heteroaryl), and $-NR^6$ -(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

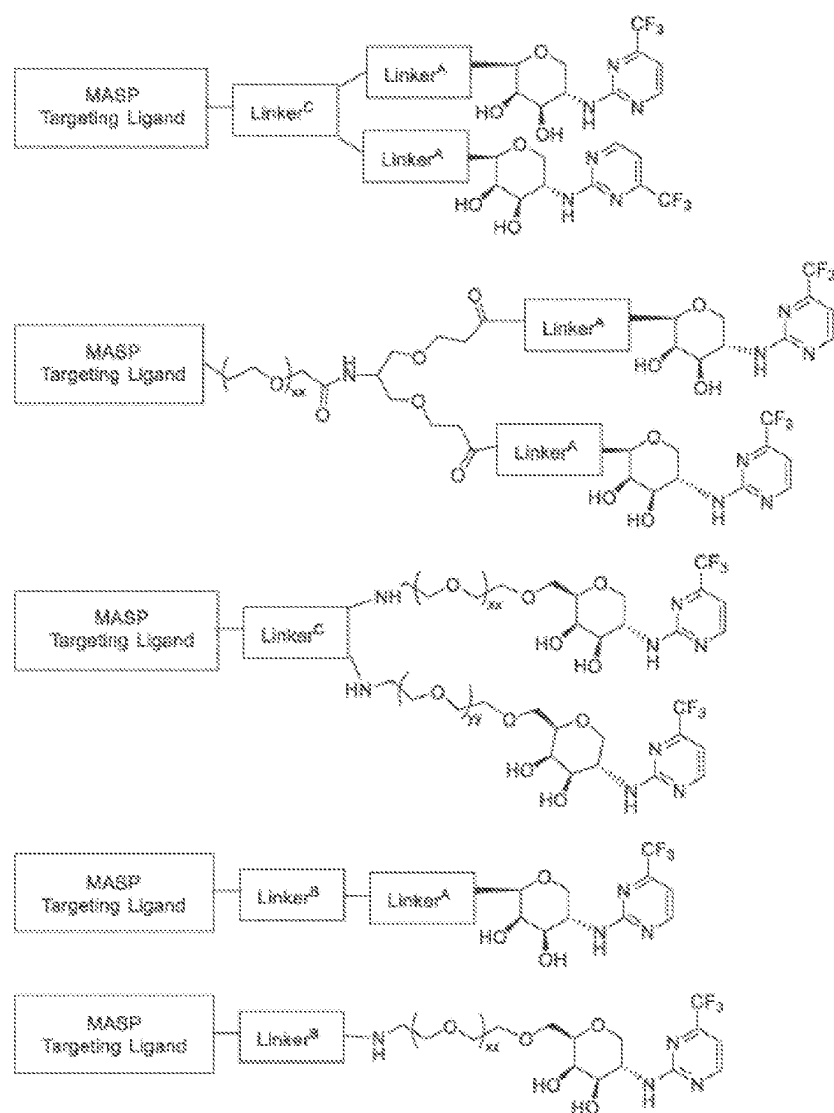
In certain embodiments, the compound of Formula II is selected from:

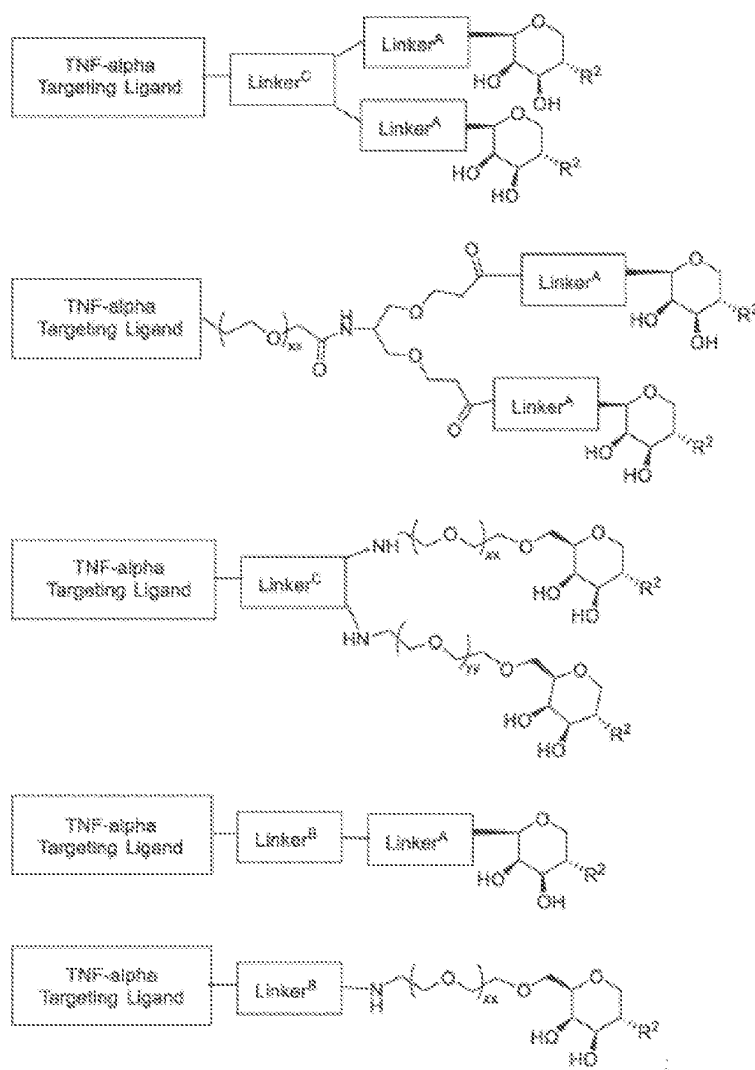




wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$ -(5-membered heteroaryl), and $-NR^6$ -(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

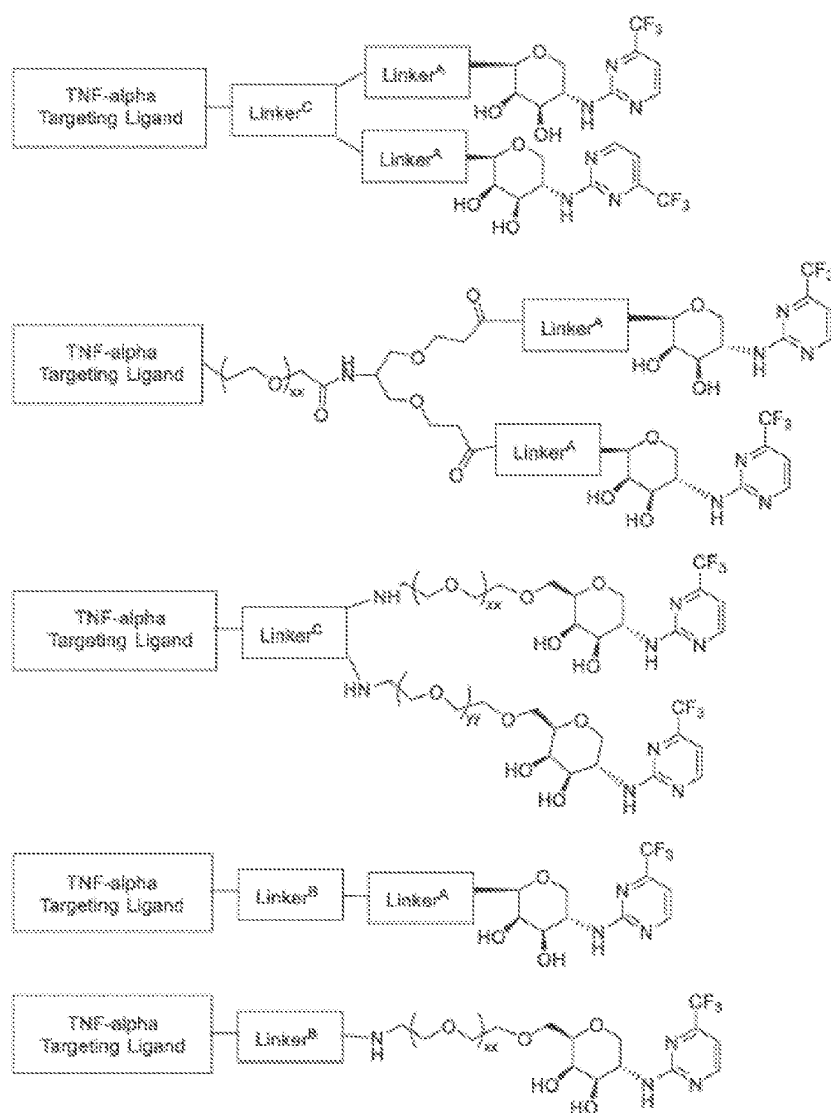
In certain embodiments, the compound of Formula II is selected from:

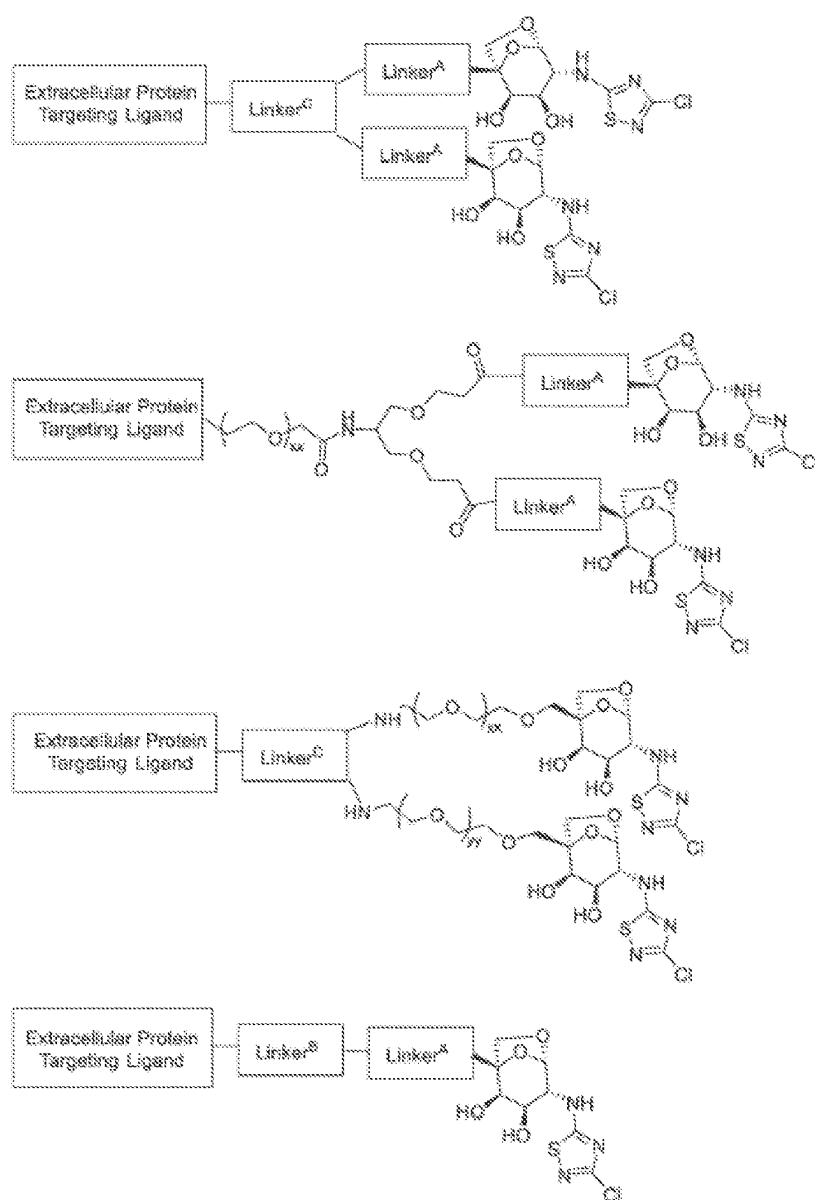


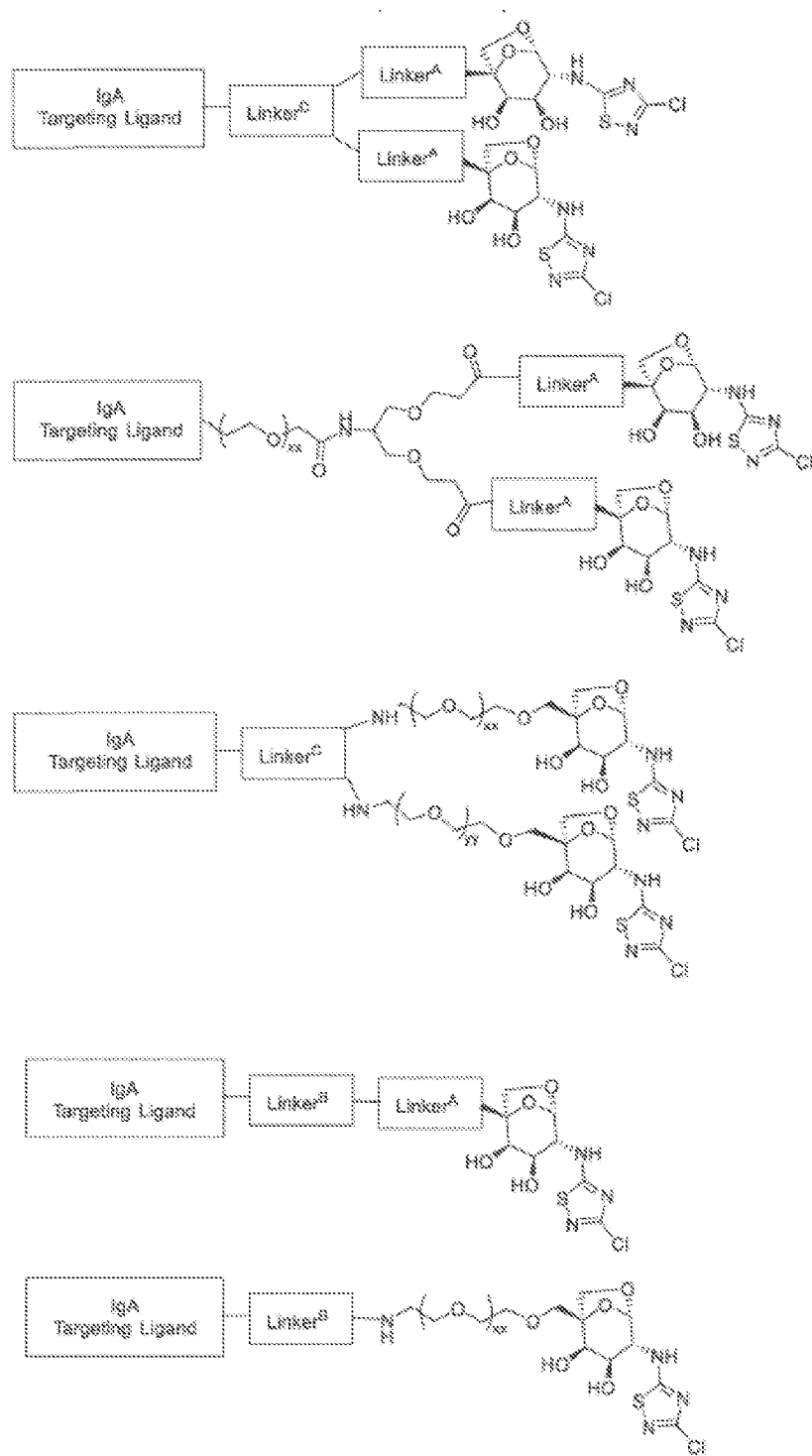


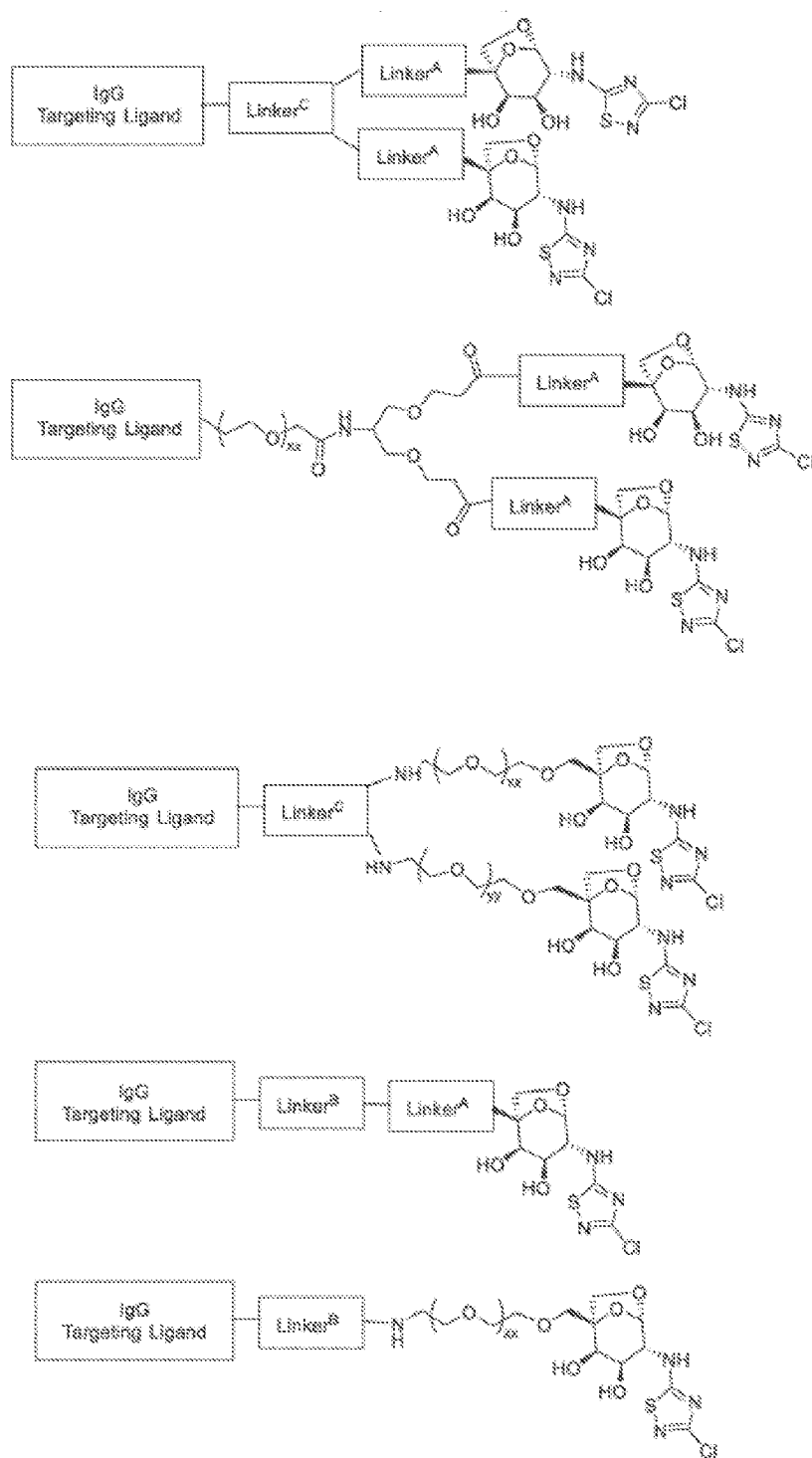
wherein in certain embodiments R^2 is selected from $-\text{NR}^6\text{COR}^{10}$, $-\text{NR}^6$ -(5-membered heteroaryl), and $-\text{NR}^6$ -(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1,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

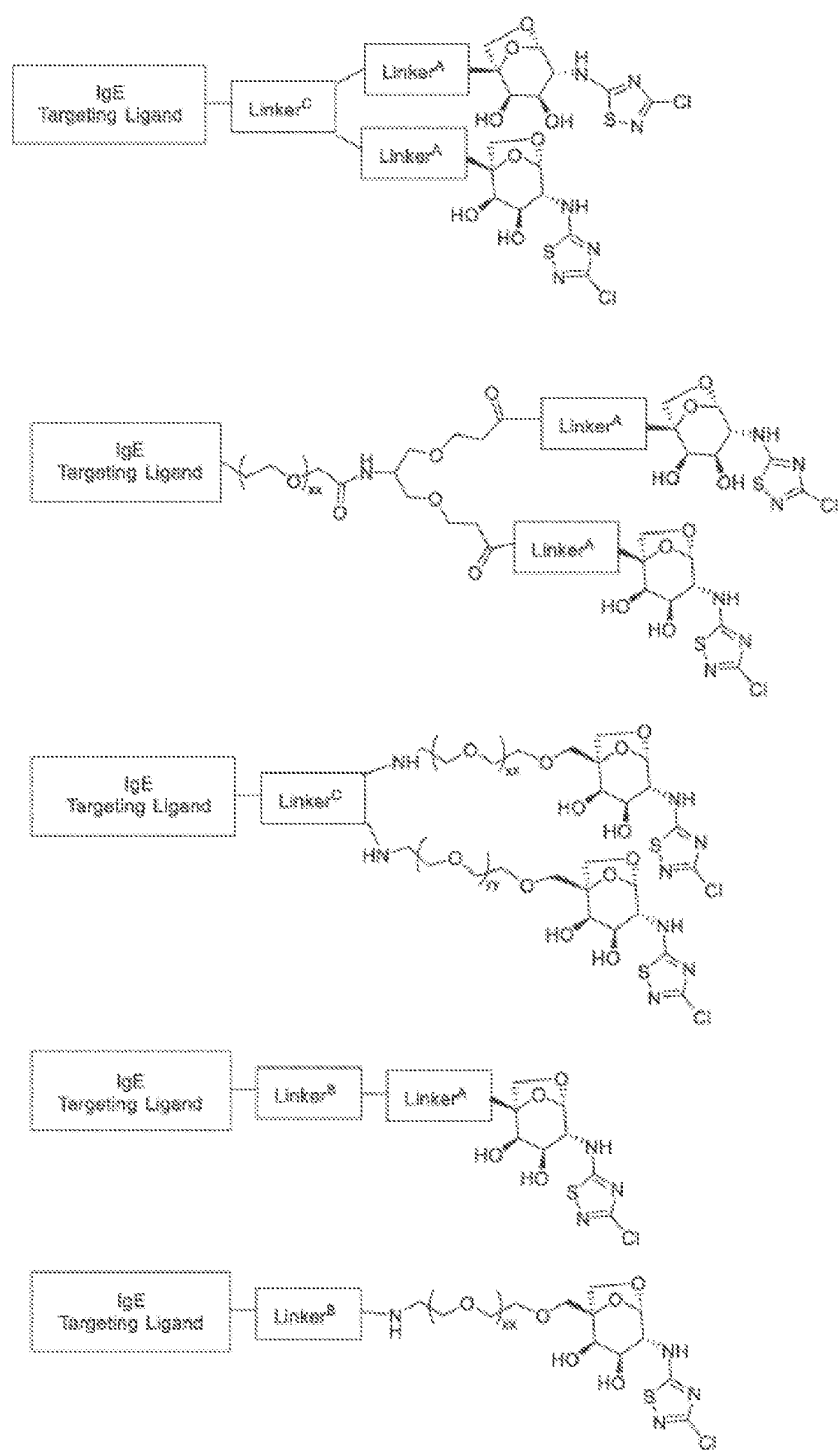
In certain embodiments, the compound of Formula II is selected from:

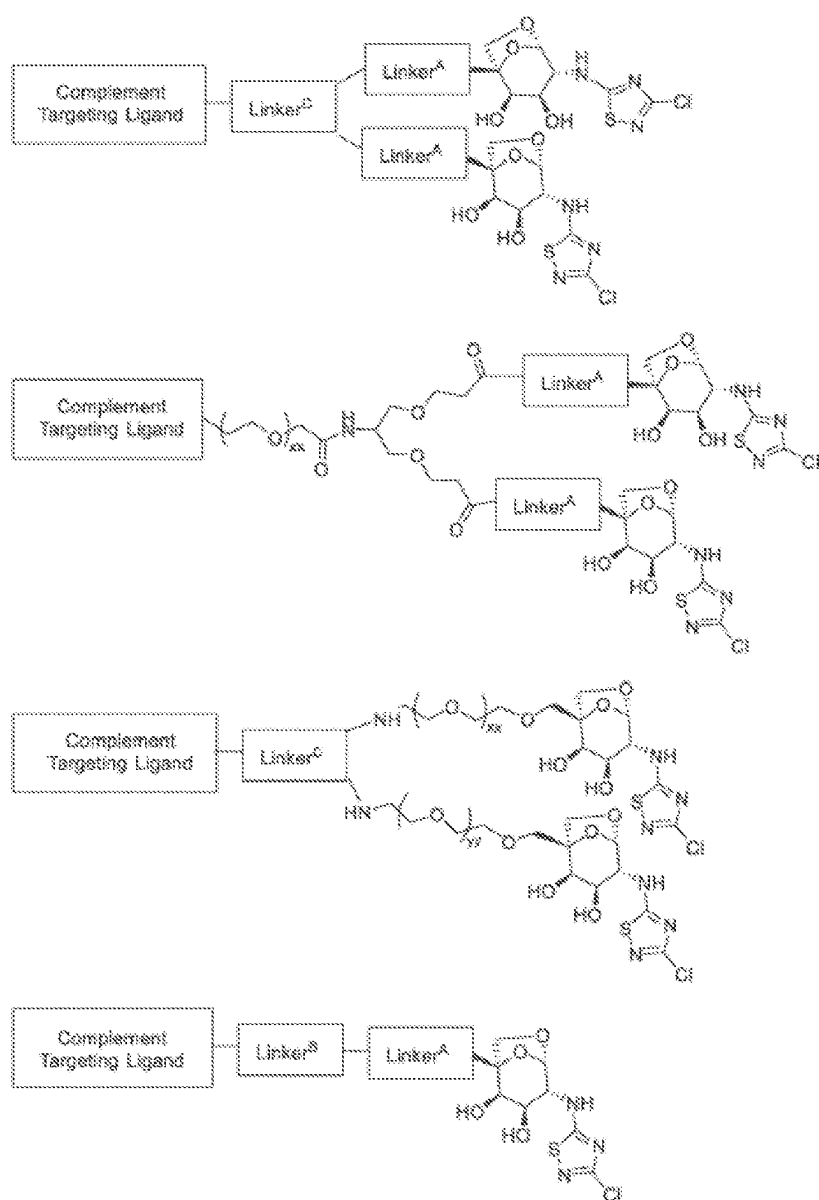


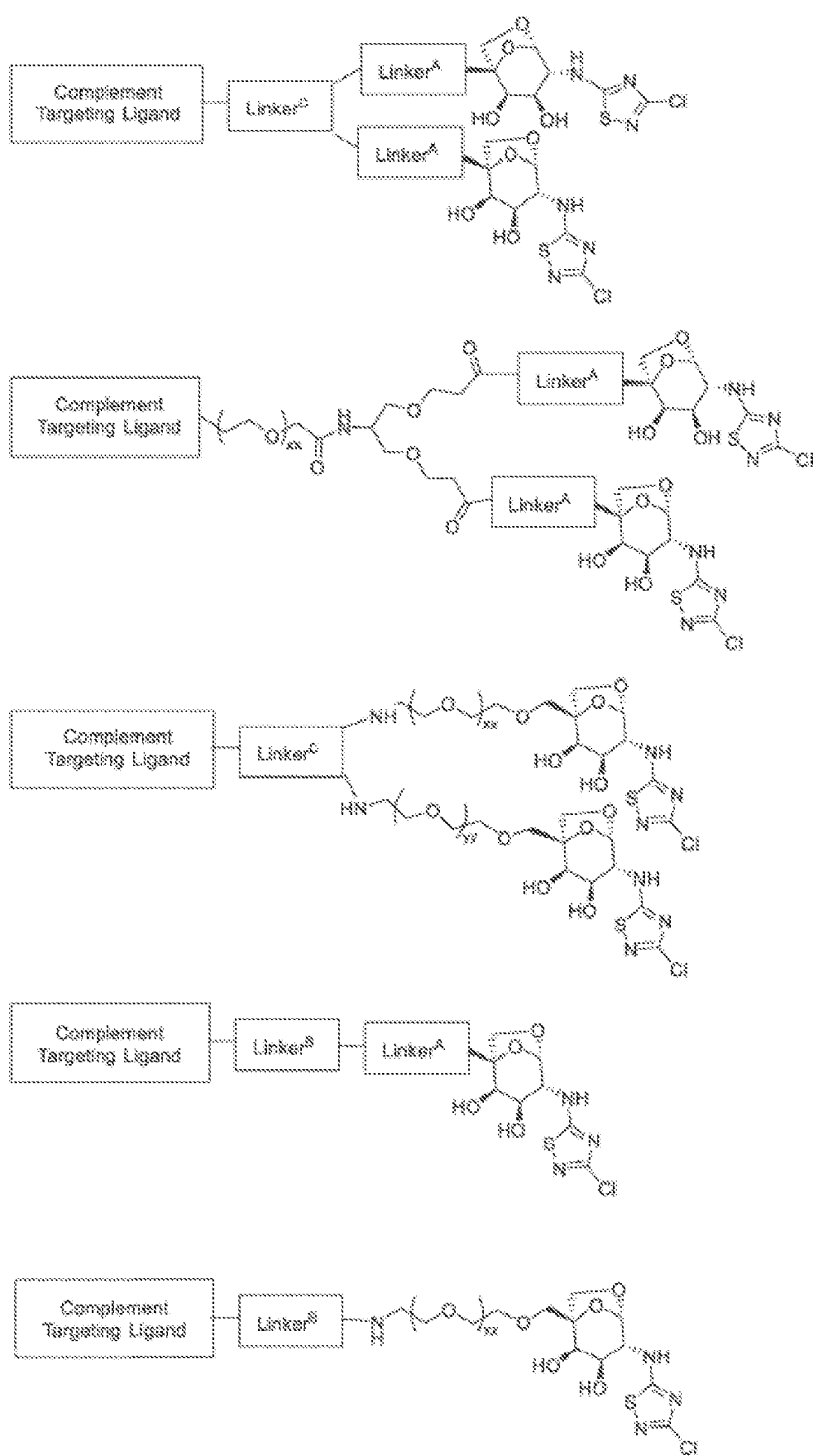


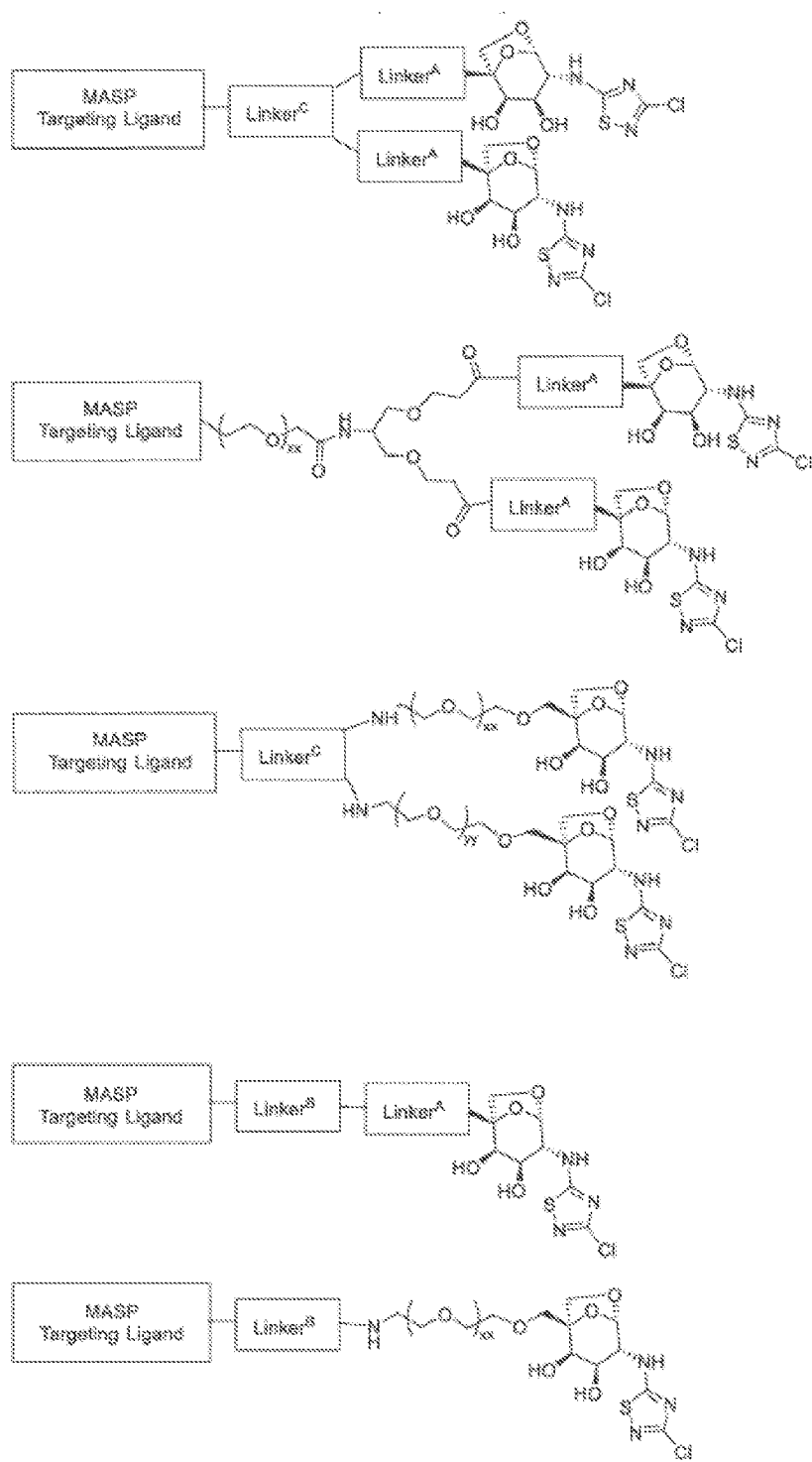


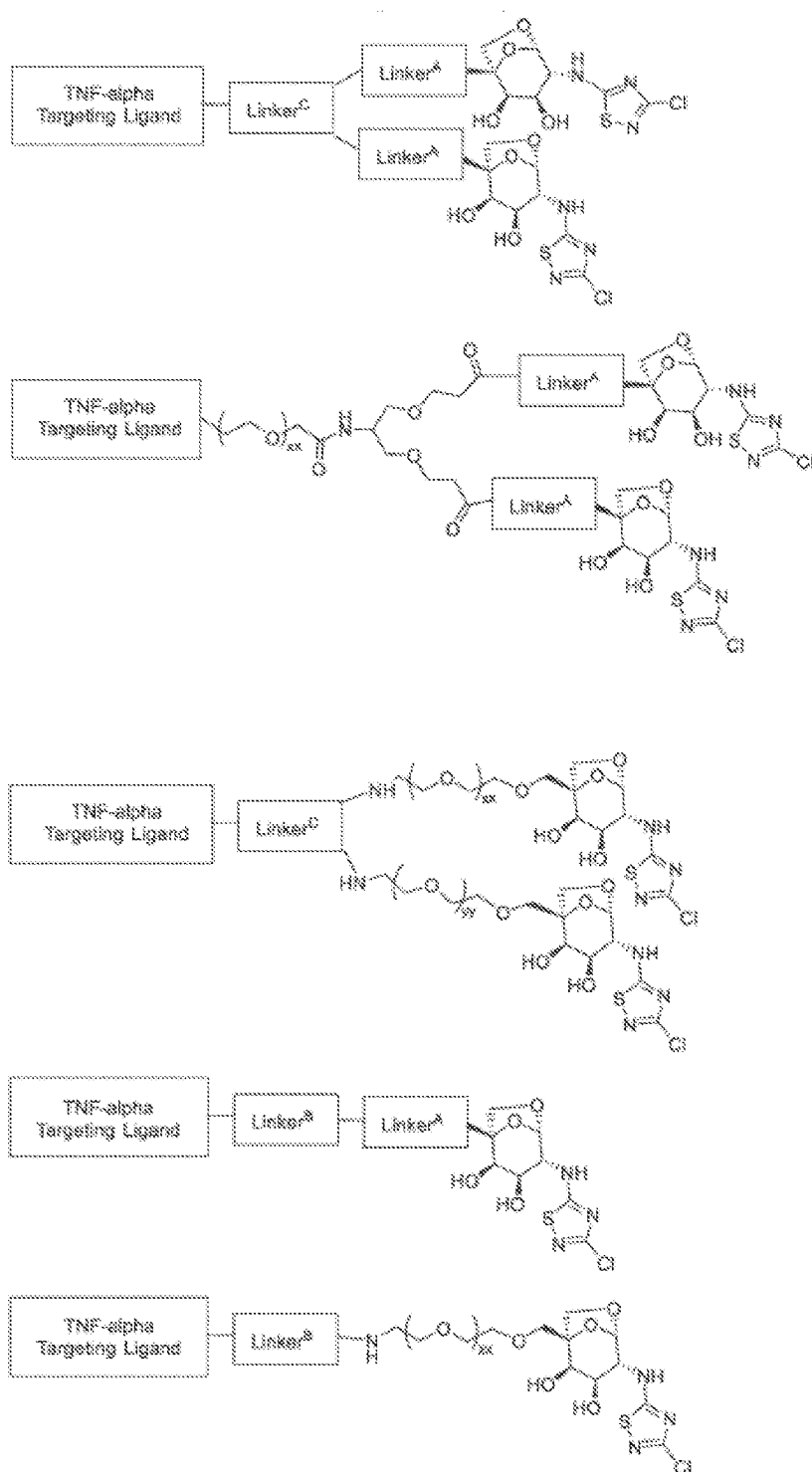


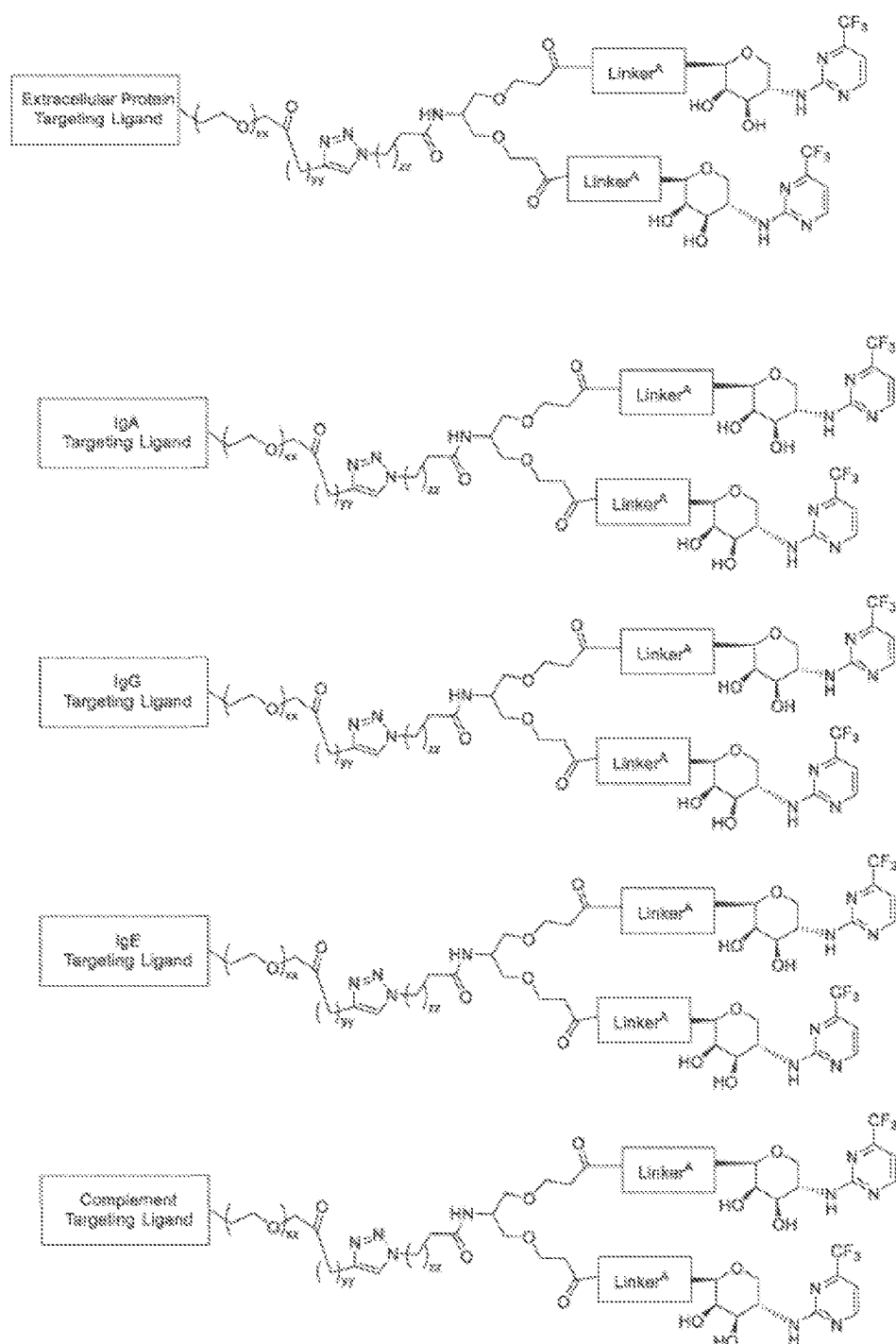


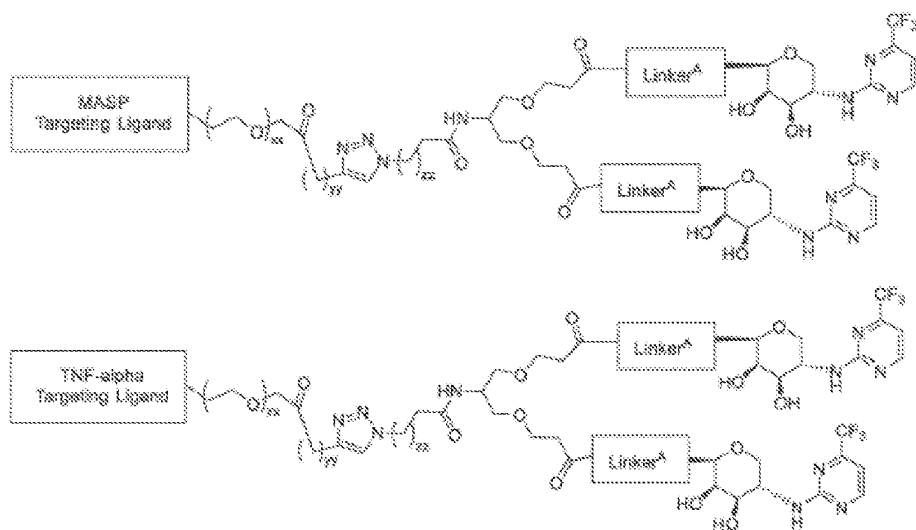




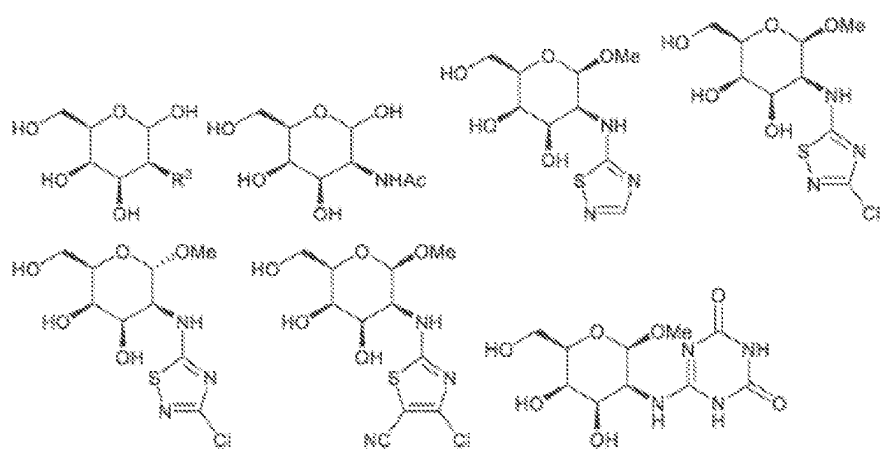


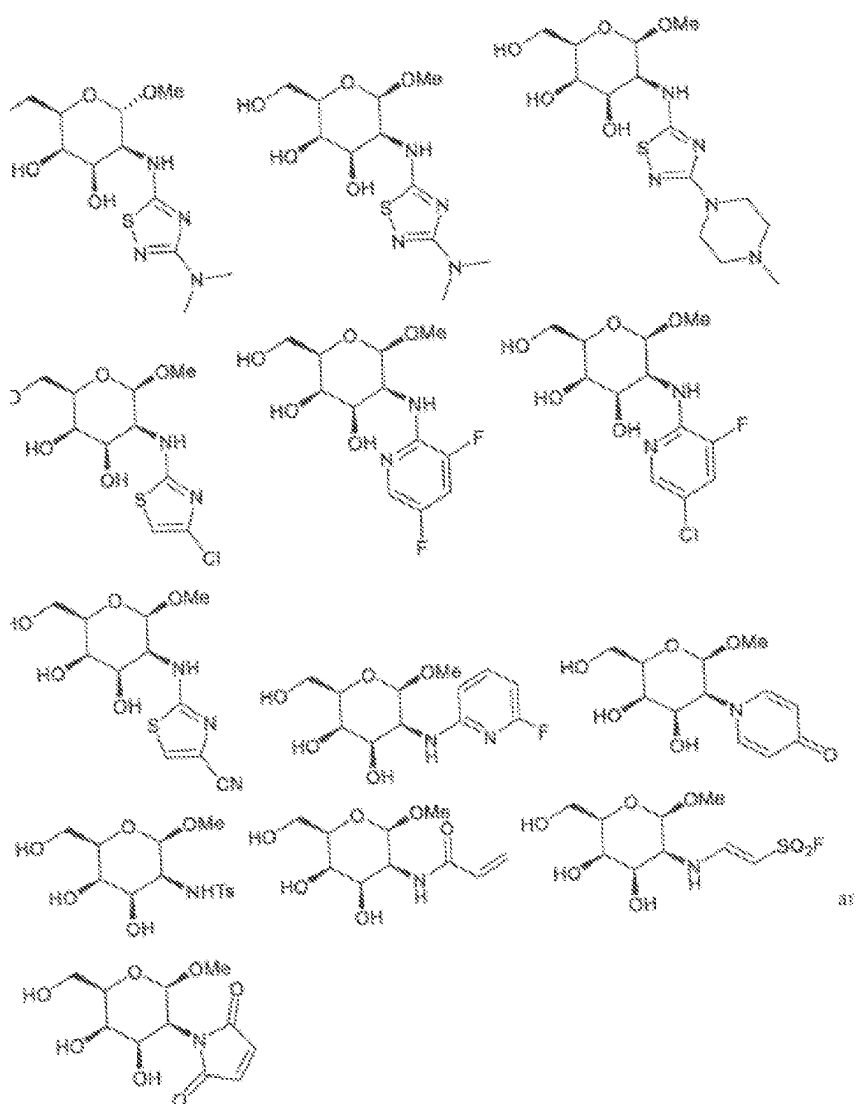


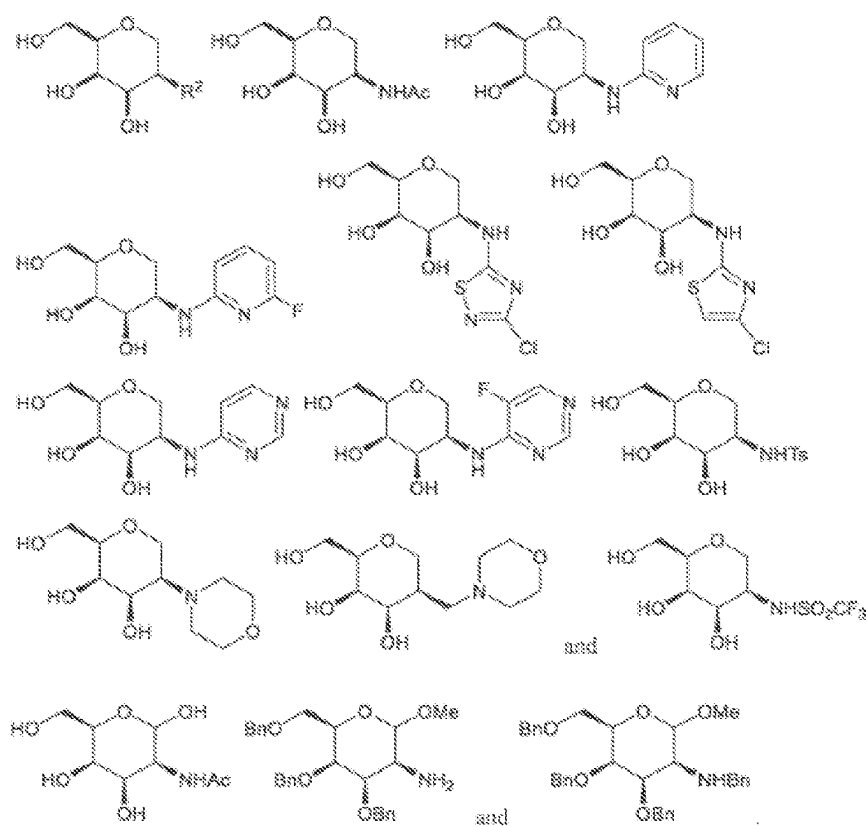


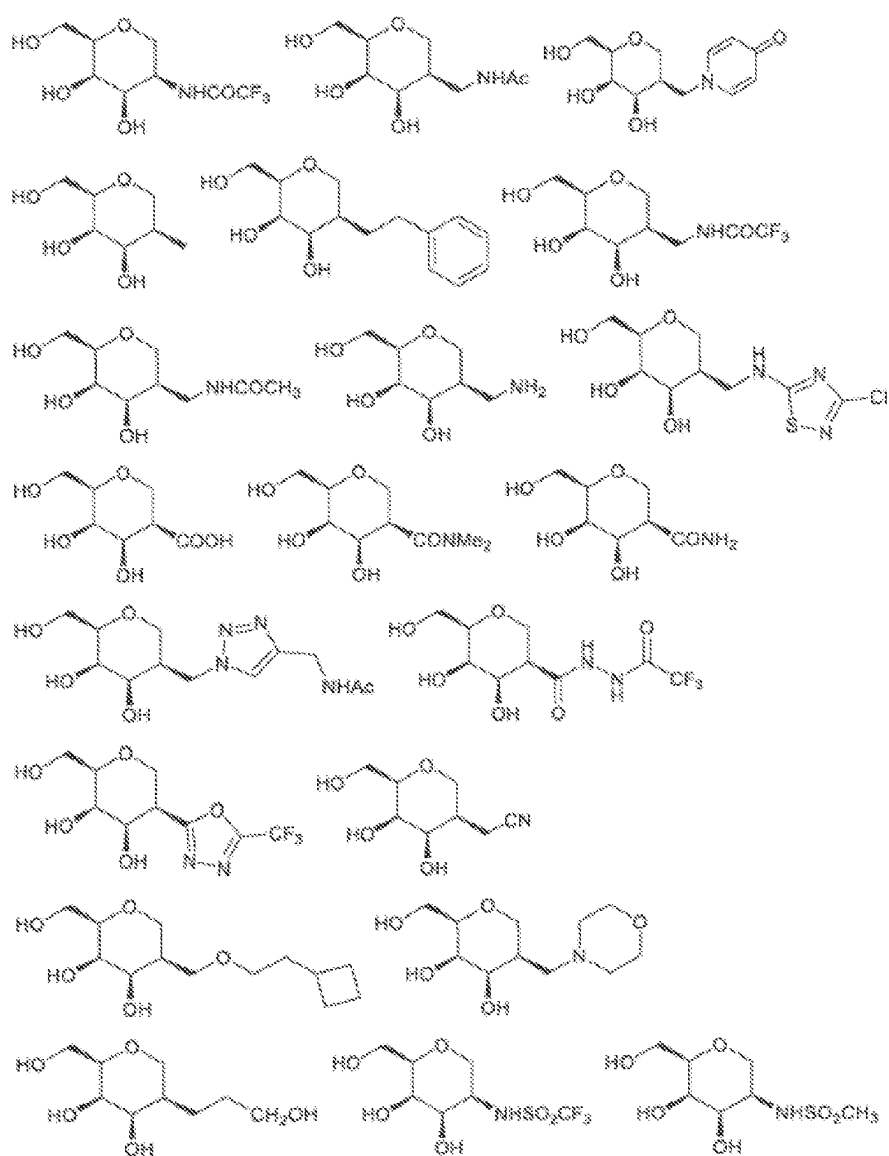


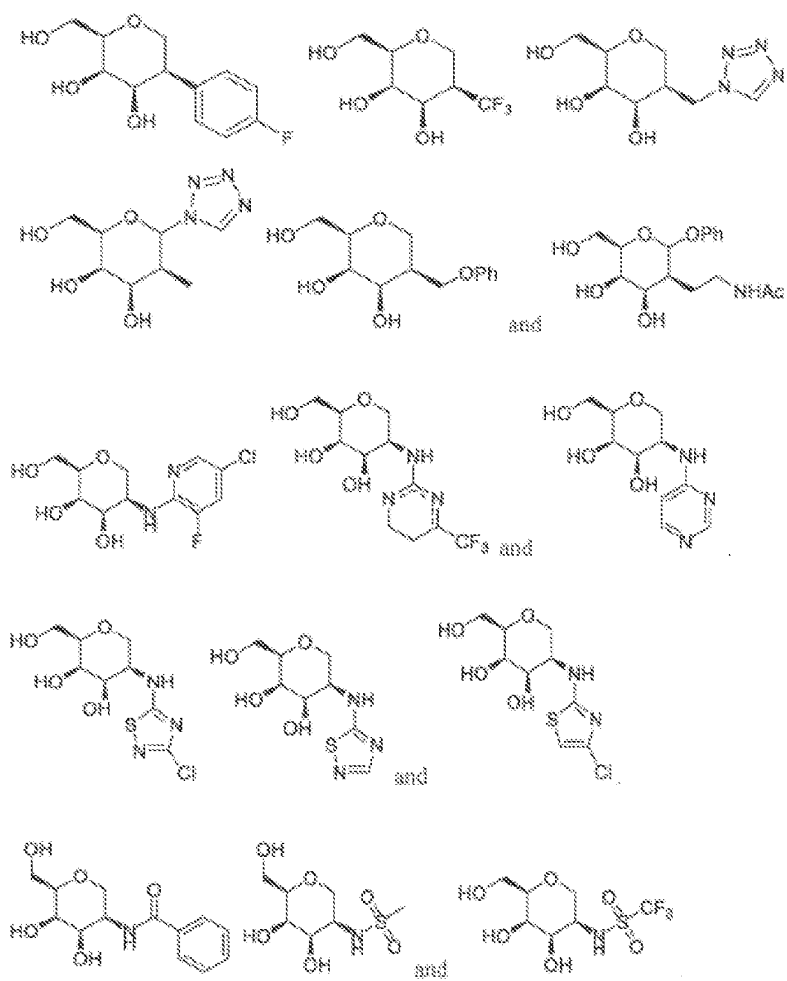
In certain embodiments, an ASGPR ligand useful for incorporation into a compound of Formula II is selected from:

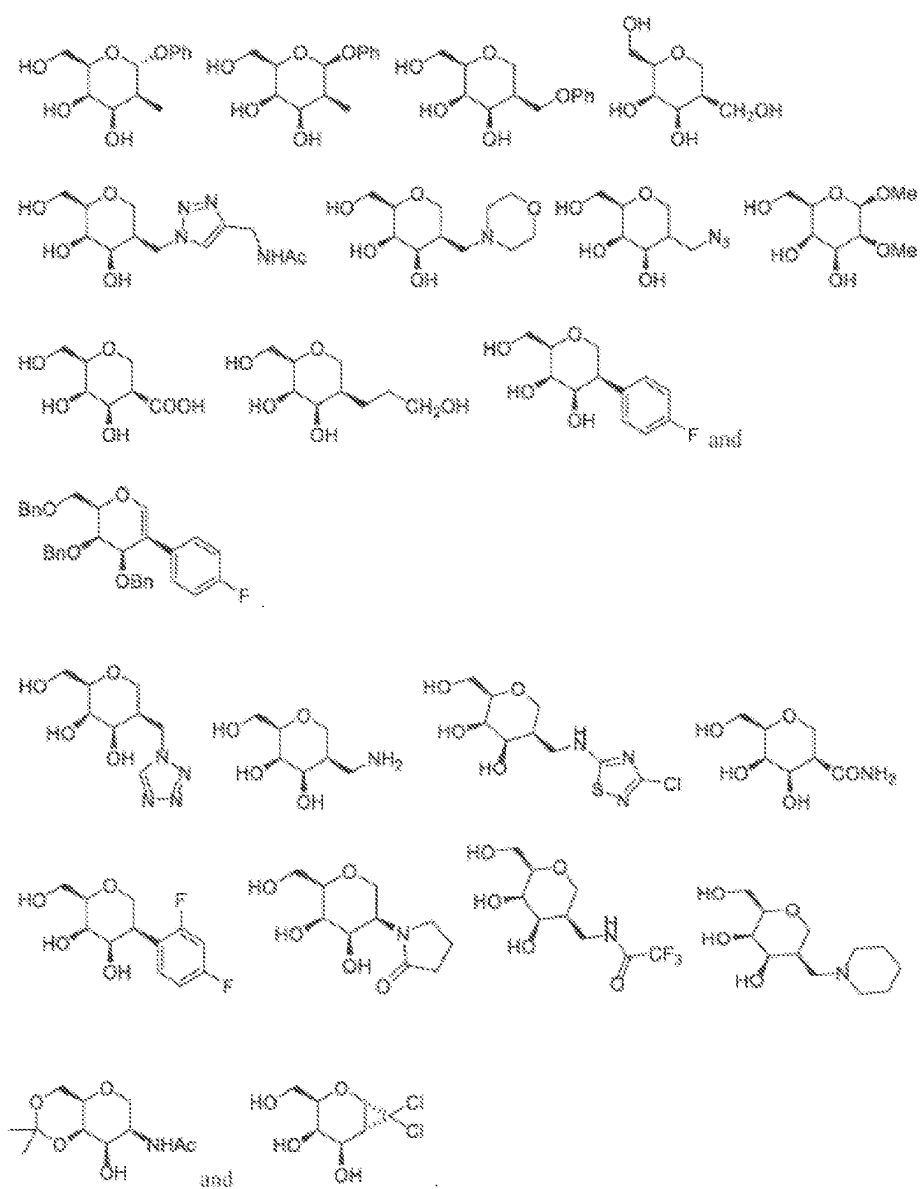


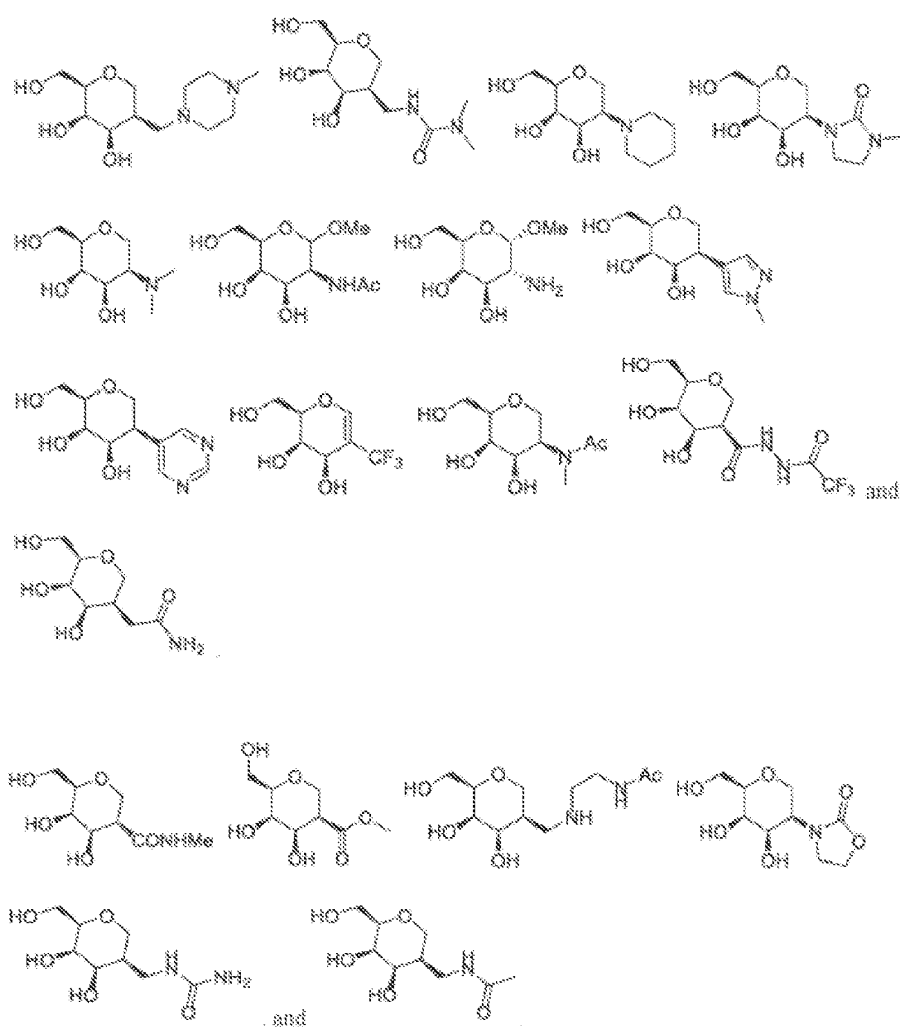


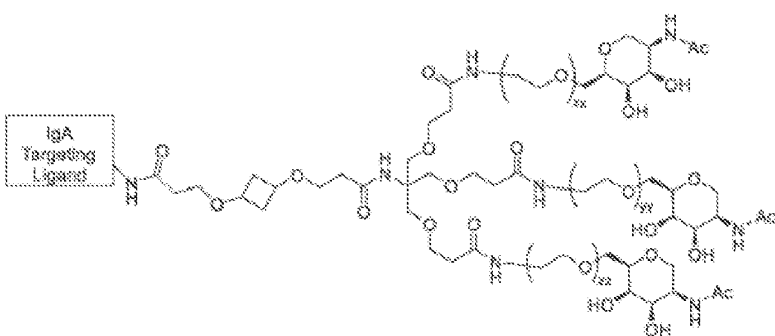
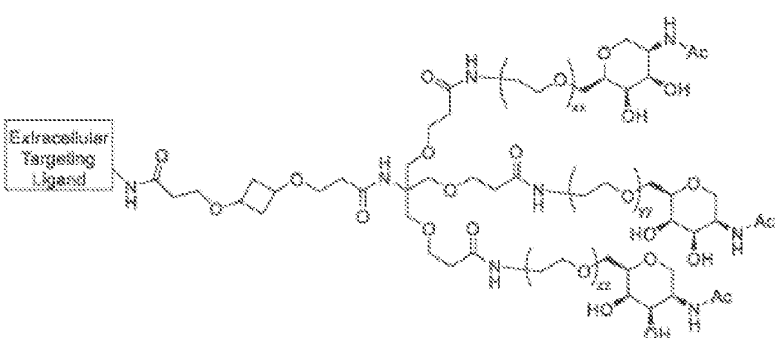
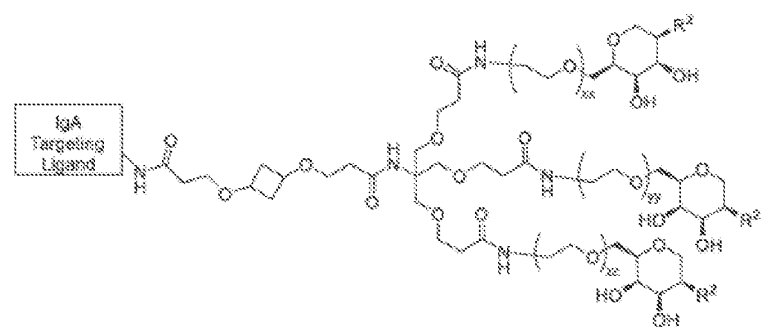
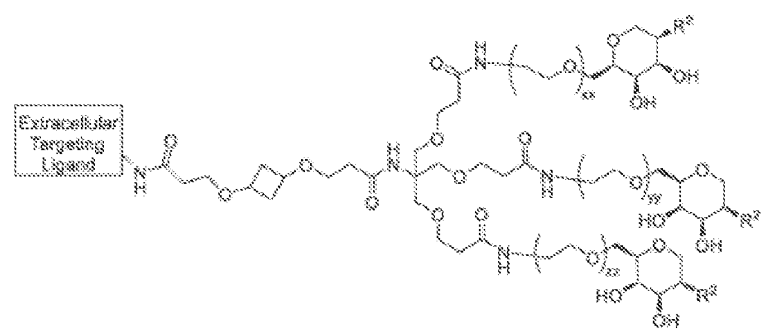


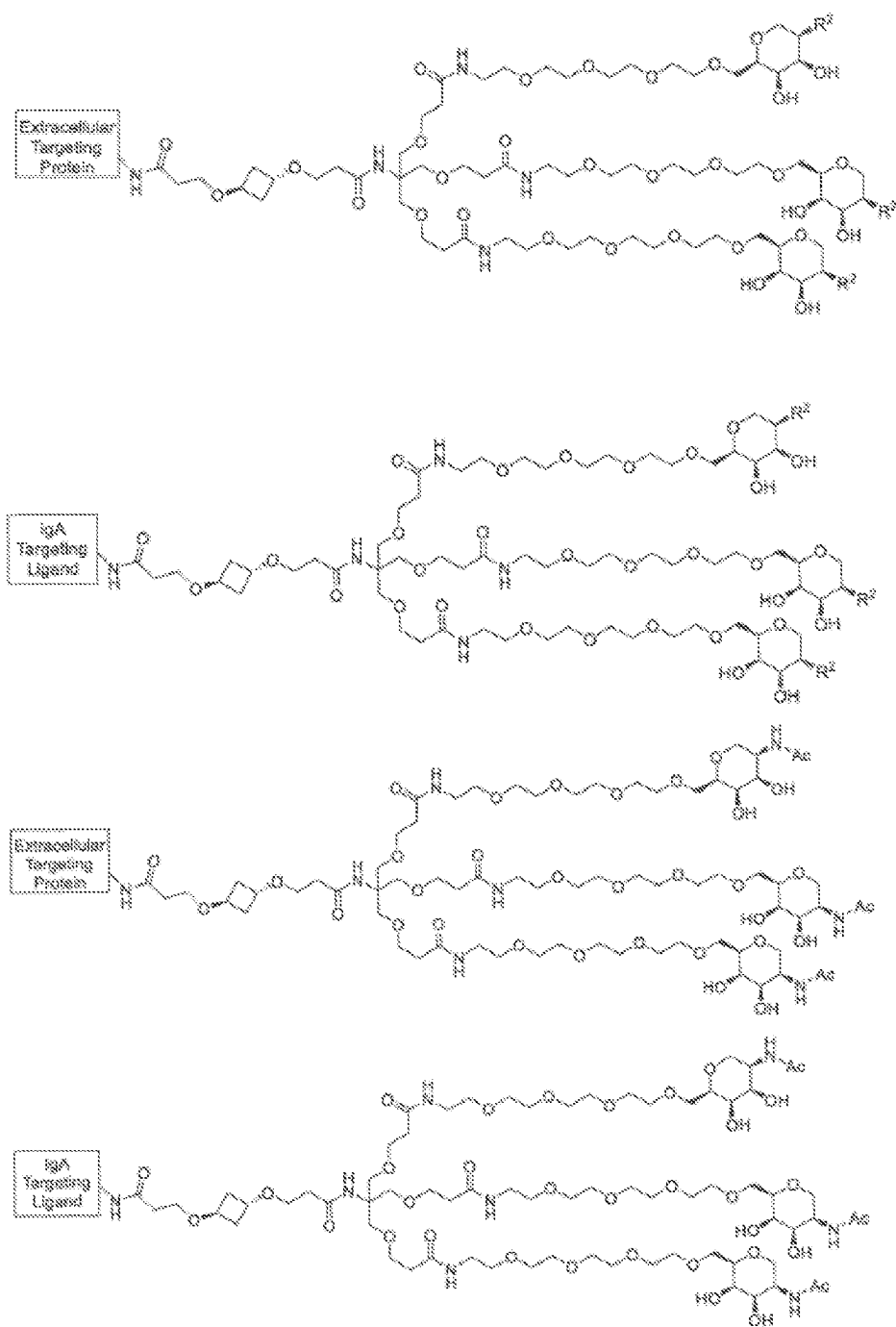


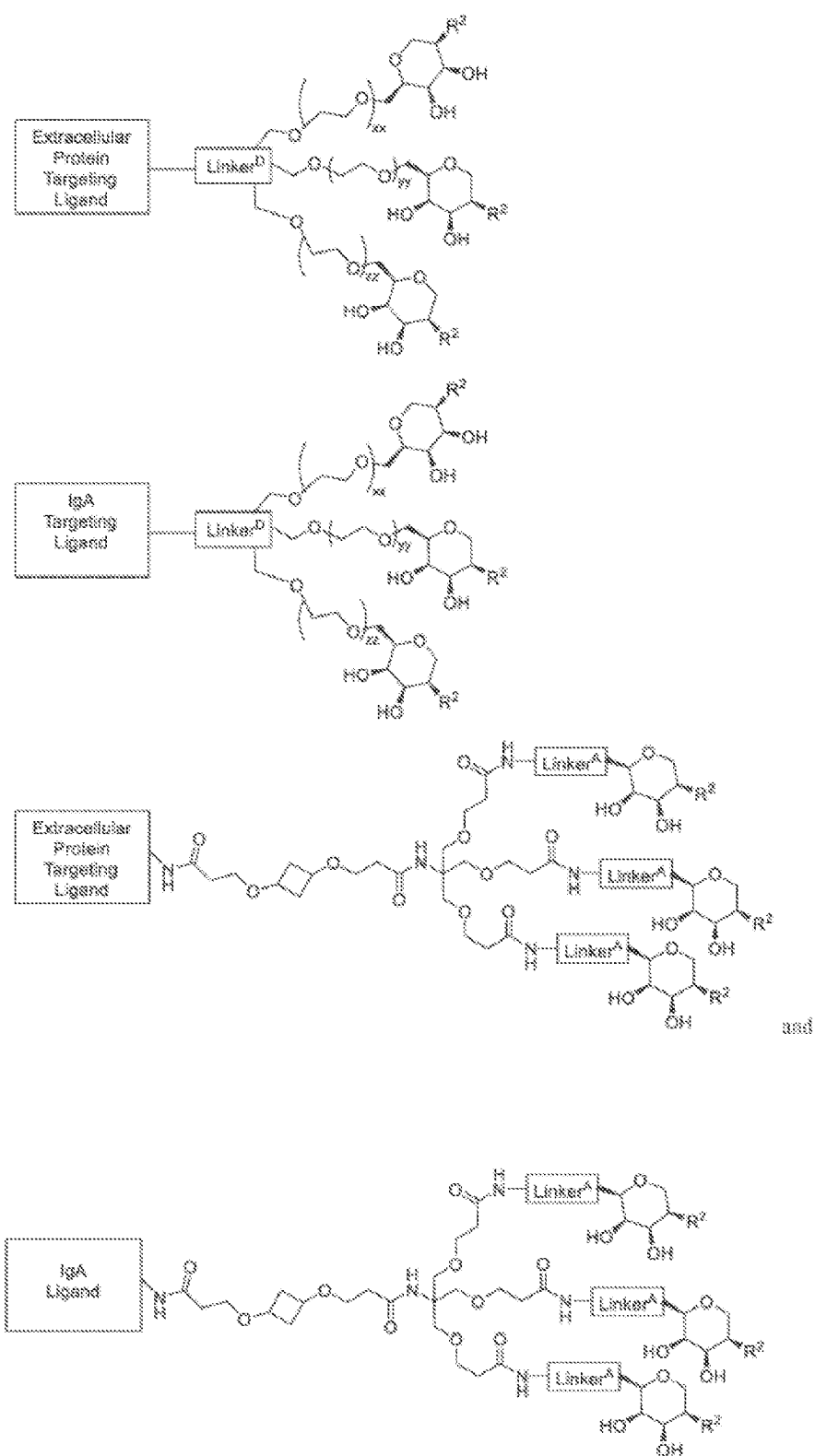


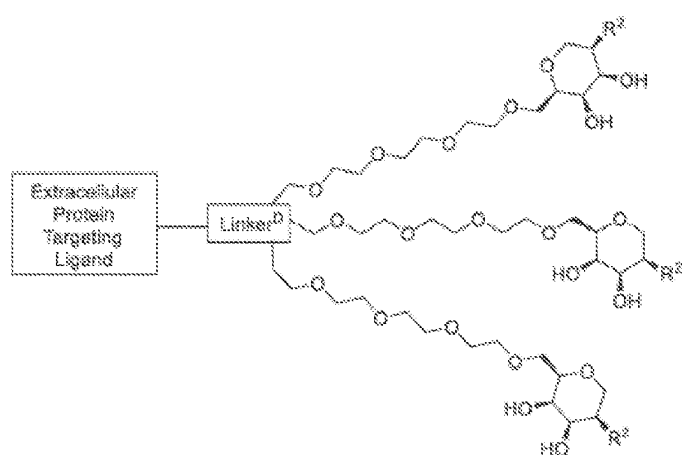


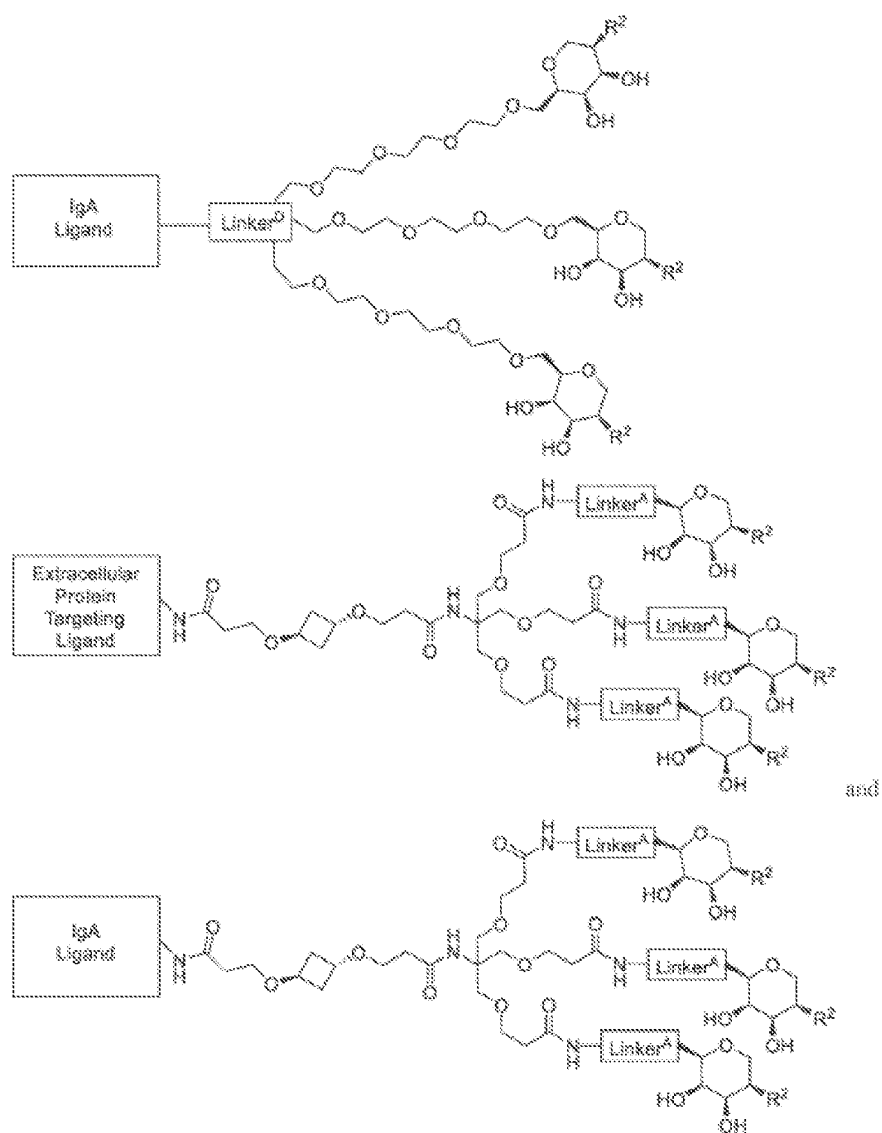


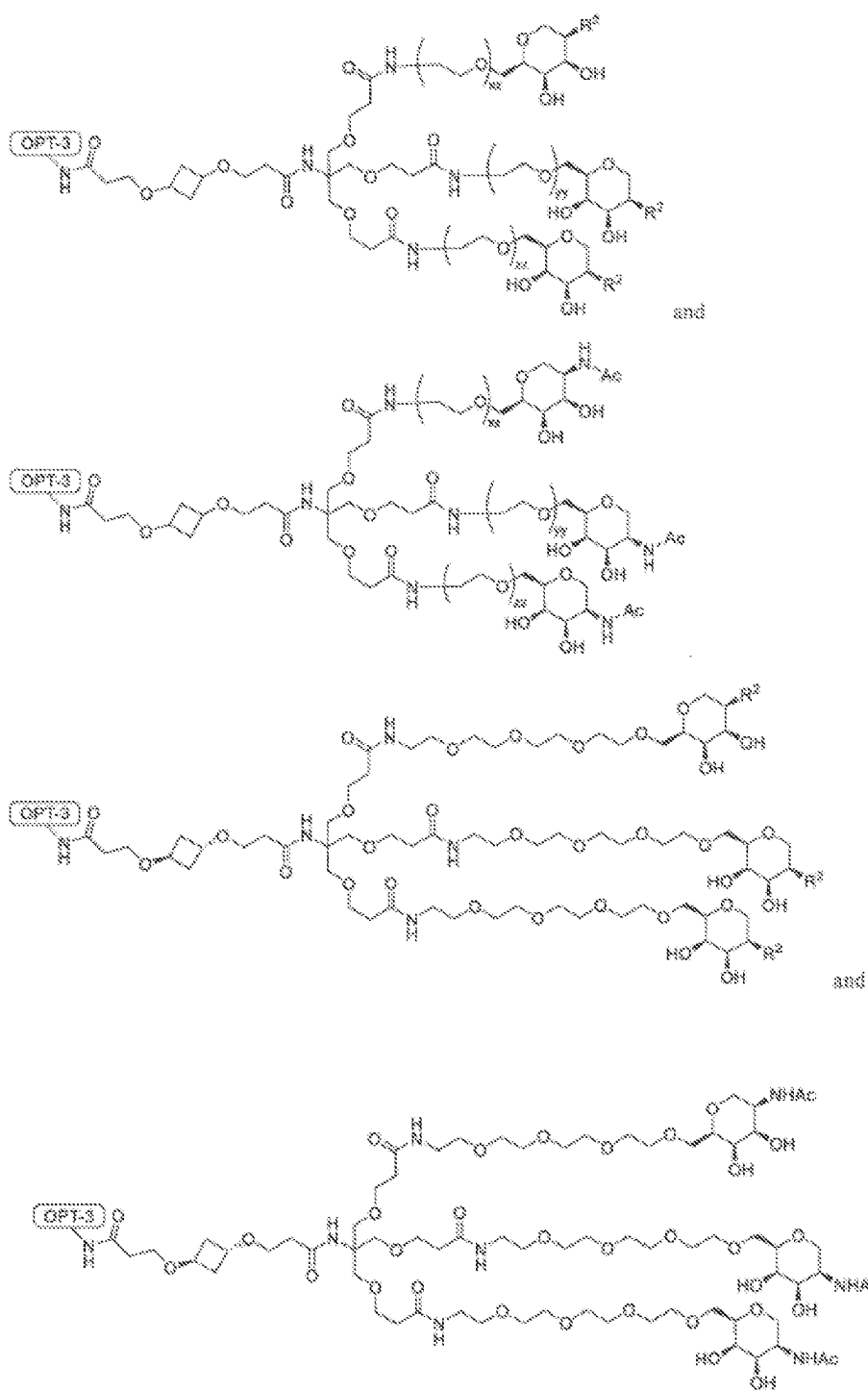












5

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

In certain embodiments, in the compound of Formula II, R¹ is hydrogen.

In certain embodiments, in the compound of Formula II, R¹ is



In certain embodiments, in the compound of Formula II, R¹ is



In certain embodiments, in the compound of Formula II, R¹ is



In certain embodiments, in the compound of Formula II, R¹ is



5 In certain embodiments, in the compound of Formula II, R¹ is



In certain embodiments, in the compound of Formula II, R¹ is



In certain embodiments, in the compound of Formula II, R¹ is C₀-C₆alkyl-cyano optionally substituted with 1, 2, 3, or 4 substituents.

10 In certain embodiments, in the compound of Formula II, R¹ is alkyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R¹ is alkenyl optionally substituted with 1, 2, 3, or 4 substituents. In certain embodiments, in the compound of Formula II, R¹ is alkynyl optionally substituted with 1, 2, 3, or 4 substituents. In certain embodiments, in the compound of Formula II, R¹ is haloalkyl optionally substituted with 1, 2, 3, or 4 substituents. In certain embodiments, in the compound of Formula II, R¹ is F.

In certain embodiments, in the compound of Formula II, R¹ is Cl.

In certain embodiments, in the compound of Formula II, R¹ is Br.

In certain embodiments, in the compound of Formula II, R¹ is aryl optionally substituted with 1, 2, 3, or 4 substituents.

20 In certain embodiments, in the compound of Formula II, R¹ is arylalkyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R¹ is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents.

25 In certain embodiments, in the compound of Formula II, R¹ is heteroaryl alkyl optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R¹ is heterocycle optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R¹ is heterocycloalkyl optionally substituted with 1, 2, 3, or 4 substituents.

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

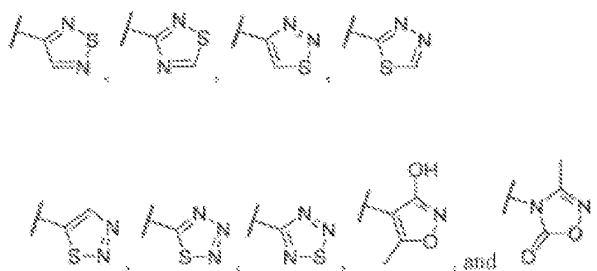
In certain embodiments, in the compound of Formula II, R^1 is -O-alkenyl, -O-alkynyl, C₀-C₆alkyl-OR⁶, C₀-C₆alkyl-SR⁶, C₀-C₆alkyl-NR⁶R⁷, C₀-C₆alkyl-C(O)R³, C₀-C₆alkyl-S(O)R³,
 5 C₀-C₆alkyl-C(S)R³, C₀-C₆alkyl-S(O)₂R³, C₀-C₆alkyl-N(R⁸)-C(O)R³, C₀-C₆alkyl-N(R⁸)-S(O)R³, C₀-C₆alkyl-N(R⁸)-C(S)R³, C₀-C₆alkyl-N(R⁸)-S(O)₂R³, 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, or C₀-C₆alkyl-O-S(O)₂R³, each of which is optionally substituted with 1, 2, 3, or 4 substituents.

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

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

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

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



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

In certain embodiments, in the compound of Formula II, R^2 is -NR⁸-S(O)-R³ optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -NR⁸-C(S)-R³ optionally substituted with 1, 2, 3, or 4 substituents.

25 In certain embodiments, in the compound of Formula II, R^2 is -NR⁸-S(O)(NR⁶)-R³ optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -N=S(O)(R³)₂ optionally substituted with 1, 2, 3, or 4 substituents.

In certain embodiments, in the compound of Formula II, R^2 is -NR⁸C(O)NR⁹S(O)₂R³

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

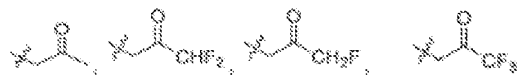
In certain embodiments, in the compound of Formula II, R^2 is $-O$ -heteroaryl optionally substituted with 1, 2, 3, or 4 substituents.

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

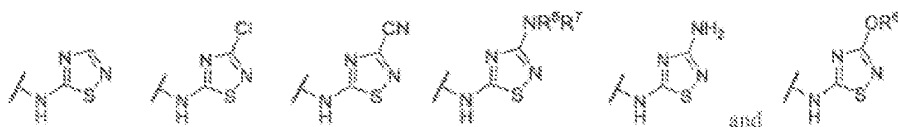
In certain embodiments, in the compound of Formula II, R^2 is $-O$ -alkynyl optionally

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

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

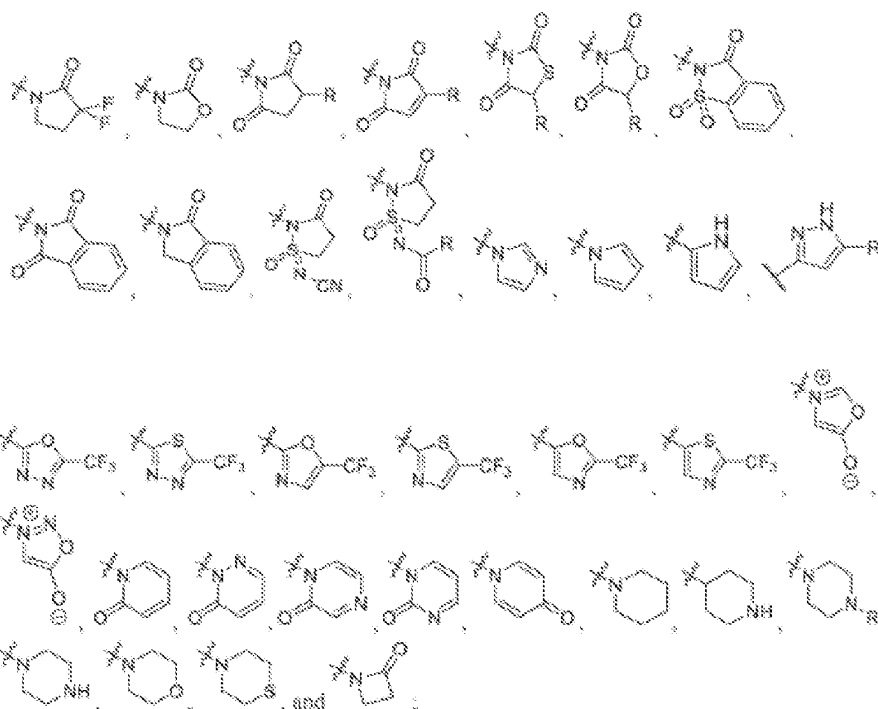


In certain embodiments, in the compound of Formula II, R^2 is selected from



5

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

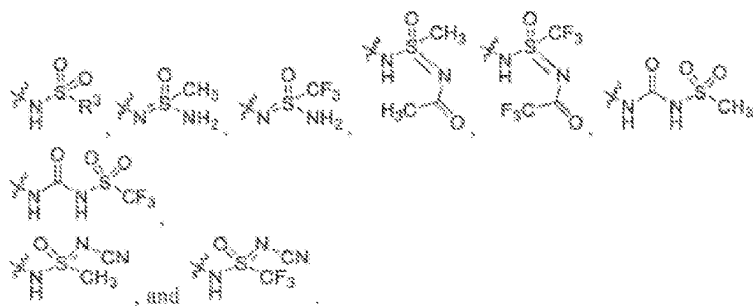


wherein

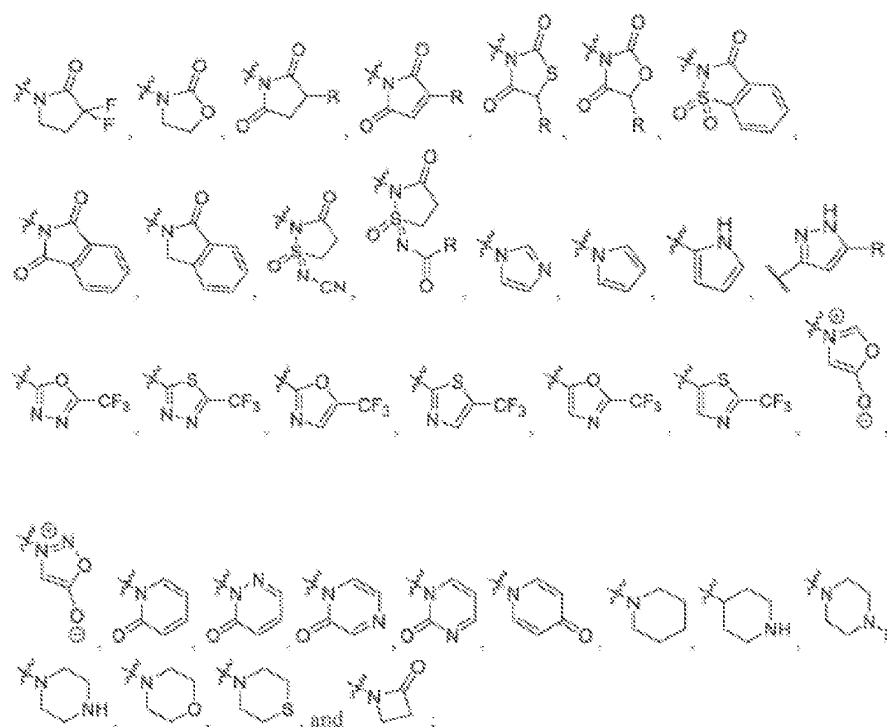
R is an optional substituent as defined herein.

10

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



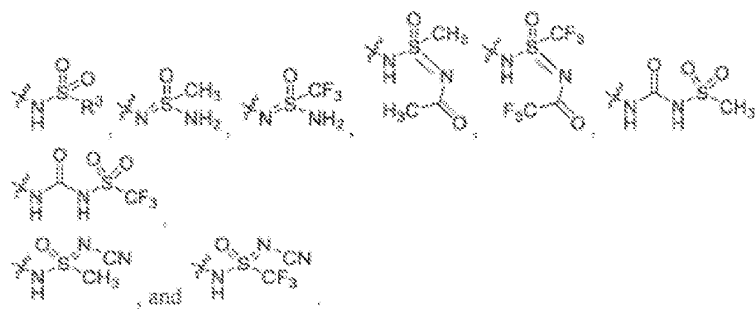
In certain embodiments, in the compound of Formula II, R^{2A} is selected from



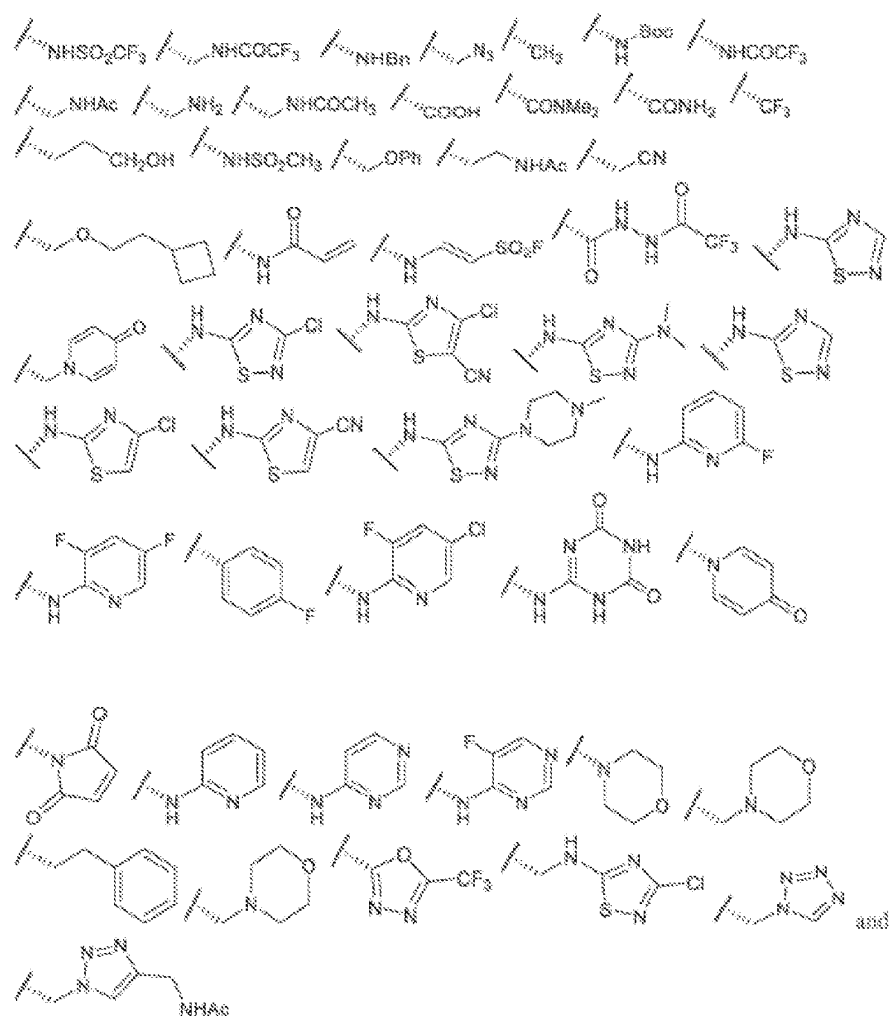
wherein R

5 is an optional substituent as defined herein.

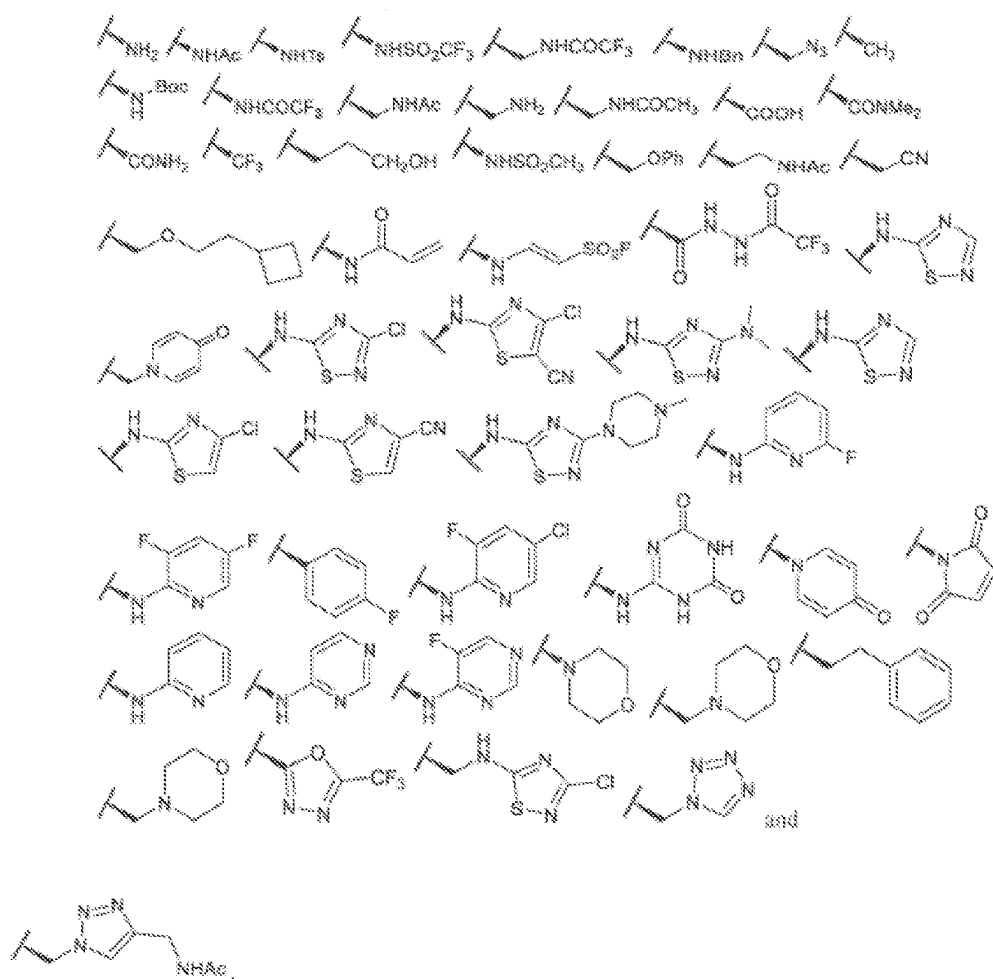
In certain embodiments, in the compound of Formula II, R^{2A} is selected from



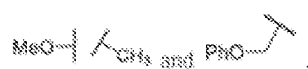
In certain embodiments, in the compound of Formula II, R^2 is selected from



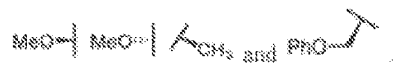
In certain embodiments, in the compound of Formula II, R^2 is selected from



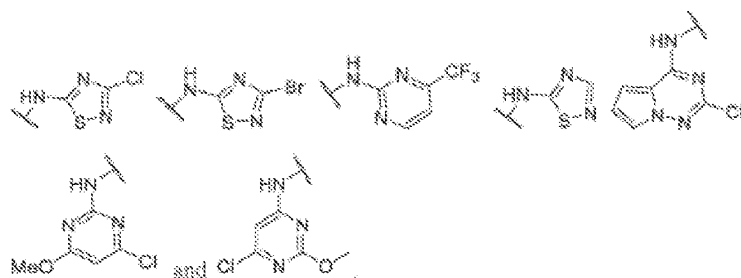
In certain embodiments, in the compound of Formula II, R^2 is selected from



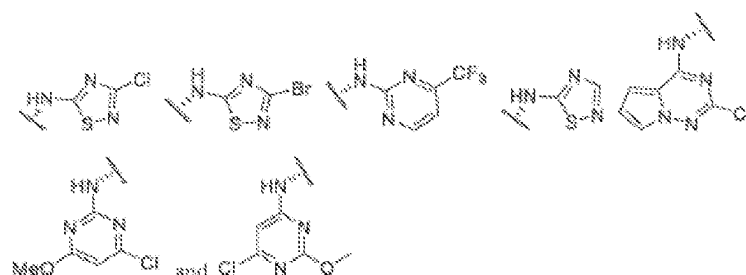
5 In certain embodiments, in the compound of Formula II, R^2 is selected from



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



In certain embodiments, in the compound of Formula II, R² is selected from

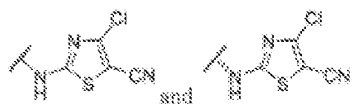


In certain embodiments, in the compound of Formula II, R² is selected from

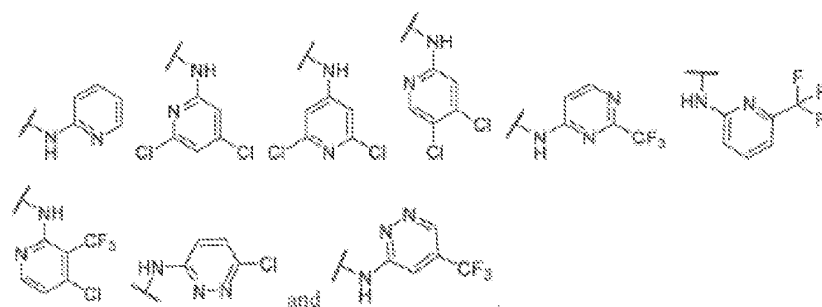


5

In certain embodiments, in the compound of Formula II, R² is selected from

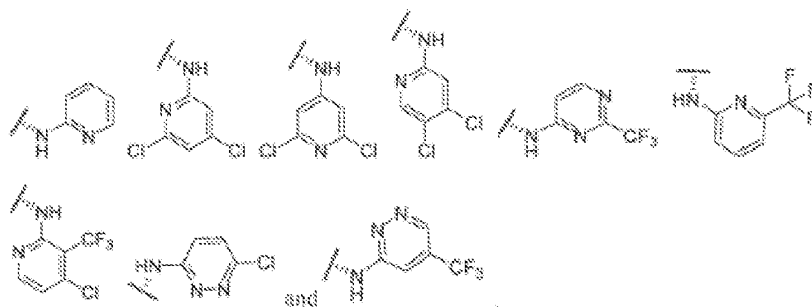


In certain embodiments, in the compound of Formula II, R² is selected from



10

In certain embodiments, in the compound of Formula II, R² is selected from



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

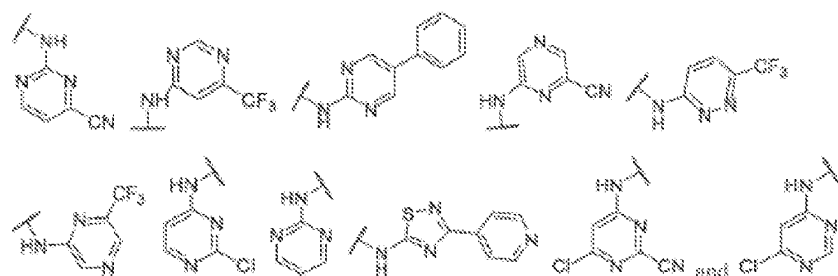


In certain embodiments, in the compound of Formula II, R^2 is selected from

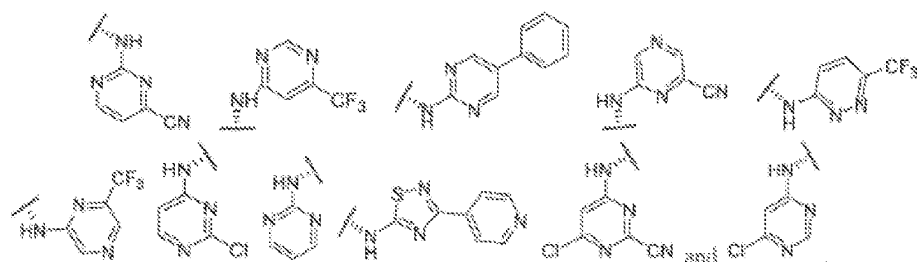


5

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

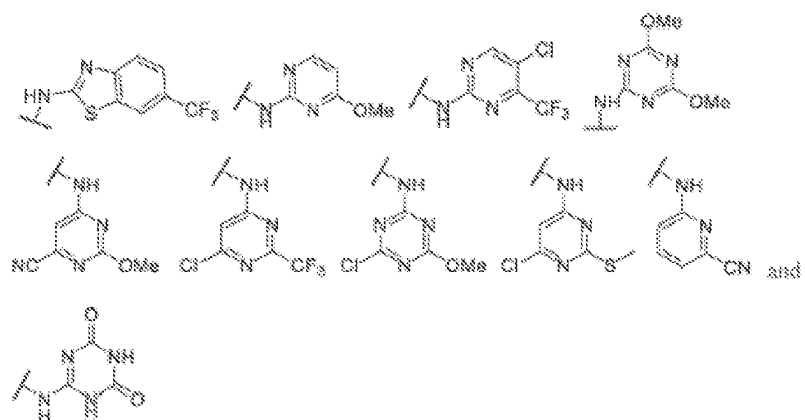


In certain embodiments, in the compound of Formula II, R^2 is selected from

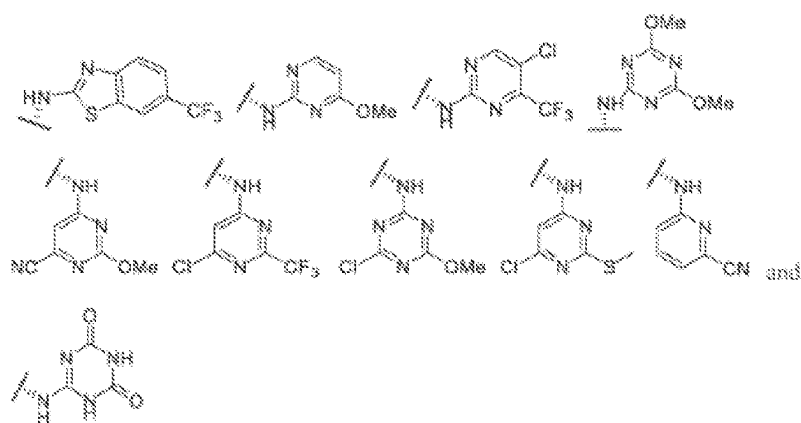


10

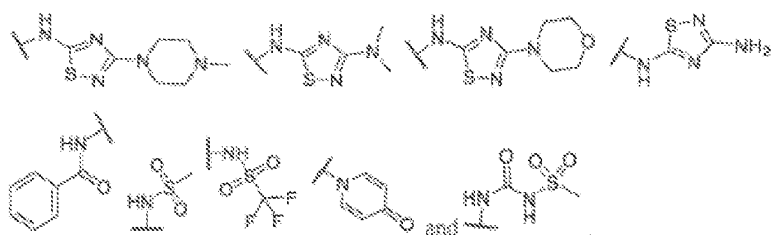
In certain embodiments, in the compound of Formula II, R^2 is selected from



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

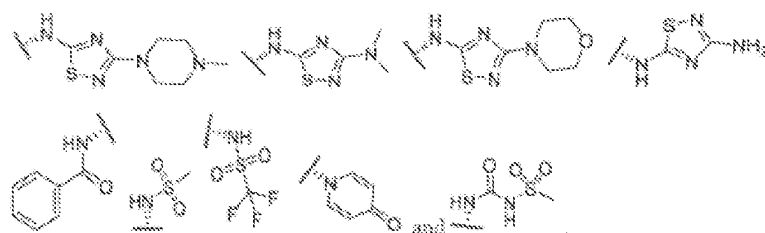


In certain embodiments, in the compound of Formula II, R^2 is selected from

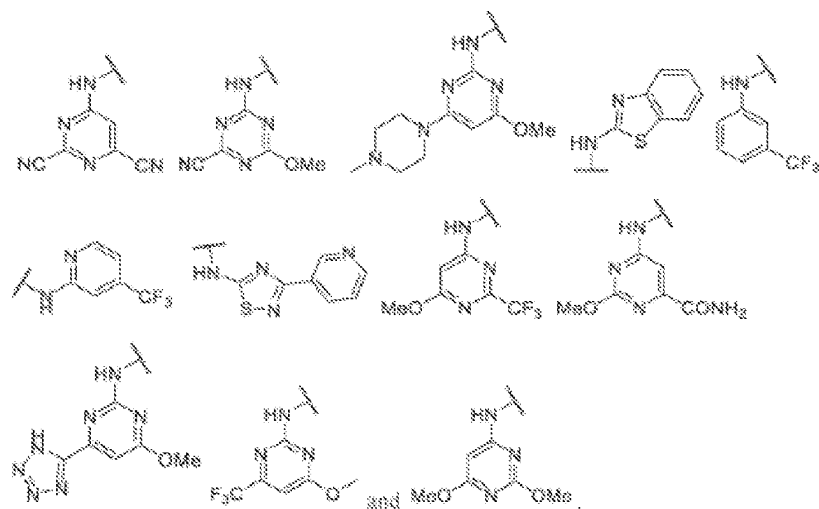


5

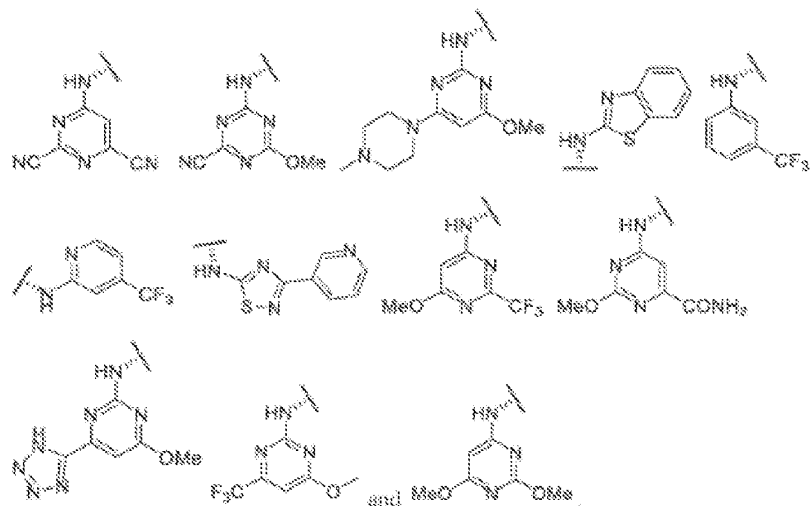
In certain embodiments, in the compound of Formula II, R^2 is selected from



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

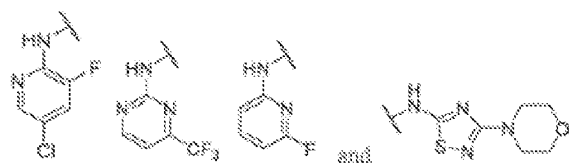


In certain embodiments, in the compound of Formula II, R^2 is selected from

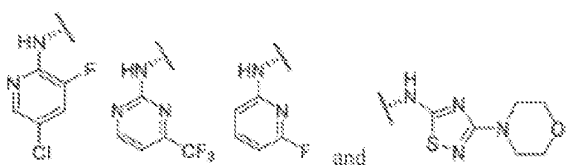


5

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



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

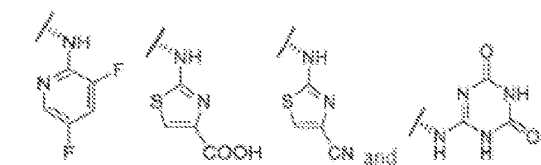


In certain embodiments, in the compound of Formula II, R^2 is selected from



5

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

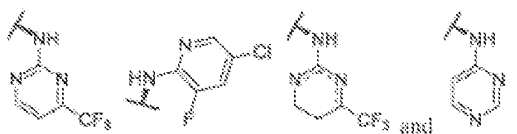


In certain embodiments, in the compound of Formula II, R^2 is selected from



10

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



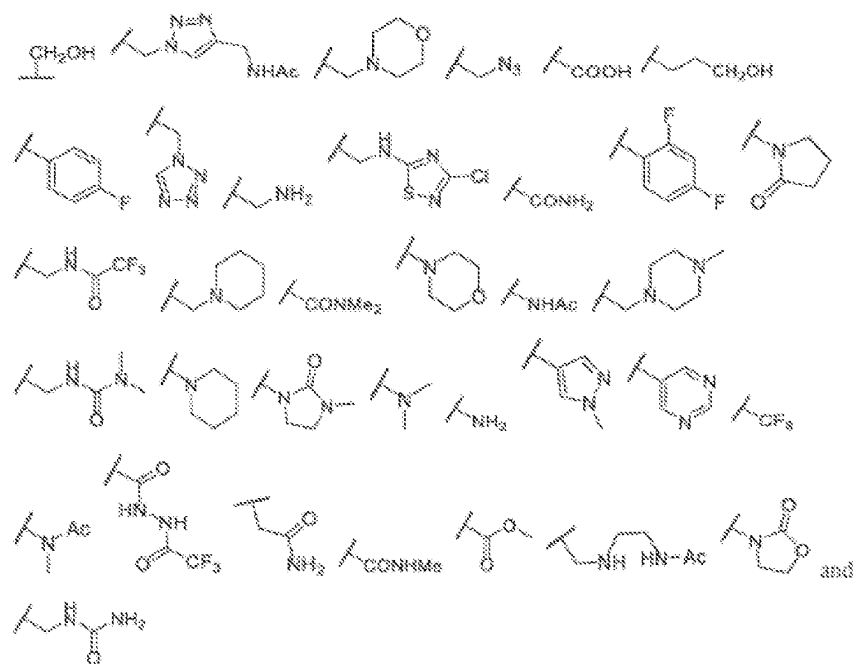
In certain embodiments, in the compound of Formula II, R^2 is selected from



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

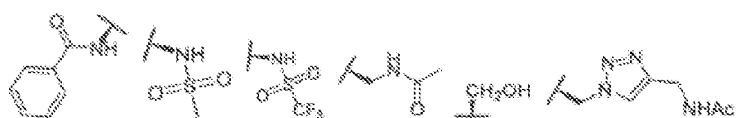


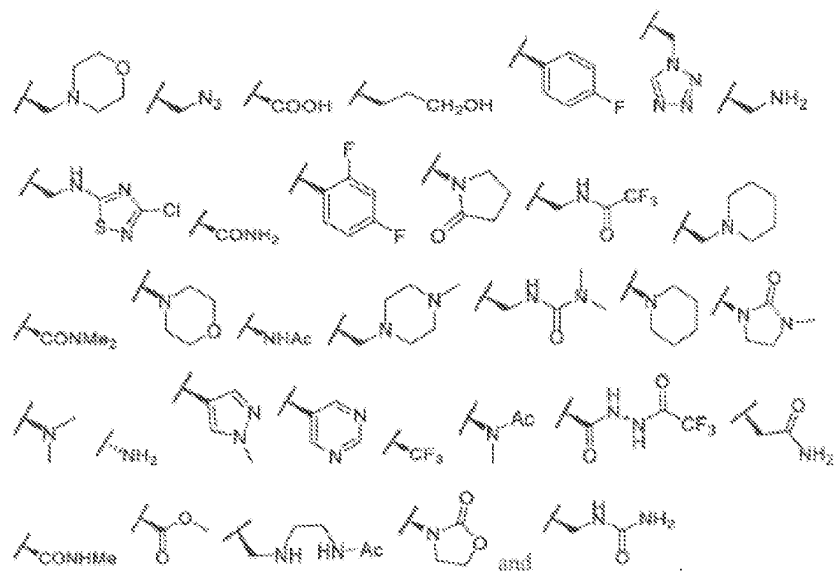
In certain embodiments, in the compound of Formula II, R^2 is selected from



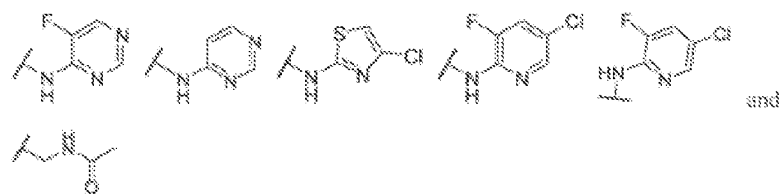
5

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

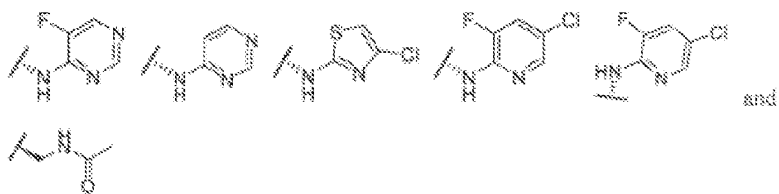




In certain embodiments, in the compound of Formula II, R² is selected from

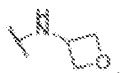


In certain embodiments, in the compound of Formula II, R² is selected from

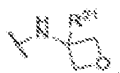


5

In certain embodiments, in the compound of Formula II, R² is selected from



In certain embodiments, in the compound of Formula II, R² is selected from



10

In certain embodiments, in the compound of Formula II, R² is selected from

In certain embodiments, in the compound of Formula II, R^2 is a spirocyclic

heterocycle, for example, and without limitation,



In certain embodiments, in the compound of Formula II, R^2 is a silicon containing

heterocycle, for example, and without limitation,

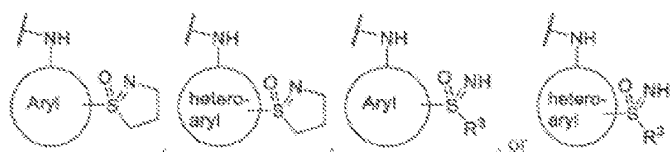


5 In certain embodiments, in the compound of Formula II, R^2 is substituted with SF_5 ,



for example, and without limitation,

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

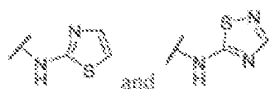


10 In certain embodiments, in the compound of Formula II, R^{10} is selected from bicyclic heterocycle.

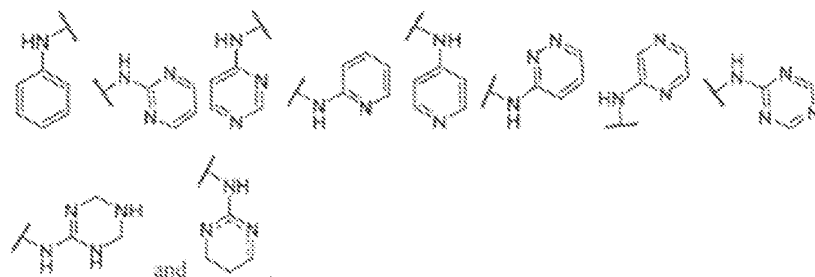
In certain embodiments, in the compound of Formula II, R^{10} is selected from spirocyclic heterocycle.

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

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



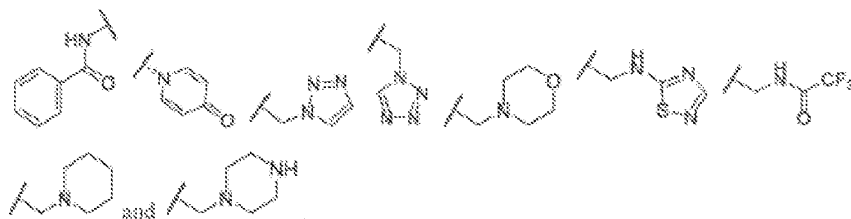
In certain embodiments, in the compound of Formula II, R^{10} is selected from



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

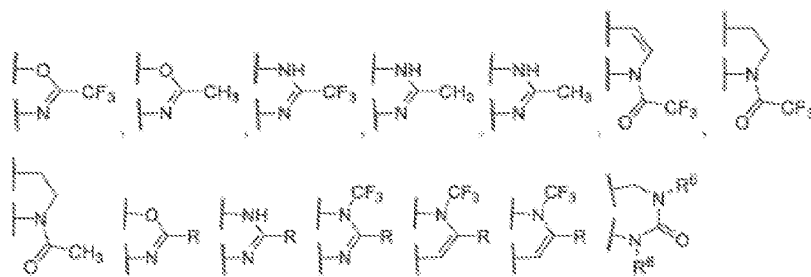


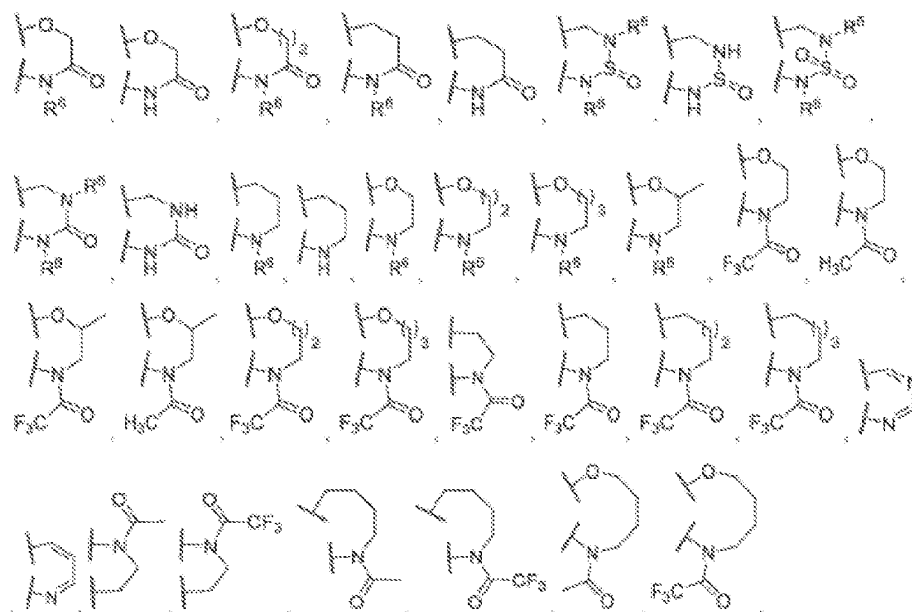
In certain embodiments, in the compound of Formula II, R^{10} is selected from



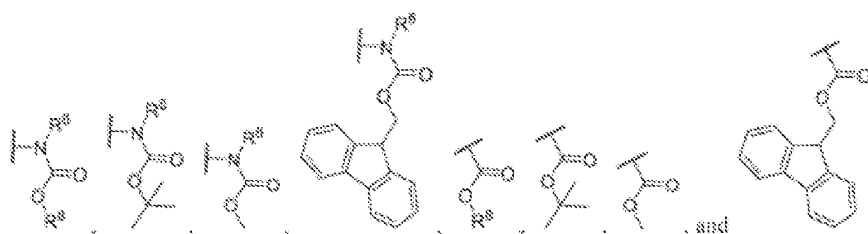
5

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





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



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

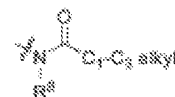


5

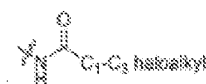
In certain embodiments, in the compound of Formula II, R^{200} is



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



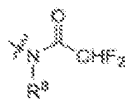
In certain embodiments, in the compound of Formula II, R^{200} is



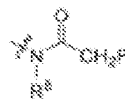
In certain embodiments, in the compound of Formula II, R^{200} is



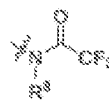
In certain embodiments, in the compound of Formula II, R^{200} is



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



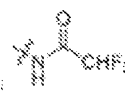
In certain embodiments, in the compound of Formula II, R^{200} is



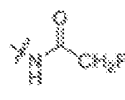
5 In certain embodiments, in the compound of Formula II, R^{200} is



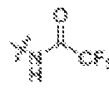
In certain embodiments, in the compound of Formula II, R^{200} is



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



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



10 *Linkers*

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



wherein:

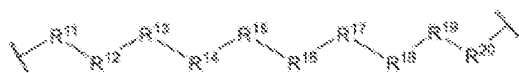
15 R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are independently at each occurrence selected from the group consisting of a bond, alkyl, -C(O)-, -C(O)O-, -OC(O)-, -SO₂-, -S(O)-, -C(S)-, -C(O)NR⁶-, -NR⁶C(O)-, -O-, -S-, -NR⁶-, -C(R²¹R²¹)-, -P(O)(R³)O-, -P(O)(R³)-, a divalent residue of a natural or unnatural amino acid, alkenyl, alkynyl, haloalkyl, alkoxy, and heterocycle, heteroaryl, -CH₂CH₂-[O-(CH₂)₂]_n-O-, CH₂CH₂-[O-(CH₂)₂]_n-NR⁶-, -CH₂CH₂-[O-

$(\text{CH}_2)_2]_n$ -, $[-(\text{CH}_2)_2-\text{O}-]_n$ -, $[-\text{O}-(\text{CH}_2)_2]_n$ -, $[-\text{O}-\text{CH}(\text{CH}_3)\text{C}(\text{O})]_n$ -, $[-\text{C}(\text{O})-\text{CH}(\text{CH}_3)-\text{O}]_n$ -,
 $[-\text{O}-\text{CH}_2\text{C}(\text{O})]_n$ -, $[-\text{C}(\text{O})-\text{CH}_2-\text{O}]_n$ -, a divalent residue of a fatty acid, a divalent
 residue of an unsaturated or saturated mono- or di-carboxylic acid; each of which is
 optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{21} ;

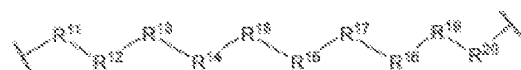
5 n is independently selected at each instance from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

R^{21} is independently at each occurrence selected from the group consisting of
 hydrogen, alkyl, alkenyl, alkynyl, F, Cl, Br, I, hydroxyl, alkoxy, azide, amino, cyano, -
 NR^6R^7 , $-\text{NR}^8\text{SO}_2\text{R}^3$, $-\text{NR}^8\text{S}(\text{O})\text{R}^3$, haloalkyl, heteroalkyl, and, heteroaryl, and heterocycle;
 and the remaining variables are as defined herein.

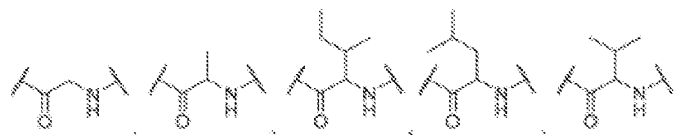
10 In certain embodiments, in the compound of Formula II, Linker^A is bond and Linker^B
 is

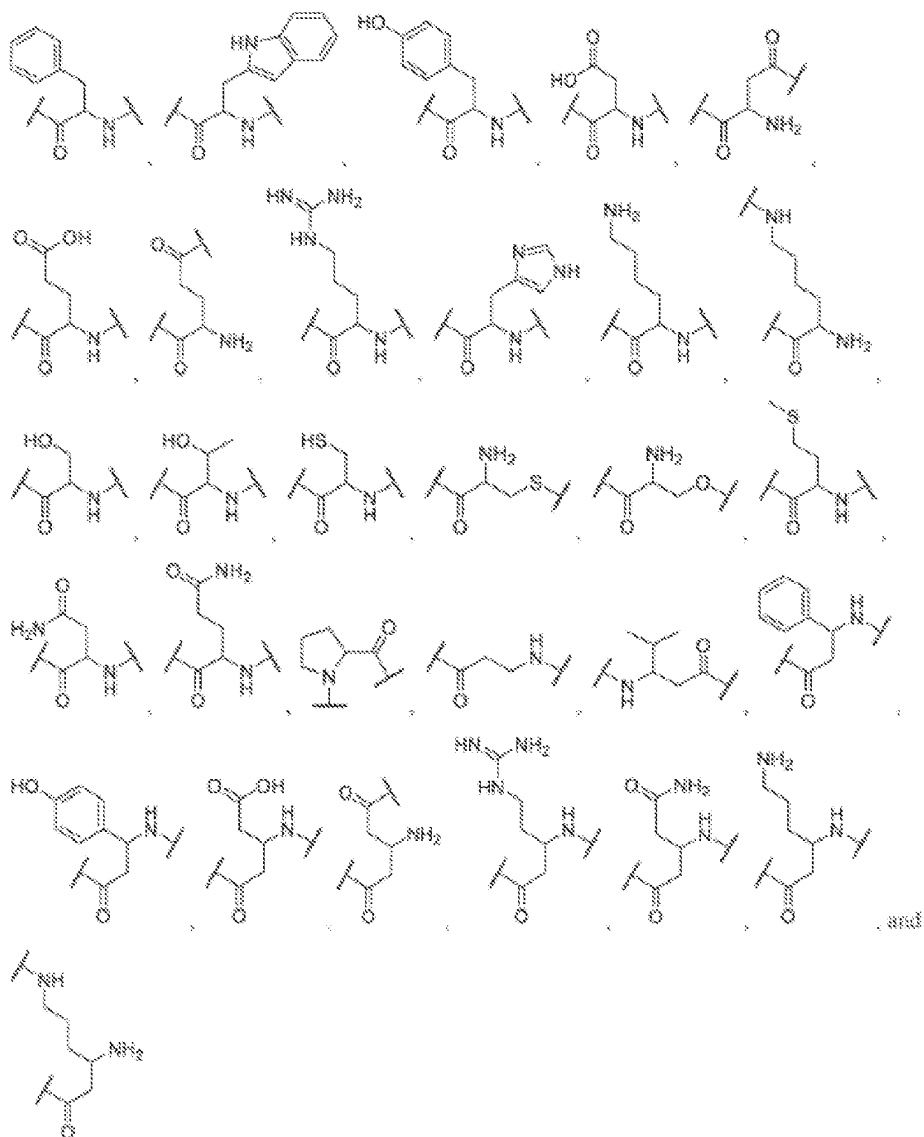


In certain embodiments, in the compound of Formula II, Linker^B is bond and Linker^A
 is



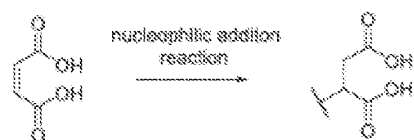
15 In certain embodiments, in the compound of Formula II, a divalent residue of an
 amino acid is selected from



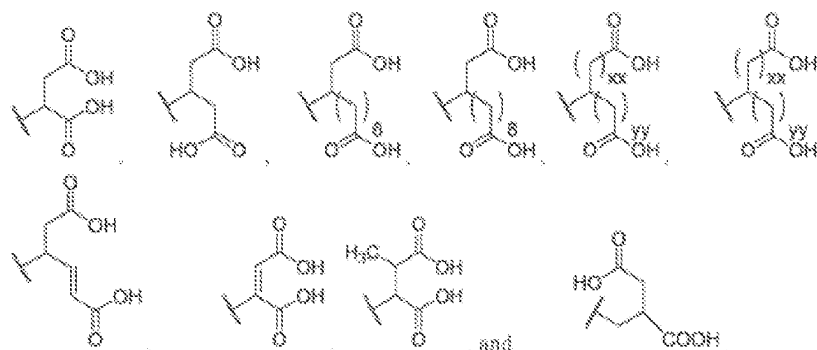


wherein the amino acid can be oriented in either direction and wherein the amino acid can be in the L- or D-form or a mixture thereof.

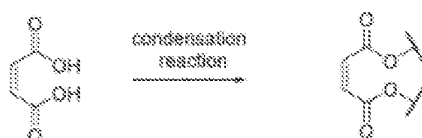
- 5 In certain embodiments, in the compound of Formula II, a divalent residue of a dicarboxylic acid is generated from a nucleophilic addition reaction:



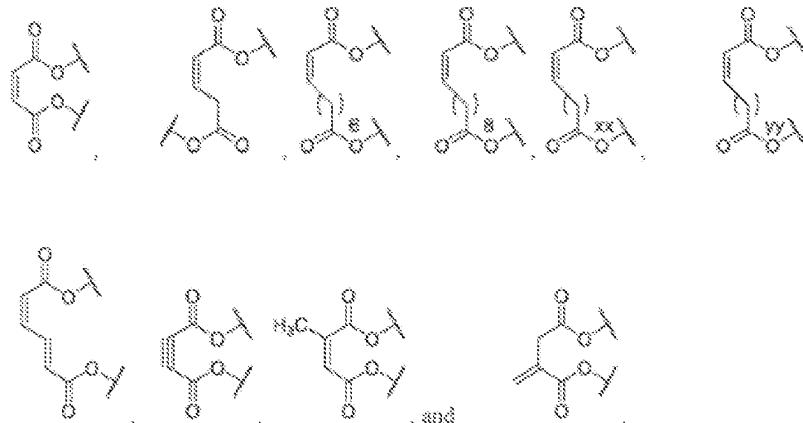
Non-limiting embodiments of a divalent residue of a dicarboxylic acid generated from a nucleophilic addition reaction include:



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

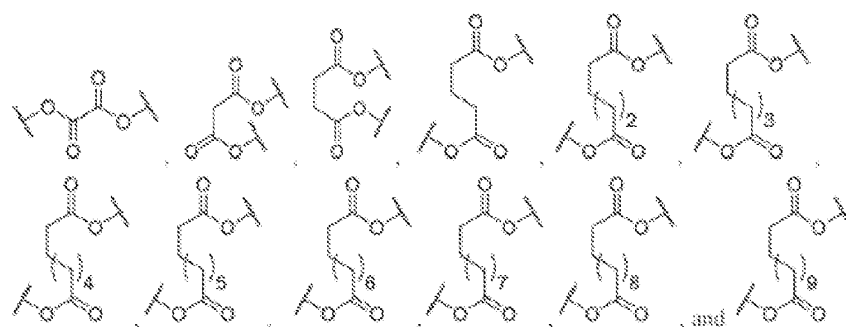


Non-limiting embodiments of a divalent residue of a dicarboxylic acid generated from a condensation include:

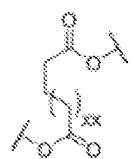


10

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

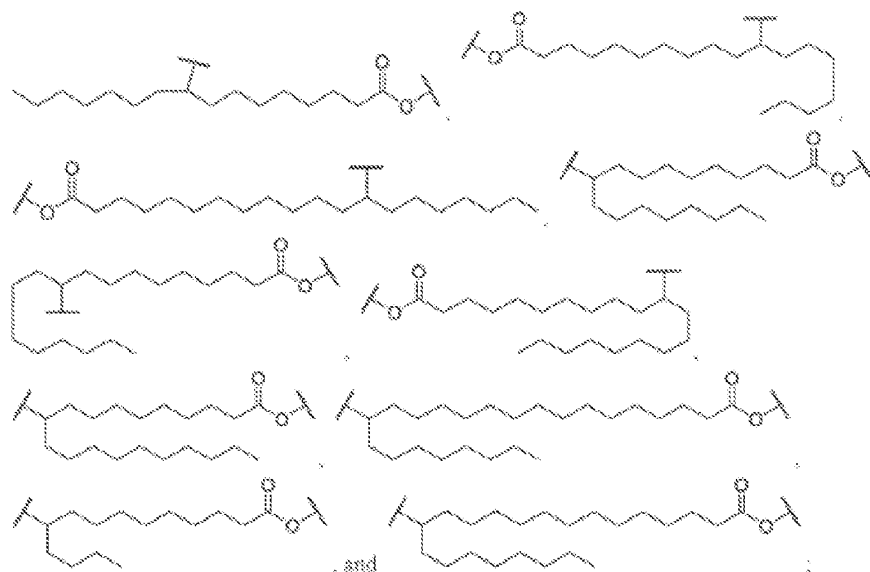


Non-limiting embodiments of a divalent residue of a saturated dicarboxylic acid include:



- 5 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 ($-\text{OC}(\text{O})(\text{CH}_2)_{16}\text{CH}_2-$),
- 10 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 ($-\text{C}(\text{O})(\text{CH}_2)_7(\text{CH})_2\text{CH}_2(\text{CH})_2(\text{CH}_2)_4\text{CH}_2-$), docosahexaenoic acid

($-\text{C}(\text{O})(\text{CH}_2)_2(\text{CHCHCH}_2)_6\text{CH}_2-$), eicosapentaenoic acid ($-\text{C}(\text{O})(\text{CH}_2)_3(\text{CHCHCH}_2)_5\text{CH}_2-$), alpha-linolenic acid ($-\text{C}(\text{O})(\text{CH}_2)_7(\text{CHCHCH}_2)_3\text{CH}_2-$),

5 stearidonic acid

($-\text{C}(\text{O})(\text{CH}_2)_4(\text{CHCHCH}_2)_4\text{CH}_2-$), gamma-linolenic acid ($-\text{C}(\text{O})(\text{CH}_2)_4(\text{CHCHCH}_2)_3(\text{CH}_2)_3\text{CH}_2-$), arachidonic acid ($-\text{C}(\text{O})(\text{CH}_2)_3(\text{CHCHCH}_2)_4(\text{CH}_2)_4\text{CH}_2-$), docosatetraenoic acid

($-\text{C}(\text{O})(\text{CH}_2)_5(\text{CHCHCH}_2)_4(\text{CH}_2)_4\text{CH}_2-$), palmitoleic acid ($-\text{C}(\text{O})(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_5\text{CH}_2-$), vaccenic acid ($-\text{C}(\text{O})(\text{CH}_2)_9\text{CHCH}(\text{CH}_2)_5\text{CH}_2-$), paullinic acid

10 ($-\text{C}(\text{O})(\text{CH}_2)_3(\text{CHCHCH}_2)_4(\text{CH}_2)_4\text{CH}_2-$), docosatetraenoic acid

($-\text{C}(\text{O})(\text{CH}_2)_5(\text{CHCHCH}_2)_4(\text{CH}_2)_4\text{CH}_2-$), palmitoleic acid ($-\text{C}(\text{O})(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_5\text{CH}_2-$), vaccenic acid ($-\text{C}(\text{O})(\text{CH}_2)_9\text{CHCH}(\text{CH}_2)_5\text{CH}_2-$), paullinic acid

acid

($-\text{C}(\text{O})(\text{CH}_2)_{11}\text{CHCH}(\text{CH}_2)_5\text{CH}_2-$), oleic acid ($-\text{C}(\text{O})(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_7\text{CH}_2-$), elaidic acid

elaidic acid

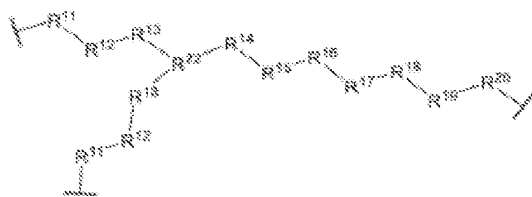
15 ($-\text{C}(\text{O})(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_7\text{CH}_2-$), gondoic acid ($-\text{C}(\text{O})(\text{CH}_2)_9\text{CHCH}(\text{CH}_2)_7\text{CH}_2-$), gadoleic acid ($-\text{C}(\text{O})(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_9\text{CH}_2-$), nervonic acid ($-\text{C}(\text{O})(\text{CH}_2)_{13}\text{CHCH}(\text{CH}_2)_3\text{CH}_2-$), mead acid ($-\text{C}(\text{O})(\text{CH}_2)_3(\text{CHCHCH}_2)_3(\text{CH}_2)_6\text{CH}_2-$), myristoleic acid ($-\text{C}(\text{O})(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_3\text{CH}_2-$), and erucic acid ($-\text{C}(\text{O})(\text{CH}_2)_{11}\text{CHCH}(\text{CH}_2)_7\text{CH}_2-$).

gadoleic acid ($-\text{C}(\text{O})(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_9\text{CH}_2-$), nervonic acid ($-\text{C}(\text{O})(\text{CH}_2)_{13}\text{CHCH}(\text{CH}_2)_3\text{CH}_2-$), mead acid ($-\text{C}(\text{O})(\text{CH}_2)_3(\text{CHCHCH}_2)_3(\text{CH}_2)_6\text{CH}_2-$), myristoleic acid ($-\text{C}(\text{O})(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_3\text{CH}_2-$), and erucic acid ($-\text{C}(\text{O})(\text{CH}_2)_{11}\text{CHCH}(\text{CH}_2)_7\text{CH}_2-$).

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

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

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

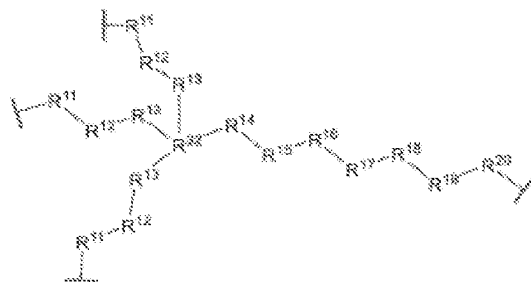


wherein:

R^{22} is independently at each occurrence selected from the group consisting of alkyl, -C(O)N-, -NC(O)-, -N-, -C(R^{21})-, -P(O)O-, -P(O)-, -P(O)(NR⁶R⁷)N-, alkenyl, haloalkyl, aryl, heterocycle, and heteroaryl, each of which is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{21} ;

and the remaining variables are as defined herein.

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



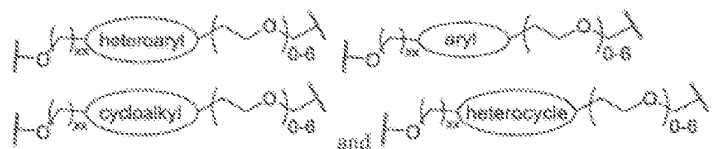
wherein:

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

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

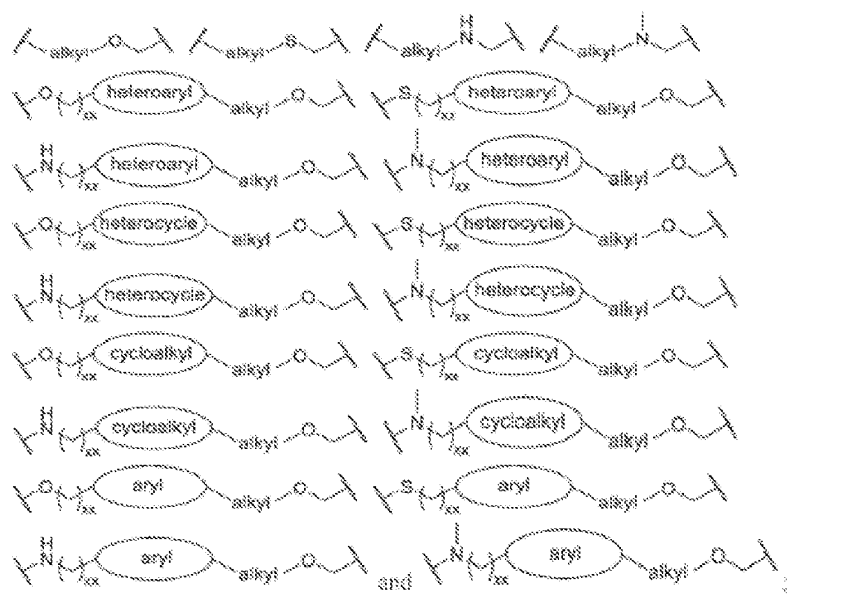
all other variables are as defined herein.

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



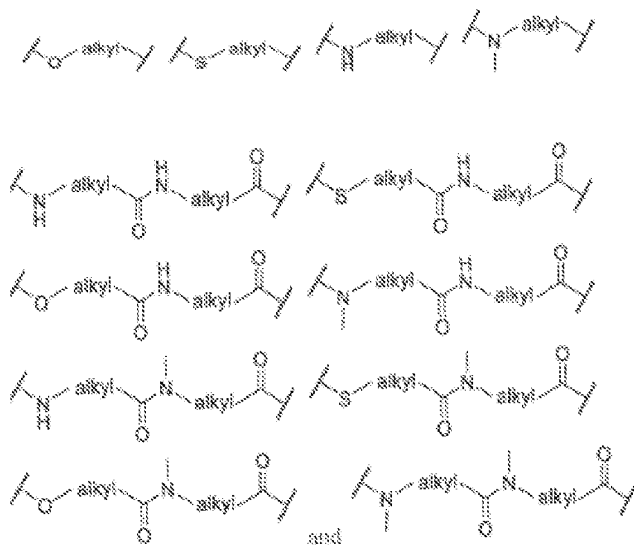
wherein each heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, and, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence.

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

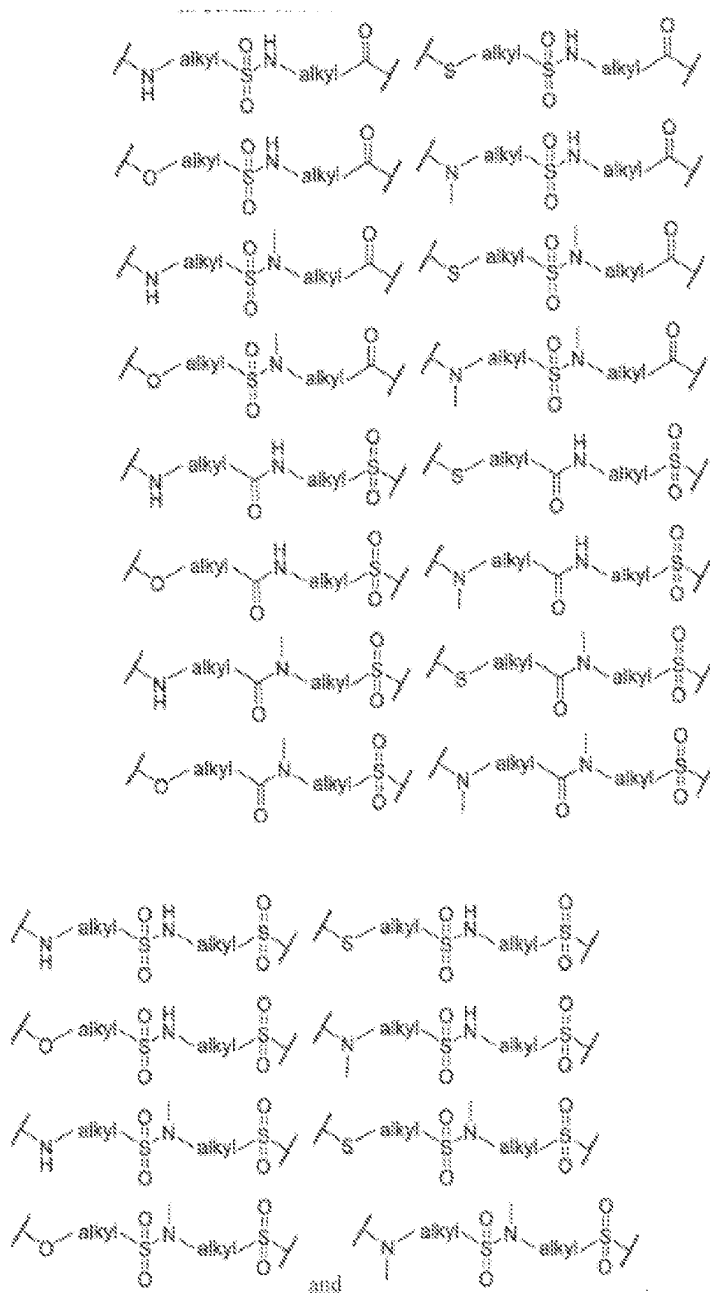


wherein each heteroaryl, heterocycle, cycloalkyl, and and can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence.

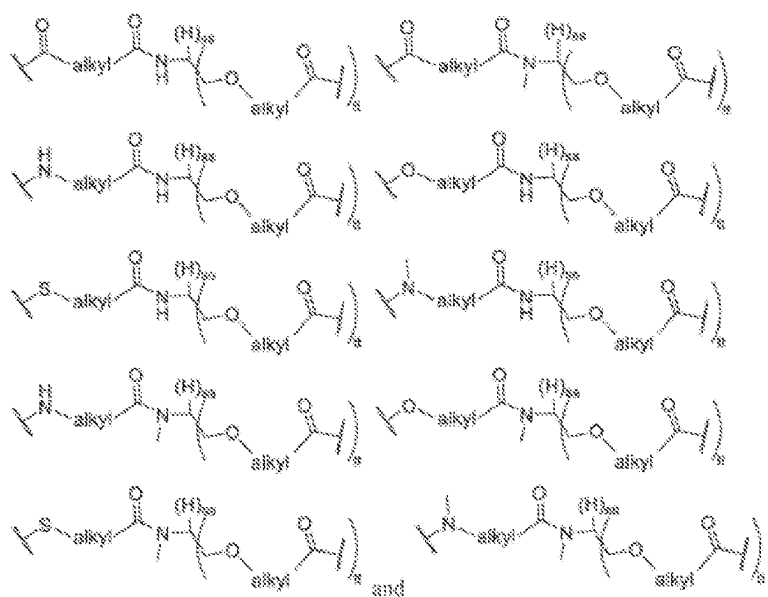
- 5 In certain embodiments, in the compound of Formula II, Linker^B is selected from:



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

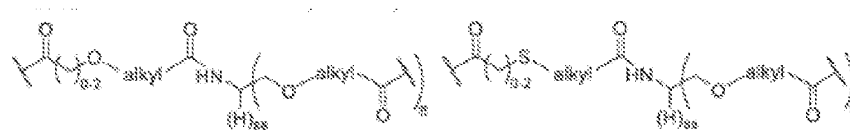


In certain embodiments, in the compound of Formula II, Linker^B, Linker^C, or Linker^D is selected from:

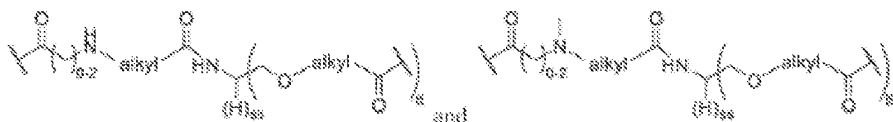


wherein tt is independently selected from 1, 2, or 3 and ss is 3 minus tt (3-tt).

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

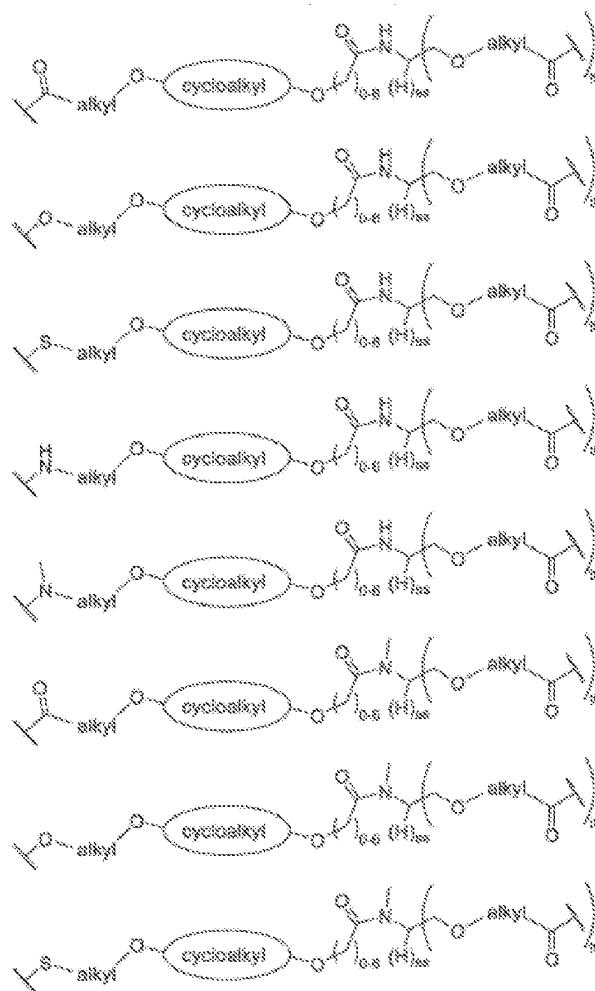


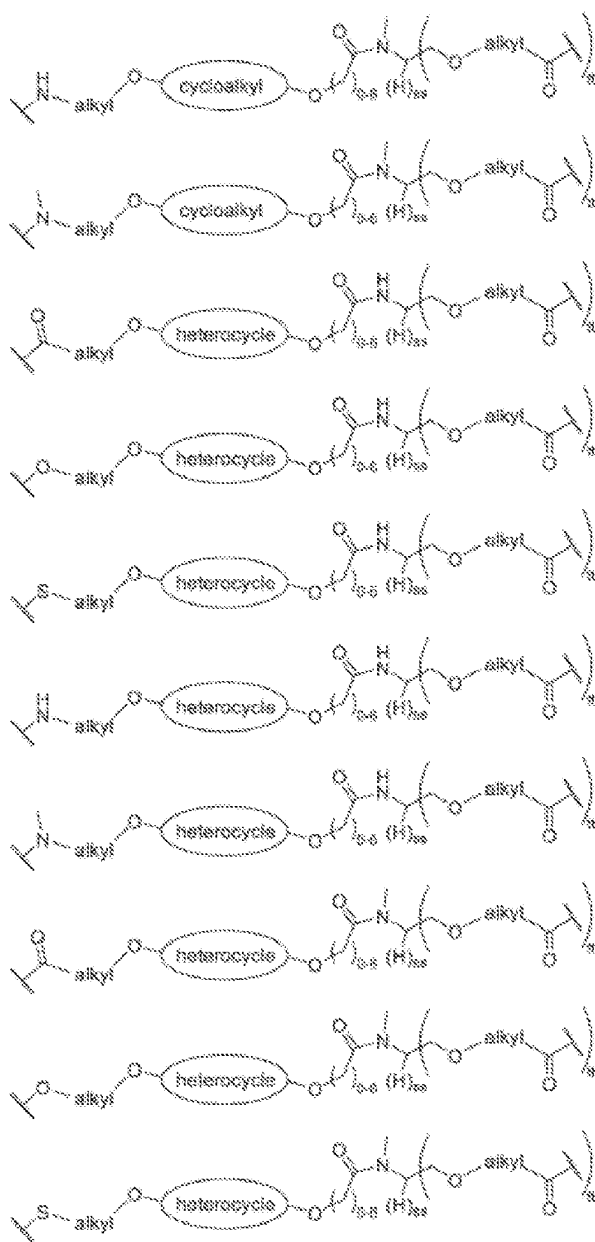
5

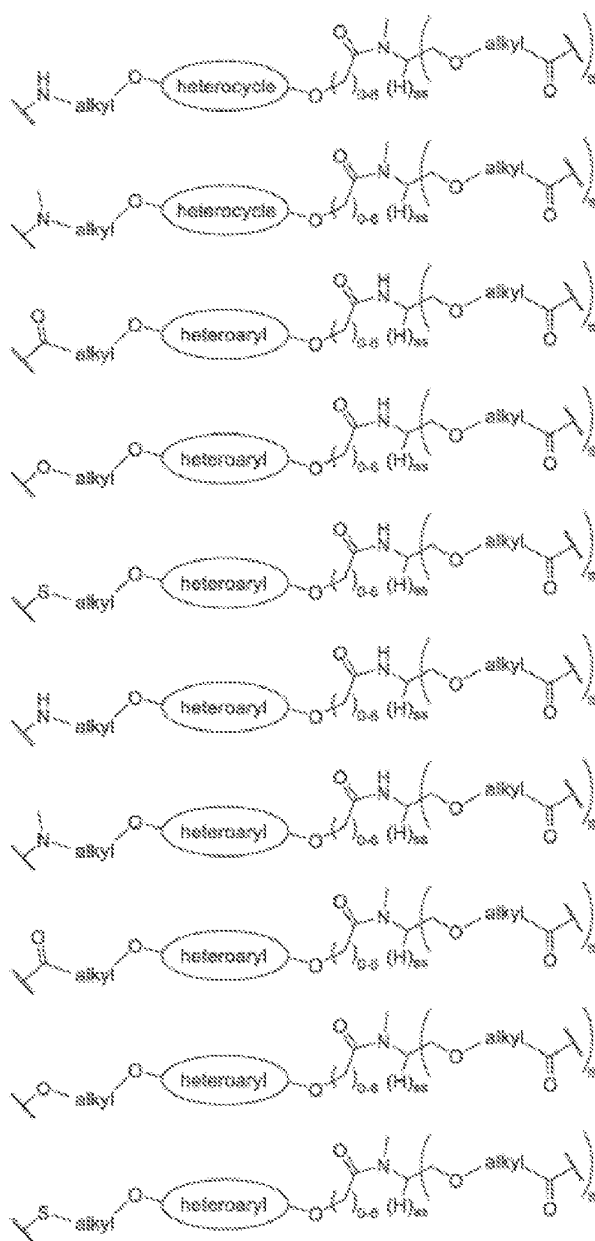


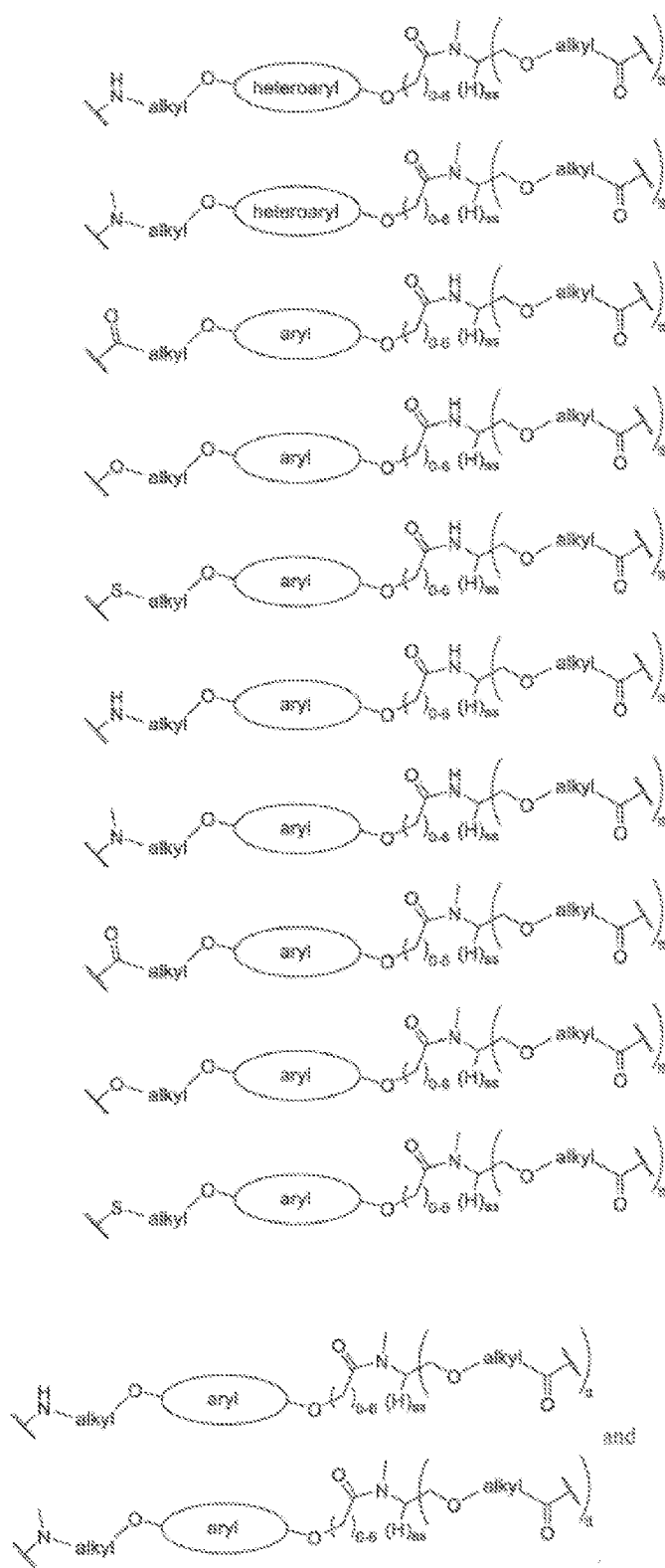
wherein tt and ss are as defined herein.

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



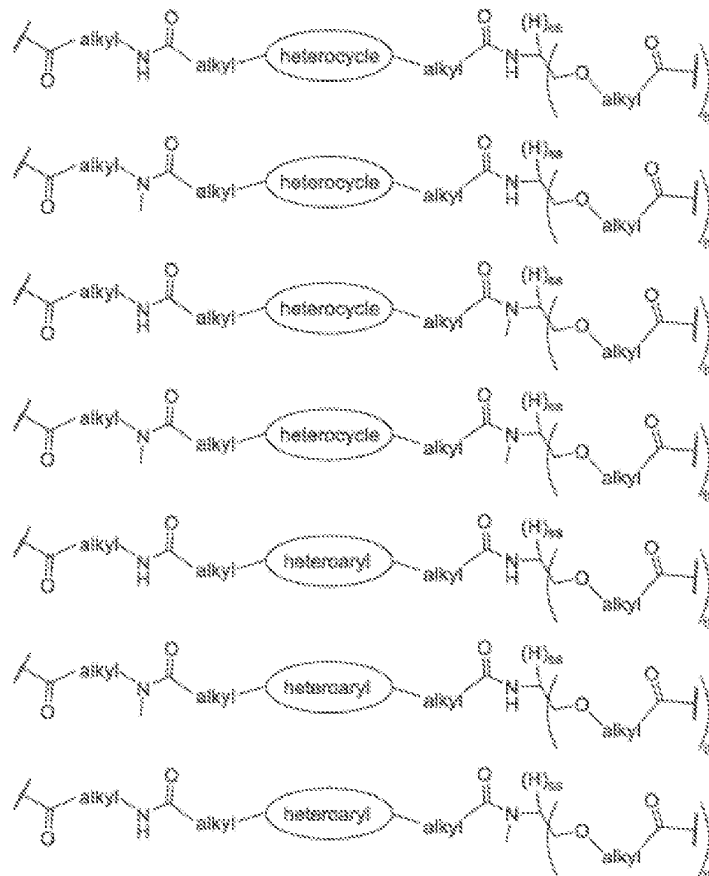


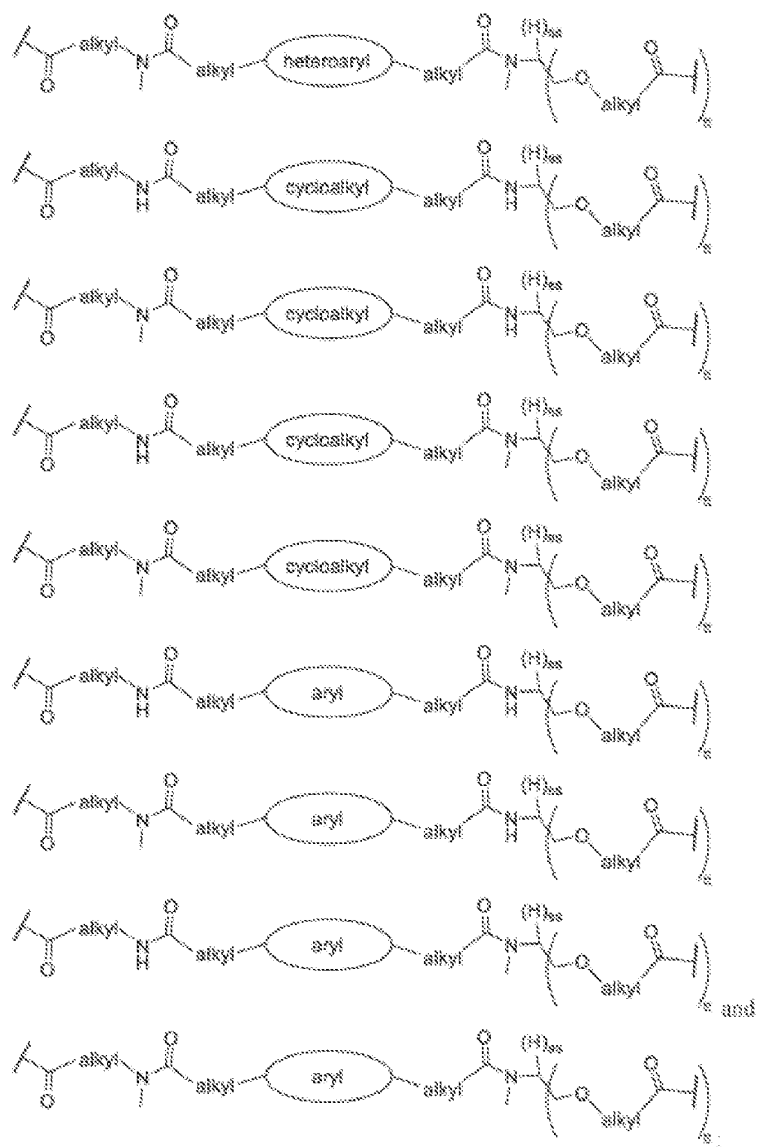




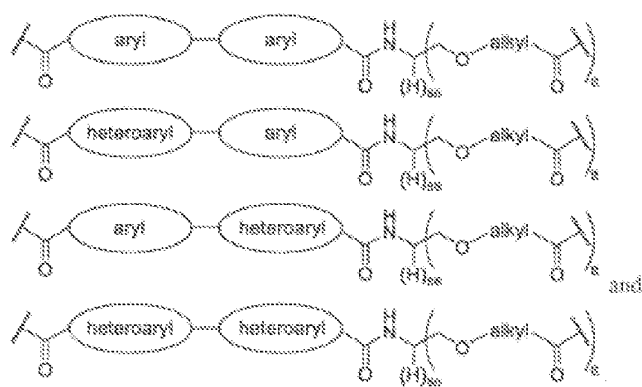
wherein each heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence; and tt and ss are as defined herein.

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



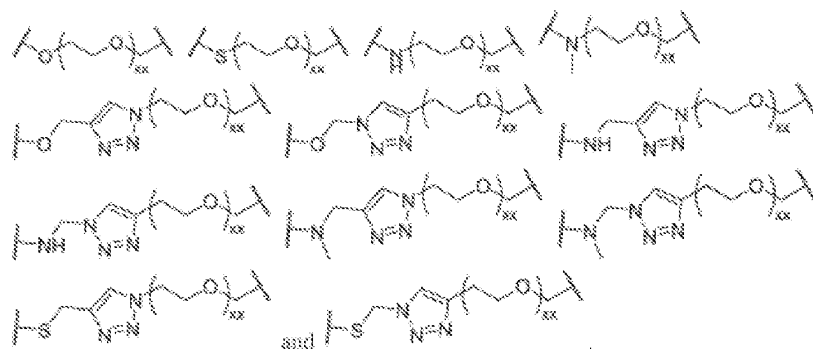


- 5 In certain embodiments, in the compound of Formula II, Linker^B, Linker^C, or Linker^D is selected from:

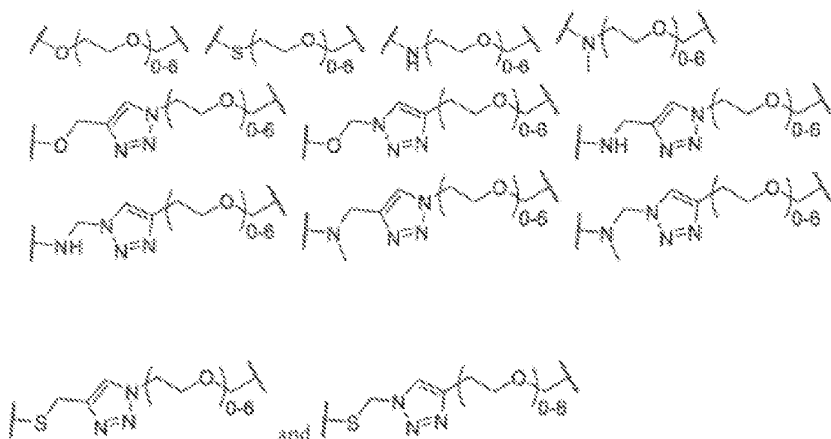


wherein each heteroaryl and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence; and tt and ss are as defined herein.

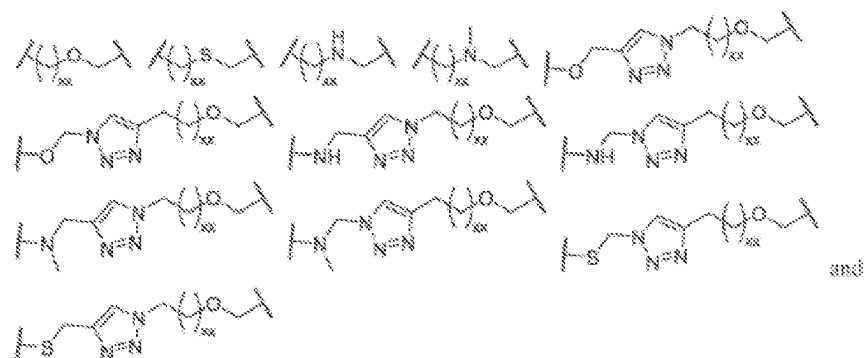
5 In certain embodiments, in the compound of Formula II, Linker^A is selected from:



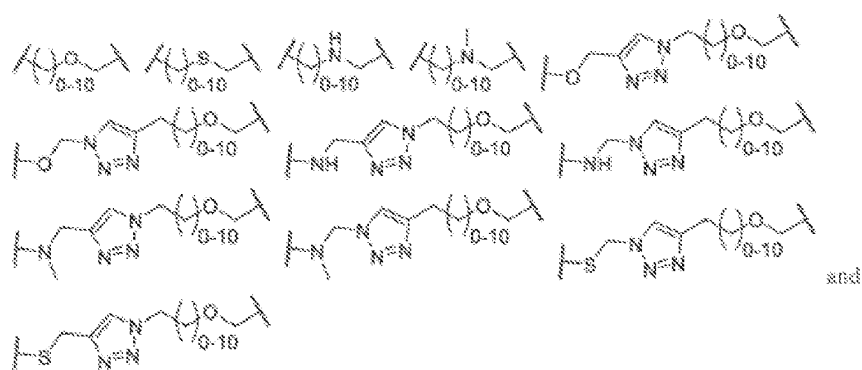
In certain embodiments, in the compound of Formula II, Linker^A is selected from:



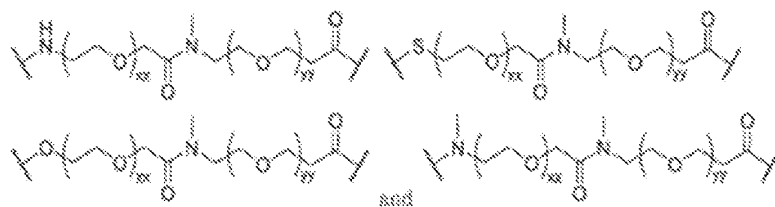
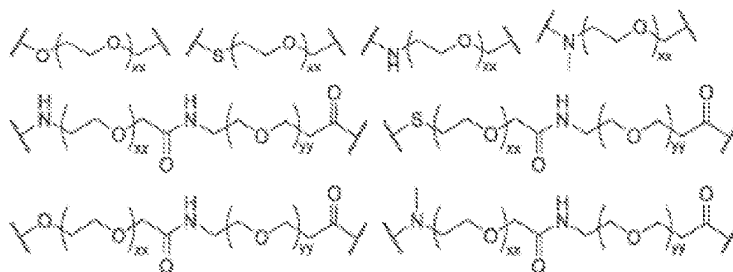
10 In certain embodiments, in the compound of Formula II, Linker^A is selected from:



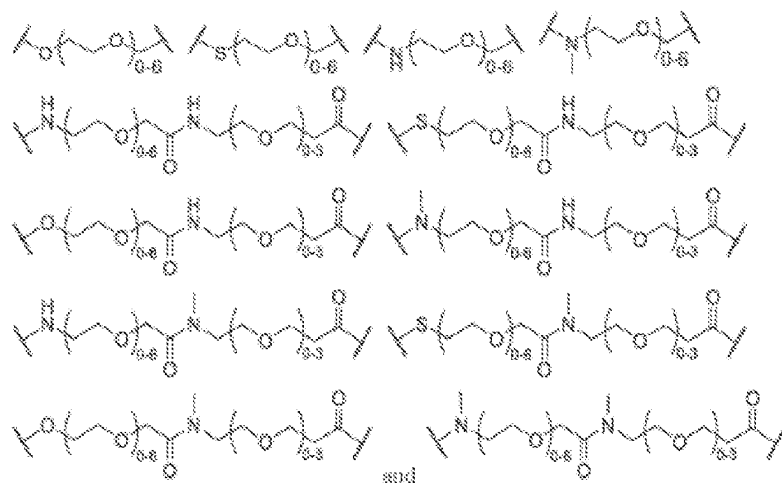
In certain embodiments, in the compound of Formula II, Linker^A is selected from:



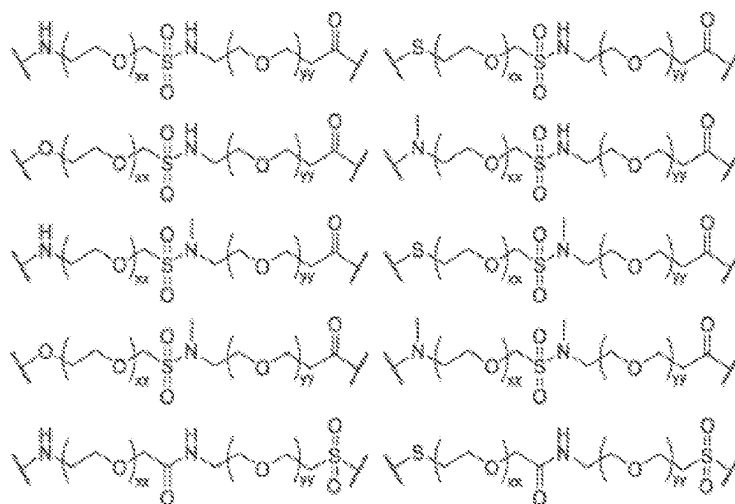
In certain embodiments, in the compound of Formula II, Linker^B is selected from:

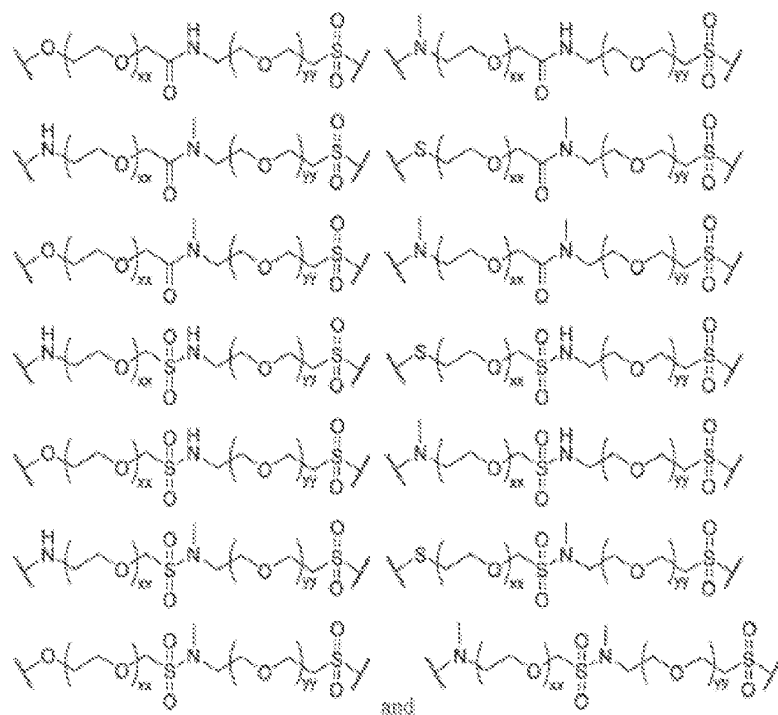


In certain embodiments, in the compound of Formula II, Linker^B is selected from:

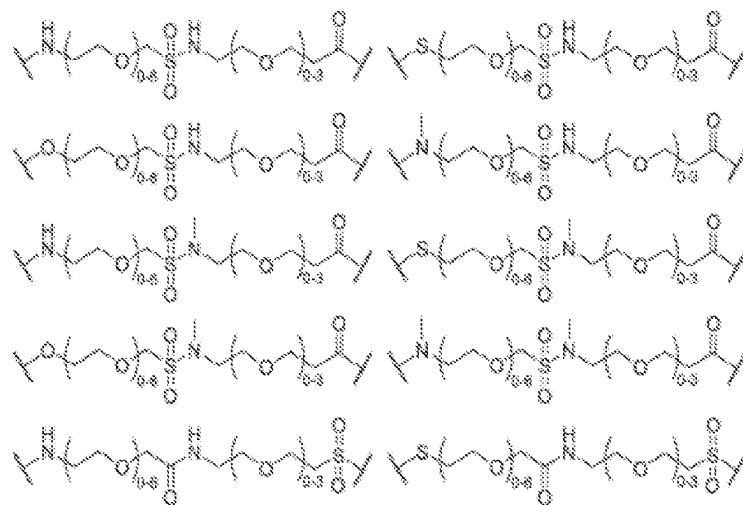


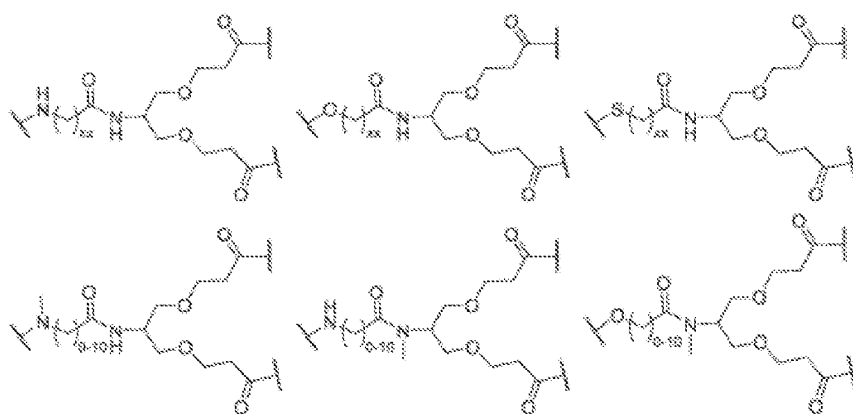
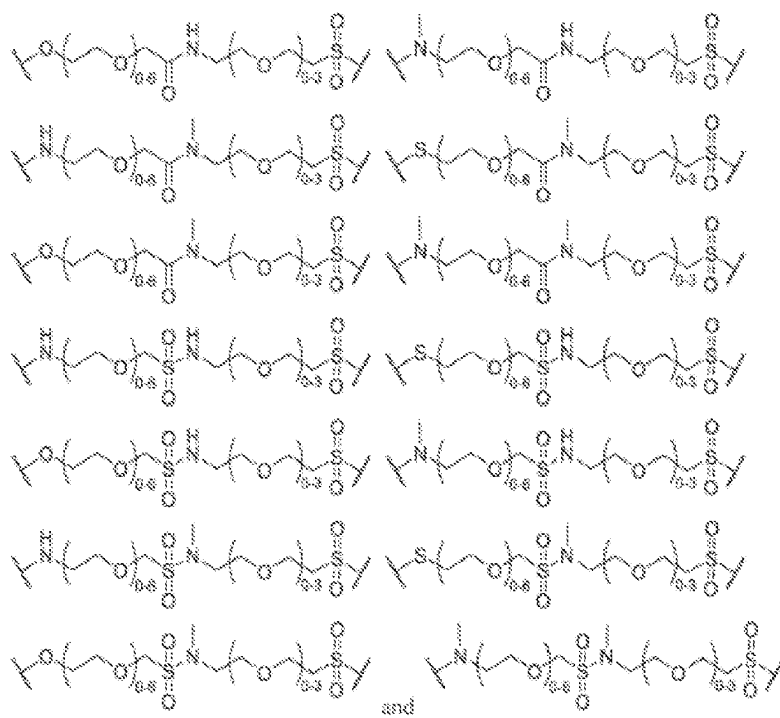
In certain embodiments, in the compound of Formula II, Linker^B is selected from:



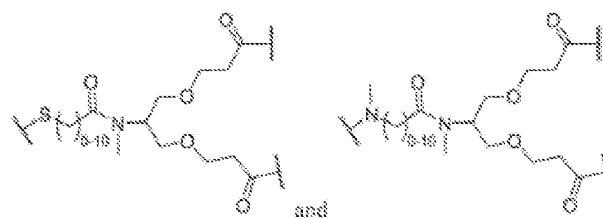


In certain embodiments, in the compound of Formula II, Linker^B is selected from:



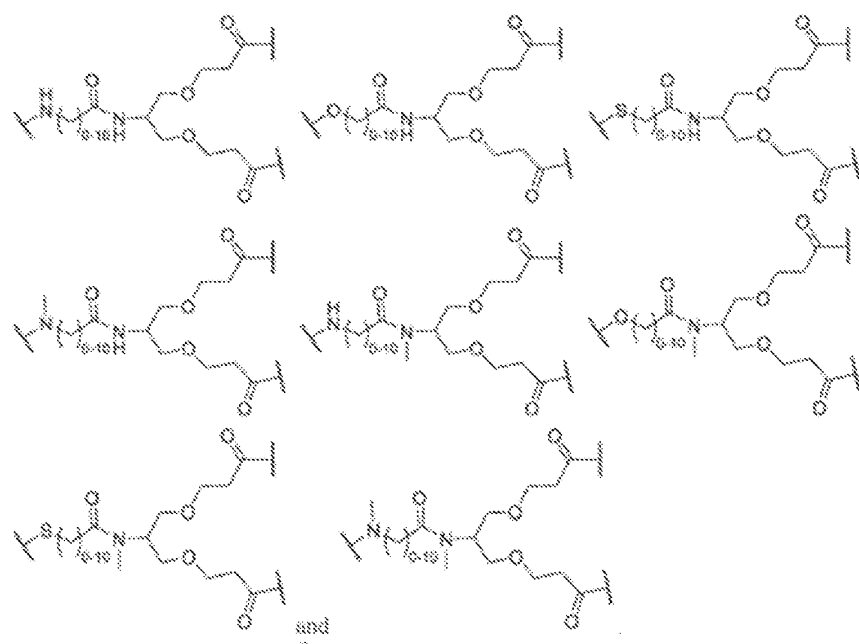


In certain embodiments, in the compound of Formula II, Linker^C is selected from:

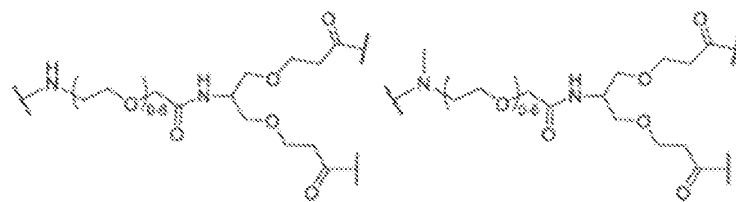


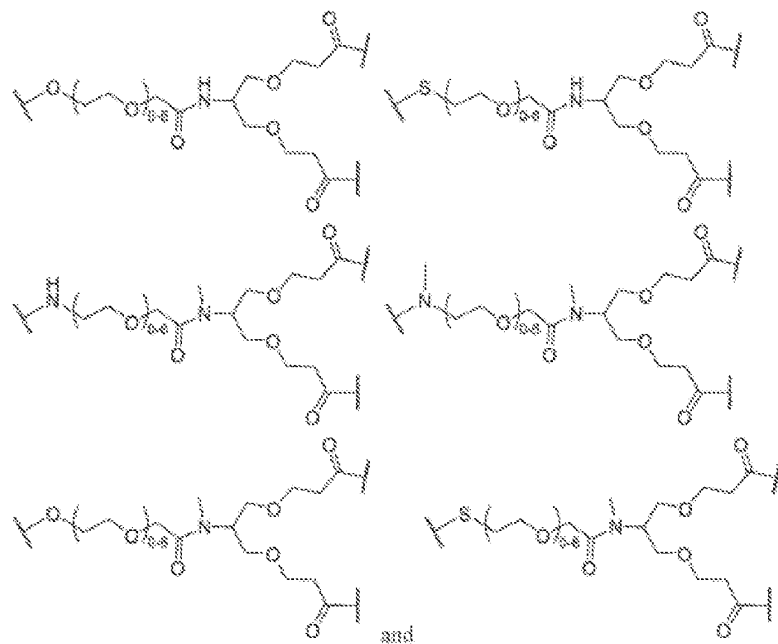
5

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

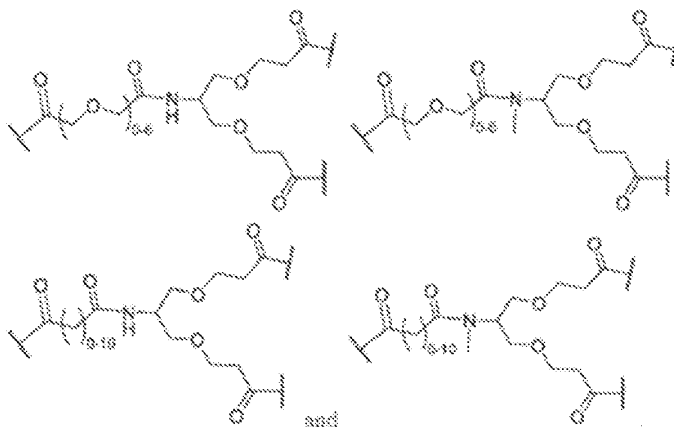


In certain embodiments, in the compound of Formula II, Linker^C is selected from:

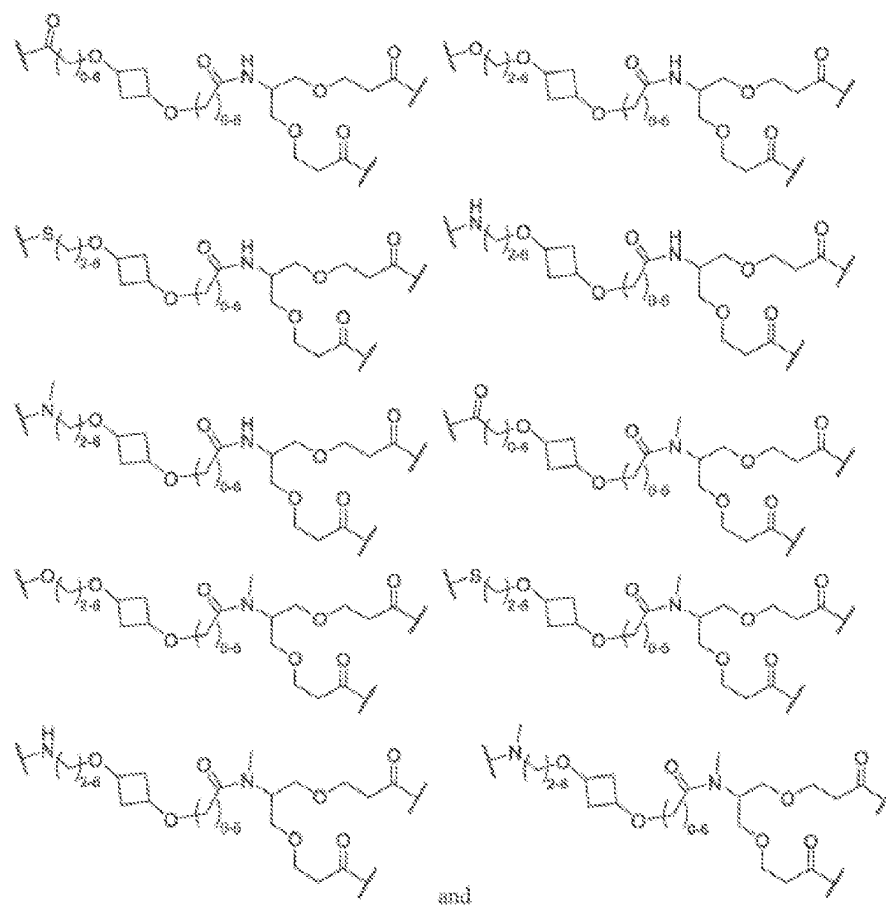




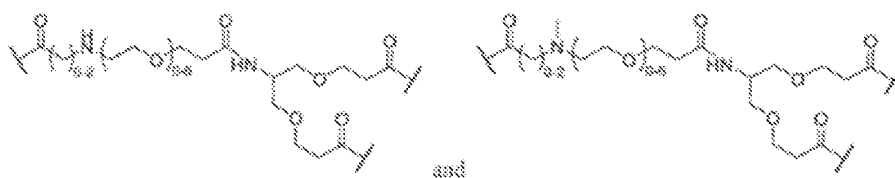
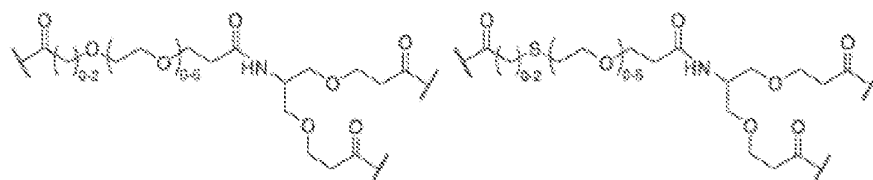
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



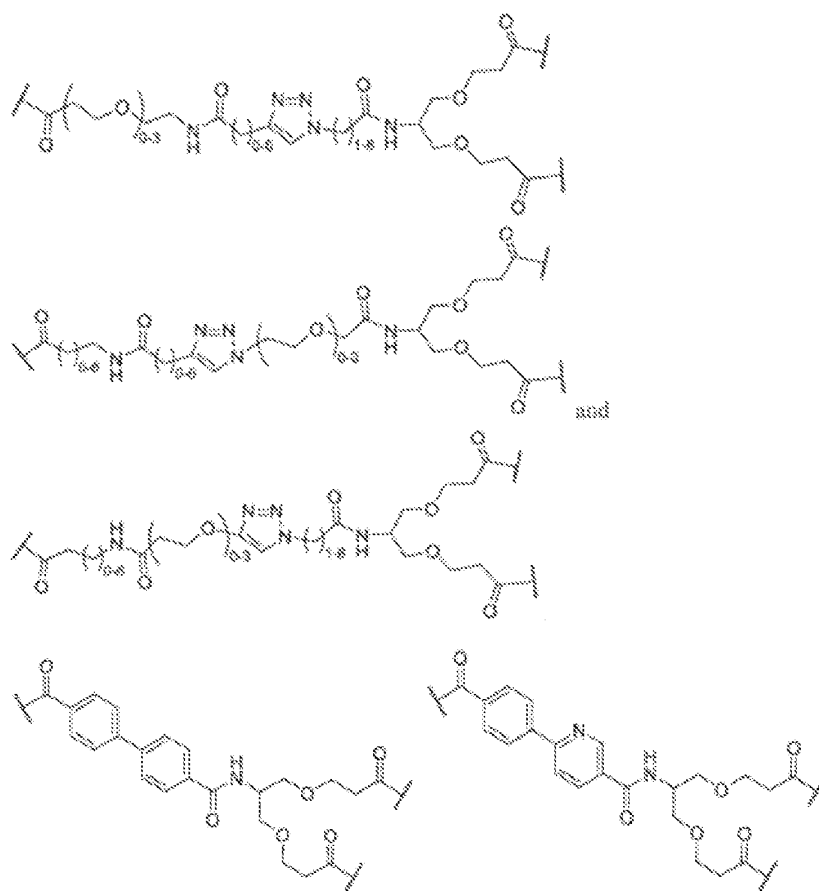
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



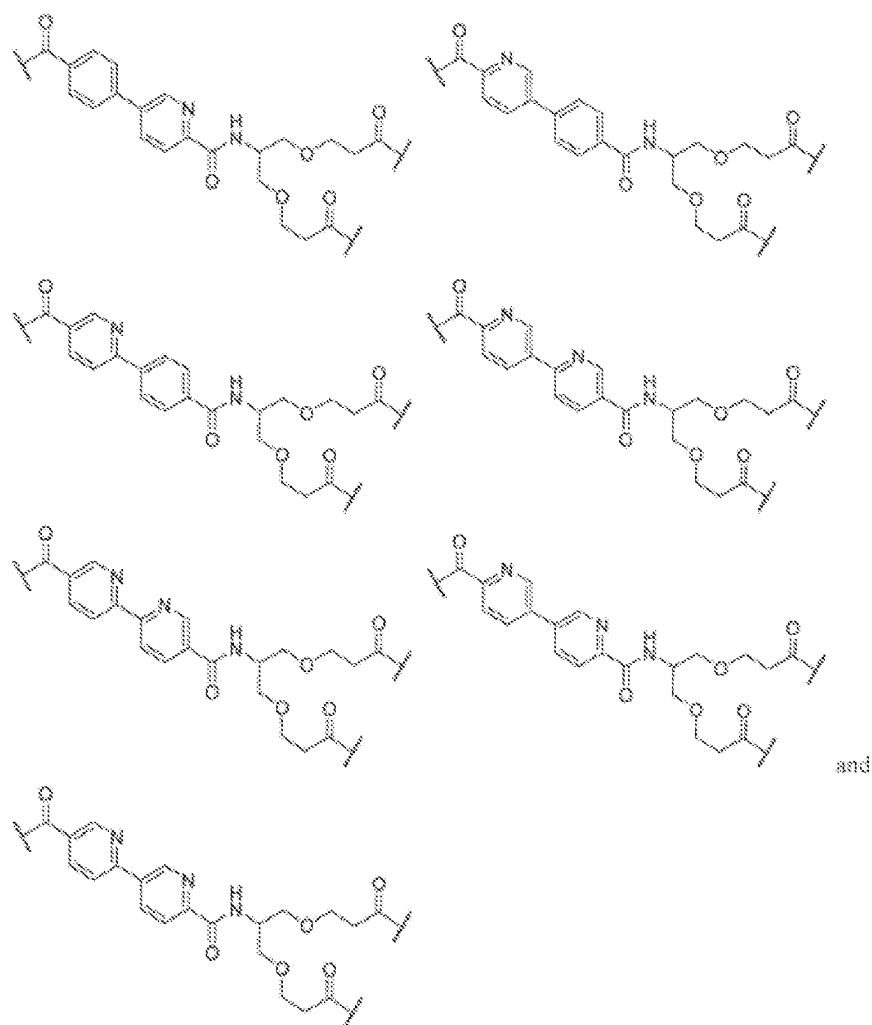
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



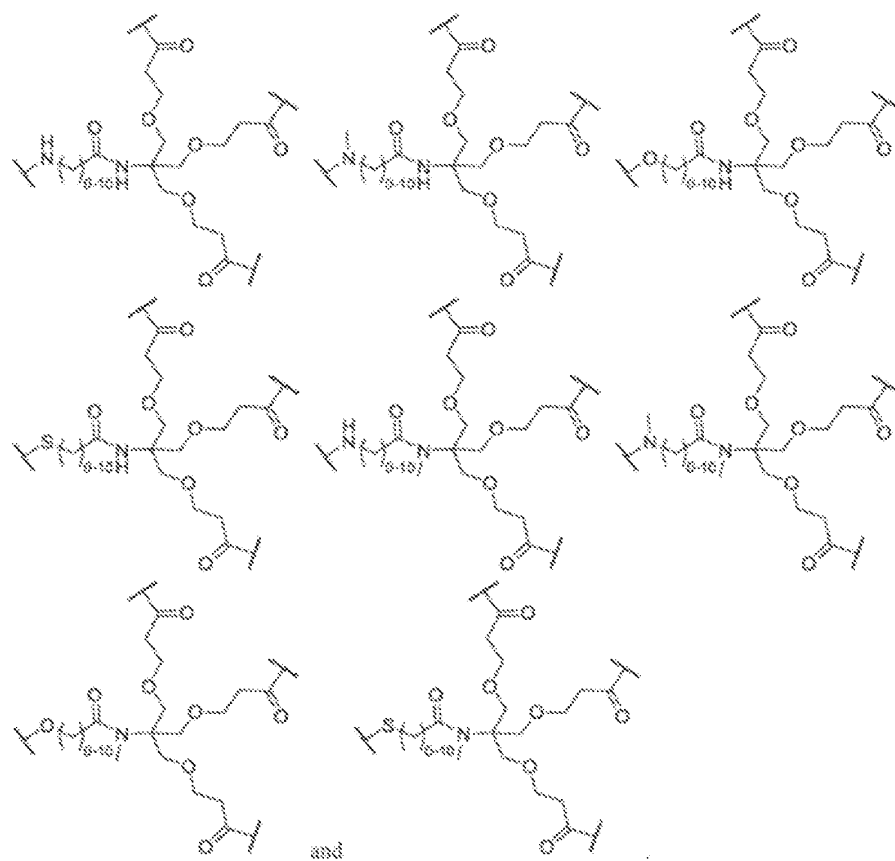
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



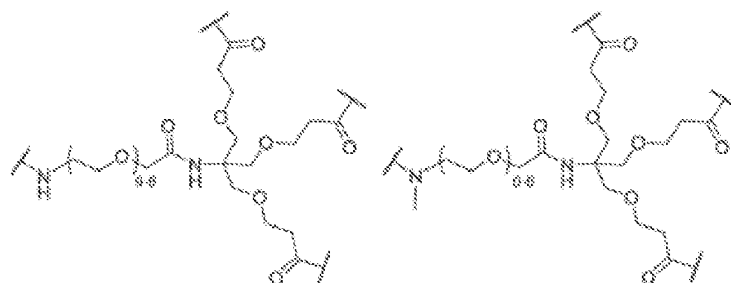
In certain embodiments, in the compound of Formula II, Linker^C is selected from:

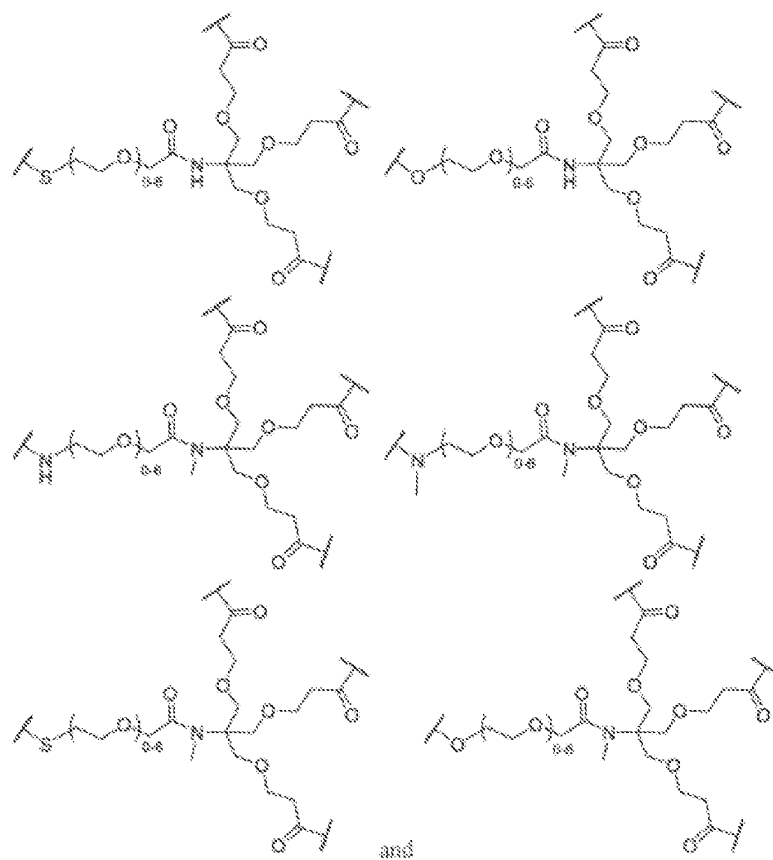


In certain embodiments, in the compound of Formula II, Linker^D is selected from:

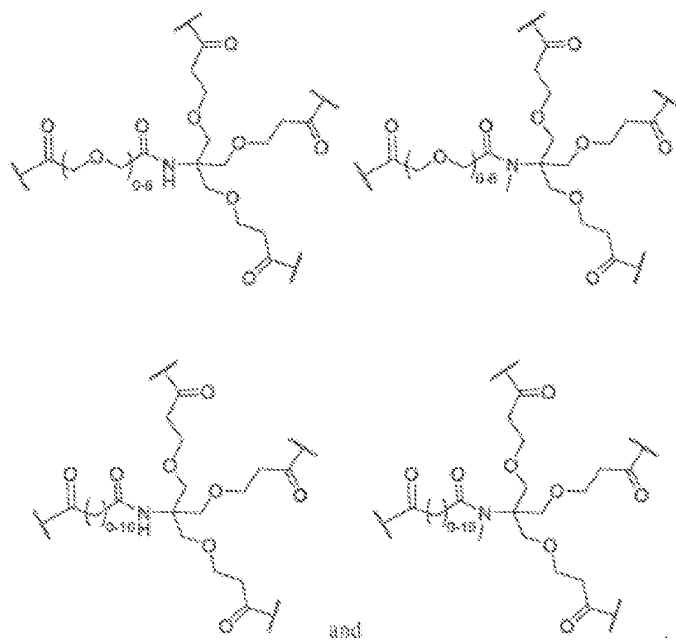


In certain embodiments, in the compound of Formula II, Linker^D is selected from:

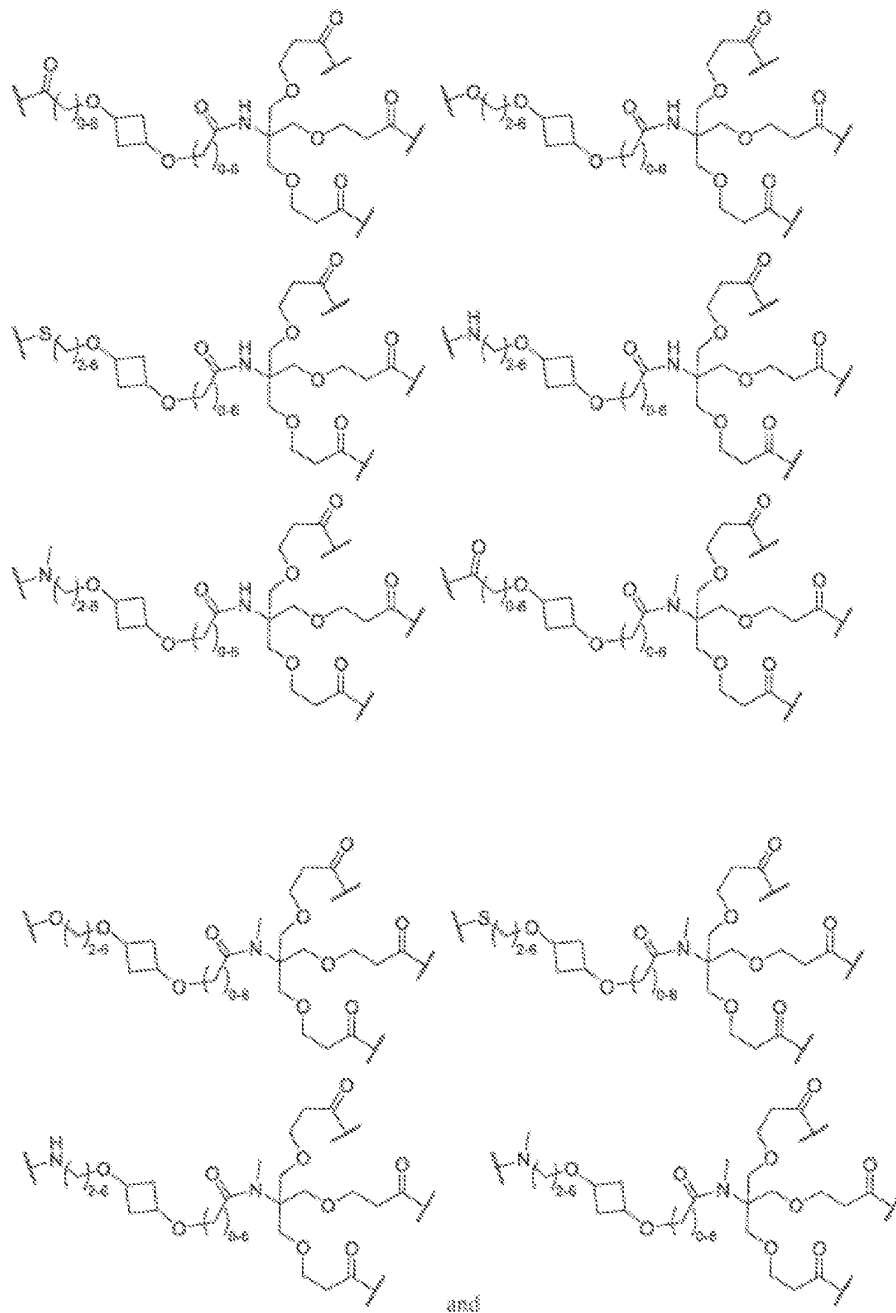




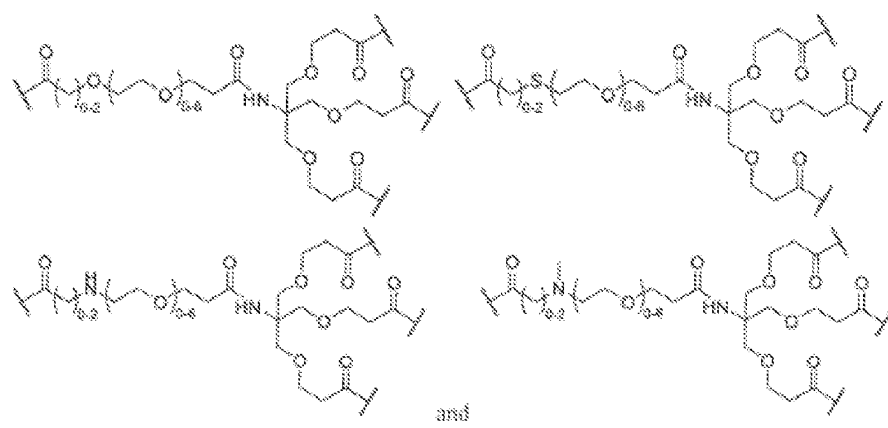
In certain embodiments, in the compound of Formula II, LinkerD is selected from:



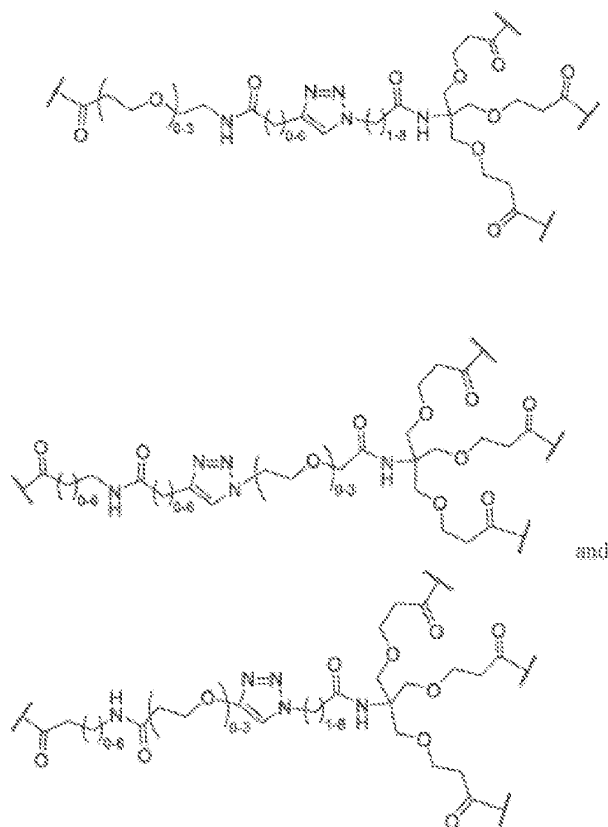
In certain embodiments, in the compound of Formula II, Linker^D is selected from:



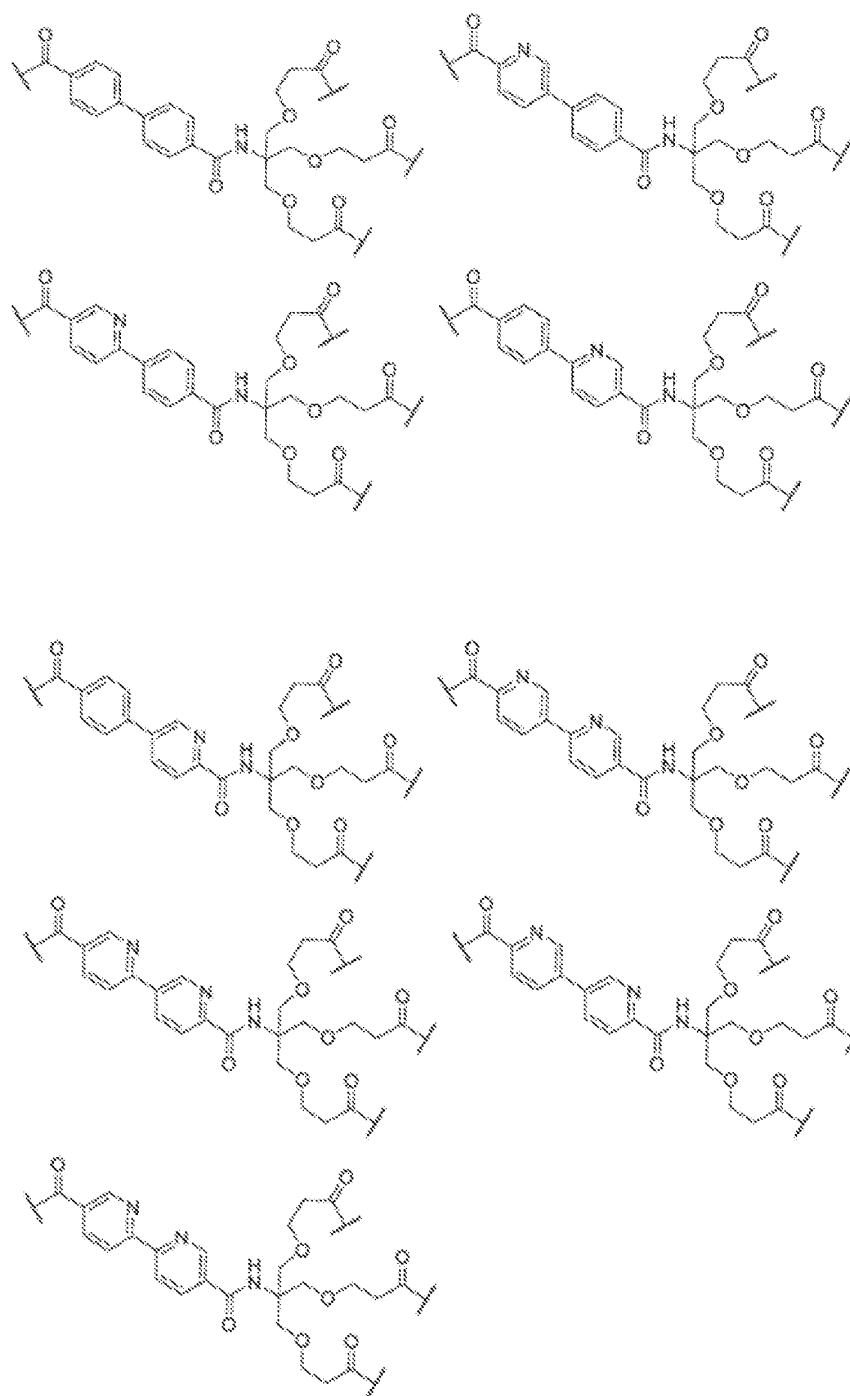
In certain embodiments, in the compound of Formula II, Linker^D is selected from:



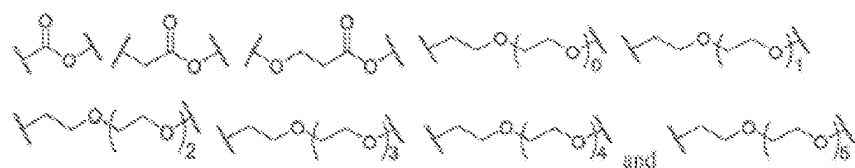
In certain embodiments, in the compound of Formula II, Linker^D is selected from:



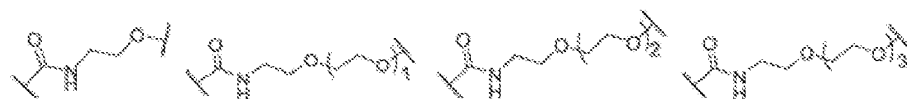
5 In certain embodiments, in the compound of Formula II, Linker^D is selected from:



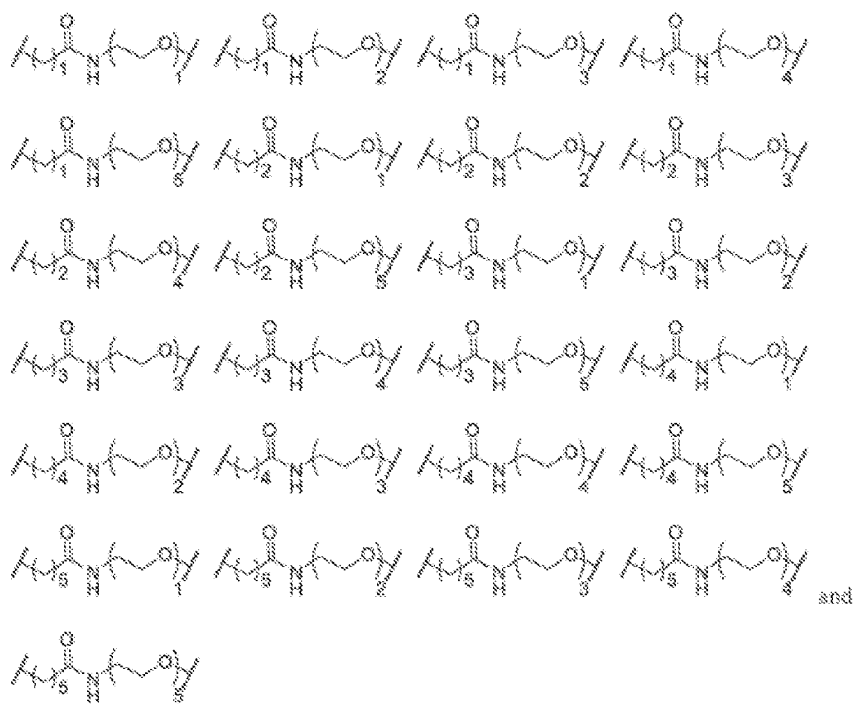
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



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

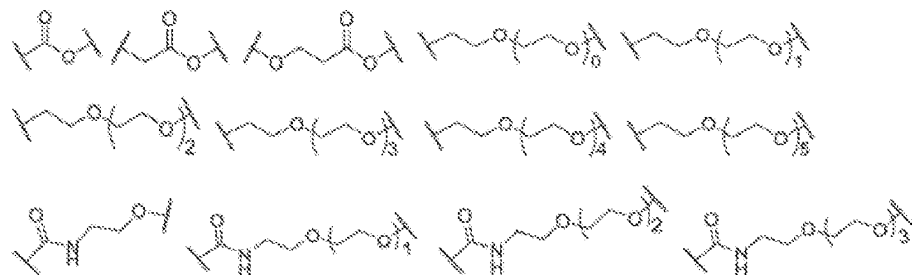


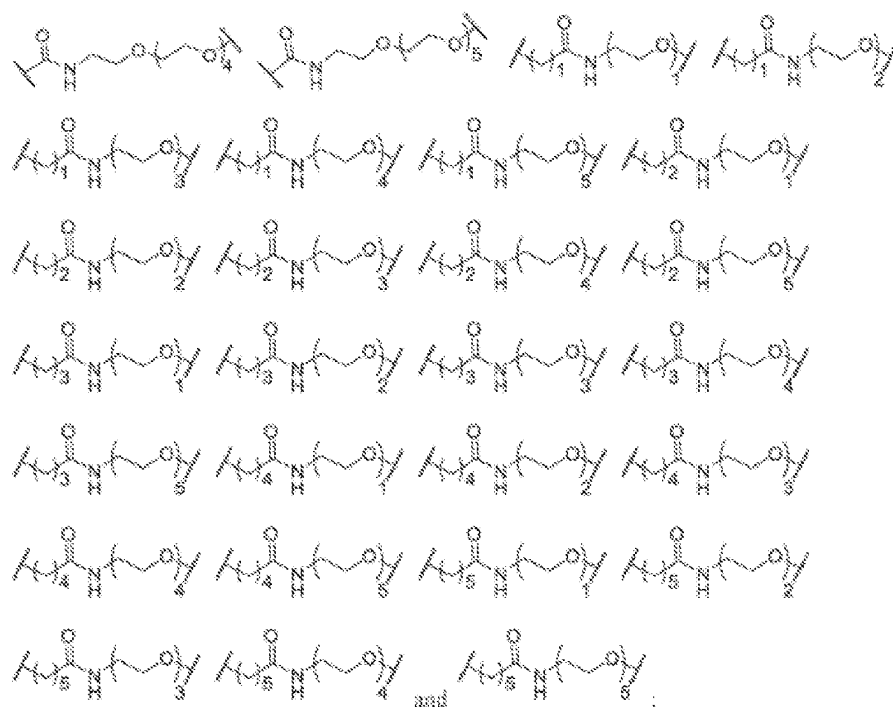
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



5

In certain embodiments, the Linker^A is selected from





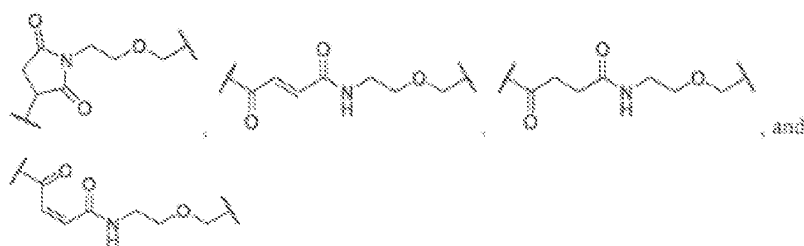
wherein each is optionally substituted with 1, 2, 3, or 4 substituents selected from R²¹.

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

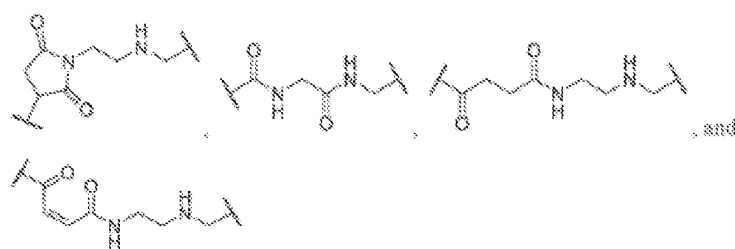


5

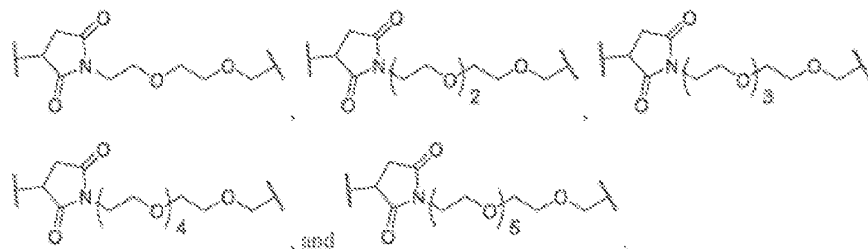
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



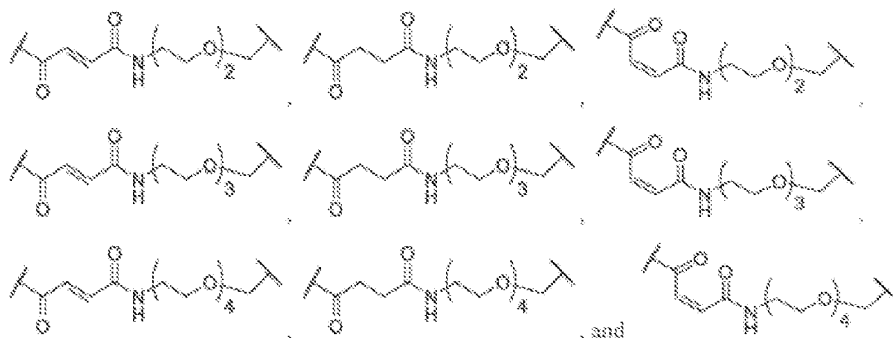
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



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

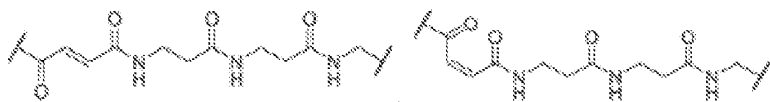


In certain embodiments, in the compound of Formula II, the Linker^A is selected from



5

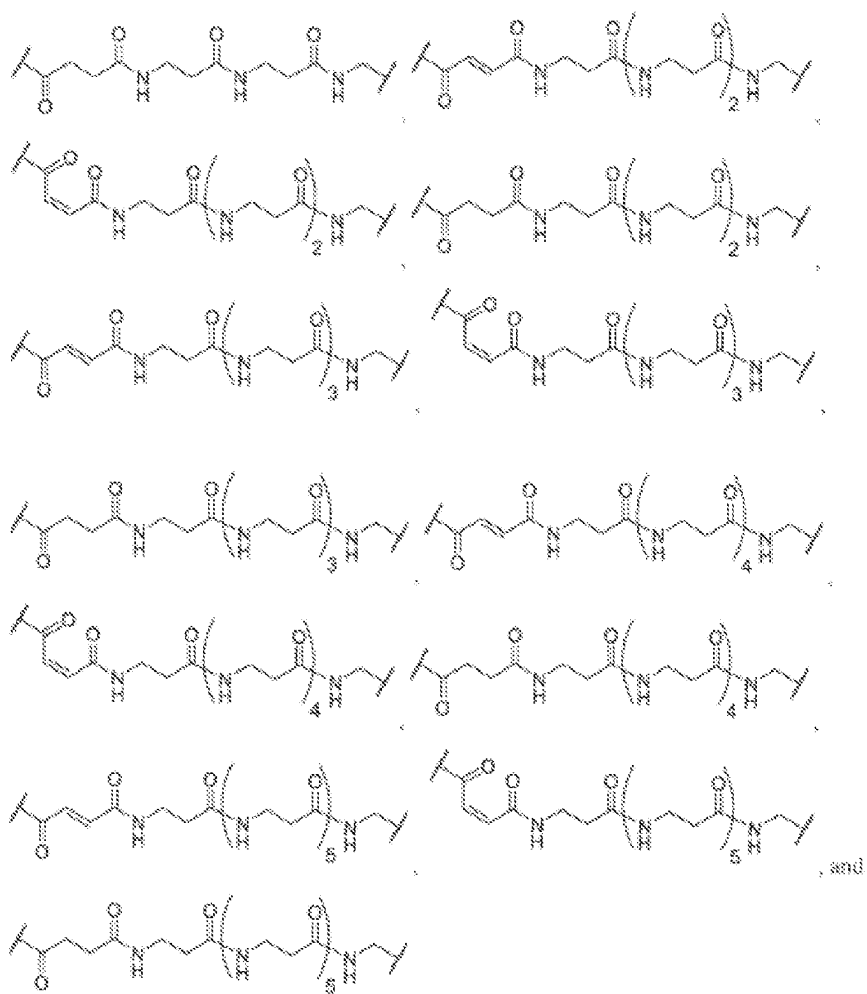
In certain embodiments, in the compound of Formula II, the Linker^A is selected from

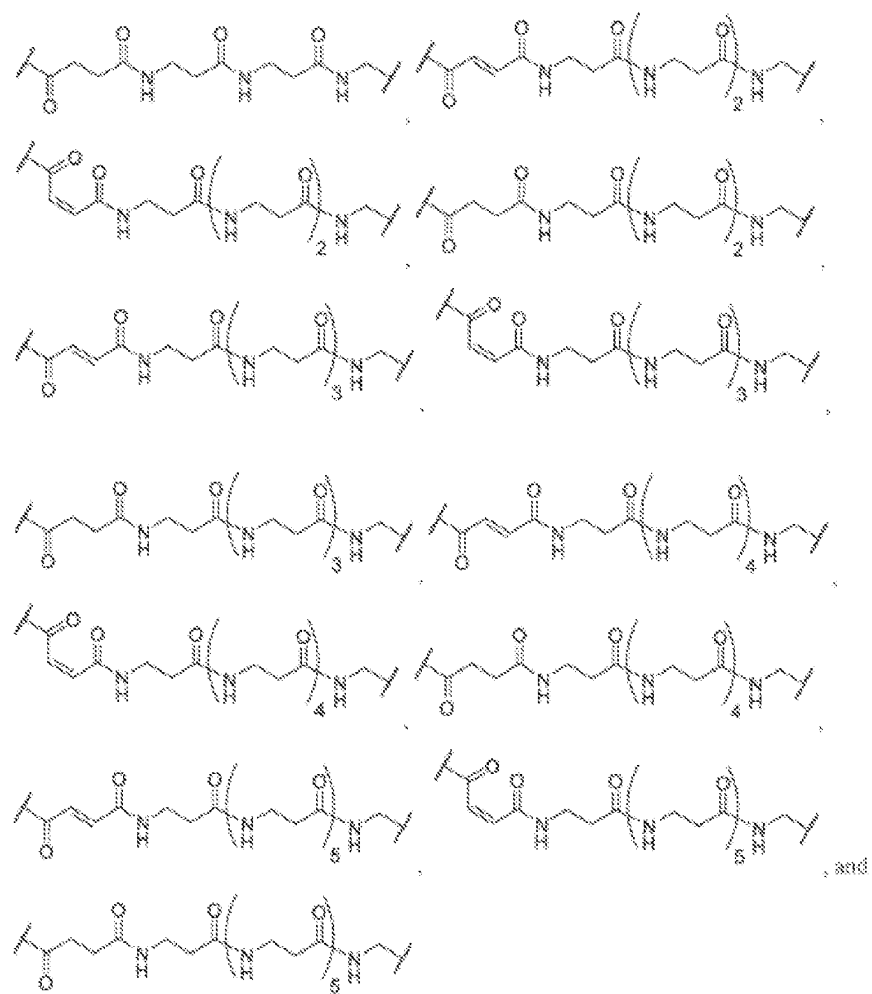


In certain embodiments, in the compound of Formula II, the Linker^A is selected from

10

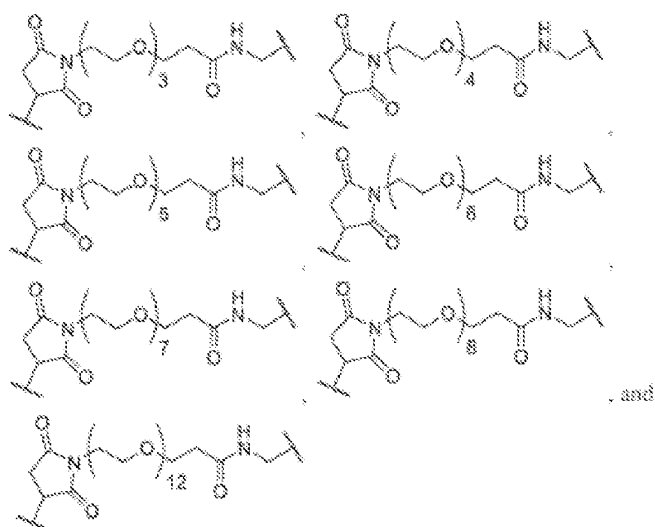
In certain embodiments, in the compound of Formula II, the Linker^A is selected from





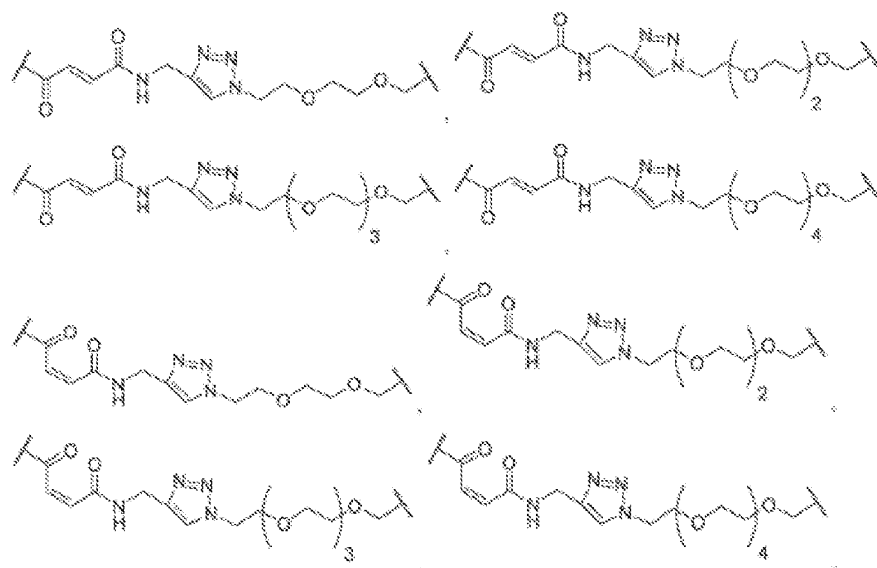
In certain embodiments, in the compound of Formula II, the Linker^A is selected from

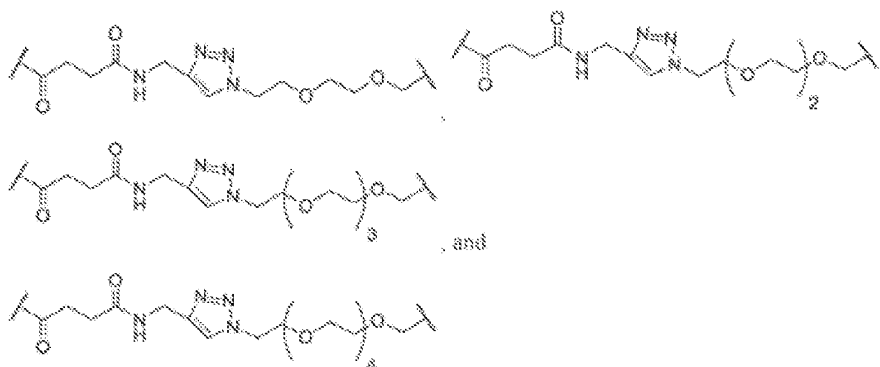




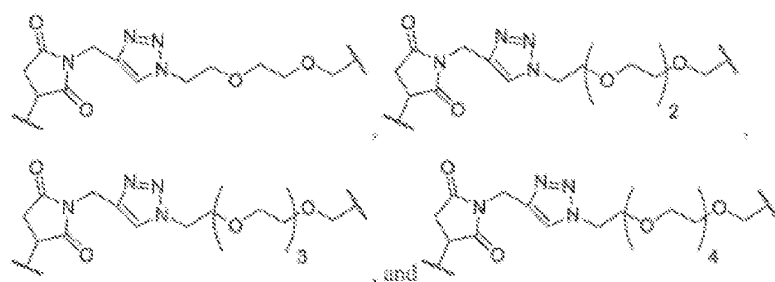
, and

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

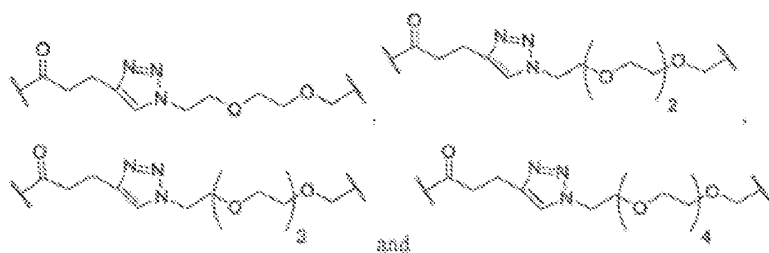




In certain embodiments, in the compound of Formula II, the Linker^A is selected from

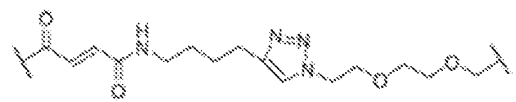


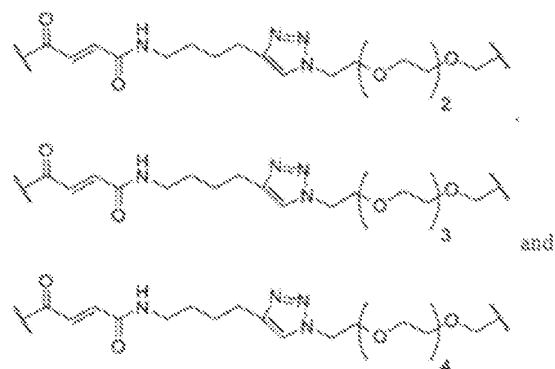
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



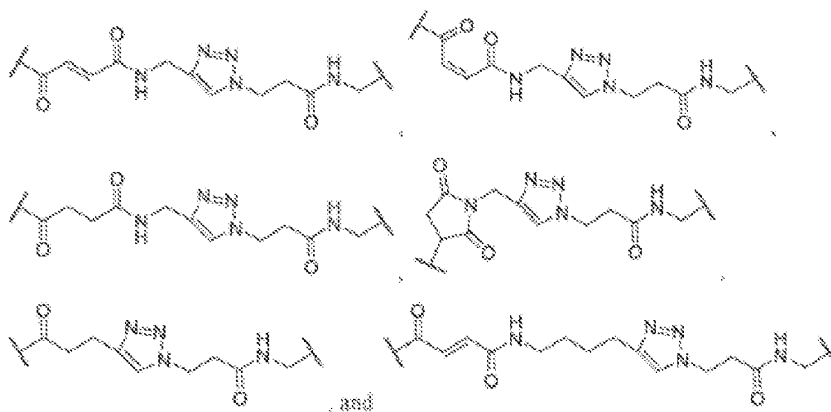
5

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

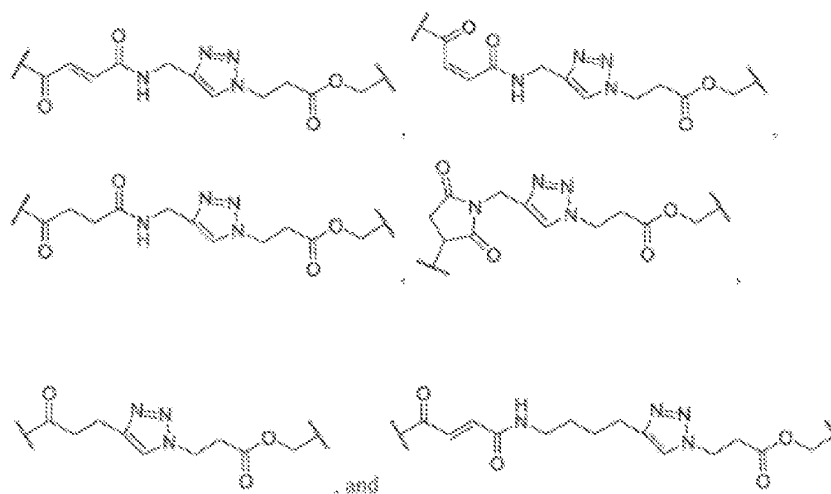




In certain embodiments, in the compound of Formula II, the Linker^A is selected from

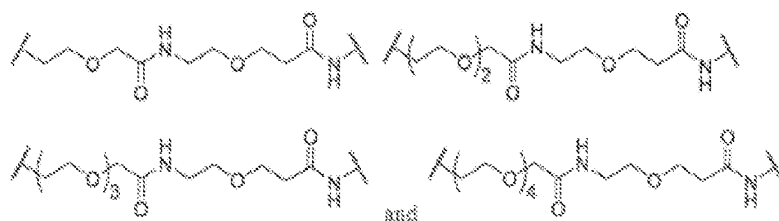


In certain embodiments, in the compound of Formula II, the Linker^A is selected from

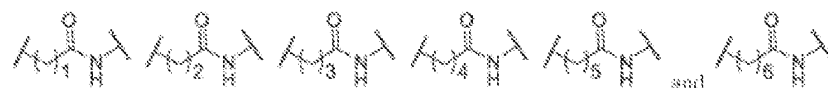


5

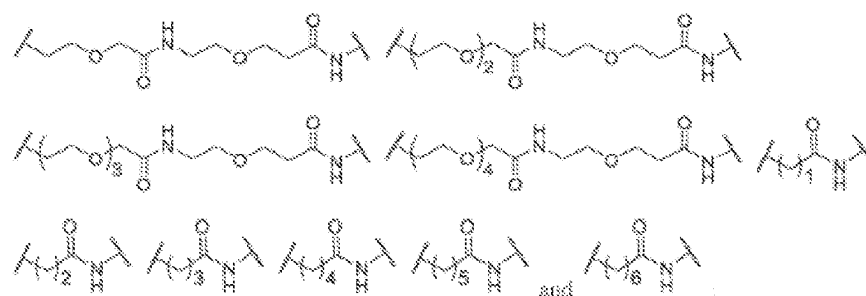
In certain embodiments, in the compound of Formula II, the Linker^B is selected from



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



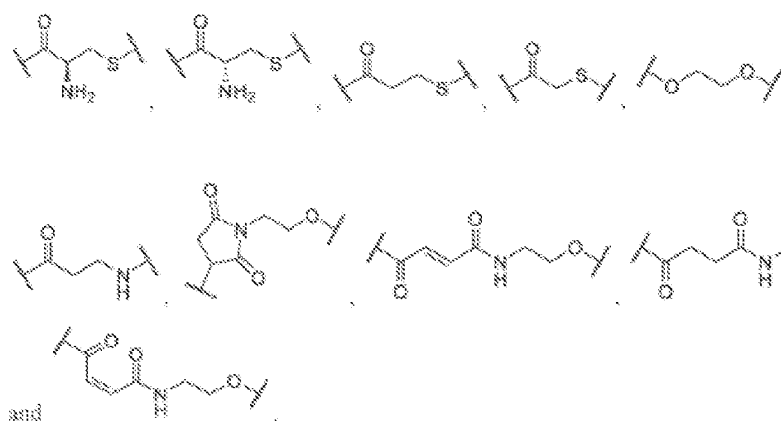
In certain embodiments, in the compound of Formula II, the Linker^B is selected from



5

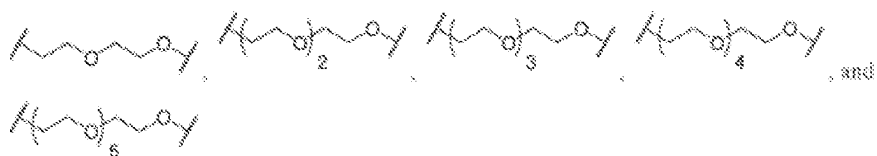
In certain embodiments, in the compound of Formula II, the Linker^B is selected from wherein each is optionally substituted with 1, 2, 3, or 4 substituents selected from R²¹.

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

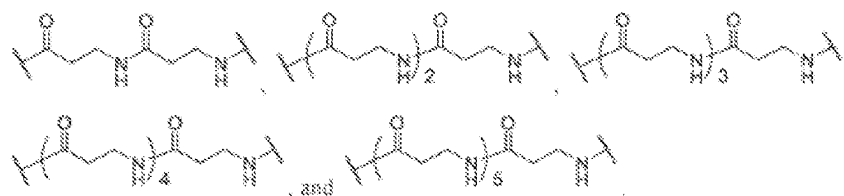


10

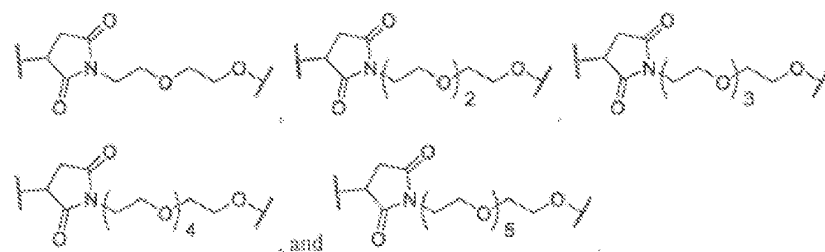
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



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

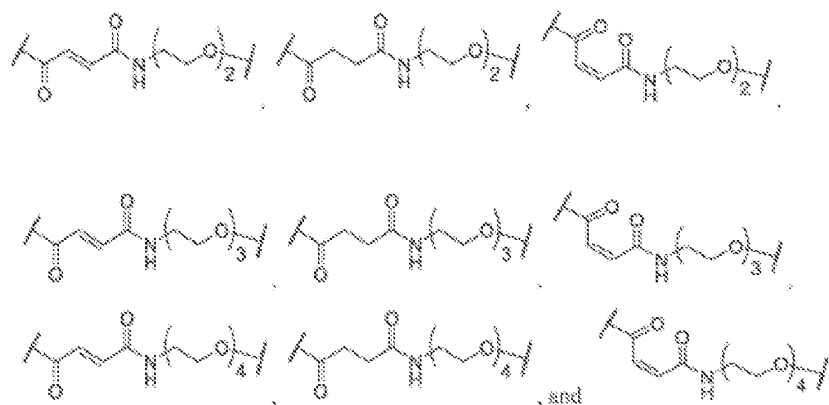


In certain embodiments, in the compound of Formula II, the Linker^B is selected from:

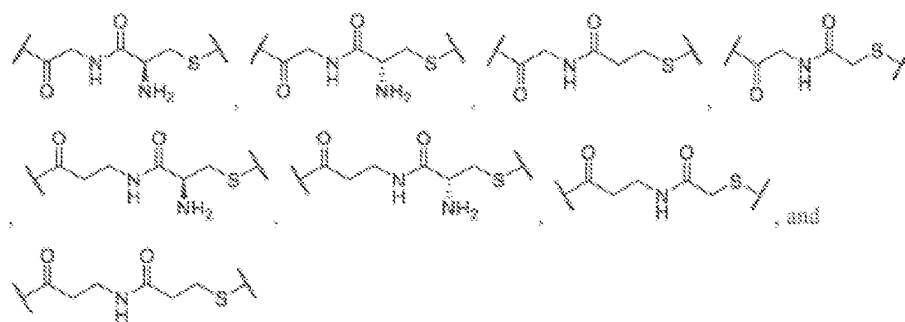


5

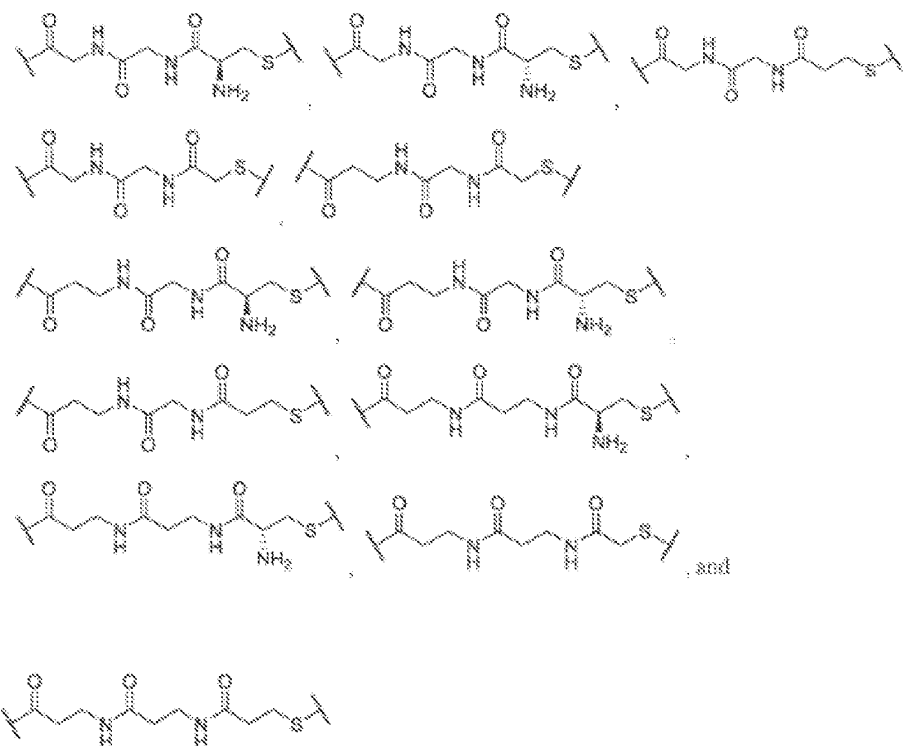
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



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

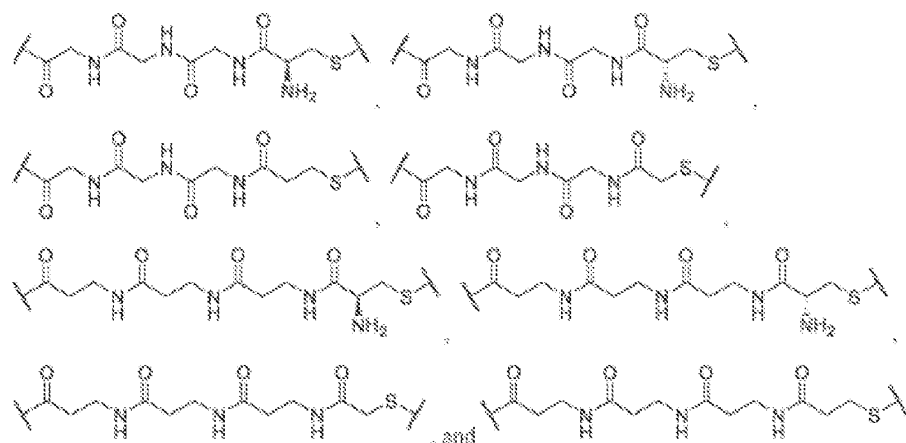


In certain embodiments, in the compound of Formula II, the Linker^B is selected from:

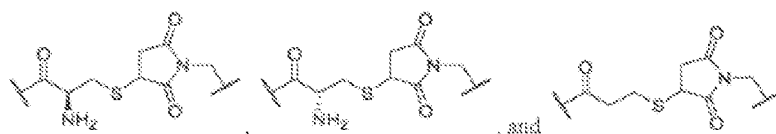


5

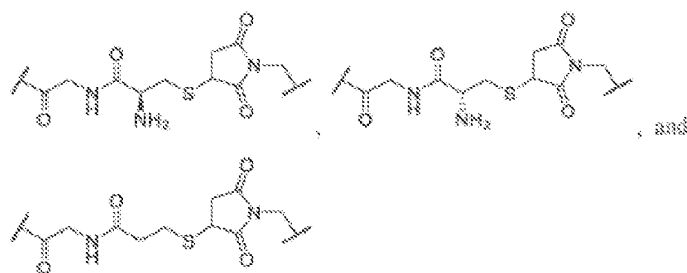
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



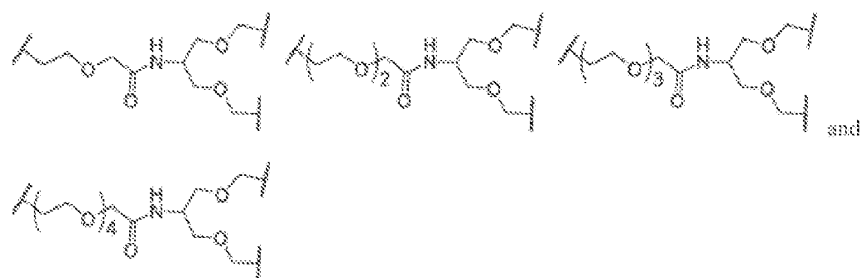
In certain embodiments, in the compound of Formula II, Linker^B-Linker^A is selected from:



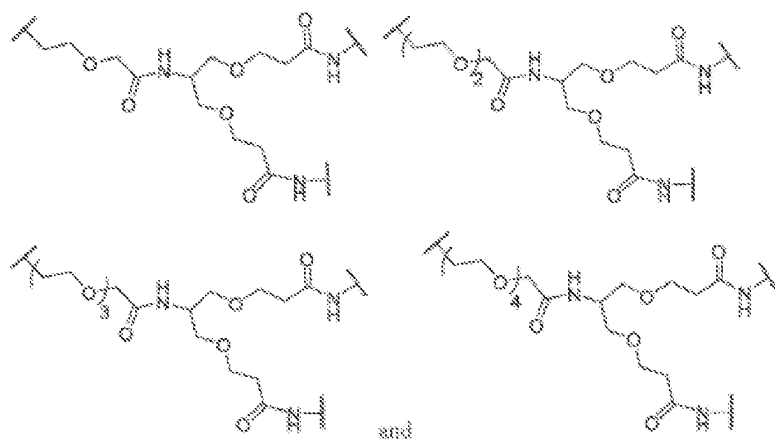
5 In certain embodiments, in the compound of Formula II, Linker^B-Linker^A is selected from:



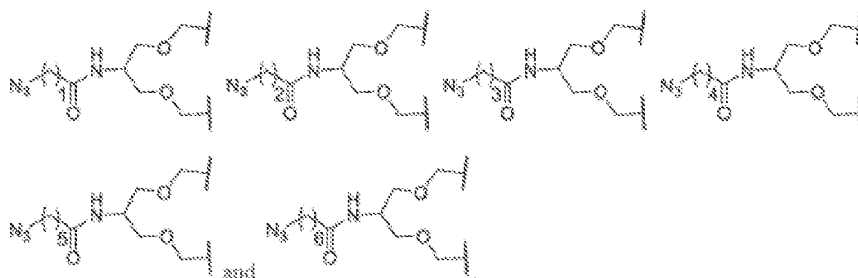
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



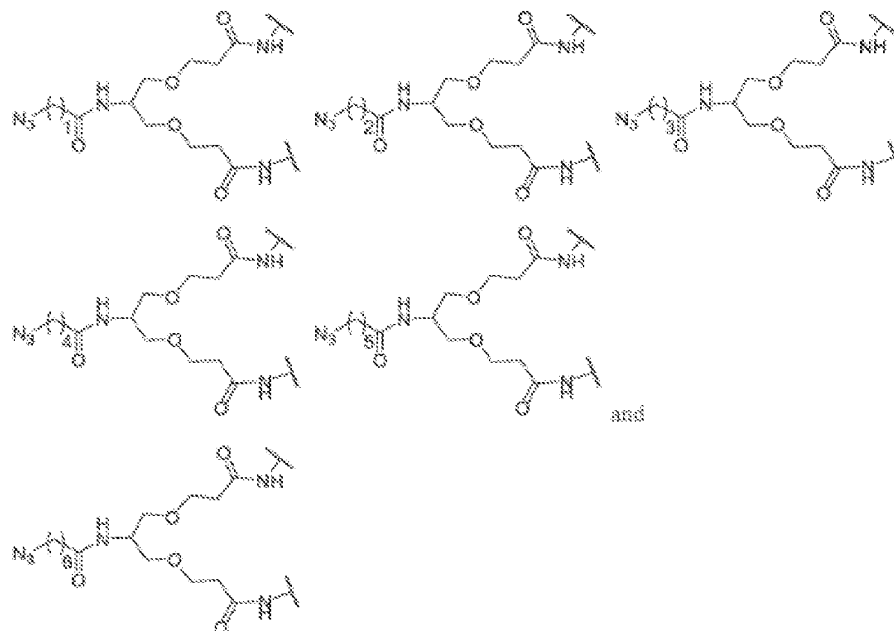
10 In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



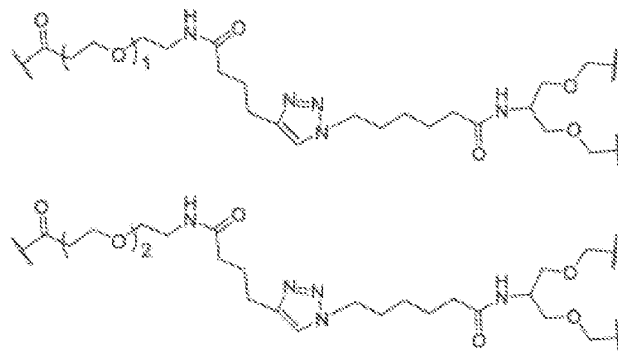
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



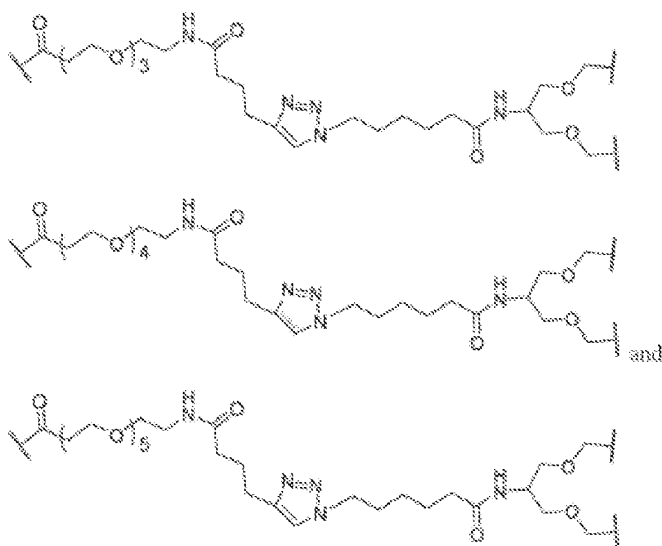
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



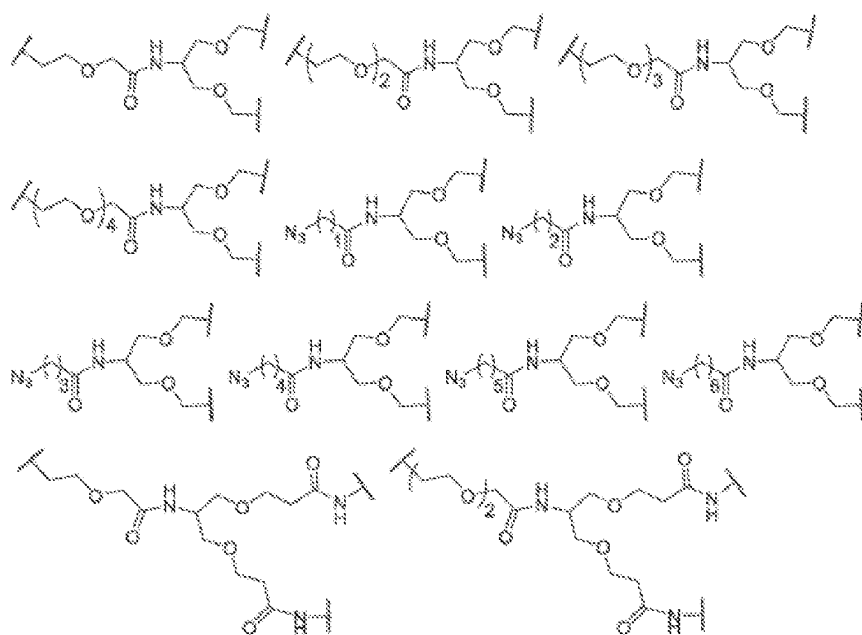
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:

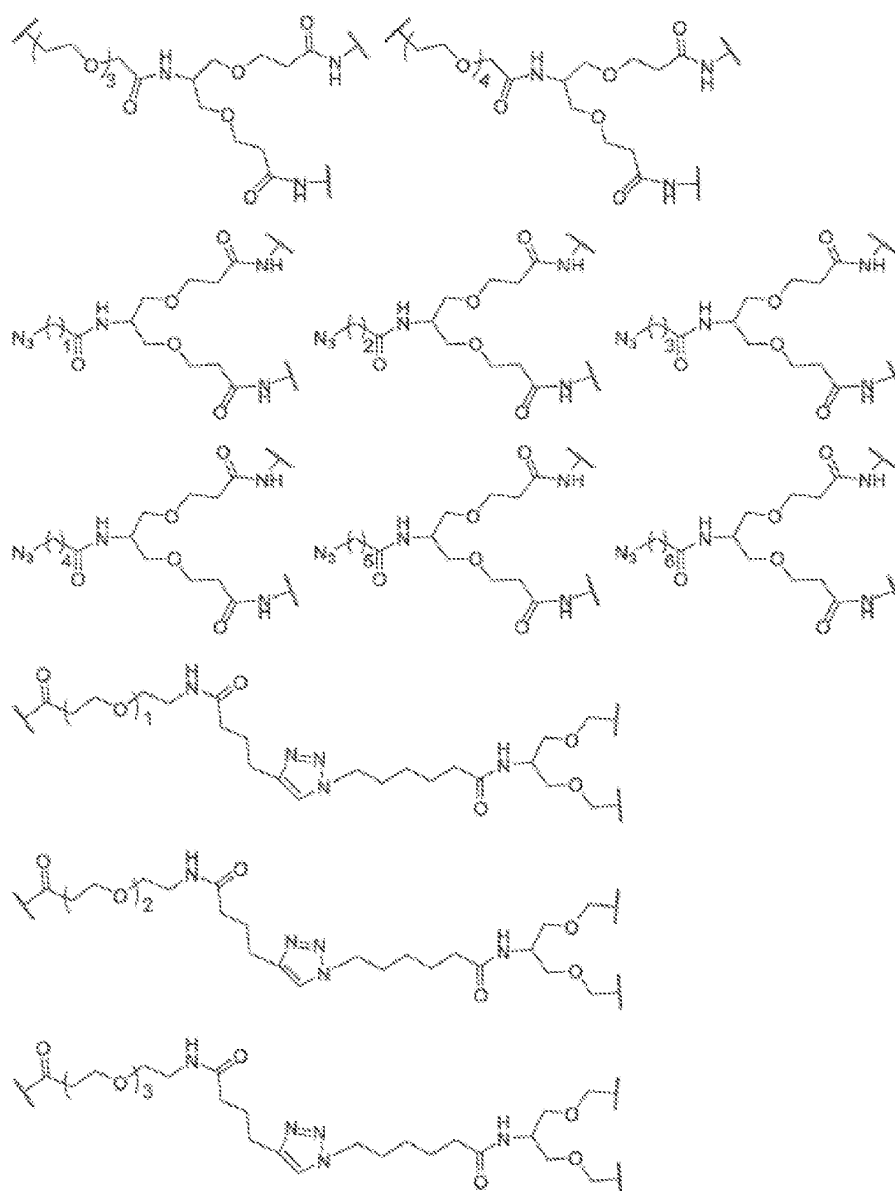


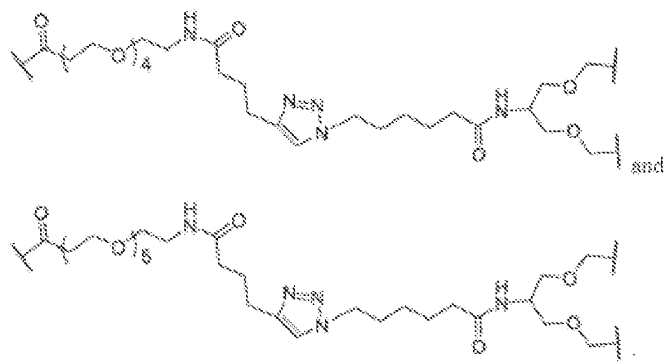
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



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

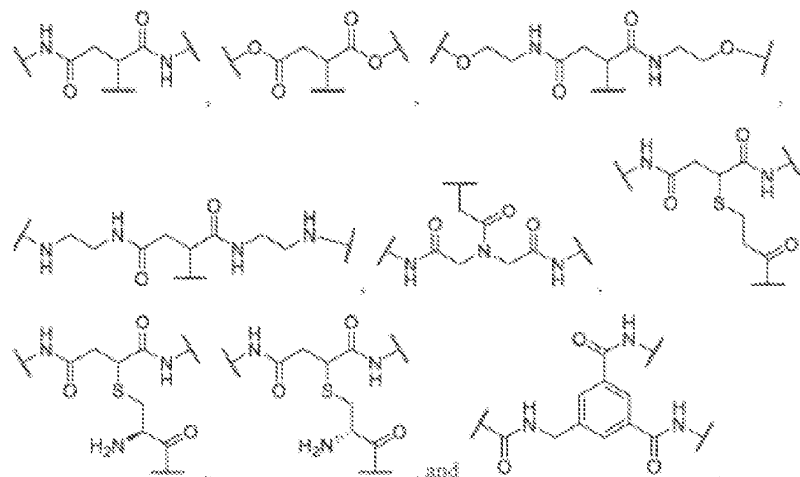




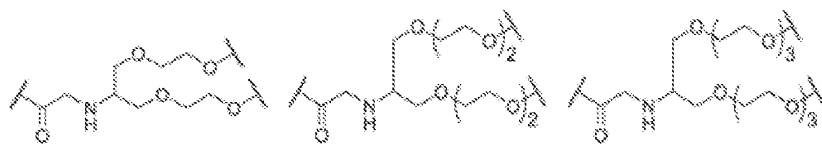


In certain embodiments, in the compound of Formula II, the Linker^C is selected from:
 wherein each is optionally substituted with 1, 2, 3, or 4 substituents substituent selected from R²¹.

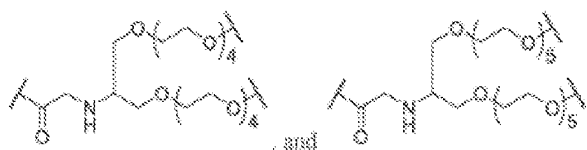
5 In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



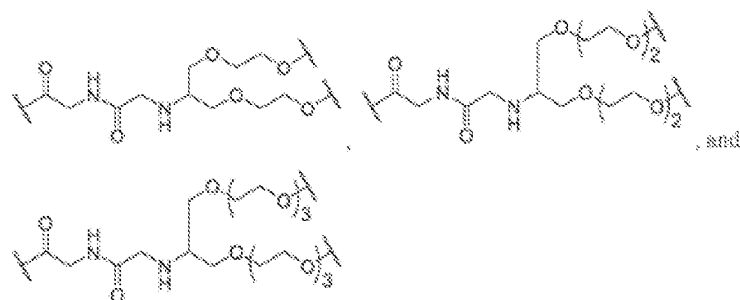
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



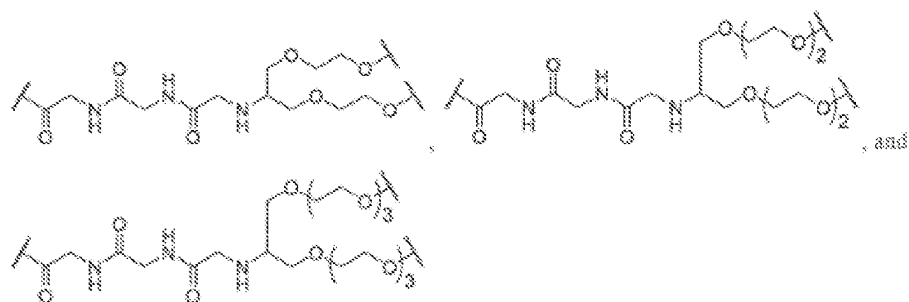
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



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

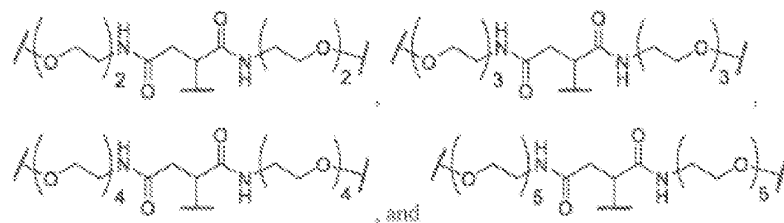


In certain embodiments, in the compound of Formula II, the Linker^C is selected from:

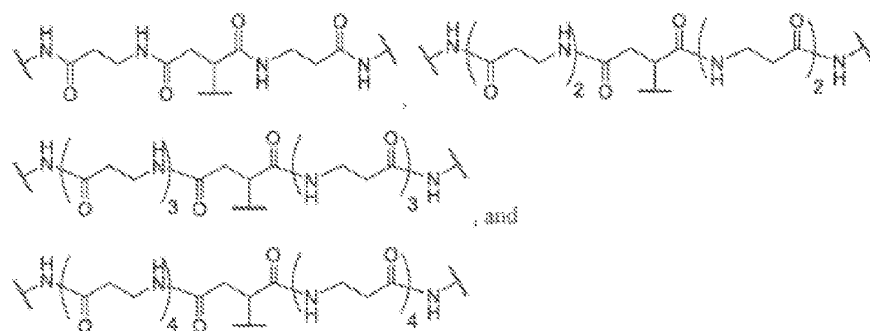


5

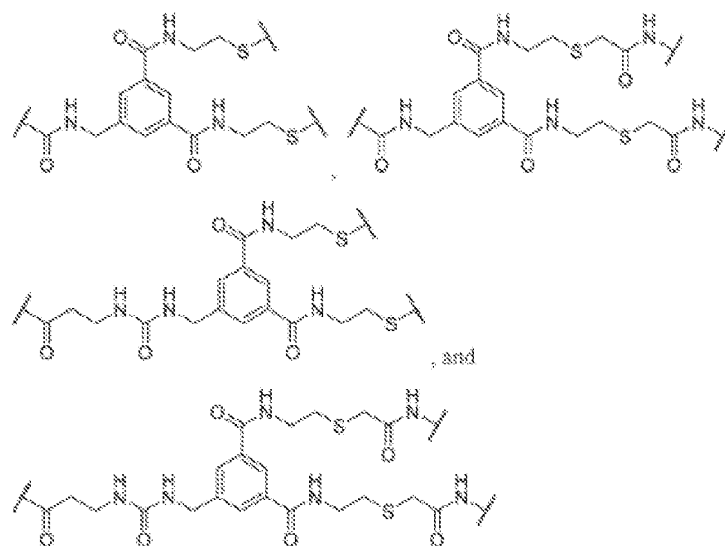
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



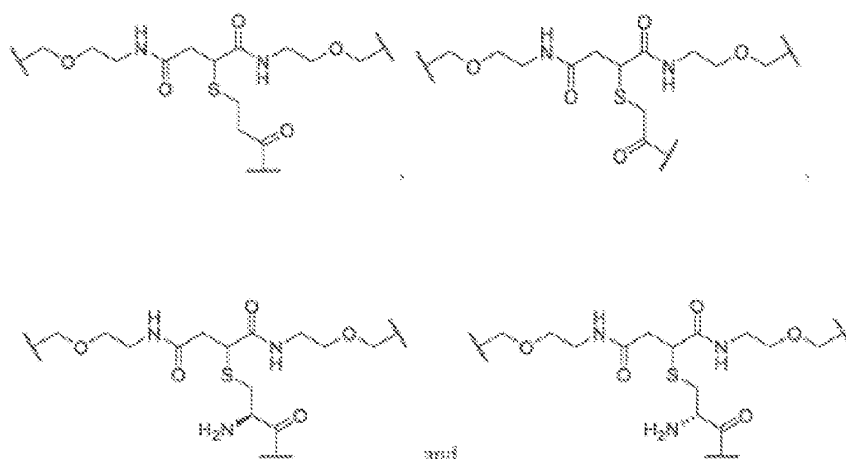
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



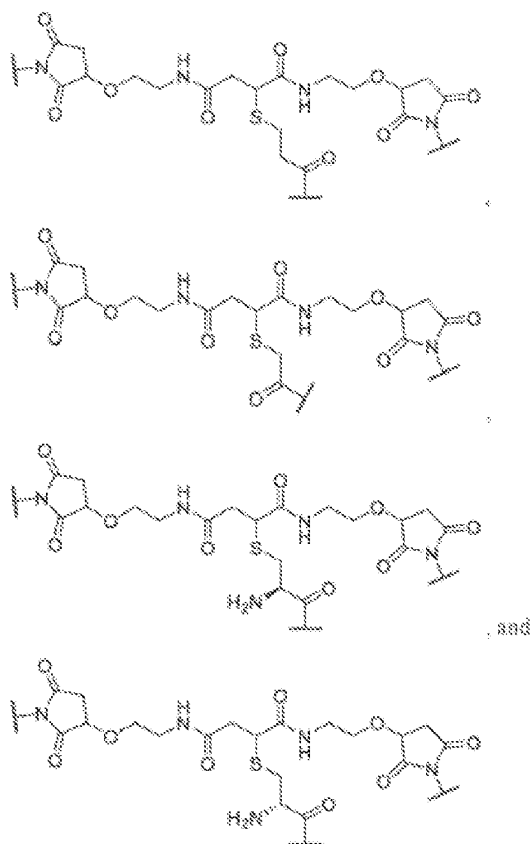
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



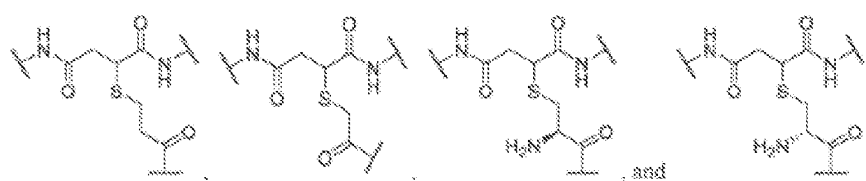
In certain embodiments, in the compound of Formula II, Linker^C-(Linker^A)₂ is
5 selected from:



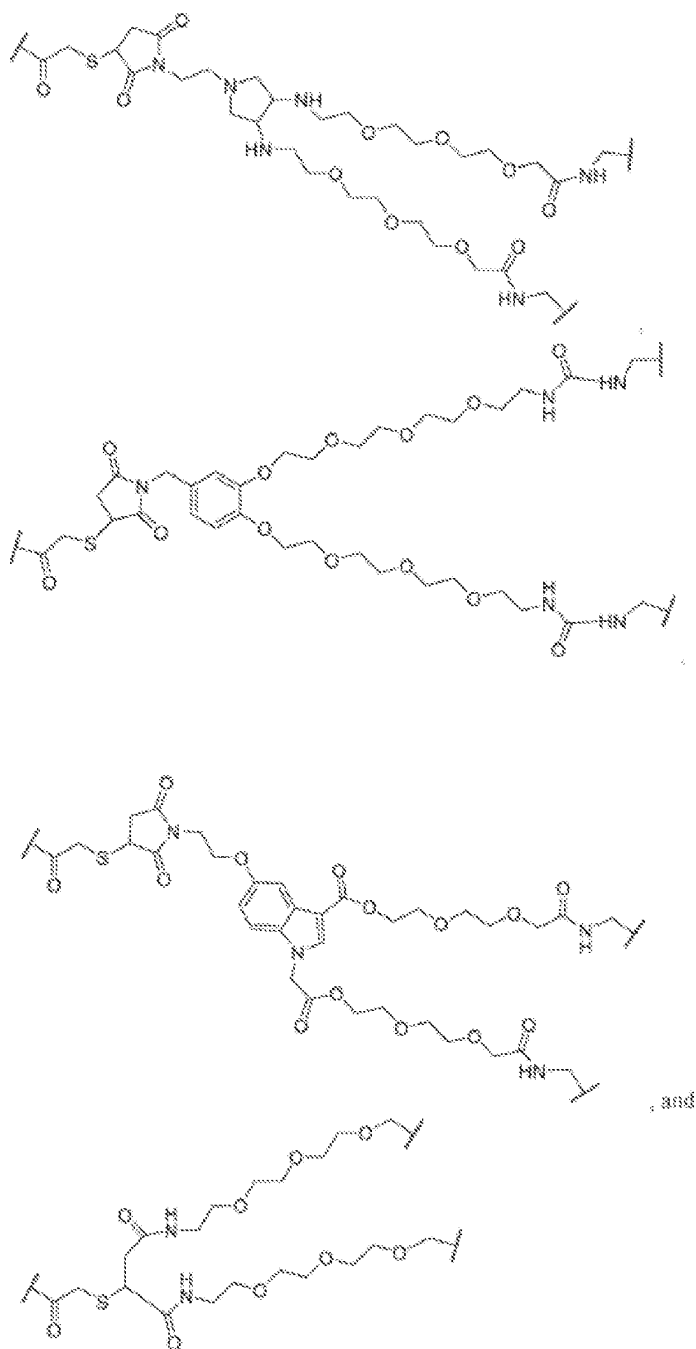
In certain embodiments, in the compound of Formula II, Linker^C-(Linker^A)₂ is selected from:



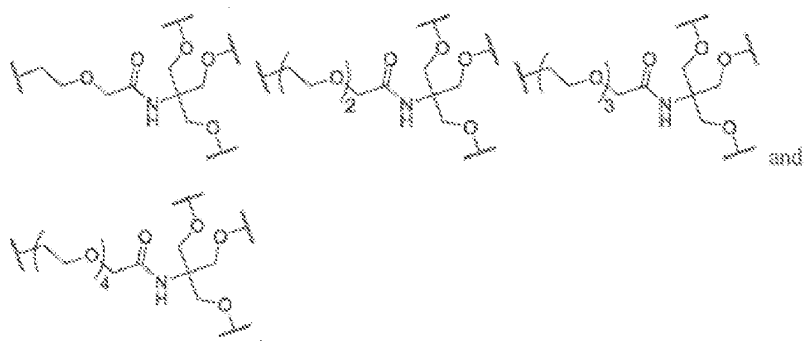
5 In certain embodiments, in the compound of Formula II, Linker^C-(Linker^A)₂ is selected from:



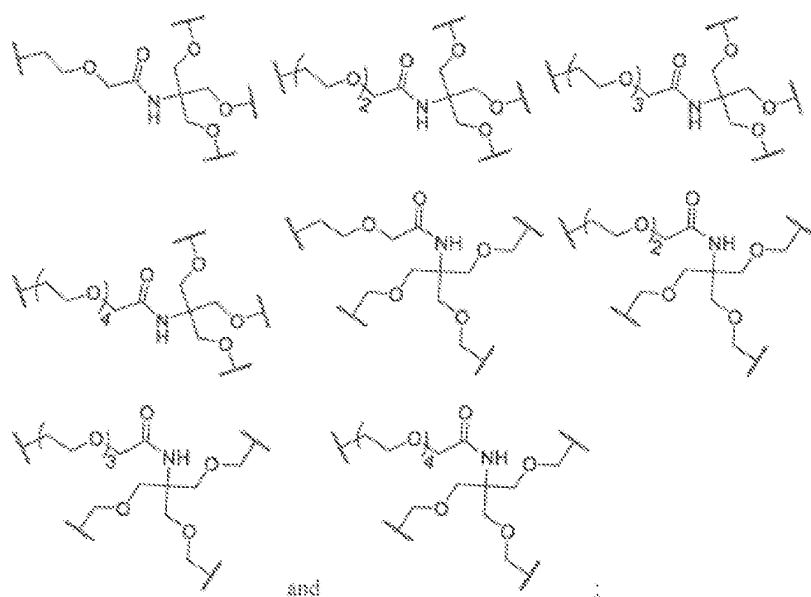
In certain embodiments, in the compound of Formula II, Linker^C-(Linker^A)₂ is selected from:



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



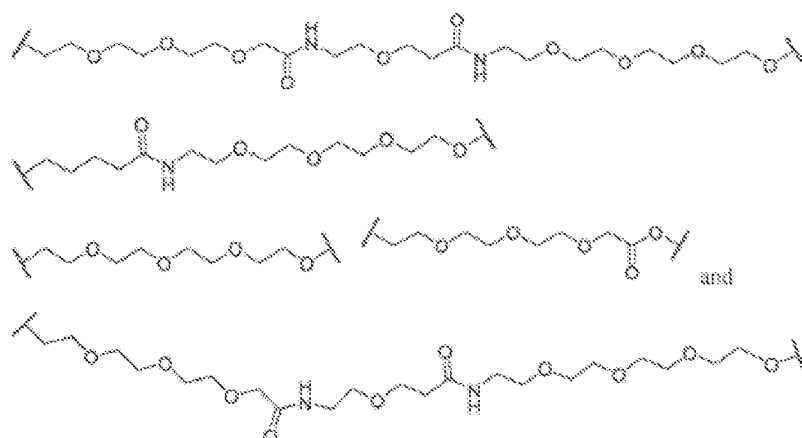
In certain embodiments, in the compound of Formula II, Linker^D is selected from:



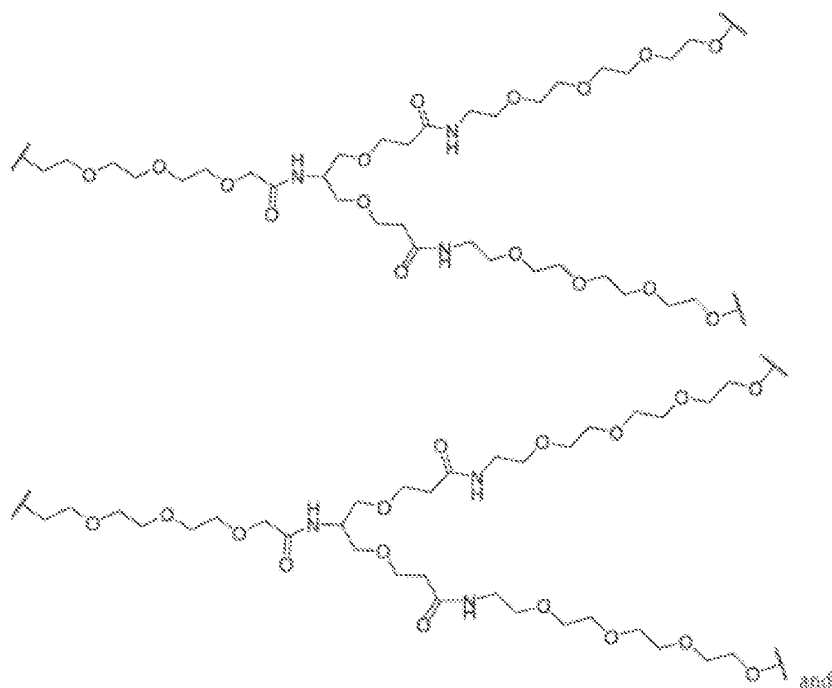
wherein each is optionally substituted with 1, 2, 3, or 4 substituents are selected from

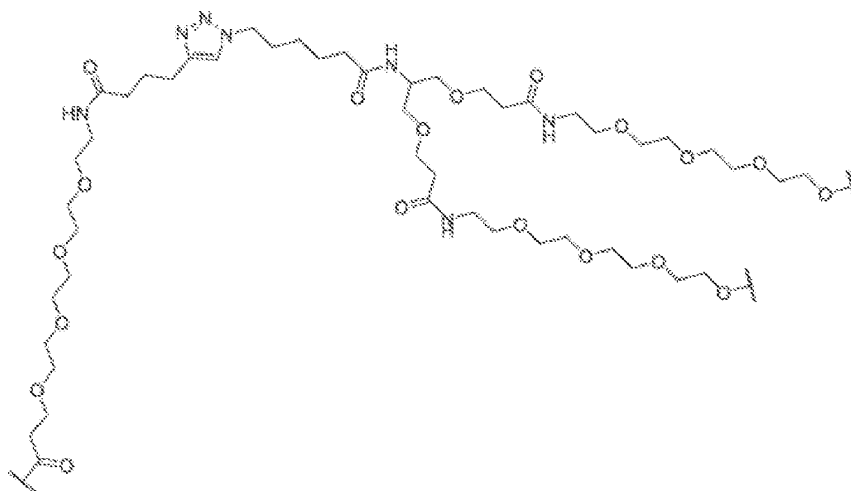
5 R²¹.

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

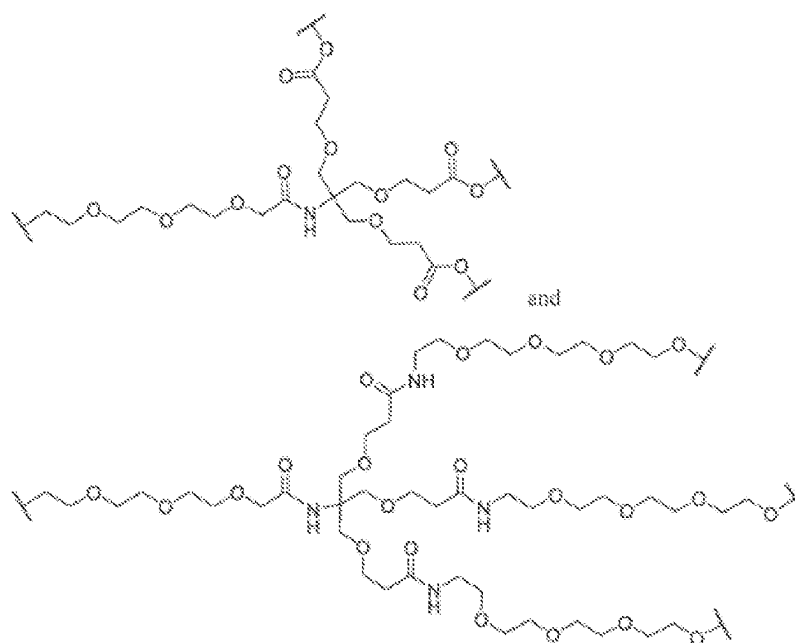


In certain embodiments, in the compound of Formula II, Linker^C-(Linker^A) is selected from





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



- 5 In various embodiments, 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.

In various embodiments, in the compound of Formula II, 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.

In various embodiments, in the compound of Formula II, 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.

In various embodiments, in the compound of Formula II, R⁸ and R⁹ are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle.

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

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

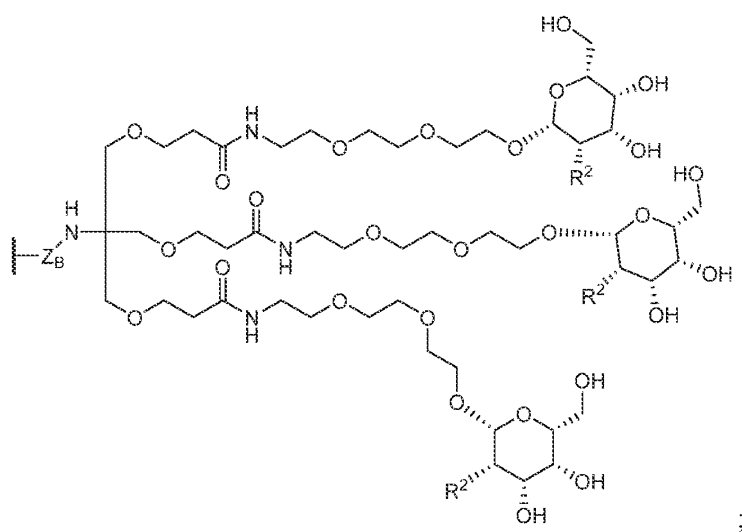
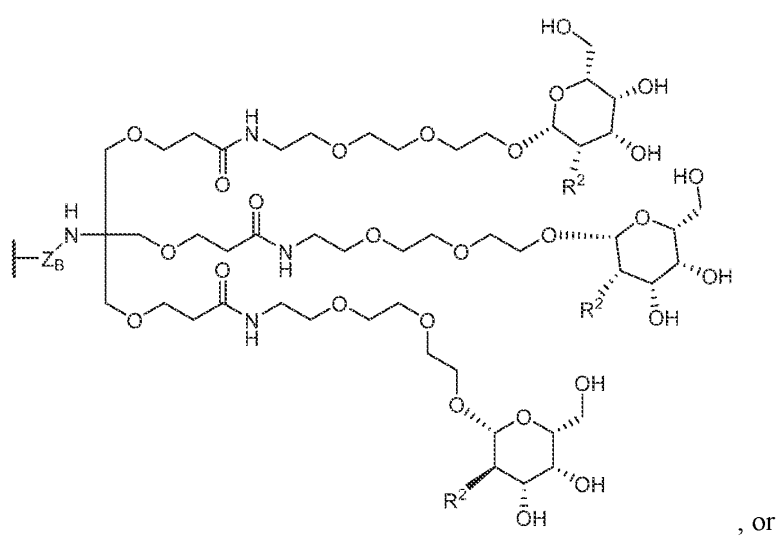
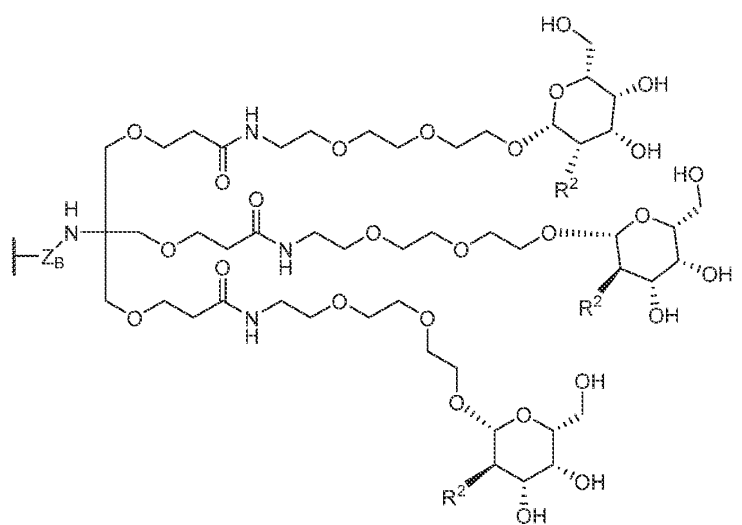


Formula II-A

wherein:

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

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

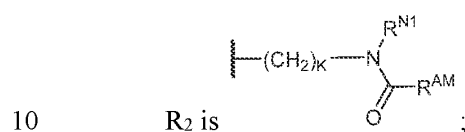


each [CON] is an optional connector chemical moiety which, when present, connects the [LIN] to [CPBM] or to [ASGPBM];

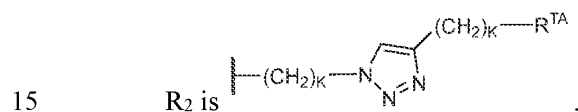
[LIN] is [LINKER] or [LINKER-2], each of which is a chemical moiety having a valency from 1 to 15, which covalently attaches to one or more [ASGPBM] or [CPBM] groups, optionally through a [CON], wherein the [LIN] optionally itself contains one or more [CON] groups;

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

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



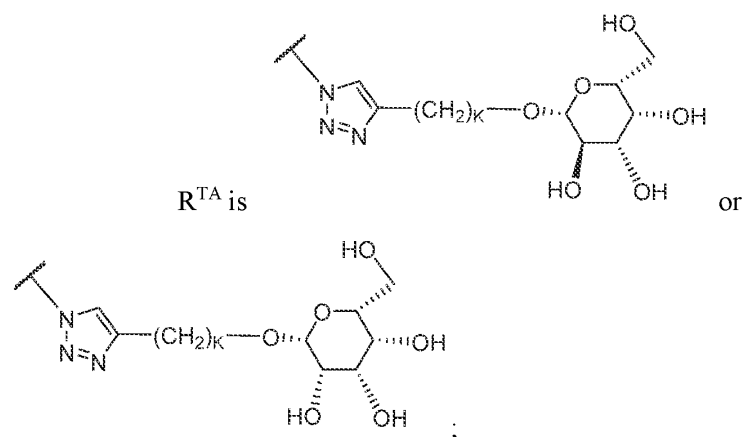
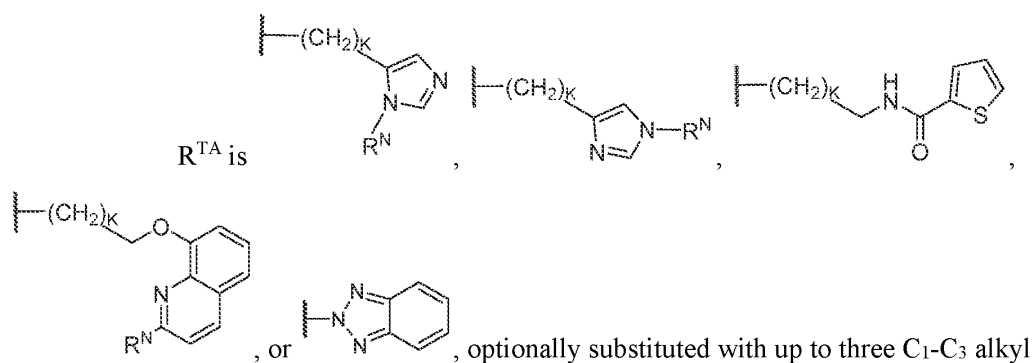
wherein R^{AM} is H, C_1 - C_4 alkyl optionally substituted with up to 3 halo groups and one or two hydroxyl groups, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O-(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, $-O-C(O)-(C_1-C_4 \text{ alkyl})$ optionally substituted with 1-3 halo groups, $-C(O)-(C_1-C_4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



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 heteroaryl atoms, each of the aryl or heteroaryl groups being optionally substituted with up to three CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KO(C_1-C_4 \text{ alkyl})$ 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 from 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



5

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

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

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

k' is an integer ranging from 1 to 15;

j' is an integer ranging from 1 to 15;

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

15 i_L is 0 to 15;

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

or a salt, stereoisomer, or solvate thereof.

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

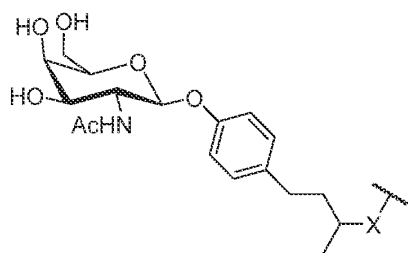
20 D. Other-Based ASGPR-Binding Moieties

In some embodiments, the ASGPR binding moieties can be any of the moieties

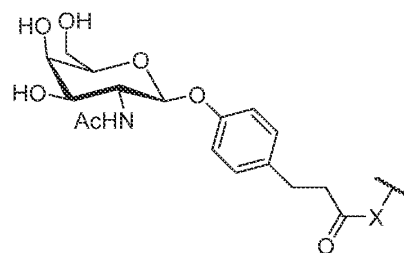
- described in: Reshitko, G. S., et al., “Synthesis and Evaluation of New Trivalent Ligands for Hepatocyte Targeting via the Asialoglycoprotein Receptor,” *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00202; Majouga, A. G., et al., “Identification of Novel Small-Molecule ASGP-R Ligands,” *Current 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

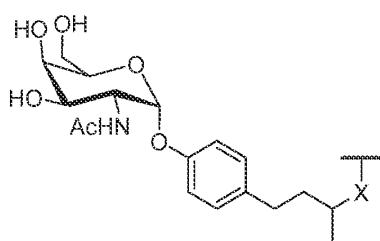
- In some embodiments, the ASGPR binding moiety can be a moiety having the structure of M1, M2, M3, or M4, or a combination thereof. In the structures of M1, M2, M3, and M4, X is independently at each occurrence O, NH, or S. In various embodiments, compounds of Formula I or Formula II can have one, two, or three ASGPR binding moieties with the structure of M1, M2, M3, or M4.



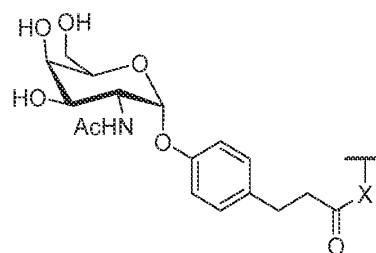
M1



M2



M3

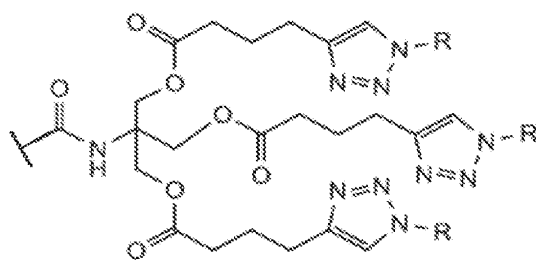


M4.

In various embodiments, ASGPR binding moieties M1 to M4 can be conjugated to any suitable [CON], [Linker], or [Linker-2] as described herein and in Congdon, M. D., et al.,
 5 “Enhanced Binding and Reduced Immunogenicity of Glycoconjugates Prepared via Solid-State Photoactivation of Aliphatic Diazirine Carbohydrates,” *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00555.

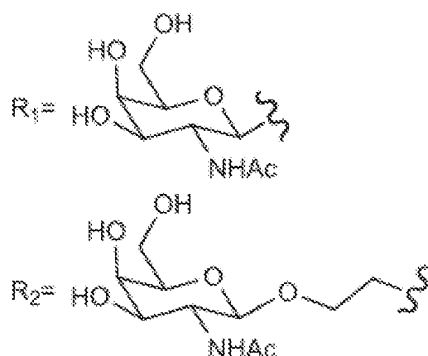
2. Trivalent Triazole-Based Moieties

10 In some embodiments, the ASGPR binding moiety can be a moiety having the structure of M5:



, M5.

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



15

In various embodiments, compounds of Formula I or Formula II contain an ASGPR

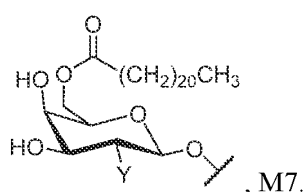
binding moiety with the structure of M5. In various embodiments, each R in M5 is R₁. In various embodiments, each R in M5 is R₂.

In various embodiments, ASGPR binding moiety M5 can be conjugated/bonded to any suitable [CON], [Linker], or [Linker-2] as described herein and in Reshitko, G. S., et al.,

- 5 “Synthesis and Evaluation of New Trivalent Ligands for Hepatocyte Targeting via the Asialoglycoprotein Receptor,” *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00202.

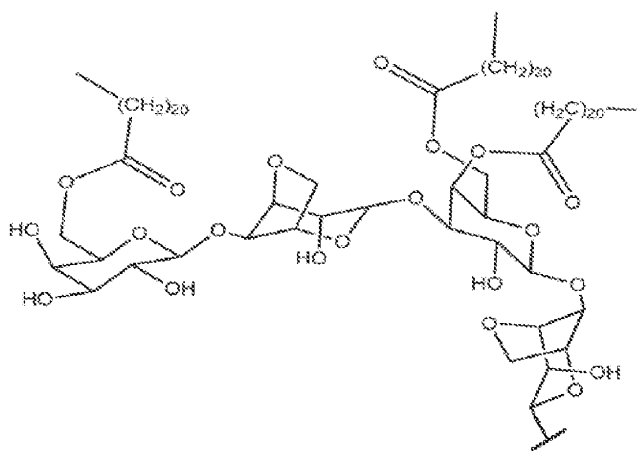
3. Galactose- and Agarose-derived Behenic Acid Ester Moieties

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



In the structure M7, Y is OH or NHAc.

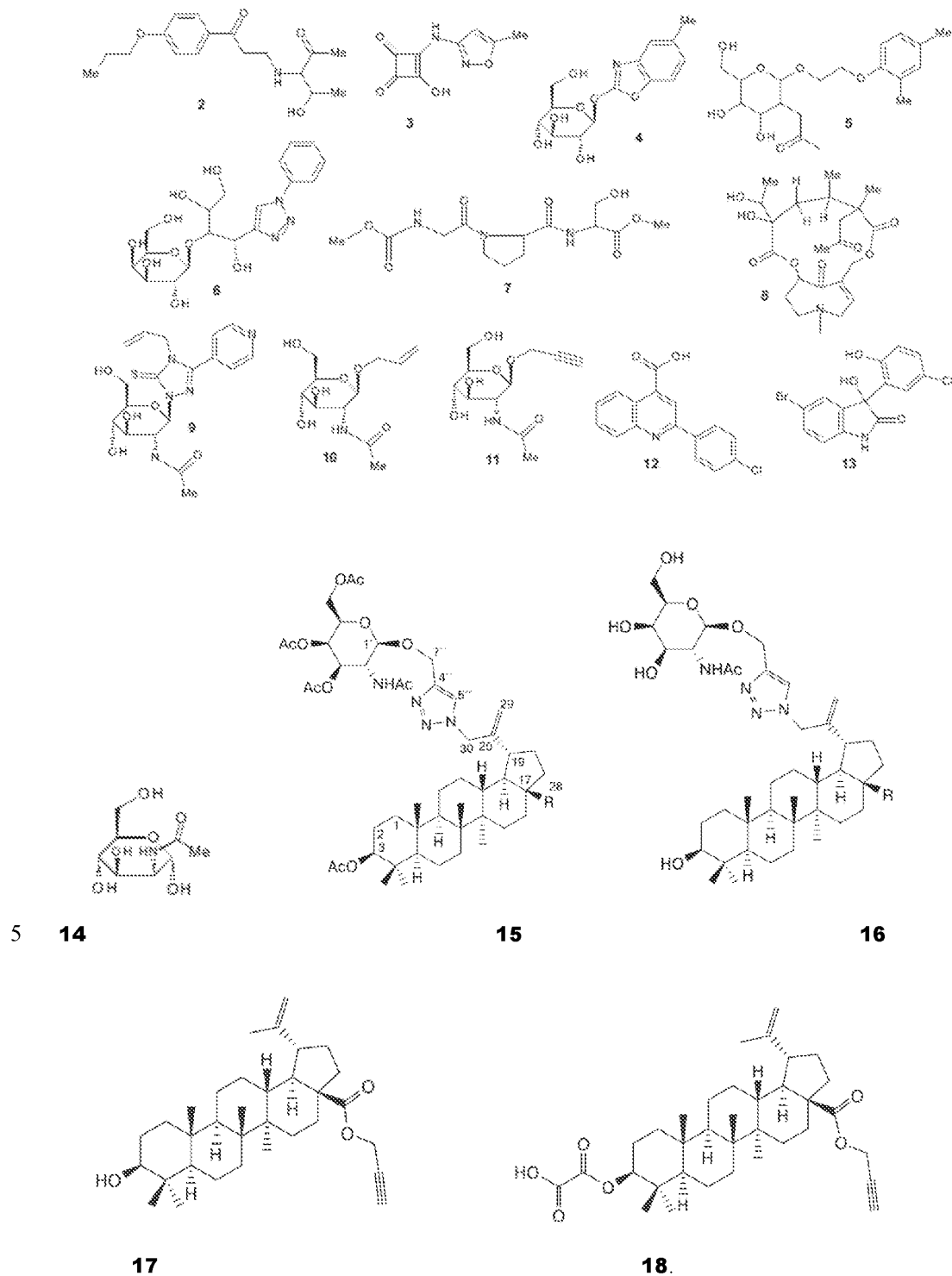
In various embodiments, the ASGPR binding moiety can be the agarose behenic acid ester-derived moiety M8:



- 15 In various embodiments, ASGPR binding moieties M7 and M8 can be conjugated to any suitable [CON], [Linker], or [Linker-2] 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.
- 20

4. Other Small Molecule ASGPR Binding Moieties

In various embodiments, the ASGPR binding moiety 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 [CON], [Linker], or [Linker-2] 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:

- 5 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**
- 10 can be attached through any suitable reactive group contained therein. Without limitation, compounds 2-13 can be attached to a CON], [Linker], or [Linker-2] 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
- 15 [CON], [Linker], or [Linker-2] 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,
- 20 oxidations, alkylations, rearrangement reactions (e.g. Claisen, Cope, etc.), and the like.

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

25 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,

30 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 substitution can be direct substitution, whereby the hydrogen atom is replaced by a functional group or substituent, or
 5 an indirect substitution, whereby an intervening linker group replaces the hydrogen atom, and the substituent or functional group is bonded to the intervening linker group. A non-limiting example of direct substitution is: $RR-H \rightarrow RR-Cl$, wherein RR is an organic moiety/fragment/molecule. A non-limiting example of indirect substitution is: $RR-H \rightarrow RR-(LL)_{zz}-Cl$, wherein RR is an organic moiety/fragment/molecule, LL is an intervening linker
 10 group, and 'zz' is an integer from 0 to 100 inclusive. When zz is 0, LL is absent, and direct substitution results. The intervening linker group LL is at each occurrence independently selected from the group consisting of -H, -O-, -OR-, -S-, -S(=O)-, -S(=O)₂-, -SR-, -N(R)-, -NR₂-, -CR=, -C≡, -CH₂-, -CHR-, -CR₂-, -CH₃-, -C(=O)-, -C(=NR)-, and combinations thereof. (LL)_{zz} can be linear, branched, cyclic, acyclic, and combinations thereof.

15 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
 20 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,
 25 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,
 30 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)hydrocarbyl, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl; or wherein two R groups bonded to a nitrogen atom or to

adjacent nitrogen atoms can together with the nitrogen atom or atoms form a heterocyclyl.

The term "alkyl" as used herein refers to straight chain and branched alkyl groups and cycloalkyl groups having from 1 to 40 carbon atoms, 1 to about 20 carbon atoms, 1 to 12 carbons or, in some embodiments, from 1 to 8 carbon atoms. Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. As used herein, the term "alkyl" encompasses n-alkyl, isoalkyl, and anteisoalkyl groups as well as other branched chain forms of alkyl.

Representative substituted alkyl groups can be substituted one or more times with any of the groups listed herein, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

The term "alkenyl" as used herein refers to straight and branched chain and cyclic alkyl groups as defined herein, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to 40 carbon atoms, or 2 to about 20 carbon atoms, or 2 to 12 carbon atoms or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to vinyl, $-\text{CH}=\text{C}=\text{CCH}_2$, $-\text{CH}=\text{CH}(\text{CH}_3)$, $-\text{CH}=\text{C}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{C}(\text{CH}_3)=\text{CH}(\text{CH}_3)$, $-\text{C}(\text{CH}_2\text{CH}_3)=\text{CH}_2$, 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

5 "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.

10 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, decalanyl, 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, 15 but not limited to, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups or mono-, di- or tri-substituted norbornyl or cycloheptyl groups, which can be substituted with, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups. The term "cycloalkenyl" alone or in combination denotes a cyclic alkenyl group.

The term "heterocycloalkyl" as used herein refers to a cycloalkyl group as defined 20 herein in which one or more carbon atoms in the ring are replaced by a heteroatom such as O, N, S, P, and the like, each of which may be substituted as described herein if an open valence is present, and each may be in any suitable stable oxidation state.

The term "aryl" as used herein refers to cyclic aromatic hydrocarbon groups that do not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, 25 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 30 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.

5 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
10 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
15 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
20 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
25 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,
30 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, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl,

3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl, (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), and the like.

The term "heterocyclalkyl" 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 heterocyclalkyl group as defined herein. Representative heterocyclalkyl groups include, but are not limited to, furan-2-yl methyl, furan-3-yl methyl, pyridine-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

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

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

The term "alkoxy" as used herein refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined herein. Examples of linear alkoxy groups

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

The term "amine" as used herein refers to primary, secondary, and tertiary amines having, *e.g.*, the formula $N(\text{group})_3$ 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, heterocyclamines and the like; and R_3N wherein each R is independently selected, such as trialkylamines, dialkylarylamines, alkyl diarylamines, triarylamines, and the like. The term "amine" also includes ammonium ions as used herein.

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

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

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

The terms "epoxy-functional" or "epoxy-substituted" as used herein refers to a functional group in which an oxygen atom, the epoxy substituent, is directly attached to two

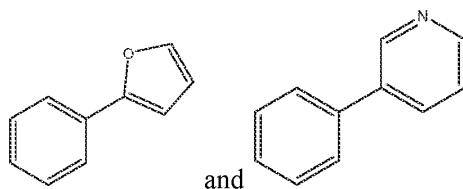
adjacent carbon atoms of a carbon chain or ring system. Examples of epoxy-substituted functional groups include, but are not limited to, 2,3-epoxypropyl, 3,4-epoxybutyl, 4,5-epoxypentyl, 2,3-epoxypropoxy, epoxypropoxypropyl, 2-glycidoxyethyl, 3-glycidoxypropyl, 4-glycidoxybutyl, 2-(glycidoxycarbonyl)propyl, 3-(3,4-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.

As used herein, the term "C₆₋₁₀-5-6 membered heterobiaryl" means a C₆₋₁₀ aryl moiety covalently bonded through a single bond to a 5- or 6-membered heteroaryl moiety. The C₆₋₁₀ aryl moiety and the 5-6-membered heteroaryl moiety can be any of the suitable aryl and heteroaryl groups described herein. Non-limiting examples of a C₆₋₁₀-5-6 membered heterobiaryl include



When the C₆₋₁₀-5-6 membered heterobiaryl is listed as a substituent (*e.g.*, as an "R" group), the C₆₋₁₀-5-6 membered heterobiaryl is bonded to the rest of the molecule through the C₆₋₁₀ moiety.

As used herein, the term "5-6 membered- C₆₋₁₀ heterobiaryl " is the same as a C₆₋₁₀-5-6 membered heterobiaryl, except that when the 5-6 membered- C₆₋₁₀ heterobiaryl is listed as a substituent (*e.g.*, as an "R" group), the 5-6 membered- C₆₋₁₀ heterobiaryl is bonded to the rest of the molecule through the 5-6-membered heteroaryl moiety.

5 As used herein, the term "C₆₋₁₀- C₆₋₁₀ biaryl" means a C₆₋₁₀ aryl moiety covalently bonded through a single bond to another C₆₋₁₀ aryl moiety. The C₆₋₁₀ aryl moiety can be any of the suitable aryl groups described herein. Non-limiting example of a C₆₋₁₀- C₆₋₁₀ biaryl include biphenyl and binaphthyl.

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

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

The term “anticancer agent” or “additional anticancer agent” refers to a compound other than the chimeric compounds according to the present disclosure which may be used in combination with a compound according to the present disclosure for the treatment of cancer. Exemplary anticancer agents which may be coadministered in combination with one or more

5 chimeric compounds according to the present disclosure include, for example, antimetabolites, inhibitors of topoisomerase I and II, alkylating agents and microtubule inhibitors (e.g., taxol), among others. Exemplary anticancer compounds for use in the present disclosure may include everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107,

10 TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhibitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT

15 inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatinib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab (Arzerra), zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490,

20 cilengitide, gimatecan, IL13-PE38QQR, INO 1001, IPdR₁ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS- 100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib, PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N -[4-[2-(2-

25 amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d [pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrozole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)-indolyl]-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t)

30 6,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH₂ acetate [C₅₉H₈₄N₁₈O₁₄ -(C₂H₄O₂)_x where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-

- 166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl
analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib,
KRN951, aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-
Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine,
5 chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine,
dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone,
fluoxymesterone, flutamide, gemcitabine, gleevac, hydroxyurea, idarubicin, ifosfamide,
imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine,
mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin,
10 pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab,
streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine,
13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine,
floxuridine, 5-deoxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycorformycin,
calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat,
15 COL-3, neovastat, BMS-275291, squalamine, endostatin, SU5416, SU6668, EMD121974,
interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxifene, spironolactone,
finasteride, cimitidine, trastuzumab, denileukin difitox, gefitinib, bortezomib, paclitaxel,
irinotecan, topotecan, doxorubicin, docetaxel, vinorelbine, bevacizumab (monoclonal
antibody) and erbitux, cremophor-free paclitaxel, epithilone B, BMS- 247550, BMS-310705,
20 droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant,
acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, PTK787/ZK 222584,
VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-
23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684,
LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin,
25 granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte
macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-
2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase,
lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-
transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen
30 mustard, methylprednisolone, ibritumomab tiuxetan, androgens, decitabine,
hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate,
mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89,
casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant,
diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol,

droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa and darbepoetin alfa, vemurafenib among others, including immunotherapy agents such as IDO inhibitors (an inhibitor of indoleamine 2,3-dioxygenase (IDO) pathway) such as Indoximod (NLG-8187), Navoximod (GDC-0919) and NLG802, PDL1 inhibitors (an inhibitor of programmed death-ligand 1) including, for example, nivolumab, durvalumab and atezolizumab, PD1 inhibitors such as pembrolizumab (Merck) and CTLA-4 inhibitors (an inhibitor of cytotoxic T-lymphocyte associated protein 4/cluster of differentiation 152), including ipilimumab and tremelimumab, among others.

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

Without not being limited by way of theory, compounds according to the present disclosure which contain a CPBM binding moiety (CPBM) and CRBM/ASGPR binding
20 moiety selectively bind to circulating proteins and through that binding, facilitate the introduction of the cellular protein into hepatocytes or other cells (degrading cells) which bind the CRBM/ASGPRBM selectively, where, the circulating protein, inside the hepatocyte or other degrading cell is degraded and removed from circulation. Thus, compounds according to the present disclosure both bind to MIF proteins and remove the MIF proteins
25 from circulation resulting in a dual action which is particularly effective for treating disease states and conditions.

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

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

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

Sterile injectable forms of the compositions of this disclosure may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

The pharmaceutical compositions of this disclosure may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used

include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

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

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

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

Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

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

The pharmaceutical compositions of this disclosure may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing

benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

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

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

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

A patient or subject (e.g. a human) suffering from an autoimmune disease, an
30 inflammatory disease or cancer can be treated by administering to the patient (subject) an effective amount of a chimeric/bi-functional compound according to the present disclosure including pharmaceutically acceptable salts, solvates or polymorphs, thereof optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with other known pharmaceutical agents, preferably agents which can assist in treating autoimmune

and/or inflammatory diseases or cancer, including metastatic cancer or recurrent cancer or ameliorating the secondary effects and/or symptoms associated with these disease states and/or conditions. This treatment can also be administered in conjunction with other conventional therapies, such as radiation treatment or surgery for cancer.

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

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

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

20 The active ingredient is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30 mM, preferably about 0.1-30 μ M. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient. Oral administration is also appropriate to generate effective plasma concentrations
25 of active agent.

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

doses to be administered at varying intervals of time.

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

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

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

The active compound or pharmaceutically acceptable salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as other anticancer agents, anti-inflammatory agents, immunosuppressants, antibiotics, antifungals, or antiviral compounds. In certain preferred
25 aspects of the disclosure, one or more chimeric/bi-functional CPBM binding compound according to the present disclosure is co-administered with another anticancer agent and/or another bioactive agent, as otherwise described herein.

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

syringes or multiple dose vials made of glass or plastic.

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

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

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

20

Chemical Synthesis

FIGs. 1, 7, and 13 attached hereto identify particular compounds according to the present disclosure which exhibit activity in binding to and reducing and/or eliminating unwanted circulating proteins for therapeutic and/or diagnostic purposes. These compounds
25 are based upon an MIF, anti-DNP IgG, or IgG binding moiety to which is covalently attached an ASPGR group such as GN₃ or AcF3-3 group through a linker which contains from 1 to 100 ethylene glycol groups, more often from 1 to 15 ethylene glycol groups, from 1 to 10 ethylene glycol groups, often from 2 to 10 ethylene glycol groups which are optionally attached through a [CON] group, such as a 1,2,3-triazole or other [CON] group as described herein.

30 FIG. 16 shows the synthesis of azide/amide carboxylic end capped PEG linker intermediates which may be condensed onto an alkynyl precursor (e.g. NVS alkyne precursor of Figure 5) to provide carboxylic acid capped intermediate which can be used to provide bifunctional molecules.

FIG. 17 describes a general method for conversion of PEG molecules into hydroxyl

azides. The PEG compound is tosylated (TsCl, DCM, in the presence of base) at reduced temperature and further reacted with sodium azide at elevated temperature in a non-nucleophilic solvent. The final azidoalcohol is used in subsequent figures.

FIG. 18 describes the synthesis of a mesylated azide from a starting PEG molecule
5 employing the same synthetic steps to reach the intermediate azido alcohol. This is then treated with MsCl in pyridine to afford the final compound.

FIG. 19 shows the synthesis of the GalNAc ASGPR ligand linked through PEG to a terminating amine. Pentaacetyl galactosamine is reacted with TMSOTf at elevated temperature in DCE to produce a bicyclic intermediate, which is then reacted with an azido
10 alcohol to give an azide intermediate (TMSOTf, DCE). This molecule is then subjected to a Staudinger reduction to give an amine which is used in subsequent figures.

FIG. 20 shows the synthesis of a higher affinity bicyclic ASGPR ligand. Galactose pentaacetate is treated with HBr/AcOH to give the brominated intermediate, which is treated with Zn and CuSO₄ (water/AcOH) to give the galactal. This is treated with ammonium
15 cerium nitrate and sodium azide at reduced temperature (MeCN) to give the disubstituted intermediate compound. This is then treated with strong base (NaOMe/MeOH) to give the triol azide intermediate. This compound is silylated completely (TMSCl/pyr) then the primary alcohol is deprotected (potassium carbonate, MeOH, lowered temperature) and oxidized (Dess-Martin Periodinane, DCM). Treatment with strong base (NaOEt/HOEt) and
20 paraformaldehyde gives the tetraol intermediate, which is cyclized in strong acid (H₂SO₄/water) to give the bicyclic azide ligand.

FIG. 21 shows the synthesis of a trifluoro-acetate derivative of the bicyclic ASGPR ligand. The triol azide is reduced (Pd/C, MeOH) to give the intermediate amine, which is then peracylated with trifluoroacetic anhydride. The esters are hydrolyzed with strong base
25 (NaOMe/HOMe) to give the intermediate amide, which is protected using dimethoxypropane in the presence of camphorsulfonic acid in DMF at elevated temperature. This is then reacted with a mesylated azido alcohol in the presence of strong base (NaH/DMF) to give an intermediate azide that is reduced (Lindlar's catalyst, MeOH) to give the final amine.

FIG. 22 shows the synthesis of the MIF-targeting linker to a monovalent linker, which
30 is synthesized through analogous methods as described in a previous figure. The boc-protected methyl ester is deprotected with TFA in DCM, then coupled to the MIF-targeting carboxylic acid (HBTU, DIPEA, DMF). Subsequent hydrolysis with strong base (NaOH/dioxane/H₂O) gives the MIF-targeting carboxylic acid.

FIG. 23 shows the synthesis of the di-carboxylic acid MIF targeting motif, which is

synthesized as described in previous figures.

FIG. 24 shows the synthesis of a tris base-derived trivalent linker. Tris base is treated with di-*t*-butyl dicarbonate in the presence of base to give the boc protected triol, which is then reacted with acrylonitrile in the presence of base (dioxane/H₂O) to give a trinitrile intermediate. This is then converted to the methyl ester through treatment with strong acid in methanol. The amine is then reacted with Cbz-glycine through a DCC-mediated amide formation, and deprotected to give a tricarboxylic acid that is used in subsequent figures.

FIG. 25 describes the synthesis of an ASGPR-targeting moiety employing three GalNAc ASGPR ligands. The tricarboxylic acid is reacted with amine-terminated protected GalNAc (amide bond formation in the presence of HBTU and DIPEA), then deprotected by reduction (Pd/C, solvent) and treatment with strong base (NaOMe/MeOH).

FIG. 26 shows the synthesis of the tri-carboxylic acid MIF targeting motif, which is synthesized as described in previous figures.

FIG. 27 shows the synthesis of the MIF NVS alkyne precursor which can be reacted with an azido reactant containing a carboxylic acid (as set forth in subsequent figures) to provide MIF-NVS-carboxylic acid capped reactants to produce bifunctional compounds according to the present disclosure.

FIG. 28 shows the synthesis of the MIF-targeting moiety terminating in a carboxylic acid. 2-chloroquinolin-6-ol is reacted with ethyl 4-bromobutanoate in the presence of base (DMF, elevated temperature) to give an aryl chloride that then undergoes Sonogashira coupling at elevated temperature with ethynyltrimethylsilane. The intermediate silylated compound is deprotected with TBAF (DCM/THF). A click reaction then forms a triazole between the alkyne intermediate and *in situ* synthesized 4-azido-2-fluorophenol to give an ethyl ester intermediate that is hydrolyzed with strong base (NaOH/dioxane) to give the carboxylic acid that is used in subsequent figures.

FIG. 29 describes the synthesis of the bifunctional molecule MIF-NVS-PEG_n-GN₃ through HBTU-mediated coupling in DMF of the ASGPR-targeting amine and the MIF targeting carboxylic acid prepared by first forming the MIF-targeting carboxylic acid by condensing the reactant azido PEG-carboxylic acid onto the MIF moiety containing a alkyne terminated PEG group.

FIG. 30 describes the synthesis of bifunctional molecules MIF-GN₃ and MIF-PEG_n-GN₃ through HATU-mediated coupling (DMF, DIPEA) of ASGPR-targeting amine and MIF-targeting carboxylic acid.

FIG. 31 describes the synthesis of the bifunctional molecule targeting MIF and

ASGPR, containing one bicyclic ASGPR AcF3 ligands. MIF-binding mono-carboxylic acid is treated with HBTU, DIPEA, the amine terminated ligand, and DMF to give the amide, which is then deprotected with 1M HCl to give the final compound.

FIG. 32 describes the synthesis of the bifunctional molecule targeting MIF and ASGPR, containing two bicyclic ASGPr ligands. It is synthesized as described above.

FIG. 33 describes the synthesis of the bifunctional molecule targeting MIF and ASGPR, containing three bicyclic ASGPr ligands. It is synthesized as described above.

FIG. 34 shows the synthesis of DNP-GN3. 2,4-dinitro chlorobenzene was treated with an amino carboxylic acid in the presence of weak base to give the di-nitro aniline carboxylic acid intermediate. Further steps were carried out as described for previous molecules.

FIG. 35 shows the synthesis of DNP-AcF3-3, which was carried out with methods analogous previous compounds.

FIG. 36 shows the synthetic scheme used to obtain IBA-GN3. Pentaethylene glycol was treated with tosyl chloride in the presence of base to give the mono-tosylated alcohol, which was then treated with sodium azide at elevated temperature to give the azidoalcohol. This compound was then oxidized using Jones reagent, then reduced with Palladium on carbon under hydrogen atmosphere to give a carboxylic acid-amine. Separately, indole butyric acid was treated with N-hydroxysuccinimide, EDC, and DIPEA to give the NHS-ester indole, which was then reacted with the above carboxylic acid-amine. The product was again reacted with N-hydroxysuccinimide, EDC, and DIPEA to give a NHS ester. This NHS ester was reacted with NH₂-GN3, which was prepared as described previously. The subsequent amide was deprotected with NaOMe in MeOH to give compound IBA-GN3.

FIG. 37 shows the synthesis of triazine-GN3. Cyanuric chloride was treated with (4-(methoxycarbonyl)phenyl)methanaminium in THF and diisopropylethylamine at -78° C to give the mono-substituted product. This was then treated with cyclohexylmethanamine at room temperature to afford the second substitution. The final substitution was accomplished under elevated temperature with (1S,2S,4R)-bicyclo[2.2.1]heptan-2-amine to give the trisubstituted triazine. Deprotection with lithium hydroxide followed by amide coupling with a monoprotected diamine gave the Boc-protected derivative, which was deprotected and reacted with glutaric anhydride to give a carboxylic acid that was converted to an NHS ester using standard coupling conditions. This was reacted with NH₂-GN3 to give the final product.

FIG. 38 shows the synthetic scheme used to access FcIII-GN3. The hexynyl peptide was prepared using standard solid phase peptide synthesis techniques. The peptide was

removed from Rink resin using Reagent L, then oxidized using ammonium bicarbonate buffer (pH8-9) in MeOH under air to give the cyclic peptide. The peptide was reacted with GN3-azide, which was described previously, to give the product triazole FcIII-GN3.

FIG. 39 shows the synthetic scheme used to access FcIII-4c-GN3, which was
5 accomplished using methods described above.

FIGs. 40-43 describe the synthesis of bifunctional molecules targeting MIF and ASGPr, containing three bicyclic ASGPR ligands with different substitutions on the 2-amine of the sugar. They are synthesized through analogous methods described above as set forth in the attached figures.

FIG. 44 shows the synthesis of compound MIF-18-3. Tri-acyl galactal was
10 deprotected with ammonia in methanol, then tri-benzyl protected with benzylbromide in the presence of base. The alkene was hydrolyzed overnight with HCl in THF/H₂O, then oxidized with PCC to give an aldehyde. Sodium azide was then added alpha to the carbonyl with KHMDS and TIBSN₃ at lowered temperature. The intermediated was then treated with p-
15 OMePhMgBr in THF and toluene to give an intermediate alcohol, which was then reduced using Et₃SiH in the presence of BF₃-Et₂O at reduced temperature. The resulting azide was then reduced with Lindlar's catalyst under a hydrogen atmosphere to give the corresponding amine, which was acylated with trifluoroacetic acid in pyridine. The benzyl groups were then removed with Pd(OH₂) on carbon in MeOH at reflux, and the resulting tri-ol protected as an
20 acetal with dimethoxypropane and camphorsulfonic acid at elevated temperature. The remainder of the synthesis was carried out as described for previous molecules.

FIG. 45 shows the synthesis of compound MIF-31-3. Galactosamine hydrochloride was fully protected with acetic anhydride, then treated with allyl alcohol in the presence of BF₃ etherate to give the allyl intermediate. Treatment with pivaloyl chloride in pyridine gave a
25 di-Piv protected intermediate, which was treated with triflic anhydride and subsequently subjected to hydrolysis in water at elevated temperature. The pivaloyl groups were removed by treatment with NaOMe in MeOH to give the allyl triol intermediate. Subsequent steps were performed as described for previous molecules.

FIG. 46 shows the synthesis of compound MIF-15-3, which was synthesized using
30 procedures analogous to compounds described above.

FIG. 47 shows the synthesis of compound MIF-19-3. The molecule is synthesized through a late stage triazole-forming click reaction between the triazide and propionic acid in methanol in the presence of THPTA, copper sulfate, water, and sodium ascorbate. All other reactions are performed as described above.

FIG. 48 shows the synthesis of compound MIF-16-3, which was synthesized using procedures analogous to compounds described above.

FIG. 49 shows the synthesis of compound MIF-20-3, which was synthesized using procedures analogous to compounds described above.

5 FIG. 50 shows the synthesis of compound MIF-14-3, which was synthesized using procedures analogous to compounds described above.

FIG. 51 shows the synthesis of compound MIF-21-3, which was synthesized using procedures analogous to compounds described above.

FIG. 52 shows the synthesis of compounds MIF-NVS-PEGN-GN3. PEG compounds
10 were treated with tosyl chloride in the presence of base, then subsequently treated with sodium azide at elevated temperature to give azido alcohols. These intermediates were oxidized using Jones reagent to give carboxylic acid azides. Separately, diethylene glycol was treated with base and propargyl bromide to give an alkynyl alcohol, which was then tosylated in the presence of base and subsequently treated with sodium iodide to give an iodinated
15 intermediate. This iodinated compound was then treated with 4-N-boc-aminophenol in the presence of base, which gave an ether intermediate that was treated with hydrochloric acid in dioxane to give an amino alkyne. This amine was reacted with 2-hydroxy-4-(tert-butyltrimethylsiloxy) benzaldehyde in the presence of sodium borohydride to give the cyclic intermediate, which was then treated with TBAF in THF to give the resulting alcohol. CuI-mediated cyclization was then performed between this alkyne and the above-described azide
20 in acetonitrile. The resulting carboxylic acid was reacted with NH₂-GN₃ as described in previous schemes.

FIGs. 53-66 show the synthesis of a number of MIF-binding compounds with various ASGPRBM moieties. These are synthesized through methods analogous to those laid out
25 above.

FIGs. 70-88 show the synthesis of a number of further bifunctional compounds according to the present disclosure.

Examples

30 Proper protein secretion and turnover is a necessary process for maintaining homeostasis. Newly synthesized proteins targeted for secretion are first trafficked to the endoplasmic reticulum, where they are post-translationally modified with N-linked glycan chains terminating in sialic acids. As proteins age, terminal sialic acid residues are removed by circulating endogenous glycosidases. This natural protein aging process unmasks

galactose and N-acetylgalactose (GalNAc) residues, which bind the asialoglycoprotein receptor (ASGPR) on the surface of hepatocytes.

The ASGPR is a C-type lectin that removes aged circulating proteins with exposed GalNAc residues from circulation by trafficking them to lysosomes. Multiple galactose or GalNAc residues displayed on the protein surface are necessary for high-affinity binding to – and subsequent endocytosis by – ASGPR. Once these proteins are endocytosed, they are released from the ASGPR through depletion of calcium from the endosome and changes in binding site amino acid protonation changes due to a decrease in pH; the ASGPR is recycled back to the hepatocyte surface. Endocytosed proteins are trafficked to late endosomes, which are fused with lysosomes. Lysosomal proteases then degrade endocytosed proteins, permanently removing them from circulation.

Non-glycosylated proteins are not known to be natural target for the ASGPR. One such protein is macrophage inhibitory factor (MIF), a 12.5 kDa protein with possible catalytic activity. Genetic depletion or antibody neutralization of MIF has been shown to have positive results in models of sepsis, multiple sclerosis, rheumatoid arthritis, and burn recovery. We propose a bifunctional molecule for degrading circulating MIF that takes advantage of ASGPR as an entryway for proteins into the endosomal-lysosomal degradation pathway. The bicyclic ASGPR-binding molecules in MIF-AcF2 and MIF-AcF3 have been reported previously as high affinity binders for the ASGPR.

20

Biological Data

A number of compounds according to the present disclosure are tested to determine their biological activity. Active compounds are shown in **FIGURES 1, 7 and 13** hereof. The results of the biological experiments are described herein below.

FIGURE 1 shows representative compounds according to the present disclosure. Note that the figure discloses compound 3w (negative control for MIF inhibition), **MIF-NVS-PEGnGN3, MIFGN3, MIF-PEGnGN3, MIF-AcF3-1, MIF-AcF3-2 and MIF-AcF3-3**. Note that n in the PEG linker preferably ranges from 1-12, 1 to 10, 2 to 8, 2 to 6, 2 to 5 or 1, 2, 3 or 4.

In an experiment the results of which are shown in **FIGURE 2, A**, fluorescence polarization data of MIF-FITC binding to human MIF indicates that the MIF-binding moiety of the present disclosure binds MIF. **B**, Bifunctional molecules WJ-PEG4-GN3, WJ-PEG2-GN3, and NVS-PEG3-GN3 bound competitively with MIF-FITC, indicating that the bifunctional molecules maintain the ability to bind human MIF.

30

In an experiment the results of which are presented in **FIGURE 3**, bifunctional molecules were able to deplete human MIF from the supernatant of culture HepG2 cells. Briefly, human MIF (100 nM) was added to cell culture media in the presence of negative control MIF inhibitor 3w as well as bifunctional molecules MIF-NVS-PEGn-GN3, MIF-GN3, MIF-PEGn-Gn3, MIF-AcF3-1, MIF-AcF3-2, and MIF-AcF3-3. All molecules utilized a known MIF-binding ligand. Experiments were performed in 96 well plates (approximate surface area .3 cm²). HepG2 cells were grown to 90% confluency in RPMI media, then washed with PBS (2x) and treated with serum-free media (optimem + .1% BSA, + Pen/Strep) containing 100 nM huMIF (Cayman Chemical) and compounds (when applicable).

Compounds were diluted from 1mM stock solutions in DMSO. After 24 hours, a sample of the supernatant (2 uL) was collected, diluted 1:100, and analyzed for MIF content by sandwich ELISA (and incubated for 24 hours in the presence or absence of compound). Remaining MIF levels were determined by sandwich ELISA (biolegend monoclonal anti-MIF and biotinylated anti-MIF antibodies). Data represents the average of at least 3 biological replicates, and error bars represent a standard deviation. After 24 hours, up to 95.3% of the MIF had been depleted from cell culture media (in the case of MIF-AcF3-3).

FIGURE 4 shows the results of an experiment to determine whether or not MIF internalized by HepG2 cells is trafficked to lysosomes. In this experiment, cells were incubated with rhuMIF (Cayman) at a concentration of 100 nM with 200 nM MIF-GN3. After 12 hours, cells were fixed with formaldehyde, permeabilized, and probed with anti-Lamp2 antibody (mouse monoclonal, Abcam), polyclonal rabbit anti-MIF antibody (Thermo) and with Alexa-488 labeled anti-mouse antibody and Alexa 568-labeled anti-rabbit antibody, evidencing internalization in lysosomes.

FIGURE 5 shows that MIF-GN3 mediates the depletion of injected human MIF from mice. Human MIF has a half-life of approximately 40 minutes in mice. In this experiment, human recombinant MIF (Cayman chemical) was co-injected into mice with an anti-DNP IgG, which was used as an injection positive control. In particular, nude mice were injected with 5µg recombinant human MIF and 200µg anti-DNP IgG as an injection control (**FIGURE 4**). MIF-GN₃ was then injected at the concentration shown and blood drawn every twenty minutes over the course of two hours. Serum was diluted 1:100 and analyzed for MIF content by sandwich ELISA (biolegend monoclonal anti-MIF and biotinylated anti-MIF antibodies). The levels of the injected IgG were not significantly different between testing groups. In the mice treated with MIF-GN₃, a moderate increase in huMIF levels up to 20 ng/ml was seen, while in mice injected with PBS negative control, serum levels of up to 150

ng/ml were observed, evidencing a substantial decrease in huMIF levels as a consequence of the administration of MIF-GN₃.

FIGURE 6 shows that MIF-GN₃ is able to delay tumor growth in a mouse model of prostate cancer. In this experiment, nude mice were engrafted with PC3 human prostate cancer cells. Treatment was then initiated immediately with either a non-bifunctional MIF inhibitor (3w), an anti-MIF antibody, or MIF-GN₃. MIF-GN₃ showed a slowing of tumor growth over the course of the experiment, comparable to the MIF-neutralizing antibody. 3w did not inhibit tumor growth, validating the necessity of degrading MIF for therapeutic efficacy.

FIGURE 7 shows molecules DNP-GN₃ and DNP-AcF₃-3, which are bifunctional molecules that bind to anti-DNP IgG and ASGPR. These compounds were used in several of the experiments as described below.

FIGURE 8 shows that DNP-GN₃ and DNP-AcF₃-3 mediate the formation of a ternary complex between HepG2 cells and anti-DNP, thus validating the bifunctional character of the molecules. In this experiment, ASGPR-expressing HepG2 cells were incubated with bifunctional molecules and alexa-488 labeled anti-DNP (Thermo). The readout is mean fluorescence intensity of the cell population. Fluorescence was measured using a flow cytometer.

In a further experiment, the results presented in **FIGURE 9** show that DNP-GN₃ and DNP-AcF₃-3 mediate the uptake of alexa 488-labeled anti-DNP by HepG2 cells. The assay carried out in this experiment was as is described above for MIF uptake. Readout is percentage of Alexa 488-positive cells after 6 hours. Fluorescence was measured using a flow cytometer.

FIGURE 10 shows that DNP-GN₃ and DNP-AcF₃-3 mediate the localization of alexa 568 labeled anti-DNP to late endosomes and lysosomes. This experiment was carried out as described above for the MIF colocalization studies.

The experimental results presented in **FIGURE 11** show that DNP-AcF₃-3 mediates the degradation of alexa 488-labeled anti-DNP in HepG2 cells. In this experiment, cells were incubated with 1 uM alexa 488-labeled anti-DNP (Thermo) and 200 nM DNP-AcF₃-3. Cells were lysed (RIPA in PBS, containing protease inhibitors) at the given time and assayed by SDS-PAGE gel. Readout is fluorescence of protein fragments.

The results presented in **FIGURE 12** evidence that DNP-GN₃ mediates the depletion of anti-DNP from mouse serum. Mice were injected with anti-DNP on day 0, then treated with the given compounds each day for 6 days. Serum IgG levels were measured by ELISA.

DNP-(OH)₃ is used as a non-bifunctional control molecule.

FIGURE 13 shows the structures of IgG-degrading molecules IBA-GN3, Triazine-GN3, FcIII-GN3, and FcIII-4c-GN3.

FIGURE 14 shows that FcIII-GN3 mediates the uptake of human IgG into HepG2 cells. This experiment was performed as described above.

FIGURE 15 shows that FcIII-GN3 mediates the localization of IgG to late endosomes in HepG2 cells. Experiment performed as described above.

Additional Biological Data for Compounds With Varying CRBM Groups

Cells lines are chosen which express the cellular receptor at high levels. These cells are all known in the art and most are commercially available. Cells are treated with bifunctional molecule and target protein. Target proteins in cell supernatant and/or cell lysate are measured by ELISA. Molecules give time- and concentration- dependent uptake of target proteins as measured by ELISA.

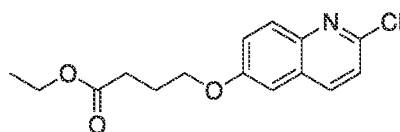
Alternatively, target proteins are labeled with NHS-fluorophores and are taken up by cells. This uptake is time- and concentration-dependent. Uptake is measured by flow analysis, which counts cells according to their fluorescence. Uptake of the fluorophore-protein conjugate is correlated with increased cell brightness.

Additionally, compounds are assayed for their ability to lead to localization of target protein to lysosomes. Cells are treated with target protein and compound, incubated for several hours (generally about 6-24 hours), and fixed using standard methods (paraformaldehyde, acetone). Lysosomes and target protein are localized using orthogonal primary antibodies (anti-Lamp2 and anti-target protein) and then fluorescently-labeled secondary antibodies are added. Colocalization of fluorescence corresponds to target protein localization to lysosomes, indicating that they are endocytosed and trafficked to degradation organelles.

Compounds are also assayed in mice, wherein target protein is injected and the mice are then treated with compounds consistent with activity of the compounds in *in vitro* or cell based assays. Compound treatment over several weeks leads to decreases in the levels of circulating target protein.

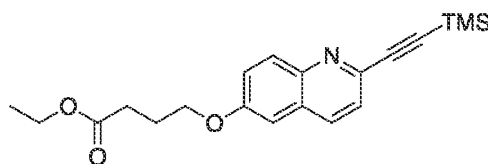
1. MIF binding molecule (Figure 13)

MIF-1



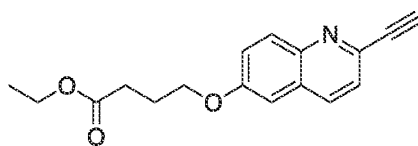
2-chloroquinolin-6-ol (1.00 g, 5.57 mmol) and K_2CO_3 (1.53 g, 11.1 mmol, 2.0 eq) were dissolved in DMF (20 mL). Ethyl bromobutyrate (1.63 g, 8.35 mmol, 1.5eq) was then added and the mixture stirred at 80° for 12 hours. The reaction was diluted into ethyl acetate and washed with water (2x) and brine (3x). The organic layer was dried over sodium sulfate and evaporated to give compound 30, which was used in the next step without further purification. ^1H NMR (400 MHz, chloroform-*d*) δ 7.98 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 9.2 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.07 (d, J = 2.7 Hz, 1H), 4.20 – 4.09 (m, 5H), 2.56 (t, J = 7.2 Hz, 2H), 2.19 (t, J = 6.7 Hz, 2H), 1.26 (t, J = 7.1 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.24, 157.46, 148.18, 143.87, 137.83, 130.05, 128.06, 123.40, 122.67, 106.20, 77.48, 77.16, 76.84, 67.30, 60.69, 30.87, 24.63, 14.39. HRMS: $[M+H]^+$ Expected 294.090, found 294.11.

MIF-2



Compound 30 (1.52 g, 5.17 mmol) was dissolved in THF (20 mL) and triethylamine (2.88 mL, 20.7 mmol, 4 eq). Copper (I) iodide (49.0 mg, 0.258 mmol, .05 eq), $Pd(PPh_3)_2Cl_2$ (181 mg, .258 mmol, .05 eq), and TMS-acetylene (1.07 mL, 762 mg, 7.75 mmol, 1.5 eq) were then added and the reaction was stirred under pressure at 65° for 16 hours. The reaction mixture was filtered through celite, washed ethyl acetate, and evaporated. The residue was purified on silica (50% ethyl acetate in hexanes) to give compound 31. ^1H NMR (500 MHz, chloroform-*d*) δ 8.00 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.5 Hz, 1H), 7.43 – 7.33 (m, 1H), 7.04 (d, J = 2.2 Hz, 1H), 4.15 (dt, J = 12.7, 6.5 Hz, 4H), 2.56 (t, J = 7.2 Hz, 2H), 2.24 – 2.13 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.30 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.07, 124.73, 105.65, 67.11, 60.51, 30.67, 24.42, 14.21, -0.27. HRMS: $[M+H]^+$ Expected 356.168, found 356.505.

MIF-3

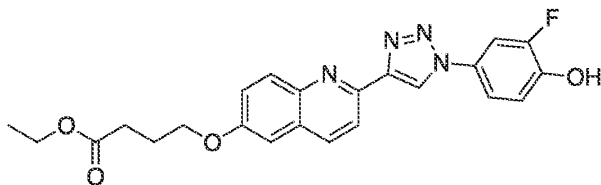


Procedure

Compound 31 (1.57 g, 4.42 mmol) was dissolved in DCM (45 mL) and TBAF (5.3 mL, 1M
 5 in THF, 5.30 mmol, 1.2 eq) was added dropwise. After 1 minute of stirring 10% citric acid
 (50 mL) was added and the reaction stirred for 30 minutes. The organic phase was washed
 with water (1x), dried, and evaporated to give compound 32, which was used in the next step
 without further purification. ¹H NMR (600 MHz, chloroform-*d*) δ 8.11 – 8.00 (m, 1H), 7.51
 (d, *J* = 8.4 Hz, 1H), 7.38 (dd, *J* = 9.3, 2.3 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 4.15 (p, *J* = 6.6,
 10 6.0 Hz, 3H), 3.43 – 3.36 (m, 1H), 2.56 (t, *J* = 7.2 Hz, 1H), 2.22 – 2.14 (m, 1H), 1.73 – 1.64
 (m, 1H), 1.47 (q, *J* = 7.4 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 2H), 1.02 (t, *J* = 7.3 Hz, 1H). ¹³C NMR
 (151 MHz, CDCl₃) δ 173.06, 137.60, 129.91, 128.64, 124.50, 123.18, 122.48, 105.99,
 105.58, 77.20, 76.99, 76.77, 67.12, 60.51, 59.14, 30.67, 24.42, 24.22, 19.80, 14.21, 13.69.
 HRMS: [M+H]⁺ Expected 284.129, found 284.327.

15

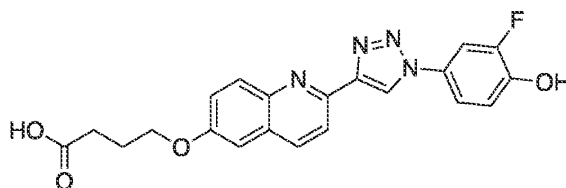
MIF-4



2-fluoro-4-iodophenol (126 mg, 0.529 mmol) and sodium azide (38 mg, 0.528 mmol, 1.0 eq)
 were dissolved in DMSO (2.5 mL) and stirred for two hours at 70°. Compound 32 (150 mg,
 20 0.529 mmol, 1 eq), trans-*N,N'*-dimethylcyclohexane-1,2-diamine (11 mg, 0.079 mmol, .15
 eq), sodium ascorbate (10 mg, 0.053 mmol, 0.1 eq), copper (I) iodide (15 mg, 0.079 mmol,
 0.15 eq), and H₂O (2.5 mL) were then added, and the mixture stirred at 70° overnight. The
 reaction was diluted with ethyl acetate and washed with H₂O (1x) and brine (1x). The organic
 layer was dried over sodium sulfate, evaporated, and purified on silica (DCM/EtOAc) to give
 25 compound 33. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.46 (s, 1H), 9.32 (s, 1H), 8.39 (d, *J* = 8.6
 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.95 (dd, *J* = 11.6, 2.6 Hz, 2H), 7.77 – 7.71 (m, 1H), 7.43
 (dd, *J* = 4.8, 2.0 Hz, 2H), 7.16 (t, *J* = 9.0 Hz, 1H), 4.17 (d, *J* = 6.3 Hz, 2H), 4.13 – 4.07 (m,
 3H), 3.17 (d, *J* = 5.2 Hz, 3H), 2.53 (d, *J* = 7.3 Hz, 3H), 2.07 (t, *J* = 6.8 Hz, 2H), 1.19 (d, *J* =

7.1 Hz, 3H), 0.94 (d, $J = 7.3$ Hz, 1H). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ 172.96, 156.95, 151.95, 150.34, 148.62, 145.98, 143.82, 136.47, 130.40, 129.01, 123.19, 121.83, 119.06, 118.62, 117.31, 109.87, 109.72, 107.12, 67.43, 60.35, 49.03, 40.48, 40.36, 40.22, 40.09, 39.95, 39.81, 39.67, 39.53, 30.61, 24.58, 23.48, 14.56, 13.93. HRMS: Expected 437.163, found 437.164.

MIF-5



Compound 33 (90 mg, .206 mmol) was dissolved in dioxane (6 mL) and 2M NaOH (3 mL). The reaction was stirred for 2.5 hours at room temperature, at which time the reaction was diluted with water and the pH adjusted to 3-4 with 1M HCl. The mixture was cooled to 4° and filtered to give compound 34, which was used without further purification.

15 **2. GaINAc spacer (Figure 14)**



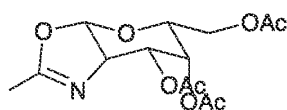
Triethylene glycol (17.5 mL, 19.7 g, 131.13 mmol, 5 eq) was dissolved in DCM (150 mL) and trimethylamine (5.48 mL, 3.98 g, 1.5 eq) and cooled to 0°. TsCl (5.00 g, 26.23 mmol, 1 eq) was then added and the reaction mixture stirred at room temperature for 18 hours. The reaction was diluted into DCM and washed with water (3x) and brine (1x). The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product was purified on silica (0-5% MeOH in DCM) to give compound 64 (6.89 g, 22.6 mmol) in 85% yield. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.30 (m, 2H), 4.23 – 4.14 (m, 2H), 3.71 (td, *J* = 5.3, 4.3 Hz, 4H), 3.66 – 3.55 (m, 6H), 2.45 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 144.98, 133.09, 129.95, 128.09, 72.58, 70.91, 70.44, 69.28, 68.84, 61.88, 21.76.



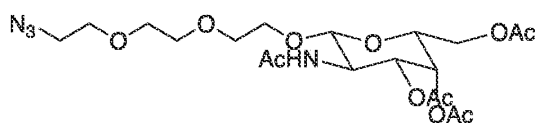
30 Compound 64 (2.00 g, 6.57 mmol) and sodium azide (.470 g, 7.23 mmol, 1.1 eq) were

dissolved in DMF (40 mL) and stirred overnight at 60°. 25 mL of DMF was then removed by rotary evaporation, and the resulting mixture diluted into water and extracted with ethyl acetate (2x). The organic layers were washed with brine (3x), dried over sodium sulfate, and evaporated. The crude product was purified on silica (0-5% MeOH in DCM) to give
 5 compound 65 (932 mg, 5.32 mmol) in 81% yield.

3. GaINAc ASGPR ligand (Figure 15)

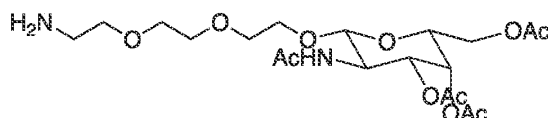


10 Galactosamine pentaacetate (100 mg, .257 mmol) was dissolved in dichloroethane (1 mL) and stirred at room temperature before the addition of TMSOTf (70 μ L, 86.0 mg, .387 mmol, 1.5 eq). The reaction was stirred at 50° for 90 minutes, then allowed to cool to room temperature and stirred for a further 12 hours. The reaction was poured into ice cold saturated sodium bicarbonate and extracted into DCM. The organic layer was washed with water (2x),
 15 dried over sodium sulfate, and evaporated to give compound 66 (.236 mmol, 77.7 mmol, 92%) as a dark gum, which was used without further purification. ¹H NMR (400 MHz, chloroform-*d*) δ 5.98 (d, *J* = 6.8 Hz, 1H), 5.45 (t, *J* = 3.0 Hz, 1H), 4.90 (dd, *J* = 7.4, 3.3 Hz, 1H), 4.29 – 4.20 (m, 1H), 4.17 (d, *J* = 6.9 Hz, 1H), 4.10 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.99 (td, *J* = 7.1, 1.4 Hz, 1H), 2.11 (s, 3H), 2.05 (m, *J* = 7.6 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ
 20 170.46, 170.13, 169.78, 166.35, 121.82, 118.64, 101.41, 71.76, 69.44, 65.25, 63.53, 61.56, 46.82, 20.77, 20.68, 20.54, 14.41, 8.64, -0.06.



Compound 66 (200 mg, .607 mmol) and compound 65 (160 mg, .913 mmol, 1.5 eq) were
 25 dissolved in 1,2-dichloroethane (5 mL). 4 Å molecular sieves were then added, and the reaction stirred for 30 minutes. TMSOTf (55 μ L, 67.5 mg, .304 mmol, .5 eq) was then added to the mixture, and the reaction stirred overnight. The mixture was diluted into DCM, washed with 1M sodium bicarbonate (1x) and water (1x), then dried over magnesium concentrate and concentrated. The curde oil was purified on silica gel (50-100% EtoAc in DCM) to give
 30 compound 67 (245 mg, .486 mmol) in 80.1% yield. ¹H NMR (400 MHz, chloroform-*d*) δ

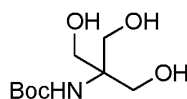
6.13 (d, $J = 9.3$ Hz, 1H), 5.31 (dd, $J = 3.4, 1.1$ Hz, 1H), 5.05 (dd, $J = 11.2, 3.4$ Hz, 1H), 4.77 (d, $J = 8.6$ Hz, 1H), 4.28 – 4.04 (m, 3H), 3.93 – 3.79 (m, 3H), 3.78 – 3.58 (m, 8H), 3.43 (dt, $J = 28.2, 4.9$ Hz, 4H), 2.15 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.24, 170.09, 169.99, 101.84, 72.06, 71.27, 70.50, 70.29, 70.27, 70.20, 70.00, 69.98, 69.67, 69.37, 68.18, 66.30, 61.38, 61.17, 50.32, 50.26, 50.11, 22.80, 20.37, 20.31. HRMS: $[\text{M}+\text{Na}]^+$ 527.207 found 527.203



Compound 67 (1.80 g, 3.57 mmol) was dissolved in THF (35 mL). Triphenylphosphine (1.40 g, 5.35 mmol, 1.5 eq) and water (257 μL , 14.28 mmol, 4 eq) were then added and the reaction stirred at room temperature under nitrogen for 36 hours. The solvent was removed and the crude product used in the next step without further purification.

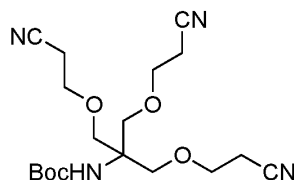
4. Tris Valent Glycine (Figure 16)

15



Tris base (5.00 g, 41.3 mmol) was dissolved in dichloromethane (80 mL) and trimethylamine (20 mL). Di-tert-butyl dicarbonate (10.81 g, 49.6 mmol, 1.2 eq) was then added, and the reaction stirred for 4 hours. The mixture was evaporated and the residue portioned between ethyl acetate and water. The organic fraction was washed with water (1x), 1M HCl (2x), saturated sodium bicarbonate (1x), and brine (1x) before drying over sodium sulfate and evaporation to give compound 23 (9.04g, 40.9 mmol) in 99% yield, which was used without purification in further steps.

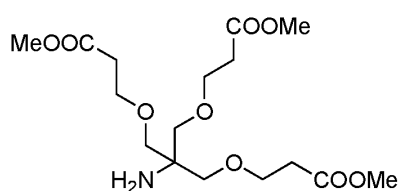
20



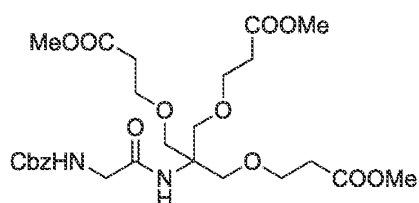
25

Compound 27 (9.04 g, 40.9 mmol) was dissolved in a mixture of dioxane (17 mL) and

aqueous KOH (4.98 g, 88.7 mmol, 2.46 mL). Acrylonitrile (8.84 mL, 7.16 g, 135.0 mmol, 3.3 eq) was then added dropwise over a period of 2.5 hours, and the reaction stirred under nitrogen for 24 hours. The reaction was neutralized with the addition of 2M HCl (30 mL) and portioned between DCM and water. The organic layer was washed with water (2x) and brine (1x), dried over sodium sulfate, and evaporated. The crude mixture was purified on silica (0-80% EtOAc in hexanes) to give compound 20 (7.87g, 20.7 mmol) in 59% yield. ¹H NMR (400 MHz, chloroform-*d*) δ 4.84 (s, 1H), 3.73 (s, 6H), 3.65 (t, *J* = 6.1 Hz, 6H), 2.57 (t, *J* = 6.1 Hz, 6H), 1.35 (s, 9H).



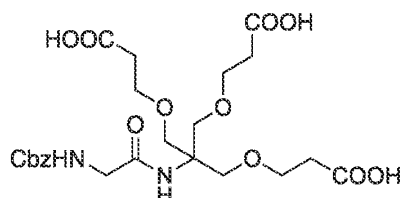
Compound 28 (7.87 g, 20.7 mmol) was dissolved in MeOH (40 mL) and concentrated sulfuric acid (10 mL) was added. The reaction was stirred at reflux under nitrogen for 24 hours, then neutralized with sodium bicarbonate. Methanol was evaporated, and the residue partitioned between water and ethyl acetate. The ethyl acetate layer was washed with sodium bicarbonate (1x) and brine (1x), then dried over sodium sulfate. The crude residue was purified on silica (10% MeOH in DCM) to give compound 29 (5.50 g, 14.5 mmol) in 70% yield. ¹H NMR (400 MHz, chloroform-*d*) δ 3.79 – 3.64 (m, 15H), 3.32 (s, 6H), 2.56 (t, *J* = 6.3 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 172.03, 72.52, 66.77, 56.10, 51.62, 34.80.



Compound 70 (723 mg, 1.90 mmol) was dissolved in MeCN (25 mL). HOBT (291 mg, 1.90 mmol, 1 eq), Cbz-glycine (397 mg, 1.90 mmol, 1 eq), and DCC (392 mg, 1.90 mmol, 1 eq) were then added, and the reaction stirred overnight. MeCN was then evaporated, and the residue adsorbed onto silica and purified using a gradient of 0-75% EtOAc in hexanes. Compound 71 (866 mg, 1.52 mmol) was recovered in 80% yield. ¹H NMR (600 MHz, Chloroform-*d*) δ 7.33 (dd, *J* = 24.9, 4.4 Hz, 5H), 6.33 (s, 1H), 5.55 (s,

1H), 5.12 (s, 2H), 3.86 (d, $J = 5.1$ Hz, 2H), 3.68 (t, $J = 5.5$ Hz, 2H), 3.49 (s, 1H), 2.53 (t, $J = 6.1$ Hz, 6H). ^{13}C NMR (151 MHz, cdCl_3) δ 172.14, 168.67, 156.32, 136.41, 128.45, 128.05, 127.98, 69.04, 66.85, 66.71, 59.83, 51.69, 44.55, 34.64. HRMS Expected: $[\text{M}+\text{H}]^+ 571.250$, found 571.243.

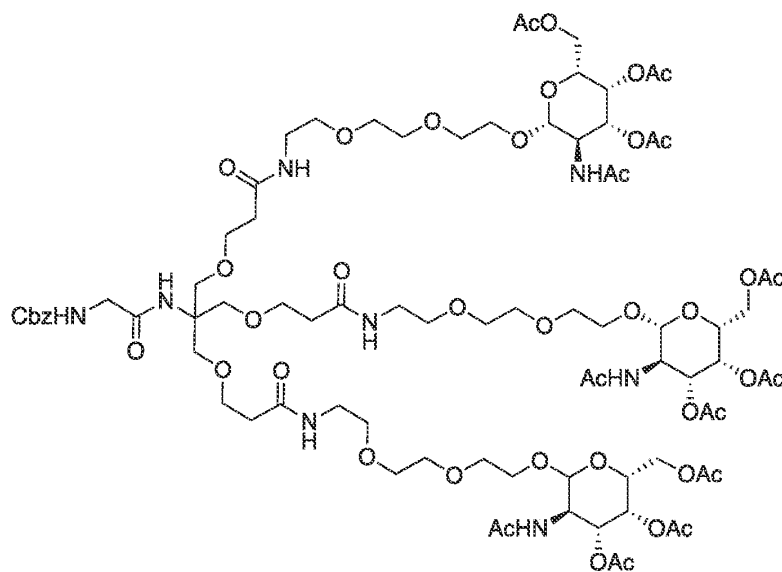
5



Compound 71 (100 mg, 0.175 mmol) was dissolved in dioxane (2 mL) and 2M NaOH (2 mL). The reaction was stirred for 3 hours, then acidified and extracted twice into ethyl acetate. The organic fraction was washed with 1M HCl, then dried over sodium sulfate and evaporated to give compound 72, which was used in further steps without purification.

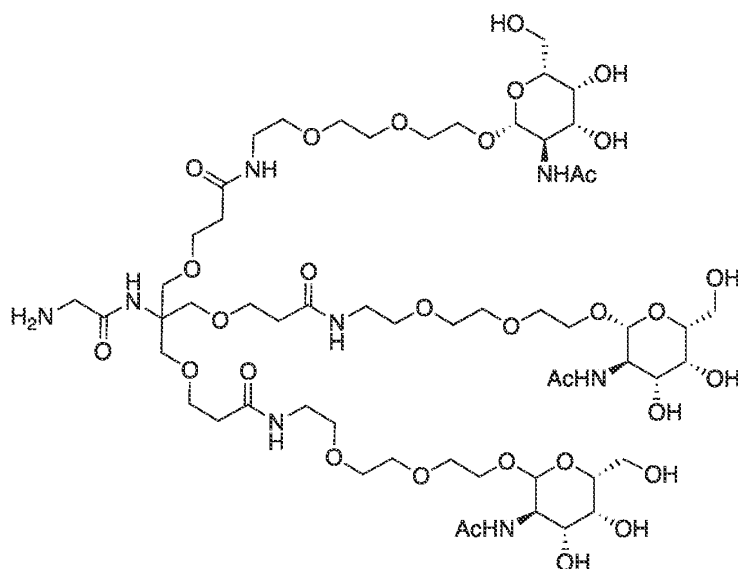
10

5. GaINAc trivalent (Figure 17)



15 Compound 72 (372 mg, 0.704 mmol, 1 eq) was dissolved in DMF (40 mL) and DIPEA (981 μL , 728 mg, 5.632 mmol, 8 eq). HBTU (1.01 g, 2.67 mmol, 3.8 eq) was then added, and the reaction stirred for 10 minutes at room temperature before the addition of compound 68 (1.28 g, 2.67 mmol, 3.8 eq). The reaction was stirred for two hours, then diluted into DCM and washed with H_3PO_4 (1M, 1x), NaHCO_3 (1M, 1x), and brine (1x). The organic layer was dried

over sodium sulfate and evaporated onto silica. The residue was purified (0-20% MeOH in DCM) to give compound 73 (831 mg, .436 mmol) in 62% yield. ¹H NMR (500 MHz, DMSO-d₆) δ 7.91 (t, J = 5.7 Hz, 3H), 7.80 (d, J = 9.2 Hz, 3H), 7.39 - 7.28 (m, 6H), 7.12 (s, 1H), 5.21 (d, J = 3.4 Hz, 3H), 5.02 (s, 2H), 4.97 (dd, J = 11.2, 3.4 Hz, 3H), 4.55 (d, J = 8.5 Hz, 3H), 4.10 - 3.99 (m, 9H), 3.92 - 3.84 (m, 3H), 3.81 - 3.75 (m, 3H), 3.62 - 3.46 (m, 35H), 3.39 (t, J = 6.1 Hz, 6H), 3.23 - 3.16 (m, 6H), 2.30 (t, J = 6.4 Hz, 6H), 2.10 (s, 9H), 1.99 (s, 9H), 1.89 (s, 9H), 1.77 (s, 9H). ¹³C NMR (126 MHz, DMSO) δ 170.40, 170.16, 170.09, 169.79, 169.48, 169.04, 156.60, 137.23, 128.50, 127.94, 127.84, 101.12, 72.50, 70.65, 70.07, 69.93, 69.86, 69.77, 69.59, 69.29, 68.50, 67.51, 66.89, 65.59, 61.63, 60.38, 59.84, 49.50, 43.77, 38.68, 36.01, 22.95, 20.68, 20.62, 20.60.

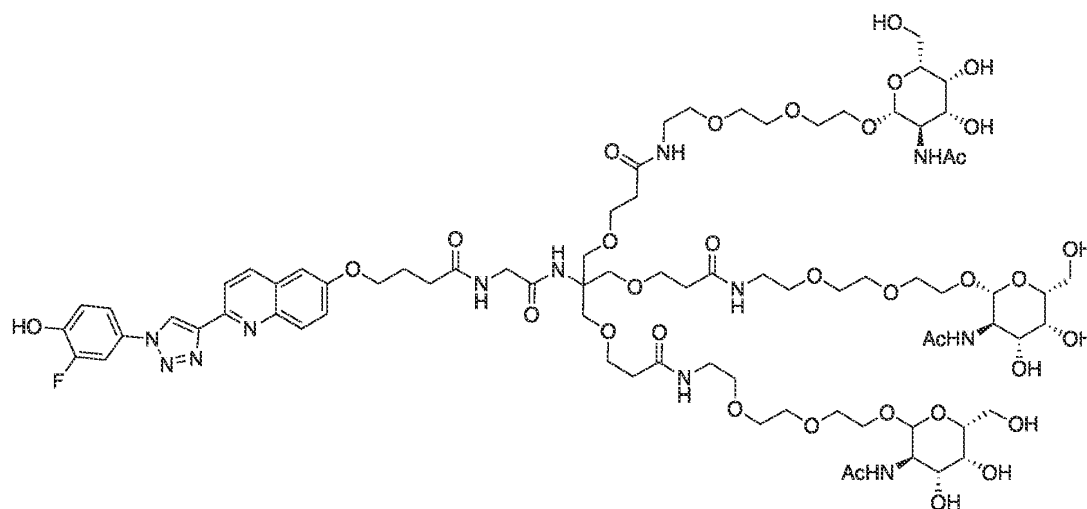


Compound 73 (710 mg, 0.372 mmol) was dissolved in dry methanol (90 mL) and cooled to 0° under nitrogen. Pd/C (71.0 mg, 10% w/w) was then added, and the reaction stirred under hydrogen (1 atm) at 0° for 16 hours. Upon completion, the reaction was filtered through celite and methanol evaporated to give compound 74 (657 mg, 0.370 mmol) in 99.5% yield, which was used without further purification.

Compound 74 (441 mg, .248 mmol) was dissolved in methanol (15 mL) and cooled to 0°. Sodium methoxide solution (400 μL, 5.4M in MeOH) was then added, and the reaction stirred for 30 minutes. Dowex 50WX8 was then added until the solution was weakly acidic. The resin was filtered off and washed thoroughly with methanol. The combined methanol fractions were evaporated under reduced pressure to give compound 75 (274 mg, 0.196

mmol) in 79% yield. Compound 75 was used in further steps without purification.

6. MIF-GN3 (Figure 18)



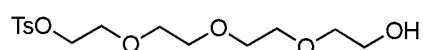
5

Compound 34 (23.5 mg, 0.0575 mmol, 1.1 eq) and HATU (20.0 mg, 0.0522 mmol, 1 eq) were dissolved in dry DMF (5 mL) and DIPEA (23.3 μ L, 16.9 mg, 0.131 mmol, 2.5 eq) and stirred for 10 minutes at room temperature. Compound 75 (73.0 mg, 0.0522 mmol) was then added, and the reaction stirred for 30 minutes. The mixture was loaded directly onto HPLC and purified (20-30% MeCN in water, 3% TFA) to give compound 76 (12 mg, 0.0067 mmol) in 12.8% yield. Expected $[M+H]^+$ 1787.801, found 1787.823.

10

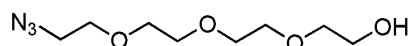
7. Bicyclic ASGPR Spacer (Figure 19)

15

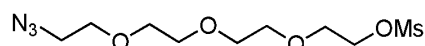


20

Tetraethylene glycol (50.0 g, 258 mmol) was dissolved in THF (1 mL), cooled to 0°, and stirred. NaOH (1.65 g, 41.3 mmol, 1.6eq) in water (1 mL) was then added, followed by the dropwise addition of p-toluenesulfonyl chloride (4.92 g, 25.8 mmol, 1 eq) in THF (3 mL). The reaction mixture was stirred at 0° for 4 hours, then diluted into DCM. The organic layer was washed with ice-cold water (2x), brine (1x), and dried over sodium sulfate to give compound 16 (8.84 g, 25.4 mmol, 99% yield), which was used in further steps without purification.

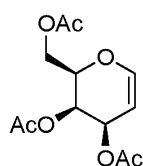


Compound 16 (8.84 g, 25.4 mmol) was dissolved in 100% ethanol (200 mL) and sodium azide (4.128 g, 63.5 mmol, 2.5 eq) was added. The reaction was heated to reflux for 16 hours, then cooled to room temperature before the addition of water (150 mL). Ethanol was then evaporated under reduced pressure and the product extracted into ethyl acetate (2x). The organic layer was washed with water (1x) and brine (1x), dried over sodium sulfate, and evaporated to give compound 17 (4.82 g, 22.1 mmol) as a yellow oil in 87% yield. ¹H NMR (400 MHz, Chloroform-*d*) δ 3.69 – 3.64 (m, 2H), 3.61 (m, *J* = 4.2 Hz, 10H), 3.57 – 3.51 (m, 2H), 3.33 (td, *J* = 5.0, 2.3 Hz, 2H), 2.81 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 72.47, 70.65, 70.63, 70.59, 70.52, 70.28, 69.99, 61.60, 50.59.



Compound 17 (5.00 g, 22.8 mmol) was dissolved in pyridine (50 mL). Methanesulfonyl chloride (3.14 g, 27.4 mmol, 1.2 eq) was then added and the reaction stirred for six hours under nitrogen. The mixture was then diluted into ethyl acetate, washed with water (3x), 5M HCl (2x), saturated sodium bicarbonate (1x), and brine (1x), dried over sodium sulfate, and evaporated to give compound 18 (5.71 g, 19.2 mmol) in 84% yield. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.41 – 4.33 (m, 2H), 3.81 – 3.72 (m, 2H), 3.70 – 3.59 (m, 10H), 3.38 (t, *J* = 5.0 Hz, 2H), 3.06 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 70.79, 70.75, 70.71, 70.15, 69.39, 69.11, 50.77, 37.78. HRMS: Expected 298.107, found 298.105.

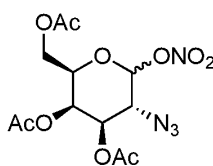
8. Bicyclic ASGPR Precursor (Figure 20)



Pentaacetyl galactose (25.0 g, 64.0 mmol) was dissolved in 33% HBr in HOAc (30 mL) and stirred under nitrogen for 2 hours. The reaction was diluted into EtOAc (500 mL) and washed with water (3x), saturated sodium bicarbonate (1x), and brine (1x). The organic layer was dried over sodium sulfate and evaporated to give compound 1 as a pale yellow oil in

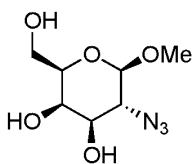
quantitative yield. The compound was used without further purification.

Compound 1 (26.34 g, 64.06 mmol) was dissolved in acetic acid (510 mL) and zinc (67.01 g, 1024 mmol) added. The mixture was stirred vigorously. A solution of CuSO₄ (2.96 g, 18.6 mmol) in aqueous NaH₂PO₄ (128 mL, 0.1M, 1.53 g) was then added, and the reaction stirred for 1 hour. The reaction mixture was filtered over celite and the resulting water/AcOH mixture evaporated to give a white solid. The white solid was dissolved in EtOAc (2x, 300 mL each), water (300 mL), and EtOAc (1x, 300 mL). The layers were separated and the organic layer further washed with water (2x), saturated sodium bicarbonate (2x), and brine (1x). The organic solution was dried over sodium sulfate, evaporated, and purified on silica (15-25% EtOAc in Hexanes) to give compound 2 in 84% yield (14.64 g, 53.76 mmol). ¹H NMR (400 MHz, Chloroform-*d*) δ 6.46 (dd, *J* = 6.3, 1.8 Hz, 1H), 5.54 (qd, *J* = 2.8, 1.2 Hz, 1H), 5.41 (dt, *J* = 4.7, 1.7 Hz, 1H), 4.71 (ddd, *J* = 6.3, 2.7, 1.5 Hz, 1H), 4.33 (ddt, *J* = 7.0, 5.6, 1.4 Hz, 1H), 4.29 – 4.15 (m, 2H), 2.11 (s, 3 H), 2.06 (s, 3H), 2.00 (s, 3H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 170.33, 170.06, 169.97, 145.30, 98.80, 72.69, 63.82, 63.59, 61.85, 20.66, 20.64, 20.58. HRMS: [M+Na]⁺ Expected 295.079, found 295.078

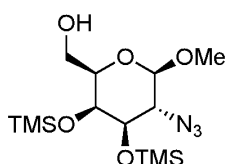


Compound 2 (12.0 g, 44 mmol) was dissolved in acetonitrile (250 mL) and cooled to -10°. In a separate nitrogen-flushed flask at -10°, NaN₃ (4.3 g, 66 mmol) and ceric ammonium nitrate (87.0 g, 158 mmol) were mixed and stirred vigorously. The solution of compound 2 in acetonitrile was added dropwise via cannula, and the mixture allowed to slowly reach room temperature. The reaction mixture was allowed to stir for a total of 12 hours before dilution with ethyl acetate (500 mL) and washing with water (3x) and brine (1x). The organic layer was dried over sodium sulfate, evaporated, and purified on silica (20-50% EtOAc in hexanes) to give compound 3 in 79% yield (13.1g, 34.9 mmol). ¹H NMR (400 MHz, Chloroform-*d*) δ 6.31 (d, *J* = 4.1 Hz, 1H), 5.60 (d, *J* = 8.8 Hz, 1H), 5.43 (dd, *J* = 3.4, 1.3 Hz, 1H), 5.32 (t, *J* = 3.3 Hz, 1H), 5.16 (dt, *J* = 11.6, 3.4 Hz, 1H), 4.96 (dd, *J* = 10.6, 3.3 Hz, 1H), 4.39 – 4.28 (m, 1H), 4.14 – 4.00 (m, 5H), 3.76 (ddd, *J* = 13.5, 9.6, 4.7 Hz, 1H), 2.19 – 2.05 (m, 6H), 2.05 – 1.88 (m, 12H). ¹³C NMR (101 MHz, CDCl₃) δ 170.15-169.06, 97.91, 97.79, 96.91, 71.68, 71.45, 69.35, 68.42, 66.98, 66.53, 65.85, 64.75, 61.07, 60.84, 57.38, 55.82, 55.08, 20.31-

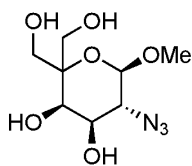
20.20. HRMS: $[M+Na]^+$ expected 399.076, found 399.073



Sodium methoxide solution was prepared from ice-cold dry methanol (50 mL) and sodium hydride (2.296 g, 95.67 mmol, 3 eq) and added to a solution of compound 3 (12.00 g, 31.89 mmol) in dry methanol (100 mL). After thirty minutes of stirring, the reaction was confirmed neutralized by the addition of acetic acid and directly loaded onto silica gel. The reaction mixture was purified over a gradient of 0-20% MeOH in DCM to give compound 4 (6.64 g, 30.3 mmol) in 95% yield. ^{13}C NMR (101 MHz, cd_3od) δ 102.60, 100.87, 98.59, 75.65, 74.62, 71.43, 70.41, 68.82, 67.81, 67.69, 67.47, 67.37, 63.73, 62.96, 60.75, 60.43, 59.54, 55.42, 53.69, 45.94. HRMS: $[M+Na]^+$ expected 242.075, found 242.072.

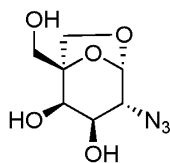


Compound 4 (5.00 g, 22.8 mmol) was dissolved in pyridine (100 mL) and stirred under nitrogen. Trimethylsilylchloride (10.43 mL, 8.929 g, 82.18 mmol, 3.6 eq) was added dropwise and the mixture stirred for 6 hours. The reaction was diluted into ethyl acetate and washed with water (2x) and brine (1x). The organic layer was dried over sodium sulfate and evaporated to give the tri-TMS intermediate. Residual pyridine was removed by co-evaporating with toluene (3x). The intermediate was taken up into dry MeOH (45 mL) and cooled to 0° before potassium carbonate (40 mg) was added. The reaction was closely monitored over 1.5 hours and quenched with acetic acid (17 μL) once TLC showed complete consumption of starting material. The product was then dry loaded onto silica and purified with a gradient of 0-50% EtOAc in hexane to give compound 5 (6.55 g, 18.0 mmol) in 79% yield. ^{13}C NMR (101 MHz, cdcl_3) δ 103.36, 75.29, 73.71, 72.37, 71.41, 70.94, 70.38, 64.04, 62.49, 62.15, 61.05, 60.36, 57.15, 55.17, 34.60, 31.52, 25.21, 22.59, 20.93, 14.11, 14.05, 0.85, 0.57, 0.55, 0.52, 0.22, 0.14, 0.01, -0.07. HRMS: $[M+Na]^+$ 386.154, found 386.156.



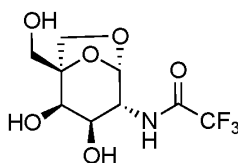
Compound 5 (7.00 g, 19.3 mmol) was dissolved in DCM (100 mL) and stirred under nitrogen. Dess-Martin periodane (9.82 g, 23.2 mmol, 1.2 eq) was added and the mixture stirred for 2 hours. The reaction was diluted into DCM and washed with water (2x) and brine (1x). The organic layer was dried over sodium sulfate and evaporated to give the intermediate aldehyde.

Compound 6 was dissolved in molecular sieve-dried EtOH (100 mL). Paraformaldehyde (36.50 g, 384.9 mmol, 20 eq) and 21% sodium ethoxide solution (14.5 mL, 38.5 mmol, 2 eq) were added and the reaction stirred for 8 hours. The solvent was evaporated and the product adsorbed onto silica. The product was purified using a gradient of 0-25% MeOH in DCM to afford compound 7 (2.981 g, 11.97 mmol) in 62% yield. HRMS: $[M+Na]^+$ expected 272.086 (+Na), found 272.083.



L6-7 (500 mg, 2.00 mmol) was dissolved in water (4.5 mL) and sulfuric acid (0.5 mL). The reaction was sealed in a microwave vial and heated at 100° for 40 minutes. The reaction was cooled to 0°, then diluted with MeOH (10 mL) and neutralized by the addition of concentrated ammonia solution. Salts were filtered off and washed several times with methanol. The filtrate was adsorbed onto silica and purified on a gradient of 0-15% MeOH in DCM to give compound L6-8 (347 mg, 1.60 mmol) in 80% yield. ^{13}C NMR (101 MHz, CD_3OD) δ 102.70, 85.32, 71.03, 69.59, 69.49, 66.07, 61.85.

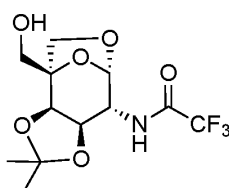
9. Bicyclic ASGPR ligand CF3 (Figure 21)



Compound (400 mg, 1.84 mmol) was dissolved in methanol (30 mL) and the reaction flask purged with nitrogen. Lindlar's catalyst (40.0 mg, 10 wt%) was then added, and the reaction mixture stirred under a 1 atm hydrogen atmosphere (balloon) for 6 hours. The reaction was filtered over celite and evaporated to give compound 10 (351 mg, 1.84 mmol) in quantitative yield, which was used in the next reaction without further purification.

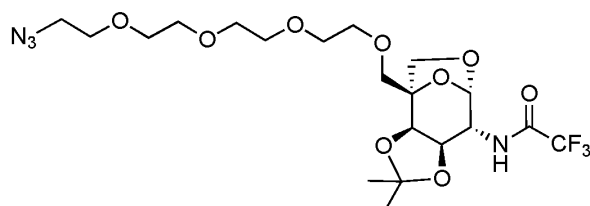
Compound (351 mg, 1.84 mmol) was dissolved in pyridine (15 mL) and treated with trifluoroacetic anhydride (1.24 mL, 1.85 g, 8.83 mmol, 4.8 eq). The reaction was stirred for 6 hours, then diluted into ethyl acetate and washed with 1M HCl (1x), saturated sodium bicarbonate (1x), and brine (1x). The organic layer was dried over sodium sulfate and evaporated to give compound 11 (1.01 g, 1.75 mmol) in 95% yield, which was used in further steps without purification.

Compound 11 (1.01 g, 1.75 mmol) was dissolved in methanol (25 mL) and dry sodium methoxide (86.2 mg, 1.60 mmol, 4 eq) was added. The reaction was stirred for one hour at room temperature, then neutralized with acetic acid and evaporated onto silica. The crude mixture was purified on silica (0-15% MeOH in DCM) to give compound 12 (482 mg, 1.68 mmol) in 96% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.51 (d, *J* = 6.6 Hz, 1H), 5.15 (s, 1H), 4.98 – 4.90 (m, 1H), 4.87 (d, *J* = 5.6 Hz, 1H), 4.75 – 4.70 (m, 1H), 3.86 – 3.80 (m, 2H), 3.80 – 3.70 (m, 2H), 3.67 – 3.54 (m, 3H). ¹³C NMR (101 MHz, DMSO) δ 157.47, 157.11, 117.74, 114.87, 100.28, 84.21, 68.77, 68.28, 66.00, 60.51, 55.95, 40.56, 40.35, 40.15, 39.94, 39.73, 39.52, 39.31. HRMS: [M+H]⁺ Expected 288.069, found 288.064.

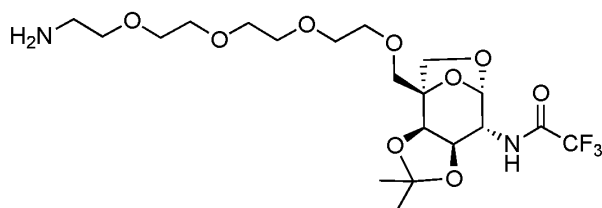


Compound 12 (110 mg, .383 mmol) was dissolved in DMF (8 mL) and dimethoxypropane (236 μL, 200 mg, 1.92 mmol, 5 eq) and camphorsulfonic acid (45 mg, .192 mmol, .5 eq) were added. The reaction was stirred at 70° overnight, then DMF evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate (1x) and brine (1x), then evaporated onto silica and purified (0-5% MeOH in DCM) to give compound 13 (99.1 mg, .303 mmol) in 79% yield. ¹H NMR (400 MHz,

Chloroform-*d*) δ 6.87 (d, J = 9.0 Hz, 1H), 5.35 (d, J = 2.1 Hz, 1H), 4.18 – 4.11 (m, 2H), 4.11 – 4.03 (m, 2H), 3.84 (t, J = 8.2 Hz, 2H), 3.74 (d, J = 7.9 Hz, 1H), 2.66 (d, J = 6.6 Hz, 1H), 1.52 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.87, 157.50, 157.12, 156.75, 119.93, 117.07, 114.21, 112.04, 111.35, 100.22, 81.55, 75.57, 75.00, 68.44, 60.96, 55.16, 27.67, 26.16. HRMS: $[\text{M}+\text{H}]^+$ Expected 328.101, found 328.095.

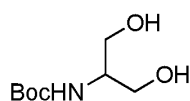


Compound 13 (99.1 mg, .303 mmol) was dissolved in DMF (5 mL) and treated with sodium hydride (8.7 mg, .364 mmol, 1.2 eq), then stirred under nitrogen for 15 minutes. Compound 18 (108 mg, .364 mmol, 1.2 eq) was then added, and the reaction stirred for 1 hour. The reaction was neutralized by the dropwise addition of acetic acid. The solvent was removed under reduced pressure and the residue taken up into ethyl acetate and washed with brine (4x), and the organic layer was dried over sodium sulfate and evaporated onto silica. The crude mixture was purified on silica (50-100% EtOAc in hexanes) to give compound 14 (131 mg, .248 mmol) in 82% yield. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.75 (d, J = 8.3 Hz, 1H), 5.29 (s, 1H), 4.40 (t, J = 6.7 Hz, 1H), 4.30 (d, J = 5.9 Hz, 1H), 3.88 – 3.66 (m, 5H), 3.64 – 3.48 (m, 14H), 3.39 (t, J = 5.0 Hz, 2H), 1.41 (s, 3H), 1.28 (s, 3H).

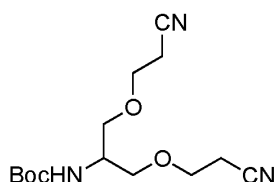


Compound 14 (131 mg, .240 mmol) was dissolved in methanol (10 mL) and stirred under a nitrogen atmosphere. Lindlar's catalyst (13.1 mg, 10 wt%) was then added, and the reaction stirred for 6 hours under H_2 atmosphere (1 atm). The reaction was then filtered over celite and the solvent evaporated to give compound 15 (120 mg, 0.240 mmol) in quantitative yield, which was used without further purification. HRMS: $[\text{M}+\text{H}]^+$ Expected 503.222, found 503.223.

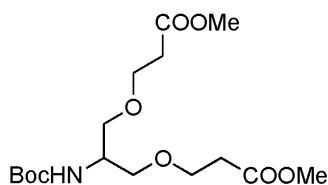
10. MIF binding divalent (Figure 23)



- 5 Serinol (2.00 g, 22.0 mmol) was dissolved in dichloromethane (40 mL) and trimethylamine (10 mL). Di-tert-butyl dicarbonate (5.76 g, 26.4 mmol, 1.2 eq) was then added, and the reaction stirred for 4 hours. The mixture was evaporated and the residue portioned between ethyl acetate and water. The organic fraction was washed with water (1x), 1M HCl (2x), saturated sodium bicarbonate (1x), and brine (1x) before drying over sodium sulfate and
- 10 evaporation to give compound 23 (3.99 g, 20.9 mmol) in 95% yield, which was used without purification in further steps.



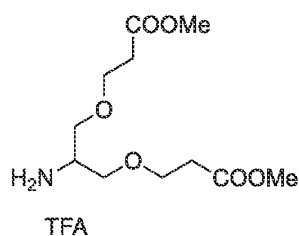
- Compound 23 (3.99 g, 20.9 mmol) was dissolved in a mixture of dioxane (12 mL) and
- 15 aqueous KOH (1.63 g, 29 mmol, 2.4 mL). Acrylonitrile (3.02 mL, 2.44 g, 46.0 mmol, 2.2 eq) was then added dropwise over a period of 2.5 hours, and the reaction stirred under nitrogen for 24 hours. The reaction was neutralized with the addition of 2M HCl (16 mL) and portioned between DCM and water. The organic layer was washed with water (2x) and brine (1x), dried over sodium sulfate, and evaporated. The crude mixture was purified on silica (20-
- 20 100% EtOAc in hexanes) to give compound 20 (4.96 g, 16.7 mmol) in 80% yield. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.91 (d, *J* = 8.9 Hz, 1H), 3.94 – 3.81 (m, 1H), 3.68 (t, *J* = 6.1 Hz, 4H), 3.65 – 3.48 (m, 4H), 2.60 (t, *J* = 6.1 Hz, 4H), 1.42 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 171.11, 155.31, 117.88, 79.70, 69.12, 65.53, 49.24, 28.30, 18.83, 14.16.



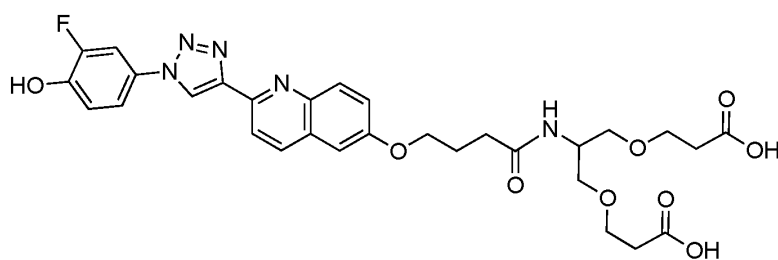
25

Compound 24 (4.96 g, 16.7 mmol) was dissolved in methanol (40 mL) and concentrated sulfuric acid (10 mL) was added. The mixture was heated at reflux for 24 hours under a nitrogen atmosphere, then cooled to room temperature. Excess sodium bicarbonate was then added, followed by di-tert-butyl dicarbonate (4.37 g, 20.04 mmol, 1.2 eq), and the reaction stirred at room temperature for 6 hours. The cloudy mixture was portioned between water and ethyl acetate, and the organic fraction washed with water (1x), 0.5M HCl (2x), saturated sodium bicarbonate (1x), and brine (1x), dried over sodium sulfate, and evaporated.

Compound 20 was purified over a gradient of 0-10% MeOH in DCM on silica, and recovered in 74% yield (4.50 g, 12.4 mmol). ¹H NMR (400 MHz, Chloroform-*d*) δ 4.90 (d, *J* = 8.6 Hz, 1H), 3.82 (br s, 1H), 3.70 – 3.59 (m, 10H), 3.51 – 3.34 (m, 4H), 2.51 (t, *J* = 6.3 Hz, 4H), 1.38 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 171.86, 155.34, 79.20, 69.19, 66.41, 51.58, 49.29, 34.75, 28.28.



Compound 25 (1.00 g, 2.75 mmol) was dissolved in dry MeOH (10 mL) and TFA (1 mL) and stirred for 15 minutes. Volatiles were evaporated under reduced pressure to give compound 26 as the TFA salt (1.04 g) in quantitative yield.



Compound 34 (50.0 mg, .123 mmol) was dissolved in DMF (5 mL) and DIPEA (214 uL, 159 mg, 1.23 mmol, 10 eq) and stirred under nitrogen. HBTU (102.4 mg, .270 mmol, 2.2 eq) was then added, and the reaction stirred for 15 minutes. Compound 26 (102 mg, .270 mmol, 2.2 eq) dissolved in DMF (1 mL) was then added dropwise, and the reaction stirred for 1 hour.

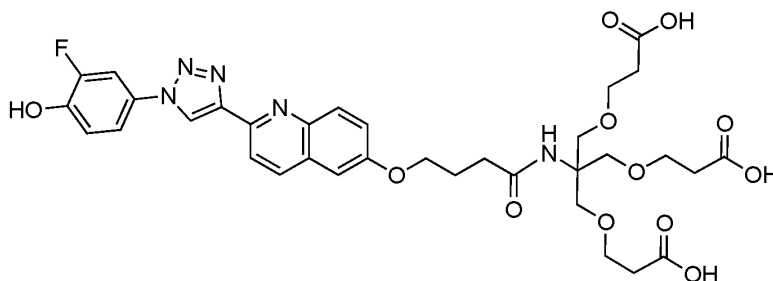
The mixture was diluted into ethyl acetate, and washed with 1M HCl (2x) and brine (5x). The organic layer was evaporated to give a gummy residue, which was purified on reverse phase HPLC (35-45% MeCN in water, .1% TFA) to give compound 40 (62.6 mg, .0959 mmol) in 78% yield. HRMS: expected 654.258, found 654.259.

5

Compound 40 (62.6 mg, .0959 mmol) was dissolved in dioxane (1.8 mL) and 1M NaOH (0.2 mL) was added. The solution was stirred at room temperature for 2 hours, then acidified (pH 3) and evaporated. The residue was resuspended in EtOAc, washed with 1M HCl, and dried over sodium sulfate. The organic layer was evaporated to give compound 41 as an oil (57.6 mg, .0921 mmol) in 96% yield, which was used without further purification.

10

11. MIF binding trivalent (Figure 23)



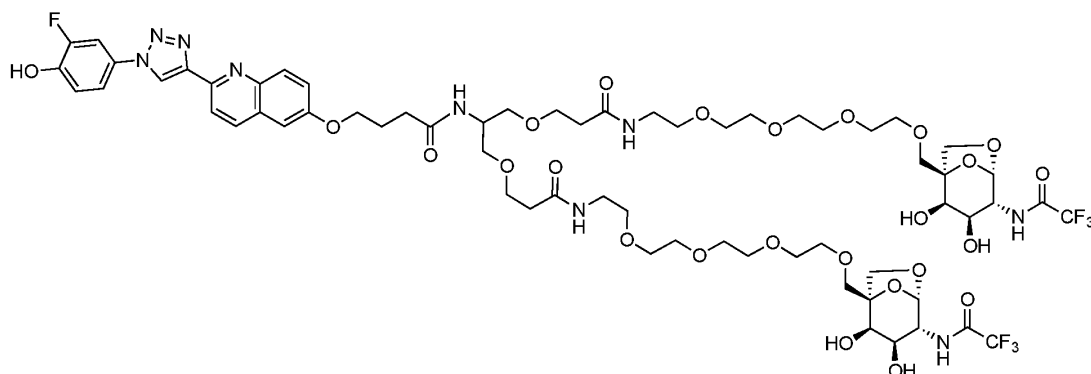
Compound 34 (50.0 mg, .123 mmol) was dissolved in DMF (5 mL) and DIPEA (214 μ L, 159 mg, 1.23 mmol, 10 eq) and stirred under nitrogen. HBTU (154 mg, .405 mmol, 3.3 eq) was then added, and the reaction stirred for 15 minutes. Compound 29 (200 mg, 0.405 mmol, 3.3 eq) dissolved in DMF (1 mL) was then added dropwise, and the reaction stirred for 1 hour. The mixture was diluted into ethyl acetate, and washed with 1M HCl (2x) and brine (5x). The organic layer was evaporated to give a gummy residue, which was purified on reverse phase HPLC (35-50% MeCN in water, .1% TFA) to give compound 44 (79.3 mg, 0.103 mmol) in 84% yield. HRMS: $[M+H]^+$ expected 770.305, found 770.308.

20

Compound 44 (79.3 mg, 0.103 mmol) was dissolved in dioxane (1.8 mL) and 1M NaOH (0.2 mL) was added. The solution was stirred at room temperature for 2 hours, then acidified (pH 3) and evaporated. The residue was resuspended in EtOAc, washed with 1M HCl, and dried over sodium sulfate. The organic layer was evaporated to give compound 41 as an oil (68.9 mg, .0948 mmol) in 92% yield, which was used without further purification.

25

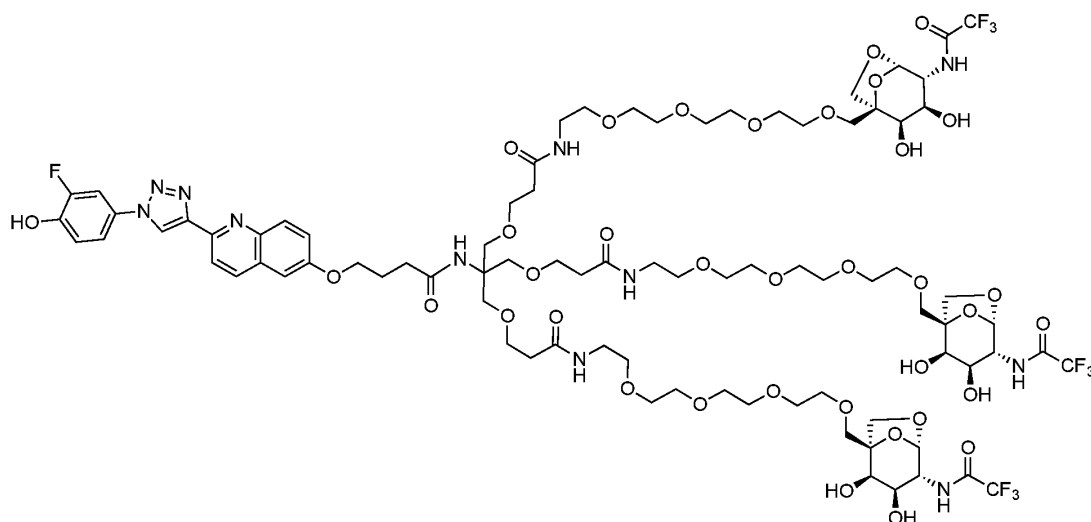
12. MIF-AcF3-2 (Figure 24)



Compound 41 (57.6 mg, 0.0921 mmol) was dissolved in DMF (1.8 mL) and DIPEA (0.2 mL). HBTU (84.0 mg, 0.222 mmol, 2.4 eq) was then added, and the reaction stirred for 15 minutes before the addition of compound 15 (111 mg, 0.222 mmol, 2.4 eq). The reaction was stirred for 1 hour, then evaporated to give a red residue which was used in the next reaction without purification.

Compound 42 (crude, .0921 mmol scale) was dissolved in 1M HCl (1 mL) and stirred for 2
10 hours. The reaction was purified directly by HPLC (20-40% MeCN in H₂O, +3% TFA) to
give compound 43 (44.66 mg, 0.0295 mmol) in 32% yield. HRMS Expected (H) 1514.570,
found 1514.561.

13. MIF-AcF3-3 (Figure 25)



Compound 45 (68.9 mg, .0948 mmol) was dissolved in DMF (1.8 mL) and DIPEA (.2 mL).

HBTU (126 mg, .333 mmol, 3.6 eq) was then added, and the reaction stirred for 15 minutes before the addition of compound 15 (167 mg, .333 mmol, 3.6 eq). The reaction was stirred for 1 hour, then evaporated to give a reddish residue which was used in the next reaction without purification.

5

Compound 38 (crude, .0948 mmol scale) was dissolved in 1M HCl (1 mL) and stirred for 2 hours. The reaction was purified directly by HPLC (20-40% MeCN in H₂O, +3% TFA) to give compound 39 (78.1 mg, 0.0379 mmol) in 40% yield. HRMS expected (2H, /2) 1030.891, found 1030.903.

10

Synthesis of MIF-AcF2-3, MIF-Ac-3, MIF-Et-3

Set forth in figures 26-29 are the chemical syntheses of MIF-AcF2-3, MIF-Ac-3, MIF-Et-3 and MIF-EtF3-3 produced using analogous methods to those presented above with minor variation.

15

Set forth in FIGURES 30-66 and 70-88 are chemical synthetic schemes which provide additional compounds according to the present disclosure. The schemes in these FIGURES evidence the exemplary synthetic chemistry which can be used to synthesis compounds according to the present disclosure.

20

Peptide Synthesis

N-linked non-cyclized peptides, C-amide terminating, without amine-containing (side-chain) amino acids.

25

Peptides are synthesized on 200 μ mol scale using Rink amide resin. Standard fmoc amino acids with sidechains protected using acid-labile protecting groups are utilized for all couplings. Between each deprotection, coupling, and capping reaction resin was washed 5x with DMF, 5x with DCM, and 5x with DMF. Resin is Fmoc deprotected (20% piperidine in DMF, 2 x 3 minute incubations on rotator) and is coupled to the first amino acid (4 eq oxyma, 4 eq Fmoc-protected amino acid, 4 eq DIC in DMF) overnight. The resin is then washed and treated with 10% acetic anhydride in pyridine to cap any unreacted amines (10 minutes on rotator). The resulting resin-amino acid conjugate is Fmoc deprotected as described above and coupled to the next amino acids (4 eq oxyma, 4 eq Fmoc-protected amino acid, 4 eq DIC

30

in DMF) for 40 minutes. The resin is then capped as above. Subsequent iterative deprotection, coupling and capping steps provide the final peptides. Following the last amino acid, {2-[2-(Fmoc-amino)ethoxy]ethoxy}acetic acid is coupled to the peptide and Fmoc deprotected to give an N terminal amine. Peptides are cleaved from resin using 90%TFA, 5%
5 TIPS, 5% water (2hr treatment), ether precipitated, and purified using RPHPLC to 95% purity, then reacted with carboxylic acids to provide the bifunctional compounds. Alternatively, these peptides are treated with succinic anhydride to afford a terminal carboxylic acid for coupling with amines; azidoacetic acid to generate a terminal alkyne; or 5-hexynoic acid to generate a terminal alkyne. Copper-mediated cross coupling is used in the
10 case of terminal azides or alkynes to give triazole-linked bifunctional molecules.

N-linked disulfide cyclized peptides, C-amide terminating, without amine-containing (sidechain) amino acids.

15 As above, but following cleavage from resin the peptides are then resuspended in PBS pH 8, MeOH/ammonium bicarbonate, or another acceptable buffer to provide the oxidized peptide containing a disulfide. Alternatively, iodine is used to oxidatively cyclize the peptides.

N-linked non-cyclized peptides, C-amide terminating with amine-containing (sidechain) amino acids.

As above, but amino acids containing amines are protected on their sidechains with Cbz which is removed under reductive conditions (H₂, Pd/C) at a later step in the synthesis.

N-linked disulfide cyclized peptides, C-amide terminating with amine-containing (sidechain) amino acids.

As above, but amino acids containing amines are protected on their sidechains with Cbz which is removed under reductive conditions (H₂, Pd/C) at a later step in the synthesis.
30 Following cleavage from resin the peptides are then resuspended in PBS pH 8, MeOH/ammonium bicarbonate, or another acceptable buffer to provide the oxidized peptide containing a disulfide. Alternatively, iodine is used to oxidatively cyclize the peptides.

C-linked non-cyclized peptides, without carboxylic acid-containing (sidechain) amino

acids.

Peptides are synthesized on 200 μ mol scale using 2-chlorotrityl resin. Standard fmoc amino acids with sidechains protected using acid-labile protecting groups are utilized for all

5 couplings. Between each deprotection, coupling, and capping reaction resin was washed 5x with DMF, 5x with DCM, and 5x with DMF. Resin is treated with 4 eq 2,4,6-collidine in DCM with the first amino acid (4 eq) of the sequence overnight. The resin is then capped by treatment with methanol in DIPEA/DCM for 1hr at RT. The amino acid is then deprotected (20% piperidine in DMF, 2 x 3 minute incubations on rotator) and is coupled to the first

10 amino acid (4 eq oxyma, 4 eq Fmoc-protected amino acid, 4 eq DIC in DMF) overnight. The resin is then washed and treated with 10% acetic anhydride in pyridine to cap any unreacted amines (10 minutes on rotator). The resulting resin-amino acid conjugate is Fmoc deprotected as described above and coupled to the next amino acids (4 eq oxyma, 4 eq Fmoc-protected amino acid, 4 eq DIC in DMF) for 40 minutes. The resin is then capped as above. Subsequent

15 iterative deprotection, coupling and capping steps provide the final peptides. Following the last amino acid, peptides are optionally capped with acetic anhydride, propionic anhydride, or another suitable activated acid. Peptides are cleaved from resin using hexafluoroisopropanol (20%) in DCM for 1.5 hr at room temperature and ether precipitated. Peptides are then purified using RPHPLC to 95% purity, then reacted with carboxylic acids to provide the

20 bifunctional compounds. Alternatively, these peptides are treated with N-boc-ethylenediamine and subsequently HCl/DCM to afford a terminal amine for coupling with carboxylic acids. Alternatively, these peptides are treated with 3-azidopropan-1-amine under standard coupling conditions (HBTU, DIPEA, DMF) to generate a terminal azide. Alternatively, these peptides are treated with 4-pentyn-1-amine under standard amide

25 coupling conditions (HBTU, DIPEA, DMF) to give a C terminal alkyne. Copper-mediated cross coupling is used in the case of terminal azides or alkynes to give triazole-linked bifunctional molecules.

30 **C-linked disulfide cyclized peptides. Without carboxylic acid-containing (sidechain) amino acids.**

As above, but following cleavage from resin the peptides are then resuspended in PBS pH 8, MeOH/ammonium bicarbonate, or another acceptable buffer to provide the oxidized peptide containing a disulfide. Alternatively, iodine is used to oxidatively cyclize the peptides.

C-linked non-cyclized peptides. With carboxylic acid-containing (sidechain) amino acids.

- 5 As above, but amino acids containing carboxylic acids are protected on their sidechains with Bz which is removed under reductive conditions (H₂, Pd/C) at a later step in the synthesis.

C-linked disulfide cyclized peptides. With carboxylic acid-containing (sidechain) amino acids.

- 10 As above, but amino acids containing carboxylic acids are protected on their sidechains with Bz which is removed under reductive conditions (H₂, Pd/C) at a later step in the synthesis. Following cleavage from resin the peptides are then resuspended in PBS pH 8, MeOH/ammonium bicarbonate, or another acceptable buffer to provide the oxidized peptide containing a disulfide. Alternatively, iodine is used to oxidatively cyclize the peptides.

15

- The foregoing outlines features of several embodiments so that those skilled in the art may better understand the aspects of the present disclosure. Those skilled in the art should appreciate that they may readily use the present disclosure as a basis for designing or modifying other processes and structures for carrying out the same purposes and/or achieving
- 20 the same advantages of the embodiments introduced herein. Those skilled in the art should also realize that such equivalent constructions do not depart from the spirit and scope of the present disclosure, and that they may make various changes, substitutions, and alterations herein without departing from the spirit and scope of the present disclosure.

CLAIMS

What is claimed is:

1. A bifunctional compound, or a salt, stereoisomer, or solvate thereof, of chemical structure:



wherein:

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

[CRBM] is a Cellular Receptor Binding Moiety which binds to asialoglycoprotein receptors of hepatocytes or other cell receptors in the subject,

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

[LINKER] is a chemical moiety having a valency from 1 to 15, which covalently attaches to one or more [CRBM] or [CPBM] groups, optionally through a [CON], wherein the [LINKER] optionally itself contains one or more [CON] groups,

k' is an integer ranging from 1 to 15,

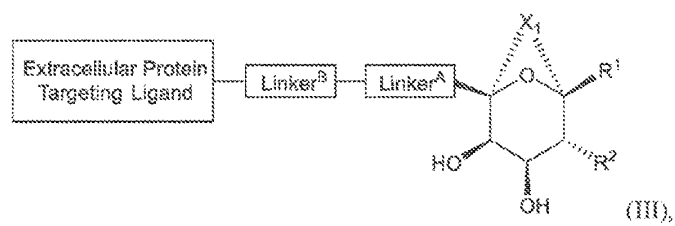
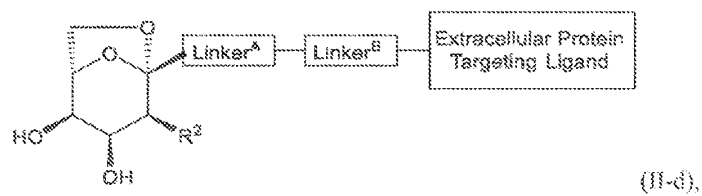
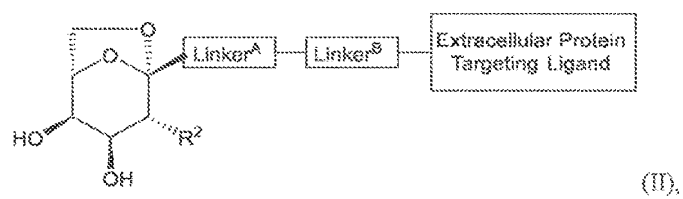
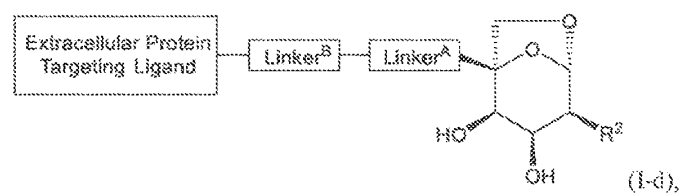
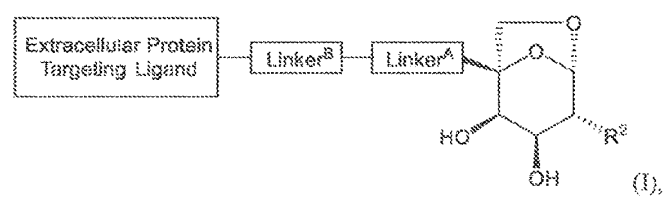
j' is an integer ranging from 1 to 15,

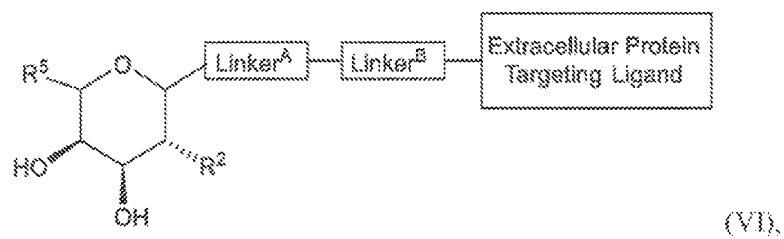
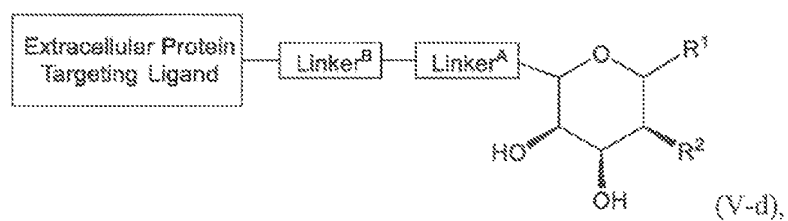
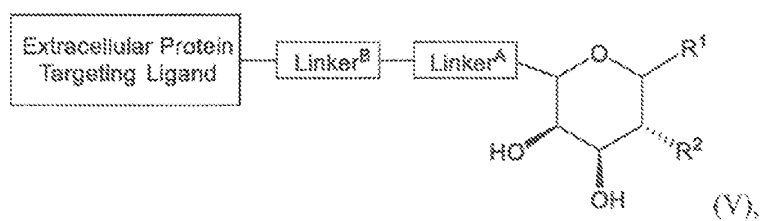
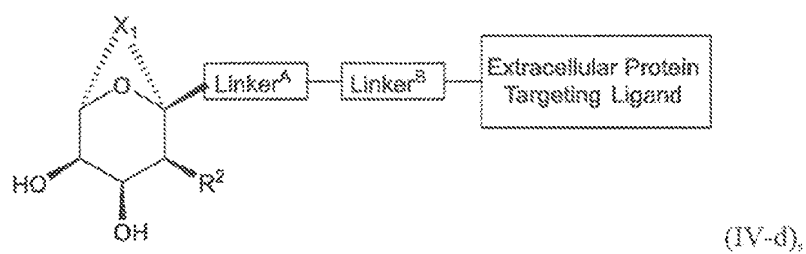
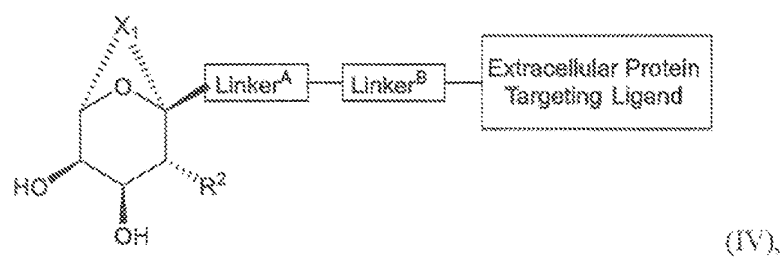
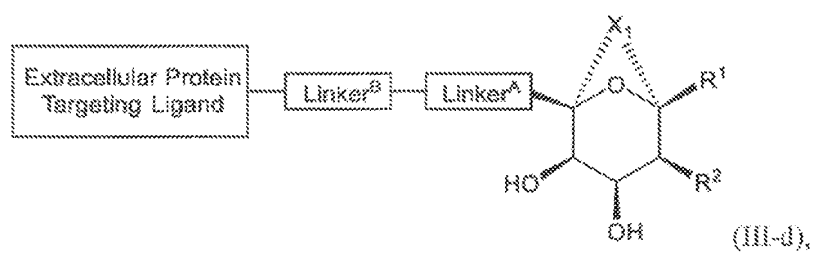
h and h' are each independently an integer ranging from 0 to 15,

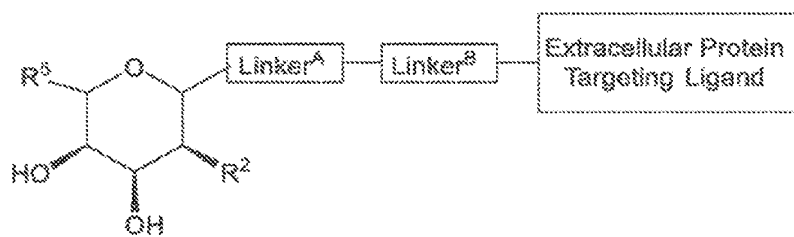
i_L is 0 to 15,

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

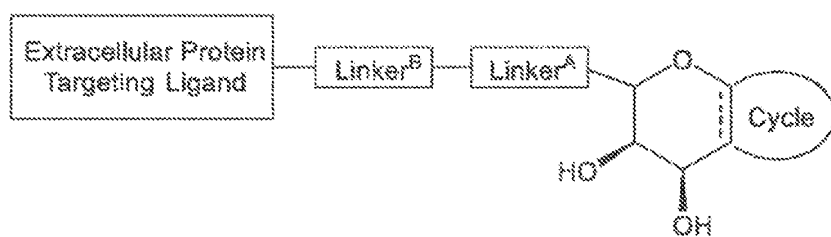
wherein the bifunctional compound is selected from the group consisting of:



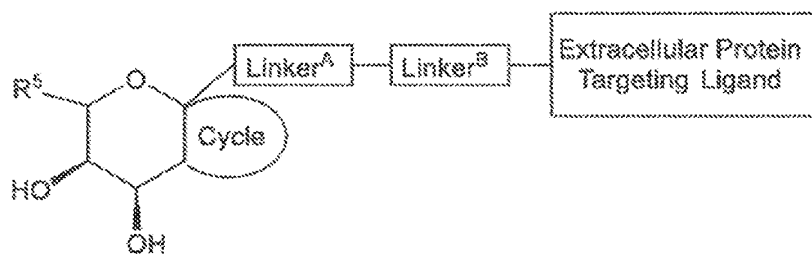




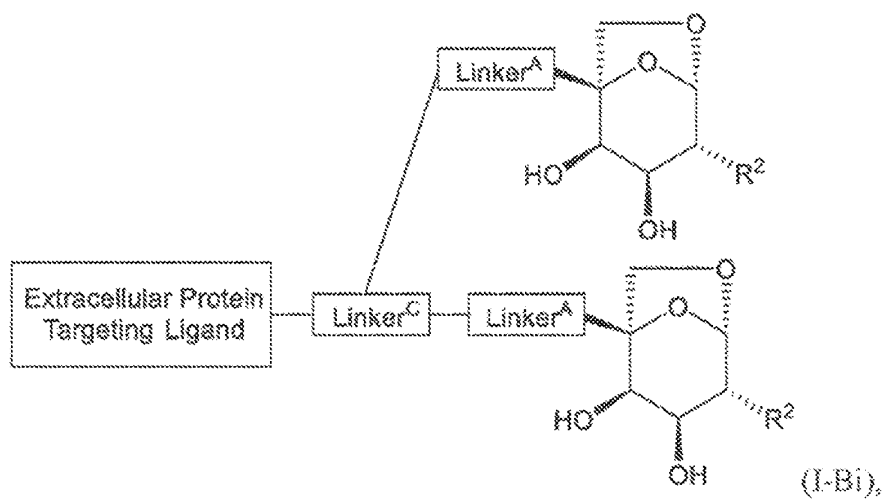
(VI-d),



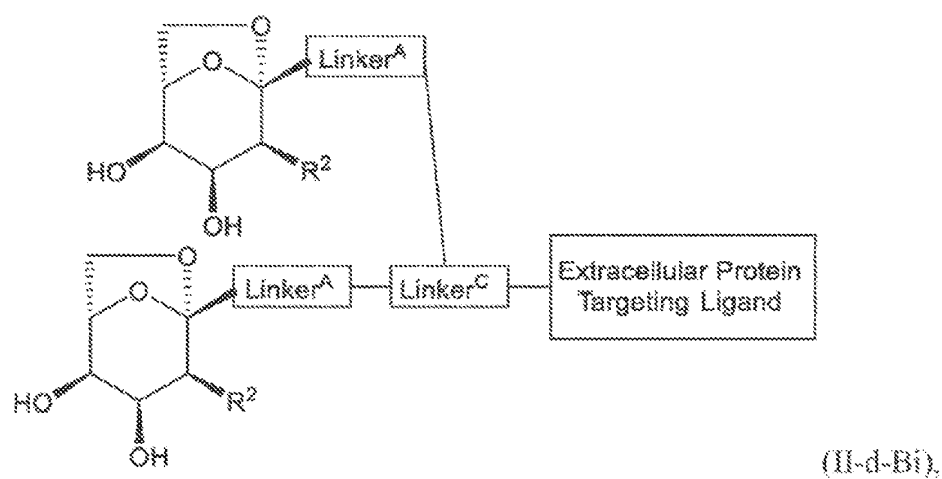
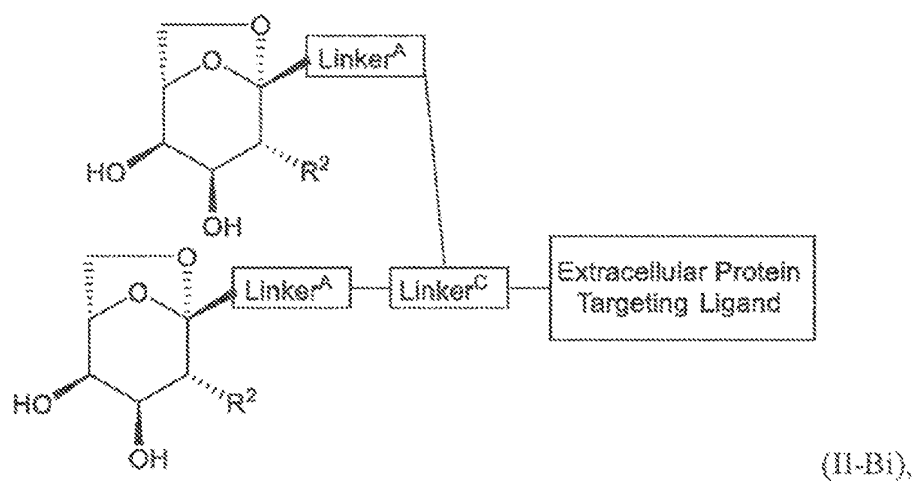
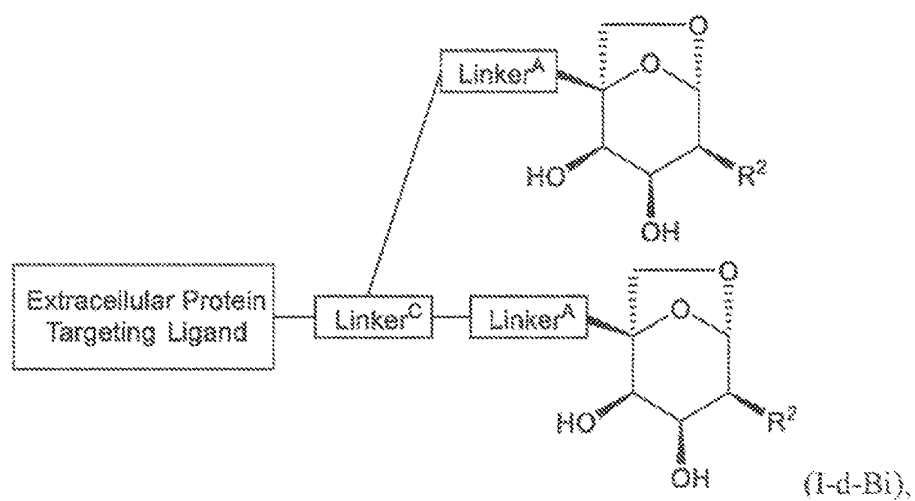
(VII),

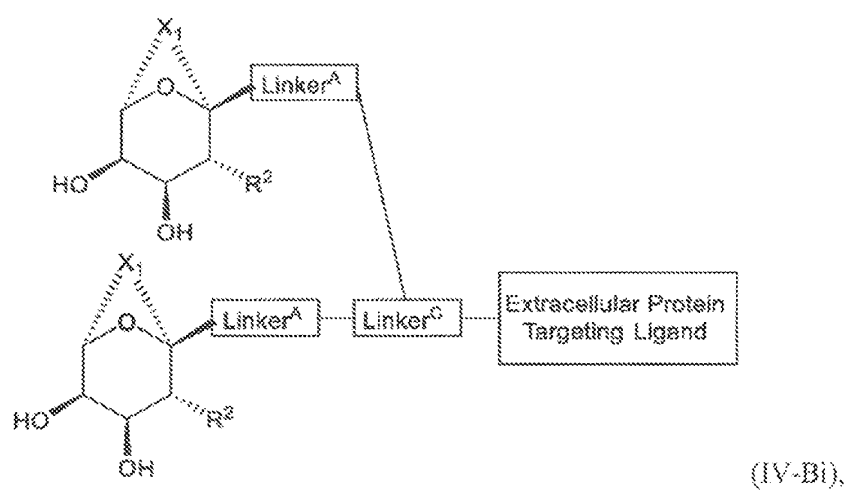
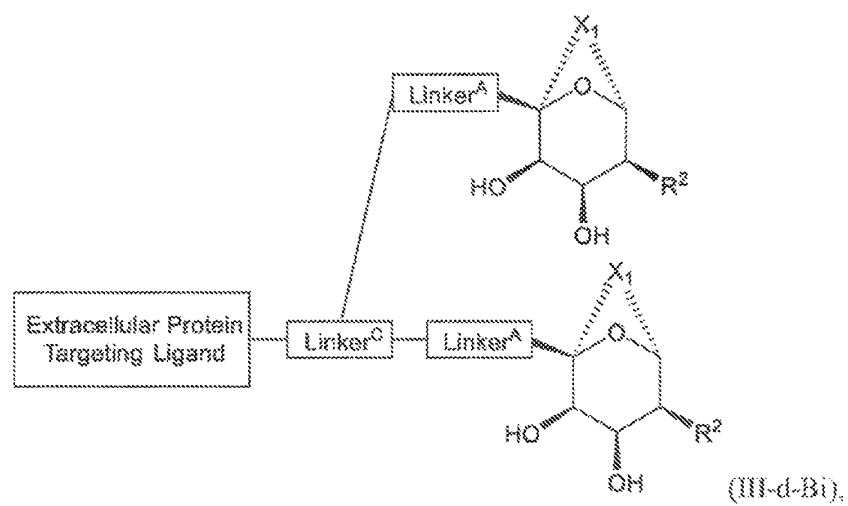
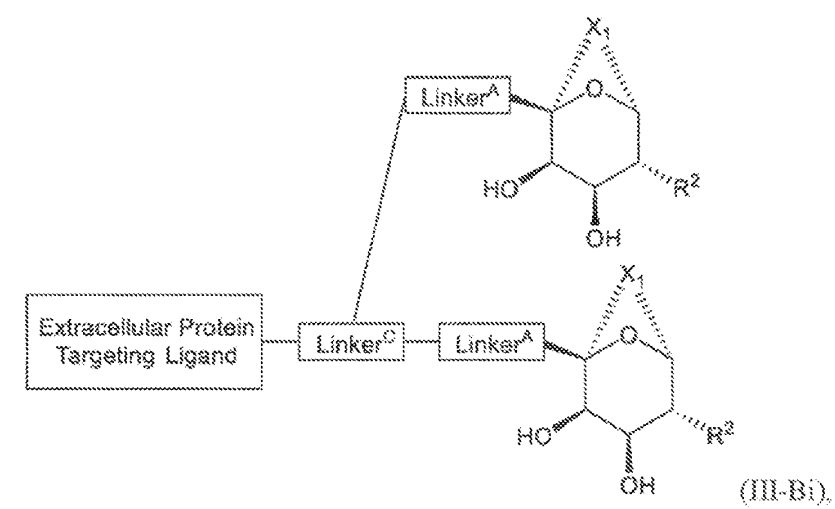


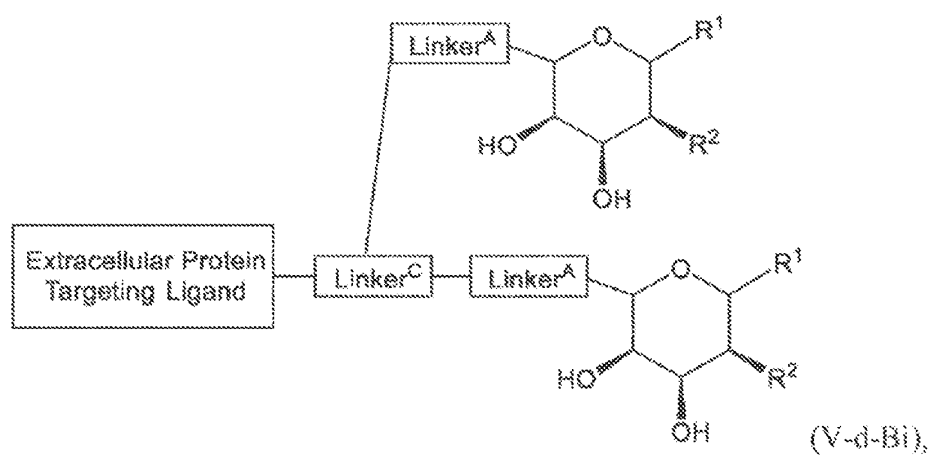
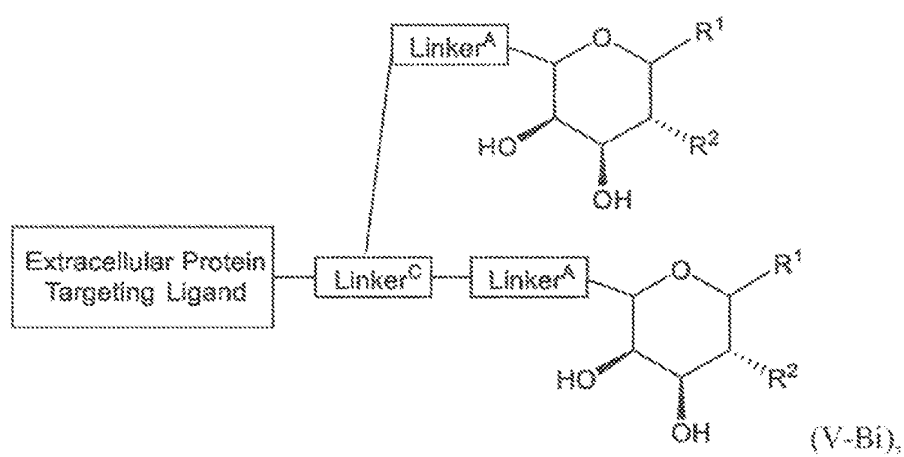
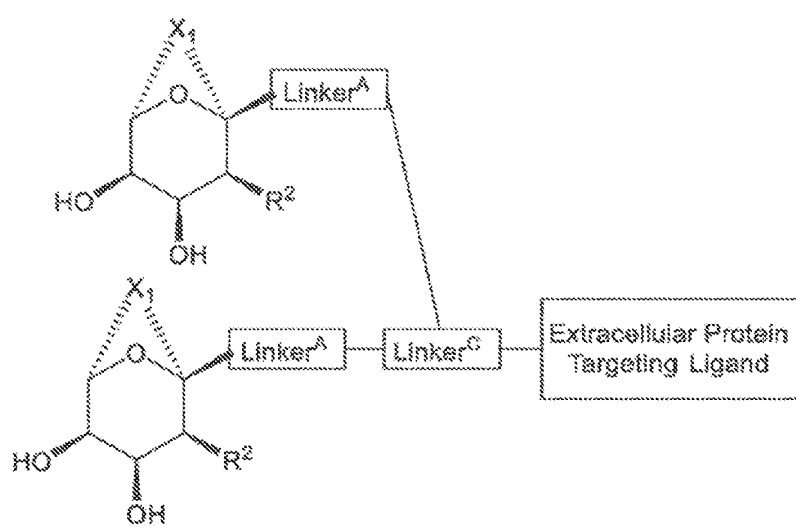
(VIII),

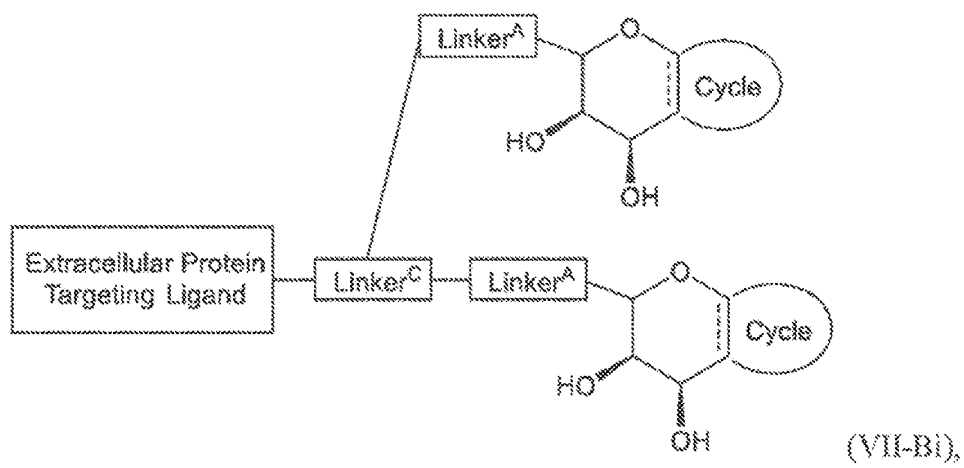
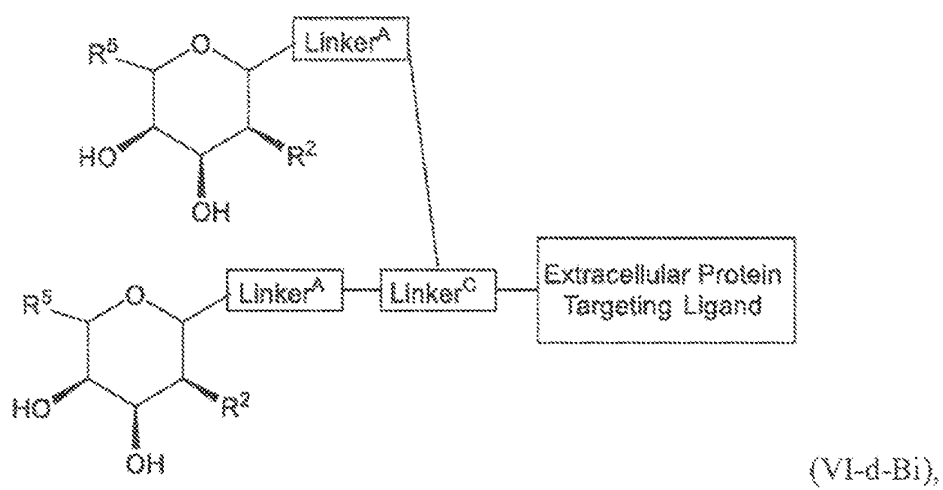
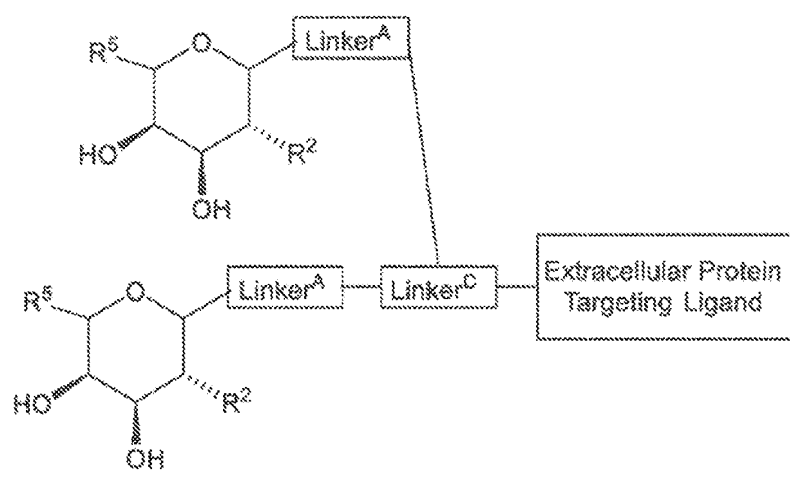


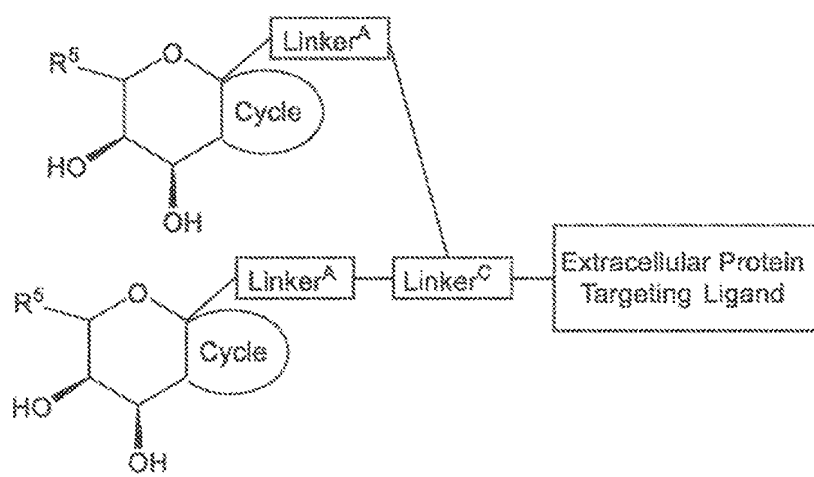
(I-Bi),



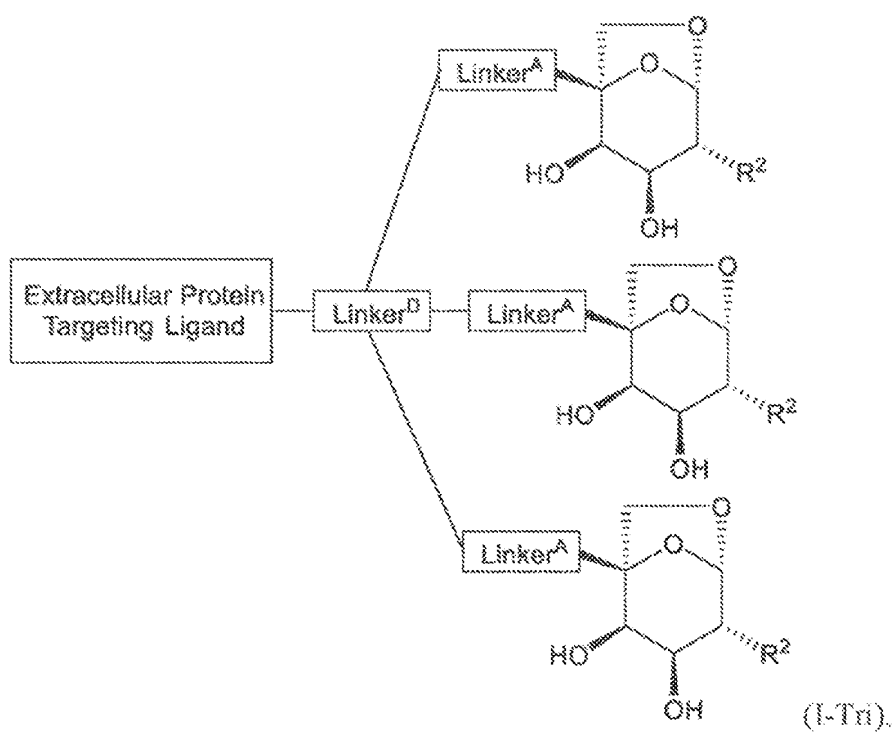


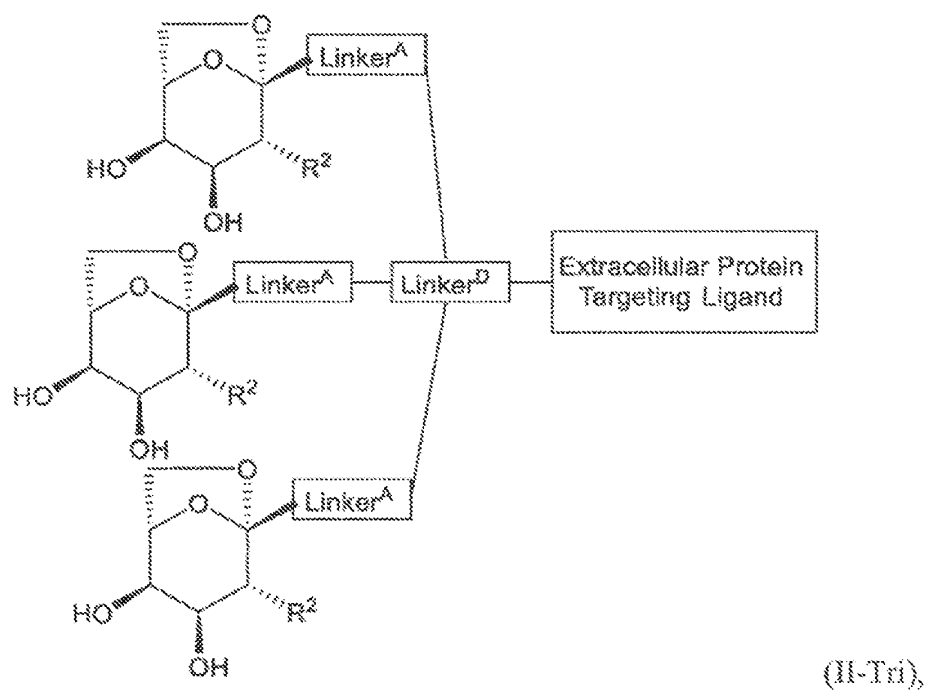
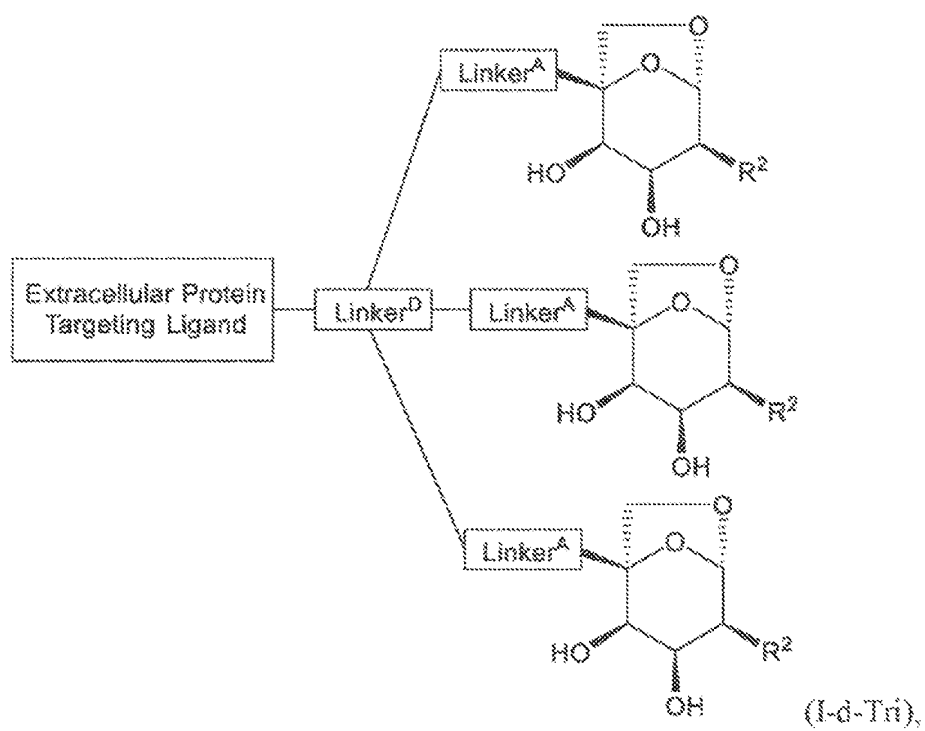


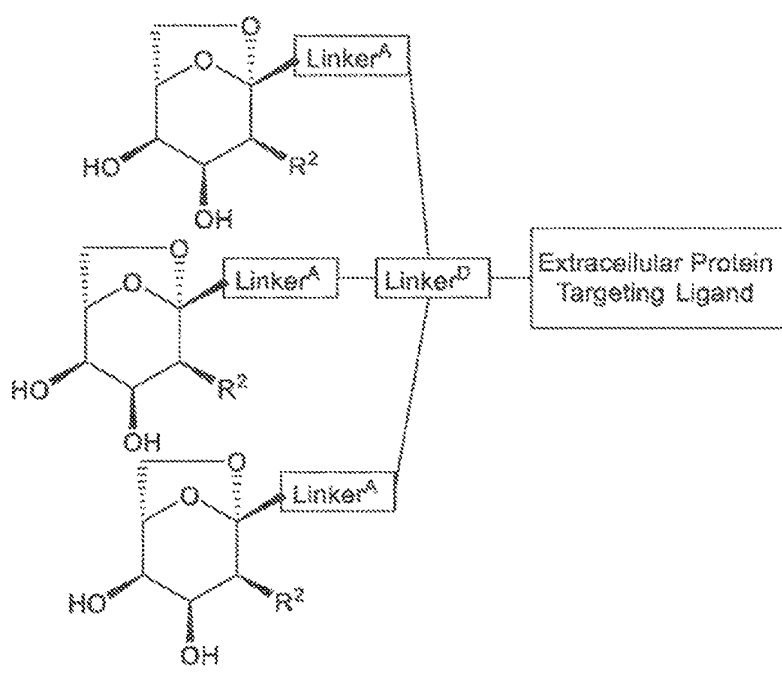




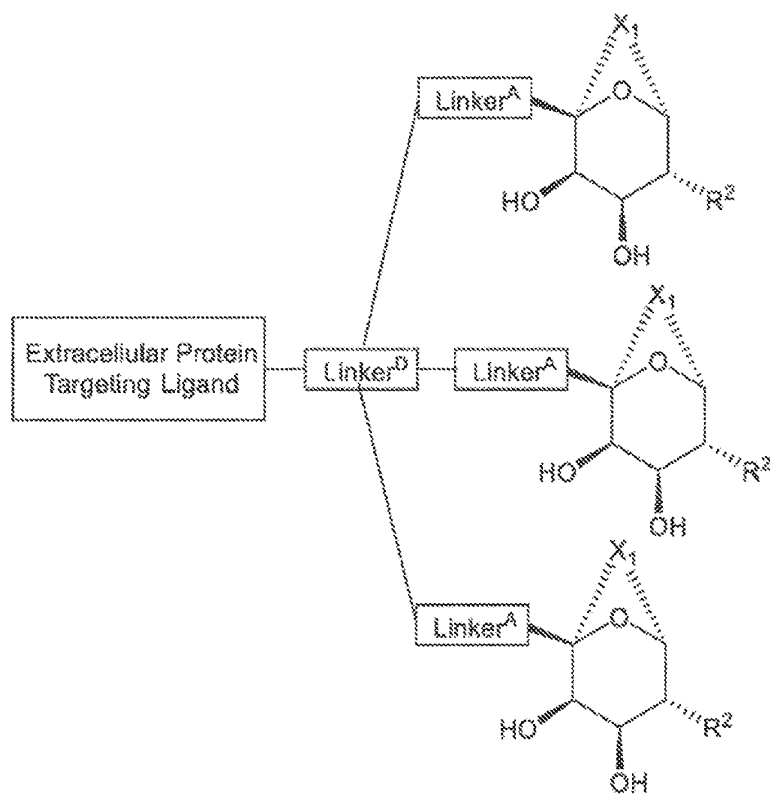
(VIII-Bi).



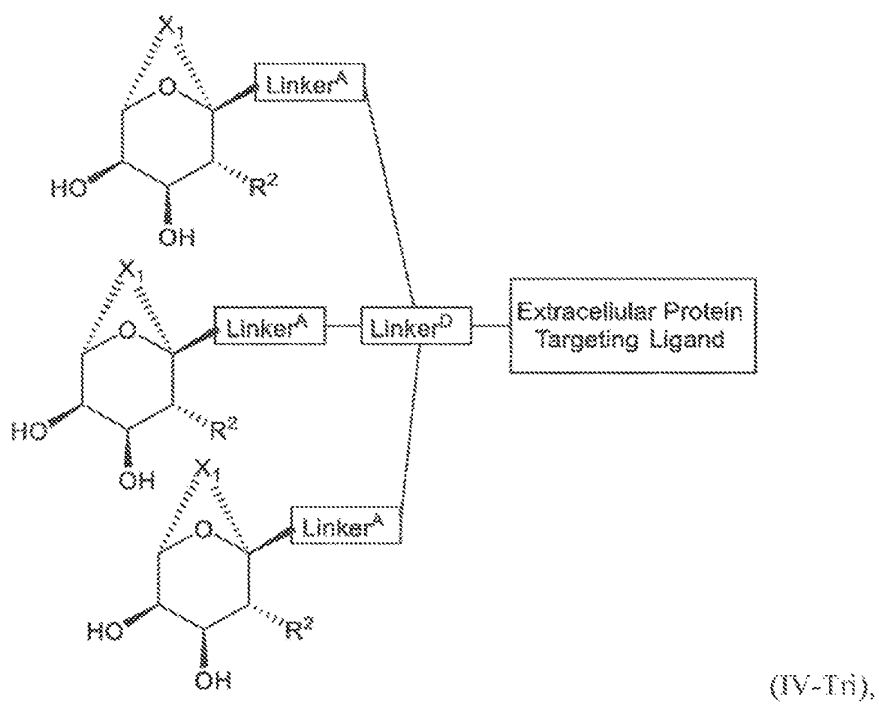
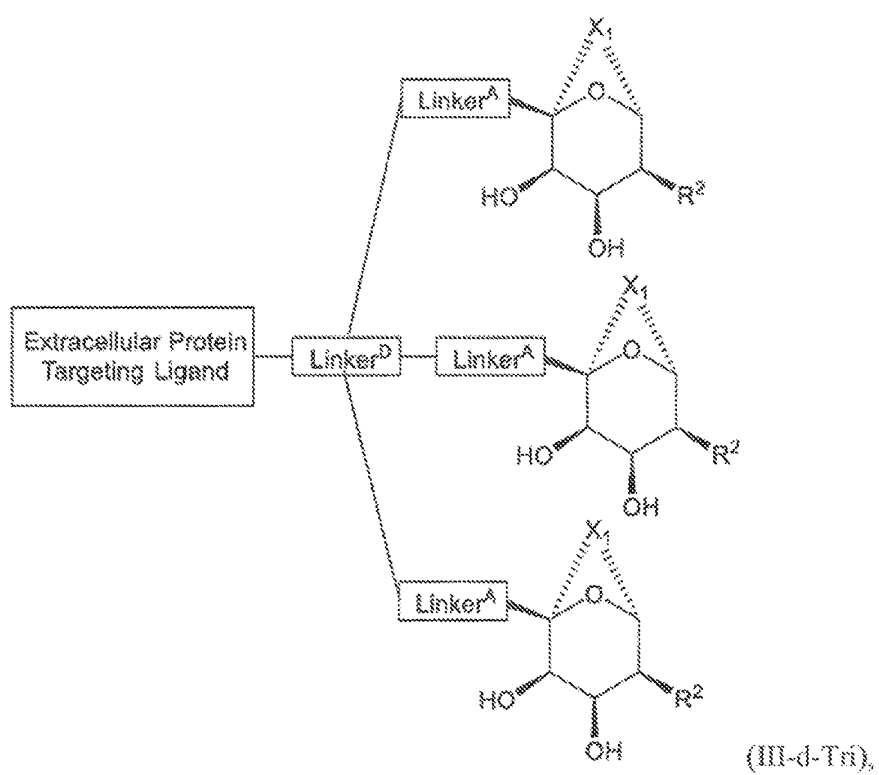


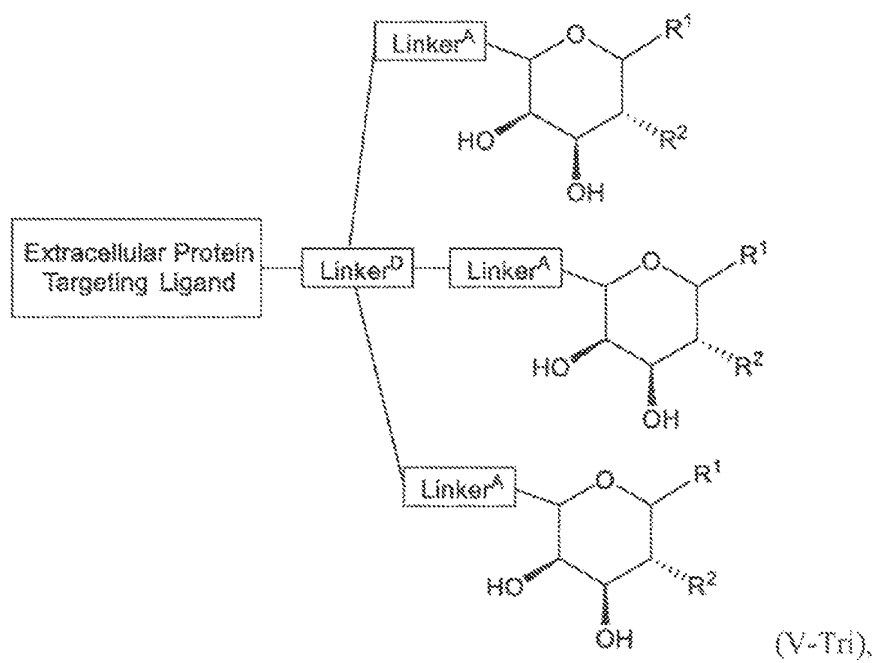
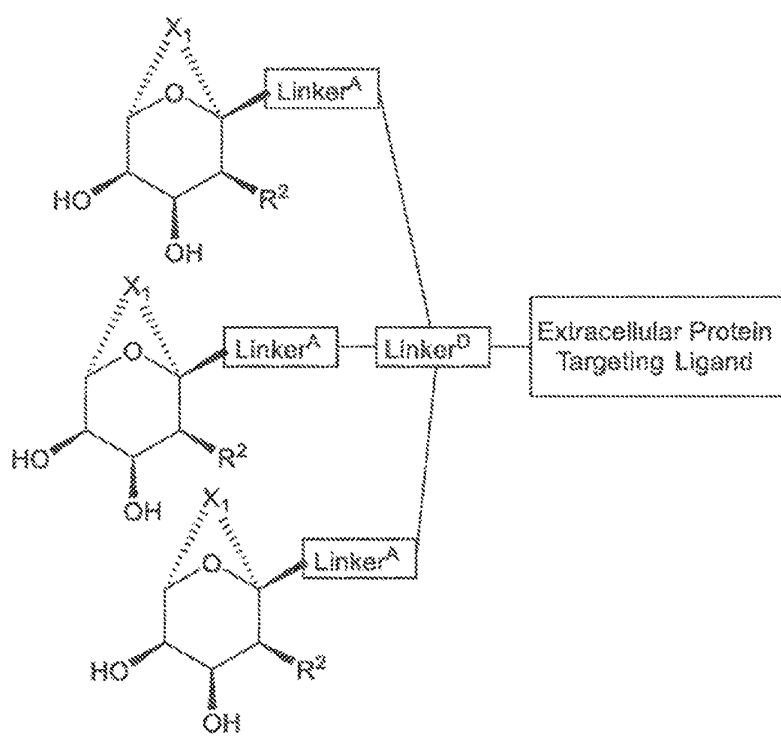


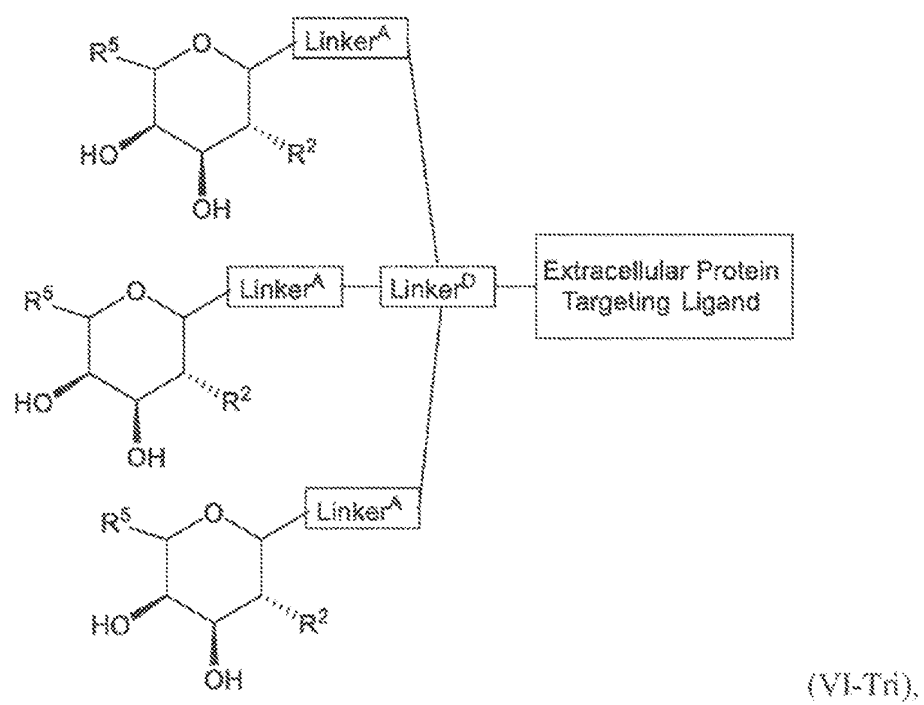
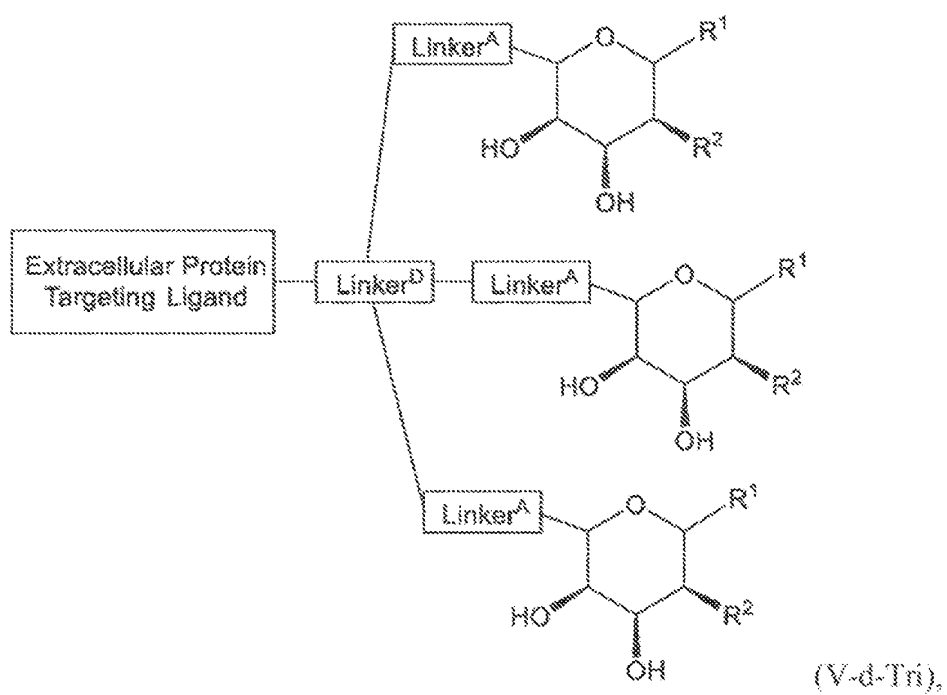
(II-d-Tri),

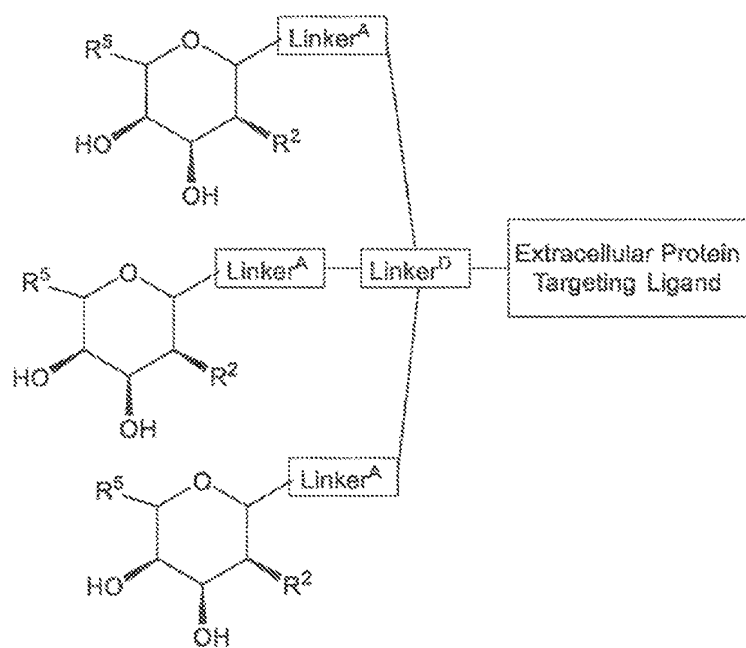


(III-Tri),

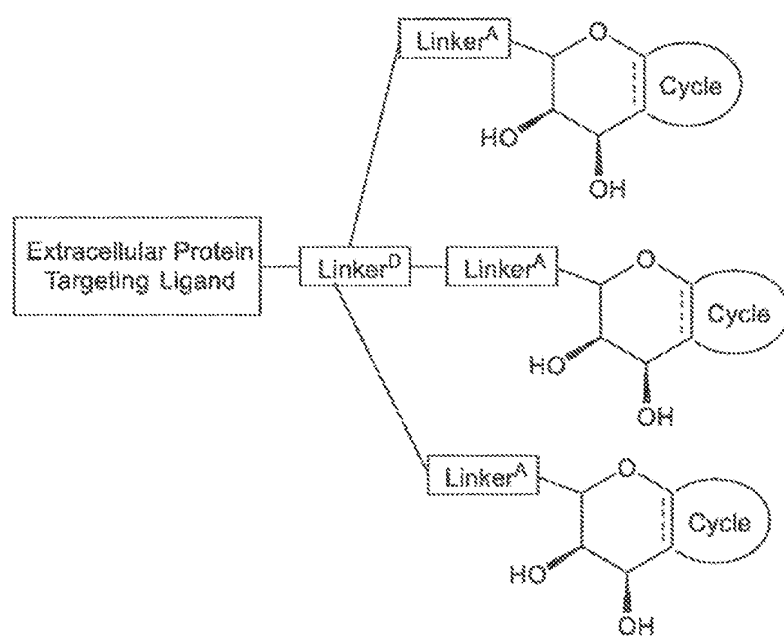






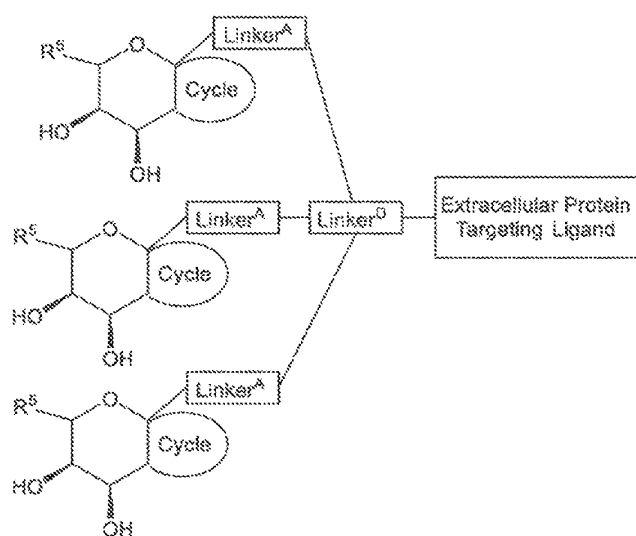


(VI-d-Tri),



(VII-Tri),

or



(VIII-Tri).

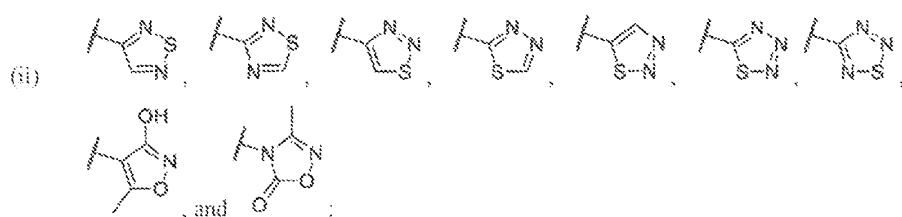
wherein:

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

X^1 is 1 to 5 groups independently selected from O, S, N(R^6), and C(R^4)(R^4), wherein if X^1 is 1 group then X^1 is O, S, N(R^6), or C(R^4)(R^4), if X^1 is 2 groups then no more than 1 group of X^1 is O, S, or N(R^6), if X^1 is 3, 4, or 5 groups then no more than 2 groups of X^1 are O, S, or N(R^6);

R^2 is selected from

- (i) aryl, heterocycle, and heteroaryl containing 1 or 2 heteroatoms independently selected from N, O, and S, each of which aryl, heterocycle, and heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents;



- (iii) $-NR^8-S(O)-R^3$, $-NR^8-C(S)-R^3$, $-NR^8-S(O)(NR^6)-R^3$, $-N=S(O)(R^3)_2$, $-NR^8C(O)NR^9S(O)_2R^3$, $-NR^8-S(O)-R^{10}$, and $-NR^8-C(NR^6)-R^3$ each of which is optionally substituted with 1, 2, 3, or 4 substituents; and

(iv) hydrogen, R^{10} , alkyl-C(O)- R^3 , -C(O)- R^3 , alkyl, haloalkyl, -OC(O) R^3 , and -NR⁸-C(O) R^{10} ;

R^{10} is selected from aryl, alkyl-NR⁵-C(O)- R^3 , alkyl-aryl, alkyl-heteroaryl with 1, 2, or 4 heteroatoms, alkyl-cyano, alkyl-OR⁶, alkyl-NR⁶R⁸, NR⁸-NR⁶-C(O) R^3 , NR⁸-S(O)₂- R^3 , alkenyl, allyl, alkynyl, -NR⁶-alkenyl, -O-alkenyl, -NR⁶-alkynyl, -NR⁶-heteroaryl, -NR⁶-aryl, -O-heteroaryl, -O-aryl, and -O-alkynyl, each of which R^{10} is optionally substituted with 1, 2, 3, or 4 substituents;

R^1 and R^5 are independently selected from 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) R^3 , C₀-C₆alkyl-S(O) R^3 , C₀-C₆alkyl-C(S) R^3 , C₀-C₆alkyl-S(O)₂ R^3 , C₀-C₆alkyl-N(R⁸)-C(O) R^3 , C₀-C₆alkyl-N(R⁸)-S(O) R^3 , C₀-C₆alkyl-N(R⁸)-C(S) R^3 , C₀-C₆alkyl-N(R⁸)-S(O)₂ R^3 , C₀-C₆alkyl-O-C(O) R^3 , C₀-C₆alkyl-O-S(O) R^3 , C₀-C₆alkyl-O-C(S) R^3 , -N=S(O)(R^3)₂, C₀-C₆alkylN₃, and C₀-C₆alkyl-O-S(O)₂ R^3 , each of which is optionally substituted with 1, 2, 3, or 4 substituents;

R^3 at each occurrence is independently selected from hydrogen, alkyl, heteroalkyl, haloalkyl (including -CF₃, -CHF₂, -CH₂F, -CH₂CF₃, -CH₂CH₂F, and -CF₂CF₃), arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, -OR⁸, and -NR⁸R⁹;

R^4 is independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, -OR⁶, -NR⁶R⁷, C(O) R^3 , S(O) R^3 , C(S) R^3 , and S(O)₂ R^3 ;

R^6 and R^7 are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, haloalkyl, heteroaryl, heterocycle, -alkyl-OR⁸, -alkyl-NR⁸R⁹, C(O) R^3 , S(O) R^3 , C(S) R^3 , and S(O)₂ R^3 ;

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

Cycle is a 3-8 membered fused cyclic group optionally substituted with 1, 2, 3, or 4 substituents,

each Linker^A is a bond or a moiety that covalently links the ASGPR ligand to Linker^B;

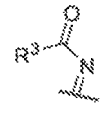
Linker^B is a bond or a moiety that covalently links Linker^A to an Extracellular Protein Targeting Ligand;

Linker^C is a chemical group that links each Linker^A to the Extracellular Protein Targeting Ligand; and

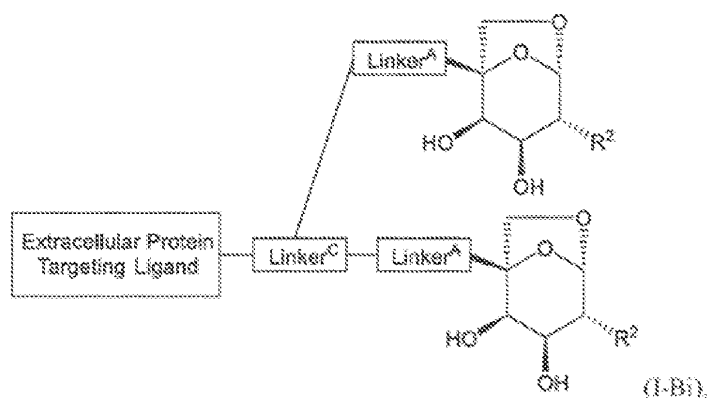
Linker^D is a chemical group that links each Linker^A to the Extracellular Protein Targeting Ligand; and

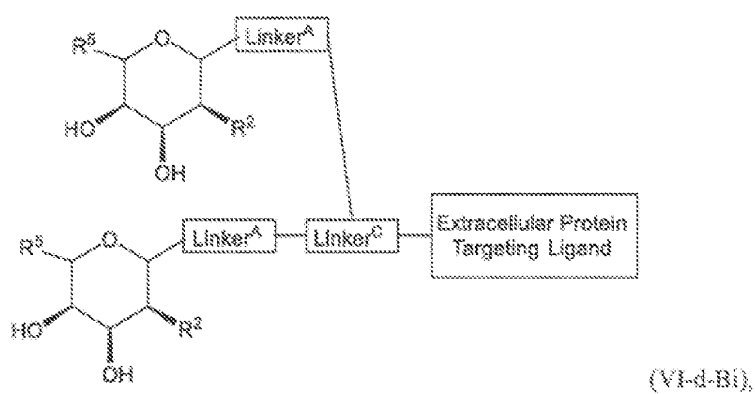
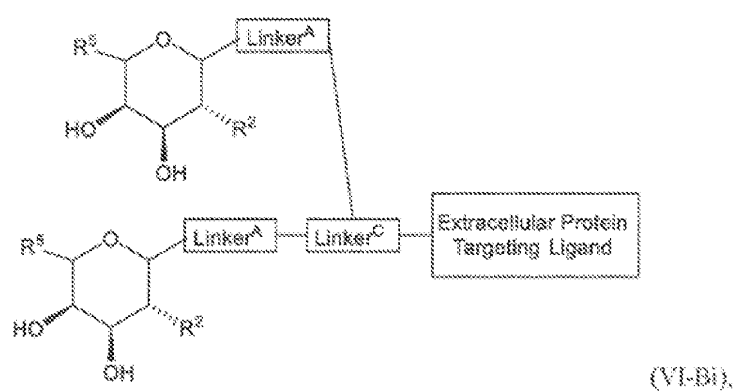
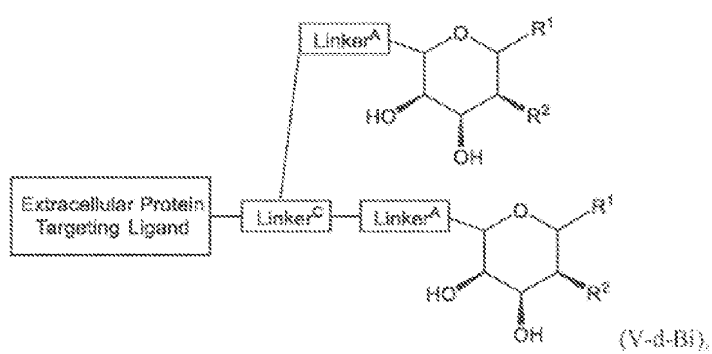
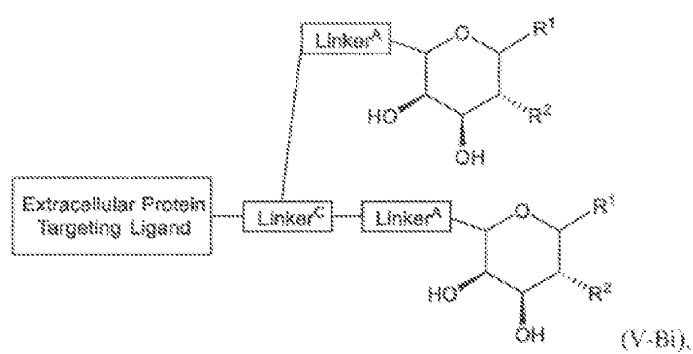
wherein, when R² is NR⁶-alkenyl, -NR⁷-alkynyl, -NR⁸-C(O)R¹⁰, -NR⁸-S(O)₂-alkenyl, -NR⁸-S(O)₂-alkynyl, -NR⁶-heteroaryl, or -NR⁶-aryl, then Extracellular Protein Targeting Ligand does not comprise an oligonucleotide; and

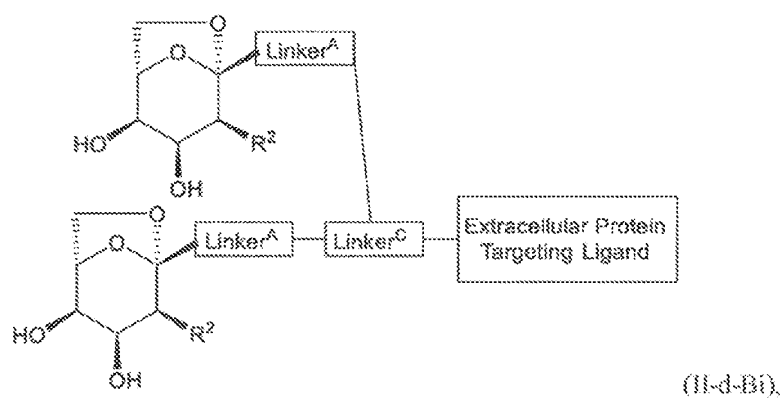
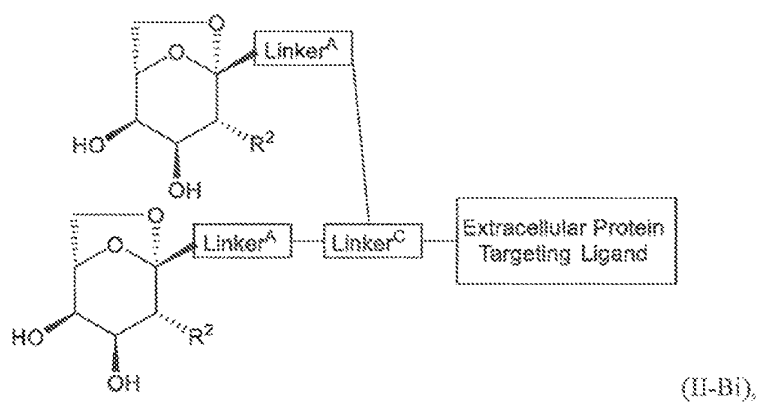
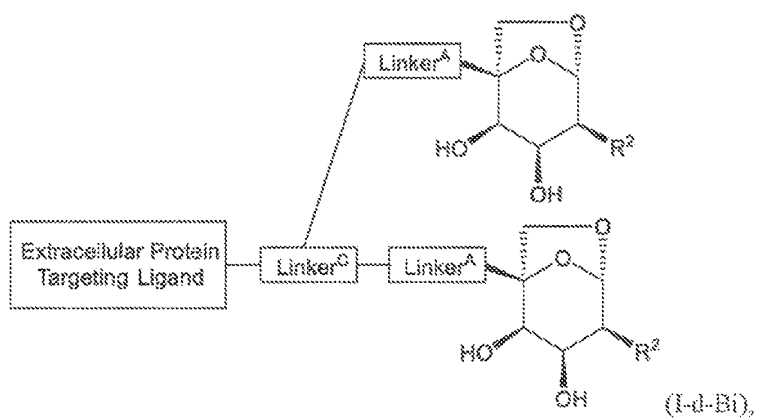
the optional substituents are selected from alkyl, alkenyl, alkynyl, haloalkyl, -OR⁶, F, Cl,

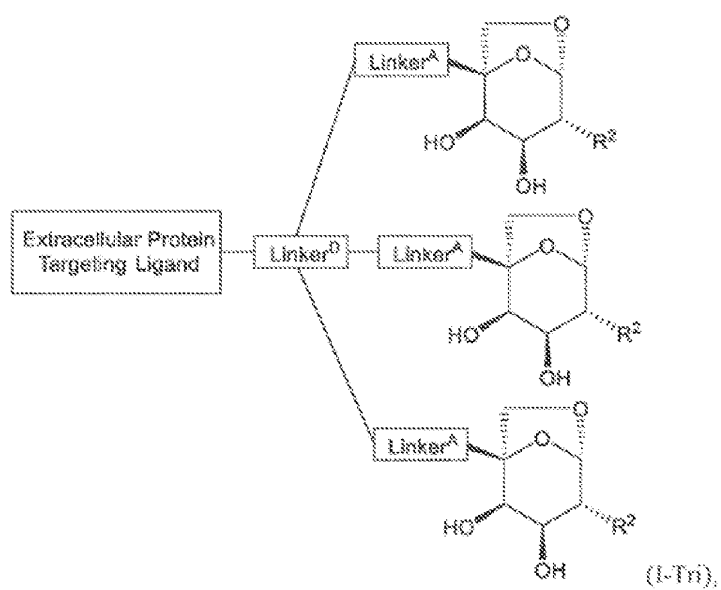
Br, I, -NR⁶R⁷, heteroalkyl, cyano, nitro, C(O)R³, , , , and , as allowed by valence such that a stable compound results.

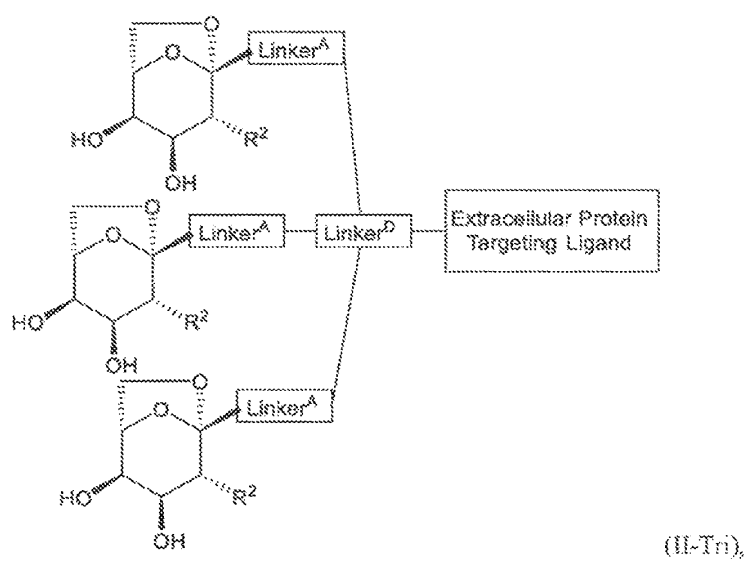
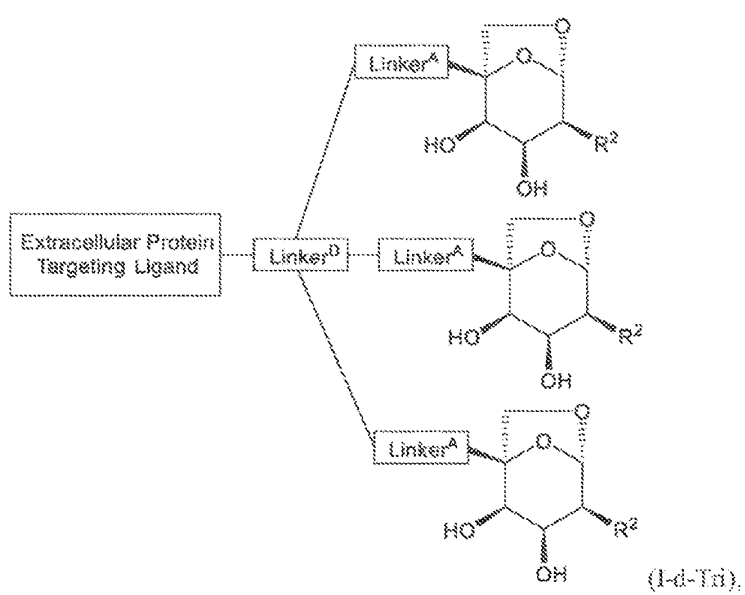
2. The bifunctional compound of claim 1, which is selected from the group consisting of:

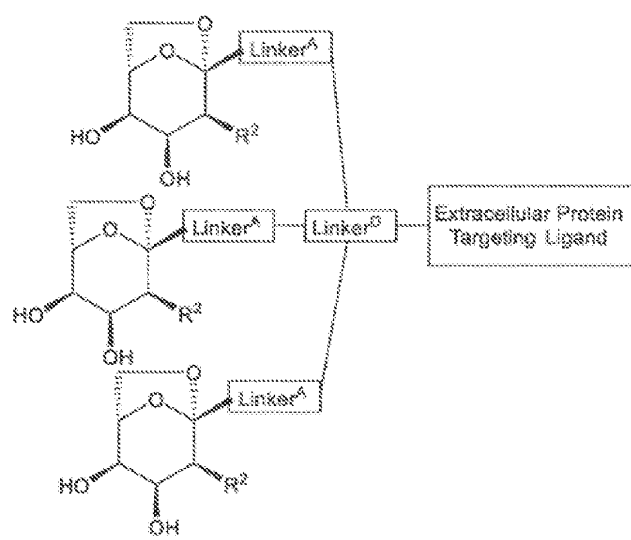




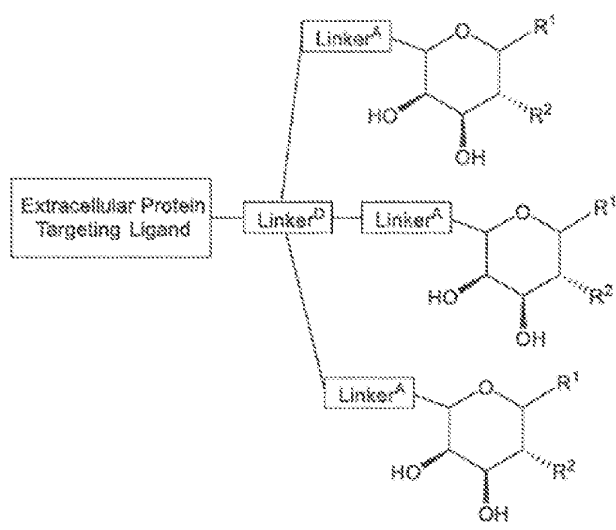




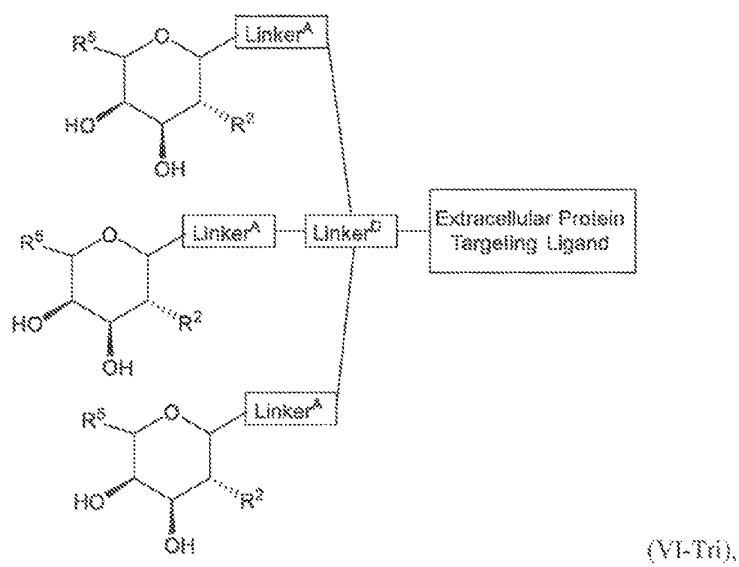
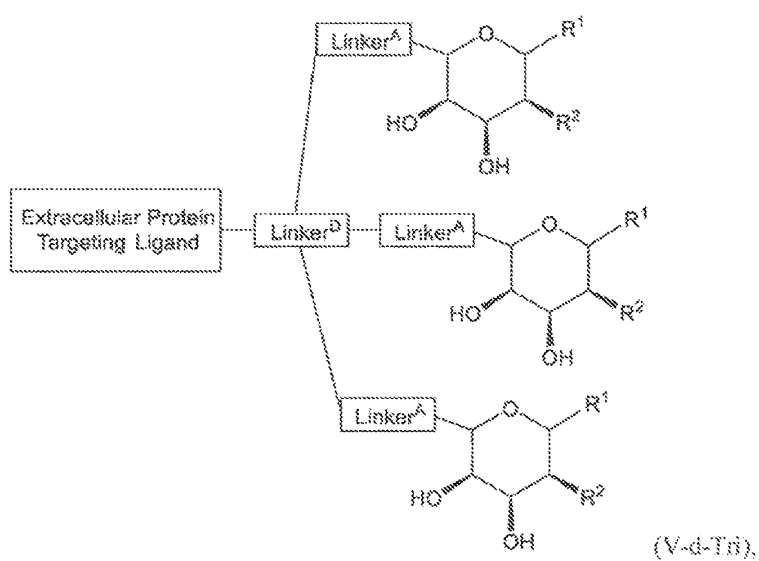




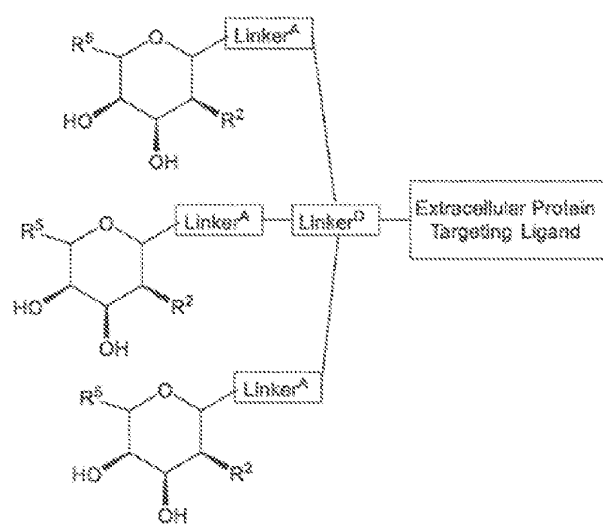
(II-d-Tri).



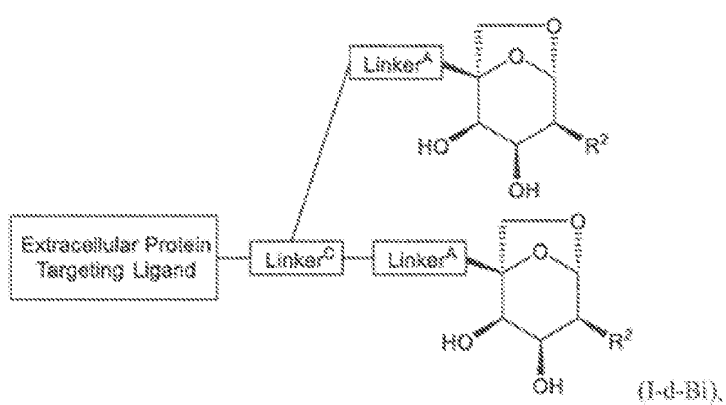
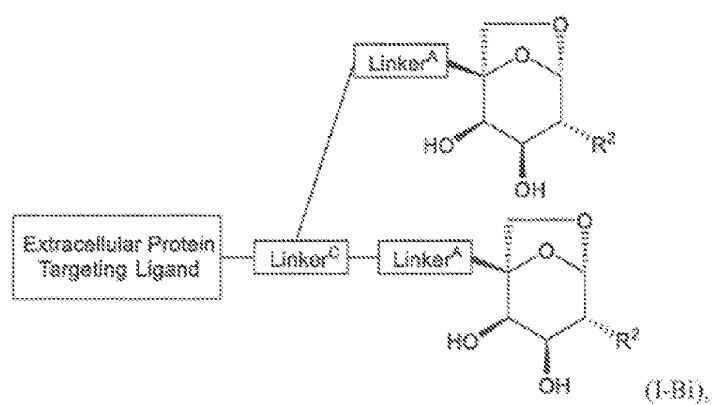
(V-Tri).

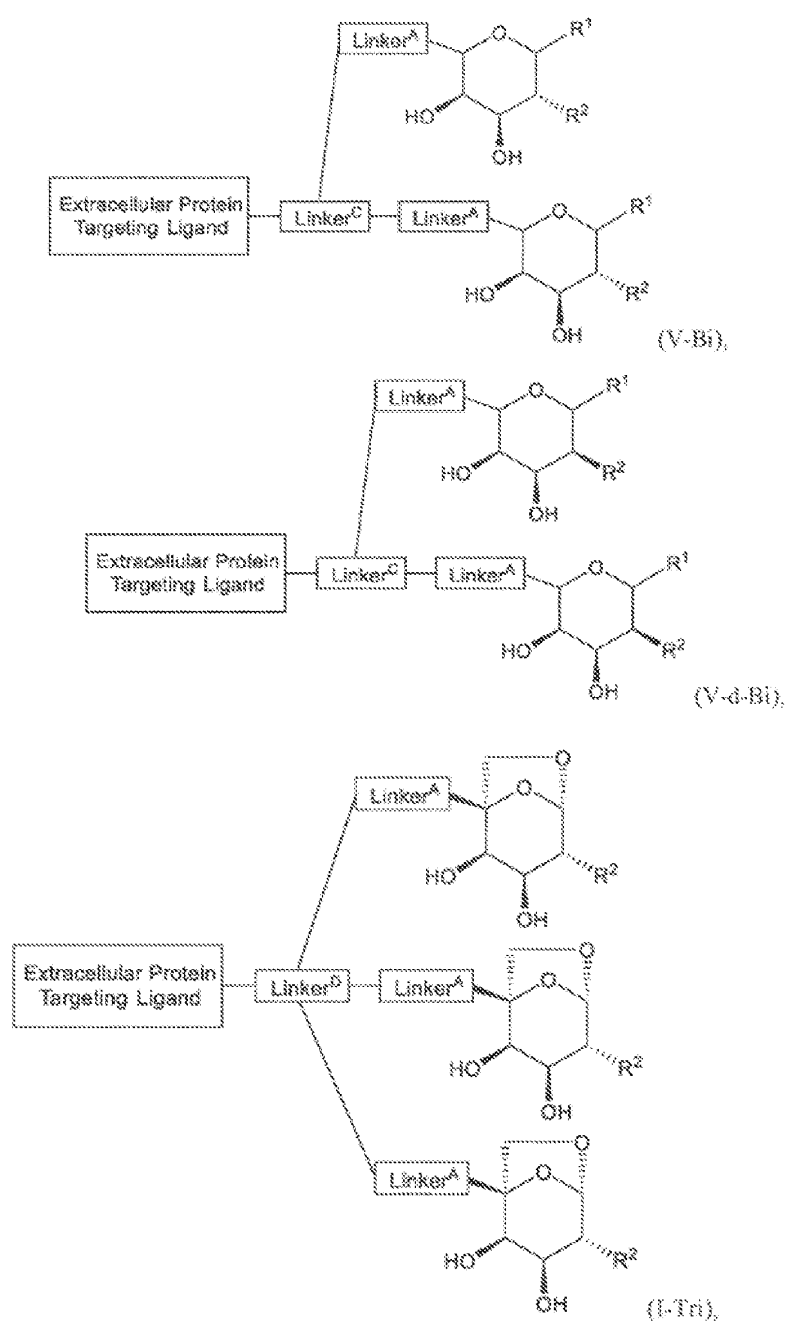


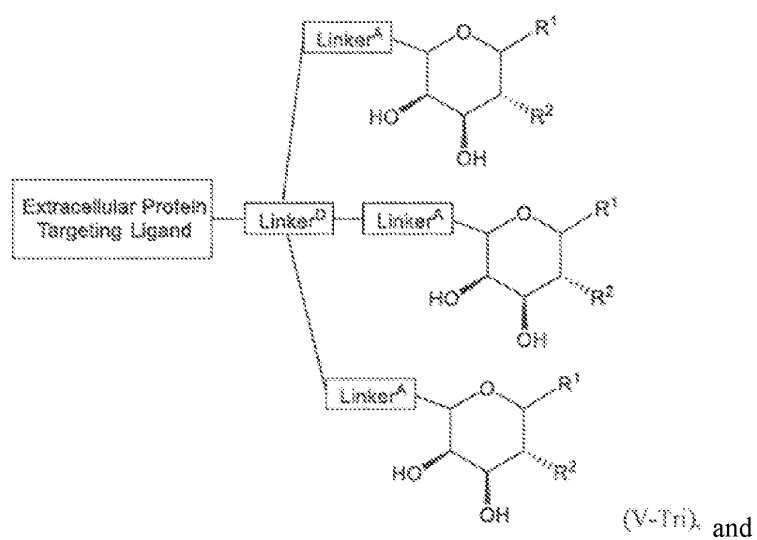
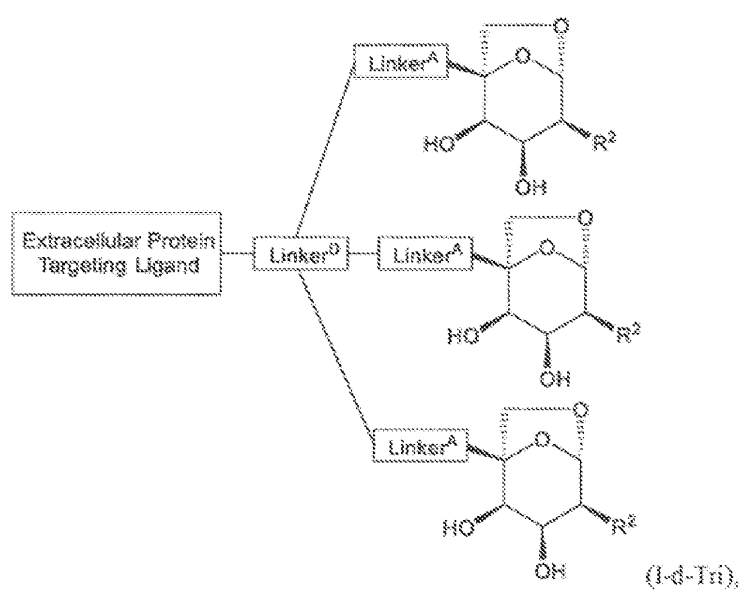
and

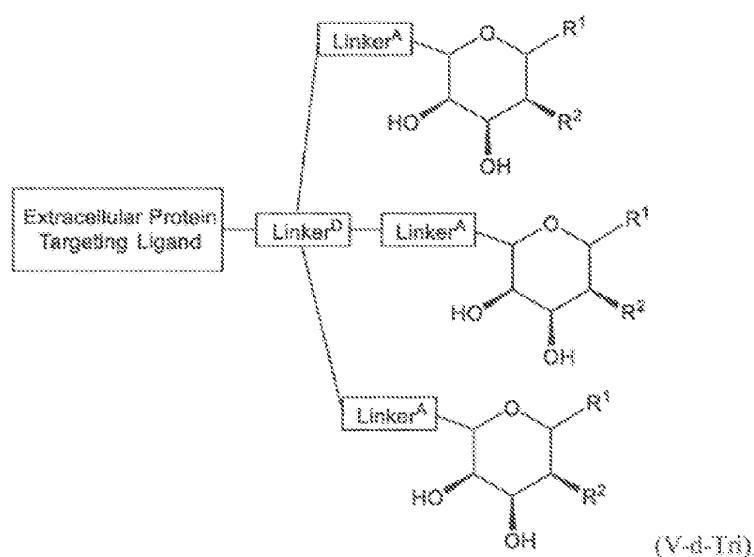


3. The bifunctional compound of claim 1, which is selected from the group consisting of:

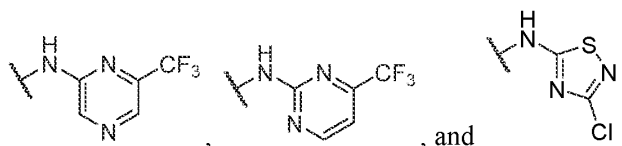








4. The bifunctional compound of any one of claims 1-3, wherein R^1 is H.
5. The bifunctional compound of any one of claims 1-4, wherein R^2 is R^{10} .
6. The bifunctional compound of any one of claims 1-5, wherein R^{10} is $-NR^6$ -heteroaryl.
7. The bifunctional compound of any one of claims 1-6, wherein R^6 is H.
8. The bifunctional compound of any one of claims 1-7, wherein $-NR^6$ -heteroaryl is selected from the group consisting of:



9. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is a MIF binding moiety.
10. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is an IgG binding moiety.
11. The bifunctional compound of any one of claims 1-8, wherein the Extracellular

Protein Targeting Ligand is a CD40L binding moiety.

12. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is a TNFalpha binding moiety.

13. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is a PCSK9 binding moiety.

14. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is a VEGF binding moiety.

15. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is a TGFbeta binding moiety.

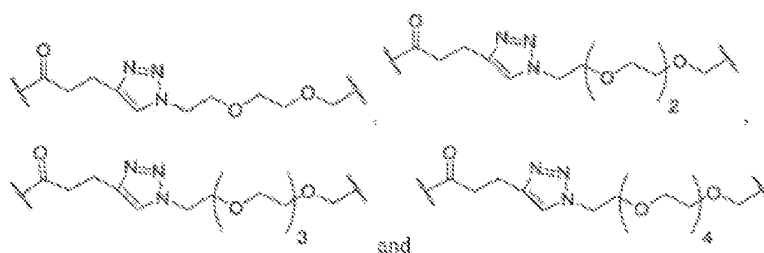
16. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is a TSP-1 binding moiety.

17. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is a uPAR binding moiety.

18. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is a PSMA binding moiety.

19. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is an IL-2 binding moiety.

20. The bifunctional compound of any one of claims 1-19, wherein Linker^A is selected from the group consisting of



21. A pharmaceutical composition comprising a therapeutically effective amount of a bifunctional compound of any one of claims 1-20 and a pharmaceutically acceptable carrier, additive, or excipient,

optionally further comprising an additional bioactive agent that is effective to treat, ameliorate, and/or prevent cancer, autoimmune disease, or inflammatory disease in a patient or that is associated with the upregulation of a circulating protein in the patient.

22. The composition of claim 21, wherein at least one applies:

- (a) the circulating protein is MIF, IgG, CD40L, TNFalpha, PCSK9, VEGF, TGFbeta, TSP-1, uPAR, PSMA, or IL-2;
- (b) the composition comprises an additional anticancer agent selected from the group consisting of: everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhibitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab (Arzerra), zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, ginatecan, IL13-PE38QQR, INO 1001, IPdR₁ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel,

atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib, PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrozole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)-indolyl]-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D-Ser(Bu t) 6, Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH₂ acetate [C₅₉H₈₄N₁₈Oi₄-(C₂H₄O₂)_x where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714, TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib, amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevec, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deoxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxifene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox, gefitinib, bortezomib, paclitaxel, irinotecan, topotecan,

doxorubicin, docetaxel, vinorelbine, bevacizumab, erbitux, cremophor-free paclitaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zoledronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11 , dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa and darbepoetin alfa, vemurafenib, immunotherapy agents PDL1 inhibitors, PD1 inhibitors, and CTLA-4 inhibitors.

23. A method of treating, ameliorating, and/or preventing a disease state or condition which is associated with the upregulation of a circulating protein in a patient or subject, the method comprising:

administering to the patient or subject a therapeutically effective amount of a bifunctional compound of any one of claims 1-20, wherein the circulating protein is MIF, IgG, CD40L, TNFalpha, PCSK9, VEGf, TGFbeta, TSP-1, uPAR, PSMA or IL-2.

24. The method of claim 23, wherein the disease state or condition is cancer, an autoimmune disease, or an inflammatory disease.

25. The method of claim 24,

wherein the disease state or condition is systemic lupus erythematosus, Sjogren syndrome, Hashimoto thyroiditis, rheumatoid arthritis, juvenile (type 1) diabetes, polymyositis, scleroderma, Addison's disease, vitiligo, pernicious anemia, glomerulonephritis, pulmonary fibrosis, Autoimmune polyendocrine syndrome (APS) types 1, 2 and 3, autoimmune pancreatitis (AIP), diabetes mellitus type 1, autoimmune thyroiditis, Ord's thyroiditis, Grave's disease, autoimmune oophoritis, endometriosis, autoimmune orchitis, Sjogren's syndrome, autoimmune enteropathy, coeliac disease, Crohn's disease, microscopic colitis, ulcerative colitis, autophospholipid syndrome (APIS), aplastic anemia, autoimmune hemolytic anemia, autoimmune lymphoproliferative syndrome, autoimmune neutropenia, autoimmune thrombocytopenic purpura, cold agglutinin disease, essential mixed cryoglobulinemia, Evans syndrome, pernicious anemia, pure red cell aplasia, thrombocytopenia, adiposis dolorosa, adult-onset Still's disease, ankylosing spondylitis, CREST syndrome, drug-induced lupus, enthesitis-related arthritis, eosinophilic fasciitis, Felty syndrome, AgG4-related disease, juvenile arthritis, Lyme disease (chronic), mixed connective tissue disease (MCTD), palindromic rheumatism, Parry Romberg syndrome, Parsonage-Turner syndrome, psoriatic arthritis, reactive arthritis, relapsing polychondritis, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schnitzler syndrome, systemic lupus erythematosus, undifferentiated connective tissue disease (UCTD), dermatomyositis, fibromyalgia, myositis, inclusion body myositis, myasthenia gravis, neuromyotonia, paraneoplastic cerebellar degeneration, polymyositis, acute disseminated encephalomyelitis (ADEM), acute motor axonic neuropathy, anti-NMDA receptor encephalitis, Balo concentric sclerosis, Bickerstaff's encephalitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, Hashimoto's encephalopathy, idiopathic inflammatory demyelinating diseases, Lambert-Eaton myasthenic syndrome, multiple sclerosis, pattern II, Oshtoran Syndrome, Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS), progressive inflammatory neuropathy, restless leg syndrome, stiff person syndrome, Sydenham chorea, transverse myelitis, autoimmune retinopathy, autoimmune uveitis, Cogan syndrome, Graves ophthalmopathy, intermediate uveitis, ligneous conjunctivitis, Mooren's ulcer, neuromyelitis optica, opsoclonus myoclonus syndrome, optic neuritis, scleritis, Susac's syndrome, sympathetic ophthalmia, Tolosa-Hunt syndrome, autoimmune inner ear disease (AIED), Ménière's disease, Bechet's disease, Eosinophilic granulomatosis with polyangiitis (EGPA), giant cell arteritis, granulomatosis with polyangiitis (GPA), IgA vasculitis (IgAV), Kawasaki's disease, leukocytoclastic vasculitis,

lupus vasculitis, rheumatoid vasculitis, microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), polymyalgia rheumatica, urticarial vasculitis, vasculitis, primary immune deficiency, chronic fatigue syndrome, complex regional pain syndrome, eosinophilic esophagitis, gastritis, interstitial lung disease, POEMS syndrome, Raynaud's syndrome, primary immunodeficiency, and pyoderma gangrenosum, or

wherein the disease state or condition is Alzheimer's disease, Parkinson's disease, Huntington's disease, other ataxias, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, lupus, multiple sclerosis, chronic obstructive pulmonary disease/COPD, pulmonary fibrosis, cystic fibrosis, Sjogren's disease, hyperglycemic disorders, diabetes (I and II), pancreatic β -cell death and related hyperglycemic disorders, including severe insulin resistance, hyperinsulinemia, insulin-resistant diabetes, dyslipidemia, metabolic syndrome, liver disease, renal disease, cardiovascular disease, muscle degeneration and atrophy, low grade inflammation, gout, silicosis, atherosclerosis and associated conditions, stroke, age-associated dementia, sporadic form of Alzheimer's disease, depression, stroke, spinal cord injury, and arteriosclerosis.

26. A method of removing excess circulating protein in a patient or subject, the method comprising:

administering to the patient or subject a therapeutically effective amount of a bifunctional compound of any one of claims 1-20, wherein the circulating protein is MIF, IgG, CD40L, TNF α , PCSK9, VEGf, TGF β , TSP-1, uPAR, PSMA or IL-2.