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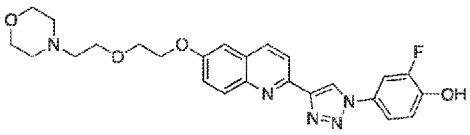
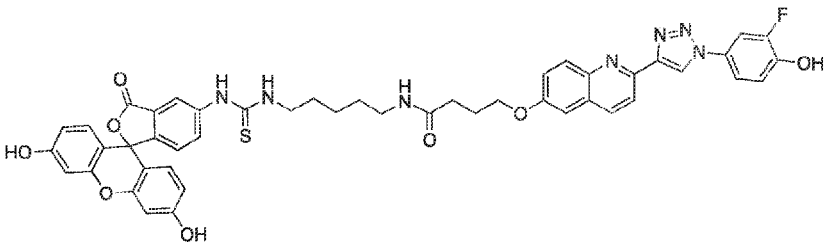
(54) Title: BI-FUNCTIONAL MOLECULES TO DEGRADE CIRCULATING PROTEINS

FIGURE 1



3w (negative control MIF inhibitor)



MIF-FITC (fluorescent MIF binder)

(57) Abstract: Described herein is a bi-functional compound for removing macrophage migration inhibitory factor (MIF) or immunoglubin G (IgG). Further described herein is a pharmaceutical composition which comprise these bi-functional compounds. Further described herein is a method for treating disease states and/or conditions with the compounds or the composition. The disease states and/or conditions are mediated through MIF/IgG or where MIF/IgG is a contributing factor to the development and perpetuation of diseases and/or conditions, such as autoimmune diseases and cancer, among others.

[Continued on next page]

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26 October 2023 (26.10.2023)

TITLE

BI-FUNCTIONAL MOLECULES TO DEGRADE CIRCULATING PROTEINS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Application No. 17/695,259, filed March 15, 2022, which application is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

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

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 12, 2023, is named 47162-7240WO2_Sequence Listing.xml and is 30.8 kilobytes in size.

BACKGROUND

MIF is a proinflammatory pluripotent cytokine which contributes to the development and perpetuation of many diseases. These include atherosclerosis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), sepsis, inflammatory bowel disease (IBD), among others. In addition, MIF has been shown to participate in the progression of various cancers, including colon cancer, prostate cancer, breast cancer, lung cancer, cervical and adenocarcinoma, among others. In pre-clinical models, inhibition of MIF has been shown to attenuate symptoms and delay disease progression in the above-mentioned diseases.

MIF and IgG significantly contribute to the pathologic process of a number of diseases. MIF neutralizing antibodies and small molecule MIF inhibitors have been developed, where IgG is upregulated in autoimmune and other diseases and causes untoward effects. Because MIF acts through various pathways, a MIF inhibitor is sometimes required to be able to interrupt multiple protein-protein interactions (PPIs), posing a challenge for drug development. In the case of IgG, the removal of IgG molecules which are upregulated and contributing to autoimmune and/or other diseases is sometimes useful to inhibit and/or

ameliorate the effects of the disease state. Therefore, a novel approach where MIF or IgG can be degraded as well as inhibited can overcome this difficulty and potentially provide a more robust therapeutic response. Encouraged by preliminary results with bi-functional MIF and IgG degraders, the present inventors decided to further test them in clinical-relevant *in vivo* models and potentially develop them into therapeutics that target MIF or IgG in diseases. They also intend to use this basic bifunctional molecule strategy to target other circulating proteins of interest to degradation via the ASGPr.

Therefore, there is a need for molecules that can eliminate MIP and/or IgG. The present disclosure addresses this need.

BRIEF SUMMARY

In some aspects, the present disclosure is directed to bifunctional small molecules which can be used to inhibit and remove MIF or IgG. In some embodiments, the present disclosure aims to establish a general small molecule strategy to target the selective degradation of MIF or IgG, which contributes to the development and perpetuation of many diseases. In some embodiments, the bifunctional molecule construct contains a MIF binding motif derived from known small molecule ligands of MIF of a IgG binding motif which comprises a ligand which binds IgG. These moieties are referred to herein generically as macrophage migration inhibitory factor binding moiety (MIFBM) or alternatively, immunoglobulin G binding moiety (IgGBM). In some embodiments, the other end of the bifunctional molecule is a motif that binds to hepatocyte asialoglycoprotein receptor (ASGPr), which is a triantennary N-acetylgalactosamine or other moiety as described herein. The instant specification sometimes refer to these moieties generically as asialoglycoprotein receptor binding moiety (ASGPRBM). The motifs which are used to provide bifunctional compounds according to some embodiments, (MIFBM or IgGBM) and (ASGPRBM), are covalently linked via a linker such as a polyethylene glycol (PEG) or other linker as described herein with adjustable length or other linker as described herein, which optionally contains one or more connector molecule(s) which connects the linker to the MIFBM or IgGBM and/or the ASGPRBM.

In some embodiments, thje bifunctional compounds selectively bind to MIF or IgG in circulation and form a protein complex. When this protein complex passes through the liver, the asialoglycoprotein receptor binding moiety of the molecule (ASGPRBM), such as a triantennary N-Acetylgalactosamine or other motif as described herein, will engage the endo-lysosomal pathway of hepatocytes through the ASGPr. As a consequence of this mechanism,

MIF or IgG is eliminated from circulation by hepatocytes, thus resulting in lowered levels of MIF or IgG with the result being that corresponding disease symptoms are attenuated and/or eliminated from a patient or subject administered the present compounds. In certain instances, the MIF is substantially reduced or eliminated or the compromising IgG substantially reduced, 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 MIF or IgG of the prior art. The small molecule based approach of the current disclosure overcomes the limitations of traditional antibody-based strategies, including lack of oral bioavailability, low-temperature storage requirements, immunogenicity, and high-cost.

Furthermore, the compounds and methods of the present disclosure are expected to have a more lasting effect compared to the conventional inhibitory approach because MIF or IgG is substantially reduced or 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 states and/or conditions can be targeted by inhibiting and degrading MIF or IgG. Thus, previously discovered non-inhibitory protein binders, presently of little value in therapy, 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 [MIFBM/IgGBM] is a MIF or IgG binding moiety which binds respectively to circulating MIF or IgG, which are related to a disease state and/or condition and is to be removed by the action of hepatocytes on circulating protein (in some embodiments, the compounds selectively bind to MIF or IgG in plasma);

[ASGPRBM] is a binding moiety which binds to hepatocytes through asialoglycoprotein receptors which are on the surface of hepatocytes, such as in a patient or subject;

each [CON] is an optional connector chemical moiety which, when present, connects

directly to [MIFBM/IgGBM] or to [ASGPRBM] or connects the [LINKER] to [MIFBM/IgGBM] or to [ASGPRBM] and

[LINKER] is a chemical moiety having a valency ranging from 1 to 15, such as ranging from 1 to 10, ranging from 1 to 5 or 1, 2 or 3, which covalently attaches to one or more [ASGPRM] and/or [MIFBM/IgGBM] 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 ranging from 1 to 15, such as ranging from 1 to 10, ranging from 1 to 5, ranging from 1 to 3 or 1, 2 or 3;

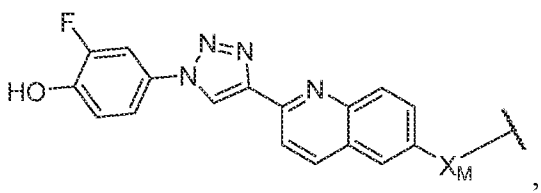
j' is an integer ranging from 1 to 15, such as ranging from 1 to 10, ranging from 1 to 5, ranging from 1 to 3 or 1, 2 or 3;

h and h' are each independently an integer ranging from 0 to 15, such as ranging from 1 to 15, ranging from 1 to 10, ranging from 1 to 5, ranging from 1 to 3 or 1, 2 or 3, optionally h and/or h' is at least 1;

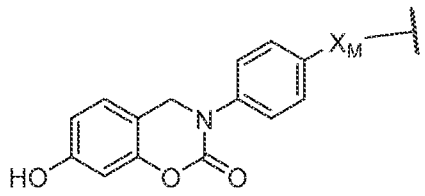
i_L is an integer ranging from 0 to 15, such as ranging from 1 to 15, ranging from 1 to 10, ranging from 1 to 5, ranging from 1 to 3, or 1, 2 or 3, optionally i_L is an integer ranging from 1 to 5 or 1, 2 or 3 with the proviso that at least one of h, h' and i_L is at least 1, or

a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

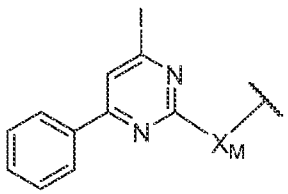
In some embodiments [MIFBM] is a moiety according to the chemical structure:



,



,or



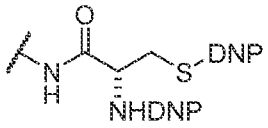
;

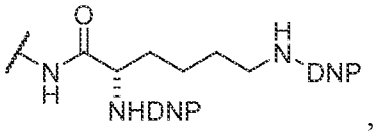
wherein X_M is $-(CH_2)_{IM}$, $-O-(CH_2)_{IM}$, $S-(CH_2)_{IM}$, $NR_M-(CH_2)_{IM}$, $C(O)-(CH_2)_{IM}-$, a polyethylene glycol (PEG) group containing from 1 to 8, such as 1-4 ethylene glycol residues or a $-C(O)(CH_2)_{IM}NR_M$ group;

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

IM is 0-6, such as 1, 2, 3 or 4, such as 1.

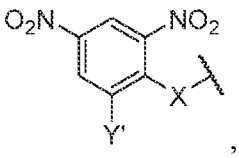
In some embodiments, [IgGMB] is a group according to the chemical structure:



or


,

wherein DNP is a 2,4-dinitrophenyl group; or

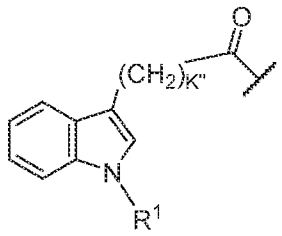
a group according to the chemical structure: 

,

wherein Y' is H or NO_2;

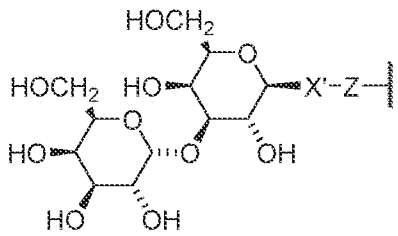
X is O, CH_2, NR^1, S(O), $S(O)_2$, -$S(O)_2O$, -$OS(O)_2$, or $OS(O)_2O$; and

R^1 is H, a C_1-C_3 alkyl group, or a -C(O)(C_1-C_3) group; or

a group according to the chemical structure: 

wherein R^1 is the same as above; and

K" is 1-5 (such as 3-5, such as 4), or

a group represented by the chemical formula: 

;

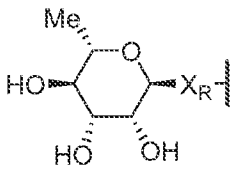
wherein X' is CH_2, O, N-$R^{1'}$, or S;

$R^{1'}$ is H or C_1-C_3 alkyl; and

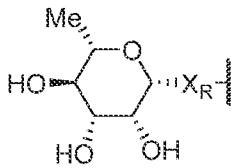
Z is a bond, a monosaccharide, disaccharide, oligosaccharide, such as a sugar group selected from the monosaccharides, including aldoses and ketoses, and disaccharides, including those disaccharides described herein. Monosaccharide aldoses include monosaccharides such as aldotriose (D-glyceraldehdye, 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 (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 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 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), gentiobiluose (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.

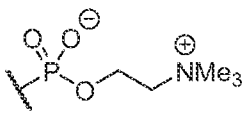
In some embodiments [IgGBM] is a group according to the chemical structure:



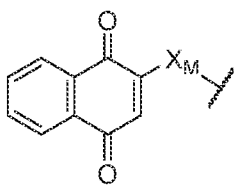
α-L-Rhamnose



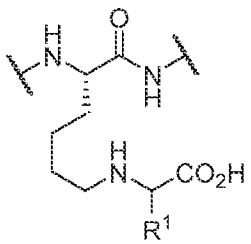
β-L-Rhamnose



Phosphoryl Choline



Menadione



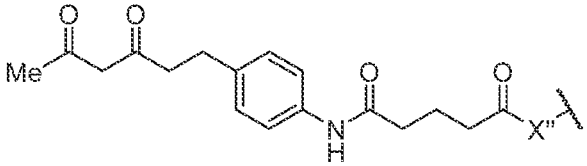
Carboxyethyl Lysine (R^1 = Me)

wherein X_R is O, S or NR^1; and

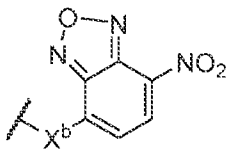
X_M is O, NR^1 or S, and

R^1 is H or a C_1-C_3 alkyl group.

In some embodiments [IgGBM] is a group according to the chemical structure:



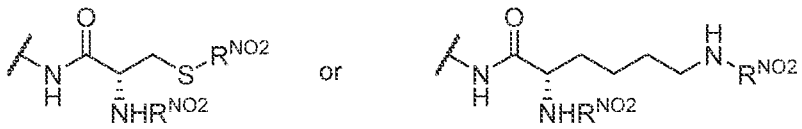
wherein X" is O, CH_2, NR^1, S; and

R^1 is H, a C_1-C_3 alkyl group or a -C(O)(C_1-C_3) group; or 

wherein X^b is a bond, O, CH_2 or NR^1 or S; and

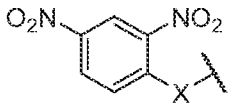
R^1 is the same as above; or

a group according to the chemical structure:



where R^{N02} 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

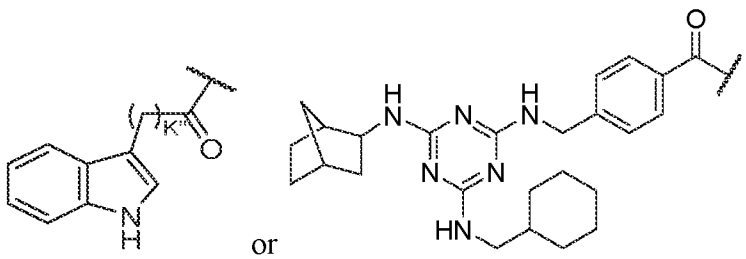
a dinitrophenyl group according to the chemical structure:



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.

In some embodiments [IgGBM] is a group according to the chemical structure:



where K'" is 1-4 (such as 2-3, such as 3), or a

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 [ASGPRBM] group through an amine group, such as a primary or secondary alkyl amine group which is

optionally substituted on the amine group with a C_1-C_3 alkyl group.

In some embodiments [IgGBM] is a peptide according to the sequence (all references cited are incorporated by reference herein):

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);

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);

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;

HFRRHL (Menegatti, et al., *J. Chromatogr.* A 2016, 1445, 93–104) SEQ IDNO: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, 158–167);

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);

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;

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;

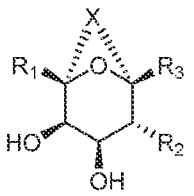
FYCHTIDE (Zhao, et al., *J. Chromatogr.* A 2014, 1359, 100–111) SEQ ID NO:16;

Dual 1/3 (Zhao, et al., *J. Chromatogr.* A 2014, 1369, 64–72);

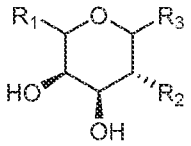
RRGW (Tsai, et al., *Anal. Chem.* 2014, 86, 2931–2938) SEQ ID NO:17;

KHRFNKD (Yoo and Choi, *BioChip J.* 2015, 10, 88–94) SEQ ID NO:18;

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



or



where X is 1-4 atoms in length and comprises O, S, $N(R^{N1})$ or $C(R^{N1})(R^{N1})$ groups such that

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

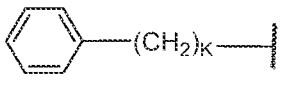
when X is 2 atoms in length, no more than 1 atom of X is O, S or $N(R^{N1})$,

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

where R^{N1} is H or a C_1-C_3 alkyl group optionally substituted with from 1-3 halo groups, such as F (in some embodiments, R^{N1} is H or methyl);

R_1 and R_3 are each independently H, -$(CH_2)_K$OH, -$(CH_2)_K$OC_1-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups,

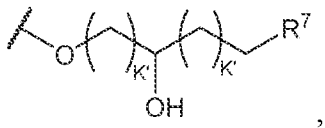
-$(CH_2)_K$vinyl, O-$(CH_2)_K$vinyl, -$(CH_2)_K$alkynyl, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, O-C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, -C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, or

R_1 and R_3 are each independently a 

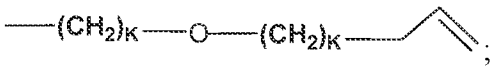
group, which is optionally substituted with up to three (such as 1) halo groups (such as F), C_1-C_4 alkyl groups, each of which is optionally substituted with from one to three halo groups, such as F, or one or two hydroxyl groups, or O-C_1-C_4 alkyl groups, each of which alkyl groups is optionally

substituted with from one to three halo groups, such as F, or one or two hydroxyl groups, and K is independently an integer ranging from 0-4 (such as 0, 1, 2, 3 or 4), or

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

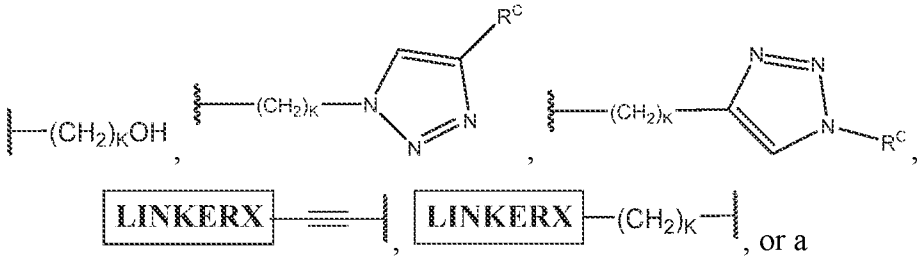


, where R^7 is O-C_1-C_4 alkyl, which is optionally substituted with from 1 to 3 halo groups, such as F and 1 or 2 hydroxy groups, or R^7 is a $-NR^{N3}R^{N4}$ group or a

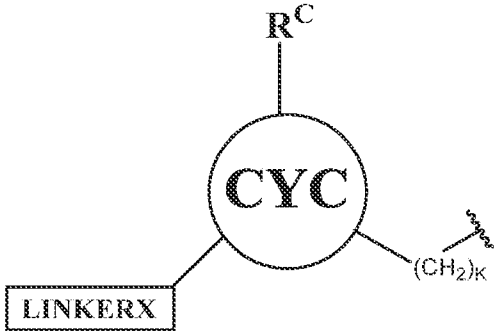


;

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

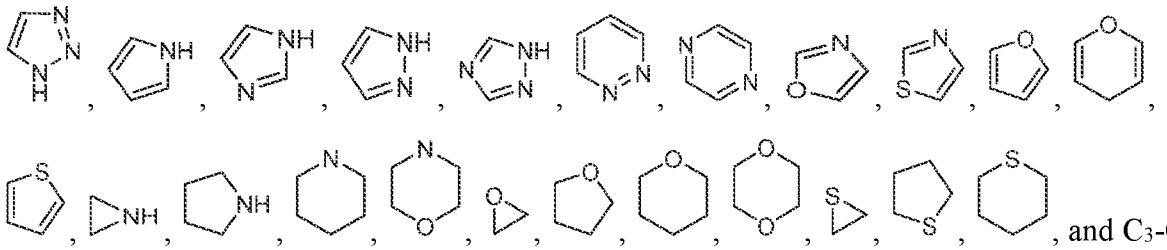


, or a



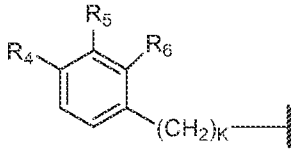
group,

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



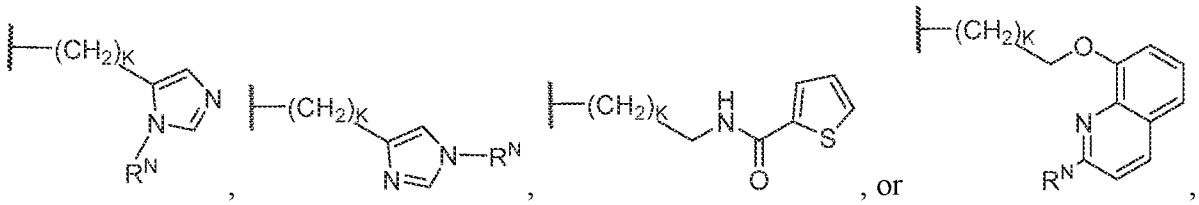
, and C_3-C_8 saturated carbocyclic, wherein each of LINKERX, R^C, and $-(CH_2)_K$- are attached to an open valence in CYC, including N-H;

R^C is absent, H, C_1-C_4 alkyl which is optionally substituted with from 1-3 halo (such as F) groups or 1-2 hydroxyl groups, or a group according to the structure:



where R_4, R_5 and R_6 are each independently, H, halo (F, Cl, Br, I), CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KOC_1$-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, I) groups, C_1-C_3 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, I) groups, -O-C_1-C_3-alkyl, which is optionally substituted with from 1-3 halo, such as F groups, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O$-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, O-C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, -C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, or

R^C is

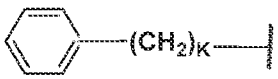


where R^N, R^{N1} and R^{N2} are each independently H or a C_1-C_3 alkyl group which is optionally substituted with from one to three halo groups, such as F, or one or two hydroxyl groups;

K is independently an integer ranging from 0-4 (0, 1, 2, 3 or 4);

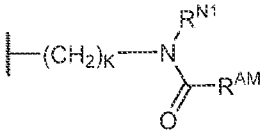
K' is an integer ranging from 1-4, such as 1;

R^{N3} is H, or a C_1-C_3 alkyl group which is optionally substituted with 1-3 halo groups, such as F or 1 or 2 hydroxy groups; and

R^{N4} is H, a C_1-C_3 alkyl group which is optionally substituted with 1-3 halo groups, such as F or 1 or 2 hydroxy groups, or R^{N4} is a  group, where K is sometimes 1;

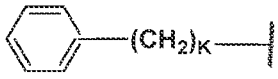
LINKERX is a linker group which is comprises to at least one [MIFBM/IgGBM] group and links the [MIFBM/IgGBM] group to the [ASGPRBM] through one or more optional [CON] groups, or

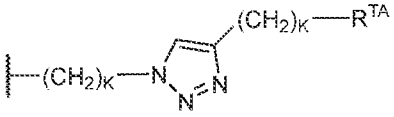
LINKERX is a linker group which contains at least one or more functional groups which can be used to covalently bond the linker group to at least one [MIFBM/IgGBM] group or optional [CON] group;

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

R^{AM} is H, a C_1-C_4 alkyl group optionally substituted with up to 3 halo groups (such as F) and one or two hydroxyl groups, a -$(CH_2)_K$COOH group, a -$(CH_2)_K$C(O)O-C_1-C_4 alkyl group which is optionally substituted with from 1-3 halo, such as F groups, a

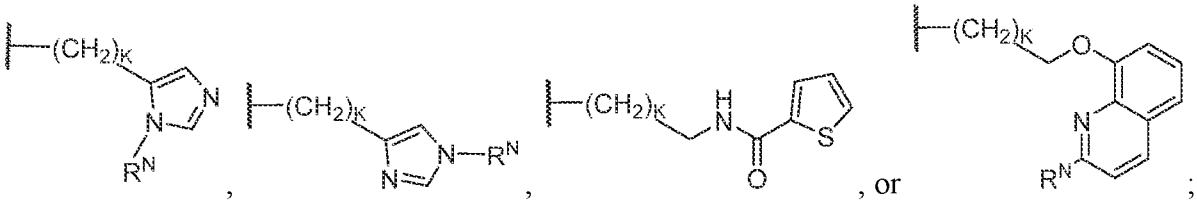
O-C(O)-C_1-C_4 alkyl group, which is optionally substituted with from 1-3 halo, such as F groups, a -C(O)-C_1-C_4 alkyl group, which is optionally substituted with from 1-3 halo, such as F groups, a -$(CH_2)_K$-$NR^{N3}R^{N4}$ group where R^{N3} is H, or a C_1-C_3 alkyl group which is optionally substituted with 1-3 halo groups, such as F or 1 or 2 hydroxy groups; and

R^{N4} is H, a C_1-C_3 alkyl group which is optionally substituted with 1-3 halo groups, such as F or 1 or 2 hydroxy groups, or R^{N4} is a  group (K is sometimes 1), or

R_2 is a  group,

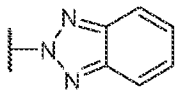
where R^{TA} is H, CN, $NR^{N1}R^{N2}$, -$(CH_2)_K$OH, -$(CH_2)_K$OC_1-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, O-C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, -C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F 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 said aryl or heteroaryl groups being optionally substituted with up to three (such as 1) CN, $NR^{N1}R^{N2}$, -$(CH_2)_K$OH, -$(CH_2)_K$OC_1-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, C_1-C_3 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups or 1 or 2 hydroxy groups, -O-C_1-C_3-alkyl, which is optionally substituted with from 1-3 halo, such as F groups, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, O-C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups or -$(CH_2)_K$C(O)-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, or

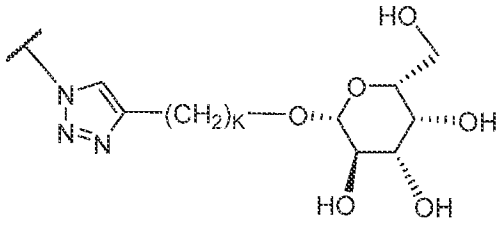
R^{TA} is



;

or

R^{TA} is a  group which is optionally substituted with up to three, such as 1 C_1-C_3 alkyl groups which are optionally substituted with up to three halo (such as F)

groups, or R^{TA} is a  group,

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 from one to three halo groups, such as F, or one or two hydroxyl groups and

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

and K is independently 0-4 (0, 1, 2, 3 or 4).

In some embodiments, [CON] is a connector moiety (including a [MULTICON]) as otherwise described herein.

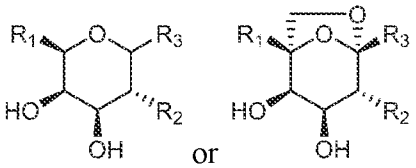
In some embodiments, [LINKER] is a linking moiety as otherwise described herein which links [MIFBM/IgGBM] to the [ASGPRBM] group and optionally contains one or more connector moieties (which optionally connect(s) more than one chemical moiety to provide said linking moiety or which connects said linking moiety to said [MIFBM/IgGBM] group or said [ASGPRBM] group, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

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

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

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

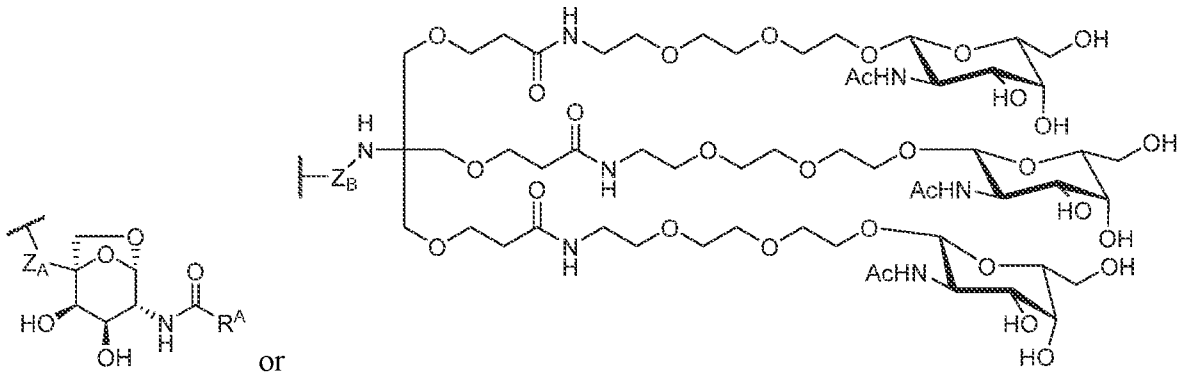
In embodiments, the [ASGPRBM] group is a group according to the chemical structure:



where R_1, R_2 and R_3 are the same as above, or

a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

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



;

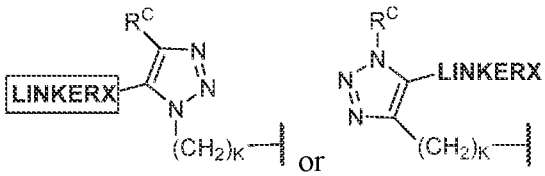
where R^A is a C_1-C_3 alkyl group which is optionally substituted with 1-5 halo (such as F) groups (In some embodiments, R^A is a methyl or ethyl group which is optionally substituted with from 1-3 fluoro groups);

Z_A is -$(CH_2)_{IM}$, -O-$(CH_2)_{IM}$, S-$(CH_2)_{IM}$, NR_M-$(CH_2)_{IM}$, C(O)-$(CH_2)_{IM}$-, a PEG group containing from 1 to 8, such as 1-4 ethylene glycol residues or a -C(O)$(CH_2)_{IM}NR_M$ group (In some embodiments, a PEG containing group comprising from 1 to 8 ethylene glycol, such as 2-4 ethylene glycol residues) 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

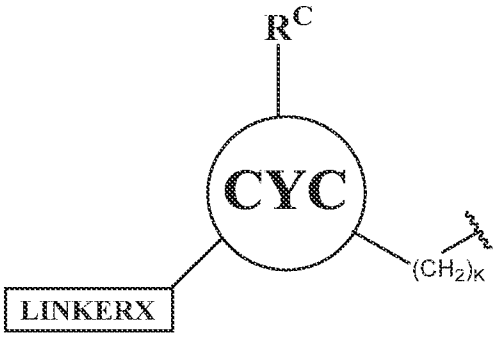
same as above.

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

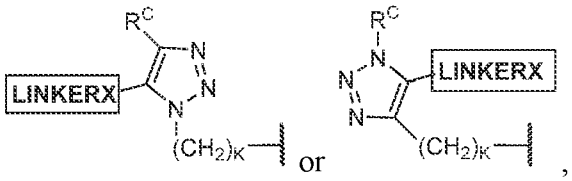


,where R^C, LINKERX and K are the same as above.

In some embodiments, in the above-described compounds,



is



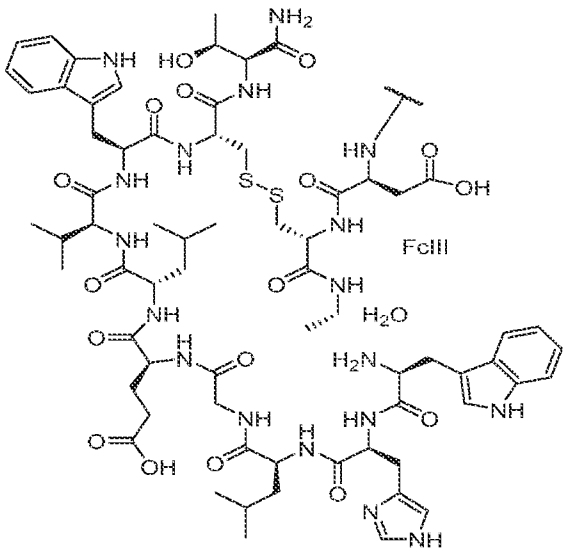
,

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

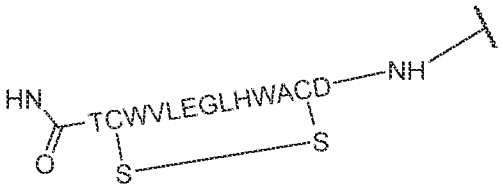
In some embodiments, the compounds include the compounds which are presented in FIGURES 1, 7 and 13. In some embodiments, additional compounds are presented in FIGURES 16-66 and include final compounds set forth therein and intermediates which are used to make final compounds pursuant to the present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

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

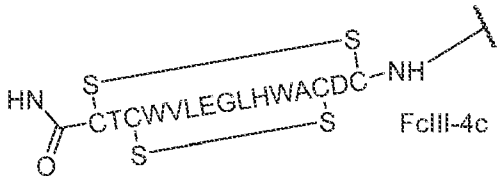
In some embodiments, the IgGBM group is a FCIII group according to the chemical



structure: FCIII, which can be represented as



(SEQ ID NO:19)

or a FcIII-4c peptide represented as 

. (SEQ ID NO:20).

In some aspects, 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 some aspects, the present disclosure is directed to a method of treating a disease state or condition where MIF is related to or contributes to a disease state and or condiiton 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. In some embodiments, the method of treatment 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 MIF associated with the disease state and/or condition from the circulation of the patient or subject.

In experiments, bi-functional molecules of the present disclosure, MIF-GN_3 were able to induce the degradation of human MIF injected in mice. Additional work focuses on the evaluation of MIF-GN_3 in autoimmune disease models as well as seeking to optimize the bi-functional MIF degrader using different MIF and ASGPr ligands. IgG-targeting molecules were able to recapitulate our results with MIF in cell culture and mediated the removal of IgG from mouse serum. Thus, the present disclosure provides a useful platform for the development of new therapeutics for these critical diseases.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 shows representative compounds according to some embodiments. 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 sometimes ranges from 1-12, such as 1 to 10, 2 to 8, 2 to 6, 2 to 5 or 1, 2, 3 or 4.

FIGURE 2 shows fluorescence polarization data of MIF-FITC binding to human MIF, indicating that our MIF-binding moiety binds MIF, in accordance with some embodiments. 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.

FIGURE 3 shows that bifunctional molecules are able to deplete human MIF from the supernatant of culture HepG2 cells, in accordance with some embodiments.

FIGURE 4 shows that MIF internalized by HepG2 cells is trafficked to lysosomes, in accordance with some embodiments.

FIGURE 5 shows that MIF-GN3 mediates the depletion of injected human MIF from mice, in accordance with some embodiments.

FIGURE 6 shows that MIF-GN3 is able to delay tumor growth in a mouse model of prostate cancer, in accordance with some embodiments.

FIGURE 7 shows molecules DNP-GN3 and DNP-AcF3-3, which are bifunctional moelcules that bind to anti-DNP IgG and ASGPR, in accordance with some embodiments.

FIGURE 8 shows that DNP-GN3 and DNP-AcF3-3 mediate the formation of a ternary complex between HepG2 cells and anti-DNP, in accordance with some embodiments.

FIGURE 9 shows that DNP-GN3 and DNP-AcF3-3 mediate the uptake of alexa 488-labeled anti-DNP by HepG2 cells, in accordance with some embodiments.

FIGURE 10 shows that DNP-GN3 and DNP-AcF3-3 mediate the localization of

alexa 568 labeled anti-DNP to late endosomes and lysosomes, in accordance with some embodiments.

FIGURE 11 shows that DNP-AcF3-3 mediates the degradation of alexa 488-labeled anti-DNP in HepG2 cells, in accordance with some embodiments.

FIGURE 12 shows that DNP-GN3 mediates the depletion of anti-DNP from mouse serum, in accordance with some embodiments.

FIGURE 13 shows the structures of IgG-degrading molecules IBA-GN3, Triazine-GN3, FcIII-GN3, and FcIII-4c-GN3, in accordance with some embodiments.

FIGURE 14 shows that FcIII-GN3 mediates the uptake of human IgG into HepG2 cells, in accordance with some embodiments. Experiment performed as described above.

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

FIGURES 16-18 show the synthesis of PEG linkers used in several molecules , in accordance with some embodiments.

FIGURES 19-21 show the synthesis of ASGPR-binding precursors and ligands used in several molecules , in accordance with some embodiments.

FIGURES 22-26 show the synthesis of valency linkers used in several molecules , in accordance with some embodiments.

FIGURES 27-28 show the synthesis of MIF ligands used in several bifunctional molecules, in accordance with some embodiments.

FIGURE 29 describes the synthesis of the bifunctional molecule MIF-NVS-PEGn-GN3, in accordance with some embodiments.

FIGURE 30 describes the synthesis of bifunctional molecules MIF-GN3 and MIF-PEGn-GN3, in accordance with some embodiments.

FIGURE 31 describes the synthesis of the bifunctional molecule targeting MIF and ASGPR, containing one bicyclic ASGPR AcF3 ligands, in accordance with some embodiments.

FIGURE 32 describes the synthesis of the bifunctional molecule targeting MIF and ASGPR, containing two bicyclic ASGPr AcF3 ligands, in accordance with some embodiments.

FIGURE 33 describes the synthesis of the bifunctional molecule targeting MIF and ASGPR, containing three bicyclic ASGPr ligands, in accordance with some embodiments.

FIGURE 34 shows the synthesis of DNP-GN3, in accordance with some

embodiments.

FIGURE 35 shows the synthesis of DNP-AcF3-3, in accordance with some embodiments.

FIGURE 36 shows the synthetic scheme used to obtain IBA-GN3, in accordance with some embodiments.

FIGURE 37 shows the synthesis of triazine-GN3, in accordance with some embodiments.

FIGURE 38 shows the synthetic scheme used to access FcIII-GN3, in accordance with some embodiments.

FIGURE 39 shows the synthetic scheme used to access FcIII-4c-GN3, in accordance with some embodiments.

FIGURES 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, in accordance with some embodiments.

FIGURE 44 shows the synthesis of compound MIF-18-3, in accordance with some embodiments.

FIGURE 45 shows the synthesis of compound MIF-31-3, in accordance with some embodiments.

FIGURE 46 shows the synthesis of compound MIF-15-3, in accordance with some embodiments.

FIGURE 47 shows the synthesis of compound MIF-19-3, in accordance with some embodiments.

FIGURE 48 shows the synthesis of compound MIF-16-3, in accordance with some embodiments.

FIGURE 49 shows the synthesis of compound MIF-20-3, in accordance with some embodiments.

FIGURE 50 shows the synthesis of compound MIF-14-3, in accordance with some embodiments.

FIGURE 51 shows the synthesis of compound MIF-21-3, in accordance with some embodiments.

FIGURES 52-66 show the synthesis of a number of MIF-binding compounds with various ASGPRBM moieties, in accordance with some embodiments.

FIGURE 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, such as

a primary or secondary alkyl amine group which is optionally substituted on the amine group with a C_1-C_3 alkyl group, in accordance with some embodiments.

FIGURE 68 shows exemplary R_1 and R_3 substituents on ASGPRBM groups, in accordance with some embodiments.

FIGURE 69 shows exemplary R_2 substituents on ASGPRBM groups, in accordance with some embodiments.

DETAILED DESCRIPTION

In some aspects, the present disclosure provides bi-functional molecules that utilize the endo-lysosomal machinery in the liver to eliminate MIF and/or IgG. In some embodiments, the present disclosure utilizes bi-functional molecules to target MIF or IgG and is modular and versatile. This offers convenience to apply medicinal chemistry to optimize the molecules. For example, in preliminary experiments, incorporation of more optimized ASGPr binding motifs have been shown to enhance MIF or IgG degradation *in vitro*. Since the bi-functional molecule is capable of degrading MIF or IgG, it does not require the MIF-binding motif (MIFBM) or the IgG binding moiety (IgGBM)to be an inhibitor, but in practice many of these binders will function as inhibitors of MIF or IgG. The reality of this dual inhibitory action opens up opportunity for the development of potent MIF or IgG binders, which might have been overlooked before for not being able to inhibit various PPIs. Compared to monoclonal antibodies, the small molecule approach of the present disclosure enables simpler, cheaper and more consistent manufacturing practices and provides for a therapeutic approach with fewer potential immugenic side effects.

In some aspects, the present disclosure is directed to bi-functional compounds which find use as pharmaceutical agents in the treatment of disease states and/or conditions which are mediated through macrophage migration inhibitory factor (MIF) or Immunoglobulin G (IgG). In some aspects, the present disclosure is directed to pharmaceutical compositions which comprise these bi-functional compounds as well as methods for treating disease states and/or conditions which are mediated through MIF or IgG or where MIF and IgG are contributing factors to the development and perpetuation of diseases and/or conditions, especially including autoimmune diseases and cancer, among others. In some aspects, present disclosure provides a molecular strategy to lower plasma MIF level or IgG levels in patients with autoimmune diseases or certain types of cancers and other diseases. The bi-functional molecule construct is comprised of a MIF-targeting motif that is derived from small molecule MIF ligands or an IgG-binding motif which binds to IgG, and an ASGPr-

targeting motif that binds to hepatocyte asialoglycoprotein receptor (ASGPr). The compounds selectively bind MIF or IgG in plasma and subsequently engage the endo-lysosomal pathway of hepatocytes through ASGPr. As a consequence, MIF or IgG is internalized and degraded by hepatocytes, thus resulting in potential attenuation of corresponding disease symptoms which are modulated through MIF and/or IgG.

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

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise (such as in the case of a group containing a number of carbon atoms), between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the 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 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, some exemplary methods and materials are now described.

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

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

Definition

The term “compound”, as used herein, unless otherwise indicated, refers to any specific chemical compound disclosed herein and includes tautomers, regioisomers, geometric isomers, stereoisomers and where applicable, optical isomers (enantiomers) thereof, as well as pharmaceutically acceptable salts and derivatives (including prodrug

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

The term "patient" or "subject" is used throughout the specification within context to describe an animal, generally a mammal, such as 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 of numerous disease states including autoimmune diseease states and/or conditions and inflammatory disease states and/or conditions as well as cancer, including especially for use in reducing the likelihood of metastasis or recurrence of a cancer.

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

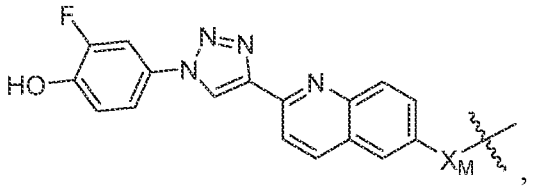
The terms “treat”, “treating”, and “treatment”, etc., as used herein, refer to any action providing a benefit to a patient at risk for a disease state or condition for which a MIF protein may be removed, such as an autoimmune disease including rheumatoid arthritis (RA) or systemic lupus erythematosus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

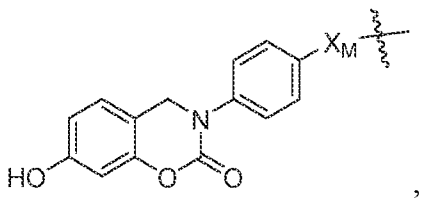
As used in this application, the terms “about” and “approximately” are used as equivalents. Any numerals used in this application with or without about/approximately are meant to cover any normal fluctuations appreciated by one of ordinary skill in the relevant.

The term “macrophage migration inhibitory factor binding moiety” or “MIFBM” 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 MIF protein which is associated with or contributes to a disease state or condition as otherwise described herein. In the present disclosure, the MIFBM is capable of binding to the circulating MIF protein, forming a complex with the present compounds, and delivering the bound protein to a hepatocyte whereupon the other end of the bifunctional molecule which contains an asialoglycoprotein receptor binding moiety (ASGPRBM) and can bind to the surface of a hepatocyte, respectively. Once attached to the hepatocyte, the bifunctional molecule to which is bound circulating protein is internalized by the hepatocyte through an 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

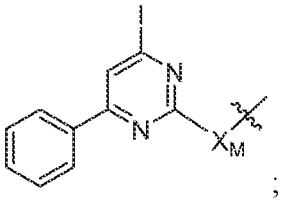
describe a moiety which binds to circulating IgG immunoglobulin, forming a complex with bifunctional molecules according to the present disclosure to be ultimately destroyed in hepatocytes. In certain instances in describing the present disclosure, the terms MIFBM and IgGBM are used synonymously.

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. In some embodiments, MIFBMs include moieties according to the chemical structures:





, or



;

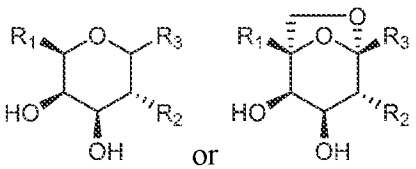
wherein X_M is $-(CH_2)_{IM}$, $-O-(CH_2)_{IM}$, $S-(CH_2)_{IM}$, $NR_M-(CH_2)_{IM}$, $C(O)-(CH_2)_{IM}-$, a PEG group containing from 1 to 8, such as 1-4 ethylene glycol residues or a $-C(O)(CH_2)_{IM}NR_M$ group;

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

IM is 0-6, such as 1, 2, 3 or 4.

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 bound to the MIHBM moiety through a linker. The ASGPRBM 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 MIF protein is taken into the hepatocytes 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 comprises O, S, $N(R^{N1})$ or $C(R^{N1})(R^{N1})$ groups such that

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

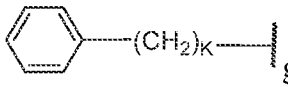
when X is 2 atoms in length, no more than 1 atom of X is O, S or $N(R^{N1})$,

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

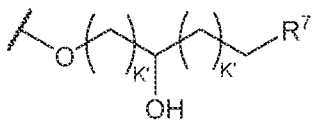
where R^{N1} is H or a C_1-C_3 alkyl group optionally substituted with from 1-3 halo groups, such as F (in some embodiments, R^{N1} is H or methyl);

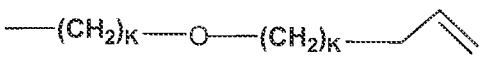
R_1 and R_3 are each independently H, $-(CH_2)_KOH$, $-(CH_2)_KOC_1$-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups,

$-(CH_2)_K$vinyl, O-$(CH_2)_K$vinyl, $-(CH_2)_K$alkynyl, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O$-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, O-C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, -C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, or

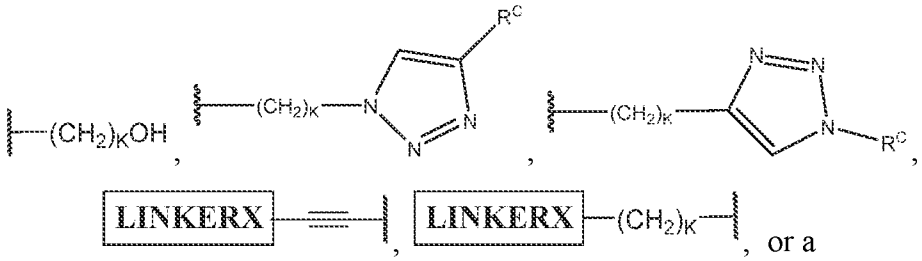
R_1 and R_3 are each independently a  group, which is optionally substituted with up to three (such as 1) halo groups (such as F), C_1-C_4 alkyl groups, each of which is optionally substituted with from one to three halo groups, such as F, or one or two hydroxyl groups, or O-C_1-C_4 alkyl groups, each of which alkyl groups is optionally substituted with from one to three halo groups, such as F, or one or two hydroxyl groups, and K is independently an integer ranging from 0 to 4 (0, 1, 2, 3 or 4), or

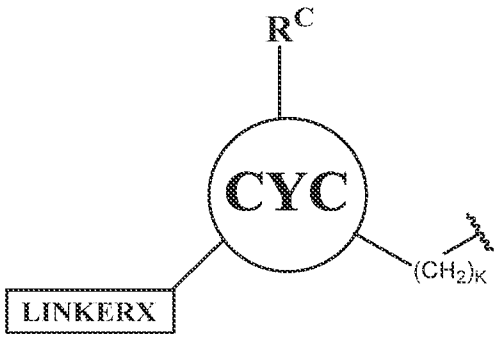
R_1 and R_3 are each independently a group according to the chemical structure:

 , where R^7 is O-C_1-C_4 alkyl, which is optionally substituted with from 1 to 3 halo groups, such as F and 1 or 2 hydroxy groups, or R^7 is a

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

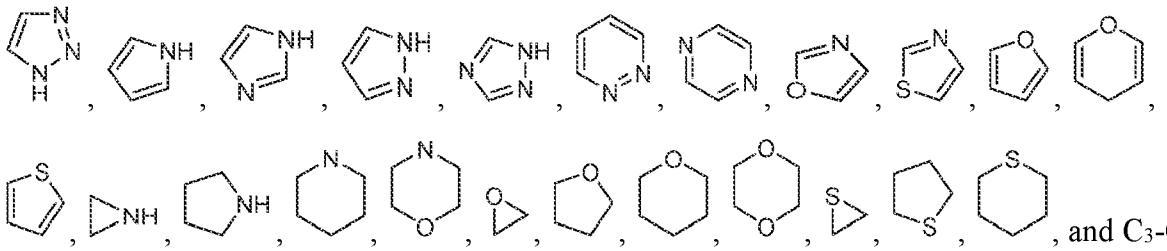
or R_1 and R_3 are each independently a group according to the structure:





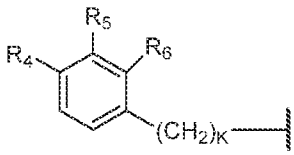
group,

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



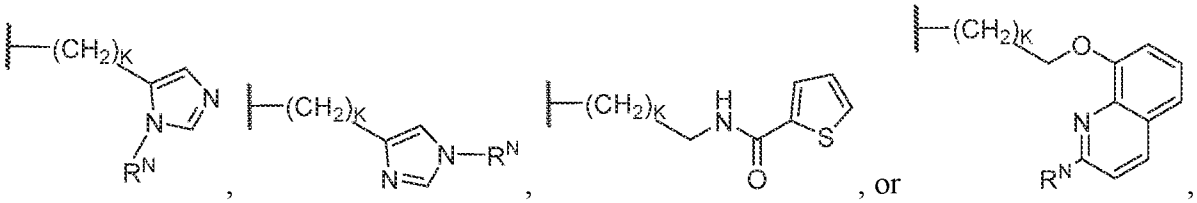
, and C_3-C_8 saturated carbocyclic, wherein each of LINKERX, R^C, and $-(CH_2)_K$- are attached to an open valence in CYC, including N-H;

R^C is absent, H, C_1-C_4 alkyl which is optionally substituted with from 1-3 halo (such as fluoro) groups or 1-2 hydroxyl groups, or a group according to the structure:



where R_4, R_5 and R_6 are each independently, H, halo (F, Cl, Br, I), CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KOC_1$-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, C_1-C_3 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, -O-C_1-C_3-alkyl, which is optionally substituted with from 1-3 halo, such as F groups, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O$-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, O-C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, -C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, or

R^C is

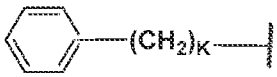


where R^N, R^{N1} and R^{N2} are each independently H or a C_1-C_3 alkyl group which is optionally substituted with from one to three halo groups, such as F, or one or two hydroxyl groups;

K is independently an integer ranging from 0 to 4 (0, 1, 2, 3 or 4);

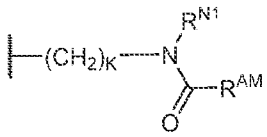
K' is an integer ranging from 1-4, such as 1;

R^{N3} is H, or a C_1-C_3 alkyl group which is optionally substituted with 1-3 halo groups, such as F or 1 or 2 hydroxy groups; and

R^{N4} is H, a C_1-C_3 alkyl group which is optionally substituted with 1-3 halo groups, such as F or 1 or 2 hydroxy groups, or R^{N4} is a  group, where K is sometimes 1;

LINKERX is a linker group which is comprises to at least one [MIFBM/IgGBM] group and links the [MIFBM/IgGBM] group to the [ASGPRBM] through one or more optional [CON] groups, or

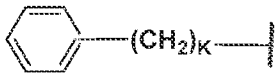
LINKERX is a linker group which contains at least one or more functional groups which can be used to covalently bond the linker group to at least one [MIFBM/IgGBM] group or optional [CON] group;

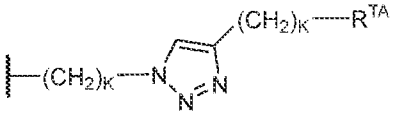
R_2 is a  group where R^{N1} and K are the same as above;

R^{AM} is H, a C_1-C_4 alkyl group optionally substituted with up to 3 halo groups (such as F) and one or two hydroxyl groups, a -$(CH_2)_K$COOH group, a -$(CH_2)_K$C(O)O-C_1-C_4 alkyl group which is optionally substituted with from 1-3 halo, such as F groups, a

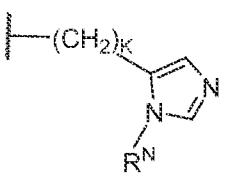
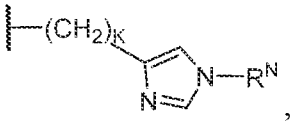
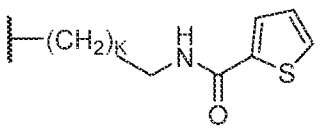
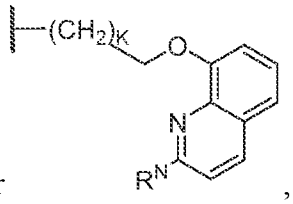
O-C(O)-C_1-C_4 alkyl group, which is optionally substituted with from 1-3 halo, such as F groups, a -C(O)-C_1-C_4 alkyl group, which is optionally substituted with from 1-3 halo, such as F groups, a -$(CH_2)_K$-$NR^{N3}R^{N4}$ group where R^{N3} is H, or a C_1-C_3 alkyl group which is optionally substituted with 1-3 halo groups, such as F or 1 or 2 hydroxy groups; and

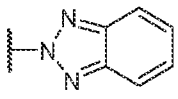
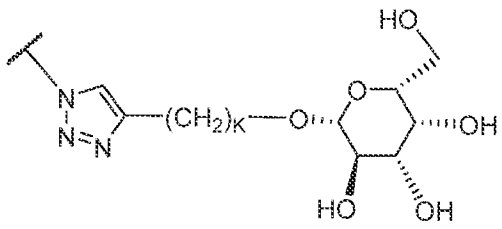
R^{N4} is H, a C_1-C_3 alkyl group which is optionally substituted with 1-3 halo groups,

such as F or 1 or 2 hydroxy groups, or R^{N4} is a  group (K is sometimes 1), or

R_2 is a  group,

where R^{TA} is H, CN, $NR^{N1}R^{N2}$, -$(CH_2)_K$OH, -$(CH_2)_K$OC_1-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, O-C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups, -C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F 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 said aryl or heteroaryl groups being optionally substituted with up to three (such as 1) CN, $NR^{N1}R^{N2}$, -$(CH_2)_K$OH, -$(CH_2)_K$OC_1-C_4 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups, C_1-C_3 alkyl, which is optionally substituted with from 1-3 halo (F, Cl, Br, or I) groups or 1 or 2 hydroxy groups, -O-C_1-C_3-alkyl, which is optionally substituted with from 1-3 halo, such as F groups, -$(CH_2)_K$COOH, -$(CH_2)_K$C(O)O-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, O-C(O)-C_1-C_4 alkyl, which is optionally substituted with from 1-3 halo, such as F groups or -$(CH_2)_K$C(O)-C_1-C_4 alkyl which is optionally substituted with from 1-3 halo, such as F groups, or R^{TA} is

 ,  ,  , or  ,

(in some embodiments, R^{TA} is a  group which is optionally substituted with up to three, such as 1 C_1-C_3 alkyl groups which are optionally substituted with up to three halo (such as F) groups, or R^{TA} is a  group,)

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 from one to three halo groups, such as F, or one or two hydroxyl groups and

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

and K is independently 0-4 (0, 1, 2, 3 or 4).

In some embodiments, [CON] is a connector moiety (including a [MULTICON]) as otherwise described herein.

In some embodiments, [LINKER] is a linking moiety as otherwise described herein which links [MIFBM/IgGBM] to the [ASGPRBM] 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 [MIFBM/IgGBM] group or said [ASGPRBM] group, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

In some embodiments, X is -O-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-O-, -S-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-S-, N(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-N(R^{N1}) or C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}) when X is 2 atoms in length,

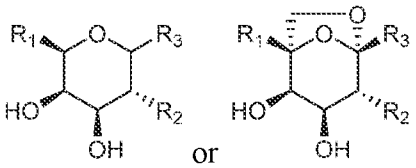
X is -O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-, -O-C(R^{N1})(R^{N1})-O-, -O-C(R^{N1})(R^{N1})-S-, -O-C(R^{N1})(R^{N1})-N(R^{N1})-, -S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1}), C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-S, -S-C(R^{N1})(R^{N1})-S-,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

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

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

In embodiments, the [ASGPRBM] group is a group according to the chemical

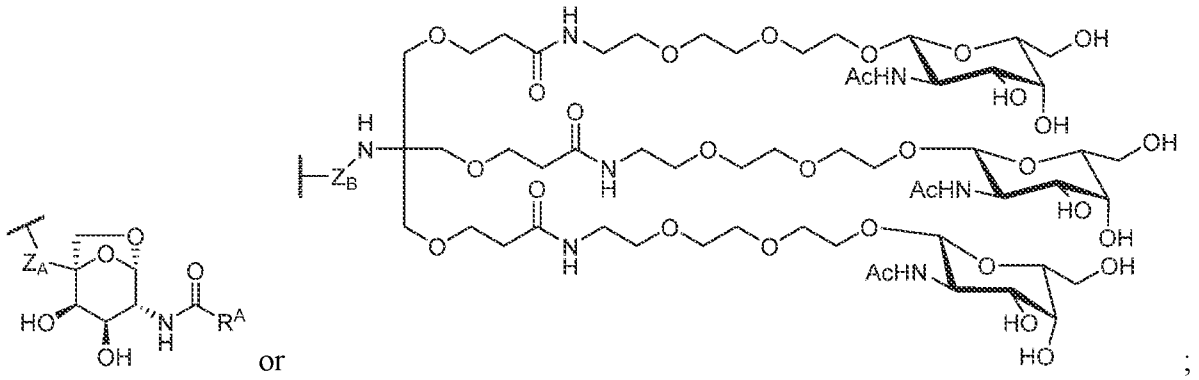
structure:



where R_1, R_2 and R_3 are the same as above, or

a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

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

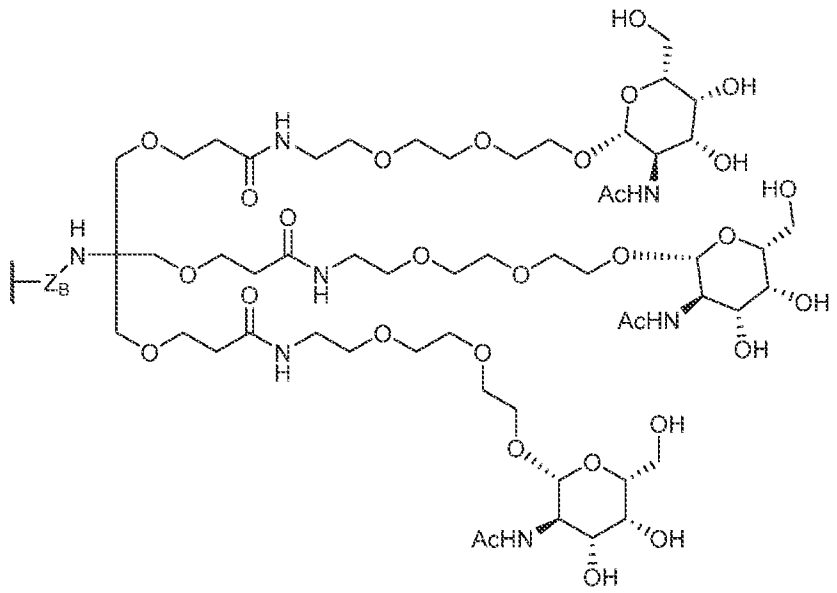


where R^A is a C_1-C_3 alkyl group which is optionally substituted with 1-5 halo (such as fluoro) groups (in some embodiments, R^A is a methyl or ethyl group which is optionally substituted with from 1-3 fluoro groups);

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 polyethylene glycol (PEG) group containing from 1 to 8, such as 1-4 ethylene glycol residues or a $-C(O)(CH_2)_{IM}NR_M$ group (such as a PEG containing group comprising from 1 to 8 ethylene glycol, such as 2-4 ethylene glycol residues) 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 some embodiments, ASPGRM group set forth above is 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, gliobastomas, 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 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, vtiligo, pernicious anemia, glomerulonephritis, and pulmonary fibrosis, among numerous others.

A more complete list of autoimmune diseases which may be treated by compounds and pharmaceutical compositions according to the present disclosure includes Addison's Disease, Autoimmune polyendodrine syndrome (APS) types 1, 2 and 3, autoimmune pancreatitis (AIP), diabetes mellitus type 1, autoimmune thyroiditis, Ord's thyroiditis, Grave's disease, autoimmune oophoritis, endometriosis, autoimmune orchitis, Sjogren's syndrome, autoimmune enteropathy, coeliac disease, Crohns' disease, microscopic colitis, ulcerative colitis, autophospholipid syndrome (APlS), aplastic anemia, autoimmune hemolytica anemia, autoimmune lymphoproliferative syndrome, autoimmune neutropenia, autoimmune thrombocytopenic purpura, cold agglutinin disease, essential mixed cryoglulinemia, Evans sndrome, pernicious anemia, pure red cell aplasia, thrombocytopenia, adiposis dolorosa, adult-onset Still's disease, anklyosing spondylitis, CREST syndrome, drug-induced lupus, enthesitis-related arthritis, esosiniphilic fasciitis, Felty syndrome, AgG4-related disease, juvenile arthritis, Lyme disease (chronic), mixed connective tissue dease (MCTD), palindromic rheurmatism, 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), dematomyositis, fibromyalgia, myositis, inclusion body myositis, myasthenia gravis, neuromyotonia, paraneoplastic cerebellar degeneration, polymysositis, acute disseminated encephalomyelitis (ADEM), acute motor axonic neuropathy, anti-NMDA receptor encephalitis, Balo concentric sclerosis, Bickerstaff's encephalitis, chronic inflamatory demyelinating polyneuropathy, Guillain-Barré syndome,

Hashimoto's encephalopathy, idiopathic inflammatory demyelinating diseases, Lambert-Eaton myasthenic syndrome, mutiple sclerosis, pattern II, Oshtoran Syndrome, Pendiatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS), progressive inflammatory neuropathy, restless leg syndrome, stiff person syndrome, Syndenham chorea, transverse myelitis, autoimmune retinopathy, autoimmune uveitis, Cogan syndrome, Graves ophthalmopathy, intermediate uveitis, ligneous conjunctivitis, Mooren's ulcer, neuromyelitis optica, opsoclonus myoclonus syndrome, optic neuritis, scleritis, Susac's syndrome, sympathetic ophthalmia, Tolosa-Hunt syndrome, autoimmune inner ear disease (AIED), Méniére's disease, Behçet's disease, Eosiniphilic granulomatosis with polyangiitis (EGPA), giant cell arteritis, granulomatosis with polyangiitis (GPA),IgA vasculitis (IgAV), Kawasaki's disease, leukocytoclastic vasculitis, lupus vasculitis, rheumatoid vasculitis, microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), polymyalgia rheumatica, urticarial vasculitis, vasculitis, primary immune deficiency, chronic fatigue syndrome, complex regional pain syndrome, eosiniphilic esopagitis, gastritis, interstitial lung disease, POEMS syndrome, Raynaud's syndrome, primary immunodeficiency and pyoderma gangrenosum, among others.

The term “inflammatory disease” is used to describe a disease or illness with acute, but more often chronic inflammation as a principal manifestation of the disease or illness. Inflammatory diseases include diseases of neurodegeneration (including, for example, Alzheimer’s disease, Parkinson’s disease, Huntington’s disease; other ataxias), diseases of compromised immune response causing inflammmation (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 pulmony disease/COPD, pulmonary fibrosis, cystic fibrosis, Sjogren’s disease; hyperglycemic disorders, diabetes (I and II), affecting lipid metabolism islet function and/or structure, pancreatic β-cell death and related hyperglycemic disorders, including severe insulin resistance, hyperinsulinemia, insulin-resistant diabetes (e.g. Mendenhall's Syndrome, Werner Syndrome, leprechaunism, and lipoatrophic diabetes) and *dyslipidemia* (e.g. hyperlipidemia as expressed by obese subjects, elevated low-density lipoprotein (LDL), depressed high-density lipoprotein (HDL), elevated triglycerides and metabolic syndrome, liver disease, renal disease (apoptosis in plaques, glomerular disease), cardiovascular disease (especially including infarction, ischemia, stroke, pressure overload and complications during reperfusion), muscle degeneration and atrophy, low grade inflammation, gout, silicosis,

atherosclerosis and associated conditions such as cardiac and neurological (both central and peripheral) manifestations including stroke, age-associated dementia and sporadic form of Alzheimer's disease, and psychiatric conditions including depression), stroke and spinal cord injury, arteriosclerosis, among others. In these diseases, elevated MIF is very often observed, making these disease states and/or conditions response to therapy using compounds and/or pharmaceutical compositions according to the present 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 macrophage migration inhibitory factor binding moiety (MIFBM) to the asialoglycoprotein receptor binding moiety (ASGPRBM), optionally through at least one (such as 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 MIFBM and the ASGPRBM ranges from about 5Å to about 50Å or more in length, about 6Å to about 45Å in length, about 7Å to about 40Å in length, about 8Å to about 35Å in length, about 9Å to about 30Å in length, about 10Å to about 25Å in length, about 7Å to about 20 Å in length, about 5Å to about 16Å in length, about 5Å to about 15Å in length, about 6Å to about 14Å in length, about 10Å to about 20Å in length, about 11Å to about 25Å in length, etc. Linkers which are based upon ethylene glycol units and are between 2 and 15 glycol units, 1 and 8 glycol units, 1, 2, 3, 4, 5, and 6 glycol units in length may be used, although the length of certain linkers may be far greater. By having a linker with a length as otherwise disclosed herein, the MIFBM group and the ASGPRBM group may be situated to advantageously take advantage of the biological activity of compounds according to the present disclosure which bind to asialoglycoprotein receptors on hepatocytes resulting in the selective and targeted degradation of MIF circulating proteins within the lysosomal degradation mechanism or other degradation mechanism of the hepatocytes. The selection of a linker component is based on its documented properties of biocompatibility, solubility in aqueous and organic media, and low immunogenicity/antigenicity. Although numerous linkers may be used as otherwise described herein, a linker based upon polyethyleneglycol (PEG) linkages, polypropylene glycol linkages, or polyethyleneglycol-co-polypropylene oligomers (up to about 100 units, about 1 to 100, about 1 to 75, about 1 to 60, about 1 to 50, about 1 to 35, about 1 to 25, about 1 to 20, about 1 to 15, 2 to 10, about 4 to 12, about 1 to 8, 1 to 3, 1 to 4, 2 to 6, 1 to 5, etc.) may be favored as a linker because of the chemical and biological characteristics of these molecules. Polyethylene (PEG) linkages of between 2 and 15 ethylene glycol units are

sometimes used. 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.) may be covalently attached at either end of the linker group to attach to a 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, such as D- or L- amino acids, such as 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 (such as 1 or 2 connecting groups at one or both ends of the polyamino acid linker).

Exemplary linkers include those according to the chemical structures:

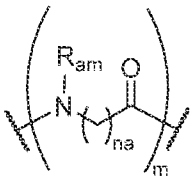
or a polypropylene glycol or polypropylene-co-polyethylene glycol linker having between 1 and 100 alkylene glycol units, such as about 1 to 75, about 1 to 60, about 1 to 50, about 1 to 45, about 1 to 35, about 1 to 25, about 1 to 20, about 1 to 15, 2 to 10, about 4 to 12, about 5 to 10, about 4 to 6,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

where R_a is H, C_1-C_3 alkyl or alkanol or forms a cyclic ring with R^3 (proline) and R^3 is a side chain derived from a D- or L amino acid (such as a naturally occurring L-amino acid), such as selected from the group consisting of alanine (methyl), arginine (propyleneguanidine), asparagine (methylenecarboxyamide), aspartic acid (ethanoic acid), cysteine (thiol, reduced or oxidized di-thiol), glutamine (ethylcarboxyamide), glutamic acid (propanoic acid), glycine (H), histidine (methyleneimidazole), isoleucine (1-methylpropane), leucine (2-methylpropane), lysine (butyleneamine), methionine (ethylmethylthioether), phenylalanine (benzyl), proline hydroxyproline (R^3 forms a cyclic ring with R_a and the adjacent nitrogen group to form a pyrrolidine or hydroxypyrrolidine group), serine (methanol), threonine (ethanol, 1-hydroxyethane), tryptophan (methyleneindole), tyrosine (methylene phenol) or valine (isopropyl);

m (within the context of this use) is an integer ranging from 1 to 100, such as from 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.

Other exemplary linkers include a polyethylene glycol linker containing from 1 to 1 to 100, such as 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 MIFBM and/or the ASGPRBM group. Still other linkers comprise amino acid residues (D or L) which are bonded to MIFBM and/or ASGPRBM moieties as otherwise described herein. In another embodiment, as otherwise described herein, the amino acid has anywhere from 1-15 methylene groups separating the amino group from the acid (acyl) group in providing a linker to the MIFBM and/or the ASGPRBM group, wherein the linker contains from 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5 amino acid groups linked together through peptide linkages to form the linker. This linker is represented by the chemical structure:



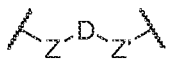
,

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

na is an integer ranging from 1 to 15, such as 1-12, 1-10, 1-8, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11;

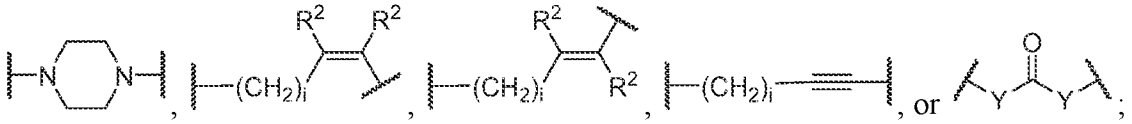
m is an integer ranging from 1 to 100, such as 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 12, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 51 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5.

or another 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), MIFBM or ASGPRBM;

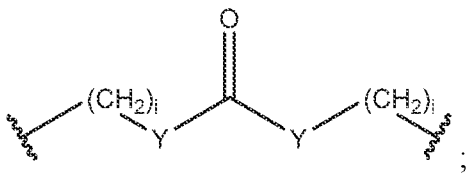
each R is H, or a C_1-C_3 alkyl or alkanol group;

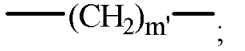
each R^2 is independently H or a C_1-C_3 alkyl group;

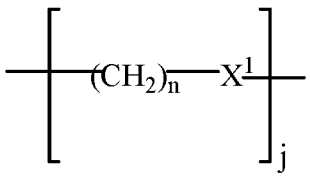
each Y is independently a bond, O, S or N-R;

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

D is


;


;


or

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

j is an integer ranging from 1 to 100, such as 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;

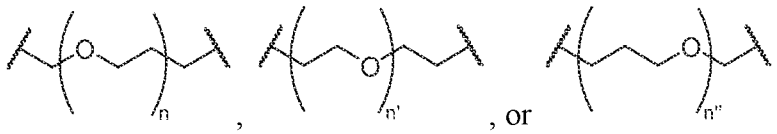
m' is an integer ranging from 1 to 100, such as 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;

n is an integer ranging from 1 to 100, such as 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;

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

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

Other linkers which are included herein include linkers according to the chemical structure:

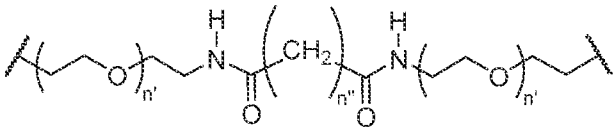

;

where each n and n' is independently an integer ranging from 1 to 25, such as 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

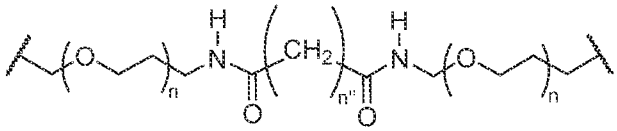
each n" is independently an integer ranging from 0 to 8, such as 1 to 7, or 1, 2, 3, 4, 5 or 6.

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 (especially a diamide [CON]

group as otherwise described herein) connecting a first and second (PEG) linker group include the following structures:



or



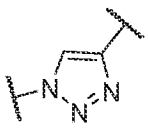
;

where each n and n' is independently an integer ranging from 1 to 25, such as 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 an integer ranging from 0 to 8, such as 1 to 7, or 1, 2, 3, 4, 5 or 6. Noted is that each of these linkers may also contain alkylene groups containing from 1 to 4 methylene groups at the distal ends of each linker group in order to facilitate connection of the linker group.

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

PEG-[CON]-PEG

wherein each PEG is independently a polyethylene glycol group containing from 1-12 ethylene glycol residues and [CON] is a connector group as otherwise set forth herein, such as a

triazole group  .

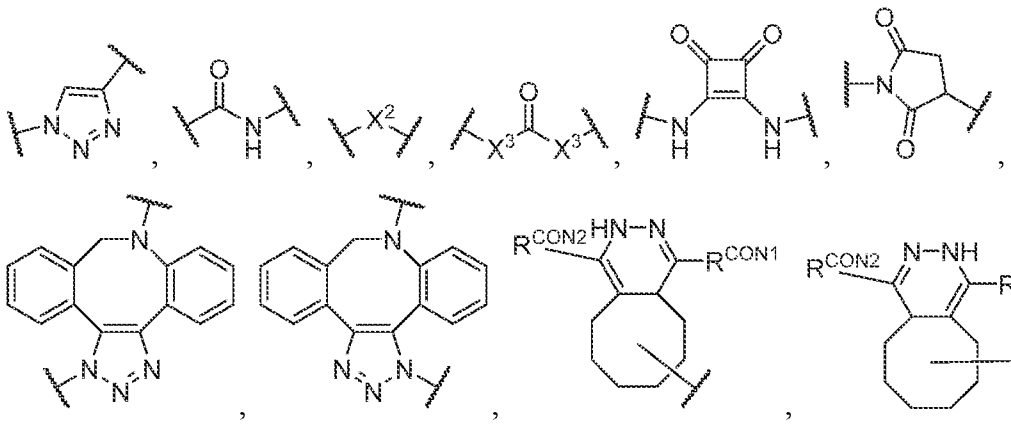
The term "connector", symbolized in the generic formulas by "CON" or [CON], is used to describe a chemical moiety which is optionally included in bifunctional compounds according to the present disclosure which forms from the reaction product of an activated linker with a MIFBM moiety (which also is sometimes activated for covalently bonding the linker with the moiety) or a ASGPRBM group with an activated linker. The connector group is often the resulting moiety which forms from the facile condensation of two or more separate chemical fragments which contain reactive groups which can provide connector groups as otherwise described to produce bifunctional or multifunctional compounds according to the present 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. 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 ASGPRBM/FCRNBM moiety) within the same molecule. It is noted that there may be some overlap between the description of the connector group and the linker group such that the connector group is actually incorporated or forms part of the linker, especially with respect to more common connector groups such as amide groups, oxygen (ether), sulfur (thioether) or amine linkages, urea or carbonate –OC(O)O- groups or as otherwise described herein. It is further noted that a connector (or linker) may be connected to MIFBM, ASGPRBM or a linker at positions which are represented as being linked to another group using the symbol

.

Where two or more such groups are present in a linker or connector, any of an ASGPRBM, a linker or a MIFBM 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.

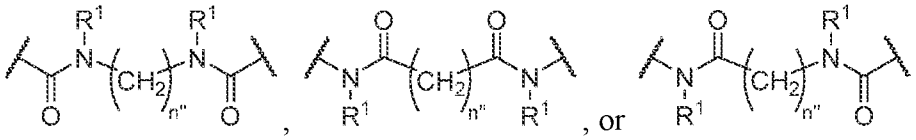
Common connector groups which are used in the present disclosure include the following chemical groups:



, 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:



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

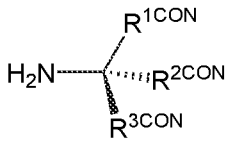
X^3 is O, S, NR^4;

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; and

n" is independently an integer ranging from 0 to 8, such as 1 to 7, or 1, 2, 3, 4, 5 or 6;

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



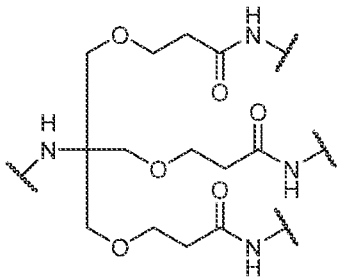
where R^{1CON}, R^{2CON} and R^{3CON} are each independently H, $-(CH_2)_{MC1}$, $-(CH_2)_{MC1a}C(O)_{XA}(NR^4)_{XA}-(CH_2)_{MC1a}$,$-(CH_2)_{MC1a}(NR^4)_{XA}C(O)_{XA}-(CH_2)_{MC1a}$ or $-(CH_2)_{MC1a}O-(CH_2)_{MC1}-C(O)NR^4-$, with the proviso that R^{1CON}, R^{2CON} and R^{3CON} are not simultaneously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

each MC1 is independently an integer ranging from 1 to 4, such as 1 or 2;

each MC1a is independently an integer ranging from 0 to 4, such as 0, 1 or 2; and

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

The triazole group, indicated above, is an exemplary connector group. An additional exemplary connector group is



which is linked to at least one MIFBM and/or at least one ASPRGBM (such as 3 ASPRGBM moieties). This connector group may be used to form GN_3.

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 MIFBM group or a ASGPRBM. 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;

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

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

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

In the compound of Formula II, yy is independently selected from 0, 1, 2, 3, 4, 5, 6, 7,

8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25.

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

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

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

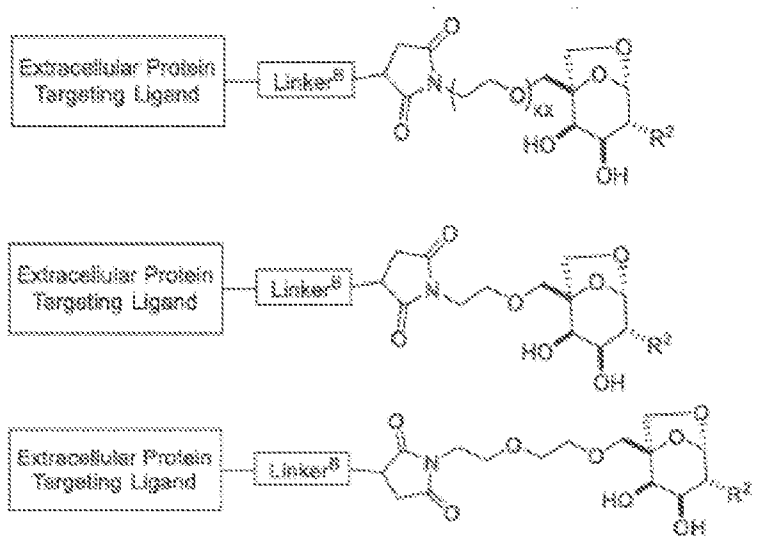
R^4 is independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, $-OR^6$, $-NR^6R^7$,

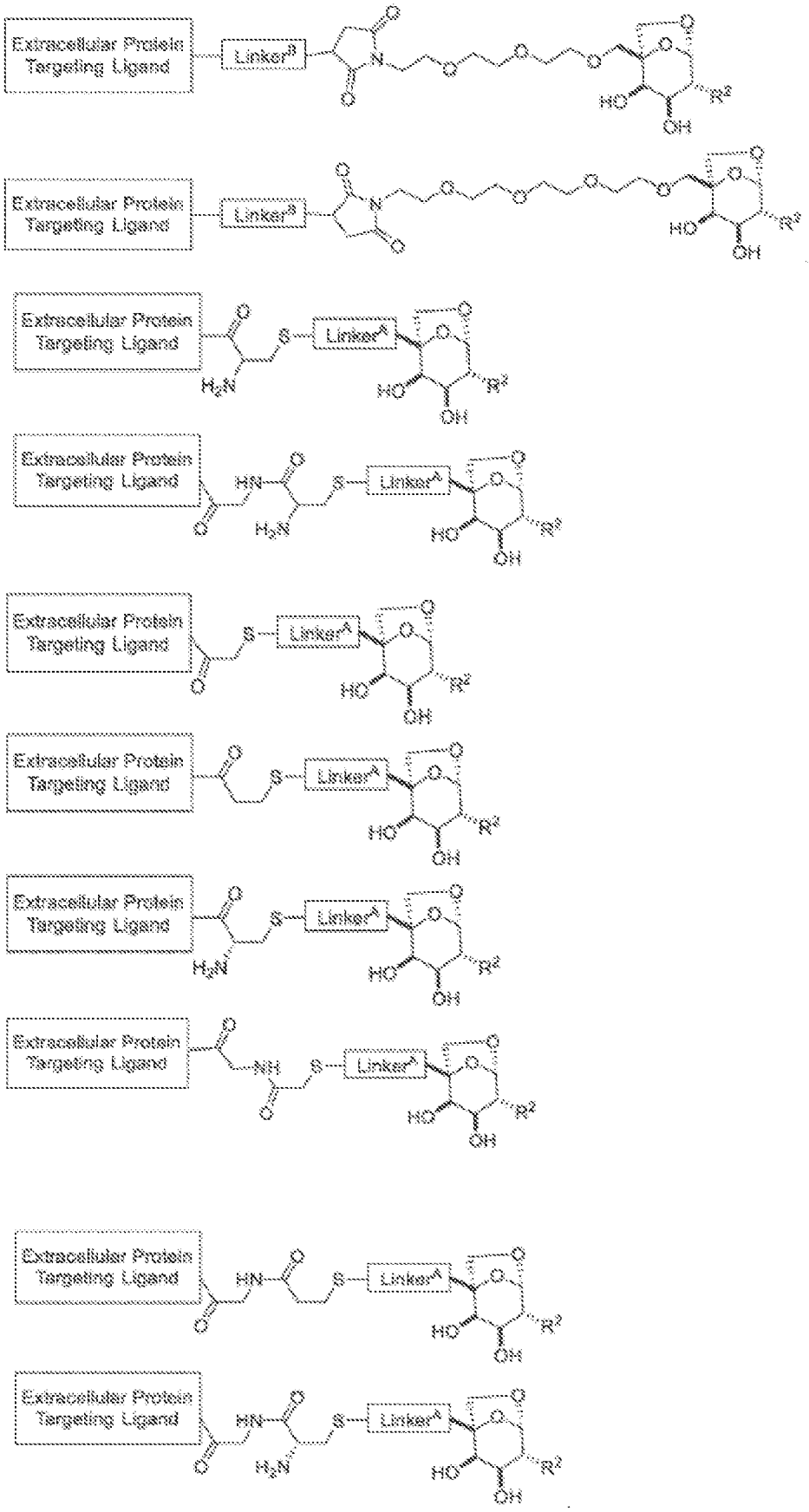
R^6 and R^7 are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroaryl alkyl, alkenyl, alkynyl, and, haloalkyl, heteroaryl, heterocycle, -alkyl-OR^8, -alkyl-NR^8R^9, $C(O)R^3$, $S(O)R^3$, $C(S)R^3$, and $S(O)_2R^3$;

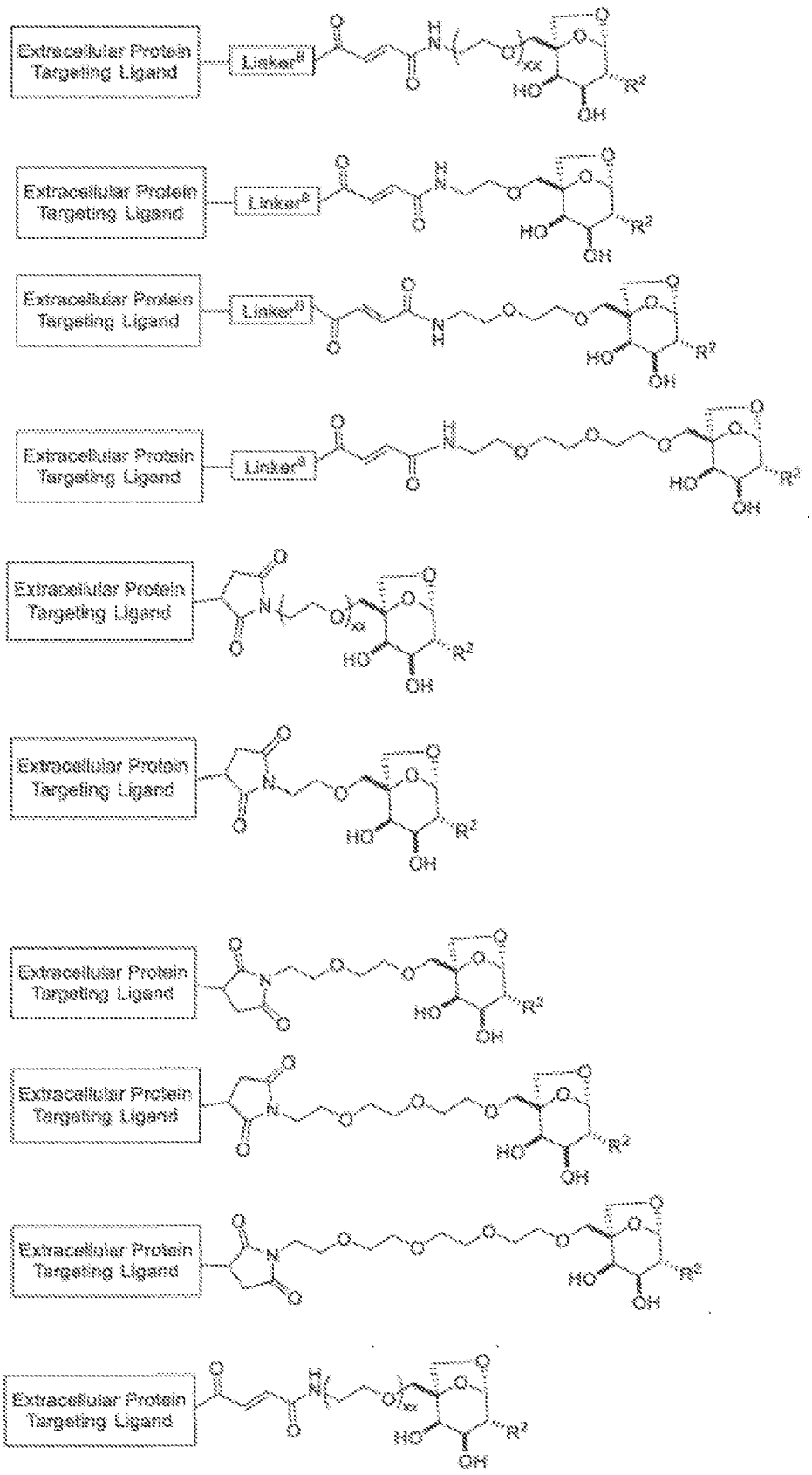
R^8 and R^9 are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle.

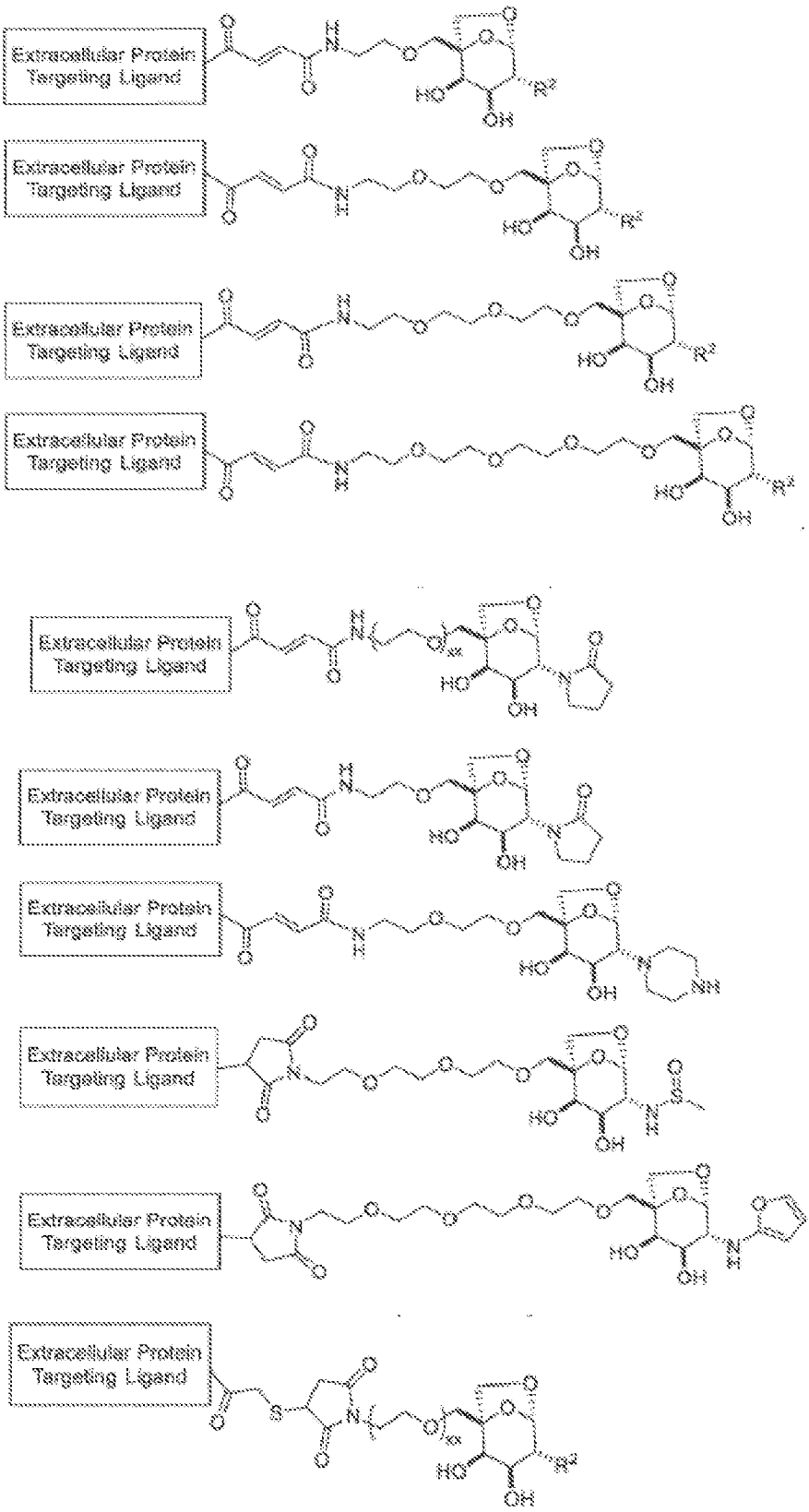
A. Galactose-Based ASGPR-Binding Cellular Receptor Binding Moieties of Formula II

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




Extracellular Protein Targeting Ligand
Linker
HO
OH
R²
H₂N
HN
S
NH
O


Extracellular Protein Targeting Ligand
Linker
HO
OH
R²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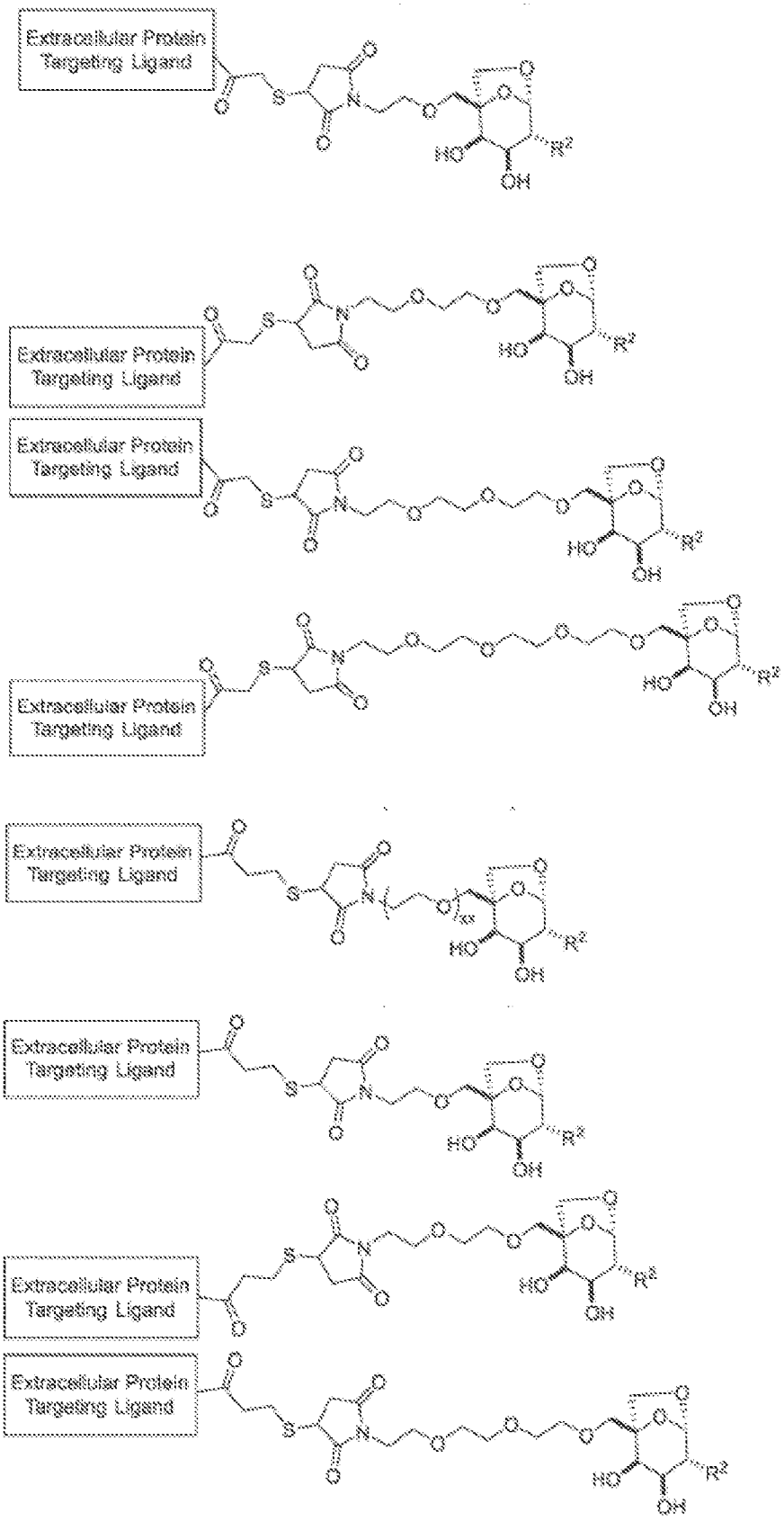
Extracellular Protein Targeting Ligand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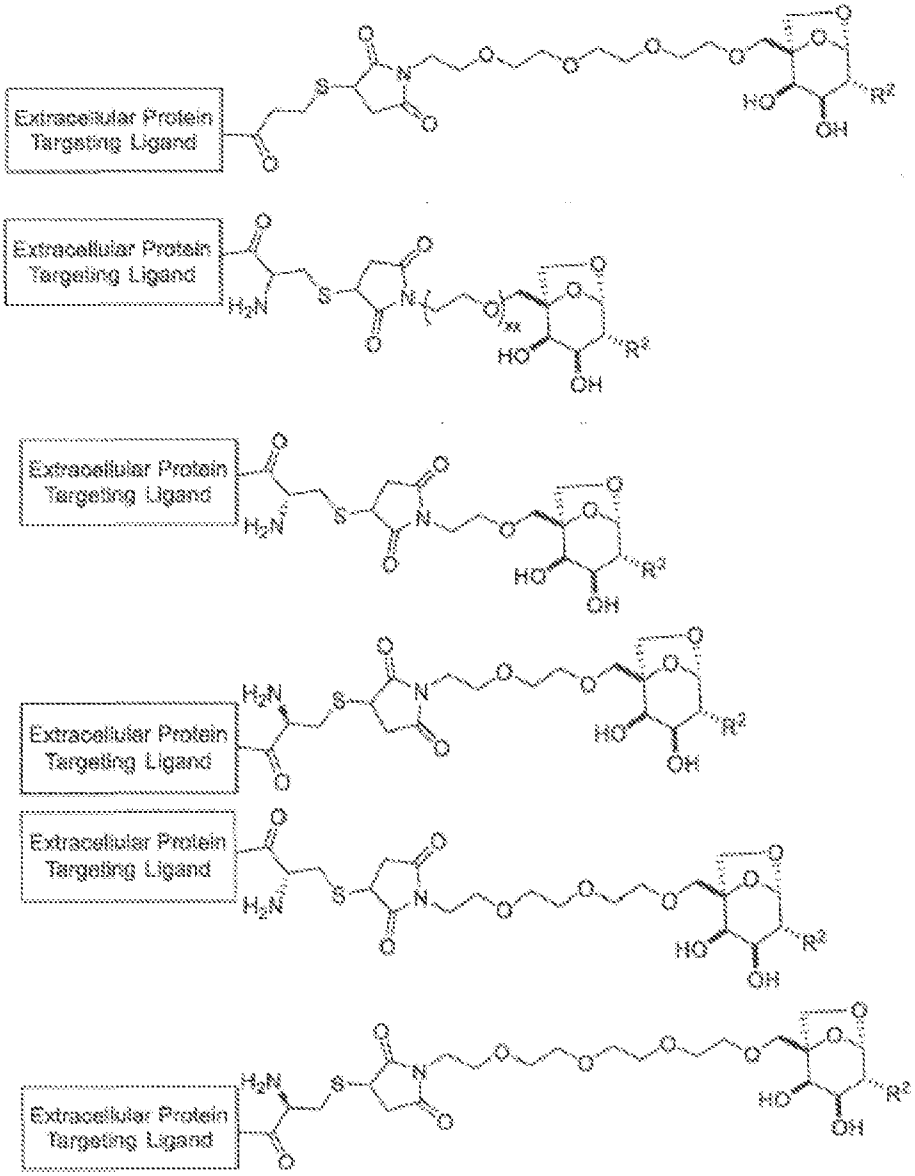
Extracellular Protein Targeting Ligand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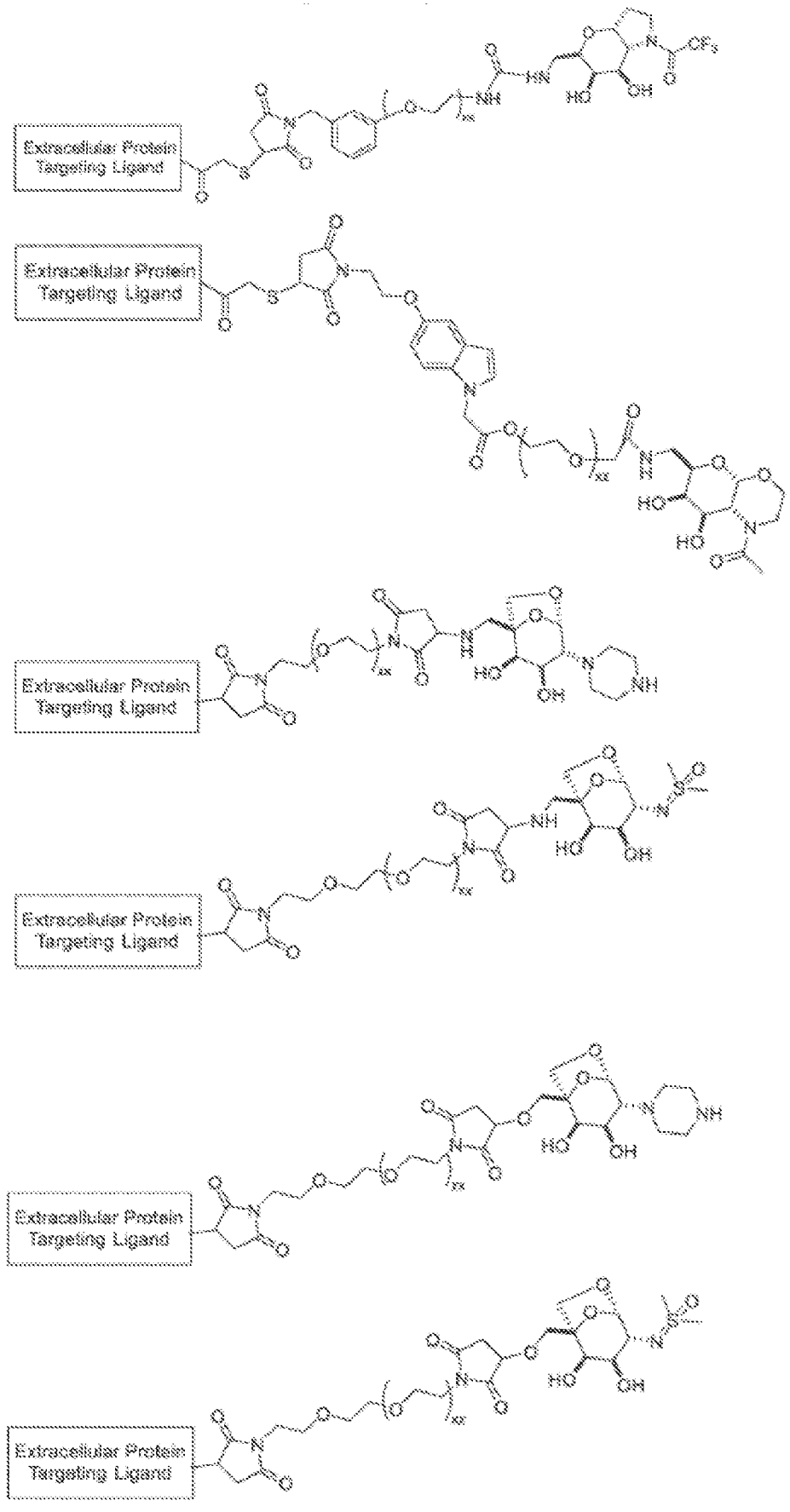
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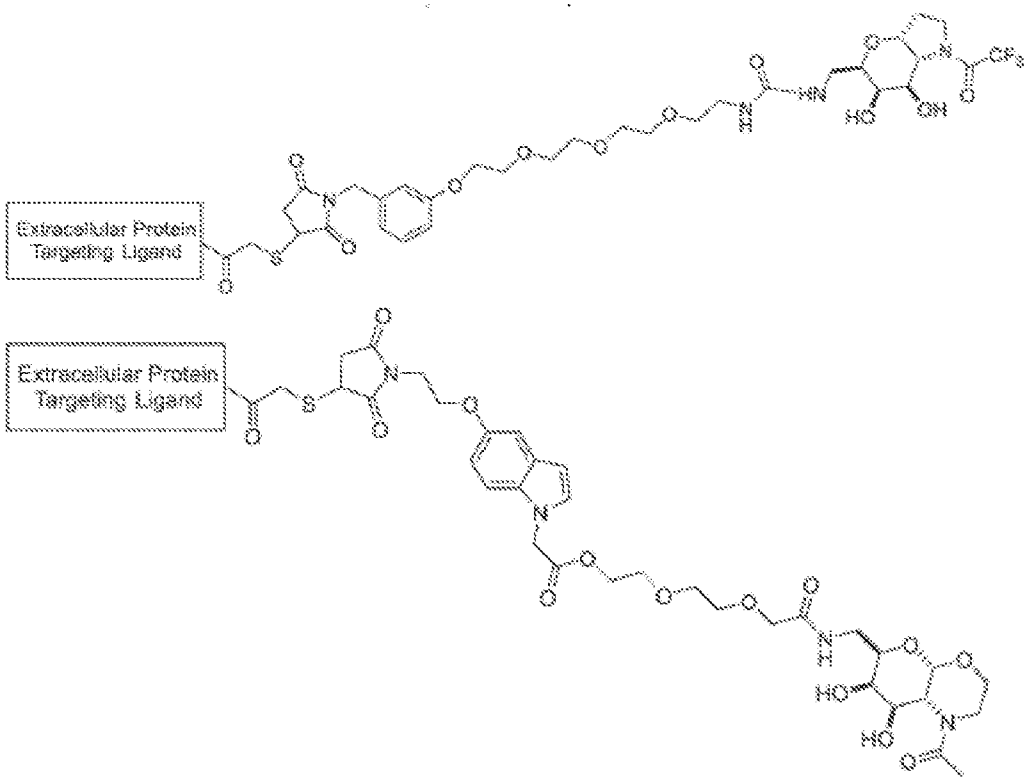
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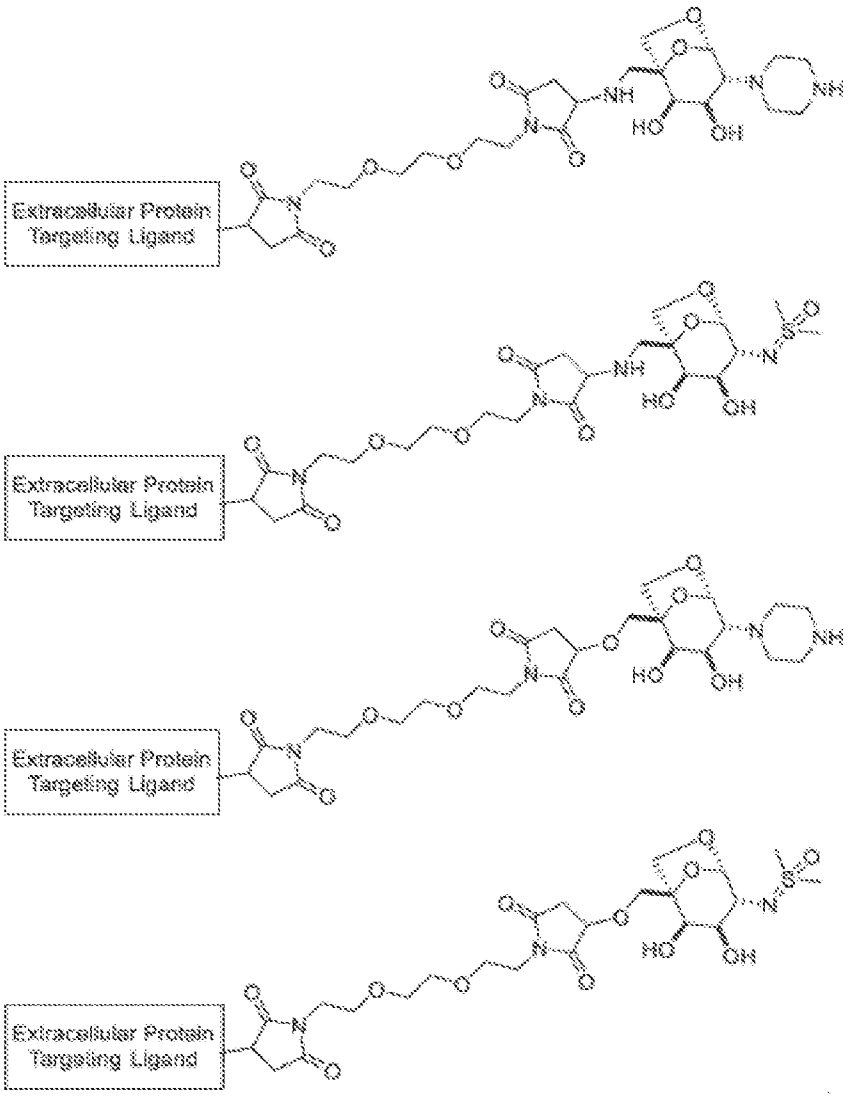
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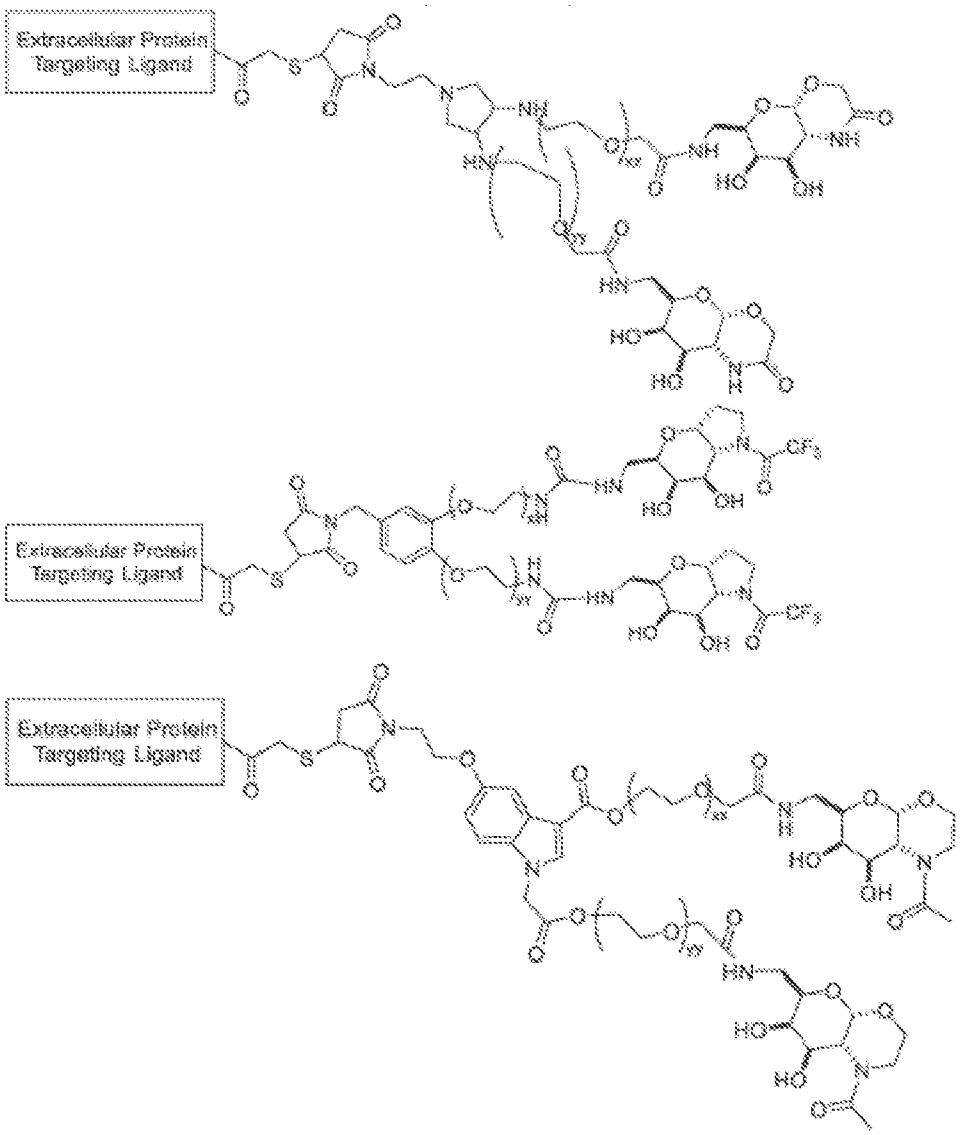
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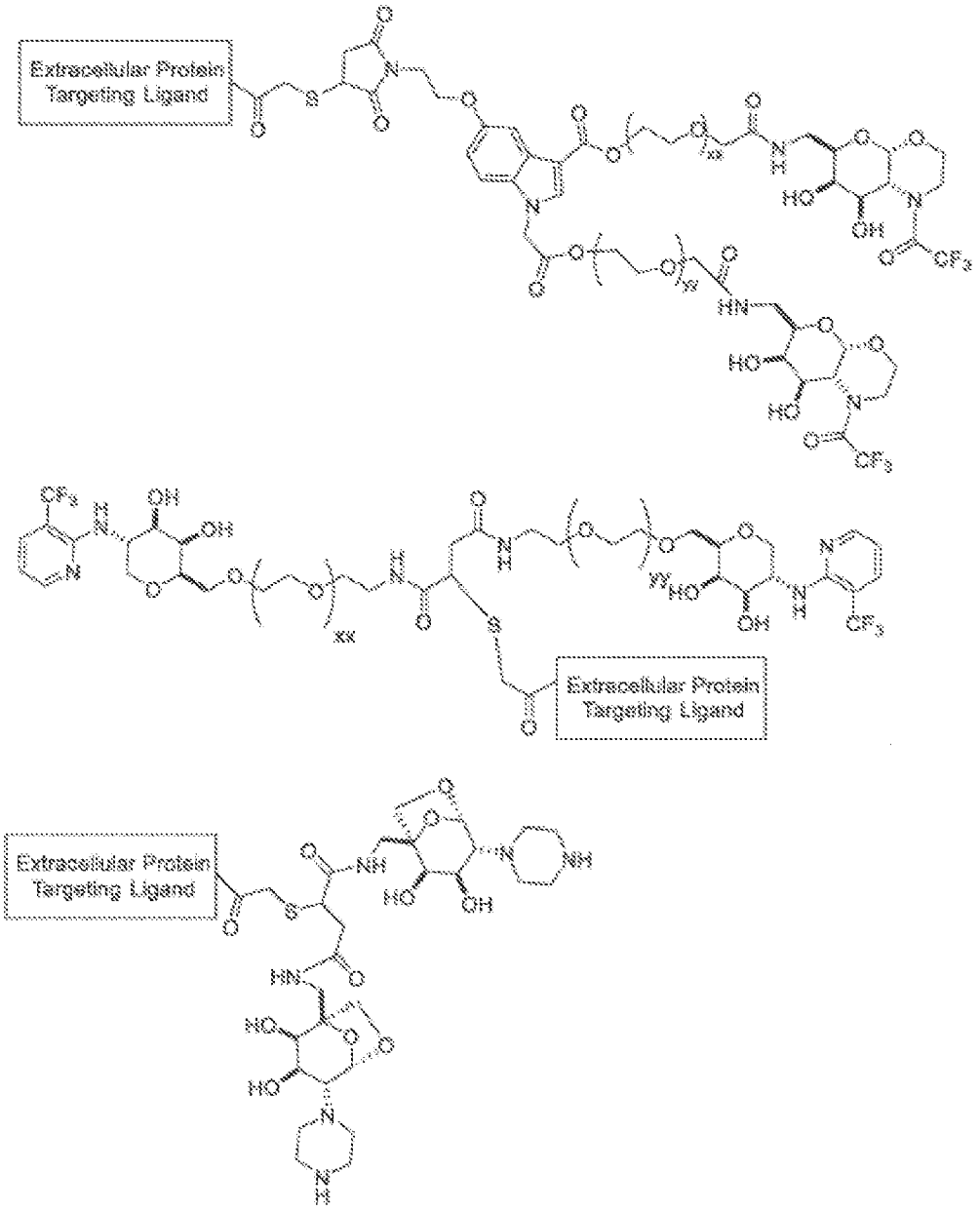
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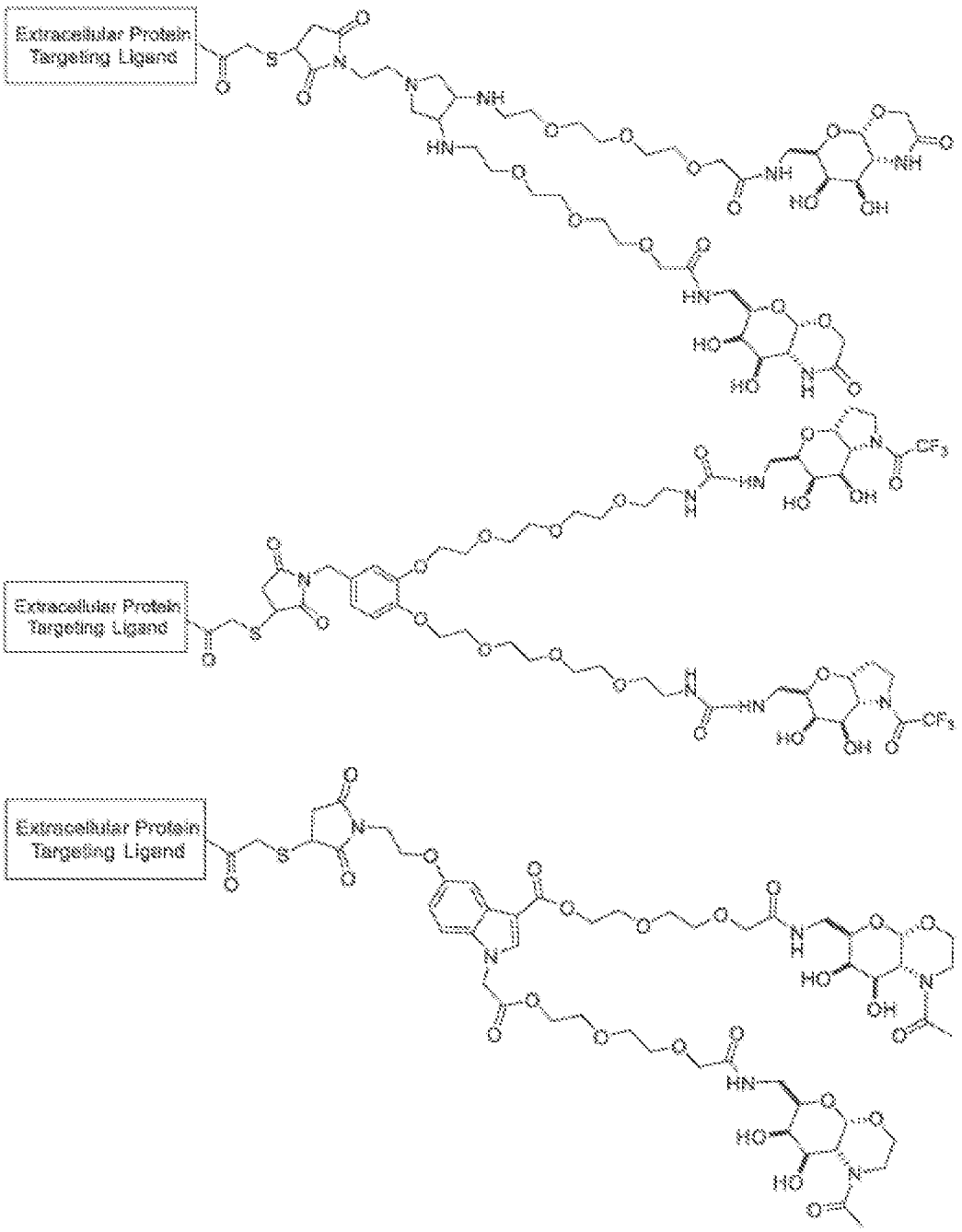
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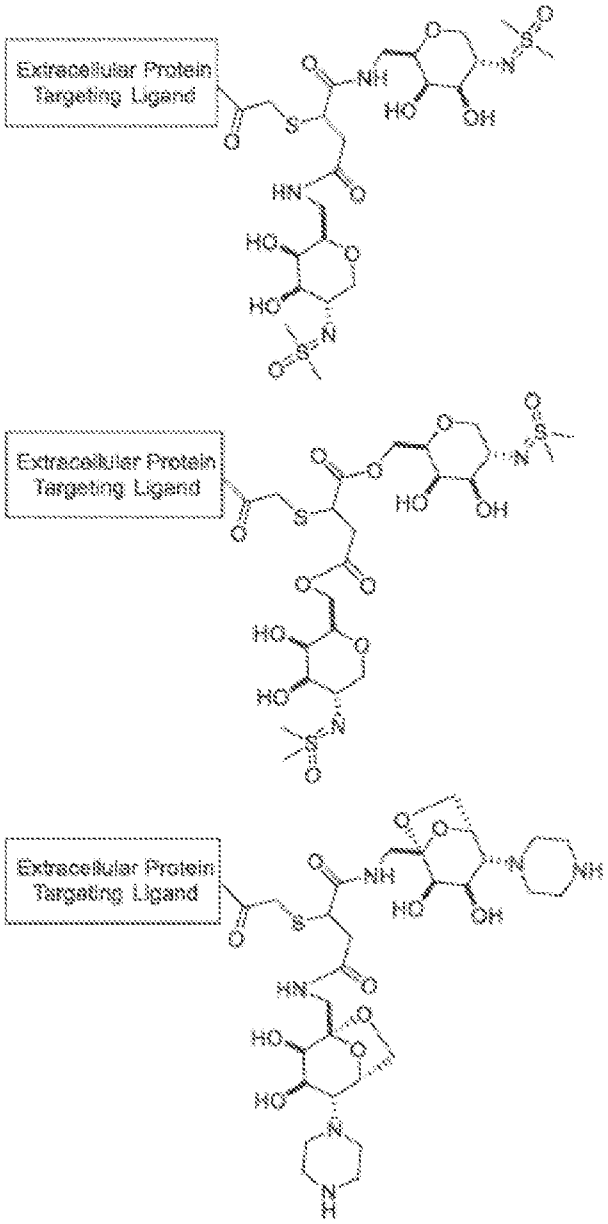
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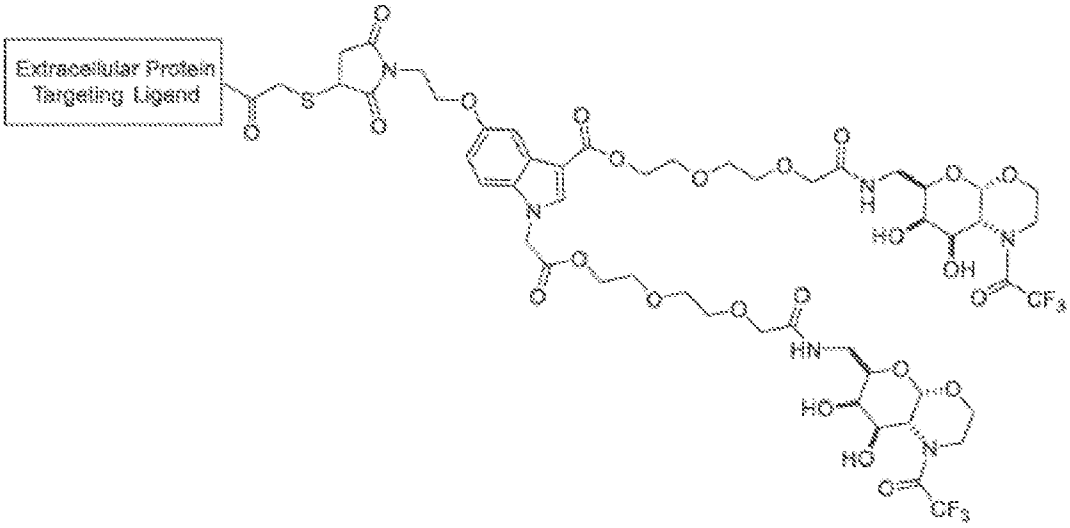
Extracellular Protein Targeting Ligand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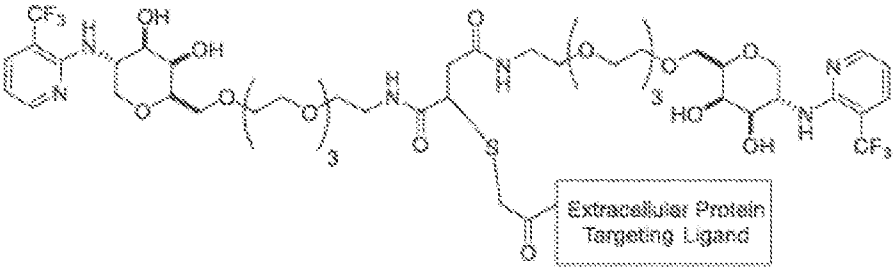
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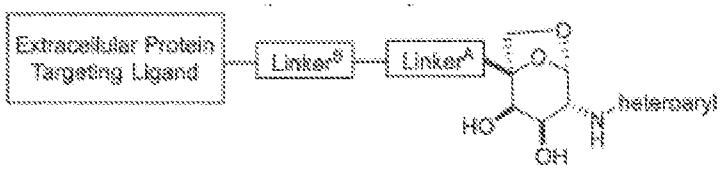
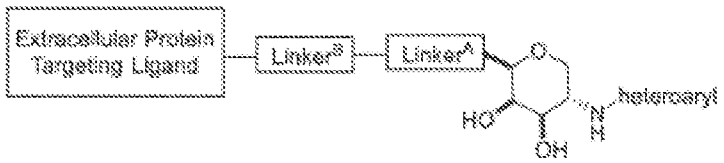
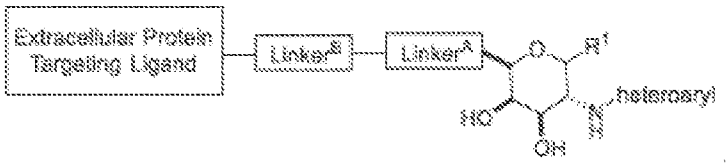
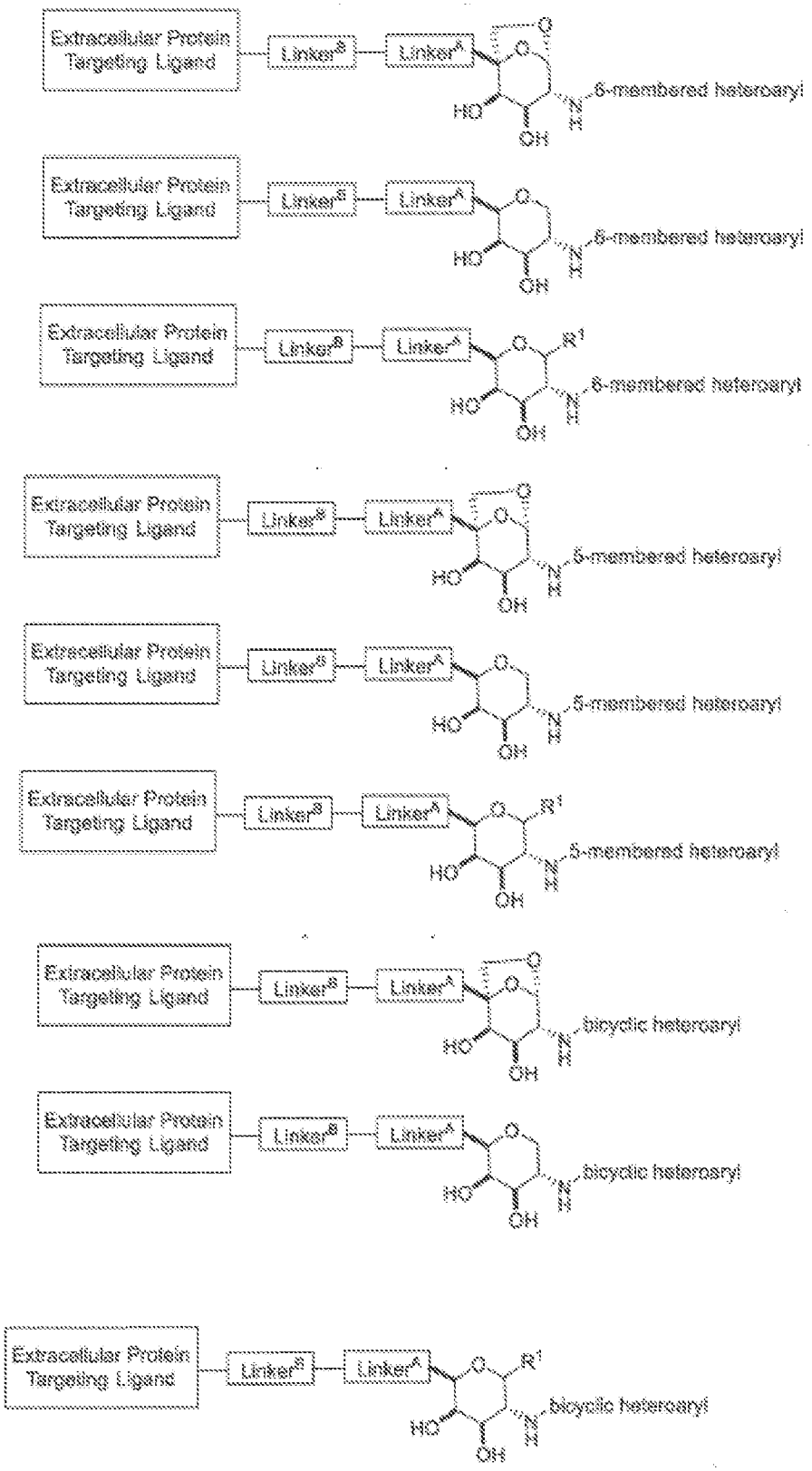
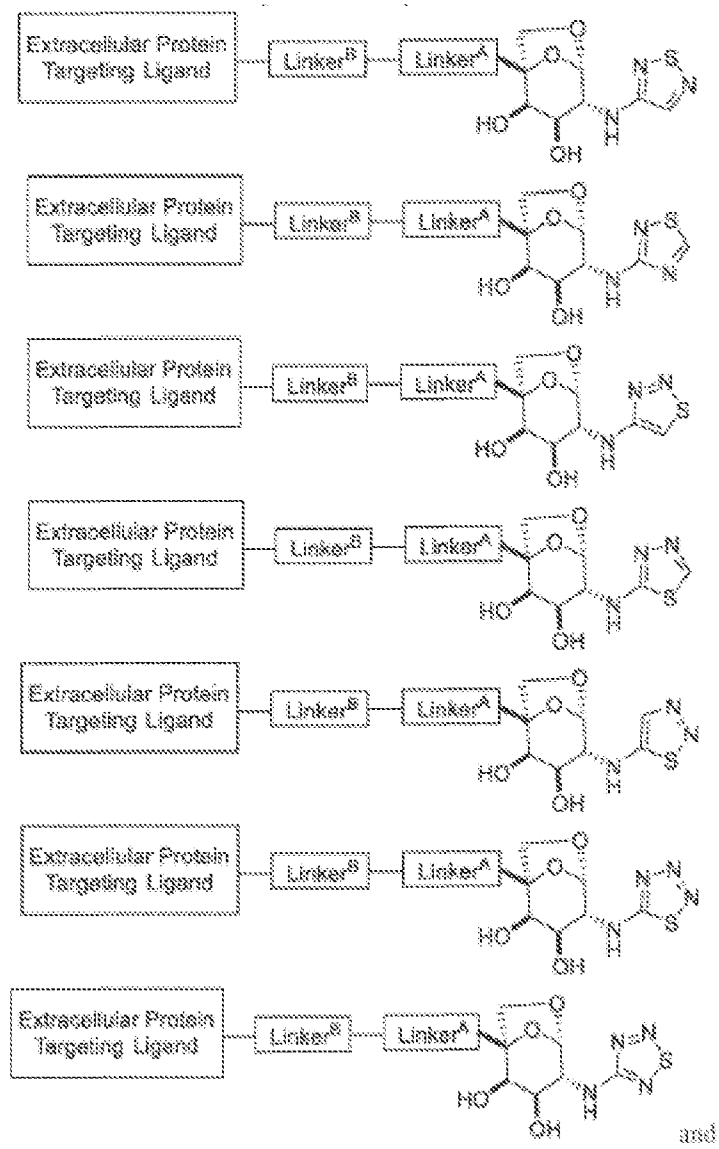

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
heteroaryl

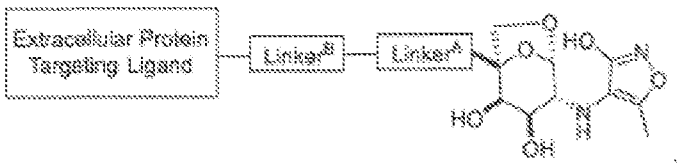

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
heteroaryl

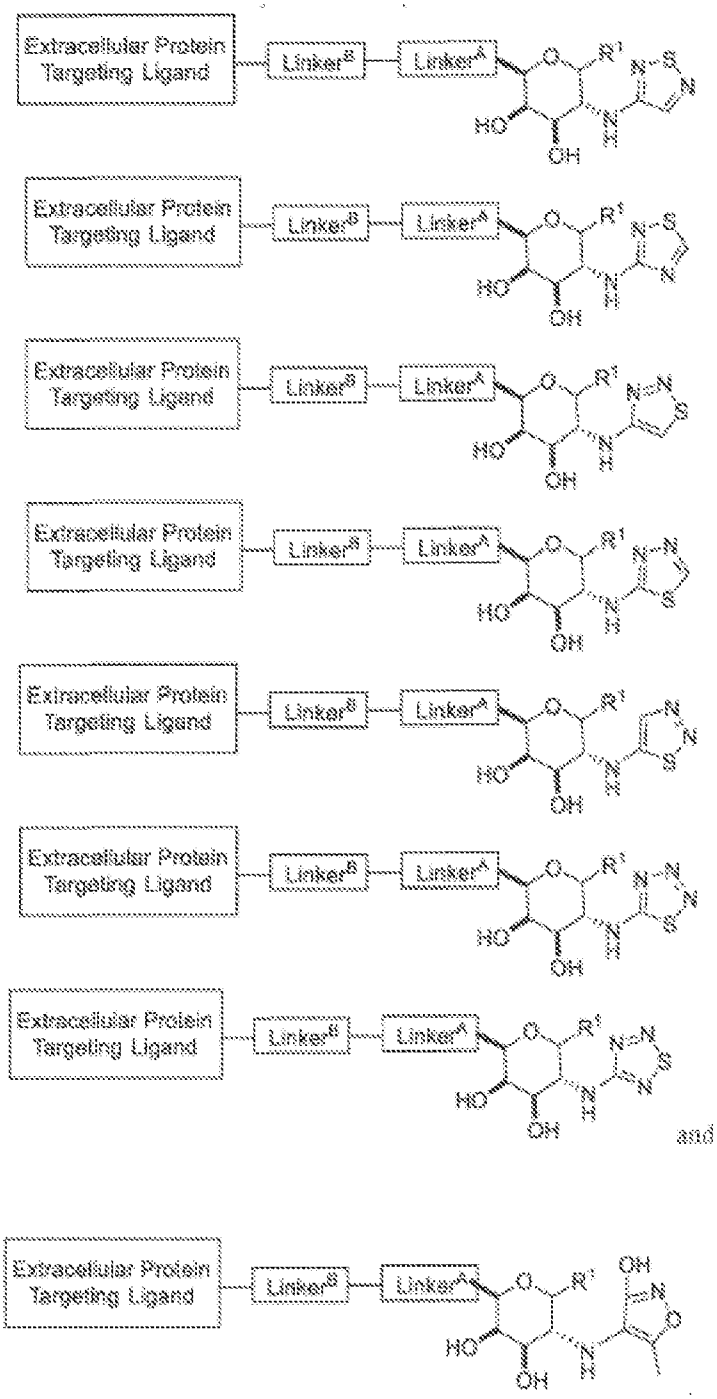

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
heteroaryl

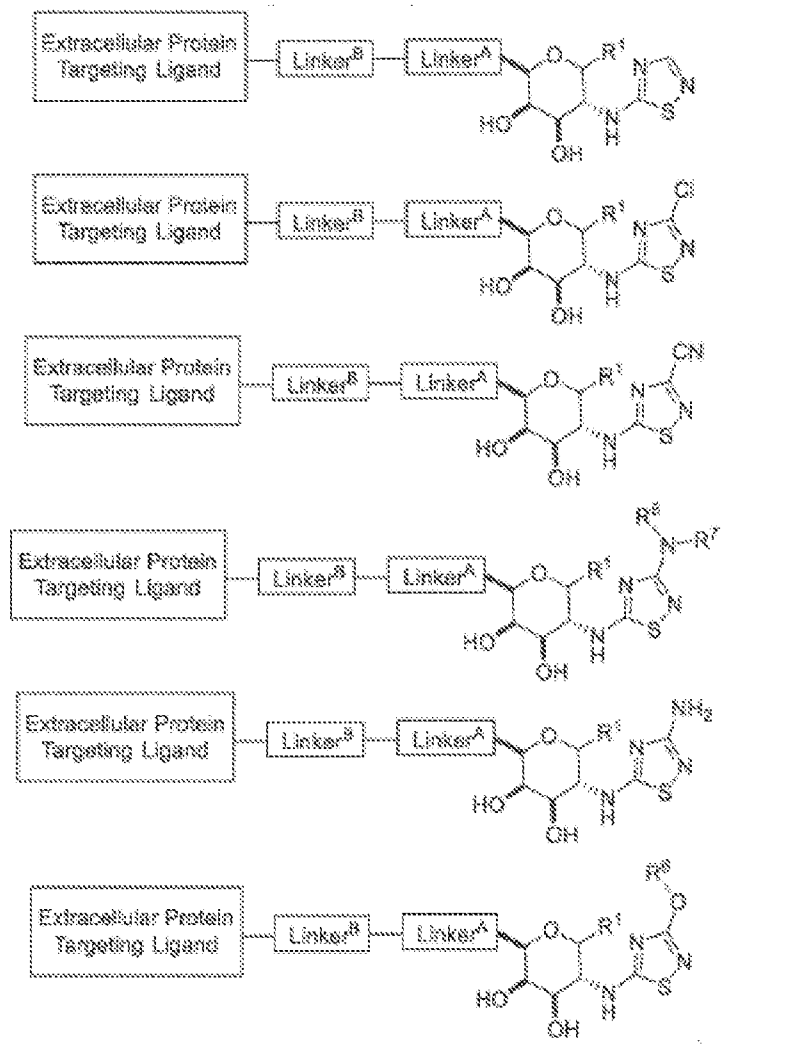

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
6-membered heteroaryl
5-membered heteroaryl
bicyclic heteroaryl
HO
OH
N
H
O
R^1


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

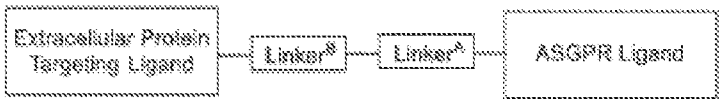
and

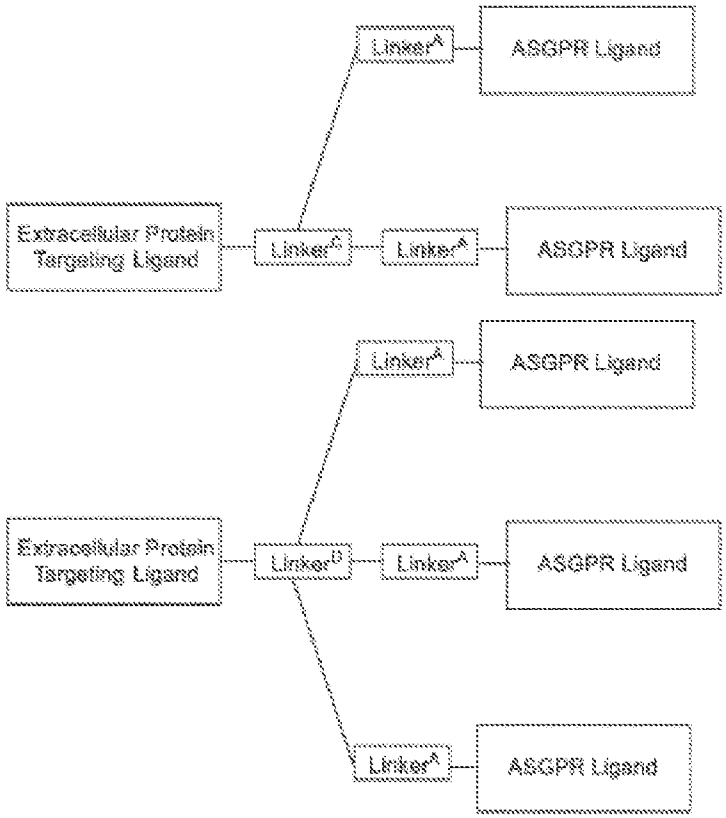

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
N
H
O
N


Extracellular Protein Targeting Ligand
Linker^B
Linker^A
and

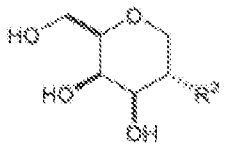


In certain embodiments, the compound of Formula II has one of the following structures:



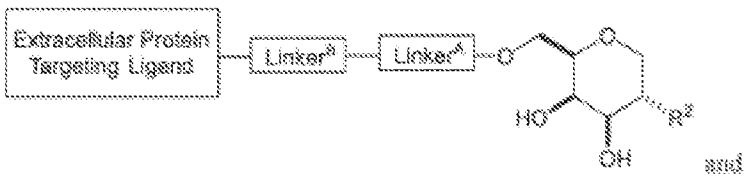


In various embodiments, the ASGPR ligand is linked at either the C^1 or C^5 (R^1 or R^5) position to form a degrading compound. In various embodiments, the ASGPR ligand is linked at C^6 position to form a degrading compound. For example, when the ASGPR ligand is



,

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



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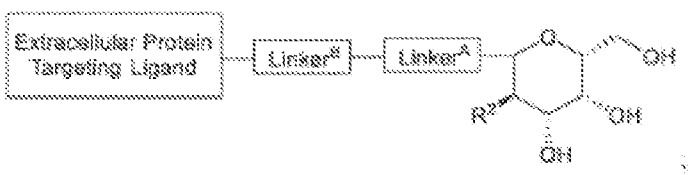
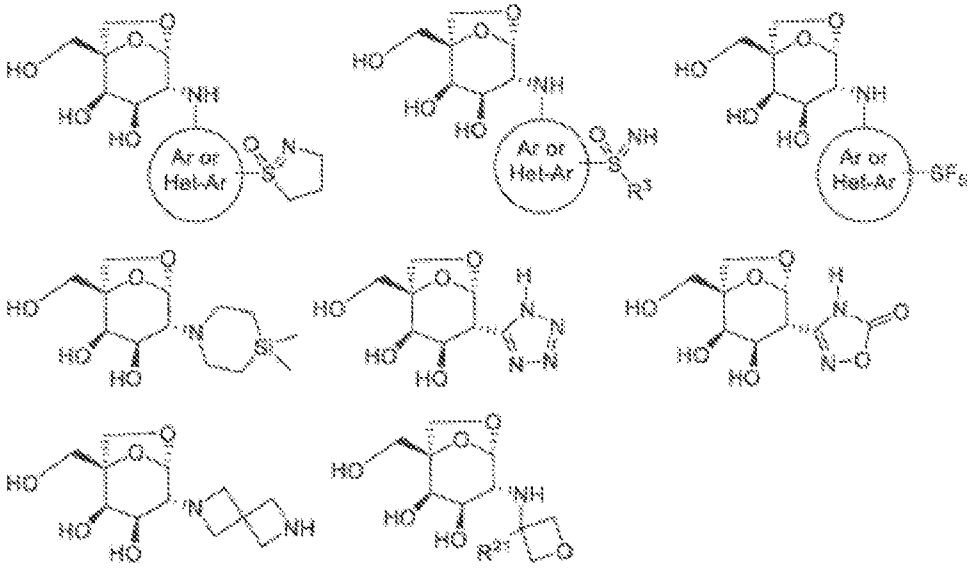


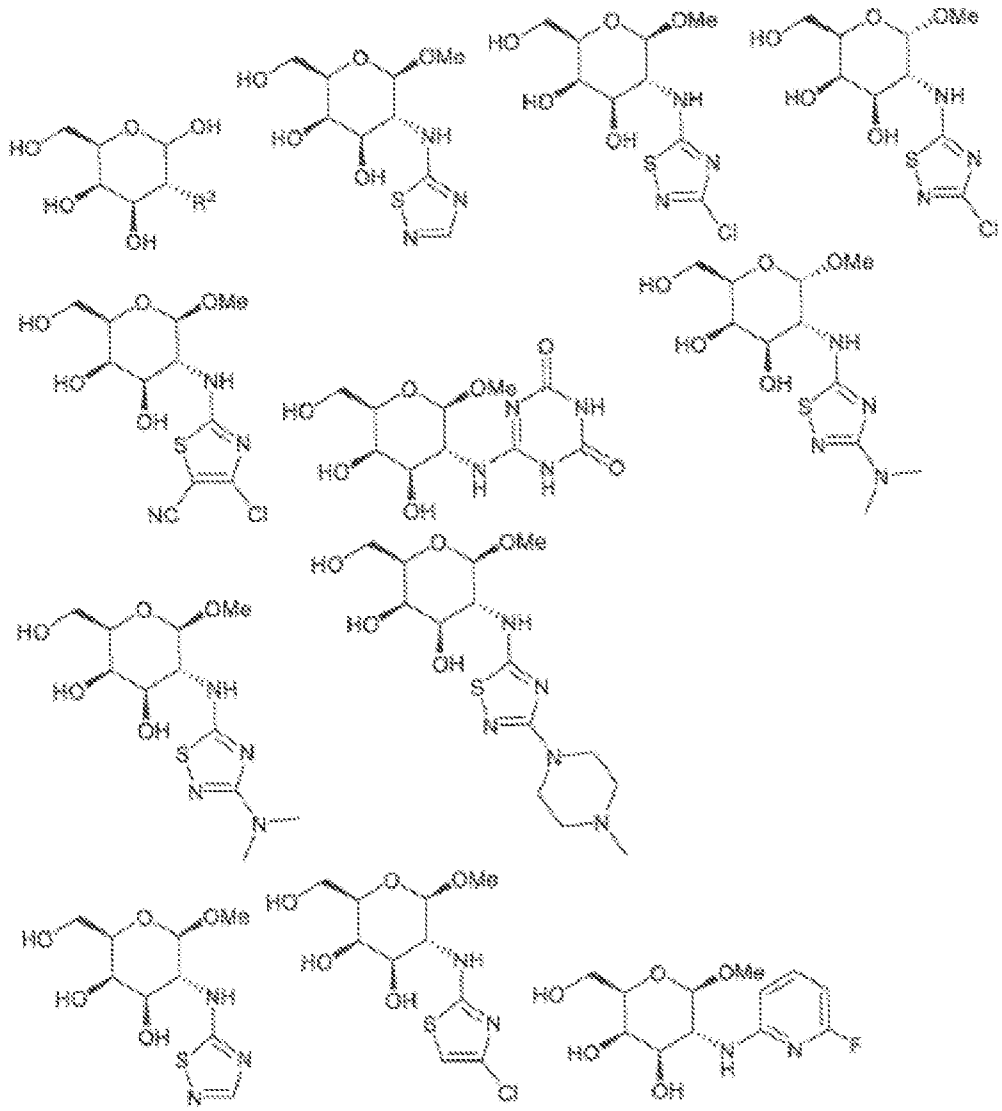
or the bi- or tri- substituted versions thereof or pharmaceutically acceptable salts thereof, where the bi- or tri- substitution

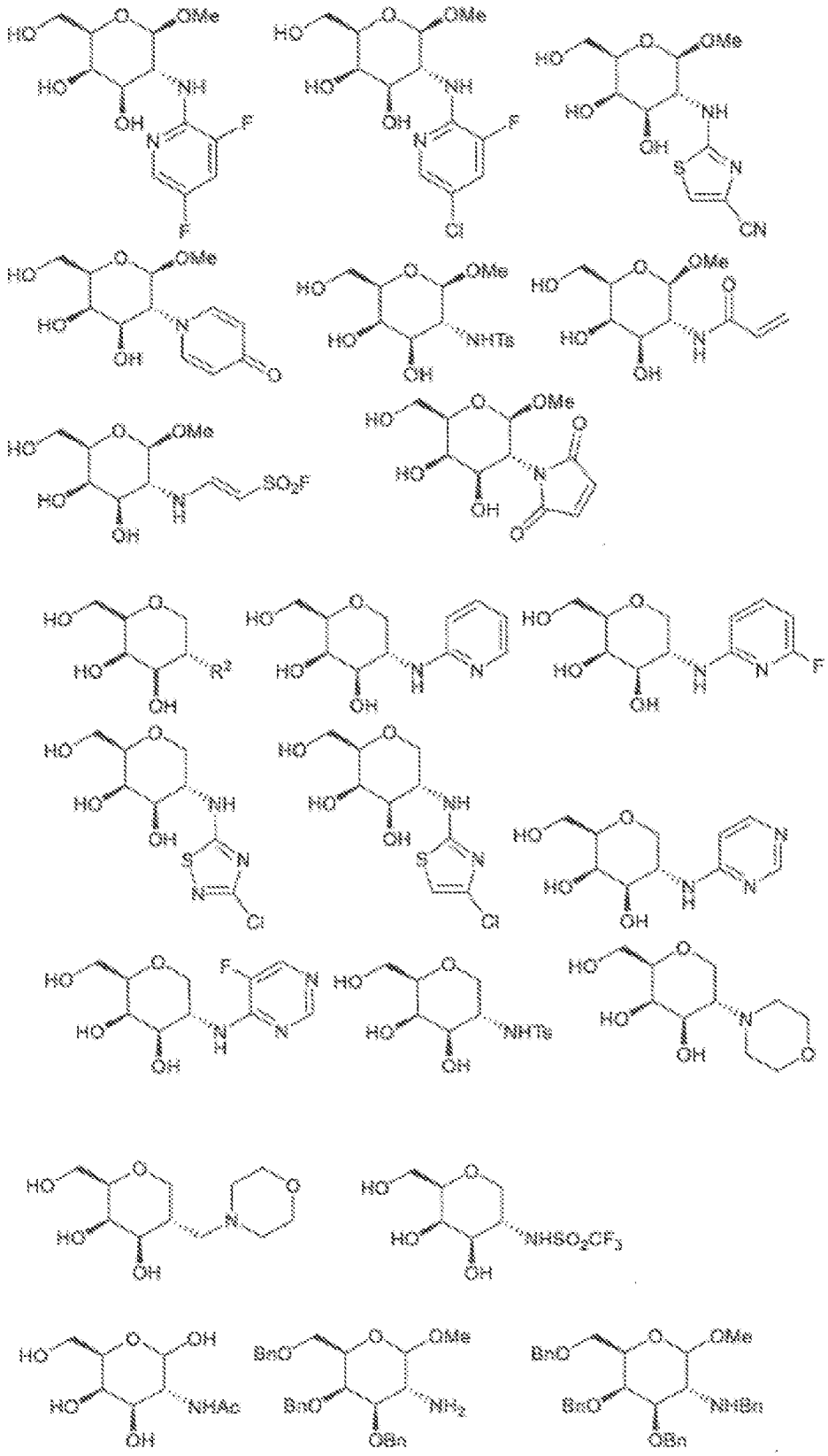
refers to the number additional galactose derivatives attached to a linker moiety.

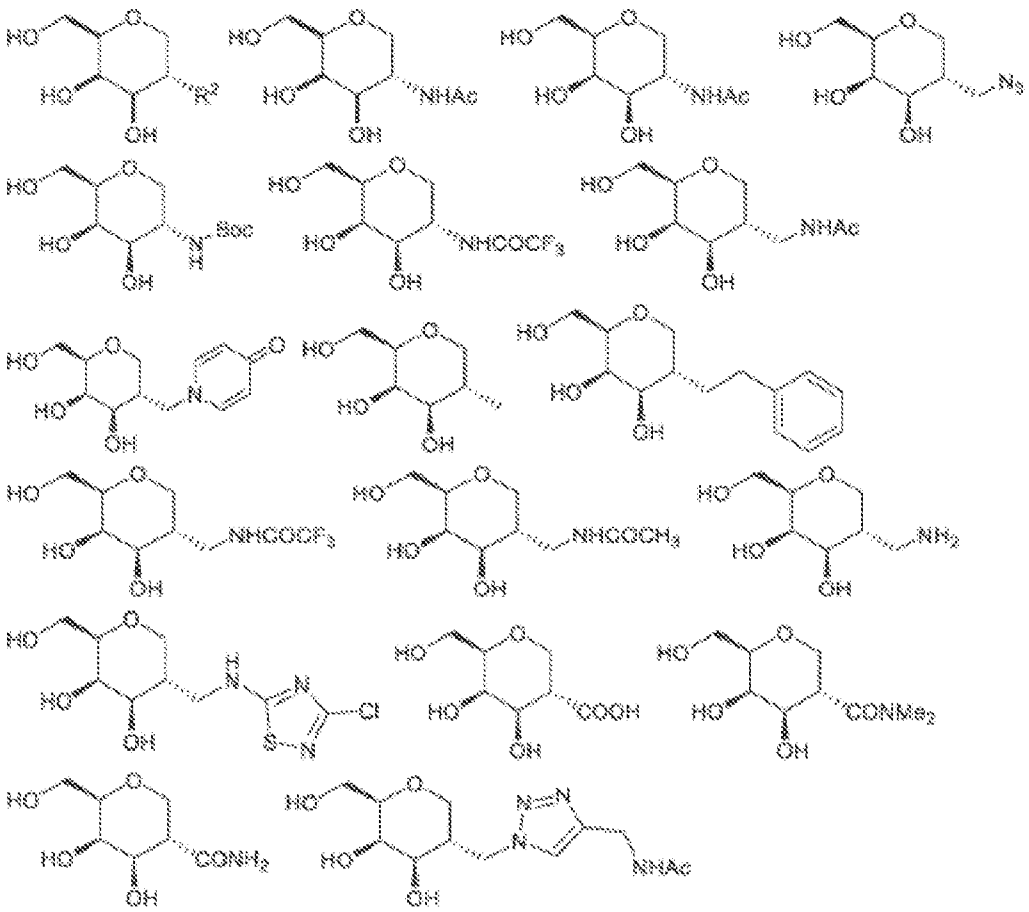
In any of the embodiments herein where an ASGPR ligand is drawn for use in a degrader the ASGPR ligand is typically linked through to the Extracellular Protein Targeting Ligand in the C^5 position (e.g., which can refer to the adjacent C^6 carbon hydroxyl or other functional moiety that can be used for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

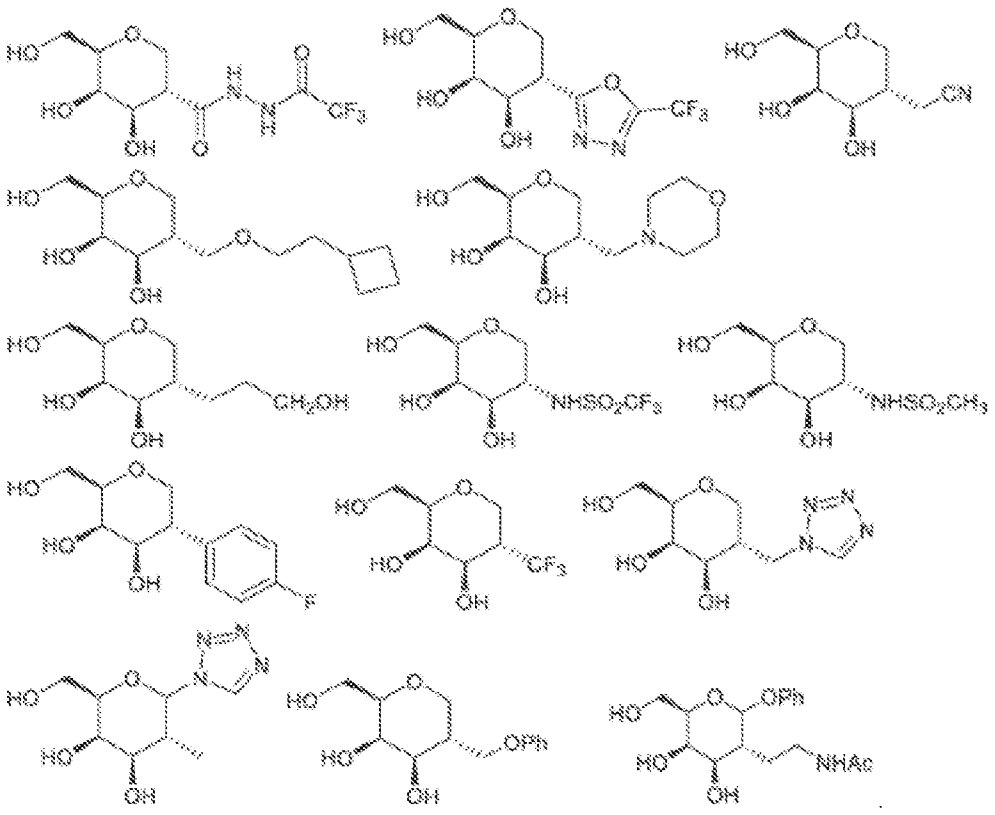
In various embodiments, the ASGPR ligand is not linked in the C^3 or C^4 position, because these positions chelate with the calcium for ASGPR binding in the liver. In certain embodiments, an ASGPR ligand useful for incorporation into a compound of Formula II is selected from:

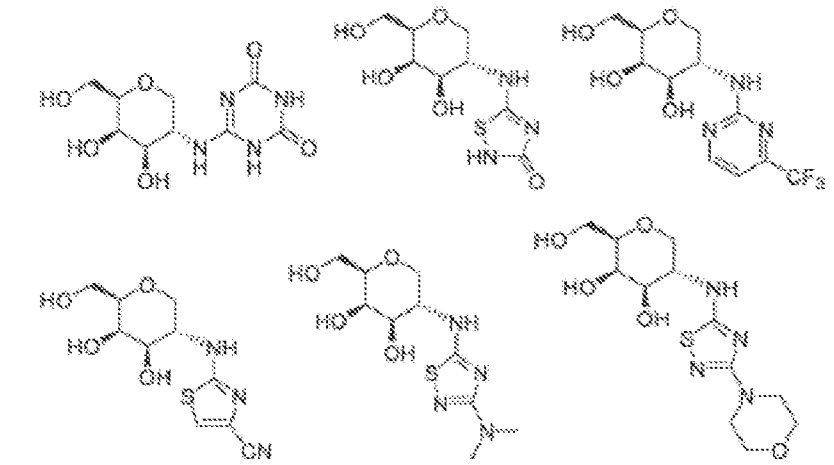


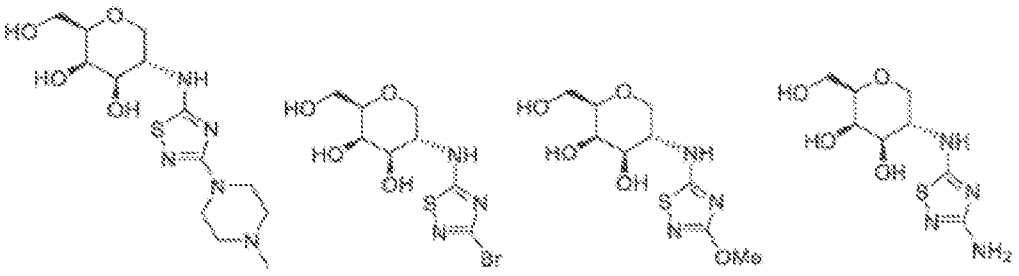


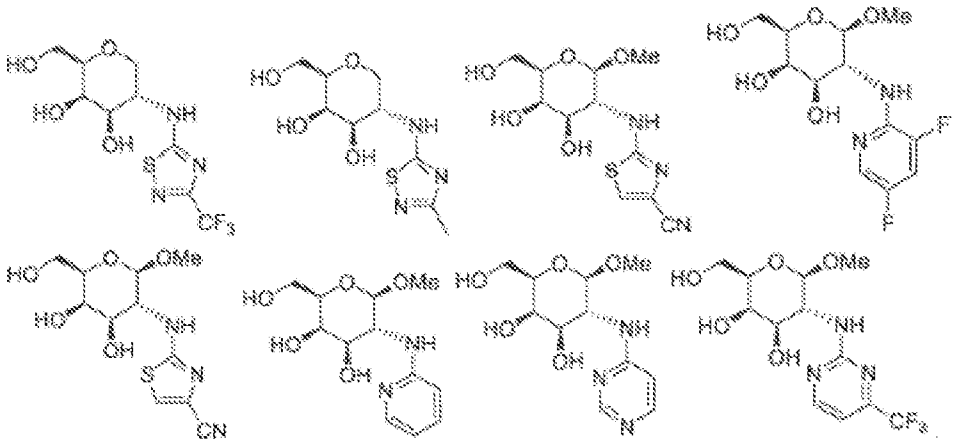


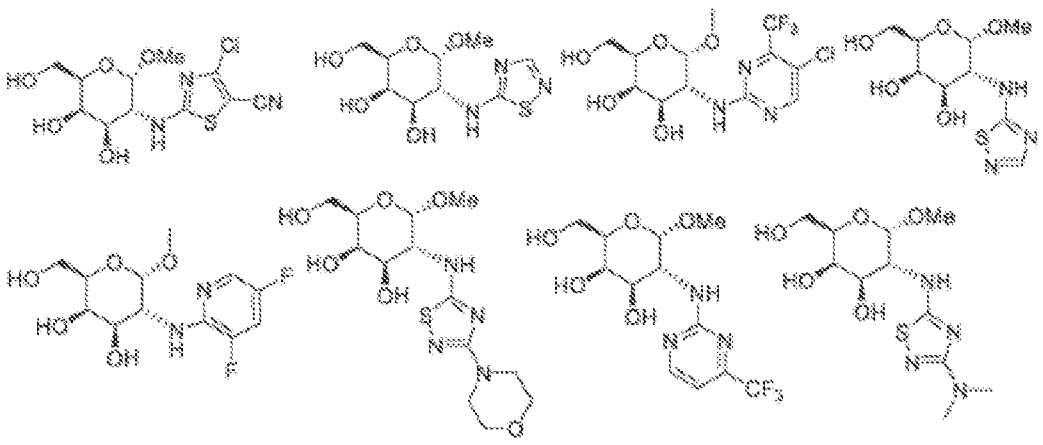


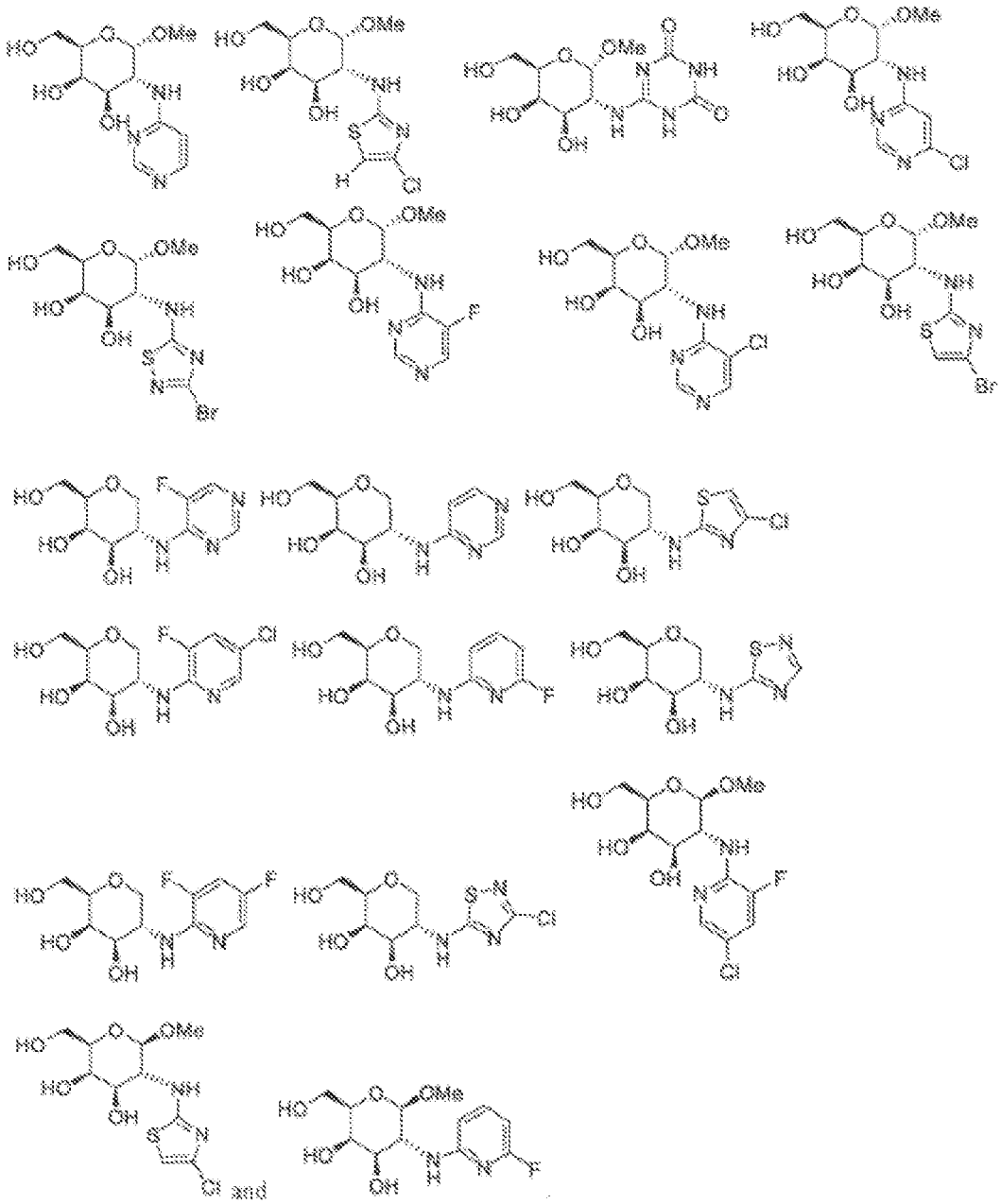












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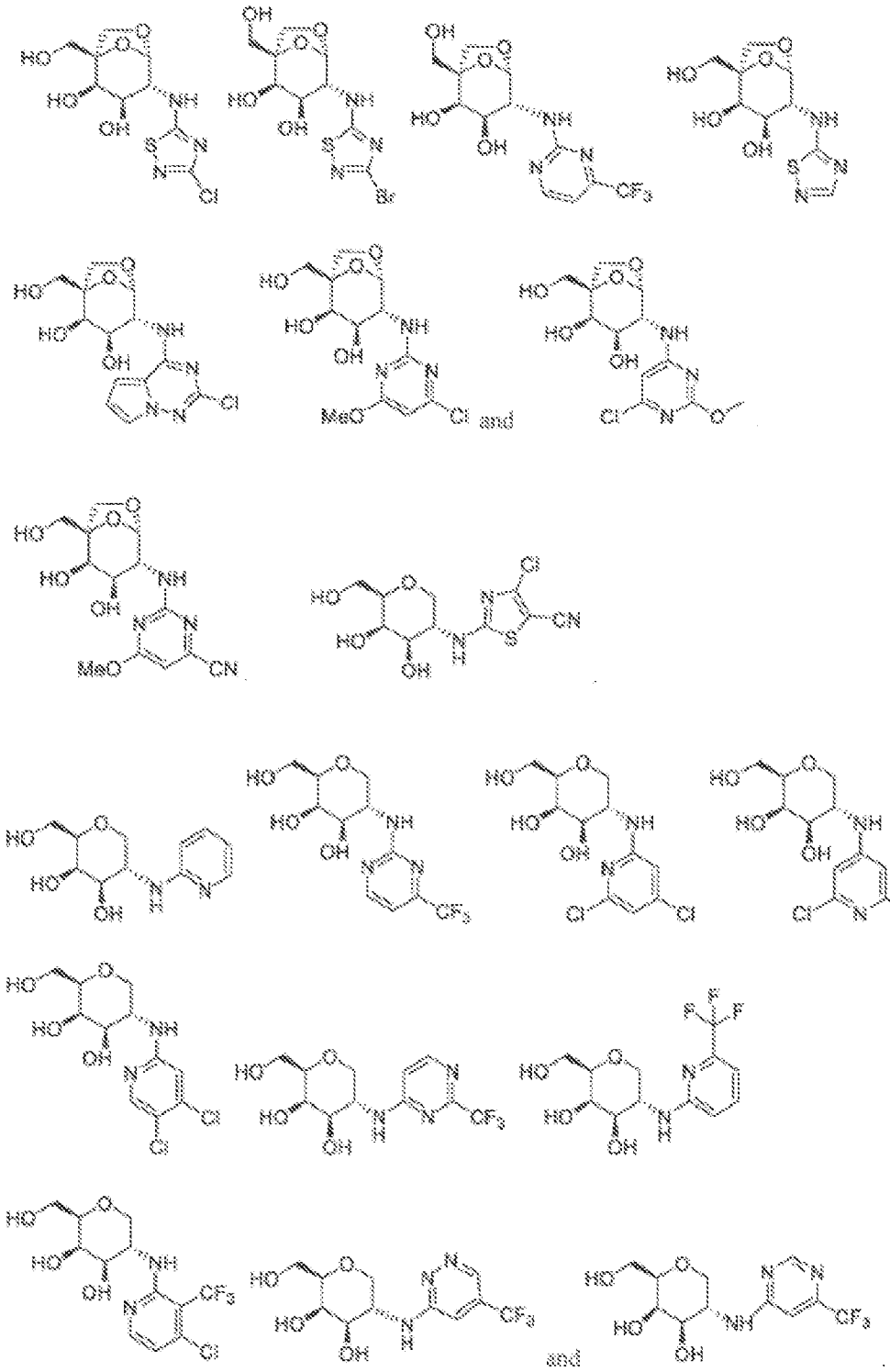
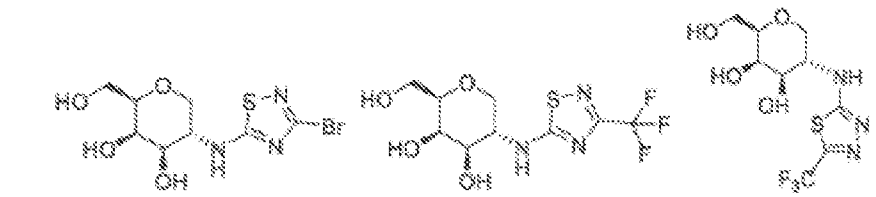
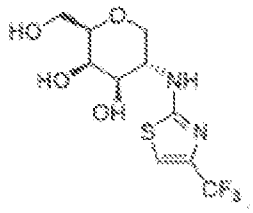
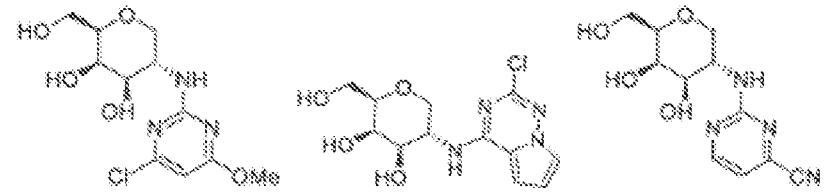
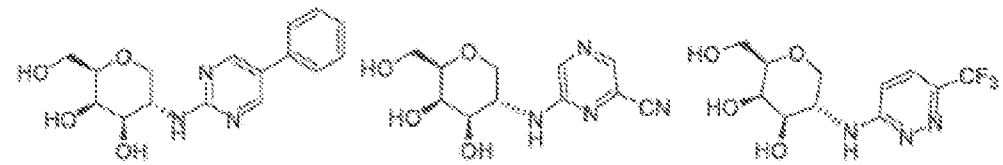
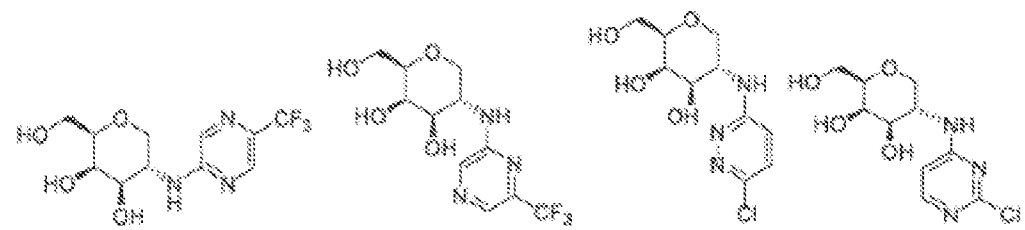


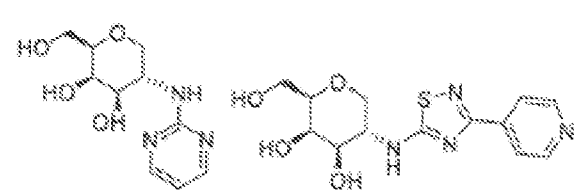


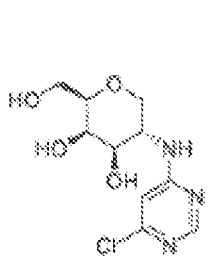


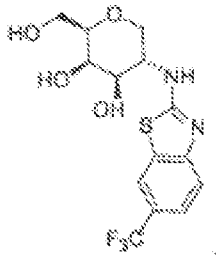


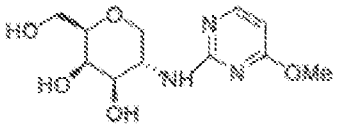


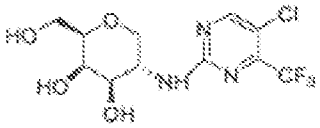


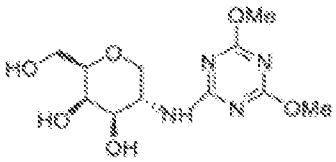


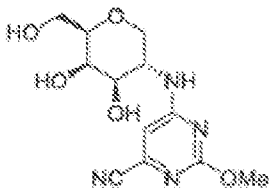


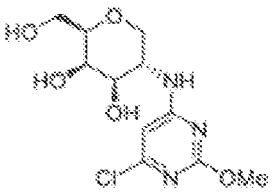


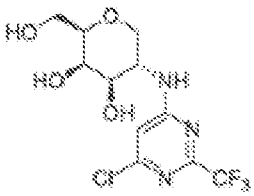


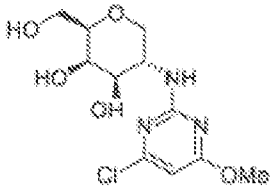


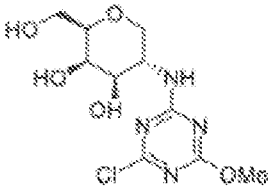


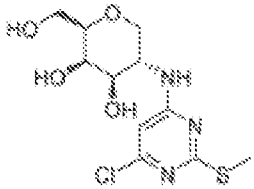


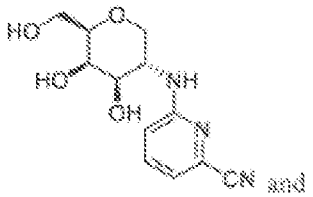




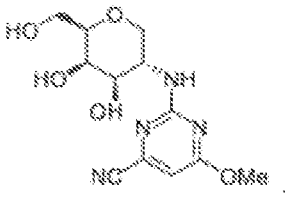


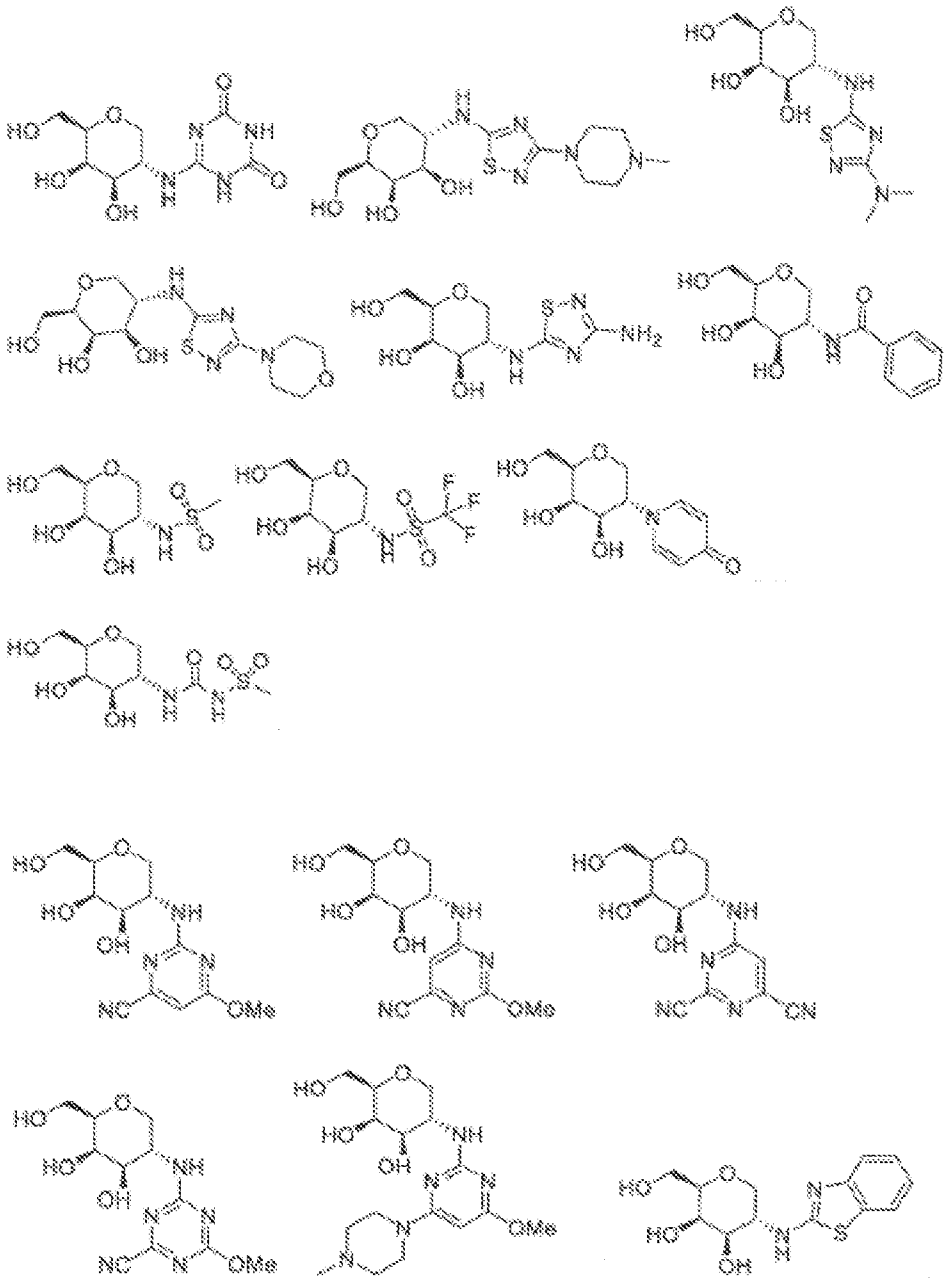


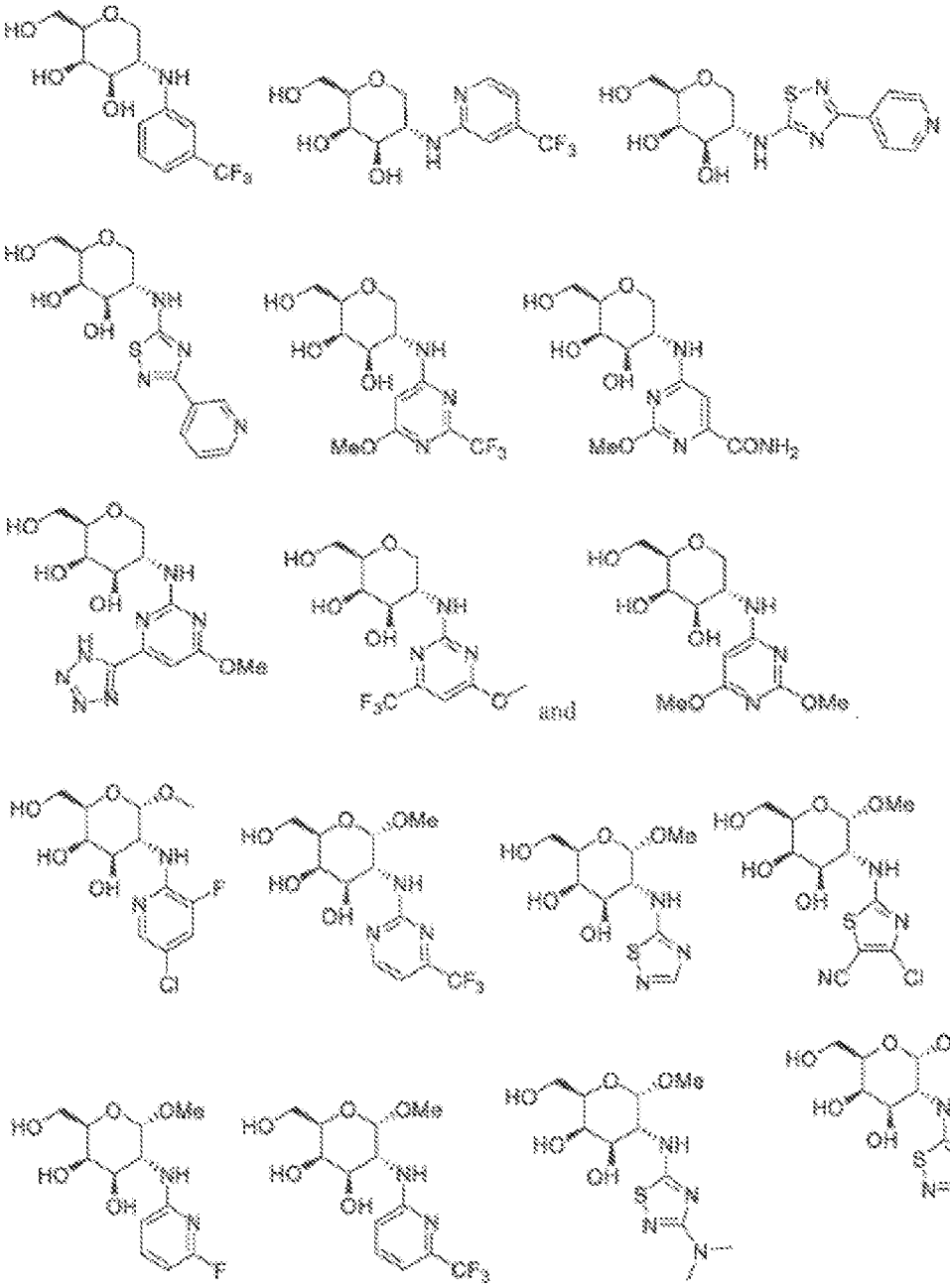


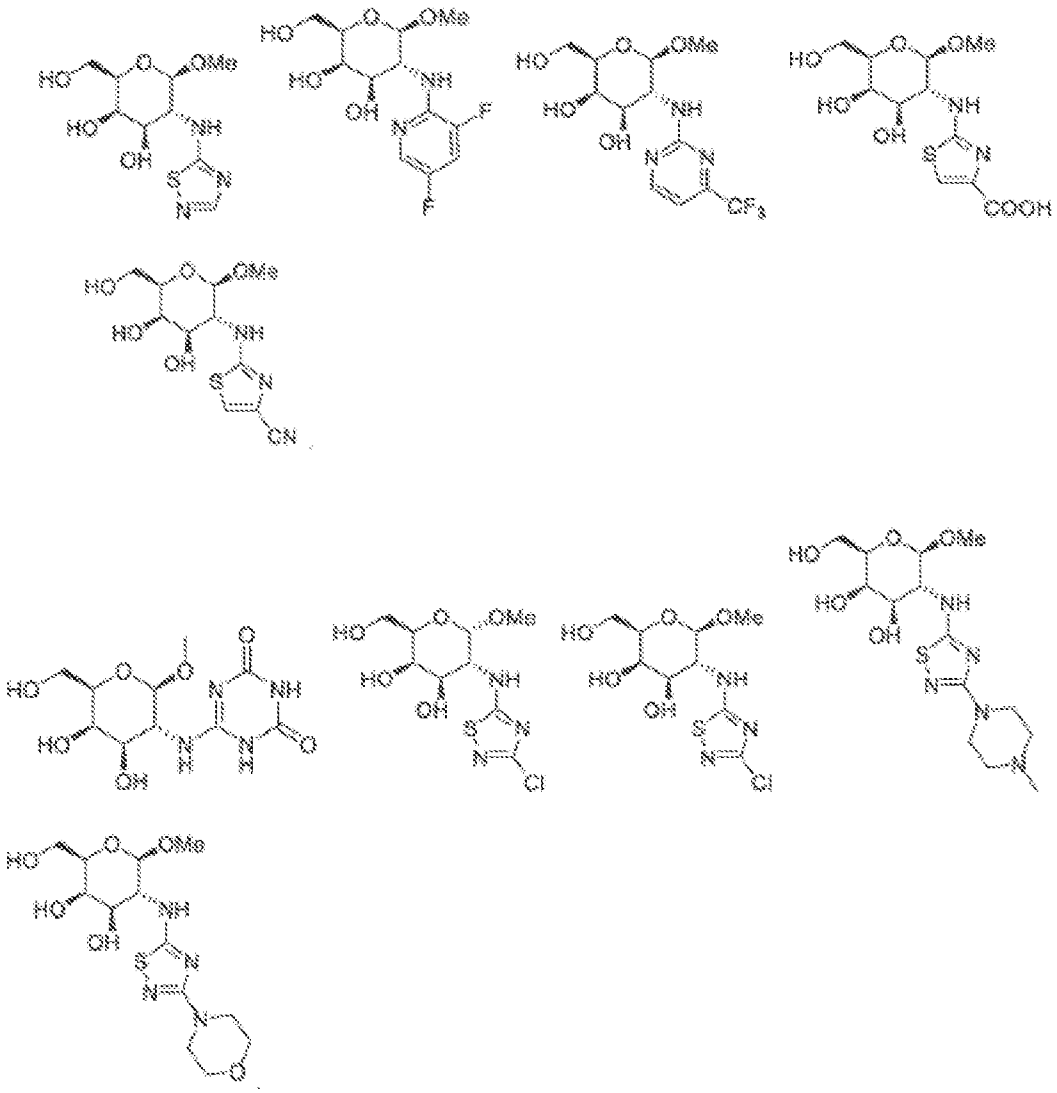


and

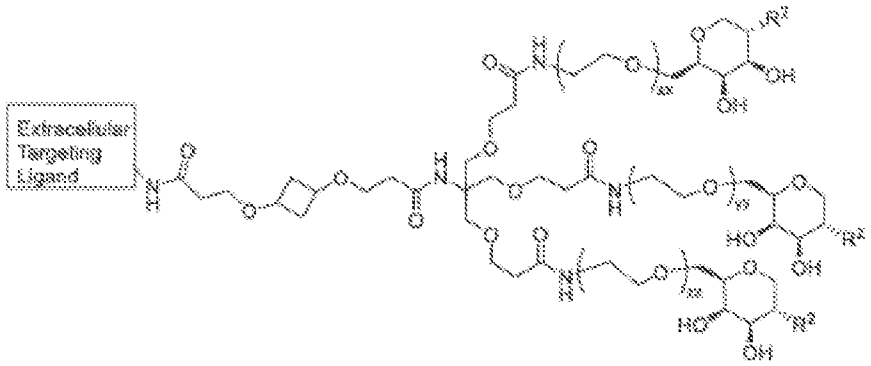


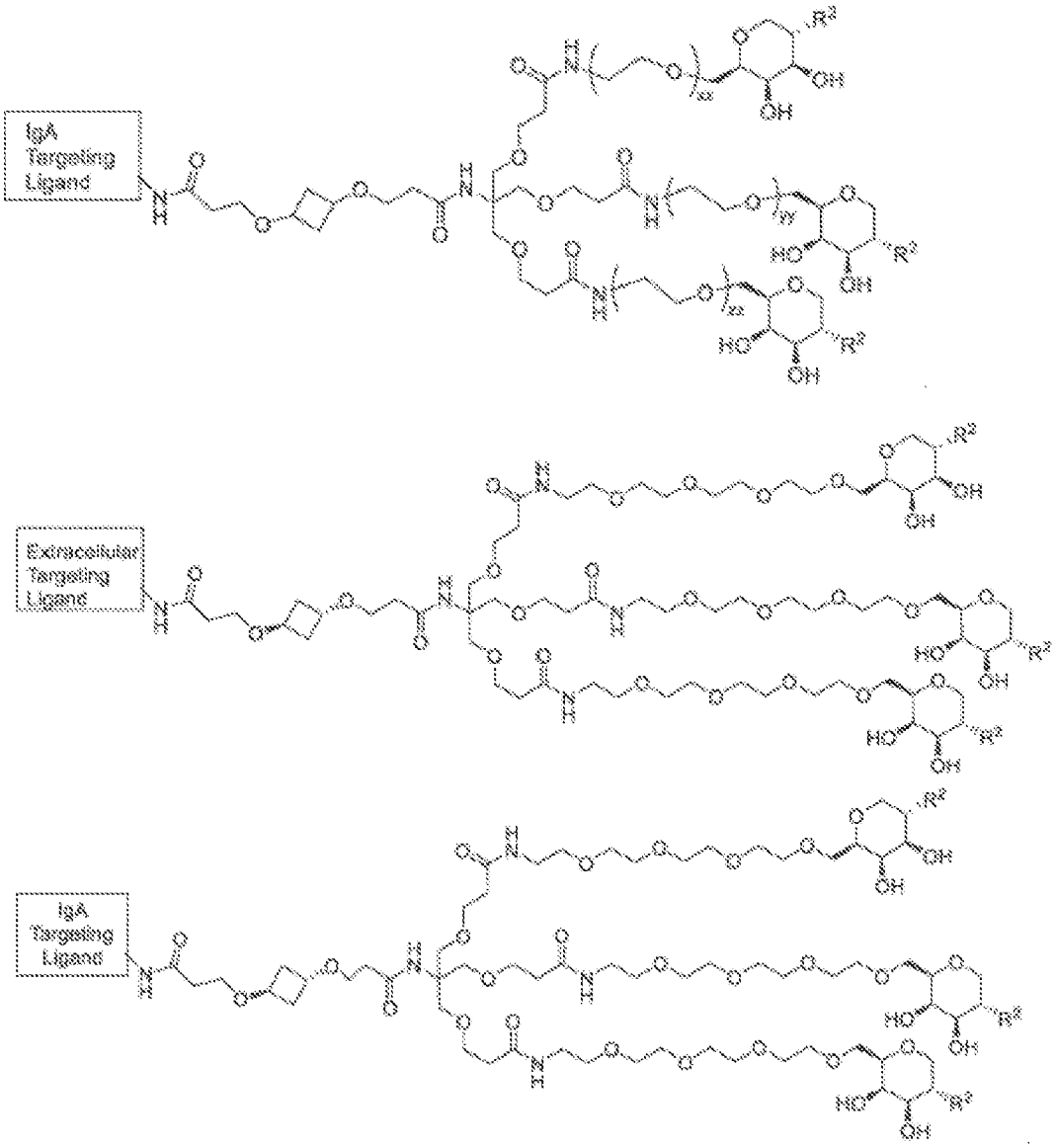


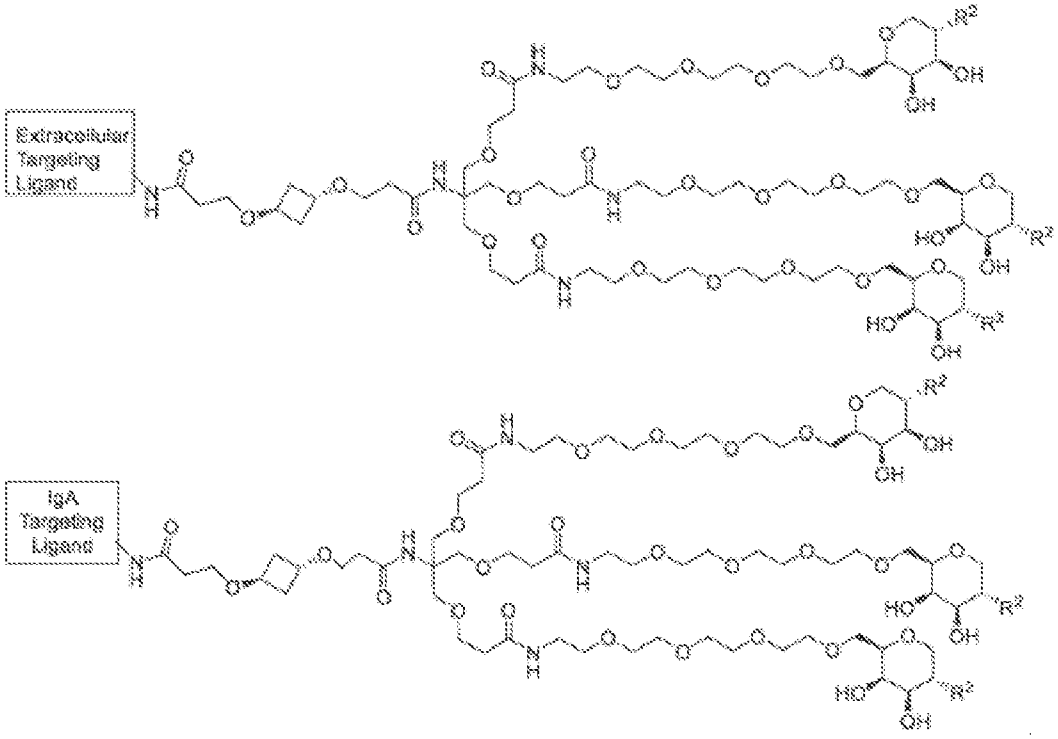


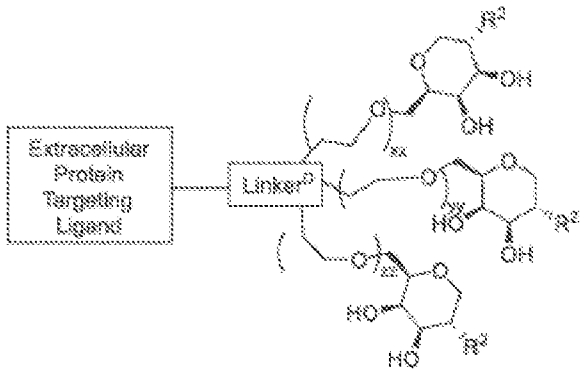


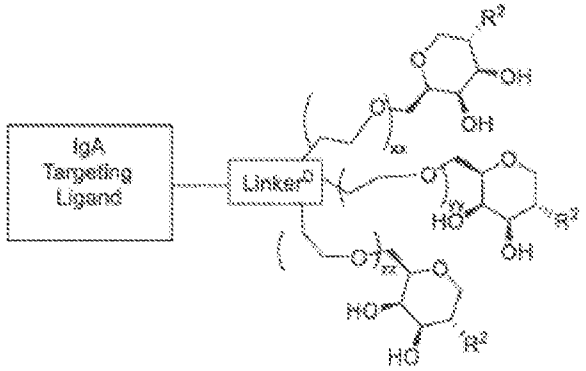
In certain embodiments, the compound of Formula II is selected from:

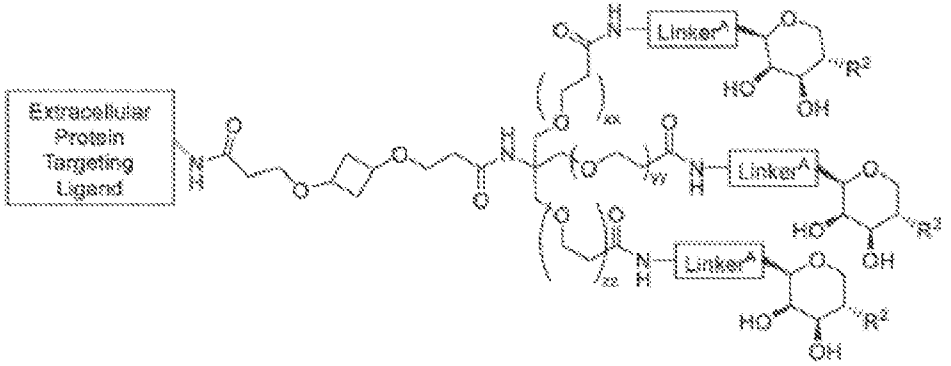


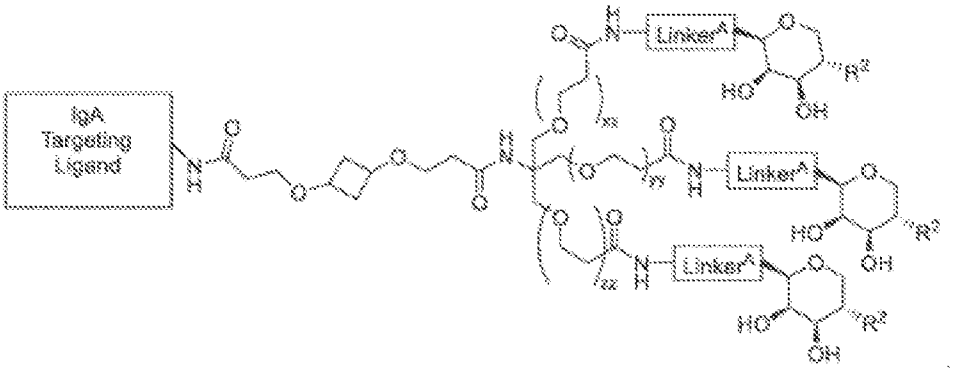

IgA Targeting Ligand
Extracellular Targeting Ligand
IgA Targeting Ligand

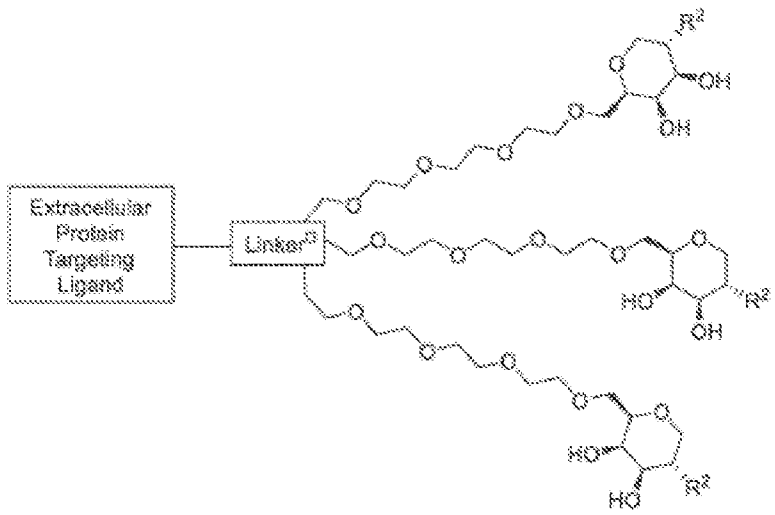

Extracellular Targeting Ligand
IgA Targeting Ligand

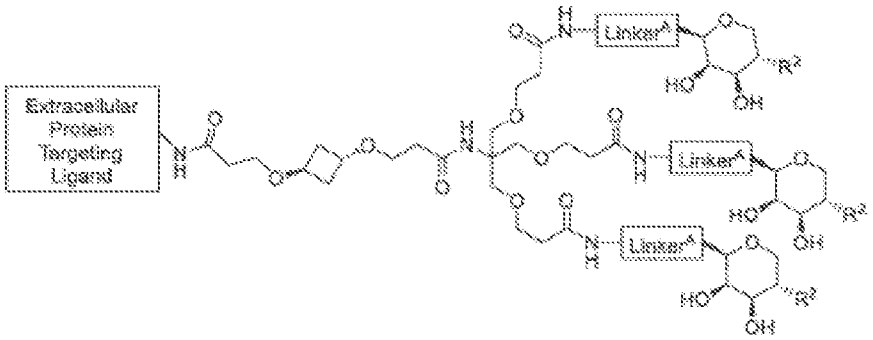

Extracellular Protein Targeting Ligand
Linker
R²
OH
HO


IgA Targeting Ligand
Linker
R²
OH
HO


Extracellular Protein Targeting Ligand
Linker
R²
OH
HO

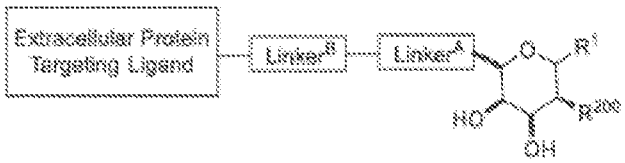

IgA Targeting Ligand
Linker
R²
OH
HO

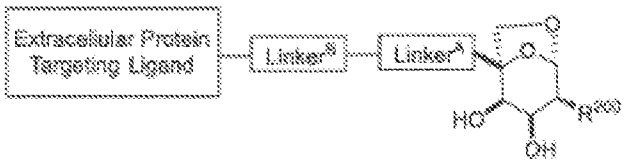


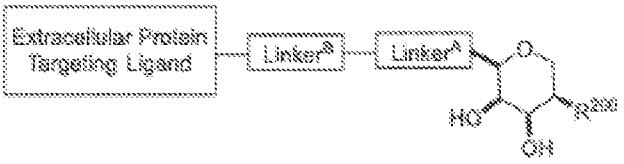


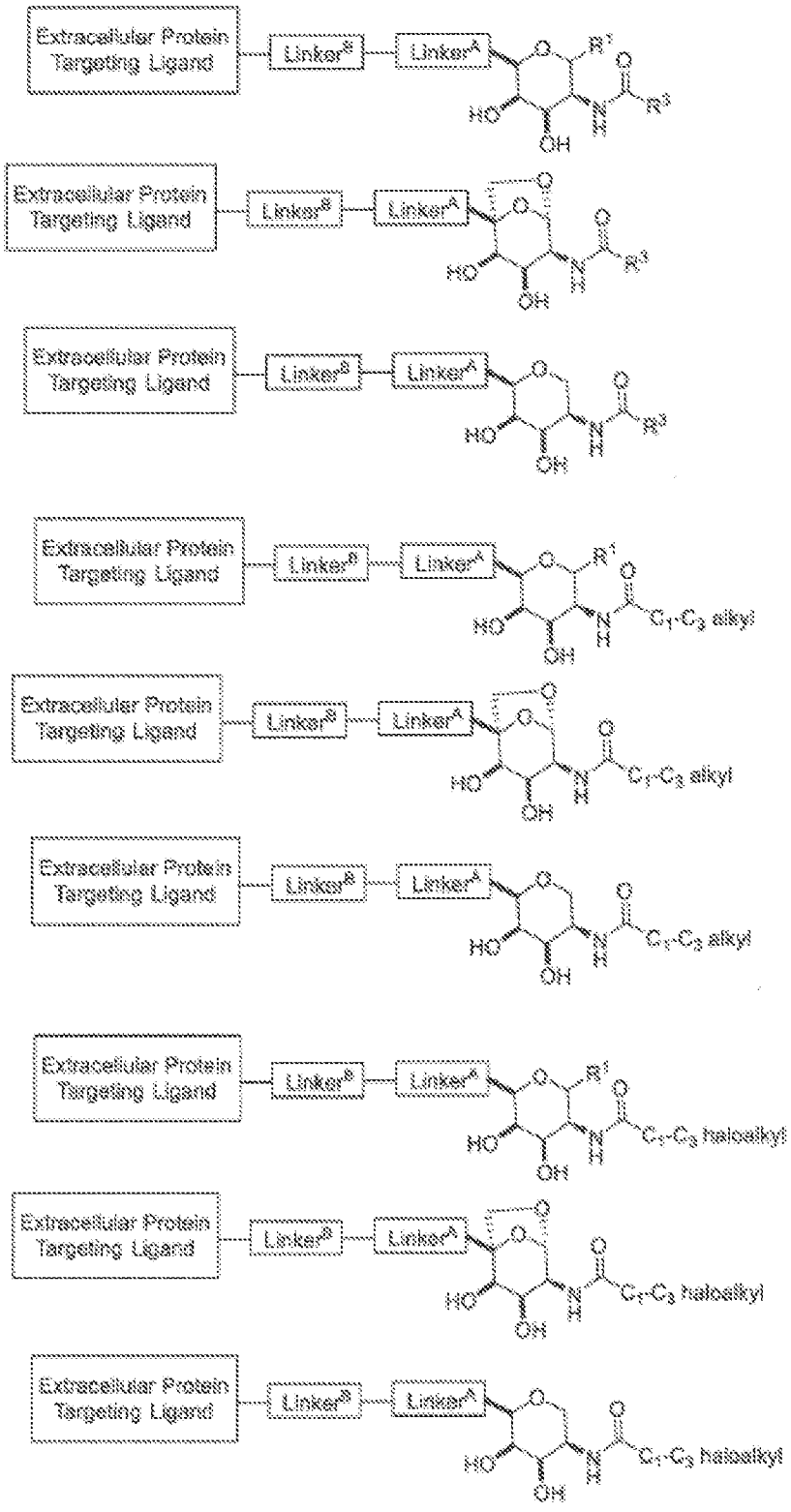
B. Talose-Based ASGPR-Binding Cellular Receptor Binding Moieties of Formula II

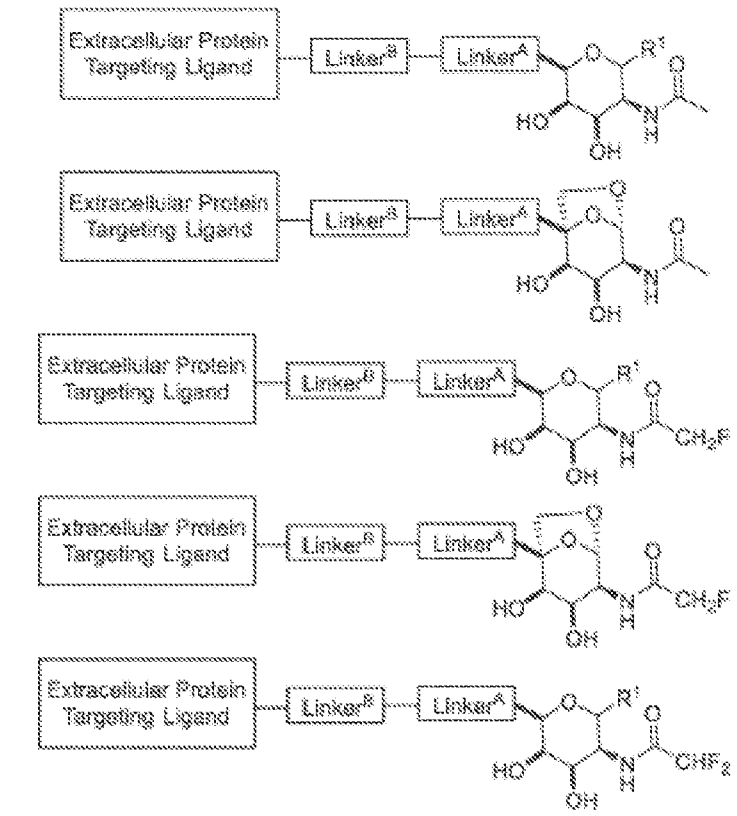
In certain embodiments, the compound of Formula II is selected from:

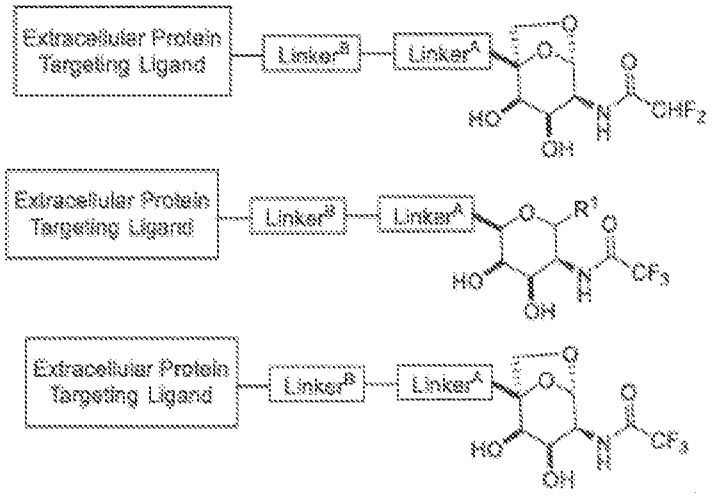


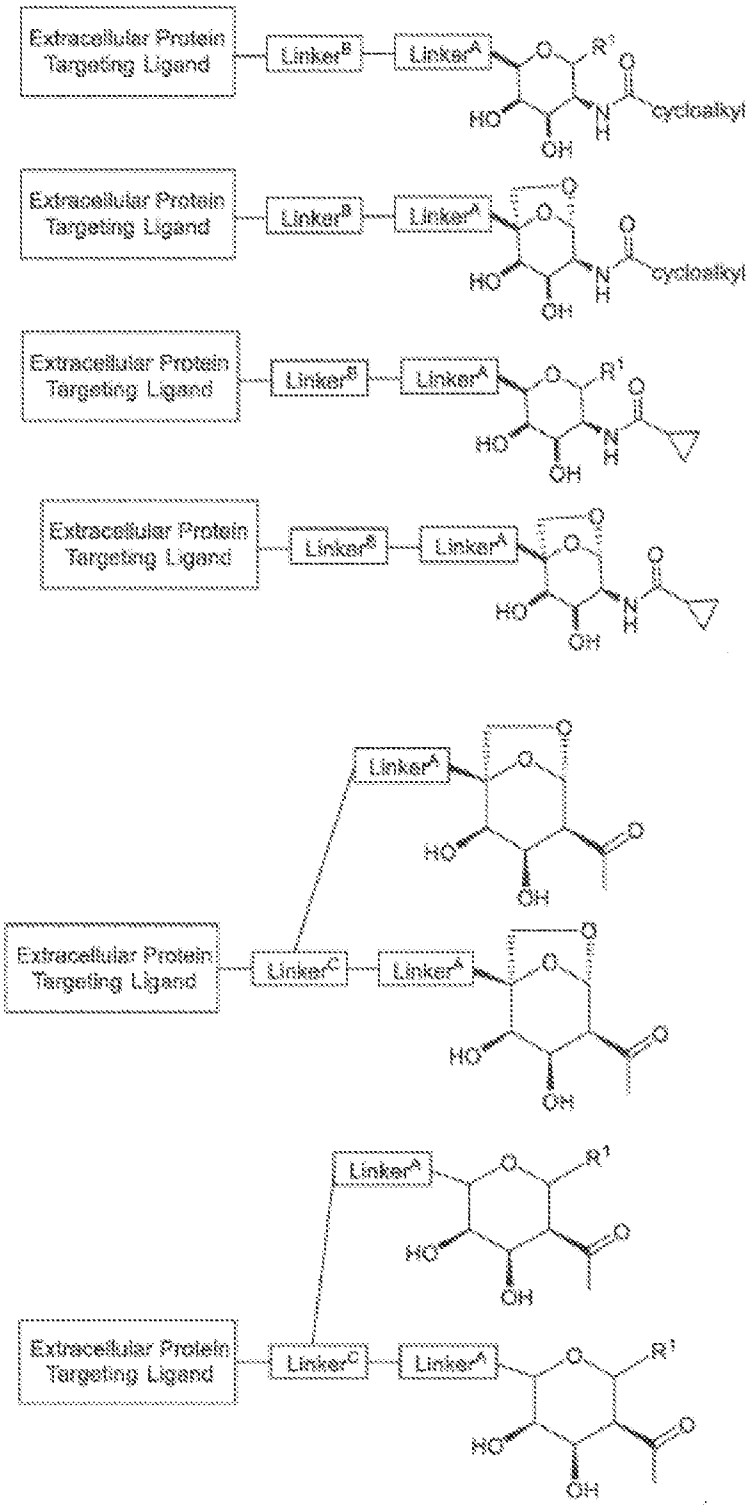


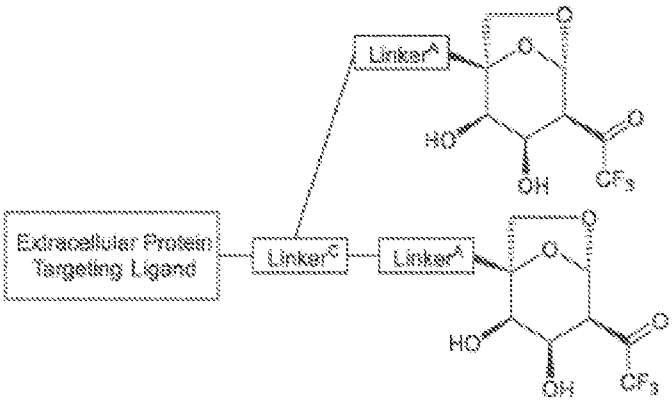


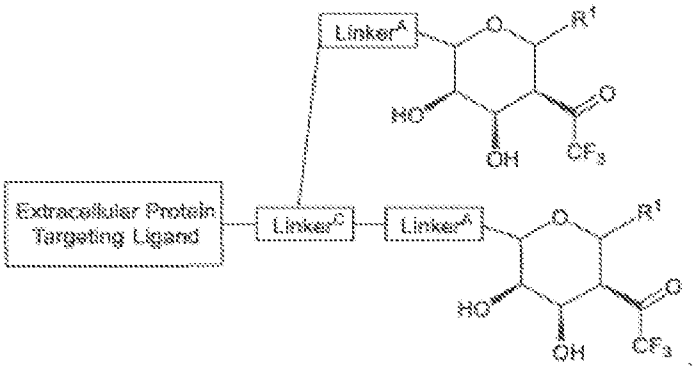

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
C1-C3 alkyl
C1-C3 haloalkyl

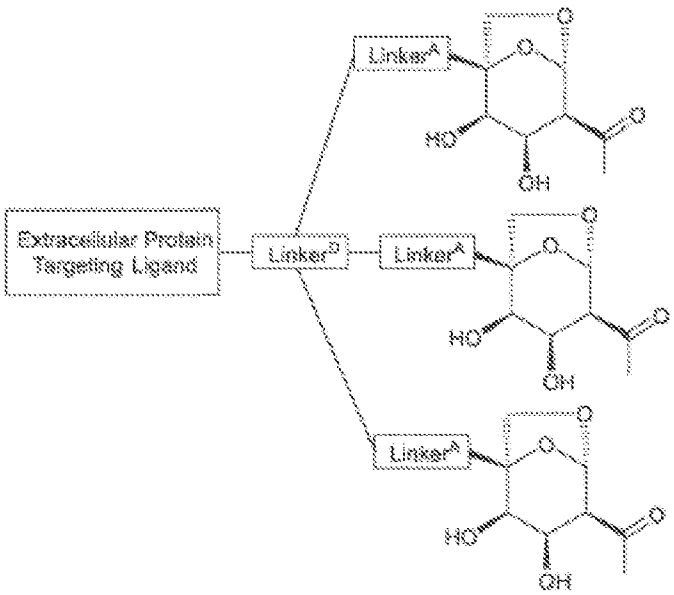

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
N
H
O
R'
CH2F
CHF2
CF3

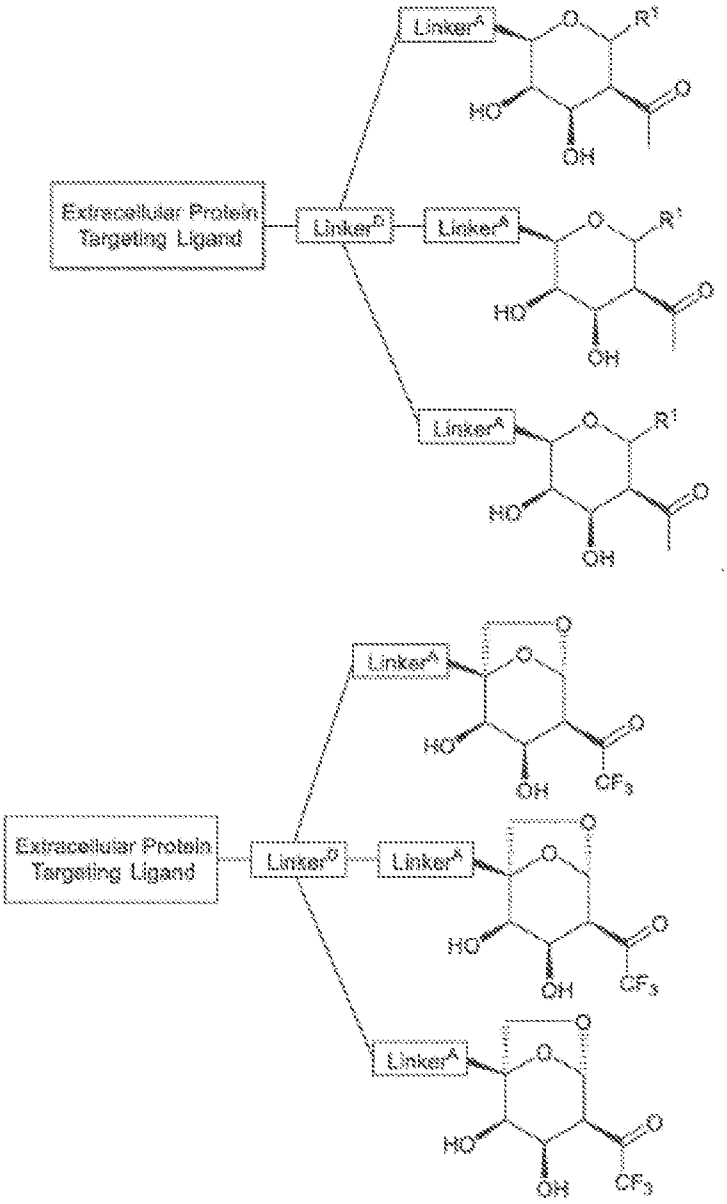

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
N
H
O
R'
CHF2
CF3

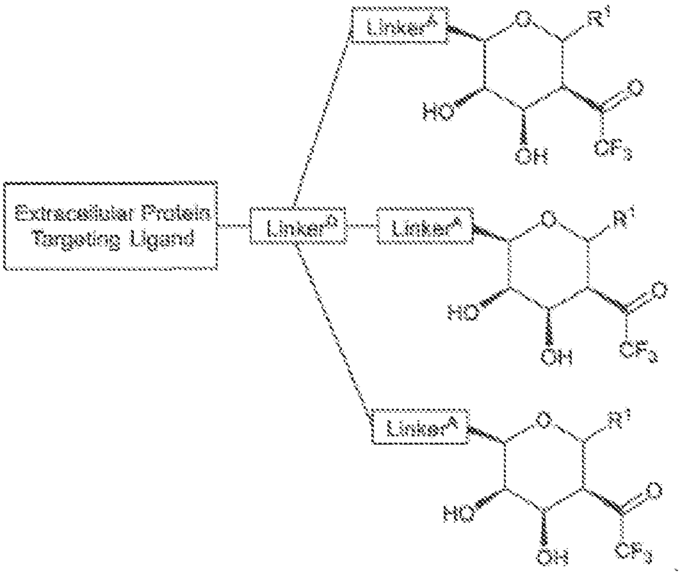

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Linker^C
cycloalkyl
HO
OH
N
H
O

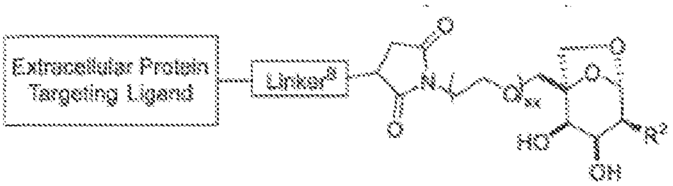

Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
HO
OH
O
CF3

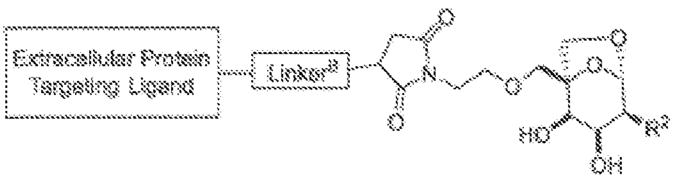

Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
R'
HO
OH
O
CF3

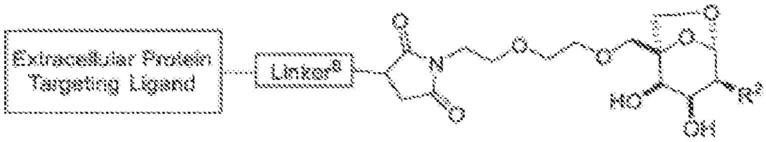

Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
Linker^A
HO
OH
O

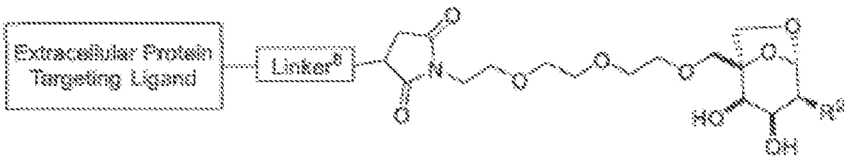

Extracellular Protein Targeting Ligand
Linker^D
Linker^A
R^1
HO
OH
O
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
HO
OH
CF3
O

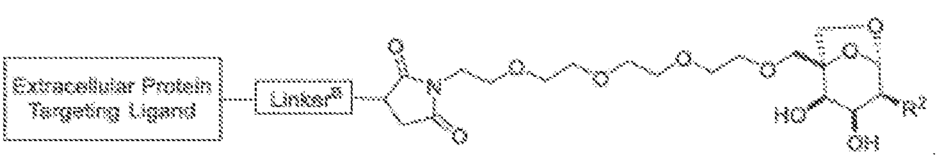

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Linker^A
Linker^A

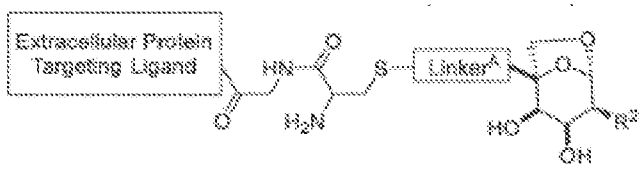

Extracellular Protein Targeting Ligand
Linker^B

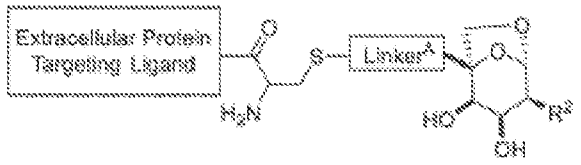

Extracellular Protein Targeting Ligand
Linker^B

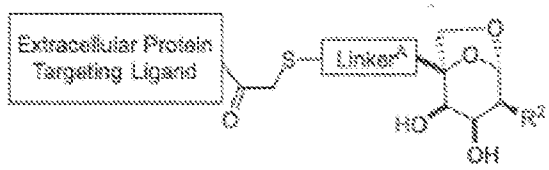

Extracellular Protein Targeting Ligand
Linker^B

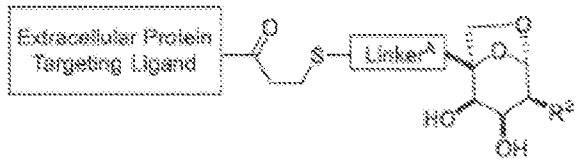

Extracellular Protein Targeting Ligand
Linker^B

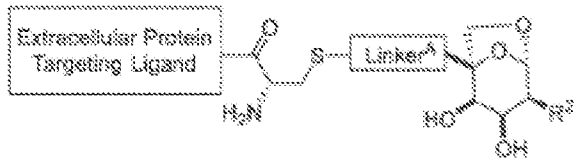

Extracellular Protein Targeting Ligand
Linker^B

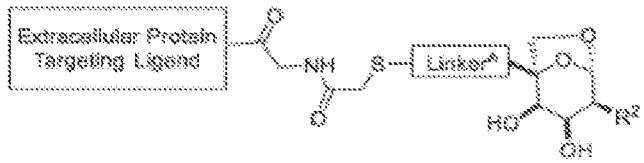

Extracellular Protein Targeting Ligand
HN
O
S
Linker^A
O
HO
OH
R^2
H_2N

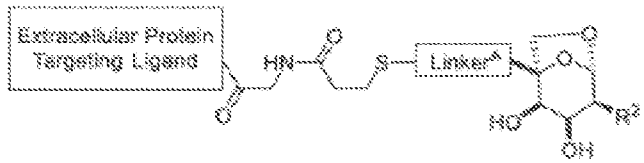

Extracellular Protein Targeting Ligand
O
S
Linker^A
O
HO
OH
R^2
H_2N

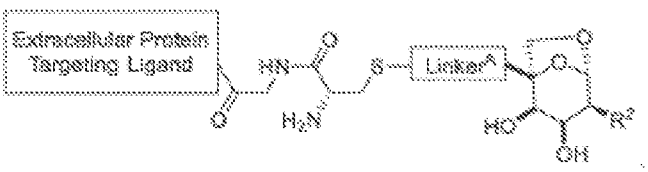

Extracellular Protein Targeting Ligand
S
Linker^A
O
HO
OH
R^2


Extracellular Protein Targeting Ligand
O
S
Linker^A
O
HO
OH
R^2


Extracellular Protein Targeting Ligand
O
S
Linker^A
O
HO
OH
R^2
H_2N


Extracellular Protein Targeting Ligand
NH
S
Linker^A
O
HO
OH
R^2


Extracellular Protein Targeting Ligand
HN
O
S
Linker^A
O
HO
OH
R^2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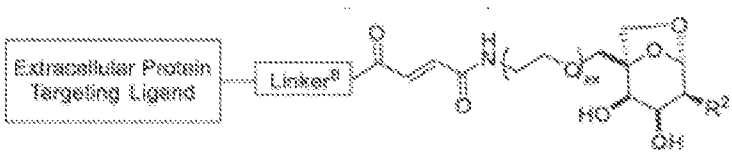
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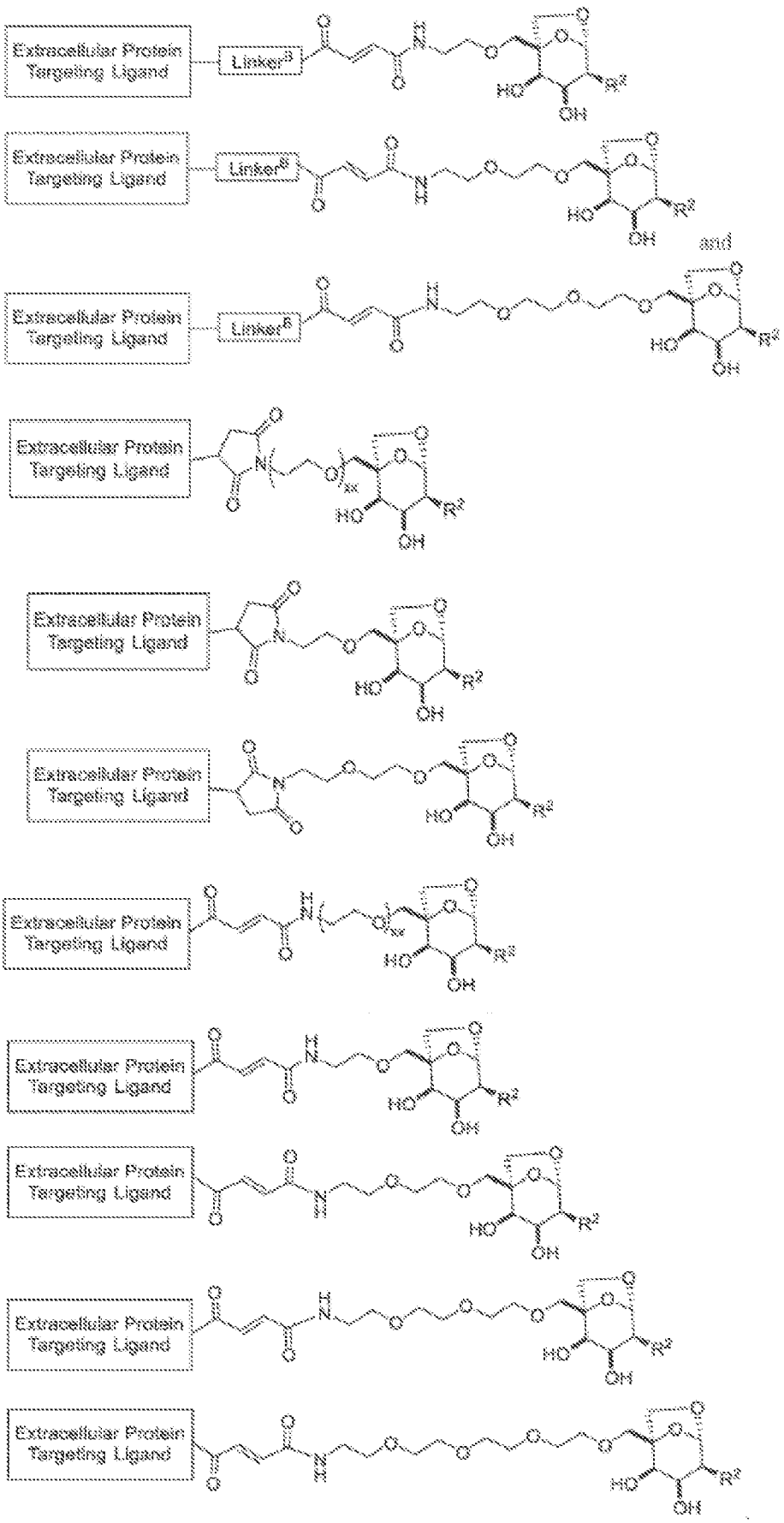
O
HO
OH
R^2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Linker
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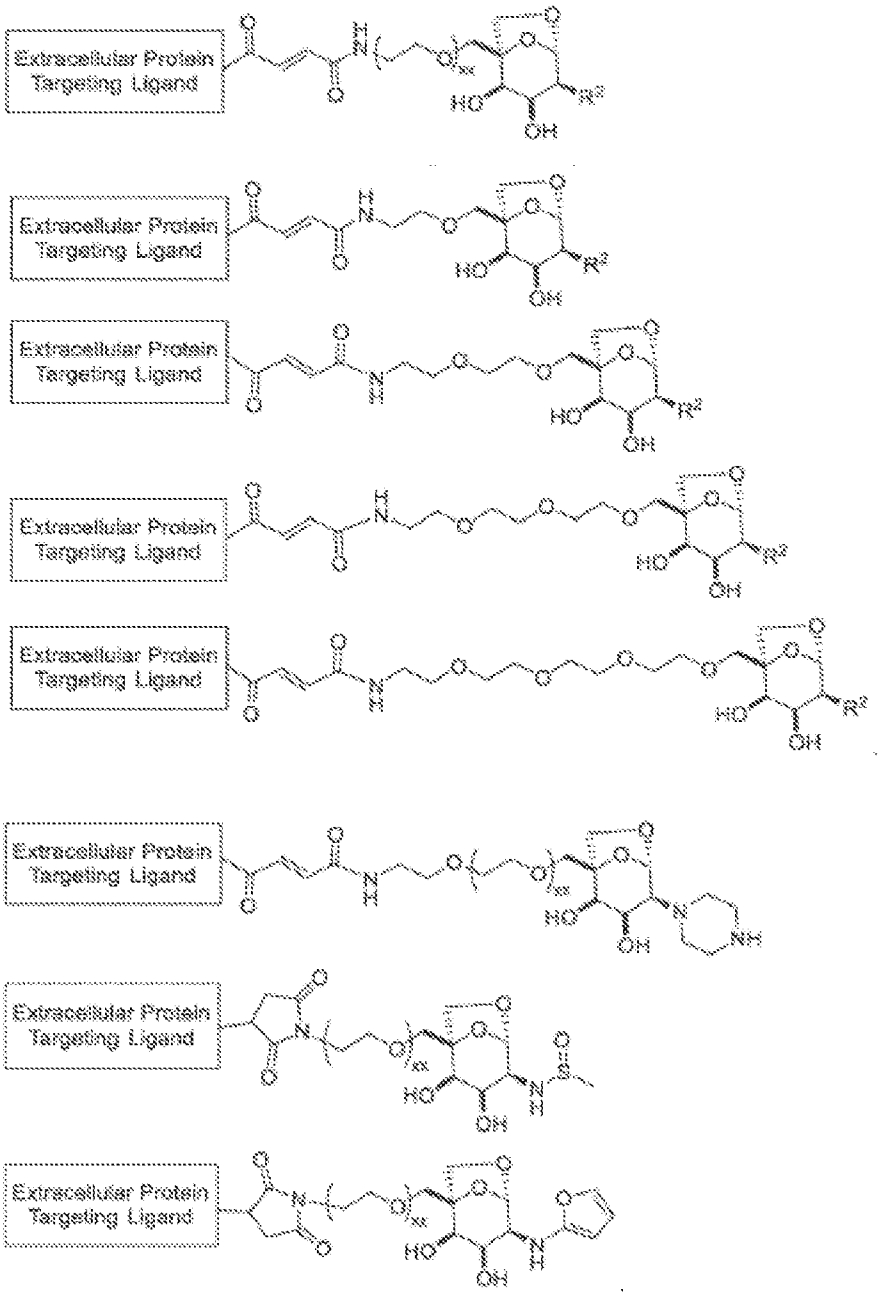
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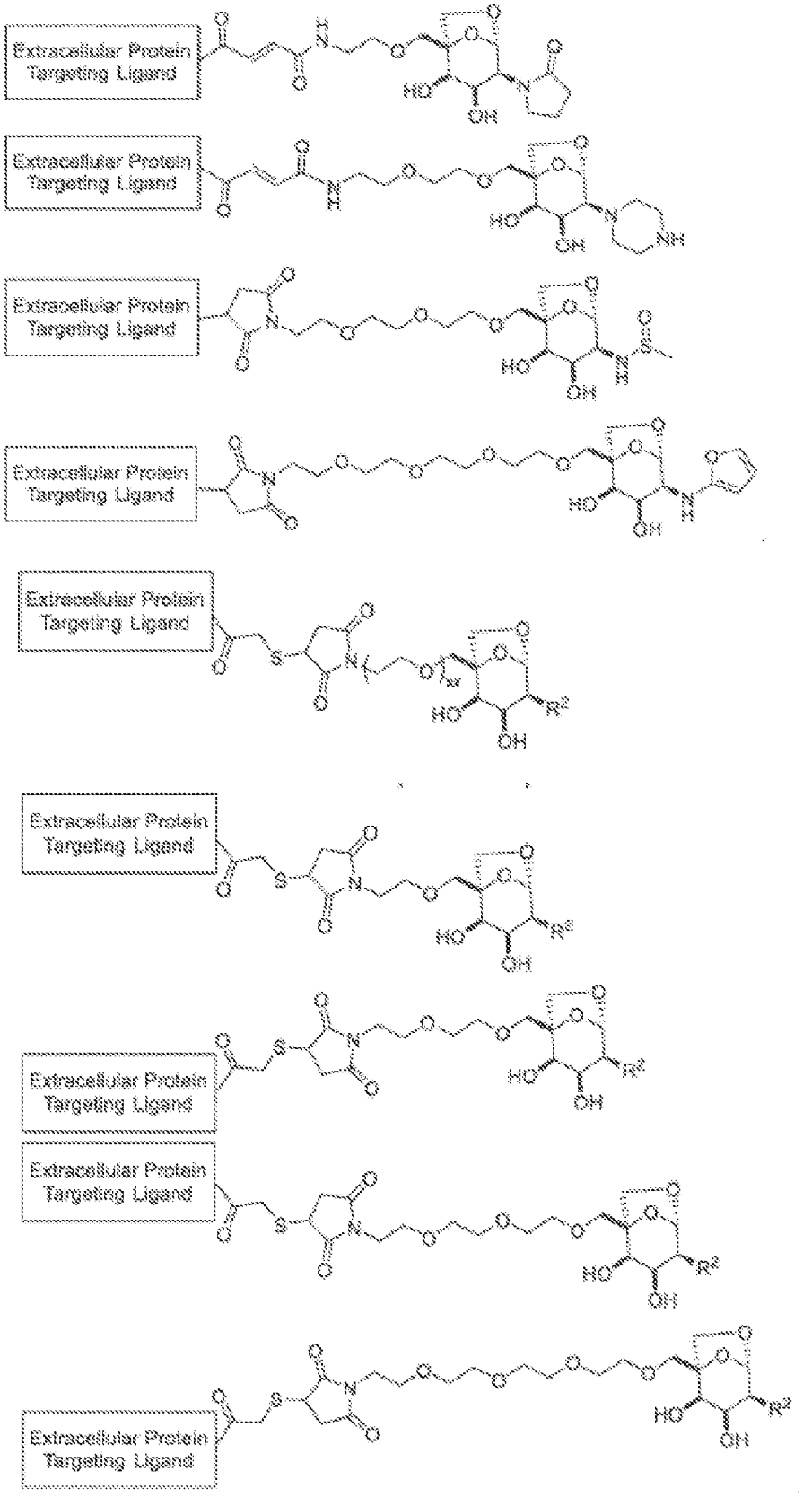
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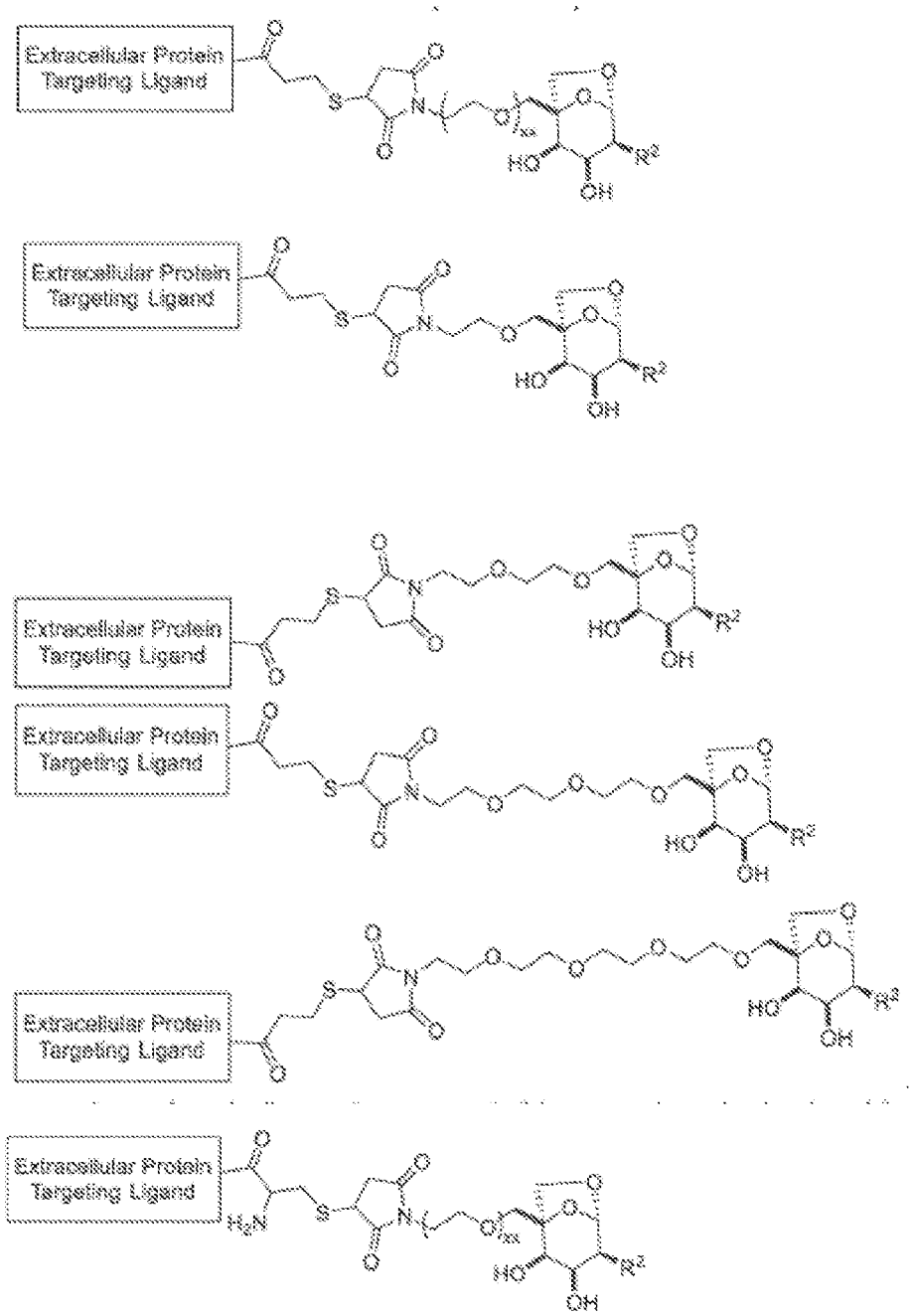
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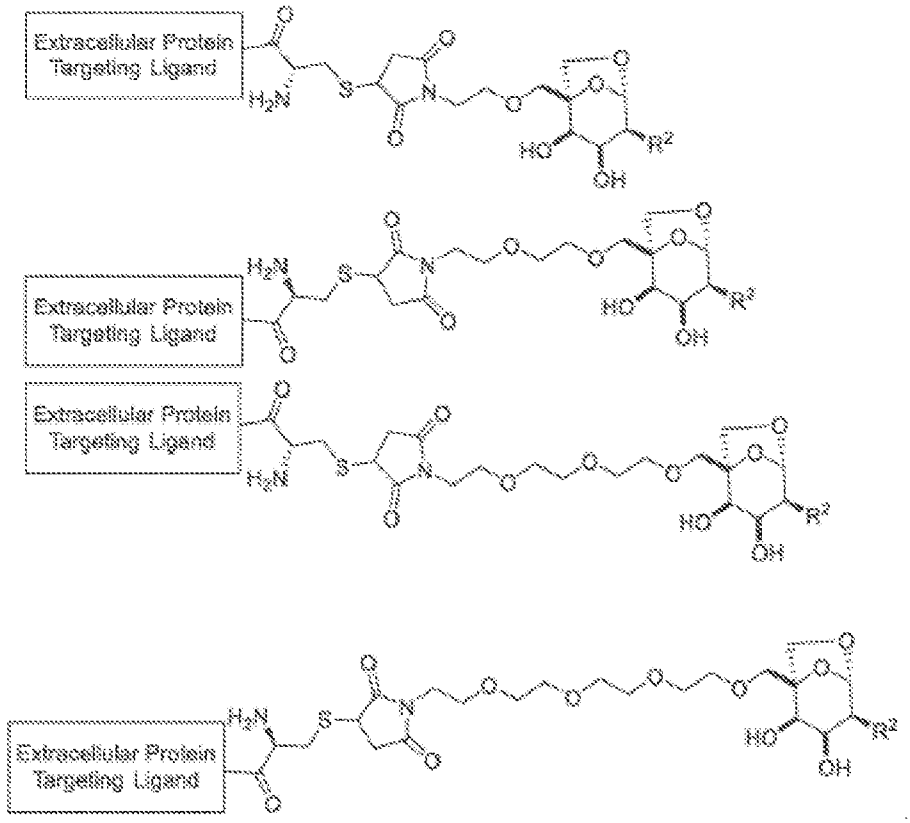
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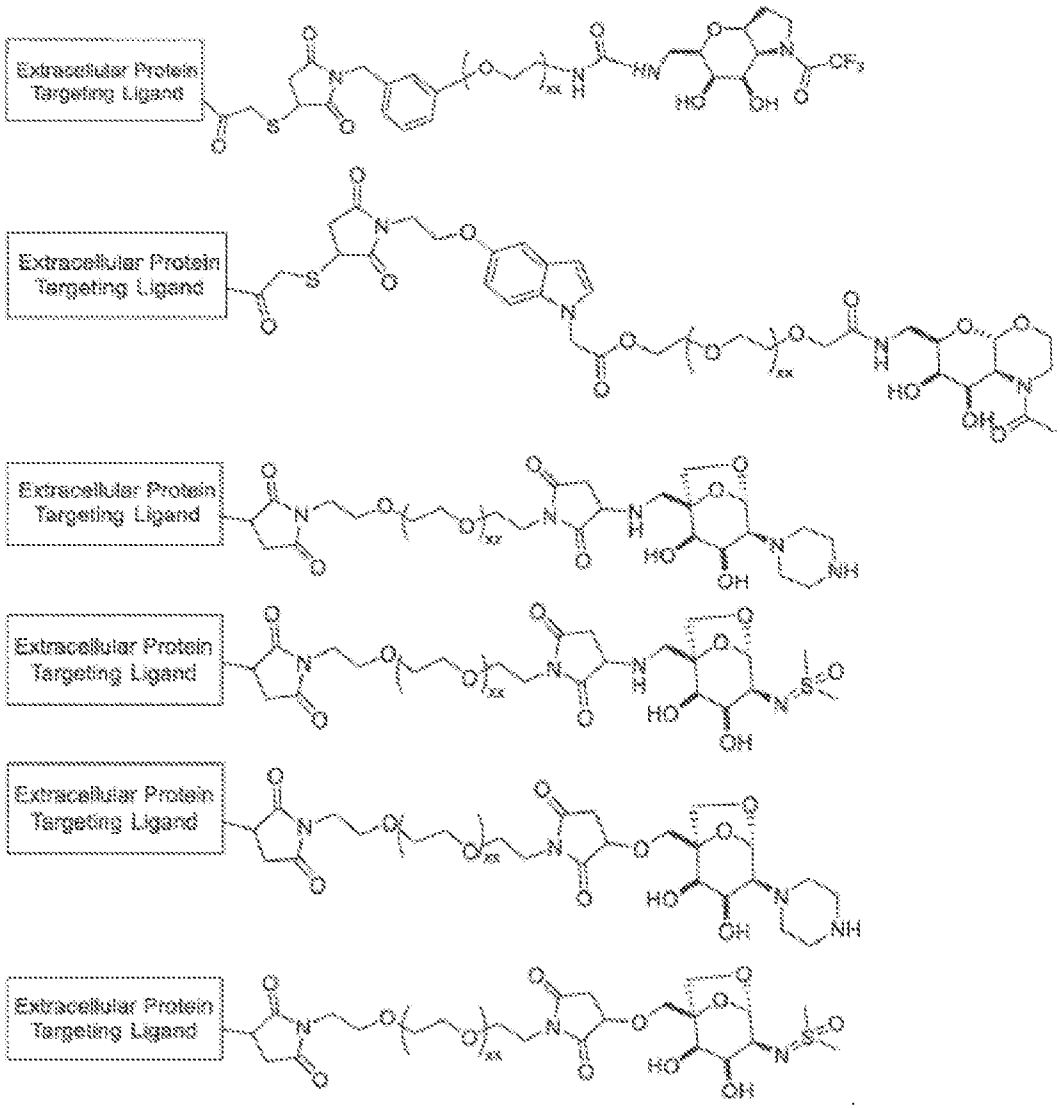
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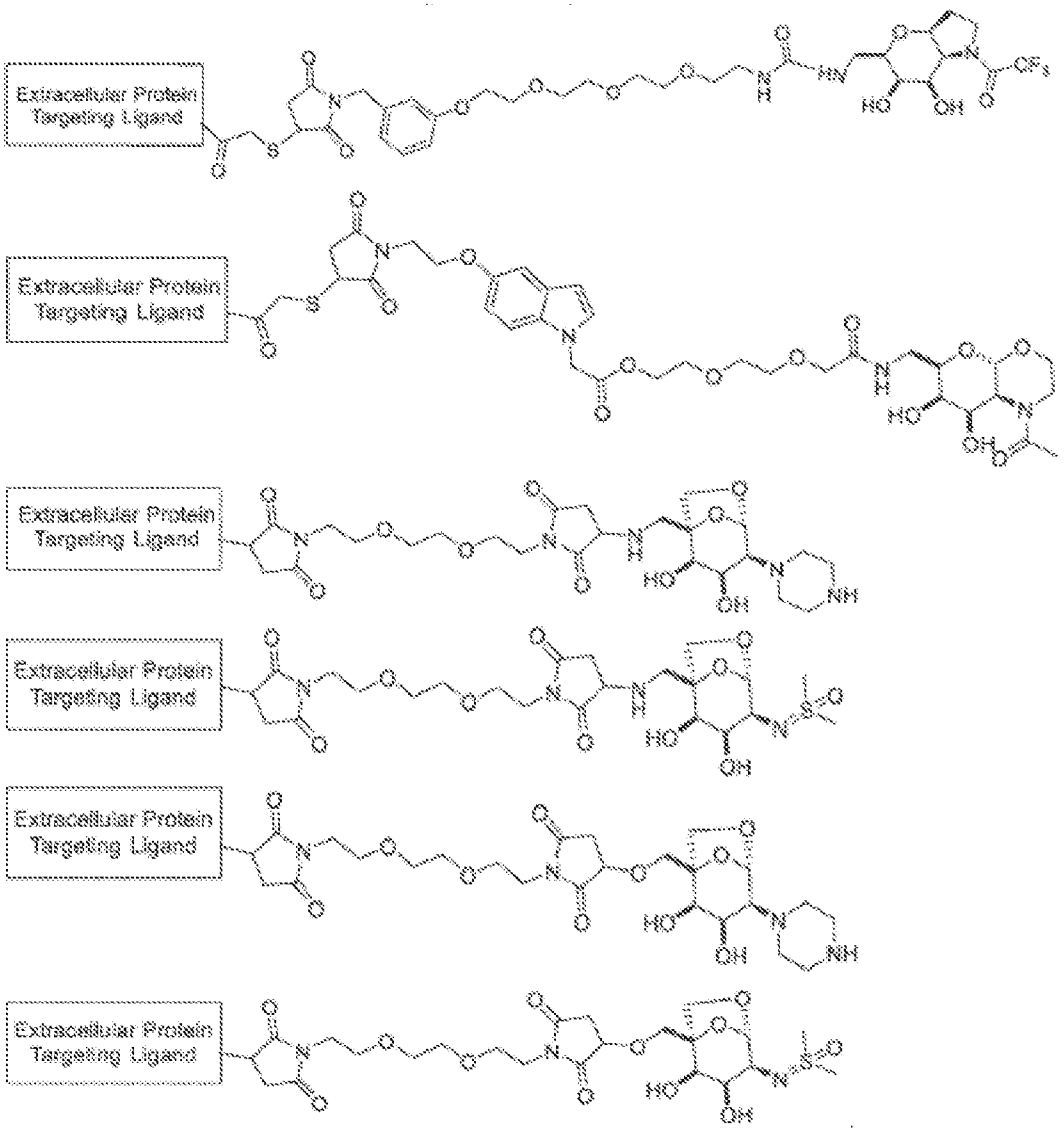
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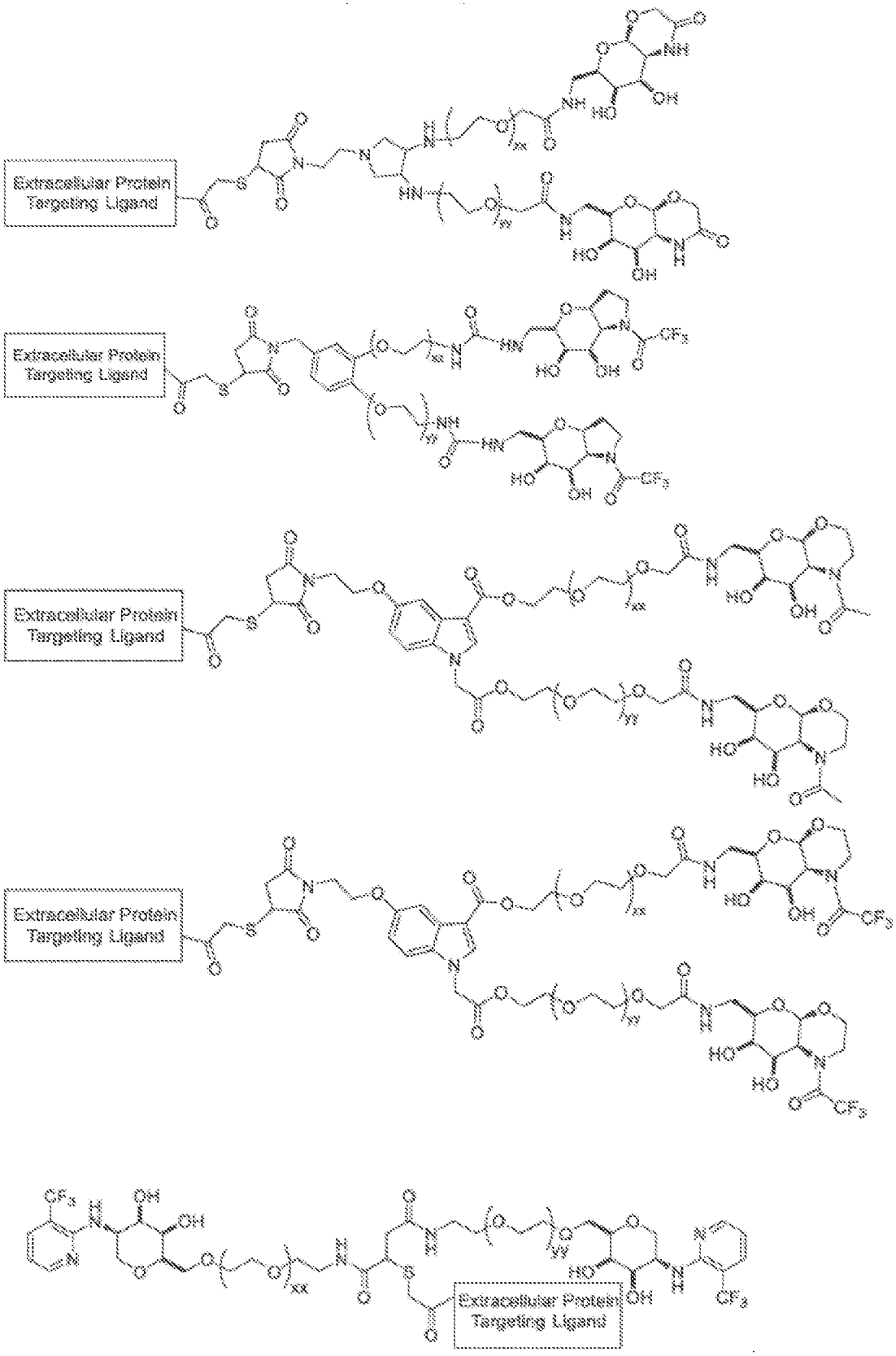
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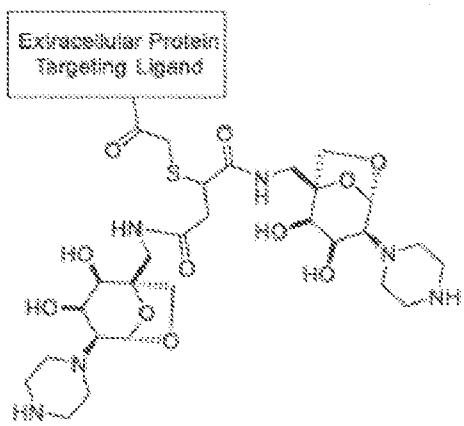
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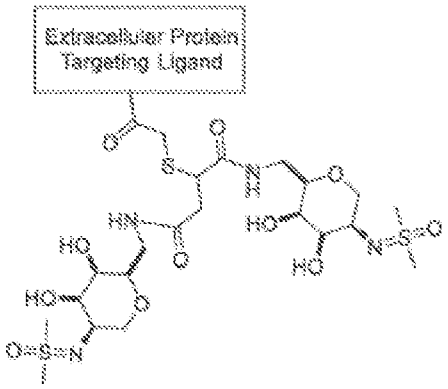
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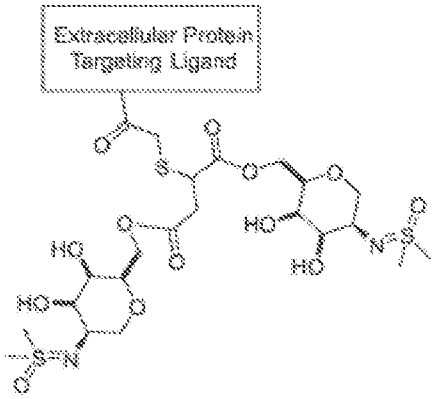
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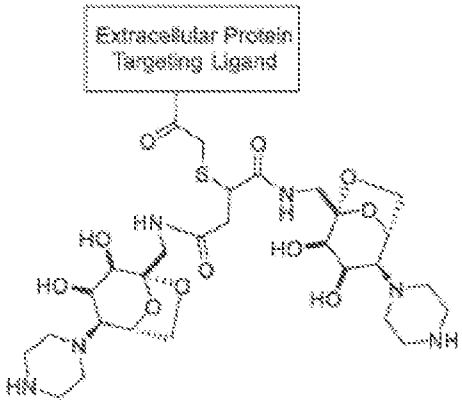
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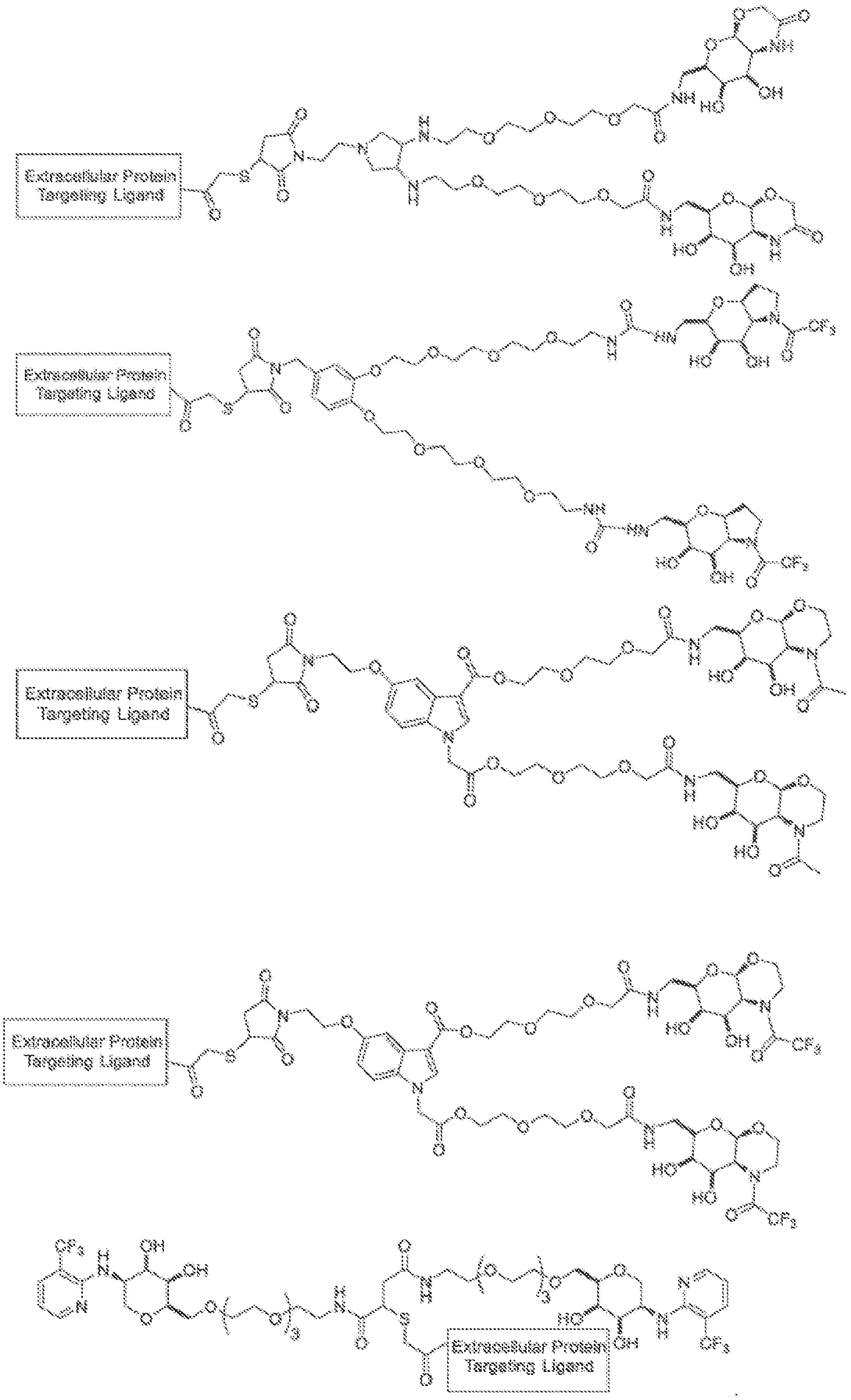
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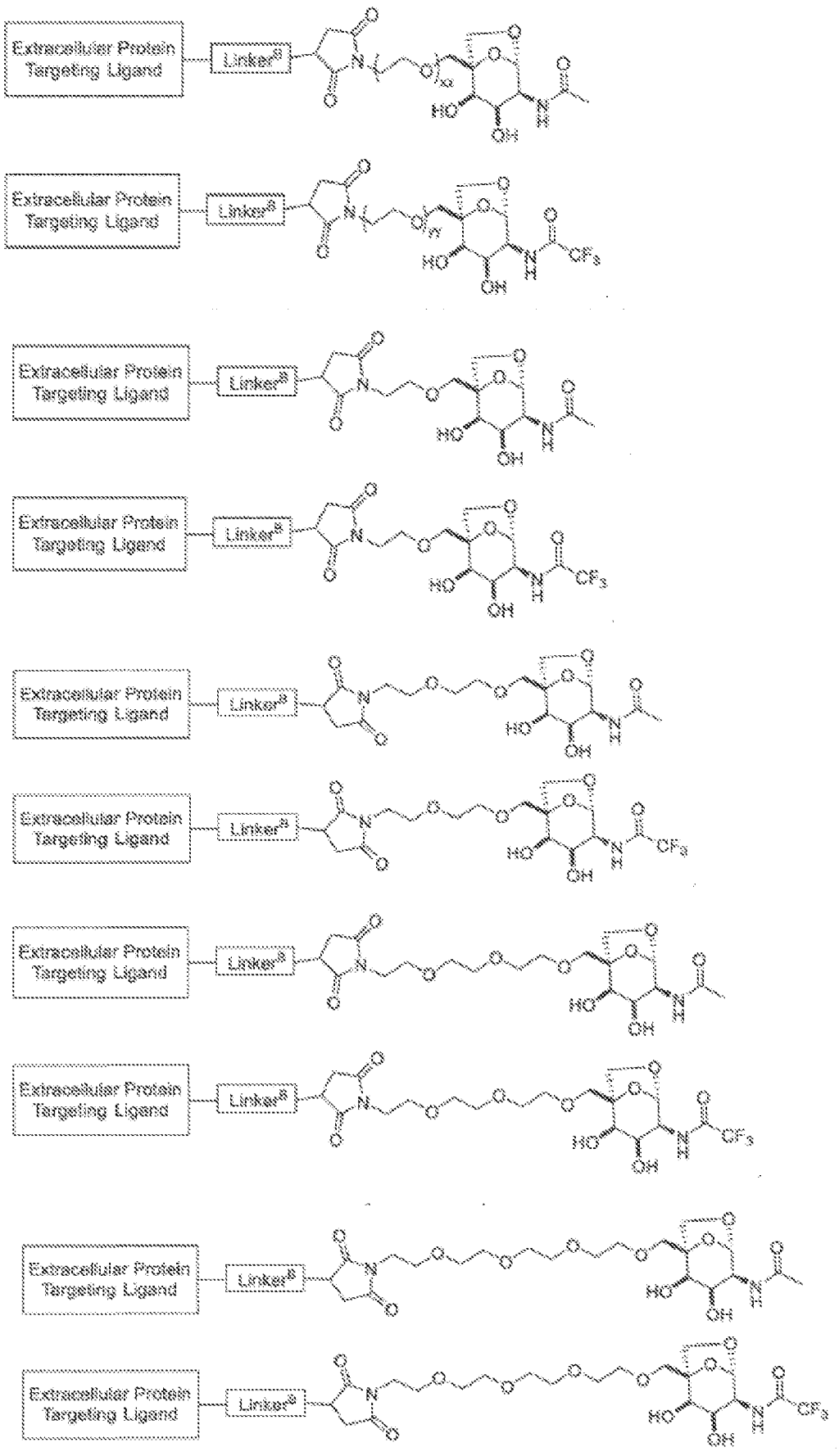
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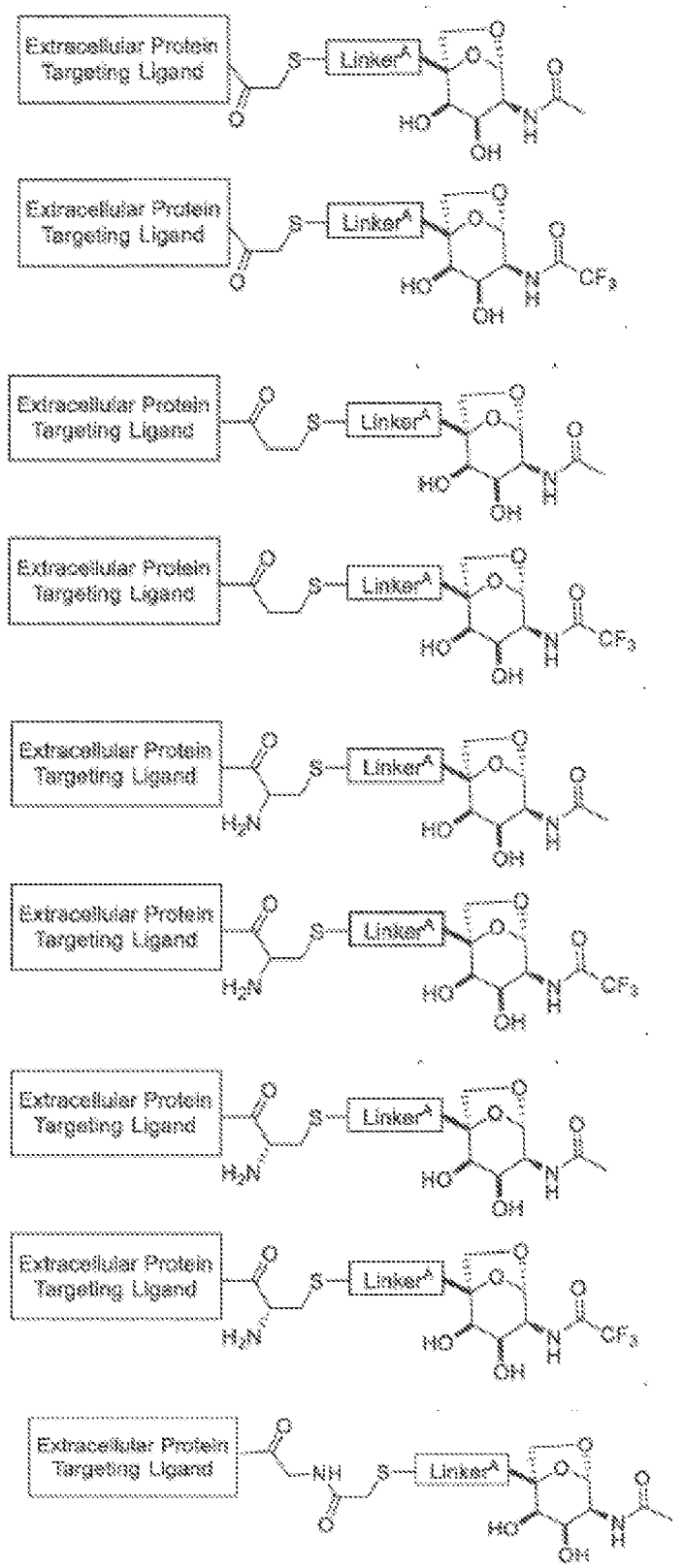
Extracellular Protein Targeting Ligand
Linker
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NH
CF3
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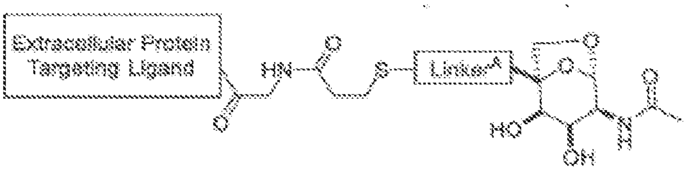
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HO
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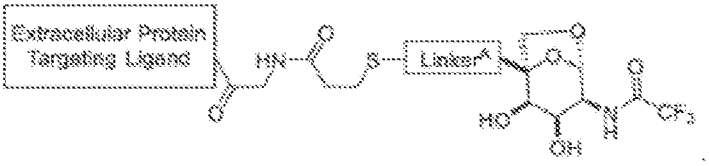
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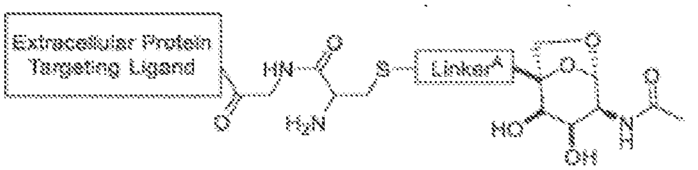
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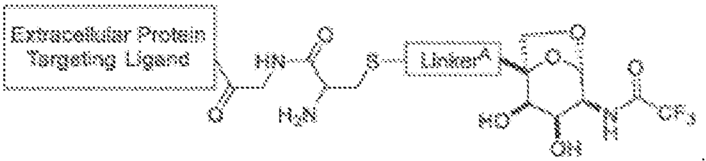
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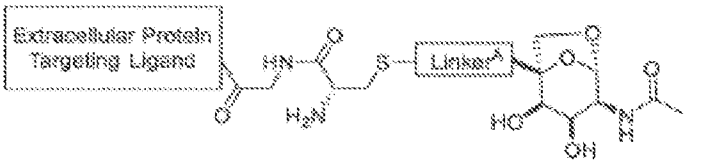
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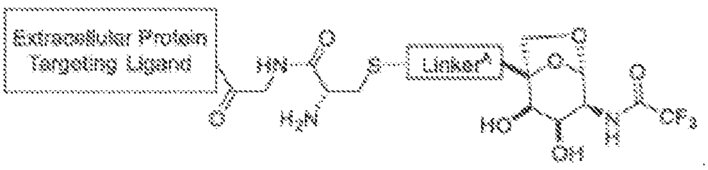
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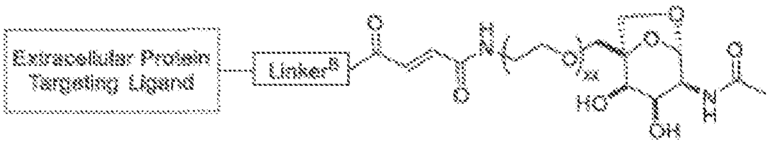
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HO
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N
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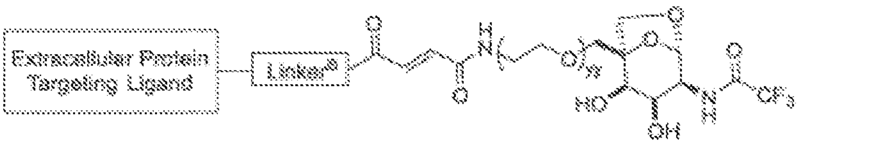
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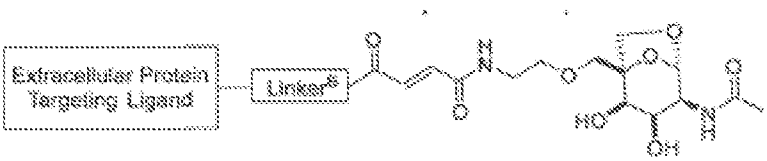
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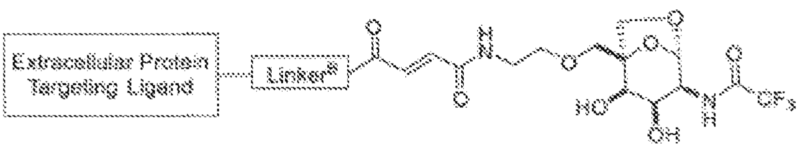
H
HO
OH
N
H

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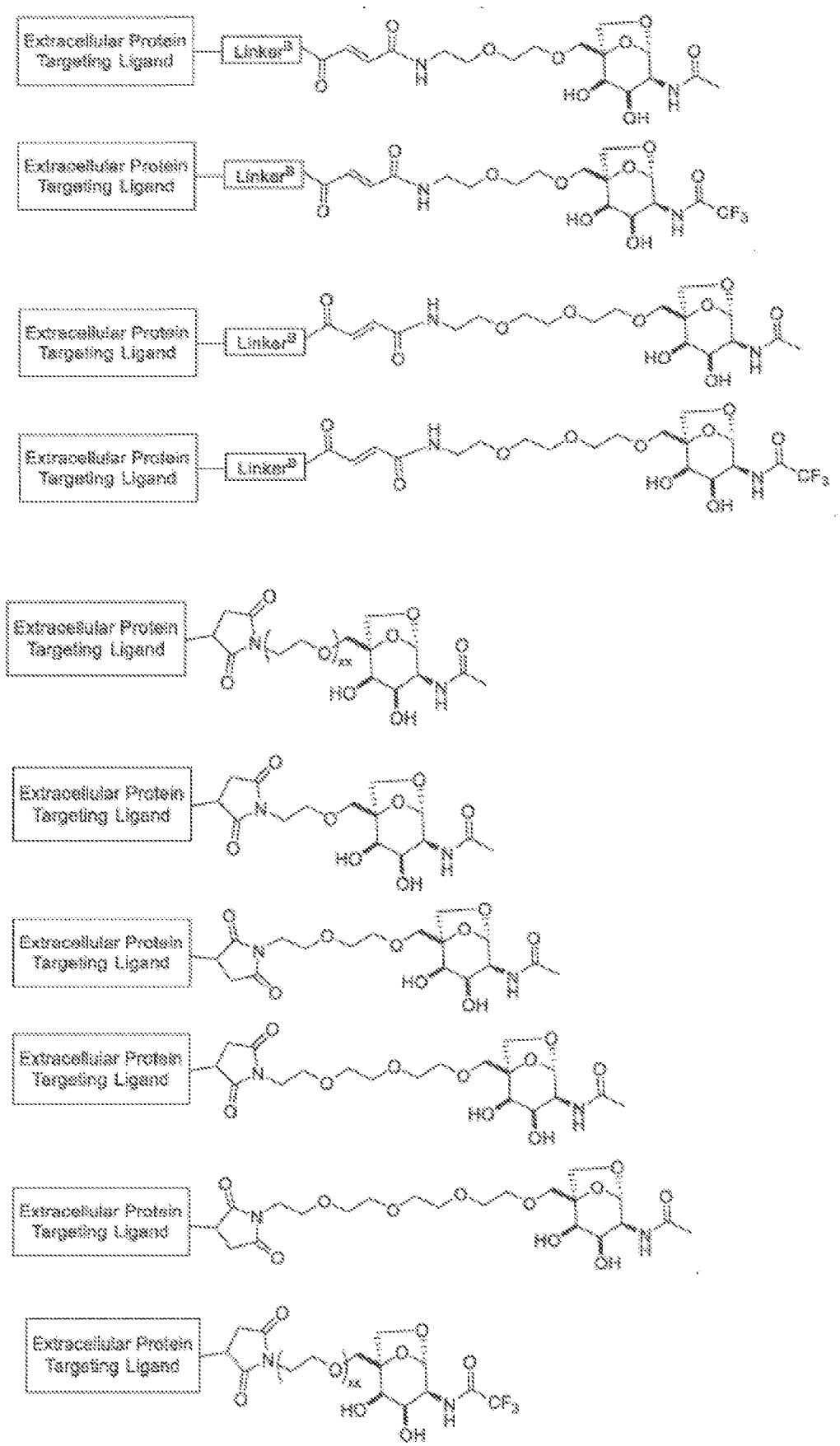
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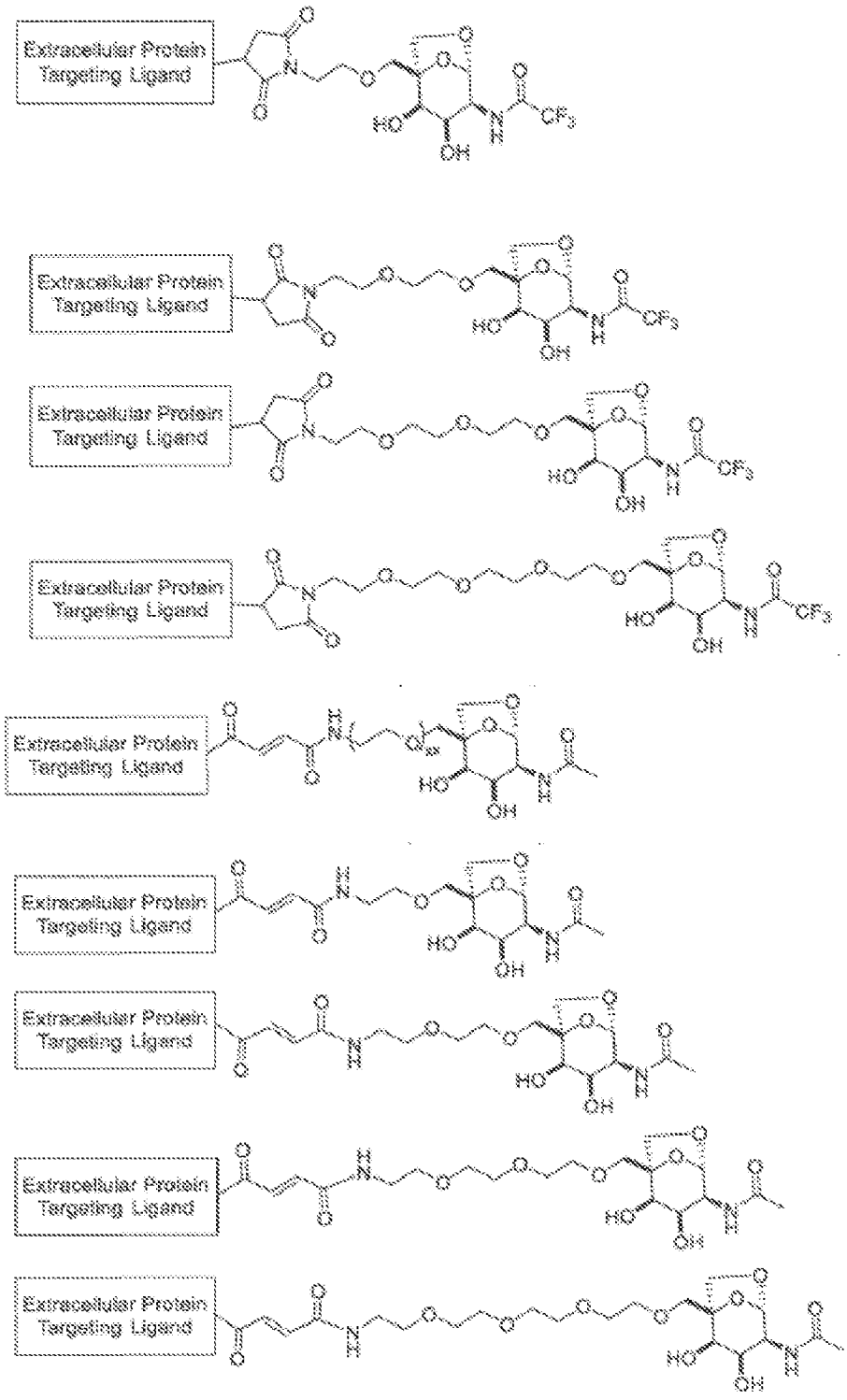
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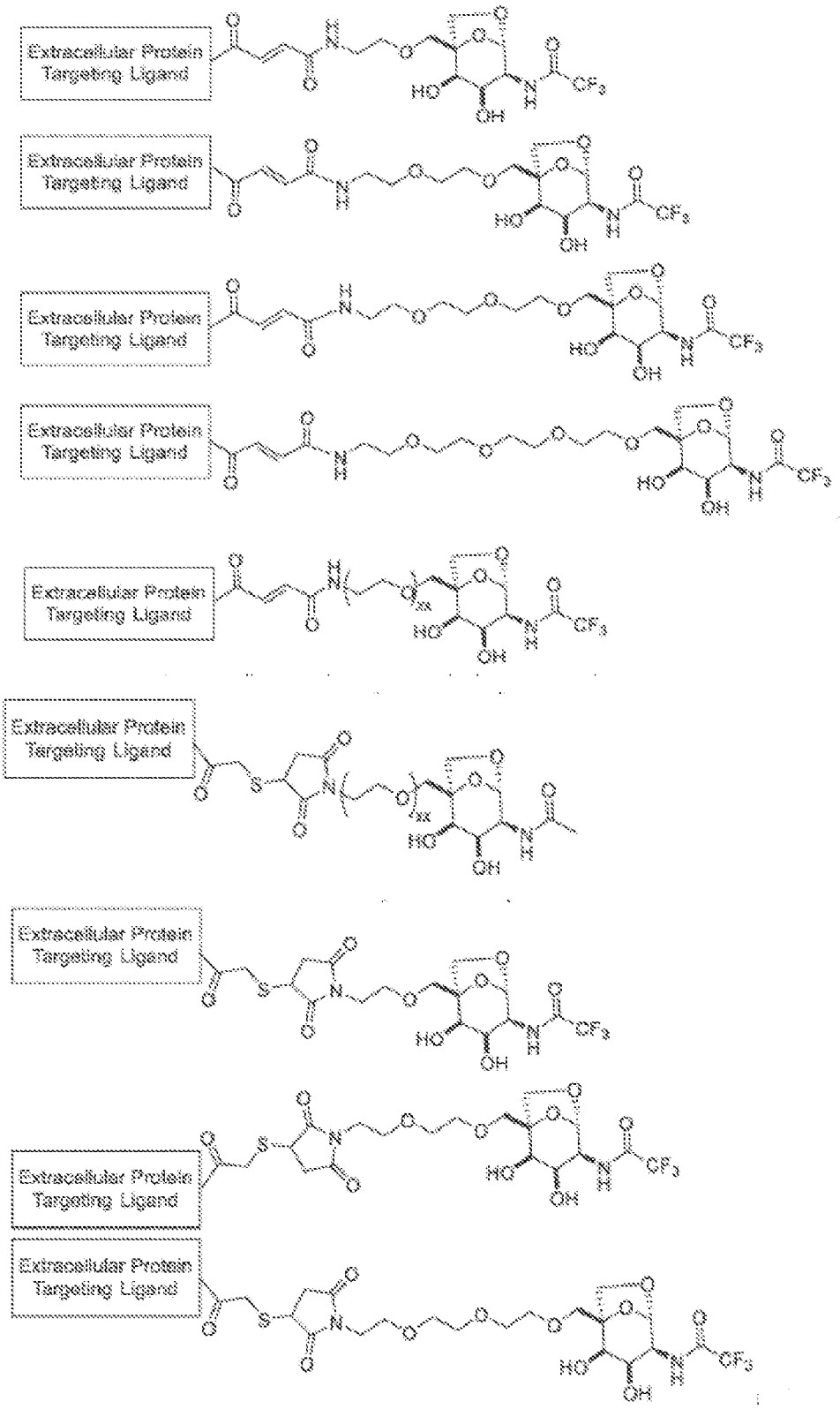
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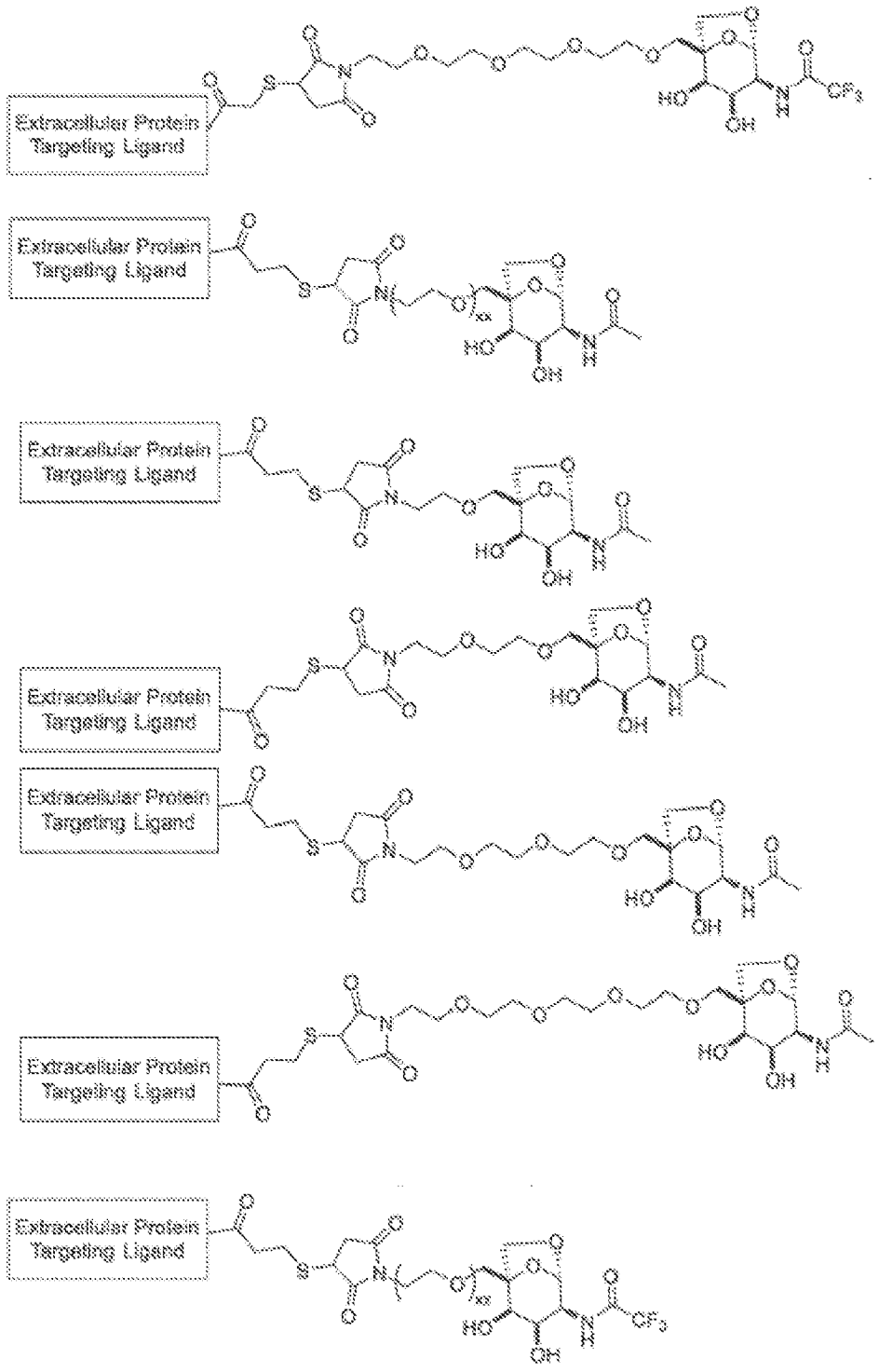
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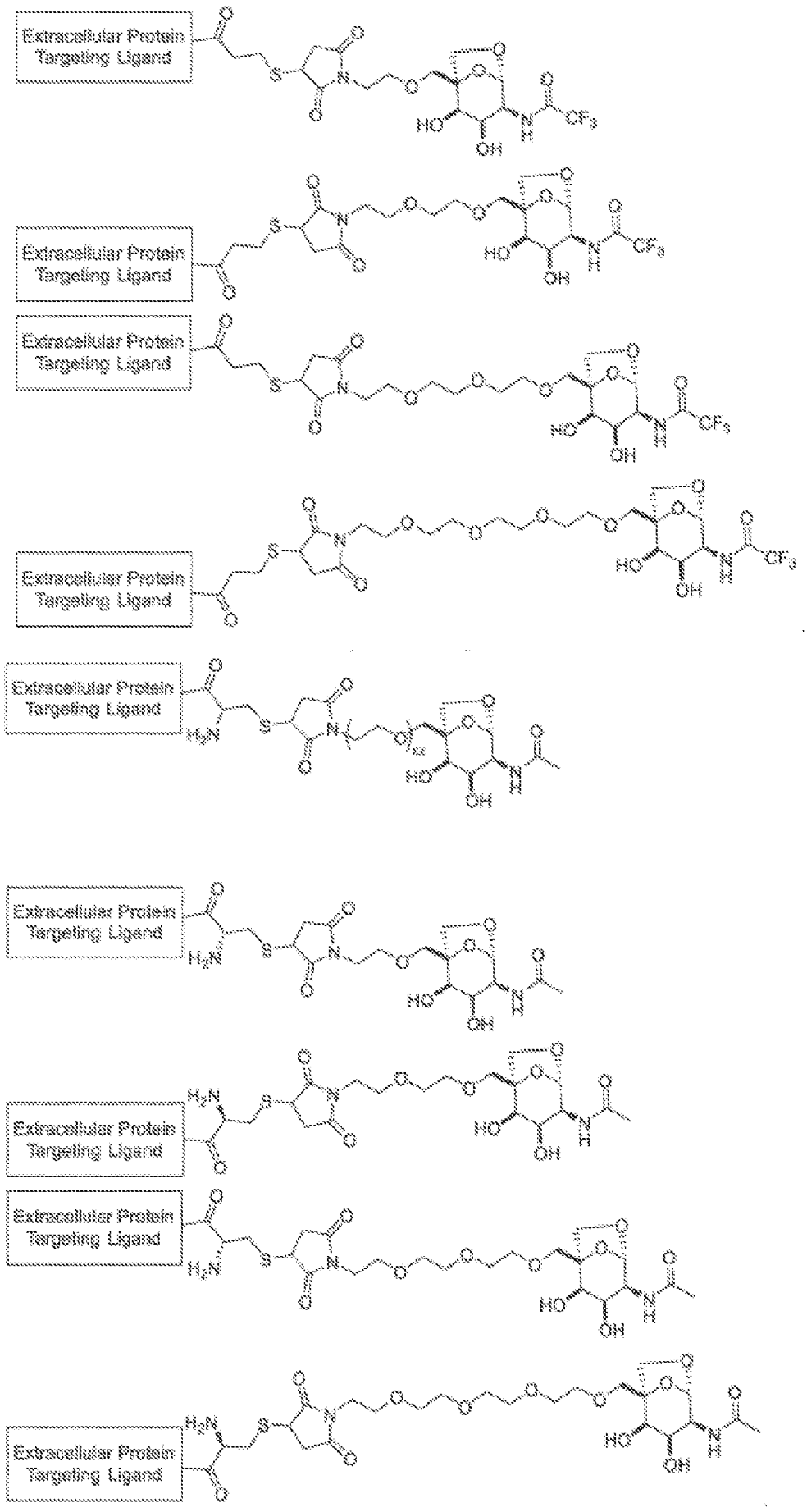
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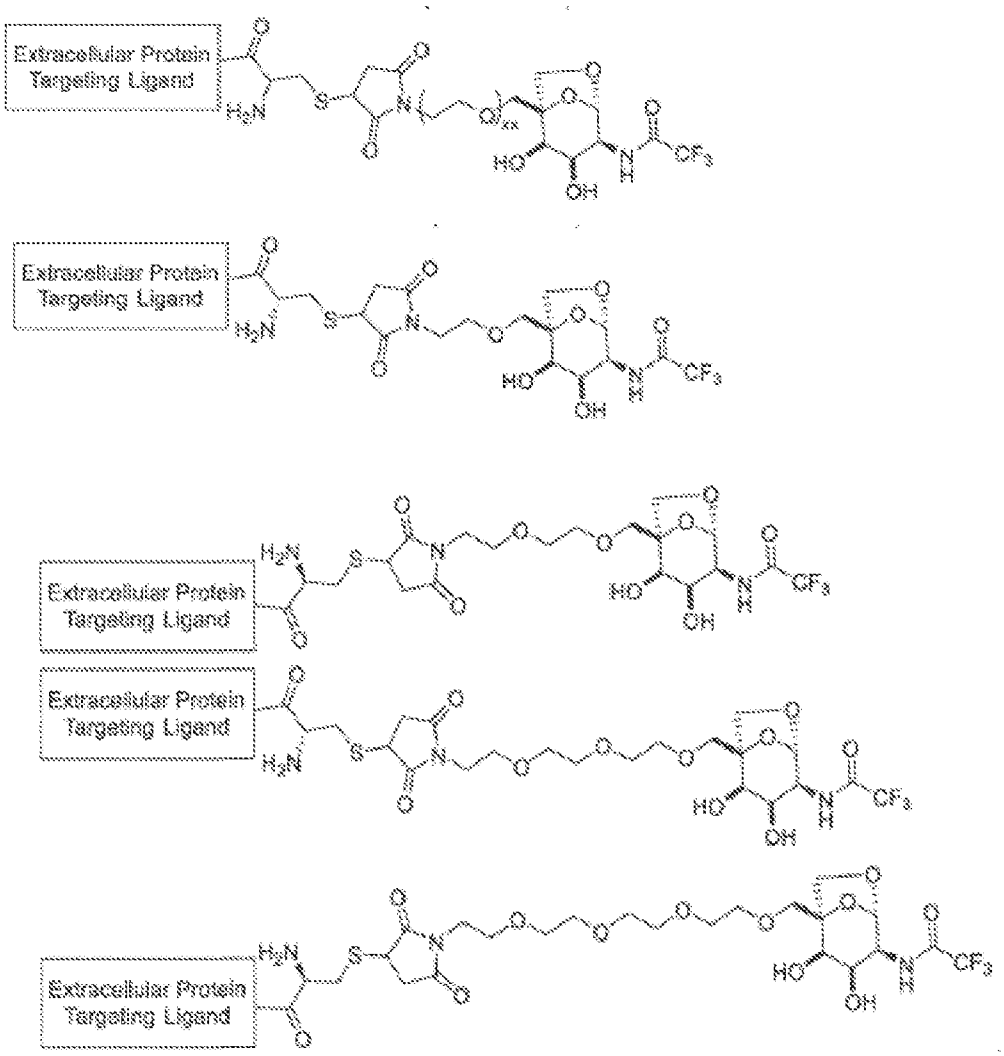
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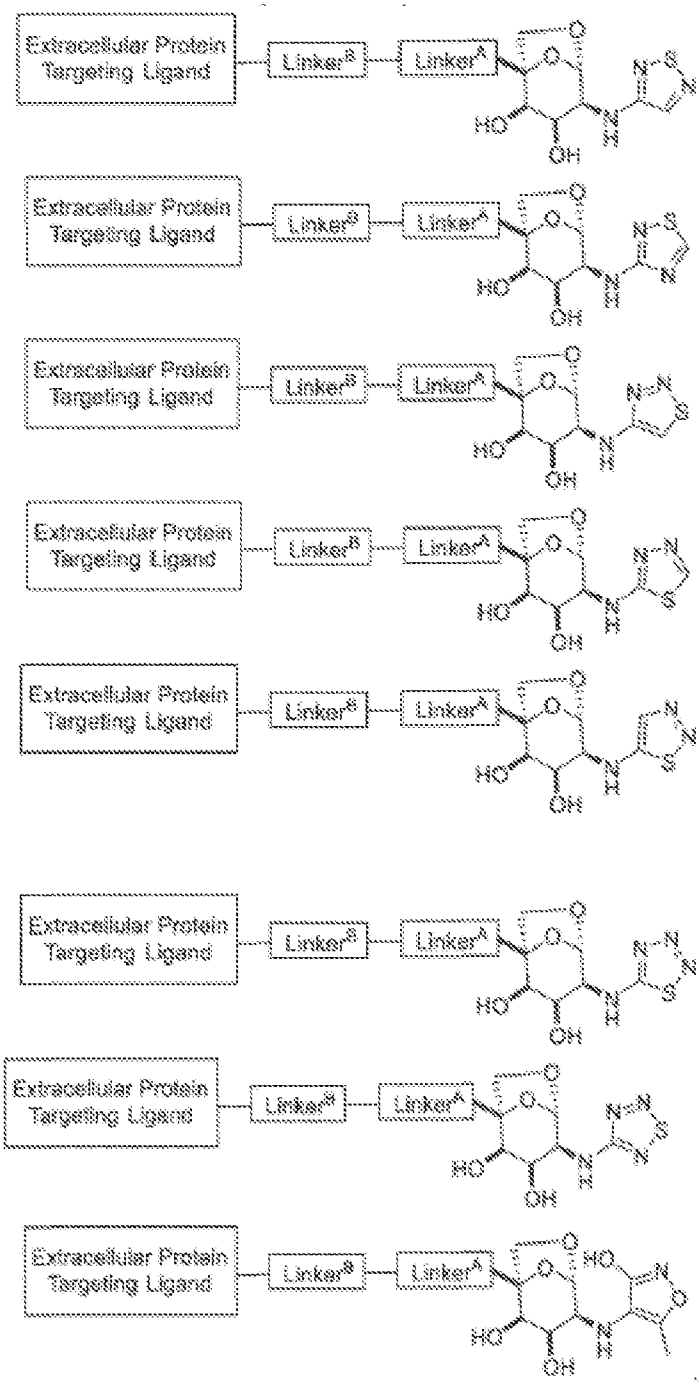
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^B
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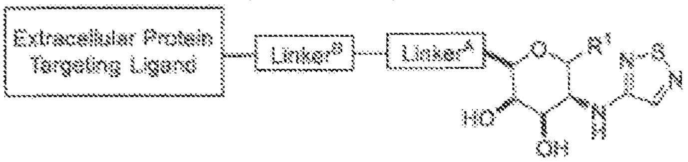
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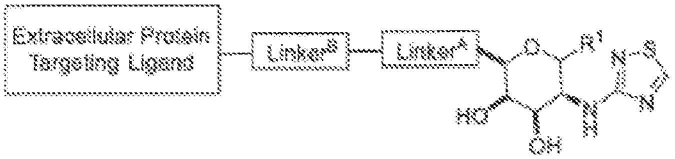
Linker^A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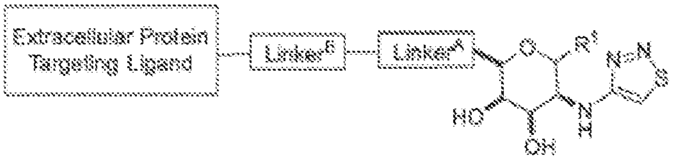
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Linker^B
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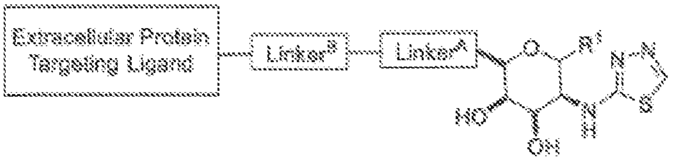
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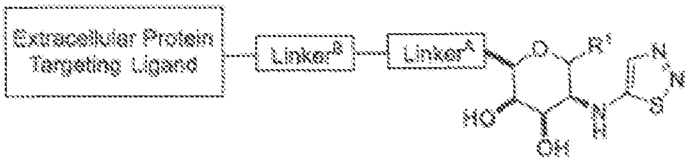
Linker^B
Linker^A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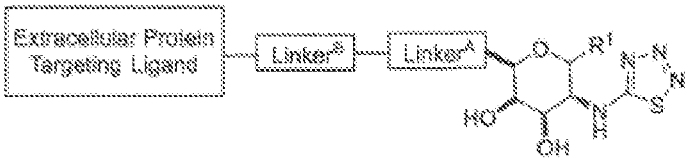
Linker^B
Linker^A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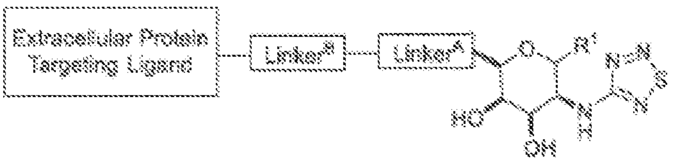
Linker^A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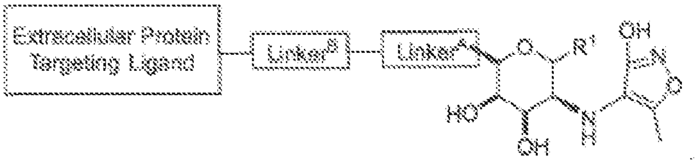
Linker^B
Linker^A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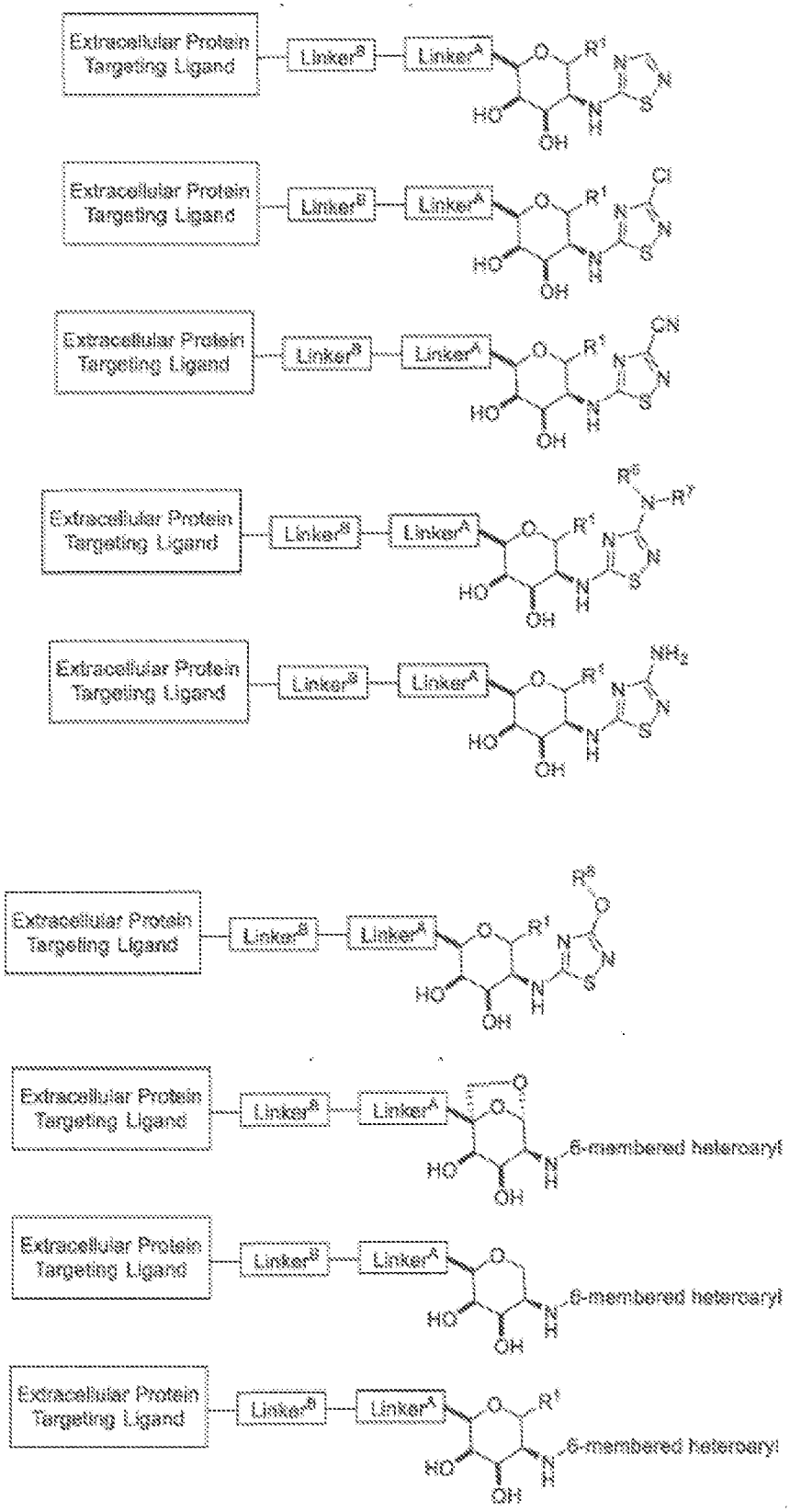
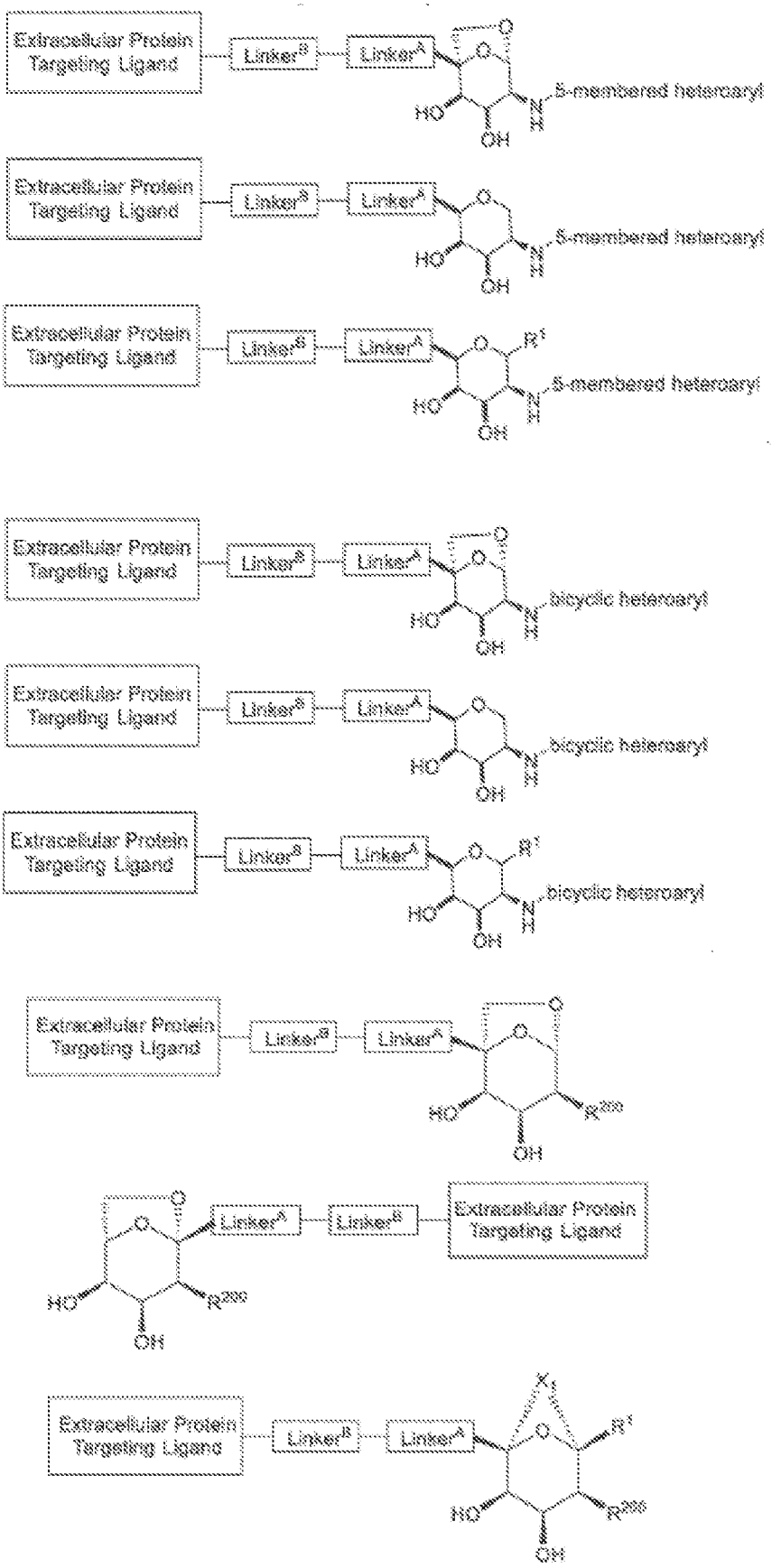
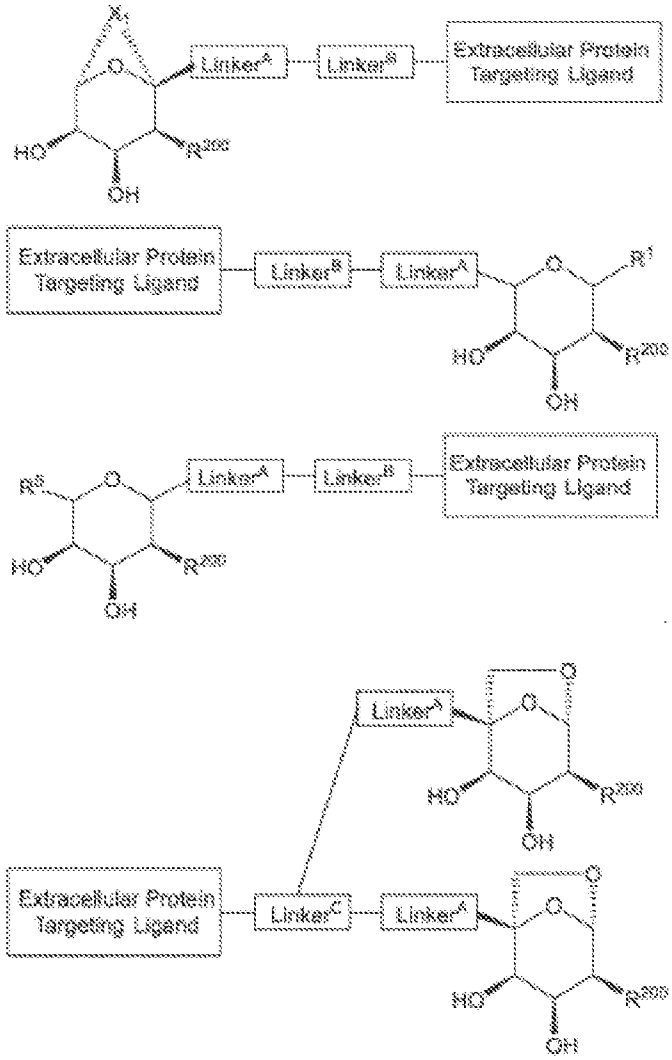
Linker^B
Linker^A


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


Extracellular Protein Targeting Ligand
Linker^B
Linker^A
5-membered heteroaryl
bicyclic heteroaryl
R^1
R^200
HO
OH
O
N
H


Extracellular Protein Targeting Ligand
Linker
Linker
HO
OH
O
Extracellular Protein Targeting Ligand
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Linker
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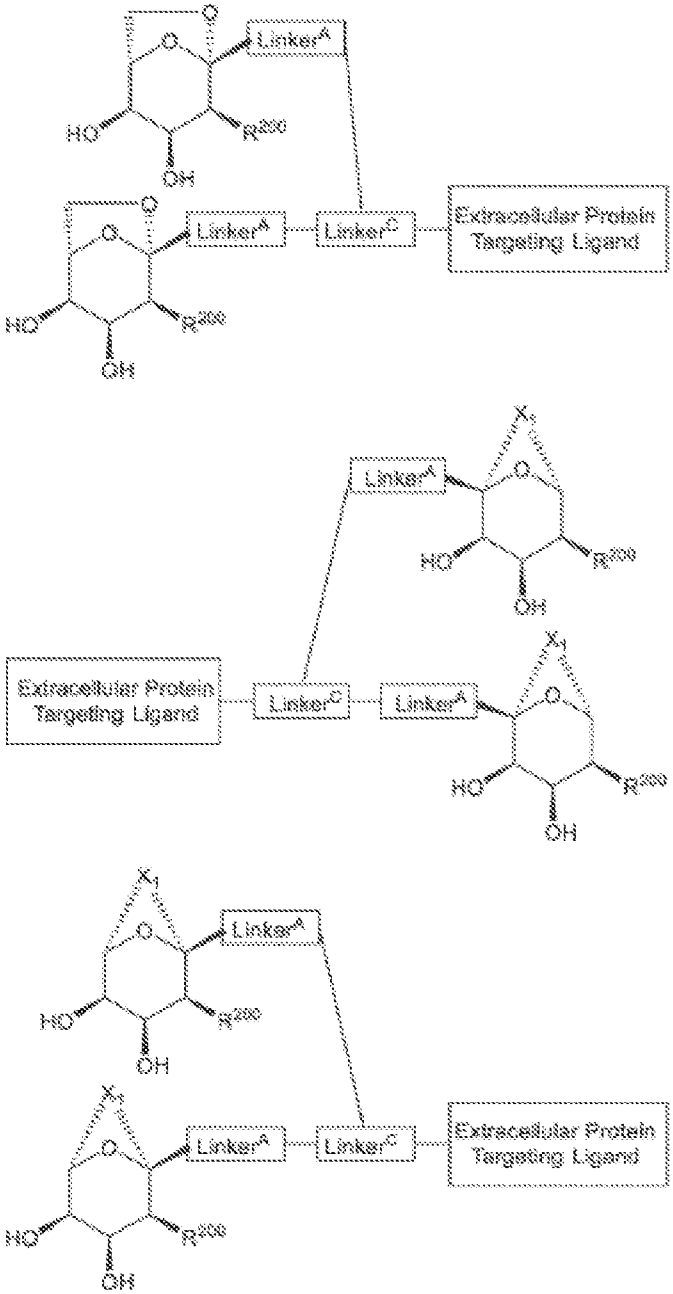
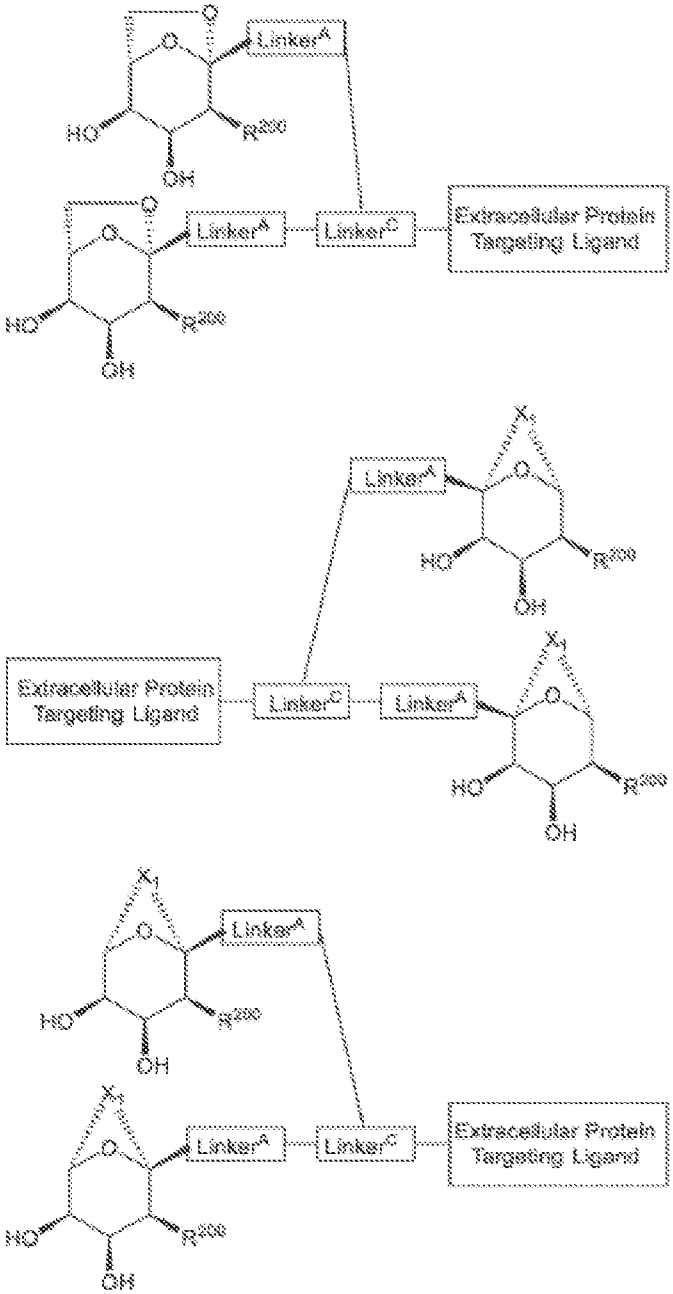
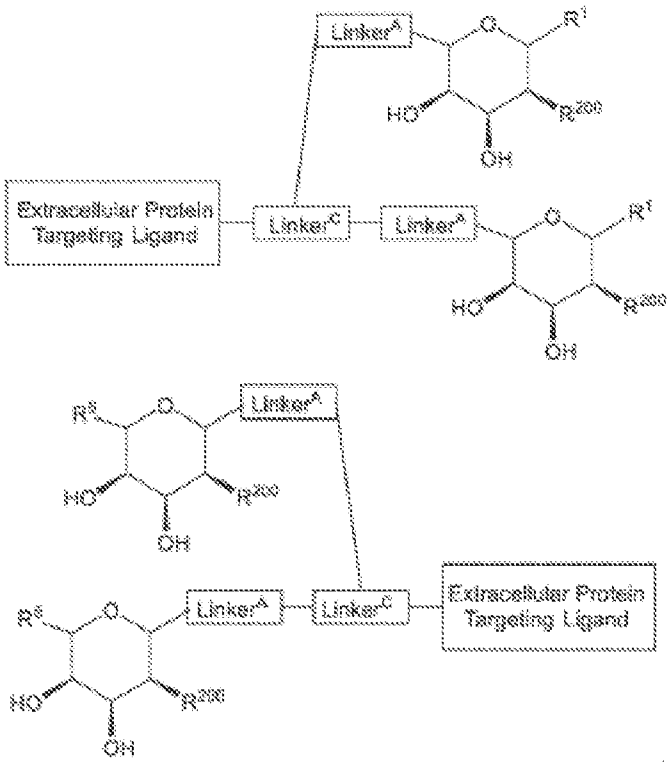
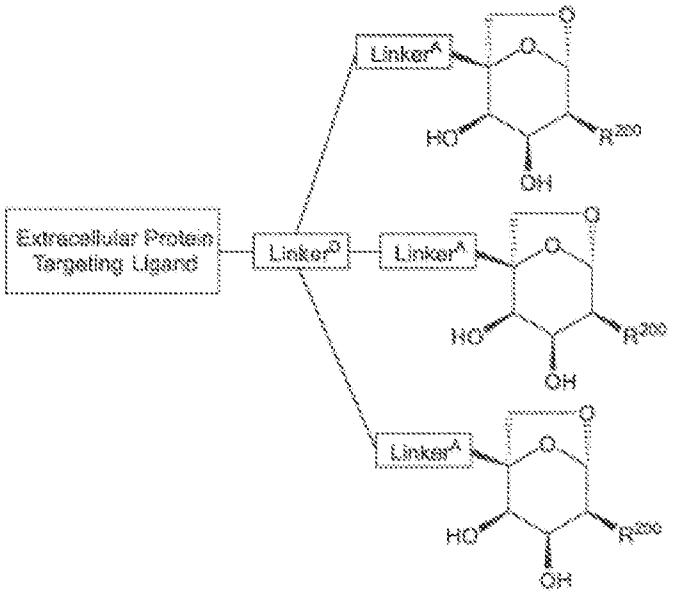
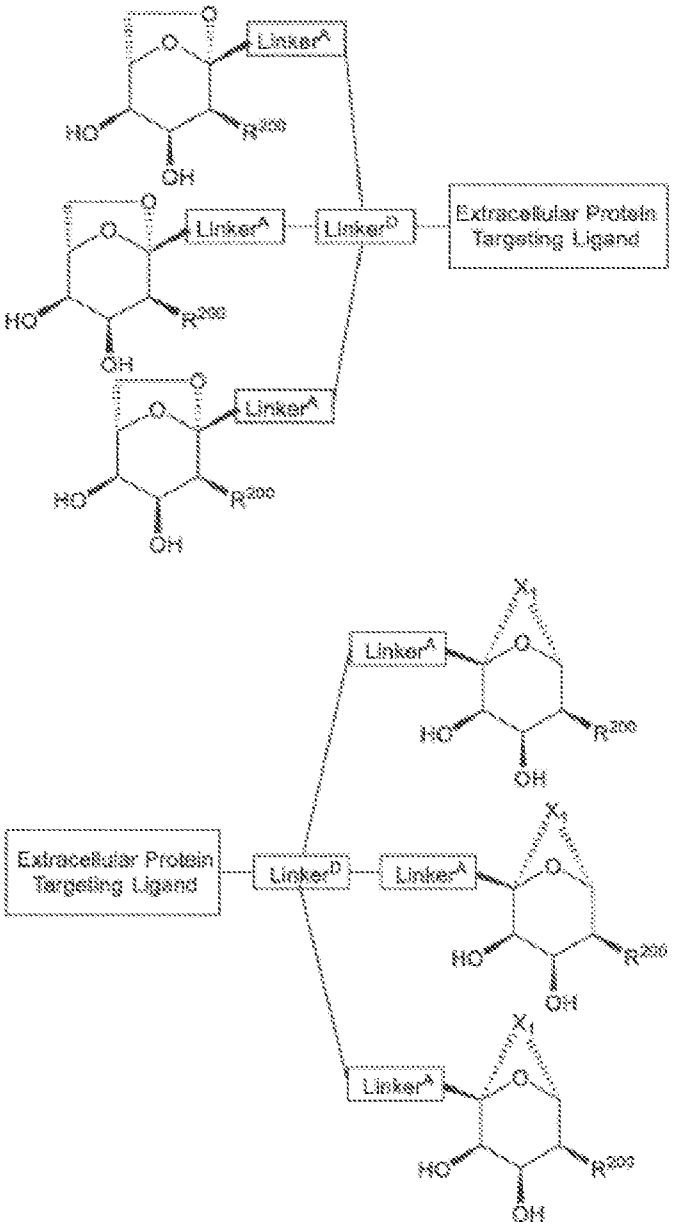
OH
O
Linker
HO
OH
O
Extracellular Protein Targeting Ligand
Linker
Linker
HO
OH
O

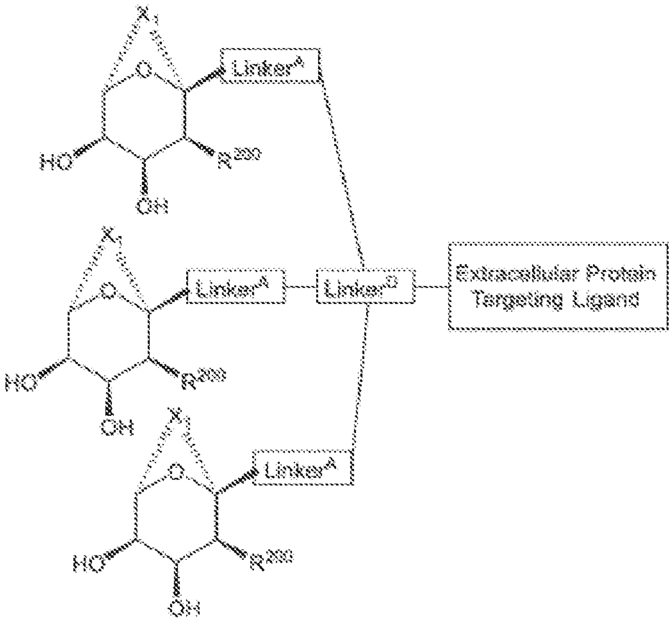

Linker^A
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
Linker^A
Linker^C
Extracellular Protein Targeting Ligand

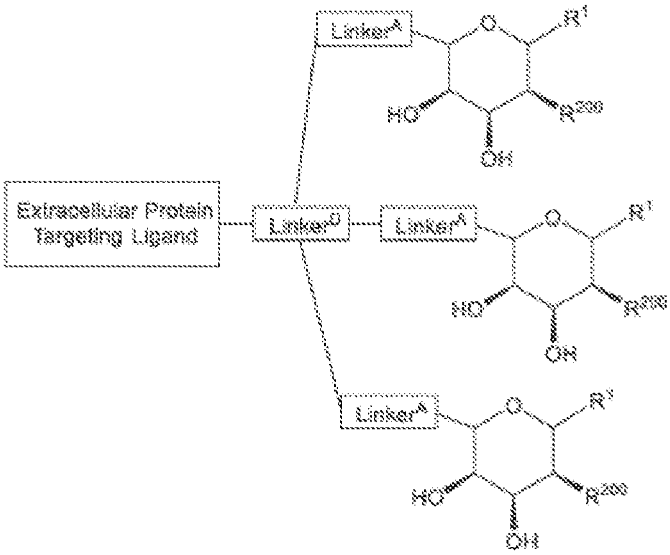

Linker^A
HO
R^200
OH
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
X1
Linker^A
HO
R^200
OH
Extracellular Protein Targeting Ligand
Linker^C
Linker^A
X1
HO
R^200
OH
Linker^A
X1
HO
R^200
OH
Linker^A
Linker^C
Extracellular Protein Targeting Ligand

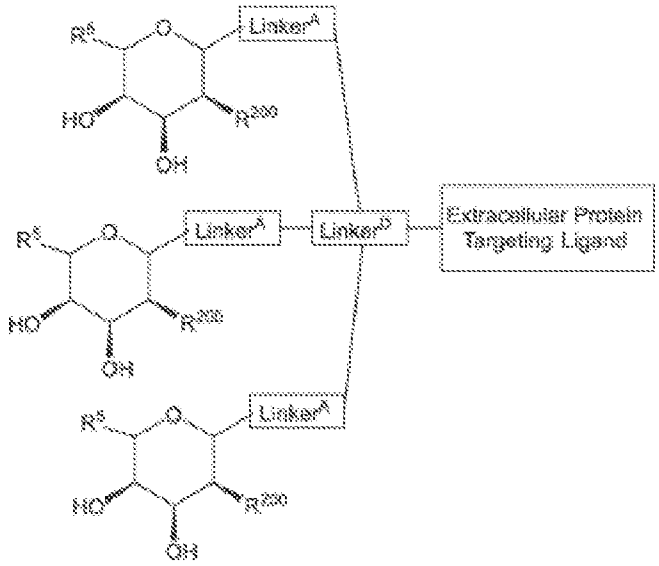

Linker^A
Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
Linker^A
Linker^C
Extracellular Protein Targeting Ligand


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

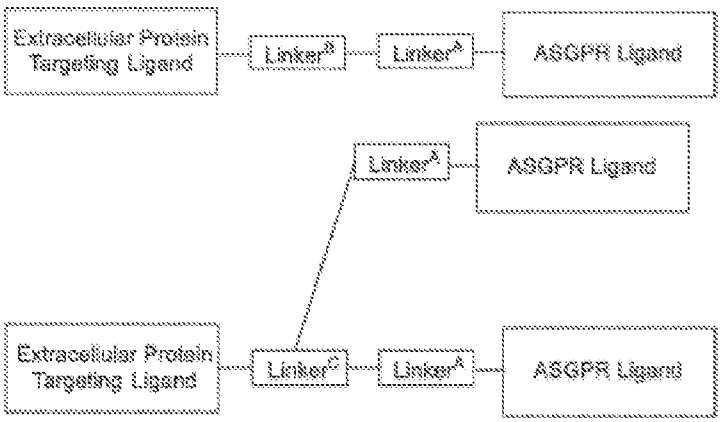

Linker^A
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
Linker^A
Linker^A
Linker^D
Linker^A
Extracellular Protein Targeting Ligand


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

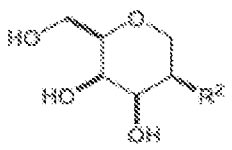

Linker^A
R^1
R^200
HO
OH
Extracellular Protein Targeting Ligand
Linker^D



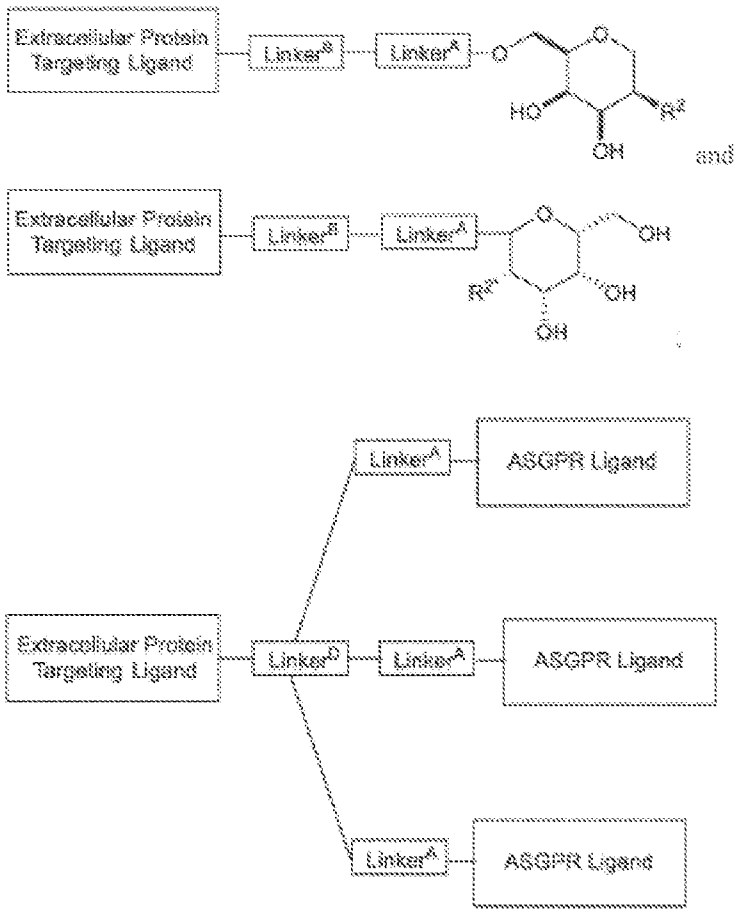
In certain embodiments, the compound of Formula II is an Extracellular Protein degrading compound in which the ASGPR ligand is a ligand as described herein



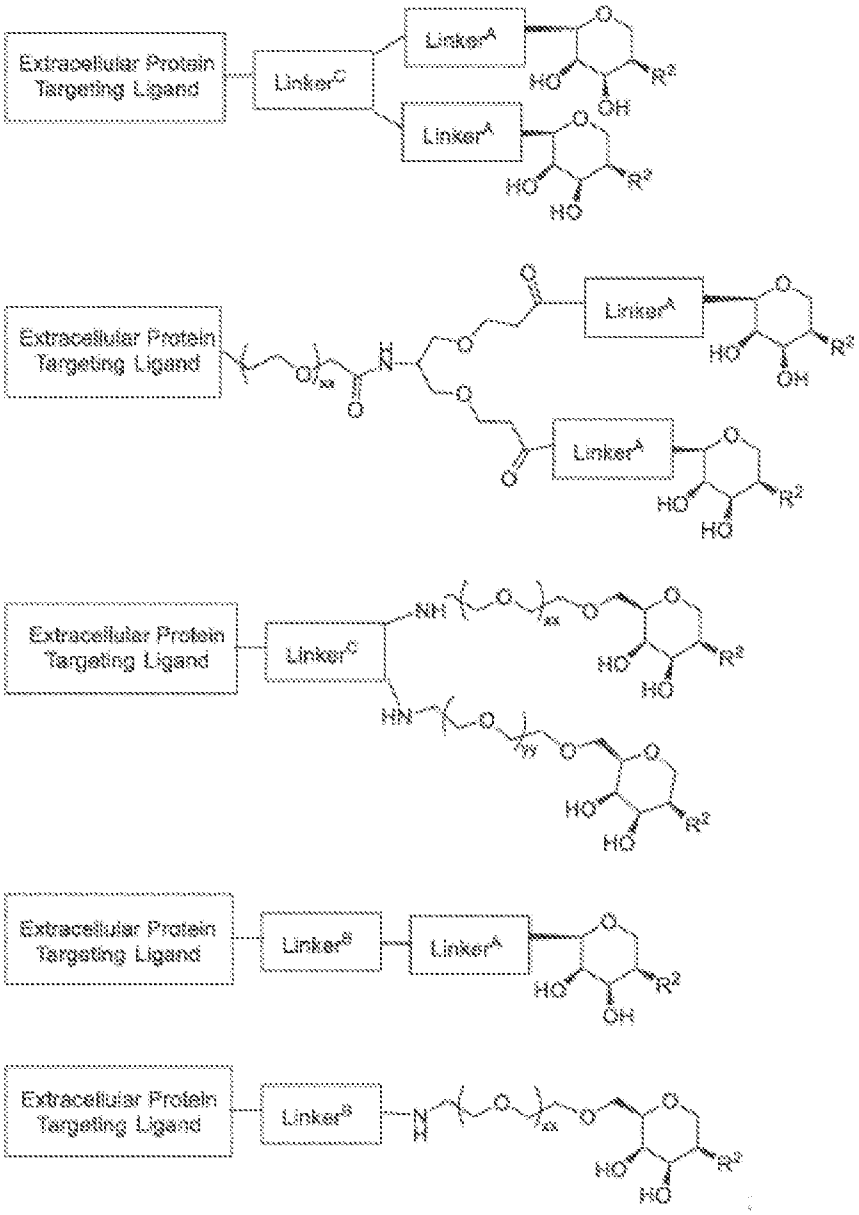
In certain embodiments, in the compound of Formula II, the ASGPR ligand is linked at either the C1 or C5 (R^1 or R^5) position to form a degrading compound. In certain embodiments, in the compound of Formula II, the ASGPR ligand is linked at C6. In various embodiments, when the ASGPR ligand is



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

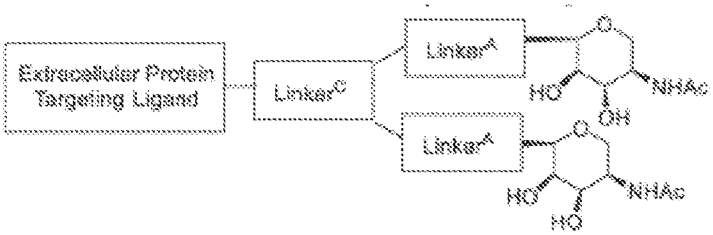


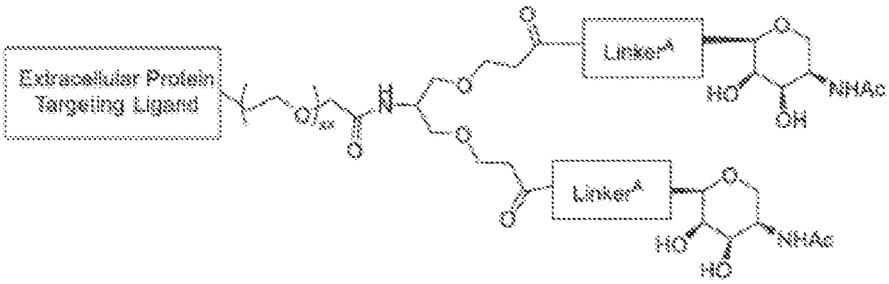
or the bi- or tri- substituted versions thereof or pharmaceutically acceptable salts thereof, where the bi- or tri- substitution refers to the number additional galactose derivatives attached to a linker moiety. In certain embodiments the compound of Formula II is selected from:

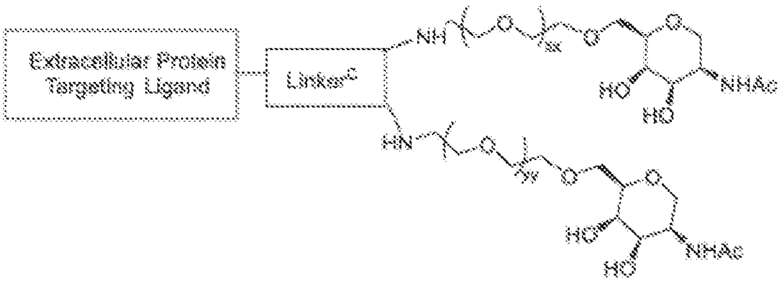


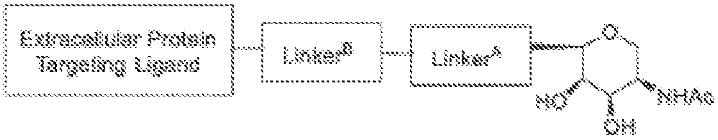
wherein in certain embodiments R^2 is selected from $-NR^6COR^3$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

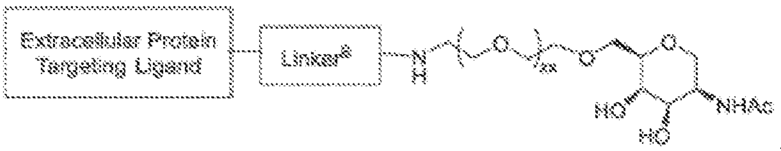
In certain embodiments, the compound of Formula II is selected from:

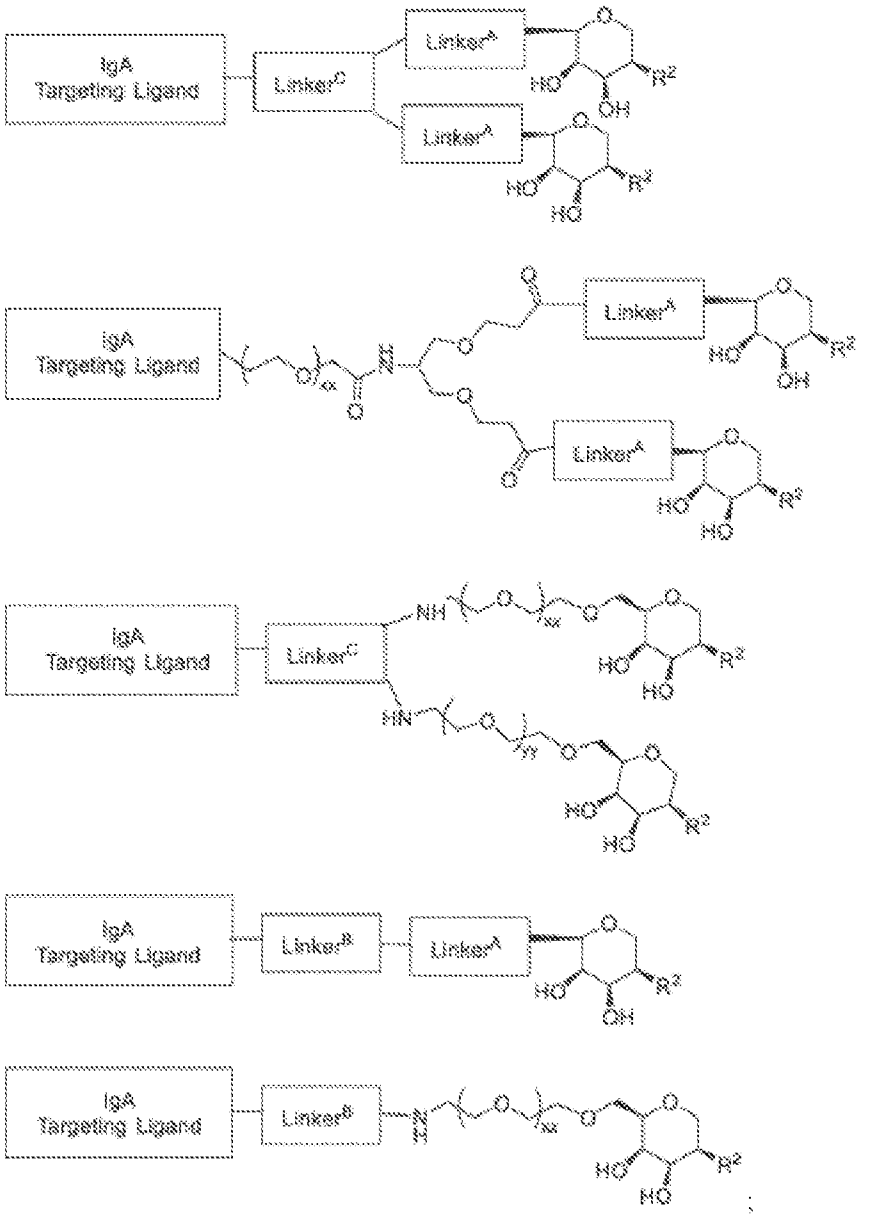

Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
HO
OH
NHAc
HO
HO
NHAc


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


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

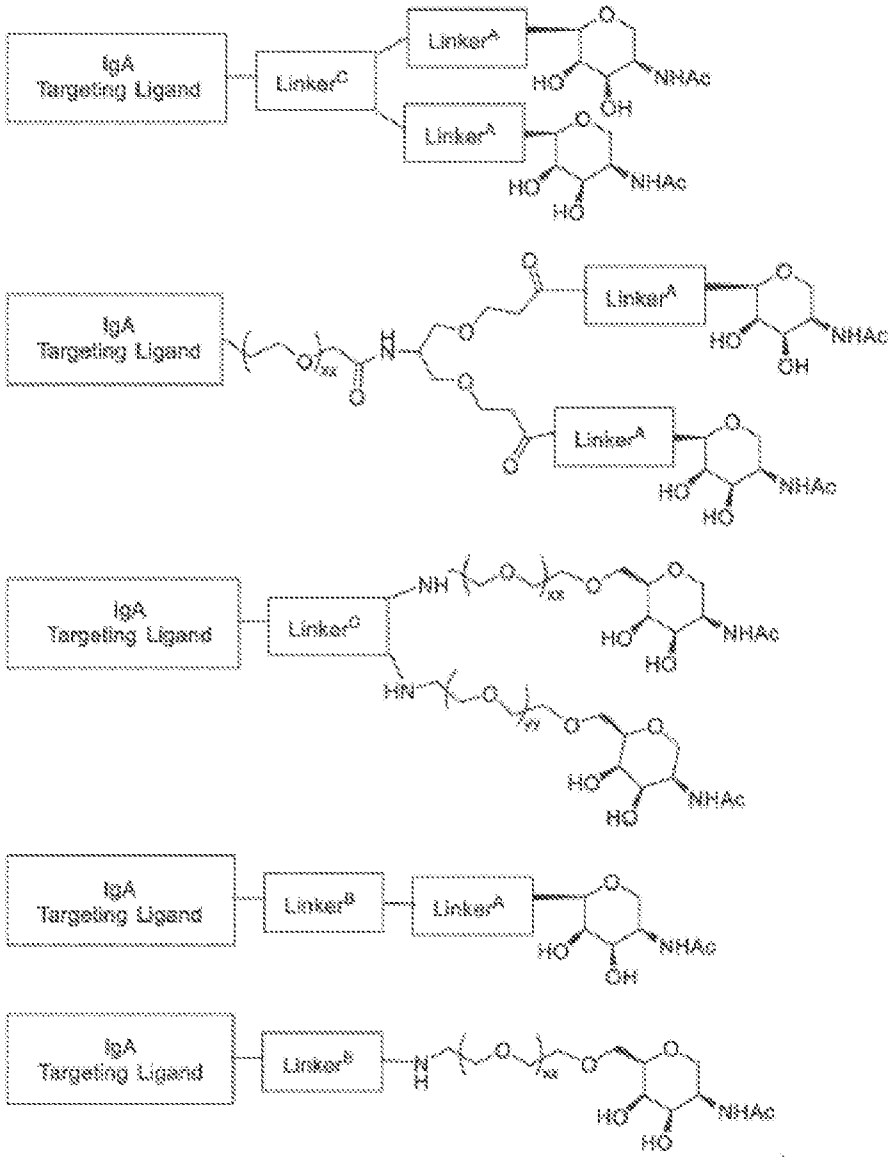

Extracellular Protein Targeting Ligand
Linker^B
Linker^A
HO
OH
NHAc

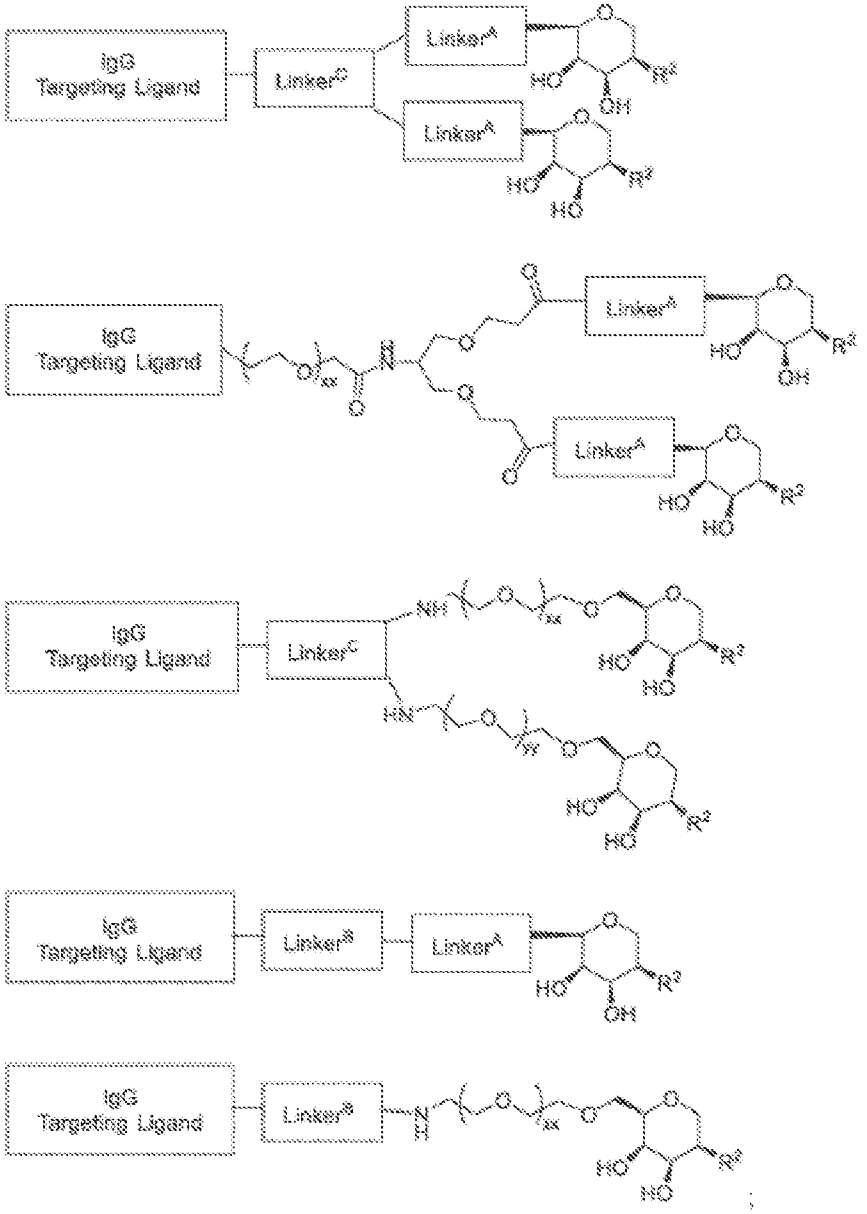

Extracellular Protein Targeting Ligand
Linker^B
HO
HO
NHAc



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

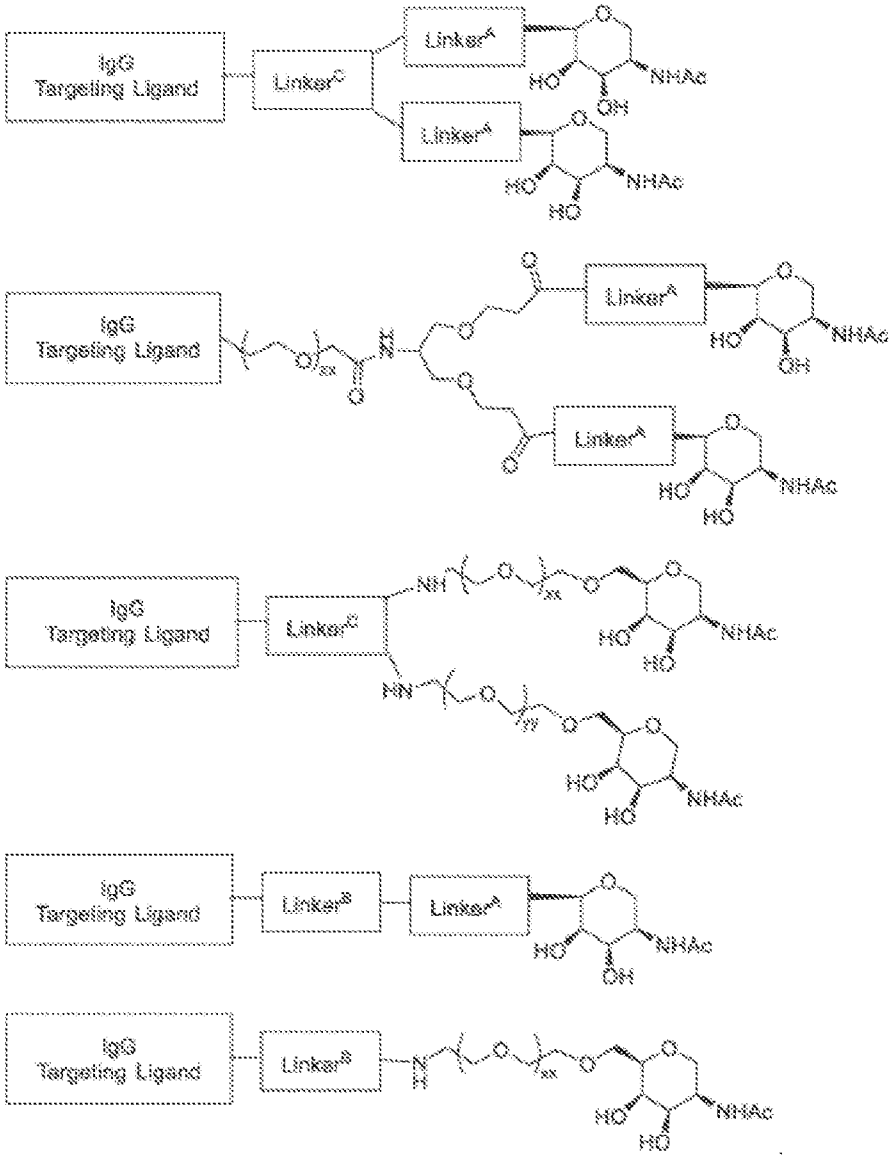
In certain embodiments, the compound of Formula II is selected from:

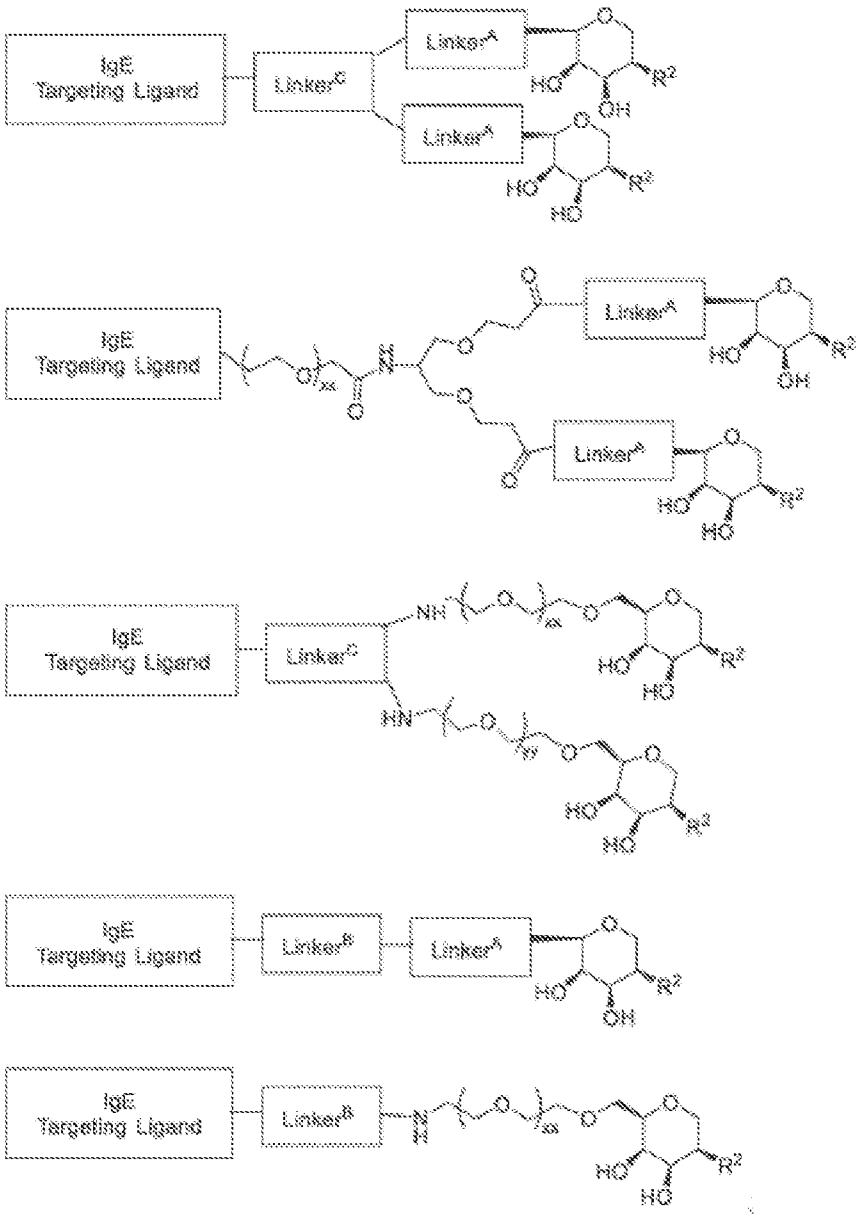

IgA Targeting Ligand
Linker^C
Linker^A
Linker^A
HO
NHAc
OH
HO
NHAc
HO
IgA Targeting Ligand
Linker^A
Linker^A
IgA Targeting Ligand
Linker^C
NH
HN
IgA Targeting Ligand
Linker^B
Linker^A
IgA Targeting Ligand
Linker^B
N
H



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

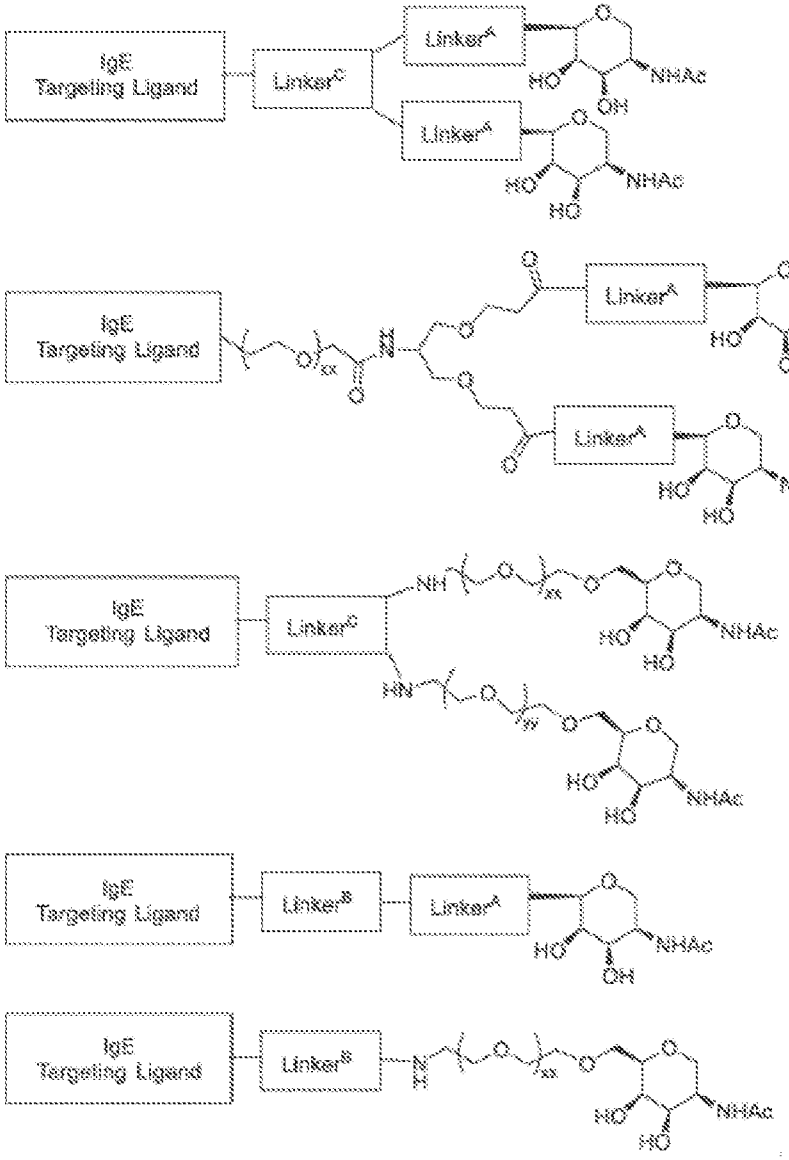
In certain embodiments, the compound of Formula II is selected from:

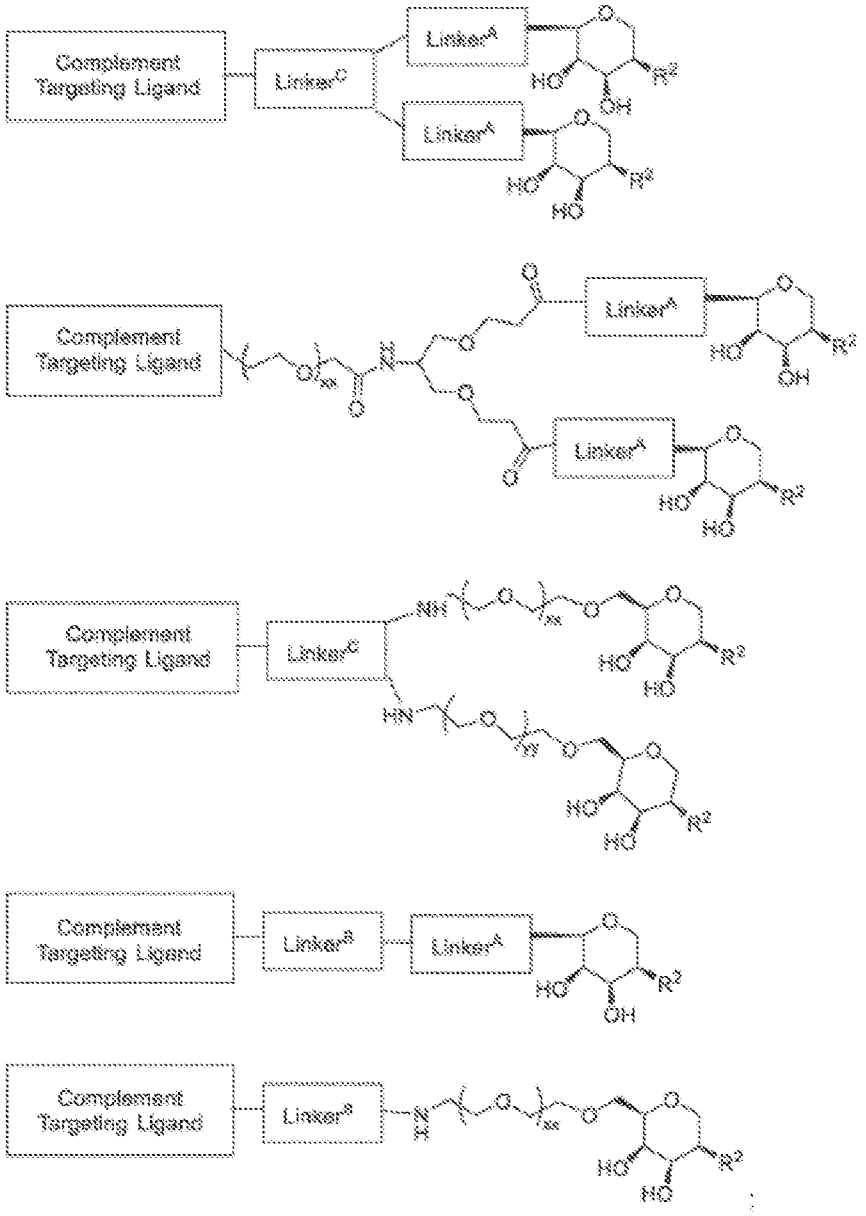

IgG Targeting Ligand
Linker^C
Linker^A
NHAc
HO
OH
IgG Targeting Ligand
Linker^A
NHAc
HO
OH
IgG Targeting Ligand
Linker^C
NH
HN
NHAc
HO
IgG Targeting Ligand
Linker^B
Linker^A
NHAc
HO
OH
IgG Targeting Ligand
Linker^B
NHAc
HO



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

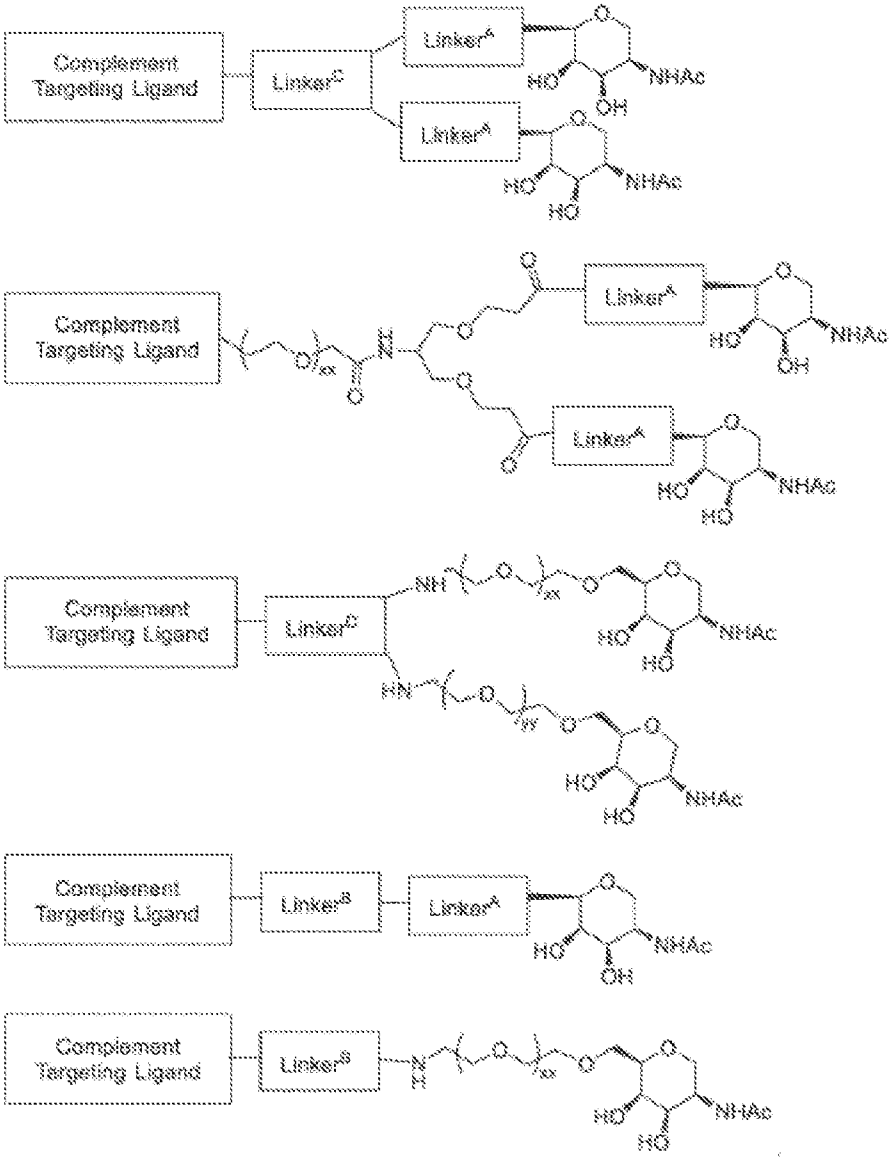
In certain embodiments, the compound of Formula II is selected from:

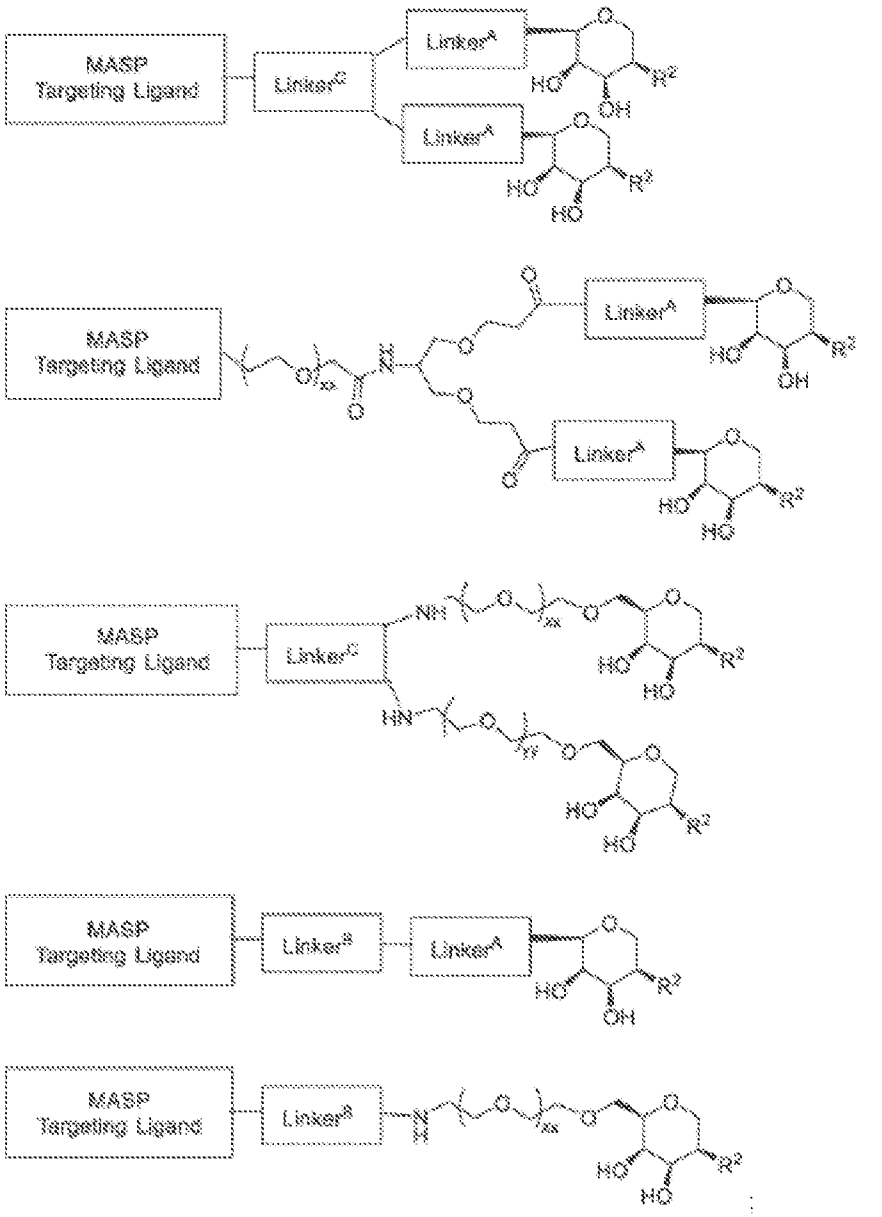

IgE Targeting Ligand
Linker^C
Linker^A
Linker^A
HO
NHAc
OH
HO
NHAc
HO
IgE Targeting Ligand
Linker^A
Linker^A
HO
NHAc
OH
HO
NHAc
HO
IgE Targeting Ligand
Linker^C
NH
HN
HO
NHAc
HO
HO
NHAc
HO
IgE Targeting Ligand
Linker^B
Linker^A
HO
NHAc
OH
IgE Targeting Ligand
Linker^B
N
H
HO
NHAc
HO



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

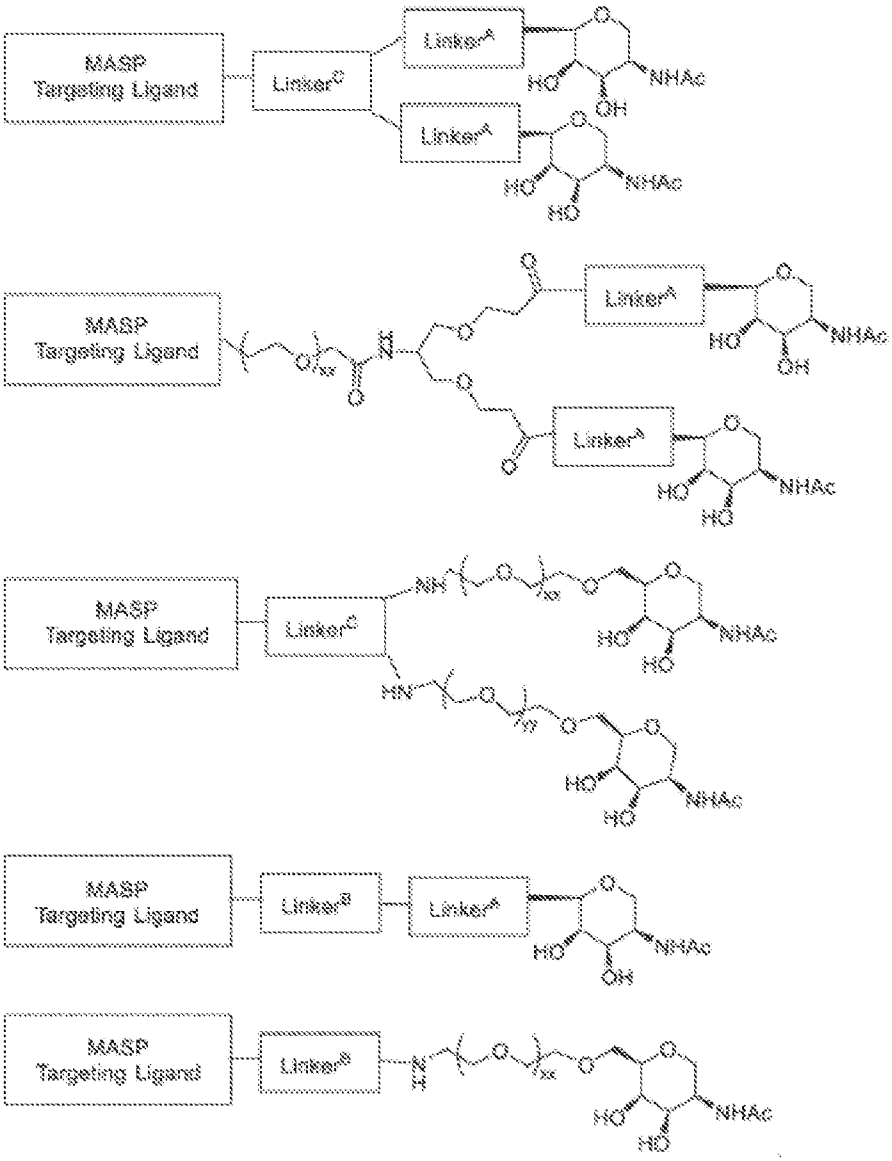
In certain embodiments, the compound of Formula II is selected from:

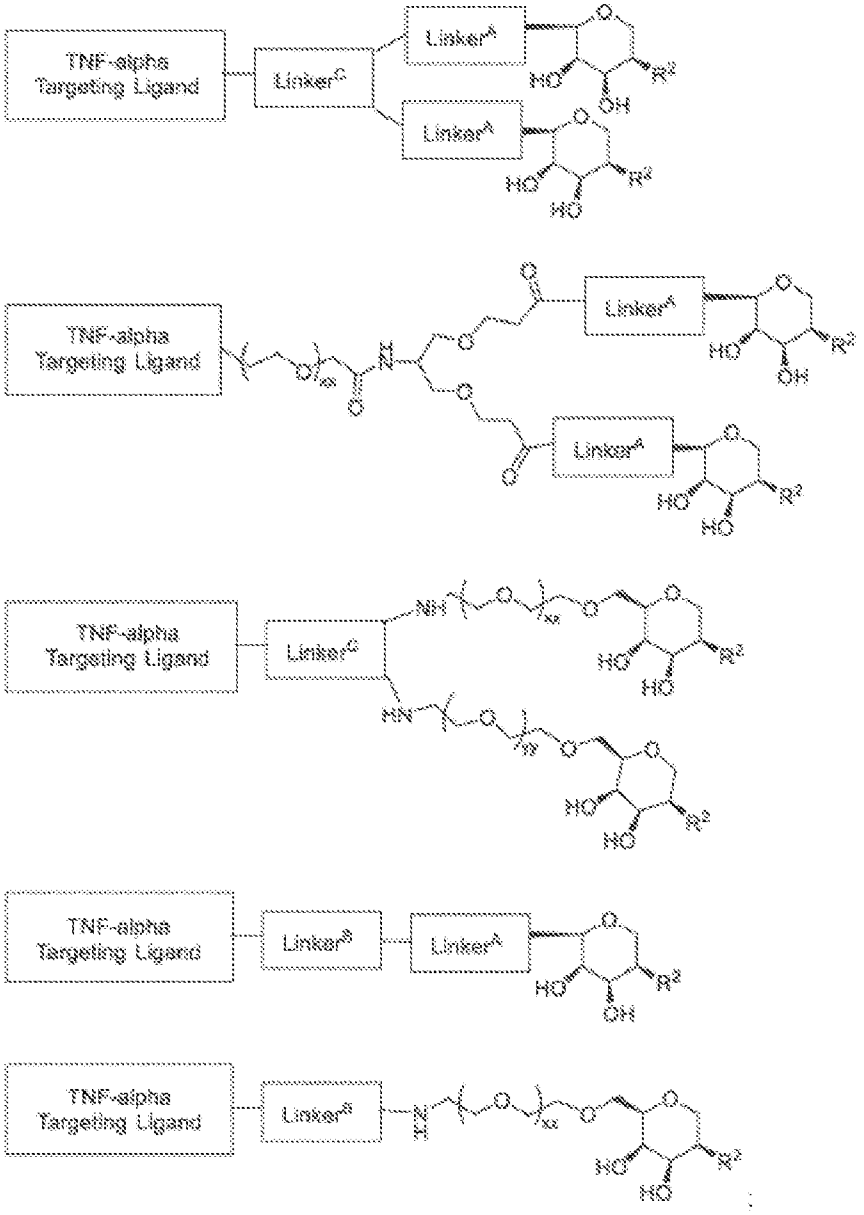

Complement Targeting Ligand
Linker^C
Linker^A
Linker^A
HO
NHAc
OH
HO
HO
Complement Targeting Ligand
Linker^A
Linker^A
HO
NHAc
OH
HO
NHAc
HO
Complement Targeting Ligand
Linker^C
NH
HN
HO
NHAc
HO
HO
NHAc
HO
Complement Targeting Ligand
Linker^B
Linker^A
HO
NHAc
OH
Complement Targeting Ligand
Linker^B
NH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



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

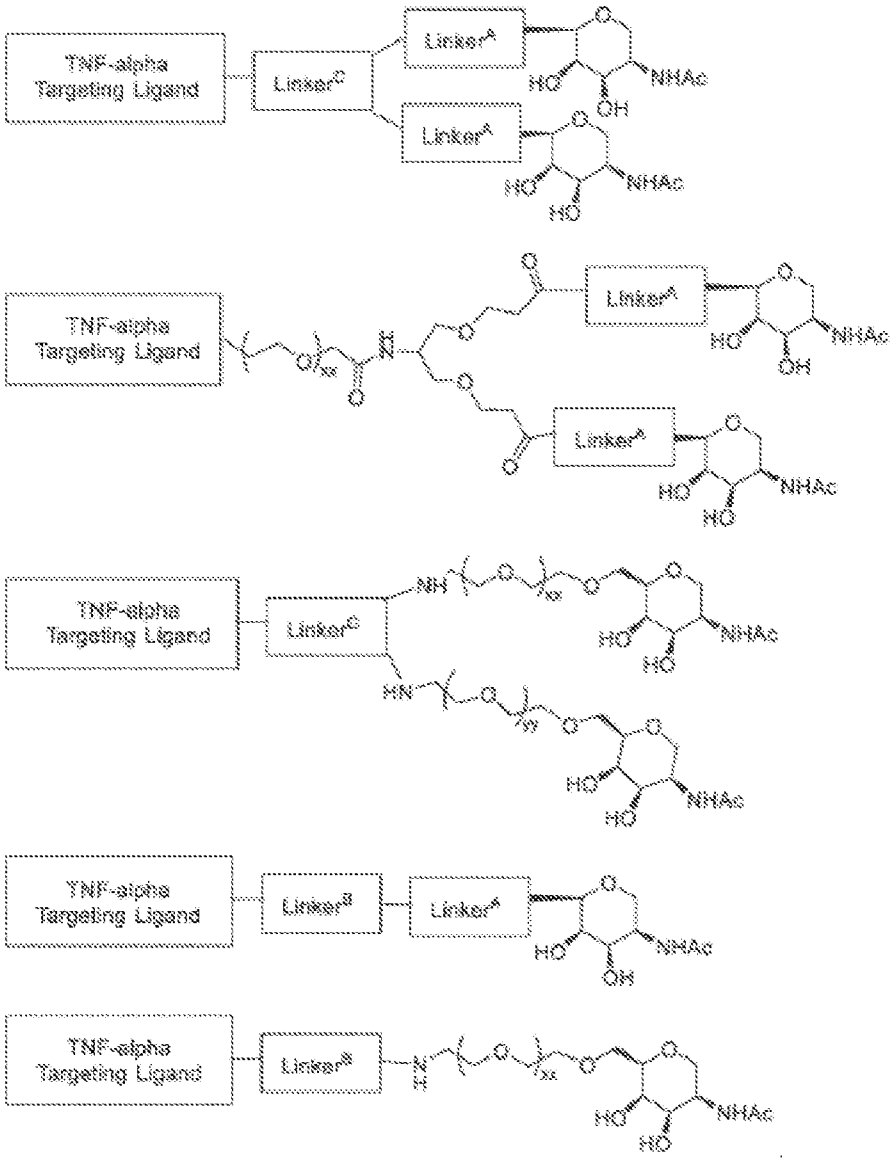
In certain embodiments, the compound of Formula II is selected from:

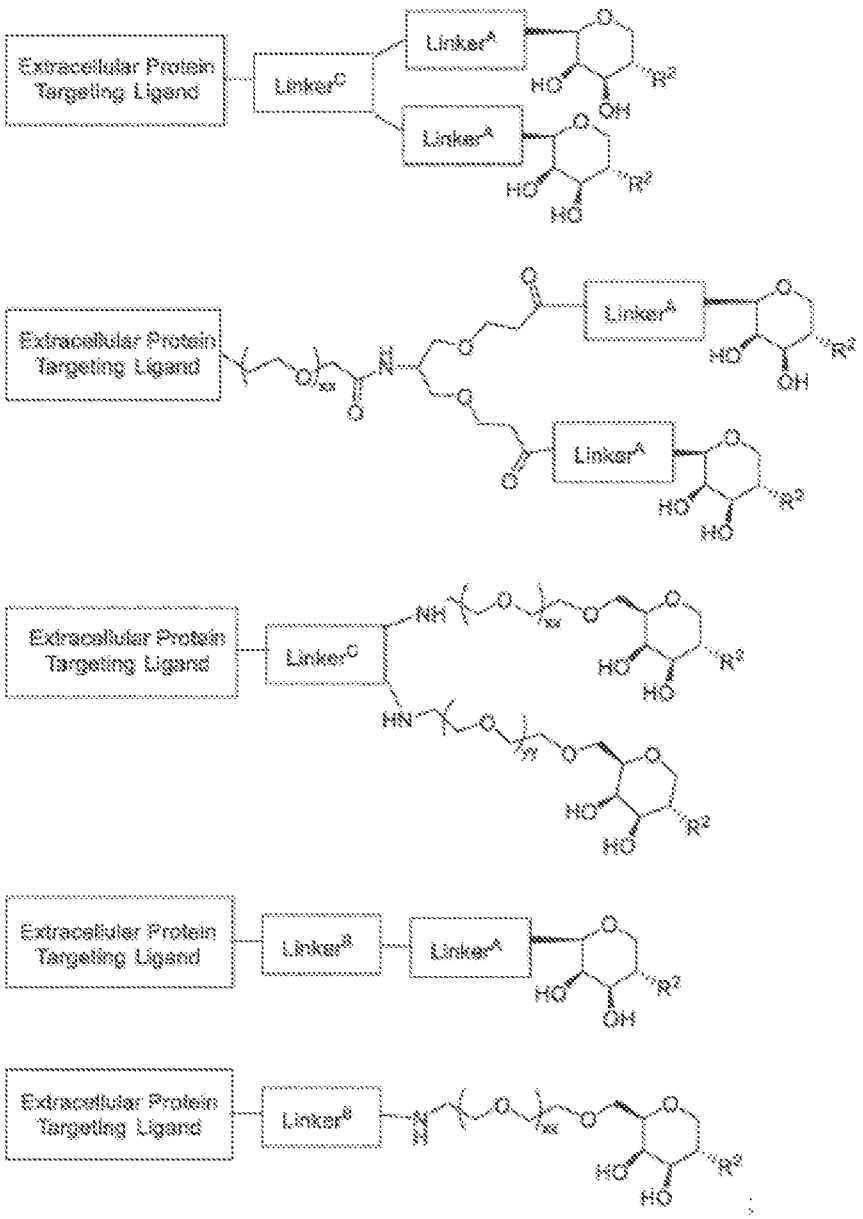

MASP Targeting Ligand
Linker^C
Linker^A
Linker^A
MASP Targeting Ligand
Linker^A
Linker^A
MASP Targeting Ligand
Linker^C
MASP Targeting Ligand
Linker^B
Linker^A
MASP Targeting Ligand
Linker^B



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

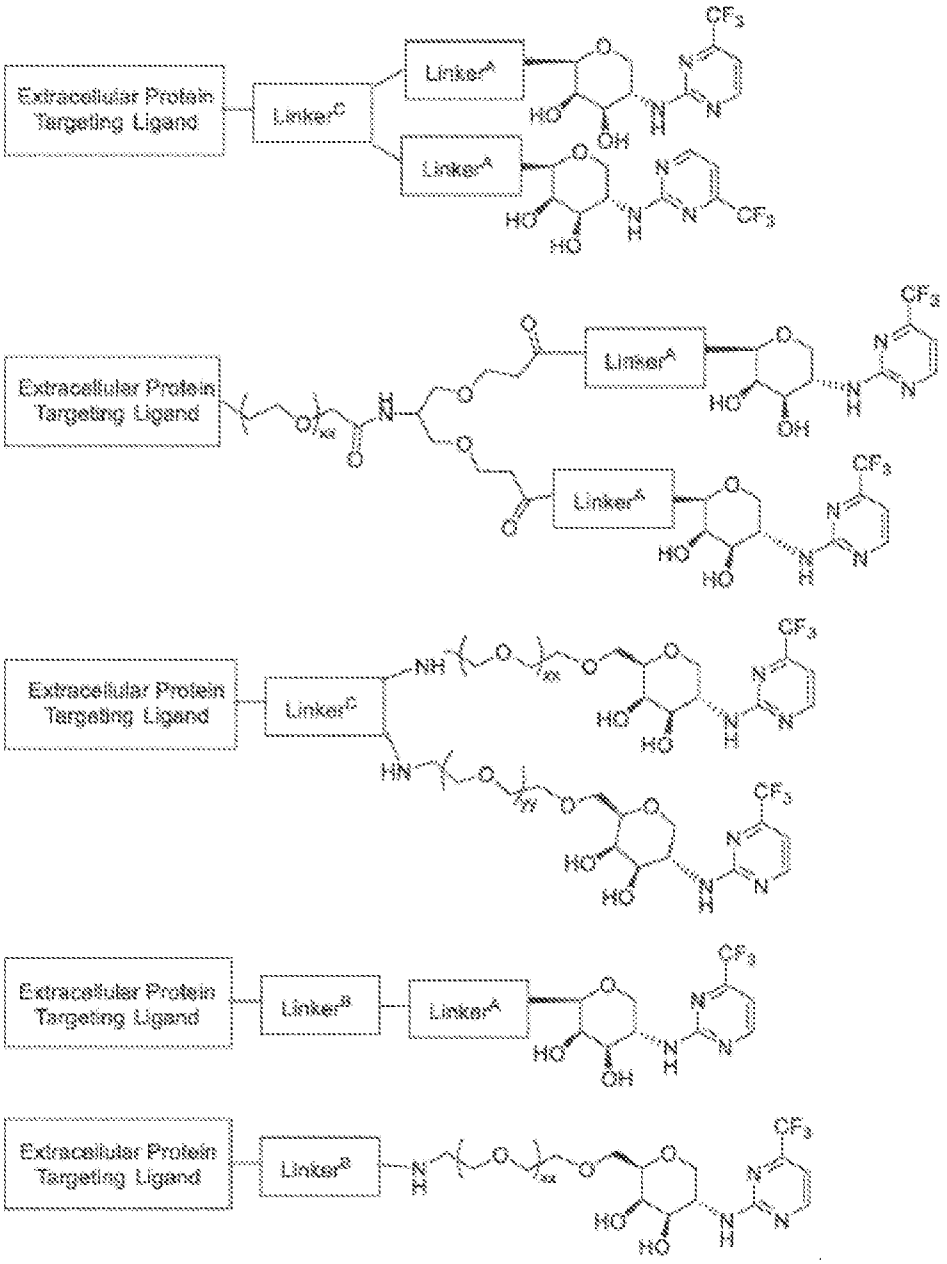
In certain embodiments, the compound of Formula II is selected from:

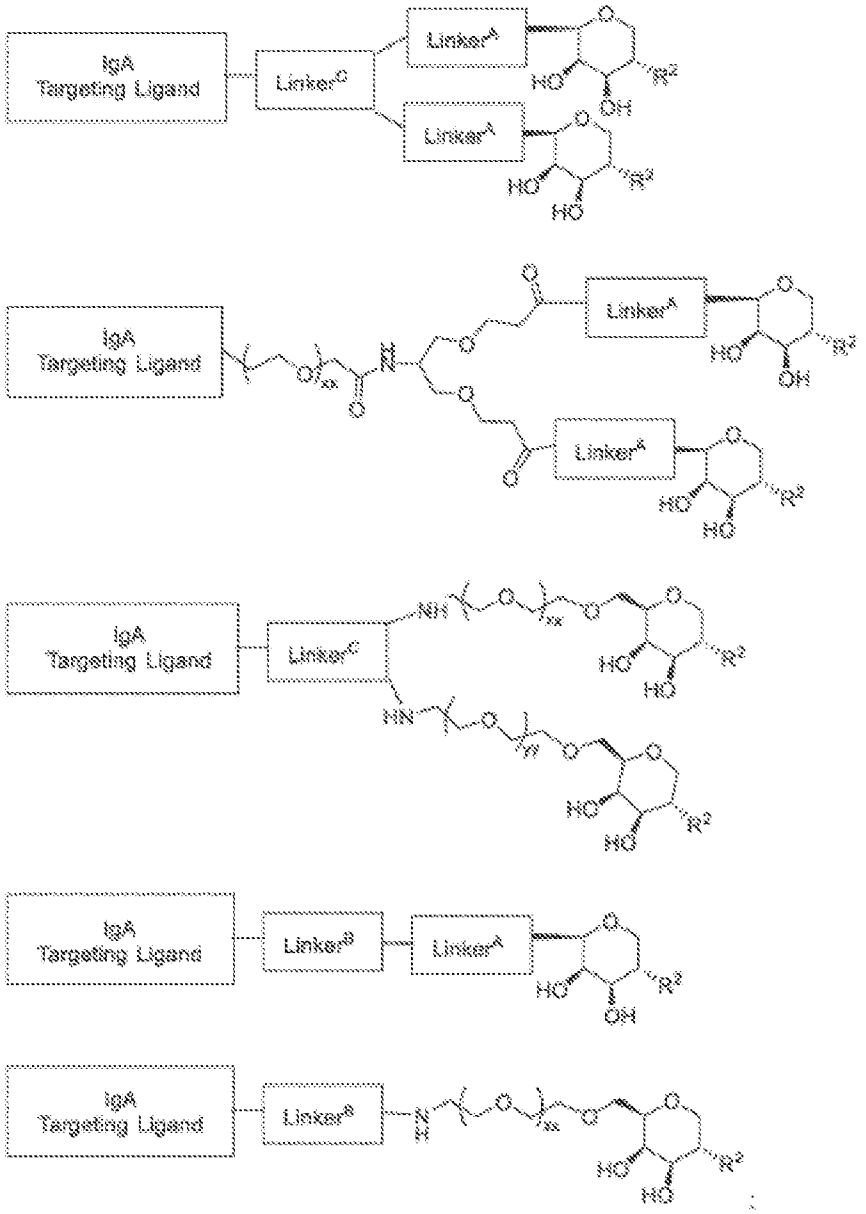

TNF-alpha Targeting Ligand
Linker^C
Linker^A
Linker^A
HO
NHAc
OH
HO
HO
TNF-alpha Targeting Ligand
Linker^A
Linker^A
HO
NHAc
OH
HO
NHAc
HO
TNF-alpha Targeting Ligand
Linker^C
NH
HN
HO
NHAc
HO
HO
NHAc
HO
TNF-alpha Targeting Ligand
Linker^B
Linker^A
HO
NHAc
OH
TNF-alpha Targeting Ligand
Linker^B
HO
NHAc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



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

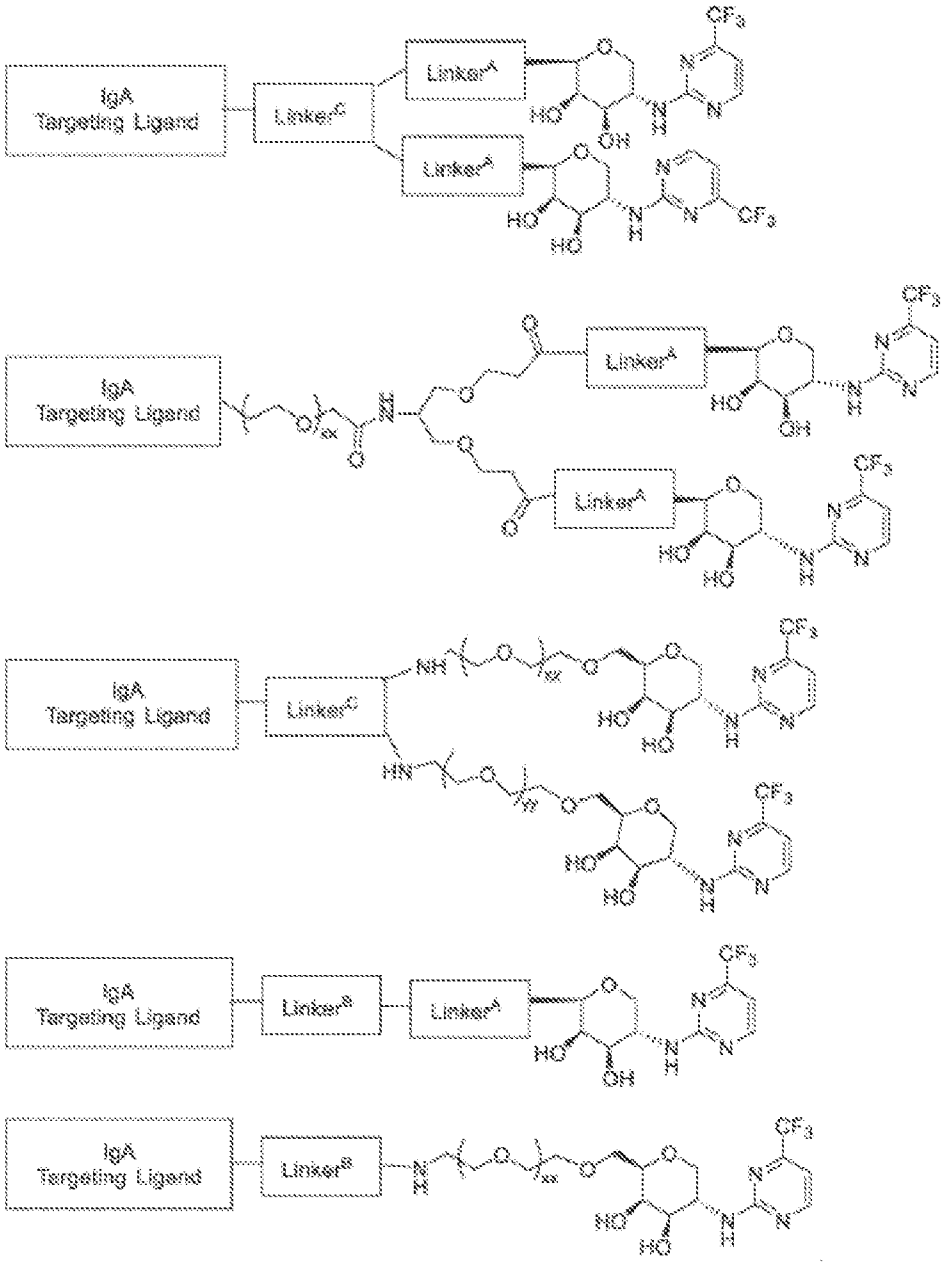
In certain embodiments, the compound of Formula II is selected from:

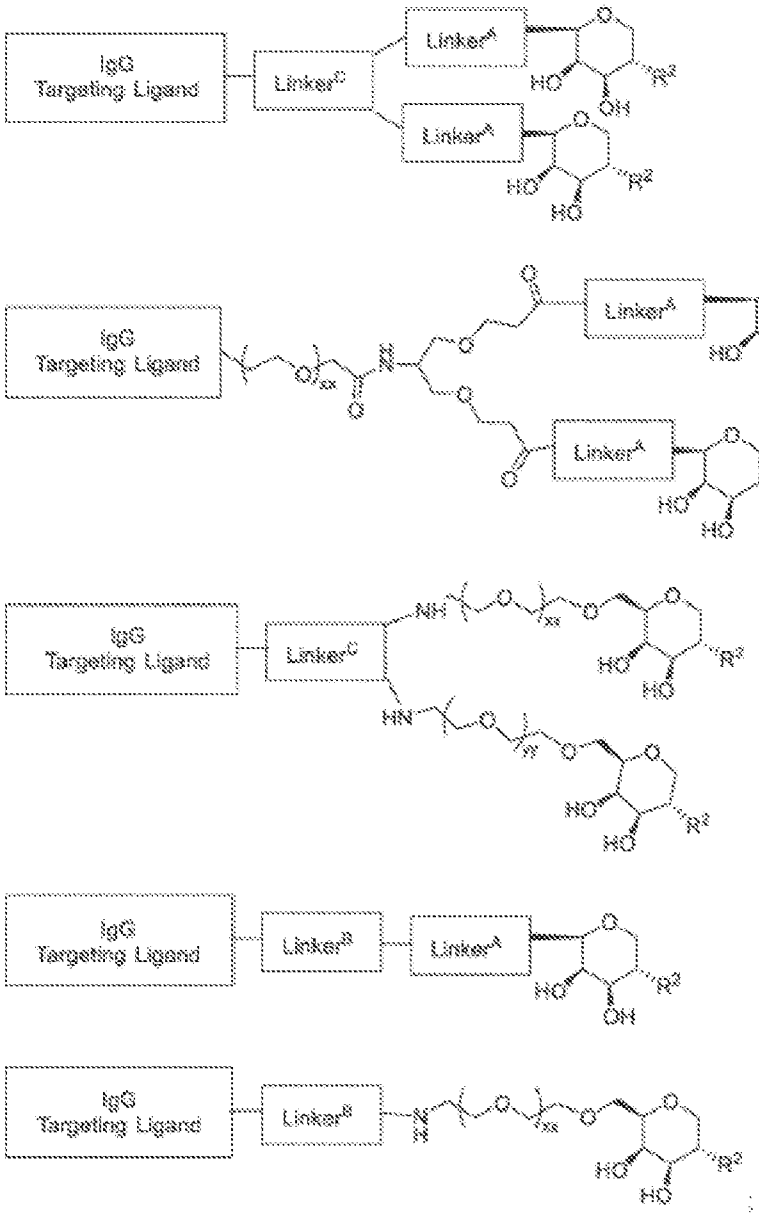

Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^C
Extracellular Protein Targeting Ligand
Linker^B
Linker^A
Extracellular Protein Targeting Ligand
Linker^B

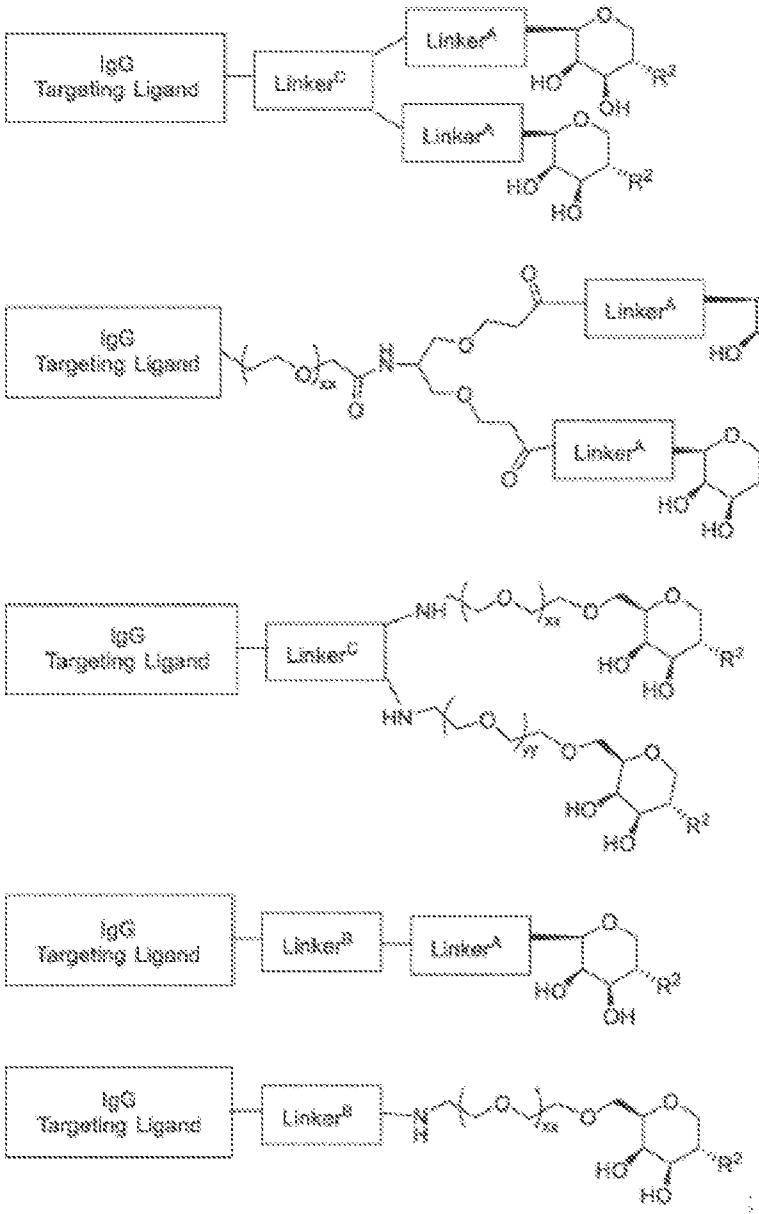


wherein in certain embodiments R^2 is selected from $-NR^bCOR^{10}$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

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

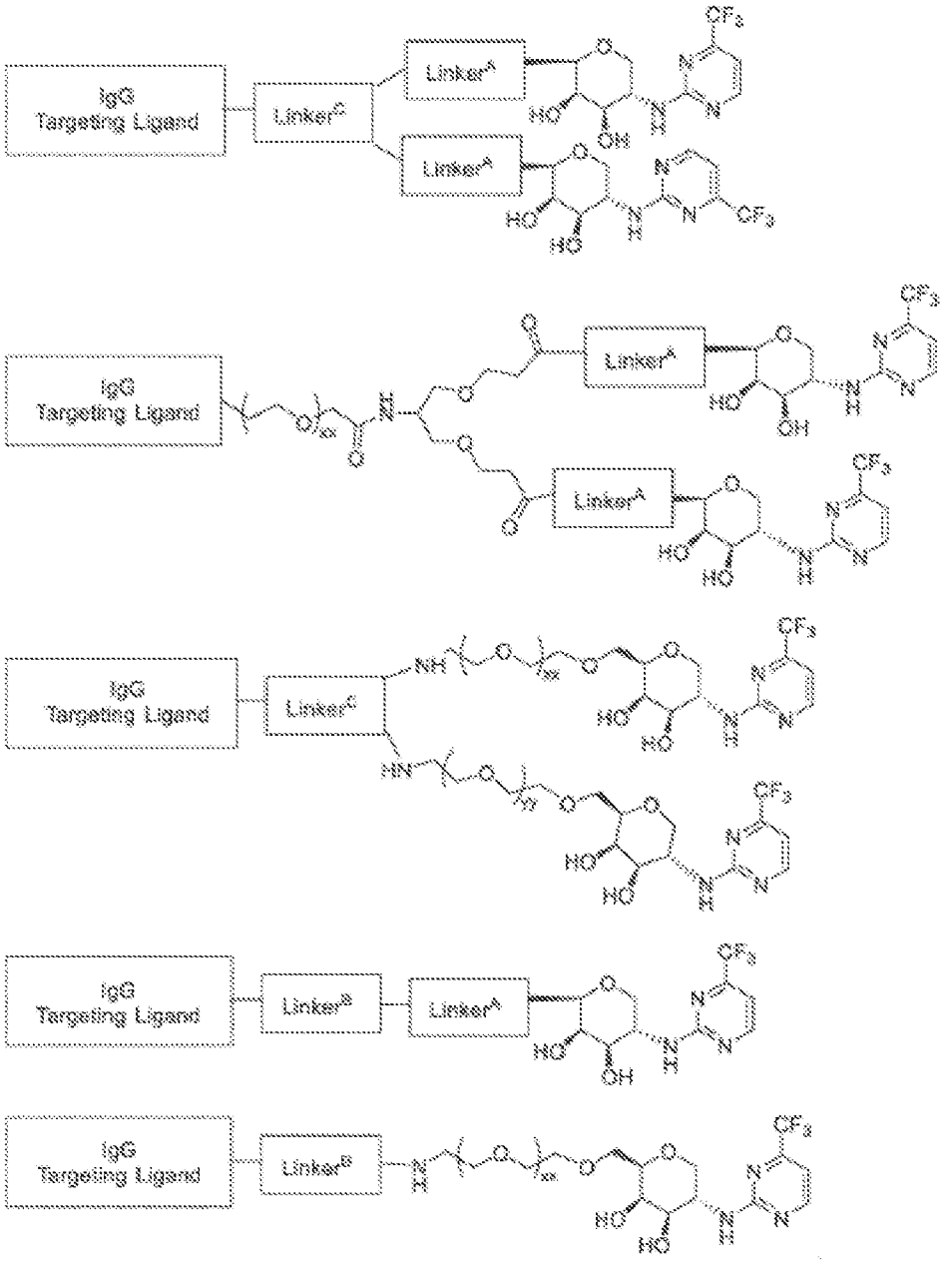

IgA Targeting Ligand
Linker^C
Linker^A
Linker^A
IgA Targeting Ligand
Linker^A
Linker^A
IgA Targeting Ligand
Linker^C
IgA Targeting Ligand
Linker^B
Linker^A
IgA Targeting Ligand
Linker^B

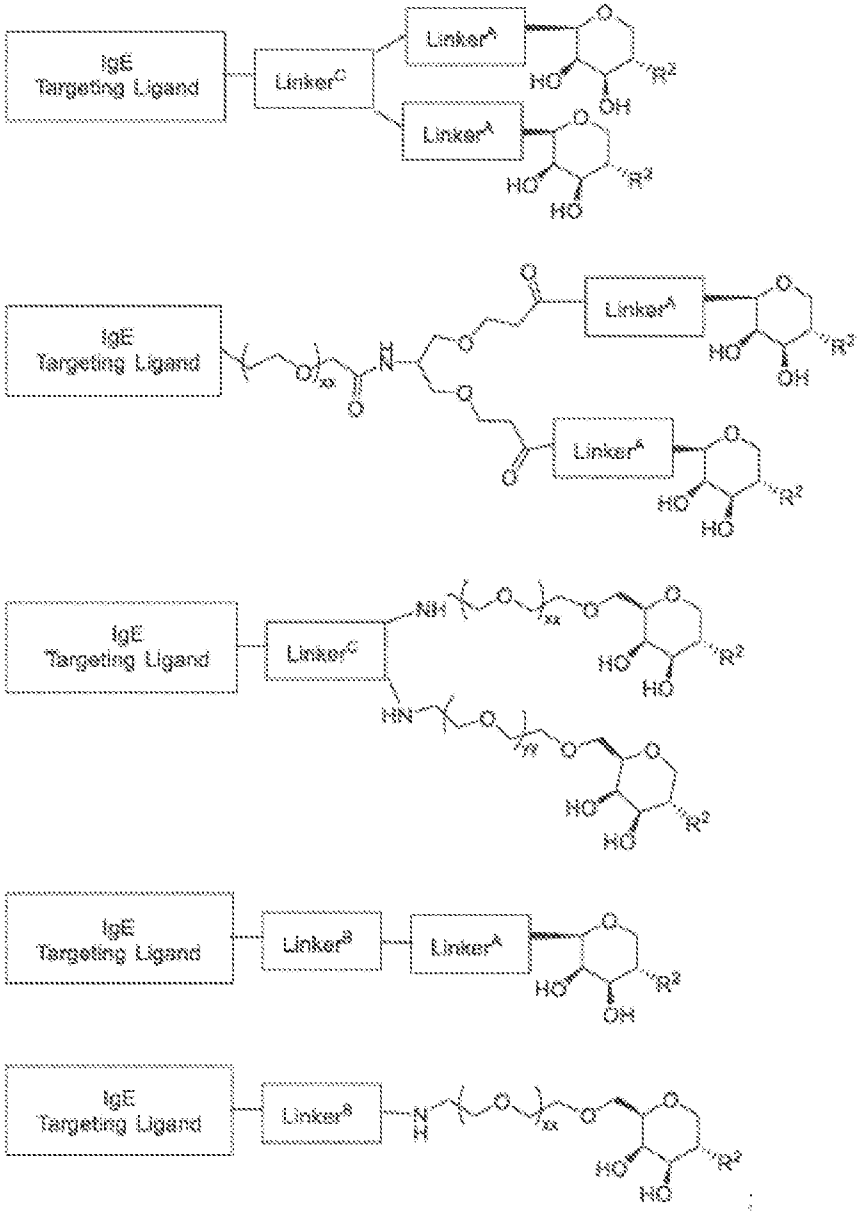

IgG Targeting Ligand
Linker^C
Linker^A
Linker^A
IgG Targeting Ligand
Linker^A
Linker^A
IgG Targeting Ligand
Linker^C
IgG Targeting Ligand
Linker^B
Linker^A
IgG Targeting Ligand
Linker^B



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

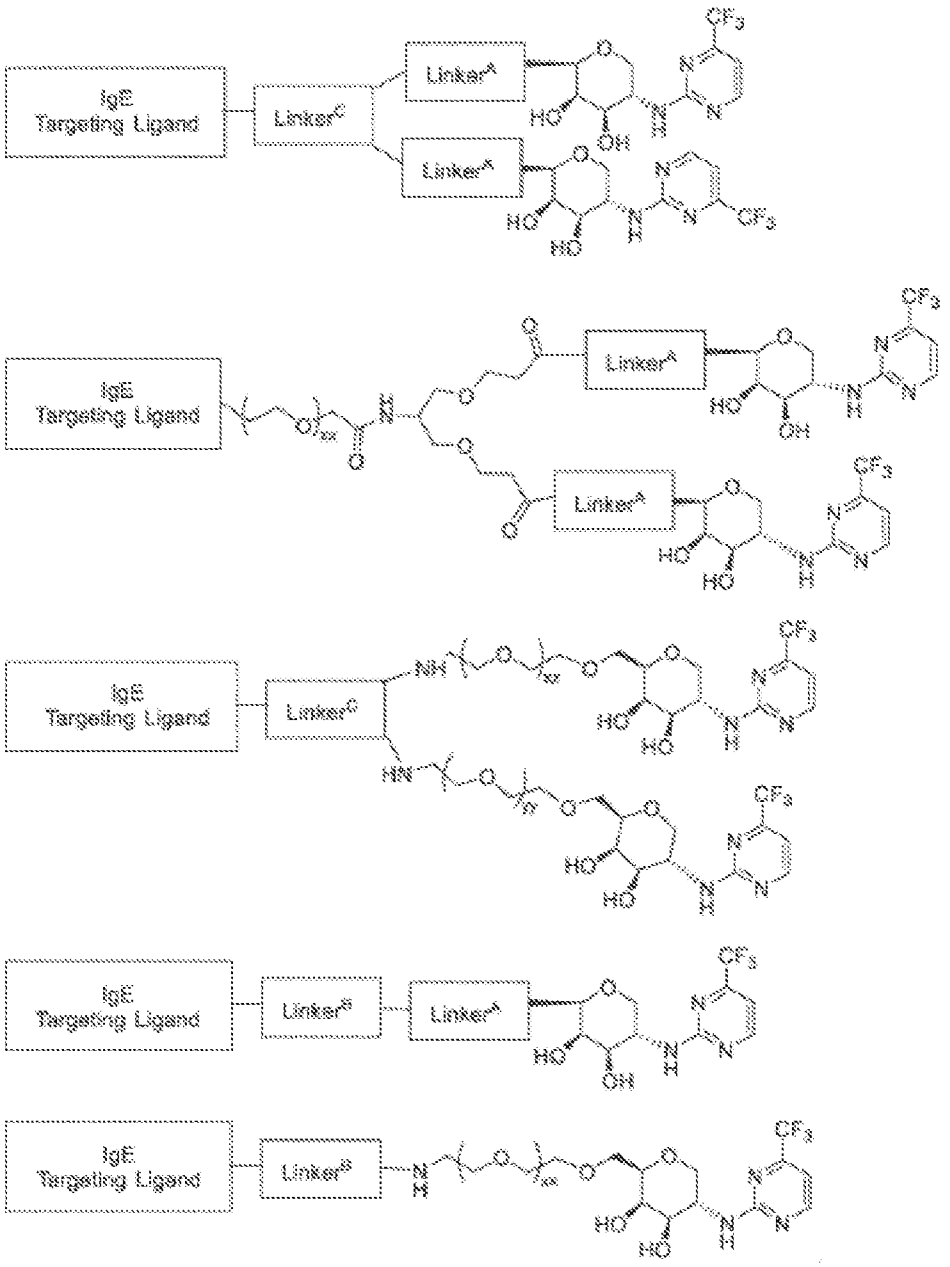
In certain embodiments, the compound of Formula II is selected from:

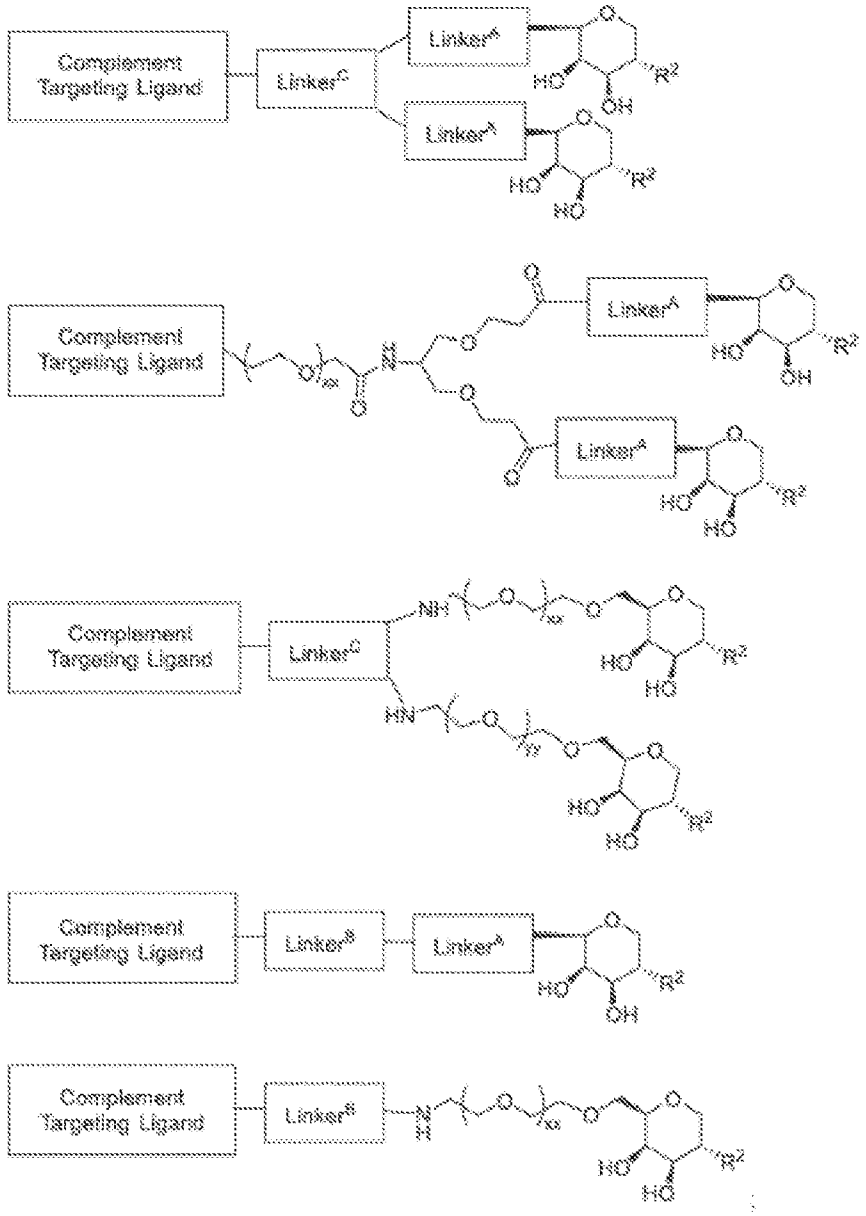

IgG
Targeting Ligand
Linker^C
Linker^A
Linker^A
IgG
Targeting Ligand
Linker^A
Linker^A
IgG
Targeting Ligand
Linker^C
IgG
Targeting Ligand
Linker^B
Linker^A
IgG
Targeting Ligand
Linker^B



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

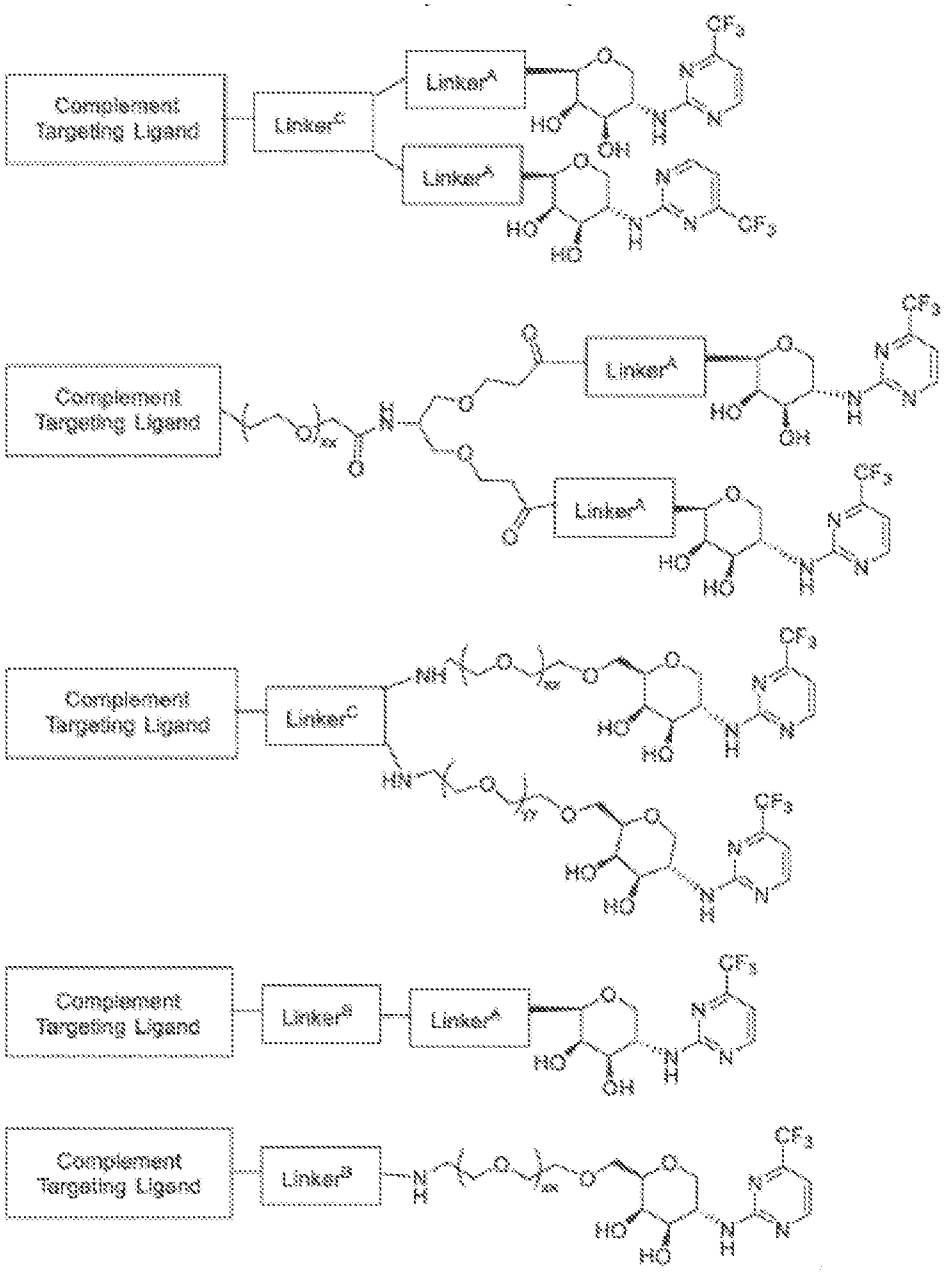
In certain embodiments, the compound of Formula II is selected from:

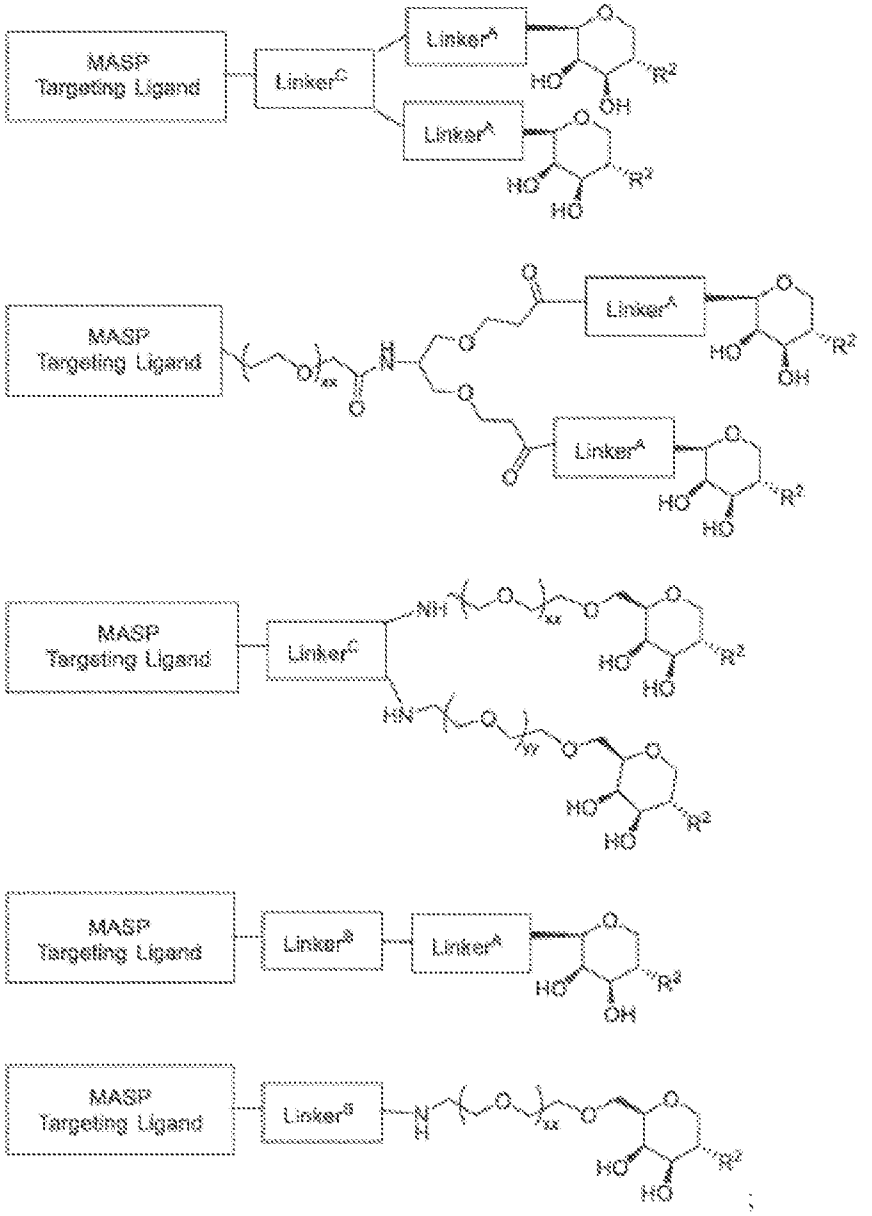

IgE Targeting Ligand
Linker^C
Linker^A
Linker^A
IgE Targeting Ligand
Linker^A
Linker^A
IgE Targeting Ligand
Linker^C
IgE Targeting Ligand
Linker^B
Linker^A
IgE Targeting Ligand
Linker^B



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

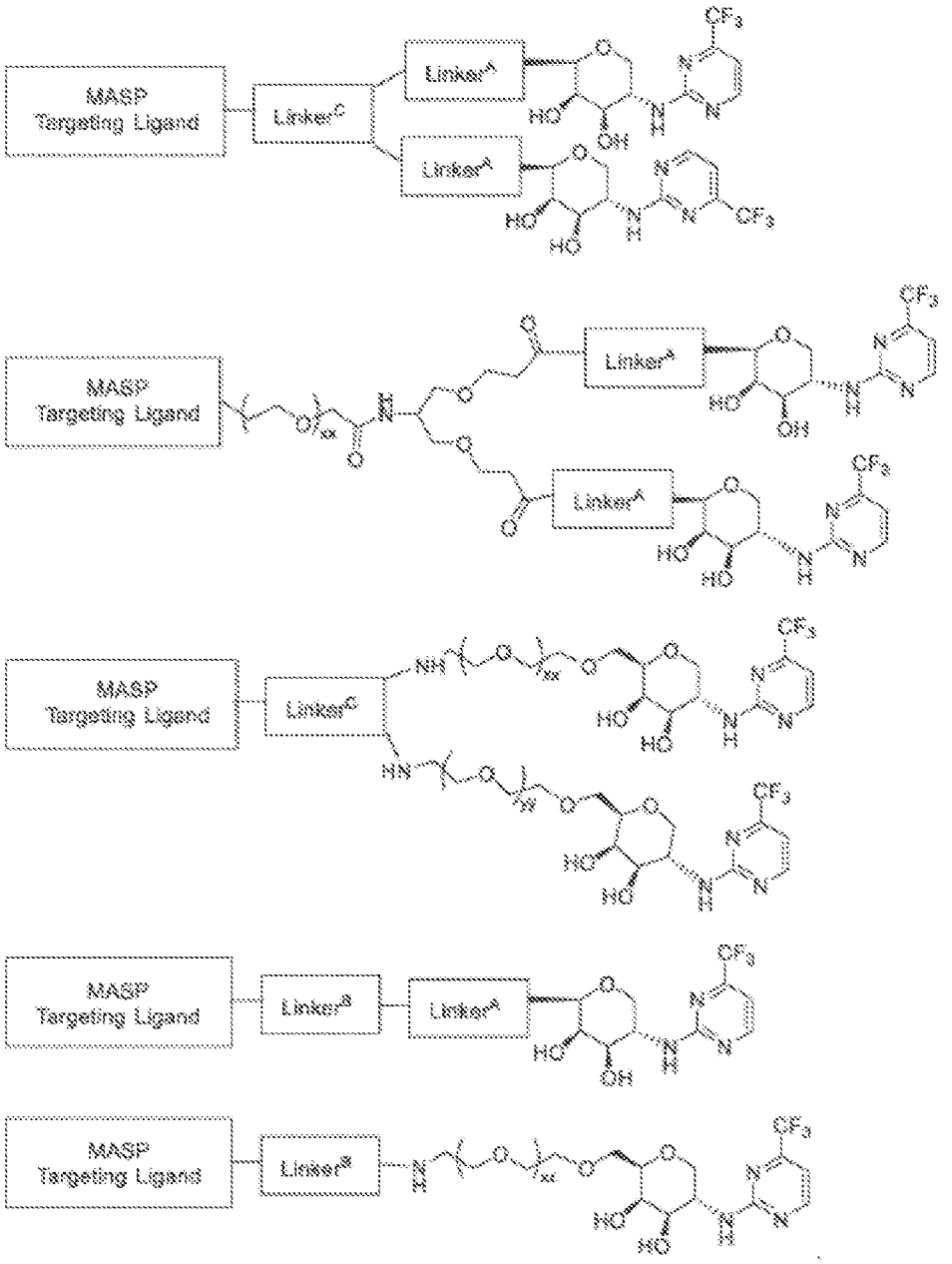
In certain embodiments, the compound of Formula II is selected from:

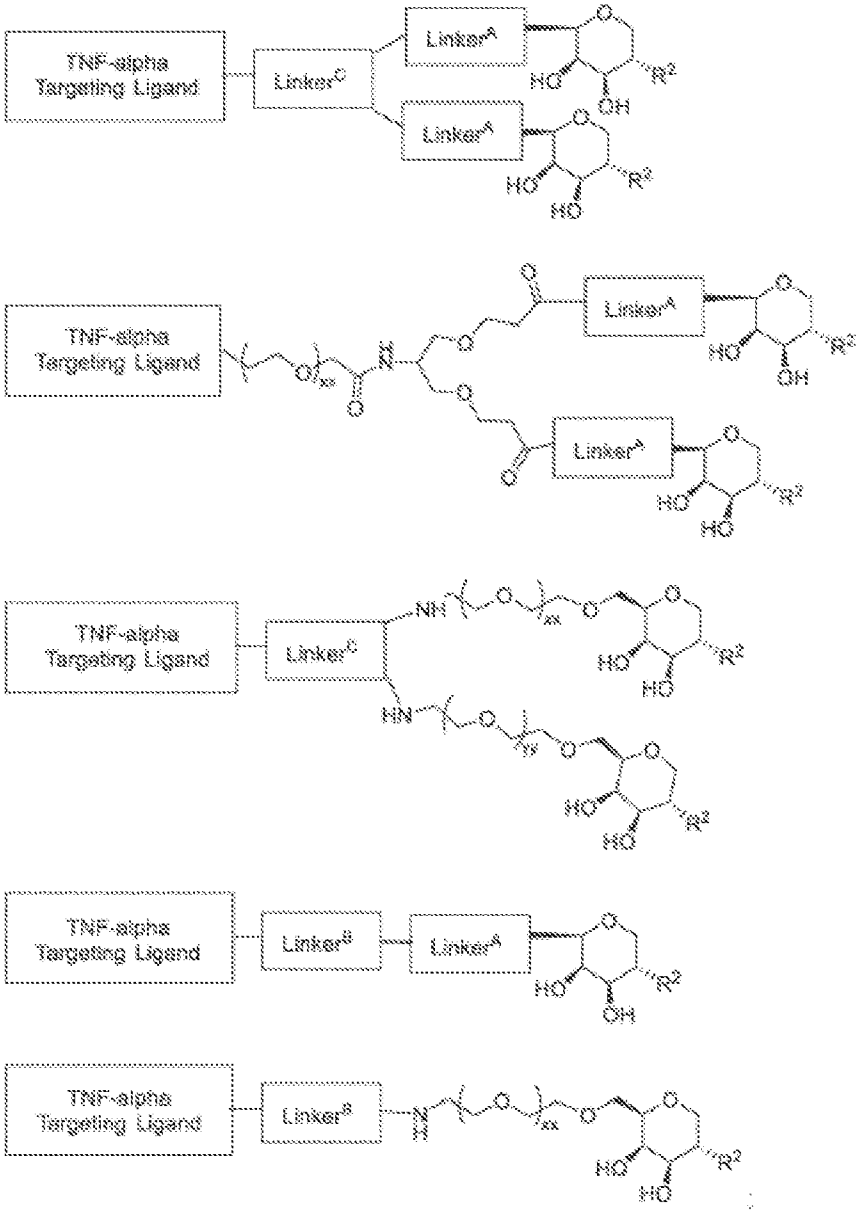

Complement Targeting Ligand
Linker^C
Linker^A
Linker^A
Complement Targeting Ligand
Linker^A
Linker^A
Complement Targeting Ligand
Linker^C
Complement Targeting Ligand
Linker^B
Linker^A
Complement Targeting Ligand
Linker^B



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

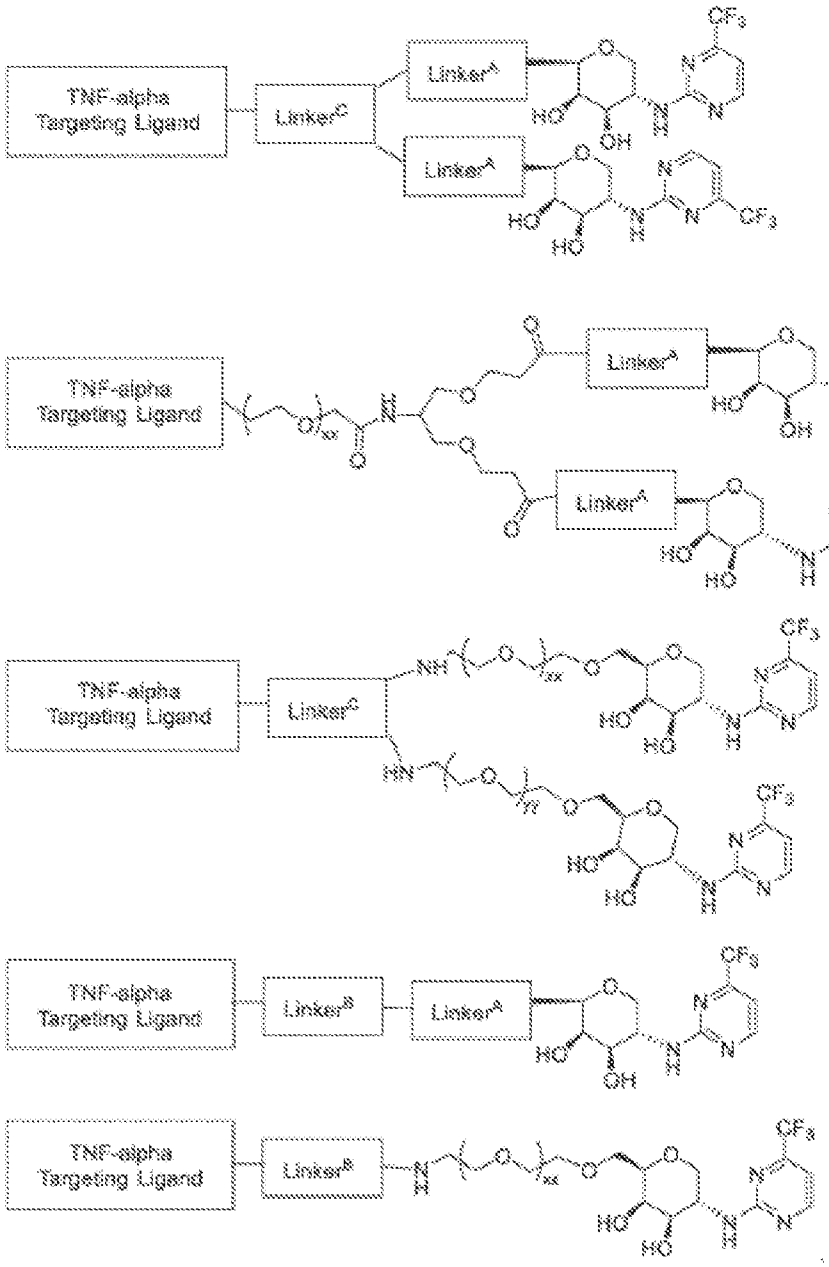
In certain embodiments, the compound of Formula II is selected from:

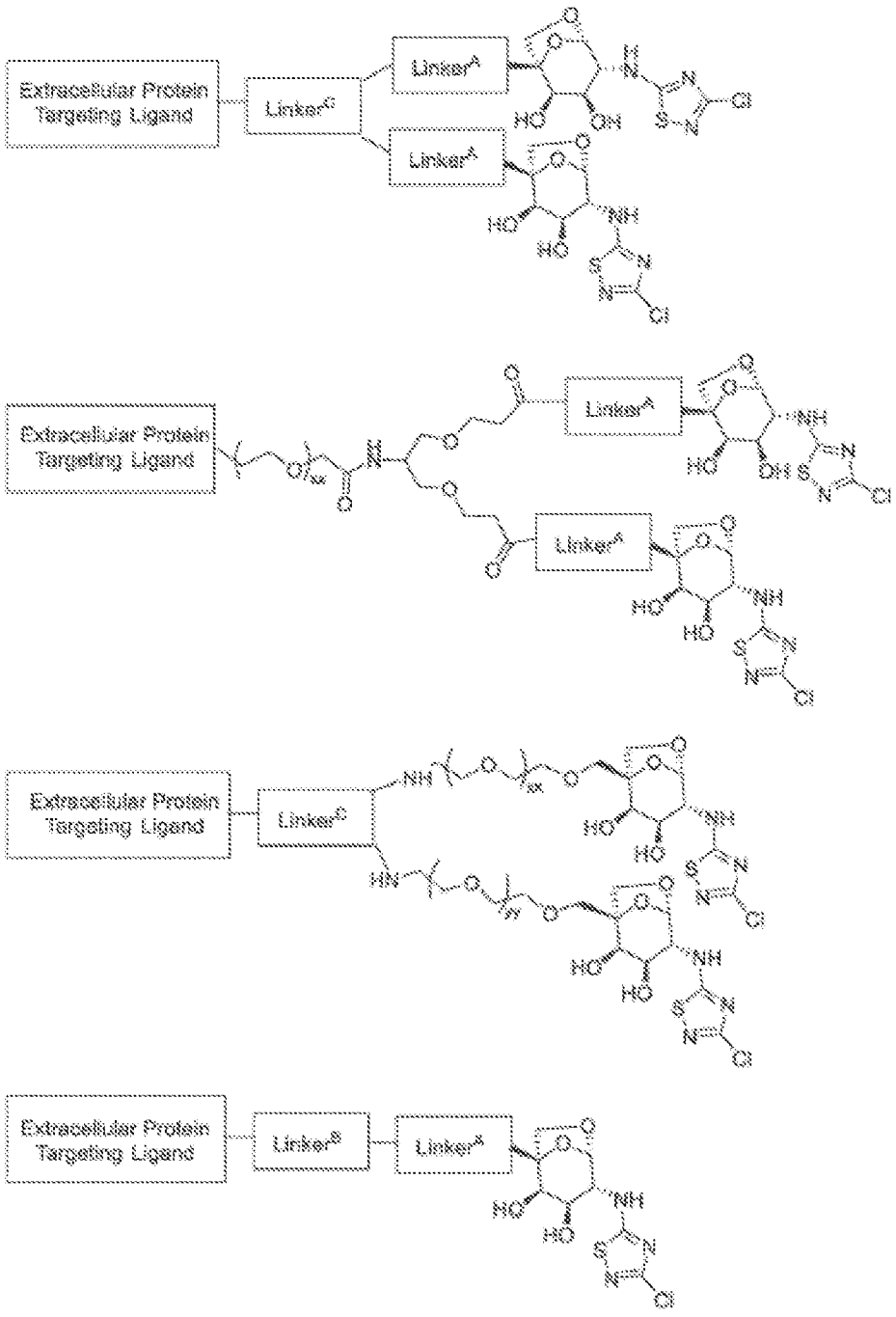

MASP Targeting Ligand
Linker^C
Linker^A
Linker^A
MASP Targeting Ligand
Linker^A
Linker^A
MASP Targeting Ligand
Linker^C
MASP Targeting Ligand
Linker^B
Linker^A
MASP Targeting Ligand
Linker^B

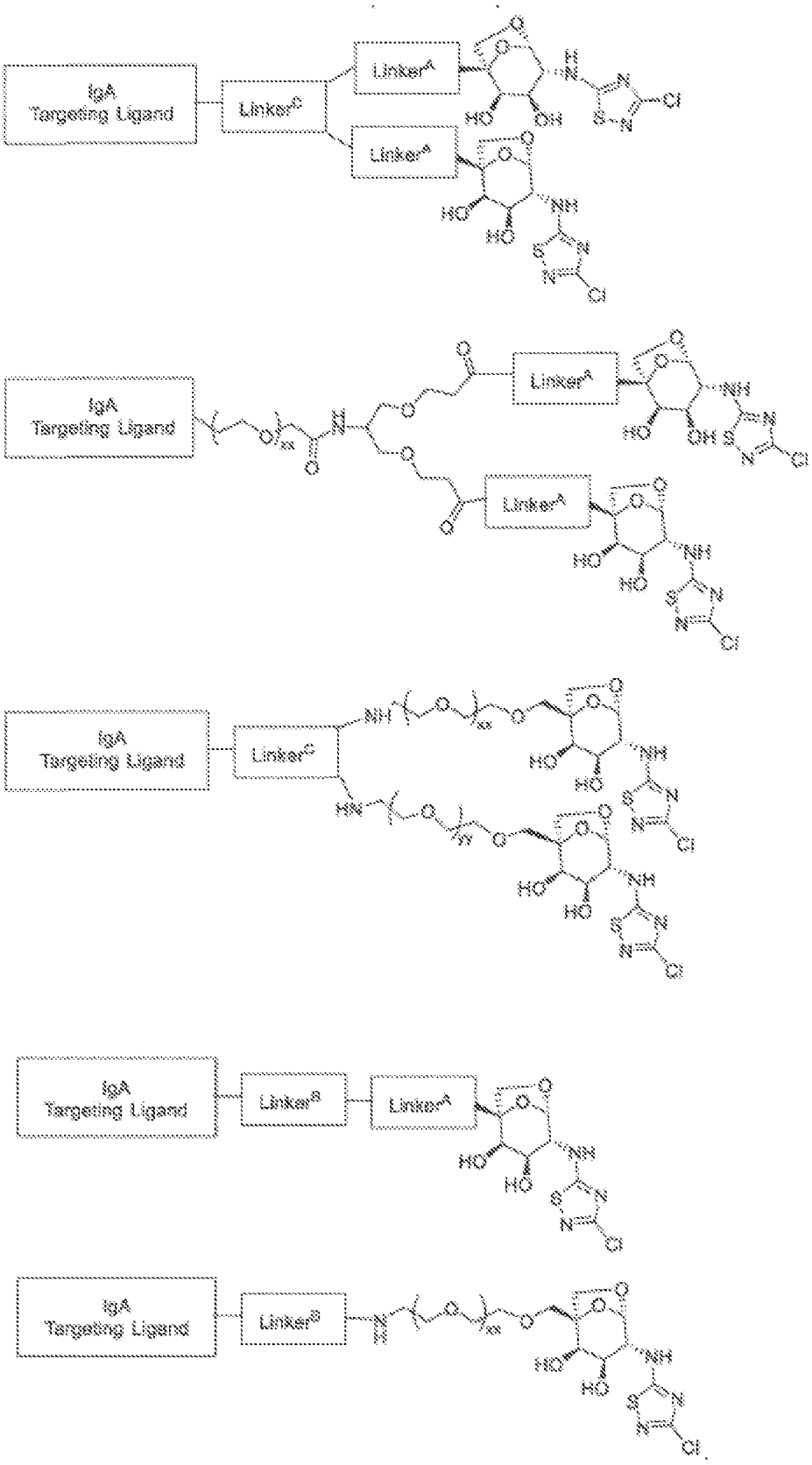


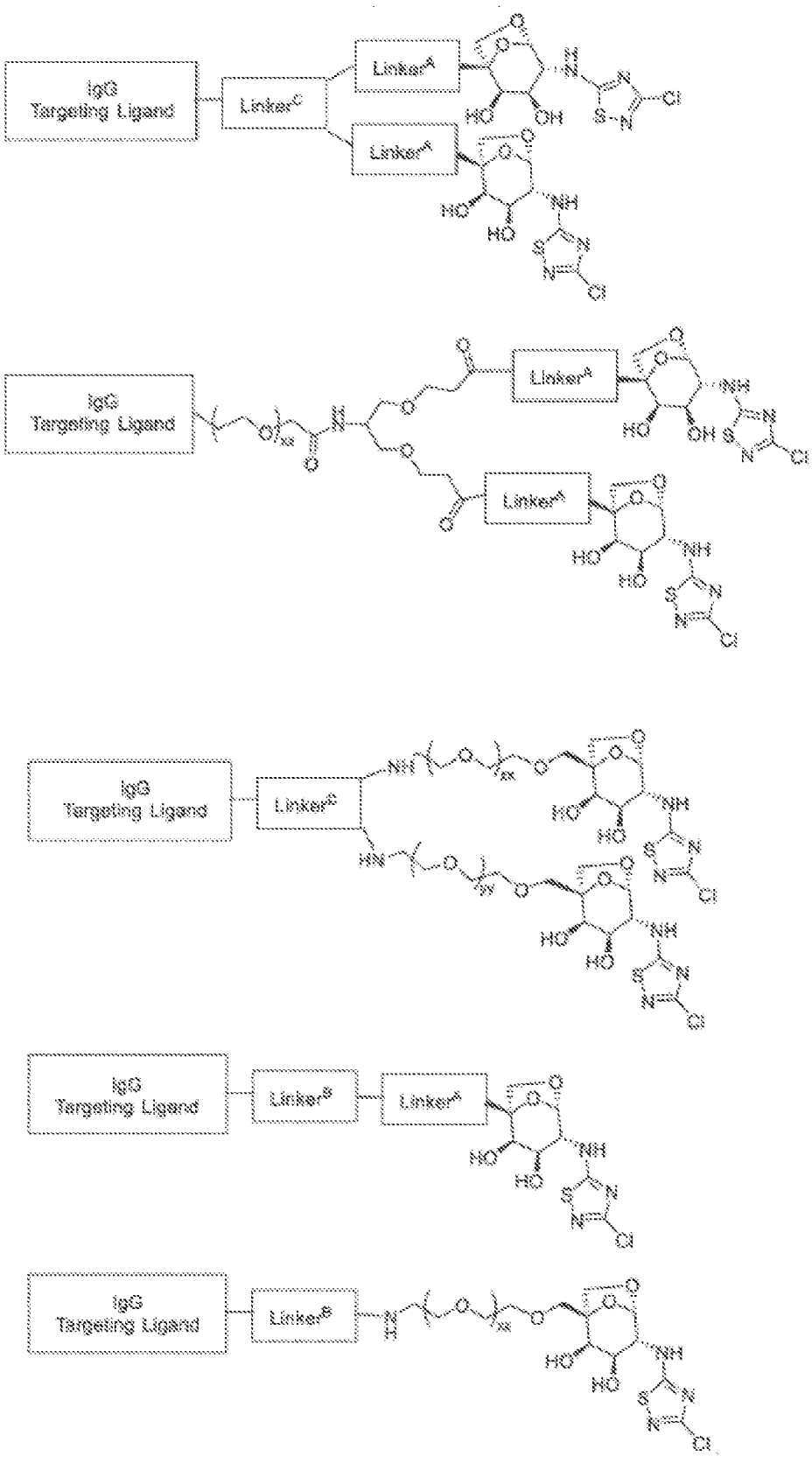
wherein in certain embodiments R^2 is selected from $-NR^6COR^{10}$, $-NR^6$-(5-membered heteroaryl), and-NR^6-(6-membered heteroaryl), each of which R^2 groups is optionally substituted with 1, 2, 3, or 4 independent, substituents as described herein, for example 1, 2, 3, or 4 substituents independently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

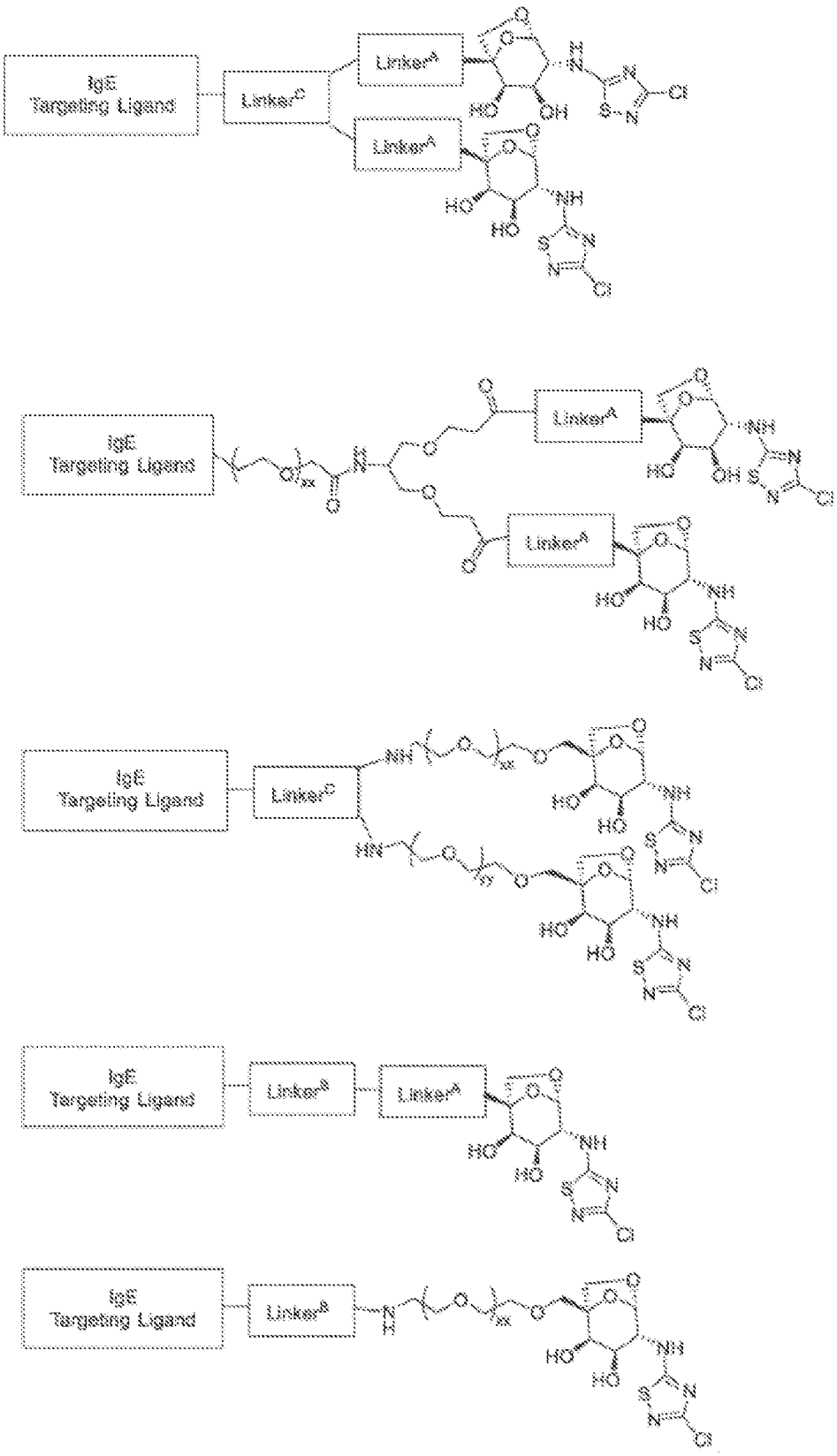
In certain embodiments, the compound of Formula II is selected from:

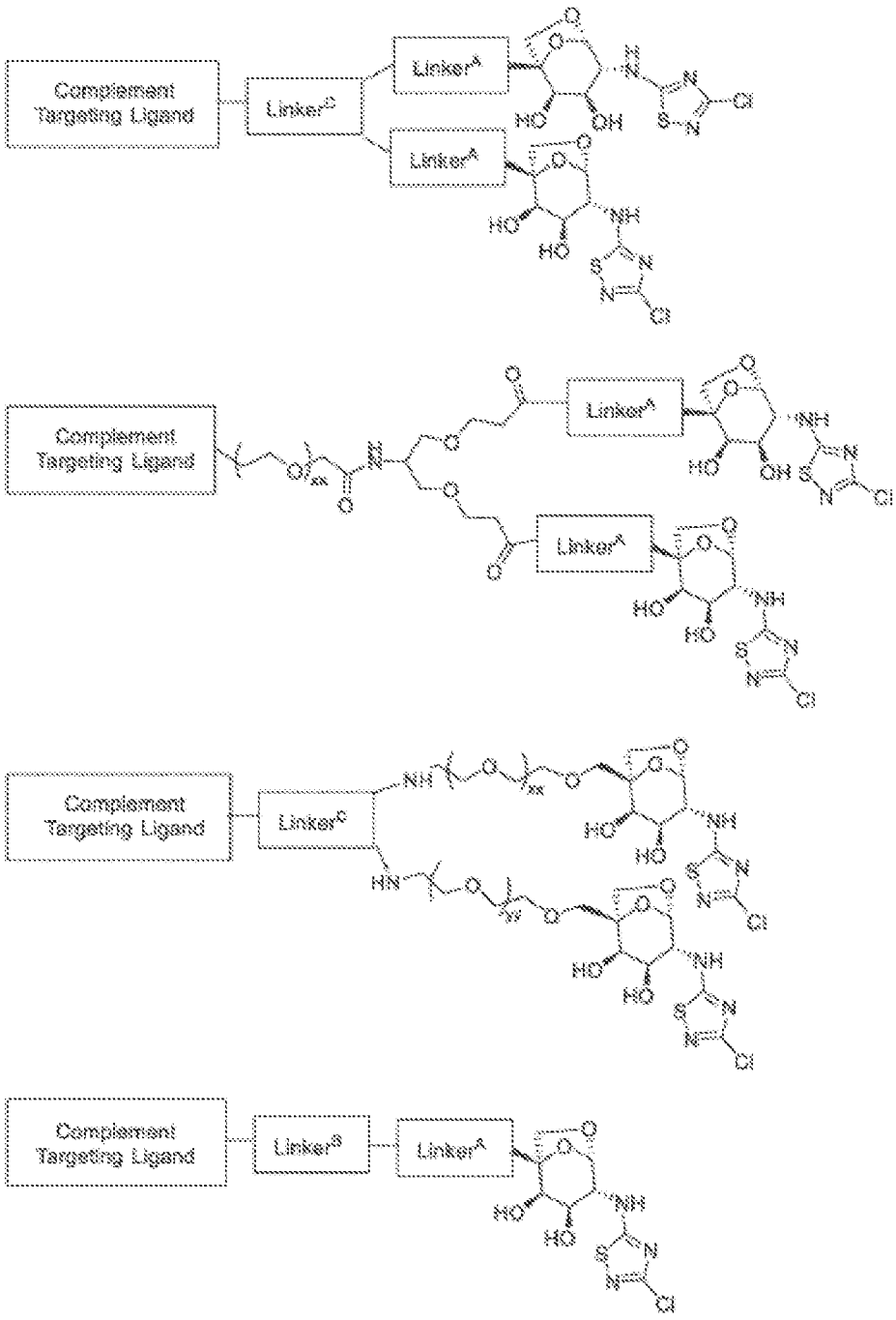

TNF-alpha Targeting Ligand
Linker^C
Linker^A
Linker^A
TNF-alpha Targeting Ligand
Linker^A
Linker^A
TNF-alpha Targeting Ligand
Linker^C
TNF-alpha Targeting Ligand
Linker^B
Linker^A
TNF-alpha Targeting Ligand
Linker^B

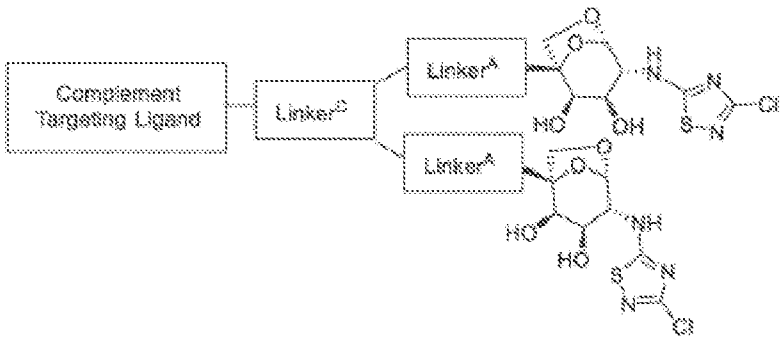

Extracellular Protein Targeting Ligand
Linker^C
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^A
Linker^A
Extracellular Protein Targeting Ligand
Linker^C
Extracellular Protein Targeting Ligand
Linker^B
Linker^A

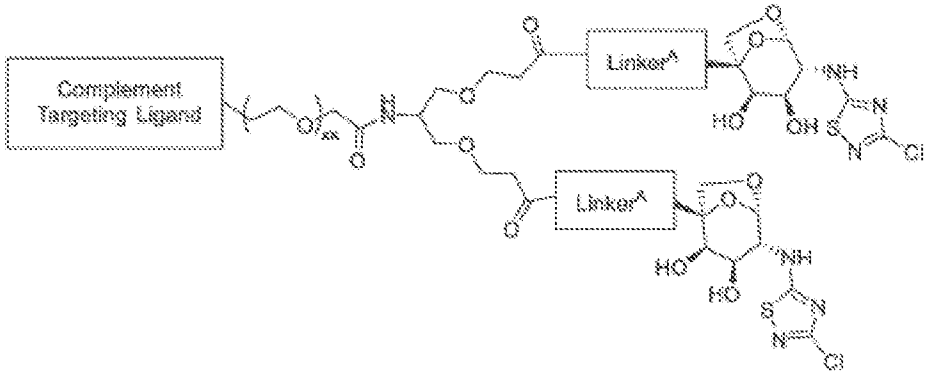

IgA Targeting Ligand
Linker^C
Linker^A
Linker^A
IgA Targeting Ligand
Linker^A
Linker^A
IgA Targeting Ligand
Linker^C
IgA Targeting Ligand
Linker^B
Linker^A
IgA Targeting Ligand
Linker^B

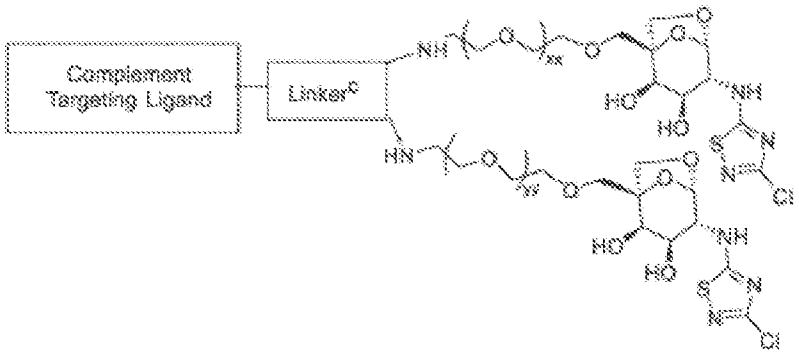

IgG Targeting Ligand
Linker^C
Linker^A
Linker^A
IgG Targeting Ligand
Linker^A
Linker^A
IgG Targeting Ligand
Linker^C
IgG Targeting Ligand
Linker^B
Linker^A
IgG Targeting Ligand
Linker^B

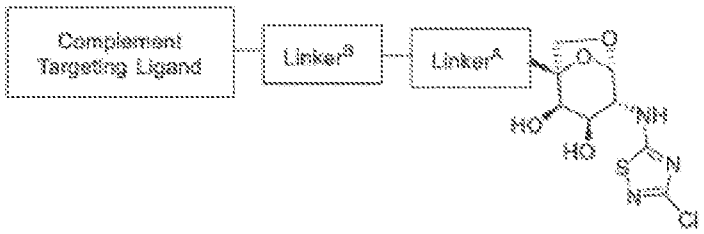

IgE Targeting Ligand
Linker^C
Linker^A
Linker^A
IgE Targeting Ligand
Linker^A
Linker^A
IgE Targeting Ligand
Linker^C
IgE Targeting Ligand
Linker^B
Linker^A
IgE Targeting Ligand
Linker^B

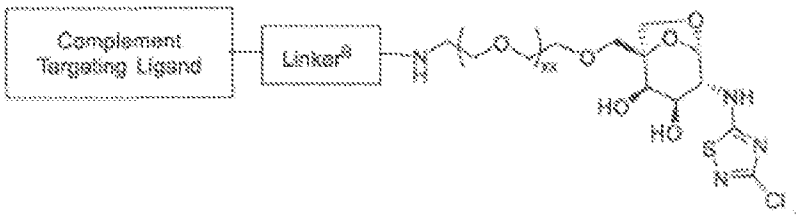

Complement Targeting Ligand
Linker^C
Linker^A
Linker^A
Complement Targeting Ligand
Linker^A
Linker^A
Complement Targeting Ligand
Linker^C
Complement Targeting Ligand
Linker^B
Linker^A

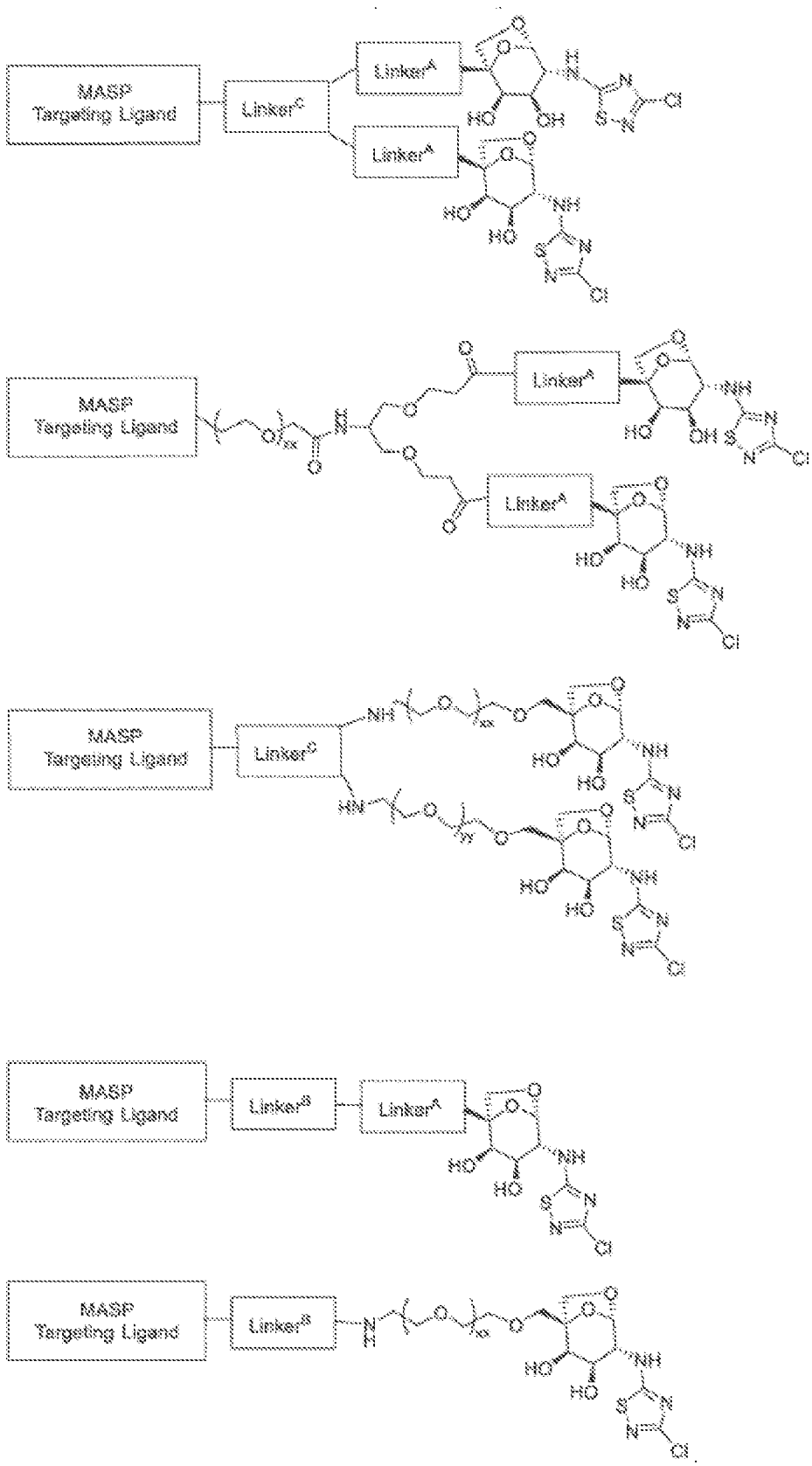

Complement Targeting Ligand
Linker^C
Linker^A
Linker^A

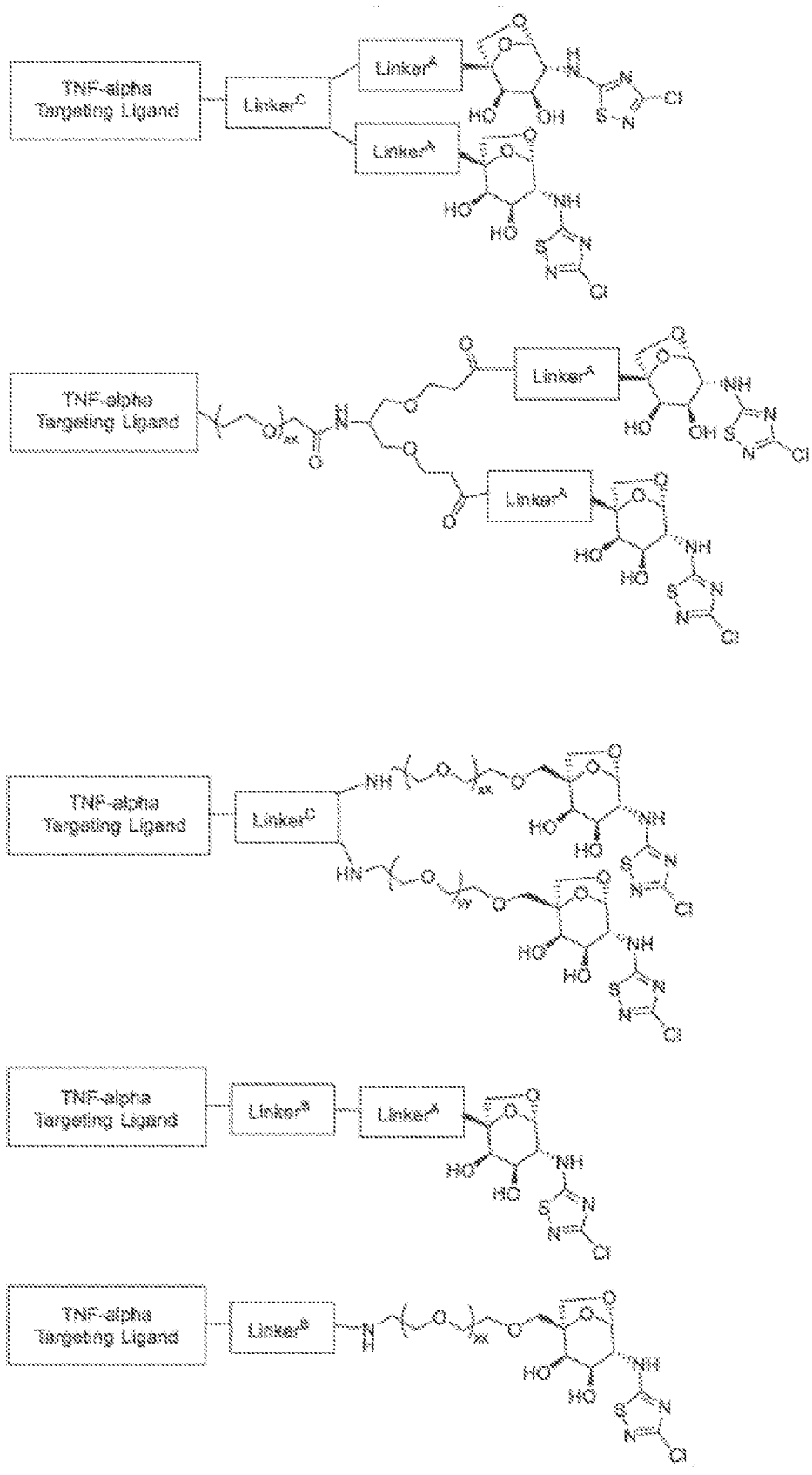

Complement Targeting Ligand
Linker^A
Linker^A

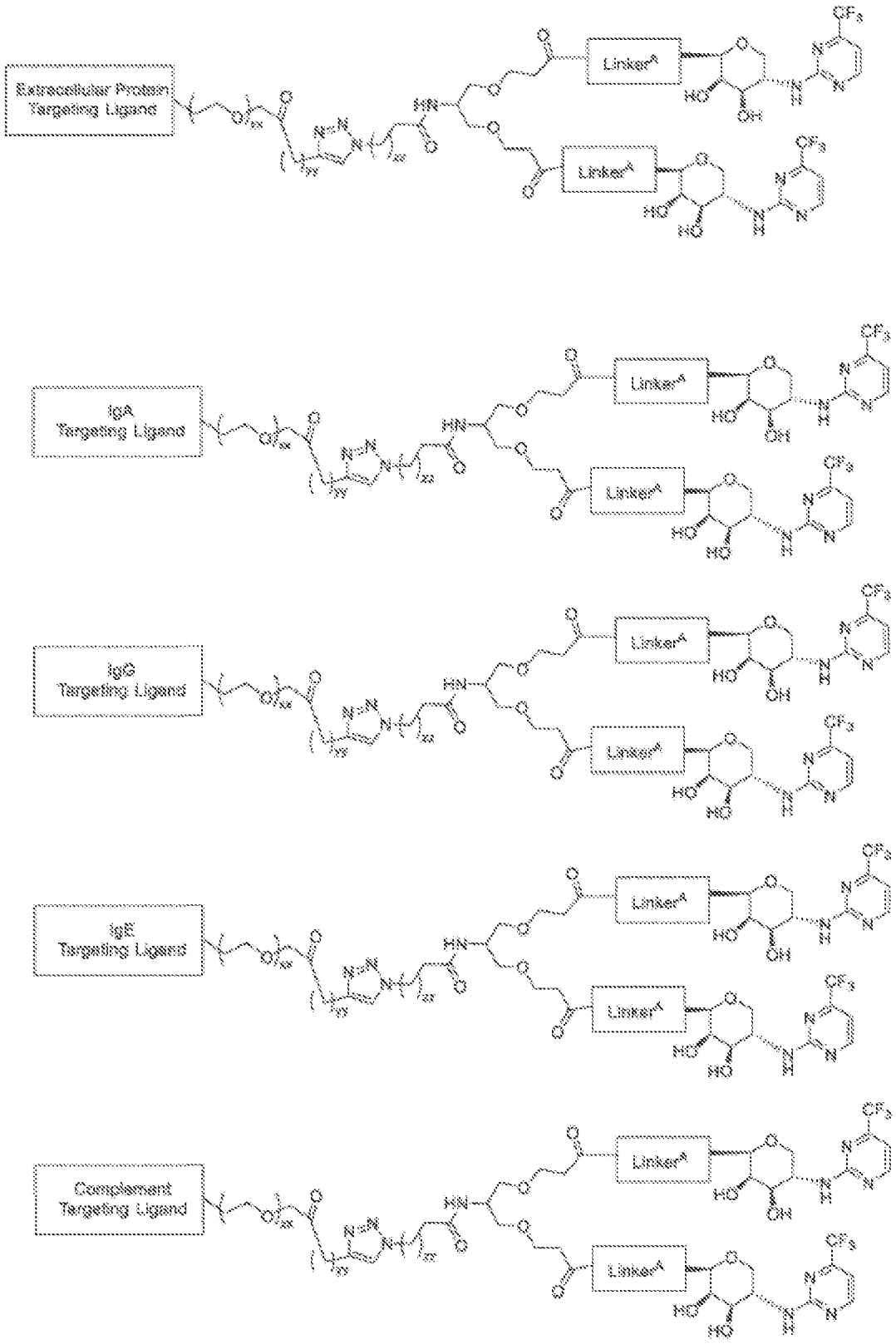

Complement Targeting Ligand
Linker^C

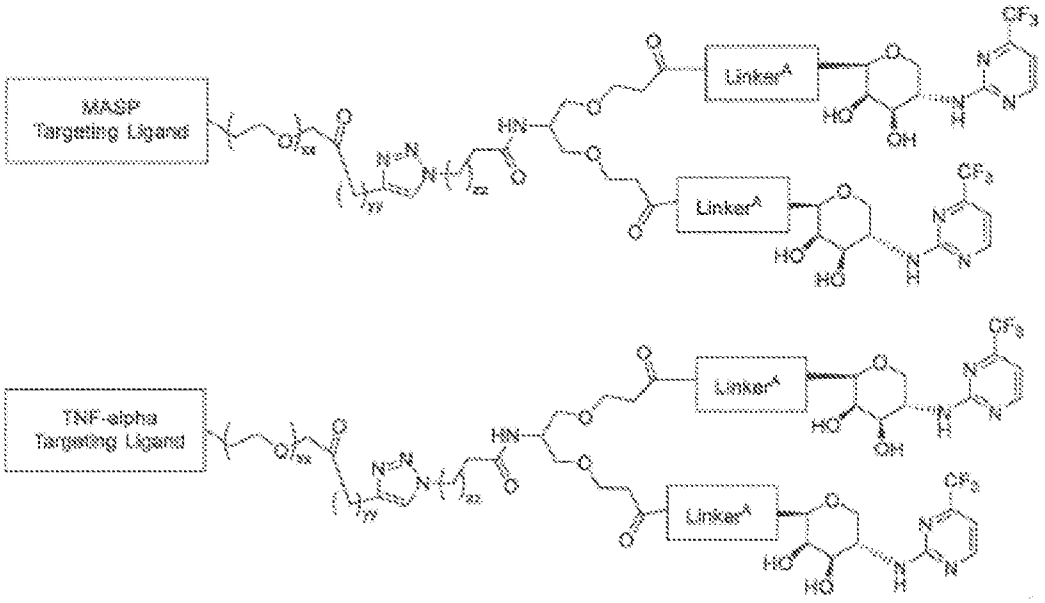

Complement Targeting Ligand
Linker^B
Linker^A


Complement Targeting Ligand
Linker^B

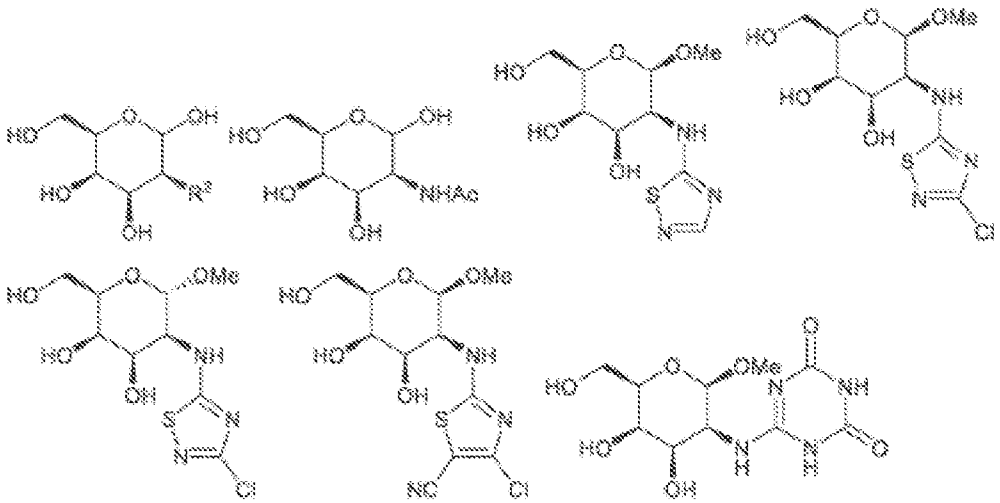

MASP Targeting Ligand
Linker^C
Linker^A
Linker^A
MASP Targeting Ligand
Linker^A
Linker^A
MASP Targeting Ligand
Linker^C
MASP Targeting Ligand
Linker^B
Linker^A
MASP Targeting Ligand
Linker^B

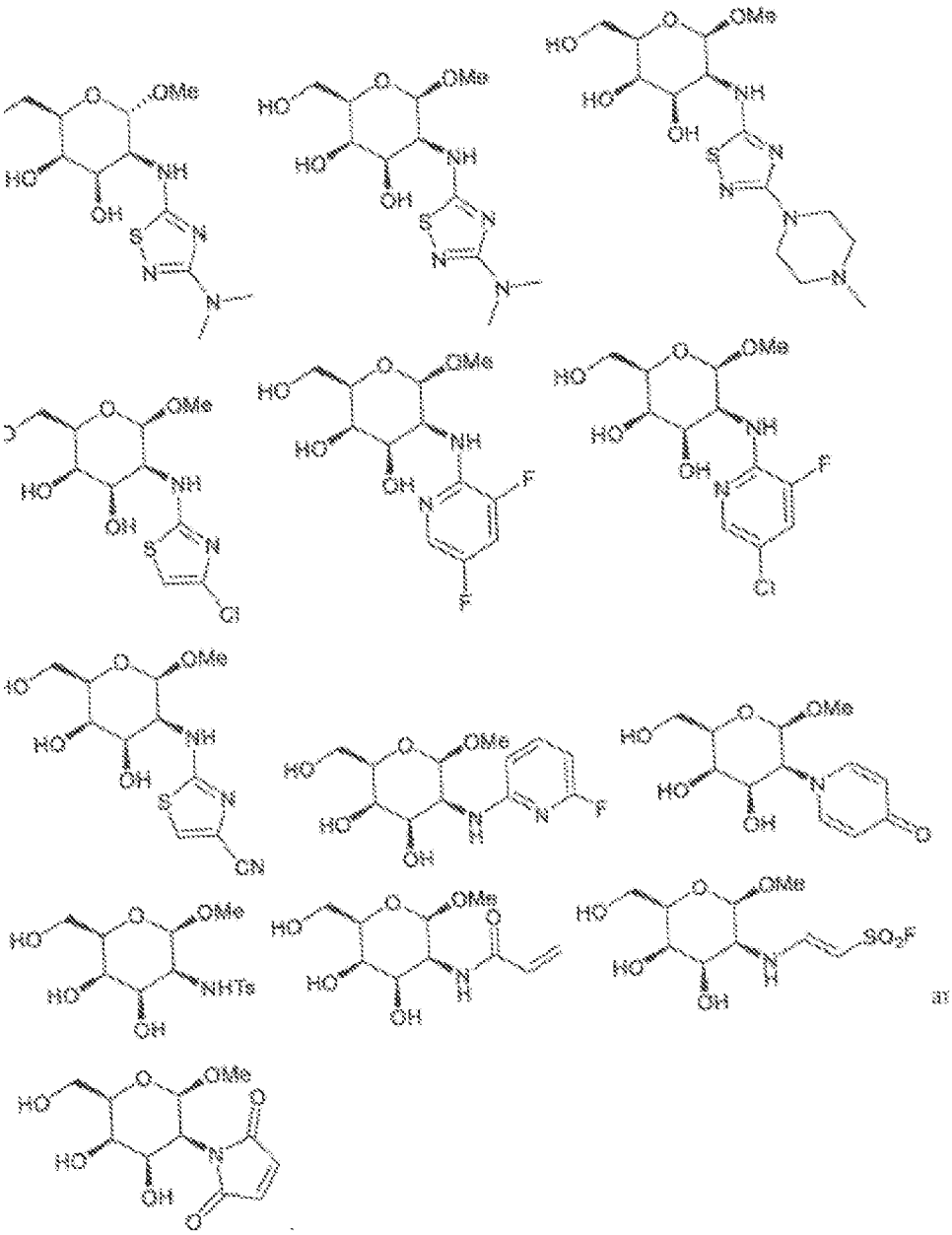

TNF-alpha Targeting Ligand
Linker^C
Linker^A
Linker^A
TNF-alpha Targeting Ligand
Linker^A
Linker^A
TNF-alpha Targeting Ligand
Linker^C
TNF-alpha Targeting Ligand
Linker^B
Linker^A
TNF-alpha Targeting Ligand
Linker^B

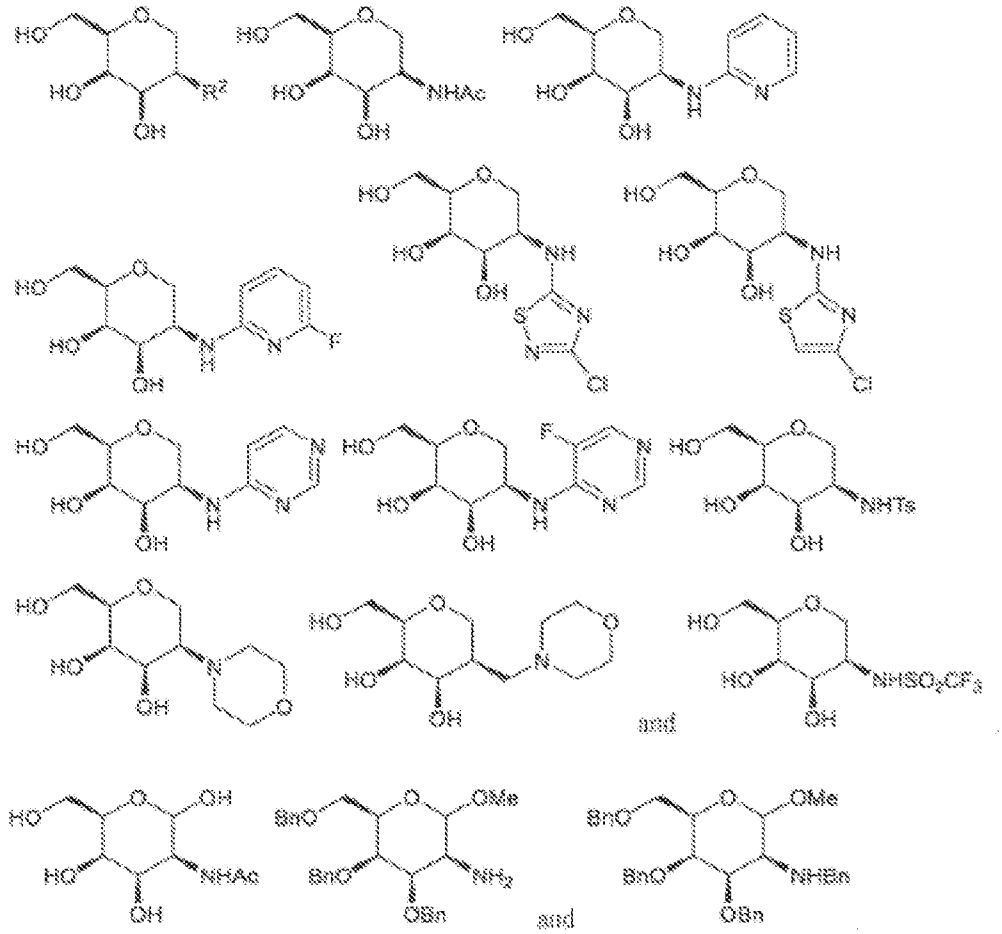

Extracellular Protein Targeting Ligand
IgA Targeting Ligand
IgG Targeting Ligand
IgE Targeting Ligand
Complement Targeting Ligand
Linker
HO
OH
HN
N
O
CF3

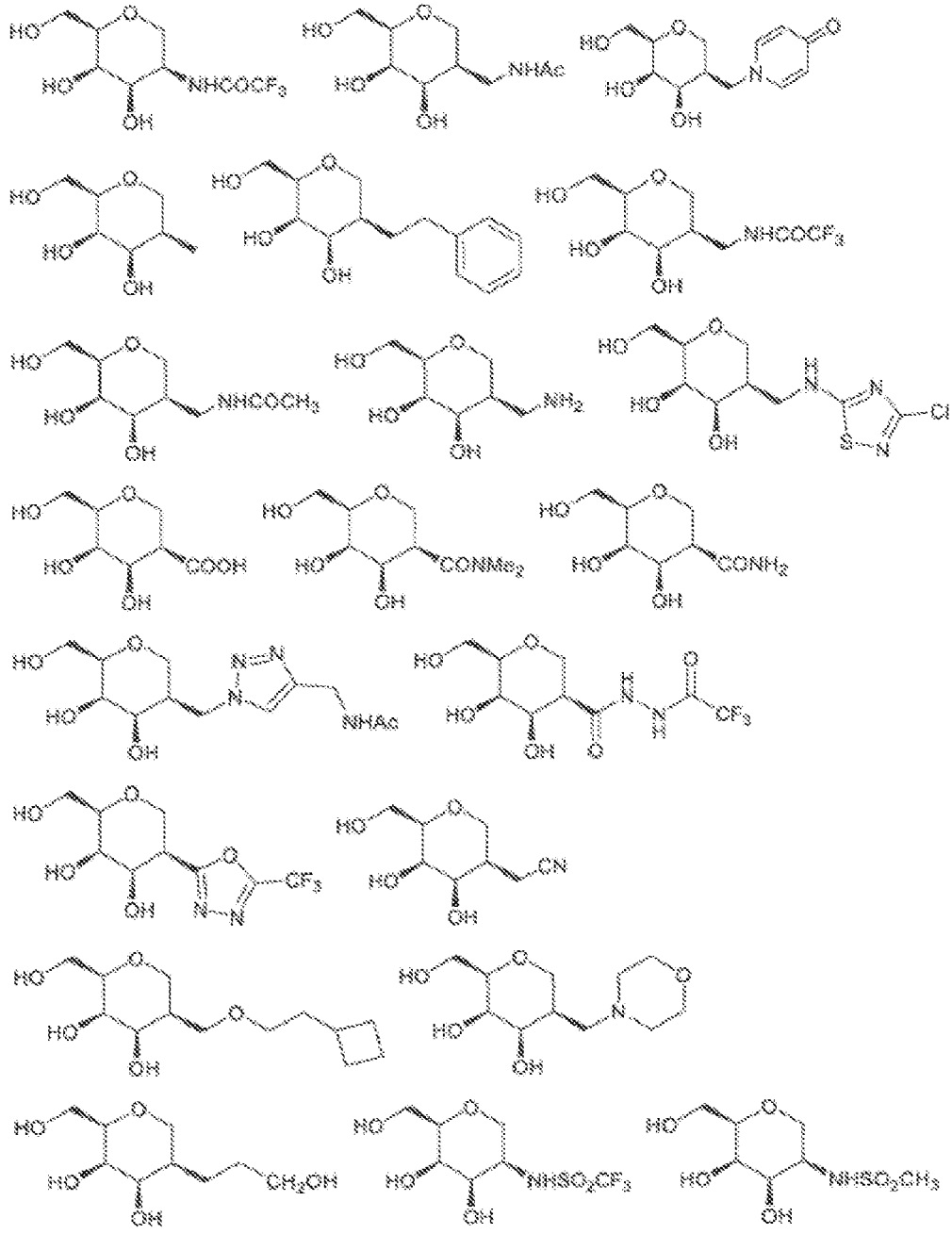


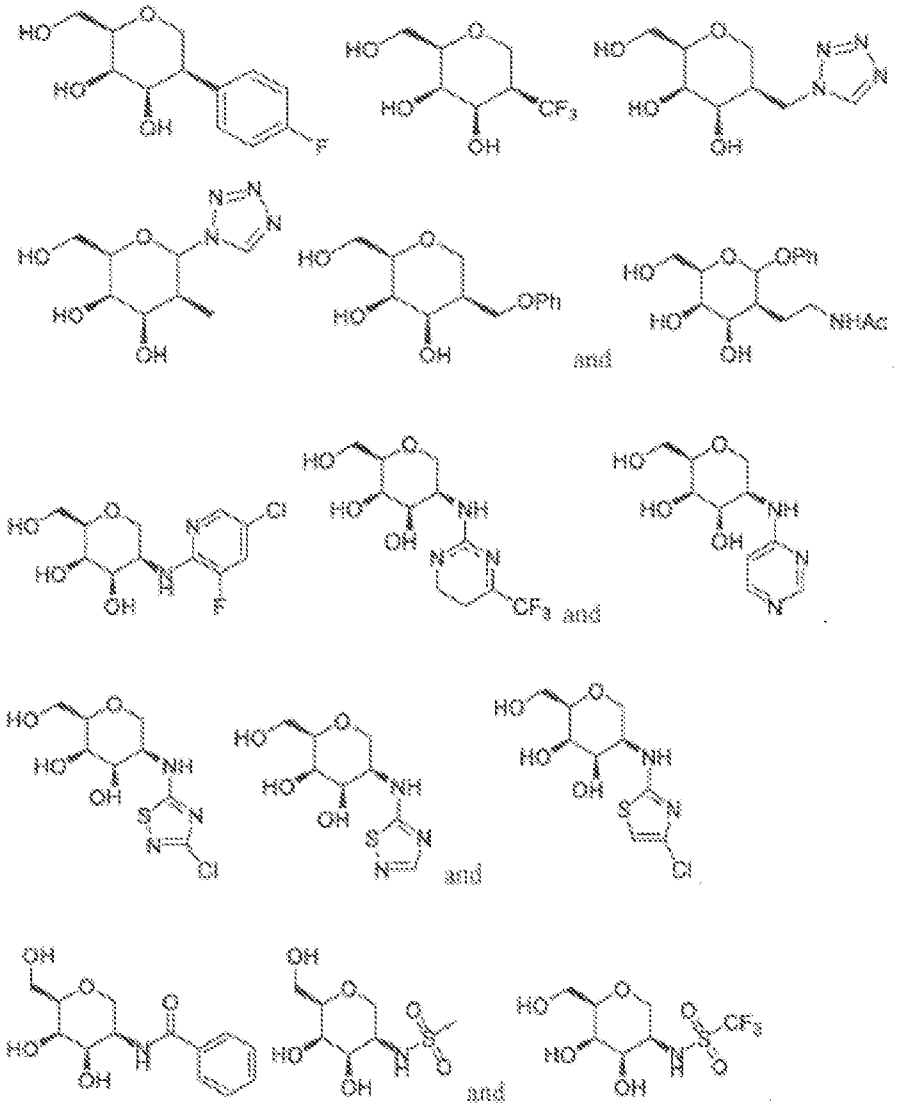
In certain embodiments, an ASGPR ligand useful for incorporation into a compound of Formula II is selected from:

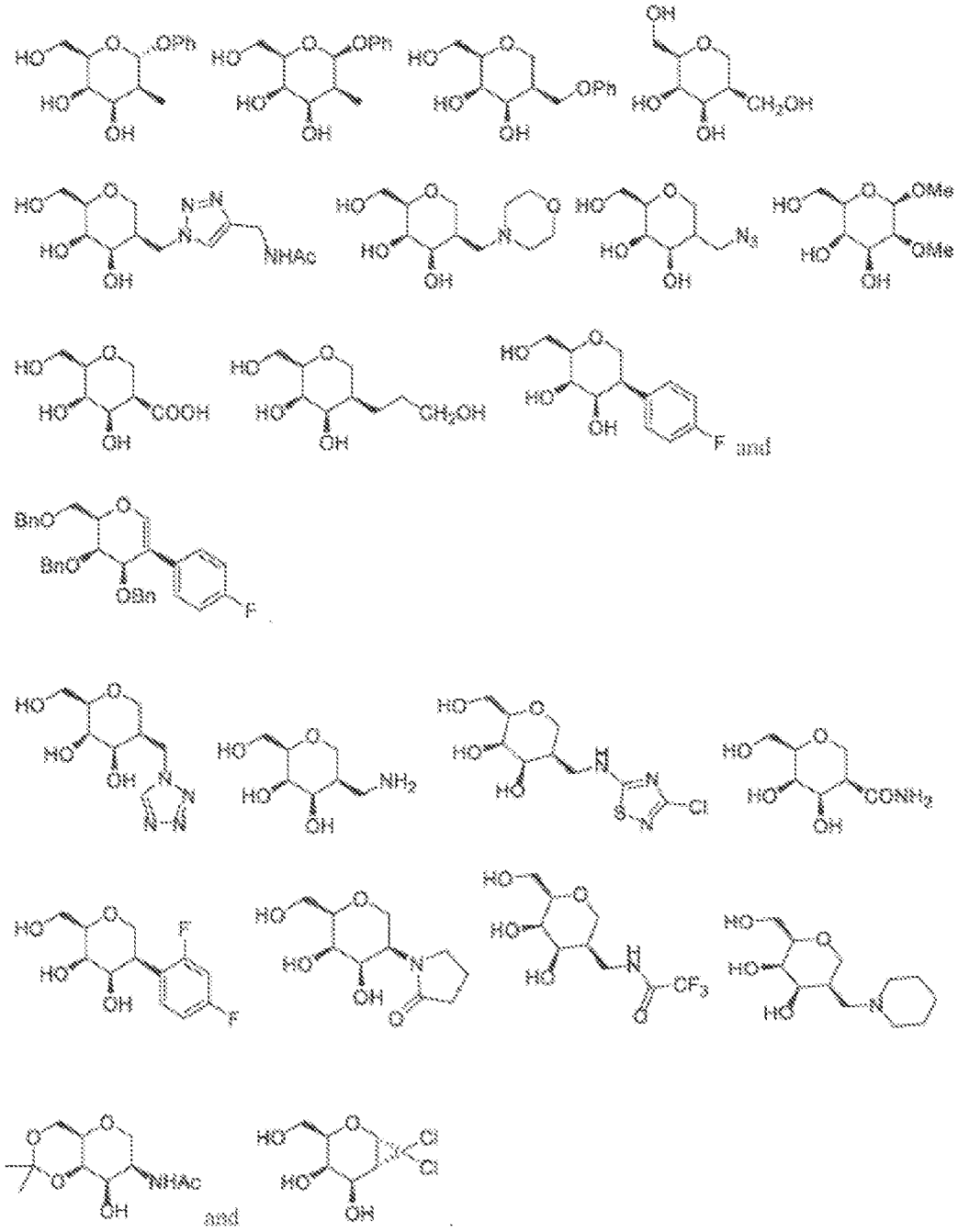


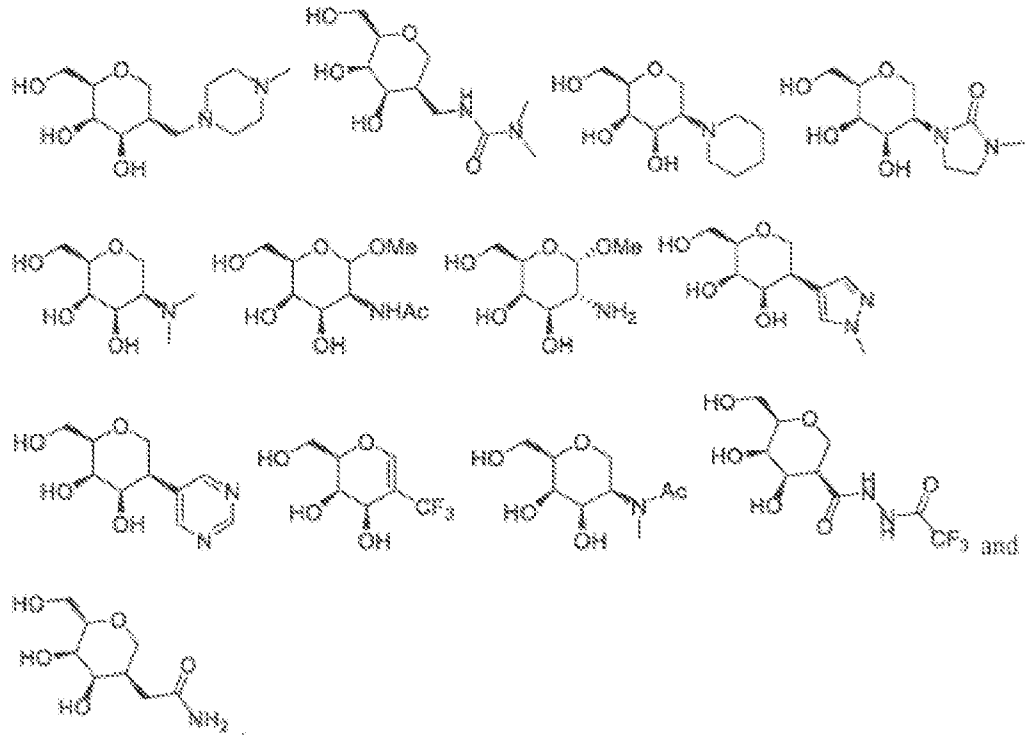




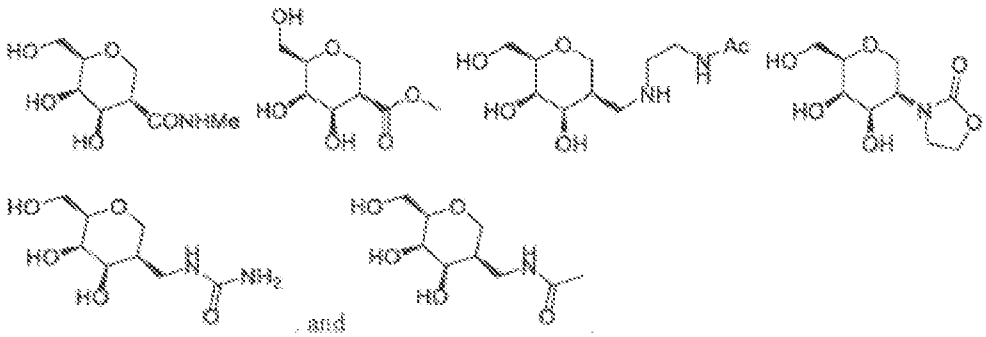




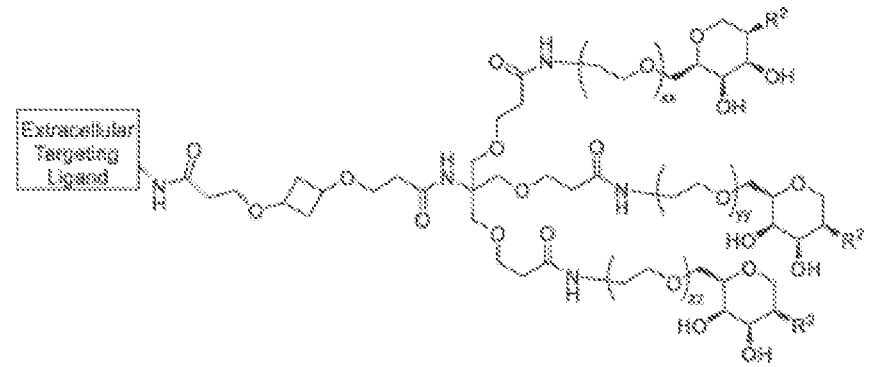


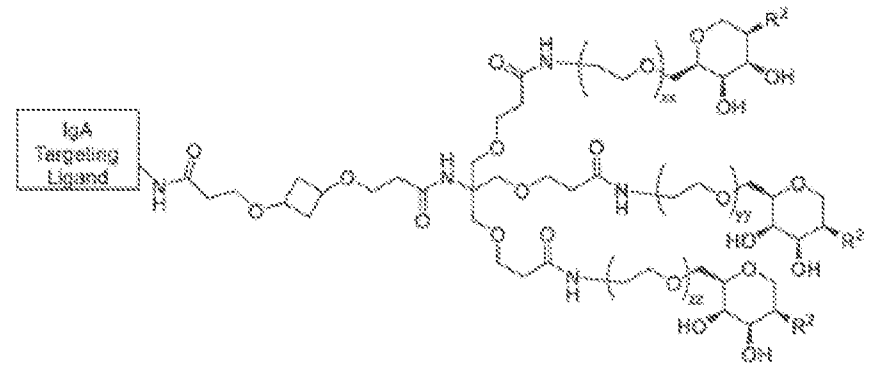


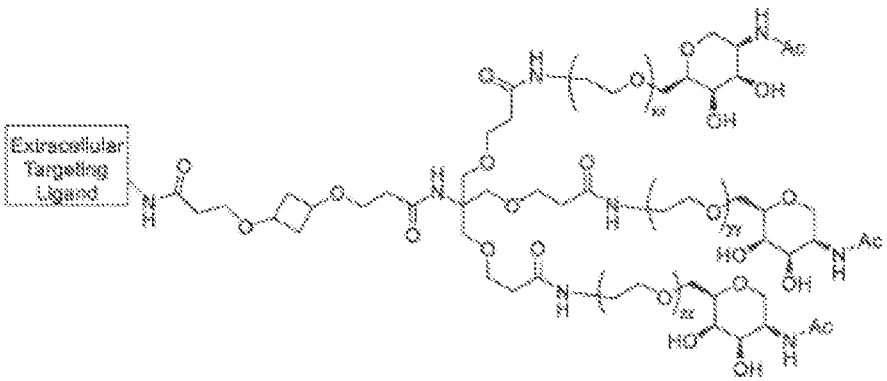
and

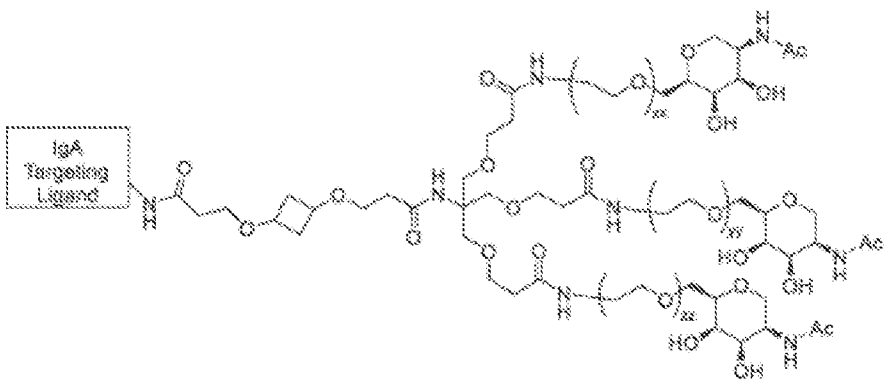


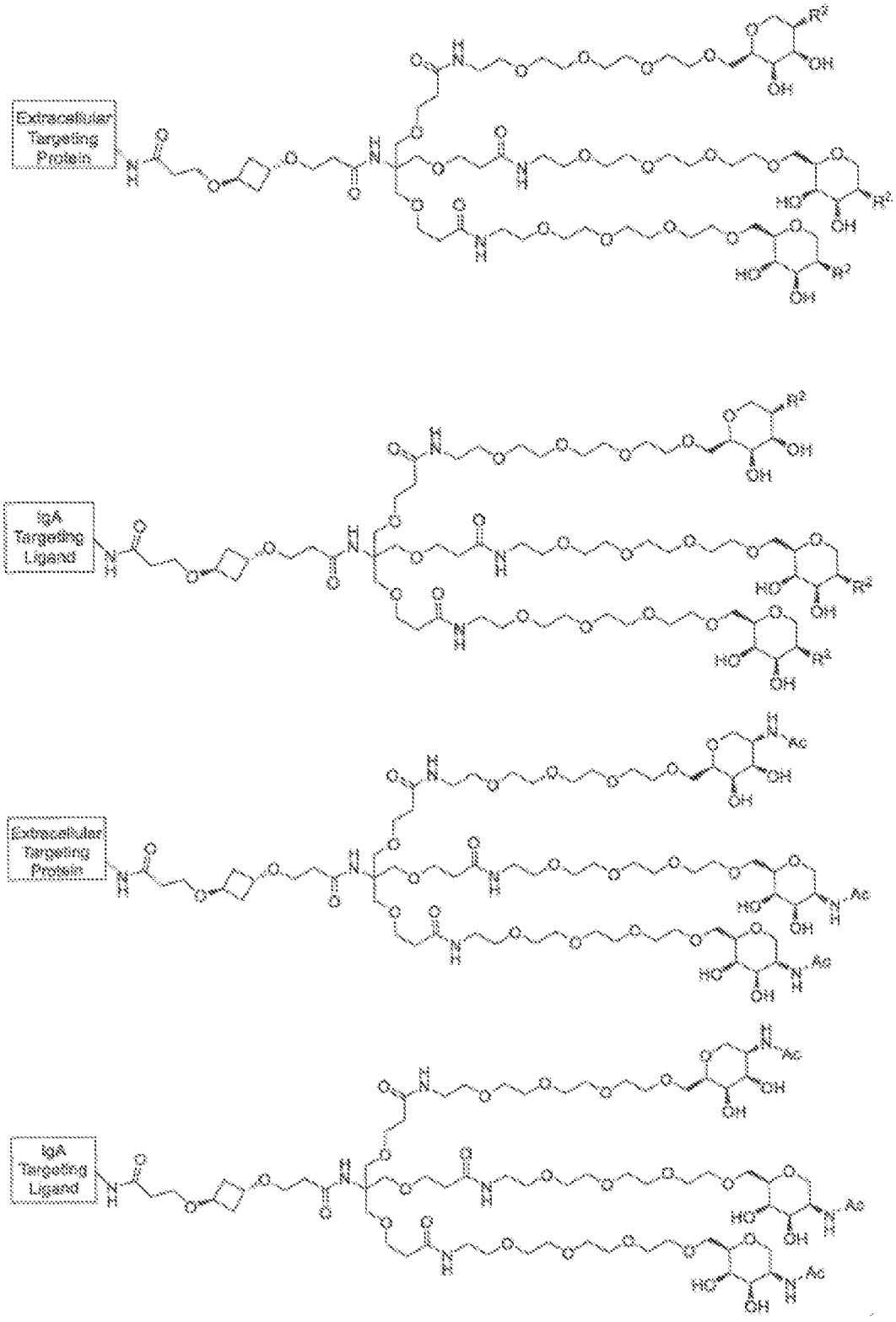
and

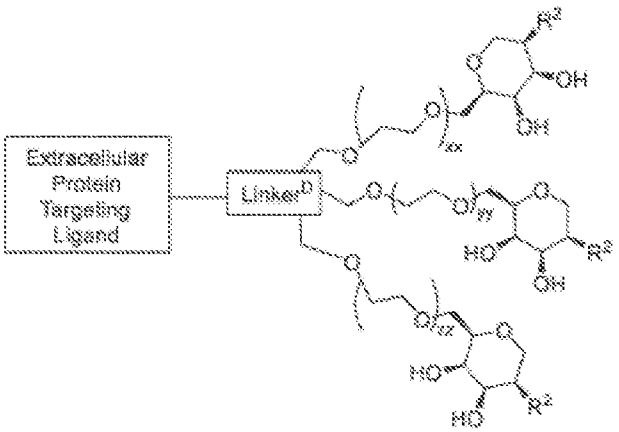

Extracellular Targeting Ligand

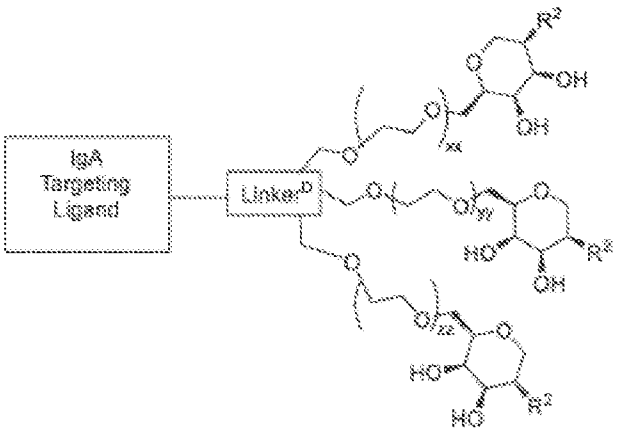

IgA Targeting Ligand

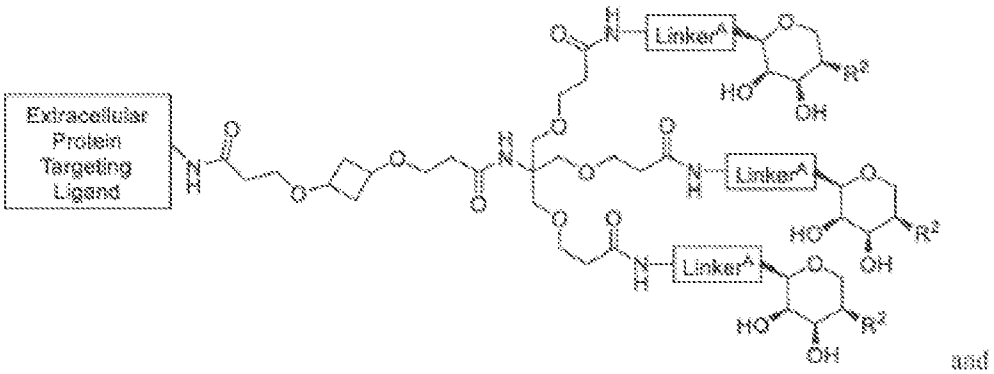

Extracellular Targeting Ligand


IgA Targeting Ligand

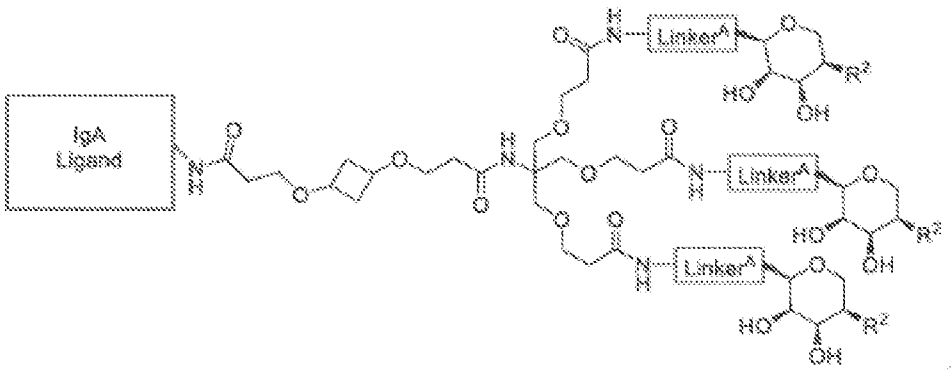

Extracellular Targeting Protein
IgA Targeting Ligand
Extracellular Targeting Protein
IgA Targeting Ligand

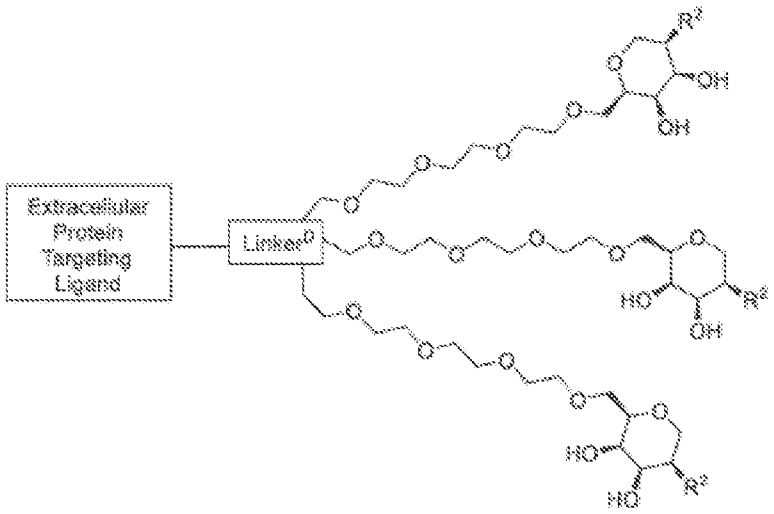

Extracellular Protein Targeting Ligand
Linker^D

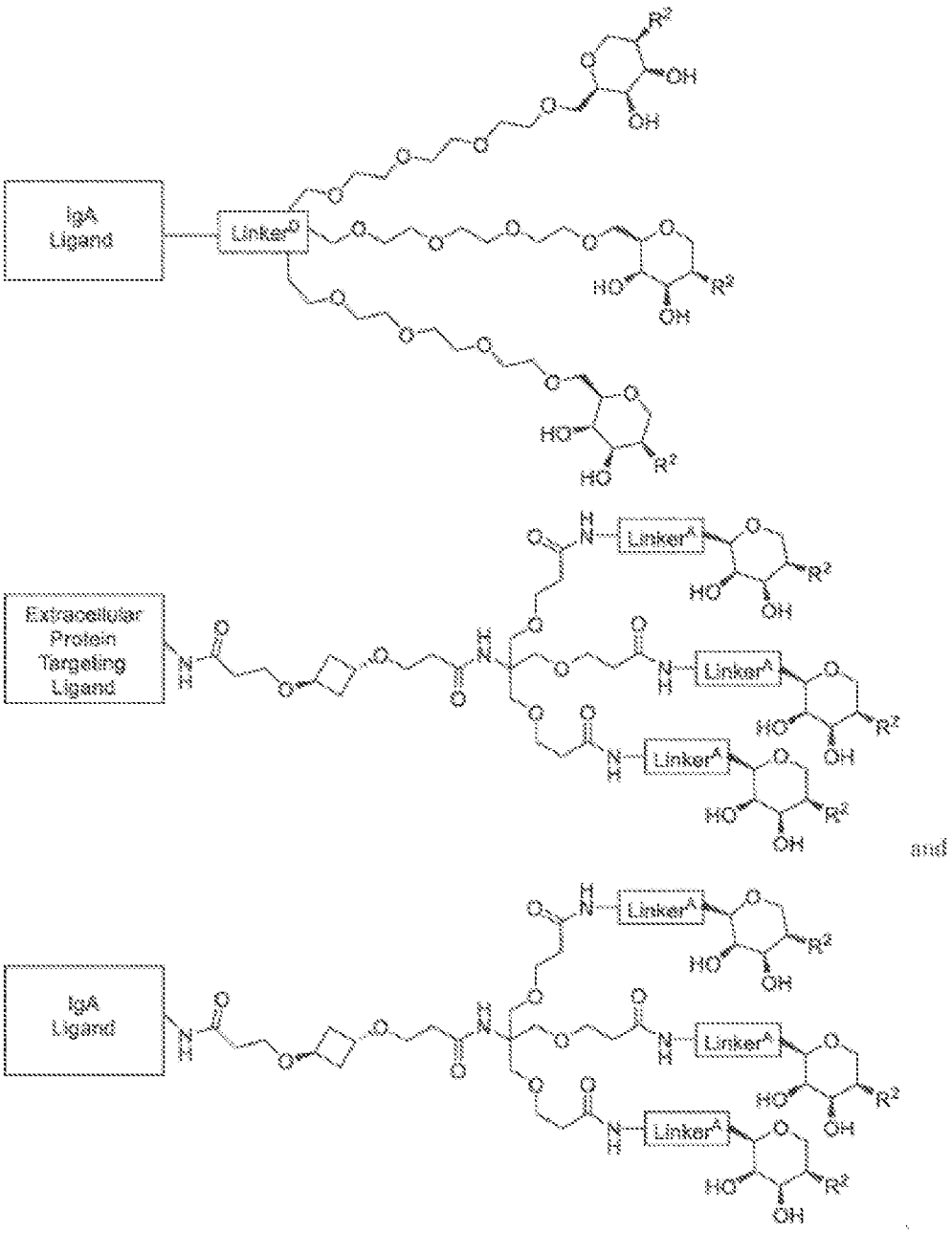

IgA Targeting Ligand
Linker^D


Extracellular Protein Targeting Ligand
Linker^A

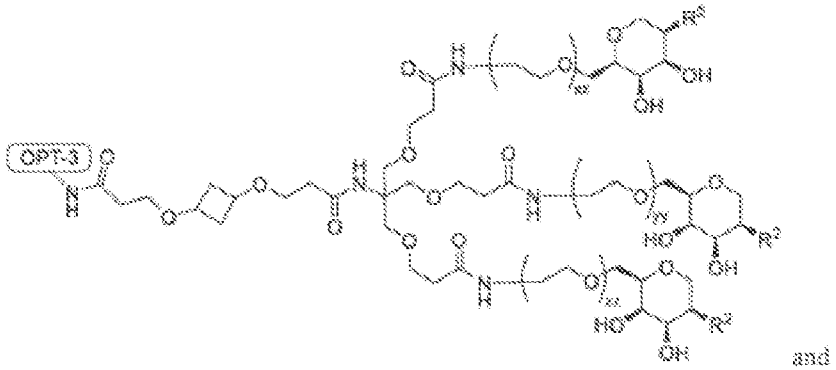
and


IgA Ligand
Linker^A


Extracellular Protein Targeting Ligand
Linker
OH
HO
R²


IgA Ligand
Linker
Extracellular Protein Targeting Ligand
Linker
IgA Ligand
Linker

and



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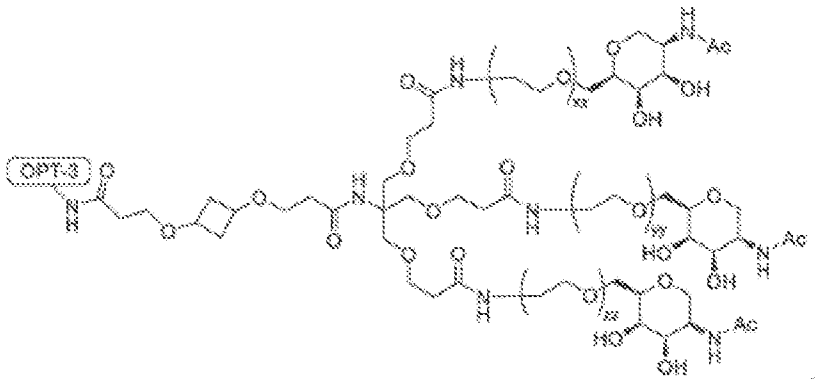

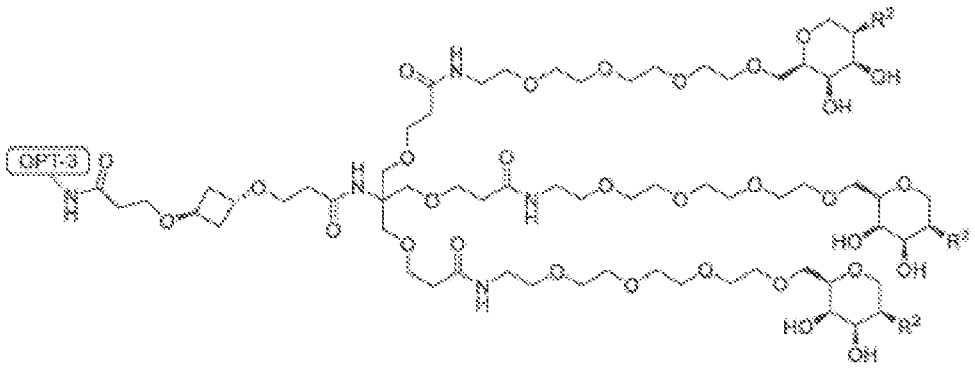

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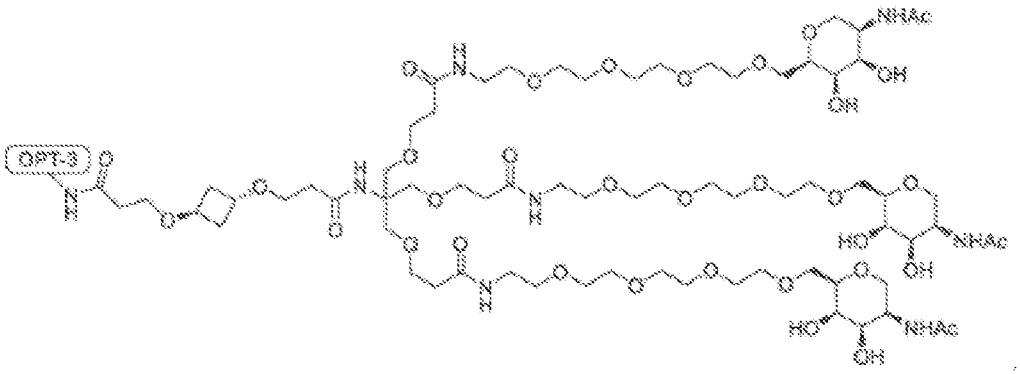
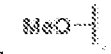
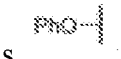
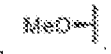


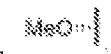
C. The ASGPR Ligand/Binding Moiety in Compounds of Formula II

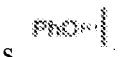
In certain embodiments, in the compound of Formula II, R^1 is hydrogen.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

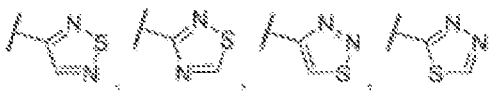
In certain embodiments, in the compound of Formula II, R^1 is -O-alkenyl, -O-alkynyl, C_0-C_6alkyl-OR^6, C_0-C_6alkyl-SR^6, C_0-C_6alkyl-NR^6R^7, C_0-C_6alkyl-$C(O)R^3$, C_0-C_6alkyl-$S(O)R^3$, C_0-C_6alkyl-$C(S)R^3$, C_0-C_6alkyl-$S(O)_2R^3$, C_0-C_6alkyl-$N(R^8)$-$C(O)R^3$, C_0-C_6alkyl-$N(R^8)$-$S(O)R^3$,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

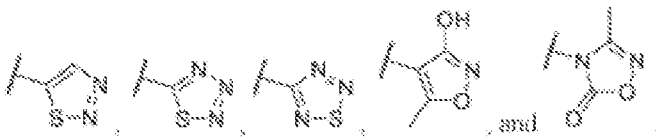
In certain embodiments, in the compound of Formula II, R^2 is aryl optionally substituted with 1, 2, 3, or 4 substituents.

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

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

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





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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

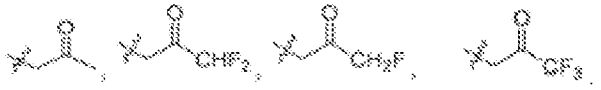
In certain embodiments, in the compound of Formula II, R^2 is -O-heteroaryl optionally substituted with 1, 2, 3, or 4 substituents.

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

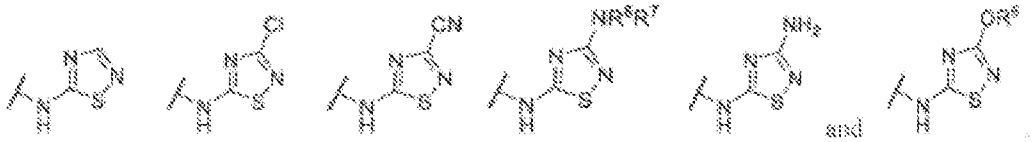
In certain embodiments, in the compound of Formula II, R^2 is -O-alkynyl optionally

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

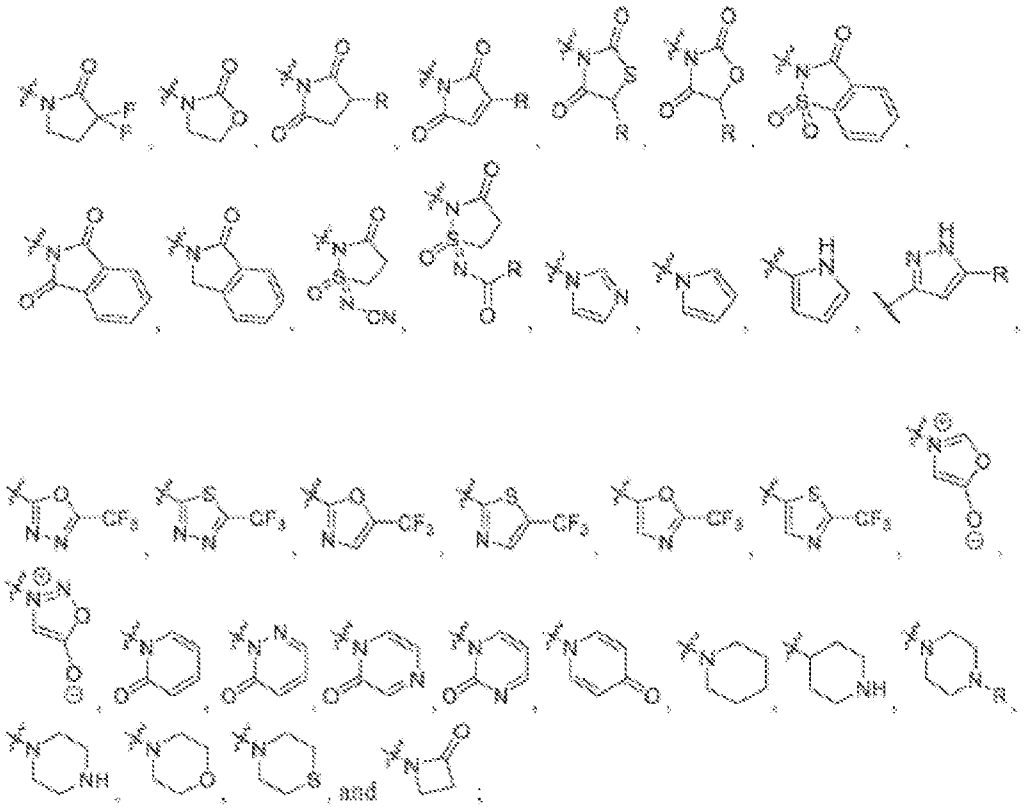
In certain embodiments, in the compound of Formula II, R^2 is selected from and



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

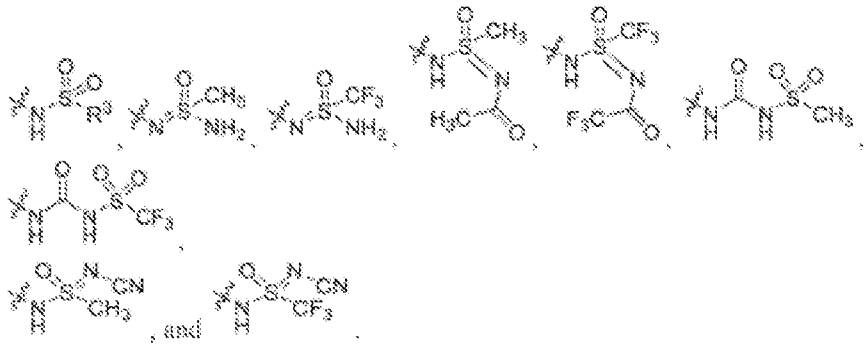


In certain embodiments, in the compound of Formula II, R^2 is selected from

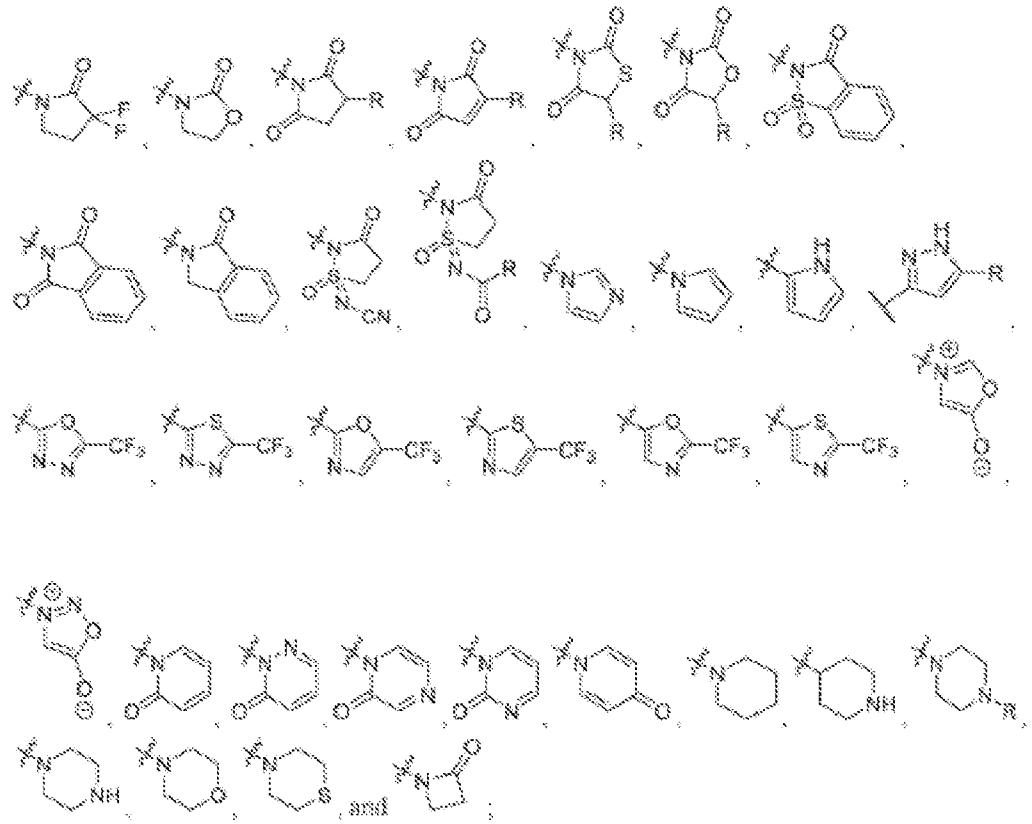


wherein R is an optional substituent as defined herein.

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

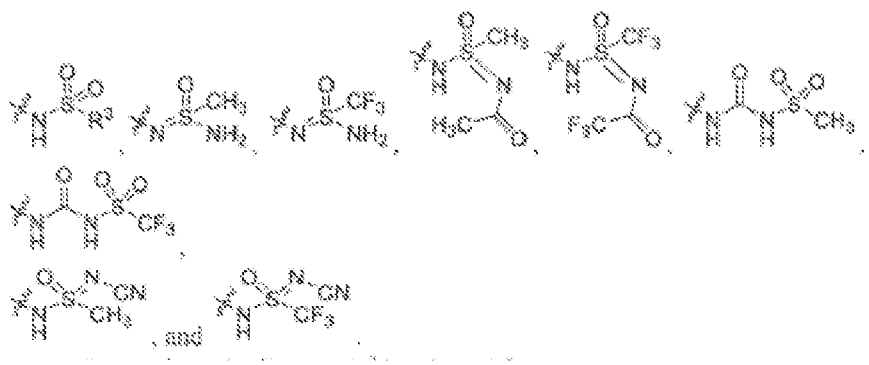


In certain embodiments, in the compound of Formula II, R^{2A} is selected from

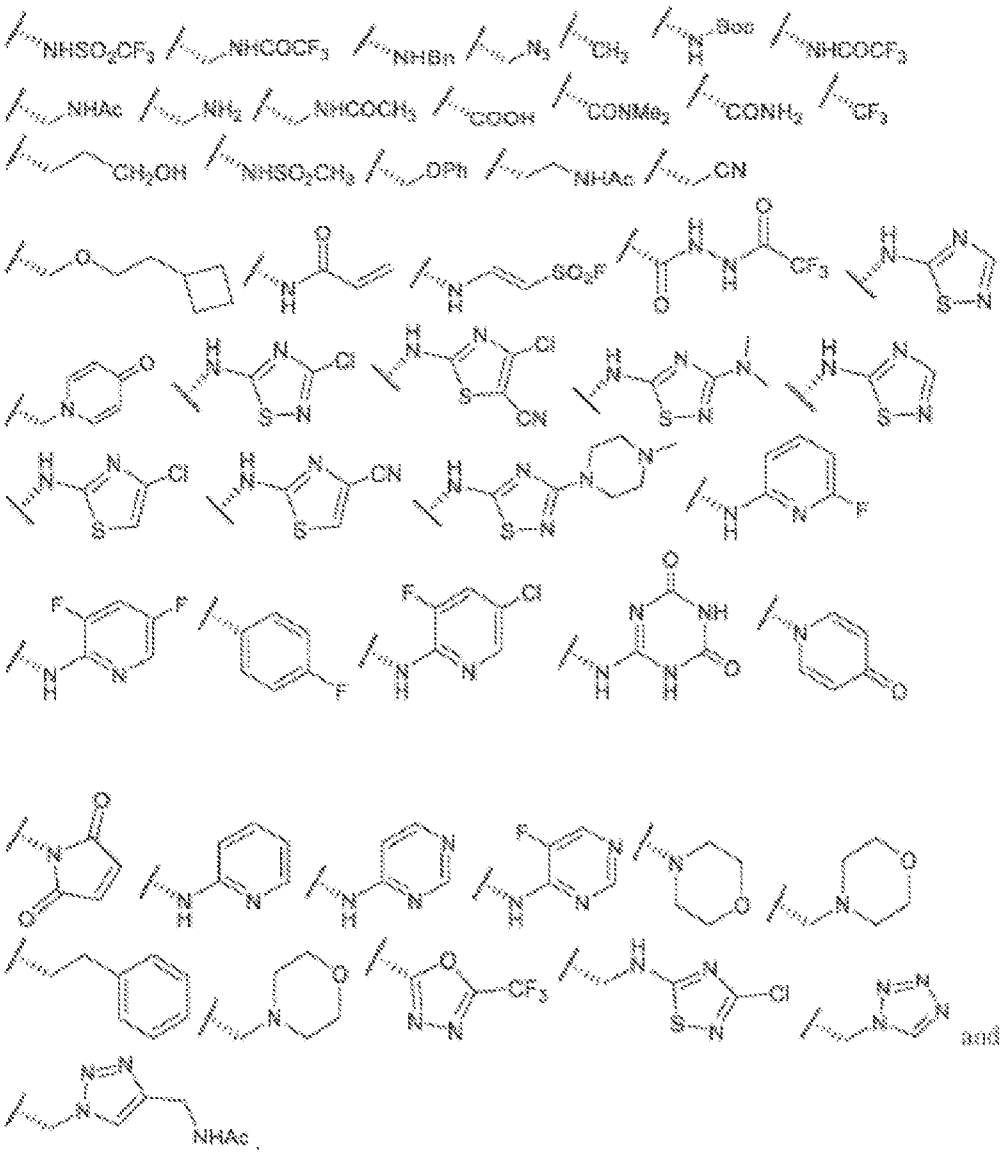


wherein R is an optional substituent as defined herein.

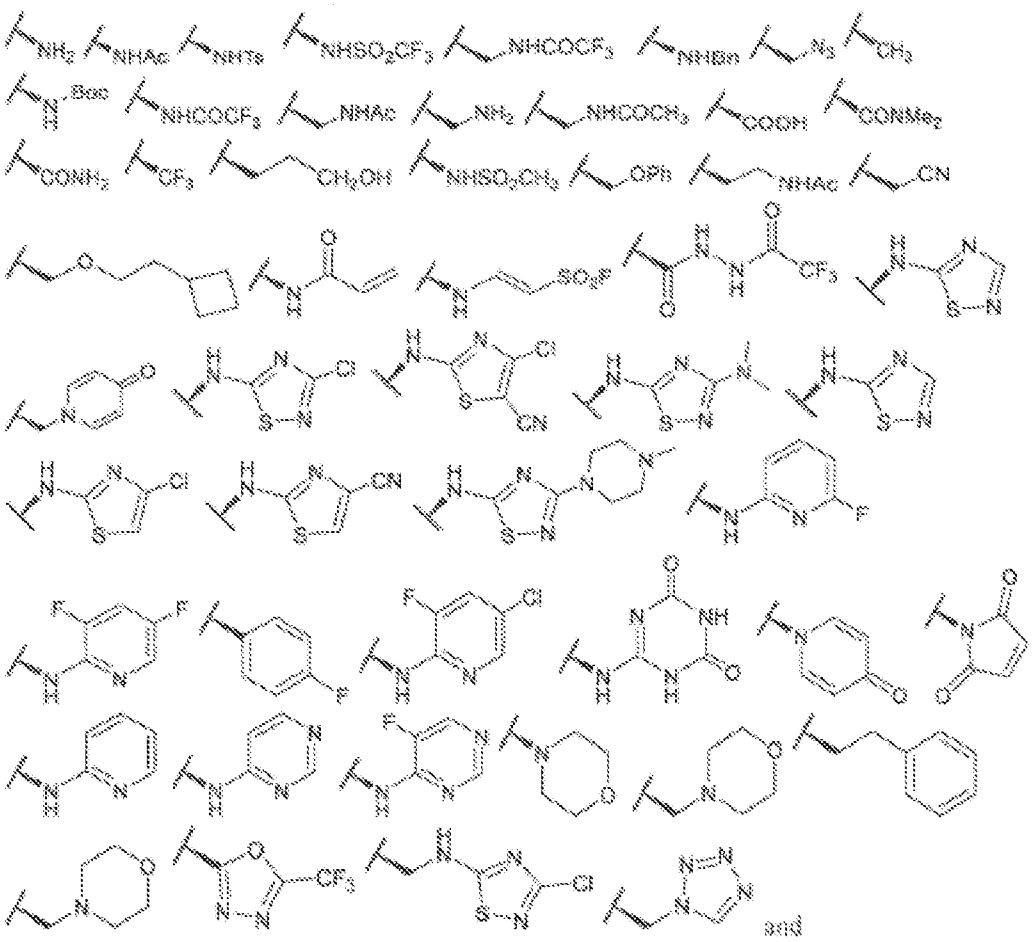
In certain embodiments, in the compound of Formula II, R^{2A} is selected from



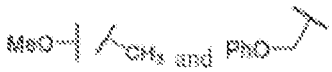
In certain embodiments, in the compound of Formula II, R^2 is selected from



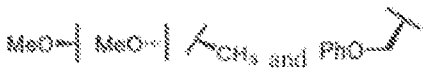
In certain embodiments, in the compound of Formula II, R^2 is selected from



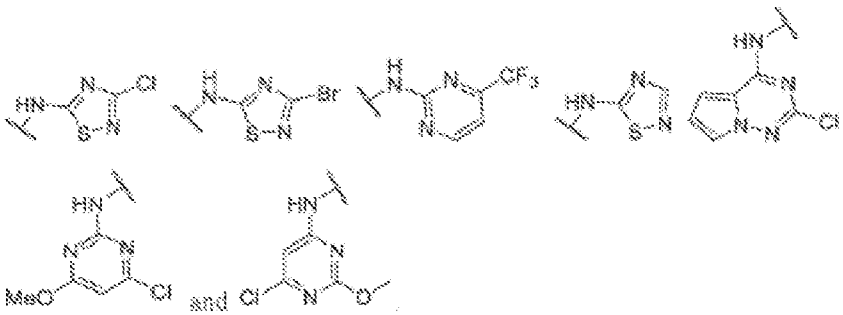
In certain embodiments, in the compound of Formula II, R^2 is selected from



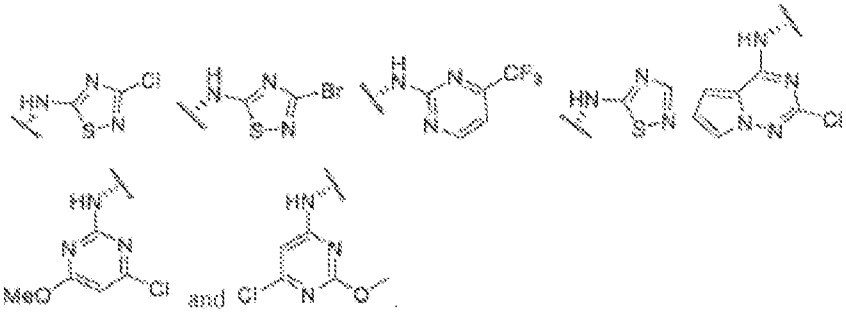
In certain embodiments, in the compound of Formula II, R^2 is selected from



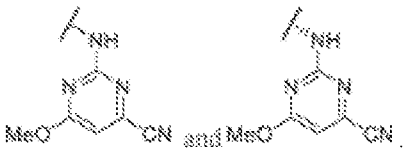
In certain embodiments, in the compound of Formula II, R^2 is selected from



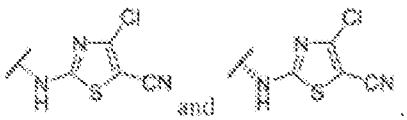
In certain embodiments, in the compound of Formula II, R^2 is selected from



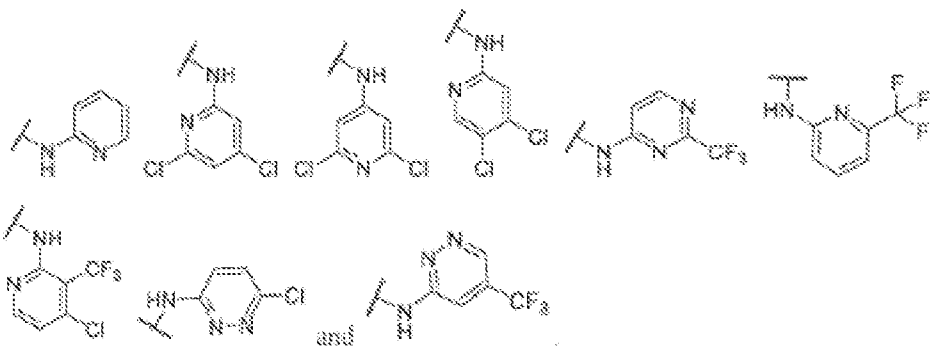
In certain embodiments, in the compound of Formula II, R^2 is selected from



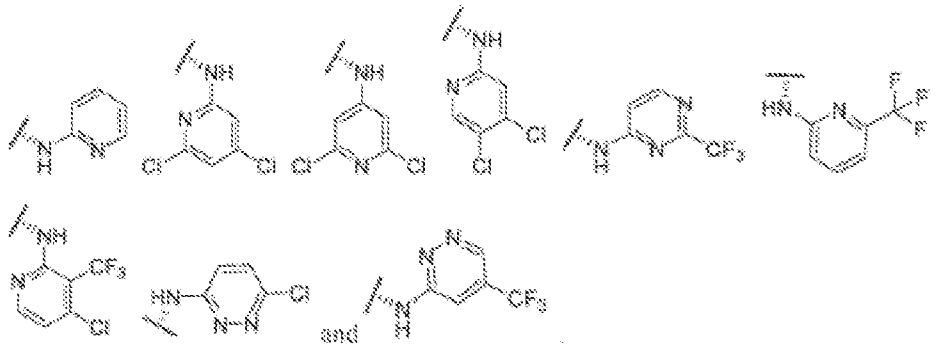
In certain embodiments, in the compound of Formula II, R^2 is selected from



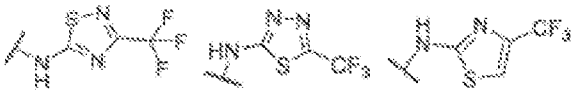
In certain embodiments, in the compound of Formula II, R^2 is selected from



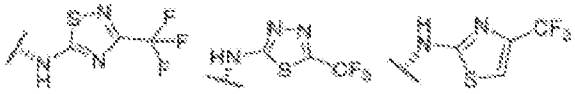
In certain embodiments, in the compound of Formula II, R^2 is selected from



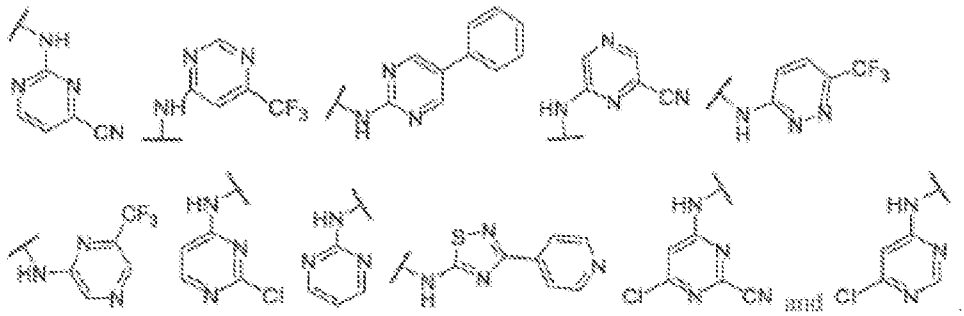
In certain embodiments, in the compound of Formula II, R^2 is selected from



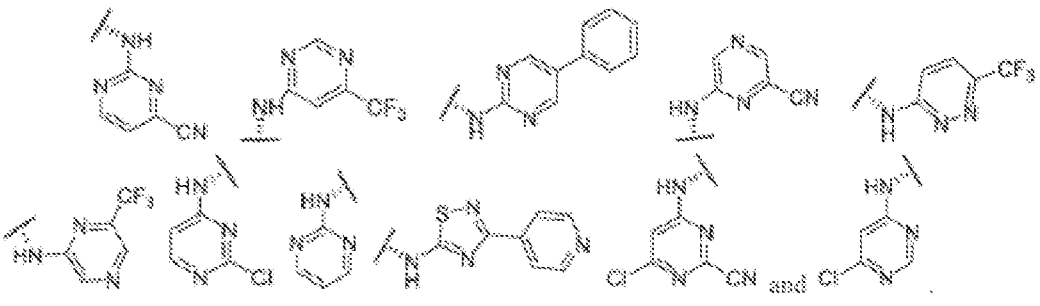
In certain embodiments, in the compound of Formula II, R^2 is selected from



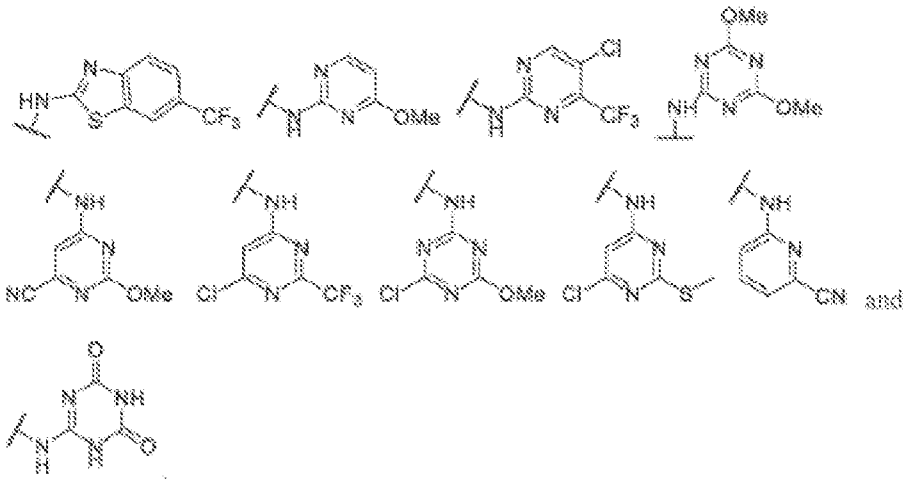
In certain embodiments, in the compound of Formula II, R^2 is selected from



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



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



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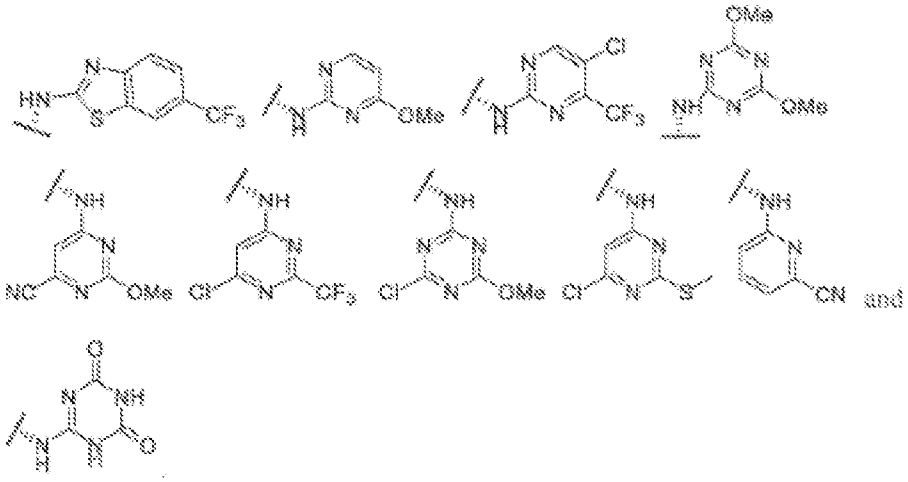
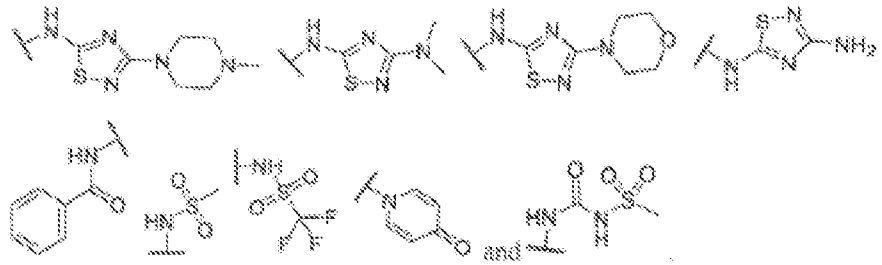
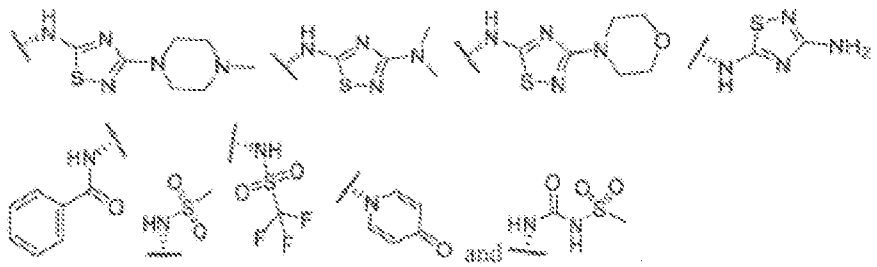


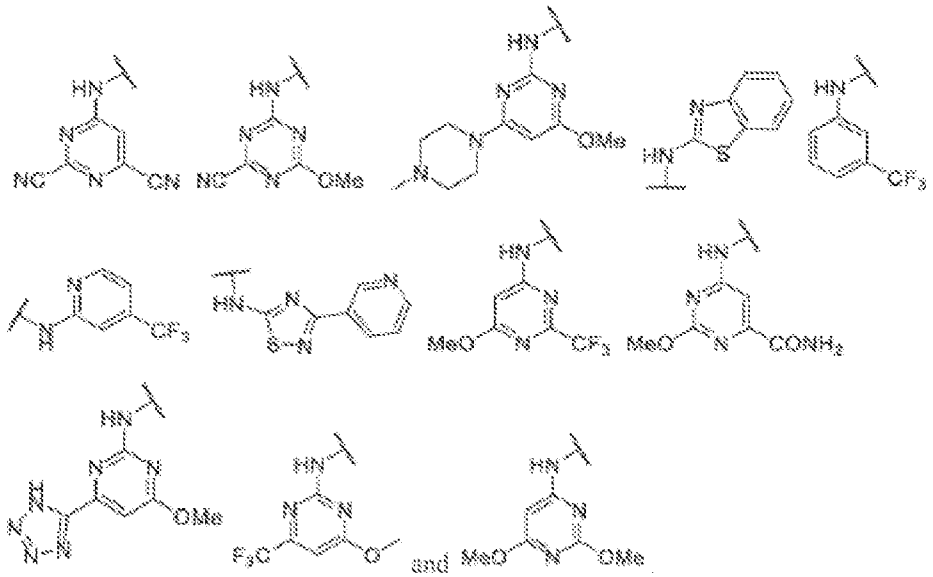
In certain embodiments, in the compound of Formula II, R^2 is selected from



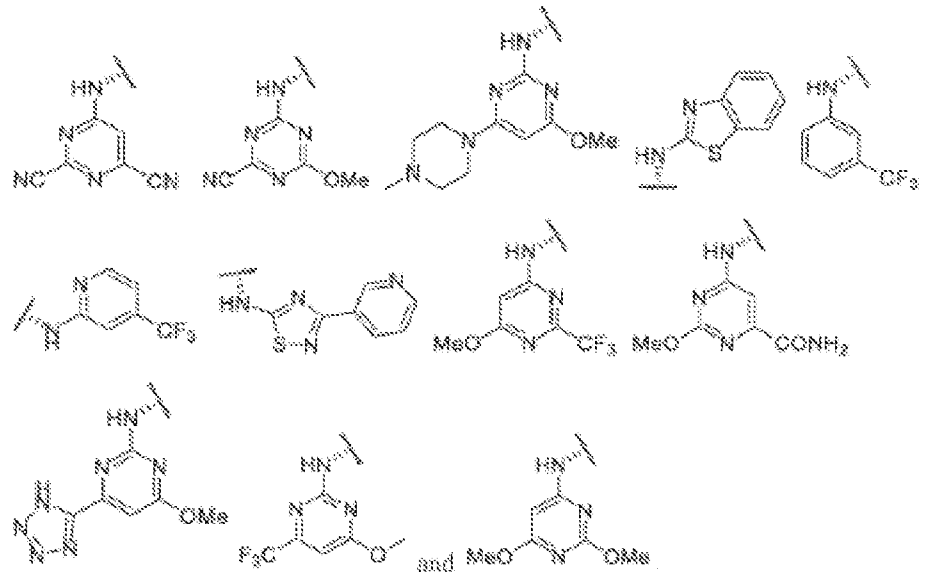
In certain embodiments, in the compound of Formula II, R^2 is selected from



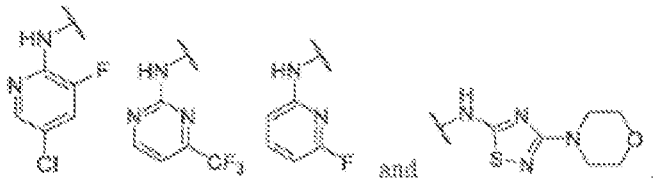
In certain embodiments, in the compound of Formula II, R^2 is selected from



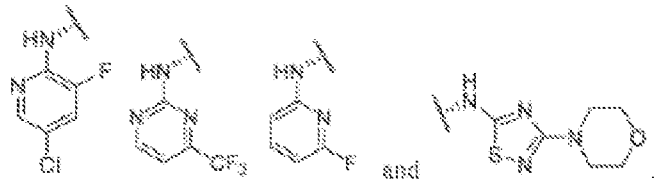
In certain embodiments, in the compound of Formula II, R^2 is selected from



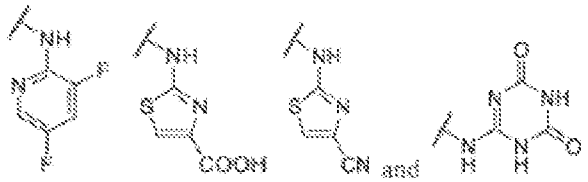
In certain embodiments, in the compound of Formula II, R^2 is selected from



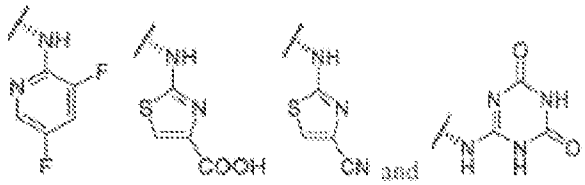
In certain embodiments, in the compound of Formula II, R^2 is selected from



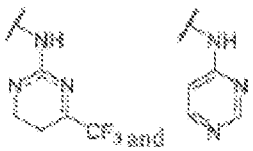
In certain embodiments, in the compound of Formula II, R^2 is selected from



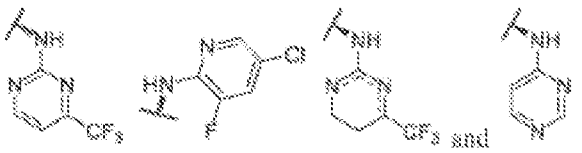
In certain embodiments, in the compound of Formula II, R^2 is selected from



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



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



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

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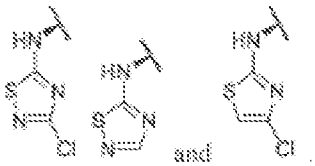
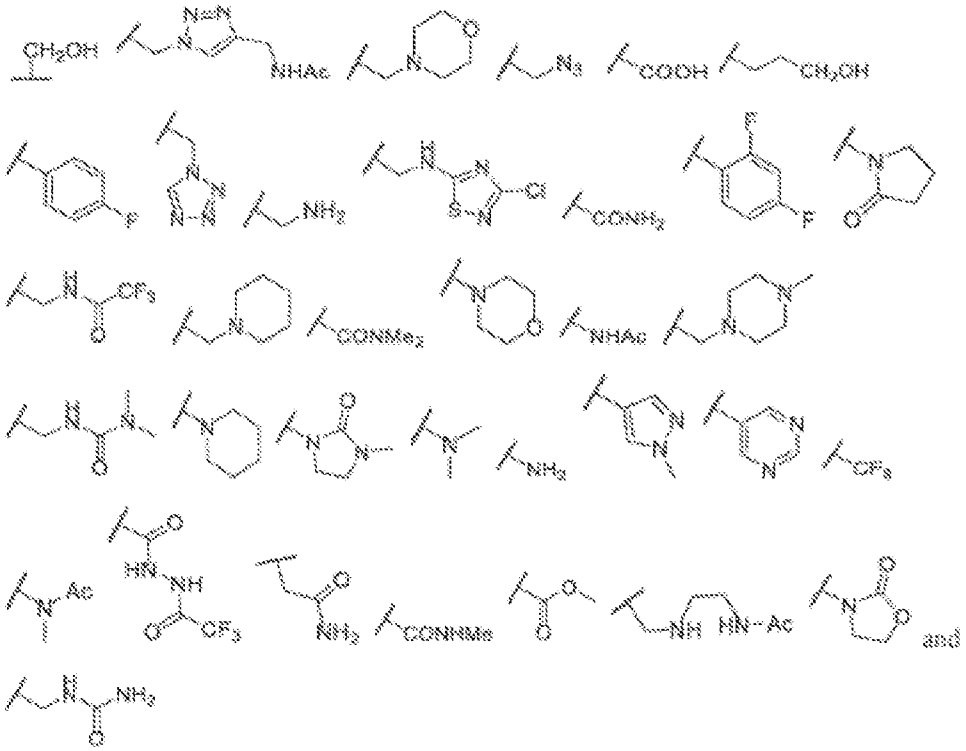
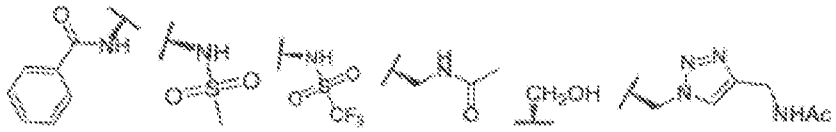
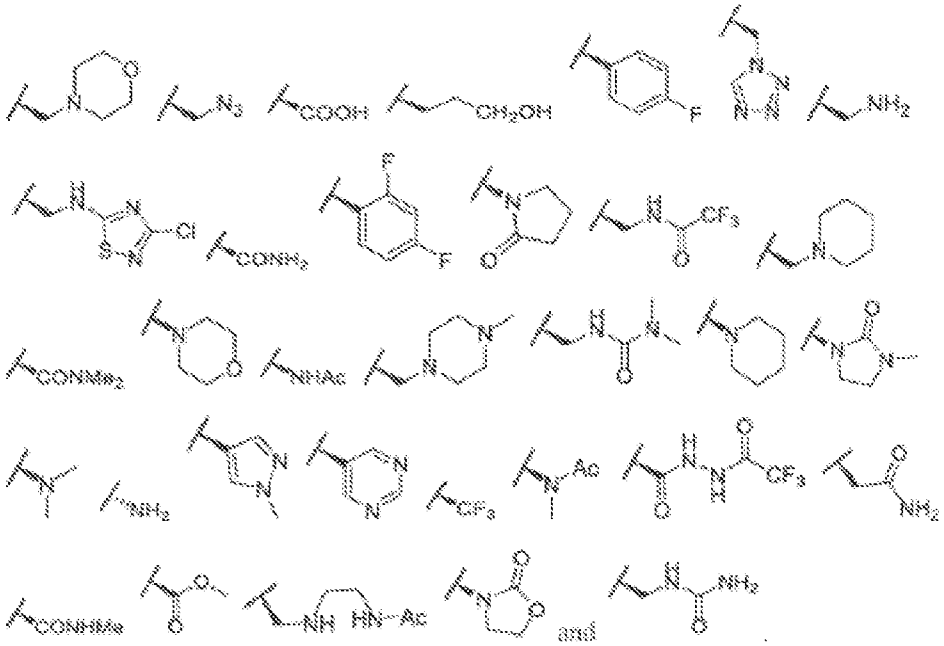


In certain embodiments, in the compound of Formula II, R^2 is selected from

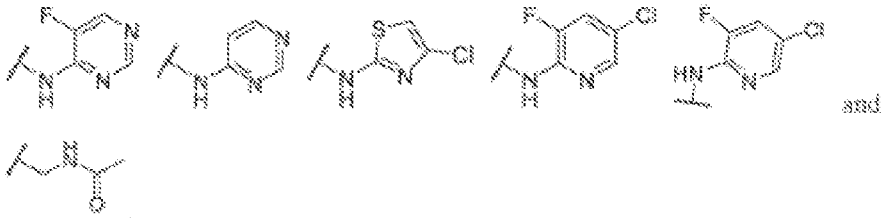


In certain embodiments, in the compound of Formula II, R^2 or R^{2A} is selected from

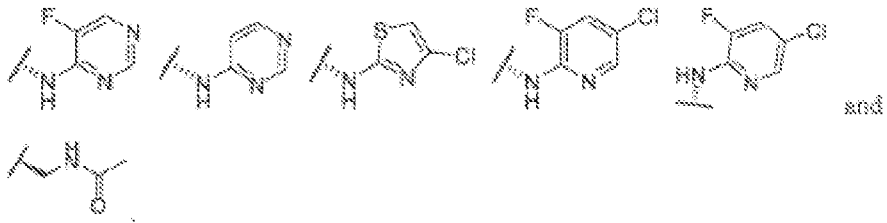




In certain embodiments, in the compound of Formula II, R^2 is selected from



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



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

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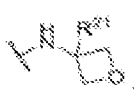
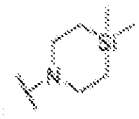
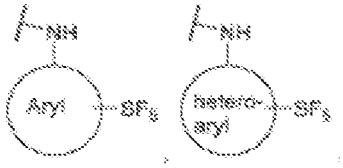


In certain embodiments, in the compound of Formula II, R^2 is selected from

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

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

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

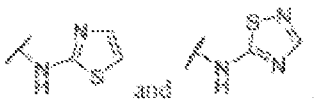
In certain embodiments, in the compound of Formula II, R^2 is substituted with a sulfoxime, for example, and without limitation,

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

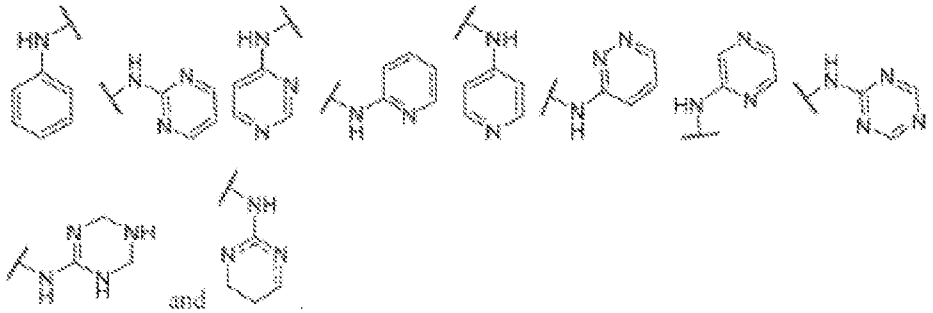
In certain embodiments, in the compound of Formula II, R^{10} is selected from spirocyclic heterocycle.

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

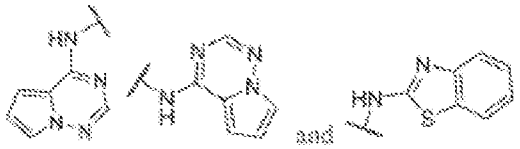
In certain embodiments, in the compound of Formula II, R^{10} is selected from



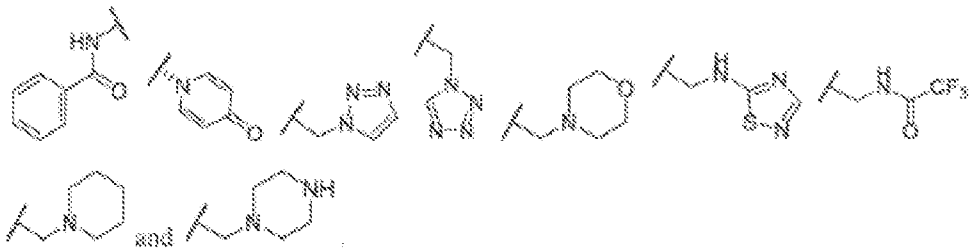
In certain embodiments, in the compound of Formula II, R^{10} is selected from



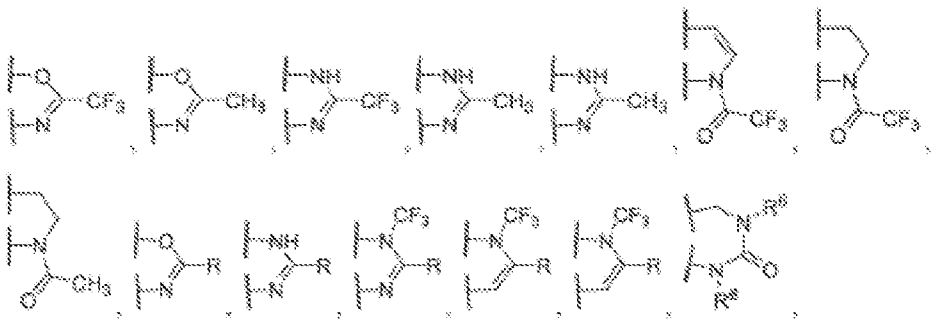
In certain embodiments, in the compound of Formula II, R^{10} is selected from

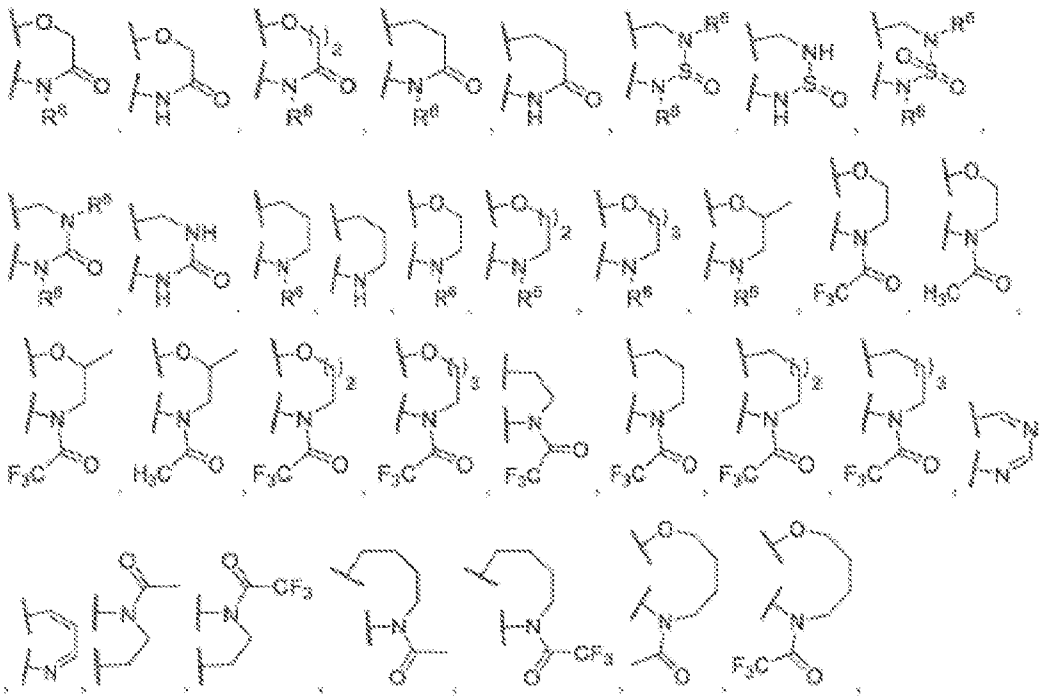


In certain embodiments, in the compound of Formula II, R^{10} is selected from

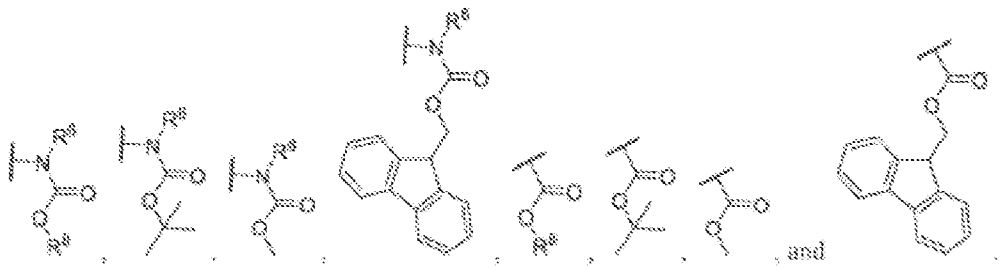


In certain embodiments, in the compound of Formula II, Cycle is selected from

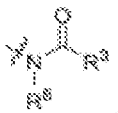


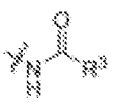


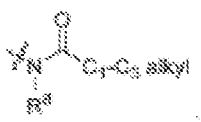
In certain embodiments, in the compound of Formula II, R^{30} is selected from:

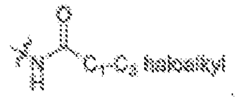


In certain embodiments, in the compound of Formula II, R^{200} is



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

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

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

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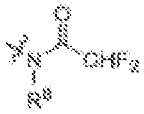
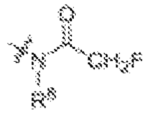
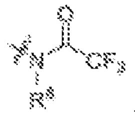
In certain embodiments, in the compound of Formula II, R^{200} is 

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

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

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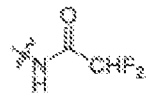
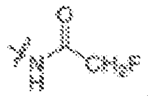
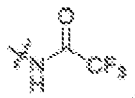
In certain embodiments, in the compound of Formula II, R^{200} is 

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

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

Linkers

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


;

wherein:

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

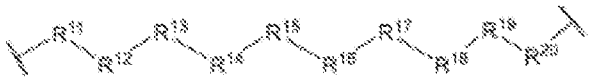
divalent residue of a natural or unnatural amino acid, alkenyl, alkynyl, haloalkyl, alkoxy, and, heterocycle, heteroaryl, $-CH_2CH_2-[O-(CH_2)_2]_n-O-$, $CH_2CH_2-[O-(CH_2)_2]_n-NR^6-$, $-CH_2CH_2-[O-(CH_2)_2]_n-$, $-[-(CH_2)_2-O-]_n-$, $-[O-(CH_2)_2]_n-$,$-[O-CH(CH_3)C(O)]_n-$, $-[C(O)-CH(CH_3)-O]_n-$,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

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

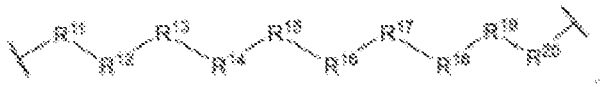
R^{21} is independently at each occurrence selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, F, Cl, Br, I, hydroxyl, alkoxy, azide, amino, cyano, $-NR^6R^7$, $-NR^8SO_2R^3$, $-NR^8S(O)R^3$, haloalkyl, heteroalkyl, and, heteroaryl, and heterocycle;

and the remaining variables are as defined herein.

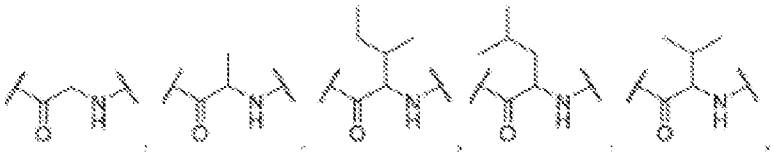
In certain embodiments, in the compound of Formula II, $Linker^A$ is bond and $Linker^B$ is

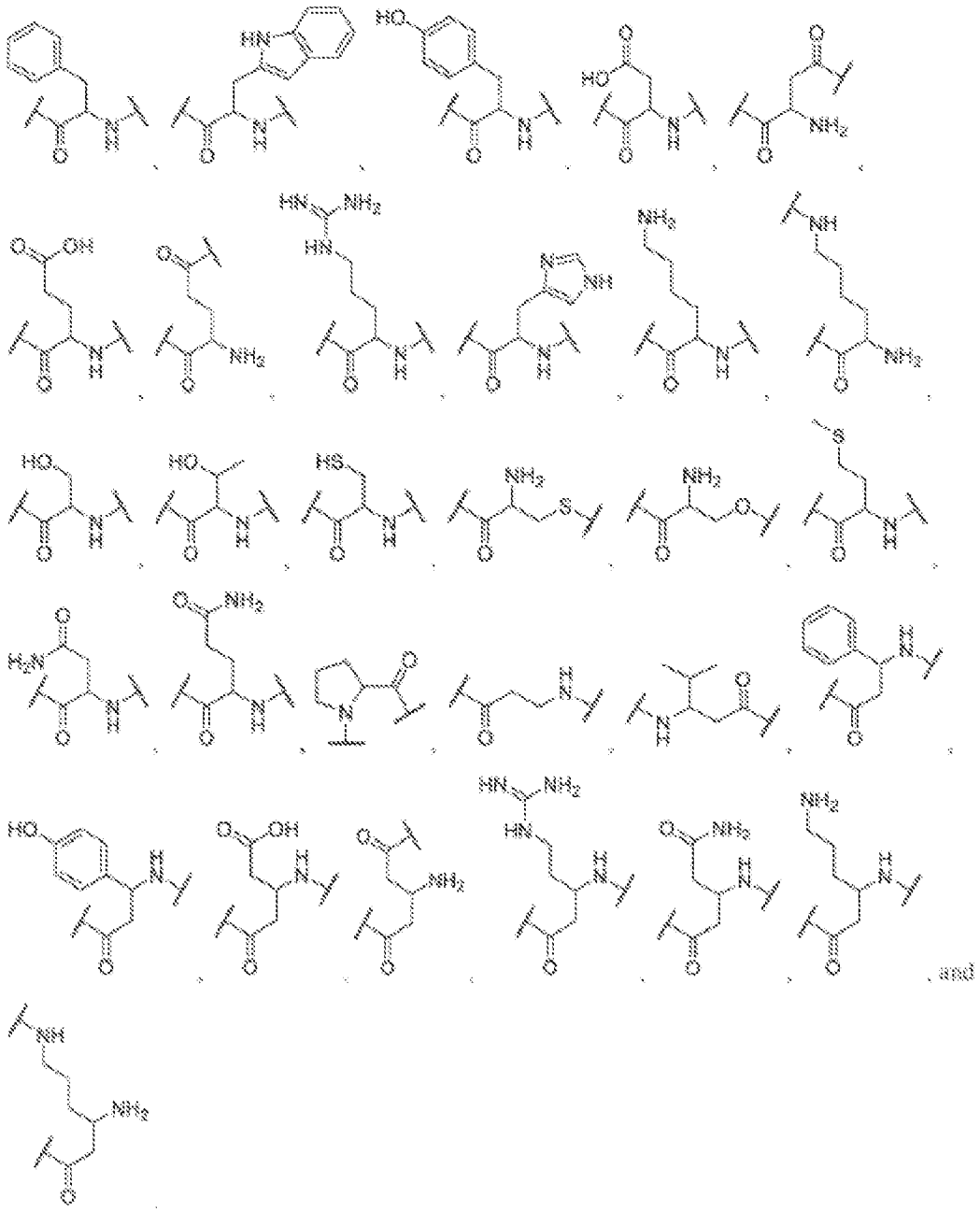


In certain embodiments, in the compound of Formula II, $Linker^B$ is bond and $Linker^A$ is



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



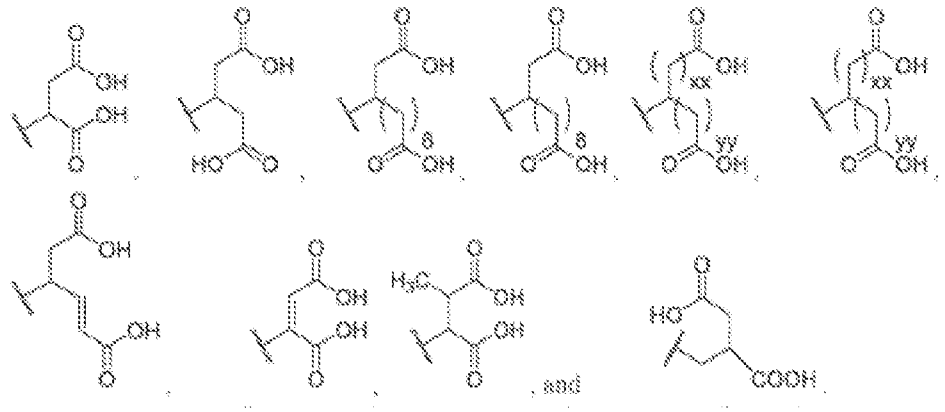


,

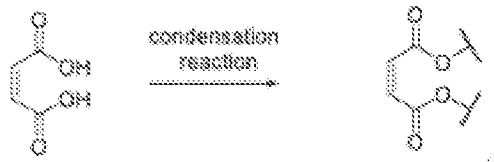
wherein the amino acid can be oriented in either direction and wherein the amino acid can be in the L- or D-form or a mixture thereof.

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

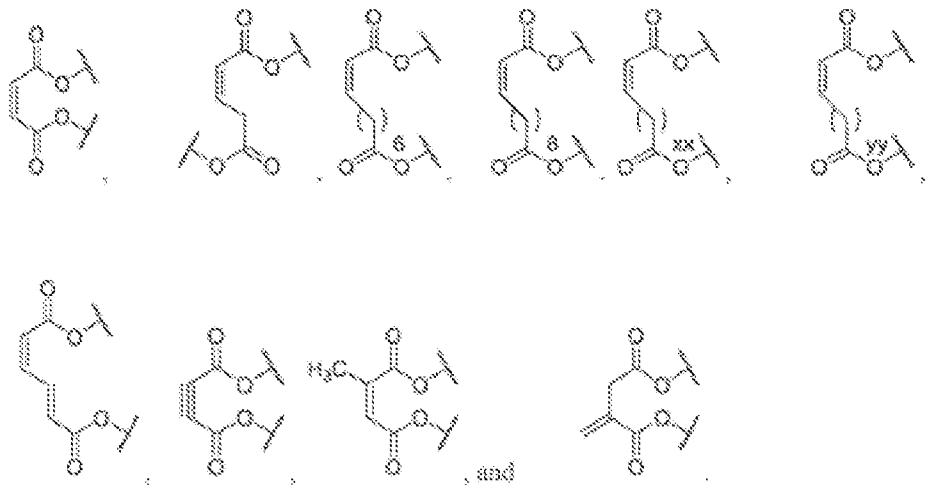
Non-limiting embodiments of a divalent residue of a dicarboxylic acid generated from a nucleophilic addition reaction include:



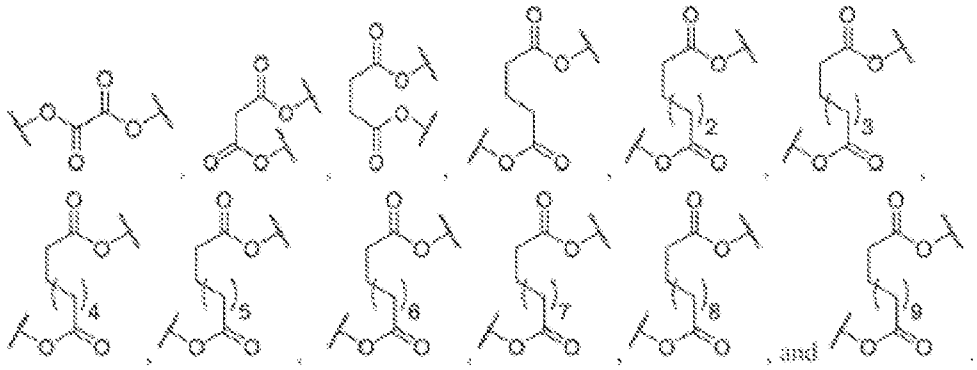
In certain embodiments, in the compound of Formula II, a divalent residue of a dicarboxylic acid is generated from a condensation reaction:



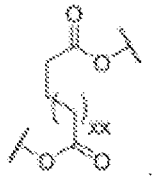
Non-limiting embodiments of a divalent residue of a dicarboxylic acid generated from a condensation include:



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

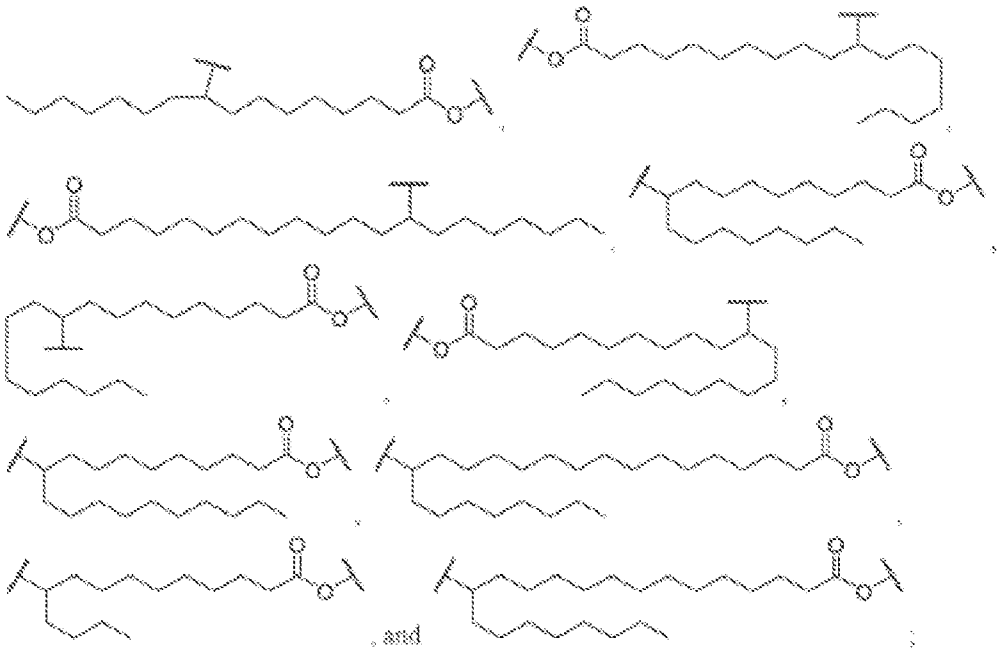


Non-limiting embodiments of a divalent residue of a saturated dicarboxylic acid include:



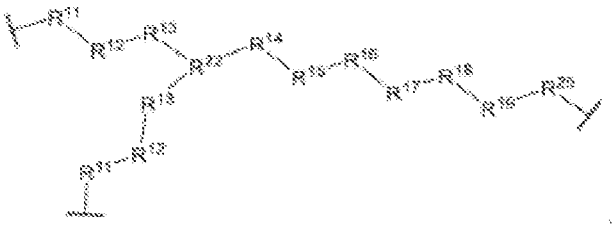
Non-limiting embodiments of a divalent residue of a saturated monocarboxylic acid is selected from butyric acid (-OC(O)$(CH_2)_2CH_2$-), caproic acid (-OC(O)$(CH_2)_4CH_2$-), caprylic acid (-OC(O)$(CH_2)_5CH_2$-), capric acid (-OC(O)$(CH_2)_8CH_2$-), lauric acid (-OC(O)$(CH_2)_{10}CH_2$-), myristic acid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

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



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

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

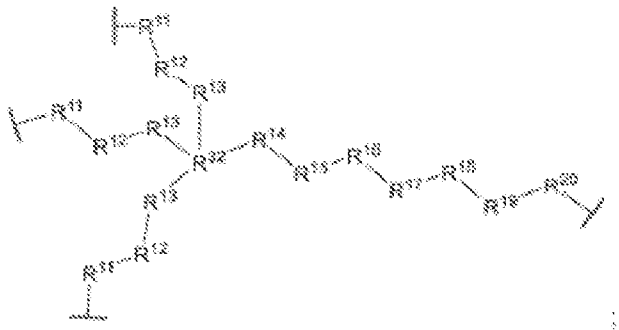


wherein:

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

and the remaining variables are as defined herein.

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



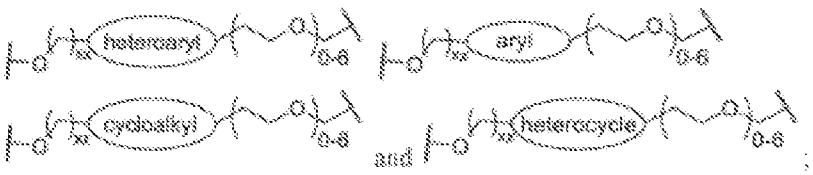
wherein:

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

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

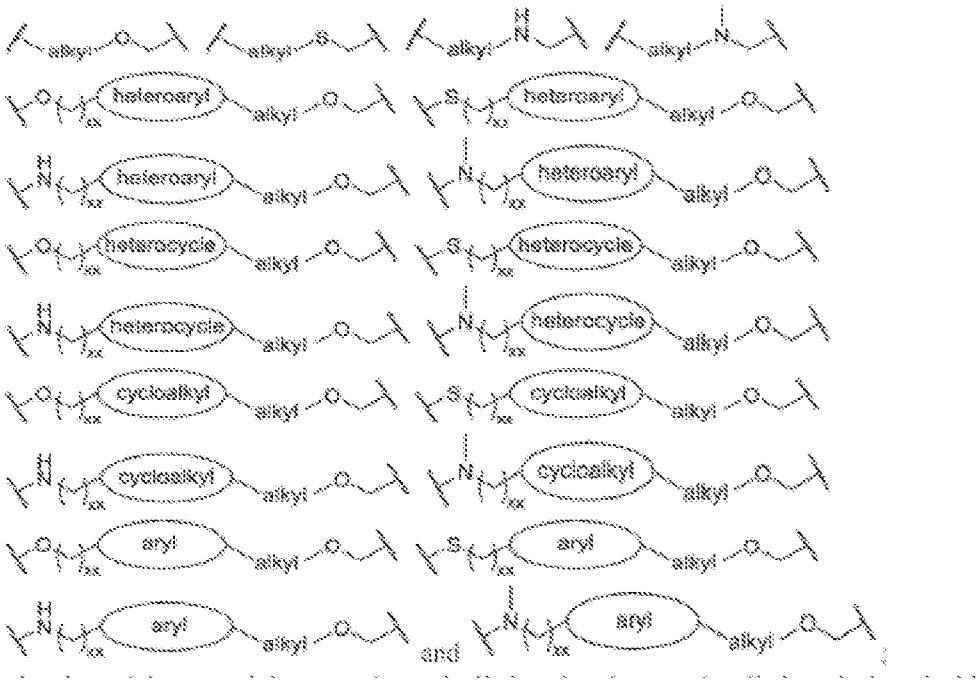
all other variables are as defined herein.

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



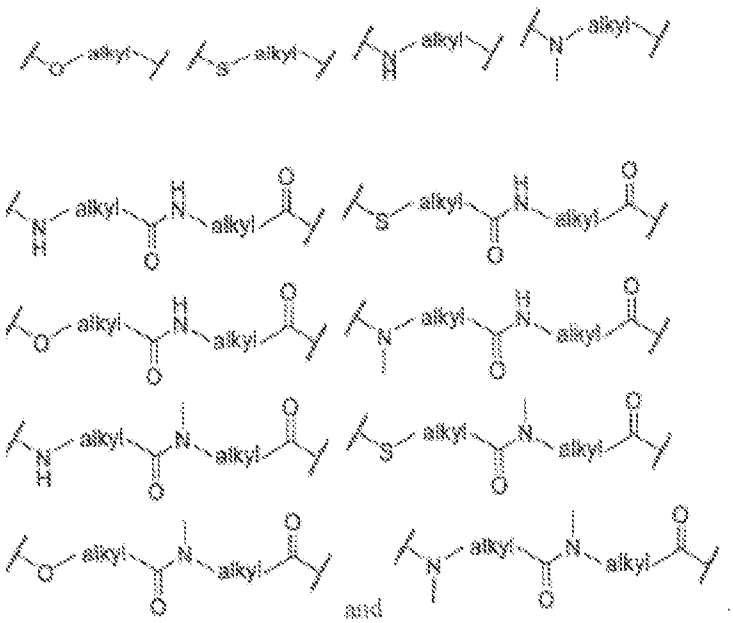
wherein each heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, and, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence.

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

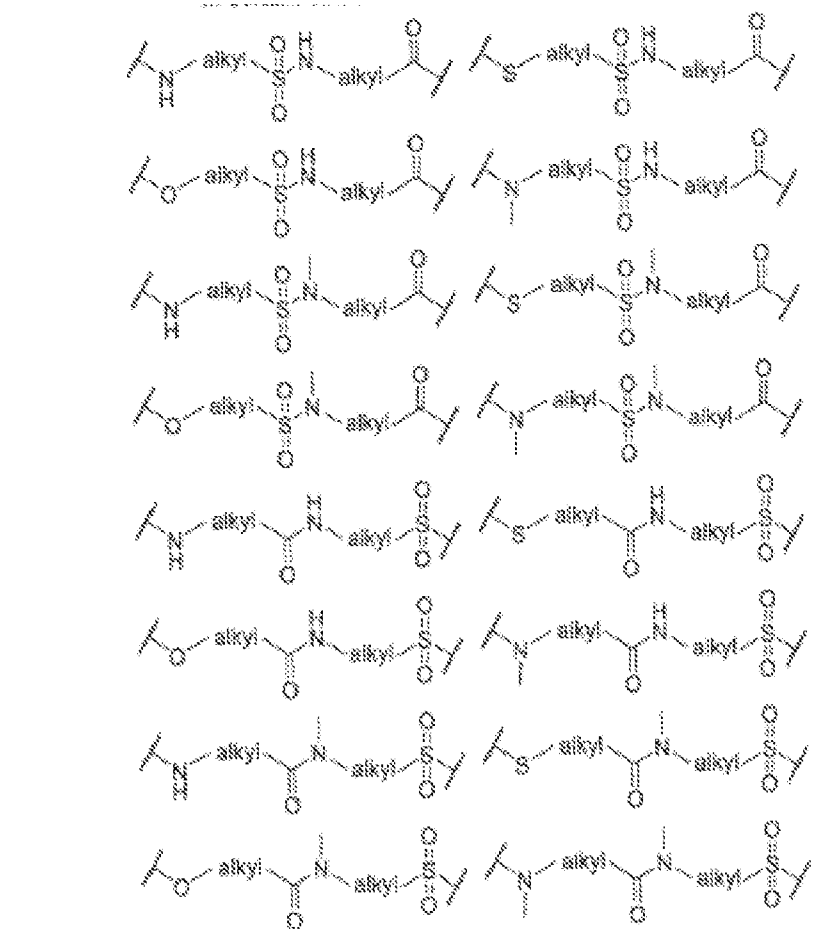


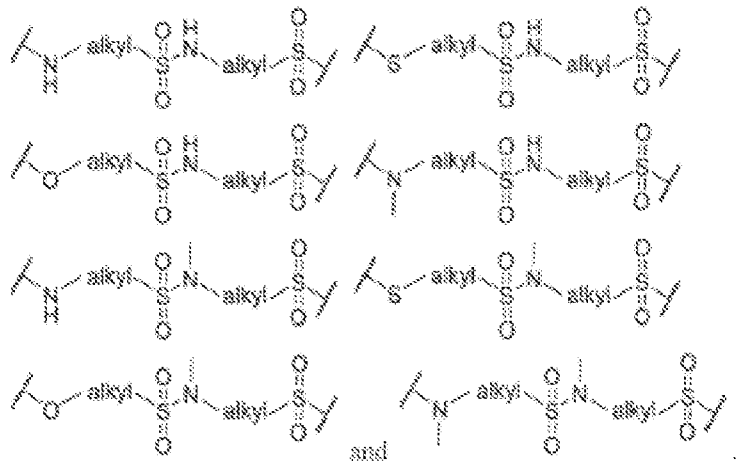
wherein each heteroaryl, heterocycle, cycloalkyl, and and can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence.

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



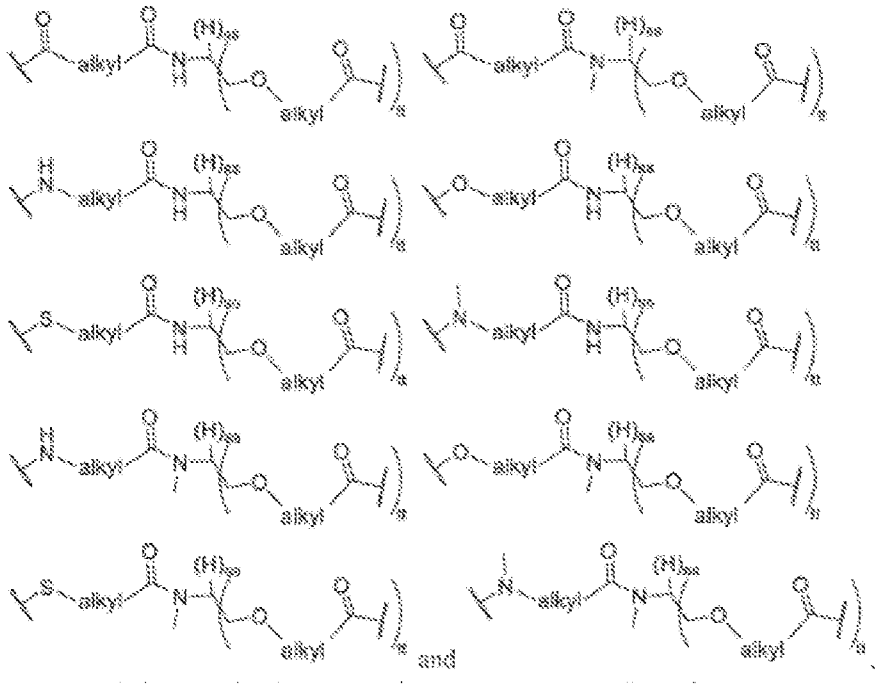
In certain embodiments, in the compound of Formula II, Linker^B is selected from:





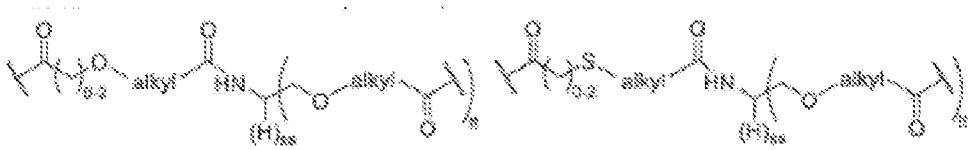
and

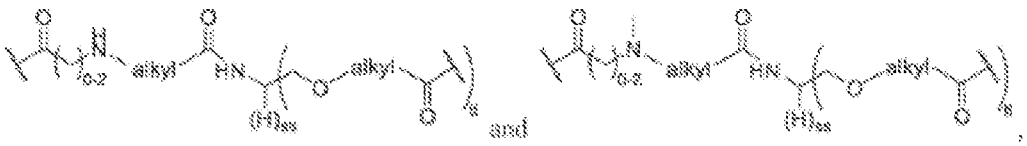
In certain embodiments, in the compound of Formula II, Linker^{B}, Linker^{C}, or Linker^{D} is selected from:



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

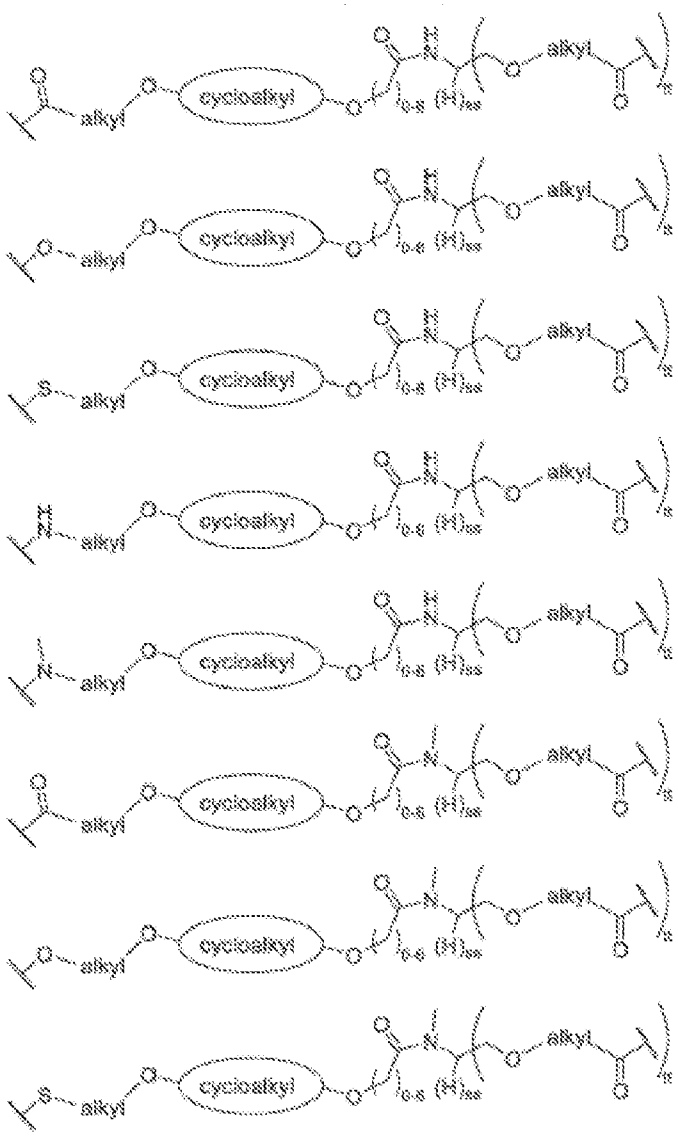
In certain embodiments, in the compound of Formula II, Linker^B, Linker^C, or Linker^D is selected from:

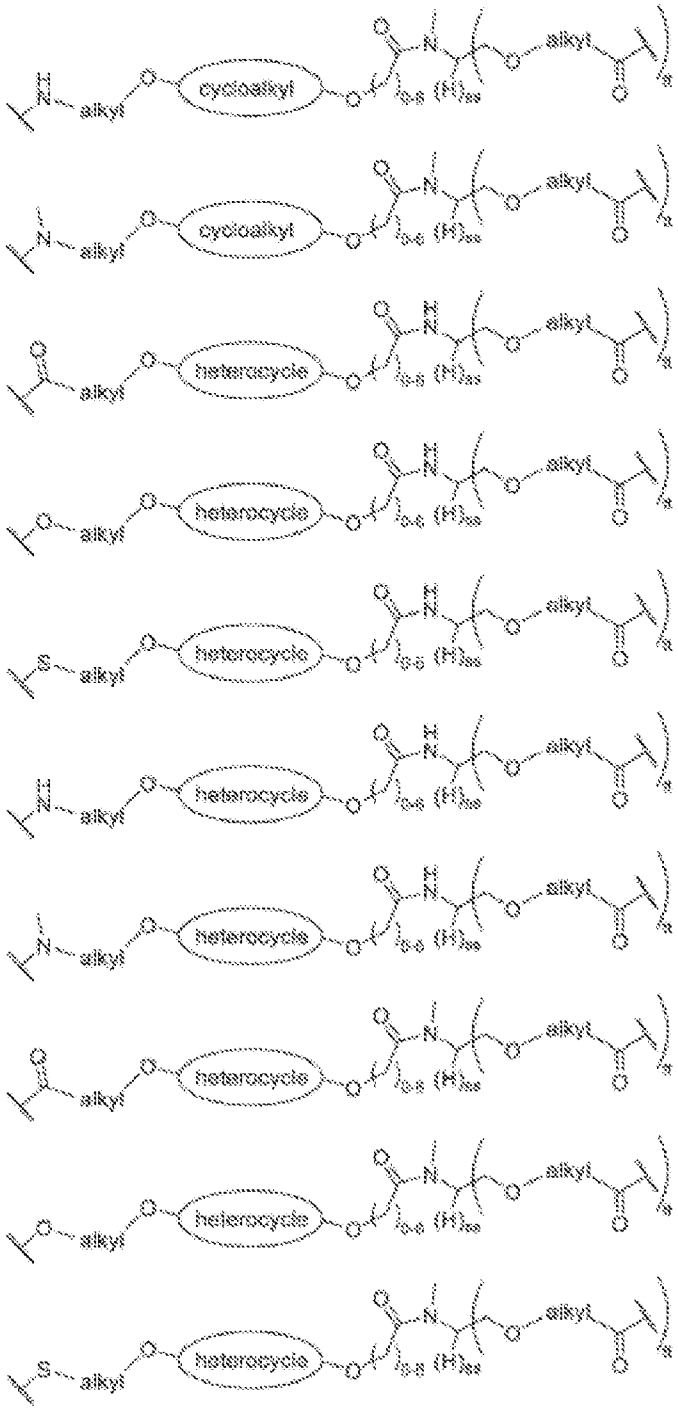


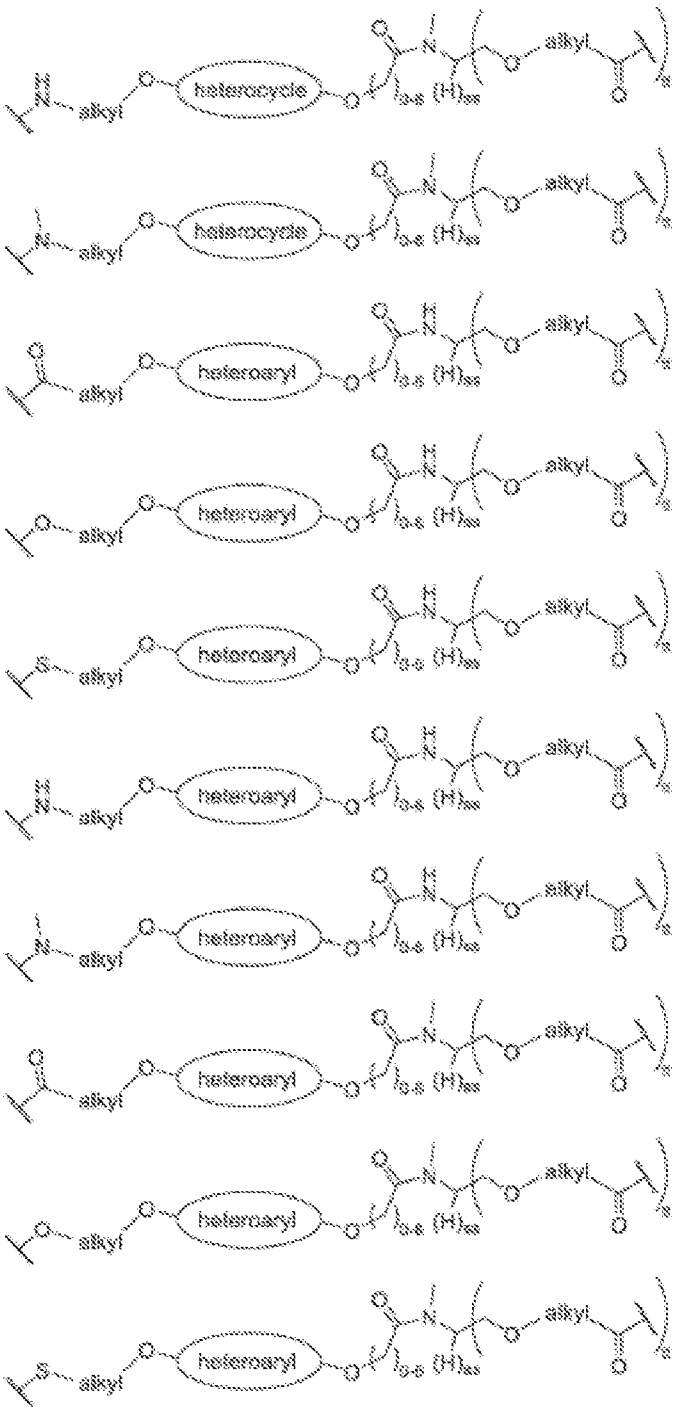


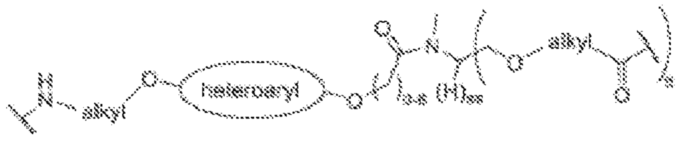
wherein tt and ss are as defined herein.

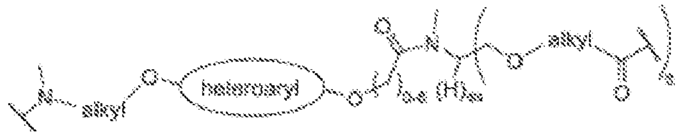
In certain embodiments, in the compound of Formula II, Linker^B, Linker^C, or Linker^D is selected from:

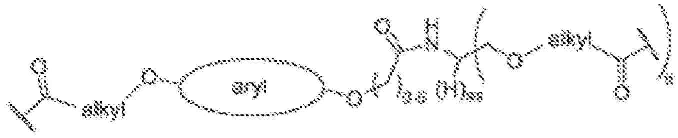

cycloalkyl
alkyl

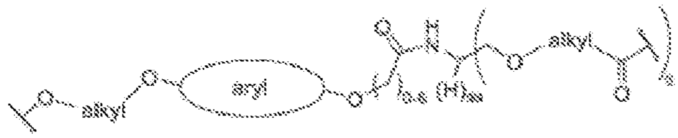

cycloalkyl
heterocycle
alkyl

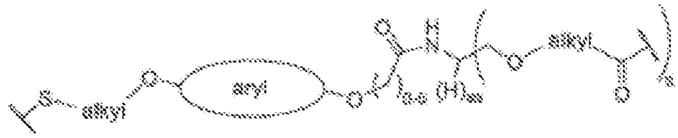

heterocycle
heteroaryl
alkyl

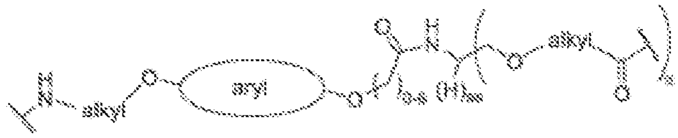

heteroaryl
alkyl

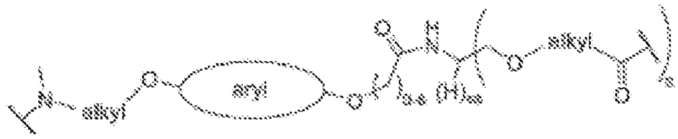

heteroaryl
alkyl


aryl
alkyl


aryl
alkyl


aryl
alkyl


aryl
alkyl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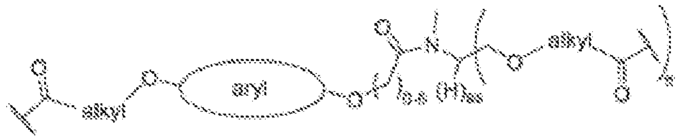
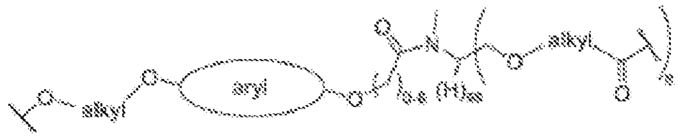
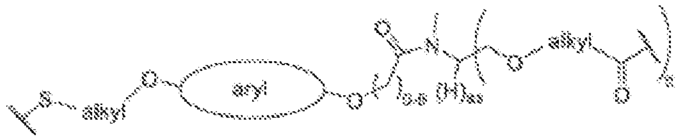
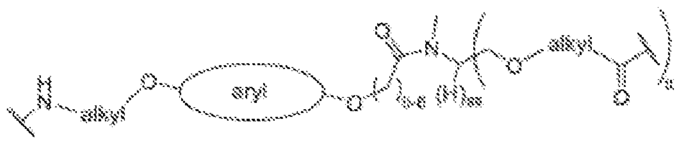
alkyl

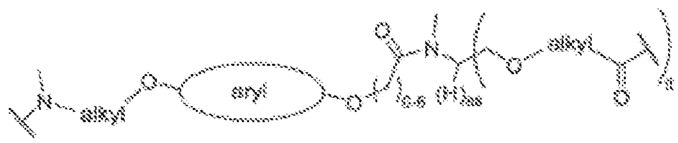

aryl
alkyl


aryl
alkyl


aryl
alkyl


aryl
alkyl

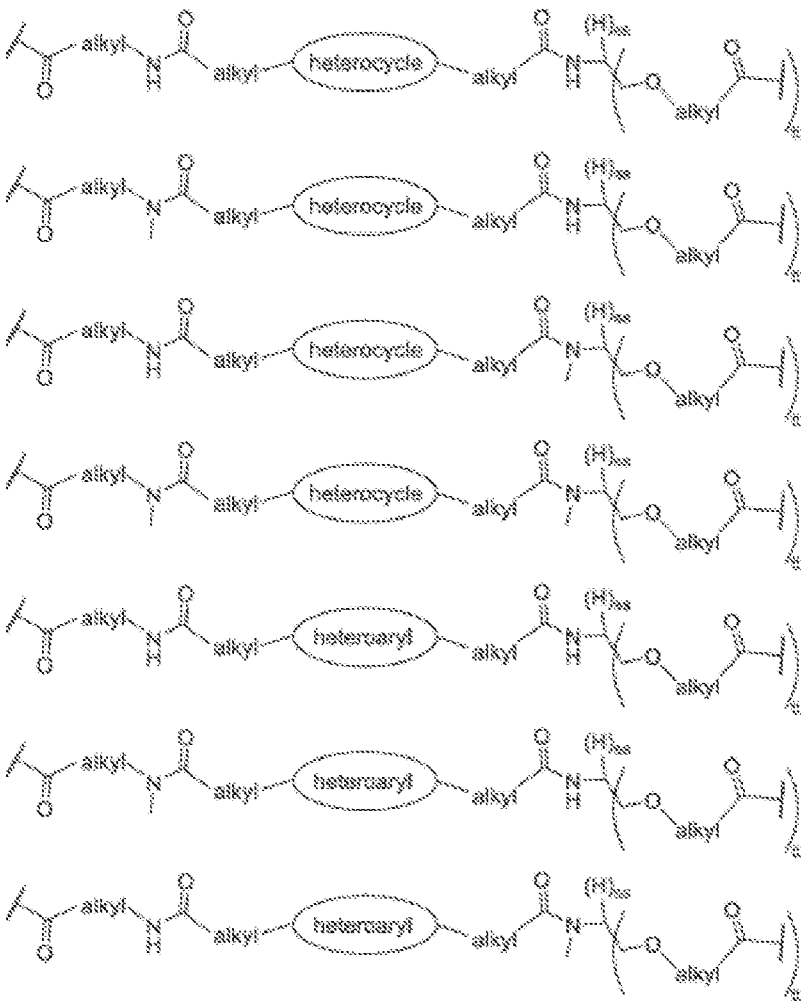
and

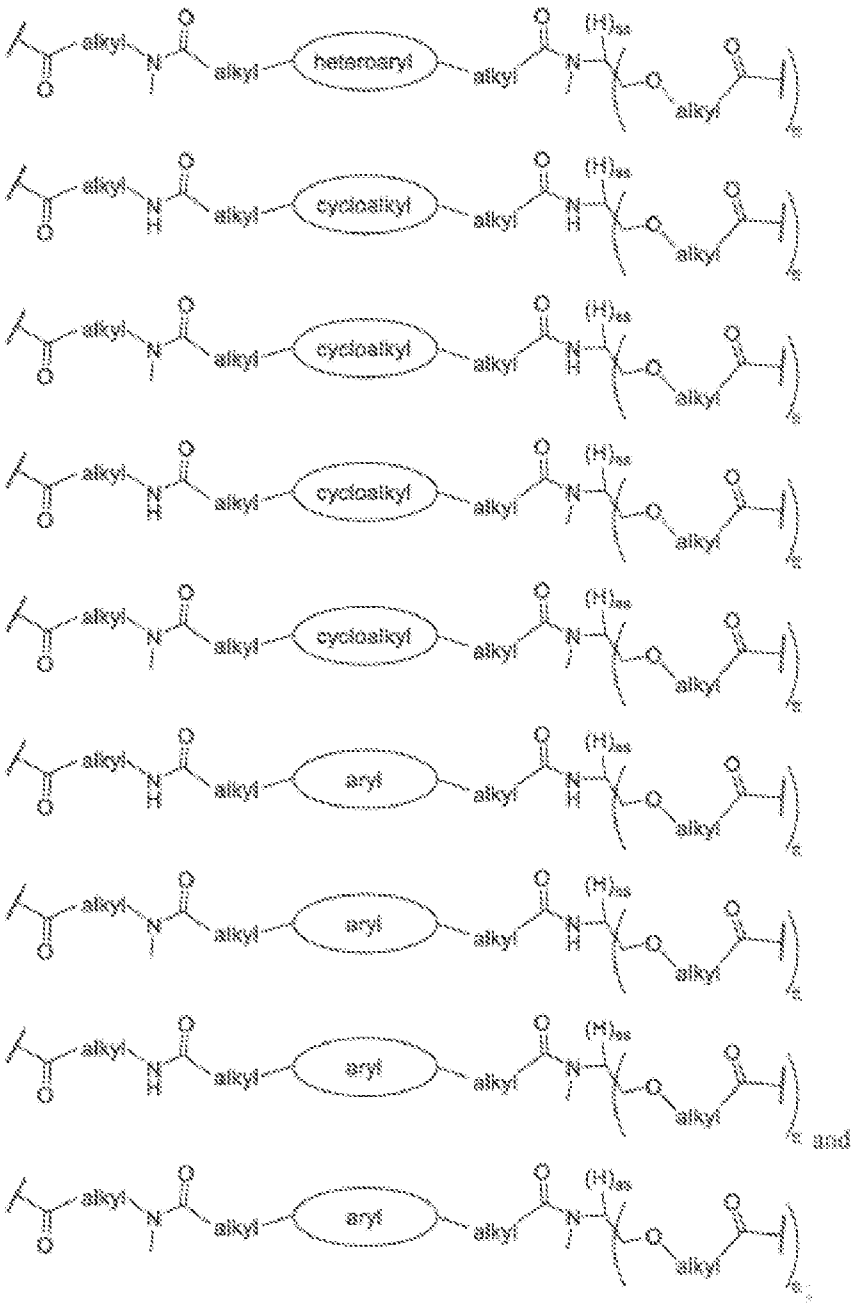

aryl
alkyl

;

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

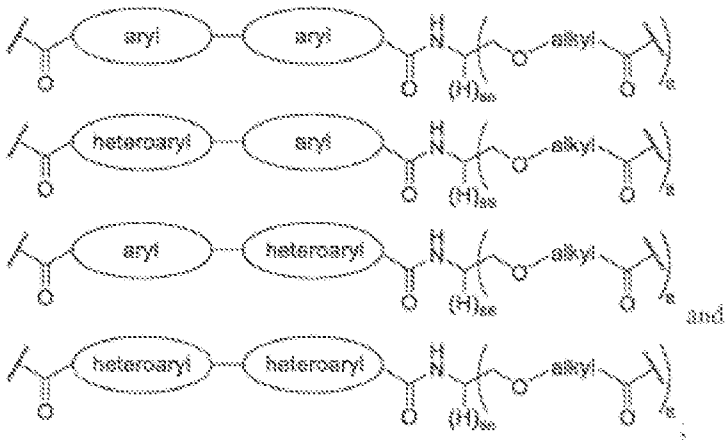
In certain embodiments, in the compound of Formula II, Linker^B, Linker^C, or Linker^D is selected from:





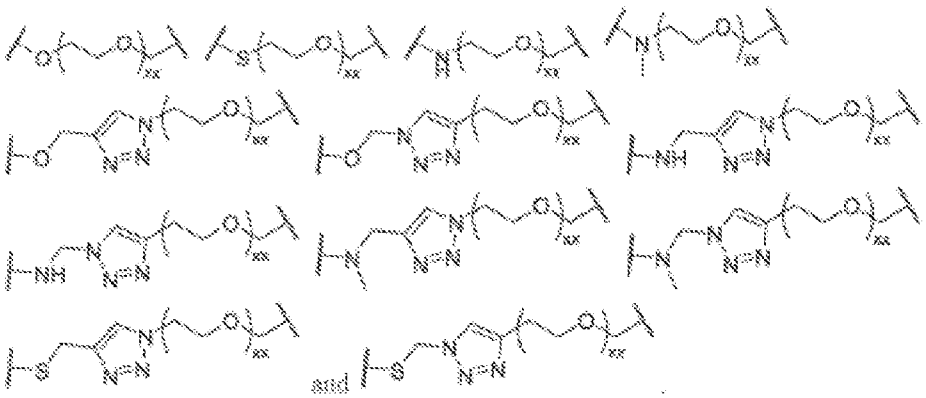
wherein each heteroaryl, heterocycle, cycloalkyl, and aryl can optionally be substituted with 1, 2 3, or 4 of any combination of halogen, alkyl, haloalkyl, and, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence: and tt and ss are as defined herein.

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

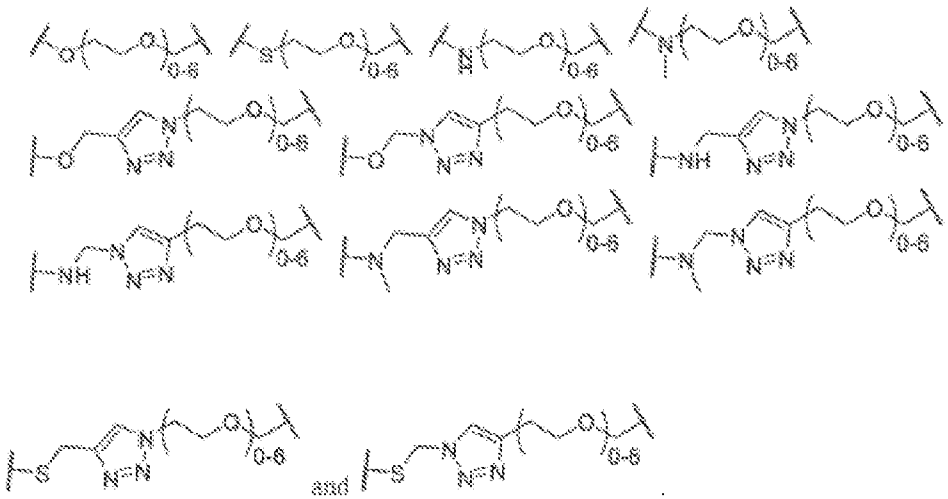


wherein each heteroaryl and aryl can optionally be substituted with 1, 2, 3, or 4 of any combination of halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocycle, or cycloalkyl, as allowed by valence; and tt and ss are as defined herein.

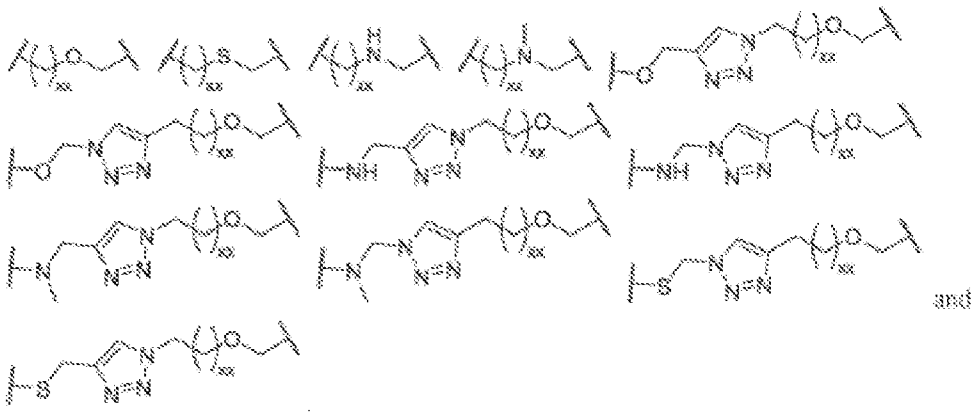
In certain embodiments, in the compound of Formula II, Linker^A is selected from:



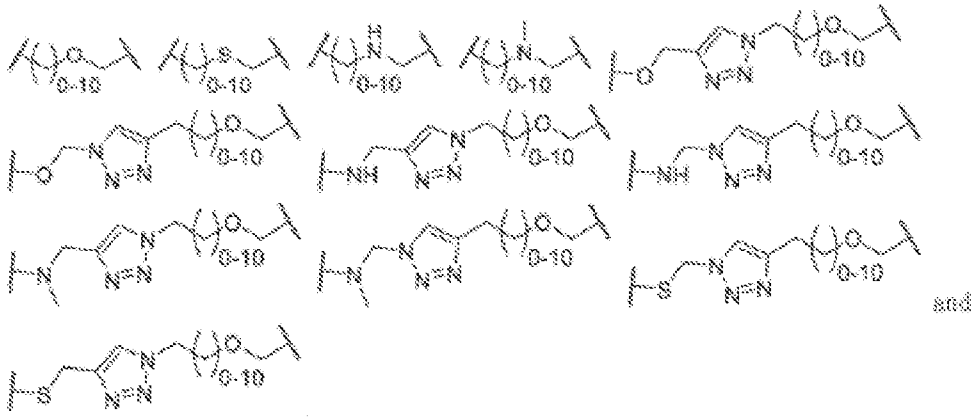
In certain embodiments, in the compound of Formula II, Linker^A is selected from:



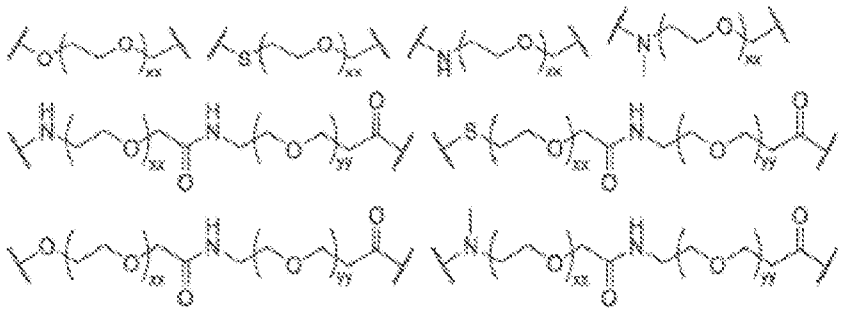
In certain embodiments, in the compound of Formula II, Linker^A is selected from:

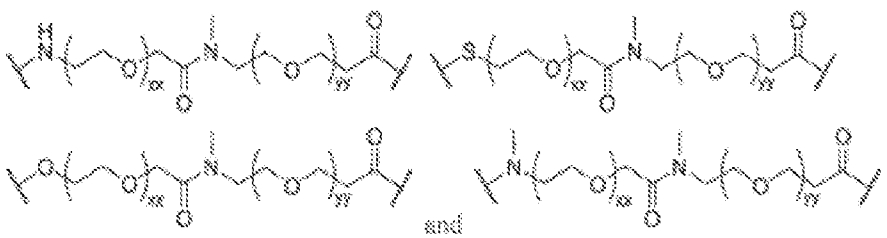


In certain embodiments, in the compound of Formula II, Linker^{A} is selected from:

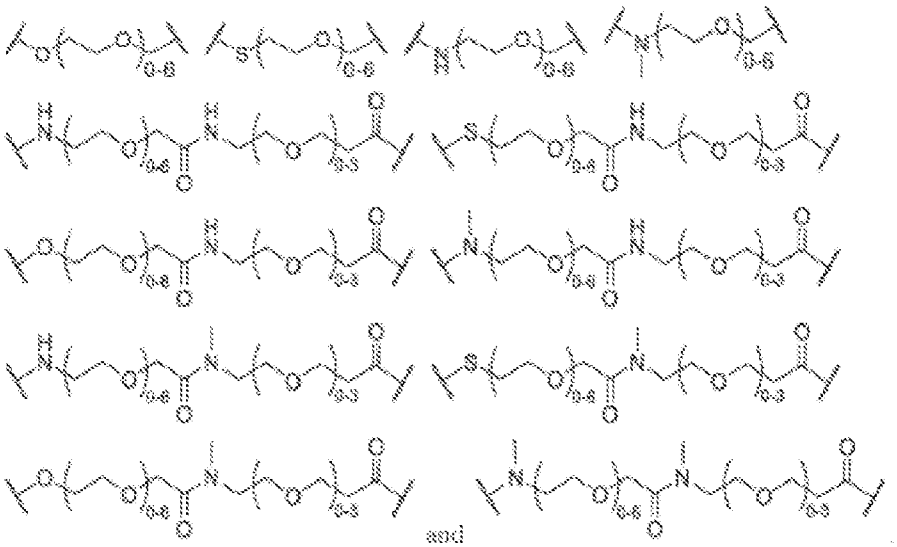


In certain embodiments, in the compound of Formula II, Linker^{B} is selected from:

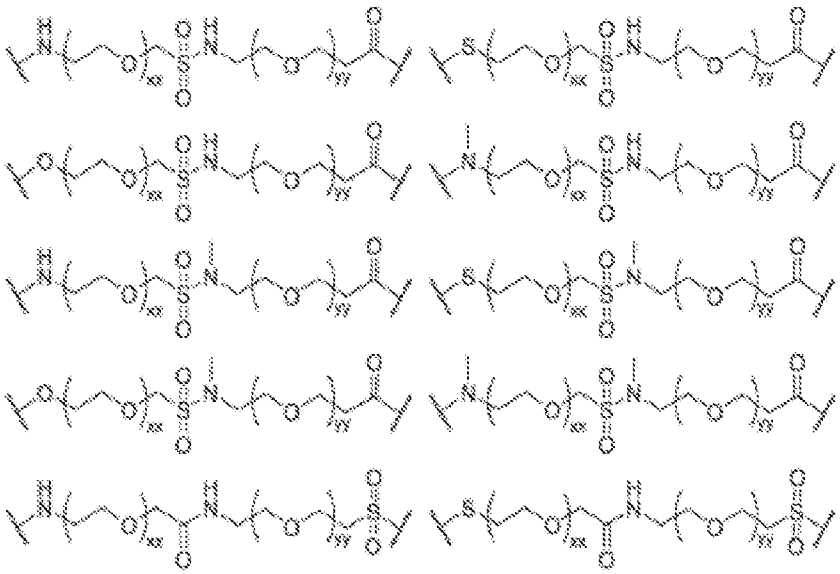


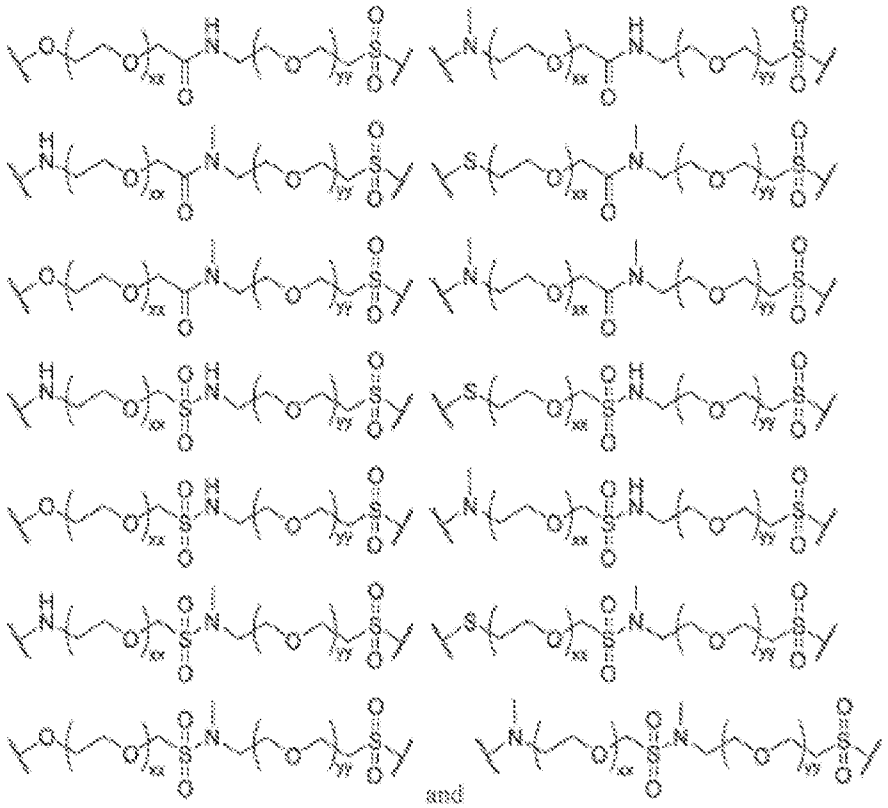


In certain embodiments, in the compound of Formula II, Linker^{B} is selected from:

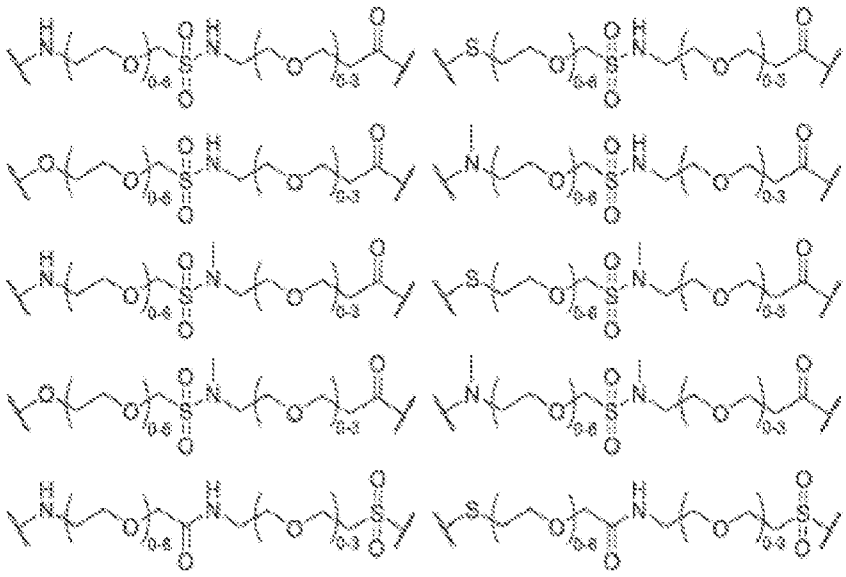


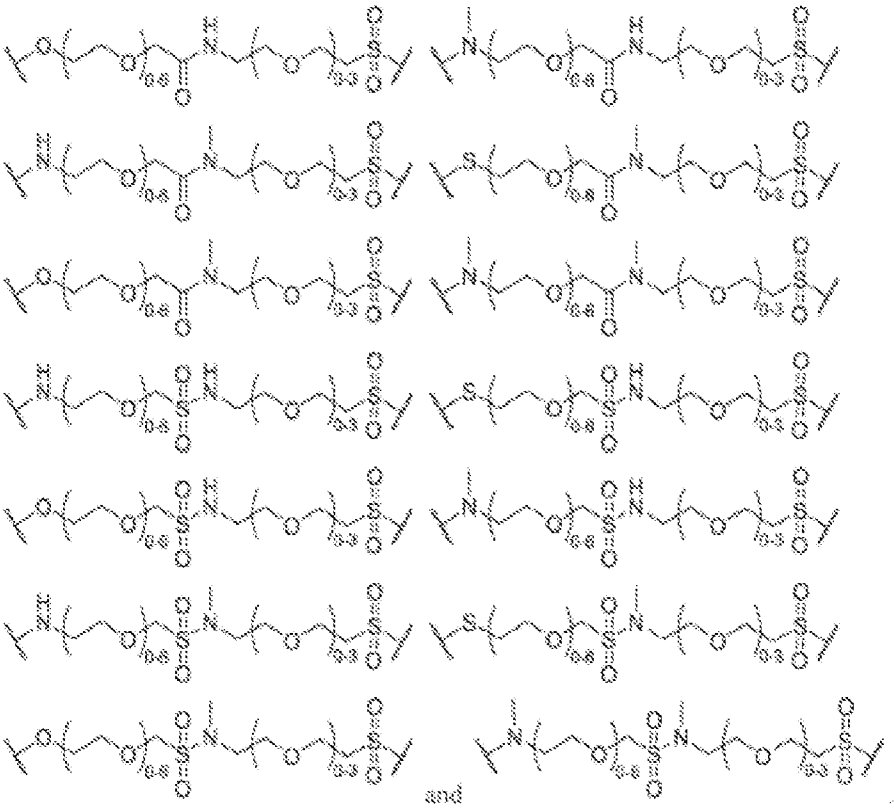
In certain embodiments, in the compound of Formula II, Linker^{B} is selected from:



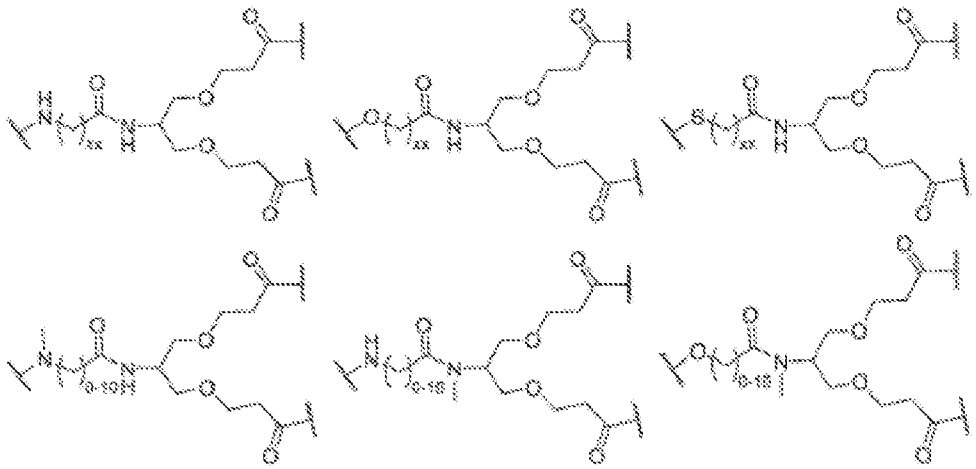


In certain embodiments, in the compound of Formula II, Linker^{B} is selected from:

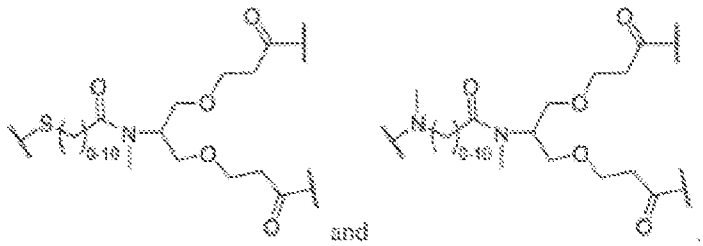




and

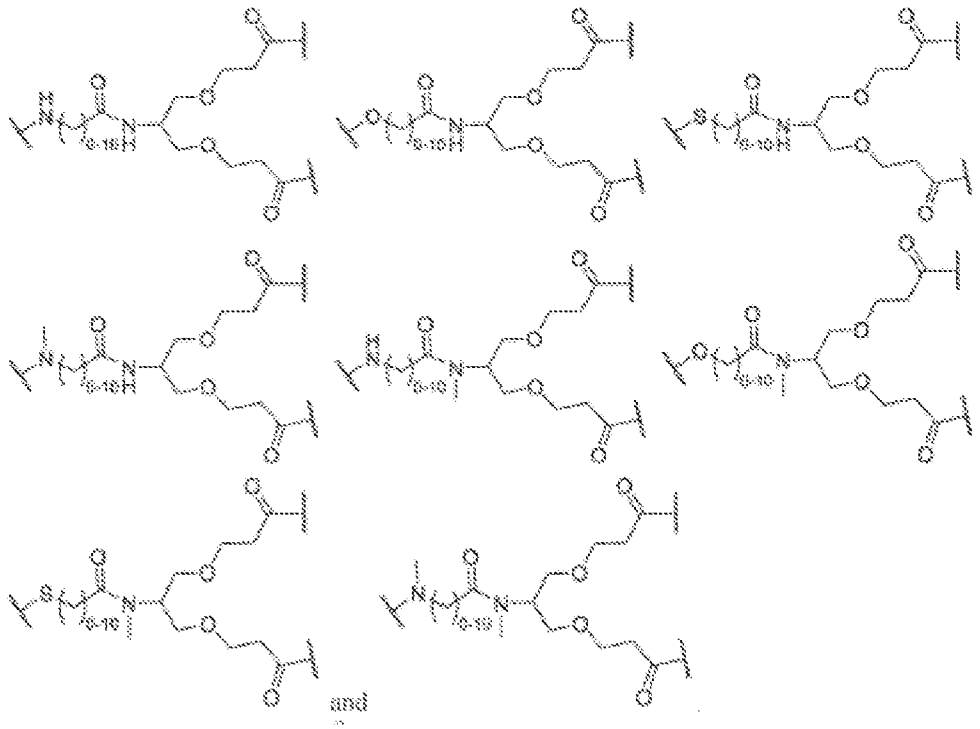


In certain embodiments, in the compound of Formula II, Linker^C is selected from:

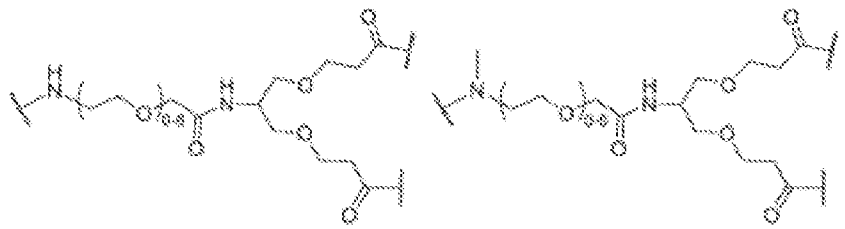


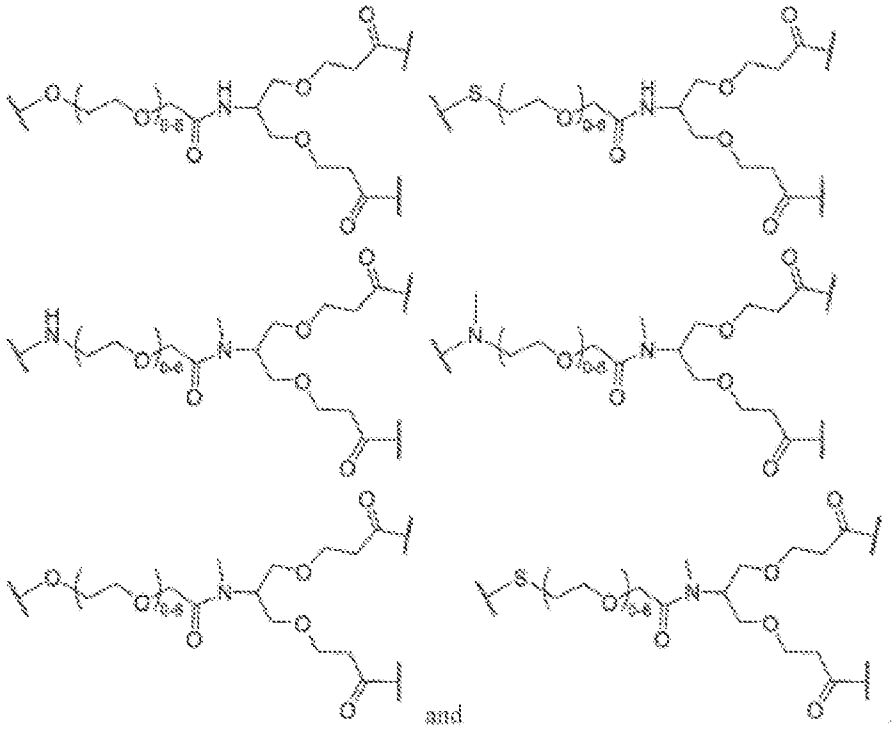
and

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

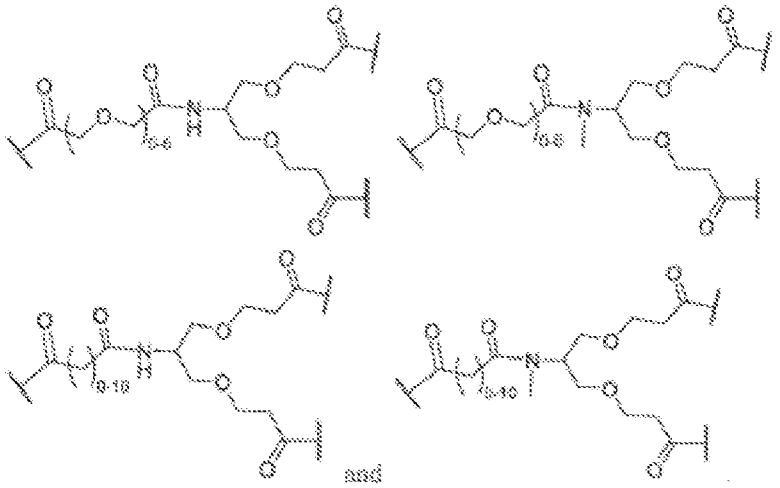


In certain embodiments, in the compound of Formula II, Linker^C is selected from:

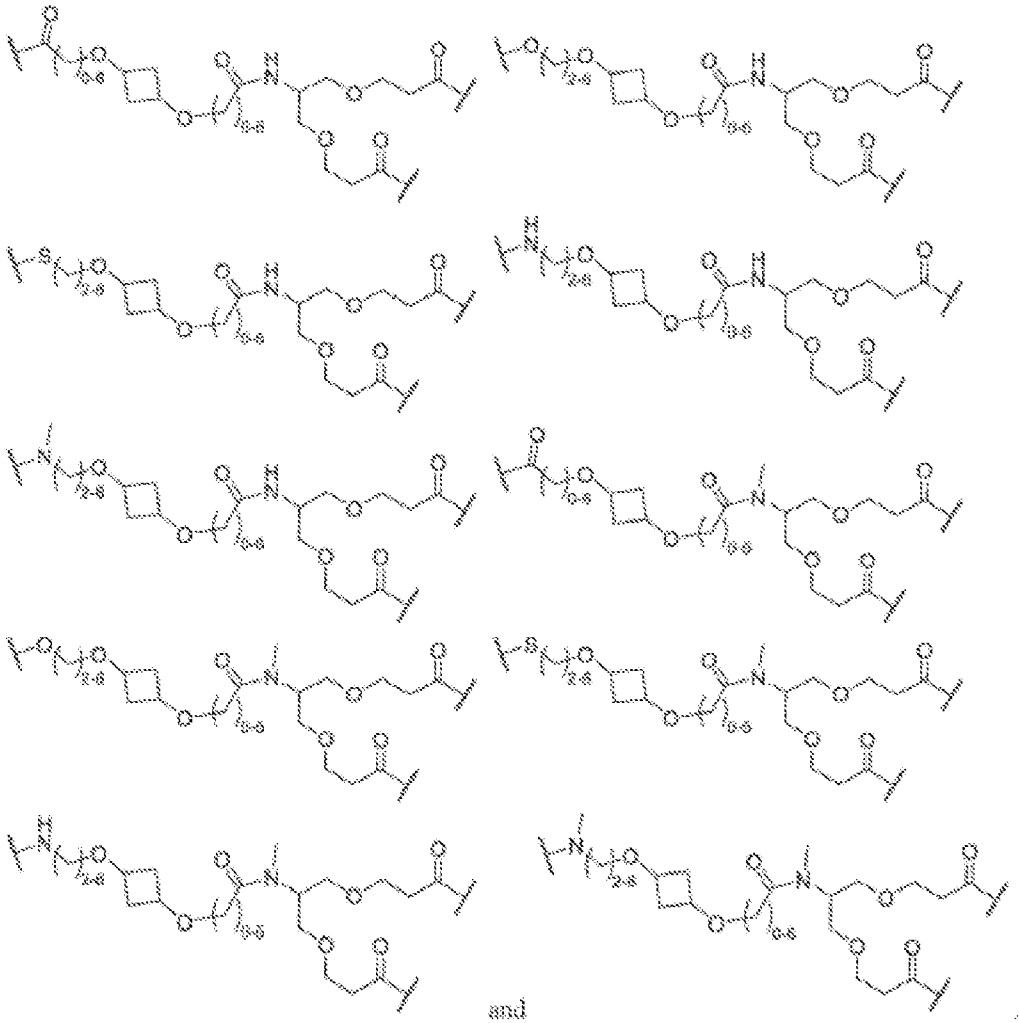




In certain embodiments, in the compound of Formula II, Linker^C is selected from:

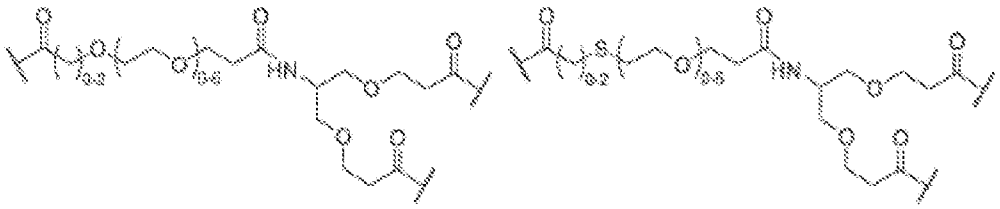


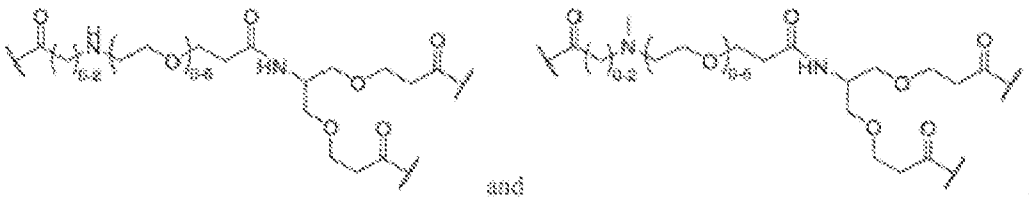
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



and

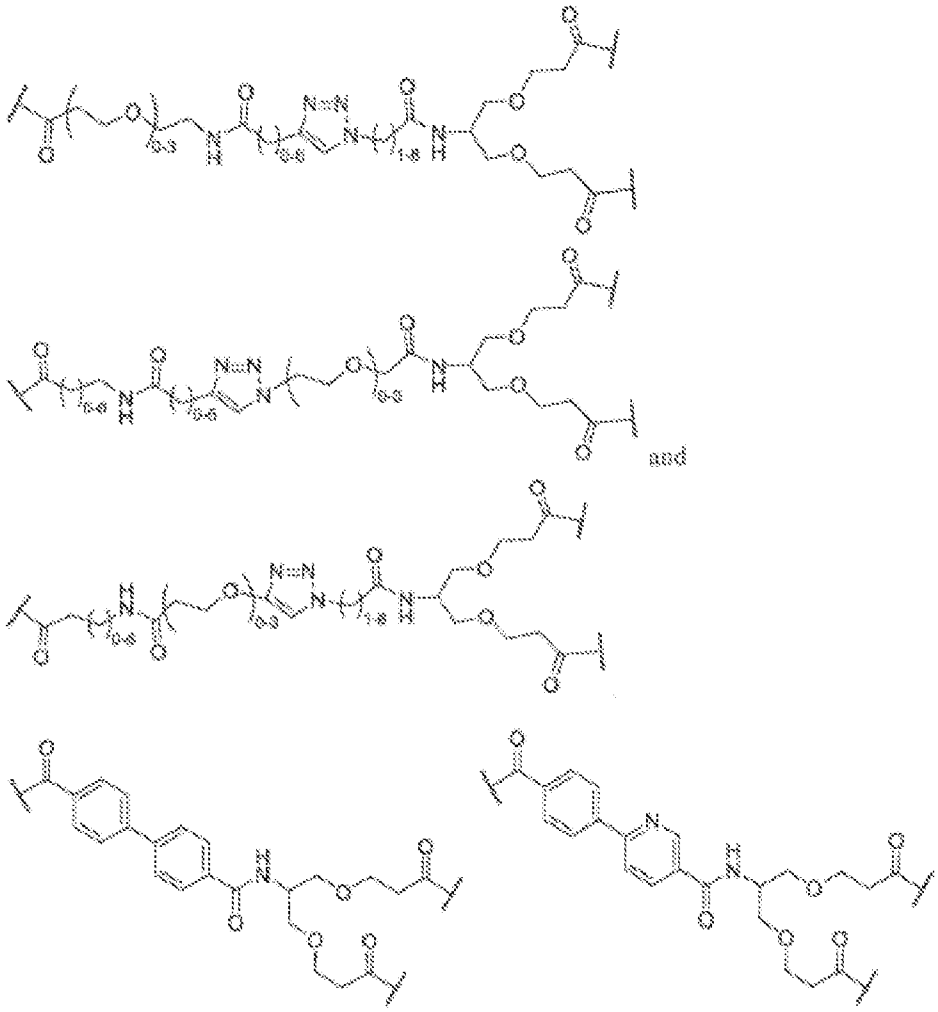
In certain embodiments, in the compound of Formula II, Linker^C is selected from:



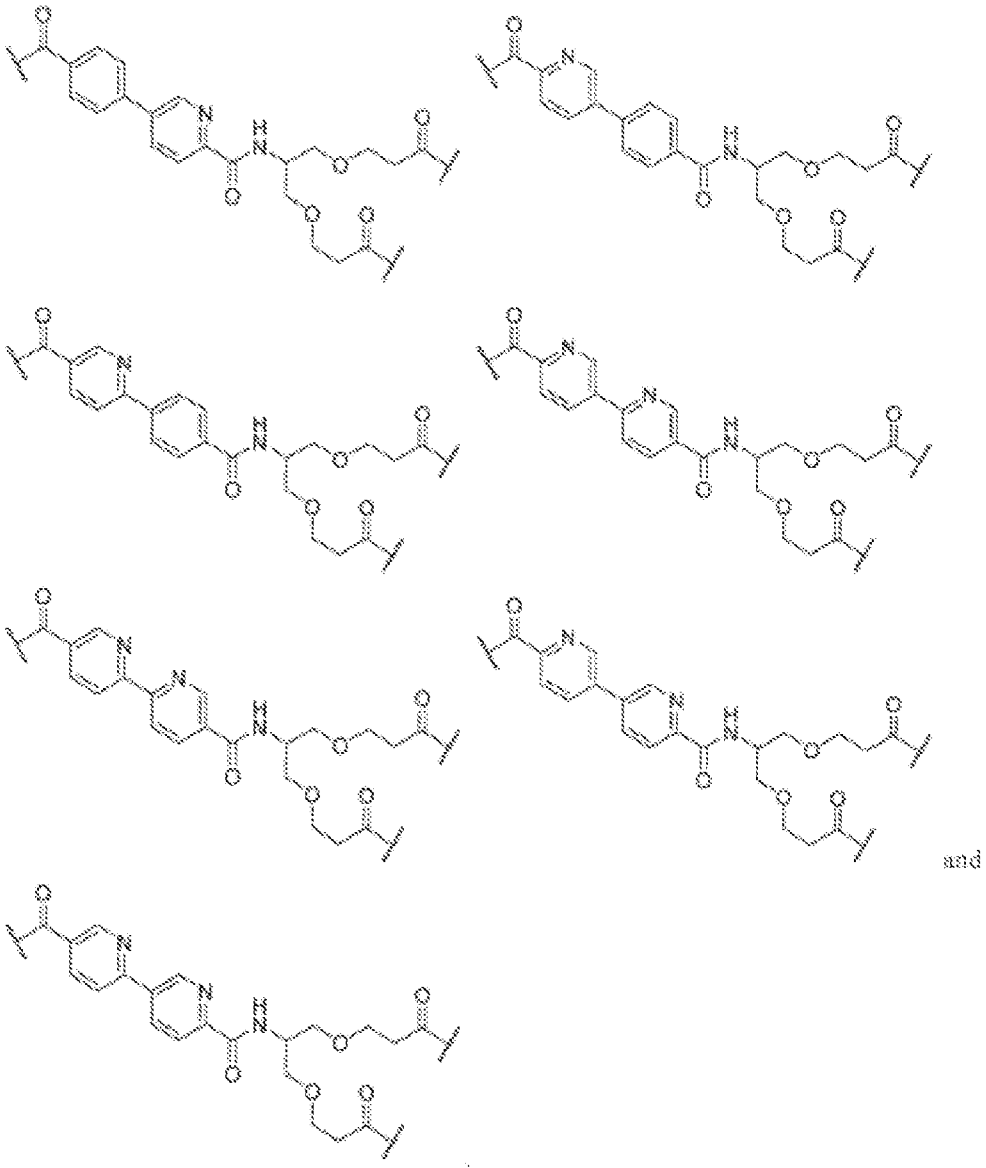


and

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

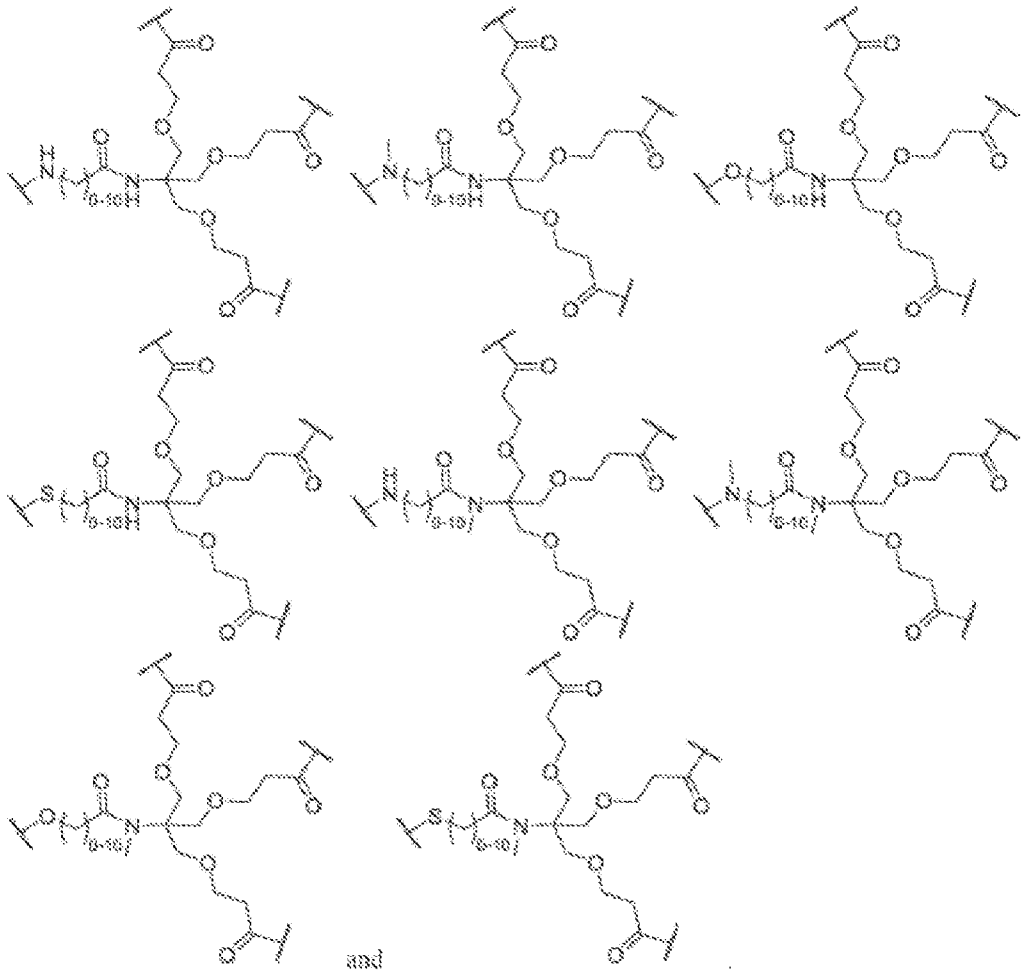


In certain embodiments, in the compound of Formula II, Linker^C is selected from:



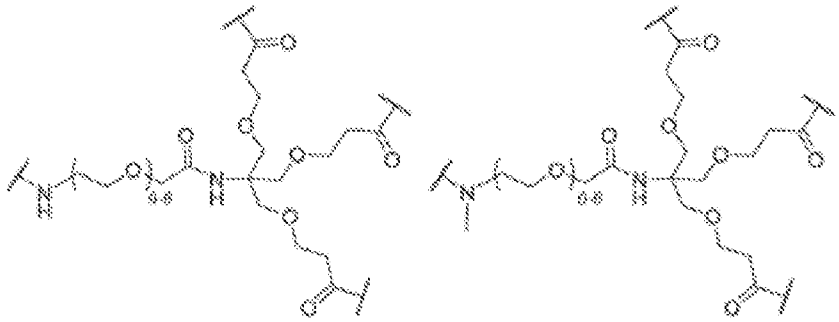
and

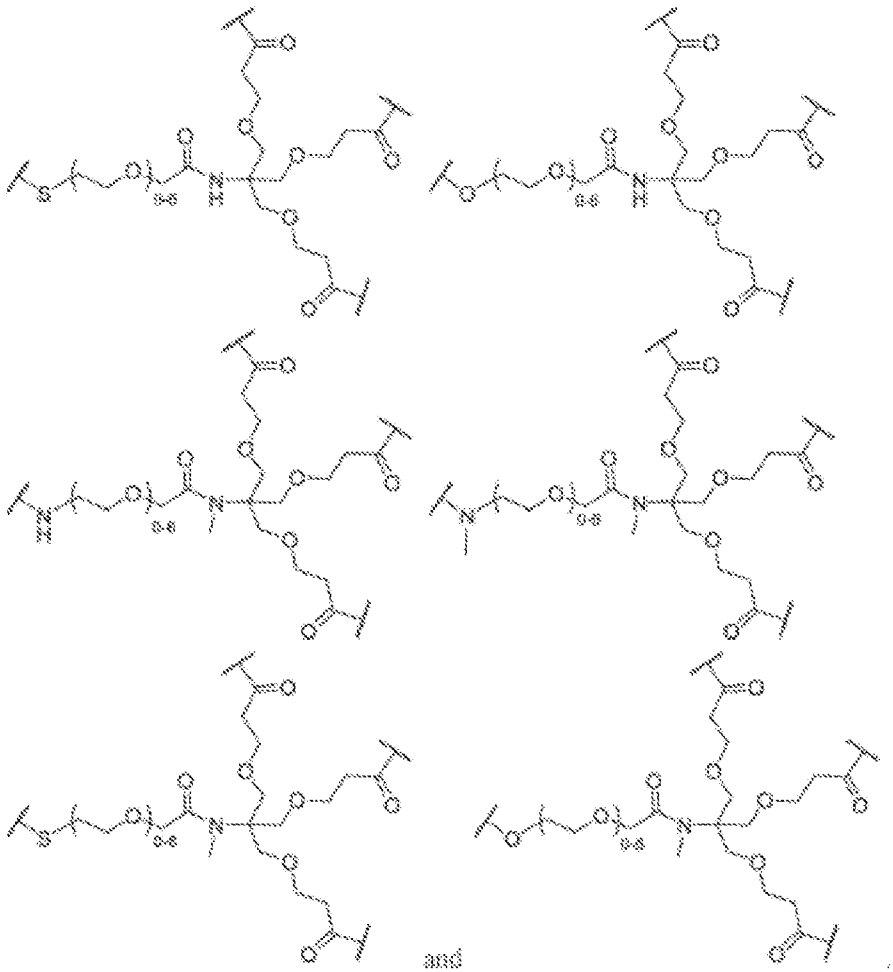
In certain embodiments, in the compound of Formula II, $Linker^D$ is selected from:



and

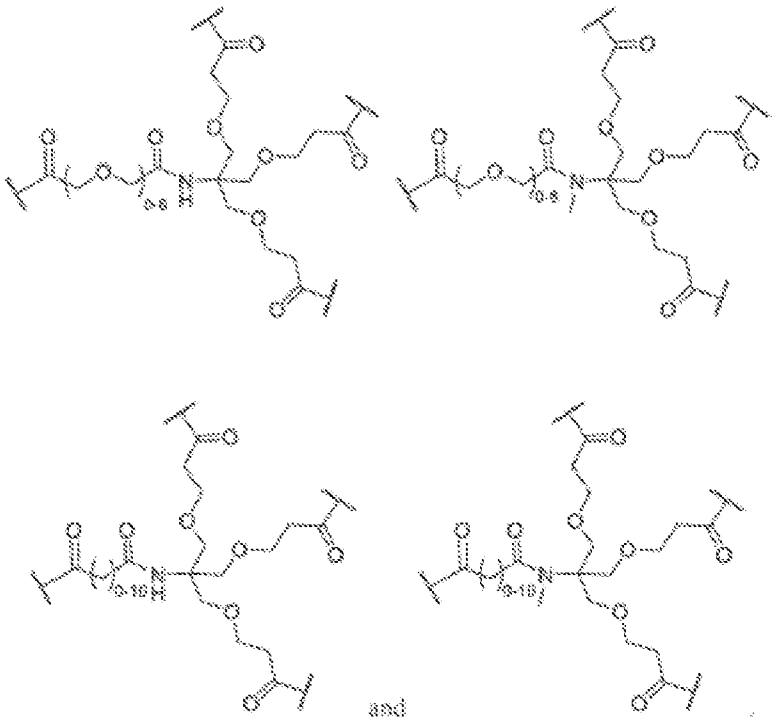
In certain embodiments, in the compound of Formula II, $Linker^D$ is selected from:





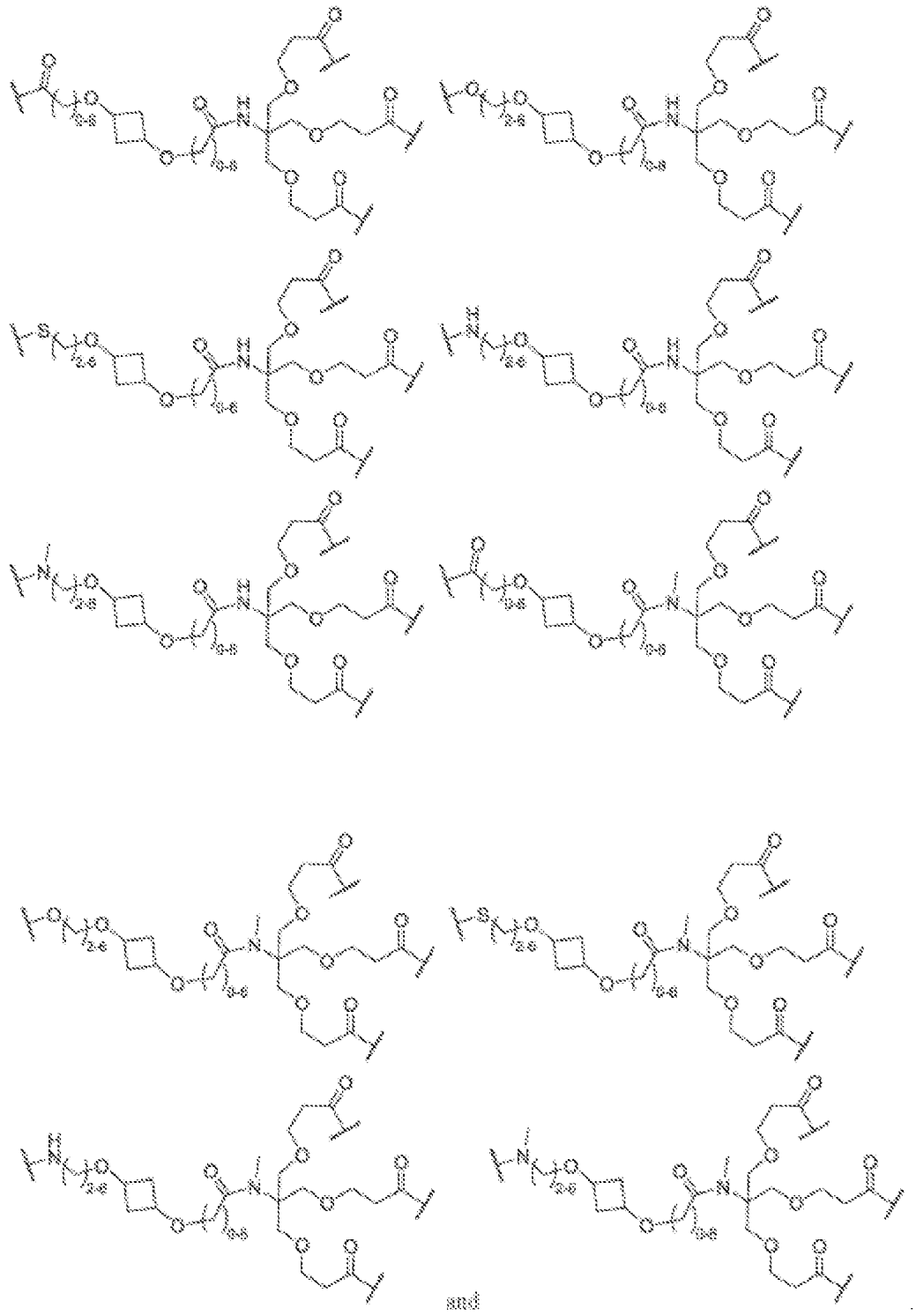
and

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



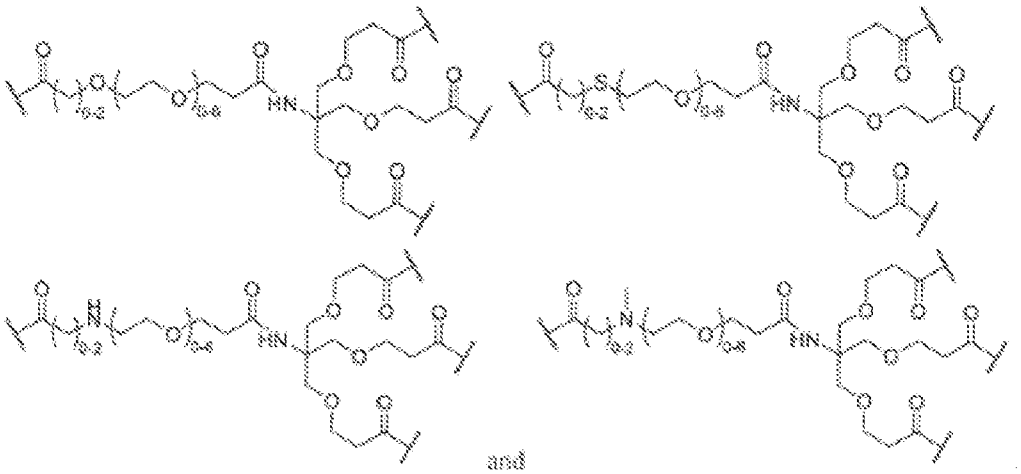
and

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



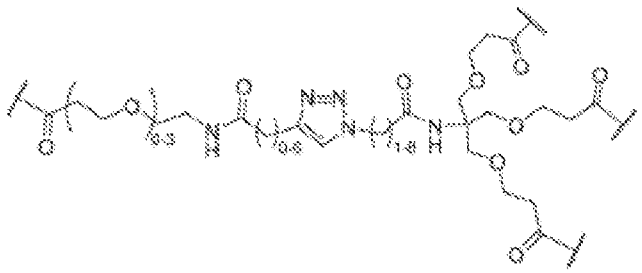
and

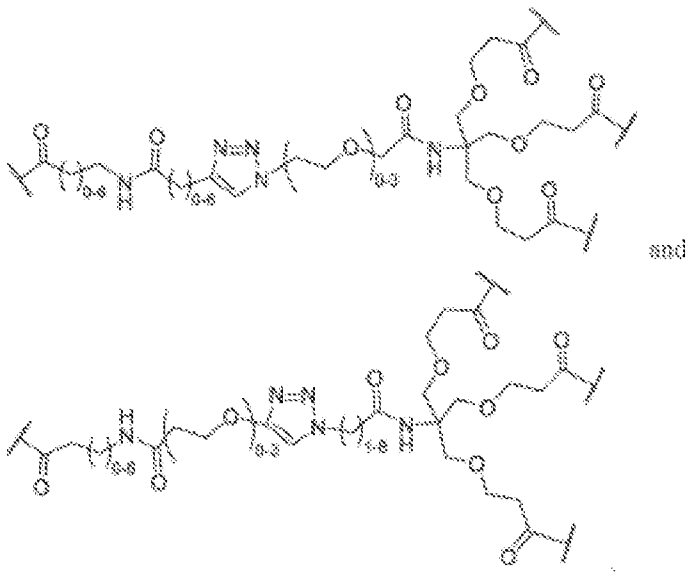
In certain embodiments, in the compound of Formula II, $Linker^D$ is selected from:



and

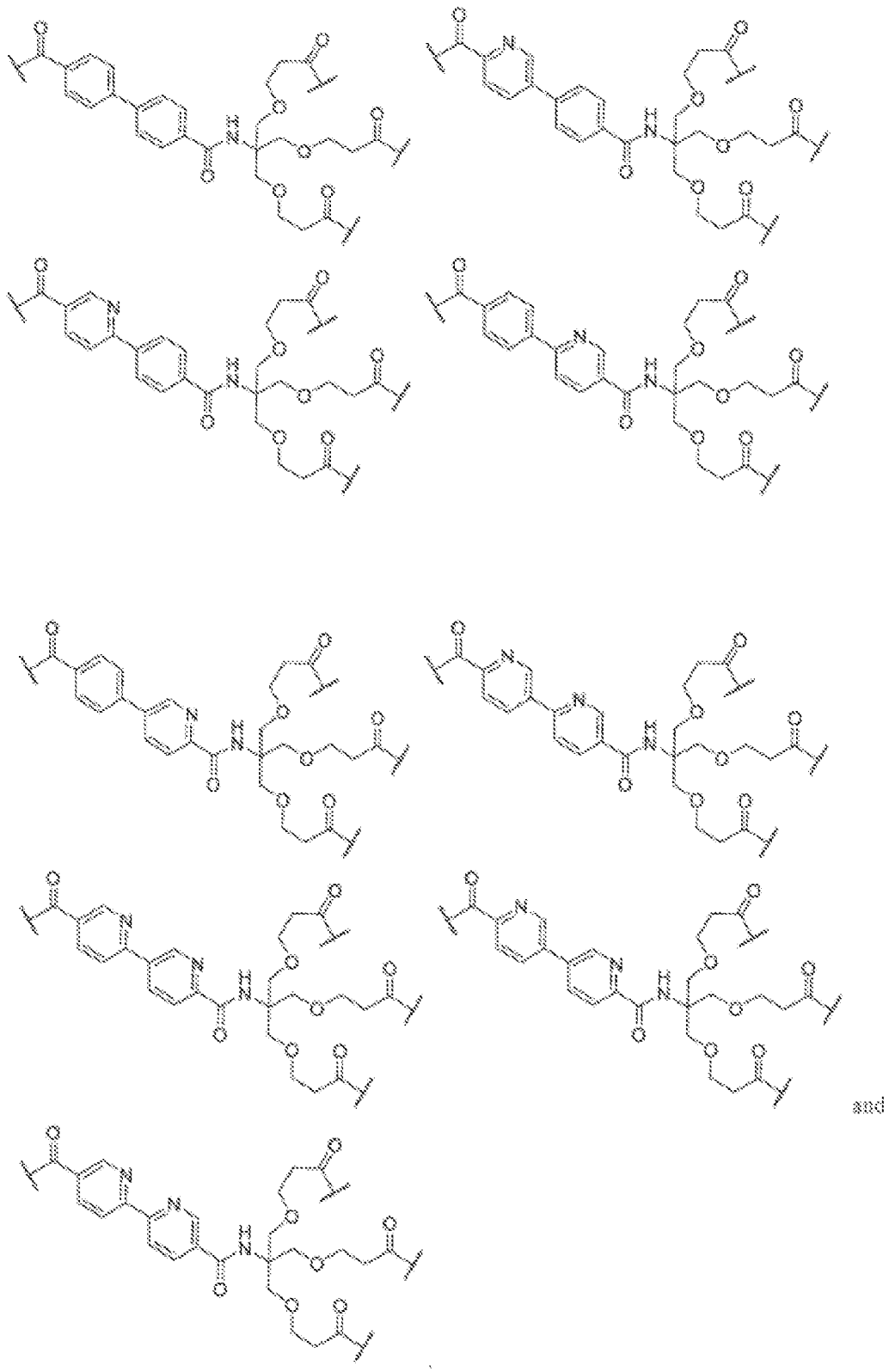
In certain embodiments, in the compound of Formula II, Linker^D is selected from:



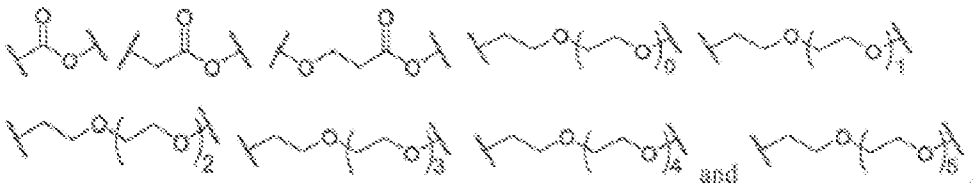


and

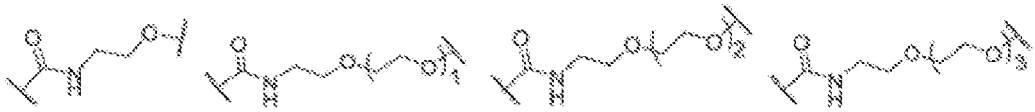
In certain embodiments, in the compound of Formula II, Linker^D is selected from:



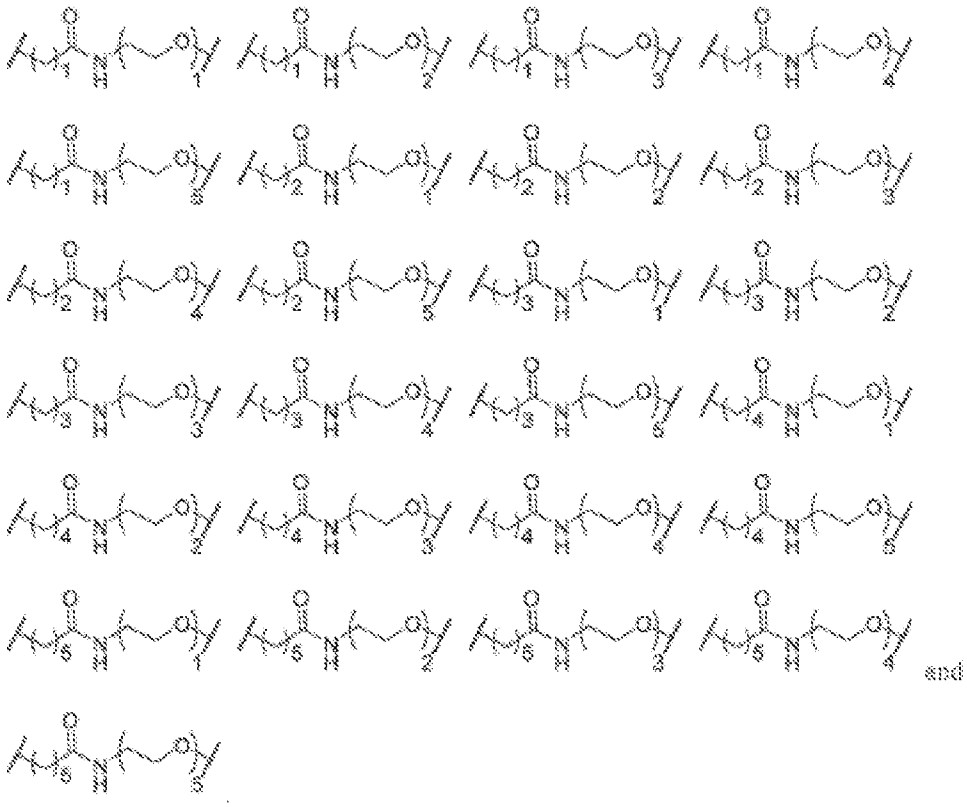
In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from



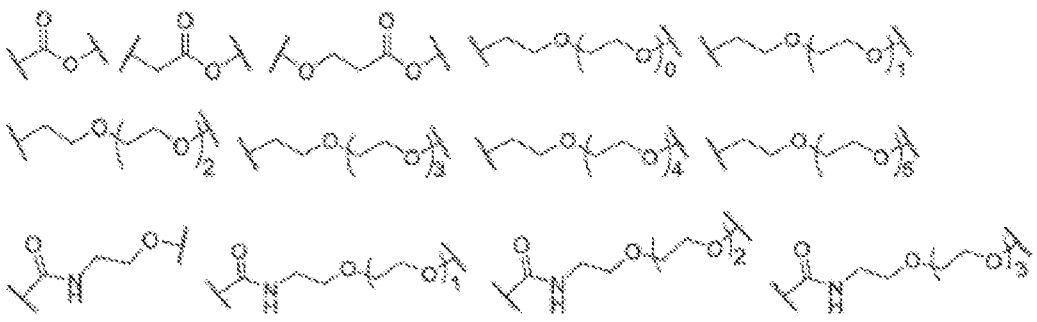
In certain embodiments, in the compound of Formula II, the Linker^A is selected from

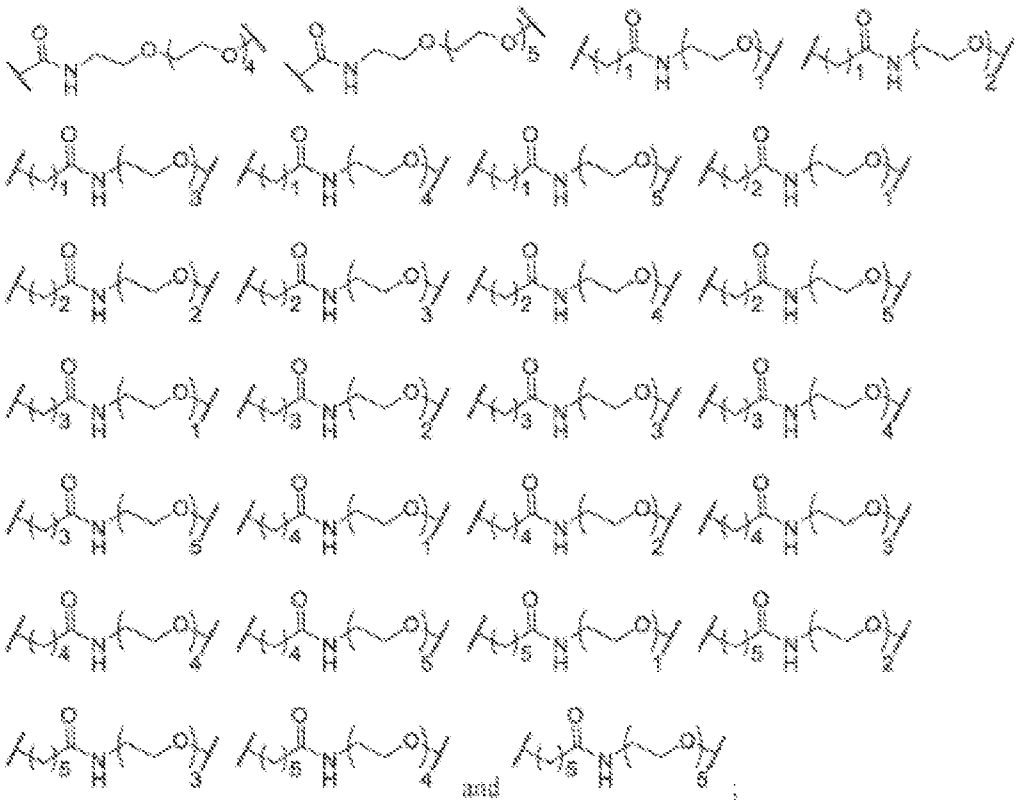


In certain embodiments, in the compound of Formula II, the Linker^A is selected from



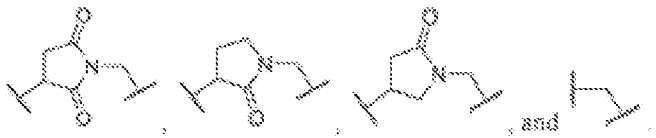
In certain embodiments, the Linker^A is selected from



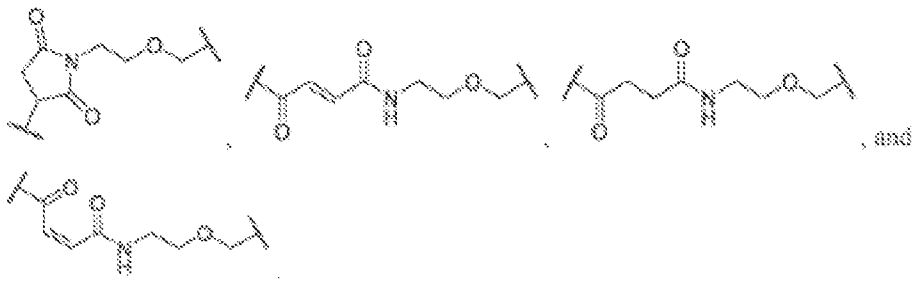


wherein each is optionally substituted with 1, 2, 3, or 4 substituents substituent selected from R^{21}.

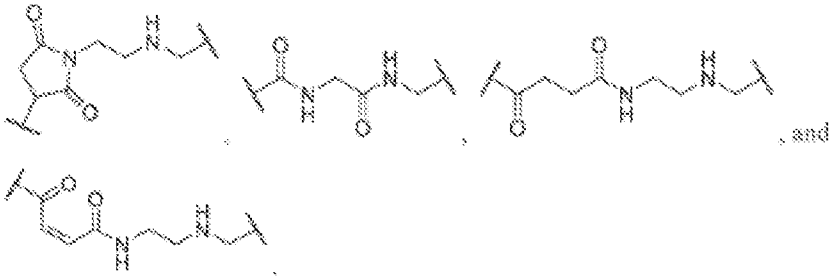
In certain embodiments, in the compound of Formula II, $Linker^A$ is selected from:



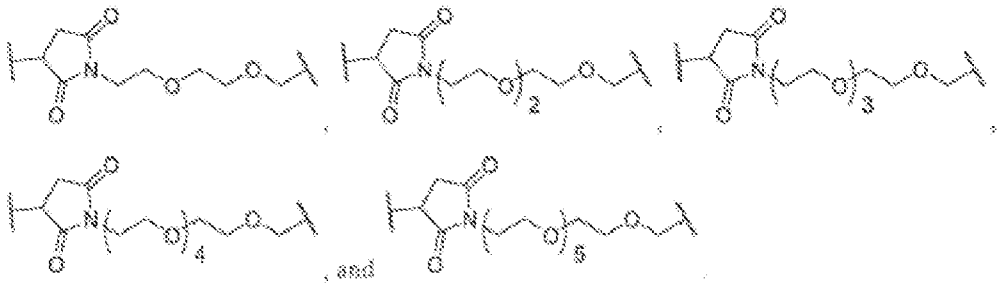
In certain embodiments, in the compound of Formula II, the $Linker^A$ is selected from



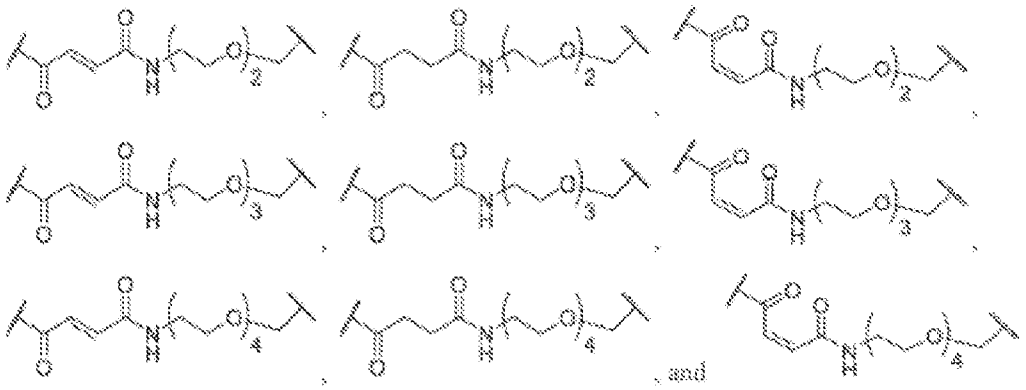
In certain embodiments, in the compound of Formula II, the $Linker^A$ is selected from



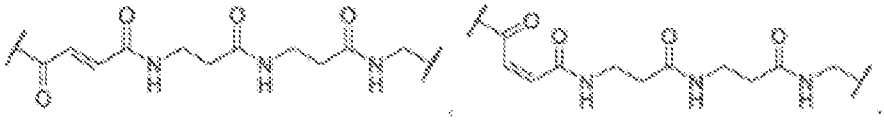
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



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

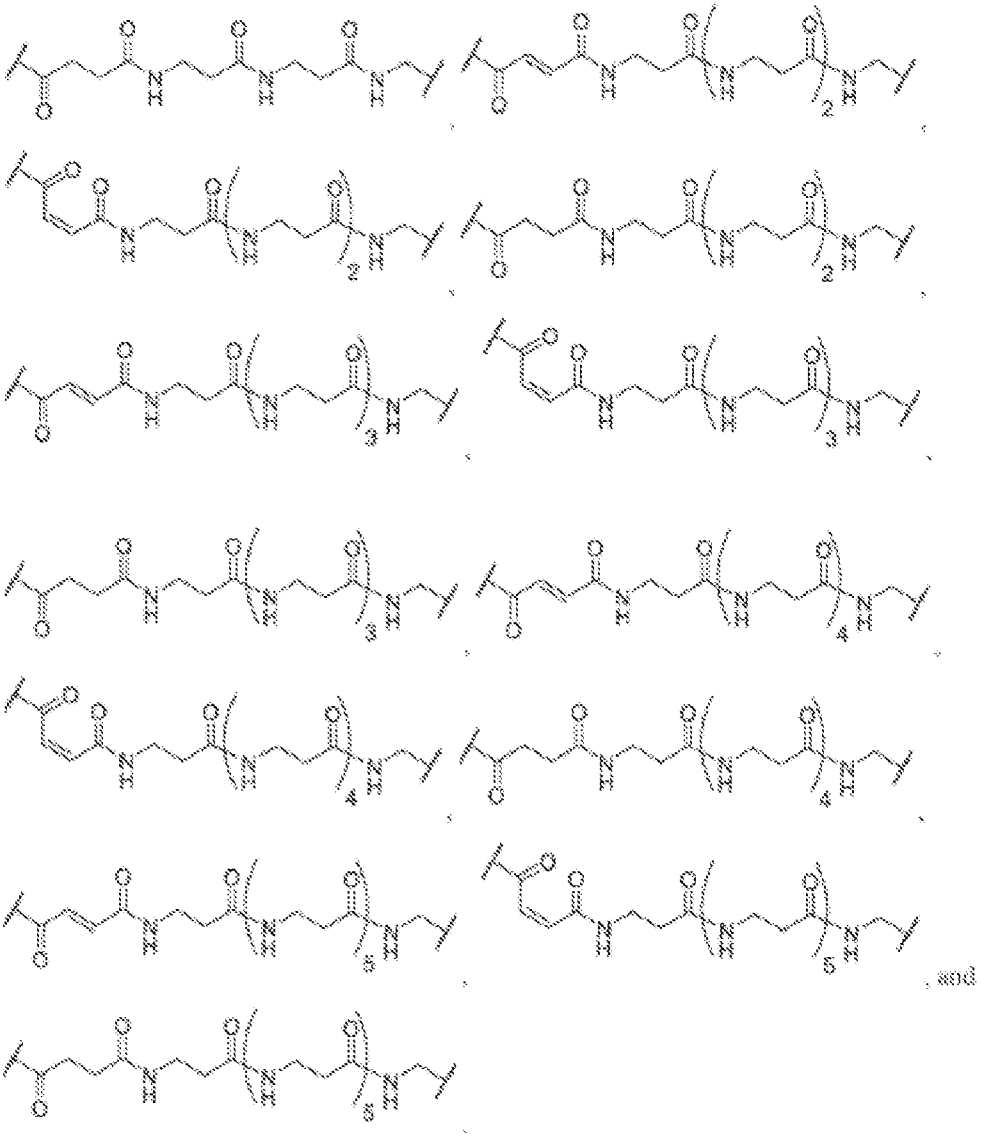


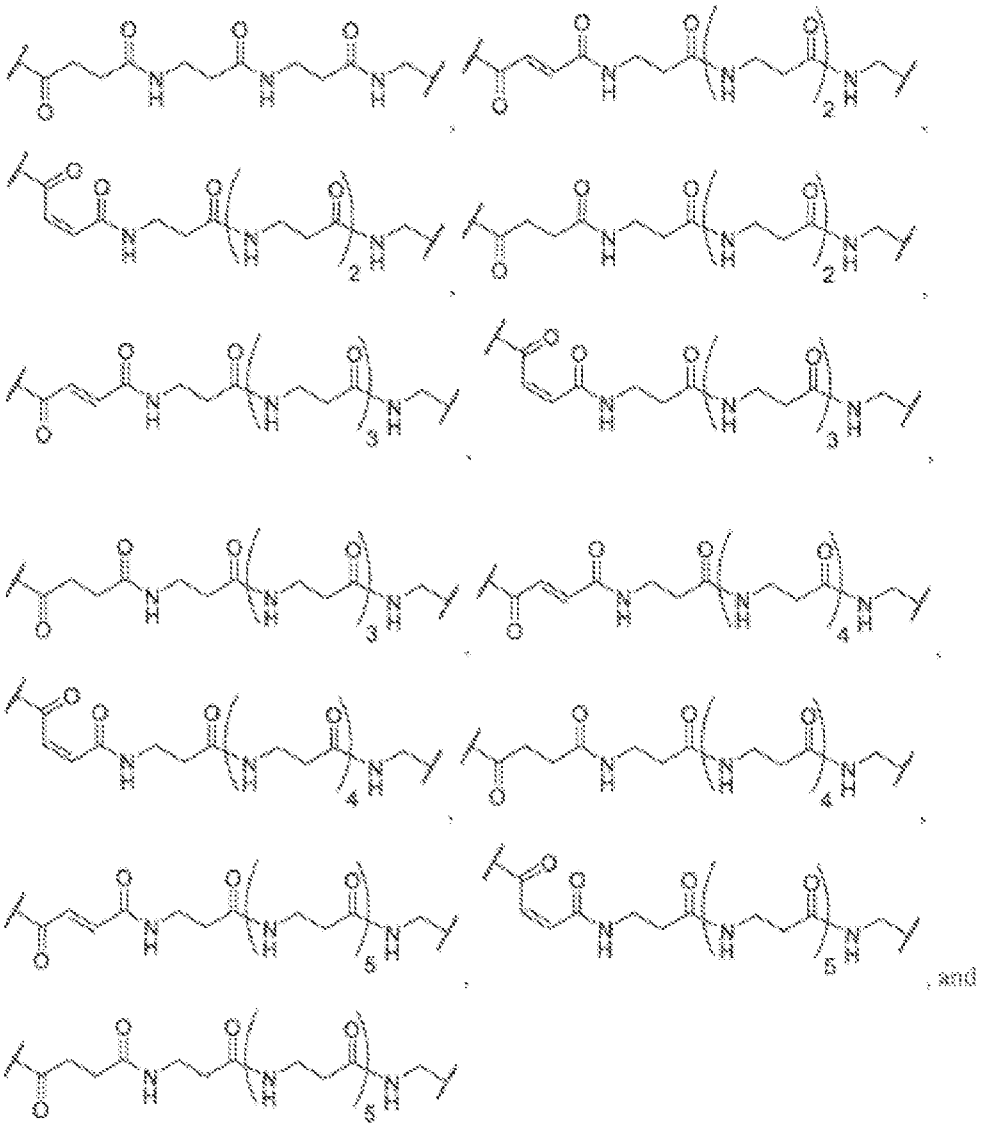
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



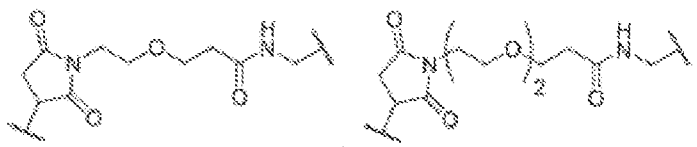
In certain embodiments, in the compound of Formula II, the Linker^A is selected from

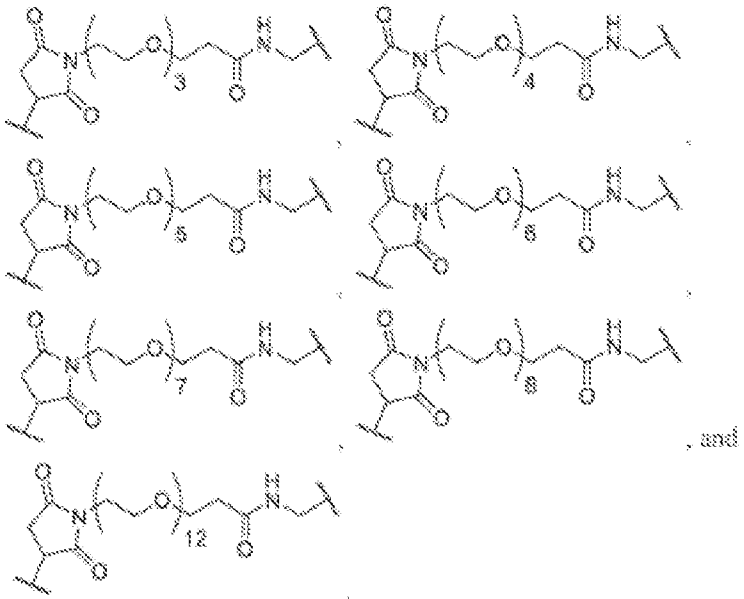
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



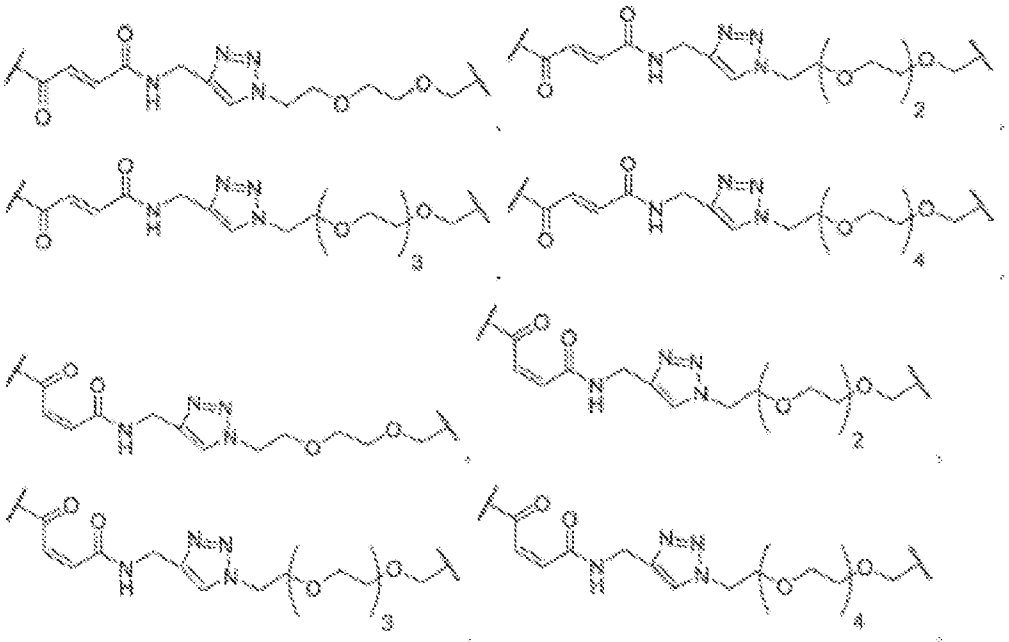


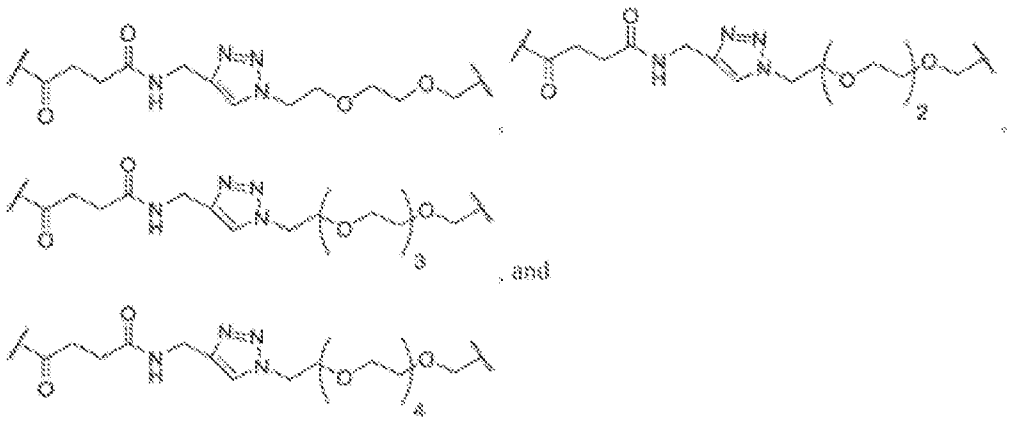
In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from



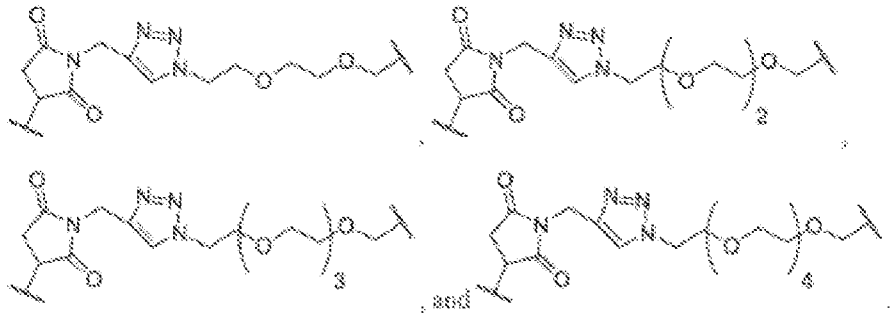


In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from

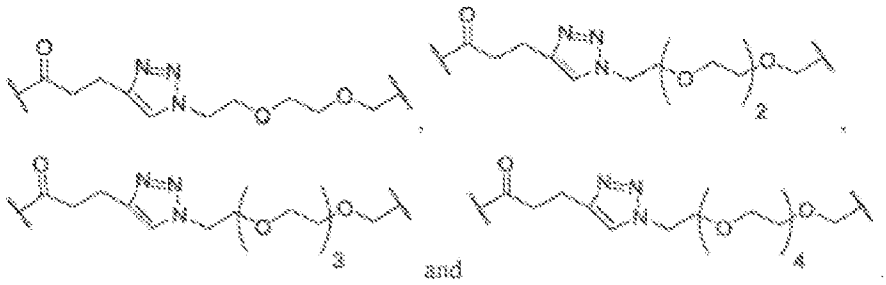




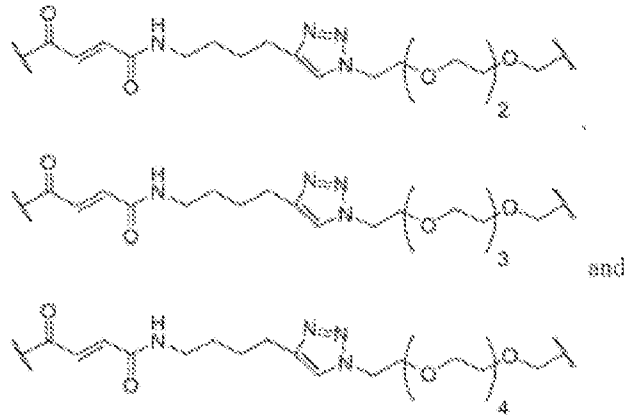
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



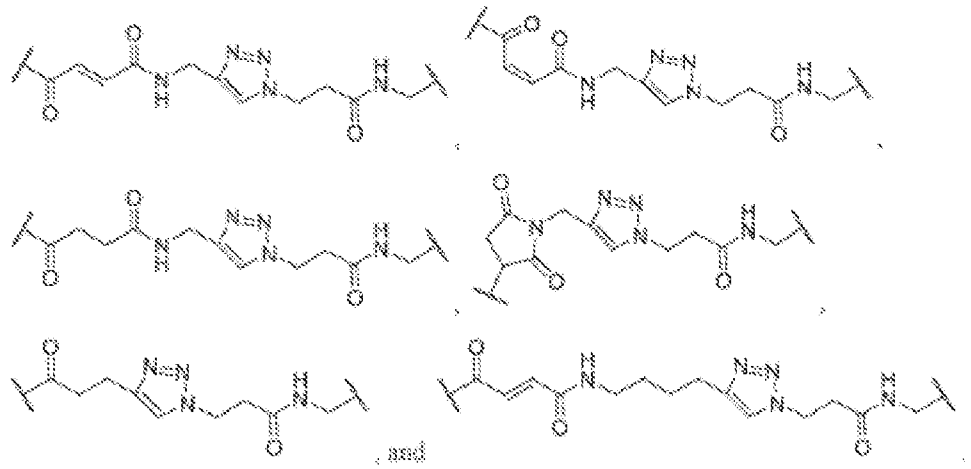
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



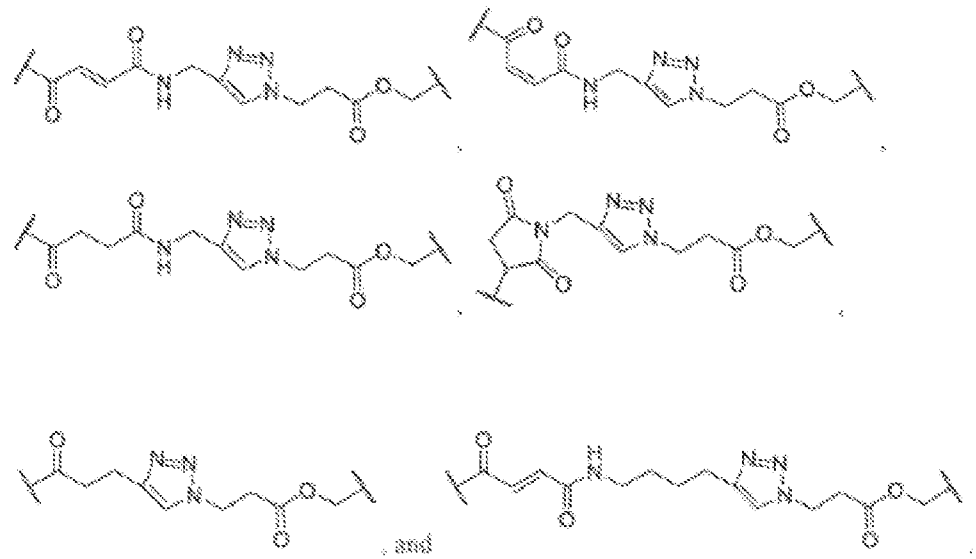
In certain embodiments, in the compound of Formula II, the Linker^A is selected from



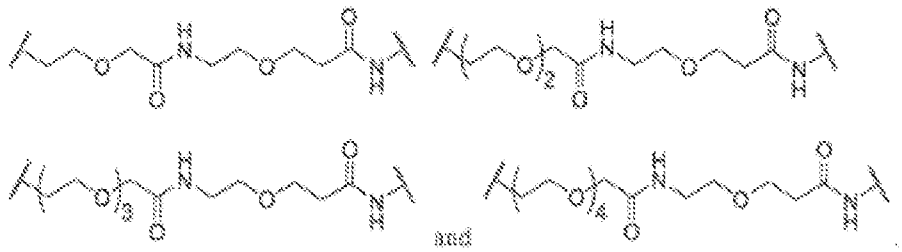
In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from



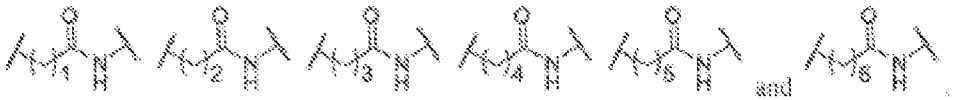
In certain embodiments, in the compound of Formula II, the Linker^{A} is selected from



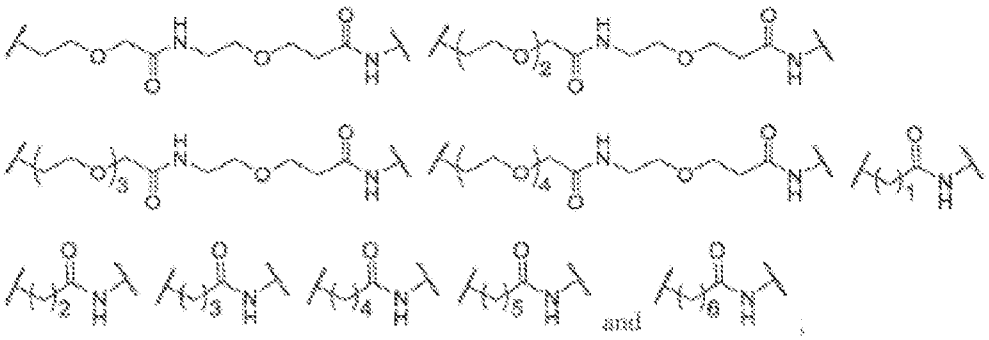
In certain embodiments, in the compound of Formula II, the Linker^{B} is selected from



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

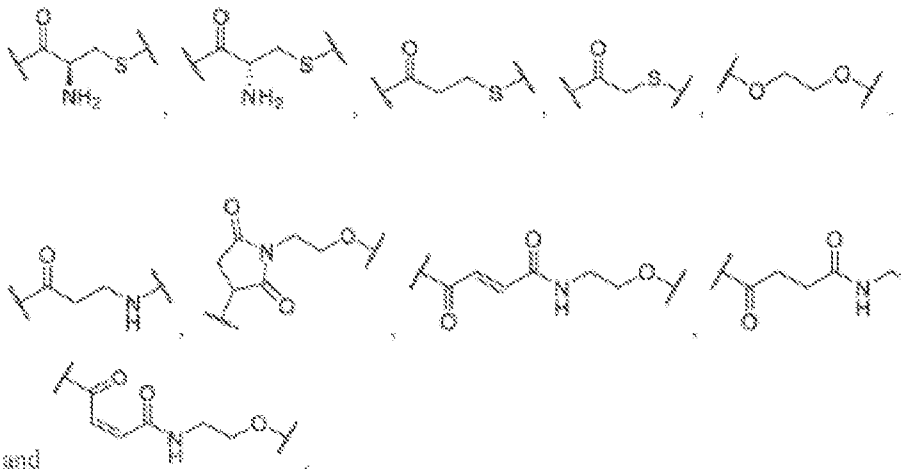


In certain embodiments, in the compound of Formula II, the Linker^B is selected from

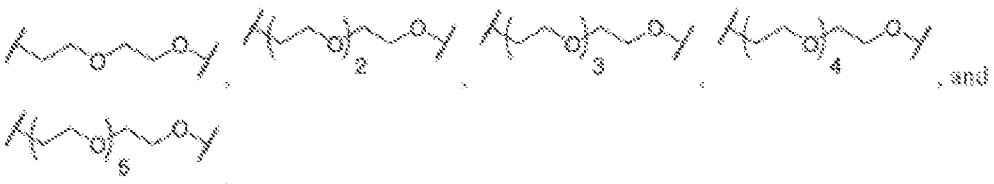


In certain embodiments, in the compound of Formula II, the Linker^B is selected from wherein each is optionally substituted with 1, 2, 3, or 4 substituents substituent selected from R^{21}.

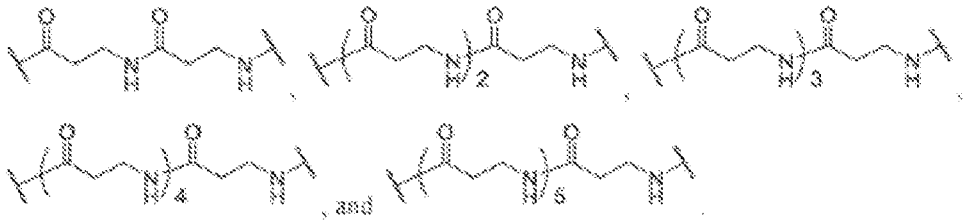
In certain embodiments, in the compound of Formula II Linker^B is selected from:



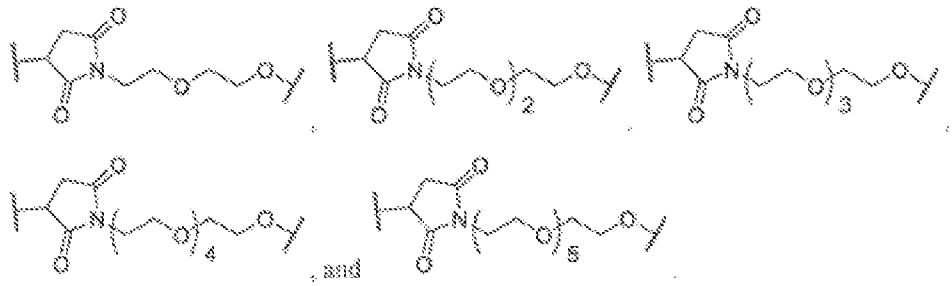
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



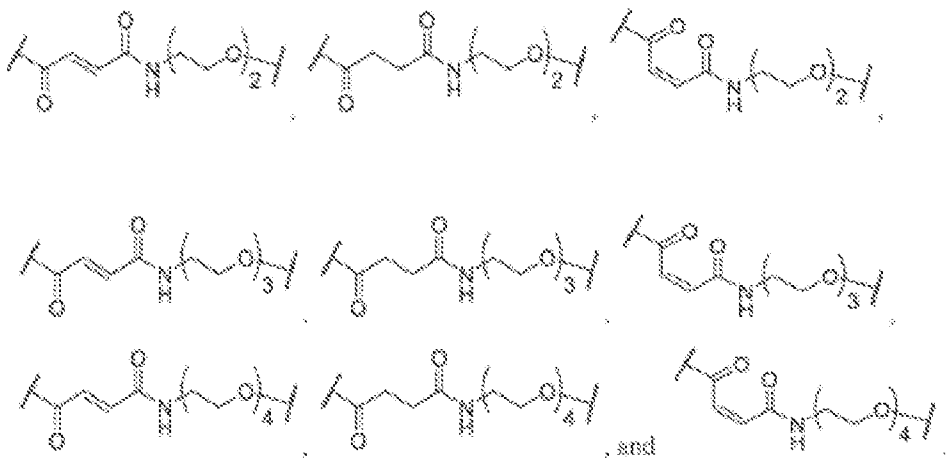
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



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

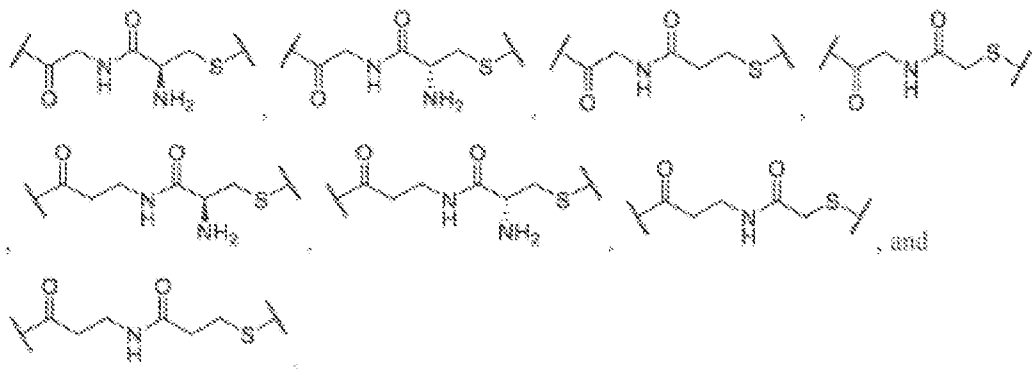


In certain embodiments, in the compound of Formula II, the Linker^B is selected from:

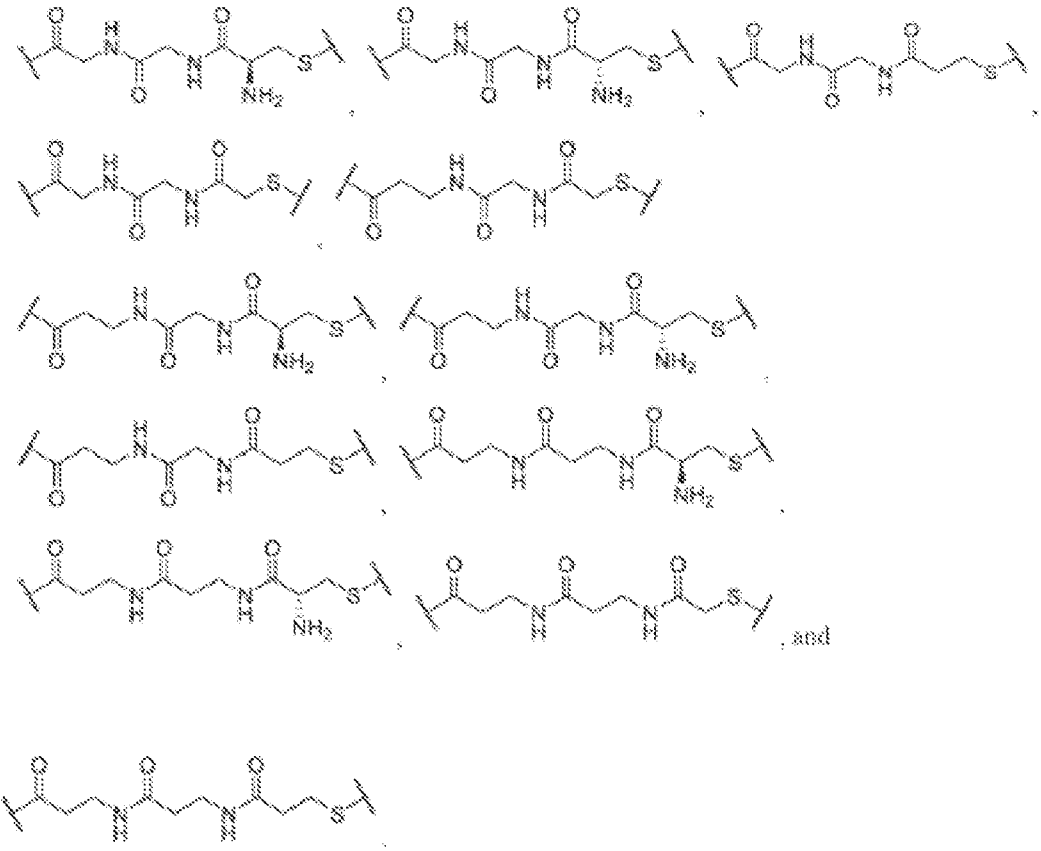


In certain embodiments, in the compound of Formula II, the Linker^B is selected from:

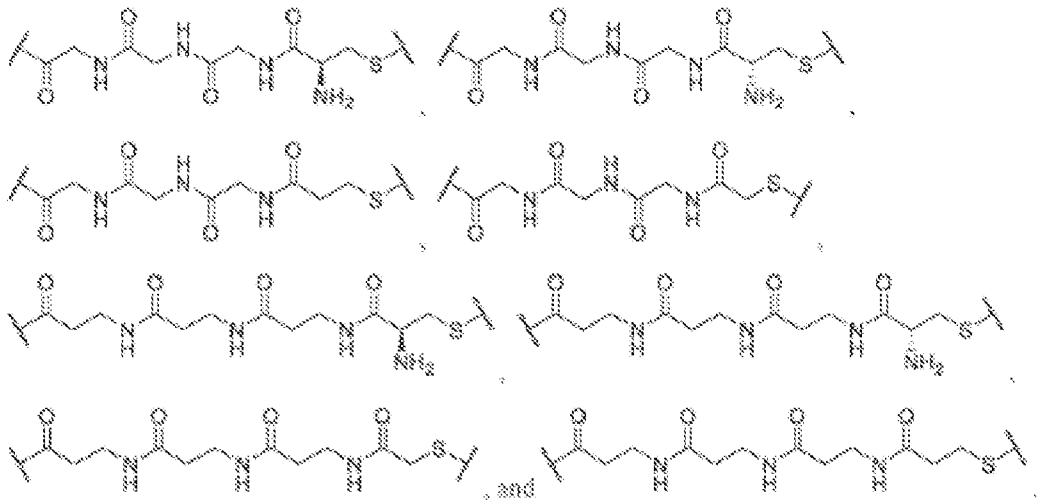
In certain embodiments, in the compound of Formula II, the Linker^B is selected from:



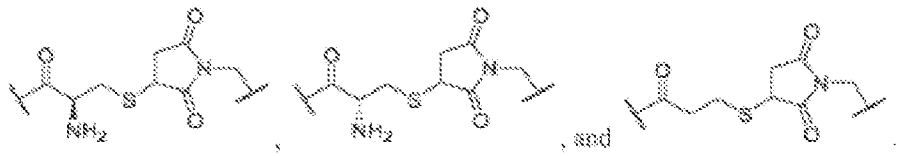
In certain embodiments, in the compound of Formula II, the Linker^{B} is selected from:



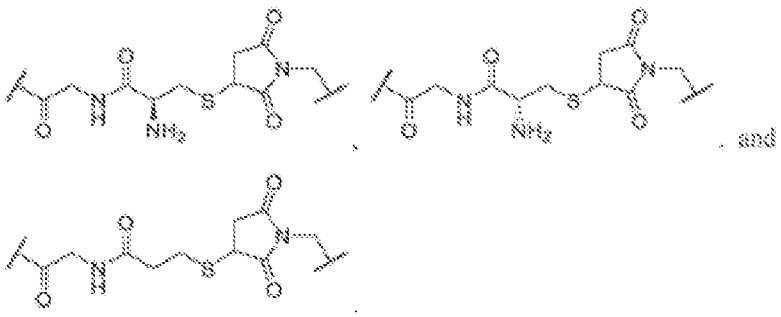
In certain embodiments, in the compound of Formula II, the Linker^{B} is selected from:



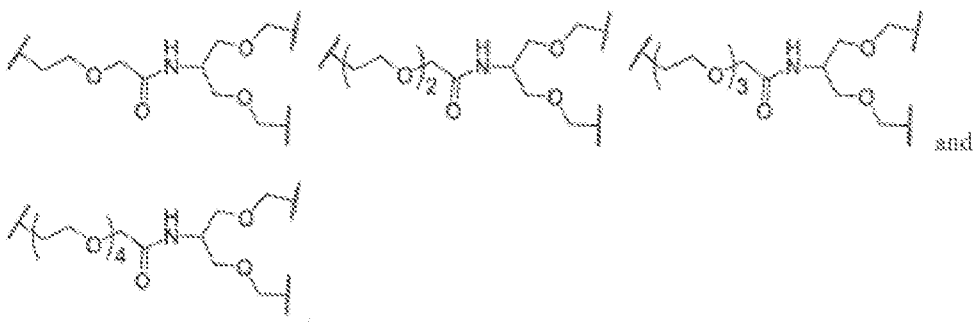
In certain embodiments, in the compound of Formula II, Linker^{B}-Linker^{A} is selected from:



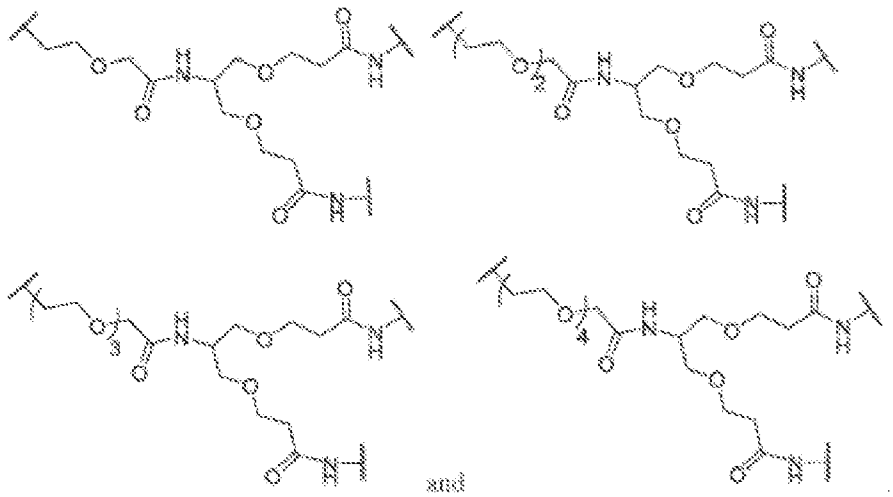
In certain embodiments, in the compound of Formula II, Linker^{B}-Linker^{A} is selected from:



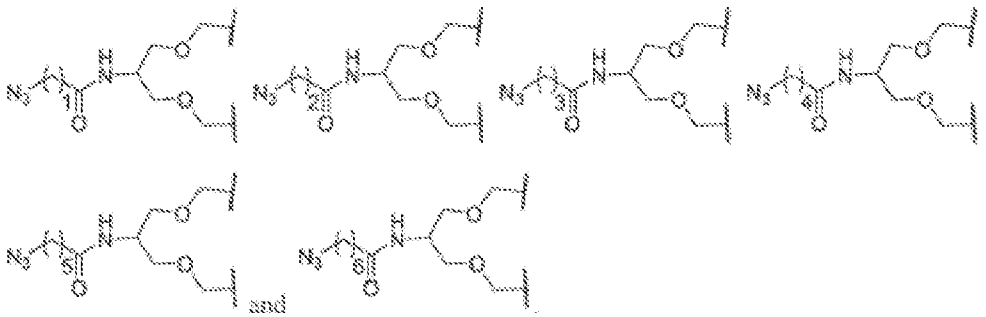
In certain embodiments, in the compound of Formula II, the Linker^{C} is selected from:



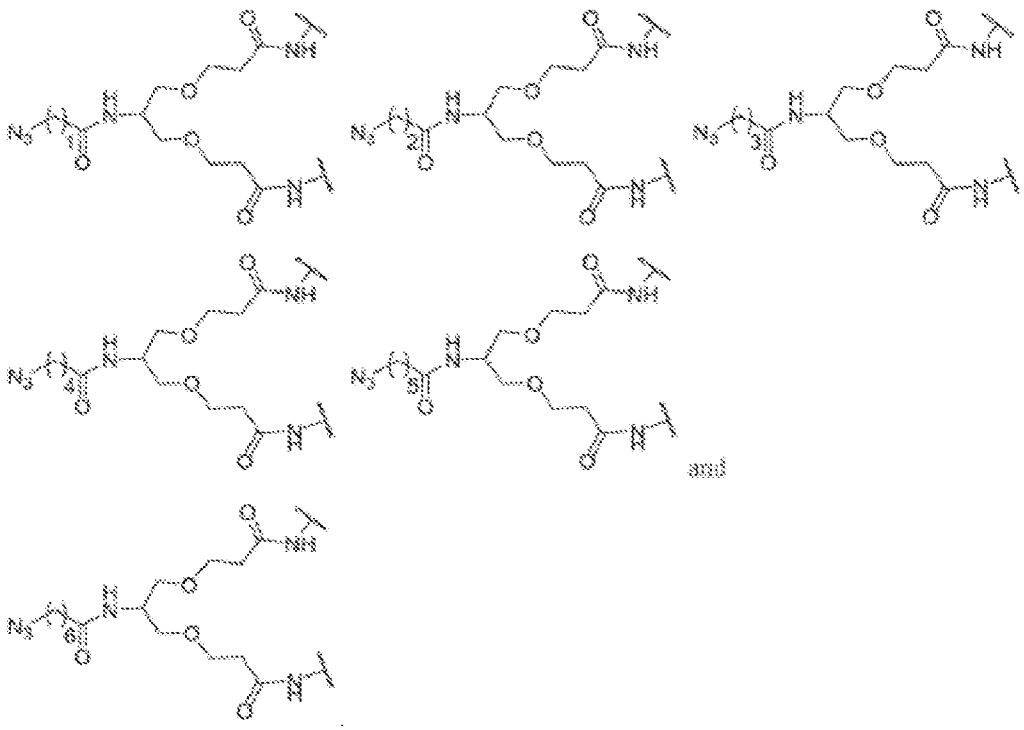
In certain embodiments, in the compound of Formula II, the Linker^{C} is selected from:



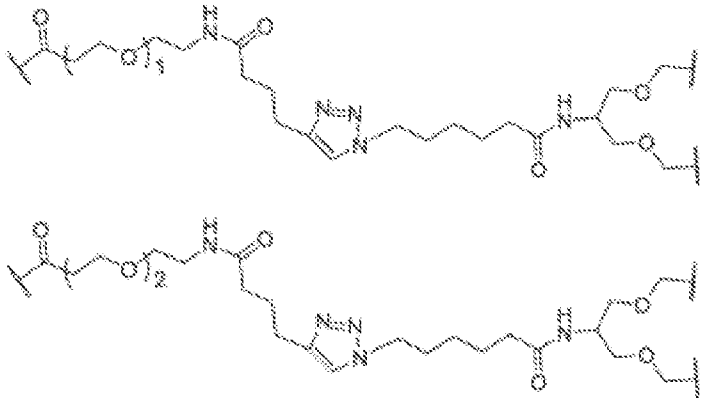
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



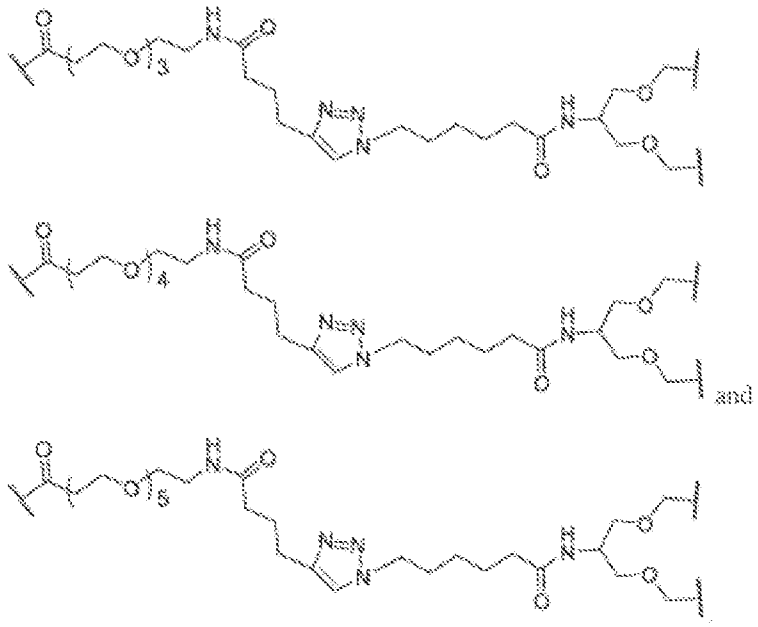
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



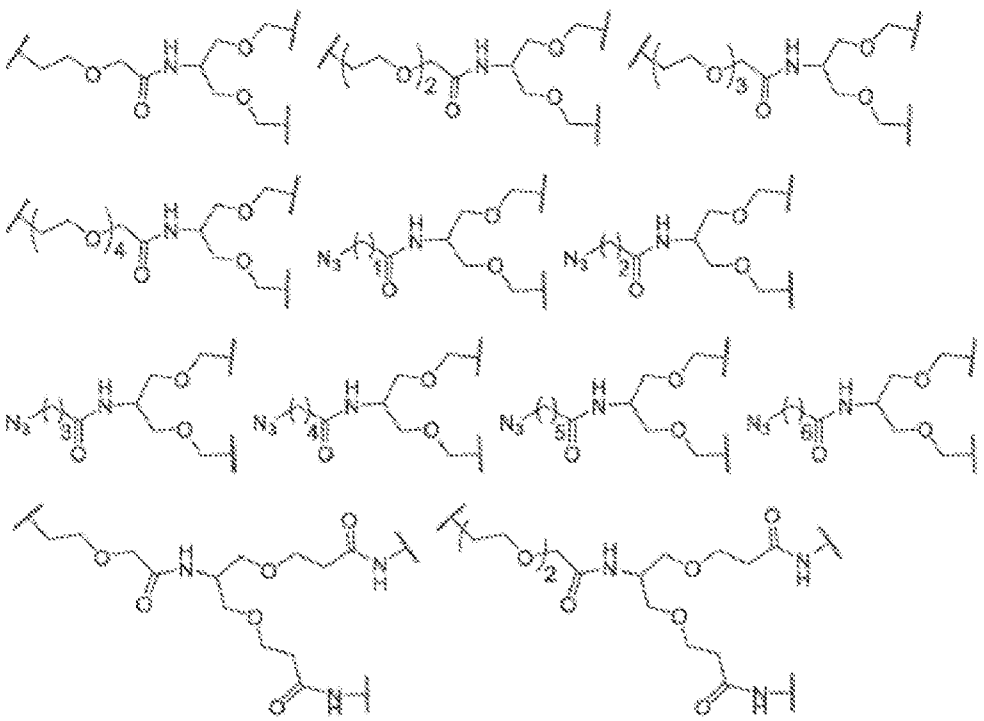
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:

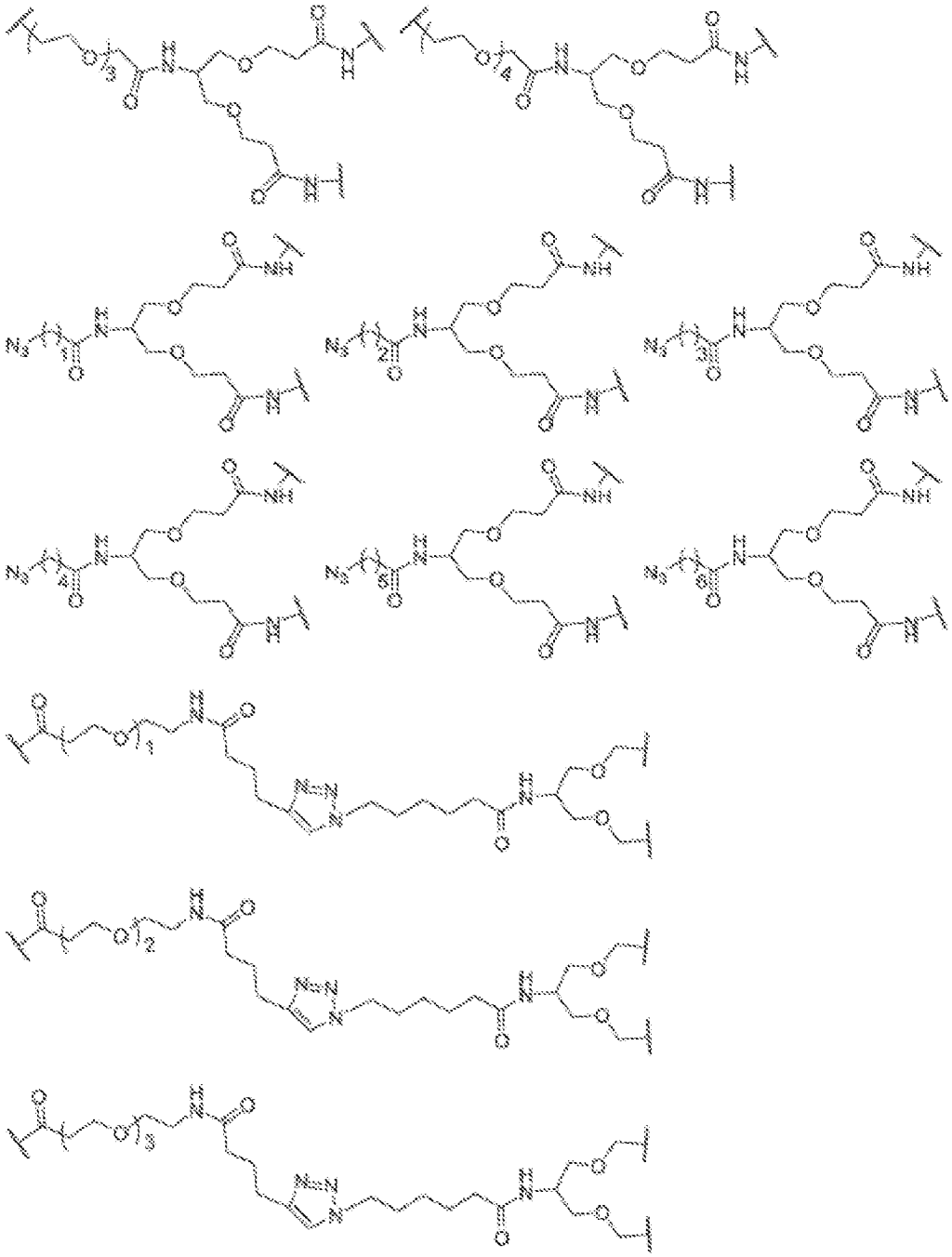


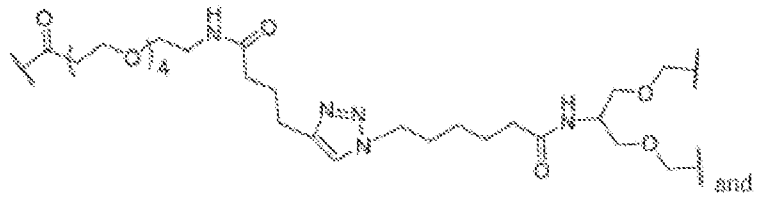
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



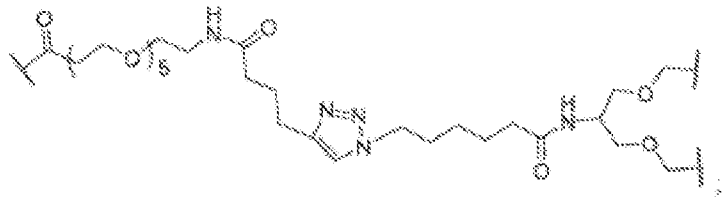
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



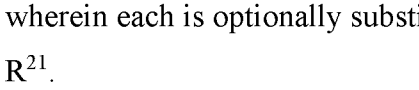




and

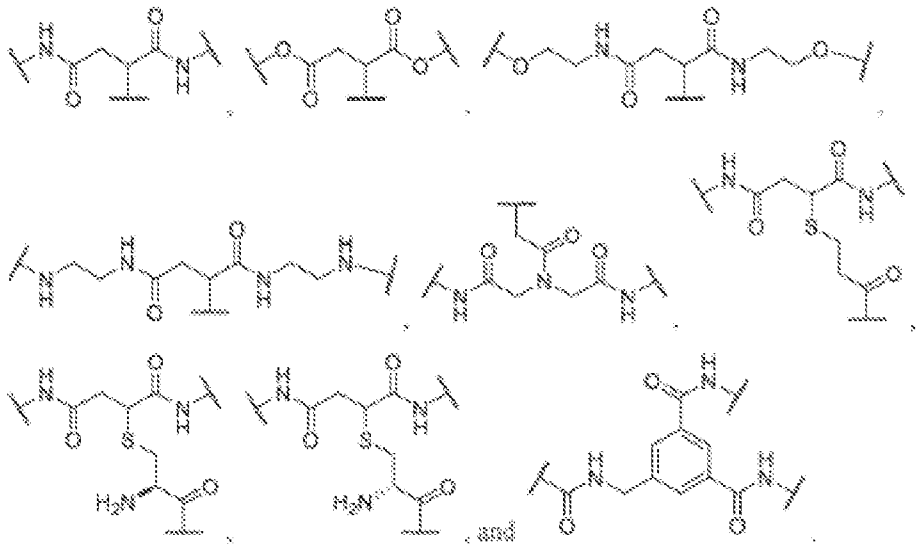


In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



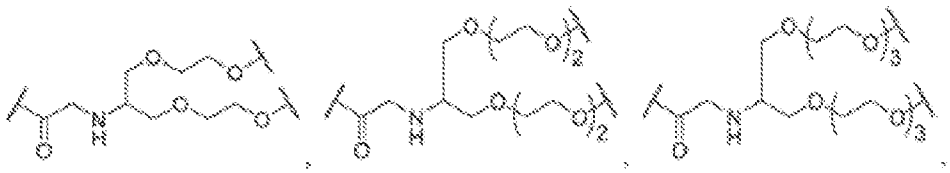
wherein each is optionally substituted with 1, 2, 3, or 4 substituents substituent selected from R^{21}.

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

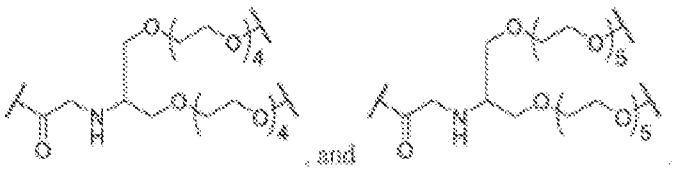


and

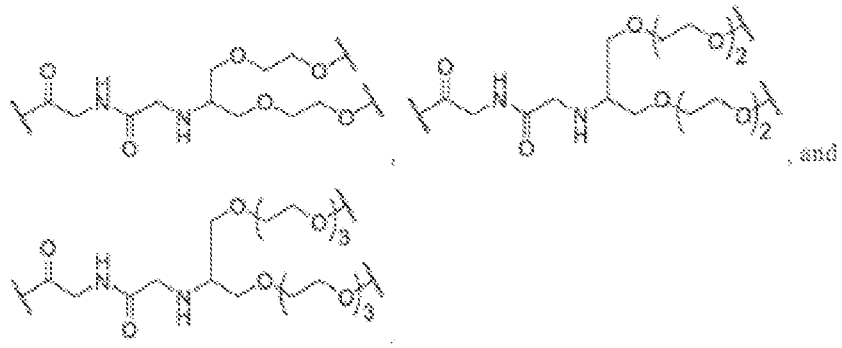
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



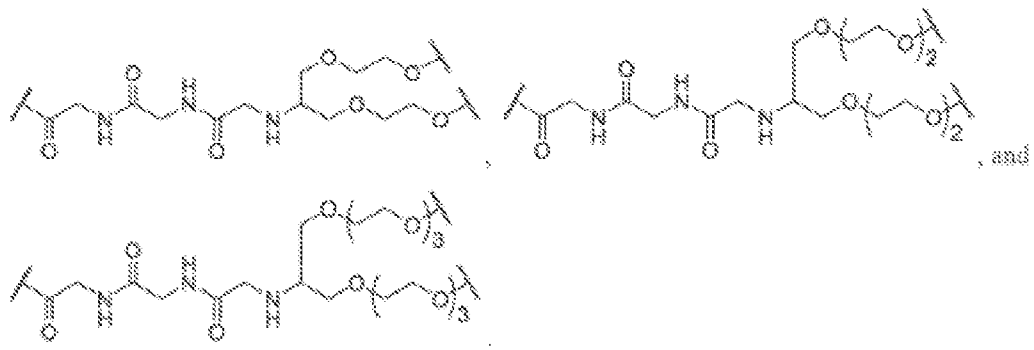
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



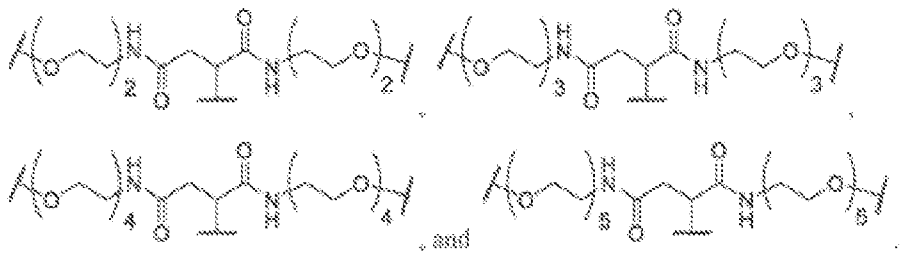
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



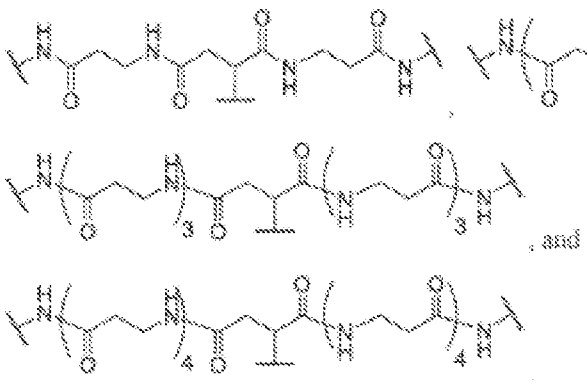
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



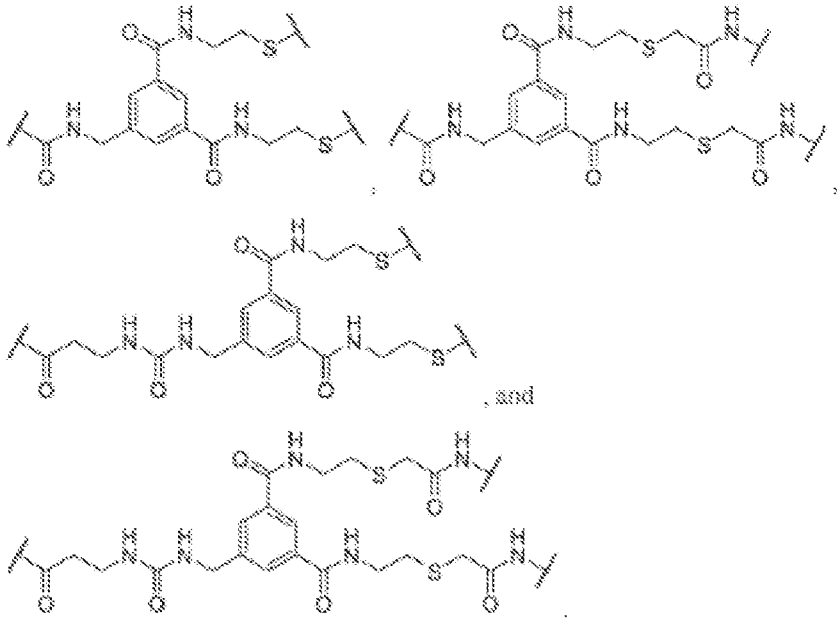
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



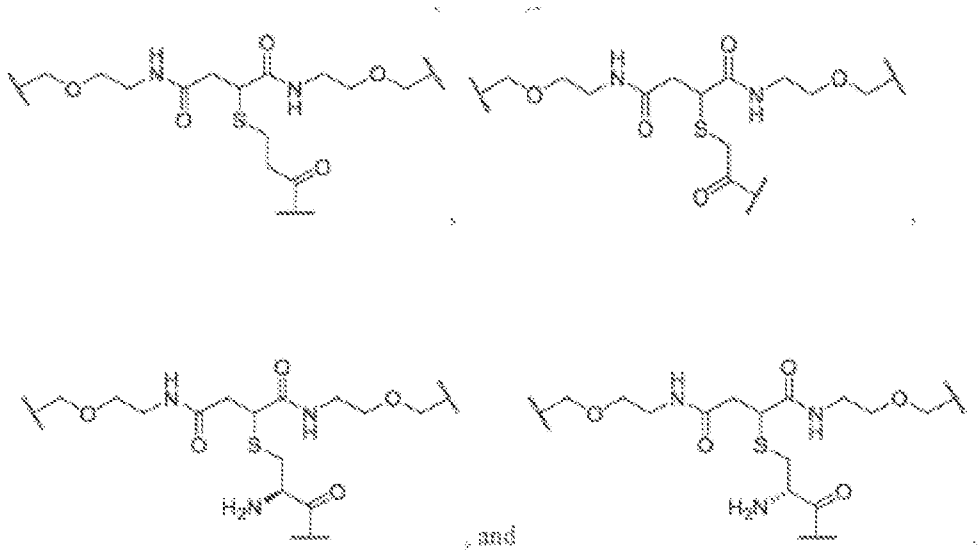
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



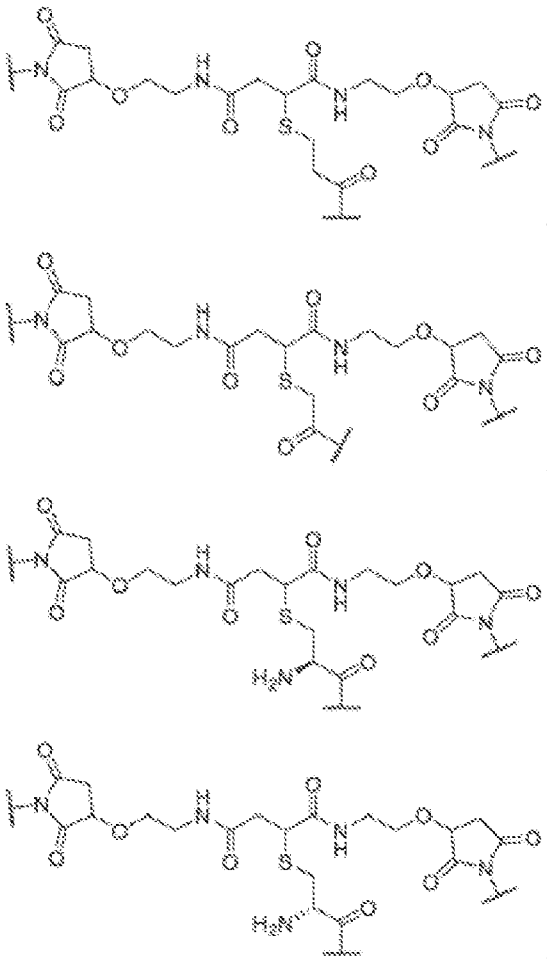
In certain embodiments, in the compound of Formula II, the Linker^C is selected from:



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

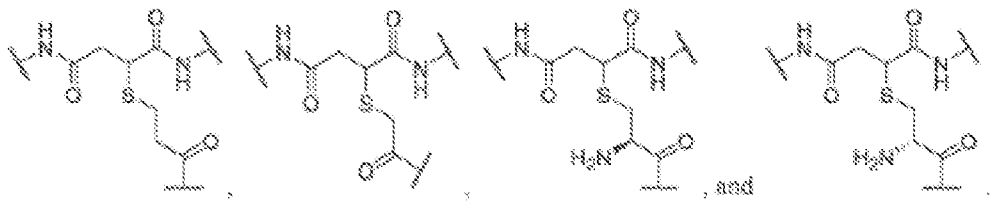


In certain embodiments, in the compound of Formula II, $Linker^C$ -$(Linker^A)_2$ is selected from:



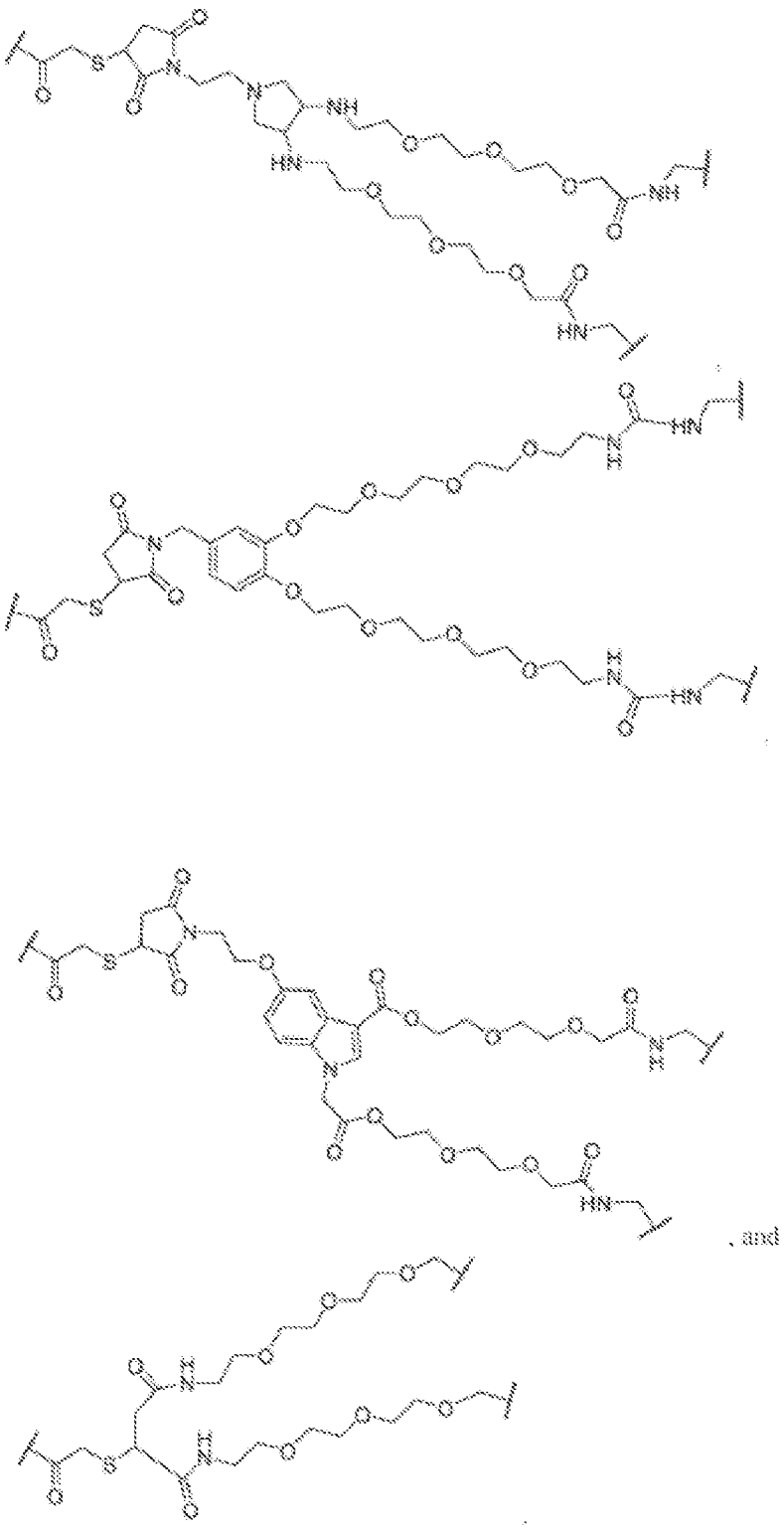
, and

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

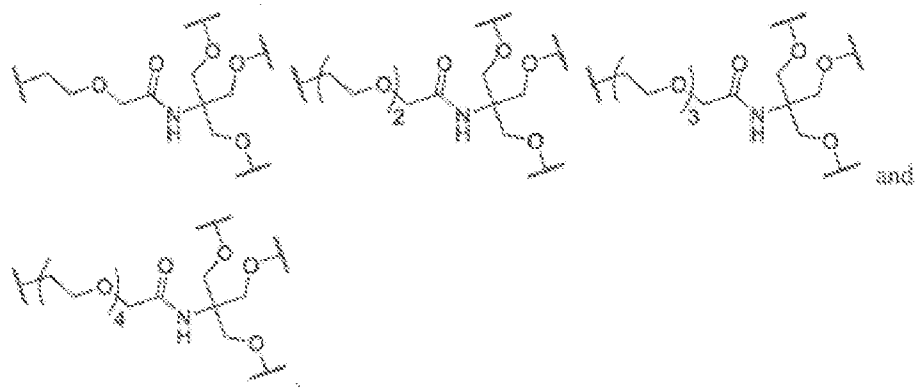


, and

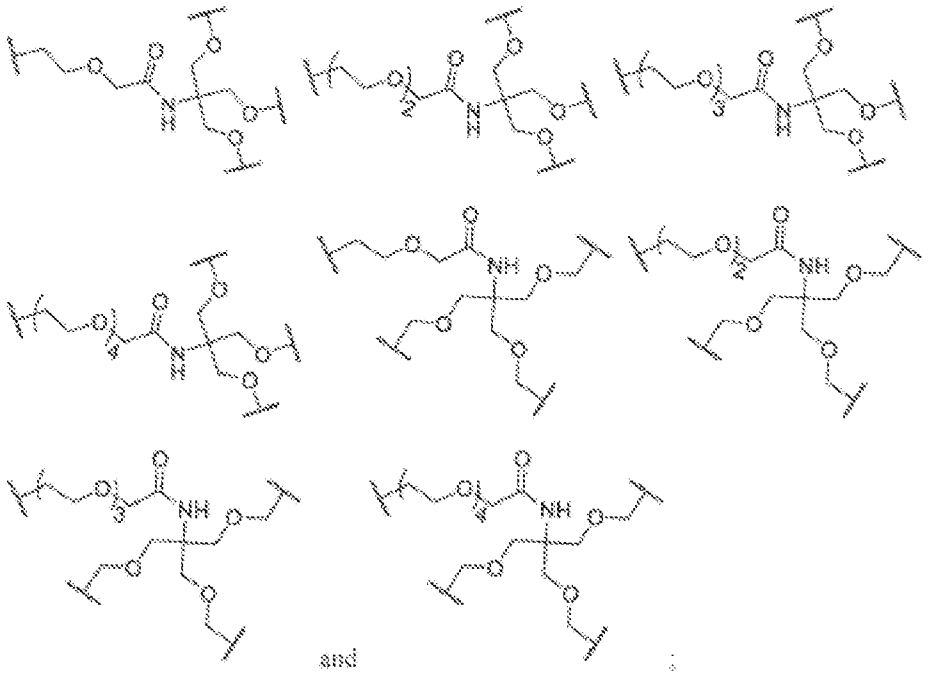
In certain embodiments, in the compound of Formula II, $Linker^C$-$(Linker^A)_2$ is selected from:



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

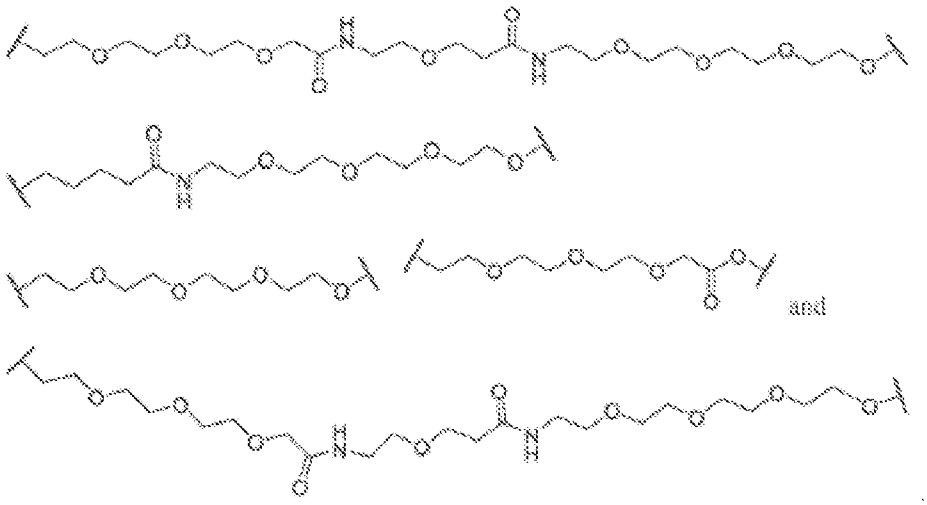


In certain embodiments, in the compound of Formula II, Linker^{D} is selected from:

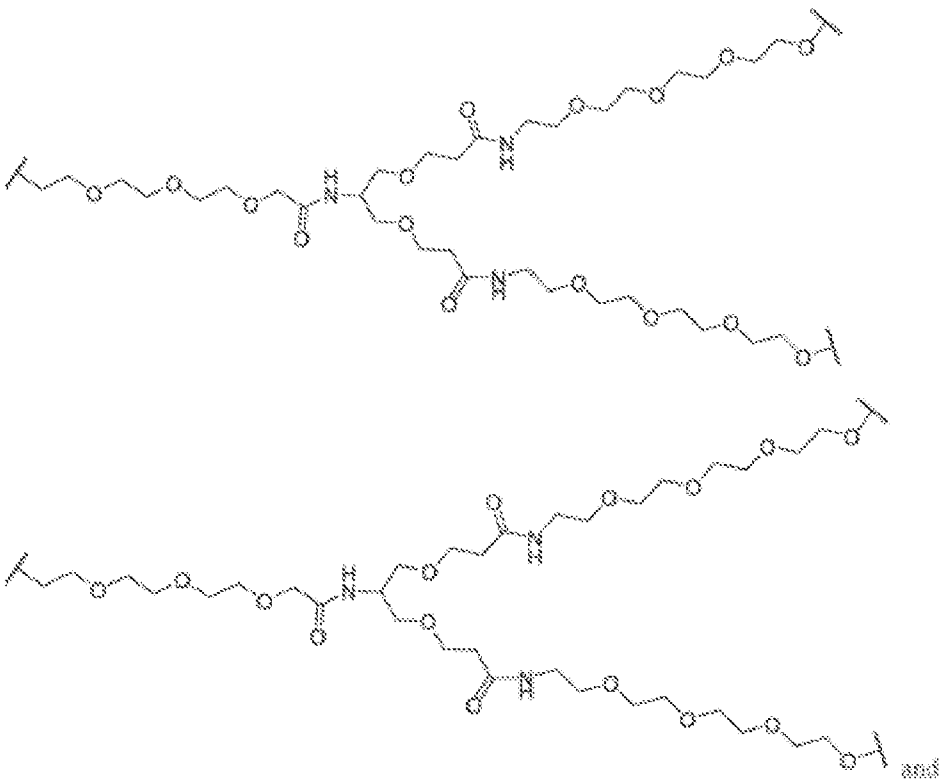


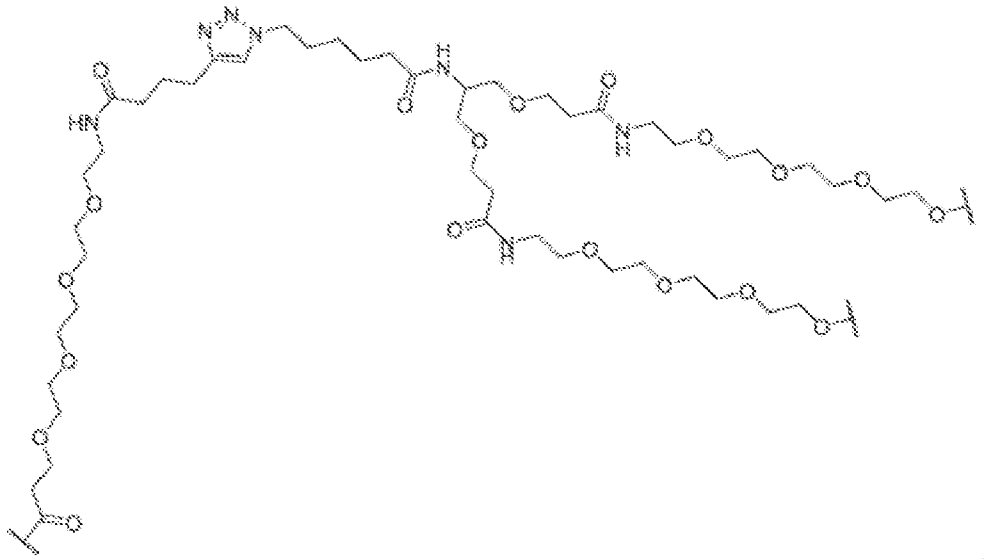
wherein each is optionally substituted with 1, 2, 3, or 4 substituents are selected from R^{21}.

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

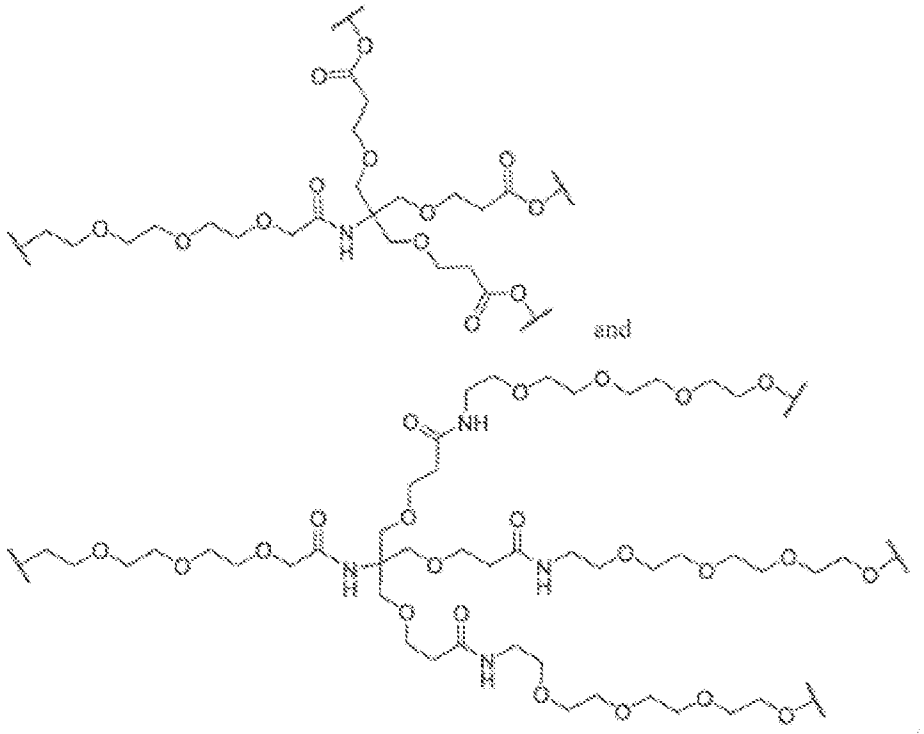


In certain embodiments, in the compound of Formula II, $Linker^{C}$-($Linker^{A}$) is selected from





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



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

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

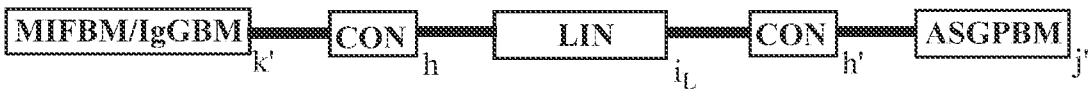
from hydrogen, heteroalkyl, , C0-C6alkyl-cyano, alkyl, alkenyl, alkynyl, haloalkyl, F, Cl, Br, I, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocycloalkyl, haloalkoxy, -O-alkenyl, -O-alkynyl, C0-C6alkyl- OR^6, C0-C6alkyl-SR^6, C0-C6alkyl-NR^6R^7, C0-C6alkyl-$C(O)R^3$, C0-C6alkyl-$S(O)R^3$, C0-C6alkyl- $C(S)R^3$, C0-C6alkyl-$S(O)_2R^3$, C0-C6alkyl-$N(R^8)$-$C(O)R^3$, C0-C6alkyl-$N(R^8)$-$S(O)R^3$, C0-C6alkyl- $N(R^8)$-$C(S)R^3$, C0-C6alkyl-$N(R^8)$-$S(O)_2R^3$ 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-C6alkylN_3, and C0-C6alkyl-O-$S(O)_2R^3$, each of which is optionally substituted with 1, 2, 3, or 4 substituents.

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

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

In various embodiments, the compound of Formula II has the structure of Formula II-A. In various embodiments, in the compound of Formula II-A, [MIFBM] and [IgGBM] are as defined herein.

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

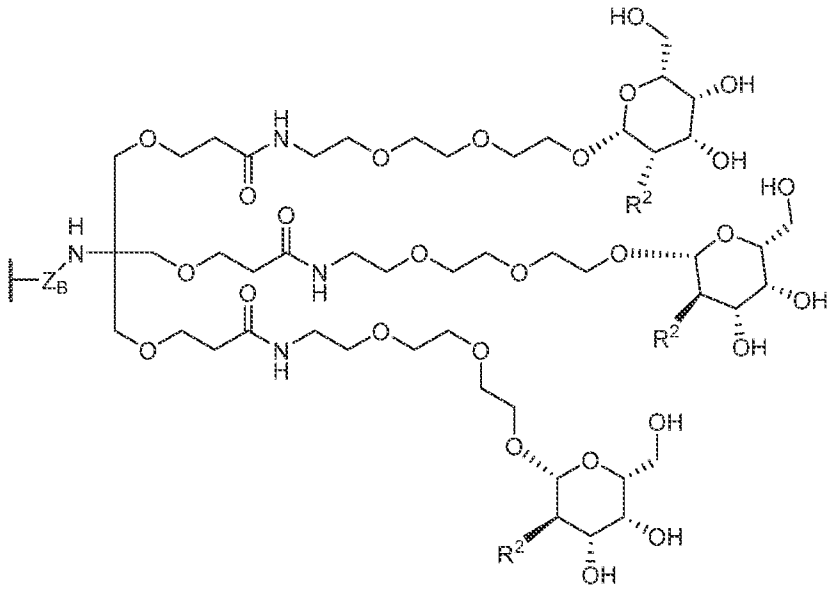


Formula II-A

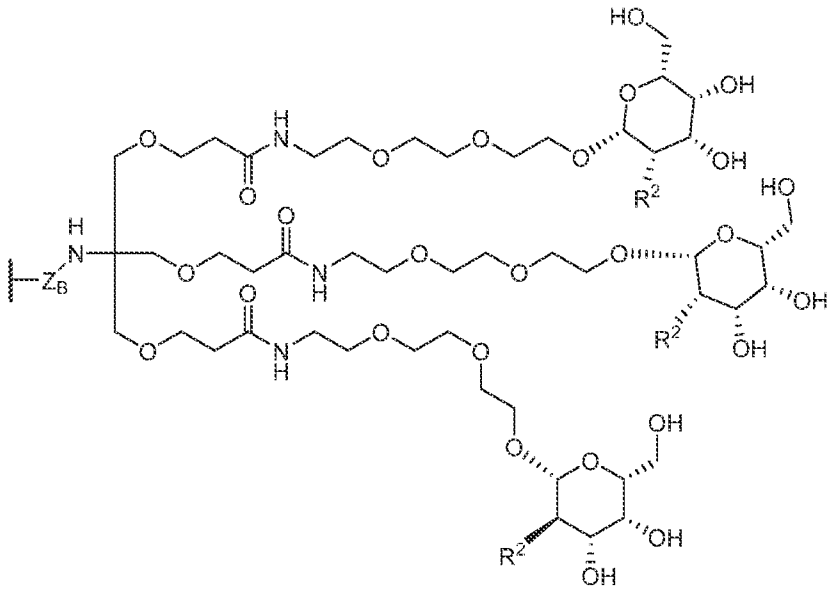
wherein:

[MIFBM/IgGBM] is a MIF or IgG Binding Moiety which binds respectively to circulating MIF or IgG in a subject, each of which is related to a disease state or condition and is to be removed by action of hepatocytes or other cells of the subject;

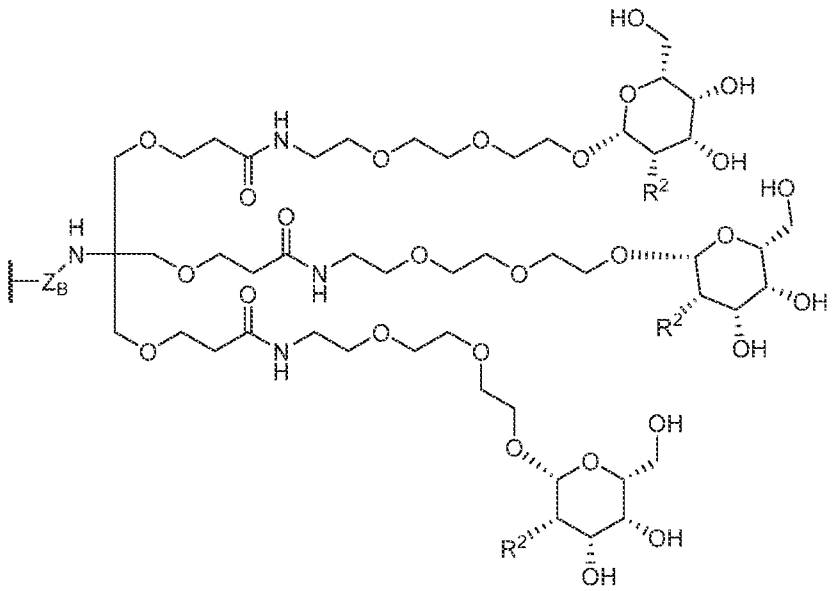
[ASGPBM] is an asialoglycoprotein receptor binding moiety having the structure selected from



,



, or



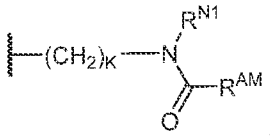
;

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

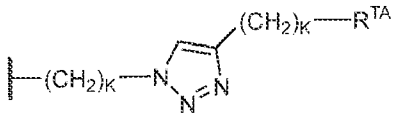
[LIN] is [LINKER] or [LINKER-2], each of which is a chemical moiety having a valency from 1 to 15, which covalently attaches to one or more [ASGPBM] or [CPBM] groups, optionally through a [CON], wherein the [LIN] optionally itself contains one or more [CON] groups;

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

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

R_2 is  ;

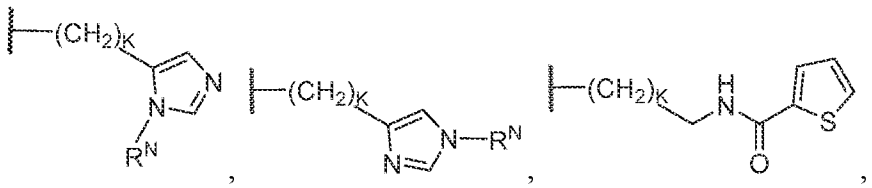
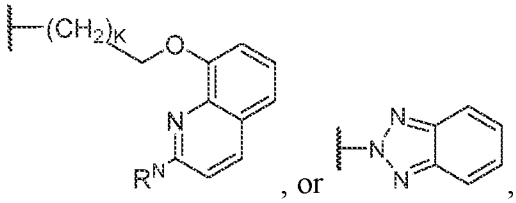
wherein R^{AM} is H, C_1-C_4 alkyl optionally substituted with up to 3 halo groups and one or two hydroxyl groups, $-(CH_2)_KCOOH$, $-(CH_2)_KC(O)O$-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, -O-C(O)-(C_1-C_4 alkyl) optionally substituted with 1-3 halo groups, -C(O)-(C_1-C_4 alkyl)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

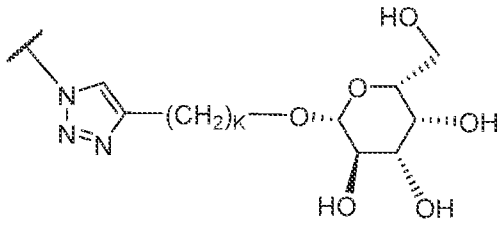
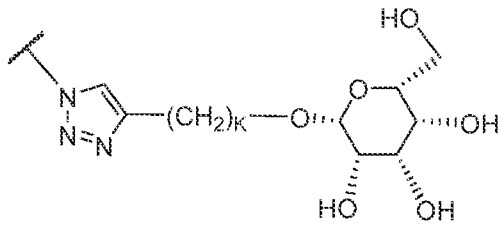
R_2 is  ,

wherein

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

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

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

R^{TA} is  or  .

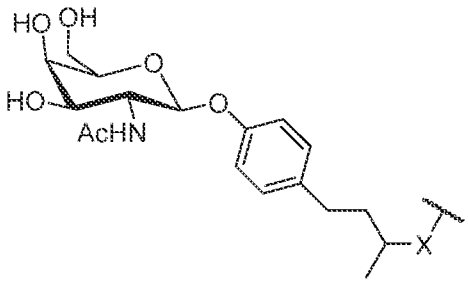
D. Other-Based ASGPR-Binding Moieties

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

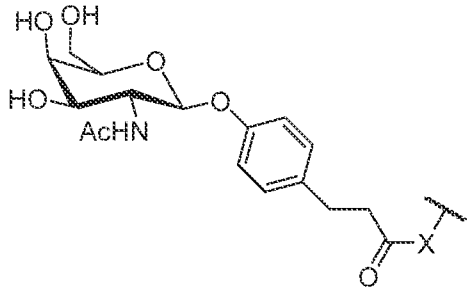
silico and *in vitro* assessment," Carbohydrate Research 509 (2021) 108417, doi: 10.1016/j.carres.2021.108417. The following ASGPR binding moieties are illustrative and not intended to be limiting.

1. GalNAc-Tyrosine Based Moieties

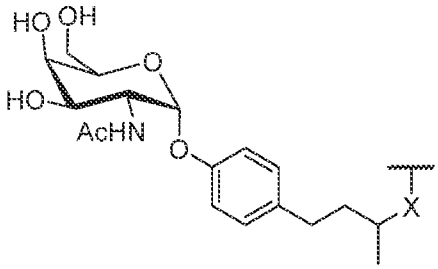
In some embodiments, the ASGPR binding moiety can be a moiety having the structure of M1, M2, M3, or M4, or a combination thereof. In the structures of M1, M2, M3, and M4, X is independently at each occurrence O, NH, or S. In various embodiments, compounds of Formula I or Formula II can have one, two,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



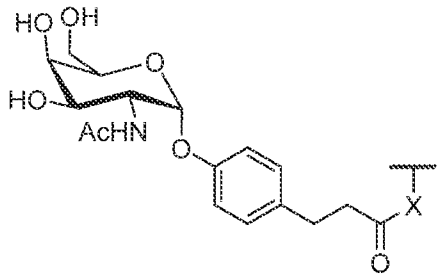
M1



M2



M3

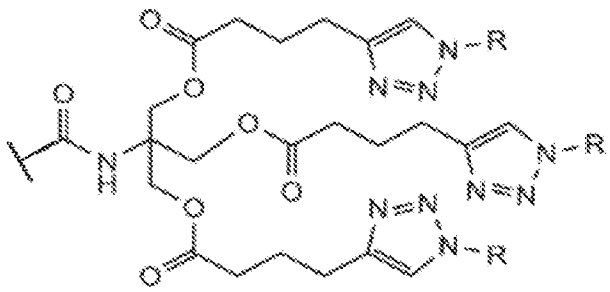


M4.

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., "Enhanced Binding and Reduced Immunogenicity of Glycoconjugates Prepared via Solid-State Photoactivation of Aliphatic Diazirine Carbohydrates," *Bioconjugate Chem*, doi: 10.1021/acs.bioconjchem.0c00555.

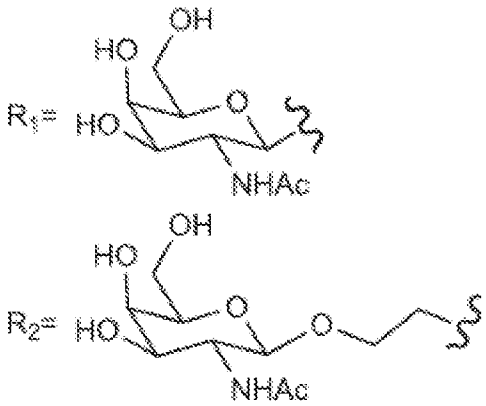
2. Trivalent Triazole-Based Moieties

In some embodiments, 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 R_1 or R_2,

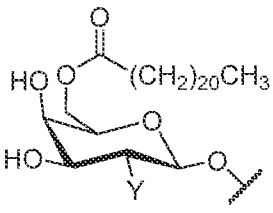


In various embodiments, compounds of Formula I or Formula II contain an ASGPR binding moiety with the structure of M5. In various embodiments, each R in M5 is R_1. In various embodiments, each R in M5 is R_2.

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

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

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

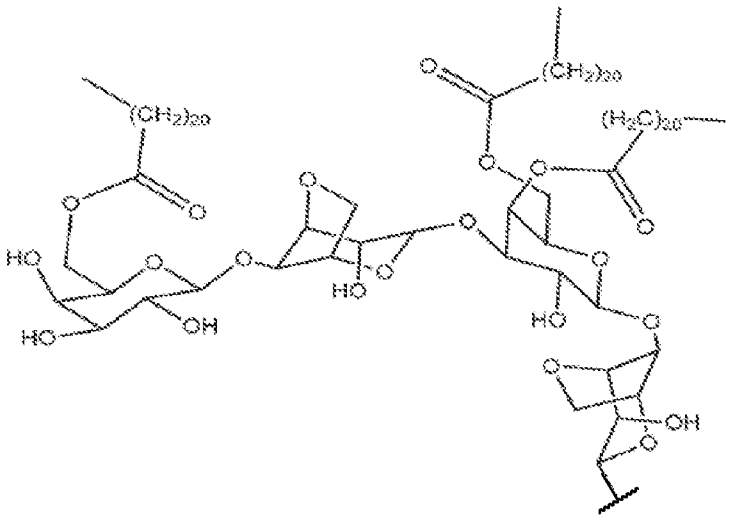


, M7.

In the structure M7, Y is OH or NHAc.

In various embodiments, the ASGPR binding moiety can be the agarose behenic acid

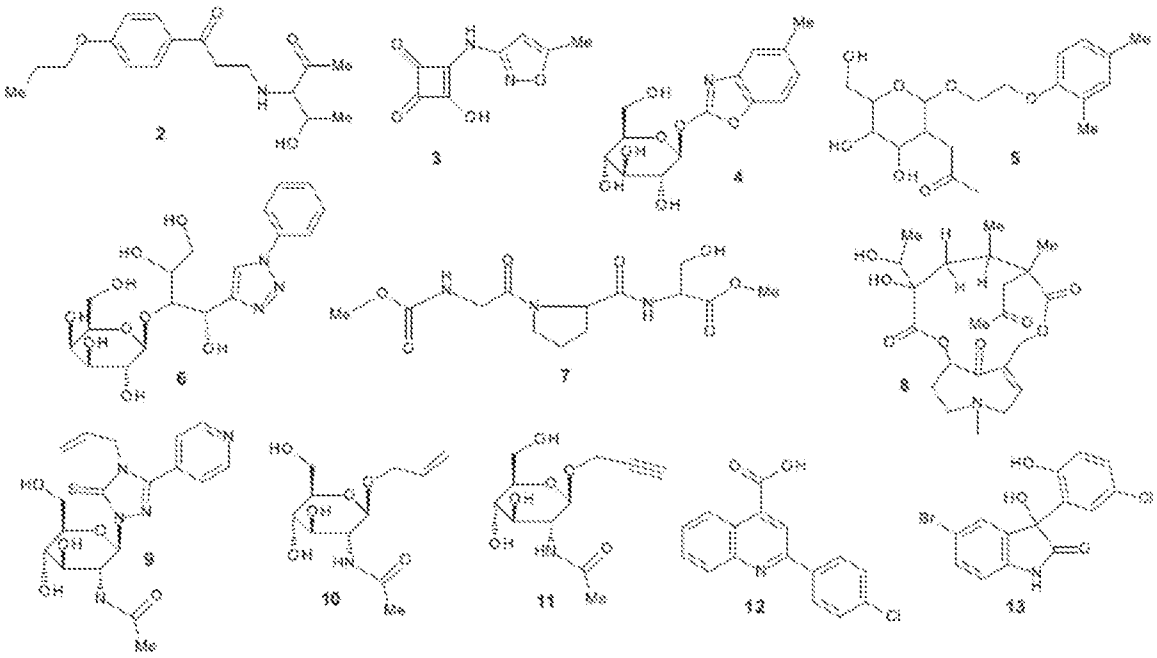
ester-derived moiety M8:

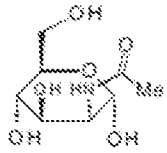


In various embodiments, ASGPR binding moieties M7 and M8 can be conjugated to any suitable [CON], [Linker], or [Linker-2] as described herein and in Dhawan, V., et al., "Polysaccharide conjugates surpass monosaccharide ligands in hepatospecific targeting – Synthesis and comparative in silico and *in vitro* assessment," Carbohydrate Research 509 (2021) 108417, doi: 10.1016/j.carres.2021.108417.

4. Other Small Molecule ASGPR Binding Moieties

In various embodiments, the ASGPR binding moiety can be any of the compounds **2-18** below:





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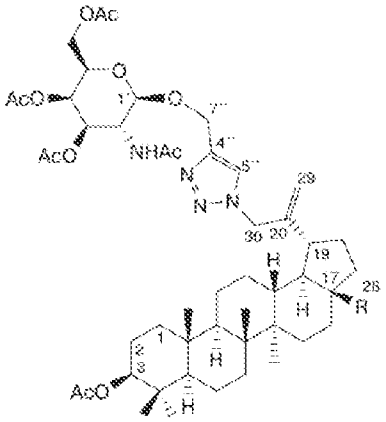

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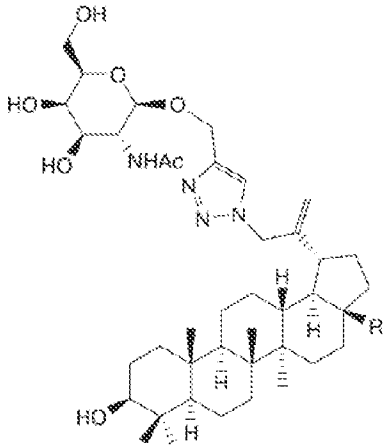
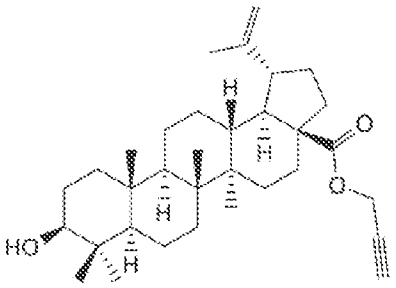


16



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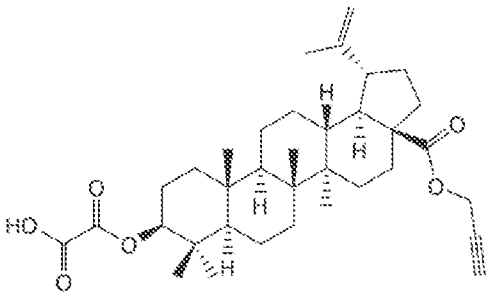


18.

In various embodiments, in compounds **15** and **16**, R is CH_2OAc, COOH, or CH_2OH. 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: 10.2174/1567201813666160719144651; Olshanova, A. S., et al., "Synthesis of a new betulinic acid glycoconjugate with N-acetyl-D-galactosamine for the targeted delivery to hepatocellular carcinoma cells," *Russian Chemical Bulletin, International Edition*, Vol. 69, No. 1, pp. 158—163, January 2020; Yamansarov, E. Yu., et al., "New ASGPR-targeted ligands based on glycoconjugated natural triterpenoids," Russian Chemical Bulletin, International Edition, Vol. 68, No. 12, pp. 2331—2338, December 2019. Compounds **2-18** can be attached through any suitable reactive group contained therein. Without limitation, compounds 2-13 can be attached to a 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 [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, oxidations, alkylations, rearrangement reactions (e.g. Claisen, Cope, etc.), and the like.

The term "pharmaceutically acceptable salt" or "salt" is used throughout the specification to describe a salt form of one or more of the compositions herein which are presented to increase the solubility of the compound in saline for parenteral delivery or in the gastric juices of the patient's gastrointestinal tract in order to promote dissolution and the bioavailability of the compounds. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium, magnesium and ammonium salts, among numerous other acids well known in the pharmaceutical art. In some embodiments, sodium and potassium salts are used as neutralization salts of carboxylic acids and free acid phosphate containing compositions according to the present 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.

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 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

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, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab (Arzerra), zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111 , 131-I-TM-601 , ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001 , IPdR$_1$ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311 , romidepsin, ADS- 100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901 , AZD-6244, capecitabine, L-Glutamic acid, N -[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11 , CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)-indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t) 6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH $_2$ acetate [$C_{59}H_{84}N_{18}Oi_4$ -($C_2H_4O_2$)$_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine,

chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevac, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291 , squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, irinotecan, topotecan, doxorubicin, docetaxel, vinorelbine, bevacizumab (monoclonal antibody) and erbitux, cremophor-free paclitaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001 , ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11 , dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa and darbepoetin alfa, vemurafenib among others, including immunotherapy agents such as IDO inhibitors (an inhibitor of indoleamine 2,3-dioxygenase (IDO) pathway) such as Indoximod

(NLG-8187), Navoximod (GDC-0919) and NLG802, PDL1 inhibitors (an inhibitor of programmed death-ligand 1) including, for example, nivolumab, durvalumab and atezolizumab, PD1 inhibitors such as pembrolizumab (Merck) and CTLA-4 inhibitors (an inhibitor of cytotoxic T-lymphocyte associated protein 4/cluster of differentiation 152), including ipilimumab and tremelimumab, among others.

In addition to anticancer agents, a number of other agents may be coadministered 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 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 MIF binding moiety (MIFBM) or antibody binding moiety and ASGPR binding moiety selectively bind to liver cells and through that binding, facilitate the introduction of the MIFBM group into hepatocytes which bind the ASGPRBM selectively, where, the MIF protein, inside the hepatocyte is degraded and removed from circulation. Thus, compounds according to the present disclosure both bind to MIF proteins and remove the MIF proteins from circulation resulting in a dual action which is particularly effective for treating disease states and conditions.

Pharmaceutical compositions comprising combinations of an effective amount of at least one compound disclosed herein, often a bi-functional chimeric compound (containing at least one MIFBM group or antibody binding moiety and at least one ASGPRBM) according to the present 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.

In some embodiments, the compositions of the present disclosure are 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. In some embodiments, 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 as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this 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 depending upon the host and disease treated, the particular mode of administration. In some embodiments, the compositions are formulated to contain between about 0.05 milligram to

about 1.5 grams, from 0.1 milligram to 1 gram, 0.5 milligrm to 750 milligrams, more often about 1 milligram to about 600 milligrams, and even more often about 10 milligrams to about 500 milligrams of active ingredient, alone or in combination with at least one additional compound which may be used to treat cancer, prostate cancer or metastatic prostate cancer or a secondary effect or condition thereof.

Methods of treating patients or subjects in need for a particular disease state or condition as otherwise described herein, especially cancer, comprise administration of an effective amount of a pharmaceutical composition comprising therapeutic amounts of one or more of the novel compounds described herein and optionally at least one additional bioactive (e.g., anti-cancer, anti-inflammatory) agent. 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 0.01, 0.1, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90 or 100 mg/kg of patient/day or in some embodiments, greater than 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 200 mg/kg of the novel compounds can be administered to a patient receiving these compositions.

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

A patient or subject (e.g. a human) suffering from an autoimmune disease, an inflammatory disease or cancer can be treated by administering to the patient (subject) an effective amount of a chimeric/bi-functional compound according to the present 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, exemplary 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 assocated with these disease states and/or conditions. This treatment can also be administered in conjunction with other conventional therapies, such as radiation treatment or surgery for cancer.

The present compounds, alone or in combination with other agents as described herein, can be administered by any appropriate route, for example, orally, parenterally,

intravenously, intradermally, subcutaneously, or topically, in liquid, cream, gel, or solid form, or by aerosol form.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount for the desired indication, without causing serious toxic effects in the patient treated. An exemplary 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, such as 0.1 to 100 mg/kg per day, such as 0.5 to about 25 mg per kilogram body weight of the recipient/patient per day. Some exemplary dosages will range from about 0.01-3% wt/wt in a suitable carrier.

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

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

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

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

composition.

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

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

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

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

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

In certain embodiments, the active compounds are prepared with carriers that will

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

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

Chemical Synthesis

FIGURES 1, 7, and 13 attached hereto identifies exemplary 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 are based upon an MIF, anti-DNP IgG, or IgG binding moiety to which is covalently attached an ASPGR group such as GN_3 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.

FIGURE 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.

FIGURE 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.

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

FIGURE 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 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.

FIGURE 20 shows the synthesis of a higher affinity bicylic 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 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 paraformaldehyde gives the tetraol intermediate, which is cyclized in strong acid (H2SO4/water) to give the bicyclic azide ligand.

FIGURE 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 trifuloroacetic anhydride. The esters are hydrolyzed with strong base (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 a mesylated azdio 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.

FIGURE 22 shows the synthesis of the MIF-targeting linker to a monovalent linker, which is synthesized through analagous 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.

FIGURE 23 shows the synthesis of the di-carboxylic acid MIF targeting motif, which is synthesized as described in previous figures.

FIGURE 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.

FIGURE 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).

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

FIGURE 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 the bifunctional compounds.

FIGURE 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 evelvated 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.

FIGURE 29 describes the synthesis of the bifunctional molecule MIF-NVS-PEGn-GN3 through HBTU-mediated coupling in DMF of the ASPGR-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.

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

FIGURE 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.

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

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

FIGURE 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 analine carboxylic acid intermediate. Further steps were carried out as described for previous molecules.

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

FIGURE 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.

FIGURE 37 shows the synthesis of triazine-GN3. Cyanuric chloride was treated with (4-(methoxycarbonyl)phenyl)methanaminium in THF and diisopropylethlamine 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.

FIGURE 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.

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

FIGURES 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 analagous methods described above as set forth in the attached figures.

FIGURE 44 shows the synthesis of compound MIF-18-3. Tri-acyl galactal was 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-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 acetal with dimethoxypropane and camphorsulfonic acid at elevated temperature. The remainder of the synthesis was carried out as described for previous molecules.

FIGURE 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 ehtrate to give the allyl intermediate. Treatment with pivaloyl chloride in pyridine gave a 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.

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

FIGURE 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 propiolic acid in methanol in the presence of THPTA, copper sulfate, water, and sodium ascorbate. All other reactions are performed as described above.

FIGURE 48 shows the synthesis of compound MIF-16-3, which was synthesized

using procedures analogous to compounds described above.

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

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

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

FIGURES 52-66 show the synthesis of a number of MIF-binding compounds with various ASGPRBM moieties. These are synthesized through methods analogous to those laid out above.

Examples

The instant specification further describes in detail by reference to the following experimental examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless so specified. Thus, the instant specification should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Proper protein section 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(1). As proteins age, terminal sialic acid residues are removed by circulating endogenous glycosydases(2). This natural protein aging process unmasks galactose and N-acetylgalactose (GalNAc) residues, which bind the asialoglycoprotein receptor (ASGPR) on the surface of hepatocytes(3-5).

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(6, 7). 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 (12); the ASGPR is recycled back to the hepatocyte surface(13). Endocytosed proteins are trafficked to late endosomes, which are fused with lysosomes. Lysosomal proteases then degrade endocytosed proteins, permanently removing them from circulation(14).

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 (15). Genetic depletion or antibody neutralization of MIF has been shown to have positive results in models of sepsis(16), multiple schlorosis(17), rheumatoid arthritis(18), and burn recovery(21). A bifunctional molecule for degrading cicrulating MIF that takes advantage of ASGPR as an entryway for proteins into the endosomal-lysosomal degradation pathway was proposed. The bicyclic ASGPR-binding molecules in MIF-AcF2 and MIF-AcF3 have been reported previously as high affinity binders for the ASGPR (22, 23).

Example 1: Biological Data

In Example 1, exemplary compounds according to some embodiments were 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 exemplary 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 sometimes ranges from 1-12, such as 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.

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 cm^2). 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-GN_3 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-GN_3, 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-GN_3.

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.

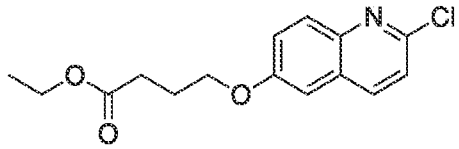
FIGURE 15 shows that FcIII-GN3 mediates the localization of IgG to late endosomes in HepG2 cells. Experiment performed as described above.

Example 2: Experimental Chemistry

In Example 2, synthesis and characterization of exemplary compounds according to some embodiments will be described.

Example 2-1. MIF binding molecule (Figure 13)

Example 2-1-1: MIF-1



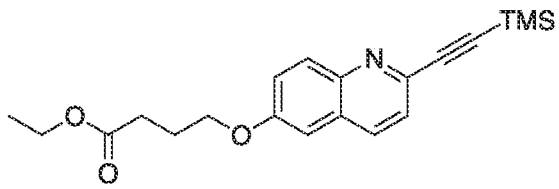
2-chloroquinolin-6-ol (1.00 g, 5.57 mmol) and K_2CO_3 (1.53 g, 11.1 mmol, 2.0 eq) were dissolved in DMF (20 mL). Ethyl bromobutyrate (1.63 g, 1.2mL, 8.35 mmol, 1.5eq) was then added and the mixture stirred at 80° for 12 hours. The reaction was diluted into ethyl acetate and washed with water (2x) and 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.

^{1}H 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

Example 2-1-2: MIF-2



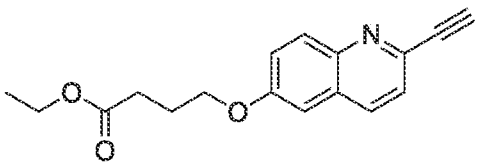
Compound 30 (1.52 g, 5.17 mmol) was dissolved in THF (20 mL) and triethylamine (2.88 mL, 20.7 mmol, 4 eq). Copper (I) iodide (49.0 mg, .258 mmol, .05 eq), $Pd(PPh_3)_2Cl_2$ (181 mg, .258 mmol, .05 eq), and TMS-acetylene (1.07 mL, 762 mg, 7.75 mmol, 1.5 eq) were then added and the reaction was stirred 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.

^{1}H 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

Example 2-1-3: MIF-3



Procedure

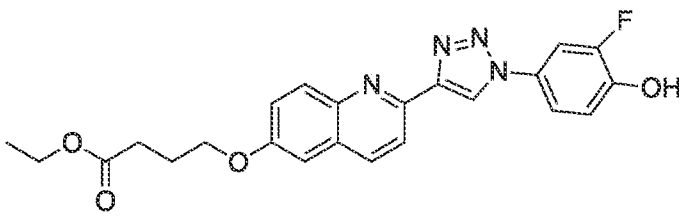
Compound 31 (1.57 g, 4.42 mmol) was dissolved in DCM (45 mL) and TBAF (5.3 mL, 1M in THF, 5.30 mmol, 1.2 eq) was added dropwise. After 1 minute of stirring 10% citric acid (50 mL) was added and the reaction stirred for 30 minutes. The organic phase was washed with water (1x), dried, and evaporated to give compound 32, which was used in the next step without further purification.

^{1}H 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, 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).

CNMR: ^{13}C NMR (151 MHz, cdcl$_3$) 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

Example 2-1-4:* MIF-*4



2-fluoro-4-iodophenol (126 mg, .529 mmol) and sodium azide (38 mg, .528 mmol, 1.0 eq) were dissolved in DMSO (2.5 mL) and stirred for two hours at 70°. Compound 32 (150 mg, .529 mmol, 1 eq), trans-N,N'-dimethylcyclohexane-1,2-diamine (11 mg, .079

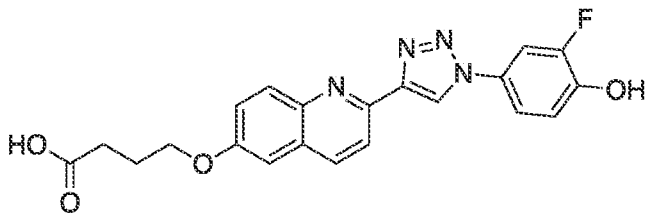
mmol, .15 eq), sodium ascorbate (10 mg, .053 mmol, .1 eq), copper (I) iodide (15 mg, .079 mmol, .15 eq), and H_2O (2.5 mL) were then added, and the mixture stirred at 70° overnight. The reaction was diluted with ethyl acetate and washed with H_2O (1x) and brine (1x). The organic layer was dried over sodium sulfate, evaporated, and purified on silica (DCM/EtOAc) to give compound 33.

^{1}H 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, dmso) 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

Example 2-1-5: 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.

Example 2-2. 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

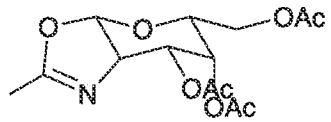
hours. The reaction was diluted into DCM and washed with water (3x) and brine (1x). The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product was purified on silica (0-5% MeOH in DCM) to give compound 64 (6.89 g, 22.6 mmol) in 85% yield.

^{1}H 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).

^{13}C NMR (101 MHz, cdcl$_3$) δ 144.98, 133.09, 129.95, 128.09, 72.58, 70.91, 70.44, 69.28, 68.84, 61.88, 21.76.

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 compound 65 (932 mg, 5.32 mmol) in 81% yield.

Example 2-3. GalNAc ASGPR ligand (Figure 15)

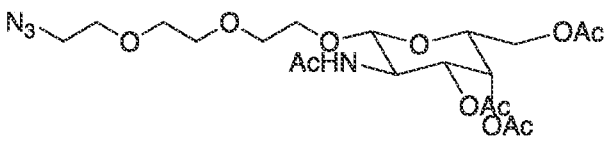


[0001] Galactosamine pentaacetate (100 mg, .257 mmol) was dissolved in dichloroethane (1 mL) and stirred at room temperature before the addition of TMSOTf (70 uL, 86.0 mg, .387 mmol, 1.5 eq). The reaction was stirred at 50° for 90 minutes, then allowed to cool to room temperature and stirred for a further 12 hours. The reaction was poured into ice cold saturated sodium bicarbonate and extracted into DCM. The organic layer was washed with water (2x), 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.

^{1}H 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).

^{13}C NMR (101 MHz, cdcl$_3$) δ 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.

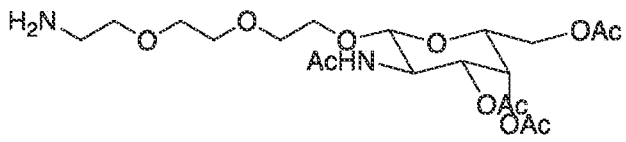


Compound 66 (200 mg, .607 mmol) and compound 65 (160 mg, .913 mmol, 1.5 eq) were dissolved in 1,2-dichloroethane (5 mL). 4 Å molecular sieves were then added, and the reaction stirred for 30 minutes. TMSOTf (55 uL, 67.5 mg, .304 mmol, .5 eq) was then added to the mixture, and the reaction stirred overnight. 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 compound 67 (245 mg, .486 mmol) in 80.1% yield.

^{1}H 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)

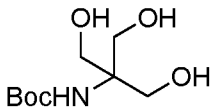
^{13}C NMR (101 MHz, cdcl$_3$) δ 170.24, 170.09, 169.99, 101.84, 72.06, 71.27, 70.50, 70.29, 70.27, 70.20, 70.00, 69.98, 69.67, 69.37, 68.18, 66.30, 61.38, 61.17, 50.32, 50.26, 50.11, 22.80, 20.37, 20.31

HRMS: $[M+Na]^+$ 527.207 found 527.203



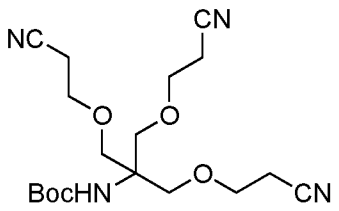
Compound 67 (1.80 g, 3.57 mmol) was dissolved in THF (35 mL). Triphenylphosphine (1.40 g, 5.35 mmol, 1.5 eq) and water (257 uL, 14.28 mmol, 4 eq) were then added and the reaction stirred at room temperature under nitrogen for 36 hours. The solvent was removed and the crude product used in the next step without further purification.

Example 2-4. Tris Valent Glycine (Figure 16)



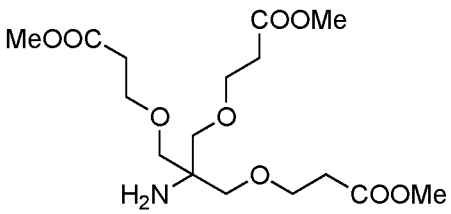
Tris base (5.00 g, 41.3 mmol) was dissolved in dichloromethane (80 mL) and

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.



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). Acrylonitrilte (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.

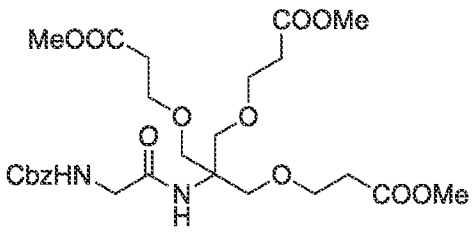
HNMR: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.84 (s, 1H), 3.73 (s, 6H), 3.65 (t, *J* = 6.1 Hz, 6H), 2.57 (t, *J* = 6.1 Hz, 6H), 1.35 (s, 9H).



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 partioned 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.

HNMR: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.79 – 3.64 (m, 15H), 3.32 (s, 6H), 2.56 (t, *J* = 6.3 Hz, 6H).

CNMR: ^{13}C NMR (101 MHz, cdcl$_3$) δ 172.03, 72.52, 66.77, 56.10, 51.62, 34.80.

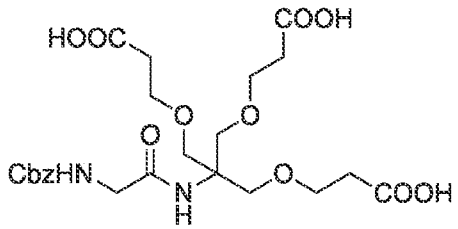


Compound 70 (723 mg, 1.90 mmol) was dissolved in MeCN (25 mL). HOBT (291 mg, 1.90 mmol, 1 eq), Cbz-glycine (397 mg, 1.90 mmol, 1 eq), and DCC (392 mg, 1.90 mmol, 1 eq) were then added, and the reaction stirred overnight. MeCN was then evaporated, and the residue adsorbed onto silica and purified using a gradient of 0-75% EtOAc in hexanes. Compound 71 (866 mg, 1.52 mmol) was recovered in 80% yield.

^{1}H 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, 21H), 3.49 (s, 1H), 2.53 (t, *J* = 6.1 Hz, 6H).

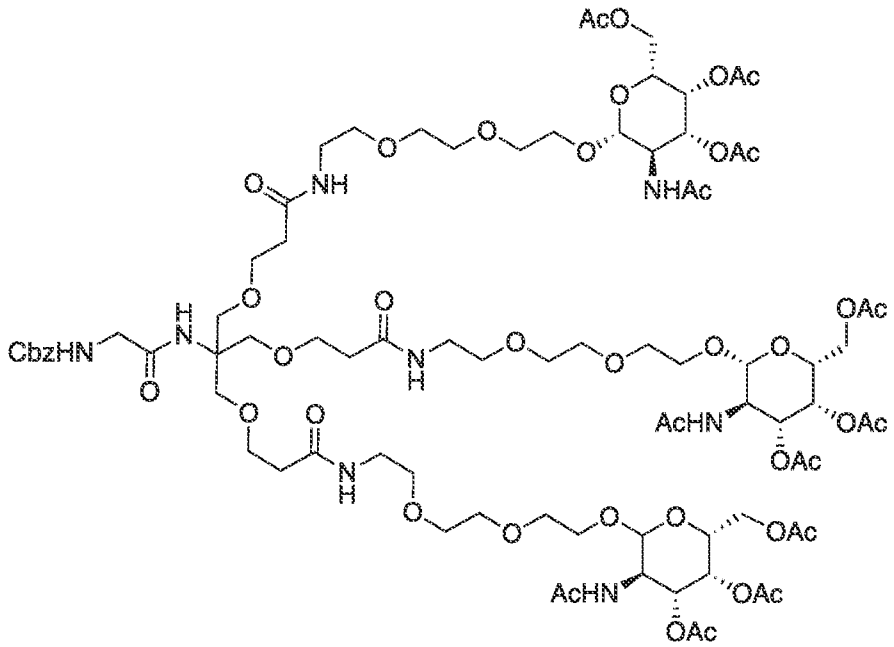
^{13}C NMR (151 MHz, cdcl$_3$) δ 172.14, 168.67, 156.32, 136.41, 128.45, 128.05, 127.98, 69.04, 66.85, 66.71, 59.83, 51.69, 44.55, 34.64.

Expected: $[M+H]^+$ 571.250, found 571.243



Compound 71 (100 mg, .175 mmol) was dissolved in dioxane (2 mL) and 2M NaOH (2mL). 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.

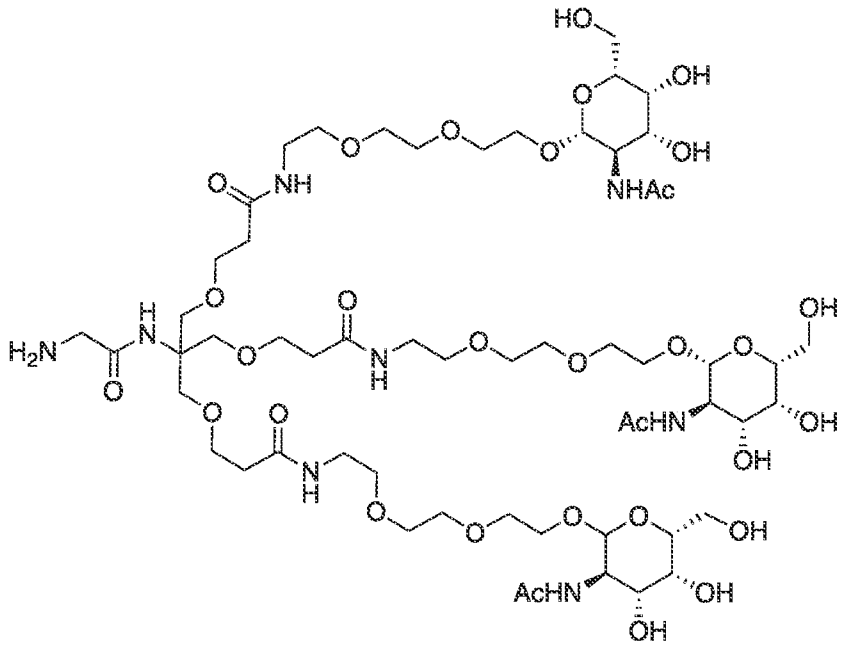
Example 2-5. GaINAc trivalent (Figure 17)



Compound 72 (372 mg, .704 mmol, 1 eq) was dissolved in DMF (40 mL) and DIPEA (981 uL, 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 H3PO4 (1M, 1x), NaHCO3 (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.

^{1}H NMR (500 MHz, DMSO-d_6) 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).

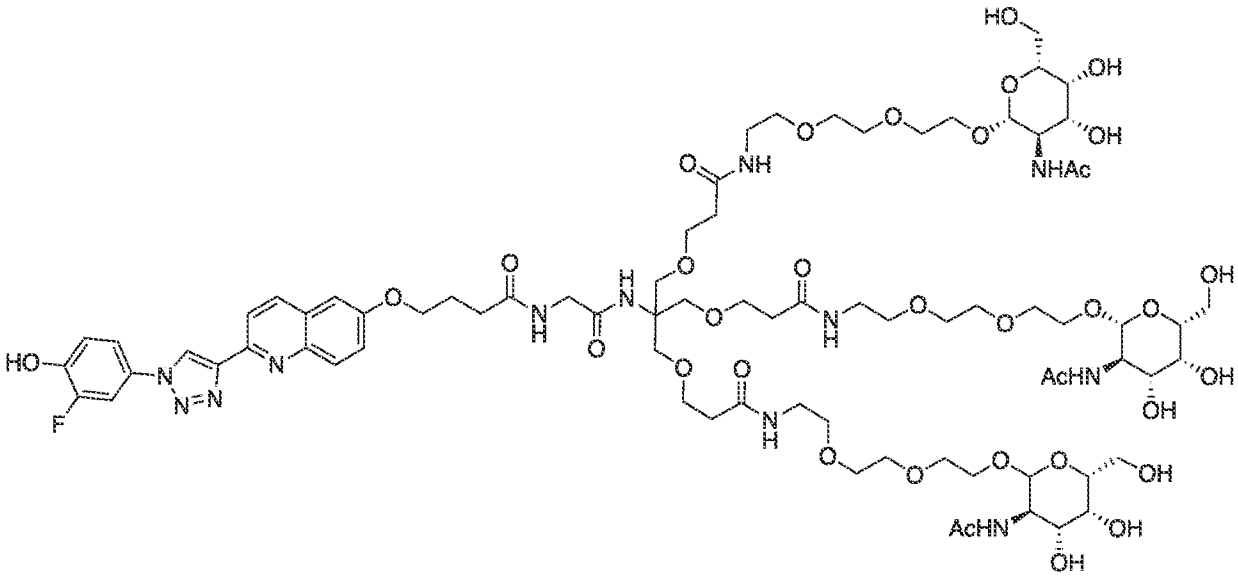
^{13}C NMR (126 MHz, dmso) δ 170.40, 170.16, 170.09, 169.79, 169.48, 169.04, 156.60, 137.23, 128.50, 127.94, 127.84, 101.12, 72.50, 70.65, 70.07, 69.93, 69.86, 69.77, 69.59, 69.29, 68.50, 67.51, 66.89, 65.59, 61.63, 60.38, 59.84, 49.50, 43.77, 38.68, 36.01, 22.95, 20.68, 20.62, 20.60.



Compound 73 (710 mg, .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, .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 uL, 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, .196 mmol) in 79% yield. Compound 75 was used in further steps without purification.

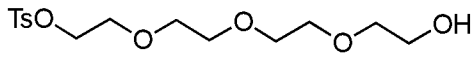
Example 2-6. MIF-GN3 (Figure 18)



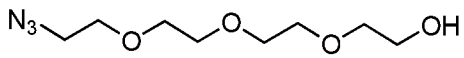
Compound 34 (23.5 mg, .0575 mmol, 1.1 eq) and HATU (20.0 mg, .0522 mmol, 1 eq) were dissolved in dry DMF (5 mL) and DIPEA (23.3 uL, 16.9 mg, .131 mmol, 2.5 eq) and stirred for 10 minutes at room temperature. Compound 75 (73.0 mg, .0522 mmol) was then added, and the reaction stirred for 30 minutes. The mixture was loaded directly onto HPLC and purified (20-30% MeCN in water, 3% TFA) to give compound 76 (12 mg, .0067 mmol) in 12.8% yield.

Expected $[M+H]^+$ 1787.801, found 1787.823

Example 2-7. Bicyclic ASGPR Spacer (Figure 19)



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.

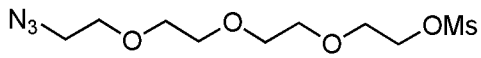


Compound 16 (8.84 g, 25.4 mmol) was dissolved in 100% ethanol (200 mL) and

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.

HNMR: ^{1}H 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).

CNMR: ^{13}C NMR (101 MHz, cdcl$_3$) δ 72.47, 70.65, 70.63, 70.59, 70.52, 70.28, 69.99, 61.60, 50.59.



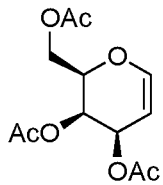
Compound 17 (5.00 g, 22.8 mmol) was dissolved in pyridine (50 mL). Methanesulfonyl chloride (3.14 g, 27.4 mmol, 1.2 eq) was then added and the reaction stirred for six hours under nitrogen. The mixture was then diluted into ethyl acetate, washed with water (3x), .5M HCl (2x), saturated sodium bicarbonate (1x), and brine (1x), dried over sodium sulfate, and evaporated to give compound 18 (5.71 g, 19.2 mmol) in 84% yield.

HNMR: ^{1}H 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).

CNMR: ^{13}C NMR (101 MHz, cdcl$_3$) δ 70.79, 70.75, 70.71, 70.15, 69.39, 69.11, 50.77, 37.78.

HRMS: Expected 298.107, found 298.105

Example 2-8. 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.

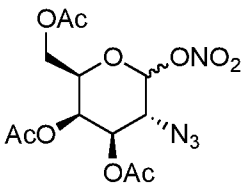
Compound 1 (26.34 g, 64.06 mmol) was dissolved in acetic acid (510 mL) and zinc

(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, .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).

^{1}H 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).

^{13}C 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

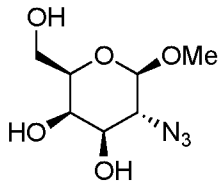


Procedure: Compound 2 (12.0 g, 44 mmol) was dissolved in acetonitrile (250 mL) and cooled to -10°. In a separate nitrogen-flushed flask at -10°, NaN_3 (4.3 g, 66 mmol) and ceric ammonium nitrate (87.0 g, 158 mmol) were mixed and stirred vigorously. The solution of compound 2 in acetonitrile was added 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).

^{1}H 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).

^{13}C NMR (101 MHz, $cdcl_3$) 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.

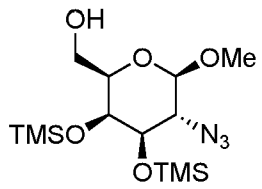
HRMS: $[M+Na]^+$ expected 399.076, found 399.073



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.

CNMR: ^{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

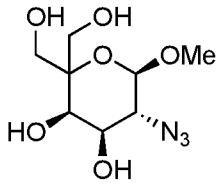


Compound 4 (5.00 g, 22.8 mmol) was dissolved in pyridine (100 mL) and stirred under nitrogen. Trimetylsilylchloride (10.43 mL, 8.929 g, 82.18 mmol, 3.6 eq) was added dropwise and the mixture stirred for 6 hours. The reaction was diluted into ethyl acetate and washed with water (2x) and brine (1x). The organic layer was dried over sodium sulfate and evaporated to give the tri-TMS intermediate. Residual pyridine was removed by coevaporating 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 uL) 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.

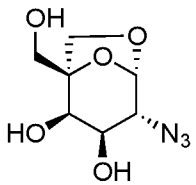
HRMS: $[M+Na]^+$ 386.154, found 386.156



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.

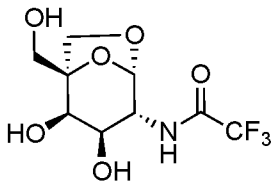
HRMS: $[M+Na]^+$ expected 272.086 (+Na), found 272.083



L6-7 (500 mg, 2.00 mmol) was dissolved in water (4.5 mL) and sulfuric acid (.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

Example 2-9. 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.

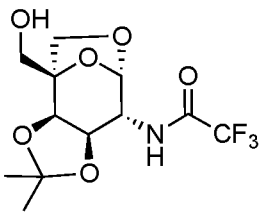
Compound (351 mg, 1.84 mmol) was dissolved in pyridine (15 mL) and treated with trifluoroacetic anhydride (1.24 mL, 1.85 g, 8.83 mmol, 4.8 eq). The reaction was stirred for 6 hours, then diluted into ethyl acetate and washed with 1M HCl (1x), saturated sodium bicarbonate (1x), and brine (1x). The organic 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.

^{1}H 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).

^{13}C 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



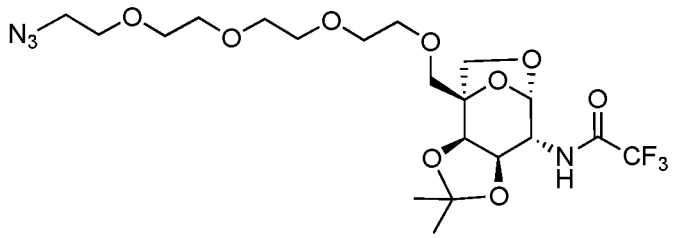
Compound 12 (110 mg, .383 mmol) was dissolved in DMF (8 mL) and dimethoxypropane (236 uL, 200 mg, 1.92 mmol, 5 eq) and camphorsulfonic acid (45 mg, .192 mmol, .5 eq) were added. The reaction was stirred at 70° overnight, then DMF

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.

HNMR: ^{1}H 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).

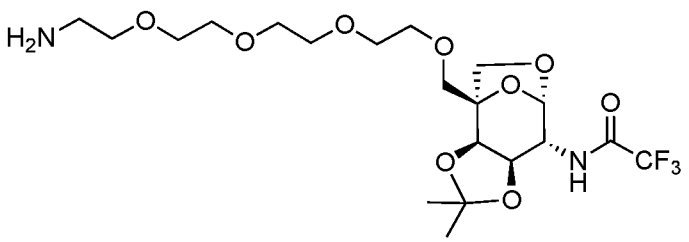
CNMR: ^{13}C NMR (101 MHz, cdcl$_3$) δ 157.87, 157.50, 157.12, 156.75, 119.93, 117.07, 114.21, 112.04, 111.35, 100.22, 81.55, 75.57, 75.00, 68.44, 60.96, 55.16, 27.67, 26.16.

HRMS: $[M+H]^+$ 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.

HNMR: ^{1}H NMR (400 MHz, 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).

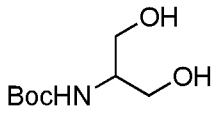


Compound 14 (131 mg, .240 mmol) was dissolved in methanol (10 mL) and stirred

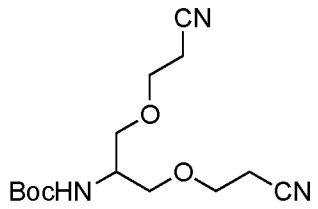
under a nitrogen atmosphere. Lindlar catalyst (13.1 mg, 10 wt%) was then added, and the reaction stirred for 6 hours under H_2 atmosphere (1 atm). The reaction was then filtered over celite and the solvent evaporated to give compound 15 (120 mg, .240 mmol) in quantitative yield, which was used without further purification.

HRMS: $[M+H]^+$ Expected 503.222, found 503.223

Example 2-10. MIF binding divalent (Figure 23)



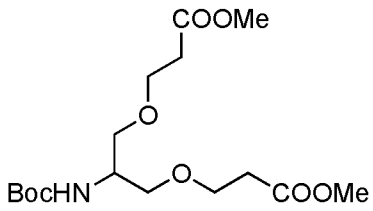
Serinol (2.00 g, 22.0 mmol) was dissolved in dichloromethane (40 mL) and trimethylamine (10 mL). Di-tert-butyl dicarbonate (5.76 g, 26.4 mmol, 1.2 eq) was then added, and the reaction stirred for 4 hours. The mixture was evaporated and the residue portioned between ethyl acetate and water. The organic fraction was washed with water (1x), 1M HCl (2x), saturated sodium bicarbonate (1x), and brine (1x) before drying over sodium sulfate and 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 aqueous KOH (1.63 g, 29 mmol, 2.4 mL). Acrylonitrilte (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 (20-100% EtOAc in hexanes) to give compound 20 (4.96 g, 16.7 mmol) in 80% yield.

HNMR: ^{1}H 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).

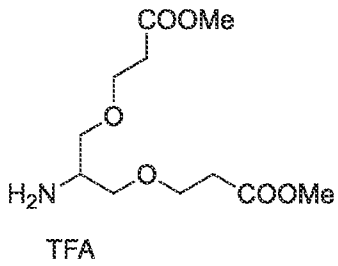
CNMR: ^{13}C NMR (101 MHz, cdcl$_3$) δ 171.11, 155.31, 117.88, 79.70, 69.12, 65.53, 49.24, 28.30, 18.83, 14.16.



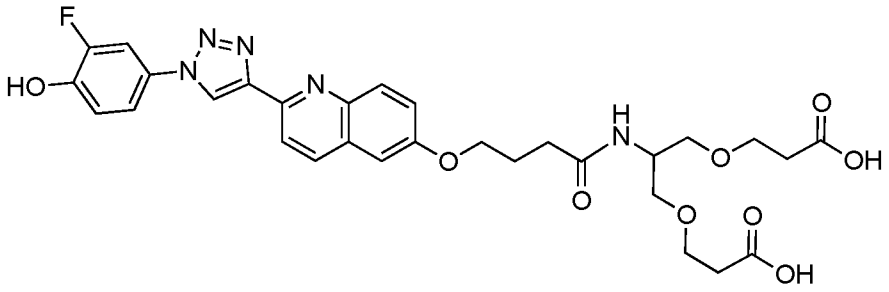
Compound 24 (4.96 g, 16.7 mmol) was dissolved in methanol (40 mL) and concentrated sulfuric acid (10 mL) was added. The mixture was heated at reflux for 24 hours under a nitrogen atmosphere, then cooled to room temperature. Excess sodium bicarbonate was then added, followed by di-tert-butyl dicarbonate (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), .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).

HNMR: ^{1}H 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).

CNMR: ^{13}C NMR (101 MHz, cdcl$_3$) 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.

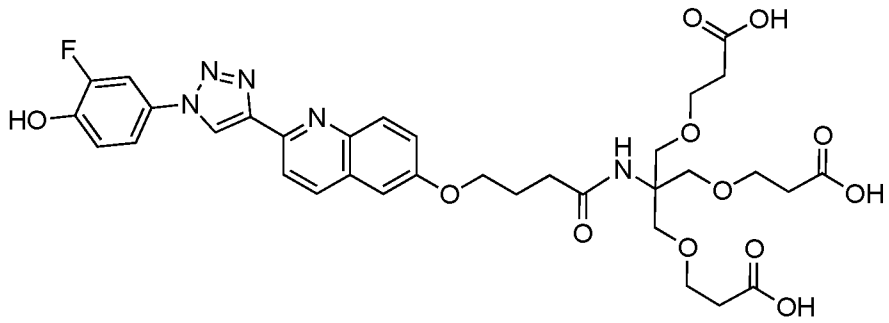


Compound 34 (50.0 mg, .123 mmol) was dissolved in DMF (5 mL) and DIPEA (214 uL, 159 mg, 1.23 mmol, 10 eq) and stirred under nitrogen. HBTU (102.4 mg, .270 mmol, 2.2 eq) was then added, and the reaction stirred for 15 minutes. Compound 26 (102 mg, .270 mmol, 2.2 eq) dissolved in DMF (1 mL) was then added 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

Compound 40 (62.6 mg, .0959 mmol) was dissolved in dioxane (1.8 mL) and 1M NaOH (.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.

Example 2-11. MIF binding trivalent (Figure 23)



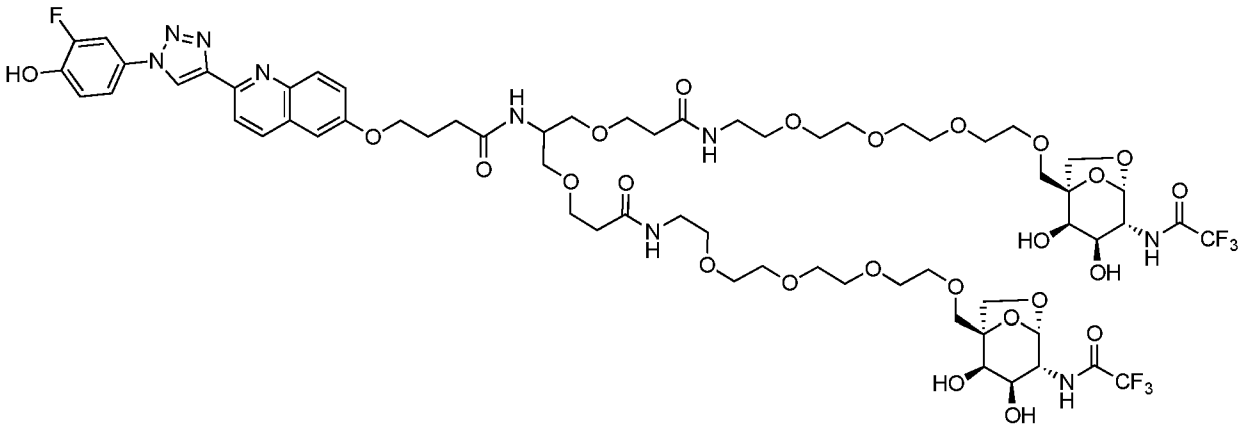
Compound 34 (50.0 mg, .123 mmol) was dissolved in DMF (5 mL) and DIPEA (214 uL, 159 mg, 1.23 mmol, 10 eq) and stirred under nitrogen. HBTU (154 mg, .405 mmol, 3.3 eq) was then added, and the reaction stirred for 15 minutes. Compound 29 (200 mg, .405 mmol, 3.3 eq) dissolved in DMF (1 mL) was then added 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, .103 mmol) in 84% yield.

HRMS: $[M+H]^+$ expected 770.305, found 770.308

Compound 44 (79.3 mg, .103 mmol) was dissolved in dioxane (1.8 mL) and 1M NaOH (.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.

Example 2-12. MIF-AcF3-2 (Figure 24)

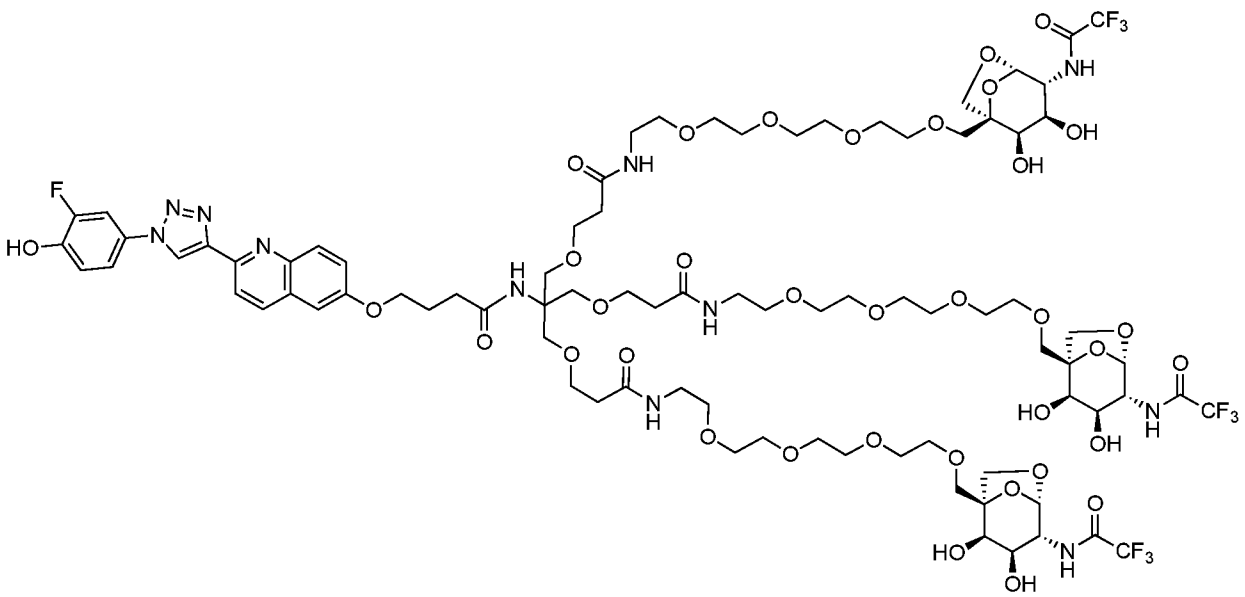


Compound 41 (57.6 mg, .0921 mmol) was dissolved in DMF (1.8 mL) and DIPEA (.2 mL). HBTU (84.0 mg, .222 mmol, 2.4 eq) was then added, and the reaction stirred for 15 minutes before the addition of compound 15 (111 mg, .222 mmol, 2.4 eq). The reaction was stirred for 1 hour, then evaporated to give a red 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 hours. The reaction was purified directly by HPLC (20-40% MeCN in H_2O, +3% TFA) to give compound 43 (44.66 mg, .0295 mmol) in 32% yield.

Expected (H) 1514.570, found 1514.561

Example 2-13. 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.

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 H_2O, +3% TFA) to give compound 39 (78.1 mg, .0379 mmol) in 40% yield.

Expected (2H, /2) 1030.891 Found 1030.903

Example 2-14. Synthesis of MIF-AcF2-3, MIF-Ac-3, MIF-Et-3

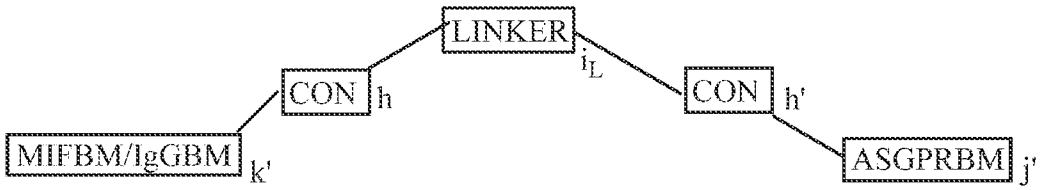
Set forth in figures 26-29 are the chemical syntheses of MIF-AcF2-3, MIF-Ac-3, MIF-Et-3 and MIF-EtF3-3 produced using analogous methods to those presented above with minor variation.

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 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, according to the chemical structure:



wherein:

[MIFBM/IgGBM] is a MIF or IgG binding moiety which binds respectively to circulating MIF or IgG, each of which is related to a disease state and/or condition and is to be removed by the action of hepatocytes on circulating protein;

[ASGPRBM] is a binding moiety which binds to hepatocytes through asialoglycoprotein receptors which are on the surface of hepatocytes, preferably in a patient or subject;

Each [CON] is an optional connector chemical moiety which, when present, connects directly to [MIFBM/IgGBM] or to [ASGPRBM] or connects the [LINKER] to [MIFBM/IgGBM] or to [ASGPRBM] and

[LINKER] is a chemical moiety having a valency from 1 to 15, often 1 to 10, more often 1 to 5 or 1, 2 or 3, which covalently attaches to one or more [ASGPRM] and/or [MIFBM/IgGBM] group, optionally through a [CON], including a [MULTICON] group, wherein said linker optionally itself contains one or more [CON] or [MULTICON] group(s);

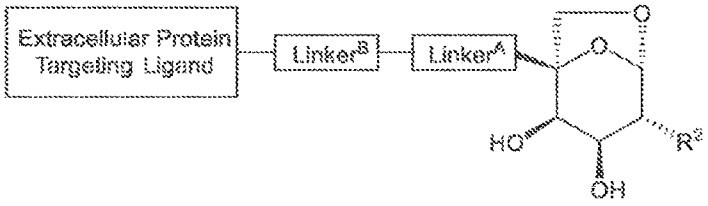
k' is 1 to 15, 1 to 10, 1 to 5, 1 to 3 or 1, 2 or 3;

j' is 1 to 15, 1 to 10, 1 to 5, 1 to 3 or 1, 2 or 3;

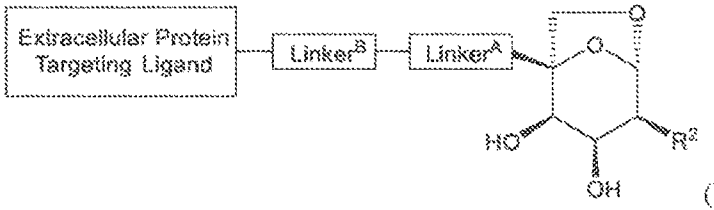
h and h' are each independently 0 to 15;

i_L is 0 to 15, often 1 to 15, 1 to 10, 1 to 5, 1 to 3, or 1, 2 or 3, preferably i_L is 1 to 5 or 1, 2 or 3 with the proviso that at least one of h, h' and i_L is preferably at least 1,

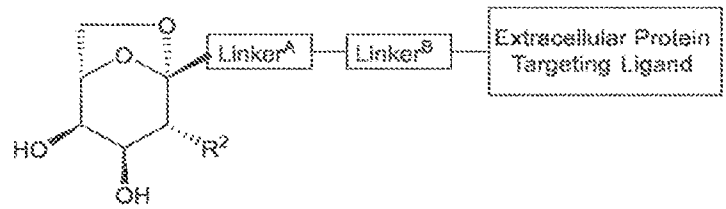
wherein the compound is selected from the group consisting of:



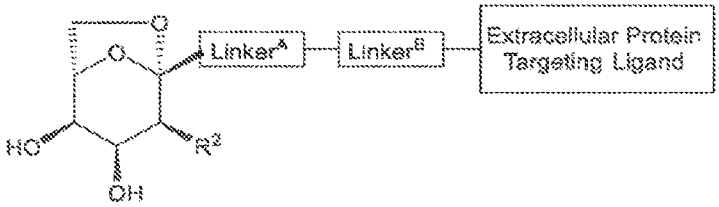
(I),



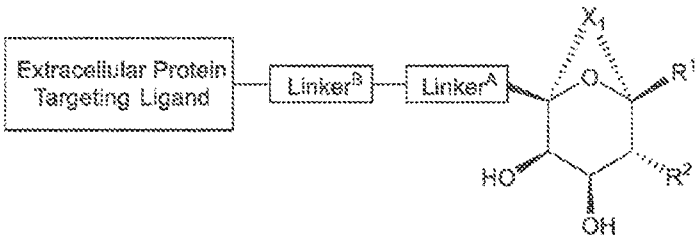
(I-d),



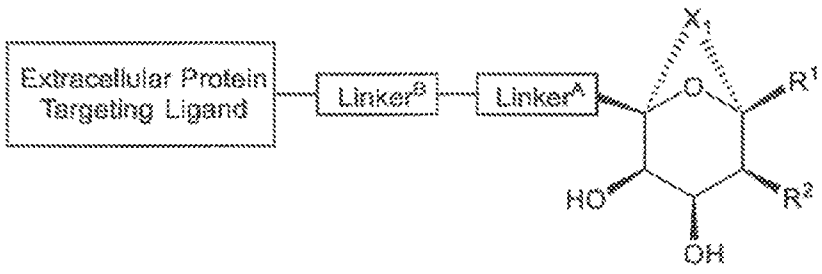
(II),



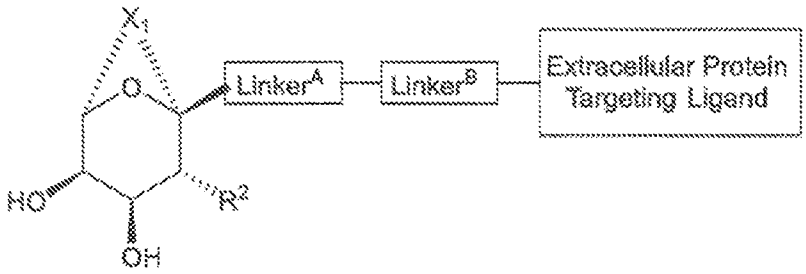
(II-d),



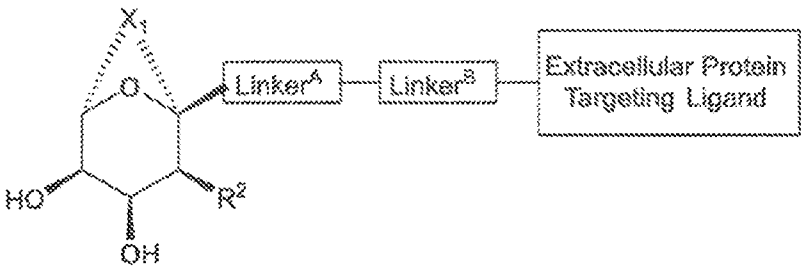
(III),



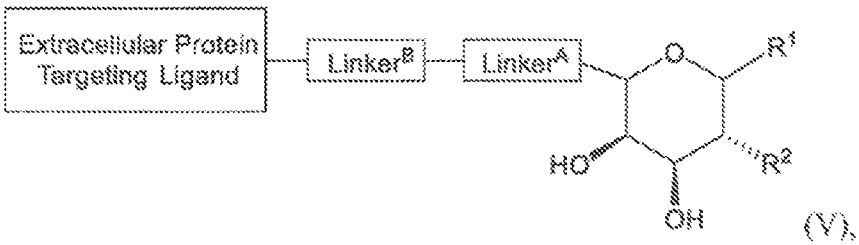
(III-d),



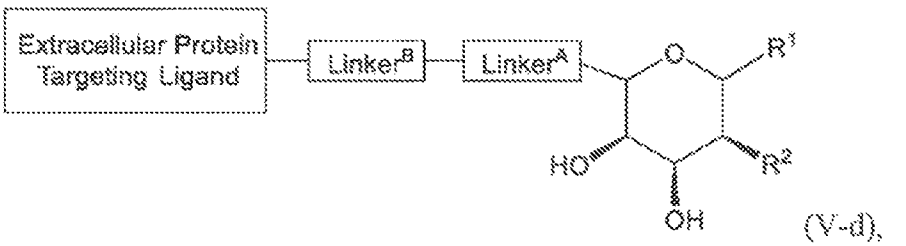
(IV),



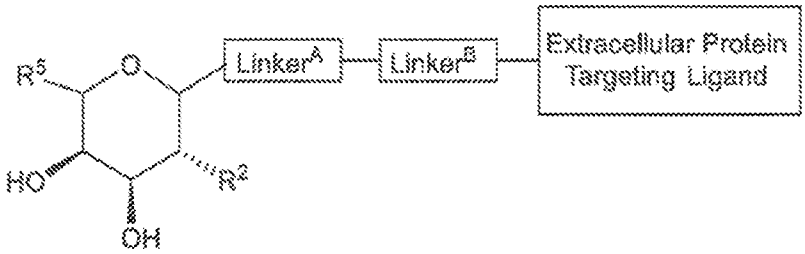
(IV-d),



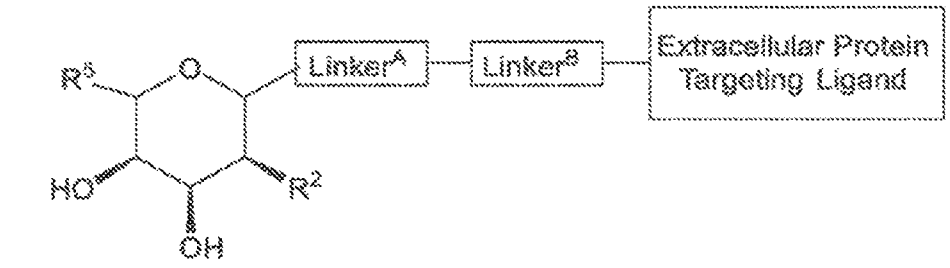
(V),



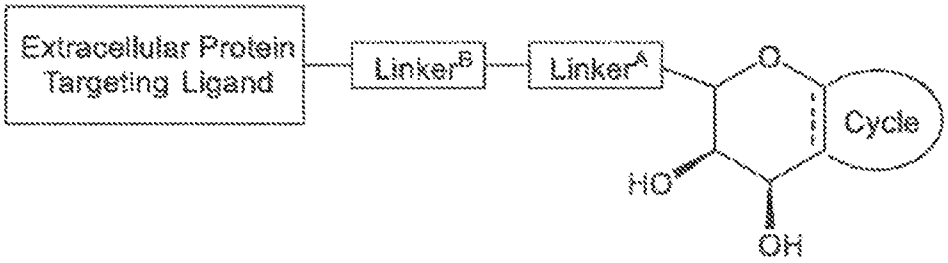
(V-d),



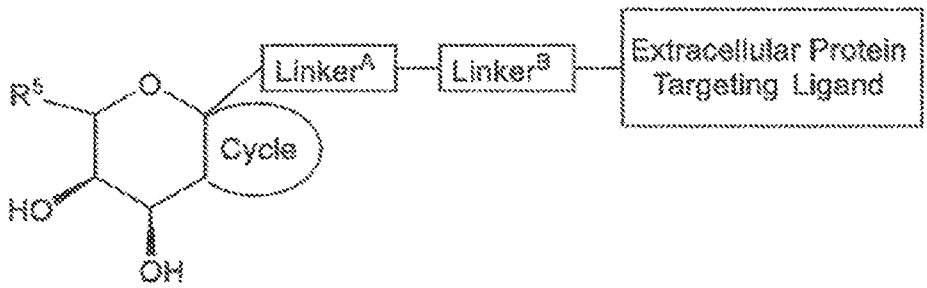
(VI),



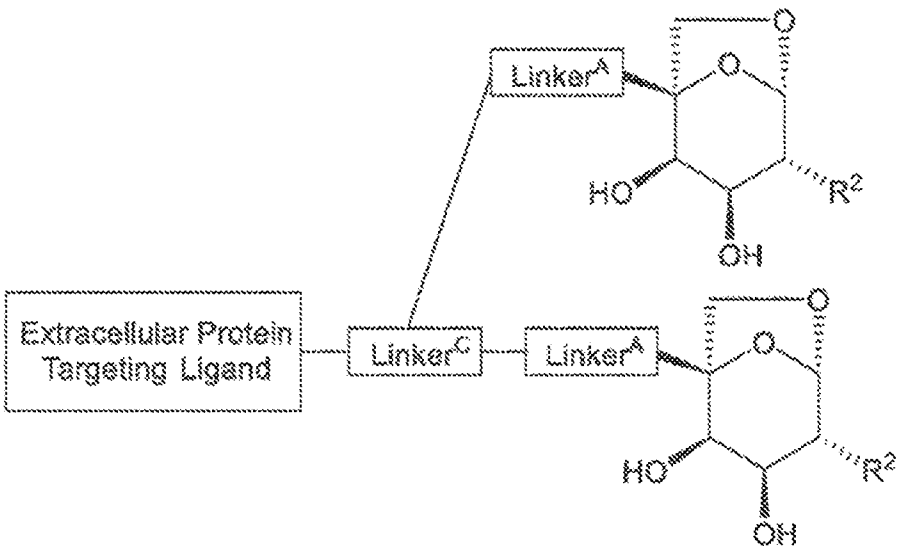
(VI-d),



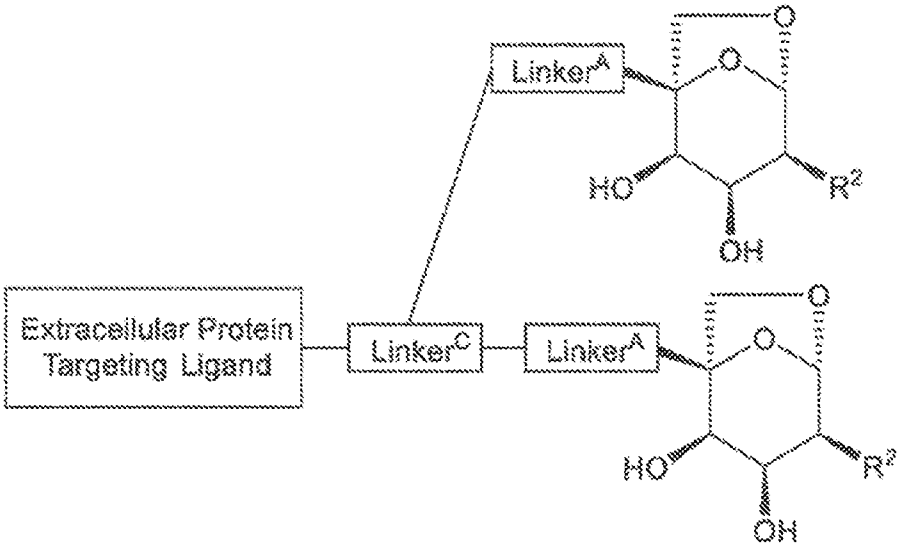
(VII),



(VIII),



(I-Bi),



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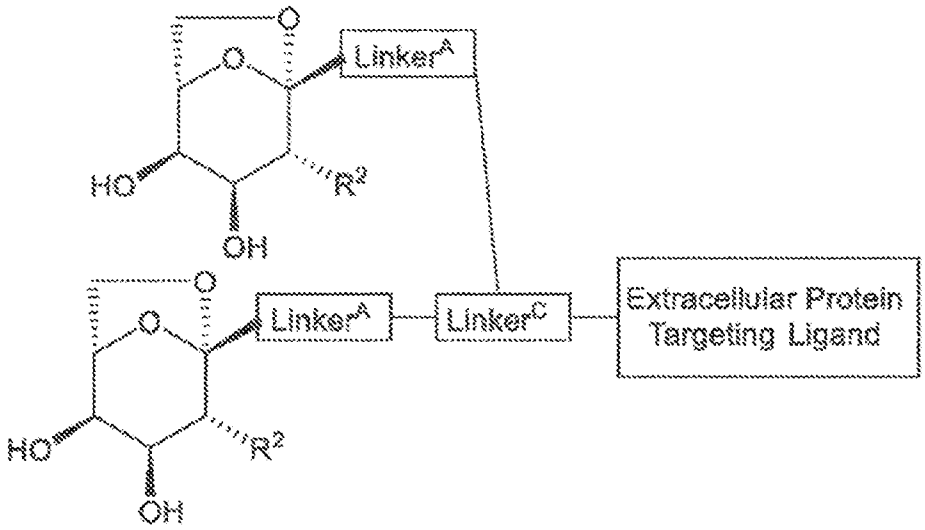

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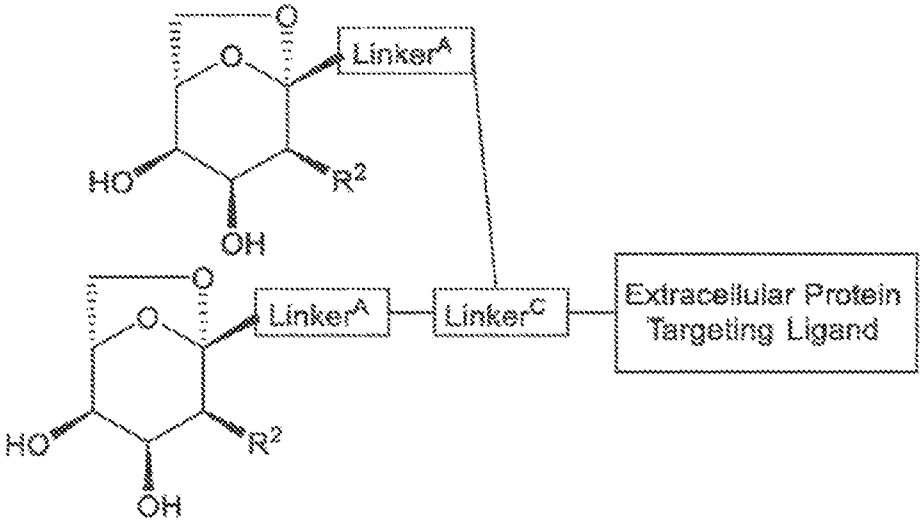

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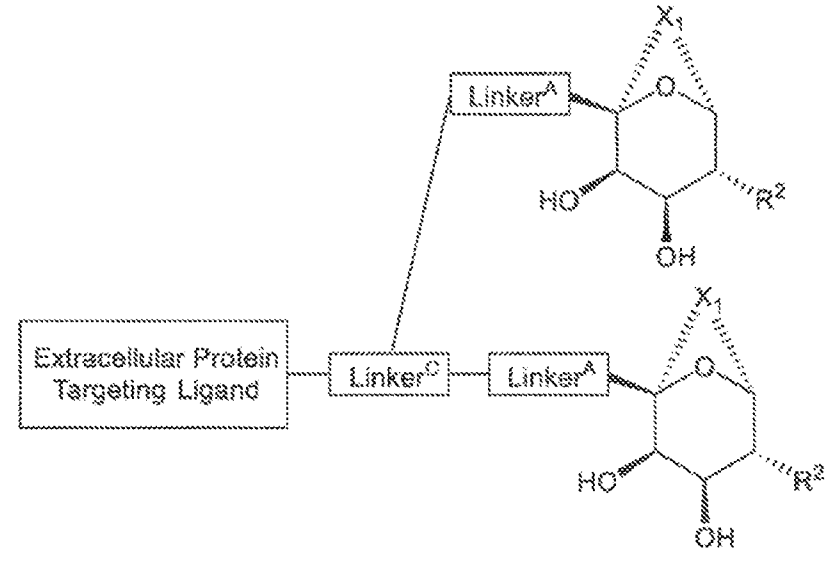
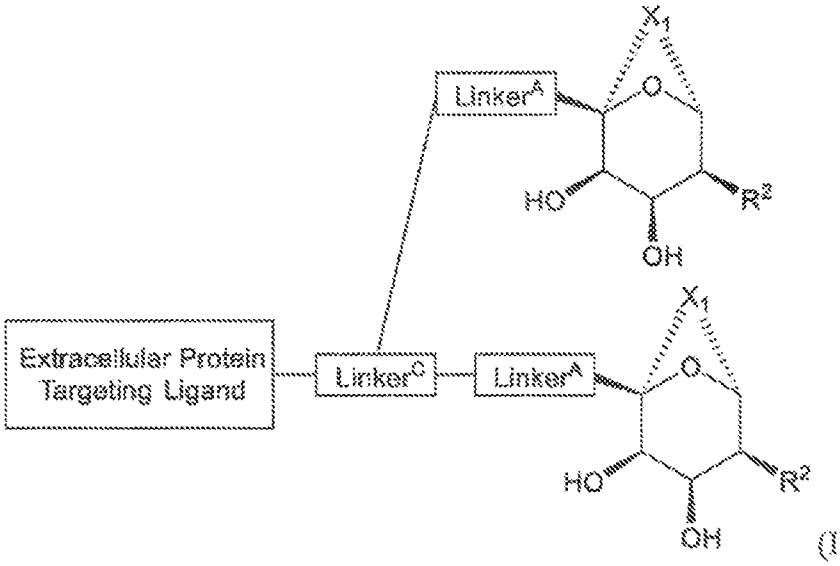


(III-Bi),



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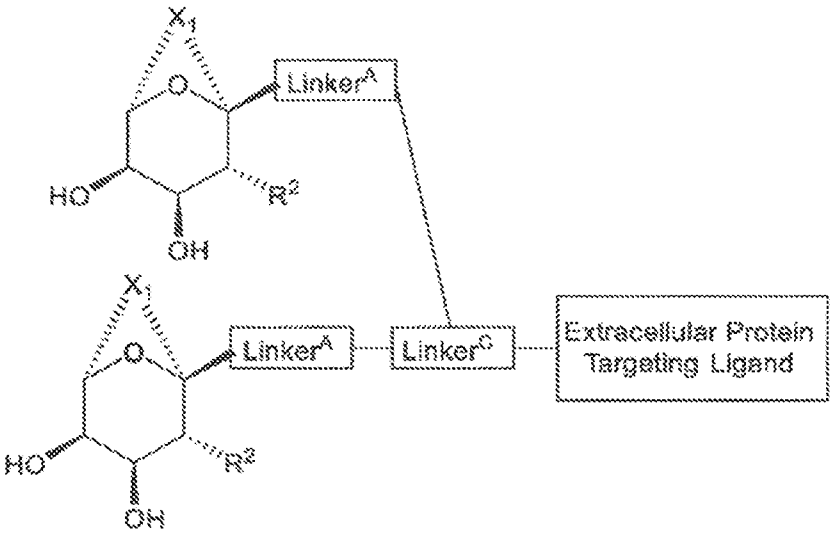

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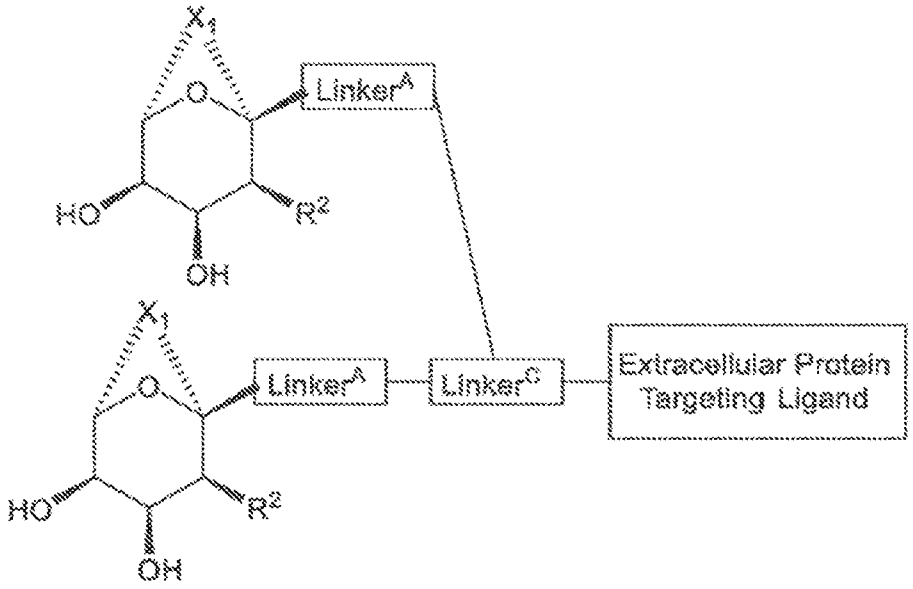

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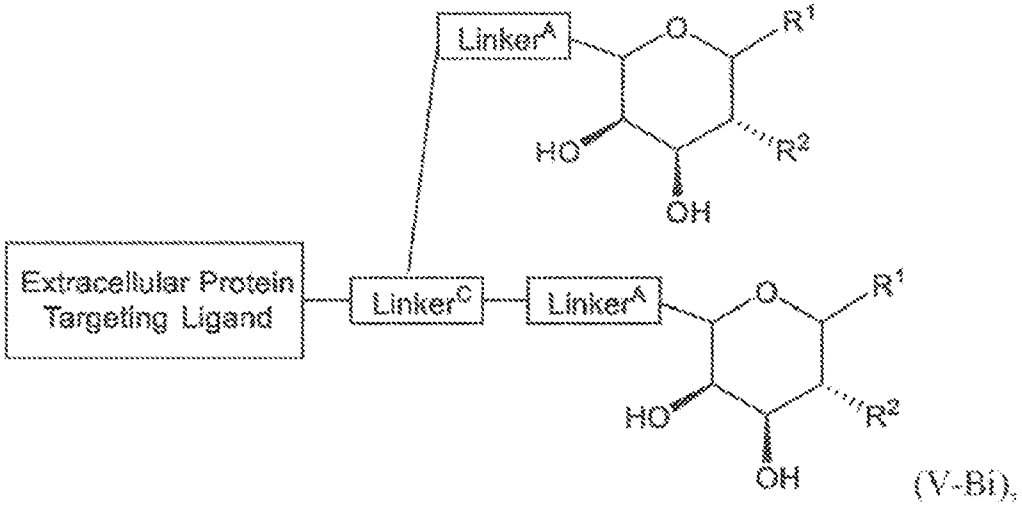
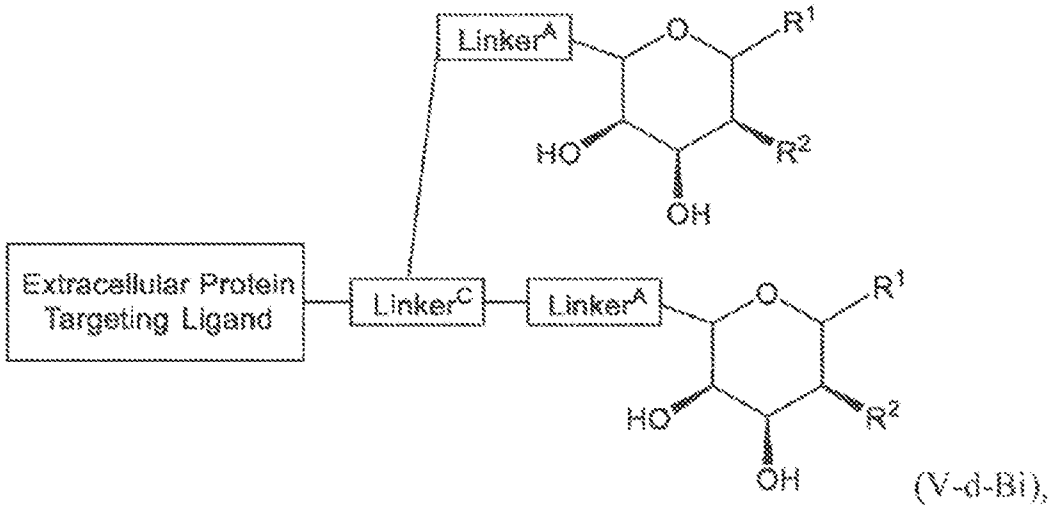
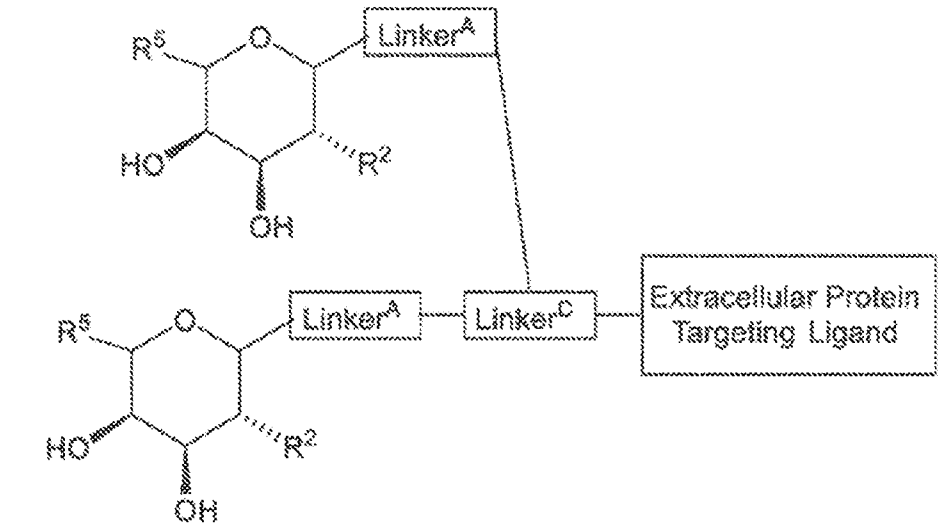


(V-Bi),



(V-d-Bi),



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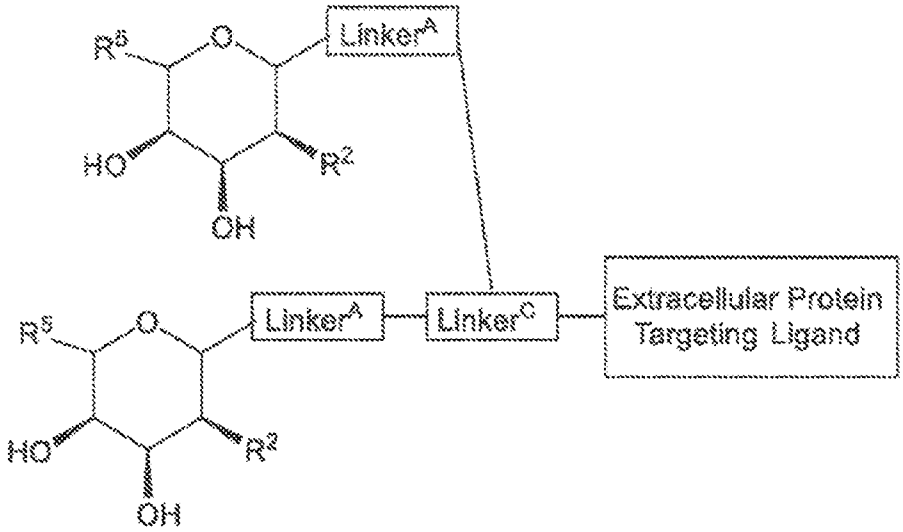
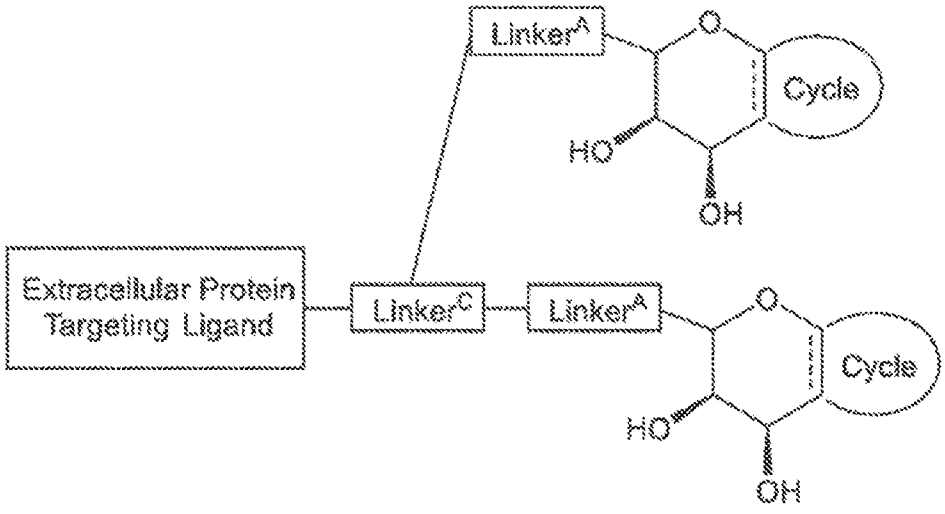
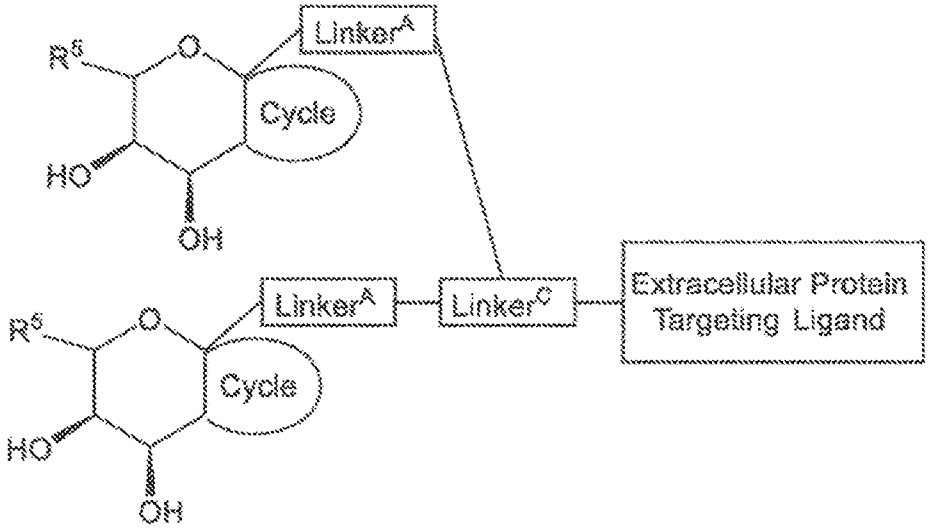


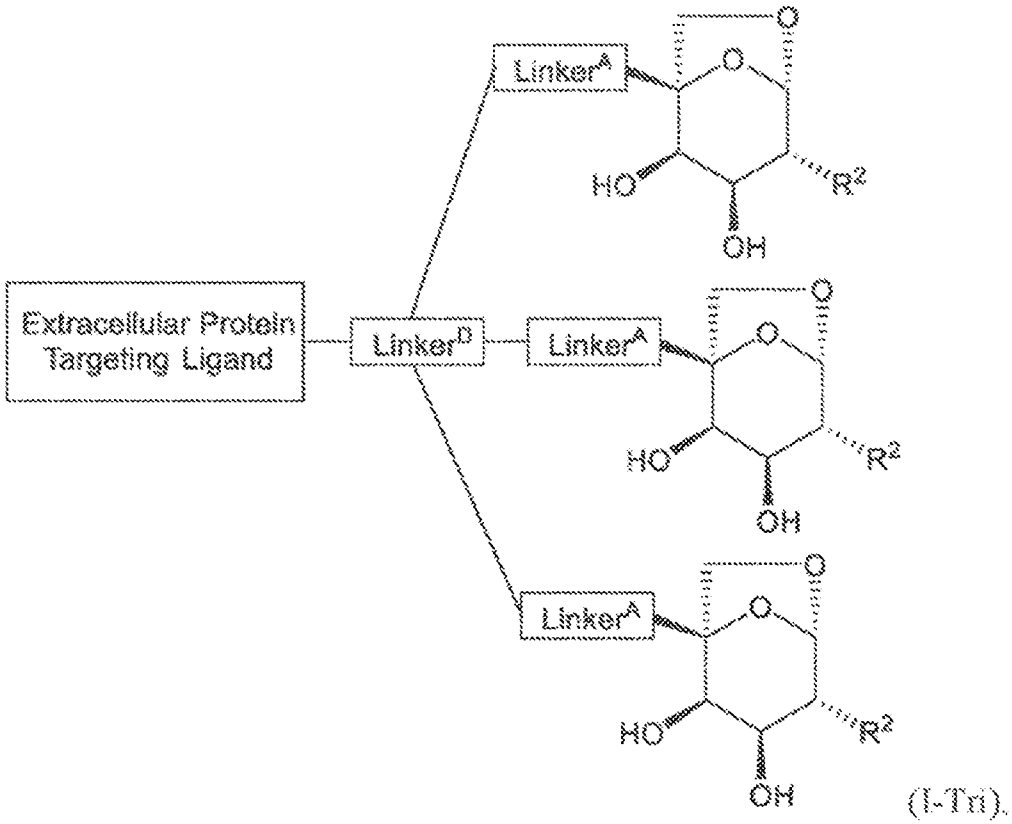
(VI-d-Bi),



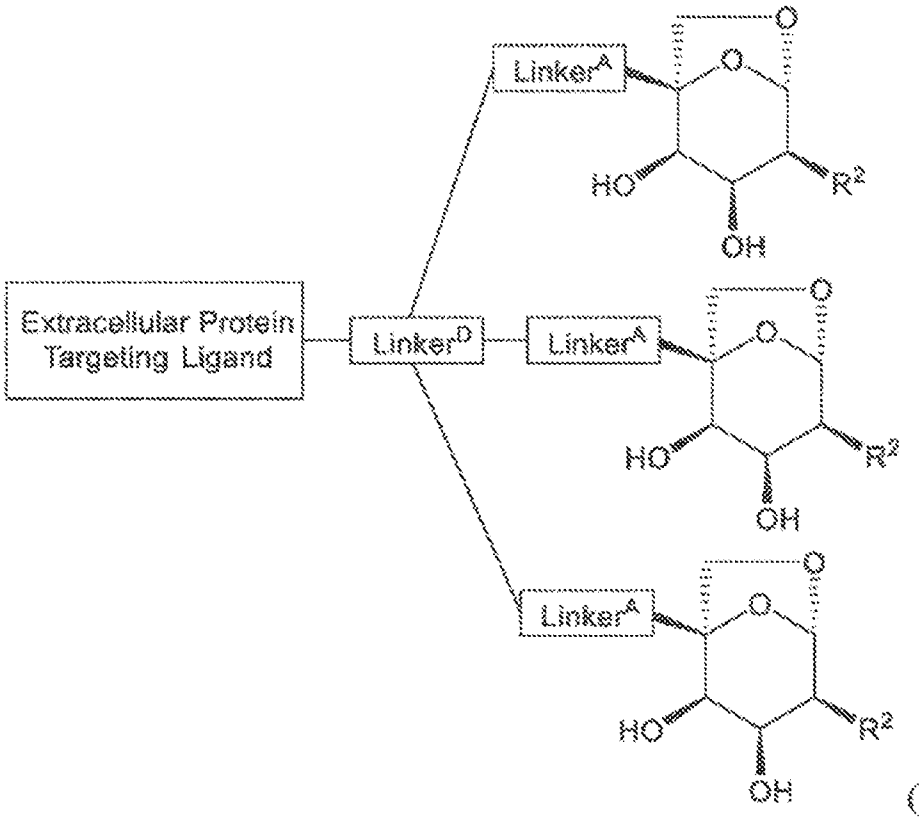
(VII-Bi),


R6
O
Linker^A
Cycle
HO
OH
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
R6
O
Cycle
HO
OH

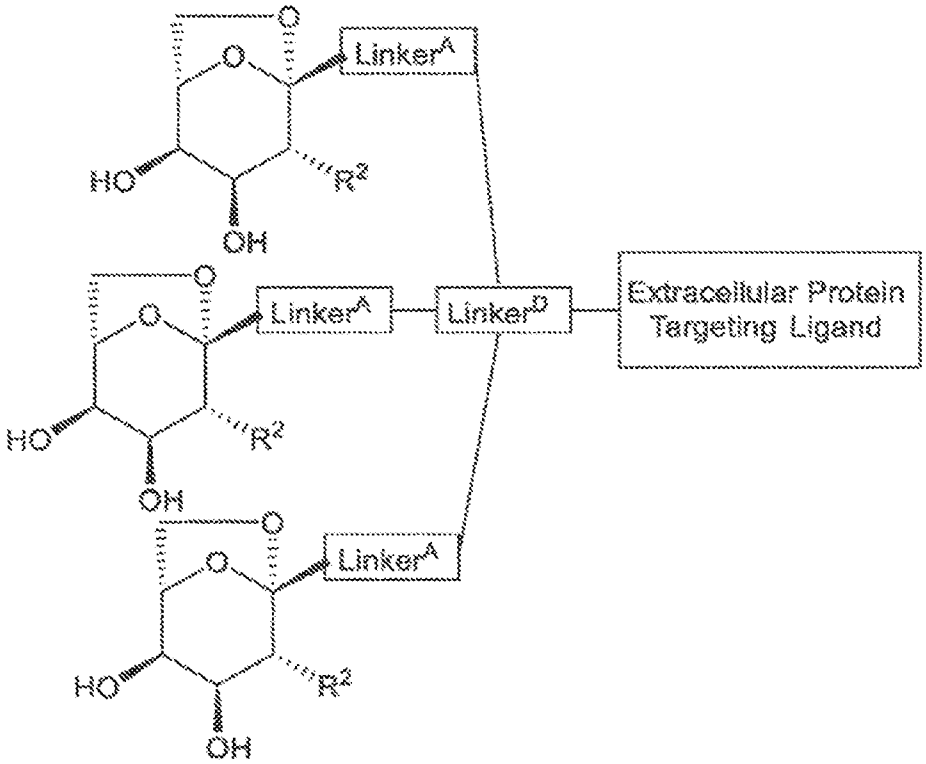
(VIII-Bi),


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A
O
HO
R2
OH

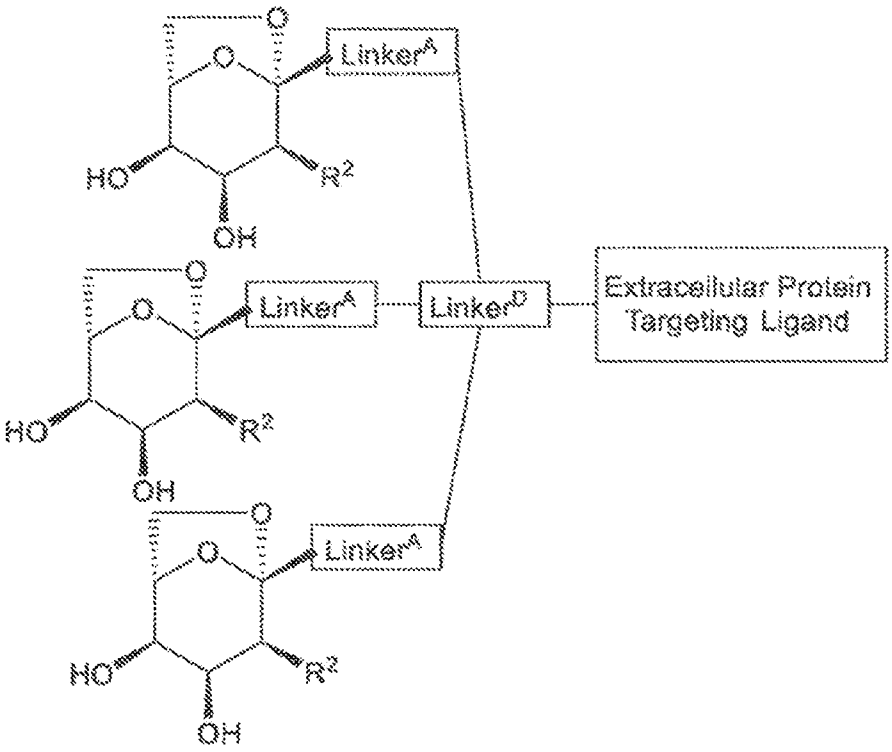
(I-Tri).


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A
HO
R^2
OH

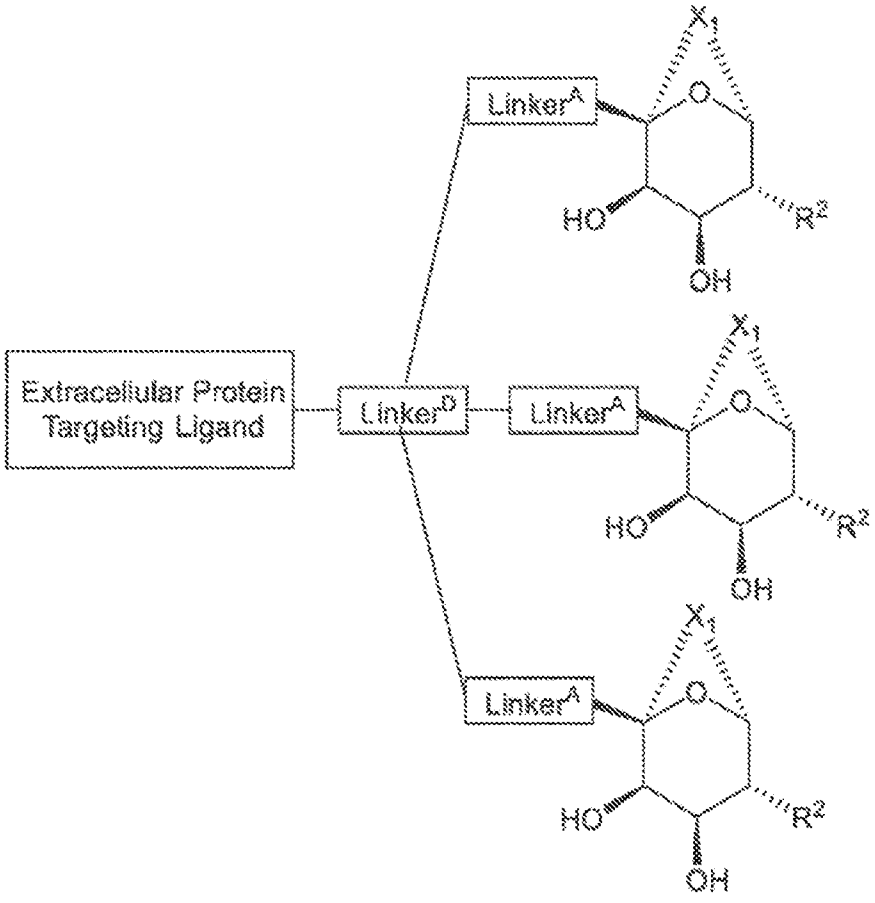
(I-d-Tri),


Linker^A
Linker^A
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
HO
R^2
OH

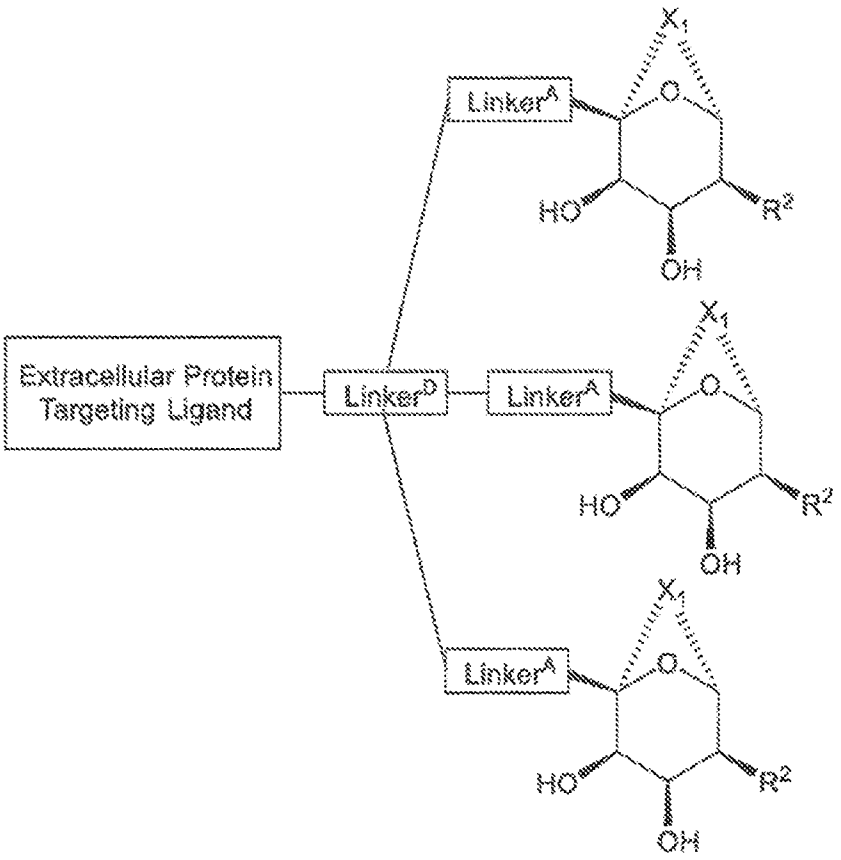
(II-Tri),



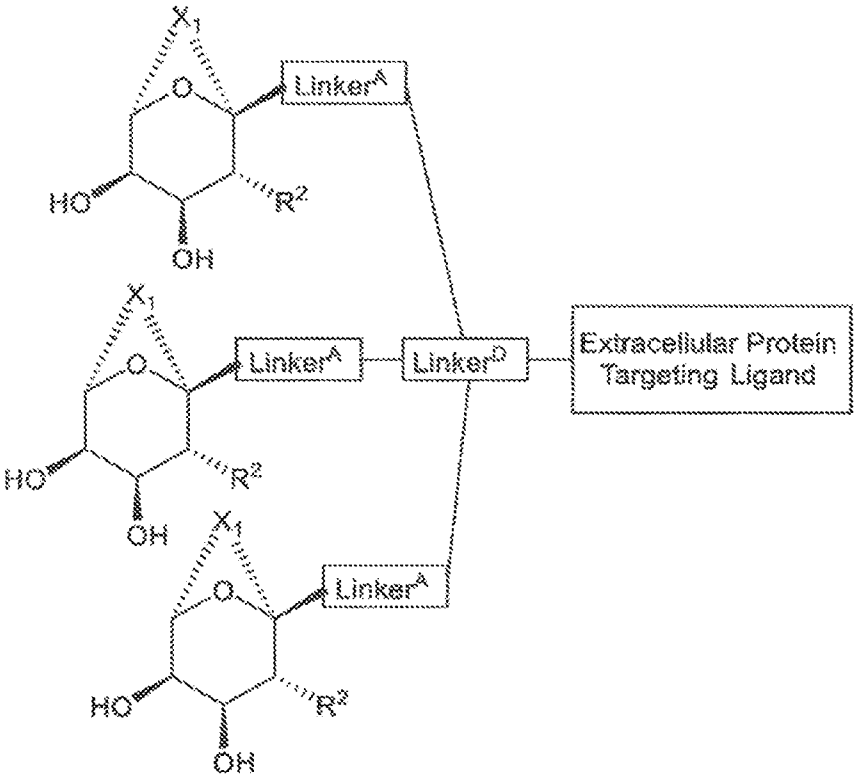
(II-d-Tri),



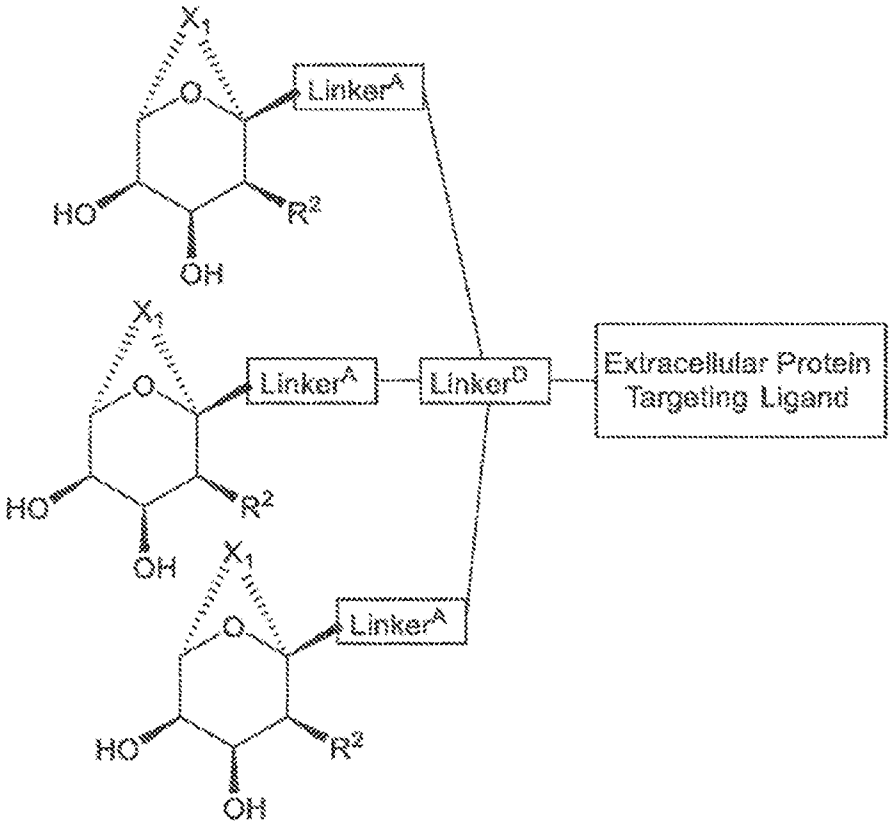
(III-Tri),



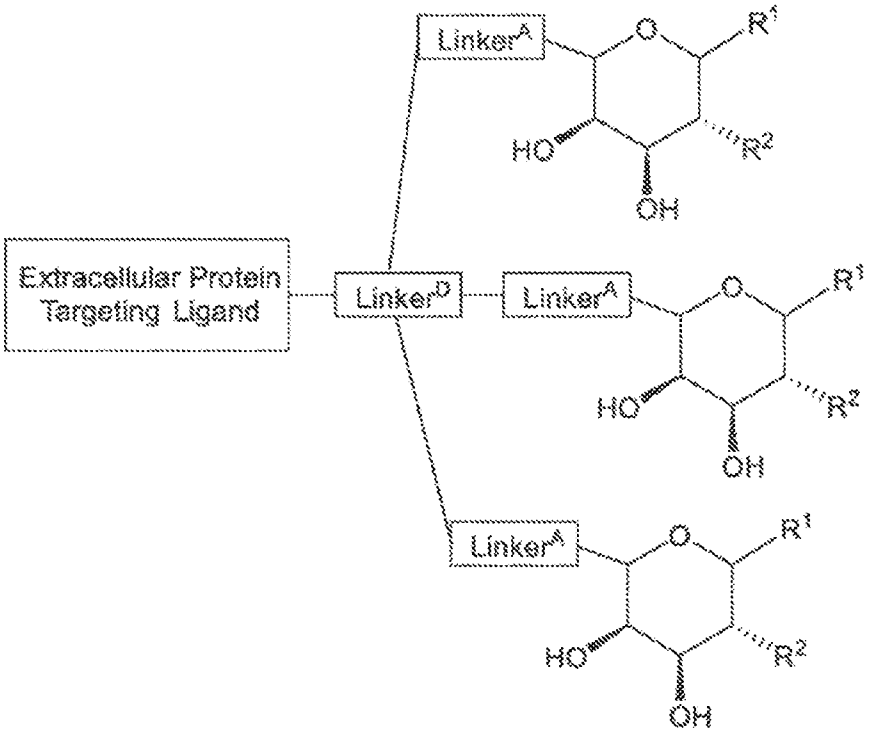
(III-d-Tri),



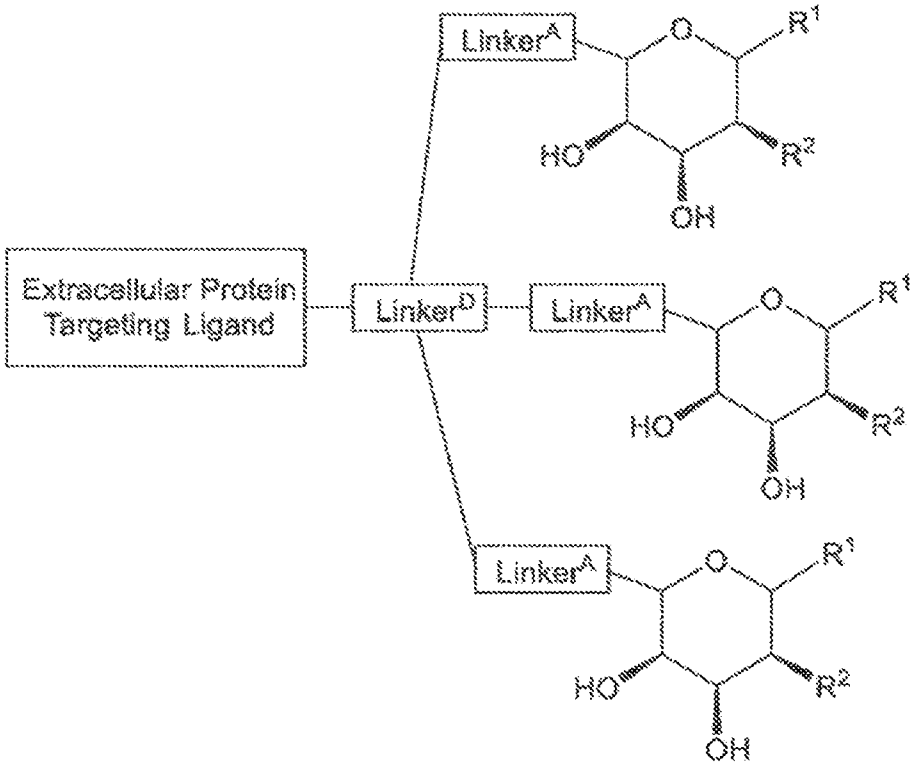
(IV-Tri),


X1
O
Linker^A
HO
R^2
OH
Linker^A
Linker^D
Extracellular Protein Targeting Ligand

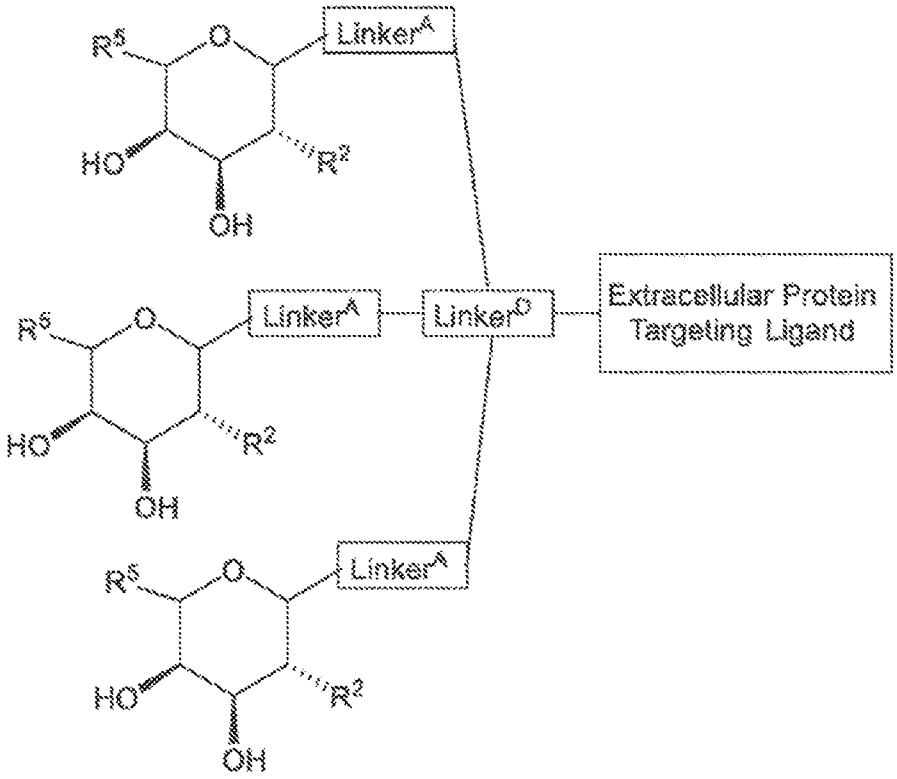
(IV-d-Tri),


Linker^A
O
R^1
HO
R^2
OH
Extracellular Protein Targeting Ligand
Linker^D
Linker^A

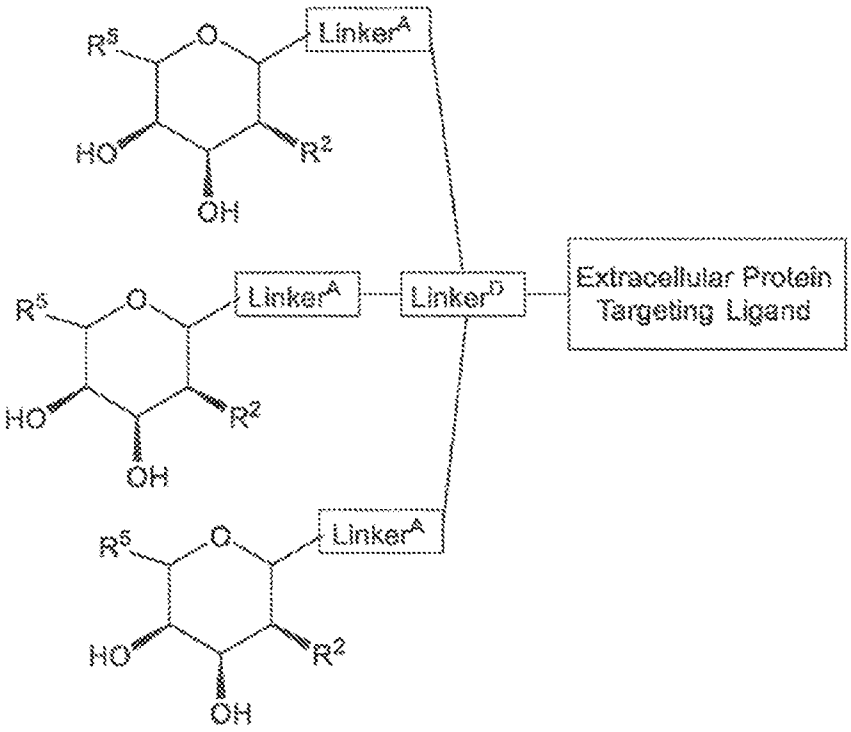
(V-Tri).


Linker^A
O
R^1
HO
R^2
OH
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
O
R^1
HO
R^2
OH
Linker^A
O
R^1
HO
R^2
OH

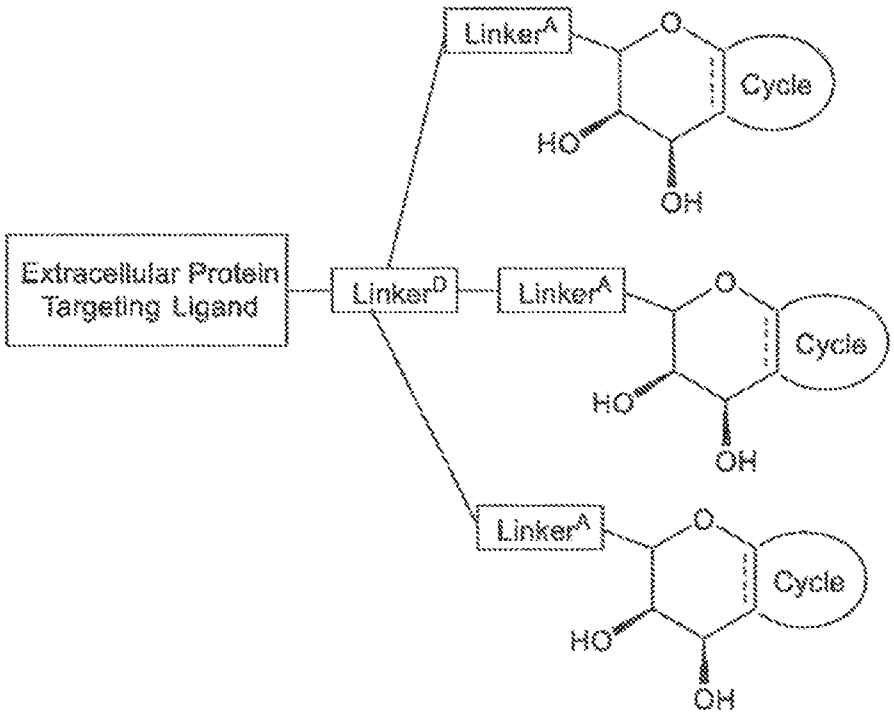
(V-d-Tri),


R^5
O
Linker^A
HO
R^2
OH
R^5
O
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
HO
R^2
OH
R^5
O
Linker^A
HO
R^2
OH

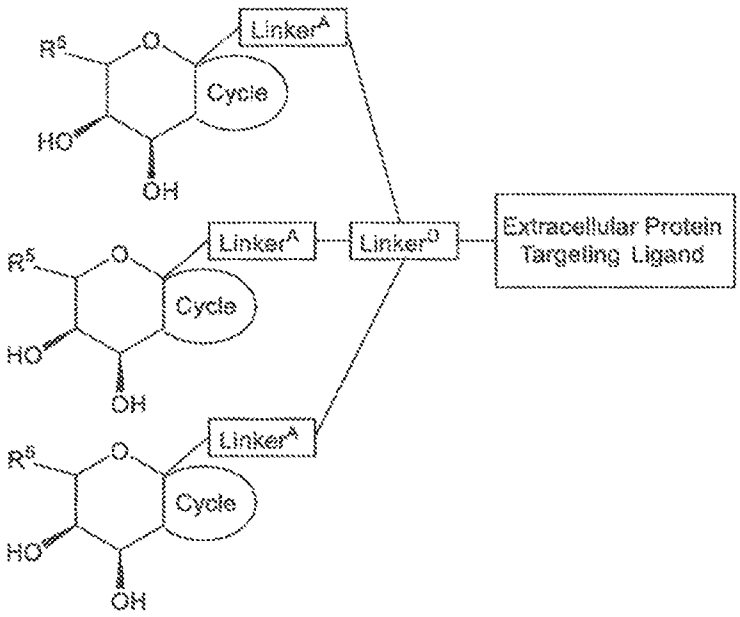
(VI-Tri).



(VI-d-Tri),



(VII-Tri), or



(VIII-Tri),

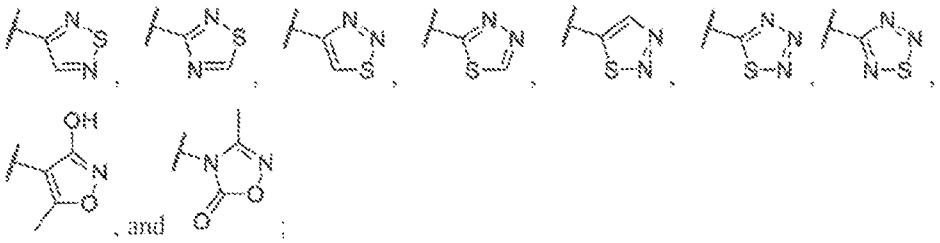
wherein:

Extracellular Protein Targeting Ligand is a MIF or IgG Binding Moiety, which binds respectively to circulating MIF or IgG in a subject, each of which is related to a disease state or condition and is to be removed by 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;

(ii)  , and ;

(iii) $-NR^8-S(O)-R^3$, $-NR^8-C(S)-R^3$, $-NR^8-S(O)(NR^6)-R^3$, $-N=S(O)(R^3)_2$, $-NR^8C(O)NR^8S(O)_2R^3$, $-NR^8-S(O)_2-R^{10}$, and $-NR^8-C(NR^6)-R^3$ each of which is optionally substituted with 1, 2, 3, or 4 substituents; and

(iv) hydrogen, R^{10}, alkyl-C(O)-R^3, -C(O)-R^3, alkyl, haloalkyl, -OC(O)R^3, and -NR^8-C(O)R^{10};

R^{10} is selected from aryl, alkyl-NR^8-C(O)-R^3, alkyl-aryl, alkyl-heteroaryl with 1, 2, or 4 heteroatoms, alkyl-cyano, alkyl-OR^6, alkyl-NR^6R^8, NR^8-NR^6-C(O)R^3, NR^8-$S(O)_2$-R^3, alkenyl, allyl, alkynyl, -NR^6-alkenyl, -O-alkenyl, -NR^6-alkynyl, -NR^6-heteroaryl, -NR^6-aryl, -O-heteroaryl, -O-aryl, and -O-alkynyl, each of which R^{10} is optionally substituted with 1, 2, 3, or 4 substituents;

R^1 and R^5 are independently selected from hydrogen, heteroalkyl, C_0-C_6alkyl-cyano, alkyl, alkenyl, alkynyl, haloalkyl, F, Cl, Br, I, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocycloalkyl, haloalkoxy, -O-alkenyl, -O-alkynyl, C_0-C_6alkyl-OR^6, C_0-C_6alkyl-SR^6, C_0-C_6alkyl-NR^6R^7, C_0-C_6alkyl-C(O)R^3, C_0-C_6alkyl-S(O)R^3, C_0-C_6alkyl-C(S)R^3, C_0-C_6alkyl-$S(O)_2R^3$, C_0-C_6alkyl-$N(R^8)$-C(O)R^3, C_0-C_6alkyl-$N(R^8)$-S(O)R^3, C_0-C_6alkyl-$N(R^8)$-C(S)R^3, C_0-C_6alkyl-$N(R^8)$-$S(O)_2R^3$ C_0-C_6alkyl-O-C(O)R^3, C_0-C_6alkyl-O-S(O)R^3, C_0-C_6alkyl-O-C(S)R^3, -N=S(O)$(R^3)_2$, C_0-C_6alkylN_3, and C_0-C_6alkyl-O-$S(O)_2R^3$, each of which is optionally substituted with 1, 2, 3, or 4 substituents;

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

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

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

R^8 and R^9 are independently selected at each occurrence from 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,

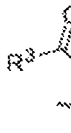
each $Linker^A$ is a bond or a moiety that covalently links the ASGPR ligand to $Linker^B$;

$Linker^B$ is a bond or a moiety that covalently links $Linker^A$ to an Extracellular Protein Targeting Ligand;

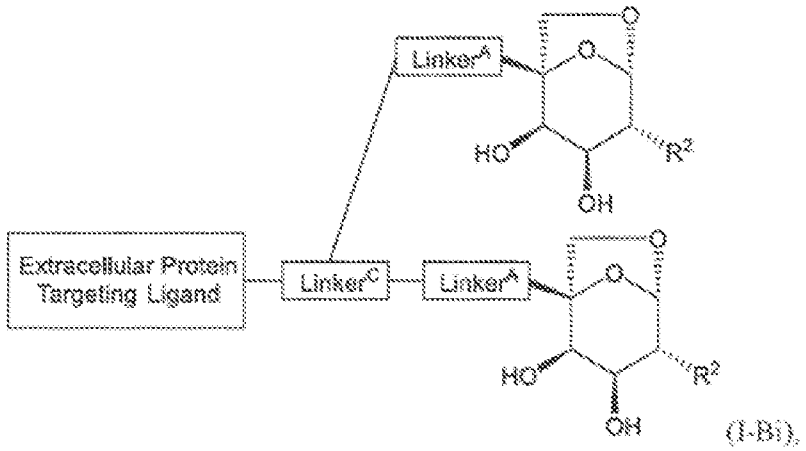
Linker^C is a chemical group that links each Linker^A to the Extracellular Protein Targeting Ligand; and

Linker^B is a chemical group that links each Linker^A to the Extracellular Protein Targeting Ligand; and

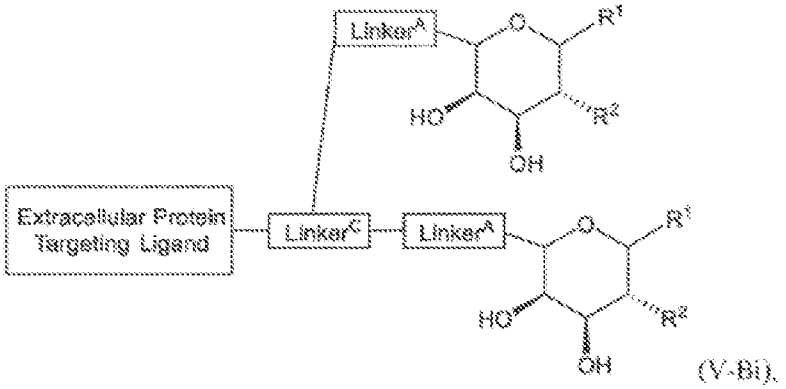
wherein, when R^2 is NR^6-alkenyl, -NR^6-alkynyl,-NR^8-C(O)R^{10}, -NR^8-S(O)$_2$-alkenyl, -NR^8-S(O)$_2$-alkynyl, -NR^6-heteroaryl, or -NR^6-aryl, then Extracellular Protein Targeting Ligand does not comprise an oligonucleotide; and

the optional substituents are selected from alkyl, alkenyl, alkynyl, haloalkyl, -OR^6, F, Cl, Br, I, -NR^6R^7, heteroalkyl, cyano, nitro, C(O)R^3,  ,  ,  , and  , as allowed by valence such that a stable compound results.

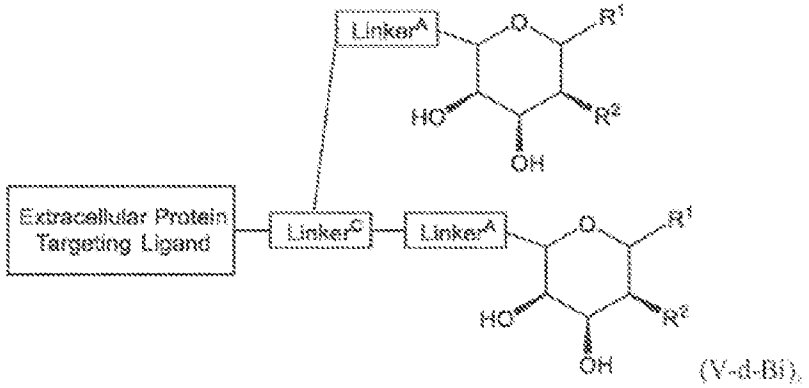
2. The bifunctional compound of claim 1, which is selected from the group consisting of:



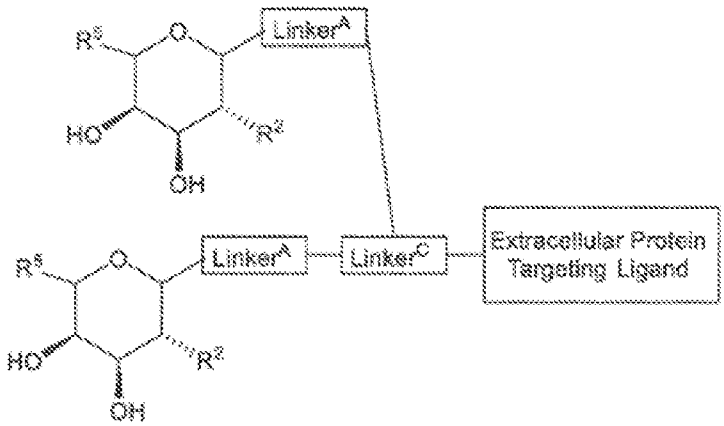
(I-Bi).



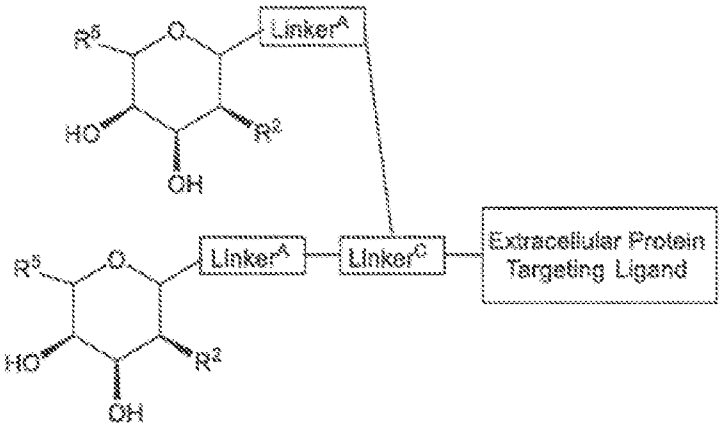
(V-Bi),



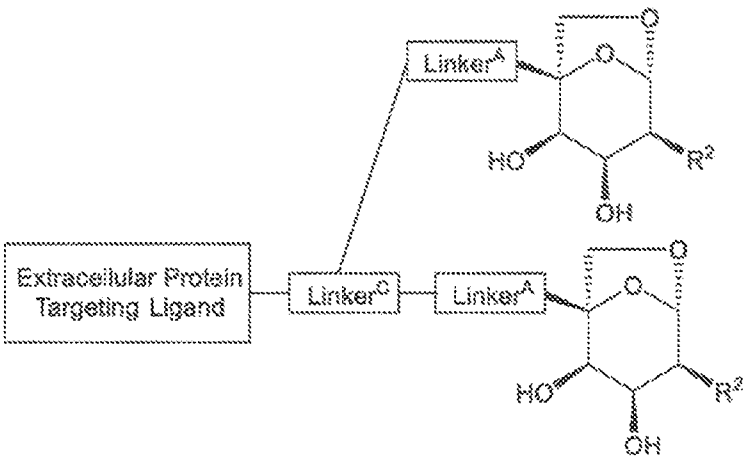
(V-d-Bi),



(VI-Bi),



(VI-d-Bi),



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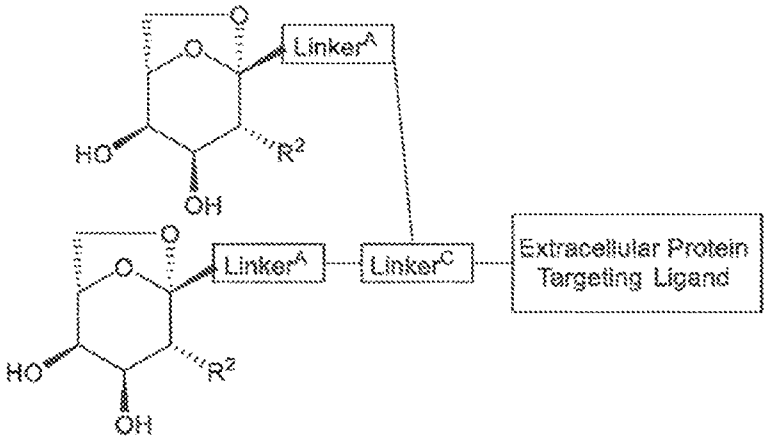
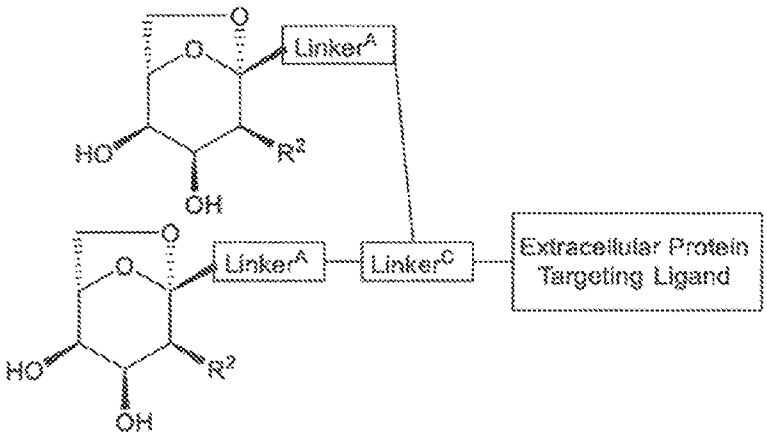
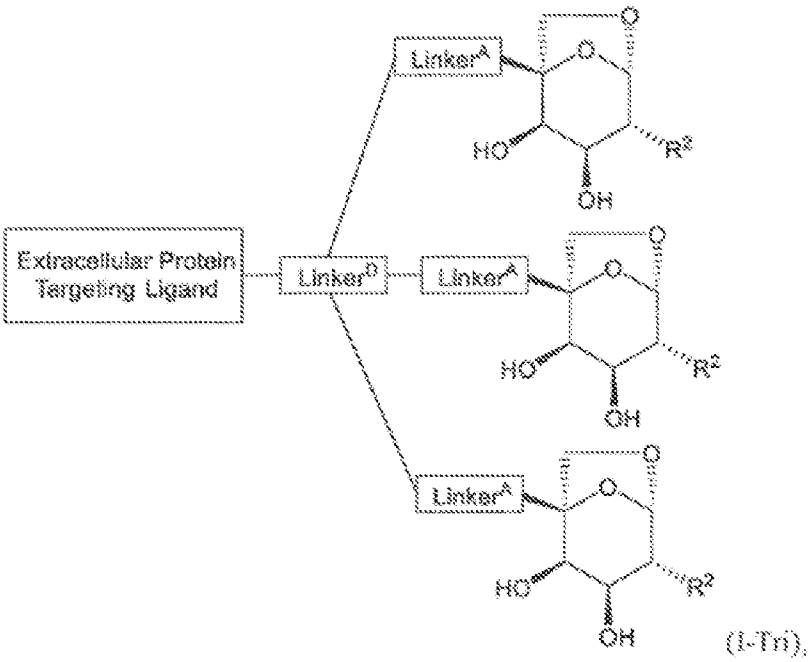


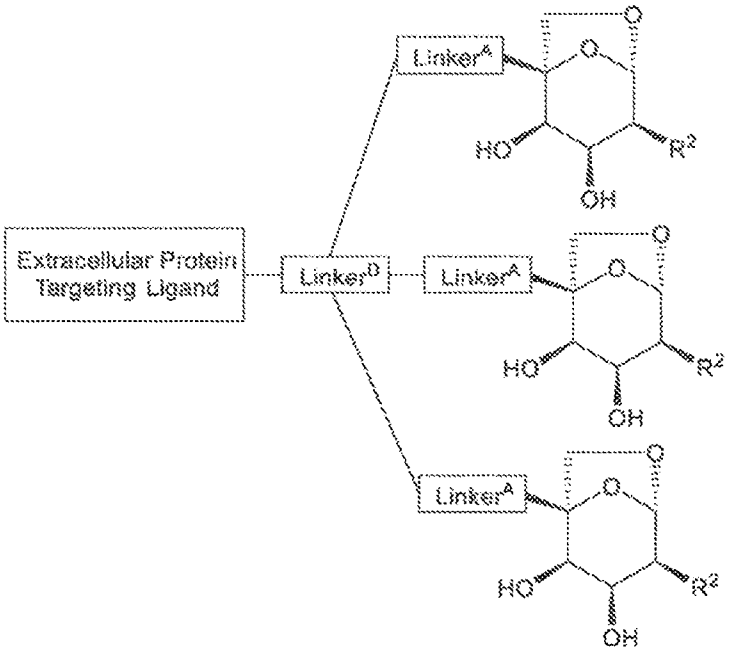
(I-Bi),



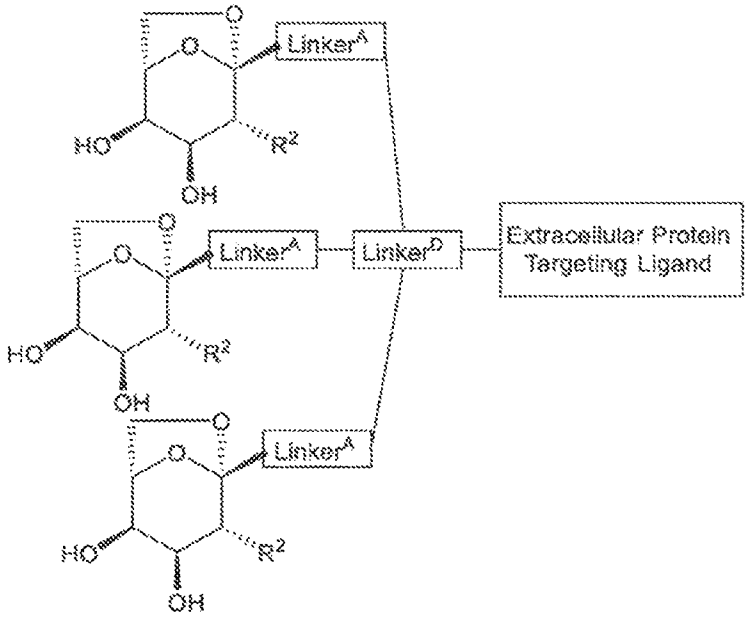
(II-d-Bi),


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A
HO
R^2
OH
O

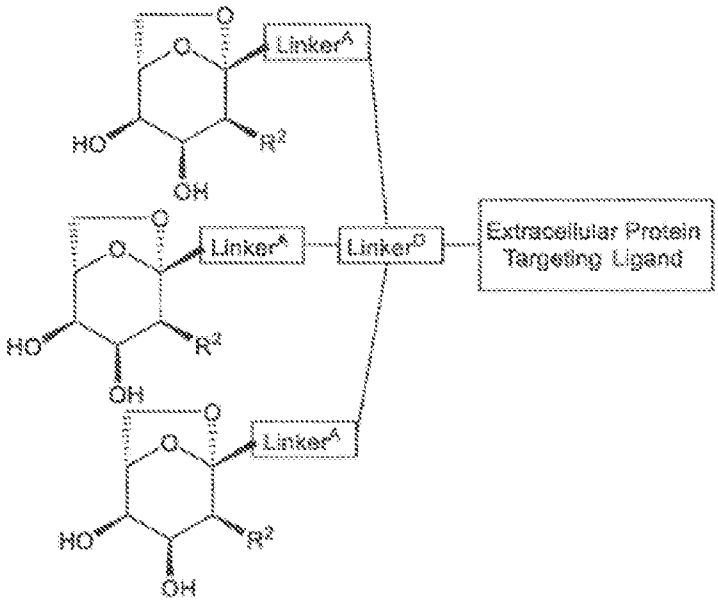
(I-Tn),


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A
HO
R^2
OH

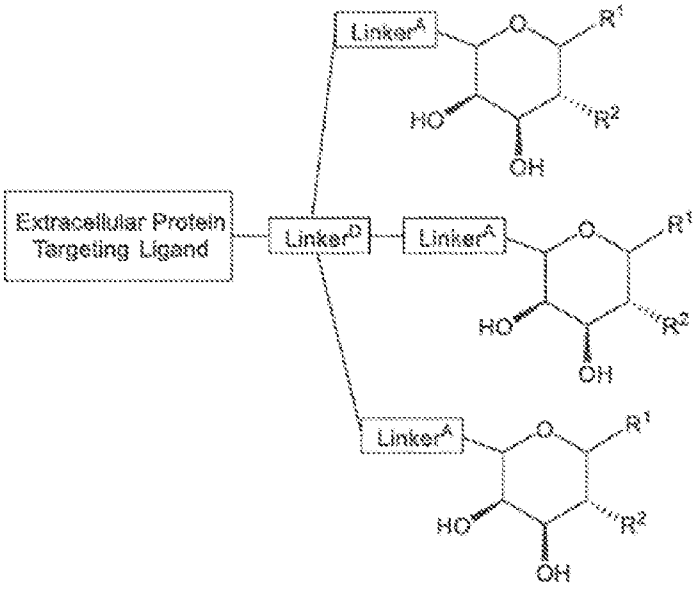
(I-d-Tri),


Linker^A
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
Linker^A
HO
R^2
OH

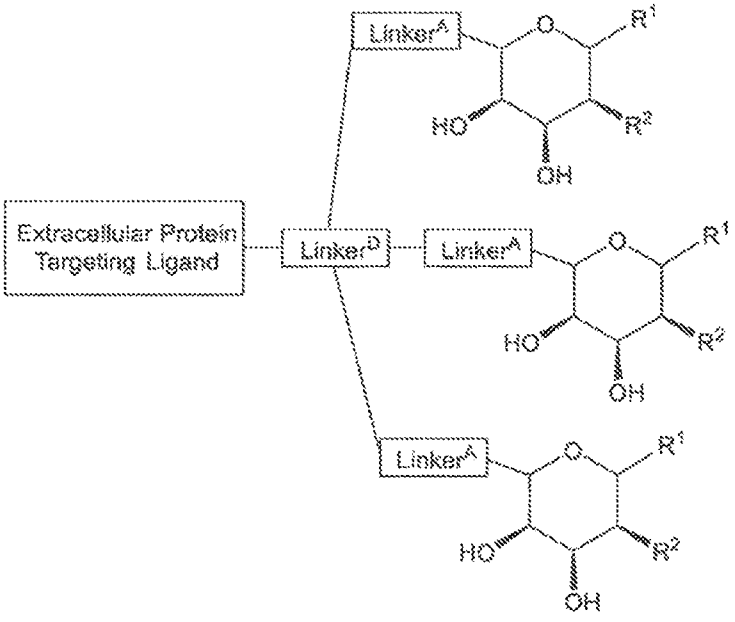
(II-Tri),


Linker^A
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
Linker^A
HO
R^2
OH

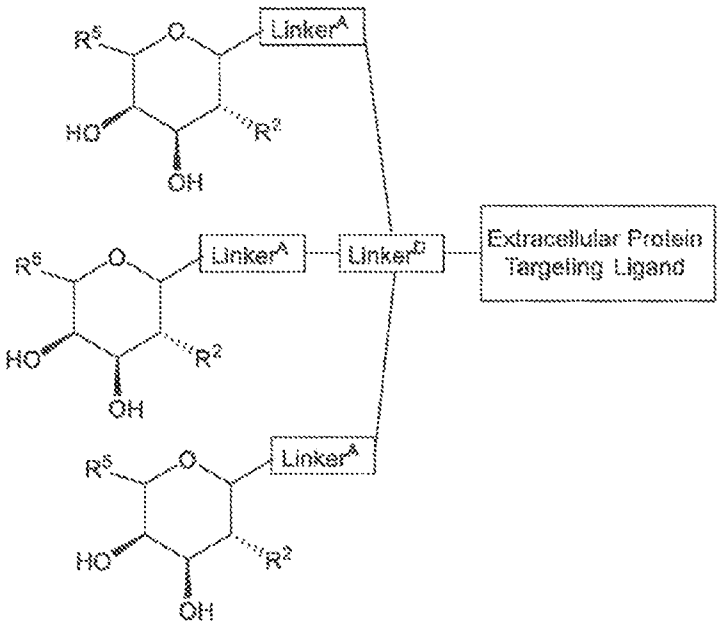
(II-d-Tn),


Linker^A
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
HO
R^1
R^2
OH

(V-Tn),

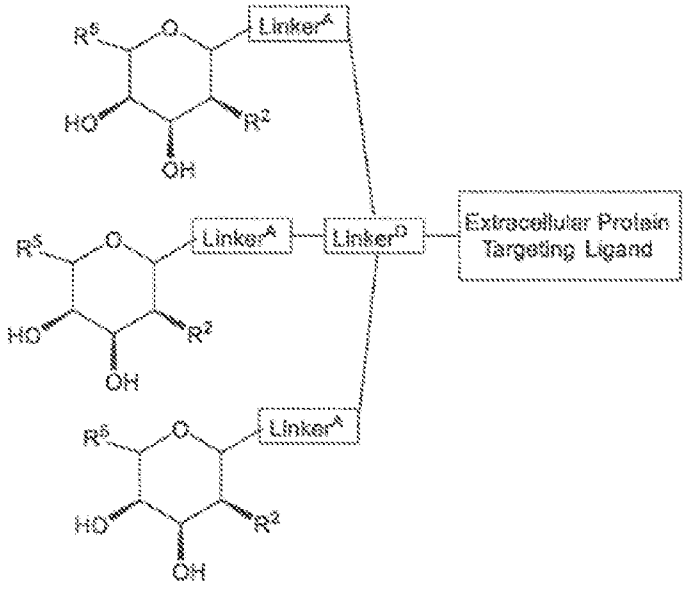


(V-d-Tri),



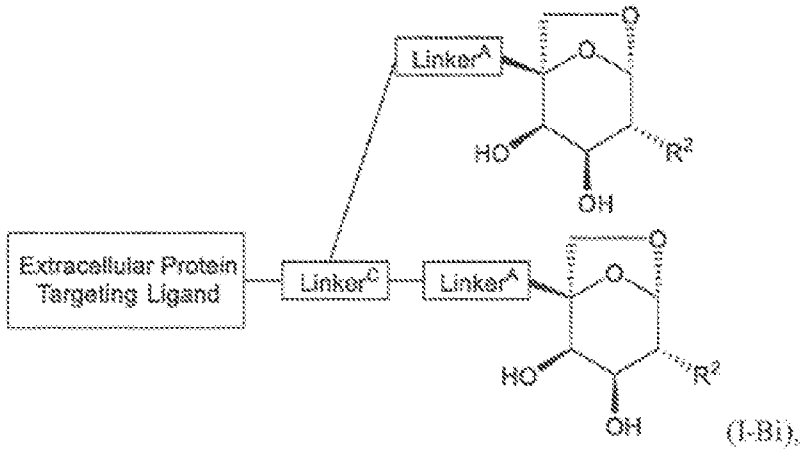
(VI-Tri),

and

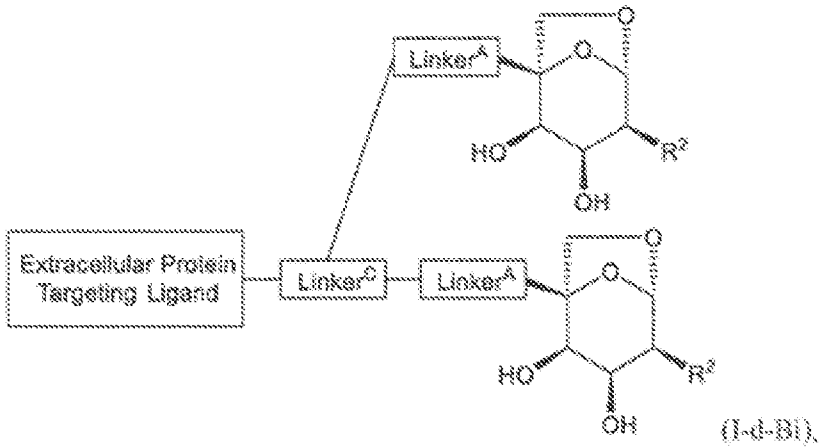


(VI-d-TrI).

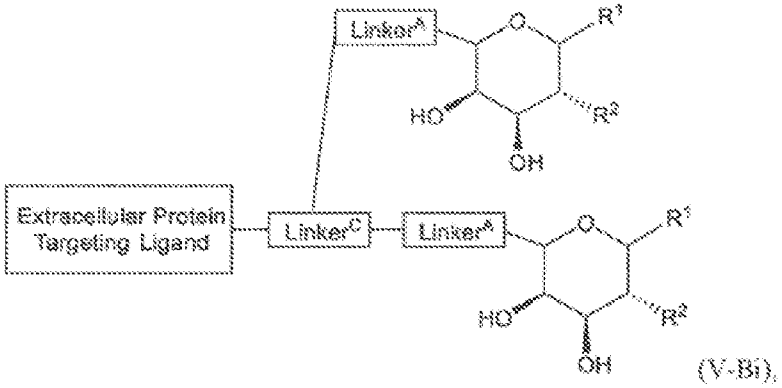
3. The bifunctional compound of claim 1, which is selected from the group consisting of:



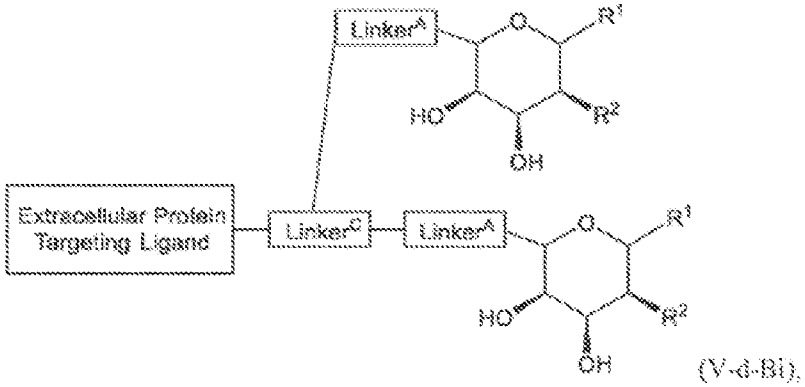
(I-Bi),



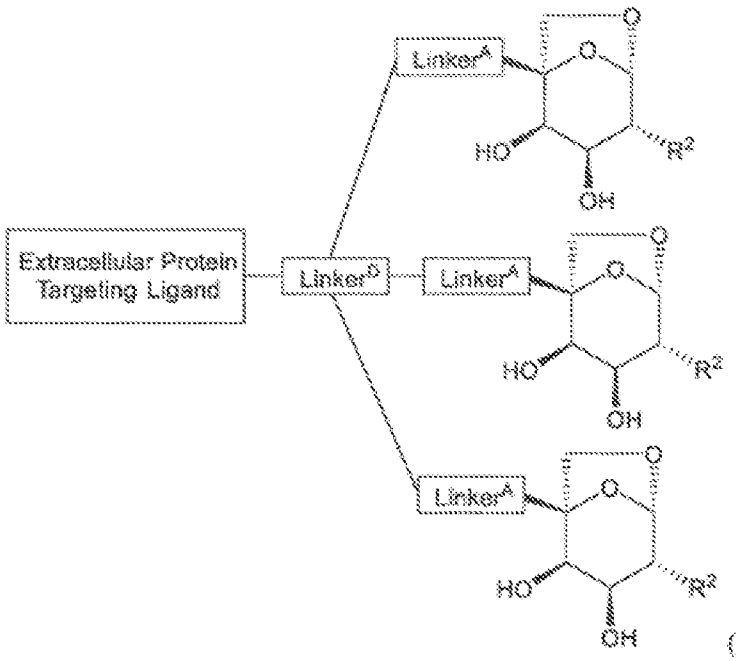
(I-d-Bi),



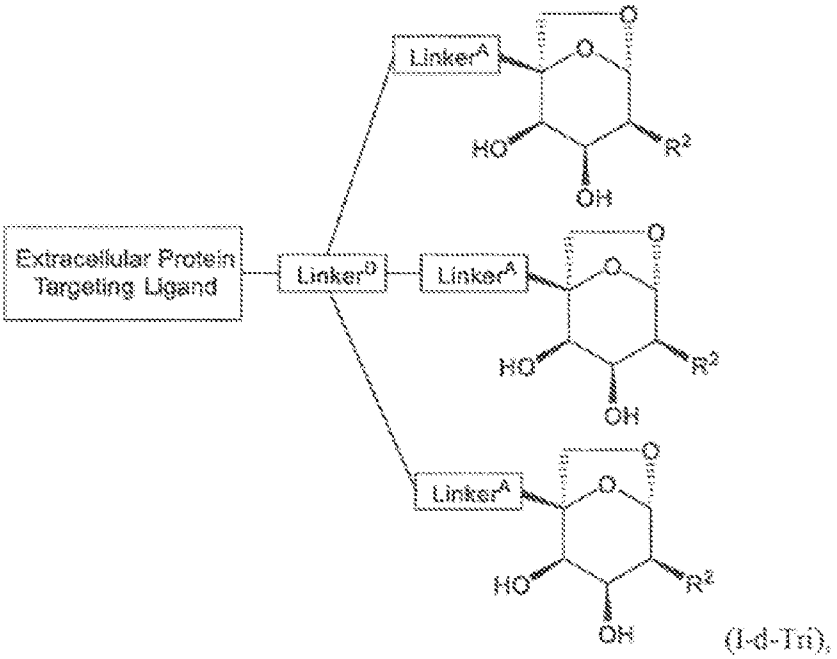
(V-Bi),



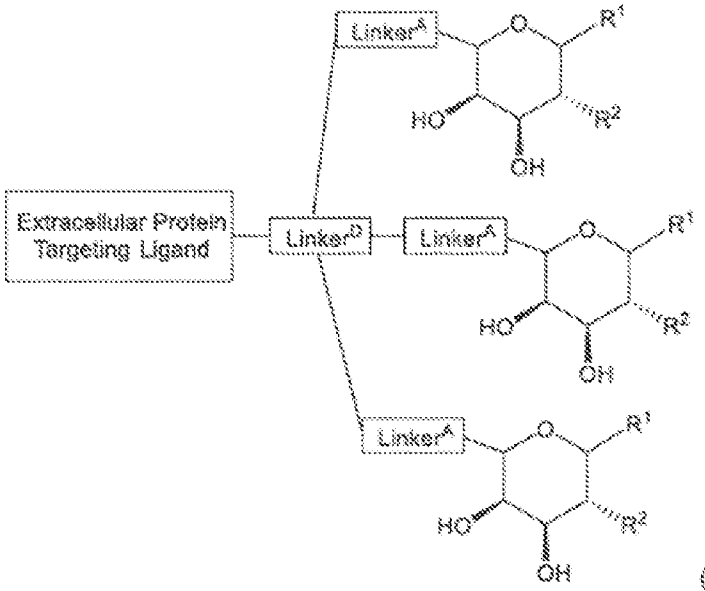
(V-d-Bi),



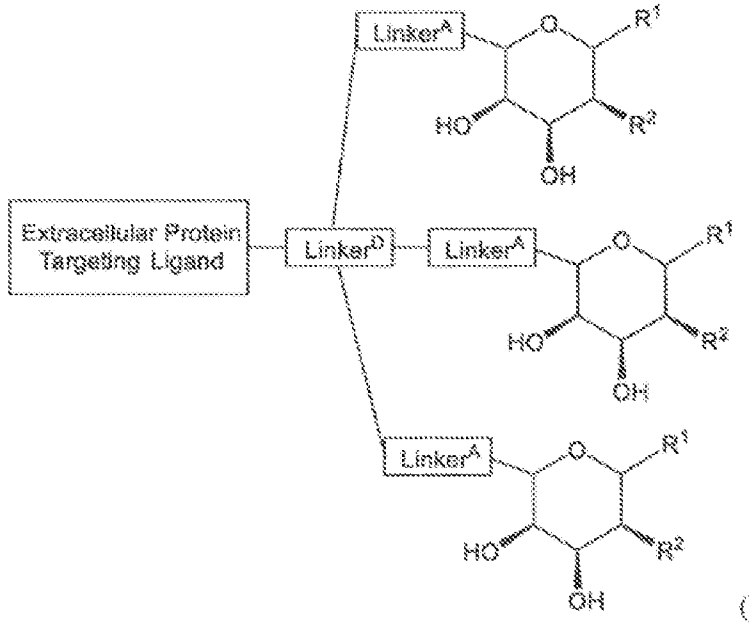
(I-Tri),


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
HO
R^2
OH
O

(I-d-Tn),


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
HO
R^1
R^2
OH
O

(V-Tn), and



(V-d-Tri).

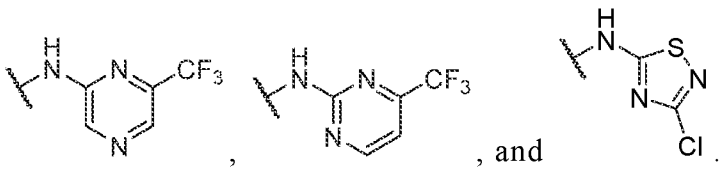
4. The bifunctional compound of any one of claims 1-3, wherein R^1 is H.

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:

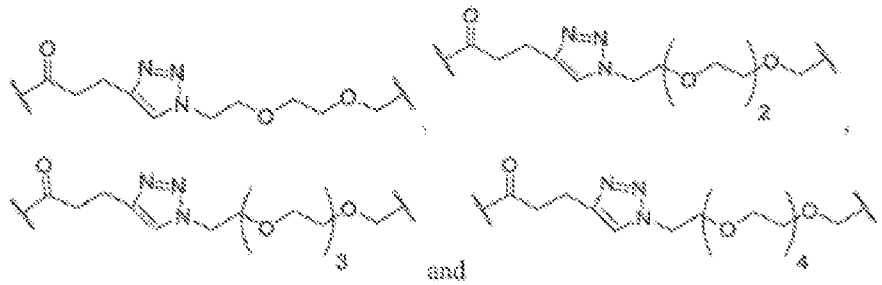


9. The bifunctional compound of any one of claims 1-8, wherein the Extracellular Protein Targeting Ligand is a MIF binding moiety.

10. The bifunctional compound of any one of claims 1-9, wherein the Extracellular Protein Targeting Ligand is an IgG binding moiety.

11. The bifunctional compound of any one of claims 1-10, wherein $Linker^A$ is selected

from the group consisting of



and

12. A pharmaceutical composition comprising a therapeutically effective amount of a bifunctional compound of any one of claims 1-11, in combination with a pharmaceutically acceptable carrier, additive, or excipient, optionally further comprising an additional bioactive agent effective to treat, ameliorate, and/or prevent cancer, autoimmune disease, or inflammatory disease in the patient or subject or which is associated with the upregulation of MIF or IgG in the patient or subject.

13. The composition of claim 12, wherein the additional anticancer agent is selected from the group consisting of: everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab (Arzerra), zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601 , ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001 , IPdR$_1$ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311 , romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N -[4-[2-(2-

amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11 , CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)-indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t) 6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH_2 acetate [$C_{59}H_{84}N_{18}Oi_4$ -($C_2H_4O_2$)x where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevac, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, irinotecan, topotecan, doxorubicin, docetaxel, vinorelbine, bevacizumab, erbitux, cremophor-free paclitaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor,

zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa and darbepoetin alfa, vemurafenib, PD-L1 checkpoint inhibitor, PD-1 checkpoint inhibitor, or CTLA-4 checkpoint inhibitor.

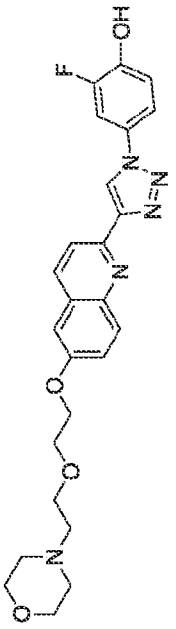
14. A method of removing excess circulating MIF or IgG in a patient or subject, the method comprising administering to the patient or subject a therapeutically effective amount of a bifunctional compound of any one of claims 1-11.

15. A method of treating, ameliorating, and/or preventing a disease state or condition which is associated with the upregulation of MIF or IgG 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 1-11.

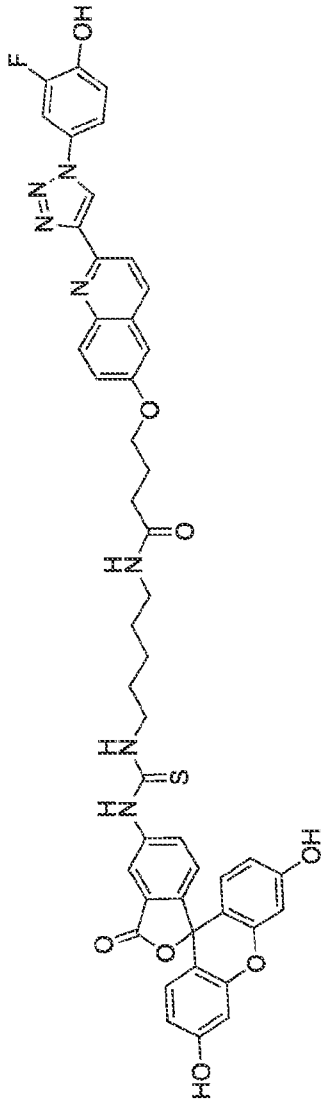
16. The method of claim 15, wherein the disease state or condition is cancer, an autoimmune disease, or an inflammatory disease.

17. A method of treating, ameliorating, or preventing cancer, an autoimmune disease, or an inflammatory disease in a subject or patient, the method comprising administering to the subject or patient a therapeutically effective amount of a bifunctional compound of any one of claims 1-11.

FIGURE 1

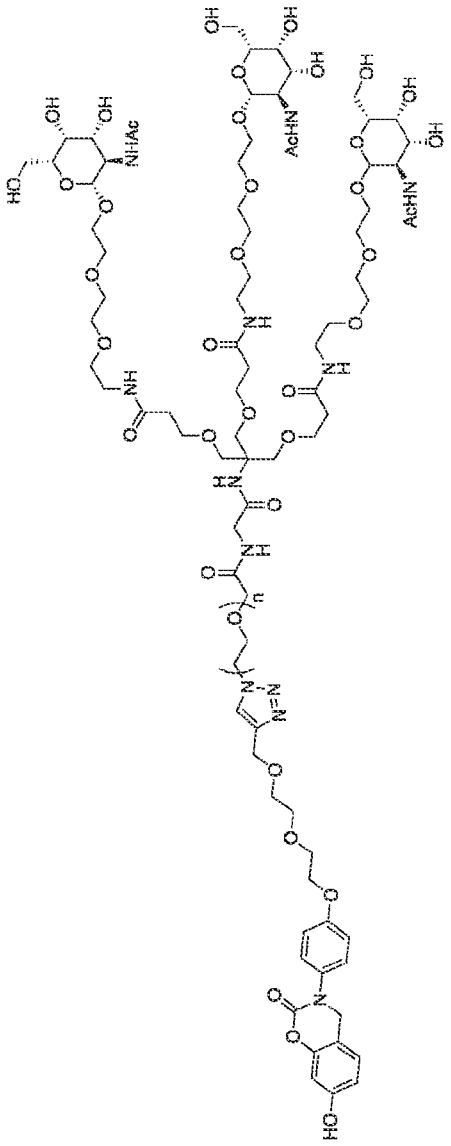


3w (negative control MIF inhibitor)

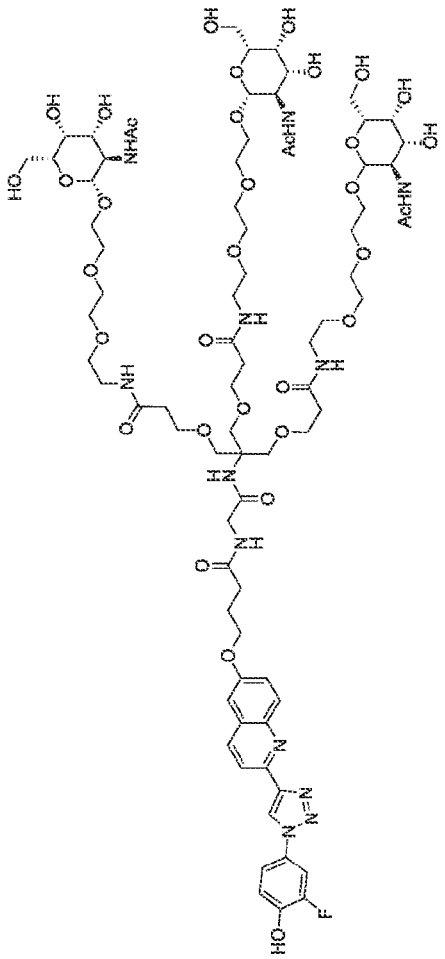


MIF-FITC (fluorescent MIF binder)

FIGURE 1 (Cont'd)

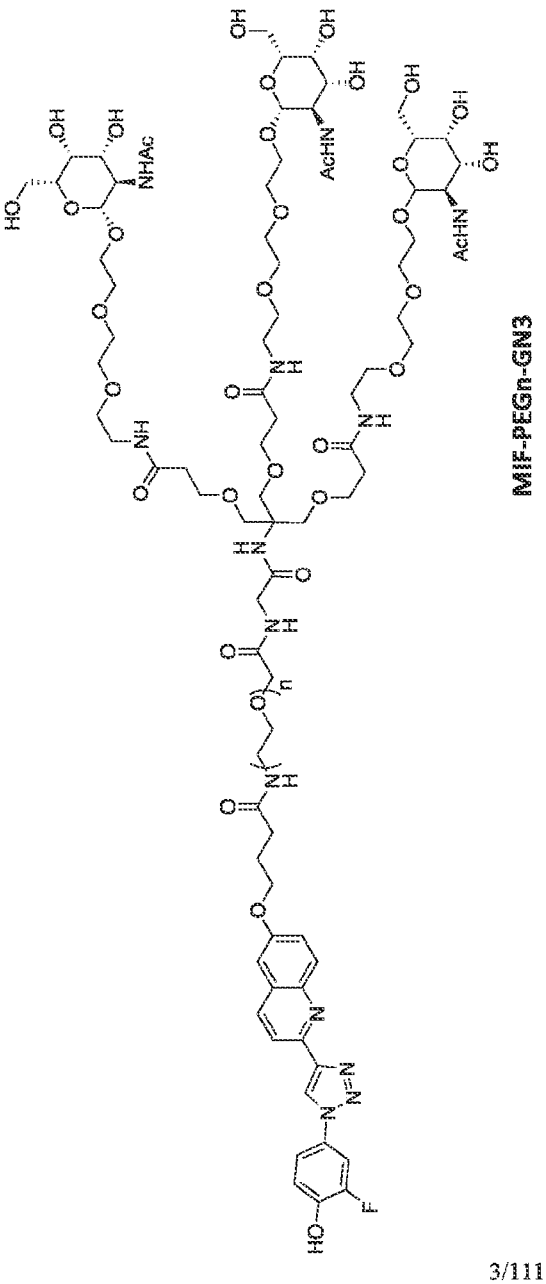


MIF-NVS-PEGn-GN3

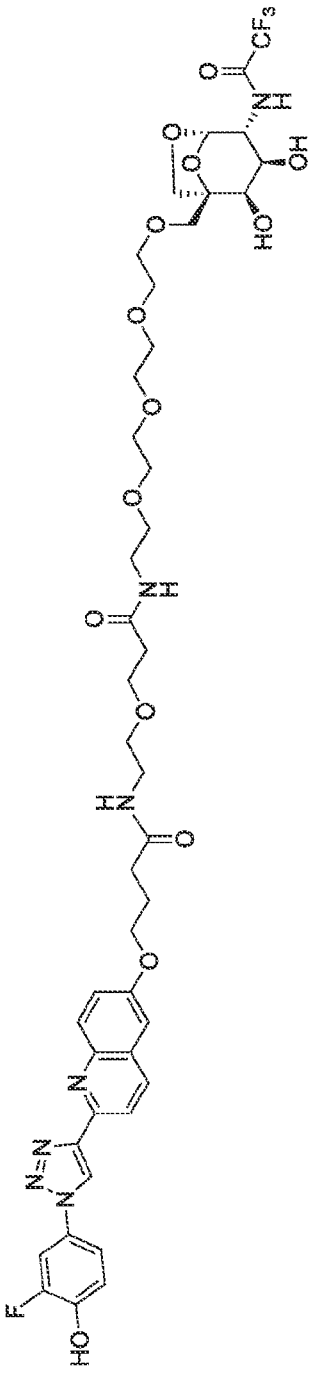


MIF-GN3

FIGURE 1 (Cont'd)

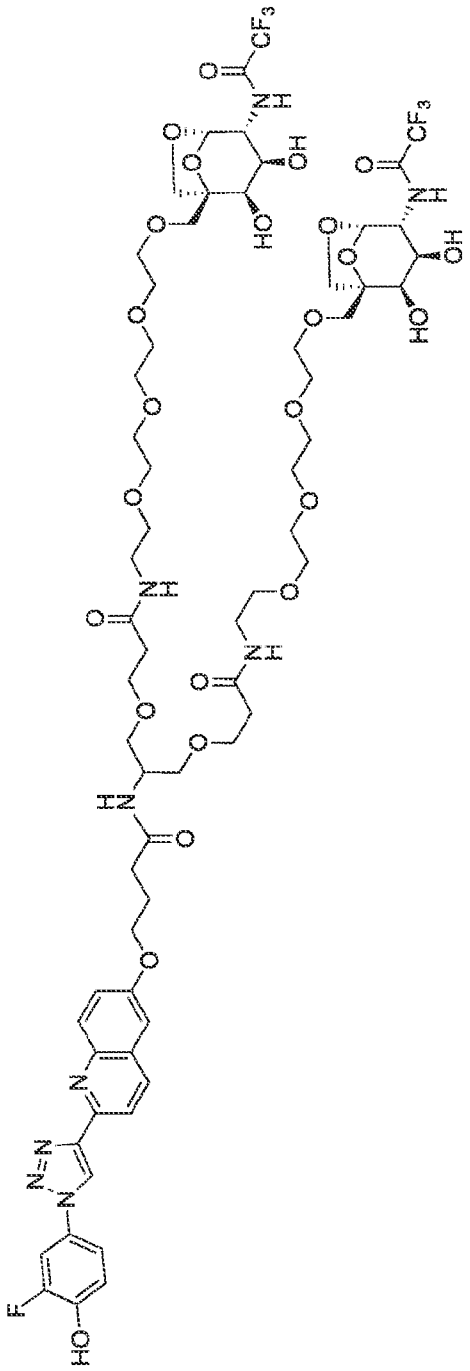


MIF-PEGn-GN3



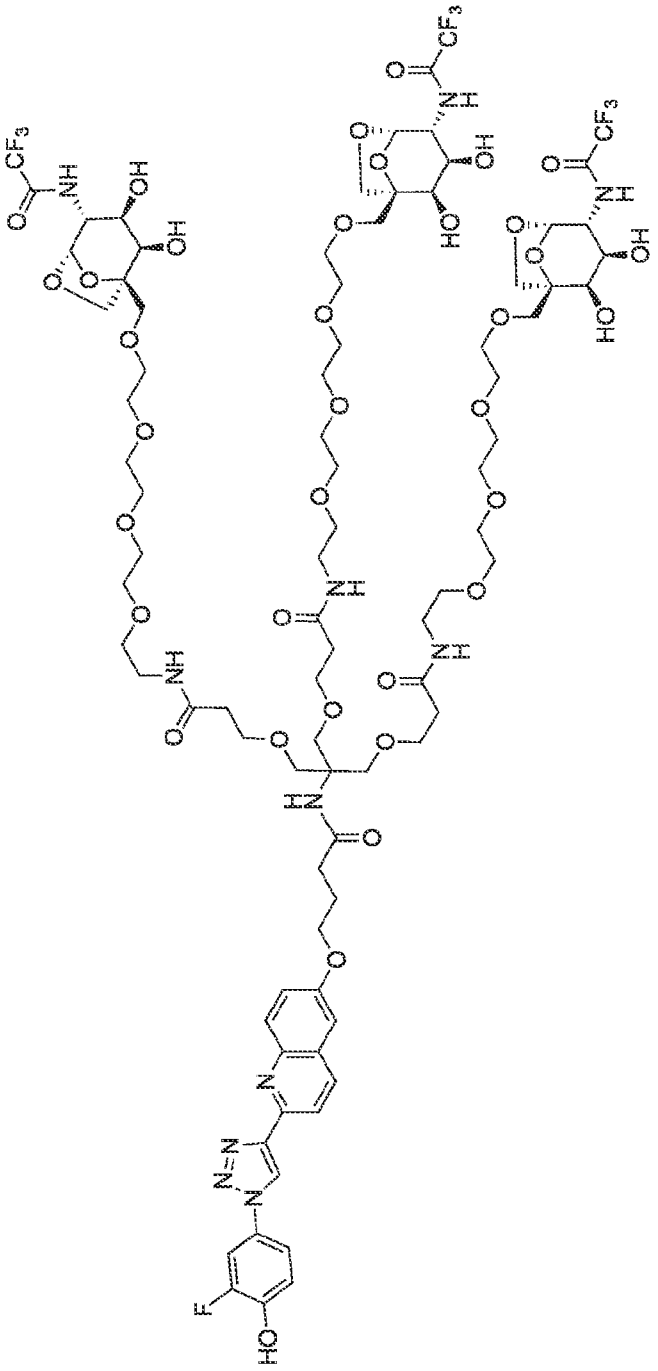
MIF-AcF3-1

FIGURE 1 (Cont'd)



MIF-AcF3-2

FIGURE 1 (Cont'd)



MIF-AcF3-3

FIGURE 2

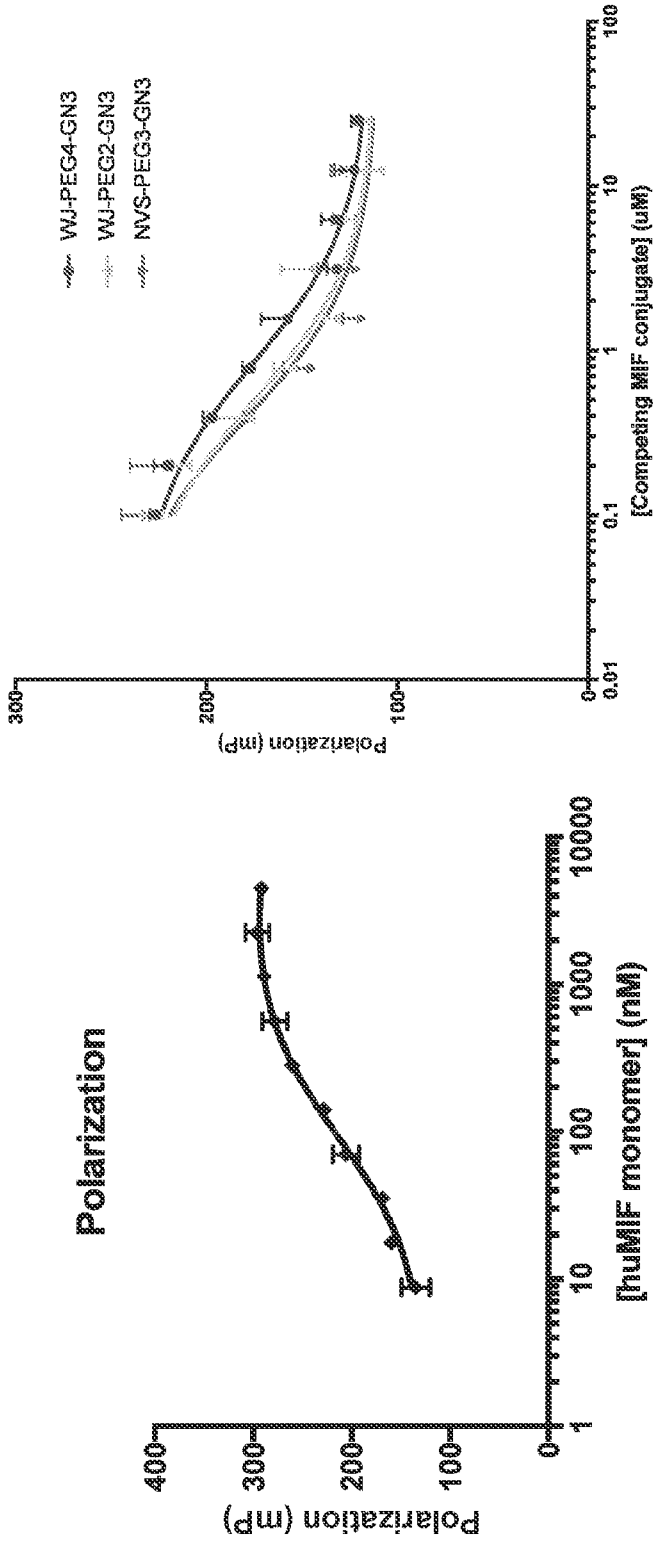

Polarization
Polarization (mP)
400
300
200
100
0
1
10
100
1000
10000
[huMIF monomer] (nM)
WJ-PEG4-GN3
WJ-PEG2-GN3
NVS-PEG3-GN3
Polarization (mP)
300
200
100
0
0.01
0.1
1
10
100
[Competing MIF conjugate] (uM)

FIGURE 3

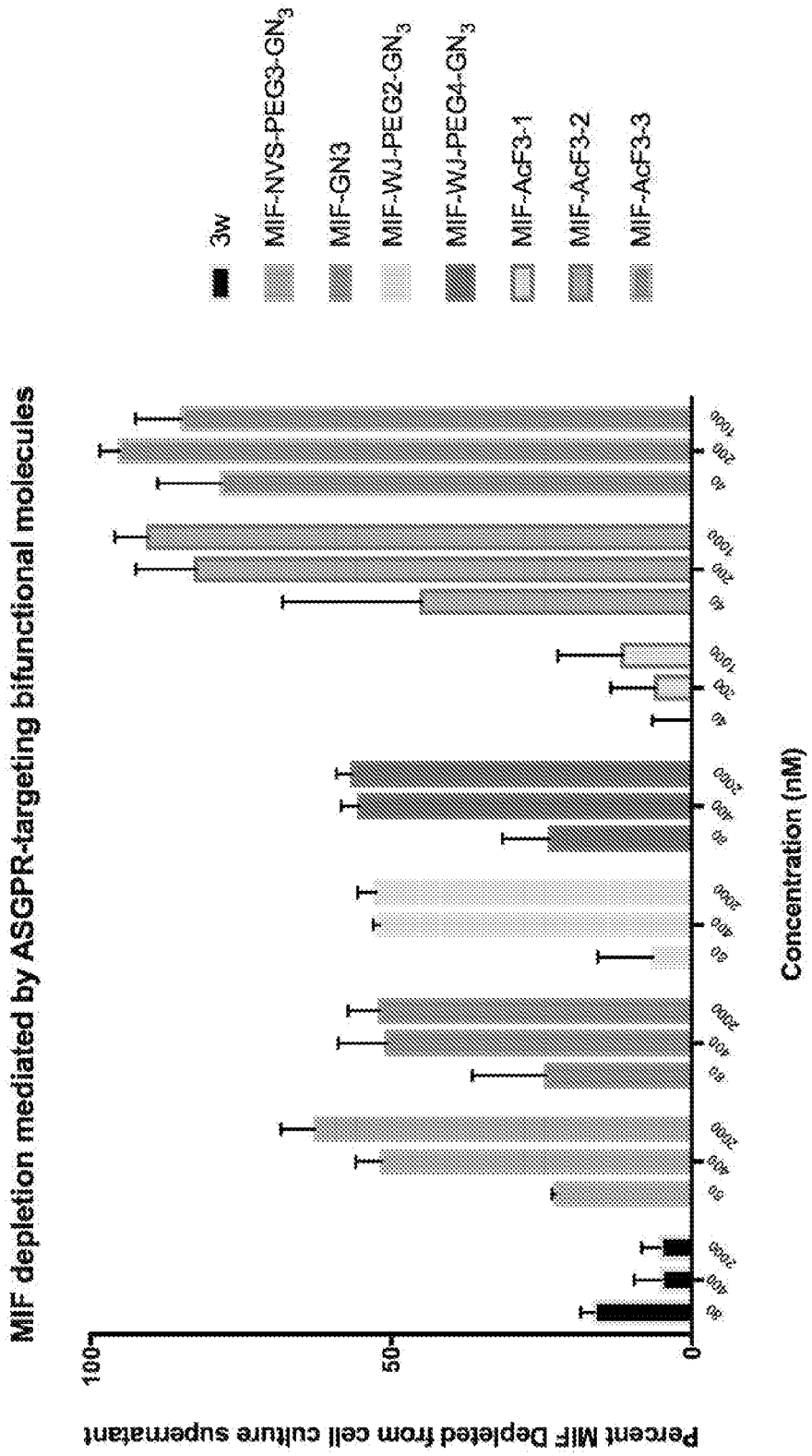

MIF depletion mediated by ASGPR-targeting bifunctional molecules
Percent MIF Depleted from cell culture supernatant
100
50
0
Concentration (nM)
3w
MIF-NVS-PEG3-GN3
MIF-GN3
MIF-WJ-PEG2-GN3
MIF-WJ-PEG4-GN3
MIF-AcF3-1
MIF-AcF3-2
MIF-AcF3-3

FIGURE 4

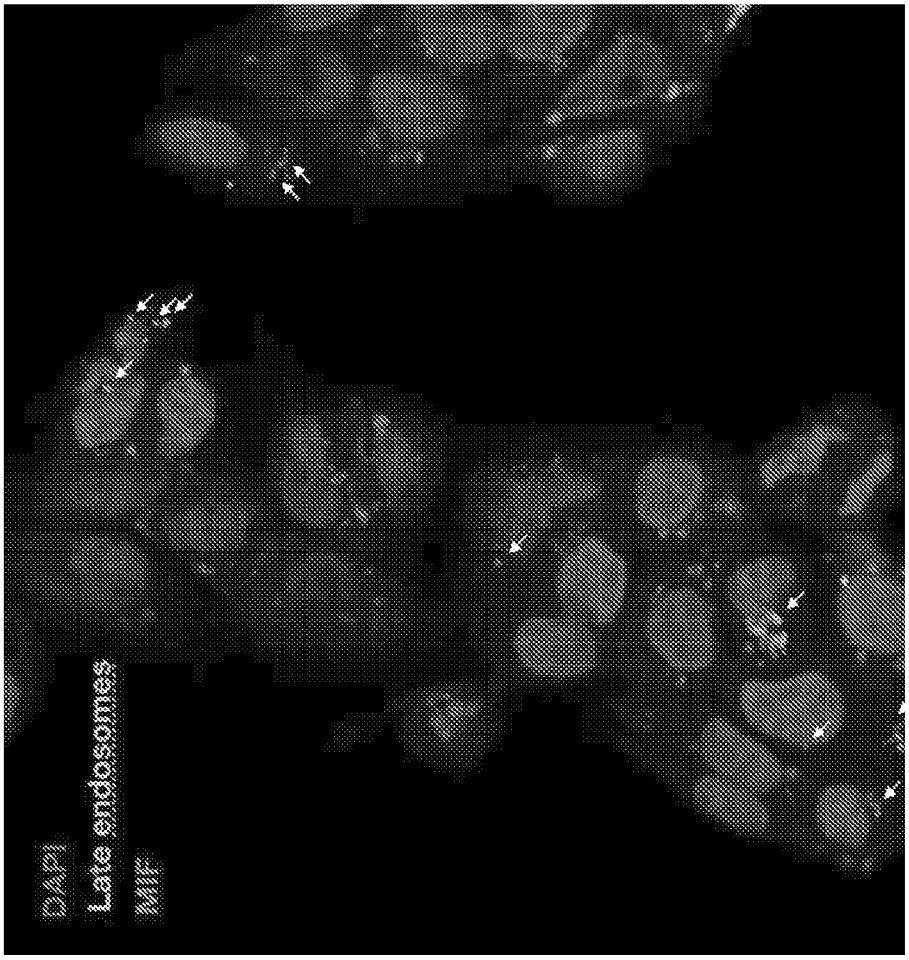


FIGURE 5

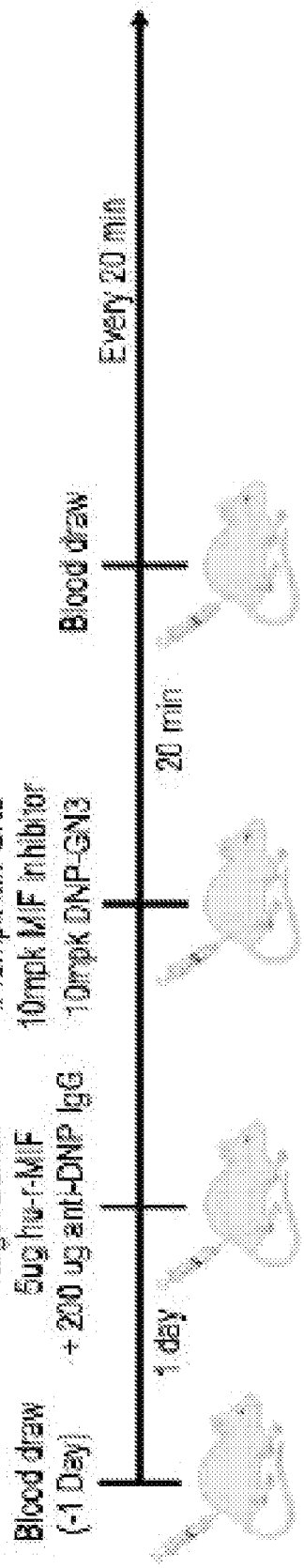

Blood draw
(-1 Day)
1 day
Target admin
Sug hu-r-M/F
+ 200 ug anti-DNP IgG
Drug admin
1/10mpk MIFGN3
10mpk M/F inhibitor
10mpk DNP-GN3
20 min
Blood draw
Every 20 min

FIGURE 5 (Cont'd)

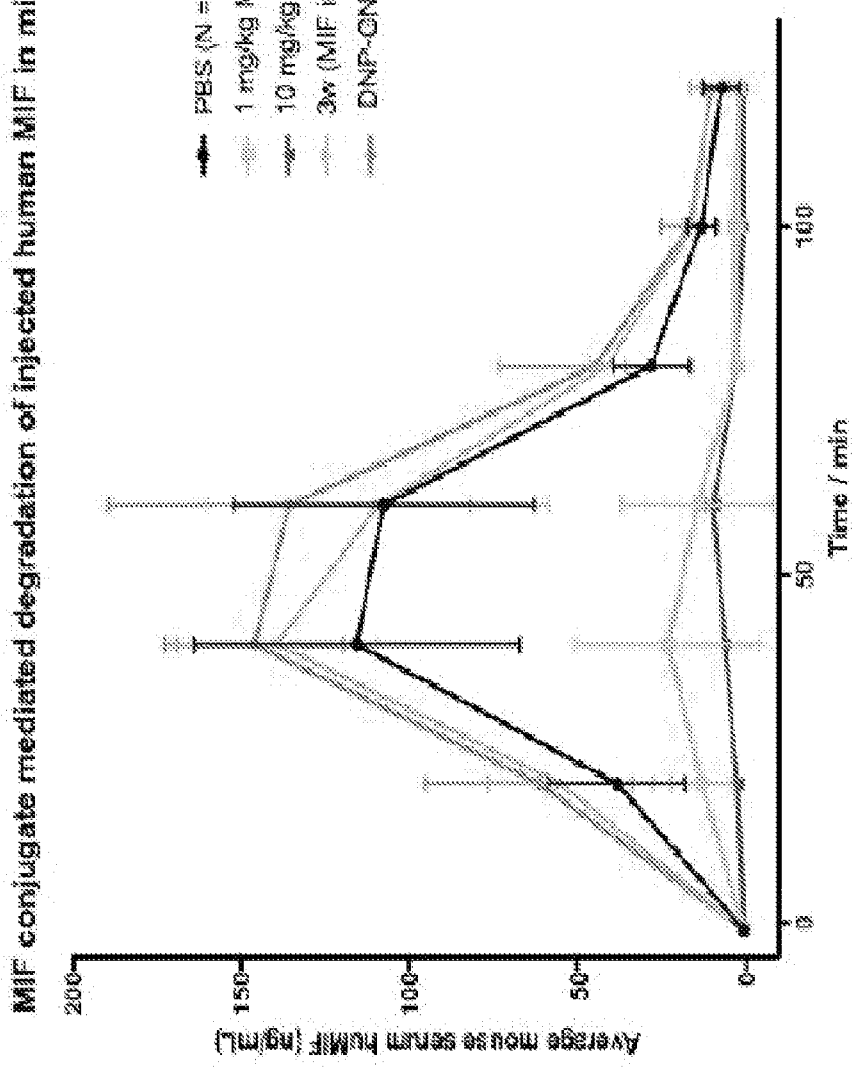


FIGURE 5 (Cont'd)

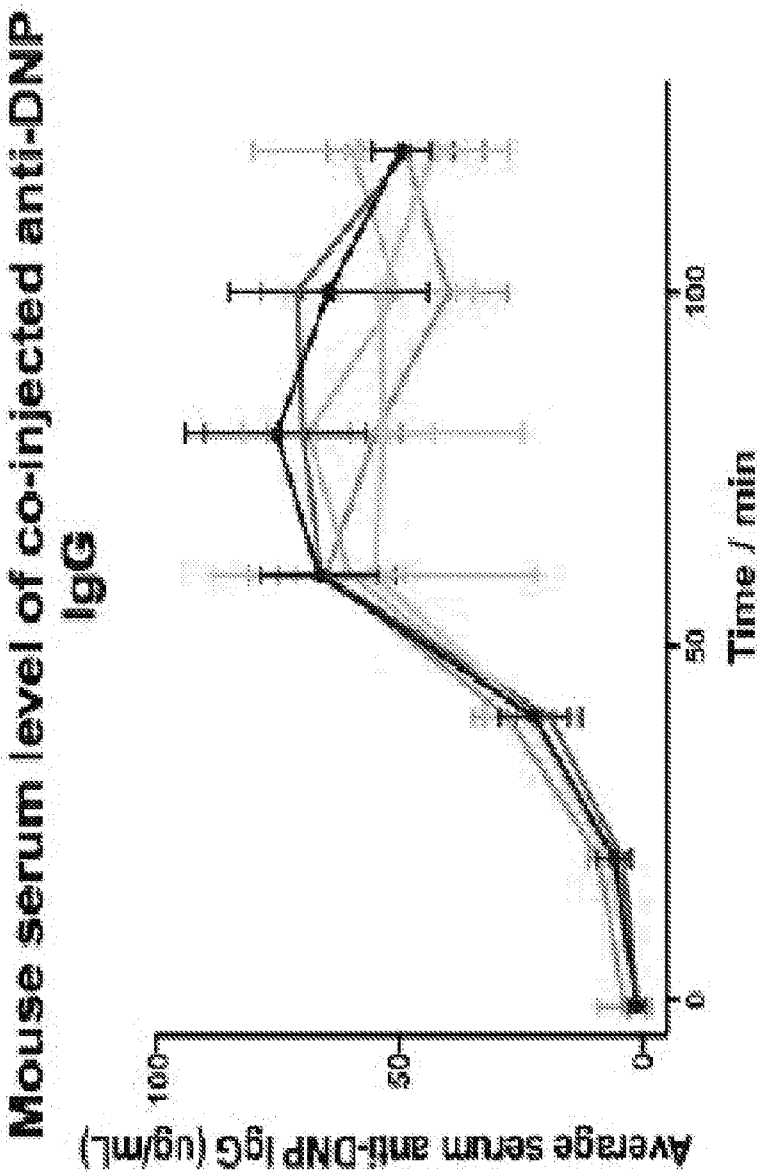


FIGURE 6

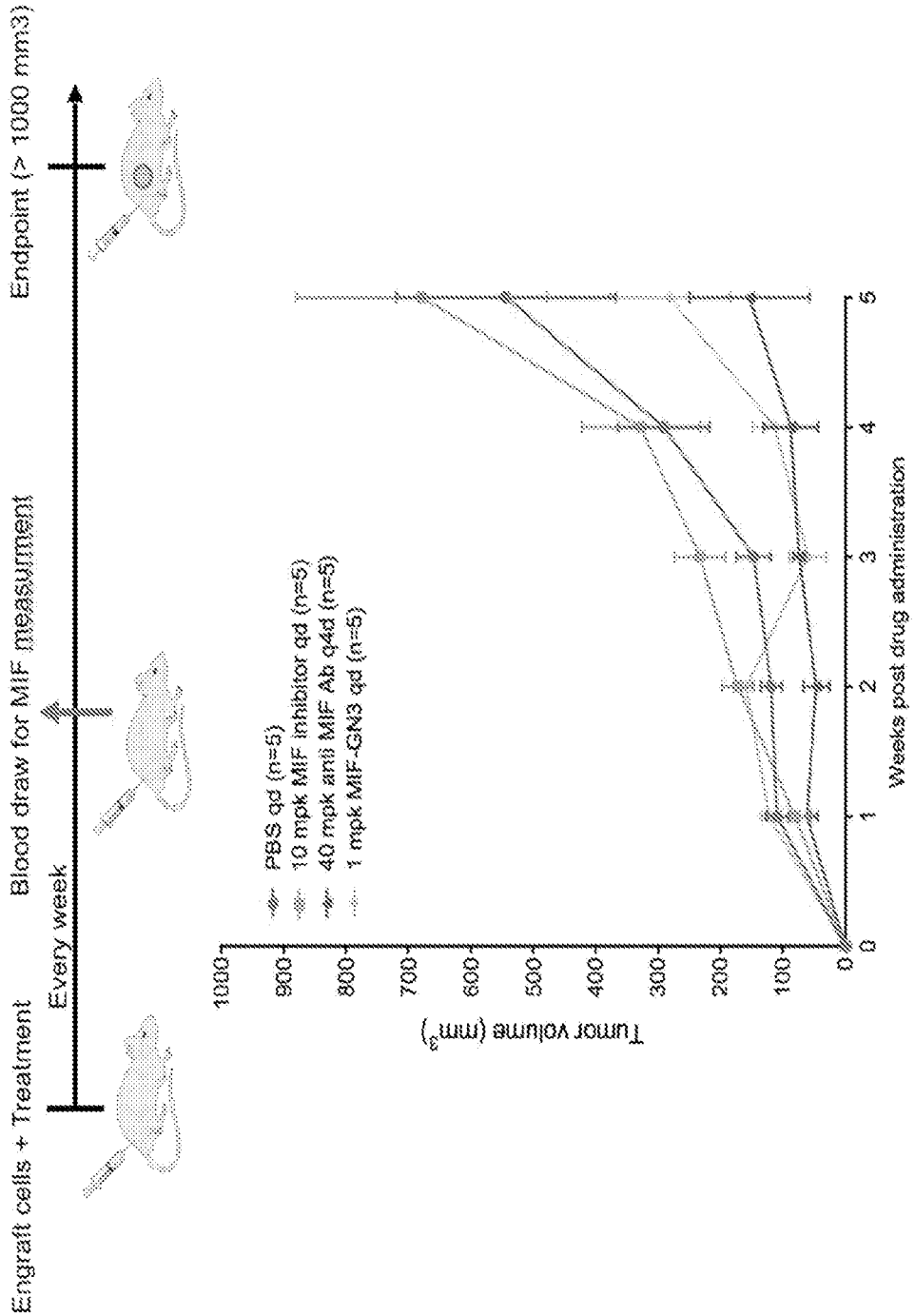

Engraft cells + Treatment
Every week
Blood draw for MIF measurment
Endpoint (> 1000 mm3)
PBS qd (n=5)
10 mpk MIF inhibitor qd (n=5)
40 mpk anti MIF Ab q4d (n=5)
1 mpk MIF-GM3 qd (n=5)
Tumor volume (mm3)
Weeks post drug administration

FIGURE 7

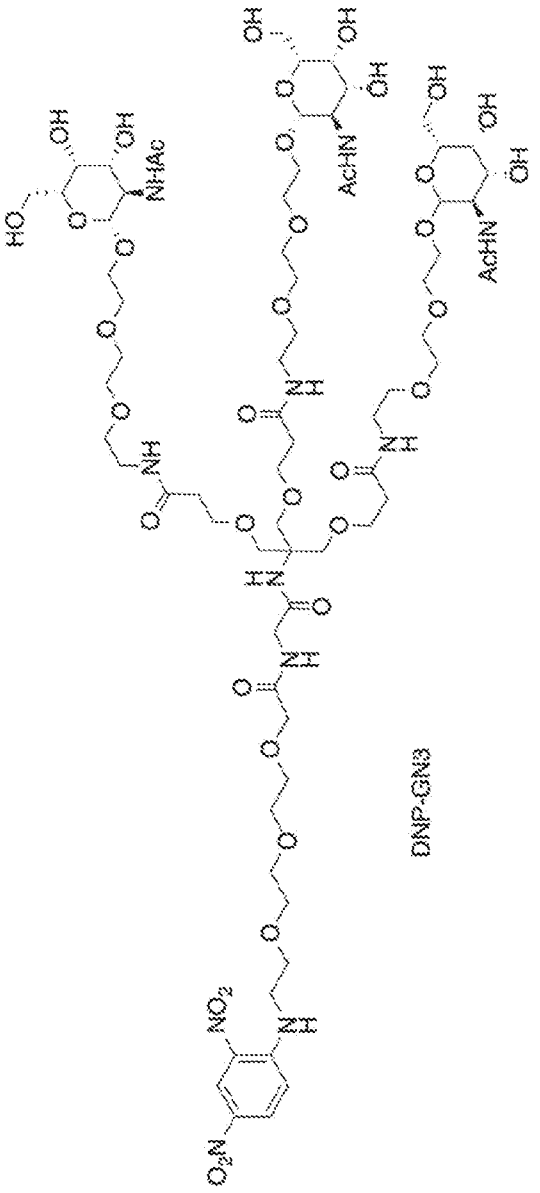


FIGURE 7 (Cont'd)

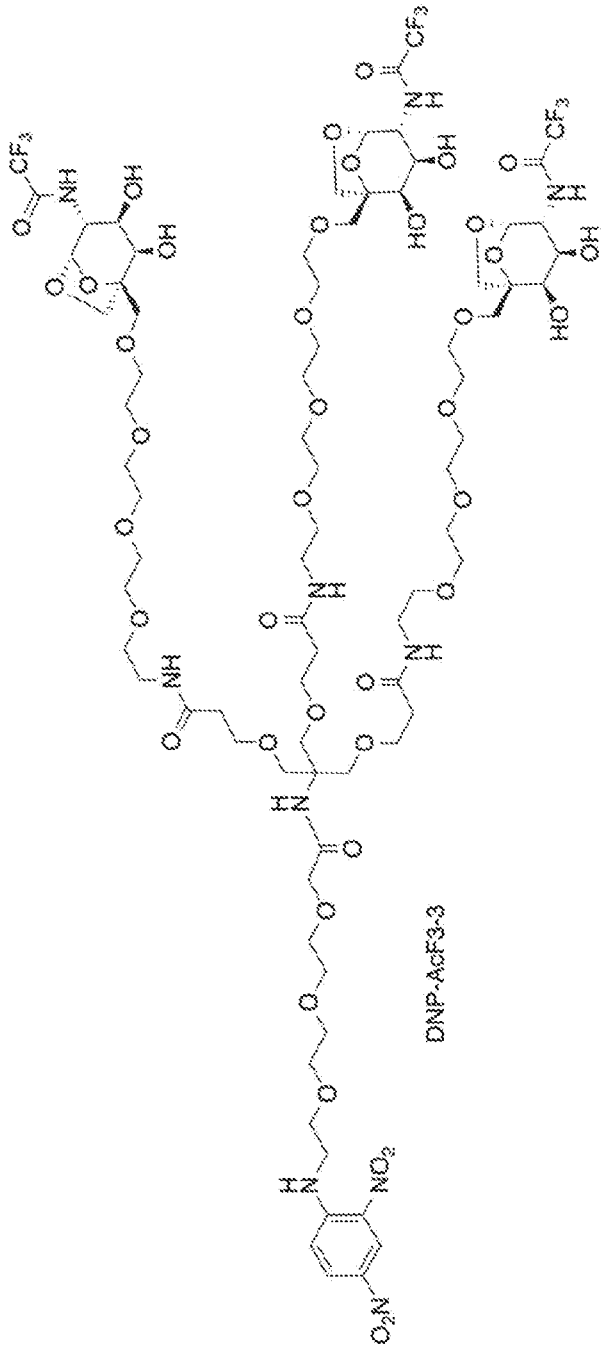


FIGURE 8

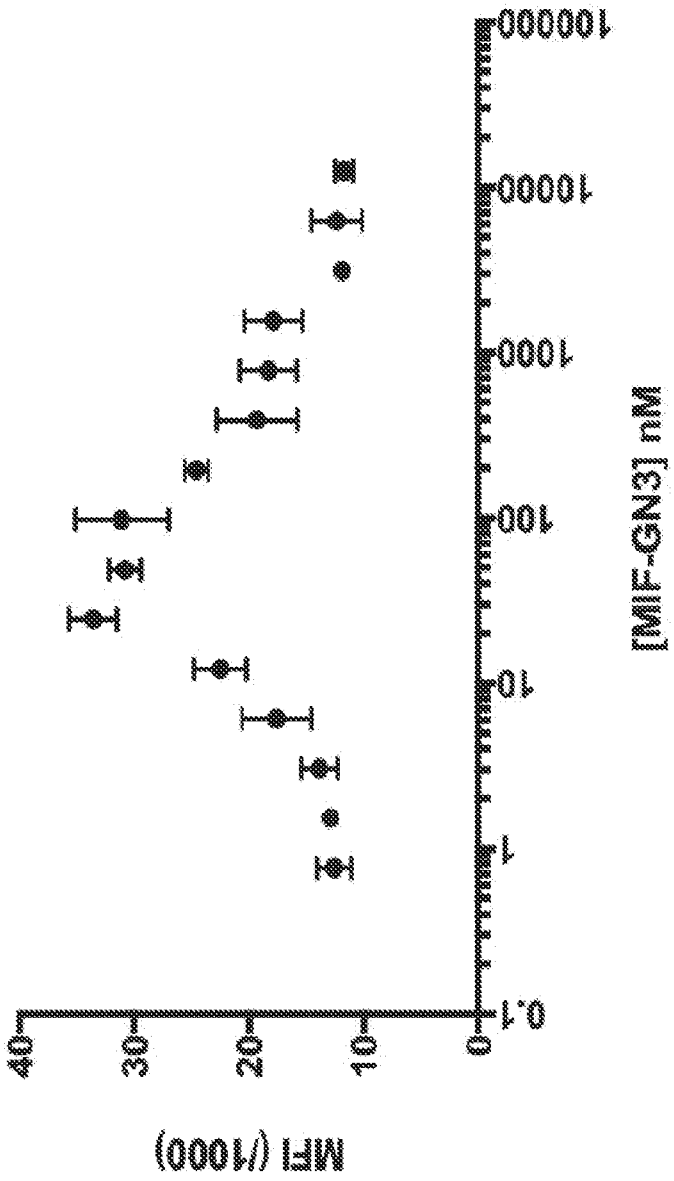


FIGURE 8 (Cont'd)

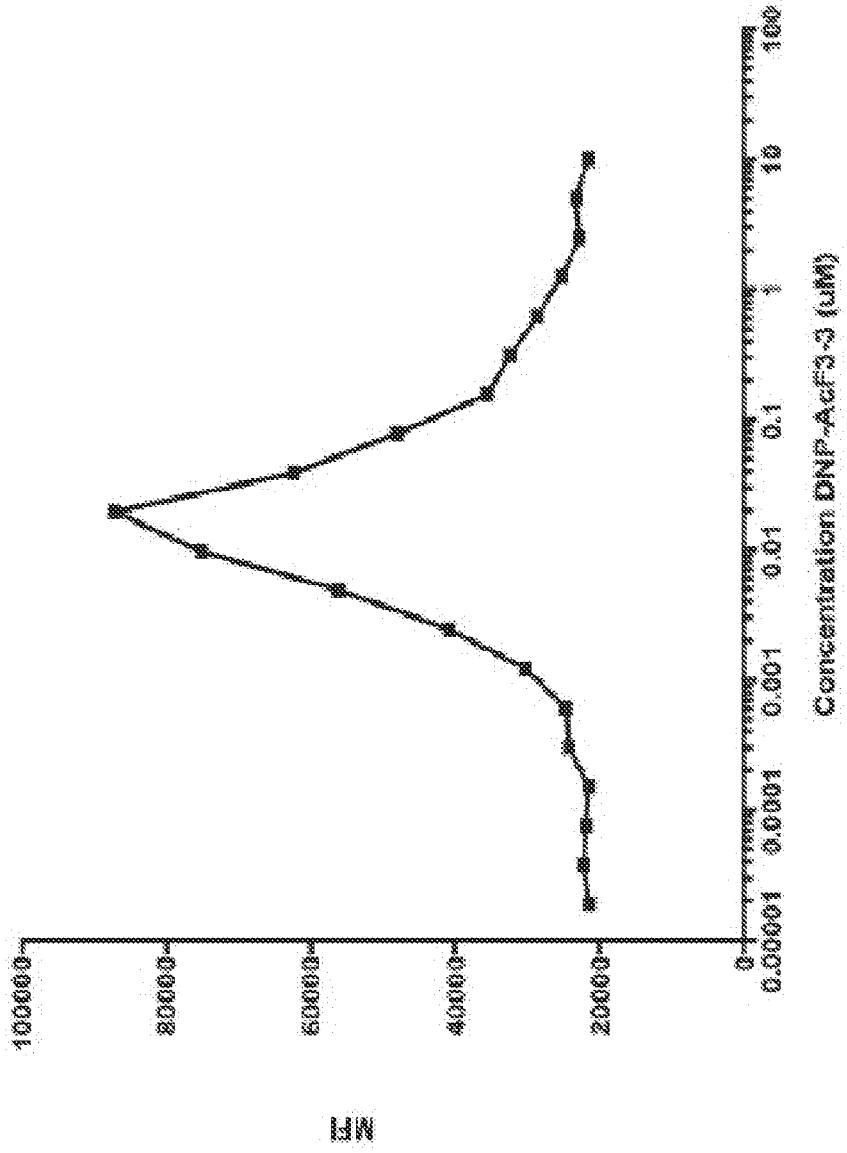


FIGURE 9

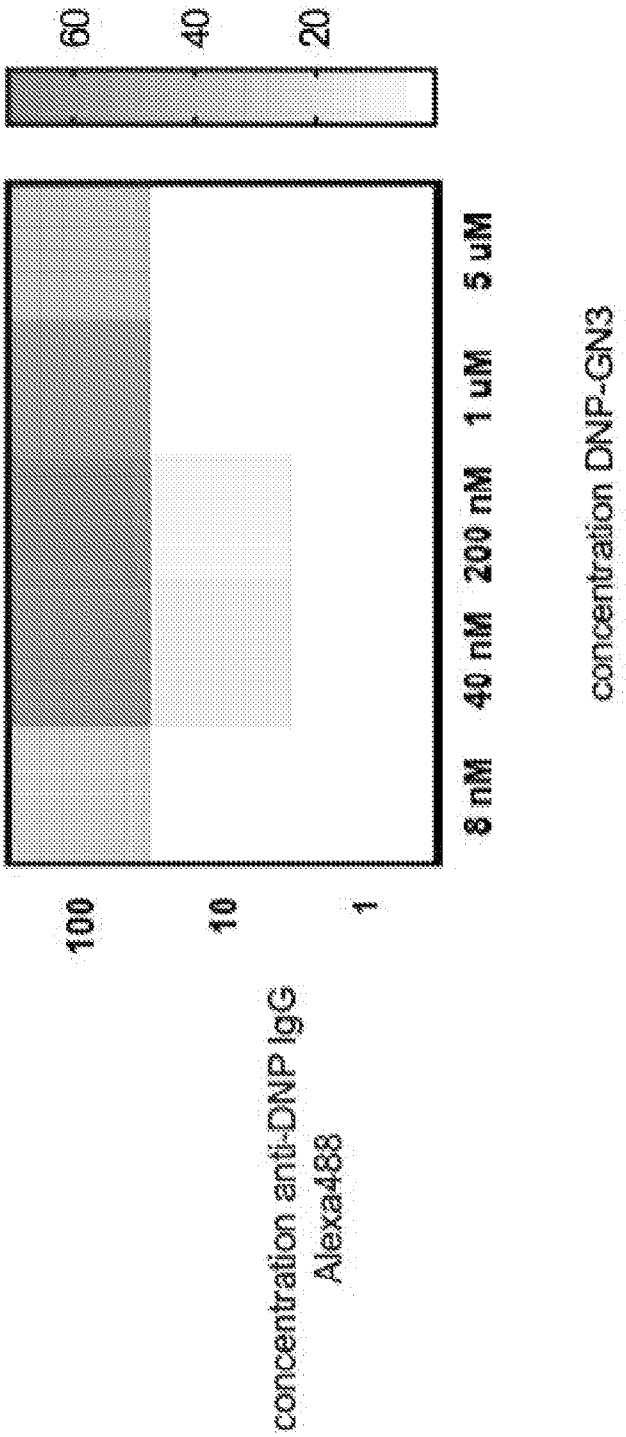

60
40
20
100
10
1
8 nM
40 nM
200 nM
1 uM
5 uM
concentration anti-DNP IgG Alexa488
concentration DNP-GN3

FIGURE 9 (Cont'd)

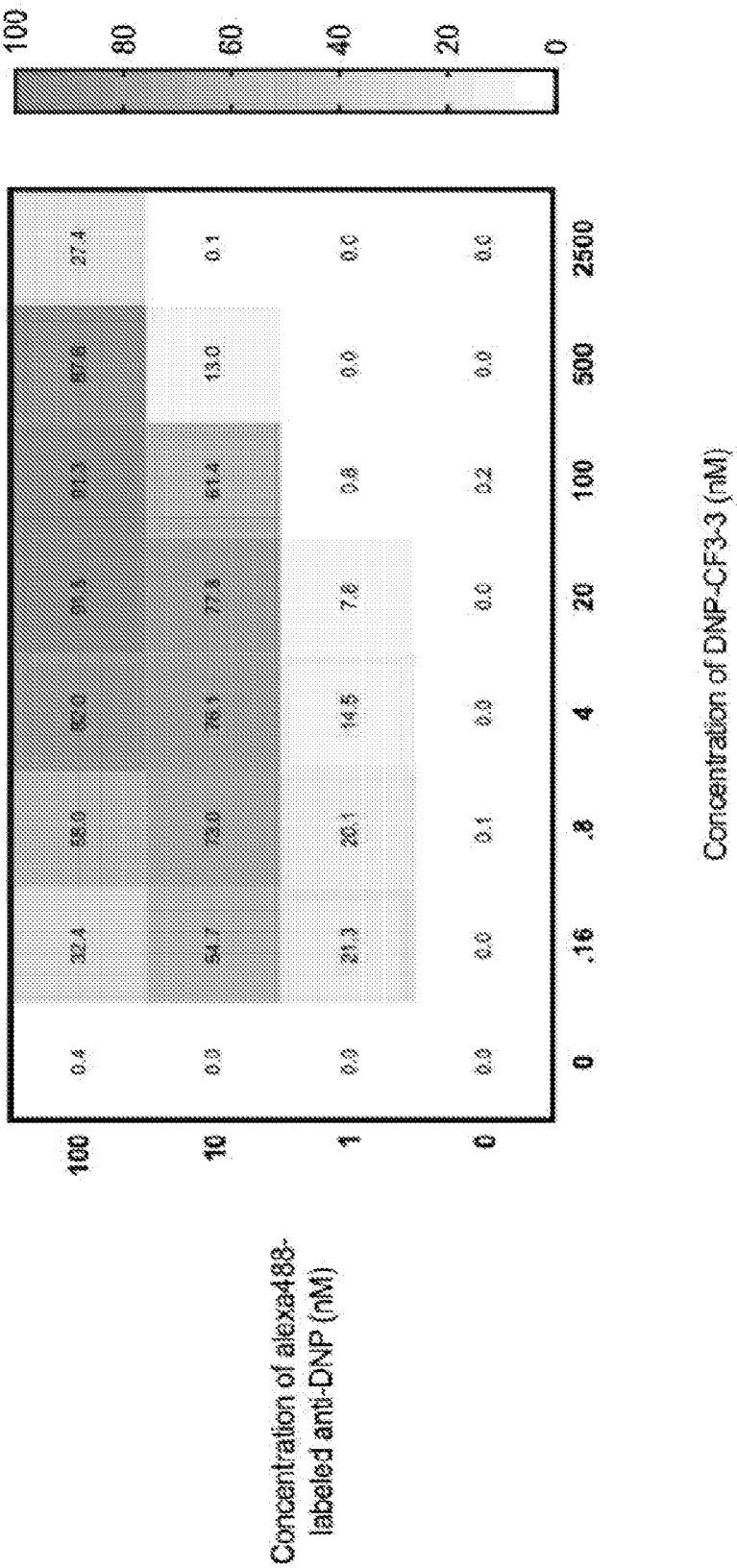


FIGURE 10

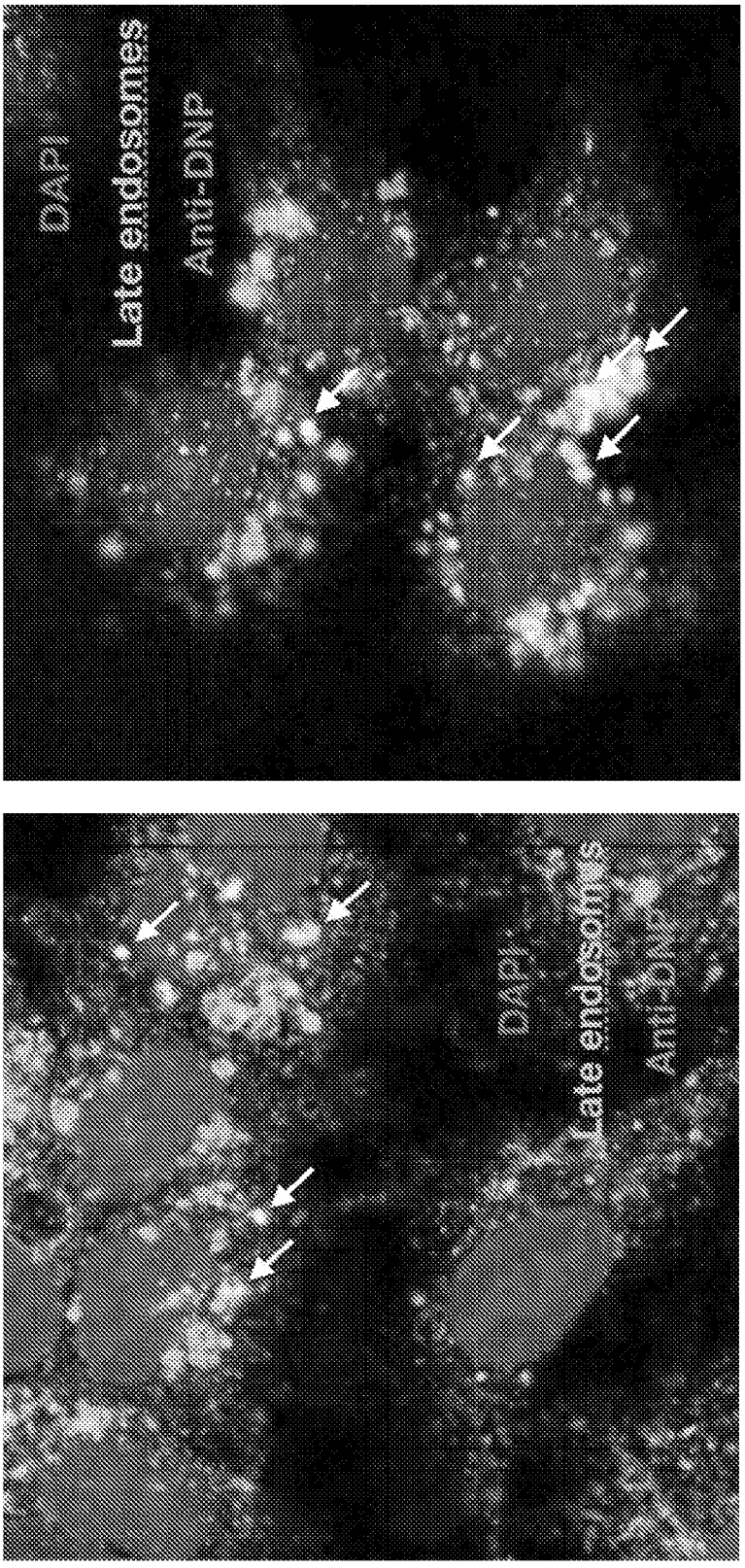

DAPI
Late endosomes
Anti-DNP
DNP-AcF3-3
DAPI
Late endosomes
Anti-DNP
DNP-GN3

FIGURE 11

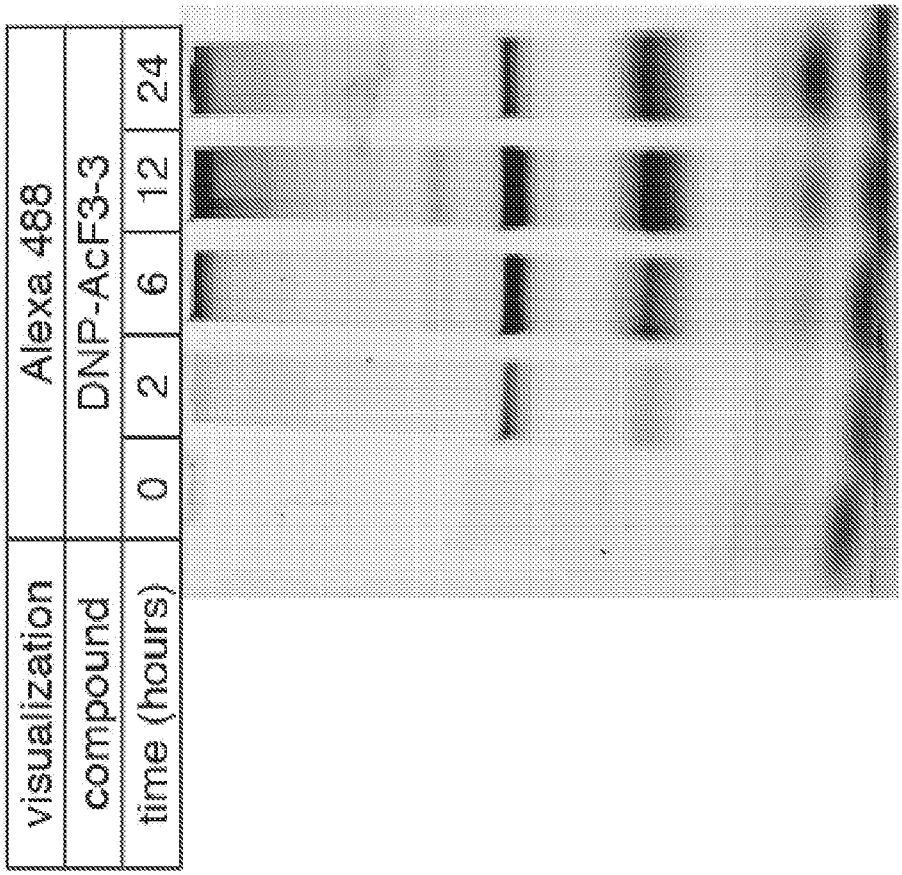

visualization
Alexa 488
compound
DNP-AcF3-3
time (hours)
0
2
6
12
24
50 kDa
25 kDa

FIGURE 12

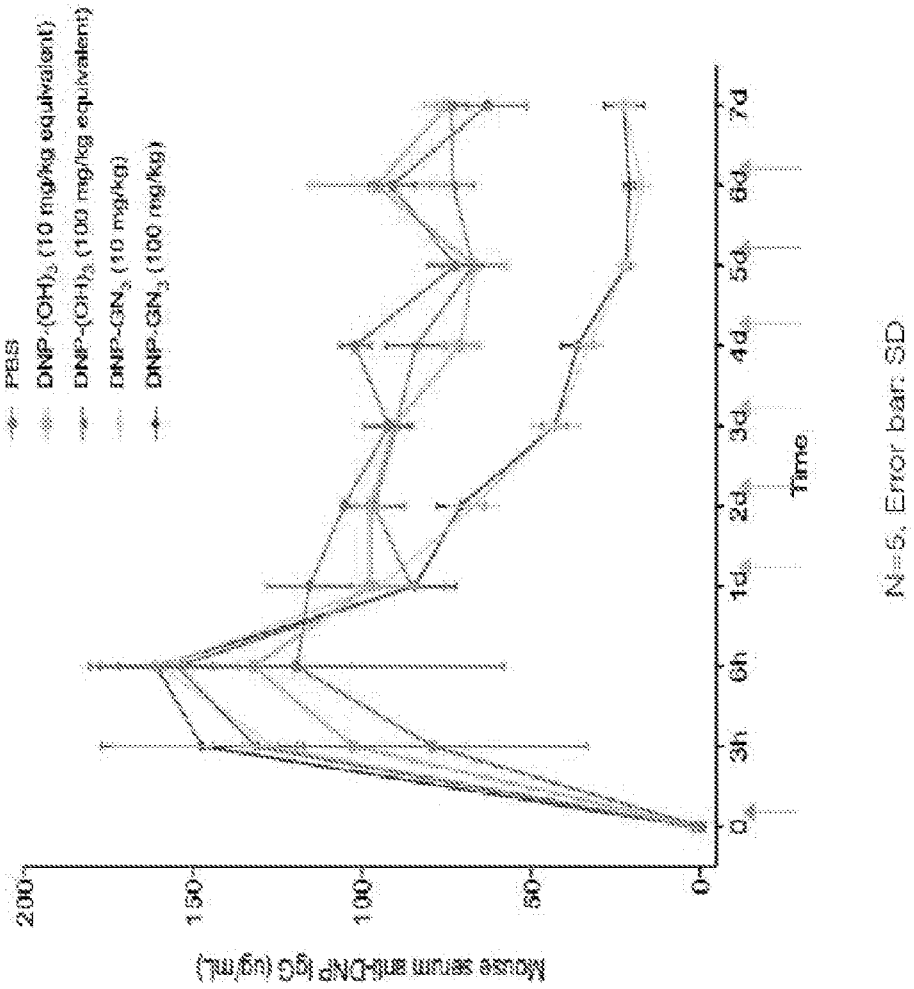

PBS
DNP-(OH)3 (10 mg/kg equivalent)
DNP-(OH)3 (100 mg/kg equivalent)
DNP-GN3 (10 mg/kg)
DNP-GN3 (100 mg/kg)
Mouse serum anti-DNP IgG (ug/mL)
200
150
100
50
0
0d
3h
6h
1d
2d
3d
4d
5d
6d
7d
Time
N=5, Error bar: SD

FIGURE 13

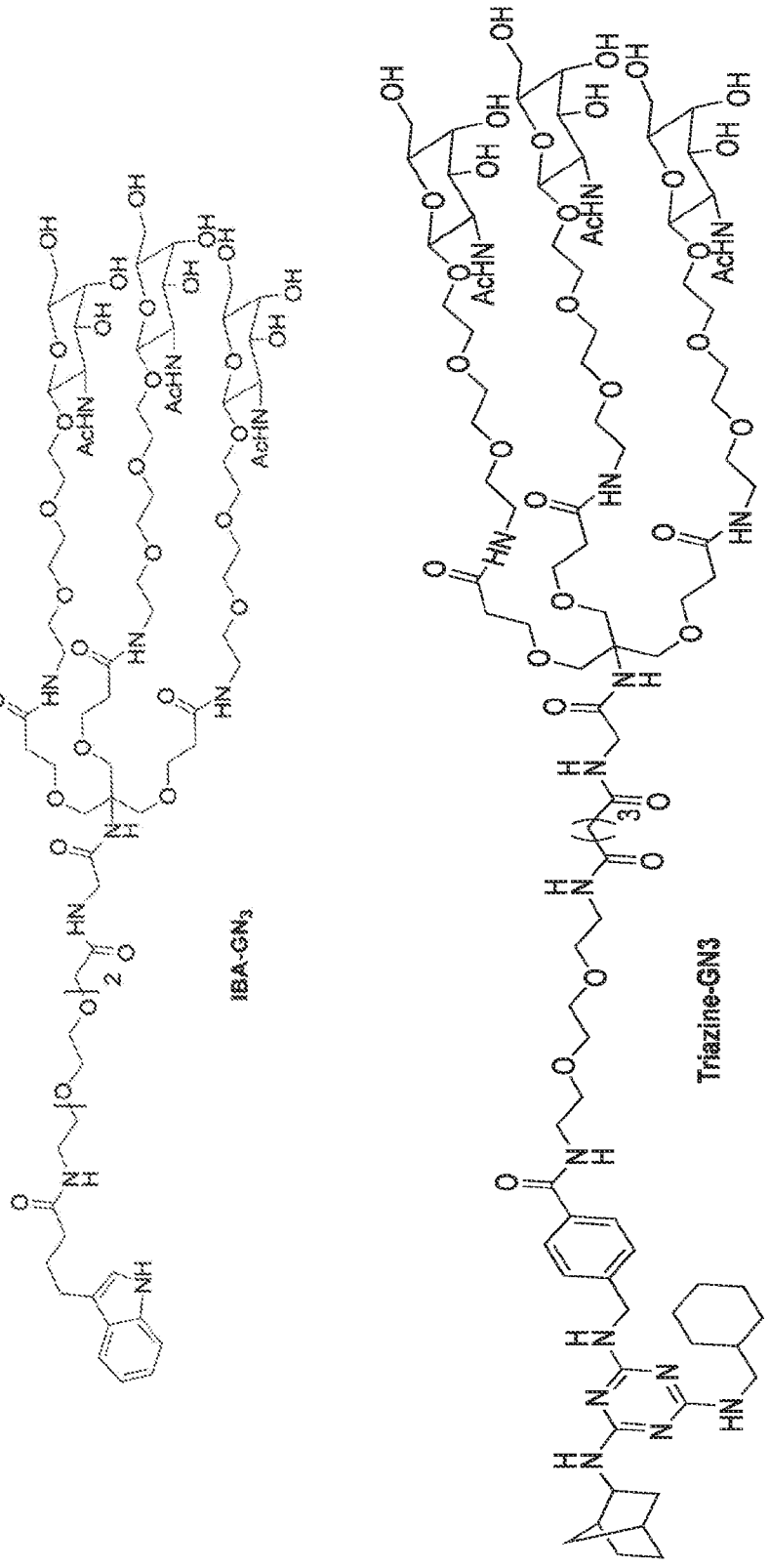
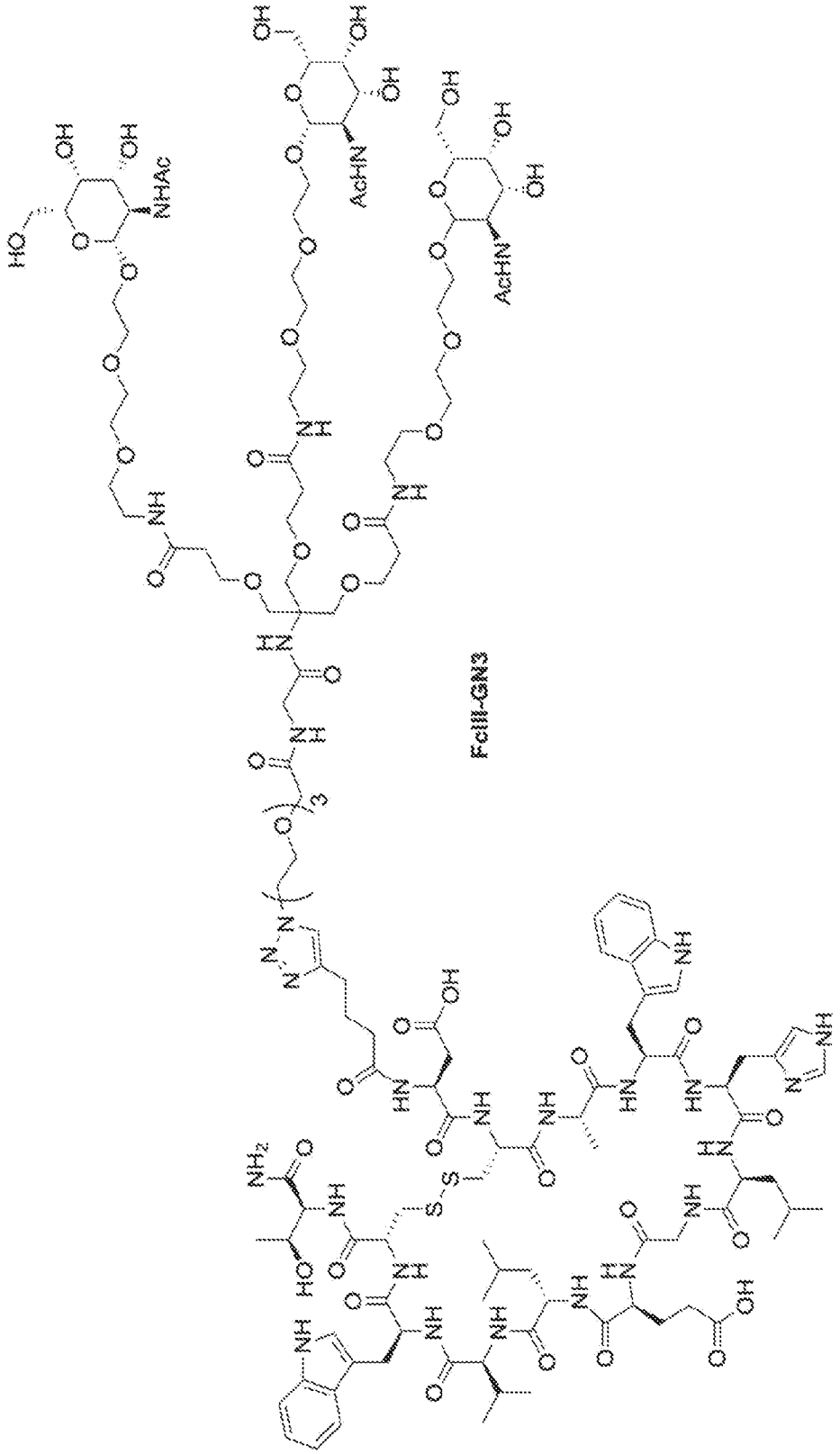
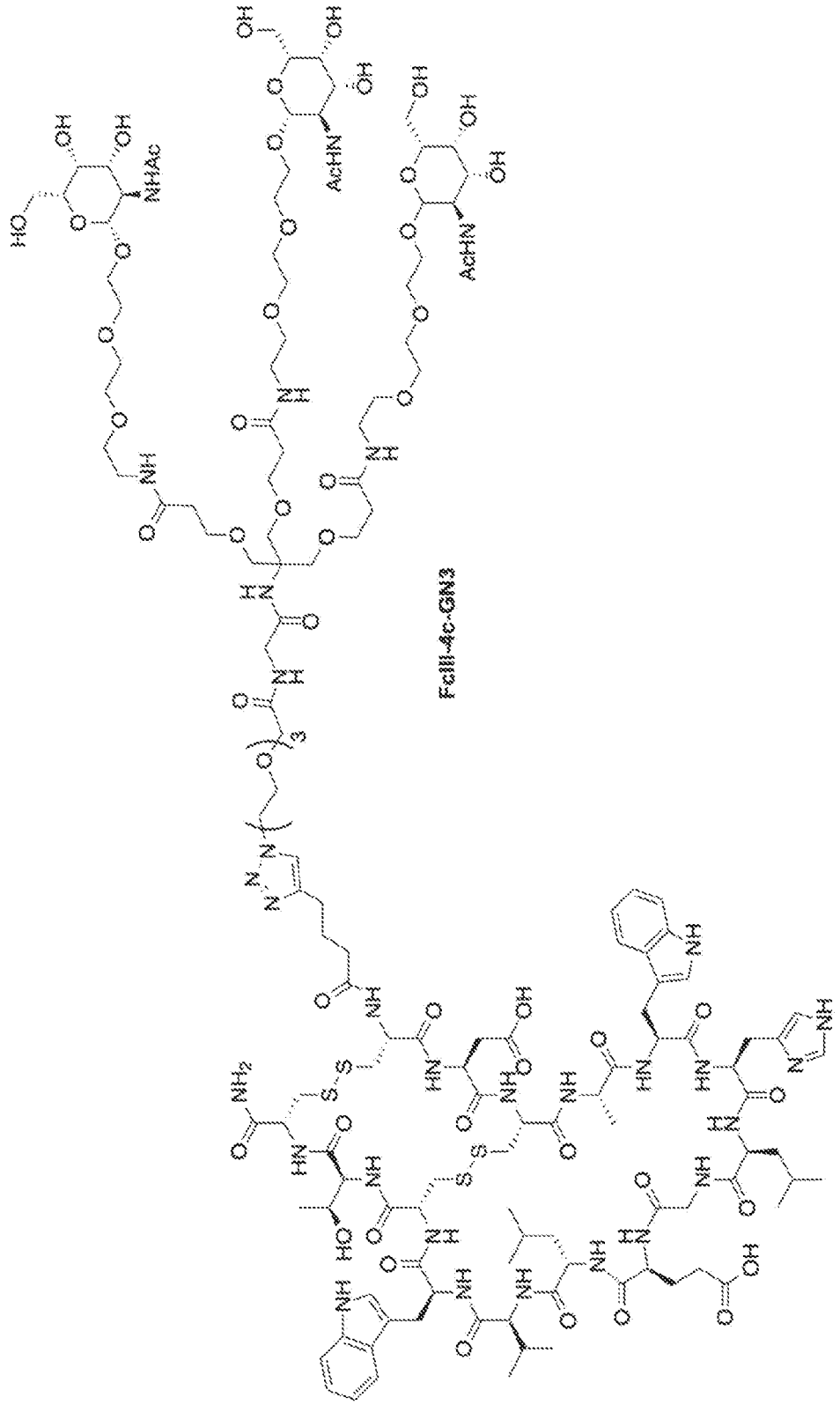


FIGURE 13 (Cont'd)



FcIII-GN3

FIGURE 13 (Cont'd)



FcIII-4c-GN3

FIGURE 14

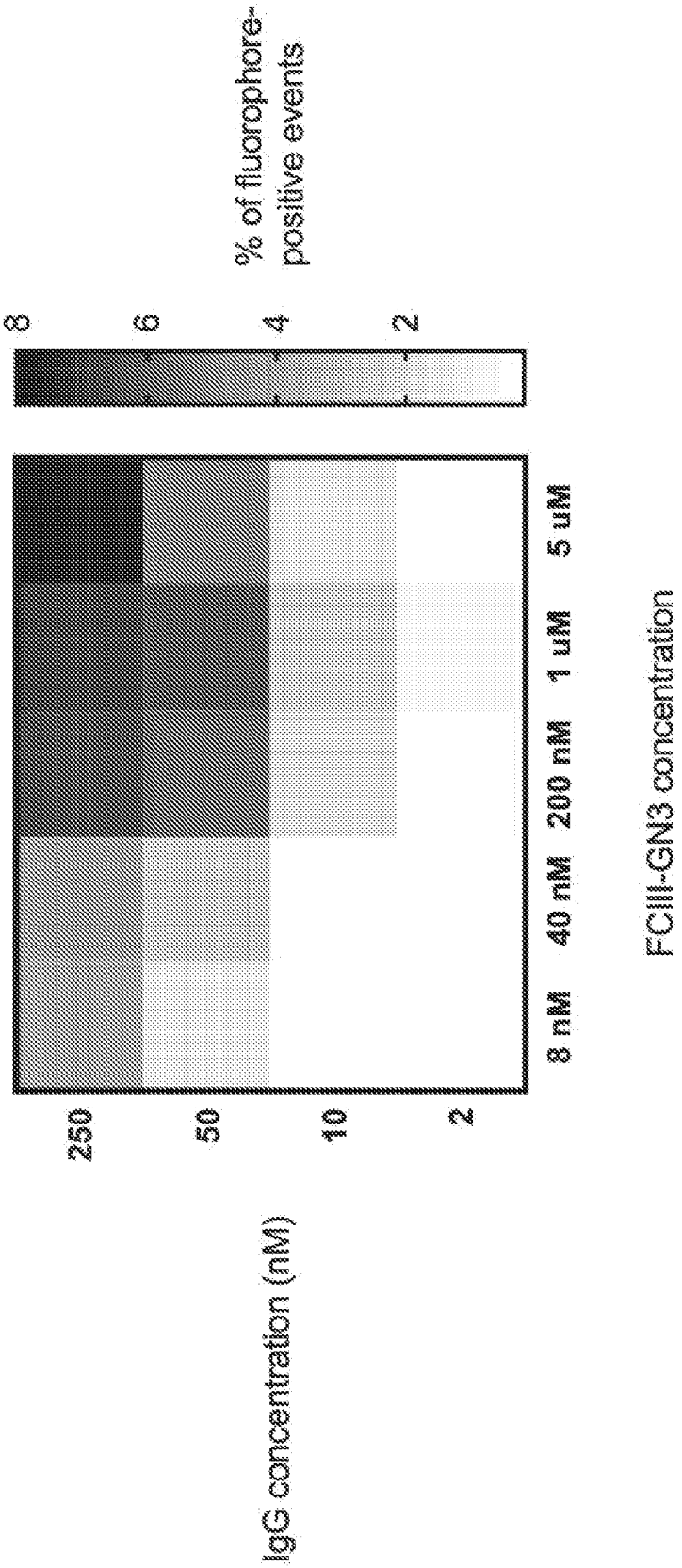

% of fluorophore-positive events
8
6
4
2
IgG concentration (nM)
250
50
10
2
8 nM
40 nM
200 nM
1 uM
5 uM
FCIII-GN3 concentration

FIGURE 15

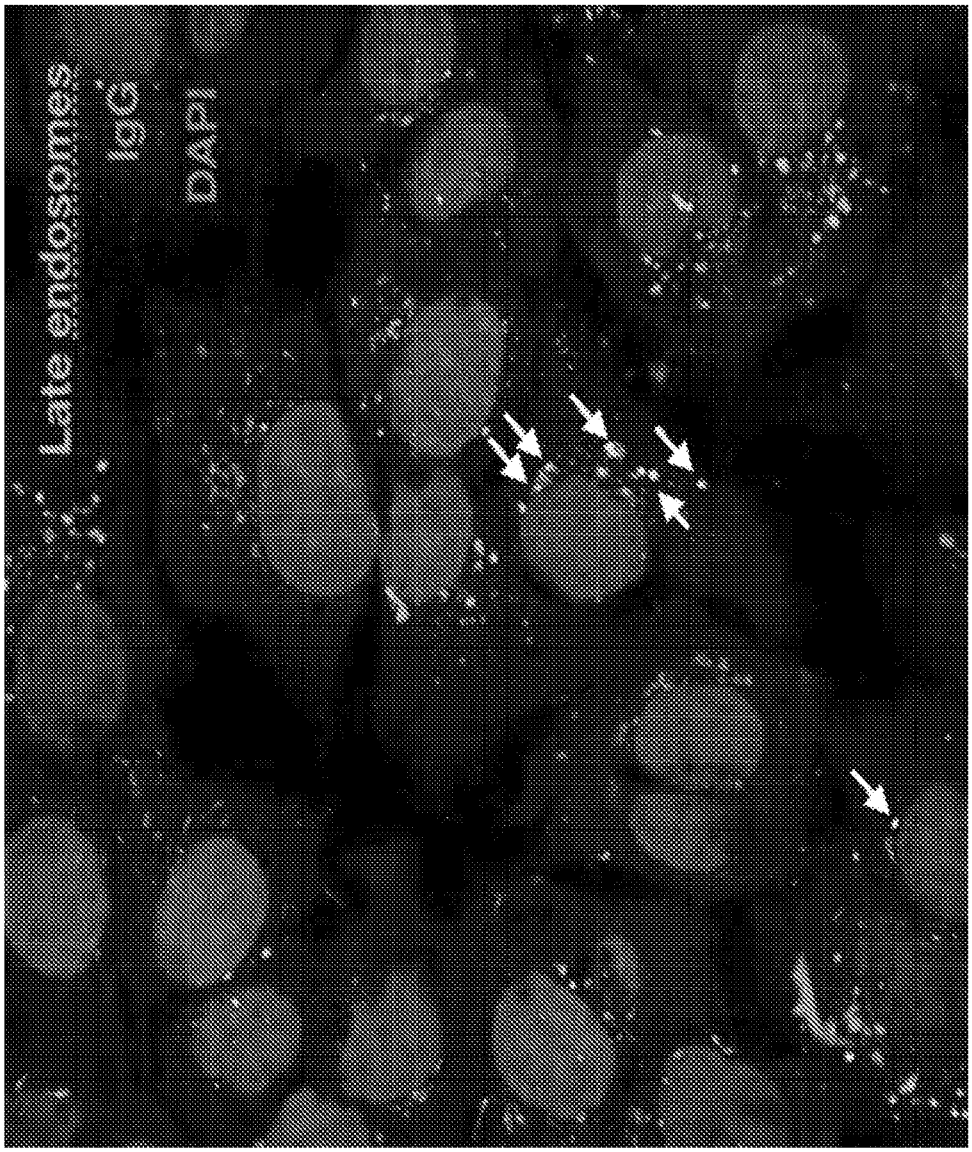


FIGURE 16

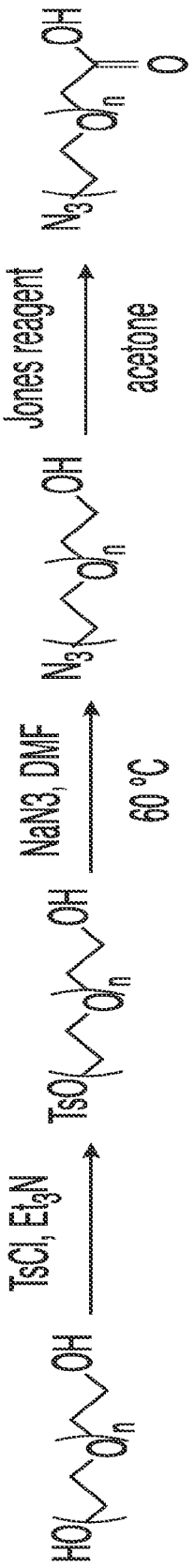

HO
OH
n
TsCl, Et3N
TsO
OH
n
NaN3, DMF
60 °C
N3
OH
n
Jones reagent
acetone
N3
OH
n
O

FIGURE 17

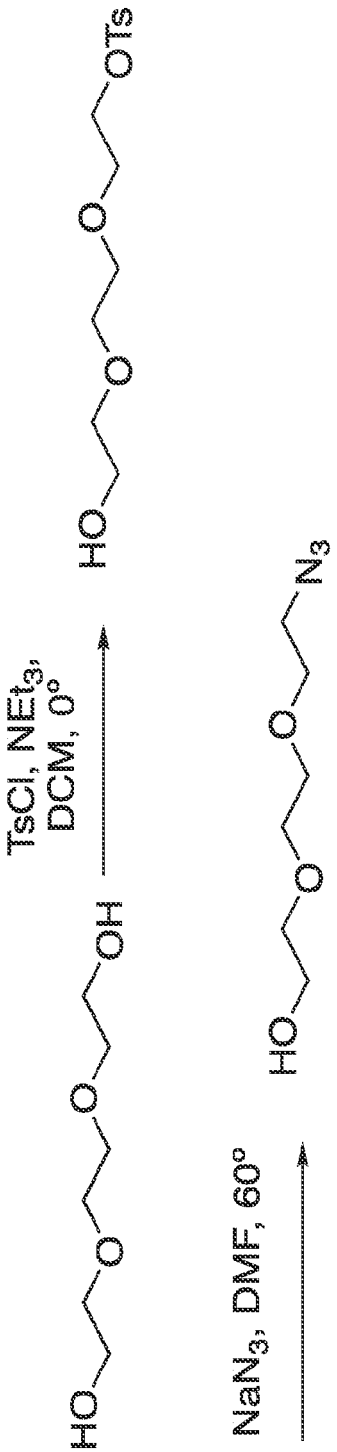


FIGURE 18

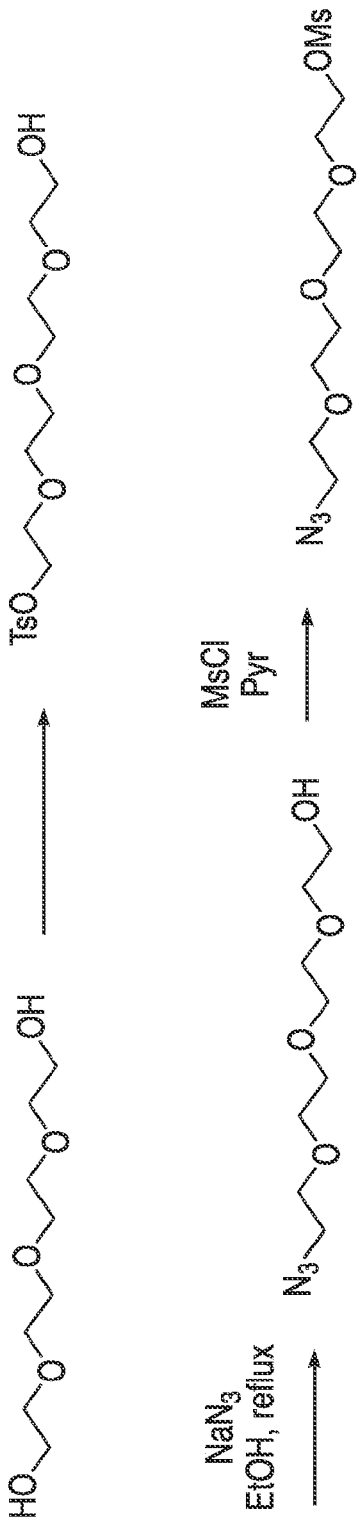

TsCl, NaOH
THF, Water, 0°
MsCl
Pyr
NaN3
EtOH, reflux
HO
OH
TsO
OH
N3
OH
N3
OMs

FIGURE 19

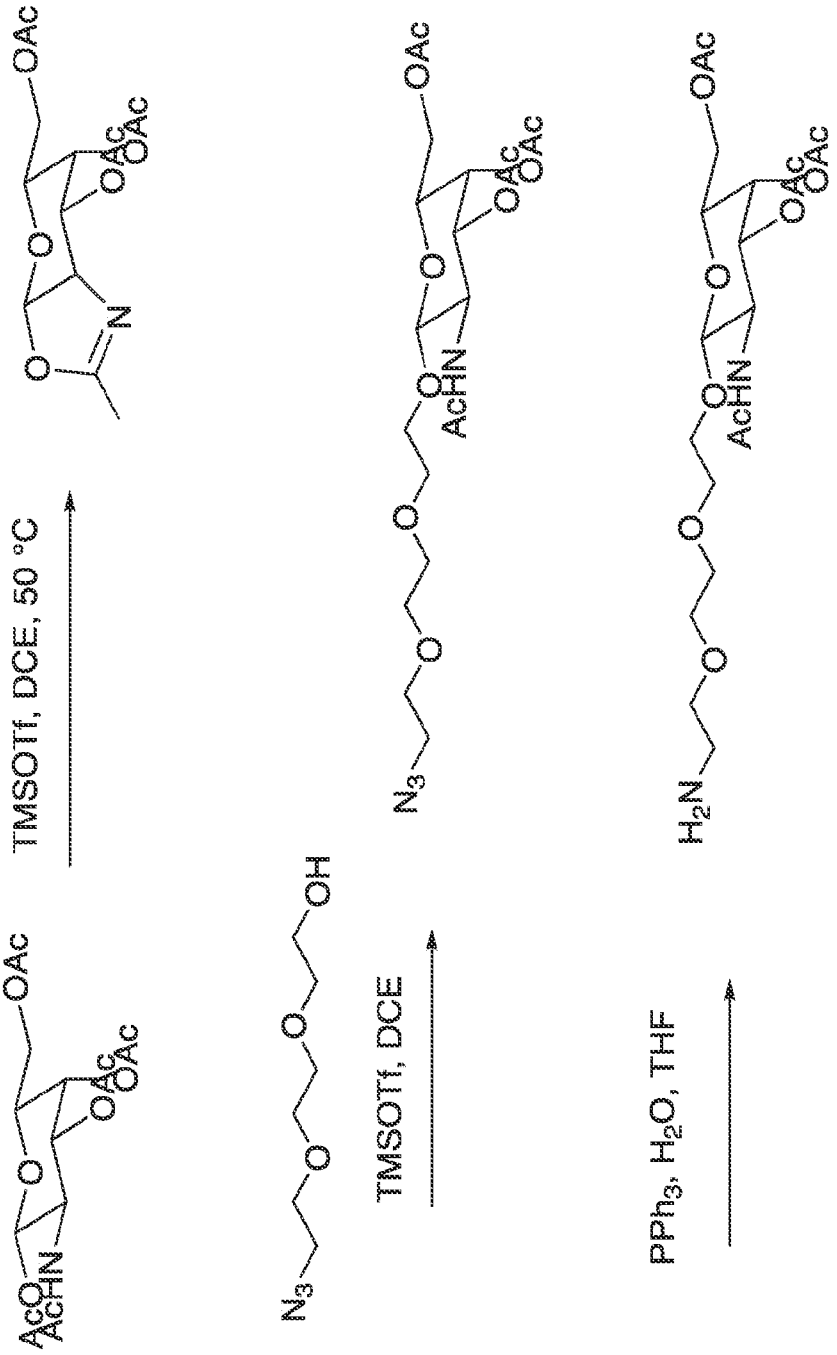


FIGURE 20

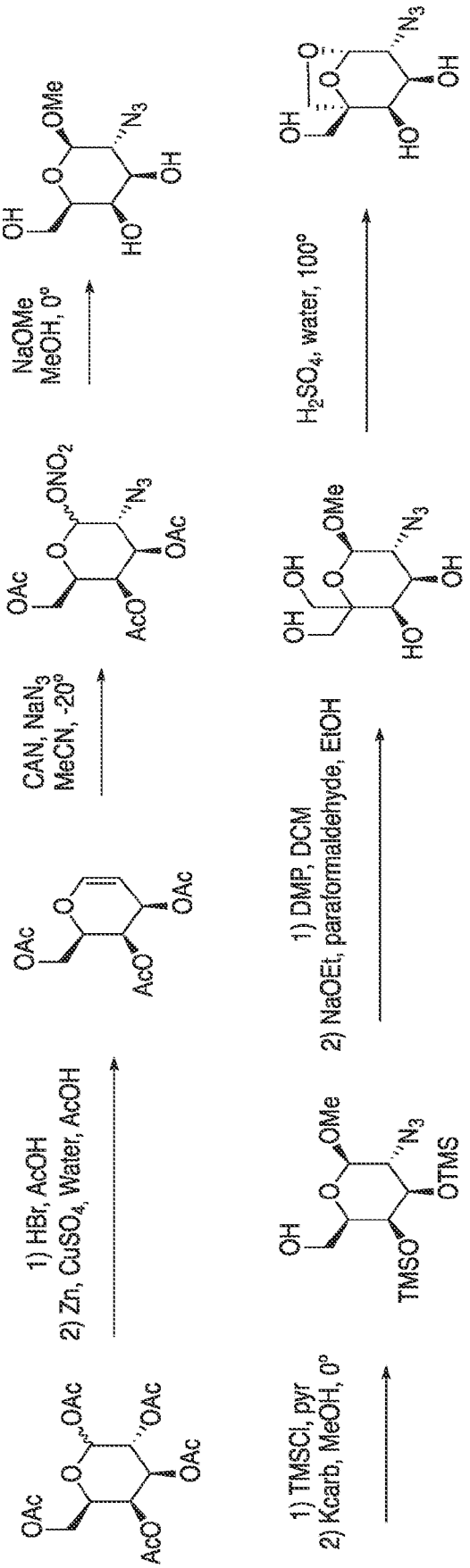

1) TMSCl, pyr
2) Kcarb, MeOH, 0°
1) HBr, AcOH
2) Zn, CuSO4, Water, AcOH
1) DMP, DCM
2) NaOEt, paraformaldehyde, EtOH
CAN, NaN3
MeCN, -20°
NaOMe
MeOH, 0°
H2SO4, water, 100°

FIGURE 21

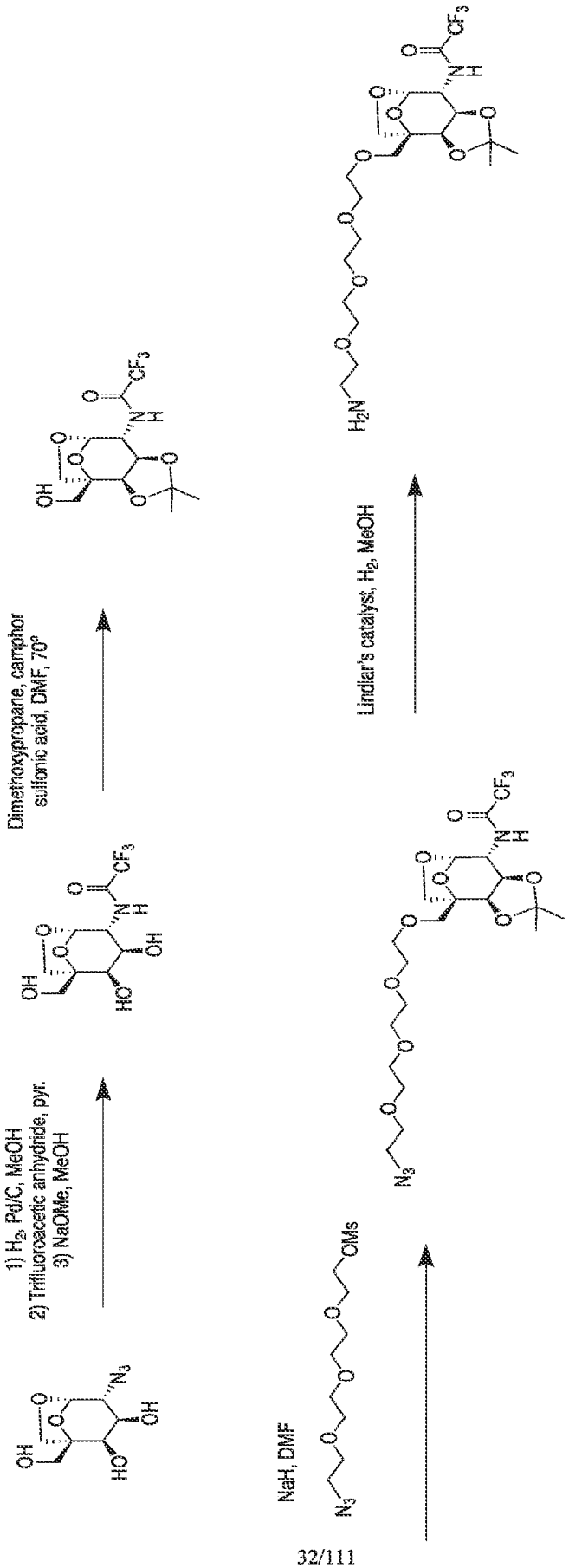

1) H_2, Pd/C, MeOH
2) Trifluoroacetic anhydride, pyr.
3) NaOMe, MeOH
Dimethoxypropane, camphor sulfonic acid, DMF, 70°
Lindlar's catalyst, H_2, MeOH
NaH, DMF

FIGURE 22

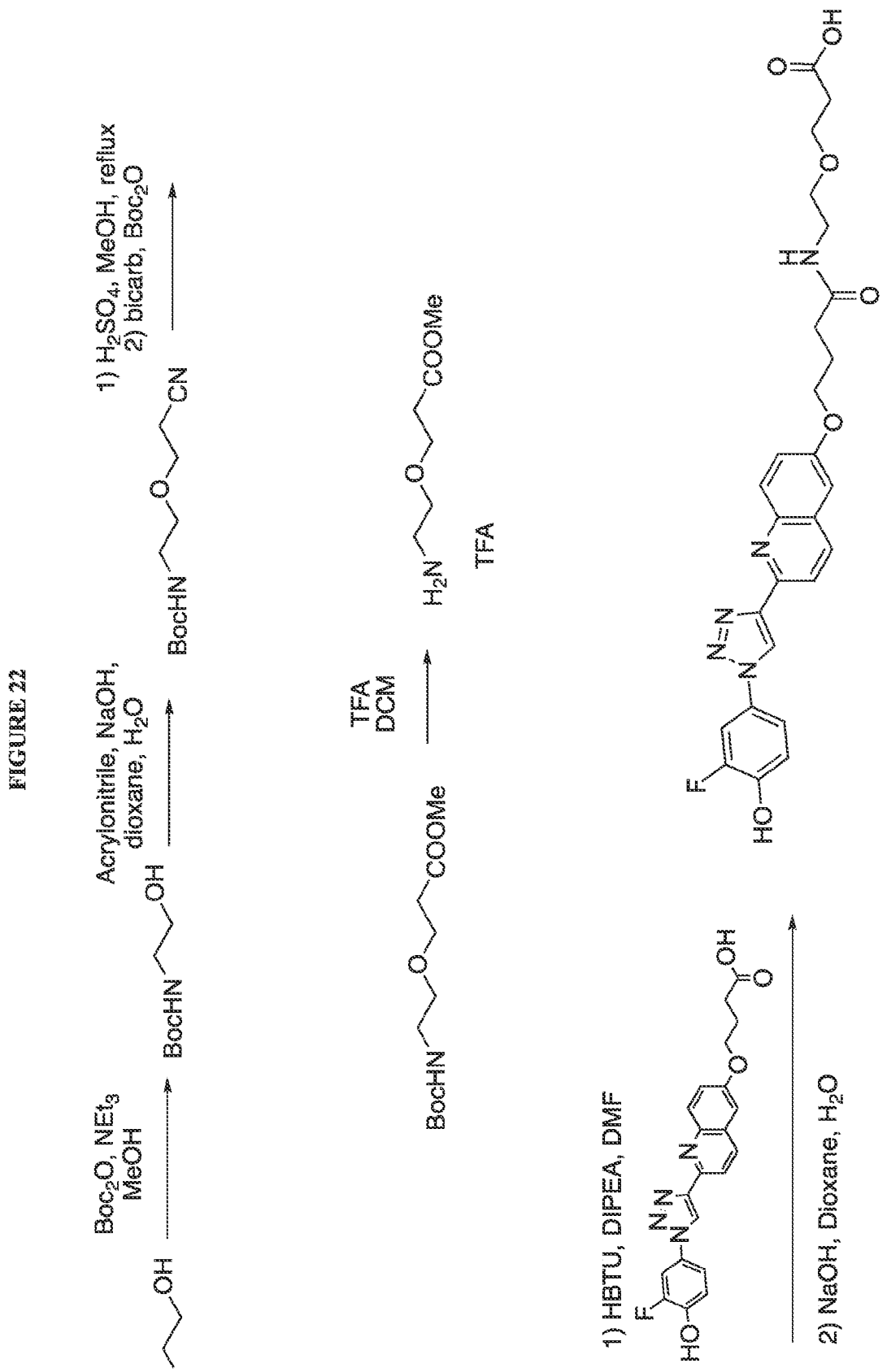

Boc2O, NEt3
MeOH
Acrylonitrile, NaOH,
dioxane, H2O
1) H2SO4, MeOH, reflux
2) bicarb, Boc2O
TFA
DCM
TFA
1) HBTU, DIPEA, DMF
2) NaOH, Dioxane, H2O

FIGURE 23

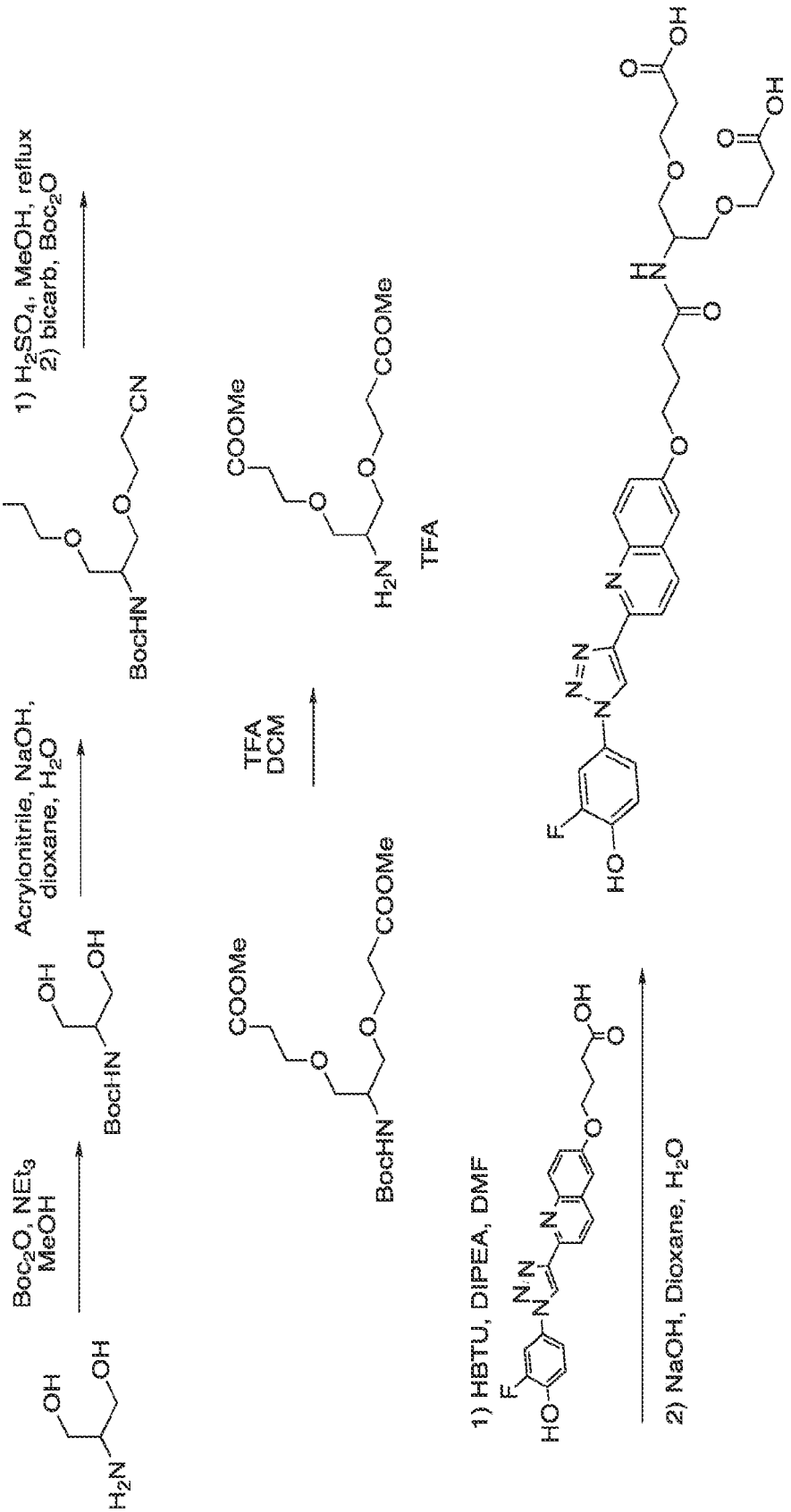

Boc2O, NEt3
MeOH
Acrylonitrile, NaOH,
dioxane, H2O
1) H2SO4, MeOH, reflux
2) bicarb, Boc2O
TFA
DCM
TFA
1) HBTU, DIPEA, DMF
2) NaOH, Dioxane, H2O

FIGURE 24

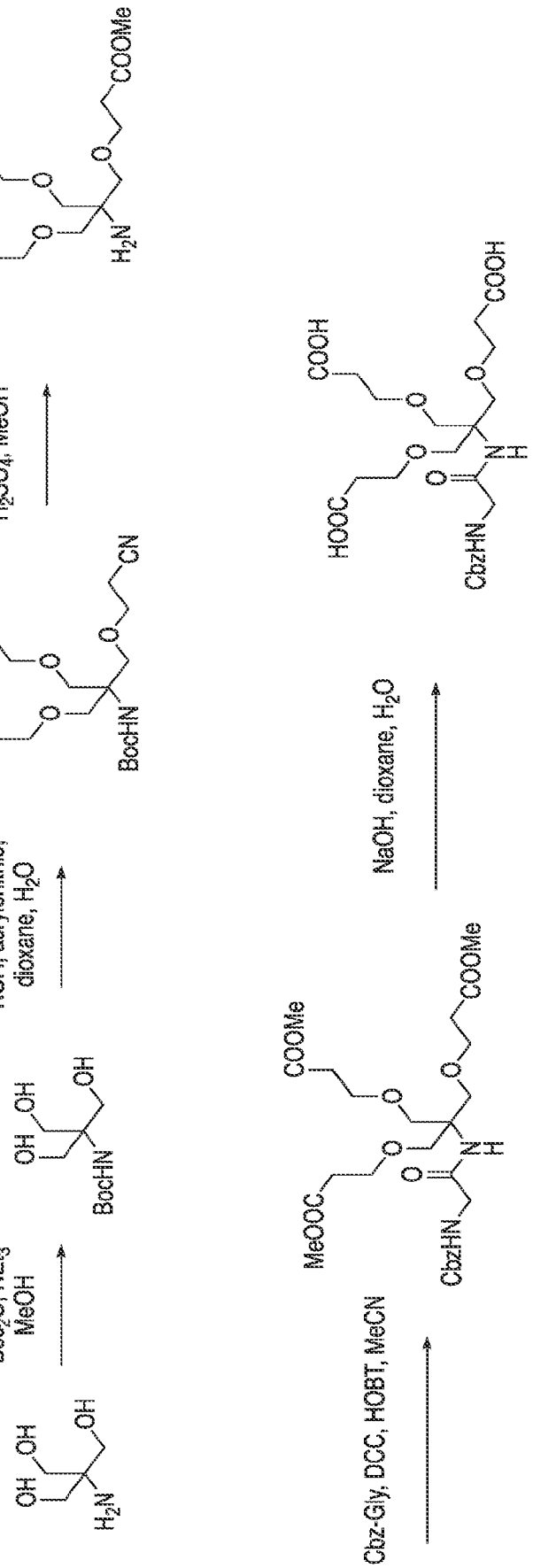

Boc2O, NEt3
MeOH
KOH, acrylonitrile,
dioxane, H2O
H2SO4, MeOH
Cbz-Gly, DCC, HOBT, MeCN
NaOH, dioxane, H2O
H2N
BocHN
NC
CN
MeOOC
COOMe
HOOC
COOH
CbzHN

FIGURE 25

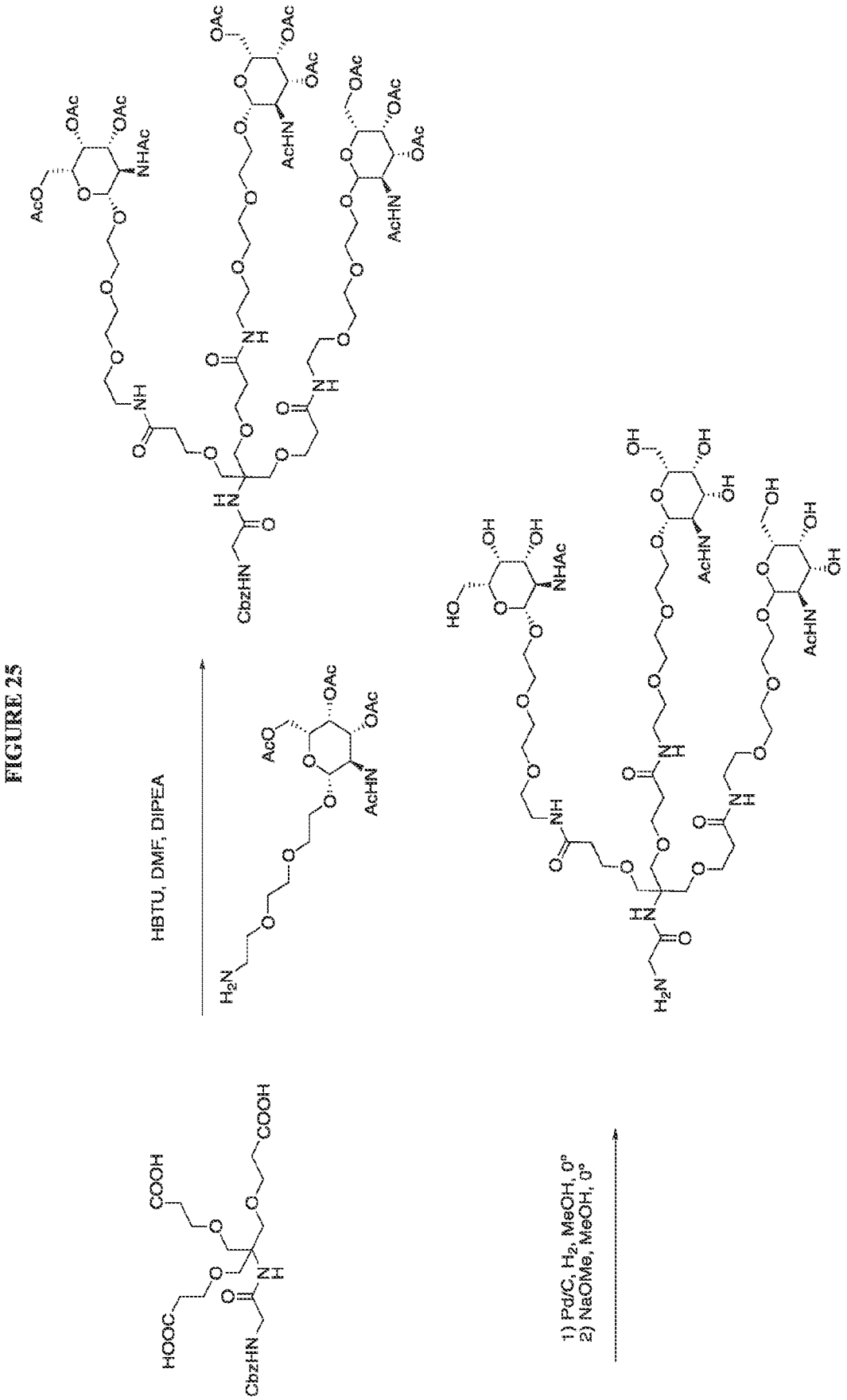


FIGURE 26

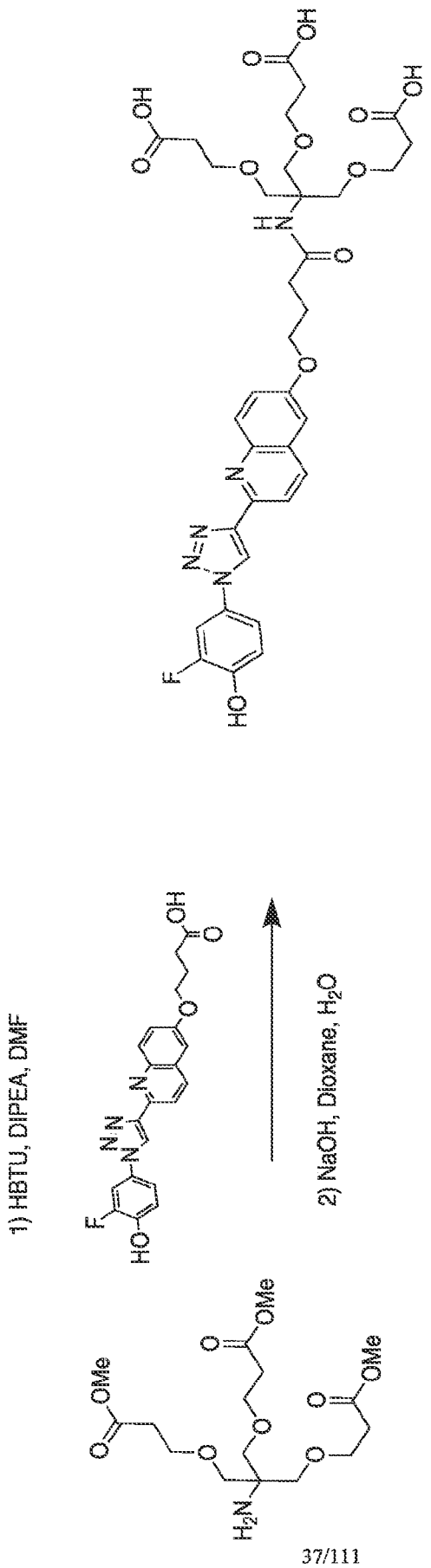


FIGURE 27

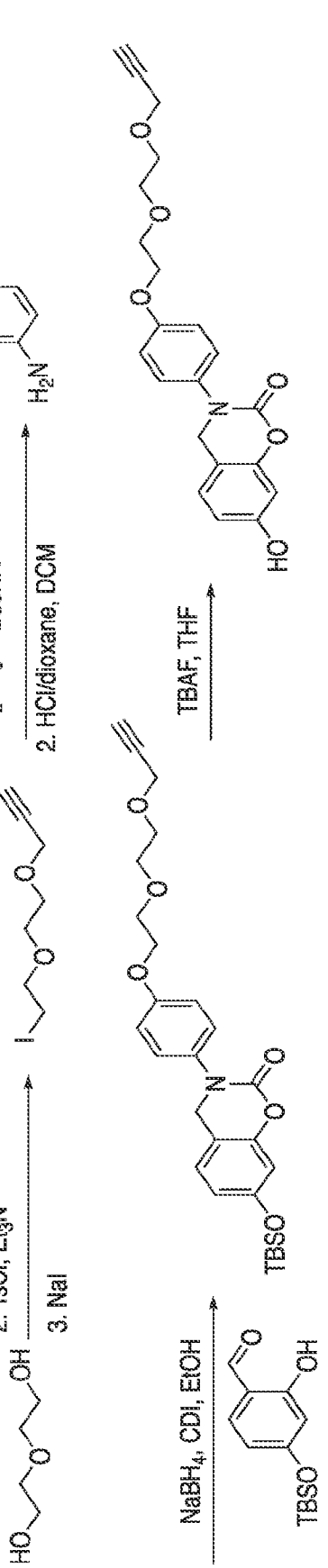

1. NaH, propargyl bromide
2. TsCl, Et3N
3. NaI
1. K2CO3, BocHN
2. HCl/dioxane, DCM
TBAF, THF
NaBH4, CDI, EtOH
TBSO
OH
HO
H2N

FIGURE 28

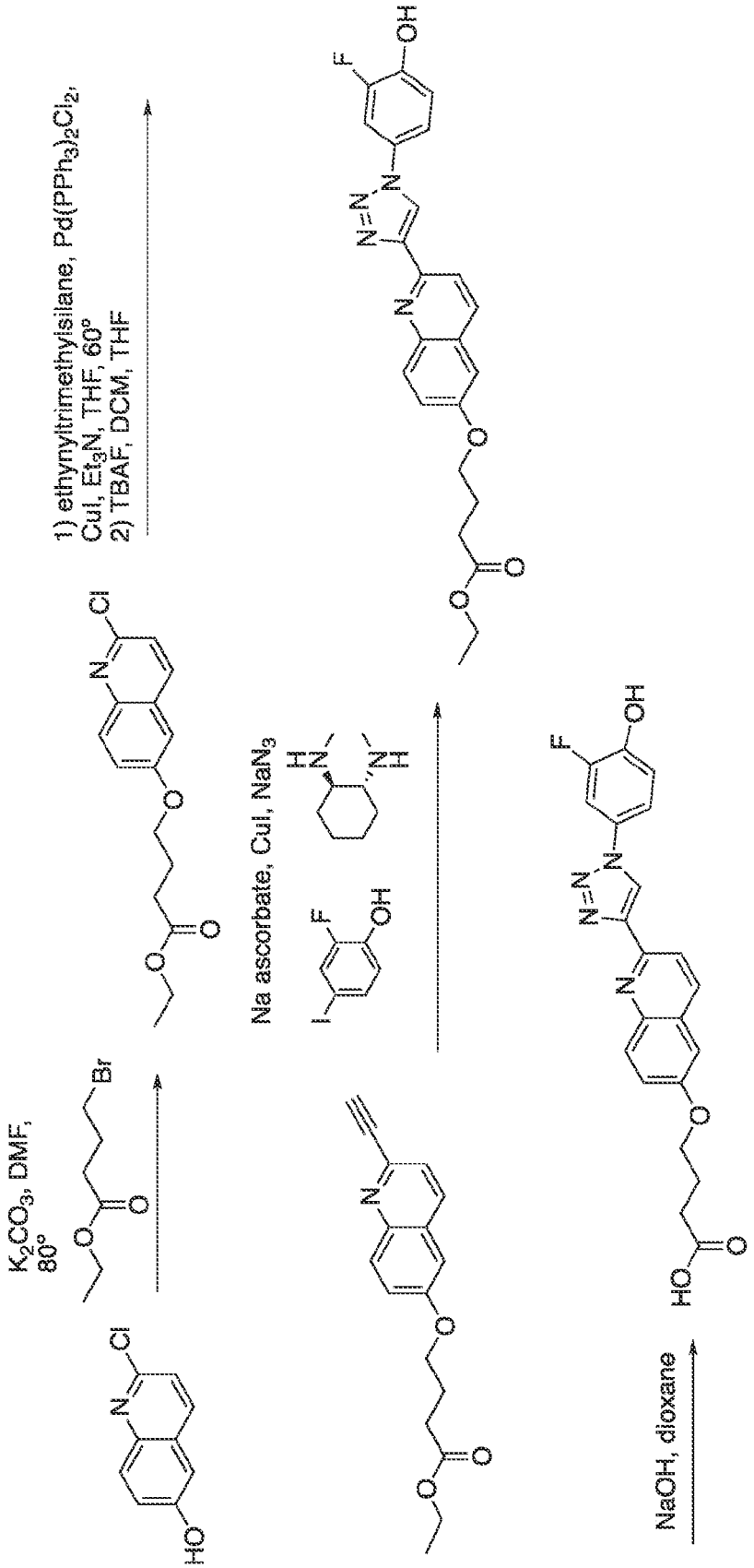

K2CO3, DMF, 80°
1) ethynyltrimethylsilane, Pd(PPh3)2Cl2, CuI, Et3N, THF, 60°
2) TBAF, DCM, THF
Na ascorbate, CuI, NaN3
NaOH, dioxane

FIGURE 29

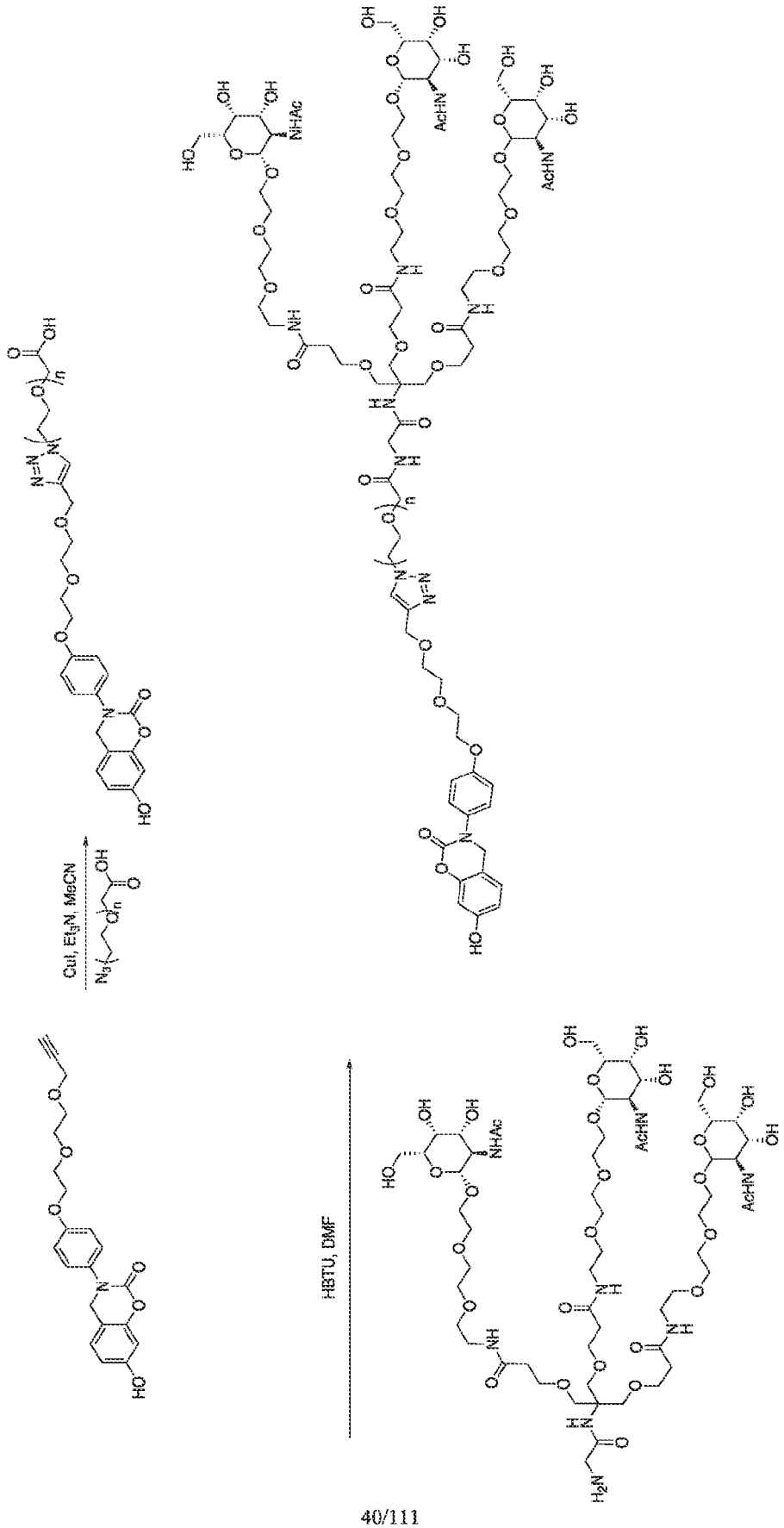


FIGURE 30

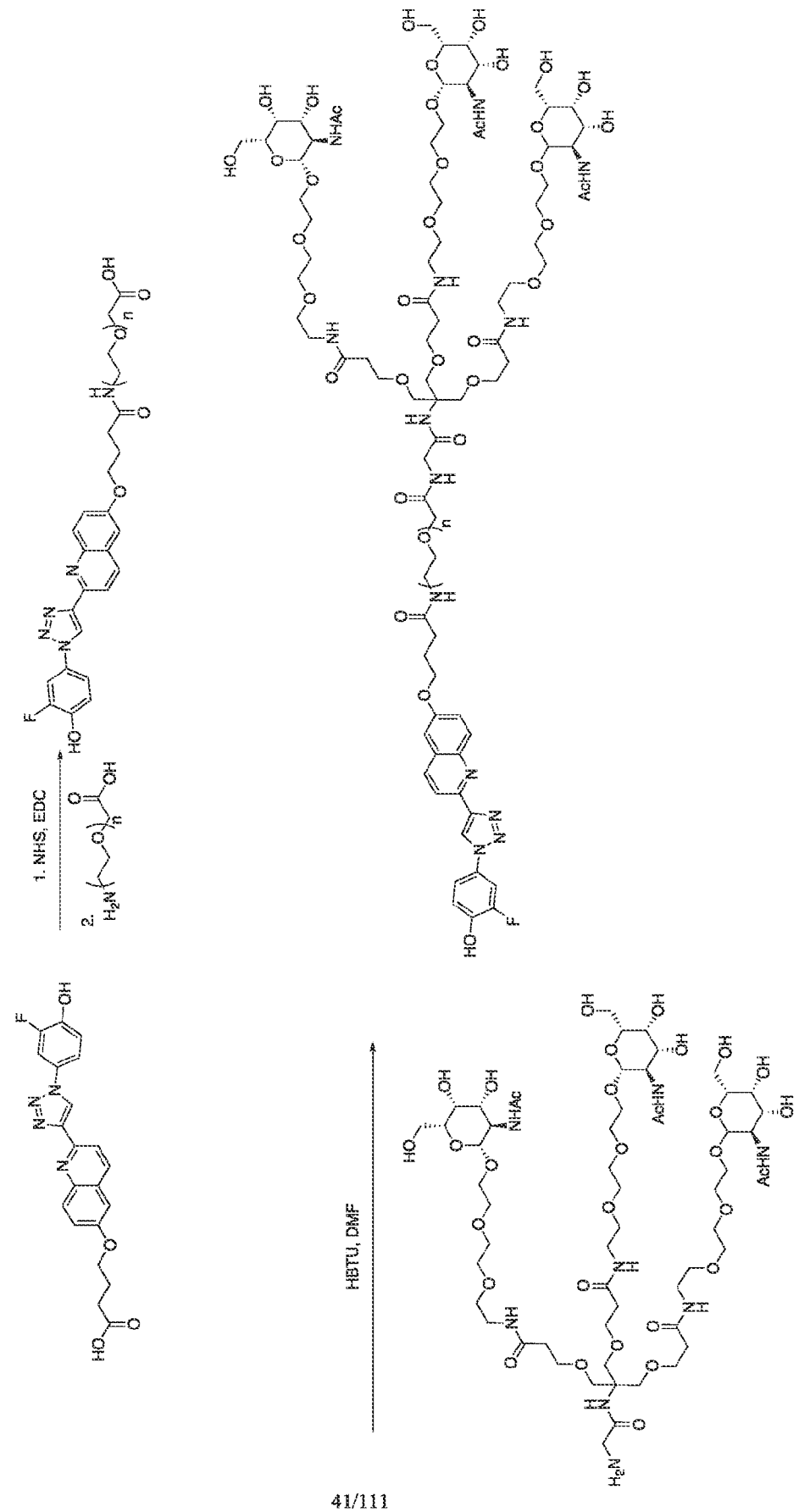


FIGURE 31

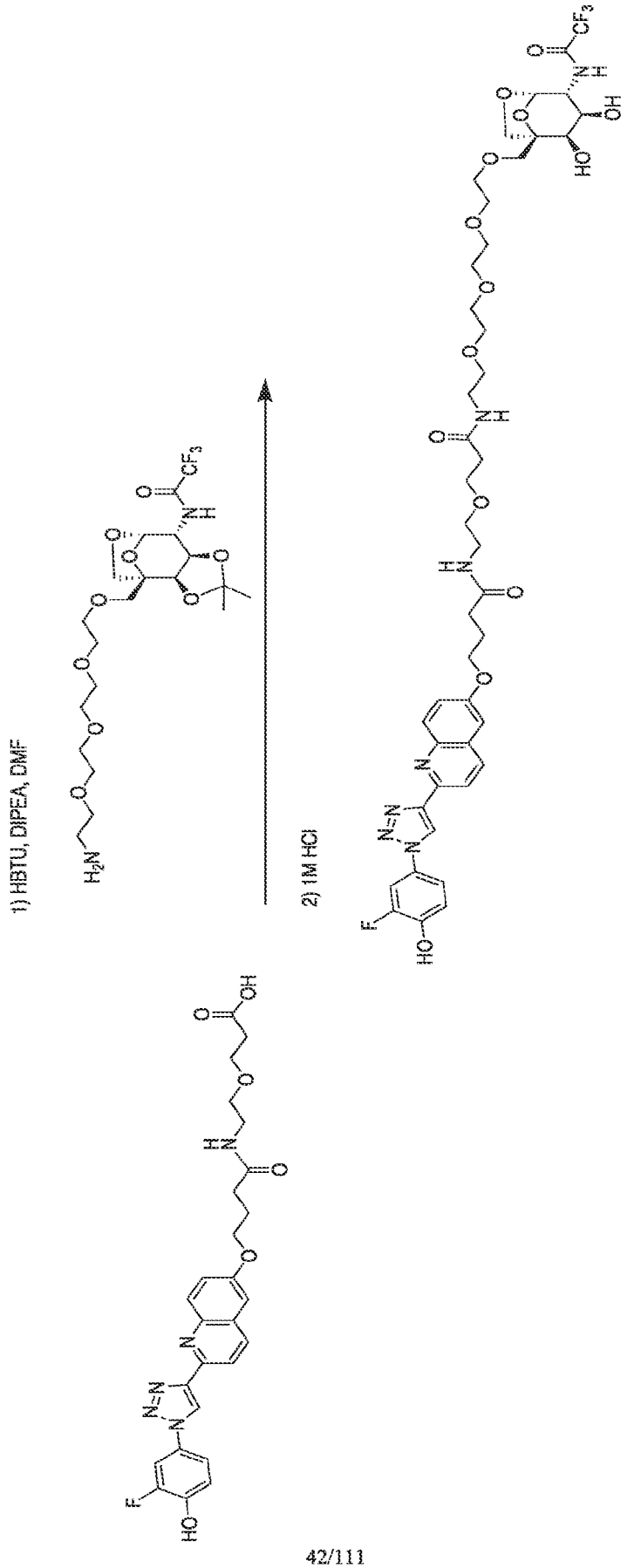


FIGURE 32

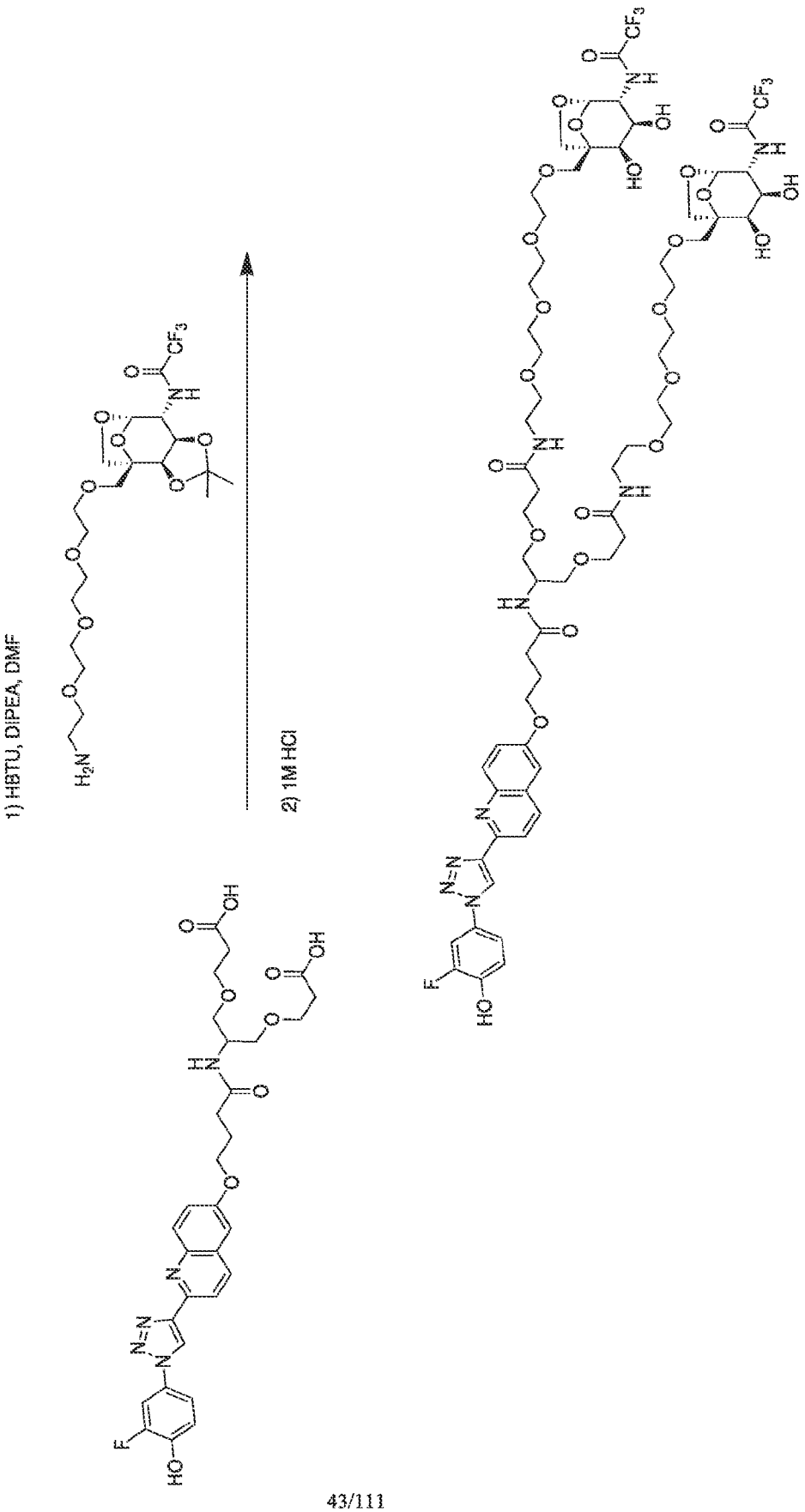


FIGURE 33

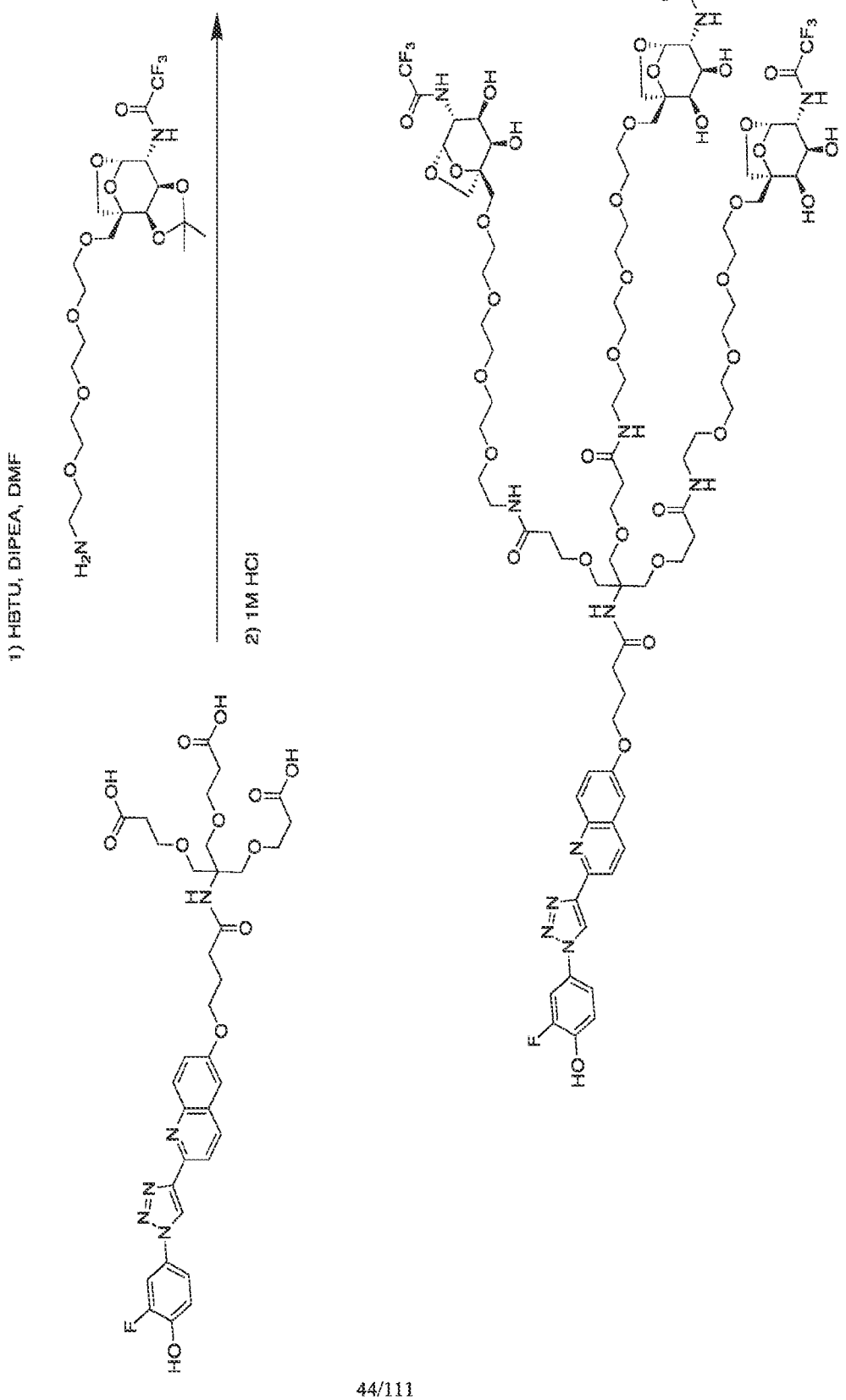


FIGURE 34

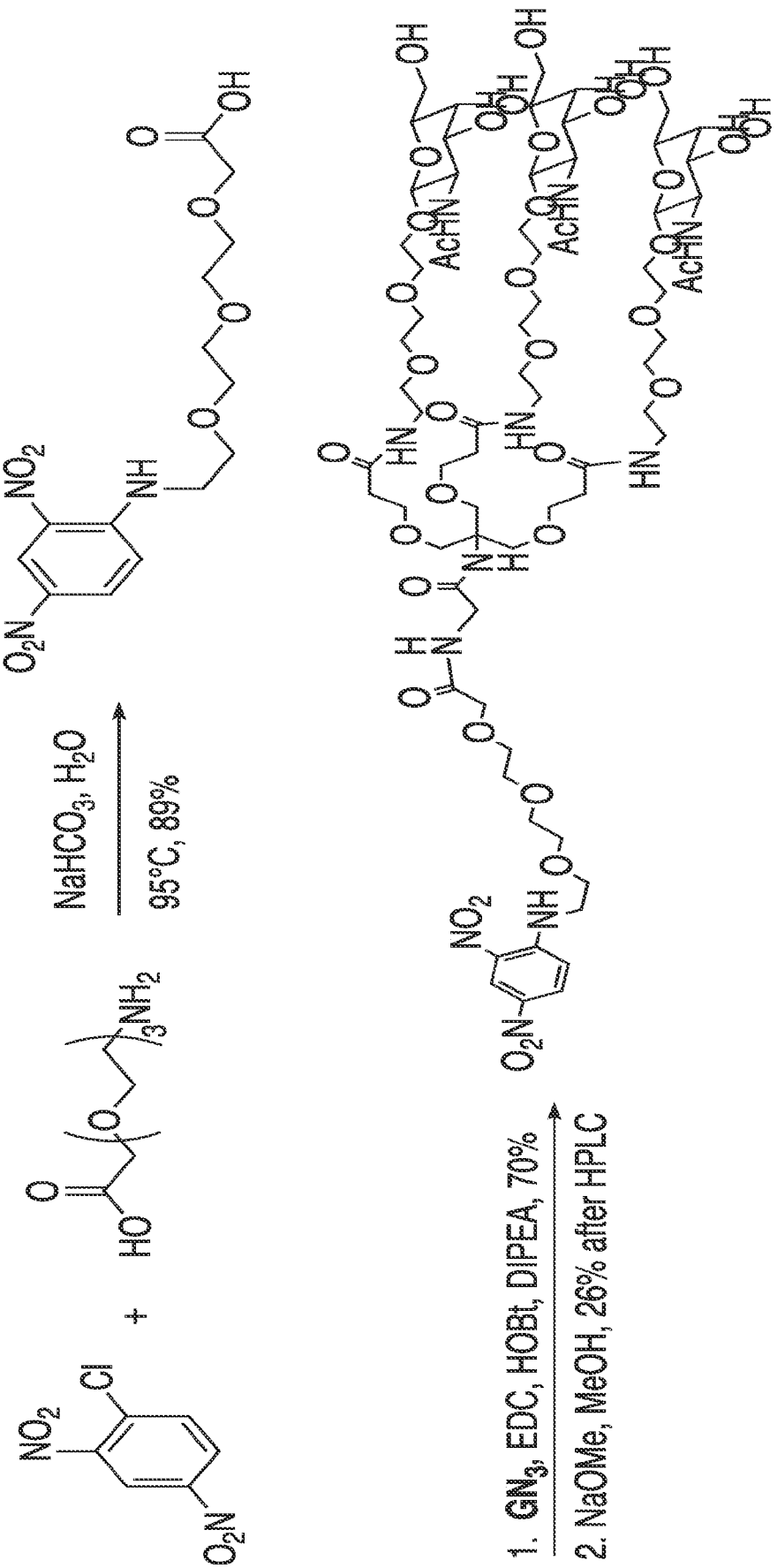

NaHCO3, H2O
95°C, 89%
1. GN3, EDC, HOBt, DIPEA, 70%
2. NaOMe, MeOH, 26% after HPLC

FIGURE 35

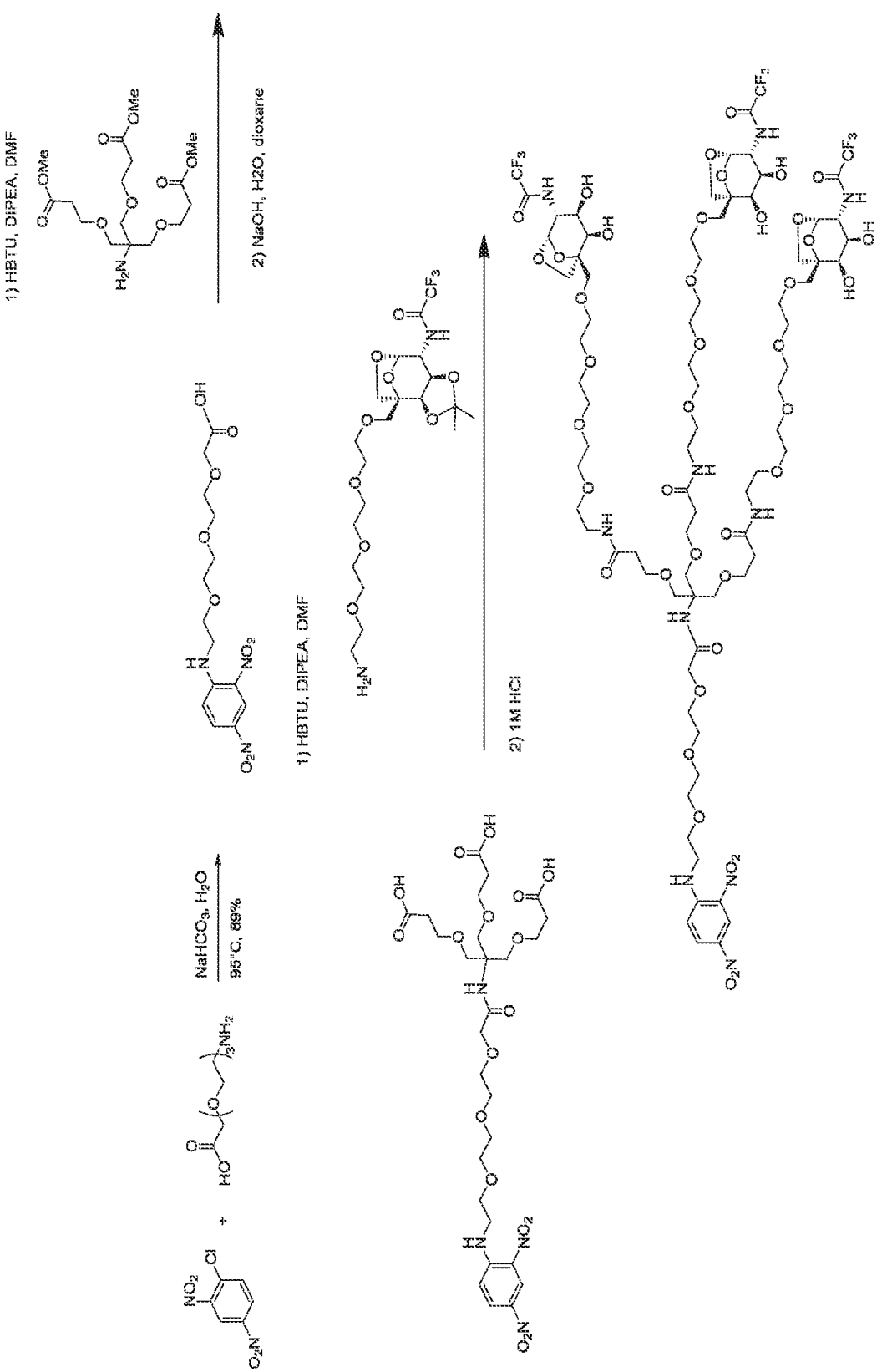

1) HBTU, DIPEA, DMF
2) NaOH, H2O, dioxane
NaHCO3, H2O
95°C, 89%
1) HBTU, DIPEA, DMF
2) 1M HCl

FIGURE 36

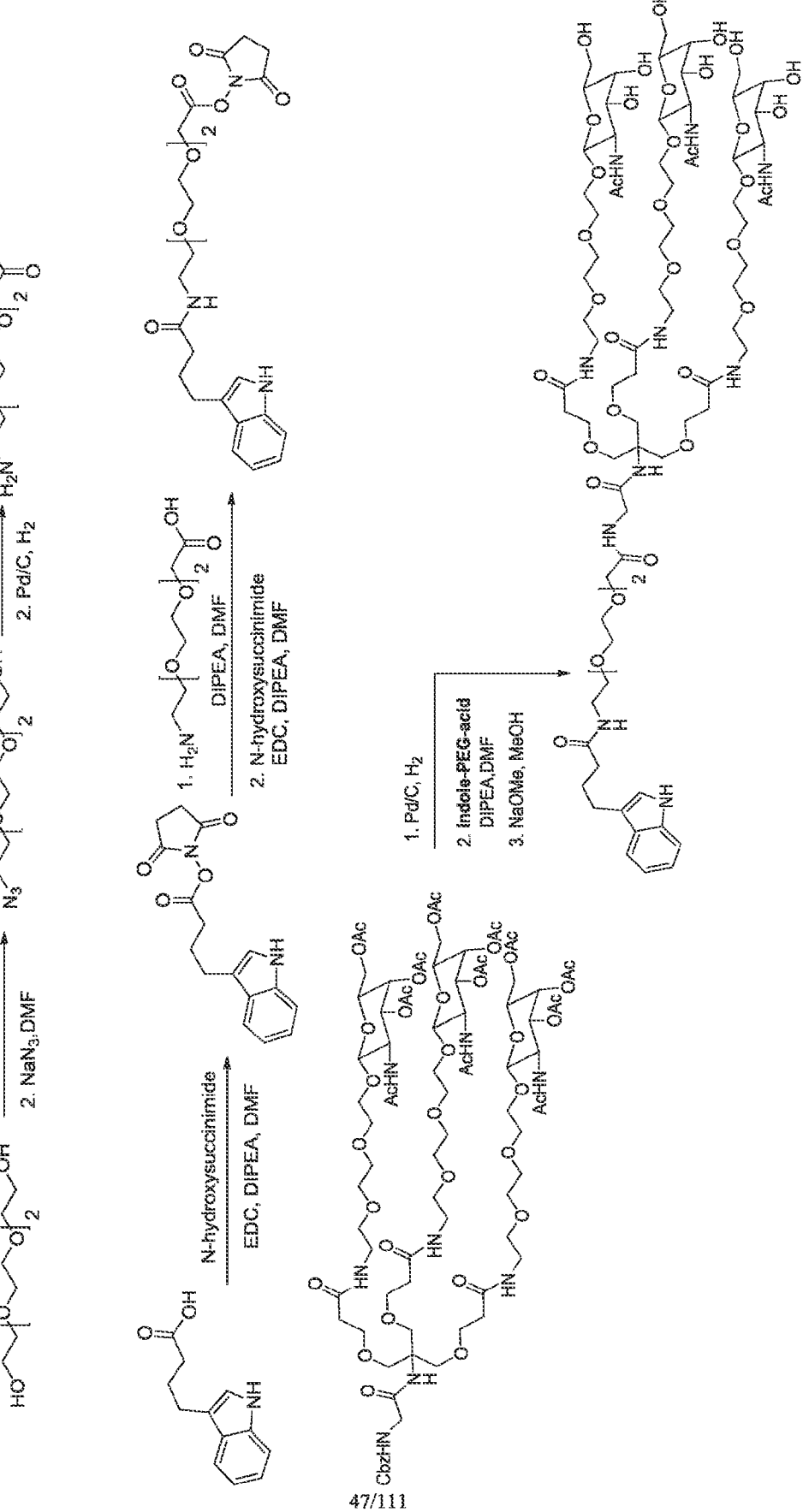

1. TsCl, THF, Et3N
2. NaN3, DMF
1. Jones
2. Pd/C, H2
N-hydroxysuccinimide
EDC, DIPEA, DMF
1. H2N
DIPEA, DMF
2. N-hydroxysuccinimide
EDC, DIPEA, DMF
1. Pd/C, H2
2. indole-PEG-acid
DIPEA, DMF
3. NaOMe, MeOH

FIGURE 37

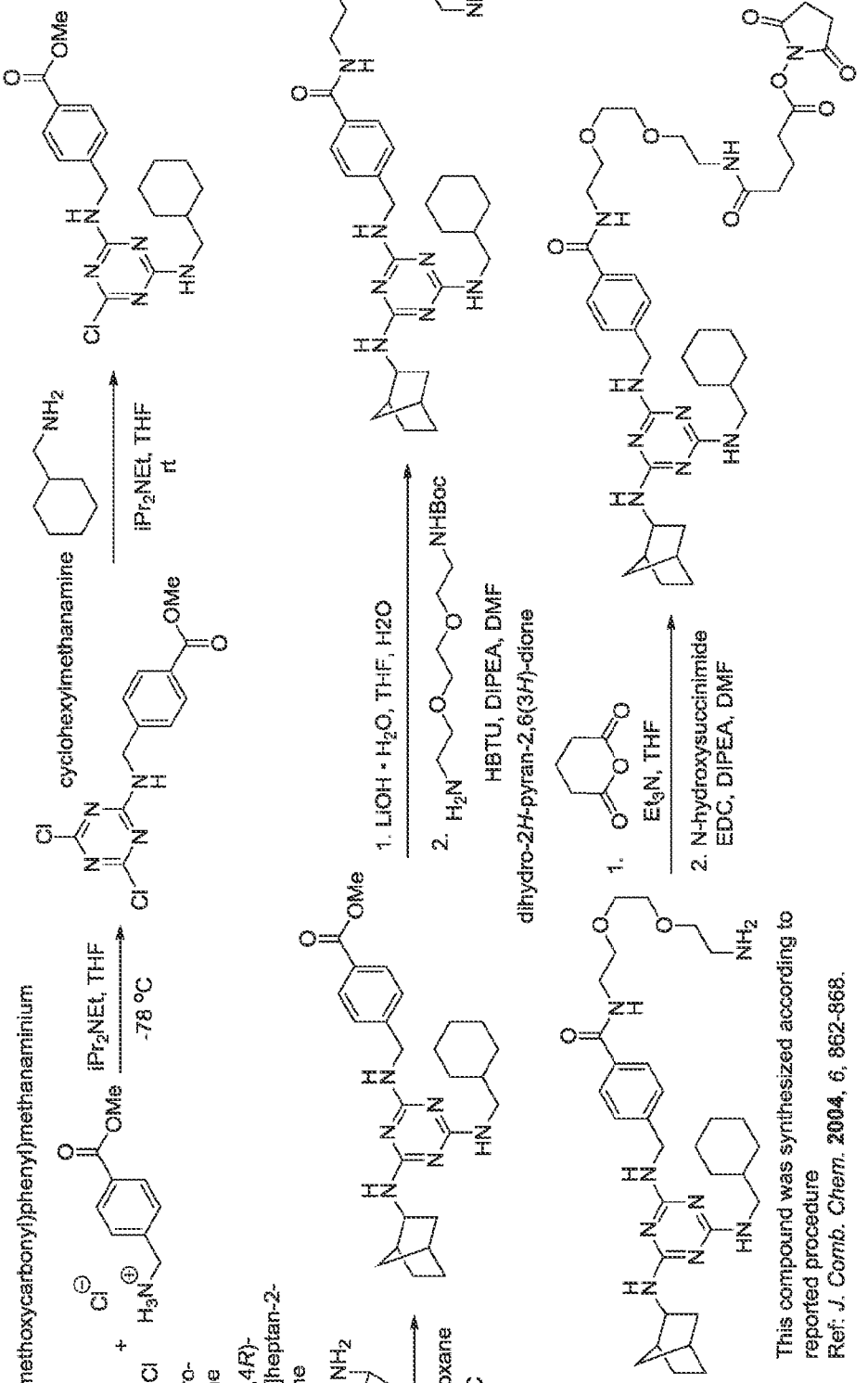

(4-(methoxycarbonyl)phenyl)methanaminium
2,4,6-trichloro-1,3,5-triazine
iPr2NEt, THF
-78 °C
cyclohexylmethanamine
iPr2NEt, THF
rt
(1S,2S,4R)-bicyclo[2.2.1]heptan-2-amine
iPr2NEt, Dioxane
140 °C
1. LiOH • H2O, THF, H2O
2. H2N
HBTU, DIPEA, DMF
dihydro-2H-pyran-2,6(3H)-dione
1.
Et3N, THF
2. N-hydroxysuccinimide
EDC, DIPEA, DMF
TFA
CH2Cl2
This compound was synthesized according to reported procedure
Ref: J. Comb. Chem. 2004, 6, 862-868.

FIGURE 37 (Cont'd)

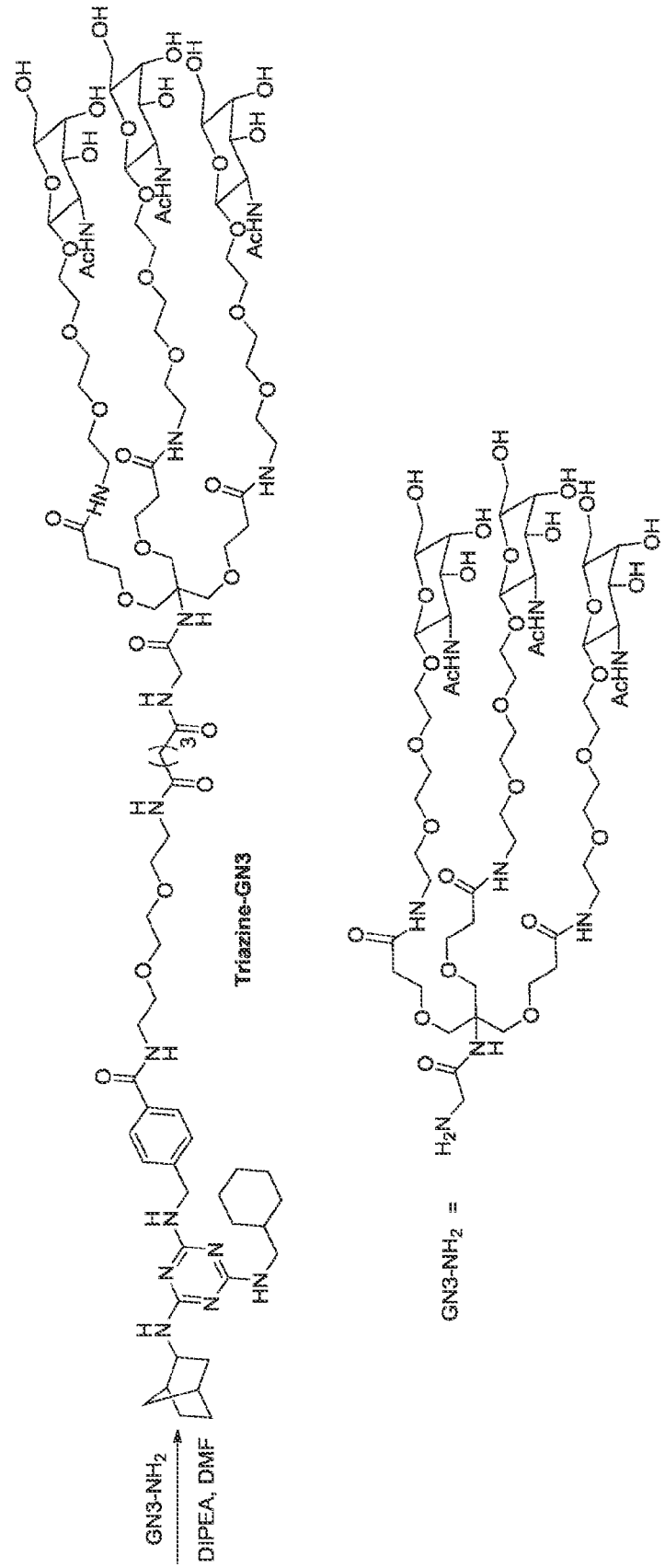


FIGURE 38

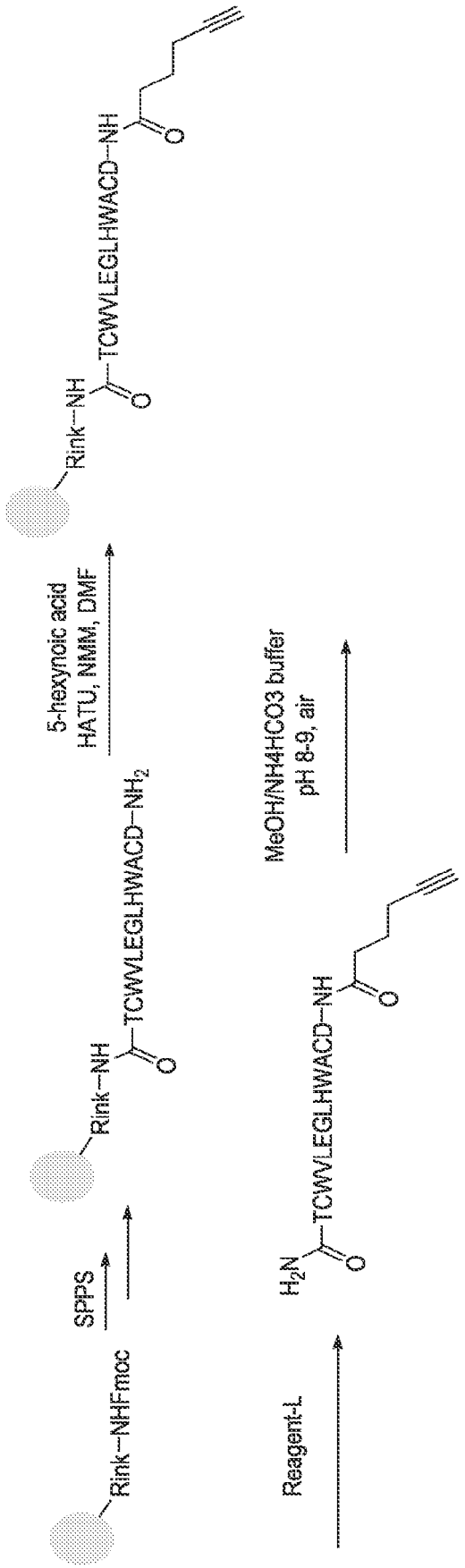

Rink–NHFmoc
SPPS
Rink–NH
TCWVLEGLHWACD–NH2
5-hexynoic acid
HATU, NMM, DMF
Rink–NH
TCWVLEGLHWACD–NH
Reagent-L
H2N
TCWVLEGLHWACD–NH
MeOH/NH4HCO3 buffer
pH 8-9, air

FIGURE 38 (Cont'd)

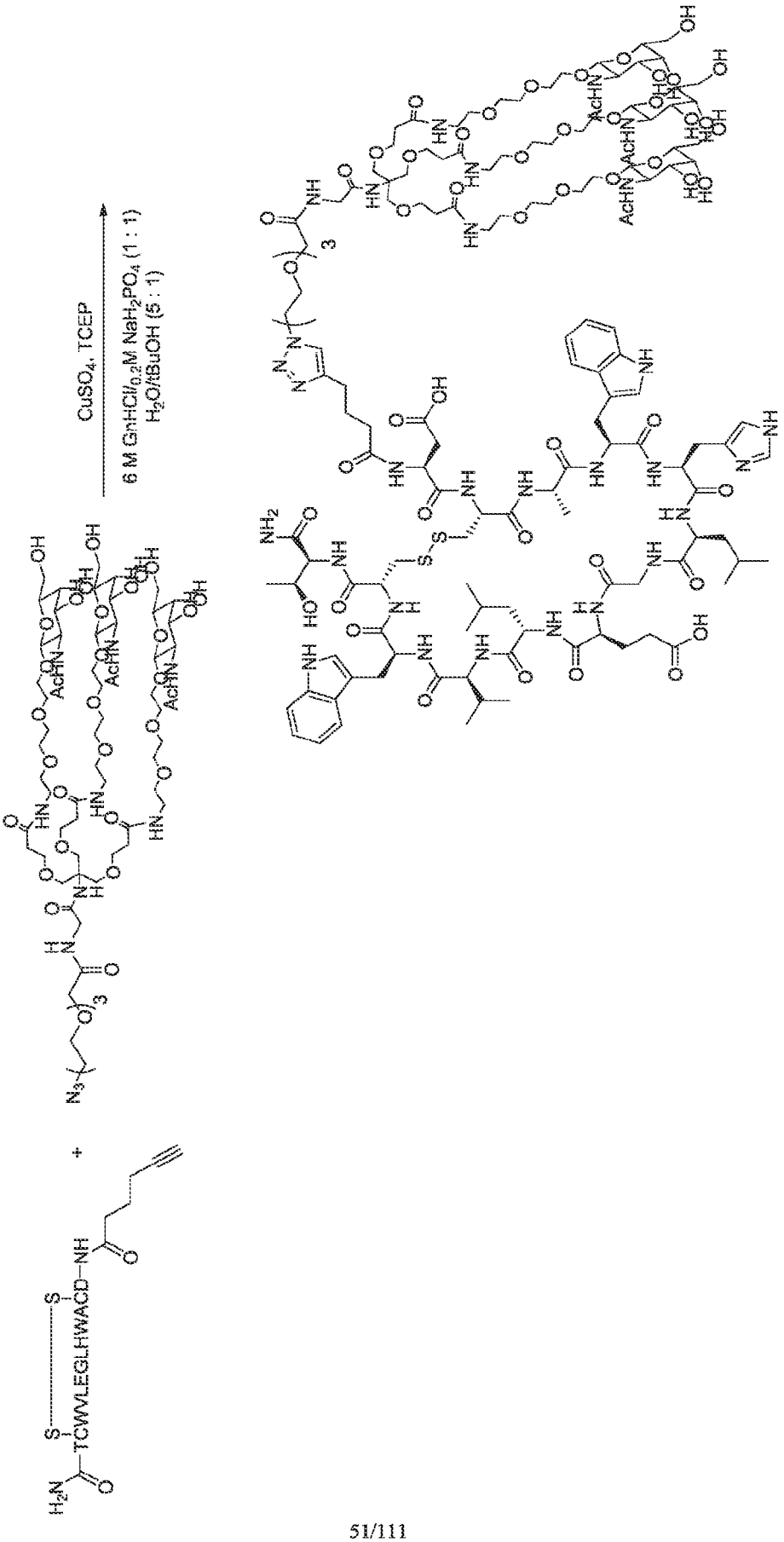


FIGURE 39

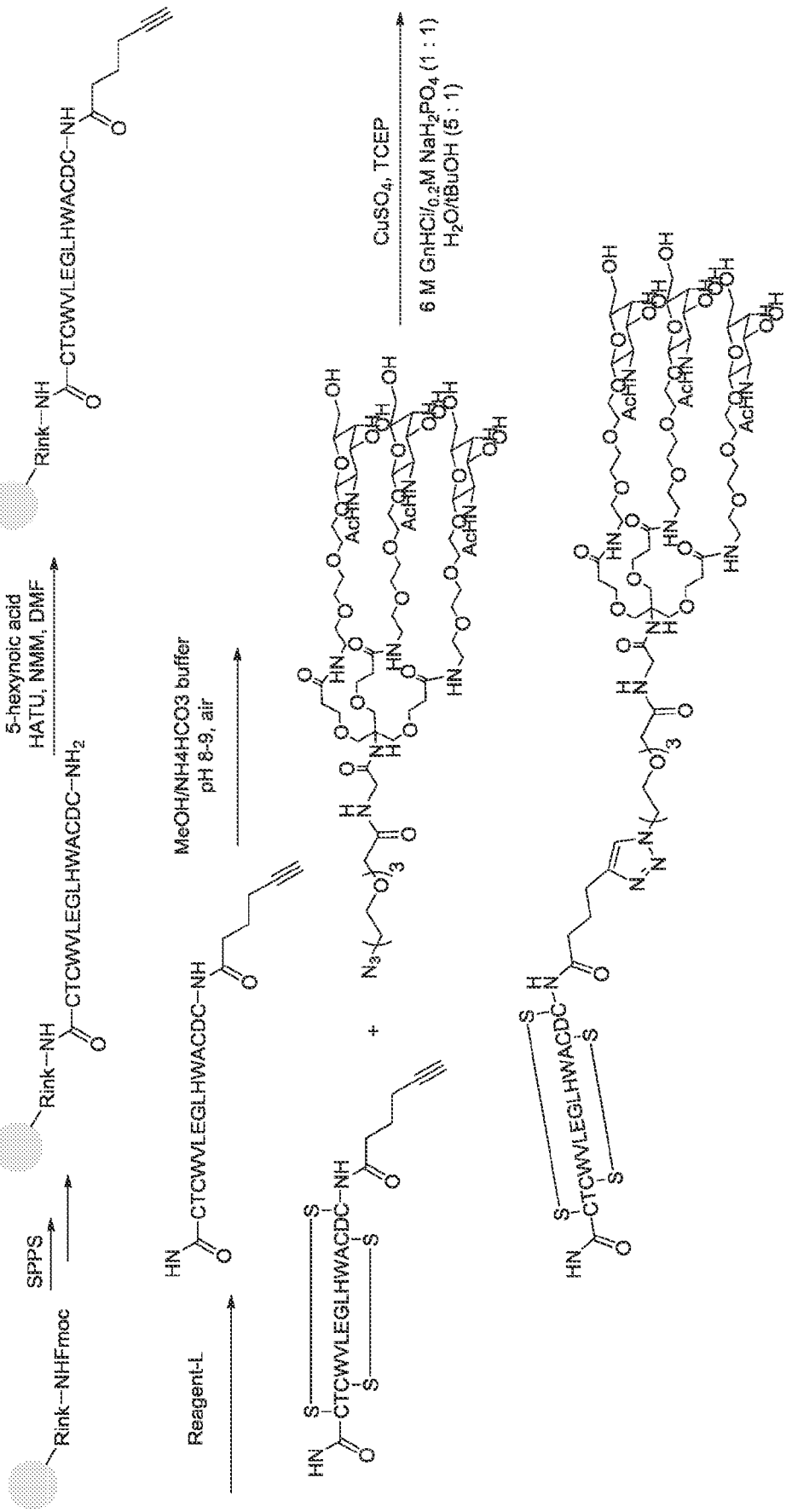

Rink–NHFmoc
SPPS
Rink–NH
CTCWVLEGLHWACDC–NH2
5-hexynoic acid
HATU, NMM, DMF
CTCWVLEGLHWACDC–NH
Reagent-L
MeOH/NH4HCO3 buffer
pH 8-9, air
CuSO4, TCEP
6 M GnHCl/0.2M NaH2PO4 (1 : 1)
H2O/tBuOH (5 : 1)

FIGURE 40

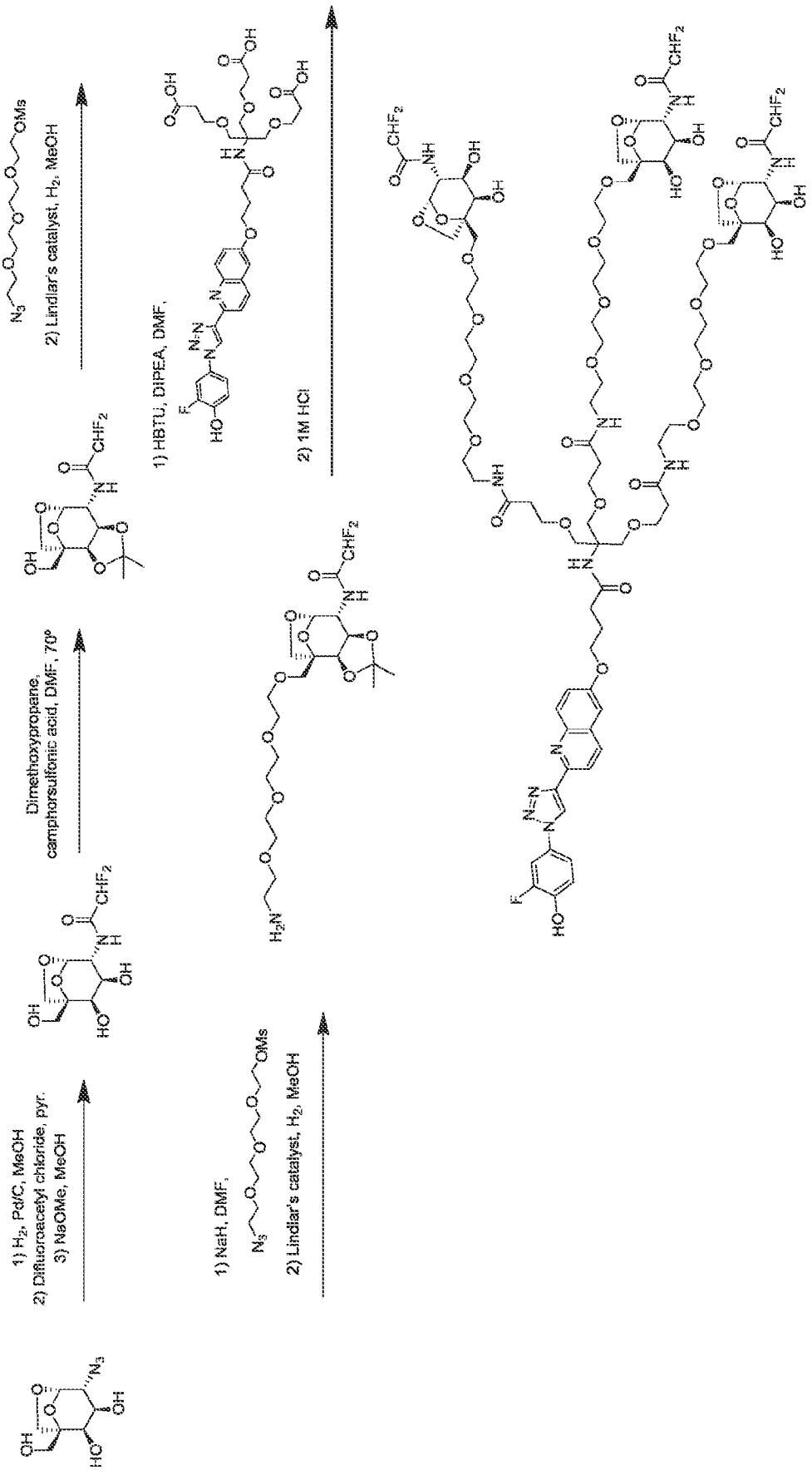

1) H2, Pd/C, MeOH
2) Difluoroacetyl chloride, pyr.
3) NaOMe, MeOH
Dimethoxypropane,
camphorsulfonic acid, DMF, 70°
1) NaH, DMF,
2) Lindlar's catalyst, H2, MeOH
1) HBTU, DIPEA, DMF,
2) 1M HCl
1) NaH, DMF,
2) Lindlar's catalyst, H2, MeOH

FIGURE 41

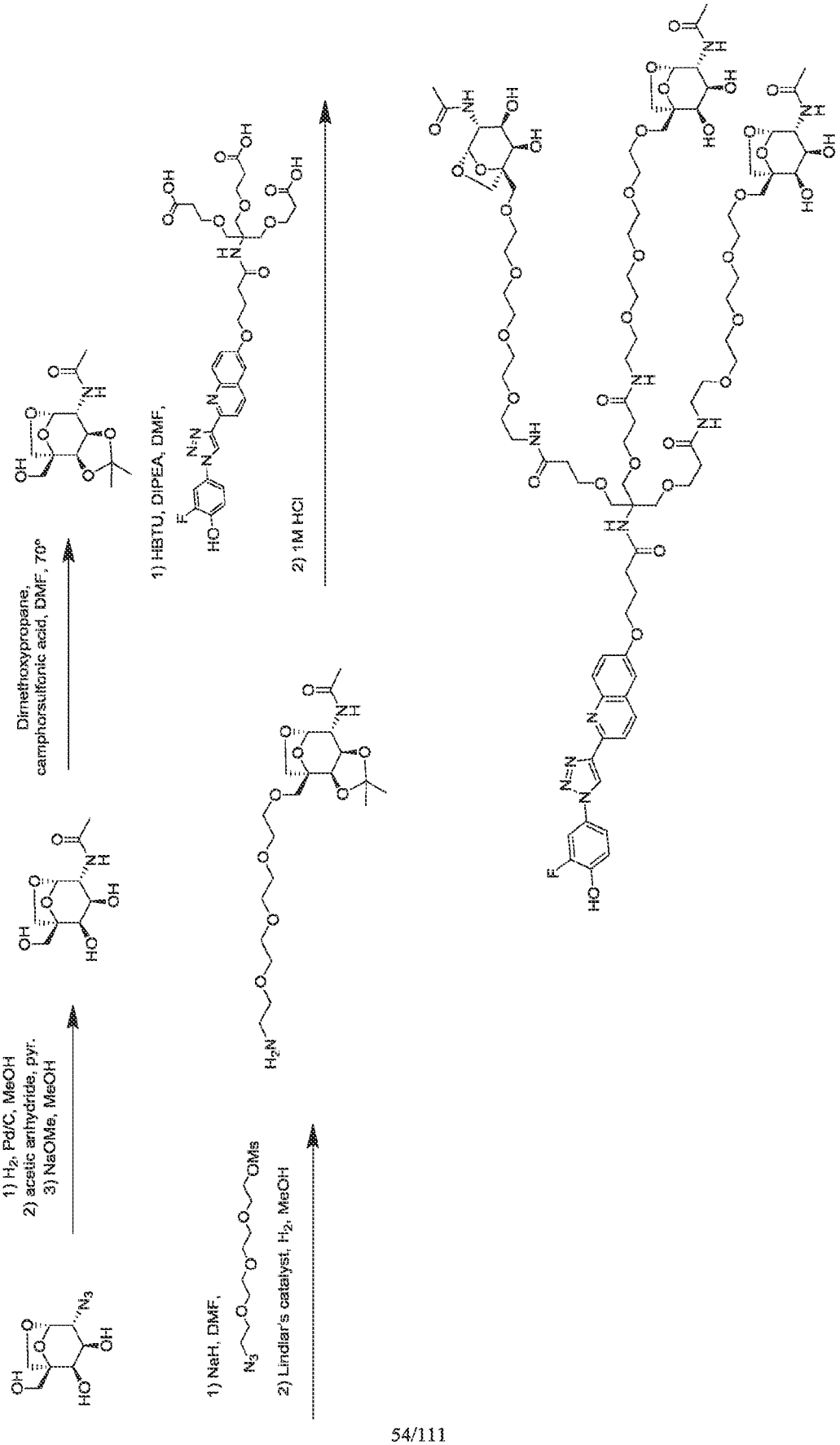

1) H_2, Pd/C, MeOH
2) acetic anhydride, pyr.
3) NaOMe, MeOH
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) NaH, DMF,
2) Lindlar's catalyst, H_2, MeOH
1) HBTU, DIPEA, DMF,
2) 1M HCl

FIGURE 42

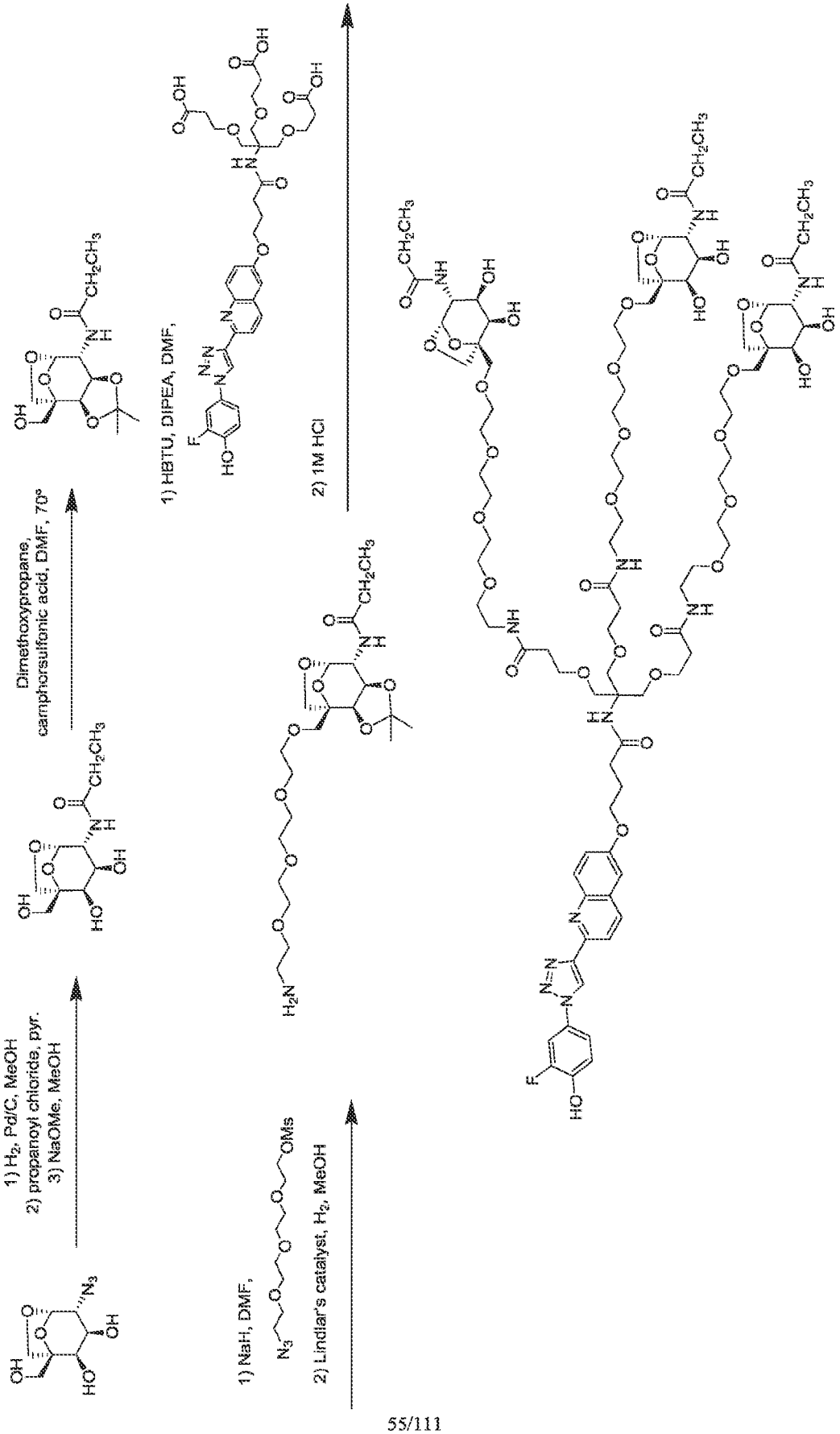

1) H_2, Pd/C, MeOH
2) propanoyl chloride, pyr.
3) NaOMe, MeOH
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) HBTU, DIPEA, DMF,
2) 1M HCl
1) NaH, DMF,
2) Lindlar's catalyst, H_2, MeOH

FIGURE 43

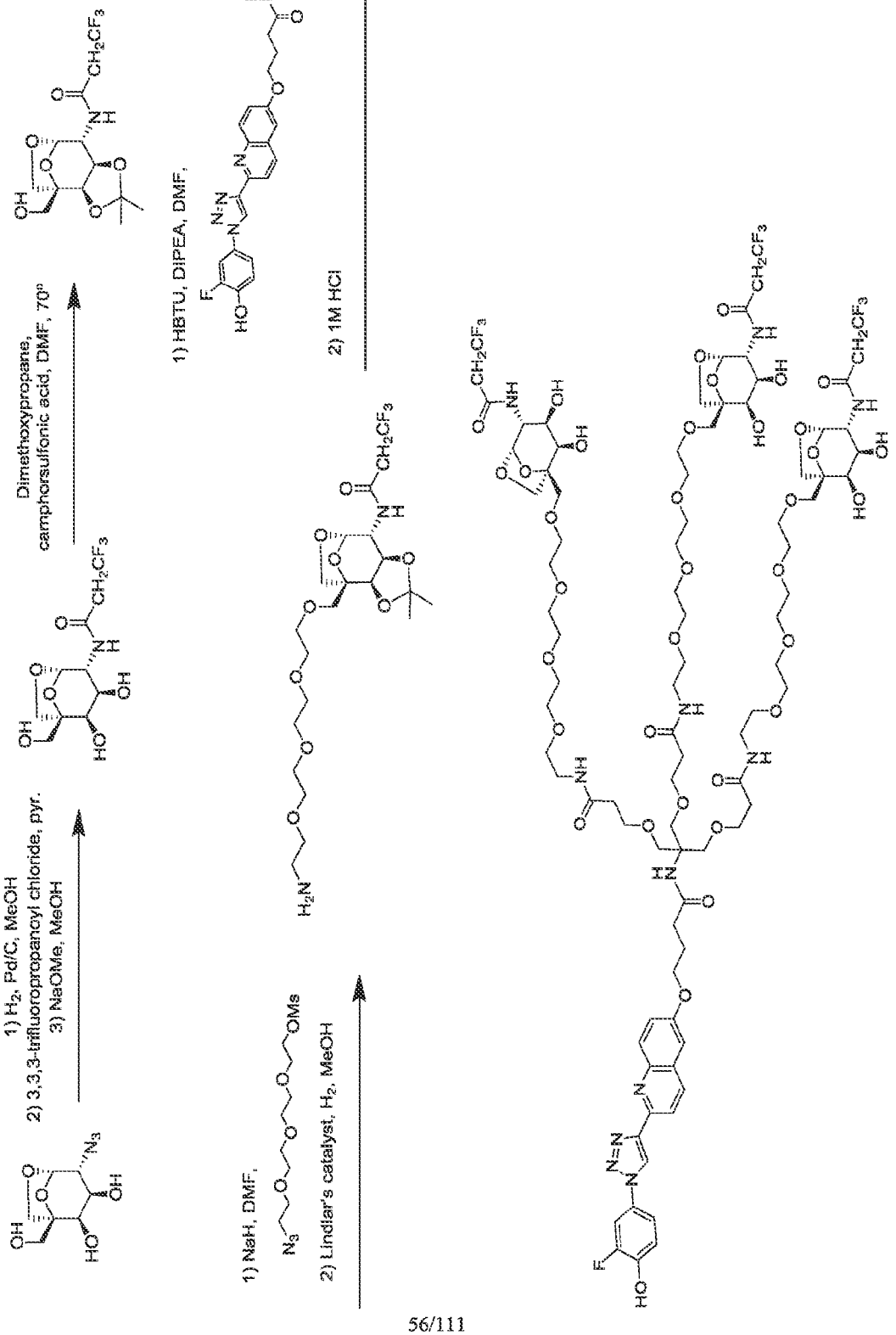

1) H_2, Pd/C, MeOH
2) 3,3,3-trifluoropropanoyl chloride, pyr.
3) NaOMe, MeOH
Dimethoxypropane,
camphorsulfonic acid, DMF, 70°
1) HBTU, DIPEA, DMF,
2) 1M HCl
1) NaH, DMF,
2) Lindlar's catalyst, H_2, MeOH

FIGURE 44

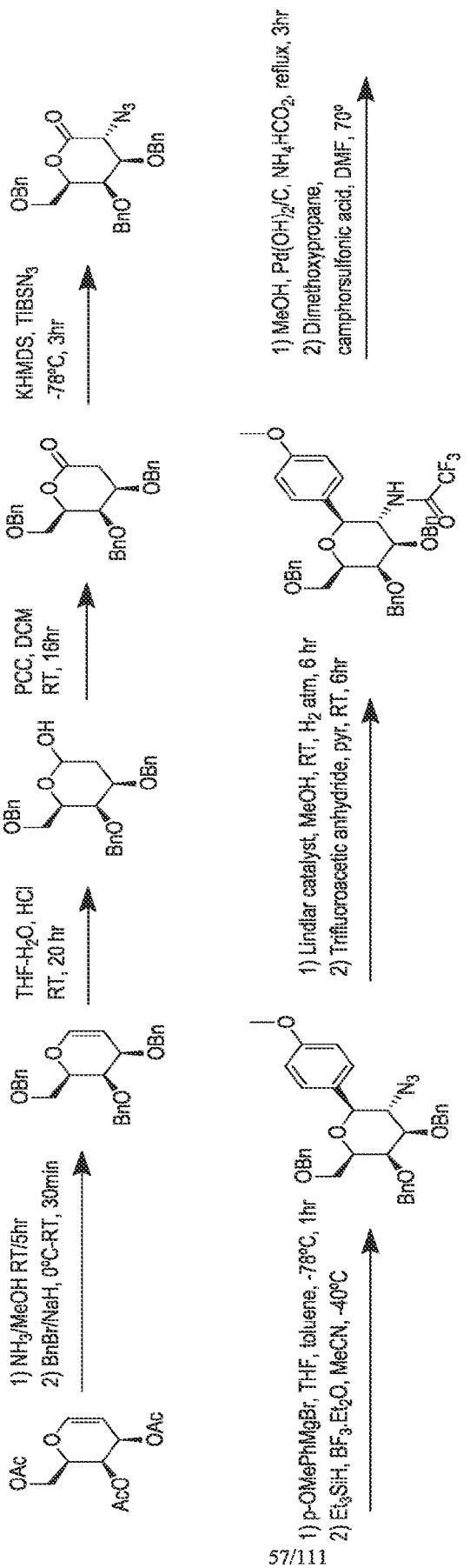

1) NH3/MeOH RT/5hr
2) BnBr/NaH, 0°C-RT, 30min
THF-H2O, HCl
RT, 20 hr
PCC, DCM
RT, 16hr
KHMDS, TIBSN3
-78°C, 3hr
1) MeOH, Pd(OH)2/C, NH4HCO2, reflux, 3hr
2) Dimethoxypropane,
camphorsulfonic acid, DMF, 70°
1) Lindlar catalyst, MeOH, RT, H2 atm, 6 hr
2) Trifluoroacetic anhydride, pyr, RT, 6hr
1) p-OMePhMgBr, THF, toluene, -78°C, 1hr
2) Et3SiH, BF3.Et2O, MeCN, -40°C

FIGURE 44 (Cont'd)

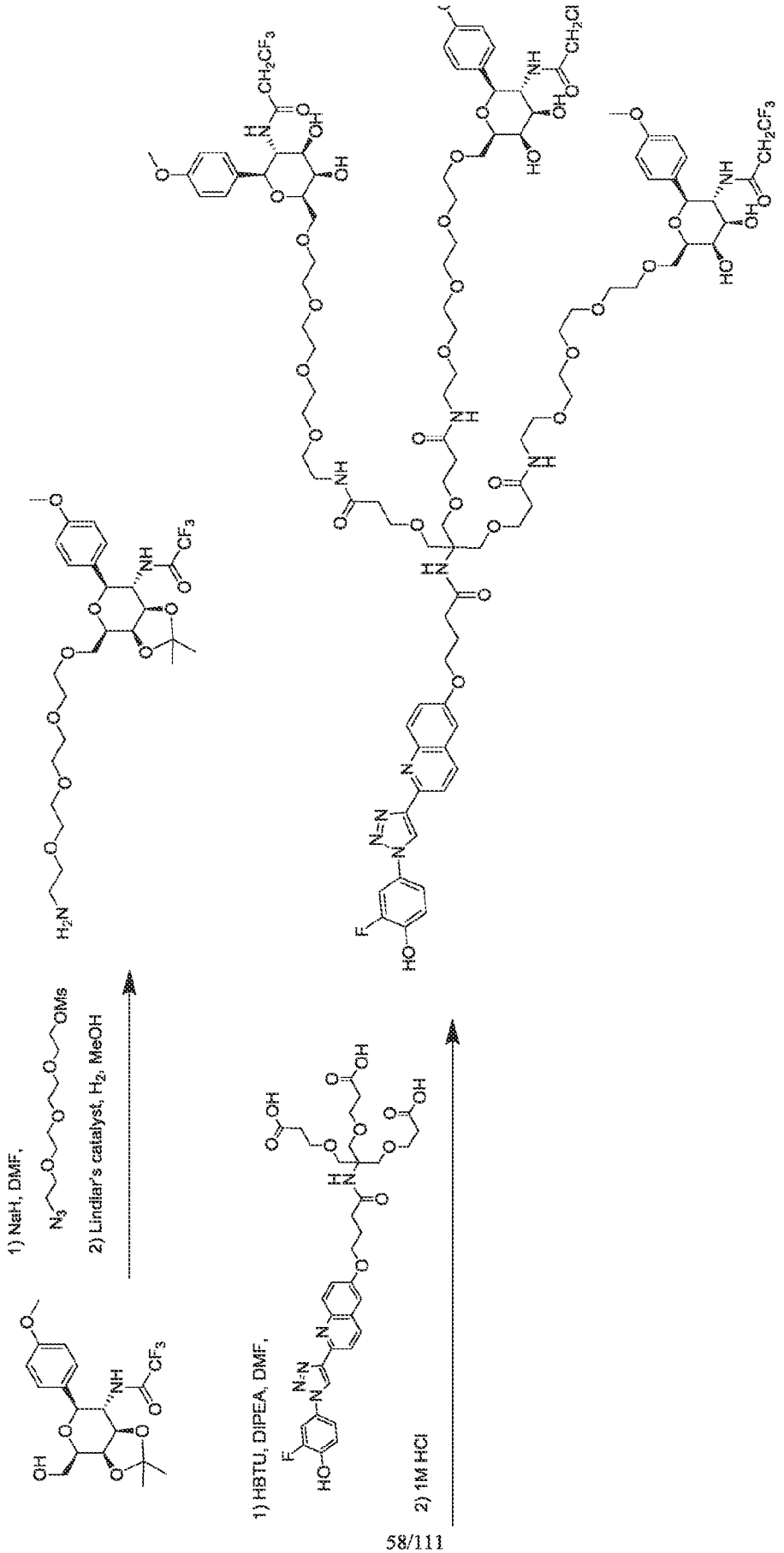


FIGURE 45

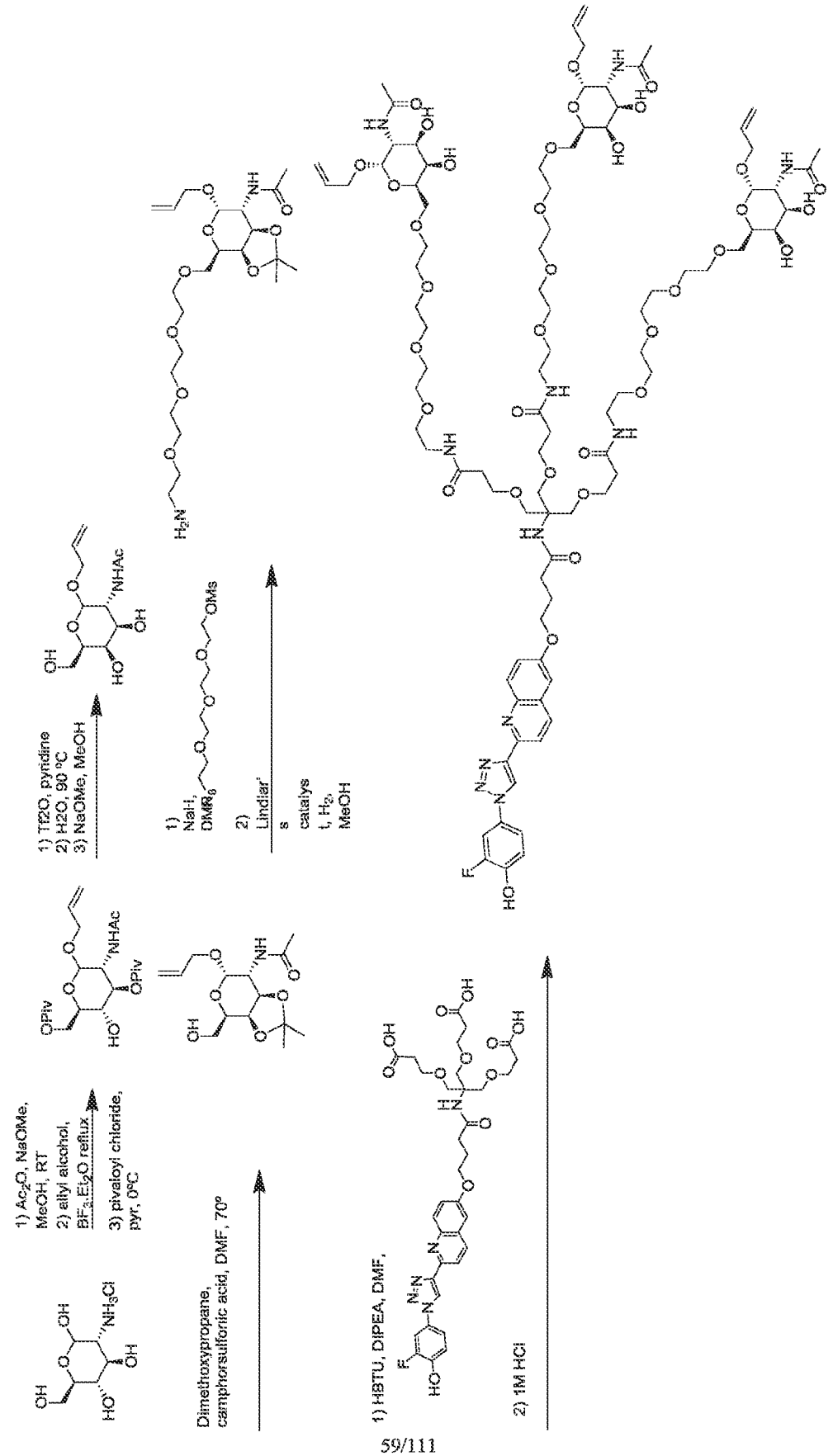

1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
1) NaH, DMF
2) Lindlar's catalys t, H2, MeOH
1) HBTU, DIPEA, DMF,
2) 1M HCl

FIGURE 46

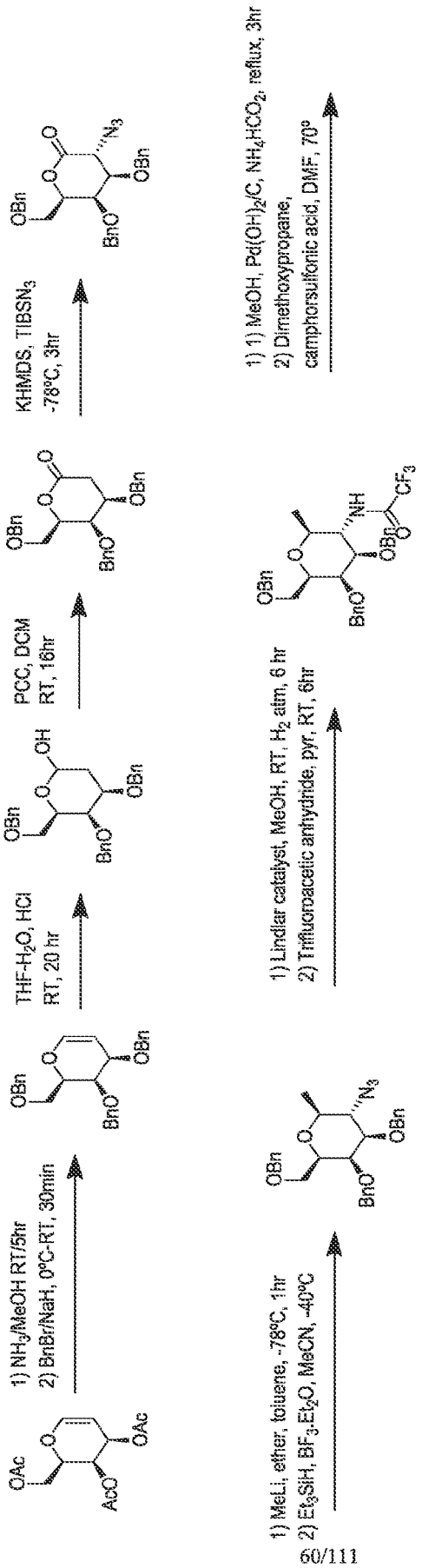

1) NH3/MeOH RT/5hr
2) BnBr/NaH, 0°C-RT, 30min
THF-H2O, HCl
RT, 20 hr
PCC, DCM
RT, 16hr
KHMDS, TIBSN3
-78°C, 3hr
1) 1) MeOH, Pd(OH)2/C, NH4HCO2, reflux, 3hr
2) Dimethoxypropane,
camphorsulfonic acid, DMF, 70°
1) MeLi, ether, toluene, -78°C, 1hr
2) Et3SiH, BF3.Et2O, MeCN, -40°C
1) Lindlar catalyst, MeOH, RT, H2 atm, 6 hr
2) Trifluoroacetic anhydride, pyr, RT, 6hr

FIGURE 46 (Cont'd)

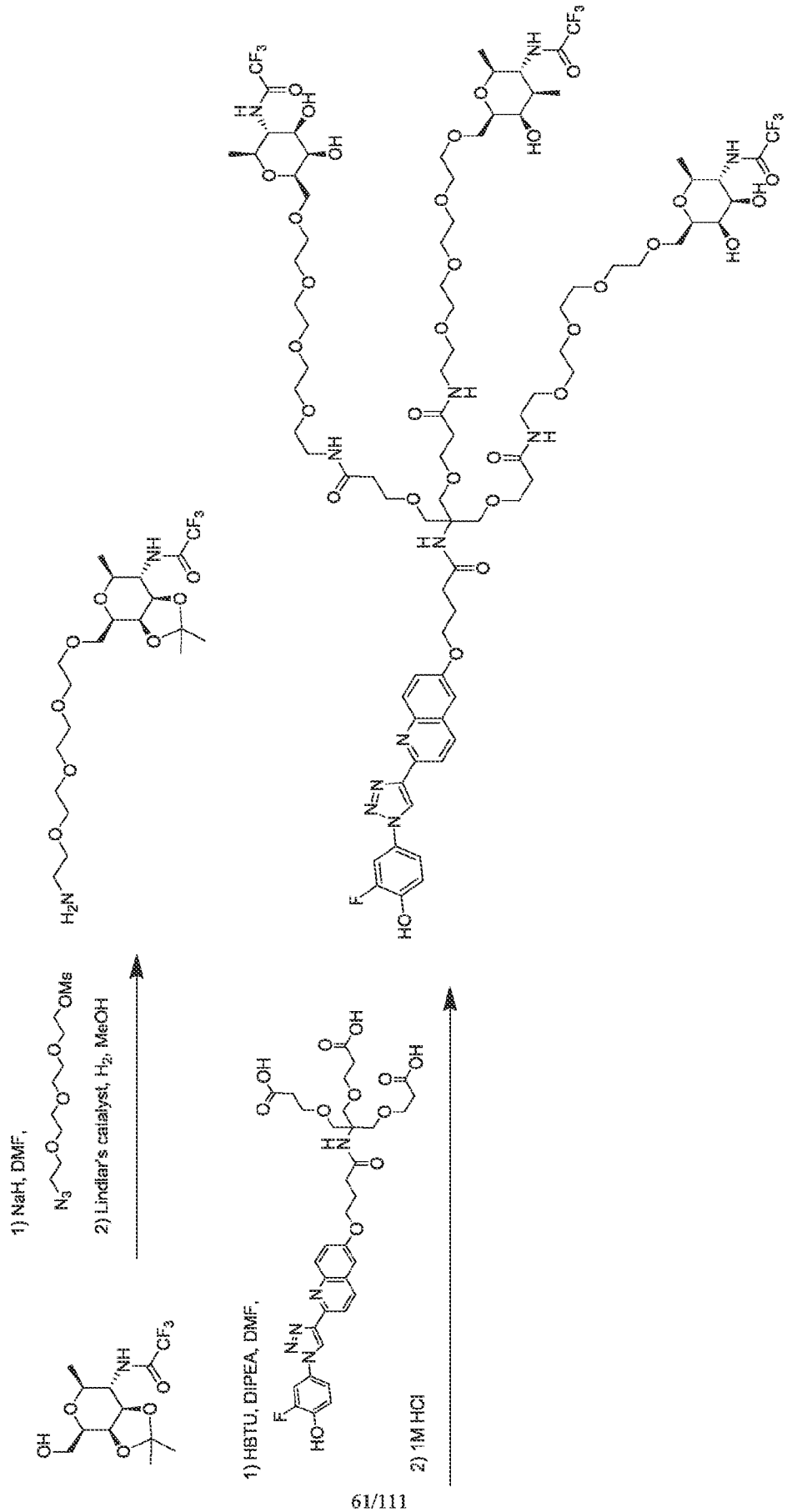


FIGURE 47

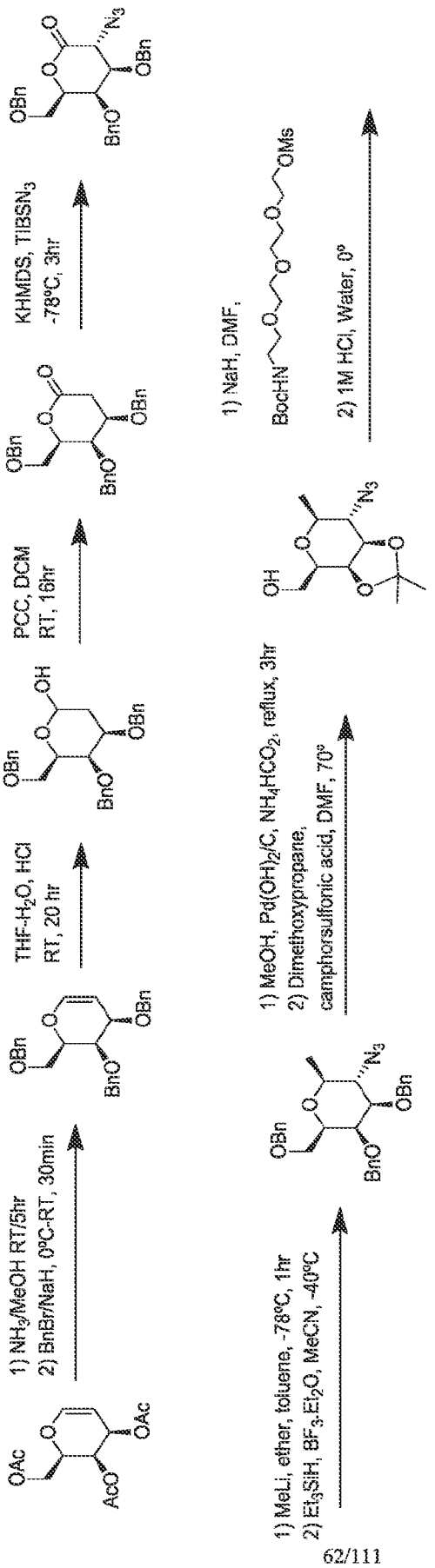

1) NH3/MeOH RT/5hr
2) BnBr/NaH, 0°C-RT, 30min
THF-H2O, HCl
RT, 20 hr
PCC, DCM
RT, 16hr
KHMDS, TIBSN3
-78°C, 3hr
1) MeLi, ether, toluene, -78°C, 1hr
2) Et3SiH, BF3.Et2O, MeCN, -40°C
1) MeOH, Pd(OH)2/C, NH4HCO2, reflux, 3hr
2) Dimethoxypropane,
camphorsulfonic acid, DMF, 70°
1) NaH, DMF,
2) 1M HCl, Water, 0°
OAc
AcO
OBn
BnO
OH
N3
BocHN
OMs

FIGURE 47 (Cont'd)

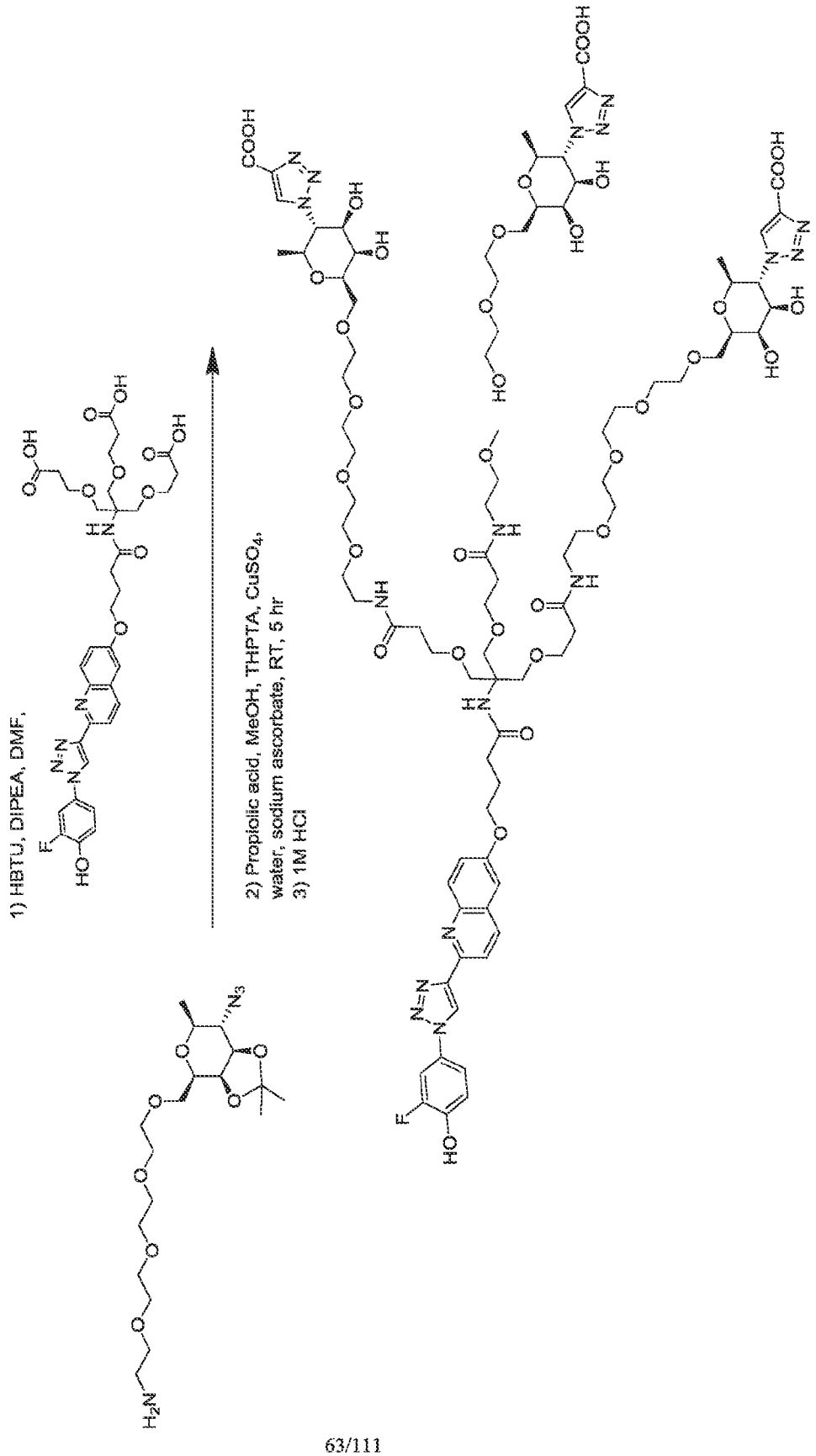


FIGURE 48

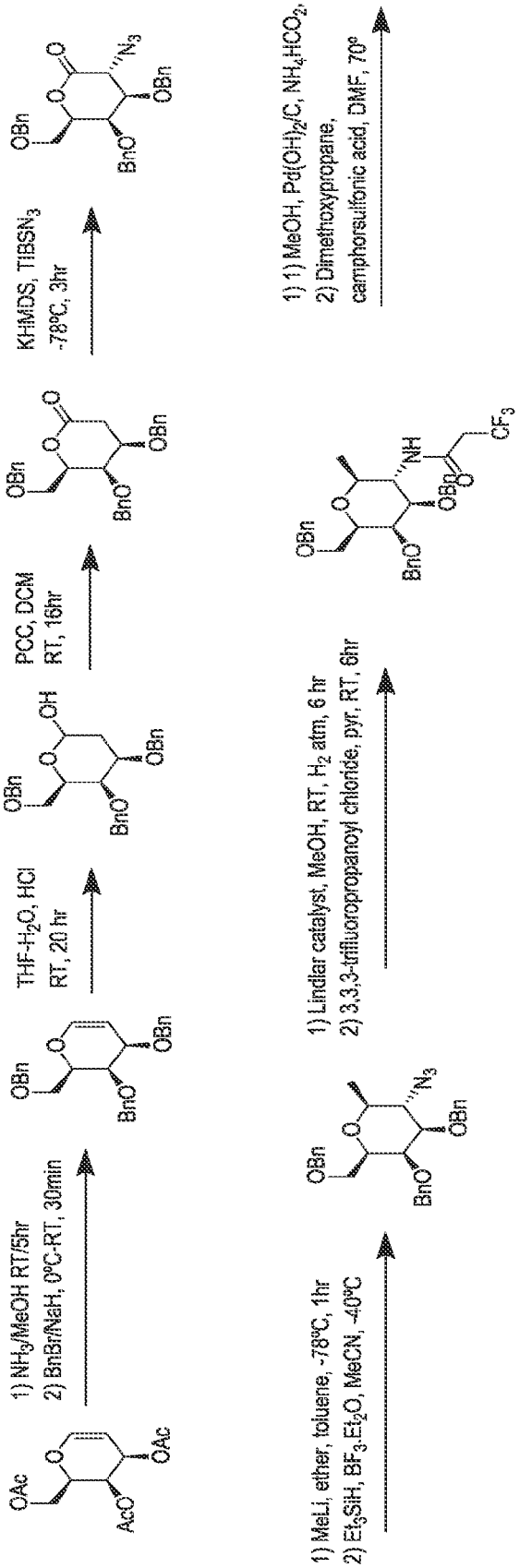

1) NH2OH/MeOH RT/5hr
2) BnBr/NaH, 0°C-RT, 30min
THF-H2O, HCl
RT, 20 hr
PCC, DCM
RT, 16hr
KHMDS, TIBSN3
-78°C, 3hr
1) 1) MeOH, Pd(OH)2/C, NH4HCO2, reflux, 3h
2) Dimethoxypropane,
camphorsulfonic acid, DMF, 70°
1) MeLi, ether, toluene, -78°C, 1hr
2) Et3SiH, BF3.Et2O, MeCN, -40°C
1) Lindlar catalyst, MeOH, RT, H2 atm, 6 hr
2) 3,3,3-trifluoropropanoyl chloride, pyr, RT, 6hr

FIGURE 48 (Cont'd)

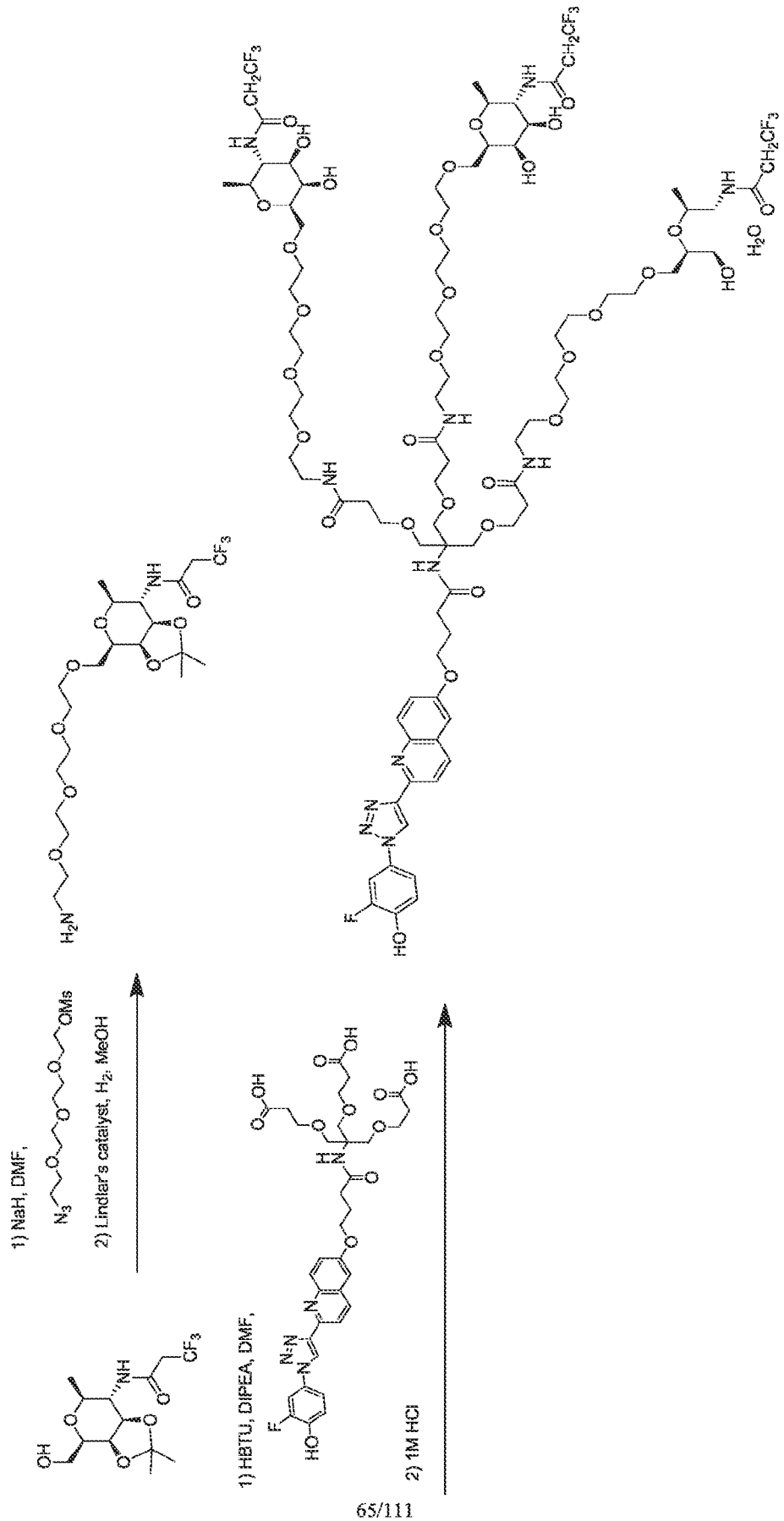


FIGURE 49

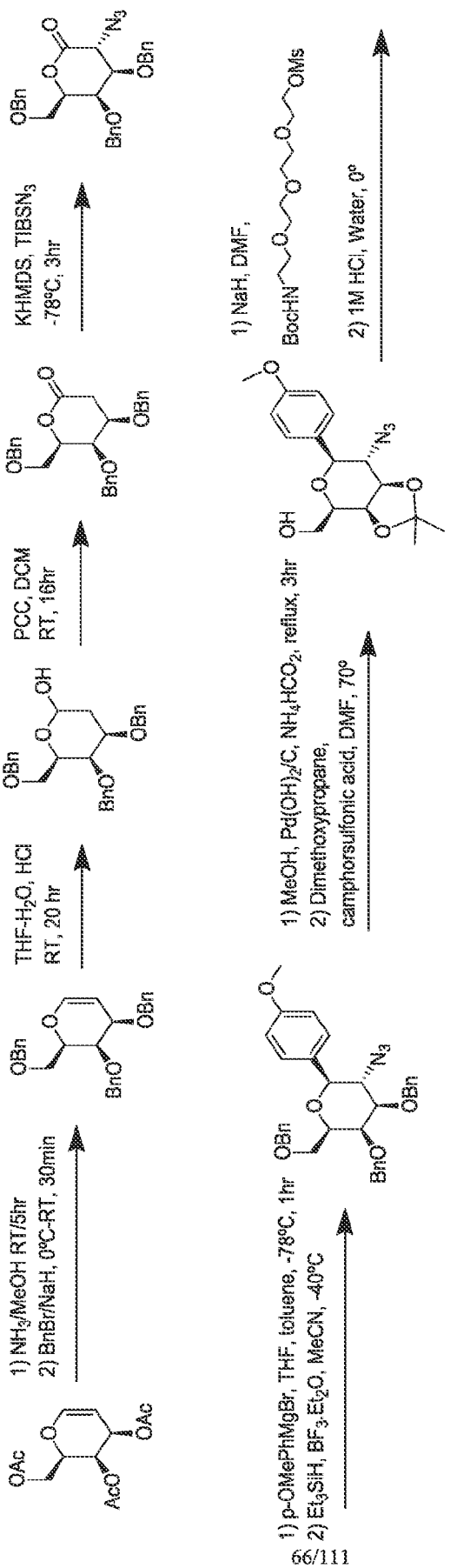

1) NH3/MeOH RT/5hr
2) BnBr/NaH, 0°C-RT, 30min
THF-H2O, HCl
RT, 20 hr
PCC, DCM
RT, 16hr
KHMDS, TIBSN3
-78°C, 3hr
1) p-OMePhMgBr, THF, toluene, -78°C, 1hr
2) Et3SiH, BF3.Et2O, MeCN, -40°C
1) MeOH, Pd(OH)2/C, NH4HCO2, reflux, 3hr
2) Dimethoxypropane,
camphorsulfonic acid, DMF, 70°
1) NaH, DMF,
2) 1M HCl, Water, 0°

FIGURE 49 (Cont'd)

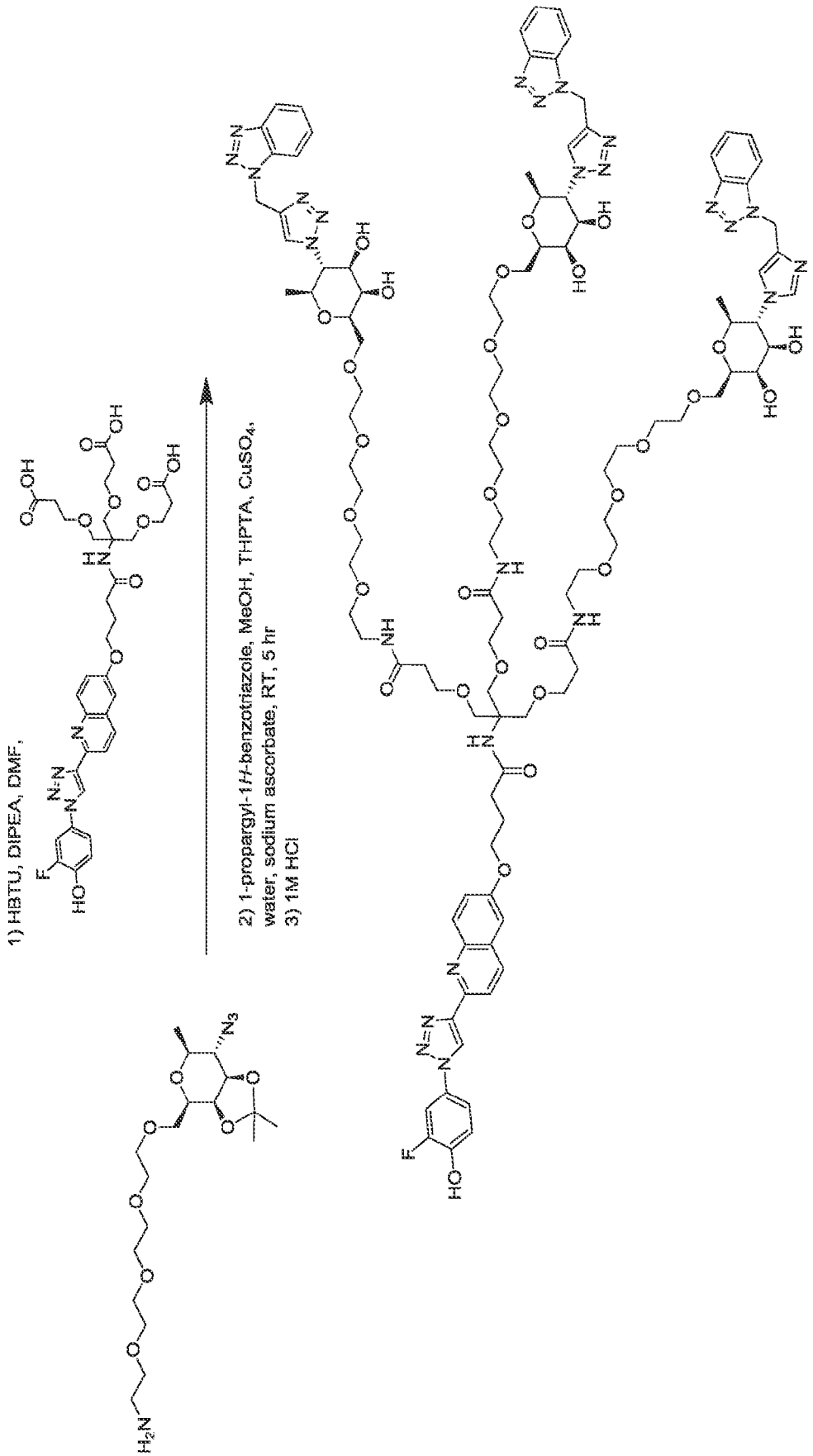


FIGURE 50

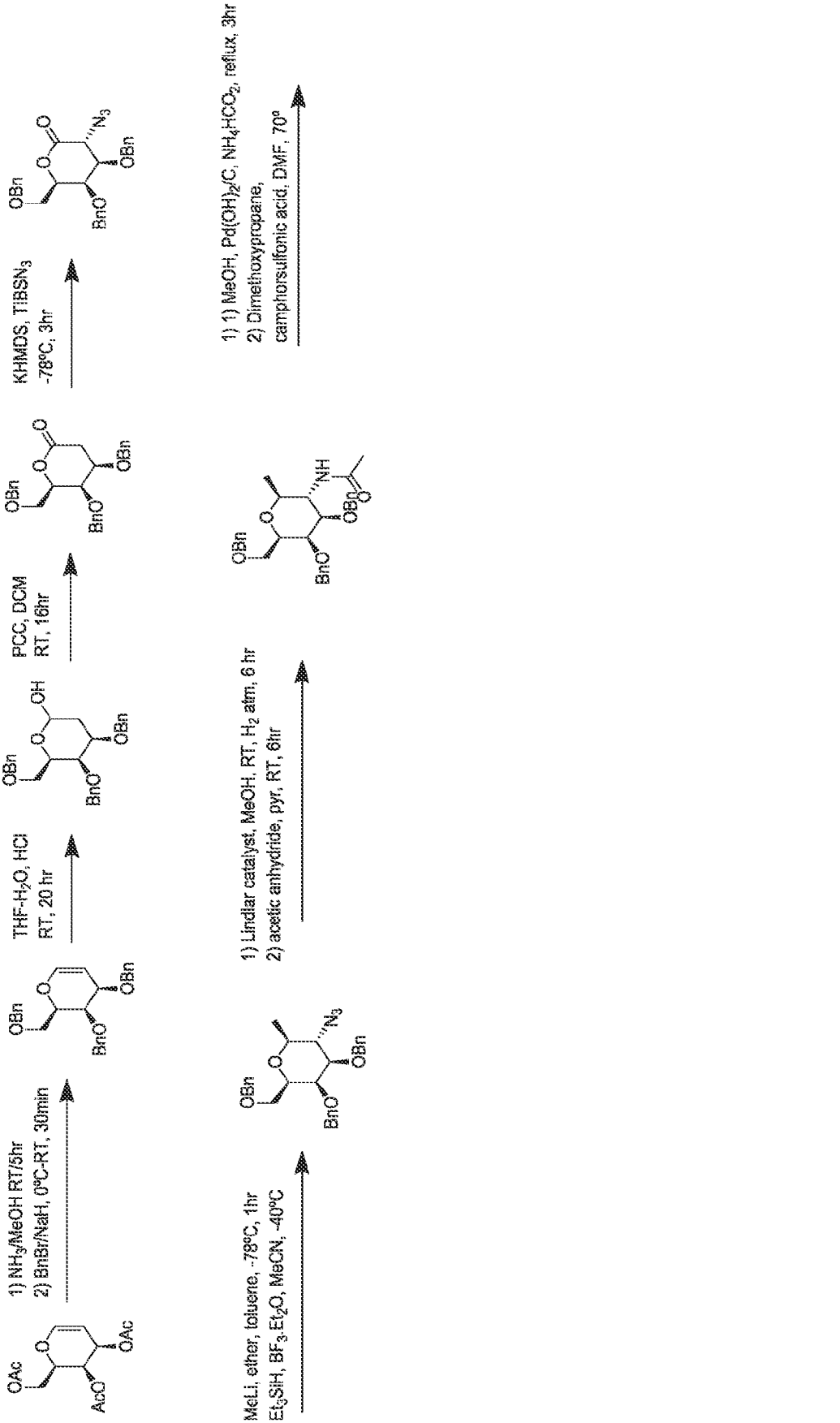

1) MeLi, ether, toluene, -78°C, 1hr
2) Et3SiH, BF3.Et2O, MeCN, -40°C
1) NH3/MeOH RT/5hr
2) BnBr/NaH, 0°C-RT, 30min
THF-H2O, HCl
RT, 20 hr
PCC, DCM
RT, 16hr
KHMDS, TIBSN3
-78°C, 3hr
1) Lindlar catalyst, MeOH, RT, H2 atm, 6 hr
2) acetic anhydride, pyr, RT, 6hr
1) 1) MeOH, Pd(OH)2/C, NH4HCO2, reflux, 3hr
2) Dimethoxypropane,
camphorsulfonic acid, DMF, 70°

FIGURE 50 (Cont'd)

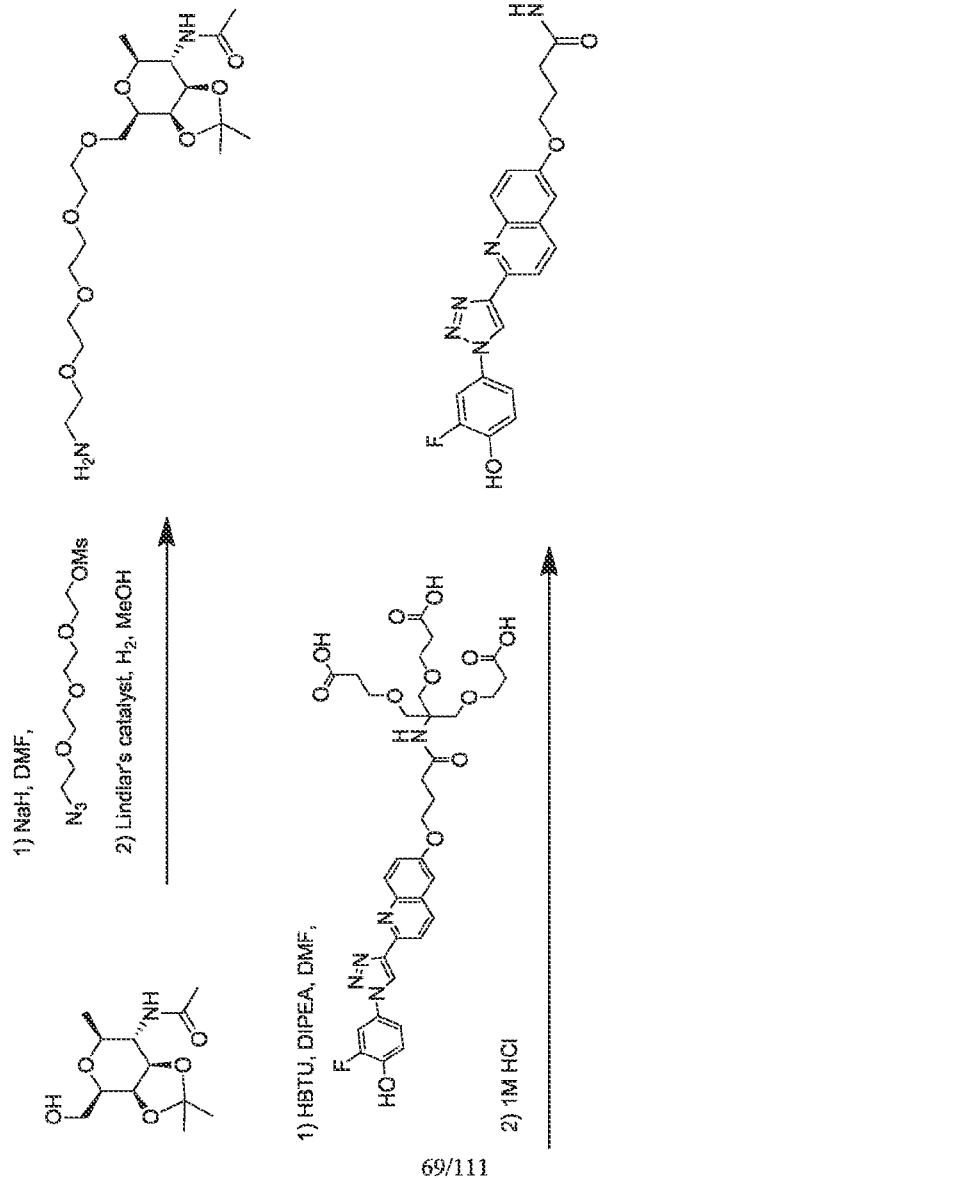


FIGURE 51

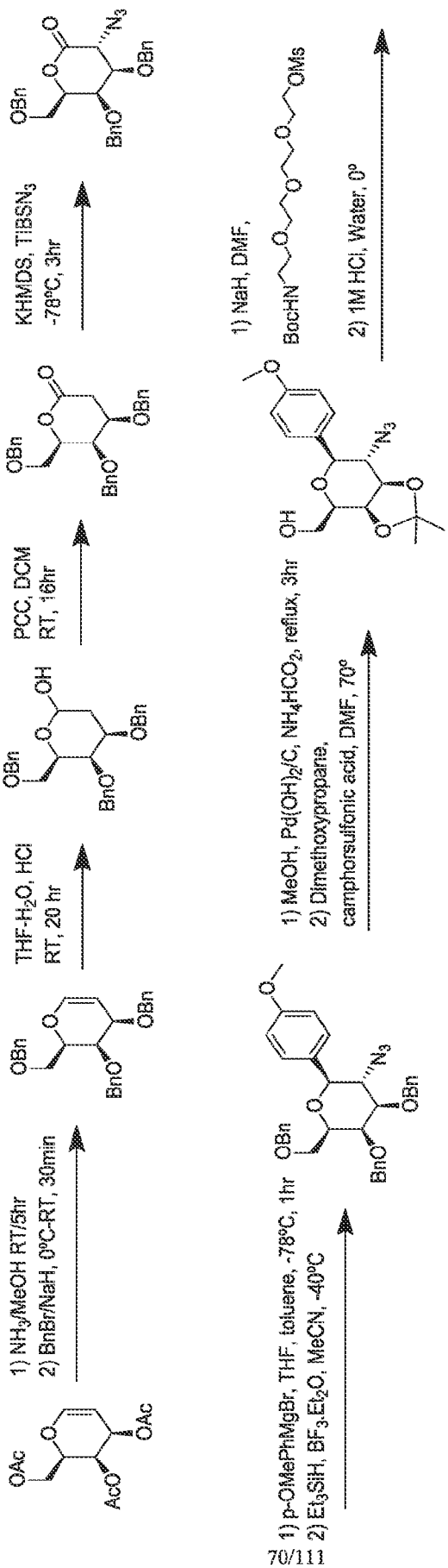

1) NH3/MeOH RT/5hr
2) BnBr/NaH, 0°C-RT, 30min
THF-H2O, HCl
RT, 20 hr
PCC, DCM
RT, 16hr
KHMDS, TIBSN3
-78°C, 3hr
1) p-OMePhMgBr, THF, toluene, -78°C, 1hr
2) Et3SiH, BF3.Et2O, MeCN, -40°C
1) MeOH, Pd(OH)2/C, NH4HCO2, reflux, 3hr
2) Dimethoxypropane,
camphorsulfonic acid, DMF, 70°
1) NaH, DMF,
2) 1M HCl, Water, 0°
OAc
AcO
OBn
BnO
OH
N3
BocHN
OMs

FIGURE S1 (Cont'd)

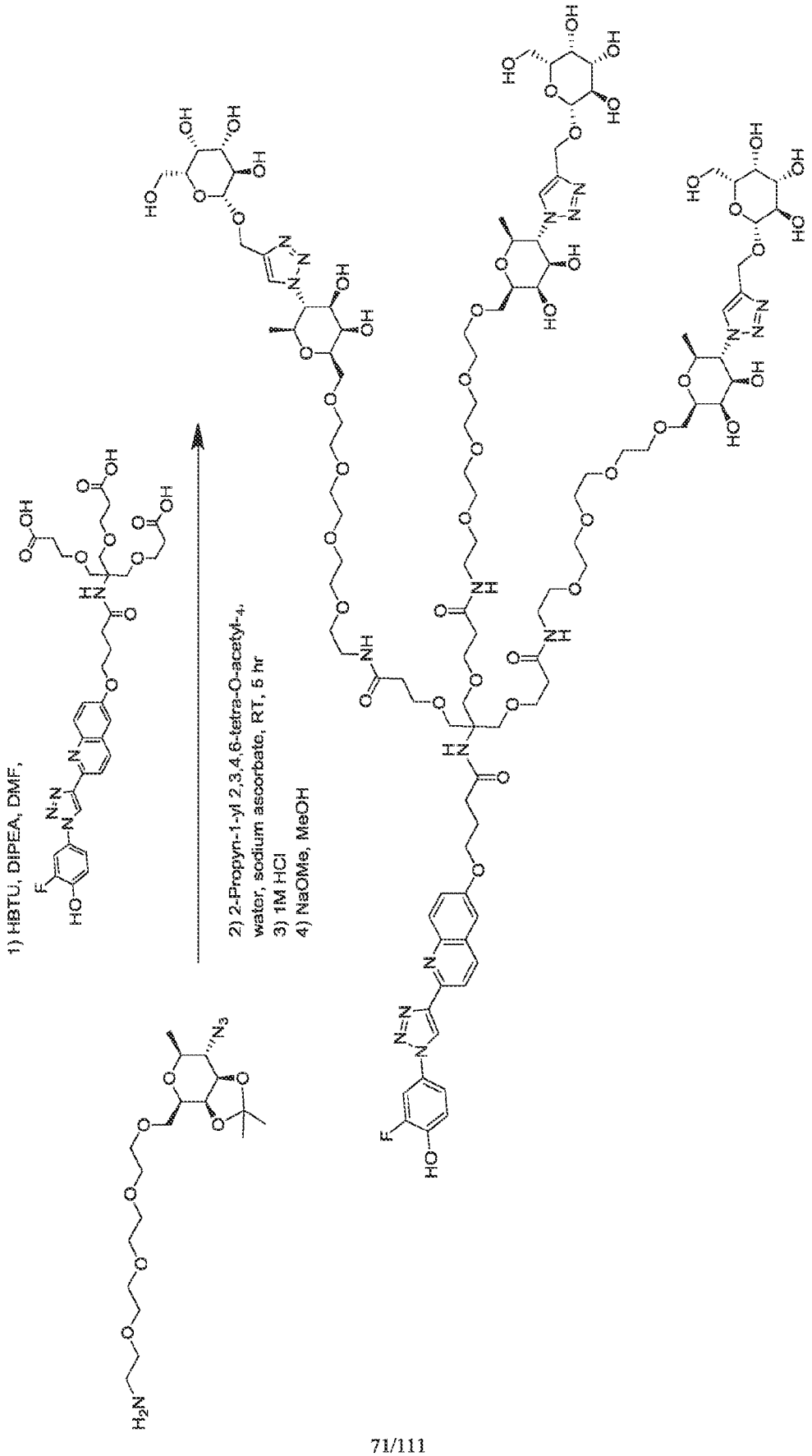


FIGURE 52

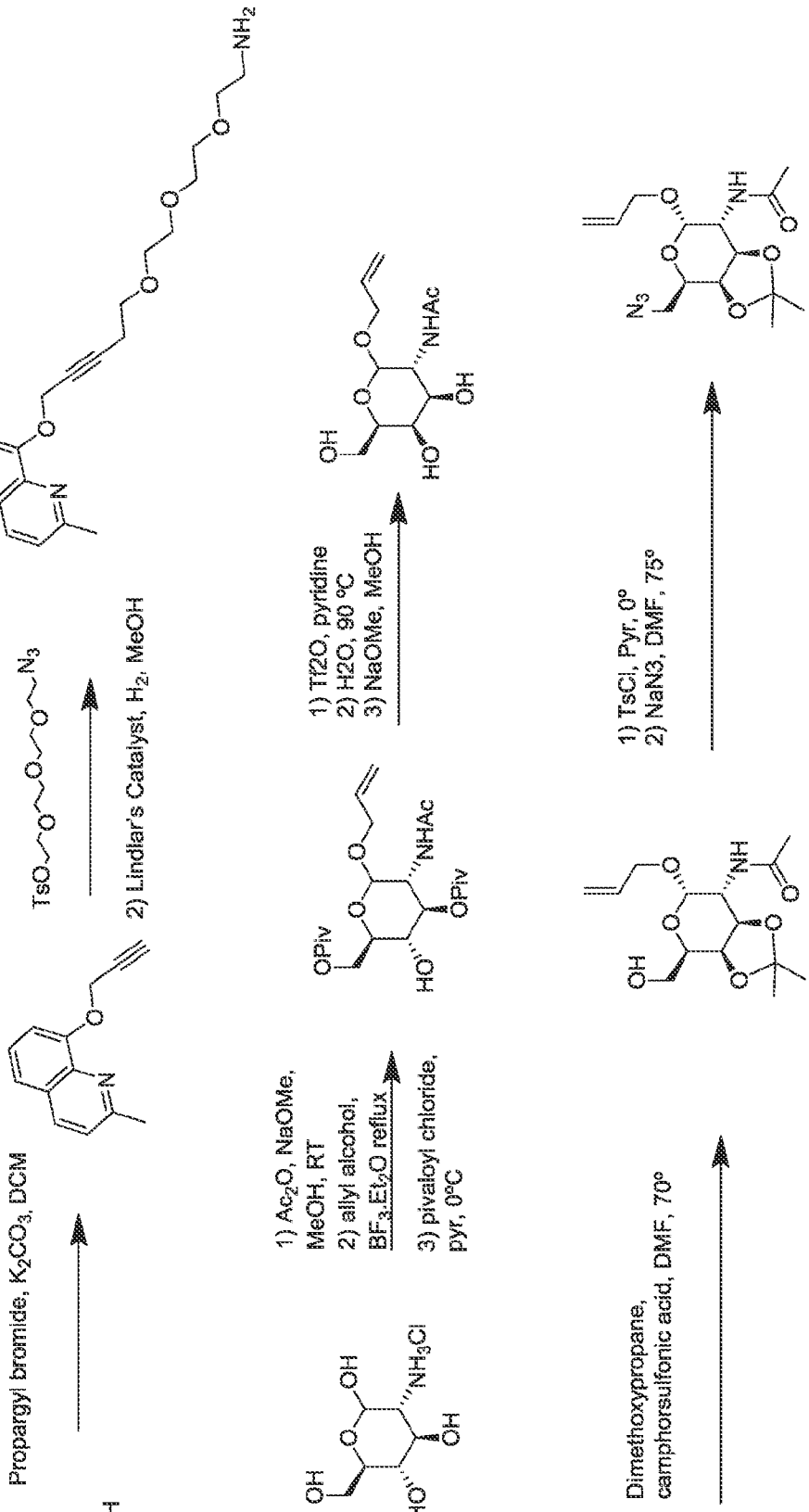

Propargyl bromide, K_2CO_3, DCM
1) NaH, DMF, 0°
2) Lindlar's Catalyst, H_2, MeOH
1) Ac_2O, NaOMe, MeOH, RT
2) allyl alcohol, $BF_3.Et_2O$ reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf_2O, pyridine
2) H_2O, 90 °C
3) NaOMe, MeOH
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) TsCl, Pyr, 0°
2) NaN_3, DMF, 75°

FIGURE S2 (Cont'd)

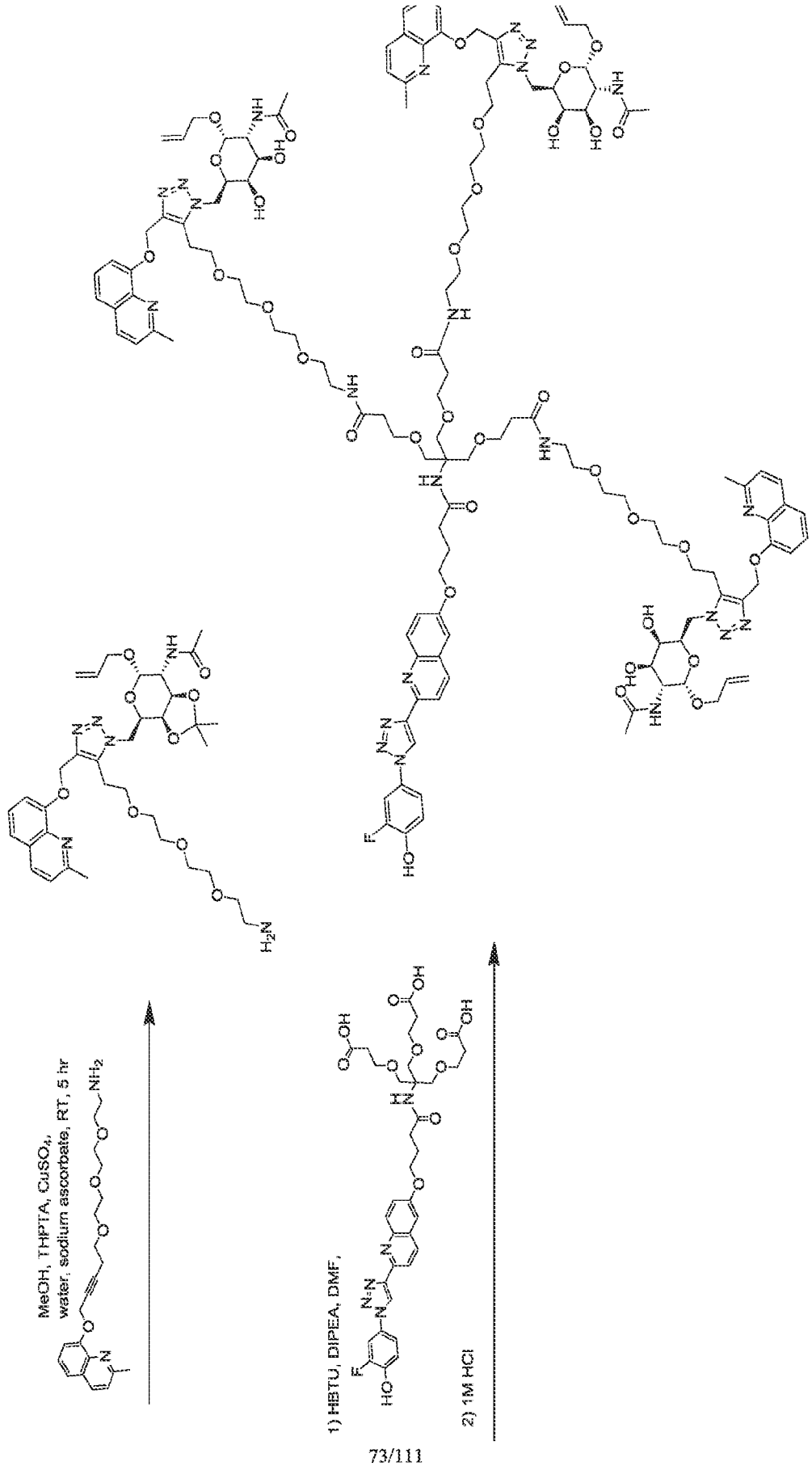


FIGURE 53

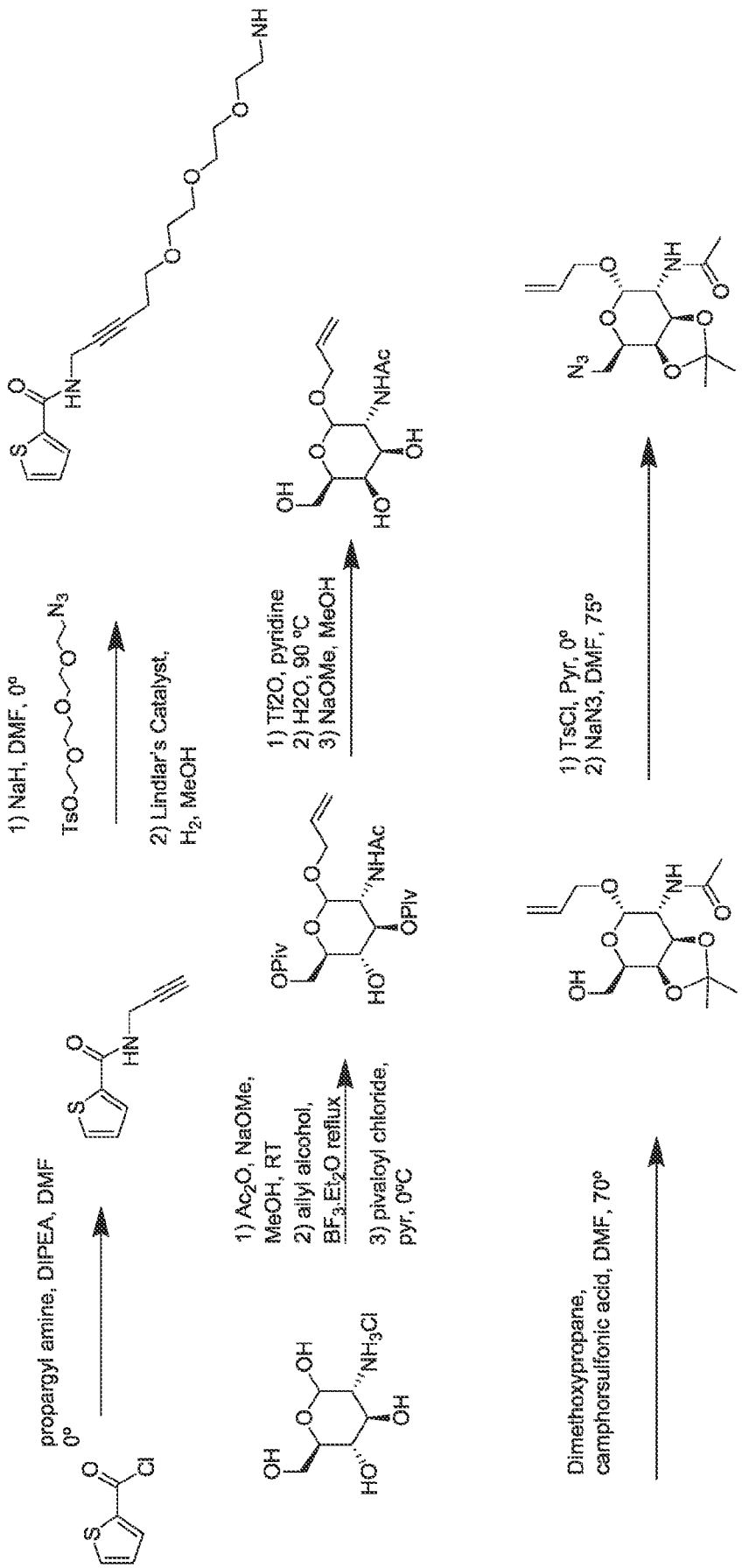

propargyl amine, DIPEA, DMF
0°
1) NaH, DMF, 0°
2) Lindlar's Catalyst, H2, MeOH
1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
1) TsCl, Pyr, 0°
2) NaN3, DMF, 75°
Dimethoxypropane, camphorsulfonic acid, DMF, 70°

FIGURE S3 (Cont'd)

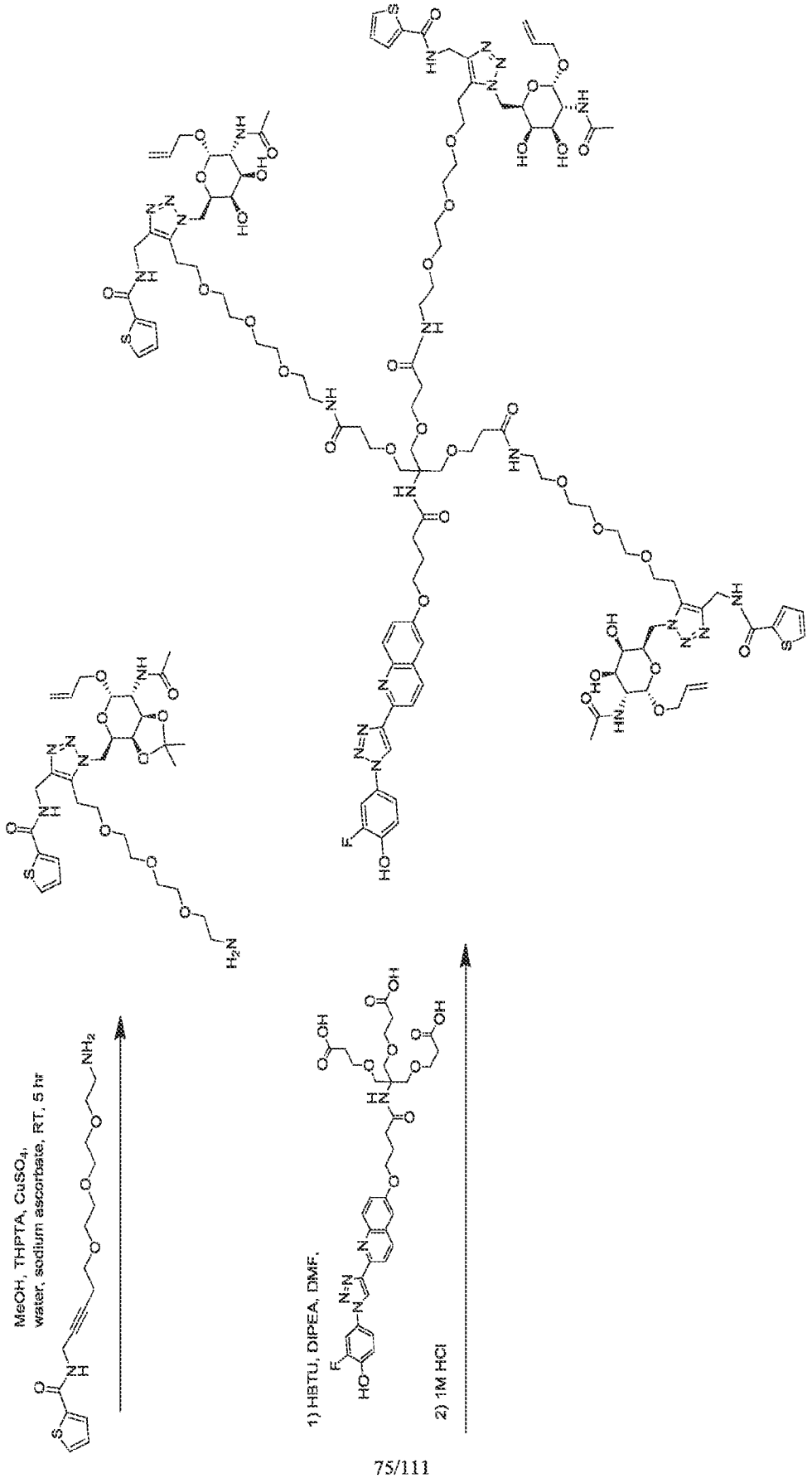


FIGURE 54

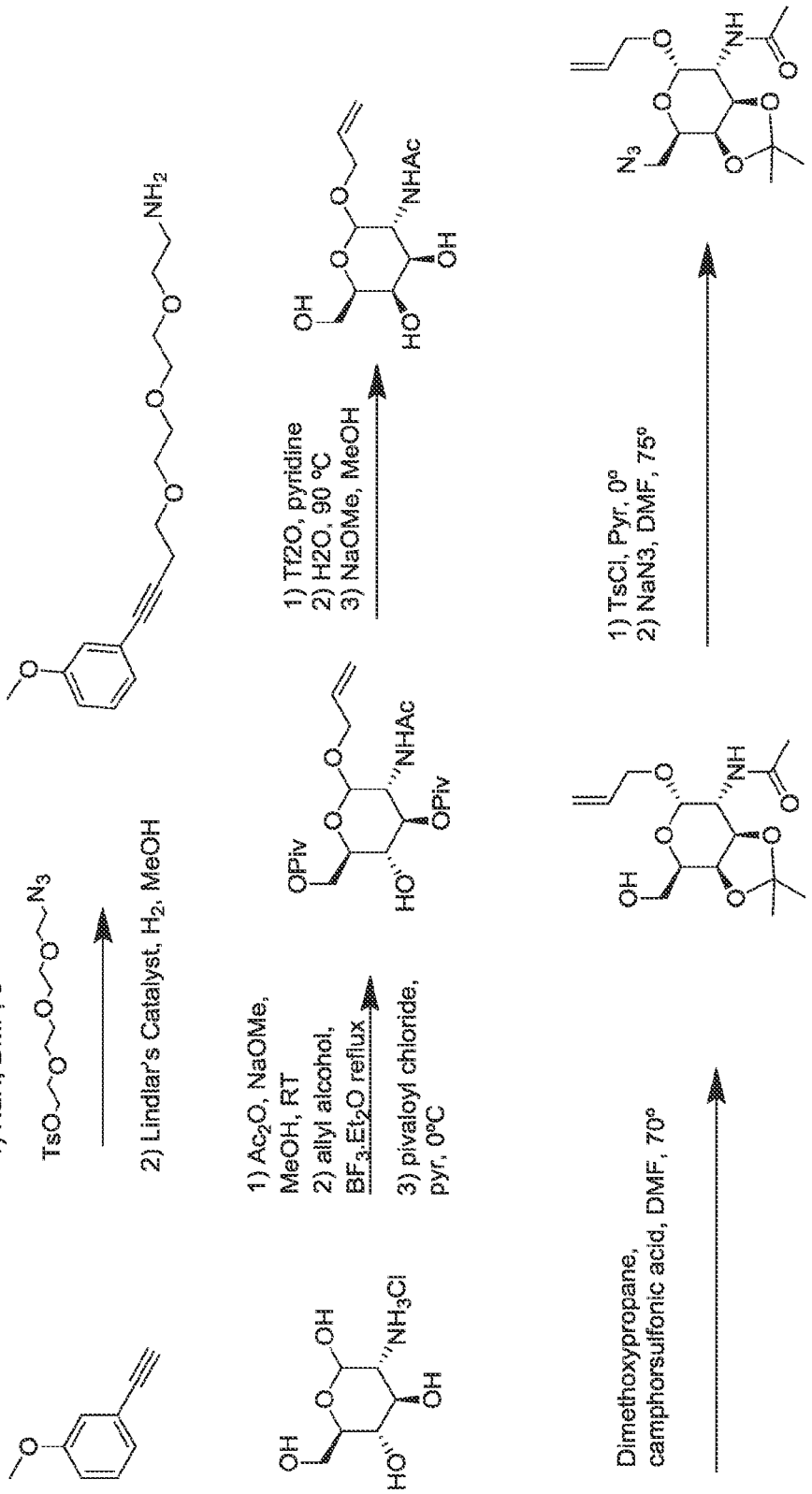

1) NaH, DMF, 0°
TsO
N3
2) Lindlar's Catalyst, H2, MeOH
NH2
1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
NH3Cl
OPiv
NHAc
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
OH
1) TsCl, Pyr, 0°
2) NaN3, DMF, 75°
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
NH
N3

FIGURE 54 (Cont'd)

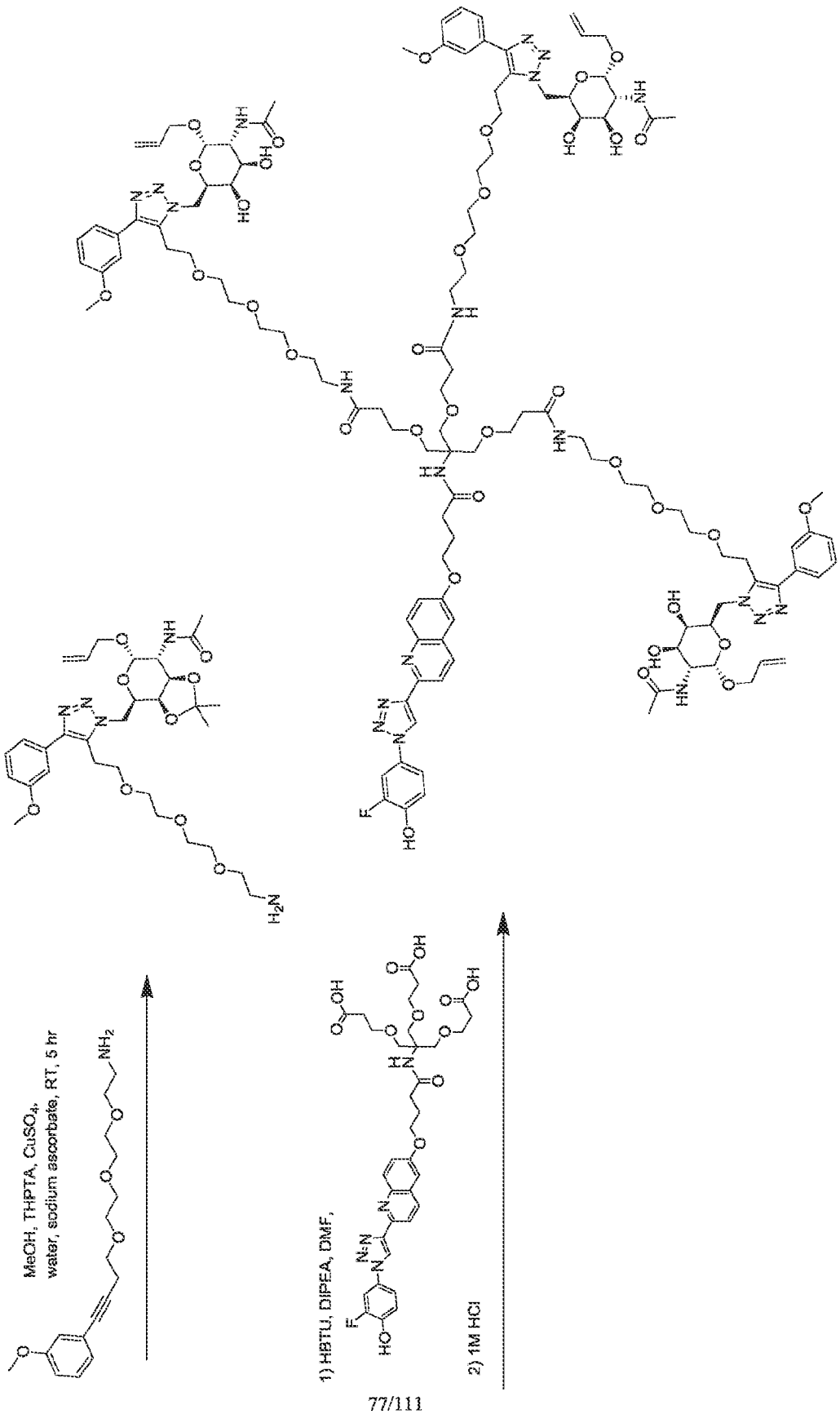


FIGURE 55

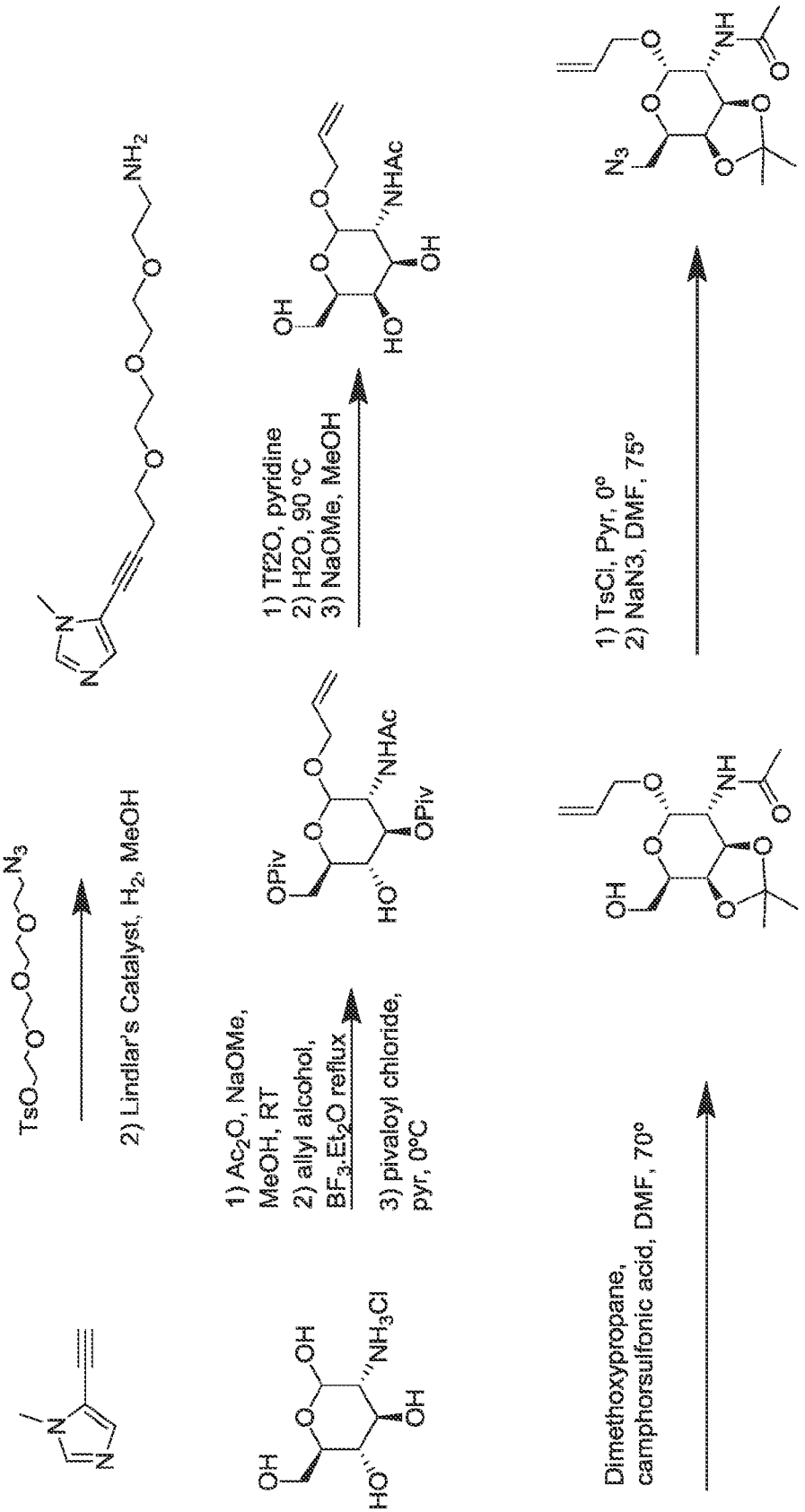

1) NaH, DMF, 0°
TsO
N3
2) Lindlar's Catalyst, H2, MeOH
NH2
1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
OPiv
NHAc
HO
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
OH
NHAc
HO
OH
NH3Cl
HO
OH
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) TsCl, Pyr, 0°
2) NaN3, DMF, 75°
N3
NH

FIGURE 55 (Cont'd)

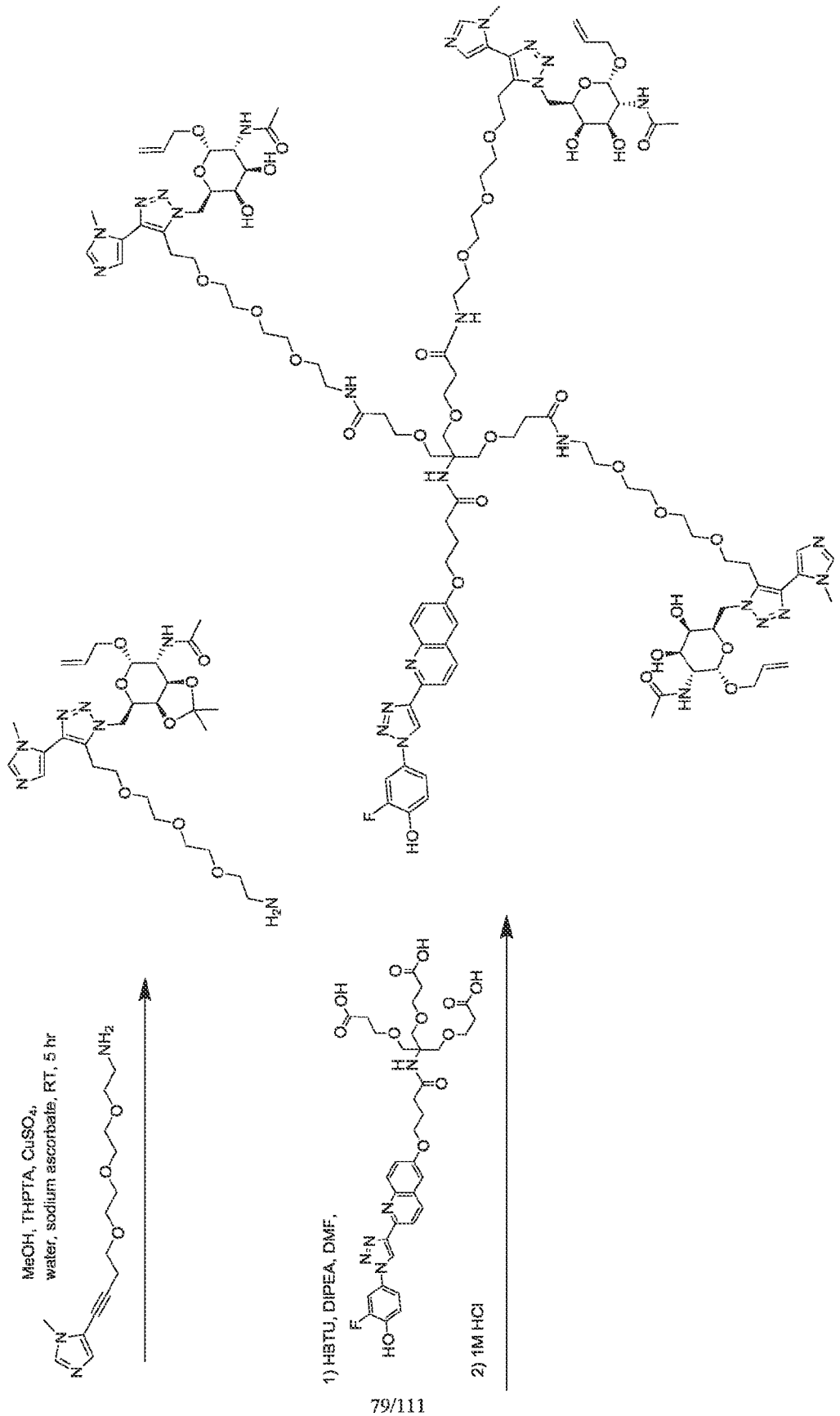


FIGURE 56

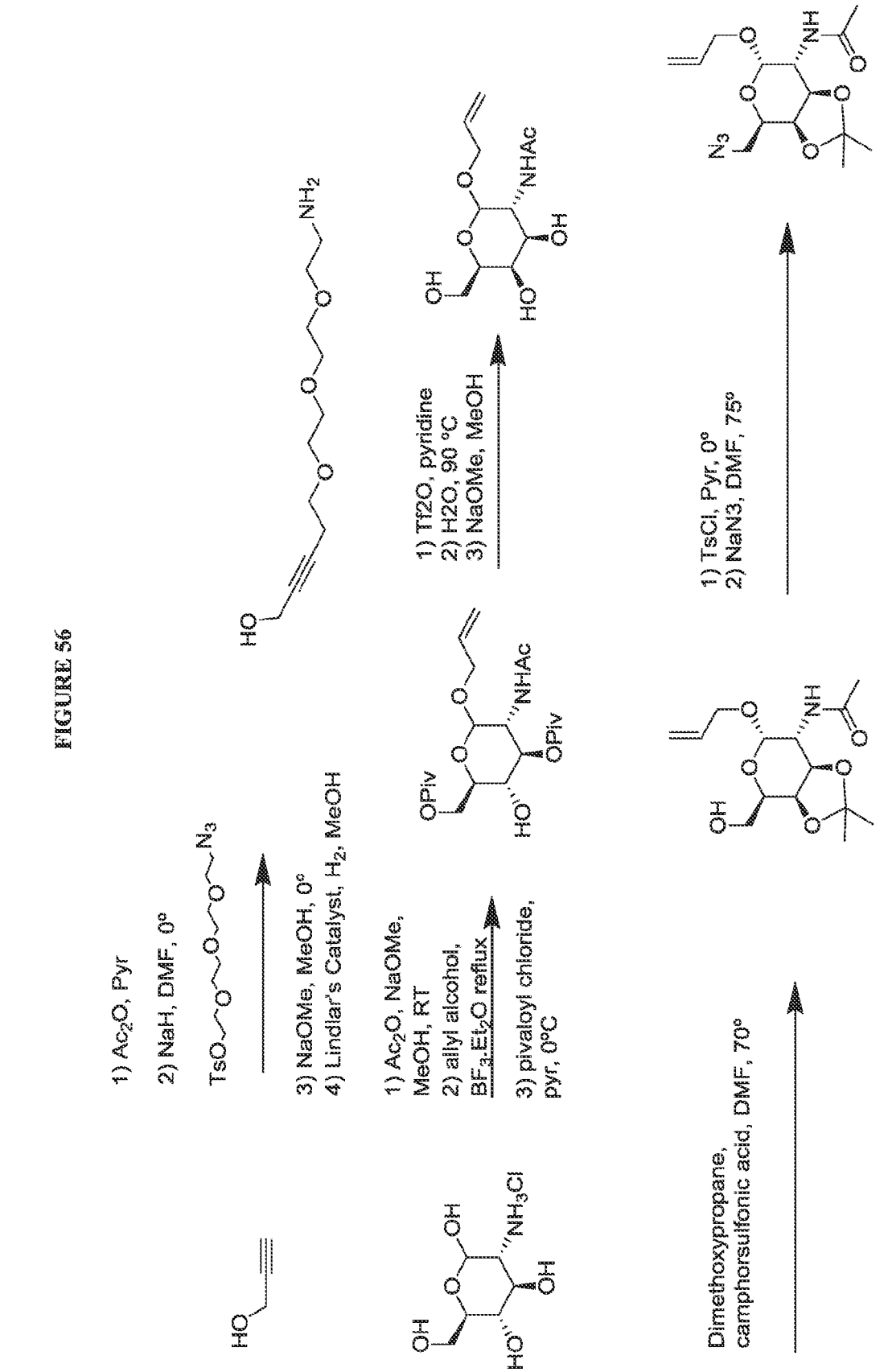

1) Ac2O, Pyr
2) NaH, DMF, 0°
TsO
N3
3) NaOMe, MeOH, 0°
4) Lindlar's Catalyst, H2, MeOH
HO
NH2
1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
OPiv
NHAc
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
OH
1) TsCl, Pyr, 0°
2) NaN3, DMF, 75°
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
NH3Cl

FIGURE 56 (Cont'd)

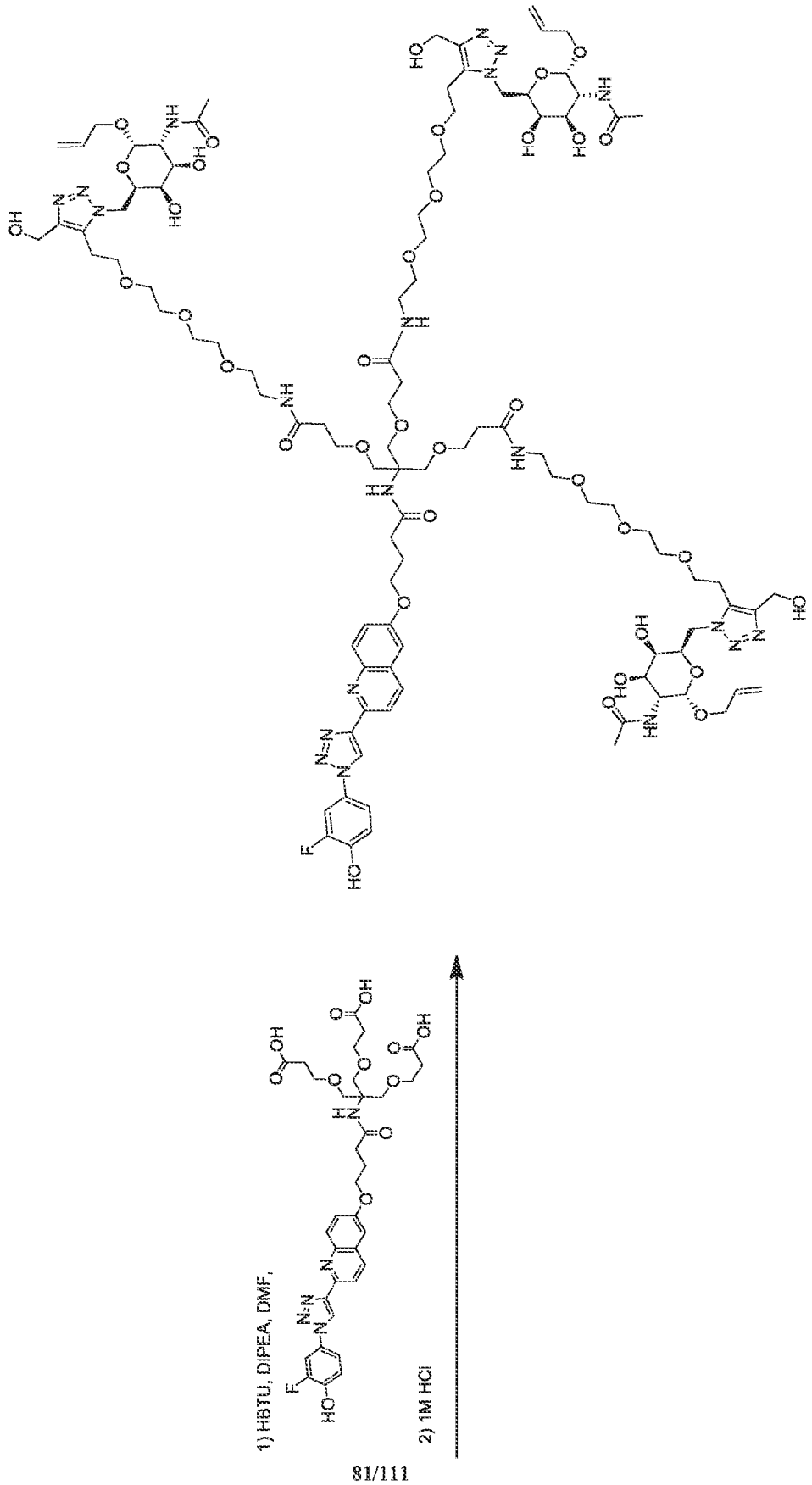


FIGURE 57

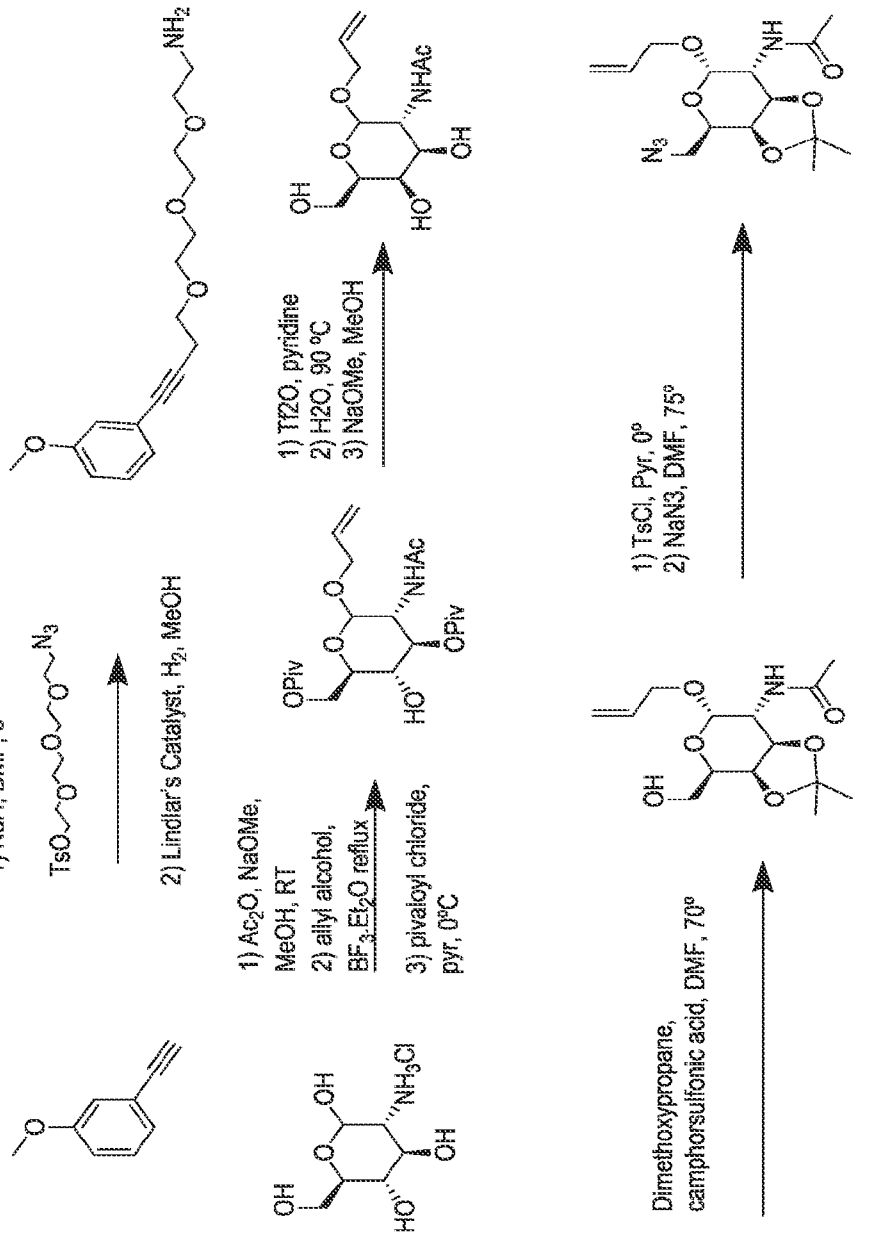

1) NaH, DMF, 0°
2) Lindlar's Catalyst, H2, MeOH
1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
1) TsCl, Pyr, 0°
2) NaN3, DMF, 75°
1) mCPBA, DCM, 0°
2) BnNH2, LiClO4, MeCN, 70°
Dimethoxypropane, camphorsulfonic acid, DMF, 70°

FIGURE 57 (Cont'd)

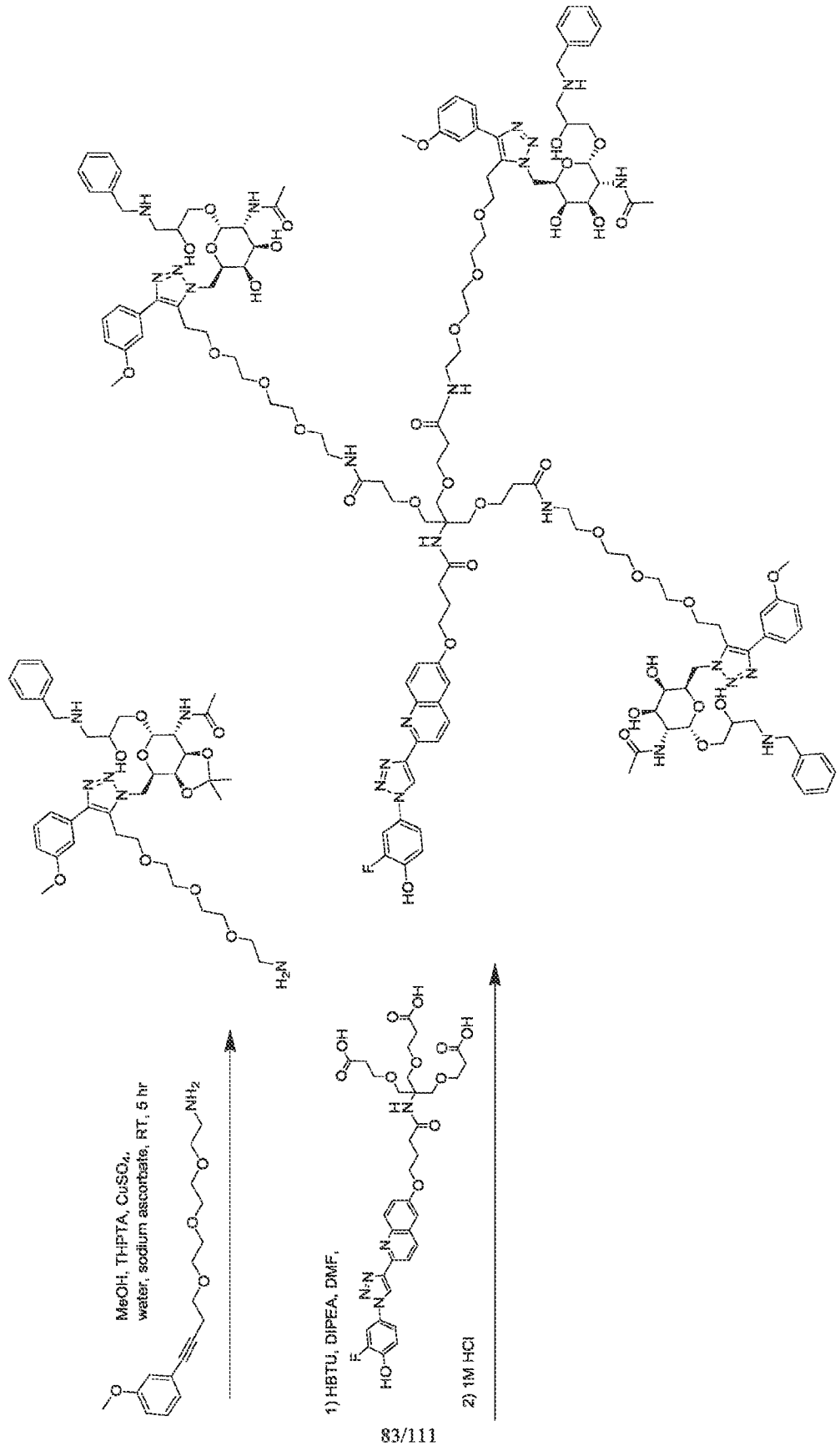


FIGURE 58

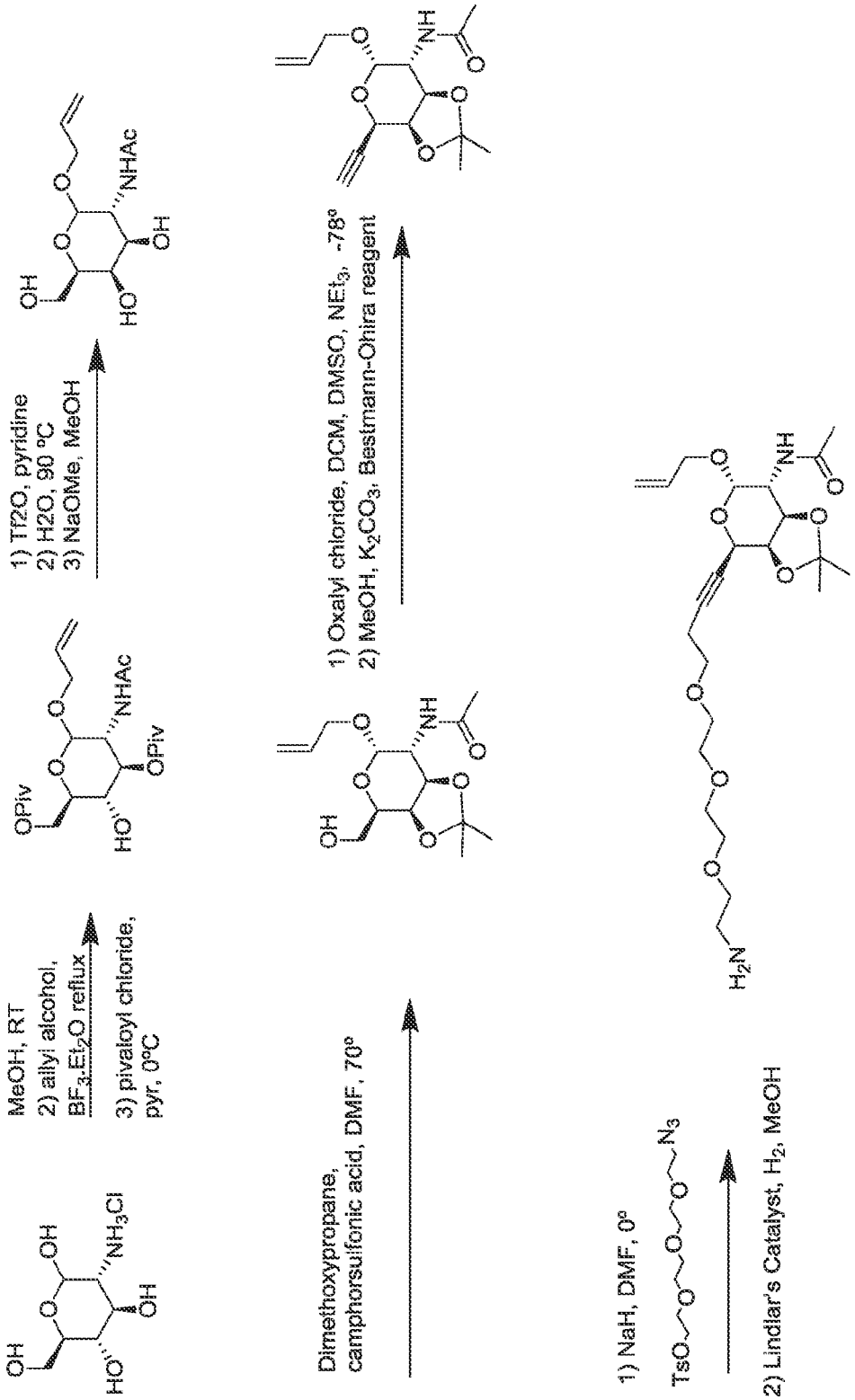

1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
1) Oxalyl chloride, DCM, DMSO, NEt3, -78°
2) MeOH, K2CO3, Bestmann-Ohira reagent
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) NaH, DMF, 0°
2) Lindlar's Catalyst, H2, MeOH

FIGURE 58 (Cont'd)

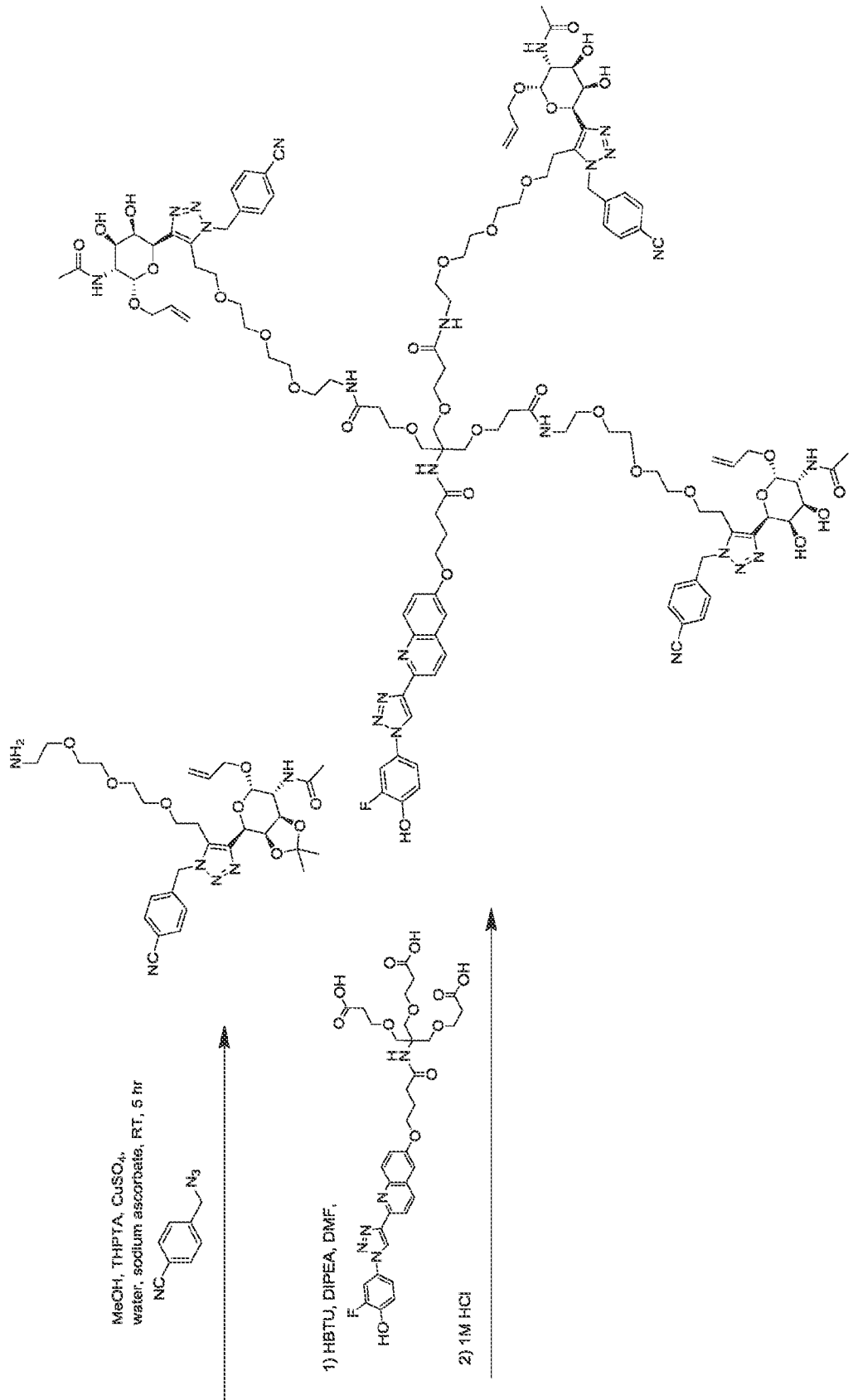


FIGURE 59

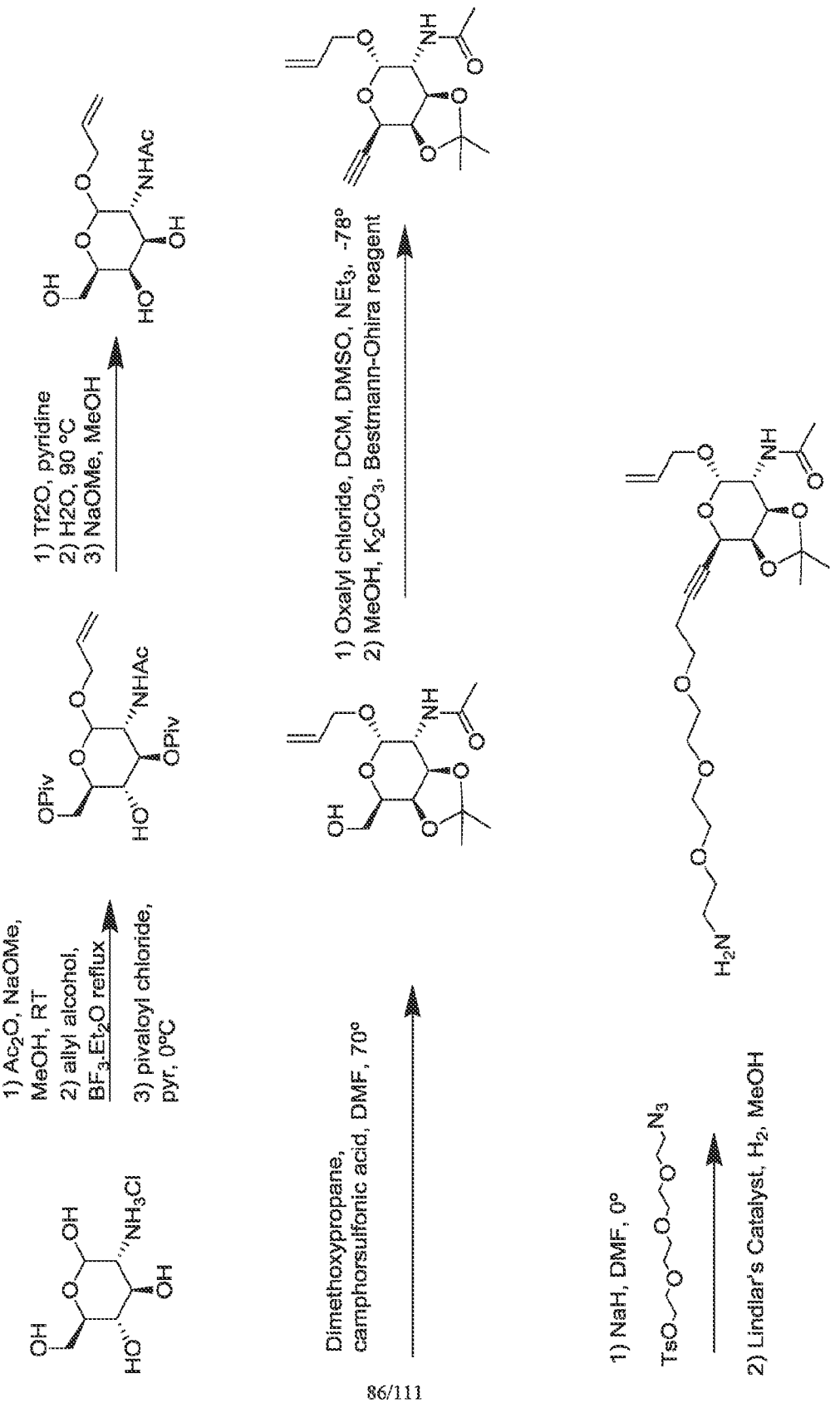

1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
1) Oxalyl chloride, DCM, DMSO, NEt3, -78°
2) MeOH, K2CO3, Bestmann-Ohira reagent
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) NaH, DMF, 0°
2) Lindlar's Catalyst, H2, MeOH

FIGURE 59 (Cont'd)

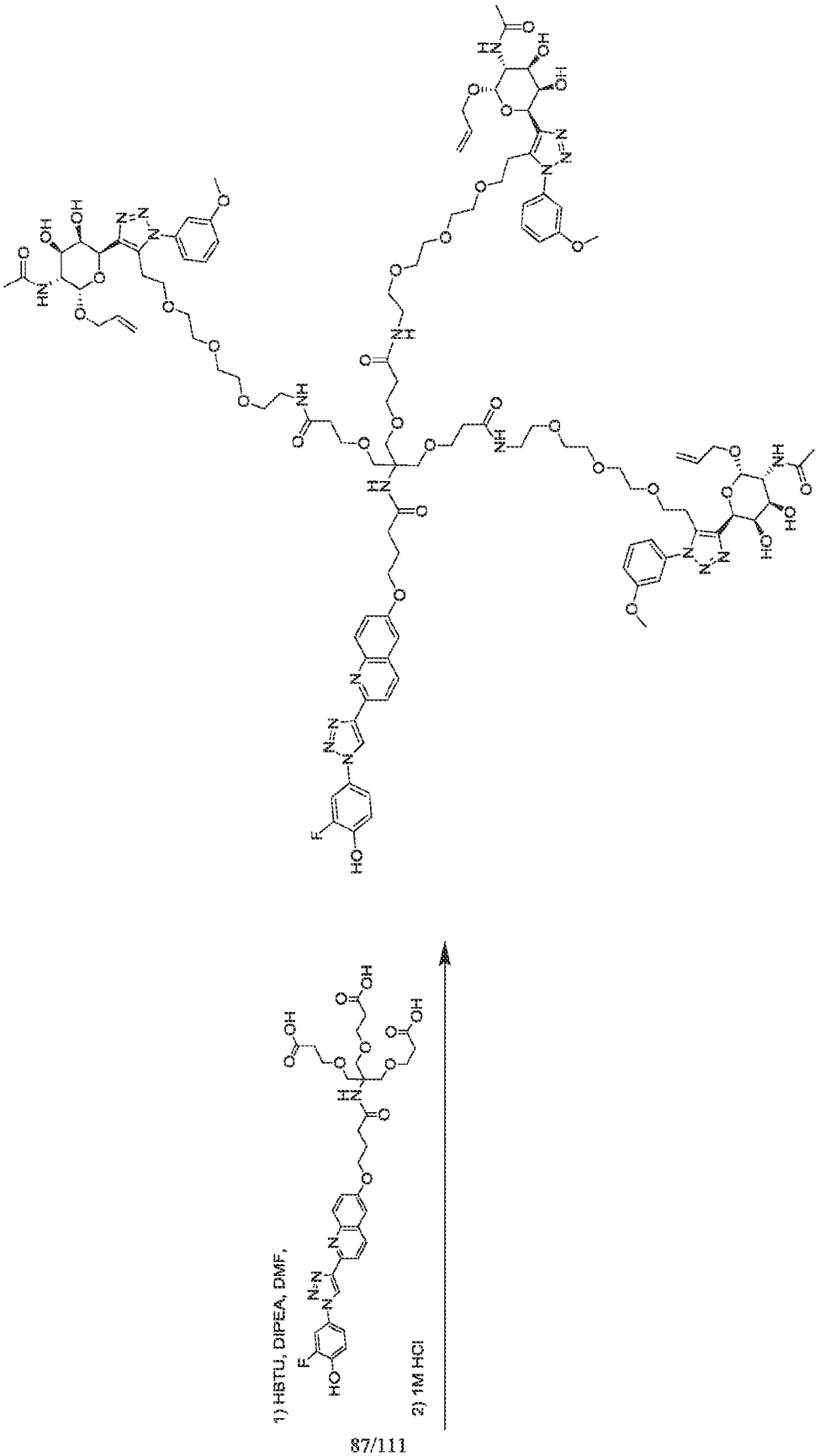


FIGURE 60

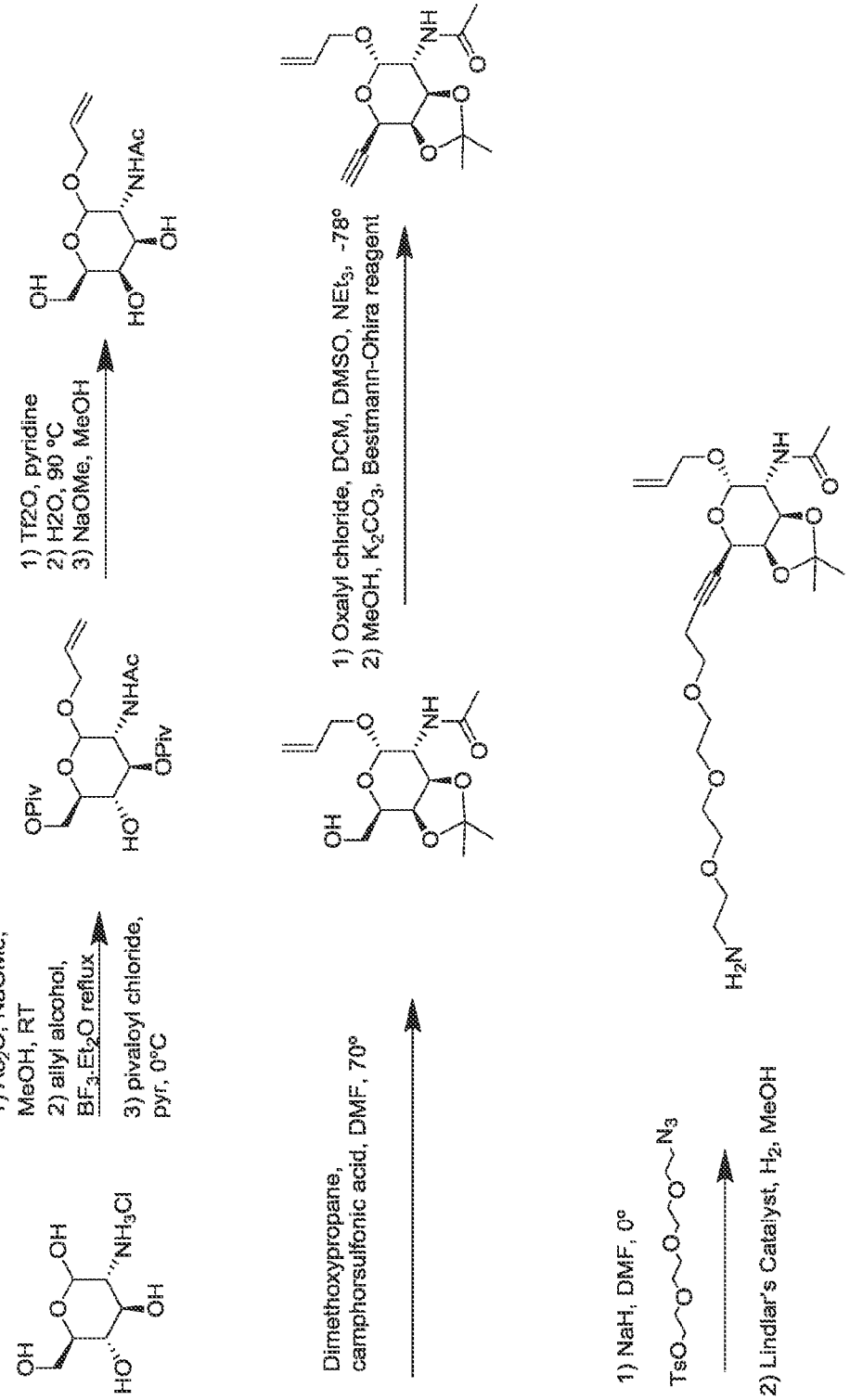

1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) Oxalyl chloride, DCM, DMSO, NEt3, -78°
2) MeOH, K2CO3, Bestmann-Ohira reagent
1) NaH, DMF, 0°
2) Lindlar's Catalyst, H2, MeOH

FIGURE 60 (Cont'd)

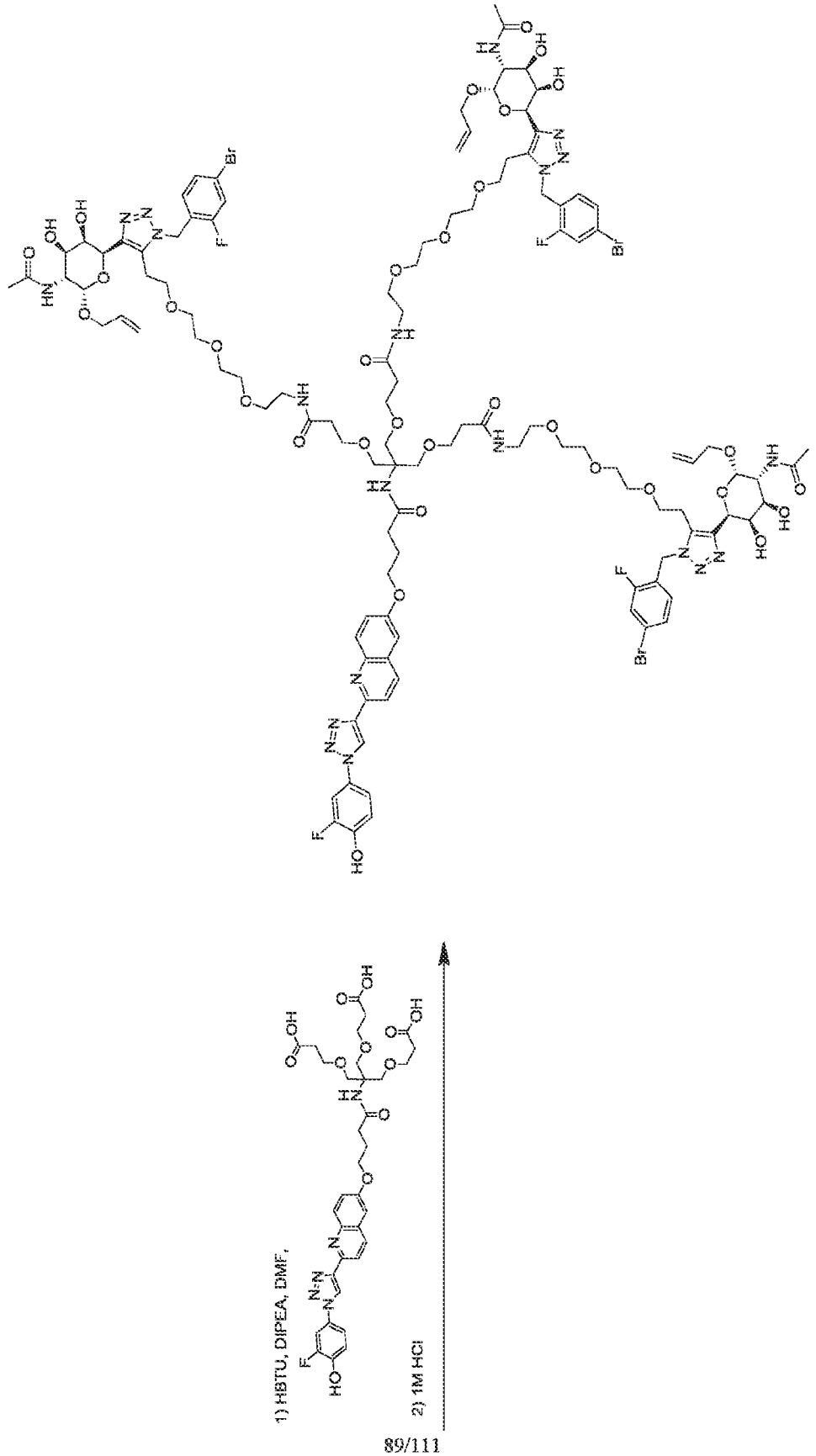


FIGURE 61

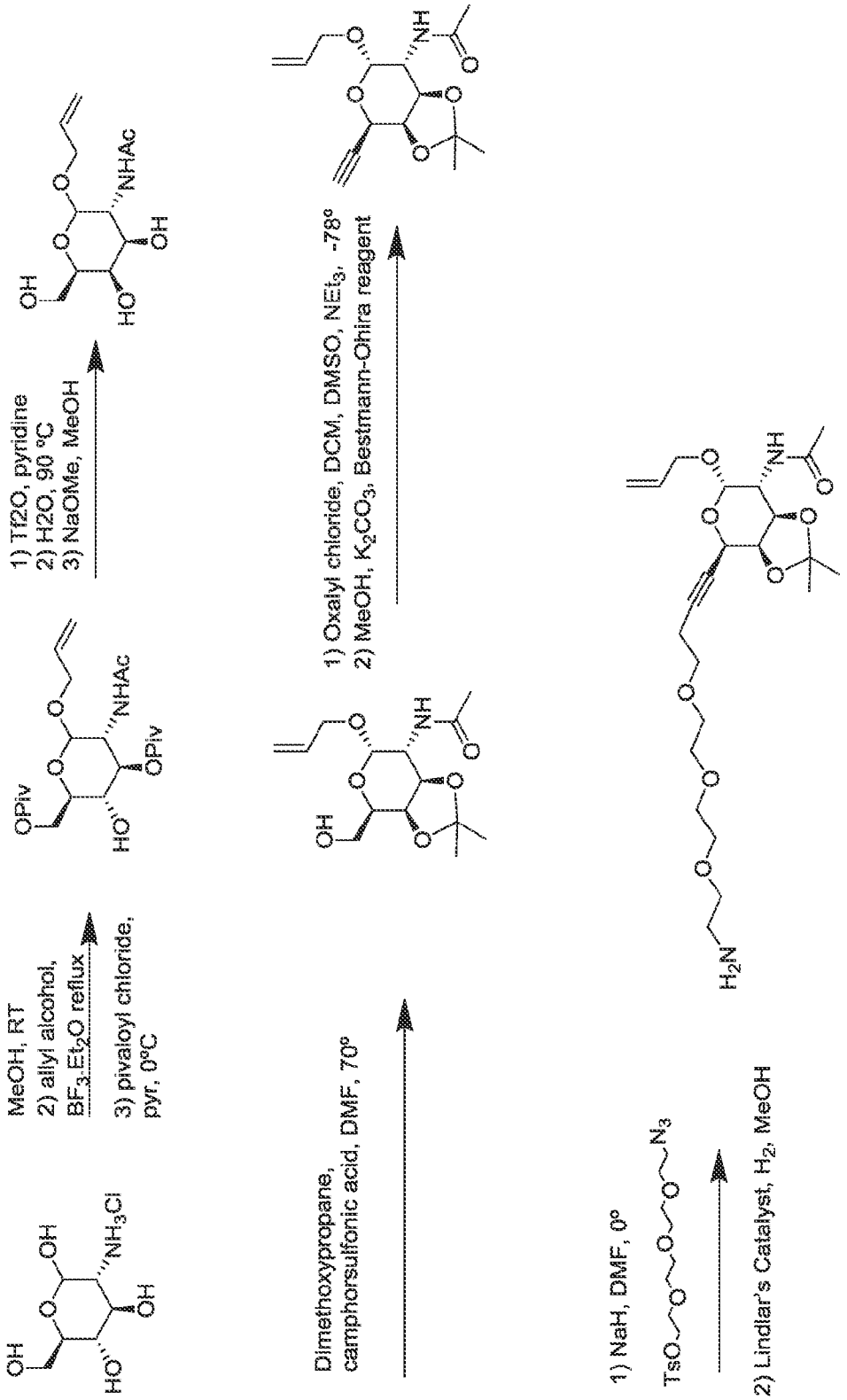

1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
1) Oxalyl chloride, DCM, DMSO, NEt3, -78°
2) MeOH, K2CO3, Bestmann-Ohira reagent
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) NaH, DMF, 0°
2) Lindlar's Catalyst, H2, MeOH

FIGURE 61 (Cont'd)

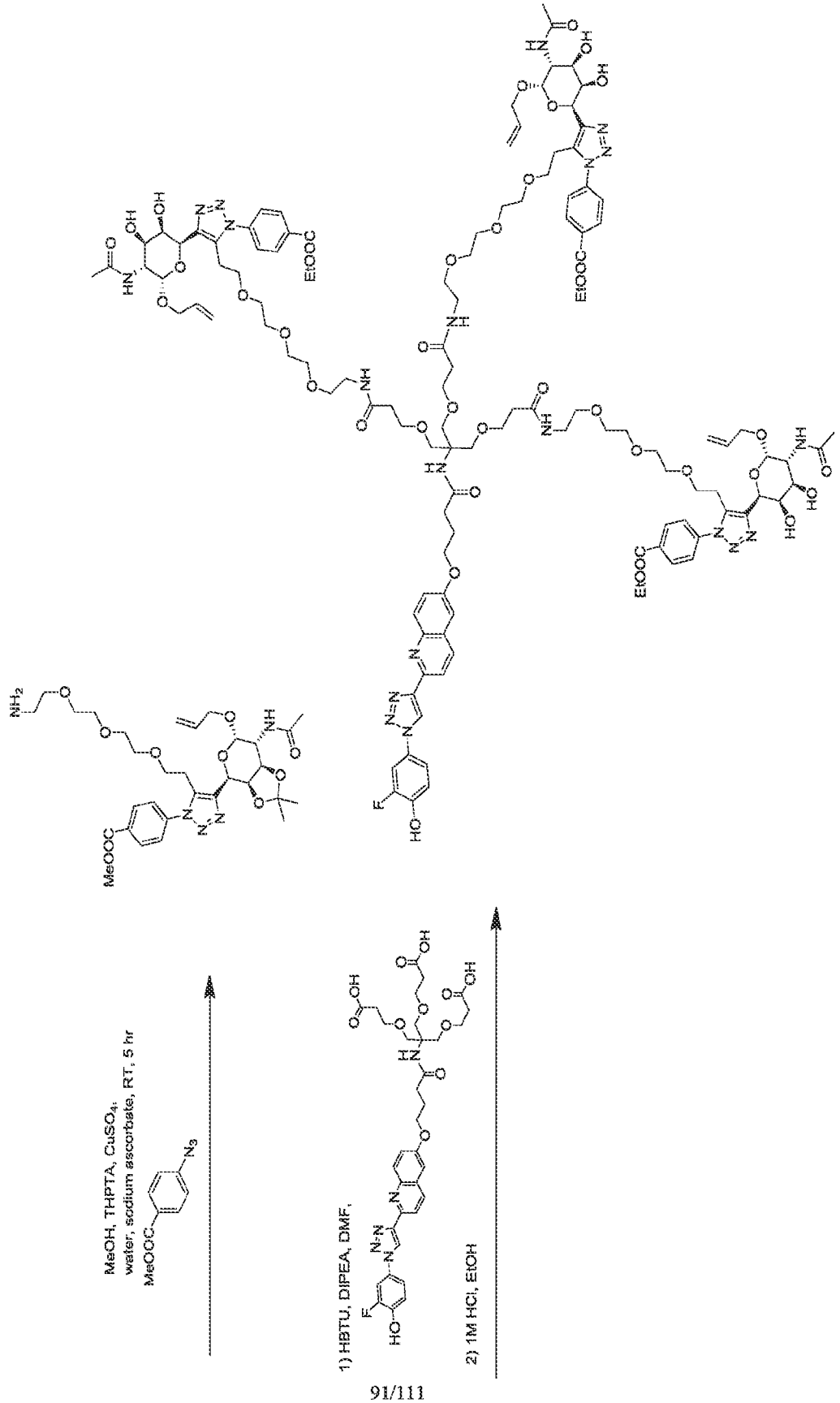


FIGURE 62

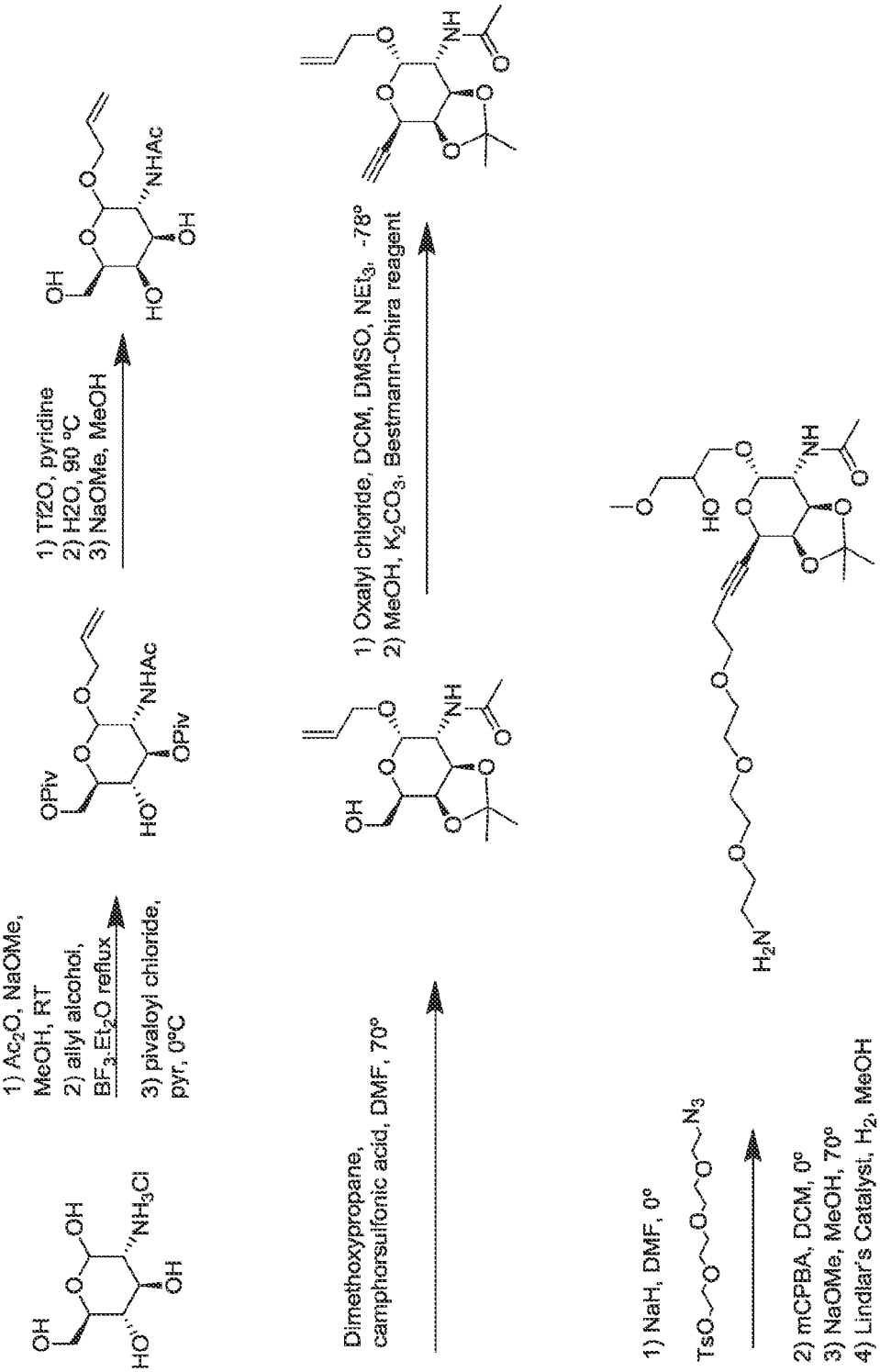
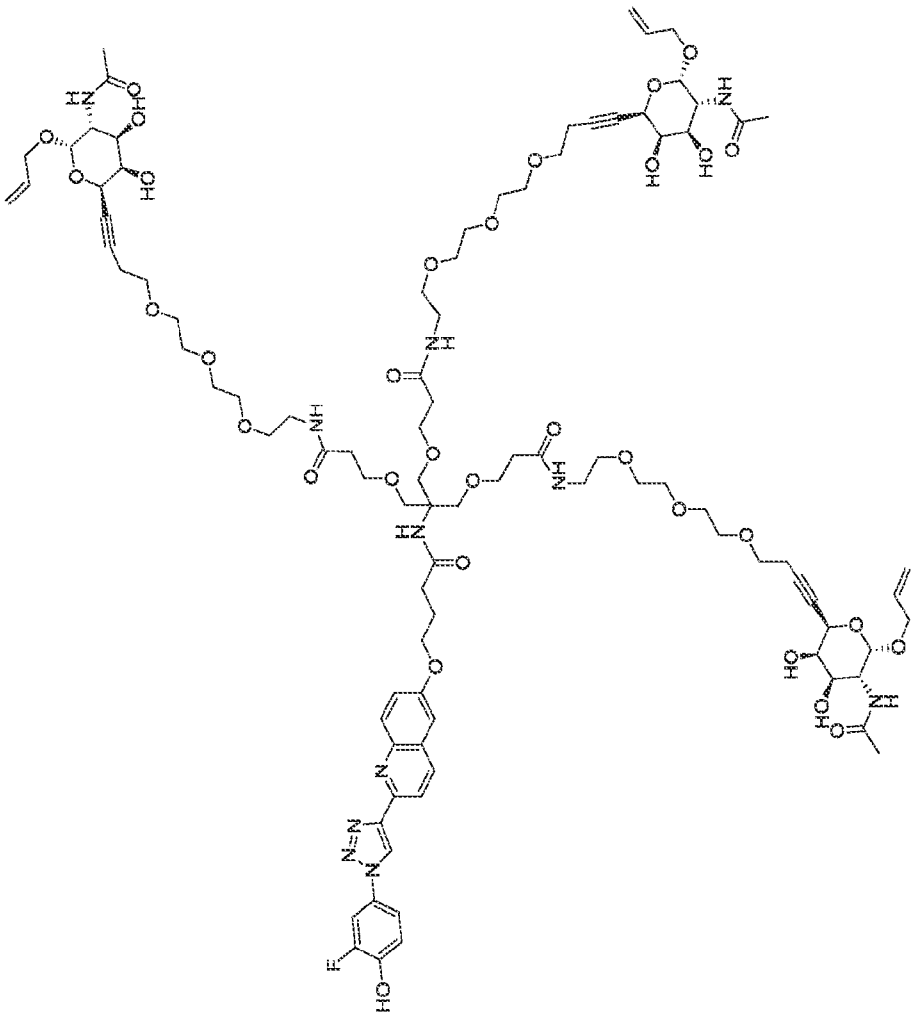

1) Ac_2O, NaOMe, MeOH, RT
2) allyl alcohol, BF_3-Et_2O reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) Oxalyl chloride, DCM, DMSO, NEt_3, -78°
2) MeOH, K_2CO_3, Bestmann-Ohira reagent
1) NaH, DMF, 0°
2) mCPBA, DCM, 0°
3) NaOMe, MeOH, 70°
4) Lindlar's Catalyst, H_2, MeOH

FIGURE 62 (Cont'd)



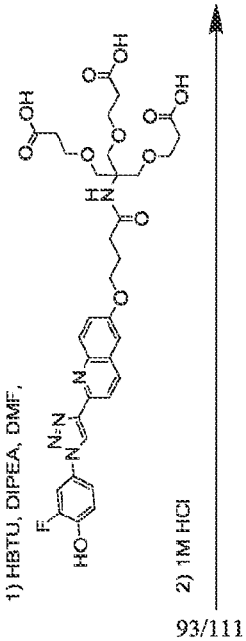


FIGURE 63

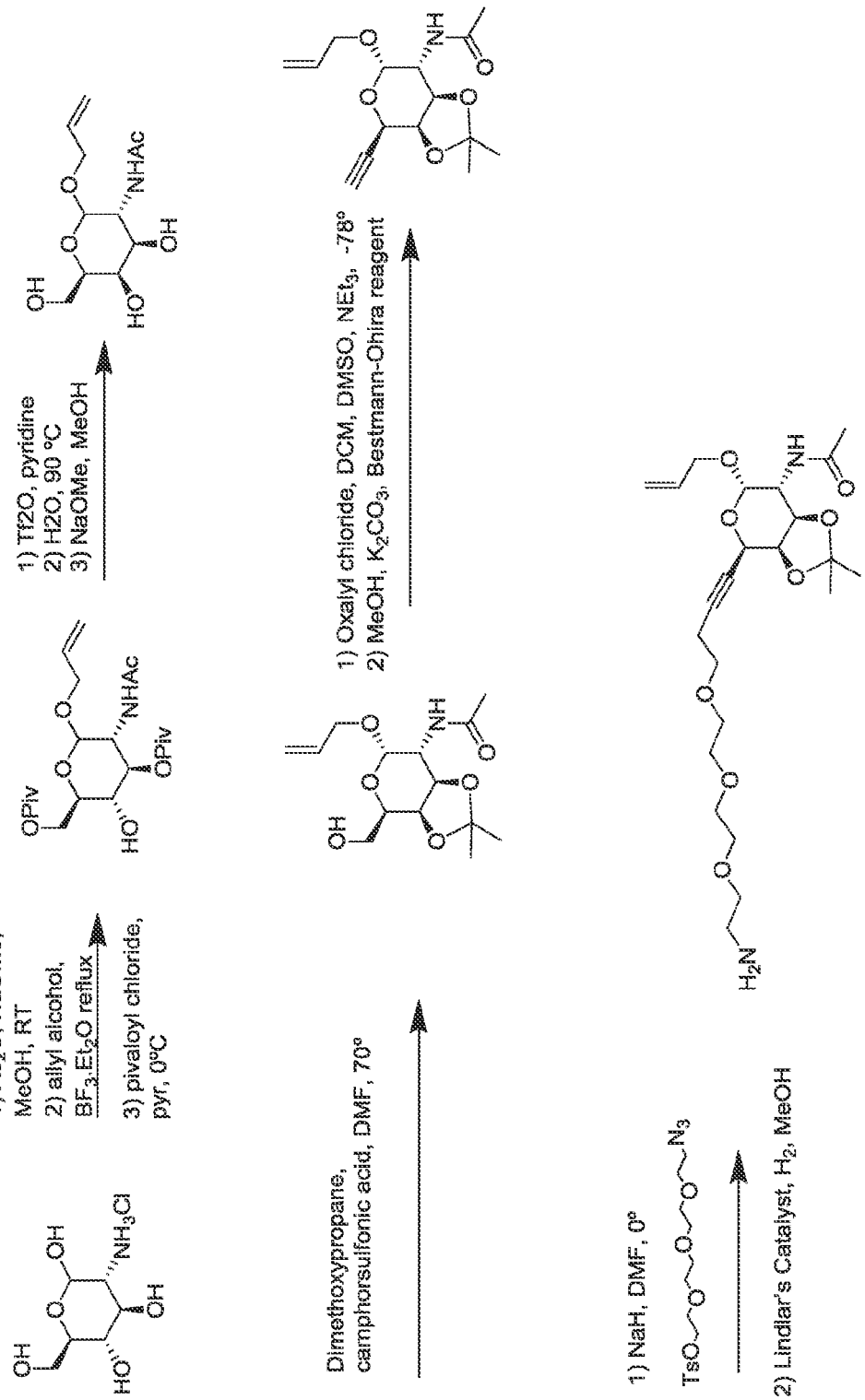
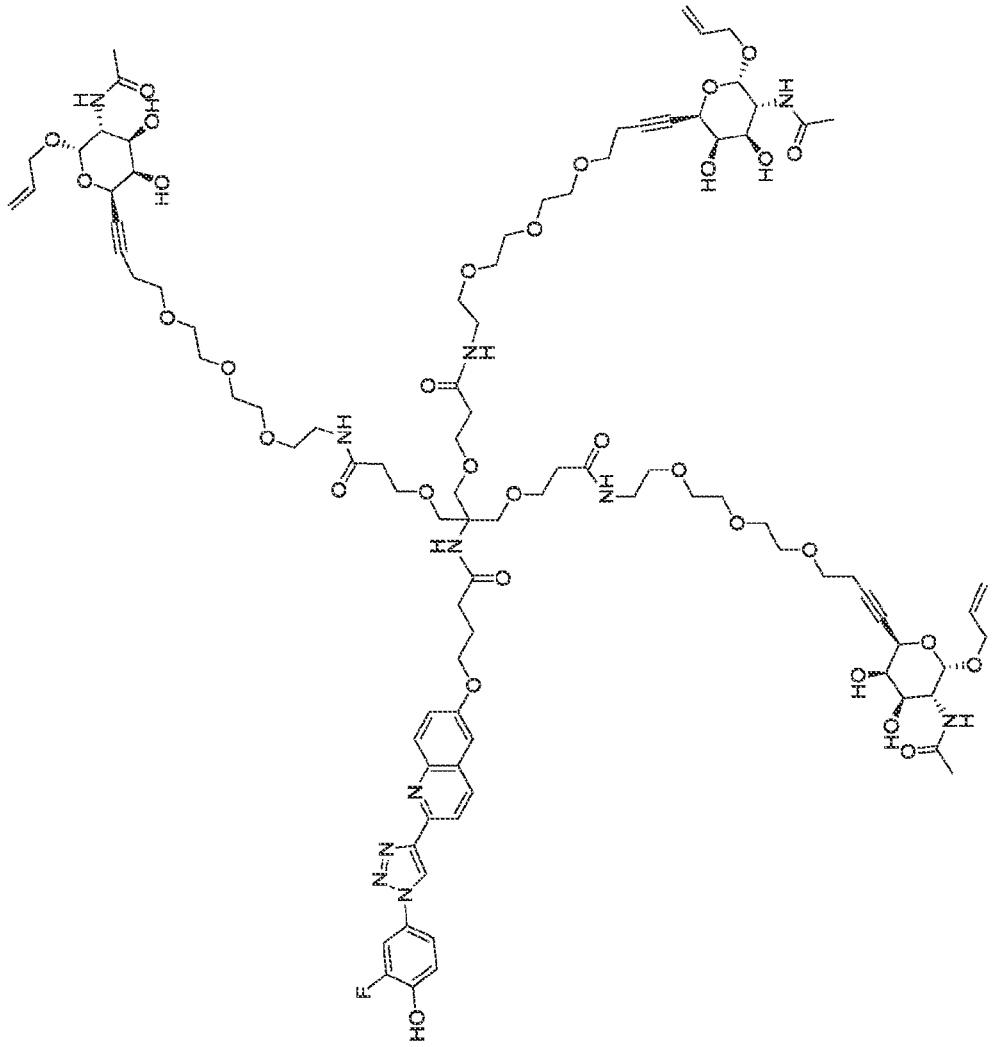

1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
1) Oxalyl chloride, DCM, DMSO, NEt3, -78°
2) MeOH, K2CO3, Bestmann-Ohira reagent
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) NaH, DMF, 0°
2) Lindlar's Catalyst, H2, MeOH

FIGURE 63 (Cont'd)



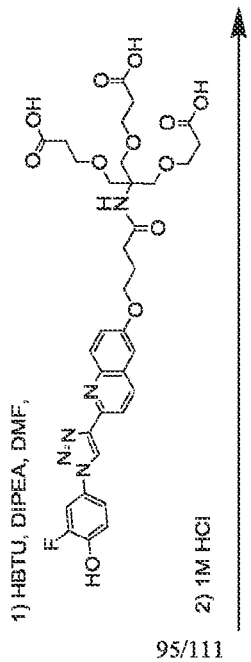


FIGURE 64

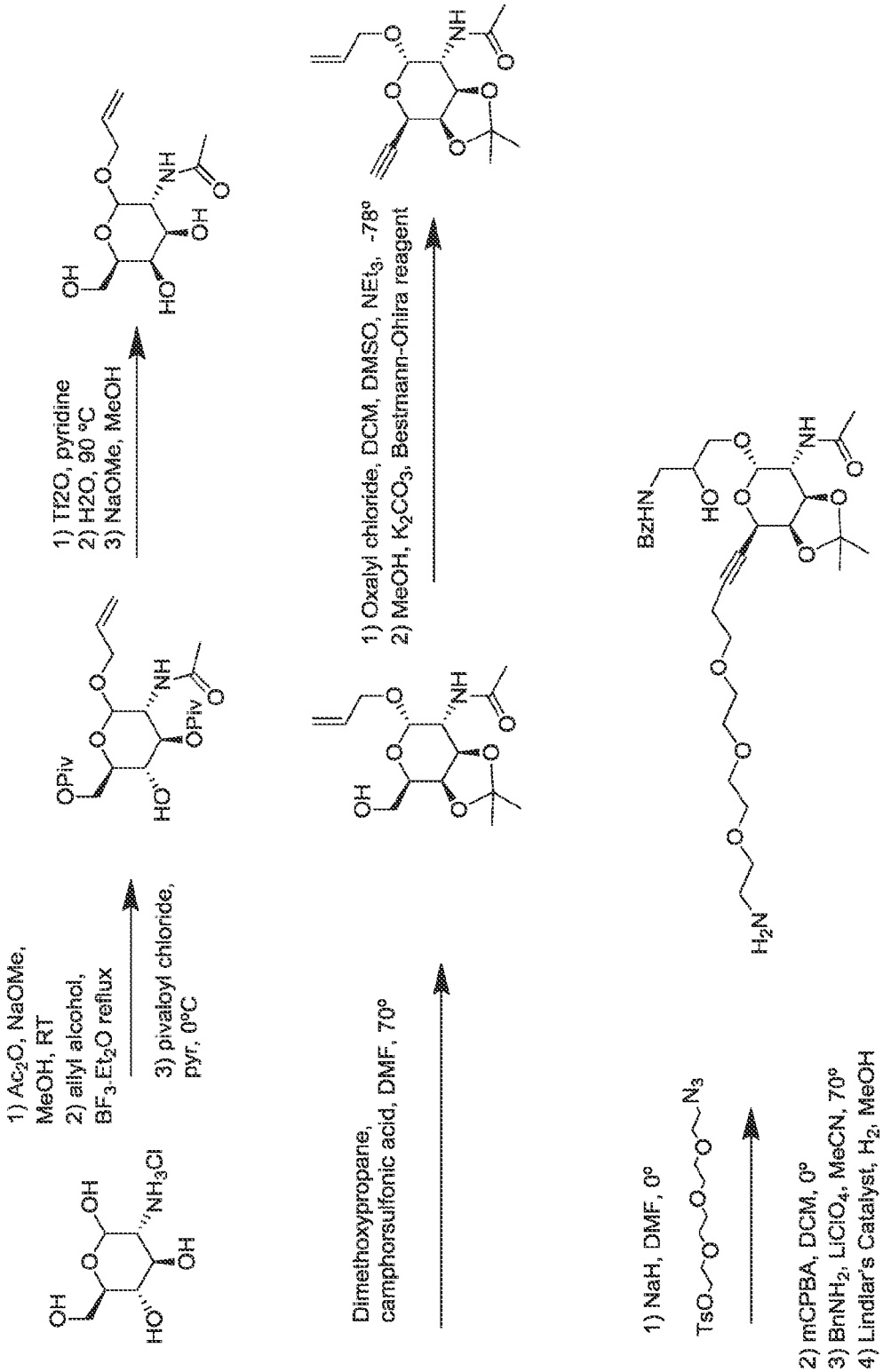

1) Ac2O, NaOMe, MeOH, RT
2) allyl alcohol, BF3.Et2O reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
1) Oxalyl chloride, DCM, DMSO, NEt3, -78°
2) MeOH, K2CO3, Bestmann-Ohira reagent
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) NaH, DMF, 0°
2) mCPBA, DCM, 0°
3) BnNH2, LiClO4, MeCN, 70°
4) Lindlar's Catalyst, H2, MeOH

FIGURE 64 (Cont'd)

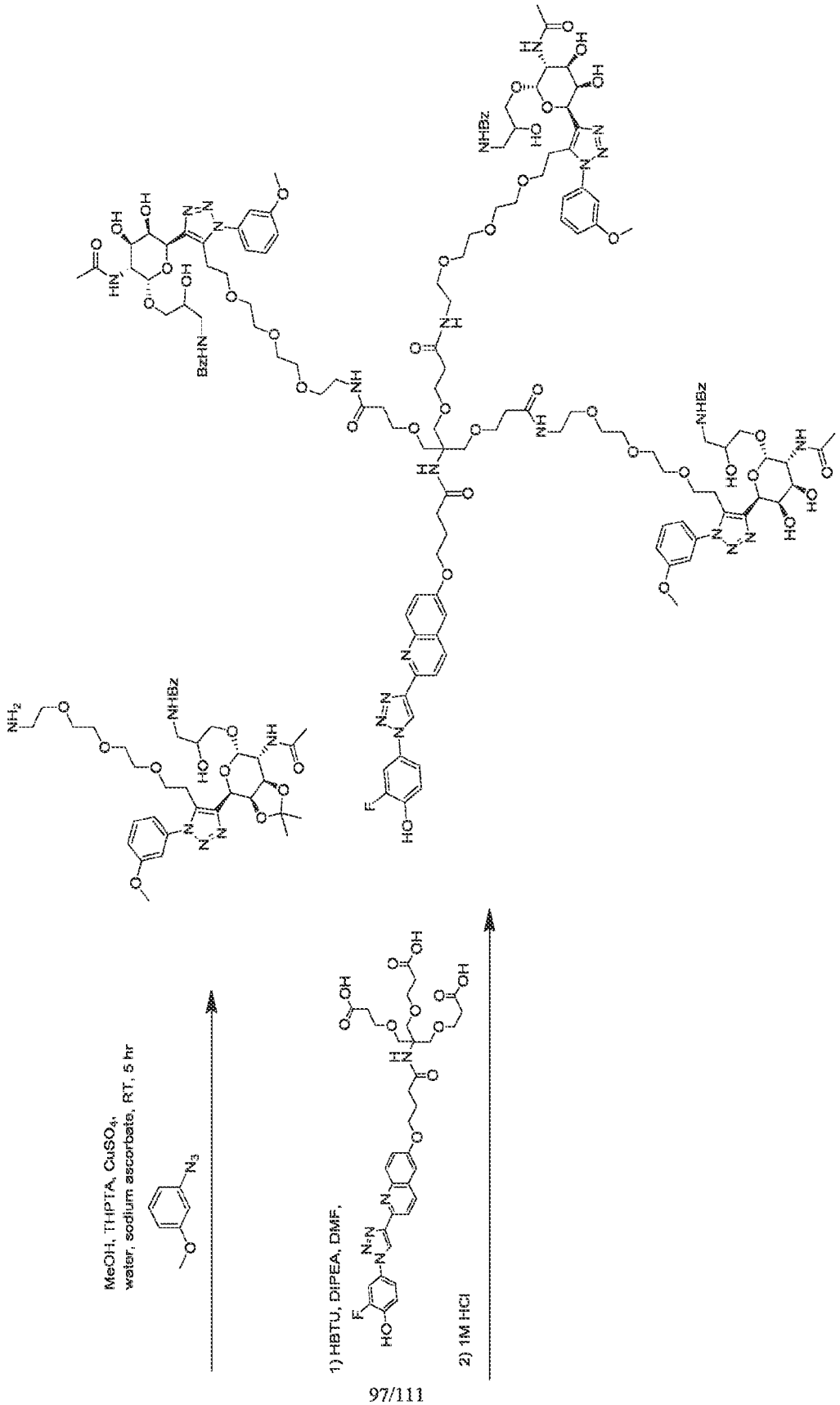


FIGURE 65

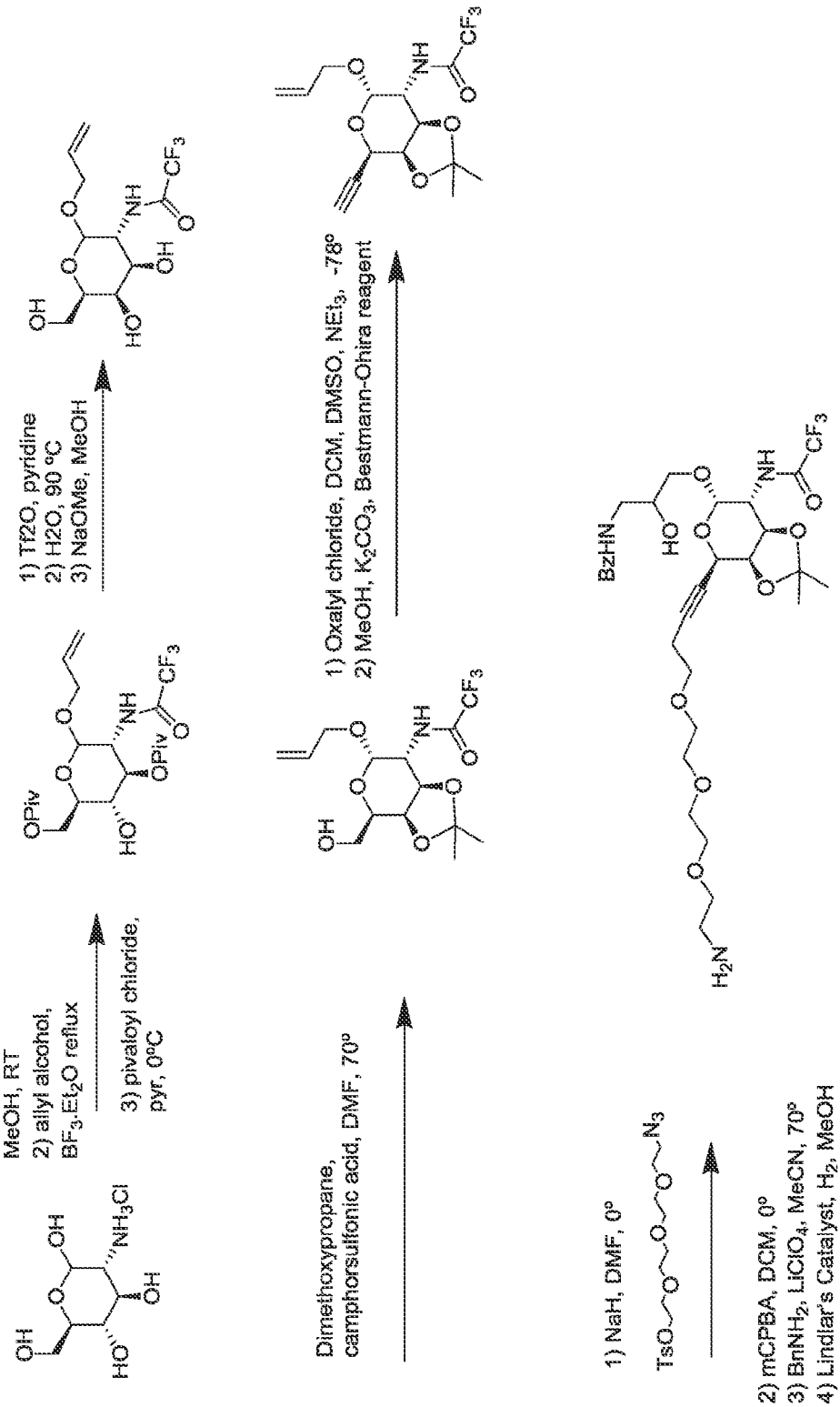

1) Trifluoroacetic anhydride, NaOMe, MeOH, RT
2) allyl alcohol, $BF_3.Et_2O$ reflux
3) pivaloyl chloride, pyr, 0°C
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) Oxalyl chloride, DCM, DMSO, NEt_3, -78°
2) MeOH, K_2CO_3, Bestmann-Ohira reagent
1) NaH, DMF, 0°
2) mCPBA, DCM, 0°
3) $BnNH_2$, $LiClO_4$, MeCN, 70°
4) Lindlar's Catalyst, H_2, MeOH

FIGURE 65 (Cont'd)

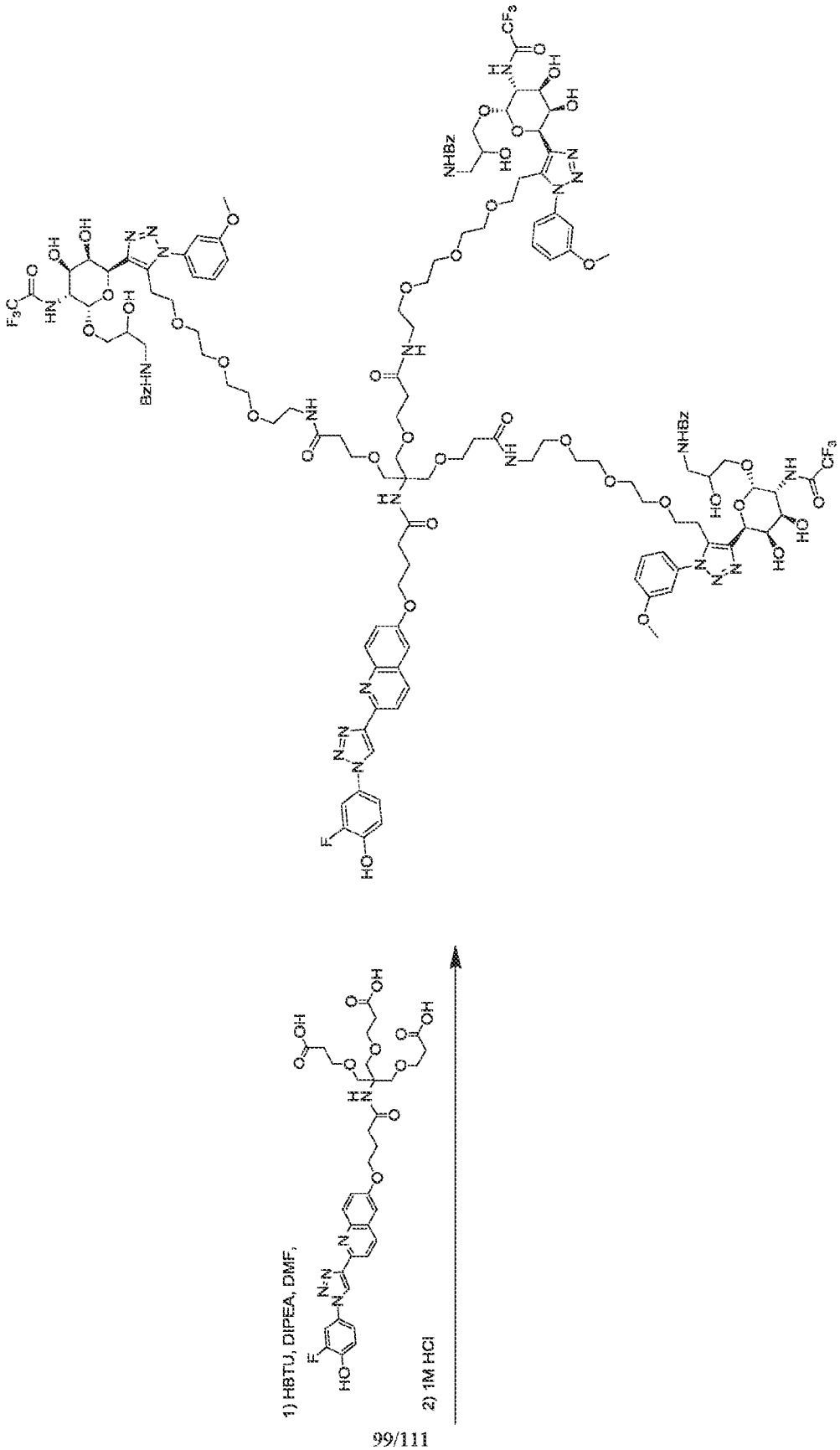


FIGURE 66

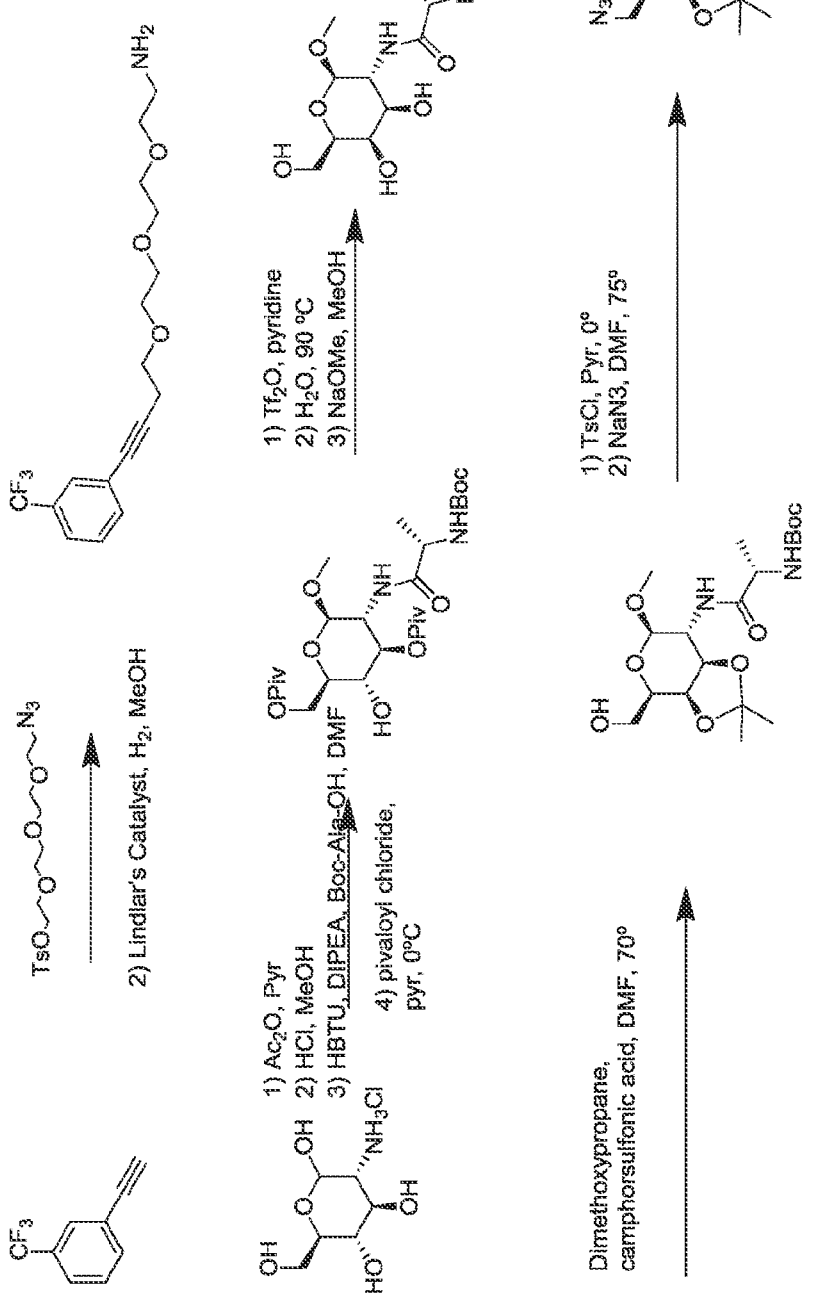

1) NaH, DMF, 0°
TsO
N3
2) Lindlar's Catalyst, H2, MeOH
CF3
NH2
1) Ac2O, Pyr
2) HCl, MeOH
3) HBTU, DIPEA, Boc-Ala-OH, DMF
4) pivaloyl chloride, pyr, 0°C
OH
NH3Cl
HO
OPiv
NHBoc
1) Tf2O, pyridine
2) H2O, 90 °C
3) NaOMe, MeOH
OH
HO
NH
NHBoc
Dimethoxypropane, camphorsulfonic acid, DMF, 70°
1) TsCl, Pyr, 0°
2) NaN3, DMF, 75°
N3
NH
NHBoc

FIGURE 66 (Cont'd)

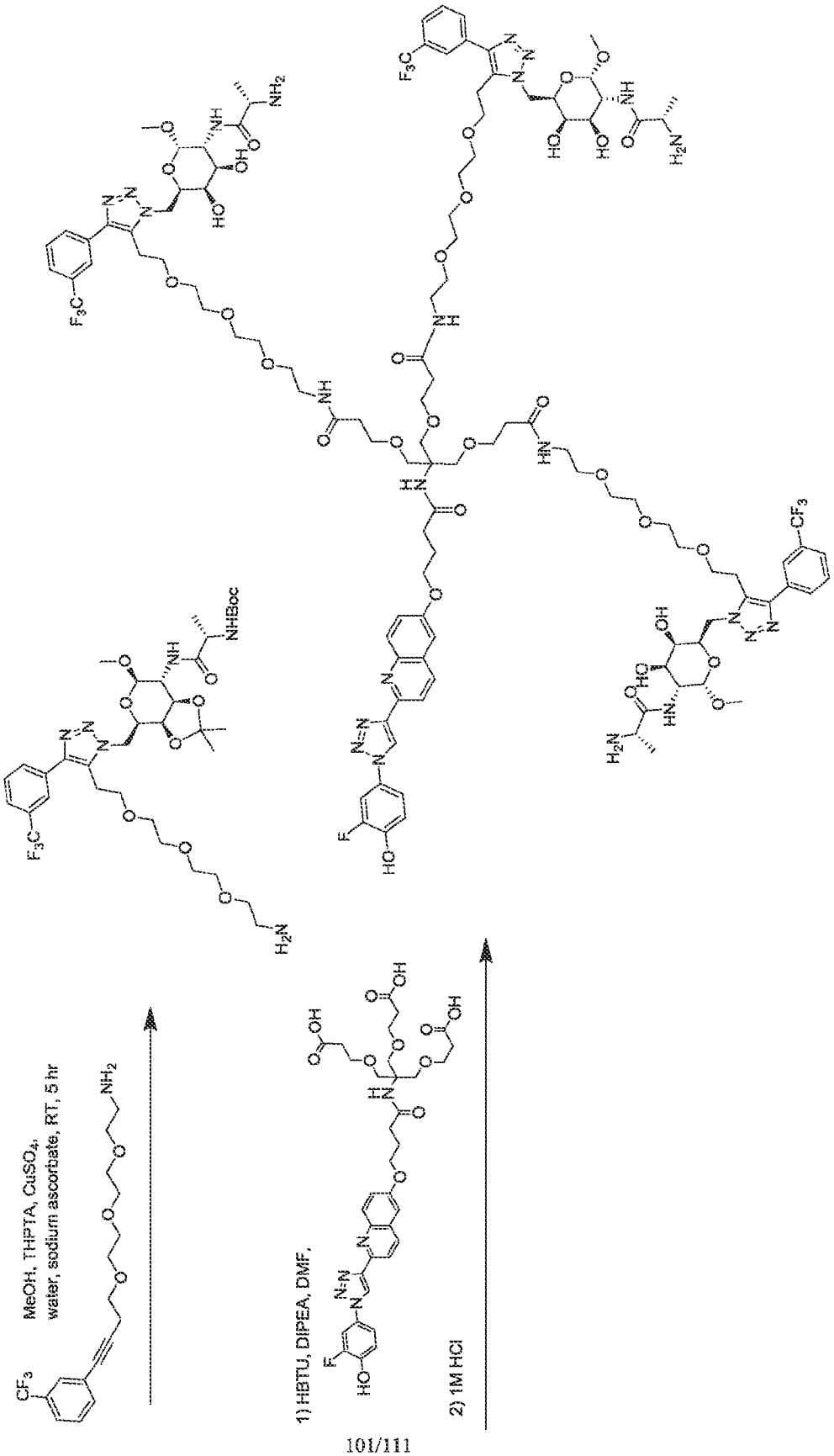


FIGURE 67

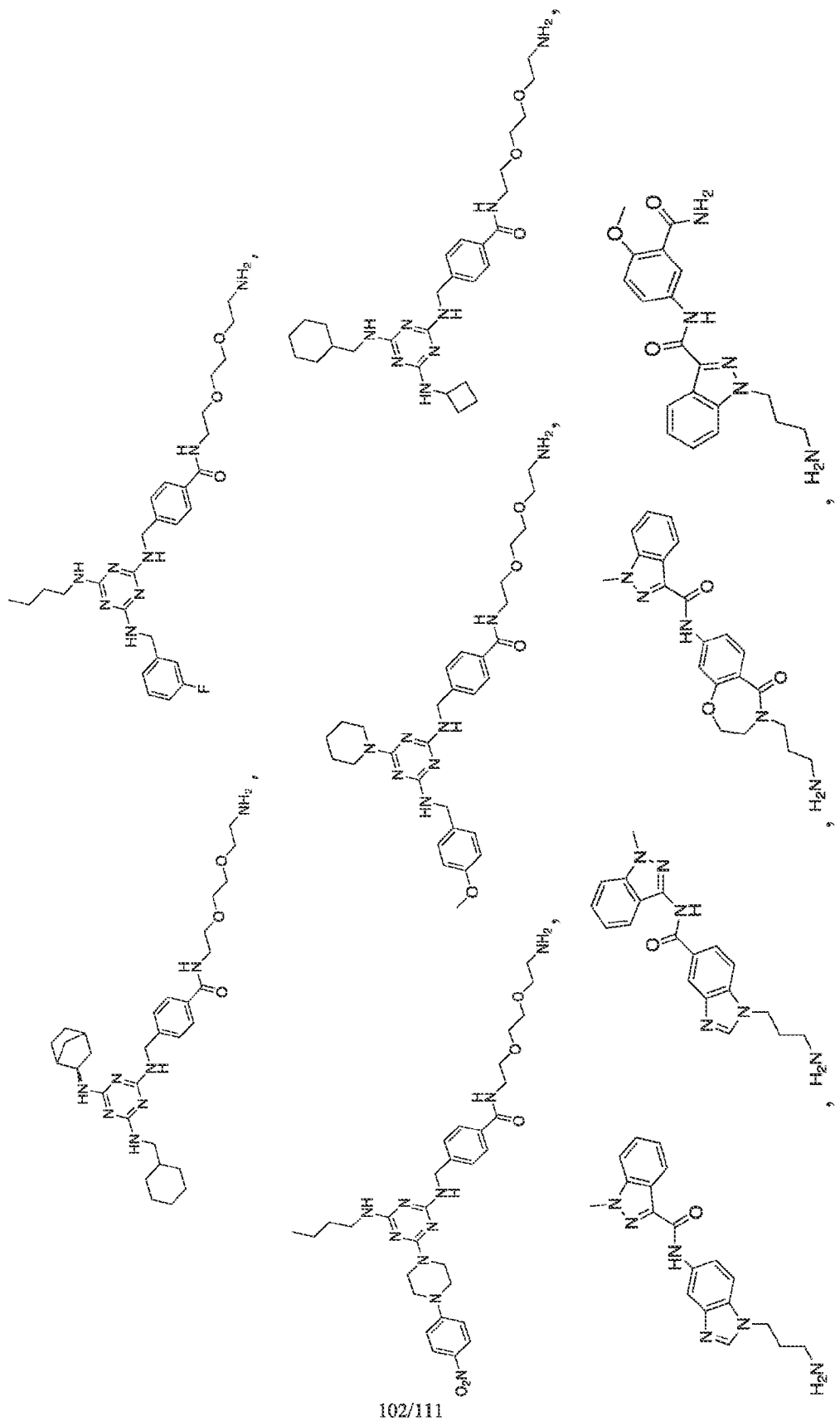


FIGURE 67 (Cont'd)

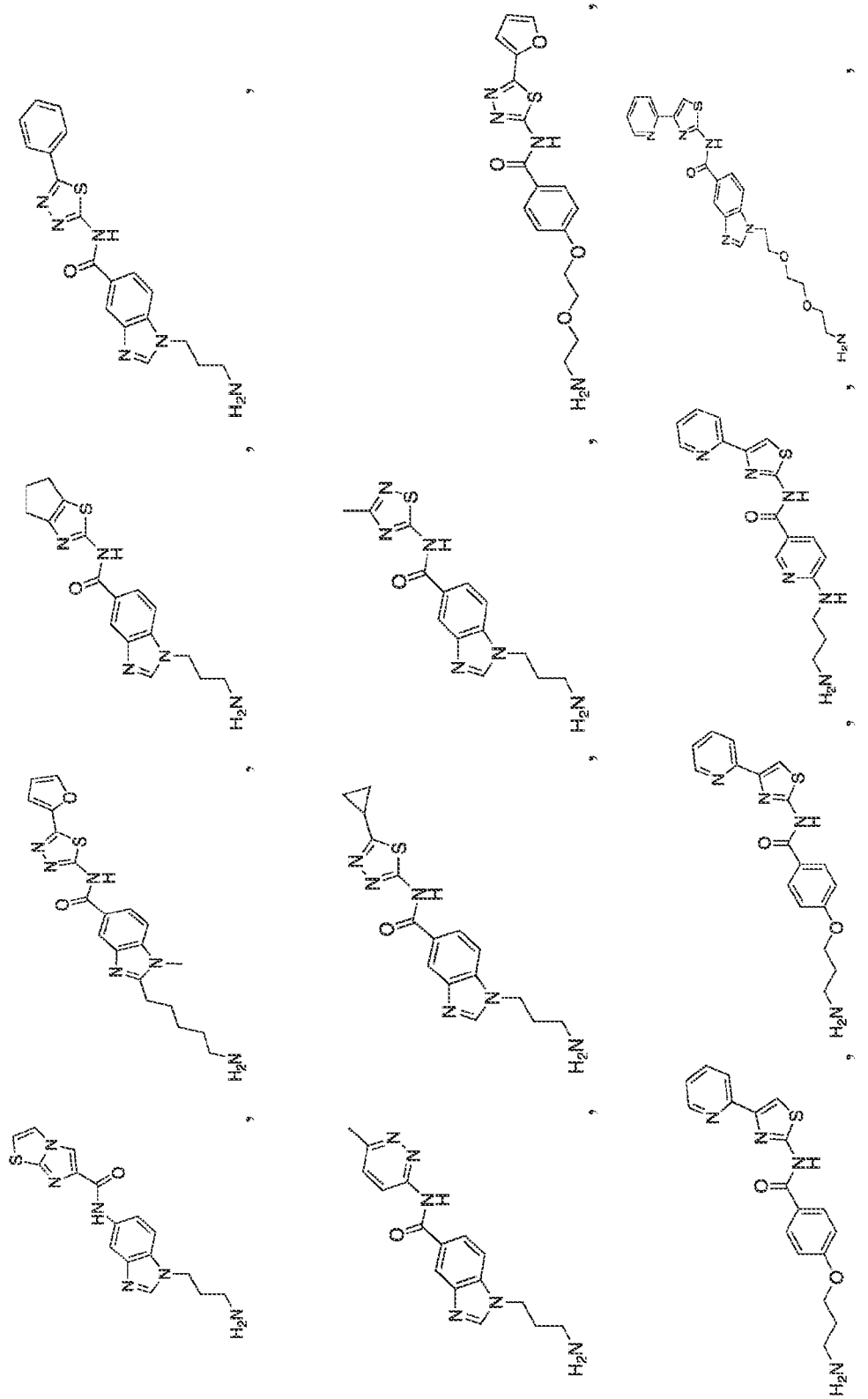


FIGURE 67 (Cont'd)

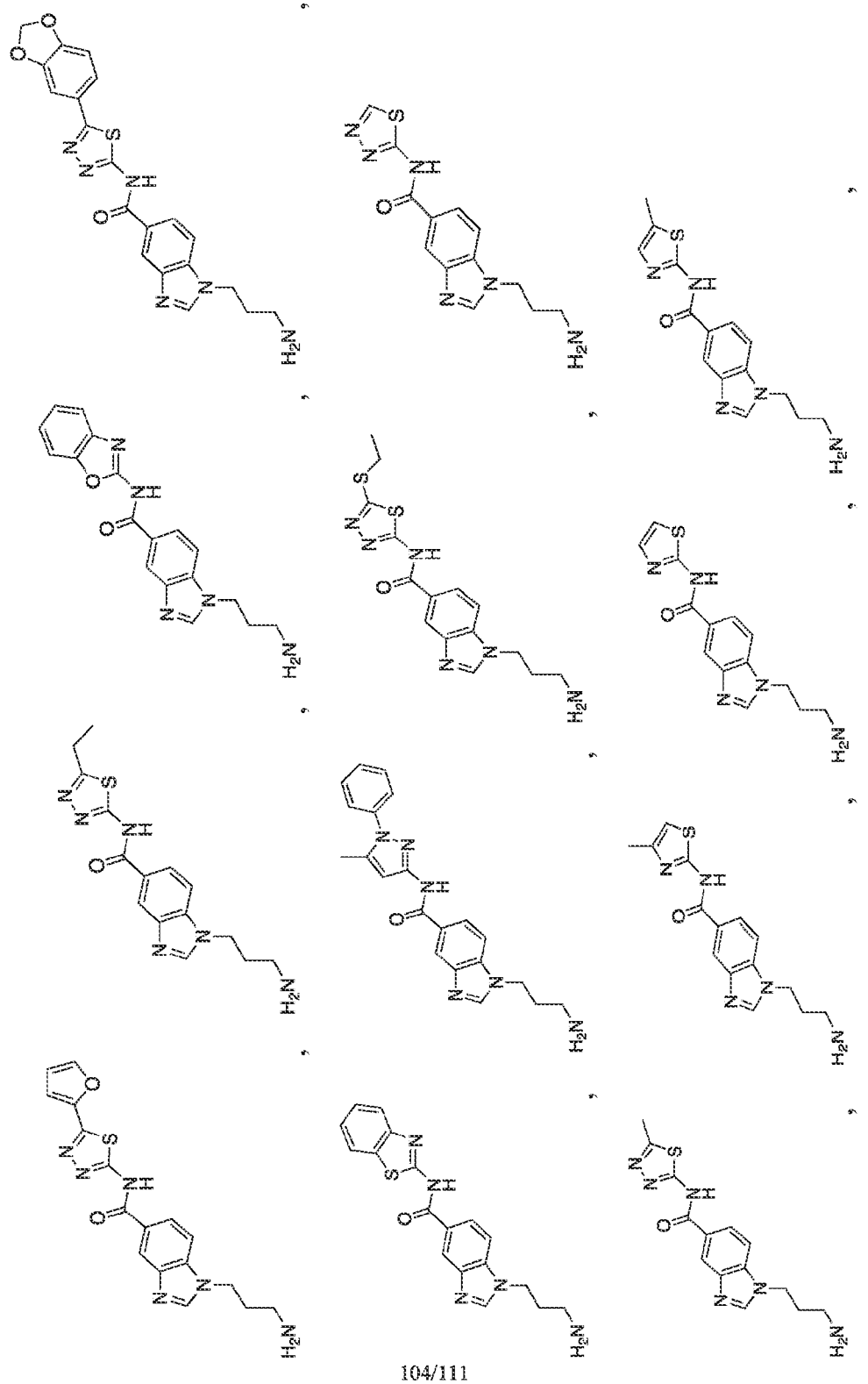


FIGURE 67 (Cont'd)

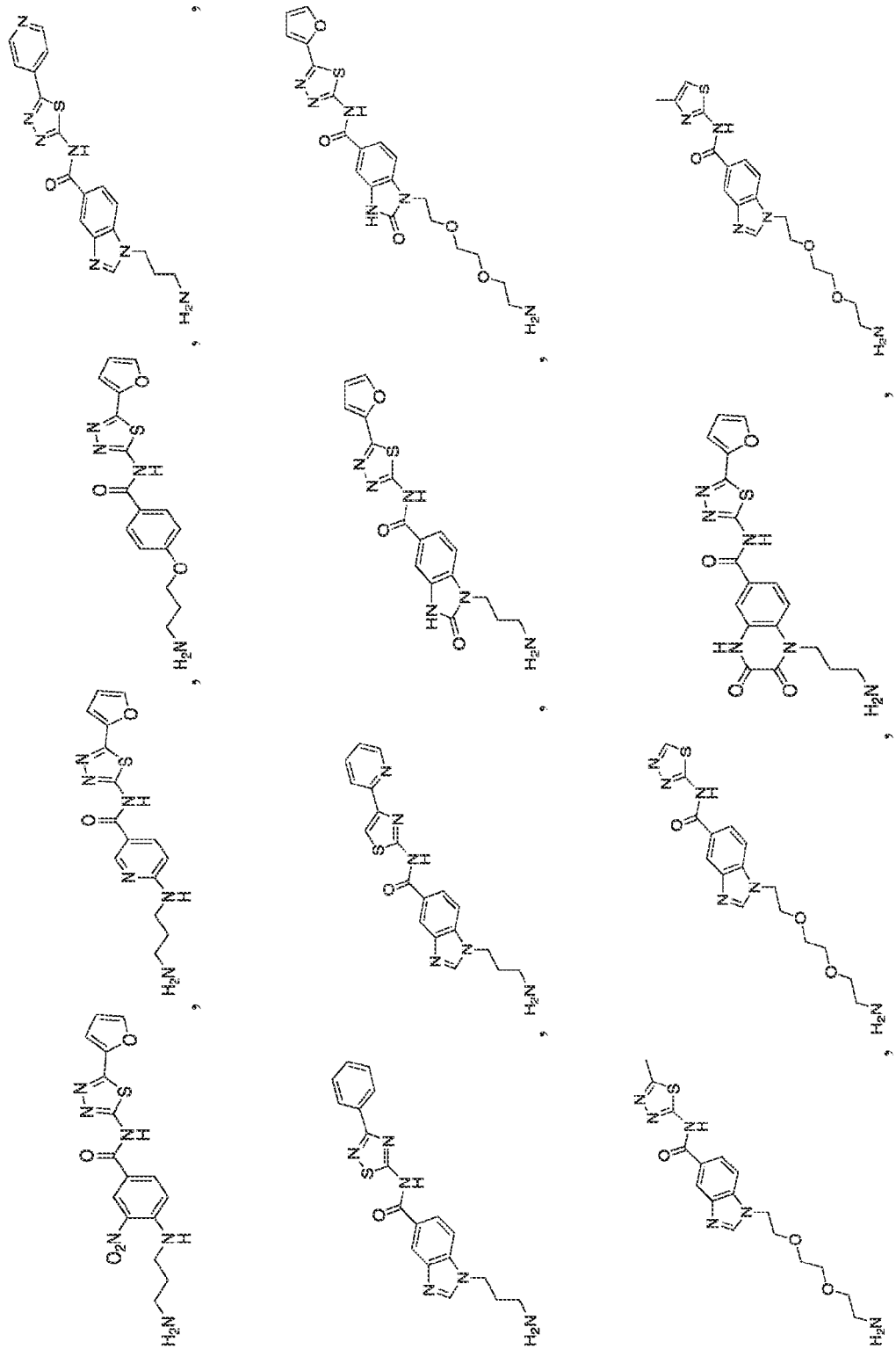


FIGURE 67 (Cont'd)

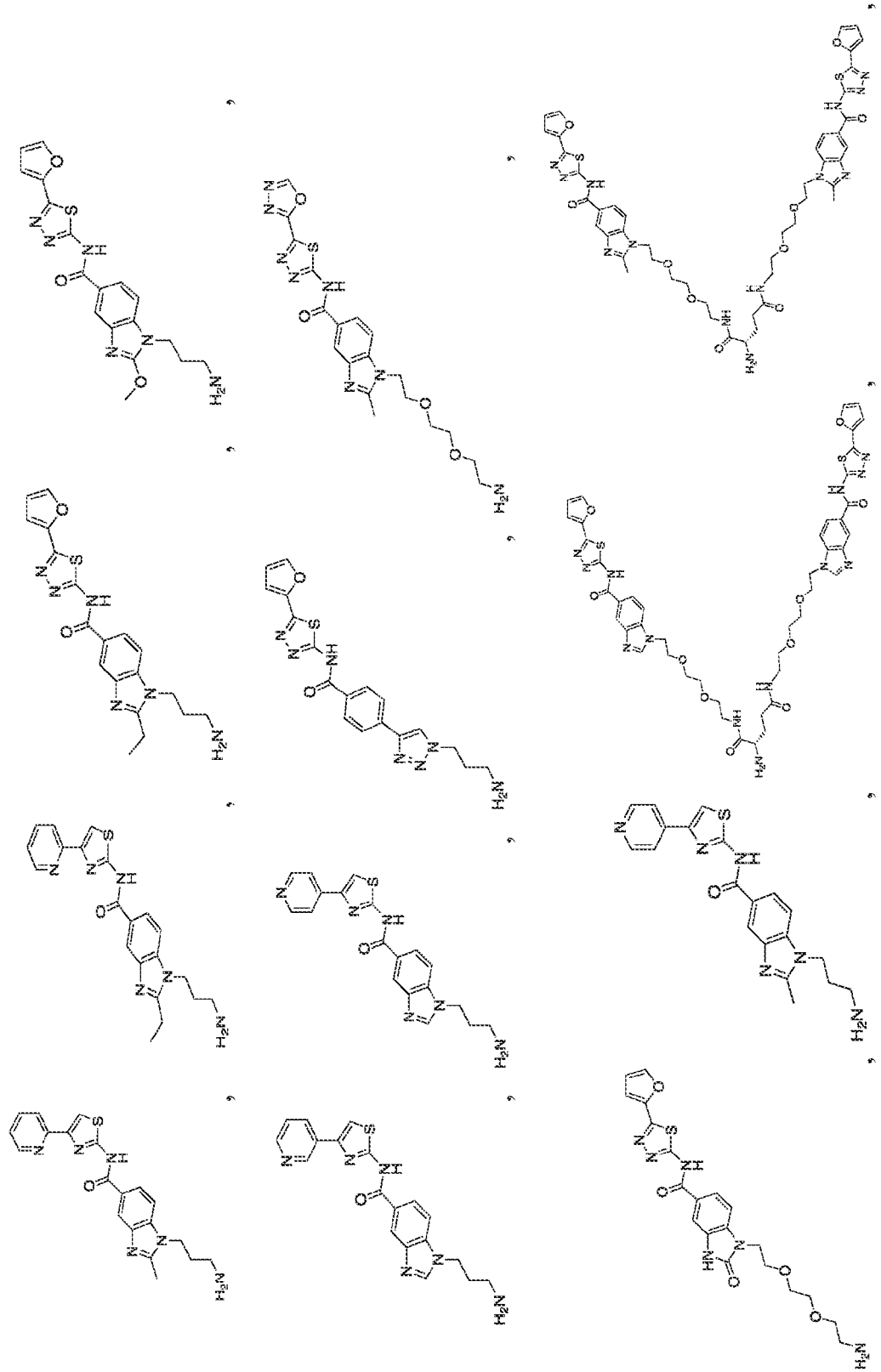


FIGURE 67 (Cont'd)

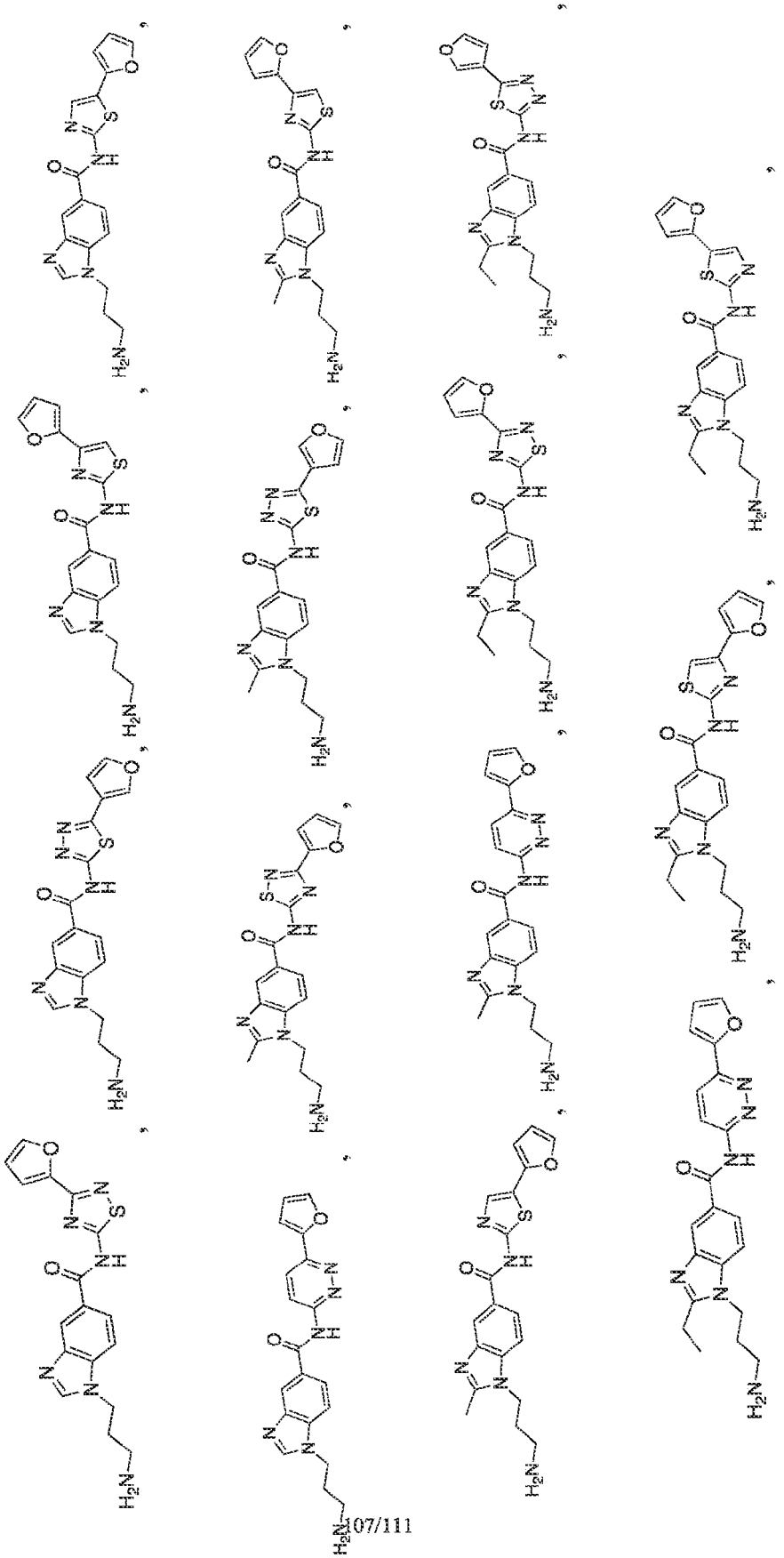
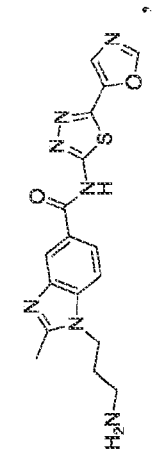
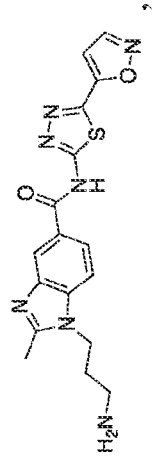
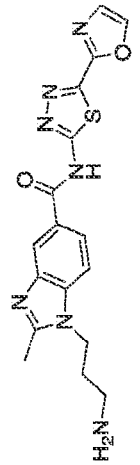


FIGURE 67 (Cont'd)







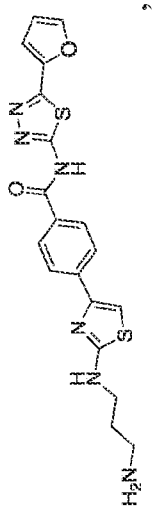


FIGURE 68

Exemplary R_1 and R_3 substituents/moieties for the [ASGPRBM] group

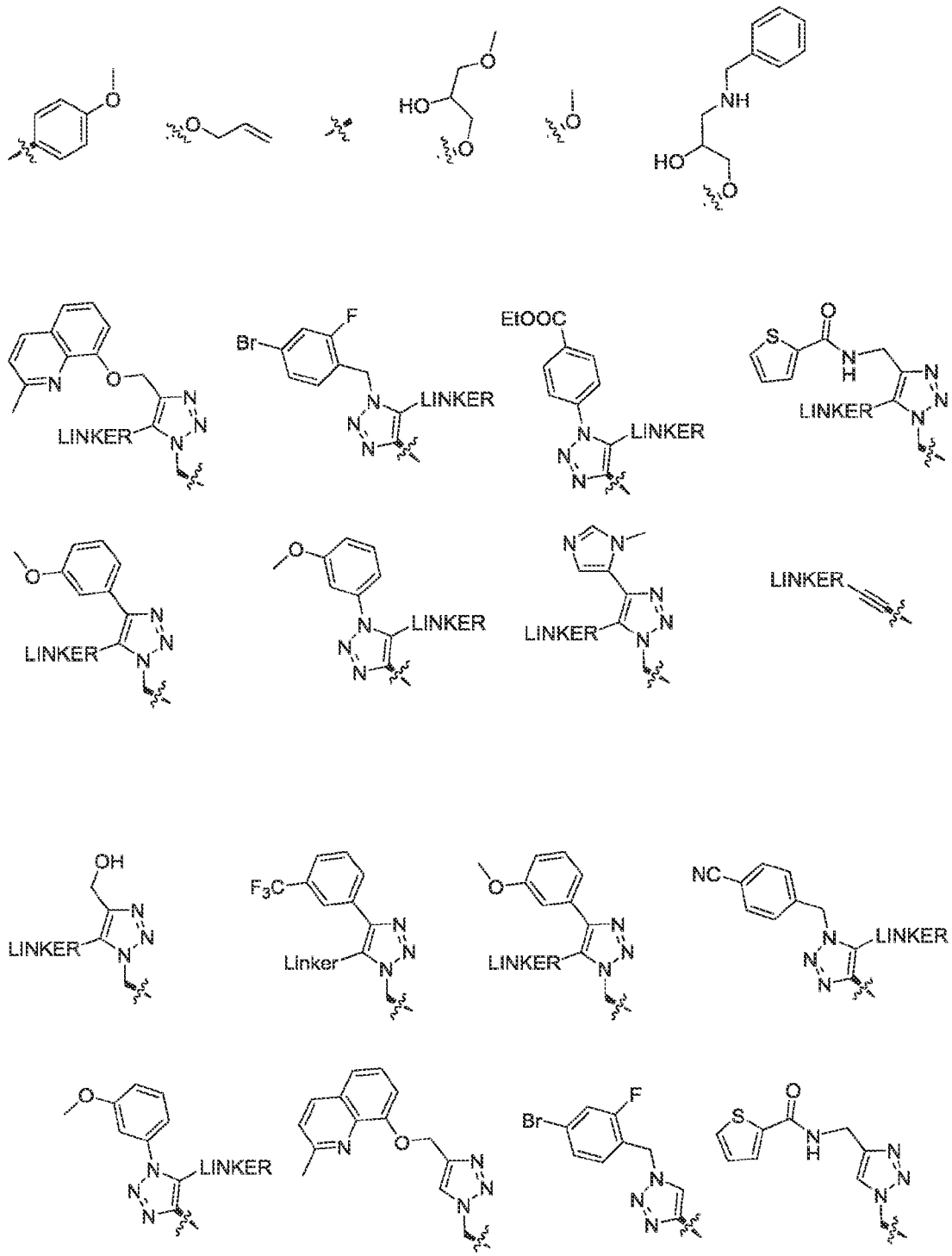


FIGURE 68 (Cont'd)

Exemplary R_1 and R_3 substituents/moieties for the [ASGPRBM] group

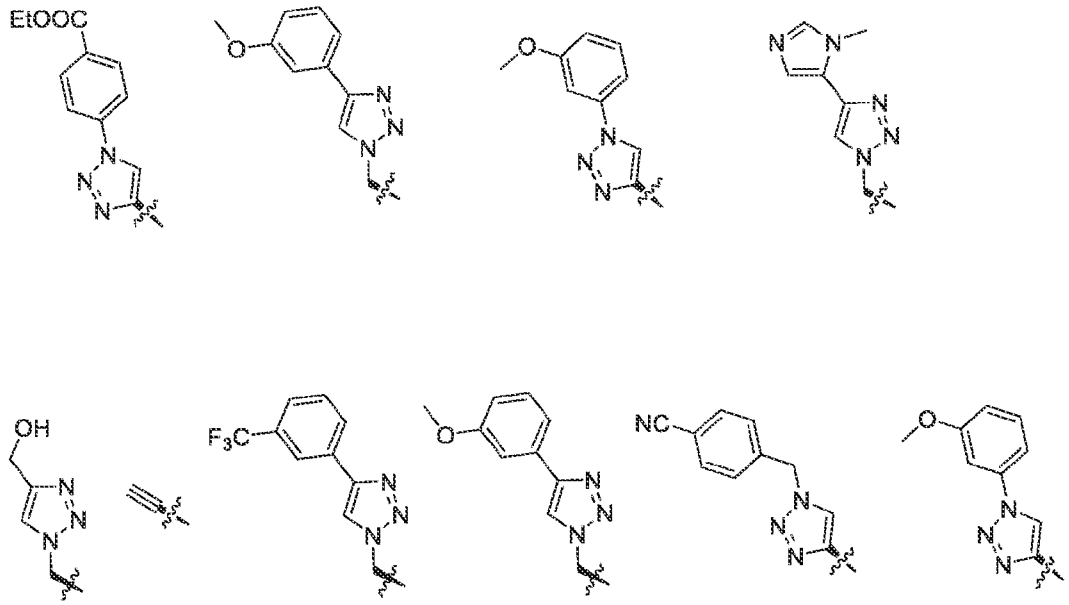
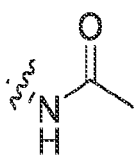
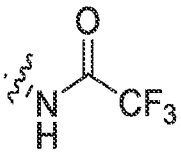
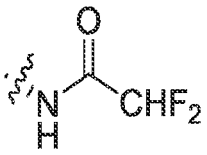


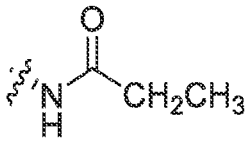
FIGURE 69

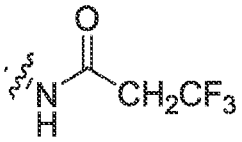
Exemplary R_2 substituents/moieties for the [ASGPRBM] group

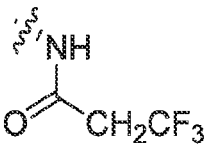


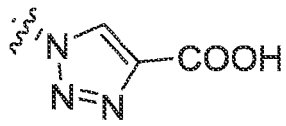


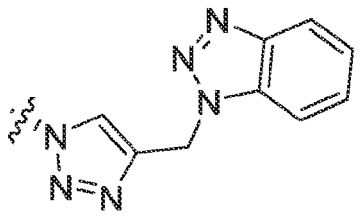


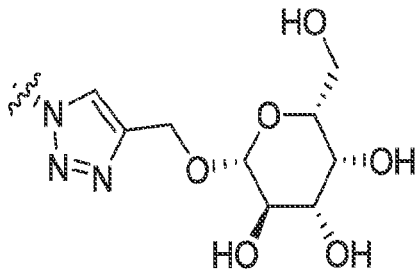


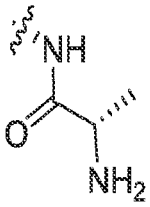












Sequence Listing

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1-2	DTD Version	V1_3
1-3	Software Name	WIPO Sequence
1-4	Software Version	2.2.0
1-5	Production Date	2023-03-14
1-6	Original free text language code	
1-7	Non English free text language code	
2	**General Information**	
2-1	Current application: IP Office	US
2-2	Current application: Application number	
2-3	Current application: Filing date	
2-4	Current application: Applicant file reference	047162-7240WO2
2-5	Earliest priority application: IP Office	US
2-6	Earliest priority application: Application number	US 17/695,259
2-7	Earliest priority application: Filing date	2022-03-15
2-8en	Applicant name	Yale University
2-8	Applicant name: Name Latin	
2-9en	Inventor name	
2-9	Inventor name: Name Latin	
2-10en	Invention title	Bi-functional Molecules To Degrade Circulating Proteins
2-11	Sequence Total Quantity	20

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3-1-1	Sequence Number [ID]	1	
3-1-2	Molecule Type	AA	
3-1-3	Length	10	
3-1-4	Features Location/	**REGION 1..10**	
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		source 1..10	
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	NonEnglishQualifier Value		
3-1-5	Residues	TWKTSRISIF	10
3-2	**Sequences**		
3-2-1	Sequence Number [ID]	2	
3-2-2	Molecule Type	AA	
3-2-3	Length	10	
3-2-4	Features Location/	**REGION 1..10**	
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3-3	**Sequences**		
3-3-1	Sequence Number [ID]	3	
3-3-2	Molecule Type	AA	
3-3-3	Length	12	
3-3-4	Features Location/	**REGION 1..12**	
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		organism=synthetic construct	
	NonEnglishQualifier Value		
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3-4-3	Length	4	
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3-5-3	Length	6	
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3-5-5	Residues	HWRGWV	6
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3-6-2	Molecule Type	AA	
3-6-3	Length	6	
3-6-4	Features Location/	**REGION 1..6**	
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		mol_type=protein	
		organism=synthetic construct	
	NonEnglishQualifier Value		

3-6-5	Residues	HYFKFD	6
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3-7-2	Molecule Type	AA	
3-7-3	Length	6	
3-7-4	Features Location/	**REGION 1..6**	
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3-7-5	Residues	HFRRHL	6
3-8	**Sequences**		
3-8-1	Sequence Number [ID]	8	
3-8-2	Molecule Type	AA	
3-8-3	Length	6	
3-8-4	Features Location/	**REGION 1..6**	
	Qualifiers	note=Chemically Synthesized	
		SITE 3	
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		source 1..6	
		mol_type=protein	
		organism=synthetic construct	
	NonEnglishQualifier Value		
3-8-5	Residues	HWXGWV	6
3-9	**Sequences**		
3-9-1	Sequence Number [ID]	9	
3-9-2	Molecule Type	AA	
3-9-3	Length	8	
3-9-4	Features Location/	**REGION 1..8**	
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		REGION 1..8	
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		SITE 2	
		note=misc_feature - Ser is N-acetylated	
		SITE 8	
		note=misc_feature - C(=O)OH of Lys bonds to lactic acid-Glu	
		source 1..8	
		mol_type=protein	
		organism=synthetic construct	
	NonEnglishQualifier Value		
3-9-5	Residues	ASRWHYFK	8
3-10	**Sequences**		
3-10-1	Sequence Number [ID]	10	
3-10-2	Molecule Type	AA	
3-10-3	Length	8	
3-10-4	Features Location/	**REGION 1..8**	
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		REGION 1..8	
		note=misc_feature - Ala and Glu of Lys-lactic acid-Glu form a ring	
		SITE 2	
		note=misc_feature - Xaa = N-acetylated 2,3-diaminopropionic acid	
		SITE 8	
		note=misc_feature - C(=O)OH of Lys bonds to lactic acid-Glu	
		source 1..8	
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3-11-3	Length	7	
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		REGION 1..7	
		note=misc_feature - Glutaric acid forms a ring between Lys and Met	
		source 1..7	
		mol_type=protein	
		organism=synthetic construct	
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3-11-5	Residues	MWFRHYK	7
3-12	**Sequences**		
3-12-1	Sequence Number [ID]	12	
3-12-2	Molecule Type	AA	
3-12-3	Length	8	
3-12-4	Features Location/	**REGION 1..8**	
	Qualifiers	note=Chemically Synthesized	
		source 1..8	
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		organism=synthetic construct	
	NonEnglishQualifier Value		
3-12-5	Residues	NKFRGKYK	8
3-13	**Sequences**		
3-13-1	Sequence Number [ID]	13	
3-13-2	Molecule Type	AA	
3-13-3	Length	8	
3-13-4	Features Location/	**REGION 1..8**	
	Qualifiers	note=Chemically Synthesized	
		source 1..8	
		mol_type=protein	
		organism=synthetic construct	
	NonEnglishQualifier Value		
3-13-5	Residues	NARKFYKG	8
3-14	**Sequences**		
3-14-1	Sequence Number [ID]	14	
3-14-2	Molecule Type	AA	
3-14-3	Length	8	
3-14-4	Features Location/	**REGION 1..8**	
	Qualifiers	note=Chemically Synthesized	
		source 1..8	
		mol_type=protein	
		organism=synthetic construct	
	NonEnglishQualifier Value		
3-14-5	Residues	FYWHCLDE	8
3-15	**Sequences**		
3-15-1	Sequence Number [ID]	15	
3-15-2	Molecule Type	AA	
3-15-3	Length	8	
3-15-4	Features Location/	**REGION 1..8**	
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		source 1..8	
		mol_type=protein	
		organism=synthetic construct	
	NonEnglishQualifier Value		
3-15-5	Residues	FYCHWALE	8
3-16	**Sequences**		
3-16-1	Sequence Number [ID]	16	
3-16-2	Molecule Type	AA	
3-16-3	Length	8	
3-16-4	Features Location/	**REGION 1..8**	
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		organism=synthetic construct	
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3-16-5	Residues	FYCHTIDE	8
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3-17-2	Molecule Type	AA	
3-17-3	Length	4	
3-17-4	Features Location/	**REGION 1..4**	
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		organism=synthetic construct	
	NonEnglishQualifier Value		
3-17-5	Residues	RRGW	4
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3-18-2	Molecule Type	AA	
3-18-3	Length	7	
3-18-4	Features Location/	**REGION 1..7**	
	Qualifiers	note=Chemically Synthesized	
		source 1..7	
		mol_type=protein	
		organism=synthetic construct	
	NonEnglishQualifier Value		
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3-19-2	Molecule Type	AA	
3-19-3	Length	13	
3-19-4	Features Location/	**REGION 1..13**	
	Qualifiers	note=Chemically Synthesized	
		REGION 2..12	
		note=misc_feature - Cys and Cys form a ring	
		SITE 13	
		note=misc_feature - terminus is C(=O)NH2	
		source 1..13	
		mol_type=protein	
		organism=synthetic construct	
	NonEnglishQualifier Value		
3-19-5	Residues	DCAWHLGELV WCT	13
3-20	**Sequences**		
3-20-1	Sequence Number [ID]	20	
3-20-2	Molecule Type	AA	
3-20-3	Length	15	
3-20-4	Features Location/	**REGION 1..15**	
	Qualifiers	note=Chemically Synthesized	
		REGION 1..15	
		note=misc_feature - Cys and Cys form a ring	
		REGION 3..13	
		note=misc_feature - Cys and Cys form a ring	
		SITE 15	
		note=misc_feature - terminus is C(=O)NH2	
		source 1..15	
		mol_type=protein	
		organism=synthetic construct	
	NonEnglishQualifier Value		
3-20-5	Residues	CDCAWHLGEL VWCTC	15