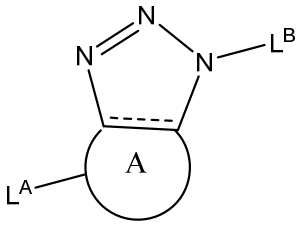
CLAIMS

1. A compound of Formula Ia, or a pharmaceutically acceptable salt thereof, having the structure:

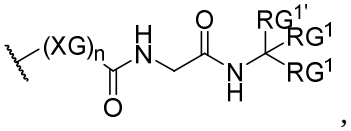


Formula Ia,

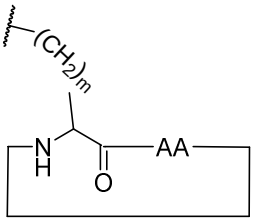
wherein:

⁼⁼⁼⁼ is a carbon-carbon single or double bond;

A is a C_{6-18} aryl, C_{6-18} heterocyclyl, C_{6-18} biaryl, or C_{6-18} heterobiaryl, each of which is optionally substituted by 1-6 substituents selected from the group consisting of F, Cl, Br, I, ORG, $OC(O)N(RG)_2$, CN, NO, NO_2, ONO_2, CF_3, OCF_3, RG, $N(RG)_2$, SRG, SORG, SO_2RG, $SO_2N(RG)_2$, and SO_3RG;

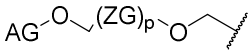
L^A is an ASGPR binding moiety with the structure 

,

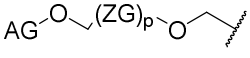
L^B is an anti-β_1AR binding moiety with the structure 

,

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

$RG^{1'}$ is 

;

each occurrence of R^1 is independently hydrogen or 

;

AG is an aminosaccharide;

each occurrence of RG is independently H, optionally substituted C_{1-10} alkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{6-18} aryl, or optionally substituted C_{5-18} heteroaryl;

each occurrence of XG is independently selected from the group consisting of $-CH_2-$, -C(=O)-, -NH-, and -O-;

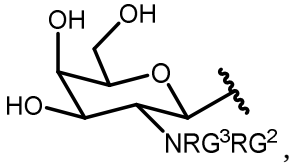
each occurrence of ZG is independently selected from the group consisting of -CH_2-, -C(=O)-, -NH-, and -O-;

m is an integer from 2 to 10;

n is an integer from 1 to 100; and

p is an integer from 1 to 50.

2. The compound of claim 1, wherein AG has the structure:

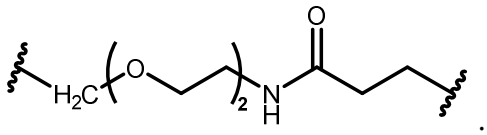


wherein RG^2 and RG^3 are each independently selected from the group consisting of hydrogen and -C(=O)R, which is optionally substituted by 1-5 groups selected from the group consisting of halogen, optionally substituted C_{1-10} alkyl, optionally substituted C_{1-10} alkoxy, optionally substituted C_{1-10} aminoalkyl, and combinations thereof, or

RG^2 and RG^3 taken together with the nitrogen atom to which they are attached, form a C5 heterocycle that is optionally substituted by 1-5 substituents selected from the group consisting of optionally substituted C_{1-10} alkyl, optionally substituted C_{1-10} alkoxy, optionally substituted C_{1-10} aminoalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{5-10} heteroaryl, halogen, and combinations thereof.

3. The compound of claim 2, wherein RG^2 is hydrogen and RG^3 is $C(=O)CH_3$.

4. The compound of claim 1, wherein each occurrence of $(ZG)_p$ independently has the structure:



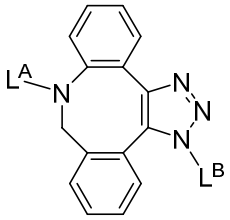
5. The compound of claim 1, wherein $(XG)_n$ is selected from the group consisting of -$O(CH_2)_3$-, -NH-$(CH_2CH_2O)_3$-CH_2-, and =N*$(C=O)(CH_2)_2C(=O)NHCH_2CH_2$-$(OCH_2CH_2)_4$-, wherein =N* is a ring nitrogen in A.

6. The compound of claim 1, wherein AA is a (6,12) cyclic peptide.

7. The compound of claim 6, wherein AA is at least 95% homologous to SEQ ID NO:1.

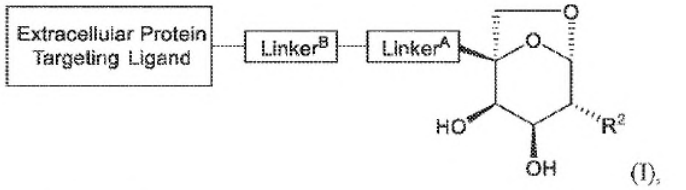
8. The compound of claim 6, wherein AA is an amino acid sequence of SEQ ID NO: 1.

9. The compound of claim 1, having the structure

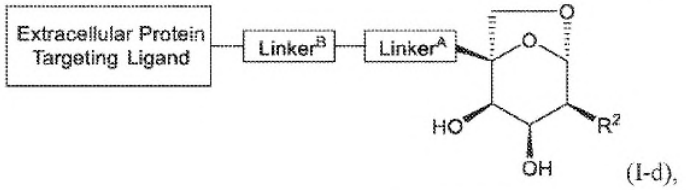


.

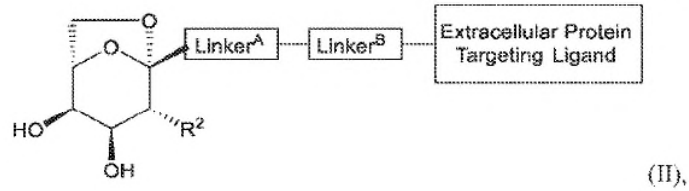
10. The compound of claim 1, having one of the following formulae:



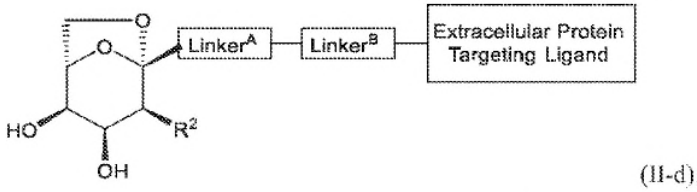
(I),



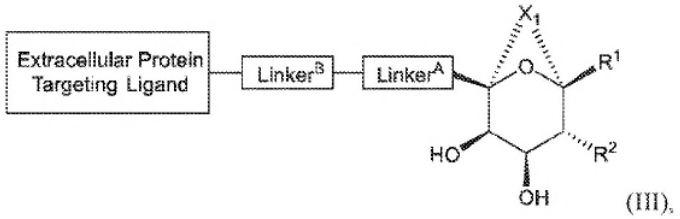
(I-d),



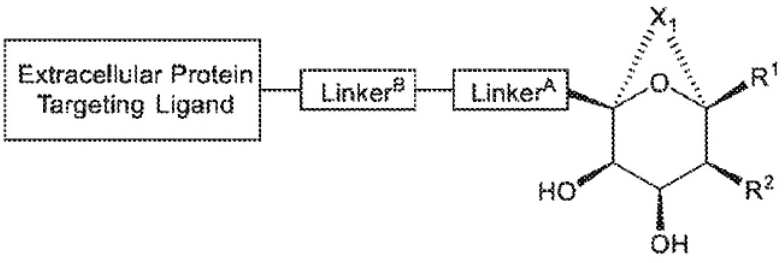
(II),



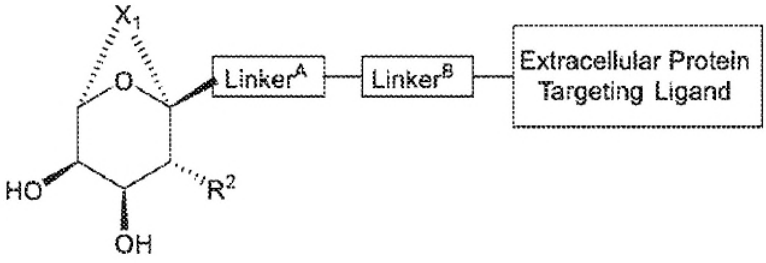
(II-d),



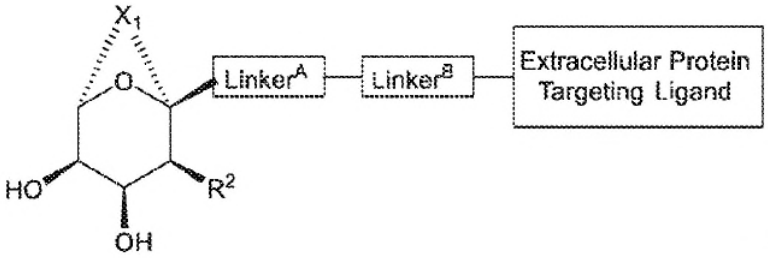
(III),



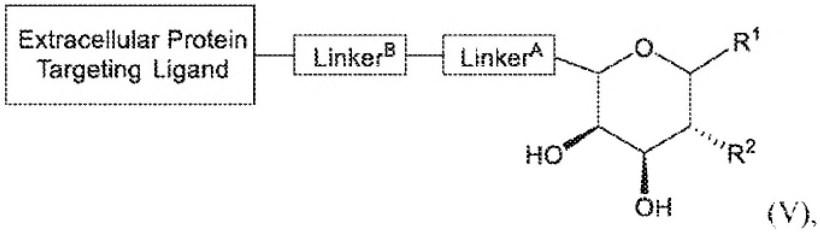
(III-d),



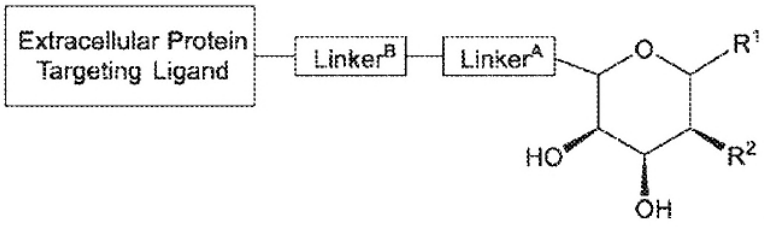
(IV),



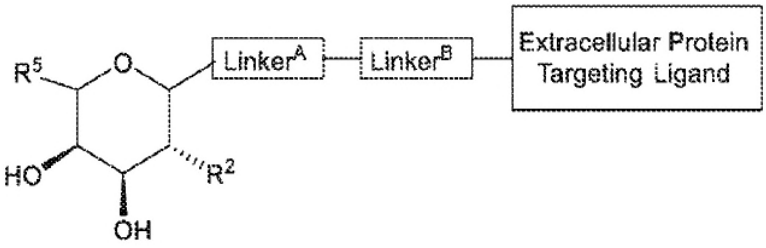
(IV-d),



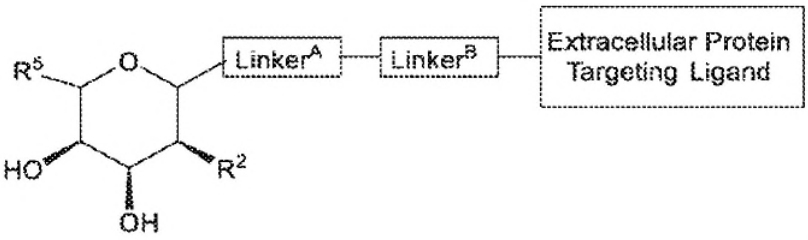
(V),



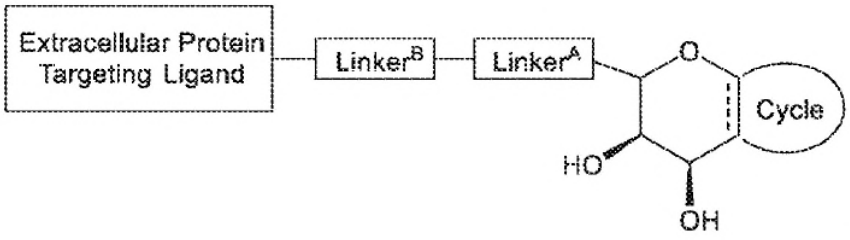
(V-d),



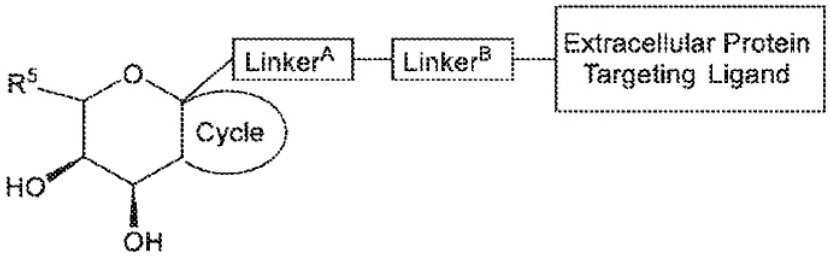
(VI),



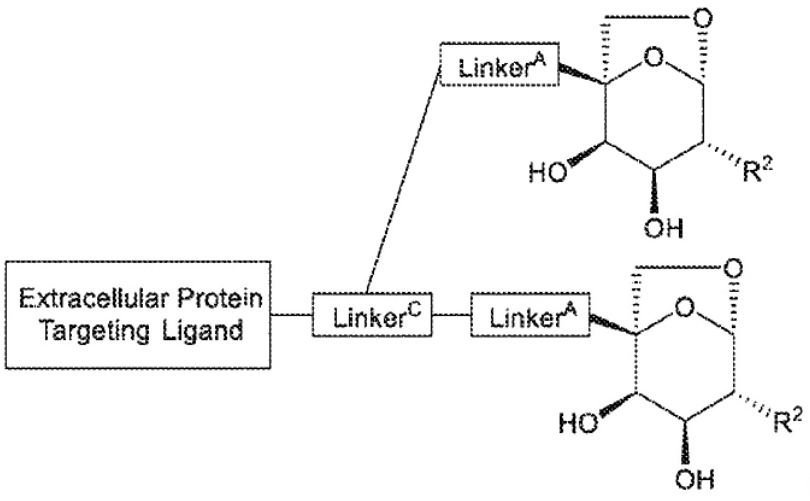
(VI-d),



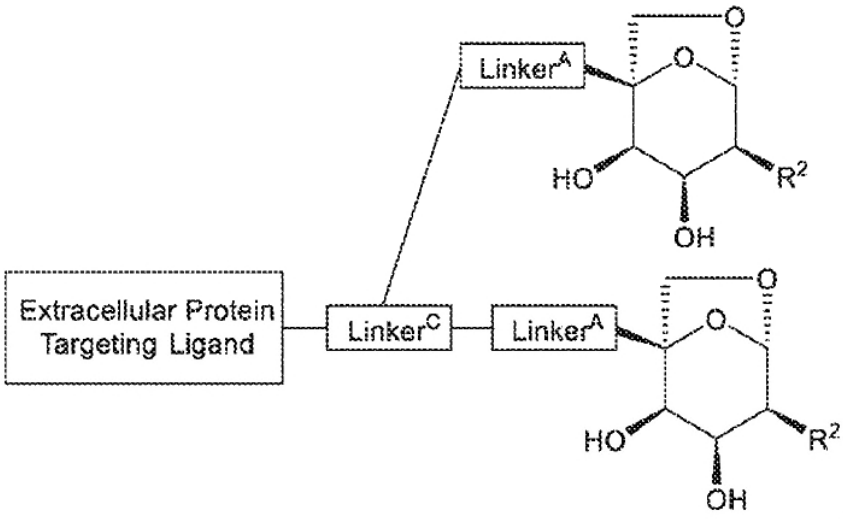
(VII),



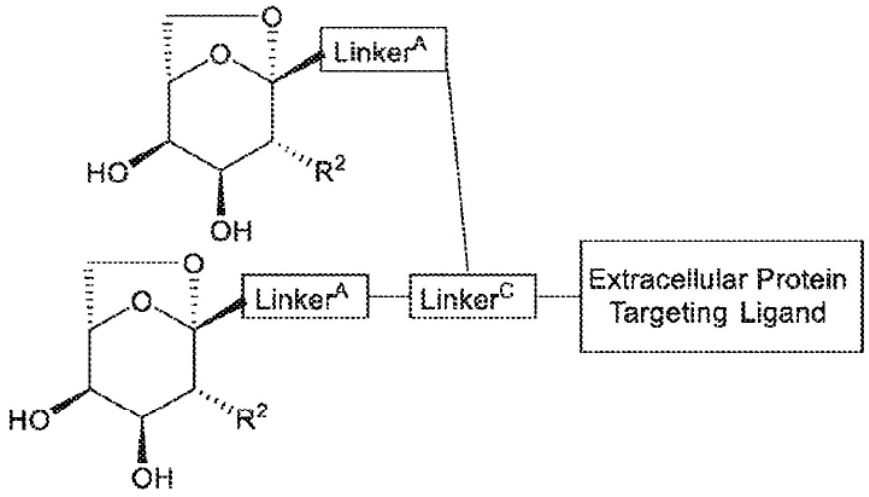
(VIII),



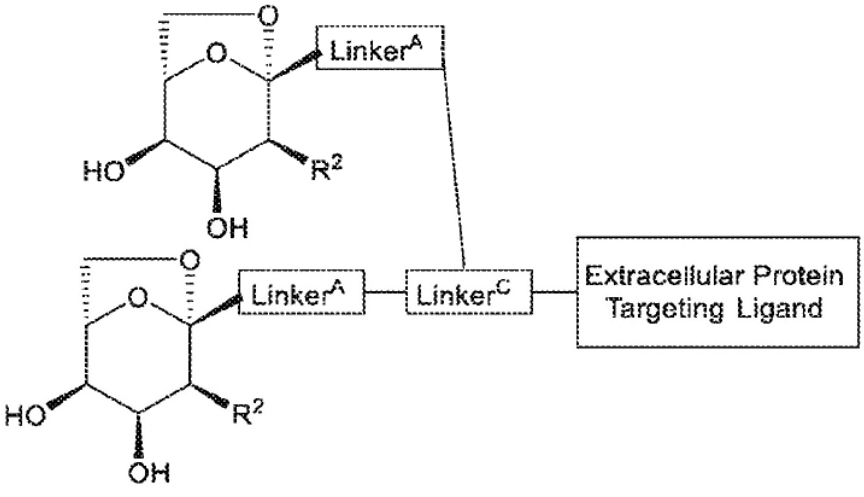
(I-Bi),



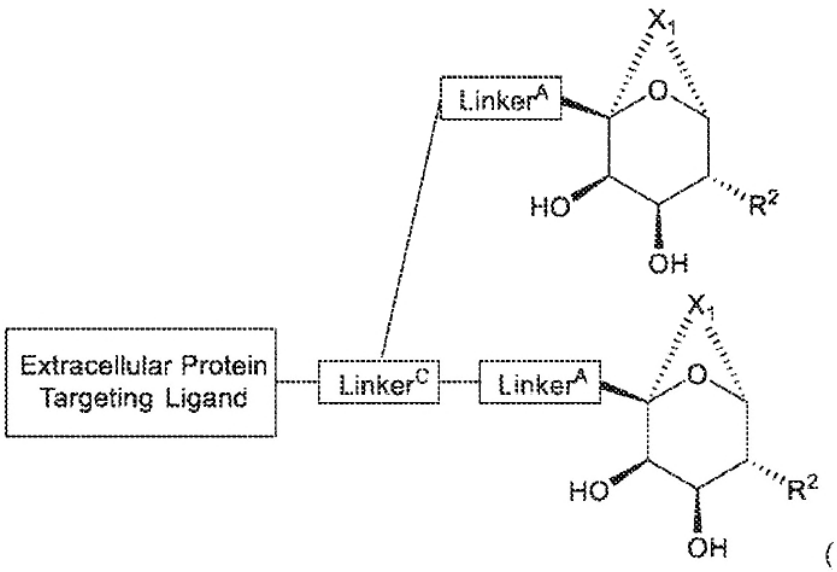
(I-d-Bi),



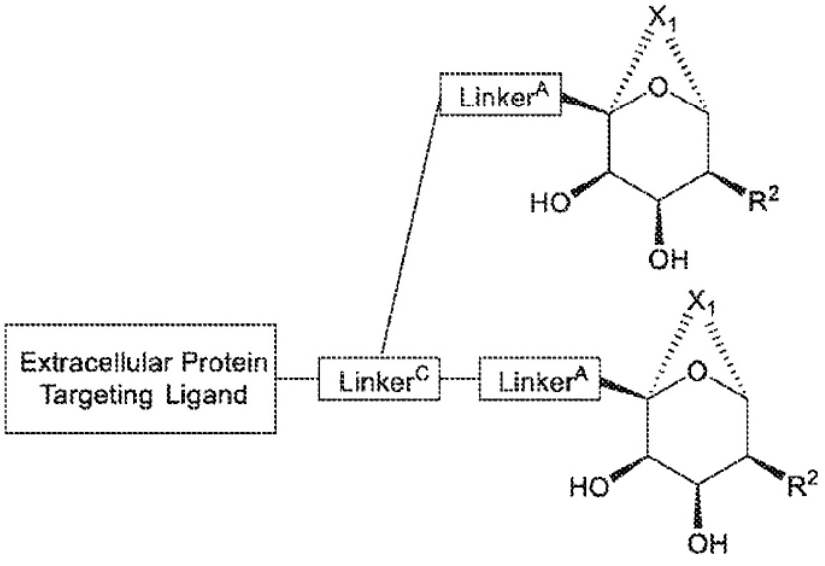
(II-Bi),



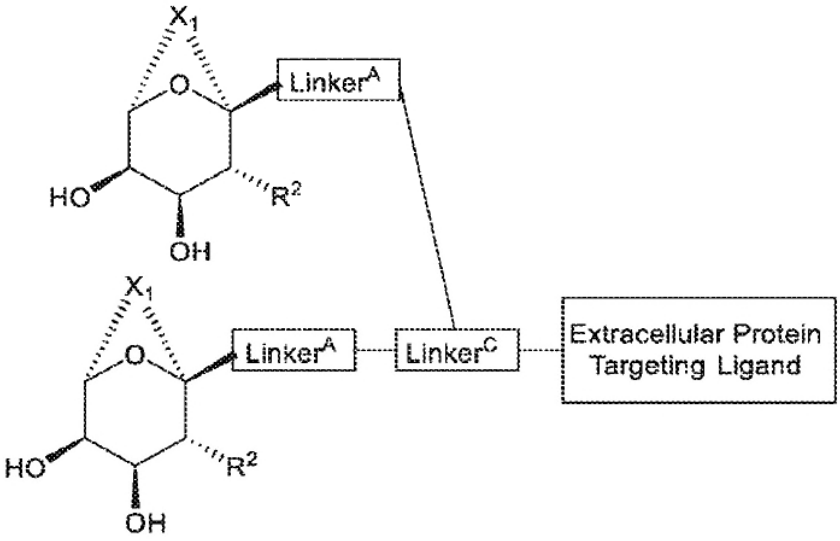
(II-d-Bi),



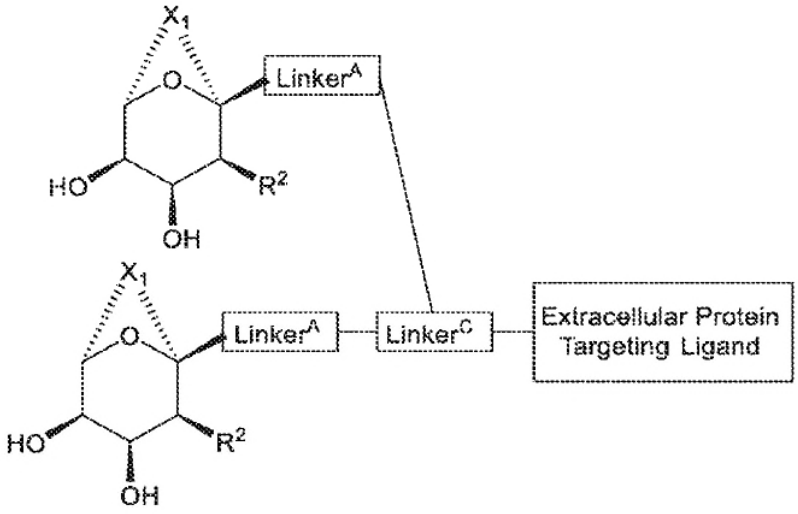
(III-Bi),



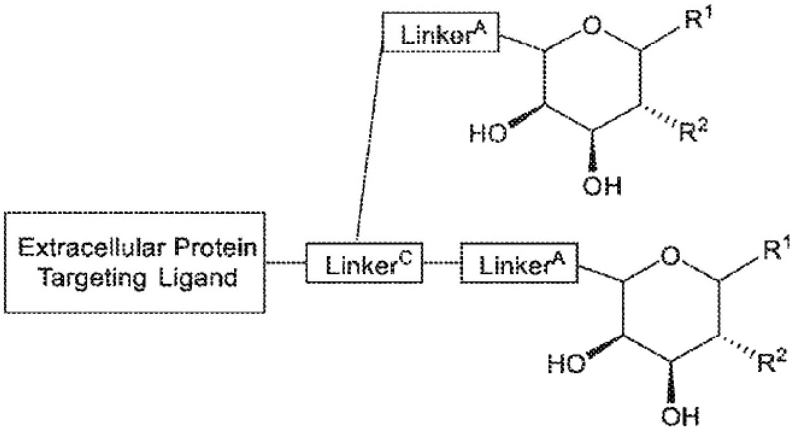
(III-d-Bi),



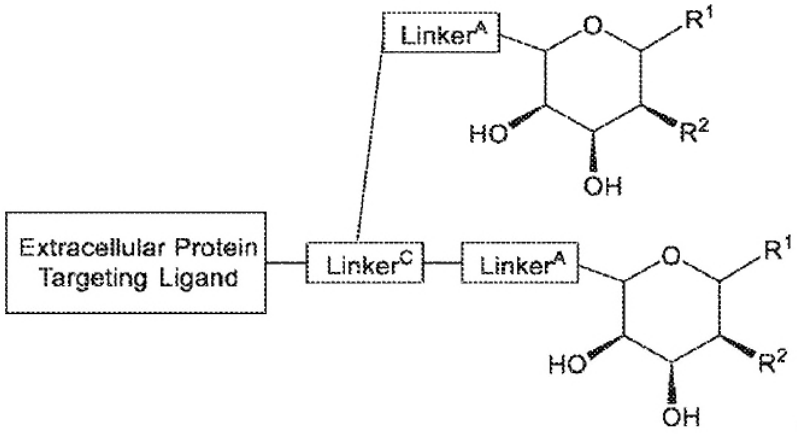
(IV-Bi),



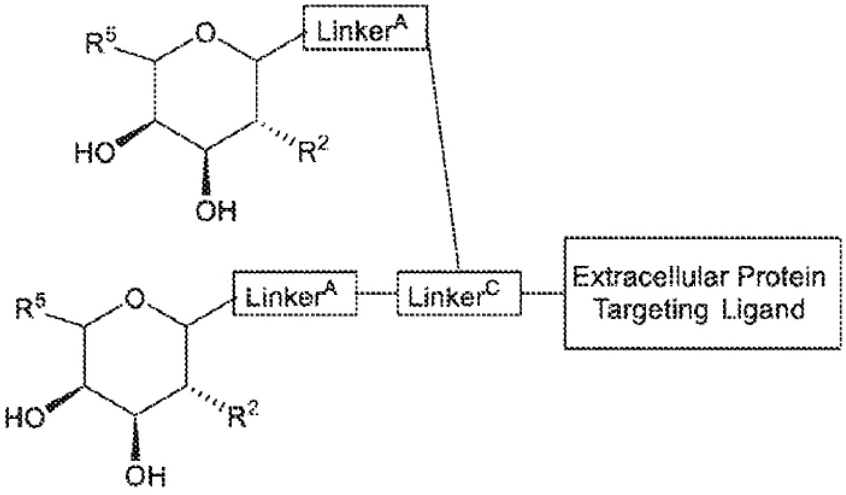
(IV-d-Bi),



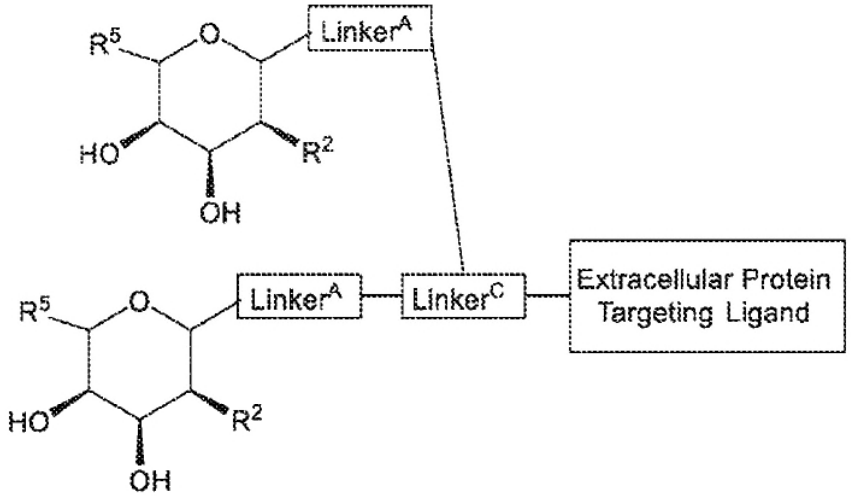
(V-Bi),



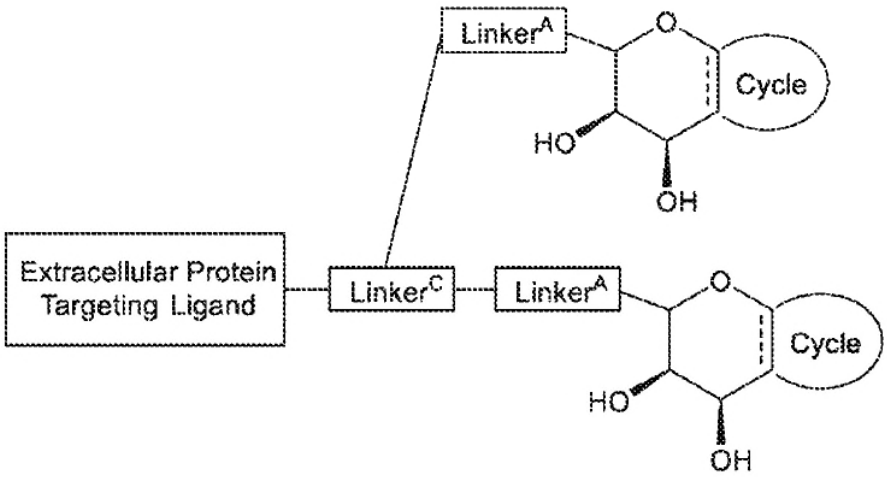
(V-d-Bi),



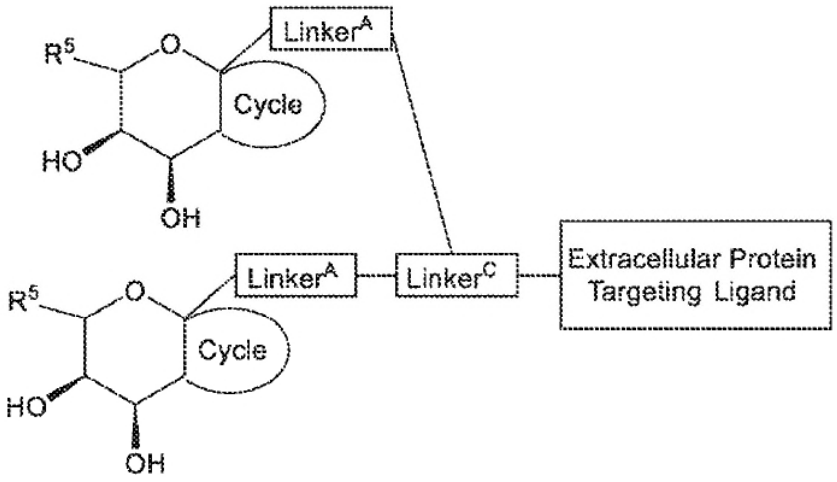
(VI-Bi),



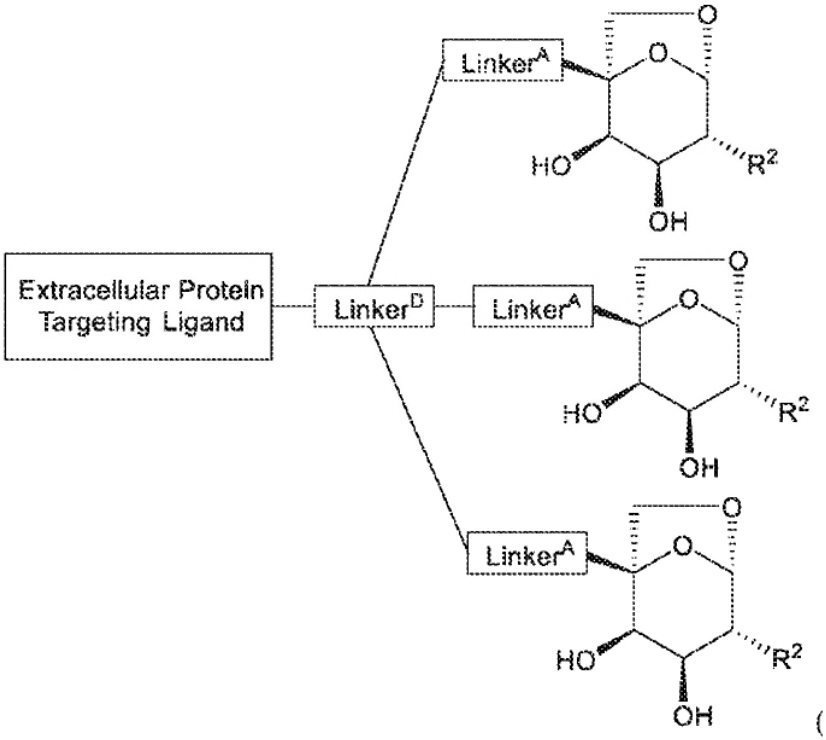
(VI-d-Bi),



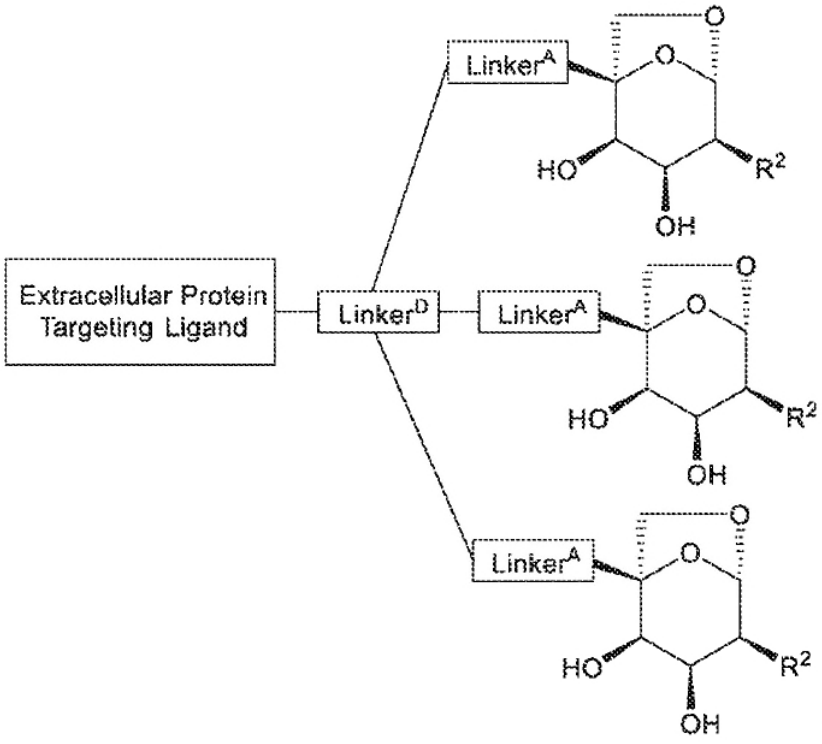
(VII-Bi),


Linker^A
R^5
O
Cycle
HO
OH
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
R^5
O
Cycle
HO
OH

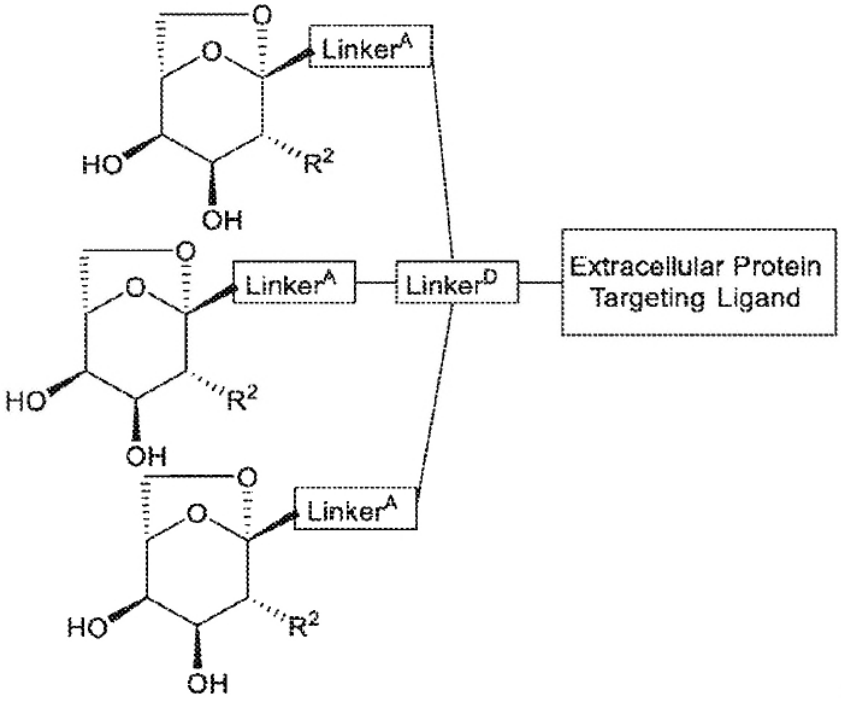
(VIII-Bi),


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

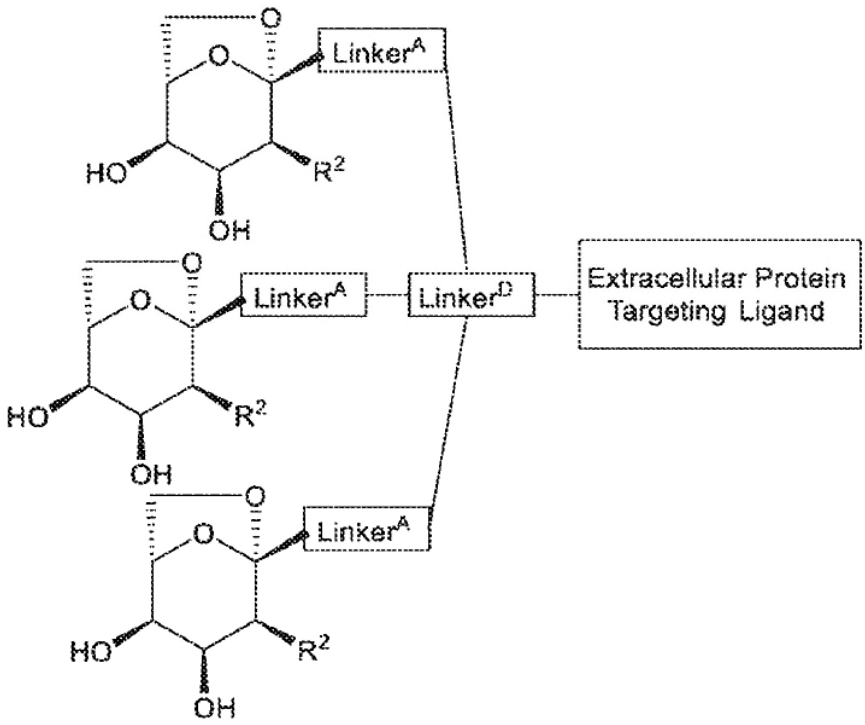
(I-Tri),


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

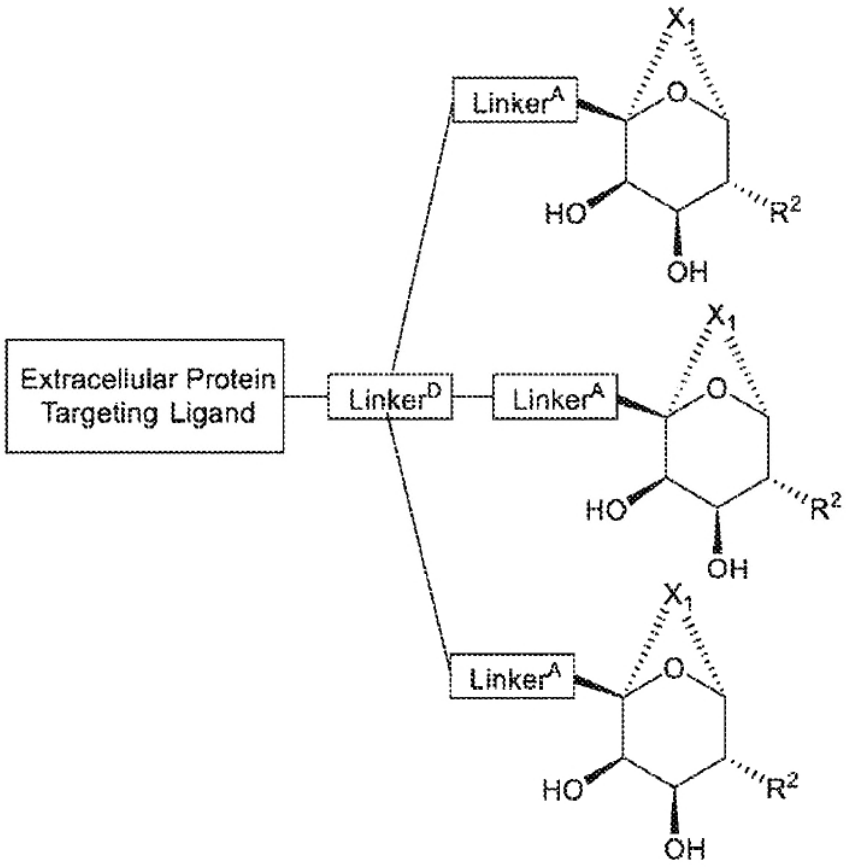
(I-d-Tri),


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

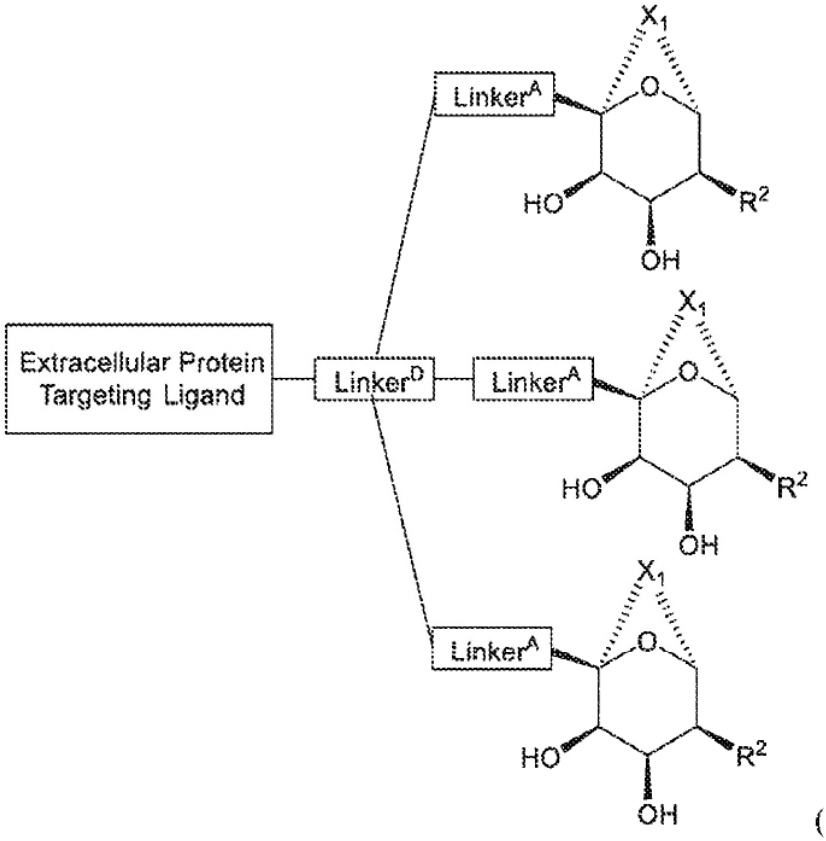
(II-Tri),



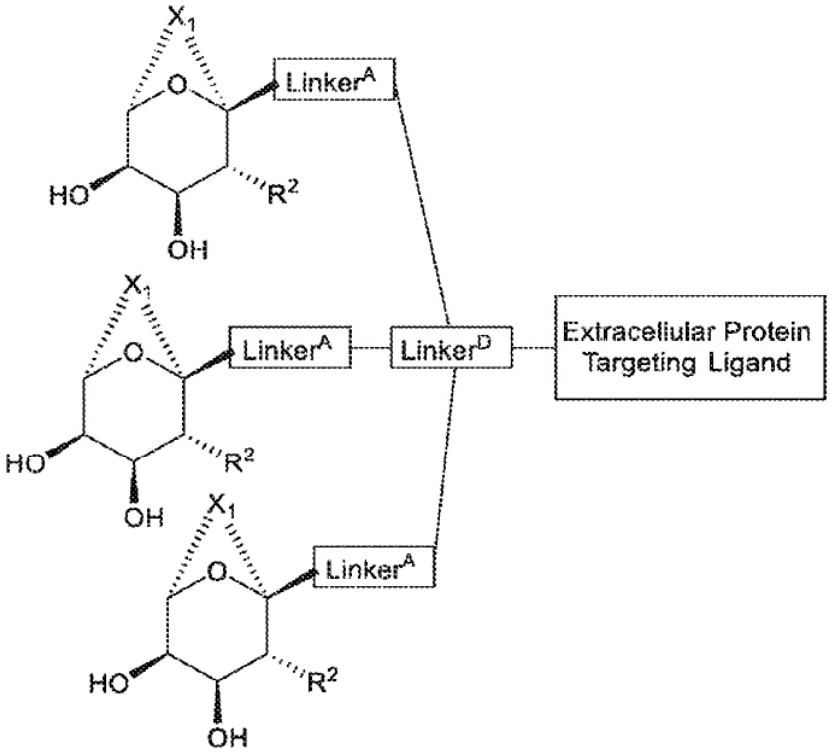
(II-d-Tri),



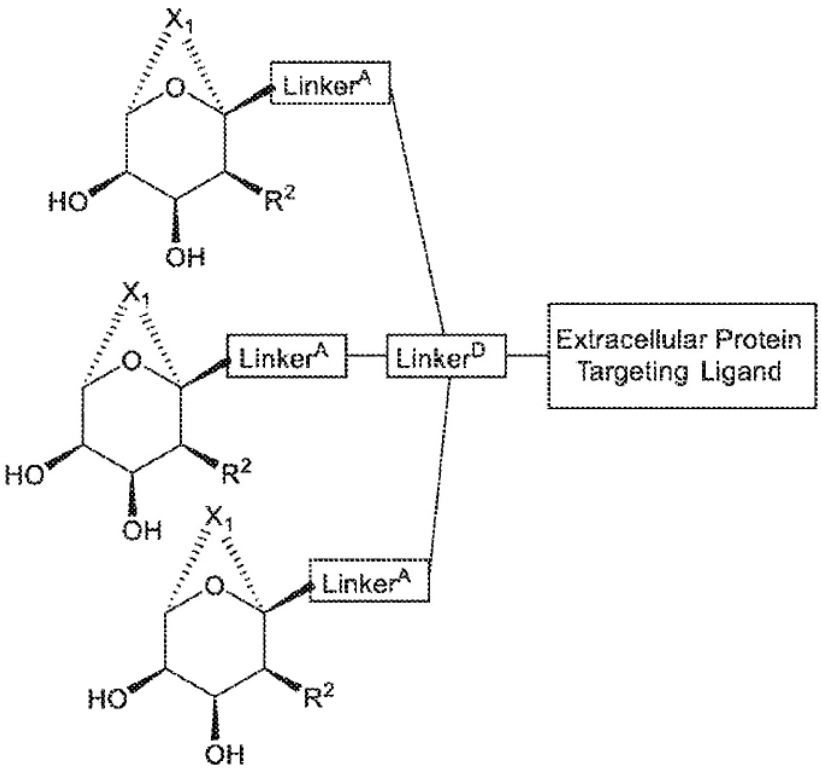
(III-Tri),



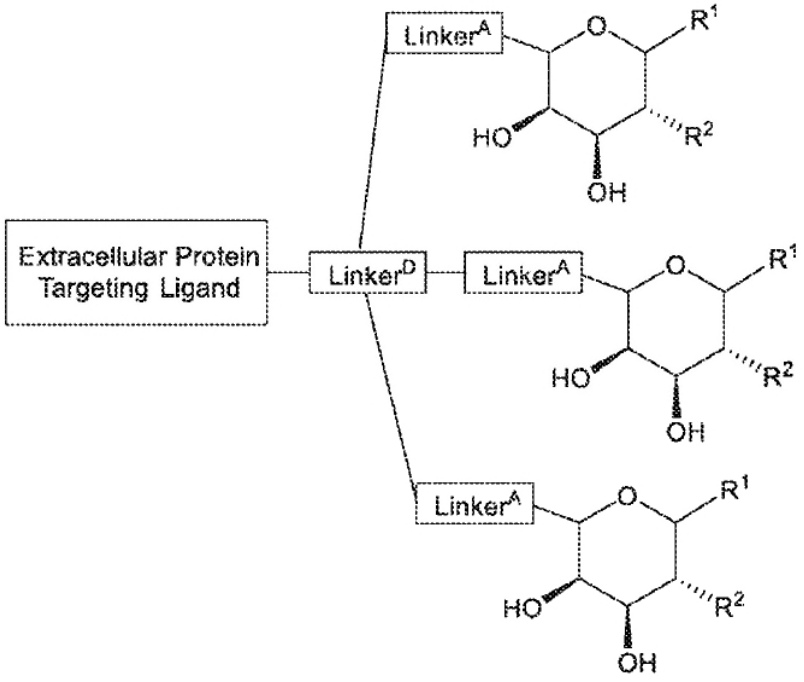
(III-d-Tri),



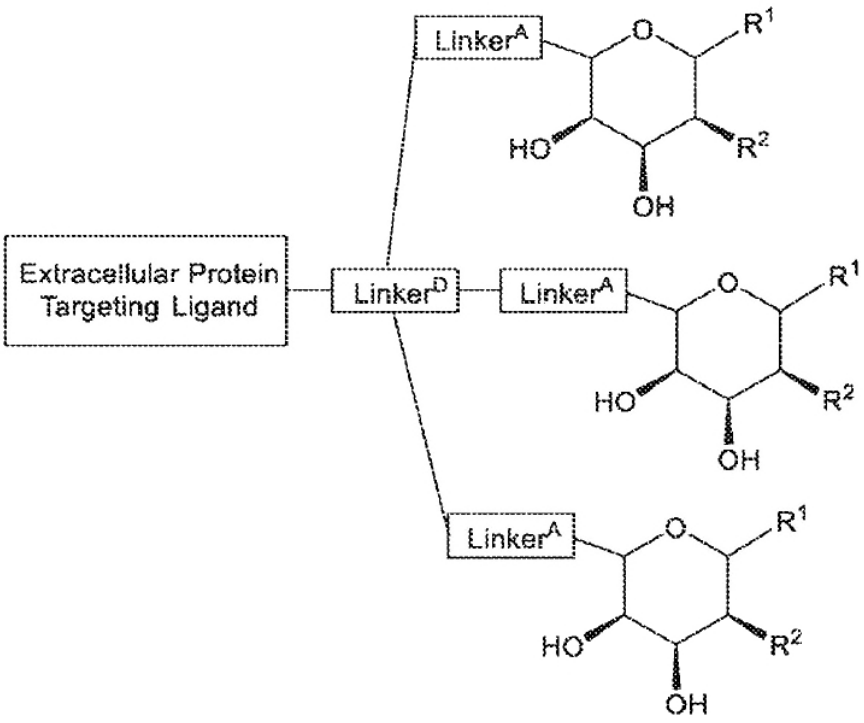
(IV-Tri),


X1
O
Linker^A
HO
R2
OH
X1
O
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
HO
R2
OH
X1
O
Linker^A
HO
R2
OH

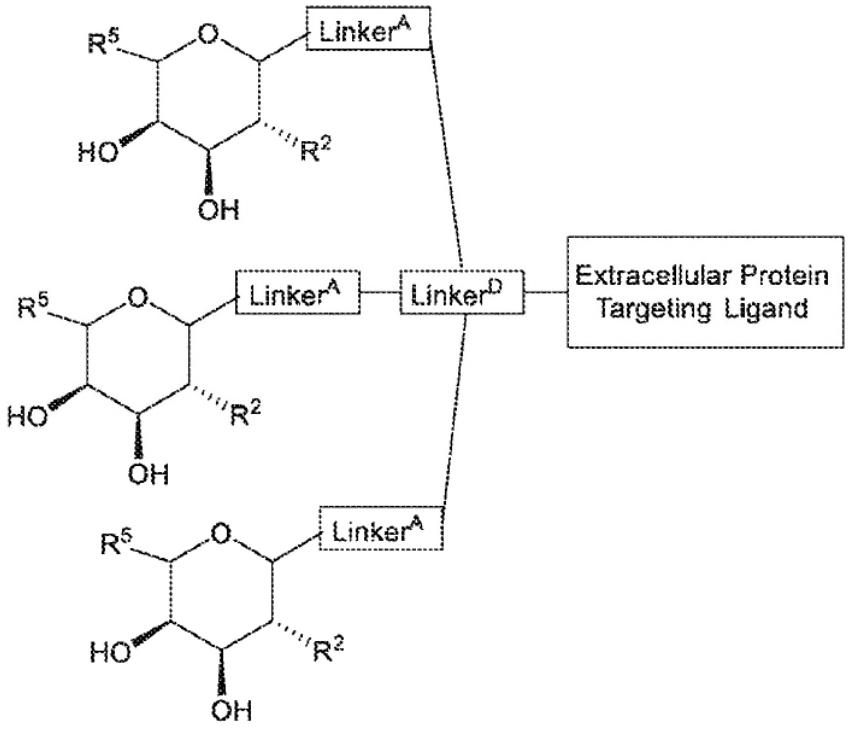
(IV-d-Tri),


Linker^A
O
R1
HO
R2
OH
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
O
R1
HO
R2
OH
Linker^A
O
R1
HO
R2
OH

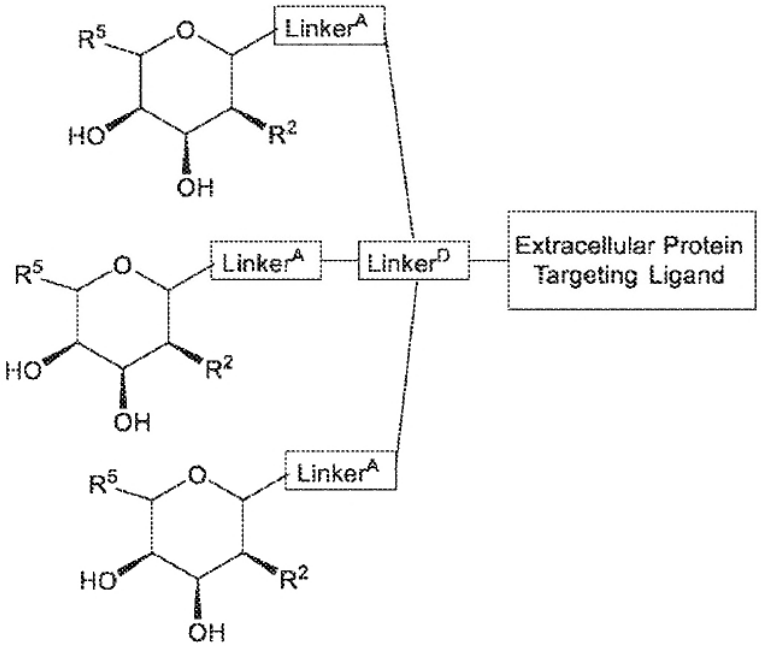
(V-Tri),


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

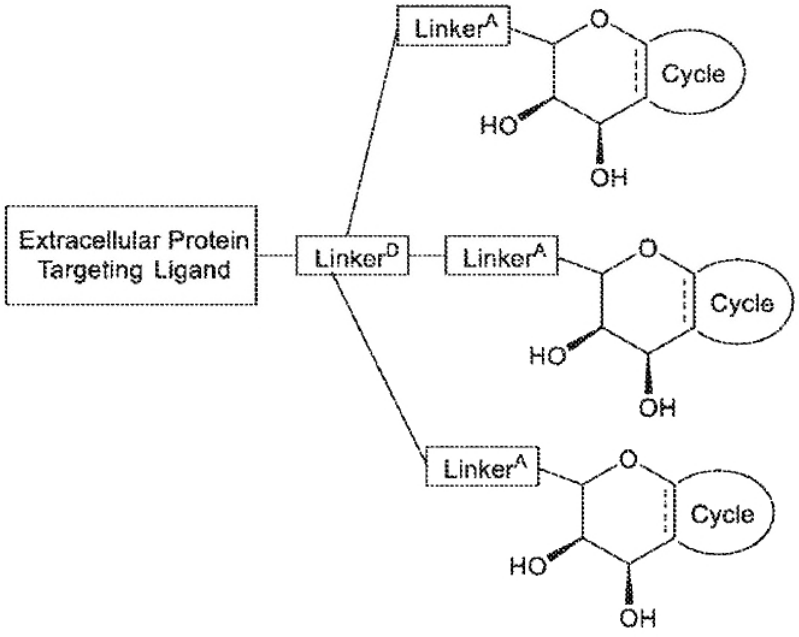
(V-d-Tri),


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

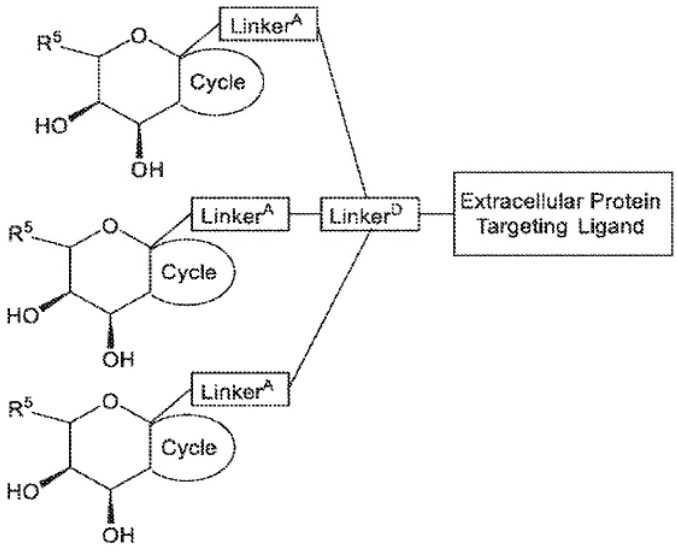
(VI-Tri),



(VI-d-Tri),



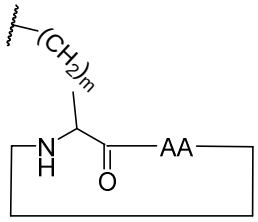
(VII-Tri), or



(VIII-Tri),

or a pharmaceutically acceptable salt thereof, wherein:

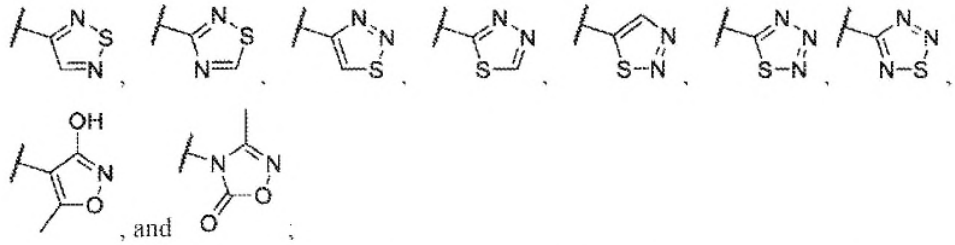
Extracellular Protein Targeting Ligand is an anti-b_1AR binding moiety L^B with the

structure ;

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) $-NR^8-S(O)-R^3$, $-NR^8-C(S)-R^3$, $-NR^8-S(O)(NR^6)-R^3$, $-N=S(O)(R^3)_2$, $-NR^8C(O)NR^9S(O)_2R^3$, $-NR^8-S(O)_2-R^{10}$, and $-NR^8-C(NR^6)-R^3$ each of which is optionally substituted with 1, 2, 3, or 4 substituents; and

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

R^{10} is selected from 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,

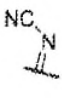
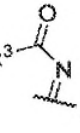
each $Linker^A$ is a bond or a moiety that covalently links the ASGPR ligand to $Linker^B$;

$Linker^B$ 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^D 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.

11. Use of the compound of any of claims 1-10 in the manufacture of a pharmaceutical composition for preventing, treating, and/or ameliorating heart failure in a subject, wherein the pharmaceutical composition comprises at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of any of claims 1-10, and wherein the pharmaceutical composition is to be administered to the subject.

12. The use of claim 11, wherein the heart failure is dilated cardiomyopathy (DCM).

13. The use of claim 11, wherein the pharmaceutical composition is to be administered by a route selected from the group consisting of oral, transdermal, transmucosal, (intra)nasal, (trans)rectal, intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical.

14. The use of claim 13, wherein the composition is to be administered intravenously.

15. The use of claim 11, wherein the composition is to be administered in a dose of 0.01 mg/kg to 20 mg/kg.

16. The use of claim 11, wherein the subject is a mammal.

17. The use of claim 16, wherein the subject is human.

18. The compound of any of claims 1-10 for use in therapy.