CLAIMS

What is claimed is:

1. A compound comprising formula (I), or a salt, geometric isomer, stereoisomer, or solvate thereof:

$$[\text{Protein binder}]_{k'}—[\text{CON}]_{h}—[\text{Linker}]_{i}—[\text{CON}]_{h'}—[\text{CRBM}]_{j'} \quad \text{(I)},$$

wherein:

the Protein binder is a molecule that binds to an extracellular protein;

the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface of a degrading cell in a subject, whereby binding of (I) leads to endocytosis and degradation of the extracellular protein;

each CON is independently a bond or a group that covalently links a Protein binder to an CRBM, a Protein binder to a Linker, and/or a Linker to a CRBM;

the Linker is a group having a valence ranging from 1 to 15;

k' is an integer ranging from 1 to 15;

h is an integer ranging from 0 to 15;

i is an integer ranging from 0 to 15;

h' is an integer ranging from 0 to 15;

j is an integer ranging from 1 to 15.

2. A compound comprising formula (II), or a salt, geometric isomer, stereoisomer, or solvate thereof:

$$[\text{TNF binder}]_{k'}—[\text{CON}]_{h}—[\text{Linker}]_{i}—[\text{CON}]_{h'}—[\text{CRBM}]_{j'} \quad \text{(II)},$$

wherein:

the TNF binder is a molecule that binds to TNF;

the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface of a degrading cell in a subject, whereby binding of (II) leads to endocytosis and degradation of TNF;

each CON is independently a bond or a group that covalently links a TNF binder to an CRBM, a TNF binder to a Linker, and/or a Linker to a CRBM;

the Linker is a group having a valence ranging from 1 to 15;

k' is an integer ranging from 1 to 15;

h is an integer ranging from 0 to 15;

i is an integer ranging from 0 to 15;

h’ is an integer ranging from 0 to 15;

j is an integer ranging from 1 to 15.

3. A compound comprising formula (III), or a salt, geometric isomer, stereoisomer, or solvate thereof:

$$[AATM]_{k'}—[CON]_{h}—[Linker]_{i}—[CON]_{h'}—[CRBM]_{j'} \text{ (III)},$$

wherein:

the AATM is a molecule that binds to an autoantibody;

the CRBM is a cellular receptor binding moiety that binds to at least one receptor on the surface of a degrading cell in a subject, whereby binding of (III) leads to endocytosis and degradation of the autoantibody;

each CON is independently a bond or a group that covalently links an AATM to an CRBM, an AATM to a Linker, and/or a Linker to a CRBM;

the Linker is a group having a valence ranging from 1 to 15;

k’ is an integer ranging from 1 to 15;

h is an integer ranging from 0 to 15;

i is an integer ranging from 0 to 15;

h’ is an integer ranging from 0 to 15;

j is an integer ranging from 1 to 15.

4. The compound of any one of claims 1-3, wherein the valence of the Linker is 1, 2, or 3.

5. The compound of any one of claims 1-3, wherein k’ is 1, 2, or 3.

6. The compound of any one of claims 1-3, wherein j is 1, 2, or 3.

7. The compound of any one of claims 1-3, wherein h is 1, 2, or 3.

8. The compound of any one of claims 1-3, wherein h’ is 1, 2, or 3.

9. The compound of any one of claims 1-3, wherein i is 1, 2, or 3.

10. The compound of any one of claims 1-3, wherein at least one of h, h’, and i is at least

1.

11. The compound of any one of claims 1-3, wherein k', j', h, h', and i are each independently 1, 2, or 3.

12. The compound of any one of claims 1-3, wherein k' is 1, and j' is 1, 2, or 3.

13. The compound of claim 1, which is:

[Protein binder]—$[CON]_{0-1}$—[Linker]—$[CON]_{0-1}$—[CRBM] (Ia).

14. The compound of claim 2, which is:

[TNF binder]—$[CON]_{0-1}$—[Linker]—$[CON]_{0-1}$—[CRBM] (IIa).

15. The compound of claim 3, which is:

[AATM]—$[CON]_{0-1}$—[Linker]—$[CON]_{0-1}$—[CRBM] (IIIa).

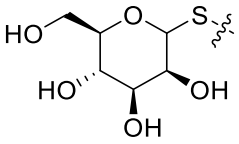
16. The compound of any one of claims 1-3, wherein the degrading cell comprises a hepatocyte.

17. The compound of any one of claims 1-3, wherein the CRBM is a folic acid (folate) receptor binder, mannose receptor binder, mannose-6-phosphate (M6P) receptor binder, low density lipoprotein receptor-related protein 1 (LRP1) receptor binder, low density lipoprotein receptor (LDLR) binder, FcγRI receptor binder, transferrin receptor binder, macrophage scavenger receptor binder, G-Protein coupled receptor binder, or asialoglycoprotein receptor (ASGPR) binder.

18. The compound of any one of claims 1-3, wherein the CRBM is:

(a) a folic acid (folate) receptor binder comprising at least one of folic acid, methotrexate, premetrexed, or a biologically active fragment thereof;

(b) a mannose receptor binder comprising at least one of: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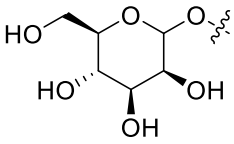
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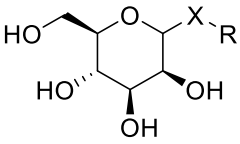
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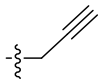
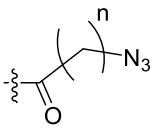
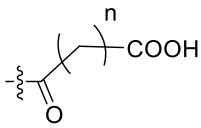
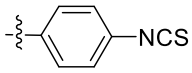
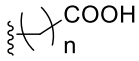
wherein: X is S or O, R is selected from the group consisting of: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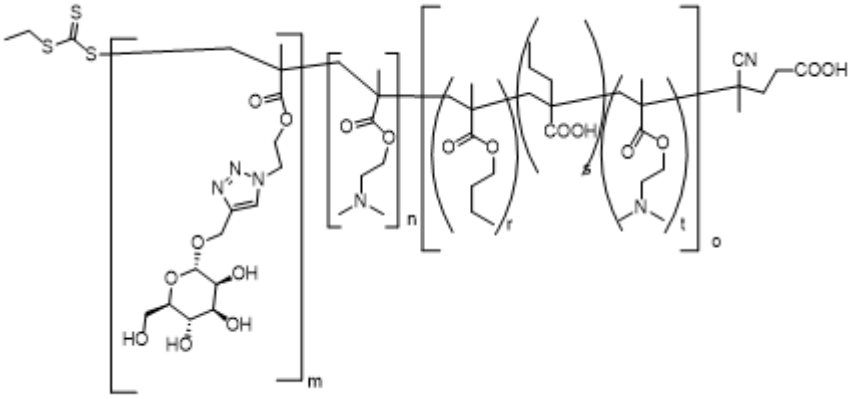
and each occurrence of 'n' is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; and

a polymeric molecule selected from the group consisting of: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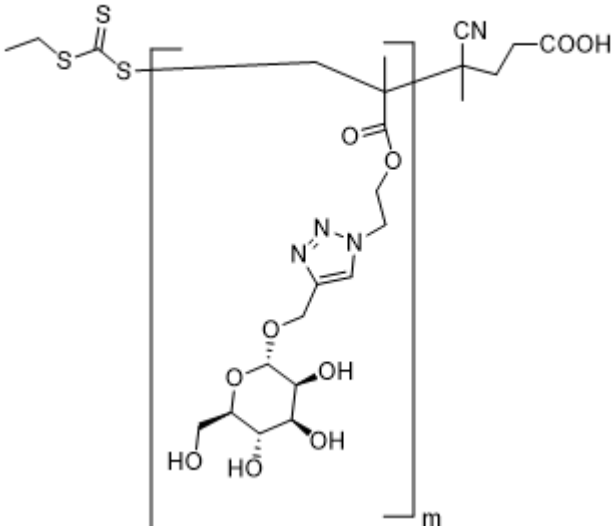
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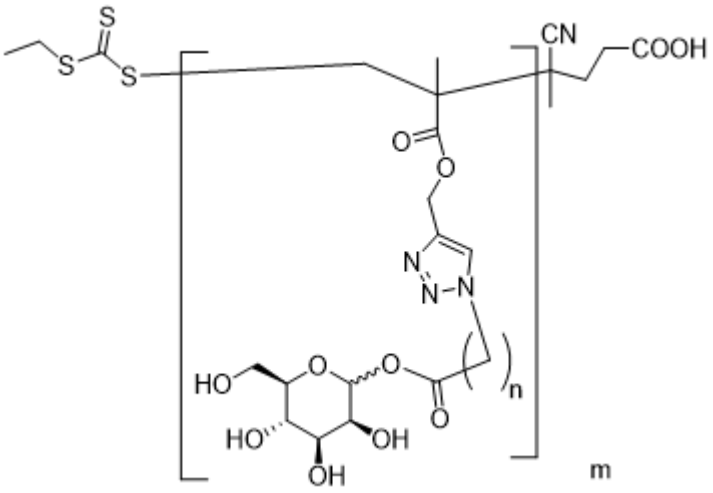
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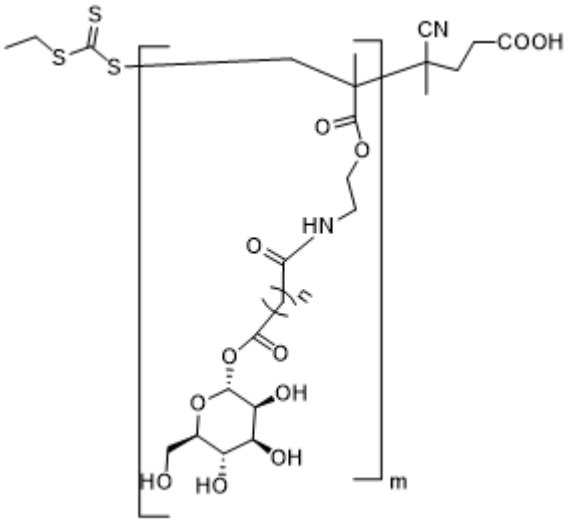
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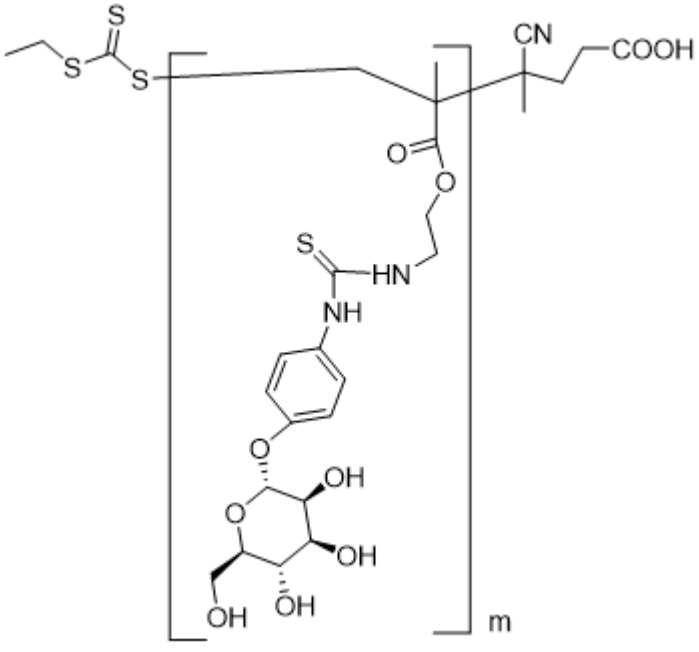
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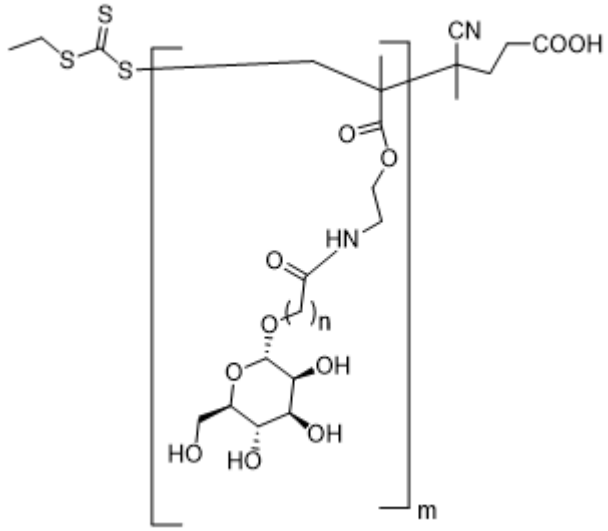

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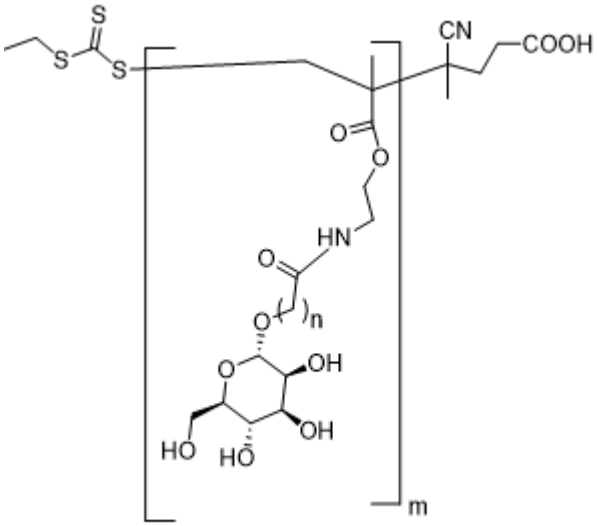
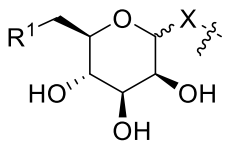


, wherein

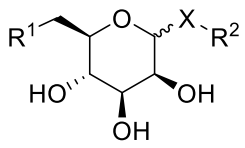
m is an integer from 1 to 100,

r, s, t, and o are each independently an integer from 0 to 100, and the COOH in the polymeric molecule is derivatized with the Protein binder, the TNF binder, or the AATM;

(c) a mannose-6-phosphate (M6P) receptor binder comprising at least one of:

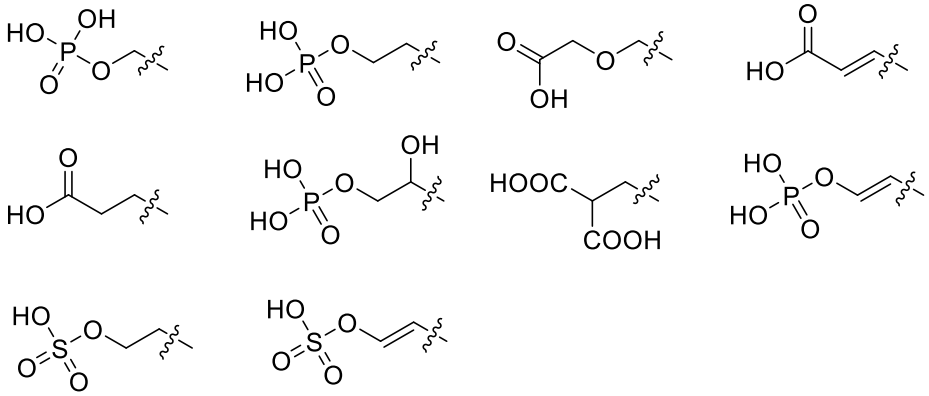


and



,

wherein X is O or S, R^1 is selected from the group consisting of:



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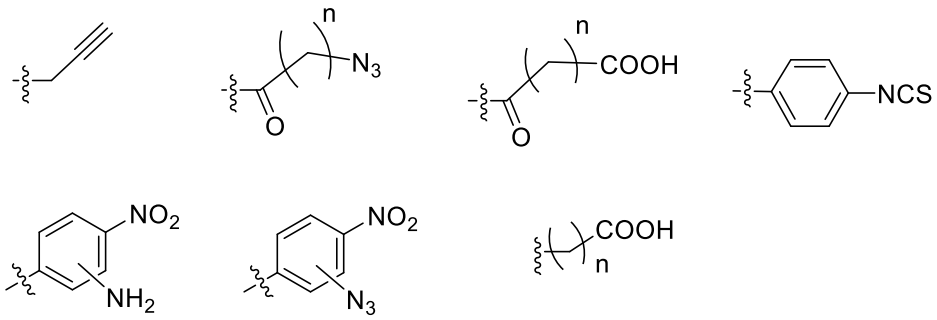
R^2 is selected from the group consisting of:



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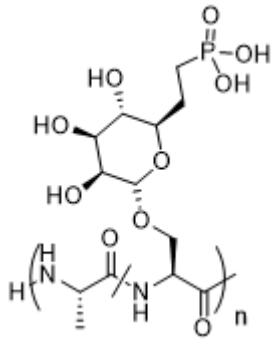
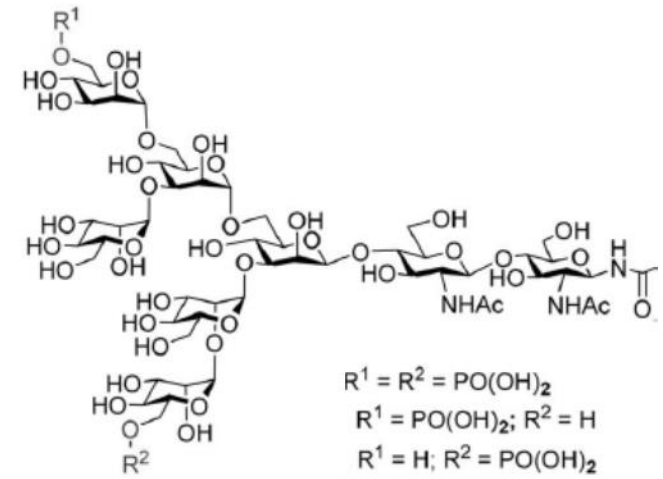
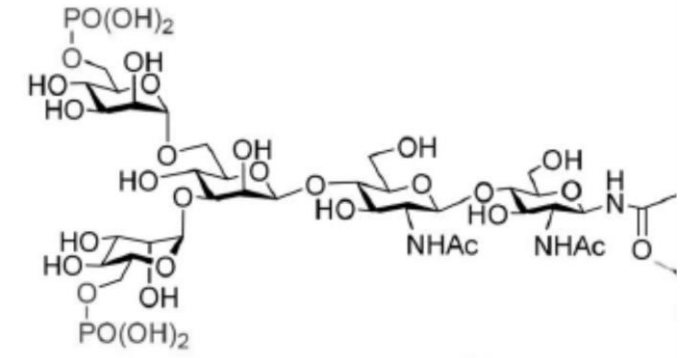
and each occurrence of 'n' is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

a polymeric molecule  , wherein n is an integer from 1 to 100;

a compound selected from:





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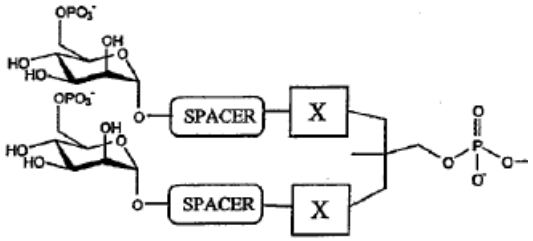
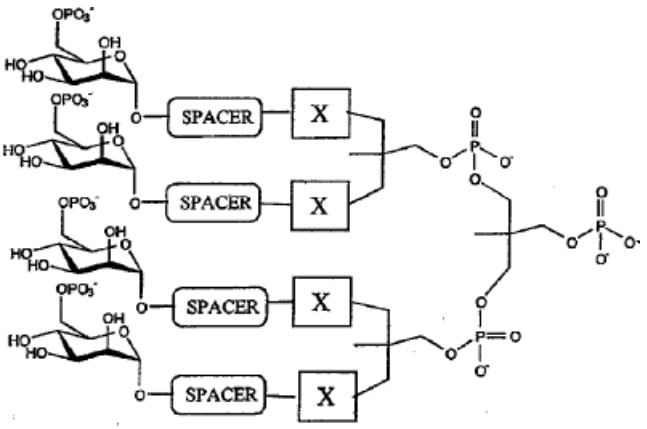
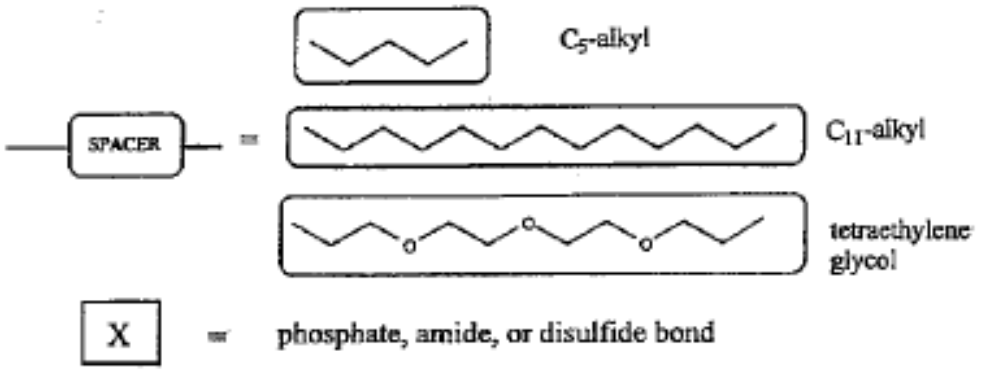
a compound selected from:







;

(d) a low density lipoprotein receptor-related protein 1 (LRP1) receptor binder comprising at least one amino acid sequence of SEQ ID NOs:1-9;

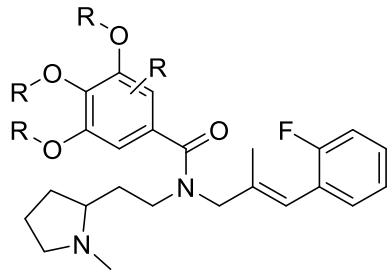
(e) a low density lipoprotein receptor (LDLR) binder comprising at least one amino acid sequence of SEQ ID NOs:10-35;

(f) a FcγRI receptor binder comprising at least one amino acid sequence of SEQ ID NOs:36-52;

(g) a transferrin receptor binder comprising at least one amino acid sequence of SEQ ID NOs:53-59 and 74;

(h) a macrophage scavenger receptor binder comprising at least one amino acid sequence of SEQ ID NOs:60-65;

(i) a G-protein coupled receptor binder comprising at least one of:



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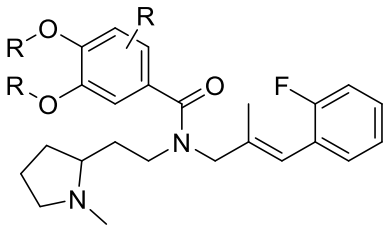
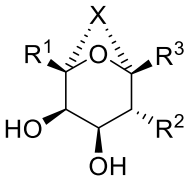


,

wherein each occurrence of R is independently H or C_1-C_6 alkyl;

(j) an asialoglycoprotein receptor (ASGPR) binder comprising:



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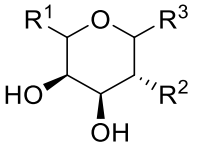


,

wherein:

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

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

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

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

wherein each occurrence of R^{N1} is independently H or C_1-C_3 alkyl optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxyl groups;

R^1 and R^3 are each independently H, -$(CH_2)_K$OH, -$(CH_2)_K$O(C_1-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, C_1-C_4 alkyl optionally substituted with 1-3 independently selected halogens, -$(CH_2)_K$(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) optionally substituted with 1-3 independently selected halogens, -OC(=O)(C_1-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, or -C(=O)(C_1-C_4 alkyl) optionally substituted with 1-3 independently selected halogens; or

R^1 and R^3 are each independently Ph$(CH_2)_K$-, which is optionally substituted with: 1-3 independently selected halogens; C_1-C_4 alkyl optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxyl groups; or C_1-C_4 alkoxy optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxyl groups; or

R^1 and R^3 are each independently a group of structure:

-O-$(CH_2)_K$'-CH(OH)-(CH_2)K'-R^7,

wherein:

R^7 is: C_1-C_4 alkoxy optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxy groups; -$NR^{N3}R^{N4}$; or -$(CH_2)_K$'-O-$(CH_2)_K$-CH_2-CH=CH_2;

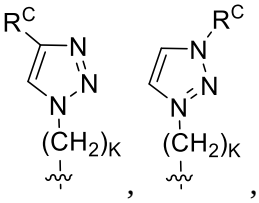
K is 0, 1, 2, 3, or 4;

K' is 1, 2, 3, or 4;

each occurrence of R^{N3} is independently H or C_1-C_3 alkyl optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxyl groups;

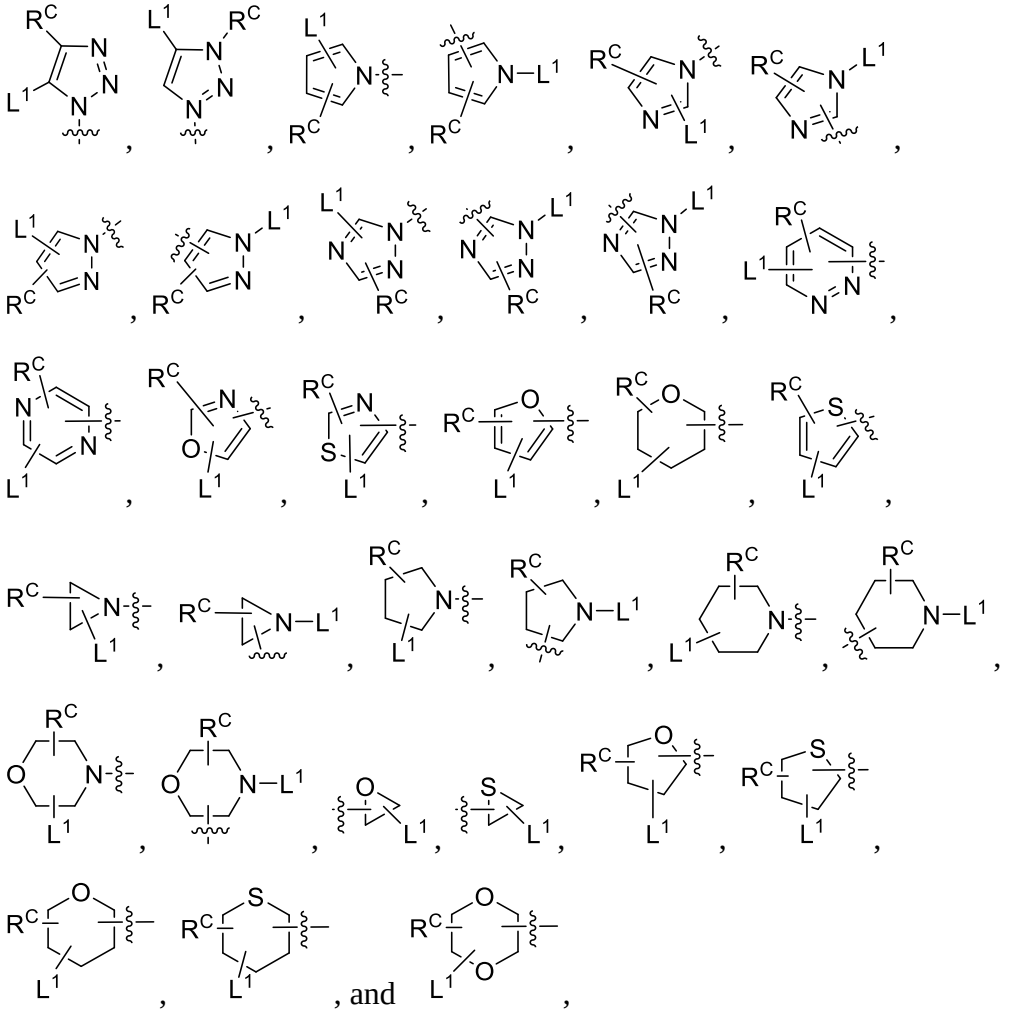
each occurrence of R^{N4} is independently H, C_1-C_3 alkyl optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxyl groups, or Ph-$(CH_2)_K$-; or

R^1 and R^3 are each independently selected from the group consisting of:



-$(CH_2)_K$OH, , , -≡-, L^1-$(CH_2)_K$-, and CYC-$(CH_2)_K$-,

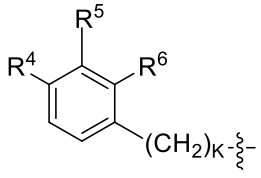
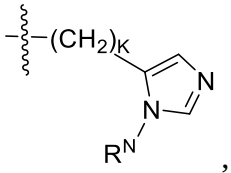
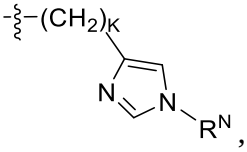
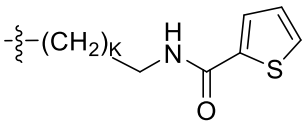
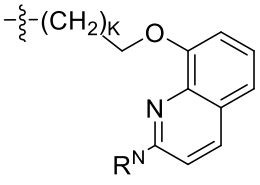
wherein CYC is selected from the group consisting of:



wherein:

the bond marked with ~~~ indicating the site on CYC whereto -$(CH_2)_K$ is connected;

L^1 is a bond, -Linker, -CON-Linker, or -CON-Linker-CON;

R^C is absent, H, C_1-C_4 alkyl optionally substituted with 1-3 optionally substituted halogens and/or 1-2 hydroxyl groups, or a group of structure:  ,  ,  ,  , or  ,

wherein:

R^4, R^5, and R^6 are each independently H, F, Cl, Br, I, CN, $NR^{N1}R^{N2}$, -$(CH_2)_K$OH, -$(CH_2)_K$O(C_1-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, C_1-C_3 alkyl optionally substituted with 1-3 independently selected halogens, C_1-C_3-alkoxy optionally substituted with 1-3 independently selected halogens, -$(CH_2)_K$COOH, -$(CH_2)_K$C(=O)O-(C_1-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, O-C(=O)-(C_1-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, or -C(=O)-(C_1-C_4 alkyl) optionally substituted with 1-3 independently selected halogens;

each occurrence of R^N is independently H or C_1-C_3 alkyl optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxyl groups;

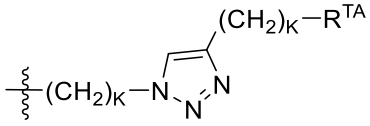
each occurrence of R^{N2} is independently H or C_1-C_3 alkyl optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxyl groups;

or

R^1 and R^3 are each independently (C_3-C_8 saturated carbocyclic)-$(CH_2)_K$-, wherein the carbocyclic is further substituted with -L^1 and -R^C;

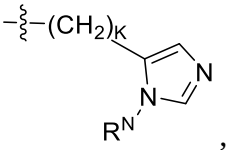
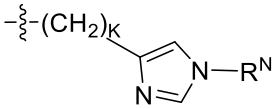
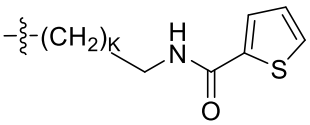
R^2 is $-(CH_2)_K-N(R^{N1})-C(=O)R^{AM}$, wherein:

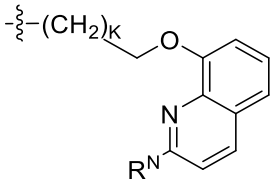
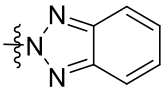
R^{AM} is H, C_1-C_4 alkyl optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxyl groups, $-(CH_2)_KCOOH$, $-(CH_2)_KC(=O)O(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, $-OC(=O)(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, $-C(=O)(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, or $-(CH_2)_K-NR^{N3}R^{N4}$; or

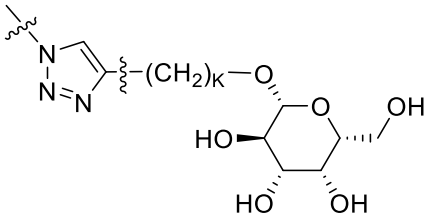
R^2 is  , wherein:

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 independently selected halogens, C_1-C_4 alkyl optionally substituted with 1-3 independently selected halogens, $-(CH_2)_KCOOH$, $-(CH_2)_KC(=O)O(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, $-OC(=O)(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, or $-C(=O)(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, or

R^{TA} is C_3-C_{10} aryl or a 3- to 10-membered heteroaryl group containing 1-5 non-carbon ring atoms, each of the aryl or heteroaryl groups being optionally substituted with 1-3 groups independently selected from CN, $NR^{N1}R^{N2}$, $-(CH_2)_KOH$, $-(CH_2)_KO(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, C_1-C_3 alkyl optionally substituted with 1-3 independently selected halogens and/or 1-2 hydroxyl groups, $-(C_1$-C_3-alkoxy) optionally substituted from 1-3 independently selected halogens, $-(CH_2)_KCOOH$, $-(CH_2)_KC(=O)O-(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, $-OC(=O)(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, or $-(CH_2)_KC(=O)-(C_1$-C_4 alkyl) optionally substituted with 1-3 independently selected halogens, or

R^{TA} is  ,  ,  ,


, or  optionally substituted with 1-3 C_1-C_3 alkyl groups optionally substituted with 1-3 independently selected halogens, or

R^{TA} is  , wherein each $-(CH_2)_K$ group is optionally substituted with 1-4 C_1-C_3 alkyl groups optionally substituted with 1-3 fluoro groups or 1-2 hydroxyl groups.

19. The compound of claim 18, wherein:

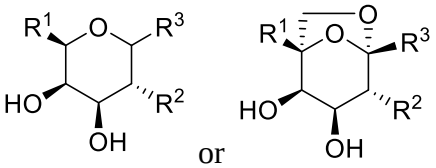
the X in ASGPRBM is -O-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-O-, -S-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-S-, -N(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-N(R^{N1})-, or -C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, when X is 2 atoms in length;

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

the X in ASGPRBM is -O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -O-C(R^{N1})(R^{N1})-O-C(R^{N1})(R^{N1})-, -S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, -C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, -S-C(R^{N1})(R^{N1})-S-C(R^{N1})(R^{N1})-, -N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})- C(R^{N1})(R^{N1})-, or -C(R^{N1})(R^{N1})-N(R^{N1})-C(R^{N1})(R^{N1})-C(R^{N1})(R^{N1})-, when X is 4 atoms in length.

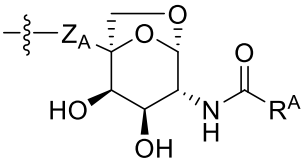
20. The compound of claim 18, wherein X is OCH_2 and R^{N1} is H, or wherein X is CH_2O and R^{N1} is H.

21. The compound of claim 18, wherein the ASGPRBM comprises the structure:



.

22. The compound of claim 18, wherein the ASGPRBM group comprises:



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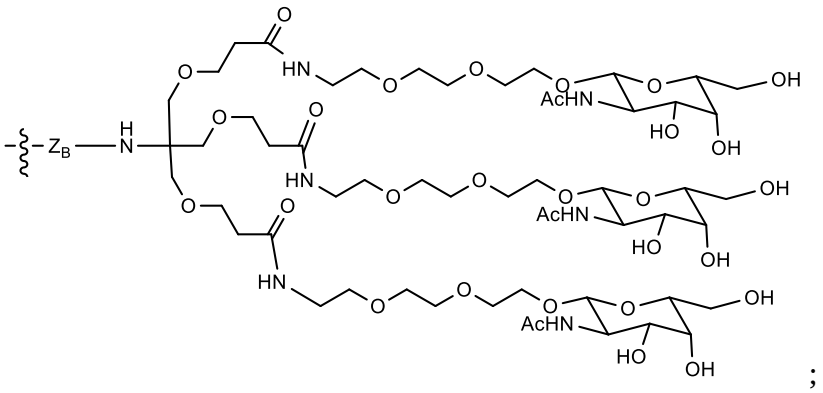


;

wherein:

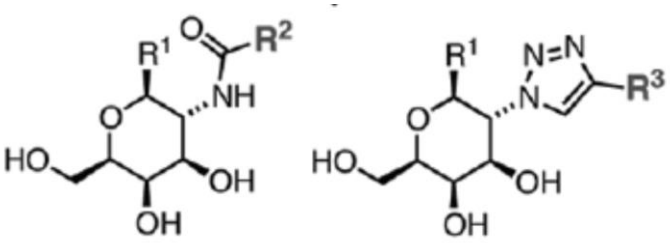
R^A is C_1-C_3 alkyl optionally substituted with 1-5 independently selected halogens;

Z_A is -$(CH_2)_{IM}$-, -O-$(CH_2)_{IM}$-, -S-$(CH_2)_{IM}$-, -NR^M-$(CH_2)_{IM}$-, -C(=O)-$(CH_2)_{IM}$-, a PEG group containing from 1 to 8 ethylene glycol residues, or -C(O)$(CH_2)_{IM}NR^M$-;

Z_B is absent, -$(CH_2)_{IM}$-, -C(=O)-$(CH_2)_{IM}$-, or -C(=O)$(CH_2)_{IM}$-NR^M-;

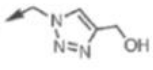
R^M is H or C_1-C_3 alkyl optionally substituted with 1-2 hydroxyl groups; and

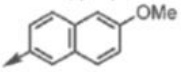
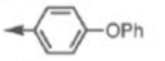
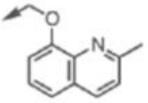
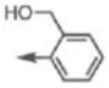
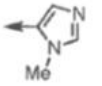
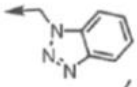
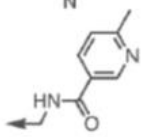
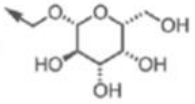
each occurrence of IM is independently 0, 1, 2, 3, 4, 5, or 6;

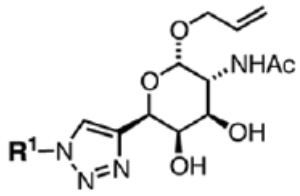


3 **4**

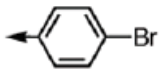
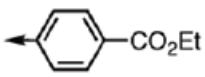
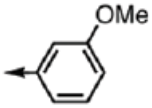
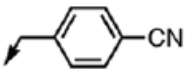
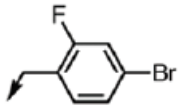
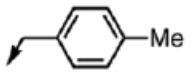
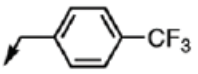
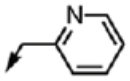
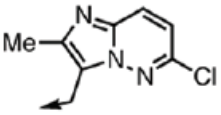
	R¹
a	Me
b	4-OMePh

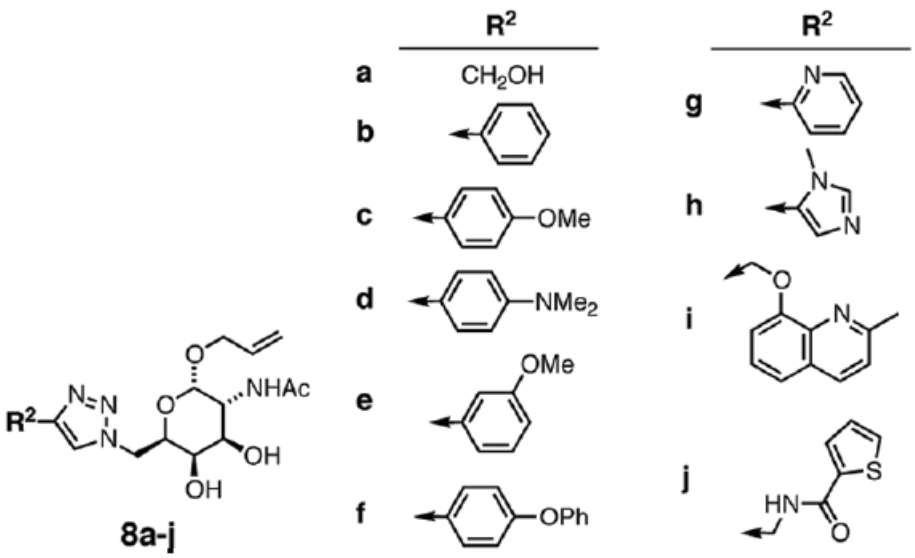
#	R²
1	Me
2	*n*-C_3H_7
3	*i*-Pr
4	*t*-Bu
5	CCl_3
6	CF_3
7	O*t*-Bu
8	CH_2CO_2H
9	CH_2NH_2
10	CH_2CF_3
11	2-furyl
12	Ph
13	4-OMePh
14	3-OMePh
15	4-CNPh
16	3-pyridyl
17	

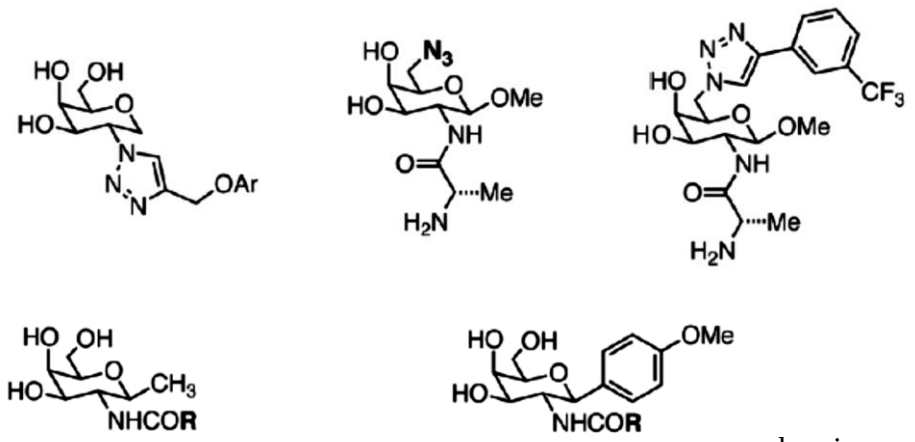
#	R³
1	Ph
2	4-OMePh
3	3-OMePh
4	3-NH_2Ph
5	4-NMe_2Ph
6	2-pyridyl
7	
8	
9	
10	
11	
12	
13	
14	
15	CH_2OH
16	CH_2NH_2
17	CH_2NHMe
18	CH_2NMe_2
19	CO_2H
20	$CH_2NHCOPh$
21	$CH_2NHCOMe$



6a-j

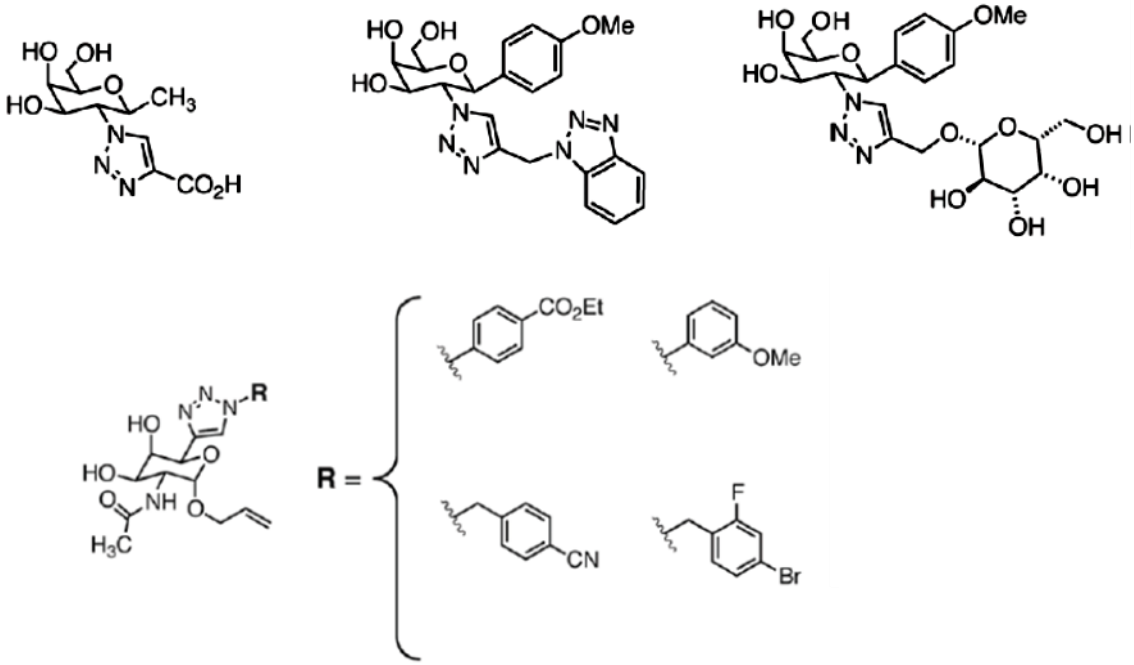
	R¹
a	Me
b	
c	
d	
e	
f	
g	
h	
i	
j	



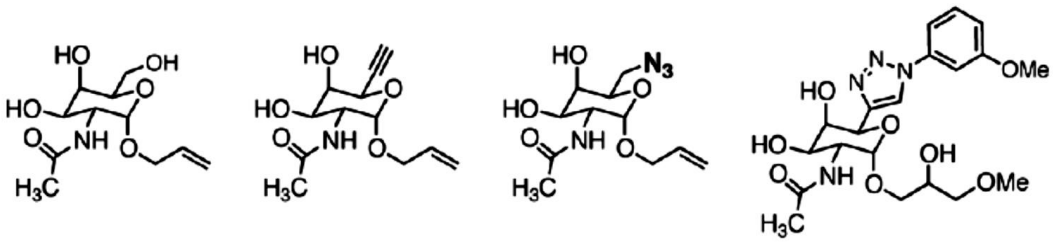


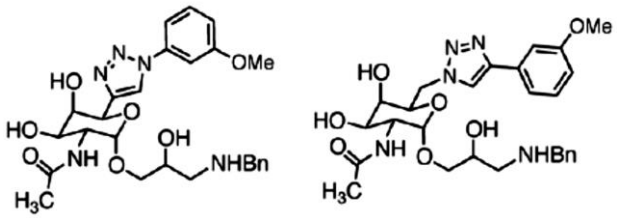
wherein

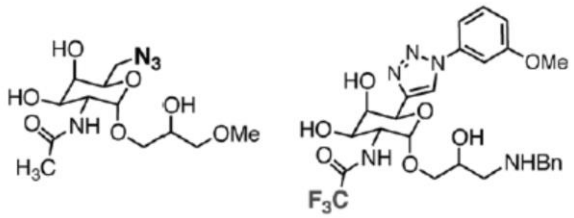
R = CH_3, CF_3, or CH_2CF_3;











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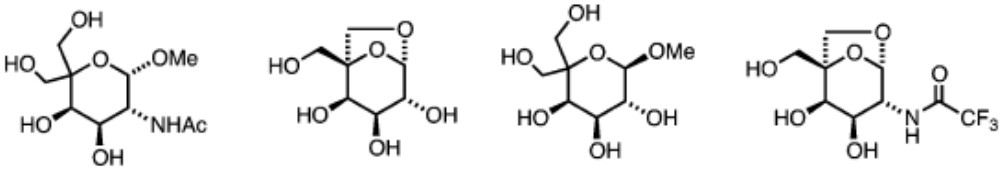
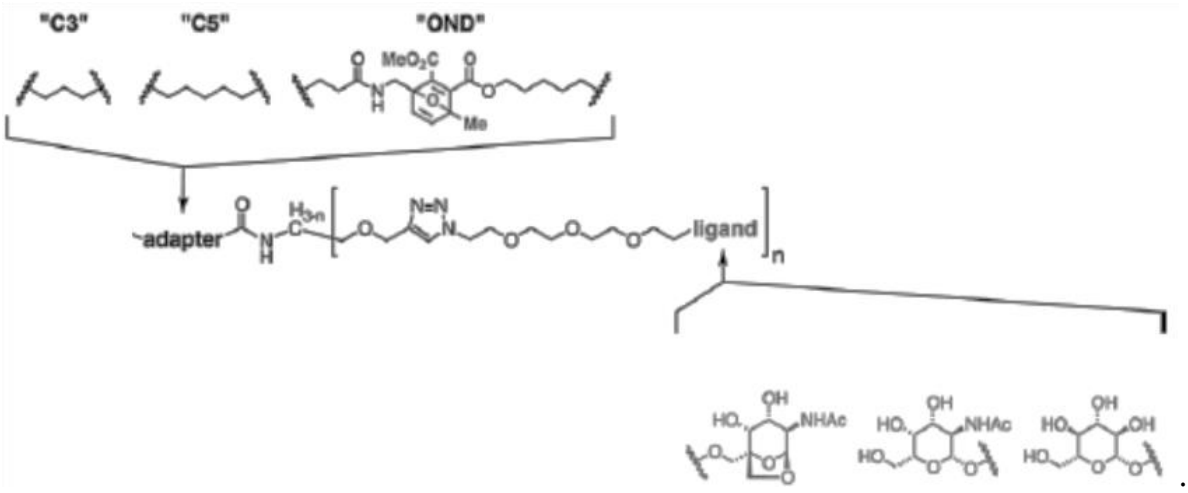


	R
16a	Et
16b	*n*-C_3H_7
16c	*n*-C_4H_9
16d	*n*-C_5H_{11}
16e	*n*-C_6H_{13}
16f	$(CH_2CH_2O)_4Me$

, or



23. The compound of any one of claims 1-3, wherein the Linker is a polyethylene glycol containing linker having 1-12 ethylene glycol residues.

24. The compound of any one of claims 1-3,

wherein the Linker comprises the structure:

$-CH_2CH_2(OCH_2CH_2)_mOCH_2-$, $-(CH_2)_mCH_2-$, $-[N(R^a)-CH(R^b)(C=O)]_m-$,

or a polypropylene glycol or polypropylene-co-polyethylene glycol group containing 1-100 alkylene glycol units;

wherein each R^a is independently H, C_1-C_3 alkyl, or C_1-C_6 alkanol, or combines with R^b to form a pyrrolidine or hydroxypyrroline group;

wherein each R^b is independently selected from the group consisting of hydrogen, methyl, isopropyl, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-(CH_2)_3$-guanidine, $-CH_2C(=O)NH_2$, $-CH_2C(=O)OH$, $-CH_2SH$, $-(CH_2)_2C(=O)NH_2$, $-(CH_2)_2C(=O)OH$, $-(CH_2)$imidazole, $-(CH_2)_4NH_2$, $-CH_2CH_2SCH_3$, benzyl, $-CH_2OH$, $-CH(OH)CH_3$, $-(CH_2)$imidazole, or $-(CH_2)$phenol; and

wherein m is an integer ranging from 1 to 15; or

wherein the Linker comprises the structure

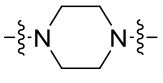
$-[N(R'-(CH_2)_{1\text{-}15}-C(=O)]-$,

wherein R' is H or a C_1-C_3 alkyl optionally substituted with 1-2 hydroxyl groups, and m is an integer ranging from 1 to 100; or

wherein the Linker comprises the structure:

-Z-D-Z'-,

wherein:

Z and Z' are each independently a bond, -$(CH_2)_i$-O-, -$(CH_2)_i$-S-, -$(CH_2)_i$-N(R)-,  , -$(CH_2)_i$-$C(R^2)$=$C(R^2)$- (cis or trans), -$(CH_2)_i$-≡-, or -Y-C(=O)-Y-;

each R is independently H, C_1-C_3 alkyl, or C_1-C_6 alkanol;

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

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

each i is independently 0 to 100;

D is a bond, -$(CH_2)_i$-Y-C(=O)-Y-$(CH_2)_i$-, -$(CH_2)_{m'}$-, or -[$(CH_2)_n$-X_1)]$_j$-, with the proviso that Z, Z', and D are not each simultaneously bonds;

X^1 is O, S, or N(R);

j is an integer ranging from 1 to 100;

m' is an integer ranging from 1 to 100;

n is an integer ranging from 1 to 100; or

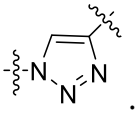
wherein the Linker comprises the structure:

-CH_2-$(OCH_2CH_2)_n$-CH_2-, -$(CH_2CH_2O)_{n'}CH_2CH_2$-, or -$(CH_2CH_2CH_2O)_n$-,

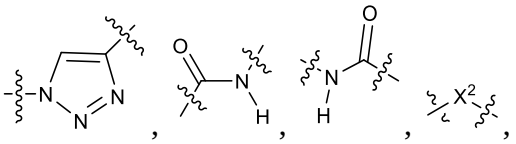
wherein each n and n' is independently an integer ranging from 1 to 25; or

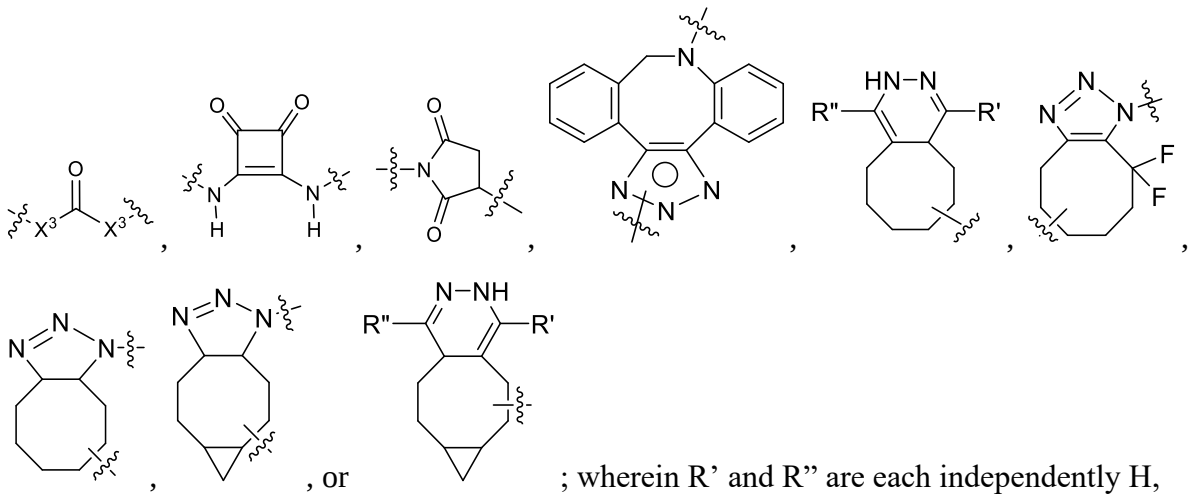
wherein the Linker comprises a structure:

-PEG-CON-PEG-

wherein each PEG is independently a polyethylene glycol group containing from 1-12 ethylene glycol residues and CON is a triazole group  .

25. The compound of any one of claims 1-3,

wherein the CON comprises a structure:  ,



; wherein R’ and R” are each independently H, methyl, or a bond; or

wherein the CON comprises a structure:

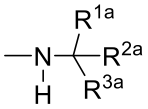
$-C(=O)-N(R^1)-(CH_2)_{n"}-N(R^1)C(=O)-$,

$-N(R^1)-C(=O)(CH_2)_{n"}-C(=O)N(R^1)-$, or

$-N(R^1)-C(=O)(CH_2)_{n"}-N(R^1)C(=O)-$;

wherein each R^1 is independently H or C_1-C_3 alkyl, and n” is independently an integer from 0 to 8, in certain embodiments 1 to 7, in certain embodiments 1, 2, 3, 4, 5 or 6; or

wherein the CON comprises a structure:



wherein:

R^{1a}, R^{2a} and R^{3a} are each independently H, $-(CH_2)_{M1}-$, $-(CH_2)_{M2}C(=O)_{M3}(NR^4)_{M3}-(CH_2)_{M2}-$, $-(CH_2)_{M2}(NR^4)_{M3}C(O)_{M3}-(CH_2)_{M2}-$, or $-(CH_2)_{M2}O-(CH_2)_{M1}-C(O)NR^4-$, with the proviso that R^{1a}, R^{2a} and R^{3a} are not simultaneously H;

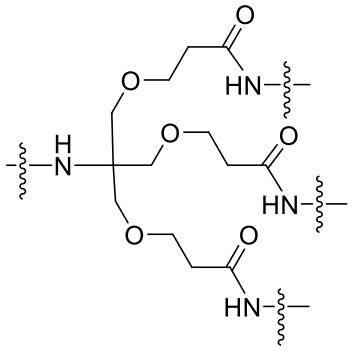
each M1 is independently 1, 2, 3, or 4;

each M2 is independently 0, 1, 2, 3, or 4;

each M3 is independently 0 or 1; and

each R^4 is independently H, C_1-C_3 alkyl, C_1-C_6 alkanol, or $-C(=O)(C_1$-C_3 alkyl), with the proviso that M2, and M3 within the same R^{1a}, R^{2a} and R^{3a} cannot all be simultaneously 0; or

wherein the CON comprises a structure:



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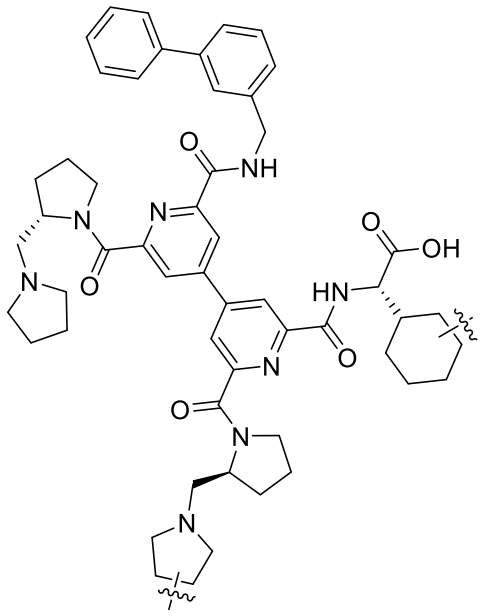
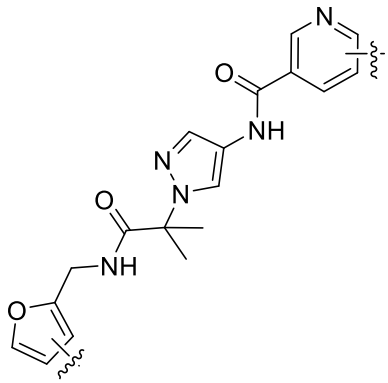
26. The compound of claim 1,

wherein the Protein binder that binds to CD40L comprises:



;

wherein the Protein binder that binds to PCSK9 comprises:



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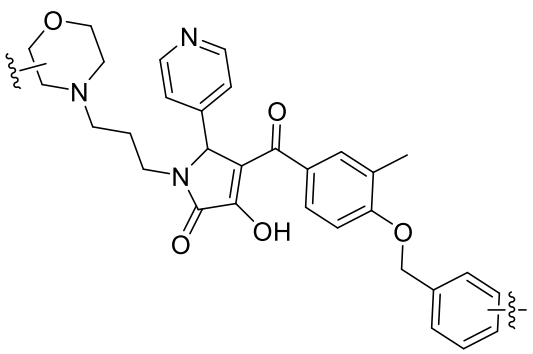
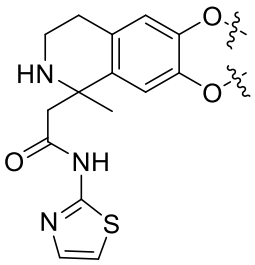


,

〰 NH-TVFTSWEEYLDWV-X (SEQ ID NO:66), wherein X = OH or NH_2;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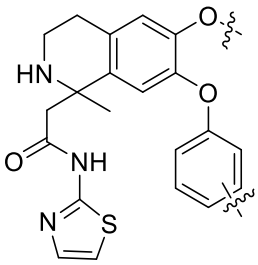
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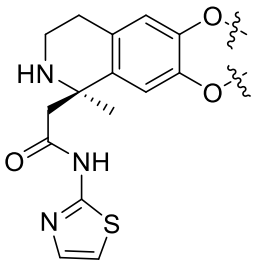
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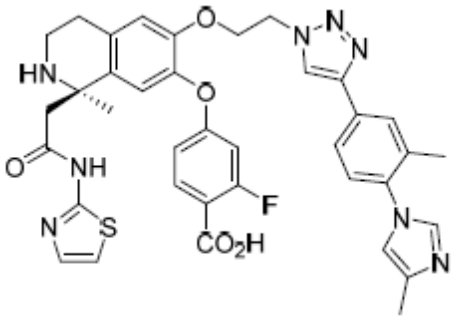
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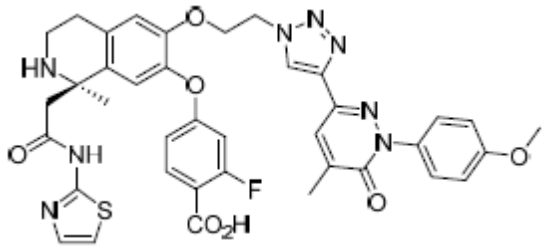
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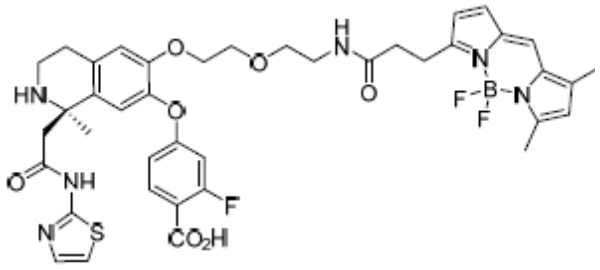
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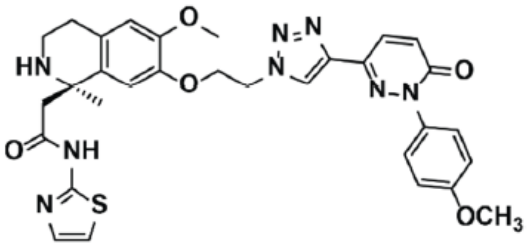
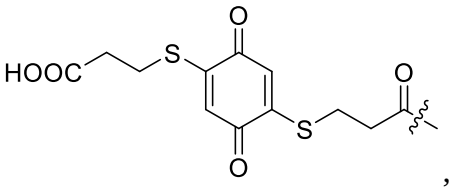

;

wherein the Protein binder that binds to VEGF comprises:

〰 NH-VEPNCDIHVMWEWECFERL-X (SEQ ID NO:67), wherein X = OH or NH_2,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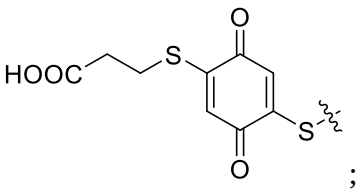
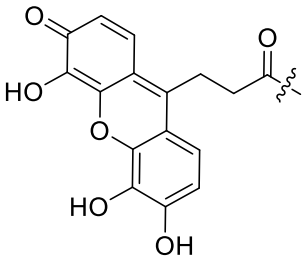

;

wherein the Protein binder that binds to TGF-beta comprises:

〰 NH-KRFKQDGGC-X (SEQ ID NO:68), wherein X = OH or NH_2;



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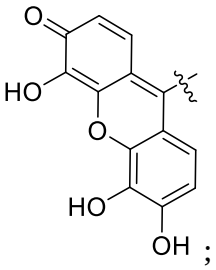
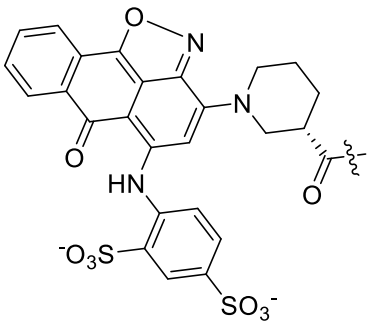


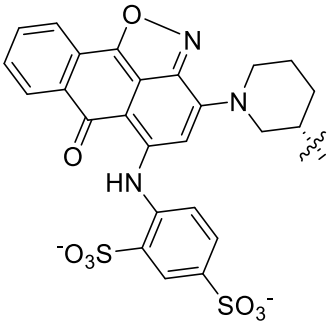
;

wherein the Protein binder that binds to TSP-1 comprises:

NH-RGQILSKLRL-X (SEQ ID NO:69), wherein X = OH or NH_2;

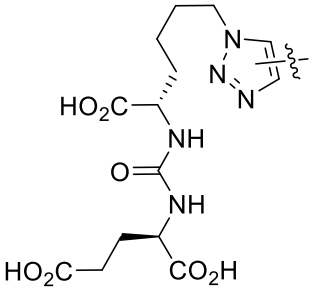
wherein the Protein binder that binds to soluble uPAR comprises:



or


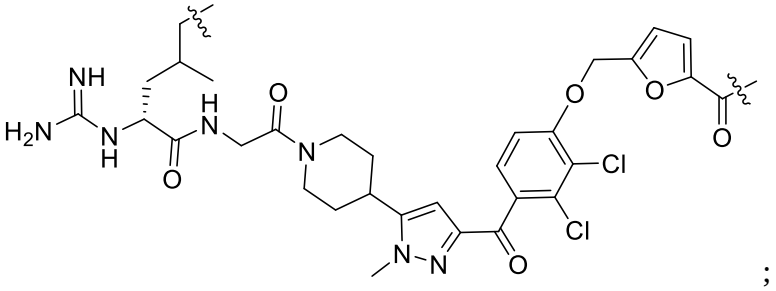
;

wherein the Protein binder that binds to soluble PSMA comprises:



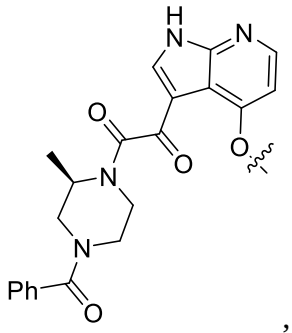
;

wherein the Protein binder that binds to IL-2 comprises:



;

wherein the Protein binder that binds to GP120 comprises: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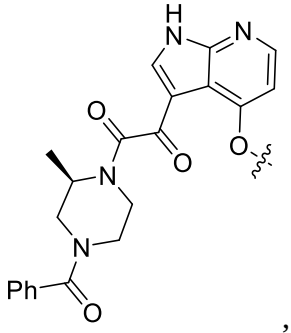
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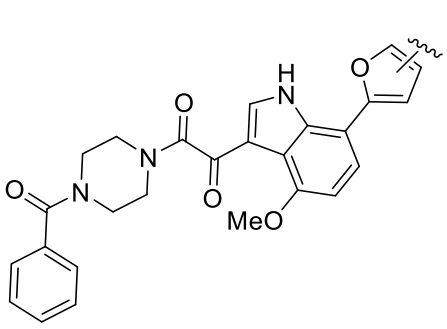
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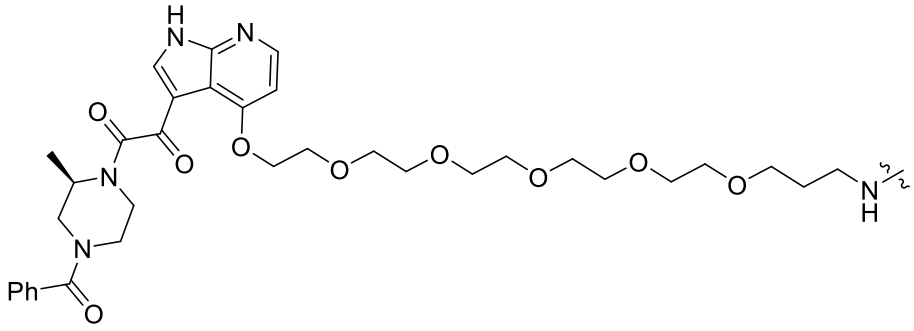
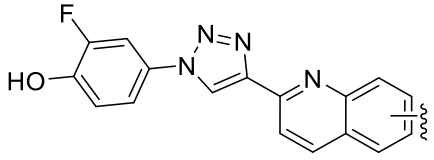

;

wherein the Protein binder that binds to MIF comprises: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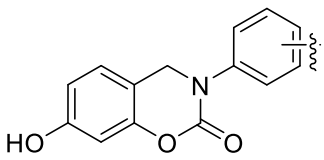
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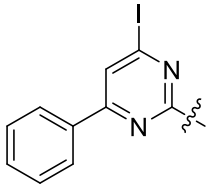
;

wherein the Protein binder that binds to IgA comprises:

STFCLLGQKDQSYCFTI SEQ ID NO:70),

HMRCLHYKGRRVCFLL (SEQ ID NO:71),

KTMCLRYNHDKVCFRI (SEQ ID NO:72),

LVLCLVHRTSKHRKCFVI (SEQ ID NO:73),

A2-3a: SDVCLRYRGRPVCFQV (SEQ ID NO:75),

Opt-1: HMVCLAYRGRPVCFAL (SEQ ID NO:76),

Opt-2: HMVCLSYRGRPVCFSL (SEQ ID NO:77),

Opt-3: HQVCLSYRGRPVCFST (SEQ ID NO:78),

RDVCLRYRGRPVCFQV (SEQ ID NO:79),

HDVCLRYRGRPVCFQV (SEQ ID NO:80),

ADVCLRYRGRPVCFQV (SEQ ID NO:81),

SAVCLRYRGRPVCFQV (SEQ ID NO:82),

SMVCLRYRGRPVCFQV (SEQ ID NO:83),

SDRCLRYRGRPVCFQV (SEQ ID NO:84),
SDACLRYRGRPVCFQV (SEQ ID NO:85),
SDVCARYRGRPVCFQV (SEQ ID NO:86),
SDVCLNYRGRPVCFQV (SEQ ID NO:87),
SDVCLHYRGRPVCFQV (SEQ ID NO:88),
SDVCLAYRGRPVCFQV (SEQ ID NO:89),
SDVCLRARGRPVCFQV (SEQ ID NO:90),
SDVCLRYAGRPVCFQV (SEQ ID NO:91),
SDVCLRYRARPVCFQV (SEQ ID NO:92),
SDVCLRYRGSPVCFQV (SEQ ID NO:93),
SDVCLRYRGAPVCFQV (SEQ ID NO:94),
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SDVCLRYRGRPVCFAV (SEQ ID NO:102),
SDVCLRYRGRPVCFQW (SEQ ID NO:103),
SDVCLRYRGRPVCFQL (SEQ ID NO:104),
SDVCLRYRGRPVCFQA (SEQ ID NO:105),
GRYQCQYRIGHYRFRYSD (SEQ ID NO:106),
GRYQAQYRIGHYRFRYSD (SEQ ID NO:107),
GRYQCQYRIGHYRFRYSD (SEQ ID NO:108),
CLIPS-CHYRFRC (SEQ ID NO:109),
CLIPS-CRIGHYRFRC (SEQ ID NO:110),
CLIPS-YQACHYRFRC (SEQ ID NO:111),
CLIPS-RYQAQCRIGHYRFC (SEQ ID NO:112),
CLIPS-GRYQCQYRIGHYRFRYCD (SEQ ID NO:113),
CLIPS-GRYQACYRIGHYRFRCSD (SEQ ID NO:114),
CLIPS-GRYQAQCRIGHYRFCYSD (SEQ ID NO:115),
RYQAQCRIGHYRFC (SEQ ID NO:116),
GRYQCQYRIGHYRFRYCD (SEQ ID NO:117),

GRYQACYRIGHYRFRCSD (SEQ ID NO:118),

GRYQAQCRIGHYRFCYSD (SEQ ID NO:119), each of which can be acyclic or cyclic.

27. The compound of claim 2,

wherein the TNF binder comprises the amino acid sequence of at least one of:

STPTRYS (SEQ ID NO:120),

CALWHWWHC (SEQ ID NO:121),

C(T/S)WLHWWAC (SEQ ID NO:122),

(L/M)HEL(Y/F)(L/M)X(W/Y/F) (SEQ ID NO:123),

D-DDDEK QLKER WYKRW LEYLD EFKKN (SEQ ID NO:124),

D-TEEEK QLKEW WYKHW QEYLE EFKKN (SEQ ID NO:125),

GACPPCLWQVLCGGSGSGSG (SEQ ID NO:126),

HIHDDLLRYYGW linear (SEQ ID NO:127) or tetra branched (SEQ ID NO:128) peptide,

KRWSRYF (SEQ ID NO:129),

HIHDDLLRYYGW (SEQ ID NO:127),

YCWSQYLCY (SEQ ID NO:130),

DFLPHYKNTSLGHRP (SEQ ID NO:131),

YCLYQSWCY (SEQ ID NO:132);

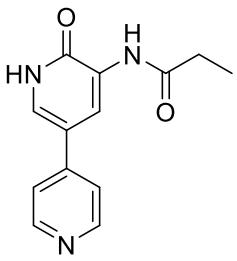
or

wherein the TNF binder comprises at least one of:

TNFR1, TNFR2, P51, P52, anticachexin C1, anticachexin C2, adalimumab, infliximab, etanercept, golimumab, certolizumab;

or

wherein the TNF binder comprises at least one of: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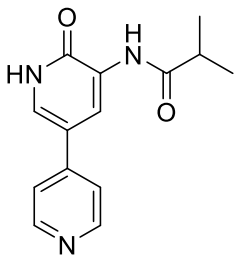
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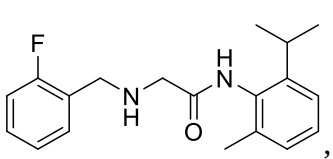
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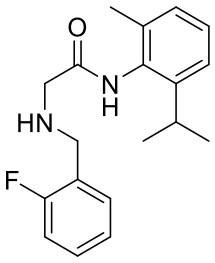
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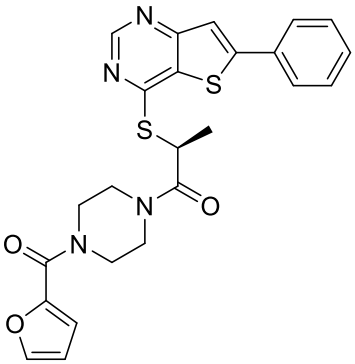
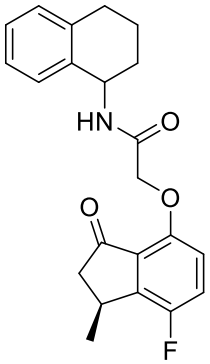
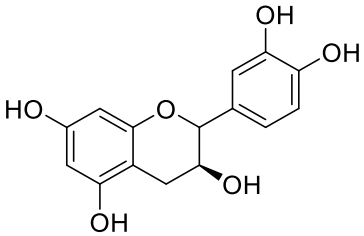
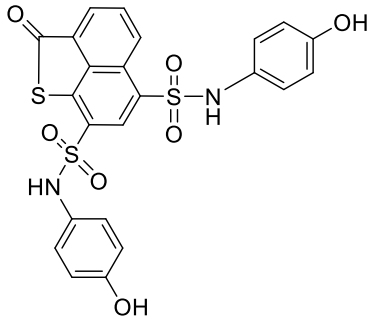
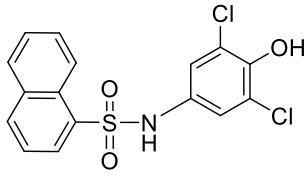
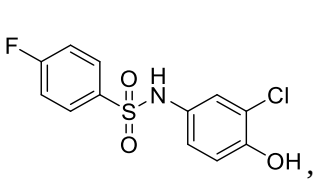



;

or

wherein the TNF binder comprises at least one of: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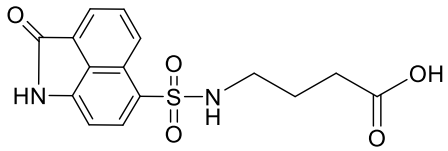
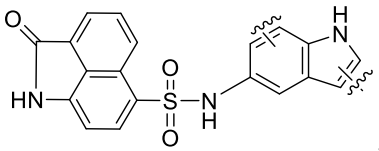
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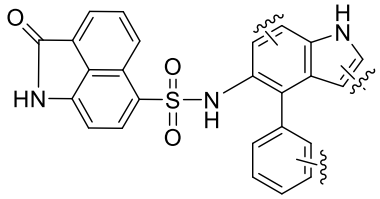
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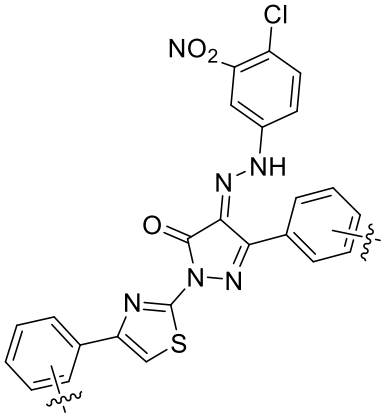
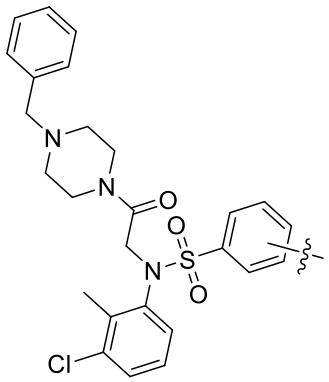
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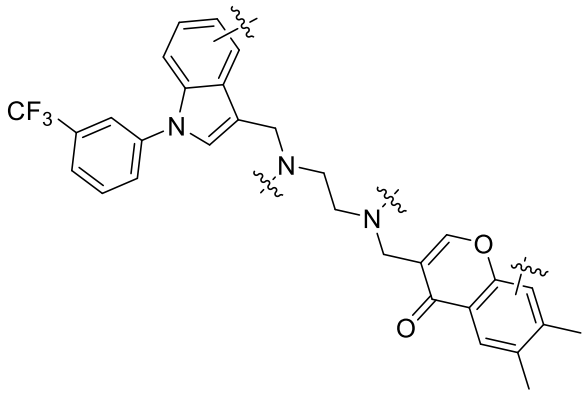
;

or

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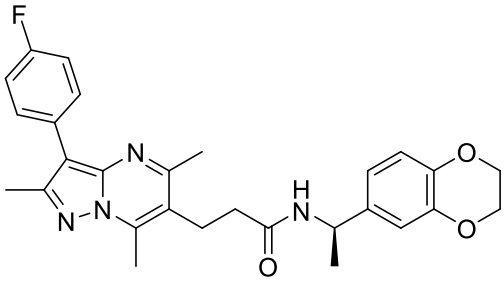
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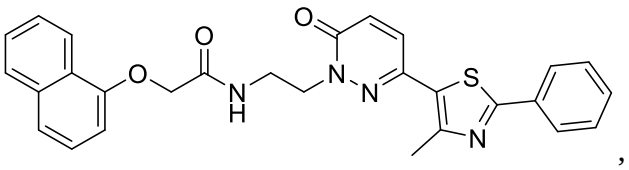
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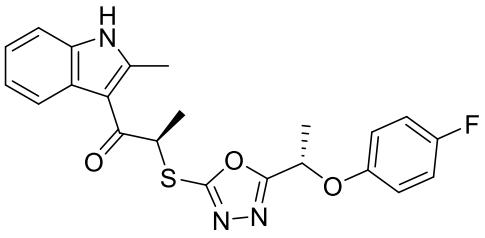
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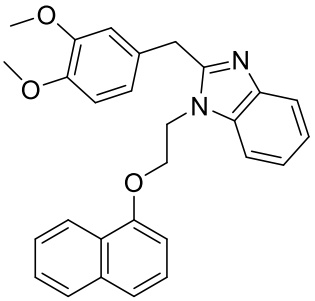
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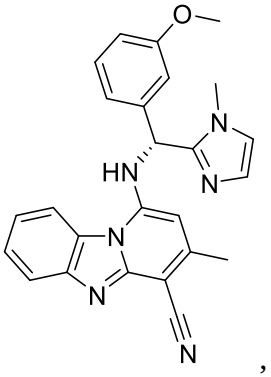
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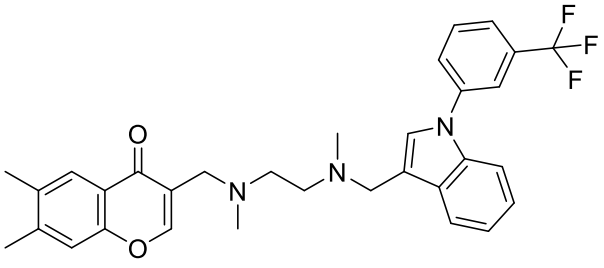
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or

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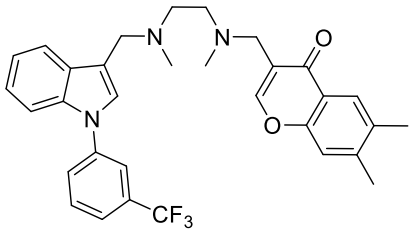
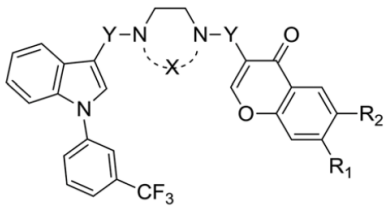
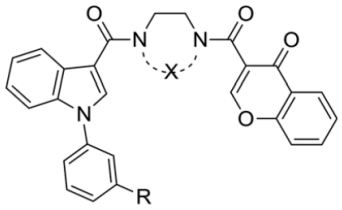


SPD-304



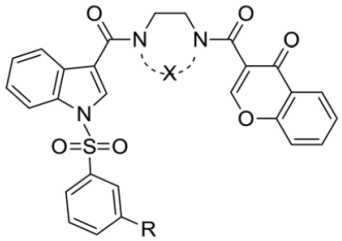
1, 2a-e



3a-d

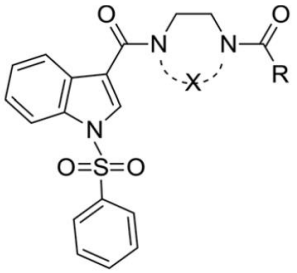
1: R_1=R_2 = CH_3, X = CH_3,CH_3, Y = CH_2
2a: R_1=R_2 = CH_3, X =  , Y = CH_2
2b: R_1 =H, R_2 = CH_3, X = CH_3,CH_3, Y = CH_2
2c: R_1 =H, R_2 = CH_3, X =  , Y = CH_2
2d: R_1=R_2 = CH_3, X= CH_3,CH_3, Y = C =O
2e: R_1=R_2 = CH_3, X=  , Y = C=O

3a: R = NO_2, X = CH_3,CH_3
3b: R = NO_2, X = 
3c: R = NH_2, X = CH_3,CH_3
3d: R = NH_2, X = 

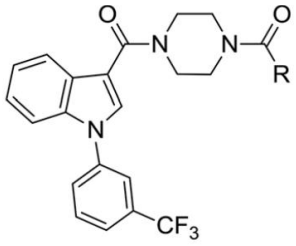


4a-f

4a: R = H, X = CH_3,CH_3
4b: R = H, X =
4c: R = NO_2, X = CH_3,CH_3
4d: R = NO_2, X =
4e: R = NH_2, X = CH_3,CH_3
4f: R = NH_2, X =



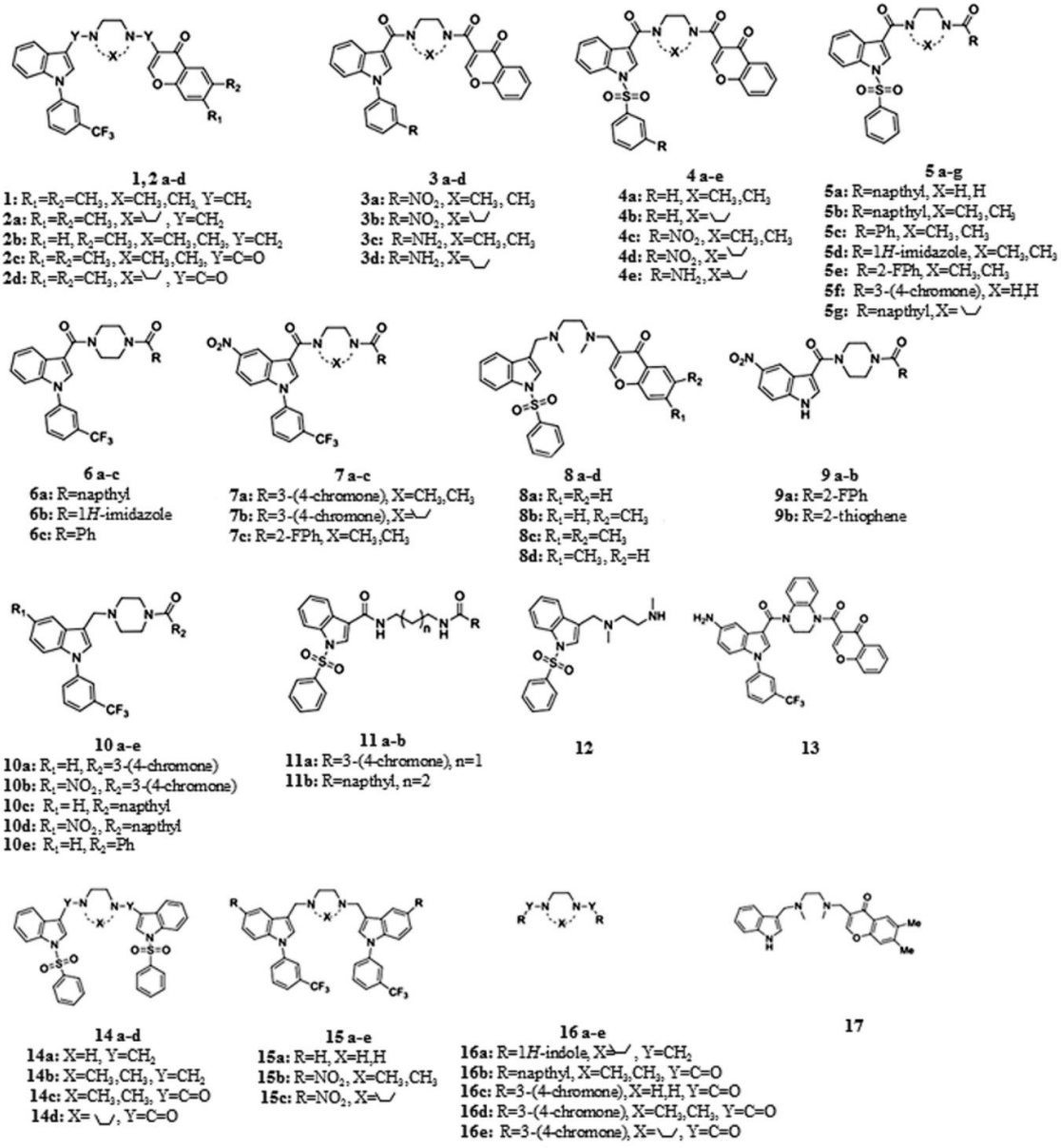
5a-g



6a-c

5a: R = napthyl, X = H, H
5b: R = napthyl, X = CH_3, CH_3
5c: R = Ph, X = CH_3, CH_3
5d: R = 1*H*-imidazole, X = CH_3, CH_3
5e: R = 2-FPh, X = CH_3, CH_3
5f: R = 2-thiophene, X = CH_3, CH_3
5g: R = napthyl, X=

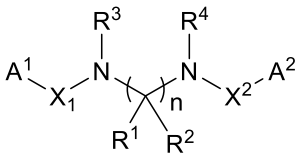
6a: R = napthyl
6b: R = 1*H*-imidazole
6c: R = Ph



;

or

wherein the TNF binder comprises at least one of:

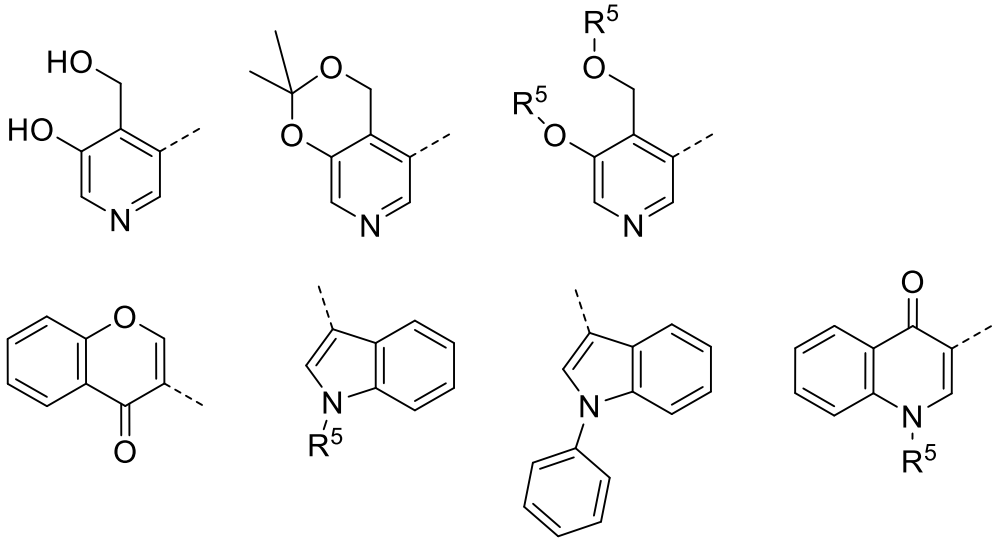


(2a)

wherein:

A^1 and A^2 are independently a substituted or unsubstituted phenyl group, wherein the substituents comprise at least one of F, Cl, Br, I, OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with at least one OH, C_1-C_4 fluoroalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, benzyloxy, and the following heterocyclic rings optionally substituted with at least

one of F, Cl, Br, I, OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with at least one OH, C_1-C_4 fluoroalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy, or



(dotted lines indicate point of attachment);

each R^5 is independently hydrogen or optionally substituted C_1-C_4 alkyl;

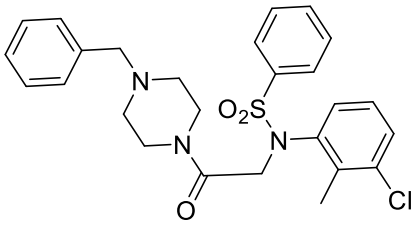
R^1 and R^2 are independently hydrogen or optionally substituted C_1-C_4 alkyl;

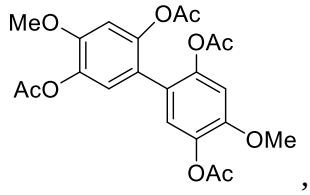
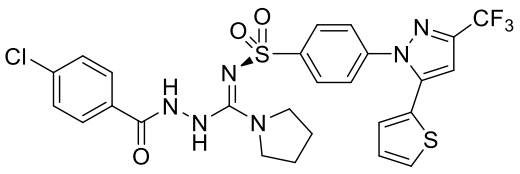
X^1 and X^2 are independently carbonyl or CH_2;

n is 2, 3, or 4;

R^3 and R^4 are independently hydrogen or optionally substituted C_1-C_4 alkyl, or R^3 and R^4 can combine to form a heterocyclyl ring;

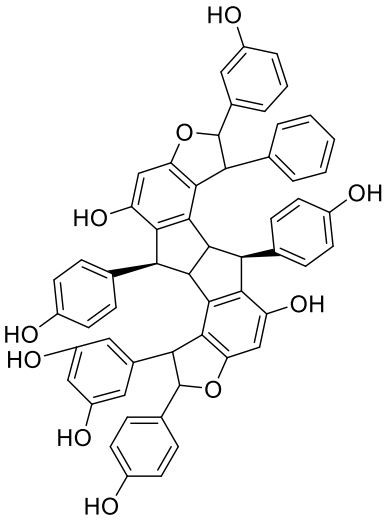
or

wherein the TNF binder comprises at least one of IA-14069, 

,  ,  ;

or

wherein the TNF binder comprises at least one of: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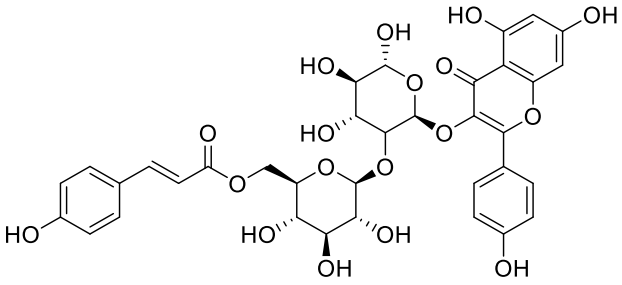
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or

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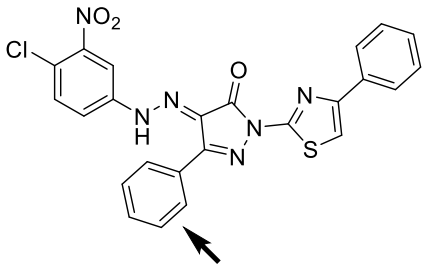
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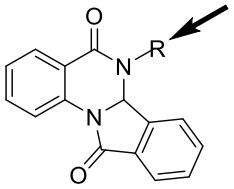
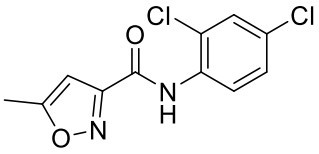

R= CH_2Ph, C_6H_4OMe-p, C_6H_4Cl-p, H
,

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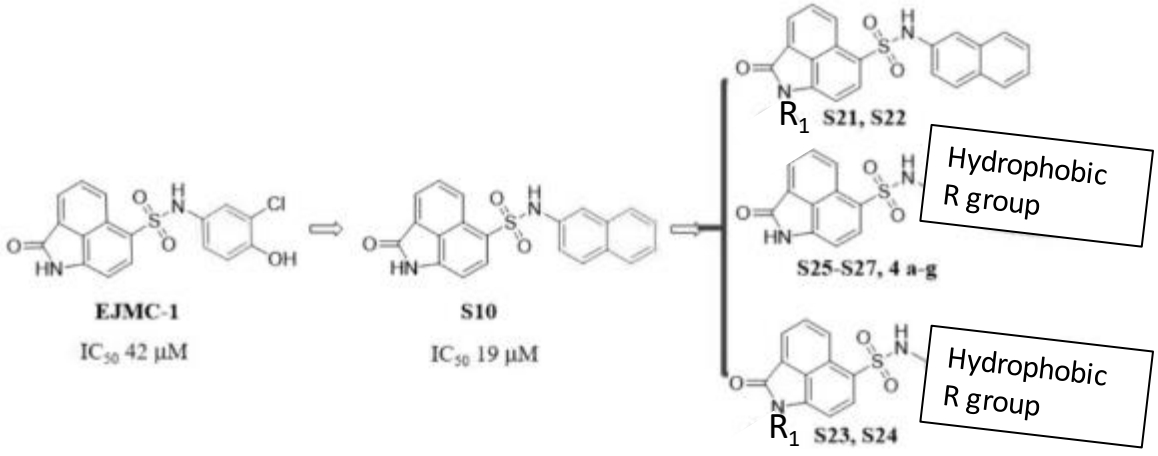
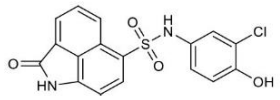
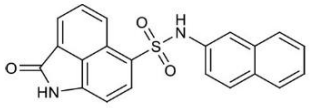
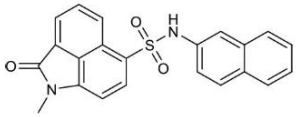
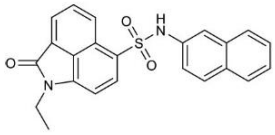
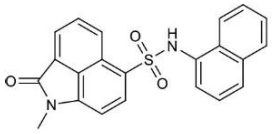
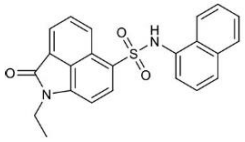
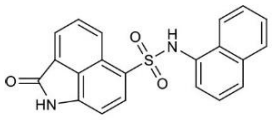
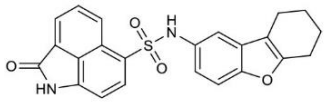
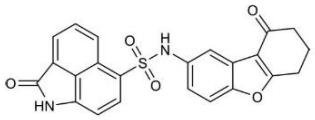
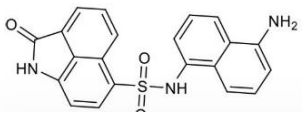
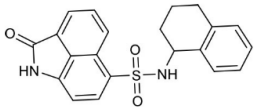
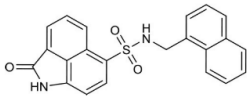
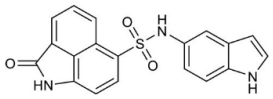
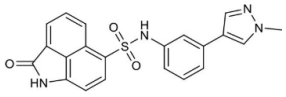
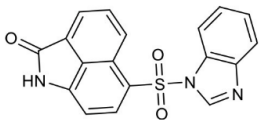
or

wherein the TNF binder comprises at least one of:



,

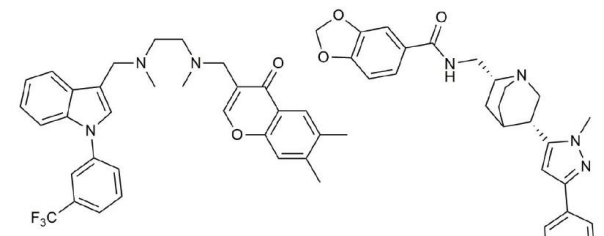
Compound	Structure
EJMC-1	
S10	
S21	
S22	
S23	
S24	
S25	
S26	
S27	
4a	

Compound	Structure
4c	
4d	
4e	
4f	
4g	

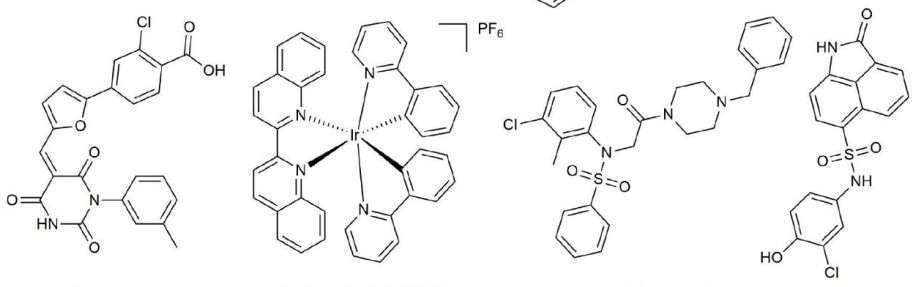
;

or

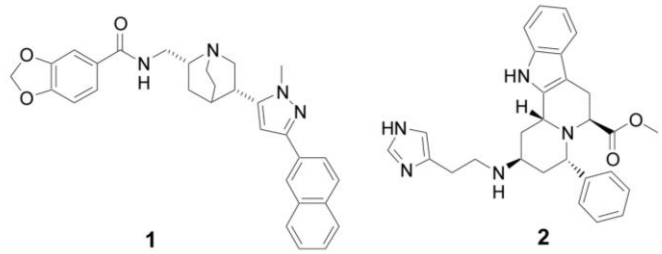
wherein the TNF binder comprises at least one of:



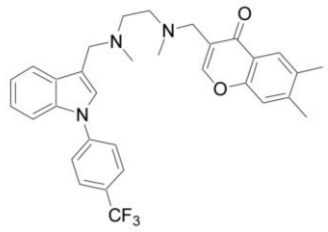
SPD304 **Quinuclidine 1** **Indoloquinolizidine 2**



Oxole-1 **$[Ir(ppy)_2(biq)]PF_6$** **Benzenesulfonamide-1** **EJMC-1**



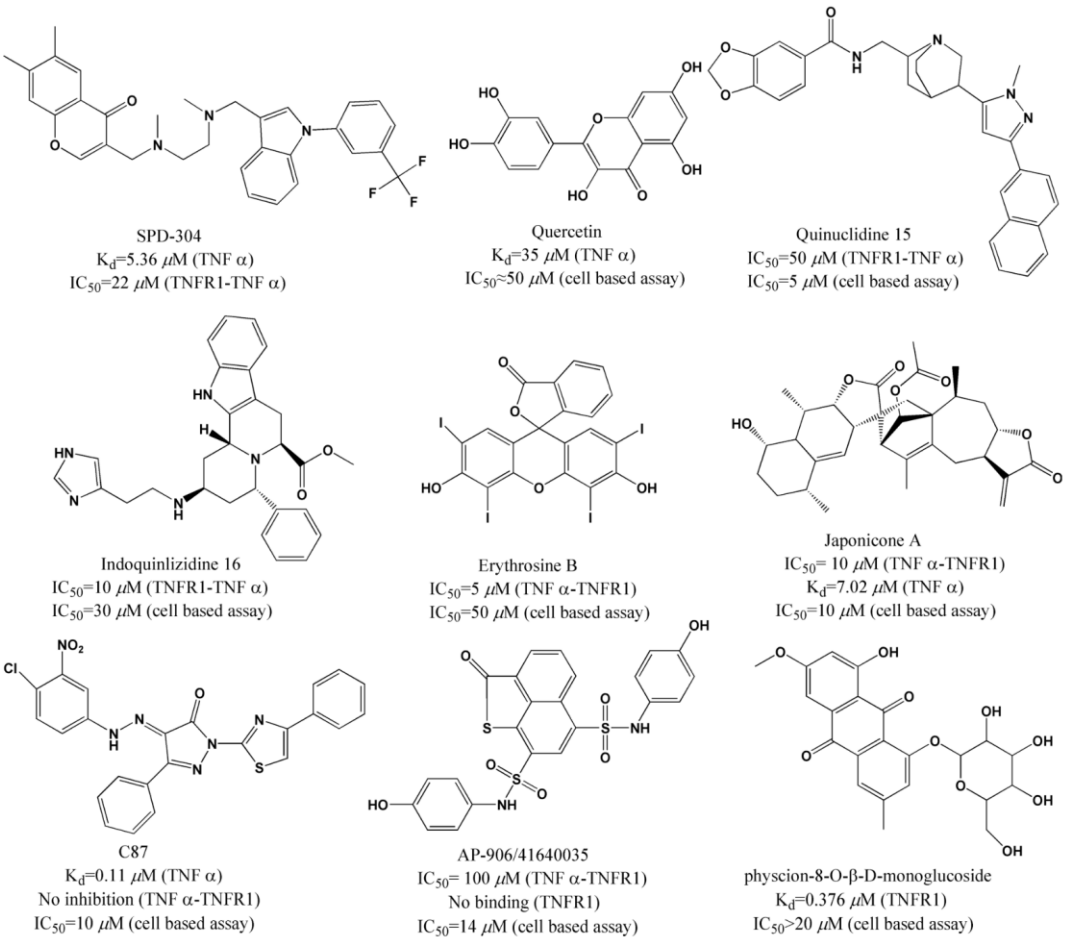
1 **2**



SPD304 ;

or

wherein the TNF binder comprises at least one of:



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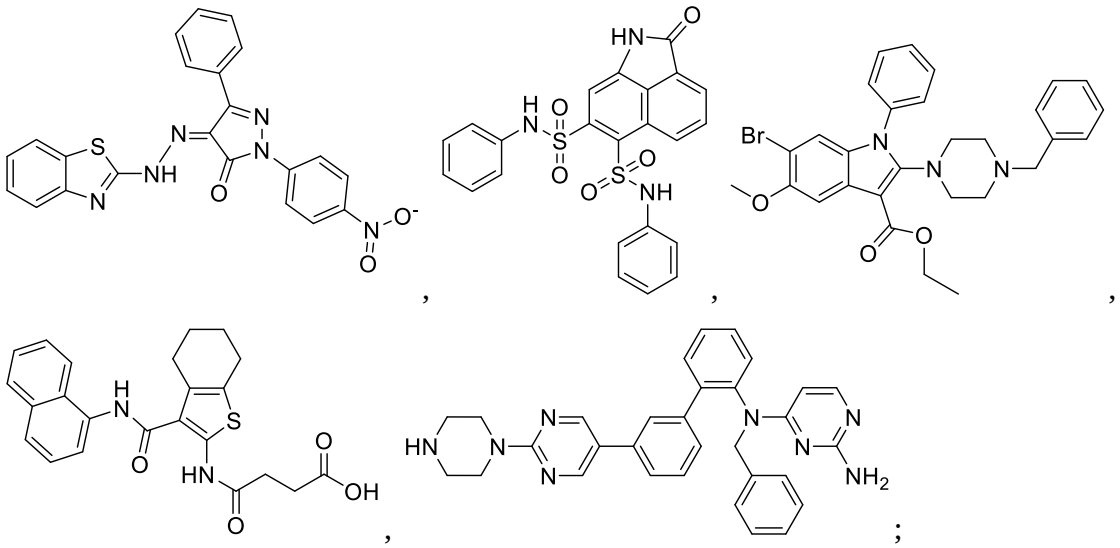
or

wherein the TNF binder comprises at least one of: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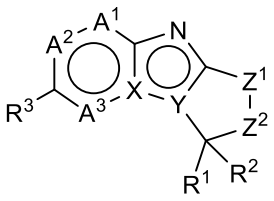
,
;

or

wherein the TNF binder comprises at least one of:



(2b),

wherein:

R^1 is H, OH, F or optionally substituted (C_1-C_3)alkyl;

R^2 is optionally substituted aryl, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted heteroaryl or optionally substituted heterocyclyl; or

R^1 and R^2 together can form an optionally substituted saturated or partially saturated carbocyclic ring or optionally substituted saturated or partially saturated heterocyclic ring;

up to two of A^1, A^2, and A^3 are N, and the rest are independently $C(R^{A2})$;

X is N and Y is C, wherein:

Z^1 is —$C(R^z)_2$— and Z^2 is —$C(R^z)_2$—, —$N(R^{z1})^-$ or —O—; or

Z^1 is —CH_2— and Z^2 is —Z^{2a}—Z^{2b}—,

wherein Z^{2a} is attached to Z^1 and Z^{2b} is attached to $C(R^1)(R^2)$; and Z^{2a} and Z^{2b} are independently —$C(R^z)_2$—, —$C(R^z)_2C(R^z)_2$—, —O— or —$N(R^{z1})$— provided that one of Z^{2a} and Z^{2b} is —$C(R^z)_2$— or —$C(R^z)_2C(R^z)_2$—; or —Z^{2a}—Z^{2b}— form —$N(R^{z1})C(O)$— or —$C(O)N(R^{z1})$—;

or

X is C and Y is N, provided that R^1 is not —OH or —F, wherein:

Z^1 is —$C(R^z)_2$— and Z^2 is —$C(R^z)_2$—; or

Z^1 is —$C(R^z)_2$— and Z^2 is —Z^{2a}—Z^{2b}—,

wherein Z^{2a} is attached to Z^1 and Z^{2b} is attached to $C(R^1)(R^2)$, and Z^{2a} is —$C(R^z)_2$—, —$C(R^z)_2C(R^z)_2$—, —O— or —$N(R^{z1})$, and Z^{2b} is —$C(R^z)_2$—, or —Z^{2a}—Z^{2b}— form —$N(R^{z1})C(O)$— or —$C(O)N(R^{z1})$—;

R^3 is —R^{3a}—R^{3b}, wherein:

R^{3a} is an optionally substituted aryl, optionally substituted saturated or partially saturated heterocyclyl or optionally substituted heteroaryl;

R^{3b} is H, —CF_3, —CN, —C(O)OH, —$N(R^a)(R^b)$, —$C(O)N(R^a)(R^b)$, —C(O)-optionally substituted heterocyclyl, —$O(R^a)$, —$S(O)_2$(C_1-C_3)alkyl, —$S(O)_2N(R^c)(R^d)$, —S—(C_1-C_3)alkyl, —$S(O)_2$—R^c optionally substituted (C_1-C_5)alkyl, —$(CH_2)_p$-optionally substituted (C_3-C_6)cycloalkyl, —$(CH_2)_p$-optionally substituted heteroaryl

or —$(CH_2)_p$-optionally substituted saturated, unsaturated or partially saturated heterocyclyl; provided that $R3^b$ is not H or methoxy when R^2 is optionally substituted phenyl;

R^a and R^b are independently selected from H, optionally substituted $(C_1$-$C_5)$alkyl, —C(O)— optionally substituted $(C_1$-$C_5)$alkyl, optionally substituted —$(CH_2)_p$—$(C_3$-$C_6)$cycloalkyl and —$(CH_2)_p$-optionally substituted heterocyclyl;

R^c and R^d are independently selected from H, optionally substituted $(C_1$-$C_5)$alkyl, optionally substituted —$(CH_2)_p$—$(C_3$-$C_6)$cycloalkyl and —$(CH_2)_p$-optionally substituted heterocyclyl;

R^{A2} is independently H, CF_3, halo or $(C_1$-$C_3)$alkyl;

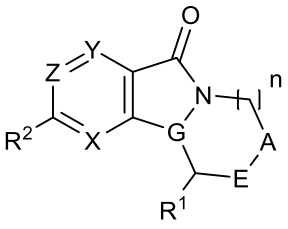
R^z is independently H, F, CF_3, —OH or $(C_1$-$C_3)$alkyl;

R^{z1} is independently H or $(C_1$-$C_3)$alkyl; and

p is independently 0, 1 or 2;

or

wherein the TNF binder comprises at least one of:



(2c),

wherein:

X, Y, and Z are independently CR^4 or N; provided that Y and Z are not both N;

A is —$C(R^z)_2$—;

E is CH_2 or O and G is CH; or E is CH_2 and G is CH or N;

R^1 is optionally substituted aryl or optionally substituted heteroaryl;

R^2 is —R^{2a}-R^{2b}, wherein:

R^{2a} is an optionally substituted saturated, unsaturated or partially saturated heterocyclyl or optionally substituted heteroaryl;

R^{2b} is —$N(R^a)(R^b)$, —$O(R^a)$, optionally substituted $(C_1$-$C_5)$alkyl, optionally substituted $(C_3$-$C_6)$cycloalkyl, —$(CH_2)_p$-optionally substituted heteroaryl or —$(CH_2)_p$-optionally substituted heterocyclyl; wherein

R^a and R^b are independently selected from H, optionally substituted $(C_1$-$C_5)$alkyl, and —$(CH_2)_n$-optionally substituted heterocyclyl;

R^4 is independently H, halo, CF_3, or $(C_1$-$C_3)$alkyl;

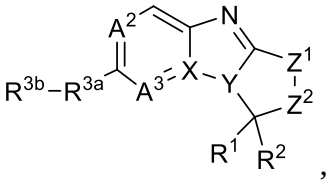
R^z is independently H, halo, CF_3, or (C_1-C_3)alkyl;

n is 0 or 1; and

p is 0 or 1.

28. The compound of claim 27,

wherein the compound of formula (1a) comprises one of the following:



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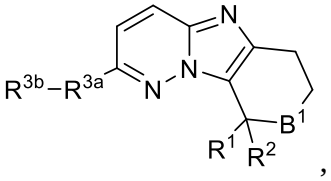

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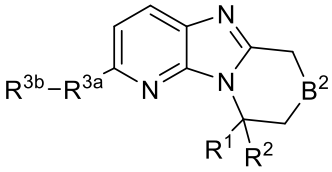

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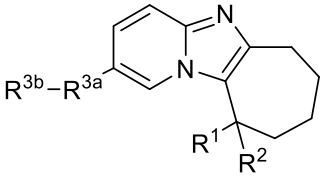
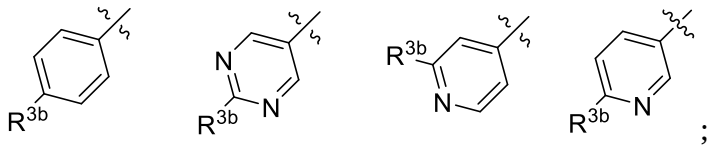


,

wherein:

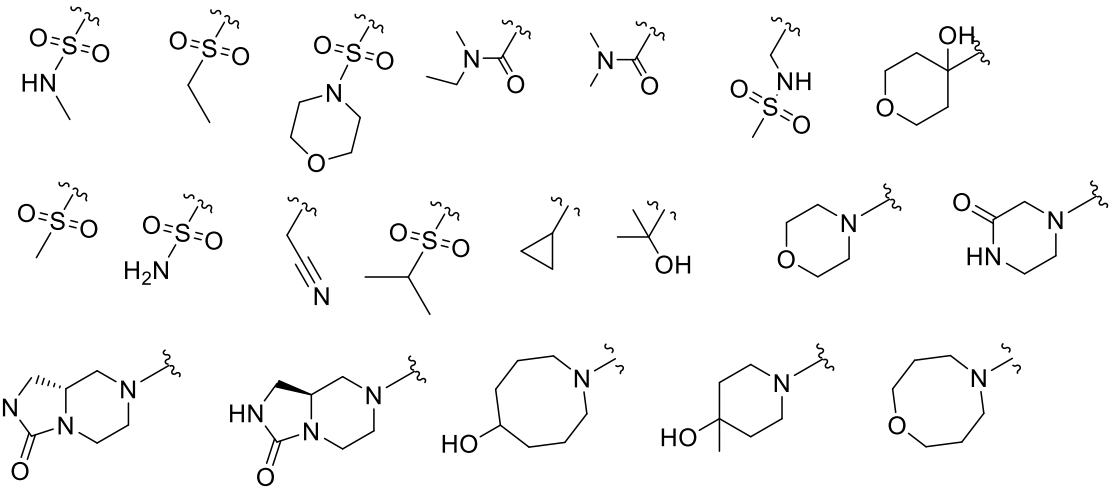
A^2 is CH or N; A^3 is CH or N; B^1 is CH_2 or O; B^2 is CH_2 or O; X is C or N; Y is C or N; Z^1 is CH_2 or O; and Z^2 is CH_2 or O;

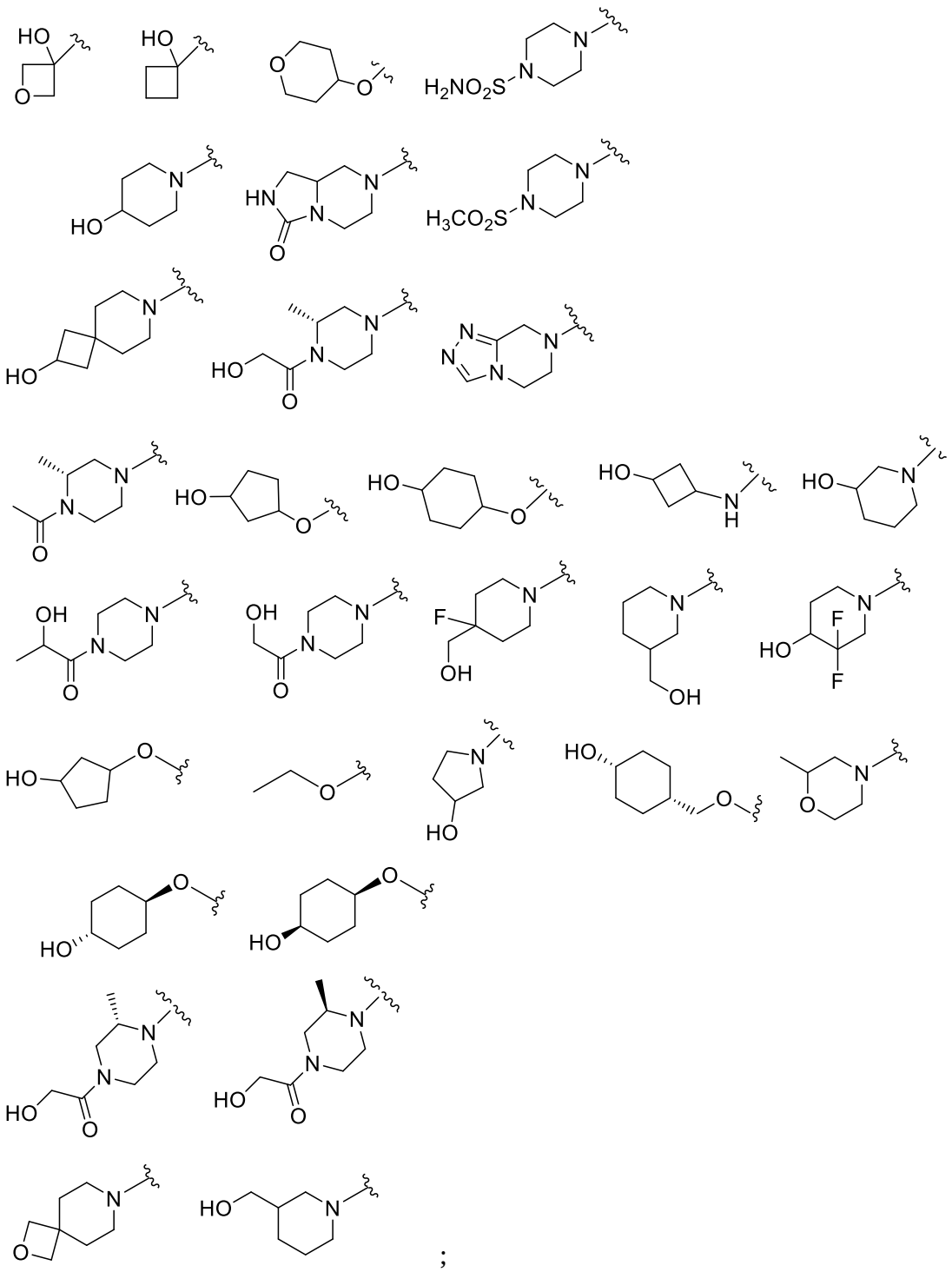
R^{3a} is selected from the group consisting of:



;

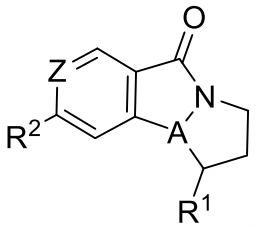
R^{3b} is selected from the group consisting of:



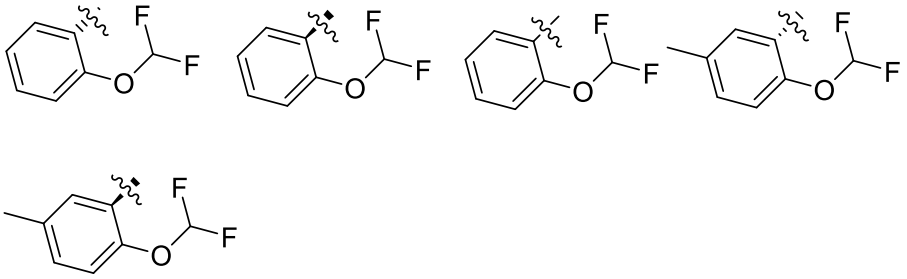


;

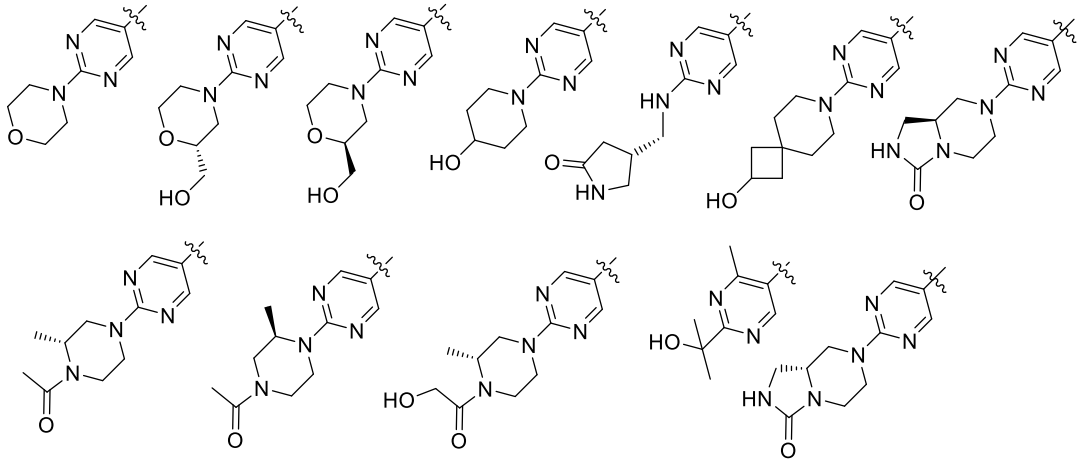
or



wherein the compound of formula (2a) comprises , wherein G is N or CH; Z is CH or CF; R^1 is selected from the group consisting of

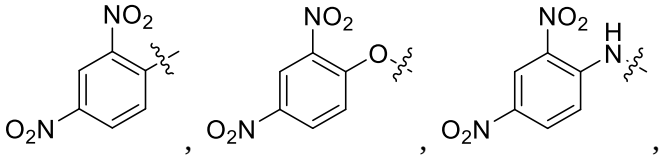


; and R^2 is selected from the group consisting of



.

29. The compound of claim 3, wherein the AATM comprises one of the following: a FcRn antagonist,



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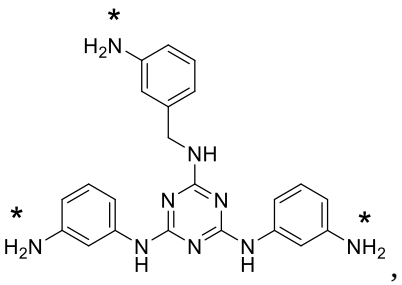

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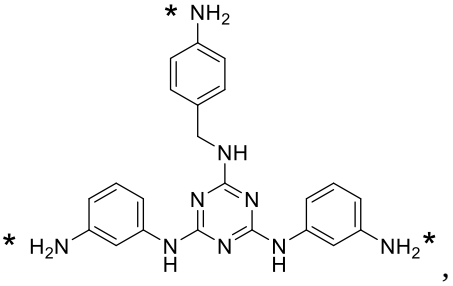

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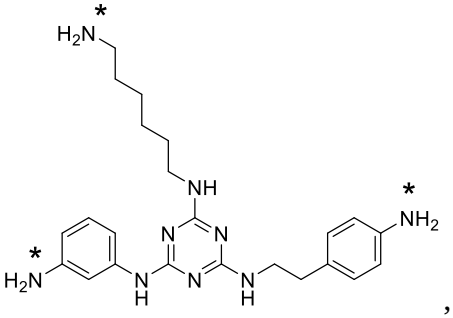

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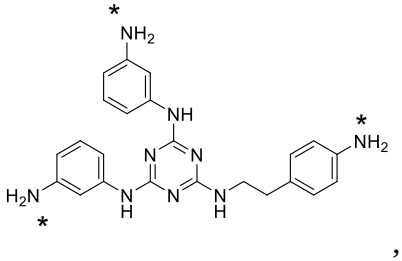

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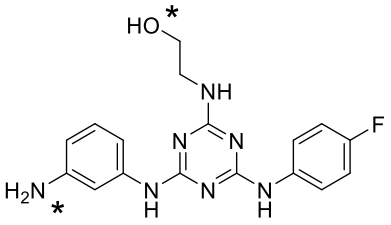
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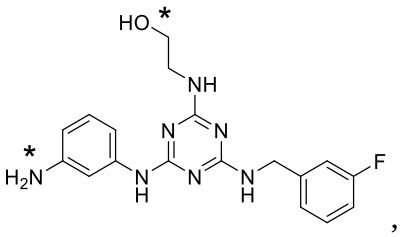
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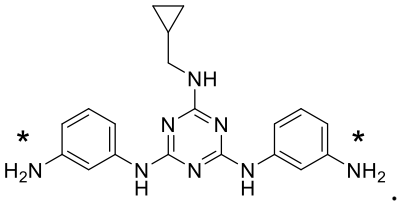
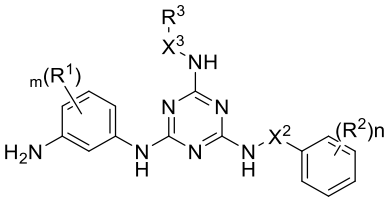
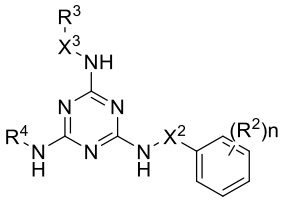

.

cyclic peptide FcIII, or any reduced form thereof,

cyclic peptide FcIII-4C (amide), or any reduced form thereof,

a compound of formula (3a) or (3b):


(3a) or

(3b)

wherein:

each occurrence of R^1 is independently F, Cl, Br, I, CN, NO_2, R, OR, C_1-C_6 haloalkyl, C_3-C_8 halocycloalkyl, C_1-C_6 haloalkoxy, C_3-C_8 halocycloalkoxy, $-N(R)_2$, -SR, -S(=O)R, $-S(=O)_2R$, $-S(=O)_2N(R)_2$, -C(=O)R, -C(=O)OR, -OC(=O)R, $-C(=O)N(R)_2$, $-N(R)S(=O)_2R$, -N(R)C(=O)OR, -N(R)C(=O)R, and $-N(R)C(=O)N(R)_2$, wherein each occurrence of R is independently H, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

m is 0, 1, 2, 3, or 4;

X^2 is a bond, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

each occurrence of R^2 is independently F, Cl, Br, I, CN, NO_2, R, OR, C_1-C_6 haloalkyl, C_3-C_8 halocycloalkyl, C_1-C_6 haloalkoxy, C_3-C_8 halocycloalkoxy, $-N(R)_2$, -SR, -S(=O)R, $-S(=O)_2R$, $-S(=O)_2N(R)_2$, -C(=O)R, -C(=O)OR, -OC(=O)R, $-C(=O)N(R)_2$, $-N(R)S(=O)_2R$, -N(R)C(=O)OR, -N(R)C(=O)R, and $-N(R)C(=O)N(R)_2$, wherein each occurrence of R is independently H, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

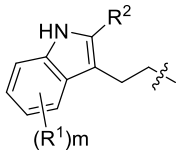
n is 0, 1, 2, 3, or 4;

X^3 is a bond, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^3 is H, R, -OH, -NH_2, -NHR, -C(=O)OH, or -SH, wherein each occurrence of R is C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

R^4 is cycloalkyl, including polycyclic cycloalkyl, which is optionally substituted with 1-4 groups independently selected from the group consisting of F, Cl, Br, I, CN, NO_2, R, OR, C_1-C_6 haloalkyl, C_3-C_8 halocycloalkyl, C_1-C_6 haloalkoxy, C_3-C_8 halocycloalkoxy, -$N(R)_2$, -SR, -S(=O)R, -$S(=O)_2$R, -$S(=O)_2N(R)_2$, -C(=O)R, -C(=O)OR, -OC(=O)R, -$C(=O)N(R)_2$, -$N(R)S(=O)_2$R, -N(R)C(=O)OR, -N(R)C(=O)R, and -$N(R)C(=O)N(R)_2$, wherein each occurrence of R is independently H, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

a compound of formula:



,

wherein:

each occurrence of R^1 is independently F, Cl, Br, I, CN, NO_2, R, OR, C_1-C_6 haloalkyl, C_3-C_8 halocycloalkyl, C_1-C_6 haloalkoxy, C_3-C_8 halocycloalkoxy, -$N(R)_2$, -SR, -S(=O)R, -$S(=O)_2$R, -$S(=O)_2N(R)_2$, -C(=O)R, -C(=O)OR, -OC(=O)R, -$C(=O)N(R)_2$, -$N(R)S(=O)_2$R, -N(R)C(=O)OR, -N(R)C(=O)R, and -$N(R)C(=O)N(R)_2$, wherein each occurrence of R is independently H, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl;

m is 0, 1, 2, 3, or 4;

each occurrence of R^2 is independently H, F, Cl, Br, I, CN, NO_2, R, OR, C_1-C_6 haloalkyl, C_3-C_8 halocycloalkyl, C_1-C_6 haloalkoxy, C_3-C_8 halocycloalkoxy, -$N(R)_2$, -SR, -S(=O)R, -$S(=O)_2$R, -$S(=O)_2N(R)_2$, -C(=O)R, -C(=O)OR, -OC(=O)R, -$C(=O)N(R)_2$, -$N(R)S(=O)_2$R, -N(R)C(=O)OR, -N(R)C(=O)R, and -$N(R)C(=O)N(R)_2$, wherein each occurrence of R is independently H, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl.

30. The compound of claim 29, wherein the FcRn antagonist comprises rozanolixizumab or efgartigimod.

31. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound of any one of claims 1-3.

32. The pharmaceutical composition of claim 31, further comprising another therapeutically active agent that treats, ameliorates, and/or prevents a disease or disorder.

33. The compound of any one of claims 1-3 for use in the treatment, amelioration and/or prevention of ~~A method of treating, ameliorating, and/or preventing~~ a disease or disorder in a subject, ~~the method comprising administering~~wherein a therapeutically effective amount of at least one compound of any one of claims 1-3 is to be administered to the subject.

34. Use of the compound in any one of claims 1-3 in the manufacture of a medicament for the treatment, amelioration and/or prevention of a disease or disorder in a subject~~The method of claim 33~~, wherein the disease or disorder comprises an autoimmune disease, cancer, or inflammation, and wherein a therapeutically effective amount of at least one compound of any one of claims 1-3 is to be administered to the subject.~~.~~

35. The ~~method~~ use of claim 34, wherein the autoimmune disease comprises 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, Crohn's 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 syndrome, pernicious anemia, pure red cell aplasia, thrombocytopenia, adiposis dolorosa, adult-onset Still's disease, ankylosing spondylitis, CREST syndrome, drug-induced lupus, enthesitis-related arthritis, eosinophilic fasciitis, Felty syndrome, AgG4-related disease, juvenile arthritis, Lyme disease (chronic), mixed connective tissue disease (MCTD), palindromic rheumatism, Parry Romberg syndrome, Parsonage-Turner syndrome, psoriatic arthritis, reactive arthritis, relapsing polychondritis, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schnitzler syndrome, systemic lupus erythematosus, undifferentiated connective tissue disease (UCTD), dermatomyositis,

fibromyalgia, myositis, inclusion body myositis, myasthenia gravis, neuromyotonia, paraneoplastic cerebellar degeneration, polymyositis, acute disseminated encephalomyelitis (ADEM), acute motor axonic neuropathy, anti-NMDA receptor encephalitis, Balo concentric sclerosis, Bickerstaff's encephalitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, Hashimoto's encephalopathy, idiopathic inflammatory demyelinating diseases, Lambert-Eaton myasthenic syndrome, multiple sclerosis, pattern II, Oshtoran Syndrome, Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS), progressive inflammatory neuropathy, restless leg syndrome, stiff person syndrome, 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, Eosinophilic granulomatosis with polyangiitis (EGPA), giant cell arteritis, granulomatosis with polyangiitis (GPA), IgA vasculitis (IgAV), IgA nephropathy, Kawasaki's disease, leukocytoclastic vasculitis, lupus vasculitis, rheumatoid vasculitis, microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), polymyalgia rheumatica, urticarial vasculitis, vasculitis, primary immune deficiency, chronic fatigue syndrome, complex regional pain syndrome, eosinophilic esophagitis, gastritis, interstitial lung disease, POEMS syndrome, Raynaud's syndrome, primary immunodeficiency, or pyoderma gangrenosum.

36. The ~~method~~ use of claim 34, wherein the cancer comprises prostate cancer, metastatic prostate cancer, stomach cancer, colon cancer, rectal cancer, liver cancer, pancreatic cancer, lung cancer, breast cancer, cervix uteri cancer, corpus uteri cancer, ovary cancer, testis cancer, bladder cancer, renal cancer, brain/CNS cancer, head and neck cancer, throat cancer, 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, or lymphoma.

37. The ~~method~~ use of claim 34, wherein the inflammation comprises inflammatory diseases of neurodegeneration, diseases of compromised immune response causing inflammation, chronic inflammatory diseases, hyperglycemic disorders, diabetes (I and II),

pancreatic β-cell death and related hyperglycemic disorders, liver disease, renal disease, cardiovascular disease, muscle degeneration and atrophy, low grade inflammation, gout, silicosis, atherosclerosis and associated conditions, stroke and spinal cord injury, or arteriosclerosis.

38. The ~~method~~ use of claim 3~~4~~43, wherein ~~the subject is further administered~~ at least one additional therapeutic agent that treats, ameliorates, and/or prevents the disease or disorder is to be administered to the subject.

39. The ~~method~~ use of claim ~~33~~34, wherein the subject is a mammal.

40. The ~~method~~ use of claim ~~33~~34, wherein the subject is a human.