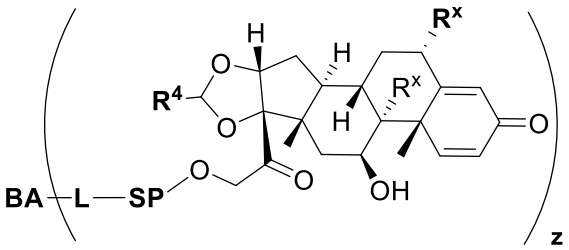
m is 0 or 1;

z is an integer selected from 1-30, inclusive;

L is a linker; and

BA is a binding agent.

[0007a] One aspect is directed to a Compound of Formula (**III**)



(**III**);

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

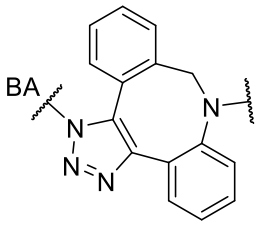
wherein

$\mathbf{R^4}$ is alkyl, aryl, arylalkyl, or an N-containing heterocycloalkyl;

either both $\mathbf{R^x}$ are hydrogen or both $\mathbf{R^x}$ are fluoro;

SP is -C(O)-C_1-C_{10}-alkylene-C(O)-;

L is a linker of the formula $–L^1-L^2-(L^3)_{0-1}$-; where $\mathbf{L^1}$ is attached to **BA** and $\mathbf{L^3}$ is attached to **SP**;

$\mathbf{L^1}$ is a reactive group residue selected from the group consisting of 

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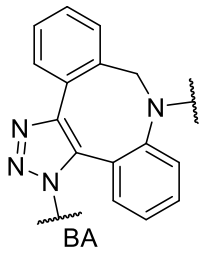
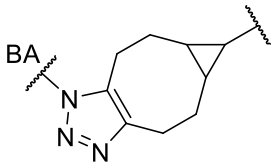
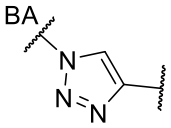
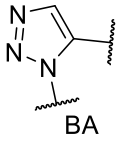


, 

, 

, and 

where 

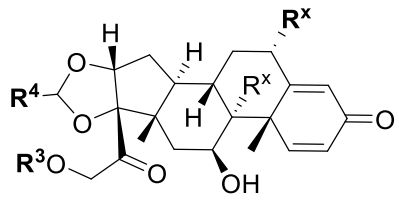
is a bond to the binding agent;

$\mathbf{L^2}$ is a connecting linker; and

$\mathbf{L^3}$, when present, is a self-immolative linker; and

BA is a binding agent.

[0008] A second example is directed to a Compound according to Formula (**I**):



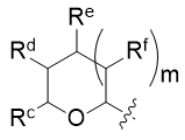
(**I**);

or a pharmaceutically acceptable salt, solvate, stereoisomer, or derivative thereof,

wherein:

$\mathbf{R^4}$ is alkyl, aryl, arylalkyl, or an N-containing heterocycloalkyl;

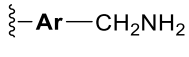
a) both $\mathbf{R^x}$ are hydrogen; and

$\mathbf{R^3}$ is -C(O)$\mathbf{R^Z}$; -(C_1-C_{10}-alkylene)-N$\mathbf{R^{50}}$C(O)-(C_1-C_{10}-alkylene)-N$\mathbf{R^{50a}}\mathbf{R^{50b}}$; -$CH_2NH_2$; or 

;

$\mathbf{R^Z}$ is -C_{4-10}-alkylene-C(O)OH; -(C_1-C_{10}-alkylene)-N$\mathbf{R^{50}}$C(O)-(C_1-C_{10}-alkylene)-N$\mathbf{R^{50a}}\mathbf{R^{50b}}$

where each C_1-C_{10}-alkylene is independently optionally substituted with one or more

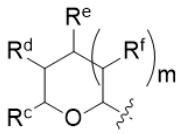
hydroxy;  where where **Ar** is optionally substituted aryl or heteroaryl; or

N**R**^{15}**R**^{15a};

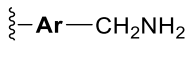
R^{15} is H or C_1-C_6alkyl and **R**^{15a} is -(C_1-C_{10}-alkylene)-SH or -(C_{1-6}-alkylene)-C(O)NHNH_2;

b) both **R**^{x} are fluoro; and

R^{3} is -C(O)**R**^{Z}**;** -(C_1-C_{10}-alkylene)-N**R**^{50}C(O)-(C_1-C_{10}-alkylene)-N**R**^{50a}**R**^{50b}; -CH_2NH_2; or



;

R^{Z} is -C_{4-10}-alkylene-C(O)OH; -(C_1-C_{10}-alkylene)-N**R**^{50}C(O)-(C_1-C_{10}-alkylene)-N**R**^{50a}**R**^{50b} where each C_1-C_{10}-alkylene is independently optionally substituted with one or more hydroxy;  where where **Ar** is optionally substituted aryl or heteroaryl; or

N**R**^{16}**R**^{16a};

$\mathbf{R^d}$, $\mathbf{R^e}$, and $\mathbf{R^f}$ are independently -H, -OH, hydroxyalkyl, alkoxycarbonyl, -C(O)OH, or $-CH_2O\mathbf{R^g}$, where each $\mathbf{R^g}$ is independently $-CH_2C(O)OH$ or $-CH_2C(O)O$(alkyl); and

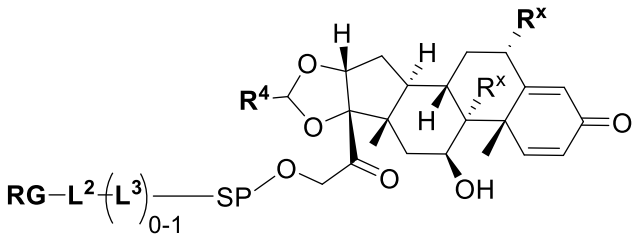
m is 0 or 1;

RG is a reactive group;

$\mathbf{L^2}$ is connecting linker; and

$\mathbf{L^3}$, when present, is a self-immolative linker.

[0009a] Another aspect is directed to a Compound of Formula (**II**)



(**II**);

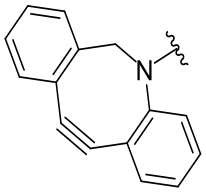
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,

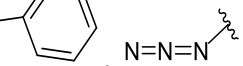
wherein

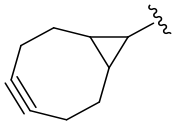
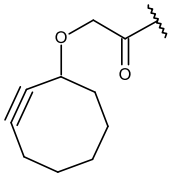
$\mathbf{R^4}$ is alkyl, aryl, arylalkyl, or an N-containing heterocycloalkyl;

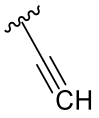
either both $\mathbf{R^x}$ are hydrogen or both $\mathbf{R^x}$ are fluoro;

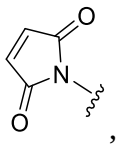
SP is $-C(O)-C_1-C_{10}$-alkylene-C(O)-;

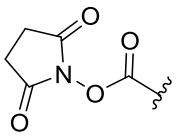
RG is a reactive group selected from the group consisting of 

, 

, 
, 

, 

, 

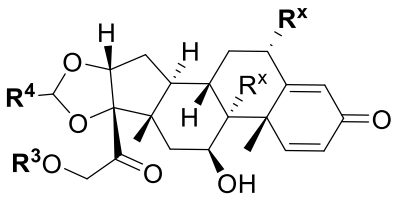
, and 

;

L[2] is a connecting linker; and

L[3], when present, is a self-immolative linker.

[0009b] Another aspect is directed to a Compound according to Formula (**I**)



(**I**);

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

wherein

R4 is alkyl, aryl, arylalkyl, or an N-containing heterocycloalkyl;

a) both $\mathbf{R^x}$ are hydrogen or both $\mathbf{R^x}$ are fluoro;

$\mathbf{R^3}$ is -C(O)$\mathbf{R^Z}$**;** and

$\mathbf{R^Z}$ is -$C_{4\text{-}10}$-alkylene-C(O)OH.

[00010] Another example is directed to pharmaceutical compositions comprising the Compound of Formula (**I**), Formula I-P, Formula I-P-1, Formula (**III**-P), Formula III-P-1, Formula (3000), or Formula (**III**) and a pharmaceutically acceptable carrier, diluent, and/or excipient.

[00011] Another example is directed to methods useful for the treatment of various diseases, disorders, or conditions comprising administering a Compound of Formula I, Formula I-P, Formula I-P-1, Formula (**III**-P), Formula III-P-1, Formula (3000), or Formula (**III**) or administering a pharmaceutical composition comprising a Compound of Formula I, Formula I-P, Formula I-P-1, Formula (**III**-P), Formula III-P-1, Formula (3000), or Formula (**III**) and a pharmaceutically acceptable carrier, diluent, and/or excipient.

[0011a] Another aspect is directed to use of a compound of Formula (III) as defined herein in the manufacture of a medicament for the treatment of a disease, disorder, or condition associated with glucocorticoid receptor signaling wherein the disease, disorder, or condition, is an inflammatory disease, disorder, or condition.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[0010] FIGS. 1A, 1B, and 1C, and 2 show GR activation of steroid-ADCs as tested in Example 7.

[0011] FIG. 3 shows Scheme 1. Synthesis of Spacer-Budesonide 1c-1e, 1g-1i, and 1j-1l.

DETAILED DESCRIPTION

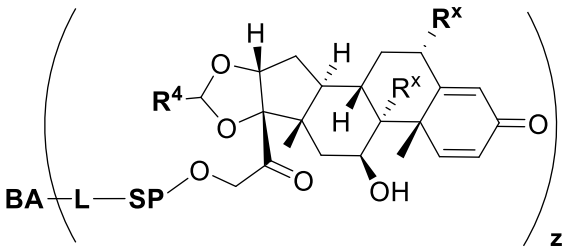
A. DEFINITIONS

[0012] As used herein, "alkyl" refers to a monovalent and saturated hydrocarbon radical moiety. Unless specified otherwise, Alkyl is unsubstituted and can be linear, branched, or cyclic, *i.e.*, cycloalkyl. Alkyl includes, but is not limited to, those having 1–20 carbon atoms, *i.e.*, $C_{1–20}$ alkyl; 1–12 carbon atoms, *i.e.*, $C_{1–12}$ alkyl; 1–8 carbon atoms, *i.e.*, $C_{1–8}$ alkyl; 1–6 carbon atoms, *i.e.*, $C_{1–6}$ alkyl; and 1–3 carbon atoms, *i.e.*, $C_{1–3}$ alkyl. Cycloalkyl, which is a subset of alkyl includes, but is not limited to, groups having 3–20 carbon atoms, *i.e.*, $C_{3–20}$ alkyl; 3–12 carbon atoms, *i.e.*, $C_{3–12}$ alkyl; 3-10 carbon atoms, *i.e.*, $C_{3–10}$ alkyl; 3–8 carbon

CLAIMS

What is claimed is:

1. A Compound of Formula (**III**)



(**III**);

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

wherein

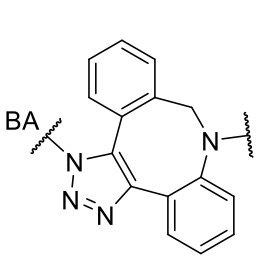
$\mathbf{R^4}$ is alkyl, aryl, arylalkyl, or an N-containing heterocycloalkyl;

either both $\mathbf{R^x}$ are hydrogen or both $\mathbf{R^x}$ are fluoro;

SP is -C(O)-C_1-C_{10}-alkylene-C(O)-;

L is a linker of the formula $–L^1$-L^2-$(L^3)_{0\text{-}1}$-; where $\mathbf{L^1}$ is attached to **BA** and $\mathbf{L^3}$ is attached to **SP**;

$\mathbf{L^1}$ is a reactive group residue selected from the group consisting of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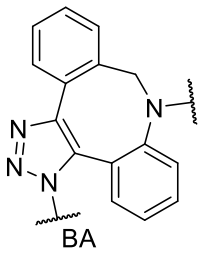
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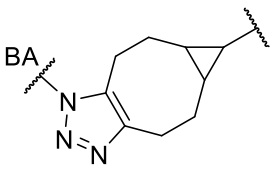
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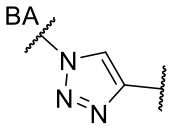
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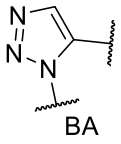

where

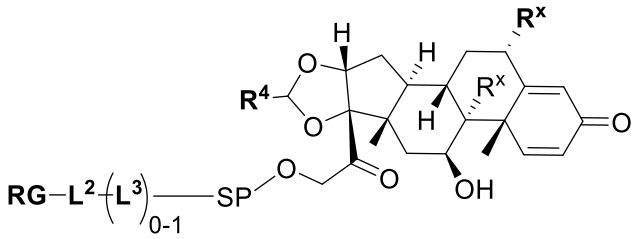
is a bond to the binding agent;

$\mathbf{L^2}$ is a connecting linker; and

$\mathbf{L^3}$, when present, is a self-immolative linker; and

BA is a binding agent.

2. A Compound of Formula (**II**)



(**II**);

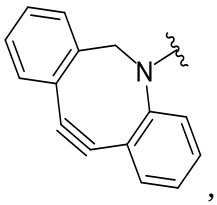
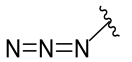
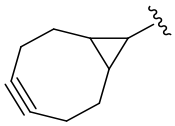
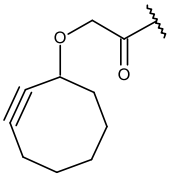
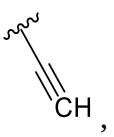
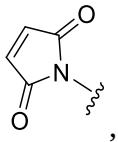
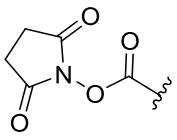
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,

wherein

R4 is alkyl, aryl, arylalkyl, or an N-containing heterocycloalkyl;

either both **Rx** are hydrogen or both **Rx** are fluoro;

SP is -C(O)-C_1-C_{10}-alkylene-C(O)-;

RG is a reactive group selected from the group consisting of , , , , , , and ;

L2 is a connecting linker; and

L3, when present, is a self-immolative linker.

3. The Compound of Claim 1 or 2, where **R4** is linear or branched alkyl.

4. The Compound of Claim 1 or 2, where **R4** is aryl.

5. The Compound of Claim 1 or 2, where **R4** is arylalkyl.

6. The Compound of Claim 1 or 2, where **R4** is N-containing heterocycloalkyl.

7. The Compound of any one of Claims 1-6, where R^4 is in the (*R*)-configuration.

8. The Compound of any one of Claims 1-7, where **SP** is -C(O)-C_2-C_5-alkylene-C(O)-.

9. The Compound of any one of Claims 1-8, where **SP** is -C(O)-CH_2CH_2-C(O)-.

10. The Compound of any one of Claims 1-9, where both **Rx** are hydrogen.

11. The Compound of any one of Claims 1-9, where both $\mathbf{R^x}$ are fluoro.

12. The Compound of Formula (**III**) of any one of Claims 1 or 3-11, where **z** is selected from one to ten, inclusive.

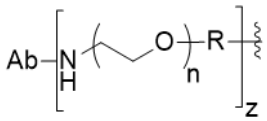
13. The Compound of Formula (**III**) of any one of Claims 1 or 3-11, where **z** is selected from two to four, inclusive.

14. The Compound of Formula (**III**) of any one of Claims 1 or 3-13, where **z** is four.

15. The Compound of Formula (**III**) of any one of Claims 1 or 3-13, where **z** is two.

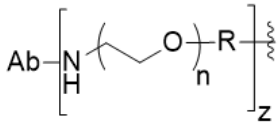
16. The Compound of Formula (**III**) of any one of Claims 1 or 3-15, where **BA** comprises an antibody, an antibody fragment, or an antigen binding fragment thereof.

17. The Compound of Formula (**III**) of any one of Claims 1 or 3-15, where **BA** comprises an antibody or antigen binding fragment thereof having the following structure



where **Ab** is a monoclonal antibody, polyclonal antibody, antibody fragment, or bispecific antibody; **R** is $C_{2\text{-}4}$-alkylene, **n** is an integer selected from one to ten, inclusive, and **z** is an integer selected from one to ten, inclusive.

18. The Compound of Formula (**III**) of any one of Claims 1 or 3-15, where **BA** comprises an antibody or antigen binding fragment having the following structure



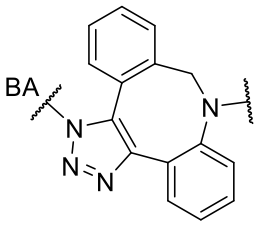
where **Ab** is a monoclonal antibody, polyclonal antibody, antibody fragment, or bispecific antibody; **R** is $C_{2\text{-}4}$-alkylene; and **n** is an integer selected from two to four, inclusive.

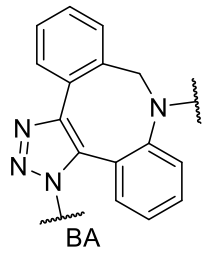
19. The Compound of Formula (**III**) of any one of Claims 1 or 3-18, where **BA** comprises an antibody or antigen binding fragment thereof that binds macrophage scavenger receptor 1 (MSR1).

20. The Compound of Formula (**III**) of any one of Claims 1 or 3-19, where **L** is $\mathbf{-L^1-L^2-}$, where $\mathbf{L^1}$ is attached to **BA** and $\mathbf{L^2}$ is attached to **SP**; and where $\mathbf{L^1}$ is a reactive group residue; and $\mathbf{L^2}$ is connecting linker.

21. The Compound of Formula (**III**) of any one of Claims 1 or 3-19, where **L** is -$\mathbf{L^1}$-$\mathbf{L^2}$-$\mathbf{L^3}$-.

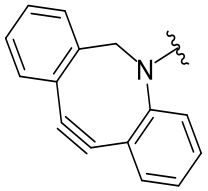
22. The Compound of Formula (**III**) of Claim 20 or 21 where $\mathbf{L^1}$ is selected from

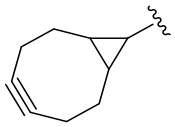
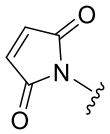


and


where

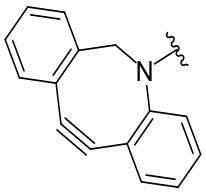

is a bond to BA.

23. The Compound of Formula (**II**) of any one of Claims 2-11, where **RG** is selected from the group consisting of


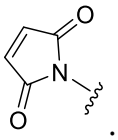
,

, and


.

24. The Compound of Formula (**II**) of any one of Claims 2-11, where **RG** is

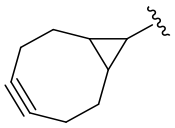


.

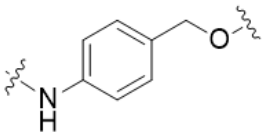
25. The Compound of Formula (**II**) of any one of Claims 2-11, where **RG** is


.

26. The Compound of Formula (**II**) of any one of Claims 2-11, where **RG** is


.

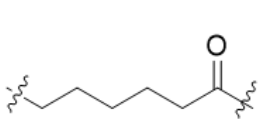
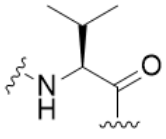
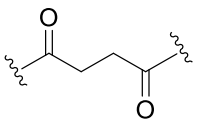
27. The Compound of any one of claims 1-26, where for the Compound of Formula (**III**), **L** is -$\mathbf{L^1}$-$\mathbf{L^2}$-$\mathbf{L^3}$-)$_{0\text{-}1}$-; and where

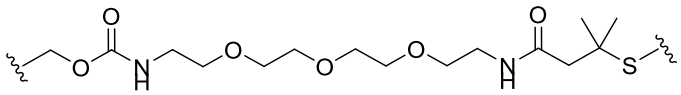
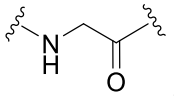
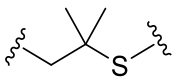
L³ in the Compound of Formula (**II**) or (**III**) is  where the -NH-group is attached to **L²**, when **SP** is -C(O)-C_1-C_{10}-alkylene-C(O)-; or

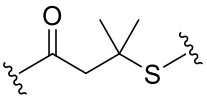
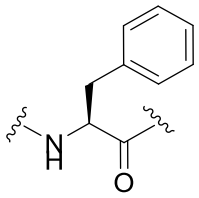
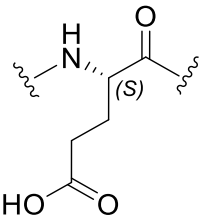
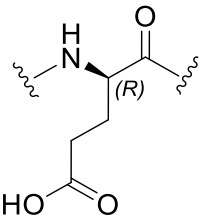
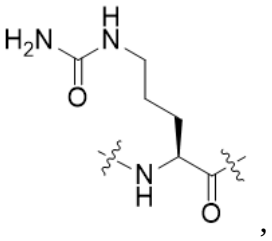
L³ in the Compound of Formula (**II**) or (**III**) is absent.

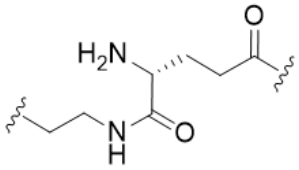
28. The Compound of any one of claims 1-27, where for the Compound of Formula (**III**), **L** is -**L¹**-**L²**-**L³**)$_{0\text{-}1}$-; and where **L²** in the Compound of Formula (**II**) or (**III**) comprises PEG, a di-peptide residue, a tripeptide residue, a tetrapeptide residue, a pentapeptide residue, -C(O)CH_2CH_2C(O)-, a cyclodextrin (CD) residue, or -$CH_2CH_2CH_2CH_2CH_2$C(O)-, or any combination thereof.

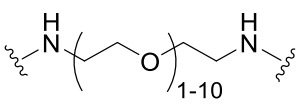
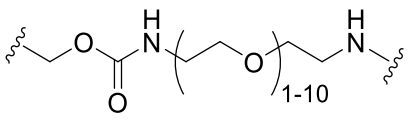
29. The Compound of any one of claims 1-27, where for the Compound of Formula (**III**) **L** is -**L¹**-**L²**-(**L³**)$_{0\text{-}1}$-; and where **L²** in the Compound of Formula (**II**) or (**III**) comprises

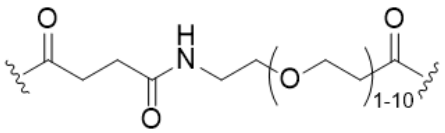
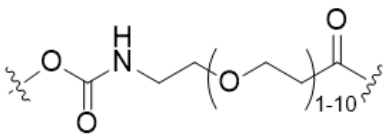
, , ,

, , ,

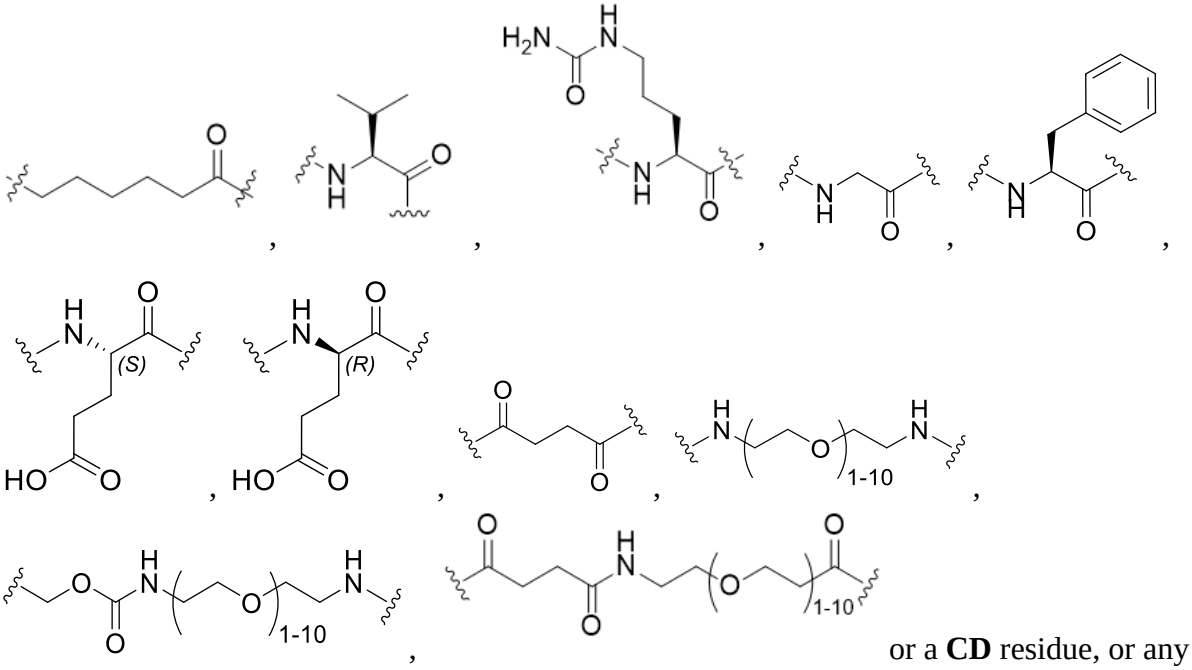
, , , , ,

,

-C(O)CH_2CH_2C(O)NH-, , ,

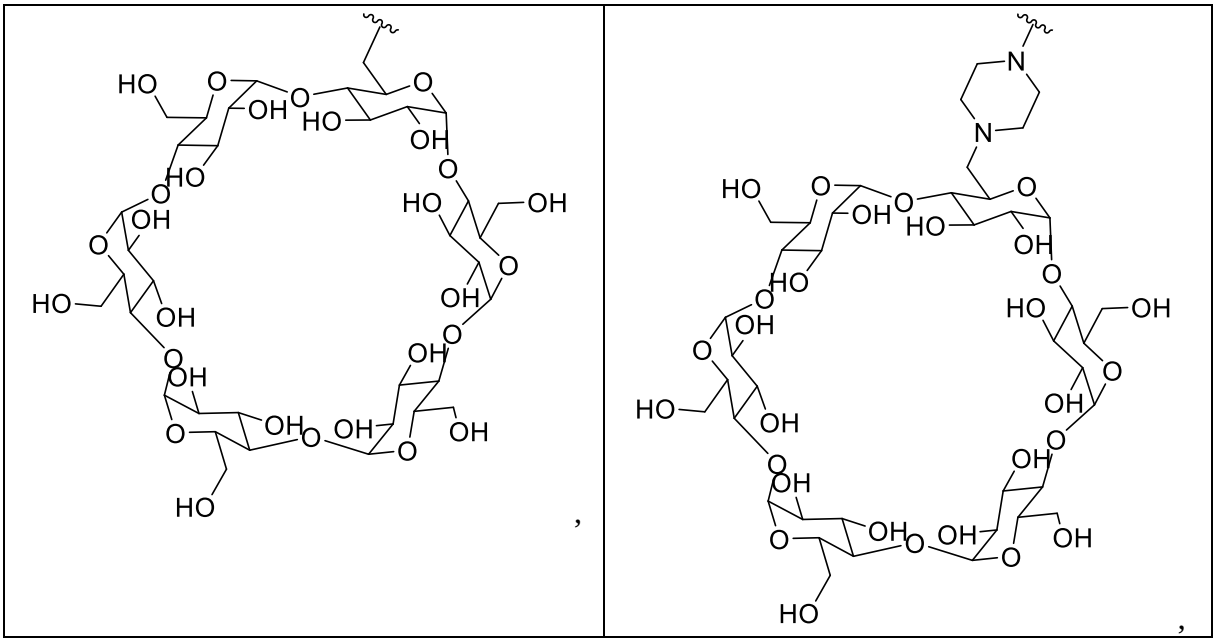
, , or a cyclodextrin residue (**CD**); or any combination thereof.

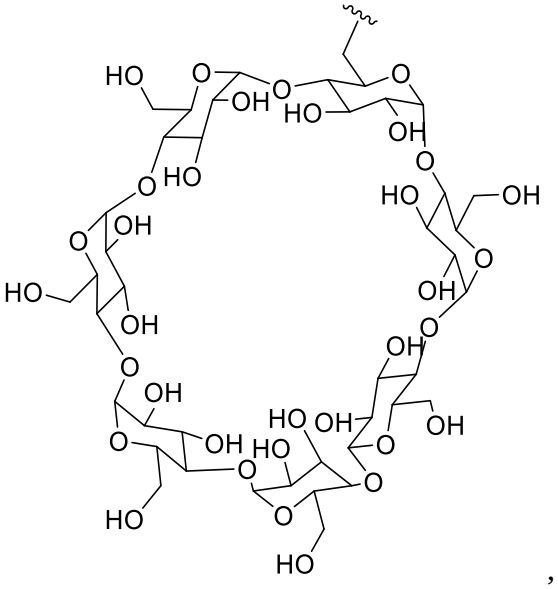
30. The Compound of any one of claims 1-27, where for the Compound of Formula (**III**), **L** is -$\mathbf{L^1}$-$\mathbf{L^2}$-$\mathbf{L^3}$)$_{0\text{-}1}$-; and where $\mathbf{L^2}$ in the Compound of Formula (**II**) or (**III**) comprises



or a **CD** residue, or any combination thereof.

31. The compound of any one of claims 28-30, wherein **CD** is selected from the group consisting of

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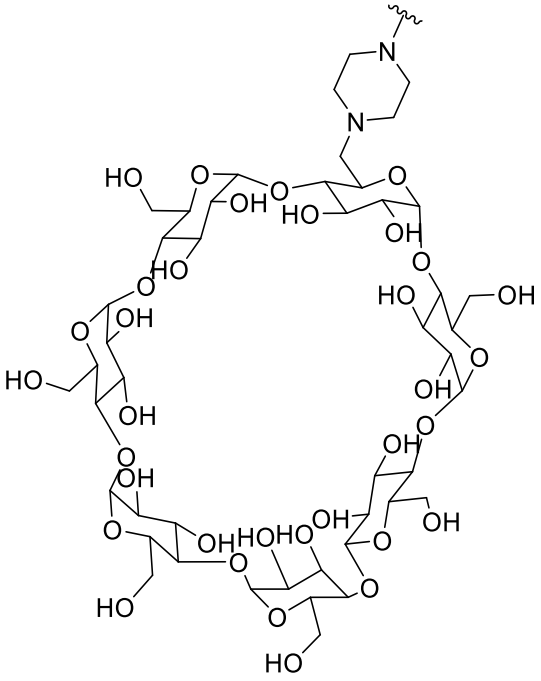
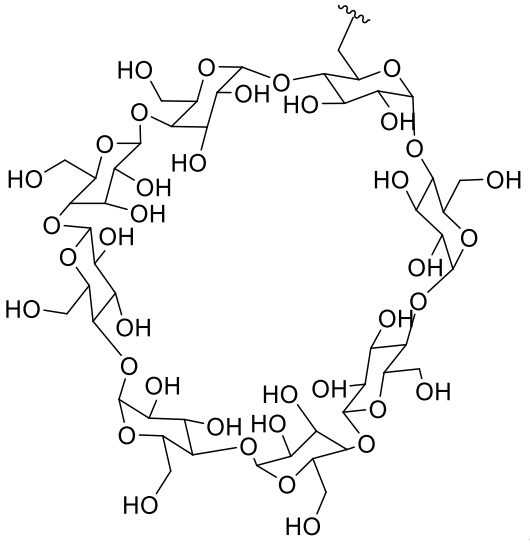
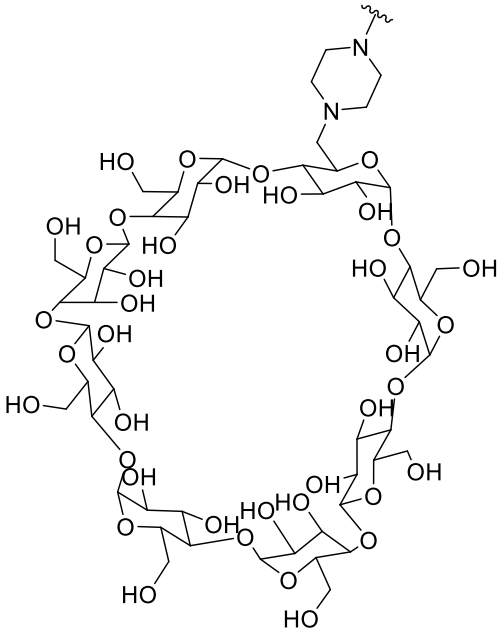
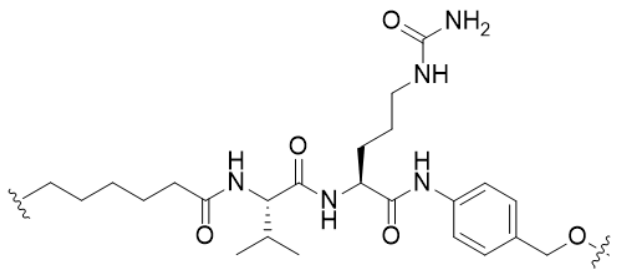
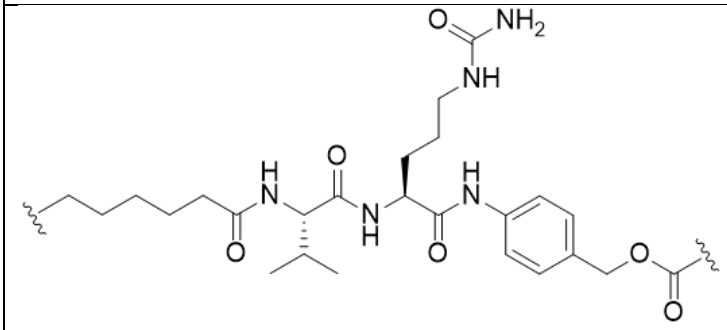
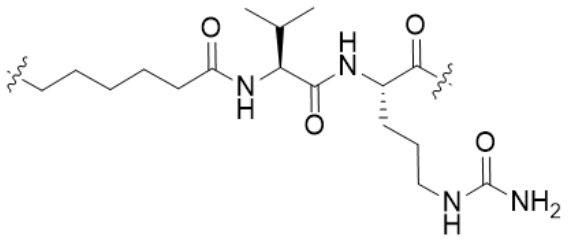
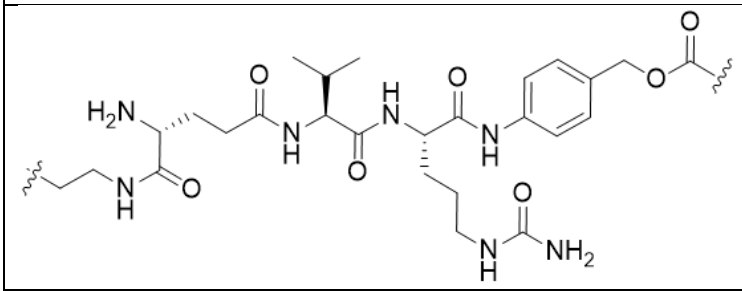

,

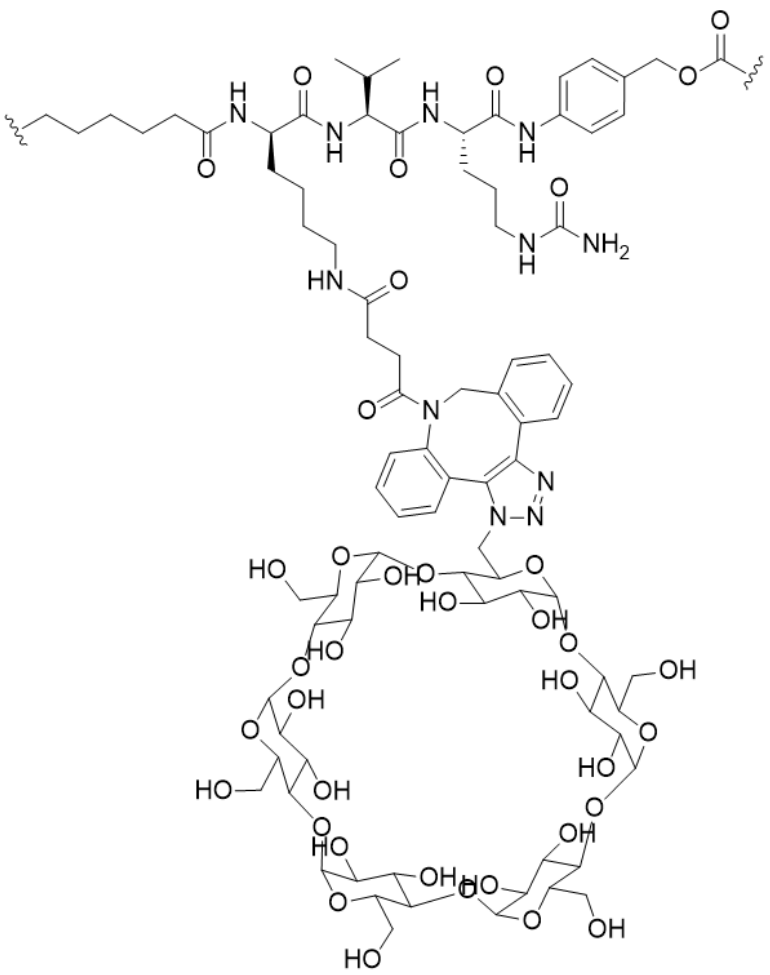

,

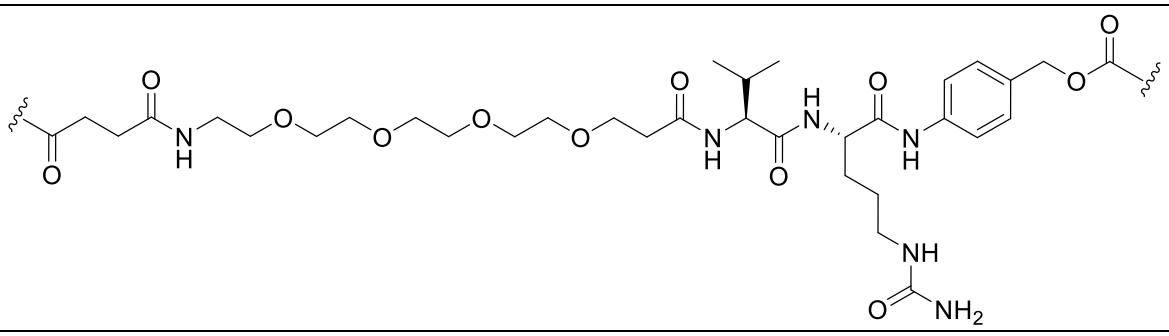
and

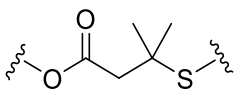

.

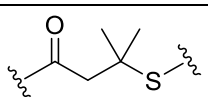
32. The Compound of any one of Claims 1-26, where for the Compound of Formula (**III**), **L** is -$\mathbf{L^1}$-$\mathbf{L^2}$-$\mathbf{L^3}$)$_{0\text{-}1}$-; and where -$\mathbf{L^2}$-($\mathbf{L^3}$)$_{0\text{-}1}$- in the Compound of Formula (**II**) or (**III**) comprises

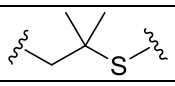





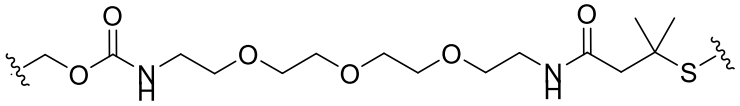


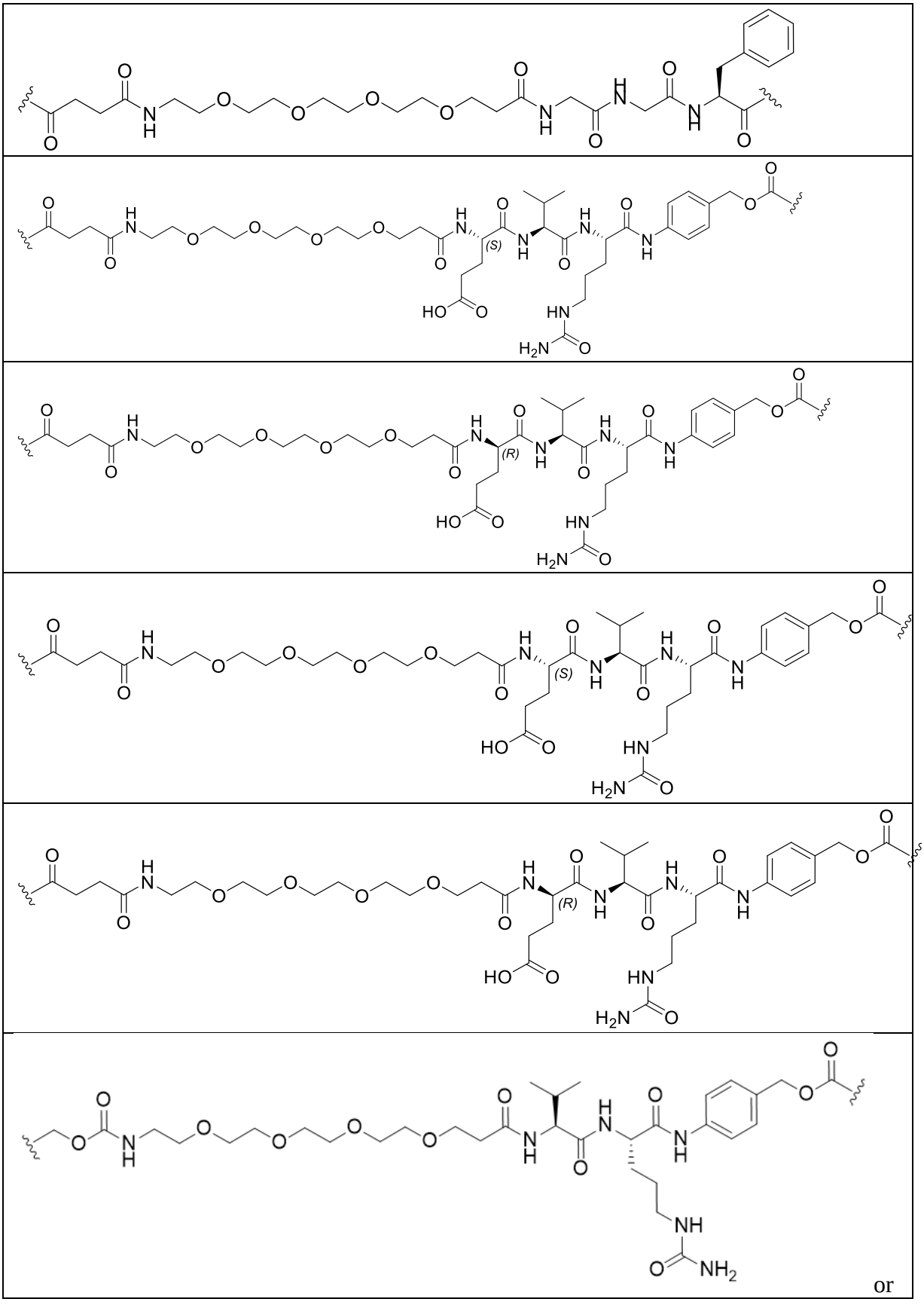


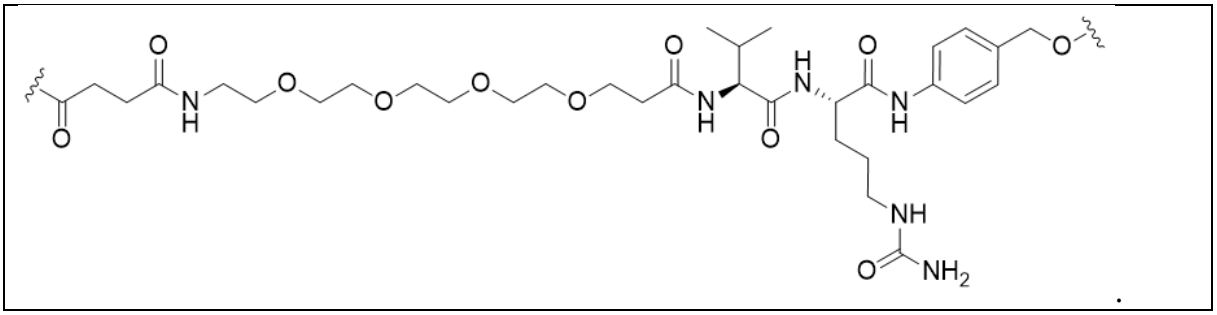




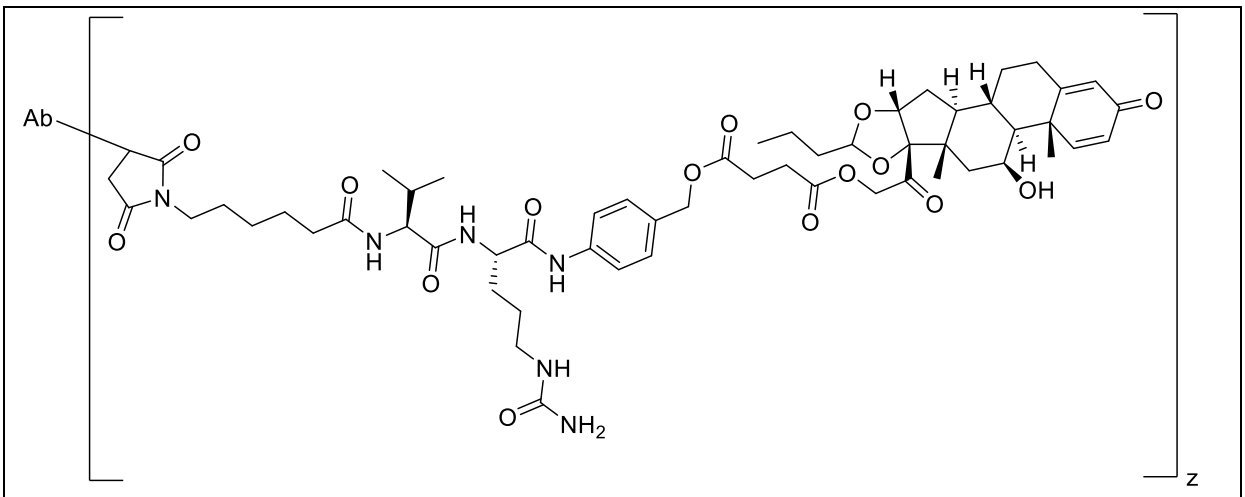




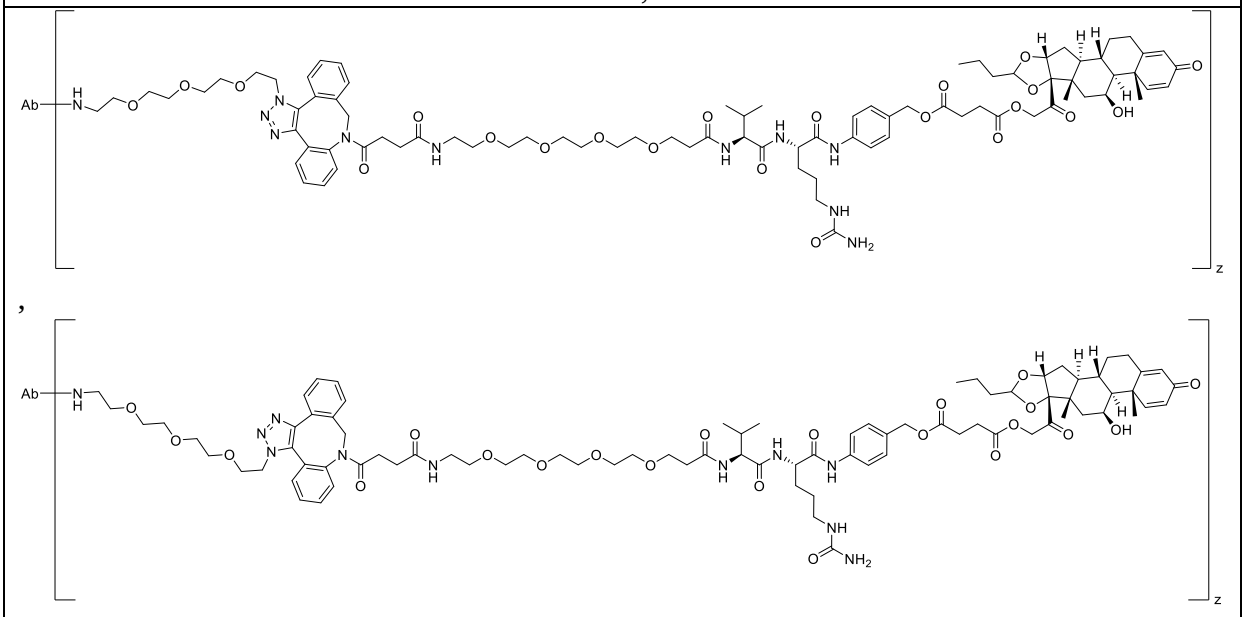

or



33. The compound of claim 1, wherein the compound is

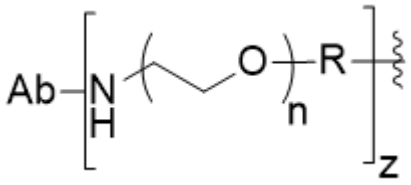


wherein the linker-payload is connected to Ab through a side chain of a cysteine residue; or a stereoisomer or mixture of stereoisomers thereof;



or a mixture thereof;

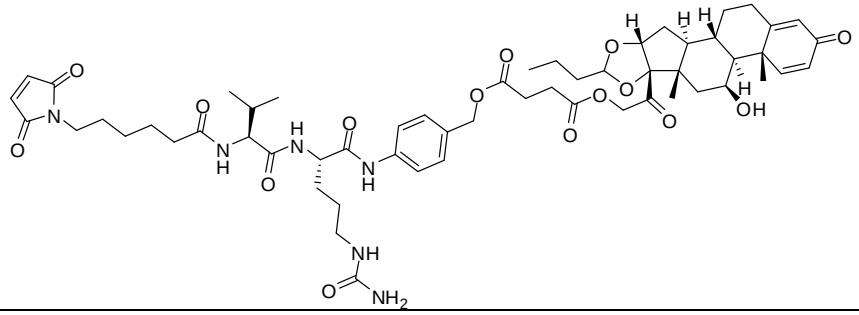
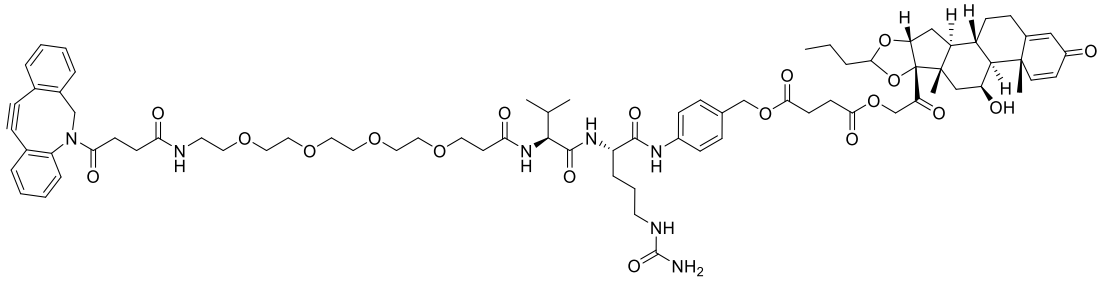
where **BA** comprises an antibody or antigen binding fragment having the following structure



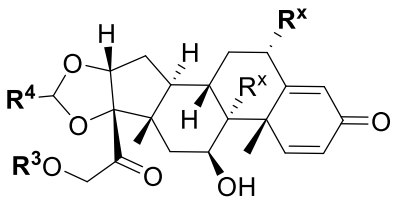
where **Ab** is a monoclonal antibody, polyclonal antibody, antibody fragment, or bispecific antibody; **R** is C_{2-4}-alkylene; and **n** is an integer selected from two to four, inclusive.

34. The compound of claim 33, wherein **Ab** is an antibody or antigen binding fragment thereof that binds macrophage scavenger receptor 1 (MSR1).

35. The compound of claim 2, wherein the compound is selected from the group consisting of

2f	
2g	

36. A Compound according to Formula (**I**)



(**I**);

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

wherein

R^4 is alkyl, aryl, arylalkyl, or an N-containing heterocycloalkyl;

a) both **R^x** are hydrogen or both **R^x** are fluoro;

$\mathbf{R^3}$ is -C(O)$\mathbf{R^Z}$**;** and

$\mathbf{R^Z}$ is -$C_{4\text{-}10}$-alkylene-C(O)OH.

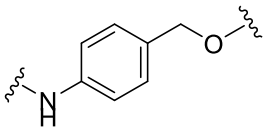
37. The Compound of Claim 36, where $\mathbf{R^4}$ is alkyl.

38. The Compound of Claim 36 or 37, where $\mathbf{R^4}$ is in the (*R*)-configuration.

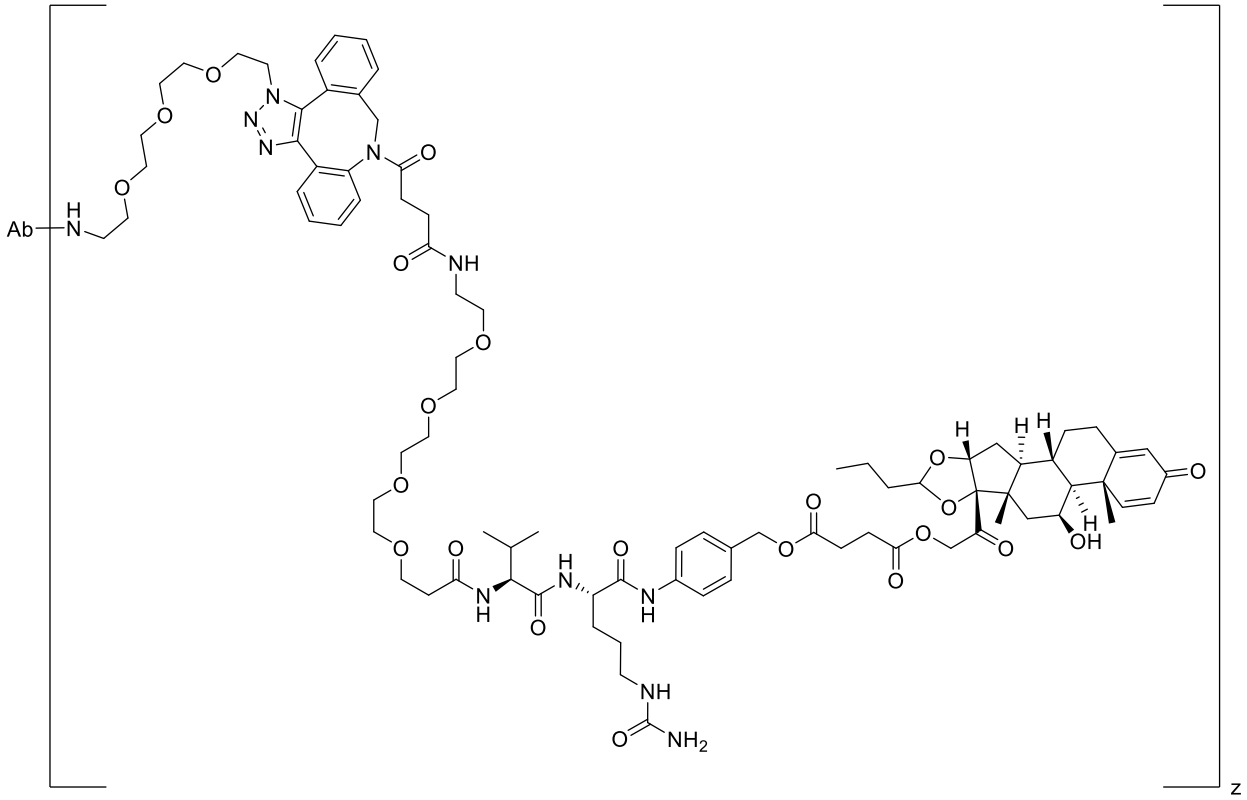
39. The compound of any one of Claims 36-38, where both $\mathbf{R^x}$ are fluoro.

40. Use of a compound of Formula (III) of any one of claims 1-21 and 27-34 in the manufacture of a medicament for the treatment of a disease, disorder, or condition associated with glucocorticoid receptor signaling wherein the disease, disorder, or condition, is an inflammatory disease, disorder, or condition.

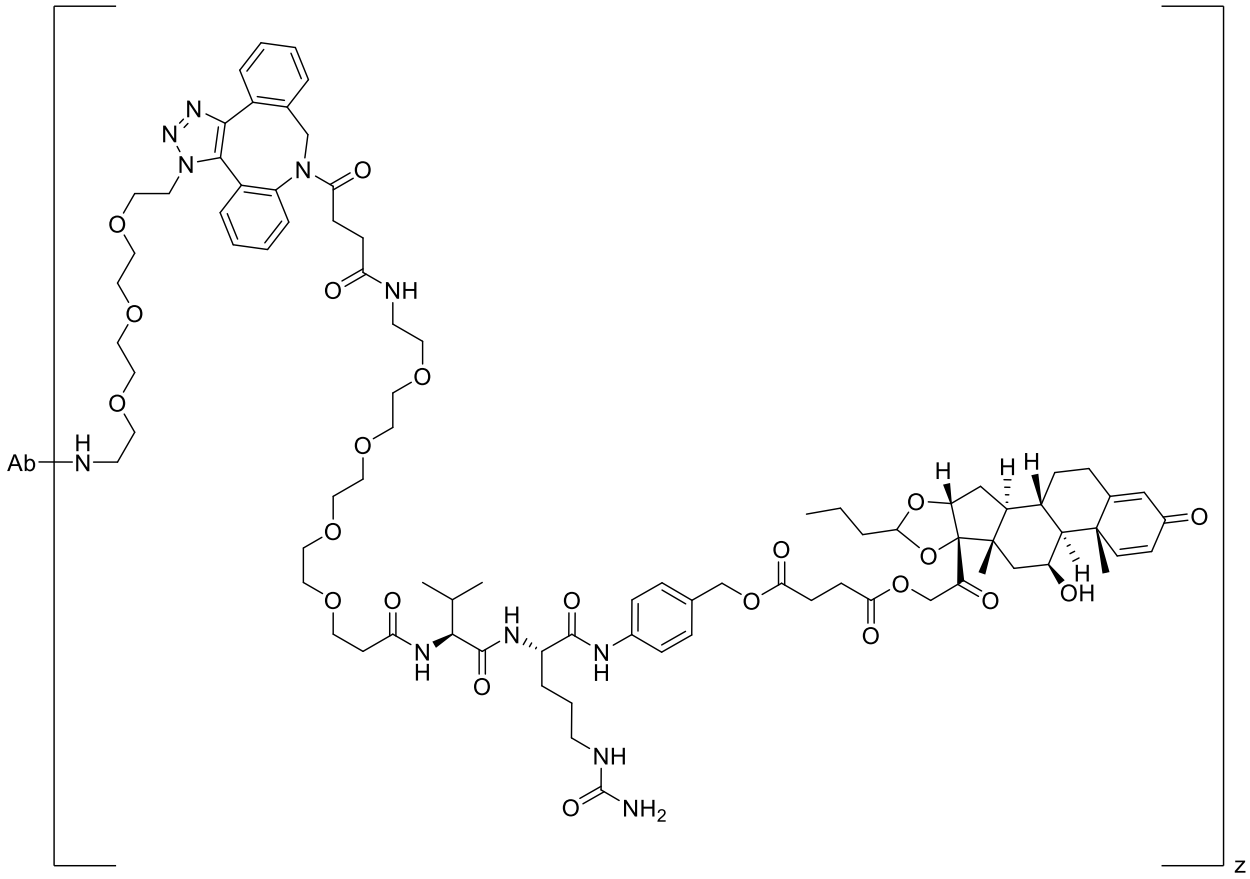
41. The use of claim 40, wherein side effects associated with administration of an unconjugated steroid payload of said compound are reduced.

42. The Compound of claim 1, wherein for the Compound of Formula (**III**), **L** is -$\mathbf{L^1}$-$\mathbf{L^2}$-$\mathbf{L^3}$)$_{0\text{-}1}$-; **SP** is -C(O)-C_1-C_{10}-alkylene-C(O)-; and $\mathbf{L^3}$ is  where the -NH- group is attached to $\mathbf{L^2}$.

43. The Compound of claim 1 selected from the group consisting of



; and



;

wherein **Ab** is an antibody or an antigen binding fragment thereof; and

z is an integer from one to four.