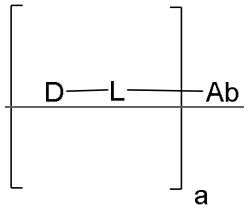
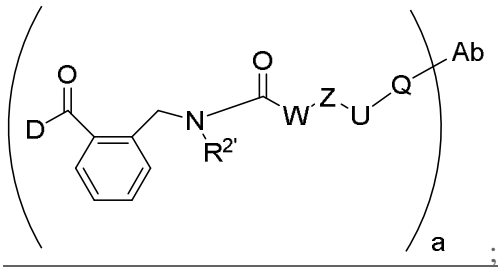
~~WHAT IS CLAIMED IS:~~

CLAIMS

1. A compound of the formula ~~(I):~~:



~~(I),~~



;

or a pharmaceutically acceptable salt thereof, wherein:

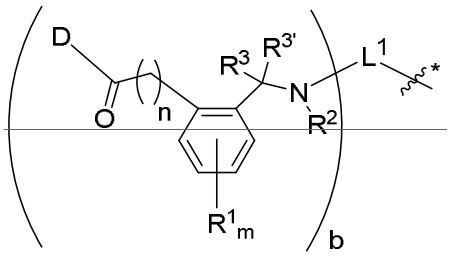
~~a is an integer from 1 to 20;~~

~~Ab is an anti-CCR2 antibody, anti-CCR2 antibody fragment, or an anti-CCR2 antigen-binding fragment;~~

~~D is a modulator of STING activity comprising an amino group on a guanine base, a guanine base derivative, an adenine base, or an adenine base derivative; and~~

~~L is a linker that, is covalently bonded to Ab; and is also covalently bonded to said amino group on D.~~

~~2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein D-L is represented by the formula (Ia):~~



~~(Ia);~~

~~wherein:~~

~~denotes the point of attachment to Ab;~~

~~b is an integer from 1 to 20;~~

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

~~n is 0 or 1;~~

~~each R^1 is independently selected from C_1-C_4alkyl, O-C_1-C_4alkyl, and halogen;~~

~~R^2 is selected from C_1-C_4alkyl and $-(CH_2CH_2O)_s$-CH_3, wherein s is an integer from 1 to 10;~~

~~R^3 and $R^{3'}$ are each independently selected from hydrogen and C_1-C_3alkyl; and~~

~~L^1 is a cleavable linker fragment.~~

~~3. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein:~~

a is an integer from 1 to 8;

~~b~~Ab is an ~~integer from 1 to 10; and~~

~~m is 0.~~

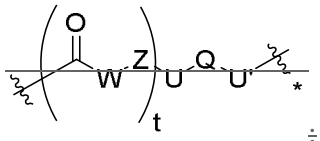
~~4. A compound of claim 2~~anti-CCR2 antibody or ~~3, or a pharmaceutically acceptable salt thereof, wherein:~~

~~m is 0;~~

~~n is 0; and~~

~~R^3 and $R^{3'}$ are each hydrogen.~~

~~5. A compound of any one of claims 2 to 4, or a pharmaceutically acceptable salt thereof, wherein L^+ is~~



~~wherein:~~

~~ is the point of attachment to the nitrogen atom of formula (Ia);~~

~~ is the point of attachment to Ab;~~

~~t is~~ an ~~integer from 1 and 10~~anti-CCR2 antigen-binding fragment;

$R^{2'}$ is C_1-C_4alkyl;

W is ~~absent or a self-immolative group;~~

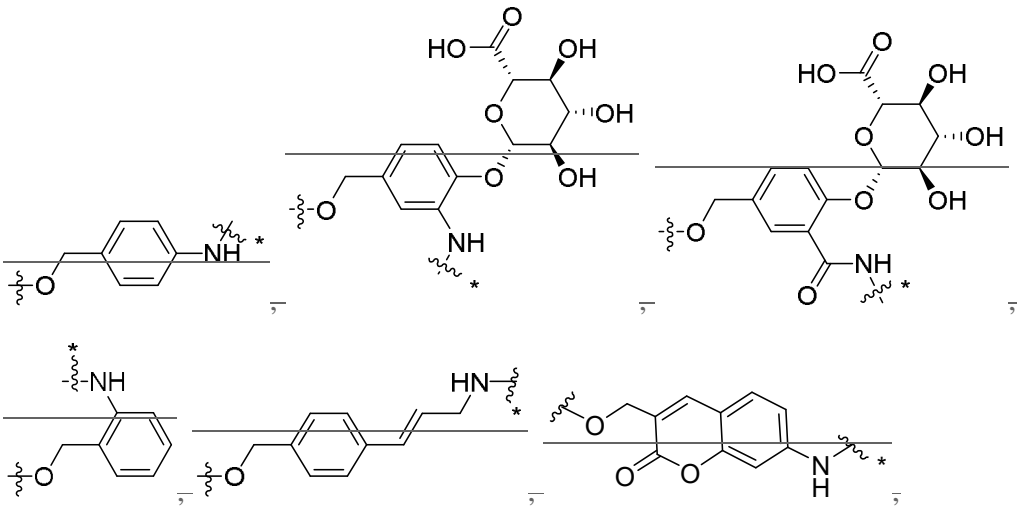
~~Z is absent or a peptide of 2 to 5 amino acids;~~

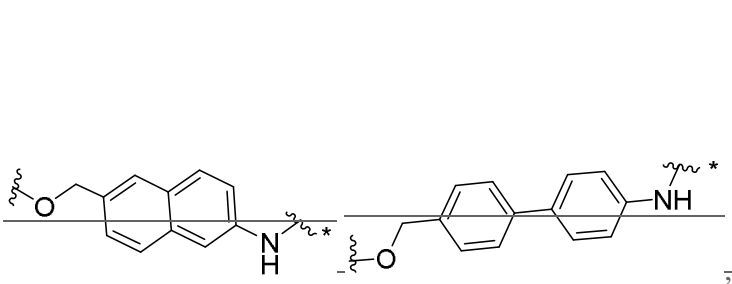
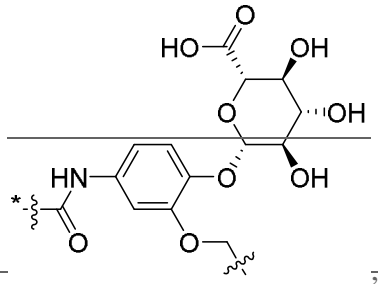
~~U and U' are independently absent or a spacer; and~~

~~Q is a heterobifunctional group;~~

~~1.~~ ~~provided that W and Z are not both absent.~~

~~6. A compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein W is a self-immolative group~~ selected from~~:~~

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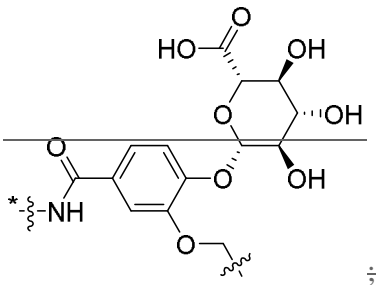
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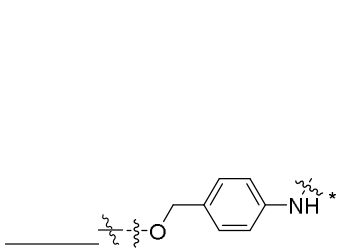
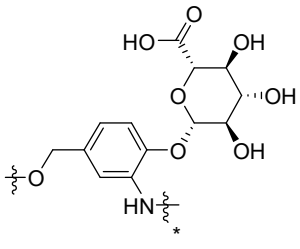
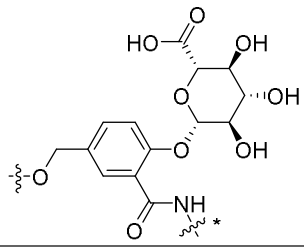
wherein:

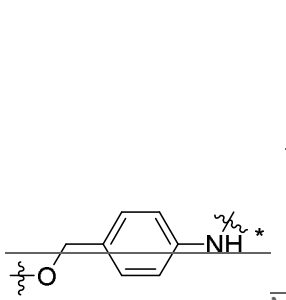
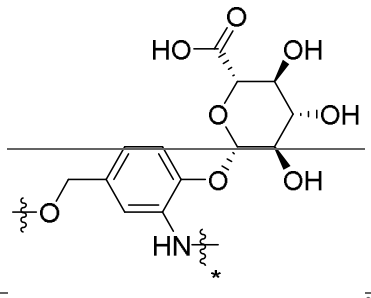



, and

; wherein

is the point of attachment to the carbonyl group; and

is the point of attachment to Z.;

7. A compound of claim 5 or 6, or a pharmaceutically acceptable salt thereof, wherein W is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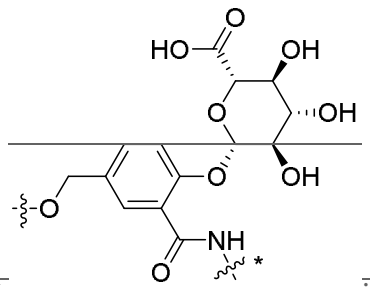
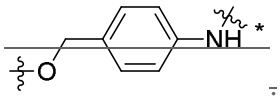

.

8. A compound of any one of claims 5 to 7, or a pharmaceutically acceptable salt thereof, wherein W is



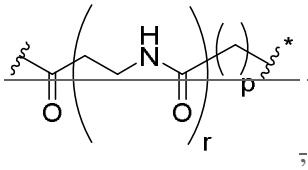
9. A compound of any one of claims 5 to 8, or a pharmaceutically acceptable salt thereof, wherein Z is a peptide capable of being enzymatically cleaved.

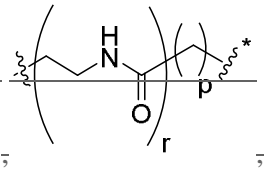
10. A compound of any one of claims 5 to 9, or a pharmaceutically acceptable salt thereof, wherein Z is cathepsin cleavable.

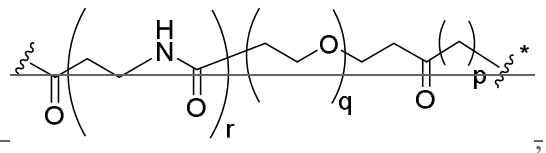
11. A compound of any one of claims 5 to 10, or a pharmaceutically acceptable salt thereof, wherein Z is a two-amino acid peptide selected from Val-Cit, Cit-Val, Val-Ala, Ala-Val, Phe-Lys, and Lys-Phe.

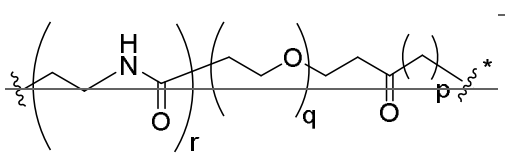
12. A compound of any one of claims 5 to 11, or a pharmaceutically acceptable salt thereof, wherein Z is Ala-Val or Val-Ala.

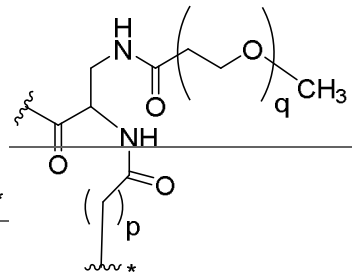
13. A compound of any one of claims 5 to 12, or a pharmaceutically acceptable salt thereof, wherein U' is absent and U is selected from

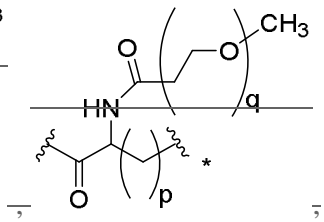


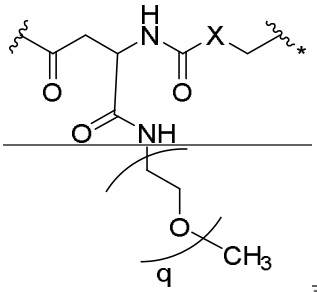


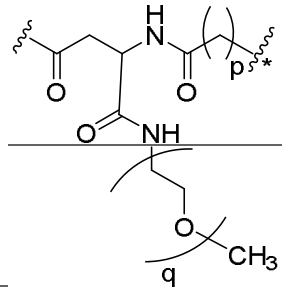












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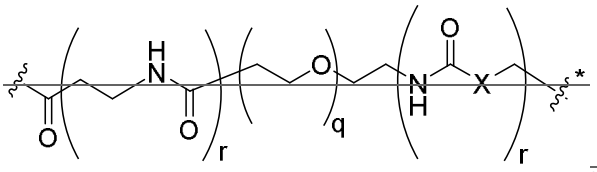
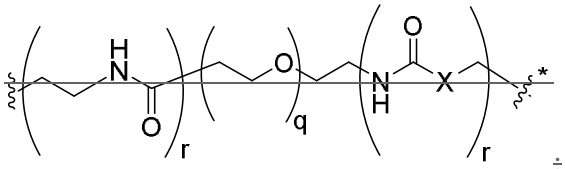


~~, and~~



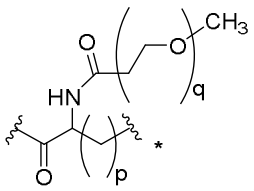
~~;~~

~~wherein:~~

~~is the point of attachment to Z;~~

~~is the point of attachment to Q;~~

Z is Ala-Val or Val-Ala;

U is  ; wherein

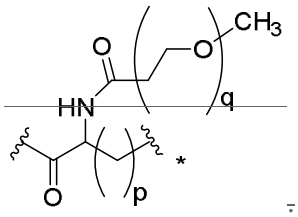
p is an integer from 1 to 6;

q is an integer from 1 to 20;

~~X is O or $-CH_2-$; and~~

~~each r is independently 0 or 1.~~

~~14. A compound of any one of claims 5 to 13, or a pharmaceutically acceptable salt thereof, wherein U' is absent and U is:~~



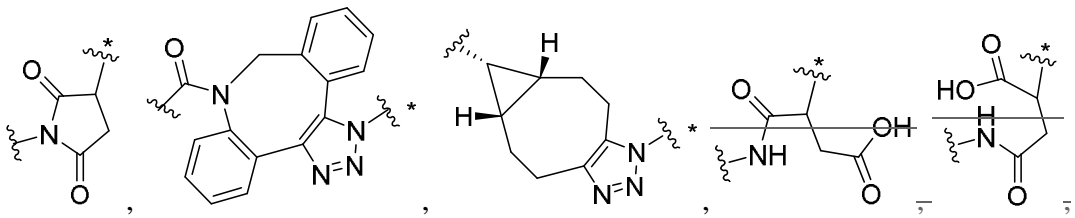
15. A compound of any one of claims 5 to 14, or a pharmaceutically acceptable salt thereof, wherein Q is a heterobifunctional group which is attached to U' or, when U' is absent, is attached to Ab through chemical or enzyme-mediated conjugation.

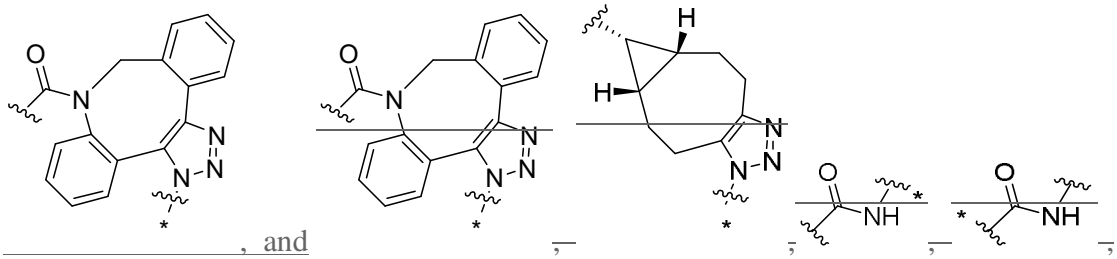
A compound of any one of claims 5 to 15, or a pharmaceutically acceptable salt thereof, wherein is the point of attachment to Z;

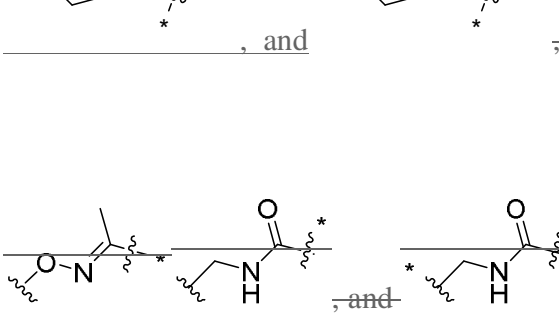
is the point of attachment to Q;

Q is selected from

16. Q is selected from







wherein

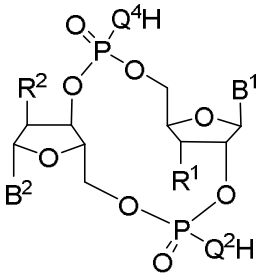
~~is the point of attachment to U or, when U is absent, the point of attachment to Z; and~~

~~is~~ the point of attachment to ~~U', or, when U' is absent,~~ U;

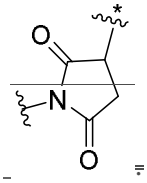
is the point of attachment to Ab~~.~~;

~~17. A compound A compound of any one of claims 5 to 16, or a pharmaceutically acceptable salt thereof, wherein Q is:~~

and



D is ; wherein:



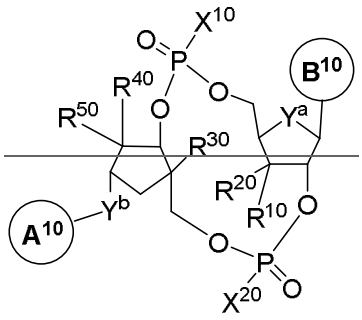
~~18. A compound of any one of claims 5 to 17, or a pharmaceutically acceptable salt thereof, wherein t is 1.~~

~~19. A compound of any one of claims 2 to 18, or a pharmaceutically acceptable salt thereof, wherein R^2 is CH_3, and R^3 and $R^{3'}$ are each hydrogen.~~

~~20. A compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein a is from 2 to 6.~~

21. A compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein b is 1.

22. A compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein the amino-substituted compound that modulates STING activity is a compound of formula (II):



(II),

wherein:

X^{10} is SH or OH;

X^{20} is SH or OH;

Y^a is O, S, or CH_2;

Y^b is O, S, NH, or NR^a, wherein R^a is C_1-C_4alkyl;

R^{10} is hydrogen, fluoro, OH, NH_2, OR^b, or NHR^b;

R^{20} is hydrogen or fluoro;

R^{30} is hydrogen; R^{40} is hydrogen, fluoro, OH, NH_2, OR^b, or NHR^b; or R^{30} and R^{40} are taken together to form CH_2O;

R^{50} is hydrogen or fluoro;

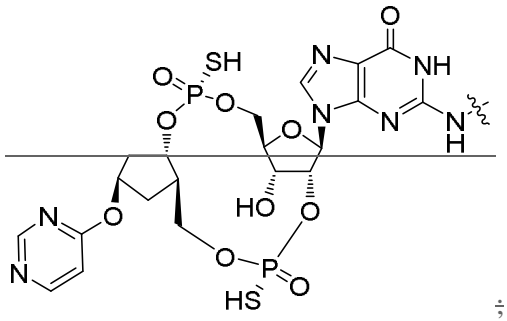
R^b is C_1-C_6alkyl, halo(C_1-C_6)alkyl, or C_3-C_6cycloalkyl;

Ring A^{10} is an optionally substituted 5- or 6-membered monocyclic heteroaryl ring containing 1-4 heteroatoms selected from N, O, or S, or an optionally substituted 9 or 10 membered bicyclic heteroaryl ring containing 1-5 heteroatoms selected from N, O, or S; wherein ring A^{10} comprises at least one N atom in the ring, and wherein Y^b is attached to a carbon atom of ring A^{10}; and

~~Ring B^{10} is an optionally substituted 9 or 10-membered bicyclic heteroaryl ring containing from 2 to 5 heteroatoms selected from N, O, or S; wherein ring B^{10} comprises at least two N atoms in the ring;~~

~~provided that either ring A^{10} or ring B^{10} is attached to 'L' in formula (I) through the amino group.~~

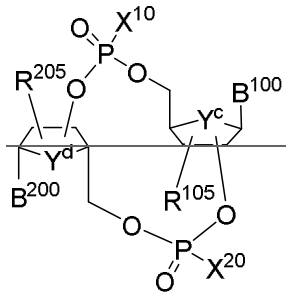
~~23. A compound of claim any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein the amino-substituted compound that modulates STING activity is~~



~~;~~

~~wherein $\sim$ is the point of attachment to 'L' in formula (I).~~

~~24. A compound of any one of claims 1 to 21, wherein the amino-substituted compound that modulates STING activity is a compound of formula (III):~~



~~(III) ;~~

~~or a pharmaceutically acceptable salt thereof; wherein~~

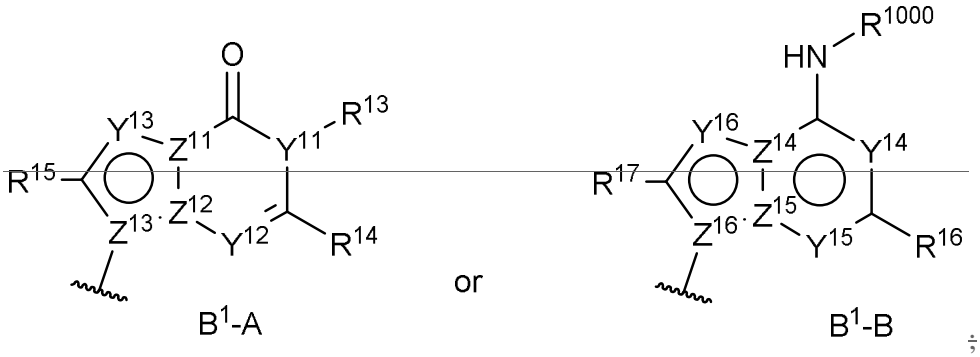
~~X^{10} is SH or OH;~~

~~X^{20} is SH or OH;~~

~~Y^e is O, S, or CH_2;~~

~~Y^d is O, S, or CH_2;~~

~~B^{100} is a group represented by formula (B^1-A) or formula (B^1-B):~~



;

~~R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are each independently a hydrogen atom or a substituent;~~

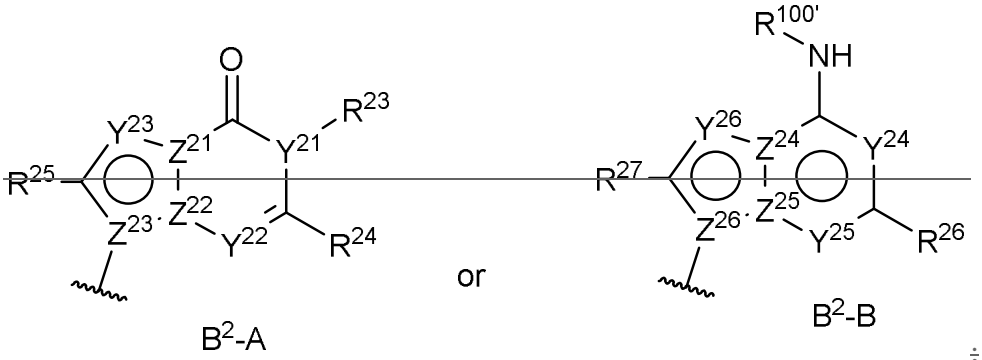
~~R^{1000} is hydrogen or a bond to the carbonyl group of formula (I);~~

~~Y^{11}, Y^{12}, Y^{13}, Y^{14}, Y^{15} and Y^{16} are each independently N or CR^{1a}, wherein R^{1a} is hydrogen or a substituent;~~

~~Z^{11}, Z^{12}, Z^{13}, Z^{14}, Z^{15} and Z^{16} are each independently N or C;~~

~~R^{105} is a hydrogen atom or a substituent;~~

~~B^{200} is a group represented by formula (B^2-A) or formula (B^2-B):~~



;

~~R^{23}, R^{24}, R^{25}, R^{26} and R^{27} are each independently a hydrogen atom or a substituent;~~

~~$R^{100'}$ is hydrogen or a bond to the carbonyl group of formula (I);~~

~~Y^{21}, Y^{22}, Y^{23}, Y^{24}, Y^{25} and Y^{26} are each independently N or CR^{2a}, wherein R^{2a} is hydrogen or a substituent;~~

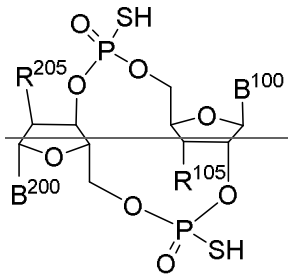
~~Z^{21}, Z^{22}, Z^{23}, Z^{24}, Z^{25} and Z^{26} are each independently N or C; and~~

~~R^{205} is a hydrogen atom or a substituent; wherein R^{105} and R^{205} are each independently attached to 2- or 3-position of the 5-membered ring they are attached to respectively;~~

~~provided that:~~

~~one of B^{100} or B^{200} is attached to 'L' in formula (I) through the amino group.~~

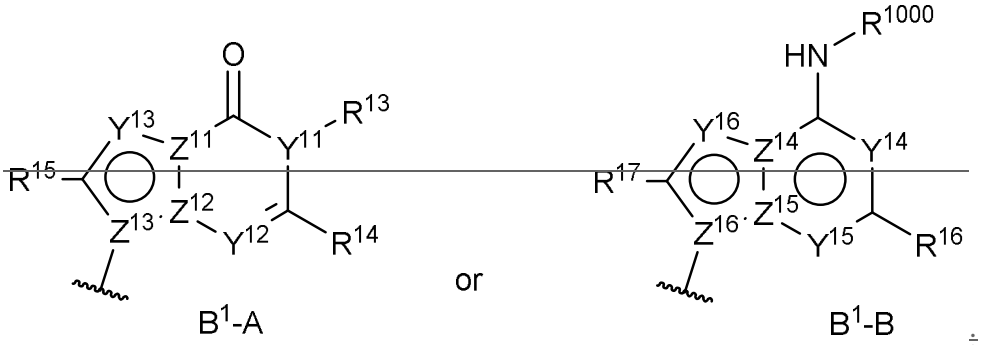
~~25. A compound of any one of claims 1 to 21 and 24, or a pharmaceutically acceptable salt thereof, wherein the amino-substituted compound that modulates STING activity is a compound of formula (IIIa):~~



~~(IIIa);~~

~~or a pharmaceutically acceptable salt thereof; wherein~~

~~B^{100} is a group represented by formula (B^1-A) or formula (B^1-B):~~



;

~~R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are each independently a hydrogen atom or a substituent;~~

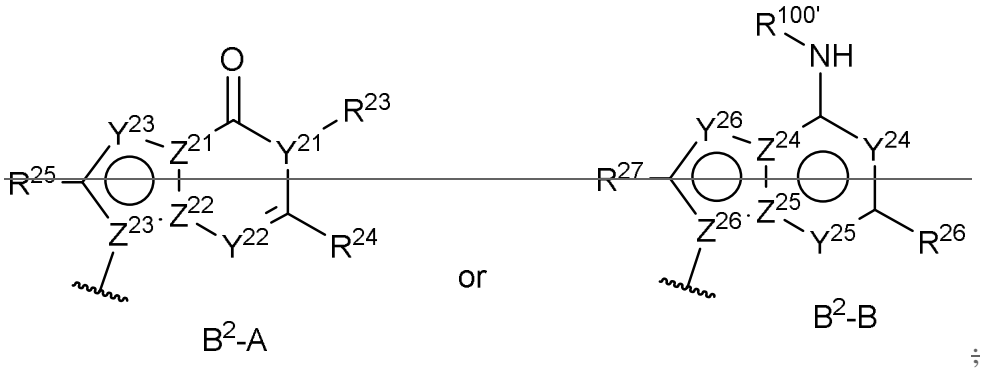
~~R^{1000} is hydrogen or a bond to the carbonyl group of formula (I);~~

~~Y^{11}, Y^{12}, Y^{13}, Y^{14}, Y^{15} and Y^{16} are each independently N or CR^{1a}, wherein R^{1a} is hydrogen or a substituent;~~

~~Z^{11}, Z^{12}, Z^{13}, Z^{14}, Z^{15} and Z^{16} are each independently N or C;~~

~~R^{105} is a hydrogen atom or a substituent;~~

~~B^{200} is a group represented by formula (B^2-A) or formula (B^2-B):~~



;

~~R^{23}, R^{24}, R^{25}, R^{26} and R^{27} are each independently a hydrogen atom or a substituent;~~

~~$R^{100'}$ is hydrogen or a bond to the carbonyl group of formula (I);~~

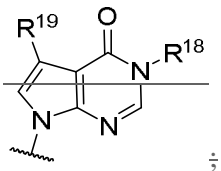
~~Y^{21}, Y^{22}, Y^{23}, Y^{24}, Y^{25} and Y^{26} are each independently N or CR^{2a}, wherein R^{2a} is hydrogen or a substituent;~~

~~Z^{21}, Z^{22}, Z^{23}, Z^{24}, Z^{25} and Z^{26} are each independently N or C; and~~

~~R^{205} is a hydrogen atom or a substituent; wherein R^{105} and R^{205} are each independently attached to 2- or 3-position of the 5-membered ring they are attached to respectively;~~

~~provided that:~~

~~one of B^{100} or B^{200} is:~~



;

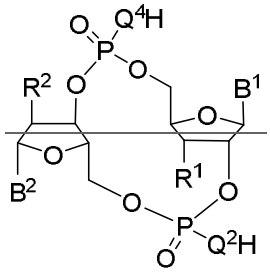
~~wherein:~~

~~R^{18} is hydrogen or C_{1-6}-alkyl;~~ and

~~R^{19} is a halogen atom;~~

~~and the other is attached to the 'L' group in formula (I) through an –NH- group.~~

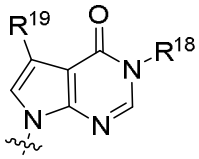
~~26. A compound of any one of claims 1 to 21, and 24, or a pharmaceutically acceptable salt thereof, wherein the amino-substituted compound that modulates STING activity is a compound of formula of formula (IV):~~



~~(IV),~~

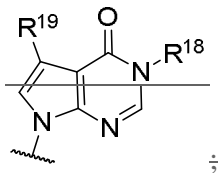
~~or a pharmaceutically acceptable salt thereof, wherein:~~

R^1 and R^2 are each independently a hydroxy group or a halogen atom;



B^1 is: ; wherein

R^{18} is hydrogen or C_{1-6} alkyl;~~B^1 is:~~

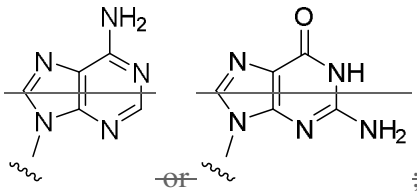


~~;~~

~~R^{18} is hydrogen or C_{1-6} alkyl;~~

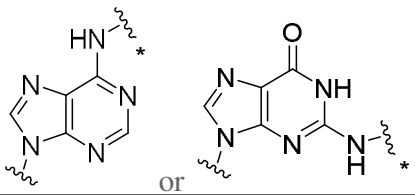
R^{19} is a halogen atom; and

~~B^2 is:~~



~~or~~ ~~; and~~

is the point of attachment to D; and



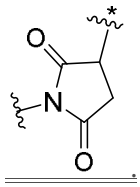
B^2 is: or ; wherein

is the point of attachment to D; and

~~*~~ is the point of attachment to the parent molecular moiety; and

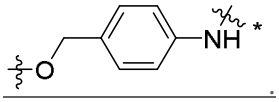
Q^2 and Q^4 are each independently an oxygen atom or a sulfur atom.

~~27.~~2. A compound of ~~any one of claims~~claim 1~~ to 21 and 24 to 26~~, or a pharmaceutically acceptable salt thereof, wherein ~~the amino-substituted compound that modulates STING activity~~Q is~~:~~



.

3. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein W is

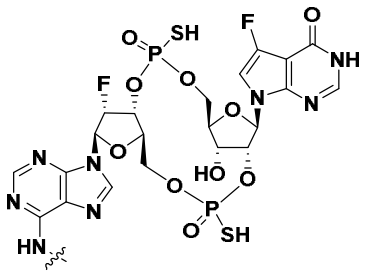


.

4. A compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^2 is –CH_3.

5. A compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein a is an integer from 2 to 6.

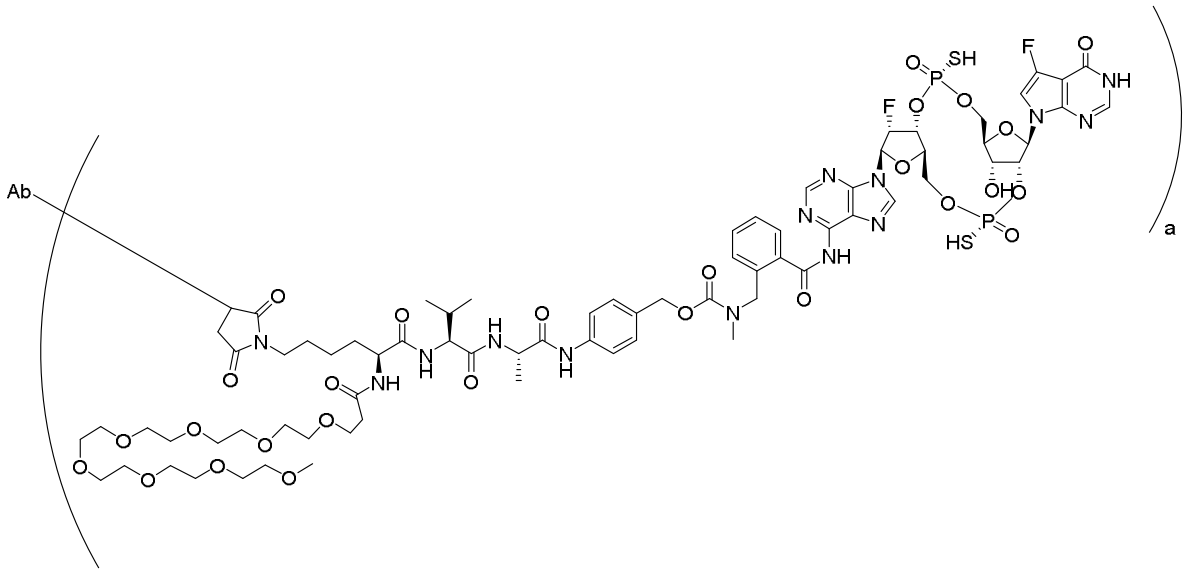
6. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein D is:



;

or a pharmaceutically acceptable salt thereof, wherein ~ is the point of attachment to ~~L~~the parent molecular moiety.

~~28.~~7. A compound of ~~any one of claims~~claim 1~~ to 21 and 24 to 26~~, or a pharmaceutically acceptable salt thereof, of formula (VI):



;

(VI);

wherein a is an integer from 1 to ~~6~~8.

~~29. A compound of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein Ab is an antibody or fragment thereof that binds human CCR2 or a portion thereof, and is capable of blocking binding of a chemokine to CCR2 and inhibiting a function of CCR2.~~

~~30.~~8. A compound of claim ~~29~~7, or a pharmaceutically acceptable salt thereof, wherein the antibody is~~ selected from the group consisting of~~ monoclonal antibody 1D9 or an antibody which can compete with 1D9 for binding to human CCR2 or a portion of CCR2~~; MC-21; STI-B020X; UniTI-101; and 4.40A68G~~.

~~31. A compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein the antibody is monoclonal antibody 1D9 or an antibody which can compete with 1D9 for binding to human CCR2 or a portion of CCR2.~~

~~32. A compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof, wherein the antibody is a chimeric antibody, a humanized antibody, a human antibody, a mouse antibody, a rat antibody, a goat antibody, or a rabbit antibody.~~

~~33.~~9. A compound of claim ~~31~~7, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody~~, anti-CCR2 antibody fragment,~~ or anti-CCR2 antigen-binding fragment comprises a light chain CDR1 comprising amino acids 24-39 of SEQ ID NO: 1; a light chain CDR2 comprising amino acids 55-61 of SEQ ID NO: 1; a light chain CDR3 comprising amino acids 94-102 of SEQ ID NO: 1; a heavy chain CDR1 comprising amino acids 31-35 of SEQ ID NO:2; a heavy chain CDR2 comprising amino acids 50-68 of SEQ ID NO:2; and a heavy chain CDR3 comprising amino acids 101-106 of SEQ ID NO:2.

~~34.~~10. A compound of claim ~~31~~ 7, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody~~, anti-CCR2 antibody fragment~~, or anti-CCR2 antigen-binding fragment comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2~~.~~ and a light chain variable region, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 1.

~~35.~~ 11. A compound of claim ~~31~~9, or a pharmaceutically acceptable salt thereof, wherein the ~~antibody, the~~ anti-CCR2 antibody~~, anti-CCR2 antibody fragment, or anti-CCR2 antigen-binding fragment comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 1.~~

~~36. A compound of claim 31, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody, anti-CCR2 antibody fragment, or anti-CCR2 antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 2.~~

~~37. A compound of claim 31, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody, anti-CCR2 antibody fragment, or anti-CCR2 antigen-binding fragment comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 1.~~

~~38. A compound of claim 31, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody, anti-CCR2 antibody fragment, or anti-CCR2 antigen-binding fragment comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 and a light chain variable region, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 1.~~

~~39. A compound of anyone of claims claim 31 to 38, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody, anti-CCR2 antibody fragment,~~ or anti-CCR2 antigen-binding fragment further comprises a heavy chain constant region selected from human immunoglobulins IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions~~.~~

~~40. A compound of anyone of claims claim 31 to 39, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody, anti-CCR2 antibody fragment, or anti-CCR2 antigen-binding fragment further comprises~~ and a light chain constant region selected from the group consisting of human immunoglobulins IgGκ and IgGλ light chain constant regions.

~~41.~~12. A compound of claim ~~31~~10, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody~~, anti-CCR2 antibody fragment,~~ or anti-CCR2 antigen-binding fragment ~~binds to the same epitope as an antibody comprising~~further comprises a ~~variable~~ heavy chain constant region ~~of SEQ ID NO: 2~~selected from human

immunoglobulins IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions and a ~~variable~~ light chain constant region ~~of SEQ ID NO: 1.~~selected from the group consisting of human immunoglobulins IgGκ and IgGλ light chain constant regions.

~~42. A compound of claim 31, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody comprises a heavy chain region of SEQ ID NO: 3.~~

~~43. A compound of claim 31, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody comprises a light chain region of SEQ ID NO: 4.~~

~~44.~~13. A compound of claim ~~31~~7, or a pharmaceutically acceptable salt thereof, wherein the anti-CCR2 antibody comprises a heavy chain region of SEQ ID NO: 3 and a light chain region of SEQ ID NO: 4.

~~45.~~14. A pharmaceutical composition comprising a compound of ~~any one of claims 1 to 44~~claim 1, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

~~46. The pharmaceutical composition of claim 45 further comprising an anti-PD-1 antibody.~~

~~47. The pharmaceutical composition of claim 46, wherein the anti-PD-1 antibody is selected from the group consisting of Pembrolizumab, Nivolumab, Cemiplimab, Pimivalimab, Spartalizumab, Camrelizumab, Sintilimab, Tislelizumab, Toripalimab, Dostarlimab, Ezabenlimab, INCMGA0012, AMP-224, AMP-514, SYM-021, LZM-009, CS-1003, SYN-125, GNR-051, MW-11, TY-101, BAT-1306, F520, Sasanlimab, Penpulimab, Pucotenlimab, CX-188, Zimberelimab, and Tebotelimab.~~

~~48. The pharmaceutical composition of claim 45 further comprising an anti-PD-L1 antibody.~~

~~49. The pharmaceutical composition of claim 48, wherein the anti-PD-L1 antibody is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, Cosibelimab,~~

~~MSB-2311, ZKAB-001, FAZ-053, MDX-1105, CBT-502, IMC-001, RC-98, KL-A167, GR-1405, Lodapolimab, Sugemalimab, Envafolimab, Opucolimab, and Garivulimab.~~

~~50. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a pharmaceutically acceptable amount of a compound of any one of claims 1 to 44.~~

~~51. A method for stimulating an immune response in a subject in need thereof, the method comprising administering to the subject a pharmaceutically acceptable amount of a compound of any one of claims 1 to 44.~~

~~52. The method of claim 50 or 51, further comprising administering to the subject an anti-PD-1 antibody.~~

~~53. The method of claim 50 or 51, further comprising administering to the subject an anti-PD-L1 antibody.~~

~~54. The method of claim 52, wherein the anti-PD-1 antibody is selected from the group consisting of Pembrolizumab, Nivolumab, Cemiplimab, Pimivalimab, Spartalizumab, Camrelizumab, Sintilimab, Tislelizumab, Toripalimab, Dostarlimab, Ezabenlimab, INCMGA0012, AMP-224, AMP-514, SYM-021, LZM-009, CS-1003, SYN-125, GNR-051, MW-11, TY-101, BAT-1306, F520, Sasanlimab, Penpulimab, Pucotenlimab, CX-188, Zimberelimab, and Tebotelimab.~~

~~55. The method of claim 53, wherein the anti-PD-L1 antibody is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, Cosibelimab, MSB-2311, ZKAB-001, FAZ-053, MDX-1105, CBT-502, IMC-001, RC-98, KL-A167, GR-1405, Lodapolimab, Sugemalimab, Envafolimab, Opucolimab, and Garivulimab.~~

~~56. The method of any of claims 52-55, wherein the anti-PD-1 antibody or the anti-PD-L1 antibody is administered simultaneously with the compound of any one of claims 1 to 44.~~

~~57. The method of any of claims 52-55, wherein the anti-PD-1 antibody or the anti-PD-L1 antibody is administered sequentially with the compound of any one of claims 1 to 44.~~

~~58. The method of any of claims 50-57 further comprising administering radiation to the subject.~~

~~59. The method of claim 58 wherein the radiation is particle radiation.~~

~~60. The method of claim 58 or 59 wherein the radiation is administered by external beam radiation.~~