CYTOTOXICITY TARGETING CHIMERAS FOR CCR2-EXPRESSING CELLS

FIELD OF THE DISCLOSURE

The present disclosure relates to heterobifunctional molecules, referred to as cytotoxicity targeting chimeras (CyTaCs) or antibody recruiting molecules (ARMs) that are able to simultaneously bind a target cell-surface protein as well as an exogenous antibody protein. The present disclosure also relates to agents capable of binding to a receptor on a surface of a pathogenic cell and inducing the depletion of the pathogenic cell in a subject for use in the treatment of cancer, inflammatory diseases, autoimmune diseases, viral infection, or bacterial infection.

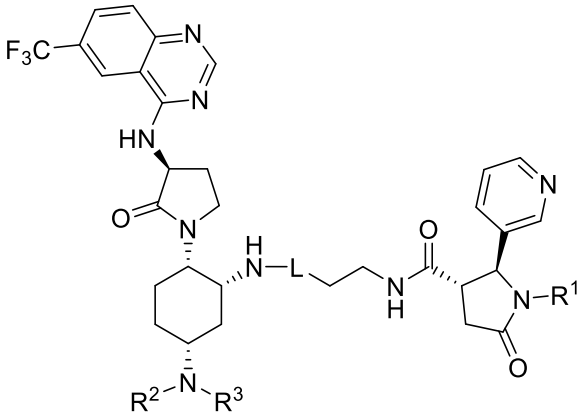
BACKGROUND

Cell-surface proteins and their ligands play key roles in a range of inflammatory, infectious, and autoimmune diseases as well tumor initiation, growth and metastasis. Antibody-based therapeutics have promising properties as drug candidates for these indications due to their selectivity for pathogenic cell-surface targets and their ability to direct immune surveillance to target-expressing tissues or cells to induce depletion of the pathogenic cells. Examples of such depletion mechanisms include antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependant cytotocity (CDC). However, antibody-based therapeutics often suffer from a lack of bioavailability, high cost, thermal instability, and difficult manufacturing due to their size, complexity and peptide based structures. Conversely, small molecule therapeutics often provide affordability, stability, and the convenience of oral dosing, but may suffer from poor selectivity and off-target effects, while also lacking the immune control of therapeutic antibodies.

Accordingly, a need exists for improved therapeutic approaches that target pathogenic cells for use in the treatment of disease. Such compositions and related methods are provided in the present disclosure.

SUMMARY

In an aspect of the present disclosure, there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

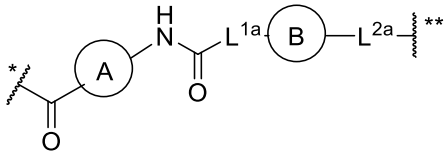
wherein:

R^1 is C_{1-4} alkyl or C_{3-6} cycloalkyl;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is hydrogen or C_{1-4} alkyl;

L is a divalent linker of Formula (L-a), (L-b), (L-c), (L-d), (L-e), (L-f), (L-g), (L-h), (L-i), (L-j), (L-k), (L-m), (L-n-i), (L-n-ii), (L-n-iii), or (L-n-iv):



(L-a), or a stereoisomer thereof,

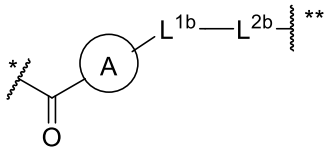
wherein:

Ring A and Ring B are each independently C_{4-6} cycloalkylene;

L^{1a} is C_{3-5} linear alkylene, wherein 1 or 2 methylene units are replaced with -O- or -NR^a-;

each R^a is independently hydrogen or C_{1-3} alkyl; and

L^{2a} is -O-, -NHC(O)-, or -CH_2-O-;



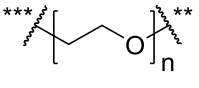
(L-b), or a stereoisomer thereof,

wherein:

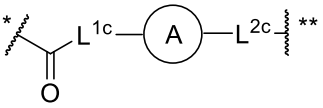
Ring A is C_{4-6} cycloalkylene or C_{7-9} bridged bicyclic cycloalkylene;

L^{1b} is -CH_2-NH-C(O)-, -NHC(O)-, or -C(O)NH-;

L^{2b} is C_{6-12} linear alkylene, wherein 1, 2, 3, or 4 methylene units are replaced with -O-, -NR^{1b}-, -C(O)NR^{1b}-, or -NR^{1b}C(O)-; or

L^{2b} is , wherein n is 1, 2, 3, or 4, and  represents a covalent bond to L^{1b}; and

each R^{1b} is independently hydrogen or C_{1-3} alkyl;



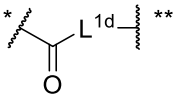
(L-c), or a stereoisomer thereof,

wherein:

L^{1c} is C_{2-10} linear alkylene, wherein 1, 2, or 3 methylene units are replaced with -O-, -NH-, -NHC(O)-, or -C(O)NH-;

Ring A is C_{4-6} cycloalkylene or C_{7-9} bridged bicyclic cycloalkylene; and

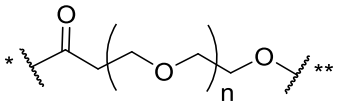
L^{2c} is -O- or a saturated C_{2-10} linear alkylene, wherein 1, 2, or 3 methylene units are replaced with -O-, -NH-, -NHC(O)-, or -C(O)NH-;



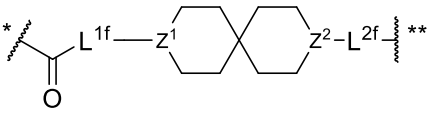
(L-d)

wherein:

L^{1d} is C_{12-22} linear alkylene, wherein 1, 2, 3, 4, or 5 methylene units are replaced with -NH-, -O-, -C(O)NH-, -NHC(O)-, or -NHC(O)-NH-;



(L-e), wherein n is an integer of 3 to 50;



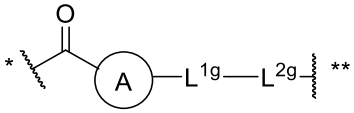
(L-f), or a stereoisomer thereof,

wherein:

L^{1f} is a bond; C_{1-6} linear alkylene, wherein 0, 1, or 2 methylene units are replaced with -O-, -NH-, or -C(O)-; or -(C_{3-6} cycloalkylene)-NHC(O)-;

L^{2f} is a bond, -NHC(O)-, -C(O)NH-, or a C_{1-6} linear alkylene, wherein 0, 1, or 2 methylene units are replaced with -O-; and

each of Z^1 and Z^2 is independently N or CH;

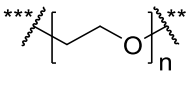
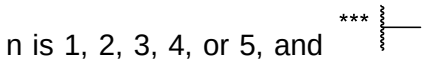


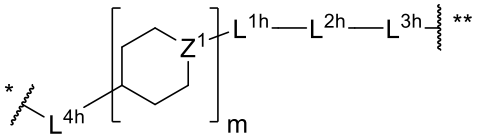
(L-g),

wherein:

Ring A is a 5 to 6 membered heteroarylene having 1 or 2 nitrogen ring atoms;

L^{1g} is a bond, $-CH_2-$, -NH-, or -O-; and

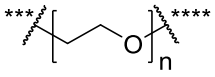
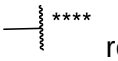
L^{2g} is  wherein n is 1, 2, 3, 4, or 5, and  represents a covalent bond to L^{1g};

 (L-h), or a stereoisomer thereof,

wherein:

each Z^1 is independently N or CH;

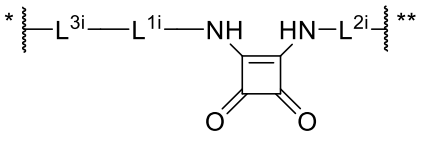
L^{1h} is a bond, -C(O)-, -C(O)-NH-, or -NHC(O)-;

L^{2h} is C_{2-10} linear alkylene or  , wherein n is 1, 2, 3, or 4, and  represents a covalent bond to L^{1h} and  represents a covalent bond to L^{3h};

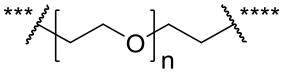
L^{3h} is a bond, $-C(O)CH_2-$, -O-(C_{3-6} cycloalkylene)-O-, or $-C(O)NH(CH_2)_3OCH_2-$;

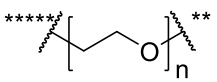
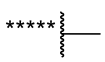
L^{4h} is a bond, $-C(O)-$, $-CH_2C(O)-$, or $-C(O)CH_2-$; and

m is 1, 2, or 3;

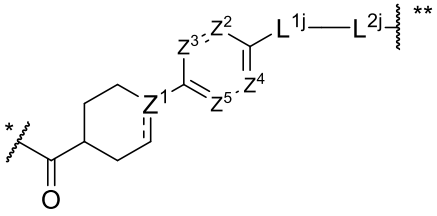
 (L-i)

wherein:

L^{1i} is a bond, C_{1-12} linear alkylene, or  , wherein n is 1, 2, 3, 4, or 5, and  represents a covalent bond to L^{3i} and  represents a covalent bond to NH;

L^{2i} is a bond, C_{1-12} linear alkylene, or  , wherein n is 1, 2, 3, 4, or 5, and  represents a covalent bond to HN; and

L^{3i} is a bond or -C(O)-;



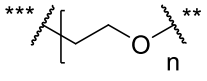
(L-j), or a stereoisomer thereof,

wherein:

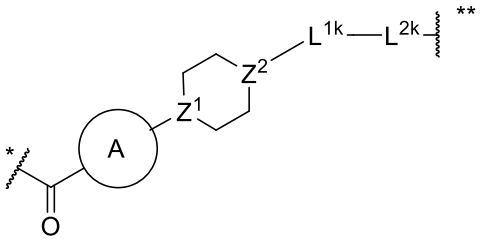
Z^1 is C, CH, or N;

each of Z^2, Z^3, Z^4 and Z^5 is independently CH or N, provided that no more than two of Z^2, Z^3, Z^4 and Z^5 are N;

L^{1j} is -NH-, -C(O)NH-, -NHC(O)-, or -O-;

L^{2j} is C_{1-6} linear alkylene or , wherein n is 1 or 2, and  represents a covalent bond to L^{1j}; and

 represents a single bond or a double bond;



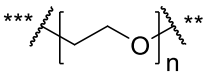
(L-k), or a stereoisomer thereof,

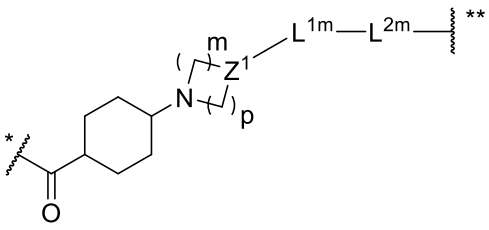
wherein:

Ring A is phenyl or a 5 or 6 membered heteroarylene having 1 or 2 nitrogen ring atoms;

each of Z^1 and Z^2 is independently CH or N;

L^{1k} is a bond, -C(O)-, -C(O)NH- or -NHC(O)-; and

L^{2k} is a C_{3-8} straight chain alkylene or , wherein n is 1, 2, or 3, and  represents a covalent bond to L^{1k};



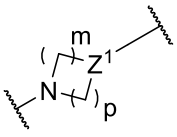
(L-m), or a stereoisomer thereof,

wherein:

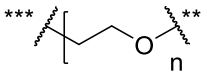
Z^1 is CH or N;

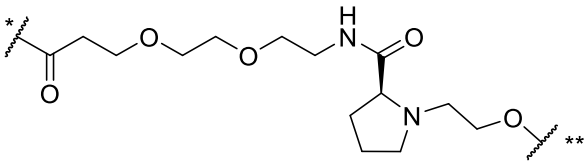
m is 1 or 2;

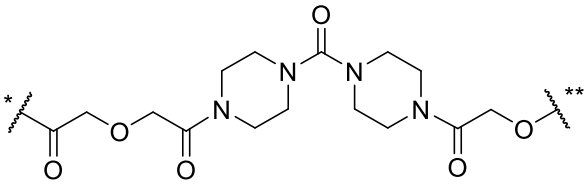
p is 1 or 2;

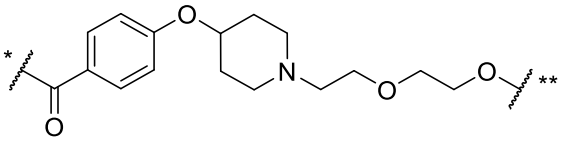
0, 1, or 2 hydrogen atoms of  are replaced with F;

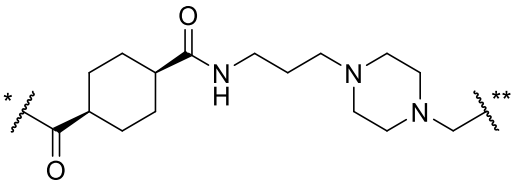
L^{1m} is a bond, -C(O)-, -C(O)NH-, -NHC(O)-, $-S(O)_2NH-$ or $-NHS(O)_2-$; and

L^{2m} is C_{3-6} linear alkylene, C_{3-6} cycloalkylene, or , wherein n is 1 or 2, and *** represents a covalent bond to L^{1m};

 (L-n-i);

 (L-n-ii);

 (L-n-iii); or

 (L-n-iv),

wherein each * represents a covalent bond to the NH group of Formula (I), and each ** represents a covalent bond to the methylene group of Formula (I).

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for treating and/or preventing a disease or disorder in a patient in need thereof, wherein the compound is to be administered with an anti-cotinine antibody, or antigen-binding fragment thereof, and wherein the disease

or disorder is selected from a cancer, an inflammatory disease, an autoimmune disease, a viral infection, or a bacterial infection.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for increasing antibody-dependent cell cytotoxicity (ADCC) of C-C motif chemokine receptor 2 (CCR2)-expressing cells, wherein the cells are to be contacted with the compound and an anti-cotinine antibody, or antigen-binding fragment thereof, and wherein the CCR2-binding moiety of the compound binds the CCR2 expressed on the cells.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for depleting C-C motif chemokine receptor 2 (CCR2)-expressing cells, wherein the cells are to be contacted with the compound and an anti-cotinine antibody, or antigen-binding fragment thereof, wherein the CCR2-binding moiety of the compound binds the CCR2 expressed on the cells.

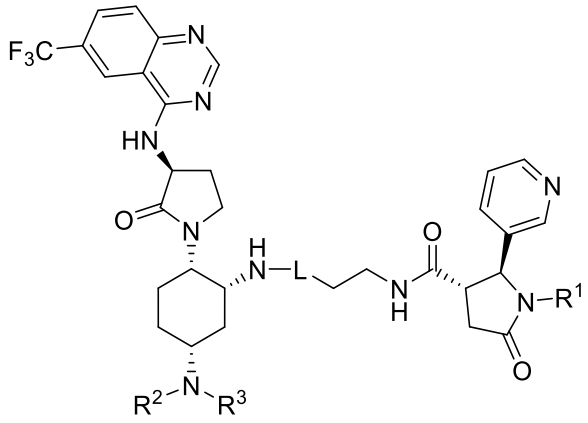
In a further aspect of the present disclosure, there is provided a combination comprising the compound disclosed herein and an anti-cotinine antibody, or antigen-binding fragment thereof.

In another aspect of the present disclosure, there is provided a compound disclosed herein, or a combination disclosed herein, for use in therapy.

In one example, the present disclosure provides a heterobifunctional molecule referred to as a cytoxicity targeting chimera (CyTaC) or an antibody recruiting molecule (ARM), wherein the ARM comprises a moiety that binds a target cell-surface protein on a cell and a moiety that binds an exogenous antibody. In a further example, the ARM comprises a divalent linker that links the target-binding moiety to the antibody-binding moiety. In a further example, the

target-binding moiety is a C-C chemokine receptor type 2 (CCR2)-binding moiety. In a further example, the exogenous antibody is an anti-cotinine antibody, or antigen-binding fragment thereof.

In a further example, the ARM is a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is C_{1-4} alkyl or C_{3-6} cycloalkyl;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is hydrogen or C_{1-4} alkyl; and

L is a divalent linker as described herein.

In one example, the present disclosure provides a method of treating and/or preventing a disease or disorder in a patient in need thereof, comprising: administering to the patient a compound of Formula (I) as disclosed herein and an anti-cotinine antibody, or antigen-binding fragment thereof.

In one example, the present disclosure provides a method of increasing antibody-dependent cell cytotoxicity (ADCC) of CCR2-expressing cells comprising: contacting the cells with a compound of Formula (I) as disclosed herein and an anti-cotinine antibody, or antigen-binding fragment thereof.

In one example, the present disclosure provides a method of depleting CCR2-expressing cells comprising: contacting the cells with a compound of Formula (I) as disclosed herein and an anti-cotinine antibody, or antigen-binding fragment thereof.

In one example, the present disclosure provides a compound of Formula (I) as disclosed herein for use in therapy. In a further example, the present disclosure provides a combination comprising a compound of Formula (I) as disclosed herein and an anti-cotinine antibody, or antigen-binding fragment thereof, for use in therapy.

In one example, the present disclosure provides a combination comprising a compound of Formula (I) as disclosed herein and an anti-cotinine antibody, or antigen-binding fragment thereof, for use in the treatment of a disease or disorder.

In one example, the present disclosure provides use of a compound of Formula (I) as disclosed herein in the manufacture of a medicament for the treatment of a disease or disorder. In a further example, the present disclosure provides use of a combination comprising a compound of Formula (I) as disclosed herein and an anti-cotinine antibody, or antigen-binding fragment thereof, in the manufacture of a medicament for the treatment of a disease or disorder.

In one example, the present disclosure provides a combination comprising a compound of Formula (I) as disclosed herein and an anti-cotinine antibody, or antigen-binding fragment thereof.

BRIEF DESCRIPTION OF THE FIGURES

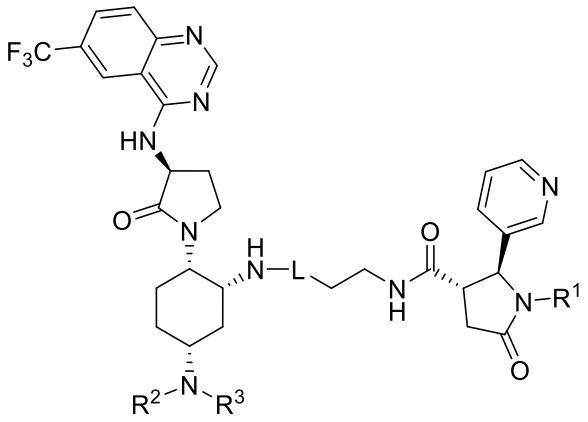
FIGURES 1A-1C: Analysis of MC38 tumor bearing mice (Human CCR2 knock-in C57 mice) dosed with ARM compound (compound of Example 36) in the presence of anti-cotinine antibody as described in Example 204; **FIGURE 1A** shows tumor volume of tumor bearing mice treated with ARM compound in the presence of anti-cotinine antibody at various concentrations of ARM and antibody over time as described in Example 204; **FIGURE 1B** shows blood drug concentration of the ARM compound at various time points post-dosing in mice (see FIGURE 1A for legend key); and **FIGURE 1C** shows % depletion of CCR2 expressing cells as determined by flow cytometry.

FIGURES 2A-2B: Tumor growth in human CCR2 knock-in mice inoculated with MC38 tumors dosed with anti-cotinine antibody and ARM compound (compound of Example 36) either with or without depletion of CD4 and CD8 T cells as described in Example 209; **FIGURE 2A** shows tumor growth in the presence of CD4 and CD8 T cells; **FIGURE 2B** shows tumor growth with depletion of CD4 and CD8 T cells; the results demonstrate that tumor growth inhibition of the antibody/ARM compound is dependent upon the presence of CD4 and CD8 T cells.

FIGURES 3A-3B: Alternative dosing strategy of small molecule ARM compound to anti-cotinine antibody, as described in Example 206, with anti-cotinine antibody and small molecule ARM compound (Example 1) co-dosed or sequentially dosed intravenously; **FIGURE 3A** shows blood concentration of small molecule ARM compound at various timepoints following administration (each time point representative of three animals tested, except for the 168 hour timepoint which is representative of 6 animals tested); **FIGURE 3B**

CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

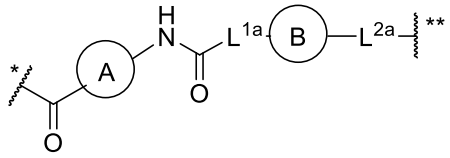
wherein:

R^1 is C_{1-4} alkyl or C_{3-6} cycloalkyl;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is hydrogen or C_{1-4} alkyl;

L is a divalent linker of Formula (L-a), (L-b), (L-c), (L-d), (L-e), (L-f), (L-g), (L-h), (L-i), (L-j), (L-k), (L-m), (L-n-i), (L-n-ii), (L-n-iii), or (L-n-iv):



(L-a), or a stereoisomer thereof,

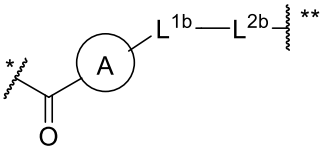
wherein:

Ring A and Ring B are each independently C_{4-6} cycloalkylene;

L^{1a} is C_{3-5} linear alkylene, wherein 1 or 2 methylene units are replaced with -O- or $-NR^a-$;

each R^a is independently hydrogen or C_{1-3} alkyl; and

L^{2a} is -O-, -NHC(O)-, or $-CH_2-O-$;



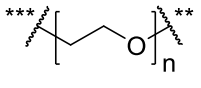
(L-b), or a stereoisomer thereof,

wherein:

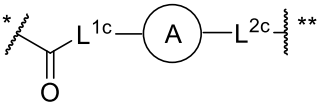
Ring A is C_{4-6} cycloalkylene or C_{7-9} bridged bicyclic cycloalkylene;

L^{1b} is $-CH_2-NH-C(O)-$, $-NHC(O)-$, or $-C(O)NH-$;

L^{2b} is C_{6-12} linear alkylene, wherein 1, 2, 3, or 4 methylene units are replaced with $-O-$, $-NR^{1b}-$, $-C(O)NR^{1b}-$, or $-NR^{1b}C(O)-$; or

L^{2b} is , wherein n is 1, 2, 3, or 4, and  represents a covalent bond to L^{1b}; and

each R^{1b} is independently hydrogen or C_{1-3} alkyl;



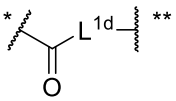
(L-c), or a stereoisomer thereof,

wherein:

L^{1c} is C_{2-10} linear alkylene, wherein 1, 2, or 3 methylene units are replaced with $-O-$, $-NH-$, $-NHC(O)-$, or $-C(O)NH-$;

Ring A is C_{4-6} cycloalkylene or C_{7-9} bridged bicyclic cycloalkylene; and

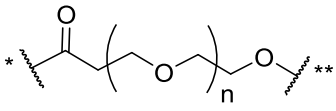
L^{2c} is $-O-$ or a saturated C_{2-10} linear alkylene, wherein 1, 2, or 3 methylene units are replaced with $-O-$, $-NH-$, $-NHC(O)-$, or $-C(O)NH-$;

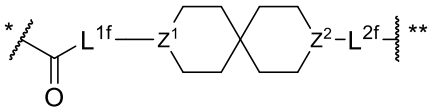


(L-d)

wherein:

L^{1d} is C_{12-22} linear alkylene, wherein 1, 2, 3, 4, or 5 methylene units are replaced with -NH-, -O-, -C(O)NH-, -NHC(O)-, or -NHC(O)-NH-;


(L-e), wherein n is an integer of 3 to 50;

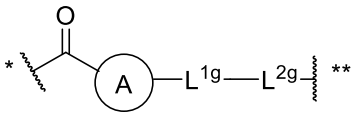

(L-f), or a stereoisomer thereof,

wherein:

L^{1f} is a bond; C_{1-6} linear alkylene, wherein 0, 1, or 2 methylene units are replaced with -O-, -NH-, or -C(O)-; or -(C_{3-6} cycloalkylene)-NHC(O)-;

L^{2f} is a bond, -NHC(O)-, -C(O)NH-, or a C_{1-6} linear alkylene, wherein 0, 1, or 2 methylene units are replaced with -O-; and

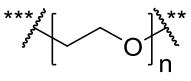
each of Z^1 and Z^2 is independently N or CH;

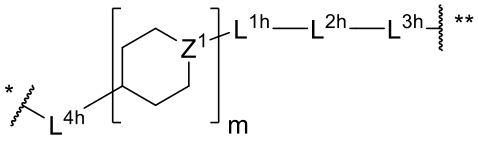

(L-g),

wherein:

Ring A is a 5 to 6 membered heteroarylene having 1 or 2 nitrogen ring atoms;

L^{1g} is a bond, -CH_2-, -NH-, or -O-; and

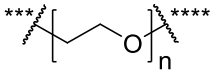
L^{2g} is  wherein n is 1, 2, 3, 4, or 5, and  represents a covalent bond to L^{1g};


(L-h), or a stereoisomer thereof,

wherein:

each Z^1 is independently N or CH;

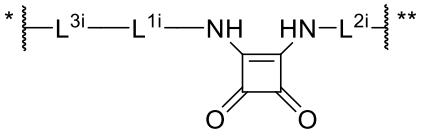
L^{1h} is a bond, -C(O)-, -C(O)-NH-, or -NHC(O)-;

L^{2h} is C_{2-10} linear alkylene or , wherein n is 1, 2, 3, or 4, and *** represents a covalent bond to L^{1h} and **** represents a covalent bond to L^{3h};

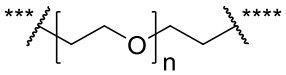
L^{3h} is a bond, -C(O)CH_2-, -O-(C_{3-6} cycloalkylene)-O-, or -C(O)NH$(CH_2)_3OCH_2$-;

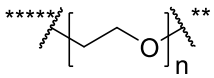
L^{4h} is a bond, -C(O)-, -CH_2C(O)-, or -C(O)CH_2-; and

m is 1, 2, or 3;

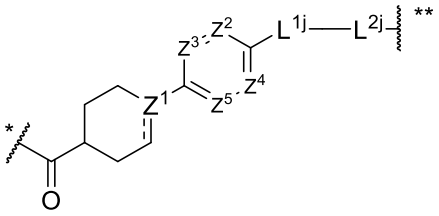

(L-i)

wherein:

L^{1i} is a bond, C_{1-12} linear alkylene, or , wherein n is 1, 2, 3, 4, or 5, and *** represents a covalent bond to L^{3i} and **** represents a covalent bond to NH;

L^{2i} is a bond, C_{1-12} linear alkylene, or , wherein n is 1, 2, 3, 4, or 5, and ***** represents a covalent bond to HN; and

L^{3i} is a bond or -C(O)-;



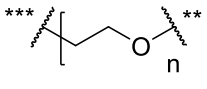
(L-j), or a stereoisomer thereof,

wherein:

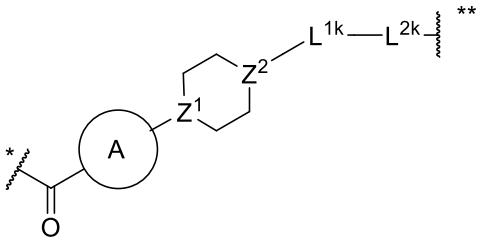
Z^1 is C, CH, or N;

each of Z^2, Z^3, Z^4 and Z^5 is independently CH or N, provided that no more than two of Z^2, Z^3, Z^4 and Z^5 are N;

L^{1j} is -NH-, -C(O)NH-, -NHC(O)-, or -O-;

L^{2j} is C_{1-6} linear alkylene or , wherein n is 1 or 2, and  represents a covalent bond to L^{1j}; and

 represents a single bond or a double bond;



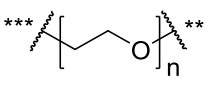
(L-k), or a stereoisomer thereof,

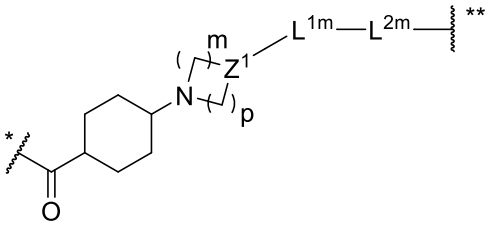
wherein:

Ring A is phenyl or a 5 or 6 membered heteroarylene having 1 or 2 nitrogen ring atoms;

each of Z^1 and Z^2 is independently CH or N;

L^{1k} is a bond, -C(O)-, -C(O)NH- or -NHC(O)-; and

L^{2k} is a C_{3-8} straight chain alkylene or , wherein n is 1, 2, or 3, and  represents a covalent bond to L^{1k};



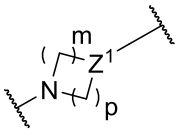
(L-m), or a stereoisomer thereof,

wherein:

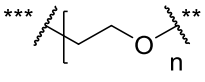
Z^1 is CH or N;

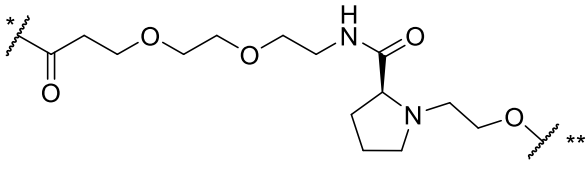
m is 1 or 2;

p is 1 or 2;

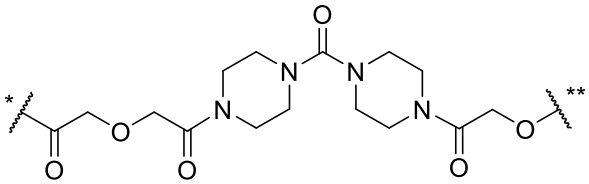
0, 1, or 2 hydrogen atoms of  are replaced with F;

L^{1m} is a bond, -C(O)-, -C(O)NH-, -NHC(O)-, $-S(O)_2NH-$ or $-NHS(O)_2-$; and

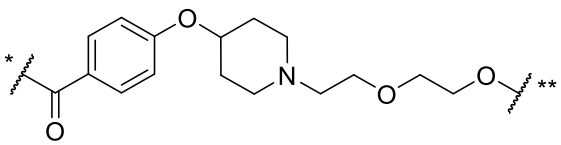
L^{2m} is C_{3-6} linear alkylene, C_{3-6} cycloalkylene, or , wherein n is 1 or 2, and *** represents a covalent bond to L^{1m};



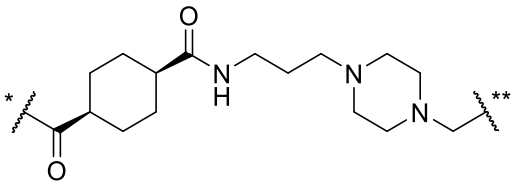
(L-n-i);



(L-n-ii);



(L-n-iii); or



(L-n-iv),

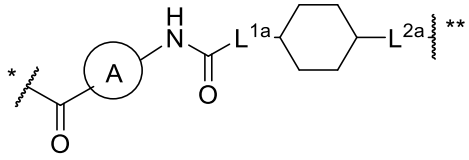
wherein each * represents a covalent bond to the NH group of Formula (I), and each ** represents a covalent bond to the methylene group of Formula (I).

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-CH_3$.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^2 is isopropyl and R^3 is methyl.

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^2 is t-butyl and R^3 is hydrogen.

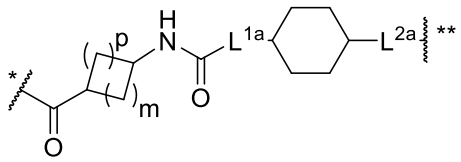
5. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-a-i):



(L-a-i), or a stereoisomer thereof,

wherein Ring A, L^{1a}, L^{2a}, *, and ** are as defined for Formula (L-a).

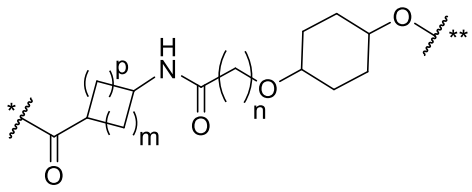
6. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-a-ii):



(L-a-ii), or a stereoisomer thereof,

wherein L^{1a}, L^{2a}, *, and ** are as defined for Formula (L-a); p is 1 or 2; and m is 1 or 2.

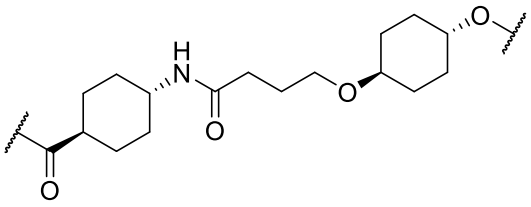
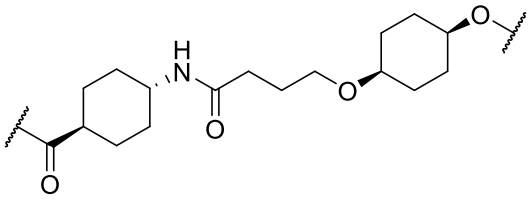
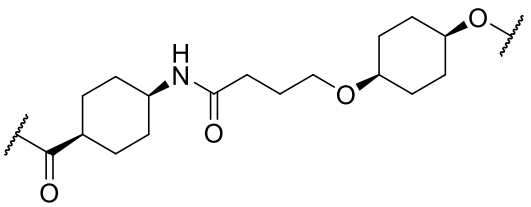
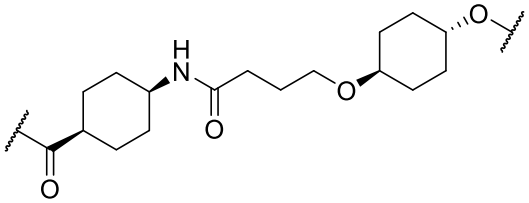
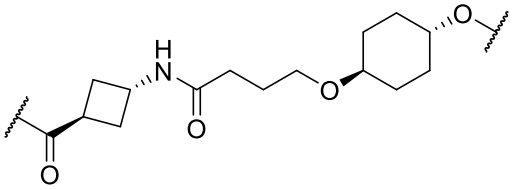
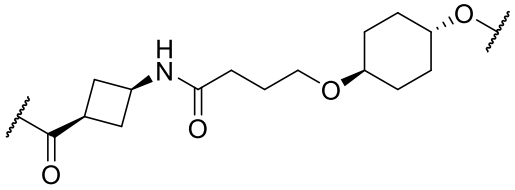
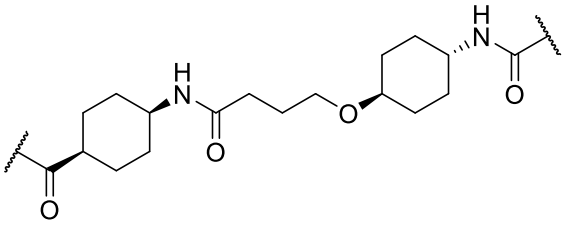
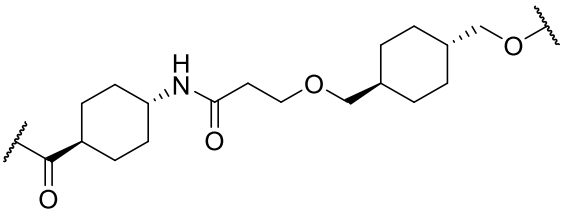
7. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-a-iii):

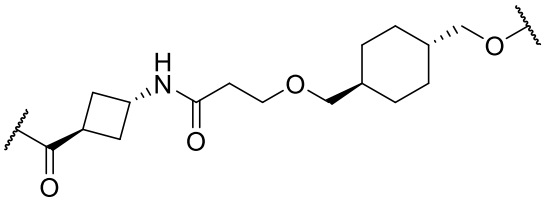
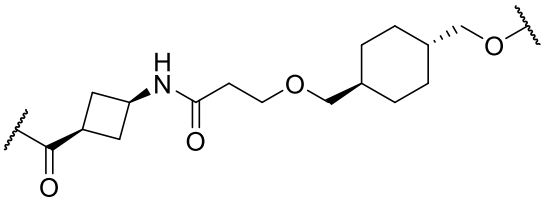
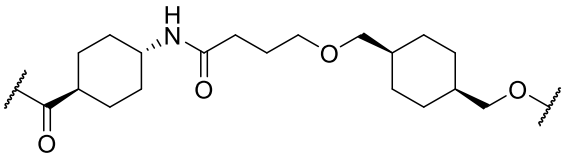
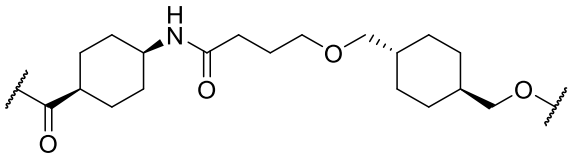
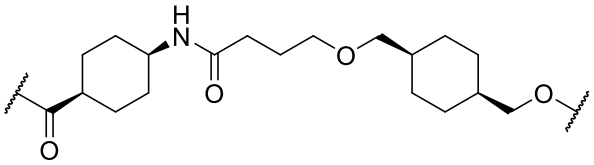
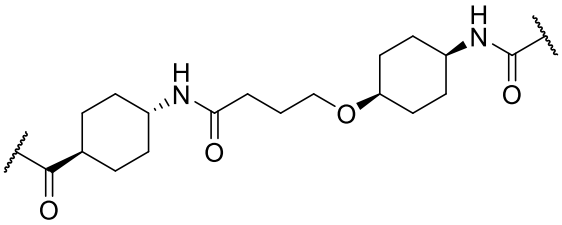
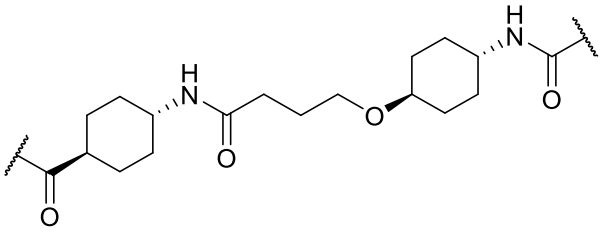
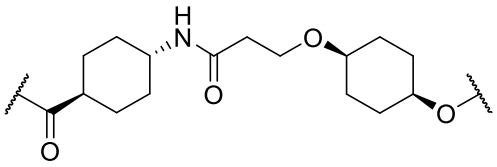
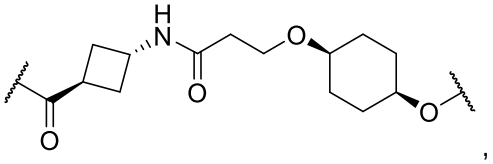
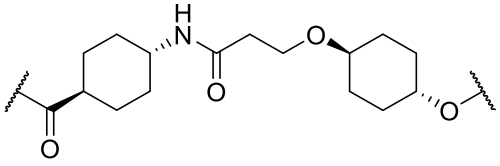
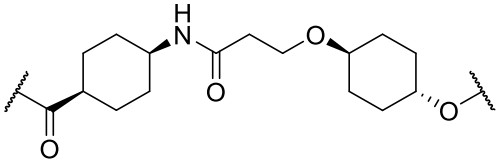
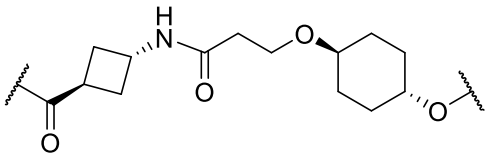
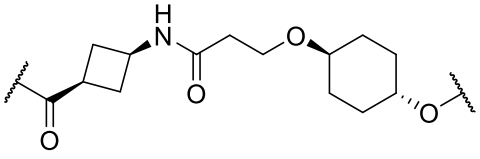


(L-a-iii), or a stereoisomer thereof,

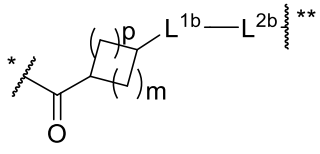
wherein p is 1 or 2; m is 1 or 2; n is 1, 2, or 3; and  and  are as defined for Formula (L-a).

8. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-a) selected from the group consisting of:


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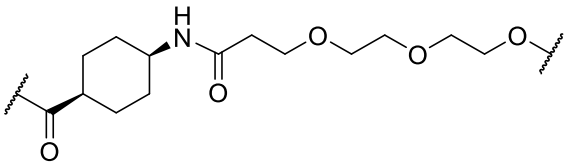
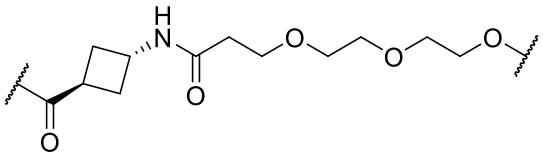
9. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-b-i):

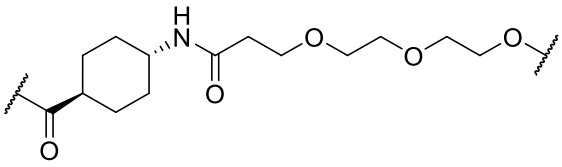
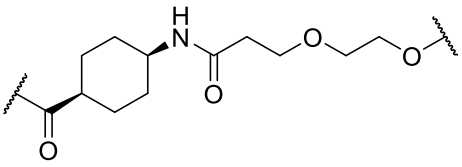


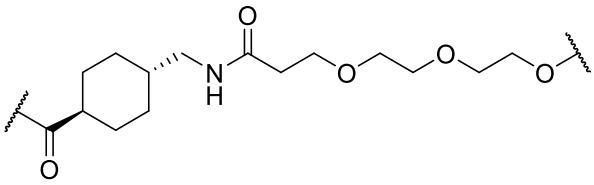
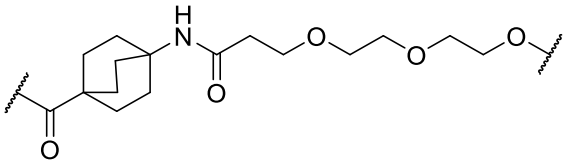
(L-b-i), or a stereoisomer thereof,

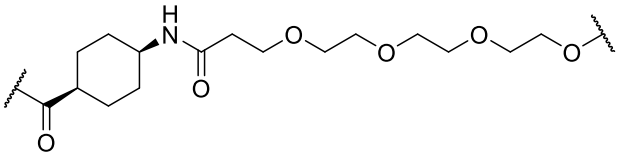
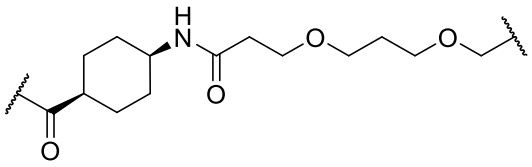
wherein L^{1b}, L^{2b}, , and  are as defined for Formula (L-b); p is 1 or 2; and m is 1 or 2.

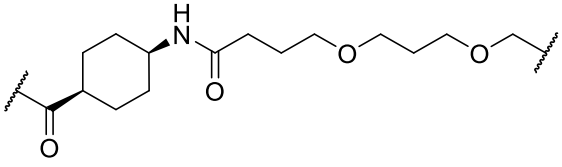
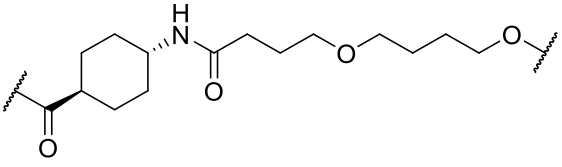
10. The compound of any one of claims 1 to 4, or 9, wherein L is a divalent linker of Formula (L-b) selected from the group consisting of:

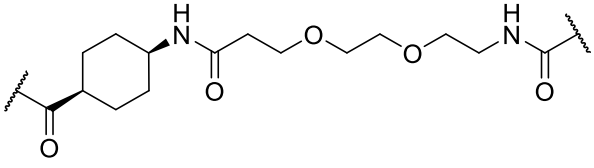
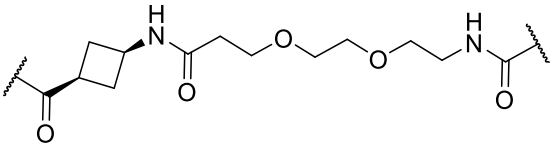
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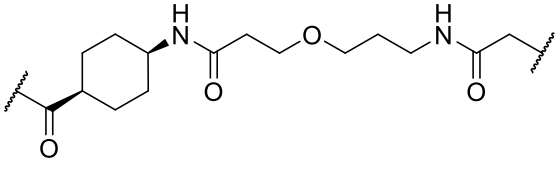
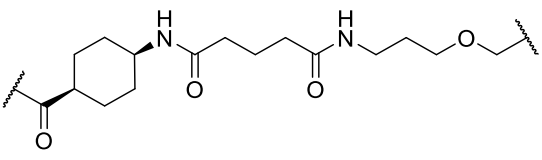
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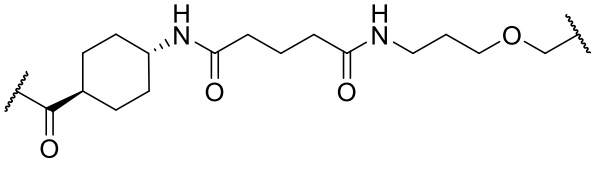
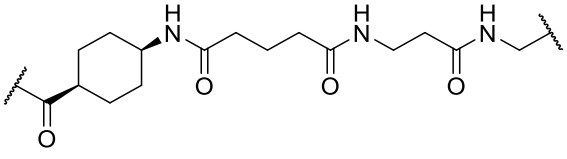
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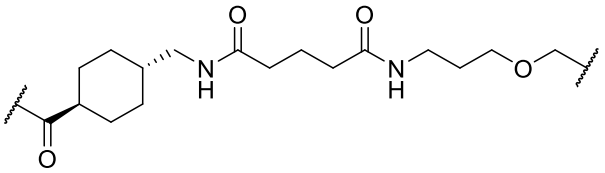
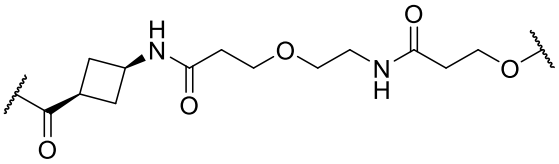
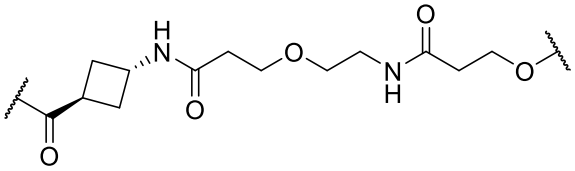
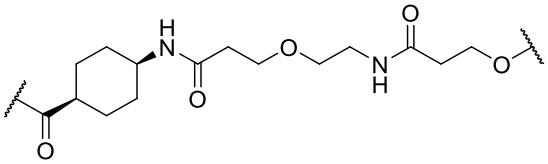
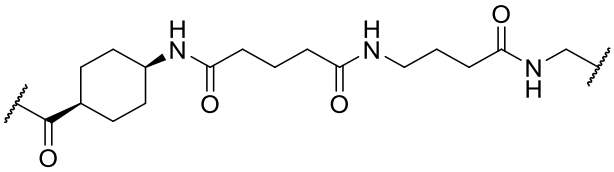
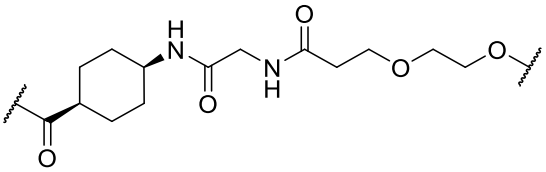
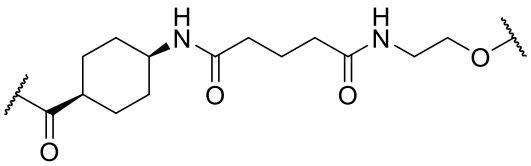
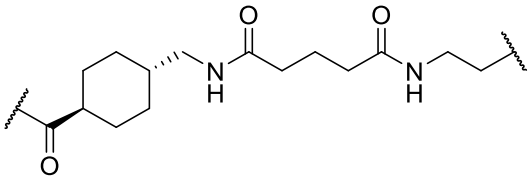
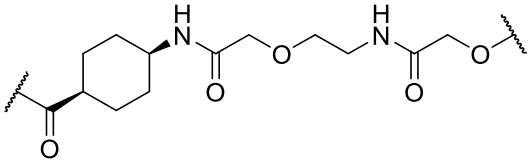
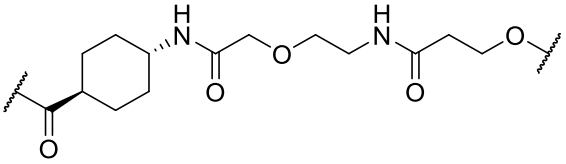
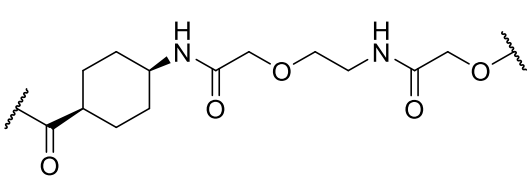
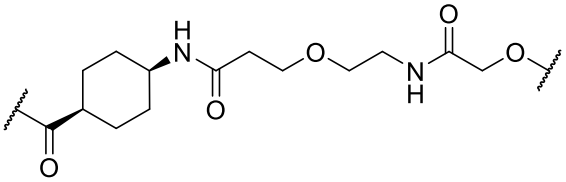
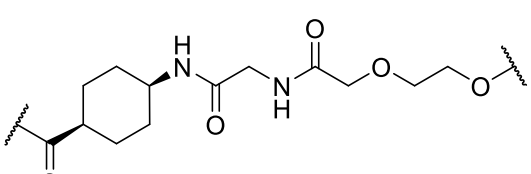
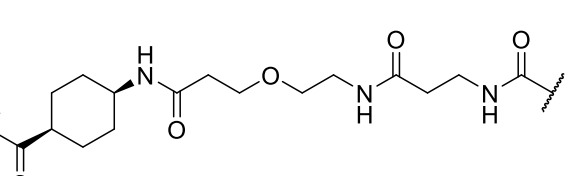
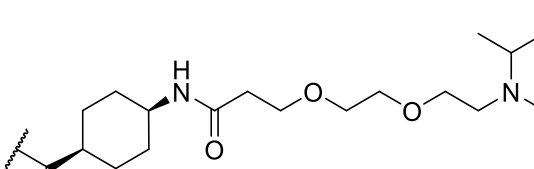
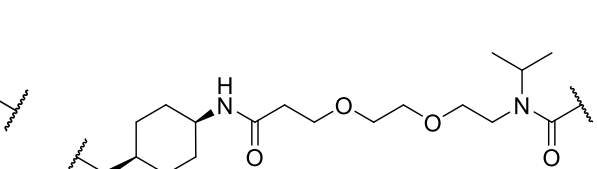
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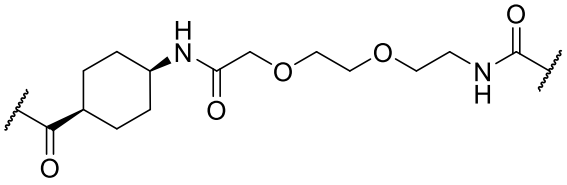
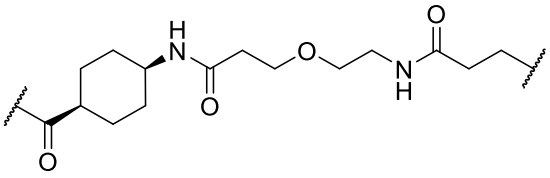
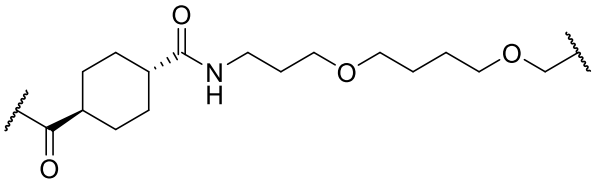
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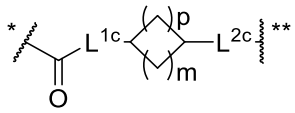

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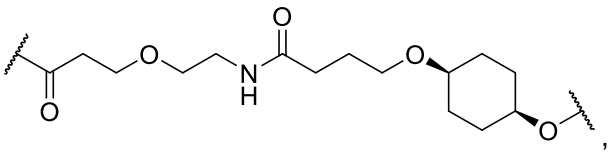
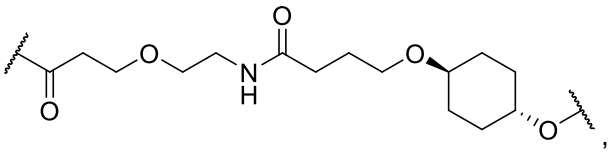
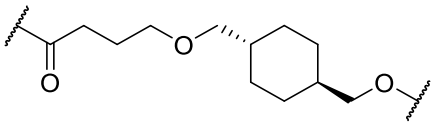
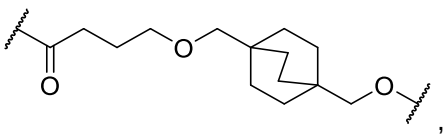
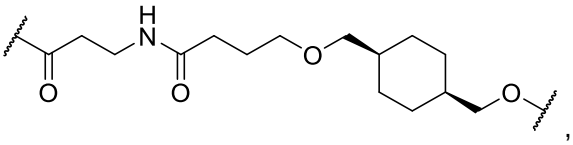
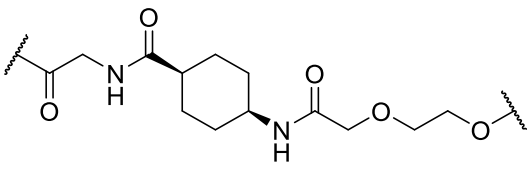
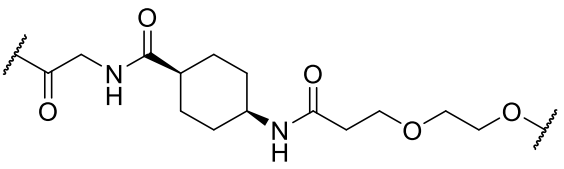


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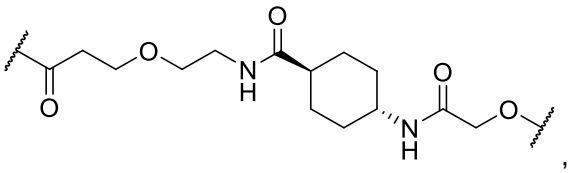
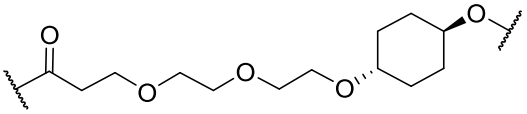
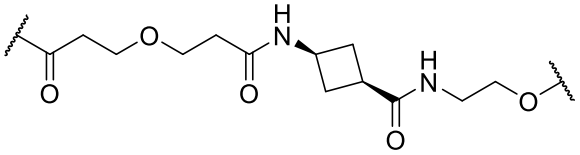
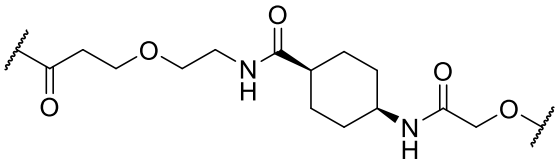
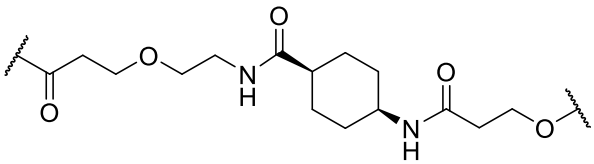
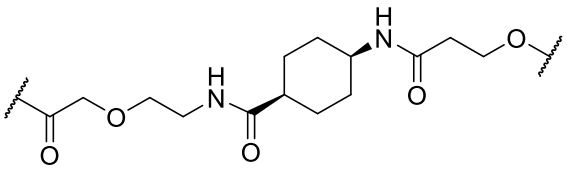
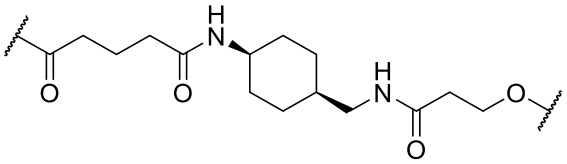
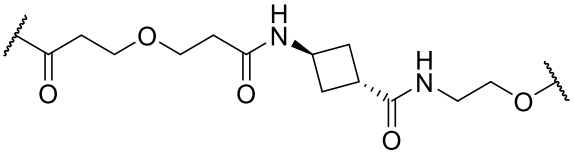
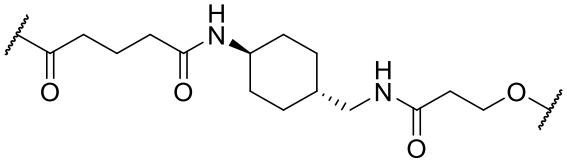
11. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-c-i):


(L-c-i), or a stereoisomer thereof,

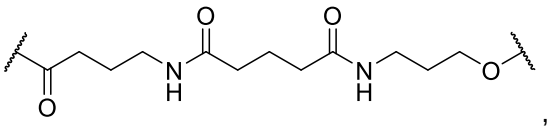
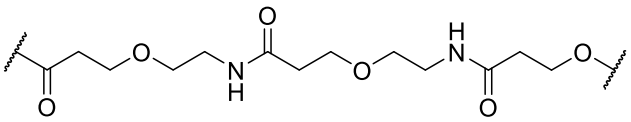
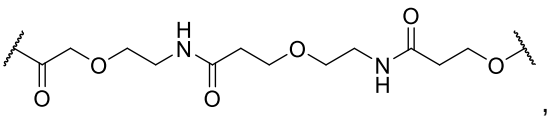
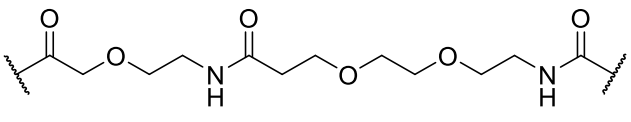
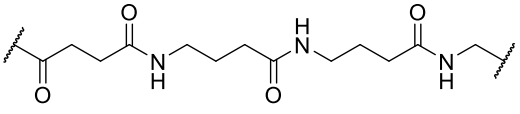
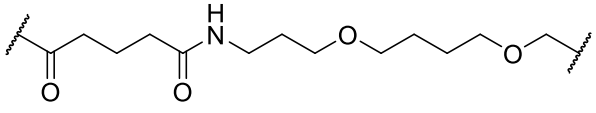
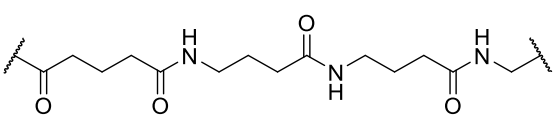
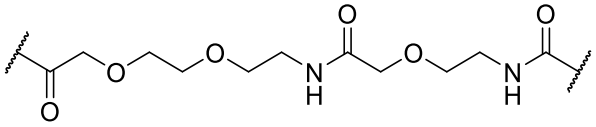
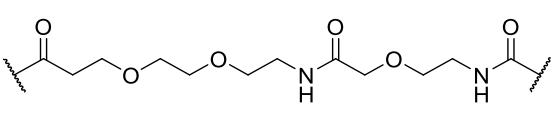
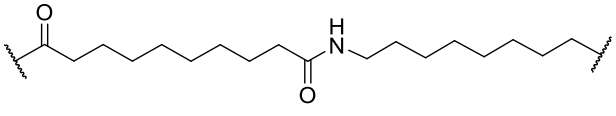
wherein L^{1c}, L^{2c}, , and  are as defined for Formula (L-c); p is 1 or 2; and m is 1 or 2.

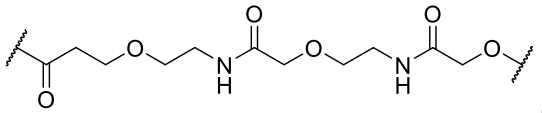
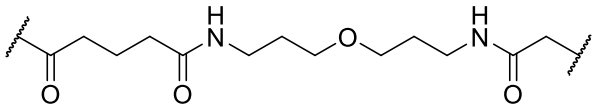
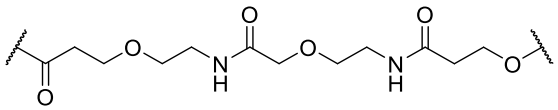
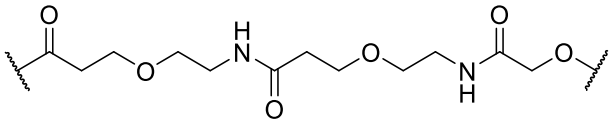
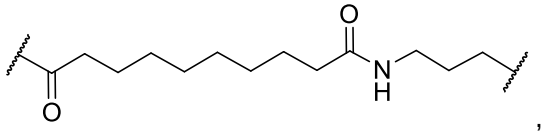
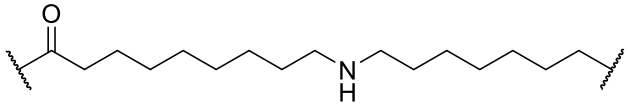
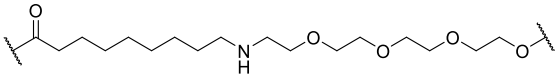
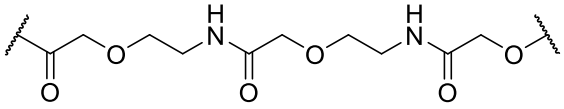
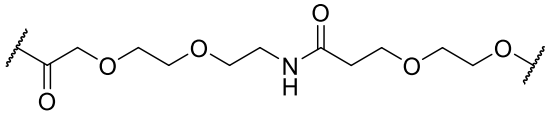
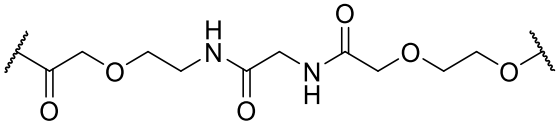
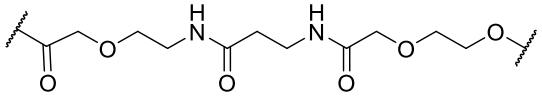
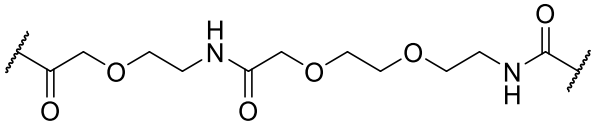
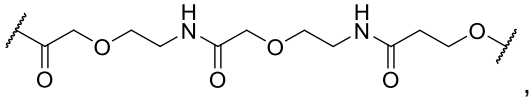
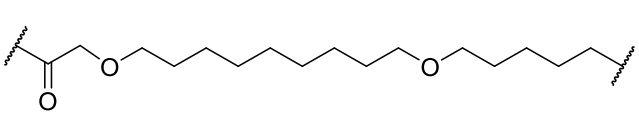
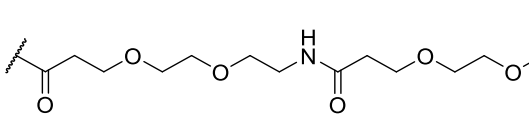
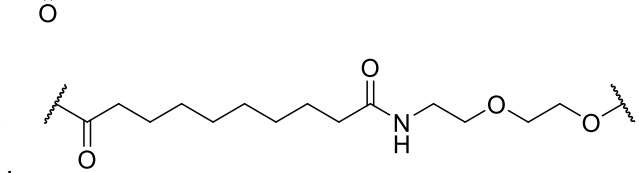
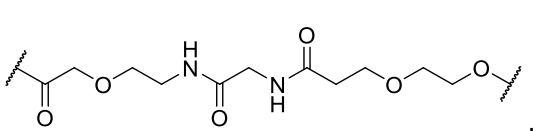
12. The compound of any one of claims 1 to 4, wherein L is a divalent linker of Formula (L-c) selected from the group consisting of:

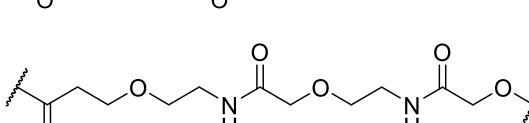
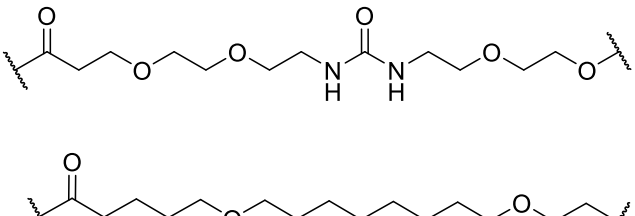

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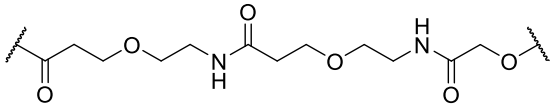
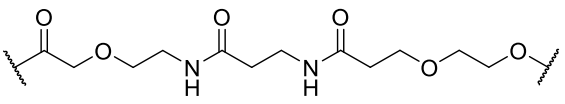
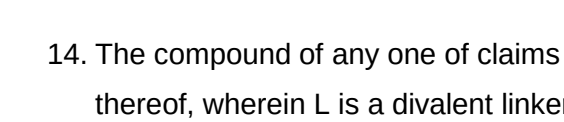
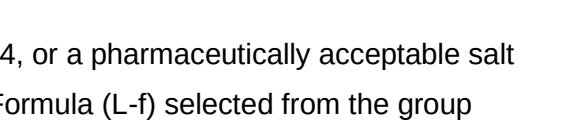
13. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-d) selected from the group consisting of:


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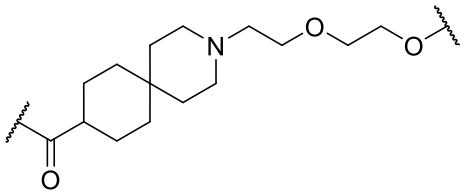
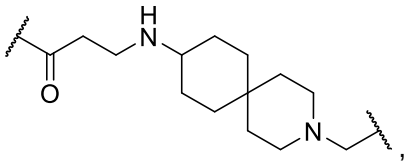
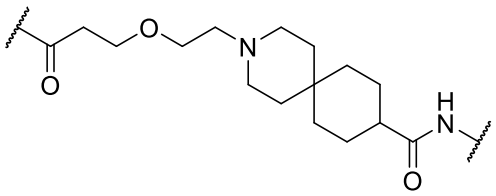
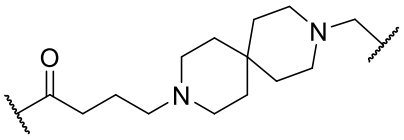
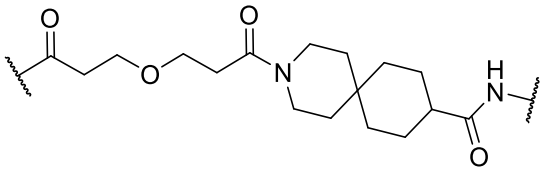
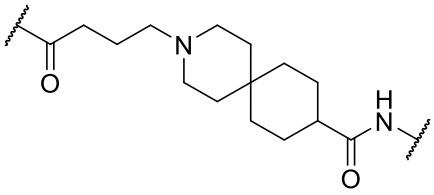
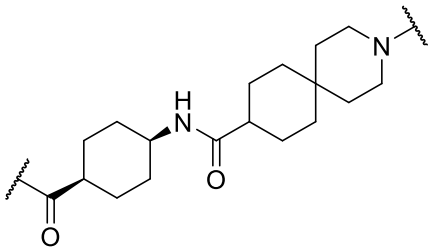

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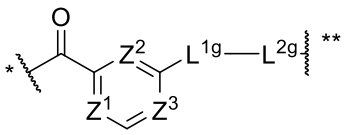
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14. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-f) selected from the group consisting of:

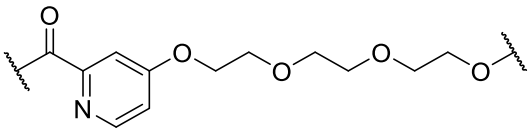
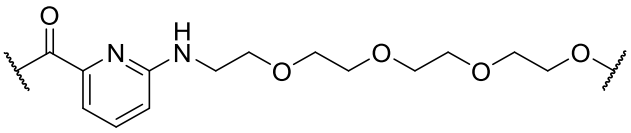
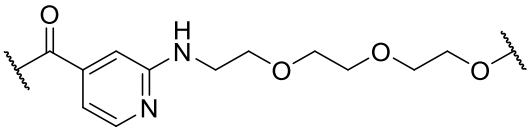
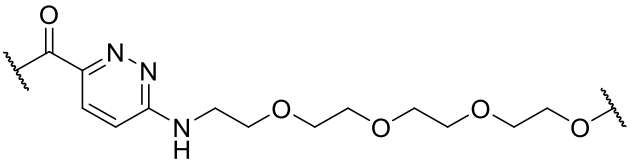
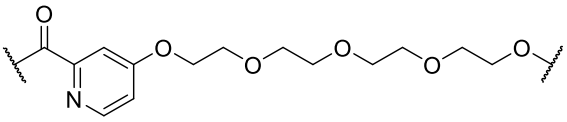
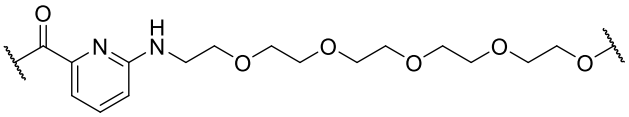
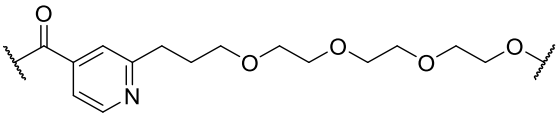
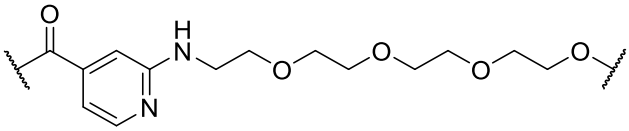
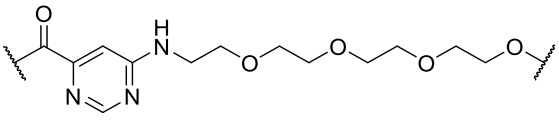
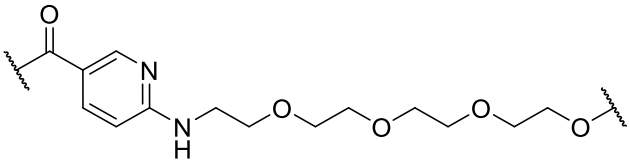






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15. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-g-i):

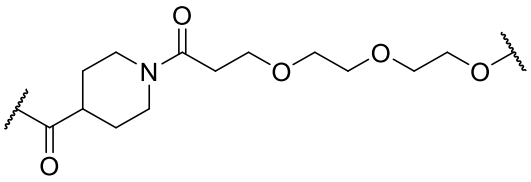
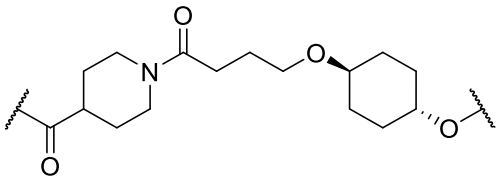
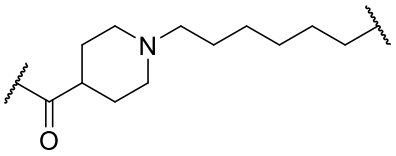
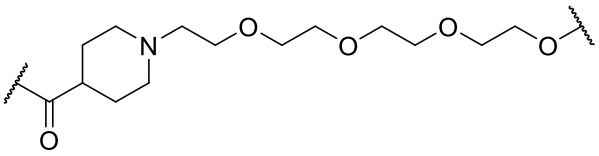
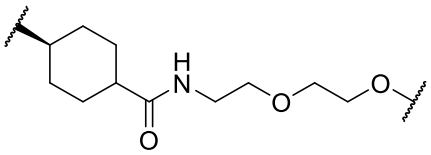
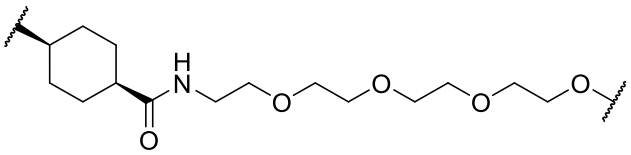
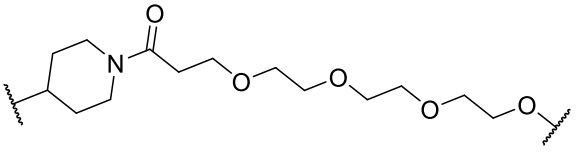
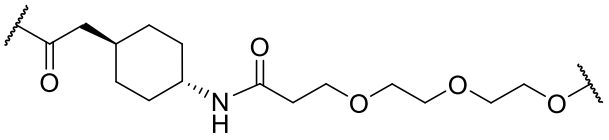
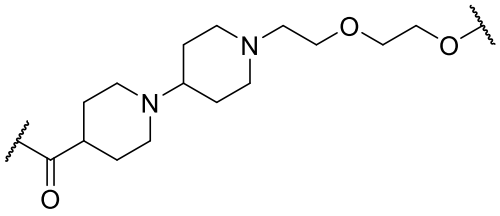
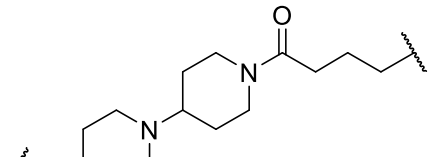
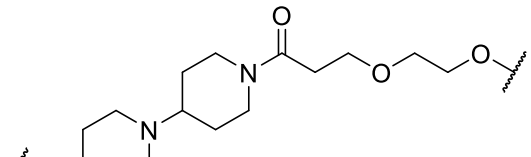
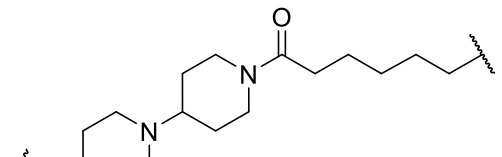
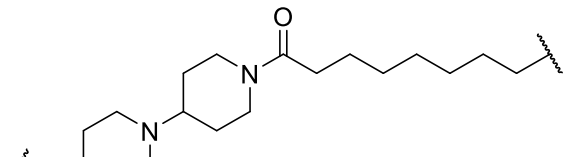
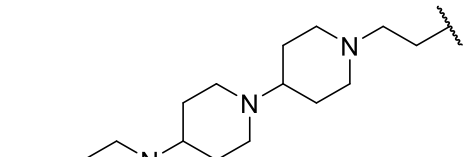
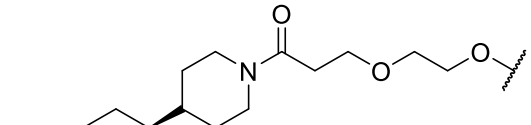

(L-g-i),

wherein L^{1g}, L^{2g}, , and  are as defined for Formula (L-g); Z^1, Z^2, and Z^3 are each independently selected from N or CH, provided that one or two of Z^1, Z^2, and Z^3 is N.

16. The compound of any one of claims 1 to 4, or 15, wherein L is a divalent linker of Formula (L-g) selected from the group consisting of:

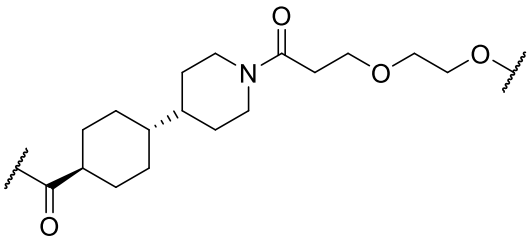
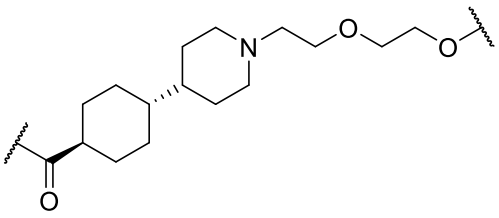
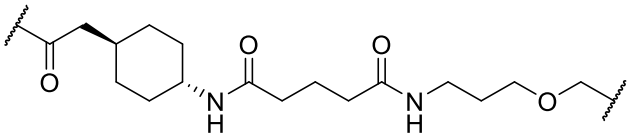

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17. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-h) selected from the group consisting of:

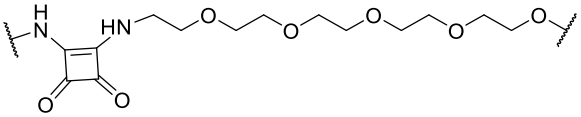
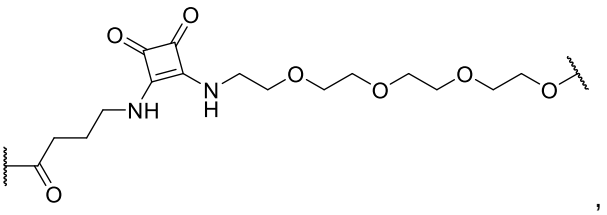
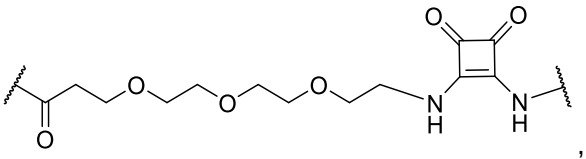
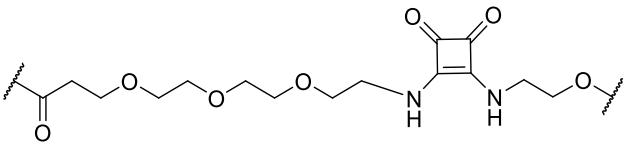
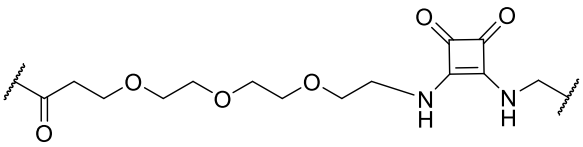

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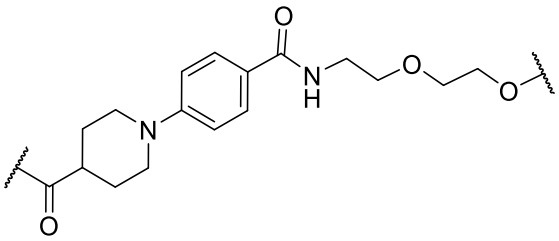
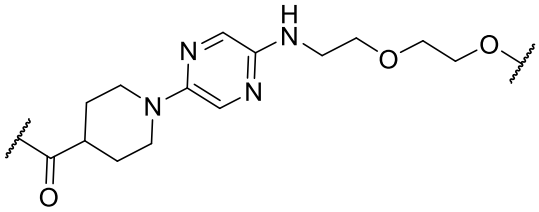
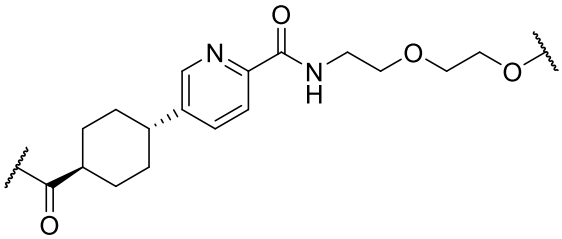
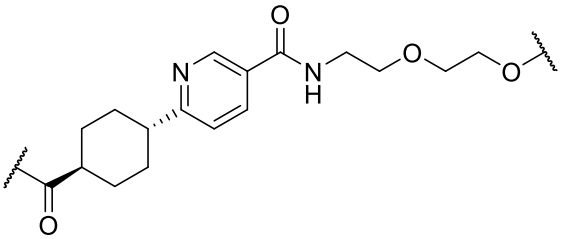
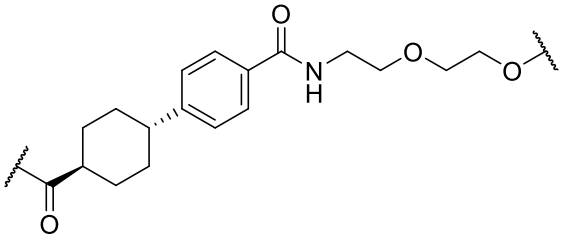
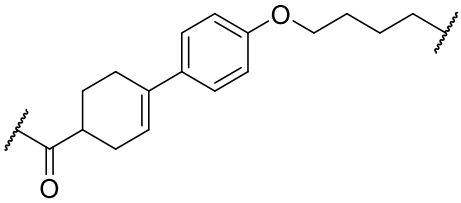
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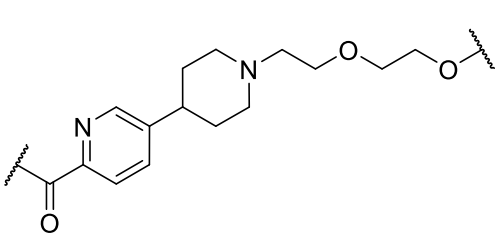
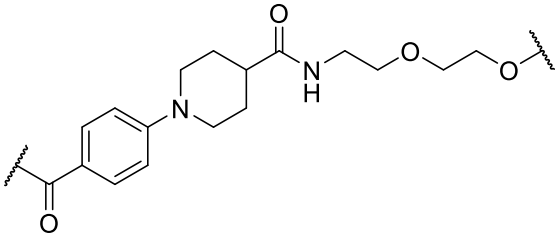
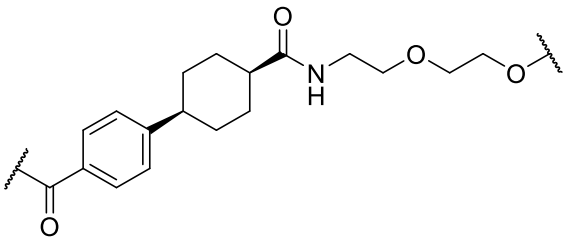
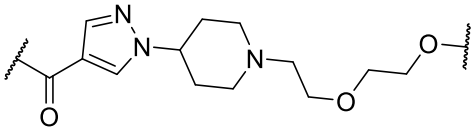
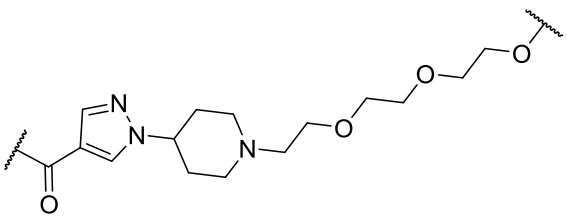
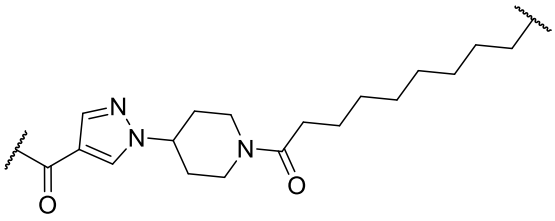
18. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-i) selected from the group consisting of:


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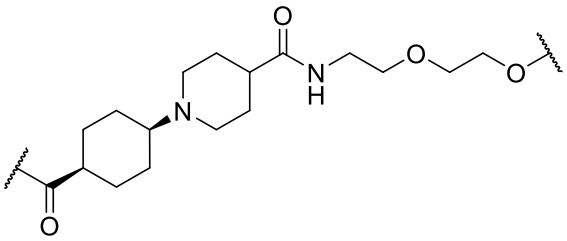
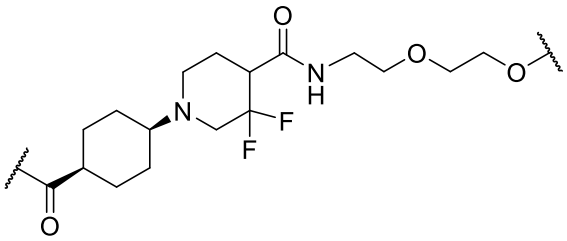
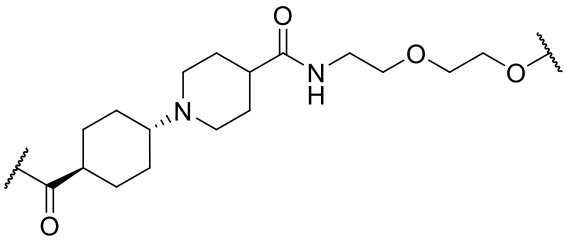
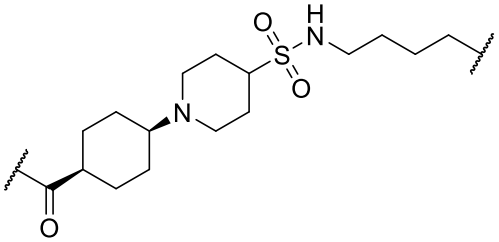
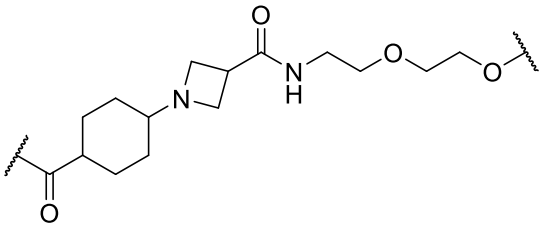
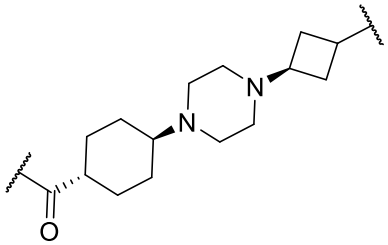
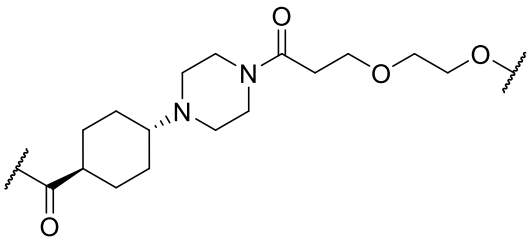
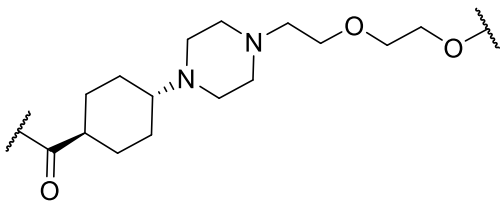
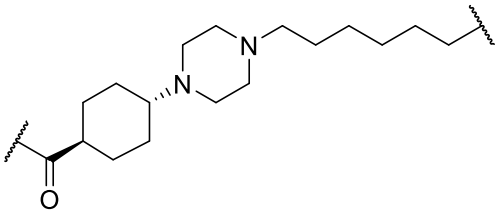
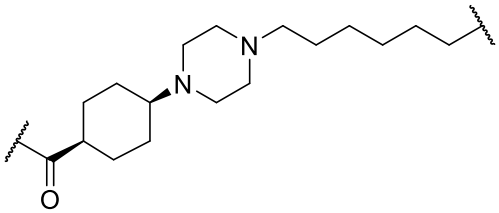
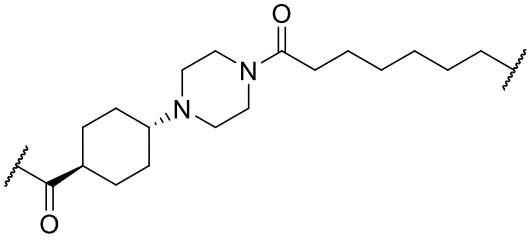
19. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-j) selected from the group consisting of:


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20. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-k) selected from the group consisting of:

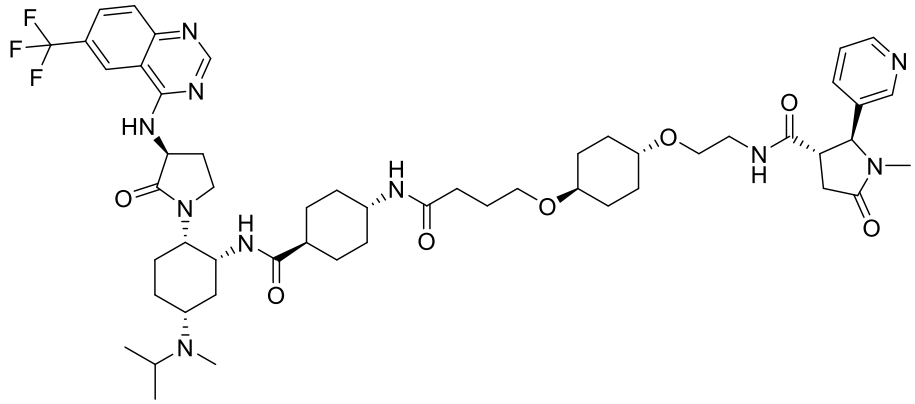
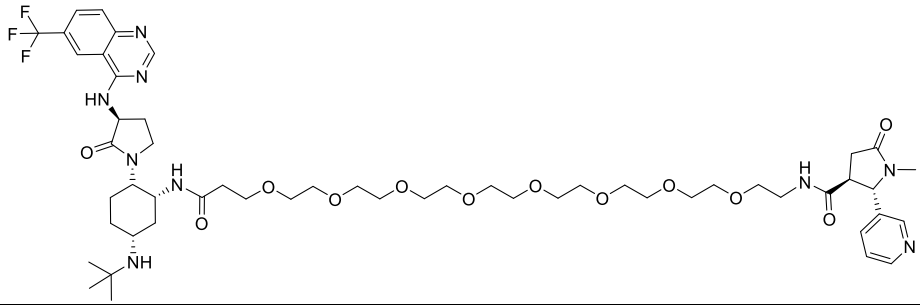

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21. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L is a divalent linker of Formula (L-m) selected from the group consisting of:


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22. The compound of claim 1, wherein the compound is selected from a compound as listed in Table 1.

23. The compound of claim 1, wherein the compound is selected from the group consisting of:

Example No:	Structure:
1	
36	

24. Use of a compound of any one of claims 1-24, in the manufacture of a medicament for treating and/or preventing a disease or disorder in a patient in need thereof, wherein the compound is to be administered with an anti-cotinine antibody, or antigen-binding fragment thereof, and wherein the disease or disorder is selected from a cancer, an inflammatory disease, an autoimmune disease, a viral infection, or a bacterial infection.

25. The use of claim 24, wherein the disease or disorder is mediated by chemokine receptor 2 (CCR2) and/or is associated with CCR2-positive pathogenic cells.

26. The use of claim 24 or 25, wherein the disease is a cancer that is a solid tumor.

27. The use of any one of claims 24 to 26, wherein the cancer is selected from non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), colorectal cancer (CRC), cervical squamous cell carcinoma (CESC), head and neck squamous cell

carcinoma (HNSC), pancreatic cancer, metastatic castration-resistant prostate cancer (mCRPC), ovarian cancer, bladder cancer, or breast cancer.

28. The use of any one of claims 24 to 27, wherein the compound and the antibody, or antigen-binding fragment thereof, are to be administered simultaneously.

29. The use of any one of claims 24 to 27, wherein the compound and the antibody, or antigen-binding fragment thereof, are to be administered sequentially.

30. Use of a compound of any one of claims 1 to 23, in the manufacture of a medicament for increasing antibody-dependent cell cytotoxicity (ADCC) of C-C motif chemokine receptor 2 (CCR2)-expressing cells, wherein the cells are to be contacted with the compound and an anti-cotinine antibody, or antigen-binding fragment thereof, and wherein the CCR2-binding moiety of the compound binds the CCR2 expressed on the cells.

31. Use of a compound of any one of claims 1 to 23, in the manufacture of a medicament for depleting C-C motif chemokine receptor 2 (CCR2)-expressing cells, wherein the cells are to be contacted with the compound and an anti-cotinine antibody, or antigen-binding fragment thereof, wherein the CCR2-binding moiety of the compound binds the CCR2 expressed on the cells.

32. The use of claim 30 or 31, wherein the CCR2-expressing cells are myeloid-derived suppressor cells (MDSCs), T regulatory cells (Tregs), neutrophils, macrophages, B regulatory cells (Bregs), CD8 regulatory cells, (CD8regs), exhausted T cells, or cancer-associated fibroblasts (CAFs).

33. The use of any one of claims 24 to 32, wherein the anti-cotinine antibody has a heavy chain and a light chain, the heavy chain comprising a CDR1 having SEQ ID NO: 1, a CDR2 having SEQ ID NO: 2, and a CDR3 having SEQ ID NO: 3, and the light chain comprising a CDR1 having SEQ ID NO: 4, a CDR2 having SEQ ID NO: 5, and a CDR3 having SEQ ID NO: 6.

34. The use of any one of claims 24 to 33, wherein the anti-cotinine antibody has a heavy chain and a light chain, the heavy chain comprising a heavy chain variable region (VH) having SEQ ID NO: 7, and the light chain comprising a light chain variable region (VL) having SEQ ID NO: 8.

35. The use of any one of claims 24 to 34, wherein the anti-cotinine antibody is of IgG1 isotype comprising a substitution in an Fc region to increase ADCC activity.

36. The use of claim 35, wherein the the substitution in the Fc region is S239D/I332E, wherein residue numbering is according to the EU Index.

37. The use of any one of claims 24 to 36, wherein the anti-cotinine antibody has a heavy chain comprising SEQ ID NO: 9 and a light chain comprising SEQ ID NO: 10.

38. A combination comprising the compound of any one of claims 1 to 23 and an anti-cotinine antibody, or antigen-binding fragment thereof.

39. The combination of claim 38, wherein the anti-cotinine antibody has a heavy chain and a light chain, the heavy chain comprising a CDR1 having SEQ ID NO: 1, a CDR2 having SEQ ID NO: 2, and a CDR3 having SEQ ID NO: 3, and the light chain comprising a CDR1 having SEQ ID NO: 4, a CDR2 having SEQ ID NO: 5, and a CDR3 having SEQ ID NO: 6.

40. The combination of claim 38 or 39, wherein the anti-cotinine antibody has a heavy chain and a light chain, the heavy chain comprising a heavy chain variable region (VH) having SEQ ID NO: 7, and the light chain comprising a light chain variable region (VL) having SEQ ID NO: 8.

41. The combination of any one of claims 38 to 40, wherein the anti-cotinine antibody is of IgG1 isotype comprising a substitution in an Fc region to increase ADCC activity.

42. The combination of any one of claims 38 to 41, wherein the substitution in the Fc region is S239D/I332E, wherein residue numbering is according to the EU Index.

43. The combination of any one of claims 38 to 42, wherein the anti-cotinine antibody has a heavy chain comprising SEQ ID NO: 9 and a light chain comprising SEQ ID NO: 10.

44. A compound of any one of claims 1-23, or a combination of any one of claims 38-43, for use in therapy.