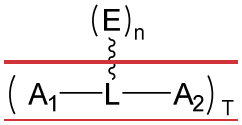
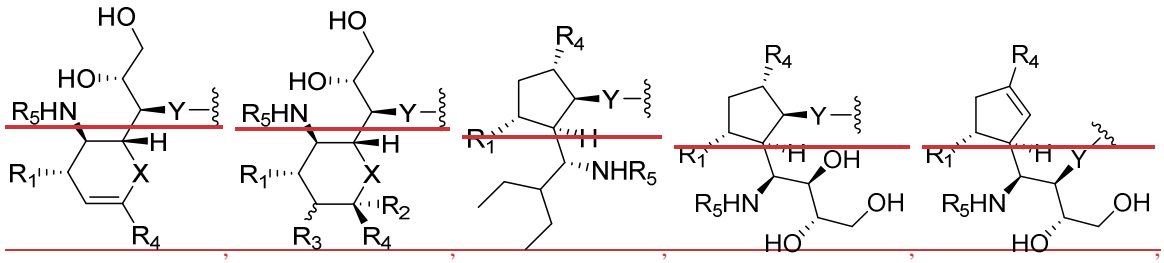
In one aspect, the present disclosure refers to a conjugate described by formula (D-I):

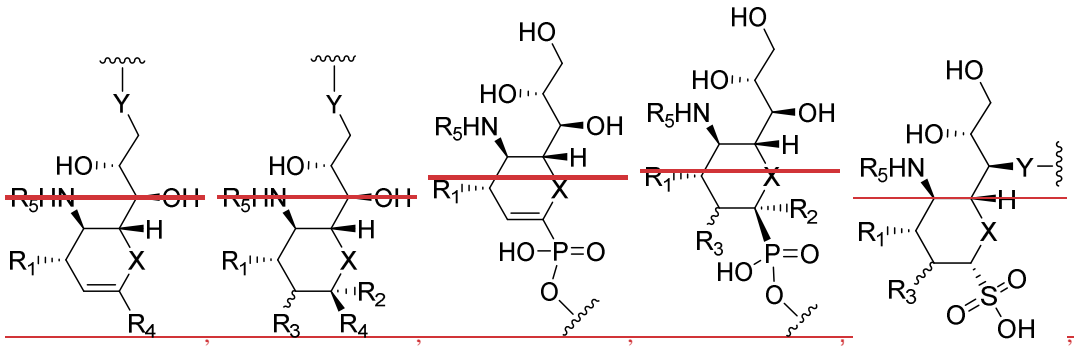


(D-I)

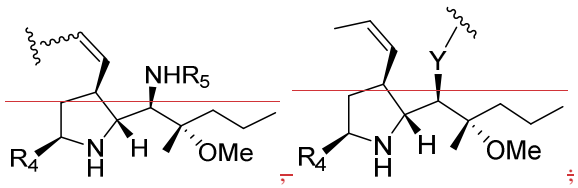
wherein each A_1 and each A_2 is independently selected from any one of formulas (A-I)-(A-XII):



(A-I), (A-II), (A-III), (A-IV), (A-V),



(A-VI), (A-VII), (A-VIII), (A-IX), (A-X),



(A-XI), (A-XII);

wherein R_1 is selected from -OH, $-NH_2$, $-NHC(=NH)NH_2$, and $-NHC(=NH)NHR_6$;

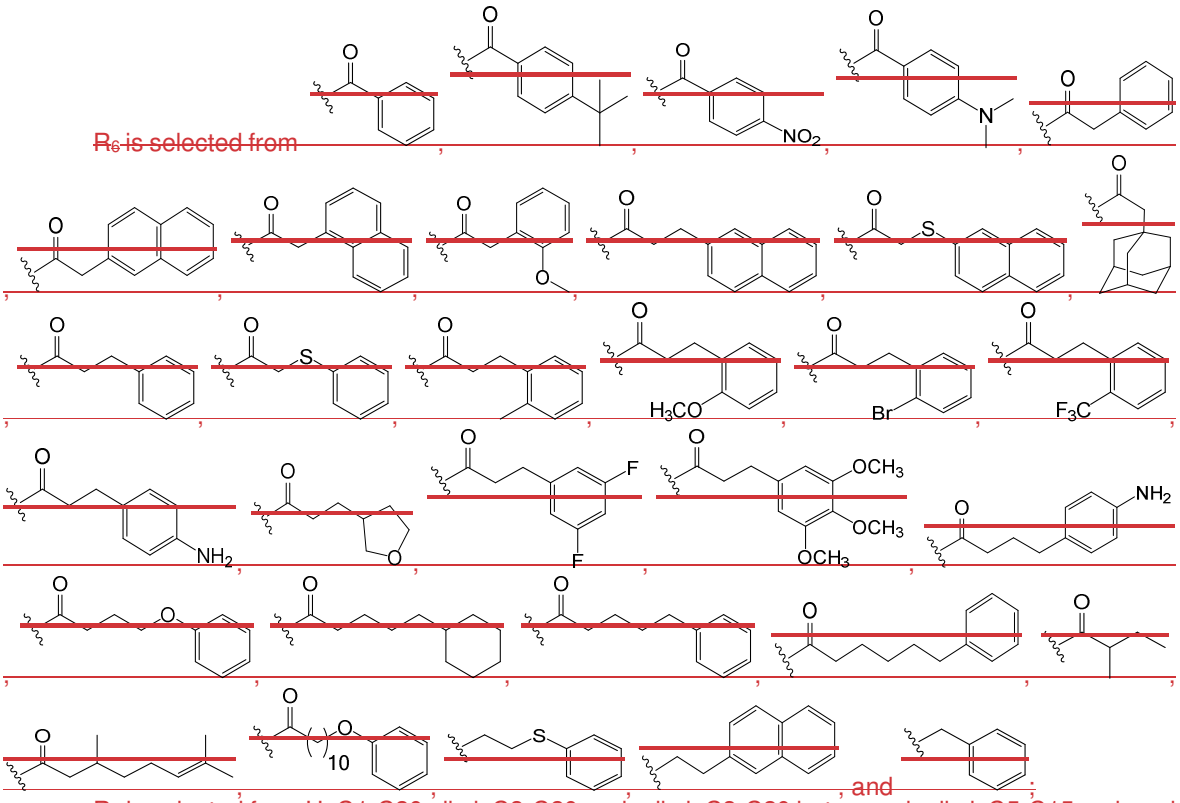
R_2 and R_3 are each independently selected from -H, -OH, -F, -Cl, and -Br;

R_4 is selected from $-CO_2H$, $-P(=O)(OH)_2$, and $-SO_3H$;

R_5 is selected from $-COCH_3$, $-COCF_3$, and $-SO_2CH_3$;

X is selected from -O- and -S-;

Y is selected from -O-, -S-, $-NR_7$-, $-O(C=O)NR_7$-, $-O(C=S)NR_7$-, $-O(C=O)O$-, $-O(C=O)$-, $-NH(C=O)O$-, $-NH(C=O)$-, $-NH(C=NH)$-, $-NH(C=O)NR_7$-, $-NH(C=NH)NR_7$-, $-NH(C=S)NR_7$-, $-NH(C=S)$-, $-OCH_2(C=O)NR_7$-, $-NH(SO_2)$-, $-NH(SO_2)NR_7$-, $-OR_8$-, $-NHR_8$-, and $-SR_8$-;

~~R_6 is selected from~~ 

~~R_7 is selected from H, C1-C20 alkyl, C3-C20 cycloalkyl, C3-C20 heterocycloalkyl; C5-C15 aryl, and C2-C15 heteroaryl;~~

~~R_8 is selected from C3-C20 heterocycloalkyl, C5-C15 aryl, and C2-C15 heteroaryl;~~

~~each E comprises an Fc domain monomer;~~

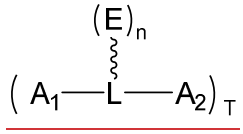
~~n is 1 or 2;~~

~~T is the number of A_1-L-A_2 moieties conjugated to each E and each T is, independently, an integer from 1 to 20; and~~

~~L is a linker covalently attached to each of E, A_1, and A_2,~~

~~or a pharmaceutically acceptable salt thereof.~~

In one aspect, the present disclosure refers to a conjugate described by formula (D-I):



(D-I)

wherein each A_1 and each A_2 is zanamivir;

E comprises an Fc domain monomer;

n is 1 or 2;

T is an integer from 1 to 20; and

L is a linker covalently attached to each of E, A_1, and A_2, wherein L is covalently attached to each of A_1 and A_2 at position C7 or position C9 of zanamivir;

or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to a population of conjugates as disclosed herein, wherein the average value of T is 1 to 5.

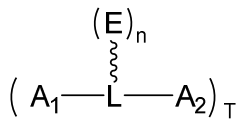
In one aspect, the present disclosure refers to a pharmaceutical composition comprising a conjugate or population of conjugates as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In one aspect, the present disclosure refers to the pharmaceutical composition as disclosed herein for use in therapy.

In one aspect, the present disclosure refers to use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject having a viral infection or presumed to have a viral infection.

In one aspect, the present disclosure refers to use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for prophylactic treatment of a subject at risk of developing a viral infection.

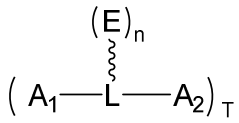
In another example, the disclosure features a conjugate described by formula (D-I):



(D-I)

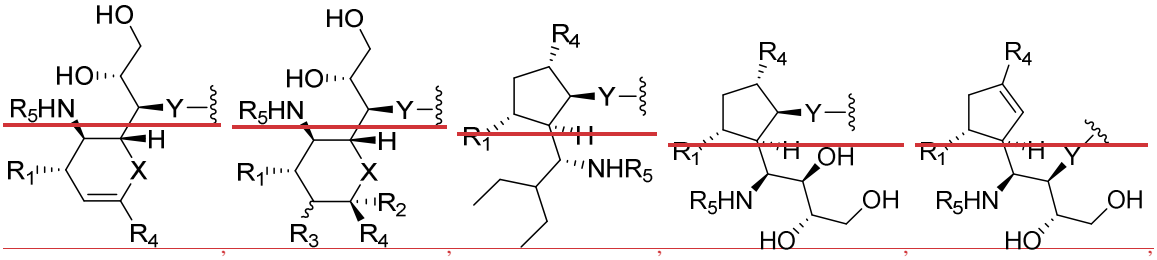
CLAIMS

1. A conjugate described by formula (D-I):

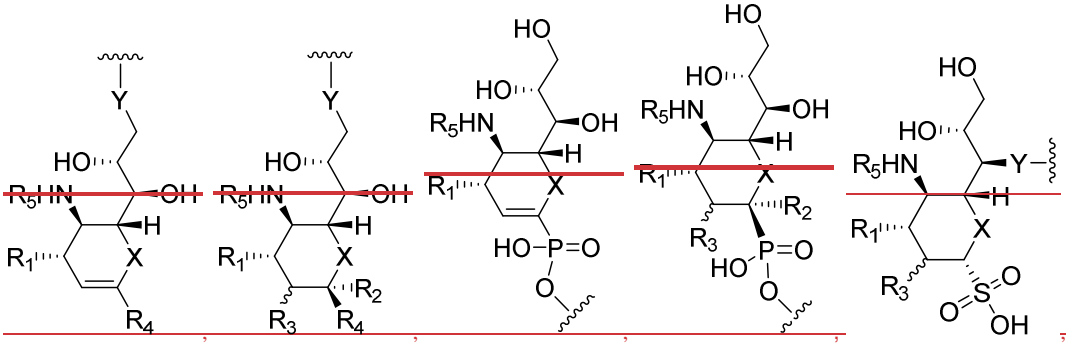


(D-I)

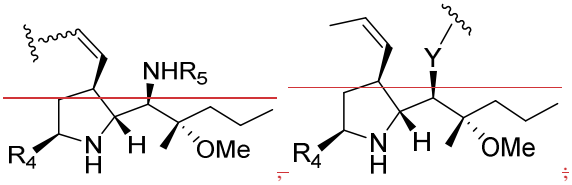
wherein each A_1 and each A_2 is zanamivir;~~independently selected from any one of formulas (A-I)-(A-XII):~~



(A-I) (A-II) (A-III) (A-IV) (A-V)



(A-VI) (A-VII) (A-VIII) (A-IX) (A-X)



(A-XI) (A-XII)

~~wherein R_1 is selected from -OH, -NH_2, -NHC(=NH)NH_2, and -NHC(=NH)NHR_6;~~

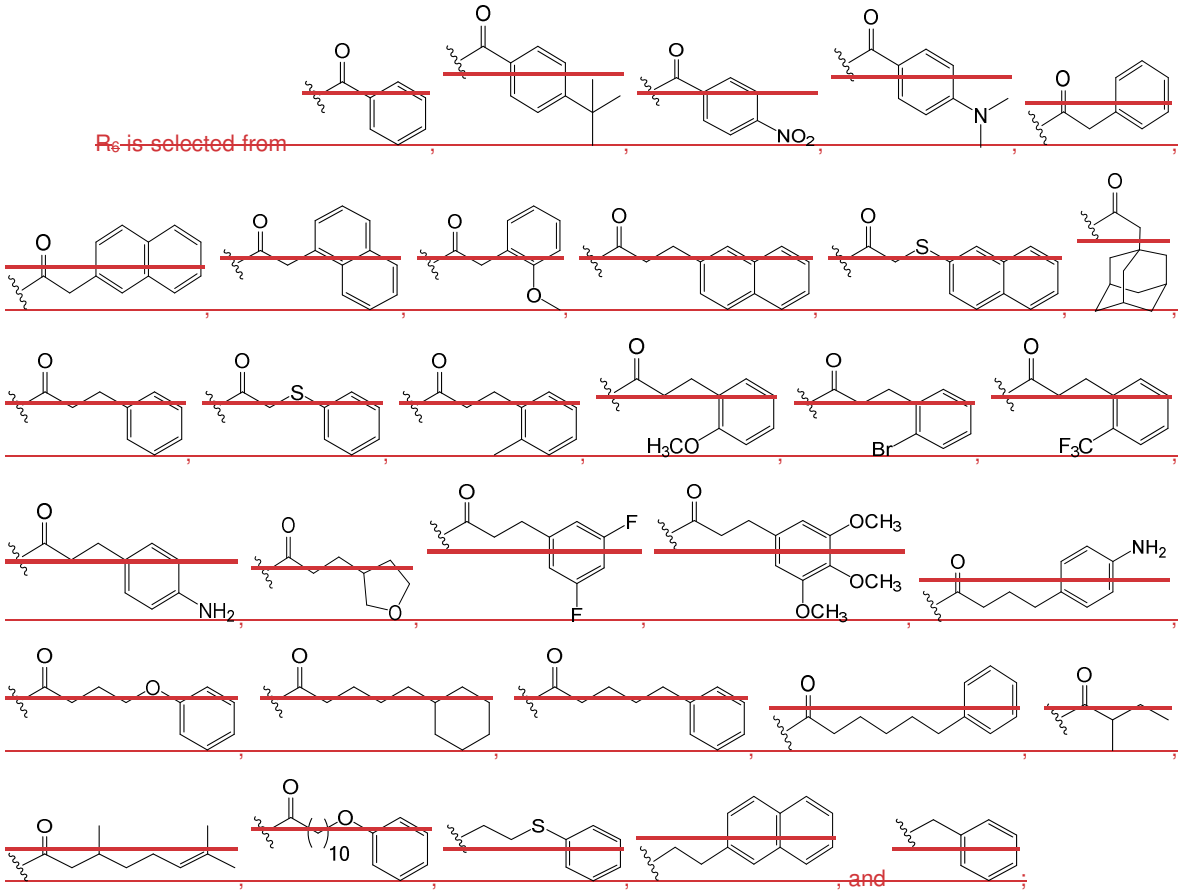
~~R_2 and R_3 are each independently selected from -H, -OH, -F, -Cl, and -Br;~~

~~R_4 is selected from -CO_2H, -P(=O)$(OH)_2$, and -SO_3H;~~

~~R_5 is selected from -$COCH_3$, -$COCF_3$, and -SO_2CH_3;~~

~~X is selected from -O- and -S-;~~

~~Y is selected from -O-, -S-, -NR_7-, -O(C=O)NR_7-, -O(C=S)NR_7-, -O(C=O)O-, -O(C=O)-, -NH(C=O)O-, -NH(C=O)-, -NH(C=NH)-, -NH(C=O)NR_7-, -NH(C=NH)NR_7-, -NH(C=S)NR_7-, -NH(C=S)-, -OCH_2(C=O)NR_7-, -NH(SO_2)-, -NH(SO_2)NR_7-, -OR_8-, -NHR_8-, and -SR_8-;~~

R_6 is selected from , and ;

R_7 is selected from H, C1-C20 alkyl, C3-C20 cycloalkyl, C3-C20 heterocycloalkyl; C5-C15 aryl, and C2-C15 heteroaryl;

R_8 is selected from C3-C20 heterocycloalkyl, C5-C15 aryl, and C2-C15 heteroaryl;

each E comprises an Fc domain monomer;

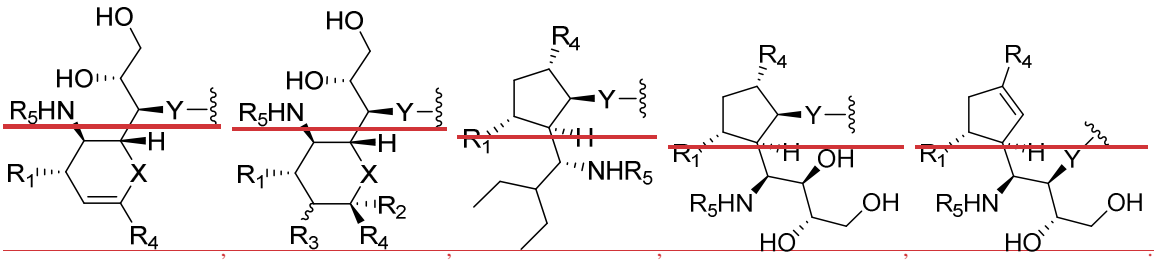
n is 1 or 2;

T is the number of A_1-L-A_2 moieties conjugated to each E and each T is, independently, an integer from 1 to 20; and

L is a linker covalently attached to each of E, A_1, and A_2, wherein L is covalently attached to each of A_1 and A_2 at position C7 or position C9 of zanamivir;

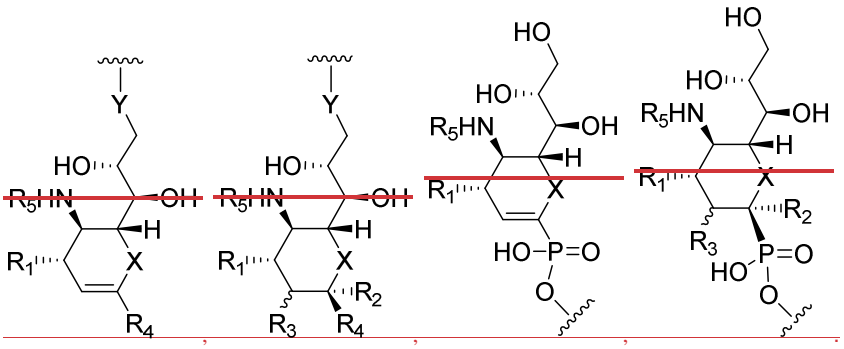
or a pharmaceutically acceptable salt thereof.

~~2. The conjugate of claim 1, wherein each A_1 and each A_2 is independently selected from any one of formulas (A-I)-(A-V):~~



~~(A-I) (A-II) (A-III) (A-IV) (A-V)~~

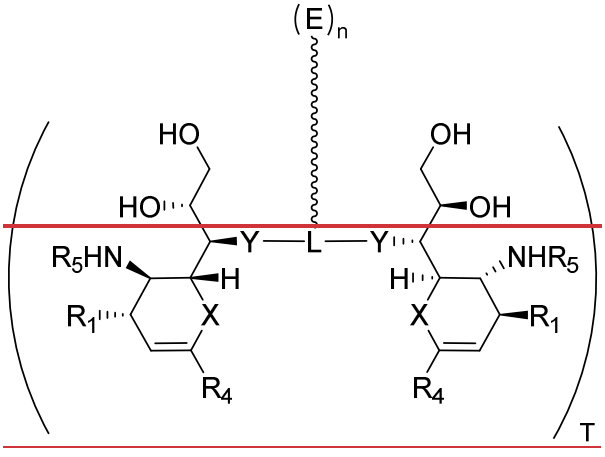
~~3. The conjugate of claim 1, wherein each A_1 and each A_2 is independently selected from any one of formulas (A-VI)-(A-IX):~~



~~(A-VI) (A-VII) (A-VIII) (A-IX)~~

42. The conjugate of claim 1, wherein Y is selected from -O-, -NR_7-, -O(C=O)NR_7-, or -NH(C=O)-,OCH_2(C=O)NR_7-, wherein R_7 is selected from H and C1-C20 alkyl.

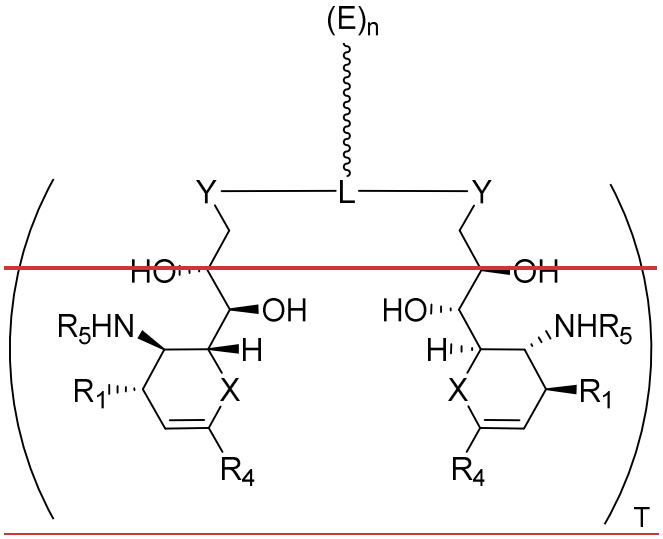
~~5. The conjugate of claim 1, wherein the conjugate is described by formula (D-II):~~



~~(D-II)~~

~~or a pharmaceutically acceptable salt thereof.~~

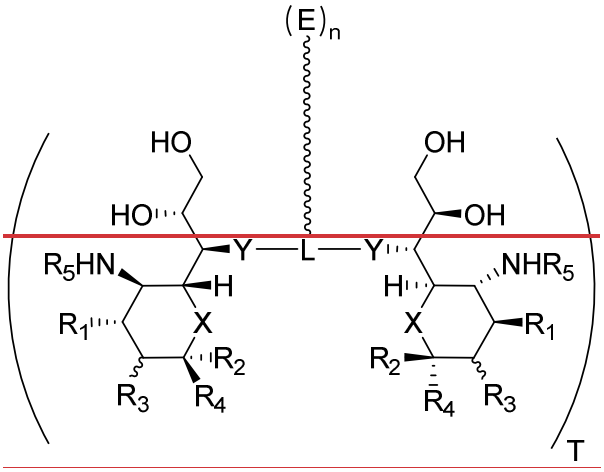
6. The conjugate of claim 1, wherein the conjugate is described by formula (D-III):



(D-III)

or a pharmaceutically acceptable salt thereof.

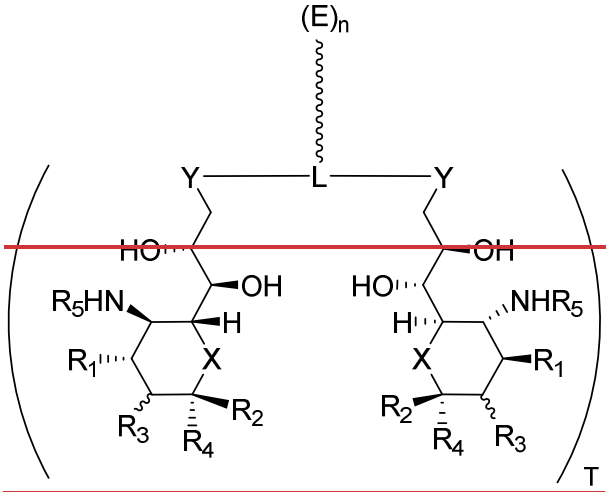
7. The conjugate of claim 1, wherein the conjugate is described by formula (D-V):



(D-V)

or a pharmaceutically acceptable salt thereof.

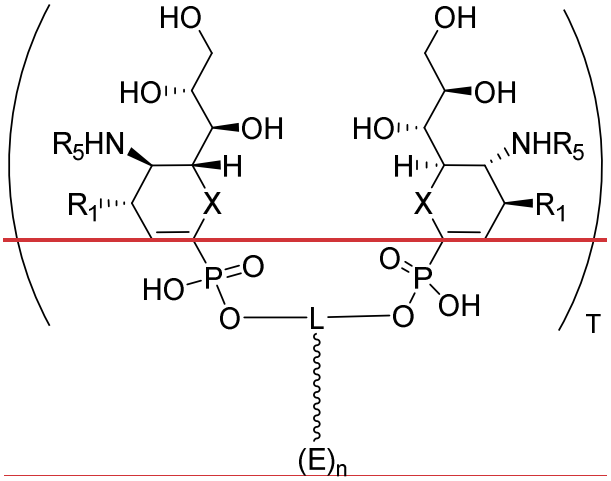
8. The conjugate of claim 1, wherein the conjugate is described by formula (D-VI):



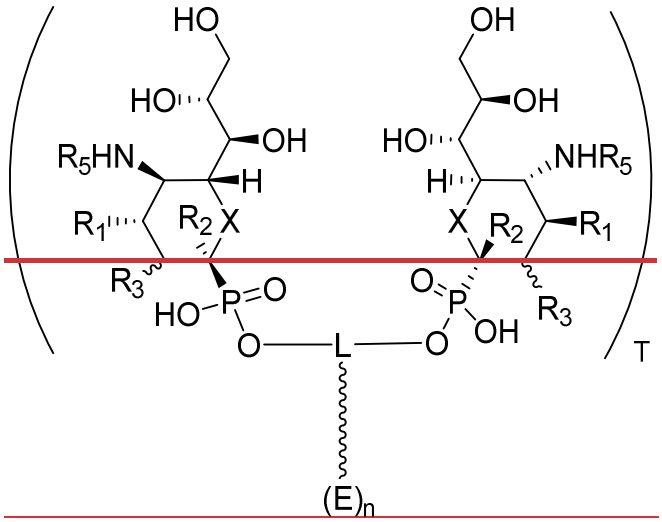
(D-VI)

or a pharmaceutically acceptable salt thereof.

9. The conjugate of claim 1, wherein the conjugate is described by formula (D-IV) or (D-VII):



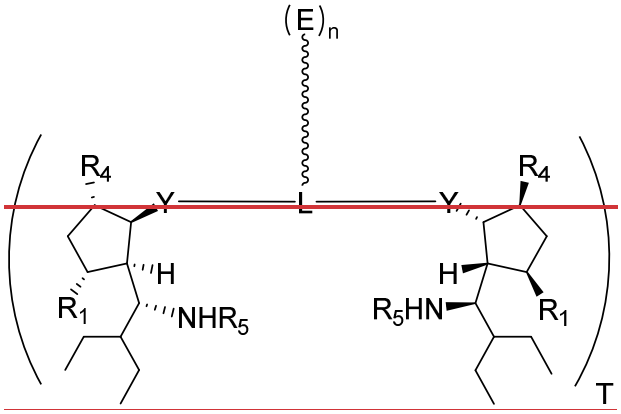
(D-IV),



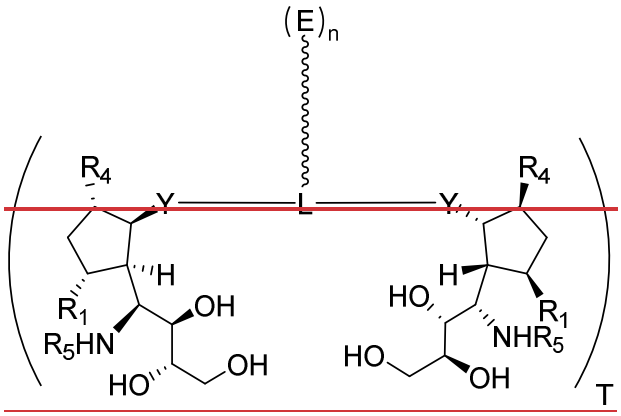
(D-VII)

or a pharmaceutically acceptable salt thereof.

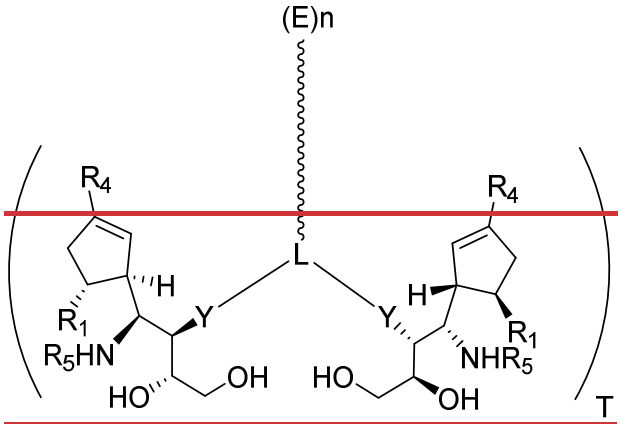
10. The conjugate of claim 1, wherein the conjugate is described by formula (D-VIII), (D-IX), or (D-X):



(D-VIII),



(D-IX),



~~(D-X)~~

~~or a pharmaceutically acceptable salt thereof.~~

~~11~~3. The conjugate of ~~any one of claims 1-10~~claim 1 or 2, wherein L comprises one or more optionally substituted C1-C20 alkylene, optionally substituted C1-C20 heteroalkylene, optionally substituted C2-C20 alkenylene, optionally substituted C2-C20 heteroalkenylene, optionally substituted C2-C20 alkynylene, optionally substituted C2-C20 heteroalkynylene, optionally substituted C3-C20 cycloalkylene, optionally substituted C3-C20 heterocycloalkylene, optionally substituted C4-C20 cycloalkenylene, optionally substituted C4-C20 heterocycloalkenylene, optionally substituted C8-C20 cycloalkynylene, optionally substituted C8-C20 heterocycloalkynylene, optionally substituted C5-C15 arylene, optionally substituted C2-C15 heteroarylene, O, S, NR^i, P, carbonyl, thiocarbonyl, sulfonyl, phosphate, phosphoryl, or imino,

wherein R^i is H, optionally substituted C1-C20 alkyl, optionally substituted C1-C20 heteroalkyl, optionally substituted C2-C20 alkenyl, optionally substituted C2-C20 heteroalkenyl, optionally substituted C2-C20 alkynyl, optionally substituted C2-C20 heteroalkynyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C5-C15 aryl, or optionally substituted C2-C15 heteroaryl.

~~12~~4. The conjugate of claim ~~11~~3, wherein L is oxo substituted.

~~13~~5. The conjugate of any one of claims 1-~~12~~4, wherein the L comprises no more than 250 atoms.

~~14~~6. The conjugate of any one of claim~~s~~ 1-~~13~~5, wherein L is covalently attached to the nitrogen atom of a surface exposed lysine of E.

~~15~~7. The conjugate of any one of claim~~s~~ 1-~~13~~5, wherein L is covalently attached to the sulfur atom of a surface exposed cysteine of E.

~~16~~8. The conjugate of claim ~~15~~7, wherein n is 2, and each E dimerizes to form an Fc domain.

~~17~~9. The conjugate of any one of claims 1-~~16~~8, wherein each T is, independently, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

~~18~~10. A population of conjugates of any one of claims 1-~~17~~9, wherein the average value of T is 1 to 5.

~~19~~11. A pharmaceutical composition comprising a conjugate or population of conjugates of any of claims 1-~~18~~10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

~~20~~12. The pharmaceutical composition of claim ~~19~~ 11 for use in therapy.

~~21~~13. Use of the pharmaceutical composition of claim ~~19~~ 11 in the manufacture of a medicament for treating a subject having a viral infection or presumed to have a viral infection.

~~22~~14. Use of the pharmaceutical composition of claim ~~19~~ 11 in the manufacture of a medicament for prophylactic treatment of a subject at risk of developing a viral infection.

~~23~~15. The use of claim ~~21~~ 13 or ~~22~~14, wherein the viral infection is caused by influenza virus or parainfluenza virus.

~~24~~16. The use of any one of claims ~~21~~13-~~23~~15, wherein the viral infection is influenza virus A, B, or C, or parainfluenza virus.

~~25~~17. The use of any one of claims ~~21~~13-~~24~~16, wherein the conjugate of composition is to be administered intramuscularly, intravenously, intradermally, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subcutaneously, subconjunctival, intravesicularlly, mucosally, intrapericardially, intraumbilically, intraocularally, orally, locally, by inhalation, by injection, or by infusion.

~~26~~18. The use of any one of claims ~~21~~13-~~25~~17, wherein the subject is to be treated with a second therapeutic agent.

~~27~~19. The use of claim ~~26~~18, wherein the second therapeutic agent is an antiviral agent.

~~28~~20. The use of claim ~~27~~19, wherein the antiviral agent is selected from oseltamivir, zanamivir, peramivir, laninamivir, amantadine, and rimantadine.

~~29~~21. The use of claim ~~26~~18, wherein the second therapeutic agent is an antiviral vaccine.

~~30~~22. The use of claim ~~29~~21, wherein the antiviral vaccine elicits an immune response in the subject against influenza virus A, B, or C, or parainfluenza virus.