cell membranes in endosomes, allowing the release of the ribonucleoprotein complex into the cytoplasm.

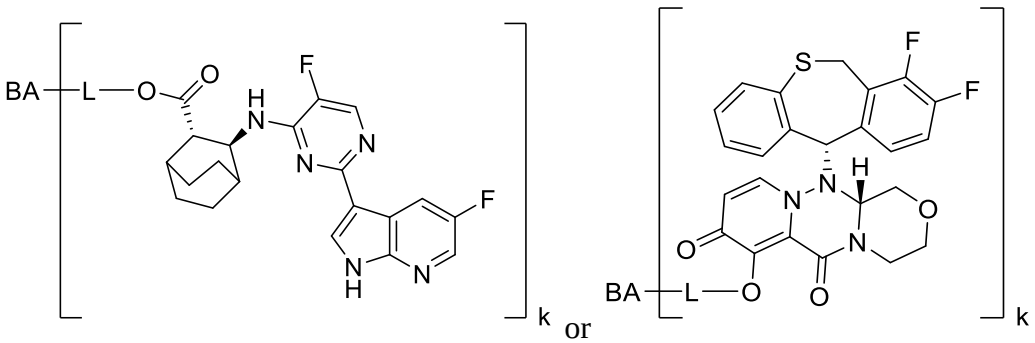
[0007] Currently, there are eighteen subtypes defined by their hemagglutinin proteins (H1 -H18). The eighteen HAs can be classified into two groups. Group 1 consists of H1, H2, H5, H6, H8, H9, H11, H12, H13, H16, H17, and H18 subtypes, and group 2 includes H3, H4, H7, H10, H14, and H15 subtypes.

[0008] Despite decades of research, there are no marketed antibodies or antibody-drug conjugates (ADCs) that broadly neutralize or inhibit influenza A virus infection or attenuate disease caused by influenza A virus. Therefore, there is a need to identify new antibodies and ADCs that neutralize multiple subtypes of influenza A virus and can be used as medicaments for prevention or therapy of influenza A infection.

SUMMARY

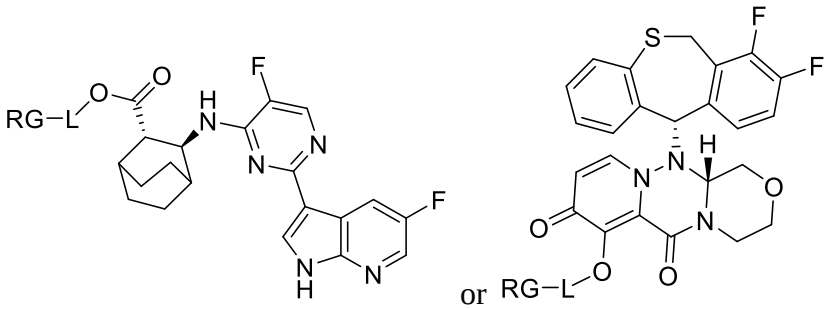
[0009] Provided herein are compounds useful, for example, in antiviral treatments. In one aspect, provided herein is an antibody-drug conjugate comprising an anti-influenza antibody or antigen-binding fragment thereof conjugated to an antiviral compound. In certain examples, the compounds include VX-787 and derivatives thereof, baloxavir and derivatives thereof, and/or baloxavir marboxil and derivatives thereof. In one example, provided is an antibody-drug conjugate including an anti-influenza antibody or antigen-binding fragment thereof conjugated to a payload (e.g., an antiviral compound), linker-payload (e.g., linker-antiviral compound), and/or compound as described herein.

[0010] In another aspect, provided herein are compounds having the following structure



wherein **L** is a linker; **BA** is a binding agent; and **k** is an integer from one to thirty.

[0011] There is also provided linker-payloads (e.g., linker-antiviral compounds). In another aspect, provided herein is a linker-antiviral compound having the following structure



or a pharmaceutically acceptable salt thereof, wherein **L** is a linker; and **RG** is a reactive moiety.

[0011a] In another aspect, provided herein is an antibody-drug conjugate comprising an antibody, or an antigen binding fragment thereof, where the antibody or antigen binding fragment thereof is conjugated to a compound as defined herein.

[0012] In another example, set forth herein are methods for making the payloads or compounds, linker-payloads, or antibody-drug conjugates, and compositions described herein.

[0012a] In another aspect, provided herein is a method of preparing an antibody-drug conjugate comprising contacting a binding agent with a linker-antiviral compound as defined herein.

[0013] In another example, provided herein are methods for the treatment, prophylaxis, reduction, or inhibition of a disease, disorder, or condition associated with an infection, as described herein, in a subject including administering to the subject an effective amount of a payload (e.g., antiviral compound), linker-payload (e.g., linker-antiviral compound), antibody-drug conjugate, or pharmaceutical composition as described herein.

[0013a] In another aspect, provided herein is a pharmaceutical composition comprising the antibody-drug conjugate or compound as defined herein, and a pharmaceutically acceptable excipient, carrier, or diluent.

[0013b] In another aspect, provided herein is the antibody-drug conjugate or compound as defined herein, or the pharmaceutical composition as defined herein for use in the treatment, prophylaxis, reduction, or inhibition of a disease, disorder, or condition associated with an infection.

[0013c] In another aspect, provided herein is use of the antibody-drug conjugate or compound as defined herein, or the pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment, prophylaxis, reduction, or inhibition of an influenza infection.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[0014] FIG. 1A shows the intensity-weighted average linker-payload (e.g., linker-antiviral compound) loadings as measured by LC-MS for 11729-Q295-**11**. FIG. 1B shows the intensity-weighted average linker-payload (e.g., linker-antiviral compound) loadings as measured by LC-MS for Isotype Control-Q295-**11**.

[0015] FIG. 2A shows the intensity-weighted average linker-payload (e.g., linker-antiviral compound) loadings as measured by LC-MS for 11729-HC-Cterm-**11**. FIG. 2B shows the intensity-weighted average linker-payload (e.g., linker-antiviral compound) loadings as measured by LC-MS for Isotype Control-HC-Cterm-**11**.

[0016] FIG. 3 shows ELISA sub-nanomolar specific binding of 11729-HC-Cterm-**11,** 11729-HC-Nterm-**11,** 11729-LC-Cterm-**11**, and 11729-LC-Nterm-**11** to influenza A-infected cells.

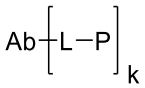
[0017] FIG. 4 shows comparative antiviral efficacy against influenza A infection between 11729-HC-Cterm-**11**, 11729-LC-Cterm-**11**, 11729-LC-Nterm-**11**, mAb11729, and an isotype control antibody and Isotype Control-HC-Cterm-**11**.

WHAT IS CLAIMED IS:

1. An antibody-drug conjugate comprising an anti-influenza antibody or antigen-binding fragment thereof conjugated to an antiviral compound.

2. The antibody-drug conjugate of claim 1, wherein the anti-influenza antibody or antigen-binding fragment thereof is conjugated to the antiviral compound via a linker.

3. The antibody-drug conjugate of claim 1 having the following structure



wherein **Ab** is an anti-influenza antibody or an antigen binding fragment thereof;
L is a linker;
P is an antiviral compound; and
k is an integer from one to thirty.

4. The antibody-drug conjugate of claim 3, wherein **P** is an influenza inhibitor.

5. The antibody-drug conjugate of claim 3, wherein **P** is a polymerase inhibitor.

6. The antibody-drug conjugate of claim 3, wherein **P** is VX-787, a derivative thereof, or a residue thereof.

7. The antibody-drug conjugate of claim 3, wherein **P** is baloxavir, a derivative thereof, or a residue thereof.

8. The antibody-drug conjugate of claim 3, wherein **Ab** is an anti-hemagglutinin antibody or an antigen binding fragment thereof.

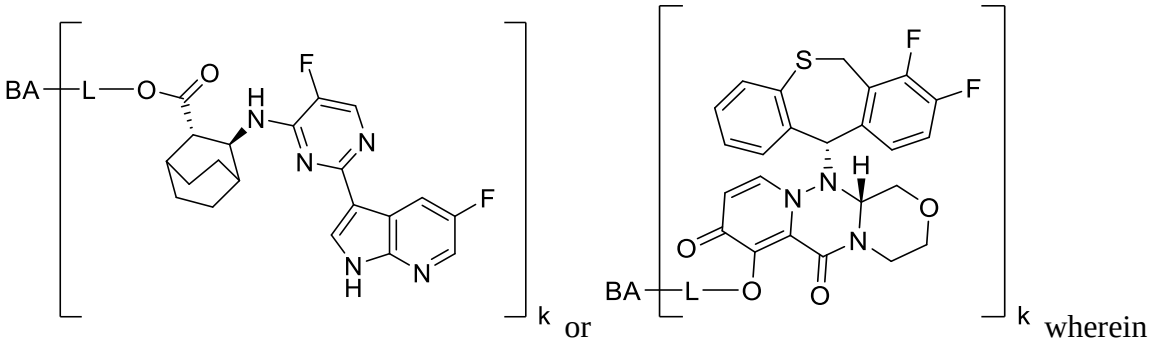
9. The antibody-drug conjugate of claim 8, wherein **P** is an influenza inhibitor.

10. The antibody-drug conjugate of claim 8, wherein **P** is a polymerase inhibitor.

11. The antibody-drug conjugate of claim 8, wherein **P** is VX-787, a derivative thereof, or a residue thereof.

12. The antibody-drug conjugate of claim 8, wherein **P** is baloxavir, a derivative thereof, or a residue thereof.

13. A compound having the following structure



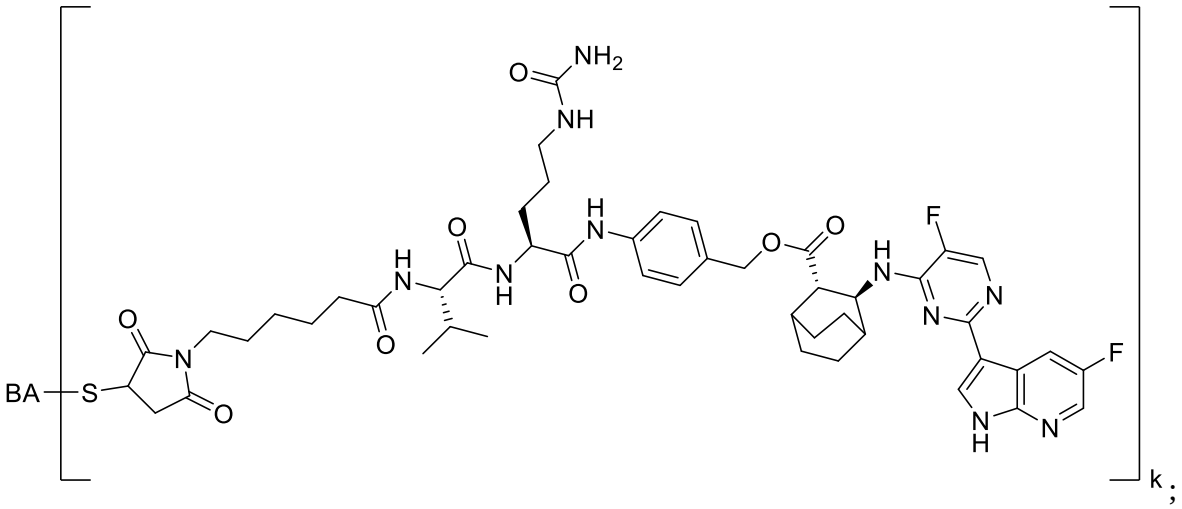
wherein

L is a linker;

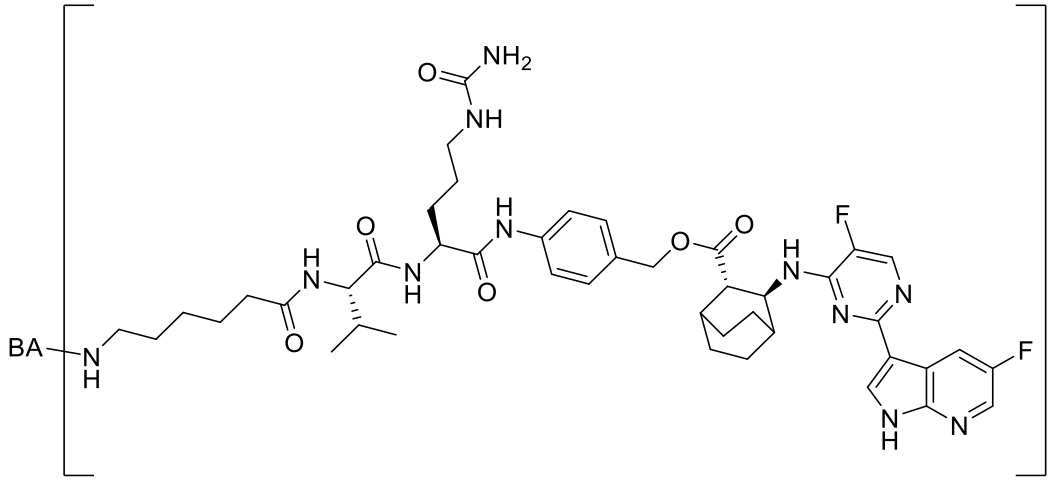
BA is a binding agent; and

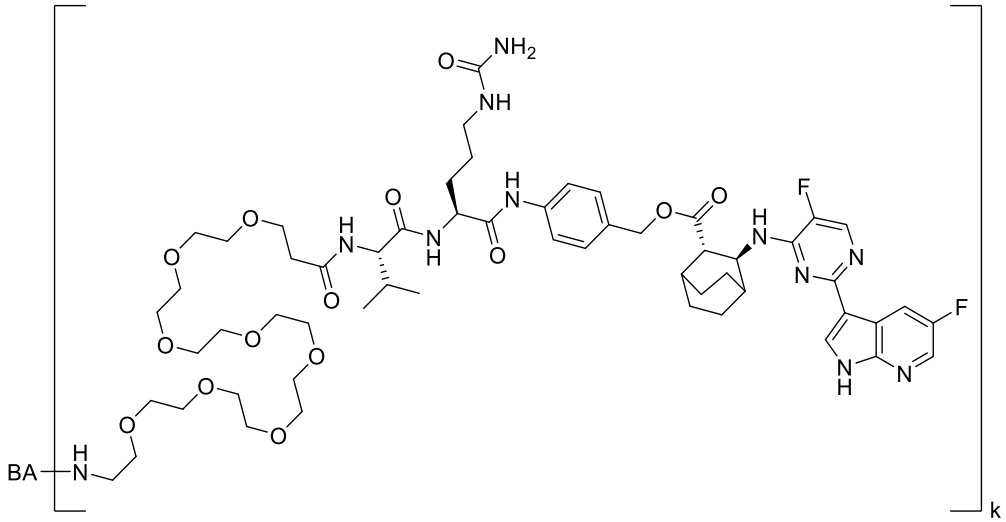
k is an integer from one to thirty.

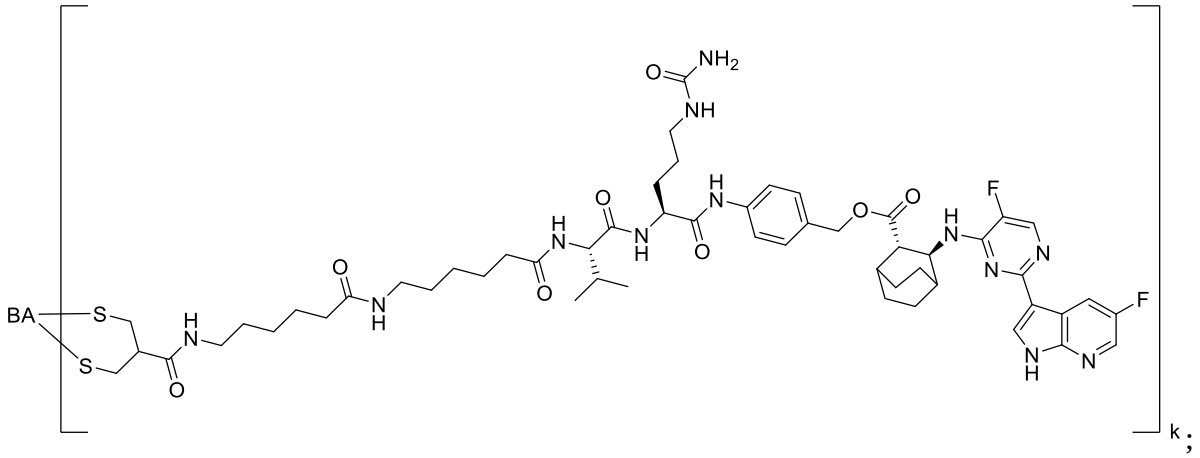
14. The compound of claim 13, selected from the group consisting of



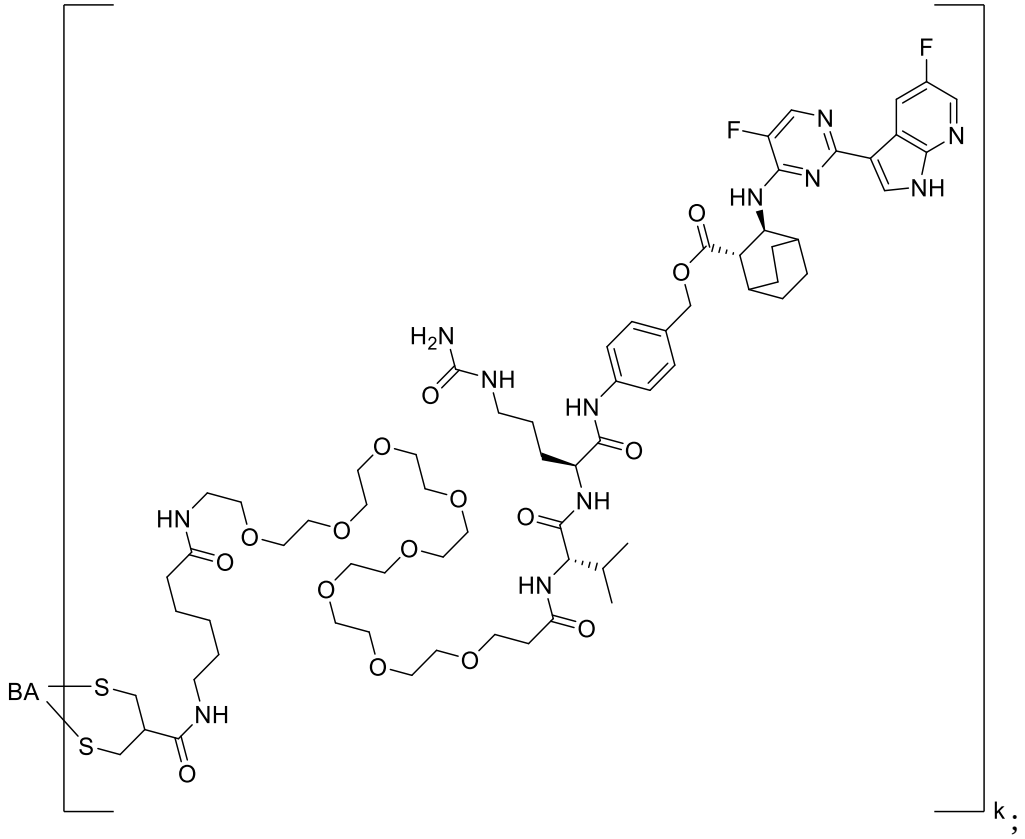
;







and



wherein

BA is an antibody or an antigen binding fragment thereof; and

k is an integer from one to thirty.

15. The compound of claim 13, wherein **BA** is an antibody or antigen-binding fragment thereof.

16. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least one glutamine residue used for conjugation.

17. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least two glutamine residues used for conjugation.

18. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least three glutamine residues used for conjugation.

19. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least four glutamine residues available for conjugation.

20. The antibody-drug conjugate or compound of claim 19, wherein **Ab** or **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof, wherein conjugation is at two Q295 residues in the EU numbering system; and **k** is two.

21. The antibody-drug conjugate or compound of claim 19, wherein **Ab** or **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising an antibody heavy chain, wherein conjugation is at the C-terminus of the heavy chain; and **k** is two.

22. The antibody-drug conjugate or compound of claim 21, wherein the conjugation is via a glutamine.

23. The antibody-drug conjugate or compound of claim 21, wherein conjugation is via a glutamine in a LLQGA (SEQ ID NO: 297) sequence at the C-terminus of the antibody heavy chain.

24. The antibody-drug conjugate or compound of claim 19, wherein conjugation is at two Q295 residues and two N297Q residues; and **k** is 4.

25. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is mAb11729.

26. A pharmaceutical composition comprising the antibody-drug conjugate or compound of any preceding claim, and a pharmaceutically acceptable excipient, carrier, or diluent.

27. The pharmaceutical composition of claim 26, wherein the pharmaceutical composition is formulated for an administration selected from the group consisting of oral, intravenous, intraperitoneal, inhalation, and intranasal.

28. The antibody-drug conjugate or compound of any one of claims 1 to 26, or the pharmaceutical composition of claim 26 or 27 for use in the treatment, prophylaxis, reduction, or inhibition of a disease, disorder, or condition associated with an infection.

29. The antibody-drug conjugate, compound, or pharmaceutical composition for use of claim 28, wherein the infection is a viral infection.

30. The antibody-drug conjugate, compound, or pharmaceutical composition for use of claim 29, wherein the infection is influenza virus infection.

31. The antibody-drug conjugate, compound, or pharmaceutical composition for use of claim 29, wherein the infection is influenza A virus infection.

32. The antibody-drug conjugate, compound, or pharmaceutical composition for use of claim 29, wherein the infection is influenza B virus.

33. The antibody-drug conjugate, compound, or pharmaceutical composition for use of claim 29, wherein the infection is influenza A virus infection and influenza B virus infection.

34. The antibody-drug conjugate, compound, or pharmaceutical composition for use of any one of claims 28-33, wherein side effects of the antibody-drug conjugate, compound, or pharmaceutical composition are reduced when compared to administration of the unconjugated antiviral compound to a comparable subject.

35. Use of the antibody-drug conjugate or compound of any one of claims 1 to 26, or the pharmaceutical composition of claim 26 or 27 in the manufacture of a medicament for the treatment, prophylaxis, reduction, or inhibition of an influenza infection.

36. The use of claim 35, wherein the influenza infection is caused by influenza A virus infection.

37. The use of claim 35, wherein the influenza infection is caused by an influenza A Group 1 virus.

38. The use of claim 35, wherein the influenza infection is caused by an influenza A H1 virus.

39. The use of claim 35, wherein the influenza infection is caused by an influenza A Group 2 virus.

40. The use of claim 35, wherein the influenza infection is caused by an influenza A H3 virus.

41. The use of claim 35, wherein the influenza infection is caused by an unknown or undetermined influenza virus.

42. The use of claim 35, wherein the influenza infection is caused by influenza B virus infection.

43. The use of claim 35, wherein the influenza infection is caused by influenza A virus infection and influenza B virus infection.

44. The use of any one of claims 28-43, wherein the antibody-drug conjugate, compound, or pharmaceutical composition is to be administered in combination with a supplementary therapeutic agent.

45. The use of claim 44, wherein the supplementary therapeutic is selected from the group consisting of an anti-viral drug, an anti-inflammatory drug, an antibody that binds specifically to influenza HA, a vaccine for influenza, a dietary supplement, and a palliative therapy to treat an influenza infection.

46. The use of claim 45, wherein the anti-inflammatory drug is selected from the group consisting of corticosteroids and non-steroidal anti-inflammatory drugs.

47. The use of claim 46, wherein the dietary supplement is an anti-oxidant.

48. The use of any one of claims 44-47, wherein the supplementary therapeutic agent is to be administered via a different route of administration as the antibody-drug conjugate, compound, or pharmaceutical composition.

49. The use of any one of claims 44-48, wherein the supplementary therapeutic agent is to be administered orally.

50. The use of claim 45, wherein the anti-viral drug is oseltamivir.

51. The use of claim 50, wherein the oseltamivir is to be administered prior to administration of the antibody-drug conjugate, compound, or pharmaceutical composition.

52. The use of claim 50, wherein the oseltamivir is to be administered concurrently with the antibody-drug conjugate, compound, or pharmaceutical composition.

53. The use of claim 50, wherein the oseltamivir is to be administered after administration of the antibody-drug conjugate, compound, or pharmaceutical composition.

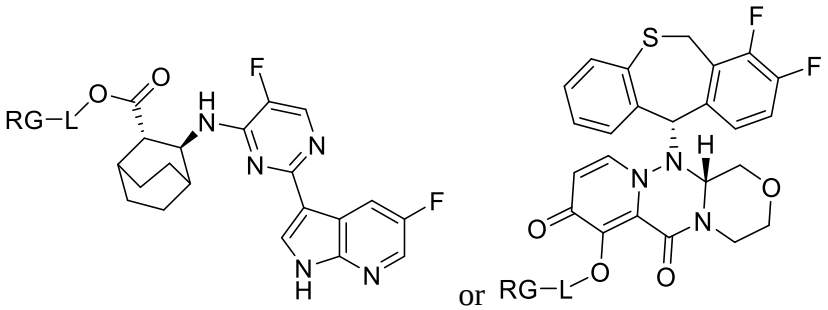
54. The use of claim 45, wherein the anti-viral drug is an anti-influenza A drug or an anti-influenza B drug.

55. The use of claim 54, wherein the anti-influenza A drug or the anti-influenza B drug is an antibody or antigen-binding portion thereof.

56. The use of claim 55, wherein the antibody binds specifically to influenza A HA or to influenza B HA.

57. The use of any one of claims 28-56, wherein the antibody-drug conjugate, compound, or pharmaceutical composition is to be administered subcutaneously, intravenously, intradermally, intramuscularly, intranasally, or orally.

58. A linker-antiviral compound having the following structure

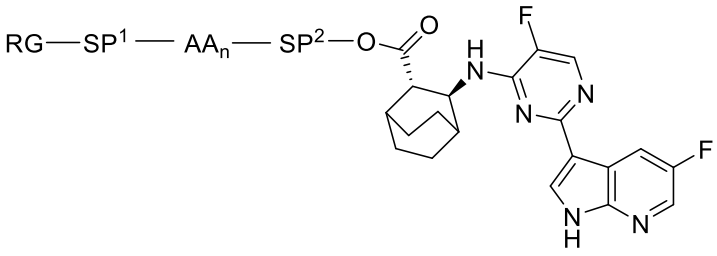


or a pharmaceutically acceptable salt thereof, wherein

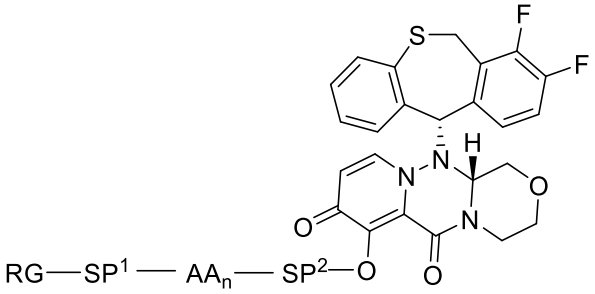
L is a linker; and

RG is a reactive moiety.

59. The linker-antiviral compound of claim 58, wherein the linker-payload is



or



or a pharmaceutically acceptable salt thereof, wherein

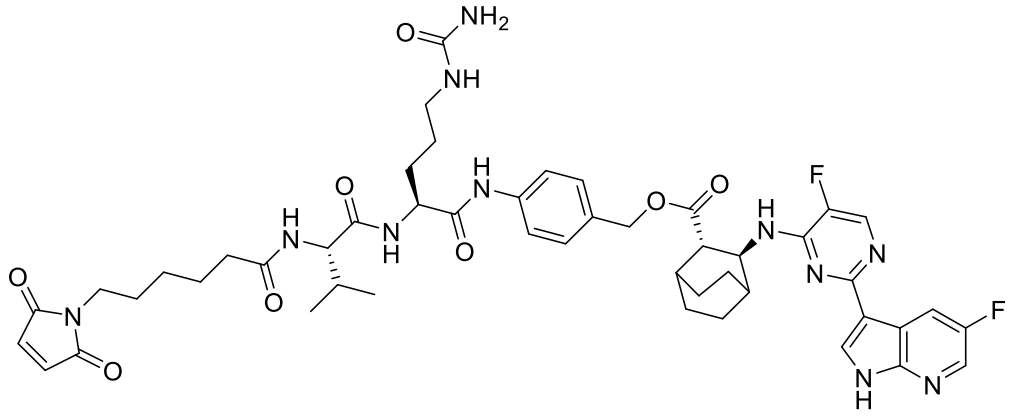
SP[1] and **SP[2]**, when present, are spacer groups;

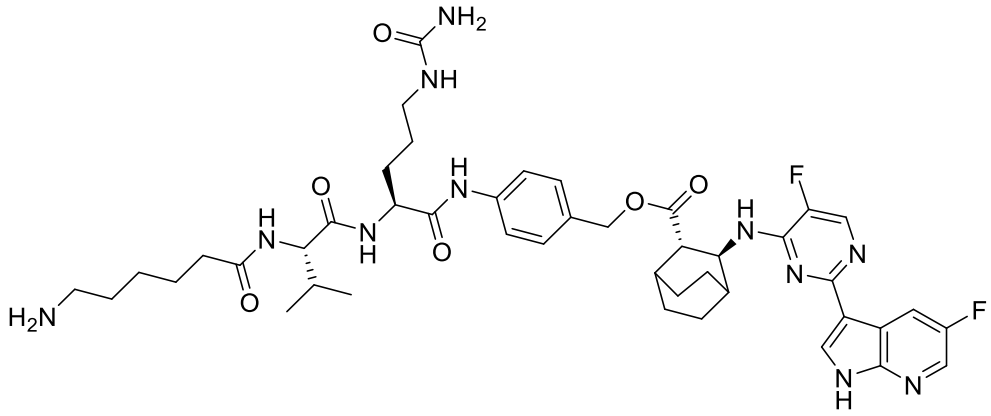
RG is a moiety reactive with an antibody or an antigen binding fragment thereof;

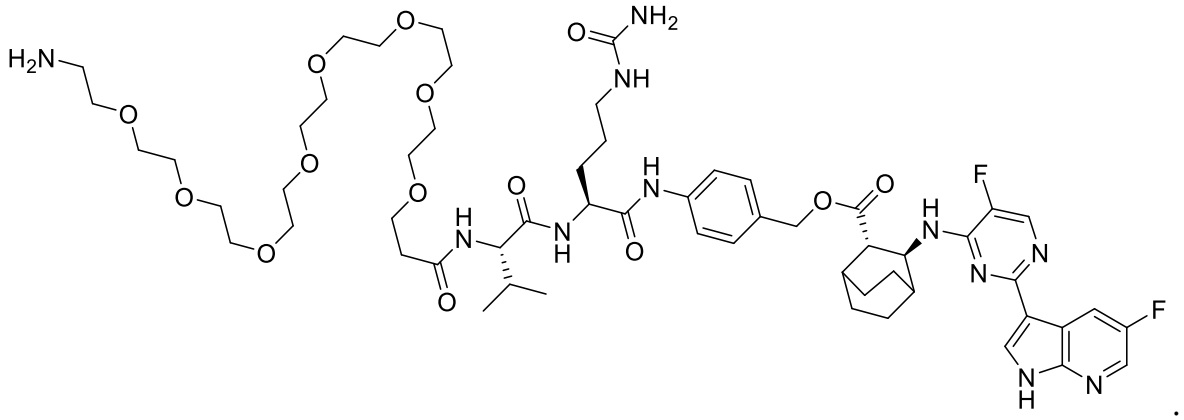
each **AA** is an amino acid; and

n is an integer from one to ten.

60. The linker-antiviral compound of claim 59, selected from the group consisting of

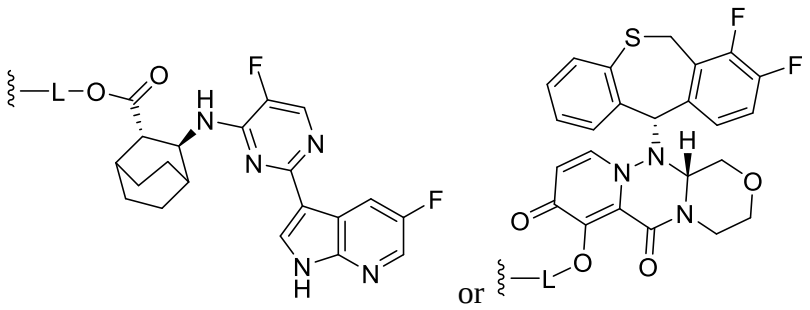

;


; and


.

61. An antibody-drug conjugate comprising an antibody, or an antigen binding fragment thereof, where the antibody or antigen binding fragment thereof is conjugated to a compound of claim 58.

62. The antibody-drug conjugate of claim 61, wherein the conjugated compound is selected from



wherein **L** is a linker.

63. A method of preparing an antibody-drug conjugate comprising contacting a binding agent with a linker-antiviral compound of claim 58.

64. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is an anti-influenza A antibody or an antigen binding fragment thereof.

65. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is an anti-influenza A Group 1 antibody or an antigen binding fragment thereof.

66. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is an anti-influenza H1 antibody or an antigen binding fragment thereof.

67. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is an anti-influenza A Group 2 antibody or an antigen binding fragment thereof.

68. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is an anti-influenza H3 antibody or an antigen binding fragment thereof.

69. The antibody-drug conjugate or compound of any of the preceding claims, wherein **Ab** or **BA** is an anti-influenza B antibody or an antigen binding fragment thereof.

70. The antibody-drug conjugate of any preceding claim, comprising an anti-influenza antibody or antigen-binding fragment thereof conjugated to an antiviral compound via a linker, wherein the antibody-drug conjugate binds to and/or inhibits polymerase basic protein 2 (PB2) (VX-787), polymerase acid protein (PA) (baloxavir marboxil), and/or polymerase basic protein 1 (PB1).

71. The antibody-drug conjugate or compound of any preceding claim, wherein the antibody-drug conjugate or compound comprises an antibody heavy chain and further comprises a pentapeptide at the C-terminus of the antibody heavy chain.

72. The antibody-drug conjugate or compound of claim 71, wherein the pentapeptide comprises the amino acid sequence LLQGA (SEQ ID NO: 297).

73. The antibody-drug conjugate of any preceding claim, wherein the antibody or antigen binding fragment thereof comprises a LCVR further comprising an amino acid sequence set forth in SEQ ID NO: 26; and a HCVR further comprising an amino acid sequence set forth in SEQ ID NO: 18 .

74. The antibody-drug conjugate of any preceding claim, wherein the antibody or antigen binding fragment thereof is the antibody mAb11729.

75. The antibody-drug conjugate of any preceding claim, wherein the antibody comprises
(a) a HCDR1 that comprises an amino acid sequence set forth in SEQ ID NO: 20;
(b) a HCDR2 that comprises an amino acid sequence set forth in SEQ ID NO: 22;
(c) a HCDR3 that comprises an amino acid sequence set forth in SEQ ID NO: 24;
(d) a LCDR1 that comprises an amino acid sequence set forth in SEQ ID NO: 28;
(e) a LCDR2 that comprises an amino acid sequence set forth in SEQ ID NO: 30; and
(f) a LCDR3 that comprises an amino acid sequence set forth in SEQ ID NO: 32 .

PROTEIN-ANTIVIRAL COMPOUND CONJUGATES

ABSTRACT

Provided herein are compounds, compositions, and uses for the treatment of diseases and disorders associated with influenza, including VX-787 and derivatives thereof, baloxavir and derivatives thereof, and baloxavir marboxil and derivatives thereof, and protein (*e.g.*, antibody) drug conjugates thereof.

[no suitable figure]