

SUBSTITUTED HETEROCYCLICS WITH THERAPEUTIC ACTIVITY IN HIV

GOVERNMENT SUPPORT.

[001] This invention was made with government support under Grant Number R01AI104416 awarded by the National Institutes of Health. The Government has certain rights in the invention.

RELATED APPLICATIONS

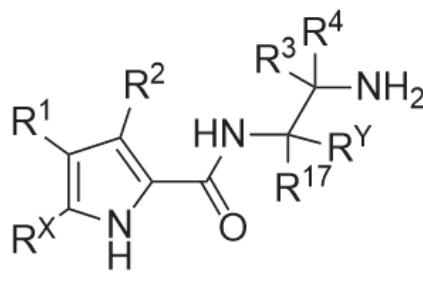
[002] This application claims the benefit of U.S. Provisional Patent Application No. 62/937,665, filed November 19, 2019, which is incorporated herein by reference in its entirety.

BACKGROUND

[003] Human immunodeficiency virus (HIV) is known to cause AIDS. Human immunodeficiency virus type 1 (HIV-1) cell entry process is thought to start when its surface envelope glycoproteins gp120 bind to the host cell primary receptor CD4. The binding triggers conformational changes in gp120 that facilitate its binding to the host cell co-receptor (secondary) CCR5 or CXCR4. There is no drug available yet that targets HIV-1 gp120.

SUMMARY

[003a] [In one aspect, provided herein is a compound of Formula \(I\):](#)



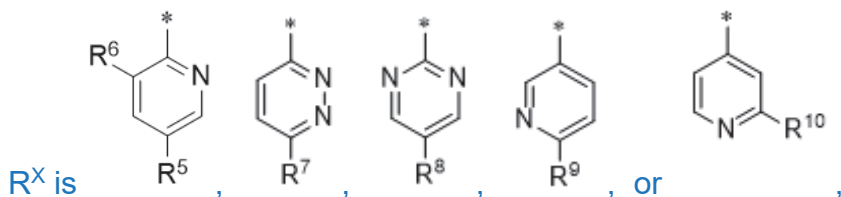
[\(I\).](#)

[or a pharmaceutically acceptable salt thereof.](#)

wherein:

each of R¹, R², R³, and R⁴, is, independently, H or C₁₋₃ alkyl;

R¹⁷ is H or CH₃;

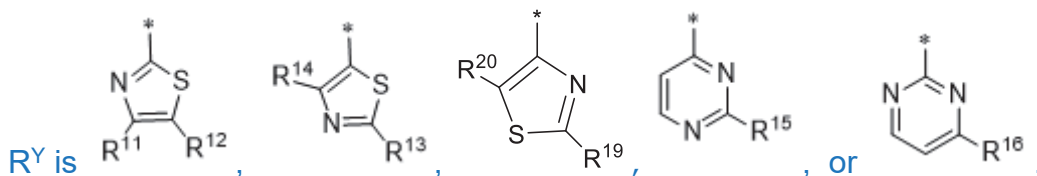


wherein * indicates the point of attachment;

each of R⁵, R⁷, R⁸, and R⁹ is H, CH₃, halogen, or CF₃;

R⁶ is H or halogen; and

R¹⁰ is H, halogen, CF₃, OCH₃ or OCF₃; and



wherein * indicates the point of attachment: and

each of R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁹, and R²⁰, is, independently, H, CH₂OH, CH₂CH₂OH, (CH₂)₃OH or CH(OH)CH₂OH.

[003b] In another aspect, provided herein is a composition, comprising the compound as disclosed herein.

[003c] In another aspect, provided herein is a pharmaceutical composition, comprising the compound as disclosed herein and a pharmaceutically acceptable carrier.

[003d] In another aspect, provided herein is use of a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for inhibiting HIV in a subject in need thereof, wherein a therapeutically effective amount of the compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein is to be administered to the subject.

[003e] In another aspect, provided herein is use of a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a HIV injection in a subject in need thereof, wherein a therapeutically effective amount of the compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein is to be administered to the subject.

[003f] In another aspect, provided herein is use of a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for eradicating, reducing, or slowing a HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein is to be administered to the subject.

[003g] In another aspect, provided herein is use of a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for reducing the viral load associated with a HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein is to be administered to the subject.

[003h] In another aspect, provided herein is use of a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for reducing reoccurrence of a HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein is to be administered to the subject.

[003i] In another aspect, provided herein is use of a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for reducing an adverse physiological impact of a HIV infection in a subject in need thereof, wherein a therapeutically effect amount of the compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein is to be administered to the subject.

[003j] In another aspect, provided herein is use of a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for inducing remission of an organ injury from a HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein is to be administered to the subject.

[003k] In another aspect, provided herein is use of a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for reducing the physiological impact of long-term antiviral therapy for HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein is to be administered to the subject.

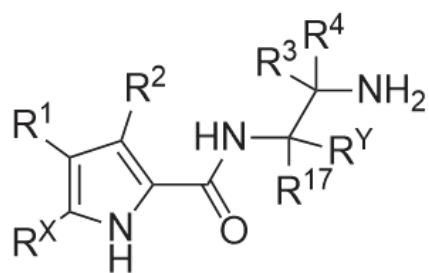
[003l] In another aspect, provided herein is use of a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for prophylactically treating a HIV infection in a subject in need thereof, wherein the subject is afflicted with a latent HIV infection, and wherein a therapeutically effective amount of the compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein is to be administered to the subject.

[003m] In another aspect, provided herein is a kit, comprising a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein, and instructions for use thereof.

[003n] In another aspect, provided herein is a compound as disclosed herein, the composition as disclosed herein, or the pharmaceutical composition as disclosed herein for use in therapy.

[004] Disclosed herein are anti-HIV compounds and methods of treating HIV infection utilizing them. Generally, the compounds are heterocyclic substituted pyrrole carboxamides.

[005] In some embodiments, the anti-HIV compounds are represented by Formula (I):

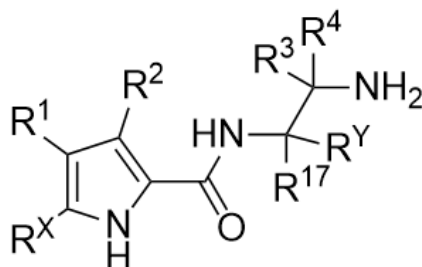


Formula (I)

CLAIMS

What is claimed is:

1. A compound of Formula (I):



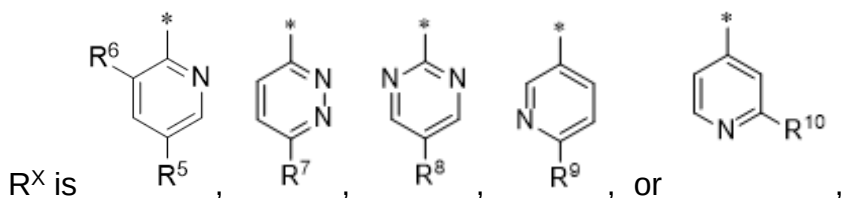
(I),

or a pharmaceutically acceptable salt thereof,

wherein:

each of R¹, R², R³, and R⁴, is, independently, H or C₁₋₃ alkyl;

R¹⁷ is H or CH₃;

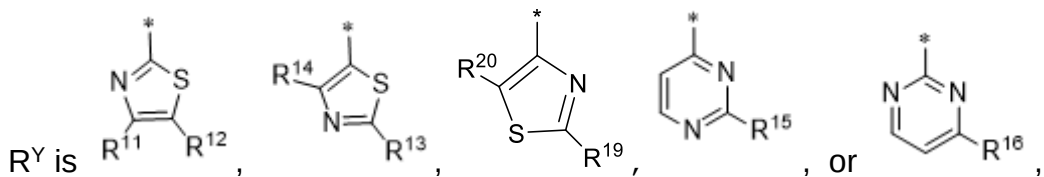


wherein * indicates the point of attachment;

each of R⁵, R⁷, R⁸, and R⁹ is H, CH₃, halogen, or CF₃;

R⁶ is H or halogen; and

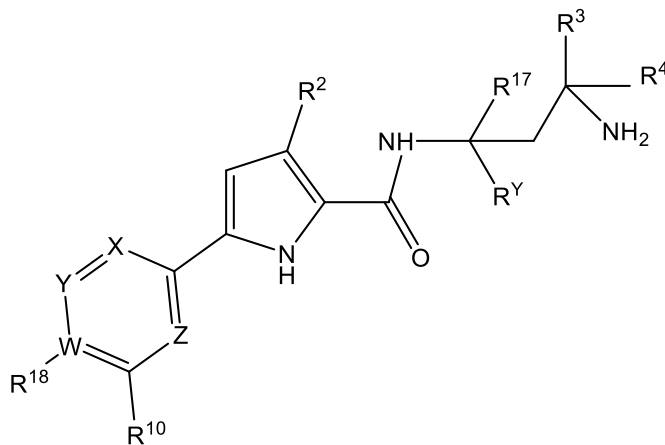
R¹⁰ is H, halogen, CF₃, OCH₃ or OCF₃; and



wherein * indicates the point of attachment: and

each of R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{19} , and R^{20} , is, independently, H, CH_2OH , CH_2CH_2OH , $(CH_2)_3OH$ or $CH(OH)CH_2OH$.

2. The compound of claim 1, having a structure of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof,

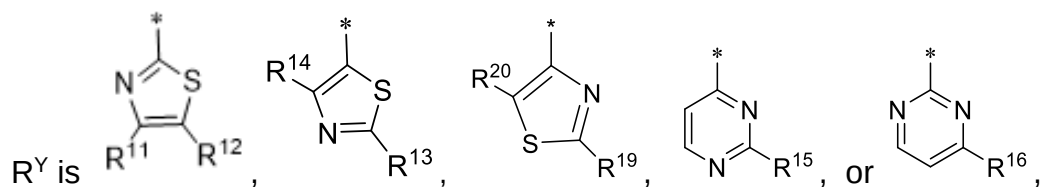
wherein:

W is C or N;

X, Y, and Z are independently CH or N, and at least one of W, X, Y, or Z is N; if more than one of W, X, Y, or Z is N, then only X and Y, or X and Z, are both N;

each of R^2 , R^3 , and R^4 , is, independently, H or CH_3 ;

R^{10} is H when X is N, and is H or OCH_3 when X is CH;



wherein * indicates the point of attachment

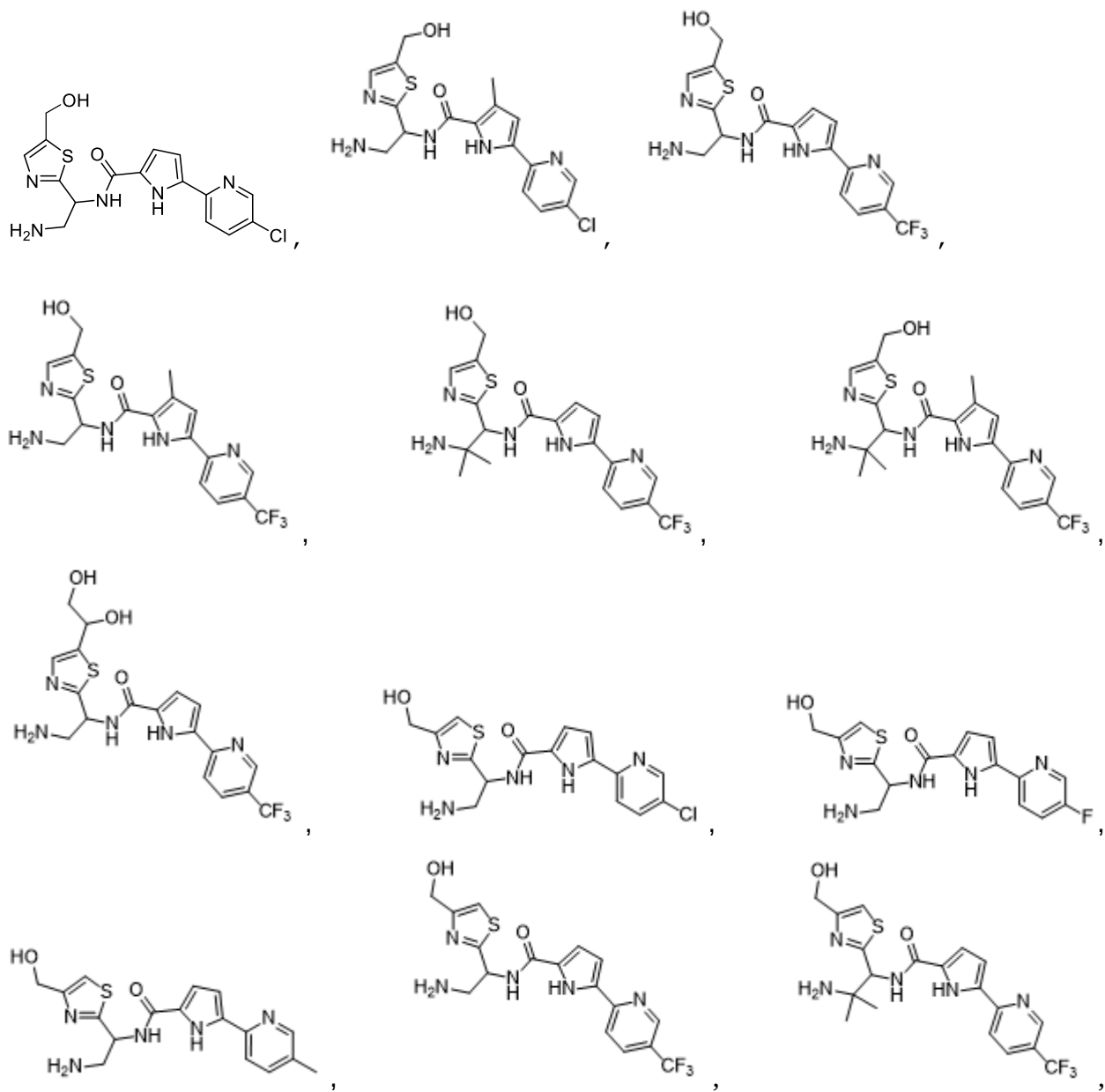
Each of R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{19} , and R^{20} , independently, H, CH_2OH , $(CH_2)_2OH$, $(CH_2)_3OH$ or $CH(OH)CH_2OH$;

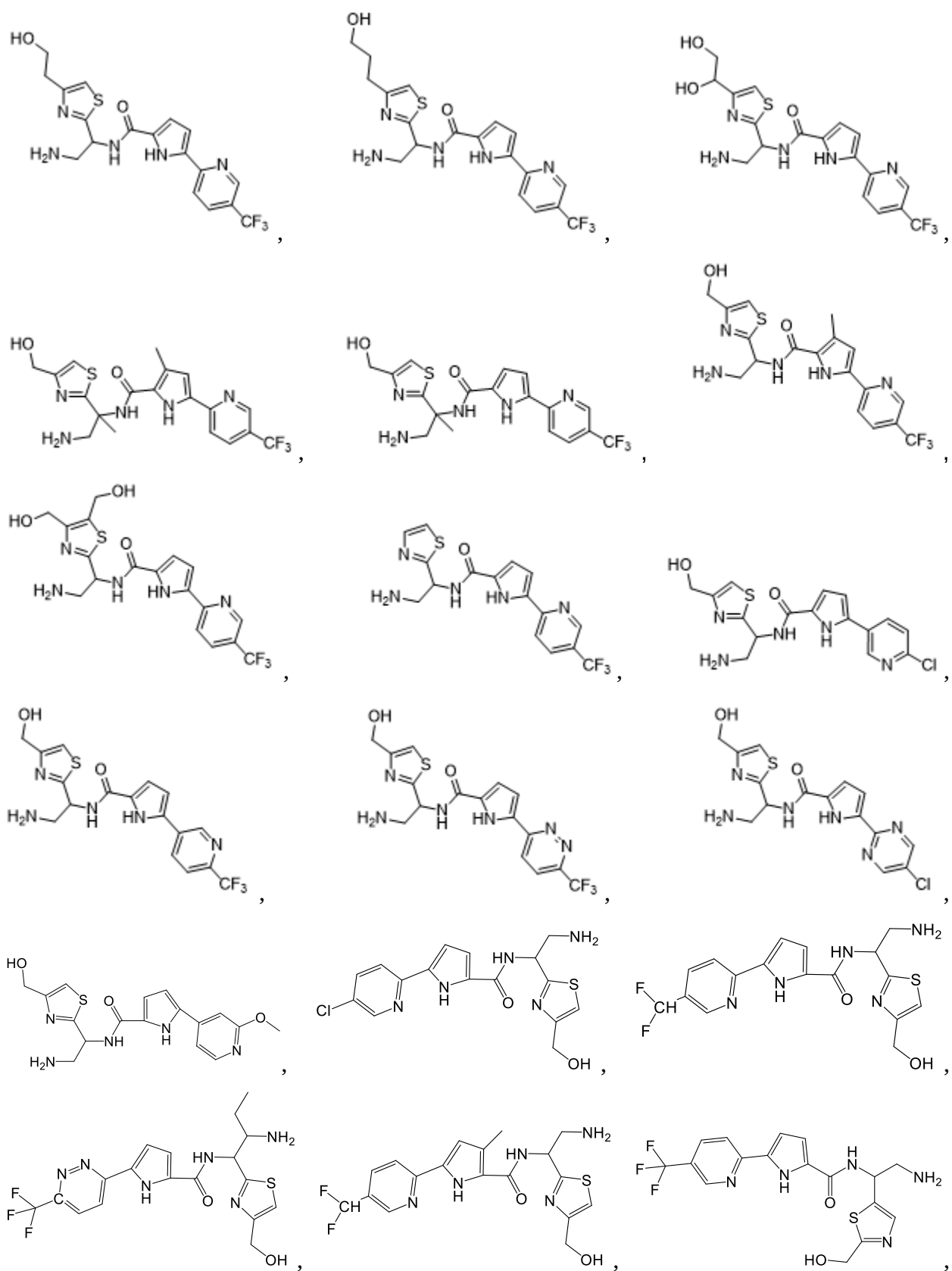
R^{17} is H or CH_3 ; and

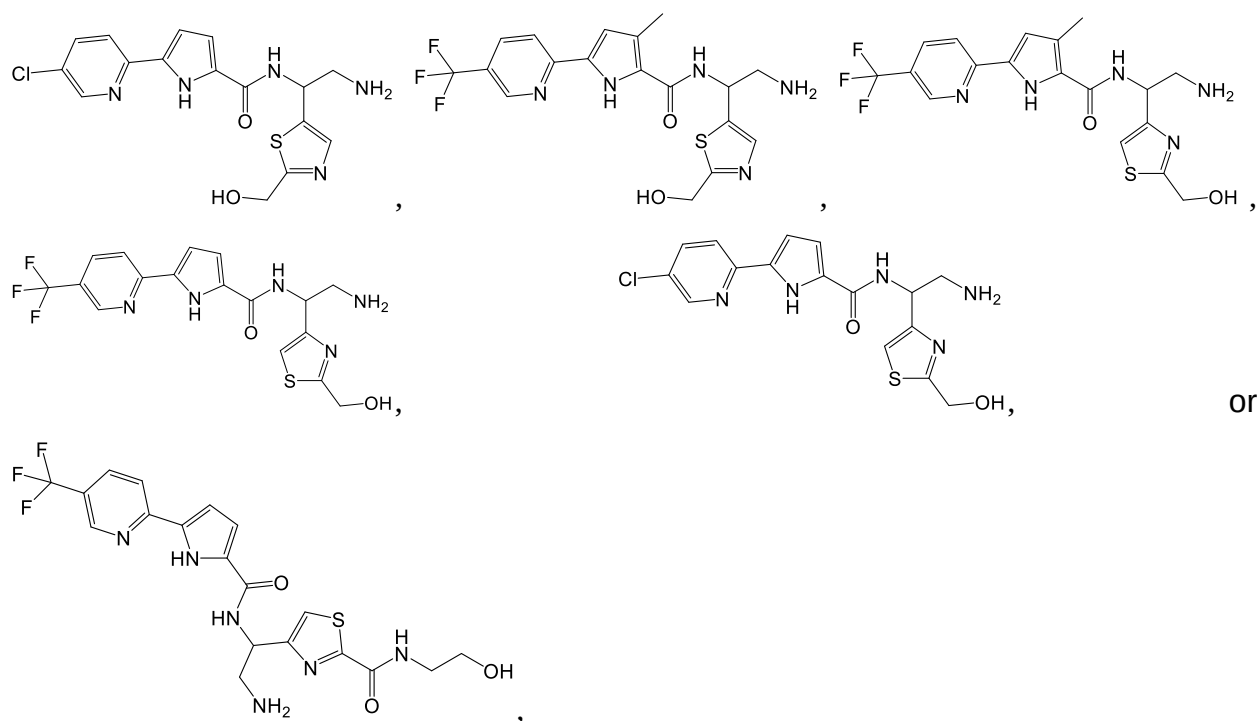
R¹⁸ is absent when W is N, and is H, CH₃, Cl, F, CH₂F, CHF₂, or CF₃ when W is

C.

3. The compound of claim 2, wherein the compound is:







or a pharmaceutically acceptable salt thereof.

4. A composition, comprising the compound of any one of claims 1–3.
5. A pharmaceutical composition, comprising the compound of any one of claims 1–3 and a pharmaceutically acceptable carrier.
6. Use of A method of inhibiting HIV in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 in the manufacture of a medicament for inhibiting HIV in a subject in need thereof, wherein a therapeutically effective amount of the compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 is to be administered to the subject.
7. Use of A method of treating an HIV infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 in the manufacture of a medicament for treating a HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound of any one of

claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 is to be administered to the subject.

8. ~~Use of A method of eradicating, reducing, or slowing an HIV infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of~~ a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 in the manufacture of a medicament for eradicating, reducing, or slowing a HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 is to be administered to the subject.

9. ~~Use of A method of reducing the viral load associated with an HIV infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of~~ a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 in the manufacture of a medicament for reducing the viral load associated with a HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 is to be administered to the subject.

10. ~~Use of A method of reducing reoccurrence of an HIV infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of~~ a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 in the manufacture of a medicament for reducing reoccurrence of a HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 is to be administered to the subject.

11. ~~Use of A method of reducing an adverse physiological impact of an HIV infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of~~ a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 in the manufacture of a medicament for reducing an adverse physiological impact of a HIV infection in a subject in need thereof,

wherein a therapeutically effect amount of the compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 is to be administered to the subject.

12. Use of A method of inducing remission of an organ injury from an HIV infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 in the manufacture of a medicament for inducing remission of an organ injury from a HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 is to be administered to the subject.

13. Use of A method of reducing the physiological impact of long-term antiviral therapy for HIV infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 in the manufacture of a medicament for reducing the physiological impact of long-term antiviral therapy for HIV infection in a subject in need thereof, wherein a therapeutically effective amount of the compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 is to be administered to the subject.

14. Use of A method of prophylactically treating an HIV infection in a subject in need thereof, wherein the subject is afflicted with a latent HIV infection, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 in the manufacture of a medicament for prophylactically treating a HIV infection in a subject in need thereof, wherein the subject is afflicted with a latent HIV infection, and wherein a therapeutically effective amount of the compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 is to be administered to the subject.

15. A kit, comprising a compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5, and instructions for use thereof.

16. A compound of any one of claims 1–3, the composition of claim 4, or the pharmaceutical composition of claim 5 for use in therapy.