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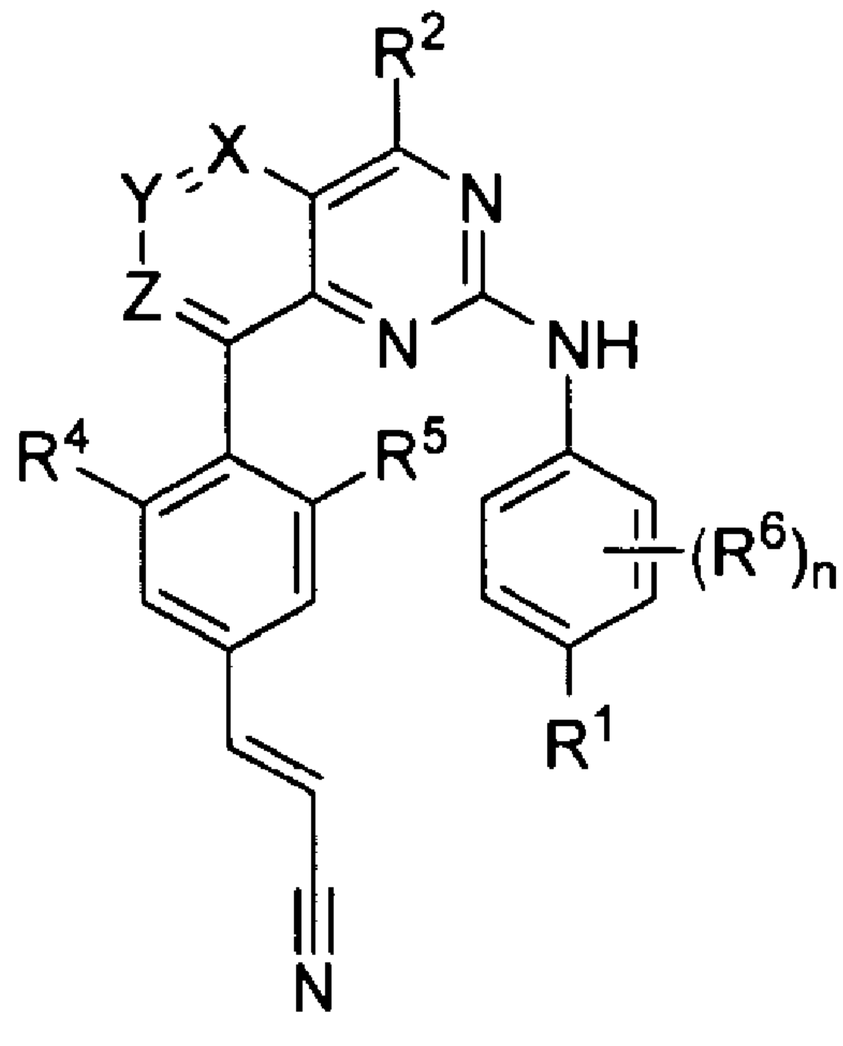
(54) Titre : COMPOSES DE PYRIMIDINE FUSIONNES POUR LE TRAITEMENT DU VIH
(54) Title: FUSED PYRIMIDINE COMPOUNDS FOR THE TREATMENT OF HIV



(I)

(57) Abrégé/Abstract:
Described herein are compounds of Formula (I) and tautomers and pharmaceutical salts thereof, compositions and formulations containing such compounds, and methods of using and making such compounds.

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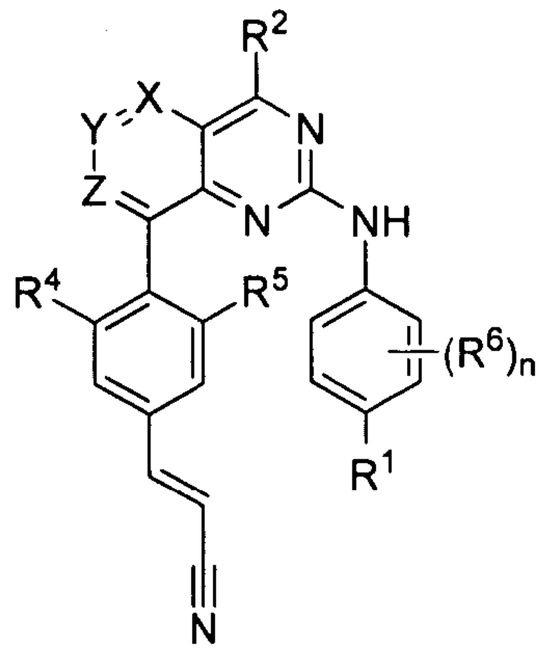
(54) Title: FUSED PYRIMIDINE COMPOUNDS FOR THE TREATMENT OF HIV

(57) Abstract: Described herein are compounds of Formula (I) and tautomers and pharmaceutical salts thereof, compositions and formulations containing such compounds, and methods of using and making such compounds.



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WO 2016/105532 A1

FUSED PYRIMIDINE COMPOUNDS FOR THE TREATMENT OF HIV

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit to U.S. Application Serial No. 62/096,820, filed December 24, 2014, the disclosure of which is herein incorporated by reference in its entirety.

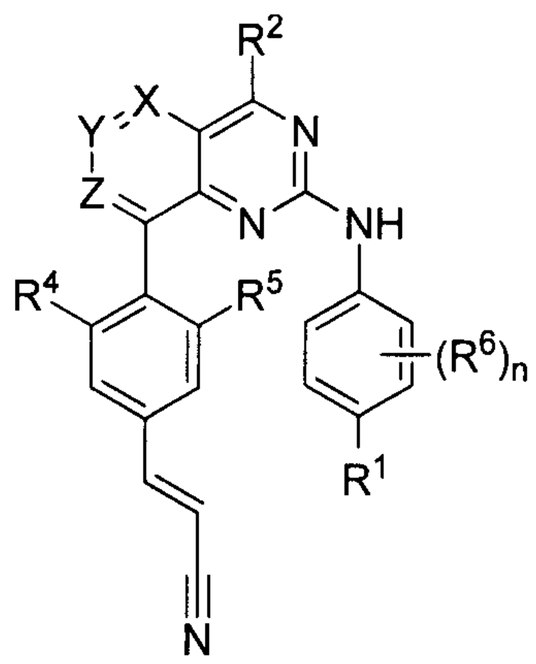
BACKGROUND

[0002] While progress has been made in treating HIV and AIDS, HIV infection remains a global health concern. As part of such treatments, non-nucleoside reverse transcriptase inhibitors (NNRTIs) have often been employed, particularly as part of highly active antiretroviral therapy (HAART) treatment regimens. Though potent, drawbacks exist for many of the known NNRTIs as their use has been associated with mutations in the HIV virus that may result in drug resistance. As such, there remains a need for further development of potent NNTRIs.

[0003] Described herein are compounds of Formula (I) and pharmaceutically acceptable salts thereof, compositions and formulations containing such compounds, or pharmaceutically acceptable salts thereof, and methods of using and making such compounds, or pharmaceutically acceptable salts thereof.

SUMMARY

[0004] In certain embodiments, the present disclosure relates to compounds of Formula (I)

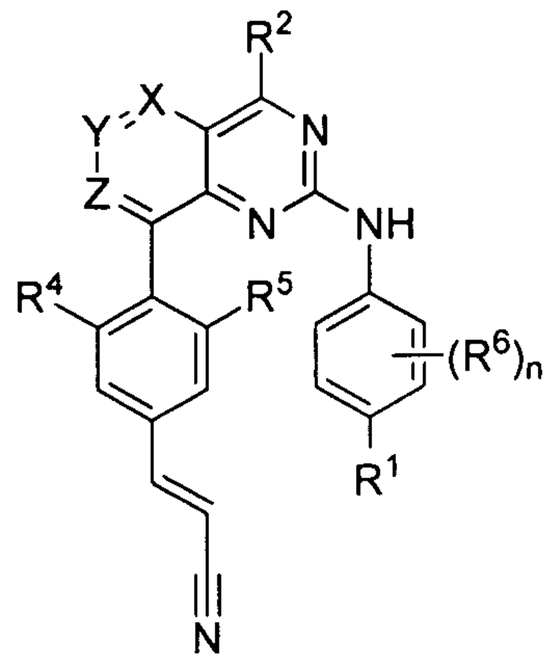


(I)

or a tautomer thereof,

What is claimed is:

1. A compound of Formula (I),



(I)

or a tautomer thereof,

wherein:

X is N, Y is CR^3, and Z is CR^3; or X is CR^3, Y is CR^3, and Z is N; or X is CR^3, Y is N, and Z is CR^3;

R^1 is –H, –CN, $–OR^a$, C_{1-6} haloalkyl, or halogen;

R^2 is –H, $–NR^bR^c$, $–OR^a$, or C_{1-10} alkyl which is optionally substituted with 1, 2, 3, 4 or 5 R^{20} groups, which may be the same or different;

each R^3 is independently -H, $-OR^a$, halogen, $–NR^aR^b$, $–C(O)OR^a$, -CN, -NHC(O)NR^aR^b, -OC(O)NR^aR^b, $-CH_2C(O)NR^aR^b$, C_{1-10} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^{20} groups which may be the same or different, or C_{1-10} heteroalkyl optionally substituted with 1, 2, 3, 4 or 5 R^{20} groups, which may be the same or different;

R^4 and R^5 are independently halogen, $–OR^a$, or C_{1-10} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^{20} groups, which may be the same or different;

each R^6 is independently halogen, $–OR^a$, or C_{1-10} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^{20} groups, which may be the same or different;

n is an integer from 0 to 4;

each R^{20} is independently C_{1-10} alkyl, C_{1-10} heteroalkyl, aryl, heteroaryl, halogen, $–OR^a$, $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^aR^b$, $–OC(O)NR^aR^b$, $–NR^aC(O)OR^b$, $–S(O)_{0-2}R^a$, $–S(O)_2F$, $–S(O)_2NR^aR^b$, $–NR^aS(O)_2R^b$, $–N_3$, –CN, or $–NO_2$,

wherein each C_{1-10} alkyl, C_{1-10} heteroalkyl, aryl, or heteroaryl is optionally substituted with 1, 2, 3, 4 or 5 halogen, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-S(O)_{0-2}R^a$, $-S(O)_2F$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-N_3$, $-CN$, or $-NO_2$ groups, which may be the same or different;

each R^a and R^b is independently $-H$, $-NH_2$, C_{1-10} alkyl, C_{1-10} heteroalkyl, aryl, or heteroaryl , each of which is optionally substituted with 1, 2, 3, 4 or 5 R^{21} groups, which may be the same or different; or R^a and R^b together with the atoms to which they are attached form a C_{1-10} heterocycloalkyl; and

R^{21} is C_{1-6} alkyl, $-CN$, aryl, heteroaryl, or halogen;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is $-H$, $-NR^aR^b$, or $-OH$.

3. The compound of claim 1 or 2, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is $-NH_2$ or $-OH$.

4. The compound of any one of claims 1 to 3, or a tautomer or pharmaceutically acceptable salt thereof, wherein each R^3 is independently $-H$, $-OR^a$, halogen, $-NR^aR^b$, $-C(O)OR^a$, or $-C(O)NR^aR^b$.

5. The compound of any one of claims 1 to 4, or a tautomer or pharmaceutically acceptable salt thereof, wherein each R^3 is independently $-H$, $C(O)OR^a$, or $-C(O)NR^aR^b$.

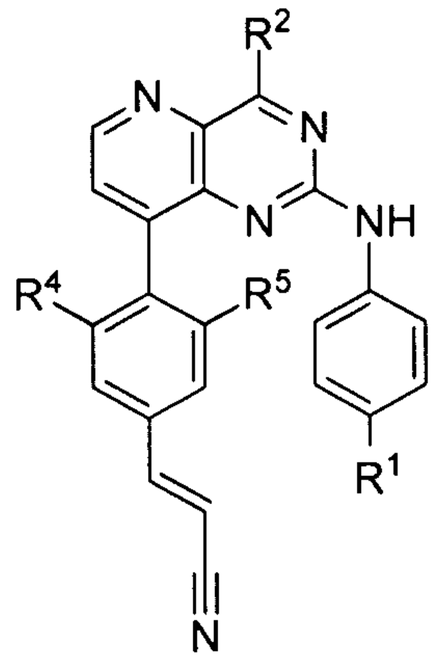
6. The compound of any one of claims 1 to 5, or a tautomer or pharmaceutically acceptable salt thereof, wherein each R^3 is $-H$.

7. The compound of any one of claims 1 to 6, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are each independently halogen, $-O-C_{1-6}$ alkyl, or C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^{20} groups, which may be the same or different.

8. The compound of any one of claims 1 to 7, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are each independently C_{1-3} alkyl.

9. The compound of any one of claims 1 to 8, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^1 is –H, –CN, –O-C_{1-6} alkyl, –C_{1-3} haloalkyl, or halogen.

10. The compound of any one of claims 1 to 9, wherein the compound of Formula I is a compound of Formula Ia:



(Ia);

or a tautomer or pharmaceutically acceptable salt thereof.

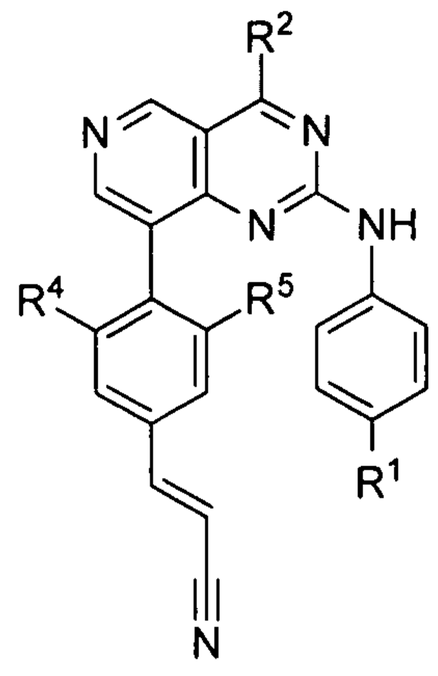
11. The compound of any one of claims 1 to 10, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are -CH_3.

12. The compound of any one of claims 1 to 11, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is -NH_2.

13. The compound of any one of claims 1 to 12, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^1 is –H, –CN, –O-C_{1-3} alkyl, -CF_3, or halogen.

14. The compound of any one of claims 1 to 13, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^1 is –CN.

15. The compound of any one of claims 1 to 9, wherein the compound of Formula I is a compound of Formula Ib:



(Ib);

or a tautomer or pharmaceutically acceptable salt thereof.

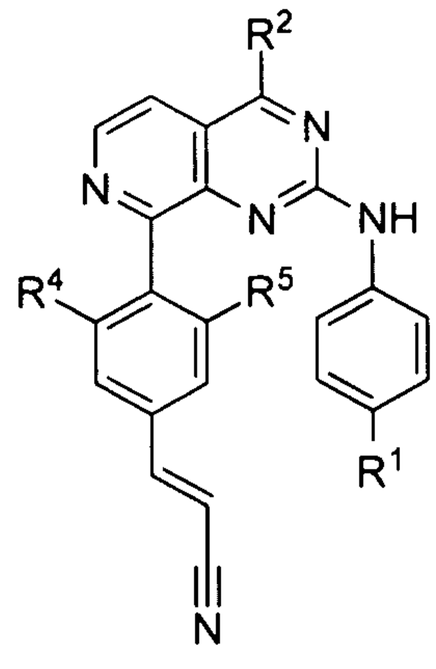
16. The compound of claim 15, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are $-CH_3$.

17. The compound of claim 15 or 16, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is $-NH_2$.

18. The compound of any one of claims 15 to 17, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^1 is –H, –CN, –O-C_{1-3} alkyl, $-CF_3$, or halogen.

19. The compound of any one of claims 15 to 18, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^1 is –CN.

20. The compound of any one of claims 1 to 9, wherein the compound of Formula I is a compound of Formula Ic:



(Ic);

or a tautomer or pharmaceutically acceptable salt thereof.

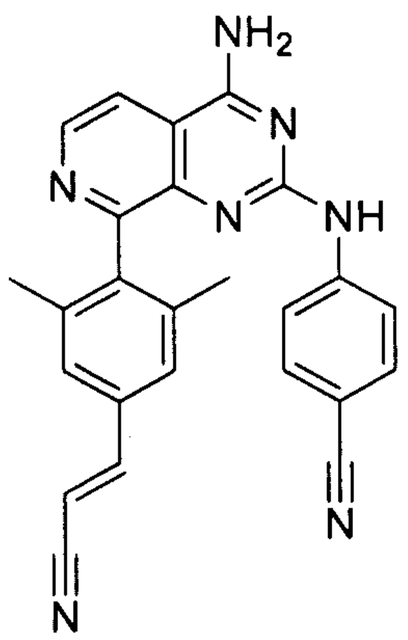
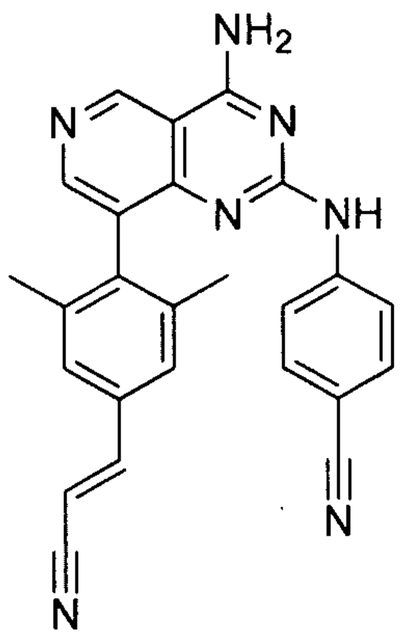
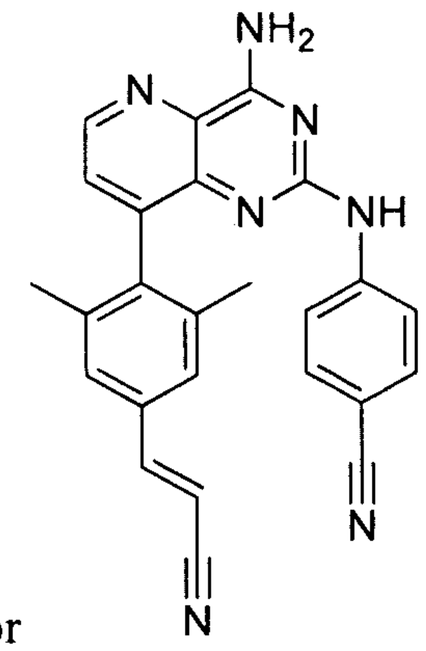
21. The compound of claim 20, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are $-CH_3$.

22. The compound of claim 20 or 21, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^2 is $-NH_2$.

23. The compound of any one of claims 20 to 22, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^1 is –H, –CN, –O-C_{1-3} alkyl, $-CF_3$, or halogen.

24. The compound of any one of claims 20 to 23, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^1 is –CN.

25. The compound of any one of the preceding claims, wherein the compound is selected from:


; 
; or 
; or a tautomer or pharmaceutically acceptable salt thereof.

26. A pharmaceutical composition comprising a compound of any of claims 1-25, or a tautomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

27. An article of manufacture comprising a unit dosage of a compound of any of claims 1-25 or a tautomer or pharmaceutically acceptable salt thereof.

28. A method of inhibiting reverse transcriptase in a subject in need thereof, comprising administering a compound of any of claims 1-25, or a tautomer or pharmaceutically acceptable salt thereof, to the subject.

29. A method for treating or preventing an HIV infection in a subject comprising administering to the subject a compound of any of claims 1-25, or a tautomer or pharmaceutically acceptable salt thereof.

30. A method for treating or preventing an HIV infection in a subject comprising administering to the subject in need thereof a compound of any of claims 1-25, or a tautomer or pharmaceutically acceptable salt thereof, in combination with a therapeutically effective

amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof.

31. A compound of any of claims 1-25, or a tautomer or pharmaceutically acceptable salt thereof for use in medical therapy.

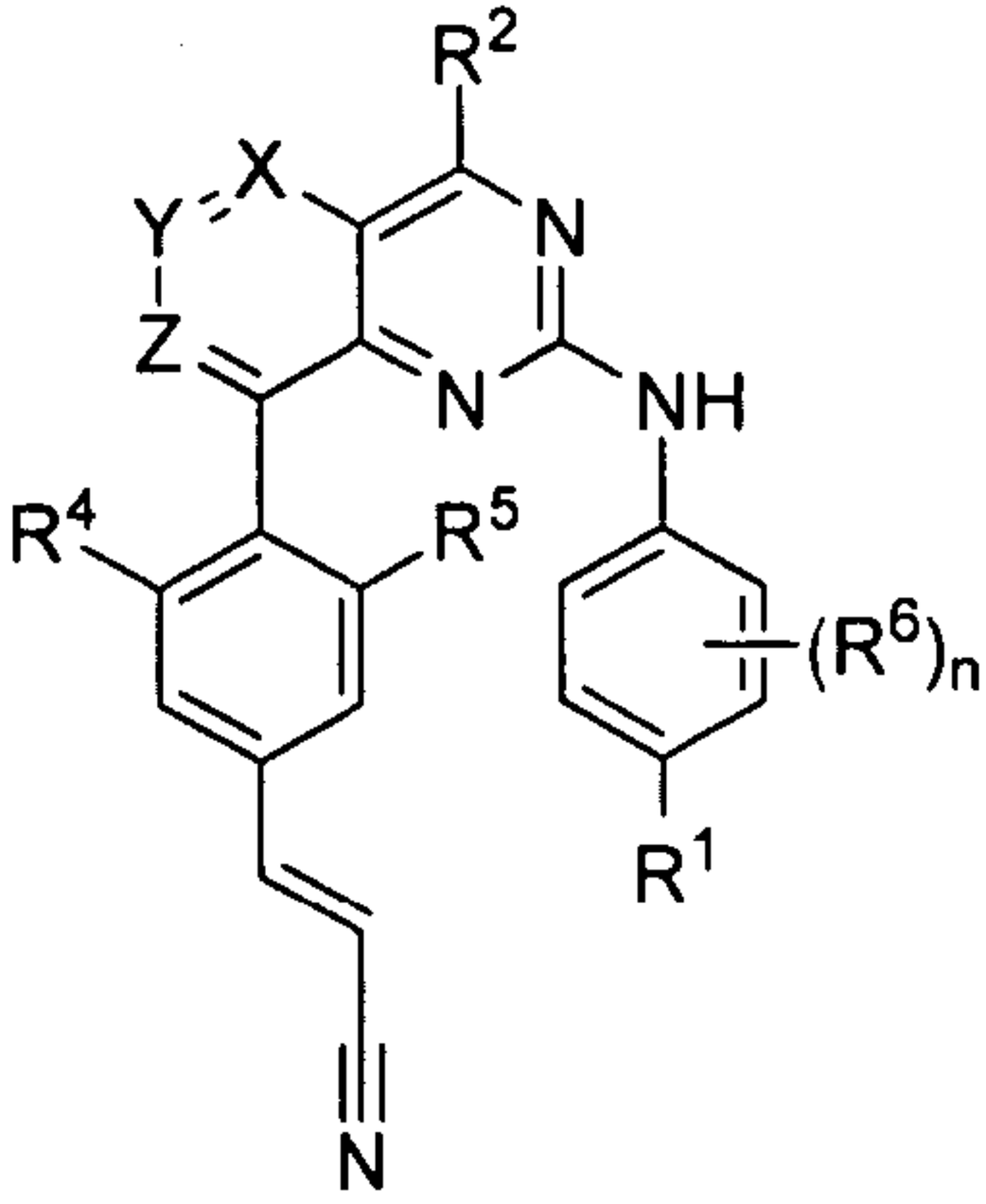
32. A compound of any of claims 1-25, or a tautomer or a pharmaceutically acceptable salt thereof, for use in treating or preventing an HIV virus infection in a subject.

33. The use of a compound of any of claims 1-25 or a tautomer or pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating or preventing an HIV virus infection in a subject.

34. The use of a compound of any of claims 1-25, or a tautomer or a pharmaceutically acceptable salt thereof, for treating or preventing an HIV virus infection in a subject.

35. The use of a compound of any of claims 1-25, or a tautomer or a pharmaceutically acceptable salt thereof, for inhibiting HIV reverse transcriptase in a subject.

36. The use of a compound of any of claims 1-25, or a tautomer or a pharmaceutically acceptable salt thereof, for inhibiting HIV reverse transcriptase *in vitro*.



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