A class of compounds being investigated for HSV treatment are the helicase-primase inhibitors. Helicase-primase inhibitors are antiviral agents with a novel mechanism of action against HSV1 and 2. They inhibit the viral heterotrimeric complex consisting of helicase, primase, and cofactor subunits that have functions essential for viral DNA replication. They are not nucleoside analogues and do not require phosphorylation by TK to inhibit HSV replication and they are therefore potentially active against TK-deficient HSV, which as described above, is a major mechanism of resistance to nucleoside analogues, such as acyclovir.

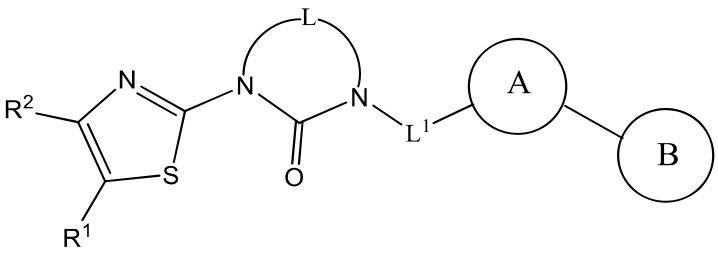
Two examples of helicase-primase inhibitors are BILS-179 BS and amenamevir (Katsumata et al. (2018) Biochem Pharm 158 p201-206). BILS-179 BS has been dosed orally but was suspended from early clinical trials due to adverse events.

One example of a helicase-primase inhibitor is pritelivir, a thiazolylamide derivative with the chemical name N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl] acetamide. This compound has been disclosed in WO200053591. WO2001047904 discloses thiazolyl amide derivatives and their use as antiviral medicaments. WO2000053591 discloses thiazolyl derivatives and their utilization as antiviral agents. WO2017174640 discloses aminothiazole derivatives useful as antiviral agents. WO2019068817 discloses enantiomers of substituted thiazoles as antiviral compounds.

There is still a need for additional antiviral compounds for the treatment and prophylaxis of HSV infections that have an improved profile with respect to safety, potency, selectivity and/or bioavailability.

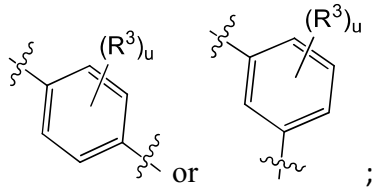
SUMMARY

In an aspect, there is provided a compound of Formula I

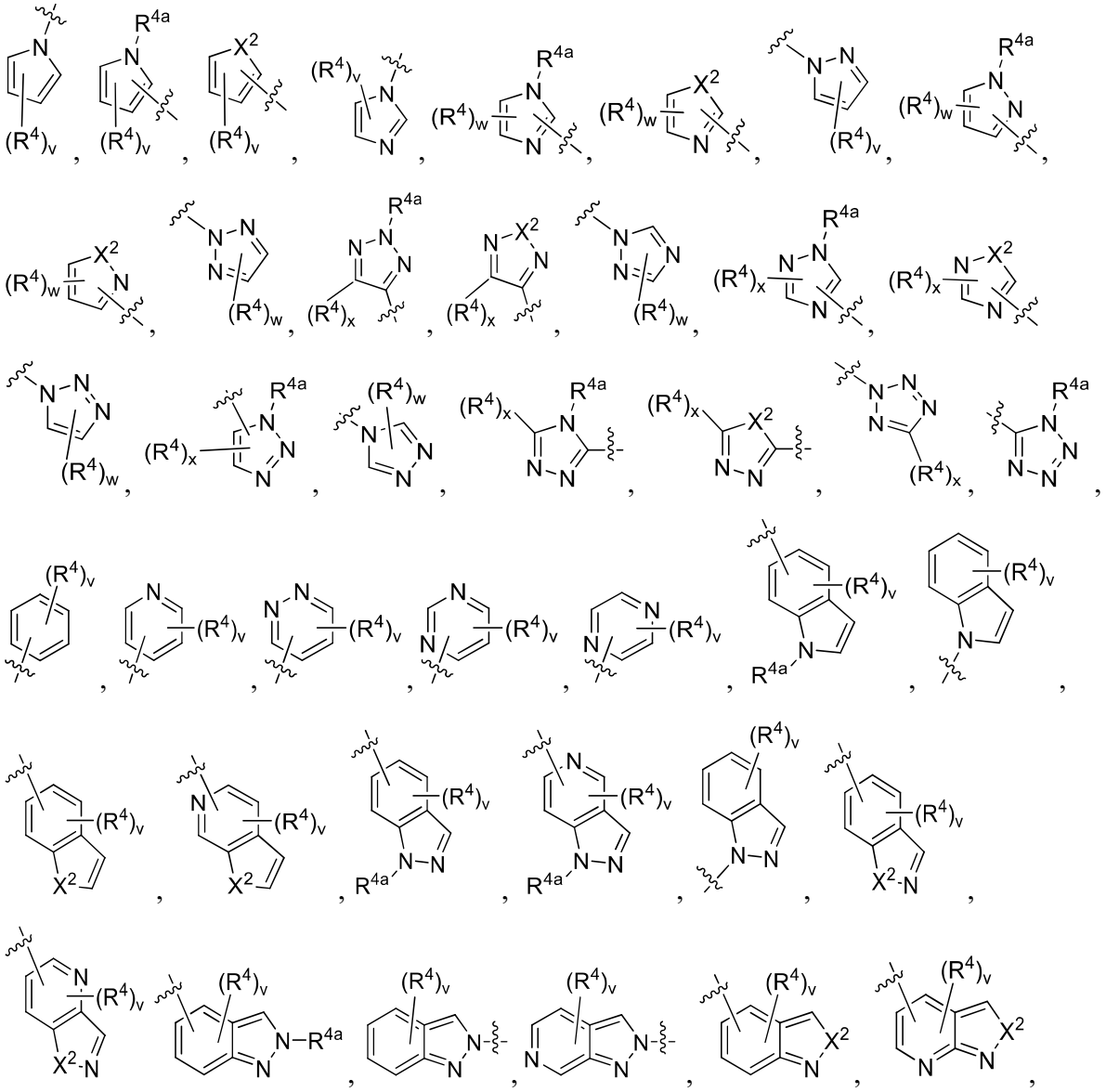


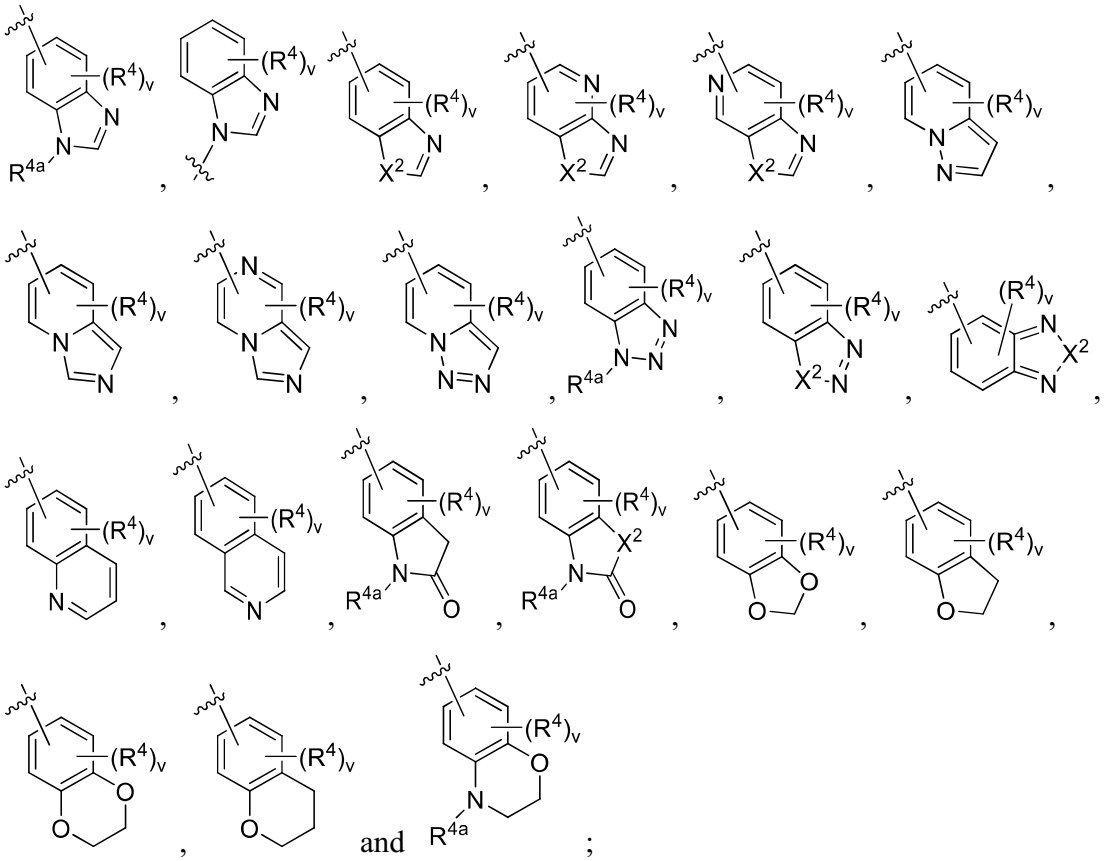
Formula II

or a pharmaceutically acceptable salt thereof, wherein:

A is  or ;

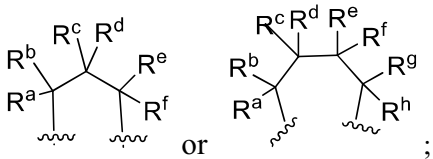
B is selected from the group consisting of:

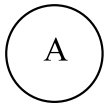
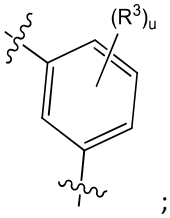




X^2 and X^4 are independently selected from the group consisting of O and S;

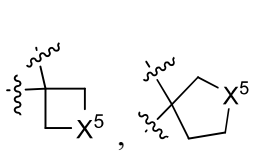
X^5 is CH_2, CF_2, O, S or NR^y,

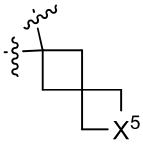
L is  ;

L^1 is a bond; or L^1 is -CH_2- when  is  ;

R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are independently selected from the group consisting of hydrogen, halo, CN, OH, NR^nR^m, -C(O)OH, -C(O)OC_{1-4}alkyl , -C(O)NR^nR^m, -$SO_2NR^nR^m$, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, and C_{1-4}alkoxy; or two R-

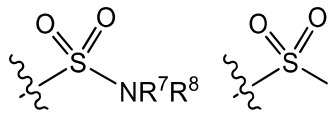
groups together with the carbon atom to which they are attached form a C_{3-6}monocycloalkyl,

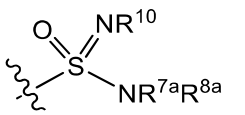
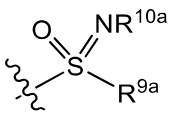
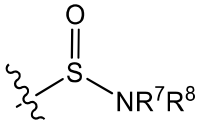
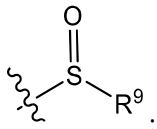



group;

R^n and R^m are independently selected for each occurrence from the group consisting or hydrogen and C_{1-4}alkyl;

R^y is hydrogen, C_{1-4}alkyl or acetyl;

R^1 is 

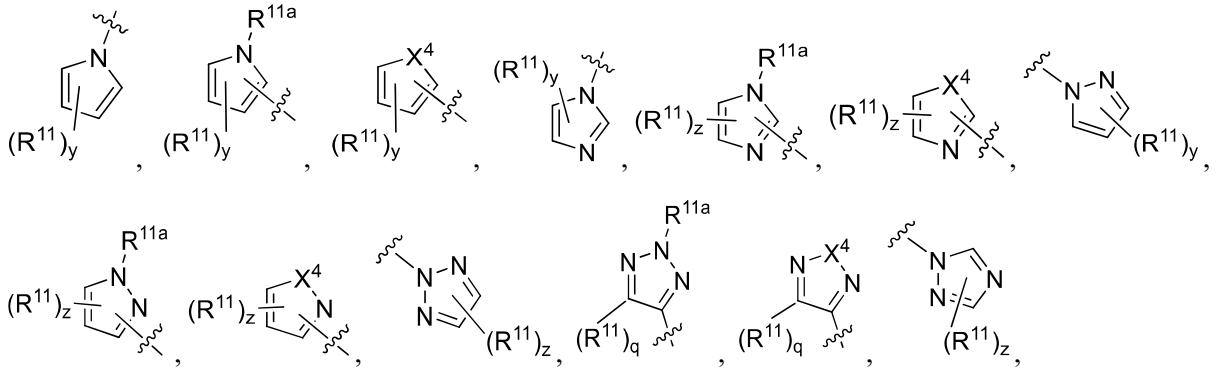



or

;

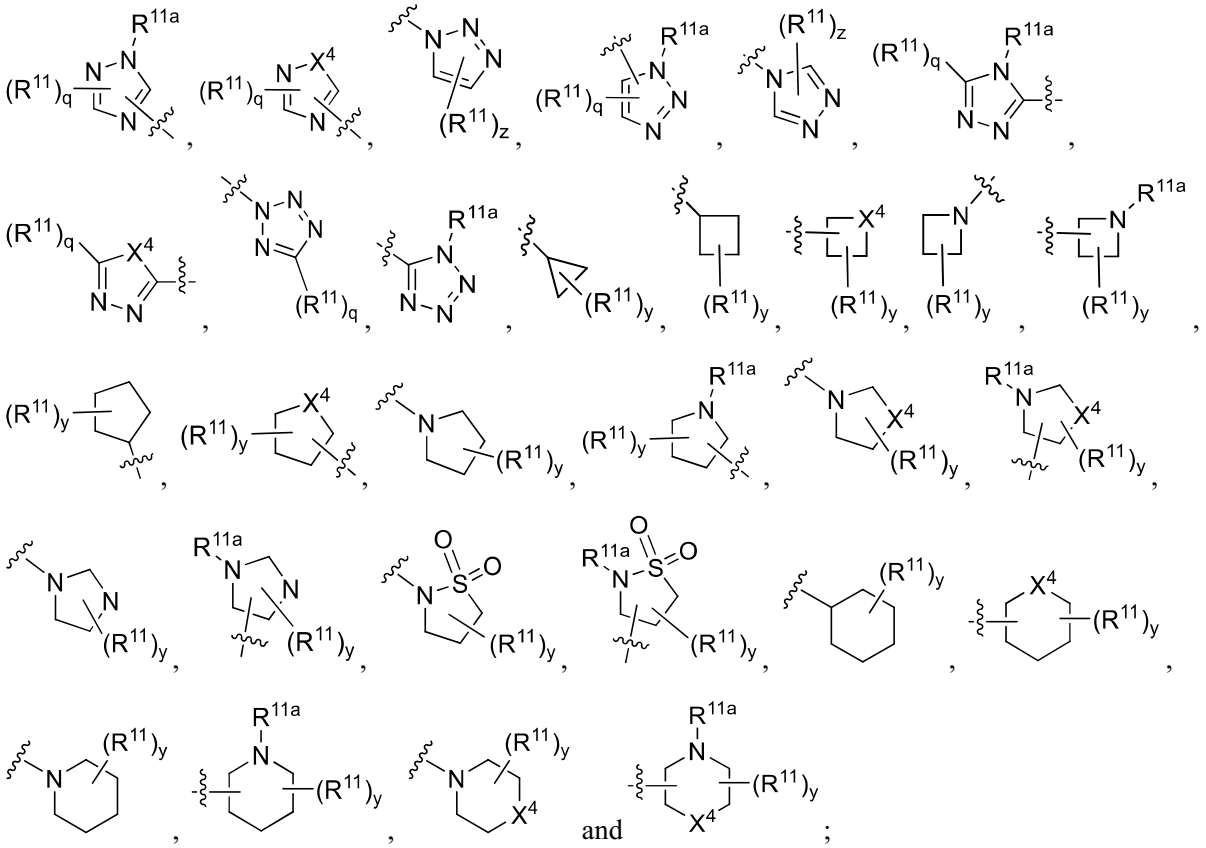
R^2 is hydrogen, halo, CN, OH, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl or haloC_{1-4}alkoxy;

R^4 is independently selected for each occurrence from the group consisting of halo, CN, OH, NR^nR^m, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl optionally substituted with hydroxyC_{1-3}alkyl, cyclopropyl optionally substituted with halo or cyano, and R^{4b}, provided that only one R^4 group can be R^{4b};

R^{4a} is hydrogen, C_{1-4}alkyl, halo C_{1-4}alkyl and hydroxyC_{1-4}alkyl;

R^{4b} is selected from the group consisting of:





R^7 and R^8 are independently selected from the group consisting of hydrogen, OH, acetyl, C_{1-10}alkyl, haloC_{1-10}alkyl, hydroxyC_{1-10}alkyl, C_{1-4}alkoxyC_{1-10}alkyl, C_{3-6}monocycloalkyl, phenyl, pyridyl or indolyl; or R^7 and R^8 together with the N-atom to which they are attached form an arizidinyl, azetidinyl, pyrrolidinly, piperidinyl, morpholinyl or thiomorpholinyl group, wherein the arizidinyl, azetidinyl, pyrrolidinly or piperidinyl group is optionally substituted with halo, CN or OH;

R^{7a} and R^{8a} are independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}monocycloalkyl, or R^7 and R^8 together with the N atom to which they are attached form an arizidinyl, azetidinyl, pyrrolidinyl, or piperidinyl morpholinyl or thiomorpholinyl group;

R^9 and R^{9a} are independently selected from the group consisting or C_{1-4}alkyl and haloC_{1-4}alkyl;

R^{10} and R^{10a} are independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{11} is independently selected from the group consisting of halo, CN, OH, NR^nR^m, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{3-6}monocycloalkyl;

R^{11a} is hydrogen, C_{1-4}alkyl, halo C_{1-4}alkyl and hydroxyC_{1-4}alkyl;

q and x are independently selected from the group consisting of 0 and 1;

w and z are independently selected from the group consisting of 0, 1 and 2; and

v and y are independently selected from the group consisting of 0, 1, 2 and 3

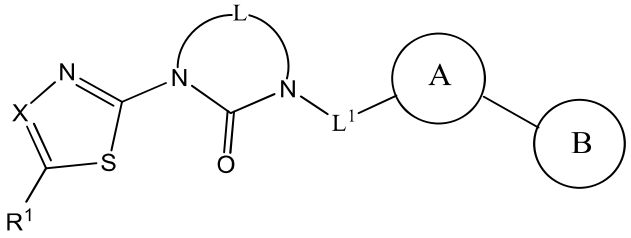
In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of an HSV infection.

In another aspect, there is provided the use of a pharmaceutical composition as defined above in the manufacture of a medicament for the treatment or prophylaxis of an HSV infection.

In another aspect, there is provided the compound as defined above for the use as a medicament.

In one example, the present disclosure provides a compound of Formula I



Formula I

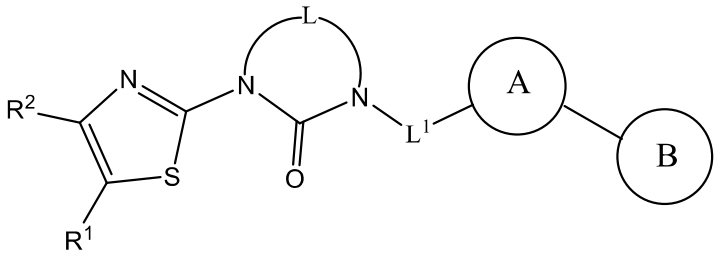
or a pharmaceutically acceptable salt thereof, wherein the variables are as described herein.

In another example, the disclosure provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another example, the disclosure provides a method of treating an HSV infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of compound of Formula I, or a pharmaceutically acceptable salt thereof.

In another example, the disclosure provides a method of treating an HSV infection in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another example, the present disclosure provides a compound of Formula II



Formula II

or a pharmaceutically acceptable salt thereof, wherein the variables are as described herein.

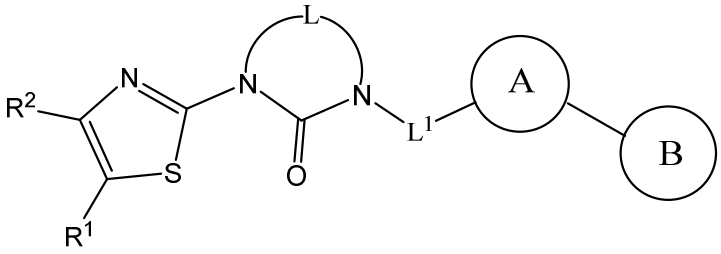
In another example, the disclosure provides pharmaceutical compositions comprising a compound of Formula II, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another example, the disclosure provides a method of treating an HSV infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of compound of Formula II, or a pharmaceutically acceptable salt thereof.

In another example, the disclosure provides a method of treating an HSV infection in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula II, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

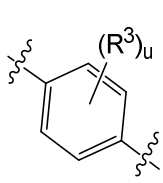
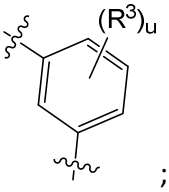
CLAIMS:

1. A compound of Formula I

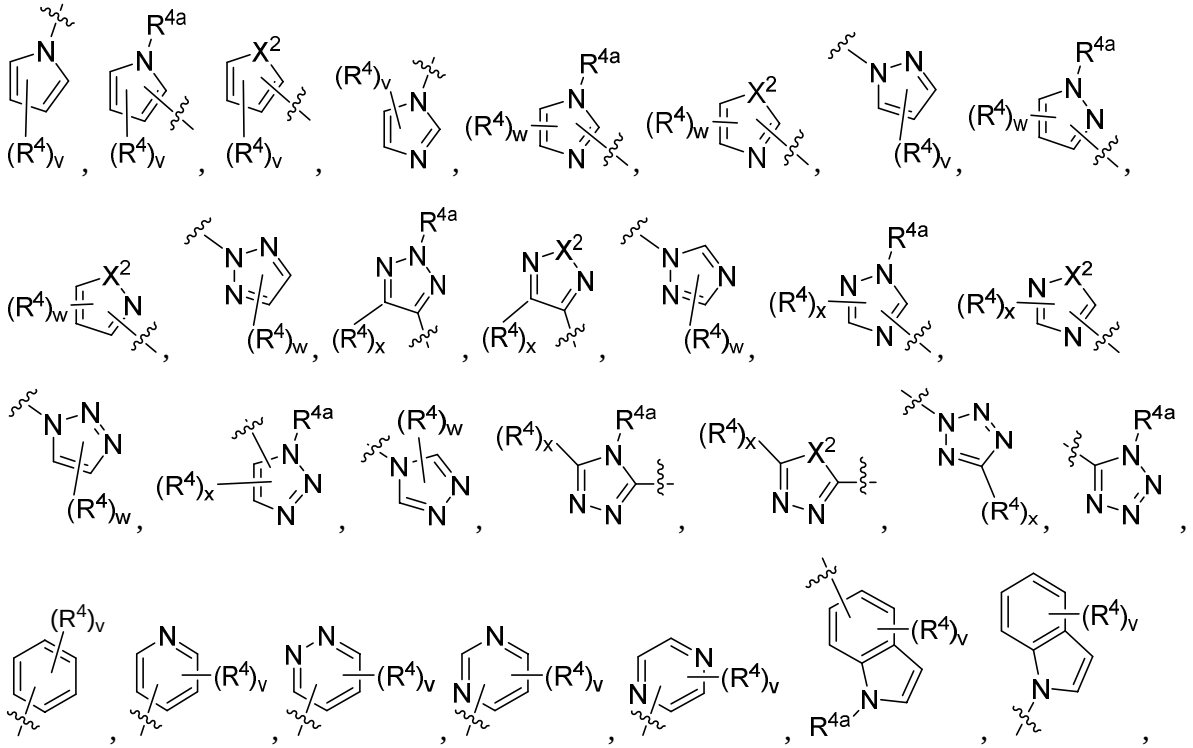


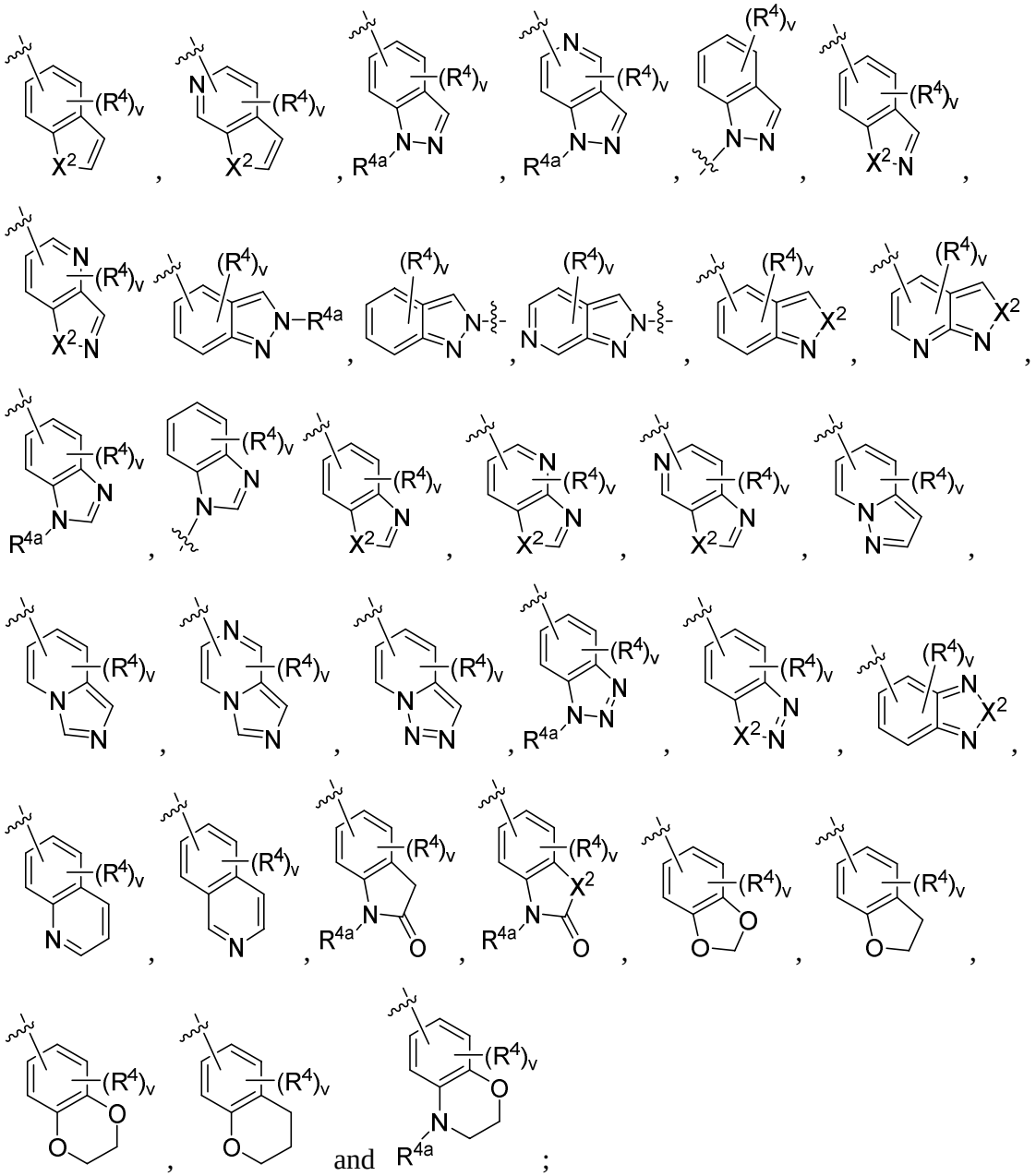
Formula II

or a pharmaceutically acceptable salt thereof, wherein:

A is  or  ;

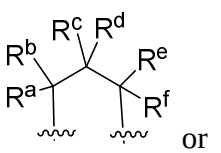
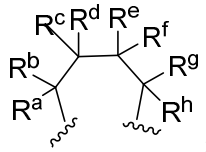
B is selected from the group consisting of:

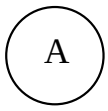
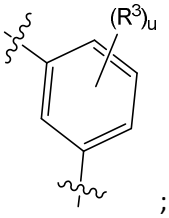




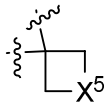
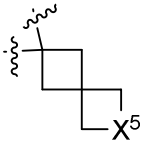
X^2 and X^4 are independently selected from the group consisting of O and S;

X^5 is CH_2, CF_2, O, S or NR^y,

L is  or ;

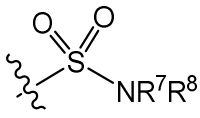
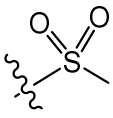
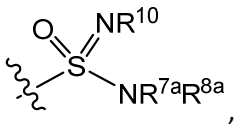
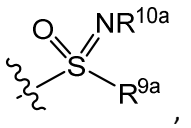
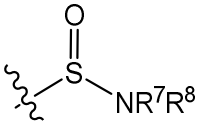
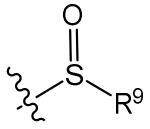
L^1 is a bond; or L^1 is $-CH_2-$ when  is ;

R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are independently selected from the group consisting of hydrogen, halo, CN, OH, NR^nR^m, -C(O)OH, $-C(O)OC_{1-4}$alkyl , $-C(O)NR^nR^m$, $-SO_2NR^nR^m$, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, and C_{1-4}alkoxy; or two R-groups together with the carbon atom to which they are attached form a C_{3-6}monocycloalkyl,

 ,  or  group;

R^n and R^m are independently selected for each occurrence from the group consisting or hydrogen and C_{1-4}alkyl;

R^y is hydrogen, C_{1-4}alkyl or acetyl;

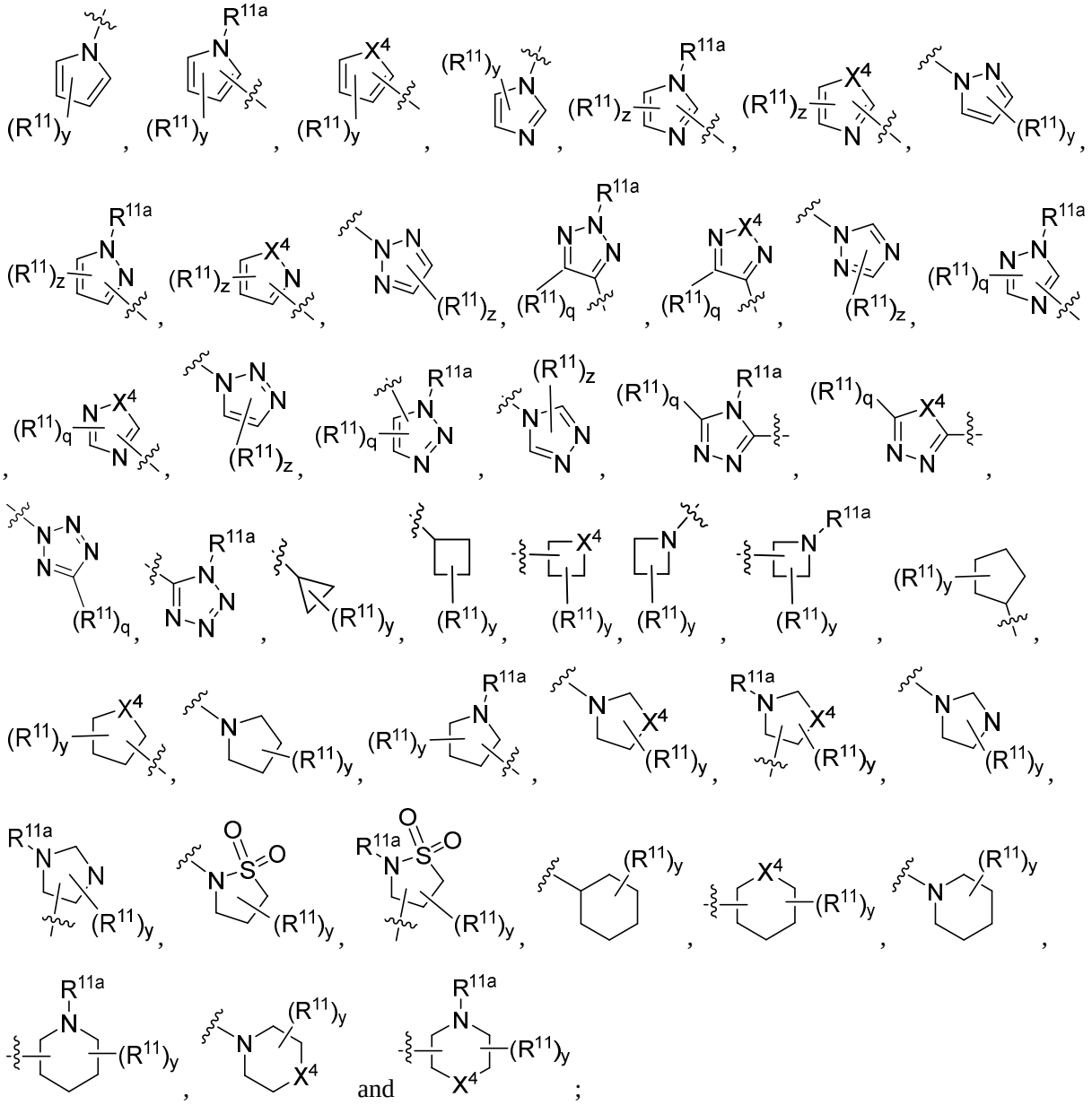
R^1 is  ,  ,  ,  ,  or ;

R^2 is hydrogen, halo, CN, OH, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl or haloC_{1-4}alkoxy;

R^4 is independently selected for each occurrence from the group consisting of halo, CN, OH, NR^nR^m, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl optionally substituted with hydroxyC_{1-3}alkyl, cyclopropyl optionally substituted with halo or cyano, and R^{4b}, provided that only one R^4 group can be R^{4b};

R^{4a} is hydrogen, C_{1-4}alkyl, halo C_{1-4}alkyl and hydroxyC_{1-4}alkyl;

R^{4b} is selected from the group consisting of:



and ;

R^7 and R^8 are independently selected from the group consisting of hydrogen, OH, acetyl, C_{1-10}alkyl, haloC_{1-10}alkyl, hydroxyC_{1-10}alkyl, C_{1-4}alkoxyC_{1-10}alkyl, C_{3-6}monocycloalkyl, phenyl, pyridyl or indolyl; or R^7 and R^8 together with the N-atom to which they are attached form an arizidinyl, azetidinyl, pyrrolidinly, piperidinyl, morpholinyl or thiomorpholinyl group, wherein the arizidinyl, azetidinyl, pyrrolidinly or piperidinyl group is optionally substituted with halo, CN or OH;

R^{7a} and R^{8a} are independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}monocycloalkyl, or R^7 and R^8 together with the N atom to which they are attached form an arizidinyl, azetidinyl, pyrrolidinyl, or piperidinyl morpholinyl or thiomorpholinyl group;

R^9 and R^{9a} are independently selected from the group consisting or C_{1-4}alkyl and haloC_{1-4}alkyl;

R^{10} and R^{10a} are independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{11} is independently selected from the group consisting of halo, CN, OH, NR^nR^m, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{3-6}monocycloalkyl;

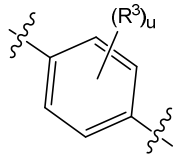
R^{11a} is hydrogen, C_{1-4}alkyl, halo C_{1-4}alkyl and hydroxyC_{1-4}alkyl;

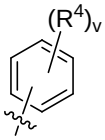
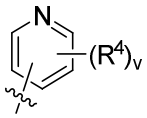
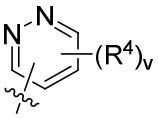
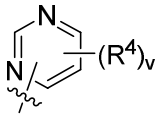
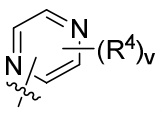
q and x are independently selected from the group consisting of 0 and 1;

w and z are independently selected from the group consisting of 0, 1 and 2; and

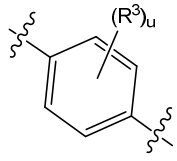
v and y are independently selected from the group consisting of 0, 1, 2 and 3.

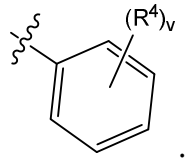
2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein:

A is ; and

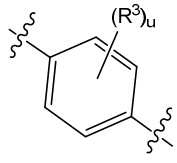
B is selected from the group consisting of: , , ,  and .

3. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein:

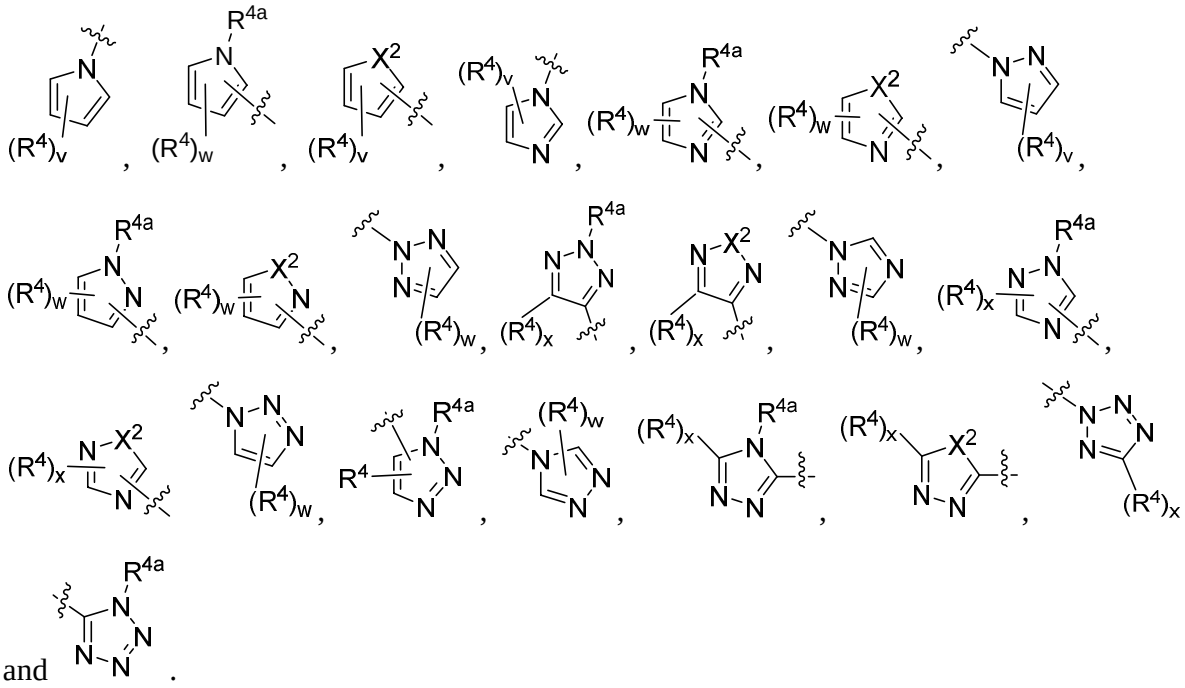
A is ; and

B is .

4. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein:

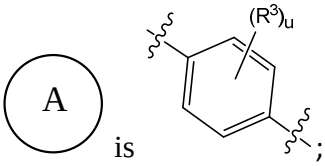
A is ; and

B is selected from the group consisting of:

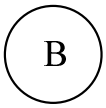


and .

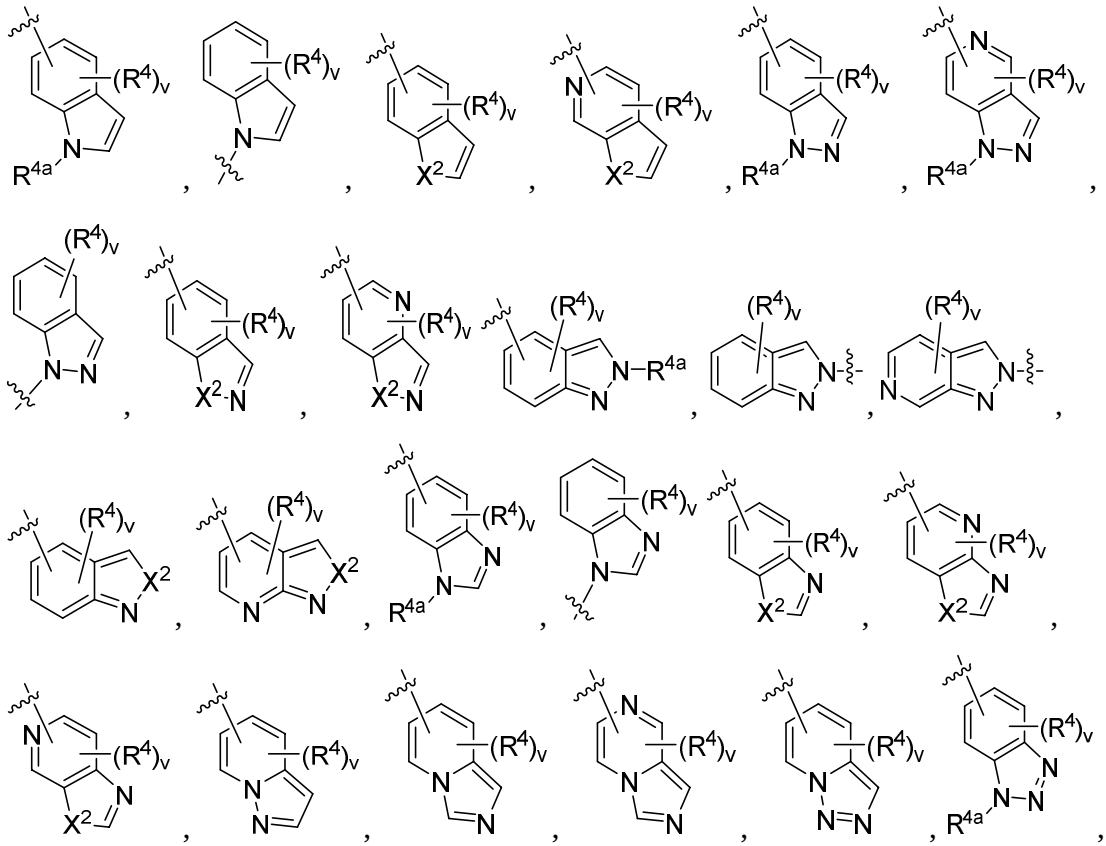
5. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein:

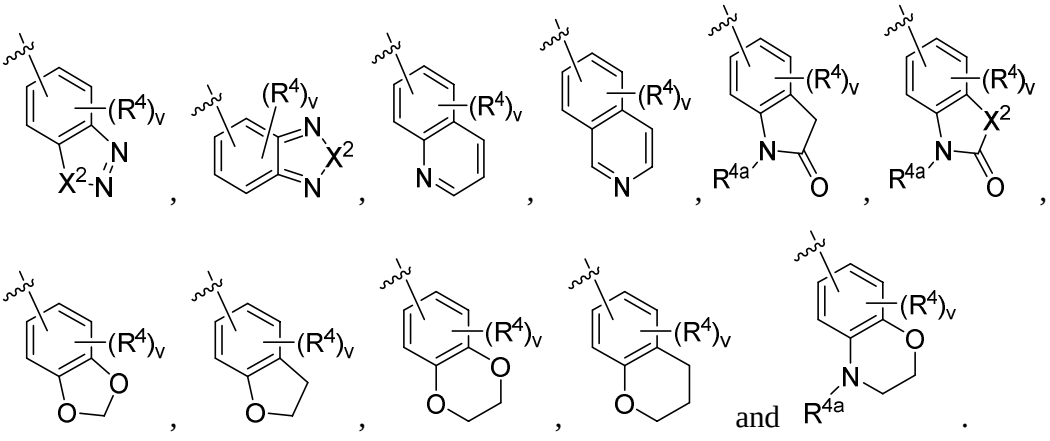


is ; and



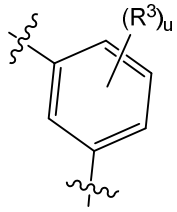
is selected from the group consisting of:

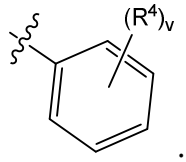


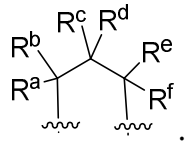


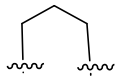
and .

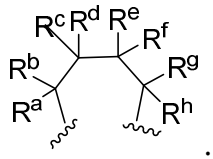
6. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein:

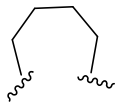
A is ; and

B is .

7. The compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein: L is .

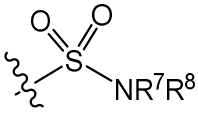
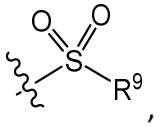
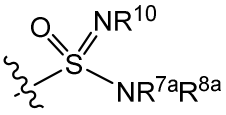
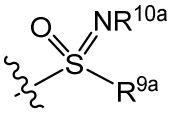
8. The compound of claims 7, or a pharmaceutically acceptable salt thereof, wherein: L is .

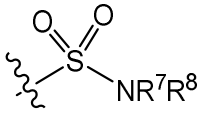
9. The compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein: L is .

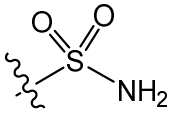
10. The compound of claims 9, or a pharmaceutically acceptable salt thereof, wherein: L is .

11. The compound according to any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein: R^2 is H, Cl, F, CH_3 or CF_3.

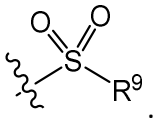
12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein: R^2 is CH_3.

13. The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein: R^1 is , ,  or .

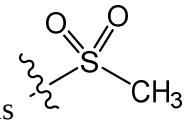
14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein: R^1 is .

15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein: R^1 is R^1 is .

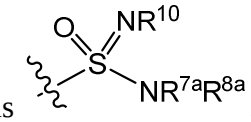
16. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is .

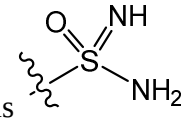
17. The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is .

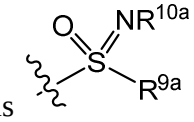
18. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is .

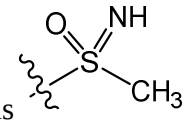
19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is .

20. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is .

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is .

22. The compound according to any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^3 is halo for each occurrence and u is 0, 1, 2 or 3.

23. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein: u is 0.

24. The compound according to any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein: R^4 is independently selected for each occurrence from the group consisting of halo, CN, methyl, CHF_2, CF_3, acetylenyl, and cyclopropyl.

25. The compound according to any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein: R^4 is independently selected from halo for all occurrences.

26. A pharmaceutical composition comprising a compound according to any one of claims 1-25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

27. Use of a compound according to any one of claims 1-25, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of an HSV infection.

28. Use of a pharmaceutical composition of claim 26 in the manufacture of a medicament for the treatment or prophylaxis of an HSV infection.

29. The use of claim 27 or 28, wherein infection is an HSV-1 infection.

30. The use of claim 27 or 28, wherein infection is an HSV-2 infection.

31. The compound according to any one of claims 1-25 for the use as a medicament.