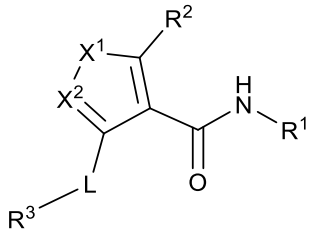
α can result in poor tolerability, and many patients are unable to complete therapy. Moreover, only a small percentage of patients are considered appropriate for interferon therapy, as only a small subset of patients is likely to have a sustained clinical response to a course of interferon therapy. As a result, interferon-based therapies are used in only a small percentage of all diagnosed patients who elect treatment.

Thus, current HBV treatments can range from palliative to watchful waiting. Nucleotide analogs suppress virus production, treating the symptom, but leave the infection intact. Interferon α has severe side effects and less tolerability among patients and is successful as a finite treatment strategy in only a small minority of patients. There is a clear on-going need for more effective treatments for HBV infections.

SUMMARY

The present disclosure provides, in part, 5-membered heteroaryl carboxamide compounds and pharmaceutical compositions thereof, useful for disruption of HBV core protein assembly, and methods of treating HBV infections.

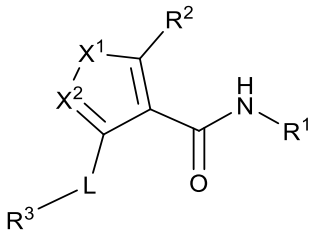
In one example, the disclosure provides a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, where the variables are described in the detailed description.

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



Formula I

, or a pharmaceutically acceptable salt thereof, wherein:

X^1 is NR^{x1};

X^2 is N;

X^3 is O, NR^7, CR^4R^8, C(O), $S(O)_t$, $C=CR^4R^0$ or $C=NR^4$;

X^4 and X^6 are independently O or S;

X^5 is O, S or NR^0;

L is a bond or C_{1-6}alkylene;

L^1 is a bond, C_{1-6}alkylene, O, NR^c, C(O), $C(O)NR^c$, $S(O)_t$ or $S(O)_tNR^c$;

R^{x1} independently is selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^a, R^b and R^c is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^d is hydrogen, OH, C_{1-6}alkyl or C_{1-6} alkoxy;

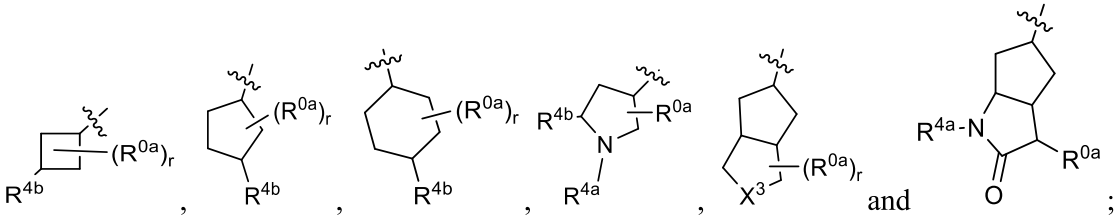
R^0, R^6, R^8 and R^{11} is independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, $R^dN=$, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} monocycloalkyl, haloC_{1-6} alkyl, hydroxyC_{1-6} alkyl-, $R^aR^bNC_{1-6}$ alkyl-, HOC(O)C_{1-6} alkyl-, $R^aR^bNC_{1-6}$ alkylNR^c-, C_{1-6} alkylNR^aC_{1-6} alkylNR^c-, C_{1-6} alkoxy, haloC_{1-6} alkoxy, hydroxyC_{1-6} alkoxy-, $R^aR^bNC_{1-6}$ alkoxy-, C_{1-6}alkoxyC_{1-6} alkyl-, haloC_{1-6} alkoxyC_{1-6} alkyl-, $R^aR^bNC(O)$-, C_{1-6} alkyl$C(O)$-, C_{1-6} alkoxy$C(O)$-, C_{1-6} alkyl$C(O)O$-, C_{1-6} alkyl$S(O)_q$-, C_{1-6} alkyl$S(O)_tNR^c$-, C_{1-6} alkyl$S(O)_tC_{1-6}$ alkyl-, C_{1-6} alkyl$S(O)_tNR^aC_{1-6}$ alkyl-, C_{3-6} cycloalkyl$S(O)_tC_{1-6}$ alkyl-, C_{1-6} alkyl$C(O)C_{1-6}$ alkyl-, and C_{1-6} alkyl$C(O)OC_{1-6}$ alkyl-;

R^{0a} is independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, R^aR^bN-, C_{1-6}alkyl and haloC_{1-6}alkyl;

R^1 is a phenyl, naphthyl, C_{3-6} monocycloalkyl, C_{3-6} monoheterocycloalkyl, or 5-6 membered monocyclic heteroaryl, wherein: the phenyl, C_{3-6} monocycloalkyl, C_{3-6} monoheterocycloalkyl, or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

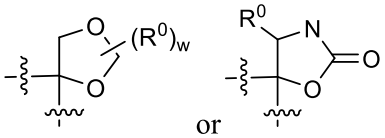
R^2 is R^aR^bN;

R^3 is selected from the group consisting of:


and ;

R^4 is R^5, R^6 or R^5-L^1-;

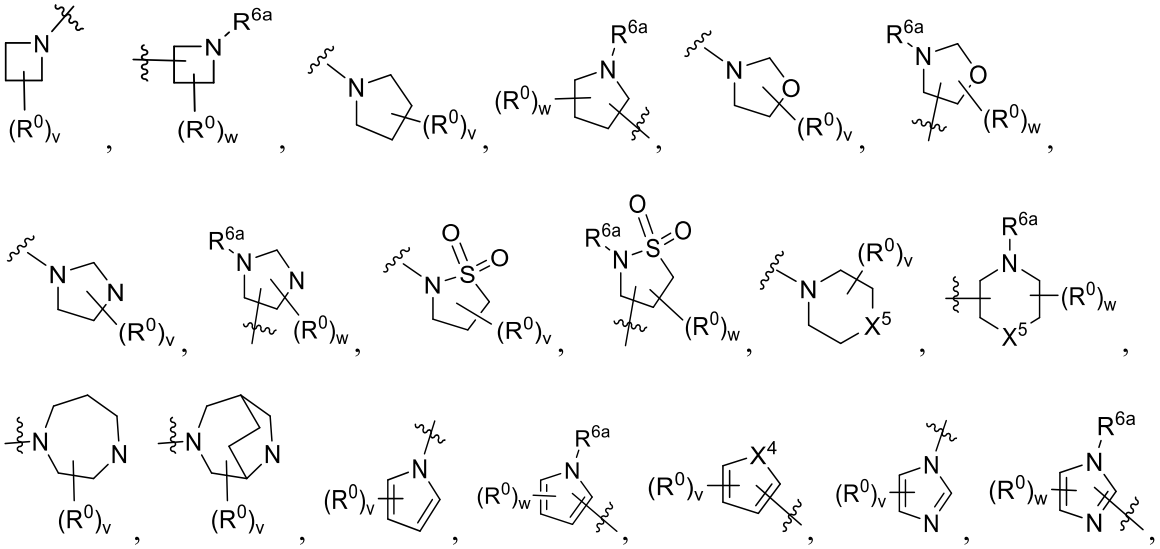
or R^4 and R^8 together with the carbon atom to which they are attached form a

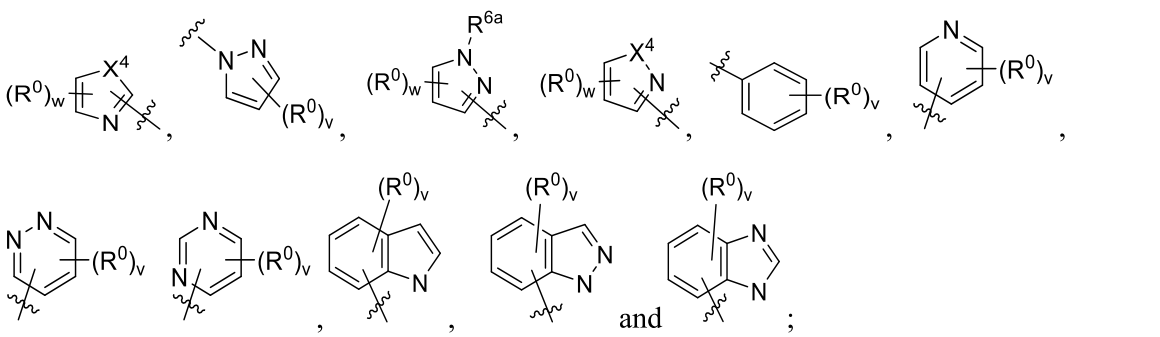

group;

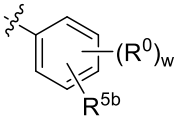
R^{4a} is hydrogen or C_{1-6}alkyl;

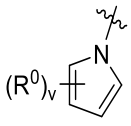
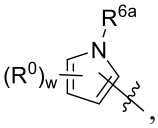
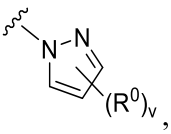
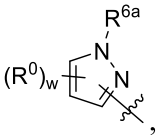
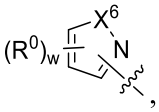
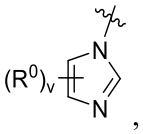
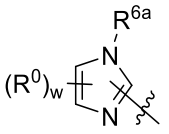
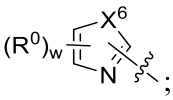
R^{4b} is R^5, R^{5a}, R^6 or R^5-L^1-;

R^5 is selected from the group consisting of:




and ;

R^{5a} is 
;

R^{5b} is , , , , , ,  or ;

R^{6a} is hydrogen or C_{1-6}alkyl;

R^7 is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxyC_{1-6} alkyl-, $NR^aR^bC(O)$-, $R^{7a}C(O)$-, C_{1-6} alkyloxyC(O)-, C_{1-6} alkyl$S(O)_q$- or C_{1-6} haloalkyl$S(O)_q$-;

R^{7a} is C_{1-6}alkyl or C_{3-6}monocycloalkyl;

q, r, t, and w is independently selected for each occurrence from 0, 1 and 2; and

v is independently selected for each occurrence from 0, 1, 2 and 3.

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

In another example, the disclosure provides a method of treating an HBV 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 HBV 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 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 treating Hepatitis B (HBV) infection in a subject in need thereof.

In another aspect, there is provided the use of a therapeutically effective amount of pharmaceutical composition as defined above in the manufacture of a medicament for treating Hepatitis B (HBV) infection in a subject in need thereof.

In another aspect, there is provided a pharmaceutical composition 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 treating Hepatitis B (HBV) infection in a subject in need thereof.

In another aspect, there is provide the use of a therapeutically effective amount of pharmaceutical composition as defined above in the manufacture of a medicament for treating Hepatitis B (HBV) infection in a subject in need thereof.

BRIEF DESCRIPTION OF DRAWINGS

FIGURE 1 shows the ORTEP plot for compound CP-AIA-227-2.

FIGURE 2 shows the relative stereochemistry scheme of compound CP-AIA-227-2.

DETAILED DESCRIPTION

The features and other details of the disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

I. Definitions

The term “alkenyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 carbon atoms, referred to herein as C_{2-6}alkenyl. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc….

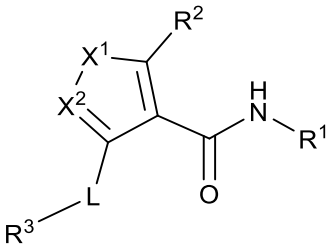
The term “alkoxy” as used herein refers to a straight or branched alkyl group attached to oxygen (i.e., alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 1-4 carbon atoms, referred to herein as C_{1-6}alkoxy and C_{1-4}alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc….

The term “alkoxyalkyl” as used herein refers to an alkyl group substituted with an alkoxy group. Examples include, but are not limited to, $CH_3CH_2OCH_2$-, $CH_3OCH_2CH_2$- and CH_3OCH_2-.

The term “alkyl” as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6 or 1-4 carbon atoms, referred to herein as C_{1-6} alkyl and C_{1-4} alkyl, respectively. Exemplary alkyl

CLAIMS:

1. A compound of Formula I



Formula I

, or a pharmaceutically acceptable salt thereof, wherein:

X^1 is NR^{x1};

X^2 is N;

X^3 is O, NR^7, CR^4R^8, C(O), $S(O)_t$, $C=CR^4R^0$ or $C=NR^4$;

X^4 and X^6 are independently O or S;

X^5 is O, S or NR^0;

L is a bond or C_{1-6}alkylene;

L^1 is a bond, C_{1-6}alkylene, O, NR^c, C(O), $C(O)NR^c$, $S(O)_t$ or $S(O)_tNR^c$;

R^{x1} independently is selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^a, R^b and R^c is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl and C_{3-6} monocycloalkyl;

R^d is hydrogen, OH, C_{1-6}alkyl or C_{1-6} alkoxy;

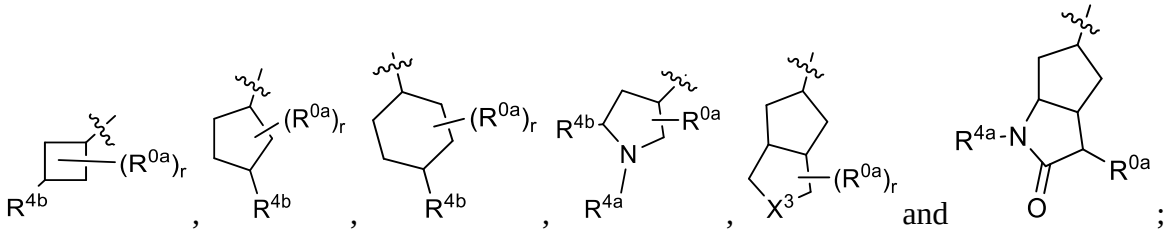
R^0, R^6, R^8 and R^{11} is independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, oxo, $R^dN=$, hydrazino, formyl, azido, silyl, siloxy, HOC(O)-, R^aR^bN-, $R^aR^bNS(O)_t$-, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} monocycloalkyl, haloC_{1-6} alkyl, hydroxyC_{1-6} alkyl-, $R^aR^bNC_{1-6}$ alkyl-, $HOC(O)C_{1-6}$ alkyl-, $R^aR^bNC_{1-6}$ alkylNR^c-, C_{1-6} alkylNR^aC_{1-6} alkylNR^c-, C_{1-6} alkoxy, haloC_{1-6} alkoxy, hydroxyC_{1-6} alkoxy-, $R^aR^bNC_{1-6}$ alkoxy-, C_{1-6}alkoxyC_{1-6} alkyl-, haloC_{1-6} alkoxyC_{1-6} alkyl-, $R^aR^bNC(O)$-, C_{1-6} alkyl$C(O)$-, C_{1-6} alkoxy$C(O)$-, C_{1-6} alkyl$C(O)O$-, C_{1-6} alkyl$S(O)_q$-, C_{1-6} alkyl$S(O)_tNR^c$-, C_{1-6} alkyl$S(O)_tC_{1-6}$ alkyl-, C_{1-6} alkyl$S(O)_tNR^aC_{1-6}$ alkyl-, C_{3-6} cycloalkyl$S(O)_tC_{1-6}$ alkyl-, C_{1-6} alkyl$C(O)C_{1-6}$ alkyl-, and C_{1-6} alkyl$C(O)OC_{1-6}$ alkyl-;

R^{0a} is independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, R^aR^bN-, C_{1-6}alkyl and haloC_{1-6}alkyl;

R^1 is a phenyl, naphthyl, C_{3-6} monocycloalkyl, C_{3-6} monoheterocycloalkyl, or 5-6 membered monocyclic heteroaryl, wherein: the phenyl, C_{3-6} monocycloalkyl, C_{3-6} monoheterocycloalkyl, or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

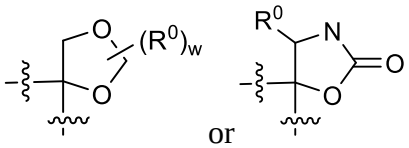
R^2 is R^aR^bN;

R^3 is selected from the group consisting of:


, and ;

R^4 is R^5, R^6 or R^5-L^1-;

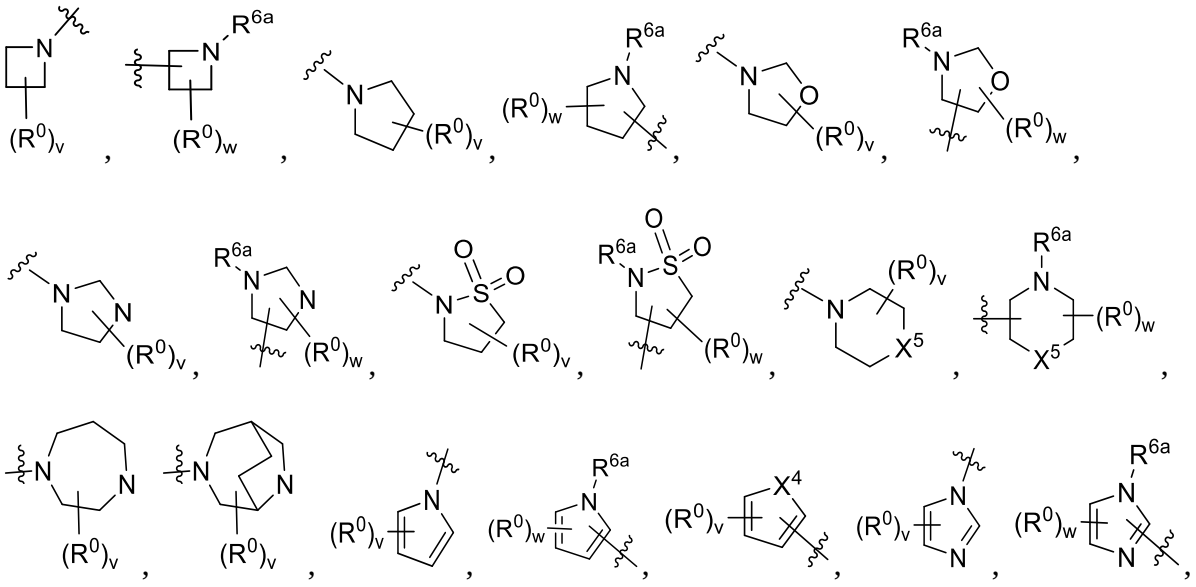
or R^4 and R^8 together with the carbon atom to which they are attached form a

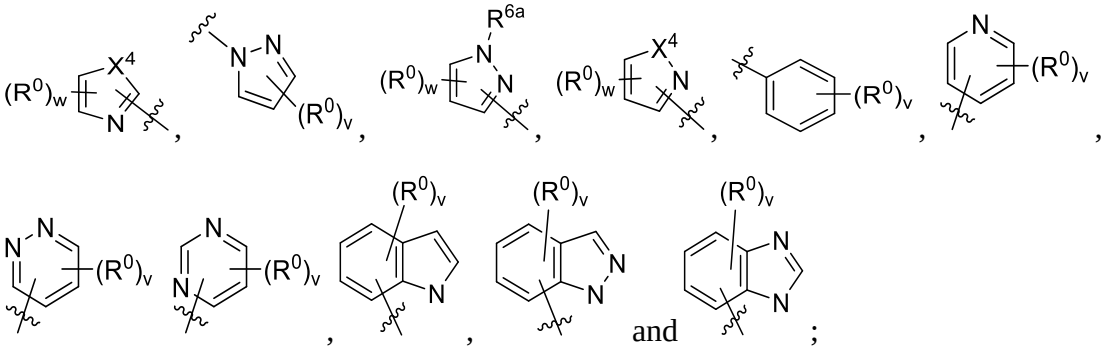

group;

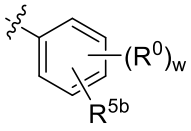
R^{4a} is hydrogen or C_{1-6}alkyl;

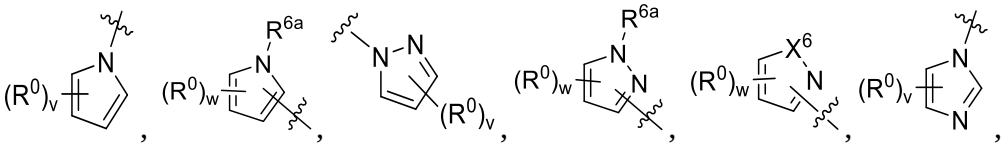
R^{4b} is R^5, R^{5a}, R^6 or R^5-L^1-;

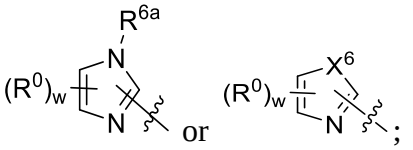
R^5 is selected from the group consisting of:





R^{5a} is ;

R^{5b} is 

 or ;

R^{6a} is hydrogen or C_{1-6}alkyl;

R^7 is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxyC_{1-6} alkyl-, $NR^aR^bC(O)$-, $R^{7a}C(O)$-, C_{1-6} alkyloxyC(O)-, C_{1-6} alkyl$S(O)_q$- or C_{1-6} haloalkyl$S(O)_q$-;

R^{7a} is C_{1-6}alkyl or C_{3-6}monocycloalkyl;

q, r, t, and w is independently selected for each occurrence from 0, 1 and 2; and

v is independently selected for each occurrence from 0, 1, 2 and 3.

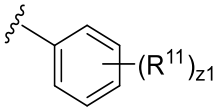
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{x1} is hydrogen or methyl.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{x1} is methyl.

4. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein is L is a bond.

5. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein L^1 is a bond.

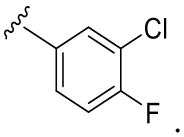
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is NH_2.

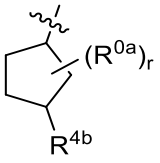
7. The compound according to any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, wherein: R^1 is ;

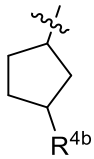
R^{11} is independently selected for each occurrence from the group consisting of halogen, CN, C_{1-6} alkyl and haloC_{1-6} alkyl; and

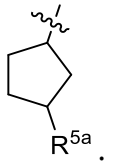
z1 is 0, 1, 2 or 3.

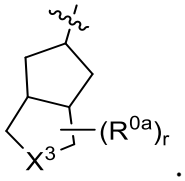
8. The compound of Claim 7, or a pharmaceutically acceptable salt thereof, wherein for each occurrence R^{11} is independently selected from the group consisting of F, Cl, Br and I.

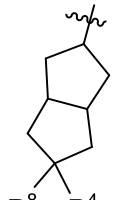
9. The compound of Claim 8, or a pharmaceutically acceptable salt thereof, wherein R^1 is .

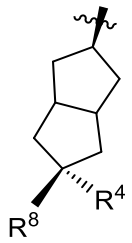
10. The compound according to any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^3 is .

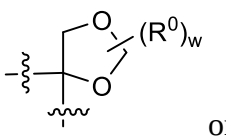
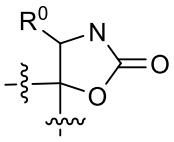
11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein R^3 is .

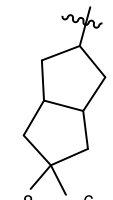
12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^3 is .

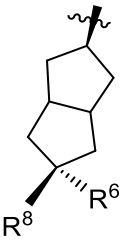
13. The compound according to any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^3 is .

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein R^3 is .

15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein R^3 is .

16. The compound of claim 14 or 15, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^8 together with the carbon atom to which they are attached form a  or  group.

17. The compound of claim 14 or 15, or a pharmaceutically acceptable salt thereof, wherein R^3 is .

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein R^3 is .

19. The compound of claim 17 or 18, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-6} alkyl$S(O)_tC_{1-6}$ alkyl- or C_{1-6} alkyl$S(O)_tNR^aC_{1-6}$ alkyl-.

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-6} alkyl$S(O)_tC_{1-6}$ alkyl-, and t is 1 or 2.

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein t is 2.

22. The compound according to any one of claims 17-21, or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen, OH or C_{1-6} alkoxy.

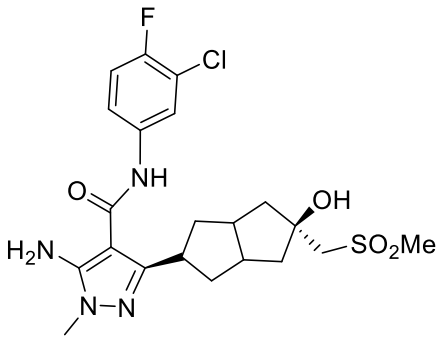
23. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein R^8 is OH.

24. A pharmaceutical composition comprising the compound according to any one of claims 1-23, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

25. Use of a compound according to any one of claims 1-23, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating Hepatitis B (HBV) infection in a subject in need thereof.

26. Use of a therapeutically effective amount of pharmaceutical composition of claim 24 in the manufacture of a medicament for treating Hepatitis B (HBV) infection in a subject in need thereof.

27. A compound



or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising the compound according to claim 27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

29. Use of a compound according to claim 27 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating Hepatitis B (HBV) infection in a subject in need thereof.

30. Use of a therapeutically effective amount of pharmaceutical composition of claim 28 in the manufacture of a medicament for treating Hepatitis B (HBV) infection in a subject in need thereof.