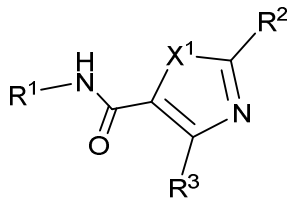
therapy. Moreover, only a small percentage of patients are considered appropriate for interferon therapy, as only a small subset of patients is likely to have a sustained clinical response to a course of interferon therapy. As a result, interferon-based therapies are used in only a small percentage of 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-membed heteroaryl carboxamide compounds and pharmaceutical compositions thereof, useful for disruption of HBV core protein assembly, and methods of treating HBV infections.

In one aspect, the disclosure provides a compound of Formula I



Formula I

, or a pharmaceutically acceptable salt thereof, wherein:

L is C_{1-4}alkylene or haloC_{1-4}alkylene;

L^1 and L^2 are independently a bond, C_{1-6}alkylene, O, NR^c, C(O), C(O)O, C(O)NR^c, $S(O)_t$ or $S(O)_tNR^c$;

X^1 is NR^{x1};

X^3 is CR^4R^8;

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

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

R^a, R^b and R^c are 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^{x1} is hydrogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, haloC_{1-4} alkyl, or C_{3-6} monocycloalkyl; or R^{x1} and R^2 together form a -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -CH_2CH_2O-, -CH_2OCH_2-, -$CH_2CH_2CH_2O$- -$CH_2CH_2OCH_2$-, -CH_2CH_2-NH- -CH_2NHCH_2-, -$CH_2CH_2CH_2NH$- or -$CH_2CH_2NHCH_2$- group;

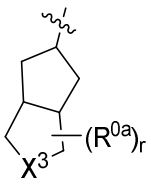
R^{0a} is independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, R^aR^bN-, C_{1-4}alkyl and haloC_{1-4}alkyl;

R^{4a} and R^{6a} are independently hydrogen or C_{1-4} alkyl;

R^0, R^6 and R^{11} are 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, 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-;

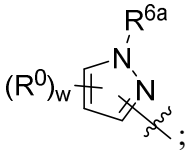
R^1 is a phenyl or 5-6 membered monocyclic heteroaryl, wherein the phenyl or 5-6 membered monocyclic heteroaryl is optionally substituted with one, two, or three independently selected R^{11} groups;

R^2 and R^8 are independently selected from the group consisting of hydrogen, halo, CN, OH, R^aR^bN, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}monocycloalkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy;

R^3 is 

;

R^4 is R^5-L^1-, R^6 or R^9;

R^5 is ;

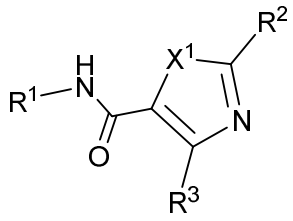
R^9 is $R^{14}S(O)_q$-L-, $R^{14}S(O)_qNH$-L-, or $R^{14}C(O)NH$-L-;

R^{14} is R^aR^bN-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or R^5-L^1-;

q, r, t, and w are 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 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 another aspect, the disclosure provides a pharmaceutical composition comprising a compound as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, the disclosure provides a use of a compound as described above, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of Hepatitis B (HBV) infection.

In another aspect, the disclosure provides a use of a pharmaceutical composition as described above in the manufacture of a medicament for the treatment of Hepatitis B (HBV) infection.

In another aspect, the disclosure provides a compound as described above, or a pharmaceutically acceptable salt thereof for use in therapy.

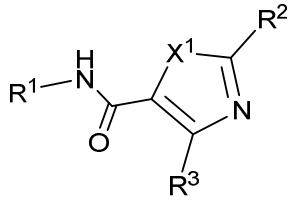
In another aspect, the disclosure provides a pharmaceutical composition as described above for use in therapy.

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

CLAIMS:

1. A compound of Formula I



Formula I

, or a pharmaceutically acceptable salt thereof, wherein:

L is C_{1-4}alkylene or haloC_{1-4}alkylene;

L^1 and L^2 are independently a bond, C_{1-6}alkylene, O, NR^c, C(O), C(O)O, C(O)NR^c, $S(O)_t$ or $S(O)_tNR^c$;

X^1 is NR^{x1};

X^3 is CR^4R^8;

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

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

R^a, R^b and R^c are 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^{x1} is hydrogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, haloC_{1-4} alkyl, or C_{3-6} monocycloalkyl; or R^{x1} and R^2 together form a $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2O-$, $-CH_2OCH_2-$, $-CH_2CH_2CH_2O-$ $-CH_2CH_2OCH_2-$, $-CH_2CH_2-NH-$ $-CH_2NHCH_2-$, $-CH_2CH_2CH_2NH-$ or $-CH_2CH_2NHCH_2-$ group;

R^{0a} is independently selected for each occurrence from the group consisting of hydrogen, halogen, OH, CN, NO_2, R^aR^bN-, C_{1-4}alkyl and haloC_{1-4}alkyl;

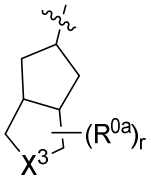
R^{4a} and R^{6a} are independently hydrogen or C_{1-4} alkyl;

R^0, R^6 and R^{11} are 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, 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-,

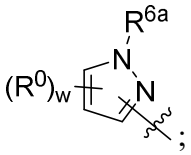
C_{1-6}alkoxyC_{1-6}alkyl-, haloC_{1-6}alkoxyC_{1-6}alkyl-, $R^aR^bNC(O)$-, C_{1-6}alkylC(O)-, C_{1-6}alkoxyC(O)-, C_{1-6}alkylC(O)O-, C_{1-6}alkylS(O)$_q$-, C_{1-6}alkylS(O)$_t$NR^c-, C_{1-6}alkylS(O)$_t$$C_{1-6}$alkyl-, C_{1-6}alkylS(O)$_t$NR^aC_{1-6}alkyl-, C_{3-6}cycloalkylS(O)$_t$$C_{1-6}$alkyl-, C_{1-6}alkylC(O)C_{1-6}alkyl-, and C_{1-6}alkylC(O)OC_{1-6}alkyl-;

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

R^2 and R^8 are independently selected from the group consisting of hydrogen, halo, CN, OH, R^aR^bN, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}monocycloalkyl, C_{1-4}alkoxy, and haloC_{1-4}alkoxy;

R^3 is ;

R^4 is R^5-L^1-, R^6 or R^9;

R^5 is ;

R^9 is $R^{14}S(O)_q$-L-, $R^{14}S(O)_q$NH-L-, or R^{14}C(O)NH-L-;

R^{14} is R^aR^bN-, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or R^5-L^1-;

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

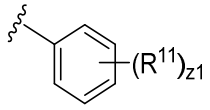
v is independently selected for each occurrence from 0, 1, 2 and 3.

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

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

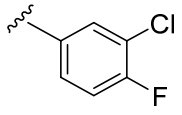
4. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein r is 0.

5. The compound according to any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

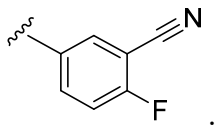
6. The compound according to any one of Claims 1-5, or a pharmaceutically acceptable salt thereof, wherein: R^1 is 

; 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.

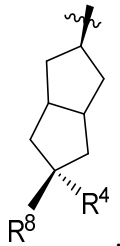
7. The compound of Claim 6, or a pharmaceutically acceptable salt thereof, wherein for each occurrence R^{11} is independently selected from the group consisting of CN, F, Cl, Br and I.

8. The compound of Claim 7, or a pharmaceutically acceptable salt thereof, wherein R^1 is 

.

9. The compound of Claim 7, 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 according to any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^4 is R^6.

12. The compound according to any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^4 is R^5-L^1-.

13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein L^1 is a bond.

14. The compound according to any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^4 is R^9.

15. The compound according to any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen, OH or C_{1-6} alkoxy.

16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R^8 is OH.

17. A pharmaceutical composition comprising the compound according to any one of claims 1-16, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

18. Use of a compound according to any one of claims 1-16, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of Hepatitis B (HBV) infection.

19. Use of a pharmaceutical composition of claim 17 in the manufacture of a medicament for the treatment of Hepatitis B (HBV) infection.

20. A compound according to any one of claims 1-16, or a pharmaceutically acceptable salt thereof for use in therapy.

21. A pharmaceutical composition of claim 17 for use in therapy.