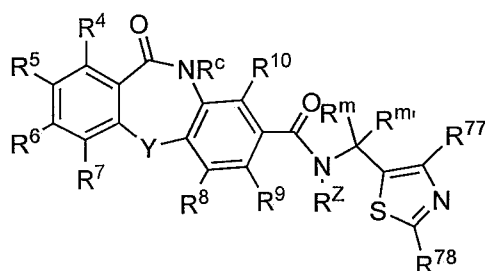


[0008] $R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^c, R^m, R^{m'}, R^{77}, R^{78}, R^Z$ and Y are defined herein.

Also provided herein are methods of treating viral infections, such as hepatitis B, comprising administering to patient a disclosed compound.

[0008a] In one aspect of the present disclosure, there is provided a compound represented by:



wherein

Y is selected from the group consisting of $S(O)_y$, $C=O$, $C(R^{11})_2$, NR_Y and O wherein y is 0, 1, or 2;

R^{11} , for each occurrence, is selected from the group consisting of H, halogen, and C_{1-6} alkyl (optionally substituted with one, two, or three halogens);

R_Y is selected from the group consisting of H, methyl, ethyl, propyl, propenyl, butyl, phenyl and benzyl, wherein R_Y when not H may be optionally substituted by hydroxyl;

R^Z is selected from the group consisting of H, methyl, ethyl, propyl, phenyl and benzyl;

$R^{m'}$ and R^m are each independently selected from the group consisting of H, C_{1-6} alkyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), and C_{2-6} alkenyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl);

R^c is selected from the group consisting of H, C_{1-6} alkyl and C_{2-6} alkenyl;

R^{77} is selected from the group consisting of H, halogen, cyano, and C_{1-6} alkyl;

R^{78} is selected from the group consisting of H, halogen, cyano, C_{1-6} alkyl, carboxy, $-C(O)-O-C_{1-6}$ alkyl; $-NR'R''$; phenyl (optionally substituted with one, two, three or four substituents each independently selected from the group consisting of R^{73}); benzyl

(optionally substituted with one or more substituents each independently selected from the group consisting of R^{73}), 4-7 membered heterocycle (optionally substituted with one or more substituents each independently selected from the group consisting of R^{73}); 4-6 membered monocyclic heteroaryl (optionally substituted with one or more substituents each independently selected from the group consisting of R^{73}); 9-10 membered bicyclic heteroaryl (optionally substituted with one or more substituents each independently selected from the group consisting of R^{73}), X^2-R^{79} , and $X^2-C_{1-6}alkylene-R^{79}$;

X^2 is selected from the group consisting of $S(O)_w$ (wherein w is 0, 1, or 2), O, $-C(O)-$ and NR' ;

R^{79} is selected from the group consisting of H, hydroxyl, halogen, $C_{1-6}alkyl$, $-C(O)-O-C_{1-6}alkyl$, heterocycle (optionally substituted by one or more substituents selected from the group consisting of halogen, $NR'R'$, $-C(O)-O-C_{1-6}alkyl$, carboxy and $C_{1-6}alkyl$), $-C(O)-NR'R''$, $-C(=NH)-NR'R''$, heteroaryl, phenyl (optionally substituted by one or more substituents selected from the group consisting of halogen, $NR'R'$, $-C(O)-O-C_{1-6}alkyl$, carboxy, $C_{1-6}alkoxy$, and $C_{1-6}alkyl$), $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, carboxy, $NR'R''$, $-C(O)-C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, $-NR'-C(O)-C_{1-6}alkyl$, $NR'-C(O)-O-C_{1-6}alkyl$, $-S(O)_w-C_{1-6}alkyl$ (where w is 0, 1 or 2), $-S(O)_w-NR'R''$ (where w is 0, 1 or 2), and $-NR'-S(O)_w-C_{1-6}alkyl$ (where w is 0, 1 or 2));

R^{73} is selected from the group consisting of H, halogen, hydroxyl, nitro, cyano, carboxy, oxo, $C_{1-6}alkyl$, $-C(O)-O-C_{1-6}alkyl$, heterocycle (optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxyl, oxo, $NR'R'$, $-C(O)-O-C_{1-6}alkyl$, carboxy and $C_{1-6}alkyl$), $-C(O)-NR'-C_{1-6}alkyl$, $-C(=NH)-NR'R''$, heteroaryl, phenyl, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, carboxy, oxo, $NR'R''$, $-C(O)-C_{1-6}alkyl$, $-C_{3-6}cycloalkyl$, $NR'-C(O)-C_{1-6}alkyl$, $NR'-C(O)-O-C_{1-6}alkyl$, $-S(O)_w-C_{1-6}alkyl$ (where w is 0, 1 or 2), $-S(O)_w-NR'R''$ (where w is 1, 2 or 3), $-NR'-S(O)_w-C_{1-6}alkyl$ (where w is 0, 1 or 2), $C(O)-NR'-C_{1-6}alkyl$, $C(O)-C_{1-3}alkylene-NR'-C(O)-O-C_{1-6}alkyl$, X^2-R^{79} ; and $X^2-C_{1-6}alkylene-R^{79}$;

R' is selected, independently for each occurrence, from H, methyl, ethyl, cyclopropyl, cyclobutyl, and propyl;

R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, (optionally substituted by hydroxyl), butyl (optionally substituted by hydroxyl), $-C(O)-$

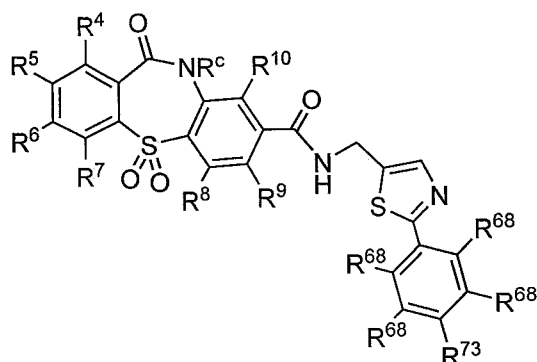
methyl and $-C(O)$ -ethyl, or R' and R'' taken together with the nitrogen to which they are attached may form a 4-7 membered heterocycle optionally substituted by one, two or more substituents selected from the group consisting of halogen, hydroxyl, NH_2 , $-C(O)-O-C_{1-3}alkyl$, $-C(O)-C_{1-3}alkyl$, carboxy, oxo, and $C_{1-3}alkyl$;

each of moieties R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} is independently selected for each occurrence from the group consisting of hydrogen, $C_{1-6}alkyl$, $C_{1-6}alkoxy$, $C_{2-6}alkynyl$, $C_{2-6}alkenyl$, halogen, hydroxyl, nitro, cyano, and $NR'R''$;

wherein for each occurrence, $C_{1-6}alkyl$, $C_{2-6}alkenyl$ or $C_{2-6}alkynyl$ may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, $C_{3-6}cycloalkyl$, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $C_{1-3}alkoxy$, $NR'R''$, $-NR'-S(O)_w-C_{1-2}alkyl$ (where w is 0, 1 or 2), $NR'-C(O)-C_{1-3}alkyl$, $NR'-C(O)-O-C_{1-3}alkyl$, and $S(O)_w-NR'R''$ (where w is 0, 1 or 2); $C_{1-6}alkoxy$ may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, $C_{1-3}alkyl$, $NR'R''$, $-NR'-S(O)_w-C_{1-2}alkyl$ (where w is 0, 1 or 2), and $S(O)_w-NR'R''$ (where w is 0, 1 or 2); $C_{1-6}alkylene$ may be optionally substituted by a substituent selected from the group consisting of $C_{3-6}cycloalkyl$, hydroxyl, cyano, and halogen;

and pharmaceutically acceptable salts and N-oxides thereof.

[0008b] In another aspect of the present disclosure, there is provided a compound represented by:



wherein

R^{73} is selected from the group consisting of heterocycle (optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxyl, oxo,

NR'R', -C(O)-O-C₁₋₆alkyl, carboxy and C₁₋₆alkyl), -C(O)-NR'-C₁₋₆alkyl, -C(=NH)-NR'R'', heteroaryl (optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxyl, NR'R', -C(O)-O-C₁₋₆alkyl, carboxy and C₁₋₆alkyl), phenyl (optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxyl, oxo, NR'R', -C(O)-O-C₁₋₆alkyl, carboxy and C₁₋₆alkyl), C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, carboxy, -C(O)-C₁₋₆alkyl, -C₃₋₆cycloalkyl, NR'-C(O)-C₁₋₆alkyl, NR'-C(O)-O-C₁₋₆alkyl, -S(O)_w-C₁₋₆alkyl (where w is 0, 1 or 2), -S(O)_w-NR'R'' (where w is 0, 1 or 2), -NR'-S(O)_w-C₁₋₆alkyl (where w is 0, 1 or 2), C(O)-NR'-C₁₋₆alkyl, C(O)-C₁₋₃alkylene-NR'-C(O)-O-C₁₋₆alkyl, X²-R⁷⁹; and X²-C₁₋₆alkylene-R⁷⁹;

R⁶⁸ is independently selected for each occurrence from the group consisting of H, halogen, hydroxyl, C₁₋₆alkyl and C₁₋₆alkoxy;

X² is selected from the group consisting of S(O)_w (wherein w is 0, 1, or 2), O, -C(O)- and NR';

R⁷⁹ is selected from the group consisting of H, hydroxyl, halogen, C₁₋₆alkyl, -C(O)-O-C₁₋₆alkyl, heterocycle (optionally substituted by one or more substituents selected from the group consisting of halogen, NR'R', -C(O)-O-C₁₋₆alkyl, carboxy and C₁₋₆alkyl), -C(O)-NR'R'', -C(=NH)-NR'R'', heteroaryl, phenyl (optionally substituted by one or more substituents selected from the group consisting of halogen, NR'R', -C(O)-O-C₁₋₆alkyl, carboxy, C₁₋₆alkoxy, and C₁₋₆alkyl), C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, carboxy, NR'R'', -C(O)-C₁₋₆alkyl, C₃₋₆cycloalkyl, -NR'-C(O)-C₁₋₆alkyl, NR'-C(O)-O-C₁₋₆alkyl, -S(O)_w-C₁₋₆alkyl (where w is 0, 1 or 2), -S(O)_w-NR'R'' (where w is 0, 1 or 2), and -NR'-S(O)_w-C₁₋₆alkyl (where w is 0, 1 or 2));

R' is selected, independently for each occurrence, from H, methyl, ethyl, cyclopropyl, cyclobutyl, and propyl;

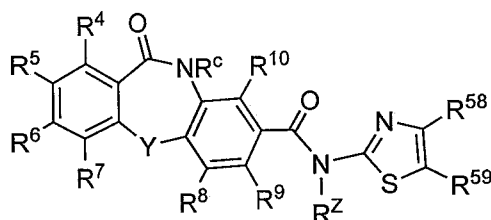
R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl, (optionally substituted by hydroxyl), butyl (optionally substituted by hydroxyl), -C(O)-methyl and -C(O)-ethyl, or R' and R'' taken together with the nitrogen to which they are attached may form a 4-7 membered heterocycle optionally substituted by one, two or more substituents selected from the group consisting of halogen, hydroxyl, NH₂, -C(O)-O-C₁₋₃alkyl, -C(O)-C₁₋₃alkyl, carboxy, oxo, and C₁₋₃alkyl;

each of moieties R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkynyl, C_{2-6} alkenyl, halogen, hydroxyl, nitro, cyano, and $NR'R''$;

wherein for each occurrence, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{3-6} cycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-3} alkoxy, $NR'R''$, $-NR'-S(O)_w-C_{1-2}$ alkyl (where w is 0, 1 or 2), $NR'-C(O)-C_{1-3}$ alkyl, $NR'-C(O)-O-C_{1-3}$ alkyl, and $S(O)_w-NR'R''$ (where w is 0, 1 or 2); C_{1-6} alkoxy may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{1-3} alkyl, $NR'R''$, $-NR'-S(O)_w-C_{1-2}$ alkyl (where w is 0, 1 or 2), and $S(O)_w-NR'R''$ (where w is 0, 1 or 2); C_{1-6} alkylene may be optionally substituted by a substituent selected from the group consisting of C_{3-6} cycloalkyl, hydroxyl, cyano, and halogen;

and pharmaceutically acceptable salts and N-oxides thereof.

[0008c] In a further aspect of the present disclosure, there is provided a compound represented by:



wherein

Y is selected from the group consisting of $S(O)_y$, $C=O$, $C(R^{11})_2$, NR_Y and O wherein y is 0, 1, or 2;

R_Y is selected from the group consisting of H, methyl, ethyl, propyl, propenyl, butyl, phenyl and benzyl;

R^Z is selected from the group consisting of H, methyl, ethyl, propyl, phenyl and benzyl;

R^c is selected from the group consisting of H, C_{1-6} alkyl and C_{2-6} alkenyl;

X^2 is selected from the group consisting of $S(O)_w$ (wherein w is 0, 1, or 2), O, $-C(O)-$ and NR' ;

R^{58} and R^{59} are each independently selected from the group consisting of H, halogen, hydroxyl, nitro, cyano, carboxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $NR'R''$, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkoxy, phenyl, heteroaryl, C_{3-6} cycloalkyl, $-S(O)_w-C_{1-6}$ alkyl (where w is 0, 1 or 2), $-S(O)_w-NR'R''$ (where w is 0, 1 or 2), and $-NR'-S(O)_w-C_{1-6}$ alkyl (where w is 0, 1 or 2); or form a phenyl, heterocyclic or heteroaryl ring (optionally substituted by one, two, or three substituents selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, halogen, hydroxyl, nitro, cyano, and $NR'R''$) and fused to the ring to which they are attached;

R' is selected, independently for each occurrence, from H, methyl, ethyl, cyclopropyl, cyclobutyl, and propyl;

R'' is selected, independently for each occurrence, from H, methyl, ethyl, propyl (optionally substituted by hydroxyl), butyl (optionally substituted by hydroxyl), $-C(O)-$ methyl and $-C(O)-$ ethyl, or R' and R'' taken together with the nitrogen to which they are attached may

form a 4-6 membered heterocycle optionally substituted by one or more substituents selected from the group consisting of halogen, NH_2 , $-C(O)-O-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, carboxy and C_{1-6} alkyl;

R^{11} , for each occurrence, is selected from the group consisting of H, halogen, and C_{1-6} alkyl (optionally substituted with one, two, or three halogens);

each of moieties R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, halogen, hydroxyl, nitro, cyano, and $NR'R''$;

wherein for each occurrence, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl may be optionally substituted with one, two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, carboxy, C_{3-6} cycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-3} alkoxy, $NR'R''$, $-NR'-S(O)_w-C_{1-2}$ alkyl (where w is 0, 1 or 2), $NR'-C(O)-C_{1-3}$ alkyl, $NR'-C(O)-O-C_{1-3}$ alkyl, $-NR'-S(O)_w$, and $S(O)_w-NR'R''$; C_{1-6} alkoxy may be optionally substituted with one, two, three or more substituents selected from the group consisting of

halogen, hydroxyl, nitro, cyano, carboxy, C₁₋₃alkyl, NR'R'', -NR'-S(O)_w-C₁₋₂alkyl (where w is 0, 1 or 2), and S(O)_w-NR'R'' (where w is 0, 1 or 2); C₁₋₆alkylene may be optionally substituted by a substituent selected from the group consisting of C₃₋₆cycloalkyl, hydroxyl, cyano, and halogen;

and pharmaceutically acceptable salts and N-oxides thereof.

[0008d] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition comprising a compound disclosed herein, and a pharmaceutically acceptable excipient.

[0008e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating a hepatitis B infection.

[0008f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein and optionally one or more additional compounds, in the manufacture of a medicament for treating a hepatitis B infection.

[0008g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein and another HBV capsid assembly promoter, in the manufacture of a medicament for treating a hepatitis B infection.

[0008h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein and one or more other HBV agents each selected from the group consisting of HBV capsid assembly promoters, HBF viral polymerase interfering nucleosides, viral entry inhibitors, HBsAg secretion inhibitors, disruptors of nucleocapsid formation, cccDNA formation inhibitors, antiviral core protein mutant, HBc directed transbodies, RNAi targeting HBV RNA, immunostimulants, TLR-7/9 agonists, cyclophilin inhibitors, HBV vaccines, SMAC mimetics, epigenetic modulators, kinase inhibitors, and STING agonists, in the manufacture of a medicament for treating a hepatitis B infection.

[0008i] In another aspect of the present disclosure, there is provided a compound disclosed herein for use in treating a hepatitis B infection.

[0009] For example, the present disclosure is directed in part to compounds having allosteric effector properties against Hepatitis B virus Cp, a protein found as a dimer, a multimer, and as the protein shell of the HBV core. Without being bound by theory, disclosed compounds may ultimately target multimerization of viral core proteins, which is central to HBV infection, where the core protein multimerizes into shell, or capsid, and/or disclosed compounds may for example, ultimately target interaction of viral core proteins with other macromolecules, such as host or viral nucleic acid, host proteins, or other viral proteins. For example, disclosed compounds may be considered in some embodiments CpAM -- core protein allosteric modifiers. CpAM interaction with core protein can allosterically favor an assembly-active form of Cp dimer and lead to viral capsid assembly at an inappropriate time or place or lead to non-standard intersubunit interactions, all resulting in defective capsids. CpAMs may additionally or alternatively affect steps of "upstream" of capsid assembly by altering the concentrations or nature of Cp available as dimer as compared to capsid or other multimeric forms. Disclosed compounds or CpAMs may, in some embodiments, noticeably affect functions upstream of viral assembly such as modulation of cccDNA transcription, RNA stability and/or protein-protein interactions.

DETAILED DESCRIPTION

[00010] The features and other details of the disclosure will now be more particularly described. Before further description of the present invention, 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.

Definitions

24 form a 4-6 membered heterocycle optionally substituted by one or more substituents selected
 25 from the group consisting of halogen, NH_2 , $-\text{C}(\text{O})-\text{O}-\text{C}_{1-6}\text{alkyl}$, $-\text{C}(\text{O})-\text{C}_{1-6}\text{alkyl}$, carboxy and
 26 $\text{C}_{1-6}\text{alkyl}$;

27 R^{11} , for each occurrence, is selected from the group consisting of H, halogen, and C_{1-6}
 28 alkyl (optionally substituted with one, two, or three halogens);

29 each of moieties R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} is independently selected for each
 30 occurrence from the group consisting of hydrogen, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkynyl}$, $\text{C}_{2-6}\text{alkenyl}$, halogen,
 31 hydroxyl, nitro, cyano, and $\text{NR}'\text{R}''$;

32 wherein for each occurrence, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$ or $\text{C}_{2-6}\text{alkynyl}$ may be optionally
 33 substituted with one, two, three or more substituents selected from the group consisting of
 34 halogen, hydroxyl, nitro, cyano, carboxy, $\text{C}_{3-6}\text{cycloalkyl}$, $\text{C}_{2-4}\text{alkenyl}$, $\text{C}_{2-4}\text{alkynyl}$, $\text{C}_{1-3}\text{alkoxy}$,
 35 $\text{NR}'\text{R}''$, $-\text{NR}'-\text{S}(\text{O})_w-\text{C}_{1-2}\text{alkyl}$ (where w is 0, 1 or 2), $\text{NR}'-\text{C}(\text{O})-\text{C}_{1-3}\text{alkyl}$, $\text{NR}'-\text{C}(\text{O})-\text{O}-\text{C}_{1-3}$
 36 alkyl , $-\text{NR}'-\text{S}(\text{O})_w$, and $\text{S}(\text{O})_w-\text{NR}'\text{R}''$; $\text{C}_{1-6}\text{alkoxy}$ may be optionally substituted with one,
 37 two, three or more substituents selected from the group consisting of halogen, hydroxyl, nitro,
 38 cyano, carboxy, $\text{C}_{1-3}\text{alkyl}$, $\text{NR}'\text{R}''$, $-\text{NR}'-\text{S}(\text{O})_w-\text{C}_{1-2}\text{alkyl}$ (where w is 0, 1 or 2), and $\text{S}(\text{O})_w-$
 39 $\text{NR}'\text{R}''$ (where w is 0, 1 or 2); $\text{C}_{1-6}\text{alkylene}$ may be optionally substituted by a substituent
 40 selected from the group consisting of $\text{C}_{3-6}\text{cycloalkyl}$, hydroxyl, cyano, and halogen;
 41 and pharmaceutically acceptable salts and N-oxides thereof.

1 23. The compound of claim 22, wherein Y may be selected from the group consisting of $\text{S}(\text{O})_y$,
 2 $\text{C}=\text{O}$, $\text{C}(\text{R}^{11})_2$, NR_Y and O wherein y is 0, 1, or 2.

1 24. A pharmaceutically acceptable composition comprising a compound of any one of claims
 2 1-23, and a pharmaceutically acceptable excipient.

1 25. Use of a compound of any one of claims 1-23 in the manufacture of a medicament for
 2 treating a hepatitis B infection.

1 26. Use of a compound of any one of claims 1-23 and optionally one or more additional
 2 compounds, in the manufacture of a medicament for treating a hepatitis B infection.

27. Use of a compound of any one of claims 1-23 and another HBV capsid assembly promoter, in the manufacture of a medicament for treating a hepatitis B infection.
28. Use of a compound of any one of claims 1-23 and one or more other HBV agents each selected from the group consisting of HBV capsid assembly promoters, HBF viral polymerase interfering nucleosides, viral entry inhibitors, HBsAg secretion inhibitors, disruptors of nucleocapsid formation, cccDNA formation inhibitors, antiviral core protein mutant, HBc directed transbodies, RNAi targeting HBV RNA, immunostimulants, TLR-7/9 agonists, cyclophilin inhibitors, HBV vaccines, SMAC mimetics, epigenetic modulators, kinase inhibitors, and STING agonists, in the manufacture of a medicament for treating a hepatitis B infection.
29. A compound of any one of claims 1-23 for use in treating a hepatitis B infection.