In addition, heteroaryldihydropyrimidines (HAPs) were identified as a class of HBV inhibitors in tissue culture and animal models (Weber et al., Antiviral Res. 54: 69–78).

WO2013/006394, published on January 10, 2013, relates to a subclass of sulfamoyl-arylamides active against HBV.

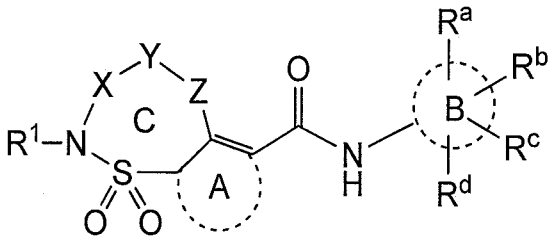
WO2013/096744, published on June 26, 2013 relates to compounds active against HBV.

Amongst the problems which HBV direct antivirals may encounter are toxicity, mutagenicity, lack of selectivity, poor efficacy, poor bioavailability, low solubility and difficulty of synthesis.

There is a need for additional HBV inhibitors that may overcome at least one of these disadvantages or that have additional advantages such as increased potency or an increased safety window.

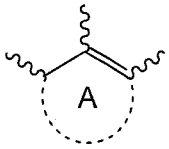
SUMMARY

The present disclosure relates to a compound of Formula (I-A)

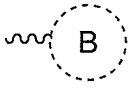


(I-A)

or a stereoisomer or tautomeric form thereof, wherein



represents a monocyclic 5 or 6 membered aryl optionally containing one or two heteroatoms, such aryl optionally being substituted with one or more substituents each independently selected from the group consisting of C_1-C_3alkyl, in particular methyl, C_3-C_4cycloalkyl, -CN and halogen;



represents a 6 membered aryl optionally containing one nitrogen atom;

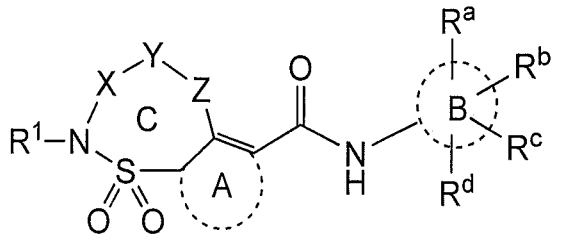
X represents $-CR^2R^3-$;

wherein R^9 and R^{10} are each independently selected from hydrogen and C_1-C_3alkyl optionally substituted with one or more fluoro substituents;

each R^8 is independently selected from the group consisting of -OH, fluoro, methoxy, oxo, -C(=O)OC_1-C_4alkyl, C_1-C_4alkyloxyC_1-C_4alkyloxy, and C_1-C_4alkyl optionally substituted with one or more substituents each independently selected from fluoro and/or –OH;

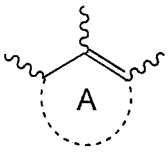
or a pharmaceutically acceptable salt or a solvate thereof.

In one aspect, the present disclosure relates to a compound of Formula (I-A)



(I-A)

or a stereoisomer or tautomeric form thereof, wherein



represents a monocyclic 5 or 6 membered aryl optionally containing one or two heteroatoms, such aryl optionally being substituted with one or more substituents each independently selected from the group consisting of C_1-C_3alkyl, C_3-C_4cycloalkyl, -CN and halogen;



represents a phenyl or pyridyl;

X represents $–CR^2R^3–$;

Y represents C_1-C_7alkanediyl or C_2-C_7alkenediyl, each optionally substituted with one or more substituents each independently selected from the group consisting of C_1-C_4alkyl, fluoro, and -OH;

Z represents a heteroatom or a single bond;

R^a, R^b, R^c and R^d are each independently selected from the group consisting of hydrogen, halogen, -CHF_2, -CF_2-methyl, -CH_2F, -CF_3, -OCF_3, -CN, C_3-C_4cycloalkyl and -C_1-C_4alkyl;

R^1 is hydrogen or C_1-C_{10}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of -OH, fluoro, and oxo;

R^2 is selected from the group consisting of hydrogen; C_1-C_{10}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of –OH, fluoro, methoxy, oxo, and -C(=O)OC_1-C_4alkyl; C_1-C_3alkyl-R^7; C_2-C_4alkynyl; a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N; and monocyclic aryl optionally containing one or two heteroatoms; wherein the C_1-C_3alkyl-R^7, 3-7 membered saturated ring or the monocyclic aryl are each optionally substituted with one or more R^8 substituents;

R^3 is hydrogen or C_{1-6}alkyl optionally substituted with -OH;

or R^2 and R^3 taken together with the carbon atom to which they are attached form a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, and optionally being substituted with one or more substituents each independently selected from the group consisting of -OH, fluoro, methoxy, oxo, -C(=O)OC_1-C_4alkyl, benzyl, and C_1-C_4alkyl optionally substituted with one or more substituents each independently selected from fluoro and/or –OH;

R^7 represents a monocyclic aryl optionally containing one or two heteroatoms, and optionally being substituted with one or two substituents each independently selected from the group consisting of halo and C_{1-3}alkyl; a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N; or –NR^9R^{10};

wherein R^9 and R^{10} are each independently selected from hydrogen and C_1-C_3alkyl optionally substituted with one or more fluoro substituents;

each R^8 is independently selected from the group consisting of -OH, fluoro, methoxy, oxo, -C(=O)OC_1-C_4alkyl, C_1-C_4alkyloxyC_1-C_4alkyloxy, and C_1-C_4alkyl optionally substituted with one or more substituents each independently selected from fluoro and/or –OH;

or a pharmaceutically acceptable salt or a solvate thereof.

The disclosure further relates to a pharmaceutical composition comprising a compound of Formula (I-A), and a pharmaceutically acceptable carrier.

The disclosure also relates to the compounds of Formula (I-A) for use as a medicament, preferably for use in the prevention or treatment of an HBV infection in a mammal.

In another aspect, the present disclosure relates to a compound as defined herein, or a pharmaceutical composition as defined herein, for use as a medicament.

In another aspect, the present disclosure relates to a compound as defined herein, or a pharmaceutical composition as defined herein, for use in the prevention or treatment of an HBV infection in a mammal.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as defined herein, and a pharmaceutically acceptable carrier.

The present disclosure relates to a combination of a compound of Formula (I-A), and another HBV inhibitor.

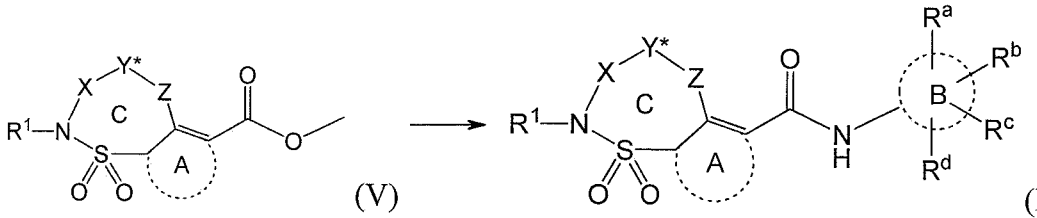
In another aspect, the present disclosure relates to a product containing (a) a compound as defined herein or the pharmaceutical composition as defined herein, and (b) another HBV inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of HBV infections.

In another aspect, the present disclosure relates to use of a compound as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for treating a warm-blooded animal, in particular a human, infected by HBV, or being at risk of infection by HBV.

In another aspect, the present disclosure relates to use of (a) a compound as defined herein or a pharmaceutical composition as defined herein, and (b) another HBV inhibitor, in the manufacture of a combined preparation for simultaneous, separate or sequential use in the treatment of HBV infections.

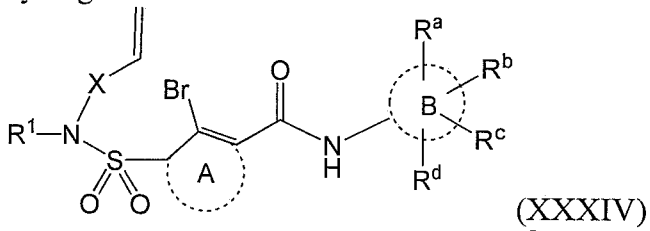
In another aspect, the present disclosure relates to a process for the preparation of a compound as defined herein, comprising the step of

(a) reacting a compound of Formula (V) with an amine of Formula (VI) in the presence of a base in a solvent to form a compound of Formula (Ia) and optionally subjecting the compound of Formula (Ia) to hydrogenation

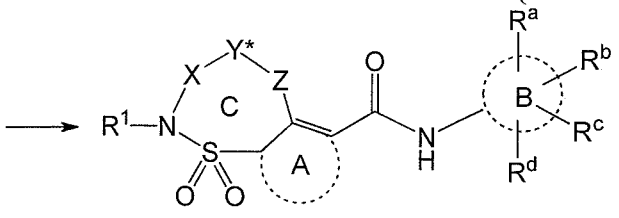


(V) (Ia), or

(b) subjecting a compound of Formula (XXXIV) to Heck conditions to form a compound of Formula (Ia) and optionally subjecting the compound of Formula (Ia) to hydrogenation

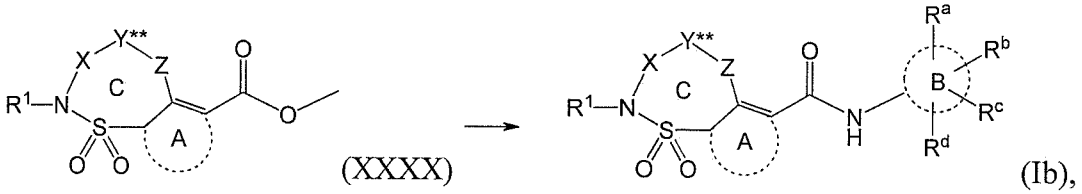


(XXXIV)



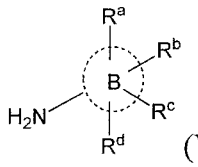
(Ia), or

(c) reacting a compound of Formula (XXXX) with an amine of Formula (VI) in the presence of a suitable base in a suitable solvent



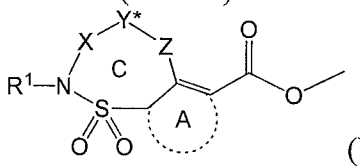
(XXXX) (Ib),

wherein the amine of Formula (VI) is

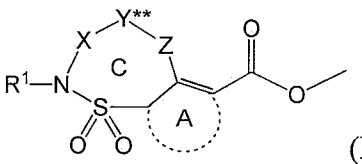


(VI); in (a) and (c) Y* is C_2-C_7alkenediyl; in (b) Y* is –CH=CH-; Y** is C_1-C_7alkanediyl; in (a) and (c) Z is as defined herein; in (b) Z is a single bond; and all other variables are as defined herein.

In another aspect, the present disclosure relates to a compound of Formula (V) or Formula (XXXX)



(V),

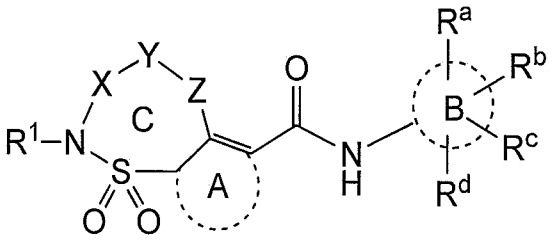


(XXXX), wherein Y^* is C_2-C_7alkenediyl, Y** is C_1-C_7alkanediyl, and all other variables are as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

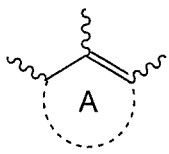
The present invention relates to a compound of Formula (I-A) as defined hereinbefore.

More in particular, the present invention relates to a compound of Formula (I-A)



(I-A)

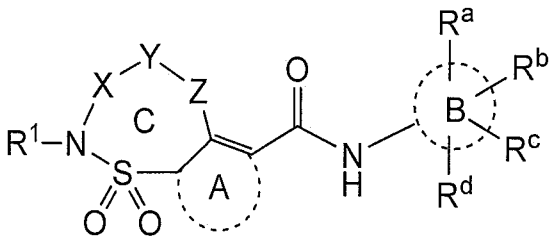
or a stereoisomer or tautomeric form thereof, wherein



represents a monocyclic 5 or 6 membered aryl optionally containing one or two heteroatoms, such aryl optionally being substituted with one or more

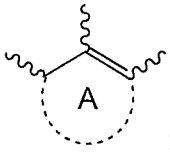
Claims

1. A compound of Formula (I-A)



(I-A)

or a stereoisomer or tautomeric form thereof, wherein



represents a monocyclic 5 or 6 membered aryl optionally containing one or two heteroatoms, such aryl optionally being substituted with one or more substituents each independently selected from the group consisting of C_1-C_3alkyl, C_3-C_4cycloalkyl, -CN and halogen;



represents a phenyl or pyridyl;

X represents $-CR^2R^3-$;

Y represents C_1-C_7alkanediyl or C_2-C_7alkenediyl, each optionally substituted with one or more substituents each independently selected from the group consisting of C_1-C_4alkyl, fluoro, and -OH;

Z represents a heteroatom or a single bond;

R^a, R^b, R^c and R^d are each independently selected from the group consisting of hydrogen, halogen, $-CHF_2$, $-CF_2$-methyl, $-CH_2F$, $-CF_3$, $-OCF_3$, -CN, C_3-C_4cycloalkyl and -C_1-C_4alkyl;

R^1 is hydrogen or C_1-C_{10}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of -OH, fluoro, and oxo;

R^2 is selected from the group consisting of hydrogen; C_1-C_{10}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of –OH, fluoro, methoxy, oxo, and -C(=O)OC_1-C_4alkyl; C_1-C_3alkyl-R^7; C_2-C_4alkynyl; a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N; and monocyclic aryl optionally containing one or two heteroatoms; wherein the C_1-C_3alkyl-R^7, 3-7 membered saturated ring or the monocyclic aryl are each optionally substituted with one or more R^8 substituents;

R^3 is hydrogen or C_{1-6}alkyl optionally substituted with -OH;

or R^2 and R^3 taken together with the carbon atom to which they are attached form a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, and optionally being substituted with one or more substituents each independently selected from the group consisting of -OH, fluoro, methoxy, oxo, -C(=O)OC_1-C_4alkyl, benzyl, and C_1-C_4alkyl optionally substituted with one or more substituents each independently selected from fluoro and/or –OH;

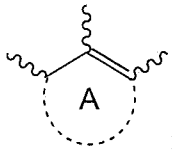
R^7 represents a monocyclic aryl optionally containing one or two heteroatoms, and optionally being substituted with one or two substituents each independently selected from the group consisting of halo and C_{1-3}alkyl; a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N; or $-NR^9R^{10}$;

wherein R^9 and R^{10} are each independently selected from hydrogen and C_1-C_3alkyl optionally substituted with one or more fluoro substituents;

each R^8 is independently selected from the group consisting of -OH, fluoro, methoxy, oxo, -C(=O)OC_1-C_4alkyl, C_1-C_4alkyloxyC_1-C_4alkyloxy, and C_1-C_4alkyl optionally substituted with one or more substituents each independently selected from fluoro and/or –OH;

or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1, wherein



represents a monocyclic 5 or 6 membered aryl optionally containing one or two heteroatoms, such aryl optionally being substituted with one or more substituents each independently selected from the group consisting of C_1-C_3alkyl;



represents a phenyl or pyridyl;

X represents $-CR^2R^3-$;

Y represents C_1-C_7alkanediyl or C_2-C_7alkenediyl each optionally being substituted with one or more substituents each independently selected from C_1-C_4alkyl and -OH;

Z represents a heteroatom or a single bond;

R^a, R^b, R^c and R^d are each independently selected from the group consisting of Hydrogen, halogen, $-CHF_2$, $-CF_2$-methyl, $-CH_2F$, $-CF_3$, $-OCF_3$, -CN, C_3-C_4cycloalkyl and -C_1-C_4alkyl;

R^1 is Hydrogen or C_1-C_6alkyl, such C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of -OH, Fluoro, oxo, and C_1-C_4alkyl optionally substituted with one or more Fluoro and/or -OH;

R^2 is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_3alkyl-R^7, a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, and monocyclic aryl optionally containing one or two heteroatoms, such C_1-C_3alkyl-R^7, 3-7 membered saturated ring or monocyclic aryl optionally being substituted with one or more R^8;

R^3 is hydrogen or C_{1-6}alkyl;

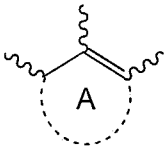
or R^2 and R^3 taken together form together with the carbon atom to which they are attached a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more R^8;

R^7 represents a monocyclic aryl optionally containing one or two heteroatoms; a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N; or $-NR^9R^{10}$;

wherein R^9 and R^{10} are each independently selected from Hydrogen and C_1-C_3alkyl;

each R^8 independently is selected from the group consisting of -OH, Fluoro, methoxy, oxo, -C(=O)OC_1-C_4alkyl and C_1-C_4alkyl optionally substituted with one or more substituents each independently selected from Fluoro and/or –OH.

3. The compound according to claim 1 or 2, wherein



represents a monocyclic 5 or 6 membered aryl optionally containing one or two heteroatoms, such aryl optionally being substituted with one or more substituents each independently selected from the group consisting of C_1-C_3alkyl, C_3-C_4cycloalkyl, -CN and halogen;



represents a phenyl or pyridyl;

X represents $-CR^2R^3-$;
Y represents C_1-C_7alkanediyl or C_2-C_7alkenediyl each optionally being substituted with one or more substituents each independently selected from C_1-C_4alkyl and -OH;
Z represents a heteroatom or a single bond;

R^a, R^b, R^c and R^d are each independently selected from the group consisting of hydrogen, halogen, $-CHF_2$, $-CF_2$-methyl, $-CH_2F$, $-CF_3$, $-OCF_3$, -CN, C_3-C_4cycloalkyl and -C_1-C_4alkyl;

R^1 is Hydrogen or C_1-C_6alkyl, such C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of -OH, Fluoro, oxo, and C_1-C_4alkyl optionally substituted with one or more Fluoro and/or -OH;

R^2 is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_3alkyl-R^7, a 3-7 membered saturated ring optionally containing one or more heteroatoms each

independently selected from the group consisting of O, S and N, and monocyclic aryl optionally containing one or two heteroatoms, such C_1-C_3alkyl-R^7, 3-7 membered saturated ring or monocyclic aryl optionally being substituted with one or more R^8;

R^3 is hydrogen;

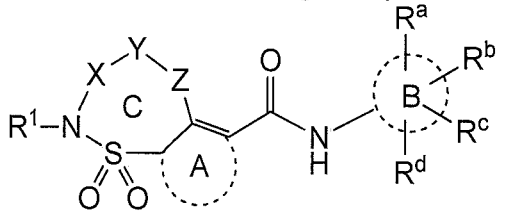
or R^2 and R^3 taken together form together with the carbon atom to which they are attached a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more R^8;

R^7 represents a monocyclic aryl optionally containing one or two heteroatoms; a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N; or $-NR^9R^{10}$;

wherein R^9 and R^{10} are each independently selected from Hydrogen and C_1-C_3alkyl;

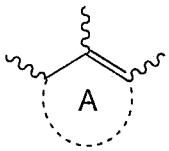
each R^8 independently is selected from the group consisting of -OH, Fluoro, methoxy, oxo, -C(=O)OC_1-C_4alkyl and C_1-C_4alkyl optionally substituted with one or more substituents each independently selected from Fluoro and/or –OH.

4. The compound according to any one of claims 1 to 3, having Formula (A)



(A)

or a stereoisomer or tautomeric form thereof, wherein:



represents a monocyclic 5 or 6 membered aryl optionally containing one or two heteroatoms, such aryl optionally substituted with one or more methyl, -CN or halogen;



represents a phenyl or pyridyl;

X represents $-CR^2R^3-$;
Y represents a C_1-C_7alkanediyl or C_2-C_7alkenediyl each optionally substituted with one or more C_1-C_4alkyl or -OH;
Z represents a heteroatom or a single bond;

R^a, R^b, R^c and R^d are independently selected from the group consisting of Hydrogen, halogen, $-CHF_2$, $-CF_2$-methyl, $-CH_2F$, $-CF_3$, $-OCF_3$, -CN, C_3-C_4cycloalkyl and -C_1-C_4alkyl;

R^1 is hydrogen or C_1-C_6alkyl, such C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of -OH, Fluoro, oxo, and C_1-C_4alkyl optionally substituted with one or more Fluoro and/or -OH;

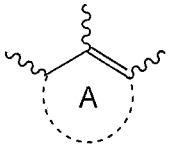
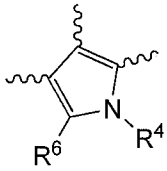
R^2 is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_3alkyl-R^7, a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, and monocyclic aryl optionally containing one or two heteroatoms, such C_1-C_3alkyl-R^7, 3-7 membered saturated ring or monocyclic aryl optionally being substituted with one or more R^8;

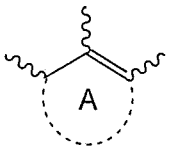
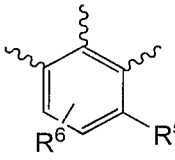
R^3 is hydrogen;

or R^2 and R^3 taken together form together with the carbon atom to which they are attached a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally substituted with one or more R^8;

R^7 represents a monocyclic aryl optionally containing one or two heteroatoms;

each R^8 independently is selected from the group consisting of -OH, Fluoro, methoxy, oxo, -C(=O)OC_1-C_4alkyl and C_1-C_4alkyl optionally substituted with one or more Fluoro and/or –OH;
or a pharmaceutically acceptable salt or a solvate thereof.

5. The compound according to any one of claims 1 to 3, wherein  represents , wherein R^4 is hydrogen, -C_1-C_3alkyl or C_3-C_4cycloalkyl; and R^6 is selected from hydrogen, methyl, -CN and halogen.

6. The compound according to any one of claims 1 to 4, wherein  represents , wherein R^5 is hydrogen or halogen; and R^6 is selected from hydrogen, methyl, -CN and halogen.

7. The compound according to any one of claims 1 to 6, wherein ring C consists of 6 to 8 atoms.

8. The compound according to claim 5 or 7, wherein R^4 is methyl.

9. The compound according to any one of claims 5 to 8 wherein R^6 is hydrogen.

10. The compound according to claim 1, wherein R^2 is C_1-C_6alkyl optionally substituted with one or more substituents each independently selected from the group consisting of –OH, fluoro, and methoxy.

11. The compound according to any one of claims 1 to 10, wherein  represents phenyl, and R^a is selected from hydrogen and halogen; R^b is hydrogen or a halogen; R^c is selected from halogen, CH_3, CHF_2, CF_3, and -CN; and R^d is selected from hydrogen and halogen.

12. The compound according to claim 1 wherein R^2 is C_1-C_4alkyl optionally substituted with one or more Fluoro.

13. The compound according to claim 1 wherein R^2 is C_1-C_6alkyl optionally substituted with one or more –OH substituents.

14. The compound according to any one of the previous claims wherein R^1 is hydrogen.

15. A compound according to claim 1, wherein the compound is
(3S)-*N*-(3-cyano-4-fluoro-phenyl)-7-methyl-1,1-dioxo-3-(3-pyridylmethyl)-3,4-dihydro-2H-pyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide;
(3R)-3-[(1S)-1-hydroxyethyl]-7-methyl-1,1-dioxo-*N*-(3,4,5-trifluorophenyl)-2,3-dihydropyrrolo[3,4-f]thiazepine-6-carboxamide;
(3R)-*N*-[3-(difluoromethyl)-4-fluoro-phenyl]-3-(1-hydroxy-1-methyl-ethyl)-7-methyl-1,1-dioxo-3,4-dihydro-2H-pyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide;
(3R)-*N*-(3-cyano-4-fluoro-phenyl)-3-(1-hydroxy-1-methyl-ethyl)-7-methyl-1,1-dioxo-3,4-dihydro-2H-pyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide;
(3S)-*N*-(3-cyano-4-fluoro-phenyl)-3,7-dimethyl-1,1-dioxo-2,3,4,5-tetrahydropyrrolo[3,4-f]thiazepine-6-carboxamide;
N-[3-(difluoromethyl)-4-fluoro-phenyl]-3-(1-hydroxy-1-methyl-ethyl)-7-methyl-1,1-dioxo-2,3,4,5-tetrahydropyrrolo[3,4-f]thiazepine-6-carboxamide;
N-[3-(difluoromethyl)-4-fluoro-phenyl]-3-[(2,5-dimethylpyrazol-3-yl)methyl]-3,7-dimethyl-1,1-dioxo-2,4-dihydropyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide; or
N-[3-(difluoromethyl)-4-fluoro-phenyl]-3,7-dimethyl-3-[(1-methylimidazol-2-yl)methyl]-1,1-dioxo-2,4-dihydropyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide,
or a stereoisomer thereof, or a pharmaceutically acceptable salt or a solvate thereof.

16. A compound according to claim 1, wherein the compound is
(3S)-*N*-(3-cyano-4-fluoro-phenyl)-7-methyl-1,1-dioxo-3-(3-pyridylmethyl)-3,4-dihydro-2H-pyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide,
or a pharmaceutically acceptable salt or a solvate thereof.

17. A compound according to claim 1, wherein the compound is
(3R)-3-[(1S)-1-hydroxyethyl]-7-methyl-1,1-dioxo-*N*-(3,4,5-trifluorophenyl)-2,3-dihydropyrrolo[3,4-f]thiazepine-6-carboxamide,
or a pharmaceutically acceptable salt or a solvate thereof.

18. A compound according to claim 1, wherein the compound is
(3R)-*N*-[3-(difluoromethyl)-4-fluoro-phenyl]-3-(1-hydroxy-1-methyl-ethyl)-7-methyl-1,1-dioxo-3,4-dihydro-2H-pyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide,
or a pharmaceutically acceptable salt or a solvate thereof.

19. A compound according to claim 1, wherein the compound is (3R)-*N*-(3-cyano-4-fluoro-phenyl)-3-(1-hydroxy-1-methyl-ethyl)-7-methyl-1,1-dioxo-3,4-dihydro-2H-pyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide, or a pharmaceutically acceptable salt or a solvate thereof.

20. A compound according to claim 1, wherein the compound is (3S)-*N*-(3-cyano-4-fluoro-phenyl)-3,7-dimethyl-1,1-dioxo-2,3,4,5-tetrahydropyrrolo[3,4-f]thiazepine-6-carboxamide, or a pharmaceutically acceptable salt or a solvate thereof.

21. A compound according to claim 1, wherein the compound is *N*-[3-(difluoromethyl)-4-fluoro-phenyl]-3-(1-hydroxy-1-methyl-ethyl)-7-methyl-1,1-dioxo-2,3,4,5-tetrahydropyrrolo[3,4-f]thiazepine-6-carboxamide, being the enantiomer having a retention time of 3.74 min determined by Supercritical fluid chromatography Method R, or a pharmaceutically acceptable salt or a solvate thereof.

22. A compound according to claim 1, wherein the compound is *N*-[3-(difluoromethyl)-4-fluoro-phenyl]-3-[(2,5-dimethylpyrazol-3-yl)methyl]-3,7-dimethyl-1,1-dioxo-2,4-dihydropyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide, being the enantiomer having a retention time of 5.13 min determined by Supercritical fluid chromatography Method R, or a pharmaceutically acceptable salt or a solvate thereof.

23. A compound according to claim 1, wherein the compound is *N*-[3-(difluoromethyl)-4-fluoro-phenyl]-3,7-dimethyl-3-[(1-methylimidazol-2-yl)methyl]-1,1-dioxo-2,4-dihydropyrrolo[3,4-b][1,4,5]oxathiazepine-6-carboxamide, or a stereoisomer thereof, or a pharmaceutically acceptable salt or a solvate thereof.

24. A compound as defined in any one of claims 1 to 23 or a pharmaceutical composition as defined in claim 26, for use as a medicament.

25. A compound as defined in any one of claims 1 to 23 or a pharmaceutical composition as defined in claim 26, for use in the prevention or treatment of an HBV infection in a mammal.

26. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 23, and a pharmaceutically acceptable carrier.

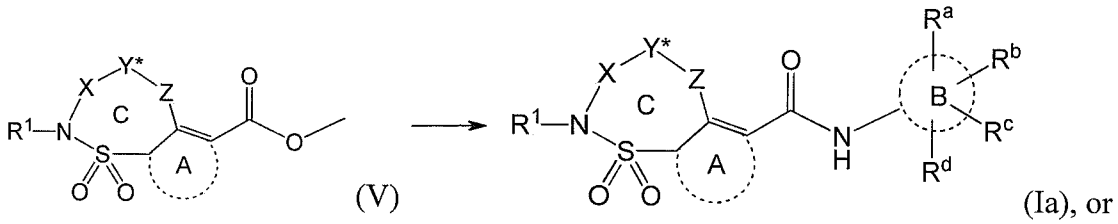
27. A product containing (a) a compound as defined in any one of claims 1 to 23 or a pharmaceutical composition as defined in claim 26, and (b) another HBV inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of HBV infections.

28. Use of a compound as defined in any one of claims 1 to 23 or a pharmaceutical composition as defined in claim 26 in the manufacture of a medicament for treating a warm-blooded animal, in particular a human, infected by HBV, or being at risk of infection by HBV.

29. Use of (a) a compound as defined in any one of claims 1 to 23 or a pharmaceutical composition as defined in claim 26, and (b) another HBV inhibitor, in the manufacture of a combined preparation for simultaneous, separate or sequential use in the treatment of HBV infections.

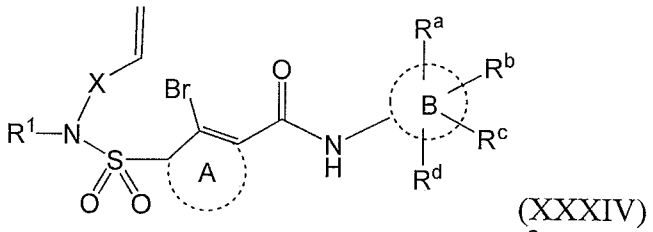
30. A process for the preparation of a compound as defined in any one of claims 1 to 23, comprising the step of

(a) reacting a compound of Formula (V) with an amine of Formula (VI) in the presence of a base in a solvent to form a compound of Formula (Ia) and optionally subjecting the compound of Formula (Ia) to hydrogenation

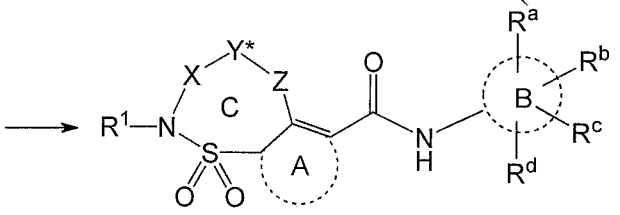


(V) (Ia), or

(b) subjecting a compound of Formula (XXXIV) to Heck conditions to form a compound of Formula (Ia) and optionally subjecting the compound of Formula (Ia) to hydrogenation

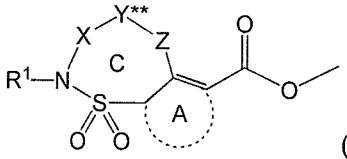


(XXXIV)

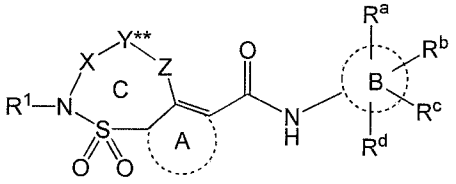


(Ia), or

(c) reacting a compound of Formula (XXXX) with an amine of Formula (VI) in the presence of a suitable base in a suitable solvent

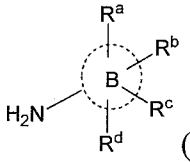


(XXXX)



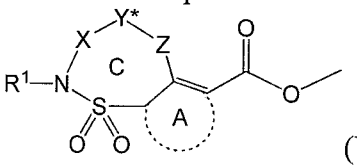
(Ib),

wherein the amine of Formula (VI) is

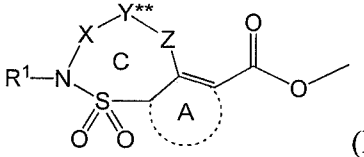


(VI); in (a) and (c) Y* is C_2-C_7alkenediyl; in (b) Y* is –CH=CH-; Y** is C_1-C_7alkanediyl; in (a) and (c) Z is as defined in any one of claims 1 to 23; in (b) Z is a single bond; and all other variables are as defined in any one of claims 1 to 23.

31. A compound of Formula (V) or Formula (XXXX)



(V),



(XXXX), wherein Y^* is C_2-C_7alkenediyl, Y** is C_1-C_7alkanediyl, and all other variables are as defined in any one of claims 1 to 23.