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.

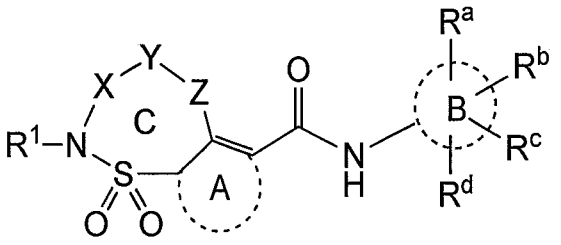
WO2013/096744, published on June 26, 2013 relates to compounds active against HBV.

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.

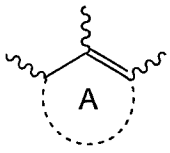
SUMMARY

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, 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.

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, for use as a medicament.

In another aspect, the present disclosure relates to a compound 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.

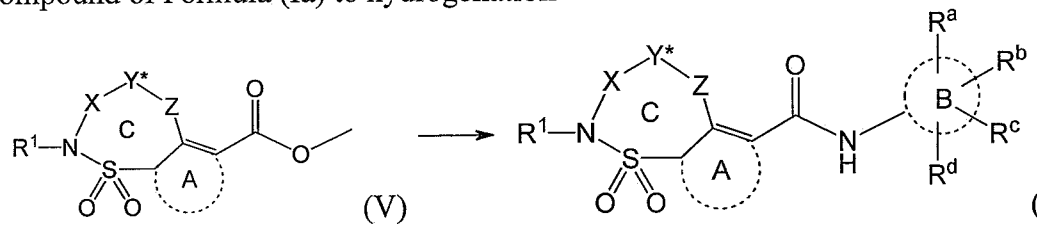
The present disclosure relates to a combination of a compound of Formula (I-A), and another HBV inhibitor.

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.

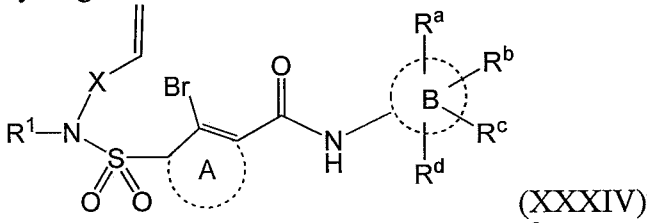
In another aspect, the present disclosure relates to a process for the preparation of a compound as defined herein, comprising the step of

(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

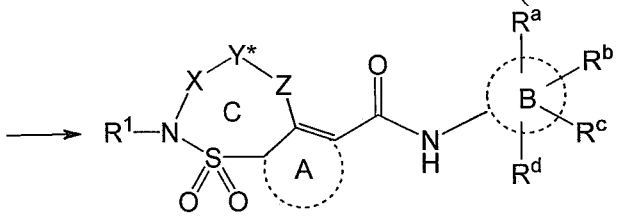


(V) (Ia), or

(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

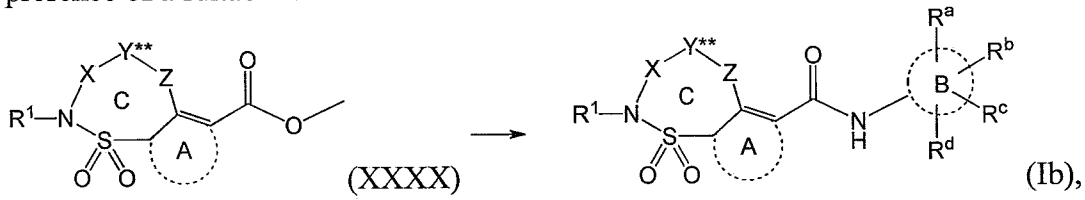


(XXXIV)



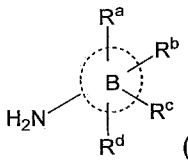
(Ia), or

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



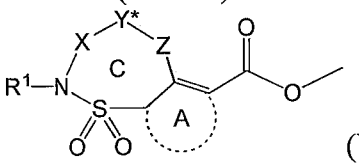
(XXXX) (Ib),

wherein the amine of Formula (VI) is

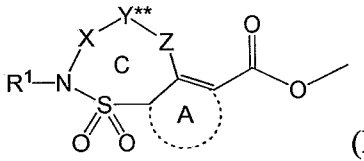


(VI), Y* is C_2-C_7alkenediyl, Y** is C_1-C_7alkanediyl, and all other variables are as defined herein.

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



(V),

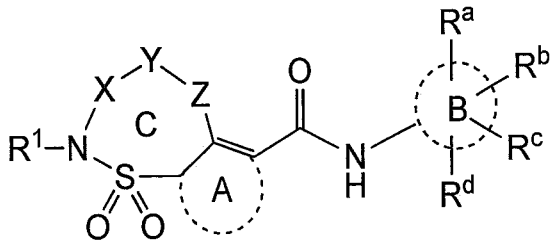


(XXXX), wherein Y^* is C_2-C_7alkenediyl, Y** is C_1-C_7alkanediyl, and all other variables are as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

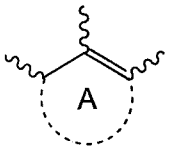
The present invention relates to a compound of Formula (I-A) as defined hereinbefore.

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

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

15. A compound as defined in any one of claims 1 to 14, for use as a medicament.

16. A compound as defined in any one of claims 1 to 14, for use in the prevention or treatment of an HBV infection in a mammal.

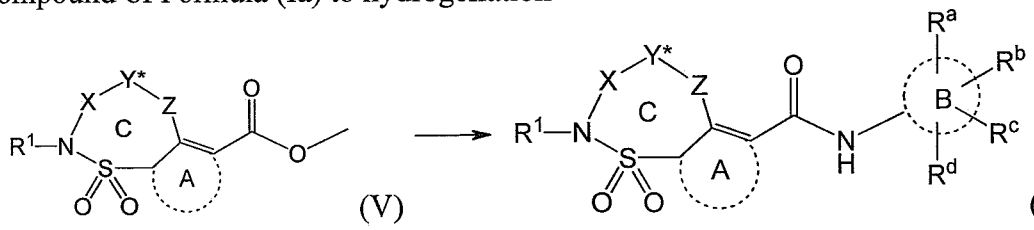
17. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 14, and a pharmaceutically acceptable carrier.

18. A product containing (a) a compound as defined in any one of claims 1 to 14 or the pharmaceutical composition of claim 17, and (b) another HBV inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of HBV infections.

19. Use of a compound as defined in any one of claims 1 to 14 or a pharmaceutical composition as defined in claim 17 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.

20. A process for the preparation of a compound as defined in any one of claims 1 to 14, 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



(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