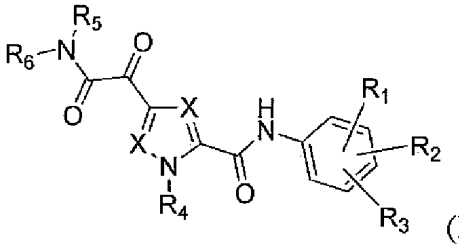
Amongst the problems which HBV direct antivirals may encounter are toxicity, mutagenicity, lack of selectivity, poor efficacy, poor bioavailability, low solubility and difficulty of synthesis.

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.

Description

The present disclosure, in one aspect, relates to a compound of Formula (IA)



(IA)

or a stereoisomer or tautomeric form thereof, wherein:

Each X independently represents CR^7;

R^1, R^2 and R^3 are independently selected from the group consisting of Hydrogen, Fluoro, Chloro, Bromo, $-CHF_2$, $-CH_2F$, $-CF_3$, -CN, C_1-C_3alkyl or C_3-C_4cycloalkyl;

R^4 is Hydrogen C_1-C_3alkyl or C_3-C_4cycloalkyl;

R^5 is Hydrogen;

R^6 is selected from the group consisting of C_1-C_6alkyl and 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 C_1-C_6alkyl or 3-7 membered saturated ring optionally substituted with one or more substituents selected from the group consisting of Fluoro, C_3-C_4cycloalkyl, $-OR^8$, oxo, -CN, $-C(=O)-OR^8$, $-C(=O)-N(R^8)_2$ or C_1-C_3alkyl optionally substituted with one or more Fluoro;

Each R^7 independently represents hydrogen, C_3-C_4cycloalkyl, -CN, Fluoro, Chloro, Bromo or C_1-C_3alkyl optionally substituted with one or more Fluoro;

R^8 represents hydrogen or C_1-C_3alkyl;

or a pharmaceutically acceptable salt or a solvate thereof.

The disclosure relates to a pharmaceutical composition comprising a compound of Formula (IA), and a pharmaceutically acceptable carrier. The disclosure, in another aspect, relates to a pharmaceutical composition comprising a compound as defined herein, and a pharmaceutically acceptable carrier.

The disclosure also relates to the compounds of Formula (IA) for use as a medicament, preferably for use in the prevention or treatment of an HBV infection in a mammal. The disclosure, in another aspect, relates to a compound as defined herein for use in the prevention or treatment of an HBV infection in a mammal.

The disclosure further relates to a combination of a compound of Formula (IA), and another HBV inhibitor.

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

Definitions

The term "C_{1-3}alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 3. In case C_{1-3}alkyl is coupled to a further radical, it refers to a Formula C_nH_{2n}. C_{1-3}alkyl groups comprise from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. C_{1-3}alkyl includes all linear, or branched alkyl groups with between 1 and 3 carbon atoms, and thus includes such as for example methyl, ethyl, *n*-propyl, and *i*-propyl.

C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as the group defined for C_{1-3}alkyl and butyl and the like.

C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylbutyl and the like.

As used herein, the term "3-7 membered saturated ring" means saturated cyclic hydrocarbon with 3, 4, 5, 6 or 7 carbon atoms and is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Such saturated ring optionally contains one or more heteroatoms, such that at least one carbon atom is replaced by a heteroatom selected from N, O and S, in particular from N and O. Examples include oxetane, tetrahydro-2H-pyranyl, piperidinyl, tetrahydrofuranyl, morpholinyl, thiolane 1,1-dioxide and pyrrolidinyl. Preferred are saturated cyclic hydrocarbon with 3 or 4 carbon atoms and 1 oxygen atom. Examples include oxetane, and tetrahydrofuranyl.

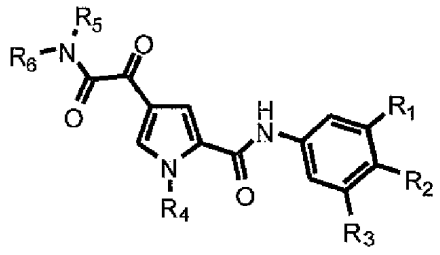
It should be noted that different isomers of the various heterocycles may exist within the definitions as used throughout the specification. For example, pyrrolyl may be

4. A compound according to any one of the previous claims wherein R^6 is a 3-7 membered saturated ring optionally containing one oxygen, such 3-7 membered saturated ring optionally substituted with one or more substituents selected from Fluoro or C_1-C_3alkyl optionally substituted with one or more.

5. A compound according to any one of the previous claims wherein R^6 is a 4 or 5 membered saturated ring optionally containing one oxygen, such 4 or 5 membered saturated ring optionally substituted with one or more substituents selected from C_1-C_3alkyl optionally substituted with one or more Fluoro or Fluoro.

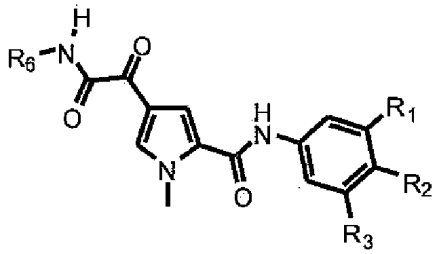
6. A compound according to any one of claims 1 to 3, wherein R^6 is a branched C_1-C_6alkyl optionally substituted with one or more Fluoro.

7. A compound according to any one of the previous claims with Formula (Ia).



(Ia)

8. A compound according to any one of the previous claims with Formula (Ib).



(Ib)

9. A compound according to any one of the previous claims for use in the prevention or treatment of an HBV infection in a mammal.

10. A pharmaceutical composition comprising a compound according to any of claims 1 to 8, and a pharmaceutically acceptable carrier.

11. A product containing (a) a compound of Formula (IA) as defined in any one of claims 1 to 8, and (b) another HBV inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of HBV infections.