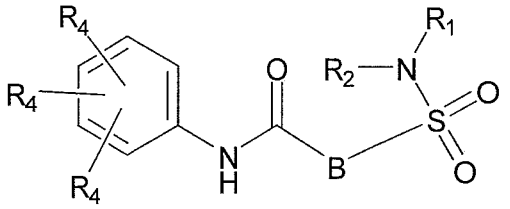
There is a need for additional HBV inhibitors that may overcome at least one of these disadvantages or that have additional advantages such as increased potency or an increased safety window.

Description

The present disclosure relates to compounds of Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 represents hydrogen or C_1-C_3alkyl;

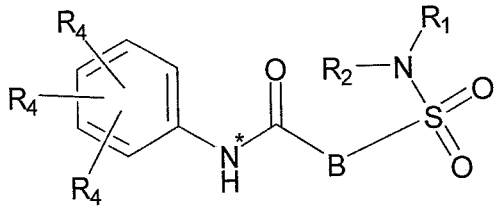
R_2 represents C_1-C_6alkyl, C_1-C_6alkenyl, C_1-C_6alkyl-R_5, C(=O)-R_5, CFH_2, CF_2H, CF_3, a dihydro-indenyl or tetrahydronaphtalenyl moiety optionally substituted with OH, or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring, C_1-C_6alkyl-R_5 or C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;
Or R_1 and R_2 together with the Nitrogen to which they are attached form a 6-10 membered bicyclic or bridged ring or a 5-7 membered saturated ring, such bicyclic, bridged or saturated ring moiety optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyl, C_1-C_4alkenyl, OH, CN, CFH_2, CF_2H, CF_3 , HC≡C or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N, such C_1-C_4alkyl optionally substituted with OH;

R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3, phenyl, pyridyl or 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 substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

or a pharmaceutically acceptable salt or a solvate thereof.

According to one aspect, the disclosure relates to a compound of Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 and R_2 together with the Nitrogen to which they are attached form a 1,4-dioxa-8-azaspiro[4.5]decyl moiety or a 5-7 membered saturated ring, such saturated ring moiety optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, C_1-C_4alkenyl, OH, CN, CFH_2, CF_2H, CF_3 , HC≡C or a 3-5 membered saturated ring

optionally containing one or more heteroatoms each independently selected from the group consisting of O and N, such C_1-C_4alkyl optionally substituted with OH;

R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3, phenyl, pyridyl or 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 substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

or a pharmaceutically acceptable salt or a solvate thereof.

According to another aspect, the disclosure further relates to a pharmaceutical composition comprising a compound of Formula (I), and a pharmaceutically acceptable carrier.

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

The disclosure relates to a combination of a compound of Formula (I), and another HBV inhibitor. According to another aspect, there is provided a product containing (a) a compound as defined herein, and (b) another HBV inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of HBV infections. According to another aspect, there is provided use of (a) a compound as defined herein, and (b) another HBV inhibitor, in the manufacture of a medicament for combined therapy 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

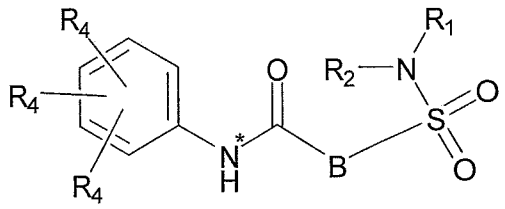
linear, or branched alkyl groups with between 1 and 3 carbon atoms, and thus includes such as for example methyl, ethyl, *n*-propyl, and *i*-propyl.

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.

Claims

1. A compound of Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 and R_2 together with the Nitrogen to which they are attached form a 1,4-dioxa-8-azaspiro[4.5]decyl moiety or a 5-7 membered saturated ring, such saturated ring moiety optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, C_1-C_4alkenyl, OH, CN, CFH_2, CF_2H, CF_3 , HC≡C or a 3-5 membered saturated ring

optionally containing one or more heteroatoms each independently selected from the group consisting of O and N, such C_1-C_4alkyl optionally substituted with OH;

R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3, phenyl, pyridyl or 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 substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

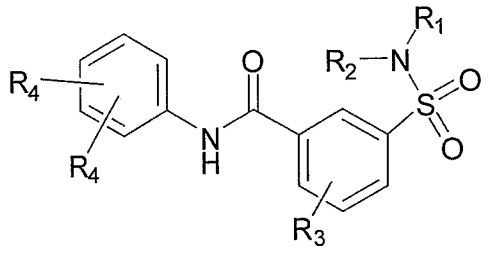
or a pharmaceutically acceptable salt or a solvate thereof.

2. A compound according to claim 1, wherein at least one R_4 represents Fluor, and one other R_4 is selected from the group consisting of C_1-C_3alkyl, C_1-C_3alkenyl, CHF_2 or cyclopropyl.

3. A compound according to claim 1 or 2 wherein one R_4 represents Fluor and one other R_4 is selected from the group consisting of methyl or CHF_2 and wherein the location of said Fluor is on the *para* position and the location of said methyl or CHF_2 is on the *meta* position related to the Nitrogen(*).

4. The compound according to any one of the preceding claims, wherein B represents phenyl or thiophene, optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3.

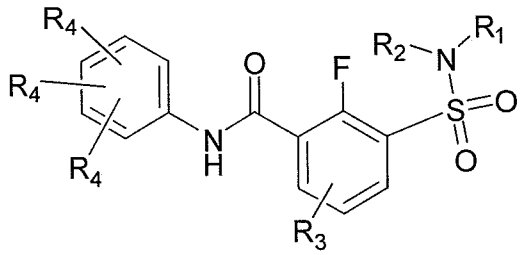
5. A compound according to any one of the preceding claims, which is of Formula (Ib)



(Ib)

wherein R_1, R_2, R_4 are defined as in any one of the previous claims and R_3 is selected from the group comprising hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H, CF_3.

6. A compound according to any one of the preceding claims 1 to 4, which is of Formula (Id)

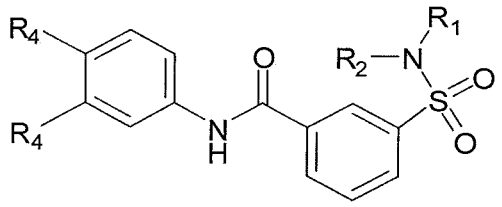


(Id)

wherein R_1, R_2, R_4 are defined as in any one of the previous claims 1 to 4 and R_3 is selected from the group comprising hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H, CF_3.

7. A compound according to claim 5 or 6, wherein R_3 represents hydrogen.

8. A compound according to any one of the preceding claims 1 to 4, which is of Formula (Ic)



(Ic)

wherein R_1, R_2, R_4 are defined as in any one of the previous claims 1 to 4.

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 one of claims 1 to 8, and a pharmaceutically acceptable carrier.

11. A product containing (a) a compound 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.

12. Use of a compound according to any one of claims 1 to 8 in the manufacture of a medicament for the prevention or treatment of an HBV infection in a mammal.

13. Use of (a) a compound as defined in any one of claims 1 to 8, and (b) another HBV inhibitor, in the manufacture of a medicament for combined therapy of HBV infections.