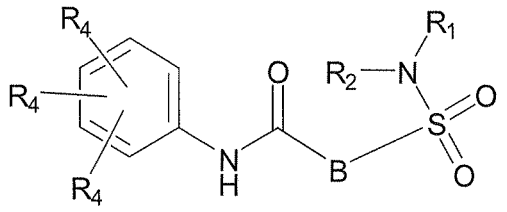
There is a need for additional HBV inhibitors that may overcome at least one of these disadvantages or that have additional advantages such as increased potency or an increased safety window.

Description

~~According to one aspect, t~~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;

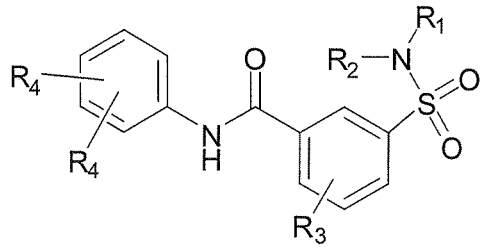
R_2 represents C_1-C_6alkyl, C_1-C_6alkenyl, C_1-C_6alkyl-R_5, C(=O)-R_5, CFH_2, CF_2H, CF_3, a dihydro-indenyl or tetrahydronaphtalenyl moiety optionally substituted with OH, or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting 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 (Ib)



(Ib)

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-R_5, a dihydro-indenyl or tetrahydronaphtalenyl moiety, all optionally substituted with OH, or a 3-7 membered saturated ring containing one N, such 3-7 membered saturated ring or C_1-C_6alkyl-R_5 optionally being substituted with one or more substituents each independently selected from the group consisting of C_1-C_4alkyloxycarbonyl, and C_1-C_4alkyl,;

Or R_1 and R_2 together with the Nitrogen to which they are attached form a 6-10 membered bicyclic or bridged ring containing one O, 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;

R_3 is selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H, and CF_3;

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;

R_5 represents phenyl or pyridyl;

or a pharmaceutically acceptable salt or a solvate thereof.

According to another aspect, the disclosure further relates to a pharmaceutical composition comprising a compound as defined herein~~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 a compound as defined herein for use as a medicine. According to another aspect, the disclosure relates to use of a compound ~~of Formula (I)~~ as defined herein in the manufacture of a medicament for ~~use in~~ 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 combined preparation ~~product~~ containing (a) a compound ~~of Formula (I)~~as defined herein, and (b) another HBV inhibitor, ~~as a combined preparation~~ for ~~simultaneous, separate or sequential~~ use in the treatment of HBV infections, said treatment comprising the simultaneous, separate or sequential use of said compound and said HBV inhibitor.

Definitions

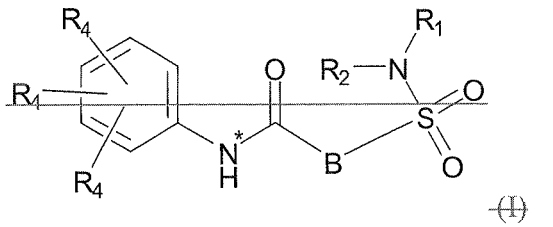
The term "C_{1-3}alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 3. In case C_{1-3}alkyl is coupled to a further radical, it refers to a Formula C_nH_{2n}.. C_{1-3}alkyl groups comprise from 1 to 3 carbon atoms, more 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.

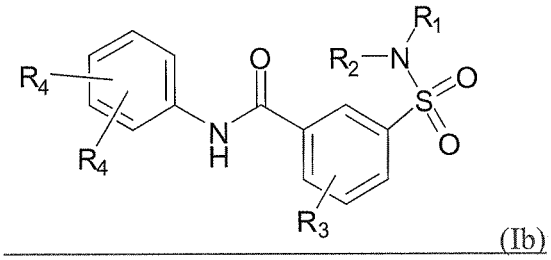
C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylbutyl and the like.

Claims

1. A compound of Formula (Ib)



~~(I)~~



(Ib)

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, all 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, or 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,~~ and 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;

R_3 is selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H, and CF_3;

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;

~~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, or 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;

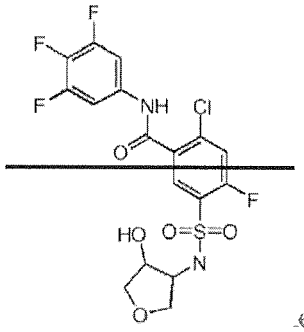
or a pharmaceutically acceptable salt or a solvate thereof.

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.

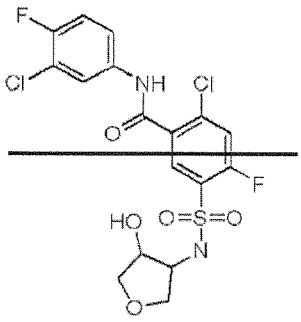
3.2. A compound according to claim 1 or 2 wherein one R_4 represents Fluor and one other R_4 is selected from the group consisting of methyl or CHF_2 and wherein the location of said Fluor is on the *para* position and the location of said methyl or CHF_2 is on the *meta* position related to the Nitrogen(*).

4. The compound according to any one of claims1 to 3, wherein R_2 represents a 4-7 membered saturated ring containing carbon and one or more oxygen atoms, such 4-7 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, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

5. The compound according to any one of claims1 to 3, wherein R_2 represents a 4-7 membered saturated ring containing carbon and one or more oxygen atoms, such 4-7 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, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3 wherein such compound is not

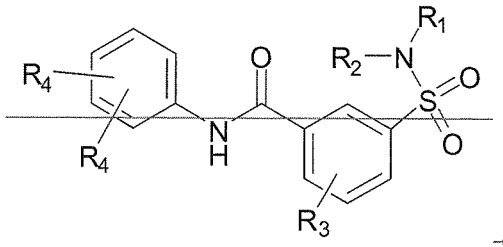


or



6. 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.

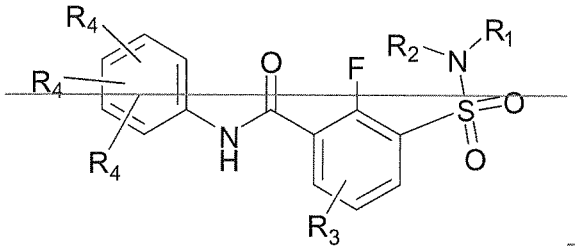
7. A compound for according to any one of the preceding claims, which is of Formula (Ib)



(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.

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

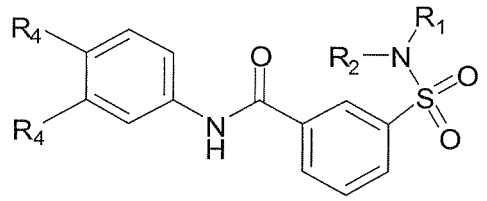


(Id)

~~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.~~

~~9. A compound according to claim 7 or 8, wherein R_3 represents hydrogen.~~

~~10.~~3. A compound ~~for~~ according to any one of the preceding claims, which is of Formula (Ic)



(Ic)

wherein R_1, R_2, R_4 are defined as in any one of the previous claims

4. A compound according to any one of the previous claims for use as a medicine.

~~11.~~5. Use of a ~~A~~ compound according to any one of ~~the previous~~ claims 1 to 3 in the manufacture of a medicament for ~~use in~~ the prevention or treatment of an HBV infection in a mammal.

~~12.~~6. A pharmaceutical composition comprising a compound according to any of claims 1 to ~~10~~3, and a pharmaceutically acceptable carrier.

~~13.~~7. A combined preparation~~product~~ containing (a) a compound ~~of formula I~~ as defined in any one of claims 1 to ~~10~~3, and (b) another HBV inhibitor, ~~as a combined preparation~~ for ~~simultaneous, separate or sequential~~ use in the treatment of HBV infections, said treatment comprising the simultaneous, separate or sequential use of said compound and said HBV inhibitor.