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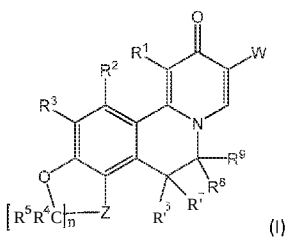
(54) Title: 8,9-FUSED 2-OXO-6,7-DIHYDROPYRIDO-ISOQUINOLINE COMPOUNDS AS ANTIVIRALS



(I)

(57) Abstract: The invention provides compounds of Formula (I) as described herein, along with pharmaceutically acceptable salts, pharmaceutical compositions containing such compounds, and methods to use these compounds, salts and compositions for treating viral infections, particularly infections caused by hepatitis B virus, and reducing the occurrence of serious conditions associated with HBV.

8,9-FUSED 2-OXO-6,7-DIHYDROPYRIDO-ISOQUINOLINE COMPOUNDS AS ANTIVIRALS

FIELD OF THE INVENTION

The present invention relates to novel polycyciic pyridone compounds that are inhibitors of hepatitis virus replication, and are thus useful to treat viral infections, and particularly hepatitis B virus (HBV). The invention provides novel pyridone compounds as disclosed herein, pharmaceutical compositions containing such compounds, and methods of using these compounds and compositions in the treatment and prevention of HBV infections.

BACKGROUND

Globally, over 400 million people are chronically infected with hepatitis B virus (HBV), and more than 12 million reside in the United States alone. Of those chronically infected patients, up to 40 percent will eventually develop complications of liver failure from cirrhosis or development of hepatocellular carcinoma (HCC). HBV belongs to the family of Hepadnaviridae, a group of small hepatotropic DNA viruses that replicate through the reverse transcription of an RNA intermediate. The 3.2-kb HBV genome in viral particles is in a circular, partially double-stranded DNA conformation (relaxed circular DNA or rcDNA). The HBV genome consists of four overlapping open reading frames (ORFs), which encode for the core, polymerase (Pol), envelope, and X proteins. rcDNA is transcriptionally inert and must be converted into covalently closed circular DNA (cccDNA) in the nucleus of infected cells before viral RNAs can be transcribed. cccDNA is the only template for HBV transcription and, because HBV RNA templates genomic reverse transcription, its persistence is required for persistent infection.

The envelope of HBV comprises a mixture of surface antigen proteins (HBsAg). The HBsAg coat is a mixture of three overlapping proteins: ail three share a common region, which corresponds to the smallest of the three proteins (SHBsAg). The mixture consists mostly of SHBsAg, but also includes Medium HBsAg, which comprises SHBsAg plus an additional polypeptide segment, and Large HBsAg, which comprises M HBsAg plus another added polypeptide segment. In addition to forming the infectious virion particle, the S, M and L HBsAg proteins also assemble into a subviral particle knows as the 22-nm particle, which is not infectious but contains the same proteins that envelope the infectious virus pat icles. indeed, these subviral, non-infectious particles have been used as a vaccine, since they contain the same antigenic surface proteins as the infectious HBV virion, and thus elicit antibodies that recognize the infectious agent. Interestingly, these subviral particles greatly outnumber infectious virions, and are believed to protect the infectious

virions from the immune system of the infected host. By sheer numbers, they may act as decoys, distracting immune responses from the infectious virus particles, but in addition they are reported to suppress the function of immune cells (monocytes, dendritic cells and natural killer cells) and may thus impair the immune response to HBV. Because these subviral particles protect infectious HBV from the host immune system, reducing the level of subviral particles has been recognized as a viable therapeutic approach. See, e.g., WO2015/113990.

One of the key diagnostic symptoms of chronic HBV is the high serum levels of the hepatitis B surface antigen (HBsAg). Clinical data in recent years suggest that sustained virologic response is often associated with on-treatment HBsAg decline during the early phase of the treatment as early as week 8, while sustained exposure to HBsAg and other viral antigens may lead to HBV-specific immune-tolerance. Chronic HB patients who experienced larger and faster decreases in serum HBsAg levels achieved significantly higher rate (~40%) of sustained virologic response as defined by sustained viral control post treatment.

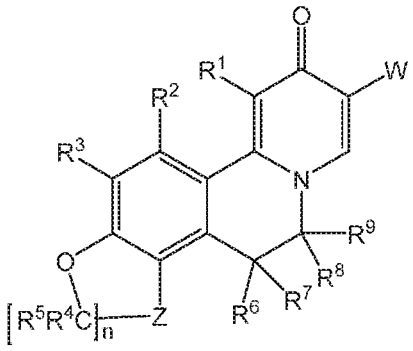
Current treatment options for HBV include interferon therapies and nucleoside/nucleotide inhibitors of the viral DNA polymerase, such as entecavir and tenofovir. These focus on reduction in the level of viremia and toleration of hepatic dysfunction, and may have adverse side-effects and also select for drug-resistant virus variants during long term therapy. More importantly, these therapies cannot eradicate the intrahepatic HBV cccDNA pool in chronic hepatitis B patients or limit the transcription of HBsAg from the pre-existing cccDNA, nor do they affect the secretion of synthesized HBsAg into patients' blood to counteract the host innate immune response. As a result, these HBV treatments are in most cases life-long therapies, and discontinuation often leads to virological relapse.

Accordingly, there remains a need for more effective treatments for HBV, especially for treating chronic HBV infections (cHBV). The invention provides compounds that are believed to operate by suppression of the secretion of the 22 nm subviral particles containing HBsAg. These compounds are useful to treat HBV infections and to reduce the incidence of serious liver disorders caused by HBV infections.

SUMMARY

The present invention provides novel compounds that inhibit secretion of HBsAg from cells infected with hepatitis B virus and thereby reduce viral load and viral replication in patients having chronic HBV infection. Thus the compounds of the invention are suitable for treatment of patients with HBV, including cHBV.

In one aspect, the invention provides compounds of Formula (I):



(I) wherein:

W is -COOR^{10}, -C(0)NH-S0$_2$R, -C(0)NH-S0$_2$NR$_2$, 5-tetrazolyl, or 1,2,4-oxadiazol-3-yl-5(4H)-one;

R^{10} is H or d-C$_6$ alkyl that is optionally substituted with one or two groups selected from halo, -OR, oxo, CN, -NR$_2$, COOR, and CONR$_2$;

R^1 is H, halo, or d-C$_3$ alkyl;

R^2 is H, halo, CN, d-C$_3$ alkyl, d-C$_3$ haloalkyi, or d-C$_3$ alkoxy;

R^3 is H, OH, halo, CN, d-C$_3$ alkyl, C$_3$-C$_6$ cycloalkyl, d-C$_3$ haloalkyi, C$_1$-C$_3$ alkoxy, or d-C$_3$ haloalkoxy;

each R^4 and R^5 is independently selected from H, R^{11}, OH, -OR^{11}, -SR^{11}, -S0$_2$R^{11}, and -NRR^{11}, provided that not more than one group represented by R^4 and R^5 is OH;

R^{11} is d-C$_4$ alkyl, optionally substituted with up to three groups selected from halo, CN, -OR, C$_1$-C$_3$ haloalkoxy, -NR$_2$, -S0$_2$R, and a 4-7 membered heterocyclic group containing one or two heteroatoms selected from N, O and S as ring members that is optionally substituted with one or two groups selected from halo, oxo, CN, R, -OR, and -NR$_2$;

n is 1 or 2;

Z is O or CR$_2$;

R is independently selected at each occurrence from H and d-C$_3$ alkyl optionally substituted with one to three groups selected from halo, -OH, d-C$_3$ alkoxy, oxo, CN, -NH$_2$, -NH(C$_1$-C$_3$ alkyl), -N(d-C$_3$ alkyl)$_2$, and cyclopropyl;

and two R groups directly attached to the same atom, which may be C or N, can optionally be taken together to form a 3-6 membered ring that can optionally contain an added heteroatom selected from N, O and S as a ring member, and can

be substituted by up to two groups selected from -OH, oxo, C_1-C_3 alkyl, and d-d alkoxy;

R^6 is H, halo, d-d alkoxy, or d-d alkyl;

R^7 is H, halo, d-d alkoxy, or d-d alkyl;

R^8 is H or d-d alkyl optionally substituted with up to three groups selected from halo, d-d haloalkyl, OH, d-d alkoxy, and 3-7 membered cycloalkyl;

R^9 is H or d-d alkyl;

or a pharmaceutically acceptable salt thereof.

The invention also provides pharmaceutical compositions containing the novel compounds as well as methods to use the compounds and compositions to inhibit hepatitis B virus replication, and to treat disease conditions associated with or caused by HBV. Further objects of this invention are described in the following description and the examples.

DETAILED DESCRIPTION

For purposes of interpreting this specification, the following definitions will apply, and whenever appropriate, terms used in the singular will also include the plural.

Terms used in the specification have the following meanings unless the context clearly indicates otherwise:

As used herein, the term "subject" refers to an animal. In certain aspects, the animal is a mammal. A subject also refers to for example, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a human. A "patient" as used herein refers to a human subject.

As used herein, the term "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or

"treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

As used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

"Optionally substituted" means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter. The number, placement and selection of substituents is understood to encompass only those substitutions that a skilled chemist would expect to be reasonably stable; thus 'oxo' would not be a substituent on an aryl or heteroaryl ring, for example, and a single carbon atom would not have three hydroxy or amino substituents. Unless otherwise specified, optional substituents are typically up to four groups selected from halo, oxo, CN, amino, hydroxy, -C_{1-3} alkyl, -OR*, -NR^*_2,-SR*, -SO_2R^*, -COOR*, and -$CONR^*_2$, where each R* is independently H or C_{1-3} alkyl.

"Aryl" as used herein refers to a phenyl or naphthyl group unless otherwise specified. Aryl groups unless otherwise specified may be optionally substituted with up to four groups selected from halo, CN, amino, hydroxy, C_{1-3} alkyl, -OR*, -NR^*_2,-SR*, -SO_2R^*, -COOR*, and -$CONR^*_2$, where each R* is independently H or C_{1-3} alkyl.

"Halo" or "halogen", as used herein, may be fluorine, chlorine, bromine or iodine.

"C_{1-6} alkyl" or "C^Ce alkyl", as used herein, denotes straight chain or branched alkyl having 1-6 carbon atoms. If a different number of carbon atoms is specified, such as C_4 or C_3, then the definition is to be amended accordingly, such as "C_{1-4} alkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

"C_{1-6} alkylene" or "C_1-C_6 alkylene", as used herein, denotes straight chain or branched alkyl having 1-6 carbon atoms and two open valences for connection to two other groups. If a different number of carbon atoms is specified, such as C_4 or C_3, then the definition is to be amended accordingly, such as "C_{1-4} alkylene" will represent methylene (-CH_2-), ethylene (-CH_2CH_2-), straight chain or branched propylene (-$CH_2CH_2CH_2$- or -CH_2-CHMe-CH_2-), and the like.

" C_{1-6} alkoxy", as used herein, denotes straight chain or branched alkoxy (-O-Alkyl) having 1-6 carbon atoms. If a different number of carbon atoms is specified, such as C_4 or

C_3, then the definition is to be amended accordingly, such as " C_{i-4} alkoxy" will represent methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy.

" C_{1-4} Haloalkyl" or "C_1-C_4 haloalkyl" as used herein, denotes straight chain or branched alkyl having 1-4 carbon atoms wherein at least one hydrogen has been replaced with a halogen. The number of halogen replacements can be from one up to the number of hydrogen atoms on the unsubstituted alkyl group. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly. Thus " C_{i-4} haloalkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl that have at least one hydrogen substituted with halogen, such as where the halogen is fluorine: CF_3CF_2-, $(CF_3)_2CH$-, CH_3-CF_2-, CF_3CF_2-, CF_3, CF_2H-, $CF_3CF_2CH(CF_3)$- or $CF_3CF_2CF_2CF_2$-.

"C_{3-8} cycloalkyl" as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. If a different number of carbon atoms is specified, such as C_3-C_6, then the definition is to be amended accordingly.

"4- to 8-Membered heterocyclyl", "5- to 6- membered heterocyclyl", "3- to 10-membered heterocyclyl", "3- to 14-membered heterocyclyl", "4- to 14-membered heterocyclyl" and "5- to 14-membered heterocyclyl", refers, respectively, to 4- to 8-membered, 5- to 6-membered , 3- to 10-membered , 3- to 14-membered , 4- to 14-membered and 5- to 14-membered heterocyclic rings; unless otherwise specified, such rings contain 1 to 7, 1 to 5, or 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur as ring members, and the rings may be saturated, or partially saturated but not aromatic. The heterocyclic group can be attached to another group at a nitrogen or a carbon atom. The term "heterocyclyl" includes single ring groups, fused ring groups and bridged groups. Examples of such heterocyclyl include, but are not limited to pyrrolidine, piperidine, piperazine, pyrrolidinone, morpholine, tetrahydrofuran , tetrahydrothiophene, tetrahydrothiopyran, tetrahydropyran, 1,4-dioxane, 1,4-oxathiane, 8-aza-bicyclo[3.2.1 Joctane, 3,8-diazabicyclo[3.2.1 Joctane, 3-Oxa-8-aza-bicyclo[3.2.1 Joctane, 8-Oxa-3-aza-bicyclo[3.2. 1]octane, 2-Oxa-5-aza-bicyclo[2.2. 1]heptane, 2,5-Diaza-bicyclo[2.2.1]heptane, azetidine, ethylenedioxo, oxetane or thiazole. In certain embodiments, if not otherwise specified, heterocyclic groups have 1-2 heteroatoms selected from N, O and S as ring members, and 4-7 ring atoms, and are optionally substituted with up to four groups selected from halo, oxo, CN, amino, hydroxy, C_{1-3} alkyl, -OR*, -NR^*_2,-SR*, -$S0_2R^*$, -COOR*, and -$CONR^*_2$, where each R* is independently H or C_{1-3} alkyl. In particular, heterocyclic groups containing a sulfur atom are optionally substituted with one or two oxo groups on the sulfur.

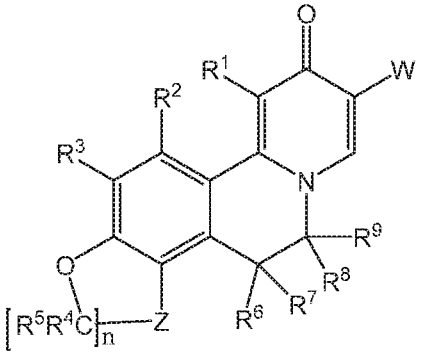
"Heteroaryl" is a completely unsaturated (aromatic) ring. The term "heteroaryl" refers to a 5-14 membered monocyclic- or bicyclic- or tricyclic-aromatic ring system, having

1 to 8 heteroatoms selected from N, O or S. Typically, the heteroaryl is a 5-10 membered ring or ring system (e.g., 5-7 membered monocyclic group or an 8-10 membered bicyclic group), often a 5-6 membered ring containing up to four heteroatoms selected from N, O and S, though often a heteroaryl ring contains no more than one divalent O or S in the ring. Typical heteroaryl groups include furan, isothiazole, thiadiazole, oxadiazole, indazole, indole, quinoline, 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5- pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-(1,2,4-triazolyl), 4- or 5-(1,2, 3-triazolyl), tetrazolyl, triazine, pyrimidine, 2-, 3-, or 4-pyridyl, 3- or 4-pyridazinyl, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, and 2-, 4-, or 5-pyrimidinyl. Heteroaryl groups are optionally substituted with up to four groups selected from halo, CN, amino, hydroxy, C_{1-3} alkyl, -OR*, -NR^*_2,-SR*, -$S0_2R^*$, -COOR*, and -CONR*2, where each R* is independently H or C_{1-3} alkyl.

The term "hydroxy" or "hydroxyl" refers to the group -OH.

Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments. The following enumerated embodiments are representative of the invention:

1. A compound of formula (I):



(I) wherein:

W is -$COOR^{10}$, -C(0)NH-$S0_2R$, -C(0)NH-$S0_2NR_2$, 5-tetrazolyl, or 1,2,4-oxadiazol-3-yl-5(4H)-one;

R^{10} is H or C_1-C_6 alkyl that is optionally substituted with one or two groups selected from halo, -OR, oxo, CN, -NR_2, COOR, and $CONR_2$;

R^1 is H, halo, or d-d alkyl;

R^2 is H, halo, CN, d-C_3 alkyl, d-C_3 haloalkyl, or d-C_3 alkoxy;

R^3 is H, OH, halo, CN, d-C_3 alkyl, C_3-C_6 cycloalkyl, d-C_3 haloalkyl, C_1-C_3 alkoxy, or d-C_3 haloalkoxy;

each R^4 and R^5 is independently selected from H, R^{11}, OH, -OR ^{11}, -SR^{11}, -S0 $_2$R^{11}, and -NRR ^{11}, provided that not more than one group represented by R^4 and R^5 is OH;

R^{11} is *C^-C4* alkyl, optionally substituted with up to three groups selected from halo, CN, -OR, C_1-C_3 haloalkoxy, -NR_2, -S0 $_2$R, and a 4-7 membered heterocyclic group containing one or two heteroatoms selected from N, O and S as ring members that is optionally substituted with one or two groups selected from halo, oxo, CN, R, -OR, and -NR_2;

n is 1 or 2;

Z is O or CR_2;

R is independently selected at each occurrence from H and C_1-C_3 alkyl optionally substituted with one to three groups selected from halo, -OH, C_1-d alkoxy, oxo, CN, -NH_2, -NH(C_1-C_3 alkyl), -N(C $_{1-C\ 3}$ alkyl)$_2$, and cyclopropyl;

and two R groups directly attached to the same atom, which may be C or N, can optionally be taken together to form a 3-6 membered ring that can optionally contain an added heteroatom selected from N, O and S as a ring member, and can be substituted by up to two groups selected from -OH, oxo, C_1-C_3 alkyl, and **C1-C3** alkoxy;

R^6 is H, halo, C_1-C_3 alkoxy, or C_1-C_6 alkyl;

R^7 is H, halo, C_1-C_3 alkoxy, or C_1-C_6 alkyl;

R^8 is H or C_1-C_6 alkyl optionally substituted with up to three groups selected from halo, C_1-C_2 haloalkyl, OH, C_1-C_3 alkoxy, and 3-7 membered cycloalkyl;

R^9 is H or C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to embodiment 1 or a pharmaceutically acceptable salt thereof, wherein R^1 is H.

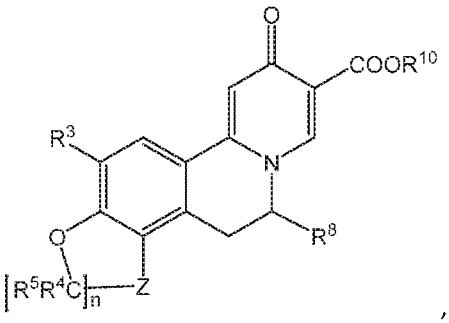
3. A compound according to cl embodiment aim 1 or embodiment 2 or a pharmaceutically acceptable salt thereof, wherein R^2 is H or halo. In certain embodiments, R^2 is H.

4. A compound according to any one of embodiments 1 to 3 or a pharmaceutically acceptable salt thereof, wherein R^3 is C_1-C_3 alkoxy or halo. In particular embodiments, R^3 is -OMe (methoxy) or Cl.

5. A compound according to any of the preceding embodiments or a pharmaceutically acceptable salt thereof, wherein W is $COOR^{10}$, where R^{10} is H or C_1-C_6 alkyl. In some embodiments, R^{10} is H. Furthermore, in some of these embodiments Z is CH_2.

6. A compound according to any of the preceding embodiments or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are both H.

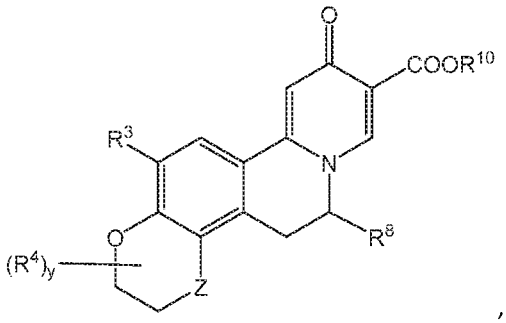
7. A compound according to any of the preceding embodiments or a pharmaceutically acceptable salt thereof, which is of the formula:



,

wherein R^8 is C_1-C_6 alkyl optionally substituted with up to three groups selected from halo, OH, and C_1-C_3 alkoxy. In some of these embodiments, n is 1. In other of these embodiments, n is 2.

8. A compound according to any of embodiments 1-7, which is of the formula:



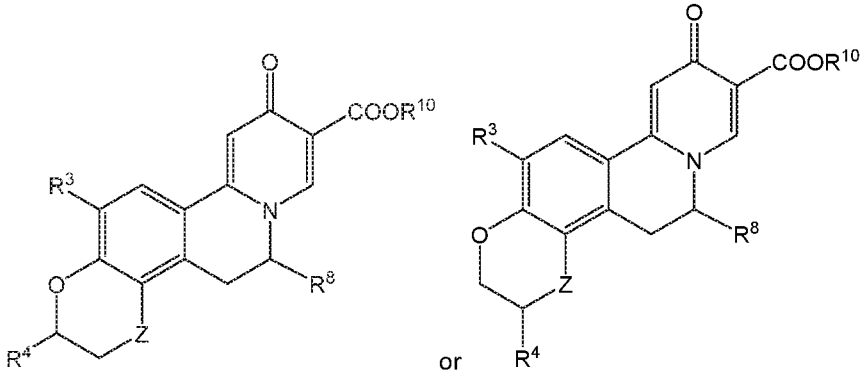
,

wherein R^4 is selected from H, R^{11}, and -OR^{11};

y is 1 or 2;

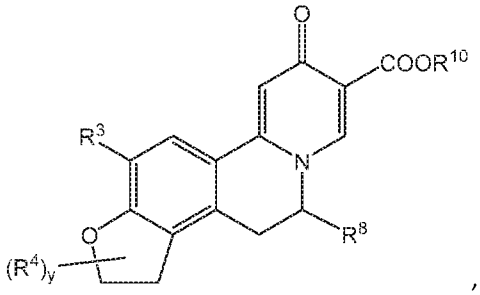
or a pharmaceutically acceptable salt thereof.

In particular embodiments of these compounds, the compound is of one of these two formulas:



In some of these embodiments, Z is CH_2.

9. A compound according to any of embodiments 1-7, which is of the formula:

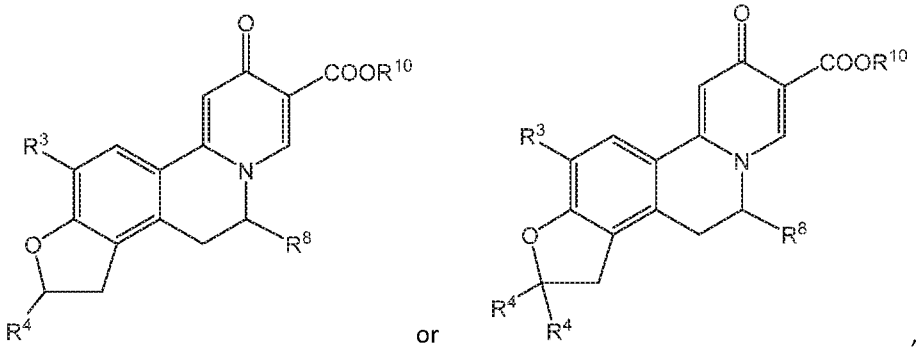


wherein R^4 is selected from H, R^{11}, and $-OR^{11}$;

y is 1 or 2;

or a pharmaceutically acceptable salt thereof.

In some of these embodiments, the compound is of one of the following two formulas:



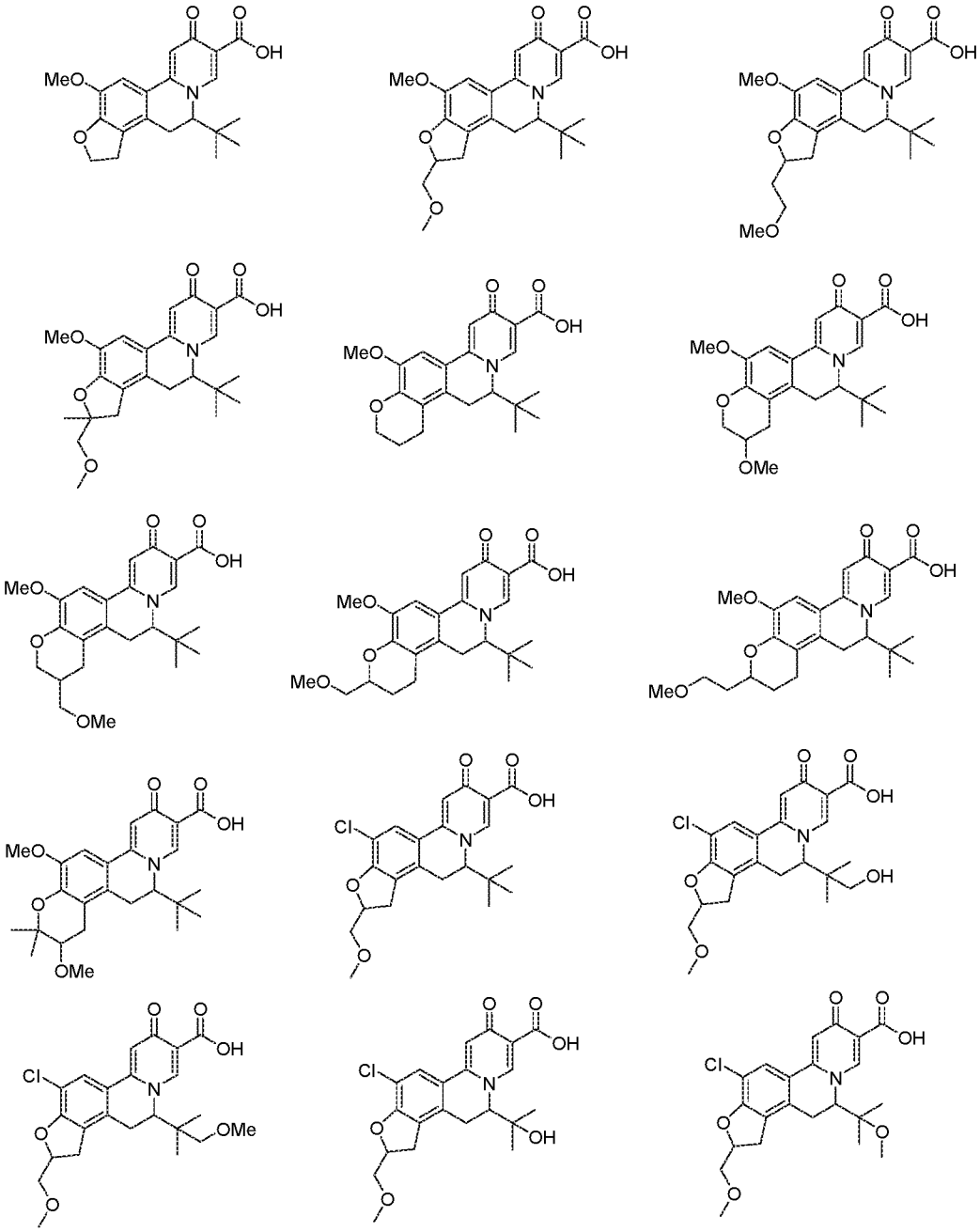
where R^4 is selected from R^{11} and $-OR^{11}$.

10. A compound according to any of the preceding embodiments or a pharmaceutically acceptable salt thereof, wherein each R^{11} is C_1-C_4 alkyl, substituted with up to two groups selected from -OR, C_1-C_3 haloalkoxy, and halo.

11. A compound according to any of embodiments 1-10 or a pharmaceutically acceptable salt thereof, wherein each R^{11} is selected from -CH_2OMe, -CH_2CH_2OMe, -$CH_2CH_2CH_2OMe$, -CH_2-OEt, -CH_2-OH, -CH_2CH_2-OH, and -$CH_2CH_2CH_2$-OH.

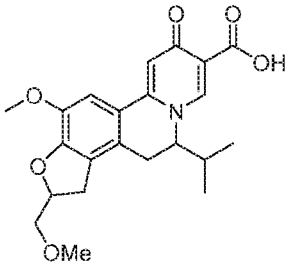
12. A compound according to any of the preceding embodiments or a pharmaceutically acceptable salt thereof, wherein R^8 is isopropyl, t-butyl, 2-methoxyprop-2-yl, 2-hydroxyprop-2-yl, 2-hydroxymethylprop-2-yl, or 2-methoxymethylprop-2-yl.

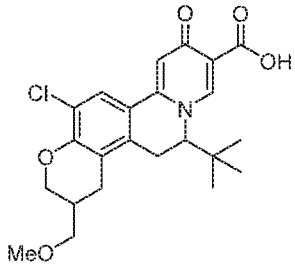
13. A compound selected from:

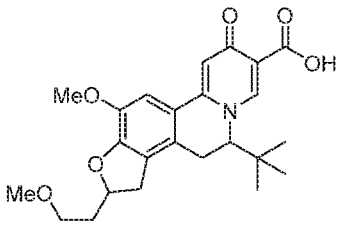


or a pharmaceutically acceptable salt thereof.

14. The compound of embodiment 1, which is selected from:



,


and


,

and the pharmaceutically acceptable salts thereof.

15. A pharmaceutical composition, comprising a compound of any of the preceding embodiments admixed with at least one pharmaceutically acceptable carrier.

16. A method to treat a hepatitis B infection, which comprises administering to a patient having a hepatitis B infection a compound of any of embodiments 1-14 or a pharmaceutical composition of embodiment 15.

17. The method of embodiment 16, wherein the compound of any one of embodiments 1-14 or the pharmaceutical composition of embodiment 15 is used in combination with an additional therapeutic agent selected from an interferon or peginterferon, an HBV polymerase inhibitor, a viral entry inhibitor, a viral maturation inhibitor, a capsid assembly inhibitor, an HBV core modulator, a reverse transcriptase inhibitor, a TLR-agonist, or an immunomodulator.

18. A method to inhibit replication of hepatitis B virus, which comprises contacting the hepatitis B virus, either in vitro or in vivo, with a compound according to any one of embodiments 1-14.

20. A compound of any of embodiments 1-14 for use in therapy. Alternatively, this can be use of a compound of any of embodiments 1-14 in the manufacture of a medicament.

21. The compound of embodiment 20 for use to treat a subject infected with hepatitis B virus (HBV). Alternatively, this can be the use of embodiment 20 in the manufacture of a medicament for treatment of a hepatitis B virus infection.

22. A pharmaceutical combination, comprising a compound of any of embodiments 1-14 and at least one additional therapeutic agent. Preferably, the additional therapeutic agent is an antiviral.

Another embodiment of the invention provides a compound as described above, or a pharmaceutically acceptable salt thereof, for use as a medicament. In one aspect, the medicament is for treatment of a subject having an HBV infection. In a particular embodiment, the subject is a human diagnosed with chronic HBV.

Also within the scope of this invention is the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament. Preferably, the medicament is for the treatment or prevention of a viral disease and/or infection in a human being, including HBV.

Included within the scope of this invention is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. Optionally, the composition comprises two or more pharmaceutically acceptable carriers and/or excipients.

According to a further aspect of this embodiment the pharmaceutical composition according to this invention further comprises a therapeutically effective amount of at least one other antiviral agent. Preferably, the other antiviral agent is one useful to treat HBV.

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of a HBV infection in a human being having or at risk of having the infection.

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of HBV infection in a human being having or at risk of having the disease.

Another aspect of the invention involves a method of treating or preventing a hepatitis B viral disease and/or infection in a human being by administering to the human being an antivirally effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof, or a composition comprising a compound of the invention, as described above, alone or in combination with at least one other antiviral agent, administered together or separately.

An additional aspect of this invention refers to an article of manufacture comprising a composition effective to treat a hepatitis B viral disease and/or infection; and packaging material comprising a label which indicates that the composition can be used to treat disease and/or infection by a hepatitis B virus; wherein the composition comprises a compound of formula (I) according to this invention or a pharmaceutically acceptable salt thereof.

Still another aspect of this invention relates to a method of inhibiting the replication of HBV, comprising exposing the virus to an effective amount of the compound of formula (I), or a salt thereof, under conditions where replication of the virus is inhibited. This method can be practiced in vitro or in vivo.

Further included in the scope of the invention is the use of a compound of formula (I), or a salt thereof, to inhibit the replication of HBV.

In all of the embodiment referring to a compound of Formula (I), the compound of Formula (I) can be a compound according to any of embodiments 1-14 described above.

In some embodiments, the compound of Formula (I) is co-administered with or used in combination with at least one additional therapeutic agent selected from: an interferon or peginterferon , an HBV polymerase inhibitor, a viral entry inhibitor, a viral maturation inhibitor, a capsid assembly inhibitor, an HBV core modulator, a reverse transcriptase inhibitor, a TLR-agonist, or an immunomodulator. Optionally, the compound of Formula (I) may be prepared for simultaneous or sequential use in combination with an additional therapeutic agent; or the compound of Formula (I) may be combined into a pharmaceutical combination comprising a compound of Formula (I) and at least one additional therapeutic agent. Some particular therapeutic agents that may be used in combination with the compounds of the invention include immunomodulators described herein, interferon alfa 2a, interferon alfa-2b, pegylated interferon alfa-2a, pegylated interferon alfa-2b, TLR-7 and TLR-9 agonists, entecavir, tenofovir, cidofovir, telbivudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine, apricitabine, atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, adefovir, efavirenz, nevirapine, delavirdine, and etravirine. Suitable core modulators are disclosed in WO2013/096744; suitable HBV capsid inhibitors are described in US2015/0252057.

These additional agents may be combined with the compounds of this invention to create a single pharmaceutical dosage form. Alternatively these additional agents may be separately administered to the patient as part of a multiple dosage form, for example, using a kit. Such additional agents may be administered to the patient prior to, concurrently with, or following the administration of a compound of the invention, or a pharmaceutically acceptable salt thereof. Alternatively, these additional therapeutic agents may be administered separately from and optionally by different routes of administration and on different dosing schedules from the compound of the invention, provided the compound of the invention and the additional therapeutic agent are used concurrently for treatment of an HBV infection or a disorder caused or complicated by an HBV infection.

The dose range of the compounds of the invention applicable per day is usually from 0.01 to 100 mg/kg of body weight, preferably from 0.1 to 50 mg/kg of body weight. Each dosage unit may conveniently contain from 5% to 95% active compound (w/w). Preferably such preparations contain from 20% to 80% active compound.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the combination will be

administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

When the composition of this invention comprises a combination of a compound of the invention and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of a virus in a human being, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a human being. Such agents can be selected from entecavir, tenofovir, cidofovir, telbivudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine, apricitabine, atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, adefovir, efavirenz, nevirapine, delavirdine, and etravirine, and immunomodulators described herein including interferons and pegylated interferons, TLR-7 agonists, and TLR-9 agonists.

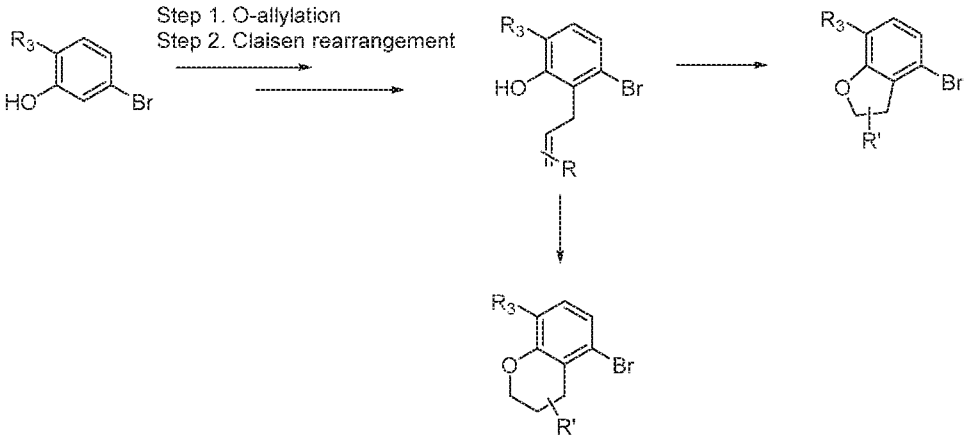
Many compounds of the invention contain one or more chiral centers. These compounds may be made and used as single isomers or as mixtures of isomers. Methods for separating the isomers, including diastereomers and enantiomers, are known in the art, and examples of suitable methods are described herein. In certain embodiments, the compounds of the invention are used as a single substantially pure isomer, meaning at least 90% of a sample of the compound is the specified isomer and less than 10% of the sample is any other isomer or mixture of isomers. Preferably, at least 95% of the sample is a single isomer. Selection of a suitable isomer is within the ordinary level of skill, as one isomer will typically be more active in the in vivo or in vitro assay described herein for measuring HBV activity, and will be the preferred isomer. Where in vitro activity differences between isomers are relatively small, e.g. less than about a factor of 4, a preferred isomer may be selected based on activity level against viral replication in cell culture, using methods such as those described herein: the isomer having a lower MIC (minimum inhibitory concentration) or EC-50 is preferred.

The compounds of the invention may be synthesized by the general synthetic routes illustrated below, specific examples of which are described in more detail in the Examples.

A versatile intermediate useful to make many compounds of the invention is readily prepared from meta-bromophenols as illustrated in Scheme 1. This provides an ortho-allylphenol, which can be used by known methods to form benzo-dihydrofuran and benzo-dihydropyran compounds. The choice of conditions for this cyclization can provide further opportunities to functionalize the newly-formed ring. The Examples that follow illustrate such methods, and persons of skill in the art will recognize modifications and variations that can

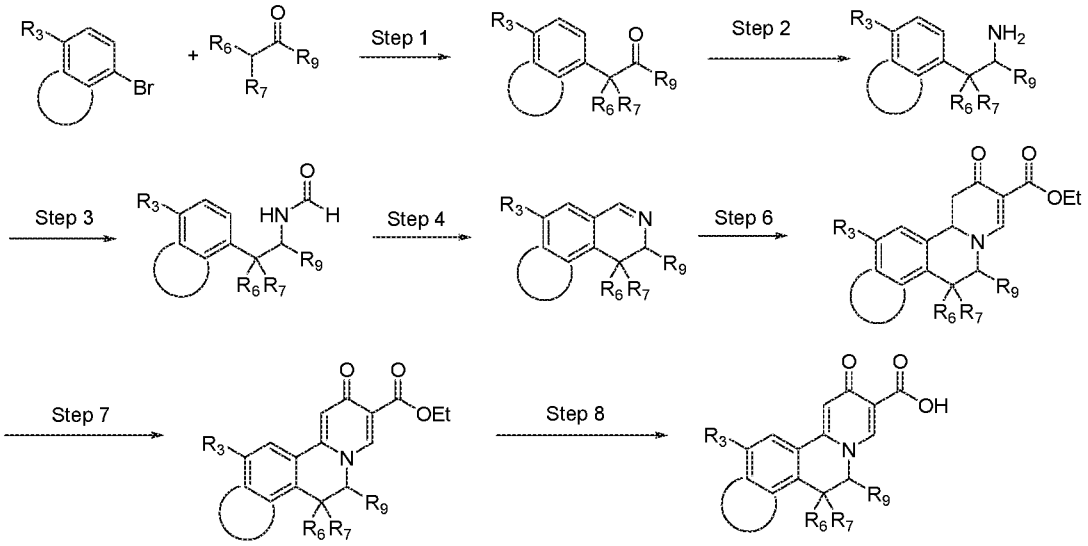
be used to make many other compounds within the scope of the invention. Some intermediates useful to synthesize compounds of Formula (I) are known in the art. Additional guidance for synthesis of the compounds of Formula (I) and synthetic intermediates useful for these syntheses are disclosed in published PCT applications WO2015/113990 and WO2015/173164.

Scheme 1. General method to synthesize key intermediates.



These and similar brominated bicyclic compounds can be elaborated to provide compounds of Formula (I) by methods such as those illustrated in Scheme 2 and the Examples herein. Step 1 in this scheme can be accomplished by a palladium-catalyzed coupling of the arylbromide with an enolate. Step 2 involves a reductive amination to convert the carbonyl from step 1 into an amine. The amine can then be formylated by conventional methods, and cyclized under electrophilic conditions (e.g., heating with $POCl_3$) to provide the dihydroisoquinoline. In steps 6 and 7, the pyridone is constructed by cyclocondensation of the dihydroisoquinoline by heating with ethyl (Z)-2-(ethoxymethylene)-3-oxobutanoate, followed by mild oxidation to convert the dihydropyridone to a pyridone. Finally, if desired, the ester can be hydrolyzed to give the free acid (step 8).

Scheme 2. General method to synthesize compounds of Formula (I).



The term "an optical isomer" or "a stereoisomer" refers to any of the various stereoisomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. The term "chiral" refers to molecules which have the property of non-superimposability on their mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-.

Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The

present invention is meant to include all such possible stereoisomers, including racemic mixtures, diasteriomeric mixtures and optically pure forms. Optically active (R)- and (S)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration . If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration . All tautomeric forms are also intended to be included.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers or diastereomers, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound . In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid , diacetyl tartaric acid, di-O.O'-p-toluoyl tartaric acid, mandelic acid, malic acid or camphor-1 0-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Furthermore, the compounds of the present invention , including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization . The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The compounds of the present invention , including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

As used herein, the terms "salt" or "salts" refers to an acid addition or base addition salt of a compound of the present invention. "Salts" include in particular "pharmaceutically acceptable salts". The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of

the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, subsalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts:

Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Any formula given herein is intended to represent unlabeled forms as well as isotopically labeled forms of the compounds of the present invention having up to three atoms with non-natural isotope distributions, e.g., sites that are enriched in deuterium or ^{13}C or ^{15}N. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number other than the natural-abundance mass distribution. Examples of isotopes that can be usefully over-incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes, such as ^{3}H and ^{14}C, or those in which non-radioactive isotopes, such as ^{2}H and ^{13}C are present at levels substantially above normal isotope distribution. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C, for example), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F labeled compound of the present invention may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent typically employed. Labeled samples may be useful with quite low isotope incorporation, such as where a radiolabel is used to detect trace amounts of the compound.

Further, more extensive substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D), may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the present invention, and typically a sample of a compound having deuterium as a substituent has at least 50% deuterium incorporation at the labeled position(s). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least

4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d^6-acetone, d^6-DMSO.

Compounds of the present invention that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of the present invention by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of the present invention with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of the present invention.

Methods of Use

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

The compounds of the invention can be administered by known methods, including oral, parenteral, inhalation, and the like. In certain embodiments, the compound of the invention is administered orally, as a pill, lozenge, troche, capsule, solution, or suspension. In other embodiments, a compound of the invention is administered by injection or infusion. Infusion is typically performed intravenously, often over a period of time between about 15 minutes and 4 hours. In other embodiments, a compound of the invention is administered intranasally or by inhalation; inhalation methods are particularly useful for treatment of respiratory infections. Compounds of the present invention exhibit oral bioavailability, so oral administration is sometimes preferred.

In certain embodiments of the present invention, a compound of the present invention is used in combination with a second antiviral agent, such as those named herein.

By the term "combination", is meant either a fixed combination in one dosage unit form, as separate dosage forms suitable for use together either simultaneously or sequentially, or as a kit of parts for the combined administration where a compound of the

present invention and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g., synergistic, effect, or any combination thereof.

The second antiviral agent may be administered in combination with the compounds of the present inventions wherein the second antiviral agent is administered prior to, simultaneously, or after the compound or compounds of the present invention. When simultaneous administration of a compound of the invention with a second agent is desired and the route of administration is the same, then a compound of the invention may be formulated with a second agent into the same dosage form. An example of a dosage form containing a compound of the invention and a second agent is a tablet or a capsule.

In some embodiments, a combination of a compound of the invention and a second antiviral agent may provide synergistic activity. The compound of the invention and second antiviral agent may be administered together, separate but simultaneously, or sequentially.

An "effective amount" of a compound is that amount necessary or sufficient to treat or prevent a viral infection and/or a disease or condition described herein. In an example, an effective amount of a compound of Formula I is an amount sufficient to treat viral infection in a subject. In another example, an effective amount is an amount sufficient to treat HBV in a subject in need of such treatment. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound of the invention. For example, the choice of the compound of the invention can affect what constitutes an "effective amount." One of ordinary skill in the art would be able to study the factors contained herein and make the determination regarding the effective amount of the compounds of the invention without undue experimentation.

The regimen of administration can affect what constitutes an effective amount. The compound of the invention can be administered to the subject either prior to or after the onset of a viral infection. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compound(s) of the invention can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

Compounds of the invention may be used in the treatment of states, disorders or diseases as described herein, or for the manufacture of pharmaceutical compositions for use in the treatment of these diseases. The invention provides methods of use of compounds of the present invention in the treatment of these diseases or for preparation of pharmaceutical compositions having compounds of the present invention for the treatment of these diseases.

The language "pharmaceutical composition" includes preparations suitable for administration to mammals, e.g., humans. When the compounds of the present invention

are administered as pharmaceuticals to mammals, e.g., humans, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of at least one compound of Formula (I) or any subgenus thereof as active ingredient in combination with a pharmaceutically acceptable carrier, or optionally two or more pharmaceutically acceptable carriers.

The phrase "pharmaceutically acceptable carrier" is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present invention to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth ; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations. Typically, pharmaceutically acceptable carriers are sterilized and/or substantially pyrogen-free.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, a-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, inhalation, topical, transdermal, buccal, sublingual, rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and

may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound that produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored base, for example, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant

(for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro¬encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluent commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed , groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring , coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth , and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a

suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration may comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable carriers such as sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, glycol ethers, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable

mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc., administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Intravenous infusion is sometimes a preferred method of delivery for compounds of the invention. Infusion may be used to deliver a single daily dose or multiple doses. In some embodiments, a compound of the

invention is administered by infusion over an interval between 15 minutes and 4 hours, typically between 0.5 and 3 hours. Such infusion may be used once per day, twice per day or up to three times per day.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound , drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration .

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention , which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration , without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration , the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed , the age, sex, weight, condition , general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required . For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved .

In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated effects, will range from about 0.0001 to about 100 mg per kilogram of

body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 0.1 to about 20 mg per kg per day. An effective amount is that amount which prevents or treats a viral infection, such as HBV.

Treatment with a compound or composition described herein may be repeated daily for a period sufficient to reduce or substantially eliminate an HBV infection or viral load. For example, treatment may be continued for a week, or two weeks, or 3-4 weeks, or 4-8 weeks, or 8-12 weeks, or longer, e.g., until viral load or other measure of infection shows a substantial reduction in viral load or viral activity or other signs or symptoms of HBV infection. The skilled treating physician can readily determine a suitable duration of treatment.

If desired, the effective daily dose of the active compound may be administered as a single dose per day, or as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Compounds delivered orally or by inhalation, are commonly administered in one to four doses per day. Compounds delivered by injection are typically administered once per day, or once every other day. Compounds delivered by infusion are typically administered in one to three doses per day. When multiple doses are administered within a day, the doses may be administered at intervals of about 4 hours, about 6 hours, about 8 hours or about 12 hours.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical composition such as those described herein. Thus methods of using the compounds of the invention include administering the compound as a pharmaceutical composition, wherein at least one compound of the invention is admixed with a pharmaceutically acceptable carrier prior to administration.

Use of Compounds of the Invention in combination with immunomodulators

The compounds and compositions described herein can be used or administered in combination with one or more therapeutic agents that act as immunomodulators, e.g., an activator of a costimulatory molecule, or an inhibitor of an immune-inhibitory molecule, or a vaccine. The Programmed Death 1 (PD-1) protein is an inhibitory member of the extended CD28/CTLA4 family of T cell regulators (Okazaki et al. (2002) Curr Opin Immunol 14: 391 779-82; Bennett et al. (2003) J. Immunol. 170:71 1-8). PD-1 is expressed on activated B cells, T cells, and monocytes. PD-1 is an immune-inhibitory protein that negatively regulates TCR signals (Ishida, Y. et al. (1992) EMBO J. 11:3887-3895; Blank, C. et al. (Epub 2006 Dec. 29) Immunol. Immunother. 56(5):739-745), and is up-regulated in chronic infections. The interaction between PD-1 and PD-L1 can act as an immune checkpoint, which can lead to, e.g., a decrease in infiltrating lymphocytes, a decrease in T-cell receptor

mediated proliferation, and/or immune evasion by cancerous or infected cells (Dong et al. (2003) J. Mol. Med. 81:281-7; Blank et al. (2005) Cancer Immunol. Immunother. 54:307-314; Konishi et al. (2004) Clin. Cancer Res. 10:5094-100). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1 or PD-L2; the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwai et al. (2002) Proc. Nat'l. Acad. Sci. USA 99: 12293-7; Brown et al. (2003) J. Immunol. 170: 1257-66). Immunomodulation can be achieved by binding to either the immune-inhibitory protein (e.g., PD-1) or to binding proteins that modulate the inhibitory protein (e.g., PD-L1, PD-L2).

In one embodiment, the combination therapies of the invention include an immunomodulator that is an inhibitor or antagonist of an inhibitory molecule of an immune checkpoint molecule. In another embodiment the immunomodulator binds to a protein that naturally inhibits the immuno-inhibitory checkpoint molecule. When used in combination with antiviral compounds, these immunomodulators can enhance the antiviral response, and thus enhance efficacy relative to treatment with the antiviral compound alone.

The term "immune checkpoints" refers to a group of molecules on the cell surface of CD4 and CD8 T cells. These molecules can effectively serve as "brakes" to down-modulate or inhibit an adaptive immune response. Immune checkpoint molecules include, but are not limited to, Programmed Death 1 (PD-1), Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), B7H1, B7H4, OX-40, CD137, CD40, and LAG3, which directly inhibit immune cells. Immunotherapeutic agents which can act as immune checkpoint inhibitors useful in the methods of the present invention, include, but are not limited to, inhibitors of PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta. Inhibition of an inhibitory molecule can be performed by inhibition at the DNA, RNA or protein level. In some embodiments, an inhibitory nucleic acid (e.g., a dsRNA, siRNA or shRNA), can be used to inhibit expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is a polypeptide, e.g., a soluble ligand, or an antibody or antigen-binding fragment thereof, that binds to the inhibitory molecule.

By "in combination with," it is not intended to imply that the therapy or the therapeutic agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope described herein. The immunomodulator can be administered concurrently with, prior to, or subsequent to, one or more compounds of the invention, and optionally one or more additional therapies or therapeutic agents. The therapeutic agents in the combination can be administered in any order. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. It will further be appreciated that the therapeutic agents utilized in this combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that each of the therapeutic agents utilized in combination be utilized at levels that do not exceed the levels at which

they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

In certain embodiments, the antiviral compounds described herein are administered in combination with one or more immunomodulators that are inhibitors of PD-1 , PD-L1 and/or PD-L2. Each such inhibitor may be an antibody, an antigen binding fragment thereof, an immunoadhesin , a fusion protein , or an oligopeptide. Examples of such immunomodulators are known in the art.

In some embodiments, the immunomodulator is an anti-PD-1 antibody chosen from MDX-1 106, Merck 3475 or CT- 011.

In some embodiments, the immunomodulator is an immunoadhesin (e.g. , an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-LI or PD-L2 fused to a constant region (e.g. , an Fc region of an immunoglobulin sequence).

In some embodiments, the immunomodulator is a PD-1 inhibitor such as AMP-224.

In some embodiments, the the immunomodulator is a PD-LI inhibitor such as anti-PD-LI antibody.

In some embodiments, the immunomodulator is an anti-PD-LI binding antagonist chosen from YW243. 55. S70, MPDL3280A, MEDI-4736, MSB-001 071 8C, or MDX-1 105. MDX-1 105, also known as BMS-936559, is an anti-PD-LI antibody described in WO2007/005874. Antibody YW243.55.S70 is an anti-PD-LI described in WO 201 0/077634.

In some embodiments, the immunomodulator is nivolumab (CAS Registry Number: 94641 4-94-4). Alternative names for nivolumab include MDX-1 106, MDX-1 106-04, ONO-4538, or BMS-936558. Nivolumab is a fully human lgG4 monoclonal antibody which specifically blocks PD-1 . Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD-1 are disclosed in US 8,008,449, EP21 6 1336 and WO2006/1 2 1168.

In some embodiments, the immunomodulator is an anti-PD-1 antibody Pembrolizumab. Pembrolizumab (also referred to as Lambrolizumab, MK-3475, MK03475, SCH-900475 or KEYTRUDA®; Merck) is a humanized lgG4 monoclonal antibody that binds to PD-1 . Pembrolizumab and other humanized anti-PD-1 antibodies are disclosed in Hamid, O. et al. (201 3) New England Journal of Medicine 369 (2): 134-44, US 8,354,509, WO2009/1 14335, and WO201 3/0791 74.

In some embodiments, the immunomodulator is Pidilizumab (CT-01 1; Cure Tech), a humanized lgG1 k monoclonal antibody that binds to PD1 . Pidilizumab and other humanized anti-PD-1 monoclonal antibodies are disclosed in WO2009/1 0161 1.

Other anti-PD1 antibodies useful as immunomodulators for use in the methods disclosed herein include AMP 514 (Amplimmune) , and anti-PD1 antibodies disclosed in US 8,609,089, US 201 0028330, and/or US 201 201 14649. In some embodiments, the anti-PD-LI antibody is MSB001 071 8C. MSB001 071 8C (also referred to as A09-246-2; Merck

Serono) is a monoclonal antibody that binds to PD-L1 .

In some embodiments, the immunomodulator is MDPL3280A (Genentech / Roche), a human Fc optimized lgG1 monoclonal antibody that binds to PD-L1 . MDPL3280A and other human monoclonal antibodies to PD-L1 are disclosed in U.S. Patent No.: 7,943,743 and U.S Publication No.: 201 20039906. Other anti-PD-L1 binding agents useful as immunomodulators for methods of the invention include YW243.55.S70 (see WO20 10/077634), MDX-1 105 (also referred to as BMS-936559), and anti-PD-L1 binding agents disclosed in WO2007/005874.

In some embodiments, the immunomodulator is AMP-224 (B7-DCIg; Amplimmune; e.g., disclosed in WO201 0/027827 and WO201 1/066342), is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD1 and B7-H1 .

In some embodiments, the immunomodulator is an anti-LAG-3 antibody such as BMS-98601 6. BMS-98601 6 (also referred to as BMS98601 6) is a monoclonal antibody that binds to LAG-3. BMS-98601 6 and other humanized anti-LAG-3 antibodies are disclosed in US 201 1/01 50892, WO201 0/01 9570, and WO201 4/00821 8

In certain embodiments, the combination therapies disclosed herein include a modulator of a costimulatory molecule or an inhibitory molecule, e.g., a co-inhibitory ligand or receptor.

In one embodiment, the costimulatory modulator, e.g., agonist, of a costimulatory molecule is chosen from an agonist (e.g., an agonistic antibody or antigen-binding fragment thereof, or soluble fusion) of OX40, CD2, CD27, CDS, ICAM-1 , LFA-1 (CD1 1a/CD1 8), ICOS (CD278), 4-1 BB (CD1 37), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD1 60, B7-H3 or CD83 ligand .

In another embodiment, the combination therapies disclosed herein include an immunomodulator that is a costimulatory molecule, e.g., an agonist associated with a positive signal that includes a costimulatory domain of CD28, CD27, ICOS and/or GITR.

Exemplary GITR agonists include, e.g., GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies), such as, a GITR fusion protein described in U.S. Patent No.: 6,111,090, European Patent No.: 090505B1 , U.S Patent No.: 8,586,023, PCT Publication Nos.: WO 201 0/0031 18 and 201 1/090754, or an anti-GITR antibody described, e.g., in U.S. Patent No.: 7,025,962, European Patent No.: 19471 83B1 , U.S. Patent No.: 7,81 2,135, U.S. Patent No.: 8,388,967, U.S. Patent No.: 8,591 ,886, European Patent No.: EP 1866339, PCT Publication No.: WO 201 1/028683, PCT Publication No. :WO 201 3/039954, PCT Publication No.: WO2005/0071 90, PCT Publication No.: WO 2007/1 33822, PCT Publication No.: WO2005/055808, PCT Publication No.: WO 99/401 96, PCT Publication No.: WO 2001 /03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/1 15451 , U.S. Patent No.: 7,61 8,632, and PCT Publication No.: WO 201 1/051 726.

In one embodiment, the immunomodulator used is a soluble ligand (e.g., a CTLA-4-lg), or an antibody or antibody fragment that binds to PD-L1, PD-L2 or CTLA4. For example, the anti-PD-1 antibody molecule can be administered in combination with an anti-CTLA-4 antibody, e.g., ipilimumab, for example. Exemplary anti-CTLA4 antibodies include Tremelimumab (IgG2 monoclonal antibody available from Pfizer, formerly known as ticilimumab, CP-675,206); and Ipilimumab (CTLA-4 antibody, also known as MDX-010, CAS No. 477202-00-9).
In one embodiment, an anti-PD-1 antibody molecule is administered after treatment with a compound of the invention as described herein.

In another embodiment, an anti-PD-1 or PD-L1 antibody molecule is administered in combination with an anti-LAG-3 antibody or an antigen-binding fragment thereof. In another embodiment, the anti-PD-1 or PD-L1 antibody molecule is administered in combination with an anti-TIM-3 antibody or antigen-binding fragment thereof. In yet other embodiments, the anti-PD-1 or PD-L1 antibody molecule is administered in combination with an anti-LAG-3 antibody and an anti-TIM-3 antibody, or antigen-binding fragments thereof. The combination of antibodies recited herein can be administered separately, e.g., as separate antibodies, or linked, e.g., as a bispecific or trispecific antibody molecule. In one embodiment, a bispecific antibody that includes an anti-PD-1 or PD-L1 antibody molecule and an anti-TIM-3 or anti-LAG-3 antibody, or antigen-binding fragment thereof, is administered. In certain embodiments, the combination of antibodies recited herein is used to treat a cancer, e.g., a cancer as described herein (e.g., a solid tumor). The efficacy of the aforesaid combinations can be tested in animal models known in the art. For example, the animal models to test the synergistic effect of anti-PD-1 and anti-LAG-3 are described, e.g., in Woo et al. (2012) Cancer Res. 72(4):917-27).

Exemplary immunomodulators that can be used in the combination therapies include, but are not limited to, e.g., afutuzumab (available from Roche®); pegfilgrastim (Neulasta®); lenalidomide (CC-5013, Revlimid®); thalidomide (Thalomid®), actimid (CC4047); and cytokines, e.g., IL-21 or IRX-2 (mixture of human cytokines including interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics).

Exemplary doses of such immunomodulators that can be used in combination with the antiviral compounds of the invention include a dose of anti-PD-1 antibody molecule of about 1 to 10 mg/kg, e.g., 3 mg/kg, and a dose of an anti-CTLA-4 antibody, e.g., ipilimumab, of about 3 mg/kg.

Examples of embodiments of the methods of using the antiviral compounds of the invention in combination with an immunomodulator include these, which may be used along with a compound of Formula I or any subgenus or species thereof that is disclosed herein:

i. A method to treat a viral infection in a subject, comprising administering to the subject a compound of Formula (I) as described herein, and an immunomodulator.

ii. The method of embodiment i, wherein the immunomodulator is an activator of a costimulatory molecule or an inhibitor of an immune checkpoint molecule.

iii. The method of either of embodiments i and ii, wherein the activator of the costimulatory molecule is an agonist of one or more of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD1 1a/CD1 8), ICOS (CD278), 4-1 BB (CD1 37), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD1 60, B7-H3 and CD83 ligand.

iv. The method of any of embodiments i-iii above, wherein the inhibitor of the immune checkpoint molecule is chosen from PD-1, PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD1 60, 2B4 and TGFR beta.

v. The method of any of any of embodiments i-iii, wherein the inhibitor of the immune checkpoint molecule is chosen from an inhibitor of PD-1, PD-L1, LAG-3, TIM-3 or CTLA4, or any combination thereof.

vi. The method of any of embodiments i-v, wherein the inhibitor of the immune checkpoint molecule is a soluble ligand or an antibody or antigen-binding fragment thereof, that binds to the immune checkpoint molecule.

vii. The method of any of embodiments i-vi, wherein the antibody or antigen-binding fragment thereof is from an lgG1 or lgG4 (e.g., human lgG1 or lgG4).

viii. The method of any of embodiments i-vii, wherein the antibody or antigen-binding fragment thereof is altered, e.g., mutated, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function.

ix. The method of any of embodiments i-viii, wherein the antibody molecule is a bispecific or multispecific antibody molecule that has a first binding specificity to PD-1 or PD-L1 and a second binding specifity to TIM-3, LAG-3, or PD-L2.

x. The method of any of embodiments i-ix, wherein the immunomodulator is an anti-PD-1 antibody chosen from Nivolumab, Pembrolizumab or Pidilizumab.

xi. The method of any of embodiments i-x, wherein the immunomodulator is an anti-PD-L1 antibody chosen from YW243.55.S70, MPDL3280A, MEDI-4736, MSB-001 071 8C, or MDX-1 105.

xii. The method of any of embodiments i-x, wherein the immunomodulator is an anti-LAG-3 antibody molecule.

xiii. The method of embodiment xii, wherein the anti-LAG-3 antibody molecule is BMS-98601 6.

xiv. The method of any of embodiments i-x, wherein the immunomodulator is an anti-PD-1 antibody molecule administered by injection (e.g., subcutaneously or intravenously) at a dose of about 1 to 30 mg/kg, e.g., about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5

mg/kg, or about 3 mg/kg., e.g., once a week to once every 2, 3, or 4 weeks.

xv. The method of embodiment xiv, wherein the anti-PD-1 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week.

xvi. The method of embodiment xv, wherein the anti-PD-1 antibody molecule, e.g., nivolumab, is administered intravenously at a dose from about 1 mg/kg to 3 mg/kg, e.g., about 1 mg/kg, 2 mg/kg or 3 mg/kg, every two weeks.

xvii. The method of embodiment xv, wherein the anti-PD-1 antibody molecule, e.g., nivolumab, is administered intravenously at a dose of about 2 mg/kg at 3-week intervals.

The compounds as described herein may be synthesized by the general synthetic routes below, specific examples of which are described in more detail in the Examples.

General Synthetic Procedures

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesize the compounds of the invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). General methods for synthesis of compounds of the invention are illustrated by the Examples below, and by methods disclosed in published PCT applications WO2015/113990 and WO2015/173164.

LIST OF ABBREVIATIONS

Ac	acetyl
ACN	Acetonitrile
AcOEt / EtOAc	Ethyl acetate
AcOH	acetic acid
aq	aqueous
Bn	benzyl
Bu	butyl (nBu = n-butyl, tBu = tert-butyl)
CDI	Carbonyldiimidazole
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
Boc20	di-tert-butyl dicarbonate
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DiBAI-H	Diisobutylaluminum Hydride
DIPEA	N-Ethyldiisopropylamine
DMA	N,N-dimethylacetamide

DMAP	Dimethylaminopyridine
DMF	N,N'-Dimethylformamide
DMSO	Dimethylsulfoxide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	Electrospray ionisation
Et_20	Diethylether
Et_3N	Triethylamine
Ether	Diethylether
EtOAc	Ethyl acetate
EtOH	Ethanol
FA	Formic acid
FC	Flash Chromatography
h	hour(s)
HCI	Hydrochloric acid
HOBt	1-Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
H_20	Water
IPA	isopropanol
L	liter(s)
LC-MS	Liquid Chromatography Mass Spectrometry
LiHMDS	Lithium bis(trimethylsilyl)amide
Me	methyl
Mel	Iodomethane
MeOH	Methanol
mg	milligram
min	minute(s)
mL	milliliter
MS	Mass Spectrometry
Pd/C	palladium on charcoal
PG	protecting group
Ph	phenyl
Ph_3P	triphenyl phosphine
Prep	Preparative
Rf	ratio of fronts
RP	reverse phase
Rt	Retention time
rt	Room temperature
SFC	Supercritical Fluid Chromatography

SiO_2	Silica gel
T3P®	Propylphosphonic acid anhydride
TBAF	Tetrabutylammonium fluoride
TBDMS	t-Butyldimethylsilyl
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TsCl	toluene sulfonyl chloride

Within the scope of this text, a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group," unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as e.g., Science of Synthesis: Houben-Weyl Methods of Molecular Transformation . Georg Thieme Verlag , Stuttgart, Germany. 2005. 4 1627 pp. (URL: http://www.science-of-synthesis.com (Electronic Version, 48 Volumes)); J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981 , in "Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition , Volume 15/1 , Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosauren, Peptide, Proteine" (Amino acids, Peptides, Proteins), Verlag Chemie, Weinheim, Deerfield Beach , and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e., without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (e.g. , by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g. , the sodium salt of 2-ethyl hexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine,

stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, e.g., by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, e.g., a free carboxy group and a free amino group, may be formed, e.g., by the neutralization of salts, such as acid addition salts, to the isoelectric point, e.g., with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallization and/or chromatographic separation, for example over silica gel or by, e.g., medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallization, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, e.g., using chromatographic methods, distribution methods, (re-) crystallization, and the like.

EXAMPLES

The invention is illustrated by the following examples, which should not be construed as limiting. The assays used to demonstrate the efficacy of compounds of Formula (I) in these assays are generally regarded as predictive of efficacy in subjects.

General Conditions:

Mass spectra were run on LC-MS systems using electrospray ionization. These were WATERS Acquity Single Quard Detector. $[M+H]^+$ refers to mono-isotopic molecular weights. NMR spectra were run on open access Varian 400 or Varian 500 NMR spectrometers. Spectra were measured at 298K and were referenced using the solvent peak. Chemical shifts for ^1H NMR are reported in parts per million (ppm).

Mass spectra were run on LC-MS systems with one of the following conditions:

1. Waters Acquity UPLC-H class system equipped with SQD detector.

Column: ACQUITY UPLC HSS C18 (50*2.1) mm, 1.8u.

Column temperature: Ambient.

Mobile Phase: A) 0.1 % FA + 5mM Ammonium Acetate in Water.

B) 0.1 % FA in Acetonitrile.

Gradient: 5-5% solvent B in 0.40 min, 5-35% solvent B in 0.80 min, 35-55%solvent B in 1.2 min,

55-1 00%solvent B in 2.5 min.

Flow rate: 0.55ml_/min.

Compounds were detected by a Waters Photodiode Array Detector.

2. Waters LCMS system equipped with ZQ 2000 detector.

Column: X-BRIDGE C18 (50*4.6) mm, 3.5u.

Column temperature: Ambient.

Mobile Phase: A) 0.1 % NH_3 in Water.

B) 0.1 % NH_3 in Acetonitrile.

Gradient: 5-95% solvent B in 5.00 min.

Flow rate: 1.OmL/min.

Compounds were detected by a Waters Photodiode Array Detector.

3. Waters ACQUITY UPLC system and equipped with a ZQ 2000 MS system.

Column: Kinetex by Phenomenex, 2.6 urn, 2.1 x 50mm

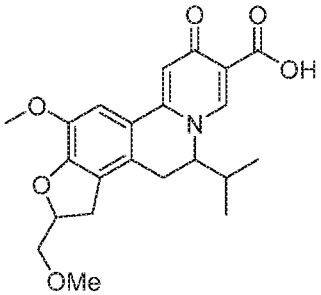
Column temperature: 50 °C

Gradient: 2-88% (or 00-45%, or 65-95%) solvent B over a 1.29 min period

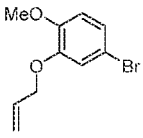
Flow rate: 1.2ml_/min.

Compounds were detected by a Waters Photodiode Array Detector.

Example 1.1 Synthesis of 5-isopropyl-12-methoxy-2-(methoxymethyl)-9-oxo-2, 3,4,9-tetrahydro-5H-furo[3,2-f]pyrido[2,1 -a]isoquinoline-8-carboxylic acid [1.1]



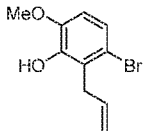
Step 1: 2-(Allyloxy)-4-bromo-1-methoxybenzene [1.1a]



A round bottom flask was charged with 5-bromo-2-methoxyphenol (15.0 g, 73.9 mmol), allylbromide (11.6 g, 96 mmol), K_2C0_3 (20.4 g, 148 mmol) and acetone (185 ml_). The mixture was heated at 60 oC for 3 hours. After cooled to rt, the mixture was filtered and the

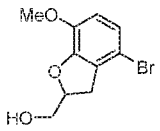
filtrate was concentrated to give product (17.9 g, 100% yield). The mixture was continued to the next step with no further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 3.84 (s, 3 H), 4.49 - 4.63 (m, 2 H), 5.31 (m, 1 H), 5.41 (m, 1 H), 5.92 - 6.16(m, 1 H), 6.74 (m, 1 H), 6.98 (m, 1 H), 7.01 -7.04 (m, 1H).

Step 2. 2-Allyl-3-bromo-6-methoxyphenol [1.1b]



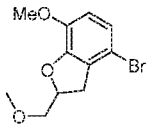
A sealed tube was charged with 2-(allyloxy)-4-bromo-1 -methoxybenzene (14.0 g) and DMF (14.4 ml_) and then purged with nitrogen. The solution was heated at 200 oC for 3 hours. The solvent was then removed under reduced pressure and the residue was purified by silica gel column chromatography, EtOAc/heptane 0 to 50%, to give product (12 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 3.57 (dt, J=6.09, 1.38 Hz, 2 H), 3.87 (s, 3 H), 4.98 - 5.14 (m, 2 H), 5.80 (s, 1 H), 5.95 (m, 1 H), 6.63 (d, J=8.71 Hz, 1 H), 7.06 (d, J=8.66 Hz, 1 H).

Step 3. (4-Bromo-7-methoxy-2,3-dihydrobenzofuran-2-yl)methanol [1.1c]



To a solution of 2-allyl-3-bromo-6-methoxyphenol (5.7g, 23.45 mmol) in DCM (47 ml_) at 0 °C was added mCPBA (12.14 g, 50%, 35.2 mmol) and the resulting mixture was stirred at rt for 2 hours. The reaction was quenched by adding sat. aq. $Na_2S_2O_3$ solution, and sat. aq. $NaHCO_3$ solution and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in MeOH (50 ml_) and K_2CO_3 (9.7 g, 70 mmol) was added. The mixture was then stirred at rt for 2 hours and then filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography, EtOAc/heptane 0 to 60% to give product (3.9 g, 64 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): 3.01 - 3.44 (m, 2 H), 3.70 - 3.81 (m, 1 H), 3.85 (s, 3 H), 3.88 - 4.05 (m, 1 H), 4.88 - 5.10 (m, 1 H), 6.64 (d, J=8.61 Hz, 1 H), 6.94 (d, J=8.66 Hz, 1 H).

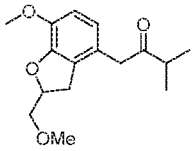
Step 4. 4-Bromo-7-methoxy-2-(methoxymethyl)-2,3-dihydrobenzofuran [1.1d]



To a solution of (4-Bromo-7-methoxy-2,3-dihydrobenzofuran-2-yl)methanol (3.9 g, 15 mmol) in DMF (15 mL) at 0 °C was added NaH (1.2 g, 60%, 30 mmol). After stirring at rt for 20 mins, the mixture was placed in an ice water bath and MeI (6.4 g, 45 mmol) was added and the mixture was stirred at rt for 2 hours. The reaction was quenched by adding sat. aq. NH_4Cl solution. The mixture was then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated . The residue was purified by silica

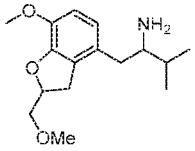
gel column chromatography, EtOAc/heptane 0 to 40% to give product (3.6 g, 88% yield). LCMS (m/z): 273.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 3.05 - 3.16 (m, 1 H), 3.20 - 3.34 (m, 1 H), 3.37 - 3.52 (m, 3 H), 3.55 - 3.71 (m, 2 H), 3.83 (s, 3 H), 5.01 (ddt, J=9.58, 7.90, 4.90, 4.90 Hz, 1 H), 6.62 (d, J=8.66 Hz, 1 H) 6.91 (d, J=8.66 Hz, 1 H).

Step 5. 1-(7-methoxy-2-(methoxymethyl)-2,3-dihydrobenzofuran-4-yl)-3-methylbutan-2-one [1.1e]



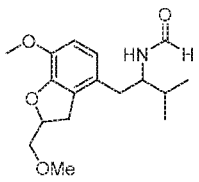
A sealed tube was charged with 4-Bromo-7-methoxy-2-(methoxymethyl)-2,3-dihydrobenzofuran (600 mg, 2.2 mmol), $Pd_2(dba)_3$ (60 mg, 0.066 mmol), xantphos (76 mg, 0.132 mmol), sodium tert-butoxide (697 mg, 7.25 mmol) and was flushed under nitrogen. Toluene (7.3 m) and 3-methylbutan-2-one (568 mg, 6.6 mmol) was added. The resulting mixture was heated at 70 °C for 6 hours. After cooled at rt, the mixture was diluted with EtOAc and washed with sat. aq NH_4Cl solution, water, brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography, EtOAc/heptane 0 to 50% to give product (400 mg, 65% yield). ^1H NMR (400 MHz, $CDCl_3$): 1.10 (s, 6 H) 2.71 (spt, J=6.90 Hz, 1 H) 2.97 (dd, J=15.43, 7.75 Hz, 1 H) 3.14 (dd, J=15.41, 9.44 Hz, 1 H) 3.41 (s, 3 H), 3.56 - 3.71 (m, 4 H) 3.84 (s, 3 H) 4.91 - 5.04 (m, 1 H) 6.58 - 6.64 (m, 1 H) 6.67 - 6.73 (m, 1 H) 10.07 - 10.83 (m, 1 H). LCMS (m/z): 279.5 $[M+H]^+$

Step 6. 1-(7-methoxy-2-(methoxymethyl)-2,3-dihydrobenzofuran-4-yl)-3-methylbutan-2-amine [1.1f]



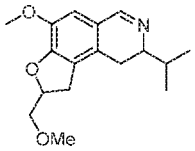
To a solution of **1.1e** (400 mg, 1.4 mmol) in MeOH (4.8 mL) was added ammonium acetate (775 mg, 10 mmol) and sodium cyanoborohydride (181 mg, 2.9 mmol). After being stirred at rt for 18 hours, the reaction was quenched by adding 10% NaOH aq solution and stirred at rt for 30 mins. The mixture was then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude material was continued to the next step with no further purification. LCMS (m/z): 280.2 $[M+H]^+$

Step 7. N-(1-(7-methoxy-2-(methoxymethyl)-2,3-dihydrobenzofuran-4-yl)-3-methylbutan-2-yl)formamide [1.1g]



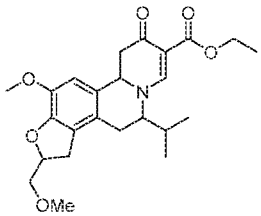
A mixture of formic acid (264 mg, 5.7 mmol) and acetic anhydride (292 mg, 2.86 mmol) was heated at 60 °C for 30 mins. After cooled at rt, the mixture was added to a solution of **1.1e** (400mg, 1.4 mmol) in dioxane (2.8 mL) and the resulting solution was stirred at 60 °C for 2 hours. The solvent was removed and the residue was purified by silica gel column chromatography, acetone/heptane 0 to 60% to give product (400 mg, 91% yield). LCMS (m/z): 308.7 $[M+H]^+$.

Step 8. 8-isopropyl-4-methoxy-2-(methoxymethyl)-1 ,2,8,9-tetrahydrofuro[3,2-fjisoquinoline [1.1h]



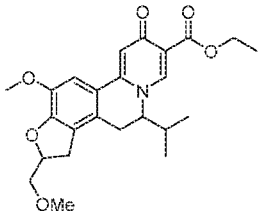
$POCl_3$ (203 mg, 1.3 mmol) was added to a solution of **1.1g** (370 mg, 1.2 mmol) in CH_3CN (4.0 mL) and the resulting solution was stirred at 70 °C for 2 hours. The solvent was then removed under reduced pressure and the remaining material was dissolved in EtOAc, basified by adding ammonium hydroxide solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography, acetone/heptane 20% to 100% to give product (300 mg, 86%). LCMS (m/z): 291.5 $[M+H]^+$.

Step 9. ethyl 5-isopropyl-1 2-methoxy-2-(methoxymethyl)-9-oxo-2, 3,4,9, 10,1 0a-hexahydro-5H-furo[3,2-f]pyrido[2,1 -a]isoquinoline-8-carboxylate [1.1i]



A solution of **1.1h** (300 mg, 1.0 mmol) and ethyl (Z)-2-(ethoxymethylene)-3-oxobutanoate (579 mg, 3.1 mmol) in EtOH (2.0 mL) was heated at 110 °C for 18 hours. The solvent was the removed under reduced pressure and the crude material was continued to the next step with no further purification. LCMS (m/z): 430.2 $[M+H]^+$.

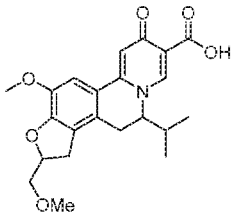
Step 10. Ethyl 5-isopropyl-1 2-methoxy-2-(methoxymethyl)-9-oxo-2,3,4,9-tetrahydro-5H-furo[3,2-f]pyrido[2,1-a]isoquinoline-8-carboxylate [1.1j]



p-Chloroanil (306 mg) was added to a solution of **1.1i** (445 mg, 1.0 mmol) in DME (2.0 mL) and the resulting solution was stirred at 100 °C for 2 hours. After cooling to rt, the mixture

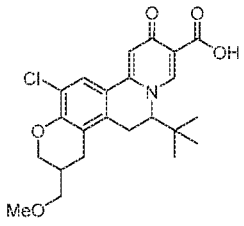
was concentrated and the remaining material was purified by silica gel column chromatography, EtOac/heptane 0 to 40% to give product (300 mg, 68% yield). LCMS (m/z): 428.6 $[M+H]^+$.

Step 11. 5-isopropyl-12-methoxy-2-(methoxymethyl)-9-oxo-2,3,4,9-tetrahydro-5H-furo[3,2-f]pyrido[2,1-a]isoquinoline-8-carboxylic acid [1.1]

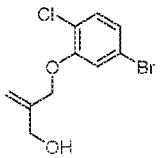


A solution of LiOH (0.23 mL, 1.0 M solution in water, 0.23 mmol) was added to a solution of 1.1j (100 mg, 0.234 mmol) in THF (0.46 mL) and the resulting solution was stirred at rt for 1 hour. The solution was then acidified by adding 1.0 N HCl aq solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in DMSO and purified by reverse phase HPLC to give product (40 mg, 42%). LCMS (m/z): 400.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): 0.67-0.69 (m, 3 H), 0.81-0.85 (m, 3 H), 1.55 - 1.68 (m, 1 H), 2.91 - 3.14 (m, 2 H), 3.18-3.34 (m, 2 H), 3.29 (m, 3 H), 3.52 - 3.59 (m, 2 H), 3.85 (m, 3 H), 4.41-4.45 (m, 1 H), 5.04 - 5.17 (m, 1 H), 7.38 (s, 1 H), 7.44 (s, 1 H), 8.74 (s, 1 H)

Example 2.1. 6-(tert-butyl)-13-chloro-3-(methoxymethyl)-10-oxo-3,4,5,10-tetrahydro-2H,6H-pyrano[3,2-f]pyrido[2,1-a]isoquinoline-9-carboxylic acid [2.1]



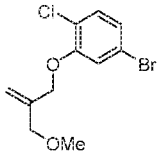
Step 1. 2-((5-bromo-2-chlorophenoxy)methyl)prop-2-en-1-ol [2.1a]



To a solution of 5-bromo-2-chlorophenol (5.0 g, 24.1 mmol) in DMF (48 mL) at 0 °C was added NaH (1.15 g, 60% in mineral oil, 28.9 mmol) and the solution was then stirred at rt for 30 mins. 5-methylene-1,3,2-dioxathiane 2-oxide (3.2 g, 24.1 mmol) was then added and the resulting mixture was heated at 55 °C for 4 hours. The reaction was quenched by adding sat. aq. NH_4Cl solution. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by

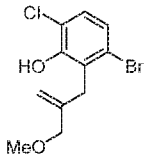
silica gel column chromatography, EtOAc/heptane 0 to 60% to give product (4.0 g, 60%). LCMS (m/z): 400.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 4.29 (s, 2 H) 4.65 (s, 2 H) 5.33 (d, J=1 .03 Hz, 2 H) 7.01 - 7.10 (m, 2 H) 7.22 (d, J=8.41 Hz, 1 H).

Step 2. 4-bromo-1-chloro-2-((2-(methoxymethyl)allyl)oxy)benzene [2.1 b]



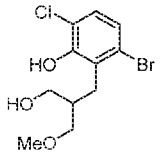
To a solution of **2.1 a** (3.9 g, 14.0 mmol) in DMF (14 mL) at 0 °C was added NaH (0.84 g, 60% in mineral oil, 21 mmol). After stirring at rt for 20 mins, MeI (4.0 g, 28.1 mmol) was added and the resulting mixture was stirred at rt for 2 hours. The reaction was quenched by adding sat. aq. NH_4Cl solution and then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography, EtOAc/heptane 0 to 40% to give product (4.0 g, 98% yield). ^1H NMR (400 MHz, $CDCl_3$): 3.36 (s, 3 H), 3.98 - 4.11 (m, 2 H), 4.59 (s, 2 H), 5.30 (d, J=1 .03 Hz, 1 H), 5.39 (s, 1 H), 7.03 (dd, J=8.39, 2.13 Hz, 1 H), 7.07 (d, J=2.10 Hz, 1 H), 7.21 (d, J=8.41 Hz, 1 H).

Step 3. 3-bromo-6-chloro-2-(2-(methoxymethyl)allyl)phenol [2.1 c]



A solution of **2.1 b** (3.9 g) in DMF (4.0 mL) was heated at 200 °C for 3 hours. After being cooled to rt, the material was purified by silica gel column chromatography, EtOAc/heptane 0 to 40% to give product. LCMS (m/z): 293.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 3.42 (s, 3 H) 3.61 (s, 2 H) 3.94 (s, 2 H) 4.97 (d, **J=1 .12** Hz, 1 H) 5.12 (d, J=1 .08 Hz, 1 H) 7.26 (s, 1 H) 7.29 (s, 1 H).

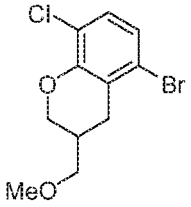
Step 4. 3-bromo-6-chloro-2-(3-hydroxy-2-(methoxymethyl)propyl)phenol [2.1 d]



To a solution of **2.1 c** (3.5 g, 12.0 mmol) in THF (30.0 mL) at 0 °C was added borane-methyl sulfide complex (2.28 ml, 24.0 mmol). After stirring at rt for 2 hours, the solution was cooled in an ice water bath and quenched by slow adding 5 mL of water followed by NaOH (5.0 M solution in water, 12 mL, 60.0 mmol) and sodium perborate (9.2 g, 60 mmol). The resulting mixture was heated at 50 °C for 1 hour and then at rt acidified by adding 5.0 N HCl solution. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column

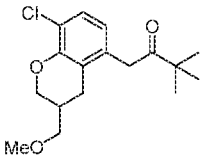
chromatography, EtOAc/heptane 0 to 60% to give product (3.2 g, 86% yield). LCMS (m/z): 311.0 $[M+H]^+$.

Step 5. 5-bromo-8-chloro-3-(methoxymethyl)chromane [2.1e]



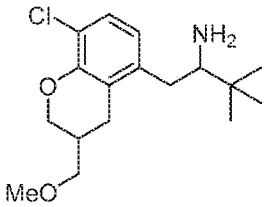
To a solution of **2.1d** (3.2 g, 10.3 mmol) in DCM (50 mL) at 0 °C was added PPh_3 (3.5 g, 13.4 mmol) followed by diethyl azodicarboxylate (2.16 g, 12.4 mmol). After stirring at rt for 18 hours, the solvent was removed and to the remaining residue was added diethyl ether. The white precipitate was filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography, EtOAc/heptane 0 to 30% to give product (2.4 g, 80 % yield). LCMS (m/z): 291.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 2.30 - 2.42 (m, 1 H) 2.47 - 2.59 (m, 1 H) 2.85 (ddd, J=17.20, 5.91, 1.39 Hz, 1 H) 3.37 (s, 3 H) 3.39 - 3.49 (m, 2H) 3.99 (dd, J=10.71, 8.31 Hz, 1 H) 4.26 - 4.45 (m, 1 H) 7.02 - 7.11 (m, 2 H)

Step 6. 1-(8-chloro-3-(methoxymethyl)chroman-5-yl)-3,3-dimethylbutan-2-one [2.1f]



A sealed tube was charged with **2.1e** (2.4 g, 8,2 mmol), $Pd_2(dba)_3$ (226 mg, 0.25 mmol), xantphos (286 mg, 0.49 mmol), sodium tert-butoxide (1.98 g, 20.6 mmol) and was flushed under nitrogen. THF (16.5 mL) and 3,3-dimethylbutan-2-one (2.5 g, 24.7 mmol) was added. The resulting mixture was heated at 70 °C for 18 hours. After cooled at rt, the mixture was diluted with EtOAc and washed with sat. aq NH_4Cl solution, water, brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography, EtOAc/heptane 0 to 50% to give product (2.1 g, 82% yield). LCMS (m/z): 311.7 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 1.09 - 1.31 (m, 9 H) 2.25 - 2.46 (m, 2 H) 2.53 - 2.75 (m, 1 H) 3.34 (s, 2 H) 3.35 - 3.47 (m, 2 H) 3.76 (s, 2 H) 3.95 - 4.11 (m, 1 H) 4.34 (dd, J=10.66, 3.03 Hz, 1 H) 6.55 (d, J=8.12 Hz, 1 H) 7.13 (d, J=8.07 Hz, 1 H).

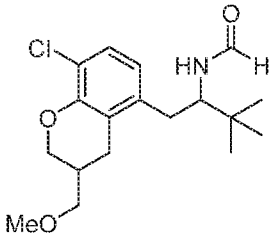
Step 7. 1-(8-chloro-3-(methoxymethyl)chroman-5-yl)-3,3-dimethylbutan-2-amine [2.1g]



To a solution of **2.1f** (2.1 g, 6.8 mmol) in MeOH (20 mL) was added ammonium acetate (5.2 g, 67.6 mmol) and sodium cyanoborohydride (849 mg, 13.5 mmol). After stirred at 60 °C for

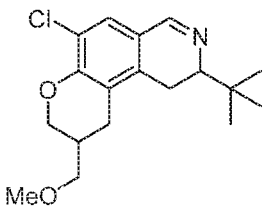
18 hours, the reaction was quenched by adding 10% NaOH aq solution and stirred at rt for 30 mins. The mixture was then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude material was continued to the next step with no further purification. LCMS (m/z): 312.1 $[M+H]^+$

Step 8. Synthesis of N-(1-(8-chloro-3-(methoxymethyl)chroman-5-yl)-3,3-dimethylbutan-2-yl)formamide [2.1 h]



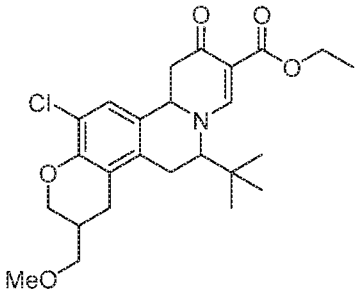
To a solution of **2.1 g** (2.1 g, 6.73 mmol) in DMF at 0 °C was added EDC (2.58 g, 13.47 mmol) and DIPEA (3.53 ml, 20.2 mmol) followed by dropwise addition of formic acid (1.2 g, 26.9 mmol) and the resulting mixture was stirred at rt for 1 hours. The solvent was then removed under reduced pressure and water was added. The precipitate was collected by filtration. The collected solid was purified by silica gel column chromatography, EtOAc/heptane, 0 to 100%. To give product (1.7 g, 74% yield). LCMS (m/z): 340.3 $[M+H]^+$.

Step 9. Synthesis of 2-(tert-butyl)-6-chloro-9-(methoxymethyl)-1,8,9,10-tetrahydro-2H-pyrano[3,2-f]isoquinoline [2.1 i]



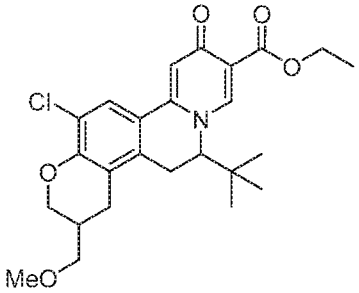
$POCl_3$ (840 mg, 5.5 mmol) was added to a solution of **2.1 h** (1.7 g, 5.0 mmol) in CH_3CN (25.0 mL) and the resulting solution was stirred at 70 °C for 1 hour. The solvent was then removed under reduced pressure and the remaining material was dissolved in EtOAc, and basified by adding ammonium hydroxide solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography, EtOAc/heptane 20% to 100% to give product (1.4 g, 87%). LCMS (m/z): 322.4 $[M+H]^+$.

Step 10. ethyl 6-(tert-butyl)-13-chloro-3-(methoxymethyl)-10-oxo-3,4,5,10,11,11a-hexahydro-2H,6H-pyrano[3,2-f]pyrido[2,1-a]isoquinoline-9-carboxylate [2.1j]



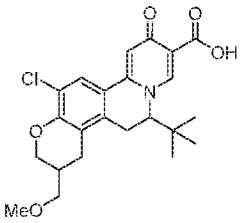
A solution of **2.1 i** (1.4g, 4.3 mmol) and ethyl (Z)-2-(ethoxymethylene)-3-oxobutanoate (2.4 g, 13.0 mmol) in EtOH (4.3 ml_) was heated at 110 °C for 18 hours. The solvent was then removed under reduced pressure and the crude material was continued to the next step with no further purification. LCMS (m/z): 462.3 $[M+H]^+$.

Step 11. ethyl 6-(tert-butyl)-1 3-chloro-3-(methoxymethyl)-1 0-oxo-3,4,5,1 0-tetrahydro-2H,6H-pyrano[3,2-f]pyrido[2,1 -a]isoquinoline-9-carboxylate [2.1 k]



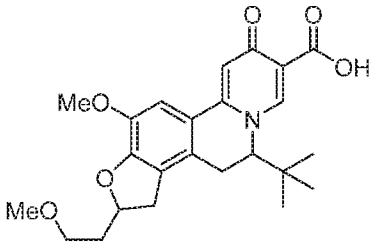
p-Chloroanil (1.3 g, 5.2 mmol) was added to a solution of **2.1j** (2.0 g, 4.3 mmol) in DME (4.3 ml_) and the resulting solution was stirred at 100 °C for 1 hours. After cooling to rt, the precipitate was collected by filtration and washed with diethyl ether to give product (1.1 g, 55% yield). LCMS (m/z): 460.3 $[M+H]^+$.

Step 12. 6-(tert-butyl)-1 3-chloro-3-(methoxymethyl)-1 0-oxo-3,4,5,1 0-tetrahydro-2H,6H-pyrano[3,2-f]pyrido[2,1 -a]isoquinoline-9-carboxylic acid [2.1]

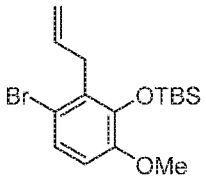


To a solution of **2.1 k** (100 mg, 0.217 mmol) in THF was added LiOH (1.0 M in water, 0.43 mmol) and the mixture was stirred at rt for 1 hour. The solution was concentrated and the remaining solution was acidified by adding 1.0 N HCI aq. solution. The precipitate was collected by filtration and further purified by reverse phase HPLC, CH_3CN/water with TFA as modifier to give product (70 mg, 74% yield). LCMS (m/z): 432.6 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-c/6): 0.73 (m, 9 H), 2.28 - 2.66 (m, 2 H), 2.75 - 2.99 (m, 1 H), 3.16 - 3.24 (m, 2 H), 3.29 (m, 3 H), 3.34 - 3.46 (m, 2 H), 3.99 - 4.15 (m, 1 H), 4.34 - 4.49 (m, 1 H), 4.64-4.66 (br, 1 H), 7.39 (s, 1 H), 8.06 (s, 1 H), 8.75 (s, 1 H).

Example 3. Synthesis of 5-(tert-butyl)-12-methoxy-2-(2-methoxyethyl)-9-oxo-2,3,4,9-tetrahydro-5H-furo[3,2-f]pyrido[2,1-a]isoquinoline-8-carboxylic acid [3]

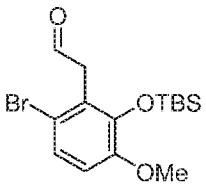


Step 1: (2-allyl-3-bromo-6-methoxyphenoxy)(tert-butyl)dimethylsilane [3a]



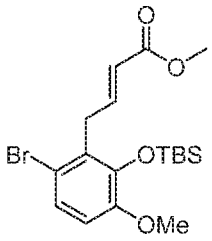
To the solution of **1.1b** (23 g) in dry DCM (230 mL) was added TBSOTf (30 g, 1.20 eq) and TEA (14.3 g. 1.5 eq) at 0 °C. After stirring at rt for 3 hours, cold water was added and the reaction mixture was extracted in EtOAc. The organic layers were combined, washed with water, brine, dried over Na_2SO_4 and concentrated. ^{1}H NMR (400 MHz, DMSO-d_6): 7.16 (m, 1 H), 6.87 (m, 1 H), 5.84 (m, 1 H), 5.01 (m, 1 H), 4.85 (m, 1 H), 3.76 (m, 3 H), 3.50 (m, 2 H), 0.94 (m, 9 H), 0.21 - 0.10 (m, 6 H).

Step 2: 2-(6-bromo-2-((tert-butyldi methylsilyl)oxy)-3-methoxyphenyl) acetaldehyde [3b]



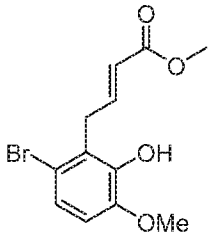
To the solution of **3a** (23.0 g, 1.0 eq) in dioxane/water (460 mL, 1/1) was added OsO_4 (0.33 mg, solution in water) at 0°C followed by the addition of 2,6-lutidine (13.8 g). After stirring at 0 °C for 30 mins, $NaIO_4$ was added and the mixture was stirred at rt for 3 hours. The reaction mixture was then filtered and the filtrate was extracted with EtOAc. The organic layer was washed with 10% NH_4Cl aq. solution, water, brine, dried over Na_2SO_4 and concentrated to give product 22.0 g (95% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 9.69 (s, 1 H), 7.20 (m, 1 H), 6.93 (m, 1 H), 3.93 (m, 2 H), 3.77 (s, 3 H), 0.96 - 0.86 (s, 9 H), 0.19 - 0.11 (s, 6H).

Step-3: methyl (E)-4-(6-bromo-2-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl) but-2-enoate. [3c]



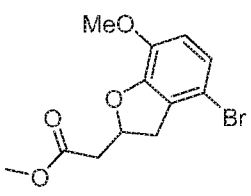
A mixture of 2-(6-bromo-2-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl) acetaldehyde (20.0 g) and methyl (triphenyl phosporanylidine)acetate (20.46 g) in toluene (400 ml_) was stirred at rt for 15 hr. The reaction mixture was then concentrated and the residue was purified by silica gel column chromatography (EtOAc/hexane, 0-13%) to give product 8.6 g (38% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 7.19 (t, J = 8.2 Hz, 1 H), 6.98 - 6.88 (m, 2 H), 5.53 (m, 1 H), 3.78 (s, 3 H), 3.69 - 3.45 (m, 5 H), 0.96 - 0.85 (s, 9 H), 0.20 - 0.08 (s, 6H).

Step 4: methyl (E)-4-(6-bromo-2-hydroxy-3-methoxyphenyl)but-2-enoate [3d]



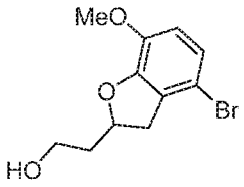
TBAF (40.7 ml_, 1.0 M in THF) was added to a solution of methyl (E)-4-(6-bromo-2-hydroxy-3-methoxyphenyl)but-2-enoate (8.6 g, 1.0 eq) in THF (100 mL) at 0°C and the solution was then stirred at rt for 1 h. The reaction mixture was then filtered and the filtrate was partitioned between water and EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc. The organic layer was washed with 10 % $NaHC0_3$ aq. solution, water, brine, dried over Na_2S0_4 and concentrated to give product 4.05 g (95% yield). ^{1}H NMR (400 MHz, DMSO): 9.26 (s, 1H), 7.051 - 7.057 (d, 1H), 7.029-7.036(d, 1H) 6.79-6.89 (m, 2H), 3.80 (s, 3H), 3.7 (s, 3H), 3.63 - 3.68 (d, 2H).

Step 5: methyl 2-(4-bromo-7-methoxy-2,3-dihydrobenzofuran-2-yl)acetate. [3e]



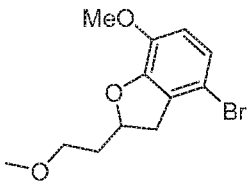
A mixture of methyl (E)-4-(6-bromo-2-hydroxy-3-methoxyphenyl)but-2-enoate (7.0 g, 1.0 eq) and PTSA (16.0 g, 4.0 eq) in toluene (140ml_) was heated at reflux for 15 hs. After cooling to rt, cold water was added to above reaction mixture. The mixture was extracted with EtOAc. The combined organic layer was washed with 10 % $NaHC0_3$ aq. solution, water, brine, dried over Na_2S0_4 and concentrated to give product 6.0 g. ^{1}H NMR (400 MHz, DMSO-d_6): 6.95 (t, *J* = 12.0 Hz, 1 H), 6.82 (t, *J* = 11.4 Hz, 1 H), 5.26 - 5.10 (m, 1 H), 3.84 - 3.72 (m, 3 H), 3.67 - 3.53 (m, 3 H), 3.06 - 2.72 (m, 3 H).

Step 6: 2-(4-bromo-7-methoxy-2,3-dihydrobenzofuran-2-yl)ethan-1 -ol [3f]



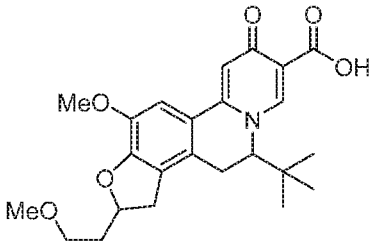
$UAIH_4$ (9.96 mL, 1.0 M in THF) was added to a solution of methyl 2-(4-bromo-7-methoxy-2,3-dihydrobenzofuran-2-yl)acetate (3.0 g, 1.0 eq) in THF (60 mL) at 0 °C. After completion of reaction, reaction mass was quenched by adding Na_2S0_4 aq. solution. The mixture was then filtered, and the solids were washed with EtOAc . The filtrate was concentrated to give product (5.50g). ^{1}H NMR (400 MHz, DMSO): 6.94 (d, *J* = 8.6 Hz, 1H), 6.77 (dd, *J* = 17.2, 6.9 Hz, 1H), 4.94 (dq, *J* = 15.9, 7.9 Hz, 1H), 3.56 (t, *J* = 6.2 Hz, 2H), 3.43 - 3.24 (m, 3H), 2.87 (dd, *J* = 15.9, 8.0 Hz, 1H), 1.97 - 1.75 (m, 2H).

Step 7: 4-bromo-7-methoxy-2-(2-methoxyethyl)-2,3-dihydrobenzofuran [3g]



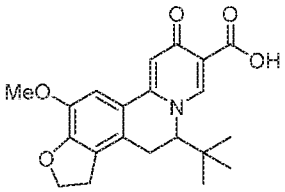
NaH (0.25 g) was added to a solution of (2-(4-bromo-7-methoxy-2,3-dihydrobenzofuran-2-yl)ethan-1 -ol (1.9 g, 1.0 eq) in THF (40mL) at 0 °C. After 30 min, MeI (1.08 g, 1.1 eq) was added and the resulting mixture was stirred at 0 °C for 2 hours. The reaction was quenched by adding water and the mixture was then extracted with EtOAc. The organic layers were combined, washed with water then brine, dried over Na_2S0_4, and concentrated to give product 1.9 g (65%). LCMS (m/z): 287.1 5 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): 6.93 (m, 1 H), 6.81 - 6.72 (m, 1 H), 4.92 (m, 1 H), 3.75 (s, 3 H), 3.53 - 3.42 (m, 2 H), 3.33 - 3.27 (m, 1 H), 3.25 (s, 3 H), 2.87 (m, 1 H), 2.01 - 1.88 (m, 2 H).

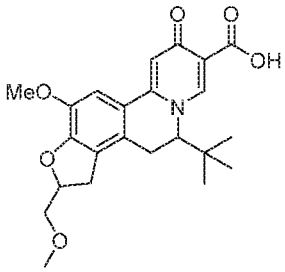
Step 8. 5-(tert-butyl)-1 2-methoxy-2-(2-methoxyethyl)-9-oxo-2,3,4,9-tetrahydro-5H-furo[3,2-f]pyrido[2,1 -a]isoquinoline-8-carboxylic acid [3]

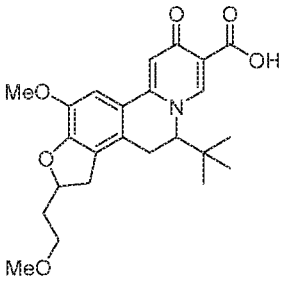


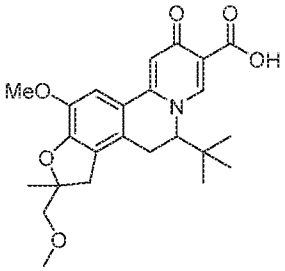
Compound 3 was synthesized from 3g by the method described in the synthesis of 1.1, Step 4-11. LCMS (m/z): 427.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO): 16.70 (d, J = 40.4 Hz, 1H), 8.69 (d, J = 18.0 Hz, 1H), 7.42 (d, J = 5.1 Hz, 2H), 5.10 - 4.99 (m, 1H), 4.58 (d, J = 6.0 Hz, 1H), 3.78 (d, J = 68.8 Hz, 3H), 3.47 (dd, J = 13.3, 7.4 Hz, 2H), 3.27 (t, J = 4.6 Hz, 3H), 3.10 - 2.78 (m, 3H), 2.04 - 1.80 (m, 2H), 1.09 - 0.25 (m, 9H).

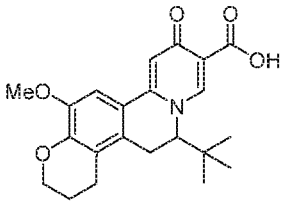
The following compounds can be made by similar methods to those illustrated above using starting materials that are known in the art:

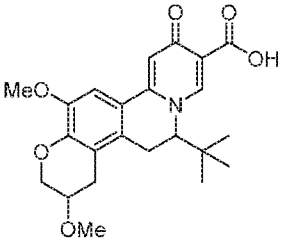


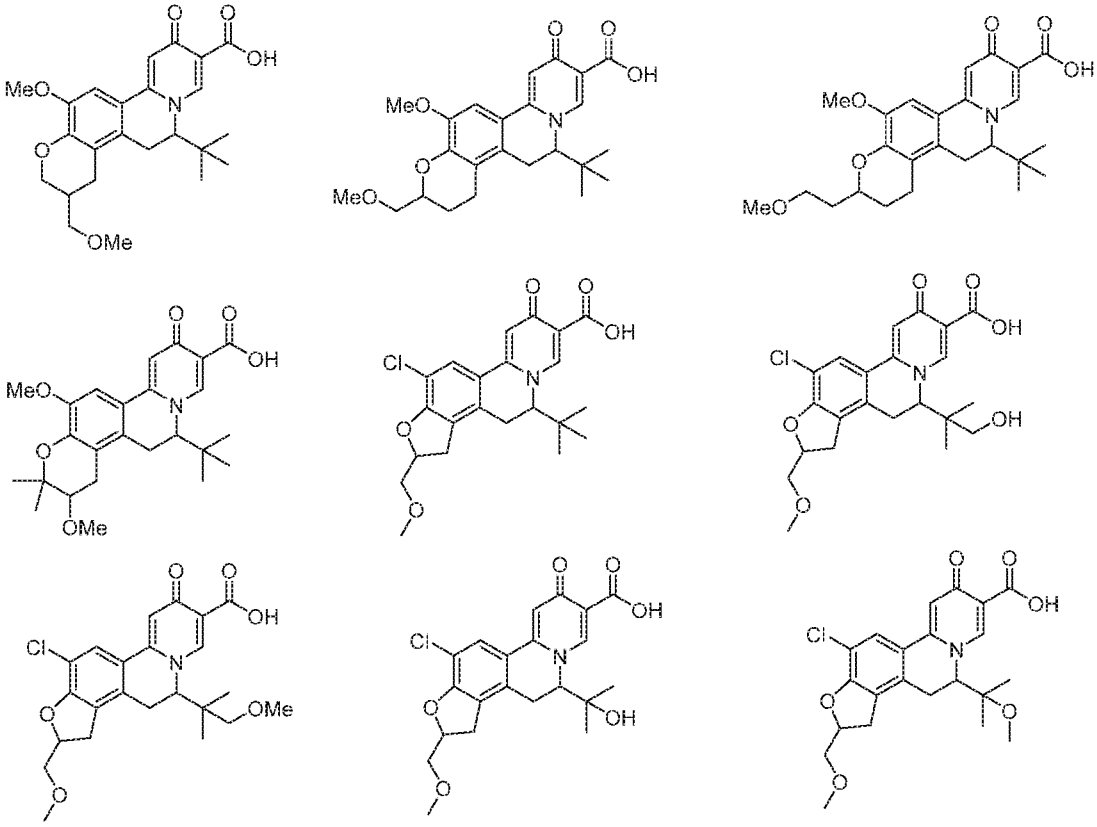












BIOLOGICAL EXAMPLES

HBV Cell Line

HepG2-Clone42, a Tet-inducible HBV-expressing cell line with a stably integrated 1.3mer copy of the HBV ayw strain, was generated based on the Tet-inducible HepAD38 cell line with slight modifications. Ladner SK, et al., *Antimicrobial Agents and Chemotherapy.* 41(8):1715-1720 (1997). HepG2-Clone42 cells were cultured in DMEM/F-12 + Glutamax™ (Life Technologies, Carlsbad, CA, USA), supplemented with 10% fetal bovine serum (Life Technologies), G-418 (Corning, Manassas, VA, USA) at a final concentration of 0.5 mg/mL, and 5 μg/mL Doxycycline (Sigma, St. Louis, MO, USA) and maintained in 5% $C0_2$ at 37°C.

HBsAg Assay

HepG2-Clone42 cells were seeded into black clear-bottom 96-well plates at a concentration of 6.0 x 10^4 cells/well. 24 hours post-seeding, the cells were treated with 200 μl/well of media containing five-fold serial dilutions of compounds in DMSO. DMSO alone was used as the no drug control. The final DMSO concentration in all wells was 0.5%.

The HBsAg ELISA kit (Alpha Diagnostic International, San Antonio, TX, USE, Catalog # 4110) was used to determine the level (semi-quantitative) of secreted HBV sAg. The HBSAg ELISA assay was performed following the manufacturer's protocol as described.

Step 1. Pipet 100 µL each of compound or DMSO treated samples into HBsAg ELISA plates. Seal plates and incubate at room temp for 60 minutes.

Step 2. Aspirate samples and wash three times with Wash Buffer. Dispense 100 µL of antibody-HRP conjugate to each well. Incubate at room temp for 30 minutes.

Step 3. Aspirate samples and wash three times with Wash Buffer. Add 100 µL of TMB Substrate to all wells and incubate 15 minutes at room temp.

Step 4. Dispense 100 µL of Stop Solution to each well. Measure absorbance of ELISA plate at 450 nm.

Dose Response Curves

Dose-response curves were generated and the EC_{50} value was defined as the compound concentration at which HBsAg secretion was reduced 50% compared to the DMSO control.

EC_{50} values were determined as follows:

1. Determine the percent of HBsAg secretion inhibition. Calculate the percent inhibition on of HBsAg secretion inhibition using the following equation:

$$100 \times (Xc - M_B)/(M_D - M_B)$$

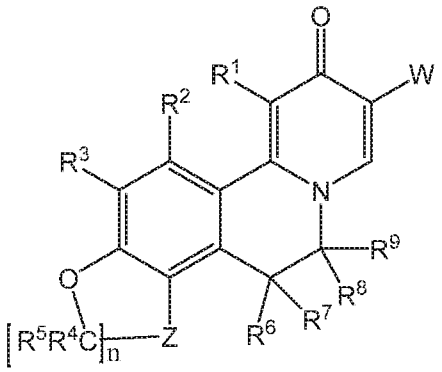
where X_c is the absorbance signal from compound-treated well; M_B is average absorbance signal (background signal) for column 12 (no cells + HBsAg ELISA sample buffer) and M_D is average absorbance signal from DMSO-treated wells. Then calculate EC_{50} values by non-linear regression using a four parameter curve logistic equation.

The curve fit model employed is XLFit Dose Response One Site Model 204: y = (A+((B-A)/(1 +(1 0^((C-x)*D))))) where A is the minimum y value, B is the maximum y value, C is the logEC50 value, and D is the slope factor.

For the compound 1.1 of Example 1.1: EC_{50} in the HBsAg assay was 20 nM.
For the compound 2.1 of Example 2.1: EC_{50} in the HBsAg assay was 3 nM.
For the compound 3 of Example 3: EC50 in the HBsAg assay was 1 nM.

CLAIMS

1. A compound of formula (I):



(I) wherein:

R^1 is H, halo, or d-d alkyl;

R^2 is H, halo, CN, d-C $_3$ alkyl, d-C $_3$ haloalkyi, or d-C $_3$ alkoxy;

R^3 is H, OH, halo, CN, d-C $_3$ alkyl, C_3-C_6 cycloalkyl, d-C $_3$ haloalkyi, C_1-C_3 alkoxy, or d-C $_3$ haloalkoxy;

each R^4 and R^5 is independently selected from H, R^{11}, OH, -OR ^{11}, -SR^{11}, -S0 $_2$R^{11}, and -NRR ^{11}, provided that not more than one group represented by R^4 and R^5 is OH;

R^{11} is d-C $_4$ alkyl, optionally substituted with up to three groups selected from halo, CN, -OR, C_1-C_3 haloalkoxy, -NR_2, -S0 $_2$R, and a 4-7 membered heterocyclic group containing one or two heteroatoms selected from N, O and S as ring members that is optionally substituted with one or two groups selected from halo, oxo, CN, R, -OR, and -NR_2;

n is 1 or 2;

Z is O or CR_2;

R is independently selected at each occurrence from H and d-C $_3$ alkyl optionally substituted with one to three groups selected from halo, -OH, d-C $_3$ alkoxy, oxo, CN, -NH_2, -NH(C_1-C_3 alkyl), -N(d-C $_3$ alkyl)$_2$, and cyclopropyl;

and two R groups directly attached to the same atom, which may be C or N, can optionally be taken together to form a 3-6 membered ring that can optionally contain an added heteroatom selected from N, O and S as a ring member, and can be substituted by up to two groups selected from -OH, oxo, C_1-C_3 alkyl, and d-C $_3$ alkoxy;

R^6 is H, halo, d-C $_3$ alkoxy, or d-C $_6$ alkyl;

R^7 is H, halo, d-C $_3$ alkoxy, or d-C $_6$ alkyl;

R^8 is H or d-C $_6$ alkyl optionally substituted with up to three groups selected from halo, d-C $_2$ haloalkyl, OH, d-C $_3$ alkoxy, and 3-7 membered cycloalkyl;

R^9 is H or C_1-C_4 alkyl;

W is -COOR ^{10}, -C(0)NH-S0 $_2$R, -C(0)NH-S0 $_2$NR_2, 5-tetrazolyl, or 1,2,4-oxadiazol-3-yl-5(4H)-one;

R^{10} is H or d-d alkyl that is optionally substituted with one or two groups selected from halo, -OR, oxo, CN, -NR_2, COOR, and CONR_2;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R^1 is H.

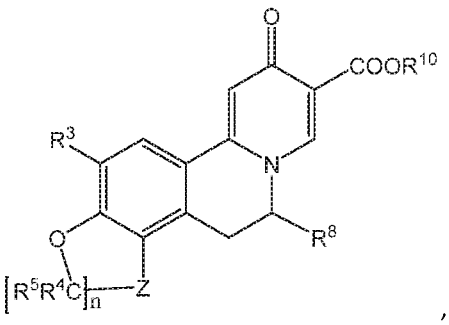
3. A compound according to claim 1 or claim 2 or a pharmaceutically acceptable salt thereof, wherein R^2 is H or halo.

4. A compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein R^3 is d-d alkoxy or halo.

5. A compound according to any of the preceding claims or a pharmaceutically acceptable salt thereof, wherein W is COOR^{10}, where R^{10} is H or d-C $_6$ alkyl.

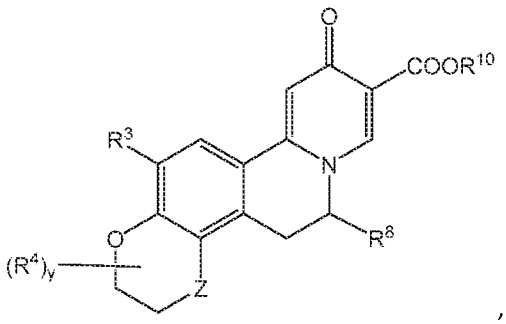
6. A compound according to any of the preceding claims or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are both H.

7. A compound according to any of the preceding claims or a pharmaceutically acceptable salt thereof, which is of the formula:



wherein R^8 is C_1-C_6 alkyl optionally substituted with up to three groups selected from halo, OH, and C_1-C_3 alkoxy.

8. A compound according to any of claims 1-7, which is of the formula:

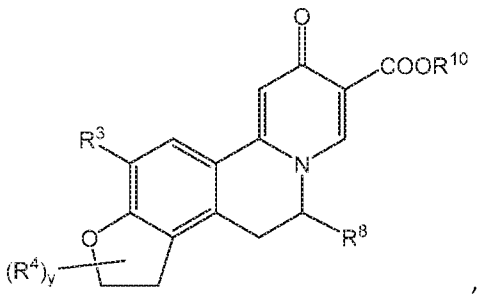


wherein R^4 is selected from H, R^{11}, and $-OR^{11}$;

y is 1 or 2;

or a pharmaceutically acceptable salt thereof.

9. A compound according to any of claims 1-7, which is of the formula:



wherein R^4 is selected from H, R^{11}, and -OR^{11};

y is 1 or 2;

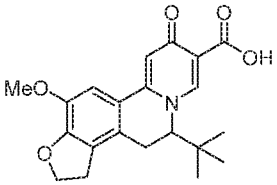
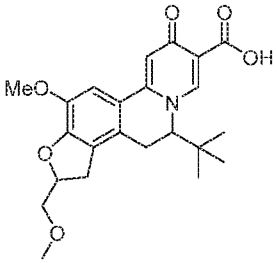
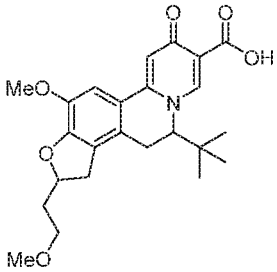
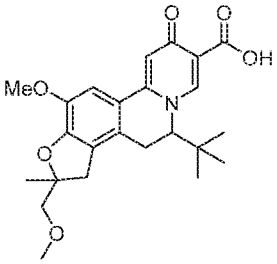
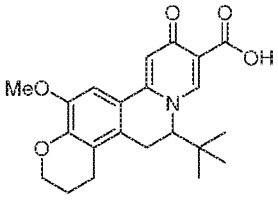
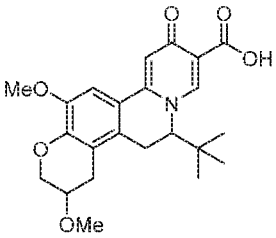
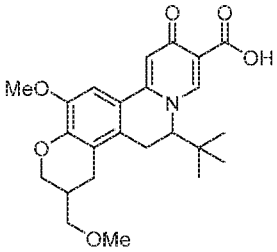
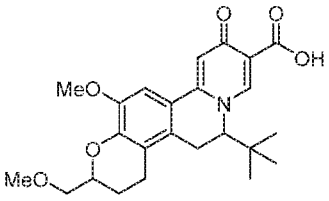
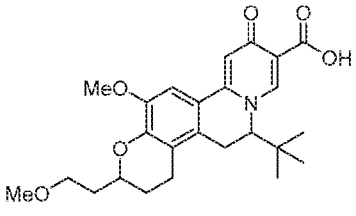
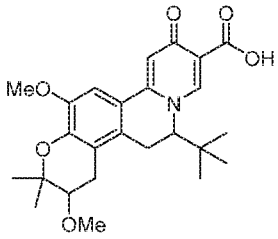
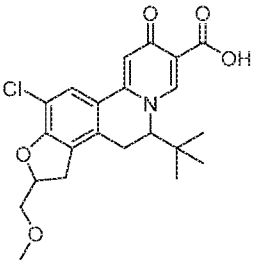
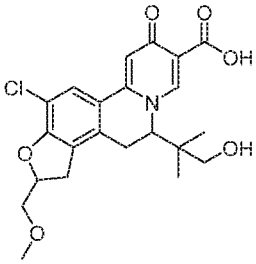
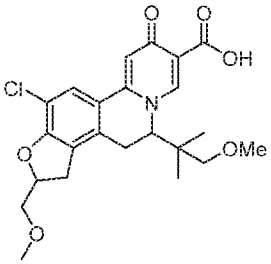
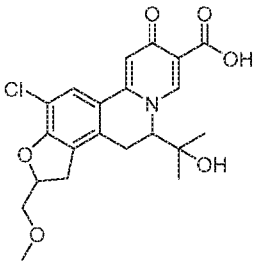
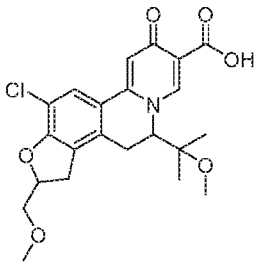
or a pharmaceutically acceptable salt thereof.

10. A compound according to any of the preceding claims or a pharmaceutically acceptable salt thereof, wherein each R^{11} is C_1-C_4 alkyl, substituted with up to two groups selected from -OR, C_1-C_3 haloalkoxy, and halo.

11. A compound according to any of claims 1-10 or a pharmaceutically acceptable salt thereof, wherein each R^{11} is selected from -CH_2OMe, -CH_2CH_2OMe, -$CH_2CH_2CH_2OMe$, -CH_2-OEt, -CH_2-OH, -CH_2CH_2-OH, and -$CH_2CH_2CH_2$-OH.

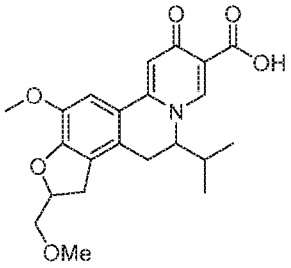
12. A compound according to any of the preceding claims or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from isopropyl, t-butyl, 2-methoxyprop-2-yl, 2-hydroxyprop-2-yl, 2-hydroxymethylprop-2-yl and 2-methoxymethylprop-2-yl.

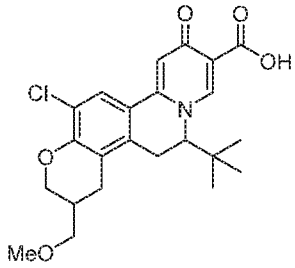
13. A compound selected from:

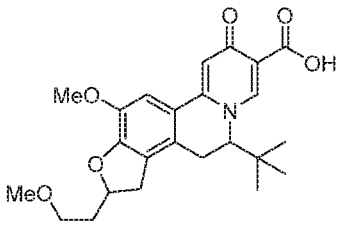
















or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, which is selected from:



,


and


,

and the pharmaceutically acceptable salts thereof.

15. A pharmaceutical composition, comprising a compound of any of the preceding claims admixed with at least one pharmaceutically acceptable carrier.

16. A method to treat a hepatitis B infection, which comprises administering to a patient having a hepatitis B infection a compound of any of claims 1-14 or a pharmaceutical composition of claim 15.

17. The method of claim 16, wherein the compound of any one of claims 1-14 or the pharmaceutical composition of claim 15 is used in combination with an additional therapeutic agent selected from an interferon or peginterferon, an HBV polymerase inhibitor, a viral entry inhibitor, a viral maturation inhibitor, a capsid assembly inhibitor, an HBV core modulator, a reverse transcriptase inhibitor, a TLR-agonist, or an immunomodulator.

18. A method to inhibit replication of hepatitis B virus, which comprises contacting the hepatitis B virus, either in vitro or in vivo, with a compound according to any one of claims 1-14.

20. A compound of any of claims 1-14 for use in therapy.

21. The compound of claim 20 for use to treat a subject infected with hepatitis B virus (HBV).

22. A pharmaceutical combination, comprising a compound of any of claims 1-14 and at least one additional therapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053369

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/04 A61K45/06 A61K31/4355 A61P31/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/113990 Al (HOFFMANN LA ROCHE [CH] ; HOFFMANN LA ROCHE [US]) 6 August 2015 (2015-08-06) cited in the application in particular the whole document; in particular the claims and the examples (e.g. 78, 82, 83, 99, 100, 113, 216)	1-22
A	WO 2015/173164 Al (HOFFMANN LA ROCHE [CH] ; HOFFMANN LA ROCHE [US]) 19 November 2015 (2015-11-19) cited in the application in particular the whole document, in particular the claims; example 4	1-22

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2017	02/08/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hani sch , Inken

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RAY-LING HUANG ET AL: "Screening of 25 compounds isolated fromPhyllanthus species for anti-human hepatitis B virus in vitro", PHYTOTHERAPY RESEARCH., vol. 17, no. 5, 1 May 2003 (2003-05-01), pages 449-453, XP055393275, GB ISSN: 0951-418X, D0I: 10. 1002/ptr. 1167 in particular compounds 2, 3 in figure 1, table 1; results page 451 right-hand column ----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/053369

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015113990 Al	06-08-2015	AU 2015212903 Al	19-05-2016
		CA 2931329 Al	06-08-2015
		CN 105899508 A	24-08-2016
		CR 20160241 A	15-07-2016
		EA 201691261 Al	30-11-2016
		EP 3099685 Al	07-12-2016
		JP 2017504633 A	09-02-2017
		PE 06862016 Al	23-07-2016
		PH 12016501254 Al	15-08-2016
		SG 11201605970Q A	30-08-2016
		TW 201540715 A	01-11-2015
		US 2015210682 Al	30-07-2015
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		EP 3143020 Al	22-03-2017
		JP 2017515844 A	15-06-2017
		KR 20160148715 A	26-12-2016
		US 2017057952 Al	02-03-2017
		W0 2015173164 Al	19-11-2015