

ANTIVIRAL 1,3-DI-OXO-INDENE COMPOUNDS
CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. 119(e) of United States Provisional Application Serial No. 63/497,972 filed on April 24, 2023, which is hereby incorporated by reference in its entirety.

FIELD

[0002] The present disclosure relates to novel 1,3-dioxoindene compounds that are inhibitors of poliovirus.

BACKGROUND

[0003] Picornaviruses are non-enveloped, positive single-stranded RNA viruses with an RNA genome 7.2-8.5 Kb long. These viruses are very small and globular in shape with a size of about 22~30 nm, and were first identified a long time ago. Among the viruses belonging to the family Picornaviridae are enteroviruses including rhinovirus, poliovirus, coxsackievirus A, coxsackievirus B, and echovirus, and hepatitis A virus.

[0004] The diseases that picornaviruses cause are varied, ranging from respiratory diseases to digestive diseases, to circulatory diseases and to dermal diseases, examples of which include poliomyelitis, paralysis, acute hemorrhagic conjunctivitis, viral meningitis, hand-foot-and-mouth disease, vesicular disease, hepatitis A, myositis, myocarditis, pancreatitis, diabetes, epidemic myalgia, encephalitis, cold, herpangina, and foot-and-mouth disease. However, there are no therapeutics for curing these diseases. Most of the drugs under development are uncoating inhibitors. Viruses belonging to the family Picornaviridae cause various diseases including the aforementioned respiratory diseases, which evoke hygienic, social and economic issues. Picornaviruses are the main causative agents of waterborne diseases. Being very stable and difficult to disinfect, the RNA viruses incessantly cause related diseases.

[0005] Human rhinoviruses (hRV) have been recently associated with the majority of asthma exacerbations, and are known to exist even in bronchial tissues of many stable asthma patients. Comparison of respective bronchial mucosa biopsy specimens taken from asthma and non-asthma patients showed significantly higher frequencies of detection of human rhinoviruses in the lower respiratory tract of asthma patients, compared to non-asthma patients. It has also been

reported that there is correlation between the presence of human rhinovirus and the clinical severity of asthma. In addition, rhinoviruses cause chronic obstructive pulmonary disease, pneumonia, sinusitis, and otitis media as well as asthma.

[0006] There remains a need for new treatments and therapies against poliovirus.

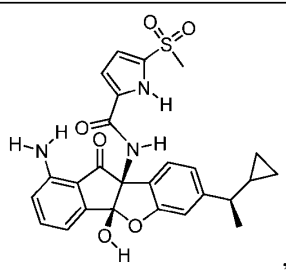
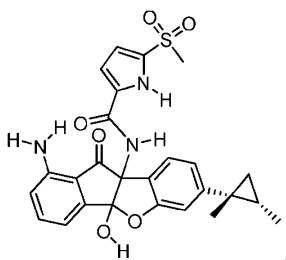
[0007] Leading to the present disclosure, intensive and thorough research into effective virustatics against picornaviruses including coxsackie-, entero-, echo-, polio-, and rhinoviruses, culminated in the finding that novel 1,3-dioxindene derivatives exhibit highly inhibitory activity against picornaviruses including coxsackie-, entero-, echo-, polio-, and rhinoviruses.

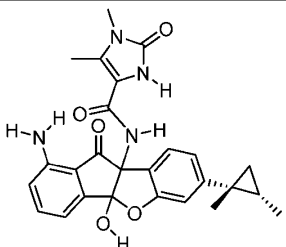
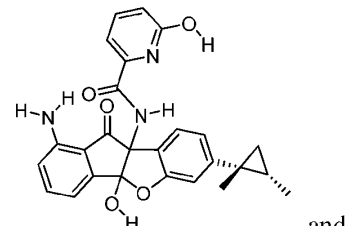
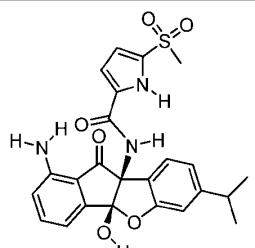
SUMMARY

[0008] The present disclosure provides novel compounds with antiviral activity *in vitro*. The disclosure also provides pharmaceutical compositions containing the novel compounds as well as methods to use the compounds and compositions to inhibit virus replication or reactivation, and to treat disease conditions associated with or caused by viruses.

[0009] In one aspect, the disclosure provides a compound of Table 1, or a pharmaceutically acceptable salt thereof, selected from:

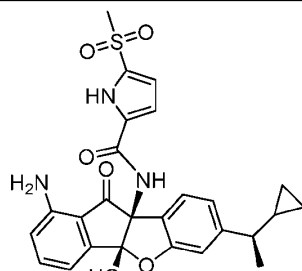
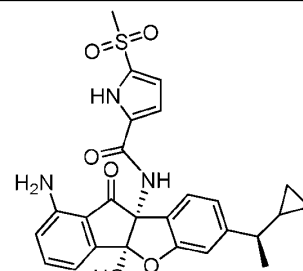
Table 1

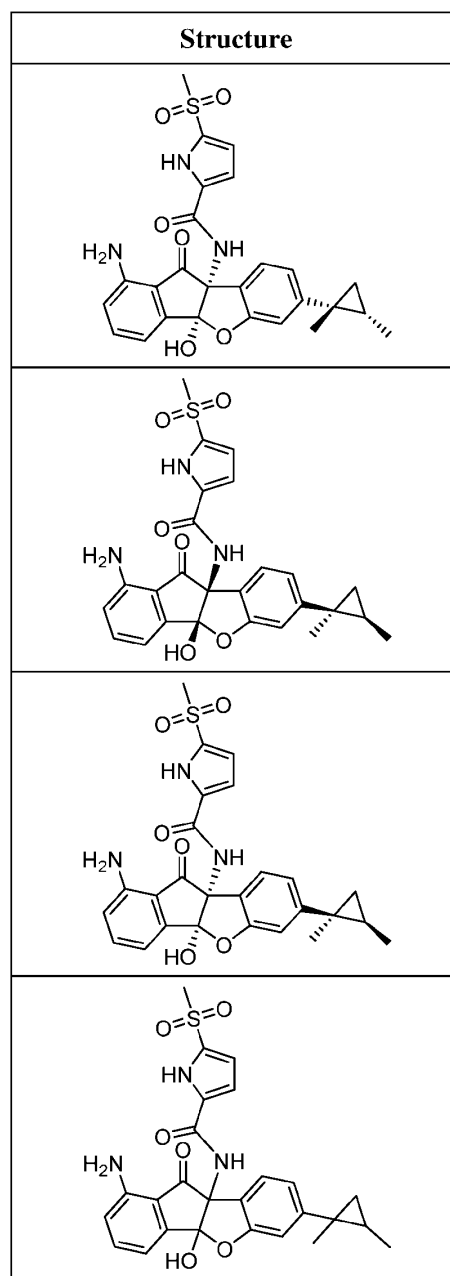
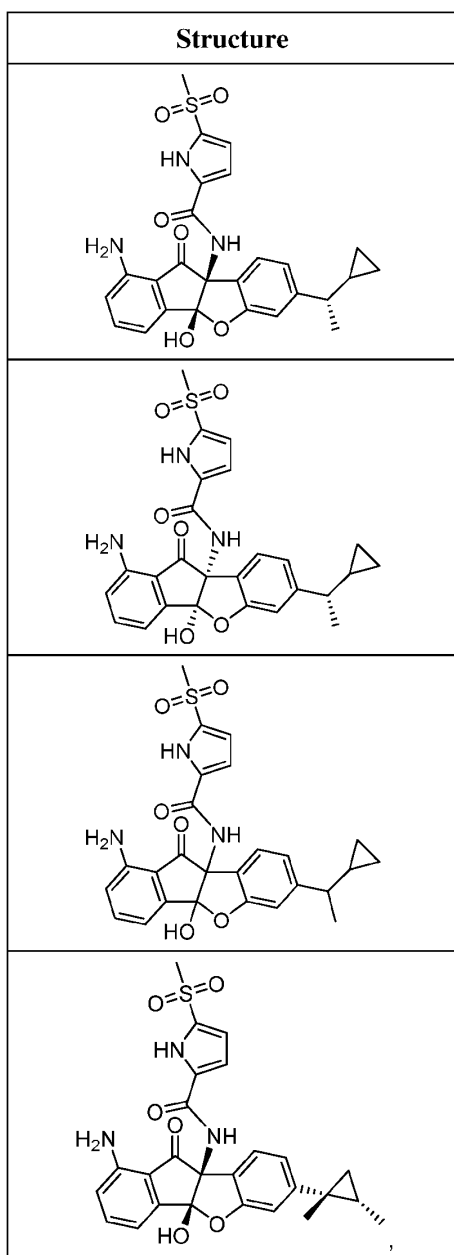
Ex.	Structure
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2	

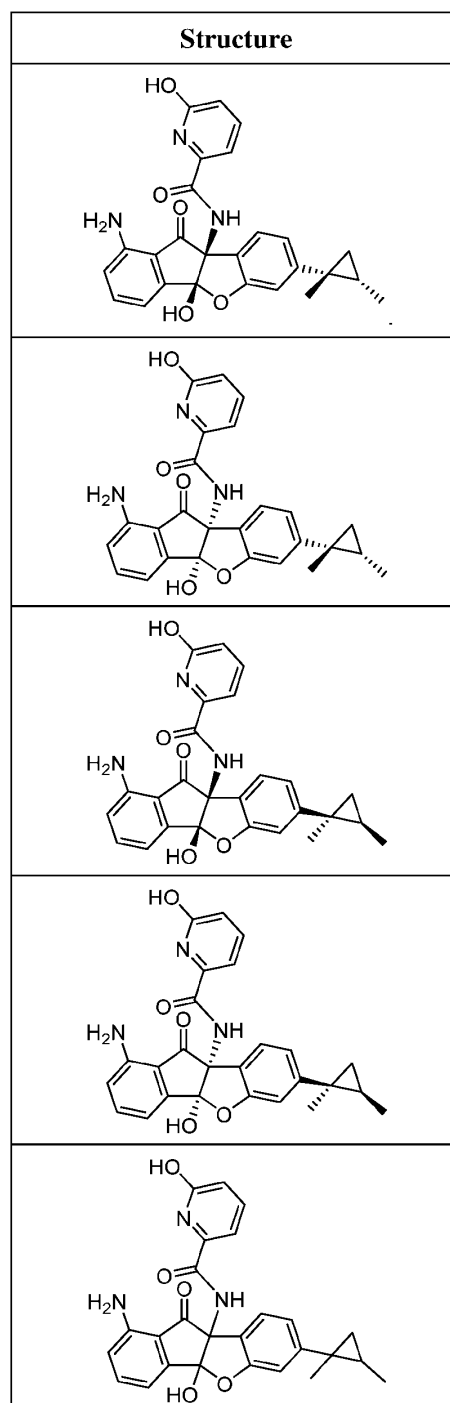
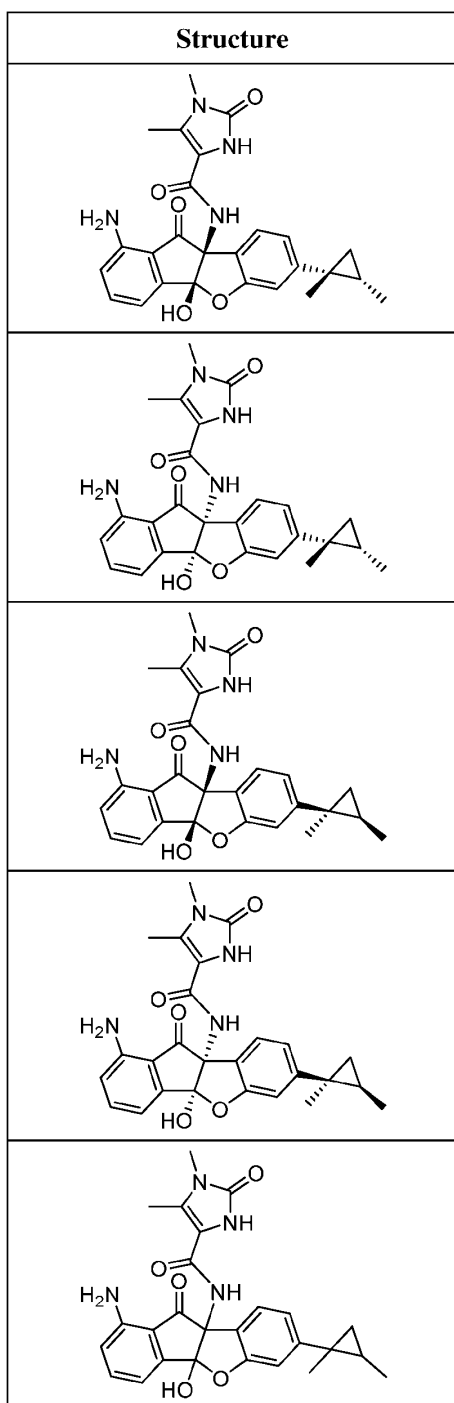
Ex.	Structure
3	
4	
5	

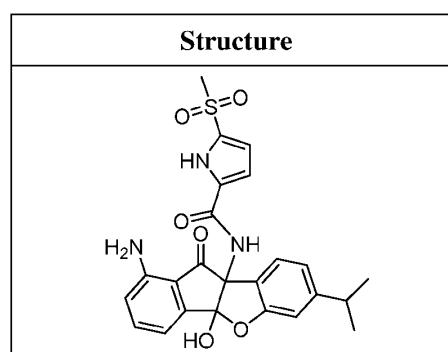
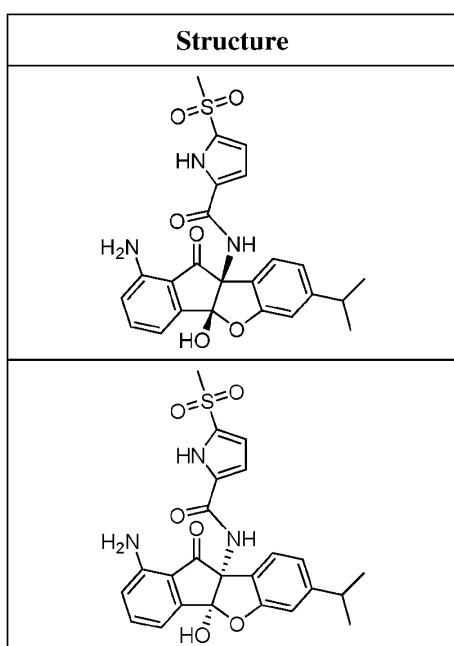
[0010] In one aspect, the disclosure provides a compound of Table 2, or a pharmaceutically acceptable salt thereof, selected from:

Table 2

Structure	Structure
	







DETAILED DESCRIPTION

[0011] For purposes of interpreting this specification, the following definitions will apply, and whenever appropriate, terms used in the singular will also include the plural.

[0012] Terms used in the specification have the following meanings unless the context clearly indicates otherwise:

[0013] 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, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

[0014] 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.

[0015] 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

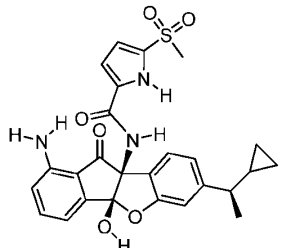
the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treating” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treating” or “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.

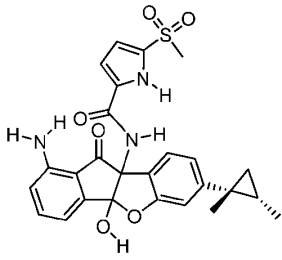
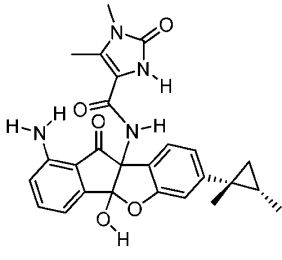
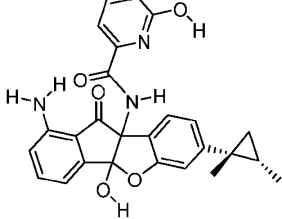
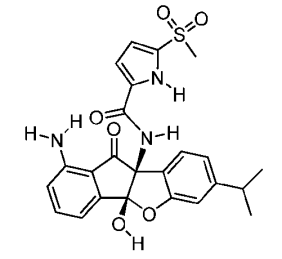
[0016] As used herein, the term “a,” “an,” “the” and similar terms used in the context of the present disclosure (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

[0017] 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 disclosure and does not pose a limitation on the scope of the disclosure otherwise claimed.

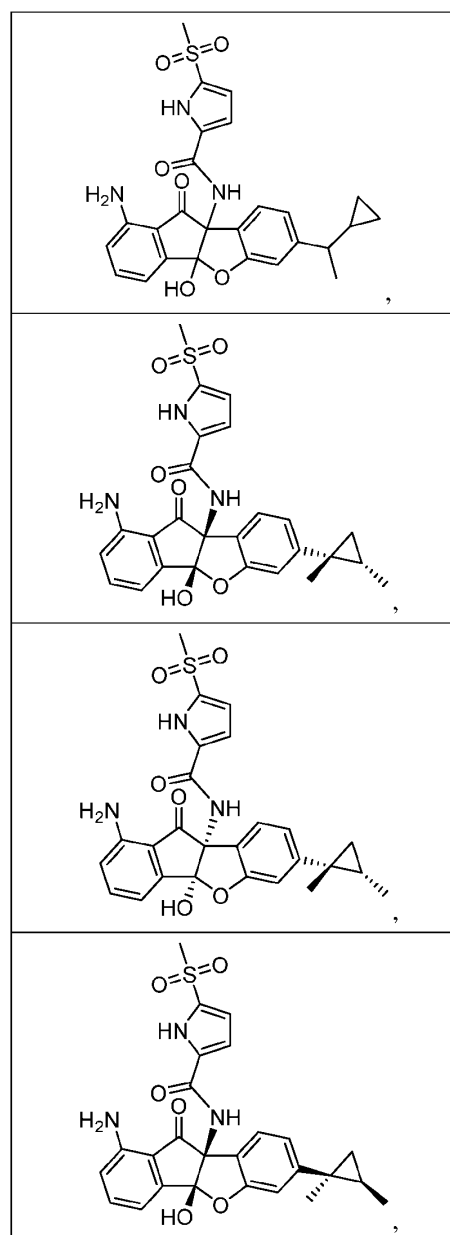
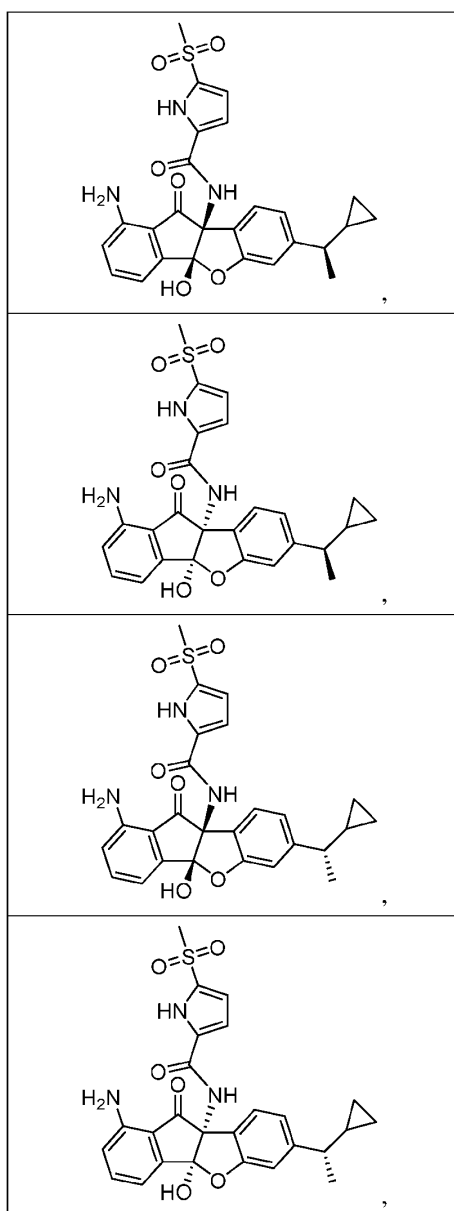
[0018] Various embodiments of the disclosure are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments. The following enumerated embodiments are representative of the disclosure:

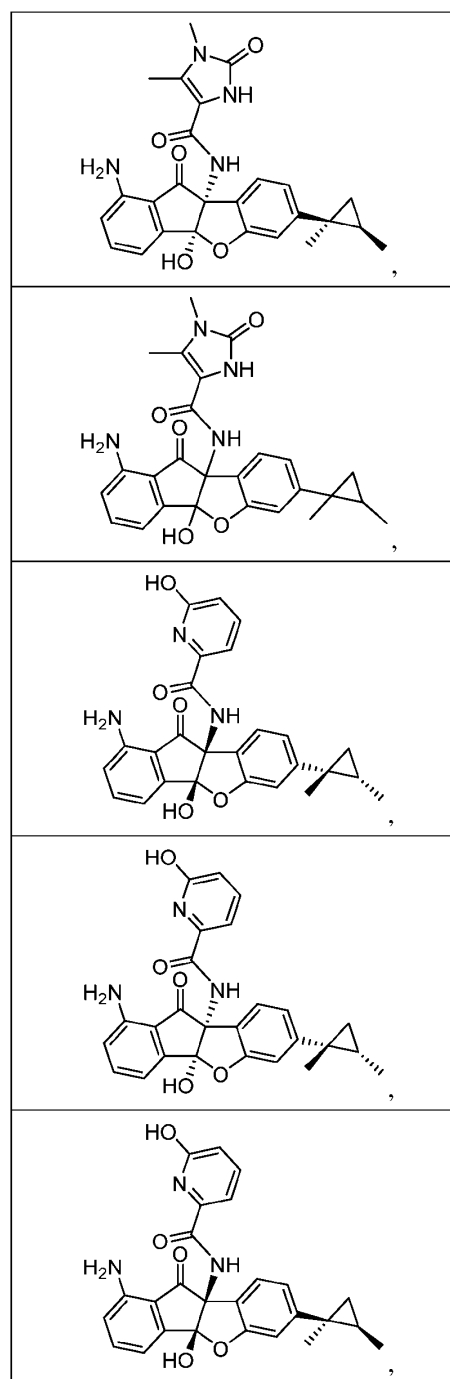
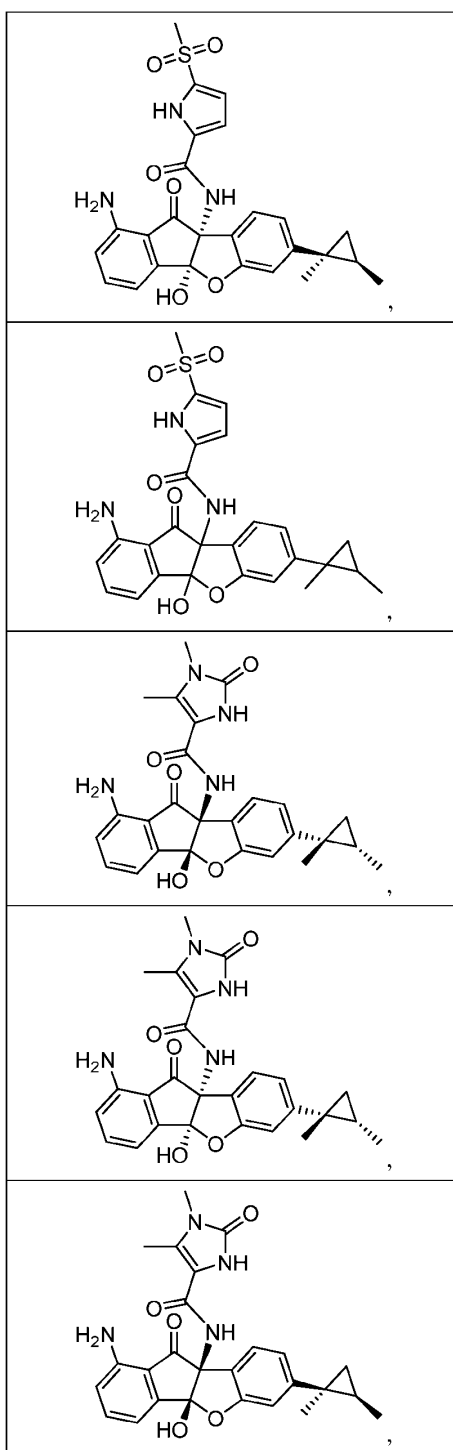
[0019] Embodiment 1. A compound, or a pharmaceutically acceptable salt thereof, selected from:

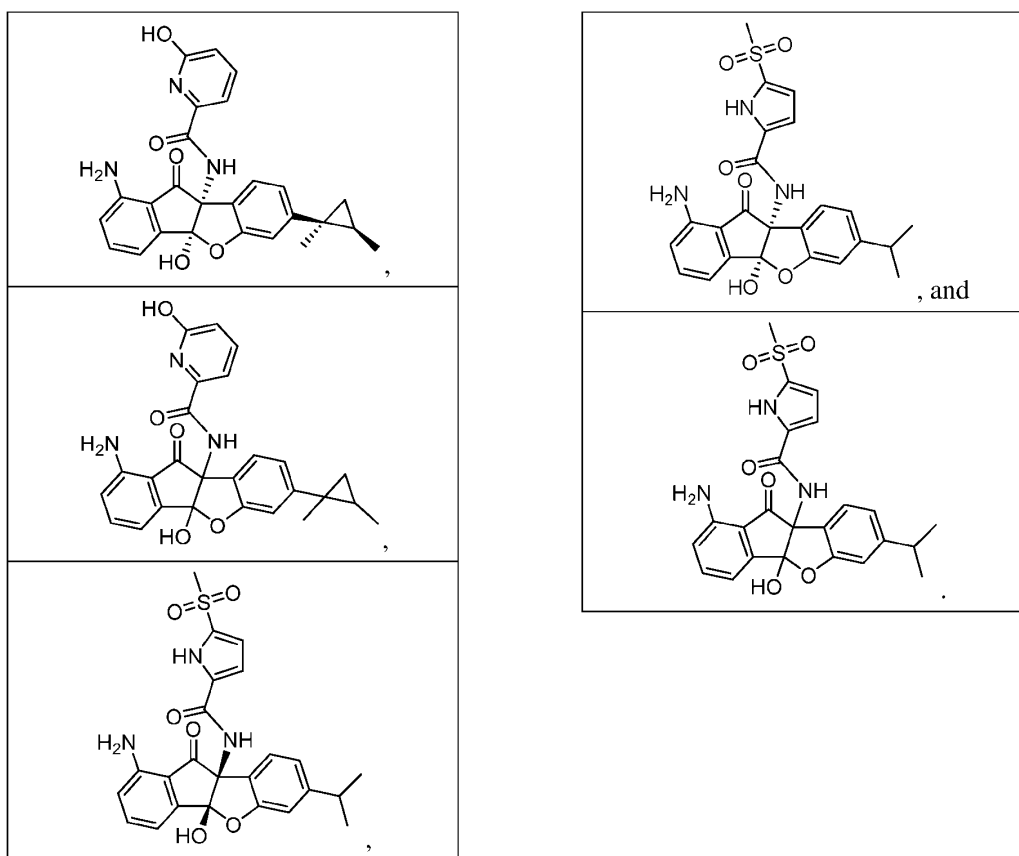
	N-((4bR,9bR)-1-amino-7-((R)-1-cyclopropylethyl)-4b-hydroxy-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxamide,
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	N-(1-amino-7-((1R,2S)-1,2-dimethylcyclopropyl)-4b-hydroxy-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxamide,
	N-(1-amino-7-((1R,2S)-1,2-dimethylcyclopropyl)-4b-hydroxy-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-1,5-dimethyl-2-oxo-2,3-dihydro-1H-imidazole-4-carboxamide,
	N-(1-amino-7-((1R,2S)-1,2-dimethylcyclopropyl)-4b-hydroxy-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-6-hydroxypicolinamide,
	N-((4bR,9bR)-1-amino-4b-hydroxy-7-isopropyl-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxamide.

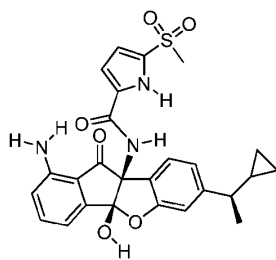
[0020] Embodiment 2. A compound, or a pharmaceutically acceptable salt thereof, selected from:



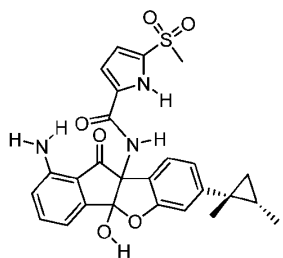




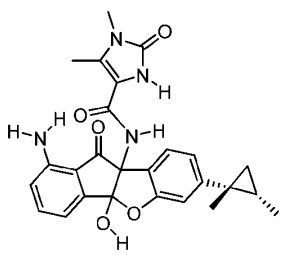
[0021] Embodiment 3. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



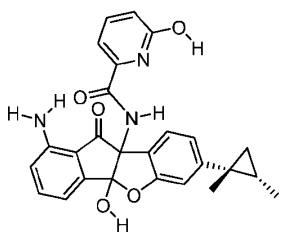
[0022] Embodiment 4. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



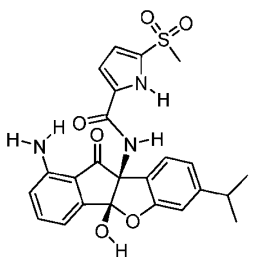
[0023] Embodiment 5. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



[0024] Embodiment 6. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



[0025] Embodiment 7. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



[0026] Embodiment 8. A pharmaceutical composition for prevention or treatment of a viral disease, comprising the compound of any one of Embodiments 1-7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or excipient.

[0027] Embodiment 9. A combination comprising a compound of any one of Embodiments 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Embodiment 8, and one or more therapeutically active agents.

[0028] Embodiment 10. A method of treating a viral disease comprising administering to a subject a therapeutically effective amount of a compound of any one of Embodiments 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Embodiment 8, or a combination of Embodiment 9.

[0029] Embodiment 11. Use of a compound of any one of Embodiments 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Embodiment 8, or a combination of Embodiment 9, for the prevention or treatment of a viral disease.

[0030] Embodiment 12. Use of a compound of any one of Embodiments 1-7 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Embodiment 8, or a combination of Embodiment 9, for the manufacture of a medicament for the treatment of a viral disease.

[0031] Embodiment 13. The pharmaceutical composition as set forth in Embodiment 8, or the combination of Embodiment 9, or the method of Embodiment 10, or the use of Embodiment 11 or Embodiment 12, wherein the viral disease is caused by poliovirus.

[0032] Embodiment 14. The pharmaceutical composition as set forth in Embodiment 8, or the combination of Embodiment 9, or the method of Embodiment 10, or the use of Embodiment 11 or Embodiment 12, wherein the viral disease is caused by coxsackievirus.

[0033] Embodiment 15. The pharmaceutical composition as set forth in Embodiment 8, or the combination of Embodiment 9, or the method of Embodiment 10, or the use of Embodiment 11 or Embodiment 12, wherein the viral disease is caused by echovirus.

[0034] Embodiment 16. The pharmaceutical composition as set forth in Embodiment 8, or the combination of Embodiment 9, or the method of Embodiment 10, or the use of Embodiment 11 or Embodiment 12, wherein the viral disease is caused by enterovirus.

[0035] Embodiment 17. The pharmaceutical composition as set forth in Embodiment 8, or the combination of Embodiment 9, or the method of Embodiment 10, or the use of Embodiment 11 or Embodiment 12, wherein the viral disease is caused by rhinovirus.

[0036] Embodiment 18. The pharmaceutical composition as set forth in Embodiment 8, or the combination of Embodiment 9, or the method of Embodiment 10, or the use of Embodiment 11 or Embodiment 12, wherein the viral disease is caused by picornavirus.

[0037] Embodiment 19. The pharmaceutical composition as set forth in Embodiment 8, or the combination of Embodiment 9, or the method of Embodiment 10, or the use of Embodiment 11 or Embodiment 12, wherein the viral disease is poliomyelitis, paralysis, acute haemorrhagic conjunctivitis, viral meningitis, hand-foot-and-mouth disease, vesicular disease, hepatitis A, myositis, myocarditis, pancreatitis, diabetes, epidemic myalgia, encephalitis, flu, herpangina, foot-and-mouth disease, asthma, chronic obstructive pulmonary disease, pneumonia, sinusitis or otitis media.

[0038] Another embodiment provides a compound as described above, or a pharmaceutically acceptable salt thereof, as a medicament.

[0039] Also within the scope is the use of a compound described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a viral disease and/or infection in a human being.

[0040] Included within the scope is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0041] According to a further aspect of this embodiment the pharmaceutical composition further comprises a therapeutically effective amount of at least one other antiviral agent.

[0042] The disclosure also provides the use of a pharmaceutical composition as described hereinabove for the treatment of a viral infection or other virus in a human being having or at risk of having the infection.

[0043] The disclosure also provides the use of a pharmaceutical composition as described hereinabove for the treatment of viral disease or other virus infection in a human being having or at risk of having the disease.

[0044] Another aspect involves a method of treating or preventing a virus disease and/or infection in a human being by administering to the human being an antivirally effective amount

of a compound described herein, a pharmaceutically acceptable salt thereof, or a composition as described above, alone or in combination with at least one other antiviral agent, administered together or separately.

[0045] Still another aspect relates to an article of manufacture comprising a composition effective to treat a poliovirus 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 virus; wherein the composition comprises a compound described herein according to this disclosure or a pharmaceutically acceptable salt thereof.

[0046] An additional aspect refers to an article of manufacture comprising a composition effective to treat a herpesvirus 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 virus; wherein the composition comprises a compound described herein according to this disclosure or a pharmaceutically acceptable salt thereof.

[0047] Still another aspect relates to a method of inhibiting the replication of a virus, comprising exposing the virus to an effective amount of a compound described herein, or a salt thereof, under conditions where replication of the virus is inhibited. This method can be practiced in vitro or in vivo.

[0048] Further included in the scope is the use of a compound described herein, or a salt thereof, to inhibit the replication of a virus.

[0049] In one embodiment, is provided a pharmaceutical composition comprising a compound described herein and another therapeutic agent(s). Optionally, the pharmaceutical composition may comprise a pharmaceutically acceptable carrier, as described above. In some embodiments, the compound described herein is co-administered with at least one additional agent selected from: including another virus inhibitor.

[0050] These additional agents may be combined with the compounds described herein 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 described herein, or a pharmaceutically acceptable salt thereof.

[0051] The dose range of the compounds described herein applicable per day is usually from 0.01 to 100 mg/kg of body weight, e.g. from 0.1 to 50 mg/kg of body weight. Each dosage unit may conveniently contain from 5% to 95% active compound (w/w). Sometimes such preparations contain from 20% to 80% active compound.

[0052] 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.

[0053] When the composition described herein comprises a combination of a compound described herein 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 sometimes between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

[0054] 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.

[0055] Many compounds described herein 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 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. In some embodiments, 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 herpesvirus DNA polymerase in vitro assay described herein and will be the single isomer. Where in vitro activity differences between isomers are relatively small, e.g. less than about a factor of 4, a single isomer may be selected based on activity level against viral replication in cell culture, using methods such as those described herein: e.g. the isomer having a lower IC₅₀ or EC₅₀.

[0056] The compounds described herein may be synthesized by the general synthetic routes below, specific examples of which are described in more detail in the Examples.

[0057] Also provided are methods of making compounds as described herein and intermediates useful for preparation of compounds described herein. The disclosure thus also includes a method to make a compound described herein. The disclosure further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed in situ under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure material.

[0058] The disclosure relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the disclosure is produced under the process conditions and processed further in situ.

[0059] The term “an optical isomer” or “a stereoisomer” refers to any of the various stereoisomeric configurations which may exist for a given compound described herein 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 disclosure 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*)-.

[0060] 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 disclosure is meant to include all such possible stereoisomers, including racemic mixtures, diastereomeric 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.

[0061] 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.

[0062] 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 described herein 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-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent.

[0063] Furthermore, the compounds described herein, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds described herein may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the disclosure embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound described herein (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.

[0064] The compounds described herein, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

[0065] As used herein, the terms “salt” or “salts” refers to an acid addition or base addition salt of a compound described herein. “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 described herein and, which typically are not biologically or otherwise undesirable. In many cases, the compounds described herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0066] 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, chlorotheophyllonate, 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, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

[0067] Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

[0068] 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.

[0069] 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.

[0070] 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, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

[0071] The pharmaceutically acceptable salts of the present disclosure 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).

[0072] Any formula given herein is intended to represent unlabeled forms as well as isotopically labeled forms of the compounds described herein 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 described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{125}I respectively. The disclosure includes various isotopically labeled compounds described herein, for example those into which radioactive isotopes, such as ^3H and ^{14}C , or those in which non-radioactive isotopes, such as ^2H 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 ^2H or ^3H), 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 described herein may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds described herein 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.

[0073] Further, more extensive substitution with heavier isotopes, particularly deuterium (i.e., ^2H 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 described herein, 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 described herein 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).

[0074] Pharmaceutically acceptable solvates in accordance with the disclosure include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O , d^6 -acetone, d^6 -DMSO.

[0075] Compounds described herein 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 described herein by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds described herein 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 disclosure further provides co-crystals comprising a compound described herein.

[0076] 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 disclosure and does not pose a limitation on the scope of the disclosure otherwise claimed.

[0077] The compounds described herein can be administered by known methods, including oral, parenteral, inhalation, and the like. In certain embodiments, the compound described herein is administered orally, as a pill, lozenge, troche, capsule, solution, or suspension. In other embodiments, a compound described herein 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 described herein is administered intranasally or by inhalation; inhalation methods are particularly useful for treatment of respiratory infections. Compounds described herein exhibit oral bioavailability, so in some embodiments, the compound may be administered orally.

[0078] A compound described herein may also be used in combination with other agents (combination partners), e.g., an additional antiviral agent, for treatment of a viral infection in a subject.

[0079] 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 described herein 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.

[0080] In certain embodiments of the present disclosure, a compound described herein is used in combination with a second antiviral agent, such as those named herein.

[0081] The second antiviral agent may be administered in combination with the compounds described herein wherein the second antiviral agent is administered prior to, simultaneously, or after the compound or compounds described herein. When simultaneous administration of a compound described herein with a second agent is desired and the route of administration is the

same, then a compound described herein may be formulated with a second agent into the same dosage form. An example of a dosage form containing a compound described herein and a second agent is a tablet or a capsule.

[0082] In some embodiments, a combination of a compound described herein and a second antiviral agent may provide synergistic activity. The compound described herein and second antiviral agent may be administered together, separate but simultaneously, or sequentially.

[0083] 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 viral inhibitor of a compound described herein is an amount sufficient to treat viral infection in a subject. In another example, an effective amount of the inhibitor is an amount sufficient to treat a viral infection, 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 described herein. For example, the choice of the compound described herein 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 described herein without undue experimentation.

[0084] The regimen of administration can affect what constitutes an effective amount. The compound described herein 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) described herein can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

[0085] Compounds described herein 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 disclosure provides methods of use of compounds described herein in the treatment of these diseases or for preparation of pharmaceutical compositions having compounds described herein for the treatment of these diseases.

[0086] The language “pharmaceutical composition” includes preparations suitable for administration to mammals, *e.g.*, humans. When the compounds described herein 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% (*e.g.*, 0.5 to 90%) of at least

one compound described herein or any subgenus thereof as active ingredient in combination with a pharmaceutically acceptable carrier, or optionally two or more pharmaceutically acceptable carriers.

[0087] The phrase “pharmaceutically acceptable carrier” is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds described herein 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.

[0088] 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.

[0089] 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, α -tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0090] Formulations of the present disclosure 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, sometimes from about 5 per cent to about 70 per cent, sometimes from about 10 per cent to about 30 per cent.

[0091] Methods of preparing these formulations or compositions include the step of bringing into association a compound described herein 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 described herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0092] Formulations of the disclosure 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 described herein as an active ingredient. A compound described herein may also be administered as a bolus, electuary or paste.

[0093] In solid dosage forms of the disclosure 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 as 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.

[0094] 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.

[0095] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present disclosure, 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 e.g., 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.

[0096] Liquid dosage forms for oral administration of the compounds described herein 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.

[0097] 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.

[0098] 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.

[0099] Formulations of the pharmaceutical compositions described herein for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds described herein 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.

[0100] Formulations described herein 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.

[0101] Dosage forms for the topical or transdermal administration of a compound described herein 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.

[0102] The ointments, pastes, creams and gels may contain, in addition to an active compound described herein, 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.

[0103] Powders and sprays can contain, in addition to a compound described herein, 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.

[0104] Transdermal patches have the added advantage of providing controlled delivery of a compound described here into 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.

[0105] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this disclosure.

[0106] Pharmaceutical compositions described herein suitable for parenteral administration may comprise one or more compounds described herein 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.

[0107] Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions described herein 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] The preparations described herein 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.

[0112] 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 method of delivery for compounds described herein. Infusion may be used to deliver a single daily dose or multiple doses. In some embodiments, a compound described herein 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.

[0113] 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.

[0114] 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.

[0115] Regardless of the route of administration selected, the compounds described herein, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions described herein, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

[0116] Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein 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.

[0117] The selected dosage level will depend upon a variety of factors including the activity of the particular compound described herein 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.

[0118] 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 described herein 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.

[0119] In general, a suitable daily dose of a compound described herein 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 described herein 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, sometimes from about 0.01 to about 50 mg per kg per day, and still sometimes 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.

[0120] 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.

[0121] While it is possible for a compound described herein to be administered alone, sometimes the compound may be administered as a pharmaceutical composition such as those described herein. Thus methods of using the compounds described herein include administering the compound as a pharmaceutical composition, wherein at least one compound described herein is admixed with a pharmaceutically acceptable carrier prior to administration.

General Synthetic Procedures

[0122] 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.

[0123] All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesize the compounds described herein 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).

List Of Abbreviations

Ac	acetyl
EtOAc	ethyl acetate
DCM	dichloromethane
DEA	diethanolamine
DIPEA / DIEA	<i>N</i> -ethyldiisopropylamine

DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOH	ethanol
h	hour(s)
HATU	O-(7-azabenzotriazole-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography
IPA	isopropanol
L	liter(s)
LCMS	liquid chromatography mass spectrometry
mg	milligram
min	minute(s)
mL	milliliter
R _t	retention time
THF	tetrahydrofuran

[0124] Compounds described herein are prepared from commonly available compounds using procedures known to those skilled in the art in view of the examples provided herein.

[0125] Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds described herein 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. 41627 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/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, 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).

[0126] Salts of compounds described herein having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds described herein 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 sometimes being used. Acid addition salts of compounds described herein are obtained in customary manner, e.g., by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds described herein 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.

[0127] 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.

[0128] Mixtures of isomers obtainable according to the disclosure 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.

[0129] 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.

High Resolution Mass Spectrometry by LC-MS

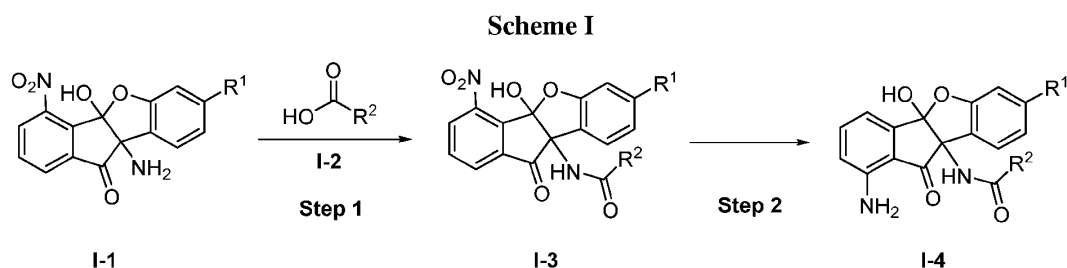
[0130] ESI-MS data were recorded using a LTQ-XL Orbitrap mass spectrometer (ThermoFisher Scientific) with electrospray ionization source. The resolution of the MS system was approximately 30000. The compound was infused into the mass spectrometer by UPLC (Acquity, Waters) from sample probe. The separation was performed on Acquity UPLC BEH C18 1x50 mm column at 0.15 mL/min flow rate with the gradient from 5% to 95% in 3 min. Solvent A was water with 0.1% trifluoroacetic acid and solvent B was 75% methanol and 25% Isopropyl alcohol with 0.1% trifluoroacetic acid. The mass accuracy of the system has been found to be <5 ppm.

EXAMPLES

[0131] The disclosure is further illustrated by the following examples, which should not be construed as limiting. The assays used throughout the Examples are well established in the art: demonstration of efficacy in these assays is generally regarded as predictive of efficacy in subjects.

General Synthesis

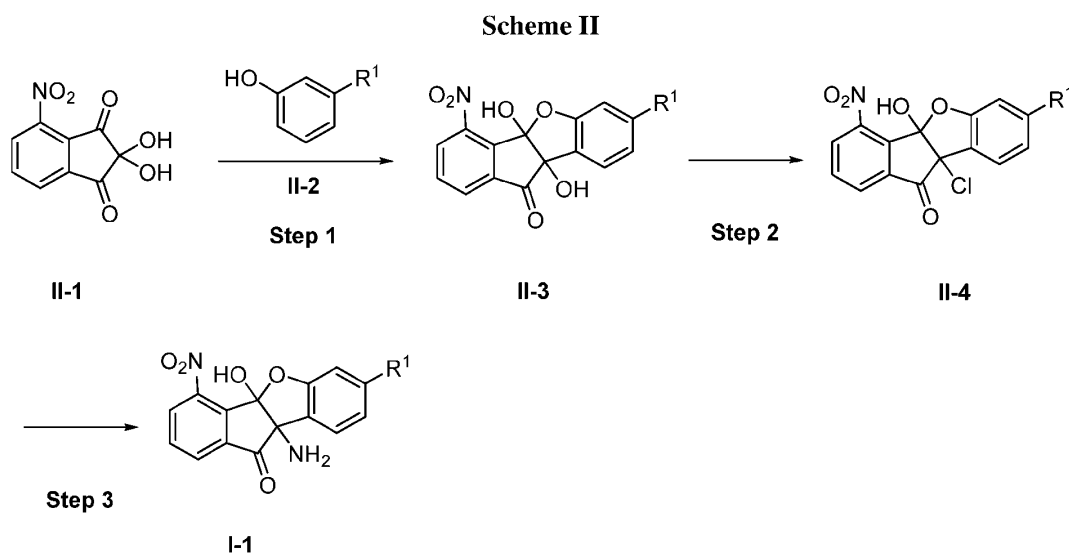
[0132] The compounds of Table 1 and Table 2 were, or can be, prepared according to the procedure described below in Scheme I using the appropriate starting materials and reagents, where R¹ and R² are each independently defined in the compounds described herein and the examples below. Additional information regarding the synthesis, including intermediates, reagents, or methods, may be found in WO2021/214080, which is hereby incorporated by reference.



[0133] Step 1: Compound I-2 (e.g., 1.2 eq) is dissolved in solvent (e.g., DMF, 0.1 M) and the solution is cooled to 0 °C. EDCI (e.g., 1.5 eq) and HOBT (e.g., 1.5 eq) are added at 0 °C. After stirring at 0 °C for 10 min, Compound I-1 (e.g., 1.0 eq) and DIPEA (e.g., 2.5 eq) are added. The solution is stirred at 25 °C overnight (e.g., 16 h). H₂O is added and extracted with EA. The organic layer is washed with brine, dried over anhydrous Na₂SO₄, concentrated *in vacuo*, and purified by silica gel column chromatography to provide Compound I-3.

[0134] Step 2: Compound I-3 (e.g., 1 eq) is dissolved in EtOH:H₂O (e.g., 0.03 M, 10:1). Fe (e.g., 3 eq) and concentrated HCl (e.g., 1 drop) are added to the solution. The solution is heated at 90 °C for 3 h and cooled to room temperature. The reaction mixture is evaporated *in vacuo*. The crude is diluted with EtOAc and filtered through the pad of celite. The solution is evaporated *in vacuo* and purified by silica gel column chromatography to give the desired product.

[0135] Additional information regarding the synthesis, including intermediates, reagents, or methods for preparing compounds of Formula I-1 for use in Scheme I can be found in WO2021/214080 and US20140114068, which are hereby incorporated by reference. One such method is shown below in Scheme II, where R¹ is defined in the compounds described herein and the examples below.



[0136] Step 1: Compound II-1 is reacted with Compound II-2 in acetic acid to provide Compound II-3.

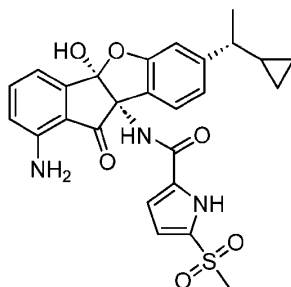
[0137] Step 2: Compound II-3 is reacted with oxalyl chloride in a solvent (e.g., DMF (10 vol.), DCM/DMF) at elevated temperature (e.g., 40 °C) to provide compound II-4.

[0138] Step 3: Compound II-4 is reacted with NH₃ in IPA (e.g., 2 M) in a solvent (e.g., THF) at -40 °C to 0 °C over 2 hours to provide Compound I-1.

[0139] Appropriate starting materials and reagents can be purchased or prepared by methods known to one of skill in the art. Upon each reaction completion, each of the intermediate or final compounds can be recovered, and optionally purified, by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration and the like.

[0140] The compounds of Table 1 were prepared and characterized according to procedures similar to as those described above or known in the art using the appropriate starting materials and reagents.

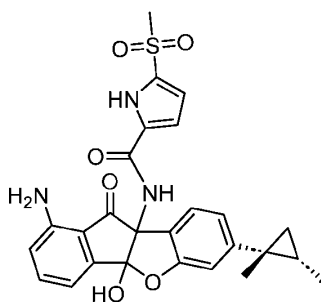
Example 1: N-((4b*R*,9b*R*)-1-amino-7-((*R*)-1-cyclopropylethyl)-4b-hydroxy-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxamide



[0141] Example 1 was prepared according to the General Synthesis and Scheme I above using (4b*R*,9b*R*)-9b-amino-7-((*R*)-1-cyclopropylethyl)-4b-hydroxy-4-nitro-4b,9b-dihydro-10H-indeno[1,2-b]benzofuran-10-one and 5-(methylsulfonyl)-1H-pyrrole-2-carboxylic acid as Compound I-1 and Compound I-2, respectively, and according to the General Synthesis and Scheme II above using (*R*)-3-(1-cyclopropylethyl)phenol as Compound II-2, with further purification by chiral HPLC under the following conditions (Injection volume: 2 μ L; Column: CHIRALPAK AD-3 (0.46 x 5 cm, 3 μ m); Mobile phase: hexane (0.1% DEA):EtOH 50:50; Flow rate: 1.0 mL/min; Wavelength: 256 nm), to give the title compound (*R*_t= 5.7 min).

[0142] LCMS-ESI⁺ (*m/z*): [*M*+*H*]⁺ calcd for C₂₆H₂₆N₃O₆S: 508.15; found: 507.9.

Example 2: N-(1-amino-7-((1*R*,2*S*)-1,2-dimethylcyclopropyl)-4b-hydroxy-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxamide

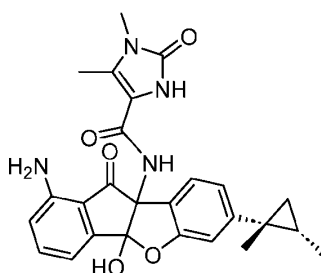


[0143] Example 2 was prepared according to the General Synthesis and Schemes I and II above using 9b-amino-7-((1*R*,2*S*)-1,2-dimethylcyclopropyl)-4b-hydroxy-4-nitro-4b,9b-dihydro-10H-indeno[1,2-b]benzofuran-10-one and 5-(methylsulfonyl)-1H-pyrrole-2-carboxylic acid as

Compound I-1 and Compound I-2, respectively, and according to the General Synthesis and Scheme II above using 3-((1*R*,2*S*)-1,2-dimethylcyclopropyl)phenol as Compound II-2.

[0144] LCMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₂₆H₂₆N₃O₆S: 508.15; found: 507.9.

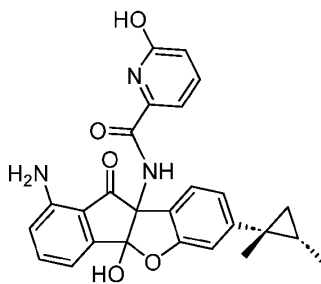
Example 3: N-(1-amino-7-((1*R*,2*S*)-1,2-dimethylcyclopropyl)-4b-hydroxy-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-1,5-dimethyl-2-oxo-2,3-dihydro-1H-imidazole-4-carboxamide



[0145] Example 3 was prepared according to the General Synthesis and Schemes I and II above using 9b-amino-7-((1*R*,2*S*)-1,2-dimethylcyclopropyl)-4b-hydroxy-4-nitro-4b,9b-dihydro-10H-indeno[1,2-b]benzofuran-10-one and 1,5-dimethyl-2-oxo-2,3-dihydro-1H-imidazole-4-carboxylic acid as Compound I-1 and Compound I-2, respectively, and according to the General Synthesis and Scheme II above using 3-((1*R*,2*S*)-1,2-dimethylcyclopropyl)phenol as Compound II-2.

[0146] LCMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₂₆H₂₇N₄O₅: 475.20; found: 474.9.

Example 4: N-(1-amino-7-((1*R*,2*S*)-1,2-dimethylcyclopropyl)-4b-hydroxy-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-6-hydroxypicolinamide

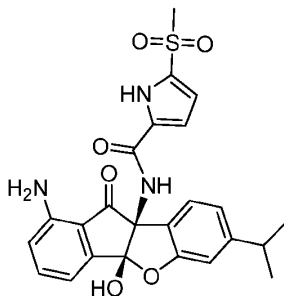


[0147] Example 4 was prepared according to the General Synthesis and Schemes I and II above using 9b-amino-7-((1*R*,2*S*)-1,2-dimethylcyclopropyl)-4b-hydroxy-4-nitro-4b,9b-dihydro-10H-indeno[1,2-b]benzofuran-10-one and 6-hydroxypicolinic acid as Compound I-1 and

Compound I-2, respectively, and according to the General Synthesis and Scheme II above using 3-((1R,2S)-1,2-dimethylcyclopropyl)phenol as Compound II-2.

[0148] LCMS-ESI⁺ (m/z): [M+H]⁺ calcd for C₂₆H₂₄N₃O₅: 458.17; found: 457.9.

Example 5: N-((4bR,9bR)-1-amino-4b-hydroxy-7-isopropyl-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxamide



[0149] 5-(methylsulfonyl)-1H-pyrrole-2-carboxylic acid (227 mg, 1.2 mmol) was dissolved in DMF (10 mL, 0.1 M). The solution was cooled to 0 °C. EDCI (288 mg, 1.5 mmol) and HOBT (203 mg, 1.5 mmol) were added at 0 °C. After stirring at 0 °C for 10 min, 9b-amino-4b-hydroxy-7-isopropyl-4-nitro-4b,9b-dihydro-10H-indeno[1,2-b]benzofuran-10-one (340 mg, 1.0 mmol) and DIPEA (0.44 mL, 2.5 mmol) were added. The solution was stirred at 25 °C for 16 h. H₂O was added and extracted with EA. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo, and purified by silica gel column chromatography to give N-(4b-hydroxy-7-isopropyl-4-nitro-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxamide.

[0150] N-(4b-hydroxy-7-isopropyl-4-nitro-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxamide (149 mg, 0.29 mmol) was dissolved in EtOH:H₂O (10 mL, 0.03 M, 10:1). Fe (49 mg, 0.90 mmol) and 1 drop of conc. HCl were added to the solution. The solution was heated at 90 °C for 3 h and cooled to room temperature. The reaction mixture was evaporated in vacuo. The crude was diluted with EtOAc and filtered through the pad of celite. The solution was evaporated in vacuo and purified by silica gel column chromatography to give the racemate, which was separated by SFC (AS column; 5mL/min, CO₂/MeOH=80:20; SFC-X5; C2_A20; Rt=1.68 min and 3.28 min) to afford N-((4bR,9bR)-1-amino-4b-hydroxy-7-isopropyl-10-oxo-4b,10-dihydro-9bH-indeno[1,2-b]benzofuran-9b-yl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxamide.

[0151] LCMS-ESI⁺ (m/z): [M+H]⁺ calcd for C₂₄H₂₄N₃O₆S: 482.14; found: 481.9.

[0152] ¹H NMR: (300 MHz – MeOD) δ 7.46 (t, J = 7.7 Hz, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.82 (d, J = 3.9 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.79 (d, J = 3.9 Hz, 1H), 6.74 (d, J = 7.3 Hz, 1H), 6.68 (s, 1H), 3.14 (s, 3H), 2.84 (hept, J = 7.0 Hz, 1H), 1.19 (d, J = 6.9 Hz, 6H)

Biochemical Assays

Biochemical Example 1: Determination of Drug Efficacy Against Picornaviruses Using Cytopathic Effect (CPE) Inhibition Assay

[0153] Bioactivity of the compounds described herein can be determined using the following methods.

[0154] In the assay, HeLa (human cervical cancer cells), MRC-5 (human fetal lung fibroblast cells), and RD cells (derived from human rhabdomyosarcoma) can be employed. For comparison, ribavirin (Riv), Pleconaril (pleco), and BTA-798 (BTA) are used as controls. Reagents can be dissolved at a concentration of 10-40 mg/mL in 100% dimethyl sulfoxide (DMSO). Water-soluble reagents can be dissolved in PBS (-) solution and stored at -20 °C. On the day of the experiment, they can be used in 3 fold to 5 fold concentrations in such a manner that the concentration of dimethyl sulfoxide in each well is between 0.5% and 1%.

[0155] Pharmaceutical efficacy is determined using a virus-induced cytopathic effect (CPE) inhibition assay. In this regard, after cells suitable for viruses are grown in 96-well plates, dilutions of viruses in DME supplemented with 2% FBS (DME/2% FBS) or MEM supplemented with 2% FBS (MEM/2% FBS) are inoculated in an amount of 100:1 with a concentration corresponding to 100 CCID₅₀ (50% cell culture infective dose) into each well of the plates, and incubated for 30 min-1 hr at 33 °C or 37 °C to allow the viruses to adsorb onto the cells. The culture medium is removed before aliquots of drug dilutions with various concentrations are added in an amount of 100 μL to each well. While HRV (human rhinovirus) is grown at 33 °C, the other viruses are incubated in a 37 °C CO₂ incubator for 2-3 days. Alternatively, the cells are cultured for 2-3 days without removal of the medium after they are added with 50 μL of each drug dilution having a 2-fold higher concentration and then with 50 μL of the virus dilution. Viruses are incubated in host HeLa cells at 37 °C for 2-3 days in DME/2% or MEM/2% FBS.

[0156] For HeLa cells, the drugs are measured for EC₅₀ (50% maximal effective concentration), which is the concentration of a drug inducing a response halfway between the

baseline and maximum, using an MTT assay. With regard to RD and MRC-5 cells, CPE is determined using FDA (fluorescein diacetate) or MTT. In order to determine the effect of drug toxicity on efficacy results, at the time of inoculation with the virus, mock-infection is also included. A virus-free medium is added to a cell culture, which is then subjected to the same treatment as the mock-infected cells inoculated with the virus. That is, the medium is removed after one hour of incubation, and dilutions of drugs in the medium are added once more. Following incubation for 2-3 days, the cells are observed under a microscope and the drugs are determined for CC_{50} (50% cytotoxic concentration) at which 50% of the cells are killed, using an MTT assay in which counts of viable cells in mock-infected wells containing drugs are compared to those of viable cells in control wells containing no drugs. In an FDA hydrolysis assay, FDA is added to each well after removal of the medium, and incubated for 20-30 min before fluorescence intensity is measured using a spectrofluorometer to determine CPE in the same manner as in MTT. That is, the survival rate (% survival) of mock-infected cells for cytotoxicity measurement is calculated using the Mathematical Formula 1 below:

$$\text{Cell Drug} = \text{Survival by } [A (\text{Drug}) - A (\text{Background solution}) / A (\text{Cell control}) - A (\text{Background} \times 100\% \text{ Solution})]$$

[0157] While 100% cell survival means no cytotoxicity of the drug, the highest cytotoxicity is reflected by 0% cell survival. The 50% cytotoxic concentration is defined as the concentration required to reduce the cell number by 50%. This concentration of the drug is represented as CC_{50} . Higher values mean lower cytotoxicity.

[0158] In addition, antiviral effects can be calculated using Mathematical Formula 2 below:
 $\text{Antiviral Effect} = [A (\text{Drug/Virus}) - A (\text{Virus Control}) / A (\text{Cell control}) - A (\text{Virus Control})]$

[0159] If the survival rate is 100%, its antiviral effect is 100% whereas if the survival rate is 0%, its antiviral effect is none. While the concentration of a drug at which the cell in a well infected with a virus can exhibit 50% survival rate is calculated as EC_{50} , the lower this value is, the more superior the antiviral effect is.

[0160] In Table 1 below are listed LC_{50} concentrations that exhibit cytotoxicity against the compounds in some examples and EC_{50} concentrations that exhibit activities against a number of rhinoviruses belonging to the picornaviruses.

Determination of Drug Effect Against Picornaviruses Using Multicycle Cytopathic Effect (CPE) Reduction Assay

[0161] The multicycle CPE reduction assay is used to conduct determination of drug efficacy against picornaviruses. The antiviral activity of a compound is initially determined by the CPE reduction assay based on MIS [3-(4, 5-dimethyl thiazol-2-yl)-5-(3-carboxy methoxy phenyl)-2-(4-sulfophenyl)-2H-tetrazolium.

[0162] Specifically, cells grown to confluence in 96-well plates are infected with 100 50% cell culture infected doses (CCID₅₀) of virus. After an adsorption period of 2 hrs at 37 °C, the virus is removed and serial dilutions of the compounds are added. The cultures are further incubated at 37 °C for 3 days until complete CPE is observed in the infected and untreated virus control (VC). After removal of the medium, 90 µL of a culture medium and 10 µL of MTS-phenazine methosulfate (Promega, Leiden, The Netherlands) are added to each well. After an incubation period of 2 hrs at 37 °C, the optical density (OD) of each well is read at 498 nm in a microplate reader.

[0163] The % CPE values for evaluating antiviral activity are calculated using Mathematical Formula 3 below:

$$\% \text{ CPE} = 100 \times [\text{OD (CC)} - \text{OD (Virus + Compound)}] / [\text{OD (CC)} - \text{OD (VC)}]$$

[0164] The % CPE value for measuring cytotoxicity of a drug is calculated by Mathematical Formula 4 below:

$$\% \text{ CPE} = 100 \times [\text{OD (CC)} - \text{OD (Virus + Compound)}] / [\text{OD (CC)} - \text{OD (Blank)}]$$

[0165] In Mathematical Formulae 3 and 4 above,

OD (CC) represents the OD of the background cell culture that is neither induced by a virus nor treated by chemical,

OD (VC) represents the OD of the control cell culture that is induced by a virus but not treated by chemical,

OD (Virus+Compound) represents the OD of the cell culture infected by a virus that has been treated with a concentrated compound,

OD (Compound) represents the OD of the cell culture that has been treated with a concentrated compound only, and

OD (Blank) represents the OD of the well to which only the cell culture has been added.

[0166] The effective concentration (EC₅₀) represents the concentration of a drug at which 50% of cells are allowed to survive by CPE of an induced virus, and the cytotoxicity concentration

(CC₅₀) represents the concentration of a drug at which a compound has killed 50% of cells, and they were calculated by the logarithmic interpolation.

Biochemical Example 2: In Vitro poliovirus type 1 (POV1) antiviral assay

[0167] Compounds were tested for in vitro antiviral activity against poliovirus type 1 (POV-1; Mahoney) in Vero 76 cells. Test media was MEM supplemented with 2% FBS and 50 µg/mL gentamicin.

[0168] Compounds were solubilized in DMSO. Compounds were serially diluted using eight half-log dilutions in test media so that the starting (high) test concentration was 50 µM. Each dilution was added to 5 wells of a 96-well plate with 80-100% confluent cells. Three wells of each dilution were infected with virus, and two wells remained uninfected as toxicity controls. Six wells were infected and untreated as virus controls, and six wells were uninfected and untreated as cell controls. Virus was prepared to achieve a MOI of 0.002. Enviroxime was tested in parallel as a positive control. Plates were incubated at 37±2°C, 5% CO₂. On day 3 post-infection, once untreated virus control wells reached maximum CPE, plates were stained with neutral red dye for approximately 2 hours (±15 minutes). Supernatant dye was removed and wells rinsed with PBS, and the incorporated dye was extracted in 50:50 Sorensen citrate buffer/ethanol for >30 minutes and the optical density was read on a spectrophotometer at 540 nm. Optical densities were converted to percent of cell controls and normalized to the virus control, then the concentration of test compound required to inhibit CPE by 50% (EC₅₀) was calculated by regression analysis. The concentration of compound that would cause 50% cell death in the absence of virus was similarly calculated (CC₅₀). The selective index (SI) is the CC₅₀ divided by EC₅₀.

[0169] In vitro antiviral results against vaccinia virus are shown in Table 3.

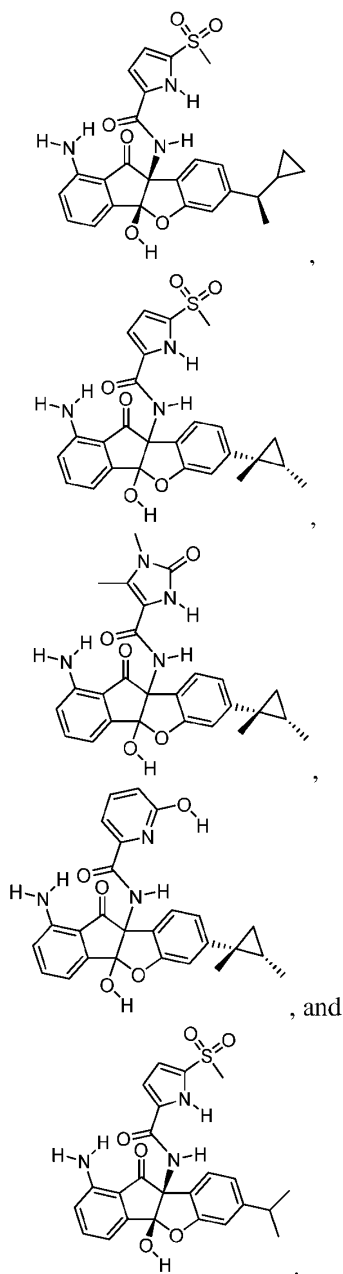
Table 3: Table of Bioactivity Data

Example No.	POV1 EC ₅₀ (nM)
1	80
2	110
3	340
4	60
5	16

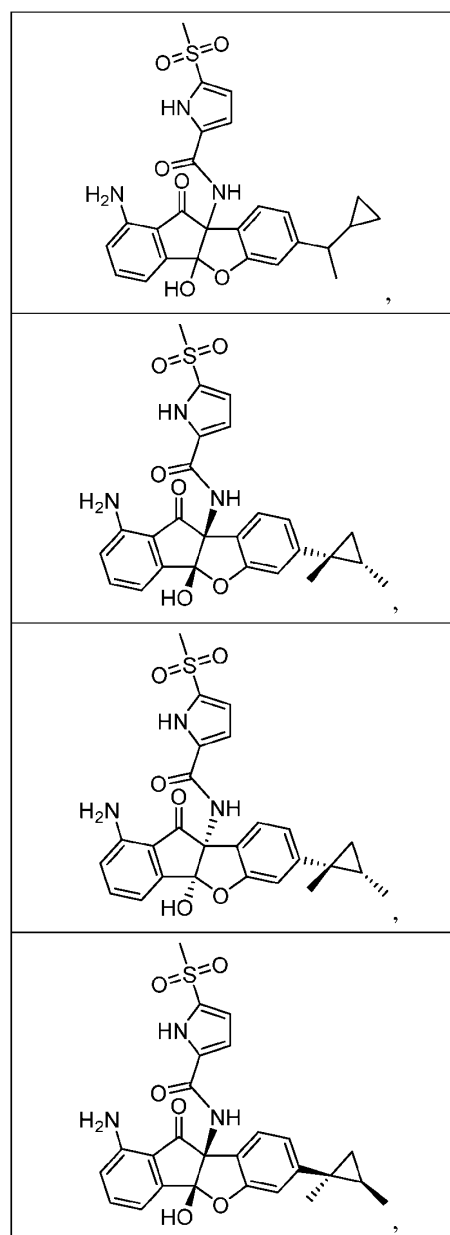
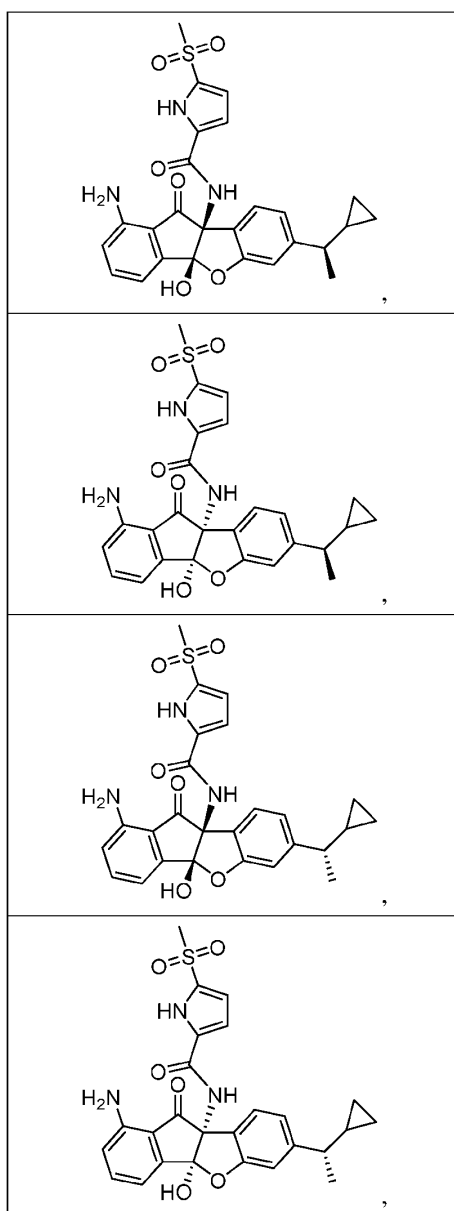
[0170] As is indicated in Table 3 above, compounds according to the present disclosure exhibit antiviral activity against poliovirus-1 (POV1).

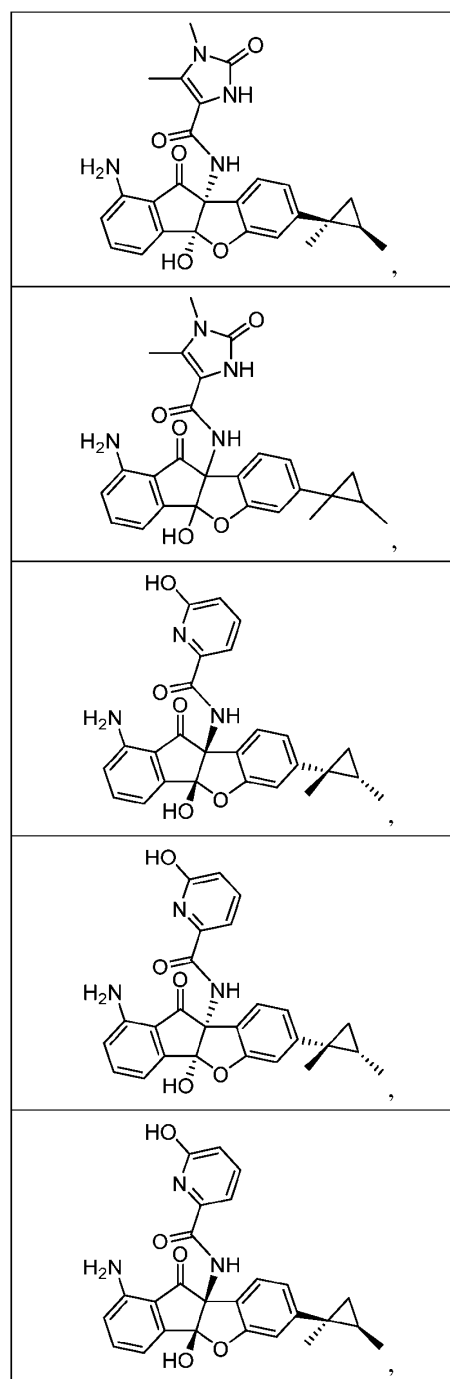
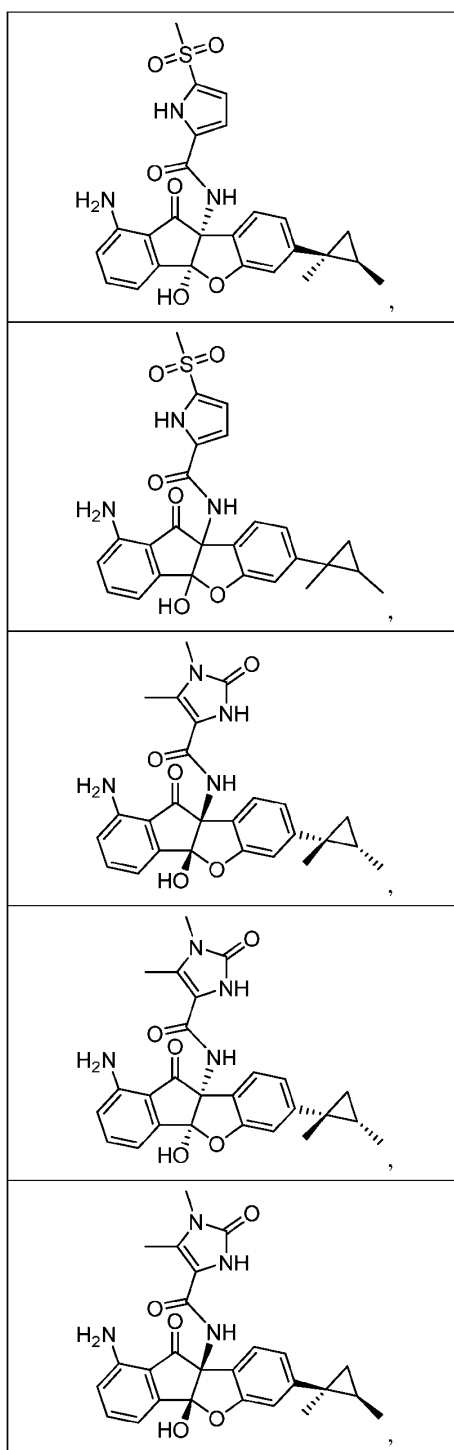
CLAIMS

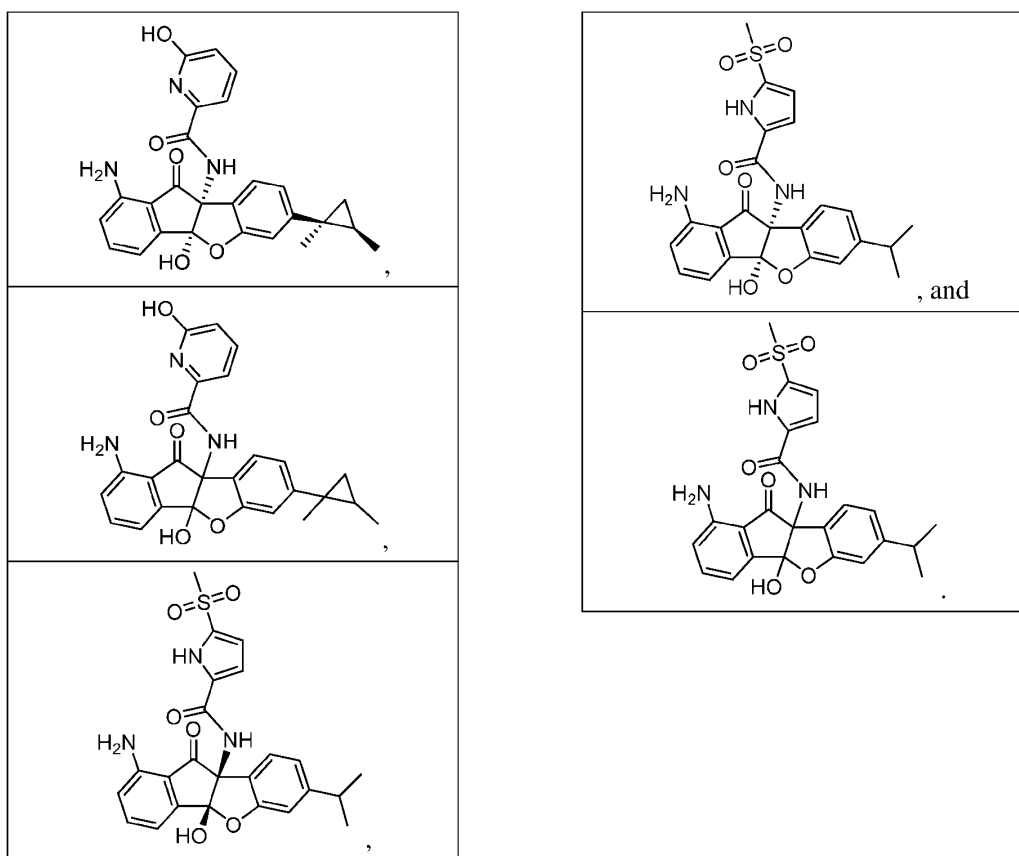
1. A compound, or a pharmaceutically acceptable salt thereof, selected from:



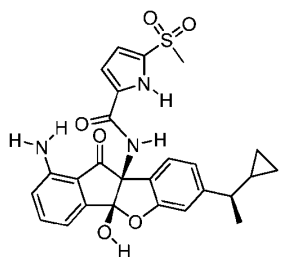
2. A compound, or a pharmaceutically acceptable salt thereof, selected from:



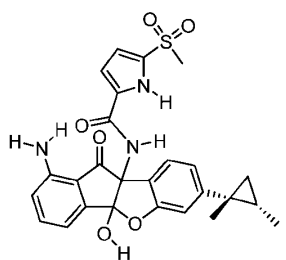




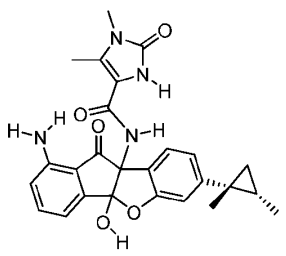
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



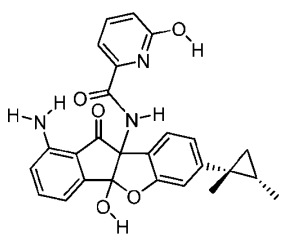
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



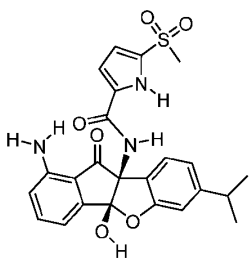
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:



8. A pharmaceutical composition for prevention or treatment of a viral disease, comprising the compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or excipient.
9. A combination comprising a compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8, and one or more therapeutically active agents.
10. A method of treating a viral disease comprising administering to a subject a therapeutically effective amount of a compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8, or a combination of claim 9.
11. Use of a compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8, or a combination of claim 9, for the prevention or treatment of a viral disease.
12. Use of a compound of any one of claims 1-7 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8, or a combination of claim 9, for the manufacture of a medicament for the prevention or treatment of a viral disease.
13. The pharmaceutical composition as set forth in claim 8, or the combination of claim 9, or the method of claim 10, or the use of claim 11 or 12, wherein the viral disease is caused by poliovirus.

14. The pharmaceutical composition as set forth in claim 8, or the combination of claim 9, or the method of claim 10, or the use of claim 11 or 12, wherein the viral disease is caused by coxsackievirus.

15. The pharmaceutical composition as set forth in claim 8, or the combination of claim 9, or the method of claim 10, or the use of claim 11 or 12, wherein the viral disease is caused by echovirus.

16. The pharmaceutical composition as set forth in claim 8, or the combination of claim 9, or the method of claim 10, or the use of claim 11 or 12, wherein the viral disease is caused by enterovirus.

17. The pharmaceutical composition as set forth in claim 8, or the combination of claim 9, or the method of claim 10, or the use of claim 11 or 12, wherein the viral disease is caused by rhinovirus.

18. The pharmaceutical composition as set forth in claim 8, or the combination of claim 9, or the method of claim 10, or the use of claim 11 or 12, wherein the viral disease is caused by picornavirus.

19. The pharmaceutical composition as set forth in claim 8, or the combination of claim 9, or the method of claim 10, or the use of claim 11 or 12, wherein the viral disease is poliomyelitis, paralysis, acute hemorrhagic conjunctivitis, viral meningitis, hand-foot-and-mouth disease, vesicular disease, hepatitis A, myositis, myocarditis, pancreatitis, diabetes, epidemic myalgia, encephalitis, flu, herpangina, foot-and-mouth disease, asthma, chronic obstructive pulmonary disease, pneumonia, sinusitis, or otitis media.