

TITLE OF THE INVENTION

Substituted Polycyclic Carboxylic Acids, Analogues Thereof, and Methods Using Same

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 62/793,578, filed January 17, 2019, which is hereby incorporated by reference in its entirety herein.

BACKGROUND OF THE INVENTION

- 10 Hepatitis B is one of the world's most prevalent diseases. Although most individuals resolve the infection following acute symptoms, approximately 30% of cases become chronic. 350-400 million people worldwide are estimated to have chronic hepatitis B, leading to 0.5-1 million deaths per year, due largely to the development of hepatocellular carcinoma, cirrhosis, and/or other complications. Hepatitis B is caused by hepatitis B virus
15 (HBV), a noncytopathic, liver tropic DNA virus belonging to *Hepadnaviridae* family.

- A limited number of drugs are currently approved for the management of chronic hepatitis B, including two formulations of alpha-interferon (standard and pegylated) and five nucleoside/nucleotide analogues (lamivudine, adefovir, entecavir, telbivudine, and tenofovir) that inhibit HBV DNA polymerase. At present, the first-line treatment choices are entecavir,
20 tenofovir, or peg-interferon alfa-2a. However, peg-interferon alfa-2a achieves desirable serological milestones in only one third of treated patients and is frequently associated with severe side effects. Entecavir and tenofovir require long-term or possibly lifetime administration to continuously suppress HBV replication, and may eventually fail due to emergence of drug-resistant viruses.

- 25 HBV is an enveloped virus with an unusual mode of replication, centering on the establishment of a covalently closed circular DNA (cccDNA) copy of its genome in the host cell nucleus. Pregenomic (pg) RNA is the template for reverse transcriptional replication of HBV DNA. The encapsidation of pg RNA, together with viral DNA polymerase, into a nucleocapsid is essential for the subsequent viral DNA synthesis.

- 30 Aside from being a critical structural component of the virion, the HBV envelope is a major factor in the disease process. In chronically infected individuals, serum levels of HBV surface antigen (HBsAg) can be as high as 400 µg/ml, driven by the propensity for infected cells to secrete non-infectious subviral particles at levels far in excess of infectious (Dane) particles. HBsAg comprises the principal antigenic determinant in HBV infection and is

composed of the small, middle and large surface antigens (S, M and L, respectively). These proteins are produced from a single open reading frame as three separate N-glycosylated polypeptides through utilization of alternative transcriptional start sites (for L and M/S mRNAs) and initiation codons (for L, M and S).

5 Although the viral polymerase and HBsAg perform distinct functions, both are essential proteins for the virus to complete its life cycle and be infectious. HBV lacking HBsAg is completely defective and cannot infect or cause infection. HBsAg protects the virus nucleocapsid, begins the infectious cycle, and mediates morphogenesis and secretion of newly forming virus from the infected cell.

10 People chronically infected with HBV are usually characterized by readily detectable levels of circulating antibody specific to the viral capsid (HBc), with little, if any detectable levels of antibody to HBsAg. There is evidence that chronic carriers produce antibodies to HBsAg, but these antibodies are complexed with the circulating HBsAg, which can be present in mg/mL amounts in a chronic carrier's circulation. Reducing the amount of
15 circulating levels of HBsAg might allow any present anti-HBsA to manage the infection. Further, even if nucleocapsids free of HBsAg were to be expressed or secreted into circulation (perhaps as a result of cell death), the high levels of anti-HBc would quickly complex with them and result in their clearance.

 Studies have shown that the presence of subviral particles in a culture of infected
20 hepatocytes may have a transactivating function on viral genomic replication, and the circulating surface antigen suppresses virus-specific immune response. Furthermore, the scarcity of virus-specific cytotoxic T lymphocytes (CTLs), that is a hallmark of chronic HBV infection, may be due to repression of MHC I presentation by intracellular expression of L and M in infected hepatocytes. Existing FDA-approved therapies do not significantly affect
25 HBsAg serum levels.

 Hepatitis D virus (HDV) is a small circular enveloped RNA virus that can propagate only in the presence of the hepatitis B virus (HBV). In particular, HDV requires the HBV surface antigen protein to propagate itself. Infection with both HBV and HDV results in more severe complications compared to infection with HBV alone. These complications
30 include a greater likelihood of experiencing liver failure in acute infections and a rapid progression to liver cirrhosis, with an increased chance of developing liver cancer in chronic infections. In combination with hepatitis B virus, hepatitis D has the highest mortality rate of all the hepatitis infections. The routes of transmission of HDV are similar to those for HBV. Infection is largely restricted to persons at high risk of HBV infection, particularly injecting

DETAILED DESCRIPTION OF THE INVENTION

The invention relates, in certain aspects, to the discovery of certain substituted tricyclic compounds that are useful to treat and/or prevent HBV and/or HBV-HDV infection and related conditions in a subject. In certain embodiments, the compounds inhibit and/or
5 reduce HBsAg secretion in a HBV-infected subject. In other embodiments, the compounds reduce or minimize levels of HBsAg in a HBV-infected subject. In yet other embodiments, the compounds reduce or minimize levels of HBeAg in a HBV-infected subject. In yet other
10 embodiments, the compounds reduce or minimize levels of hepatitis B core protein in a HBV-infected subject. In yet other embodiments, the compounds reduce or minimize levels of pg RNA in a HBV-infected subject. In yet other embodiments, the HBV-infected subject is further HDV-infected.

Definitions

As used herein, each of the following terms has the meaning associated with it in this
15 section.

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in animal pharmacology, pharmaceutical science, separation science, and organic chemistry are
20 those well-known and commonly employed in the art. It should be understood that the order of steps or order for performing certain actions is immaterial, so long as the present teachings remain operable. Moreover, two or more steps or actions can be conducted simultaneously or not.

The following non-limiting abbreviations are used herein: cccDNA, covalently
25 closed circular DNA; HBc, hepatitis B capsid; HBV, hepatitis B virus; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B virus surface antigen; pg RNA, pregenomic RNA.

As used herein, the articles “a” and “an” refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

30 As used herein, the term “alkenyl,” employed alone or in combination with other terms, means, unless otherwise stated, a stable monounsaturated or diunsaturated straight chain or branched chain hydrocarbon group having the stated number of carbon atoms. Examples include vinyl, propenyl (or allyl), crotyl, isopentenyl, butadienyl, 1,3-pentadienyl, 1,4-pentadienyl, and the higher homologs and isomers. A functional group representing an

alkene is exemplified by $-\text{CH}_2-\text{CH}=\text{CH}_2$.

As used herein, the term “alkoxy” employed alone or in combination with other terms means, unless otherwise stated, an alkyl group having the designated number of carbon atoms, as defined elsewhere herein, connected to the rest of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy (or isopropoxy), and the higher homologs and isomers. A specific example is (C_1-C_3) alkoxy, such as, but not limited to, ethoxy and methoxy.

As used herein, the term “alkyl” by itself or as part of another substituent means, unless otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms designated (*i.e.*, C_1-C_{10} means one to ten carbon atoms) and includes straight, branched chain, or cyclic substituent groups. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, neopentyl, hexyl, and cyclopropylmethyl. A specific embodiment is (C_1-C_6) alkyl, such as, but not limited to, ethyl, methyl, isopropyl, isobutyl, *n*-pentyl, *n*-hexyl, and cyclopropylmethyl.

As used herein, the term “alkynyl” employed alone or in combination with other terms means, unless otherwise stated, a stable straight chain or branched chain hydrocarbon group with a triple carbon-carbon bond, having the stated number of carbon atoms. Non-limiting examples include ethynyl and propynyl, and the higher homologs and isomers. The term “propargylic” refers to a group exemplified by $-\text{CH}_2-\text{C}\equiv\text{CH}$. The term “homopropargylic” refers to a group exemplified by $-\text{CH}_2\text{CH}_2-\text{C}\equiv\text{CH}$.

As used herein, the term “aromatic” refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, *i.e.*, having $(4n+2)$ delocalized π (pi) electrons, where ‘*n*’ is an integer.

As used herein, the term “aryl” employed alone or in combination with other terms means, unless otherwise stated, a carbocyclic aromatic system containing one or more rings (typically one, two or three rings) wherein such rings may be attached together in a pendent manner, such as a biphenyl, or may be fused, such as naphthalene. Examples include phenyl, anthracyl, and naphthyl. Aryl groups also include, for example, phenyl or naphthyl rings fused with one or more saturated or partially saturated carbon rings (*e.g.*, bicyclo[4.2.0]octa-1,3,5-trienyl, or indanyl), which can be substituted at one or more carbon atoms of the aromatic and/or saturated or partially saturated rings.

As used herein, the term “aryl- (C_1-C_6) alkyl” refers to a functional group wherein a one to six carbon alkanediyl chain is attached to an aryl group, *e.g.*, $-\text{CH}_2\text{CH}_2$ -phenyl or $-\text{CH}_2$ -phenyl (or benzyl). Specific examples are aryl- CH_2 - and aryl- $\text{CH}(\text{CH}_3)$ -. The term

“substituted aryl-(C₁-C₆)alkyl” refers to an aryl-(C₁-C₆)alkyl functional group in which the aryl group is substituted. A specific example is [substituted aryl]-(CH₂)-. Similarly, the term “heteroaryl-(C₁-C₆)alkyl” refers to a functional group wherein a one to three carbon alkanediyl chain is attached to a heteroaryl group, *e.g.*, -CH₂CH₂-pyridyl. A specific example is heteroaryl-(CH₂)-. The term “substituted heteroaryl-(C₁-C₆)alkyl” refers to a heteroaryl-(C₁-C₆)alkyl functional group in which the heteroaryl group is substituted. A specific example is [substituted heteroaryl]-(CH₂)-.
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In one aspect, the terms “co-administered” and “co-administration” as relating to a subject refer to administering to the subject a compound and/or composition of the invention along with a compound and/or composition that may also treat or prevent a disease or disorder contemplated herein. In certain embodiments, the co-administered compounds and/or compositions are administered separately, or in any kind of combination as part of a single therapeutic approach. The co-administered compound and/or composition may be formulated in any kind of combinations as mixtures of solids and liquids under a variety of solid, gel, and liquid formulations, and as a solution.
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As used herein, the term “cycloalkyl” by itself or as part of another substituent refers to, unless otherwise stated, a cyclic chain hydrocarbon having the number of carbon atoms designated (*i.e.*, C₃-C₆ refers to a cyclic group comprising a ring group consisting of three to six carbon atoms) and includes straight, branched chain, or cyclic substituent groups. Examples of (C₃-C₆)cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Cycloalkyl rings can be optionally substituted. Non-limiting examples of cycloalkyl groups include: cyclopropyl, 2-methyl-cyclopropyl, cyclopropenyl, cyclobutyl, 2,3-dihydroxycyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctanyl, decalanyl, 2,5-dimethylcyclopentyl, 3,5-dichlorocyclohexyl, 4-hydroxycyclohexyl, 3,3,5-trimethylcyclohex-1-yl, octahydropentalenyl, octahydro-1*H*-indenyl, 3a,4,5,6,7,7a-hexahydro-3*H*-inden-4-yl, decahydroazulenyl; bicyclo[6.2.0]decanyl, decahydronaphthalenyl, and dodecahydro-1*H*-fluorenyl. The term “cycloalkyl” also includes bicyclic hydrocarbon rings, non-limiting examples of which include bicyclo-[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, 1,3-dimethyl[2.2.1] heptan-2-yl, bicyclo[2.2.2]octanyl, and bicyclo[3.3.3]undecanyl.
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As used herein, a “disease” is a state of health of a subject wherein the subject cannot maintain homeostasis, and wherein if the disease is not ameliorated then the subject’s health continues to deteriorate.

As used herein, a “disorder” in a subject is a state of health in which the subject is able to maintain homeostasis, but in which the subject’s state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the subject’s state of health.

5 As used herein, the term “halide” refers to a halogen atom bearing a negative charge. The halide anions are fluoride (F^-), chloride (Cl^-), bromide (Br^-), and iodide (I^-).

As used herein, the term “halo” or “halogen” alone or as part of another substituent refers to, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

As used herein, the term “Hepatitis B virus” (or HBV) refers to a virus species of the genus Orthohepadnavirus, which is a part of the Hepadnaviridae family of viruses, and that is capable of causing liver inflammation in humans.

As used herein, the term “Hepatitis D virus” (or HDV) refers to a virus species of the genus Deltaviridae, which is capable of causing liver inflammation in humans. The HDV particle comprises an envelope, which is provided by HBV and surrounds the RNA genome and the HDV antigen. The HDV genome is a single, negative stranded, circular RNA molecule nearly 1.7 kb in length. The genome contains several sense and antisense open reading frames (ORFs), only one of which is functional and conserved. The RNA genome is replicated through an RNA intermediate, the antigenome. The genomic RNA and its complement, the antigenome, can function as ribozymes to carry out self-cleavage and self-ligation reactions. A third RNA present in the infected cell, also complementary to the genome, but 800 bp long and polyadenylated, is the mRNA for the synthesis of the delta antigen (HDAg).

As used herein, the term “heteroalkenyl” by itself or in combination with another term refers to, unless otherwise stated, a stable straight or branched chain monounsaturated or diunsaturated hydrocarbon group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. Up to two heteroatoms may be placed consecutively. Examples include -CH=CH-O-CH₃, -CH=CH-CH₂-OH, -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, and -CH₂-CH=CH-CH₂-SH.

As used herein, the term “heteroalkyl” by itself or in combination with another term refers to, unless otherwise stated, a stable straight or branched chain alkyl group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may be optionally

oxidized and the nitrogen heteroatom may be optionally quaternized. The heteroatom(s) may be placed at any position of the heteroalkyl group, including between the rest of the heteroalkyl group and the fragment to which it is attached, as well as attached to the most distal carbon atom in the heteroalkyl group. Examples include: -OCH₂CH₂CH₃, -CH₂CH₂CH₂OH, -CH₂CH₂NHCH₃, -CH₂SCH₂CH₃, and -CH₂CH₂S(=O)CH₃. Up to two heteroatoms may be consecutive, such as, for example, -CH₂NH-OCH₃, or -CH₂CH₂SSCH₃.

As used herein, the term “heteroaryl” or “heteroaromatic” refers to a heterocycle having aromatic character. A polycyclic heteroaryl may include one or more rings that are partially saturated. Examples include tetrahydroquinoline and 2,3-dihydrobenzofuryl.

As used herein, the term “heterocycle” or “heterocyclyl” or “heterocyclic” by itself or as part of another substituent refers to, unless otherwise stated, an unsubstituted or substituted, stable, mono- or multi-cyclic heterocyclic ring system that comprises carbon atoms and at least one heteroatom selected from the group consisting of N, O, and S, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen atom may be optionally quaternized. The heterocyclic system may be attached, unless otherwise stated, at any heteroatom or carbon atom that affords a stable structure. A heterocycle may be aromatic or non-aromatic in nature. In certain embodiments, the heterocycle is a heteroaryl.

Examples of non-aromatic heterocycles include monocyclic groups such as aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazoline, pyrazolidine, dioxolane, sulfolane, 2,3-dihydrofuran, 2,5-dihydrofuran, tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydropyridine, 1,4-dihydropyridine, piperazine, morpholine, thiomorpholine, pyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane, homopiperazine, homopiperidine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin and hexamethyleneoxide.

Examples of heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl (such as, but not limited to, 2- and 4-pyrimidinyl), pyridazinyl, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

Examples of polycyclic heterocycles include indolyl (such as, but not limited to, 3-, 4-, 5-, 6- and 7-indolyl), indolinyl, quinolyl, tetrahydroquinolyl, isoquinolyl (such as, but not limited to, 1- and 5-isoquinolyl), 1,2,3,4-tetrahydroisoquinolyl, cinnolinyl, quinoxalinyl (such as, but not limited to, 2- and 5-quinoxalinyl), quinazolinyl, phthalazinyl, 1,8-naphthyridinyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarin, 1,5-naphthyridinyl, benzofuryl (such as, but

not limited to, 3-, 4-, 5-, 6- and 7-benzofuryl), 2,3-dihydrobenzofuryl, 1,2-benzisoxazolyl, benzothienyl (such as, but not limited to, 3-, 4-, 5-, 6-, and 7-benzothienyl), benzoxazolyl, benzothiazolyl (such as, but not limited to, 2-benzothiazolyl and 5-benzothiazolyl), purinyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl.

The aforementioned listing of heterocyclyl and heteroaryl moieties is intended to be representative and not limiting.

As used herein, the term “pharmaceutical composition” or “composition” refers to a mixture of at least one compound useful within the invention with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a subject.

As used herein, the term “pharmaceutically acceptable” refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound useful within the invention, and is relatively non-toxic, *i.e.*, the material may be administered to a subject without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the invention within or to the subject such that it may perform its intended function. Typically, such constructs are carried or transported 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, including the compound useful within the invention, and not injurious to the subject. Some examples of materials that may 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; surface active agents; 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. As used herein, “pharmaceutically acceptable carrier” also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound useful within the invention, and are

5 physiologically acceptable to the subject. Supplementary active compounds may also be incorporated into the compositions. The “pharmaceutically acceptable carrier” may further include a pharmaceutically acceptable salt of the compound useful within the invention. Other additional ingredients that may be included in the pharmaceutical compositions used in the practice of the invention are known in the art and described, for example in Remington’s

10 Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

As used herein, the language “pharmaceutically acceptable salt” refers to a salt of the administered compound prepared from pharmaceutically acceptable non-toxic acids and/or bases, including inorganic acids, inorganic bases, organic acids, inorganic bases, solvates

15 (including hydrates), and clathrates thereof.

As used herein, a “pharmaceutically effective amount,” “therapeutically effective amount,” or “effective amount” of a compound is that amount of compound that is sufficient to provide a beneficial effect to the subject to which the compound is administered.

The term “prevent,” “preventing,” or “prevention” as used herein means avoiding or

20 delaying the onset of symptoms associated with a disease or condition in a subject that has not developed such symptoms at the time the administering of an agent or compound commences. Disease, condition and disorder are used interchangeably herein.

As used herein, the term “RNA Destabilizer” refers to a molecule, or a salt or solvate thereof, that reduces the total amount of HBV RNA in mammalian cell culture or in a live

25 human subject. In a non-limiting example, an RNA Destabilizer reduces the amount of the RNA transcript(s) encoding one or more of the following HBV proteins: surface antigen, core protein, RNA polymerase, and e antigen.

By the term “specifically bind” or “specifically binds” as used herein is meant that a first molecule preferentially binds to a second molecule (*e.g.*, a particular receptor or

30 enzyme), but does not necessarily bind only to that second molecule.

As used herein, the terms “subject” and “individual” and “patient” can be used interchangeably, and may refer to a human or non-human mammal or a bird. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and murine mammals. In certain embodiments, the subject is human.

As used herein, the term “substituted” refers to that an atom or group of atoms has replaced hydrogen as the substituent attached to another group.

As used herein, the term “substituted alkyl,” “substituted cycloalkyl,” “substituted alkenyl,” “substituted alkynyl,” or “substituted acyl” refers to alkyl, cycloalkyl, alkenyl, alkynyl, or acyl, as defined elsewhere herein, substituted by one, two or three substituents independently selected from the group consisting of halogen, -OH, alkoxy, tetrahydro-2-H-pyran-2-yl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, 1-methyl-imidazol-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, -C(=O)OH, -C(=O)O(C₁-C₆)alkyl, trifluoromethyl, -C≡N, -C(=O)NH₂, -C(=O)NH(C₁-C₆)alkyl, -C(=O)N((C₁-C₆)alkyl)₂, -SO₂NH₂, -SO₂NH(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -C(=NH)NH₂, and -NO₂, in certain embodiments containing one or two substituents independently selected from halogen, -OH, alkoxy, -NH₂, trifluoromethyl, -N(CH₃)₂, and -C(=O)OH, in certain embodiments independently selected from halogen, alkoxy, and -OH. Examples of substituted alkyls include, but are not limited to, 2,2-difluoropropyl, 2-carboxycyclopentyl and 3-chloropropyl.

For aryl, aryl-(C₁-C₃)alkyl and heterocycl-yl groups, the term “substituted” as applied to the rings of these groups refers to any level of substitution, namely mono-, di-, tri-, tetra-, or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. In certain embodiments, the substituents vary in number between one and four. In other embodiments, the substituents vary in number between one and three. In yet another embodiment, the substituents vary in number between one and two. In yet other embodiments, the substituents are independently selected from the group consisting of C₁-C₆ alkyl, -OH, C₁-C₆ alkoxy, halogen, amino, acetamido, and nitro. As used herein, where a substituent is an alkyl or alkoxy group, the carbon chain may be branched, straight or cyclic.

Unless otherwise noted, when two substituents are taken together to form a ring having a specified number of ring atoms (*e.g.*, two groups taken together with the nitrogen to which they are attached to form a ring having from 3 to 7 ring members), the ring can have carbon atoms and optionally one or more (*e.g.*, 1 to 3) additional heteroatoms independently selected from nitrogen, oxygen, or sulfur. The ring can be saturated or partially saturated, and can be optionally substituted.

Whenever a term or either of their prefix roots appear in a name of a substituent the name is to be interpreted as including those limitations provided herein. For example, whenever the term “alkyl” or “aryl” or either of their prefix roots appear in a name of a substituent (*e.g.*, arylalkyl, alkylamino) the name is to be interpreted as including those

limitations given elsewhere herein for “alkyl” and “aryl” respectively.

In certain embodiments, substituents of compounds are disclosed in groups or in ranges. It is specifically intended that the description include each and every individual subcombination of the members of such groups and ranges. For example, the term “C₁₋₆ alkyl” is specifically intended to individually disclose C₁, C₂, C₃, C₄, C₅, C₆, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₃-C₆, C₃-C₅, C₃-C₄, C₄-C₆, C₄-C₅, and C₅-C₆ alkyl.

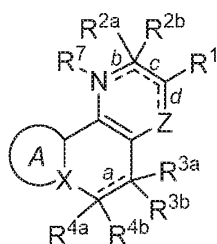
The terms “treat,” “treating” and “treatment,” as used herein, means reducing the frequency or severity with which symptoms of a disease or condition are experienced by a subject by virtue of administering an agent or compound to the subject.

Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual and partial numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

Compounds

The invention includes certain compound recited herein, as well as any salt, solvate, geometric isomer (such as, in a non-limiting example, any geometric isomer and any mixtures thereof, such as, in a non-limiting example, mixtures in any proportions of any geometric isomers thereof), stereoisomer (such as, in a non-limiting example, any enantiomer or diastereoisomer, and any mixtures thereof, such as, in a non-limiting example, mixtures in any proportions of any enantiomers and/or diastereoisomers thereof), tautomer (such as, in a non-limiting example, any tautomer and any mixtures thereof, such as, in a non-limiting example, mixtures in any proportions of any tautomers thereof), and any mixtures thereof.

The invention includes a compound of formula (I), or a salt, solvate, geometric isomer, stereoisomer, tautomer and any mixtures thereof.



(I), wherein:

- R¹ is selected from the group consisting of H; halogen; -OR⁸; -C(R⁹)(R⁹)OR⁸ (such as, for example, -CH₂OR⁸, such as, for example, -CH₂OH); -C(=O)R⁸; -C(=O)OR⁸ (such as, for example, -C(=O)OH or -C(=O)O-(C₁-C₆ alkyl)); -C(=O)NH-OR⁸ (such as, for example, -C(=O)NH-OH); -C(=O)NHNHR⁸; -C(=O)NHNHC(=O)R⁸; -C(=O)NHS(=O)₂R⁸; -CH₂C(=O)OR⁸; -CN; -NH₂; -N(R⁸)C(=O)H; -N(R⁸)C(=O)R¹⁰; -N(R⁸)C(=O)OR¹⁰; -N(R⁸)C(=O)NHR⁸; -NR⁹S(=O)₂R¹⁰; -P(=O)(OR⁸)₂; -B(OR⁸)₂; 2,5-dioxo-pyrrolidin-1-yl; 2H-tetrazol-5-yl; 3-hydroxy-isoxazol-5-yl; 1,4-dihydro-5-oxo-5H-tetrazol-1-yl; pyridin-2-yl optionally substituted with C₁-C₆ alkyl; pyrimidin-2-yl optionally substituted with C₁-C₆ alkyl; (pyridin-2-yl)methyl; (pyrimidin-2-yl)methyl; (pyrimidin-2-yl)amino; bis-(pyrimidin-2-yl)-amino; 5-R⁸-1,3,4-thiadiazol-2-yl; 5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl; 1H-1,2,4-triazol-5-yl; 1,3,4-oxadiazol-2-yl; 1,2,4-oxadiazol-5-yl; and 3-R¹⁰-1,2,4-oxadiazol-5-yl;

R^{2a}, R^{2b}, R⁷, bond *b*, bond *c*, bond *d*, and Z are selected such that:

- (i) Z is selected from the group consisting of N and CR¹²;
 R^{2a} and R^{2b} combine to form =O;
 bond *b* is a single bond; bond *c* is a single bond; bond *d* is a double bond; and
 R⁷ is selected from the group consisting of H, optionally substituted C₁-C₆ alkyl (*e.g.*, optionally substituted benzyl, or C₁-C₆ alkyl optionally substituted with 1-3 independently selected halogen groups), and optionally substituted C₃-C₈ cycloalkyl;
 or
- (ii) Z is selected from the group consisting of N and CR¹²;
 R^{2a} is selected from the group consisting of H, halogen, and optionally substituted C₁-C₆ alkoxy;
 R^{2b} is null;
 bond *b* is a double bond; bond *c* is a single bond; bond *d* is a double bond; and
 R⁷ is null;
 or
- (iii) Z is C(=O);
 R^{2a} is selected from the group consisting of H, halogen, and optionally substituted C₁-

C₆ alkoxy;

R^{2b} is null;

bond *b* is a single bond; bond *c* is a double bond; bond *d* is a single bond; and

R⁷ is selected from the group consisting of H, optionally substituted C₁-C₆ alkyl (*e.g.*,

optionally substituted benzyl, or C₁-C₆ alkyl optionally substituted with 1-3

independently selected halogen groups), and optionally substituted C₃-C₈ cycloalkyl;

R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of H,

alkyl-substituted oxetanyl, optionally substituted C₁-C₆ alkyl (*e.g.*, optionally substituted with

1-3 groups independently selected from the group consisting of F, Cl, Br, I, OH, and OMe),

and optionally substituted C₃-C₈ cycloalkyl (*e.g.*, optionally substituted with 1-3 groups

independently selected from the group consisting of F, Cl, Br, I, OH, and OMe);

or one pair selected from the group consisting of R^{3a} / R^{3b}, R^{4a} / R^{4b}, and R^{3a} / R^{4a}

combine to form a divalent group selected from the group consisting of C₁-C₆

alkanediyl, -(CH₂)_nO(CH₂)_n-, -(CH₂)_nNR⁹(CH₂)_n-, -(CH₂)_nS(CH₂)_n-, -

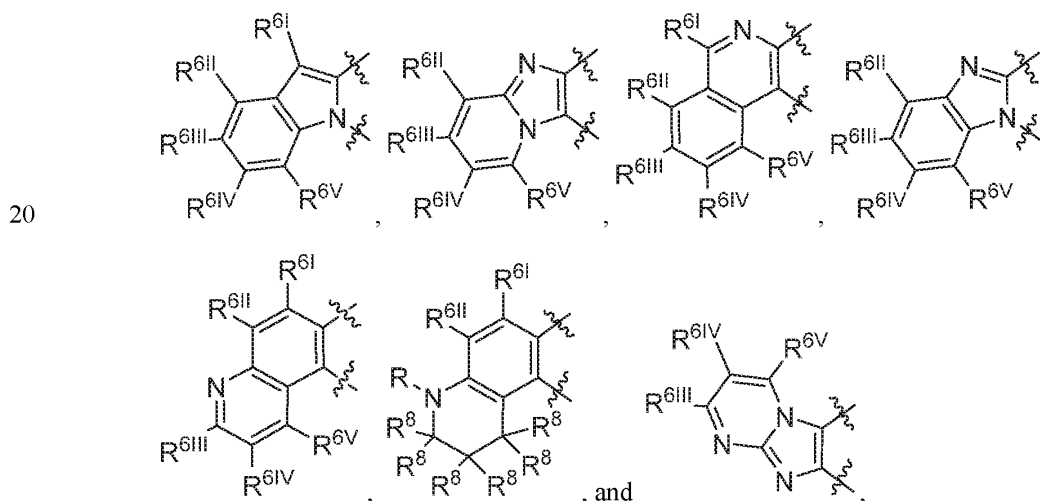
(CH₂)_nS(=O)(CH₂)_n-, and -(CH₂)_nS(=O)₂(CH₂)_n-, wherein each occurrence of *n* is

independently selected from the group consisting of 1 and 2 and wherein each

divalent group is optionally substituted with at least one C₁-C₆ alkyl or halogen;

bond *a* is single; or bond *a* is double and R^{3b} and R^{4b} are both null;

X is C or N, and ring *A* is selected from the group consisting of:



R^{6I}, R^{6II}, R^{6III}, R^{6IV}, and R^{6V} are independently selected from the group consisting of H, halogen, -CN, optionally substituted C₁-C₆ alkyl (*e.g.*, C₁-C₆ hydroxyalkyl, alkoxy-C₁-C₆ alkyl, and/or C₁-C₆ haloalkyl), optionally substituted C₁-C₆ alkenyl, optionally substituted C₃-

C₈ cycloalkyl, optionally substituted heteroaryl (*e.g.*, triazolyl, thiazolyl, or oxazolyl), optionally substituted heterocyclyl (*e.g.*, morpholinyl, or pyrrolidinyl), -OR, C₁-C₆ haloalkoxy, -N(R)(R), -NO₂, -S(=O)₂N(R)(R), acyl, and C₁-C₆ alkoxy carbonyl,

each occurrence of R is independently selected from the group consisting of H, optionally substituted C₁-C₆ alkyl, C₁-C₆ haloalkyl, R'-substituted C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, optionally substituted (C₁-C₆ alkoxy)-C₁-C₆ alkyl, optionally substituted C₃-C₈ cycloalkyl, and optionally substituted C₁-C₆ acyl;

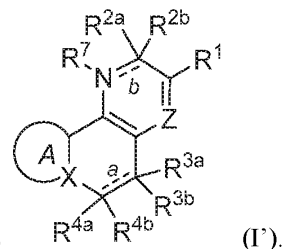
each occurrence of R' is selected from the group consisting of -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -NHC(=O)O^tBu, -N(C₁-C₆ alkyl)C(=O)O^tBu, and a 5- or 6-membered heterocyclic group (such as, but not limited to, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, and so forth), which is optionally N-linked;

each occurrence of R⁸ is independently selected from the group consisting of H, optionally substituted C₁-C₆ alkyl, and optionally substituted C₃-C₈ cycloalkyl;

each occurrence of R⁹ is independently selected from the group consisting of H and C₁-C₆ alkyl (*e.g.*, methyl or ethyl);

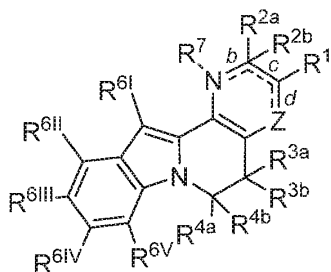
each occurrence of R¹⁰ is independently selected from the group consisting of optionally substituted C₁-C₆ alkyl and optionally substituted phenyl; and,

R¹² is selected from the group consisting of H, OH, halogen, C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkyl (*e.g.*, optionally substituted with 1-3 independently selected halogen groups), and optionally substituted C₃-C₈ cycloalkyl.

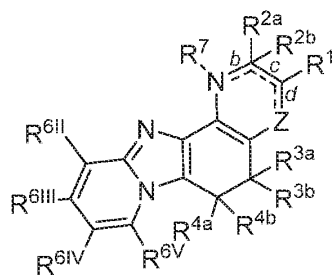


In certain embodiments, the compound of formula (I) is

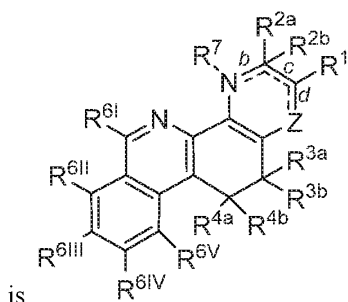
In certain embodiments, the compound of formula (I) is



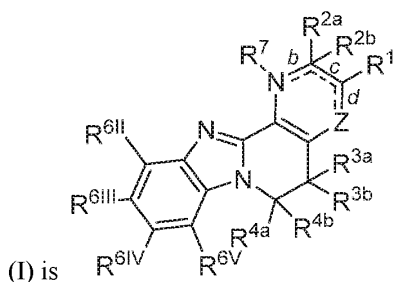
(Ia). In other embodiments, the compound of formula (I) is



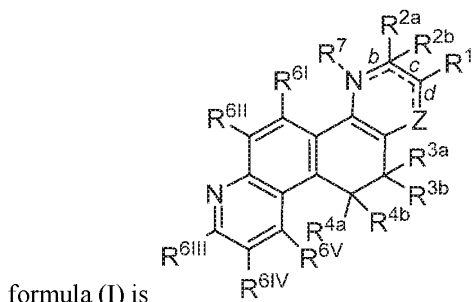
(Ib). In yet other embodiments, the compound of formula (I)



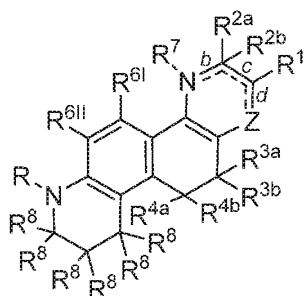
is (Ic). In yet other embodiments, the compound of formula



(I) is (Id). In yet other embodiments, the compound of

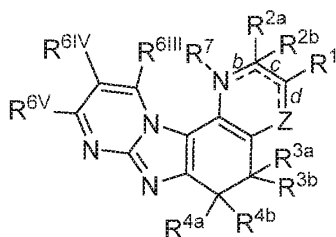


formula (I) is (Ie). In yet other embodiments, the compound



of formula (I) is

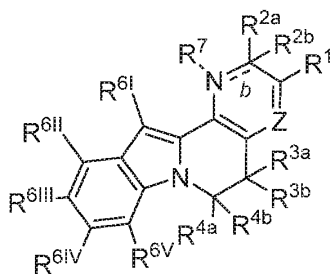
(If). In yet other embodiments, the compound



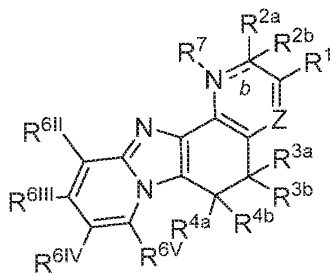
of formula (I) is

(Ig).

In certain embodiments, the compound of formula (I) is

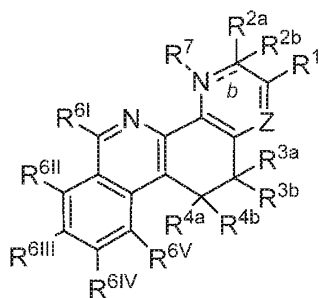


(Ia'). In other embodiments, the compound of formula (I) is



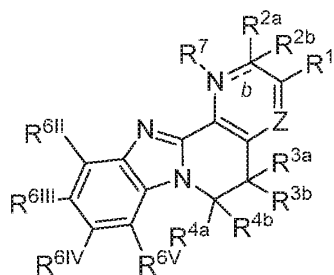
5

(Ib'). In yet other embodiments, the compound of formula



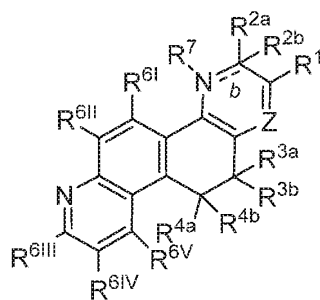
(I) is

(Ic'). In yet other embodiments, the compound of



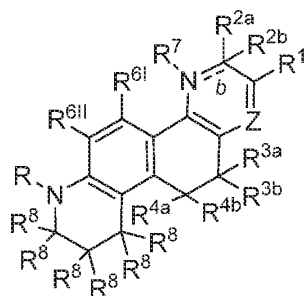
formula (I) is

(Id'). In yet other embodiments, the compound



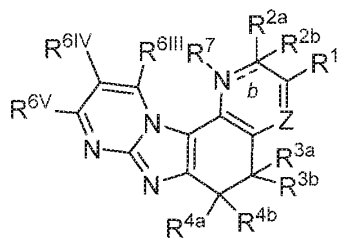
of formula (I) is

(Ie'). In yet other embodiments, the



compound of formula (I) is

(If'). In yet other embodiments, the



5 compound of formula (I) is

(Ig').

In certain embodiments, in any of (I), (Ia)-(Ig), and (Ia')-(Ig'), at least one of R^{3a} or R^{3b} is independently optionally substituted C₁-C₆ alkyl or optionally substituted C₃-C₈ cycloalkyl. In certain embodiments, in any of (I), (Ia)-(Ig), and (Ia')-(Ig'), at least one of R^{3a} or R^{3b} is independently selected from the group consisting of n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and t-butyl. In certain embodiments, in any of (I), (Ia)-(Ig), and (Ia')-(Ig'), at least one of R^{3a} or R^{3b} is n-propyl. In certain embodiments, in any of (I), (Ia)-(Ig), and (Ia')-(Ig'), at least one of R^{3a} or R^{3b} is isopropyl. In certain embodiments, in any of (I), (Ia)-(Ig), and (Ia')-(Ig'), at least one of R^{3a} or R^{3b} is n-butyl. In certain embodiments, in any of (I), (Ia)-(Ig), and (Ia')-(Ig'), at least one of R^{3a} or R^{3b} is isobutyl. In certain embodiments, in any of (I), (Ia)-(Ig), and (Ia')-(Ig'), at least one of R^{3a} or R^{3b} is sec-butyl. In certain embodiments, in any of (I), (Ia)-(Ig), and (Ia')-(Ig'), at least one of R^{3a} or R^{3b} is t-butyl.

In certain embodiments, each occurrence of alkyl, alkenyl, cycloalkyl, or acyl is independently optionally substituted with at least one substituent selected from the group consisting of C₁-C₆ alkyl, halogen, -OR'', phenyl (thus yielding, in non-limiting examples, optionally substituted phenyl-(C₁-C₃ alkyl), such as, but not limited to, benzyl or substituted benzyl), and -N(R'')(R''), wherein each occurrence of R'' is independently H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl.

In certain embodiments, each occurrence of aryl or heteroaryl is independently optionally substituted with at least one substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, -CN, -OR'', -N(R'')(R''), -NO₂, -S(=O)₂N(R'')(R''), acyl, and C₁-C₆ alkoxy carbonyl, wherein each occurrence of R'' is independently H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl.

In certain embodiments, each occurrence of aryl or heteroaryl is independently optionally substituted with at least one substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, -CN, -OR'', -N(R'')(R''), and C₁-C₆ alkoxy carbonyl, wherein each occurrence of R'' is independently H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl.

In certain embodiments, R¹ is selected from the group consisting of H; halogen; -C(=O)OR⁸; -C(=O)NH-OR⁸; -C(=O)NHNHR⁸; -C(=O)NHNHC(=O)R⁸; -C(=O)NHS(=O)₂R⁸; -CN; and 1H-1,2,4-triazol-5-yl. In certain embodiments, R¹ is H. In certain embodiments, R¹ is halo. In certain embodiments, R¹ is -C(=O)OR⁸ (such as, for example, -C(=O)OH or -C(=O)O-C₁-C₆ alkyl). In certain embodiments, R¹ is -C(=O)OH. In certain embodiments, R¹ is -C(=O)O(C₁-C₆ alkyl). In certain embodiments, R¹ is -C(=O)NH-OR⁸ (such as, for example, -C(=O)NH-OH). In certain embodiments, R¹ is -C(=O)NHNHR⁸.

In certain embodiments, R^1 is $-C(=O)NHNHC(=O)R^8$. In certain embodiments, R^1 is $-C(=O)NHS(=O)_2R^8$. In certain embodiments, R^1 is 1H-1,2,4-triazol-5-yl. In certain embodiments, R^1 is selected from the group consisting of $-C(=O)OH$, $-C(=O)OMe$, $-C(=O)OEt$, $-C(=O)O-nPr$, $-C(=O)O-iPr$, $-C(=O)O-cyclopentyl$, and $-C(=O)O-cyclohexyl$.

5 In certain embodiments, R^{2a} and R^{2b} combine to form $=O$. In certain embodiments, R^{2a} is C_1-C_6 alkoxy and R^{2b} is null. In certain embodiments, R^{2a} is H and R^{2b} is null. In certain embodiments, R^{2a} is halogen and R^{2b} is null.

In certain embodiments, bond a is a single bond. In other embodiments, bond a is a double bond.

10 In certain embodiments, bond b is a single bond. In other embodiments, bond b is a double bond.

In certain embodiments, bond c is a single bond. In other embodiments, bond c is a double bond.

15 In certain embodiments, bond d is a single bond. In other embodiments, bond d is a double bond.

In certain embodiments, R^{3a} is H. In certain embodiments, R^{3a} is not H. In certain embodiments, R^{3a} is alkyl-substituted oxetanyl. In certain embodiments, R^{3a} is optionally substituted C_1-C_6 alkyl. In certain embodiments, R^{3a} is optionally substituted C_3-C_8 cycloalkyl. In certain embodiments, R^{3b} is H. In certain embodiments, R^{3b} is not H. In certain embodiments, R^{3b} is alkyl-substituted oxetanyl. In certain embodiments, R^{3b} is optionally substituted C_1-C_6 alkyl. In certain embodiments, R^{3b} is optionally substituted C_3-C_8 cycloalkyl. In certain embodiments, R^{4a} is H. In certain embodiments, R^{4a} is not H. In certain embodiments, R^{4a} is alkyl-substituted oxetanyl. In certain embodiments, R^{4a} is optionally substituted C_1-C_6 alkyl. In certain embodiments, R^{4a} is optionally substituted C_3-C_8 cycloalkyl. In certain embodiments, R^{4b} is H. In certain embodiments, R^{4b} is not H. In certain embodiments, R^{4b} is alkyl-substituted oxetanyl. In certain embodiments, R^{4b} is optionally substituted C_1-C_6 alkyl. In certain embodiments, R^{4b} is optionally substituted C_3-C_8 cycloalkyl.

30 In certain embodiments, the C_1-C_6 alkyl is optionally substituted with 1-3 groups independently selected from the group consisting of F, Cl, Br, I, OH, and OMe. In certain embodiments, the C_3-C_8 cycloalkyl is optionally substituted with 1-3 groups independently selected from the group consisting of F, Cl, Br, I, OH, and OMe.

In certain embodiments, R^{3a} is H and R^{3b} is H. In certain embodiments, R^{3a} is H and R^{3b} is isopropyl. In certain embodiments, R^{3a} is H and R^{3b} is tert-butyl. In certain

embodiments, R^{3a} is methyl and R^{3b} is isopropyl. In certain embodiments, R^{3a} is methyl and R^{3b} is tert-butyl. In certain embodiments, R^{3a} is methyl and R^{3b} is methyl. In certain embodiments, R^{3a} is methyl and R^{3b} is ethyl. In certain embodiments, R^{3a} is ethyl and R^{3b} is ethyl.

5 In certain embodiments, R^{4a} is H and R^{4b} is H. In certain embodiments, R^{4a} is H and R^{4b} is isopropyl. In certain embodiments, R^{4a} is H and R^{4b} is tert-butyl. In certain embodiments, R^{4a} is methyl and R^{4b} is isopropyl. In certain embodiments, R^{4a} is methyl and R^{4b} is tert-butyl. In certain embodiments, R^{4a} is methyl and R^{4b} is methyl. In certain
10 embodiments, R^{4a} is methyl and R^{4b} is ethyl. In certain embodiments, R^{4a} is ethyl and R^{4b} is ethyl.

In certain embodiments, one pair selected from the group consisting of R^{3a} / R^{3b} , R^{4a} / R^{4b} , and R^{3a} / R^{4a} combine to form C_1 - C_6 alkanediyl. In certain embodiments, one pair selected from the group consisting of R^{3a} / R^{3b} , R^{4a} / R^{4b} , and R^{3a} / R^{4a} combine to form -
(CH_2)_nO(CH_2)_n-, which is optionally substituted with at least one C_1 - C_6 alkyl or halogen,
15 wherein each occurrence of n is independently selected from the group consisting of 1 and 2. In certain embodiments, one pair selected from the group consisting of R^{3a} / R^{3b} , R^{4a} / R^{4b} , and R^{3a} / R^{4a} combine to form -(CH_2)_nNR⁹(CH_2)_n-, which is optionally substituted with at least one C_1 - C_6 alkyl or halogen, wherein each occurrence of n is independently selected from the group consisting of 1 and 2.

20 In certain embodiments, R^{3a} and R^{3b} are independently selected from the group consisting of H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, hydroxymethyl, 2-hydroxy-ethyl, 2-methoxy-ethyl, methoxymethyl, 2-methyl-1-methoxy-prop-2-yl, 2-methyl-1-hydroxy-prop-2-yl, and trifluoroethyl. In certain embodiments, R^{4a} and R^{4b} are independently selected from the group consisting of H, methyl, ethyl, n-propyl,
25 isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, hydroxymethyl, 2-hydroxy-ethyl, 2-methoxy-ethyl, methoxymethyl, and 2-methyl-1-methoxy-prop-2-yl. In certain embodiments, R^{4a} is selected from the group consisting of H, methyl, ethyl, 2-hydroxy-ethyl, and 2-methoxy-ethyl. In certain embodiments, R^{3a} and R^{3b} combine to form 1,1-methanediyl (*i.e.*, an exocyclic double bond). In certain embodiments, R^{3a} and R^{3b} combine to form 1,2-
30 ethanediyl. In certain embodiments, R^{3a} and R^{3b} combine to form 1,3-propanediyl. In certain embodiments, R^{3a} and R^{3b} combine to form 1,4-butanediyl. In certain embodiments, R^{3a} and R^{3b} combine to form 1,5-pentanediyl. In certain embodiments, R^{3a} and R^{3b} combine to form 1,6-hexanediyl. In certain embodiments, R^{3a} and R^{4a} combine to form 1,2-ethanediyl. In certain embodiments, R^{3a} and R^{4a} combine to form 1,2-propanediyl. In certain embodiments,

R^{3a} and R^{4a} combine to form 1,3-propanediyl. In certain embodiments, R^{3a} and R^{4a} combine to form (1-methyl or 2-methyl)-1,4-butanediyl. In certain embodiments, R^{3a} and R^{4a} combine to form (1,1-dimethyl / 1,2-dimethyl / 1,3-dimethyl / or 2,2-dimethyl)-1,3-propanediyl. In certain embodiments, R^{3a} and R^{4a} combine to form 1,5-pentanediy. In certain embodiments, R^{3a} and R^{4a} combine to form 1,6-hexanediy.

In certain embodiments, R^{6I} is H. In certain embodiments, R^{6I} is halo. In certain embodiments, R^{6I} is $-CN$. In certain embodiments, R^{6I} is optionally substituted C_1-C_6 alkyl (e.g., C_1-C_6 hydroxyalkyl, alkoxy- C_1-C_6 alkyl, and/or C_1-C_6 haloalkyl). In certain embodiments, R^{6I} is optionally substituted C_3-C_8 cycloalkyl. In certain embodiments, R^{6I} is –
 10 OR. In certain embodiments, R^{6I} is C_1-C_6 haloalkoxy.

In certain embodiments, R^{6II} is H. In certain embodiments, R^{6II} is halo. In certain embodiments, R^{6II} is $-CN$. In certain embodiments, R^{6II} is optionally substituted C_1-C_6 alkyl (e.g., C_1-C_6 hydroxyalkyl, alkoxy- C_1-C_6 alkyl, and/or C_1-C_6 haloalkyl). In certain embodiments, R^{6II} is optionally substituted C_3-C_8 cycloalkyl. In certain embodiments, R^{6II} is –
 15 –OR. In certain embodiments, R^{6II} is C_1-C_6 haloalkoxy. In certain embodiments, R^{6II} is fluoromethoxy. In certain embodiments, R^{6II} is difluoromethoxy. In certain embodiments, R^{6II} is trifluoromethoxy. In certain embodiments, R^{6II} is methoxy. In certain embodiments, R^{6II} is ethoxy. In certain embodiments, R^{6II} is 2-methoxyethoxy. In certain embodiments, R^{6II} is 2-ethoxyethoxy. In certain embodiments, R^{6II} is 3-methoxypropoxy. In certain
 20 embodiments, R^{6II} is 3-ethoxypropoxy. In certain embodiments, R^{6II} is fluoro. In certain embodiments, R^{6II} is chloro. In certain embodiments, R^{6II} is bromo.

In certain embodiments, R^{6III} is H. In certain embodiments, R^{6III} is halo. In certain embodiments, R^{6III} is $-CN$. In certain embodiments, R^{6III} is optionally substituted C_1-C_6 alkyl (e.g., C_1-C_6 hydroxyalkyl, alkoxy- C_1-C_6 alkyl, and/or C_1-C_6 haloalkyl). In certain
 25 embodiments, R^{6III} is C_1-C_6 alkoxy. In certain embodiments, R^{6III} is methoxy. In certain embodiments, R^{6III} is optionally substituted C_3-C_8 cycloalkyl. In certain embodiments, R^{6III} is –OR. In certain embodiments, R^{6III} is C_1-C_6 haloalkoxy.

In certain embodiments, R^{6IV} is H. In certain embodiments, R^{6IV} is halo. In certain embodiments, R^{6IV} is $-CN$. In certain embodiments, R^{6IV} is optionally substituted C_1-C_6
 30 alkyl (e.g., C_1-C_6 hydroxyalkyl, alkoxy- C_1-C_6 alkyl, and/or C_1-C_6 haloalkyl). In certain embodiments, R^{6IV} is optionally substituted C_3-C_8 cycloalkyl. In certain embodiments, R^{6IV} is –OR. In certain embodiments, R^{6IV} is C_1-C_6 haloalkoxy.

In certain embodiments, R^{6I} is selected from the group consisting of H, F, Cl, Br, I, CN, methoxy, ethoxy, n-propoxy, isopropoxyl, n-butoxy, sec-butoxy, isobutoxy, t-butoxy, 2-

methoxy-ethoxy, 2-hydroxy-ethoxy, 3-methoxy-prop-1-yl, 3-hydroxy-prop-1-yl, 3-methoxy-prop-1-oxy, 3-hydroxy-prop-1-oxy, 4-methoxy-but-1-yl, 4-hydroxy-but-1-yl, 4-methoxy-but-1-oxy, 4-hydroxy-but-1-oxy, 2-hydroxy-ethoxy, 3-hydroxy-prop-1-yl, 4-hydroxy-but-1-yl, 3-hydroxy-2,2-dimethyl-prop-1-oxy, cyclopropylmethoxy, difluoromethoxy, trifluoromethoxy,
 5 2,2,2-trifluoroethoxy, and 2-(2-haloethoxy)-ethoxy.

In certain embodiments, R^{6II} is selected from the group consisting of H, F, Cl, Br, I, CN, amino, methylamino, dimethylamino, methoxyethylamino, pyrrolidinyl, methoxy, ethoxy, n-propoxy, isopropoxyl, n-butoxy, sec-butoxy, isobutoxy, t-butoxy, 2-methoxy-ethoxy, 2-hydroxy-ethoxy, 3-methoxy-prop-1-yl, 3-hydroxy-prop-1-yl, 3-methoxy-prop-1-oxy, 3-hydroxy-prop-1-oxy, 4-methoxy-but-1-yl, 4-hydroxy-but-1-yl, 4-methoxy-but-1-oxy, 4-hydroxy-but-1-oxy, 2-hydroxy-ethoxy, 3-hydroxy-prop-1-yl, 4-hydroxy-but-1-yl, 3-hydroxy-2,2-dimethyl-prop-1-oxy, cyclopropylmethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 2-(2-haloethoxy)-ethoxy, 2-(N-morpholino)-ethyl, 2-(N-morpholino)-ethoxy, 3-(N-morpholino)-prop-1-yl, 3-(N-morpholino)-prop-1-oxy, 4-(N-morpholino)-but-1-yl, 4-(N-morpholino)-but-1-oxy, 2-amino-ethyl, 2-(NHC(=O)O^tBu)-ethyl, 2-amino-ethoxy, 2-(NHC(=O)O^tBu)-ethoxy, 3-amino-prop-1-yl, 3-(NHC(=O)O^tBu)-prop-1-yl, 3-amino-prop-1-oxy, 3-(NHC(=O)O^tBu)-prop-1-oxy, 4-amino-but-1-yl, 4-(NHC(=O)O^tBu)-but-1-yl, 4-amino-but-1-oxy, and 4-(NHC(=O)O^tBu)-but-1-oxy.
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In certain embodiments, R^{6III} is selected from the group consisting of H, F, Cl, Br, I, CN, amino, methylamino, dimethylamino, methoxyethylamino, pyrrolidinyl, methoxy, ethoxy, n-propoxy, isopropoxyl, n-butoxy, sec-butoxy, isobutoxy, t-butoxy, 2-methoxy-ethoxy, 2-hydroxy-ethoxy, 3-methoxy-prop-1-yl, 3-hydroxy-prop-1-yl, 3-methoxy-prop-1-oxy, 3-hydroxy-prop-1-oxy, 4-methoxy-but-1-yl, 4-hydroxy-but-1-yl, 4-methoxy-but-1-oxy, 4-hydroxy-but-1-oxy, 2-hydroxy-ethoxy, 3-hydroxy-prop-1-yl, 4-hydroxy-but-1-yl, 3-hydroxy-2,2-dimethyl-prop-1-oxy, cyclopropylmethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 2-(2-haloethoxy)-ethoxy, 2-(N-morpholino)-ethyl, 2-(N-morpholino)-ethoxy, 3-(N-morpholino)-prop-1-yl, 3-(N-morpholino)-prop-1-oxy, 4-(N-morpholino)-but-1-yl, 4-(N-morpholino)-but-1-oxy, 2-amino-ethyl, 2-(NHC(=O)O^tBu)-ethyl, 2-amino-ethoxy, 2-(NHC(=O)O^tBu)-ethoxy, 3-amino-prop-1-yl, 3-(NHC(=O)O^tBu)-prop-1-yl, 3-amino-prop-1-oxy, 3-(NHC(=O)O^tBu)-prop-1-oxy, 4-amino-but-1-yl, 4-(NHC(=O)O^tBu)-but-1-yl, 4-amino-but-1-oxy, and 4-(NHC(=O)O^tBu)-but-1-oxy.
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In certain embodiments, R^{6IV} is selected from the group consisting of H, F, Cl, Br, I, CN, methoxy, ethoxy, n-propoxy, isopropoxyl, n-butoxy, sec-butoxy, isobutoxy, t-butoxy, 2-methoxy-ethoxy, 2-hydroxy-ethoxy, 3-methoxy-prop-1-yl, 3-hydroxy-prop-1-yl, 3-methoxy-

prop-1-oxy, 3-hydroxy-prop-1-oxy, 4-methoxy-but-1-yl, 4-hydroxy-but-1-yl, 4-methoxy-but-1-oxy, 4-hydroxy-but-1-oxy, 2-hydroxy-ethoxy, 3-hydroxy-prop-1-yl, 4-hydroxy-but-1-yl, 3-hydroxy-2,2-dimethyl-prop-1-oxy, cyclopropylmethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, and 2-(2-haloethoxy)-ethoxy.

- 5 In certain embodiments, R^{6I} is H, R^{6II} is H, R^{6III} is 3-methoxy-propoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is methoxymethyl, R^{6III} is 3-methoxy-propoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is methoxy, R^{6III} is 3-methoxy-propoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is chloro, R^{6III} is 3-methoxy-propoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is isopropyl, R^{6III} is 3-methoxy-propoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is methoxy, R^{6III} is methoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is chloro, R^{6III} is methoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is cyclopropyl, R^{6III} is methoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is difluoromethoxy, R^{6III} is H, R^{6IV} is H, and R^{6V} is H. In certain embodiments, R^{6I} is H, R^{6II} is methoxy, R^{6III} is H, R^{6IV} is H, and R^{6V} is H. In certain
- 10 R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is methoxy, R^{6III} is methoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is chloro, R^{6III} is methoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is cyclopropyl, R^{6III} is methoxy, and R^{6IV} is H. In certain embodiments, R^{6I} is H, R^{6II} is difluoromethoxy, R^{6III} is H, R^{6IV} is H, and R^{6V} is H. In certain embodiments, R^{6I} is H, R^{6II} is methoxy, R^{6III} is H, R^{6IV} is H, and R^{6V} is H. In certain
- 15 embodiments, R^{6I} is H, R^{6II} is ethoxy, R^{6III} is H, R^{6IV} is H, and R^{6V} is H. In certain embodiments, R^{6I} is H, R^{6II} is 2-methoxyethoxy, R^{6III} is H, R^{6IV} is H, and R^{6V} is H. In certain embodiments, R^{6I} is H, R^{6II} is difluoromethoxy, R^{6III} is H, R^{6IV} is H, and R^{6V} is H. In certain embodiments, R^{6I} is H and R^{6II} is difluoromethoxy. In certain embodiments, R^{6II} is methoxy, R^{6III} is H, R^{6IV} is H, and R^{6V} is H. In certain embodiments, R^{6II} is methoxy, R^{6III} is methoxyH, R^{6IV} is H, and R^{6V} is H. In certain embodiments, R^{6II} is difluoromethoxy, R^{6III} is H, R^{6IV} is H, and R^{6V} is H. In certain embodiments, R^{6II} is chloro, R^{6III} is H, R^{6IV} is H, R^{6V} is H, and R^{6VI} is H.

- In certain embodiments, R^{6II} is methoxy, R^{6III} is 3-methoxy-propoxy, and R^{6IV} is H. In certain embodiments, R^{6II} is 3-methoxy-propoxy, R^{6III} is methoxy, and R^{6IV} is H. In certain
- 25 certain embodiments, R^{6II} is chloro, R^{6III} is 3-methoxy-propoxy, and R^{6IV} is H. In certain embodiments, R^{6II} is cyclopropyl, R^{6III} is 3-methoxy-propoxy, and R^{6IV} is H. In certain embodiments, R^{6II} is methoxy, R^{6III} is methoxy, and R^{6IV} is H. In certain embodiments, R^{6II} is chloro, R^{6III} is methoxy, and R^{6IV} is H. In certain embodiments, R^{6II} is cyclopropyl, R^{6III} is methoxy, and R^{6IV} is H.

- 30 In certain embodiments, each occurrence of R is independently selected from the group consisting of H, C₁-C₆ alkyl, R'-substituted C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, optionally substituted (C₁-C₆ alkoxy)-C₁-C₆ alkyl, optionally substituted C₃-C₈ cycloalkyl, and C₁-C₆ alkyl. In certain embodiments, R is H. In certain embodiments, R is methyl. In certain embodiments, R is ethyl. In certain embodiments, R is acetyl. In certain

embodiments, R is 2-methoxyethoxy. In certain embodiments, R is 2-ethoxyethoxy. In certain embodiments, R is 3-methoxypropoxy. In certain embodiments, R is 3-ethoxypropoxy. In certain embodiments, each occurrence of R⁷ is independently selected from the group consisting of -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -NHC(=O)O^tBu, -N(C₁-C₆ alkyl)C(=O)O^tBu, or a 5- or 6-membered heterocyclic group (such as, but not limited to, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, and so forth), which is optionally N-linked.

In certain embodiments, R^{6II} and R^{6III} combine to form a divalent group selected from the group consisting of -O(CR⁹R¹¹)O-, -O(CR⁹R¹¹)(CR⁹R¹¹)O-, -O(CR⁹R¹¹)(CR⁹R¹¹)-, and -O(CR⁹R¹¹)(CR⁹R¹¹)(CR⁹R¹¹)-.
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In certain embodiments, R^{6III} and R^{6IV} combine to form a divalent group selected from the group consisting of -O(CR⁹R¹¹)O-, -O(CR⁹R¹¹)(CR⁹R¹¹)O-, -O(CR⁹R¹¹)(CR⁹R¹¹)-, and -O(CR⁹R¹¹)(CR⁹R¹¹)(CR⁹R¹¹)-.
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In certain embodiments, R⁷ is H. In certain embodiments, R⁷ is optionally substituted C₁-C₆ alkyl (*e.g.*, optionally substituted with 1-3 independently selected halogen groups). In certain embodiments, R⁷ is optionally substituted C₃-C₈ cycloalkyl. In certain embodiments, R⁷ is optionally substituted benzyl. In certain embodiments, R⁷ is methyl. In certain embodiments, R⁷ is ethyl. In certain embodiments, R⁷ is n-propyl. In certain embodiments, R⁷ is isopropyl.
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In certain embodiments, each occurrence of R⁸ is independently selected from the group consisting of H, optionally substituted C₁-C₆ alkyl, and optionally substituted C₃-C₈ cycloalkyl. In certain embodiments, each occurrence of R⁸ is H.

In certain embodiments, each occurrence of R⁹ is independently selected from the group consisting of H and C₁-C₆ alkyl (*e.g.*, methyl or ethyl).
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In certain embodiments, each occurrence of R¹⁰ is independently selected from the group consisting of optionally substituted C₁-C₆ alkyl and optionally substituted phenyl.

In certain embodiments, Z is N. In certain embodiments, Z is CR¹². In certain embodiments, Z is C(=O).

In certain embodiments, R¹² is H. In certain embodiments, R¹² is OH. In certain embodiments, R¹² is halo. In certain embodiments, R¹² is C₁-C₆ alkoxy. In certain embodiments, R¹² is optionally substituted C₁-C₆ alkyl (*e.g.*, optionally substituted with 1-3 independently selected halogen groups). In certain embodiments, R¹² is optionally substituted C₃-C₈ cycloalkyl. In certain embodiments, R¹² is F. In certain embodiments, R¹² is methoxy. In certain embodiments, R¹² is ethoxy. In certain embodiments, R¹² is methyl.
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In certain embodiments, R¹² is ethyl. In certain embodiments, R¹² is n-propyl. In certain embodiments, R¹² is isopropyl.

In certain embodiments, the compounds of the invention, or a salt, solvate, stereoisomer (such as, in a non-limiting example, an enantiomer or diastereoisomer thereof),
 5 any mixture of one or more stereoisomers (such as, in a non-limiting example, mixtures in any proportion of enantiomers thereof, and/or mixtures in any proportion of diastereoisomers thereof), tautomer, and/or any mixture of tautomers thereof, are recited in Table 1.

In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-
 10 tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-11-ethoxy-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-
 15 h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-4-hydroxy-11-(2-methoxyethoxy)-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-
 20 tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-11-
 25 (difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is 11-(difluoromethoxy)-(R)-5-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain
 30 5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-isopropyl-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain
 embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-

- 5-(tert-butyl)-10,11-dimethoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is 11-(difluoromethoxy)-(R)-6-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain
- 5 embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain
- embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt,
- 10 solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-
- 15 tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt,
- solvate, geometric isomer, or tautomer thereof, is (R)-6-(tert-butyl)-12-(difluoromethoxy)-7-
- 20 hydroxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-6-(tert-butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the
- compound, or a salt, solvate, geometric isomer, or tautomer thereof, is 1-acetyl-(R)-6-(tert-
- 25 butyl)-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-6-(tert-butyl)-12-(difluoromethoxy)-1-methyl-9-oxo-
- 1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain
- embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-
- 30 6-(tert-butyl)-12-(difluoromethoxy)-1-ethyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate,
- geometric isomer, or tautomer thereof, is (R)-6-(tert-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the
- compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-6-(tert-butyl)-12-

- (difluoromethoxy)-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-6-(tert-butyl)-12-(difluoromethoxy)-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate,
- 5 geometric isomer, or tautomer thereof, is (R)-12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-12-(tert-butyl)-6-methoxy-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer
- 10 thereof, is (R)-12-(tert-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (R)-6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric
- 15 isomer, or tautomer thereof, is (R)-6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer,
- 20 or tautomer thereof, is (S)-5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-11-ethoxy-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer
- 25 thereof, is (S)-5-(tert-butyl)-4-hydroxy-11-(2-methoxyethoxy)-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate,
- 30 geometric isomer, or tautomer thereof, is (S)-6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate,

- geometric isomer, or tautomer thereof, is 11-(difluoromethoxy)-(S)-5-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-isopropyl-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-10,11-dimethoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is 11-(difluoromethoxy)-(S)-6-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-6-(tert-butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is 1-acetyl-(S)-6-(tert-butyl)-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer,

- or tautomer thereof, is (S)-6-(tert-butyl)-12-(difluoromethoxy)-1-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-6-(tert-butyl)-12-(difluoromethoxy)-1-ethyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-6-(tert-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-6-(tert-butyl)-12-(difluoromethoxy)-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-6-(tert-butyl)-12-(difluoromethoxy)-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-12-(tert-butyl)-6-methoxy-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-12-(tert-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid. In certain embodiments, the compound, or a salt, solvate, geometric isomer, or tautomer thereof, is (S)-6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid.
- 25 The compounds of the invention may possess one or more stereocenters, and each stereocenter may exist independently in either the (*R*) or (*S*) configuration. In certain embodiments, compounds described herein are present in optically active or racemic forms. The compounds described herein encompass racemic, optically active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful
- 30 properties described herein. Preparation of optically active forms is achieved in any suitable manner, including by way of non-limiting example, by resolution of the racemic form with recrystallization techniques, synthesis from optically active starting materials, chiral synthesis, or chromatographic separation using a chiral stationary phase. A compound illustrated herein by the racemic formula further represents either of the two enantiomers or

mixtures thereof, or in the case where two or more chiral center are present, all diastereomers or mixtures thereof.

In certain embodiments, the compounds of the invention exist as tautomers. All tautomers are included within the scope of the compounds recited herein.

- 5 Compounds described herein also include isotopically labeled compounds wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds described herein include and are not limited to ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{36}Cl , ^{18}F , ^{123}I , ^{125}I , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , and ^{35}S .
- 10 In certain embodiments, substitution with heavier isotopes such as deuterium affords greater chemical stability. Isotopically labeled compounds are prepared by any suitable method or by processes using an appropriate isotopically labeled reagent in place of the non-labeled reagent otherwise employed.

- In certain embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.
- 15

In all of the embodiments provided herein, examples of suitable optional substituents are not intended to limit the scope of the claimed invention. The compounds of the invention may contain any of the substituents, or combinations of substituents, provided herein.

20

Salts

- The compounds described herein may form salts with acids or bases, and such salts are included in the present invention. The term “salts” embraces addition salts of free acids or bases that are useful within the methods of the invention. The term “pharmaceutically acceptable salt” refers to salts that possess toxicity profiles within a range that affords utility in pharmaceutical applications. In certain embodiments, the salts are pharmaceutically acceptable salts. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present invention, such as for example utility in process of synthesis, purification or formulation of compounds useful within the methods of the invention.
- 25
- 30

Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include sulfate, hydrogen sulfate, hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids (including hydrogen phosphate and dihydrogen phosphate). Appropriate

organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (or pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, sulfanilic, 2-hydroxyethanesulfonic, trifluoromethanesulfonic, p-toluenesulfonic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric, galacturonic acid, glycerophosphonic acids and saccharin (*e.g.*, saccharinate, saccharate). Salts may be comprised of a fraction of one, one or more than one molar equivalent of acid or base with respect to any compound of the invention.

Suitable pharmaceutically acceptable base addition salts of compounds of the invention include, for example, ammonium salts and metallic salts including alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (or N-methylglucamine) and procaine. All of these salts may be prepared from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

Combination Therapies

In one aspect, the compounds of the invention are useful within the methods of the invention in combination with one or more additional agents useful for treating HBV and/or HDV infections. These additional agents may comprise compounds or compositions identified herein, or compounds (*e.g.*, commercially available compounds) known to treat, prevent, or reduce the symptoms of HBV and/or HDV infections.

Non-limiting examples of one or more additional agents useful for treating HBV and/or HDV infections include: (a) reverse transcriptase inhibitors; (b) capsid inhibitors; (c) cccDNA formation inhibitors; (d) RNA destabilizers; (e) oligomeric nucleotides targeted against the HBV genome; (f) immunostimulators, such as checkpoint inhibitors (*e.g.*, PD-L1 inhibitors); and (g) GalNAc-siRNA conjugates targeted against an HBV gene transcript.

(a) Reverse Transcriptase Inhibitors

In certain embodiments, the reverse transcriptase inhibitor is a reverse-transcriptase inhibitor (NARTI or NRTI). In other embodiments, the reverse transcriptase inhibitor is a

nucleotide analog reverse-transcriptase inhibitor (NtARTI or NtRTI).

Reported reverse transcriptase inhibitors include, but are not limited to, entecavir, clevudine, telbivudine, lamivudine, adefovir, and tenofovir, tenofovir disoproxil, tenofovir alafenamide, adefovir dipovoxil, (1*R*,2*R*,3*R*,5*R*)-3-(6-amino-9*H*-9-puriny1)-2-fluoro-5-
 5 (hydroxymethyl)-4-methylenecyclopentan-1-ol (described in U.S. Patent No. 8,816,074, incorporated herein in its entirety by reference), emtricitabine, abacavir, elvucitabine, ganciclovir, lobucavir, famciclovir, penciclovir, and amdoxovir.

Reported reverse transcriptase inhibitors further include, but are not limited to, entecavir, lamivudine, and (1*R*,2*R*,3*R*,5*R*)-3-(6-amino-9*H*-9-puriny1)-2-fluoro-5-
 10 (hydroxymethyl)-4-methylenecyclopentan-1-ol.

Reported reverse transcriptase inhibitors further include, but are not limited to, a covalently bound phosphoramidate or phosphonamidate moiety of the above-mentioned reverse transcriptase inhibitors, or as described in for example U.S. Patent No. 8,816,074, US Patent Application Publications No. US 2011/0245484 A1, and US 2008/0286230A1, all of
 15 which incorporated herein in their entireties by reference.

Reported reverse transcriptase inhibitors further include, but are not limited to, nucleotide analogs that comprise a phosphoramidate moiety, such as, for example, methyl (((1*R*,3*R*,4*R*,5*R*)-3-(6-amino-9*H*-purin-9-yl)-4-fluoro-5-hydroxy-2-methylenecyclopentyl) methoxy)(phenoxy) phosphoryl)-(D or L)-alaninate and methyl (((1*R*,2*R*,3*R*,4*R*)-3-fluoro-2-
 20 hydroxy-5-methylene-4-(6-oxo-1,6-dihydro-9*H*-purin-9-yl)cyclopentyl)methoxy)(phenoxy) phosphoryl)-(D or L)-alaninate. Also included are the individual diastereomers thereof, which include, for example, methyl ((*R*)-(((1*R*,3*R*,4*R*,5*R*)-3-(6-amino-9*H*-purin-9-yl)-4-fluoro-5-hydroxy-2-methylenecyclopentyl)methoxy)(phenoxy)phosphoryl)-(D or L)-alaninate and methyl ((*S*)-(((1*R*,3*R*,4*R*,5*R*)-3-(6-amino-9*H*-purin-9-yl)-4-fluoro-5-hydroxy-2-
 25 methylenecyclopentyl) methoxy)(phenoxy)phosphoryl)-(D or L)-alaninate.

Reported reverse transcriptase inhibitors further include, but are not limited to, compounds comprising a phosphonamidate moiety, such as, for example, tenofovir alafenamide, as well as those described in U.S. Patent Application Publication No. US 2008/0286230 A1, incorporated herein in its entirety by reference. Methods for preparing
 30 stereoselective phosphoramidate or phosphonamidate containing actives are described in, for example, U.S. Patent No. 8,816,074, as well as U.S. Patent Application Publications No. US 2011/0245484 A1 and US 2008/0286230 A1, all of which incorporated herein in their entireties by reference.

(b) Capsid Inhibitors

- As described herein, the term “capsid inhibitor” includes compounds that are capable of inhibiting the expression and/or function of a capsid protein either directly or indirectly. For example, a capsid inhibitor may include, but is not limited to, any compound that inhibits capsid assembly, induces formation of non-capsid polymers, promotes excess capsid assembly or misdirected capsid assembly, affects capsid stabilization, and/or inhibits encapsidation of RNA (pgRNA). Capsid inhibitors also include any compound that inhibits capsid function in a downstream event(s) within the replication process (*e.g.*, viral DNA synthesis, transport of relaxed circular DNA (rcDNA) into the nucleus, covalently closed circular DNA (cccDNA) formation, virus maturation, budding and/or release, and the like).
- For example, in certain embodiments, the inhibitor detectably inhibits the expression level or biological activity of the capsid protein as measured, *e.g.*, using an assay described herein. In certain embodiments, the inhibitor inhibits the level of rcDNA and downstream products of viral life cycle by at least 5%, at least 10%, at least 20%, at least 50%, at least 75%, or at least 90%.
- Reported capsid inhibitors include, but are not limited to, compounds described in International Patent Applications Publication Nos WO 2013006394, WO 2014106019, and WO2014089296, all of which incorporated herein in their entireties by reference.
- Reported capsid inhibitors also include, but are not limited to, the following compounds and pharmaceutically acceptable salts and/or solvates thereof: Bay-41-4109 (see Int’l Patent Application Publication No. WO 2013144129), AT-61 (see Int’l Patent Application Publication No. WO 1998033501; and King, *et al.*, 1998, Antimicrob. Agents Chemother. 42(12):3179–3186), DVR-01 and DVR-23 (see Int’l Patent Application Publication No. WO 2013006394; and Campagna, *et al.*, 2013, J. Virol. 87(12):6931, all of which incorporated herein in their entireties by reference.
- In addition, reported capsid inhibitors include, but are not limited to, those generally and specifically described in U.S. Patent Application Publication Nos. US 2015/0225355, US 2015/0132258, US 2016/0083383, US 2016/0052921 and Int’l Patent Application Publication Nos. WO 2013096744, WO 2014165128, WO 2014033170, WO 2014033167, WO 2014033176, WO 2014131847, WO 2014161888, WO 2014184350, WO 2014184365, WO 2015059212, WO 2015011281, WO 2015118057, WO 2015109130, WO 2015073774, WO 2015180631, WO 2015138895, WO 2016089990, WO 2017015451, WO 2016183266, WO 2017011552, WO 2017048950, WO2017048954, WO 2017048962, WO 2017064156 and are incorporated herein in their entirety by reference.

(c) cccDNA Formation Inhibitors

Covalently closed circular DNA (cccDNA) is generated in the cell nucleus from viral rcDNA and serves as the transcription template for viral mRNAs. As described herein, the term “cccDNA formation inhibitor” includes compounds that are capable of inhibiting the formation and/or stability of cccDNA either directly or indirectly. For example, a cccDNA formation inhibitor may include, but is not limited to, any compound that inhibits capsid disassembly, rcDNA entry into the nucleus, and/or the conversion of rcDNA into cccDNA. For example, in certain embodiments, the inhibitor detectably inhibits the formation and/or stability of the cccDNA as measured, *e.g.*, using an assay described herein. In certain embodiments, the inhibitor inhibits the formation and/or stability of cccDNA by at least 5%, at least 10%, at least 20%, at least 50%, at least 75%, or at least 90%.

Reported cccDNA formation inhibitors include, but are not limited to, compounds described in Int'l Patent Application Publication No. WO 2013130703, and are incorporated herein in their entirety by reference.

In addition, reported cccDNA formation inhibitors include, but are not limited to, those generally and specifically described in U.S. Patent Application Publication No. US 2015/0038515 A1, and are incorporated herein in their entirety by reference.

(d) RNA Destabilizer

As used herein, the term “RNA destabilizer” refers to a molecule, or a salt or solvate thereof, that reduces the total amount of HBV RNA in mammalian cell culture or in a live human subject. In a non-limiting example, an RNA destabilizer reduces the amount of the RNA transcript(s) encoding one or more of the following HBV proteins: surface antigen, core protein, RNA polymerase, and e antigen. In certain embodiments, the RNA destabilizer reduces the total amount of HBV RNA in mammalian cell culture or in a live human subject by at least 5%, at least 10%, at least 20%, at least 50%, at least 75%, or at least 90%.

Reported RNA destabilizers include compounds described in U.S. Patent No. 8,921,381, as well as compounds described in U.S. Patent Application Publication Nos. US 2015/0087659 and US 2013/0303552, all of which are incorporated herein in their entireties by reference.

In addition, reported RNA destabilizers include, but are not limited to, those generally and specifically described in Int'l Patent Application Publication Nos. WO 2015113990, WO 2015173164, US 2016/0122344, WO 2016107832, WO 2016023877, WO 2016128335, WO 2016177655, WO 2016071215, WO 2017013046, WO 2017016921, WO 2017016960, WO 2017017042, WO 2017017043, WO 2017102648, WO 2017108630, WO 2017114812, WO 2017140821, WO 2018085619, and are incorporated herein in their entirety by reference.

(e) Oligomeric Nucleotides Targeted Against the HBV Genome

Reported oligomeric nucleotides targeted against the HBV genome include, but are not limited to, Arrowhead-ARC-520 (see U.S. Patent No. 8,809,293; and Wooddell *et al.*, 2013, Molecular Therapy 21(5):973–985, all of which incorporated herein in their entireties
5 by reference).

In certain embodiments, the oligomeric nucleotides can be designed to target one or more genes and/or transcripts of the HBV genome. Oligomeric nucleotide targeted to the HBV genome also include, but are not limited to, isolated, double stranded, siRNA molecules, that each include a sense strand and an antisense strand that is hybridized to the
10 sense strand. In certain embodiments, the siRNA target one or more genes and/or transcripts of the HBV genome.

(f) Immunostimulators

Checkpoint Inhibitors

As described herein, the term “checkpoint inhibitor” includes any compound that is
15 capable of inhibiting immune checkpoint molecules that are regulators of the immune system (*e.g.*, stimulate or inhibit immune system activity). For example, some checkpoint inhibitors block inhibitory checkpoint molecules, thereby stimulating immune system function, such as stimulation of T cell activity against cancer cells. A non-limiting example of a checkpoint inhibitor is a PD-L1 inhibitor.

As described herein, the term “PD-L1 inhibitor” includes any compound that is
20 capable of inhibiting the expression and/or function of the protein Programmed Death-Ligand 1 (PD-L1) either directly or indirectly. PD-L1, also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1), is a type 1 transmembrane protein that plays a major role in suppressing the adaptive arm of immune system during pregnancy, tissue allograft
25 transplants, autoimmune disease, and hepatitis. PD-L1 binds to its receptor, the inhibitory checkpoint molecule PD-1 (which is found on activated T cells, B cells, and myeloid cells) so as to modulate activation or inhibition of the adaptive arm of immune system. In certain embodiments, the PD-L1 inhibitor inhibits the expression and/or function of PD-L1 by at least 5%, at least 10%, at least 20%, at least 50%, at least 75%, or at least 90%.

Reported PD-L1 Inhibitors include, but are not limited to, compounds recited in one
30 of the following patent application publications: US 2018/0057455; US 2018/0057486; WO 2017/106634; WO 2018/026971; WO 2018/045142; WO 2018/118848; WO 2018/119221; WO 2018/119236; WO 2018/119266; WO 2018/119286; WO 2018/121560; WO 2019/076343; WO 2019/087214; and are incorporated herein in their entirety by reference.

(g) GalNAc-siRNA Conjugates Targeted Against an HBV Gene Transcript

“GalNAc” is the abbreviation for N-acetylgalactosamine, and “siRNA” is the abbreviation for small interfering RNA. An siRNA that targets an HBV gene transcript is covalently bonded to GalNAc in a GalNAc-siRNA conjugate useful in the practice of the present invention. While not wishing to be bound by theory, it is believed that GalNAc binds to asialoglycoprotein receptors on hepatocytes thereby facilitating the targeting of the siRNA to the hepatocytes that are infected with HBV. The siRNA enter the infected hepatocytes and stimulate destruction of HBV gene transcripts by the phenomenon of RNA interference.

Examples of GalNAc-siRNA conjugates useful in the practice of this aspect of the present invention are set forth in published international application PCT/CA2017/050447 (PCT Application Publication number WO/2017/177326, published on October 19, 2017) which is hereby incorporated by reference in its entirety.

A synergistic effect may be calculated, for example, using suitable methods such as, for example, the Sigmoid- $E_{\max}$ equation (Holford & Scheiner, 1981, Clin. Pharmacokinet. 6:429-453), the equation of Loewe additivity (Loewe & Muischnek, 1926, Arch. Exp. Pathol Pharmacol. 114: 313-326) and the median-effect equation (Chou & Talalay, 1984, Adv. Enzyme Regul. 22:27-55). Each equation referred to elsewhere herein may be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to elsewhere herein are the concentration-effect curve, isobologram curve and combination index curve, respectively.

Synthesis

The present invention further provides methods of preparing the compounds of the present invention. Compounds of the present teachings can be prepared in accordance with the procedures outlined herein, from commercially available starting materials, compounds known in the literature, or readily prepared intermediates, by employing standard synthetic methods and procedures known to those skilled in the art. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be readily obtained from the relevant scientific literature or from standard textbooks in the field. It should be contemplated that the invention includes each and every one of the synthetic schemes described and/or depicted herein.

It is appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, and so forth) are given,

other process conditions can also be used unless otherwise stated. Optimum reaction conditions can vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures. Those skilled in the art of organic synthesis will recognize that the nature and order of the synthetic steps presented can be varied for the purpose of optimizing the formation of the compounds described herein.

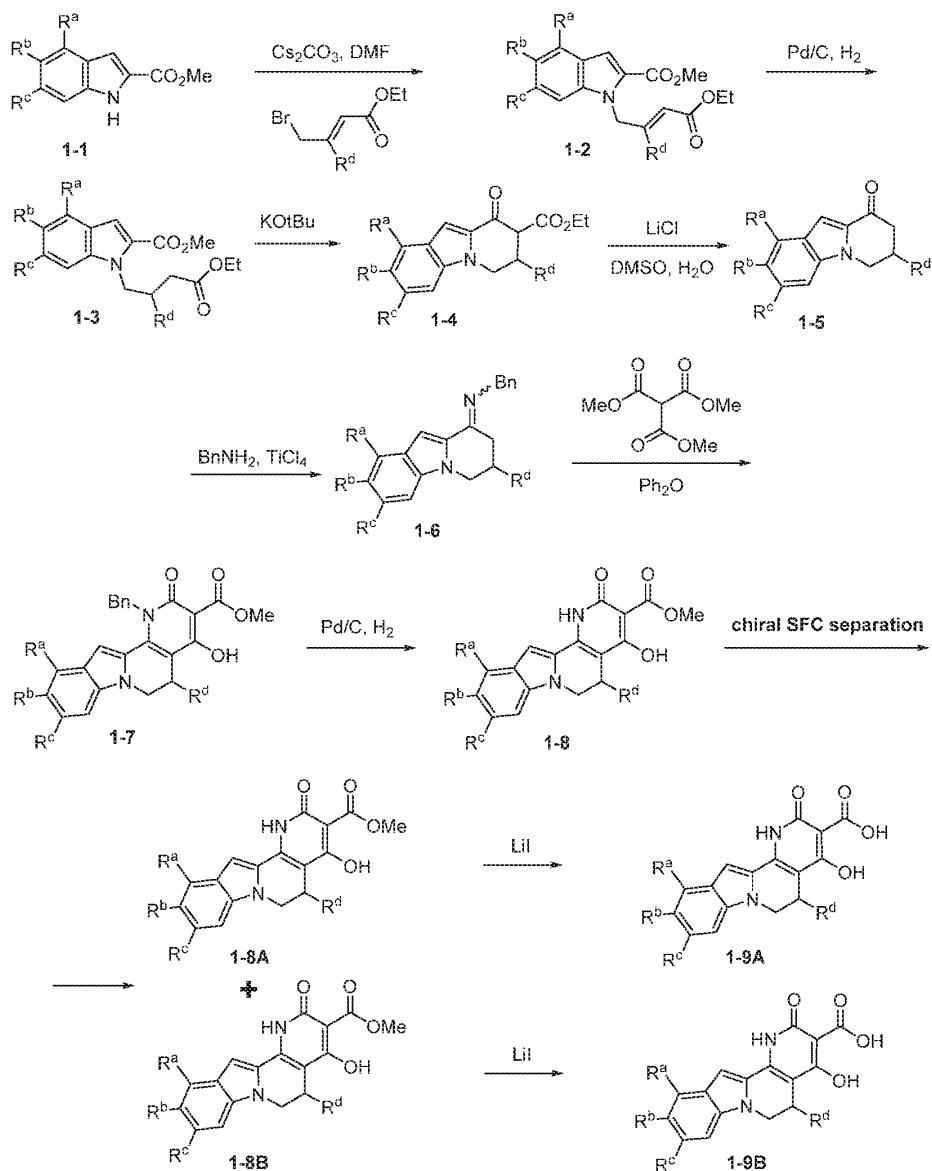
The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (*e.g.*, ^1H or ^{13}C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry, or by chromatography such as high pressure liquid chromatography (HPLC), gas chromatography (GC), gel-permeation chromatography (GPC), or thin layer chromatography (TLC).

Preparation of the compounds can involve protection and deprotection of various chemical groups. The need for protection and deprotection and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene, *et al.*, *Protective Groups in Organic Synthesis*, 2d. Ed. (Wiley & Sons, 1991), the entire disclosure of which is incorporated by reference herein for all purposes.

The reactions or the processes described herein can be carried out in suitable solvents that can be readily selected by one skilled in the art of organic synthesis. Suitable solvents typically are substantially nonreactive with the reactants, intermediates, and/or products at the temperatures at which the reactions are carried out, *i.e.*, temperatures that can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

The following Schemes illustrate non-limiting synthetic routes that allow for the preparation of certain compounds of the invention. It should be noted that substituents in these Schemes, such as but not limited to R^a - R^e , are non-limiting in nature and correspond to substituents defined elsewhere herein, as would be contemplated by one skilled in the art.

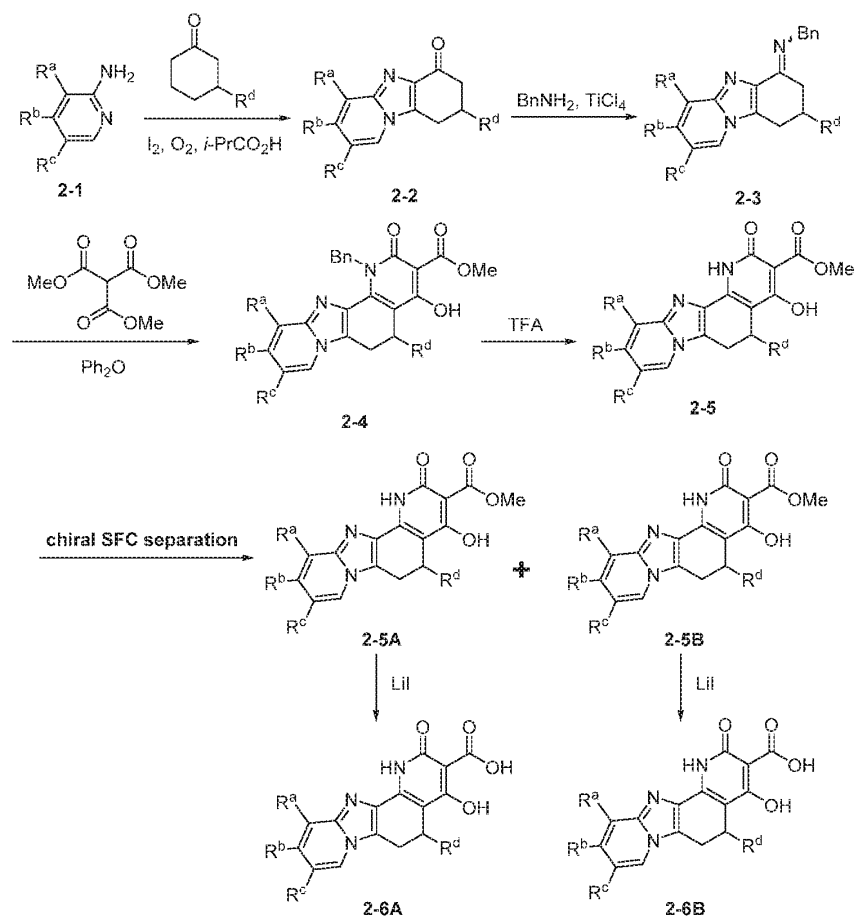
In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme I:



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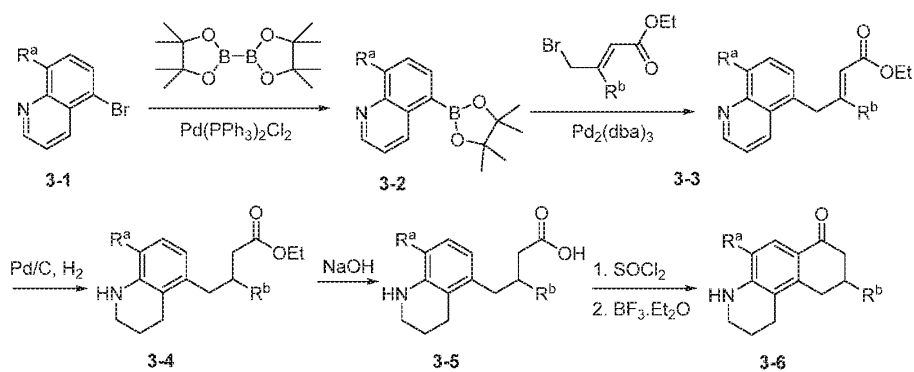
Scheme I.

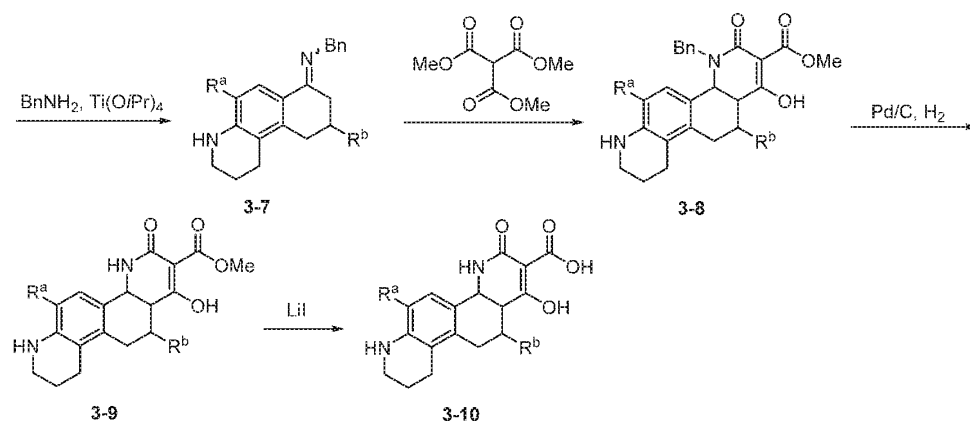
In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme II:



Scheme II.

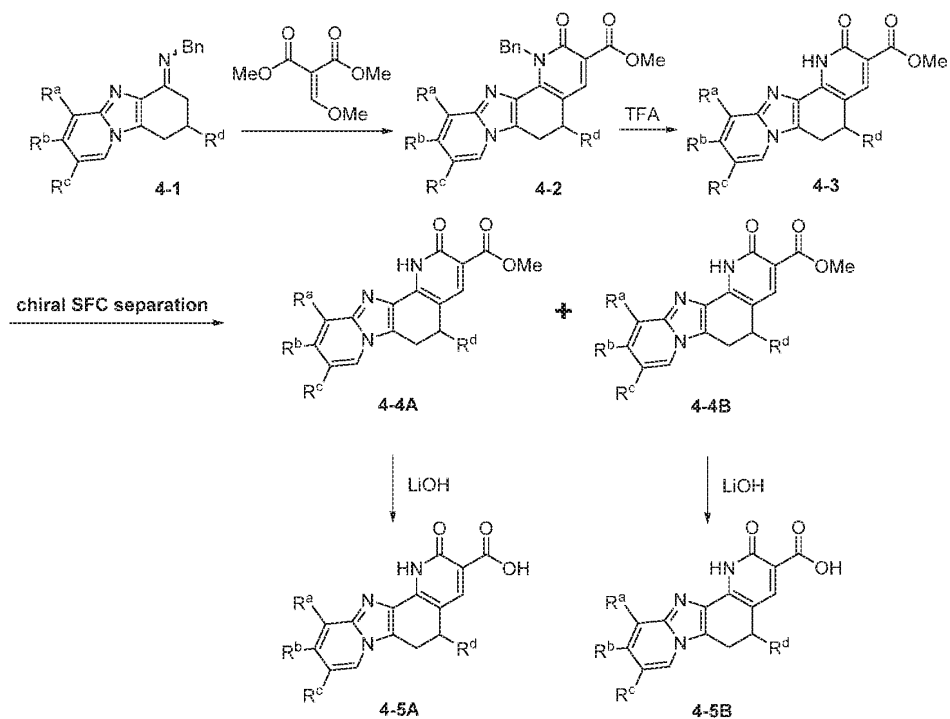
- In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme III:





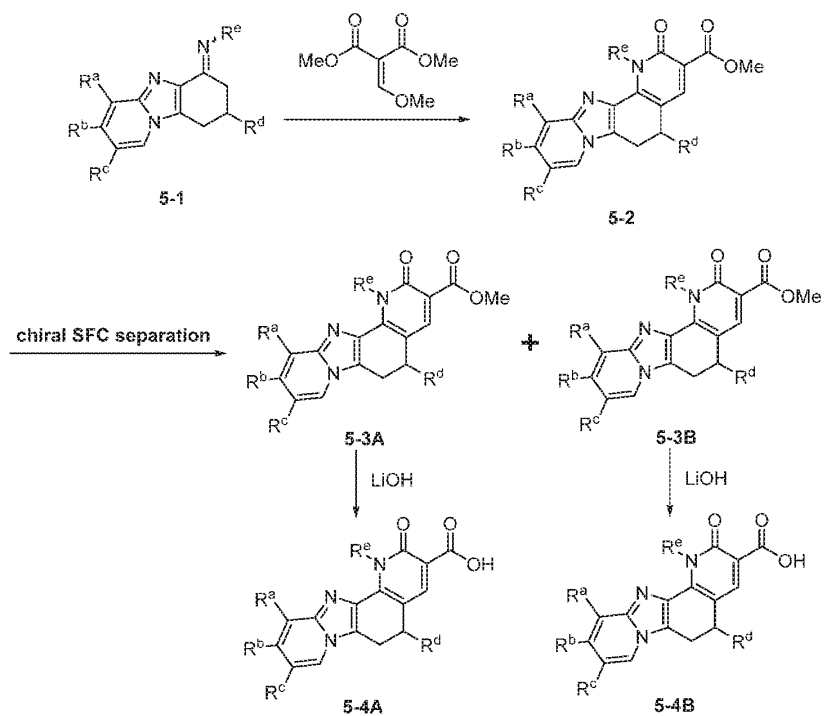
Scheme III.

In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme IV:



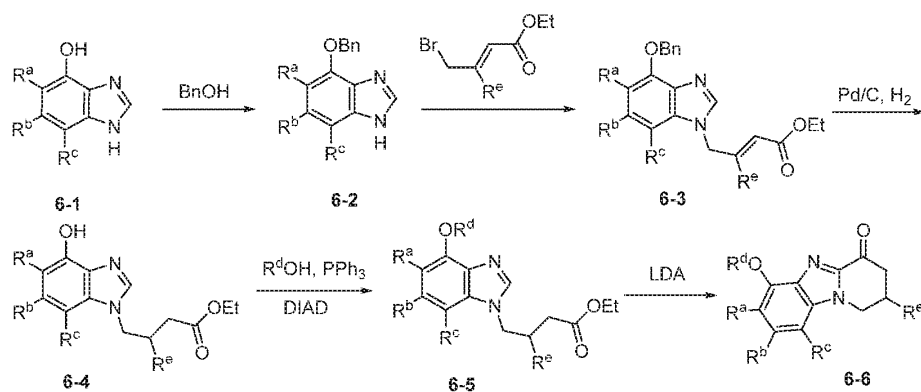
Scheme IV.

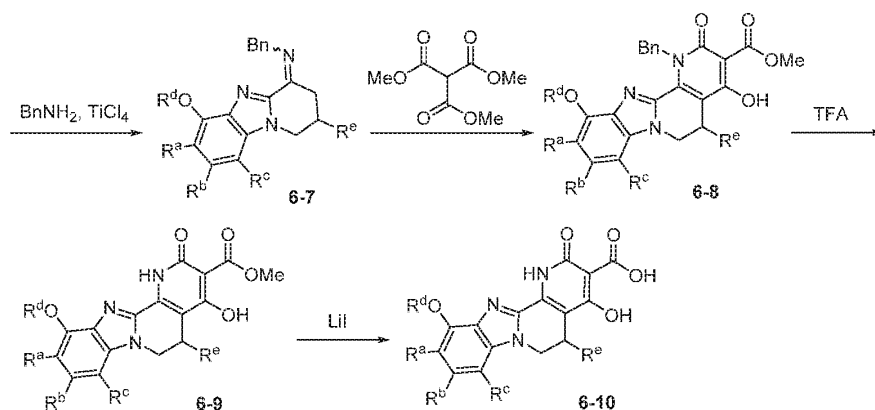
In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme V:



Scheme V.

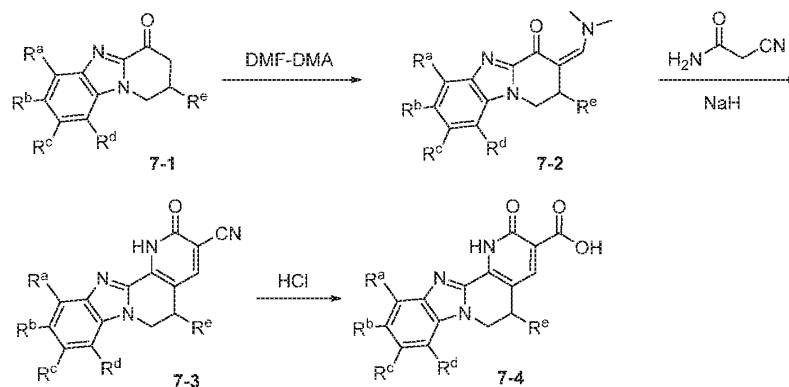
- In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme VI:





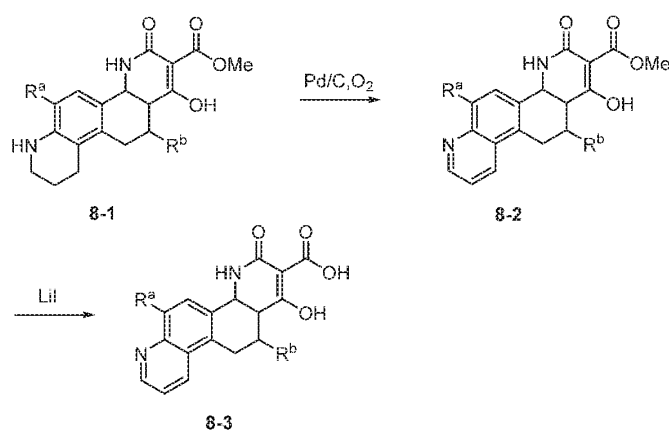
Scheme VI.

In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme VII:



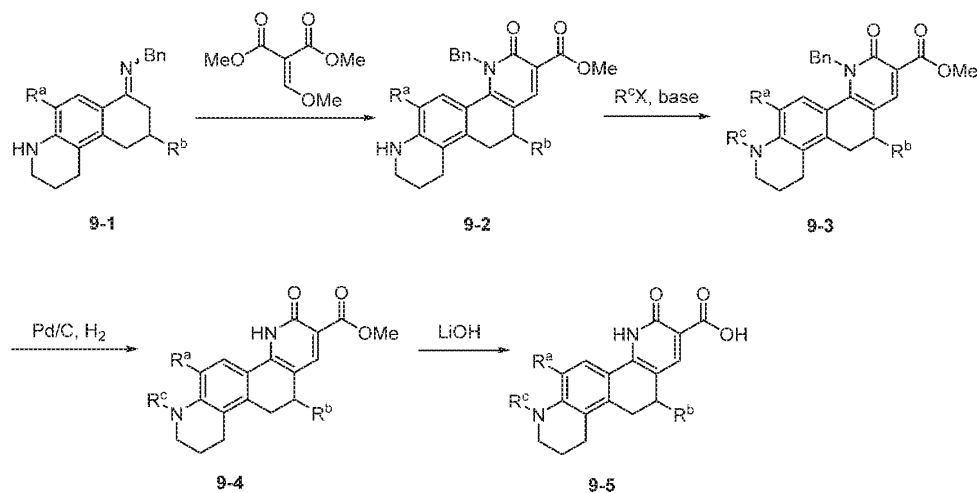
Scheme VII.

In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme VIII:

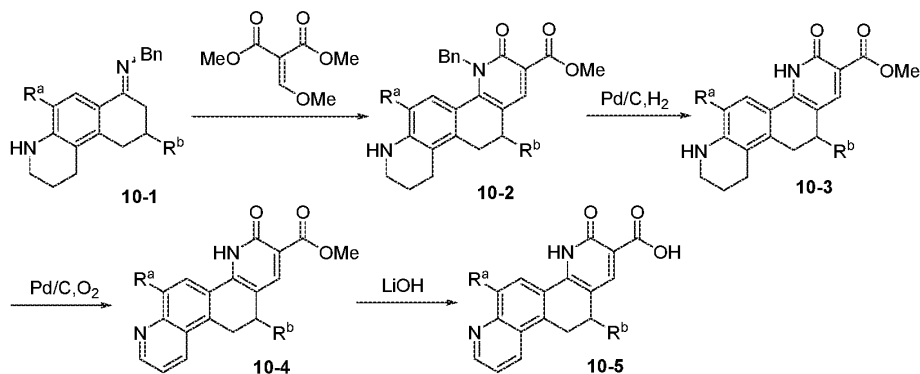


Scheme VIII.

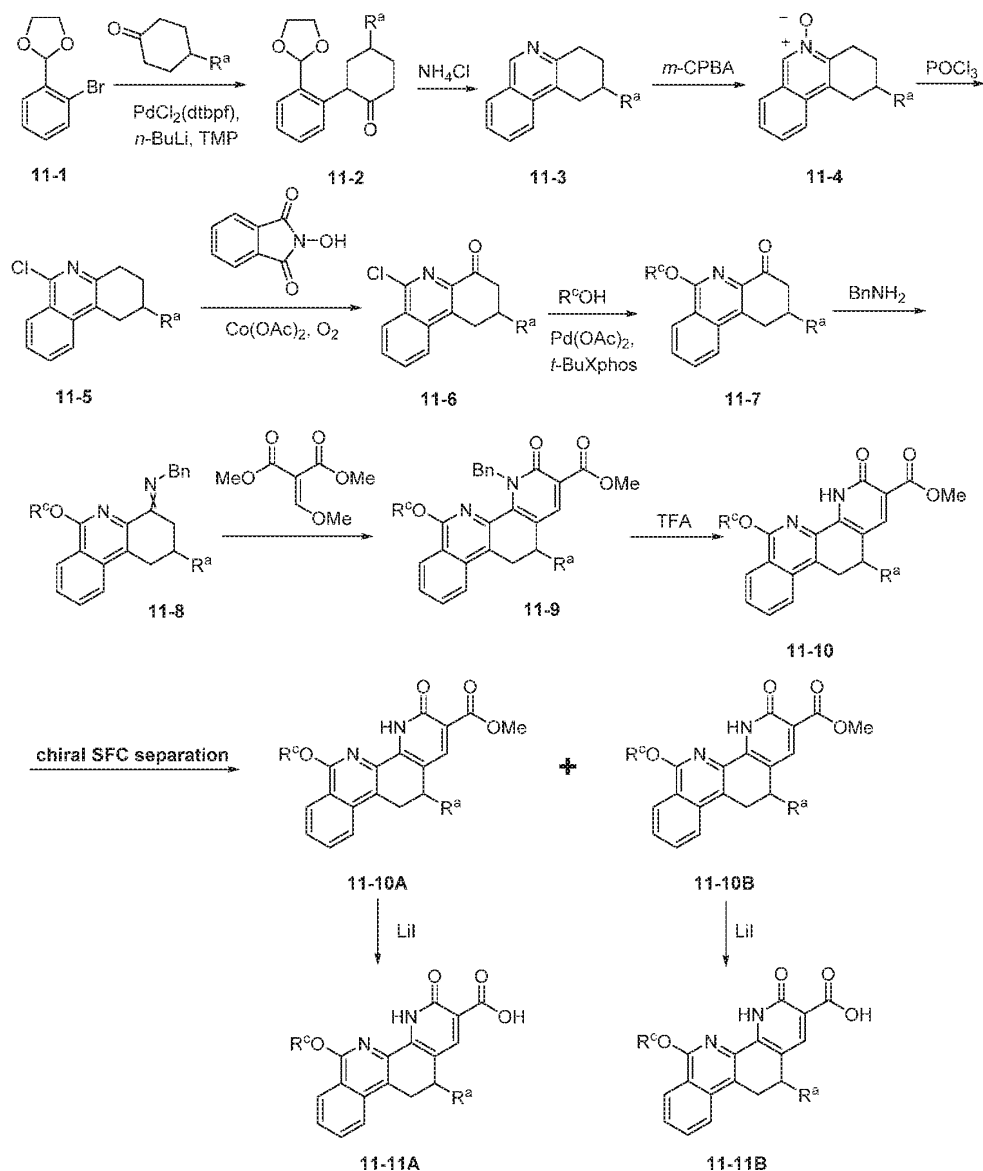
In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme IX:

**Scheme IX.**

In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme X:

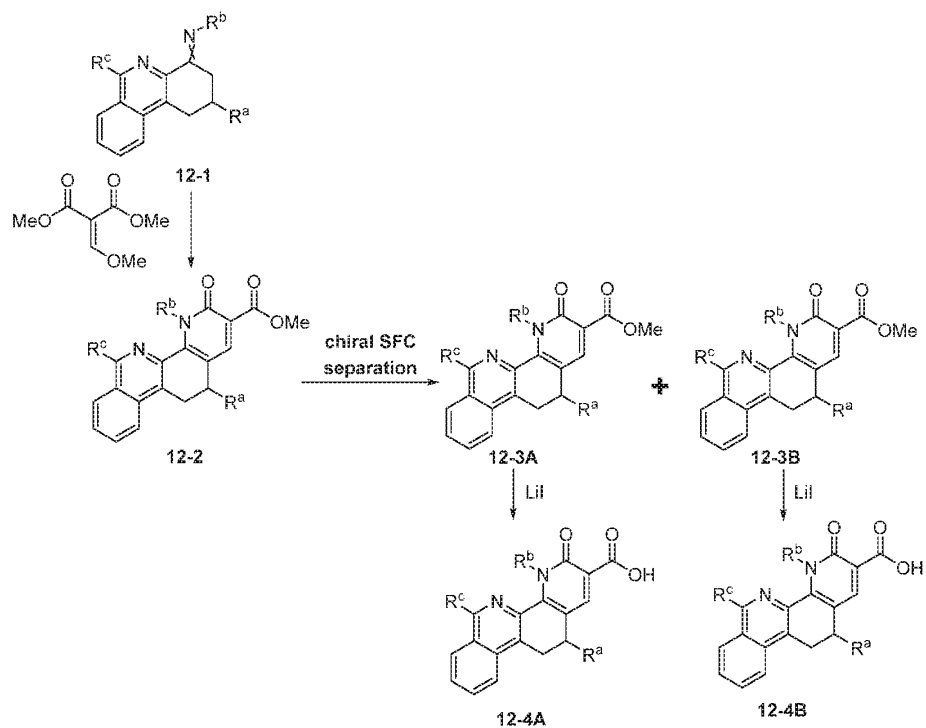
**Scheme X.**

In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme XI:

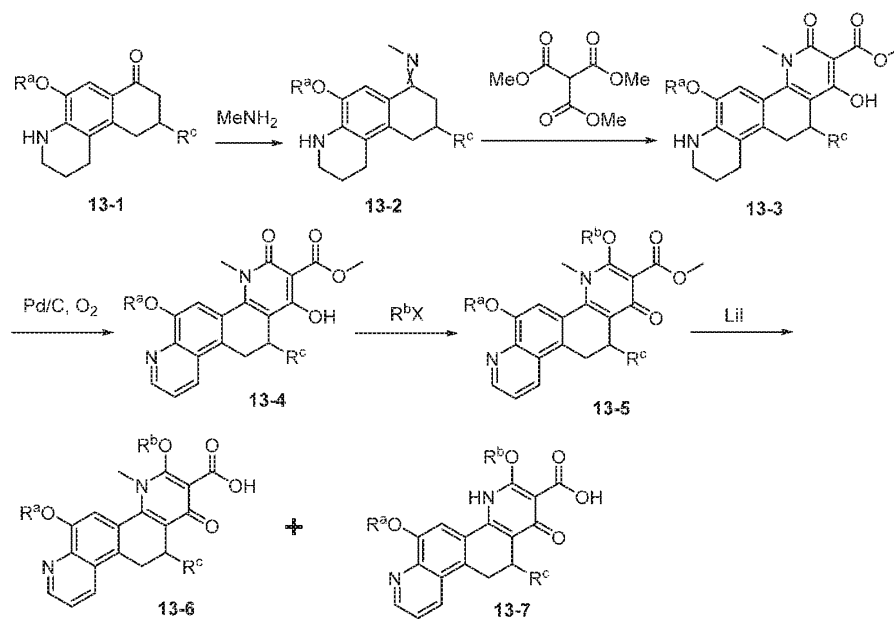


Scheme XI.

In certain embodiments, a compound of the invention can be prepared, for example,
 5 according to the illustrative synthetic methods outlined in Scheme XII:

**Scheme XII.**

In certain embodiments, a compound of the invention can be prepared, for example, according to the illustrative synthetic methods outlined in Scheme XIII:

**Scheme XIII.**

Methods

The invention provides a method of treating or preventing hepatitis virus infection in a subject. In certain embodiments, the infection comprises hepatitis B virus (HBV) infection.

- 5 In yet other embodiments, the infection comprises hepatitis D virus (HDV) infection. In other embodiments, the method comprises administering to the subject in need thereof a therapeutically effective amount of at least one compound of the invention. In yet other embodiments, the compound of the invention is the only antiviral agent administered to the subject. In yet other embodiments, the at least one compound is administered to the subject
- 10 in a pharmaceutically acceptable composition. In yet other embodiments, the subject is further administered at least one additional agent useful for treating the hepatitis virus infection. In yet other embodiments, the at least one additional agent comprises at least one selected from the group consisting of reverse transcriptase inhibitors, capsid inhibitors, cccDNA formation inhibitors, RNA destabilizers, oligomeric nucleotides targeted against the
- 15 HBV genome, immunostimulators, and GalNAc-siRNA conjugates targeted against an HBV gene transcript. In yet other embodiments, the subject is co-administered the at least one compound and the at least one additional agent. In yet other embodiments, the at least one compound and the at least one additional agent are coformulated.

- The invention further provides a method of inhibiting and/or reducing HBV surface
- 20 antigen (HBsAg) secretion either directly or indirectly in a subject. The invention further provides a method of reducing or minimizing levels of HBsAg in a HBV-infected subject. The invention further provides a method of reducing or minimizing levels of HBeAg in a HBV-infected subject. The invention further provides a method of reducing or minimizing levels of hepatitis B core protein in a HBV-infected subject. The invention further provides a
- 25 method of reducing or minimizing levels of pg RNA in a HBV-infected subject.

- In certain embodiments, the method comprises administering to the subject in need thereof a therapeutically effective amount of at least one compound of the invention. In other embodiments, the at least one compound is administered to the subject in a pharmaceutically acceptable composition. In yet other embodiments, the compound of the invention is the only
- 30 antiviral agent administered to the subject. In yet other embodiments, the subject is further administered at least one additional agent useful for treating the hepatitis infection. In yet other embodiments, the at least one additional agent comprises at least one selected from the group consisting of reverse transcriptase inhibitors, capsid inhibitors, cccDNA formation inhibitors, RNA destabilizers, oligomeric nucleotides targeted against the HBV genome,

immunostimulators, and GalNAc-siRNA conjugates targeted against an HBV gene transcript. In yet other embodiments, the subject is co-administered the at least one compound and the at least one additional agent. In yet other embodiments, the at least one compound and the at least one additional agent are coformulated.

5 In certain embodiments, the subject is infected with HBV. In other embodiments, the subject is infected with HDV. In yet other embodiments, the subject is infected with HBV and HDV.

 In certain embodiments, the subject is a mammal. In other embodiments, the mammal is a human.

10

Pharmaceutical Compositions and Formulations

 The invention provides pharmaceutical compositions comprising at least one compound of the invention or a salt or solvate thereof, which are useful to practice methods of the invention. Such a pharmaceutical composition may consist of at least one compound
15 of the invention or a salt or solvate thereof, in a form suitable for administration to a subject, or the pharmaceutical composition may comprise at least one compound of the invention or a salt or solvate thereof, and one or more pharmaceutically acceptable carriers, one or more additional ingredients, or some combination of these. At least one compound of the invention may be present in the pharmaceutical composition in the form of a physiologically acceptable
20 salt, such as in combination with a physiologically acceptable cation or anion, as is well known in the art.

 In certain embodiments, the pharmaceutical compositions useful for practicing the method of the invention may be administered to deliver a dose of between 1 ng/kg/day and 100 mg/kg/day. In other embodiments, the pharmaceutical compositions useful for practicing
25 the invention may be administered to deliver a dose of between 1 ng/kg/day and 1,000 mg/kg/day.

 The relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and condition of the subject treated and further depending
30 upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

 Pharmaceutical compositions that are useful in the methods of the invention may be suitably developed for nasal, inhalational, oral, rectal, vaginal, pleural, peritoneal, parenteral, topical, transdermal, pulmonary, intranasal, buccal, ophthalmic, epidural, intrathecal,

intravenous or another route of administration. A composition useful within the methods of the invention may be directly administered to the brain, the brainstem, or any other part of the central nervous system of a mammal or bird. Other contemplated formulations include projected nanoparticles, microspheres, liposomal preparations, coated particles, polymer
5 conjugates, resealed erythrocytes containing the active ingredient, and immunologically-based formulations.

In certain embodiments, the compositions of the invention are part of a pharmaceutical matrix, which allows for manipulation of insoluble materials and improvement of the bioavailability thereof, development of controlled or sustained release
10 products, and generation of homogeneous compositions. By way of example, a pharmaceutical matrix may be prepared using hot melt extrusion, solid solutions, solid dispersions, size reduction technologies, molecular complexes (*e.g.*, cyclodextrins, and others), microparticulate, and particle and formulation coating processes. Amorphous or crystalline phases may be used in such processes.

15 The route(s) of administration will be readily apparent to the skilled artisan and will depend upon any number of factors including the type and severity of the disease being treated, the type and age of the veterinary or human patient being treated, and the like.

The formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology and
20 pharmaceuticals. In general, such preparatory methods include the step of bringing the active ingredient into association with a carrier or one or more other accessory ingredients, and then, if necessary or desirable, shaping or packaging the product into a desired single-dose or multi-dose unit.

As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition
25 comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient that would be administered to a subject or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage. The unit dosage form may be for a single daily dose or one of multiple daily doses (*e.g.*, about 1 to 4 or more times per day). When multiple daily doses are
30 used, the unit dosage form may be the same or different for each dose.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions suitable for ethical administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical

compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions of the invention is contemplated include, but are not limited to, humans and other primates, mammals including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, and dogs.

In certain embodiments, the compositions of the invention are formulated using one or more pharmaceutically acceptable excipients or carriers. In certain embodiments, the pharmaceutical compositions of the invention comprise a therapeutically effective amount of at least one compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers, which are useful, include, but are not limited to, glycerol, water, saline, ethanol, recombinant human albumin (*e.g.*, RECOMBUMIN®), solubilized gelatins (*e.g.*, GELOFUSINE®), and other pharmaceutically acceptable salt solutions such as phosphates and salts of organic acids. Examples of these and other pharmaceutically acceptable carriers are described in Remington's Pharmaceutical Sciences (1991, Mack Publication Co., New Jersey).

The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), recombinant human albumin, solubilized gelatins, suitable mixtures thereof, and vegetable oils. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, are included in the composition. Prolonged absorption of the injectable compositions may be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate or gelatin.

Formulations may be employed in admixtures with conventional excipients, *i.e.*, pharmaceutically acceptable organic or inorganic carrier substances suitable for oral, parenteral, nasal, inhalational, intravenous, subcutaneous, transdermal enteral, or any other suitable mode of administration, known to the art. The pharmaceutical preparations may be sterilized and if desired mixed with auxiliary agents, *e.g.*, lubricants, preservatives,

stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or fragrance-conferring substances and the like. They may also be combined where desired with other active agents, *e.g.*, other analgesic, anxiolytics or hypnotic agents. As used herein, “additional ingredients” include, but are not limited to, one
5 or more ingredients that may be used as a pharmaceutical carrier.

The composition of the invention may comprise a preservative from about 0.005% to 2.0% by total weight of the composition. The preservative is used to prevent spoilage in the case of exposure to contaminants in the environment. Examples of preservatives useful in accordance with the invention include but are not limited to those selected from the group
10 consisting of benzyl alcohol, sorbic acid, parabens, imidurea and combinations thereof. One such preservative is a combination of about 0.5% to 2.0% benzyl alcohol and 0.05% to 0.5% sorbic acid.

The composition may include an antioxidant and a chelating agent which inhibit the degradation of the compound. Antioxidants for some compounds are BHT, BHA, alpha-
15 tocopherol and ascorbic acid in the exemplary range of about 0.01% to 0.3%, or BHT in the range of 0.03% to 0.1% by weight by total weight of the composition. The chelating agent may be present in an amount of from 0.01% to 0.5% by weight by total weight of the composition. Exemplary chelating agents include edetate salts (*e.g.* disodium edetate) and citric acid in the weight range of about 0.01% to 0.20%, or in the range of 0.02% to 0.10% by
20 weight by total weight of the composition. The chelating agent is useful for chelating metal ions in the composition that may be detrimental to the shelf life of the formulation. While BHT and disodium edetate are exemplary antioxidant and chelating agent, respectively, for some compounds, other suitable and equivalent antioxidants and chelating agents may be substituted therefore as would be known to those skilled in the art.

Liquid suspensions may be prepared using conventional methods to achieve
25 suspension of the active ingredient in an aqueous or oily vehicle. Aqueous vehicles include, for example, water, and isotonic saline. Oily vehicles include, for example, almond oil, oily esters, ethyl alcohol, vegetable oils such as arachis, olive, sesame, or coconut oil, fractionated vegetable oils, and mineral oils such as liquid paraffin. Liquid suspensions may further
30 comprise one or more additional ingredients including, but not limited to, suspending agents, dispersing or wetting agents, emulsifying agents, demulcents, preservatives, buffers, salts, flavorings, coloring agents, and sweetening agents. Oily suspensions may further comprise a thickening agent. Known suspending agents include, but are not limited to, sorbitol syrup, hydrogenated edible fats, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum

acacia, and cellulose derivatives such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl cellulose. Known dispersing or wetting agents include, but are not limited to, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with a fatty acid, with a long chain aliphatic alcohol, with a partial ester derived from a fatty acid and a hexitol, or with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene stearate, heptadecaethyleneoxycetanol, polyoxyethylene sorbitol monooleate, and polyoxyethylene sorbitan monooleate, respectively). Known emulsifying agents include, but are not limited to, lecithin, acacia, and ionic or non ionic surfactants. Known preservatives include, but are not limited to, methyl, ethyl, or *n*-propyl para-hydroxybenzoates, ascorbic acid, and sorbic acid. Known sweetening agents include, for example, glycerol, propylene glycol, sorbitol, sucrose, and saccharin.

Liquid solutions of the active ingredient in aqueous or oily solvents may be prepared in substantially the same manner as liquid suspensions, the primary difference being that the active ingredient is dissolved, rather than suspended in the solvent. As used herein, an “oily” liquid is one which comprises a carbon-containing liquid molecule and which exhibits a less polar character than water. Liquid solutions of the pharmaceutical composition of the invention may comprise each of the components described with regard to liquid suspensions, it being understood that suspending agents will not necessarily aid dissolution of the active ingredient in the solvent. Aqueous solvents include, for example, water, and isotonic saline. Oily solvents include, for example, almond oil, oily esters, ethyl alcohol, vegetable oils such as arachis, olive, sesame, or coconut oil, fractionated vegetable oils, and mineral oils such as liquid paraffin.

Powdered and granular formulations of a pharmaceutical preparation of the invention may be prepared using known methods. Such formulations may be administered directly to a subject, used, for example, to form tablets, to fill capsules, or to prepare an aqueous or oily suspension or solution by addition of an aqueous or oily vehicle thereto. Each of these formulations may further comprise one or more of dispersing or wetting agent, a suspending agent, ionic and non-ionic surfactants, and a preservative. Additional excipients, such as fillers and sweetening, flavoring, or coloring agents, may also be included in these formulations.

A pharmaceutical composition of the invention may also be prepared, packaged, or sold in the form of oil-in-water emulsion or a water-in-oil emulsion. The oily phase may be a vegetable oil such as olive or arachis oil, a mineral oil such as liquid paraffin, or a combination of these. Such compositions may further comprise one or more emulsifying

agents such as naturally occurring gums such as gum acacia or gum tragacanth, naturally-
occurring phosphatides such as soybean or lecithin phosphatide, esters or partial esters
derived from combinations of fatty acids and hexitol anhydrides such as sorbitan monooleate,
and condensation products of such partial esters with ethylene oxide such as polyoxyethylene
5 sorbitan monooleate. These emulsions may also contain additional ingredients including, for
example, sweetening or flavoring agents.

Methods for impregnating or coating a material with a chemical composition are
known in the art, and include, but are not limited to methods of depositing or binding a
chemical composition onto a surface, methods of incorporating a chemical composition into
10 the structure of a material during the synthesis of the material (*i.e.*, such as with a
physiologically degradable material), and methods of absorbing an aqueous or oily solution
or suspension into an absorbent material, with or without subsequent drying. Methods for
mixing components include physical milling, the use of pellets in solid and suspension
formulations and mixing in a transdermal patch, as known to those skilled in the art.

15

Administration/Dosing

The regimen of administration may affect what constitutes an effective amount. The
therapeutic formulations may be administered to the patient either prior to or after the onset
of a disease or disorder. Further, several divided dosages, as well as staggered dosages may
20 be administered daily or sequentially, or the dose may be continuously infused, or may be a
bolus injection. Further, the dosages of the therapeutic formulations may be proportionally
increased or decreased as indicated by the exigencies of the therapeutic or prophylactic
situation.

Administration of the compositions of the present invention to a patient, such as a
25 mammal, such as a human, may be carried out using known procedures, at dosages and for
periods of time effective to treat a disease or disorder contemplated herein. An effective
amount of the therapeutic compound necessary to achieve a therapeutic effect may vary
according to factors such as the activity of the particular compound employed; the time of
administration; the rate of excretion of the compound; the duration of the treatment; other
30 drugs, compounds or materials used in combination with the compound; the state of the
disease or disorder, age, sex, weight, condition, general health and prior medical history of
the patient being treated, and like factors well-known in the medical arts. Dosage regimens
may be adjusted to provide the optimum therapeutic response. For example, several divided
doses may be administered daily or the dose may be proportionally reduced as indicated by

the exigencies of the therapeutic situation. A non-limiting example of an effective dose range for a therapeutic compound of the invention is from about 0.01 mg/kg to 100 mg/kg of body weight/per day. One of ordinary skill in the art would be able to study the relevant factors and make the determination regarding the effective amount of the therapeutic compound

5 without undue experimentation.

The compound may be administered to an animal as frequently as several times daily, or it may be administered less frequently, such as once a day, once a week, once every two weeks, once a month, or even less frequently, such as once every several months or even once a year or less. It is understood that the amount of compound dosed per day may be

10 administered, in non-limiting examples, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days. For example, with every other day administration, a 5 mg per day dose may be initiated on Monday with a first subsequent 5 mg per day dose administered on Wednesday, a second subsequent 5 mg per day dose administered on Friday, and so on. The frequency of the dose is readily apparent to the skilled artisan and depends

15 upon a number of factors, such as, but not limited to, type and severity of the disease being treated, and type and age of the animal.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and

20 mode of administration, without being toxic to the patient.

A medical doctor, *e.g.*, physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required

25 in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In particular embodiments, it is especially advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be

30 treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding/formulating such a

therapeutic compound for the treatment of a disease or disorder in a patient.

In certain embodiments, the compositions of the invention are administered to the patient in dosages that range from one to five times per day or more. In other embodiments, the compositions of the invention are administered to the patient in range of dosages that include, but are not limited to, once every day, every two days, every three days to once a week, and once every two weeks. It will be readily apparent to one skilled in the art that the frequency of administration of the various combination compositions of the invention will vary from subject to subject depending on many factors including, but not limited to, age, disease or disorder to be treated, gender, overall health, and other factors. Thus, the invention should not be construed to be limited to any particular dosage regime and the precise dosage and composition to be administered to any patient will be determined by the attending physician taking all other factors about the patient into account.

Compounds of the invention for administration may be in the range of from about 1 µg to about 7,500 mg, about 20 µg to about 7,000 mg, about 40 µg to about 6,500 mg, about 80 µg to about 6,000 mg, about 100 µg to about 5,500 mg, about 200 µg to about 5,000 mg, about 400 µg to about 4,000 mg, about 800 µg to about 3,000 mg, about 1 mg to about 2,500 mg, about 2 mg to about 2,000 mg, about 5 mg to about 1,000 mg, about 10 mg to about 750 mg, about 20 mg to about 600 mg, about 30 mg to about 500 mg, about 40 mg to about 400 mg, about 50 mg to about 300 mg, about 60 mg to about 250 mg, about 70 mg to about 200 mg, about 80 mg to about 150 mg, and any and all whole or partial increments there-in-between.

In some embodiments, the dose of a compound of the invention is from about 0.5 µg and about 5,000 mg. In some embodiments, a dose of a compound of the invention used in compositions described herein is less than about 5,000 mg, or less than about 4,000 mg, or less than about 3,000 mg, or less than about 2,000 mg, or less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 200 mg, or less than about 50 mg. Similarly, in some embodiments, a dose of a second compound as described herein is less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 400 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than about 40 mg, or less than about 30 mg, or less than about 25 mg, or less than about 20 mg, or less than about 15 mg, or less than about 10 mg, or less than about 5 mg, or less than about 2 mg, or less than about 1 mg, or less than about 0.5 mg, and any and all whole or

partial increments thereof.

In certain embodiments, the present invention is directed to a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a compound of the invention, alone or in combination with a second
5 pharmaceutical agent; and instructions for using the compound to treat, prevent, or reduce one or more symptoms of a disease or disorder in a patient.

The term “container” includes any receptacle for holding the pharmaceutical composition or for managing stability or water uptake. For example, in certain embodiments, the container is the packaging that contains the pharmaceutical composition, such as liquid
10 (solution and suspension), semisolid, lyophilized solid, solution and powder or lyophilized formulation present in dual chambers. In other embodiments, the container is not the packaging that contains the pharmaceutical composition, *i.e.*, the container is a receptacle, such as a box or vial that contains the packaged pharmaceutical composition or unpackaged pharmaceutical composition and the instructions for use of the pharmaceutical composition.
15 Moreover, packaging techniques are well known in the art. It should be understood that the instructions for use of the pharmaceutical composition may be contained on the packaging containing the pharmaceutical composition, and as such the instructions form an increased functional relationship to the packaged product. However, it should be understood that the instructions may contain information pertaining to the compound’s ability to perform its
20 intended function, *e.g.*, treating, preventing, or reducing a disease or disorder in a patient.

Administration

Routes of administration of any of the compositions of the invention include inhalational, oral, nasal, rectal, parenteral, sublingual, transdermal, transmucosal (*e.g.*,
25 sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (*e.g.*, trans- and perivaginally), (intra)nasal, and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, epidural, intrapleural, intraperitoneal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration.

Suitable compositions and dosage forms include, for example, tablets, capsules,
30 caplets, pills, gel caps, troches, emulsions, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and

compositions that would be useful in the present invention are not limited to the particular formulations and compositions that are described herein.

Oral Administration

For oral application, particularly suitable are tablets, dragees, liquids, drops, capsules, caplets and gelcaps. Other formulations suitable for oral administration include, but are not limited to, a powdered or granular formulation, an aqueous or oily suspension, an aqueous or oily solution, a paste, a gel, toothpaste, a mouthwash, a coating, an oral rinse, or an emulsion. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic, generally recognized as safe (GRAS) pharmaceutically excipients which are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate.

Tablets may be non-coated or they may be coated using known methods to achieve delayed disintegration in the gastrointestinal tract of a subject, thereby providing sustained release and absorption of the active ingredient. By way of example, a material such as glyceryl monostearate or glyceryl distearate may be used to coat tablets. Further by way of example, tablets may be coated using methods described in U.S. Patents Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotically controlled release tablets. Tablets may further comprise a sweetening agent, a flavoring agent, a coloring agent, a preservative, or some combination of these in order to provide for pharmaceutically elegant and palatable preparation. Hard capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin. The capsules comprise the active ingredient, and may further comprise additional ingredients including, for example, an inert solid diluent such as calcium carbonate, calcium phosphate, or kaolin.

Hard capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin. Such hard capsules comprise the active ingredient, and may further comprise additional ingredients including, for example, an inert solid diluent such as calcium carbonate, calcium phosphate, or kaolin.

Soft gelatin capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin from animal-derived collagen or from a hypromellose, a modified form of cellulose, and manufactured using optional mixtures of gelatin, water and plasticizers such as sorbitol or glycerol. Such soft capsules comprise the active ingredient, which may be mixed with water or an oil medium such as peanut oil, liquid

paraffin, or olive oil.

For oral administration, the compounds of the invention may be in the form of tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents; fillers; lubricants; disintegrates; or wetting agents. If desired, the tablets may be coated using suitable methods and coating materials such as OPADRY® film coating systems available from Colorcon, West Point, Pa. (*e.g.*, OPADRY® OY Type, OYC Type, Organic Enteric OY-P Type, Aqueous Enteric OY-A Type, OY-PM Type and OPADRY® White, 32K18400). It is understood that similar type of film coating or polymeric products from other companies may be used.

- 10 A tablet comprising the active ingredient may, for example, be made by compressing or molding the active ingredient, optionally with one or more additional ingredients. Compressed tablets may be prepared by compressing, in a suitable device, the active ingredient in a free-flowing form such as a powder or granular preparation, optionally mixed with one or more of a binder, a lubricant, an excipient, a surface active agent, and a
- 15 dispersing agent. Molded tablets may be made by molding, in a suitable device, a mixture of the active ingredient, a pharmaceutically acceptable carrier, and at least sufficient liquid to moisten the mixture. Pharmaceutically acceptable excipients used in the manufacture of tablets include, but are not limited to, inert diluents, granulating and disintegrating agents, binding agents, and lubricating agents. Known dispersing agents include, but are not limited to, potato starch and sodium starch glycolate. Known surface-active agents include, but are not limited to, sodium lauryl sulphate. Known diluents include, but are not limited to, calcium carbonate, sodium carbonate, lactose, microcrystalline cellulose, calcium phosphate, calcium hydrogen phosphate, and sodium phosphate. Known granulating and disintegrating agents include, but are not limited to, corn starch and alginic acid. Known binding agents
- 20 include, but are not limited to, gelatin, acacia, pre-gelatinized maize starch, polyvinylpyrrolidone, and hydroxypropyl methylcellulose. Known lubricating agents include, but are not limited to, magnesium stearate, stearic acid, silica, and talc.

- Granulating techniques are well known in the pharmaceutical art for modifying starting powders or other particulate materials of an active ingredient. The powders are typically mixed with a binder material into larger permanent free-flowing agglomerates or
- 30 granules referred to as a “granulation.” For example, solvent-using “wet” granulation processes are generally characterized in that the powders are combined with a binder material and moistened with water or an organic solvent under conditions resulting in the formation of a wet granulated mass from which the solvent must then be evaporated.

Melt granulation generally consists in the use of materials that are solid or semi-solid at room temperature (*i.e.*, having a relatively low softening or melting point range) to promote granulation of powdered or other materials, essentially in the absence of added water or other liquid solvents. The low melting solids, when heated to a temperature in the melting point range, liquefy to act as a binder or granulating medium. The liquefied solid spreads itself over the surface of powdered materials with which it is contacted, and on cooling, forms a solid granulated mass in which the initial materials are bound together. The resulting melt granulation may then be provided to a tablet press or be encapsulated for preparing the oral dosage form. Melt granulation improves the dissolution rate and bioavailability of an active (*i.e.*, drug) by forming a solid dispersion or solid solution.

U.S. Patent No. 5,169,645 discloses directly compressible wax-containing granules having improved flow properties. The granules are obtained when waxes are admixed in the melt with certain flow improving additives, followed by cooling and granulation of the admixture. In certain embodiments, only the wax itself melts in the melt combination of the wax(es) and additives(s), and in other cases both the wax(es) and the additives(s) will melt.

The present invention also includes a multi-layer tablet comprising a layer providing for the delayed release of one or more compounds useful within the methods of the invention, and a further layer providing for the immediate release of one or more compounds useful within the methods of the invention. Using a wax/pH-sensitive polymer mix, a gastric insoluble composition may be obtained in which the active ingredient is entrapped, ensuring its delayed release.

Liquid preparation for oral administration may be in the form of solutions, syrups or suspensions. The liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.*, methyl or propyl para-hydroxy benzoates or sorbic acid). Liquid formulations of a pharmaceutical composition of the invention which are suitable for oral administration may be prepared, packaged, and sold either in liquid form or in the form of a dry product intended for reconstitution with water or another suitable vehicle prior to use.

Parenteral Administration

As used herein, "parenteral administration" of a pharmaceutical composition includes any route of administration characterized by physical breaching of a tissue of a subject and administration of the pharmaceutical composition through the breach in the tissue. Parenteral

administration thus includes, but is not limited to, administration of a pharmaceutical composition by injection of the composition, by application of the composition through a surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, but is not limited to, subcutaneous, intravenous, intraperitoneal, intramuscular, intrasternal injection, and kidney dialytic infusion techniques.

Formulations of a pharmaceutical composition suitable for parenteral administration comprise the active ingredient combined with a pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration. Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as in ampules or in multidose containers containing a preservative. Injectable formulations may also be prepared, packaged, or sold in devices such as patient-controlled analgesia (PCA) devices. Formulations for parenteral administration include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations. Such formulations may further comprise one or more additional ingredients including, but not limited to, suspending, stabilizing, or dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (*i.e.*, powder or granular) form for reconstitution with a suitable vehicle (*e.g.*, sterile pyrogen-free water) prior to parenteral administration of the reconstituted composition.

The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the known art, and may comprise, in addition to the active ingredient, additional ingredients such as the dispersing agents, wetting agents, or suspending agents described herein. Such sterile injectable formulations may be prepared using a non-toxic parenterally acceptable diluent or solvent, such as water or 1,3-butanediol, for example. Other acceptable diluents and solvents include, but are not limited to, Ringer's solution, isotonic sodium chloride solution, and fixed oils such as synthetic mono- or di-glycerides. Other parentally-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form in a recombinant human albumin, a fluidized gelatin, in a liposomal preparation, or as a component of a biodegradable polymer system. Compositions for sustained release or implantation may comprise pharmaceutically acceptable polymeric or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

Topical Administration

An obstacle for topical administration of pharmaceuticals is the stratum corneum layer of the epidermis. The stratum corneum is a highly resistant layer comprised of protein, cholesterol, sphingolipids, free fatty acids and various other lipids, and includes cornified and living cells. One of the factors that limit the penetration rate (flux) of a compound through the stratum corneum is the amount of the active substance that can be loaded or applied onto the skin surface. The greater the amount of active substance which is applied per unit of area of the skin, the greater the concentration gradient between the skin surface and the lower layers of the skin, and in turn the greater the diffusion force of the active substance through the skin. Therefore, a formulation containing a greater concentration of the active substance is more likely to result in penetration of the active substance through the skin, and more of it, and at a more consistent rate, than a formulation having a lesser concentration, all other things being equal.

Formulations suitable for topical administration include, but are not limited to, liquid or semi-liquid preparations such as liniments, lotions, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes, and solutions or suspensions. Topically administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

Enhancers of permeation may be used. These materials increase the rate of penetration of drugs across the skin. Typical enhancers in the art include ethanol, glycerol monolaurate, PGML (polyethylene glycol monolaurate), dimethylsulfoxide, and the like. Other enhancers include oleic acid, oleyl alcohol, ethoxydiglycol, laurocapram, alkanecarboxylic acids, dimethylsulfoxide, polar lipids, or N-methyl-2-pyrrolidone.

One acceptable vehicle for topical delivery of some of the compositions of the invention may contain liposomes. The composition of the liposomes and their use are known in the art (*i.e.*, U.S. Patent No. 6,323,219).

In alternative embodiments, the topically active pharmaceutical composition may be optionally combined with other ingredients such as adjuvants, anti-oxidants, chelating agents, surfactants, foaming agents, wetting agents, emulsifying agents, viscosifiers, buffering agents, preservatives, and the like. In other embodiments, a permeation or penetration enhancer is included in the composition and is effective in improving the percutaneous penetration of the active ingredient into and through the stratum corneum with respect to a

composition lacking the permeation enhancer. Various permeation enhancers, including oleic acid, oleyl alcohol, ethoxydiglycol, laurocapram, alkanecarboxylic acids, dimethylsulfoxide, polar lipids, or N-methyl-2-pyrrolidone, are known to those of skill in the art. In another aspect, the composition may further comprise a hydrotropic agent, which functions to
5 increase disorder in the structure of the stratum corneum, and thus allows increased transport across the stratum corneum. Various hydrotropic agents such as isopropyl alcohol, propylene glycol, or sodium xylene sulfonate, are known to those of skill in the art.

The topically active pharmaceutical composition should be applied in an amount effective to affect desired changes. As used herein “amount effective” shall mean an amount
10 sufficient to cover the region of skin surface where a change is desired. An active compound should be present in the amount of from about 0.0001% to about 15% by weight volume of the composition. For example, it should be present in an amount from about 0.0005% to about 5% of the composition; for example, it should be present in an amount of from about 0.001% to about 1% of the composition. Such compounds may be synthetically-or naturally
15 derived.

Buccal Administration

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets or lozenges made using conventional methods, and may contain, for
20 example, 0.1 to 20% (w/w) of the active ingredient, the balance comprising an orally dissolvable or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise a powder or an aerosolized or atomized solution or suspension comprising the active ingredient. Such powdered, aerosolized, or aerosolized formulations, when dispersed,
25 may have an average particle or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein. The examples of formulations described herein are not exhaustive and it is understood that the invention includes additional modifications of these and other formulations not described herein, but which are known to those of skill in the art.

Rectal Administration

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for rectal administration. Such a composition may be in the form of, for example, a suppository, a retention enema preparation, and a solution for rectal or colonic irrigation.

Suppository formulations may be made by combining the active ingredient with a non-irritating pharmaceutically acceptable excipient which is solid at ordinary room temperature (*i.e.*, about 20°C) and which is liquid at the rectal temperature of the subject (*i.e.*, about 37°C in a healthy human). Suitable pharmaceutically acceptable excipients include, but are not limited to, cocoa butter, polyethylene glycols, and various glycerides. Suppository formulations may further comprise various additional ingredients including, but not limited to, antioxidants, and preservatives.

Retention enema preparations or solutions for rectal or colonic irrigation may be made by combining the active ingredient with a pharmaceutically acceptable liquid carrier. As is well known in the art, enema preparations may be administered using, and may be packaged within, a delivery device adapted to the rectal anatomy of the subject. Enema preparations may further comprise various additional ingredients including, but not limited to, antioxidants, and preservatives.

Additional Administration Forms

Additional dosage forms of this invention include dosage forms as described in U.S. Patents Nos. 6,340,475, 6,488,962, 6,451,808, 5,972,389, 5,582,837, and 5,007,790. Additional dosage forms of this invention also include dosage forms as described in U.S. Patent Applications Nos. 20030147952, 20030104062, 20030104053, 20030044466, 20030039688, and 20020051820. Additional dosage forms of this invention also include dosage forms as described in PCT Applications Nos. WO 03/35041, WO 03/35040, WO 03/35029, WO 03/35177, WO 03/35039, WO 02/96404, WO 02/32416, WO 01/97783, WO 01/56544, WO 01/32217, WO 98/55107, WO 98/11879, WO 97/47285, WO 93/18755, and WO 90/11757.

Controlled Release Formulations and Drug Delivery Systems

In certain embodiments, the compositions and/or formulations of the present invention may be, but are not limited to, short-term, rapid-offset, as well as controlled, for example, sustained release, delayed release and pulsatile release formulations.

The term sustained release is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that may, although not necessarily, result in substantially constant blood levels of a drug over an extended time period. The period of time may be as long as a month or more and should be a release which is longer than the same amount of agent administered in bolus form.

For sustained release, the compounds may be formulated with a suitable polymer or

hydrophobic material which provides sustained release properties to the compounds. As such, the compounds for use the method of the invention may be administered in the form of microparticles, for example, by injection or in the form of wafers or discs by implantation.

In certain embodiments of the invention, the compounds useful within the invention are administered to a subject, alone or in combination with another pharmaceutical agent, using a sustained release formulation.

The term delayed release is used herein in its conventional sense to refer to a drug formulation that provides for an initial release of the drug after some delay following drug administration and that may, although not necessarily, include a delay of from about 10 minutes up to about 12 hours.

The term pulsatile release is used herein in its conventional sense to refer to a drug formulation that provides release of the drug in such a way as to produce pulsed plasma profiles of the drug after drug administration.

The term immediate release is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration.

As used herein, short-term refers to any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes and any or all whole or partial increments thereof after drug administration after drug administration.

As used herein, rapid-offset refers to any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes, and any and all whole or partial increments thereof after drug administration.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents were considered to be within the scope of this invention and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, *e.g.*, nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that, wherever values and ranges are provided herein, the description in range format is merely for convenience and brevity and should not be

construed as an inflexible limitation on the scope of the invention. Accordingly, all values and ranges encompassed by these values and ranges are meant to be encompassed within the scope of the present invention. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application. The description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range and, when appropriate, partial integers of the numerical values within ranges. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

The following examples further illustrate aspects of the present invention. However, they are in no way a limitation of the teachings or disclosure of the present invention as set forth herein.

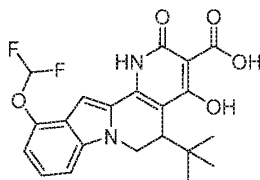
EXAMPLES

The invention is now described with reference to the following Examples. These Examples are provided for the purpose of illustration only, and the invention is not limited to these Examples, but rather encompasses all variations that are evident as a result of the teachings provided herein.

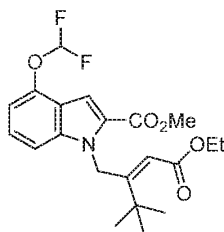
Materials & Methods

The following procedures can be utilized in preparing and/or testing exemplary compounds of the invention.

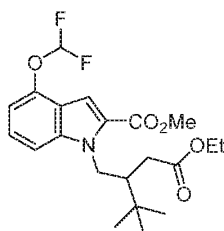
Example 1: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid



Methyl (E)-1-(2-(tert-butyl)-4-ethoxy-4-oxobut-2-en-1-yl)-4-(difluoromethoxy)-1H-indole-

2-carboxylate:

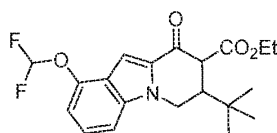
To a solution of ethyl (*E*)-3-(bromomethyl)-4,4-dimethyl-pent-2-enoate (5.73 g, 23 mmol), prepared according to the procedures by Sudalai, *et al.*, 2006, Tetrahedron 62:4907 and Ren, *et al.*, 2015, Synlett 26:2784, in DMF (50 mL) were added methyl 4-(difluoromethoxy)-1H-indole-2-carboxylate (3.7 g, 15.3 mmol) and cesium carbonate (10 g, 30.7 mmol). The reaction mixture was stirred at 50 °C for 16 h under N₂. To the reaction mixture was added H₂O (20 mL) and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with saturated aqueous brine solution (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude residue was purified by normal phase SiO₂ chromatography (0-20% EtOAc/petroleum ether) to afford methyl (*E*)-1-(2-(*tert*-butyl)-4-ethoxy-4-oxobut-2-en-1-yl)-4-(difluoromethoxy)-1H-indole-2-carboxylate as a yellow solid (3.6 g, 57% yield, m/z: 432 [M+Na]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 7.44 (s, 1H), 7.33-7.31 (m, 1H), 7.22 (t, *J* = 8 Hz, 1H), 6.83 (s, 1H), 6.65 (t, *J* = 7.4 Hz, 1H), 6.05-6.03 (m, 3H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 1.17 (t, *J* = 6.4 Hz, 3H), 0.99 (s, 9H).

Methyl 1-(2-(*tert*-butyl)-4-ethoxy-4-oxobutyl)-4-(difluoromethoxy)-1H-indole-2-carboxylate:

To a solution of methyl (*E*)-1-(2-(*tert*-butyl)-4-ethoxy-4-oxobut-2-en-1-yl)-4-(difluoromethoxy)-1H-indole-2-carboxylate (3.6 g, 8.79 mmol) in EtOH (50 mL) was added palladium on carbon (10% wt, 1.24 g, 1.14 mmol). The suspension was degassed using vacuum and purged with hydrogen gas (repeated cycle 2 times). The mixture was stirred under an atmosphere of hydrogen gas at 50 psi for 20 h. The reaction mixture was filtered through CELITE®, washed with EtOH (2 x 50 mL) and concentrated under reduced pressure

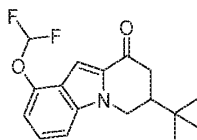
to give methyl 1-(2-(*tert*-butyl)-4-ethoxy-4-oxobutyl)-4-(difluoromethoxy)-1H-indole-2-carboxylate as a yellow oil, which was used without further purification (3.5g, 97% yield, m/z : 412 $[M + H]^+$ observed).

5 ***Ethyl 7-(tert-butyl)-1-(difluoromethoxy)-9-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-8-carboxylate:***



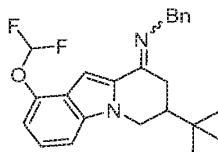
To a solution of methyl 1-(2-(*tert*-butyl)-4-ethoxy-4-oxobutyl)-4-(difluoromethoxy)-1H-indole-2-carboxylate (1.5 g, 3.65 mmol) in anhydrous THF (20 mL) was added potassium tert-butoxide (819 mg, 7.29 mmol). The reaction mixture was stirred at 80 °C for 16 h. To the mixture was added saturated aqueous ammonium chloride solution (30 mL), and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with saturated aqueous brine solution (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give ethyl 7-(*tert*-butyl)-1-(difluoromethoxy)-9-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-8-carboxylate as a brown oil, which was used without purification (1.18 g, 85% yield, m/z : 380 $[M + H]^+$ observed).

7-(tert-Butyl)-1-(difluoromethoxy)-7,8-dihydropyrido[1,2-a]indol-9(6H)-one:



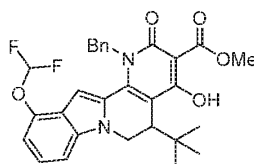
To a solution of ethyl 7-(*tert*-butyl)-1-(difluoromethoxy)-9-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-8-carboxylate (0.95 g, 2.5 mmol) in DMSO (10 mL) was added LiCl (117 mg, 2.76 mmol) and H₂O (0.06 mL, 3.26 mmol). The reaction mixture was stirred at 120 °C for 5 h. The reaction mixture was poured into H₂O (40 mL) and extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with saturated aqueous brine solution (30 mL), dried over anhydrous sodium, filtered and evaporated under reduced pressure. The crude residue was purified by normal phase SiO₂ chromatography (0-20% EtOAc/petroleum ether) to afford 7-(*tert*-butyl)-1-(difluoromethoxy)-7,8-dihydropyrido[1,2-a]indol-9(6H)-one as a light green solid (300 mg, 39% yield, m/z : 308 $[M + H]^+$ observed).

N-Benzyl-7-(tert-butyl)-1-(difluoromethoxy)-7,8-dihydropyrido[1,2-a]indol-9(6H)-imine:



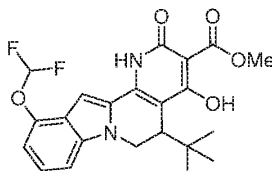
- To a solution of 7-(*tert*-butyl)-1-(difluoromethoxy)-7,8-dihydropyrido[1,2-a]indol-9(6H)-one (210 mg, 0.68 mmol), benzylamine (0.08 mL, 0.75 mmol) and triethylamine (0.25 mL, 1.78 mmol) in CH₂Cl₂ (10 mL) was added titanium(IV) chloride solution (1 M solution in CH₂Cl₂, 0.44 mL, 0.44 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred for 12 h. The reaction mixture was diluted with CH₂Cl₂ (30 mL) and then poured into H₂O (30 mL). Saturated aqueous NaHCO₃ solution was added to adjust the pH to 9. The organic layer was separated, washed with H₂O (20 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford *N*-benzyl-7-(*tert*-butyl)-1-(difluoromethoxy)-7,8-dihydropyrido[1,2-a]indol-9(6H)-imine as a brown solid (360 mg, >100% yield, m/z: 397 [M + H]⁺ observed).

Methyl 1-benzyl-5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylate:



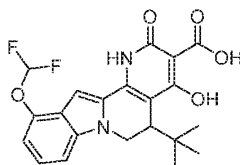
- To a solution of *N*-benzyl-7-(*tert*-butyl)-1-(difluoromethoxy)-7,8-dihydropyrido[1,2-a]indol-9(6H)-imine (270 mg, 0.68 mmol) in Ph₂O (15 mL) was added trimethyl methanetricarboxylate (259 mg, 1.36 mmol) and the reaction mixture was stirred at 220 °C in microwave reactor for 30 min. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by normal phase SiO₂ chromatography (0-50% EtOAc/petroleum ether) to afford methyl 1-benzyl-5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylate as a light green solid (210 mg, 59 % yield, m/z: 523 [M + H]⁺ observed).

Methyl 5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylate:



To a solution of methyl 1-benzyl-5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylate (150 mg, 0.29 mmol) in MeOH (10 mL) was added palladium on carbon (10% wt, 500 mg, 0.5 mmol). The suspension was degassed using vacuum and purged with hydrogen gas (repeated cycle 2
5 times). The mixture was stirred under an atmosphere of hydrogen gas at 15 psi for 4 h. The reaction mixture was filtered through CELITE®, washed with MeOH (2 x 20 mL) and concentrated under reduced pressure to afford methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylate as a light green solid, which was used without purification (85 mg, 69 % yield, *m/z*: 433 [M + H]⁺
10 observed).

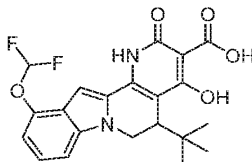
Example 1: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-5,6-dihydro-1*H*-indolo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid:



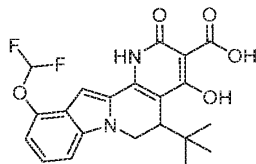
To a solution of methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylate (97 mg, 0.22 mmol) in EtOAc (1.5 mL) was added lithium iodide (60 mg, 0.45 mmol). The reaction mixture was stirred at 60 °C for 3 h. The mixture was cooled to rt and EtOAc (20 mL) was added. The organic phase was separated, washed with saturated aqueous brine solution (15 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The reaction mixture was
20 purified by reverse phase HPLC to give 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid as a light yellow solid (9.5 mg, 10% yield, *m/z*: 419 [M+H]⁺ observed). ¹H NMR (400 MHz, DMSO-*d*₆): δ 14.23 (s, 1H), 13.19 (s, 1H), 7.64-7.62 (m, 2H), 7.55-6.87 (m, 3H), 4.83-4.79 (m, 1H), 4.04-3.99 (m, 1H), 3.20-3.19 (m, 1H), 0.72 (s, 9H).

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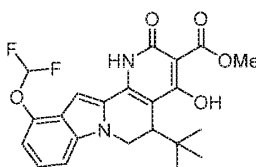
Example 2: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid (single enantiomer I)



Example 3: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid (single enantiomer II)

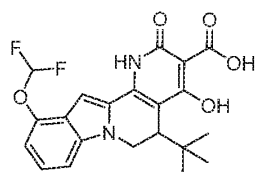


5 Methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylate:



130 mg of the mixture of enantiomers was separated by SFC (supercritical fluid chromatography) on a DAICEL CHIRALCEL OD column using 60% MeOH (0.05% isopropylamine) to give methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylate (single enantiomer I) as a yellow solid (faster eluting enantiomer, 40 mg, 31% yield, m/z : 433 $[M+H]^+$ observed), and methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylate (single enantiomer II) as a yellow solid (slower eluting enantiomer, 35 mg, 27% yield, m/z : 433 $[M+H]^+$ observed).

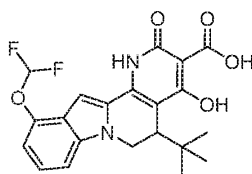
Example 2: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid (single enantiomer I):



To a solution of methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-*h*][1,7]naphthyridine-3-carboxylate (enantiomer I) (40 mg, 0.093 mmol) in EtOAc (1.5 mL) was added lithium iodide (25 mg, 0.19 mmol) under N_2 . The mixture was stirred at 60 °C for 4 h. The mixture was cooled to rt, diluted with H_2O (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with saturated aqueous brine solution (10 mL), dried with anhydrous sodium sulfate, filtered and

concentrated in vacuum. The crude was purified by reverse phase HPLC to give 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid (enantiomer I) as a yellow solid (9.2 mg, 24% yield, m/z: 419 [M+H]⁺ observed). ¹H NMR (400 MHz, DMSO-d₆): δ 14.23 (s, 1H), 13.19 (s, 1H), 7.64-7.62 (m, 2H), 7.55-6.87 (m, 3H), 4.83-4.79 (m, 1H), 4.04-3.99 (m, 1H), 3.20-3.19 (m, 1H), 0.72 (s, 9H).

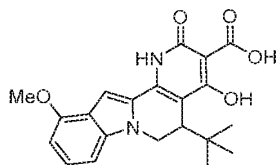
Example 3: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid (single enantiomer II):



To a solution of methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylate (enantiomer II) (35 mg, 0.081 mmol) in EtOAc (1.5 mL) was added lithium iodide (22 mg, 0.16 mmol) under N₂. The mixture was stirred at 60 °C for 4 h. The mixture was cooled to rt, diluted with H₂O (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with saturated aqueous brine solution (10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude residue was purified by reverse phase HPLC to give 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid (enantiomer II) as a yellow solid (6.1 mg, 18% yield, m/z: 419 [M+H]⁺ observed). ¹H NMR (400 MHz, DMSO-d₆): δ 14.23 (s, 1H), 13.19 (s, 1H), 7.64-7.62 (m, 2H), 7.55-6.87 (m, 3H), 4.83-4.79 (m, 1H), 4.04-3.99 (m, 1H), 3.20-3.19 (m, 1H), 0.72 (s, 9H).

The following examples were prepared in a similar manner as 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid from ethyl (*E*)-3-(bromomethyl)-4,4-dimethyl-pent-2-enoate and an appropriate indole.

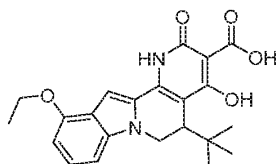
Example 4: 5-(*tert*-Butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid



m/z: 383 $[M + H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 14.08 (s, 1H), 13.10 (s, 1H), 7.57 (s, 1H), 7.29-7.22 (m, 2H), 6.60-6.58 (d, J = 6.8 Hz, 1H), 4.76-4.72 (d, J = 14 Hz, 1H), 4.00-3.91 (m, 4H), 3.16-3.15 (d, J = 4.4 Hz, 1H), 0.71 (s, 9H).

5

Example 5: 5-(*tert*-Butyl)-11-ethoxy-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h]naphthyridine-3-carboxylic acid

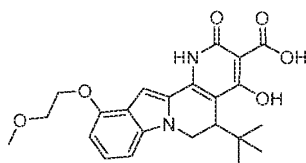


m/z: 397 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 16.03 (s, 1H), 14.08 (s, 1H), 13.02 (s, 1H), 7.61 (s, 1H), 7.37-7.06 (m, 2H), 6.56 (d, J = 7.3 Hz, 1H), 4.72 (d, J = 13.6 Hz, 1H), 4.15 (dd, J = 6.8, 2.9 Hz, 2H), 4.05-3.82 (m, 1H), 3.14 (d, J = 4.5 Hz, 1H), 1.41 (t, J = 6.9 Hz, 3H), 0.69 (s, 9H).

10

Example 6: 5-(*tert*-Butyl)-4-hydroxy-11-(2-methoxyethoxy)-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7] naphthyridine-3-carboxylic acid

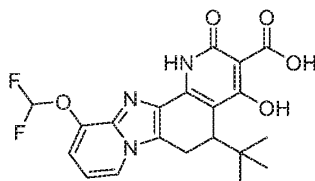
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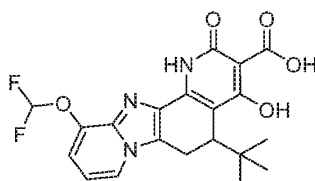
m/z: 427 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 16.04 (s, 1H), 14.07 (s, 1H), 13.05 (s, 1H), 7.63 (s, 1H), 7.47-7.04 (m, 2H), 6.58 (d, J = 7.6 Hz, 1H), 4.73 (d, J = 13.7 Hz, 1H), 4.22 (d, J = 4.6 Hz, 2H), 4.10-3.84 (m, 1H), 3.75 (s, 2H), 3.37 (s, 3H), 3.15 (d, J = 4.4 Hz, 1H), 0.70 (s, 9H).

20

Example 7: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)

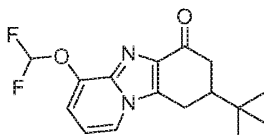


Example 8: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)



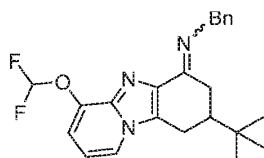
5

8-(*tert*-Butyl)-4-(difluoromethoxy)-8,9-dihydrobenzo[4,5]imidazo[1,2-a]pyridin-6(7H)-one:



- A mixture of 3-*tert*-butylcyclohexanone (6.16 g, 40 mmol), 3-(difluoromethoxy)pyridin-2-amine (4 g, 25 mmol), and iodine (634 mg, 2.5 mmol) in isobutyric acid (30 mL) was stirred under oxygen gas at 15 psi for 24 h at 110 °C. The reaction mixture was concentrated under reduced pressure and saturated aqueous sodium bicarbonate solution was added to adjust the pH to 8. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.
- The crude was purified by normal phase SiO₂ chromatography (5-50% EtOAc/petroleum ether) to afford the crude product. The crude product was further purified by reverse phase HPLC to give 8-(*tert*-butyl)-4-(difluoromethoxy)-8,9-dihydrobenzo[4,5]imidazo[1,2-a]pyridin-6(7H)-one as a brown solid (350 mg, 5% yield, m/z: 309 [M+H]⁺ observed).

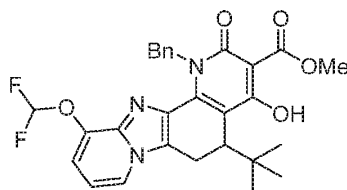
- N*-Benzyl-8-(*tert*-butyl)-4-(difluoromethoxy)-8,9-dihydrobenzo[4,5]imidazo[1,2-a]pyridin-6(7H)-imine:**



To a mixture of 8-(*tert*-butyl)-4-(difluoromethoxy)-8,9-dihydrobenzo[4,5]imidazo[1,2-

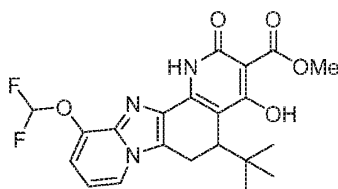
- a]pyridin-6(7H)-one (817 mg, 2.65 mmol), benzylamine (0.32 mL, 2.91 mmol) and triethylamine (0.96 mL, 6.89 mmol) in CH₂Cl₂ (10 mL) was added a solution of titanium(IV) chloride solution (1 M solution in CH₂Cl₂, 1.72 mL, 1.72 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was warmed to rt and stirred for 16 h. Saturated aqueous sodium bicarbonate solution was added to adjust the pH to 8 and the mixture was filtered. The filtrate was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic phase was washed with saturated aqueous brine solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give *N*-benzyl-8-(*tert*-butyl)-4-(difluoromethoxy)-8,9-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridin-6(7H)-imine as a yellow oil (1.03 g, >100% yield, m/z: 398 [M + H]⁺ observed).

Methyl 1-benzyl-5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylate:



- A mixture of *N*-benzyl-8-(*tert*-butyl)-4-(difluoromethoxy)-8,9-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridin-6(7H)-imine (1.03 g, 2.59 mmol) in Ph₂O (5 mL) and trimethyl methanetricarboxylate (986 mg, 5.19 mmol) was degassed using vacuum and purging with nitrogen gas (repeated cycle 3 times). The mixture was stirred at 220 °C in a microwave reactor for 15 min. The reaction mixture was concentrated under reduced pressure. The crude was purified by normal phase SiO₂ chromatography (5-30% EtOAc/petroleum ether) to afford methyl 1-benzyl-5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate as a yellow solid (600 mg, 44% yield, m/z: 524 [M + H]⁺ observed).

Methyl 5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylate:

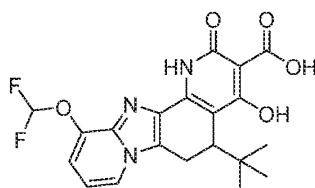


A solution of methyl 1-benzyl-5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-

tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylate (600 mg, 1.15 mmol) in trifluoroacetic acid (20 mL) was degassed using vacuum and purged with nitrogen gas (repeated cycle 3 times). The mixture was stirred at 100 °C for 24 h. The reaction mixture was concentrated under reduced pressure. Saturated aqueous sodium bicarbonate solution was added to adjust the pH to 8 and the reaction mixture extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with saturated aqueous brine solution (50 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude material was purified by normal phase SiO₂ chromatography (5-80% EtOAc/petroleum ether) to afford methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylate as a yellow solid (115 mg, 23% yield, 434 [M + H]⁺ observed).

110 mg of the mixture of enantiomers was separated by SFC (supercritical fluid chromatography) on a DAICEL CHIRALPAK AD-H column using 40% MeOH (0.1% NH₄OH modifier) to give methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylate (single enantiomer I) as a yellow solid (faster eluting enantiomer, 45 mg, 41% yield, m/z: 434 [M+H]⁺ observed) and methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylate (single enantiomer II) as a yellow solid (slower eluting enantiomer, 46 mg, 42% yield, m/z: 434 [M+H]⁺ observed).

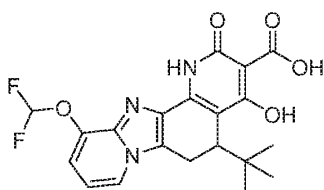
Example 7: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I):



To a solution of methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylate (enantiomer I) (45 mg, 0.105 mmol) in EtOAc (2 mL) was added lithium iodide (14 mg, 0.105 mmol) under nitrogen atmosphere. The mixture was stirred at 60 °C for 4 h. The reaction was cooled to rt, H₂O (10 mL) was added and the mixture extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with saturated aqueous brine solution (10 mL), dried with anhydrous

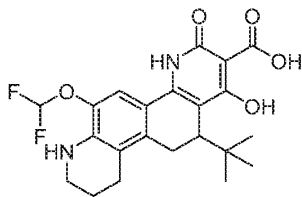
sodium sulfate, filtered and concentrated in vacuum. The reaction mixture was purified by reverse phase HPLC to give 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (enantiomer I) as a yellow solid (6.1 mg, 14% yield, *m/z*: 420 [M+H]⁺ observed). ¹H NMR (400 MHz, CD₃CN): δ 15.65 (s, 1H), 14.18 (s, 1H), 8.10-8.09 (d, *J* = 6 Hz, 1H), 7.87-7.49 (m, 1H), 7.05-7.03 (m, 1H), 6.97-6.94 (m, 1H), 3.44-3.36 (m, 2H), 3.21-3.15 (m, 1H), 0.80 (s, 9H).

Example 8: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer II):

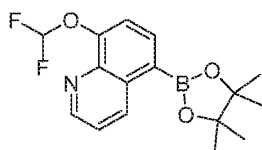


To a solution of methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate (enantiomer II) (41 mg, 0.095 mmol) in EtOAc (2 mL) was added lithium iodide (13 mg, 0.095 mmol) under a nitrogen atmosphere. The mixture was stirred at 60 °C for 4 h. The contents of the flask were cooled to rt, H₂O (10 mL) was added and the mixture extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with saturated aqueous brine solution (10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The reaction mixture was purified by reverse phase HPLC to give 5-(*tert*-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (enantiomer II) as a yellow solid (7.8 mg, 20% yield, *m/z*: 420 [M+H]⁺ observed). ¹H NMR (400 MHz, CD₃CN): δ 15.65 (s, 1H), 14.18 (s, 1H), 8.10-8.09 (d, *J* = 6 Hz, 1H), 7.87-7.49 (m, 1H), 7.05-7.03 (m, 1H), 6.97-6.94 (m, 1H), 3.44-3.36 (m, 2H), 3.21-3.15 (m, 1H), 0.80 (s, 9H).

Example 9: 6-(*tert*-Butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid

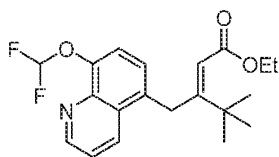


8-(Difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline:



- 5 A mixture of 5-bromo-8-(difluoromethoxy)quinoline (10 g, 36.5 mmol), bis(pinacolato) diboron (27.6 g, 72.9 mmol) and potassium acetate (10.7 g, 72.9 mmol) in 1,4-dioxane (150 mL) was degassed using nitrogen gas for 1h. Pd(PPh₃)₂Cl₂ (1.54 g, 2.18 mmol) was added, the mixture was degassed for further 15min using nitrogen gas, and then heated to 120 °C for 6 h. The reaction mixture was cooled to rt and diluted with EtOAc (100 mL).
- 10 The mixture was then filtered through CELITE® and washed with EtOAc (100 mL). Water (300mL) was added to the filtrate and stirred for 30 min. Following separation, the aqueous layer was extracted with EtOAc (120 mL). The combined organic phase was concentrated under vacuum. The crude solid was triturated with *n*-pentane (250 mL) and the resulting solid was collected by filtration to give 8-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline as a brown solid (9 g, 77 % yield, m/z: 322 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 9.17 (m, 1H), 8.97 (d, *J* = 3.6 Hz, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 7.56-7.42 (m, 2H), 7.32- 6.92 (m, 1H), 1.42 (s, 12H).
- 15

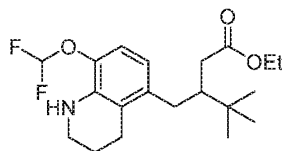
Ethyl (Z)-3-((8-(1-fluoroethoxy)quinolin-5-yl)methyl)-4,4-dimethylpent-2-enoate:



- 20 To a solution of 8-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) quinoline (9 g, 28 mmol) in dry toluene (125 mL) was added potassium carbonate (34.8 g, 252 mmol). The reaction mixture was degassed with nitrogen gas for 1h. Ethyl-(Z)-3-(bromomethyl)-4,4-dimethylpent-2-enoate (7.64 g, 30.8 mmol) and Pd₂(dba)₃ (5.7 g, 1.96 mol) were added and the mixture was further degassed using nitrogen gas for 30 min.

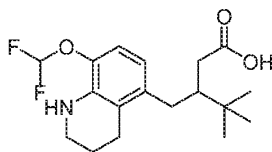
The reaction was heated to 110 °C for 16 h. The reaction mixture was cooled to rt and water (100 mL) was added. The biphasic mixture was filtered through CELITE® and extracted with EtOAc (2 x 250 mL). The combined organic phase was washed with saturated aqueous brine solution (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified by normal phase SiO₂ chromatography (0-30 % EtOAc/hexanes) to give ethyl (Z)-3-((8-(1-fluoroethoxy)quinolin-5-yl)methyl)-4,4-dimethylpent-2-enoate as a brown syrup (6.1 g, 60 % yield, m/z: 364 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 9.00 (d, *J* = 2.5 Hz, 1H), 8.56-8.43 (m, 1H), 7.54 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.21-6.78 (m, 2H), 6.24 (s, 1H), 4.41 (s, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 1.17-1.10 (m, 12H).

Ethyl 3-((8-(difluoromethoxy)-1,2,3,4-tetrahydroquinolin-5-yl)methyl)-4,4-dimethylpentanoate:



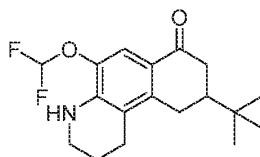
To a mixture of ethyl (Z)-3-((8-(difluoromethoxy)quinolin-5-yl)methyl)-4,4-dimethylpent-2-enoate (12 g, 33 mmol) and ethanol (250 mL) in an autoclave reactor was added palladium on carbon (20% on carbon, 7 g, 13 mmol). Following evacuation, hydrogen gas pressure of 250 psi was applied and the mixture heated to 60 °C for 16 h. The mixture was cooled to rt, filtered through CELITE®, washed with EtOH (2 x 50 mL) and concentrated under reduced pressure. The residue obtained was dissolved in EtOH (250 mL) and a fresh lot of palladium on carbon (20% on carbon, 14 g, 26 mmol) was added. Following evacuation, a hydrogen gas pressure of 380 psi was applied and the mixture heated to 60 °C for 98 h. The reaction mixture was filtered through CELITE®, washed with EtOH (2 x 50 mL) and concentrated under reduced pressure. The crude oil was purified by normal phase SiO₂ chromatography (20-35 % EtOAc/hexanes) to give ethyl 3-((8-(difluoromethoxy)-1,2,3,4-tetrahydroquinolin-5-yl)methyl)-4,4-dimethylpentanoate as a pale yellow syrup (10 g, 82 % yield, m/z: 370 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 6.74 (d, *J* = 8.1 Hz, 1H), 6.60- 6.16 (m, 2H), 3.94-3.73 (m, 2H), 3.34-3.27 (m, 2H), 2.86 (d, *J* = 11.0 Hz, 1H), 2.78-2.68 (m, 2H), 2.34-2.07 (m, 4H), 2.02-1.88 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.97 (s, 9H).

3-((8-(Difluoromethoxy)-1,2,3,4-tetrahydroquinolin-5-yl)methyl)-4,4-dimethylpentanoic acid:



To a solution of ethyl 3-((8-(difluoromethoxy)-1,2,3,4-tetrahydroquinolin-5-yl)methyl)-4,4-dimethylpentanoate (10 g, 27.1 mmol) in MeOH (100 mL) was added 1N aqueous sodium hydroxide solution (136 mL, 136 mmol) and the mixture heated to 65 °C for 3 h. The solvents were distilled off under reduced pressure and the residue obtained was acidified to pH 2 using 2N aqueous HCl solution. The mixture was then extracted with EtOAc (100 mL), washed with water (60 mL), washed with saturated aqueous brine solution (50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude solid was triturated with *n*-pentane (20 mL) and the solids collected by filtration to give 3-((8-(difluoromethoxy)-1,2,3,4-tetrahydroquinolin-5-yl)methyl)-4,4-dimethylpentanoic acid as an off-white solid (7.7 g, 85 % yield, *m/z*: 342 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 6.71 (d, *J* = 8.2 Hz, 1H), 6.56-6.12 (m, 2H), 3.32-3.14 (m, 2H), 2.86 (d, *J* = 9.2 Hz, 1H), 2.80-2.60 (m, 2H), 2.31 (d, *J* = 11.6 Hz, 1H), 2.13 (d, *J* = 13.8 Hz, 3H), 2.01-1.81 (m, 2H), 0.97 (s, 9H).

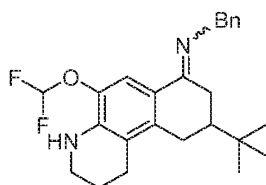
9-(*tert*-Butyl)-5-(difluoromethoxy)-1,3,4,8,9,10-hexahydrobenzo[*off*]quinolin-7(2H)-one:



To a stirred solution of 3-[[8-(difluoromethoxy)-1,2,3,4-tetrahydroquinolin-5-yl]methyl]-4,4-dimethylpentanoic acid (400 mg, 1.17 mmol) in dry CH₂Cl₂ (15 mL) at 0 °C was added thionyl chloride (0.21 mL, 2.93 mmol) dropwise. The yellow solution was stirred for 1 h at 0 °C. The solvent was removed under reduced pressure. The resulting crude oil was diluted with toluene (20 mL) and concentrated under reduced pressure (cycle repeated 2 times) to give an orange foam. The acid chloride was then dissolved in dry CH₂Cl₂ (15 mL), cooled to 0 °C, and treated with BF₃·OEt₂ (0.37 mL, 2.93 mmol). The bright red mixture was warmed to rt over 30 min. The reaction was then heated at 40 °C for 18 h. The mixture was cooled to rt, diluted with CH₂Cl₂ (15 mL) and quenched with H₂O (15 mL). The aqueous phase was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude solid was purified by normal phase SiO₂ chromatography (20-40 % EtOAc/hexanes) to give 9-(*tert*-butyl)-5-

(difluoromethoxy)-1,3,4,8,9,10-hexahydrobenzo[f]quinolin-7(2H)-one as a yellow solid (150 mg, 40 % yield, m/z : 324 $[M+H]^+$ observed). ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 6.50 (t, $J = 74.2$ Hz, 1H), 4.92 (s, 1H), 3.48-3.27 (m, 2H), 2.90 (d, $J = 16.3$ Hz, 1H), 2.79-2.61 (m, 3H), 2.39-2.28 (m, 1H), 2.22 (t, $J = 15.0$ Hz, 1H), 2.10-1.89 (m, 2H), 1.83 (t, $J =$

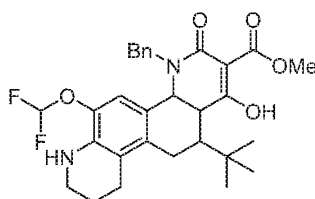
N-Benzyl-9-(*tert*-butyl)-5-(difluoromethoxy)-1,3,4,8,9,10-hexahydrobenzo[f]quinolin-7(2H)-imine:



Titanium (IV) isopropoxide (1.0 mL, 3.6 mmol) was added to a suspension of 9-(*tert*-butyl)-5-(difluoromethoxy)-1,3,4,8,9,10-hexahydrobenzo[f]quinolin-7(2H)-one (310 mg, 0.96 mmol) and benzylamine (260 μ L, 2.4 mmol) in THF (2 mL) in a microwave vial. The mixture was heated to 95 $^{\circ}C$ in a microwave reactor for 30 min. The reaction was cooled to rt, quenched with water (10 mL) and diluted with CH_2Cl_2 (20 mL). The two layers were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (2 x 20 mL). The combined organic phase was filtered through CELITE®, dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give *N*-benzyl-9-(*tert*-butyl)-5-(difluoromethoxy)-1,3,4,8,9,10-hexahydrobenzo[f]quinolin-7(2H)-imine, which was used without further purification (412 mg, 100 % yield, m/z : 413 $[M+H]^+$ observed).

Methyl 10-benzyl-6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo

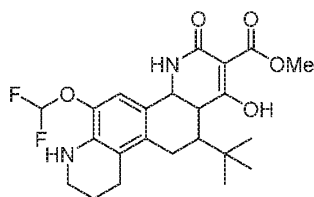
1,2,3,4,5,6,6a,9,10,10a-decahydroquinolino[7,8-f]quinoline-8-carboxylate:



A mixture of *N*-benzyl-9-(*tert*-butyl)-5-(difluoromethoxy)-1,3,4,8,9,10-hexahydrobenzo[f]quinolin-7(2H)-imine (412 mg, 0.96 mmol) and trimethyl methanetricarboxylate (548 mg, 2.88 mmol) in diglyme (5 mL) was heated at 185 $^{\circ}C$ in a microwave reactor for 1 h. The crude reaction was then diluted with EtOAc (10 mL), washed with H_2O (3 x 15 mL) and washed with saturated aqueous brine solution (10 mL). The combined organic phase was

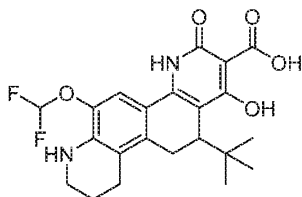
dried over anhydrous sulfate, filtered and concentrated in vacuum. The crude material was purified by normal phase SiO₂ chromatography (25-50 % EtOAc/hexanes) eluting to give methyl 10-benzyl-6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,6a,9,10,10a-decahydroquinolino[7,8-*f*]quinoline-8-carboxylate as light yellow solid (248 mg, 45 % yield, m/z: 541 [M+H]⁺ observed).

Methyl 6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,6a,9,10,10a-decahydroquinolino[7,8-*f*]quinoline-8-carboxylate:



A mixture of methyl 10-benzyl-6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,6a,9,10,10a-decahydroquinolino[7,8-*f*]quinoline-8-carboxylate (75 mg, 0.14 mmol) and palladium hydroxide on carbon (30 wt. %, 45 mg, 0.04 mmol) were dissolved in methanol (3 mL). The mixture was purged with hydrogen gas and the reaction was stirred at rt for 24 h under an atmosphere of hydrogen. The reaction mixture was filtered through CELITE® and the solvent was removed under vacuum to give methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,6a,9,10,10a-decahydroquinolino[7,8-*f*]quinoline-8-carboxylate as a yellow solid, which was used in the next step without further purification (53 mg, 85% yield, m/z: 451[M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 13.86 (s, 1H), 11.70 (s, 1H), 7.57 (s, 1H), 7.12 (t, *J* = 72 Hz, 1H), 4.80 (s, 1H), 3.88 (s, 3H), 3.46-3.29 (m, 2H), 3.15 (dd, *J* = 17 Hz, 1H), 3.06 (d, *J* = 7 Hz, 1H), 2.76 (m, 2H), 2.57 (dd, *J* = 17, 7 Hz, 1H), 2.12-2.02 (m, 1H), 1.99-1.89 (m, 1H), 0.77 (s, 9H).

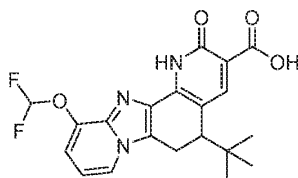
Example 9: 6-(tert-Butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid:



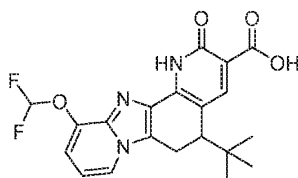
A mixture of methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,6a,9,10,10a-decahydroquinolino[7,8-*f*]quinoline-8-carboxylate (27 mg, 0.06 mmol) and lithium iodide (16 mg, 0.12 mmol) in anhydrous EtOAc (4 mL) was heated at 60

°C for 2 h. The reaction mixture was cooled to rt, diluted with EtOAc (10 mL), washed with H₂O (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude solid was purified by reverse phase HPLC purification to 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid as a yellow solid (23 mg, 89 %, *m/z*: 435 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 13.85 (s, 1H), 10.36 (s, 1H), 7.22 (s, 1H), 6.52 (t, *J* = 72 Hz, 1H), 4.89 (s, 1H), 3.45 (m, 1H), 3.36 (t, *J* = 8 Hz, 1H), 3.2 (d, *J* = 16 Hz, 1H), 3.07 (d, *J* = 8 Hz, 1H), 2.79 (m, 2H), 2.60 (dd, *J* = 16, 8 Hz, 1H), 2.08 (m, 1H), 2.02 (s, 1H), 1.97 (m, 1H), 0.76 (s, 9H).

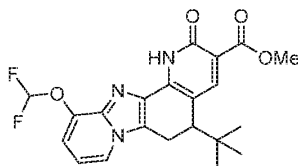
Example 10: 5-(*tert*-Butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer I)



Example 11: 5-(*tert*-Butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer II)



Methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate:

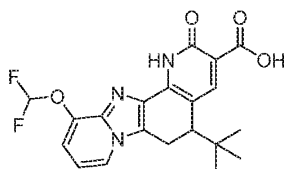


A mixture of methyl 1-benzyl-5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate (350 mg, 0.69 mmol) in TFA (10 mL) was stirred at 100 °C for 16 h under N₂. The mixture was cooled to rt and

concentrated in vacuum. The residue was diluted with sat. aqueous sodium bicarbonate solution (50 mL) and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with sat. aqueous brine solution (50 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was triturated with ethyl acetate (10 mL) at rt for 10 min. Then the mixture was filtered and the filter cake was dried in vacuum to get methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate as a yellow solid (150 mg, 51% yield, *m/z*: 418 [M+H]⁺ observed). ¹H NMR (400 MHz, MeOD): δ 8.29-8.25 (m, 2H), 7.56-7.19 (t, *J* = 7.4 Hz, 1H), 7.13-7.11 (d, *J* = 7.6 Hz, 1H), 7.04-7.00 (t, *J* = 7.6 Hz, 1H), 3.97-3.89 (m, 1H), 3.87 (s, 3H), 3.59-3.54 (d, *J* = 17.6 Hz, 1H), 3.00-2.98 (d, *J* = 4.4 Hz, 1H), 0.81 (s, 9H).

160 mg of methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate was separated by SFC (supercritical fluid chromatography) on DAICEL CHIRALPAK AD column using 60% MeOH (0.1% NH₄OH modifier) to give methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate (single enantiomer I) as a yellow solid (faster eluting enantiomer, 75 mg, 46 % yield, *m/z*: 418 [M+H]⁺ observed) and methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate (single enantiomer II) as a yellow solid (slower eluting enantiomer 70 mg, 43% yield, *m/z*: 418 [M+H]⁺ observed).

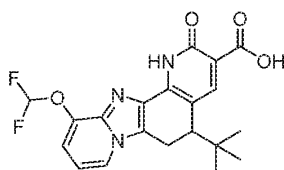
Example 10: 5-(*tert*-Butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer I)



To a mixture of methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate (enantiomer I) (75 mg, 0.18 mmol) in THF/MeOH/H₂O (3:1:1, 5 mL) was added lithium hydroxide monohydrate (38 mg, 0.90 mmol) in one portion under N₂. The mixture was stirred at rt for 12 h under N₂. 1N HCl was added to the solution to adjust the pH to 5 and the reaction was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with sat. aqueous brine solution (50 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue

was purified by reverse phase HPLC to obtain 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid as a yellow solid (47 mg, 62% yield, *m/z*: 404 [M+H]⁺ observed). ¹H NMR (400 MHz, DMSO-*d*₆): δ 15.01 (s, 1 H), 13.54 (s, 1 H), 8.52-8.50 (d, *J* = 6.4 Hz, 1 H), 8.27 (s, 1 H), 8.25-7.88 (t, *J* = 74.8 Hz, 1 H), 7.15-7.13 (d, *J* = 7.2 Hz, 1 H), 7.06-7.03 (t, *J* = 7.2 Hz, 1 H), 3.63-3.59 (d, *J* = 17.6 Hz, 1 H), 3.27-3.20 (dd, *J* = 8.4 Hz, *J* = 17.6 Hz, 1 H), 3.09-3.07 (d, *J* = 4.4 Hz, 1 H), 0.73 (s, 9 H)

Example 11: 5-(*tert*-Butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer II)



10

To a mixture of methyl 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate (enantiomer II) (70 mg, 0.18 mmol) in THF/MeOH/H₂O (3:1:1, 5 mL) was added lithium hydroxide monohydrate (35 mg, 0.84 mmol) in one portion under N₂. The mixture was stirred at rt for 12 h under N₂. 1N HCl was added to the solution to adjust the pH to 5 and the reaction was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with sat. aqueous brine solution (50 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reverse phase HPLC to obtain 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid as a yellow solid (39 mg, 55% yield, *m/z*: 404 [M+H]⁺ observed). ¹H NMR (400 MHz, DMSO-*d*₆): δ 15.01 (s, 1 H), 13.54 (s, 1 H), 8.52-8.50 (d, *J* = 6.4 Hz, 1 H), 8.27 (s, 1 H), 8.25-7.88 (t, *J* = 74.8 Hz, 1 H), 7.15-7.13 (d, *J* = 7.2 Hz, 1 H), 7.06-7.03 (t, *J* = 7.2 Hz, 1 H), 3.63-3.59 (d, *J* = 17.6 Hz, 1 H), 3.27-3.20 (dd, *J* = 8.4 Hz, *J* = 17.6 Hz, 1 H), 3.09-3.07 (d, *J* = 4.4 Hz, 1 H), 0.73 (s, 9 H)

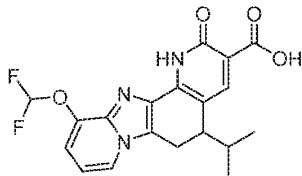
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The following examples were prepared in a similar manner as 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid from an appropriate 2-aminopyridine and cyclohexanone.

Example 12: 11-(Difluoromethoxy)-5-isopropyl-2-oxo-1,2,5,6-

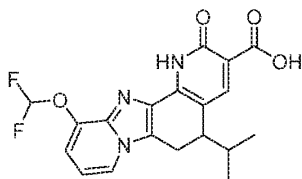
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tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)



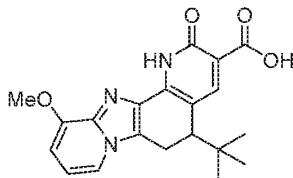
m/z: 390 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 14.91 (s, 1H), 13.64 (s, 1H),
 5 8.46-8.44 (d, $J = 6.8$ Hz, 1H), 8.32 (s, 1H), 8.29-7.92 (t, $J = 74.8$ Hz, 1H), 7.17-7.15 (d, $J = 7.6$ Hz, 1H), 7.07-7.03 (t, $J = 7.2$ Hz, 1H), 3.43-3.38 (m, 1H), 3.28-3.22 (m, 1H), 3.17-3.15 (m, 1H), 1.86-1.77 (m, 1H), 0.85-0.84 (d, $J = 6.8$ Hz, 3H), 0.73-0.71 (d, $J = 6.8$ Hz, 3H).

Example 13: 11-(Difluoromethoxy)-5-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)



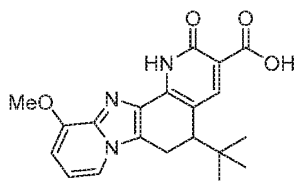
m/z: 390 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 14.91 (s, 1H), 13.64 (s, 1H),
 15 8.46-8.44 (d, $J = 6.8$ Hz, 1H), 8.32 (s, 1H), 8.29-7.92 (t, $J = 74.8$ Hz, 1H), 7.17-7.15 (d, $J = 7.6$ Hz, 1H), 7.07-7.03 (t, $J = 7.2$ Hz, 1H), 3.43-3.38 (m, 1H), 3.28-3.22 (m, 1H), 3.17-3.15 (m, 1H), 1.86-1.77 (m, 1H), 0.85-0.84 (d, $J = 6.8$ Hz, 3H), 0.73-0.71 (d, $J = 6.8$ Hz, 3H).

Example 14: 5-(tert-Butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)



m/z: 368 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 8.22-8.20 (m, 2H), 6.98-6.96 (t, $J = 7.2$ Hz, 1H), 6.75-6.73 (d, $J = 7.6$ Hz, 1H), 3.96 (s, 3H), 3.56-3.52 (d, $J = 17.6$ Hz, 1H), 3.24-3.17 (m, 1H), 3.03-3.01 (d, $J = 8$ Hz, 1H), 0.71 (s, 9H).

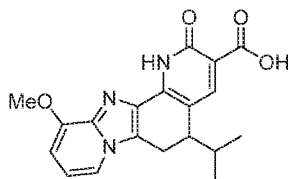
Example 15: 5-(*tert*-Butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer II)



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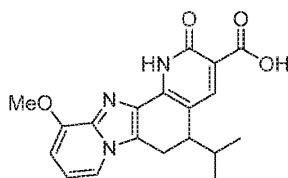
m/z : 368 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 8.22-8.20 (m, 2H), 6.98-6.96 (t, J = 7.2 Hz, 1H), 6.75-6.73 (d, J = 7.6 Hz, 1H), 3.96 (s, 3H), 3.56-3.52 (d, J = 17.6 Hz, 1H), 3.24-3.17 (m, 1H), 3.03-3.01 (d, J = 8 Hz, 1H), 0.71 (s, 9H).

Example 16: 5-Isopropyl-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer I)



m/z : 354 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 8.23 (s, 1H), 8.15 - 8.13 (d, J = 6.8 Hz, 1H), 6.98 - 6.94 (t, J = 7.6 Hz, 1H), 6.76 - 6.74 (d, J = 7.6 Hz, 1H), 3.97 (s, 3H), 3.31 - 3.17 (m, 2H), 3.10 - 3.09 (m, 1H), 1.82 - 1.74 (m, 1H), 0.83 - 0.81 (d, J = 6.4 Hz, 3H), 0.71 - 0.69 (d, J = 6.8 Hz, 3H).

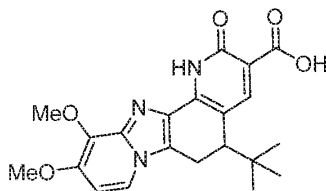
Example 17: 5-Isopropyl-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer II)



m/z : 354 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 8.23 (s, 1H), 8.15 - 8.13 (d, J = 6.8 Hz, 1H), 6.98 - 6.94 (t, J = 7.6 Hz, 1H), 6.76 - 6.74 (d, J = 7.6 Hz, 1H), 3.97 (s, 3H)

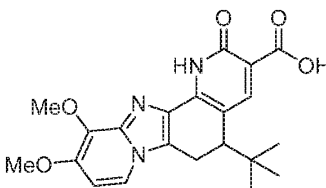
3.31 - 3.17 (m, 2H), 3.10 - 3.09 (m, 1H), 1.82 - 1.74 (m, 1H), 0.83 - 0.81 (d, $J = 6.4$ Hz, 3H), 0.71 - 0.69 (d, $J = 6.8$ Hz, 3H).

Example 18: 5-(*tert*-Butyl)-10,11-dimethoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer I)



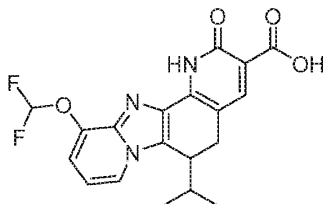
m/z: 398 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 15.15 (s, 1H), 8.38-8.36 (d, $J = 7.2$ Hz, 1H), 8.22 (s, 1H), 7.12-7.10 (d, $J = 7.2$ Hz, 1H), 4.07 (s, 3H), 3.92 (s, 3H), 3.56-3.52 (d, $J = 17.6$ Hz, 2H), 3.20-3.13 (m, 1H), 3.03-3.01 (d, $J = 8$ Hz, 1H), 0.72 (s, 9H).

Example 19: 5-(*tert*-Butyl)-10,11-dimethoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer II)



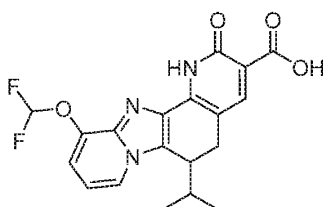
m/z: 398 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 15.15 (s, 1H), 8.38-8.36 (d, $J = 7.2$ Hz, 1H), 8.22 (s, 1H), 7.12-7.10 (d, $J = 7.2$ Hz, 1H), 4.07 (s, 3H), 3.92 (s, 3H), 3.56-3.52 (d, $J = 17.6$ Hz, 2H), 3.20-3.13 (m, 1H), 3.03-3.01 (d, $J = 8$ Hz, 1H), 0.72 (s, 9H).

Example 20: 11-(Difluoromethoxy)-6-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer I)



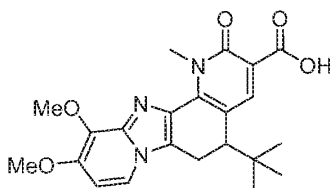
m/z: 390 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 15.25 (s, 1H), 13.73 (s, 1H), 8.47-8.45 (d, $J = 6.8$ Hz, 1H), 8.33 (s, 1H), 8.21-7.82 (t, $J = 74.8$ Hz, 1H), 7.16-7.14 (d, $J = 7.6$ Hz, 1H), 7.04-7.00 (t, $J = 7.2$ Hz, 1H), 3.41-3.38 (m, 1H), 3.29-3.24 (m, 1H), 3.16-3.10 (m, 1H), 1.92-1.83 (m, 1H), 0.84-0.82 (d, $J = 6.8$ Hz, 6H).

Example 21: 11-(Difluoromethoxy)-6-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)

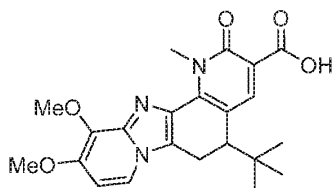


m/z: 390 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 15.25 (s, 1H), 13.73 (s, 1H), 8.47-8.45 (d, $J = 6.8$ Hz, 1H), 8.33 (s, 1H), 8.21-7.82 (t, $J = 74.8$ Hz, 1H), 7.16-7.14 (d, $J = 7.6$ Hz, 1H), 7.04-7.00 (t, $J = 7.2$ Hz, 1H), 3.41-3.38 (m, 1H), 3.29-3.24 (m, 1H), 3.16-3.10 (m, 1H), 1.92-1.83 (m, 1H), 0.84-0.82 (d, $J = 6.8$ Hz, 6H).

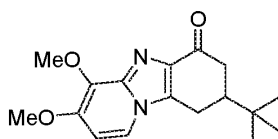
Example 22: 5-(tert-Butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)



Example 23: 5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)

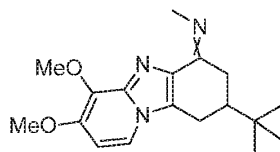


8-(tert-Butyl)-3,4-dimethoxy-8,9-dihydrobenzo[4,5]imidazo[1,2-a]pyridin-6(7H)-one:



- 5 A mixture of 3,4-dimethoxypyridin-2-amine (0.5 g, 3.24 mmol), 3-*tert*-butylcyclohexanone (1.0 g, 6.5 mmol) and I₂ (0.08 g, 0.32 mmol) in *i*-PrCO₂H (5 mL) was stirred under O₂ (15 Psi) for 16 h at 110 °C. The mixture was basified with saturated aqueous sodium bicarbonate solution to adjust the pH to 8. The mixture was combined with 6 batches that were run on the same scale and extracted with EtOAc (3 x 300 mL). The combined organic phase was dried
- 10 over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by normal phase SiO₂ chromatography (10%- 100% EtOAc/petroleum ether) to give a crude product. The residue was further purified by reverse phase HPLC to get 8-(*tert*-butyl)-3,4-dimethoxy-8,9-dihydrobenzo[4,5]imidazo[1,2-a] pyridine-6(7H)-one as a brown solid (0.52 g, 7.5% yield, m/z: 303 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 7.66-7.64 (d, *J* = 7.6 Hz, 1 H), 6.82-6.80 (d, *J* = 7.6 Hz, 1H), 4.25 (s, 3H), 4.00 (s, 3H), 3.03-3.01
- 15 (dd, *J* = 4.4 Hz, *J* = 15.6 Hz, 1H), 2.84-2.73 (m, 2H), 2.53-2.45(m, 1H), 2.29-2.22(m, 1H), 1.05 (s, 9H).

***N*-(8-(tert-butyl)-3,4-dimethoxy-8,9-dihydrobenzo[4,5]imidazo[1,2-a]pyridin-6(7H)-ylidene)methanamine:**

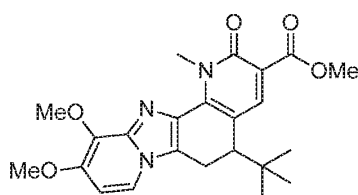


- 20 To a mixture of 8-*tert*-butyl-3,4-dimethoxy-8,9-dihydro-7H-pyrido[1,2-a]benzimidazol-6-one (320 mg, 1.06 mmol) and methyl amine (2M solution in THF, 5.3 mL, 10.6 mmol) in THF (6 mL) was added a solution of titanium (IV) isopropoxide (16 mL, 1.6 mmol) in CH₂Cl₂ (1 mL) over 30 min under N₂. The reaction mixture was stirred at rt for 12 h under
- 25 N₂. The mixture was poured into ice water (10 mL) and filtered. The filtrate was extracted

with EtOAc (2 x 30 mL). The combined organic phase was washed with saturated aqueous brine solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give *N*-(8-(*tert*-butyl)-3,4-dimethoxy-8,9-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridin-6(7H)-ylidene)methanamine as a yellow solid (400 mg, >100% yield, *m/z*: 316

5 [M+H]⁺ observed) which was used without further purification.

Methyl 5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate:

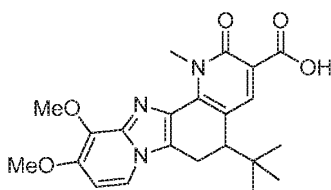


A mixture of *N*-(8-(*tert*-butyl)-3,4-dimethoxy-8,9-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridin-6(7H)-ylidene)methanamine (400 mg, 1.27 mmol) and dimethyl 2-(methoxymethylene)malonate (663 mg, 3.8 mmol) in diphenyl ether (4 mL) was stirred at 220 °C in a microwave reactor for 20 min. The mixture was cooled and purified directly by normal phase SiO₂ chromatography (20-100% EtOAc/petroleum ether; then 0-20% MeOH/CH₂Cl₂). The residue was further purified by reverse phase HPLC to get methyl 5-(*tert*-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydro pyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate as a yellow solid (50 mg, 11% yield over 2 steps).

50 mg of the racemate was separated by SFC (supercritical fluid chromatography) on a DAICEL CHIRALPAK AD-H column using 35% IPA (0.1% NH₄OH modifier) to give methyl 5-(*tert*-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-

20 tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate (single enantiomer I) as a yellow solid (faster eluting enantiomer, 17 mg, 34% yield) and methyl 5-(*tert*-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylate (single enantiomer II) as a yellow solid (slower eluting enantiomer, 17 mg, 34% yield).

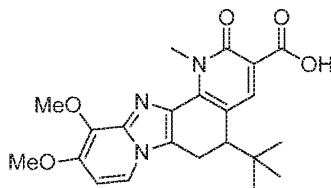
25 ***Example 22: 5-(tert-Butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-*h*]quinoline-3-carboxylic acid (single enantiomer I)***



To a mixture of methyl 5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylate (single enantiomer I) (17 mg, 0.04 mmol) in H₂O/THF/MeOH (1:1:1, 1.5 mL) was added lithium hydroxide hydrate (16 mg, 386 μ mol) in one portion. The mixture was stirred at rt for 1 h. The mixture was acidified with 1 N aqueous HCl to pH=2 and extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with saturated aqueous brine solution (10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reverse phase HPLC to give 5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid as a yellow solid (10 mg, 62% yield). m/z: 412 [M+H]⁺ observed. ¹H NMR (400 MHz, DMSO-d₆): δ 14.90 (br s, 1H), 8.43 (d, *J* = 7.2 Hz, 1H), 8.27 (s, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 4.37 (s, 3H), 4.08 (s, 3H), 3.94 (s, 3H), 3.54 (d, *J* = 17.2 Hz, 1H), 3.18 (dd, *J* = 8 Hz, *J* = 17.2 Hz, 1H), 3.04 (d, *J* = 8 Hz, 1H), 0.65 (s, 9H).

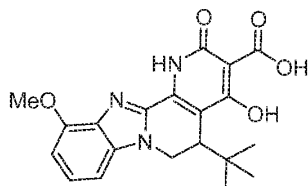
Example 23: 5-(tert-Butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-

tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)



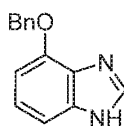
To a mixture of methyl 5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylate (single enantiomer II) (17 mg, 0.04 mmol) in H₂O/THF/MeOH (1:1:1, 1.5 mL) was added lithium hydroxide hydrate (16 mg, 386 μ mol) in one portion. The mixture was stirred at rt for 1 h. The mixture was acidified with 1 N aqueous HCl to pH=2 and extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with saturated aqueous brine solution (10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reverse phase HPLC to give 5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid as a yellow solid (8.9 mg, 53% yield). m/z: 412 [M+H]⁺ observed. ¹H NMR (400 MHz, DMSO-d₆): δ 14.90 (br s, 1H), 8.43 (d, *J* = 7.2 Hz, 1H), 8.27 (s, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 4.37 (s, 3H), 4.08 (s, 3H), 3.94 (s, 3H), 3.54 (d, *J* = 17.2 Hz, 1H), 3.18 (dd, *J* = 8 Hz, *J* = 17.2 Hz, 1H), 3.04 (d, *J* = 8 Hz, 1H), 0.65 (s, 9H).

Example 24: 5-(*tert*-Butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid



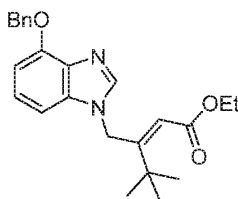
5

4-(Benzyloxy)-1H-benzo[d]imidazole:



To a mixture of 1H-benzo[d]imidazol-4-ol (40 g, 298 mmol) and benzyl alcohol (38 mL, 363 mmol) in THF (800 mL) was added PPh₃ (95.4 g, 363 mmol) and DEAD (66 mL, 363 mmol) in one portion at rt under N₂. The mixture was stirred at rt for 12 h. To the mixture was added H₂O (1 L) and extracted with EtOAc (2 x 500 mL). The combined organic phase was washed with sat. aqueous brine solution (1 L), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by normal phase SiO₂ chromatography (20-50% EtOAc/petroleum ether) to give a crude product which was further triturated with EtOAc (100 mL). The mixture was filtered, and the filter cake was dried in vacuum to afford 4-(benzyloxy)-1H-benzo[d]imidazole as a white solid (100 g, 73% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.91 (s, 1H), 7.47-7.46 (d, *J* = 7.2 Hz, 2H), 7.37-7.30 (m, 4 H), 7.18 (d, 1H), 6.81-6.80 (d, *J* = 8 Hz, 1H), 5.26 (s, 2H).

(*E*)-Ethyl 3-((4-(benzyloxy)-1H-benzo[d]imidazol-1-yl)methyl)-4,4-dimethylpent-2-enoate:

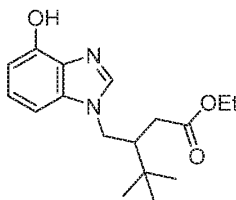


20

To a mixture of 4-(benzyloxy)-1H-benzo[d]imidazole (25 g, 111 mmol) in DMF (200 mL) was added Cs₂CO₃ (72.6 g, 223 mmol) in one portion at rt under N₂. The mixture was stirred at rt for 30 min. Then ethyl (*E*)-3-(bromomethyl)-4,4-dimethylpent-2-enoate (27.8 g, 112 mmol) was added and the mixture was heated to 50 °C for 2.5 h. The reaction mixture was

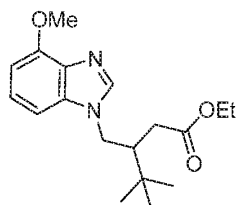
combined with another batch that was run on the same scale. Water (1 L) was added, and the mixture was extracted with EtOAc (2 x 400 mL). The combined organic phase was washed with sat. aqueous brine solution (500 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by normal phase SiO₂ chromatography (5-50% EtOAc/petroleum ether) to give (*E*)-ethyl 3-((4-(benzyloxy)-1H-benzo[d]imidazol-1-yl)methyl)-4,4-dimethylpent-2-enoate as a yellow oil (18 g, 45.9 mmol, 21% yield). ¹H NMR (400 MHz, CDCl₃): δ 8.07 (s, 1H), 7.55-7.53 (d, *J* = 6.8 Hz, 2H), 7.37-7.35 (m, 2H), 7.30 (m, 1H), 7.17-7.15 (t, *J* = 4 Hz, 1H), 6.91-6.89 (d, *J* = 7.2 Hz, 1H), 6.78-6.76 (m, 2H), 5.40 (s, 2H), 4.09-4.03 (q, *J* = 7.6 Hz, 2H), 3.08 (s, 2H), 1.25 (s, 9H), 1.21-1.18 (t, *J* = 6.8 Hz, 3H).

Ethyl 3-((4-hydroxy-1H-benzo[d]imidazol-1-yl)methyl)-4,4-dimethylpentanoate:



To a solution of (*E*)-ethyl 3-((4-(benzyloxy)-1H-benzo[d]imidazol-1-yl)methyl)-4,4-dimethylpent-2-enoate (15 g, 38.2 mmol) in MeOH (200 mL) was added palladium on carbon (10% on carbon, 5g, 5 mmol) under nitrogen atmosphere. The suspension was degassed under vacuum/hydrogen purge cycle (3 times). The mixture was stirred under H₂ atmosphere (50 Psi) at 50 °C for 16 h. The mixture was filtered through CELITE[®] and the filter cake was washed with MeOH (3 x 150 mL). The filtrate was evaporated under reduced pressure. The residue was purified by normal phase SiO₂ chromatography (20% to 50% EtOAc/petroleum ether) to afford ethyl 3-((4-hydroxy-1H-benzo[d]imidazol-1-yl)methyl)-4,4-dimethylpentanoate as a yellow solid (6 g, 20 mmol, 52% yield). ¹H NMR (400 MHz, CDCl₃): δ 11.32-11.07 (m, 1H), 7.98 (s, 1H), 7.25-7.21 (t, *J* = 8 Hz, 1H), 6.95-6.93 (d, *J* = 6.8 Hz, 1H), 6.84-6.82 (d, *J* = 7.2 Hz, 1H), 4.38-4.35 (m, 1H), 4.06-4.00 (m, 1H), 3.77 (s, 2H), 2.53-2.52 (m, 1H), 2.42-2.38 (m, 1H), 2.17-2.16 (m, 1H), 1.06-1.00 (m, 12H).

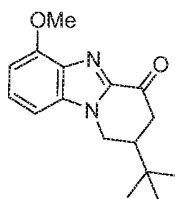
Ethyl 3-((4-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,4-dimethylpentanoate:



Ethyl 3-((4-hydroxy-1H-benzo[d]imidazol-1-yl)methyl)-4,4-dimethylpentanoate (2.5 g, 8.2

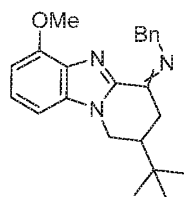
mmol) was dissolved in THF (75 mL), and MeOH (3.3 mL, 82 mmol), followed by the addition of PPh₃ (6.5 g, 24.6 mmol), DIAD (3.2 mL, 16.4 mmol). The mixture was stirred at rt for 1 h. Additional PPh₃ (6.5 g, 24.6 mmol) and DIAD (3.2 mL, 16.4 mmol) were added and the mixture was stirred at rt for 15 h. The reaction was concentrated in vacuum. The crude residue was triturated with EtOAc/petroleum ether (1:2, 100 mL). The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by normal phase SiO₂ chromatography (30% to 100% EtOAc/petroleum ether) to afford ethyl 3-((4-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,4-dimethylpentanoate as a yellow oil (2.9 g, >100% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.85 (s, 1H), 7.25-7.21 (t, *J* = 8 Hz, 1H), 7.04-7.02 (d, *J* = 7.6 Hz, 1H), 6.70-6.69 (d, *J* = 7.6 Hz, 1H), 4.37-4.33 (dd, *J* = 3.6 Hz, *J* = 14.4 Hz, 1H), 4.03-4.00 (m, 4H), 3.82-3.80 (m, 2H), 2.54-2.52 (m, 1H), 2.42-2.37 (dd, *J* = 5.2 Hz, *J* = 16.4 Hz, 1H), 2.16-2.10 (dd, *J* = 6.4 Hz, *J* = 16 Hz, 1H), 1.07-1.01 (m, 12H).

2-(*tert*-Butyl)-6-methoxy-2,3-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridin-4(1H)-one:



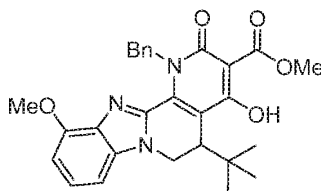
To a solution of ethyl 3-((4-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,4-dimethylpentanoate (2.4 g, 7.5 mmol) in THF (100 mL) was added LDA (2 M solution in THF, 7.9 mL) at -70 °C over 5 min. The temperature was allowed to reach -10 °C over 3 h. The reaction was quenched with saturated aqueous ammonium chloride solution (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was triturated with EtOAc/petroleum ether (1:4, 15 mL) and filtered. The filter cake was dried in vacuum to afford 2-(*tert*-butyl)-6-methoxy-2,3-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridin-4(1H)-one as a yellow solid (1.2 g, 58% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.34 (t, *J* = 8 Hz, 1H), 7.02-7.00 (d, *J* = 8.4 Hz, 1H), 6.78-6.73 (d, *J* = 8 Hz, 1H), 4.49-4.44 (dd, *J* = 4.4 Hz, *J* = 12.4 Hz, 1H), 4.05-3.97 (m, 4H), 3.02-2.98 (dd, *J* = 2.4 Hz, *J* = 13.6 Hz, 1H), 2.66-2.59 (m, 1H), 2.40-2.35 (m, 1H), 1.09 (s, 9H).

***N*-(2-(*tert*-butyl)-6-methoxy-2,3-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-4(1H)-ylidene)-1-phenylmethanamine:**



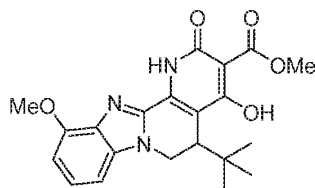
- To a mixture of 2-(*tert*-butyl)-6-methoxy-2,3-dihydrobenzo[4,5]imidazo[1,2-a] pyridine-4(1H)-one (1 g, 3.7 mmol) and benzyl amine (0.5 mL, 4.04 mmol) in CH₂Cl₂ (10 mL) was added triethylamine (1.3 mL, 9.5 mmol) under N₂. Then a solution of titanium tetrachloride (1 M solution in CH₂Cl₂, 2.4 mL) in CH₂Cl₂ (5 mL) was added at 0 °C over 30 min. The mixture was stirred at rt for 16 hours. The mixture was basified with sat. aqueous sodium bicarbonate solution to pH=8 and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic phase was washed with sat. aqueous brine solution (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to get *N*-(2-(*tert*-butyl)-6-methoxy-2,3-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-4(1H)-ylidene)-1-phenylmethanamine as a yellow solid which was used in the next step without further purification (1.3 g, >100% yield, m/z: 362 [M+H]⁺ observed).

Methyl 1-benzyl-5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylate:



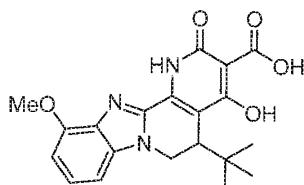
- A mixture of *N*-(2-(*tert*-butyl)-6-methoxy-2,3-dihydrobenzo[4,5]imidazo[1,2-a] pyridine-4(1H)-ylidene)-1-phenylmethanamine (1.2 g, 3.3 mmol) and trimethyl methanetricarboxylate (1.26 g, 6.6 mmol) in Ph₂O (20 mL) was stirred at 220 °C for 15 min under N₂. The mixture was cooled to rt and purified directly by normal phase SiO₂ chromatography (20-50% EtOAc/petroleum ether) to give methyl 1-benzyl-5-(*tert*-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylate as a yellow solid (300 mg, 12% yield, m/z: 488 [M+H]⁺ observed).

Methyl 5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylate:



A solution of methyl 1-benzyl-5-(*tert*-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylate (300 mg, 0.62 mmol) in TFA (5 mL) was stirred at 100 °C for 12 h. The mixture was concentrated in vacuum. To residue was basified with sat. aqueous sodium bicarbonate solution NaHCO_3 to pH=8 and the aqueous phase extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with sat. aqueous brine solution (50 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by normal phase SiO_2 chromatography (30-100% EtOAc/petroleum ether) to give methyl 5-(*tert*-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylate as a yellow solid (150 mg, 43% yield). ^1H NMR (400 MHz, CDCl_3): δ 14.19 (s, 1H), 9.59 (s, 1H), 7.37-7.33 (t, J = 8 Hz, 1H), 7.06-7.02 (d, J = 8 Hz, 1H), 6.78-6.76 (d, J = 7.6 Hz, 1H), 4.39-4.35 (m, 1H), 4.18-4.14 (m, 1H), 4.08 (s, 3H), 4.02 (s, 3H), 3.33-3.32 (d, J = 5.2 Hz, 1H), 0.83 (s, 9H).

Example 24: 5-(*tert*-Butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid:

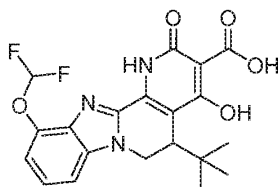


To a mixture of methyl 5-(*tert*-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylate (150 mg, 0.38 mmol) in EtOAc (5 mL) was added LiI (252 mg, 1.9 mmol) in one portion under N_2 . The mixture was stirred at 60 °C for 0.5 h. The mixture was cooled to rt and H_2O (20 mL) was added. The mixture was extracted with EtOAc (2 x 20 mL). The organic phase was filtered to remove some insoluble suspension that formed, and the filter cake was washed with EtOAc (2 x 20 mL) and $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10:1, 40 mL). The filter cake was dried to afford 5-(*tert*-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid as a light yellow solid (87 mg, 59 % yield, m/z : 384 $[\text{M}+\text{H}]^+$ observed). ^1H

NMR (400 MHz, DMSO- d_6): δ 14.75 (s, 1H), 11.18 (s, 1H), 7.37-7.19 (m, 2H), 6.81-6.71 (m, 1H), 4.71-4.64 (m, 1H), 4.15-4.02 (m, 1H), 3.97 (s, 3H), 3.28-3.16 (m, 1H), 0.70-0.67 (s, 9H).

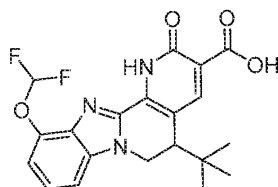
- 5 The following example was prepared in a similar manner as 5-(*tert*-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid from an appropriate benzimidazole.

10 **Example 25: 5-(*tert*-Butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid**



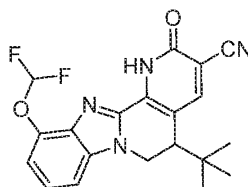
- m/z: 420 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 8.32 - 7.94 (t, J = 75.6 Hz, 1H), 7.77 - 7.75 (d, J = 8.4 Hz, 1H), 7.43 - 7.39 (t, J = 8 Hz, 1H), 7.09 - 7.07 (d, J = 8 Hz, 1H), 4.89 - 4.85 (d, J = 14.4 Hz, 1H), 4.28 - 4.23 (dd, J = 5.6 Hz, J = 5.2 Hz, 1H), 3.29 - 3.27 (d, J = 5.6 Hz, 1H), 0.73 (s, 9H).
- 15

Example 26: 5-(*tert*-Butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid



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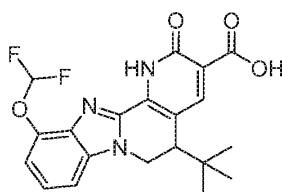
5-(*tert*-Butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*h*][1,7]naphthyridine-3-carbonitrile:



A mixture of 2-(*tert*-butyl)-6-(difluoromethoxy)-2,3-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-4(1H)-one (310 mg, 1 mmol) and N,N-dimethylformamide dimethyl acetal (10 mL) was stirred at 120 °C for 6h. After cooling, the mixture was concentrated under vacuum to give (Z)-2-(*tert*-butyl)-6-(difluoromethoxy)-3-((dimethyl amino)methylene)-2,3-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-4(1H)-one as a red solid which was used into the next step without further purification (0.36 g, >100% yield).

To a mixture of NaH (60% dispersion in mineral oil, 77 mg, 1.93 mmol) in DMF (2 mL) at 0 °C was added a solution of 2-cyanoacetamide (81 mg, 0.96 mmol), (Z)-2-(*tert*-butyl)-6-(difluoromethoxy)-3-((dimethylamino)methylene)-2,3-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-4(1H)-one (350 mg, 0.96 mmol), MeOH (0.08 mL, 1.93 mmol) and DMF (1 mL). The mixture was stirred at rt for 15 min and then heated at 95 °C for 16 h. After cooling to rt, the mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with sat. aqueous brine solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by normal phase SiO₂ chromatography (0-50% EtOAc/petroleum ether) to give a yellow oil. The crude residue was further purified by reverse phase preparative HPLC to give 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carbonitrile as a yellow solid (20 mg, 5.4 % yield, m/z: 385 [M+H]⁺ observed).

Example 26: 5-(*tert*-Butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid:

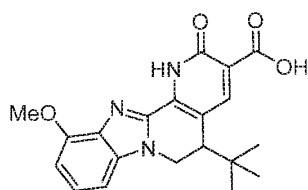


A mixture of 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carbonitrile (20 mg, 52 μmol) in conc HCl (2 mL) and 1,4-dioxane (2 mL) was stirred at 100 °C for 12 h. After cooling to rt, the reaction mixture was concentrated under vacuum. The residue was purified by reverse phase preparative HPLC to give 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid as a yellow solid (1.4 mg, 7 %, m/z: 404 [M+H]⁺ observed). ¹H NMR (400 MHz, DMSO-d₆): δ 8.44 (s, 1H), 8.33-7.95 (t, *J* = 7.4-8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.44-7.40 (t, *J* = 8.0 Hz, 1H), 7.09 (d,

$J = 8.0$ Hz, 1H), 4.91 (d, $J = 13.6$ Hz, 1H), 4.32-4.27 (m, 1H), 3.21 (d, $J = 5.2$ Hz, 2H), 0.73 (s, 9H).

- The following examples were prepared in a similar manner as 5-(*tert*-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid from an appropriate benzimidazole.

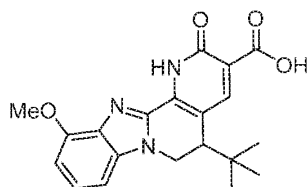
Example 27: 5-(*tert*-Butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid (single enantiomer I)



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m/z : 368 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 8.43 (s, 1H), 7.44 (d, $J = 8.4$ Hz, 1H), 7.35 (t, $J = 8$ Hz, 1H), 6.84 (d, $J = 8$ Hz, 1H), 4.83 (d, $J = 14$ Hz, 1H), 4.26 (dd, $J = 6.4$ Hz, $J = 14$ Hz, 1H), 3.97 (s, 3H), 3.16 (d, $J = 6.4$ Hz, 1H), 0.70 (s, 9H).

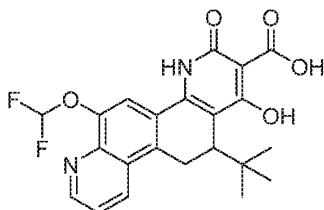
- Example 28: 5-(*tert*-Butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-*h*][1,7]naphthyridine-3-carboxylic acid (single enantiomer II)**



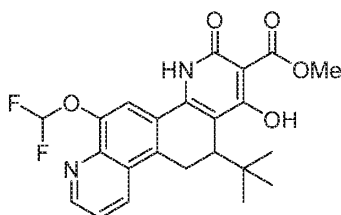
20

m/z : 368 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6): δ 8.43 (s, 1H), 7.44 (d, $J = 8.4$ Hz, 1H), 7.35 (t, $J = 8$ Hz, 1H), 6.84 (d, $J = 8$ Hz, 1H), 4.83 (d, $J = 14$ Hz, 1H), 4.26 (dd, $J = 6.4$ Hz, $J = 14$ Hz, 1H), 3.97 (s, 3H), 3.16 (d, $J = 6.4$ Hz, 1H), 0.70 (s, 9H).

Example 29: 6-(*tert*-Butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid



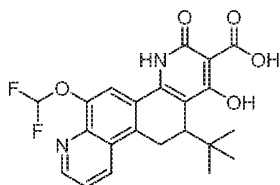
Methyl 6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,6a,9,10,10a-hexahydroquinolino[7,8-f]quinoline-8-carboxylate:



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Methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylate (103 mg, 0.24 mmol) and palladium on carbon (10% on carbon, 126 mg, 1.2 mmol) were dissolved in toluene (2 mL). The reaction was bubbled with O₂ gas for 20 min at 100 °C. The reaction was sealed and heated at 110 °C for 16h. The reaction was cooled to rt, filtered through CELITE[®] and washed with MeOH (2 x 10 mL). The filtrate was concentrated in vacuum to give methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylate as a yellow oil (40 mg, 37% yield, m/z: 445 [M+H]⁺ observed), which was used in the next step without further purification.

15 ***6-(tert-Butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid:***

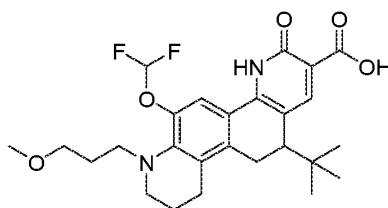


A mixture of methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,6a,9,10,10a-hexahydroquinolino[7,8-f]quinoline-8-carboxylate (40 mg, 0.09 mmol) and lithium iodide (16 mg, 0.12 mmol) in anhydrous EtOAc (4 mL) was heated at 60 °C for 2 h. The reaction mixture was cooled to rt, diluted with EtOAc (10 mL), washed with H₂O (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude solid was

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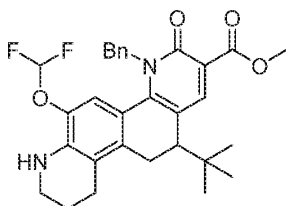
purified by reverse phase HPLC purification to 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid as a yellow solid (12 mg, 29 % yield). m/z : 431 $[M+H]^+$ observed. ^1H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.67 (d, $J = 8.3$ Hz, 1H), 7.98 (s, 1H), 7.71 (d, $J = 4.2$ Hz, 1H), 7.18 (t, $J = 74.7$ Hz, 1H), 3.85 (d, $J = 16.9$ Hz, 1H), 3.29 (d, $J = 6.6$ Hz, 1H), 3.15 (dd, $J = 16.8, 6.9$ Hz, 1H), 0.74 (s, 9H).

Example 30: 6-(*tert*-Butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid



10

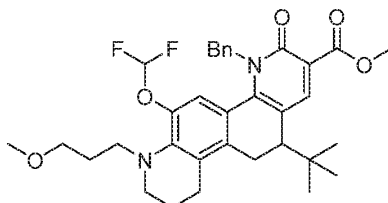
Methyl 10-benzyl-6-(*tert*-butyl)-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylate:



15 A mixture of *N*-benzyl-9-(*tert*-butyl)-5-(difluoromethoxy)-1,3,4,8,9,10-hexahydrobenzo[*f*]quinolin-7(2H)-imine (1.2 g, 2.9 mmol) and trimethyl methanetricarboxylate (1.26 g, 6.6 mmol) in Ph_2O (20 mL) was stirred at 220 °C in a microwave reactor for 15 min. The mixture was cooled to rt and purified directly by normal phase SiO_2 chromatography (10-50% EtOAc/petroleum ether) to afford methyl 10-benzyl-6-(*tert*-butyl)-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylate (250 mg, 17 % yield, m/z : 523 $[M+H]^+$ observed) as a yellow solid.

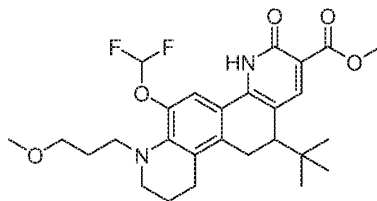
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Methyl 10-benzyl-6-(*tert*-butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylate:



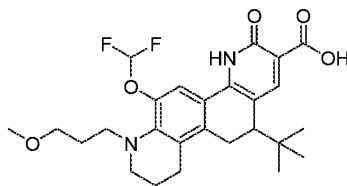
A mixture of methyl 10-benzyl-6-tert-butyl-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6-hexahydroquinolino[7,8-f]quinoline-8-carboxylate (137 mg, 0.26 mmol), 1-bromo-3-methoxy-propane (60 mg, 0.39 mmol), potassium carbonate (108 mg, 0.79 mmol) and
 5 potassium iodide (43 mg, 0.26 mmol) in DMF (2 mL) was stirred at 145 °C for 48 h. The reaction mixture was cooled to rt and concentrated in vacuum. The crude residue was purified by normal phase SiO₂ chromatography (0-30% EtOAc/Hexanes) to give methyl 10-benzyl-6-tert-butyl-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-3,4,5,6-tetrahydro-2H-quinolino[7,8-f]quinoline-8-carboxylate (40 mg, 25%, m/z: 595 [M+H]⁺ observed) as yellow
 10 solid.

Methyl 6-(tert-butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylate:



A mixture of methyl 10-benzyl-6-tert-butyl-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-3,4,5,6-tetrahydro-2H-quinolino[7,8-f]quinoline-8-carboxylate (40 mg, 0.07 mmol) and
 15 palladium on carbon (10% wt, 10 mg, 0.1 mmol) in MeOH (3 mL) was purged with hydrogen gas for 5 min. The reaction was stirred under hydrogen atmosphere for 16 h. The reaction mixture was filtered through CELITE[®] to give methyl 6-(tert-butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylate
 20 as a yellow oil (35 mg, >100% yield, m/z: 505 [M+H]⁺ observed), which was used in the next step without further purification.

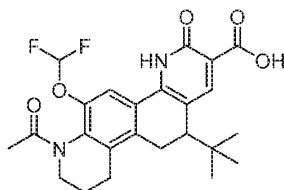
Example 30: 6-(tert-Butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid:



A mixture of methyl 6-*tert*-butyl-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-2,3,4,5,6,10-hexahydroquinolino[7,8-f]quinoline-8-carboxylate (35 mg, 0.07 mmol) and lithium hydroxide monohydrate (9 mg, 0.2 mmol) in 1,4-dioxane/water (1:1, 2 mL) was stirred at 40 °C for 2 h. The solvent was removed in vacuum and 1*N* aqueous HCl solution was added to adjust the pH to 5. The solution was extracted with CH₂Cl₂ (3 x 5 mL) and concentrated in vacuum. The crude residue was purified via reverse phase HPLC to give 6-*tert*-butyl-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-2,3,4,5,6,10-hexahydroquinolino[7,8-f]quinoline-8-carboxylic acid as a yellow solid (1.2 mg, 4 %, m/z: 491 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.55 (s, 1H), 7.04-6.55 (m, 1H), 4.42 (t, *J* = 6.4 Hz, 2H), 3.54 (t, *J* = 6.2 Hz, 2H), 3.49 (d, *J* = 0.4 Hz, 3H), 3.46-3.33 (m, 1H), 3.36 (s, 3H), 3.26 (d, *J* = 16.4 Hz, 1H), 2.85-2.57 (m, 4H), 2.03 (t, *J* = 6.3 Hz, 2H), 0.76 (s, 9H).

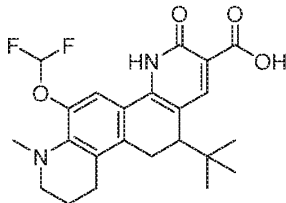
The following examples were prepared in a similar manner as 6-*tert*-butyl-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-2,3,4,5,6,10-hexahydroquinolino[7,8-f]quinoline-8-carboxylic acid from methyl 10-benzyl-6-(*tert*-butyl)-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylate and an appropriate alkylating reagent.

Example 31: 1-Acetyl-6-(*tert*-butyl)-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid



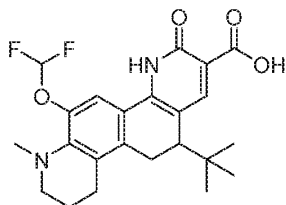
m/z: 461 [M+H]⁺ observed. ¹H NMR (400 MHz, CD₃OD) δ 8.36 (d, *J* = 2.8 Hz, 1H), 7.73 (s, 1H), 6.80 (t, *J* = 73.3 Hz, 1H), 3.43 (dd, *J* = 16.6, 13.4 Hz, 1H), 3.30 (p, *J* = 1.7 Hz, 2H), 3.15-2.50 (m, 3H), 2.40-1.76 (m, 6H), 0.75 (s, 9H).

Example 32: 6-(*tert*-Butyl)-12-(difluoromethoxy)-1-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid (single enantiomer I)



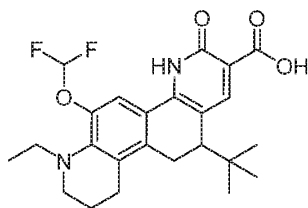
m/z: 433 [M+H]⁺ observed. ¹H NMR (400 MHz, DMSO-d₆) δ 14.81 (s, 1H), 12.99 (s, 1H),
5 8.17 (s, 1H), 7.71 (s, 1H), 7.02 (t, *J* = 74.6 Hz, 1H), 3.20-3.05 (m, 3H), 2.97 (s, 3H), 2.75-
2.60 (m, 4H), 1.95-1.70 (m, 2H), 0.67 (s, 9H).

Example 33: 6-(*tert*-Butyl)-12-(difluoromethoxy)-1-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid (single enantiomer II)



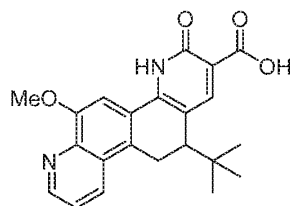
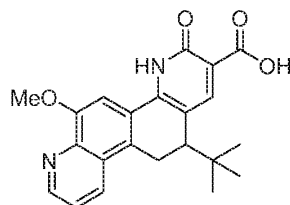
10 m/z: 433 [M+H]⁺ observed. ¹H NMR (400 MHz, DMSO-d₆) δ 14.81 (s, 1H), 12.99 (s, 1H),
8.17 (s, 1H), 7.71 (s, 1H), 7.02 (t, *J* = 74.6 Hz, 1H), 3.20-3.05 (m, 3H), 2.97 (s, 3H), 2.75-
2.60 (m, 4H), 1.95-1.70 (m, 2H), 0.67 (s, 9H).

15 **Example 34: 6-(*tert*-Butyl)-12-(difluoromethoxy)-1-ethyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid**

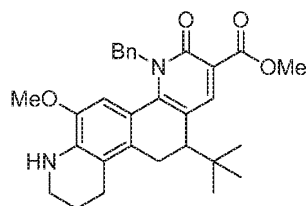


m/z: 447 [M+H]⁺ observed. ¹H NMR (400 MHz, DMSO) δ 14.81 (s, 1H), 13.01 (s, 1H), 8.17
(s, 1H), 7.68 (s, 1H), 7.08 (t, *J* = 74.3 Hz, 1H), 3.27-3.09 (m, 4H), 3.07-2.95 (m, 1H), 2.78-
20 2.60 (m, 4H), 1.93-1.83 (m, 2H), 1.14 (t, *J* = 6.6 Hz, 3H), 0.67 (s, 9H).

Example 35: 6-(*tert*-Butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-

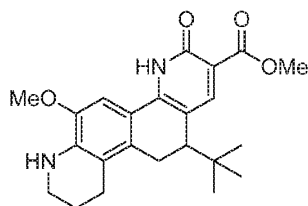
f]quinoline-8-carboxylic acid (single enantiomer I)**Example 36: 6-(tert-Butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid (single enantiomer II)**

5

Methyl 10-benzyl-6-(tert-butyl)-12-methoxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylate:

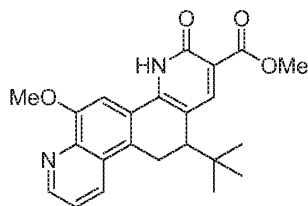
- 10 A mixture of *N*-(9-(*tert*-butyl)-5-methoxy-1,2,3,4,9,10-hexahydrobenzo[*f*]quinolin-7(8*H*)-ylidene)-1-phenylmethanamine (1.25 g, 3.3 mmol) and dimethyl 2-(methoxymethylene)malonate (1.16 g, 6.6 mmol) in diphenylether (10 mL) was stirred at 220 °C for 20 min in a microwave reactor under N₂. The mixture was cooled to rt and purified directly by normal phase SiO₂ chromatography (20-100% Ethyl acetate/petroleum ether, then
- 15 0-20% MeOH/CH₂Cl₂) to give methyl 10-benzyl-6-(*tert*-butyl)-12-methoxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylate as a yellow solid (700 mg, 43% yield, *m/z*: 487 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 8.19 (s, 1H), 7.36 (m, 2H), 7.23 (m, 3H), 6.70 (s, 1H), 5.19 (s, 1H), 3.91 (s, 3H), 3.42 - 3.39 (m, 1H), 3.32 - 3.26 (m, 1H), 3.16 (d, *J* = 16 Hz, 1H), 2.96 (s, 3H), 2.80 - 2.78 (m, 2H), 2.63 (dd, *J* = 6.4 Hz, *J* =
- 20 15.2 Hz, 1H), 2.50 (d, *J* = 6 Hz, 1H), 2.10 - 2.04 (m, 2H), 2.04 (s, 2H), 0.69 (s, 9H).

Methyl 6-(tert-butyl)-12-methoxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylate:



- To a solution of methyl 10-benzyl-6-(*tert*-butyl)-12-methoxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylate (700 mg, 1.44 mmol) in MeOH (20 mL) was added palladium hydroxide on carbon (20 wt. %, 1 g) under N₂ atmosphere. The suspension was degassed under vacuum and purged with H₂ (cycle repeated three times). The mixture was stirred under H₂ (15 psi) at rt for 2 h. The mixture was filtered, and the filter cake was washed by MeOH (2 x 50 mL). The filtrate was concentrated in vacuum to get methyl 6-(*tert*-butyl)-12-methoxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylate as a yellow solid (600 mg, crude, m/z: 397 [M+H]⁺ observed), which was used in the next step without further purification.

Methyl 6-(tert-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylate:

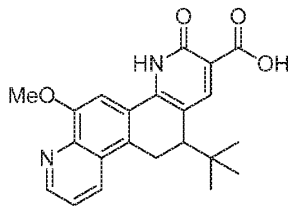


- To a solution of methyl 6-(*tert*-butyl)-12-methoxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylate (600 mg, 1.5 mmol) in *o*-xylene (12 mL) was added palladium on carbon (10 wt. %, 1 g, 10 mmol) and the mixture was heated to 100 °C. Air was bubbled into the mixture at 100 °C for 30 min and the reaction vessel was sealed and heated at 120 °C for 3.5 h. The reaction mixture was cooled, filtered through CELITE[®] and the filtrate concentrated under reduced pressure. The crude oil was purified by reverse phase HPLC to give methyl 6-(*tert*-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylate as a yellow solid (120 mg, 17% yield, m/z: 393 [M+H]⁺ observed).

- 120 mg of the mixture of enantiomers was separated by SFC (supercritical fluid chromatography) on a DAICEL CHIRALCEL OD column using 40% MeOH (0.1% NH₄OH as modifier) to give methyl 6-(*tert*-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylate (single enantiomer I) as a yellow solid

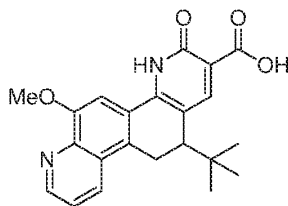
(faster eluting enantiomer, 38 mg, 32% yield, m/z : 393 $[M+H]^+$ observed) and methyl 6-(*tert*-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylate (single enantiomer II) as a yellow solid (slower eluting enantiomer, 45 mg, 38% yield, m/z : 393 $[M+H]^+$ observed).

5 **Example 35: 6-(*tert*-Butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid (single enantiomer I)**



To a mixture of methyl 6-(*tert*-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylate (faster eluting enantiomer, 38 mg, 0.1 mmol) in H₂O/THF/MeOH
 10 (1:1:1, 3 mL) was added lithium hydroxide monohydrate (40 mg, 1 mmol) in one portion. The mixture was stirred at rt for 2 h. The mixture was acidified with 1N aqueous HCl solution to pH=2, then the mixture was purified directly by reverse phase HPLC to give 6-(*tert*-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid as a yellow solid (21 mg, 56% yield, m/z : 379 $[M+H]^+$ observed). ¹H NMR (400 MHz, DMSO-
 15 d₆): δ 15.12 (br s, 1H), 13.49 (br s, 1H), 8.92 (dd, J = 1.2 Hz, J = 4 Hz, 1H), 8.81 (dd, J = 1.2 Hz, J = 8.8 Hz, 1H), 8.30 (s, 1H), 7.86 (s, 1H), 7.80 (q, J = 4 Hz, 1H), 4.08 (s, 3H), 3.84 (d, J = 17.2 Hz, 1H), 3.07 (dd, J = 7.6 Hz, J = 17.2 Hz, 1H), 2.97 (d, J = 7.2 Hz, 1H), 0.66 (s, 9H).

20 **Example 36: 6-(*tert*-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid (single enantiomer II)**

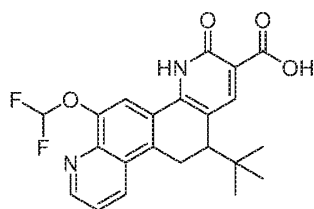


To a mixture of methyl 6-(*tert*-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylate (slower eluting enantiomer, 45 mg, 0.11 mmol) in H₂O/THF/MeOH (1:1:1, 3 mL) was added lithium hydroxide monohydrate (40 mg, 1
 25 mmol) in one portion. The mixture was stirred at rt for 2 h. The mixture was acidified with 1N aqueous HCl solution to pH=2, then the mixture was purified directly by reverse phase

HPLC to give 6-(*tert*-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid as a yellow solid (19 mg, 54% yield, m/z : 379 $[M+H]^+$ observed). ^1H NMR (400 MHz, DMSO- d_6): δ 15.12 (br s, 1H), 13.49 (br s, 1H), 8.92 (dd, $J = 1.2$ Hz, $J = 4$ Hz, 1H), 8.81 (dd, $J = 1.2$ Hz, $J = 8.8$ Hz, 1H), 8.30 (s, 1H), 7.86 (s, 1H), 7.80 (q, $J = 4$ Hz, 1H), 4.08 (s, 3H), 3.84 (d, $J = 17.2$ Hz, 1H), 3.07 (dd, $J = 7.6$ Hz, $J = 17.2$ Hz, 1H), 2.97 (d, $J = 7.2$ Hz, 1H), 0.66 (s, 9H).

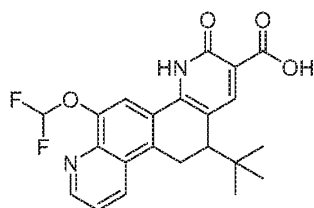
The following examples were prepared in a similar manner as 6-(*tert*-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid from an appropriate quinoline and vinyl halide coupling reagent.

Example 37: 6-(*tert*-Butyl)-12-(difluoromethoxy)-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid (single enantiomer I)



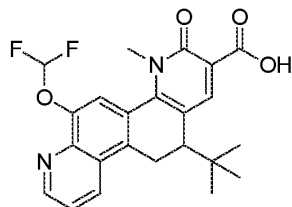
m/z : 415 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6) δ 9.03 (dd, $J = 4.1$, 1.5 Hz, 1H), 8.94 (dd, $J = 8.8$, 1.6 Hz, 1H), 8.30 (s, 1H), 8.27 (s, 1H), 7.75 (dd, $J = 8.6$, 4.1 Hz, 1H), 7.46 (t, $J = 74.6$ Hz, 1H), 3.92 (d, $J = 17.2$ Hz, 1H), 3.13 (dd, $J = 17.2$, 7.8 Hz, 1H), 2.95 (d, $J = 7.6$ Hz, 1H), 0.64 (s, 9H).

Example 38: 6-(*tert*-butyl)-12-(difluoromethoxy)-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid (single enantiomer II)



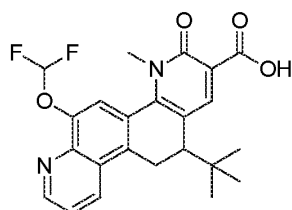
m/z : 415 $[M+H]^+$ observed. ^1H NMR (400 MHz, DMSO- d_6) δ 9.03 (dd, $J = 4.1$, 1.5 Hz, 1H), 8.94 (dd, $J = 8.8$, 1.6 Hz, 1H), 8.30 (s, 1H), 8.27 (s, 1H), 7.75 (dd, $J = 8.6$, 4.1 Hz, 1H), 7.46 (t, $J = 74.6$ Hz, 1H), 3.92 (d, $J = 17.2$ Hz, 1H), 3.13 (dd, $J = 17.2$, 7.8 Hz, 1H), 2.95 (d, $J = 7.6$ Hz, 1H), 0.64 (s, 9H).

Example 39: 6-(*tert*-Butyl)-12-(difluoromethoxy)-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid (single enantiomer I)



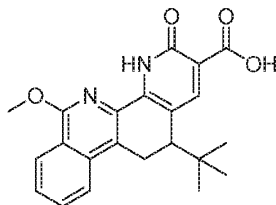
- 5 m/z: 429 [M+H]⁺ observed. ¹H NMR (400 MHz, DMSO-*d*₆): δ 14.78 (br s, 1H), 9.08 (d, *J* = 3.2 Hz, 1H), 8.99 (d, *J* = 8.8 Hz, 1H), 8.38 (s, 1H), 8.01 (s, 1H), 7.80 (q, *J* = 4 Hz, 1H), 7.48 (t, *J* = 74.8 Hz, 1H), 3.91 (d, *J* = 16.4 Hz, 1H), 3.82 (s, 3H), 3.09 (dd, *J* = 7.2 Hz, *J* = 16.4 Hz, 1H), 2.97 (d, *J* = 6.8 Hz, 1H), 0.53 (s, 9H).

10 **Example 40: 6-(*tert*-Butyl)-12-(difluoromethoxy)-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid (single enantiomer II)**



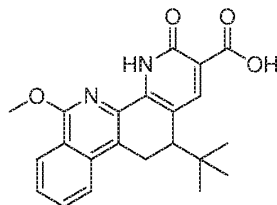
- m/z: 429 [M+H]⁺ observed. ¹H NMR (400 MHz, DMSO-*d*₆): δ 14.78 (br s, 1H), 9.08 (d, *J* = 3.2 Hz, 1H), 8.99 (d, *J* = 8.8 Hz, 1H), 8.38 (s, 1H), 8.01 (s, 1H), 7.80 (q, *J* = 4 Hz, 1H), 7.48 (t, *J* = 74.8 Hz, 1H), 3.91 (d, *J* = 16.4 Hz, 1H), 3.82 (s, 3H), 3.09 (dd, *J* = 7.2 Hz, *J* = 16.4 Hz, 1H), 2.97 (d, *J* = 6.8 Hz, 1H), 0.53 (s, 9H).
- 15

Example 41: 12-(*tert*-Butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[*c*][1,10]phenanthroline-2-carboxylic acid (single enantiomer I)

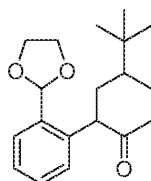


20

Example 42: 12-(*tert*-Butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[*c*][1,10]phenanthroline-2-carboxylic acid (single enantiomer II)

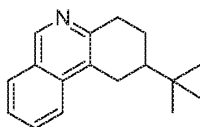


2-(2-(1,3-Dioxolan-2-yl)phenyl)-4-(tert-butyl)cyclohexanone:



- 5 To 2,2,6,6-tetramethylpiperidine (40 mL, 236 mmol) in 250 mL round bottom flask was added *n*-butyllithium (2.5 M solution in hexanes, 88 mL) dropwise at -78 °C and the reaction was stirred for 10 min at -78 °C, then for 10 min at 0 °C. After re-cooling to -78 °C, a solution of 4-(tert-butyl)cyclohexanone (26.9 g, 175 mmol) in THF (100 mL) was added dropwise. The reaction was stirred for 10 min at -78 °C before warming to 0 °C. A solution of 2-(2-
- 10 bromophenyl)-1,3-dioxolane (20 g, 87.3 mmol) in anhydrous THF (100 mL) was added via syringe, followed by [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (2.85 g, 4.37 mmol). The reaction was heated at 70 °C for 18 h. The reaction was then cooled to rt and quenched by the addition of H₂O (500 mL) and extracted with EtOAc (3 x 400 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated
- 15 under vacuum. The residue was combined with another 150g batch crude product and purified by normal phase SiO₂ chromatography (0-30% EtOAc/petroleum ether) to afford 2-(2-(1,3-dioxolan-2-yl)phenyl)-4-(tert-butyl)cyclohexanone as a dark yellow oil (68 g, 20% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.49 (d, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 5.80 (s, 1H), 4.09-3.99 (m, 1H), 3.97-3.93 (m,
- 20 4H), 2.48-2.44 (m, 2H), 2.24-2.23 (m, 2H), 1.75-1.50 (m, 3H), 0.88 (s, 9H).

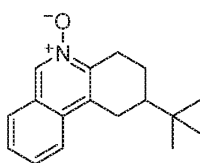
2-(tert-Butyl)-1,2,3,4-tetrahydrophenanthridine:



To a solution of 1M NH₄Cl solution in EtOH/H₂O (3:1, 560 mL) was added 2-(2-(1,3-dioxolan-2-yl)phenyl)-4-(tert-butyl)cyclohexanone (17 g, 56.2 mmol) and the reaction was

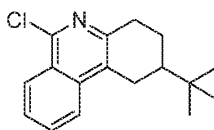
heated to 90 °C for 16 h. After cooling, 4 batches of the reaction mixture on the same scale were combined and concentrated. The residue was quenched with saturated aqueous sodium bicarbonate solution (1 L) and extracted with EtOAc (3 x 400 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by normal phase SiO₂ chromatography (0-30% EtOAc/petroleum ether) to afford 2-*tert*-butyl-1,2,3,4-tetrahydrophenanthridine as a red oil (26.1 g, 42% yield).
¹H NMR (400 MHz, CDCl₃): δ 9.08 (s, 1H), 7.96 (t, *J* = 9.2 Hz, 2H), 7.74-7.70 (m, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 3.29-3.18 (m, 3H), 2.77 (m, 1H), 2.22-2.18 (m, 1H), 1.65-1.51 (m, 2H), 1.08 (s, 9H).

10 **2-(*tert*-Butyl)-1,2,3,4-tetrahydrophenanthridine 5-oxide:**



To the solution of 2-*tert*-butyl-1,2,3,4-tetrahydrophenanthridine (8.7 g, 36.4 mmol) in CH₂Cl₂ (120 mL) was added 3-chloroperoxybenzoic acid (15.7 g, 72.7 mmol). The reaction was stirred for 16 h at room temperature. The reaction was quenched with saturated aqueous sodium sulfite solution/saturated aqueous sodium bicarbonate solution (1:1, 1 L) and stirred for 1 h at room temperature. Then the mixture was extracted with CH₂Cl₂ (4 x 500 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford 2-(*tert*-butyl)-1,2,3,4-tetrahydrophenanthridine 5-oxide as a yellow solid which was used into the next step without further purification (31 g, >100% yield, *m/z*: 256 [M+H]⁺ observed).

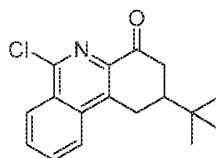
2-(*tert*-Butyl)-6-chloro-1,2,3,4-tetrahydrophenanthridine:



The solution of 2-(*tert*-butyl)-1,2,3,4-tetrahydrophenanthridine 5-oxide (31 g, 121 mmol, 51% purity) in CH₂Cl₂ (500 mL) was added phosphorus(V) oxychloride (13.5 mL, 146 mmol) at 0 °C, followed by DMF (4.7 mL, 60.7 mmol). Then the mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (pH=8) and extracted with CH₂Cl₂ (2 x 200 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by normal phase SiO₂ chromatography (0-10% EtOAc/petroleum ether) to

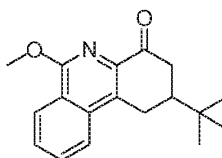
afford 2-(*tert*-butyl)-6-chloro-1,2,3,4-tetrahydrophenanthridine as a yellow solid (16.4 g, 49% yield). ¹H NMR (400 MHz, CDCl₃): δ 8.23 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.69-7.65 (m, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 3.14-2.90 (m, 3H), 2.66-2.58 (m, 1H), 2.10-2.05 (m, 1H), 1.55-1.47 (m, 1H), 1.45-1.34 (m, 1H), 0.97 (s, 9H).

5 **2-(*tert*-Butyl)-6-chloro-2,3-dihydrophenanthridin-4(1H)-one:**



To a solution of 2-(*tert*-butyl)-6-chloro-1,2,3,4-tetrahydrophenanthridine (500 mg, 1.83 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (5.2 mL, 51 mmol) was added cobalt(II) acetate (11.6 mg, 0.065 mmol) and *N*-hydroxyphthalimide (29.8 mg, 0.18 mmol). The mixture was stirred vigorously under O₂ (15 Psi) at room temperature for 16 h. The reaction mixture was quenched with H₂O (200 mL) and extracted with EtOAc (2 x 150 mL). The combined organic phase was concentrated under vacuum. The residue was purified by normal phase SiO₂ chromatography (0-50% EtOAc/petroleum ether) to afford a dark yellow solid. Then the product was triturated with EtOAc (20 mL) to give 2-(*tert*-butyl)-6-chloro-2,3-dihydrophenanthridin-4(1H)-one as a light yellow solid (0.91 g, 5% yield, *m/z*: 288 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 8.50 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.96-7.88 (m, 2H), 3.61-3.56 (m, 1H), 3.06-2.96 (m, 2H), 2.57-2.49 (m, 1H), 2.15-2.14 (m, 1H), 1.11 (s, 9H).

2-(*tert*-Butyl)-6-methoxy-2,3-dihydrophenanthridin-4(1H)-one:

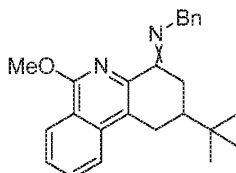


To a mixture of 2-(*tert*-butyl)-6-chloro-2,3-dihydrophenanthridin-4(1H)-one (0.33 g, 1.15 mmol) and MeOH (0.11 mL, 2.77 mmol) in toluene (6 mL) was added cesium carbonate (1.12 g, 3.44 mmol), *t*BuXPhos (97.4 mg, 0.23 mmol) and palladium(II) acetate (25.7 mg, 0.11 mmol). The reaction was stirred at 80 °C for 16 h under N₂. After cooling to rt, the mixture was diluted with H₂O (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phase was concentrated under vacuum. The residue was purified normal phase SiO₂ chromatography (0-15% EtOAc/petroleum ether) to afford 2-(*tert*-butyl)-6-methoxy-2,3-dihydrophenanthridin-4(1H)-one as a light-yellow solid (0.2 g, 61% yield). ¹H NMR (400

MHz, CDCl₃): δ 8.28 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.74 (t, J = 9.6 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 4.16 (s, 3H), 3.41-3.36 (m, 1H), 2.91-2.76 (m, 2H), 2.44-2.37 (m, 1H), 2.01-1.96 (m, 1H), 1.00 (s, 9H).

N-(2-(*tert*-Butyl)-6-methoxy-2,3-dihydrophenanthridin-4(1H)-ylidene)-1-

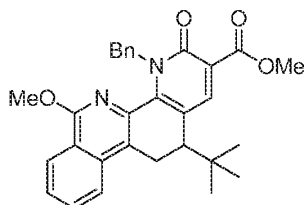
5 phenylmethanamine:



To a mixture of 2-(*tert*-butyl)-6-methoxy-2,3-dihydrophenanthridin-4(1H)-one (120 mg, 0.42 mmol) and benzylamine (69 μ L, 0.64 mmol) in THF (2 mL) was added titanium (IV) isopropoxide (0.38 mL, 1.27 mmol) and then stirred in a microwave reactor at 95 °C for 1 h.

- 10 The reaction mixture was quenched with H₂O (20 mL) and extracted with EtOAc (20 mL). The organic layer was separated, washed with H₂O (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford *N*-(2-(*tert*-butyl)-6-methoxy-2,3-dihydrophenanthridin-4(1H)-ylidene)-1-phenylmethanamine as a dark yellow oil, which was used into the next step without further purification (0.32 g, >100% yield, m/z: 373 [M+H]⁺ observed).

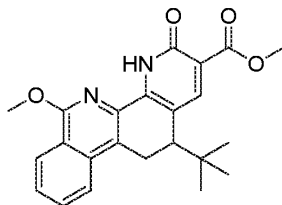
Methyl 4-Benzyl-12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate:



A mixture of *N*-(2-(*tert*-butyl)-6-methoxy-2,3-dihydrophenanthridin-4(1H)-ylidene)-1-

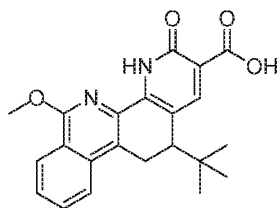
- 20 phenylmethanamine (0.32 g, 0.86 mmol) and dimethyl 2-(methoxymethylene)propanedioate (449 mg, 2.58 mmol) in diphenyl ether (4 mL) was heated to 220 °C in a microwave reactor for 30 min. After cooling to room temperature, the reaction mixture was purified directly by normal phase SiO₂ chromatography (0-100% EtOAc/petroleum ether then 0-10% MeOH/EtOAc) to afford methyl 4-benzyl-12-(*tert*-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate as a yellow solid (60 mg, 12% yield, m/z: 483 [M+H]⁺ observed).

Methyl 12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate:



- A mixture of methyl 4-benzyl-12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate (60 mg, 0.12 mmol) in TFA (5 mL) was stirred at 100 °C for 65 h. After cooling to rt, the mixture was concentrated under vacuum. Saturated aqueous sodium bicarbonate solution was added to adjust the pH to 8. The mixture was extracted with EtOAc (3 x 100 mL) and concentrated under vacuum. The residue was purified by reverse phase HPLC to give methyl 12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate as a yellow solid (30 mg, 36% yield, m/z: 393 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 8.38 (d, *J* = 8.4 Hz, 1H), 8.27 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.84 (t, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 4.27 (s, 3H), 3.98 (s, 3H), 3.75 (d, *J* = 17.6 Hz, 1H), 3.24-3.18 (m, 1H), 2.78 (d, *J* = 8.0 Hz, 1H), 0.85 (s, 9H).
- 120 mg of the mixture of enantiomers was separated by SFC (supercritical fluid chromatography) on a DAICEL CHIRALCEL OD column using 45% MeOH(0.1% NH₄OH as modifier) to give methyl 12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate (enantiomer I) as a yellow solid (faster eluting enantiomer, 10 mg, 30% yield, m/z: 393 [M+H]⁺ observed) and methyl 12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate (enantiomer II) as a yellow solid (slower eluting enantiomer, 10 mg, 30% yield, m/z: 393 [M+H]⁺ observed).

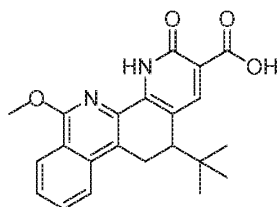
Example 41: 12-(tert-Butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid (single enantiomer I)



To a mixture of methyl 12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo

[c][1,10]phenanthroline-2-carboxylate (10 mg, 25.5 μ mol, faster eluting enantiomer) in EtOAc (5 mL) was added lithium iodide (34 mg, 0.25 mmol) and the reaction was stirred at 60 °C for 16 h. The mixture was quenched with H₂O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was concentrated under vacuum. The crude residue was purified by reverse phase HPLC to afford 12-(*tert*-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid as a yellow solid (1.2 mg, 11% yield, m/z : 379 [M+H]⁺ observed). ¹H NMR (400 MHz, CD₃CN): δ 14.57 (s, 1H), 10.91 (br s, 1H), 8.41 (s, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.94-7.91 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 4.28 (s, 3H), 3.82 (d, J = 17.6 Hz, 1H), 3.27-3.20 (m, 1H), 2.96 (d, J = 8.4 Hz, 1H), 0.82 (s, 9H).

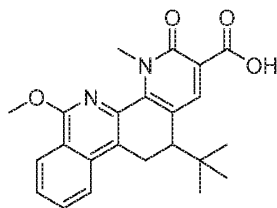
Example 42: 12-(*tert*-Butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid (single enantiomer II)



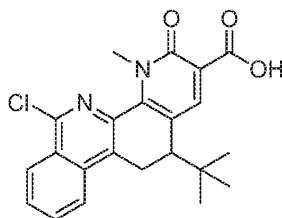
To a mixture of methyl 12-(*tert*-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate (10 mg, 25.5 μ mol, slower eluting enantiomer) in EtOAc (5 mL) was added lithium iodide (34 mg, 0.25 mmol) and the reaction was stirred at 60 °C for 16 h. The mixture was quenched with H₂O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was concentrated under vacuum. The crude residue was purified by reverse phase HPLC to afford 12-(*tert*-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid as a yellow solid (1 mg, 10% yield, m/z : 379 [M+H]⁺ observed). ¹H NMR (400 MHz, CD₃CN): δ 14.57 (s, 1H), 10.91 (br s, 1H), 8.41 (s, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.94-7.91 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 4.28 (s, 3H), 3.82 (d, J = 17.6 Hz, 1H), 3.27-3.20 (m, 1H), 2.96 (d, J = 8.4 Hz, 1H), 0.82 (s, 9H).

The following examples were prepared in a similar manner as 12-(*tert*-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid from an appropriate 2,3-dihydrophenanthridin-4(1H)-one.

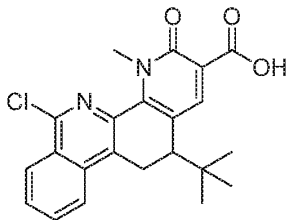
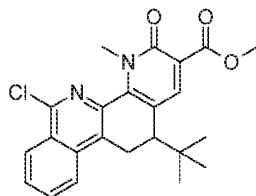
Example 43: 12-(*tert*-Butyl)-6-methoxy-4-methyl-3-oxo-3,4,11,12-

tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid

m/z: 393 [M+H]⁺ observed. ¹H NMR (400 MHz, CDCl₃): δ 8.44 (s, 1H), 8.34 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1H), 8.10 (dt, *J* = 8.8, 0.8 Hz, 1H), 7.84 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 4.14 (s, 3H), 3.69-3.70 (m, 4H), 3.15 (dd, *J* = 16.3, 7.2 Hz, 1H), 2.72 (dd, *J* = 7.1, 1.5 Hz, 1H), 0.65 (s, 9H).

Example 44: 12-(*tert*-Butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid (single enantiomer I)

10

Example 45: 12-(*tert*-Butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid (single enantiomer II)**15 Methyl 12-(*tert*-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate:**

To a mixture of *N*-(2-(*tert*-butyl)-6-chloro-2,3-dihydrophenanthridin-4(1H)-ylidene)

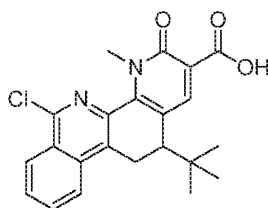
methanamine (0.62 g, 2.06 mmol) in Ph₂O (10 mL) was added dimethyl 2-(methoxy methylene)malonate (1.08 g, 6.18 mmol). The reaction mixture was then heated to 220 °C in the microwave reactor for 30 min. After cooling to room temperature, the reaction mixture combined with another batch on 470 mg scale. The combined mixture was directly

5 purified by normal phase SiO₂ chromatography (0-100% EtOAc/petroleum ether then 10% MeOH/EtOAc) to afford a dark yellow oil, which was further purified by reverse phase HPLC to give methyl 12-(*tert*-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate as a yellow solid (200 mg, 23% yield, *m/z*: 411 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃): δ 8.42 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 8.13 (s, 1H), 7.90 (t, *J* = 7.2 Hz, 1H), 7.81 (t, *J* = 7.2 Hz, 1H), 3.96 (d, *J* = 4.4 Hz, 6H), 3.80 (d, *J* = 16.4 Hz, 1H), 3.23-3.18 (m, 1H), 2.69 (d, *J* = 6.4 Hz, 1H), 0.65 (s, 9H).

200 mg of the mixture of enantiomers was separated by SFC (supercritical fluid chromatography) on a DAICEL CHIRALCEL OD column using 50% EtOH (0.1% NH₄OH

15 as modifier) to give methyl 12-(*tert*-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate (enantiomer I) as a yellow solid (faster eluting enantiomer, 80 mg, 39% yield, *m/z*: 411 [M+H]⁺ observed) and methyl 12-(*tert*-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylate (enantiomer II) as a yellow solid (slower eluting enantiomer, 70 mg, 33% yield, *m/z*: 411 [M+H]⁺ observed).

Example 44: 12-(*tert*-Butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid (single enantiomer I)



To a mixture of methyl 12-(*tert*-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydro

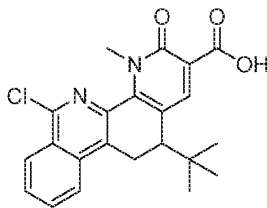
25 benzo[c][1,10]phenanthroline-2-carboxylate (70 mg, 0.17 mmol, faster eluting enantiomer) in EtOAc (5 mL) was added lithium iodide (228 mg, 1.7 mmol) and the reaction was stirred at 60 °C for 40 h. The mixture was combined with another 10 mg batch. The combined mixture was quenched with H₂O (10 mL), extracted with EtOAc (3 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase HPLC to

30 afford 12-(*tert*-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenan

throline-2-carboxylic acid as a yellow solid (31 mg, 45% yield, m/z : 397 $[M+H]^+$ observed).

^1H NMR (400 MHz, DMSO- d_6): δ 14.92 (br s, 1H), 8.60 (d, J = 8.8 Hz, 1H), 8.42 (d, J = 7.2 Hz, 2H), 8.10-8.06 (t, J = 7.2 Hz, 1H), 8.01-7.97 (t, J = 7.6 Hz, 1H), 3.95-3.91 (d, J = 19.6 Hz, 4H), 3.23 (d, J = 8.0 Hz, 1H), 3.03 (d, J = 6.4 Hz, 1H), 0.59 (s, 9H).

5 **Example 45: 12-(*tert*-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[*c*][1,10]phenanthroline-2-carboxylic acid (single enantiomer II)**

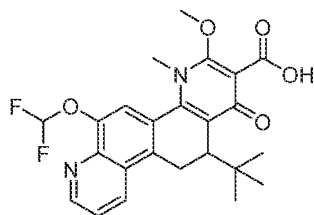


To a mixture of methyl 12-(*tert*-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[*c*][1,10]phenanthroline-2-carboxylate (70 mg, 0.17 mmol, slower eluting

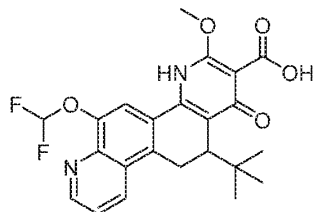
- 10 enantiomer) in EtOAc (6 mL) was added lithium iodide (228 mg, 1.70 mmol) and the reaction was stirred at 60 °C for 40 h. The mixture was quenched with H₂O (10 mL), extracted with EtOAc (3 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by reverse phase HPLC to afford 12-(*tert*-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[*c*][1,10]phenanthroline-2-
- 15 carboxylic acid as a yellow solid (39 mg, 57% yield, m/z : 397 $[M+H]^+$ observed).

^1H NMR (400 MHz, DMSO- d_6): δ 14.91 (s, 1H), 8.60 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 7.2 Hz, 1H), 8.10-8.06 (t, J = 7.2 Hz, 1H), 8.01-7.97 (t, J = 7.2 Hz, 1H), 3.95-3.91 (d, J = 19.6 Hz, 4H), 3.22 (d, J = 7.2 Hz, 1H), 3.02 (d, J = 6.4 Hz, 1H), 0.59 (s, 9H).

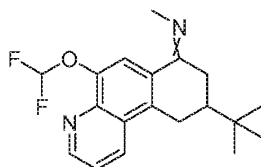
20 **Example 46: 6-(*tert*-Butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid**



Example 47: 6-(*tert*-butyl)-12-(difluoromethoxy)-9-methoxy-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylic acid



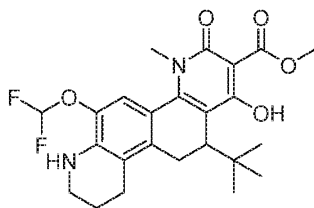
9-(tert-Butyl)-5-(difluoromethoxy)-N-methyl-7,8,9,10-tetrahydrobenzo[f]quinolin-7-amine:



- 5 To a solution of 9-(tert-butyl)-5-(difluoromethoxy)-9,10-dihydrobenzo[f]quinolin-7(8H)-one (0.57 g, 1.76 mmol) in THF (3 mL) was added Ti(IV)isopropoxide (1.8 mL, 6.17 mmol) and methylamine (2 M solution in THF, 1.76 mL, 3.53 mmol) at room temperature and the reaction was heated to 90°C for 2 h in a microwave reactor. The reaction mixture was diluted with EtOAc (100 mL) and washed with H₂O (2 x 20 mL), then saturated aqueous brine solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give 9-(tert-butyl)-5-(difluoromethoxy)-N-methyl-7,8,9,10-tetrahydrobenzo[f]quinolin-7-amine as a yellow oil (0.59 g, 100% yield, m/z: 333 [M+H]⁺ observed), which was used in the next step without further purification.

Methyl 6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-10-methyl-9-oxo-1,2,3,4,5,6,9,10-

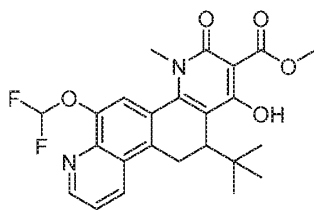
- 15 **octahydroquinolino[7,8-f]quinoline-8-carboxylate:**



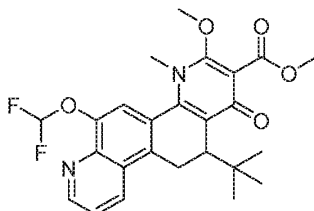
- To a solution of methyl 9-(tert-butyl)-5-(difluoromethoxy)-N-methyl-7,8,9,10-tetrahydrobenzo[f]quinolin-7-amine (0.59 g, 1.75 mmol) in diglyme (5 mL) was added trimethylmethanetricarboxylate (0.67 g, 3.51 mmol) and the reaction was heated to 170°C for 1 h in a microwave reactor. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (2 x 20 mL), washed with saturated aqueous brine solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude residue was purified by normal phase SiO₂ chromatography (0-40% EtOAc/Hexanes) to afford methyl 6-

- (*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-10-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylate (0.24 g, 30% yield, *m/z* 463 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃) δ 13.65 (s, 1H), 7.12 (s, 1H), 6.41 (t, *J* = 74.0 Hz, 1H), 4.71 (s, 1H), 3.98 (s, 3H), 3.60 (s, 3H), 3.50-3.39 (m, 1H), 3.40-3.25 (m, 1H), 3.14-3.03 (m, 2H), 2.78 (t, *J* = 7.7, 5.1 Hz, 2H), 2.58-2.46 (m, 1H), 2.14-2.01 (m, 1H), 1.99-1.91 (m, 1H), 0.63 (s, 9H).

Methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylate:



- To a solution of methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-10-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-*f*]quinoline-8-carboxylate (0.24 g, 0.52 mmol) in *o*-Xylenes (10 mL) was added palladium on carbon (10% on carbon, 0.06 g, 0.06 mmol) at rt. The reaction was evacuated, then purged with O₂ (the cycle repeated 3 times). An atmosphere of O₂ was bubbled through solvent for several minutes. The mixture was heated to 100°C for 16h. The reaction was worked up by diluting with EtOAc (100 mL) and filtering through a CELITE[®] pad. The filtrate was evaporated under reduced pressure and purified by normal phase SiO₂ chromatography (0-5% MeOH/CH₂Cl₂) to afford methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylate (0.08 g, 33% yield, *m/z*: 459 [M+H]⁺ observed).
- Methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylate:**

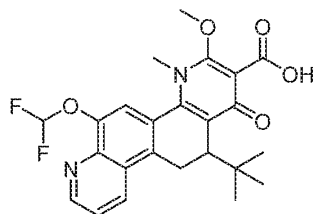


- To a solution of methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-7-hydroxy-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-*f*]quinoline-8-carboxylate (0.08 g, 0.18 mmol) in acetonitrile (10 mL) was added K₂CO₃ (0.05 g, 0.36 mmol) and iodomethane (0.03 mL, 0.54 mmol) at rt and the reaction was heated to 80 °C and stirred for 2 h. The reaction mixture

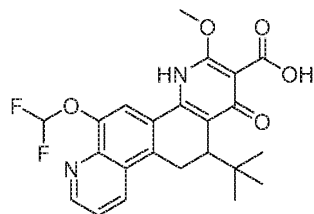
was diluted with EtOAc (100 mL), washed with water (2 x 20 ml), washed with saturated aqueous brine solution (20 ml), then dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude residue was purified by normal phase SiO₂ chromatography (0-80% EtOAc/Hexanes) to afford methyl 6-(*tert*-butyl)-12-

- 5 (difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylate (0.21 g, 25% yield *m/z*: 473 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃) δ 9.02 (d, *J* = 4.2, 1.6 Hz, 1H), 8.54 (d, *J* = 8.8, 1.6 Hz, 1H), 7.71 (s, 1H), 7.64-7.55 (m, 1H), 7.12 (m, 1H), 3.96 (s, 6H), 3.77-3.58 (m, 4H), 3.13 (d, *J* = 6.7, 1.7 Hz, 1H), 2.99 (dd, *J* = 16.1, 6.7 Hz, 1H), 0.50 (s, 9H).

- 10 **Example 46: 6-(*tert*-Butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid**



Example 47: 6-(*tert*-Butyl)-12-(difluoromethoxy)-9-methoxy-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid



15

To a solution of methyl 6-(*tert*-butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylate (0.04 g, 0.09 mmol) in EtOAc (10 mL) was added LiI (0.02 g, 0.13 mmol) at rt. The reaction was heated to 65°C for 3 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (20 ml),

- 20 washed with with saturated aqueous brine solution (20 ml), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude residue was purified by normal phase SiO₂ chromatography (0-80% EtOAc/Hexanes) to afford two products:

Example 46: 6-(*tert*-Butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid

- 25 (23 mg, 56% yield, *m/z*: 459 [M+H]⁺ observed). ¹H NMR (400 MHz, CDCl₃) δ 13.84 (s,

1H), 9.05 (d, $J = 4.2, 1.7$ Hz, 1H), 8.58 (m, 1H), 7.76 (s, 1H), 7.67-7.58 (m, 1H), 7.06 (t, 1H), 4.03 (s, 3H), 3.71 (d, $J = 16.2$ Hz, 1H), 3.65 (s, 3H), 3.26 (d, 1H), 3.07 (dd, $J = 16.3, 6.7$ Hz, 1H), 0.56 (d, $J = 0.8$ Hz, 9H).

Example 47: 6-(tert-Butyl)-12-(difluoromethoxy)-9-methoxy-7-oxo-5,6,7,10-

5 tetrahydroquinolino[7,8-*ff*]quinoline-8-carboxylic acid

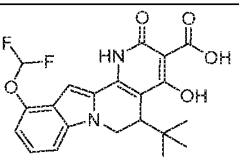
(5 mg, 12% yield, m/z : 445 $[M+H]^+$ observed). ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.76 (d, $J = 8.6$ Hz, 1H), 7.87 (s, 1H), 7.84-7.76 (m, 1H), 6.99 (t, $J = 72.9$ Hz, 1H), 3.80-3.71 (m, 4H), 3.32 (d, 1H), 3.11 (m, 1H), 0.58 (s, 9H).

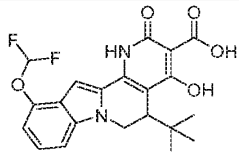
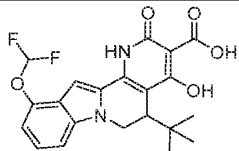
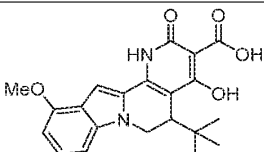
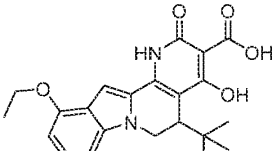
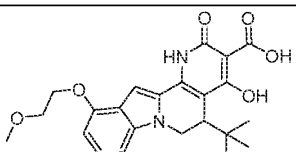
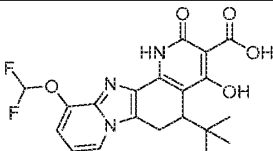
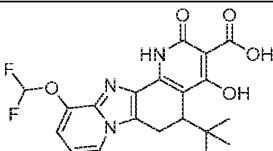
10 Example 48: Biological Examples

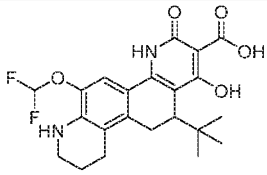
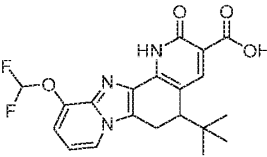
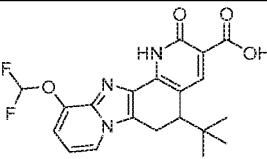
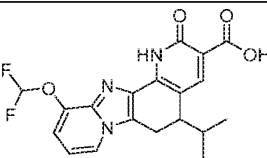
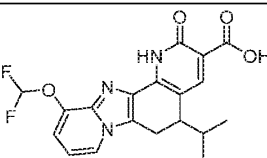
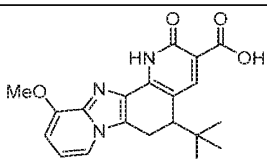
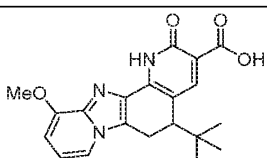
HBsAg Assay

Inhibition of HBsAg was determined in HepG2.2.15 cells. Cells were maintained in culture medium containing 10% fetal calf serum, G414, Glutamine, penicillin/streptomycin. Cells were seeded in 96-well collagen-coated plate at a density of 30,000 cells/well. Serially
 15 diluted compounds were added to cells next day at the final DMSO concentration of 0.5%. Cells were incubated with compounds for 2-3 days, after which medium was removed. Fresh medium containing compounds was added to cells for additional 3-4 days. At day 6 after exposure of compounds, supernatant was collected, the HBsAg immunoassay (microplate-based chemiluminescence immunoassay kits, CLIA, Autobio Diagnostics Co., Zhengzhou,
 20 China, Catalog # CL0310-2) was used to determine the level of HBsAg according to manufactory instruction. Dose-response curves were generated and the EC_{50} value (effective concentrations that achieved 50% inhibitory effect) were determined using XLfit software. In addition, cells were seeded at a density of 5,000 cells/well for determination of cell viability in the presence and absence of compounds by using CellTiter-Glo reagent
 25 (Promega). Tables 1-3 show EC_{50} values obtained by the HBsAg assay for selected compounds.

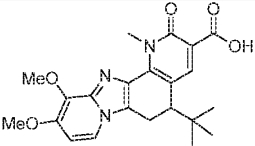
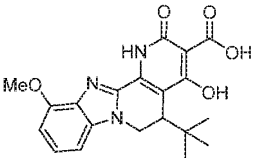
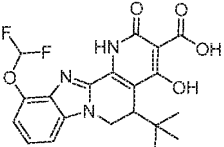
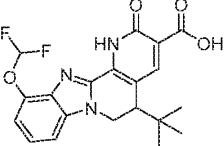
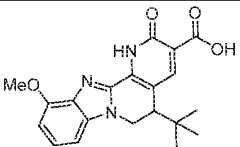
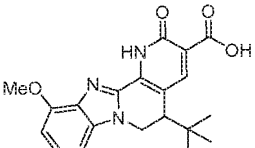
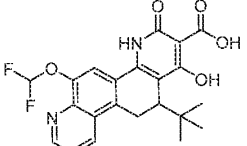
Table 1.

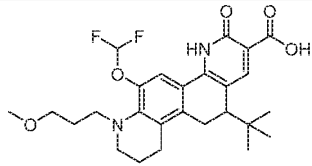
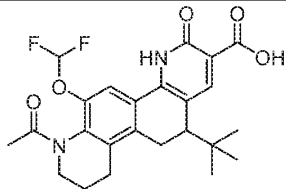
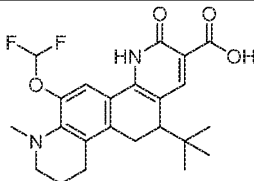
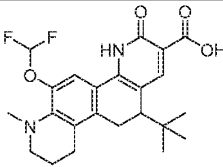
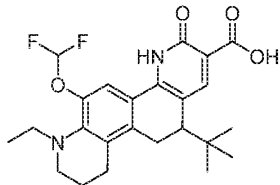
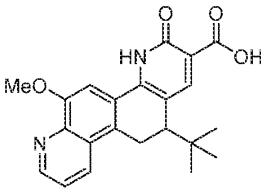
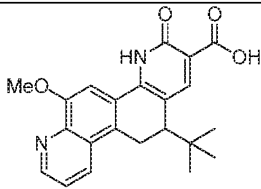
Ex. No.	Structure	Nomenclature	sAg EC_{50} , μM
1		5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid	0.009

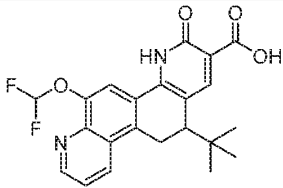
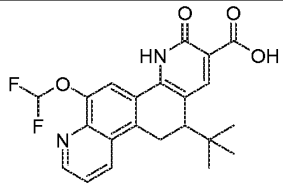
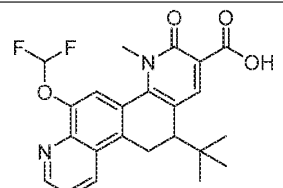
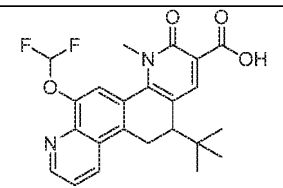
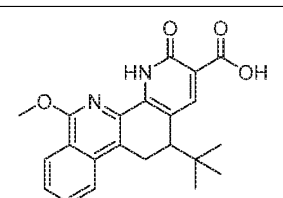
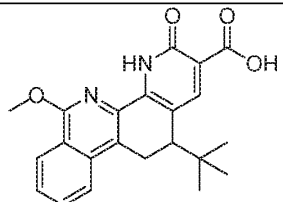
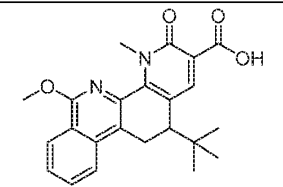
2		5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid (single enantiomer I)	1
3		5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid (single enantiomer II)	0.005
4		5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid	0.13
5		5-(tert-butyl)-11-ethoxy-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid	0.13
6		5-(tert-butyl)-4-hydroxy-11-(2-methoxyethoxy)-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid	0.76
7		5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)	0.002
8		5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)	0.22

9		6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid	0.011
10		5-(tert-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)	0.003
11		5-(tert-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)	27
12		11-(difluoromethoxy)-5-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)	0.018
13		11-(difluoromethoxy)-5-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)	1.1
14		5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)	0.012
15		5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)	1

16		5-isopropyl-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)	0.048
17		5-isopropyl-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)	10
18		5-(tert-butyl)-10,11-dimethoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)	0.005
19		5-(tert-butyl)-10,11-dimethoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)	8
20		11-(difluoromethoxy)-6-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)	0.099
21		11-(difluoromethoxy)-6-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)	6
22		5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer I)	0.11

23		5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid (single enantiomer II)	0.011
24		5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid	0.02
25		5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid	0.004
26		5-(tert-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid	0.057
27		5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid (single enantiomer I)	10
28		5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid (single enantiomer II)	0.093
29		6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid	0.001

30		6-(tert-butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid	0.2
31		1-acetyl-6-(tert-butyl)-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid	0.05
32		6-(tert-butyl)-12-(difluoromethoxy)-1-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid (single enantiomer I)	0.002
33		6-(tert-butyl)-12-(difluoromethoxy)-1-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid (single enantiomer II)	0.3
34		6-(tert-butyl)-12-(difluoromethoxy)-1-ethyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid	0.012
35		6-(tert-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid (single enantiomer I)	0.027
36		6-(tert-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid (single enantiomer II)	5.2

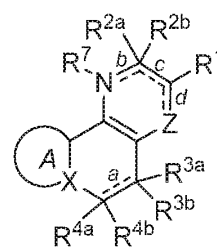
37		6-(tert-butyl)-12-(difluoromethoxy)-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid (single enantiomer I)	0.003
38		6-(tert-butyl)-12-(difluoromethoxy)-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid (single enantiomer II)	3
39		6-(tert-butyl)-12-(difluoromethoxy)-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid (single enantiomer I)	10
40		6-(tert-butyl)-12-(difluoromethoxy)-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid (single enantiomer II)	0.2
41		12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid (single enantiomer I)	0.001
42		12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid (single enantiomer II)	0.075
43		12-(tert-butyl)-6-methoxy-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid	0.023

44		12-(tert-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid (single enantiomer I)	0.009
45		12-(tert-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid (single enantiomer II)	1.0
46		6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid	0.3
47		6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid	0.14

Enumerated Embodiments

The following exemplary embodiments are provided, the numbering of which is not to be construed as designating levels of importance:

Embodiment 1 provides a compound of formula (I), or a salt, solvate, geometric



5 isomer, stereoisomer, tautomer and any mixtures thereof:

R^1 is selected from the group consisting of H; halogen; $-OR^8$; $-C(R^9)(R^9)OR^8$; $-C(=O)R^8$; $-C(=O)OR^8$; $-C(=O)NH-OR^8$; $-C(=O)NHNHR^8$; $-C(=O)NHNHC(=O)R^8$; $-C(=O)NHS(=O)_2R^8$; $-CH_2C(=O)OR^8$; $-CN$; $-NH_2$; $-N(R^8)C(=O)H$; $-N(R^8)C(=O)R^{10}$; $-N(R^8)C(=O)OR^{10}$; $-N(R^8)C(=O)NHR^8$; $-NR^9S(=O)_2R^{10}$; $-P(=O)(OR^8)_2$; $-B(OR^8)_2$; 2,5-dioxo-pyrrolidin-1-yl; 2H-tetrazol-5-yl; 3-hydroxy-isoxazol-5-yl; 1,4-dihydro-5-oxo-5H-tetrazol-1-

yl; pyridin-2-yl optionally substituted with C₁-C₆ alkyl; pyrimidin-2-yl optionally substituted with C₁-C₆ alkyl; (pyridin-2-yl)methyl; (pyrimidin-2-yl)methyl; (pyrimidin-2-yl)amino; bis-(pyrimidin-2-yl)-amino; 5-R⁸-1,3,4,-thiadiazol-2-yl; 5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl; 1H-1,2,4-triazol-5-yl; 1,3,4-oxadiazol-2-yl; 1,2,4-oxadiazol-5-yl; and 3-R¹⁰-1,2,4-oxadiazol-5-yl;

R^{2a}, R^{2b}, R⁷, bond *b*, bond *c*, bond *d*, and Z are selected such that:

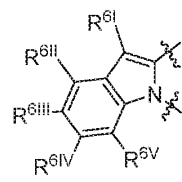
- (i) Z is selected from the group consisting of N and CR¹²; R^{2a} and R^{2b} combine to form =O; bond *b* is a single bond; bond *c* is a single bond; bond *d* is a double bond; and R⁷ is selected from the group consisting of H, optionally substituted C₁-C₆ alkyl, and optionally substituted C₃-C₈ cycloalkyl; or
- (ii) Z is selected from the group consisting of N and CR¹²; R^{2a} is selected from the group consisting of H, halogen, and optionally substituted C₁-C₆ alkoxy; R^{2b} is null; bond *b* is a double bond; bond *c* is a single bond; bond *d* is a double bond; and R⁷ is null;
- (iii) Z is C(=O); R^{2a} is selected from the group consisting of H, halogen, and optionally substituted C₁-C₆ alkoxy; R^{2b} is null; bond *b* is a single bond; bond *c* is a double bond; bond *d* is a single bond; and R⁷ is selected from the group consisting of H, optionally substituted C₁-C₆ alkyl, and optionally substituted C₃-C₈ cycloalkyl;

R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of H, alkyl-substituted oxetanyl, optionally substituted C₁-C₆ alkyl, and optionally substituted C₃-C₈ cycloalkyl;

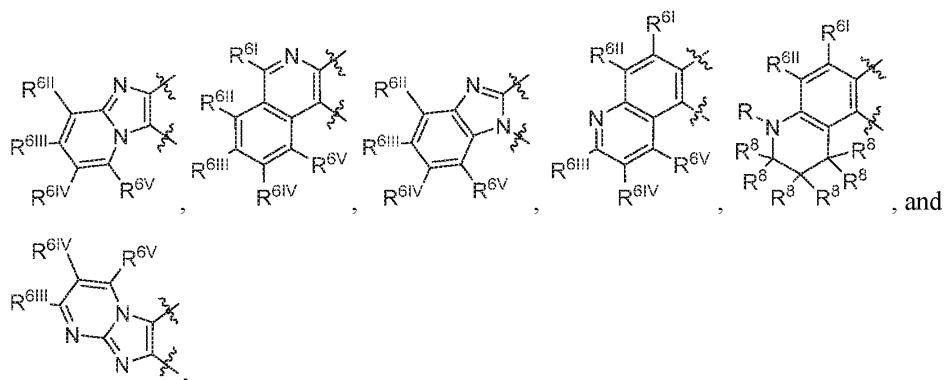
or one pair selected from the group consisting of R^{3a} / R^{3b}, R^{4a} / R^{4b}, and R^{3a} / R^{4a} combine to form a divalent group selected from the group consisting of C₁-C₆ alkanediyl, -(CH₂)_nO(CH₂)_n-, -(CH₂)_nNR⁹(CH₂)_n-, -(CH₂)_nS(CH₂)_n-, -(CH₂)_nS(=O)(CH₂)_n-, and -(CH₂)_nS(=O)₂(CH₂)_n-, wherein each occurrence of n is

independently selected from the group consisting of 1 and 2 and wherein each divalent group is optionally substituted with at least one C₁-C₆ alkyl or halogen;

bond *a* is single; or bond *a* is double and R^{3b} and R^{4b} are both null;



X is C or N, and ring *A* is selected from the group consisting of:



R^{6I} , R^{6II} , R^{6III} , R^{6IV} , and R^V are independently selected from the group consisting of H, halogen, -CN, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 alkenyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -OR, C_1 - C_6 haloalkoxy, -N(R)(R), -NO₂, -S(=O)₂N(R)(R), acyl, and C_1 - C_6 alkoxycarbonyl,

each occurrence of R is independently selected from the group consisting of H, optionally substituted C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, R' -substituted C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, optionally substituted (C_1 - C_6 alkoxy)- C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, and optionally substituted C_1 - C_6 acyl,

each occurrence of R' is selected from the group consisting of -NH₂, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)(C_1 - C_6 alkyl), -NHC(=O)O^tBu, -N(C_1 - C_6 alkyl)C(=O)O^tBu, and a 5- or 6-membered heterocyclic group, which is optionally N-linked;

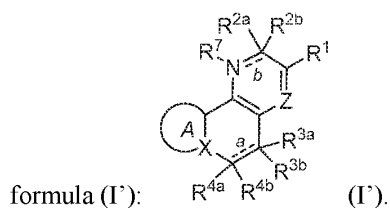
each occurrence of R^8 is independently selected from the group consisting of H, optionally substituted C_1 - C_6 alkyl, and optionally substituted C_3 - C_8 cycloalkyl;

each occurrence of R^9 is independently selected from the group consisting of H and C_1 - C_6 alkyl (*e.g.*, methyl or ethyl);

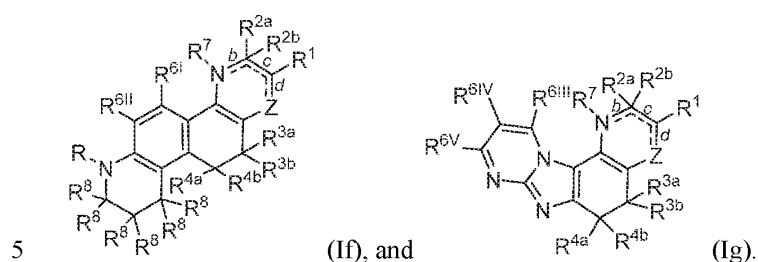
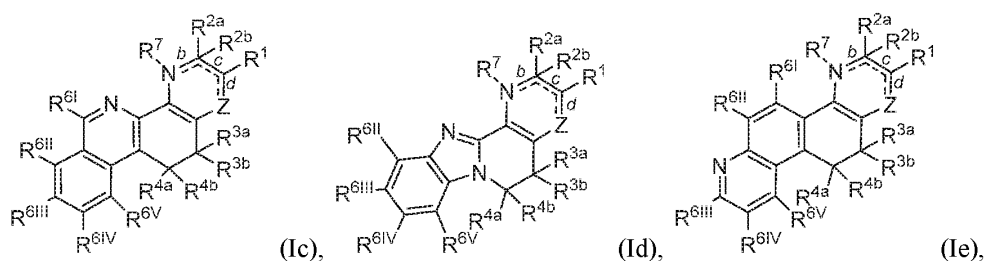
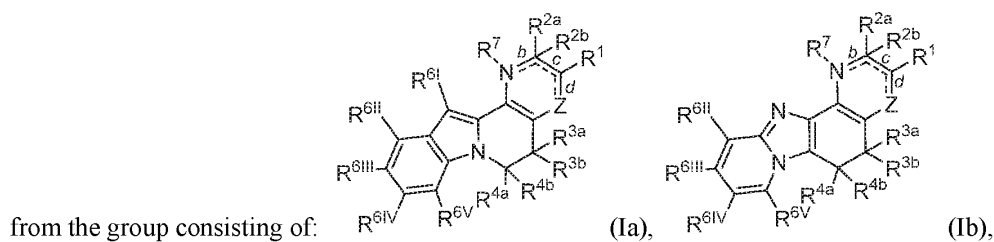
each occurrence of R^{10} is independently selected from the group consisting of optionally substituted C_1 - C_6 alkyl and optionally substituted phenyl; and,

R^{12} is selected from the group consisting of H, OH, halogen, C_1 - C_6 alkoxy, optionally substituted C_1 - C_6 alkyl, and optionally substituted C_3 - C_8 cycloalkyl.

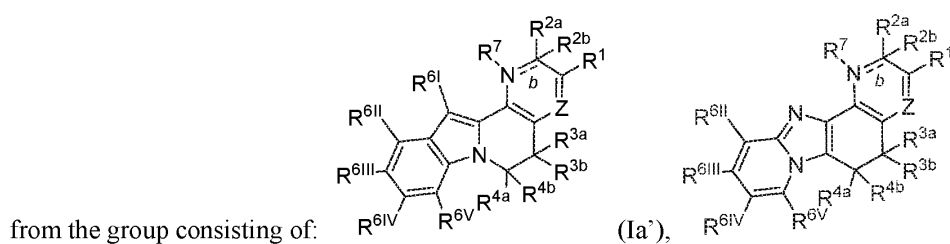
Embodiment 2 provides the compound of Embodiment 1, which is a compound of

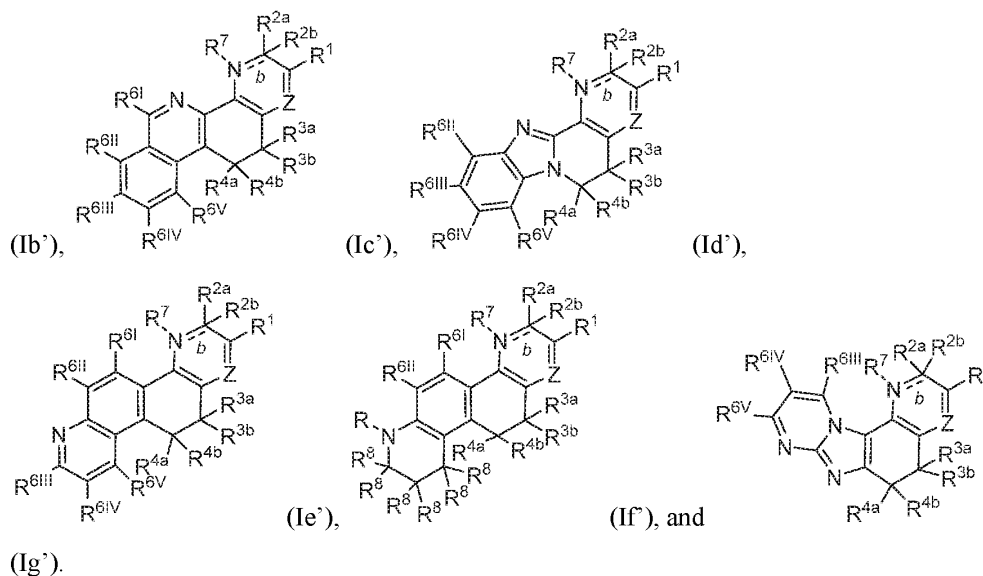


Embodiment 3 provides the compound of any of Embodiments 1-2, which is selected



Embodiment 4 provides the compound of any of Embodiments 1-3, which is selected





Embodiment 5 provides the compound of any of Embodiments 1-4, wherein at least one of R^{3a} or R^{3b} is independently selected from the group consisting of optionally substituted C₁-C₆ alkyl and optionally substituted C₃-C₈ cycloalkyl.

Embodiment 6 provides the compound of any of Embodiments 1-5, wherein each occurrence of alkyl, alkenyl, cycloalkyl, or acyl is independently optionally substituted with at least one substituent selected from the group consisting of C₁-C₆ alkyl, halogen, -OR'', phenyl, and -N(R'')(R''), wherein each occurrence of R'' is independently H, C₁-C₆ alkyl, or C₃-C₈ cycloalkyl.

Embodiment 7 provides the compound of any of Embodiments 1-6, wherein each occurrence of aryl or heteroaryl is independently optionally substituted with at least one substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, -CN, -OR'', -N(R'')(R''), -NO₂, -S(=O)₂N(R'')(R''), acyl, and C₁-C₆ alkoxycarbonyl, wherein each occurrence of R'' is independently H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl.

Embodiment 8 provides the compound of any of Embodiments 1-7, wherein each occurrence of aryl or heteroaryl is independently optionally substituted with at least one substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, -CN, -OR'', -N(R'')(R''), and C₁-C₆ alkoxycarbonyl, wherein each occurrence of R'' is independently H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl.

Embodiment 9 provides the compound of any of Embodiments 1-8, wherein at least one applies: R^{3a} is H and R^{3b} is isopropyl; R^{3a} is H and R^{3b} is tert-butyl; R^{3a} is methyl and

R^{3b} is isopropyl; R^{3a} is methyl and R^{3b} is tert-butyl; R^{3a} is methyl and R^{3b} is methyl; R^{3a} is methyl and R^{3b} is ethyl; and R^{3a} is ethyl and R^{3b} is ethyl.

Embodiment 10 provides the compound of any of Embodiments 1-9, wherein R^{3a} and R^{3b} are not H.

- 5 Embodiment 11 provides the compound of any of Embodiments 1-10, which is selected from the group consisting of: 5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid; 5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid; 5-(tert-butyl)-11-ethoxy-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-
- 10 h][1,7]naphthyridine-3-carboxylic acid; 5-(tert-butyl)-4-hydroxy-11-(2-methoxyethoxy)-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid; 5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid; 6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid; 5-(tert-butyl)-11-
- 15 (difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid; 11-(difluoromethoxy)-5-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid; 5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid; 5-isopropyl-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-
- 20 carboxylic acid; 5-(tert-butyl)-10,11-dimethoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid; 11-(difluoromethoxy)-6-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid; 5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid; 5-(tert-butyl)-4-
- 25 hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid; 5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid; 5-(tert-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid; 5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-
- 30 h][1,7]naphthyridine-3-carboxylic acid; 6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid; 6-(tert-butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid; 1-acetyl-6-(tert-butyl)-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid; 6-(tert-butyl)-12-

(difluoromethoxy)-1-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid; 6-(tert-Butyl)-12-(difluoromethoxy)-1-ethyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid; 6-(tert-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid; 6-(tert-butyl)-12-(difluoromethoxy)-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid; 6-(tert-butyl)-12-(difluoromethoxy)-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid; 12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid; 12-(tert-butyl)-6-methoxy-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid; 12-(tert-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid; 6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid; and 6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid.

Embodiment 12 provides a pharmaceutical composition comprising at least one compound of any of Embodiments 1-11 and a pharmaceutically acceptable carrier.

Embodiment 13 provides the pharmaceutical composition of Embodiment 12, further comprising at least one additional agent useful for treating hepatitis virus infection.

Embodiment 14 provides the pharmaceutical composition of Embodiment 13, wherein the at least one additional agent comprises at least one selected from the group consisting of reverse transcriptase inhibitors, capsid inhibitors, cccDNA formation inhibitors, RNA destabilizers, oligomeric nucleotides targeted against the HBV genome, immunostimulators, and GalNAc-siRNA conjugates targeted against an HBV gene transcript.

Embodiment 15 provides the pharmaceutical composition of Embodiment 14, wherein the oligomeric nucleotide comprises one or more siRNAs.

Embodiment 16 provides the pharmaceutical composition of any of Embodiments 13-15, wherein the hepatitis virus is at least one selected from the group consisting of hepatitis B virus (HBV) and hepatitis D virus (HDV).

Embodiment 17 provides a method of treating or preventing hepatitis virus infection in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of at least one compound of any of Embodiments 1-11 or at least one pharmaceutical composition of any of Embodiments 12-16.

Embodiment 18 provides the method of Embodiment 17, wherein the subject is infected with hepatitis B virus (HBV).

Embodiment 19 provides the method of any of Embodiments 17-18, wherein the subject is infected with hepatitis D virus (HDV).

Embodiment 20 provides the method of any of Embodiments 17-19, wherein the subject is infected with HBV and HDV.

5 Embodiment 21 provides a method of reducing or minimizing levels of at least one selected from the group consisting of hepatitis B virus surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), hepatitis B core protein, and pregenomic (pg) RNA, in a HBV-infected subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of at least one compound of any of Embodiments 1-11 or at least one
10 pharmaceutical composition of any of Embodiments 12-16.

Embodiment 22 provides the method of any of Embodiments 17-21, wherein the at least one compound is administered to the subject in a pharmaceutically acceptable composition.

15 Embodiment 23 provides the method of any of Embodiments 17-22, wherein the subject is further administered at least one additional agent useful for treating the hepatitis virus infection.

Embodiment 24 provides the method of Embodiment 23, wherein the at least one additional agent comprises at least one selected from the group consisting of reverse transcriptase inhibitors, capsid inhibitors, cccDNA formation inhibitors, RNA destabilizers,
20 oligomeric nucleotides targeted against the HBV genome, immunostimulators, and GalNAc-siRNA conjugates targeted against an HBV gene transcript.

Embodiment 25 provides the method of Embodiment 24, wherein the oligomeric nucleotide comprises one or more siRNAs.

25 Embodiment 26 provides the method of any of Embodiments 23-25, wherein the subject is co-administered the at least one compound and the at least one additional agent.

Embodiment 27 provides the method of any of Embodiments 23-26, wherein the at least one compound and the at least one additional agent are coformulated.

Embodiment 28 provides the method of any of Embodiments 21-27, wherein the subject is further infected with HDV.

30 Embodiment 29 provides the method of any of Embodiments 17-28, wherein the subject is a mammal.

Embodiment 30 provides the method of Embodiment 29, wherein the mammal is a human.

The disclosures of each and every patent, patent application, and publication cited

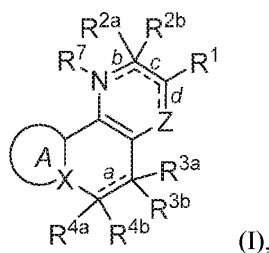
herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be

5 construed to include all such embodiments and equivalent variations.

CLAIMS

What is claimed is:

1. A compound of formula (I), or a salt, solvate, geometric isomer, stereoisomer, tautomer and any mixtures thereof:



R^1 is selected from the group consisting of H; halogen; $-OR^8$; $-C(R^9)(R^9)OR^8$; $-C(=O)R^8$; $-C(=O)OR^8$; $-C(=O)NH-OR^8$; $-C(=O)NHNHR^8$; $-C(=O)NHNHC(=O)R^8$; $-C(=O)NHS(=O)_2R^8$; $-CH_2C(=O)OR^8$; $-CN$; $-NH_2$; $-N(R^8)C(=O)H$; $-N(R^8)C(=O)R^{10}$; $-N(R^8)C(=O)OR^{10}$; $-N(R^8)C(=O)NHR^8$; $-NR^9S(=O)_2R^{10}$; $-P(=O)(OR^8)_2$; $-B(OR^8)_2$; 2,5-dioxo-pyrrolidin-1-yl; 2H-tetrazol-5-yl; 3-hydroxy-isoxazol-5-yl; 1,4-dihydro-5-oxo-5H-tetrazol-1-yl; pyridin-2-yl optionally substituted with C_1 - C_6 alkyl; pyrimidin-2-yl optionally substituted with C_1 - C_6 alkyl; (pyridin-2-yl)methyl; (pyrimidin-2-yl)methyl; (pyrimidin-2-yl)amino; bis-(pyrimidin-2-yl)-amino; 5- R^8 -1,3,4-thiadiazol-2-yl; 5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl; 1H-1,2,4-triazol-5-yl; 1,3,4-oxadiazol-2-yl; 1,2,4-oxadiazol-5-yl; and 3- R^{10} -1,2,4-oxadiazol-5-yl;

R^{2a} , R^{2b} , R^7 , bond b , bond c , bond d , and Z are selected such that:

- (i) Z is selected from the group consisting of N and CR^{12} ; R^{2a} and R^{2b} combine to form $=O$; bond b is a single bond; bond c is a single bond; bond d is a double bond; and R^7 is selected from the group consisting of H, optionally substituted C_1 - C_6 alkyl, and optionally substituted C_3 - C_8 cycloalkyl; or
- (ii) Z is selected from the group consisting of N and CR^{12} ; R^{2a} is selected from the group consisting of H, halogen, and optionally substituted C_1 - C_6 alkoxy; R^{2b} is null; bond b is a double bond; bond c is a single bond; bond d is a double bond; and R^7 is null; or
- (iii) Z is $C(=O)$;

R^{2a} is selected from the group consisting of H, halogen, and optionally substituted C_1 - C_6 alkoxy;

R^{2b} is null;

bond b is a single bond; bond c is a double bond; bond d is a single bond; and

R^7 is selected from the group consisting of H, optionally substituted C_1 - C_6 alkyl, and optionally substituted C_3 - C_8 cycloalkyl;

R^{3a} , R^{3b} , R^{4a} , and R^{4b} are each independently selected from the group consisting of H, alkyl-substituted oxetanyl, optionally substituted C_1 - C_6 alkyl, and optionally substituted C_3 - C_8 cycloalkyl;

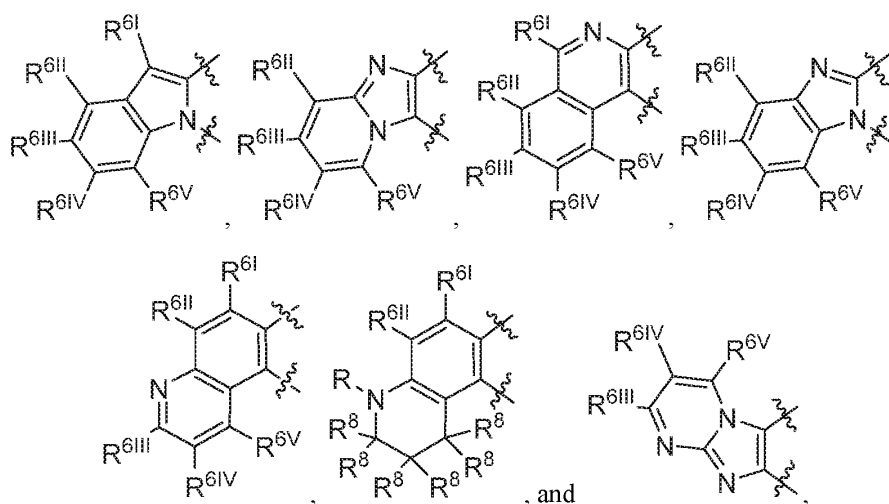
or one pair selected from the group consisting of R^{3a} / R^{3b} , R^{4a} / R^{4b} , and R^{3a} / R^{4a} combine to form a divalent group selected from the group consisting of C_1 - C_6 alkanediyl, $-(CH_2)_nO(CH_2)_n-$, $-(CH_2)_nNR^9(CH_2)_n-$, $-(CH_2)_nS(CH_2)_n-$, -

$(CH_2)_nS(=O)(CH_2)_n-$, and $-(CH_2)_nS(=O)_2(CH_2)_n-$, wherein each occurrence of n is independently selected from the group consisting of 1 and 2 and wherein each

divalent group is optionally substituted with at least one C_1 - C_6 alkyl or halogen;

bond a is single; or bond a is double and R^{3b} and R^{4b} are both null;

X is C or N, and ring A is selected from the group consisting of:



R^{6I} , R^{6II} , R^{6III} , R^{6IV} , and R^V are independently selected from the group consisting of H, halogen, $-CN$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 alkenyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-OR$, C_1 - C_6 haloalkoxy, $-N(R)(R)$, $-NO_2$, $-S(=O)_2N(R)(R)$, acyl, and C_1 - C_6 alkoxy carbonyl,

each occurrence of R is independently selected from the group consisting of H, optionally substituted C₁-C₆ alkyl, C₁-C₆ haloalkyl, R'-substituted C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, optionally substituted (C₁-C₆ alkoxy)-C₁-C₆ alkyl, optionally substituted C₃-C₈ cycloalkyl, and optionally substituted C₁-C₆ acyl,

each occurrence of R' is selected from the group consisting of -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -NHC(=O)O^tBu, -N(C₁-C₆ alkyl)C(=O)O^tBu, and a 5- or 6-membered heterocyclic group, which is optionally N-linked;

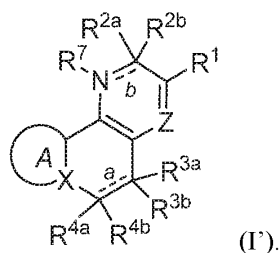
each occurrence of R⁸ is independently selected from the group consisting of H, optionally substituted C₁-C₆ alkyl, and optionally substituted C₃-C₈ cycloalkyl;

each occurrence of R⁹ is independently selected from the group consisting of H and C₁-C₆ alkyl (*e.g.*, methyl or ethyl);

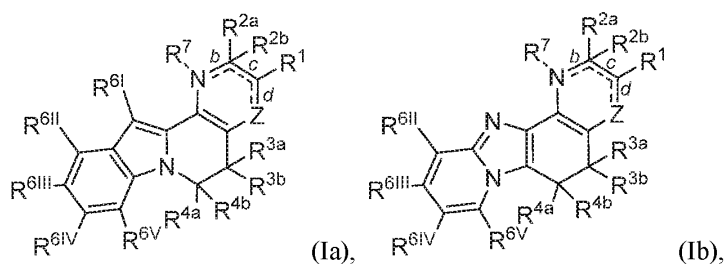
each occurrence of R¹⁰ is independently selected from the group consisting of optionally substituted C₁-C₆ alkyl and optionally substituted phenyl; and,

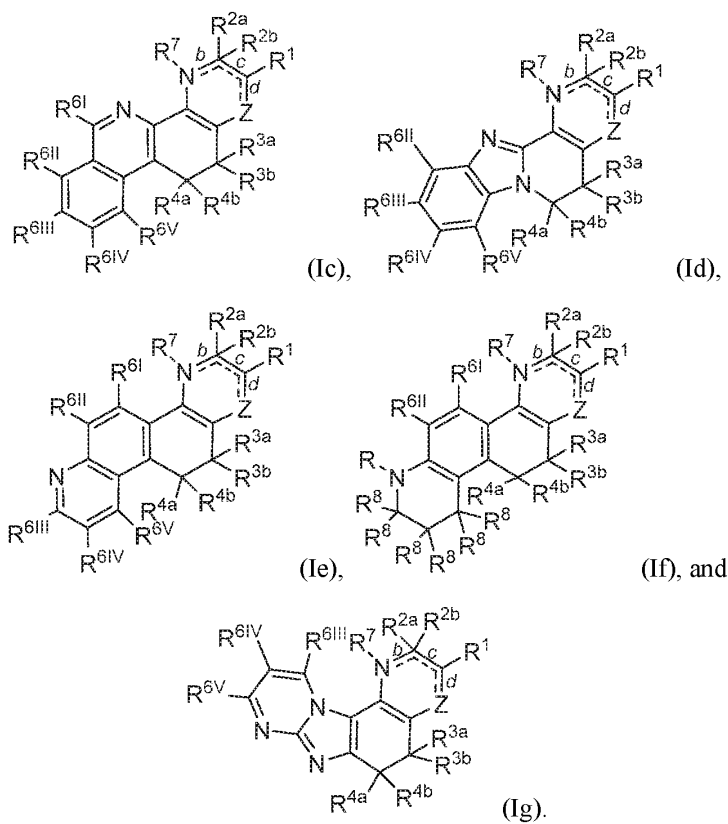
R¹² is selected from the group consisting of H, OH, halogen, C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkyl, and optionally substituted C₃-C₈ cycloalkyl.

2. The compound of claim 1, which is a compound of formula (I'):

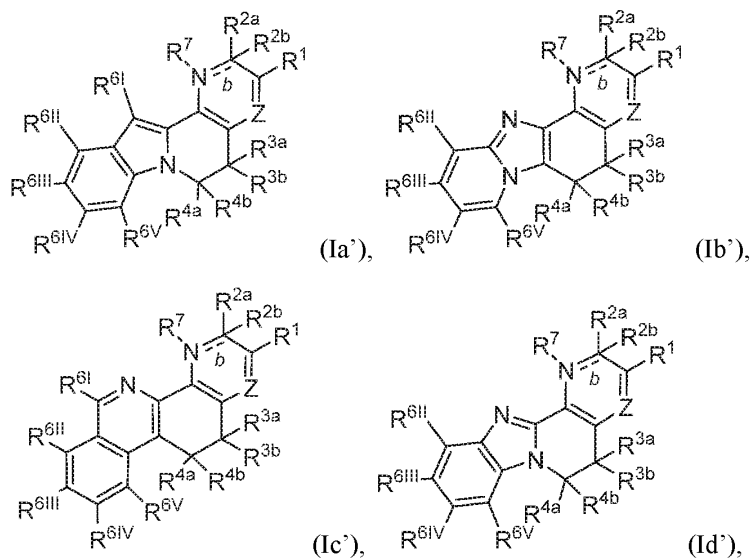


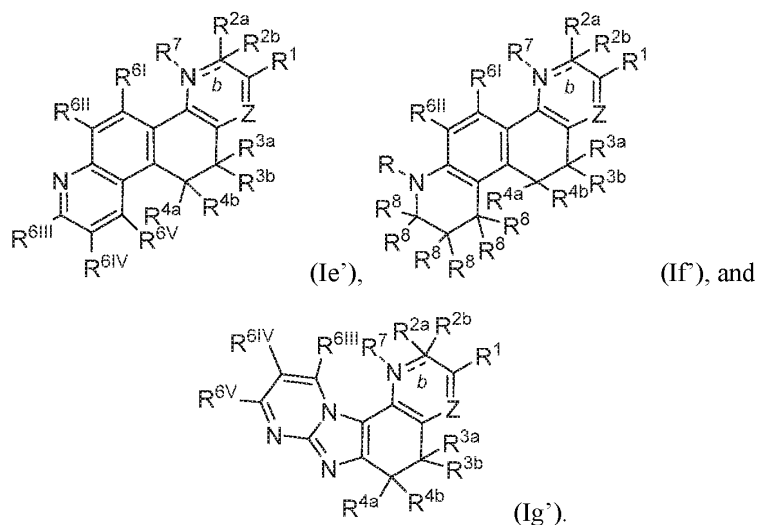
3. The compound of claim 1, which is selected from the group consisting of:





4. The compound of claim 1, which is selected from the group consisting of:





5. The compound of claim 1, wherein at least one of R^{3a} or R^{3b} is independently selected from the group consisting of optionally substituted C₁-C₆ alkyl and optionally substituted C₃-C₈ cycloalkyl.

6. The compound of claim 1, wherein each occurrence of alkyl, alkenyl, cycloalkyl, or acyl is independently optionally substituted with at least one substituent selected from the group consisting of C₁-C₆ alkyl, halogen, -OR'', phenyl, and -N(R'')(R''), wherein each occurrence of R'' is independently H, C₁-C₆ alkyl, or C₃-C₈ cycloalkyl.

7. The compound of claim 1, wherein each occurrence of aryl or heteroaryl is independently optionally substituted with at least one substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, -CN, -OR'', -N(R'')(R''), -NO₂, -S(=O)₂N(R'')(R''), acyl, and C₁-C₆ alkoxy carbonyl, wherein each occurrence of R'' is independently H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl.

8. The compound of claim 1, wherein each occurrence of aryl or heteroaryl is independently optionally substituted with at least one substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, halogen, -CN, -OR'', -N(R'')(R''), and C₁-C₆ alkoxy carbonyl, wherein each occurrence of R'' is independently H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl.

9. The compound of claim 1, wherein at least one applies: R^{3a} is H and R^{3b} is isopropyl; R^{3a} is H and R^{3b} is tert-butyl; R^{3a} is methyl and R^{3b} is isopropyl; R^{3a} is methyl and R^{3b} is tert-butyl; R^{3a} is methyl and R^{3b} is methyl; R^{3a} is methyl and R^{3b} is ethyl; and R^{3a} is ethyl and R^{3b} is ethyl.
10. The compound of claim 1, wherein R^{3a} and R^{3b} are not H.
11. The compound of claim 1, which is selected from the group consisting of:
- 5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid;
 - 5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid;
 - 5-(tert-butyl)-11-ethoxy-4-hydroxy-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid;
 - 5-(tert-butyl)-4-hydroxy-11-(2-methoxyethoxy)-2-oxo-1,2,5,6-tetrahydroindolo[1,2-h][1,7]naphthyridine-3-carboxylic acid;
 - 5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid;
 - 6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid;
 - 5-(tert-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid;
 - 11-(difluoromethoxy)-5-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid;
 - 5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid;
 - 5-isopropyl-11-methoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid;
 - 5-(tert-butyl)-10,11-dimethoxy-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid;
 - 11-(difluoromethoxy)-6-isopropyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid;
 - 5-(tert-butyl)-10,11-dimethoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',1':2,3]imidazo[4,5-h]quinoline-3-carboxylic acid;

5-(tert-butyl)-4-hydroxy-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid;

5-(tert-butyl)-11-(difluoromethoxy)-4-hydroxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid;

5-(tert-butyl)-11-(difluoromethoxy)-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid;

5-(tert-butyl)-11-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[4,5]imidazo[1,2-h][1,7]naphthyridine-3-carboxylic acid;

6-(tert-butyl)-12-(difluoromethoxy)-7-hydroxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid;

6-(tert-butyl)-12-(difluoromethoxy)-1-(3-methoxypropyl)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid;

1-acetyl-6-(tert-butyl)-12-(difluoromethoxy)-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid;

6-(tert-butyl)-12-(difluoromethoxy)-1-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid;

6-(tert-butyl)-12-(difluoromethoxy)-1-ethyl-9-oxo-1,2,3,4,5,6,9,10-octahydroquinolino[7,8-f]quinoline-8-carboxylic acid;

6-(tert-butyl)-12-methoxy-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid;

6-(tert-butyl)-12-(difluoromethoxy)-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid;

6-(tert-butyl)-12-(difluoromethoxy)-10-methyl-9-oxo-5,6,9,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid;

12-(tert-butyl)-6-methoxy-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid;

12-(tert-butyl)-6-methoxy-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid;

12-(tert-butyl)-6-chloro-4-methyl-3-oxo-3,4,11,12-tetrahydrobenzo[c][1,10]phenanthroline-2-carboxylic acid;

6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-10-methyl-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid; and

6-(tert-butyl)-12-(difluoromethoxy)-9-methoxy-7-oxo-5,6,7,10-tetrahydroquinolino[7,8-f]quinoline-8-carboxylic acid.

12. A pharmaceutical composition comprising at least one compound of claim 1 and a pharmaceutically acceptable carrier.
13. The pharmaceutical composition of claim 12, further comprising at least one additional agent useful for treating hepatitis virus infection.
14. The pharmaceutical composition of claim 13, wherein the at least one additional agent comprises at least one selected from the group consisting of reverse transcriptase inhibitors, capsid inhibitors, cccDNA formation inhibitors, RNA destabilizers, oligomeric nucleotides targeted against the HBV genome, immunostimulators, and GalNAc-siRNA conjugates targeted against an HBV gene transcript.
15. The pharmaceutical composition of claim 14, wherein the oligomeric nucleotide comprises one or more siRNAs.
16. The pharmaceutical composition of claim 13, wherein the hepatitis virus is at least one selected from the group consisting of hepatitis B virus (HBV) and hepatitis D virus (HDV).
17. A method of treating or preventing hepatitis virus infection in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of at least one compound of claim 1 or at least one pharmaceutical composition of claim 12.
18. The method of claim 17, wherein the subject is infected with hepatitis B virus (HBV).
19. The method of claim 17, wherein the subject is infected with hepatitis D virus (HDV).
20. The method of claim 17, wherein the subject is infected with HBV and HDV.
21. A method of reducing or minimizing levels of at least one selected from the group consisting of hepatitis B virus surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), hepatitis B core protein, and pregenomic (pg) RNA, in a HBV-infected subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of

at least one compound of claim 1 or at least one pharmaceutical composition of claim 12.

22. The method of claim 17 or 21, wherein the at least one compound is administered to the subject in a pharmaceutically acceptable composition.

23. The method of claim 17 or 21, wherein the subject is further administered at least one additional agent useful for treating the hepatitis virus infection.

24. The method of claim 23, wherein the at least one additional agent comprises at least one selected from the group consisting of reverse transcriptase inhibitors, capsid inhibitors, cccDNA formation inhibitors, RNA destabilizers, oligomeric nucleotides targeted against the HBV genome, immunostimulators, and GalNAc-siRNA conjugates targeted against an HBV gene transcript.

25. The method of claim 24, wherein the oligomeric nucleotide comprises one or more siRNAs.

26. The method of claim 23, wherein the subject is co-administered the at least one compound and the at least one additional agent.

27. The method of claim 23, wherein the at least one compound and the at least one additional agent are coformulated.

28. The method of claim 17 or 21, wherein the subject is further infected with HDV.

29. The method of claim 17 or 21, wherein the subject is a mammal.

30. The method of claim 29, wherein the mammal is a human.