(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 December 2011 (22.12.2011)

PCT

(10) International Publication Number
WO 2011/159920 A1

(51) International Patent Classification:
A01N 43/90 (2006.01) *A61K 31/519* (2006.01)

(21) International Application Number:
PCT/US2011/040731

(22) International Filing Date:
16 June 2011 (16.06.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/355,816 17 June 2010 (17.06.2010) US

(71) Applicant *(for all designated States except US)*: **CONCERT PHARMACEUTICALS, INC.** [US/US]; 99 Hayden Avenue, Suite 500, Lexington, MA 02421 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **MASSE, Craig** [US/US]; 122 Hamilton Street, #2, Cambridge, MA 02139 (US).

(74) Agents: **BUTEAU, Kristen, C.** et al.; Choate, Hall & Stewart LLP, Two International Place, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

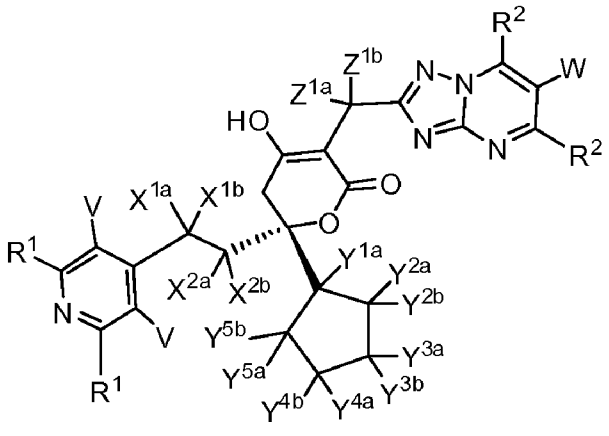
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: *[5,6]-DIHYDRO-2H-PYRAN-2-ONE DERIVATIVES*



(I)

(57) Abstract: This invention relates to novel [5,6]-dihydro-2h-pyran-2-one derivatives, tautomers thereof, and a pharmaceutical salts of the compounds or tautomers. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering a hepatitis C virus RNA polymerase inhibitor.

WO 2011/159920 A1

[5,6]-DIHYDRO-2H-PYRAN-2-ONE DERIVATIVES

Related Applications

[1] This application claims the benefit of U.S. Application No. 61/355,816, filed June 17, 2010. The entire teachings of the above application are incorporated herein by reference.

Background of the Invention

[2] Many current medicines suffer from poor absorption, distribution, metabolism and/or excretion (ADME) properties that prevent their wider use or limit their use in certain indications. Poor ADME properties are also a major reason for the failure of drug candidates in clinical trials. While formulation technologies and prodrug strategies can be employed in some cases to improve certain ADME properties, these approaches often fail to address the underlying ADME problems that exist for many drugs and drug candidates. One such problem is rapid metabolism that causes a number of drugs, which otherwise would be highly effective in treating a disease, to be cleared too rapidly from the body. A possible solution to rapid drug clearance is frequent or high dosing to attain a sufficiently high plasma level of drug. This, however, introduces a number of potential treatment problems such as poor patient compliance with the dosing regimen, side effects that become more acute with higher doses, and increased cost of treatment. A rapidly metabolized drug may also expose patients to undesirable toxic or reactive metabolites.

[3] Another ADME limitation that affects many medicines is the formation of toxic or biologically reactive metabolites. As a result, some patients receiving the drug may experience toxicities, or the safe dosing of such drugs may be limited such that patients receive a suboptimal amount of the active agent. In certain cases, modifying dosing intervals or formulation approaches can help to reduce clinical adverse effects, but often the formation of such undesirable metabolites is intrinsic to the metabolism of the compound.

[4] In some select cases, a metabolic inhibitor will be co-administered with a drug that is cleared too rapidly. Such is the case with the protease inhibitor class of drugs that are used to treat HIV infection. The FDA recommends that these drugs be co-dosed with

ritonavir, an inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4), the enzyme typically responsible for their metabolism (see Kempf, D.J. et al., Antimicrobial agents and chemotherapy, 1997, 41(3): 654-60). Ritonavir, however, causes adverse effects and adds to the pill burden for HIV patients who must already take a combination of different drugs. Similarly, the CYP2D6 inhibitor quinidine has been added to dextromethorphan for the purpose of reducing rapid CYP2D6 metabolism of dextromethorphan in a treatment of pseudobulbar affect. Quinidine, however, has unwanted side effects that greatly limit its use in potential combination therapy (see Wang, L et al., Clinical Pharmacology and Therapeutics, 1994, 56(6 Pt 1): 659-67; and FDA label for quinidine at www.accessdata.fda.gov).

[5] In general, combining drugs with cytochrome P450 inhibitors is not a satisfactory strategy for decreasing drug clearance. The inhibition of a CYP enzyme's activity can affect the metabolism and clearance of other drugs metabolized by that same enzyme. CYP inhibition can cause other drugs to accumulate in the body to toxic levels.

[6] A potentially attractive strategy for improving a drug's metabolic properties is deuterium modification. In this approach, one attempts to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites by replacing one or more hydrogen atoms with deuterium atoms. Deuterium is a safe, stable, non-radioactive isotope of hydrogen. Compared to hydrogen, deuterium forms stronger bonds with carbon. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability. At the same time, because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

[7] Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, MI et al, J Pharm Sci, 1975, 64:367-91; Foster, AB, Adv Drug Res 1985, 14:1-40 ("Foster"); Kushner, DJ et al, Can J Physiol Pharmacol 1999, 79-88; Fisher, MB et al, Curr Opin Drug Discov Devel, 2006, 9:101-09 ("Fisher")). The results have been variable and unpredictable. For some compounds deuteration caused decreased

metabolic clearance *in vivo*. For others, there was no change in metabolism. Still others demonstrated increased metabolic clearance. The variability in deuterium effects has also led experts to question or dismiss deuterium modification as a viable drug design strategy for inhibiting adverse metabolism (see Foster at p. 35 and Fisher at p. 101).

[8] The effects of deuterium modification on a drug's metabolic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. Only by actually preparing and testing a deuterated drug can one determine if and how the rate of metabolism will differ from that of its non-deuterated counterpart. *See,* for example, Fukuto et al. (J. Med. Chem. 1991, 34, 2871-76). Many drugs have multiple sites where metabolism is possible. The site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug.

[9] Filibuvir, also known as (*R*)-6-cyclopentyl-6-(2-(2,6-diethylpyridin-4-yl)ethyl)-3-((5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl)-4-hydroxy-5,6-dihydro-2H-pyran-2-one, acts as an inhibitor of the NS5B RNA polymerase of the hepatitis C virus (HCV). Filibuvir is currently in clinical trials for the treatment of hepatitis C virus (HCV).

[10] Despite the beneficial activities of filibuvir, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

Summary of the Invention

[11] This invention relates to novel 5,6-dihydro-2H-pyran-2-one derivatives and pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering an inhibitor of the NS5B RNA polymerase of the HCV virus. The compounds and compositions of the invention are useful, for example, for the treatment of chronic hepatitis C viral infection.

Definitions

[12] The term "treat" means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

[13] "Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

[14] It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of filibuvir will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada, E et al., Seikagaku, 1994, 66:15; Gannes, LZ et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725.

[15] In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

[16] The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

[17] In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3

(99.5% deuterium incorporation).

[18] The term "isotopologue" refers to a species in which the chemical structure differs from a specific compound of this invention only in the isotopic composition thereof.

[19] The term "compound," when referring to a compound of this invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues *in toto* will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues *in toto* will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

[20] The invention also provides salts of the compounds of the invention.

[21] A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

[22] Throughout the application all references to "a compound of Formula A" or "a compound of Formula I" or "a compound of the invention" or "a compound of claim" include, within the scope of each such term, synthetically feasible pharmaceutically acceptable salts of such a compound.

[23] The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to

a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A "pharmaceutically acceptable counterion" is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

[24] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

[25] The compounds of the present invention (e.g., compounds of Formula I), may contain an asymmetric carbon atom, for example, as the result of deuterium substitution or otherwise. As such, compounds of this invention can exist as either individual enantiomers, or mixtures of the two enantiomers. Accordingly, a compound of the present invention may exist as either a racemic mixture or a scalemic mixture, or as individual respective stereoisomers that are substantially free from another possible stereoisomer. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers,

more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers are present. Methods of obtaining or synthesizing an individual stereoisomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

[26] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

[27] The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

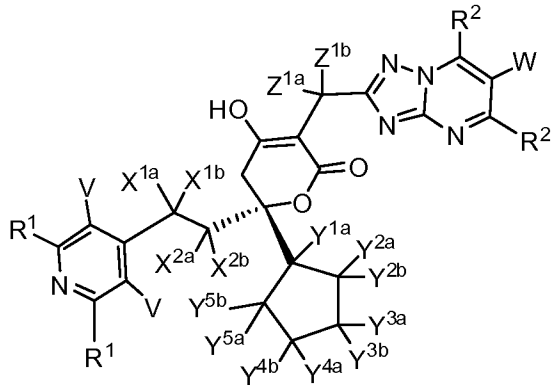
[28] "D" and "d" both refer to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers. "Tert" and "t-" each refer to tertiary. "US" refers to the United States of America.

[29] "Substituted with deuterium" refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms.

[30] Throughout this specification, a variable may be referred to generally (e.g.,"each Y") or may be referred to specifically (e.g., Y^{1a}, Y^{2a}, Y^{2b}, etc.). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

Therapeutic Compounds

[31] The present invention provides a compound of Formula I:



Formula I

or a tautomer thereof, or a pharmaceutical salt of the compound or tautomer wherein:

each R^1 is the same and is selected from CD_3CD_2-, CD_3CH_2-, CH_3CD_2-, and CH_3CH_2-;

each R^2 is the same and is selected from -CD_3, -CD_2H, -CDH_2, and -CH_3;

each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is independently hydrogen or deuterium;

each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is independently hydrogen or deuterium;

each of Z^{1a} and Z^{1b} is independently hydrogen or deuterium;

W is hydrogen or deuterium; and

each V is the same and is selected from hydrogen and deuterium,

provided that when R^1 is CH_3CH_2-, each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is hydrogen, each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is hydrogen, each of Z^{1a} and Z^{1b} is hydrogen, W is hydrogen, and each V is hydrogen, then R^2 is -CD_3, -CD_2H, or -CDH_2.

[32] In one embodiment R^1 is CD_3CD_2-, CD_3CH_2-, CH_3CD_2-, or CH_3CH_2- ; R^2 is -CD_3 or -CH_3; X^{1a} and X^{1b} are the same; X^{2a} and X^{2b} are the same; Y^{2a} and Y^{2b} are the same; Y^{3a} and Y^{3b} are the same; Y^{4a} and Y^{4b} are the same; Y^{5a} and Y^{5b} are the same and; Z^{1a} and Z^{1b} are the same.

[33] In one embodiment, each R^1 is the same and is CD_3CD_2- or CH_3CH_2- .

[34] In one embodiment, each X is the same.

[35] In one embodiment, each one of Y^{2a}, Y^{2b}, Y^{5a}, and Y^{5b} is the same.

[36] In one embodiment, each one of Y^{3a}, Y^{3b}, Y^{4a}, and Y^{4b} is the same.

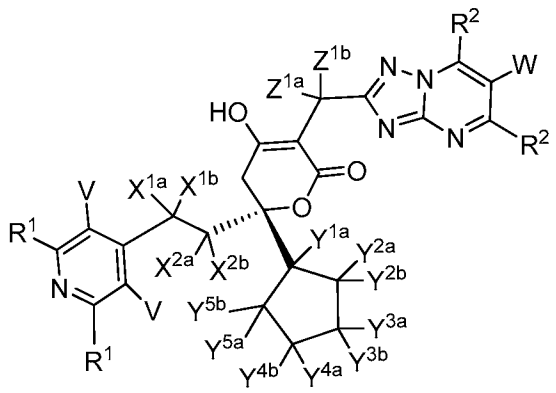
[37] In one embodiment, each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is the same.

[38] In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

[39] In one embodiment of Formula I, each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is deuterium; each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is the same; and each of Z^{1a} and Z^{1b} is the same. In one aspect, each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is deuterium. In another aspect, each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is hydrogen. In one aspect, each of Z^{1a} and Z^{1b} is deuterium. In another aspect, each of Z^{1a} and Z^{1b} is hydrogen.

[40] In one embodiment of Formula I, each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is D; each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is the same; each of Z^{1a} and Z^{1b} is the same; and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1 below, or a tautomer thereof, or a pharmaceutical salt of the compound or tautomer, wherein any atom not designated as deuterium is present at its natural isotopic abundance:

[41] Table 1. Exemplary Compounds of Formula I



Formula I

Cmpd	R^1	R^2	Each X	Each Z	W	V
100	CD_3CD_2	CD_3	D	D	D	D
101	CD_3CD_2	CD_3	H	D	D	D
102	CD_3CD_2	CD_3	D	H	D	D
103	CD_3CD_2	CD_3	H	H	D	D
104	CD_3CD_2	CH_3	D	D	H	D

Cmpd	R^1	R^2	Each X	Each Z	W	V
105	CD_3CD_2	CH_3	H	D	H	D
106	CD_3CD_2	CH_3	D	H	H	D
107	CD_3CD_2	CH_3	H	H	H	D
108	CH_3CH_2	CD_3	D	D	D	H
109	CH_3CH_2	CD_3	H	D	D	H
110	CH_3CH_2	CD_3	D	H	D	H
111	CH_3CH_2	CD_3	H	H	D	H
112	CH_3CH_2	CH_3	D	D	H	H
113	CH_3CH_2	CH_3	H	D	H	H
114	CH_3CH_2	CH_3	D	H	H	H
115	CH_3CH_2	CH_3	H	H	H	H

wherein:

"each X" refers to each of X^{1a}, X^{1b}, X^{2a}, and X^{2b};

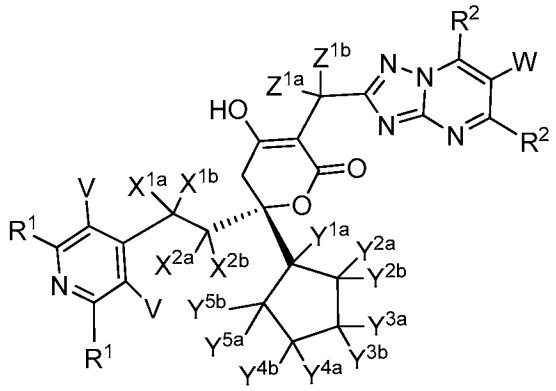
"each "Z" refers to each of Z^{1a} and Z^{1b}; and

each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is D.

[42] In one embodiment of Formula I, each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is hydrogen; each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is the same; and each of Z^{1a} and Z^{1b} is the same. In one aspect, each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is deuterium. In another aspect, each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is hydrogen. In one aspect, each of Z^{1a} and Z^{1b} is deuterium. In another aspect, each of Z^{1a} and Z^{1b} is hydrogen.

[43] In another embodiment of Formula I, each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is hydrogen; each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is the same; each of Z^{1a} and Z^{1b} is the same; and the compound is selected from any one of the compounds (Cmpd) set forth in Table 2 below, or a tautomer thereof, or a pharmaceutical salt of the compound or tautomer, wherein any atom not designated as deuterium is present at its natural isotopic abundance:

[44] Table 2. Exemplary Compounds of Formula I



Formula I

Cmpd	R^1	R^2	Each X	Each Z	W	V
200	CD_3CD_2	CD_3	D	D	D	D
201	CD_3CD_2	CD_3	D	H	D	D
202	CD_3CD_2	CD_3	H	H	D	D
203	CD_3CD_2	CH_3	D	D	H	D
204	CD_3CD_2	CD_3	H	D	D	D
205	CD_3CD_2	CH_3	D	H	H	D
206	CD_3CD_2	CH_3	H	D	H	D
207	CD_3CD_2	CH_3	H	H	H	D
208	CH_3CH_2	CD_3	D	D	D	H
209	CH_3CH_2	CD_3	D	H	D	H
210	CH_3CH_2	CD_3	H	D	D	H
211	CH_3CH_2	CD_3	H	H	D	H
212	CH_3CH_2	CH_3	D	D	H	H
213	CH_3CH_2	CH_3	D	H	H	H
214	CH_3CH_2	CH_3	H	D	H	H

wherein:

"each X" refers to each of X^{1a}, X^{1b}, X^{2a}, and X^{2b}; and

"each "Z" refers to each of Z^{1a} and Z^{1b}; and

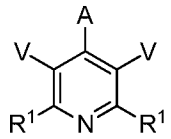
each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is H.

[45] In one embodiment of Formula I, each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is deuterium; each of X^{1a} and X^{1b} is the same, each of X^{2a} and X^{2b} is the same, and one set of either X^{1a} and X^{1b} or X^{2a} and X^{2b} is D; and each of Z^{1a} and Z^{1b} is the same. In one aspect, each of X^{1a} and X^{1b} is D and each of X^{2a} and X^{2b} is H. In another aspect,

each of X^{1a} and X^{1b} is H and each of X^{2a} and X^{2b} is D. In one aspect, each of Z^{1a} and Z^{1b} is deuterium. In another aspect, each of Z^{1a} and Z^{1b} is hydrogen.

[46] In one embodiment of Formula I, each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is hydrogen; each of X^{1a} and X^{1b} is the same, each of X^{2a} and X^{2b} is the same, and one set of either X^{1a} and X^{1b} or X^{2a} and X^{2b} is D; and each of Z^{1a} and Z^{1b} is the same. In one aspect, each of X^{1a} and X^{1b} is D and each of X^{2a} and X^{2b} is H. In another aspect, each of X^{1a} and X^{1b} is H and each of X^{2a} and X^{2b} is D. In one aspect, each of Z^{1a} and Z^{1b} is deuterium. In another aspect, each of Z^{1a} and Z^{1b} is hydrogen.

[47] In one embodiment the invention is directed to a compound of Formula IIa or a salt thereof:



IIa

wherein

each R^1 is the same and is selected from CD_3CD_2-, CD_3CH_2-, CH_3CD_2-, and CH_3CH_2-;

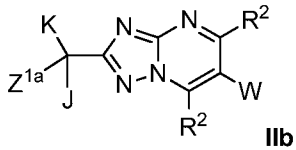
each V is the same and is selected from hydrogen and deuterium; and

A is –OH or –Br,

provided that if each R^1 is CH_3CH_2-, then each V is deuterium.

[48] In one embodiment, each R^1 is CD_3CD_2-.

[49] In one embodiment the invention is directed to a compound of Formula IIb or a salt thereof:



IIb

wherein:

each R^2 is the same and is selected from $-CD_3$, $-CD_2H$, $-CDH_2$, and $-CH_3$;

W is hydrogen or deuterium;

Z^{1a} is hydrogen or deuterium;

and either

(i) J is OH, and K and Z^{1a} are the same; or

(ii) J and K taken together with the carbon to which they are attached form C(O); provided that if each R^2 is $-CH_3$ and W is hydrogen, then Z^{1a} is deuterium.

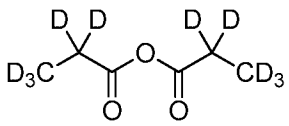
[50] The synthesis of compounds of Formula I may be readily achieved by synthetic chemists of ordinary skill by reference to the Exemplary Synthesis and Examples disclosed herein. Relevant procedures analogous to those of use for the preparation of filibuvir and intermediates thereof are disclosed, for instance in Li, H, et al, J Med Chem 2009, 52:1255-1258; Li, H, et al, Bioorg Med Chem Lett 2006, 16:834-4838; Li, H, et al, J Med Chem 2007, 50:3969-3972; Scott, R W, et al, Org Proc Res Dev 2006, 10:814-821 and PCT Publication No. WO 2006/018725.

[51] Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

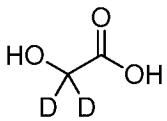
Exemplary Synthesis

[52] Compounds of Formula I may be conveniently prepared as described in the following Schemes, which are not intended to be limiting in any way.

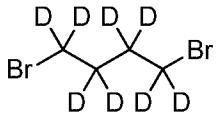
[53] The following deuterated reagents and building blocks that are useful in the preparation of the compounds of the invention are commercially available:



1



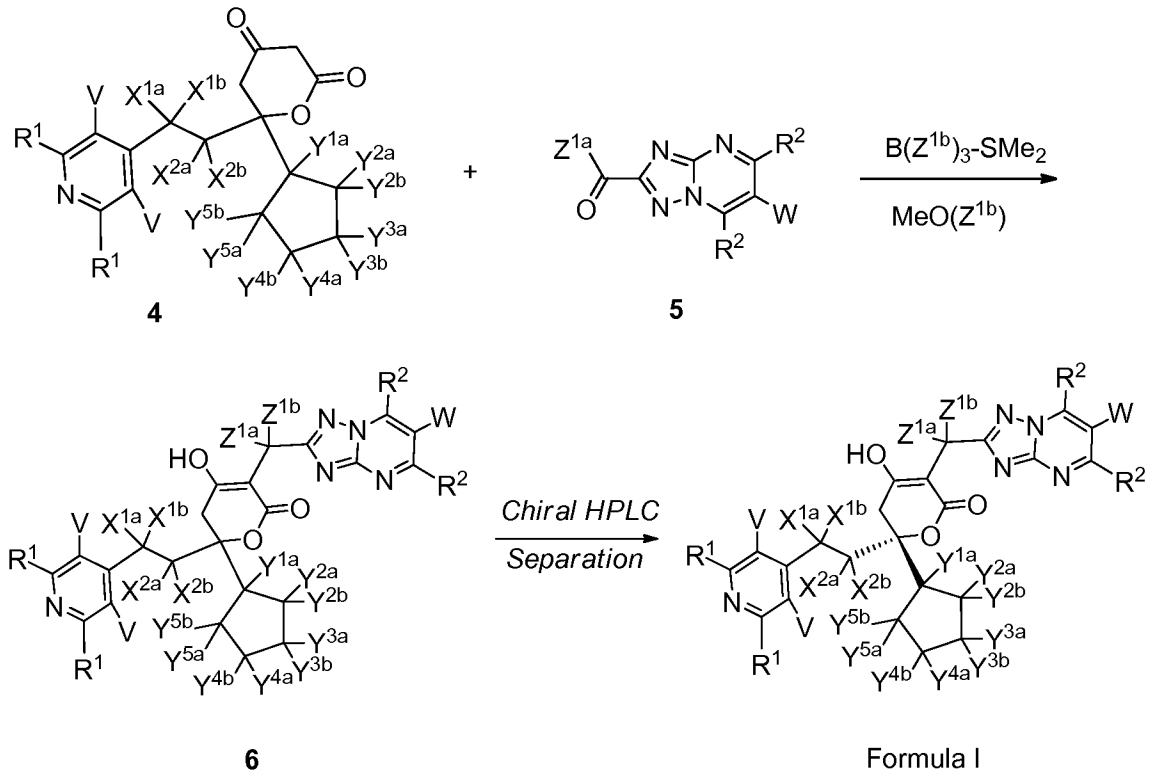
2



3

[54] A convenient method for synthesizing compounds of Formula I is depicted in Scheme 1.

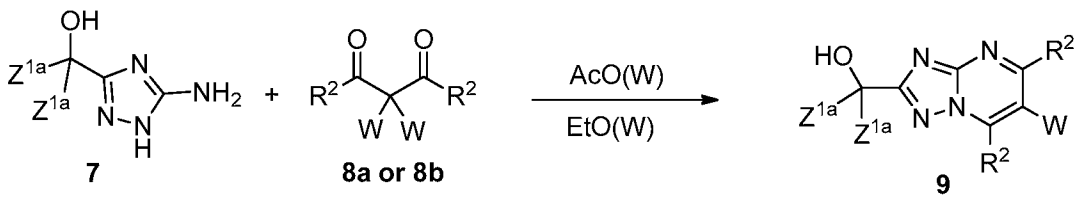
[55] Scheme 1. A Convenient Route to Compounds of Formula I.

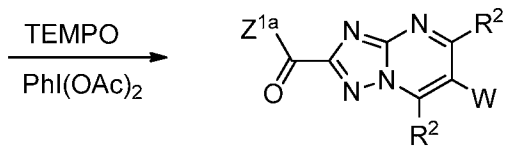


[56] Treatment of an appropriately deuterated racemic dihydropyrone **4** with appropriately deuterated triazolopyrimidinyl aldehyde **5** in the presence of borane-methyl sulfide or d3-borane-methyl sulfide in a manner analogous to the procedure described by Li, H. et al., Journal of Medicinal Chemistry 2009, 52, pp. 1255-1258 affords the racemic deuterated analogs **6**. Using the protocols of Li et al., chiral HPLC separation of racemic material affords the desired enantiomer of Formula I.

[57] The synthesis of the triazolopyrimidinyl aldehyde **5** is shown in Scheme 2, wherein $Z^{1a} = Z^{1b}$.

[58] Scheme 2. Route to Intermediates **5**.



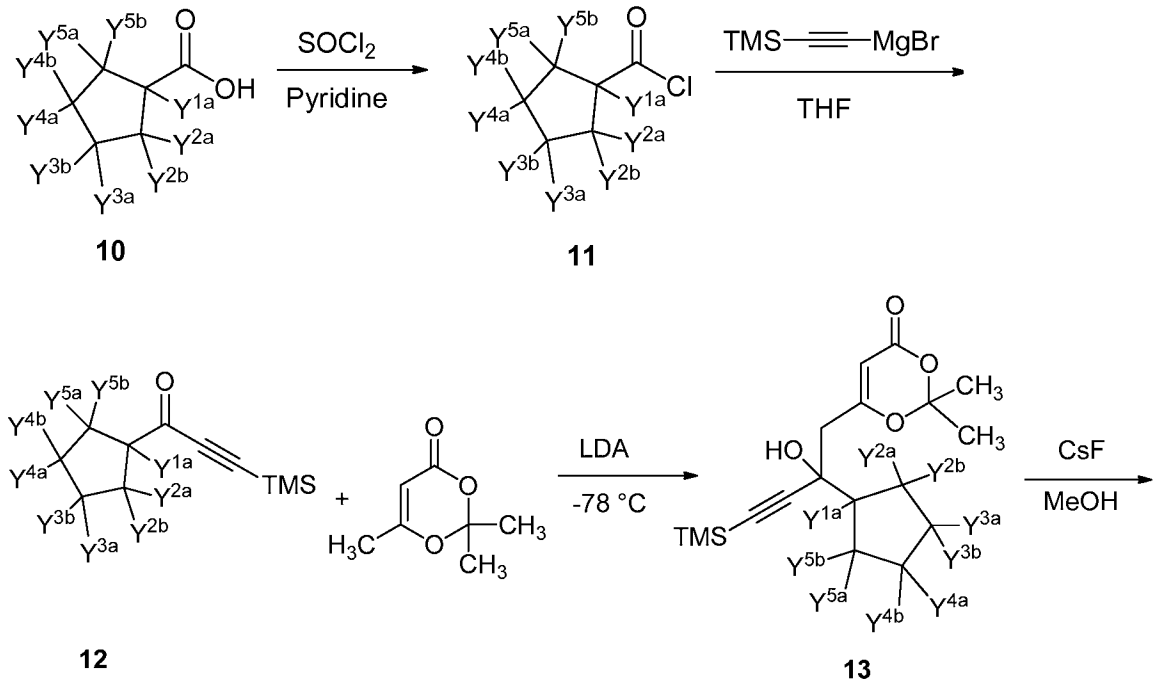


5

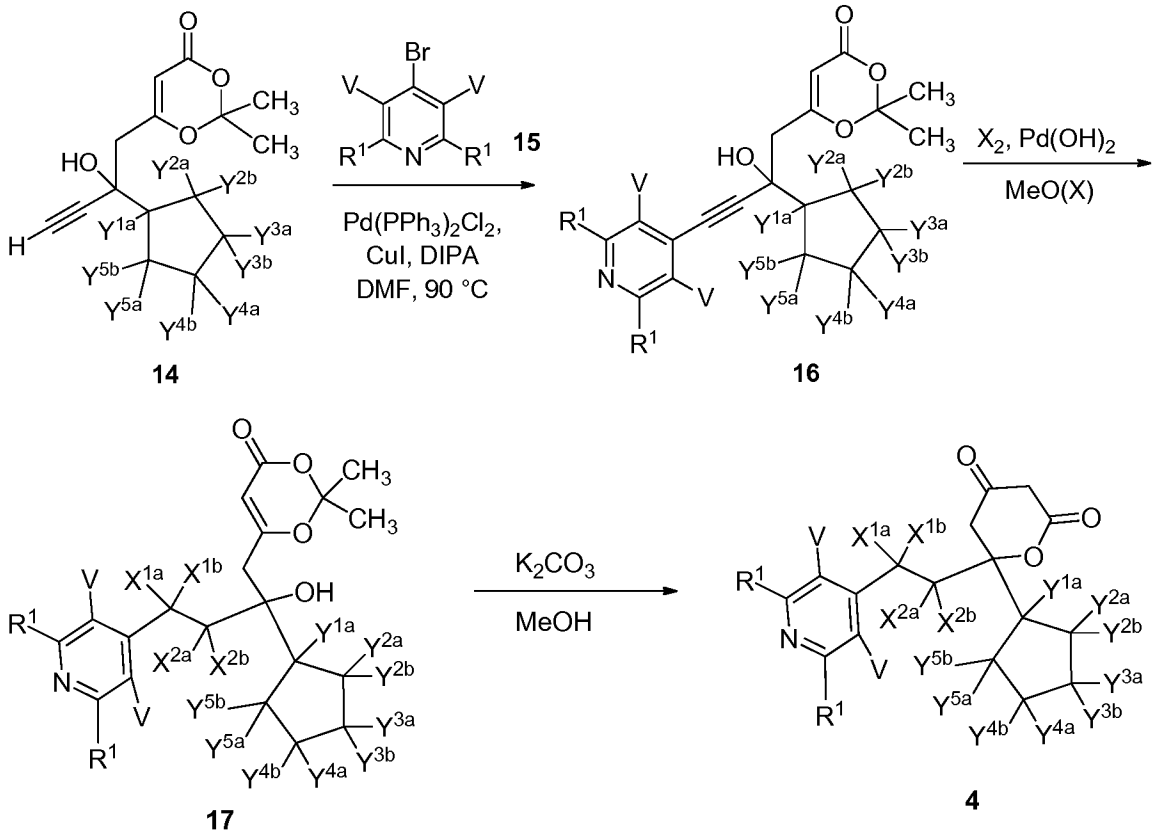
[59] Treatment of the appropriately deuterated triazole **7** (where **7** is prepared from aminoguanidine and either glycolic acid or d2-glycolic acid **2** in a manner analogous to the procedure described by Allen, CFH et al, J Org Chem 1959, 24:793-796) with either d8-acetylacetone **8a** (wherein each W is D and each R^2 is $-CD_3$) prepared according to the procedure described by Elguero, J et al, J Label Comp Radiopharm 1990, 28:967-970) or commercially available acetylacetone **8b** (wherein each W is H and each R^2 is each R^2 is $-CH_3$), in a manner analogous to the procedure described by Scott, RW et al, Org Proc Res Dev 2006, 10:814-821, gives the triazolopyrimidinyl methanol **9**. Utilizing the same methods, oxidation of **9** with 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) in the presence of iodobenzene diacetate affords **5**.

[60] The synthesis of dihydropyrone **4**, wherein $X^{1a} = X^{1b} = X^{2a} = X^{2b}$, is shown in Scheme 3.

[61] Scheme 3. Route to Intermediates **4**.



10 11 12 13

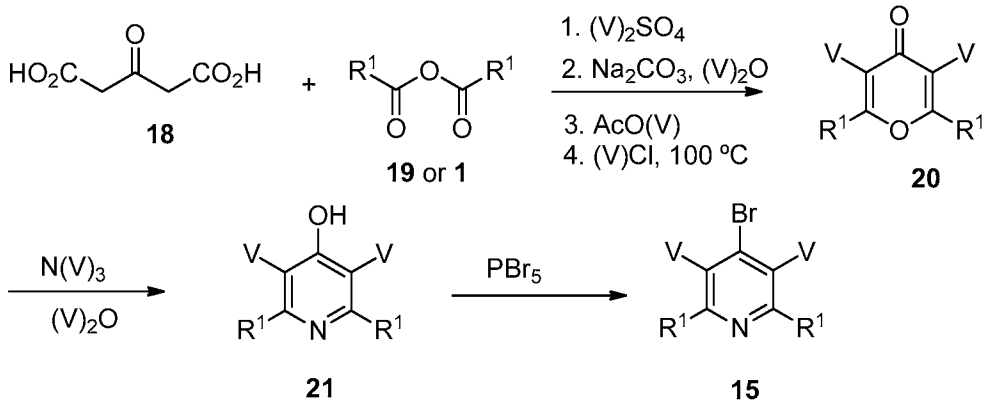


[62] Treatment of the appropriately deuterated cyclopentane carboxylic acid **10** (d9-cyclopentane carboxylic acid can be prepared from commercially available d8-1,4-dibromobutane **3** using the procedure described by Dmowski, N et al, J Fluorine Chem 2000, 102:41-146) with thionyl chloride in the presence of pyridine according to the procedure described by Beaulieu, PL et al, Bioorg Med Chem Lett 2006, 16:4987-4993 gives the acid chloride **11**. Treatment of **11** with trimethylsilyl ethynyl magnesium bromide in a manner analogous to the procedure described by Scott, RW et al, Org Proc Res Devel 2006, 10: 814-821 gives the alkynone **12** deuterated as appropriate. Treatment of the lithium enolate of 2,2,6-trimethyl-4H-1,3-dioxin-4-one (prepared by deprotonation of 2,2,6-trimethyl-4H-1,3-dioxin-4-one with lithium diisopropylamide) with **12** using a procedure analogous to that described by Li, H et al, J Med Chem 2007, 50:3969-3972 provides the tertiary alcohol intermediate **13** as a racemic mixture. Using the Scott et al protocol, deprotection of the alkynyl-trimethylsilyl group of **13** with cesium fluoride in methanol gives the terminal acetylene **14**. Sonogashira coupling of **14** with the appropriately deuterated 4-bromopyridine **15,** using a procedure analogous to that described by Li, H et al, J Med Chem 2009, 52:1255-1258, provides the propargylic

alcohol **16**. Using the aforementioned protocol from Li et al., hydrogenation or deuterogenation of **16** in the presence of a palladium catalyst gives the saturated tertiary alcohol **17** which, upon treatment with potassium carbonate in methanol, undergoes an acetonide deprotection and concomitant cyclization to provide **4**.

[63] The synthesis of 4-bromopyridine **15** wherein each R^1 is selected from CD_3CD_2- and CH_3CH_2- is shown in Scheme 4.

[64] Scheme 4. Route to Intermediates **15**.



[65] Treatment of acetonedicarboxylic acid **18** with the propionic anhydride **19** (where each R^1 is CH_3CH_2-) or **1** (where each R^1 is CD_3CD_2-) in an acidic medium, using a procedure analogous to that described by Li, H et al, J Med Chem 2009, 52:1255-1258, affords the 2,6-diethyl-4-pyrone **20**. Using the aforementioned protocol from Li et al., treatment of **20** with either ammonia or d3-ammonia in water or deuterated water, respectively gives the 2,6-diethyl-pyridin-4-ol **21**. Finally, treatment of **21** with phosphorous pentabromide affords **15**.

[66] Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene, TW et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser, L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette, L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

[67] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

Compositions

[68] The invention also provides pharmaceutical compositions comprising an effective amount of a compound of Formula I (e.g., including any of the formulae herein), or a tautomer thereof, or a pharmaceutical salt of the compound or tautomer; and a pharmaceutically acceptable carrier. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

[69] In some embodiments, the present invention provides a pyrogen-free pharmaceutical composition comprising an effective amount of a compound of Formula I (e.g., including any of the formulae herein), or a tautomer thereof, or a pharmaceutical salt of the compound or tautomer; and a pharmaceutically acceptable carrier.Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[70] If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

[71] Another known method of enhancing bioavailability is the use of an amorphous

form of a compound of this invention optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See United States patent 7,014,866; and United States patent publications 20060094744 and 20060079502.

[72] The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000).

[73] Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[74] In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

[75] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[76] Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

[77] Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

[78] Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

[79] The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is

solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[80] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz JD and Zaffaroni AC, US Patent 6,803,031, assigned to Alexza Molecular Delivery Corporation.

[81] Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

[82] Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

[83] Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

[84] According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

[85] According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

[86] According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

[87] According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

[88] Where an organ or tissue is accessible because of removal from the subject, such organ or tissue may be bathed in a medium containing a composition of this invention, a

composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

[89] In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as filibuvir. Such agents include beta blockers, aldose reductase inhibitors, NSAIDs, $5HT_{1D}$ agonists, dopamine D_2 receptor antagonists, secale alkaloids, a second calcium channel blocker and neurokinin antagonists.

[90] In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

[91] In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat the target disorder.

[92] The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., Cancer Chemother. Rep, 1966, 50: 219. Body surface area may be approximately determined from height and weight of the subject. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

[93] In one embodiment, an effective amount of a compound of this invention can range from 10 mg to 200 mg per day, from 50-100 mg/day, or from 20-50 mg/day.

[94] Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of

co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for filibuvir.

[95] For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. *See*, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

[96] Second therapeutic agents that act synergistically with the compounds of this invention allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

[97] In another embodiment, the invention provides a method of inhibiting hepatitis C virus polymerase activity comprising contacting the polymerase with one or more compounds of Formula I or or a tautomer thereof, or a pharmaceutical salt of the compound or tautomer herein.

[98] According to another embodiment, the invention provides a method of treating a subject suffering from an infection with hepatitis C virus, comprising the step of administering to the subject in need thereof an effective amount of a compound or a composition of this invention.

[99] In another embodiment, the invention provides a method of inhibiting hepatitis C virus replication in a subject previously diagnosed as being infected with hepatitis C

virus, comprising the step of administering to the subject in need thereof an effective amount of a compound or a composition of this invention.

[100] Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

[101] In another embodiment, any of the above methods of treatment comprises the further step of co-administering to the subject in need thereof one or more second therapeutic agents, for example those selected from, for example, HCV inhibitors such as ribavirin, consensus interferon (Infergen), albuferon and other Long-Acting Interferons, natural interferon, interferon omega, viramidine, telaprevir, boceprevir, PF-0341390, Debio 025, PSI-7977, TMC-435, ITX5061, VX-759, narlaprevir, BMS-790052, GS 9190, A-832, BI 207127, vaniprevir, ANA598, RG7227, IDX-184; or HIV inhibitors such as nelfinavir, delavirdine, indinavir, nevirapine, saquinavir, and tenofovir.

[102] The term "co-administered" as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

[103] Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well

within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

[104] In one embodiment of the invention, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

[105] In yet another aspect, the invention provides the use of a compound of Formula I or a tautomer thereof, or a pharmaceutical salt of the compound or tautomer, alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I or a pharmaceutically acceptable salt thereof or a tautomer thereof for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

Example 1. Evaluation of Metabolic Stability

[106] ***Microsomal Assay:*** Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, KS). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

[107] ***Determination of Metabolic Stability:*** 7.5 mM stock solutions of test compounds are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5-50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes are added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 12.5-50 μM test compound is added to the microsomes and the

mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25-1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM $MgCl_2$. The reaction mixtures are incubated at 37 °C, and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4 °C for 20 minutes after which 100 μL of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for the non-deuterated counterpart of the compound of Formula I and the positive control, 7-ethoxycoumarin (1.0 μM). Testing is done in triplicate.

[108] ***Data analysis:*** The *in vitro* $t_{1/2}$s for test compounds are calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.

in vitro $t_{1/2}$ = 0.693/k

k = -[slope of linear regression of % parent remaining(ln) vs incubation time]

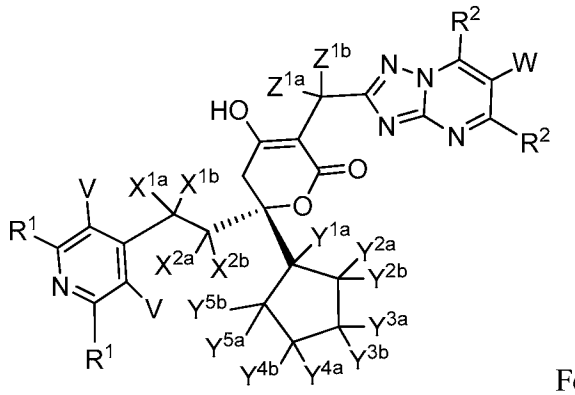
[109] Data analysis is performed using Microsoft Excel Software.

[110] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

CLAIMS

We claim:

1. A compound of Formula I :



Formula I,

or a tautomer thereof or a pharmaceutically acceptable salt of the compound or tautomer, wherein:

each R^1 is the same and is selected from CD_3CD_2-, CD_3CH_2-, CH_3CD_2-, and CH_3CH_2-;

each R^2 is the same and is selected from -CD_3, -CD_2H, -CDH_2, and -CH_3;

each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is independently hydrogen or deuterium;

each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is independently hydrogen or deuterium;

each of Z^{1a} and Z^{1b} is independently hydrogen or deuterium;

W is hydrogen or deuterium; and

each V is the same and is selected from hydrogen and deuterium,

provided that when R^1 is CH_3CH_2-, each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is hydrogen, each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is hydrogen, each of Z^{1a} and Z^{1b} is hydrogen, W is hydrogen, and each V is hydrogen, then R^2 is -CD_3, -CD_2H, or -CDH_2.

2. The compound of claim 1, wherein:

R^1 is CD_3CD_2-, CD_3CH_2-, CH_3CD_2-, or CH_3CH_2-;

R^2 is -CD_3 or -CH_3;

X^{1a} and X^{1b} are the same;

X^{2a} and X^{2b} are the same;

Y^{2a} and Y^{2b} are the same;

Y^{3a} and Y^{3b} are the same;
Y^{4a} and Y^{4b} are the same;
Y^{5a} and Y^{5b} are the same; and
each of Z^{1a} and Z^{1b} is the same.

3. The compound of claim 1 or 2, wherein R^1 is CD_3CD_2- or CH_3CH_2-.

4. The compound of any one of claims 1 to 3, wherein each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is the same.

5. The compound of any one of claims 1 to 3, wherein each of X^{1a} and X^{1b} is deuterium and each of X^{2a} and X^{2b} is hydrogen.

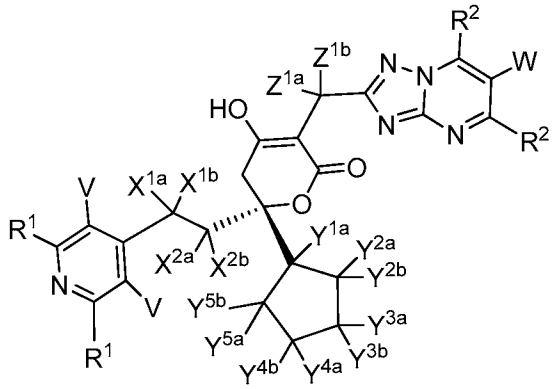
6. The compound of any one of claims 1 to 3, wherein each of X^{1a} and X^{1b} is hydrogen and each of X^{2a} and X^{2b} is deuterium.

7. The compound of any one of claims 1 to 6, wherein each one of Y^{2a}, Y^{2b}, Y^{5a}, and Y^{5b} is the same.

8. The compound of any one of claims 1 to 7, wherein each one of Y^{3a}, Y^{3b}, Y^{4a}, and Y^{4b} is the same.

9. The compound of any one of claims 1 to 8, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

10. The compound of claim 9, wherein each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is D; each of X^{1a}, X^{1b}, X^{2a}, and X^2 is the same; each of Z^{1a} and Z^{1b} is the same; and the compound is selected from any one of the compounds of formula I set forth in the table, or a tautomer thereof or a pharmaceutically acceptable salt of the compound or tautomer, wherein any atom not designated as deuterium is present at its natural isotopic abundance:



Formula I

Cmpd	R^1	R^2	Each X	Each Z	W	V
100	CD_3CD_2	CD_3	D	D	D	D
101	CD_3CD_2	CD_3	H	D	D	D
102	CD_3CD_2	CD_3	D	H	D	D
103	CD_3CD_2	CD_3	H	H	D	D
104	CD_3CD_2	CH_3	D	D	H	D
105	CD_3CD_2	CH_3	H	D	H	D
106	CD_3CD_2	CH_3	D	H	H	D
107	CD_3CD_2	CH_3	H	H	H	D
108	CH_3CH_2	CD_3	D	D	D	H
109	CH_3CH_2	CD_3	H	D	D	H
110	CH_3CH_2	CD_3	D	H	D	H
111	CH_3CH_2	CD_3	H	H	D	H
112	CH_3CH_2	CH_3	D	D	H	H
113	CH_3CH_2	CH_3	H	D	H	H
114	CH_3CH_2	CH_3	D	H	H	H
115	CH_3CH_2	CH_3	H	H	H	H

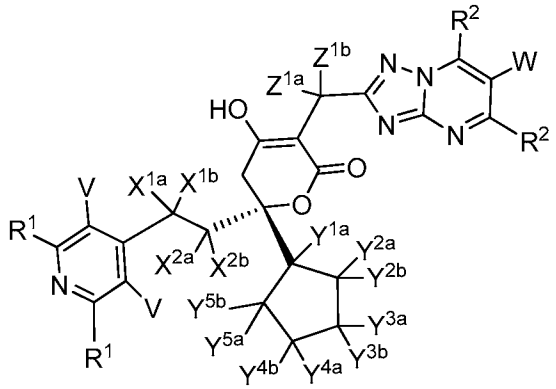
wherein:

"each X" refers to each of X^{1a}, X^{1b}, X^{2a}, and X^{2b}; and

"each "Z" refers to each of Z^{1a} and Z^{1b}.

11. The compound of claim 9, wherein each of Y^{1a}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is H; each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is the same; each of Z^{1a} and Z^{1b} is the same; and the compound is selected from any one of the compounds of formula I set forth in the table below, or a tautomer thereof or a pharmaceutically acceptable salt of the compound

or tautomer, wherein any atom not designated as deuterium is present at its natural isotopic abundance:



Formula I

Cmpd	R^1	R^2	Each X	Each Z	W	V
200	CD_3CD_2	CD_3	D	D	D	D
201	CD_3CD_2	CD_3	D	H	D	D
202	CD_3CD_2	CD_3	H	H	D	D
203	CD_3CD_2	CH_3	D	D	H	D
204	CD_3CD_2	CD_3	H	D	D	D
205	CD_3CD_2	CH_3	D	H	H	D
206	CD_3CD_2	CH_3	H	D	H	D
207	CD_3CD_2	CH_3	H	H	H	D
208	CH_3CH_2	CD_3	D	D	D	H
209	CH_3CH_2	CD_3	D	H	D	H
210	CH_3CH_2	CD_3	H	D	D	H
211	CH_3CH_2	CD_3	H	H	D	H
212	CH_3CH_2	CH_3	D	D	H	H
213	CH_3CH_2	CH_3	D	H	H	H
214	CH_3CH_2	CH_3	H	D	H	H

wherein:

"each X" refers to each of X^{1a}, X^{1b}, X^{2a}, and X^{2b}; and

"each "Z" refers to each of Z^{1a} and Z^{1b}.

12. A pharmaceutical composition comprising a compound of claim 1; and a pharmaceutically acceptable carrier.

13. A method of inhibiting the activity of a hepatitis C virus RNA polymerase comprising the step of contacting the polymerase with a compound of claim 1.

14. A method of treating a hepatitis C virus infection in a subject comprising administering to the subject in need thereof a composition of claim 12.

15. A method of inhibiting hepatitis C virus replication in a subject previously diagnosed as being infected with hepatitis C virus, comprising the step of administering to the subject in need thereof an effective amount of a composition of claim 12.

16. The method of claim 14 or 15, additionally comprising the step of co-administering to the subject in need thereof a second therapeutic selected from one or more of ribavirin, consensus interferon (Infergen), albuferon or another Long-Acting Interferon, natural interferon, interferon omega, viramidine, telaprevir, boceprevir, PF-0341390, Debio 025, PSI-7977, TMC-435, ITX5061, VX-759, narlaprevir, BMS-790052, GS 9190, A-832, BI 207127, vaniprevir, ANA598, RG7227, IDX-184, nelfinavir, delavirdine, indinavir, nevirapine, saquinavir, and tenofovir.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/40731

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90; A61K 31/519 (2011.01)
USPC - 514/262.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/262.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/93, 359 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar
Search Terms Used: Filibuvir, deuterium, oxidation, pyran-2-one, cytochrome, hepatitis, NS5B

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/0176701 A1 (Borchardt et al.) 11 August 2005 (11.08.2005) para [0006], [0110], [0114], [0120], [0277], [0306], [0314], [0337], [1146], [2696]	1-3, 12-16
Y	US 2004/0224960 A1 (Borchardt et al.) 11 November 2004 (11.11.2004) para [0005]-[0013], [0016]	1-3, 12-16
Y	US 2007/0191432 A1 (Tung) 16 August 2007 (16.08.2007) para [0003], [0011]-[0013], [0017]-[0022]	1-3, 12-16

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2011 (30.09.2011)	18 OCT 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/40731

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-11
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.