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(54) Title: ATAZANAVIR METABOLITE DERIVATIVES

(57) Abstract: The present invention provides a compound of Formula (I) or (II) or a pharmaceutically acceptable salt of any of the foregoing, wherein each of the variables is as defined herein. The compounds of the invention can be used in therapy, for example, to improve the efficacy of a therapeutic agent that is either (i) metabolized by a liver metabolic enzyme; (ii) transported by an efflux pump; or (iii) a combination of (i) and (ii), especially a HCV protease inhibitor or a HIV protease inhibitor.



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ATAZANAVIR METABOLITE DERIVATIVES

RELATED APPLICATIONS

[1] This application claims the benefit of U.S. Provisional Application No. 61/495,877, filed on June 10, 2011 and U.S. Provisional Application No. 61/495,870, filed on June 10, 2011. The entire teachings of the above applications 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 cases, a metabolic inhibitor may 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 may 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] Atazanavir sulfate, also known as (3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate is currently approved for the treatment of HIV infection.

[7] It would be useful to harness atazanavir's inhibitory effects on various metabolic enzymes and transporter proteins for use as a booster for other therapeutic agents that are labile to such metabolism and transport.

SUMMARY OF THE INVENTION

[8] The present invention provides a compound of Formula I or II or a pharmaceutically acceptable salt thereof, wherein each of the variables is as defined herein. The compounds of the invention can be used in therapy, for example, to improve the efficacy in a subject of a therapeutic agent that is (i) metabolized by a liver metabolic enzyme; (ii) transported by an efflux pump; or (iii) a combination of (i) and (ii), especially a HCV protease inhibitor or a HIV protease inhibitor.

DEFINITIONS

[9] 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.

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

[11] 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 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium).

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

[13] 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).

[14] 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.

[15] 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 45% of the compound. In other embodiments, the relative amount of such isotopologues *in toto* will be 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.

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

[17] 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.

[18] 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.

[19] 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-1,6-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.

[20] The compounds of the present invention (e.g., compounds of Formula I or II), contain asymmetric carbon atoms. 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 enantiomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

[21] 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.

[22] 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).

[23] “D” and “d” both refer to deuterium. “Stereoisomer” refers to both

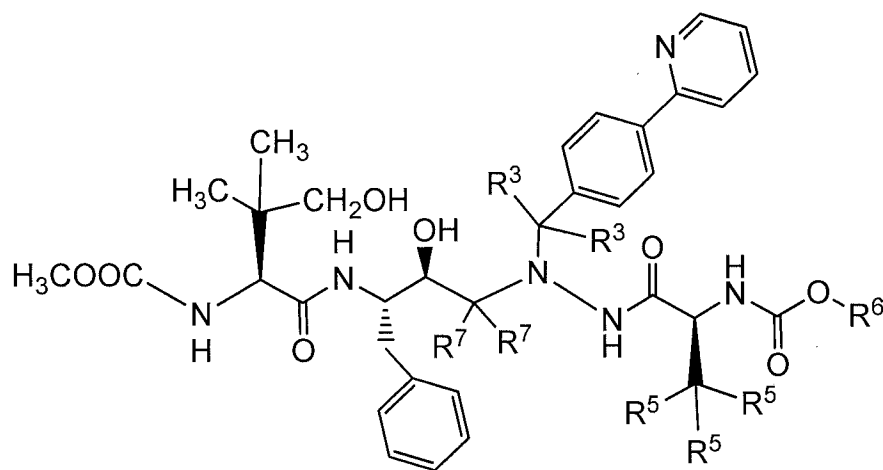
enantiomers and diastereomers. “Tert” and “t-” each refer to tertiary. “US” refers to the United States of America. “tBu” refers to t-butyl. “iPr” refers to isopropyl.

[24] “Substituted with deuterium” refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms.

[25] Throughout this specification, a variable may be referred to generally (e.g., “each R”) or may be referred to specifically (e.g., R^1 , R^2 , R^3 , 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

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



(I), or a pharmaceutically acceptable salt thereof, wherein:

each R^7 is the same and is selected from hydrogen and deuterium;

each R^3 is the same and is selected from hydrogen and deuterium;

each R^5 is the same and is selected from $-CH_3$ and $-CD_3$; and

R^6 is selected from $-CH_3$ and $-CD_3$;

provided that if each R^7 is hydrogen, each R^3 is hydrogen, and each R^5 is $-CH_3$, then R^6 is $-CD_3$.

[27] In certain embodiments each R^3 is deuterium.

[28] In certain embodiments R^6 is $-CD_3$.

[29] In one aspect of the embodiment wherein R^6 is CD_3 , each R^3 is hydrogen. In another aspect of this embodiment, each R^3 is deuterium.

[30] In one embodiment, each R^5 is CH_3 . In one aspect of this embodiment, each R^3 is deuterium, and R^6 is CD_3 . In another aspect, each R^3 is hydrogen, and R^6 is CD_3 .

[31] In one embodiment, each R^5 is CD_3 . In one aspect of this embodiment, each R^3 is deuterium, and R^6 is CD_3 .

[32] In one aspect of the embodiment wherein R^6 is $-CD_3$, each R^7 is hydrogen; in another aspect of the embodiment wherein R^6 is $-CD_3$, each R^7 is deuterium.

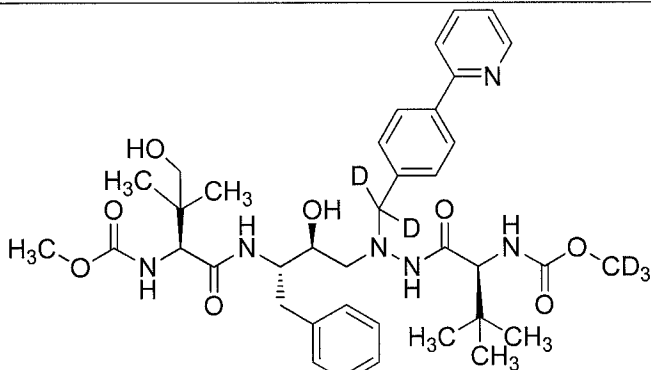
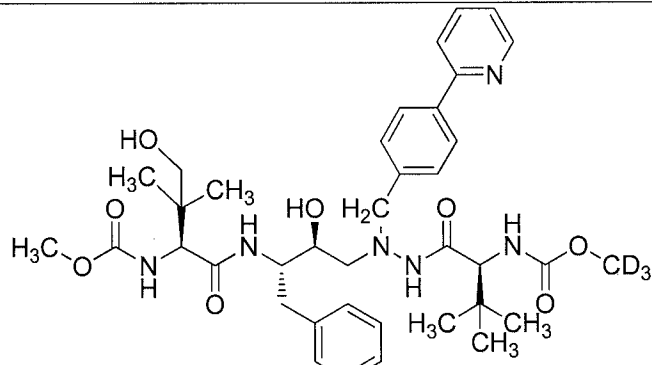
[33] In one embodiment, each R^7 is hydrogen.

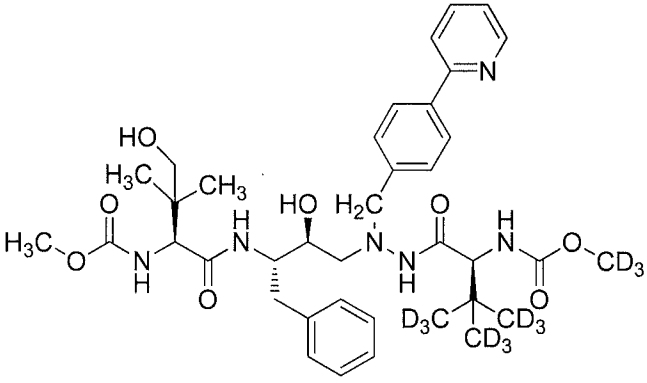
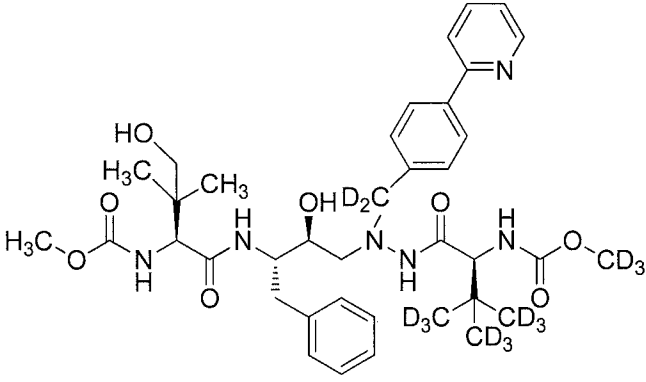
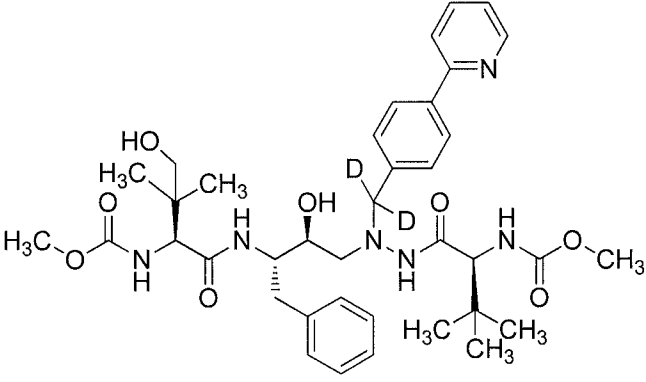
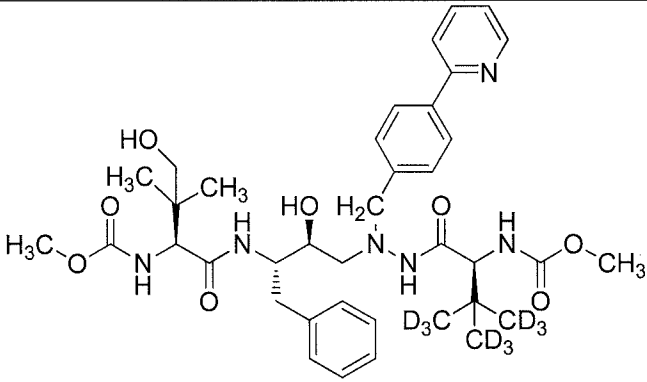
[34] In one embodiment, each R^7 is deuterium.

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

[36] Exemplary compounds of Formula I are set forth in Table 1, below:

Table 1. Exemplary Compounds of Formula I.

Compound No.	Structure
100	
101	

Compound No.	Structure
102	 Chemical structure of compound 102: A complex molecule featuring a central amide linkage. The left side includes a methyl ester group (H₃C-O-C(=O)-NH-) and a chiral center with a hydroxyl group (HO-CH-), a methyl group (CH₃), and a hydroxymethyl group (CH₂-OH). The right side includes a chiral center with a hydroxyl group (HO-CH-), a benzyl group (CH₂-C₆H₅), and a secondary amine (N-CH₂-). The secondary amine is further substituted with a 4-(pyridin-2-yl)phenyl group and a methyl ester group (H₃C-O-C(=O)-NH-). The molecule also contains several deuterium-labeled methyl groups (D₃C- and CD₃-).
120	 Chemical structure of compound 120: Similar to compound 102, but with a different substitution pattern on the right side. It features a methyl ester group (H₃C-O-C(=O)-NH-) and a chiral center with a hydroxyl group (HO-CH-), a methyl group (CH₃), and a hydroxymethyl group (CH₂-OH). The secondary amine (N-CH₂-) is substituted with a 4-(pyridin-2-yl)phenyl group and a methyl ester group (H₃C-O-C(=O)-NH-). The molecule also contains several deuterium-labeled methyl groups (D₃C- and CD₃-).
121	 Chemical structure of compound 121: Similar to compound 102, but with a different substitution pattern on the right side. It features a methyl ester group (H₃C-O-C(=O)-NH-) and a chiral center with a hydroxyl group (HO-CH-), a methyl group (CH₃), and a hydroxymethyl group (CH₂-OH). The secondary amine (N-CH₂-) is substituted with a 4-(pyridin-2-yl)phenyl group and a methyl ester group (H₃C-O-C(=O)-NH-). The molecule also contains several deuterium-labeled methyl groups (D₃C- and CD₃-).
122	 Chemical structure of compound 122: Similar to compound 102, but with a different substitution pattern on the right side. It features a methyl ester group (H₃C-O-C(=O)-NH-) and a chiral center with a hydroxyl group (HO-CH-), a methyl group (CH₃), and a hydroxymethyl group (CH₂-OH). The secondary amine (N-CH₂-) is substituted with a 4-(pyridin-2-yl)phenyl group and a methyl ester group (H₃C-O-C(=O)-NH-). The molecule also contains several deuterium-labeled methyl groups (D₃C- and CD₃-).

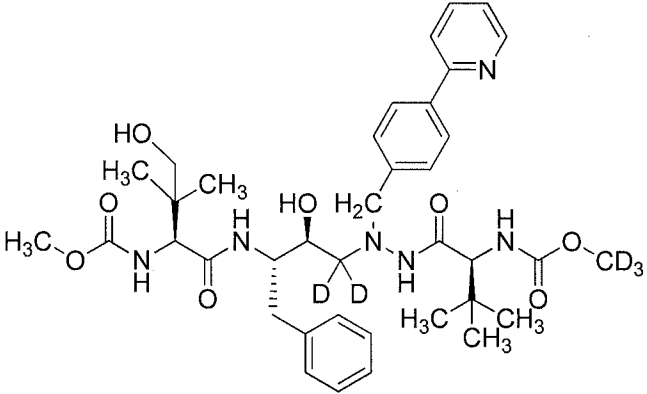
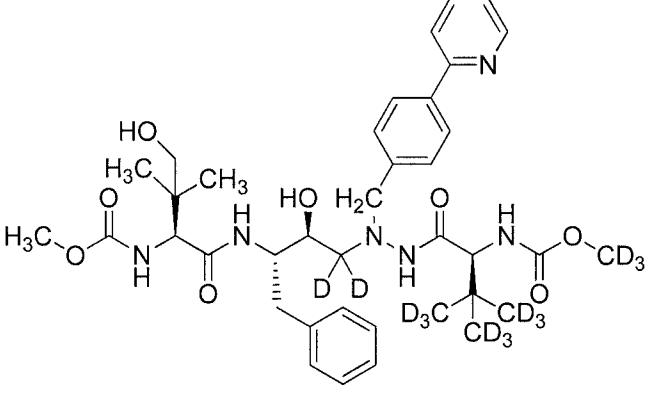
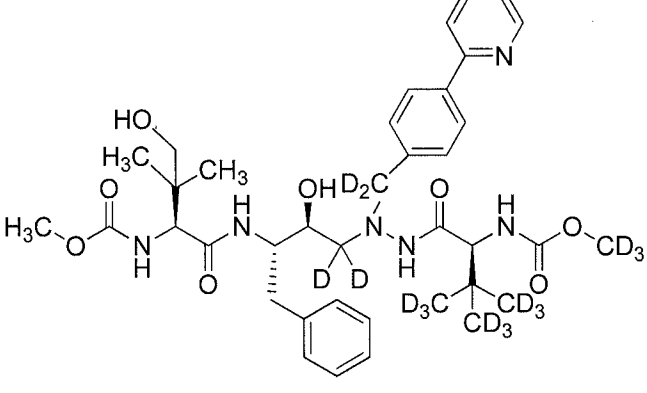
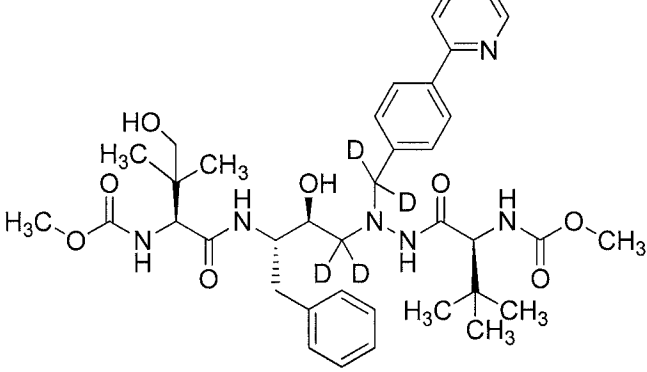
Compound No.	Structure
123	

and pharmaceutically acceptable salts thereof, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

[37] Additional exemplary compounds of Formula I are set forth in Table 2, below:

Table 2. Exemplary Compounds of Formula I.

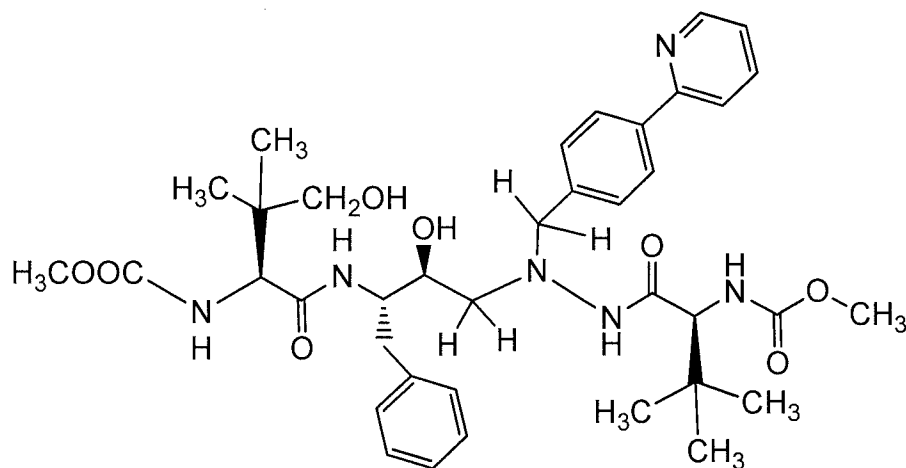
Compound No.	Structure
130	

Compound No.	Structure
131	 Chemical structure of compound 131: A complex molecule featuring a central chiral center (C2) bonded to a hydroxyl group (HO), a methyl group (H₃C), and a methyl group (CH₃). This center is part of a chain that includes a pyridine ring, a benzene ring, and a methyl ester group (O-CD₃). The structure also shows a methyl ester group (O-CD₃) and a methyl group (H₃C).
132	 Chemical structure of compound 132: A complex molecule featuring a central chiral center (C2) bonded to a hydroxyl group (HO), a methyl group (H₃C), and a methyl group (CH₃). This center is part of a chain that includes a pyridine ring, a benzene ring, and a methyl ester group (O-CD₃). The structure also shows a methyl ester group (O-CD₃) and a methyl group (H₃C).
133	 Chemical structure of compound 133: A complex molecule featuring a central chiral center (C2) bonded to a hydroxyl group (HO), a methyl group (H₃C), and a methyl group (CH₃). This center is part of a chain that includes a pyridine ring, a benzene ring, and a methyl ester group (O-CD₃). The structure also shows a methyl ester group (O-CD₃) and a methyl group (H₃C).
134	 Chemical structure of compound 134: A complex molecule featuring a central chiral center (C2) bonded to a hydroxyl group (HO), a methyl group (H₃C), and a methyl group (CH₃). This center is part of a chain that includes a pyridine ring, a benzene ring, and a methyl ester group (O-CH₃). The structure also shows a methyl ester group (O-CH₃) and a methyl group (H₃C).

Compound No.	Structure
135	
136	
137	

and pharmaceutically acceptable salts thereof, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

[38] The present invention in one embodiment provides a compound of Formula II:



(II), or

a pharmaceutically acceptable salt thereof.

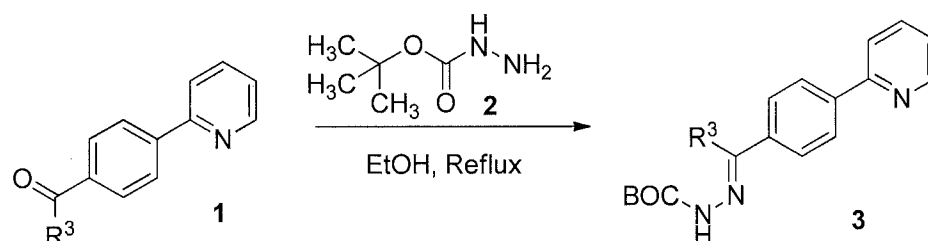
[39] The synthesis of compounds of Formula I or II may be readily achieved by synthetic chemists of ordinary skill by reference to the Exemplary Synthesis and Examples disclosed herein. Relevant procedures analogous to those of use for the preparation of compounds of Formula I or II and intermediates thereof are disclosed, for instance in PCT publications WO 97/46514 and WO 2008/156632; United States Patent 5,849,911; Bold, G et al., J Med Chem 1998, 41:3387; and Xu, Z et al., Org Process Res Dev 2002, 6:323.

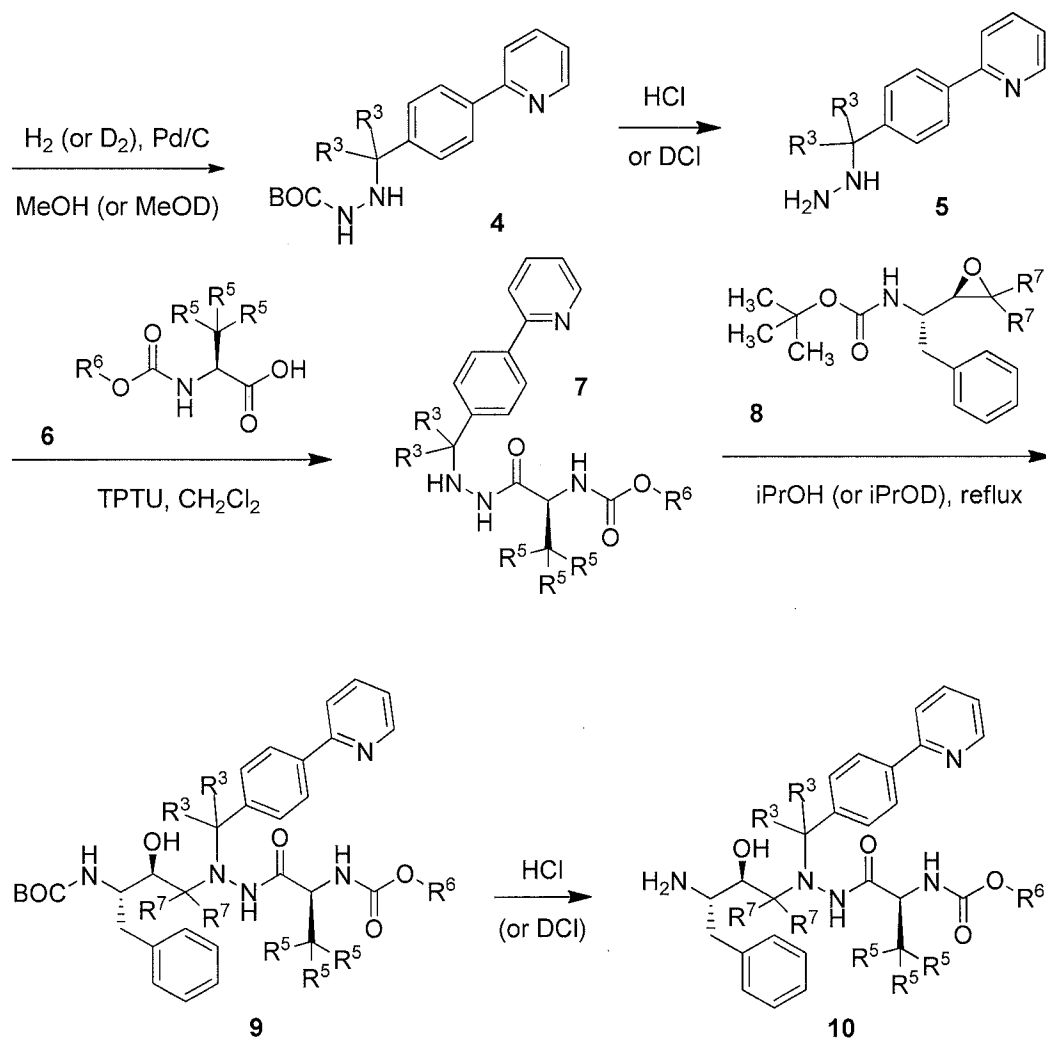
[40] Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

EXEMPLARY SYNTHESIS

[41] Compounds of Formula I may be prepared using the synthetic routes depicted in Schemes 1-3 set forth below.

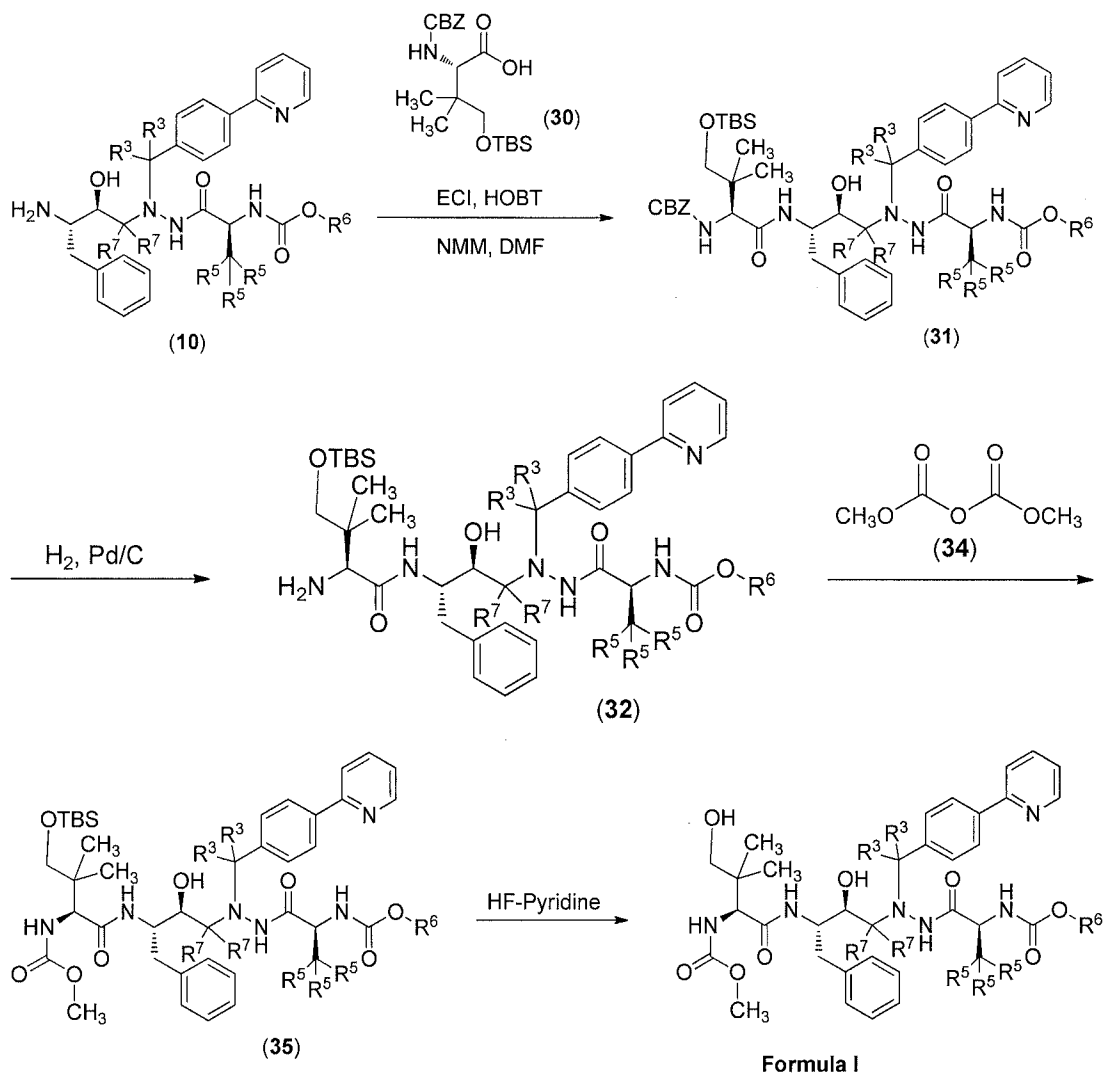
[42] Scheme 1. Synthesis of the Right-Hand Side of a Compound of Formula I



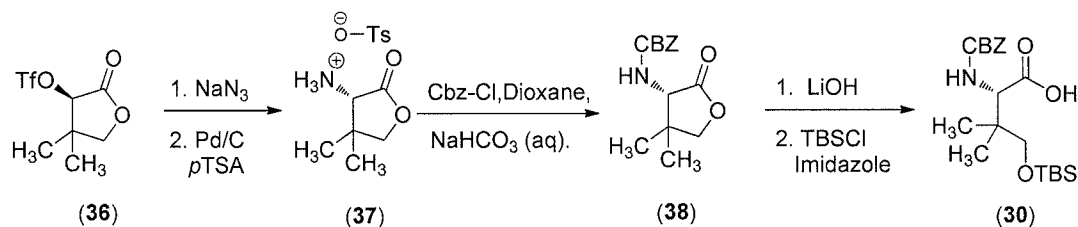


[43] Aldehyde 1 is treated with the commercially available t-butoxycarbonylhydrazide (2) to produce a BOC-protected hydrazide intermediate 3, which is then reduced using either hydrogen or deuterium gas to form the appropriate BOC-protected hydrazide 4. The BOC-protected hydrazide 4 is then deprotected with HCl or DCI to produce hydrazide 5. Hydrazide 5 is then combined with the appropriate carbamate derivative of tert-leucine 6 in the presence of O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TPTU) to produce intermediate 7. Intermediate 7 is then treated with the commercially available epoxide (8) to produce 9, which is then deprotected with hydrochloric acid or DCI to produce 10.

[44] Scheme 2. General Route to Compounds of Formula I.



[45] Scheme 2 depicts a general route to compounds of Formula I. Intermediate **31** is prepared from **10** (obtained as disclosed in Scheme 1) by reacting with **30**, which is prepared as disclosed in Scheme 3 below. **31** is then treated with hydrogen and palladium on carbon to provide **32**, which is coupled with anhydride $CH_3OCOOCOCH_3$ **34** to afford the carbamate **35**. Treatment of **35** with hydrofluoric acid affords compounds of Formula I.

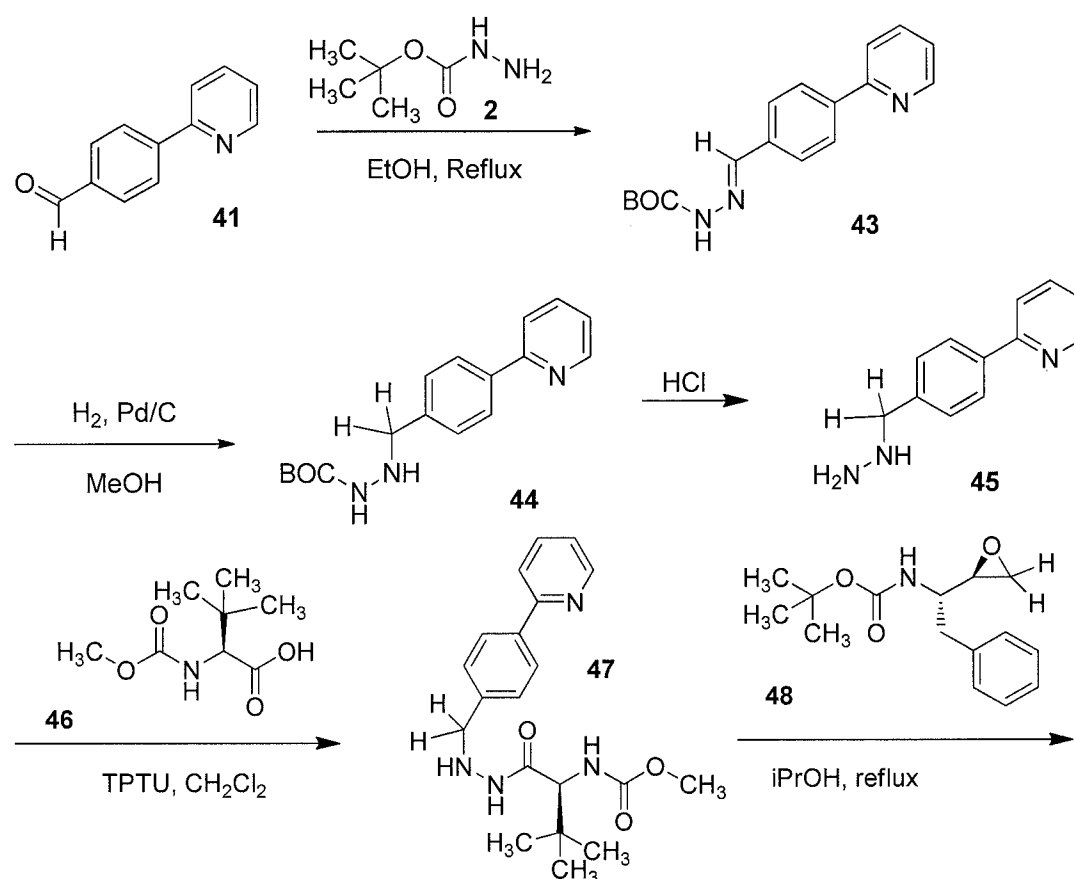
[46] Scheme 3. General Route to Intermediate **30**.

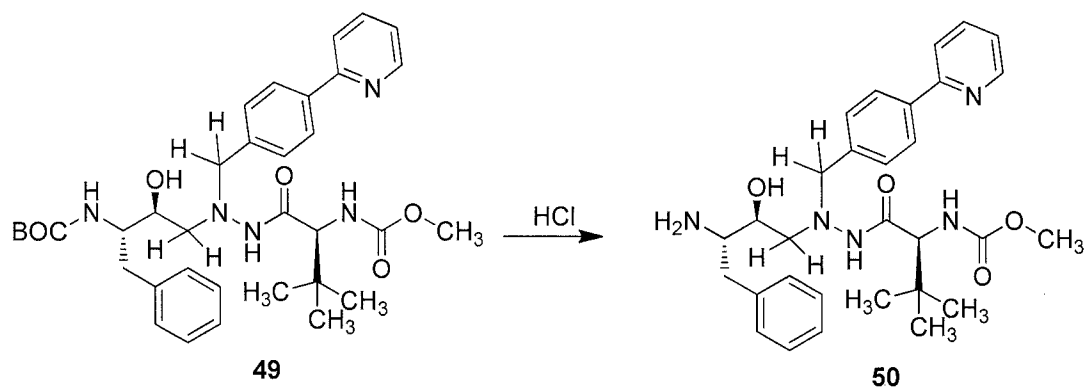
[47] Intermediate **30**, for use in preparing compounds of Formula I according to Schemes 2, may be prepared from furan **36** as shown in Scheme 3 in a manner analogous to that described in WO01/68603, line 5, page 78 through line 2, page 80, the content of that section of which is incorporated herein by reference.

[48] The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., R^1 , R^2 , R^3 , etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

[49] Compounds of Formula II may be prepared using the synthetic routes depicted in Schemes 4-6 set forth below.

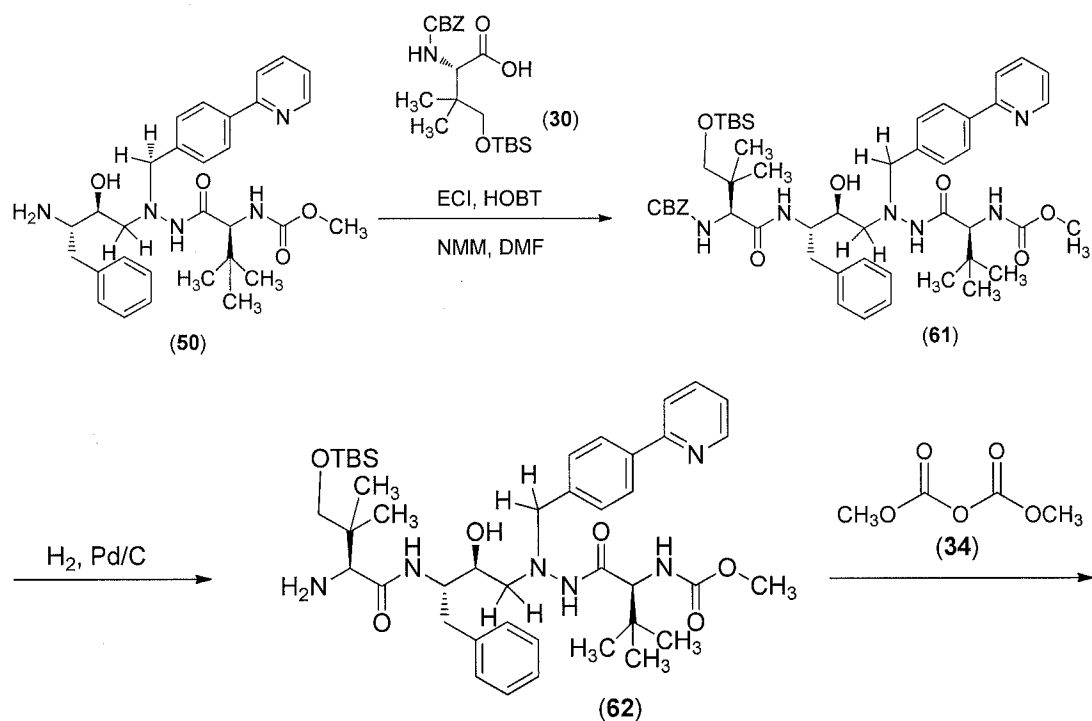
[50] Scheme 4. Synthesis of the Right-Hand Side of Compound of Formula II

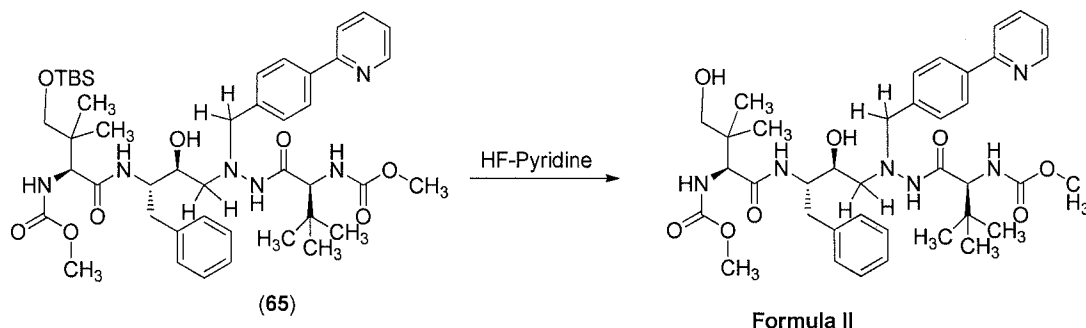




[51] Aldehyde **41** is treated with the commercially available t-butoxycarbonylhydrazide (**2**) to produce a BOC-protected hydrazide intermediate **43**, which is then reduced using hydrogen gas to form the BOC-protected hydrazide **44**. The BOC-protected hydrazide **44** is then deprotected with HCl to produce hydrazide **45**. Hydrazide **45** is then combined with the carbamate derivative of tert-leucine **46** in the presence of O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TPTU) to produce intermediate **47**. Intermediate **47** is then treated with the commercially available epoxide (**48**) to produce **49**, which is then deprotected with hydrochloric acid to produce **50**.

[52] Scheme 5. Route to Compound of Formula II.





[53] Scheme 5 depicts a route to the compound of Formula II. Intermediate **61** is prepared from **50** (obtained as disclosed above) by reacting with **30**, which is prepared as disclosed in Scheme 3 above. **61** is then treated with hydrogen and palladium on carbon to provide **62**, which is coupled with anhydride $\text{CH}_3\text{OCOOCOCH}_3$ to afford the carbamate **65**. Treatment of **65** with hydrofluoric acid affords the compound of Formula II.

[54] Additional methods of synthesizing compounds of Formula I or II and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. 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.

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

COMPOSITIONS

[56] The invention also provides pharmaceutical compositions, which may be pyrogen-free compositions, comprising an effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt of said compound; 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.

[57] 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.

[58] 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.

[59] 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 LUTROLTM and PLURONICTM (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.

[60] 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).

[61] 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.

[62] 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.

[63] In one aspect of the embodiments of the composition, each R^3 is deuterium. In one aspect of the embodiments of the composition, R^6 is $-CD_3$. In one example of the aspect wherein R^6 is CD_3 , each R^3 is hydrogen. In another example of this aspect, each R^3 is deuterium. In one aspect of the embodiments of the composition, each R^5 is CH_3 . In one example of this aspect, each R^3 is deuterium, and R^6 is CD_3 . In another example, each R^3 is hydrogen, and R^6 is CD_3 . In one aspect of the embodiments of the composition, each R^5 is CD_3 . In one example of this aspect, each R^3 is deuterium, and R^6 is CD_3 . In one example of the aspect wherein R^6 is $-CD_3$, each R^7 is hydrogen. In one aspect of the embodiments of the composition, each R^7 is hydrogen.

[64] 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.

[65] 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.

[66] 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.

[67] 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.

[68] 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.

[69] 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.

[70] 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.

[71] 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.

[72] In another embodiment, a composition of this invention further comprises a second therapeutic agent. In one aspect of this embodiment, the second therapeutic agent is a compound that is either metabolized by a liver enzyme and/or subjected to being removed from a cell by an efflux transporter protein. In a more specific embodiment, the second therapeutic agent is a compound that is either (i) metabolized by an enzyme selected from cytochrome P450 (CYP) 3A, CYP2C8, and UGT1A1;

(ii) transported by an efflux pump selected from P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP); or (iii) a combination of (i) and (ii).

In certain embodiments, the second therapeutic agent is an agent selected from an HIV protease inhibitor, an HIV integrase inhibitor, an HCV protease inhibitor. In one aspect of this embodiment, the second therapeutic agent is selected from saquinavir, indinavir, amprenavir, fosamprenavir, darunavir, lopinavir, atazanavir, elvitegravir, danoprevir, dolutegravir, and deuterated derivatives of any of the foregoing. The term “deuterated derivative” refers to a compound wherein at least one hydrogen atom bound to a carbon atom is replaced with deuterium.

[73] In certain embodiments, the second therapeutic agent is a peptide, peptidomimetic agent, and/or higher molecular weight orally available compounds the plasma level of which may be beneficially enhanced by administration of the compound of the inventions. The administration may be prior to or following the administration of a compound of this invention, or concurrently with a compound of this invention for example in a composition of this invention. Examples of such second therapeutic agents include HIV protease inhibitors such as darunavir, amprenavir, fosamprenavir, and lopinavir; mariviroc, HCV protease inhibitors such as telaprevir, VX-500, ABT-450, BI 201335, danoprevir, vaniprevir, narlaprevir, ACH-1625, GS-9256, MK-5172, and BMS-650032; aliskiren, cyclosporine, ibutamoren (Merck growth hormone secretagogue), rapamycin, temsirolimus, integrilin, vinflunine, lapatinib, and dabigatran. Agents primarily delivered by parenteral, nasal, or buccal means include nemifitide (peptidyl anti-depressant developed by Tetragenex), davenetide (Allon pro-cognitive agent), paclitaxel, cabazitaxel, docetaxel, leuprorelin, eribulin, cetrotide, echinocandin antifungals (e.g. caspofungin, micafungin, anidulafungin), azole antifungals such as posaconazole, voriconazole, and itraconazole, and ceftaroline fosamil.

[74] 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).

[75] 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 either a) treat the target disorder; or b) detectably reduce the metabolism of a second therapeutic agent co-administered with a compound of this invention. In certain embodiments, an effective amount to treat the target disorder is the same as the effective amount that reduces the metabolism of a second therapeutic agent co-administered. In yet another embodiment, an effective amount to treat the target disorder is different from the effective amount that reduces the metabolism of a second therapeutic agent co-administered. In certain embodiments, when a compound of this invention is used to reduce the metabolism of a co-administered second therapeutic agent, the compound of this invention is administered at between a 3:1 and 1:3 molar ratio of the second therapeutic agent.

[76] 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.

[77] In one embodiment, an effective amount of a compound of this invention can range from 1 mg to 1,000 mg daily. In one aspect, an effective amount of a compound of this invention can range from 50 mg to 400 mg daily. In still another aspect, an effective amount of a compound of this invention can range from 10 mg to 100 mg daily. In an alternate aspect, an effective amount of a compound of this invention can range from 3 mg to 30 mg daily. In still another alternate aspect an effective amount of a compound of this invention can range from 30 mg to 300 mg daily.

[78] 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, in certain

embodiments, guidance for selecting an effective dose can be determined by reference to the prescribing information for atazanavir.

[79] 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.*

[80] It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will 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 or 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

[81] In one embodiment, the invention provides a method of inhibiting a liver metabolic enzyme in a subject, such as a patient in need thereof, comprising the step of administering to the subject a compound of Formula I or II or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula I or II or a pharmaceutically acceptable salt thereof. In one aspect of this embodiment, the liver metabolic enzyme is selected from CYP3A, CYP2C8, and UGT1A1.

[82] In another embodiment the invention provides a method of inhibiting an efflux pump in a subject, such as a patient in need thereof, comprising the step of administering to the subject a compound of Formula I or II or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of

Formula I or II or a pharmaceutically acceptable salt thereof. In one aspect of this embodiment, the efflux pump is selected from P-gp, a MRP, and BCRP.

[83] In another embodiment, the invention provides a method of increasing the efficacy of a therapeutic agent that is (i) metabolized by a liver metabolic enzyme; (ii) transported by an efflux pump; or a combination of (i) and (ii), in a subject, such as a patient in need thereof comprising co-administering to the subject in need thereof a compound of Formula I or II or a pharmaceutically acceptable salt thereof and the therapeutic agent. In one aspect of this embodiment, the liver metabolic enzyme is selected from CYP3A, CYP2C8, and UGT1A1. In a more specific aspect, the liver metabolic enzyme is CYP3A. In one aspect of this embodiment, the efflux pump is selected from P-gp, a MRP, and BCRP. In a more specific aspect, the efflux pump is P-gp. In still another aspect of this embodiment, the therapeutic agent is selected from an HIV protease inhibitor, an HIV integrase inhibitor, an HCV protease inhibitor. In a more specific aspect of this embodiment, the therapeutic agent is selected from saquinavir, indinavir, amprenavir, fosamprenavir, darunavir, lopinavir, atazanavir, elvitegravir, danoprevir, dolutegravir, and deuterated derivatives of any of the foregoing.

[84] In another embodiment, the invention provides a method of treating an HIV infection in a subject, such as a patient in need thereof comprising the step of administering to the subject in need thereof a compound of Formula I or II or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising a compound of Formula I or II or a pharmaceutically acceptable salt thereof.

[85] In another embodiment, the invention provides a method of improving exposure to antisense RNA oligonucleotides, short interfering RNA, and chemically stabilized forms of such agents, comprising the step of administering to the subject a compound of Formula I or II or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising a compound of Formula I or II or a pharmaceutically acceptable salt thereof.

[86] In one aspect of the embodiments of the method, each R^3 is deuterium. In one aspect of the embodiments of the method, R^6 is $-CD_3$. In one example of the aspect wherein R^6 is CD_3 , each R^3 is hydrogen. In another example of this aspect, each R^3 is deuterium. In one aspect of the embodiments of the method, each R^5 is CH_3 . In one example of this aspect, each R^3 is deuterium, and R^6 is CD_3 . In another example, each

R^3 is hydrogen, and R^6 is CD_3 . In one aspect of the embodiments of the method, each R^5 is CD_3 . In one example of this aspect, each R^3 is deuterium, and R^6 is CD_3 . In one example of the aspect wherein R^6 is $-CD_3$, each R^7 is hydrogen. In one aspect of the embodiments of the method, each R^7 is hydrogen.

[87] In another aspect of this embodiment, the method comprises the additional step of co-administering to the subject a second therapeutic agent selected from an HIV protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, a nucleoside/nucleotide reverse transcriptase inhibitor, a viral entry inhibitor, an integrase inhibitor, an immune based antiretroviral agent, a viral maturation inhibitor, a cellular inhibitor, or combinations of two or more of the above. In a more specific aspect, the second therapeutic agent is selected from an HIV protease inhibitor and an HIV integrase inhibitor. In an even more specific aspect, the second therapeutic agent is selected from saquinavir, indinavir, amprenavir, fosamprenavir, darunavir, lopinavir, atazanavir, elvitegravir, dolutegravir, and deuterated derivatives of any of the foregoing.

[88] In certain embodiments, the second therapeutic agent is a peptide, peptidomimetic agent, and/or higher molecular weight orally available compounds the plasma level of which may be beneficially enhanced by administration of the compound of the inventions. The administration may be prior to or following the administration of a compound of this invention, or concurrently with a compound of this invention for example in a composition of this invention. Examples of such second therapeutic agents include HIV protease inhibitors such as darunavir, amprenavir, fosamprenavir, and lopinavir; mariviroc, HCV protease inhibitors such as telaprevir, VX-500, ABT-450, BI 201335, danoprevir, vaniprevir, narlaprevir, ACH-1625, GS-9256, MK-5172, and BMS-650032; aliskiren, cyclosporine, ibutamoren (Merck growth hormone secretagogue), rapamycin, temsirolimus, integrilin, vinflunine, lapatinib, and dabigatran. Agents primarily delivered by parenteral, nasal, or buccal means include nemifitide (peptidyl anti-depressant developed by Tetragenex), davenetide (Allon pro-cognitive agent), paclitaxel, cabazitaxel, docetaxel, leuprorelin, eribulin, cetrotide, echinocandin antifungals (e.g. caspofungin, micafungin, anidulafungin), azole antifungals such as posaconazole, voriconazole, and itraconazole, and ceftaroline fosamil.

[89] In another embodiment, the invention provides a method of treating an HCV

infection in a subject, such as a patient in need thereof, comprising the step of co-administering to the subject in need thereof (i) a compound of Formula I or II or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising a compound of Formula I or II or a pharmaceutically acceptable salt thereof ; and (ii) an HCV protease inhibitor. In a more specific aspect of this embodiment, the HCV protease inhibitor is danoprevir.

[90] 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).

[91] The term “co-administering” 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, concurrently 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.

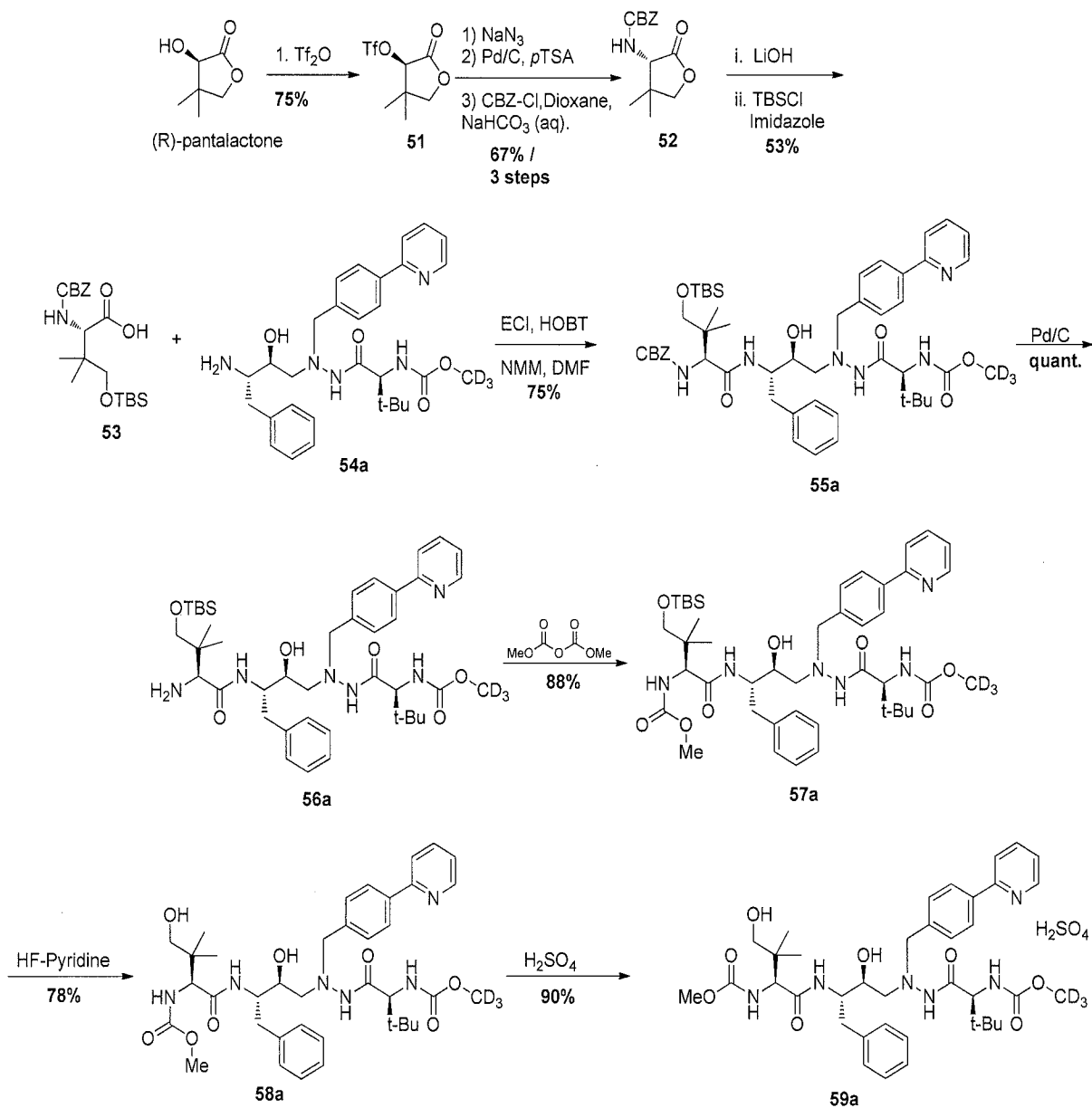
[92] Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., *Pharmacotherapy Handbook*, 2nd Edition, Appleton and Lange, Stamford, 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.

[93] 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.

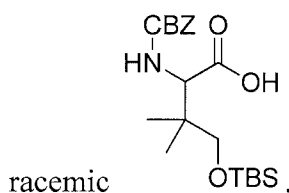
In yet another aspect, the invention provides the use of a compound of Formula I or II alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a subject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

[94] Examples

[95] Example 1: Preparation of Compound 101 (as its bisulfate salt 59a).

(S)-benzyl (4,4-dimethyl-2-oxotetrahydrofuran-3-yl)carbamate **52** was prepared according to the method described by Freskos, J. N. *Synth. Comm.* **1994**, 24, 557-563 from (R)-pantalactone *via* intermediate **51**.

Carbamate **52** was converted to the corresponding siloxy *tert*-leucine **53** by the method analogous to the one described in EP 0580402A2 for the preparation of



Amino alcohol **54a** was prepared in accordance with the procedure disclosed in US patent publication **20090036357**.

Preparation of ((5S,8S,9S,14S)-8-benzyl-9-hydroxy-1-phenyl-5-(1-tertbutyldimethylsilyloxy-2-methylpropan-2-yl)-15,15-dimethyl-3,6,13-trioxo-11-(4-(pyridin-2-yl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamic acid trideuteromethyl ester 55a: **53** (6.63 g, 16.8 mmol) was dissolved in 2-methyl THF (42 mL), cooled with an ice bath. N-methyl morpholine (1.94 mL), 1-hydroxybenzotriazole hydrate (4.09 g), and **54a** (9.44 g, 17.6 mmol) were added sequentially. In a separate flask *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (4.82 g) was dissolved in water (16.8 mL). The freshly prepared solution was added to the cooled reaction flask as a single portion. The reaction proceeded to warm to ambient temperature over 12h. Reaction progress was monitored by LCMS and TLC. Once **53** was consumed and the desired **55a** was observed by LCMS, the reaction was quenched with an aqueous solution of saturated ammonium chloride (25 mL). The volatiles were removed by concentration and the reaction was partitioned into ethyl acetate and water. The organic phase was separated and the aqueous phase was back-extracted (3 times) with ethyl acetate. The combined organics were dried over sodium sulfate, filtered and concentrated to give a white solid. Purification by gradient elution of a solution of heptanes/ethyl acetate (0-100%) through silica gel was performed by ISCO to provide the desired amide **55a** as a white solid (11.97g, 13.1 mmol, 73%) MS(ESI) 914.5 [(M+H)⁺].

Preparation of trideuteromethyl ((S)-1-(2-((2S,3S)-3-((S)-2-amino-4-tertbutyldimethylsilyloxy-3,3-dimethylbutanamido)-2-hydroxy-4-phenylbutyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate

56a: Amide **55a** (11.97 g, 13.1 mmol) was dissolved in methanol (55 mL) and a 10% by weight suspension of palladium on carbon (1.4 g) was added. The reaction was stirred under a hydrogen atmosphere for 12 hours when it was deemed complete by LCMS. The hydrogen balloon was removed, the reaction was degassed with nitrogen, and the black solution was filtered through a short pad of celite. The celite pad was washed with methanol and organics were concentrated to give free amine **56a** as a white solid (9.77 g, 12.6 mmol, 96% yield). MS(ESI) 778.5 [(MS-H)].

Preparation of ((5S,8S,9S,14S)-8-benzyl-9-hydroxy-5-(1-tertbutyldimethylsilyloxy-2-methylpropan-2-yl)-15,15-dimethyl-3,6,13-trioxo-11-(4-(pyridin-2-yl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamic acid

trideuteromethyl ester 57a: Amine **56a** (9.77 g, 12.6 mmol) was dissolved in dichloromethane (125 mL) and triethyl amine (5.2 mL) and the reaction was cooled with a wet ice bath. Dimethyl dicarbonate (2 mL) was added by syringe and the reaction was allowed to warm to ambient temperature. After conversion to the methyl carbamate was observed by LCMS, the reaction was quenched with addition of an aqueous solution of saturated ammonium chloride. The phases were separated and the organics were dried, filtered and concentrated. Purification by gradient elution of a solution of methanol/dichloromethane (0-15%) through silica gel was performed by ISCO to provide desired methyl carbamate **57a** as a white solid (9.98 g, 11.9 mmol, 95% yield) MS(ESI) 838.5 [(MS+H)⁺].

Preparation of ((5S,8S,9S,14S)-8-benzyl-9-hydroxy-5-(1-hydroxy-2-methylpropan-2-yl)-15,15-dimethyl-3,6,13-trioxo-11-(4-(pyridin-2-yl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamic acid trideuteromethyl ester 58a:

Silyl ether **57a** (4.0 g, 4.78 mmol) was dissolved in tetrahydrofuran (48 mL), the solution was cooled with a wet ice bath and a solution of hydrofluoric acid in pyridine (70%, 0.3 mL) was added. The reaction was allowed to warm to ambient temperature and stirred under a nitrogen atmosphere until conversion of ether to free alcohol **58a** was observed by LCMS. The reaction was quenched with an aqueous solution of

sodium bicarbonate and the volatiles were evaporated. The reaction was then partitioned with ethyl acetate and the aqueous phase was back-extracted (3 times). The combined organic phases were dried over sodium sulfate, filtered, and concentrated to give a white solid. Purification by gradient elution of a solution of methanol/dichloromethane (0-15%) through silica gel was performed by ISCO to provide desired methyl carbamate **58a** as a white solid (3.36 g, 4.65 mmol, 97% yield) MS(ESI) 724.1 [(MS+H)⁺].

Preparation of ((5S,8S,9S,14S)-8-benzyl-9-hydroxy-5-(1-hydroxy-2-methylpropan-2-yl)-15,15-dimethyl-3,6,13-trioxo-11-(4-(pyridin-2-yl)benzyl)-2-oxa-4,7,11,12-tetraazahexadecan-14-yl)carbamic acid trideuteromethyl ester bisulfate salt 59a: Alcohol **58a** (2.37 g, 3.28 mmol) was dissolved in methanol (33 mL), the solution was cooled with a wet ice bath and concentrated sulfuric acid (0.175 mL) was added. The reaction was allowed to warm to ambient temperature and stirred under a nitrogen atmosphere for 1h. The reaction was concentrated to give the bisulfate salt as a white solid (2.69 g, 3.28 mmol, 100% yield) MS(ESI) 724.1 [(MS+H)⁺].

[96] Example 2. Assay of Inhibition of HIV Viral Replication.

[97] The ability of the compounds of the invention to inhibit HIV viral replication is tested using the T-lymphoblastoid cell line CEM-SS.

[98] *Cell Preparation.* CEM-SS cells are passaged in T-75 flasks prior to use in the antiviral assay. On the day preceding the assay, the cells are split 1:2 to assure they are in an exponential growth phase at the time of infection. Total cell and viability quantification are performed using a hemocytometer and Trypan Blue dye exclusion. Cell viability must be greater than 95% for the cells to be utilized in the assay. The cells are re-suspended at 5×10^4 cells per mL in tissue culture medium and added to the test compound-containing microtiter plates (evaluated at various concentrations) in a volume of 50 μ L. The internal assay control is AZT and is evaluated at concentrations of 100 nM to 0.32 nM.

[99] *Virus Preparation.* The virus used for the cytoprotection assays is the lymphocyte-tropic virus HIV-1_{IIIB}. The virus is obtained from the NIH AIDS Research and Reference Reagent Program and the stock virus pool is produced in CEM-SS cells. A pre-titered aliquot of virus is removed from the freezer (-80°C) and

allowed to thaw slowly to room temperature in a biological safety cabinet. Virus is re-suspended and diluted into tissue culture medium such that the amount of virus added to each well in a volume of 50 μ L is the amount determined to yield 85 to 95% cell killing at 6 days post-infection.

[100] *Plate Format.* Each plate contains cell control wells (cells only), virus control wells (cells plus virus), test compound toxicity wells (cells plus test compound only), test compound colorimetric control wells (test compound only) and experimental wells (test compound plus cells plus virus). Samples are tested in triplicate typically with five half-log dilutions per compound.

[101] *Efficacy and Toxicity XTT.* Following incubation at 37°C in a 5% CO₂ incubator, the test plates are stained with the tetrazolium dye XTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide). XTT-tetrazolium is metabolized by the mitochondrial enzymes of metabolically active cells to a soluble formazan product. XTT solution is prepared daily as a stock of 1 mg/mL in RPMI1640. Phenazine methosulfate (PMS) solution is prepared at 0.15 mg/mL in PBS and stored in the dark at -20°C. XTT/PMS stock is prepared immediately before use by adding 40 μ L of PMS per mL of XTT solution. Fifty microliters of XTT/PMS is added to each well of the plate prior to re-incubation for 4 hr at 37°C. Plates are sealed with adhesive plate sealers and shaken gently or inverted several times to mix the soluble formazan product. The plate is read spectrophotometrically at 450/650 nm with a Molecular Devices Vmax plate reader.

[102] *Data Analysis.* Raw data is collected from the Softmax Pro 4.6 software and imported into a Microsoft Excel spreadsheet for analysis by linear curve fit calculations.

[103] **Example 3. Assay of Cytochrome P450 Inhibition.**

[104] The ability of the compounds of the invention to inhibit various cytochrome P450 metabolism is assayed as follows.

[105] Stock solutions of test compound (30 mM) are prepared in DMSO. Stock solutions of the CYP450-selective marker substrates, phenacetin (CYP1A2), tolbutamide (CYP2C9), *S*-mephenytoin (CYP2C19), dextromethorphan (CYP2D6) and midazolam (CYP3A4) are prepared in acetonitrile. Stock solution of the CYP2C8-selective marker substrate amodiaquine is prepared in methanol. Human liver microsomes are incubated with the CYP450-selective marker substrates and 1:3-

or 1:2- (for CYP2C8) serial dilutions of test compound (e.g., 0.1 - 50 μM) in 0.1 M potassium phosphate buffer, pH 7.4, with 3 mM MgCl_2 in shallow 96-well plates. The concentration of the human liver microsomes in the incubations is 0.5 mg/mL for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and 0.025 mg/mL for CYP2C8. The concentrations of the selective marker substrates in the final incubations are as follows: phenacetin (30 μM), amodiaquine (0.25 μM), tolbutamide (150 μM), *S*-mephenytoin (100 μM), dextromethorphan (8 μM), midazolam (5 μM). The reactions are initiated by the addition of NADPH and are incubated for 15 or 30 min (for *S*-mephenytoin only) at 37°C. The final incubation volume is 100 μL . The reactions are stopped by addition of 150 μL of acetonitrile with internal standard. The plates are centrifuged to pellet precipitated protein, and supernatants are analyzed by LC-MS/MS for amounts of the metabolites of the CYP450-selective substrates formed.

[106] Example 4. Enhancement of pharmacokinetic parameters for compound 200, a deuterated derivative of atazanavir, when administered with compound 101 to monkeys

Five male cyno monkeys (Grp 2) were dosed IV with either

- (a) 7.5 mg/kg of compound **200** co-dosed with 2.5 mg/kg of compound **101**, or
- (b) 7.5 mg/kg of compound **200** only.

Five male cyno monkeys (Grp 1) were dosed IV with 10 mg/kg of compound 200

Dosing solutions were prepared in saline solution at concentrations of

- (a) 3.75 mg/mL compound **200** + 1.75 mg/mL compound **200** (for co-dosing),
- or
- (b) 5 mg/mL compound **200** (for dosing of compound **200** only).

The dosing volume was 2 mL/kg.

Blood was collected pre-dose and post dose at 5 min, 15 min, 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 12 hr and 24 hr. Plasma samples were analyzed by LC-MS/MS. The limit of quantitation was 2.5 ng/mL for compound **200** and for compound **101**. The results of these dosing studies are shown in Table 2.

Table 2

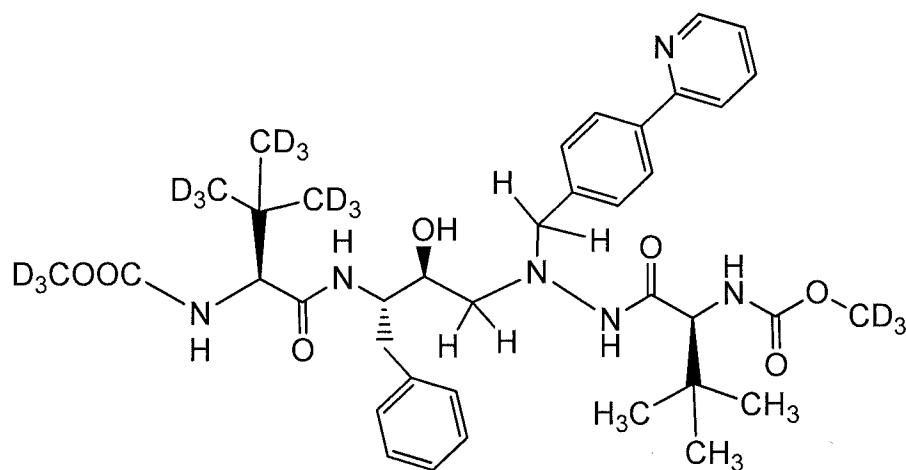
Study # (Monkey Grp #)	Compd	Dose	C _{8hr}	AUC _(0-∞)	AUC _{(0-∞)/Dose^a}	t _{1/2}
			ng/mL	hr*ng/mL		hr
CCP- 1001 (Grp 1)	Compound 200	(10 mg/kg, discrete)	13± 8	6370± 1071	637	1.40± 0.26
CCP- 1104 (Grp 2)	Compound 200	(7.5 mg/kg, discrete)	49± 13	7328± 768	977	2.19± 0.32
CCP- 1104 (Grp 2)	Compound 200	7.5 mg/kg ^b co-dosed with 2.5 mg/kg Compound 101	116± 52	8861± 1735	1478	1.99± 0.29

^a: Measured dose correction was applied when the measure dose deviated > 10% from the nominal dose

^b: measured dose = 6 mg/kg

[107] As shown in Table 2, administration of an exemplary compound of the invention (compound **101**) with a deuterated derivative of atazanavir, compound **200**, advantageously provides a substantial increase in the pharmacokinetic parameters C_{8hr}, AUC_{0-∞}, and AUC_{0-∞}/Dose of compound **200** as compared to the same parameters for compound 200 when the latter is administered discretely (i.e., in the absence of compound **101**).

[108] The structure of compound 200 is as follows:



200,

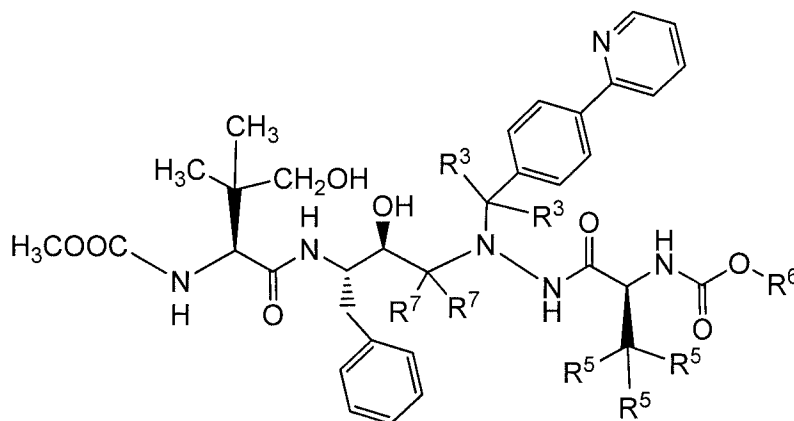
wherein any atom not designated as deuterium is present at its natural isotopic abundance.

[109] 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

What is claimed is:

1. A compound of Formula I:



(I), or a pharmaceutically acceptable salt thereof, wherein:

each R^7 is the same and is selected from hydrogen and deuterium;

each R^3 is the same and is selected from hydrogen and deuterium;

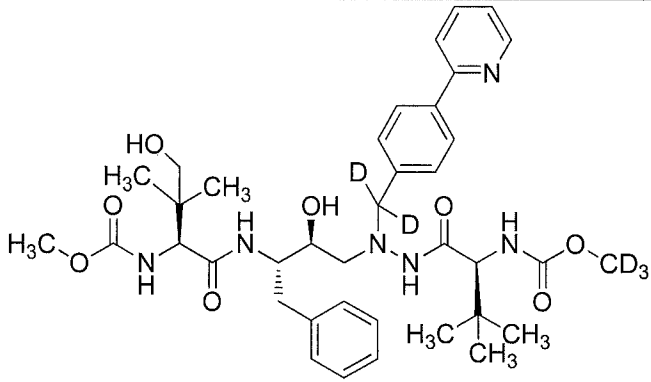
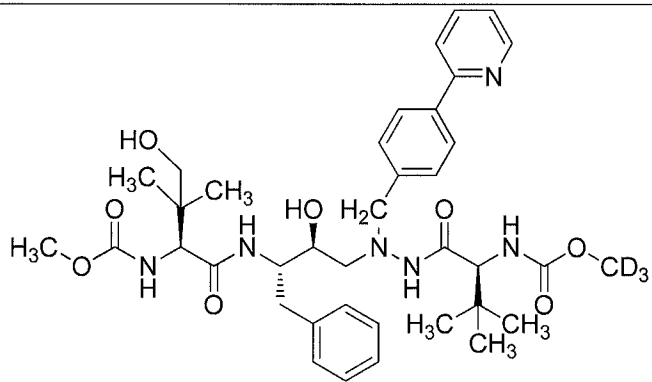
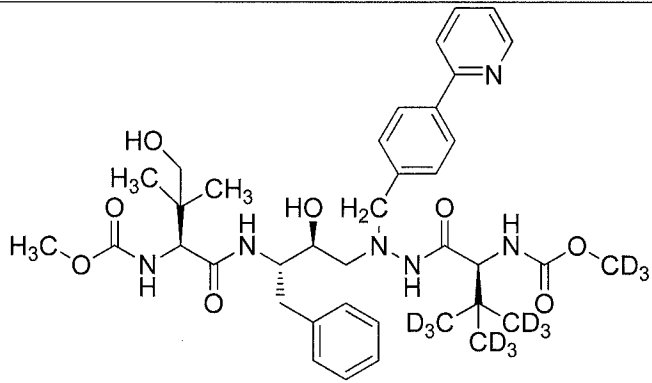
each R^5 is the same and is selected from $-\text{CH}_3$ and $-\text{CD}_3$;

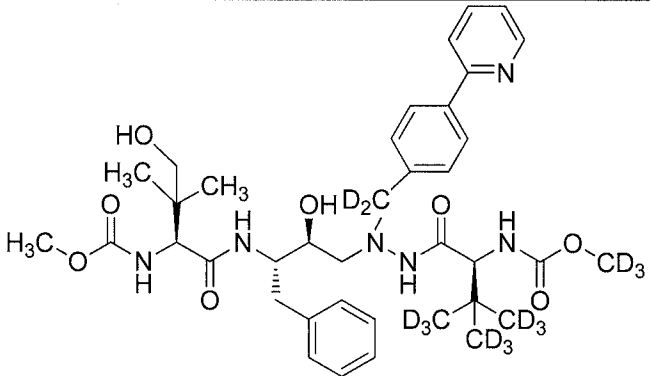
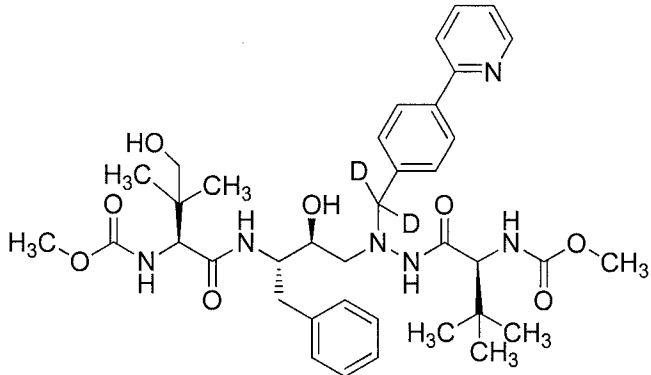
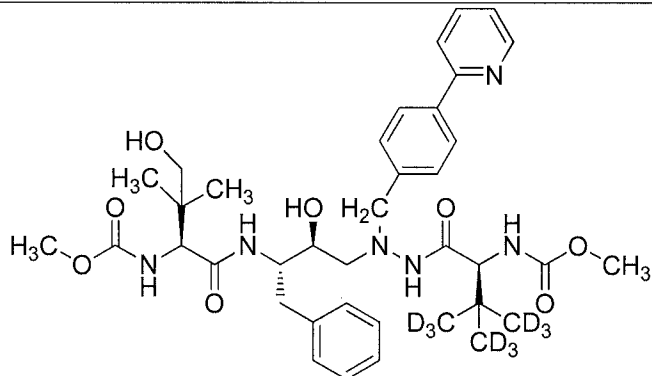
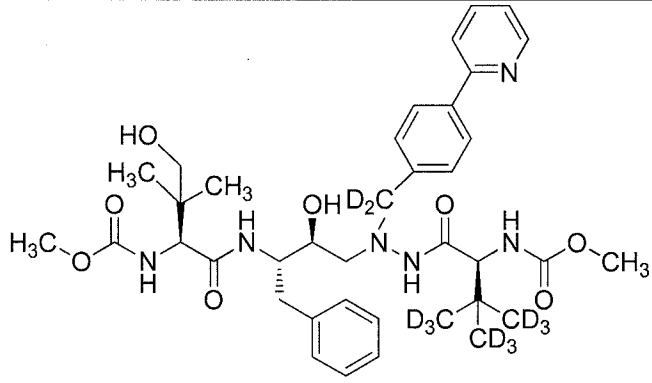
R^6 is selected from $-\text{CH}_3$ and $-\text{CD}_3$; and

provided that if each R^7 is hydrogen, each R^3 is hydrogen, and each R^5 is $-\text{CH}_3$, then R^6 is $-\text{CD}_3$.

2. The compound of claim 1, wherein R^6 is $-\text{CD}_3$.
3. The compound of claim 1 or 2, wherein each R^3 is deuterium.
4. The compound of claim 1 or 2, wherein each R^3 is hydrogen.
5. The compound of any one of claims 1 to 4, wherein each R^5 is CH_3 .
6. The compound of any one of claims 1 to 4, wherein each R^5 is CD_3 .
7. The compound of any one of the preceding claims, wherein each R^7 is hydrogen.

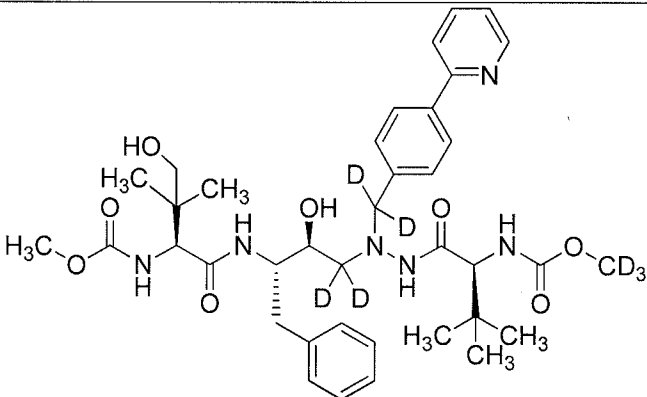
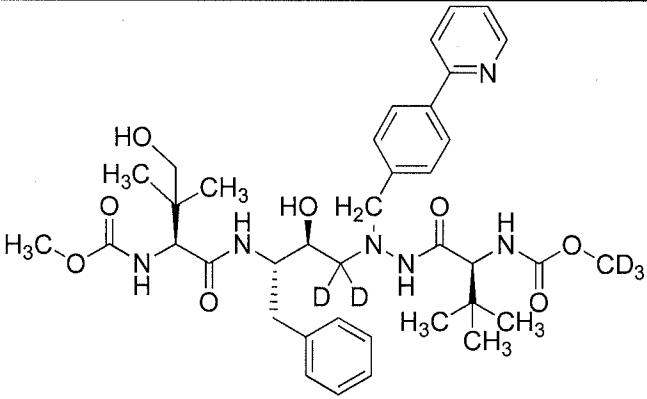
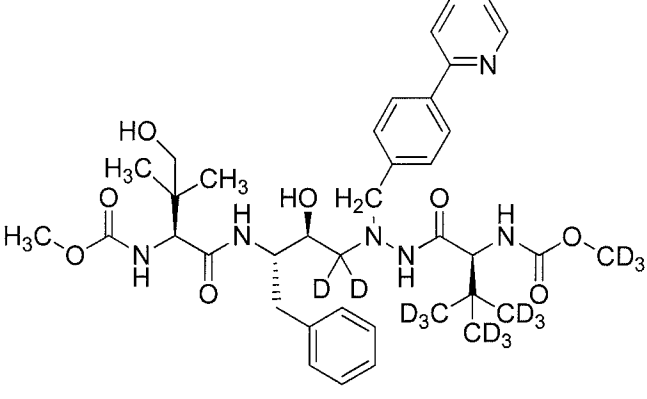
8. The compound of any one of the preceding claims, wherein any atom not designated as deuterium is present at its natural isotopic abundance.
9. The compound of claim 1, wherein the compound is any one of the compounds set forth in the table below:

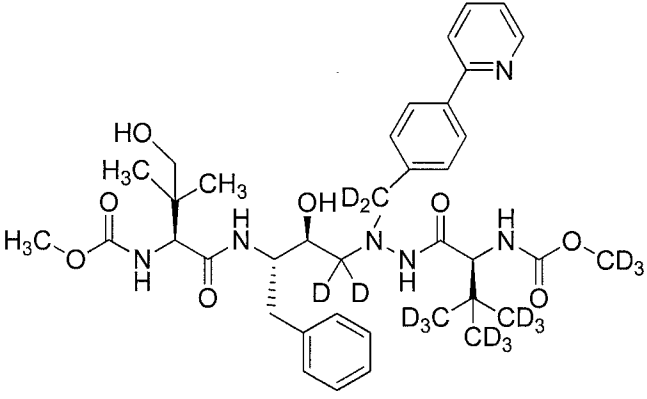
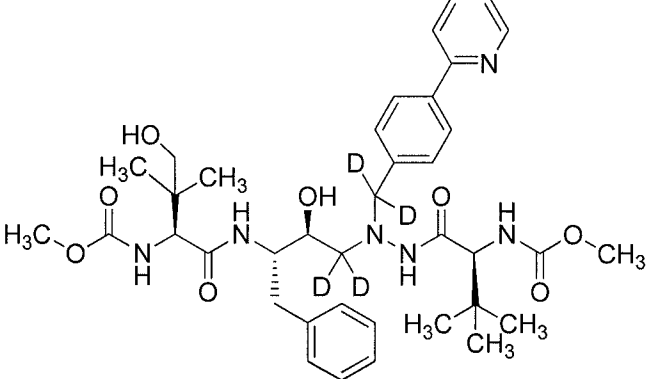
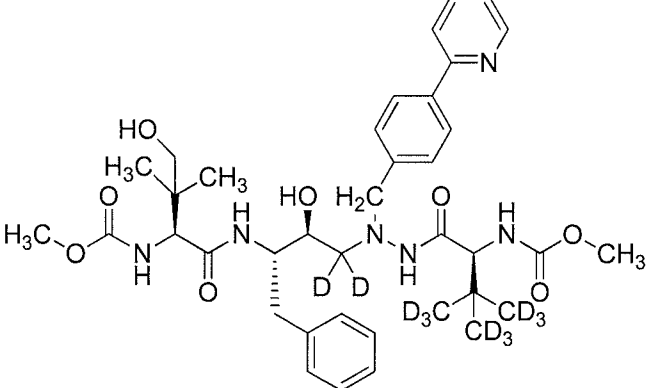
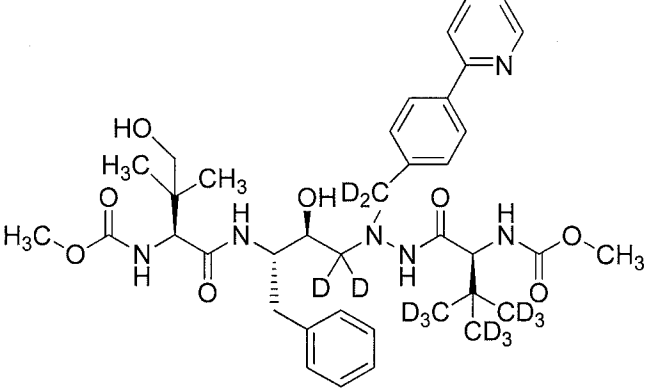
Compound No.	Structure
100	
101	
102	

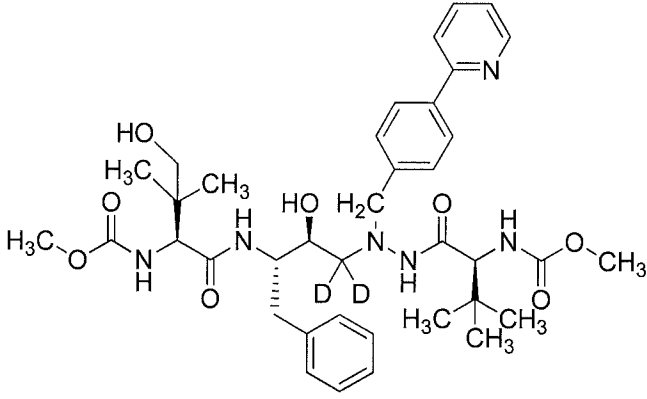
Compound No.	Structure
120	 Chemical structure of compound 120: A complex molecule featuring a central chiral center (C1) bonded to a hydroxyl group (HO), a methyl group (CH₃), and a methoxycarbonyl group (H₃C-O-C(=O)-NH-). C1 is also bonded to a chiral center (C2) which is part of a chain containing a hydroxyl group (OH), a deuterated methylene group (D₂CH₂), and a pyridine ring. The pyridine ring is substituted with a phenyl group and a pyridine ring. The chain also includes a chiral center (C3) bonded to a methyl group (CH₃) and a methoxycarbonyl group (H₃C-O-C(=O)-NH-). The chain ends with a chiral center (C4) bonded to a methyl group (CH₃) and a methoxycarbonyl group (H₃C-O-C(=O)-NH-).
121	 Chemical structure of compound 121: A complex molecule featuring a central chiral center (C1) bonded to a hydroxyl group (HO), a methyl group (CH₃), and a methoxycarbonyl group (H₃C-O-C(=O)-NH-). C1 is also bonded to a chiral center (C2) which is part of a chain containing a hydroxyl group (OH), a deuterated methylene group (D-CH₂), and a pyridine ring. The pyridine ring is substituted with a phenyl group and a pyridine ring. The chain also includes a chiral center (C3) bonded to a methyl group (CH₃) and a methoxycarbonyl group (H₃C-O-C(=O)-NH-). The chain ends with a chiral center (C4) bonded to a methyl group (CH₃) and a methoxycarbonyl group (H₃C-O-C(=O)-NH-).
122	 Chemical structure of compound 122: A complex molecule featuring a central chiral center (C1) bonded to a hydroxyl group (HO), a methyl group (CH₃), and a methoxycarbonyl group (H₃C-O-C(=O)-NH-). C1 is also bonded to a chiral center (C2) which is part of a chain containing a hydroxyl group (OH), a methylene group (H₂C), and a pyridine ring. The pyridine ring is substituted with a phenyl group and a pyridine ring. The chain also includes a chiral center (C3) bonded to a methyl group (CH₃) and a methoxycarbonyl group (H₃C-O-C(=O)-NH-). The chain ends with a chiral center (C4) bonded to a methyl group (CH₃) and a methoxycarbonyl group (H₃C-O-C(=O)-NH-).
123	 Chemical structure of compound 123: A complex molecule featuring a central chiral center (C1) bonded to a hydroxyl group (HO), a methyl group (CH₃), and a methoxycarbonyl group (H₃C-O-C(=O)-NH-). C1 is also bonded to a chiral center (C2) which is part of a chain containing a hydroxyl group (OH), a deuterated methylene group (D₂CH₂), and a pyridine ring. The pyridine ring is substituted with a phenyl group and a pyridine ring. The chain also includes a chiral center (C3) bonded to a methyl group (CH₃) and a methoxycarbonyl group (H₃C-O-C(=O)-NH-). The chain ends with a chiral center (C4) bonded to a methyl group (CH₃) and a methoxycarbonyl group (H₃C-O-C(=O)-NH-).

or a pharmaceutically acceptable salt thereof, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

10. The compound of claim 1, wherein the compound is any one of the compounds set forth in the table below:

Compound No.	Structure
130	
131	
132	

Compound No.	Structure
133	 Chemical structure of compound 133: A complex molecule featuring a central chiral center (C2) bonded to a hydroxyl group (OH), a phenyl ring, and two amide groups. The left amide group is part of a chain ending in a methyl ester (H₃C-O-CO-NH-CH(CH₃)-CH₂-OH). The right amide group is part of a chain ending in a deuterated methyl ester (H₃C-O-CO-NH-CH(CH₃)-CH₂-OH, where the methyl group is CD₃). The central chiral center is also bonded to a deuterated methyl group (CD₃) and a deuterated methyl group (CD₃).
134	 Chemical structure of compound 134: A complex molecule featuring a central chiral center (C2) bonded to a hydroxyl group (OH), a phenyl ring, and two amide groups. The left amide group is part of a chain ending in a methyl ester (H₃C-O-CO-NH-CH(CH₃)-CH₂-OH). The right amide group is part of a chain ending in a methyl ester (H₃C-O-CO-NH-CH(CH₃)-CH₂-OH). The central chiral center is also bonded to a deuterated methyl group (CD₃) and a deuterated methyl group (CD₃).
135	 Chemical structure of compound 135: A complex molecule featuring a central chiral center (C2) bonded to a hydroxyl group (OH), a phenyl ring, and two amide groups. The left amide group is part of a chain ending in a methyl ester (H₃C-O-CO-NH-CH(CH₃)-CH₂-OH). The right amide group is part of a chain ending in a methyl ester (H₃C-O-CO-NH-CH(CH₃)-CH₂-OH). The central chiral center is also bonded to a deuterated methyl group (CD₃) and a deuterated methyl group (CD₃).
136	 Chemical structure of compound 136: A complex molecule featuring a central chiral center (C2) bonded to a hydroxyl group (OH), a phenyl ring, and two amide groups. The left amide group is part of a chain ending in a methyl ester (H₃C-O-CO-NH-CH(CH₃)-CH₂-OH). The right amide group is part of a chain ending in a methyl ester (H₃C-O-CO-NH-CH(CH₃)-CH₂-OH). The central chiral center is also bonded to a deuterated methyl group (CD₃) and a deuterated methyl group (CD₃).

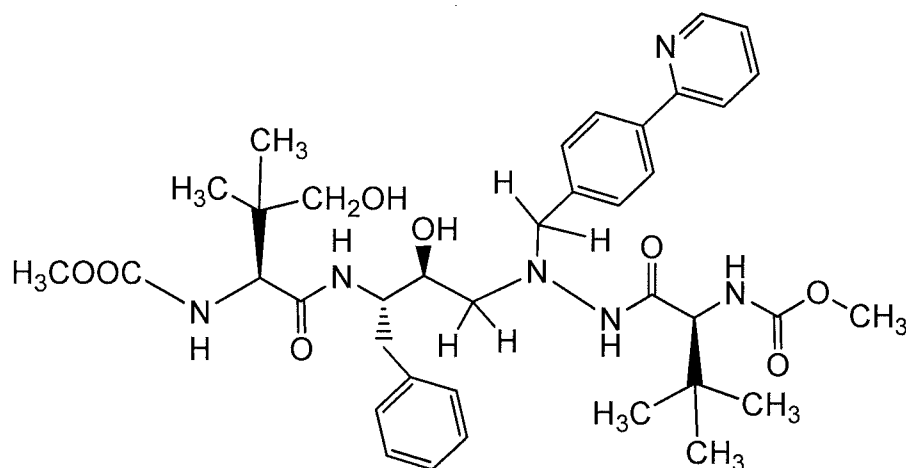
Compound No.	Structure
137	

or a pharmaceutically acceptable salt thereof, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

11. A pharmaceutical composition comprising a compound of any one of claims 1-10 or a pharmaceutically acceptable salt of any of the foregoing; and a pharmaceutically acceptable carrier.
12. A method of increasing the efficacy in a subject of a therapeutic agent that is (i) metabolized by a liver enzyme; (ii) transported by an efflux pump; or (iii) a combination of (i) and (ii), comprising co-administering to the subject a compound of any one of claims 1 to 10 or a composition of claim 11 and the therapeutic agent.
13. The method of claim 12, wherein the therapeutic agent is selected from an HIV protease inhibitor, an HIV integrase inhibitor, an HCV protease inhibitor.
14. The method of claim 13, wherein the therapeutic agent is selected from saquinavir, indinavir, amprenavir, fosamprenavir, darunavir, lopinavir, atazanavir, elvitegravir, danoprevir, dolutegravir, and deuterated derivatives of any of the foregoing.
15. A method of treating an HIV infection in a subject comprising the step of co-administering to the subject a compound of any one of claims 1 to 10 or a composition of claim 11 and a second therapeutic agent selected from an HIV

protease inhibitor and an HIV integrase inhibitor.

16. The method of claim 15, wherein the second therapeutic agent is selected from saquinavir, indinavir, amprenavir, fosamprenavir, darunavir, lopinavir, atazanavir, elvitegravir, dolutegravir, and deuterated derivatives of any of the foregoing.
17. The method of claim 15 wherein the second therapeutic agent is selected from danoprevir and deuterated derivatives of danoprevir.
18. A method of treating an HIV infection in a subject comprising the step of administering to the subject a compound of any one of claims 1 to 10 or a composition of claim 11.
19. A compound of Formula II:



(II), or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising a compound of claim 19 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.
21. A method of increasing the efficacy in a subject of a therapeutic agent that is (i) metabolized by a liver enzyme; (ii) transported by an efflux pump; or (iii) a

combination of (i) and (ii), comprising co-administering to the subject a compound of claim 19 or a composition of claim 20 and the therapeutic agent selected from an HIV protease inhibitor, an HIV integrase inhibitor, an HCV protease inhibitor.

22. A method of treating an HIV infection in a subject comprising the step of co-administering to the subject a compound of claim 19 or a composition of claim 20 and a second therapeutic agent selected from an HIV protease inhibitor and an HIV integrase inhibitor.
23. The method of claim 22, wherein the second therapeutic agent is selected from saquinavir, indinavir, amprenavir, fosamprenavir, darunavir, lopinavir, atazanavir, elvitegravir, dolutegravir, and deuterated derivatives of any of the foregoing.
24. A method of treating an HIV infection in a subject comprising the step of administering to the subject a compound of claim 19 or a composition of claim 20.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/41511

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/44; C07D 213/04; A61P 31/12 (2012.01)

USPC - 514/357; 546/332

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)

IPC(8) -A61K 31/44; C07D 213/04; A61P 31/12 (2012.01)

USPC -514/357; 546/332

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST, Google Patents, Google Scholar, WIPO (natural, isotope, abundance, liver, enzyme, efflux, pump, saquinavir, indinavir, amprenavir, fosamprenavir, darunavir, lopinavir, atazanavir, elvitegravir, dolutegravir, deuterium, formula, azapeptide, method, treat, HIV, pyridinyl, pyridin-5-yl, methanol)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0076097 A1 (CZARNIK) 19 March 2009 (19.03.2009) entire document, especially para[0003], [0005], [0021]-[0022], [0031], [0065], [0067].	1-4, 9-10, 19-24
Y	US 7,723,380 B2 (CANNIZZARO, et al.) 25 May 2010 (25.05.2010) entire document, especially col 1, ln 21-24, 44-60; col 6, ln 27-47; col 15, ln 27-44.	1-4, 9-10, 19-24

☐ 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

13 August 2012 (13.08.2012)

Date of mailing of the international search report

24 AUG 2012

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

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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/41511

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.: 5-8, 11-18
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.