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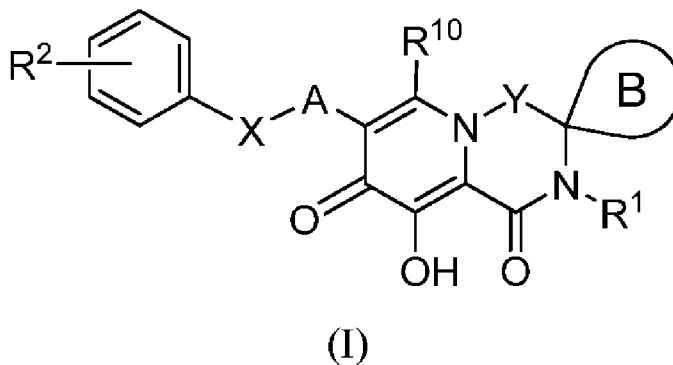
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(54) Title: SPIROCYCLIC PYRIDOTRIAZINE DERIVATIVES USEFUL AS HIV INTEGRASE INHIBITORS



(57) Abstract: The present invention relates to Spirocyclic Pyridotriazine Derivatives of Formula (I) and pharmaceutically acceptable salts thereof, wherein A, B, X, Y, R¹, R² and R¹⁰ are as defined herein. The present invention also relates to compositions comprising at least one Spirocyclic Pyridotriazine Derivative, and methods of using the Spirocyclic Pyridotriazine Derivatives for treating or preventing HIV infection in a subject.

SPIROCYCLIC PYRIDOTRIAZINE DERIVATIVES USEFUL AS HIV INTEGRASE INHIBITORS

FIELD OF THE INVENTION

5 The present invention relates to Spirocyclic Pyridotriazine Derivatives, compositions comprising at least one Spirocyclic Pyridotriazine Derivative, and methods of using the Spirocyclic Pyridotriazine Derivatives for treating or preventing HIV infection in a subject.

10 BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV), particularly the strains known as HIV type-1 (HIV-1) virus and type-2 (HIV-2) virus, is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous
15 system. A common feature of retrovirus replication is the insertion by virally-encoded integrase of +proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA and covalent joining of the recessed 3'
20 OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV
25 protease [Tohous, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)]. All three enzymes have been shown to be essential for the replication of HIV.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse
30 transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhibitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication.

The following references may be of interest as background:

International Publication Nos. WO 11/045330 and WO 11/121105 disclose macrocyclic compounds having HIV integrase inhibitory activity.

Kinzel et al., *Tet. Letters* 2007, 48(37): pp. 6552-6555 discloses the synthesis of tetrahydropyridopyrimidones as a scaffold for HIV-1 integrase inhibitors.

5 Ferrara et al., *Tet. Letters* 2007, 48(37), pp. 8379-8382 discloses the synthesis of a hexahydropyrimido[1,2-*a*]azepine-2-carboxamide derivative useful as an HIV integrase inhibitor.

Muraglia et al., *J. Med. Chem.* 2008, 51: 861-874 discloses the design and synthesis of bicyclic pyrimidinones as potent and orally bioavailable HIV-1 integrase inhibitors.

10 US2004/229909 discloses certain compounds having integrase inhibitory activity.

US 7232819 and US 2007/0083045 disclose certain 5,6-dihydroxypyrimidine-4-carboxamides as HIV integrase inhibitors.

15 US 7169780, US 7217713, and US 2007/0123524 disclose certain N-substituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamides as HIV integrase inhibitors.

US 7279487 discloses certain hydroxynaphthyridinone carboxamides that may be useful as HIV integrase inhibitors.

US 7135467 and US 7037908 disclose certain pyrimidine carboxamides that may be useful as HIV integrase inhibitors.

20 US 7211572 discloses certain nitrogenous condensed ring compounds that are HIV integrase inhibitors.

US 7414045 discloses certain tetrahydro-4H-pyrido[1,2-*a*]pyrimidine carboxamides, hexahydropyrimido[1,2-*a*]azepine carboxamides, and related compounds that may be useful as HIV integrase inhibitors.

25 US 8129385 discloses certain hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamides, and related compounds that may be useful as HIV integrase inhibitors.

30 WO 2006/103399 discloses certain tetrahydro-4H-pyrimidooxazepine carboxamides, tetrahydropyrazinopyrimidine carboxamides, hexahydropyrimidodiazepine carboxamides, and related compounds that may be useful as HIV integrase inhibitors.

US 2007/0142635 discloses processes for preparing hexahydropyrimido[1,2-*a*]azepine-2-carboxylates and related compounds.

US 2007/0149556 discloses certain hydroxypyrimidinone derivatives having HIV integrase inhibitory activity.

Various pyrimidinone compounds useful as HIV integrase inhibitors are also disclosed in US 7115601, US 7157447, US 7173022, US 7176196, US 7192948, US 7273859, and US 7419969.

US 2007/0111984 discloses a series of bicyclic pyrimidinone compounds useful as HIV integrase inhibitors.

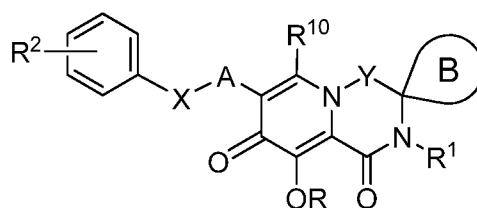
US 2006/0276466, US 2007/0049606, US 2007/0111985, US 2007/0112190, US 2007/0281917, US 2008/0004265 each disclose a series of bicyclic pyrimidinone compounds useful as HIV integrase inhibitors.

US7462608 and US7649015 each disclose phosphate and phosphonate substituted heterocycles useful as HIV nNRTI inhibitors and HIV protease inhibitors, respectively.

International Publication No. WO 2015/095258 discloses phosphate and phosphonate substituted heterocycles useful as HIV integrase inhibitors.

SUMMARY OF THE INVENTION

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



(I)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

A is -NHC(O)- or 5 or 6-membered monocyclic heteroaryl;

B is 3 to 8-membered heterocycloalkyl, which may be optionally substituted with one or more groups, each independently selected from R^6 ;

X is $\text{C}_1\text{-C}_3$ alkylene;

Y is $\text{-CH}_2\text{-}$, $\text{-CH(R}^6\text{)-}$ or $\text{-N(R}^3\text{)-}$;

R is H or benzyl;

R^1 is selected from H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{-(C}_1\text{-C}_4\text{ alkylene)-O-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-(C}_1\text{-C}_4\text{ alkylene)-S-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-(C}_1\text{-C}_4\text{ alkylene)-SO}_2\text{-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-(C}_1\text{-C}_4\text{ alkylene)-N-(C}_1\text{-C}_6\text{ alkyl)}_2$, $\text{-(C}_1\text{-C}_6\text{ alkylene)}_m\text{-Z-(C}_1\text{-C}_3\text{ alkylene)}_m\text{-R}^{11}$, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$

hydroxyalkyl, phenyl, 3 to 8-membered monocyclic heterocycloalkyl and 5 or 6-membered monocyclic heteroaryl;

R^2 represents up to 3 optional substituents, each independently selected from halo, C_1 - C_6 alkyl, $-O-(C_1-C_6 \text{ alkyl})$ and C_1 - C_6 haloalkyl;

R^3 is selected from H, C_1 - C_6 alkyl, $-SO_2R^4$, $-C(O)R^4$, $-(C_1-C_6 \text{ alkylene})_p-$
 $C(O)N(R^5)_2$, $-(C_2-C_4 \text{ alkylene})-O-(C_1-C_6 \text{ alkyl})$, $-(C_2-C_4 \text{ alkylene})-S-(C_1-C_6 \text{ alkyl})$, $-(C_2-C_4 \text{ alkylene})-SO_2-(C_1-C_6 \text{ alkyl})$, $-(C_2-C_4 \text{ alkylene})-N-(C_1-C_6 \text{ alkyl})_2$, $-(C_1-C_6 \text{ alkylene})_m-Z-(C_1-C_3 \text{ alkylene})_m-R^{11}$, C_3 - C_7 cycloalkyl, phenyl, 4 to 8-membered monocyclic heterocycloalkyl or 6-membered monocyclic heteroaryl and 8 to 10-membered bicyclic heteroaryl;

each occurrence of R^4 is independently selected from H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_7 cycloalkyl, phenyl, 3 to 8-membered monocyclic heterocycloalkyl or 6-membered monocyclic heteroaryl and 8 to 10-membered bicyclic heteroaryl, wherein said C_3 - C_7 cycloalkyl group, said phenyl group, said 3 to 8-membered monocyclic heteroaryl group, said 6-membered monocyclic heteroaryl group and said 8 to 10-membered bicyclic heteroaryl group may be optionally substituted with one or more groups, each independently selected from R^6 ;

each occurrence of R^5 is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, $-(C_1-C_6 \text{ alkylene})-N(R^7)_2$, C_1 - C_6 haloalkyl, $-C(O)O(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkylene})_m-Z-(C_1-C_3 \text{ alkylene})_m-R^{11}$, $-(C_1-C_6 \text{ alkylene})_p-R^8$ and $-(C_1-C_6 \text{ alkylene})-O-(C_1-C_6 \text{ alkyl})$;

each occurrence of R^6 is independently selected from halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-(C_1-C_6 \text{ alkylene})_m-Z-(C_1-C_3 \text{ alkylene})_m-R^{11}$, $-N(R^{20})_2$, 3 to 8-membered monocyclic heterocycloalkyl, 6 to 10-membered bicyclic heterocycloalkyl, $-O-(C_1-C_6 \text{ alkyl})$, $-O-(C_6-C_{10} \text{ aryl})$, $-O-(C_1-C_6 \text{ alkylene})-O-(C_1-C_6 \text{ alkyl})$, $-O-(C_1-C_6 \text{ haloalkyl})$, $-O-(C_1-C_6 \text{ alkylene})-O-(C_1-C_6 \text{ alkyl})$, $-S(O)_2(C_1-C_6 \text{ alkyl})$, $-NHS(O)_2-(C_1-C_6 \text{ alkyl})$, $-S(O)_2NH-(C_1-C_6 \text{ alkyl})$, $-OC(O)-(C_1-C_6 \text{ haloalkyl})$, $-(C_1-C_6 \text{ alkylene})_p-C(O)O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkylene})_p-C(O)-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkylene})_p-C(O)N(R^7)_2$, C_1 - C_6 hydroxyalkyl, $-P(O)(OR^9)_2$, and $-CN$;

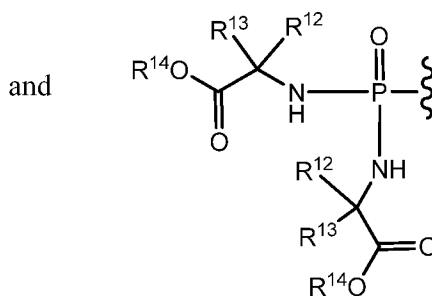
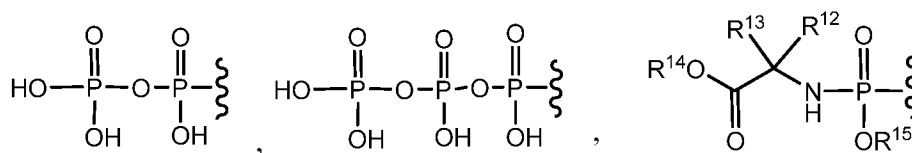
each occurrence of R^7 is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkyl, $-C(O)O(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkylene})_m-Z-(C_1-C_3 \text{ alkylene})_m-R^{11}$, $-(C_1-C_6 \text{ alkylene})_p-R^8$ and $-(C_1-C_6 \text{ alkylene})-O-(C_1-C_6 \text{ alkyl})$;

each occurrence of R^8 is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, 5 or 6-membered monocyclic heteroaryl and 3 to 8-membered monocyclic heterocycloalkyl;

each occurrence of R^9 is independently selected from H, C_1 - C_6 alkyl and $-(C_1-C_6 \text{ alkylene})_m-Z-(C_1-C_3 \text{ alkylene})_m-R^{11}$;

R^{10} is selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl and $-(C_1-C_4 \text{ alkylene})-O-(C_1-C_6 \text{ alkyl})$;

5 each occurrence of R^{11} is independently selected from $-P(O)(-OR^{18})_2$,



each occurrence of R^{12} is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, phenyl or benzyl, wherein said C_1 - C_6 alkyl may be optionally substituted with a group selected from halo, $-OR^{16}$, $-SR^{16}$, guanidino, $-N(R^{16})_2$, $-C(O)OR^{16}$, $-C(O)N(R^{16})_2$, $-NHC(O)R^{16}$, 5- or 6-membered monocyclic heteroaryl and 9- or 10-membered bicyclic heteroaryl, and wherein said phenyl group and said benzyl group may be optionally substituted with up to 2 groups, each independently selected from C_1 - C_6 alkyl, halo and $-OR^{16}$;

each occurrence of R^{13} is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, phenyl or benzyl, wherein said C_1 - C_6 alkyl may be optionally substituted with a group selected from halo, $-OR^{16}$, $-SR^{16}$, guanidino, $-N(R^{16})_2$, $-C(O)OR^{16}$, $-C(O)N(R^{16})_2$, $-NHC(O)R^{16}$, 5- or 6-membered monocyclic heteroaryl and 9- or 10-membered bicyclic heteroaryl, and wherein said phenyl group and said benzyl group may be optionally substituted with up to 2 groups, each independently selected from C_1 - C_6 alkyl, halo and $-OR^{16}$;

each occurrence of R^{14} is independently selected from H, C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, $-(C_1-C_3 \text{ alkylene})_m-(C_3-C_7 \text{ cycloalkyl})$, $-(C_1-C_3 \text{ alkylene})_m-(C_6-C_{10} \text{ aryl})$ or $-(C_1-C_3 \text{ alkylene})_m$ -adamantyl, wherein said C_1 - C_{20} alkyl group, said C_2 - C_{20} alkenyl group, said C_6 - C_{10} aryl group and said adamantyl group may be optionally substituted with up to three groups, each independently selected from halo, -

OR¹⁶, -C(O)OR¹⁶, CN, NO₂, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₇ cycloalkyl, C₆-C₁₀ aryl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, -N(R¹⁶)₂, -C(O)N(R¹⁶)₂ -SR¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -S(O)₂N(R¹⁶)₂, -NHC(O)R¹⁶, -NHC(O)OR¹⁶ and -NHC(O)N(R¹⁶)₂;

R¹⁵ is H, C₆-C₁₀ aryl, 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl, wherein said C₆-C₁₀ aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group may be optionally substituted with R¹⁷;

each occurrence of R¹⁶ is independently H, C₁-C₁₀ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, -(C₁-C₃ alkylene)_m-(C₃-C₇ cycloalkyl), -(C₁-C₃ alkylene)_m-(C₆-C₁₀ aryl), -(C₁-C₃ alkylene)_m-(4 to 7-membered heterocycloalkyl), -(C₁-C₃ alkylene)_m-(5- or 6-membered monocyclic heteroaryl) or -(C₁-C₃ alkylene)_m-(9- or 10-membered bicyclic heteroaryl), wherein said C₃-C₇ cycloalkyl group, said C₆-C₁₀ aryl group, said 4 to 7-membered heterocycloalkyl group, said 5- or 6-membered monocyclic heteroaryl group or said 9- or 10-membered bicyclic heteroaryl group may be optionally substituted with R¹⁷;

R¹⁷ represents from one to five substituent groups, each independently selected from C₁-C₆ alkyl, halo, -OR¹⁹, -SR¹⁹, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, -O-(C₁-C₆ haloalkyl), -CN, -NO₂, -N(R¹⁹)₂, -C(O)OR¹⁹, -C(O)N(R¹⁹)₂ and -NHC(O)R¹⁹;

each occurrence of R¹⁸ is independently selected from H, C₁-C₆ alkyl, C₆-C₁₀ aryl, -(C₁-C₆ alkylene)-O-(C₁-C₂₀ alkyl), -(C₁-C₆ alkylene)-O-C(O)-R¹⁶, and -(C₁-C₆ alkylene)-O-C(O)-O-R¹⁶;

each occurrence of R¹⁹ is independently H, C₁-C₁₀ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, -(C₁-C₃ alkylene)_m-(C₃-C₇ cycloalkyl), -(C₁-C₃ alkylene)_m-(C₆-C₁₀ aryl), -(C₁-C₃ alkylene)_m-(4 to 7-membered heterocycloalkyl), -(C₁-C₃ alkylene)_m-(5- or 6-membered monocyclic heteroaryl) or -(C₁-C₃ alkylene)_m-(9- or 10-membered bicyclic heteroaryl);

each occurrence of R²⁰ is independently selected from H, C₁-C₆ alkyl and -(C₁-C₆ alkylene)_m-Z-(C₁-C₃ alkylene)_m-R¹¹;

each occurrence of Z is independently selected from a bond, -O- or -N(R⁹)-;

each occurrence of m is independently 0 or 1;

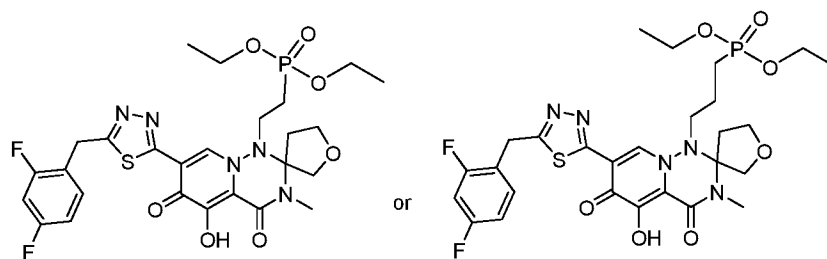
n is 1 or 2; and

each occurrence of p is independently 0 or 1,

such that at least one occurrence of R¹¹ must be present in the compound of

formula (I),

and provided that the compound of formula (I) is other than:



The Compounds of Formula (I) (also referred to herein as the “Spirocyclic Pyridotriazine Derivatives”) and pharmaceutically acceptable salts thereof may be useful, for example, for inhibiting HIV viral replication or replicon activity, and for treating or preventing HIV infection in a subject. Without being bound by any specific theory, it is believed that the Spirocyclic Pyridotriazine Derivatives inhibit HIV viral replication by inhibiting HIV Integrase.

Accordingly, the present invention provides methods for treating or preventing HIV infection in a subject, comprising administering to the subject an effective amount of at least one Spirocyclic Pyridotriazine Derivative.

The details of the invention are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein may be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes Spirocyclic Pyridotriazine Derivatives, compositions comprising at least one Spirocyclic Pyridotriazine Derivative, and methods of using the Spirocyclic Pyridotriazine Derivatives for treating or preventing HIV infection in a subject.

Definitions and Abbreviations

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "-O-alkyl," etc...

As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

A "subject" is a human or non-human mammal. In one embodiment, a subject is a human. In another embodiment, a subject is a primate. In another embodiment, a subject is a monkey. In another embodiment, a subject is a chimpanzee. In still another embodiment, a subject is a rhesus monkey.

The term "effective amount" as used herein, refers to an amount of Spirocyclic Pyridotriazine Derivative and/or an additional therapeutic agent, or a composition thereof that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a subject suffering from HIV infection or AIDS. In the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

The term "preventing," as used herein with respect to an HIV viral infection or AIDS, refers to reducing the likelihood or severity of HIV infection or AIDS.

The term "alkyl," as used herein, refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond. An alkyl group may be straight or branched and contain from about 1 to about 20 carbon atoms. In one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In different embodiments, an alkyl group contains from 1 to 6 carbon atoms (C₁-C₆ alkyl) or from about 1 to about 4 carbon atoms (C₁-C₄ alkyl). Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. An alkyl group may be unsubstituted or substituted by one or more substituents which may be the same or

different. Illustrative examples of substituents include, but are not limited to, halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and -C(O)O-alkyl. In one embodiment, an alkyl group is linear. In another
5 embodiment, an alkyl group is branched. Unless otherwise indicated, an alkyl group is unsubstituted.

The term "alkenyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and having one of its hydrogen atoms replaced with a bond. An alkenyl group may be straight or branched and contain from about 2 to
10 about 15 carbon atoms. In one embodiment, an alkenyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkenyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl. An alkenyl group may be unsubstituted or substituted by one or more substituents which may be the same or different. Illustrative
15 examples of substituents include, but are not limited to, halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and -C(O)O-alkyl. The term "C₂-C₆ alkenyl" refers to an alkenyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkenyl group is unsubstituted.

The term "alkynyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and having one of its hydrogen atoms replaced with a bond. An alkynyl group may be straight or branched and contain from about 2 to about 15
20 carbon atoms. In one embodiment, an alkynyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkynyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butyne and 3-methylbutynyl. An alkynyl group may be unsubstituted or substituted by one or more substituents which may be the same or different. Illustrative examples of substituents include, but are not limited to, halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(O)-alkyl, -O-
25 C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and -C(O)O-alkyl. The term "C₂-C₆ alkynyl" refers to
30

an alkynyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkynyl group is unsubstituted.

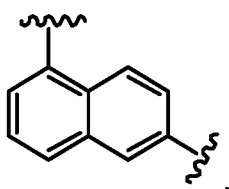
The term "alkylene," as used herein, refers to an alkyl group, as defined above, wherein one of the alkyl group's hydrogen atoms has been replaced with a bond. Non-limiting examples of alkylene groups include $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$ and $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$. In one embodiment, an alkylene group has from 1 to about 6 carbon atoms. In another embodiment, an alkylene group has from about 3 to about 5 carbon atoms. In another embodiment, an alkylene group is branched. In another embodiment, an alkylene group is linear. In one embodiment, an alkylene group is $-\text{CH}_2-$. The term "C₁-C₆ alkylene" refers to an alkylene group having from 1 to 6 carbon atoms. The term "C₁-C₃ alkylene" refers to an alkylene group having from 1 to 3 carbon atoms.

The term "alkenylene," as used herein, refers to an alkenyl group, as defined above, wherein one of the alkenyl group's hydrogen atoms has been replaced with a bond. Non-limiting examples of alkenylene groups include $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CHCH}_2-$, $-\text{CH}_2\text{CH}=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CHCH}_2-$, $-\text{CH}=\text{CHCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}-$ and $-\text{CH}(\text{CH}_3)\text{CH}=\text{CH}-$. In one embodiment, an alkenylene group has from 2 to about 6 carbon atoms. In another embodiment, an alkenylene group has from about 2 to about 4 carbon atoms. In another embodiment, an alkenylene group is branched. In another embodiment, an alkenylene group is linear. The term "C₂-C₆ alkenylene" refers to an alkenylene group having from 2 to 6 carbon atoms. The term "C₂-C₄ alkenylene" refers to an alkenylene group having from 2 to 4 carbon atoms.

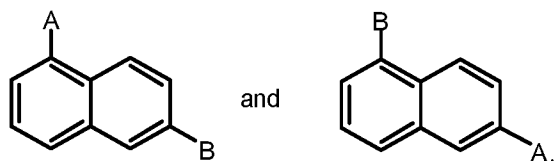
The term "aryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an aryl group contains from about 6 to about 10 carbon atoms. An aryl group may be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, an aryl group may be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of aryl groups include phenyl and naphthyl. In one embodiment, an aryl group is phenyl. Unless otherwise indicated, an aryl group is unsubstituted.

The term "arylene," as used herein, refers to a bivalent group derived from an aryl group, as defined above, by removal of a hydrogen atom from a ring carbon of an aryl group. An arylene group may be derived from a monocyclic or multicyclic ring system comprising from

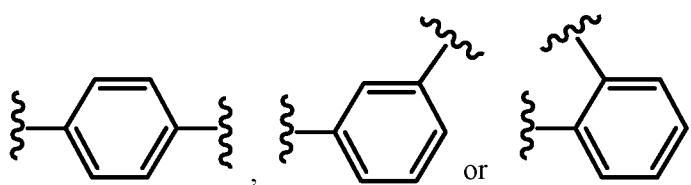
about 6 to about 14 carbon atoms. In one embodiment, an arylene group contains from about 6 to about 10 carbon atoms. In another embodiment, an arylene group is a naphthylene group. In another embodiment, an arylene group is a phenylene group. An arylene group may be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. An arylene group is divalent and either available bond on an arylene group can connect to either group flanking the arylene group. For example, the group "A-arylene-B," wherein the arylene group is:



is understood to represent both:



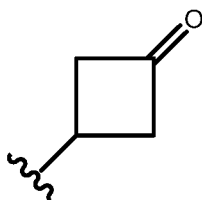
In one embodiment, an arylene group may be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of arylene groups include phenylene and naphthalene. In one embodiment, an arylene group is unsubstituted. In another embodiment, an arylene group is:



Unless otherwise indicated, an arylene group is unsubstituted.

The term "cycloalkyl," as used herein, refers to a saturated or unsaturated non-aromatic mono- or multicyclic ring system comprising from about 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl contains from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkyl contains from about 3 to about 7 ring atoms. In another embodiment, a cycloalkyl contains from about 5 to about 6 ring atoms. The term "cycloalkyl" also encompasses a cycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring, such as tetrahydronaphthalene and the like. Non-limiting examples of

monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of multicyclic cycloalkyls include 1-decalinyl, norbornyl and adamantyl. A cycloalkyl group may be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one
5 embodiment, a cycloalkyl group is unsubstituted. The term "3 to 7-membered cycloalkyl" refers to a cycloalkyl group having from 3 to 7 ring carbon atoms. Unless otherwise indicated, a cycloalkyl group is unsubstituted. A ring carbon atom of a cycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a cycloalkyl group (also referred to herein as a "cycloalkanoyl" group) includes, but is not limited to, cyclobutanoyl:



The term "halo," as used herein, means -F, -Cl, -Br or -I.

The term "haloalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a
15 haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include -CH₂F, -CHF₂, -CF₃, -CH₂Cl and -CCl₃. The term "C₁-C₆ haloalkyl" refers to a haloalkyl group having from 1 to 6 carbon atoms.

The term "hydroxyalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms have been replaced with an -
20 OH group. In one embodiment, a hydroxyalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of hydroxyalkyl groups include -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH and -CH₂CH(OH)CH₃. The term "C₁-C₆ hydroxyalkyl" refers to a hydroxyalkyl group having from 1 to 6 carbon atoms.

The term "heteroaryl," as used herein, refers to an aromatic monocyclic or
25 multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms is independently O, N or S and the remaining ring atoms are carbon atoms. In one embodiment, a heteroaryl group has 5 to 10 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroaryl group is

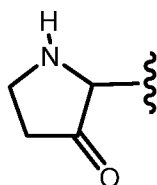
bicyclic. A heteroaryl group may be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. A heteroaryl group is joined via a ring carbon atom, and any nitrogen atom of a heteroaryl may be optionally oxidized to the corresponding N-oxide. The term "heteroaryl" also encompasses a heteroaryl group, as defined above, which is fused to a benzene ring. Non-limiting examples of heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl, 1,3,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, benzimidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like, and all isomeric forms thereof. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. In one embodiment, a heteroaryl group is a 5-membered heteroaryl. In another embodiment, a heteroaryl group is a 6-membered monocyclic heteroaryl. In another embodiment, a heteroaryl group comprises a 5- to 6-membered monocyclic heteroaryl group fused to a benzene ring. Unless otherwise indicated, a heteroaryl group is unsubstituted.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic saturated or unsaturated monocyclic or multicyclic ring system comprising 3 to about 11 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S, N or Si, and the remainder of the ring atoms are carbon atoms. A heterocycloalkyl group may be joined via a ring carbon, ring silicon atom or ring nitrogen atom. In one embodiment, a heterocycloalkyl group is monocyclic and has from about 3 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is monocyclic has from about 4 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is bicyclic and has from about 7 to about 11 ring atoms. In still another embodiment, a heterocycloalkyl group is monocyclic and has 5 or 6 ring atoms. In one embodiment, a heterocycloalkyl group is monocyclic. In another embodiment, a heterocycloalkyl group is bicyclic. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Any -NH group in a heterocycloalkyl ring may exist protected such as, for example, as an -N(BOC), -N(Cbz), -N(Tos) group and the like; such protected heterocycloalkyl groups are considered part

of this invention. The term "heterocycloalkyl" also encompasses a heterocycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring, such as dihydrobenzofuran and the like. A heterocycloalkyl group may be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein

5 below. The nitrogen or sulfur atom of the heterocycloalkyl may be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyl rings include oxetanyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, pyranal, tetrahydrothiophenyl, delta-lactam, delta-lactone and the like, and all isomers thereof.

10 A ring carbon atom of a heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyl group is:



In one embodiment, a heterocycloalkyl group is a 5-membered monocyclic heterocycloalkyl. In another embodiment, a heterocycloalkyl group is a 6-membered

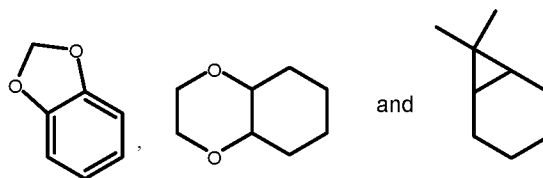
15 monocyclic heterocycloalkyl. The term "3 to 6-membered monocyclic heterocycloalkyl" refers to a monocyclic heterocycloalkyl group having from 3 to 6 ring atoms. The term "4 to 7-membered monocyclic heterocycloalkyl" refers to a monocyclic heterocycloalkyl group having from 4 to 7 ring atoms. The term "7 to 11-membered bicyclic heterocycloalkyl" refers to a bicyclic heterocycloalkyl group having from 7 to 11 ring atoms. Unless otherwise indicated, a

20 heterocycloalkyl group is unsubstituted.

The term "ring system substituent," as used herein, refers to a substituent group attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different. Illustrative examples of ring system substituents include, but are not limited to, alkyl, alkenyl, alkynyl, aryl,

25 heteroaryl, -alkylene-aryl, -arylene-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, -OH, hydroxyalkyl, haloalkyl, -O-alkyl, -O-haloalkyl, -alkylene-O-alkyl, -O-aryl, -O-alkylene-aryl, acyl, -C(O)-aryl, halo, -NO₂, -CN, -SF₅, -C(O)OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-alkylene-aryl, -S(O)-alkyl, -S(O)₂-alkyl, -S(O)-aryl, -S(O)₂-aryl, -S(O)-

heteroaryl, -S(O)₂-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, -S-alkylene-aryl, -S-alkylene-heteroaryl, -S(O)₂-alkylene-aryl, -S(O)₂-alkylene-heteroaryl, -Si(alkyl)₂, -Si(aryl)₂, -Si(heteroaryl)₂, -Si(alkyl)(aryl), -Si(alkyl)(cycloalkyl), -Si(alkyl)(heteroaryl), cycloalkyl, heterocycloalkyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(=N-CN)-NH₂, -C(=NH)-NH₂, -C(=NH)-NH(alkyl), -N(Y₁)(Y₂), -alkylene-N(Y₁)(Y₂), -C(O)N(Y₁)(Y₂) and -S(O)₂N(Y₁)(Y₂), wherein Y₁ and Y₂ may be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and -alkylene-aryl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylenedioxy, ethylenedioxy, -C(CH₃)₂- and the like which form moieties such as, for example:



The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "in substantially purified form," as used herein, refers to the physical state of a compound after the compound is isolated from a synthetic process (*e.g.*, from a reaction mixture), a natural source, or a combination thereof. The term "in substantially purified form," also refers to the physical state of a compound after the compound is obtained from a purification process or processes described herein or well-known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well-known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed “protected”, this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

When any substituent or variable (*e.g.*, alkyl, R¹, R⁷, etc.) occurs more than one time in any constituent or in Formula (I), its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term “prodrug” means a compound (*e.g.*, a drug precursor) that is transformed *in vivo* to provide a Spirocyclic Pyridotriazine Derivative or a pharmaceutically acceptable salt of the compound. The transformation may occur by various mechanisms (*e.g.*, by metabolic or chemical processes), such as, for example, through hydrolysis in blood. For example, if a Spirocyclic Pyridotriazine Derivative or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C₁–C₈)alkyl, (C₂–C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-

(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di (C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl, and the like.

5 Similarly, if a Spirocyclic Pyridotriazine Derivative contains an alcohol functional group, a prodrug may be formed by the replacement of one or more of the hydrogen atoms of the alcohol groups with a group such as, for example, (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkyl, α-amino(C₁-C₄)alkylene-aryl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

15 If a Spirocyclic Pyridotriazine Derivative incorporates an amine functional group, a prodrug may be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl-, RO-carbonyl-, NRR'-carbonyl- wherein R and R' are each independently (C₁-C₁₀)alkyl, (C₃-C₇) cycloalkyl, benzyl, a natural α-aminoacyl, -C(OH)C(O)OY¹ wherein Y¹ is H, (C₁-C₆)alkyl or benzyl, -C(OY²)Y³ wherein Y² is (C₁-C₄) alkyl and Y³ is (C₁-C₆)alkyl; carboxy (C₁-C₆)alkyl; amino(C₁-C₄)alkyl or mono-N- or di-N,N-(C₁-C₆)alkylaminoalkyl; -C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N- or di-N,N-(C₁-C₆)alkylamino morpholino; piperidin-1-yl or pyrrolidin-1-yl, and the like.

25 Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy group of a hydroxyl compound, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (*e.g.*, methyl, ethyl, n-propyl, isopropyl, t-butyl, sec-butyl or n-butyl), alkoxyalkyl (*e.g.*, methoxymethyl), aralkyl (*e.g.*, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (*e.g.*, phenyl optionally substituted with, for example, halogen, C₁₋₄alkyl, -O-(C₁₋₄alkyl) or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters, including those corresponding to both natural and non-natural amino acids (*e.g.*, L-valyl or L-isoleucyl); (4) 30 phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be

further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di (C₆₋₂₄)acyl glycerol.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of solvates include ethanolates, methanolates, and the like. A "hydrate" is a solvate wherein the solvent molecule is water.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than room temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The Spirocyclic Pyridotriazine Derivatives can form salts which are also within the scope of this invention. Reference to a Spirocyclic Pyridotriazine Derivative herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a Spirocyclic Pyridotriazine Derivative contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. In one

embodiment, the salt is a pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salt. In another embodiment, the salt is other than a pharmaceutically acceptable salt. Salts of the Compounds of Formula (I) may be formed, for example, by reacting a Spirocyclic Pyridotriazine Derivative with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, t-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Diastereomeric mixtures may be separated into their individual diastereomers on the basis of their physical chemical differences by methods well-known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers may be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction
5 with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Stereochemically pure compounds may also be prepared by using chiral starting materials or by employing salt resolution techniques. Also, some of the Spirocyclic Pyridotriazine Derivatives may be
10 atropisomers (*e.g.*, substituted biaryls) and are considered as part of this invention. Enantiomers can also be directly separated using chiral chromatographic techniques.

It is also possible that the Spirocyclic Pyridotriazine Derivatives may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. For example, all keto-enol and imine-enamine forms of the compounds are included in the
15 invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, hydrates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which
20 may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. If a Spirocyclic Pyridotriazine Derivative incorporates a double bond or a fused ring, both the *cis*- and *trans*-forms, as well as mixtures, are embraced within the scope of the invention.

Individual stereoisomers of the compounds of the invention may, for example, be
25 substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the *S* or *R* configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the
30 inventive compounds.

In the Compounds of Formula (I), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples.

Isotopically-enriched Compounds of Formula (I) may be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates. In one embodiment, a Compound of Formula (I) has one or more of its hydrogen atoms replaced with deuterium.

Polymorphic forms of the Spirocyclic Pyridotriazine Derivatives, and of the salts, solvates, hydrates, esters and prodrugs of the Spirocyclic Pyridotriazine Derivatives, are intended to be included in the present invention.

List of Abbreviations

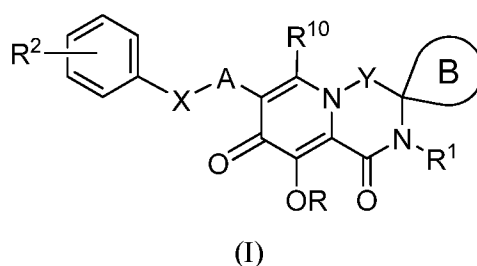
Anal.	=	analytical
Bn	=	benzyl
DCM	=	dichloromethane
DMF	=	dimethylformamide
DMSO	=	dimethylsulfoxide
EDC	=	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Ent A	=	enantiomer A
Ent B	=	enantiomer B
EtOAc	=	ethyl acetate
EtOH	=	ethanol
HOBT	=	1-hydroxy-1H-benzotriazole

	HPLC	=	high-pressure liquid chromatography
	LCMS	=	liquid chromatography-mass spectrometry
	Me	=	methyl
	MeOH	=	methanol
5	MS	=	mass spectroscopy
	NHS	=	normal human serum
	NMR	=	nuclear magnetic resonance spectroscopy
	Pd/C	=	palladium on carbon
	Pd(Ph ₃ P) ₄	=	tetrakis triphenylphosphine palladium(0)
10	RP-MPLC	=	reverse-phase medium pressure liquid chromatography
	Rt or RT	=	room temperature
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	TLC	=	thin-layer chromatography
15	TMS-Br	=	trimethylsilyl bromide

The Compounds of Formula (I)

The present invention provides Spirocyclic Pyridotriazine Derivatives of Formula

(I):



and pharmaceutically acceptable salts thereof, wherein A, B, X, Y, R, R¹, R² and R¹⁰ are defined above for the Compounds of Formula (I).

In one embodiment, A is 5 or 6-membered monocyclic heterocycle.

In another embodiment, A is 5-membered monocyclic heterocycle.

In another embodiment, A is thiadiazolyl.

In still another embodiment, A is 1,3,4-thiadiazolyl.

In another embodiment, A is -NHC(O)- .

In one embodiment, X is $\text{-CH}_2\text{-}$.

In another embodiment, X is $\text{-CH(CH}_3\text{)-}$.

5 In one embodiment, Y is $\text{-N(R}^3\text{)-}$.

In another embodiment, Y is $\text{-N(C}_1\text{-C}_6\text{ alkyl)-}$.

In another embodiment, Y is $\text{-N(CH}_3\text{)-}$.

In still another embodiment, Y is $\text{-CH(R}^6\text{)-}$.

In another embodiment, Y is $\text{-CH}_2\text{-}$.

10 In one embodiment, Y is $\text{-N(R}^3\text{)-}$, wherein R^3 is $\text{-(C}_1\text{-C}_6\text{ alkylene)}_m\text{-Z-(C}_1\text{-C}_3\text{ alkylene)}_m\text{-R}^{11}$.

In another embodiment, Y is $\text{-N(R}^3\text{)-}$, wherein R^3 is $\text{-(C}_1\text{-C}_6\text{ alkylene)-R}^{11}$.

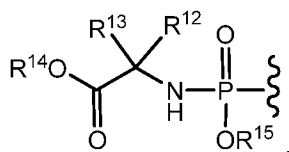
In another embodiment, Y is $\text{-N(R}^3\text{)-}$, wherein R^3 is $\text{-(C}_1\text{-C}_6\text{ alkylene)-P(O)(-OR}^{18}\text{)}_2$.

15 In still another embodiment, Y is $\text{-N(R}^3\text{)-}$, wherein R^3 is $\text{-(C}_1\text{-C}_3\text{ alkylene)-P(O)(-OH)}_2$.

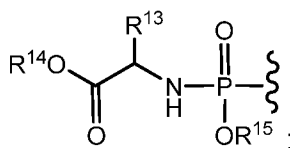
In another embodiment, Y is $\text{-N(R}^3\text{)-}$, wherein R^3 is $\text{-(C}_1\text{-C}_3\text{ alkylene)-P(O)(-OR}^{18}\text{)}_2$ and each occurrence of R^{18} is $\text{C}_1\text{-C}_6$ alkyl.

20 In another embodiment, Y is $\text{-N(R}^3\text{)-}$, wherein R^3 is $\text{-(C}_1\text{-C}_3\text{ alkylene)-P(O)(-OR}^{18}\text{)}_2$ and each occurrence of R^{18} is independently selected from H and $\text{-(C}_1\text{-C}_3\text{ alkylene)-OC(O)O-(C}_1\text{-C}_6\text{ alkyl)}$.

In yet another embodiment, Y is $\text{-N(R}^3\text{)-}$, wherein R^3 is $\text{-(C}_1\text{-C}_6\text{ alkylene)-R}^{11}$ and R^{11} is:



25 In another embodiment, Y is $\text{-N(R}^3\text{)-}$, wherein R^3 is $\text{-(C}_1\text{-C}_6\text{ alkylene)-R}^{11}$; R^{11} is:



R^{13} is C_1 - C_6 alkyl; R^{14} is C_1 - C_6 alkyl; and R^{15} is phenyl.

In one embodiment, R^1 is $-(C_1-C_6 \text{ alkylene})_m-Z-(C_1-C_3 \text{ alkylene})_m-R^{11}$.

In one embodiment, R^3 is $-(C_1-C_6 \text{ alkylene})_m-Z-(C_1-C_3 \text{ alkylene})_m-R^{11}$.

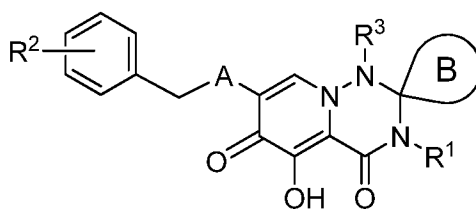
In one embodiment, R^{10} is H.

5 In another embodiment, R^{10} is C_3 - C_7 cycloalkyl.

In another embodiment, R^{10} is $-(C_1-C_4 \text{ alkylene})-O-(C_1-C_6 \text{ alkyl})$.

In another embodiment, R^{10} is $-CH_2OCH_3$.

In one embodiment, the compounds of formula (I) have the formula (Ia):

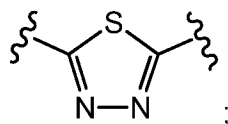


(Ia)

10 or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

A is: $-NHC(O)-$ or:



15 B is a 5 or 6-membered heterocycloalkyl, optionally substituted with R^6 ;

R^1 is C_1 - C_6 alkyl or $-(C_1-C_6 \text{ alkylene})-R^{11}$;

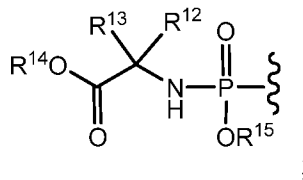
R^2 represents up to 2 optional substituents, each independently selected from

halo; and

R^3 is C_1 - C_6 alkyl or $-(C_1-C_6 \text{ alkylene})-R^{11}$;

20 R^6 is $-(C_1-C_6 \text{ alkylene})_m-R^{11}$;

each occurrence of R^{11} is independently selected from $-P(O)(-OR^{18})_2$ and:



R^{12} is independently selected from H and C_1 - C_6 alkyl;

R^{13} is independently selected from H and C_1 - C_6 alkyl;

R^{14} is C_1 - C_6 alkyl;

R^{15} is C_6 - C_{10} aryl;

each occurrence of R^{18} is independently selected from H and C_1 - C_6 alkyl; and

5 m is 0 or 1,

such that at least one occurrence of R^{11} must be present in the compound of formula (I).

In another embodiment, for the compounds of formula (I) or (Ja), R^3 is $-(C_1$ - C_6 alkylene)- R^{11} .

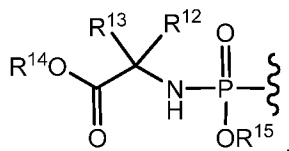
10 In another embodiment, for the compounds of formula (I) or (Ja), R^3 is $-(C_1$ - C_6 alkylene)- $P(O)(-OR^{18})_2$.

In still another embodiment, for the compounds of formula (I) or (Ja), R^3 is $-(C_1$ - C_3 alkylene)- $P(O)(-OH)_2$.

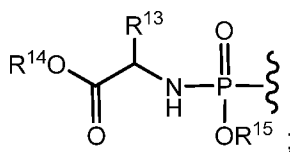
15 In another embodiment, for the compounds of formula (I) or (Ja), R^3 is $-(C_1$ - C_3 alkylene)- $P(O)(-OR^{18})_2$ and each occurrence of R^{18} is C_1 - C_6 alkyl.

In another embodiment, for the compounds of formula (I) or (Ja), R^3 is $-(C_1$ - C_3 alkylene)- $P(O)(-OR^{18})_2$ and each occurrence of R^{18} is independently selected from H and $-(C_1$ - C_3 alkylene)- $OC(O)O$ -(C_1 - C_6 alkyl).

20 In yet another embodiment, for the compounds of formula (I) or (Ja), R^3 is $-(C_1$ - C_6 alkylene)- R^{11} and R^{11} is:



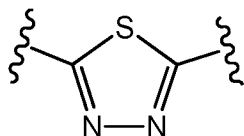
In another embodiment, for the compounds of formula (I) or (Ja), R^3 is $-(C_1$ - C_6 alkylene)- R^{11} ; R^{11} is:



25 R^{13} is C_1 - C_6 alkyl; R^{14} is C_1 - C_6 alkyl; and R^{15} is phenyl.

In one embodiment, for the compounds of formula (I) or (Ia), A is -NHC(O)- .

In another embodiment, embodiment, for the compounds of formula (I) or (Ia), A is:



5 In one embodiment, for the compounds of formula (I) or (Ia), B is 5-membered monocyclic heterocycloalkyl.

In another embodiment, for the compounds of formula (I) or (Ia), B is 6-membered monocyclic heterocycloalkyl.

10 In another embodiment, for the compounds of formula (I) or (Ia), B is tetrahydrofuranlyl.

In still another embodiment, for the compounds of formula (I) or (Ia), B is tetrahydropyranlyl.

In one embodiment, for the compounds of formula (I) or (Ia), R^1 is $\text{-(C}_1\text{-C}_6\text{ alkylene)-R}^{11}$.

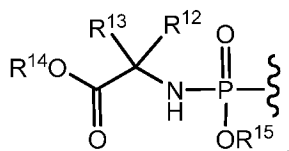
15 In another embodiment, for the compounds of formula (I) or (Ia), R^1 is $\text{-(C}_1\text{-C}_6\text{ alkylene)-P(O)(-OR}^{18}\text{)}_2$.

In still another embodiment, for the compounds of formula (I) or (Ia), R^1 is $\text{-(C}_1\text{-C}_3\text{ alkylene)-P(O)(-OH)}_2$.

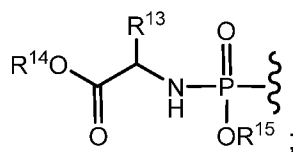
20 In another embodiment, for the compounds of formula (I) or (Ia), R^1 is $\text{-(C}_1\text{-C}_3\text{ alkylene)-P(O)(-OR}^{18}\text{)}_2$ and each occurrence of R^{18} is $\text{C}_1\text{-C}_6$ alkyl.

In another embodiment, for the compounds of formula (I) or (Ia), R^1 is $\text{-(C}_1\text{-C}_3\text{ alkylene)-P(O)(-OR}^{18}\text{)}_2$ and each occurrence of R^{18} is independently selected from H and $\text{-(C}_1\text{-C}_3\text{ alkylene)-OC(O)O-(C}_1\text{-C}_6\text{ alkyl)}$.

25 In yet another embodiment, for the compounds of formula (I) or (Ia), R^1 is $\text{-(C}_1\text{-C}_6\text{ alkylene)-R}^{11}$ and R^{11} is:



In another embodiment, for the compounds of formula (I) or (Ia), R^1 is $-(C_1-C_6 \text{ alkylene})-R^{11}$; R^{11} is:



R^{13} is C_1-C_6 alkyl; R^{14} is C_1-C_6 alkyl; and R^{15} is phenyl.

5 In one embodiment, for the compounds of formula (I) or (Ia), R^1 is C_1-C_6 alkyl.

In another embodiment, for the compounds of formula (I) or (Ia), R^1 is $-(C_2-C_4 \text{ alkylene})-O-(C_1-C_6 \text{ alkyl})$.

In another embodiment, for the compounds of formula (I) or (Ia), R^1 is selected from methyl, ethyl and n-propyl.

10 In still another embodiment, for the compounds of formula (I) or (Ia), R^1 is $-CH_2CH_2OCH_3$.

In another embodiment, for the compounds of formula (I) or (Ia), either R^1 or R^3 is $-(C_1-C_6 \text{ alkylene})-R^{11}$.

15 In one embodiment, for the compounds of formula (I) or (Ia), each occurrence of R^2 is halo.

In another embodiment, for the compounds of formula (I) or (Ia), R^2 represents 2 fluoro groups.

20 In another embodiment, for the compounds of formula (I) or (Ia), R^2 represents 2 fluoro groups in the ortho and para positions.

In one embodiment, variables A, B, X, Y, R, R^1 , R^2 and R^{10} for the Compounds of Formula (I) are selected independently of each other.

In another embodiment, the Compounds of Formula (I) are in substantially purified form.

25

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a Compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(c) The pharmaceutical composition of (b), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors, nucleoside reverse transcriptase inhibitors, CCR5 co-receptor antagonists and non-nucleoside reverse-transcriptase inhibitors.

(d) A pharmaceutical combination that is (i) a Compound of Formula (I) and (ii) a second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents; wherein the Compound of Formula (I) and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HIV replication, or for treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection.

(e) The combination of (d), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, CCR5 co-receptor antagonists, fusion and non-nucleoside reverse-transcriptase inhibitors.

(f) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

(g) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

(h) The method of (g), wherein the Compound of Formula (I) is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(i) The method of (h), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, CCR5 co-receptor antagonists, fusion and non-nucleoside reverse-transcriptase inhibitors.

(j) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

(k) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

5 The present invention also includes a compound of the present invention for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) medicine, (b) inhibiting HIV replication or (c) treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected
10 from HIV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the
15 compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate. It is understood that references to compounds would include the compound in its present form as well as in different forms, such as polymorphs, solvates and hydrates, as applicable.

It is further to be understood that the embodiments of compositions and methods
20 provided as (a) through (k) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

The Compounds of Formula (I) may be referred to herein by chemical structure and/or by chemical name. In the instance that both the structure and the name of a Compound of Formula (I) are provided and a discrepancy is found to exist between the chemical structure and
25 the corresponding chemical name, it is understood that the chemical structure will predominate.

Non-limiting examples of the Compounds of Formula (I) include compounds **3-26**, **29-36** and **39-49**, as set forth in the Examples below herein, and pharmaceutically acceptable salts thereof.

30 Uses of the Pyridotriazine Derivatives

The Spirocyclic Pyridotriazine Derivatives may be useful in human and veterinary medicine for treating or preventing HIV infection in a subject. In one embodiment, the Spirocyclic Pyridotriazine Derivatives may be inhibitors of HIV viral replication. In a specific embodiment, the Spirocyclic Pyridotriazine Derivatives are inhibitors of HIV-1. Accordingly, the Spirocyclic Pyridotriazine Derivatives may be useful for treating HIV infections and AIDS. In accordance with the invention, the Spirocyclic Pyridotriazine Derivatives may be administered to a subject in need of treatment or prevention of HIV infection.

Accordingly, in one embodiment, the invention provides methods for treating HIV infection in a subject comprising administering to the subject an effective amount of at least one Spirocyclic Pyridotriazine Derivative or a pharmaceutically acceptable salt or prodrug thereof. In a specific embodiment, the present invention provides methods for treating AIDS in a subject comprising administering to the subject an effective amount of at least one Spirocyclic Pyridotriazine Derivative or a pharmaceutically acceptable salt or prodrug thereof.

Treatment or Prevention of HIV Infection

The Spirocyclic Pyridotriazine Derivatives may be useful in the inhibition of HIV, the treatment of HIV infection and/or reduction of the likelihood or severity of symptoms of HIV infection and the inhibition of HIV viral replication and/or HIV viral production in a cell-based system. For example, the Spirocyclic Pyridotriazine Derivatives may be useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to subject blood during surgery or other medical procedures.

In one embodiment, the HIV infection has progressed to AIDS.

Accordingly, in one embodiment, the invention provides methods for treating HIV infection in a subject, the methods comprising administering to the subject an effective amount of at least one Spirocyclic Pyridotriazine Derivative or a pharmaceutically acceptable salt or prodrug thereof. In a specific embodiment, the amount administered is effective to treat or prevent infection by HIV in the subject. In another specific embodiment, the amount administered is effective to inhibit HIV viral replication and/or viral production in the subject.

The Spirocyclic Pyridotriazine Derivatives may also be useful in the preparation and execution of screening assays for antiviral compounds. For example the Spirocyclic

Pyridotriazine Derivatives may be useful for identifying resistant HIV cell lines harboring mutations, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the Spirocyclic Pyridotriazine Derivatives may be useful in establishing or determining the binding site of other antivirals to the HIV Integrase.

5

Combination Therapy

In another embodiment, the present methods for treating or preventing HIV infection can further comprise the administration of one or more additional therapeutic agents which are not Spirocyclic Pyridotriazine Derivatives.

10

In one embodiment, the additional therapeutic agent is an antiviral agent.

In another embodiment, the additional therapeutic agent is an immunomodulatory agent, such as an immunosuppressive agent.

Accordingly, in one embodiment, the present invention provides methods for treating a viral infection in a subject, the method comprising administering to the subject: (i) at least one Spirocyclic Pyridotriazine Derivative (which may include two or more different Spirocyclic Pyridotriazine Derivatives), or a pharmaceutically acceptable salt or prodrug thereof, and (ii) at least one additional therapeutic agent that is other than a Spirocyclic Pyridotriazine Derivative, wherein the amounts administered are together effective to treat or prevent a viral infection.

20

When administering a combination therapy of the invention to a subject, therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for non-limiting illustration purposes, a Spirocyclic Pyridotriazine Derivative and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (*e.g.*, a capsule, a tablet and the like).

25

In one embodiment, the at least one Spirocyclic Pyridotriazine Derivative is administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

30

In another embodiment, the at least one Spirocyclic Pyridotriazine Derivative and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating a viral infection.

5 In another embodiment, the at least one Spirocyclic Pyridotriazine Derivative and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In still another embodiment, the at least one Spirocyclic Pyridotriazine Derivative and the additional therapeutic agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a
10 viral infection.

In one embodiment, the at least one Spirocyclic Pyridotriazine Derivative and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration. In another embodiment, this composition is suitable for
15 subcutaneous administration. In still another embodiment, this composition is suitable for parenteral administration.

Viral infections and virus-related disorders that may be treated or prevented using the combination therapy methods of the present invention include, but are not limited to, those listed above.

20 In one embodiment, the viral infection is HIV infection.

In another embodiment, the viral infection is HIV infection which has progressed to AIDS.

The at least one Spirocyclic Pyridotriazine Derivative and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow
25 the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of therapy without reducing the efficacy of therapy.

In one embodiment, the administration of at least one Spirocyclic Pyridotriazine Derivative and the additional therapeutic agent(s) may inhibit the resistance of a viral infection to
30 these agents.

As noted above, the present invention is also directed to use of a compound of Formula I with one or more anti-HIV agents. An "anti-HIV agent" is any agent which is directly or indirectly effective in the inhibition of HIV reverse transcriptase or another enzyme required for HIV replication or infection, the treatment or prophylaxis of HIV infection, and/or the treatment, prophylaxis or delay in the onset or progression of AIDS. It is understood that an anti-HIV agent is effective in treating, preventing, or delaying the onset or progression of HIV infection or AIDS and/or diseases or conditions arising therefrom or associated therewith. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more anti-HIV agents selected from HIV antiviral agents, immunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS. Suitable HIV antivirals for use in combination with the compounds of the present invention include, for example, those listed in Table A as follows:

Table A

Name	Type
abacavir, ABC, Ziagen®	nRTI
abacavir + lamivudine, Epzicom®	nRTI
abacavir + lamivudine + zidovudine, Trizivir®	nRTI
amprenavir, Agenerase®	PI
atazanavir, Reyataz®	PI
AZT, zidovudine, azidothymidine, Retrovir®	nRTI
CMX-157	nRTI
darunavir, Prezista®	PI
ddC, zalcitabine, dideoxycytidine, Hivid®	nRTI
ddI, didanosine, dideoxyinosine, Videx®	nRTI
ddI (enteric coated), Videx EC®	nRTI
delavirdine, DLV, Rescriptor®	nnRTI
Dolutegravir	PI
efavirenz, EFV, Sustiva®, Stocrin®	nnRTI

efavirenz + emtricitabine + tenofovir DF, Atripla®	nnRTI + nRTI
Elvitegravir	InI
emtricitabine, FTC, Emtriva®	nRTI
emtricitabine + tenofovir DF, Truvada®	nRTI
emvirine, Coactinon®	nnRTI
enfuvirtide, Fuzeon®	FI
enteric coated didanosine, Videx EC®	nRTI
etravirine, TMC-125	nnRTI
fosamprenavir calcium, Lexiva®	PI
indinavir, Crixivan®	PI
lamivudine, 3TC, Epivir®	nRTI
lamivudine + zidovudine, Combivir®	nRTI
lopinavir	PI
lopinavir + ritonavir, Kaletra®	PI
maraviroc, Selzentry®	EI
nelfinavir, Viracept®	PI
nevirapine, NVP, Viramune®	nnRTI
raltegravir, MK-0518, Isentress®	InI
rilpivirine, TMC-278	nnRTI
Rilpivirine + emtricitabine + tenofovir, Complera	nnRTI + nRTI
ritonavir, Norvir®	PI
saquinavir, Invirase®, Fortovase®	PI
stavudine, d4T, didehydrodeoxythymidine, Zerit®	nRTI
tenofovir DF (DF = disoproxil fumarate), TDF, Viread®	nRTI
tipranavir, Aptivus®	PI

EI = entry inhibitor; FI = fusion inhibitor; InI = integrase inhibitor; PI = protease inhibitor; nRTI = nucleoside reverse transcriptase inhibitor; nnRTI = non-nucleoside reverse transcriptase inhibitor. Some of the

drugs listed in the table are used in a salt form; e.g., abacavir sulfate, indinavir sulfate, atazanavir sulfate, nelfinavir mesylate.

In one embodiment, the one or more anti-HIV drugs are selected from raltegravir, lamivudine, abacavir, ritonavir, darunavir, atazanavir, emtricitabine, tenofovir, elvitegravir, rilpivirine and lopinavir.

In another embodiment, the compound of formula (I) is used in combination with a single anti-HIV drug which is lamivudine.

In still another embodiment, the compound of formula (I) is used in combination with a single anti-HIV drug which is atazanavir.

In another embodiment, the compound of formula (I) is used in combination with a single anti-HIV drug which is darunavir.

In another embodiment, the compound of formula (I) is used in combination with a single anti-HIV drug which is rilpivirine.

In one embodiment, the compound of formula (I) is used in combination with two anti-HIV drugs which are lamivudine and abacavir.

In another embodiment, the compound of formula (I) is used in combination with two anti-HIV drugs which are emtricitabine and tenofovir.

In another embodiment, the compound of formula (I) is used in combination with two anti-HIV drugs which are ritonavir and lopinavir.

In one embodiment, the present invention provides pharmaceutical compositions comprising (i) a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof; (ii) a pharmaceutically acceptable carrier; and (iii) one or more additional anti-HIV agents selected from lamivudine, abacavir, ritonavir and lopinavir, or a pharmaceutically acceptable salt thereof, wherein the amounts present of components (i) and (iii) are together effective for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in the subject in need thereof.

In another embodiment, the present invention provides a method for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset or

progression of AIDS in a subject in need thereof, which comprises administering to the subject (i) a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof and (ii) one or more additional anti-HIV agents selected from lamivudine, abacavir, ritonavir and lopinavir, or a pharmaceutically acceptable salt thereof, wherein the amounts administered of components (i) and (ii) are together effective for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in the subject in need thereof.

It is understood that the scope of combinations of the compounds of this invention with anti-HIV agents is not limited to the HIV antivirals listed in Table A, but includes in principle any combination with any pharmaceutical composition useful for the treatment or prophylaxis of AIDS. The HIV antiviral agents and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians' Desk Reference, Thomson PDR, Thomson PDR, 57th edition (2003), the 58th edition (2004), the 59th edition (2005), and the like. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

The compounds of this invention may also be useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of HIV infection may be determined by the attending clinician, taking into consideration the approved doses and dosage regimen in the package insert; the age, sex and general health of the subject; and the type and severity of the viral infection or related disease or disorder. When administered in combination, the Spirocyclic Pyridotriazine Derivative(s) and the other agent(s) may be administered simultaneously (*i.e.*, in the same composition or in separate compositions one right after the other) or sequentially. This particularly useful when the components of the combination are

given on different dosing schedules, *e.g.*, one component is administered once daily and another component is administered every six hours, or when the pharmaceutical compositions are different, *e.g.*, one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

5

Compositions and Administration

When administered to a subject, the Spirocyclic Pyridotriazine Derivatives may be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one Spirocyclic Pyridotriazine Derivative and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, *i.e.*, oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. Powders and tablets may be comprised of from about 0.5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules may be used as solid dosage forms suitable for oral administration.

Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize therapeutic effects, *i.e.*, antiviral activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the one or more Spirocyclic Pyridotriazine Derivatives are administered orally.

In another embodiment, the one or more Spirocyclic Pyridotriazine Derivatives are administered intravenously.

In one embodiment, a pharmaceutical preparation comprising at least one Spirocyclic Pyridotriazine Derivative is in unit dosage form. In such form, the preparation is subdivided into unit doses containing effective amounts of the active components.

Compositions may be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the Spirocyclic Pyridotriazine Derivative(s) by weight or volume. In various embodiments, the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the Spirocyclic Pyridotriazine Derivative(s) by weight or volume.

The compounds of Formula I may be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions may be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. The specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In one embodiment, the daily dosage is administered in one portion. In another embodiment, the total daily dosage is administered in two divided doses over a 24 hour period. In another embodiment, the total daily dosage is administered in three divided doses over a 24 hour period. In still another embodiment, the total daily dosage is administered in four divided doses over a 24 hour period.

The amount and frequency of administration of the Spirocyclic Pyridotriazine Derivatives will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the subject as well as severity of the symptoms being treated. The compositions of the invention can further comprise one or more additional therapeutic agents, selected from those listed above herein. Accordingly, in one embodiment, the present invention provides compositions comprising: (i) at least one Spirocyclic Pyridotriazine Derivative or a pharmaceutically acceptable salt or prodrug thereof; (ii) one or more additional therapeutic agents that are not a Spirocyclic Pyridotriazine Derivative; and (iii) a pharmaceutically acceptable carrier, wherein the amounts in the composition are together effective to treat HIV infection.

Kits

In one aspect, the present invention provides a kit comprising a therapeutically effective amount of at least one Spirocyclic Pyridotriazine Derivative, or a pharmaceutically acceptable salt or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

In another aspect the present invention provides a kit comprising an amount of at least one Spirocyclic Pyridotriazine Derivative, or a pharmaceutically acceptable salt or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts of the two or more active ingredients result in a desired therapeutic effect.

In one embodiment, the one or more Spirocyclic Pyridotriazine Derivatives and the one or more additional therapeutic agents are provided in the same container. In one embodiment, the one or more Spirocyclic Pyridotriazine Derivatives and the one or more additional therapeutic agents are provided in separate containers.

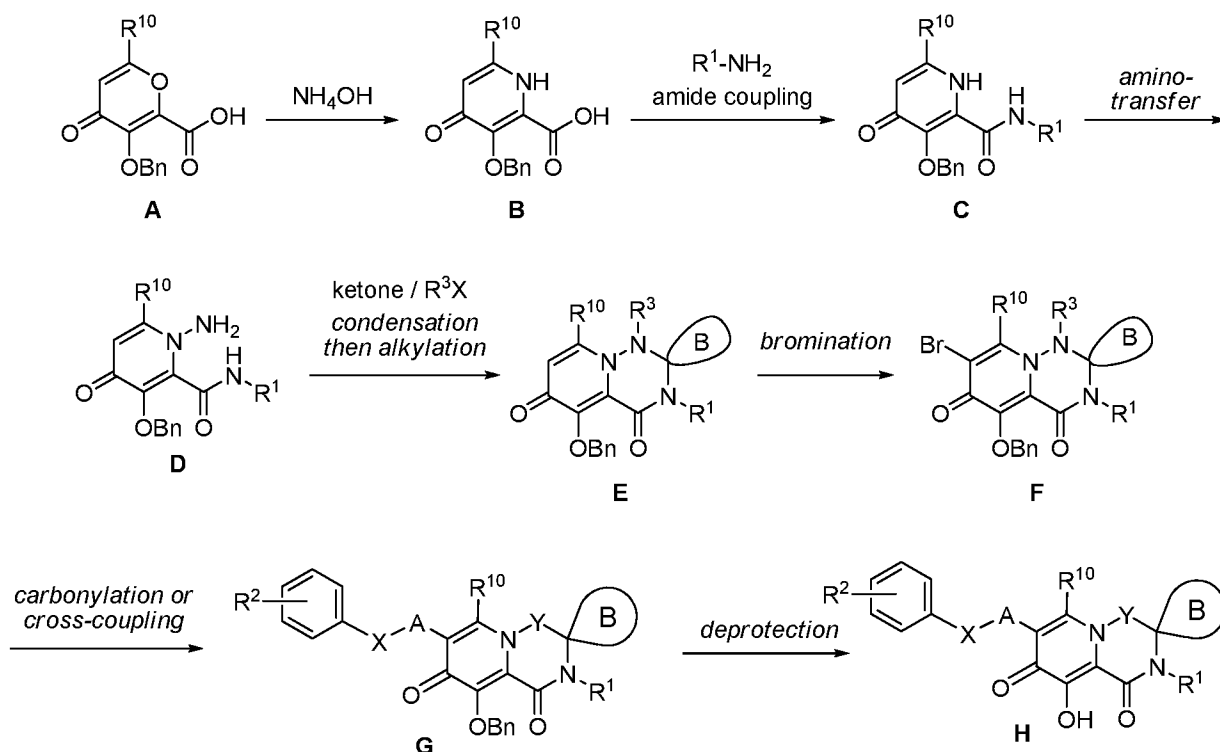
Methods For Making the Compounds of Formula (I)

The Compounds of Formula (I) may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis.

Methods useful for making the Compounds of Formula (I) are set forth in the Examples below and generalized in the Schemes below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis.

The following schemes describe general methods for preparing the compounds of Formula (I).

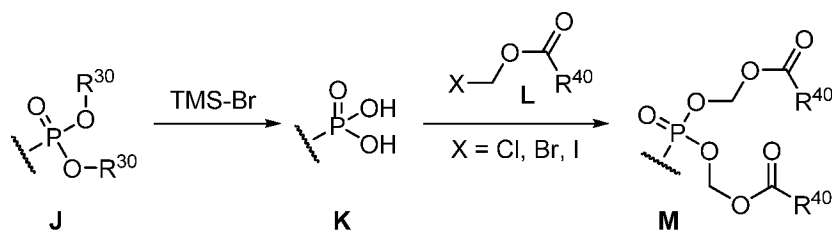
Scheme 1



wherein A, B, X, Y, R, R¹, R² and R¹⁰ are as defined above for the Compounds of Formula (I).

Scheme 1 shows a general route to prepare the compounds of this invention. A
 5 pyranone compound of formula **A** upon treatment with aqueous ammonium hydroxide provides a
 4-pyridinone of formula **B**. Treatment of **B** with a suitably functionalized amine under standard
 amide formation conditions provides **C**, which is subjected to an amino-transfer process to
 provide hydrazide compound **D**. A two-step procedure involving condensation of **D** with a
 carbocyclic or heterocyclic ketone followed by alkylation with a suitably functionalized
 10 alkylating reagent (R³X), provides **E**. Bromination of **E** provides **F** which is then subjected to a
 carbonylation or cross-coupling process to provide **G**. Deprotection of the protected hydroxyl
 group of compound **G** then provides compound **H**.

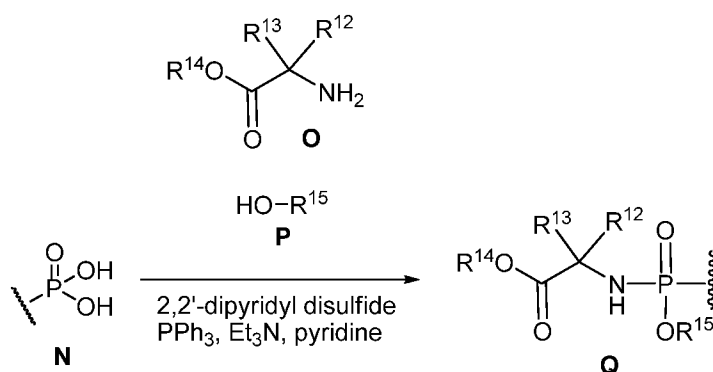
Scheme 2



wherein R³⁰ is C₁-C₆ alkyl and R⁴⁰ is C₁-C₆ alkyl.

Scheme 2 illustrates methodology useful for preparing acetal prodrugs of phosphonates. Such prodrugs may be prepared from the dialkylphosphonate **J** which is converted to the phosphonic acid **K** upon removal of the alkyl groups using TMSBr, for example. Phosphonic acids **K** may be converted to acetal prodrugs of formula **M** by reaction with a suitably functionalized halide **L** under standard conditions.

Scheme 3



wherein R¹², R¹³, R¹⁴ and R¹⁵ are as defined above for the Compounds of Formula (I).

Scheme 3 illustrates methodology useful for preparing phosphoramidate type prodrugs, which are also sometimes referred to as “McGuigan” prodrugs. A phosphate group of formula **N** can be reacted with an amino compound of formula **O** and an alcohol of formula **P** in the presence of 2,2'-dipyridyl disulfide, triphenylphosphine and triethylamine with pyridine as a solvent, to provide the corresponding phosphoramidate group of formula **Q**.

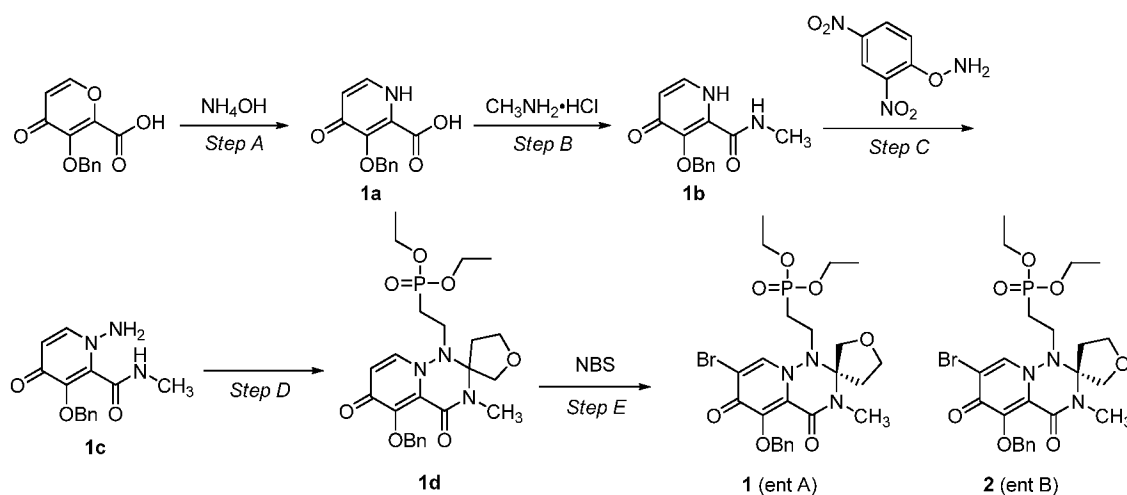
EXAMPLES

General Methods

The compounds described herein may be prepared according to the procedures of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures may be used to prepare these compounds. Concentration refers to the removal of the volatile components at reduced pressure (e.g. rotary evaporation) unless otherwise noted. All temperatures are degrees Celsius unless otherwise noted. Mass spectra (MS) were measured by electrospray ion-mass spectroscopy (ESI) in positive ion detection mode and m/z refers to the $[M+H]^+$ ion unless otherwise noted. 1H NMR spectra were recorded at 400-500 MHz at ambient temperature unless otherwise noted. When the 1H NMR spectrum exhibits conformational isomers at room temperature, brackets { } indicate groups of signals that may be assigned to the same proton and integrations are not representative of any ratio. RP-HPLC refers to reverse-phase HPLC on C18-functionalized preparative or semi-preparative columns with gradient elution using acetonitrile and water modified with trifluoroacetic acid as eluents and fractions were lyophilized or concentrated by rotary evaporation unless otherwise noted. RP-MPLC refers to reverse phase medium pressure liquid chromatography using a flash chromatography system (e.g. ISCO or Biotage) and commercial pre-packed C18-functionalized silica gel columns with gradient elution using acetonitrile and water modified with trifluoroacetic acid as eluents and fractions were lyophilized or concentrated by rotary evaporation unless otherwise noted. Compounds described herein were synthesized as the racemates unless otherwise noted in the experimental procedures and compound tables. For stereoisomers, enantiomer A refers to the earlier eluting enantiomer and enantiomer B refers to the later eluting enantiomer at the point of chiral resolution and this nomenclature is maintained through the remainder of a synthetic sequence for a given enantiomeric series regardless of the possibility that subsequent intermediates and final compounds may have the same or opposite orders of elution.

Example 1

Preparation of Intermediate Compound 1 and Intermediate Compound 2



Step A – Synthesis of Compound **1a**

3-(benzyloxy)-4-oxo-4H-pyran-2-carboxylic acid (30.00 g, 122 mmol) was taken up in 28% aqueous ammonium hydroxide (150 mL, 1079 mmol) at room temperature and the mixture was allowed to stir at room temperature for 16 hours. The reaction mixture was diluted with water to a total volume of 500 mL and then treated with 36% aqueous HCl until the pH was approximately 4 and additional water (500 mL) was added. The reaction mixture was allowed to age for 12 hours at room temperature. The solids were collected by filtration, washed with water (250 mL) and then dried under vacuum to provide **1a** which was used without further purification. Mass Calc'd for $\text{C}_{13}\text{H}_{11}\text{NO}_4$: 245.1, found 246.1 ($\text{M}+\text{H}^+$); ^1H NMR 0362764-0049-1: (400 MHz, $\text{DMSO}-d_6$) δ 7.70 (bs, 1H), 7.43-7.45 (m, 2H), 7.27-7.35 (m, 3H), 6.53 (bs, 1H), 5.07 (s, 2H).

Step B – Synthesis of Compound **1b**

A mixture of **1a** (20 g, 82 mmol) and HOBt (13.74 g, 90 mmol) in dichloromethane (100 mL) was cooled to 0°C and treated with EDC (17.20 g, 90 mmol) and N-methylmorpholine (26.9 mL, 245 mmol). After 5 minutes of stirring, methanamine hydrochloride (6.06 g, 90 mmol) was added. The reaction was allowed to stir for 20 hours while slowly warming to room temperature. The reaction mixture was concentrated to provide a viscous syrup that was taken up in DMSO (30 mL), neutralized with glacial acetic acid and purified using RP-MPLC to provide **1b**.

Mass Calc'd for $C_{14}H_{14}N_2O_3$: 258.1, found 259.1 (M+H)⁺; 1H NMR (500 MHz, DMSO) δ 8.40 (s, 1 H), 7.62 (d, J = 6.8 Hz, 1 H), 7.30-7.39 (m, 5 H), 6.42 (d, J = 6.7 Hz, 1 H), 5.32 (s, 2 H), 2.74 (d, J = 4.8 Hz, 3 H).

5 *Step C – Synthesis of Compound 1c*

A mixture of **1b** (18.10 g, 70.1 mmol) and potassium carbonate (29.1 g, 210 mmol) in *N,N*-dimethylformamide (150 mL) at 0°C was treated with O-(2,4-dinitrophenyl)hydroxylamine (27.9 g, 140 mmol) and was allowed to warm to room temperature and stir at room temperature for 48 hours. The reaction mixture was filtered through a pad of
10 celite (acetonitrile rinse) and the filtrate was neutralized with glacial acetic acid. The resulting solution was directly purified using RP-MPLC to provide **1c**, which was used without further purification. Mass Calc'd for $C_{14}H_{15}N_3O_3$: 273.1, found 274.2 (M+H)⁺; 1H NMR (500 MHz, $CDCl_3$): δ 7.61 (bs, 1 H), 7.42 (d, J = 7.6 Hz, 1 H), 7.31-7.35 (m, 5 H), 6.24 (d, J = 7.6 Hz, 1 H), 5.07 (s, 2 H), 2.64 (d, J = 4.9 Hz, 3 H).

15

Step D – Synthesis of Compound 1d

A solution of Compound **1c** (1000 mg, 3.66 mmol) in dioxane (5.0 mL) was treated at room temperature with 3-oxotetrahydrofuran (1260 mg, 14.64 mmol) and AcOH (0.050 mL). The reaction mixture was capped and stirred at room temperature for 24 hours. The
20 reaction mixture was directly applied to a dry 80g silica gel column. Gradient elution with 0 to 30% MeOH/ dichloromethane provided the intermediate that was taken up in DMSO (6 mL) and treated with diethyl 2-bromoethylphosphonate (1.330 mL, 7.32 mmol), tetrabutylammonium hydroxide triacontahydrate (585 mg, 0.732 mmol) and potassium hydroxide (616 mg, 10.98 mmol). The reaction mixture was allowed to stir at room temperature for 4 hours, neutralized
25 with glacial acetic acid and directly purified using RP-MPLC to provide Compound **1d** which was used without further purification. Mass Calc'd for $C_{24}H_{32}N_3O_7P$: 505.1, found 506.1 (M+H)⁺;

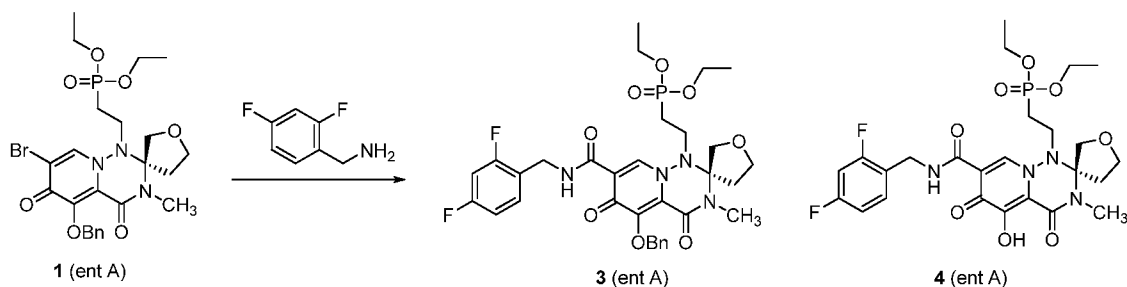
Step E – Synthesis of Intermediate Compound 1 and Intermediate Compound 2

30 Compound **1d** (1.145 g, 2.265 mmol) in DMF (10 mL) was treated at 0°C with NBS (0.887 g, 4.98 mmol). The reaction mixture was allowed to stir at room temperature for 4

hours, diluted with acetonitrile (4 mL) and directly purified using RP-HPLC to provide the product as the racemate. Mass Calc'd for $C_{24}H_{31}BrN_3O_7P$: 583.1, 585.1 Found 584.1, 586.0 $(M+H)^+$; 1H NMR (500 MHz, $CDCl_3$): δ {8.06 (s; 1 H); 7.98 (s; 1 H)}; 7.49 (t; J = 8.42 Hz; 2 H); 7.26-7.29 (m; 3 H); 5.58 (d; J = 10.64 Hz; 1 H); 5.25 (d; J = 10.59 Hz; 1 H); 4.24 (d; J = 10.2 Hz; 1 H); 4.08-4.19 (m; 5 H); 3.98-4.05 (m; 1 H); 3.81-3.92 (m; 2H); 3.76 (d; J = 10.2 Hz; 1 H); 3.13 (s; 3 H); 2.99-3.11 (m; 2 H); 2.03-2.09 (m; 1 H); 1.92-2.00 (m; 1 H); 1.33-1.40 (m; 6 H). Chiral resolution using SFC (ChiralCel OJ-H, 250×20mm, 15% isopropanol:acetonitrile (0.1% NH_3H_2O) in $SC-CO_2$, 70mL/min, 100 bar, 220 nM) provided intermediate Compound **1** (ent A, earlier eluting enantiomer) and intermediate Compound **2** (ent B, later eluting enantiomer).

Example 2

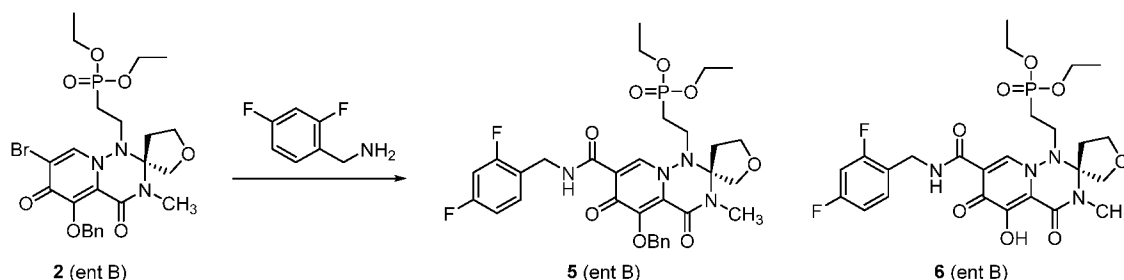
Preparation of Compound **3** and Compound **4**



The mixture of Compound **1** (ent A, 232.8 mg, 0.398 mmol) in acetonitrile (4 mL) was added palladium(II) acetate (44.7 mg, 0.199 mmol), bis(2-diphenylphosphinophenyl)ether (107 mg, 0.199 mmol), 2,4-difluorobenzylamine (0.063 mL, 0.518 mmol) and triethylamine (0.167 mL, 1.195 mmol). The resulting mixture was sub-surface sparged with nitrogen for 10 minutes. The reaction mixture was allowed to stir under carbon monoxide (1 atm) at 75 °C for 8 hours, cooled to room temperature and concentrated *in vacuo*. The residue obtained was purified using RP-HPLC to provide Compound **3**, Mass Calc'd for $C_{32}H_{37}F_2N_4O_8P$: 674.2; Found 675.2 $(M+H)^+$ and Compound **4**, Mass Calc'd for $C_{25}H_{31}F_2N_4O_8P$: 584.2; Found 584.9 $(M+H)^+$

Example 3

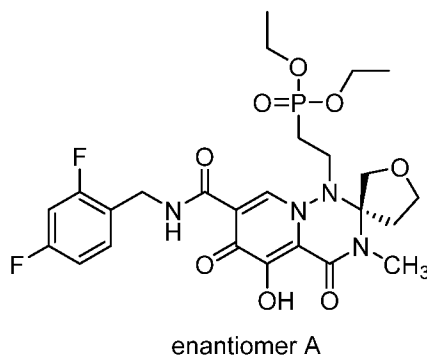
Preparation of Compound **5** and Compound **6**



The mixture of Compound **2** (ent B, 245.7 mg, 0.436 mmol) in acetonitrile (4 mL) was added palladium(II) acetate (48.9 mg, 0.218 mmol), bis(2-diphenylphosphinophenyl)ether (117 mg, 0.218 mmol), 2,4-difluorobenzylamine (0.069 mL, 0.567 mmol) and triethylamine (0.182 mL, 1.308 mmol). The resulting mixture was sub-surface sparged with nitrogen for 10 minutes. The reaction mixture was allowed to stir under carbon monoxide (1 atm) at 75 °C for 8 hours, cooled to room temperature and concentrated *in vacuo*. The residue obtained was purified using RP-HPLC to provide Compound **5**. Mass Calc'd for C₃₂H₃₇F₂N₄O₈P: 674.2; Found 675.0 (M+H)⁺ and Compound **6**, Mass Calc'd for C₂₅H₃₁F₂N₄O₈P: 584.2; Found 584.9 (M+H)⁺

Example 4

Preparation of Compound 4



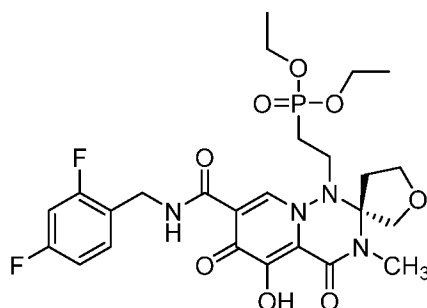
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Compound **3** (ent A, 30 mg, 0.044 mmol) in TFA (1 mL) was allowed to stir at room temperature for 2 hours, diluted with aqueous DMSO and directly purified using RP-HPLC to provide Compound **4**. Mass Calc'd for C₂₅H₃₁F₂N₄O₈P: 584.2, Found: 585.1 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ 11.64 (br s; 1 H); 10.23 (t; J = 5.6 Hz; 1 H); {8.48 (s; 1 H); 8.42 (s; 1 H)} 7.42 (q; J = 7.9 Hz; 1 H); 7.24 (t; J = 10.0 Hz; 1 H); 7.06 (t; J = 8.7 Hz; 1 H); 4.50-4.60 (m; 2 H); 3.95-4.06 (m; 4 H); 3.66-3.75 (m; 2 H); {3.15 (s; 3 H); 3.11 (s; 3 H)}; 2.95-

3.05 (m; 2 H); 2.78-2.83 (m; 1 H); 2.39-2.45 (m; 1 H); 2.24-2.29 (m; 1 H); 2.07-2.13 (m; 1 H); 1.94-2.03 (m; 1 H); 1.77-1.85 (m; 1 H); 1.25 (t; J = 7.1 Hz; 3 H); 1.21 (t; J = 7.1 Hz; 3 H).

Example 5

Preparation of Compound 6



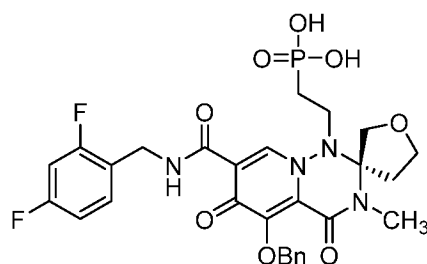
enantiomer B

6

Compound **5** (ent A, 30 mg, 0.044 mmol) in TFA (1 mL) was allowed to stir at room temperature for 2 hours, diluted with aqueous DMSO and directly purified using RP-HPLC to provide Compound **6**. Mass Calc'd for $C_{25}H_{31}F_2N_4O_8P$: 584.2, Found: 585.1 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ 11.64 (br s; 1 H); 10.23 (s; 1 H); {8.48 (s; 1 H); 8.42 (s; 1 H)}; 7.42 (q; J = 7.9 Hz; 1 H); 7.24 (t; J = 10.0 Hz; 1 H); 7.06 (t; J = 8.7 Hz; 1 H); 4.50-4.60 (m; 2 H); 3.95-4.06 (m; 4 H); 3.66-3.75 (m; 2 H); {3.15 (s; 3 H); 3.11 (s; 3 H)}; 2.96-3.03 (m; 2 H); 2.79-2.83 (m; 1 H); 2.39-2.45 (m; 1 H); 2.24-2.29 (m; 1 H); 2.07-2.13 (m; 1 H); 1.96-2.04 (m; 1 H); 1.76-1.83 (m; 1 H); 1.25 (t; J = 7.1 Hz; 3 H); 1.21 (t; J = 7.1 Hz; 3 H).

Example 6

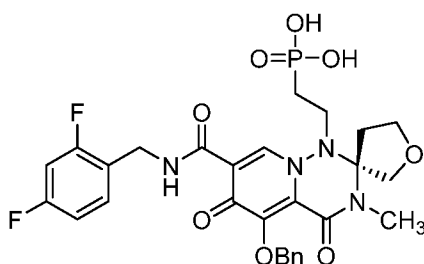
Preparation of Compound 7



enantiomer A

7

Compound **3** (ent A, 174.1 mg, 0.258 mmol) in acetonitrile (2.5 mL) was treated at room temperature with 2,6-lutidine (0.225 mL, 1.936 mmol) and TMS-Br (0.234 mL, 1.806 mmol). The reaction mixture was allowed to stir at 50 °C for 2 hours, cooled to 0 °C, quenched with water (600 uL) and allowed to stir for 1 hour at room temperature. Glacial acetic acid (2.5 mL) was added and the mixture was diluted with 10% aqueous DMSO (7.5 mL) and directly purified using RP-HPLC to provide Compound **7**. Calc'd for $C_{28}H_{29}F_2N_4O_8P$: 618.2, Found: 619.0 (M+H)⁺.

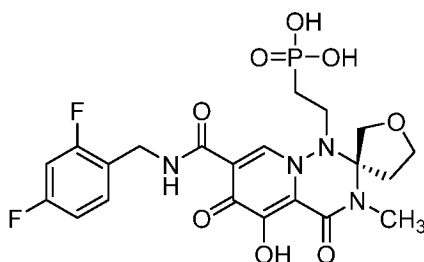
Example 7Preparation of Compound **8**

enantiomer B

8

Compound **5** (ent A, 155.1 mg, 0.230 mmol) in acetonitrile (2.5 mL) was treated at room temperature with 2,6-lutidine (0.201 mL, 1.724 mmol) and TMS-Br (0.209 mL, 1.609 mmol). The reaction mixture was allowed to stir at 50 °C for 12 hours, cooled to 0 °C, quenched with water (200 uL) and allowed to stir for 1 hour at room temperature. Glacial acetic acid (2 mL) was added and the mixture was diluted with 10% aqueous DMSO (6 mL) and directly purified using RP-HPLC to provide Compound **8**. Calc'd for $C_{28}H_{29}F_2N_4O_8P$: 618.2, Found: 619.0 (M+H)⁺.

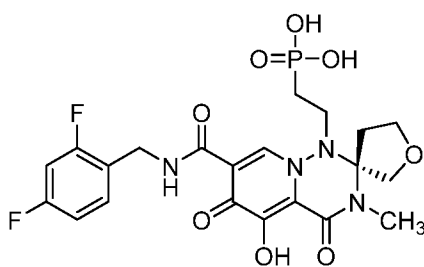
Example 8Preparation of Compound **9**



enantiomer A

9

Compound **4** (ent A, 81.3 mg, 0.139 mmol) in acetonitrile (1.5 mL) was treated at room temperature with 2,6-lutidine (0.122 mL, 1.043 mmol) and TMS-Br (0.126 mL, 0.974 mmol). The reaction mixture was allowed to stir at 50 °C for 12 hours, cooled to 0 °C, quenched with water (130 uL) and allowed to stir for 1 hour. Acetic acid (1.3 mL) was added and the mixture was diluted with 10% aq DMSO (4 mL). Direct purification using RP-HPLC provided Compound **9**. Mass Calc'd for C₂₁H₂₃F₂N₄O₈P: 528.1, Found: 529.1 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ {11.69 (s; 1 H); 11.65 (s; 1 H)}; 10.21-10.24 (m; 1 H); {8.46 (s; 1 H); 8.39 (s; 1 H)}; 7.39-7.44 (m; 1 H); 7.22-7.26 (m; 1 H); 7.06 (t; J = 8.6; 1 H); 4.49-4.58 (m; 2 H); {4.06 (td; J = 9.0; 4.4 Hz; 1 H); 3.96-4.02 (m; 1 H)}; 3.69-3.79 (m; 2 H); {3.16 (s; 3 H); 3.11 (s; 3 H)}; 2.93-2.98 (m; 2 H); 2.76-2.81 (m; 1 H); 2.29-2.36 (m; 1 H); 2.07-2.13 (m; 1 H); 1.78-1.86 (m; 1 H); 1.37-1.46 (m; 1 H).

Example 9Preparation of Compound **10**

enantiomer B

10

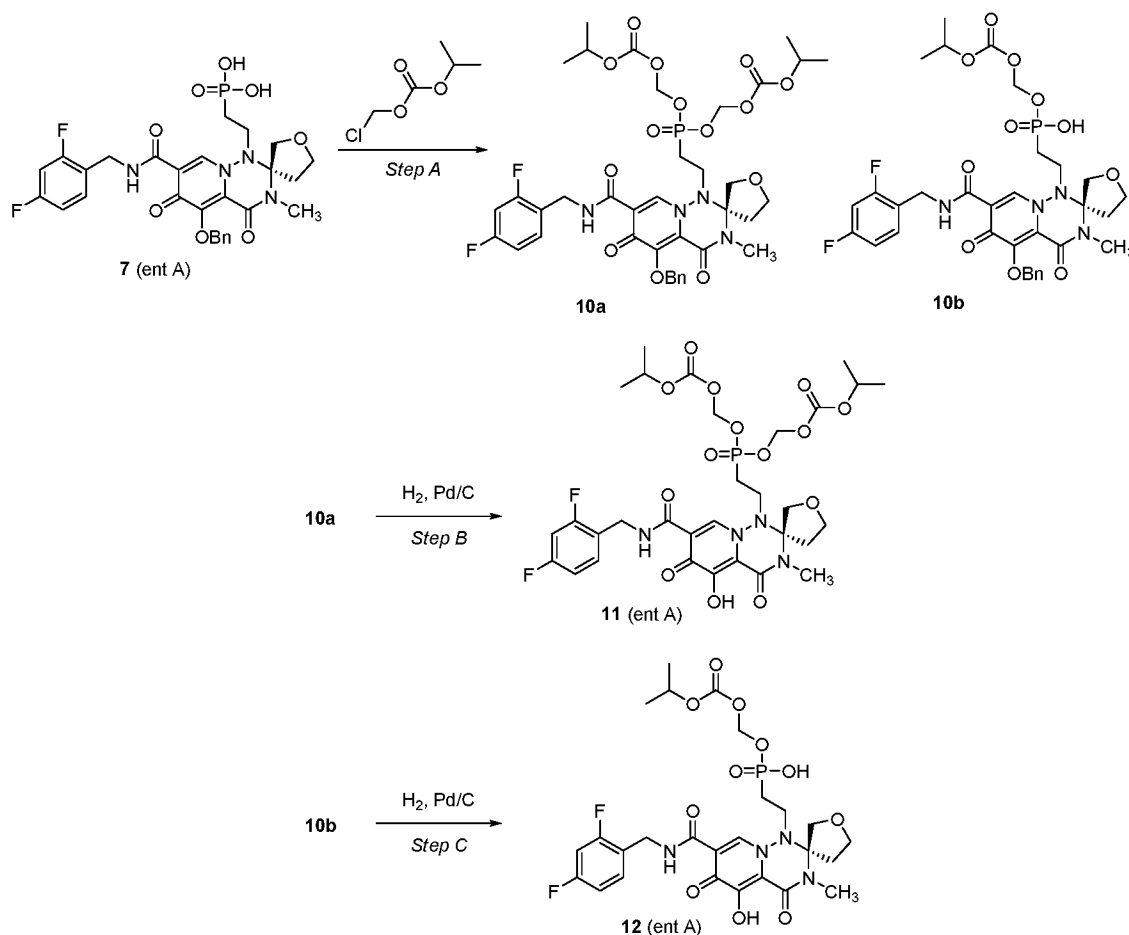
Compound **6** (ent B, 85.6 mg, 0.146 mmol) in acetonitrile (1.5 mL) was treated at room temperature with 2,6-lutidine (0.128 mL, 1.098 mmol) and TMS-Br (0.133 mL, 1.025 mmol). The reaction mixture was allowed to stir at 50 °C for 12 hours, cooled to 0 °C, quenched with water (130 uL) and allowed to stir for 1 hour. Acetic acid (1.3 mL) was added and the mixture was diluted with 10% aq DMSO (4 mL). Direct purification using RP-HPLC provided Compound **10**.

mmol). The reaction mixture was allowed to stir at 50 °C for 12 hours, cooled to 0 °C, quenched with water (130 uL) and allowed to stir for 1 hour. Acetic acid (1.3 mL) was added and the mixture was diluted with 10% aq DMSO (4 mL). Direct purification using RP-HPLC provided Compound **10**. Mass Calc'd for C₂₁H₂₃F₂N₄O₈P: 528.1, Found: 529.1 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ {11.69 (s; 1 H); 11.65 (s; 1 H)}; 10.21-10.24 (m; 1 H); {8.46 (s; 1 H); 8.39 (s; 1 H)}; 7.39-7.44 (m; 1 H); 7.22-7.26 (m; 1 H); 7.06 (t; J = 8.6 Hz; 1 H); 4.49-4.58 (m; 2 H); {4.05 (dd; J = 9.1; 4.5 Hz; 1 H); 3.98-4.02 (m; 1 H)}; 3.69-3.79 (m; 2 H); {3.16 (s; 3 H); 3.11 (s; 3 H)}; 2.92-2.97 (m; 2 H); 2.77-2.80 (m; 1 H); 2.28-2.40 (m; 1 H); 2.07-2.13 (m; 1 H); 1.75-1.86 (m; 1 H); 1.36-1.45 (m; 1 H).

10

Example 10

Preparation of Compound **11** and Compound **12**



Step A – Synthesis of Compound 10a and Compound 10b

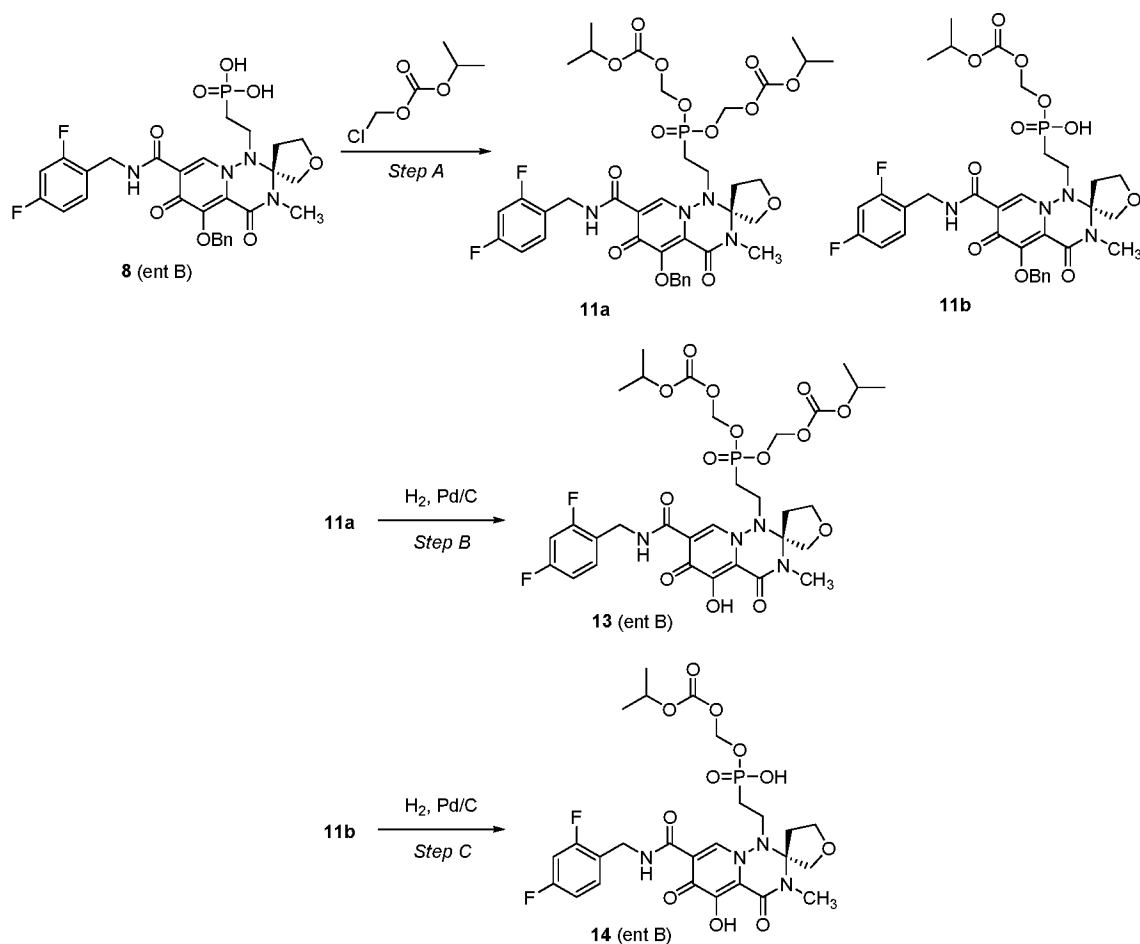
Compound 7 (ent A, 77 mg, 0.124 mmol) in *N*-methyl-2-pyrrolidinone (1.2 mL) was treated with triethylamine (0.069 mL, 0.498 mmol), tetra-*N*-butylammonium bromide (40.1 mg, 0.124 mmol). The suspension was warmed to 50 °C and allowed to stir for 5 hours, cooled to room temperature, diluted with aqueous DMSO and directly purified using RP-HPLC to provide Compound 10a, Mass Calc'd for C₃₈H₄₅F₂N₄O₁₄P: 850.3, Found: 851.2 (M+H)⁺ and Compound 10b, Mass Calc'd for C₃₃H₃₇F₂N₄O₁₁P: 734.2, Found: 735.0 (M+H)⁺

Step B – Synthesis of Compound 11

A mixture of Compound 10a (44.2 mg, 0.052 mmol) and 10% Pd/C (5 mg) in methanol (2 mL) was sub-surface sparged with nitrogen for 2 minutes and then allowed to stir under hydrogen gas (1 atm) for 16 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue obtained was purified using RP-HPLC to provide Compound 11, Mass Calc'd for C₃₁H₃₉F₂N₄O₁₄P: 760.2, Found: 761.0 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 11.65 (br s, 1H); 10.21-10.23 (m; 1 H); {8.42 (s; 1 H); 8.36 (s; 1 H)}; 7.42 (q; J = 7.9 Hz; 1 H); 7.23 (t; J = 10.0 Hz; 1 H); 7.06 (t; J = 8.6 Hz; 1 H); 5.54-5.62 (m; 4 H); 4.77-4.82 (m; 2 H); 4.49-4.59 (m; 2 H); 3.97-4.06 (m; 2 H); 3.73-3.78 (m; 1 H); 3.70 (t; J = 5.3 Hz; 1 H); {3.15 (s; 3 H); 3.10 (s; 3 H)}; 2.97-3.07 (m; 2 H); 2.77-2.82 (m; 1 H); 2.18-2.39 (m; 2 H); 2.01-2.13 (m; 1 H); 1.23 (t; J = 6.2 Hz; 12 H).

Step C – Synthesis of Compound 12

A mixture of Compound 10b (21.5 mg, 0.029 mmol) and 10% Pd/C (3.11 mg) in methanol (2 mL) was sub-surface sparged with nitrogen for 2 minutes and then allowed to stir under hydrogen gas (1 atm) for 16 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue obtained was purified using RP-HPLC to provide Compound 12, Mass Calc'd for C₂₆H₃₁F₂N₄O₁₁P: 644.2, Found: 644.9 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 10.23 (br s; 1 H); {8.45 (s; 1 H); 8.38 (s; 1 H)}; 7.42 (q; J = 7.9 Hz; 1 H); 7.23 (t; J = 10.0 Hz; 1 H); 7.06 (t; J = 8.4 Hz; 1 H); 5.50 (m; 2 H); 4.76-4.81 (m; 1 H); 4.48-4.55 (m; 2 H); 3.97-4.04 (br m; 2 H); 3.68-3.78 (m; 2 H); {3.15 (s; 3 H); 3.11 (s; 3 H)}; 2.97-3.05 (m; 2 H); 2.28-2.38 (m; 2 H); 2.08-2.12 (m; 1 H); 1.92-1.99 (m; 1 H); 1.66-1.71 (br m; 1 H); 1.22 (d; J = 6.3 Hz; 6 H).

Example 11**Preparation of Compound 13 and Compound 14****5 Step A – Synthesis of Compound 11a and Compound 11b**

Compound 8 (ent B, 59 mg, 0.095 mmol) in *N*-methyl-2-pyrrolidinone (1 mL) was treated with triethylamine (0.053 mL, 0.382 mmol), tetra-*N*-butylammonium bromide (30.8 mg, 0.095 mmol). The suspension was warmed to 50 °C and allowed to stir for 5 hours, cooled to room temperature, diluted with aqueous DMSO and directly purified using RP-HPLC to provide Compound 11a, Mass Calc'd for C₃₈H₄₅F₂N₄O₁₄P: 850.3, Found: 851.2 (M+H)⁺ and Compound 11b, Mass Calc'd for C₃₃H₃₇F₂N₄O₁₁P: 734.2, Found: 735.0 (M+H)⁺

Step B – Synthesis of Compound 13

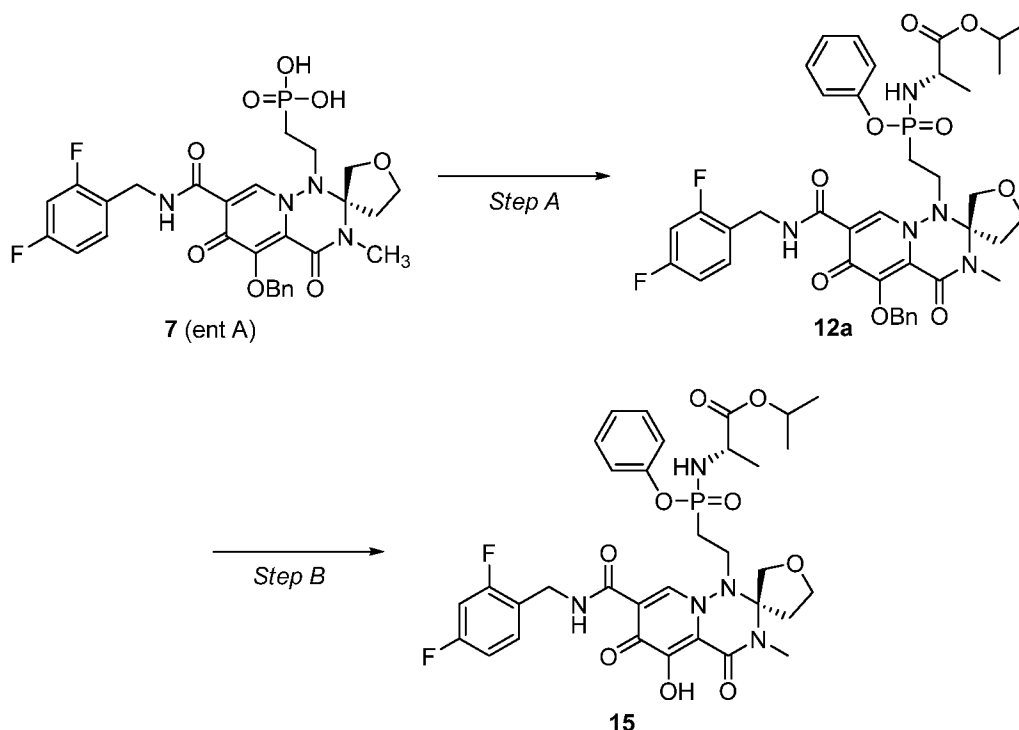
A mixture of Compound **11a** (26 mg, 0.031 mmol) and 10% Pd/C (5 mg) in methanol (2 mL) was sub-surface sparged with nitrogen for 2 minutes and then allowed to stir under hydrogen gas (1 atm) for 16 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue obtained was purified using RP-HPLC to provide Compound **13**, Mass Calc'd for C₃₁H₃₉F₂N₄O₁₄P: 760.2, Found: 760.9 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 11.65 (br s, 1H); 10.21-10.23 (m; 1 H); {8.42 (s; 1 H); 8.36 (s; 1 H)}; 7.42 (q; J = 7.9 Hz; 1 H); 7.23 (t; J = 10.0 Hz; 1 H); 7.06 (t; J = 8.6 Hz; 1 H); 5.54-5.62 (m; 4 H); 4.77-4.82 (m; 2 H); 4.49-4.59 (m; 2 H); 3.97-4.06 (m; 2 H); 3.73-3.78 (m; 1 H); 3.70 (t; J = 5.3 Hz; 1 H); {3.15 (s; 3 H); 3.10 (s; 3 H)}; 2.97-3.07 (m; 2 H); 2.77-2.82 (m; 1 H); 2.18-2.39 (m; 2 H); 2.01-2.13 (m; 1 H); 1.23 (t; J = 6.2 Hz; 12 H).

Step C – Synthesis of Compound **14**

A mixture of Compound **11b** (20.0 mg, 0.027 mmol) and 10% Pd/C (2.9 mg) in methanol (2 mL) was sub-surface sparged with nitrogen for 2 minutes and then allowed to stir under hydrogen gas (1 atm) for 16 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue obtained was purified using RP-HPLC to provide Compound **14**, Mass Calc'd for C₂₆H₃₁F₂N₄O₁₁P: 644.2, Found: 644.9 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 10.23 (br s; 1 H); {8.45 (s; 1 H); 8.38 (s; 1 H)}; 7.42 (q; J = 7.9 Hz; 1 H); 7.23 (t; J = 10.0 Hz; 1 H); 7.06 (t; J = 8.4 Hz; 1 H); 5.50 (m; 2 H); 4.76-4.81 (m; 1 H); 4.48-4.55 (m; 2 H); 3.97-4.04 (br m; 2 H); 3.68-3.78 (m; 2 H); {3.15 (s; 3 H); 3.11 (s; 3 H)}; 2.97-3.05 (m; 2 H); 2.28-2.38 (m; 2 H); 2.08-2.12 (m; 1 H); 1.92-1.99 (m; 1 H); 1.66-1.71 (br m; 1 H); 1.22 (d; J = 6.3 Hz; 6 H).

Example 12

Preparation of Compound **15**



Step A – Synthesis of Compound 12a

A mixture of Compound 7 (47.2 mg, 0.076 mmol), L-alanine isopropyl ester hydrochloride (69.3 mg, 0.413 mmol) and phenol (86 mg, 0.918 mmol) were charged to a reaction vial and flushed with nitrogen while heating to 60 °C. The reaction mixture was treated at 60 °C with 0.8 mL of a freshly prepared stock solution containing 2,2'-dipyridyl disulfide (303 mg, 1.377 mmol), triphenylphosphine (361 mg, 1.377 mmol) and triethylamine (0.384 mL, 2.75 mmol) in pyridine (1.6 mL). The reaction mixture was allowed to stir at 60 °C for 2 hours, cooled to room temperature and concentrated *in vacuo*. The residue obtained was purified using column chromatography on silica gel to provide Compound 12a that is epimeric at phosphorous. Mass Calc'd for C₄₀H₄₄F₂N₅O₉P: 807.3, Found: 808.0 (M+H)⁺

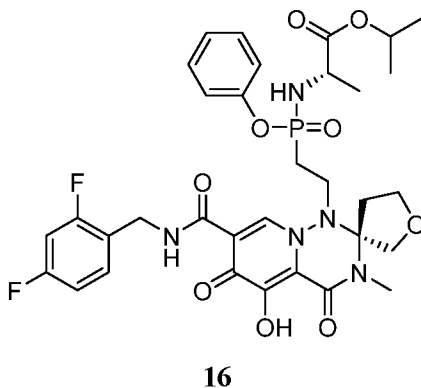
Step B – Synthesis of Compound 15

A mixture of Compound 12a (125.3 mg, 0.155 mmol) and 10% Pd/C (20 mg) in MeOH (3 mL) was sub-surface sparged with nitrogen gas for 2 minutes and then allowed to stir under hydrogen gas (1 atm) for 16 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue obtained was purified using RP-HPLC (acetonitrile/ water,

NH_4HCO_3 as modifier) to provide Compound **15**. Mass Calc'd for $\text{C}_{33}\text{H}_{38}\text{F}_2\text{N}_5\text{O}_9\text{P}$: 717.2, Found: 718.0 ($\text{M}+\text{H}$)⁺

Example 13

Preparation of Compound 16

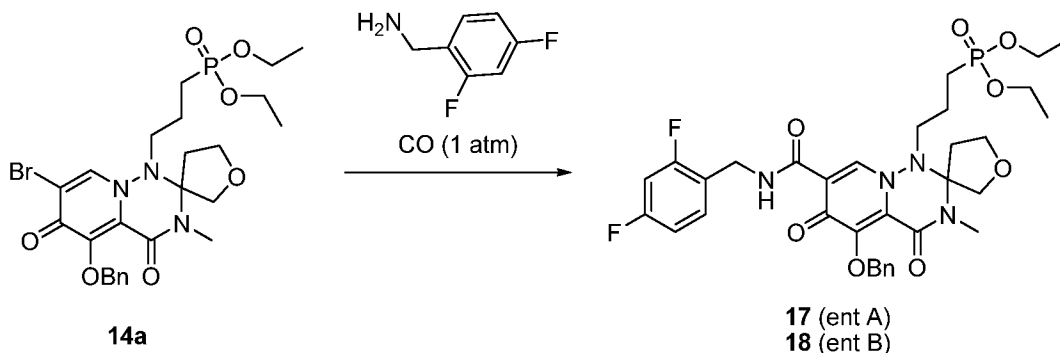


Compound **16** was prepared from Compound **8** in a similar manner to Example

12. Mass Calc'd for $\text{C}_{33}\text{H}_{38}\text{F}_2\text{N}_5\text{O}_9\text{P}$: 717.2, Found: 718.0 ($\text{M}+\text{H}$)⁺

Example 14

Preparation of Compound 17 and Compound 18

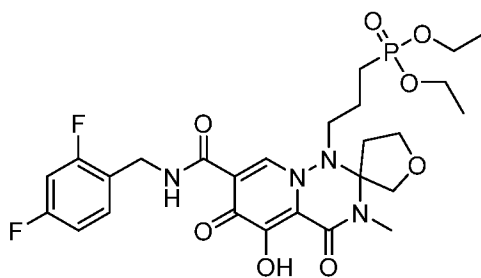


A mixture of Compound **14a**, prepared as the racemate in a similar manner to Compounds **1** and **2** in Example 1, (1.760 g, 2.94 mmol), 2,4-difluorobenzylamine (0.769 ml, 6.47 mmol) and *N,N*-diisopropylethylamine (1.541 ml, 8.82 mmol) in DMSO (10.0 mL) was sub-surface sparged with nitrogen for 15 minutes and then treated with $\text{Pd}(\text{Ph}_3\text{P})_4$ (1.020 g, 0.882 mmol) with additional sparging for 5 minutes. The reaction mixture was then allowed to stir under CO (1 atm) at 90 °C for 8 hours, cooled to room temperature and neutralized with glacial acetic acid. Direct purification using RP-HPLC provided the product as the racemate. Mass

Calc'd for $C_{33}H_{39}F_2N_4O_8P$: 688.2, Found: 689.4 ($M+H$)⁺; ¹H NMR (500 MHz, $CDCl_3$): δ 10.38-10.42 (m; 1 H); {8.39 (s; 1 H); 8.35 (s; 1 H)}; 7.46-7.50 (m; 2 H); 7.37-7.42 (m; 1 H); 7.29-7.33 (m; 3 H); 6.81-6.87 (m; 2 H); 5.52-5.55 (m; 1 H); 5.27 (d; J = 10.46 Hz; 1 H); 4.64 (d; J = 5.91 Hz; 2 H); 4.25 (d; J = 10.26 Hz; 1 H); 4.02-4.12 (m; 4 H); 3.83-3.93 (m; 2 H); 3.71 (d; J = 10.13 Hz; 1 H); 3.14 (s; 3 H); 2.82-2.91 (m; 2 H); 2.06-2.12 (m; 1 H); 1.73-1.89 (m; 4 H); 1.38-1.43 (m; 1 H); 1.29-1.34 (m; 6 H). Chiral resolution using SFC (ChiralCel OJ, 250×30mm, 5% ethanol (0.2% diethylamine) in $SC-CO_2$, 70mL/min, 140 bar, 220 nM) provided Compound **17** (ent A, earlier eluting enantiomer) and Compound **18** (ent B, later eluting enantiomer).

Example 15

Preparation of Compound **19**



enantiomer A

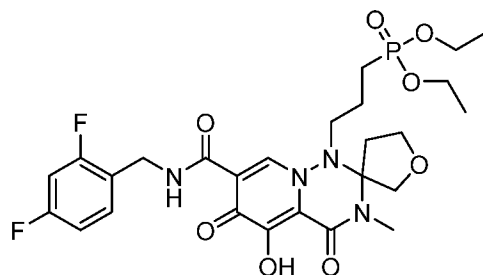
19

Compound **17** (ent A, 30 mg, 0.044 mmol) in TFA (0.5 mL) was allowed to stir at room temperature for 1 hour, diluted with acetonitrile (5 mL) and directly purified using RP-

HPLC to provide Compound **19**. Mass Calc'd for $C_{26}H_{33}F_2N_4O_8P$: 598.2, Found: 599.3 ($M+H$)⁺; ¹H NMR (500 MHz, DMSO): δ 11.74 (br s; 1 H); 10.19-10.23 (m; 1 H); {8.26-8.27 (m; 1 H); 8.18 (s; 1 H)}; 7.37-7.42 (m; 1 H); 7.21-7.25 (m; 1 H); 7.03-7.07 (m; 1 H); 4.52 (d; J = 5.54 Hz; 2 H); 4.43 (d; J = 10.58 Hz; 1 H); 3.86-4.05 (m; 4 H); 3.74-3.80 (m; 1 H); 3.69 (d; J = 9.72 Hz; 1 H); 3.64 (d; J = 10.65 Hz; 1 H); {3.13 (s; 3 H); 3.09 (s; 3 H)}; 2.88-2.96 (m; 1 H); 2.80-2.86 (m; 1 H); 2.26-2.37 (m; 1 H); 2.05-2.11 (m; 1 H); 1.69-1.87 (m; 2 H); 1.51-1.59 (m; 1 H); 1.33-1.41 (m; 1 H); 1.10-1.15 (m; 6 H).

Example 16

Preparation of Compound **20**

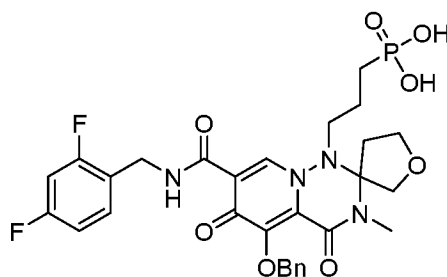


enantiomer B

20

Compound **18** (ent B, 30 mg, 0.044 mmol) in TFA (0.5 mL) was allowed to stir at room temperature for 1 hour, diluted with acetonitrile (5 mL) and directly purified using RP-

- 5 HPLC to provide Compound **20**. Mass Calc'd for $C_{26}H_{33}F_2N_4O_8P$: 598.2, Found: 599.3 $(M+H)^+$; 1H NMR (500 MHz, DMSO): δ 11.74 (br s; 1 H); 10.19-10.23 (m; 1 H); {8.26-8.27 (m; 1 H); 8.18 (s; 1 H)}; 7.37-7.42 (m; 1 H); 7.21-7.25 (m; 1 H); 7.03-7.07 (m; 1 H); 4.52 (d; J = 5.54 Hz; 2 H); 4.43 (d; J = 10.58 Hz; 1 H); 3.86-4.05 (m; 4 H); 3.74-3.80 (m; 1 H); 3.69 (d; J = 9.72 Hz; 1 H); 3.64 (d; J = 10.65 Hz; 1 H); {3.13 (s; 3 H); 3.09 (s; 3 H)}; 2.88-2.96 (m; 1 H); 2.80-2.86 (m; 1 H); 2.26-2.37 (m; 1 H); 2.05-2.11 (m; 1 H); 1.69-1.87 (m; 2 H); 1.51-1.59 (m; 1 H); 1.33-1.41 (m; 1 H); 1.10-1.15 (m; 6 H).
- 10

Example 17Preparation of Compound **21**

enantiomer A

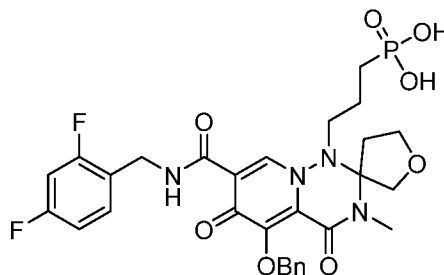
21

A solution of Compound **17** (ent A, 492 mg, 0.714 mmol) in acetonitrile (4.0 mL) was treated at room temperature with 2,6-lutidine (0.499 ml, 4.29 mmol) and TMS-Br (0.463 ml, 3.57 mmol). The resulting reaction mixture was heated at 50 °C for 1 hour, cooled to 0 °C,

quenched with water (1.0 mL) and allowed to stir for 10 minute sat 0 °C and then warmed to room temperature. The reaction mixture was directly purified using RP-HPLC to provide Compound **21**. Mass Calc'd for C₂₉H₃₁F₂N₄O₈P: 632.2, Found: 633.3 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 10.29-10.33 (m; 1 H); {8.29 (s; 1 H); 8.22 (s; 1 H)}; 7.40-7.45 (m; 3 H); 7.22-7.35 (m; 4 H); 7.07 (td; J = 8.6; 2.4 Hz; 1 H); 5.24 (app t; J = 10.1 Hz; 1 H); 5.11 (d; J = 10.7 Hz; 1 H); 4.50-4.58 (m; 2 H); {4.37 (d; J = 10.5 Hz; 1 H); 3.49 (d; J = 9.5 Hz; 1 H); }; 3.93-4.01 (m; 1 H); {3.81-3.86 (m; 1 H); 3.74-3.79 (m; 1 H)}; {3.63 (d; J = 10.5 Hz; 1 H), 3.25 (d; J = 9.5 Hz; 1 H)}; {3.07 (s; 3 H); 3.03 (s; 3 H)}; 2.77-2.87 (m; 2 H); 2.64-2.69 (m; 1 H); 2.27-2.33 (m; 1 H); 2.10-2.16 (m; 1 H); 1.63-1.66 (m; 1 H); 1.49-1.61 (m; 2 H).

Example 18

Preparation of Compound **22**



enantiomer B

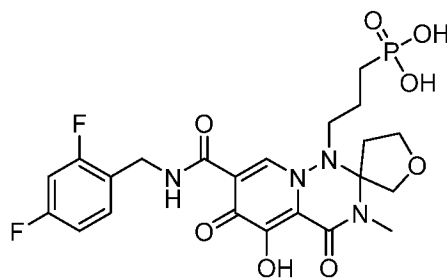
22

Compound **18** (ent B, 492 mg, 0.714 mmol) in acetonitrile (4.0 mL) was treated at room temperature with 2,6-lutidine (0.499 ml, 4.29 mmol) and TMS-Br (0.463 ml, 3.57 mmol). The resulting reaction mixture was heated at 50 °C for 1 hour, cooled to 0 °C, quenched with water (1.0 mL) and allowed to stir for 10 minutes at 0 °C and then warmed to room temperature. The reaction mixture was directly purified using RP-HPLC to provide Compound **22**. Mass Calc'd for C₂₉H₃₁F₂N₄O₈P: 632.2, Found: 633.3 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 10.29-10.33 (m; 1 H); {8.29 (s; 1 H); 8.22 (s; 1 H)}; 7.40-7.45 (m; 3 H); 7.22-7.35 (m; 4 H); 7.07 (td; J = 8.6; 2.4 Hz; 1 H); 5.24 (app t; J = 10.1 Hz; 1 H); 5.11 (d; J = 10.7 Hz; 1 H); 4.50-4.58 (m; 2 H); {4.37 (d; J = 10.5 Hz; 1 H); 3.49 (d; J = 9.5 Hz; 1 H); }; 3.93-4.01 (m; 1 H); {3.81-3.86 (m; 1 H); 3.74-3.79 (m; 1 H)}; {3.63 (d; J = 10.5 Hz; 1 H), 3.25 (d; J = 9.5 Hz; 1 H)};

{3.07 (s; 3 H); 3.03 (s; 3 H)}; 2.77-2.87 (m; 2 H); 2.64-2.69 (m; 1 H); 2.27-2.33 (m; 1 H); 2.10-2.16 (m; 1 H); 1.63-1.66 (m; 1 H); 1.49-1.61 (m; 2 H).

Example 19

Preparation of Compound 23



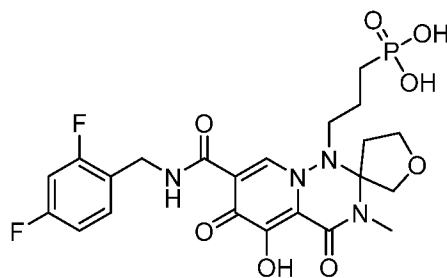
enantiomer A

23

Compound **21** (ent A, 100.3 mg, 0.159 mmol) was allowed to stir in TFA (1mL) at room temperature for 30 minutes, diluted with aqueous DMSO and directly purified using RP-HPLC to provide Compound **23**. Mass Calc'd for $C_{22}H_{25}F_2N_4O_8P$: 542.1, Found: 543.1 ($M+H$)⁺; ¹H NMR (500 MHz, DMSO): δ 10.23-10.26 (m; 1 H); {8.25 (s; 1 H); 8.17 (s; 1 H)}; 7.41 (q; J = 7.9 Hz; 1 H); 7.22-7.26 (m; 1 H); 7.06 (td; J = 8.6; 2.5 Hz; 1 H); 4.49-4.61 (m; 2 H); 4.45 (d; J = 10.7 Hz; 1 H); 3.95-4.05 (m; 1 H); 3.74-3.80 (m; 1 H); 3.65-3.69 (m; 1 H); {3.14 (s; 3 H); 3.09 (s; 3 H)}; 2.82-2.95 (m; 2 H); 2.70-2.75 (dt; J = 13.6; 6.4 Hz; 1 H); 2.30-2.36 (m; 1 H); 2.08 (dt; J = 13.3; 8.0 Hz; 1 H); 1.48-1.60 (m; 2 H); 1.38 (br s; 1 H).

Example 20

Preparation of Compound 24

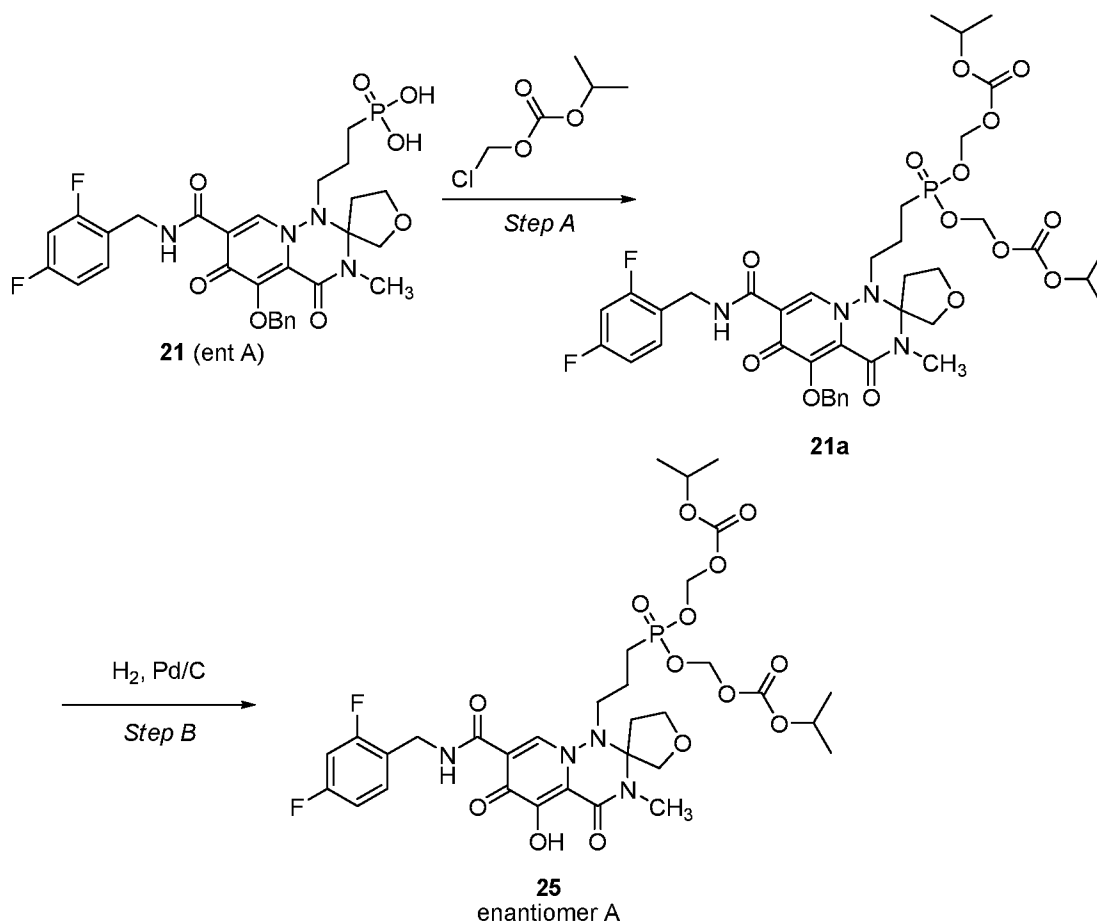


enantiomer B

24

Compound **22** (ent B, 100.9 mg, 0.160 mmol) was allowed to stir in TFA (1mL) at room temperature for 30 minutes, diluted with aqueous DMSO and directly purified using RP-HPLC to provide Compound **24**. Mass Calc'd for $C_{22}H_{25}F_2N_4O_8P$: 542.1, Found: 543.1 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 10.23-10.26 (m; 1 H); {8.25 (s; 1 H); 8.17 (s; 1 H)}; 7.41 (q; J = 7.9 Hz; 1 H); 7.22-7.26 (m; 1 H); 7.06 (td; J = 8.6; 2.5 Hz; 1 H); 4.49-4.61 (m; 2 H); 4.45 (d; J = 10.7 Hz; 1 H); 3.95-4.05 (m; 1 H); 3.74-3.80 (m; 1 H); 3.65-3.69 (m; 1 H); {3.14 (s; 3 H); 3.09 (s; 3 H)}; 2.82-2.95 (m; 2 H); 2.70-2.75 (dt; J = 13.6; 6.4 Hz; 1 H); 2.30-2.36 (m; 1 H); 2.08 (dt; J = 13.3; 8.0 Hz; 1 H); 1.48-1.60 (m; 2 H); 1.38 (br s; 1 H).

10

Example 21Preparation of Compound **25**

Step A – Synthesis of Compound 21a

Compound **21** (301.4 mg, 0.476 mmol) in acetonitrile (5 mL) was treated at room temperature with *N,N*-diisopropylethylamine (0.832 mL, 4.76 mmol), tetrabutylammonium bromide (154 mg, 0.476 mmol) and chloromethyl isopropyl carbonate (0.506 mL, 3.81 mmol).

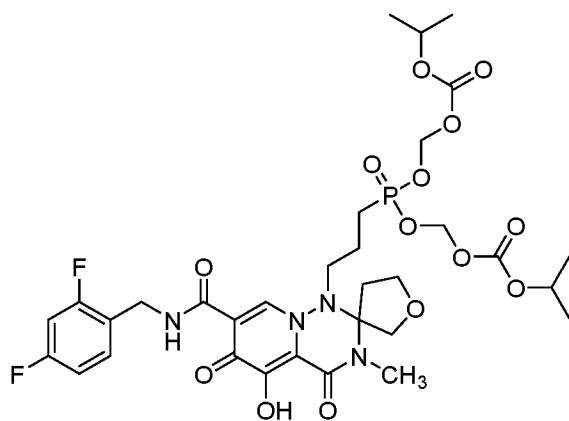
- 5 The suspension was warmed to 60 °C and allowed to stir for 24 hours, cooled to room temperature and concentrated *in vacuo*. The residue obtained was purified using column chromatography on silica gel (25% to 100% [1:3 EtOH/EtOAc]/ hexanes) to provide Compound **21a**. Mass Calc'd for C₃₉H₄₇F₂N₄O₁₄P: 864.3, Found: 865.4 (M+H)⁺.

10 *Step B – Synthesis of Compound 27*

A mixture of Compound **21a** (300 mg, 0.347 mmol) and 10% Pd/C (36.9 mg) in MeOH (3.5 mL) was sub-surface sparged with nitrogen gas for 5 minutes and then allowed to stir under hydrogen gas (1 atm) for 16 hours. The reaction mixture was filtered and the filtrate was directly purified using RP-HPLC to provide Compound **25**. Mass Calc'd for

- 15 C₃₂H₄₁F₂N₄O₁₄P: 774.2, Found: 775.2 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ 11.70 (br s; 1 H); 10.21-10.24 (m; 1 H); {8.28 (s; 1 H); 8.20 (s; 1 H)}; 7.41 (q; J = 7.9 Hz; 1 H); 7.23 (t; J = 10.0 Hz; 1 H); 7.05 (t; J = 8.3 Hz; 1 H); 5.50-5.59 (m; 4 H); 4.78-4.84 (m; 2 H); 4.53 (dd; J = 13.1; 5.7 Hz; 2 H); 4.43 (d; J = 10.6 Hz; 1 H); 3.96-4.03 (m; 1 H); 3.68-3.81 (m; 1 H); 3.63 (d; J = 10.6 Hz; 1 H); {3.14 (s; 3 H); 3.09 (s; 3 H)}; 2.71-2.94 (m; 2 H); 2.28-2.35 (m; 1 H);
20 1.99-2.12 (m; 3 H); 1.44-1.57 (br m; 2 H); 1.23 (d; J = 6.0 Hz; 12 H).

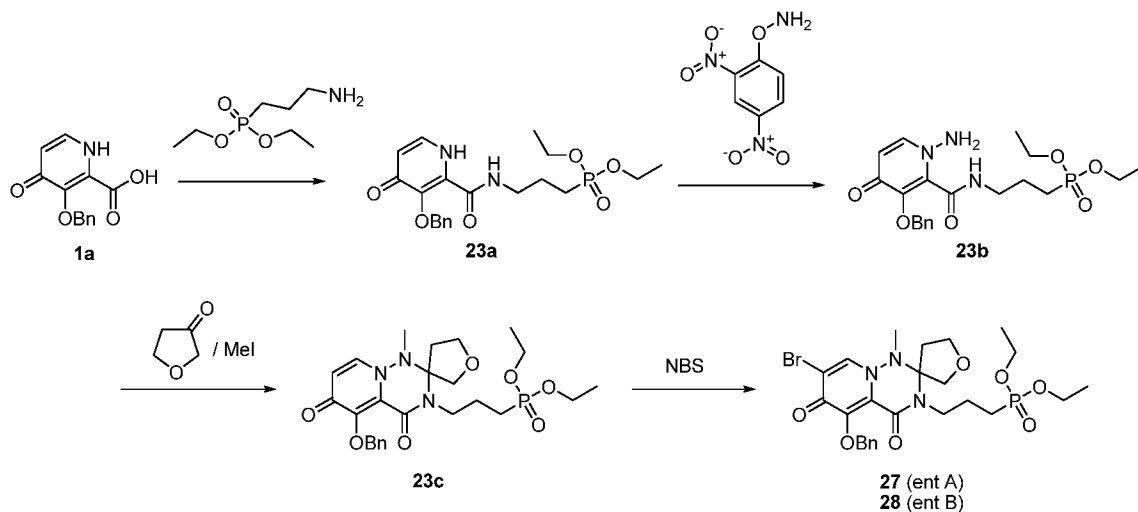
Example 22Preparation of Compound **26**

**26**

enantiomer B

Compound **26** (ent B) was prepared from Compound **22** using the method described in Example 21. Mass Calc'd for $C_{32}H_{41}F_2N_4O_{14}P$: 774.2, Found: 775.2 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ 11.70 (br s; 1 H); 10.21-10.24 (m; 1 H); {8.28 (s; 1 H); 8.20 (s; 1 H)}; 7.41 (q; J = 7.9 Hz; 1 H); 7.23 (t; J = 10.0 Hz; 1 H); 7.05 (t; J = 8.3 Hz; 1 H); 5.50-5.59 (m; 4 H); 4.78-4.84 (m; 2 H); 4.53 (dd; J = 13.1; 5.7 Hz; 2 H); 4.43 (d; J = 10.6 Hz; 1 H); 3.96-4.03 (m; 1 H); 3.68-3.81 (m; 1 H); 3.63 (d; J = 10.6 Hz; 1 H); {3.14 (s; 3 H); 3.09 (s; 3 H)}; 2.71-2.94 (m; 2 H); 2.28-2.35 (m; 1 H); 1.99-2.12 (m; 3 H); 1.44-1.57 (br m; 2 H); 1.23 (d; J = 6.0 Hz; 12 H).

10

Example 23Preparation of Intermediate Compound **27** and Intermediate Compound **28**

Step A – Synthesis of Compound 23a

A mixture of Compound **1a** (1.20 g, 4.89 mmol) and HOBT (0.787 g, 5.14 mmol) in dichloromethane (25 mL) was cooled to 0 °C and treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.985 g, 5.14 mmol) and 4-methylmorpholine (1.614 mL, 14.68 mmol). After stirring for 3 minutes, diethyl (3-aminopropyl)phosphonate (1.00 g, 5.12 mmol) was added and the mixture was allowed to slowly warm to room temperature and stir for 20 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the residue obtained was taken up in dimethylsulfoxide, neutralized with glacial acetic acid and purified using RP-MPLC to provide Compound **23a**. Mass Calc'd for C₂₀H₂₇N₂O₆P: 422.2, Found: 423.1 (M+H)⁺. ¹H NMR (500 MHz, CDCl₃): δ 8.31 (t; J = 5.9 Hz; 1 H); 7.68 (d; J = 7.1 Hz; 1 H); 7.37-7.41 (m; 5 H); 6.92 (d; J = 6.9 Hz; 1 H); 5.52 (s; 2 H); 4.03-4.14 (m; 4 H); 3.27-3.31 (m; 2 H); 1.57-1.70 (m; 4 H); 1.32 (t; J = 7.1 Hz; 6 H).

Step B – Synthesis of Compound 23b

A solution of Compound **23a** (1.730 g, 4.10 mmol) in *N,N*-dimethylformamide (15 mL) was treated with potassium carbonate (1.698 g, 12.29 mmol), O-(2,4-dinitrophenyl)-hydroxylamine (1.631 g, 8.19 mmol) and water (0.074 mL, 4.10 mmol). The reaction mixture was allowed to stir at room temperature for 48 hours, diluted with water (5 mL) and filtered through a pad of solkaflor with an acetonitrile rinse. The combined filtrates were neutralized with glacial acetic acid and directly purified using RP-MPLC to provide Compound **23b** which was used without further purification or treatment. Mass Calc'd for C₂₀H₂₈N₃O₆P: 437.2, Found: 438.3 (M+H)⁺. ¹H NMR (500 MHz, CDCl₃): δ 7.83 (s; 1 H); 7.33-7.34 (m; 3 H); 7.26 (s; 5 H); 7.00 (d; J = 7.4 Hz; 1 H); 5.20 (s; 2 H); 4.02-4.08 (m; 4 H); 3.36 (q; J = 6.1 Hz; 2 H); 1.72-1.84 (m; 4 H); 1.30 (t; J = 7.1 Hz; 6 H).

Step C – Synthesis of Compound 23c

Compound **23b** (1.260 g, 2.88 mmol) in dioxane (10.0 mL) was treated at room temperature with 3-oxotetrahydrofuran (1.115 mL, 14.40 mmol) and acetic acid (0.165 mL, 2.88 mmol). The reaction mixture was allowed to stir at room temperature for 36 hours, directly loaded onto a dry silica gel column and purified using column chromatography on silica gel (0 to 30% MeOH/ dichloromethane) to provide an intermediate residue. Mass Calc'd for

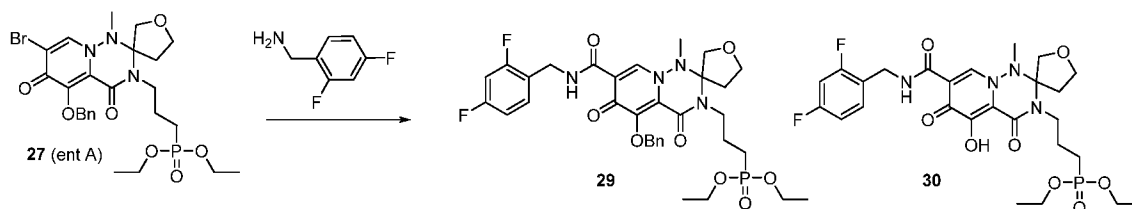
$C_{24}H_{32}N_3O_7P$: 505.2, Found: 506.2 ($M+H$)⁺. The intermediate residue obtained was taken up in dimethylsulfoxide (8.0 mL) and sequentially treated at room temperature with iodomethane (0.333 mL, 5.33 mmol), tetrabutylammonium hydroxide triacontahydrate (284 mg, 0.355 mmol) and finely-powdered potassium hydroxide (299 mg, 5.33 mmol). The reaction mixture was allowed to stir at room temperature for 6 hours, neutralized with glacial AcOH and directly purified using RP-MPLC to provide Compound **23c** which was used without further purification. Mass Calc'd for $C_{25}H_{34}N_3O_7P$: 519.2, Found: 520.3 ($M+H$)⁺.

Step D – Synthesis of Intermediate Compound 27 and Intermediate Compound 28

A solution of Compound **23c** (1.018 g, 1.959 mmol) in *N,N*-dimethylformamide (5.0 mL) was treated at room temperature with *N*-bromosuccinimide (0.698 g, 3.92 mmol), stirred at room temperature for 3 hours, diluted with water (2 mL) and directly purified using RP-MPLC to provide a residue that was purified further using column chromatography on silica gel (10 to 100% [1:3 EtOH/EtOAc]/ hexanes eluted at 100%) to provide the product as a racemate. Mass Calc'd for $C_{25}H_{33}BrN_3O_7P$: 597.1, 599.1, Found: 598.2, 600.2 ($M+H$)⁺. Chiral resolution using SFC (ChiralCel OD-H, 250×20mm, 15% methanol in SC-CO₂, 70mL/min, 100 bar, 220 nM) provided intermediate Compound **27** (ent A, earlier eluting enantiomer) and intermediate Compound **28** (ent B, later eluting enantiomer).

Example 24

Preparation of Compound **29** and Compound **30**

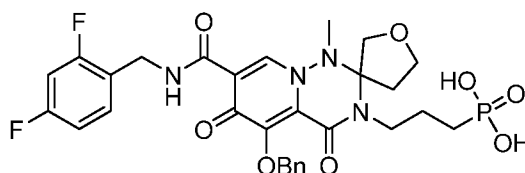


A mixture of Compound **27** (ent A, 200.4 mg, 0.335 mmol), 2,4-difluorobenzylamine (0.089 mL, 0.737 mmol), *N,N*-diisopropylethylamine (0.175 mL, 1.005 mmol) and Pd(PPh₃)₄ (193 mg, 0.167 mmol) in dimethylsulfoxide (3 mL) was sub-surface sparged with nitrogen gas for 10 minutes and then allowed to stir under carbon monoxide (1 atm) at 90 °C for 8 hours. The reaction mixture was treated with water (1 mL), stirred for 10 minutes, diluted with dimethylsulfoxide (4 mL) and directly purified using RP-HPLC to

provide Compound **29**, Mass Calc'd for $C_{33}H_{39}F_2N_4O_8P$: 688.3, Found: 689.3 (M+H)⁺, and Compound **30** Mass Calc'd for $C_{26}H_{33}F_2N_4O_8P$: 598.2, Found: 599.2 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 10.26 (q; J = 6.0 Hz; 1 H); {8.33 (s; 1 H); 8.26 (s; 1 H)}; 7.38-7.43 (m; 1 H); 7.24 (td; J = 9.9; 2.5 Hz; 1 H); 7.06 (td; J = 8.5; 2.5 Hz; 1 H); 4.53 (d; J = 5.8 Hz; 2 H); 4.27 (d; J = 10.8 Hz; 1 H); 3.95-4.03 (m; 4 H); 3.69-3.81 (m; 2 H); 3.63 (d; J = 9.8 Hz; 1 H); 3.29-3.34 (m; 2 H); {2.82 (s; 3 H); 2.73 (s; 3 H)}; 2.32-2.36 (m; 1 H); 2.05-2.11 (m; 1 H); 1.75-1.88 (m; 4 H); 1.23 (t; J = 7.0 Hz; 6 H).

Example 25

Preparation of Compound 31



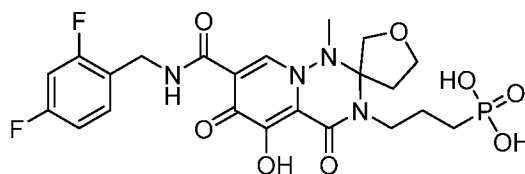
enantiomer A

31

Compound **29** (ent A, 164 mg, 0.238 mmol) in acetonitrile (2.3 mL) was treated at room temperature with 2,6-lutidine (0.208 mL, 1.786 mmol) and TMS-Br (0.216 mL, 1.667 mmol). The reaction mixture was allowed to stir at 50 °C for 2 hours, cooled to 0 °C, quenched with water (2 mL) and allowed to stir for 1 hour while warming to room temperature. The reaction mixture was directly purified using RP-HPLC to provide Compound **31**. Mass Calc'd for $C_{29}H_{31}F_2N_4O_8P$: 632.2, Found: 633.0 (M+H)⁺.

Example 26

Preparation of Compound 32



enantiomer A

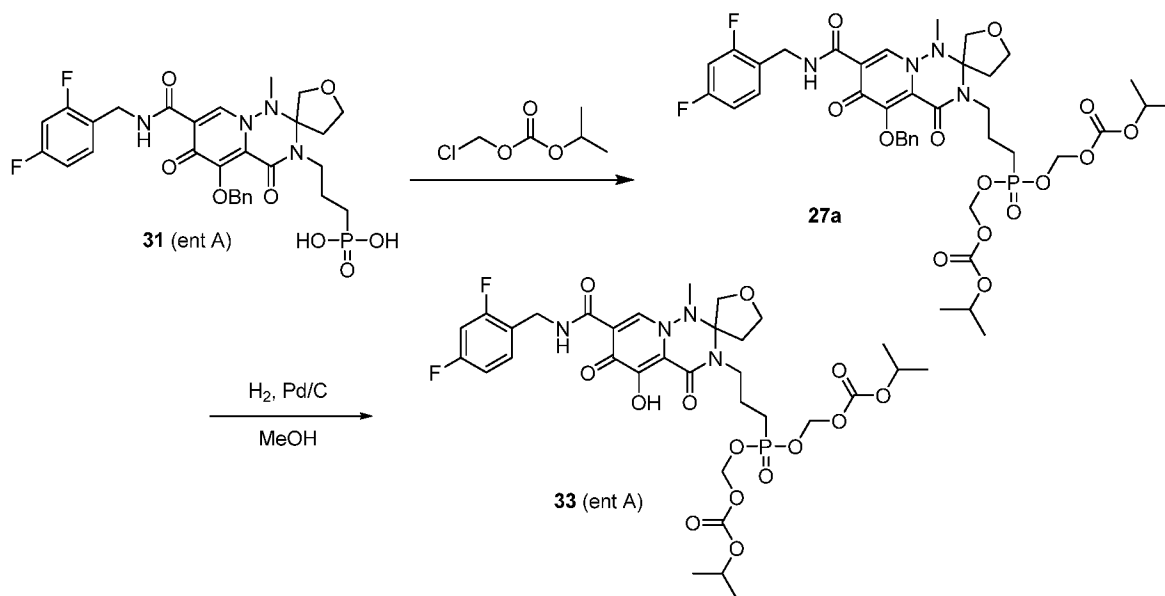
32

A solution of Compound **30** (34 mg, 0.057 mmol) in acetonitrile (1 mL) was treated at room temperature with 2,6-lutidine (0.050 mL, 0.426 mmol) and TMS-Br (0.052 mL, 0.398 mmol). The reaction mixture was allowed to stir at 50 °C for 2 hours, cooled to 0°C, quenched with water (1 mL) and allowed to stir for 1 hour while warming to room temperature.

- 5 The reaction mixture was directly purified using RP-HPLC to provide Compound **32**. Mass Calc'd for $C_{22}H_{25}F_2N_4O_8P$: 542.1, Found: 542.8 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ 10.27 (q; J = 5.9 Hz; 1 H); {8.33 (s; 1 H); 8.26 (s; 1 H)}; 7.38-7.43 (m; 1 H); 7.22-7.26 (m; 1 H); 7.04-7.08 (m; 1 H); 4.53 (d; J = 5.8 Hz; 2 H); 4.26 (d; J = 10.9 Hz; 1 H); 3.95-4.02 (m; 1 H); 3.70-3.79 (m; 2 H); 3.61 (d; J = 9.8 Hz; 1 H); 3.29-3.35 (m; 1 H); {2.82 (s; 3 H); 2.73 (s; 3 H)}; 2.32-2.38 (m; 1 H); 2.04-2.10 (m; 1 H); 1.84-1.90 (m; 1 H); 1.72-1.78 (m; 1 H); 1.54-1.64 (m; 2 H).

Example 27

Preparation of Compound **33**



Step A – Synthesis of Compound **27a**

A solution of Compound **31** (ent A, 140 mg, 0.221 mmol) in acetonitrile (2 mL) was treated with *N,N*-diisopropylethylamine (0.387 mL, 2.213 mmol), tetrabutylammonium bromide (71.3 mg, 0.221 mmol) and chloromethyl isopropyl carbonate (0.235 mL, 1.771 mmol).

- 20 The reaction mixture was allowed to stir at 60 °C for 16 hours, cooled to room temperature and

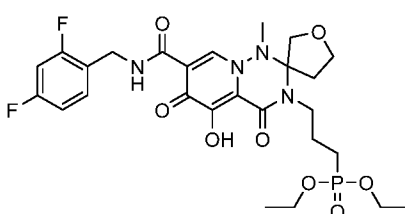
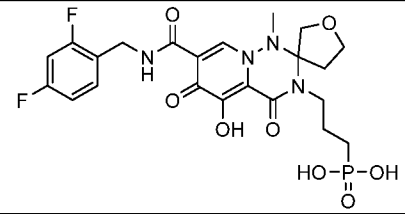
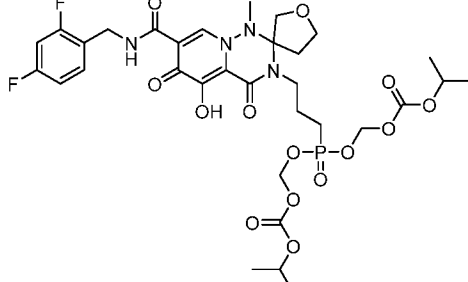
concentrated *in vacuo*. The residue obtained was purified using column chromatography on silica gel (25% to 100% [1:3 EtOH/EtOAc]/ hexanes) to provide Compound **27a**. Mass Calc'd for C₃₉H₄₇F₂N₄O₁₄P: 864.3, Found: 865.8 (M+H)⁺.

5 Step B – Synthesis of Compound 33

A mixture of Compound **27a** (100 mg, 0.116 mmol) and 10% Pd/C (12.3 mg) in MeOH (2.0 mL) was sub-surface sparged with nitrogen gas for 5 minutes and then allowed to stir under hydrogen gas (1 atm) for 16 hours. The reaction mixture was filtered and the filtrate was directly purified using RP-HPLC to provide Compound **33**. Mass Calc'd for

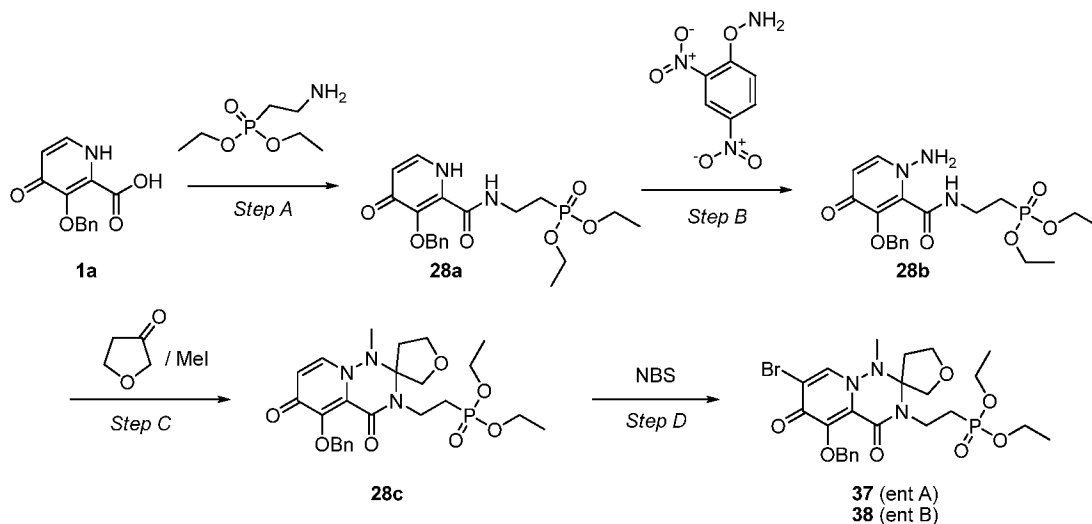
10 C₃₂H₄₁F₂N₄O₁₄P: 774.2, Found: 775.2 (M+H)⁺.

The following compounds were prepared from Compound **28** (ent B) using the methods described in Examples 24 – 27.

<u>Compound No.</u>	<u>Structure</u>	<u>Stereochemistry</u>	<u>Exact Mass [M+H]⁺</u>
34		enantiomer B	Calc'd 599.2, found 599.3
35		enantiomer B	Calc'd 543.1, found 542.9
36		enantiomer B	Calc'd 775.2, found 779.2

Example 28

Preparation of Intermediate Compound 37 and Intermediate Compound 38



5 Step A – Synthesis of Compound 28a

A mixture of Compound **1a** (1.0 g, 4.08 mmol) and HOBT (0.687 g, 4.49 mmol) in dichloromethane (20 mL) was cooled to 0 °C and treated with EDC (0.860 g, 4.49 mmol) and *N*-methylmorpholine (1.345 mL, 12.23 mmol). After 15 minutes, diethyl (2-aminoethyl)phosphonate (0.960 g, 5.30 mmol) was added and the mixture was allowed to stir for 20 hours while slowly warming to room temperature. The reaction mixture was concentrated to an amber syrup, diluted with DMSO, neutralized with glacial acetic acid and directly purified using RP-MPLC to provide Compound **28a**. Mass Calc'd for C₁₉H₂₅N₂O₆P: 408.1, Found: 409.1 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ 8.67 (t; J = 5.8 Hz; 1 H); 7.71 (dd; J = 6.8; 3.6 Hz; 1 H); 7.41-7.43 (m; 2 H); 7.32-7.36 (m; 3 H); 6.53 (t; J = 6.0 Hz; 1 H); 5.35 (s; 2 H); 3.95-4.03 (m; 4 H); 3.37-3.44 (m; 2 H); 1.92 (dt; J = 17.8; 7.7 Hz; 2 H); 1.22 (t; J = 7.0 Hz; 6 H).

Step B – Synthesis of Compound 28b

A solution of Compound **28a** (2.049 g, 5.02 mmol) in *N,N*-dimethylformamide (12 mL) was treated at room temperature with potassium carbonate (2.080 g, 15.05 mmol) and O-(2,4-dinitrophenyl)hydroxylamine (1.998 g, 10.03 mmol). The reaction mixture was allowed to stir at room temperature for 48 hours, diluted with water (5 mL) and filtered through a pad of

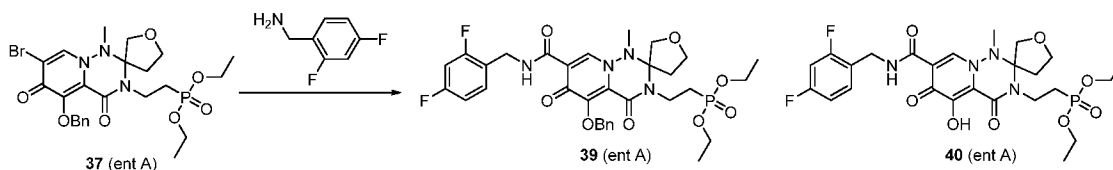
solkaflor (acetonitrile rinse). The combined filtrates were directly purified using RP-MPLC to provide Compound **28b** which was used without further purification. Mass Calc'd for $C_{19}H_{26}N_3O_6P$: 423.2, Found: 424.0 (M+H)⁺. ¹H NMR (500 MHz, CDCl₃): δ 7.85 (d; J = 6.9 Hz; 1 H); 7.34 (s; 5 H); 7.04 (d; J = 7.3 Hz; 1 H); 5.18 (s; 2 H); 4.02-4.11 (m; 4 H); 3.55-3.63 (m; 2 H); 1.95-2.02 (m; 2 H); 1.32 (t; J = 7.1 Hz; 6 H).

Step C – Synthesis of Compound 28c

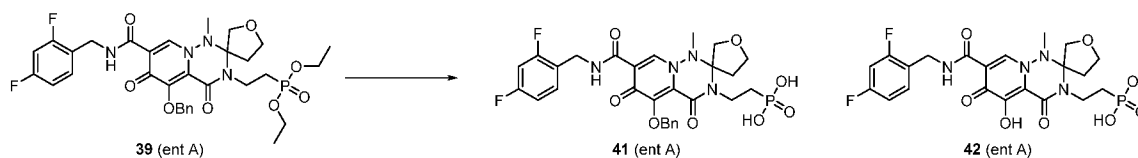
Compound **28b** (2.00 g, 4.72 mmol) in 1,4-dioxane (10.0 mL) was treated with dihydrofuran-3(2H)-one (1.097 ml, 14.17 mmol) and acetic acid (0.100 mL). The reaction mixture was allowed to stir at room temperature for 24 hours and then directly loaded onto a dry 120g silica gel column. Purification using column chromatography on silica gel (0 to 30% MeOH/ dichloromethane) provided the intermediate. Mass Calc'd for $C_{23}H_{30}N_3O_7P$: 491.2, Found: 492.0 (M+H)⁺. The intermediate was taken up in dimethylsulfoxide (8 mL) and treated, in the following order, with iodomethane (0.886 ml, 14.17 mmol), tetrabutylammonium hydroxide triacontahydrate (0.756 g, 0.945 mmol) and finely-powdered potassium hydroxide (0.795 g, 14.17 mmol). The reaction mixture was allowed to stir at room temperature for 14 hours, quenched with glacial acetic acid (2 mL) and water (1 mL) and directly purified using RP-HPLC to provide Compound **28c**. Mass Calc'd for $C_{24}H_{32}N_3O_7P$: 505.2, Found: 506.2 (M+H)⁺.

Step D – Synthesis of Intermediate Compound 37 and Intermediate Compound 38

Compound **28c** (1.65 g, 3.26 mmol) in *N,N*-dimethylformamide (10 mL) was treated at room temperature with *N*-bromosuccinimide (1.162 g, 6.53 mmol). The reaction mixture was allowed to stir at room temperature for 3 hours, diluted with acetonitrile (5 mL) and directly purified using RP-HPLC to provide the product as a racemate. Mass Calc'd for $C_{24}H_{31}BrN_3O_7P$: 583.1, 585.1 Found: 584.0, 586.0 (M+H)⁺. ¹H NMR (500 MHz, CDCl₃): δ {7.82 (s; 1 H); 7.78 (s; 1 H)}; 7.26 (s; 5 H); {5.62 (app t; J = 11.1 Hz; 2 H); 5.23 (d; J = 10.6 Hz; 1 H)}; 4.07-4.21 (m; 6 H); 3.83-3.94 (m; 3 H); {3.61 (d; J = 10.2 Hz; 1 H); 3.48 (d; J = 9.4 Hz; 1 H)}; {2.77 (s; 3 H); 2.68 (s; 3 H)}; 1.97-2.15 (m; 4 H); 1.38 (t; J = 7.1 Hz; 6 H). Chiral resolution using SFC (ChiralCel AD-H, 150×20mm, 15% ethanol (0.1% diethylamine) in SC-CO₂, 60mL/min, 100 bar, 220 nM) provided intermediate Compound **37** (ent A, earlier eluting enantiomer) and intermediate Compound **38** (ent B, later eluting enantiomer).

Example 29**Preparation of Compound 39 and Compound 40**

- 5 A mixture of Compound **37** (ent A, 451.7 mg, 0.773 mmol), 2,4-difluorobenzylamine (0.206 mL, 1.700 mmol), *N,N*-diisopropylethylamine (0.405 mL, 2.319 mmol) and Pd(PPh₃)₃ (447 mg, 0.386 mmol) in dimethylsulfoxide (8 mL) was sub-surface sparged with nitrogen gas for 10 min. The reaction mixture was allowed to stir under carbon monoxide (1 atm) at 90 °C for 8 hours, cooled to room temperature, treated with water (1 mL),
- 10 stirred for 10 minutes and then filtered. The filtrate was purified using RP-HPLC to provide Compound **39**, Mass Calc'd for C₃₂H₃₇F₂N₄O₈P: 674.2 Found: 675.2 (M+H)⁺, and Compound **40** Mass Calc'd for C₂₅H₃₁F₂N₄O₈P: 584.2 Found: 585.1 (M+H)⁺, ¹H NMR (500 MHz, DMSO): δ 10.24 (q; J = 6.1 Hz; 1 H); {8.33 (s; 1 H); 8.26 (s; 1 H);} 7.38-7.43 (m; 1 H); 7.21-7.25 (m; 1 H); 7.04-7.08 (m; 1 H); 4.54 (d; J = 6.0 Hz; 2 H); 4.36 (d; J = 11.0 Hz; 1 H); 3.96-4.08 (m; 5 H); 3.88 (br s; 1 H); 3.75-3.80 (m; 1 H); 3.64 (d; J = 13.8 Hz; 1 H); 3.45-3.50 (m; 1 H); {2.82 (s; 3 H); 2.72 (s; 3 H)}; 2.11-2.42 (m; 4 H); 1.26 (t; J = 7.1 Hz; 6 H).
- 15

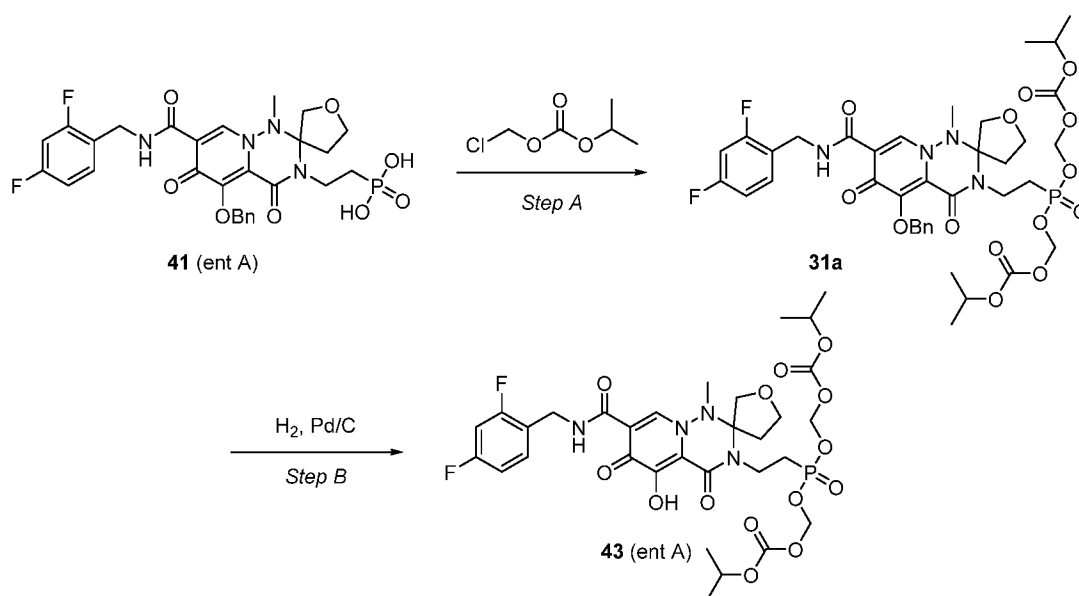
Example 30**Preparation of Compound 41 and Compound 42**

- 20 Compound **39** (ent A, 420 mg, 0.623 mmol) in acetonitrile (6 mL) was treated at room temperature with 2,6-lutidine (0.544 mL, 4.67 mmol) and TMS-Br (0.565 mL, 4.36 mmol). The reaction mixture was allowed to stir at 50 °C for 12 hours, cooled to 0°C, quenched with water (600 uL) and allowed to stir for 1 hour while warming to room temperature. The reaction
- 25 mixture was treated with glacial acetic acid (6 mL), diluted with 10% aq DMSO (6 mL) and directly purified using RP-HPLC to provide Compound **41**, Mass Calc'd for C₂₈H₂₉F₂N₄O₈P:

618.2 Found: 618.8 (M+H)⁺, and Compound **42**, Mass Calc'd for C₂₁H₂₃F₂N₄O₈P: 528.1 Found: 529.9 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ 10.25 (q; J = 6.4 Hz; 1 H); {8.32 (s; 1 H); 8.26 (s; 1 H)}; 7.41 (q; J = 7.9 Hz; 1 H); 7.23 (t; J = 10.0 Hz; 1 H); 7.06 (t; J = 8.7 Hz; 1 H); 4.53 (d; J = 5.8 Hz; 2 H); 4.32 (d; J = 10.9 Hz; 1 H); 3.97-4.04 (m; 2 H); 3.91 (br s; 1 H); 3.78 (dd; J = 8.3; 8.3 Hz; 1 H); 3.69-3.74 (m; 1 H); 3.66 (d; J = 10.9 Hz; 1 H); 3.43-3.46 (m; 1 H); {2.81 (s; 3 H); 2.72 (s; 3 H)}; 2.52-2.58 (m; 1 H); 2.31-2.40 (m; 1 H); 1.91-2.16 (m; 2 H).

Example 31

Preparation of Compound **43**



Step A – Synthesis of Compound **31a**

A mixture of Compound **41** (37 mg, 0.060 mmol), triethylamine (83 μl, 0.598 mmol) and tetra-*N*-butylammonium bromide (19.28 mg, 0.060 mmol) in *N*-methyl-2-pyrrolidinone (598 μl) was treated with chloromethylisopropylcarbonate (63.5 μl, 0.479 mmol). The reaction mixture was warmed to 50 °C, stirred for 20 hours, cooled to room temperature, diluted with aqueous dimethylsulfoxide and directly purified using RP-HPLC to provide Compound **31a**. Mass Calc'd for C₃₈H₄₅F₂N₄O₁₄P: 850.3 Found: 851.0 (M+H)⁺

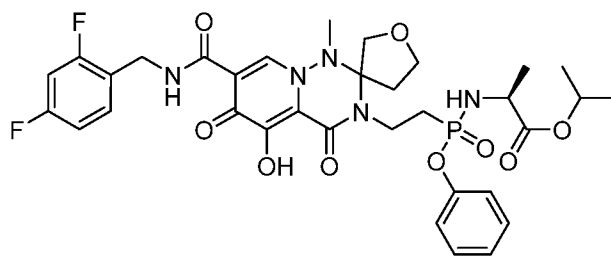
Step B – Synthesis of Compound **43**

A mixture of Compound **31a** (51 mg, 0.060 mmol) and 10% Pd/C (6.38 mg) in MeOH (2 mL) was sub-surface sparged with nitrogen gas for 2 minutes and then allowed to stir under hydrogen gas for 18 hours. The reaction mixture was filtered and the filtrate was directly purified using RP-HPLC to provide Compound **43**. Mass Calc'd for $C_{31}H_{39}F_2N_4O_{14}P$: 760.2

Found: 761.0 (M+H)⁺; ¹H NMR (500 MHz, DMSO): δ 10.23 (q; J = 5.9 Hz; 1 H); {8.32 (s; 1 H); 8.26 (s; 1 H);} 7.38-7.43 (m; 1 H); 7.23 (t; J = 10.3 Hz; 1 H); 7.05 (t; J = 8.2 Hz; 1 H); 5.59-5.64 (m; 4 H); 4.81-4.86 (m; 2 H); 4.53 (d; J = 6.0 Hz; 2 H); 4.34 (d; J = 11.0 Hz; 1 H); 3.89-4.02 (m; 2 H); 3.79 (dd; J = 8.4; 8.2 Hz; 1 H); 3.63 (d; J = 11.0 Hz; 1 H); 3.46-3.51 (m; 1 H); {2.81 (s; 3 H); 2.71 (s; 3 H)}; 2.32-2.43 (br m; 4 H); 1.25 (d; J = 6.3 Hz; 12 H).

Example 32

Preparation of Compound **44**



42

A mixture of Compound **42** (ent A, 78.1 mg, 0.148 mmol), L-Alanine isopropyl ester hydrochloride (44.6 mg, 0.266 mmol) and phenol (55.6 mg, 0.591 mmol) in a nitrogen-flushed reaction vial was heated to 60 °C and treated with 600 μ L of a stock solution containing 2,2'-dipyridyl disulfide (195 mg, 0.887 mmol), triphenylphosphine (233 mg, 0.887 mmol) and triethylamine (247 μ L, 1.774 mmol) in pyridine (1.2 mL). The reaction mixture was allowed to stir at 60 °C under nitrogen gas for 2 hours, cooled to room temperature and concentrated *in vacuo*. The residue obtained was taken up in dimethylsulfoxide (2 mL) and purified using RP-HPLC (C_{18} , acetonitrile, water, 0.05% NH_4CO_3H) to provide Compound **44** that is epimeric at phosphorous. Mass Calc'd for $C_{33}H_{38}F_2N_5O_9P$: 717.2 Found: 718.0 (M+H)⁺ ¹H NMR (500 MHz, DMSO): δ 10.33 (t; J = 5.7 Hz; 1 H); {8.26 (s; 1 H); 8.19 (s; 1 H)}; 7.33-7.43 (m; 3 H); 7.13-7.25 (m; 4 H); 7.06 (t; J = 8.7 Hz; 1 H); 5.59-5.78 (m; 1 H); 4.81-4.87 (m; 1 H); 4.53 (s; 2 H); 4.38 (d; J = 10.8 Hz; 1 H); 3.98-4.05 (m; 2 H); 3.86-3.92 (m; 1 H); 3.79 (q; J = 8.3 Hz; 1 H);

3.67-3.74 (m; 1 H); 3.55-3.62 (m; 1 H); 2.81 (s; 3 H); 2.72 (d; J = 8.7 Hz; 3 H); 2.57-2.64 (m; 1 H); 2.25-2.41 (m; 2 H); 2.08-2.14 (m; 1 H); 1.10-1.22 (m; 6 H).

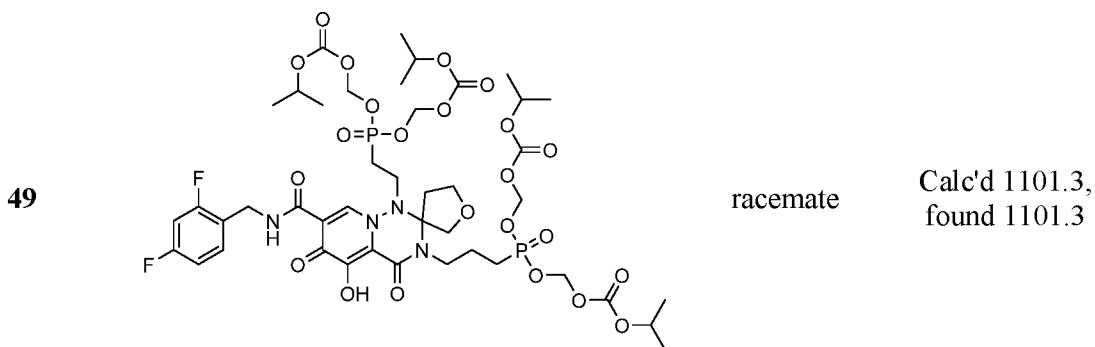
The following compounds were prepared from Compound **38** (ent B) using the methods described in Examples 29 – 32.

5

<u>Compound No.</u>	<u>Structure</u>	<u>Stereochemistry</u>	<u>Exact Mass [M+H]⁺</u>
45		enantiomer B	Calc'd 585.2, found 585.1
46		enantiomer B	Calc'd 529.1, found 528.7
47		enantiomer B	Calc'd 761.2, found 761.0
48		enantiomer B, epimers at phosphorous	Calc'd 718.2, found 718.0

The following compound was prepared using the methods described in the Examples 1 – 32 above with substitution of the appropriate reactants and reagents.

<u>Compound No.</u>	<u>Structure</u>	<u>Stereochemistry</u>	<u>Exact Mass [M+H]⁺</u>
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Example 33

Assessing Antiviral Potency Using An HIV-1 Infection Assay

HIV-1 replication was monitored using MT4-gag-GFP clone D3 (hereafter designate MT4-GFP), which are MT-4 cells modified to harbor a GFP reporter gene, the expression of which is dependent on the HIV-1 expressed proteins tat and rev. Productive infection of an MT4-GFP cell with HIV-1 results in GFP expression approximately 24h post-infection.

MT4-GFP cells were maintained at 37°C/5% CO₂/90% relative humidity in RPMI 1640 supplemented with 10% fetal bovine serum, 100 U/ml penicillin/streptomycin, and 400µg/ml G418 to maintain the reporter gene. For infections, MT4-GFP cells were placed in the same medium lacking G418 and infected overnight with H9IIIB or NL4-3 virus at an approximate multiplicity of infection of 0.01 in the same incubation conditions. Cells were then washed and resuspended in either RPMI 1640 containing no serum at 1.6 x 10⁵ cells/mL (serum free conditions), 10% normal human serum at 1.6 x 10⁵ cells/mL (10% NHS conditions) or in 100% normal human serum at 2 x 10⁵ cells/mL (100% NHS conditions). Compound plates were prepared by dispensing compounds taken up in DMSO into wells of 384 well poly D lysine-coated plates (0.2µl/well) using an ECHO acoustic dispenser. Each compound was tested in a 10 point serial 3-fold dilution (typical final concentrations: 4.2 µM – 0.21 nM). Controls included no inhibitor (DMSO only) and a combination of three antiviral agents (efavirenz, indinavir, and the integrase strand transfer inhibitor L-002254051 at final concentrations of 4µM each). Cells were added (50µL/well) to compound plates and the infected cells were maintained at 37°C/5% CO₂/90% relative humidity.

Infected cells were quantified at two time points, ~48h and ~72h post-infection, by counting the number of green cells in each well using an Acumen eX3 scanner. The increase in the number of green cells over ~24h period gives the reproductive ratio, R_0 , which is typically 5-15 and has been shown experimentally to be in logarithmic phase (data not shown). Inhibition of R_0 is calculated for each well, and IC_{50} value was determined using non-linear 4-parameter curve fitting.

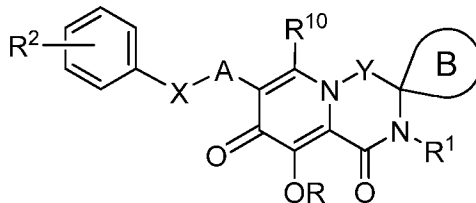
Compound	VIKING IP (nM) with 0% NHS	VIKING IP (nM) with 100% NHS
6	2.0	45.9
9	23.3	961.2
10	14.4	449.1
11	0.05	1.5
12	0.8	156.2
13	0.04	1.8
14	1.6	89.0
15	3.9	270.9
16	3.7	90.4
40	3.6	92.6
42	54.8	447.0
43	1.2	43.4
44	13.4	352.3
45	2.9	117.9
46	92.1	774.9
47	2.9	106.5
48	23.8	405.3
49	0.3	8.8

The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will
5 become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein, the entire disclosures of which are incorporated herein by reference.

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

A is -NHC(O)- or 5 or 6-membered monocyclic heteroaryl;

B is 3 to 8-membered heterocycloalkyl, which may be optionally substituted with

one or more groups, each independently selected from R^6 ;

X is $\text{C}_1\text{-C}_3$ alkylene;

Y is $\text{-CH}_2\text{-}$, $\text{-CH(R}^6\text{)-}$ or $\text{-N(R}^3\text{)-}$;

R is H or benzyl;

R^1 is selected from H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{-(C}_1\text{-C}_4\text{ alkylene)-O-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-(C}_1\text{-C}_4\text{ alkylene)-S-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-(C}_1\text{-C}_4\text{ alkylene)-SO}_2\text{-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-(C}_1\text{-C}_4\text{ alkylene)-N-(C}_1\text{-C}_6\text{ alkyl)}_2$, $\text{-(C}_1\text{-C}_6\text{ alkylene)}_m\text{-Z-(C}_1\text{-C}_3\text{ alkylene)}_m\text{-R}^{11}$, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, phenyl, 3 to 8-membered monocyclic heterocycloalkyl and 5 or 6-membered monocyclic heteroaryl;

R^2 represents up to 3 optional substituents, each independently selected from halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{-O-(C}_1\text{-C}_6\text{ alkyl)}$ and $\text{C}_1\text{-C}_6$ haloalkyl;

R^3 is selected from H, $\text{C}_1\text{-C}_6$ alkyl, $\text{-SO}_2\text{R}^4$, -C(O)R^4 , $\text{-(C}_1\text{-C}_6\text{ alkylene)}_p\text{-C(O)N(R}^5\text{)}_2$, $\text{-(C}_2\text{-C}_4\text{ alkylene)-O-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-(C}_2\text{-C}_4\text{ alkylene)-S-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-(C}_2\text{-C}_4\text{ alkylene)-SO}_2\text{-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-(C}_2\text{-C}_4\text{ alkylene)-N-(C}_1\text{-C}_6\text{ alkyl)}_2$, $\text{-(C}_1\text{-C}_6\text{ alkylene)}_m\text{-Z-(C}_1\text{-C}_3\text{ alkylene)}_m\text{-R}^{11}$, $\text{C}_3\text{-C}_7$ cycloalkyl, phenyl, 4 to 8-membered monocyclic heterocycloalkyl or 6-membered monocyclic heteroaryl and 8 to 10-membered bicyclic heteroaryl;

each occurrence of R^4 is independently selected from H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, phenyl, 3 to 8-membered monocyclic heterocycloalkyl or 6-membered monocyclic heteroaryl and 8 to 10-membered bicyclic heteroaryl, wherein said $\text{C}_3\text{-C}_7$

cycloalkyl group, said phenyl group, said 3 to 8-membered monocyclic heteroaryl group, said 6-membered monocyclic heteroaryl group and said 8 to 10-membered bicyclic heteroaryl group may be optionally substituted with one or more groups, each independently selected from R⁶;

each occurrence of R⁵ is independently selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkylene)-N(R⁷)₂, C₁-C₆ haloalkyl, -C(O)O(C₁-C₆ alkyl), -(C₁-C₆ alkylene)_m-Z-(C₁-C₃ alkylene)_m-R¹¹, -(C₁-C₆ alkylene)_p-R⁸ and -(C₁-C₆ alkylene)-O-(C₁-C₆ alkyl);

each occurrence of R⁶ is independently selected from halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -(C₁-C₆ alkylene)_m-Z-(C₁-C₃ alkylene)_m-R¹¹, -N(R²⁰)₂, 3 to 8-membered monocyclic heterocycloalkyl, 6 to 10-membered bicyclic heterocycloalkyl, -O-(C₁-C₆ alkyl), -O-(C₆-C₁₀ aryl), -O-(C₁-C₆ alkylene)-O-(C₁-C₆ alkyl), -O-(C₁-C₆ haloalkyl), -O-(C₁-C₆ alkylene)-O-(C₁-C₆ alkylene)-O-(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -NHS(O)₂(C₁-C₆ alkyl), -S(O)₂NH-(C₁-C₆ alkyl), -OC(O)-(C₁-C₆ haloalkyl), -(C₁-C₆ alkylene)_p-C(O)O-(C₁-C₆ alkyl), -(C₁-C₆ alkylene)_p-C(O)-(C₁-C₆ alkyl), -(C₁-C₆ alkylene)_p-C(O)N(R⁷)₂, C₁-C₆ hydroxyalkyl, -P(O)(OR⁹)₂, and -CN;

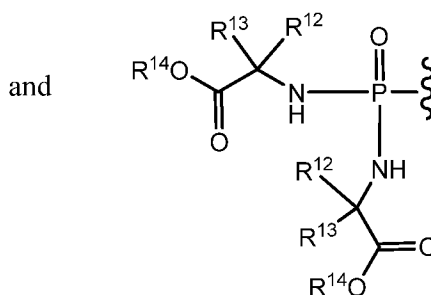
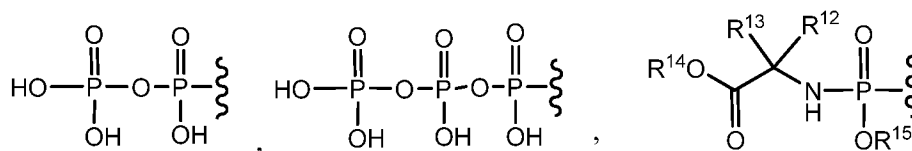
each occurrence of R⁷ is independently selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₁-C₆ haloalkyl, -C(O)O(C₁-C₆ alkyl), -(C₁-C₆ alkylene)_m-Z-(C₁-C₃ alkylene)_m-R¹¹, -(C₁-C₆ alkylene)_p-R⁸ and -(C₁-C₆ alkylene)-O-(C₁-C₆ alkyl);

each occurrence of R⁸ is independently selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, 5 or 6-membered monocyclic heteroaryl and 3 to 8-membered monocyclic heterocycloalkyl;

each occurrence of R⁹ is independently selected from H, C₁-C₆ alkyl and -(C₁-C₆ alkylene)_m-Z-(C₁-C₃ alkylene)_m-R¹¹;

R¹⁰ is selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and -(C₁-C₄ alkylene)-O-(C₁-C₆ alkyl);

each occurrence of R¹¹ is independently selected from -P(O)(-OR¹⁸)₂,



each occurrence of R^{12} is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, phenyl or benzyl, wherein said C_1 - C_6 alkyl may be optionally substituted with a group selected from halo, $-\text{OR}^{16}$, $-\text{SR}^{16}$, guanidino, $-\text{N}(\text{R}^{16})_2$, $-\text{C}(\text{O})\text{OR}^{16}$, $-\text{C}(\text{O})\text{N}(\text{R}^{16})_2$, $-\text{NHC}(\text{O})\text{R}^{16}$, 5- or 6-membered monocyclic heteroaryl and 9- or 10-membered bicyclic heteroaryl, and wherein said phenyl group and said benzyl group may be optionally substituted with up to 2 groups, each independently selected from C_1 - C_6 alkyl, halo and $-\text{OR}^{16}$;

each occurrence of R^{13} is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, phenyl or benzyl, wherein said C_1 - C_6 alkyl may be optionally substituted with a group selected from halo, $-\text{OR}^{16}$, $-\text{SR}^{16}$, guanidino, $-\text{N}(\text{R}^{16})_2$, $-\text{C}(\text{O})\text{OR}^{16}$, $-\text{C}(\text{O})\text{N}(\text{R}^{16})_2$, $-\text{NHC}(\text{O})\text{R}^{16}$, 5- or 6-membered monocyclic heteroaryl and 9- or 10-membered bicyclic heteroaryl, and wherein said phenyl group and said benzyl group may be optionally substituted with up to 2 groups, each independently selected from C_1 - C_6 alkyl, halo and $-\text{OR}^{16}$;

each occurrence of R^{14} is independently selected from H, C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, $-(\text{C}_1-\text{C}_3 \text{ alkylene})_m-(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$, $-(\text{C}_1-\text{C}_3 \text{ alkylene})_m-(\text{C}_6-\text{C}_{10} \text{ aryl})$ or $-(\text{C}_1-\text{C}_3 \text{ alkylene})_m$ -adamantyl, wherein said C_1 - C_{20} alkyl group, said C_2 - C_{20} alkenyl group, said C_6 - C_{10} aryl group and said adamantyl group may be optionally substituted with up to three groups, each independently selected from halo, $-\text{OR}^{16}$, $-\text{C}(\text{O})\text{OR}^{16}$, CN, NO_2 , C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_3 - C_7 cycloalkyl, C_6 - C_{10} aryl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, $-\text{N}(\text{R}^{16})_2$, $-\text{C}(\text{O})\text{N}(\text{R}^{16})_2$, $-\text{SR}^{16}$, $-\text{S}(\text{O})\text{R}^{16}$, $-\text{S}(\text{O})_2\text{R}^{16}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{16})_2$, $-\text{NHC}(\text{O})\text{R}^{16}$, $-\text{NHC}(\text{O})\text{OR}^{16}$ and $-\text{NHC}(\text{O})\text{N}(\text{R}^{16})_2$;

R^{15} is H, C_6 - C_{10} aryl, 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl, wherein said C_6 - C_{10} aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group may be optionally substituted with R^{17} ;

each occurrence of R^{16} is independently H, C_1 - C_{10} alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, $-(C_1-C_3 \text{ alkylene})_m-(C_3-C_7 \text{ cycloalkyl})$, $-(C_1-C_3 \text{ alkylene})_m-(C_6-C_{10} \text{ aryl})$, $-(C_1-C_3 \text{ alkylene})_m-(4 \text{ to } 7\text{-membered heterocycloalkyl})$, $-(C_1-C_3 \text{ alkylene})_m-(5\text{- or } 6\text{-membered monocyclic heteroaryl})$ or $-(C_1-C_3 \text{ alkylene})_m-(9\text{- or } 10\text{-membered bicyclic heteroaryl})$, wherein said C_3 - C_7 cycloalkyl group, said C_6 - C_{10} aryl group, said 4 to 7-membered heterocycloalkyl group, said 5- or 6-membered monocyclic heteroaryl group or said 9- or 10-membered bicyclic heteroaryl group may be optionally substituted with R^{17} ;

R^{17} represents from one to five substituent groups, each independently selected from C_1 - C_6 alkyl, halo, $-OR^{19}$, $-SR^{19}$, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, $-O-(C_1-C_6 \text{ haloalkyl})$, $-CN$, $-NO_2$, $-N(R^{19})_2$, $-C(O)OR^{19}$, $-C(O)N(R^{19})_2$ and $-NHC(O)R^{19}$;

each occurrence of R^{18} is independently selected from H, C_1 - C_6 alkyl, C_6 - C_{10} aryl, $-(C_1-C_6 \text{ alkylene})-O-(C_1-C_{20} \text{ alkyl})$, $-(C_1-C_6 \text{ alkylene})-O-C(O)-R^{16}$, and $-(C_1-C_6 \text{ alkylene})-O-C(O)-O-R^{16}$;

each occurrence of R^{19} is independently H, C_1 - C_{10} alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, $-(C_1-C_3 \text{ alkylene})_m-(C_3-C_7 \text{ cycloalkyl})$, $-(C_1-C_3 \text{ alkylene})_m-(C_6-C_{10} \text{ aryl})$, $-(C_1-C_3 \text{ alkylene})_m-(4 \text{ to } 7\text{-membered heterocycloalkyl})$, $-(C_1-C_3 \text{ alkylene})_m-(5\text{- or } 6\text{-membered monocyclic heteroaryl})$ or $-(C_1-C_3 \text{ alkylene})_m-(9\text{- or } 10\text{-membered bicyclic heteroaryl})$;

each occurrence of R^{20} is independently selected from H, C_1 - C_6 alkyl and $-(C_1-C_6 \text{ alkylene})_m-Z-(C_1-C_3 \text{ alkylene})_m-R^{11}$;

each occurrence of Z is independently selected from a bond, $-O-$ or $-N(R^9)-$;

each occurrence of m is independently 0 or 1;

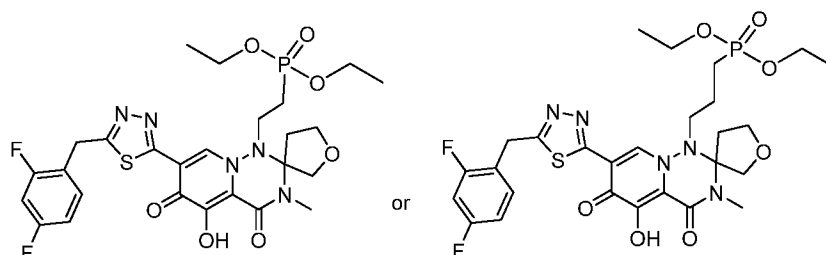
n is 1 or 2; and

each occurrence of p is independently 0 or 1,

such that at least one occurrence of R^{11} must be present in the compound of

formula (I),

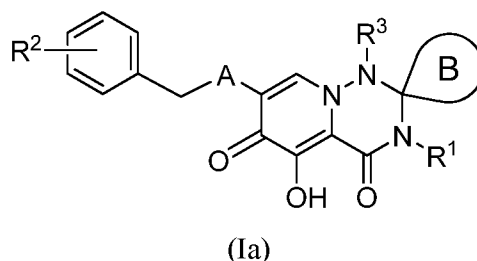
and provided that the compound of formula (I) is other than:



2. The compound of claim 1, wherein X is $-CH_2-$.

3. The compound of claim 1 or 2, wherein R^{10} is H.
4. The compound of claim 1 having the formula (Ia):

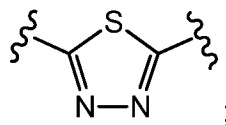
5



or a pharmaceutically acceptable salt or prodrug thereof,
wherein:

10

A is: -NHC(O)- or:



B is a 5 or 6-membered heterocycloalkyl, optionally substituted with R^6 ;

R^1 is C_1 - C_6 alkyl or $-(C_1$ - C_6 alkylene)- R^{11} ;

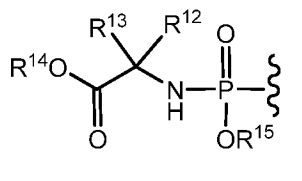
R^2 represents up to 2 optional substituents, each independently selected from

15 halo; and

R^3 is C_1 - C_6 alkyl or $-(C_1$ - C_6 alkylene)- R^{11} ;

R^6 is $-(C_1$ - C_6 alkylene) $_m$ - R^{11} ;

each occurrence of R^{11} is independently selected from $-P(O)(-OR^{18})_2$ and:



20

R^{12} is independently selected from H and C_1 - C_6 alkyl;

R^{13} is independently selected from H and C_1 - C_6 alkyl;

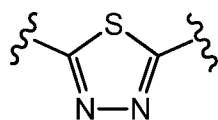
R^{14} is C_1 - C_6 alkyl;

R^{15} is C_6 - C_{10} aryl;

each occurrence of R^{18} is independently selected from H and C_1-C_6 alkyl; and
 m is 0 or 1,
 such that at least one occurrence of R^{11} must be present in the compound of formula (I).

5 5. The compound of any of claims 1 to 4, wherein A is $-NHC(O)-$.

6. The compound of any of claims 1 to 4, wherein A is:



10 7. The compound of any of claims 1 to 6, wherein B is 5-membered monocyclic heterocycloalkyl.

8. The compound of claim 7, wherein B is tetrahydrofuranyl.

15 9. The compound of claims 1 to 8, wherein B is substituted with
 $-(C_1-C_6 \text{ alkylene})_m-R^{11}$.

10. The compound of any of claims 1 to 9, wherein R^1 is selected from methyl, ethyl, and n-propyl.

20

11. The compound of any of claims 1 to 9, wherein either R^1 or R^3 is $-(C_1-C_6 \text{ alkylene})-R^{11}$.

12. The compound of any of claims 1 to 11, wherein R^2 represents two fluoro groups,
 25 in the ortho and para positions.

13. A compound being any of the compounds numbered 3-26, 29-36 and 39-49 in the above specification, or a pharmaceutically acceptable salt or prodrug thereof.

14. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

5 15. A method for the inhibition of HIV integrase in a subject in need thereof which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt or prodrug thereof.

10 16. A method for the treatment of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof, which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt or prodrug thereof.

15 17. A compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt or prodrug thereof, for use in therapy.

20 18. A compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt or prodrug thereof, for use in the preparation of a medicament for the inhibition of HIV integrase, for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof.

25 19. The pharmaceutical composition of claim 14, further comprising one or more additional therapeutic agents selected from raltegravir, lamivudine, abacavir, ritonavir, dolutegravir, arunavir, atazanavir, emtricitabine, tenofovir, elvitegravir, rilpivirine and lopinavir.

30 20. The method of claim 16, further comprising administering to the subject one or more additional therapeutic agents selected from raltegravir, abacavir, lamivudine, ritonavir and lopinavir, wherein the amounts administered of the compound of any one of claims 1 to 13 and the one or more additional therapeutic agents, are together effective to treat infection by HIV or to treat, prevent or delay the onset or progression of AIDS.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/061455

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/53; A61K 31/495; A61K 31/4985; C07D 295/00; C07D 401/02; C07D 403/02 (2017.01)

CPC - A61K 31/53; A61K 31/495; A61K 31/4985; C07D 295/00; C07D 401/02; C07D 403/02 (2017.01)

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)

See Search History document

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)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/089847 A1 (MERCK SHARP & DOHME CORP) 25 June 2015 (25.06.2015) entire document	1-3
A	US 2012/0108564 A1 (MIYAZAKI et al) 03 May 2012 (03.05.2012) entire document	1-3
A	US 7,858,788 B2 (YOSHIDA et al) 28 December 2010 (28.12.2010) entire document	1-3

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

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

"L" 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

07 February 2017

Date of mailing of the international search report

09 MAR 2017

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/061455

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.: 5-12, 14-20
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:

See Extra Sheet

Claims 1-3 have been analyzed subject to the restriction that the claims read on a compound having the formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein A is -NHC(O); B is a 3-membered heterocycloalkyl, which is unsubstituted; X is C1 alkylene; Y is -CH2-; R is H; R1 is -(C1 alkylene)m-Z-(C1 alkylene)m-R11; R2 is absent; R10 is H; m is 0; Z is a bond; R11 is -P(O)(-OR18)2; and R18 is H.

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.:
1-3

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/061455

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-4 and 13 are drawn to compounds having formula (I) and species thereof.

The first invention of Group I+ is restricted based on the proviso that at least one occurrence of R11 must be present in the compound of formula (I), and that the compound of formula (I) is other than the two compounds shown in claim 1 of the instant invention, and is restricted to a compound having the formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein A is -NHC(O); B is a 3-membered heterocycloalkyl, which is unsubstituted; X is C1 alkylene; Y is -CH2-; R is H; R1 is -(C1 alkylene)m-Z-(C1 alkylene)m-R11; R2 is absent; R10 is H; m is 0; Z is a bond; R11 is -P(O)(-OR18)2; and R18 is H. It is believed that claims 1-3 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound having the formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein A is a 5-membered monocyclic heteroaryl, which is furanyl, attached in the 2 and 5 positions; B is a 3-membered heterocycloalkyl, which is unsubstituted; X is C2 alkylene; Y is -CH(R6)-, wherein R6 is halo; R is benzyl; R1 is -(C1 alkylene)m-Z-(C1 alkylene)m-R11; R2 is absent; R10 is H; m is 0; Z is O; R11 is -P(O)(-OR18)2; and R18 is H. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for compound variables A, B, X, Y, R, R1, R2, R10, and R11.

The Groups I+ share the technical features of a core structure of formula (I). However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2015/089847 A1 to Merck Sharp and Dohme Corp. teaches a core structure of formula (I), wherein B is a 5-membered heterocycloalkyl; X is C1 alkylene; Y is -CH2-; R is H; R1 is C1 alkyl; R2 represents two substituents, which are halo; and R10 is H (Pg. 60, Table, Compound 42, See shown structure).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.