

TITLE OF THE INVENTION

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

This application claims the benefit of U.S. Provisional Application No. 60/874,629, filed December 13, 2006, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention is directed to certain substituted indazoles, benzotriazoles, and related bicyclic compounds and their pharmaceutically acceptable salts and their use for the inhibition of HIV reverse transcriptase, the prophylaxis of HIV infection and HIV replication, the treatment of HIV infection and HIV replication, the prophylaxis of AIDS, the treatment of AIDS, and the delay in the onset and/or progression of AIDS.

BACKGROUND OF THE INVENTION

The retrovirus designated human immunodeficiency virus (HIV), particularly the strains known as HIV type-1 (HIV-1) and type-2 (HIV-2) viruses, have been etiologically linked to the immunosuppressive disease known as acquired immunodeficiency syndrome (AIDS). HIV seropositive individuals are initially asymptomatic but typically develop AIDS related complex (ARC) followed by AIDS. Affected individuals exhibit severe immunosuppression which makes them highly susceptible to debilitating and ultimately fatal opportunistic infections. Replication of HIV by a host cell requires integration of the viral genome into the host cell's DNA. Since HIV is a retrovirus, the HIV replication cycle requires transcription of the viral RNA genome into DNA via an enzyme known as reverse transcriptase (RT).

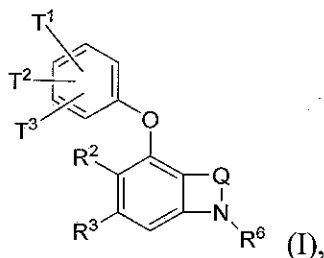
Reverse transcriptase has three known enzymatic functions: The enzyme acts as an RNA-dependent DNA polymerase, as a ribonuclease, and as a DNA-dependent DNA polymerase. In its role as an RNA-dependent DNA polymerase, RT transcribes a single-stranded DNA copy of the viral RNA. As a ribonuclease, RT destroys the original viral RNA and frees the DNA just produced from the original RNA. And as a DNA-dependent DNA polymerase, RT makes a second, complementary DNA strand using the first DNA strand as a template. The two strands form double-stranded DNA, which is integrated into the host cell's genome by the integrase enzyme.

It is known that compounds that inhibit enzymatic functions of HIV RT will inhibit HIV replication in infected cells. These compounds are useful in the treatment of HIV infection in humans. Among the compounds approved for use in treating HIV infection and AIDS are the RT inhibitors 3'-azido- 3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC), d4T, 3TC, nevirapine, delavirdine, efavirenz and abacavir.

While each of the foregoing drugs is effective in treating HIV infection and AIDS, there remains a need to develop additional HIV antiviral drugs including additional RT inhibitors. A particular problem is the development of mutant HIV strains that are resistant to the known inhibitors. The use of RT inhibitors to treat AIDS often leads to viruses that are less sensitive to the inhibitors. This resistance is typically the result of mutations that occur in the reverse transcriptase segment of the pol gene. The continued use of antiviral compounds to prevent HIV infection will inevitably result in the emergence of new resistant strains of HIV. Accordingly, there is a particular need for new RT inhibitors that are effective against mutant HIV strains.

SUMMARY OF THE INVENTION

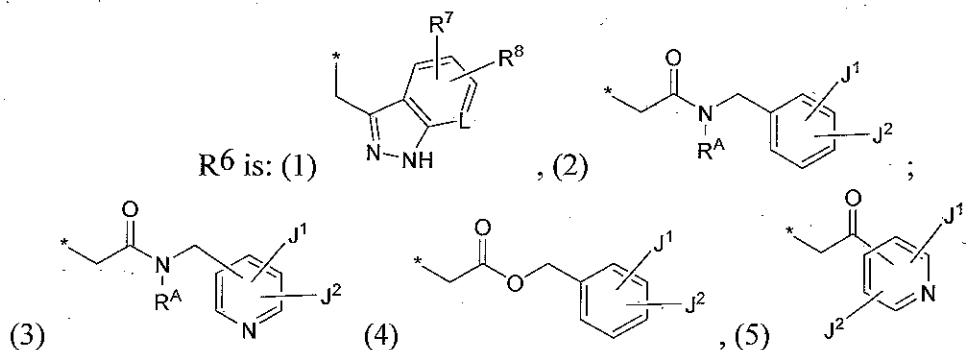
The disclosure is directed to certain indazoles, benzotriazoles, and related bicyclic compounds and their use in the inhibition of HIV reverse transcriptase, the prophylaxis of infection by HIV, the treatment of infection by HIV, and the prophylaxis, treatment, and delay in the onset or progression of AIDS and/or ARC. More particularly, the disclosure, in one aspect, includes compounds of Formula I and pharmaceutically acceptable salts thereof:

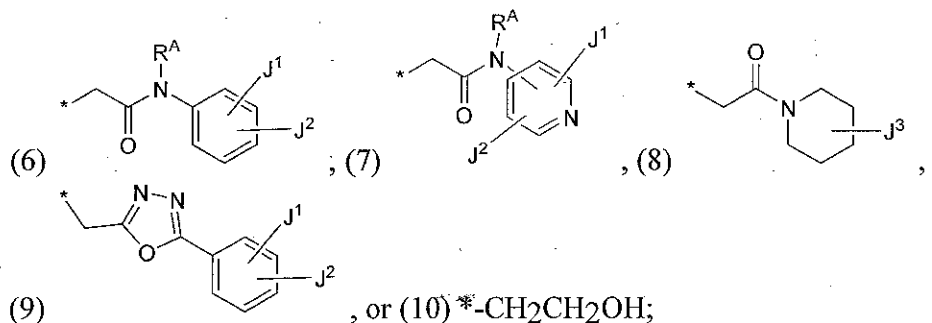


or a pharmaceutically acceptable salt thereof, wherein:

T¹ and T² and T³ are each independently H, C₁₋₄ alkyl, halogen, CN, CH=CH-CN, C(O)RA, or (CH₂)₁₋₂N(RA)RB;

R² and R³ are each independently selected from the group consisting of (1) H, (2) halogen, (3) C(O)N(RA)RB, (4) C₁₋₄ alkyl, (5) CF₃, (6) O-C₁₋₄ alkyl, and (7) OCF₃;





J1 and J2 are each independently H, halogen, CN, NO2, C1-4 alkyl, CF3, OH, O-C1-4 alkyl, OCF3, C(O)N(RA)RB, C(O)RA, CO2RA, SO2RA, or SO2N(RA)RB;

J3 is H, halogen, CN, C1-4 alkyl, OH, oxo, O-C1-4 alkyl, CF3, OCF3, C(O)NH2, C(O)N(H)CH3, C(O)N(RA)RB, C(O)RA, CO2RA, SO2RA, or SO2N(RA)RB;

L is N or N oxide;

Q is: (1) -CH(R4)-, (2) -C(R4)=C(R5)-, (3) -CH(R4)-CH(R5)-, (4) -C(R4)=C(R5)-CH2-, (5) -CH(R4)-CH(R5)-CH2-, (6) -C(R4)=C(R5)-CH=CH-, (7) -CH(R4)-CH(R5)-CH=CH-, (8) -C(R4)=C(R5)-CH2CH2-, (9) -CH(R4)-CH(R5)-CH2CH2-, (10) -C(R4)=N-, (11) -N=C(R4)-, or (12) -N=N-;

wherein the left-most atom in Q is the atom directly attached to the fused benzo;

R4 and R5 are each independently selected from the group consisting of: (1) H, (2) C1-4 alkyl, (3) O-C1-4 alkyl, (4) CF3, (5) OCF3, and (6) halogen;

R7 and R8 are each independently selected from the group consisting of: (1) H, (2) OH, (3) halogen, (4) CN, (5) NO2, (6) C1-4 alkyl, (7) O-C1-4 alkyl, (8) O(CH2)2-3N(RA)RB, (9) O(CH2)1-3C(O)RA, (10) CF3, (11) OCF3, (12) O(CH2)1-2CF3, (12) N(RC)RD, (13) N(RA)-(CH2)2-3-N(RC)RD, and (14) C(O)N(RA)RB;

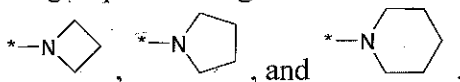
each RA is independently H or C1-4 alkyl;

each RB is independently H or C1-4 alkyl;

each RC is independently H or C1-4 alkyl;

each RD is independently H or C1-4 alkyl; and

alternatively and independently each pair of RC and RD together with the N atom to which they are both attached form a saturated monocyclic ring selected from the group consisting of:



(1) H_1

(1) $-\text{CH}(\text{R}^4)-$,

(9) $-\text{CH}(\text{R}^4)-\text{CH}(\text{R}^5)-\text{CH}_2\text{CH}_2-$,

(10) $-\text{C}(\text{R}^4)=\text{N}-$,

(11) $-\text{N}=\text{CH}-$, or

(12) $-\text{N}=\text{N}-$;

wherein the left-most atom in Q is the atom directly attached to the fused benzo;

R^4 and R^5 are each independently selected from the group consisting of:

- (1) H,
- (2) C_{1-4} alkyl,
- (3) $\text{O}-\text{C}_{1-4}$ alkyl,
- (4) CF_3 ,
- (5) OCF_3 , and
- (6) halogen;

R^7 and R^8 are each independently selected from the group consisting of:

- (1) H,
- (2) OH,
- (3) halogen,
- (4) CN,
- (5) NO_2 ,
- (6) C_{1-4} alkyl,
- (7) $\text{O}-\text{C}_{1-4}$ alkyl,
- (8) $\text{O}(\text{CH}_2)_{2-3}\text{N}(\text{R}^{\text{A}})\text{R}^{\text{B}}$,
- (9) $\text{O}(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{R}^{\text{A}}$,
- (10) CF_3 ,
- (11) OCF_3 ,
- (12) $\text{O}(\text{CH}_2)_{1-2}\text{CF}_3$,
- (12) $\text{N}(\text{R}^{\text{C}})\text{R}^{\text{D}}$,
- (13) $\text{N}(\text{R}^{\text{A}})-(\text{CH}_2)_{2-3}-\text{N}(\text{R}^{\text{C}})\text{R}^{\text{D}}$, and
- (14) $\text{C}(\text{O})\text{N}(\text{R}^{\text{A}})\text{R}^{\text{B}}$;

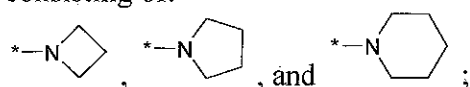
each R^{A} is independently H or C_{1-4} alkyl;

each R^{B} is independently H or C_{1-4} alkyl;

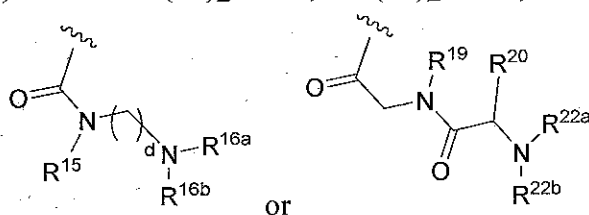
each R^C is independently H or C₁₋₄ alkyl;

each R^D is independently H or C₁₋₄ alkyl;

alternatively and independently each pair of R^C and R^D together with the N atom to which they are both attached form a saturated monocyclic ring selected from the group consisting of:



R^{9P} is $PO(OH)O^- \cdot M^+$; $PO(O^-)_2 \cdot 2M^+$; $PO(O^-)_2 \cdot M^{2+}$; or an acid salt of:



M^+ is a pharmaceutically acceptable monovalent counterion;

M^{2+} is a pharmaceutically acceptable divalent counterion;

R^{15} is H or C₁₋₄ alkyl

R^{16a} and R^{16b} are each independently H or C₁₋₄ alkyl;

R^{19} is H or C₁₋₄ alkyl;

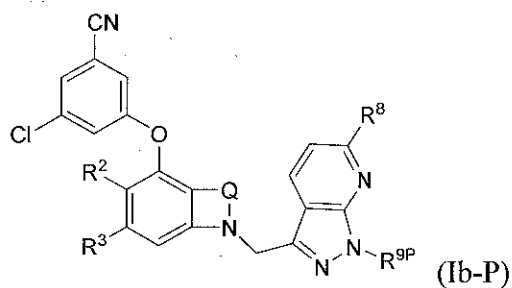
R^{20} is H or C₁₋₄ alkyl;

R^{22a} and R^{22b} are each independently H or C₁₋₄ alkyl; and

d is an integer equal to 2, 3 or 4;

and provided that (A) when Q is $-N=C(R^4)-$, then R^4 is H.

In a third aspect, there is provided a compound of Formula Ib-P:



wherein:

Q is:

- (1) -CH=CH-,
- (2) -CH=CH-CH₂-,
- (3) -CH=CH-CH=CH-,
- (4) -CH₂CH₂-CH=CH-,
- (5) -CH=CH-CH₂CH₂-,
- (6) -C(R⁴)=N-,
- (7) -N=CH-, or
- (8) -N=N-;

R² and R³ are each independently selected from the group consisting of H, Cl, Br, F and C₁₋₄ alkyl;

R⁴ is H, C₁₋₄ alkyl, Cl, Br, or F; and

R⁸ is H, OH, Cl, Br, F, CH₃, OCH₃, O(CH₂)₂₋₃NH₂, CF₃, OCF₃, OCH₂CF₃, NH₂, N(H)CH₃, N(CH₃)₂, C(O)NH₂, C(O)N(H)CH₃, or C(O)N(CH₃)₂.

In a fourth aspect, there is provided a pharmaceutical composition comprising (A) an effective amount of (i) a compound as defined above, or a pharmaceutically acceptable salt thereof, or (ii) a compound as defined above and (B) a pharmaceutically acceptable carrier.

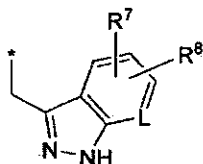
In a fifth aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt thereof, or a compound as defined above, in the manufacture of a medicament for the treatment or prophylaxis of HIV-1 infection, or the treatment or prophylaxis or delay in the onset or progression of AIDS due to HIV-1.

Other embodiments, aspects and features of the disclosure are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of Formula I above, and pharmaceutically acceptable salts thereof, are HIV reverse transcriptase inhibitors. The compounds are useful for inhibiting HIV reverse transcriptase and for inhibiting HIV replication *in vitro* and *in vivo*. More particularly, the compounds of Formula I inhibit the polymerase function of HIV-1 reverse transcriptase. Based upon the testing of representative compounds of the invention in the assays set forth in Example 6 below, it is known that compounds of Formula I inhibit the RNA-dependent DNA polymerase activity of HIV-1 reverse transcriptase. Representative compounds of the present invention also exhibit activity against drug resistant forms of HIV (e.g., mutant strains of HIV-1 in which reverse transcriptase has a mutation at lysine 103 $\rightarrow$ asparagine (K103N) and/or tyrosine 181 $\rightarrow$ cysteine (Y181C)), and thus can exhibit decreased cross-resistance against currently approved antiviral therapies.

A first embodiment of the present invention (alternatively referred to herein as "Embodiment E1") is a compound of Formula I (alternatively and more simply referred to as "Compound I") as originally defined (i.e., as defined in the Summary of the Invention), or a pharmaceutically acceptable salt thereof; and provided that (A) when Q is $-N=C(R^4)-$ and R^4 is



other than H, then R^6 is not

A second embodiment of the present invention (Embodiment E2) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein T^1 and T^2 and T^3 are each independently H, C_{1-4} alkyl, halogen, or CN; and all other variables are as originally defined or as defined in Embodiment E1.

A third embodiment of the present invention (Embodiment E3) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein T^1 and T^2 and T^3 are each independently H, CH_3 , Cl, or CN, with the proviso that at least one of T^1 and T^2 and T^3 is Cl and at least one of T^1 and T^2 and T^3 is CN; and all other variables are as originally defined or as defined in Embodiment E1.

A fourth embodiment of the present invention (Embodiment E4) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each independently selected from the group consisting of H, Cl, Br, F and C_{1-4} alkyl; and all other variables are as originally defined or as defined in any of the foregoing embodiments.

A fifth embodiment of the present invention (Embodiment E5) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^2 is Br or Cl; R^3 is H; and all other variables are as originally defined or as defined in any of the foregoing embodiments.

A sixth embodiment of the present invention (Embodiment E6) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R² is Cl; R³ is H; and all other variables are as originally defined or as defined in any of the foregoing embodiments.

5 A seventh embodiment of the present invention (Embodiment E7) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein J¹ and J² are each independently H, Cl, Br, F, CN, NO₂, C₁₋₃ alkyl, CF₃, OH, O-C₁₋₃ alkyl, OCF₃, C(O)NH₂, C(O)N(H)CH₃, C(O)N(CH₃)₂, C(O)H, C(O)CH₃, CO₂H, CO₂CH₃, SO₂CH₃, or SO₂NH₂; J³ is H, Cl, Br, F, CN, C₁₋₃ alkyl, OH, oxo, O-C₁₋₃ alkyl, CF₃, OCF₃, C(O)NH₂, C(O)N(H)CH₃, C(O)N(CH₃)₂, C(O)H, C(O)CH₃, CO₂H, CO₂CH₃, SO₂CH₃, or SO₂NH₂; and all other
10 variables are as originally defined or as defined in any of the foregoing embodiments.

An eighth embodiment of the present invention (Embodiment E8) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein Q is -CH₂CH₂CH₂-, -CH=N-, -C(Cl)=N-, -N=CH-, or -N=N-; and all other variables are as originally defined or as defined in any of the foregoing embodiments.

15 A ninth embodiment of the present invention (Embodiment E9) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁴ and R⁵ are each independently selected from the group consisting of H, C₁₋₄ alkyl, Cl, Br and F; and all other variables are as originally defined or as defined in any one of the foregoing embodiments.

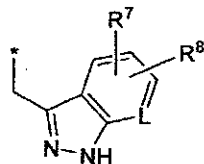
A tenth embodiment of the present invention (Embodiment E10) is a compound
20 of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁴ and R⁵ are each independently selected from the group consisting of H, CH₃, OCH₃, CF₃, OCF₃, Cl, Br and F; and all other variables are as originally defined or as defined in any one of the foregoing embodiments.

An eleventh embodiment of the present invention (Embodiment E11) is a
25 compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁴ and R⁵ are both H; and all other variables are as originally defined or as defined in any one of the foregoing embodiments.

A twelfth embodiment of the present invention (Embodiment E12) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁷ is H; R⁸ is H, OH, Cl, Br, F, CH₃, OCH₃, O(CH₂)₂₋₃NH₂, CF₃, OCF₃, OCH₂CF₃, NH₂, N(H)CH₃, N(CH₃)₂,
30 C(O)NH₂, C(O)N(H)CH₃, or C(O)N(CH₃)₂; and all other variables are as originally defined or as defined in any one of the foregoing embodiments.

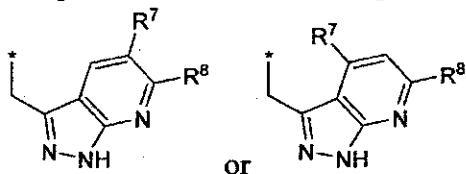
A thirteenth embodiment of the present invention (Embodiment E13) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁷ is H; R⁸ is H or NH₂; and all other variables are as originally defined or as defined in any one of the foregoing
35 embodiments.

A fourteenth embodiment of the present invention (Embodiment E14) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁶ is



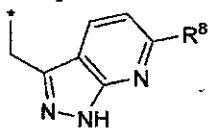
; and all other variables are as originally defined or as defined in any one of the foregoing embodiments.

A fifteenth embodiment of the present invention (Embodiment E15) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁶ is



; and all other variables are as originally defined or as defined in any one of the foregoing embodiments.

A sixteenth embodiment of the present invention (Embodiment E16) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁶ is



; and all other variables are as originally defined or as defined in any one of the foregoing embodiments.

To the extent any of the preceding or subsequent embodiments refer back to and are incorporated into Embodiment E1, the proviso set forth therein applies. It is understood, however, that the definitions of variables in the provisos set forth in Embodiment E1 can be customized to reflect the definitions of variables in the embodiments being incorporated therein. For example, the proviso set forth in Embodiment E1 can be customized to reflect the definition of R⁶ in Embodiments E14 to E16. As a particular example, when Embodiment E14 is incorporated into Embodiment E1, the proviso can be adjusted to read as follows – and provided that (A) when Q is -N=C(R⁴)-, then R⁴ is H.

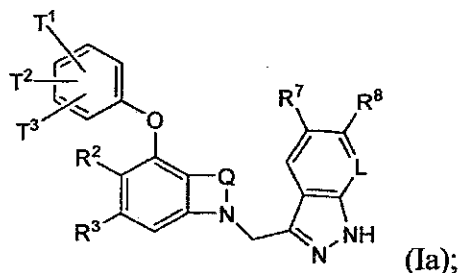
A seventeenth embodiment of the present invention (Embodiment E17) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^A and R^B are each independently H or CH₃; and all other variables are as originally defined or as defined in any of the preceding embodiments.

An eighteenth embodiment of the present invention (Embodiment E18) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^C and R^D are each independently H or C₁₋₄ alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A nineteenth embodiment of the present invention (Embodiment E19) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^C and R^D are

each independently H or CH₃; and all other variables are as originally defined or as defined in any of the preceding embodiments.

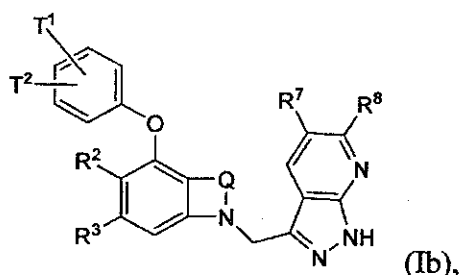
A first class of compounds of the present invention (alternatively referred to herein as Class C1) includes compounds, and pharmaceutically acceptable salts thereof, selected from compounds of Formula Ia:



wherein all variables therein are as originally defined. Sub-classes of Class C1 include the compounds of Formula Ia and their pharmaceutically acceptable salts wherein the variables are as respectively defined in each of the preceding embodiments.

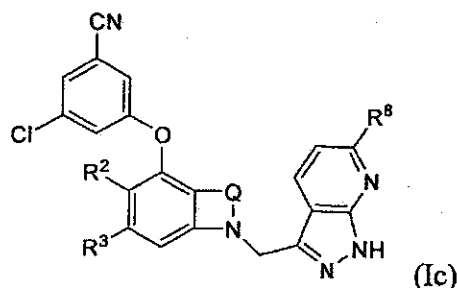
A second class of compounds of the present invention (Class C2) includes compounds of Formula Ia and pharmaceutically acceptable salts thereof, as defined in Class C1; and provided that when Q is -N=C(R⁴)-, then R⁴ is H.

A third class of compounds of the present invention (Class C3) includes compounds of Formula Ib:



and pharmaceutically acceptable salts thereof, wherein T¹ and T² are each independently H, C₁₋₄ alkyl, halogen, CN, or CH=CH-CN; and all other variables therein are as originally defined. Sub-classes of Class C3 include the compounds of Formula Ib and their pharmaceutically acceptable salts wherein the other variables are as respectively defined in each of the preceding embodiments.

A fourth class of compounds of the present invention (Class C4) includes compounds of Formula Ic:



and pharmaceutically acceptable salts thereof, wherein:

Q is: (1) $-\text{CH}=\text{CH}-$, (2) $-\text{CH}=\text{CH}-\text{CH}_2-$, (3) $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$,
(4) $-\text{CH}_2\text{CH}_2-\text{CH}=\text{CH}-$, (5) $-\text{CH}=\text{CH}-\text{CH}_2\text{CH}_2-$, (6) $-\text{C}(\text{R}^4)=\text{N}-$, (7) $-\text{N}=\text{C}(\text{R}^4)-$, or (8) $-\text{N}=\text{N}-$;

R² and R³ are each independently selected from the group consisting of H, Cl, Br, F and C₁₋₄ alkyl;

R⁴ is H, C₁₋₄ alkyl, Cl, Br, or F; and

R⁸ is H, OH, Cl, Br, F, CH₃, OCH₃, O(CH₂)₂₋₃NH₂, CF₃, OCF₃, OCH₂CF₃, NH₂, N(H)CH₃, N(CH₃)₂, C(O)NH₂, C(O)N(H)CH₃, or C(O)N(CH₃)₂.

A sub-class of Class C5 (i.e., Sub-class SC5-1) includes compounds of Formula Ic and pharmaceutically acceptable salts thereof as defined in Class C5; and provided that when Q is $-\text{N}=\text{C}(\text{R}^4)-$, then R⁴ is H.

Another sub-class of Class C5 (Sub-class SC5-2) includes compounds of Formula Ic and pharmaceutically acceptable salts thereof; wherein Q is $-\text{CH}=\text{N}-$, $-\text{C}(\text{Cl})=\text{N}-$, $-\text{N}=\text{CH}-$, or $-\text{N}=\text{N}-$; R² is Br or Cl; R³ is H; and R⁸ is H or NH₂.

A sixth class of the present invention (Class C6) includes compounds selected from the group consisting of the compounds set forth in Examples 1 to 3 below and their pharmaceutically acceptable salts.

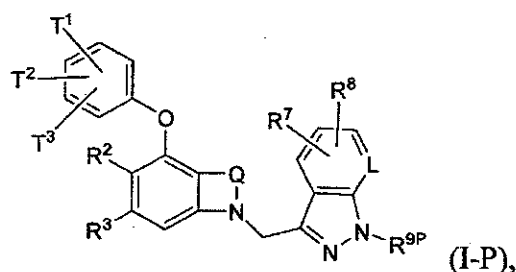
Another embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, as originally defined or as defined in any of the foregoing embodiments, classes or sub-classes, wherein the compound or its salt is in a substantially pure form. As used herein "substantially pure" means suitably at least about 60 wt.%, typically at least about 70 wt.%, preferably at least about 80 wt.%, more preferably at least about 90 wt.% (e.g., from about 90 wt.% to about 99 wt.%), even more preferably at least about 95 wt.% (e.g., from about 95 wt.% to about 99 wt.%, or from about 98 wt.% to 100 wt.%), and most preferably at least about 99 wt.% (e.g., 100 wt.%) of a product containing a compound of Formula I or its salt (e.g., the product isolated from a reaction mixture affording the compound or salt) consists of the compound or salt. The level of purity of the compounds and salts can be determined using a standard method of analysis such as thin layer chromatography, gel electrophoresis, high performance liquid chromatography, and/or mass spectrometry. If more than one method of analysis is employed and the methods provide experimentally significant

differences in the level of purity determined, then the method providing the highest purity level governs. A compound or salt of 100% purity is one which is free of detectable impurities as determined by a standard method of analysis. With respect to a compound of the invention which has one or more asymmetric centers and can occur as mixtures of stereoisomers, a substantially pure compound can be either a substantially pure mixture of the stereoisomers or a substantially pure individual diastereomer or enantiomer.

The present invention also includes prodrugs of the compounds of Formula I. The term "prodrug" refers to a derivative of a compound of Formula I, or a pharmaceutically acceptable salt thereof, which is converted *in vivo* into Compound I. Prodrugs of compounds of Formula I can exhibit enhanced solubility, absorption, and/or lipophilicity compared to the compounds per se, thereby resulting in increased bioavailability and efficacy. The *in vivo* conversion of the prodrug can be the result of an enzyme-catalyzed chemical reaction, a metabolic chemical reaction, and/or a spontaneous chemical reaction (e.g., solvolysis). When the compound contains, for example, a hydroxy group, the prodrug can be a derivative of the hydroxy group such as an ester (-OC(O)R), a carbonate ester (-OC(O)OR), a phosphate ester (-O-P(=O)(OH)₂), or an ether (-OR). Other examples include the following: When the compound of Formula I contains a carboxylic acid group, the prodrug can be an ester or an amide, and when the compound of Formula I contains a primary amino group or another suitable nitrogen that can be derivatized, the prodrug can be an amide, carbamate, urea, imine, or a Mannich base. One or more functional groups in Compound I can be derivatized to provide a prodrug thereof. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, edited by H. Bundgaard, Elsevier, 1985; J. J. Hale et al., *J. Med. Chem.* 2000, vol. 43, pp.1234-1241; C. S. Larsen and J. Ostergaard, "Design and application of prodrugs" in: Textbook of Drug Design and Discovery, 3rd edition, edited by C. S. Larsen, 2002, pp. 410-458; and Beaumont et al., *Current Drug Metabolism* 2003, vol. 4, pp. 461-458; the disclosures of each of which are incorporated herein by reference in their entireties.

Another embodiment of the present invention (alternatively referred to as "Embodiment PD1") is a prodrug of a compound of Formula I as originally defined above.

Another embodiment of the present invention (Embodiment PD2) is a compound of Formula I-P:



wherein:

T¹ and T² and T³ are each independently H, C₁₋₄ alkyl, halogen, CN, CH=CH-CN, C(O)RA, or (CH₂)₁₋₂N(RA)RB;

R² and R³ are each independently selected from the group consisting of: (1) H, (2) halogen, (3) C(O)N(RA)RB, (4) C₁₋₄ alkyl, (5) CF₃, (6) O-C₁₋₄ alkyl, and (7) OCF₃;

L is N or N oxide;

Q is: (1) -CH(R⁴)-, (2) -C(R⁴)=C(R⁵)-, (3) -CH(R⁴)-CH(R⁵)-, (4) -C(R⁴)=C(R⁵)-CH₂-, (5) -CH(R⁴)-CH(R⁵)-CH₂-, (6) -C(R⁴)=C(R⁵)-CH=CH-, (7) -CH(R⁴)-CH(R⁵)-CH=CH-, (8) -C(R⁴)=C(R⁵)-CH₂CH₂-, (9) -CH(R⁴)-CH(R⁵)-CH₂CH₂-, (10) -C(R⁴)=N-, (11) -N=CH-, or (12) -N=N-; wherein the left-most atom in Q is the atom directly attached to the fused benzo;

R⁴ and R⁵ are each independently selected from the group consisting of: (1) H, (2) C₁₋₄ alkyl, (3) O-C₁₋₄ alkyl, (4) CF₃, (5) OCF₃, and (6) halogen;

R⁷ and R⁸ are each independently selected from the group consisting of: (1) H, (2) OH, (3) halogen, (4) CN, (5) NO₂, (6) C₁₋₄ alkyl, (7) O-C₁₋₄ alkyl, (8) O(CH₂)₂₋₃N(RA)RB, (9) O(CH₂)₁₋₃C(O)RA, (10) CF₃, (11) OCF₃, (12) O(CH₂)₁₋₂CF₃, (12) N(RC)RD, (13) N(RA)-(CH₂)₂₋₃-N(RC)RD, and (14) C(O)N(RA)RB;

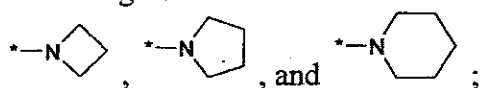
each RA is independently H or C₁₋₄ alkyl;

each RB is independently H or C₁₋₄ alkyl;

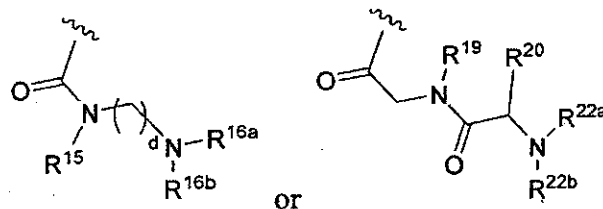
each RC is independently H or C₁₋₄ alkyl;

each RD is independently H or C₁₋₄ alkyl;

alternatively and independently each pair of RC and RD together with the N atom to which they are both attached form a saturated monocyclic ring selected from the group consisting of:



R^{9P} is PO(OH)O⁻ · M⁺; PO(O⁻)₂ · 2M⁺; PO(O⁻)₂ · M²⁺; or an acid salt of:



M⁺ is a pharmaceutically acceptable monovalent counterion;

M²⁺ is a pharmaceutically acceptable divalent counterion;

R¹⁵ is H or C₁₋₄ alkyl

R^{16a} and R^{16b} are each independently H or C₁₋₄ alkyl;

R¹⁹ is H or C₁₋₄ alkyl;

R²⁰ is H or C₁₋₄ alkyl;

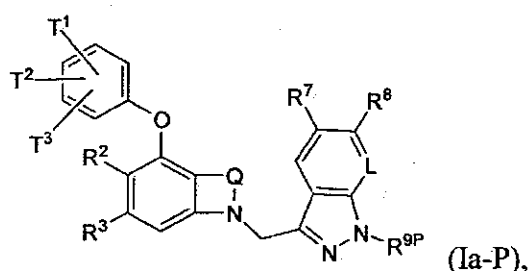
R22a and R22b are each independently H or C₁₋₄ alkyl; and

d is an integer equal to 2, 3 or 4.

Another embodiment of the present invention (Embodiment PD3) is a compound of Formula I-P wherein all of the variables are as defined in Embodiment PD2; and provided that

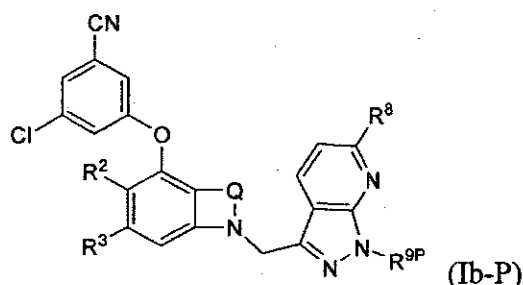
5 (A) when Q is -N=C(R⁴)-, then R⁴ is H.

Another embodiment of the present invention (Embodiment PD4) is a compound of Formula Ia-P:



wherein all of the variables are as defined in Embodiment PD2 or Embodiment PD3.

10 Another embodiment of the present invention (Embodiment PD5) is a compound of Formula Ib-P:



wherein:

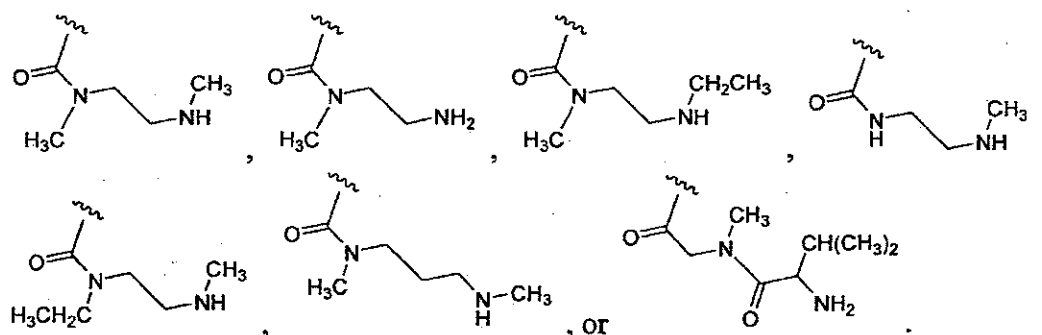
15 Q is: (1) -CH=CH-, (2) -CH=CH-CH₂-, (3) -CH=CH-CH=CH-,
(4) -CH₂CH₂-CH=CH-, (5) -CH=CH-CH₂CH₂-, (6) -C(R⁴)=N-, (7) -N=CH-, or (8) -N=N-;

R² and R³ are each independently selected from the group consisting of H, Cl, Br, F and C₁₋₄ alkyl;

R⁴ is H, C₁₋₄ alkyl, Cl, Br, or F; and

20 R⁸ is H, OH, Cl, Br, F, CH₃, OCH₃, O(CH₂)₂₋₃NH₂, CF₃, OCF₃, OCH₂CF₃,
NH₂, N(H)CH₃, N(CH₃)₂, C(O)NH₂, C(O)N(H)CH₃, or C(O)N(CH₃)₂.

Another embodiment of the present invention (Embodiment PD6) is a compound as defined in any one of Embodiments PD2, PD3, PD4, or PD5, wherein R^{9P} is an acid salt of:



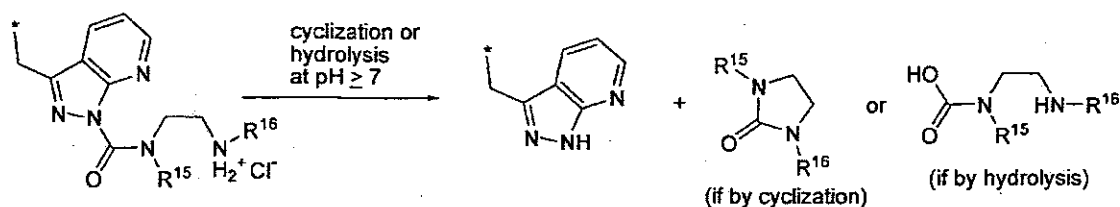
A class of the preceding embodiment (Class C1-PD6) includes compounds as defined in Embodiment PD5, wherein the acid salt in the definition of R^{9P} is a hydrochloride salt.

Another embodiment of the present invention (Embodiment PD7) is a compound selected from the group consisting of the compounds of Example 4 and Example 5.

Pharmaceutically acceptable monovalent counterions (M^+) suitable for use in the prodrugs of the invention described in Embodiments PD2 to PD5 include NH_4^+ , alkali metal cations (e.g., Na^+ or K^+), and cations from alkylamines, hydroxyalkylamines (e.g., tris(hydroxymethyl)methylamine), choline, lysine, arginine, histidine, and N-methyl-D-glucamine. Suitable divalent counterions (M^{2+}) include the cations of alkaline earth metals such as Mg^{2+} and Ca^{2+} . Additional pharmaceutically acceptable salts of basic drugs (pharmaceutically acceptable monovalent and divalent counterions) are described in P. L. Gould, *Int. J. Pharm.* 1986, vol. 33 pp. 201-217 and S. M. Berge et al., *J. Pharm. Sci.*, 1977, vol. 66, pp. 1-19.

Acid salts suitable for use in the prodrugs of the invention described in Embodiments PD2 to PD7 include the salts of organic and inorganic acids. Suitable salts of inorganic acids include the salts of hydrochloric acid, sulfuric acid, alkali metal bisulfates (e.g., KHSO_4), and the like. Suitable salts of organic acids include the salts of carboxylic acids and sulfonic acids, such as alkylcarboxylic acids (e.g., acetic acid, propanoic acid, butyric acid, etc.), fluoroalkylcarboxylic acids (e.g., trifluoroacetic acid), arylcarboxylic acids (benzoic acid), alkylsulfonic acids (e.g., ethylsulfonic acid), fluoroalkylsulfonic acids (e.g., trifluoromethylsulfonic acid), and arylsulfonic acids (e.g., benzenesulfonic acid or toluenesulfonic acid).

While not wishing to be bound by any particular theory, it is believed that the compounds set forth in Embodiments PD2 to PD7 act as prodrugs, wherein the compound is relatively stable at low pH (e.g., pH = 1 to 3) but will convert by hydrolysis or cyclization to its free base at physiological pH (e.g., a pH of greater than about 7), thereby releasing the active substance *in vivo*. This reaction is exemplified as follows for a hydrochloride salt:



Other embodiments of the present invention include the following:

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

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula I as defined above, or a prodrug or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising an effective amount of an anti-HIV agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the anti-HIV agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV reverse transcriptase inhibitors other than a compound of Formula I, HIV integrase inhibitors, HIV fusion inhibitors, and HIV entry inhibitors.

(e) A combination which is (i) a compound of Formula I as defined above, or a prodrug or pharmaceutically acceptable salt thereof, and (ii) an anti-HIV agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents; wherein Compound I and the anti-HIV agent are each employed in an amount that renders the combination effective for inhibition of HIV reverse transcriptase, for treatment or prophylaxis of infection by HIV, or for treatment, prophylaxis of, or delay in the onset or progression of AIDS.

(f) The combination of (e), wherein the anti-HIV agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV reverse transcriptase inhibitors other than a compound of Formula I, HIV integrase inhibitors, HIV fusion inhibitors, and HIV entry inhibitors.

(g) A method for the inhibition of HIV reverse transcriptase in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or a prodrug or pharmaceutically acceptable salt thereof.

(h) A method of the prophylaxis or treatment of infection by HIV (e.g., HIV-1) in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or a prodrug or pharmaceutically acceptable salt thereof.

(i) The method of (h), wherein the compound of Formula I is administered in combination with an effective amount of at least one other HIV antiviral selected from the group

consisting of HIV protease inhibitors, HIV integrase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, nucleoside HIV reverse transcriptase inhibitors, HIV fusion inhibitors, and HIV entry inhibitors.

(j) A method for the prophylaxis, treatment or delay in the onset or
5 progression of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or a prodrug or pharmaceutically acceptable salt thereof.

(k) The method of (j), wherein the compound is administered in combination
10 with an effective amount of at least one other HIV antiviral other than a compound of Formula I, selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, nucleoside HIV reverse transcriptase inhibitors, HIV fusion inhibitors, and HIV entry inhibitors.

(l) A method for the inhibition of HIV reverse transcriptase in a subject in
15 need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(m) A method for the prophylaxis or treatment of infection by HIV (e.g., HIV-
1) in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(n) A method for the prophylaxis, treatment, or delay in the onset or
20 progression of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

The present invention also includes a compound of Formula I, or a prodrug or
pharmaceutically acceptable salt thereof, (i) for use in, (ii) for use as a medicament for, or (iii) for
use in the preparation of a medicament for: (a) therapy (e.g., of the human body), (b) medicine,
25 (c) inhibition of HIV reverse transcriptase, (d) treatment or prophylaxis of infection by HIV, or
(e) treatment, prophylaxis of, or delay in the onset or progression of AIDS. In these uses, the
compounds of the present invention can optionally be employed in combination with one or more
anti-HIV agents selected from HIV antiviral agents, anti-infective agents, and
immunomodulators.

30 Additional embodiments of the invention include the pharmaceutical
compositions, combinations and methods set forth in (a)-(n) above and the uses (i)(a)-(e) through
(iii)(a)-(e) set forth in the preceding paragraph, wherein the compound of the present invention
employed therein is a compound of one of the embodiments, classes or sub-classes described
above. In all of these embodiments etc., the compound may optionally be used in the form of a
35 prodrug or pharmaceutically acceptable salt.

Additional embodiments of the present invention include each of the
pharmaceutical compositions, combinations, methods and uses set forth in the preceding

paragraphs, wherein the compound of the present invention or its salt employed therein is substantially pure. With respect to a pharmaceutical composition comprising a compound of Formula I or its prodrug or salt and a pharmaceutically acceptable carrier and optionally one or more excipients, it is understood that the term "substantially pure" is in reference to a compound of Formula I or its prodrug or salt per se.

Still additional embodiments of the present invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(n) above and the uses (i)(a)-(e) through (iii)(a)-(e) set forth above, wherein the HIV of interest is HIV-1. Thus, for example, in the pharmaceutical composition (d), the compound of Formula I is employed in an amount effective against HIV-1 and the anti-HIV agent is an HIV-1 antiviral selected from the group consisting of HIV-1 protease inhibitors, HIV-1 reverse transcriptase inhibitors other than a compound of Formula I, HIV-1 integrase inhibitors, and HIV-1 fusion inhibitors.

As used herein, the term "alkyl" refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "C₁₋₆ alkyl" (or "C₁-C₆ alkyl") refers to any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and iso- propyl, ethyl and methyl. As another example, "C₁₋₄ alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "C(O)" refers to carbonyl. The terms "S(O)₂" and "SO₂" each refer to sulfonyl.

An asterisk ("*") as the end of an open bond in a chemical group denotes the point of attachment of the group to the rest of the compound.

The term "aryl" refers to (i) phenyl, (ii) 9- or 10-membered bicyclic, fused carbocyclic ring systems in which at least one ring is aromatic, and (iii) 11- to 14-membered tricyclic, fused carbocyclic ring systems in which at least one ring is aromatic. Suitable aryls include, for example, phenyl, naphthyl, tetrahydronaphthyl (tetralinyl), indenyl, anthracenyl, and fluorenyl. A class of aryls of interest with respect to the invention is phenyl and naphthyl. An aryl of particular interest is phenyl.

Unless expressly stated to the contrary in a particular context, any of the various cyclic rings and ring systems described herein may be attached to the rest of the compound at any ring atom (i.e., any carbon atom or any heteroatom) provided that a stable compound results.

When any variable (e.g., RA or RB) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the present invention, its definition on each occurrence is independent of its definition at every other

occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring provided such ring substitution is chemically allowed and results in a stable compound.

As a result of the selection of substituents and substituent patterns, certain compounds of the present invention can exhibit tautomerism such as keto-enol tautomerism. All tautomeric forms of these compounds, whether present individually or in mixtures, are within the scope of the present invention. For example, in compounds of the present invention where a hydroxy (-OH) substituent is permitted on a heteroaromatic ring and keto-enol tautomerism is possible, it is understood that the substituent might in fact be present, in whole or in part, in the keto form.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject). The compounds of the present invention are limited to stable compounds embraced by Formula I.

As a result of the selection of substituents and substituent patterns, certain compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether individually or in mixtures, are within the scope of the present invention.

The methods of the present invention involve the use of compounds of the present invention in the inhibition of HIV reverse transcriptase (e.g., wild type HIV-1 and/or mutant strains thereof), the prophylaxis or treatment of infection by human immunodeficiency virus (HIV) and the prophylaxis, treatment or delay in the onset or progression of consequent pathological conditions such as AIDS. Prophylaxis of AIDS, treating AIDS, delaying the onset or progression of AIDS, or treating or prophylaxis of infection by HIV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the present invention can be employed to treat 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 patient blood during surgery. As another example, the present invention can also be employed to prevent transmission of HIV from a pregnant female infected with HIV to her unborn child or from an HIV-infected female who is nursing (i.e., breast feeding) a child to the child via administration of an effective amount of Compound I or a pharmaceutically acceptable salt thereof.

The compounds can be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. When compounds employed in the present invention carry an acidic moiety (e.g., -COOH or a phenolic group), suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of Formula I mean providing the compound or a prodrug of the compound to the individual in need of treatment or prophylaxis. When a compound or a prodrug thereof is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating or prophylaxis of HIV infection or AIDS), "administration" and its variants are each understood to include provision of the compound or prodrug and other agents at the same time or at different times. When the agents of a combination are administered at the same time, they can be administered together in a single composition or they can be administered separately.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients, as well as any product which results, directly or indirectly, from combining the specified ingredients.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition being prevented. The term also includes herein the amount of active compound sufficient to inhibit HIV reverse transcriptase (wild type and/or mutant

strains thereof) and thereby elicit the response being sought (i.e., an "inhibition effective amount"). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free form (i.e., the non-salt form) of the compound.

5 In the method of the present invention (i.e., inhibiting HIV reverse transcriptase, treating or prophylaxis of HIV infection or treating, prophylaxis of, or delaying the onset or progression of AIDS), the compounds of Formula I, optionally in the form of a salt/hydrate or a prodrug, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in
10 conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal
15 injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water,
20 glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other
25 ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions for use in the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th
30 edition, edited by A. R. Gennaro, Mack Publishing Co., 1990 and in Remington - The Science and Practice of Pharmacy, 21st edition, Lippincott Williams & Wilkins, 2005.

The compounds of Formula I can 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 preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single
35 dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can 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 patient to be treated. The specific dose level and frequency of dosage for any particular patient 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.

In one embodiment, a compound of Formula I such as the compound of Example 1 can be administered to adult humans orally in the form of a tablet or capsule containing the compound in an amount in a range of from about 40 mg to about 900 mg, wherein the tablet or capsule is administered once per day or twice per day. In another embodiment, a compound of Formula I such as the compound of Example 1 can be administered to adult humans orally in the form of a tablet or capsule containing the compound in an amount in a range of from about 40 mg to about 320 mg, wherein the tablet or capsule is administered once per day or twice per day.

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, anti-infectives, or vaccines useful for treating HIV infection or AIDS, such as those disclosed in Table 1 of WO 01/38332 or in the Table in WO 02/30930. 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
capravirine	nnRTI
darunavir, Prezista®	PI
ddC, zalcitabine, dideoxycytidine, Hivid®	nRTI
ddI, didanosine, dideoxyinosine, Videx®	nRTI
ddI (enteric coated), Videx EC®	nRTI

delavirdine, DLV, Rescriptor®	nnRTI
efavirenz, EFV, Sustiva®, Stocrin®	nnRTI
efavirenz + emtricitabine + tenofovir DF, Atripla®	nnRTI + nRTI
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
PPL-100 (also known as PL-462) (Ambrilia)	PI
raltegravir, MK-0518, Isentress™	InI
ritonavir, Norvir®	PI
saquinavir, Invirase®, Fortovase®	PI
stavudine, d4T, didehydrodeoxythymidine, Zerit®	nRTI
tenofovir DF (DF = disoproxil fumarate), TDF, Viread®	nRTI
tipranavir, Aptivus®	PI

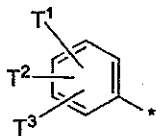
EI = entry inhibitor; FI = fusion inhibitor; InI = integrase inhibitor; PI = protease inhibitor; nRTI = nucleoside reverse transcriptase inhibitor; nnRTI = non-nucleoside reverse transcriptase inhibitor. Some of the drugs listed in the table are used in a salt form; e.g., abacavir sulfate, indinavir sulfate, atazanavir sulfate, nelfinavir mesylate.

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 and/or listed in the above-referenced Tables in WO 01/38332 and WO 02/30930, 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 subsequent editions thereof. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

Abbreviations include the following: ACN = acetonitrile; AIDS = acquired immunodeficiency syndrome; BOC or Boc = t-butyloxycarbonyl; (BOC)₂O (or BOC₂O) = di-t-butyl carbonate; Bn-p-OMe = p-methoxybenzyl; BrdUTP = bromodeoxyuridine triphosphate; n-

Bu = n-butyl; t-Bu = t-butyl; CHAPS = 3-[(3-cholamidopropyl)-dimethylammonio]-1-propane-sulfonate; DCE = 1,2-dichloroethane; DCM = dichloromethane; DMAP = 4-dimethylaminopyridine; DMF = dimethylformamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (or N,N'-dimethylpropyleneurea); DMSO = dimethylsulfoxide; dNTP = deoxynucleoside triphosphate; DPPA = diphenylphosphoryl azide; EDC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; EGTA = ethylene glycol bis(2-aminoethyl ether)-N,N,N',N'-tetraacetic acid; Et = ethyl; EtOAc = ethyl acetate; EtOH = ethanol; HOAT = 1-hydroxy-7-azabenzotriazole; HPLC = high-performance liquid chromatography; HRMS = high resolution mass spectroscopy; IPA = isopropyl alcohol; LAH = lithium aluminum hydride; LC = liquid chromatography; LDA = lithium diisopropylamide; LRMS = low resolution mass spectroscopy; MCPBA = meta-chloroperbenzoic acid; MeOH = methanol; NBS = N-bromosuccinimide; NMP = N-methyl pyrrolidinone; NMR = nuclear magnetic resonance; Ph = phenyl; PMB = para-methoxybenzyl; TEA = triethylamine; TFA = trifluoroacetic acid; THF = tetrahydrofuran; Tos = tosyl.

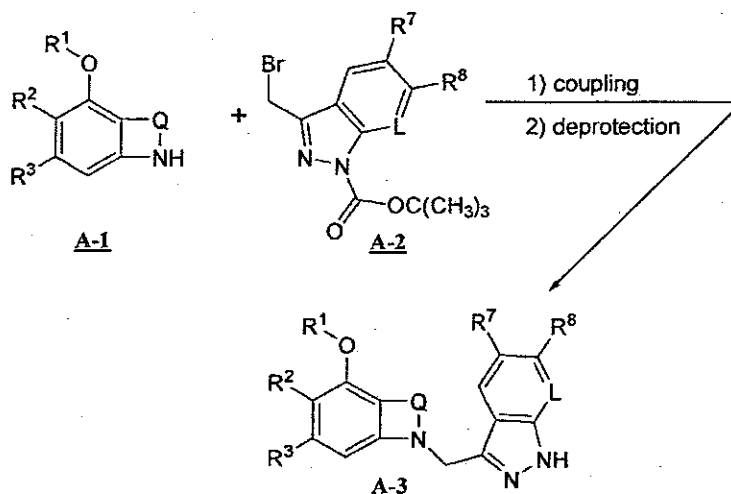
The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily obtainable starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as



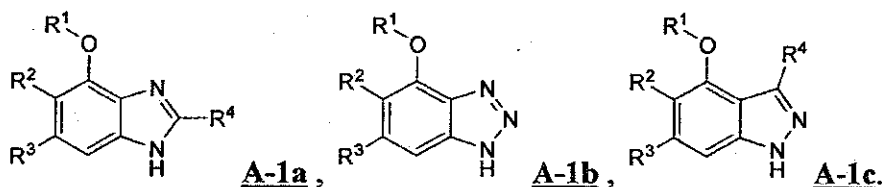
defined above. In the schemes, R¹ is

Scheme A depicts a general method suitable for the preparation of compounds of the invention, wherein the fused bicyclic A-1 is coupled with 1-Boc-1H-pyrazolo[3,4-b]pyridin-3-yl methylene bromide A-2 in the presence of a base (e.g., an alkali metal carbonate such as CsCO₃) and then the Boc protective group is removed by treating the coupled product with a suitable acid (e.g., TFA) to afford A-3.

Scheme A

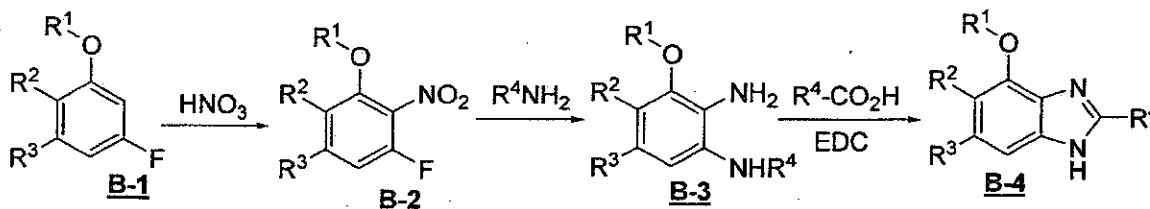


Representative examples of starting substrate **A-1** include the following:



5

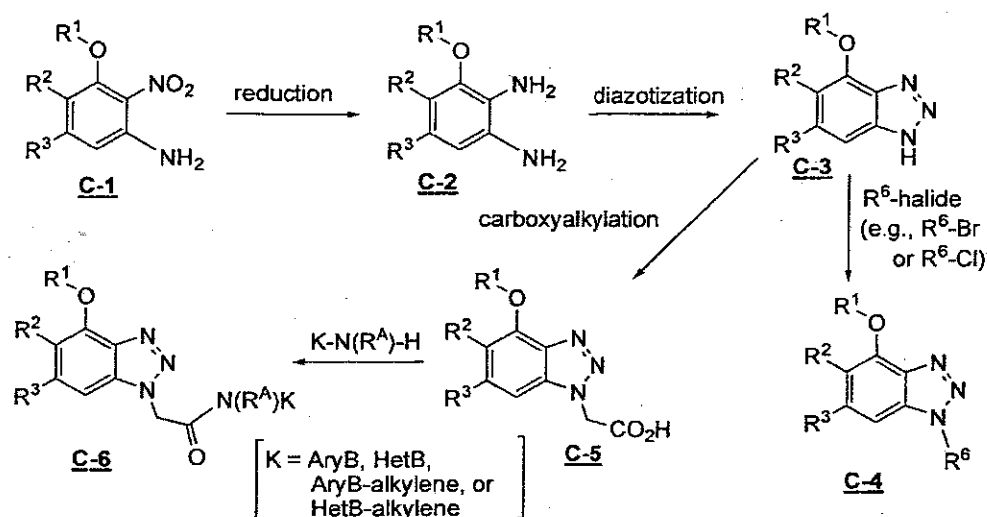
Substrates of Formula **A-1a** can be prepared in accordance with Scheme B:



Representative methods for preparing reactants of formula **A-1** and **A-2** are further described in the examples below.

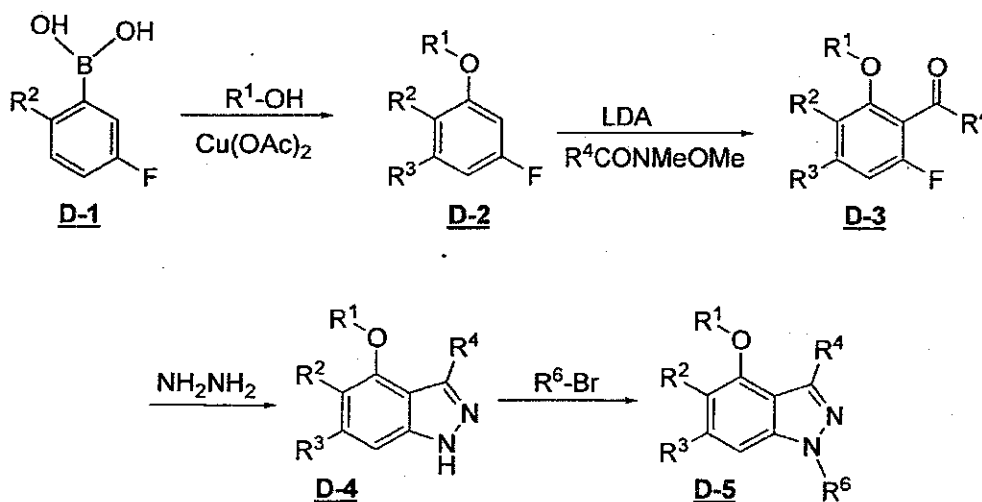
Scheme C depicts the preparation of benzotriazolyl compounds of the present invention, wherein the nitro group on the 2-amino-nitrobenzene derivative **C-1** can be reduced to the corresponding dianiline **C-2** through catalytic hydrogenation or by the action of tin II chloride. The dianiline can undergo cyclization to the corresponding triazole **C-3** upon diazotization. Alkylation of the triazole can be accomplished through reaction with a suitable electrophile such as R^6 (which may require protection) in the presence of a base to afford either **C-4** or **C-6**.

Scheme C



Scheme D depicts the preparation of benzopyrazolyl compounds of the invention wherein the arylboronic acid **D-1** can be coupled with a suitable phenol in the presence of a copper carboxylate (e.g., copper acetate) to provide the aryl ether **D-2**, which can be deprotonated and acylated to provide aldehyde or ketone **D-3**. The aldehyde or ketone can be further reacted with hydrazine to afford the corresponding benzopyrazole penultimate **D-4**, which can be alkylated with a suitable R^6 halide (R^6 may require protection) to provide the compound of the invention **D-5**.

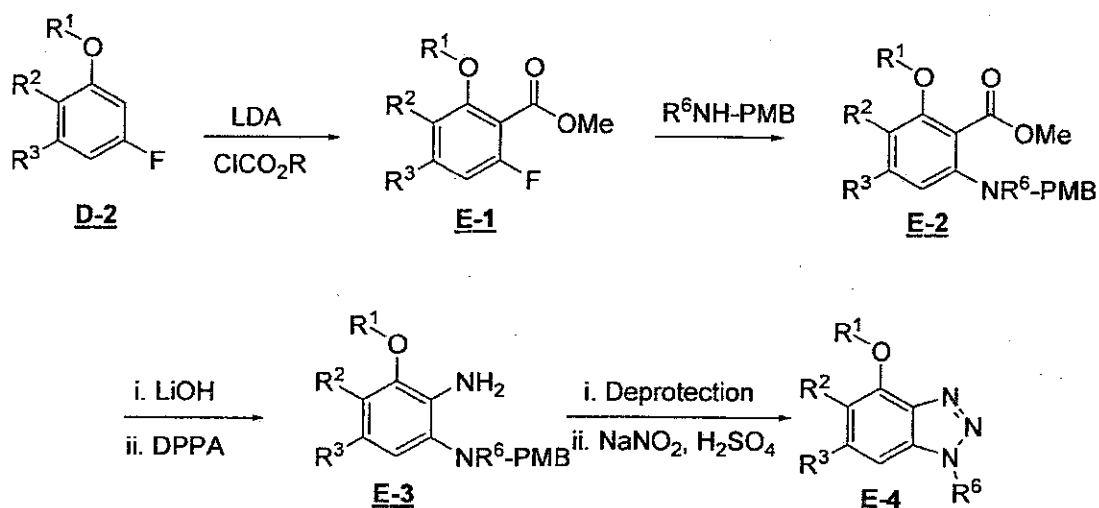
10 Scheme D



Scheme E depicts another route for preparing compounds of the invention, wherein the aryl ether **D-2** can be deprotonated and quenched with methylchloroformate to provide the ester **E-1**. Nucleophilic displacement of the fluorine in **E-1** with a suitably protected amine (exemplified by PMB in Scheme E) can provide **E-2**, which can be converted to the

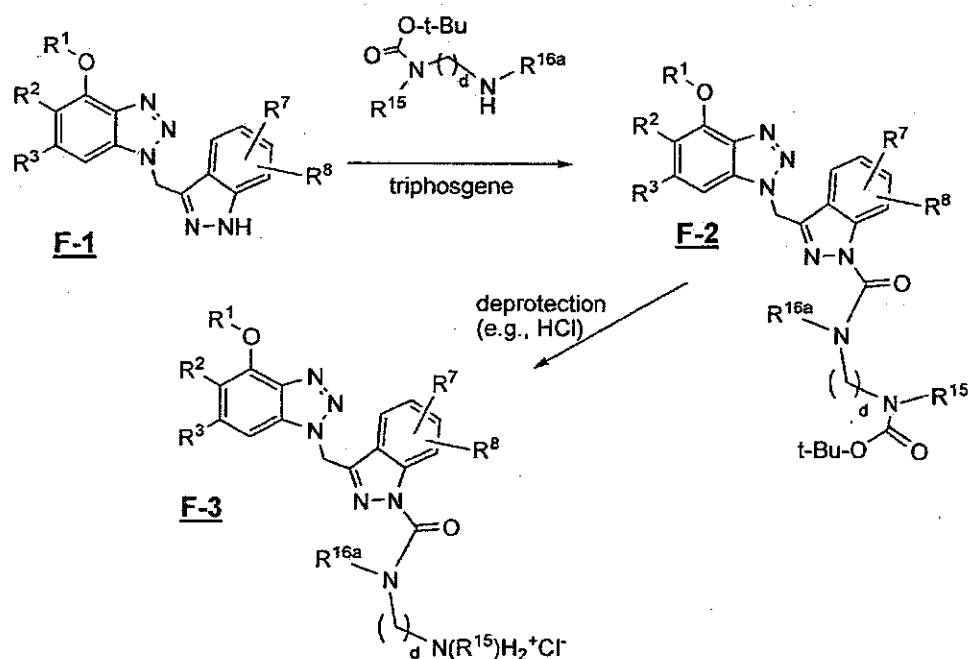
corresponding diamine **E-3** through a Curtius rearrangement. Following deprotection (e.g., treatment of the PMB with acid), the diamine can be converted to a variety of heterocycles including, for example, the triazole **E-4** shown in Scheme E.

Scheme E



Scheme F depicts a representative preparation of a pro-drug of the present invention, wherein the benzotriazolyl compound of the present invention **F-1** can be treated with a Boc-protected amine in the presence of a phosgene to afford acylated amine **F-2**, which can then be deprotected by treatment with a suitable acid (e.g., HCl or TFA) to provide desired pro-drug **F-3**.

Scheme F



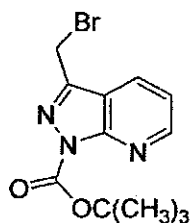
In the methods for preparing compounds of the present invention set forth in the foregoing schemes, functional groups in various moieties and substituents (e.g., R⁶, as well as other groups explicitly or implicitly referred to in the foregoing schemes) may be sensitive or reactive under the reaction conditions employed and/or in the presence of the reagents employed.

- 5 Such sensitivity/reactivity can interfere with the progress of the desired reaction to reduce the yield of the desired product, or possibly even preclude its formation. Accordingly, it may be necessary or desirable to protect sensitive or reactive groups on any of the molecules concerned. Protection can be achieved by means of conventional protective groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973 and in T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 3rd edition, 1999, and 2nd edition, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art. Alternatively the interfering group can be introduced into the molecule subsequent to the reaction step of concern.

- 15 The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention. References in the following examples to "room temperature" means a temperature of from about 20°C to about 25°C.

INTERMEDIATE 1

- 20 1-(tert-Butyl)-3-(bromomethyl)-1H-pyrazolo[3,4-b]pyridine-1-carboxylate



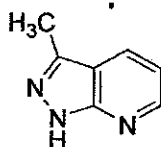
Intermediate I was prepared in accordance with the procedure described in Henke et al., *J. Med. Chem.* 1997, **40**: p. 2706. More particularly:

- 25 Step 1: 1-(2-fluoropyridine-3-yl)ethanone

- A solution of 3.13 mL (30.90 mmol) of freshly distilled diisopropylamine in 10 mL of anhydrous THF under nitrogen cooled to -78°C was treated dropwise with 19.31 mL (30.90 mmol) of a 1.6 M solution of n-BuLi in hexanes. The resulting solution was stirred at -78°C for approximately 20 minutes, and was briefly (5-10 minutes) warmed to -40°C, then re-cooled to -78°C. At 30 minutes post addition, 3.00g (30.90 mmol) of 2-fluoropyridine was added dropwise to the reaction. The resulting solution was stirred at -78°C for 30 minutes. The reaction was treated dropwise with a solution of 3.16 mL (30.90 mmol) of the Weinreb amide

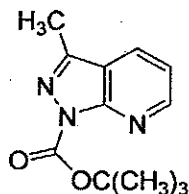
(i.e., N-methoxy-n-methylacetamide) in 30 mL of THF. The resulting solution was stirred 18 hours, allowing the bath to slowly evaporate and the reaction temperature to rise to room temperature. The reaction was treated with 5 mL of 1N HCl, and was concentrated to remove most of the THF. The residue was extracted twice with EtOAc, and the combined extracts were washed with 1N HCl, saturated aqueous NaHCO₃ solution, and brine, and were dried over anhydrous MgSO₄. Filtration and concentration of the filtrate provided a crude orange oil, which was purified by flash chromatography over silica gel with 3:1 Hexanes/EtOAc to provide 1.10 g of the title product as an orange oil. ¹H NMR (CDCl₃): δ 2.72(s,3H), 7.33(m,1H), 8.34(m,1H), 8.41(m,1H).

Step 2: 3-methyl-1H-pyrazolo[3,4-b]pyridine (36-2)



A stirred solution of 1.10g (7.91 mmol) of 1-(2-fluoropyridine-3-yl)ethanone in 5 mL of ethylene glycol under nitrogen was treated with 265 μL (8.31 mmol) of hydrazine. This solution was stirred for 2 hours at room temperature and then heated at 165°C for 1.5 hours. The solution was cooled to room temperature, poured into CH₂Cl₂ (25 mL), and extracted with H₂O (2x50 mL). The organic portions were combined, dried (MgSO₄), filtered and concentrated in vacuo to give the title product as a fluffy off-white solid. ¹H NMR (CDCl₃): δ 2.61(s, 3H), 7.14(m,1H), 8.06(dd,1H), 8.58(dd,1H), 11.18(br s, 1H).

Step 3: tert-butyl 3-methyl-1H-pyrazolo[3,4-b]pyridine-1-carboxylate



A stirred solution of 692 mg (5.20 mmol) of 3-methyl-1H-pyrazolo[3,4-b]pyridine in 25 mL of acetonitrile under nitrogen was cooled to 0°C in an ice bath, and was treated with 635 mg (5.20 mmol) of DMAP and 761 μL (5.46 mmol) of triethylamine. A solution of 1.36 g (6.24 mmol) of (BOC)₂O in 5 mL acetonitrile was then added dropwise using an addition funnel. Upon completion of addition, the ice bath was removed and the mixture was stirred for an additional 18 hours at room temperature. Solvent was removed in vacuo, and the residue was partitioned between EtOAc and H₂O. The organic layer was separated, dried (MgSO₄), filtered

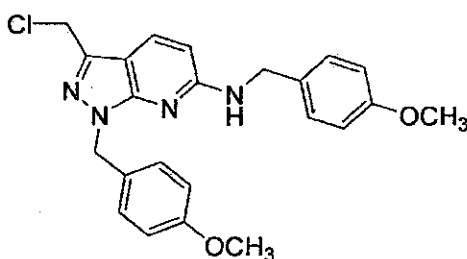
and concentrated in vacuo to an orange oil. This crude material was purified by flash chromatography over silica gel with 1:1 ethyl acetate/hexanes to give the title product as a clear oil. ^1H NMR (CDCl_3): δ 1.74(s,9H), 2.60(s,3H), 7.29(m,1H), 8.02(dd,1H), 8.74(dd,1H).

5 Step 4: 1-(tert-butyl)-3-(bromomethyl)-1H-pyrazolo[3,4-b]pyridine-1-carboxylate

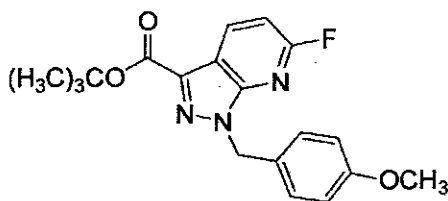
A stirred solution of 934 mg (4.00 mmol) of tert-butyl 3-methyl-1H-pyrazolo[3,4-b]pyridine-1-carboxylate in 10 mL of CCl_4 was heated to reflux, and then a mixture of 783 mg (4.40 mmol) of NBS and 97 mg (0.40 mmol) of benzoyl peroxide was added portion-wise over 5 minutes as a solid. The resulting solution was heated at reflux for 5 hours and then allowed to cool to room temperature. The reaction mixture was filtered through a pad of Celite to remove precipitated succinimide, and the filtrate was concentrated in vacuo. The crude residue was purified by flash chromatography over silica gel with 1:2 ethyl acetate/hexanes to the title product as a solid. ^1H NMR (CDCl_3): δ 1.76(s,9H), 4.78(s,2H), 7.35(q,1H), 8.24(dd,1H), 8.77(dd,1H).

INTERMEDIATE 2

3-(Chloromethyl)-N,1-bis(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridin-6-amine



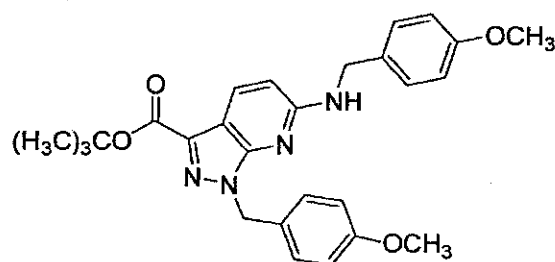
20 Step 1: tert-Butyl 6-fluoro-1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylate



To a solution of tert-butyl 6-fluoro-1H-pyrazolo[3,4-b]pyridine-3-carboxylate (29.55 g, 125 mmol) in THF (300 mL) cooled in an ice bath was added K_{Ot}Bu (13.98g, 125 mmol) at such a rate as to maintain the temperature between 5-10°C, and then 4-methoxybenzyl bromide (18.2 mL, 125 mmol) was added. The resulting mixture was stirred in an ice bath for 1 hour and then stirred at room temperature for 18 hours. The resulting suspension was quenched with saturated aqueous NH_4Cl (200 mL) and then extracted with EtOAc (2x300 mL). The

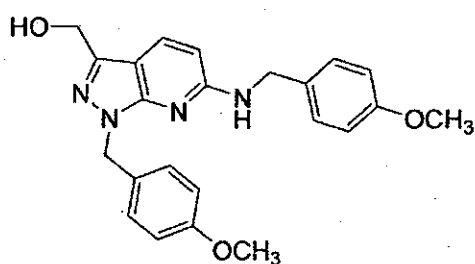
combined organic extracts were washed with brine, dried with MgSO_4 and the solvent removed in vacuo. The resulting residue was purified on a silica gel (1000g) column (0-11% EtOAc/hexanes) to give the title compound. LRMS (M+1)=380.1

- 5 Step 2: tert-Butyl 1-(4-methoxybenzyl)-6-[(4-methoxybenzyl)amino]-1H-pyrazolo[3,4-b]pyridine-3-carboxylate



- 10 To a solution of tert-butyl 6-fluoro-1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylate (2.55g, 7.14 mmol) in NMP (30 mL) was added 4-methoxybenzylamine (2.80 mL, 21.41 mmol). The resulting mixture was then heated to 80°C for 2 hours, after which the mixture was diluted with water (200 mL) and extracted with EtOAc (2x200 mL). The combined extracts were washed with water (100 mL), dried with MgSO_4 , filtered, absorbed onto silica gel (17 g) and removed the solvent in vacuo. This solid was purified on silica gel (80 g) column (0-100% EtOAc/ CH_2Cl_2) to give the title compound. LRMS (M+1)=474.0

- 15 Step 3: {1-(4-Methoxybenzyl)-6-[(4-methoxybenzyl)amino]-1H-pyrazolo[3,4-b]pyridine-3-yl}methanol



- 20 To a solution of tert-butyl 1-(4-methoxybenzyl)-6-[(4-methoxybenzyl)amino]-1H-pyrazolo[3,4-b]pyridine-3-carboxylate (2.65 g, 5.58 mmol) in 30 mL THF cooled in an ice bath was added a 2M solution of LiAlH_4 in THF (3.49 mL, 6.98 mmol). The resulting mixture was stirred cold for 20 minutes and then warmed to room temperature and then left at room temperature for 2.5 hours. The mixture was then diluted with THF (50 mL) and then treated sequentially with water (265 μL), 15% NaOH (265 μL) and water (795 μL) and then stirred for 25 30 minutes. The resulting suspension was filtered through diatomaceous earth and the resulting

cake was rinsed with THF (50 mL). The combined filtrates were preabsorbed onto silica gel (15) and the solvent removed in vacuo. This solid was purified on silica gel (80g) column (0-20% MeOH/CH₂Cl₂) to give the title compound. LRMS (M+1)=404.9

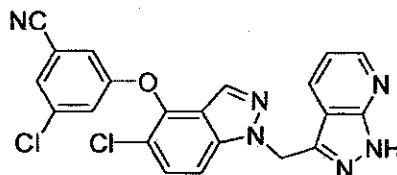
5 Step 4: 3-(Chloromethyl)-N,1-bis(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridin-6-amine

To a slurry of {1-(4-methoxybenzyl)-6-[(4-methoxybenzyl)amino]-1H-pyrazolo[3,4-b]pyridin-3-yl}methanol (1.49g, 3.68 mmol) in chloroform (15 mL) cooled in an ice bath was added thionyl chloride (538 μ L, 7.37 mmol). The resulting mixture was then allowed to warm to room temperature and left at room temperature for 30 minutes. The reaction
10 was determined by LCMS monitoring not to be complete, so the reaction mixture was re-cooled in an ice bath, treated with additional thionyl chloride (100 μ L), and then stirred at room temperature for 30 minutes. The reaction mixture was then poured into aqueous NaHCO₃, extracted into CHCl₃ and the solvent removed in vacuo. This residue was purified on a silica gel (120g) column (0-60% EtOAc/CHCl₃ to give the title compound. LRMS (M+1)=422.9

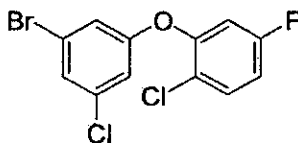
15

EXAMPLE 1

3-Chloro-5-{{[5-chloro-1-(1H-pyrazolo[3,4-b]pyridin-3-ylmethyl)-1H-indazol-4-yl]oxy}benzonitrile

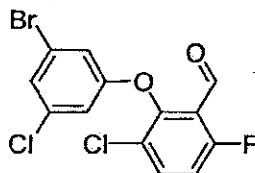


20 Step 1: 3-Bromo-5-chlorophenyl 2-chloro-5-fluorophenyl ether



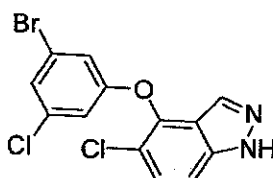
To a solution of 2-chloro-5-fluorophenol (82.3 g, 562 mmol) and 1-bromo-3-chloro-5-fluorobenzene (124g, 590 mmol) in NMP (200 mL) was added potassium carbonate (155g, 1.123mol). The resulting mixture was then heated to 140°C and maintained at 140°C for
25 30 hours, after which the mixture was poured into water (1500 mL) and extracted with EtOAc (2500 + 1500 mL). The combined extracts were washed with water and brine. This solution was concentrated on the rotary evaporator and the residue was distilled at high vacuum at 135-190°C to give the title compound as a clear, colorless liquid. ¹H NMR (CDCl₃) δ 7.45 (dd, 1H, J=9.0 and 4.5 hz), 7.28(dd, 1H, J=1.7Hz), 7.26(s, 1H), 7.00(dd, 1h, J=1.95Hz), 6.92(ddd, 1H, J=10.5,
30 7.6 and 2.7Hz), 6.89(dd, 1H, J=1.95Hz).

Step 2: 2-(3-Bromo-5-chlorophenoxy)-3-chloro-6-fluorobenzaldehyde



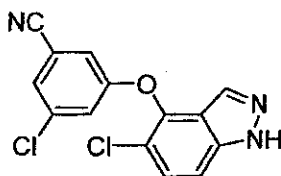
To a solution of 3-bromo-5-chlorophenyl 2-chloro-5-fluorophenyl ether (100g, 298 mmol) in THF (300 mL) cooled to -78°C over a dry ice/acetone bath was added 1.8M lithium diisopropylamide in hexanes/THF/ethylbenzene (174 mL, 313 mmol) over 10min. The resulting mixture was stirred for 20 minutes and then treated with DMF (46.1 mL, 595 mmol). The DMF-treated mixture was then removed from the cooling bath and allowed to warm to room temperature and then left at room temperature for 1 hour. The reaction mixture was then quenched with water (1000 mL) and extracted with EtOAc (3x500 mL). The combined extracts were washed with water (500 mL), dried over MgSO_4 , and concentrated in vacuo. This residue was purified on a silica gel column (0-40% $\text{CH}_2\text{Cl}_2/\text{hexanes}$) to give the title product. LRMS (M-18+1) = 346.7

Step 3: 4-(3-Bromo-5-chlorophenoxy)-5-chloro-1H-indazole



To a suspension of 2-(3-bromo-5-chlorophenoxy)-3-chloro-6-fluorobenzaldehyde (77.5g, 213 mmol) in ethanol (120 mL) was added hydrazine hydrate (31 mL, 639 mmol). The resulting mixture was then heated at reflux for 4 days, after which the mixture was cooled to room temperature, diluted with water (100 mL) and the resulting solid was filtered. The solid was absorbed onto silica gel (300g) and purified on a silica gel (1500g) column (0-40% EtOAc/ CH_2Cl_2) to give the title product as a white solid. LRMS (M+1) = 358.8

Step 4: 3-Chloro-5-[(5-chloro-1H-indazol-4-yl)oxy]benzonitrile



To a suspension of 4-(3-bromo-5-chlorophenoxy)-5-chloro-1H-indazole (40g, 112 mmol) and zinc cyanide (15.74g, 134 mmol) in DMF (400 mL) was added palladium tetrakis triphenylphosphine (38.7g, 33.5 mmol) and heated to 90°C for 1 hour. After this time, the reaction was cooled to room temperature and partitioned between saturated aq. NH₄Cl (500 mL), water (500 mL) and EtOAc (2x1000 mL). The combined extracts were dried over MgSO₄, absorbed onto silica gel (200 g) and the solvent removed in vacuo. This solid was purified on a silica gel (1000 g) column (0-10% EtOAc/CH₂Cl₂) to give the title compound as a white solid. LRMS (M+1)=303.9

Step 5: 3-Chloro-5-{[5-chloro-1-(1H-pyrazolo[3,4-b]pyridin-3-ylmethyl)-1H-indazol-4-yl]oxy}benzonitrile

To a suspension of 3-chloro-5-[(5-chloro-1H-indazol-4-yl)oxy]benzonitrile (24g, 79 mmol) and tert-butyl 3-(bromomethyl)-1H-pyrazolo[3,4-b]pyridine-1-carboxylate (= Intermediate 1; 24.63g, 79 mmol) in DMF (150 mL) at 0°C was added cesium carbonate (51.4g, 158 mmol). The resulting mixture was allowed to warm to room temperature and then stirred at room temperature for 2 hours, after which the mixture was partitioned between water (1000 mL) and EtOAc (1000 mL). The organic extract was washed with water (1000 mL) and then with brine (200 mL), dried over MgSO₄ and the solvent removed in vacuo. This residue was purified on a silica gel (500 g) column (0-10% acetonitrile/CH₂Cl₂) to give the the Boc-protected form of the title compound. This material was dissolved in TFA (50 mL) and allowed to stand at room temperature for 10 minutes, after which the solvent was removed in vacuo. The resulting solid was then preabsorbed onto silica gel (50 g) and purified on silica gel (330 g) column (10-30% acetonitrile/CH₂Cl₂) to give the title compound as a white solid.

¹H NMR (DMSO- d₆): δ 13.65 (s, 1H), 8.49 (d, J=4.6Hz, 1H), 7.91 (d, J=8.3Hz, 1H), 7.89 (s, 1H), 7.82 (d, J= 8.8Hz, 1H), 7.62 (d, J= 8.6Hz, 1H), 7.47 (m, 1H), 7.39 (m, 1H), 7.13 (dd, J= 7.7 and 4.6Hz, 1H), 6.05 (s, 2H) ppm. LRMS (M+1)= 434.7

EXAMPLE 1A

Alternative preparation of 3-chloro-5-{[5-chloro-1-(1H-pyrazolo[3,4-b]pyridin-3-ylmethyl)-1H-indazol-4-yl]oxy}benzonitrile

Step 1: 3-Bromo-5-chlorophenyl 2-chloro-5-fluorophenyl ether

A round bottom flask (100 L) was charged with K₂CO₃ (11.410 kg; 82.56 moles; 3.00 eqs.), DMSO (40 L), and 1-bromo-3-chloro-5-fluorobenzene (5.82 kg, 27.79 moles; 1.00 eq.). The resulting white slurry was degassed for 10 minutes using a subsurface stream of nitrogen, after which 2-chloro-5-fluorophenol (1.2 kg) was added through a dropping funnel. The reaction mixture was then heated to 150°C, and a second portion 2-chloro-5-fluorophenol

(4.56 kg) was added in batches of about 0.5-0.6 kg batch over 7 hours. The mixture was then aged at 150°C for 12 hours, and cooled to room temperature. About half of the mixture was transferred to an extractor (100 L) filled with water (30 L), extracted with heptane (45 L), and then washed with water (18 L). The other half of the mixture was worked up in the same manner. The combined organic layers were filtered through a silica pad (22 kg), washed with heptane (50 L), and concentrated on a rotavap with a bath temperature of 50°C-60°C to provide a clear colorless viscous oil that solidified after cooling to room temperature.

Step 2: 2-(3-Bromo-5-chlorophenoxy)-3-chloro-6-fluorobenzaldehyde

A round bottom flask was charged with diisopropylamine (1.336 kg, 13.20 moles; 1.2 eqs.) and THF (25 L), and the mixture cooled to -16°C in a dry ice/acetone bath. A solution of n-butyl lithium (2.5 M; 12.65 moles; 1.17 eqs.) in hexane was added over 25 minutes, while keeping the temperature below 1°C, after which the mixture was aged 20 minutes and then cooled to below -70°C. 3-Bromo-5-chlorophenyl 2-chloro-5-fluorophenyl ether (3.638 kg; 10.8 moles; 1.0 eq.) in THF (4 L) was then added over 35 minutes. The reaction mixture was kept below -60°C and aged for 1.5 hours, after which DMF (3.683 kg; 50.4 moles; 1.2 eq.) was added over 15 minutes. After aging the mixture a further 50 minutes, the reaction mixture was warmed to -20°C and quenched with water (5 L). The mixture was then warmed to 15°C, transferred to an extractor (100 L) filled with water (20 L), and extracted with EtOAc (28 L). The organic layer was washed with water (22 L), 1N HCl (25 L), and brine (18 L), and then concentrated to 15L. Heptane (25 L) was added to the concentrate, and the resulting solution was heated to 60°C and then concentrated to 18 L as it was cooled to 11°C. The dark yellow suspension was filtered and washed with heptane (5 L), and dried overnight to provide the title product as a solid.

Step 3: 4-(3-Bromo-5-chlorophenoxy)-5-chloro-1H-indazole

A suspension of 2-(3-bromo-5-chlorophenoxy)-3-chloro-6-fluorobenzaldehyde (4.5 kg; 12.36 moles; 1.0 eq.) in DMSO (18 L) was degassed, after which hydrazine monohydrate (6.192 kg; 123.7 moles; 10.0 eqs.) was added over 20 minutes at room temperature. The reaction solution was degassed again, stirred at room temperature for 15 minutes, heated to 73°C, and then aged for 16 hours. After the mixture was cooled to room temperature, isopropanol (15 L) and then water (40 L) were added, and the resulting mixture cooled to room temperature, filtered under pressure, and washed with isopropanol:water (1:2; 10 L), water (12 L), and heptane (12 L). The title product as a solid was obtained after drying at 30°C-35°C under vacuum for four days.

Step 4: 3-Chloro-5-[(5-chloro-1H-indazol-4-yl)oxy]benzonitrile

Bromine (154 g; 0.964 mole; 0.10 eq.) was added to a slurry of zinc (particle size < 10 microns; 192 g; 2.940 moles; 0.30 eq.) in DMF (10 L) at room temperature. The resulting mixture was then stirred fast for 30 minutes while 4-(3-bromo-5-chlorophenoxy)-5-chloro-1H-indazole (3.508 kg; 9.798 moles; 1.00 eq., zinc cyanide (690 g; 5.879 moles; 0.60 eq.), triphenylphosphine (308 g; 1.176 moles; 0.12 eq.), palladium acetate (66 g; 0.294 mole; 0.03 eq.) and DMF (11 L) were added at room temperature. The reaction mixture was then degassed for 15 minutes using a subsurface stream of nitrogen, heated to 85°C, and then aged for 4.5 hours. The reaction mixture was then cooled to room temperature and stirred overnight. The reaction mixture was then diluted with THF (18 L) and heated to 50°C, after which aqueous EDTA·3Na (0.5M, 20L) was added and the mixture aged at 50°C-60°C for 1 hour. The mixture was then filtered through solka floc and washed with THF (20L), and the filtrate transferred to an extractor (100 L) filled with brine (15L) and separated. The aqueous layer was extracted with EtOAc (15 L), and the combined organic layers were washed with a second portion of EDTA·3Na (0.5M, 20L), then water (20 L), and then brine (15 L). The solution was treated with activated carbon (Darko KB), filtered through solka floc, concentrated to a slurry of less than 10 L, switched to toluene (6 L), concentrated to half volume, heated to 40°C, added heptane (6 L), and cooled below 25°C. The resulting slurry was filtered, washed with extra toluene:heptane (1:3; 4 L), heptane (4 L), and dried to provide the title product as a solid.

Step 5: 3-chloro-5-{[5-chloro-1-(1-*t*-butyloxycarbonyl-1H-pyrazolo[3,4-*b*]pyridin-3-ylmethyl)-1H-indazol-4-yl]oxy}benzonitrile

A 4-necked round bottom flask (75 L) under nitrogen and equipped with a mechanical stirrer, a thermocouple and an addition funnel was placed on a steam bath. 3-Chloro-5-[(5-chloro-1H-indazol-4-yl)oxy]benzonitrile (2.07 kg; 6.12 moles; 1.0 eq.), 1-(*tert*-butyl)-3-(bromomethyl)-1H-pyrazolo[3,4-*b*]pyridine-1-carboxylate (2.48 kg; 7.95 moles; 1.30 eqs.) were charged to the flask, followed by the addition of DMF (11.2 L). The mixture was cooled to 3.1°C with ice-water, after which DBU (1.46 L; 9.79 moles; 1.60 eqs.) was added over 30 minutes while keeping the internal temperature below about 21°C. The reaction mixture was then cooled to 6°C and aged at that temperature until complete conversion of the indazole as determined by HPLC. MTBE (10 L), AcOEt (5 L), H₂O (10 L) were then added and the mixture transferred to an extractor (100 L). The flask was rinsed with MTBE (1.2 L), EtOAc (1.2 L) and H₂O (1.2 L), the rinse was stirred for 10 minutes, and then allowed to settle. The aqueous layer was cut away, and the organic layer was drummed off. The aqueous layer was transferred to the extractor, after which MTBE (7.4 L) and EtOAc (3.7 L) were added, and the mixture stirred for 10 minutes, and then allowed to settle. The aqueous layer was cut away. The first organic layer was transferred to the extractor, and the drum was rinsed with MTBE:EtOAc (2:1; 1.5 L). Water (11.2 L) was added to the extractor, and the mixture was stirred for 10 minutes, then allowed to

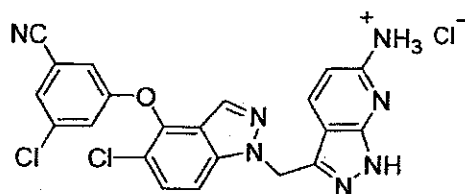
settle. The aqueous layer was cut away, the organic layer was drummed off, and the extractor was rinsed with AcOEt (1 L x 2). The combined organic layers were concentrated in vacuo with rotavap at a bath temperature of 30°C-35 °C to 4.775 kg (with solvent). The concentrate was then separated via a silica gel column (40 kg) using heptane-EtOH. The desired fractions were concentrated in a round bottom flask (75 L) using a batch concentrator to about 15 L. EtOAc (4 L) was added to the concentrate and the mixture stirred at room temperature overnight. The resulting crystalline slurry was then heated to 45°C, stirred for 40 minutes at 45°C and then allowed to cool to room temperature. The crystals were then separated by filtration using a filter pot, and the resulting wet cake was rinsed with EtOAc-heptane (1:2; 6 L) and then dried with a nitrogen stream to afford the desired title product as crystals.

Step 6: 3-Chloro-5-{{[5-chloro-1-(1*H*-pyrazolo[3,4-*b*]pyridin-3-ylmethyl)-1*H*-indazol-4-yl]oxy}benzonitrile

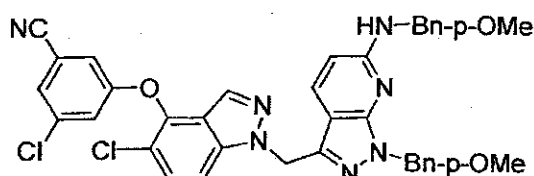
A jacketed reaction vessel (30 L) equipped with a thermocouple was charged with 3-chloro-5-{{[5-chloro-1-(1-*t*-butyloxycarbonyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-ylmethyl)-1*H*-indazol-4-yl]oxy}benzonitrile (1.338 kg; 2.499 moles; 1.0 eq.) and then with DMF (10.7 L) and IPA (2.68 L). Concentrated HCl (2.68 L) was then charged to the vessel during which time the internal temperature rose from 16°C to 44°C. The mixture was then heated to 60 °C. After 1 hour at 60°C, the suspension became a clear solution. Conversion was complete after 1.75 hours as determined by HPLC, at which point the reaction mixture was transferred into a 4-necked round bottom flask (75 L) at 55°C-60°C via an in-line filter. The reaction vessel was rinsed with IPA (2 L x 2), and the rinse transferred to the flask via the in-line filter. Filtered water (16 L) was then added to the mixture via an additional funnel while maintaining the temperature at 55°C-60°C, during which crystallization of the title product began. Upon completion of the water addition, the mixture was stirred at 55°C for 40 minutes, then cooled to room temperature and filtered with a filter pot. The wet cake was rinsed with filtered IPA:water (3:7, 10 L), and then with filtered water (7 L x 6), and then dried in a vacuum oven at 40°C for two days to afford the title product.

EXAMPLE 2

3-{{[5-Chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-indazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridin-6-aminium chloride. (Alternative name: 3-({1-[(6-Amino-1*H*-pyrazolo[3,4-*b*]pyridine-3-yl)methyl]-5-chloro-1*H*-indazol-4-yl}oxy)-5-chlorobenzonitrile, HCl salt)



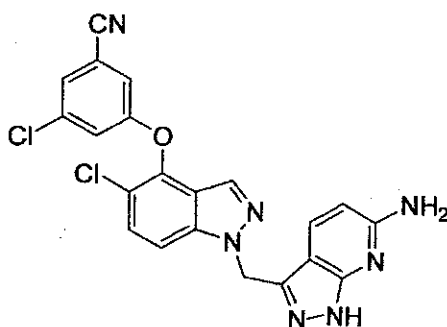
Step 1: 3-Chloro-5-{{[5-chloro-1-({1-(4-methoxybenzyl)-6-[(4-methoxybenzyl)amino]-1H-pyrazolo[3,4-b]pyridin-3-yl}methyl)-1H-indazol-4-yl]oxy} benzonitrile



5 3-chloro-5-[(5-chloro-1H-indazol-4-yl)oxy]benzonitrile (0.677 g, 2.225 mmol) and lithium tert-butoxide (0.178 g, 2.225 mmol) were dissolved in DMF (5 mL) and allowed to stir for 5 minutes. To this mixture at 0°C was added 3-(chloromethyl)-N,1-bis(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridin-6-amine (Intermediate 2; 0.896 g, 2.119 mmol) as a solution in DMF (5 mL). The mixture was then allowed to warm to room temperature overnight, after which aqueous ammonium chloride (20 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were washed with water (5 x 50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was subjected to automated silica gel chromatography eluting with a gradient of 0-10% ethyl acetate in dichloromethane to yield the title product. LRMS (M+1) = 691.8

15

Step 2: 3-({1-[(6-Amino-1H-pyrazolo[3,4-b]pyridin-3-yl)methyl]-5-chloro-1H-indazol-4-yl}oxy)-5-chlorobenzonitrile



20 3-chloro-5-{{[5-chloro-1-({1-(4-methoxybenzyl)-6-[(4-methoxybenzyl)amino]-1H-pyrazolo[3,4-b]pyridin-3-yl}methyl)-1H-indazol-4-yl]oxy} benzonitrile (0.848 g, 1.228 mmol) was dissolved in TFA (10 mL) and placed in an oil bath at 75°C. After 2.5 hours, the reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure.

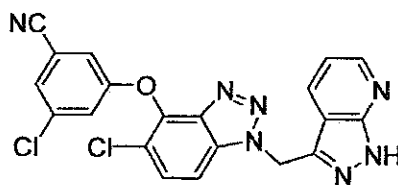
The resulting residue was suspended in a chloroform and ethyl acetate mixture (4:1, 200 mL) and aqueous sodium bicarbonate (50 mL) was added. Ethyl acetate was then added until both phases had become solutions. The organic phase was separated and the aqueous phase was washed with chloroform (2 x 100 mL). The combined organic fractions were dried over MgSO_4 , filtered and concentrated under reduced pressure. The resulting residue was subjected to automated silica gel chromatography eluting with a gradient of 0-10% methanol in chloroform to yield the title product. ^1H NMR ($\text{DMSO}-d_6$): δ 12.60 (s, 1H), 7.86 (s, 1H), 7.81-7.78 (m, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.49-7.47 (m, 1H), 7.38-7.34 (m, 2H), 6.30 (s, 2H), 6.21 (d, J = 8.8 Hz, 1H), 5.82 (s, 2H). LRMS ($M+1$) = 449.7

Step 3: 3-([5-Chloro-4-(3-chloro-5-cyanophenoxy)-1H-indazol-1-yl]methyl)-1H-pyrazolo[3,4-b]pyridin-6-aminium chloride

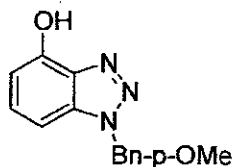
To 3-([1-[(6-amino-1H-pyrazolo[3,4-b]pyridin-3-yl)methyl]-5-chloro-1H-indazol-4-yl]oxy)-5-chlorobenzonitrile (0.936 g, 2.079 mmol) as a solution in 20% methanol in chloroform (300 mL) was added 1N HCl (2.079 mL, 2.079 mmol), and the resulting mixture was then concentrated under reduced pressure. The resulting white paste was diluted with acetonitrile (100 mL) and the solvent evaporated in vacuo. The dilution-evaporation was repeated twice more for a total of three times. The resulting residue was placed under vacuum overnight to give product. ^1H NMR ($\text{DMSO}-d_6$): δ 7.91 (s, 1H), 7.81 (s, 3H), 7.68-7.60 (m, 2H), 7.48 (s, 1H), 7.37 (s, 1H), 6.50-6.30 (m, 2H), 6.00-5.86 (m, 2H). HRMS ($M+1$) = 450.06

EXAMPLE 3

3-chloro-5-([5-chloro-1-(1H-pyrazolo[3,4-b]pyridin-3-ylmethyl)-1H-1,2,3-benzotriazol-4-yl]oxy)benzonitrile



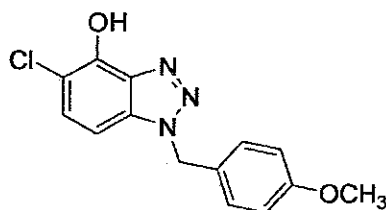
Step 1: 1-(4-methoxybenzyl)-1H-1,2,3-benzotriazol-4-ol



4-Methoxy-benzylbromide (2.976 g, 14.80 mmol) was added to a stirred suspension of 4-hydroxy-benzotriazole (2.0 g, 14.80 mmol) and cesium carbonate (9.645 g, 29.6

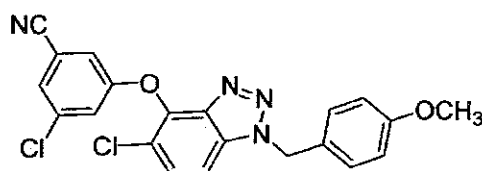
mmol) in DMF (30 mL) at room temperature and the reaction mixture was stirred for 1 hour. Aqueous ammonium chloride (30 mL) was then added to quench the reaction and the mixture was then extracted with ethyl acetate (2 x 100 mL). The organic fractions were combined and concentrated under reduced pressure. The resulting residue was subjected to reverse phase chromatography (5-95% MeCN/H₂O, 0.1% TFA). The product fractions were combined and extracted with dichloromethane (2 x 100 mL). The combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to yield the title product. ¹H NMR (DMSO d₆) δ 10.67 (s, 1, H), 7.29-7.27 (m, 3H), 7.15(d, J=8.3 Hz, 1H), 6.88-6.84(m, 2H), 6.63(d, J=7.6Hz, 1H), 5.80(s, 2H), 3.71(s, 3H).

Step 2: 5-Chloro-1-(4-methoxybenzyl)-1*H*-1,2,3-benzotriazol-4-ol



To a stirred solution of 1-(4-methoxybenzyl)-1*H*-1,2,3-benzotriazol-4-ol (0.984 g, 3.85 mmol) at 0°C in THF (15 mL) was added 1N NaOH (3.85 mL, 3.85 mmol). The resulting mixture was then stirred for several minutes, after which N-chloro-succinimide (0.515 g, 3.85 mmol) was added in one portion. The stirred reaction mixture was quenched after 5 minutes at 0°C with aqueous ammonium chloride (25 mL) and extracted with dichloromethane (2 x 100 mL). The combined extracts were concentrated under reduced pressure. The resulting residue was subjected to reverse phase chromatography (5-95% MeCN/H₂O, 0.1% TFA). The product fractions were combined and extracted with dichloromethane (2 x 100 mL). The combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to afford the title product. ¹H NMR (DMSO d₆) δ 11.61(s, 1H), 7.44(d, J=8.5Hz, 1H), 7.30 (d, J=8.5Hz, 2H), 7.23 (d, J=8.6Hz, 1H), 6.90(d, J=8.8Hz, 2H), 5.84(s, 2H), 3.71(s, 3H).

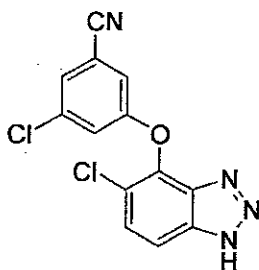
Step 3: 3-Chloro-5-[[5-chloro-1-(4-methoxybenzyl)-1*H*-1,2,3-benzotriazol-4-yl]oxy]benzonitrile



A stirred suspension of 5-chloro-1-(4-methoxybenzyl)-1*H*-1,2,3-benzotriazol-4-ol (0.050 g, 0.173 mmol), 3-fluoro-5-chloro-benzonitrile (0.081 g, 0.518 mmol) and cesium

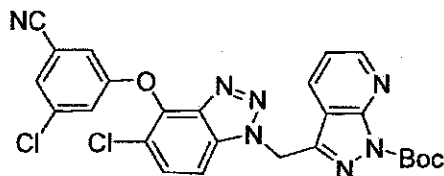
carbonate (0.068 g, 0.207 mmol) in NMP (1.5 mL) was heated at 140°C for 72 hours. The reaction mixture was then quenched with aqueous ammonium chloride (25 mL) and extracted with dichloromethane (2 x 100 mL). The combined extracts were concentrated under reduced pressure. The resulting residue was subjected to reverse phase chromatography (5-95% MeCN/H₂O, 0.1% TFA). The product fractions were combined and extracted with dichloromethane (2 x 100 mL). The combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to yield the title product. ¹H NMR (DMSO d₆) δ 7.90-7.88(m, 1H), 7.80(s, 1H), 7.79-7.75(m, 1H), 7.60-7.55(m, 2H), 7.40-7.35(d, J=6.9Hz, 2H), 6.95-6.88 (m, 2H), 5.80(s, 2H), 3.71(s, 3H).

Step 4: 3-Chloro-5-[(5-chloro-1*H*-1,2,3-benzotriazol-4-yl)oxy]benzonitrile



3-chloro-5-[[5-chloro-1-(4-methoxybenzyl)-1*H*-1,2,3-benzotriazol-4-yl]oxy]benzonitrile (0.0097 g, 0.023 mmol) was dissolved in TFA (2 mL) and heated at 75°C for 2 hours. The reaction mixture was then allowed to cool to room temperature and then concentrated under reduced pressure. The resulting residue was subjected to automated silica gel chromatography eluting with 0-25% ethyl acetate in hexanes to give the title product. LRMS (M+1) = 304.8

Step 5: *tert*-Butyl 3-[[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl]-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate



To 3-chloro-5-[(5-chloro-1*H*-1,2,3-benzotriazol-4-yl)oxy]benzonitrile (0.006 g, 0.020 mmol) and cesium carbonate (0.0077 g, 0.024 mmol) suspended in DMF (1 mL) at room temperature was added *tert*-butyl 3-(bromomethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (= Intermediate 1; 0.0068 g, 0.022 mmol) as a solution in DMF (0.5 mL). After stirring for 1 hour at room temperature, the reaction mixture was quenched with aqueous ammonium chloride

(2 mL), and the quenched mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were washed with water (3 x 10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was subjected to automated silica gel chromatography eluting with a gradient of 25-50% ethyl acetate in hexanes to afford the title product. LRMS (M+1) = 435.7

Step 6: 3-Chloro-5-{[5-chloro-1-(1*H*-pyrazolo[3,4-*b*]pyridin-3-ylmethyl)-1*H*-1,2,3-benzotriazol-4-yl]oxy} benzonitrile

tert-Butyl 3-{[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (0.001 g, 1.86 μmol) was dissolved in TFA (2 mL) at room temperature. After 5 minutes, the solvent was evaporated in vacuo to afford the title product.

¹H NMR (CDCl₃): δ 8.52-8.46 (m, 1H), 8.35 (d, *J* = 4.15 Hz, 1H), 7.59 (d, *J* = 8.79 Hz, 1H), 7.57 (d, *J* = 8.78 Hz, 1H), 7.36 (s, 1H), 7.33-7.27 (m, 1H), 6.98 (s, 1H), 6.25 (s, 2H). HRMS (M+1) = 436.05.

EXAMPLE 3A

Alternative preparation of 3-chloro-5-{[5-chloro-1-(1*H*-pyrazolo[3,4-*b*]pyridin-3-ylmethyl)-1*H*-1,2,3-benzotriazol-4-yl]oxy} benzonitrile

Step 1: 2-(3-bromo-5-chlorophenoxy)-1-chloro-3-nitrobenzene

2,3-dichloronitrobenzene (764 mg, 3.99 mmol), 3-bromo-5-chlorophenol (1.65 g, 7.98 mmol) and potassium carbonate (661 mg, 4.79 mmol) were suspended in NMP (5mL) and placed in an oil bath at 120°C. After 2 hours, the reaction was allowed to cool to room temperature, saturated aqueous ammonium chloride (10mL) was added and the mixture was extracted with ethyl acetate (2x50mL). The combined organic fractions were washed with dilute brine (4x50 mL), dried (MgSO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by automated column chromatography on silica gel (80g), eluting with 0-100% CH₂Cl₂/hexanes to yield the title compound. ¹H NMR (CD₃CN) δ 8.02 (dd, *J* = 8.3Hz, *J* = 1.5 Hz, 1H), 7.88 (dd, *J* = 8.2Hz, *J* = 1.6Hz, 1H), 7.52 (dd, *J* = 8.2Hz, *J* = 8.3Hz, 1H), 7.38 (m, 1H), 7.07 (m, 1H), 6.97 (m, 1H).

Step 2: 3-(3-bromo-5-chlorophenoxy)-4-chloro-2-nitroaniline

To copper (I) chloride (5.45 mg, 0.055 mmol) and potassium *tert*-butoxide (247 mg, 2.204 mmol) suspended in DMF (3mL) at 0°C was added 1,1,1-trimethylhydrazinium iodide (139 mg, 0.689 mmol). This mixture was allowed to stir for several minutes at which point the mixture was cooled to -40°C and 2-(3-bromo-5-chlorophenoxy)-1-chloro-3-nitrobenzene (200 mg, 0.551 mmol) as a solution in DMF (1 mL) was added dropwise. The reaction was

maintained at -40°C for 15 minutes and was then quenched at -40°C with saturated aqueous ammonium chloride (10 mL). Water (10mL) was added and the mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2x50 mL). The combined organic fractions were washed with water (3x50mL), dried (MgSO₄), filtered and the solvent was evaporated under reduced pressure. The resulting residue was purified by automated column chromatography on silica gel (40g) eluting with 0-25%EtOAc/hexanes to give the title product. LRMS (M+1) = 378.7.

Step 3: 3-(3-bromo-5-chlorophenoxy)-4-chlorobenzene-1,2-diamine

3-(3-bromo-5-chlorophenoxy)-4-chloro-2-nitroaniline (5.7 g, 15 mmol) and tin(II) chloride dihydrate (17 g, 75 mmol) were suspended in MeOH (100mL) and heated to 75°C under a reflux condenser and N₂. After 10 hours, the reaction was allowed to cool to room temperature. The reaction was concentrated under reduced pressure, diluted with ethyl acetate (150mL) and 10% aqueous sodium carbonate (250mL) was added with vigorous stirring until the pH was 10. The mixture was filtered through celite. The resulting biphasic filtrate was separated and the aqueous extracted again with ethyl acetate (150mL). The combined organic fractions were dried (MgSO₄), filtered and the solvent was evaporated under reduced pressure to yield the title product. LRMS (M+1) = 348.7.

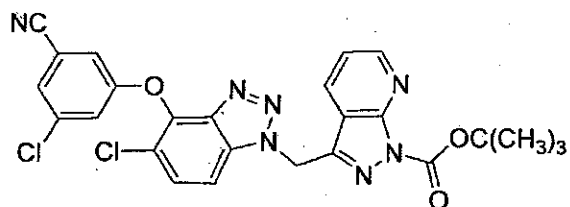
Step 4: 4-(3-bromo-5-chlorophenoxy)-5-chloro-1*H*-1,2,3-benzotriazole

3-(3-bromo-5-chlorophenoxy)-4-chlorobenzene-1,2-diamine (4.97 g, 14.3 mmol) in acetic acid (25 mL) was cooled to 15°C under N₂ and sodium nitrite (1.08g, 15.7 mmol) in water (39.3 mL) was added dropwise. After 1.5 hours, the reaction was diluted with EtOAc (300 mL), and the organic phase was separated and washed with water (3x100 mL). The organic phase was then dried (MgSO₄), filtered, concentrated to afford the title product. LRMS (M+1) = 359.7.

Step 5: 3-chloro-5-[(5-chloro-1*H*-1,2,3-benzotriazol-4-yl)oxy]benzonitrile

4-(3-bromo-5-chlorophenoxy)-5-chloro-1*H*-1,2,3-benzotriazole (5.0 g, 14 mmol), tetrakis triphenylphosphine palladium (0) (4.83 g, 4.83 mmol) and zinc cyanide (1.96 g, 16.7 mmol) were suspended in dry DMF (50 mL) under N₂ and placed in an oil bath at 90°C. After 2.5 hours, the reaction was allowed to cool to room temperature. The mixture was diluted with EtOAc (300mL) and washed with water (4x100 mL), dried (MgSO₄), filtered and concentrated with silica gel (20 g). This was purified by automated column chromatography on silica gel (120 g), eluting with 0-30%EtOAc/hexanes to deliver the title compound. LRMS (M+1) = 304.8.

Step 6: *tert*-Butyl 3-{{[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate



To 3-chloro-5-[(5-chloro-1*H*-1,2,3-benzotriazol-4-yl)oxy]benzonitrile (0.006 g, 0.020 mmol) and cesium carbonate (0.0077 g, 0.024 mmol) suspended in DMF (1 mL) at room temperature was added *tert*-butyl 3-(bromomethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (= Intermediate 1; 0.0068 g, 0.022 mmol) as a solution in DMF (0.5 mL). After stirring for 1 hour at room temperature, the reaction mixture was quenched with aqueous ammonium chloride (2 mL), and the quenched mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were washed with water (3 x 10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was subjected to automated silica gel chromatography eluting with a gradient of 25-50% ethyl acetate in hexanes to afford the title product. LRMS (M+1) = 435.7

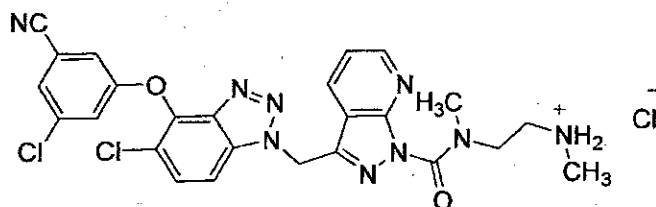
Step 7: 3-Chloro-5-{{[5-chloro-1-(1*H*-pyrazolo[3,4-*b*]pyridin-3-ylmethyl)-1*H*-1,2,3-benzotriazol-4-yl]oxy}benzonitrile

tert-Butyl 3-{{[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (0.001 g, 1.86 μmol) was dissolved in TFA (2 mL) at room temperature. After 5 minutes, the solvent was evaporated in vacuo to afford the title product.

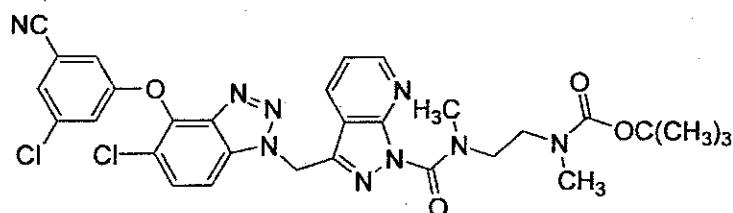
¹H NMR (CDCl₃): δ 8.52-8.46 (m, 1H), 8.35 (d, *J* = 4.15 Hz, 1H), 7.59 (d, *J* = 8.79 Hz, 1H), 7.57 (d, *J* = 8.78 Hz, 1H), 7.36 (s, 1H), 7.33-7.27 (m, 1H), 6.98 (s, 1H), 6.25 (s, 2H). HRMS (M+1) = 436.05.

EXAMPLE 4

2-[[[3-{{[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl]carbonyl](methyl)amino]-*N*-methylethanaminium chloride



Step 1: *tert*-butyl {2-[[3-{{5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)carbonyl](methyl)amino]ethyl}methyl carbamate

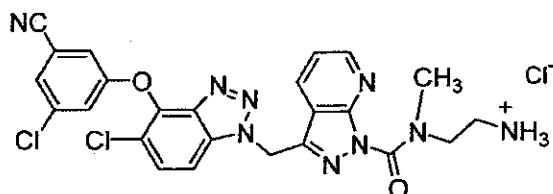


5 To a suspension of 3-chloro-5-{{5-chloro-1-(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methyl}-1*H*-1,2,3-benzotriazol-4-yl]oxy} benzonitrile (117 mg, 0.268 mmol) in dichloromethane (5mL) at 0°C was added pyridine (0.043 mL, 0.536 mmol). To this suspension was then added triphosgene (32 mg, 0.107 mmol) as a solid, in one addition, followed by addition of diisopropyl ethylamine (0.198 mL, 1.135 mmol). This suspension was allowed to stir
10 at 0°C until a solution was achieved. At this point, 2-[[*tert*-butoxycarbonyl]amino]-*N*-methylethanaminium chloride (120 mg, 0.567 mmol) was added as a solid followed by diisopropyl ethylamine (0.047 mL, 0.268 mmol). The reaction was allowed to warm to room temperature and after 10 minutes, the reaction was diluted with dichloromethane (25mL), washed with water (15mL) and the aqueous layer was re-extracted with dichloromethane (25mL). The
15 combined organic fractions were dried (MgSO₄), filtered and concentrated. The resulting residue was purified by reverse phase chromatography eluting with 30-95% MeCN/H₂O + 0.1% TFA. LRMS (M+1) = 549.6.

Step 2: 2-[[3-{{5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)carbonyl](methyl)amino]-*N*-methylethanaminium chloride
20 *tert*-butyl {2-[[3-{{5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)carbonyl](methyl)amino]ethyl}methylcarbamate (125 mg, 0.192 mmol) was dissolved in TFA (5mL). After 20 minutes, the reaction was
25 concentrated and the resulting residue was purified by reverse phase chromatography eluting with 30-95% MeCN/H₂O + 0.1% TFA. Product fractions were concentrated under reduced pressure and the resulting solid was dissolved in MeCN (3mL), cooled to -78°C and 1N HCl (5mL) added. This froze and was lyophilized to yield the title compound. ¹H NMR (DMSO-*d*₆)
30 δ 8.68 (dd, *J*=4.5Hz, *J*=1.5Hz, 1H), 8.57 (s, 1H), 8.26 (d, *J*=8.0Hz, 1H), 8.11 (s, 1H), 7.96 (m, 1H), 7.83 (d, *J*=9.0Hz, 1H), 7.72 (m, 1H), 7.58 (m, 1H), 7.44 (dd, *J*=4.6Hz, *J*=8.0Hz, 1H), 7.35 (m, 1H), 7.28 (m, 1H), 6.50 (s, 2H), 3.70 (s, 3H), 3.20 (s, 2H), 3.00 (s, 2H), 2.20 (m, 3H).

EXAMPLE 5

2-[[[3-{{[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl]carbonyl](methyl)amino]ethanaminium chloride (Alternative name: *N*-(2-aminoethyl)-3-{{[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-indazol-1-yl]methyl}-*N*-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxamide, HCl salt)



5

Step 1 *tert*-butyl {2-[[[3-{{[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl]carbonyl](methyl)amino]ethyl} carbamate

Pyridine (0.061 mL, 0.756 mmol) was added to a suspension of 3-chloro-5-{{[5-chloro-1-(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methyl]-1*H*-1,2,3-benzotriazol-4-yl]oxy} benzonitrile (165 mg, 0.378 mmol) in DCM (10 mL) at 0°C, followed by the addition in a single charge of triphosgene (45 mg, 0.151 mmol) as a solid, and then by the addition of diisopropyl ethylamine (0.198 mL, 1.135 mmol). This suspension was allowed to stir at 0°C until a solution was achieved. 2-[(*tert*-Butoxycarbonyl)amino]-*N*-methylethanaminium chloride (120 mg, 0.567 mmol) was then added as a solid followed by diisopropyl ethylamine (0.198 mL, 1.135 mmol). The reaction mixture was allowed to warm to room temperature and after 10 minutes, the reaction mixture was diluted with dichloromethane (25 mL), washed with water (15 mL), and the aqueous layer was extracted with dichloromethane (25 mL). The combined organic fractions were dried (MgSO₄), filtered and concentrated. The resulting residue was purified by automated column chromatography on silica gel (12g), eluting with 50-100% EtOAc/hexanes to afford the title compound. LRMS (M+1) = 635.6.

Step 2: 2-[[[3-{{[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl]carbonyl](methyl)amino]ethanaminium chloride

Hydrochloric acid in dioxane (4 M, 5 mL) was added to *tert*-butyl {2-[[[3-{{[5-chloro-4-(3-chloro-5-cyanophenoxy)-1*H*-1,2,3-benzotriazol-1-yl]methyl}-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl]carbonyl](methyl)amino]ethyl} carbamate (620 mg, 974 μmol) at 0°C. After 2 hours, the reaction mixture was concentrated under reduced pressure and the residue crystallized from ethanol. ¹H NMR (DMSO-*d*₆) δ 8.68 (d, *J*=4.5Hz, 1H), 8.28 (d, *J*=8.0Hz, 1H), 7.97 (d, *J*=9.1Hz, 1H), 7.90 (s, 1H), 7.82 (m, 1H), 7.55 (m, 1H), 7.43 (m, 1H), 6.50 (s, 2H), 3.65 (m, 2H), 3.1 (m, 5H).

EXAMPLE 6

ECL Assay for Inhibition of HIV Reverse Transcriptase

An assay to determine the *in vitro* inhibition of HIV reverse transcriptase by compounds of the present invention was conducted as follows: HIV-1 RT enzyme (0.1 nM) was combined with inhibitor or DMSO (10%) in assay buffer (50 mM Tris-HCl, pH 7.8, 1 mM dithiothreitol, 6 mM MgCl₂, 80 mM KCl, 0.025% CHAPS, 0.1 mM EGTA), and the mixture preincubated for 30 minutes at room temperature in microtiter plates (Costar #3359). 100 μ L reaction mixtures were initiated with a combination of primer-template substrate (10 nM final concentration) and dNTPs (0.6 μ M dNTPs, 1.25 μ M BrdUTP). The heterodimeric nucleic acid substrate was generated by annealing the DNA primer pD500 (described in Shaw-Reid et al., *J. Biol. Chem.*, 278: 2777-2780; obtained from Integrated DNA Technologies) to t500, a 500 nucleotide RNA template created by *in vitro* transcription (see Shaw-Reid et al., *J. Biol. Chem.*, 278: 2777-2780). After 1 hour incubation at 37°C, reactions were quenched by 10 μ L of 1 N NaOH. Microtiter plates were incubated for an additional 30 minutes at room temperature and then neutralized with 10 μ L of 1 N HCl. A mixture of detection buffer containing ruthenylated anti-BrdU antibody and streptavidin coated magnetic beads were added to the plate and incubated at room temperature for 1.5 hours prior to quantification via electrochemiluminescence instrument. Representative compounds of the present invention exhibit inhibition of the reverse transcriptase enzyme in this assay. For example, the title compounds set forth above in Examples 1-3 (Note – Examples 4 and 5 are prodrugs) were tested in the assay and all were found to have IC₅₀ values as reported in Table B below.

Analogous assays were conducted substituting mutant HIV strains to determine the *in vitro* inhibition of compounds of the present invention against mutant HIV reverse transcriptase. In one strain the reverse transcriptase has the Y181C mutation and in the other strain the reverse transcriptase has the K103N mutation. The mutations were generated with the QUIKCHANGE site-directed mutagenesis kit (Stratagene). Representative compounds of the present invention exhibit inhibition of the reverse transcriptase enzyme in these assays. For example, the title compounds set forth above in Examples 1-3 were tested in the assays and were found to have IC₅₀ values set forth in Table B.

Table B

Example No.	ECL Assay (WT) IC ₅₀ (nM)	ECL Assay (K103N) IC ₅₀ (nM)	ECL Assay (Y181C) IC ₅₀ (nM)
1	0.35	0.57	0.60
2	0.6	1.7	1.9
3	0.24	0.41	0.44

1. WT = wild-type

2. All the IC₅₀ values reported in the table are based on the results of at least 2 runs.

EXAMPLE 7

Assay for inhibition of HIV replication

Assays for the inhibition of acute HIV-1 infection of T-lymphoid cells

(alternatively referred to herein as the "spread assay") were conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. The assays tested for inhibition of wild type HIV-1 and of HIV strains containing the Y181C or K103N mutation. Representative compounds of the present invention exhibit inhibition of HIV replication in the assay employing wild-type HIV-1 and the mutant strains. For example, the compounds set forth in Examples 1 to 4 were found to have CIC95 values of less than 10 micromolar in the assay employing the wild type strain. The compounds of Examples 1-4 exhibited CIC95 values of less than 10 micromolar in the assay employing the Y181C mutant strain. The compounds of Examples 1 to 3 were found to have CIC95 values as set forth in Table C below in the assay employing the wild type strain. Table C also reports the CIC95 values of the compounds of Examples 1-3 obtained in the assays employing the Y181C mutant strain and the K103N mutant strain.

Table C

Example No.	Spread (WT) CIC95 (nM) (10% FBS)	Spread (K103N) CIC95 (nM) (10% FBS)	Spread (Y181C) CIC95 (nM) (10% FBS)
1	13	17	69
2	9	23	77
3	4	5	24

1. WT = wild-type

2. All the CIC95 values reported in the table are based on the results of at least 2 runs.

EXAMPLE 8

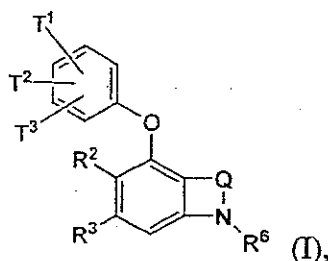
Cytotoxicity

Cytotoxicity was determined by microscopic examination of the cells in each well in the spread assay, wherein a trained analyst observed each culture for any of the following morphological changes as compared to the control cultures: pH imbalance, cell abnormality, cytostatic, cytopathic, or crystallization (i.e., the compound is not soluble or forms crystals in the well). The toxicity value assigned to a given compound is the lowest concentration of the compound at which one of the above changes is observed. Representative compounds of the present invention exhibit no cytotoxicity at concentrations of up to their CIC95 value in the spread assay of Example 7. In particular, the compounds set forth in Examples 1-3 exhibited no cytotoxicity at concentrations of up to 833 nanomolar.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims. All publications, patents and patent applications cited herein are incorporated
5 by reference in their entireties into the disclosure.

WHAT IS CLAIMED IS:

1. A compound of Formula I:

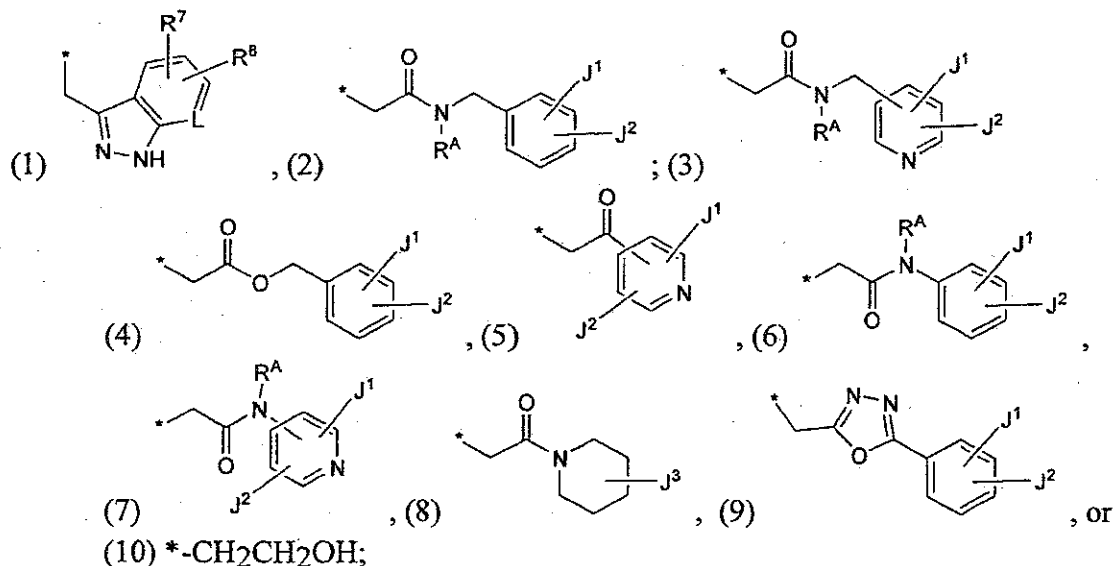


- 5 or a pharmaceutically acceptable salt thereof, wherein:

T¹ and T² and T³ are each independently H, C₁₋₄ alkyl, halogen, CN, CH=CH-CN, C(O)RA, or (CH₂)₁₋₂N(RA)RB;

- 10 R² and R³ are each independently selected from the group consisting of: (1) H, (2) halogen, (3) C(O)N(RA)RB, (4) C₁₋₄ alkyl, (5) CF₃, (6) O-C₁₋₄ alkyl, and (7) OCF₃;

R⁶ is:



- 20 J¹ and J² are each independently H, halogen, CN, NO₂, C₁₋₄ alkyl, CF₃, OH, O-C₁₋₄ alkyl, OCF₃, C(O)N(RA)RB, C(O)RA, CO₂RA, SO₂RA, or SO₂N(RA)RB;

J³ is H, halogen, CN, C₁₋₄ alkyl, OH, oxo, O-C₁₋₄ alkyl, CF₃, OCF₃, C(O)NH₂, C(O)N(H)CH₃, C(O)N(RA)RB, C(O)RA, CO₂RA, SO₂RA, or SO₂N(RA)RB;

L is N or N oxide;

Q is:

- 5 (1) -CH(R⁴)-,
- (2) -C(R⁴)=C(R⁵)-,
- (3) -CH(R⁴)-CH(R⁵)-,
- (4) -C(R⁴)=C(R⁵)-CH₂-,
- (5) -CH(R⁴)-CH(R⁵)-CH₂-,
- 10 (6) -C(R⁴)=C(R⁵)-CH=CH-,
- (7) -CH(R⁴)-CH(R⁵)-CH=CH-,
- (8) -C(R⁴)=C(R⁵)-CH₂CH₂-,
- (9) -CH(R⁴)-CH(R⁵)-CH₂CH₂-,
- (10) -C(R⁴)=N-,
- 15 (11) -N=C(R⁴)-, or
- (12) -N=N-;

wherein the left-most atom in Q is the atom directly attached to the fused benzo;

R⁴ and R⁵ are each independently selected from the group consisting of:

- 20 (1) H,
- (2) C₁₋₄ alkyl,
- (3) O-C₁₋₄ alkyl,
- (4) CF₃,
- (5) OCF₃, and
- 25 (6) halogen;

R⁷ and R⁸ are each independently selected from the group consisting of:

- (1) H,
- (2) OH,
- 30 (3) halogen,
- (4) CN,
- (5) NO₂,
- (6) C₁₋₄ alkyl,
- (7) O-C₁₋₄ alkyl,
- 35 (8) O(CH₂)₂₋₃N(R^A)R^B,
- (9) O(CH₂)₁₋₃C(O)R^A,
- (10) CF₃,

- (11) OCF_3 ,
- (12) $\text{O}(\text{CH}_2)_{1-2}\text{CF}_3$,
- (12) $\text{N}(\text{R}^{\text{C}})\text{R}^{\text{D}}$,
- (13) $\text{N}(\text{R}^{\text{A}})-(\text{CH}_2)_{2-3}-\text{N}(\text{R}^{\text{C}})\text{R}^{\text{D}}$, and
- (14) $\text{C}(\text{O})\text{N}(\text{R}^{\text{A}})\text{R}^{\text{B}}$;

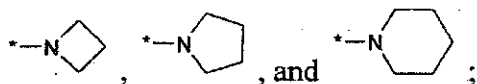
each R^A is independently H or C₁₋₄ alkyl;

each R^B is independently H or C₁₋₄ alkyl;

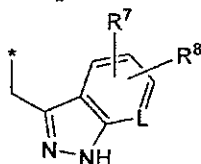
each R^C is independently H or C₁₋₄ alkyl;

each R^D is independently H or C₁₋₄ alkyl; and

- 15 alternatively and independently each pair of R^C and R^D together with the N atom to which they are both attached form a saturated monocyclic ring selected from the group consisting of:

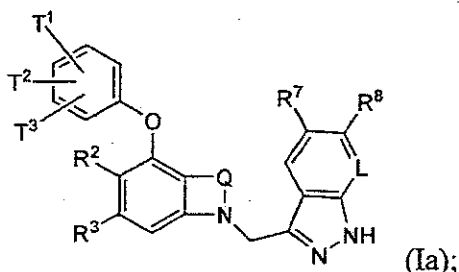


and provided that (A) when Q is $-N=C(R^4)-$ and R^4 is other than H, then R^6 is not



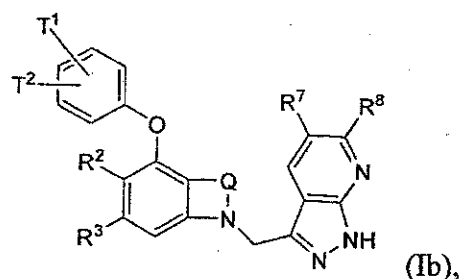
2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{N}-$, $-\text{C}(\text{Cl})=\text{N}-$, $-\text{N}=\text{CH}-$, or $-\text{N}=\text{N}-$.

3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of Formula Ia:



and provided that when Q is $-N=C(R^4)-$, then R^4 is H.

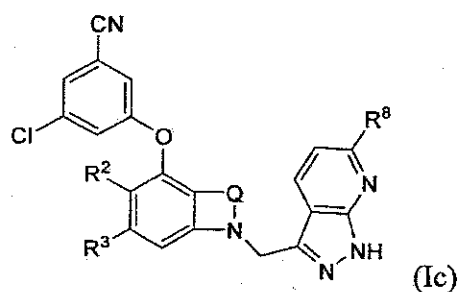
4. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of Formula Ib:



wherein T¹ and T² are each independently H, C₁₋₄ alkyl, halogen, CN, or CH=CH-CN;

and provided that when Q is -N=C(R⁴)-, then R⁴ is H.

5. A compound according to claim 4, or a pharmaceutically acceptable salt thereof, which is a compound of Formula Ic:



wherein:

Q is:

- (1) -CH=CH-,
- (2) -CH=CH-CH₂-,
- (3) -CH=CH-CH=CH-,
- (4) -CH₂CH₂-CH=CH-,
- (5) -CH=CH-CH₂CH₂-,
- (6) -C(R⁴)=N-,
- (7) -N=C(R⁴)-, or
- (8) -N=N-;

R² and R³ are each independently selected from the group consisting of H, Cl, Br, F and C₁₋₄ alkyl;

R⁴ is H, C₁₋₄ alkyl, Cl, Br, or F; and

R⁸ is H, OH, Cl, Br, F, CH₃, OCH₃, O(CH₂)₂₋₃NH₂, CF₃, OCF₃, OCH₂CF₃, NH₂, N(H)CH₃, N(CH₃)₂, C(O)NH₂, C(O)N(H)CH₃, or C(O)N(CH₃)₂.

6. A compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein:

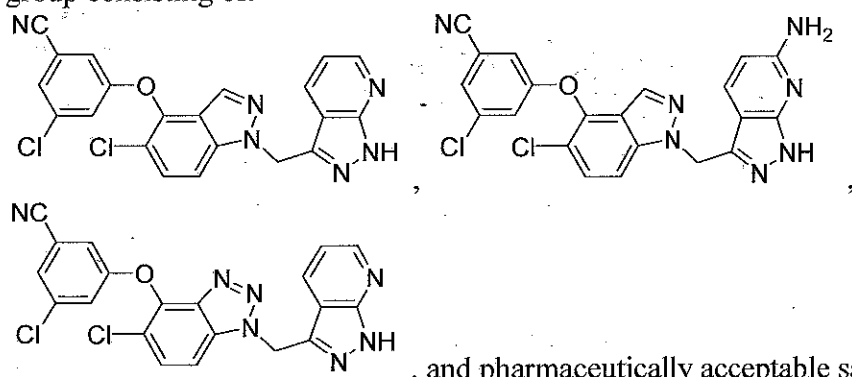
Q is -CH=N-, -C(Cl)=N-, -N=CH-, or -N=N-;

R² is Br or Cl;

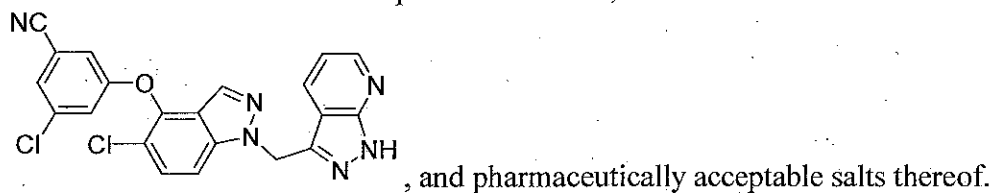
R³ is H; and

R⁸ is H or NH₂.

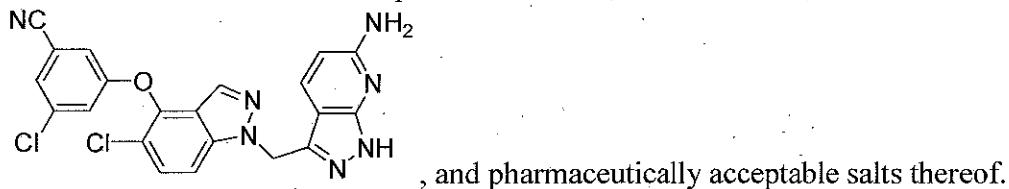
7. A compound according to claim 1, which is selected from the group consisting of:



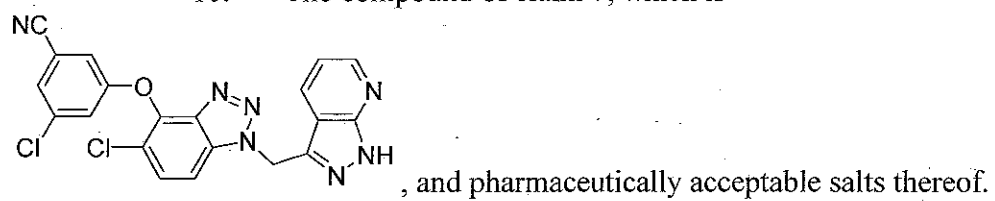
8. The compound of claim 7, which is



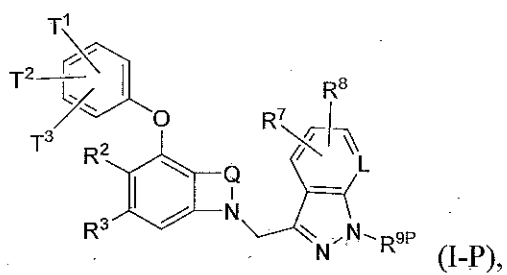
9. The compound of claim 7, which is



10. The compound of claim 7, which is



11. A compound of Formula I-P:



wherein:

T¹ and T² and T³ are each independently H, C₁₋₄ alkyl, halogen, CN, CH=CH-CN, C(O)RA, or (CH₂)₁₋₂N(RA)RB;

R² and R³ are each independently selected from the group consisting of:

- (1) H,
- (2) halogen,
- (3) C(O)N(RA)RB,
- (4) C₁₋₄ alkyl,
- (5) CF₃,
- (6) O-C₁₋₄ alkyl, and
- (7) OCF₃;

L is N or N oxide;

Q is:

- (1) -CH(R⁴)-,
- (2) -C(R⁴)=C(R⁵)-,
- (3) -CH(R⁴)-CH(R⁵)-,
- (4) -C(R⁴)=C(R⁵)-CH₂-,
- (5) -CH(R⁴)-CH(R⁵)-CH₂-,
- (6) -C(R⁴)=C(R⁵)-CH=CH-,
- (7) -CH(R⁴)-CH(R⁵)-CH=CH-,
- (8) -C(R⁴)=C(R⁵)-CH₂CH₂-,
- (9) -CH(R⁴)-CH(R⁵)-CH₂CH₂-,
- (10) -C(R⁴)=N-,
- (11) -N=CH-, or
- (12) -N=N-;

wherein the left-most atom in Q is the atom directly attached to the fused benzo;

R⁴ and R⁵ are each independently selected from the group consisting of:

- (1) H,
- (2) C₁₋₄ alkyl,
- (3) O-C₁₋₄ alkyl,
- (4) CF₃,
- (5) OCF₃, and
- (6) halogen;

R⁷ and R⁸ are each independently selected from the group consisting of:

- (1) H,
- (2) OH,
- (3) halogen,
- (4) CN,
- (5) NO₂,
- (6) C₁₋₄ alkyl,
- (7) O-C₁₋₄ alkyl,
- (8) O(CH₂)₂₋₃N(RA)RB,
- (9) O(CH₂)₁₋₃C(O)RA,
- (10) CF₃,
- (11) OCF₃,
- (12) O(CH₂)₁₋₂CF₃,
- (12) N(R^C)R^D,
- (13) N(RA)-(CH₂)₂₋₃-N(R^C)R^D, and
- (14) C(O)N(RA)RB;

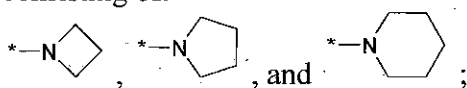
each RA is independently H or C₁₋₄ alkyl;

each RB is independently H or C₁₋₄ alkyl;

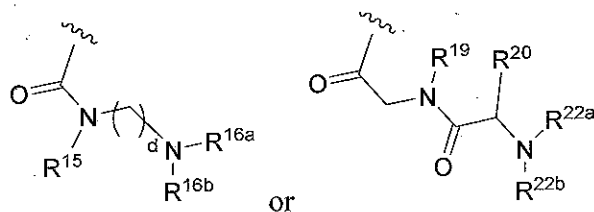
each R^C is independently H or C₁₋₄ alkyl;

each R^D is independently H or C₁₋₄ alkyl;

alternatively and independently each pair of R^C and R^D together with the N atom to which they are both attached form a saturated monocyclic ring selected from the group consisting of:



R^{9P} is PO(OH)O⁻·M⁺; PO(O⁻)₂·2M⁺; PO(O⁻)₂·M²⁺; or an acid salt of:



M⁺ is a pharmaceutically acceptable monovalent counterion;

M²⁺ is a pharmaceutically acceptable divalent counterion;

R¹⁵ is H or C₁₋₄ alkyl

R^{16a} and R^{16b} are each independently H or C₁₋₄ alkyl;

R¹⁹ is H or C₁₋₄ alkyl;

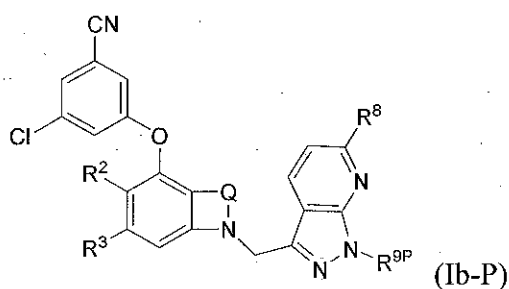
R²⁰ is H or C₁₋₄ alkyl;

R^{22a} and R^{22b} are each independently H or C₁₋₄ alkyl; and

d is an integer equal to 2, 3 or 4;

and provided that (A) when Q is -N=C(R⁴)-, then R⁴ is H.

12. A compound of Formula Ib-P:



wherein:

Q is:

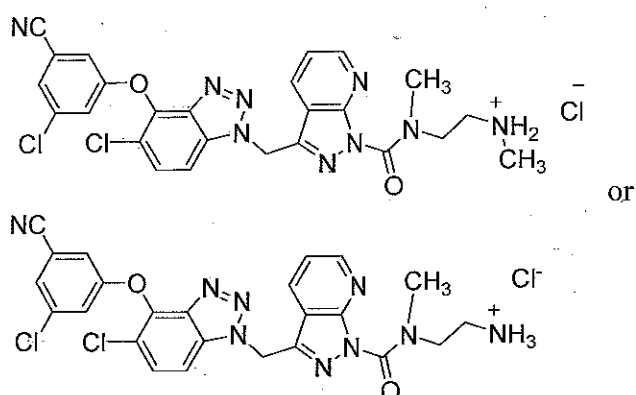
- (1) -CH=CH-,
- (2) -CH=CH-CH₂-,
- (3) -CH=CH-CH=CH-,
- (4) -CH₂CH₂-CH=CH-,
- (5) -CH=CH-CH₂CH₂-,
- (6) -C(R⁴)=N-,
- (7) -N=CH-, or
- (8) -N=N-;

R² and R³ are each independently selected from the group consisting of H, Cl, Br, F and C₁₋₄ alkyl;

R⁴ is H, C₁₋₄ alkyl, Cl, Br, or F; and

R⁸ is H, OH, Cl, Br, F, CH₃, OCH₃, O(CH₂)₂₋₃NH₂, CF₃, OCF₃, OCH₂CF₃, NH₂, N(H)CH₃, N(CH₃)₂, C(O)NH₂, C(O)N(H)CH₃, or C(O)N(CH₃)₂.

13. A compound according to claim 12, which is:



14. A pharmaceutical composition comprising (A) an effective amount of (i) a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, or (ii) a compound according to any one of claims 11 to 13 and (B) a pharmaceutically acceptable carrier.

15. Use of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 11 to 13, in the manufacture of a medicament for the treatment or prophylaxis of HIV-1 infection, or the treatment or prophylaxis or delay in the onset or progression of AIDS due to HIV-1.