TITLE OF THE INVENTION

HIV REVERSE TRANSCRIPTASE INHIBITORS

This application claims the benefit of U.S. Provisional Application Nos. 60/701,797 (filed July 22, 2005), 60/727,916 (filed October 18, 2005), and 60/790,705 (filed April 10, 2006), the disclosures of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

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

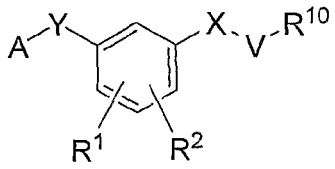
While each of the foregoing drugs is effective in treating HIV infection and AIDS, there remains a need to develop additional HIV antiviral drugs including additional RT inhibitors. A particular problem is the development of mutant HIV strains that are resistant to the known inhibitors. The use of

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.

The compounds described in this invention represent a novel structural class of non-nucleoside reverse transcriptase inhibitors.

SUMMARY OF THE INVENTION

The present invention is directed to certain substituted aromatic 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 of AIDS and/or ARC. More particularly, the present invention includes compounds of Formula Ic, and pharmaceutically acceptable salts thereof:



(Ic)

wherein:

R^1 and R^2 are independently selected from the group consisting of:

a) H,
b) C_{1-6} alkyl,
c) C_{3-6} cycloalkyl,
d) C_{1-3} fluoroalkyl,
e) NO_2,
f) halogen,
g) OR^3,
h) $O(CH_2)_sOR^3$,
i) CO_2R^3,
j) $(CO)NR^3R^4$,
k) $O(CO)NR^3R^4$,
l) $N(R^3)(CO)NR^3R^4$,
m) $N(R^3)(CO)R^4$,
n) $N(R^3)(CO)OR^3$,
o) $SO_2NR^3R^4$,
p) $N(R^3)\ SO_2R^4$,
q) $S(O)_mR^3$,

r) CN,

s) NR^3R^4,

t) $N(R^3)(CO)NR^3R^4$, and

u) $O(CO)R^3$;

A is aryl, C_{3-7} cycloalkyl, or heterocyclyl;

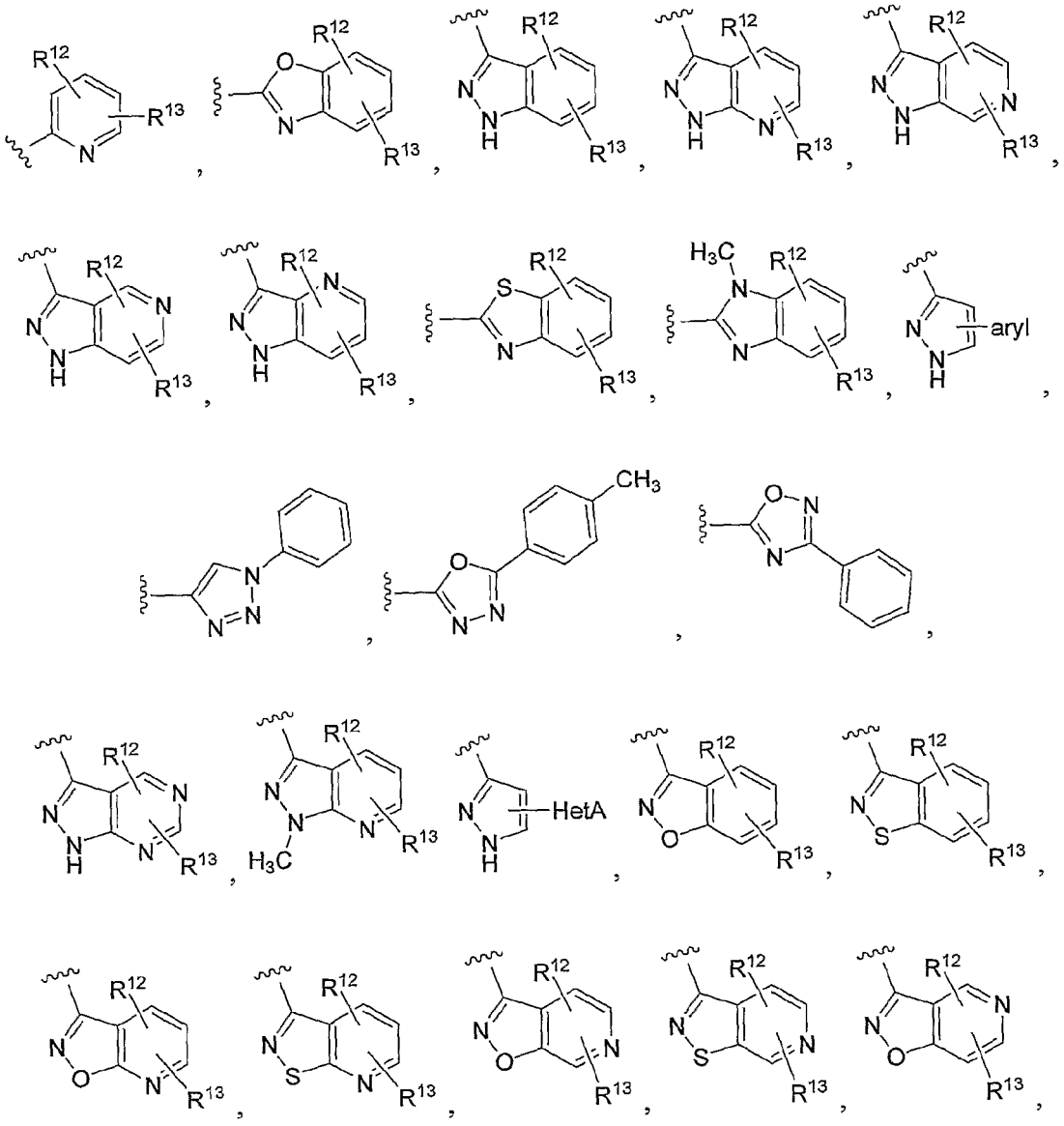
V is $-C(R^5R^6)-$;

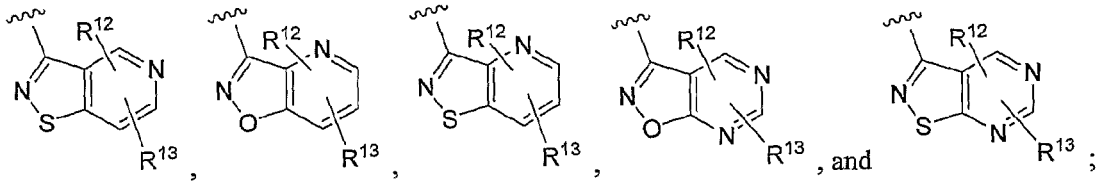
X is selected from the group consisting of -O-, -NH-, and $-C(R^5R^6)-$;

Y is selected from the group consisting of -O-, $-C(R^5R^6)-$, and $-S(O)_m-$;

R^5 and R^6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-3} fluoroalkyl, and OR^3;

R^{10} is a heterocyclyl selected from the group consisting of:





R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halogen, oxo, NO_2, CN, OR^3, $O(CH_2)_tCF_3$, CO_2R^3, $CONR^3R^4$, $O(CH_2)_tNR^3R^4$, $O(CH_2)_vCOR^3$, $S(O)_mR^3$, $SO_2NR^3R^4$, C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{3-6} cycloalkyl, and NR^3R^4;

R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-3} fluoroalkyl, and C_{3-6} cycloalkyl;

or, alternatively and optionally, when R^3 and R^4 are in an NR^3R^4 group, then:

(A) one of R^3 and R^4 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-3} fluoroalkyl, and C_{3-6} cycloalkyl, and the other of R^3 and R^4 is C_{1-6} alkyl substituted with O-C_{1-6} alkyl, $C(O)R^A$, CO_2R^A, $C(O)N(R^A)R^B$, SR^A, $S(O)R^A$, SO_2R^A, or $SO_2N(R^A)R^B$; or

(B) R^3 and R^4 together with the nitrogen atom to which they are both attached form

(i) a 4- to 7-membered, saturated or unsaturated monocyclic ring optionally containing 1 or 2 heteroatoms in addition to the nitrogen attached to R^3 and R^4 selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$, or

(ii) a 7- to 12-membered bicyclic ring system wherein each ring in (ii) is independent of, fused to, or bridged with the other ring and each ring is saturated or unsaturated, and wherein the bicyclic ring system optionally contains from 1 to 3 heteroatoms in addition to the nitrogen attached to R^3 and R^4 selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$, and

wherein the monocyclic ring or the bicyclic ring system is optionally substituted with from 1 to 3 substituents each of which is independently: (1) C_{1-6} alkyl, (2) C_{1-6} haloalkyl, (3) C_{1-6} alkyl substituted with OH, O-C_{1-6} alkyl, O-C_{1-6} haloalkyl, CN, NO_2, $N(R^A)R^B$, $C(O)N(R^A)R^B$, $C(O)R^A$, CO_2R^A, SR^A, $S(O)R^A$, SO_2R^A, or $SO_2N(R^A)R^B$, (4) O-C_{1-6} alkyl, (5) O-C_{1-6} haloalkyl, (6) OH, (7) oxo, (8) halogen, (9) CN, (10) NO_2, (11) $N(R^A)R^B$, (12) $C(O)N(R^A)R^B$, (13) $C(O)R^A$, (14) C(O)-C_{1-6} haloalkyl, (15) $C(O)OR^A$, (16) $OC(O)N(R^A)R^B$, (17) SR^A, (18) $S(O)R^A$, (19) $S(O)_2R^A$, (20) $S(O)_2N(R^A)R^B$, (21) $N(R^A)COR^B$, or (22) $N(R^A)SO_2R^B$ and

wherein each R^A is independently H or C_{1-6} alkyl, and each R^B is independently H or C_{1-6} alkyl;

HetA is heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, and pyrazinyl;

s is 1-5;

t is 2-3;

v is 1-2; and

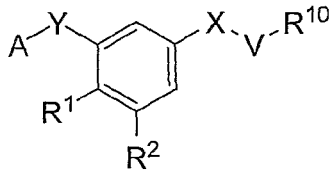
m, in each instance in which it appears, is independently selected from 0-2;
and provided that when X is -C(R^5R^6)-, then neither R^1 nor R^2 is OR^3.

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

DETAILED DESCRIPTION OF THE DISCLOSURE

The compounds of Formula Ic 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 assay set forth in Example 56 below, it is known that compounds of Formula I inhibit the RNA-dependent DNA polymerase activity of HIV-1 reverse transcriptase. Certain of the compounds of the present invention can also exhibit activity against drug resistant forms of HIV (e.g., mutant strains of HIV in which reverse transcriptase has a mutation at lysine 103 → asparagine (K103N) and/or tyrosine 181 → cysteine (Y181C)), and thus can exhibit decreased cross-resistance against currently approved antiviral therapies.

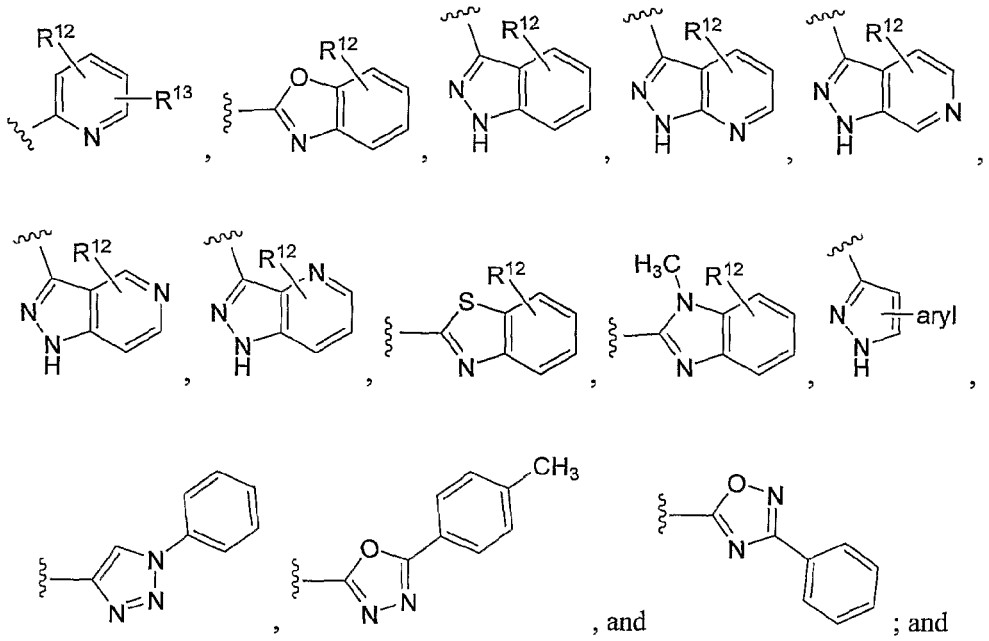
An embodiment of the present invention (alternatively referred to herein as "Embodiment E1") is a compound of Formula Ic, which is a compound of Formula Ic-1, or a pharmaceutically acceptable salt thereof:



(Ic-1) ;

wherein all variables are as originally defined above (i.e., as defined in the Summary of the Invention); and provided that when X is -C(R^5R^6)-, then neither R^1 nor R^2 is OR^3.

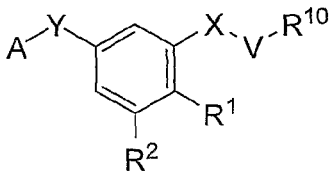
Another embodiment of the present invention (Embodiment E2) is a compound of Formula Ic-1, or a pharmaceutically acceptable salt thereof, wherein:
R^1 and R^2 are independently selected from the group consisting of hydrogen, halogen, and C_{1-6} alkyl;
A is aryl;
V is -C(R^5R^6)-;
X is selected from the group consisting of -O- and -NH-;
Y is selected from the group consisting of -O-, -CH_2-, and –$S(O)_m$-;
R^5 and R^6 are independently selected from the group consisting of hydrogen and C_{1-6} alkyl;
R^{10} is selected from the group consisting of:



R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halogen, oxo, NO_2, CN, OR^3, $O(CH_2)_tCF_3$, CO_2R^3, $CONR^3R^4$, $O(CH_2)_tNR^3R^4$, $O(CH_2)_vCOR^3$, $S(O)_mR^3$, $SO_2NR^3R^4$, C_{1-6} alkyl and C_{1-3} fluoroalkyl;

and all other variables are as originally defined.

Another embodiment of the present invention (Embodiment E3) is a compound of Formula Ic-2, or a pharmaceutically acceptable salt thereof:



(Ic-2);

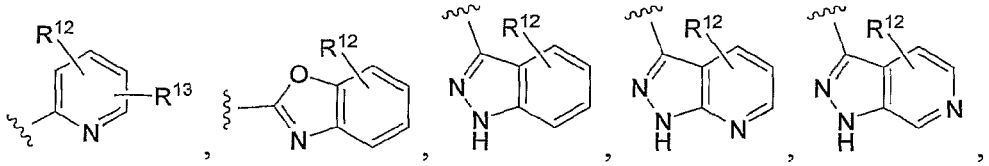
wherein all of the variables are as originally defined above; and provided that (i) when X is $-C(R^5R^6)-$, then neither R^1 nor R^2 is OR^3, and (ii) R^1 is other than H.

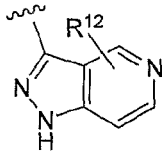
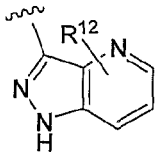
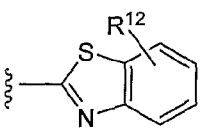
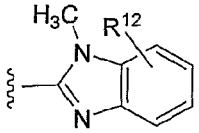
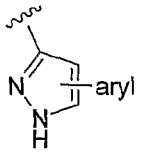
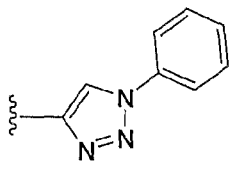
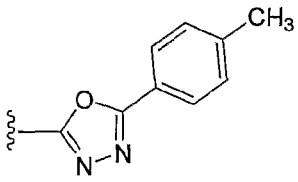
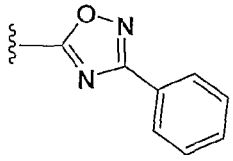
A preferred embodiment of the present invention (Embodiment E4) includes compounds of Formula Ic and pharmaceutically acceptable salts thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen, halogen, and C_{1-6} alkyl;

A is aryl;

R^{10} is selected from the group consisting of:



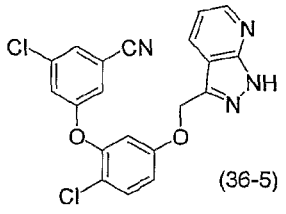
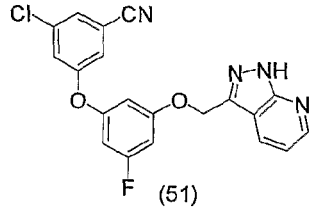
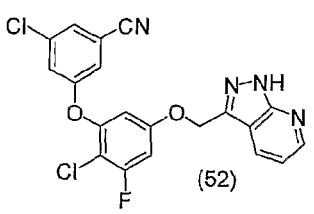
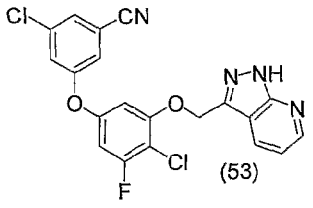
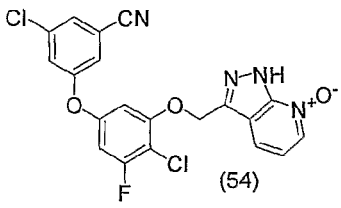









, and ; and

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halogen, oxo, NO_2, CN, OR^3, $O(CH_2)_tCF_3$, CO_2R^3, $CONR^3R^4$, $O(CH_2)_tNR^3R^4$, $O(CH_2)_vCOR^3$, $S(O)_mR^3$, $SO_2NR^3R^4$, C_{1-6} alkyl, C_{1-3} fluoroalkyl, and NR^3R^4; and all other variables are as originally defined for Formula I. A sub-embodiment is a compound of Formula Ic-1, or a pharmaceutically acceptable salt thereof, wherein all variables are as defined in Embodiment E4. Another sub-embodiment is a compound of Formula Ic-2, or a pharmaceutically acceptable salt thereof, wherein all variables are as defined in Embodiment E4; and provided that R^1 is halogen or C_{1-6} alkyl.

Another embodiment of the present invention (Embodiment E5) is a compound of Formula Ic, and pharmaceutically acceptable salts thereof, wherein V is $-CH_2-$; X is -O-; and Y is -O-; and all other variables are as defined in Embodiment E4. A sub-embodiment is a compound of Formula Ic-1, or a pharmaceutically acceptable salt thereof, wherein all variables are as defined in Embodiment E5. Another sub-embodiment is a compound of Formula Ic-2, or a pharmaceutically acceptable salt thereof, wherein all variables are as defined in Embodiment E5; and provided that R^1 is halogen or C_{1-6} alkyl.

Specific examples of compounds of Formula Ic, and pharmaceutically acceptable salts thereof, include


(36-5)

(51)

(52)

(53)

(54)

, and .

The compounds represented by the structures shown above have the following names:

(36-5) 3-chloro-5-[2-chloro-5-(1H-pyrazolo[3,4-b]pyridin-3-ylmethoxy)phenoxy]benzonitrile;

(51) 3-{5-[(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-3-fluorophenoxy}-5-chlorobenzonitrile);

(52) 3-{5-[(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chloro-3-fluorophenoxy}-5-chlorobenzonitrile;

(53) 3-{5-[(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-4-chloro-3-fluorophenoxy}-5-chlorobenzonitrile; and

(54) 3-{5-[(7-oxo-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-4-chloro-3-fluorophenoxy}-5-chlorobenzonitrile.

Each of the foregoing compounds individually, and the pharmaceutically acceptable salts thereof, is an aspect of the present invention.

Another embodiment of the present invention (Embodiment E6) is a compound of Formula Ic, or a pharmaceutically acceptable salt thereof, wherein:

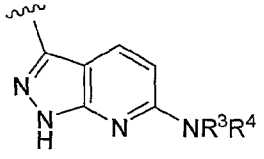
R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, and C_{1-4} alkyl;

A is phenyl optionally substituted with from 1 to 3 substituents each of which is independently halogen, C_{1-4} alkyl, or CN;

V is $-CH_2-$;

X is -O-;

Y is -O-;

R^{10} is ;

one of R^3 and R^4 is H, C_{1-4} alkyl, or C_{3-6} cycloalkyl, and the other of R^3 and R^4 is H, C_{1-4} alkyl, or C_{1-4} alkyl substituted with O-C_{1-4} alkyl, $C(O)R^A$, CO_2R^A, $C(O)N(R^A)R^B$, or SO_2R^A;

or alternatively R^3 and R^4 together with the nitrogen atom to which they are both attached form a 4- to 7-membered, saturated monocyclic ring optionally containing 1 heteroatom in addition to the nitrogen attached to R^3 and R^4 selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$, wherein the monocyclic ring is optionally substituted with 1 or 2 substituents each of which is independently: (1) C_{1-4} alkyl, (2) CF_3, (3) $(CH_2)_{1-2}T$ wherein T is OH, O-C_{1-4} alkyl, OCF_3, $N(R^A)R^B$, $C(O)N(R^A)R^B$, $C(O)R^A$, CO_2R^A, or SO_2R^A, (4) O-C_{1-4} alkyl, (5) OCF_3, (6) OH, (7) oxo, (8) halogen, (9) $C(O)N(R^A)R^B$, (10) $C(O)R^A$, (11) C(O)-CF_3, (12) $C(O)OR^A$, or (13) $S(O)_2R^A$;

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

each R^B is independently H or C_{1-4} alkyl. A sub-embodiment is a compound of Formula Ic-1, or a pharmaceutically acceptable salt thereof, wherein all variables are as defined in

Embodiment E6. Another sub-embodiment is a compound of Formula Ic-2, or a pharmaceutically acceptable salt thereof, wherein all variables are as defined in Embodiment E6; and provided that R^1 is halogen or C_{1-4} alkyl.

Another embodiment of the present invention (Embodiment E7) is a compound of Formula Ic, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chlorophenoxy}-5-chlorobenzonitrile,

3-chloro-5-(2-chloro-5-{[6-methylamino)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)benzonitrile,

3-chloro-5-(2-chloro-5-{[6-dimethylamino)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)benzonitrile,

3-chloro-5-[2-chloro-5-({6-[(2-methoxyethyl)(methyl)amino]-1H-pyrazolo[3,4-b]-pyridin-3-yl}methoxy)phenoxy)benzonitrile ,

3-chloro-5-(2-chloro-5-[(6-morpholin-4-yl-1H-pyrazolo[3,4-b]-pyridin-3-yl)methoxy]phenoxy)benzonitrile,

N2-(3-{[4-chloro-3-(3-chloro-5-cyanophenoxy)phenoxy]methyl}-1H-pyrazolo[3,4-b]pyridin-6-yl)-N2-methylglycinamide,

3-chloro-5-(2-chloro-5-{[6-(3-methoxyazetidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)benzonitrile,

3-chloro-5-(2-chloro-5-{[6-(azetidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)benzonitrile,

3-chloro-5-{2-chloro-5-[(6-piperazin-1-yl-1H-pyrazolo[3,4-b]-pyridin-3-yl)methoxy]phenoxy}benzonitrile,

3-(5-{[6-(3-aminopyrrolidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}-2-chlorophenoxy)-5-chlorobenzonitrile,

3-[5-({6-[3-(aminomethyl)azetidin-1-yl]-1H-pyrazolo[3,4-b]-pyridin-3-yl}methoxy)-2-chlorophenoxy]-5-chlorobenzonitrile,

3-(5-{[6-(3-aminoazetidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}-2-chlorophenoxy)-5-chlorobenzonitrile,

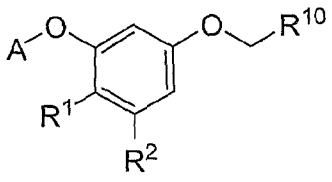
3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chloro-3-fluorophenoxy}-5-chlorobenzonitrile,

3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-3-fluorophenoxy}-5-chlorobenzonitrile, and

3-{5-[(6-amino-1H-pyrazolo[3,4-b]pyridin-3-yl)methoxy]-4-chloro-3-fluorophenoxy}-5-chlorobenzonitrile.

Each of the foregoing compounds individually, and the pharmaceutically acceptable salts thereof, is an aspect of the present invention.

Another embodiment of the present invention (Embodiment E8) is a compound of Formula Ic-1a, or a pharmaceutically acceptable salt thereof:



(Ic-1a);

wherein all of the variables are as defined in Embodiment E6.

A class of compounds of the present invention (Class C1) includes compounds of Formula Ic and their pharmaceutically acceptable salts, wherein all of the variables and provisos are as originally defined above, except that A is aryl optionally substituted with from 1 to 3 substituents each of which is independently halo, C_1-C_6 alkyl, CF_3, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -NO_2, -CN, -OH, -O-(C_1-C_6 alkyl), C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -S(O)$_{0-2}$(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-S(O)$_{0-2}$(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -C(=NH)NH_2, -O(C_1-C_6 alkylene)CF_3, -C(O)(C_1-C_6 alkyl), -C(O)H, -OC(O)(C_1-C_6 alkyl), -(C_1-C_6 alkylene)O(C_1-C_6 alkyl), -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -C(O)$_2$H, -C(O)$_2$(C_1-C_6 alkyl), -(C_1-C_6 alkylene)C(O)$_{1-2}$(C_1-C_6 alkyl), -NHC(O)O-(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl)NHC(O)NH(C_1-C_6 alkyl), -$NHSO_2NH_2$, -NH(C_1-C_6 alkyl)$NHSO_2$(C_1-C_6 alkyl), -$NHSO_2$(C_1-C_6 alkyl), -(C_1-C_6 alkyl)$NHSO_2$(C_1-C_6 alkyl), phenyl, or benzyl.

A sub-class of Class C1 (SC1) includes compounds of Formula Ic and their pharmaceutically acceptable salts, wherein all of the variables are as originally defined for Class C1, except that A is phenyl or naphthyl, wherein the phenyl or naphthyl is optionally substituted with from 1 to 3 substituents each of which is independently Cl, Br, F, CH_3, CF_3, NH_2, -NH(CH_3), -N(CH_3)$_2$, -CN, -OH, -OCH_3, cyclohexyl, ethenyl, ethynyl, -SCH_3, -S(O)$_2CH_3$, -(CH$_2$)$_{1-2}$-SCH_3, -(CH$_2$)$_{1-2}$-S(O)$_2CH_3$, -NHC(O)CH_3, -O(CH$_2$)$_{1-2}CF_3$, -C(O)CH_3, -OC(O)CH_3, -(CH$_2$)$_{1-2}OCH_3$, -C(O)NH_2, -C(O)NHCH_3, -C(O)N(CH$_3$)$_2$, -C(O)$_2$H, -C(O)$_2CH_3$, -(CH$_2$)$_{1-2}$C(O)$_2CH_3$, -NHC(O)OCH_3, -NH(CH_3)NHC(O)NH(CH_3), phenyl, or benzyl.

Other classes of the present invention are compounds of Formula Ic and their pharmaceutically acceptable salts, wherein all of the variables (and applicable provisos) are as defined in Embodiments E1 to E6 respectively, except that A is an optionally substituted aryl as defined in Class C1. Other sub-classes of the present invention are compounds of Formula Ic and their pharmaceutically acceptable salts, wherein all of the variables (and applicable provisos) are as defined in Embodiments E1 to E6 respectively, except that A is an optionally substituted phenyl or optionally substituted naphthyl as defined in sub-class SC1.

The present invention also encompasses a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of Formula Ic or a pharmaceutically acceptable crystal form or hydrate thereof. A preferred embodiment is a pharmaceutical composition of the compound of Formula Ic, comprising, in addition, a second agent.

The compounds of the present invention may have chiral centers, e.g. one chiral center (providing for two stereoisomers, (R) and (S)), or two chiral centers (providing for up to four stereoisomers, (R,R), (S,S), (R,S), and (S,R)). This invention includes all of the optical isomers and mixtures thereof. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

Tautomers of compounds defined by Formula Ic are also included within the scope of the present invention. For example, compounds including carbonyl $-CH_2C(O)-$ groups (keto forms) may undergo tautomerism to form hydroxyl $-CH=C(OH)-$ groups (enol forms). Both keto and enol forms are included within the scope of the present invention.

In addition compounds with carbon-carbon double bonds may occur in Z- and E- forms with all isomeric forms of the compounds being included in the present invention.

Another embodiment of the present invention is a compound of Formula Ic, or a pharmaceutically acceptable salt thereof, as originally defined or as defined in any of the foregoing embodiments, sub-embodiments, aspects, 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 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. A compound or salt of 100% purity is one which is free of detectable impurities as determined by one or more standard methods 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.

Abbreviations employed herein include the following: AIDS = acquired immunodeficiency syndrome; BOC (or Boc) = t-butyloxycarbonyl; DCM = dichloromethane; dGTP = deoxyguanosine triphosphate; DIEA = diisopropylethylamine; DMAP = dimethylaminopyridine; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; dNTP = deoxynucleoside triphosphate; EDC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; EGTA = ethylene glycol bis(2-aminoethyl ether)-N,N,N',N'-tetraacetic acid; EtOAc = ethyl acetate; HOBT = 1-hydroxybenzotriazole hydrate; HRMS = high resolution mass spectroscopy; LC = liquid chromatography; MeOH = methanol; MTBE = methyl t-butyl ether; NBS = N-bromosuccinimide; NMP = N-methyl pyrrolidinone; NMR = nuclear magnetic resonance; TBAF = tetrabutylammonium fluoride; TEA = triethylamine; Tf = trifluoromethanesulfonic (triflic); TFA = trifluoroacetic acid; THF = tetrahydrofuran; TMS = trimethylsilyl; UV = ultraviolet.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of Compound Ic, or a 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 Compound Ic, or a 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, and HIV integrase inhibitors.

(e) A pharmaceutical combination which is (i) a compound of Formula Ic, or a 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 the compound of Formula I and the anti-HIV agent are each employed in an amount that renders the combination effective for inhibiting HIV reverse transcriptase, for treating or prophylaxis of infection by HIV, or for treating, prophylaxis of, or delaying the onset 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, and HIV integrase inhibitors.

Additional embodiments of the invention include the pharmaceutical compositions and combinations set forth in (a)-(f) above, wherein the compound of the present invention employed therein is a compound defined in one of the embodiments, sub-embodiments, aspects, classes, or sub-classes described above. In all of these embodiments, sub-embodiments, aspects, classes and sub-classes, the compound can optionally be used in the form of a pharmaceutically acceptable salt.

The present invention also includes a method for inhibiting HIV reverse transcriptase, for treating or prophylaxis of HIV infection, or for treating, prophylaxis of, or delaying the onset of AIDS, which comprises administering to a subject in need thereof an effective amount of a compound of Formula Ic, or a pharmaceutically acceptable salt thereof.

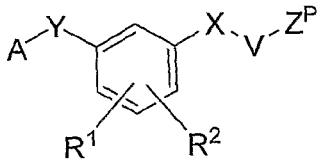
Other embodiments of the method of the present invention include those in which the compound of Formula Ic administered to the subject is the compound of Formula I, or a pharmaceutically acceptable salt thereof, as defined in the compound embodiments, sub-embodiments, aspects, classes and sub-classes set forth above.

The present invention also includes a compound of Formula Ic, or a 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) inhibiting HIV reverse transcriptase, (b) treating or prophylaxis of infection by HIV, or (c) treating, prophylaxis of, or delaying the onset of AIDS. In these uses, the compound of

Formula Ic is as originally set forth and defined above. In these uses, the compound of Formula Ic can optionally be employed in combination with one or more anti-HIV agents selected from HIV antiviral agents, anti-infective agents, and immunomodulators. Embodiments of the uses of the present invention include those in which the compound of Formula Ic is as defined in the embodiments, sub-embodiments, aspects, classes, and sub-classes set forth above.

The present invention also includes prodrugs of the compounds of Formula Ic. The term "prodrug" refers to a derivative of a compound of Formula Ic, or a pharmaceutically acceptable salt thereof, which is converted in vivo into Compound Ic. Prodrugs of compounds of Formula Ic 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). The prodrug can be, for example, a derivative of a 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.

An embodiment of the present invention (alternatively referred to as "Embodiment PD1") is a compound of Formula I-P:



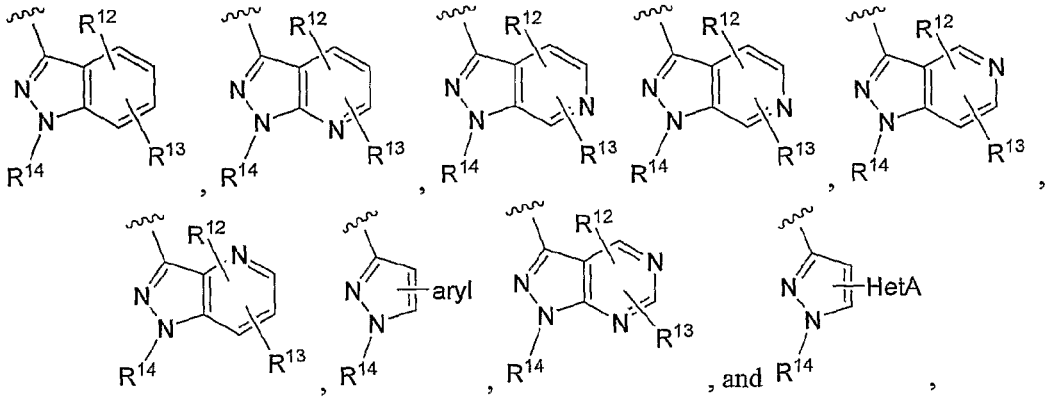
(I-P)

wherein:

R^1, R^2, A, V, X and Y and the variables defined therein (i.e., R^3, R^4, R^5, R^6, R^A, R^B and the integers s, t, v and m) have the same definitions as originally set forth above for compounds of Formula Ic;

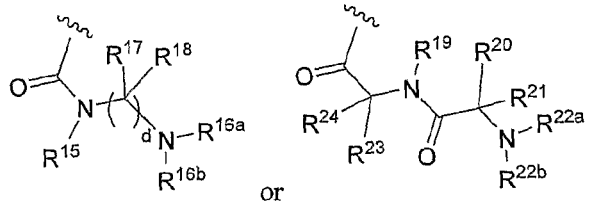
Z^P is R^{10*};

R^{10*} is a heterocycle selected from the group consisting of:



R^{12}, R^{13}, and HetA are as defined in Claim 1;

R^{14} is $PO(OH)O^-$ M^+; $PO(O^-)_2 \cdot 2M^+$; $PO(O^-)_2 \cdot M^{+2}$; or an acid salt of:



or ;

M^+ is a pharmaceutically acceptable monovalent counterion;

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

R^{15} is H, C_{1-6} alkyl, $(CH_2)_{2-3}CF_3$, AryA, or HetB;

R^{16a} and R^{16b} are each independently H, C_{1-6} alkyl, $(CH_2)_{2-3}CF_3$, AryA, or HetB;

each R^{17} is independently H or C_{1-6} alkyl;

each R^{18} is independently H or C_{1-6} alkyl;

alternatively, an R^{17} together with the R^{18} attached to the same carbon atom form a 5- or 6-membered, saturated monocyclic ring optionally containing a heteroatom, wherein the optional heteroatom is selected from N, O and S, where the S is optionally oxidized to S(O) or $S(O)_2$;

R^{19} is H or C_{1-6} alkyl;

R^{20} is H or C_{1-6} alkyl;

R^{21} is H or C_{1-6} alkyl;

R^{22a} and R^{22b} are each independently H, C_{1-6} alkyl, $(CH_2)_{2-3}CF_3$, AryA, or HetB;

R^{23} is H or C_{1-6} alkyl;

R^{24} is H or C_{1-6} alkyl;

AryA is phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently Cl, Br, F, CH_3, CF_3, NH_2, $-NH(CH_3)$, $-N(CH_3)_2$, -CN, -OH, $-OCH_3$, cyclohexyl, ethenyl, ethynyl, $-SCH_3$, $-S(O)_2CH_3$, $-(CH_2)_{1-2}-SCH_3$, $-(CH_2)_{1-2}-S(O)_2CH_3$, $-NHC(O)CH_3$, $-O(CH_2)_{1-2}CF_3$, $-C(O)CH_3$, $-OC(O)CH_3$, $-(CH_2)_{1-2}OCH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)_2H$, $-C(O)_2CH_3$, $-(CH_2)_{1-2}C(O)_2CH_3$, $-NHC(O)OCH_3$, $-NH(CH_3)NHC(O)NH(CH_3)$, phenyl, or benzyl; and

HetB is a 5- or 6-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently Cl, Br, F, CH_3, CF_3, NH_2, -NH(CH_3), -N(CH_3)$_2$, -CN, -OH, -OCH_3, cyclohexyl, ethenyl, ethynyl, -SCH_3, -S(O)$_2$$CH_3$, -($CH_2$)$_{1-2}$-S$CH_3$, -($CH_2$)$_{1-2}$-S(O)$_2$$CH_3$, -NHC(O)$CH_3$, -O($CH_2$)$_{1-2}$$CF_3$, -C(O)$CH_3$, -OC(O)$CH_3$, -($CH_2$)$_{1-2}OCH_3$, -C(O)$NH_2$, -C(O)NH$CH_3$, -C(O)N($CH_3$)$_2$, -C(O)$_2$H, -C(O)$_2$$CH_3$, -($CH_2$)$_{1-2}$C(O)$_2$$CH_3$, -NHC(O)O$CH_3$, -NH($CH_3$)NHC(O)NH($CH_3$), phenyl, or benzyl.

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

V is -CH_2-;

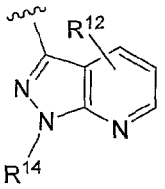
X is -O-;

Y is -O-;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, and C_{1-4} alkyl;

A is phenyl optionally substituted with from 1 to 3 substituents each of which is independently halogen, C_{1-4} alkyl, or CN;

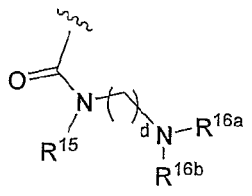
R^{10*} is:



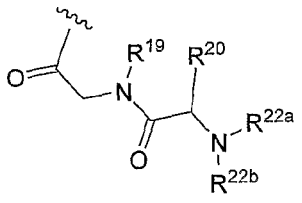
;

R^{12} is selected from the group consisting of hydrogen, halogen, oxo, NO_2, CN, OR^3, O(CH_2)$_t$$CF_3$, CO_2R^3, $CONR^3R^4$, O(CH_2)$_t$$NR^3R^4$, O($CH_2$)$_v$$COR^3$, S(O)$_m$$R^3$, $SO_2NR^3R^4$, C_{1-6} alkyl, C_{1-3} fluoroalkyl, and NR^3R^4.

R^{14} is PO(OH)O$^-$ M^+; PO(O$^-$)$_2$ $\cdot 2M^+$; PO(O$^-$)$_2$ $\cdot M^{+2}$; or an acid salt of:



or



;

M^+ is a pharmaceutically acceptable monovalent counterion;

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

R^{15} is H or C_{1-4} alkyl;

R^{16a} and R^{16b} are each independently H or C_{1-4} alkyl;

R^{19} is H or C_{1-4} alkyl;

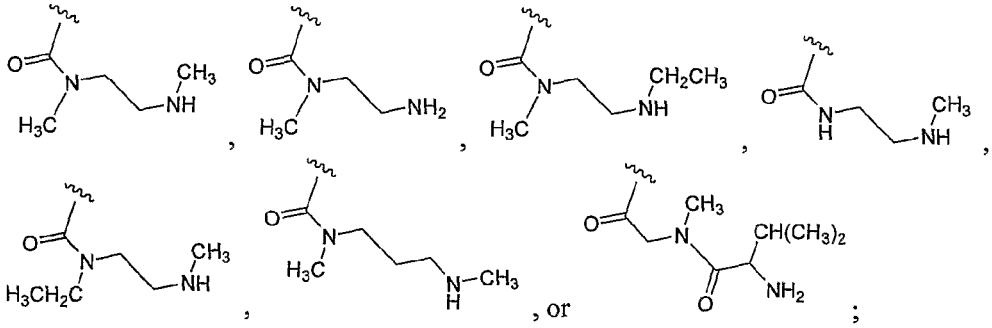
R^{20} is H or C_{1-4} alkyl; and

R^{22a} and R^{22b} are each independently H or C_{1-4} alkyl;

and all other variables are as defined in Embodiment PD1.

Another embodiment of the present invention (Embodiment PD3) is a compound of Formula I-P, wherein:

R^{14} is an acid salt of:



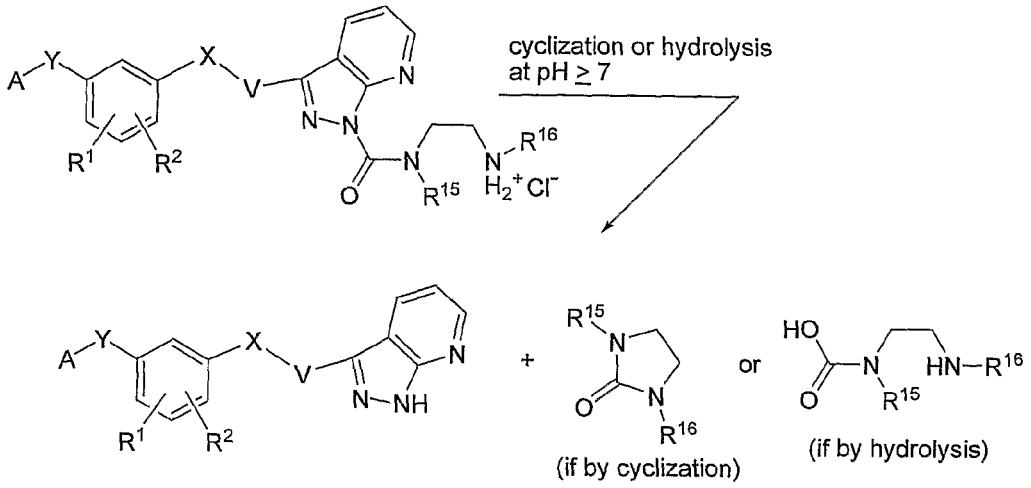
and all other variables are as defined in Embodiment PD2.

A class of the preceding embodiment (Class C8) includes compounds of Formula I-P, wherein the acid salt in the definition of R^{14} is a hydrochloride salt; and all other variables are as defined in Embodiment PD3.

Pharmaceutically acceptable monovalent counterions (M^+) suitable for use in the prodrugs of the invention described in Embodiments PD1 to PD3 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 counterion (M^{+2}) include 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 PD1 to PD3 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.), fluoroalkylcarboxlic acids (e.g., trifluoroacetic acid), arylcarboxylic acids (benzoic acid), alkylsuflonic 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 PD1 to PD3 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:



As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbon atoms. Commonly used abbreviations for alkyl groups are used throughout the specification, e.g. methyl may be represented by "Me" or CH_3, ethyl may be represented by "Et" or CH_2CH_3, propyl may be represented by "Pr" or $CH_2CH_2CH_3$, butyl may be represented by "Bu" or $CH_2CH_2CH_2CH_3$, etc. "C_{1-6} alkyl" (or "C_1-C_6 alkyl") for example, means linear or branched chain alkyl groups, including all isomers, having the specified number of carbon atoms. C_{1-6} alkyl includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. "C_{1-4} alkyl" means n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

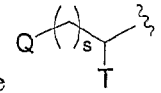
The term "alkylene" refers to both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbons, and having two terminal end chain attachments (i.e., the alkylene is divalent). For illustration, the term "unsubstituted A-C_4 alkylene-B" includes A-CH_2-CH_2-CH_2-CH_2-B, A-CH[$CH(CH_3)_2$]-B, A-$C(CH_3)(CH_2CH_3)$-B, A-$CH(CH_2CH_2CH_3)$-B, A-$CH(CH_3)CH(CH_3)$-B, A-$C(CH_3)_2CH_2$)-B, and A-$CH_2C(CH_3)_2$-B. The term "alkoxy" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

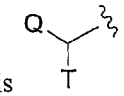
The term "alkenyl" includes both branched and straight chain unsaturated hydrocarbon groups containing at least two carbon atoms joined by a double bond. The alkene ethylene is represented, for example, by "CH_2CH_2" or alternatively, by "H_2C=CH_2", and the term "ethenyl" can be represented by "-$CHCH_2$" or "-CH=CH_2". "C_{2-5} alkenyl" (or "C_2-C_5 alkenyl") for example, means linear or branched chain alkenyl groups having from 2 to 5 carbon atoms and includes all of the pentenyl isomers, all of the butenyl isomers (e.g., 1-butenyl, 2-butenyl, 3-butenyl, 2,2-dimethylethenyl, and 2-methyl-1-propenyl), 1-propenyl, 2-propenyl, and ethenyl (or ethylenyl). Similar terms such as "C_{2-3} alkenyl" have an analogous meaning.

The term "alkynyl" includes both branched and straight chain unsaturated hydrocarbon groups containing at least two carbon atoms joined by a triple bond. The alkyne acetylene (or ethyne) is represented, for example, by "CHCH" or alternatively, by "HC≡CH", and the term "ethynyl" can be

represented by "-CCH" or "-C≡CH". "C_{2-5} alkynyl" (or "C_2-C_5 alkynyl") for example, means linear or branched chain alkynyl groups having from 2 to 5 carbon atoms and includes all of the pentynyl isomers, all of the butynyl isomers, 1-propynyl, 2-propynyl, and ethynyl (or acetylenyl). Similar terms such as "C_{2-3} alkynyl" have an analogous meaning.

Unless otherwise specifically noted as only "unsubstituted" or only "substituted", alkyl, alkylene, alkoxy, alkenyl and alkynyl groups are unsubstituted or substituted with 1 to 3 substituents on each carbon atom, with halo, C_1-C_{20} alkyl, CF_3, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, $-O(C_1$-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl) $S(O)_{0-2}$-, (C_0-C_6 alkyl)$S(O)_{0-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, $-O(C_1$-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6 alkyl)$O(C_1$-C_6 alkyl)-, (C_0-C_6 alkyl)$C(O)_{1-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, $-NH(C_1$-C_6 alkyl)NHC(O)NH(C_1-C_6 alkyl), $-NHSO_2NH_2$, $-NH(C_1$-C_6 alkyl)$NHSO_2(C_1$-C_6 alkyl), -(C_0-C_6 alkyl)$NHSO_2(C_1$-C_6 alkyl), aryl, aralkyl, heterocycle, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

The term "C_0" as employed in expressions such as "C_{0-6} alkyl" means a direct covalent bond. If C_0 necessarily results in an open valence, then it is assumed the valence is satisfied by an H. For example, (C_0-C_6 alkyl)OC(O)- becomes HOC(O)- for C_0. Similarly, when an integer defining the presence of a certain number of atoms in a group is equal to zero, it means that the atoms adjacent thereto are connected directly by a bond. For example, in the structure 

, wherein s is an integer equal to zero, 1 or 2, the structure is 

when s is zero.

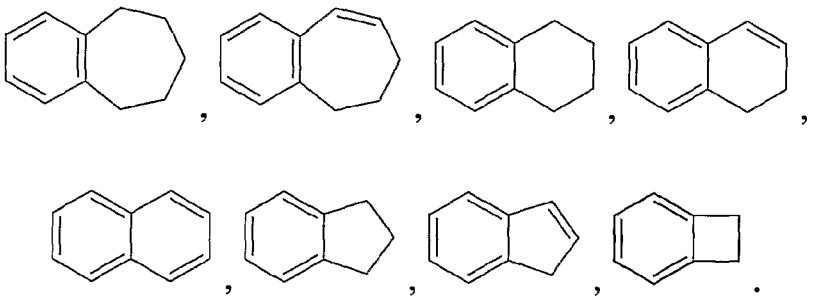
The term "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") means a cyclic ring of an alkane having three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl). The terms "C_{3-7} cycloalkyl", "C_{3-6} cycloalkyl", "C_{5-7} cycloalkyl" and the like have analogous meanings.

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

The term "C_{1-6} haloalkyl" (which may alternatively be referred to as "C_1-C_6 haloalkyl" or "halogenated C_1-C_6 alkyl") means a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "C_{1-4} haloalkyl" has an analogous meaning. The term "C_{1-3} fluoroalkyl" has an analogous meaning where the halogen substituents are restricted to fluoro, and where the number of fluoro atoms can be, for example one to seven, depending on the number of carbon atoms. Suitable fluoroalkyls include the series $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to (i) a C_3 to C_8 monocyclic, saturated or unsaturated ring or (ii) a C_7 to C_{12} bicyclic saturated or unsaturated ring system. Each ring in (ii) is either independent

of, or fused to, or bridged with, the other ring, and each ring is saturated or unsaturated. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound. The fused bicyclic carbocycles are a subset of the carbocycles; i.e., the term "fused bicyclic carbocycle" generally refers to a C_7 to C_{10} bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms are shared by each of the rings in the ring system. A fused bicyclic carbocycle in which one ring is saturated and the other is saturated is a saturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is saturated is an unsaturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is unsaturated is an unsaturated ring system. Saturated carbocyclic rings are also referred to as cycloalkyl rings, e.g., cyclopropyl, cyclobutyl, etc. Unless otherwise noted, carbocycle is unsubstituted or substituted with C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, halogen, NH_2 or OH. A subset of the fused bicyclic unsaturated carbocycles are those bicyclic carbocycles in which one ring is a benzene ring and the other ring is saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include the following:



The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. Suitable aryl groups include phenyl, naphthyl, and biphenylenyl.

The term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") broadly refers to (i) a stable 4- to 8-membered, saturated or unsaturated monocyclic ring, or (ii) a stable 7- to 12-membered bicyclic ring system, wherein each ring in (ii) is independent of, or fused to, or bridged with, the other ring or rings and each ring is saturated or unsaturated, and the monocyclic ring or bicyclic ring system contains one or more heteroatoms (e.g., from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) selected from N, O and S and a balance of carbon atoms (the monocyclic ring typically contains at least one carbon atom and the ring systems typically contain at least two carbon atoms); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. Unless otherwise specified, the heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Unless otherwise specified, when the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

Unless otherwise specifically noted as only "unsubstituted" or only "substituted", cycloalkyl, aryl and heterocycle groups are unsubstituted or substituted. As used herein, the terms "substituted C_{3-8} cycloalkyl", "substituted aryl" and "substituted heterocycle" are intended to include the cyclic group containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Preferably, the substituents are selected from the group which includes, but is not limited to, halo, C_1-C_{20} alkyl, CF_3, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, $-O(C_1$-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl) $S(O)_{0-2}$-, aryl-$S(O)_{0-2}$-, (C_0-C_6 alkyl)$S(O)_{0-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, $-O(C_1$-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6alkyl)O(C_1-C_6 alkyl)-, (C_0-C_6 alkyl)$C(O)_{1-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

Thus, a substituted cycloalkyl, substituted aryl, or substituted heterocycle can be a cycloalkyl (e.g., cyclopentyl or cyclohexyl), an aryl (e.g., phenyl or naphthyl), or a heterocycle (e.g., a heteroaryl) as defined herein substituted with from 1 to 3 substituents each of which is independently halo, C_1-C_6 alkyl, CF_3, NH_2, -$NH(C_1$-C_6 alkyl), -$N(C_1$-C_6 alkyl$)_2$, $-NO_2$, oxo, -CN, -OH, -O-(C_1-C_6 alkyl), C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-S(O)_{0-2}(C_1$-C_6 alkyl), -(C_1-C_6 alkylene)--$S(O)_{0-2}(C_1$-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), $-C(=NH)NH_2$, $-O(C_1$-C_6 alkylene)CF_3, -C(O)(C_1-C_6 alkyl), -C(O)H, -OC(O)(C_1-C_6 alkyl), -(C_1-C_6 alkylene)O(C_1-C_6 alkyl), $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl$)_2$, $-C(O)_2H$, $-C(O)_2(C_1$-C_6 alkyl), -(C_1-C_6 alkylene)$C(O)_{1-2}(C_1$-C_6 alkyl), -NHC(O)O-(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl)NHC(O)NH(C_1-C_6 alkyl), $-NHSO_2NH_2$, -NH(C_1-C_6 alkyl)$NHSO_2(C_1$-C_6 alkyl), $-NHSO_2(C_1$-C_6 alkyl), -(C_1-C_6 alkyl)$NHSO_2(C_1$-C_6 alkyl), phenyl, or benzyl.

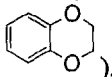
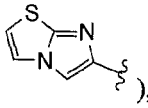
As another example, a substituted cycloalkyl, substituted aryl, or substituted heterocycle can be a cycloalkyl (e.g., cyclopentyl or cyclohexyl), an aryl (e.g., phenyl or naphthyl), or a heterocycle (e.g., a heteroaryl) as defined herein substituted with from 1 to 3 substituents each of which is independently Cl, Br, F, CH_3, CF_3, NH_2, -$NH(CH_3)$, -$N(CH_3)_2$, oxo, -CN, -OH, $-OCH_3$, cyclohexyl, ethenyl, ethynyl, $-SCH_3$, $-S(O)_2CH_3$, $-(CH_2)_{1-2}$-SCH_3, $-(CH_2)_{1-2}$-$S(O)_2CH_3$, -$NHC(O)CH_3$, $-O(CH_2)_{1-2}CF_3$, $-C(O)CH_3$, $-OC(O)CH_3$, $-(CH_2)_{1-2}OCH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)_2H$, $-C(O)_2CH_3$, $-(CH_2)_{1-2}C(O)_2CH_3$, $-NHC(O)OCH_3$, -NH(CH_3)NHC(O)NH(CH_3), phenyl, or benzyl.

Preferred sets of substituents for substituted cycloalkyl, substituted aryl, or substituted heterocycle are those set forth in the three preceding paragraphs, wherein at most 1 of the up to 3 substituents is or contains aryl (e.g., phenyl), heteroaryl, or heterocyclyl.

Saturated heterocyclics form a subset of the heterocycles; i.e., the term "saturated heterocyclic" generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is saturated. The term "saturated heterocyclic ring" refers to a 4- to 8-membered saturated monocyclic ring or a stable 7- to 12-membered bicyclic ring system which consists of carbon atoms and one or more heteroatoms selected from N, O and S. Representative examples include

piperidinyl, piperazinyl, azepanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl (or tetrahydrofuranyl).

Heteroaromatics form another subset of the heterocycles; i.e., the term "heteroaromatic" (alternatively "heteroaryl") generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is an aromatic ring system. The term "heteroaromatic ring" refers a 5- or 6-membered monocyclic aromatic ring or a 7- to 12-membered bicyclic which consists of carbon atoms and one or more heteroatoms selected from N, O and S. In the case of substituted heteroaryl rings containing at least one nitrogen atom (e.g., pyridine), such substitutions can be those resulting in N-oxide formation. Representative examples of heteroaromatic rings include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl.

Representative examples of bicyclic heterocycles include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl (i.e., ), imidazo(2,1-b)(1,3)thiazole, (i.e., ), and benzo-1,3-dioxolyl (i.e., ). In certain contexts herein,  is alternatively referred to as phenyl having as a substituent methylenedioxy attached to two adjacent carbon atoms.

Unless expressly stated to the contrary, an "unsaturated" ring is a partially or fully unsaturated ring. For example, an "unsaturated monocyclic C_6 carbocycle" refers to cyclohexene, cyclohexadiene, and benzene.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocycle described as containing from "1 to 4 heteroatoms" means the heterocycle can contain 1, 2, 3 or 4 heteroatoms. It is also understood that any range cited herein includes within its scope all of the sub-ranges within that range. Thus, for example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" is intended to include as aspects thereof, heterocyclic rings containing 2 to 4 heteroatoms, 3 or 4 heteroatoms, 1 to 3 heteroatoms, 2 or 3 heteroatoms, 1 or 2 heteroatoms, 1 heteroatom, 2 heteroatoms, 3 heteroatoms, and 4 heteroatoms. As another example, an aryl or heteroaryl described as optionally substituted with "from 1 to 3 substituents" is intended to include as aspects thereof, an aryl or heteroaryl optionally substituted with 1 to 3 substituents, 1 to 2 substituents, 2 to 3 substituents, 1 substituent, 2 substituents, and 3 substituents.

When any variable occurs more than one time in any constituent or in any formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, when V, X and Y are all $-C(R^5R^6)-$ (see Formula I, e.g.), they may be the same or different. More particularly, in one embodiment $-C(R^5R^6)-$ can

be selected from $-CH_2-$, $-CH(CH_3)-$, and $-C(CH_3)_2-$, in which case there are several possible combinations of V, X and Y, including but not limited to V = X = Y = $-CH_2-$; V = $-CH_2-$, X = $-CH(CH_3)-$, Y = $-CH_2-$; V = $-CH_2-$, X = $-CH_2-$, Y = $-CH(CH_3)-$; V = $-CH(CH_3)-$, X = $-CH_2-$, Y = $-CH_2-$; V = $-CH_2-$, X = $-CH_2-$, Y = $-C(CH_3)_2-$; V = $-CH(CH_3)-$, X = $-CH_2-$, Y = $-C(CH_3)_2-$; and so forth.

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

The term "substituted" (e.g., as in "aryl which is optionally substituted with one or more substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed.

The term "hydrate" as used herein means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

The term "clathrate" as used herein means a compound of the invention or a salt thereof in the form of a crystal lattice that contains spaces (e. g., channels) that have a guest molecule (e. g., a solvent or water) trapped within.

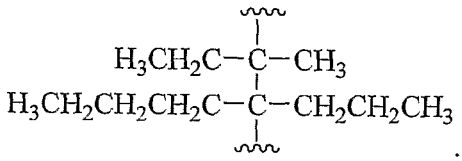
The symbol " $\}$ " or "$\sim\sim$" at the end of a bond refers to the point of attachment of a functional group or other chemical moiety to the rest of the molecule of which it is a part.

In compounds of the invention having pyridyl N-oxide moieties, the pyridyl-N-oxide portion is structurally depicted using conventional representations such as



which have equivalent meanings.

For variable definitions containing terms having repeated terms, e.g., $(CR^iR^j)_r$, where r is the integer 2, R^i is a defined variable, and R^j is a defined variable, the value of R^i may differ in each instance in which it occurs, and the value of R^j may differ in each instance in which it occurs. For example, if R^i and R^j are independently selected from the group consisting of methyl, ethyl, propyl and butyl, then $(CR^iR^j)_2$ can be



Pharmaceutically acceptable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in *Remington's Pharmaceutical Sciences*, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydro-scopicity and solubility. As will be understood by those skilled in

the art, pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts of an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate or palmoate, salicylate and stearate. Similarly pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium (especially ammonium salts with secondary amines). Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts. Also included within the scope of this invention are crystal forms, hydrates and solvates of the compounds of Formula Ic.

The method of the present invention involves the use of compounds of Formula Ic in the inhibition of HIV reverse transcriptase, the prophylaxis or treatment of infection by human immunodeficiency virus (HIV) and the prophylaxis, treatment or the delay in the onset of consequent pathological conditions such as AIDS. Prophylaxis of AIDS, treating AIDS, delaying the onset 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 a compound of Formula Ic', or a pharmaceutically acceptable salt thereof.

The compounds of Formula Ic 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. Certain of the compounds employed in the present invention carry an acidic moiety (e.g., -COOH or a phenolic group), in which case 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 Ic mean providing the compound or a prodrug of the compound to the individual in need of treatment or prophylaxis. When a compound of the invention 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 in the specified amounts, as well as any product which results, directly or indirectly, from combining the specified ingredients in the specified amounts.

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 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.

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 of AIDS), the compounds of Formula Ic, optionally in the form of a salt, 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 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 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, 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. Liquid-filled capsules can also be employed for oral administration of the compounds of the invention; e.g., a liquid-filled capsule (hard

gelatin) containing up to about 8 mg of the compound of Example 36 in Cremophor EL:Labrasol:Tween 80 1:1:1, wherein Cremophor EL (BASF, Parsipanny, NJ) is a derivative of castor oil and ethylene oxide; Labrasol (Gattefosse Corporation, Westwood, NJ) consists of caprylocaproyl macrogol-8 glycerides; and Tween 80 is polyoxyethylene sorbitan monooleate. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other 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 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 Ic 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 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. As an example, it is believed that the compound of Example 36 can be administered orally in a range of from about 0.5 to about 12 mg/kg twice per day. 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.

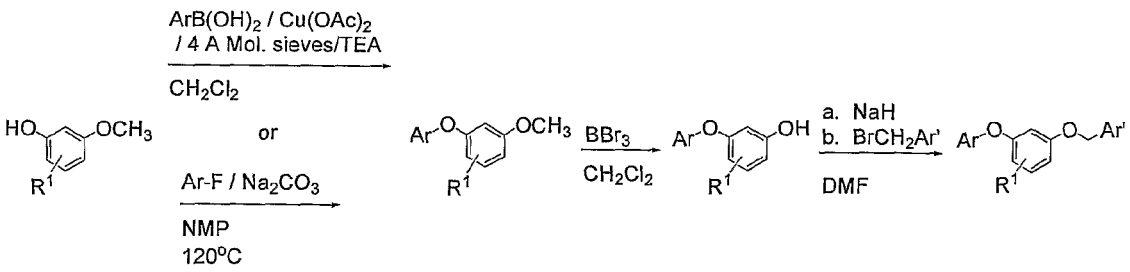
As noted above, the present invention is also directed to the use of the compounds of Formula Ic' in combination with one or more agents useful in the treatment of HIV infection or AIDS. For example, the compounds of Formula Ic can be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more HIV antiviral agents, imunomodulators, antiinfectives, 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 antiviral agents for use in combination with the compounds of Formula Ic include, for example, HIV protease inhibitors (e.g., indinavir, atazanavir, lopinavir optionally with ritonavir, saquinavir, or nelfinavir), nucleoside HIV reverse transcriptase inhibitors (e.g., abacavir, lamivudine (3TC), zidovudine (AZT), or tenofovir), non-nucleoside HIV reverse transcriptase inhibitors (e.g., efavirenz or nevirapine), and HIV integrase inhibitors such as those described in WO 02/30930, WO 03/35076, and WO 03/35077. It will be understood that the scope of combinations of compounds of Formula Ic with HIV antiviral agents,

immunomodulators, anti-infectives or vaccines is not limited to the foregoing substances or to the list 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 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, 57th edition, Thomson PDR, 2003. The dosage ranges for a compound of Formula Ic in these combinations are the same as those set forth above. All agents can optionally be used in the form of pharmaceutically acceptable salts.

Compounds of the present invention can be made by the method exemplifed in Scheme I below. The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis; Wiley & Sons: New York, Volumes 1-21; R. C. LaRock, Comprehensive Organic Transformations, 2nd edition Wiley-VCH, New York 1999; Comprehensive Organic Synthesis, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, 1991; Comprehensive Heterocyclic Chemistry, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1984, vol. 1-9; Comprehensive Heterocyclic Chemistry II, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1996, vol. 1-11; and Organic Reactions, Wiley & Sons: New York, 1991, Volumes 1-40. The following synthetic reaction scheme and examples are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to this synthetic reaction scheme can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this application.

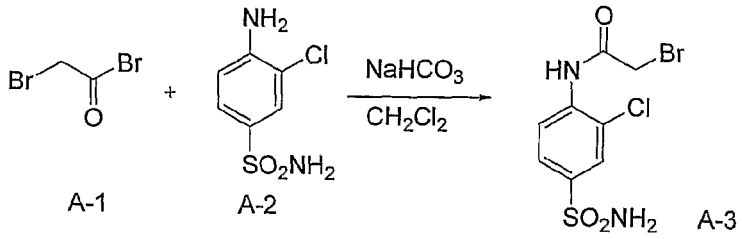
The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

Scheme I



In the scheme, Ar is an aryl or heteroaryl group as defined above.

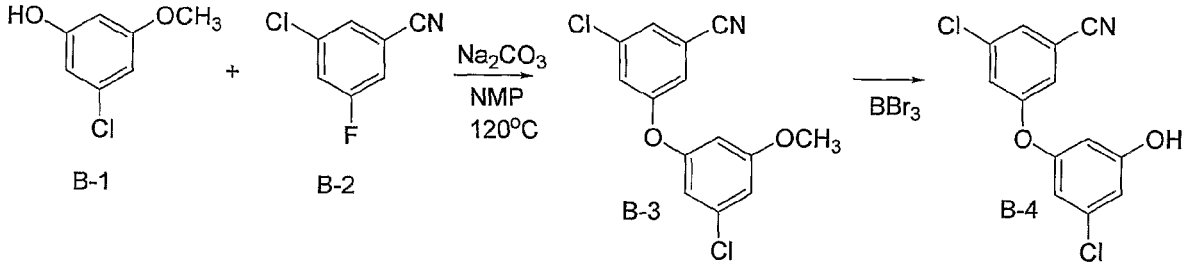
INTERMEDIATE A



N-[4-(aminosulfonyl)-2-chlorophenyl]-2-bromoacetamide

A mixture of 750mg (3.63mmol) of 4-amino-3-chlorobenzenesulfonamide (A-2) and 610mg (7.26mmol) of sodium bicarbonate in 25 mL of CH_2Cl_2 was stirred at room temperature for 18 hours. Bromoacetyl bromide (A-1) was then added, and the mixture was stirred for an additional 12 hours. The mixture was then concentrated in vacuo to a yellow oil. The oil was washed with three 25 mL portions of diethyl ether, decanted, and concentrated in vacuo to give the desired product A-3 as a tan solid. MS: M+1 = 329.0.

INTERMEDIATE B



3-chloro-5-(3-chloro-5-methoxyphenoxy)benzonitrile(B-3)

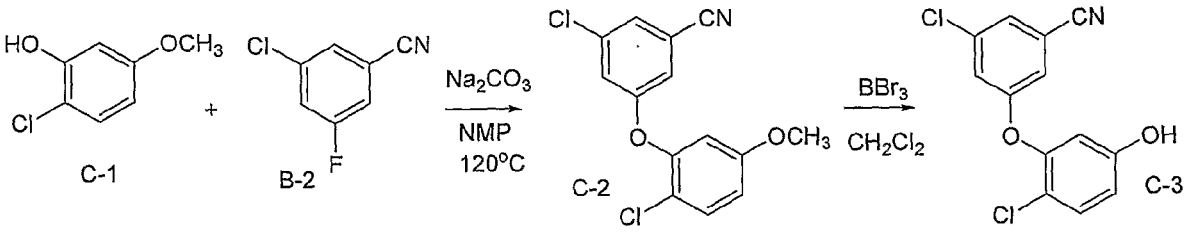
A mixture of 1.00 g(6.31 mmol) of 3-chloro-5-methoxyphenol (B-1) , of 1.28 g(8.20 mmol) 3-fluoro-5-chlorobenzonitrile (B-2) , and 2.62 g(18.93 mmol) of potassium carbonate in 10 mL of N-methylpyrrolidinone was heated at 120°C in a nitrogen atmosphere with vigorous stirring. After 6 hours, LC/MS analysis indicated that the reaction was complete. The reaction was cooled to room temperature and filtered, and the solid washed with EtOAc. The filtrate was diluted further with EtOAc, and was washed with 20 mL of 1N HCl, 20 mL of 1 N NaOH , 20 mL of water, and 20 mL of brine. The organic layer was dried(anhydrous $MgSO_4$), filtered, and the filtrate concentrated in vacuo to an orange oil. The oil was purified by flash column chromatography over silica gel with 3:1 cloroform/hexanes to give the desired product B-3 as a clear oil. MS: M+1 = 295. ^1H NMR($CDCl_3$) : 3.81 δ(s, 3H) , 6.44 m, 1H) , 6.62 (m,1H), 6.78 (m,1H), 7.14 (m,1H), 7.22(m,1H), 7.37(m,1H).

3-chloro-5-(3-chloro-5-hydroxyphenoxy)benzonitrile(B-4)

A stirred solution of 500 mg(1.70 mmol) of 3-chloro-5-(3-chloro-5-methoxyphenoxy)benzonitrile(B-3) in 5 mL CH_2Cl_2 was cooled to -20°C in a nitrogen atmosphere. The reaction was treated with 5.10 mL(5.10 mmol) of a 1M solution of boron tribromide in CH_2Cl_2, and the

resulting solution was stirred in the cold for 30 minutes, then at ambient temp. for 18 hours. The reaction was carefully poured into excess ice water with stirring, and the mixture extracted twice with diethyl ether. The combined ether extracts were washed with brine, dried (anhydrous $MgSO_4$), filtered and concentrated in vacuo to give the desired product B-4 as a yellow oil which slowly crystallized to a yellow solid . MS: M+= 280.

INTERMEDIATE C



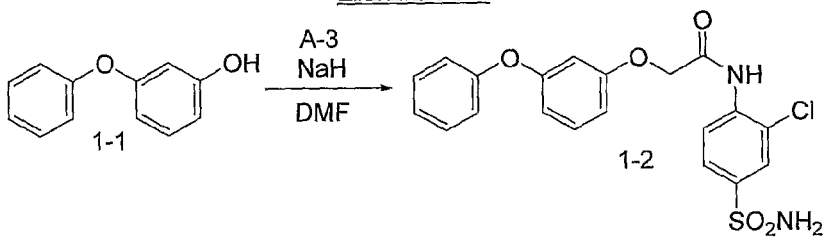
3-chloro-5-(2-chloro-5-methoxyphenoxy)benzonitrile(C-2)

In a manner identical to that described above in Intermediate B for the synthesis of B-3 , from 340 mg(2.14 mmol) of 2-chloro-5-methoxyphenol (C-1) and 433 mg(2.78 mmol) of 3-fluoro-5-chlorobenzonitrile (B-2), was obtained the desired product C-2 as a white solid. MS M+ = 293.

3-chloro-5-(2-chloro-5-hydroxyphenoxy)benzonitrile (C-3)

In a manner identical to that described in Intermediate B above for the synthesis of B-4, from 265 mg(0.90 mmol) of 3-chloro-5-(2-chloro-5-methoxyphenoxy)benzonitrile(8-2) was obtained the desired product C-3 as a pale yellow solid. MS M+ = 280.

EXAMPLE 1



N-[4-(aminosulfonyl)-2-chlorophenyl]-2-(3-phenoxyphenoxy)acetamide (1-2)

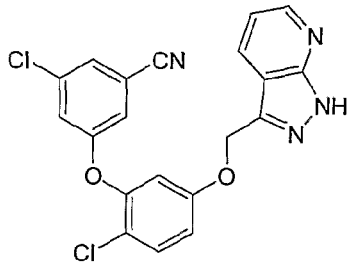
A stirred solution of 37mg (0.198 mmol) of 3-phenoxyphenol (1-1) in 1mL anhydrous DMF under nitrogen was treated with 10mg (0.397mmol) of 60% NaH dispersion. The resulting mixture was stirred at room temperature for 4 hours and then treated with 65 mg (0.198mmol) of *N*-[4-(aminosulfonyl)-2-chlorophenyl]-2-bromoacetamide (A-3). This mixture was then stirred at room temperature for an additional 4 hours. The reaction was concentrated in vacuo, and the residue was purified by reverse phase prep LC on a Gilson unit. Clean product fractions were combined and concentrated in vacuo to give the desired product 1-2 as a white solid. MS: M+1 = 433.2.

EXAMPLES 2-35

There are no examples 2 to 35.

EXAMPLE 36

3-chloro-5-[2-chloro-5-(1H-pyrazolo[3,4-b]pyridin-3-ylmethoxy)phenoxy]benzonitrile (36-5)



Step 1: 1-(2-fluoropyridine-3-yl)ethanone (36-1)

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 recooled 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 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 $NaHCO_3$ solution, and brine, and were dried over anhydrous $MgSO_4$. 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 ($CDCl_3$): 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-fluoropyridin-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 CH_2Cl_2 (25mL), and extracted with H_2O (2x50 mL). The organic portions were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give the title product as a fluffy off-white solid. ^1H NMR ($CDCl_3$): 2.61(s, 3H), 7.14(m,1H), 8.06(dd,1H), 8.58(dd,1H), 11.18(br s, 1H).

3-Methyl-1H-pyrazolo[3,4-b]pyridine can also be prepared by heating a solution of 1-(2-chloropyridin-3-yl)ethanone and aqueous hydrazine in 1-propanol at reflux and with stirring for a time

sufficient to achieve complete or nearly complete conversion of the starting substrate (e.g., about 48 hours). Cooling water can then be added to the reaction mixture to precipitate the desired product which can be isolated by filtration.

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

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 H_2O. The organic layer was separated, dried ($MgSO_4$), 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 ($CDCl_3$): 1.74(s,9H), 2.60(s,3H), 7.29(m,1H), 8.02(dd,1H), 8.74(dd,1H).

Step 4: 1-(tert-butyl)-3-(bromomethyl)- 1H-pyrazolo[3,4-b]pyridine-1-carboxylate (36-4)

A stirred solution of 934 mg (4.00mmol) 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 ($CDCl_3$): 1.76(s,9H), 4.78(s,2H), 7.35(q,1H), 8.24(dd,1H), 8.77(dd,1H).

Step 5: 3-chloro-5-[2-chloro-5-(1H-pyrazolo[3,4-b]pyridin-3-ylmethoxy)phenoxy]benzonitrile (36-5)

In a manner identical to that described above for the synthesis of *N*-[4-(aminosulfonyl)-2-chlorophenyl]-2-(3-phenoxyphenoxy)acetamide (Compound 1-2 in Example 1), from 80 mg (0.29 mmol) of 3-chloro-5-(2-chloro-5-hydroxyphenoxy)benzonitrile (C-3), 12 mg (0.30mmol) of NaH 60% dispersion, and 91 mg (0.29 mmol) of 1-(tert-butyl)-3-(bromomethyl)- 1H-pyrazolo[3,4-b]pyridine-1-carboxylate was prepared the crude Boc-protected derivative of the title product as an oil. This material was immediately dissolved in 1 mL methylene chloride/1 mL TFA, and the resulting solution stirred at room temperature overnight. The reaction was concentrated in vacuo, and the crude oil purified by reversed phase preparative LC on a Gilson apparatus to provide the title product 36-5 as an amorphous white powder after lyophilization. MS M+1 = 411. ^1H NMR (DMSO-d_6) :

5.47(s, 2H), 7.08(dd,1H), 7.12(d,1H), 7.21(q,1H), 7.37(dd,1H), 7.45(m,1H), 7.56(d,1H), 7.80(m,1H), 8.30(dd,1H), 8.54(dd,1H), 13.70(s,1H).

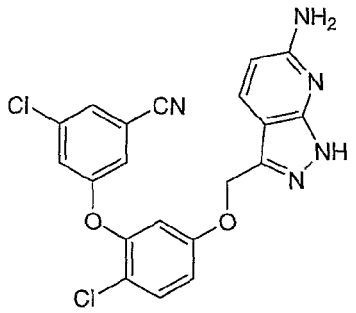
Alternative Step 5:

3-chloro-5-[2-chloro-5-(1H-pyrazolo[3,4-b]pyridin-3-ylmethoxy)phenoxy]benzonitrile (36-5) has also been prepared as follows:

3-chloro-5-(2-chloro-5-hydroxyphenoxy)benzonitrile (20.24 g), cesium fluoride (30.8 g), and 1-(tert-butyl)-3-(bromomethyl)-1H-pyrazolo[3,4-b]pyridine-1-carboxylate (22.5 g) were charged to a round bottom flask equipped with an overhead stirrer and a nitrogen inlet (the reaction was conducted under nitrogen), followed by addition of dimethylacetamide (60 mL) as solvent. The mixture was stirred at room temperature overnight, after which MTBE (500 mL) was added and the mixture transferred to an extractor containing K_2CO_3 (13 g) in water (300 mL). The organic phase was collected and washed with water (3 x 150 mL), and then collected and dried over sodium sulfate (20 g) overnight. The solvent was then switched from MTBE to THF (400 mL final volume), and sulfuric acid (10 mL) was added. After 18 hours, water (300 mL) was added and the solvent volume was reduced by concentration to 350 mL. The resulting solids were filtered and washed with water (100 mL) and the slurry washed with methanol (200 mL). The solids were placed in a round bottom flask, acetonitrile (150 mL) was added, the mixture heated to 80°C and then cooled to room temperature overnight. The solids were filtered and washed with acetonitrile to afford the title product.

EXAMPLE 37

3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chlorophenoxy}-5-chlorobenzonitrile (37-9)



Step 1: 1-(2,6-difluoropyridin-3-yl)ethanone (37-2)

A solution of freshly distilled diisopropylamine (14.7 mL, 104.3 mmol) in 10 mL of anhydrous THF was cooled to -78° and treated with 1.6 M solution of n-BuLi in hexanes (64.0 mL, 102.5 mmol). The resulting solution naturally warmed to -20° and was maintained at -20° for 1.5 hours. The solution was cooled to -78° and 2,6 difluoro pyridine (37-1) was added dropwise. The reaction was continued with stirring for 2 hours at -78 °C before a solution of 9.7 mL (86.9 mmol) of the Weinryb amide was added in 20 mL of THF. The resulting solution was warmed to ambient temperature overnight before quenching with a brine solution. The mixture was extracted with EtOAc (3x), and the

combined organic layers were washed with H_2O (1X), brine (2x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash silica gel chromatography (0-40% EtOAc/Hexane) to yield the desired product 37-2. ^1H NMR ($CDCl_3$): 2.68(s,3H), 6.95(d,1H), 8.50(q,1H).

Step 2: 6-fluoro-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (37-3)

To a stirred solution of 7.46g (47.51 mmol) of 1-(2,6-difluoropyridin-3-yl)ethanone (37-2) in 50 mL of CH_2Cl_2 under nitrogen was added dropwise titanium (IV) isopropoxide. The resulting solution was stirred vigorously for 15 minutes before hydrazine hydrate (4.62 g, 95.0 mmol) was added slowly to form a thick slurry. The reaction mixture was stirred for 1 hour before the addition of 11 mL of H_2O, and the resulting mixture stirred for 1.5 hours until completion as determined by LC/MS analysis. The solid matter was filtered off and the filterate was condensed to yield a white solid. EtOH (100 mL) was added to the crude intermediate and the mixture was heated to reflux for 6 hours. After the reaction was complete as determined by LC/MS analysis the solvent was removed to yield the desired product. No further purification was necessary. ^1H NMR ($CDCl_3$): 2.56(s, 3H), 6.78(d,1H), 8.08(t,1H).

Step 3: *tert*-butyl 6-fluoro-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (37-4)

A stirred solution of 6.67 g (44.2 mmol) of 6-fluoro-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine in 100 mL of acetonitrile under nitrogen was treated with 5.40 g (44.2 mmol) of DMAP and 6.46 mL (46.4 mmol) of triethylamine. A solution of 11.56 g (53.0 mmol) of $(BOC)_2O$ in 20 mL acetonitrile was added dropwise via a cannula and the resulting reaction mixture stirred for 1 hour until completion as determined by LC/MS analysis. The reaction was quenched with brine and extracted with EtOAc (3x). The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified via silica gel chromatography (0-70 % EtOAc/hexane) to yield the title compound. ^1H NMR ($CDCl_3$): 1.74(s,9H), 2.60(s,3H), 6.95(d,1H), 8.08(t,1H).

Step 4: *tert*-butyl 3-(bromomethyl)-6-fluoro-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (37-5)

A stirring solution of 8.88 g (35.2 mmol) of 37-4, 6.88 g (38.7 mmol) of NBS and 851 mg (3.52 mmol) of benzoyl peroxide in 250 mL of CCl_4 was heated to reflux for 6 hours. The reaction was stopped after a 66% conversion of starting material as determined by LC/MS. The reaction mixture was cooled to room temperature, filtered through a pad of Celite to remove precipitated succinimide, and the filtrate concentrated in vacuo. The crude residue was purified by silica gel chromatography (0-70 % ethyl acetate/hexanes) to afford the title product as a solid. ^1H NMR ($CDCl_3$): 1.75(s,9H), 4.75(s,2H), 7.00(d,1H), 8.30(t,1H).

Step 5: 3-chloro-5-{2-chloro-5-[(6-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]phenoxy}benzonitrile (37-7)

In a manner identical to that described above for the synthesis of 1-2, from 2.97 g (10.68 mmol) of 3-chloro-5-(2-chloro-5-hydroxyphenoxy)benzonitrile (C-3), 3.29 g (10.15 mmol) of Cs_2CO_3, and 3.34 g (10.15 mmol) of *tert*-butyl 3-(bromomethyl)-6-fluoro-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (37-5) was prepared crude 3-chloro-5-{2-chloro-5-[(1-t-butyloxycarbonyl-6-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]phenoxy}benzonitrile (37-6) as an oil. This BOC-protected material (3.66 g) was immediately dissolved in 10 mL TFA, and the resulting solution stirred for 20 minutes at room temperature. The crude reaction mixture was concentrated in vacuo and purified via silica gel chromatography (10-70% EtOAc/hexane) to yield the title compound. H^1 NMR ($CDCl_3$) : 5.47(s, 2H), 6.85(d,1H), 6.95(d,1H), 7.02(s,1H), 7.10(s,1H), 7.30(s,1H), 7.40(d,1H), 8.38(t,1H), 11.38(bs,1H).

Step 6: 3-chloro-5-[2-chloro-5-({6-[(4-methoxybenzyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}methoxy)phenoxy]benzonitrile (37-8)

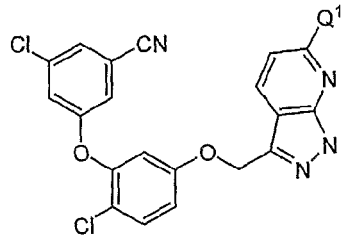
To a solution of 3-chloro-5-{2-chloro-5-[(6-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]phenoxy}benzonitrile (37-7, 200 mg, 0.467 mmol) in NMP (5 mL) was added 0.61 mL of 1-(4-methoxyphenyl)methenamine. The resulting solution was heated to 95°C for 18 hours until completion as determined by LC/MS analysis. The reaction was cooled to room temperature and diluted with (1/1) brine/H_2O solution and extracted with EtOAc (3x). The combined organic layers were washed with H_2O (4x), brine (2x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified via silica gel chromatograpy (20-100% EtOAc/hexane) to yield the title compound. ^1H NMR ($CDCl_3$) : 3.80 (s, 3H), 4.58 (d, 2H), 4.98 (t, 1H), 5.30(s, 2H), 6.30(d, 1H), 6.82(m, 1H), 6.85(d,1H), 6.92(d,1H), 7.00(s,1H), 7.10(s,1H), 7.12(m,1H), 7.25-7.35(m,3H), 7.38(d,1H), 7.80(d,1H).

Step 7: 3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chlorophenoxy}-5-chlorobenzonitrile (37-9)

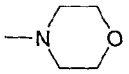
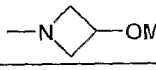
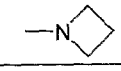
3-chloro-5-[2-chloro-5-({6-[(4-methoxybenzyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}methoxy)phenoxy]benzonitrile (37-8) was dissolved in 6 mL of TFA and heated to 60°C for 7 hours until reaction was complete as determined by LC/MS analysis. After removal of all volatile material the crude residue was purified via prep HPLC (20%-70% acetonitrile in H_2O: C18 Phenomenex Gemini) and lyophilzed from dioxane to yield the title compound in the form of a TFA salt. H^1 NMR (CD_3OD): 5.40(s 2H), 6.58(d,1H), 6.96(d,1H), 7.04(d,1H), 7.16(s,1H), 7.18(s,1H), 7.58(d,1H), 7.52(s,1H), 8.10(bs,1H).

EXAMPLES 38-44

The compounds in the following table and having the following general formula:

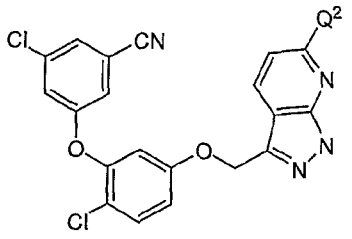


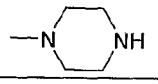
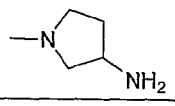
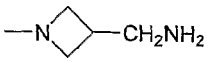
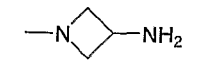
were prepared in accordance with the following procedure: To a solution of 3-chloro-5-{2-chloro-5-[(6-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]phenoxy}benzonitrile (1 eq) in NMP was added the appropriate amine (10 eq) and the resulting solution was heated to 95°C until the reaction was complete as determined by LC/MS analysis. The reaction mixture was cooled to room temperature and diluted with (1/1) brine/H_2O solution and extracted with EtOAc (3x). The combined organic layers were washed with H_2O (4x), brine (2x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography to afford the desired product.

Ex.	Compound Name	Q1	M+1
38	3-chloro-5-(2-chloro-5-{[6-methylamino)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)benzonitrile	-NHMe	440.3
39	3-chloro-5-(2-chloro-5-{[6-dimethylamino)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)benzonitrile	-NMe_2	454.3
40	3-chloro-5-[2-chloro-5-({6-[(2-methoxyethyl)(methyl)amino]-1H-pyrazolo[3,4-b]-pyridin-3-yl}methoxy)phenoxy)benzonitrile	-$NMe(CH_2CH_2OMe)$	498.3
41	3-chloro-5-(2-chloro-5-[(6-morpholin-4-yl-1H-pyrazolo[3,4-b]-pyridin-3-yl)methoxy]phenoxy)benzonitrile		496.3
42	N2-(3-{[4-chloro-3-(3-chloro-5-cyanophenoxy)phenoxy]methyl}-1H-pyrazolo[3,4-b]pyridin-6-yl)-N2-methylglycinamide	-$NMe(CH_2C(O)NH_2)$	439.8
43	3-chloro-5-(2-chloro-5-{[6-(3-methoxyazetidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)benzonitrile		495.6
44	3-chloro-5-(2-chloro-5-{[6-(azetidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)benzonitrile		465.7

EXAMPLES 45-48

The compounds in the following table were prepared in accordance with the procedures set forth in Steps 6 and 7 of Example 37 using the appropriate amine in place of 1-(4-methoxyphenyl)methenamine. All of the compounds in the table were prepared as TFA salts after reversed phase LC purification. The compound name shown in the table is the name of the free base.



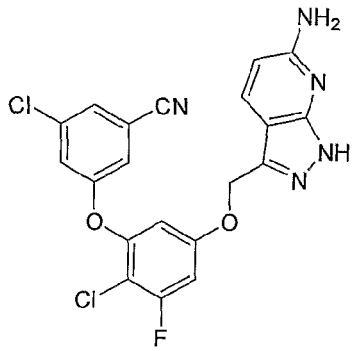
Ex.	Compound Name	Q^2	M+1
45	3-chloro-5-{2-chloro-5-[(6-piperazin-1-yl-1H-pyrazolo[3,4-b]-pyridin-3-yl)methoxy]phenoxy}benzonitrile		494.7
46	(RS) 3-(5-{[6-(3-aminopyrrolidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}-2-chlorophenoxy)-5-chlorobenzonitrile		494.7
47	3-[5-({6-[3-(aminomethyl)azetidin-1-yl]-1H-pyrazolo[3,4-b]-pyridin-3-yl}methoxy)-2-chlorophenoxy]-5-chlorobenzonitrile		494.6
48	3-(5-{[6-(3-aminoazetidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}-2-chlorophenoxy)-5-chlorobenzonitrile		480.7

EXAMPLE 49

There is no Example 49.

EXAMPLE 50

3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chloro-3-fluorophenoxy}-5-chlorobenzonitrile



Step 1: 3-fluoro-5-methoxyphenol (50-1)

Under nitrogen atmosphere, 1-fluoro-3,5-dimethoxybenzene (25g, 160 mmol) was diluted in CH_2Cl_2 (200 mL, 0.8M) and then cooled to -15°C. Next, BBr_3 (176 mL, 176 mmol, 1M in CH_2Cl_2) was slowly added to the reaction mixture. The reaction mixture was stirred at -15°C for one and a half hours and at room temperature for 10 minutes. The reaction mixture was then cooled to 0°C and slowly quenched with water (150mL). The aqueous layer was then extracted with methylene chloride

(3x100mL). The organic extracts were dried over sodium sulfate and concentrated. Silica gel chromatography (1%-30% EtOAc/Hexanes) gave the mono demethylated product (50-1) (15 g, 67%).

Step 2: 2-chloro-3-fluoro-5-methoxyphenol (50-2)

Under a nitrogen atmosphere, 3-fluoro-5-methoxyphenol (50-1) (15 g, 106 mmol) was diluted in DCE (150 mL, 0.7 M). To this solution NCS (15.5 g, 116 mmol) was added, and the reaction mixture was heated to reflux for 4 hours. The reaction was then cooled to room temperature and quenched with water (100 mL). The aqueous layer was then extracted with methylene chloride (3x50mL). The organic extracts were dried over sodium sulfate and concentrated. Silica gel chromatography (1%-30% EtOAc/Hexanes) gave 2-chloro-3-fluoro-5-methoxyphenol (50-2) (6.7 g, 36%) and 4-chloro-3-fluoro-5-methoxyphenol (50-3) (2.8 g, 15%). LCMS (ES) *m/z* 177.2 $(M)^+$. The starting material, 3-fluoro-5-methoxyphenol (50-1), was also recovered (4.3 g).

Step 3: 3-chloro-5-(2-chloro-3-fluoro-5-methoxyphenoxy)benzonitrile (50-4)

Under a nitrogen atmosphere, 2-chloro-3-fluoro-5-methoxyphenol (50-2) (6.7 g, 37.9 mmol) was diluted in NMP (40 mL, 0.95 M). To this solution Cs_2CO_3 (24.73 g, 76 mmol) was added and the reaction was allowed to stir at room temperature for 5 minutes. Then, 3-chloro-5-fluorobenzonitrile (11.81 g, 76 mmol) was added to the reaction and it was then heated to 120°C. After 2 hours the reaction was cooled to room temperature and then diluted with EtOAc (40 mL). It was partitioned with water (20 mL) and then extracted with EtOAc (3x30mL). The organic extracts were then washed with water (3x20mL) and brine (1x20mL), dried over sodium sulfate and concentrated. Silica gel chromatography (1%-15% EtOAc/Hexanes) gave 3-chloro-5-(2-chloro-3-fluoro-5-methoxyphenoxy)-benzonitrile (50-4) (10.4 g, 88%).

Step 4: 3-chloro-5-(2-chloro-3-fluoro-5-hydroxyphenoxy)benzonitrile (50-5)

Under nitrogen atmosphere, 3-chloro-5-(2-chloro-3-fluoro-5-methoxyphenoxy)-benzonitrile (50-4) (9.6 g, 30.8 mmol) was diluted in CH_2Cl_2 (60 mL, 0.5M) and then cooled to 0°C. To this solution BBr_3 (61.5 mL, 61.5 mmol, 1M in CH_2Cl_2) was slowly added to the reaction. The reaction mixture was allowed to slowly warm to room temperature and stir for 12 hours. It was then cooled to 0°C and slowly quenched with water (60mL). The aqueous layer was then extracted with methylene chloride (3x30mL). The organic extracts were dried over sodium sulfate and concentrated. Silica gel chromatography (1%-20% EtOAc/Hexanes) gave 3-chloro-5-(2-chloro-3-fluoro-5-hydroxyphenoxy)benzonitrile (50-5) (3.2 g, 35%). LCMS (ES) *m/z* 298.2 $(M)^+$.

Step 5: tert-butyl3-{[4-chloro-3-(3-chloro-5-cyanophenoxy)-5-fluorophenoxy]methyl}-6-fluoro-1H-pyrazolo[3,4-b]pyridine-1-carboxylate (50-6)

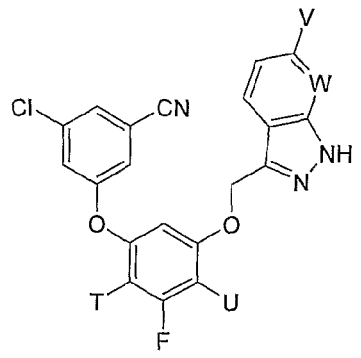
Under a nitrogen atmosphere, 3-chloro-5-(2-chloro-3-fluoro-5-hydroxyphenoxy)benzonitrile (50-5) (150 mg, 0.503 mmol) was dissolved in NMP (4 mL, 0.1 M). Next, Cs_2CO_3 (164 mg, 0.503 mmol) was added and the reaction was allowed to stir at room temperature for 15 minutes. Then, tert-butyl-3-(bromomethyl)-6-fluoro-1H-pyrazolo[3,4-b]pyridine-1-carboxylate (37-5) (166 mg, 0.503 mmol, prepared using the procedure set forth in Example 37) was added to the reaction. The reaction was stirred at room temperature for 2 hours. It was then diluted with EtOAc (4 mL). It was partitioned with water (3 mL) and then extracted with EtOAc (3x4mL). The organic extracts were then washed with water (3x4mL) and brine (1x4mL), dried over sodium sulfate and concentrated. Silica gel chromatography (1%-20% EtOAc/Hexanes) gave tert-butyl3-{[4-chloro-3-(3-chloro-5-cyanophenoxy)-5-fluorophenoxy]-methyl}-6-fluoro-1H-pyrazolo[3,4-b]pyridine-1-carboxylate (50-6) (230 mg, 85%). LCMS (ES) *m/z* 446.9 $(M\text{-}BOC)^+$.

Step 6: 3-{5-[(6-amino-1H-pyrazolo[3,4-b]pyridin-3-yl)methoxy]-2-chloro-3-fluorophenoxy}-5-chlorobenzonitrile (50-7)

Under a nitrogen atmosphere, tert-butyl3-{[4-chloro-3-(3-chloro-5-cyanophenoxy)-5-fluorophenoxy]methyl}-6-fluoro-1H-pyrazolo[3,4-b]pyridine-1-carboxylate (50-6) (230 mg, 0.420 mmol) was dissolved in NMP (4mL, 0.1 M). Next, 4-methoxybenzylamine (288 mg, 2.101 mmol) was added and the reaction was heated to 95°C for 2 hours. It was then diluted with EtOAc (4 mL). It was partitioned with water (3 mL) and then extracted with EtOAc (3x4mL). The organic extracts were then washed with water (3x4mL) and brine (1x4mL), dried over sodium sulfate and concentrated. The crude reaction material was then diluted with TFA (3mL) and heated to 65°C for 2 hours. It was then concentrated and purified on a reverse phase system (5%-95%AcCN/H_2O with 0.5% TFA) to give 3-{5-[(6-amino-1H-pyrazolo[3,4-b]pyridin-3-yl)methoxy]-2-chloro-3-fluorophenoxy}-5-chlorobenzonitrile (50-7) (8 mg, 4%). LCMS (ES) *m/z* 445.9 (M^+).

EXAMPLES 51-55

The compounds in the following table were prepared in accordance with the procedures set forth in Example 50.



Ex.	Compound Name	T	U	V	W	M+1
51	3-{5-[(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-3-fluorophenoxy}-5-chlorobenzonitrile	H	H	H	N	395.1
52	3-{5-[(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chloro-3-fluorophenoxy}-5-chlorobenzonitrile	Cl	H	H	N	429.6
53	3-{5-[(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-4-chloro-3-fluorophenoxy}-5-chlorobenzonitrile	H	Cl	H	N	429.0
54	3-{5-[(7-oxo-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-4-chloro-3-fluorophenoxy}-5-chlorobenzonitrile	H	Cl	H	N^+-O^-	445.5
55	3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-3-fluorophenoxy}-5-chlorobenzonitrile	H	H	NH_2	N	410.0

EXAMPLE 56

Assay for Inhibition of HIV Reverse Transcriptase

Assays to determine the in vitro inhibition of HIV reverse transcriptase by compounds of the present invention were conducted as follows: HIV-1 RT enzyme (1 nM) was combined with inhibitor or DMSO (5%) in assay buffer (50 mM Tris-HCl, pH 7.8, 1 mM dithiothreitol, 6 mM $MgCl_2$, 80 mM KCl, 0.2% polyethylene glycol 8000, 0.1 mM EGTA), and the mixture preincubated for 30 minutes at room temperature in microtiter Optiplates (Packard). 100 µL reaction mixtures were initiated with a combination of primer-template substrate (10 nM final concentration) and dNTPs (0.6 µM dNTPs, 0.75 µM [^{3}H]-dGTP). 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 µL streptavidin scintillation proximity assay beads (10 mg/mL, from Amersham Biosciences) in 0.5 M EDTA, pH 8. Microtiter plates were incubated an additional 10 minutes at 37°C prior to quantification via Topcount (Packard). 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 36 to 48 and 50 to 55 were tested in the assay and all were found to have IC_{50}'s less than 20 micromolar.

EXAMPLE 57

Assay for inhibition of HIV replication

Assays for the inhibition of acute HIV infection of T-lymphoid cells (also referred to as the "spread assay") were conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. Representative compounds of the present invention exhibit inhibition of HIV replication in this assay. For example, the compounds set forth in Examples 36 to 48 and 50 to 55 were found to have IC_{95}'s of less than 20 micromolar in the assay.

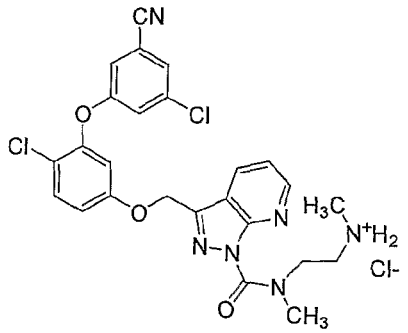
EXAMPLE 58

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 that were tested in the spread assay (see Example 57) were examined for cytotoxicity. For those compounds for which an IC_{95} value was determined in the spread assay, no cytotoxicity was exhibited at the IC_{95} concentration; i.e., their toxicity value is greater than their IC_{95} value. In particular, the compounds set forth in Examples 36 to 48 and 50 to 55 exhibited no cytotoxicity at their IC_{95} concentrations.

EXAMPLE 59

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



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

To a solution of triphosgene (63 mg, 0.212 mmol) in CH_2Cl_2 (3 mL) at 0°C was added a mixture of Hunig's base (0.305 mL, 1.75 mmol) and tert-butyl methyl[2-(methylamino)ethyl]carbamate (100mg, 0.531 mmol) in CH_2Cl_2 (2 mL) was added over 2mins. Five minutes after the addition was complete, the reaction was allowed to warm to room temperature. The 3-chloro-5-[2-chloro-5-(1H-

pyrazolo[3,4-b]pyridin-3-ylmethoxy)phenoxy]benzonitrile ((218mg, 0.531 mmol) and then pyridine (0.141mL 1.75 mmol) were added at room temperature and the resulting slurry heated at 70°C in a sealed tube. A pale yellow solution was obtained which was heated at 70°C for 16 hours. The reaction mixture was cooled to room temperature and the solvents evaporated in vacuo. The residue was dissolved in DMF (4 mL) and purified by reverse phase HPLC using a gradient elution 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid. The pure fractions were lyophilized to afford the title compound as a cream solid. MH+-BOC 524. ^{1}H NMR (400MHz) $CDCl_3$ 8.70(1H, dd, j-4.7 and 1.5Hz), 8.25(1H, dd, J=1.4, 8.1Hz), 7.42(1H, d, J=8.9Hz), 7.34(1H, t, J=1.5Hz), 7.3291H, dd, J=8.0 and 4.7Hz), 7.14(1H, t, J=2Hz), 7.01(1H, m), 6.95(1H, dd, J=8.9 and 2.9Hz), 6.80(1H, d, J=2.9Hz), 3.80-2.60(10H, m), 1.60-1.30 (9H, m).

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

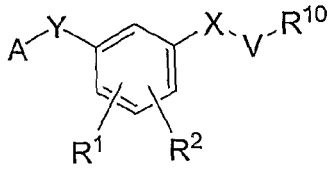
To a solution of the Boc derivative (see Step A; 39 mg, 0.062 mmol) in $CDCl_3$ (0.8 mL) at 0°C was added 4M HCl in dioxane (3.1mL 0.124 mmol). The reaction mixture was stirred for 2 hours at room temperature and the solvent evaporated in vacuo. The residue was dissolved in acetonitrile (5 mL) and lyophilized to afford the title compound as a white solid. MH+ 525. ^{1}H NMR (400MHz) d6 DMSO 8.67 (1 H d, J=4.5 and 1.0 Hz), 8.57 (2H, brs), 8.42 (1H, dd, J=1.2 and 8.0 Hz), 7.79 (1H, s), 7.56 (1H, d, J=8.9 Hz), 7.43 (1H, s), 7.41 (1H, m), 7.37 (1H, t, J=1.8 Hz), 7.15-7.05 (2H, m), 5.52 (2H, s), 3.80-3.20 (4H, m), 3.03 (3H, brs), 2.60 (3H, brs) ppm.

Oral dosing of the title compound of Example 59 to rats has been found to provide substantially higher bioavailability as compared to that obtained via analogous dosing of the compound of Example 36.

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.

WHAT IS CLAIMED IS:

1. A compound of Formula Ic, or a pharmaceutically acceptable salt thereof:



(Ic)

wherein:

R^1 and R^2 are independently selected from the group consisting of:

a) H,
b) C_{1-6} alkyl,
c) C_{3-6} cycloalkyl,
d) C_{1-3} fluoroalkyl,
e) NO_2,
f) halogen,
g) OR^3,
h) $O(CH_2)_sOR^3$,
i) CO_2R^3,
j) $(CO)NR^3R^4$,
k) $O(CO)NR^3R^4$,
l) $N(R^3)(CO)NR^3R^4$,
m) $N(R^3)(CO)R^4$,
n) $N(R^3)(CO)OR^3$,
o) $SO_2NR^3R^4$,
p) $N(R^3)\ SO_2R^4$,
q) $S(O)_mR^3$,
r) CN,
s) NR^3R^4,
t) $N(R^3)(CO)NR^3R^4$, and
u) $O(CO)R^3$;

A is aryl, C_{3-7} cycloalkyl, or heterocyclyl;

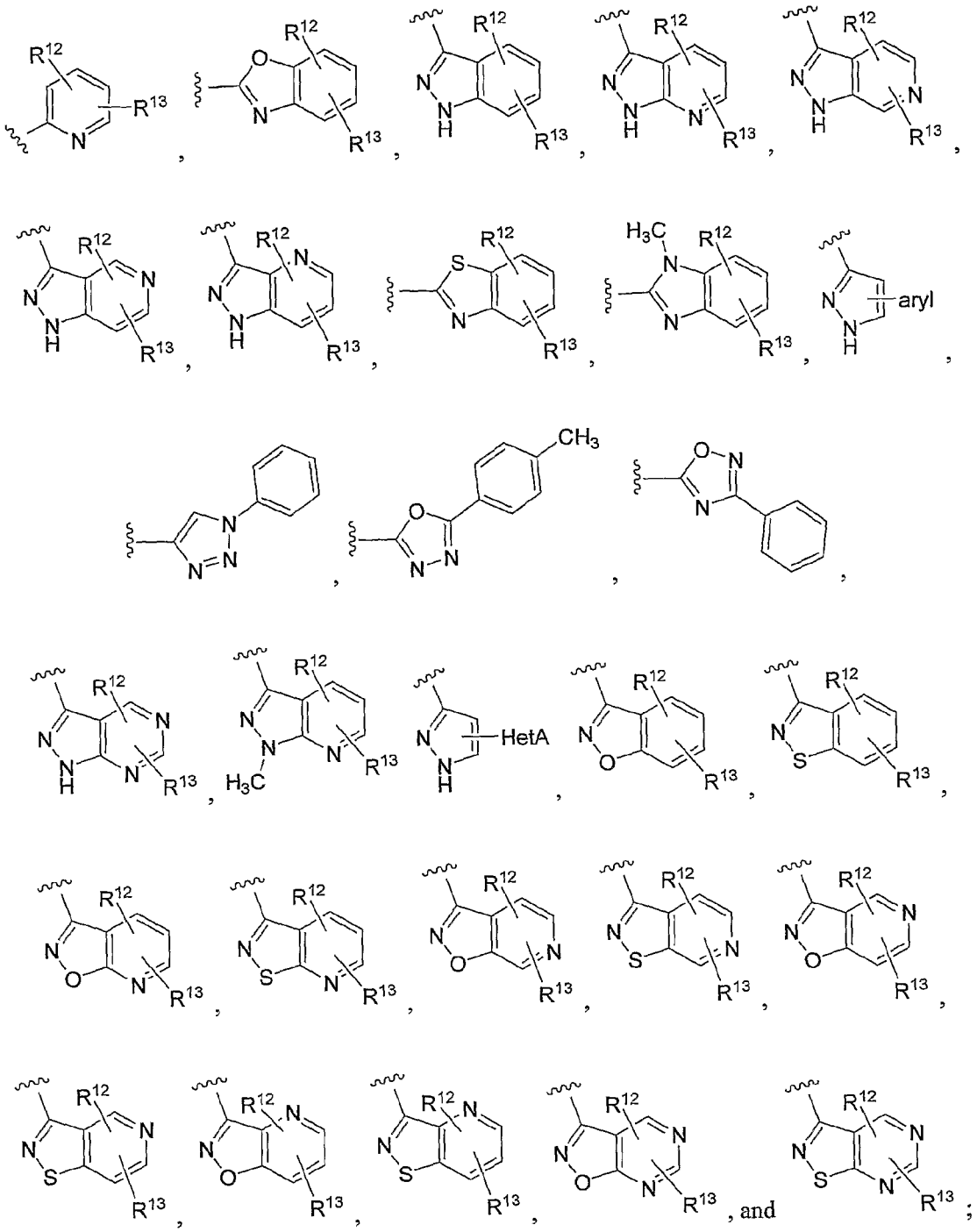
V is $-C(R^5R^6)-$;

X is selected from the group consisting of -O-, -NH-, and $-C(R^5R^6)-$;

Y is selected from the group consisting of -O-, $-C(R^5R^6)-$, and $-S(O)_m-$;

R^5 and R^6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-3} fluoroalkyl, and OR^3;

R^{10} is a heterocyclyl selected from the group consisting of:



R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halogen, oxo, NO_2, CN, OR^3, $O(CH_2)_tCF_3$, CO_2R^3, $CONR^3R^4$, $O(CH_2)_tNR^3R^4$, $O(CH_2)_vCOR^3$, $S(O)_mR^3$, $SO_2NR^3R^4$, C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{3-6} cycloalkyl, and NR^3R^4;

R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-3} fluoroalkyl, and C_{3-6} cycloalkyl;

or, alternatively and optionally, when R^3 and R^4 are in an NR^3R^4 group, then:

(A) one of R^3 and R^4 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-3} fluoroalkyl, and C_{3-6} cycloalkyl, and the other of R^3 and R^4 is C_{1-6} alkyl substituted with O-C_{1-6} alkyl, $C(O)R^A$, CO_2R^A, $C(O)N(R^A)R^B$, SR^A, $S(O)R^A$, SO_2R^A, or $SO_2N(R^A)R^B$; or

(B) R^3 and R^4 together with the nitrogen atom to which they are both attached form

(i) a 4- to 7-membered, saturated or unsaturated monocyclic ring optionally containing 1 or 2 heteroatoms in addition to the nitrogen attached to R^3 and R^4 selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$, or

(ii) a 7- to 12-membered bicyclic ring system wherein each ring in (ii) is independent of, fused to, or bridged with the other ring and each ring is saturated or unsaturated, and wherein the bicyclic ring system optionally contains from 1 to 3 heteroatoms in addition to the nitrogen attached to R^3 and R^4 selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$, and

wherein the monocyclic ring or the bicyclic ring system is optionally substituted with from 1 to 3 substituents each of which is independently: (1) C_{1-6} alkyl, (2) C_{1-6} haloalkyl, (3) C_{1-6} alkyl substituted with OH, O-C_{1-6} alkyl, O-C_{1-6} haloalkyl, CN, NO_2, $N(R^A)R^B$, $C(O)N(R^A)R^B$, $C(O)R^A$, CO_2R^A, SR^A, $S(O)R^A$, SO_2R^A, or $SO_2N(R^A)R^B$, (4) O-C_{1-6} alkyl, (5) O-C_{1-6} haloalkyl, (6) OH, (7) oxo, (8) halogen, (9) CN, (10) NO_2, (11) $N(R^A)R^B$, (12) $C(O)N(R^A)R^B$, (13) $C(O)R^A$, (14) C(O)-C_{1-6} haloalkyl, (15) $C(O)OR^A$, (16) $OC(O)N(R^A)R^B$, (17) SR^A, (18) $S(O)R^A$, (19) $S(O)_2R^A$, (20) $S(O)_2N(R^A)R^B$, (21) $N(R^A)COR^B$, or (22) $N(R^A)SO_2R^B$ and

wherein each R^A is independently H or C_{1-6} alkyl, and each R^B is independently H or C_{1-6} alkyl;

HetA is heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, and pyrazinyl;

s is 1-5;

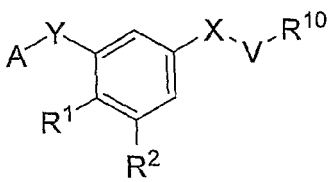
t is 2-3;

v is 1-2; and

m, in each instance in which it appears, is independently selected from 0-2;

and provided that when X is $-C(R^5R^6)-$, then neither R^1 nor R^2 is OR^3.

2. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of Formula Ic-1:



(Ic-1);

and provided that when X is -C(R^5R^6)-, then neither R^1 nor R^2 is OR^3.

3. A compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen, halogen, and C_{1-6} alkyl;

A is aryl;

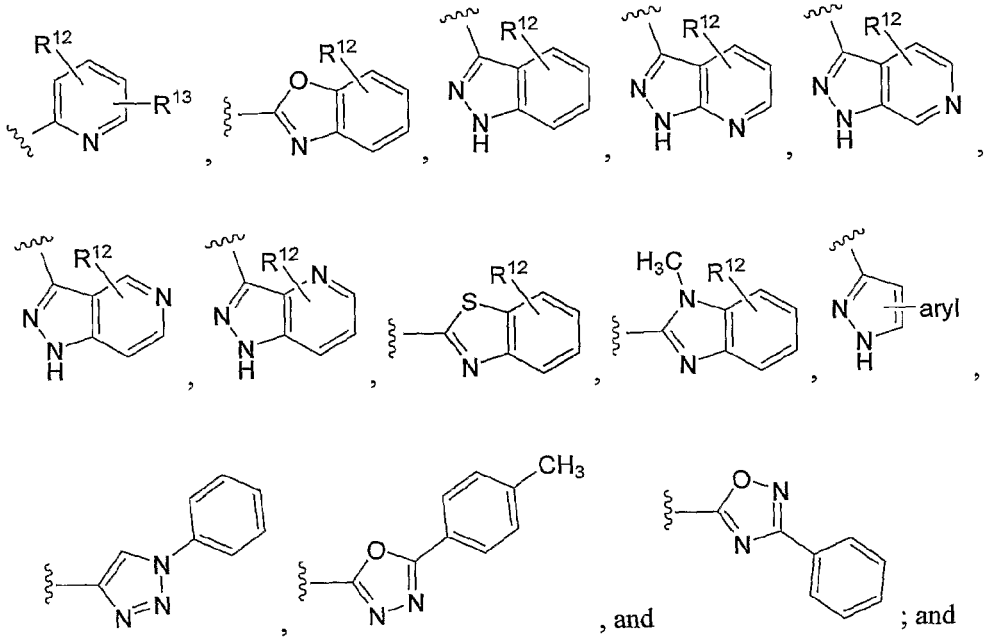
V is -C(R^5R^6)-;

X is selected from the group consisting of -O- and -NH-;

Y is selected from the group consisting of -O-, -CH_2-, and –$S(O)_m$-;

R^5 and R^6 are independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

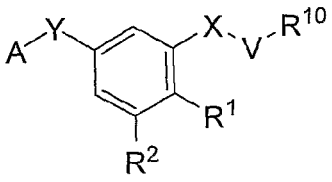
R^{10} is selected from the group consisting of:



; and

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halogen, oxo, NO_2, CN, OR^3, $O(CH_2)_tCF_3$, CO_2R^3, $CONR^3R^4$, $O(CH_2)_tNR^3R^4$, $O(CH_2)_vCOR^3$, $S(O)_mR^3$, $SO_2NR^3R^4$, C_{1-6} alkyl and C_{1-3} fluoroalkyl.

4. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of Formula Ic-2;



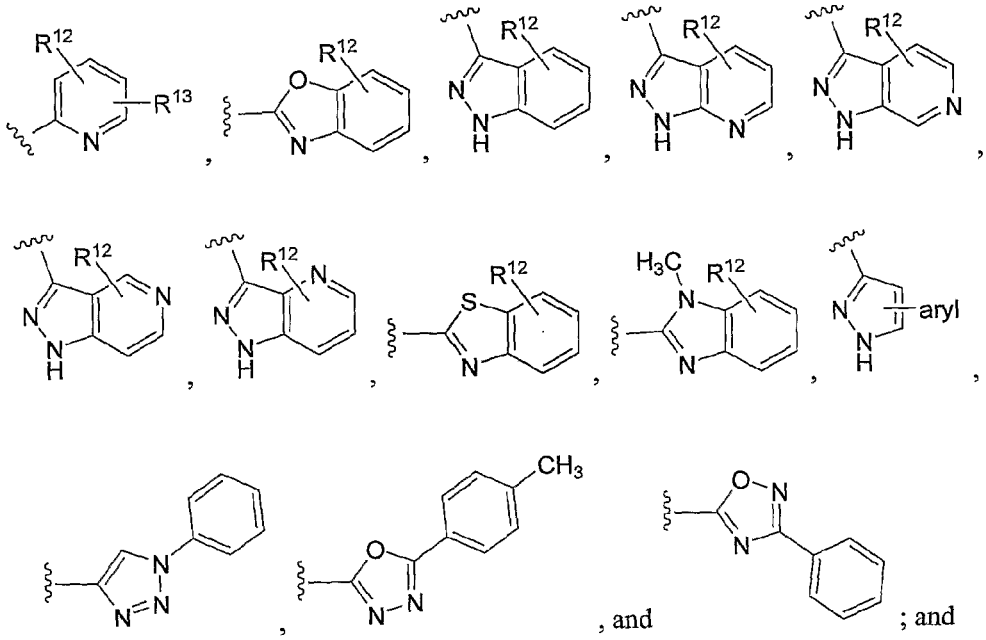
(Ic-2) ;

and provided that (i) when X is -C(R^5R^6)-, then neither R^1 nor R^2 is OR^3, and (ii) R^1 is other than H.

5. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen, halogen, and C_{1-6} alkyl;

A is aryl;

R^{10} is selected from the group consisting of:



; and

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halogen, oxo, NO_2, CN, OR^3, $O(CH_2)_tCF_3$, CO_2R^3, $CONR^3R^4$, $O(CH_2)_tNR^3R^4$, $O(CH_2)_vCOR^3$, $S(O)_mR^3$, $SO_2NR^3R^4$, C_{1-6} alkyl, C_{1-3} fluoroalkyl, and NR^3R^4.

6. A compound of Claim 5, or a pharmaceutically acceptable salt thereof, wherein:

V is $-CH_2-$;

X is -O-; and

Y is -O-.

7. A compound of Claim 6, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

3-chloro-5-[2-chloro-5-(1H-pyrazolo[3,4-b]pyridin-3-ylmethoxy)phenoxy]benzonitrile,

3-{5-[(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-3-fluorophenoxy}-5-chlorobenzonitrile,

3-{5-[(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chloro-3-fluorophenoxy}-5-chlorobenzonitrile,

3-{5-[(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-4-chloro-3-fluorophenoxy}-5-chlorobenzonitrile, and

3-{5-[(7-oxo-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-4-chloro-3-fluorophenoxy}-5-chlorobenzonitrile.

8. A compound of Claim 5, or a pharmaceutically acceptable salt thereof, wherein:

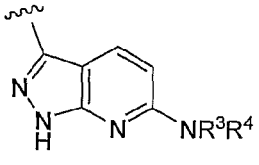
R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, and C_{1-4} alkyl;

A is phenyl optionally substituted with from 1 to 3 substituents each of which is independently halogen, C_{1-4} alkyl, or CN;

V is $-CH_2-$;

X is -O-;

Y is -O-;

R^{10} is ;

one of R^3 and R^4 is H, C_{1-4} alkyl, or C_{3-6} cycloalkyl, and the other of R^3 and R^4 is H, C_{1-4} alkyl, or C_{1-4} alkyl substituted with O-C_{1-4} alkyl, $C(O)R^A$, CO_2R^A, $C(O)N(R^A)R^B$, or SO_2R^A;

or alternatively R^3 and R^4 together with the nitrogen atom to which they are both attached form a 4- to 7-membered, saturated monocyclic ring optionally containing 1 heteroatom in addition to the nitrogen attached to R^3 and R^4 selected from N, O, and S, where the S is optionally oxidized to S(O) or $S(O)_2$, wherein the monocyclic ring is optionally substituted with 1 or 2 substituents each of which is independently: (1) C_{1-4} alkyl, (2) CF_3, (3) $(CH_2)_{1-2}T$ wherein T is OH, O-C_{1-4} alkyl, OCF_3, $N(R^A)R^B$, $C(O)N(R^A)R^B$, $C(O)R^A$, CO_2R^A, or SO_2R^A, (4) O-C_{1-4} alkyl, (5) OCF_3, (6) OH, (7) oxo, (8) halogen, (9) $C(O)N(R^A)R^B$, (10) $C(O)R^A$, (11) $C(O)-CF_3$, (12) $C(O)OR^A$, or (13) $S(O)_2R^A$;

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

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

9. A compound of Claim 8, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chlorophenoxy}-5-chlorobenzonitrile,

3-chloro-5-(2-chloro-5-{[6-methylamino)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)-benzonitrile,

3-chloro-5-(2-chloro-5-{[6-dimethylamino)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)-benzonitrile,

3-chloro-5-[2-chloro-5-({6-[(2-methoxyethyl)(methyl)amino]-1H-pyrazolo[3,4-b]-pyridin-3-yl}methoxy)phenoxy)benzonitrile,

3-chloro-5-(2-chloro-5-[(6-morpholin-4-yl-1H-pyrazolo[3,4-b]-pyridin-3-yl)methoxy]phenoxy)-benzonitrile,

N2-(3-{[4-chloro-3-(3-chloro-5-cyanophenoxy)phenoxy]methyl}-1H-pyrazolo[3,4-b]pyridin-6-yl)-N2-methylglycinamide,

3-chloro-5-(2-chloro-5-{[6-(3-methoxyazetidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)benzonitrile,

3-chloro-5-(2-chloro-5-{[6-(azetidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}phenoxy)-benzonitrile,

3-chloro-5-{2-chloro-5-[(6-piperazin-1-yl-1H-pyrazolo[3,4-b]-pyridin-3-yl)methoxy]phenoxy}-benzonitrile,

3-(5-{[6-(3-aminopyrrolidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}-2-chlorophenoxy)-5-chlorobenzonitrile,

3-[5-({6-[3-(aminomethyl)azetidin-1-yl]-1H-pyrazolo[3,4-b]-pyridin-3-yl}methoxy)-2-chlorophenoxy]-5-chlorobenzonitrile, and

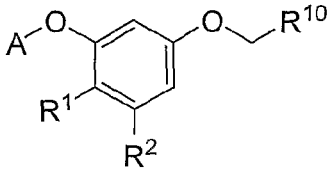
3-(5-{[6-(3-aminoazetidin-1-yl)-1H-pyrazolo[3,4-b]-pyridin-3-yl]methoxy}-2-chlorophenoxy)-5-chlorobenzonitrile,

3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-2-chloro-3-fluorophenoxy}-5-chlorobenzonitrile,

3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methoxy]-3-fluorophenoxy}-5-chlorobenzonitrile, and

3-{5-[(6-amino-1H-pyrazolo[3,4-b]pyridin-3-yl)methoxy]-4-chloro-3-fluorophenoxy}-5-chlorobenzonitrile.

10. A compound of Claim 8, or a pharmaceutically acceptable salt thereof, which is a compound of Formula Ic-1a:



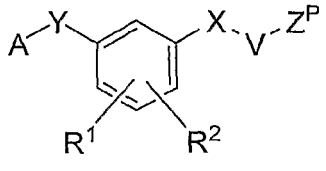
(Ic-1a).

11. A pharmaceutical composition comprising an effective amount of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. A method for inhibiting HIV reverse transcriptase, for treating or prophylaxis of HIV infection, or for treating, prophylaxis of, or delaying the onset of AIDS, which comprises administering to a subject in need thereof an effective amount of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof.

13. Use of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting HIV reverse transcriptase, for treating or prophylaxis of HIV infection, or for treating, prophylaxis of, or delaying the onset of AIDS.

14. A compound of Formula I-P:



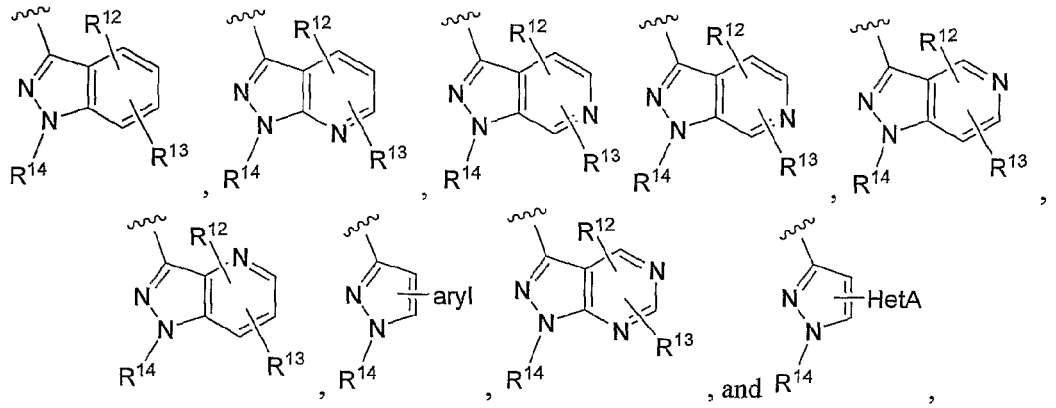
(I-P)

wherein:

R^1, R^2, A, V, X and Y have the same definition as set forth for a compound of Formula Ic of Claim 1;

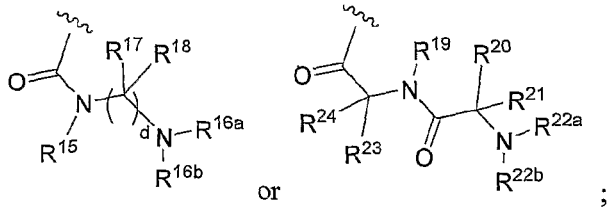
Z^P is R^{10*};

R^{10*} is a heterocycle selected from the group consisting of:



R^{12}, R^{13}, and HetA are as defined in Claim 1;

R^{14} is $PO(OH)O^-$ 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, C_{1-6} alkyl, $(CH_2)_{2-3}CF_3$, AryA, or HetB;

R^{16a} and R^{16b} are each independently H, C_{1-6} alkyl, $(CH_2)_{2-3}CF_3$, AryA, or HetB;

each R^{17} is independently H or C_{1-6} alkyl;

each R^{18} is independently H or C_{1-6} alkyl;

alternatively, an R^{17} together with the R^{18} attached to the same carbon atom form a 5- or 6-membered, saturated monocyclic ring optionally containing a heteroatom, wherein the optional heteroatom is selected from N, O and S, where the S is optionally oxidized to S(O) or $S(O)_2$;

R^{19} is H or C_{1-6} alkyl;

R^{20} is H or C_{1-6} alkyl;

R^{21} is H or C_{1-6} alkyl;

R^{22a} and R^{22b} are each independently H, C_{1-6} alkyl, $(CH_2)_{2-3}CF_3$, AryA, or HetB;

R^{23} is H or C_{1-6} alkyl;

R^{24} is H or C_{1-6} alkyl;

AryA is phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently Cl, Br, F, CH_3, CF_3, NH_2, $-NH(CH_3)$, $-N(CH_3)_2$, -CN, -OH, $-OCH_3$, cyclohexyl, ethenyl, ethynyl, $-SCH_3$, $-S(O)_2CH_3$, $-(CH_2)_{1-2}-SCH_3$, $-(CH_2)_{1-2}-S(O)_2CH_3$, $-NHC(O)CH_3$, $-O(CH_2)_{1-2}CF_3$, $-C(O)CH_3$, $-OC(O)CH_3$, $-(CH_2)_{1-2}OCH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)_2H$, $-C(O)_2CH_3$, $-(CH_2)_{1-2}C(O)_2CH_3$, $-NHC(O)OCH_3$, $-NH(CH_3)NHC(O)NH(CH_3)$, phenyl, or benzyl; and

HetB is a 5- or 6-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently Cl, Br, F, CH_3, CF_3, NH_2, $-NH(CH_3)$, $-N(CH_3)_2$, -CN, -OH, $-OCH_3$, cyclohexyl, ethenyl, ethynyl, $-SCH_3$, $-S(O)_2CH_3$, $-(CH_2)_{1-2}-SCH_3$, $-(CH_2)_{1-2}-S(O)_2CH_3$, $-NHC(O)CH_3$, $-O(CH_2)_{1-2}CF_3$, $-C(O)CH_3$, $-OC(O)CH_3$, $-(CH_2)_{1-2}OCH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)_2H$, $-C(O)_2CH_3$, $-(CH_2)_{1-2}C(O)_2CH_3$, $-NHC(O)OCH_3$, $-NH(CH_3)NHC(O)NH(CH_3)$, phenyl, or benzyl.