TITLE

TRICYCLIC 2-PYRIDONE COMPOUNDS USEFUL AS HIV REVERSE TRANSCRIPTASE INHIBITORS

FIELD OF THE INVENTION

This invention relates generally to tricyclic pyridone compounds which are useful as inhibitors of HIV reverse transcriptase, pharmaceutical compositions and diagnostic kits comprising the same, methods of using the same for treating viral infection or as assay standards or reagents, and intermediates and processes for making such tricyclic compounds.

BACKGROUND OF THE INVENTION

Two distinct retroviruses, human immunodeficiency virus (HIV) type-1 (HIV-1) or type-2 (HIV-2), have been etiologically linked to the immunosuppressive disease, 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 predisposes them to debilitating and ultimately fatal opportunistic infections.

The disease AIDS is the consequence of HIV-1 or HIV-2 virus following its complex viral life cycle. The virion life cycle involves the virion attaching itself to the host human T-4 lymphocyte immune cell through the binding of a glycoprotein on the surface of the virion's protective coat with the CD4 glycoprotein on the lymphocyte cell. Once attached, the virion sheds its glycoprotein coat, penetrates into the membrane of the host cell, and uncoats its RNA. The virion enzyme, reverse transcriptase, directs the process of transcribing the RNA into single-stranded DNA. The viral RNA is degraded and a second DNA strand is created. The now double-stranded DNA is integrated into the

human cell's genes and those genes are used for virus reproduction.

RNA polymerase transcribes the integrated viral DNA into viral mRNA. The viral RNA is translated into the precursor *gag-pol* fusion polyprotein. The polyprotein is then cleaved by the HIV protease enzyme to yield the mature viral proteins. Thus, HIV protease is responsible for regulating a cascade of cleavage events that lead to the virus particle's maturing into a virus that is capable of full infectivity.

The typical human immune system response, killing the invading virion, is taxed because the virus infects and kills the immune system's T cells. In addition, viral reverse transcriptase, the enzyme used in making a new virion particle, is not very specific, and causes transcription mistakes that result in continually changed glycoproteins on the surface of the viral protective coat. This lack of specificity decreases the immune system's effectiveness because antibodies specifically produced against one glycoprotein may be useless against another, hence reducing the number of antibodies available to fight the virus. The virus continues to reproduce while the immune response system continues to weaken. In most cases, without therapeutic intervention, HIV causes the host's immune system to be debilitated, allowing opportunistic infections to set in. Without the administration of antiviral agents, immunomodulators, or both, death may result.

There are at least three critical points in the HIV life cycle which have been identified as possible targets for antiviral drugs: (1) the initial attachment of the virion to the T-4 lymphocyte or macrophage site, (2) the transcription of viral RNA to viral DNA (reverse transcriptase, RT), and (3) the processing of gag-pol protein by HIV protease.

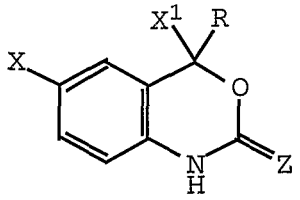
Inhibition of the virus at the second critical point, the viral RNA to viral DNA transcription process, has

provided a number of the current therapies used in treating AIDS. This transcription must occur for the virion to reproduce because the virion's genes are encoded in RNA and the host cell transcribes only DNA. By introducing drugs that block the reverse transcriptase from completing the formation of viral DNA, HIV-1 replication can be stopped.

A number of compounds that interfere with viral replication have been developed to treat AIDS. For example, nucleoside analogs, such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (ddC), 2',3'-dideoxythymidinene (d4T), 2',3'-dideoxyinosine (ddI), and 2',3'-dideoxy-3'-thia-cytidine (3TC) have been shown to be relatively effective in certain cases in halting HIV replication at the reverse transcriptase (RT) stage.

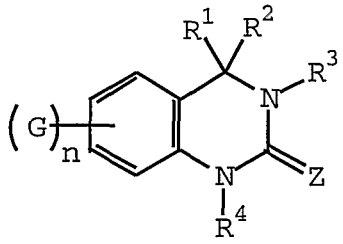
An active area of research is in the discovery of non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs). As an example, it has been found that certain benzoxazinones and quinazolinones are active in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and the treatment of AIDS.

U.S. 5,874,430 describes benzoxazinone non-nucleoside reverse transcriptase inhibitors for the treatment of HIV. U.S. 5,519,021 describe non-nucleoside reverse transcriptase inhibitors which are benzoxazinones of the formula:



wherein X is a halogen, Z may be O.

EP 0,530,994 and WO 93/04047 describe HIV reverse transcriptase inhibitors which are quinazolinones of the formula (A):



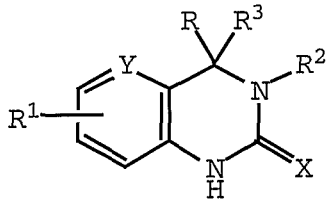
(A)

wherein G is a variety of groups, R^3 and R^4 may be H, Z may be O, R^2 may be unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted cycloalkyl, unsubstituted heterocycle, and optionally substituted aryl, and R^1 may be a variety of groups including substituted alkyl.

WO 95/12583 also describes HIV reverse transcriptase inhibitors of formula A. In this publication, G is a variety of groups, R^3 and R^4 may be H, Z may be O, R^2 is substituted alkenyl or substituted alkynyl, and R^1 is cycloalkyl, alkynyl, alkenyl, or cyano. WO 95/13273 illustrates the asymmetric synthesis of one of the compounds of WO 95/12583, (S)-(-)-6-chloro-4-cyclopropyl-3,4-dihydro-4((2-pyridy)ethynyl)-2(1H)-quinazolinone.

Synthetic procedures for making quinazolinones like those described above are detailed in the following references: Houpis et al., *Tetr. Lett.* **1994**, *35(37)*, 6811-6814; Tucker et al., *J. Med. Chem.* **1994**, *37*, 2437-2444; and, Huffman et al., *J. Org. Chem.* **1995**, *60*, 1590-1594.

DE 4,320,347 illustrates quinazolinones of the formula:



wherein R is a phenyl, carbocyclic ring, or a heterocyclic ring. Compounds of this sort are not considered to be part of the present invention.

Even with the current success of reverse transcriptase inhibitors, it has been found that HIV patients can become resistant to a given inhibitor. Thus, there is an important need to develop additional inhibitors to further combat HIV infection.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel reverse transcriptase inhibitors.

It is another object of the present invention to provide a novel method for treating HIV infection which comprises administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, including a pharmaceutically acceptable salt form thereof.

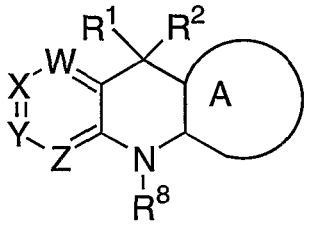
It is another object of the present invention to provide a novel method for treating HIV infection which comprises administering to a host in need thereof a therapeutically effective combination of (a) one of the compounds of the present invention and (b) one or more compounds selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors.

It is another object of the present invention to provide pharmaceutical compositions with reverse transcriptase inhibiting activity comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

It is another object of the present invention to provide novel tricyclic 2-pyridone compounds for use in therapy.

It is another object of the present invention to provide the use of novel tricyclic 2-pyridone compounds for the manufacture of a medicament for the treatment of HIV infection.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

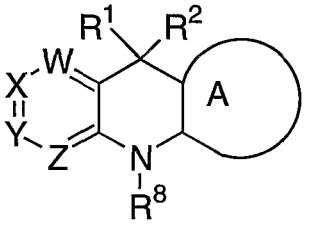


(I)

wherein R^1, R^2, R^8, A, W, X, Y, and Z are defined below, including any stereoisomeric form, mixtures of stereoisomeric forms, complexes, prodrug forms or pharmaceutically acceptable salt forms thereof, are effective reverse transcriptase inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

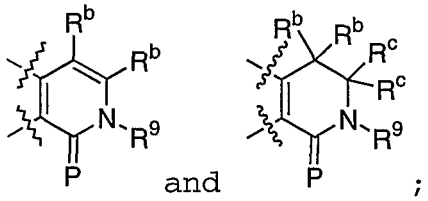
[1] Thus, in an embodiment, the present invention provides a novel compound of formula (I):



(I)

or a stereoisomeric form or mixture of stereoisomeric forms or a pharmaceutically acceptable salt form thereof, wherein:

A is a ring selected from:



;

P is O or S;

R^b, at each occurrence, is independently selected from H, F, Cl, Br, I, CN, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, C_{1-4} alkyl-O-, or C_{1-4} alkyl-NH-, NH_2;

R^c, at each occurrence, is independently selected from H, C_{1-4} alkyl, C_{1-4} alkenyl, and C_{1-4} alkynyl;

W is N or CR^3;

X is N or CR^{3a};

Y is N or CR^{3b};

Z is N or CR^{3c};

provided that if two of W, X, Y, and Z are N, then the remaining are other than N;

R^1 is selected from the group C_{1-4} alkyl substituted with 0-9 halogen, cyclopropyl, hydroxymethyl, and CN;

R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-6} alkyl substituted with 0-2 R^4, C_{2-6}haloalkyl, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, phenyl substituted with 0-2 R^{3d}, and 3-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3d};

R^3 is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, CF_3, F, Cl, Br, I, $-(CH_2)_tNR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-(CH_2)_tNHC(O)R^7$, $-(CH_2)_tNHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-S-C_{1-4}$alkyl, $-S(O)C_{1-4}$alkyl, $-S(O)_2C_{1-4}$alkyl, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

R^{3a} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, CF_3, F, Cl, Br, I, $-(CH_2)_tNR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-(CH_2)_tNHC(O)R^7$, $-(CH_2)_tNHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-S-C_{1-4}$alkyl, $-S(O)C_{1-4}$alkyl, $-S(O)_2C_{1-4}$alkyl, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^{3c} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3b} and R^{3c} together form $-OCH_2O-$;

R^{3d}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3e}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, CN, -OH, $-O-R^{11}$,

OCF_3, $-O(CO)-R^{13}$, $-OS(O)_2C_{1-4}$alkyl, $-NR^{12}R^{12a}$, $-C(O)R^{13}$, $-NHC(O)R^{13}$, $-SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-NHSO_2R^{10}$, and $-SO_2NR^{12}R^{12a}$;

R^4 is selected from the group H, F, Cl, Br, I, C_{1-6} alkyl substituted with 0-2 R^{3e}, C_{3-10} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-10 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H and C_{1-4} alkyl;

alternatively, R^5 and R^{5a}, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms;

R^6 is selected from the group H, OH, C_{1-4} alkyl, C_{1-4} alkoxy, and NR^5R^{5a};

R^7 is selected from the group H, C_{1-3} alkyl and C_{1-3} alkoxy;

R^8 is selected from the group H, (C_{1-6} alkyl)carbonyl, C_{1-6} alkoxy, (C_{1-4} alkoxy)carbonyl, C_{6-10} aryloxy, (C_{6-10} aryl)oxycarbonyl, (C_{6-10} aryl)methylcarbonyl, (C_{1-4} alkyl)carbonyloxy(C_{1-4} alkoxy)carbonyl, C_{6-10} arylcarbonyloxy(C_{1-4} alkoxy)carbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, phenyl(C_{1-4} alkoxy)carbonyl, and NR^5R^{5a}(C_{1-6} alkyl)carbonyl;

R^9 is selected from H, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, (C_{1-6} alkyl)carbonyl, C_{1-6} alkoxy, (C_{1-4} alkoxy)carbonyl, C_{6-10} aryloxy, (C_{6-10} aryl)oxycarbonyl, (C_{6-10}

aryl)methylcarbonyl, (C_{1-4} alkyl)carbonyloxy(C_{1-4} alkoxy)carbonyl, C_{6-10} arylcarbonyloxy(C_{1-4} alkoxy)carbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, phenyl(C_{1-4} alkoxy)carbonyl, and NR^5R^{5a}(C_{1-6} alkyl)carbonyl;

R^{10} is selected from the group C_{1-4} alkyl and phenyl;

R^{11} is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyl substituted with C_{3-6}cycloalkyl substituted with 0-2 R^{3e}, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocycle substituted with 0-2 R^{3e};

R^{12} and R^{12a} are independently selected from H, C_{1-6} alkyl, C_{1-6} alkyl substituted with C_{3-6}cycloalkyl substituted with 0-2 R^{3e}, and C_{3-6} carbocycle substituted with 0-2 R^{3e};

alternatively, R^{12} and R^{12a} can join to form 4-7 membered heterocyclic ring;

R^{13} is selected from the group H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, $NR^{12}R^{12a}$, C_{3-6}carbocycle, and -O-C_{3-6}carbocycle; and

t is selected from 0 and 1.

[2] In a preferred embodiment, the present invention provides compounds of formula (I), wherein:

R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-5} alkyl substituted with 0-2 R^4, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with

0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, and phenyl substituted with 0-2 R^{3d}, and 3-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3d}, wherein the heterocyclic system is selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-oxazolyl, 2-thiazolyl, 4-isoxazolyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl;

R^3 and R^{3a}, at each occurrence, are independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, $NHC(O)NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} and R^{3c}, at each occurrence, are independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^4 is selected from the group H, Cl, F, C_{1-4} alkyl substituted with 0-2 R^{3e}, C_{3-6} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

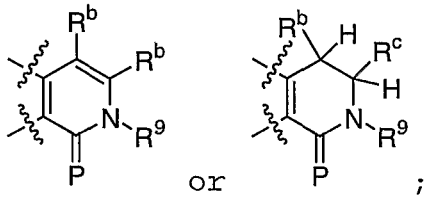
R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a}; and

R^7 is selected from the group CH_3, C_2H_5, $CH(CH_3)_2$, OCH_3, OC_2H_5, and $OCH(CH_3)_2$.

[3] In another preferred embodiment, the present invention provides compounds of formula (I), wherein:

P is O;

Ring A is:



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R^b, at each occurrence, is selected from H, F, Cl, and Br, C_{1-4} alkyl, CN, C_{1-4} alkyl-NH-, NH_2;

R^c is selected from H and methyl;

W is CR^3;

X is CR^{3a};

Y is CR^{3b};

Z is CR^{3c};

R^1 is selected from the group CF_3, C_2F_5, CHF_2, CH_2F and cyclopropyl;

R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-3} alkyl substituted with 0-2 R^4, C_{2-3} alkenyl substituted with 0-2 R^4, C_{2-3} alkynyl substituted with 0-1 R^4, and C_{3-6} cycloalkyl substituted with 0-2 R^{3d};

R^3, R^{3a}, R^{3b}, and R^{3c}, at each occurrence, are independently selected from the group H, C_{1-3} alkyl, OH, C_{1-3} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3e}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, $-NR^5R^{5a}$, $-C(O)R^6$, and $-SO_2NR^5R^{5a}$;

R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, CN, -OH, $-O-R^{11}$, , $-O(CO)-R^{13}$, $-SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, and $-NR^{12}R^{12a}$;

R^4 is selected from the group H, Cl, F, C_{1-4} alkyl substituted with 0-1 R^{3e}, C_{3-5} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-oxazolyl, 2-thiazolyl, 4-isoxazolyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl;

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5;

R^8 is H;

R^9 is H, methyl, ethyl, propyl, and i-propyl;

R^{11} is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, and C_{3-6} carbocycle substituted with 0-2 R^{3e} wherein the C_{3-6} carbocycle is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and phenyl; and

R^{12} and R^{12a} are independently selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, and C_{3-6} carbocycle substituted with 0-2 R^{3e} wherein the C_{3-6} carbocycle is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and phenyl.

[4] In another preferred embodiment, the present invention provides compounds of formula (I), wherein:

R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-3} alkyl substituted with 1 R^4, C_{2-3} alkenyl substituted with 1 R^4, and C_{2-3} alkynyl substituted with 1 R^4;

R^3, R^{3a}, R^{3b}, and R^{3c}, at each occurrence, are independently selected from the group H, C_{1-3} alkyl, OH, C_{1-3} alkoxy, F, Cl, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3e}, at each occurrence, is independently selected from the group CH_3, -OH, OCH_3, OCF_3, F, Cl, and $-NR^5R^{5a}$;

R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, -OH, CN, $-O-R^{11}$, $-O(CO)-R^{13}$, and $-NR^{12}R^{12a}$, $-SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, and $-OS(O)_2$methyl;

R^4 is selected from the group H, Cl, F, CH_3, CH_2CH_3, cyclopropyl substituted with 0-1 R^{3e}, 1-methyl-cyclopropyl substituted with 0-1 R^{3e}, cyclobutyl substituted with 0-1 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl;

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5; and

R^9 is selected from H and methyl.

[5] In another preferred embodiment, the present invention provides compounds of formula (I), wherein:

R^2 is selected from the group methyl substituted with 0-2 R^{3f}, methyl substituted with 0-2 R^4, ethyl substituted

with 0-2 R^4, propyl substituted with 0-2 R^4, ethenyl substituted with 0-2 R^4, 1-propenyl substituted with 0-2 R^4, 2-propenyl substituted with 0-2 R^4, ethynyl substituted with 0-2 R^4, 1-propynyl substituted with 0-2 R^4, 2-propynyl substituted with 0-2 R^4, and cyclopropyl substituted with 0-1 R^{3d};

R^{3e}, at each occurrence, is independently selected from the group CH_3, -OH, OCH_3, OCF_3, F, Cl, and $-NR^5R^{5a}$;

R^4 is selected from the group H, Cl, F, CH_3, CH_2CH_3, cyclopropyl substituted with 0-1 R^{3e}, 1-methyl-cyclopropyl substituted with 0-1 R^{3e}, cyclobutyl substituted with 0-1 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl ;

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5;

R^8 is H.

[6] In another preferred embodiment, the present invention provides compounds of formula (I), wherein:

R^1 is selected from methyl, ethyl, propyl, i-propyl, butyl, cyclopropyl, CF_3, CF_2CH_3, CN, and hydroxymethyl;

R^2 is selected from the group methyl substituted with 0-2 R^{3f}, methyl substituted with 0-2 R^4, ethyl substituted with 0-2 R^4, propyl substituted with 0-1 R^4, ethenyl substituted with 0-2 R^4, 1-propenyl substituted with 0-2 R^4, 2-propenyl substituted with 0-2 R^4, ethynyl substituted with 0-2 R^4, 1-propynyl substituted with 0-2 R^4;

R^3, R^{3b}, and R^{3c} are H;

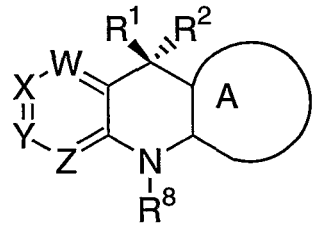
R^{3e} is CH_3;

R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, CN, -OH, $-O-R^{11}$, $-SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, and $-NR^{12}R^{12a}$;

R^4 is selected from the group H, cyclopropyl substituted with 0-1 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl;

R^{12} and R^{12a} are independently selected from H, methyl, ethyl, propyl, and i-propyl, and C_{3-6} carbocycle substituted with 0-2 R^{3e} wherein the C_{3-6} carbocycle is selected from cyclopropyl.

[7] Preferred compounds of the present invention are those compounds wherein the compound is of formula (Ic):



(Ic).

[8] Preferred compounds of the present invention include compounds of formula (I) wherein the compound of formula (I) is selected from the compounds shown in Table 1.

7-fluoro-2-methyl-5-[(6-methyl-2-pyridinyl)methyl]-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

5-(2-cyclopropylethynyl)-7-fluoro-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-propyl-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

5-butyl-7-fluoro-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(4-fluorophenylmethyl) -5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(2-pyridylmethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(isopropyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(3-pyridylmethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(4-pyridylmethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(3-propynyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(2-pyridylethynyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(2-(2-pyridyl)ethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

3-chloro-7-fluoro-5-propyl-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(3-propenyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

5-(2-cyclopropylethyl)-7-fluoro-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(ethynyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(2-ethoxyethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

5-Butyl-7-chloro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(2-pyridylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(2-cyclopropylethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-cyclopropylethynyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(N-cyclopropylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-hydroxymethyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-3-methyl-5-(2-pyridylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(2-cyclopropylethyl)-3-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(2-methoxyethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(N-methyl-N-*i*-propylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclopropylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(*n*-propylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclobutylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(*i*-butylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(*i*-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Cyano-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Cyano-5-(i-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclopropylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclopropanesulfinylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(t-butylsulfinylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(methylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(ethylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Fluoro-5-(i-propylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(t-butylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclopropylmethoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclobutoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(Cyclobutoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(Cyclopropylmethoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-3-methyl-5-(i-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-3-methyl-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Cyano-3-methyl-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-2-methyl-5-(i-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

3,7-Dichloro-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

4,7-Dichloro-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(ethoxyethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-methyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propoxymethyl)-5-methyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-cyano-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-(hydroxymethyl)-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-difluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propoxymethyl)-5-difluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(n-Butyl)-5-(1,1-difluoroethyl)-7-Fluoro-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-(1,1-difluoroethyl)-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Cyano-5-(n-butyl)-5-(1,1-difluoroethyl)-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(ethoxymethyl)-5-(1,1-difluoroethyl)-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(allyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-methyl-1-propenyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(1-propynyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyanomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(ethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(dimethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(methylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-ethoxyethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(i-propylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(diethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(cyclopropylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(pentyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-butyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(vinyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(imidazolylethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(pyrazolylethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(1,2,4-triazolylethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(methylethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(i-propylethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(pyrrolidinyl)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(methoxy)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(3-pentanylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(dimethoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-butylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyclopropylmethylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(allylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-((R)-sec-butylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-((S)-sec-butylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(diethoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

3-chloro-5-(propyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(butyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(i-propoxy)ethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propylaminomethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propoxymethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-ethoxyethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(sec-butylaminomethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyclopentylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyclobutylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(dimethylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(pyrrolidinylmethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyclopropylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(dimethoxy)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(diethoxy)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(1,3-dioxolanyl)methyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one; and

5-(2-(methoxy)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one.

The present invention also provides a novel pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of

a compound of formula (I) or a pharmaceutically acceptable salt form thereof

The compositions and methods of use comprising the compounds of the present invention include compositions and methods of use comprising the compounds of the present invention and stereoisomeric forms thereof, mixtures of stereoisomeric forms thereof, complexes thereof, crystalline forms thereof, prodrug forms thereof and pharmaceutically acceptable salt forms thereof

In another embodiment, the present invention provides a novel method for treating HIV infection which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof

In another embodiment, the present invention provides a novel method of treating HIV infection which comprises administering, in combination, to a host in need thereof a therapeutically effective amount of:

(a) a compound of formula (I); and

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors.

In another embodiment, the present invention provides a novel method of treating HIV infection which comprises administering, in combination, to a host in need thereof a therapeutically effective amount of:

(a) a compound of formula (I); and

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors, HIV protease inhibitors, CCR-5 inhibitors, and fusion inhibitors.

Preferred reverse transcriptase inhibitors useful in the above method of treating HIV infection are selected from the group AZT, ddC, ddI, d4T, 3TC, delavirdine, efavirenz, nevirapine, Ro 18,893, trovirdine, MKC-442, HBY 097, HBY1293, GW867, ACT, UC-781, UC-782, RD4-2025, MEN 10979, AG1549 (S1153), TMC-120, TMC-125, Calanolide A, and PMPA. Preferred protease inhibitors useful in the above method of treating HIV infection are selected from the group saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, palinavir, BMS-232623, GS3333, KNI-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, VX-175, MK-944, and VX-478, the CCR-5 inhibitor is selected from TAK-779 (Takeda), SC-351125 (SCH-C, Schering) and SCH-D (Schering), and the fusion inhibitor is selected from T-20 amd T1249.

In an even more preferred embodiment, the reverse transcriptase inhibitor is selected from the group AZT, efavirenz, and 3TC and the protease inhibitor is selected from the group saquinavir, ritonavir, nelfinavir, and indinavir.

In a still further preferred embodiment, the reverse transcriptase inhibitor is AZT.

In another still further preferred embodiment, the protease inhibitor is indinavir.

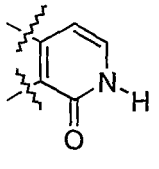
In another embodiment, the present invention provides a pharmaceutical kit useful for the treatment of HIV infection, which comprises a therapeutically effective amount of:

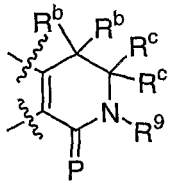
(a) a compound of formula (I); and,

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors, in one or more sterile containers.

In another embodiment, the present invention provides novel tricyclic 2-pyridone compounds for use in therapy.

In another embodiment, the present invention provides the use of novel tricyclic 2-pyridone compounds for the manufacture of a medicament for the treatment of HIV infection.

In another embodiment, the present invention provides that Ring A is  .

In another embodiment, the present invention provides that Ring A is  .

In another embodiment, the present invention provides that R^1 is CF_3, CF_2CH_3, and CHF_2.

In another embodiment, the present invention provides that R^1 is selected from the group CF_3, C_2F_5, CF_2CH_3, CHF_2, CH_2F and cyclopropyl.

In another embodiment, the present invention provides that R^1 is methyl, ethyl, propyl, i-propyl and butyl.

In another embodiment, the present invention provides that R^1 is CN and hydroxymethyl.

In another embodiment, the present invention provides that R^2 is selected from the group methyl substituted with

0-3 R^{3f}, C_{1-5} alkyl substituted with 0-2 R^4, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, and phenyl substituted with 0-2 R^{3d}, and 3-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3d}, wherein the heterocyclic system is selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-oxazolyl, 2-thiazolyl, 4-isoxazolyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl.

In another embodiment, the present invention provides that R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-3} alkyl substituted with 0-2 R^4, C_{2-3} alkenyl substituted with 0-2 R^4, C_{2-3} alkynyl substituted with 0-1 R^4, and C_{3-6} cycloalkyl substituted with 0-2 R^{3d}.

In another embodiment, the present invention provides that R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-3} alkyl substituted with 1 R^4, C_{2-3} alkenyl substituted with 1 R^4, and C_{2-3} alkynyl substituted with 1 R^4.

In another embodiment, the present invention provides that R^2 is selected from the group methyl substituted with 0-2 R^{3f}, methyl substituted with 0-2 R^4, ethyl substituted with 0-2 R^4, propyl substituted with 0-2 R^4, ethenyl substituted with 0-2 R^4, 1-propenyl substituted with 0-2 R^4, 2-propenyl substituted with 0-2 R^4, ethynyl substituted with 0-2 R^4, 1-propynyl substituted with 0-2 R^4, 2-propynyl substituted with 0-2 R^4, and cyclopropyl substituted with 0-1 R^{3d}.

In another embodiment, the present invention provides that R^2 is selected from the group methyl substituted with

0-2 R^{3f}, methyl substituted with 0-2 R^4, ethyl substituted with 0-2 R^4, propyl substituted with 0-1 R^4, ethenyl substituted with 0-2 R^4, 1-propenyl substituted with 0-2 R^4, 2-propenyl substituted with 0-2 R^4, ethynyl substituted with 0-2 R^4, 1-propynyl substituted with 0-2 R^4.

In another embodiment, R^2 is selected from the group methyl substituted with 0-2 R^{3f}, methyl substituted with 0-2 R^4, and ethyl substituted with 0-2 R^4.

In another embodiment, R^2 is R^{2c}.

In another embodiment, the present invention provides that R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, CN, -OH, -O-R^{11}, , -O(CO)-R^{13}, -SR^{11}, -S(O)R^{11}, -$S(O)_2R^{11}$, and -$NR^{12}R^{12a}$.

In another embodiment, the present invention provides that R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, -OH, CN, -O-R^{11}, -O(CO)-R^{13}, and -$NR^{12}R^{12a}$, -SR^{11}, -S(O)R^{11}, -$S(O)_2R^{11}$, and -$OS(O)_2$methyl.

In another embodiment, the present invention provides that R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, CN, -OH, -O-R^{11}, -SR^{11}, -S(O)R^{11}, -$S(O)_2R^{11}$, and -$NR^{12}R^{12a}$.

In another embodiment, the present invention provides that R^4 is selected from the group H, Cl, F, C_{1-4} alkyl substituted with 0-2 R^{3e}, C_{3-6} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e}.

In another embodiment, the present invention provides that R^4 is selected from the group H, Cl, F, C_{1-4} alkyl substituted with 0-1 R^{3e}, C_{3-5} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-oxazolyl, 2-thiazolyl, 4-isoxazolyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl.

In another embodiment, the present invention provides that R^4 is selected from the group H, Cl, F, CH_3, CH_2CH_3, cyclopropyl substituted with 0-1 R^{3e}, 1-methyl-cyclopropyl substituted with 0-1 R^{3e}, cyclobutyl substituted with 0-1 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl.

In another embodiment, the present invention provides that R^4 is selected from the group H, Cl, F, CH_3, CH_2CH_3, cyclopropyl substituted with 0-1 R^{3e}, 1-methyl-cyclopropyl substituted with 0-1 R^{3e}, cyclobutyl substituted with 0-1 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl.

In another embodiment, the present invention provides that R^8 is H.

In another embodiment, the present invention provides that R^9 is H, methyl, ethyl, propyl, and i-propyl.

The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional even more preferred embodiments of the present invention. Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments.

DEFINITIONS

It will be appreciated that the compounds of the present invention contain an asymmetrically substituted carbon atom, and may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated. All tautomers of shown or described compounds are also considered to be part of the present invention.

As used herein, the term "tricyclic 2-pyridones" is intended to include the compounds 5,10-Dihydro-2H-benzo[b][1,7]naphthyridin-1-one which are represented by the compounds of Formula I.

The processes of the present invention are contemplated to be practiced on at least a multigram scale, kilogram scale, multikilogram scale, or industrial scale. Multigram scale, as used herein, is preferably the scale wherein at

least one starting material is present in 10 grams or more, more preferably at least 50 grams or more, even more preferably at least 100 grams or more. Multikilogram scale, as used herein, is intended to mean the scale wherein more than one kilogram of at least one starting material is used. Industrial scale as used herein is intended to mean a scale which is other than a laboratory scale and which is sufficient to supply product sufficient for either clinical tests or distribution to consumers.

The present invention is intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (i.e., within) of the ring.

When any variable (e.g., R^b) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^4, then said group may optionally be substituted with up to two R^4 groups and R^4 at each occurrence is selected independently from the definition of R^4. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be

bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, the following terms and expressions have the indicated meanings.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. By way of illustration, the term "C_{1-10} alkyl" or "C_1-C_{10} alkyl" is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. "C_{1-4} alkyl" is intended to include C_1, C_2, C_3, and C_4 alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-10} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-7} cycloalkyl, is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any

stable point along the chain, such as ethenyl, propenyl and the like. C_{2-10} alkenyl, is intended to include C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkenyl groups. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. C_{2-10} alkynyl, is intended to include C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo. "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate and the like.

As used herein, "aryl" or "aromatic residue" is intended to mean an aromatic moiety containing the specified number of carbon atoms, such as phenyl or naphthyl. As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12 or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. An oxo group may be a substituent on a nitrogen heteroatom to form

an N-oxide. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 1,3-dioxolanyl, 1,3-dioxanyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl,

4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, "HIV reverse transcriptase inhibitor" is intended to refer to both nucleoside and non-nucleoside inhibitors of HIV reverse transcriptase (RT). Examples of nucleoside RT inhibitors include, but are not limited to, AZT, ddC, ddI, d4T, PMPA, and 3TC. Examples of non-nucleoside RT inhibitors include, but are no limited to, delavirdine (Pharmacia and Upjohn U90152S), efavirenz (DuPont), nevirapine (Boehringer Ingelheim), Ro 18,893 (Roche), trovirdine (Lilly), MKC-442 (Triangle), HBY 097 (Hoechst), HBY1293 (Hoechst), GW867 (Glaxo Wellcome), ACT (Korean Research Institute), UC-781 (Rega Institute), UC-782 (Rega Institute), RD4-2025 (Tosoh Co. Ltd.), MEN 10979 (Menarini Farmaceutici) AG1549 (S1153; Agouron), TMC-120, TMC-125, and Calanolide A.

As used herein, "HIV protease inhibitor" is intended to refer to compounds that inhibit HIV protease. Examples include, but are not limited, saquinavir (Roche, Ro31-8959), ritonavir (Abbott, ABT-538), indinavir (Merck, MK-639), amprenavir (Vertex/Glaxo Wellcome), nelfinavir (Agouron, AG-1343), palinavir (Boehringer Ingelheim), BMS-232623 (Bristol-Myers Squibb), GS3333 (Gilead Sciences), KNI-413 (Japan Energy), KNI-272 (Japan Energy), LG-71350 (LG

Chemical), CGP-61755 (Ciba-Geigy), PD 173606 (Parke Davis), PD 177298 (Parke Davis), PD 178390 (Parke Davis), PD 178392 (Parke Davis), U-140690 (Pharmacia and Upjohn), tipranavir (Pharmacia and Upjohn, U-140690), DMP-450 (DuPont), AG-1776, VX-175, MK-944, VX-478 and ABT-378. Additional examples include the cyclic protease inhibitors disclosed in WO93/07128, WO 94/19329, WO 94/22840, and PCT Application Number US96/03426.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists

of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention. Examples of prodrugs at R^8 and at R^9 are C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4}

alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Only stable compounds are contemplated by the present invention.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to inhibit HIV infection or treat the symptoms of HIV infection in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the effect (in this case, inhibition of HIV replication) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state

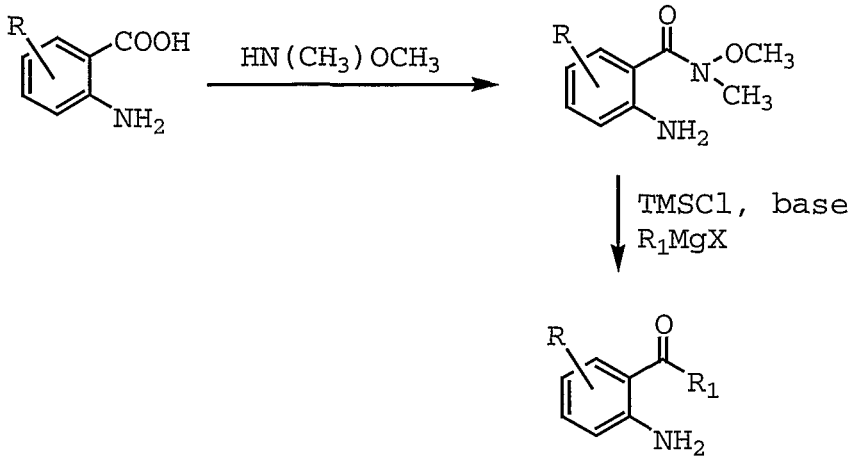
from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

SYNTHESIS

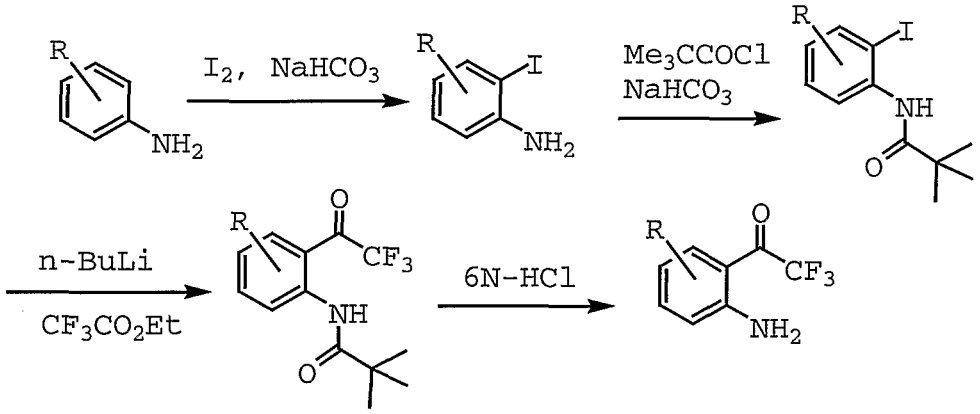
The compounds of Formula I can be prepared using the reactions and techniques described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991).

SCHEME 1



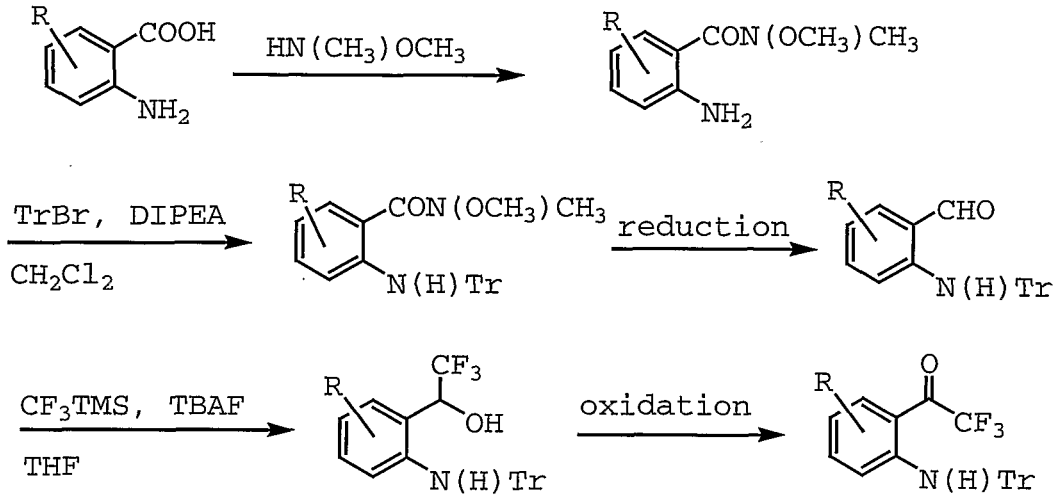
Scheme 1 illustrates a method of preparing keto-anilines from an appropriately substituted 2-aminobenzoic acid (wherein R represents R^3, R^{3a}, R^{3b}, and R^{3c}). The acid is converted to its N-methoxy-N-methyl amide derivative which can then be displaced to obtain the R^1-substituted ketone. The keto-anilines are useful intermediates for the presently claimed compounds.

SCHEME 2



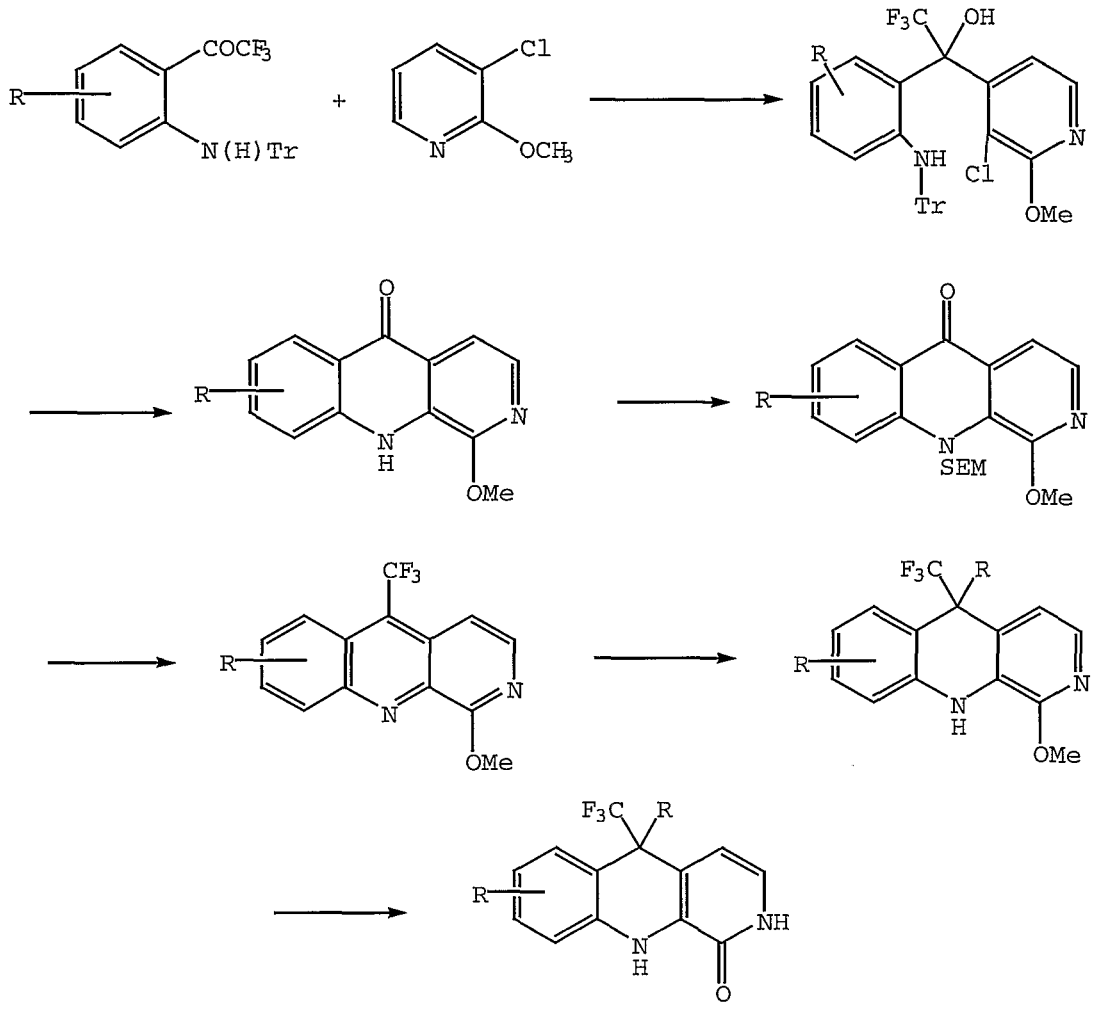
Scheme 2 describes another method of preparing keto-anilines, this time from an appropriately substituted aniline. After iodination and amine protection, a group such as trifluoromethyl can be introduced using a strong base and ethyl trifluoroacetate. Deprotection provides the keto-aniline. Additional means of preparing keto-anilines are known to one of skill in the art, e.g, Houpis et al, *Tetr. Lett.* **1994**, *35(37)*, 6811-6814, the contents of which are hereby incorporated herein by reference.

SCHEME 3



Another method of making 2-trifluoroacetylanilines is shown in Scheme 3. After forming the protected aniline, the amide is then reduced and the trifluoromethyl group added. Oxidation with an oxidant, such as MnO_2, provides the useful intermediate.

Scheme 4

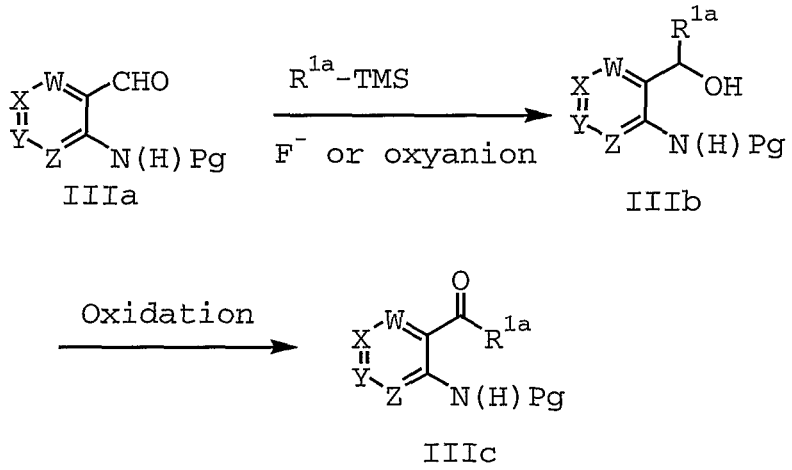


Scheme 4 describes a method of converting the protected aniline to the tricyclic structure. Metallation of the chloropyridine with LDA followed by condensation with the trifluoromethylketone gave the tertiary alcohol. Cyclization to the azaacridone was accomplished by heating in DMF with K2CO3 for base. After protection with SEM-Cl, the acridone was condensed with CF3TMS and Bu4NF to give the fully aromatic tricycle. Addition of nucloephiles such as cyanide and organometallics generated the quaternary addition products. Conversion of the methoxypyridine to the pyridone products was accomplished by heating with HCl or HBr.

While the above schemes describe methods of preparing the benzo analogs (i.e. wherein W, X, Y, and Z are all carbon), they can be modified by one skilled in the art to

prepare the heterocyclic varieties wherein W, X, Y, or Z are equal to nitrogen.

SCHEME 5

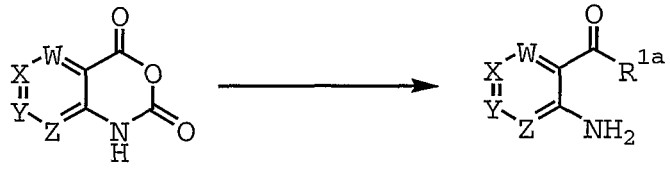


Scheme 5 illustrates specific steps for forming the aminoketone IIIc. Intermediate IIIb (R^{1a} is selected from CF_3, CF_3CF_2, and $CF_3CF_2CF_2$) is useful for making some of the presently claimed compounds. Pg is an amine protecting group as defined previously, preferably trityl (triphenylmethyl). The protected or unprotected aminobenzaldehyde, preferably protected, is treated with a perfluoralkyl trimethylsilane, preferably trifluoromethyl trimethylsilane, followed by fluoride anion, preferably tetrabutylammonium fluoride. In the same fashion, CF_3CF_2TMS, $CF_3CF_2CF_2TMS$ can also be used to prepare the appropriately substituted ketones. Other sources of fluoride anion such as sodium fluoride, potassium fluoride, lithium fluoride, cesium fluoride as well as oxyanionic species such as potassium tert-butoxide, sodium methoxide, sodium ethoxide and sodium trimethylsilanolate can also be used.. Aprotic solvents such as DMF and THF can be used, preferably THF. The amount of perfluoralkyl trimethylsilane used can be from about 1 to about 3 equivalents with an equivalent amount of fluoride anion or oxyanionic species. The reaction can be typically carried out at temperatures

between about -20°C to about 50°C, preferably about -10 to about 10°C, more preferably about 0°C.

Conversion of IIIb to IIIc can be achieved by using an oxidizing agent well known to one of skill in the art such as MnO_2, PDC, PCC, $K_2Cr_2O_7$, CrO_3, $KMnO_4$, $BaMNO_4$, $Pb(OAc)_4$, and RuO_4. A preferred oxidant is MnO_2. Such conversion can be performed in an aprotic solvent like THF, DMF, dichloromethane dichloroethane, or tetrachloroethane, preferably dichloromethane.

SCHEME 6



In addition to the methods of obtaining keto-anilines described in Schemes 1 and 2, nucleophilic opening of isatoic anhydrides can also be used as shown in Scheme 6. This reaction is accomplished by using an anionic nucleophile of the group R^{1a}. See Mack et al, *J. Heterocyclic Chem.* **1987**, *24*, 1733-1739; Coppola et al, *J. Org. Chem.* **1976**, *41(6)*, 825-831; Takimoto et al, *Fukuoka Univ. Sci. Reports* **1985**, *15(1)*, 37-38; Kadin et al, *Synthesis* **1977**, 500-501; Staiger et al, *J. Org. Chem.* **1959**, *24*, 1214-1219.

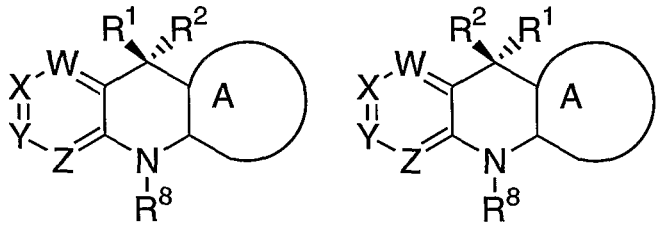
It is preferred that the stoichiometry of the isatoic anhydride reagent to nucleophile is about 1.0 to 2.1 molar equivalents. The use of 1.0 eq. or more (e.g., 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.0) of anion (or anion precursor) is preferred to force the conversion and improve the isolated yield. Preferably, the temperature used is from -20 to +35°C, with temperatures below 0°C being more preferred and -20°C being even more preferred. Reactions are run to about completion with time dependent upon *inter alia* nucleophile, solvent, and temperature. Preferably this nucleophilic addition is run in THF, but any

aprotic solvent would be suitable. Reaction with the active nucleophilic anion is the only criterion for exclusion of a solvent.

Patent Publications WO98/14436, WO98/45276, and WO01/29037 describe other methods of preparing the appropriately substituted anilines and are hereby incorporated by reference.

The keto-anilines can alsobe converted to the tricyclic compounds using procedures described in the examples.

One enantiomer of a compound of Formula I may display superior activity compared with the other. Thus, both of the following stereochemistries are considered to be a part of the present invention.



When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotheraphy*, **1995**, 2602-2605.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Abbreviations used in the Examples are defined as follows: "°C" for degrees Celsius, "d" for doublet, "dd" for doublet of doublets, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "H" for hydrogen or hydrogens, "hr" for hour or hours, "m" for multiplet, "M" for molar, "min" for minute or minutes, "MHz" for megahertz,

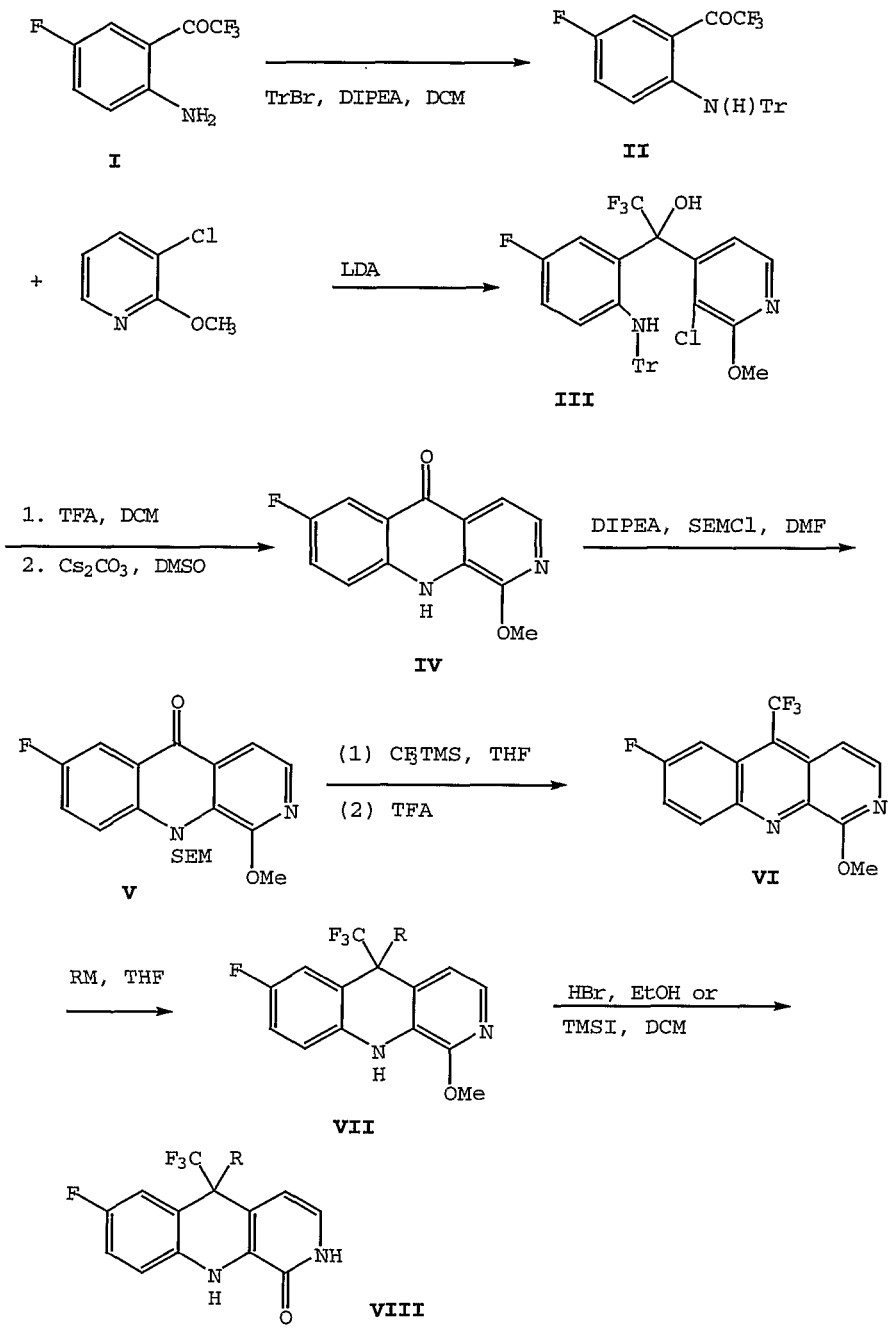
"MS" for mass spectroscopy, "nmr" or "NMR" for nuclear magnetic resonance spectroscopy, "t" for triplet, "TLC" for thin layer chromatography, "ACN" for acetic anhydride, "CDI" for carbonyl diimidazole, "DIEA" for diisopropylethylamine, "DIPEA" for diisopropylethylamine, "DMAP" for dimethylaminopyridine, "DME" for dimethoxyethane, "EDAC" for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, "LAH" for lithium aluminium hydride, "TBAF" for tetrabutylammonium fluoride, "TBS-Cl" for t-butyldimethylsilyl chloride, and "TEA" for triethylamine.

All reactions were run under a nitrogen atmosphere at room temperature and most were not optimized. The reactions were followed by TLC. Reactions run over night were done so for adequate time. Reagents were used as received. Dimethylformamide, tetrahydrofuran and acetonitrile were dried over molecular sieves. All other solvents were reagent grade. Ethanol and methanol were absolute and water was deionized. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Column chromatographies were done on flash silica gel. Exceptions to any of the conditions above are noted in the text. Ciral HPLC separations were done using chiral columns which gave the enantiomers in >99% EE.

The following methods are illustrated in the synthethic schemes that follow the methods. While the schemes are described for specific compounds, the same methods were employed to synthesize the other compounds that are listed in the table of examples.

Example 1

Compound **VIII**, wherein R=(6-methylpyrid-2-yl)methyl



Step A: Preparation of compound **II**.

To a solution of amino ketone **I** (19.4 g, 281 mmol) in dichloromethane (400 mL) at room temperature was added DIPEA (49 mL, 843 mmol) followed by trityl bromide (30.3 g, 281 mmol) and the resulting reaction mixture was allowed to stir at room temperature for 15 minutes. The reaction mixture was poured onto 3*N* HCl and extracted with dichloromethane (4x200 mL). The combined dichloromethane extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to

provide 85 g of compound **II**, (126 g theoretical, 67%). ^1H NMR (300 MHz, $CDCl_3$) δ 10.29(br s, 1H), 7.43(d, 1H, J = 6Hz), 7.3(m, 15H), 6.78(m, 1H), 6.29(m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -69.34(s, 3F), -128.28(s, 1F). Anal. ($C_{27}H_{19}NOF_4$) C, H, N.

Step B: Preparation of compound **III**.

To a solution of 2-methoxy-3-chloropyridine (11.9 g, 83.1 mmol) in THF (600 mL) at -78°C was added a *2M* solution of LDA in THF (45.6 mL, 91.4 mmol) followed by compound **II** (37.35g, 83.1 mmol), and the resulting reaction mixture was allowed to stir while warming to room temperature for 30 minutes. The reaction mixture was poured onto saturated ammonium chloride and extracted with ethyl acetate (3x200 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography (SiO_2, 10% EtOAc-hexanes eluant) provided 25.9 g of compound **III** (74.1 g theoretical, 35%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.91(d, 1H, J = 6Hz), 7.4-6.9(m, 17H), 6.51(m, 1H), 6.08(m, 1H), 4.01 (s, 3H). ^{16}F NMR (282 MHz, $CDCl_3$) δ -76.81(br s, 3F), -128.36(s, 1F). Anal. ($C_{33}H_{25}N_2O_2ClF_4$) C, H, N.

Step C: Preparation of compound **IV**.

To a solution of compound **III** (25.89 g, 43.65 mmol) in dichloromethane (225 mL) at room temperature was added TFA (225 mL) and the resulting reaction mixture was allowed to stir at room temperature for one hour. The reaction mixture was poured onto saturated sodium bicarbonate and extracted with ethyl acetate (3x200 mL). The combined ethyl acetate extracts were dried over anhydrous $NaSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc-hexanes eluant) provided 14.28 g of the deprotected compound (15.31 g theoretical, 93%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.10(d, 1H, J = 6Hz), 7.27(m, 1H), 6.9(m, 1H), 6.75(m, 1H), 6.65(m, 1H),

3.99(s, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -74.95(br s, 3F), -122.01(s, 1F). Anal. ($C_{14}H_{11}N_2O_2ClF_4$) C, H, N.

To a solution of the above deprotected compound (2.0 g, 5.70 mmol) in DMSO (40 mL) at room temperature was added cesium carbonate (9.29 g, 28.5 mmol) and the resulting reaction mixture was allowed to stir at 120°C for 8 hours. The reaction mixture was poured onto 1*N* HCl and the solids were filtered off. The residue was washed sequentially with water and ethanol and ether and dried *in vacuo* to provide 1.12 g of compound **IV** (1.39 g theoretical, 81 %). ^1H NMR (300 MHz, $CDCl_3$) δ 11.88 (br s, 1H), 8.10(m, 1H), 7.95(m, 1H), 7.85(m, 1H), 7.75(m, 1H), 7.60(m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -119.46(s, 3F), -145.79(s, 1F). Anal. ($C_{13}H_9N_2O_2F$) C, H, N.

Step D: Preparation of compound **V**.

To a solution of compound **IV** (2.31 g, 9.45 mmol) in DMF (40 mL) at room temperature was added DIPEA (8.24 mL, 47.3 mmol) followed by SEMCl (3.35 mL, 18.9 mmol), and the resulting reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was poured onto water and extracted with ethyl acetate (2x50 mL). The combined ethyl acetate extracts were dried over anhydrous $NaSO_4$ and concentrated *in vacuo*. Chromatography (SiO_2, 20% acetone-hexanes eluant) provided 5.04 g of compound **V** (5.21 g theoretical, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.1-8.0(m, 2H), 7.9-7.8(m, 2H), 7.5-7.4(m, 1H), 5.83(s, 2H), 4.15(s, 3H), 3.6 m, 2H), (1.0(m, 2H), 0.01(s, 9H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -119.02(s, 1F). Anal. ($C_{19}H_{23}N_2O_3SiF_4$) C, H, N.

Step E: Preparation of compound **VI**.

To a solution of compound **V** (5.04 g, 13.46 mmol), in THF (60 mL) at room temperature was added CF_3TMS (6.0 mL, 40.4 mmol) followed by TBAF (4.04 mL, 4.04 mmol) and the

resulting reaction mixture was allowed to stir at 0°C for 30 minutes. The reaction mixture was poured onto water and extracted with ethyl acetate (2x100 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a brown oil which was used in the next step without further purification.

A solution of the above brown oil (crude product, 13.46 mmol) in TFA (70 mL) was allowed to stir at room temperature for 30 minutes. The reaction mixture was concentrated in vacuo. The residue was taken up in THF (70 mL), methanol (70 mL), and saturated sodium bicarbonate (70 mL), and the resulting reaction mixture was allowed to stir at room temperature for 5 minutes. The reaction mixture was poured onto water and extracted with ethyl acetate (2x100 mL). The combined ethyl acetate extracts were dried over $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20-30% EtOAc-hexanes eluant) provided 3.52 g of compound **VI** (3.99 g theoretical, 93%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.6-8.5(m, 1H), 8.1-8.0(m, 2H), 7.8-7.6(m, 1H), 4.32(s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -52.42(s, 3F), -104.57(s, 1F). Anal. ($C_{14}H_8N_2OF_4$) C, H, N.

Step F: Preparation of compound **VII** (R=(6-methylpyrid-2-yl)methyl).

To a solution of lutidine (275 µl, 2.36 mmol) in THF (3 mL) at -78°C was added a *2M* solution of LDA in THF (1.18 mL, 2.36 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 15 minutes. Thereafter, compound **VI** (175 mg, 0.59 mmol) was added and the resulting reaction mixture was allowed to stir at -78°C for 30 minutes. The reaction mixture was poured onto saturated NH_4Cl and thereafter partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and

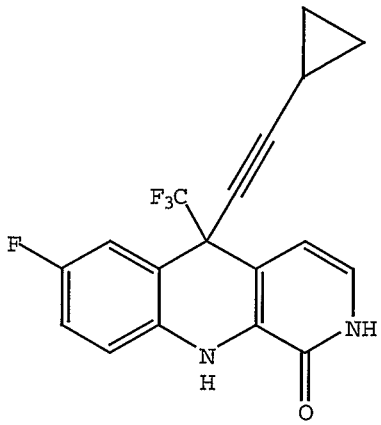
concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 30 mg of compound **VIIa** (238 g theoretical, 13%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.63(d, 1H, J = 6Hz), 7.3(m, 1H), 7.1-7.0(m, 2H), 6.95(s, 1H), 6.8-6.6(m, 2H), 6.4(d, 1H, J = 8Hz), 4.03(s, 3H), 2.38 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.02(s, 3F), -122.84(s, 1F). Anal. ($C_{21}H_{17}N_3OF_4$) C, H, N.

Step G: Preparation of compound of formula **VIII** (R=(6-methylpyrid-2-yl)methyl).

To a solution of **VII** (R=(6-methylpyrid-2-yl)methyl) (30 mg, 0.074 mmol) in ethanol (1 mL) was added a 48% aqueous solution of HBr (1 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, EtOAc eluant) provided 23 mg of compound **VIII** (R=(6-methylpyrid-2-yl)methyl)(29 mg theoretical, 79%). ^1H NMR (300 MHz, acetone-d_6) δ 8.15 (br s, 1H), 7.4(m, 1H), 7.35(m, 2H), 7.0-6.85(m, 2H), 6.8-6.75(m, 1H), 6.5-6.6(m, 1H), 4.03(m, 2H), 2.23(s, 3H). ^{19}F NMR (282 MHz, acetone-d_6) δ -76.08(s, 3F), -124.98(s, 1F). Anal. ($C_{20}H_{15}N_3O_1F_4$) C, H, N.

Example 2

Compound **VIII**, wherein R=cyclopropylacetylenyl



Step F: Preparation of compound **VII** (R=cyclopropylacetylenyl).

To a solution of cyclopropylacetylene (167 µl, 1.52 mmol) in THF (2 mL) at 0°C was added a 1.6*M* solution of *n*BuLi in THF (0.85 mL, 1.36 mmol) and the resulting reaction mixture was allowed to stir at 0°C for 20 minutes. Thereafter, the reaction mixture was cooled to -78°C and compound **VI** (100 mg, 0.34 mmol) was added and the resulting reaction mixture was warmed to 0°C and allowed to stir with warming to room temperature over a period of several hours. The reaction mixture was quenched with saturated NH_4Cl and poured onto water and extracted with ethyl acetate (2x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and dried in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 30 mg of the title compound (238 g theoretical, 13%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.8(d, 1H, J = 6Hz), 7.5(m, 1H), 7.25(m, 1H), 7.1(m, 1H), 6.85-6.8(m, 1H), 6.75(br s, 1H), 4.06(s, 3H), 1.48(s, 3H), 1.4(m, 1H), 0.9(m, 2H), 0.8(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -77.30(s, 3F), -122.50(s, 1F). High resolution mass spec: calculated for $C_{19}H_{15}N_2OF_4$ $(M+H)^+$: 363.1121, found 363.1128.

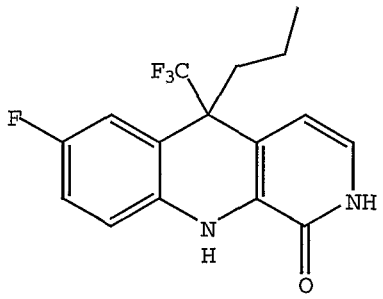
Step G: Preparation of compound of formula **VIII** (R=cyclopropylacetylenyl).

To a solution of compound **VII** (R=cyclopropylacetylenyl)(18 mg, 0.05 mmol) in

dichloromethane (1 mL) at room temperature was added TMSI (100 µl of a 1*M* solution in dichloromethane, 0.01 mmol) and the resulting reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was poured onto water and extracted with ethyl acetate (2x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc-hexanes eluant) provided 3 mg of the title compound (17 mg theoretical, 18%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.5(m, 1H), 7.35(br s, 1H), 7.05-7.0(m, 1H), 6.95-6.85 (m, 2H), 6.85-6.8(m, 1H),4.06(s, 3H), 1.57(s, 3H), 1.4 (m, 1H), 0.9(m, 2H), 0.8(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -77.26(s, 3F), -121.64(s, 1F). High resolution mass spec: calculated for $C_{18}H_{13}N_2OF_4$ $(M+H)^+$: 349.0964, found 349.0939.

Example 3

Compound **VIII**, wherein R=n-propyl



Step F: Preparation of compound of formula **VII** (R=n-propyl).

To a solution of **VI** (175 mg, 0.59 mmol) in THF (2 mL) at -78°C was added a 2*M* solution of *n*-propyl magnesium chloride in ether (1.48 mL, 2.95 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 15 minutes. The reaction mixture was quenched with saturated NH_4Cl and poured onto water and extracted with ethyl acetate (2x50 mL). Chromatography (SiO_2, 20% EtOAc-hexanes eluant) provided 144 mg of compound **VIIc** (201 g theoretical, 72%).

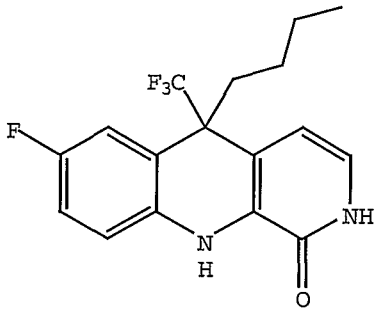
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8(d, 1H, J = 6Hz), 7.5(m, 1H), 7.25(m, 1H), 7.1(m, 1H), 6.85-6.8(m, 1H), 6.75(br s, 1H), 4.06(s, 3H), 1.48(s, 3H), 1.4(m, 1H), 0.9(m, 2H), 0.8(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.15(s, 3F), -122.88(s, 1F). High resolution mass spec: calculated for $C_{17}H_{17}N_2OF_4$ $(M+H)^+$: 341.1277, found 341.1282.

Step G: Preparation of compound of formula **VIII** (R=n-propyl).

To a solution of **VII** (R=n-propyl)(144 mg, 0.42 mmol) in ethanol (2 mL) at room temperature was added a 48% aqueous solution of HBr (2 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 84 mg of the title compound (137 mg theoretical, 61%). ^{1}H NMR (300 MHz, acetone-d_6) δ 11.56 (br s, 1H), 8.74(br s, 1H), 7.44(m, 1H), 7.2(m, 1H), 7.05-6.95(m, 2H), 6.42(m, 1H), 6.5-6.6(m, 1H), 4.03(m, 2H), 2.4(m, 2H), 1.05(m, 3H). ^{19}F NMR (282 MHz, acetone -d_6) δ -76.48(s, 3F), -124.44(s, 1F). Anal. ($C_{16}H_{14}N_2OF_4$) C, H, N.

Example 4

Compound **VIII**, wherein R=n-butyl



Step F: Preparation of compound of formula **VII** (R=n-butyl)

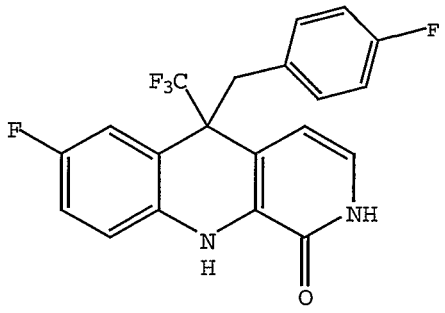
To a solution of **VI** (500 mg, 1.69 mmol) in THF (8 mL) at -78°C was added a 2*M* solution of *n*-butyl magnesium chloride in ether (4.22 mL, 8.44 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 15 minutes. The reaction mixture was quenched with saturated NH_4Cl and poured onto water and extracted with ethyl acetate (2x50 mL). Chromatography (SiO_2, 10% EtOAc-hexanes eluant) provided 337 mg of compound **VII** (R=n-butyl)(599 mg theoretical, 56%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.70(d, 1H, J = 6Hz), 7.1(m, 1H), 7.0-6.95(m, 1H), 6.85(m, 1H), 6.8(m, 1H), 6.7(br s, 1H), 4.06(s, 3H), 2.4(m, 2H), 1.35(m, 2H), 1.1 (m, 2H), 0.8(t, 3H, J = 7Hz)), 0.8(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.12(s, 3F), -122.86(s, 1F). Anal. ($C_{18}H_{18}N_2OF_4$) C, H, N.

Step G: Preparation of compound of formula **VIII** (R=n-butyl).

To a solution of **VII** (R=n-butyl)(64 mg, 0.18 mmol) in ethanol (2 mL) at room temperature was added a 48% aqueous solution of HBr (2 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 36 mg of the title compound (61 mg theoretical, 59%). ^1H NMR (300 MHz, $CDCl_3$) δ 12.5(br s, 1H), 7.55(br s, 1H), 7.1(m, 1H), 7.0-6.8(m, 3H), 6.35(m, 1H), 2.3(m, 2H), 1.35 (m, 2H), 1.05(m, 2H), 0.8(t, 3H, J = 7Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.84(s, 3F), -122.14(s, 1F). Anal. ($C_{17}H_{16}N_2OF_4$) C, H, N.

Example 5

Compound **VIII**, wherein R=4-fluorophenylmethyl



Step F: Preparation of compound of formula **VII**(R=4-fluorophenylmethyl).

To a solution of **VI** (196 mg, 0.66 mmol) in THF (2 mL) at -78°C was added a 0.25*M* solution of *p*-fluorophenylmagnesium chloride in ether (13.2 mL, 3.3 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 45 minutes. The reaction mixture was quenched with saturated NH_4Cl and poured onto water and extracted with ethyl acetate (2x50 mL). Chromatography (SiO_2, 20% EtOAc-hexanes eluant) provided 153 mg of compound **VII** (R=4-fluorophenylmethyl)(268 mg theoretical, 57%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.73(d, 1H, J = 6Hz), 7.3(m, 1H), 7.1(m, 1H), 6.95(m, 1H), 6.8-6.6(m, 5H), 6.55(br s, 1H), 3.99(s, 3H), 3.7(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.25(s, 3F), -116.27(s, 1F), -122.53(s, 1F). Anal. ($C_{21}H_{15}N_2OF_5$) C, H, N.

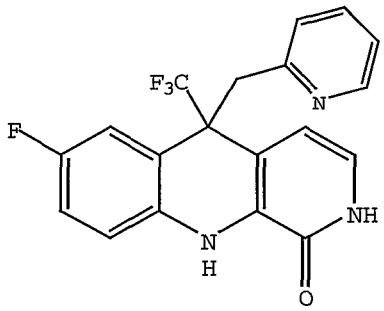
Step G: Preparation of compound of formula **VIII**(R=4-fluorophenylmethyl).

To a solution of **VII** (R=4-fluorophenylmethyl)(153 mg, 0.38 mmol) in ethanol (4 mL) at room temperature was added a 48% aqueous solution of HBr (4 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 89 mg of the title compound (149 mg

theoretical, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.0(br s, 1H), 7.3(m, 1H), 7.0(m, 1H), 6.9(m, 1H), 6.85-6.7(m, 5H), 6.55(m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.89(s, 3F), -116.01(s, 1F), -121.68(s, 1F). Anal. ($C_{20}H_{13}N_2OF_5$) C, H, N.

Example 6

Compound **VIII**, wherein R=2-pyridylmethyl



Step F: Preparation of compound of formula **VII** (R=2-pyridylmethyl).

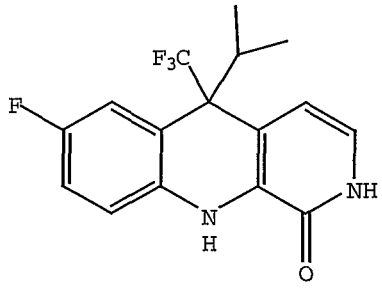
To a solution of 2-picoline (134 µl, 1.36 mmol) in THF (2 mL) at -78°C was added a 2*M* solution of LDA in THF (0.76 mL, 1.52 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 15 minutes. Thereafter, compound **VI** (100 mg, 0.34 mmol) was added and the resulting reaction mixture was allowed to stir at -78°C for 30 minutes. The reaction mixture was poured onto saturated NH_4Cl and thereafter partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 111 mg of compound **VII** (R=2-pyridylmethyl)(132 mg theoretical, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.3(d, 1H, J = 5Hz), 7.64(d, 1H, J = 6Hz), 7.3(m, 2H), 7.1(m, 1H), 6.95(m, 1H), 6.8-6.6(m, 2H), 4.1(m, 2H), 4.02(s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.99(s, 3F), -122.57(s, 1F). Anal. ($C_{20}H_{15}N_3OF_4$) C, H, N.

Step G: Preparation of compound of formula **VIII** (R=2-pyridylmethyl).

To a solution of **VII** (R=2-pyridylmethyl)(111 mg, 0.28 mmol) in ethanol (2 mL) was added a 48% aqueous solution of HBr (2 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, EtOAc eluant) provided 77 mg of the title compound (105 mg theoretical, 73%). ^1H NMR (300 MHz, DMSO-d_6) δ 11.7(br s, 1H), 9.0 (br s, 1H), 8.3(d, 1H, J = 4Hz), 7.5(m, 1H), 7.45(m, 1H), 7.25(m, 1H), 7.05-6.95(m, 3H), 6.8(d, 1H, J = 7Hz), 6.45(d, 1H, J = 7Hz), 4.0(m, 2H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -74.98(s, 3F), -123.69(s, 1F). Anal. ($C_{19}H_{13}N_3OF_4$) C, H, N.

Example 7

Compound **VIII**, wherein R=*i*-propyl



Step F: Preparation of compound of formula **VII**(R=i-propyl).

To a solution of **VI** (175 mg, 0.59 mmol) in THF (2 mL) at -78°C was added a 2*M* solution of isopropyl magnesium chloride in ether (1.48 mL, 2.95 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 15 minutes. The reaction mixture was quenched with saturated NH_4Cl and poured onto water and extracted with ethyl acetate (2x50 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography

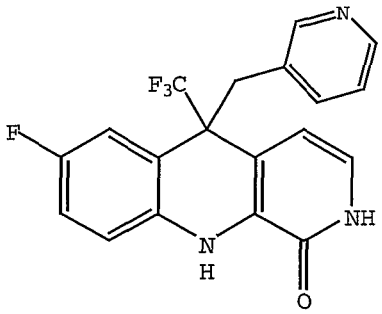
(SiO_2, 20% EtOAc-hexanes eluant) provided 144 mg of compound **VII** (R=i-propyl)(201 mg theoretical, 72%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.6(d, 1H, J = 6Hz), 7.3(m, 1H), 7.05(m, 1H), 6.95(m, 1H), 6.65(m, 1H), 4.04(s, 3H), 2.6(m, 1H), 1.05(m, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.80(s, 3F), -122.85(s, 1F). High resolution mass spec: calculated for $C_{17}H_{17}N_2OF_4$ $(M+H)^+$: 341.1277, found 341.1276.

Step G: Preparation of compound of formula **VIII**(R=i-propyl).

To a solution of **VII** (R=i-propyl)(144 mg, 0.42 mmol) in ethanol (2 mL) at room temperature was added a 48% aqueous solution of HBr (2 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 63 mg of the title compound (137 mg theoretical, 46%). ^1H NMR (300 MHz, acetone-d_6) δ 11.0 (br s, 1H), 8.3 (br s, 1H), 7.4-7.2(m, 2H), 7.1(m, 1H), 6.95(d, 1H, J = 7Hz), 6.4(m, 1H), 2.7(m, 1H), 1.0(m, 6H). ^{19}F NMR (282 MHz, acetone-d_6) δ -65.46(s, 3F), -124.43(s, 1F). Anal. ($C_{16}H_{14}N_2OF_4$) C, H, N.

Example 8

Compound **VIII**, wherein R=3-pyridylmethyl



Step F: Preparation of compound of formula **VII** (3-pyridylmethyl).

To a solution of 3-picoline (230 µl, 2.36 mmol) in THF (3 mL) at -78°C was added a 2*M* solution of LDA in THF (1.33 mL, 2.66 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 15 minutes. Thereafter, compound **VI** (175 mg, 0.59 mmol) was added and the resulting reaction mixture was allowed to stir at -78°C for 30 minutes. The reaction mixture was poured onto saturated NH_4Cl and thereafter partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 8 mg of compound **VII** (3-pyridylmethyl)(230 mg theoretical, 3%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.25(d, 1H, J = 6Hz), 8.1(m, 1H0, 7.69(d, 1H, J = 6Hz), 7.3(m, 1H), 7.1(m, 2H), 6.9(m, 2H), 6.7(m, 1H), 6.55(br s, 1H), 4.01(s, 3H), 3.75(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.42(s, 3F), -122.07(s, 1F). High resolution mass spec: calculated for $C_{20}H_{16}N_3OF_4$ $(M+H)^+$: 390.1230, found 390.1248.

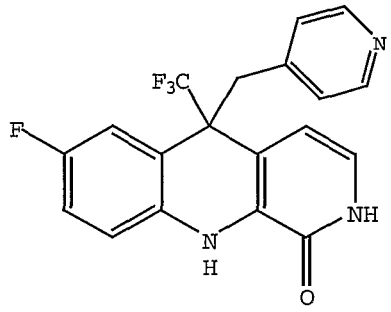
Step G: Preparation of compound of formula **VIII** (3-pyridylmethyl).

To a solution of **VII** (3-pyridylmethyl)(8 mg, 0.02 mmol) in ethanol (1 mL) was added a 48% aqueous solution of HBr (1 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 5% MeOH-dichloromethane eluant) provided 4 mg of the title compound (7.5 mg theoretical, 53%). ^1H NMR (300 MHz, acetone-d_6) δ 11.0(br s, 1H), 8.4 (br s, 1H), 8.2(m, 2H), 7.6(m, 1H), 7.4-7.2(m, 2H), 7.15-7.0(m, 3H), 6.65(m, 1H),

3.95(m, 2H). ^{19}F NMR (282 MHz, acetone-d_6) δ -74.81(s, 3F), -124.05(s, 1F). High resolution mass spec: calculated for $C_{19}H_{14}N_3OF_4$ $(M+H)^+$: 376.1073, found 376.1060.

Example 9

Compound **VIII**, wherein R=4-pyridylmethyl



Step F: Preparation of compound of formula **VII** (R=4-pyridylmethyl).

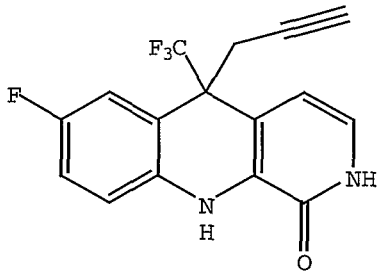
To a solution of 4-picoline (230 µl, 2.36 mmol) in THF (3 mL) at -78°C was added a 2*M* solution of LDA in THF (1.33 mL, 2.66 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 15 minutes. Thereafter, compound **VI** (175 mg, 0.59 mmol) was added and the resulting reaction mixture was allowed to stir at -78°C for 30 minutes. The reaction mixture was poured onto saturated NH_4Cl and thereafter partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 116 mg of compound **VII** (R=4-pyridylmethyl)(230 g theoretical, 50%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.25(m, 1H), 7.68(d, 1H, J = 6Hz), 7.25(m, 1H), 7.05-6.95(m, 2H), 6.8-6.65(m, 3H), 4.0(s, 3H), 3.75(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.83(s, 3F), -122.13(s, 1F). Anal. ($C_{20}H_{15}N_3OF_4$) C, H, N.

Step G: Preparation of compound of formula **VIII** (R=4-pyridylmethyl).

To a solution of **VII** (R=4-pyridylmethyl)(116 mg, 0.30 mmol) in ethanol (2 mL) was added a 48% aqueous solution of HBr (2 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, EtOAc eluant) provided 93 mg of the title compound (113 mg theoretical, 82%). ^1H NMR (300 MHz, acetone-d_6) δ 10.65(br s, 1H), 8.2 (m, 3H), 7.5(m, 1H), 7.3(m, 1H), 7.1-6.9(m, 4H), 6.6(m, 1H), 3.95(m, 2H). ^{19}F NMR (282 MHz, acetone-d_6) δ -75.45(s, 3F), -124.13(s, 1F). Anal. ($C_{19}H_{13}N_3OF_4$) C, H, N.

Example 10

Compound **VIII**, wherein R=3-propynyl



Step F: Preparation of compound of formula **VII** (R=3-propynyl).

To a solution of 1-TMS-1-propyne (300 µl, 2.02 mmol) in THF (3 mL) at -78°C was added a 2*M* solution of LDA in THF (1.14 mL, 2.28 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 20 minutes. Thereafter, compound **VI** (150 mg, 0.51 mmol) was added and the resulting reaction mixture was allowed to stir at -78°C 30 minutes. The reaction mixture was poured onto saturated NH_4Cl and thereafter partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20%

EtOAc-hexanes eluant) provided 102 mg of compound **VII** (R=3-propynyl)(207 mg theoretical, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72(d, 1H, J = 6Hz), 7.2(m, 1H), 7.0(m, 1H), 6.9(m, 1H), 6.8(m, 1H), 6.75(br s, 1H), 4.07(s, 3H), 3.35(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.68(s, 3F), -123.05(s, 1F). High resolution mass spec: calculated for $C_{20}H_{21}N_2OSiF_4$ $(M+H)^+$: 409.1359, found 409.11365.

Step G: Preparation of compound of formula **VIII** (R=3-propynyl).

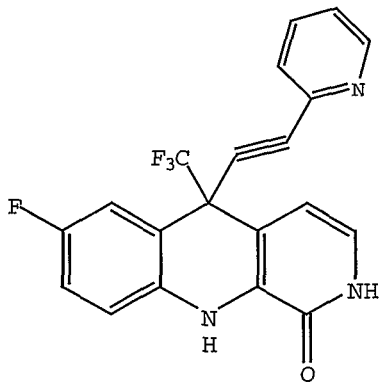
To a solution of compound **VII** (R=3-propynyl)(102 mg, 0.25 mmol) in dichloromethane (5 mL) at room temperature was added TMSI (2 ml of a 1*M* solution in dichloromethane, 2 mmol) and the resulting reaction mixture was allowed to stir at room temperature for 4 hours. The reaction mixture was poured onto water and extracted with dichloromethane (2x25 mL). The combined dichloromethane extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc-hexanes eluant) provided 66 mg of the trimethylsilyl protected compound (99 mg theoretical, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.4(br s, 1H), 7.5(br s, 1H), 7.15(m, 1H), 7.05(m, 1H), 7.0-6.85 (m, 2H), 6.4(d, 1H, J = 7Hz), 3.3(m, 2H), 0.05(s, 9H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.37(s, 3F), -122.19(s, 1F). Anal. ($C_{19}H_{18}N_2OSiF_4$) C, H, N.

To a solution of the above trimethylsilyl protected compound (66 mg, 0.17 mmol) in methanol (1 mL) at room temperature was added potassium carbonate (117 mg, 0.85 mmol) and the resulting reaction mixture was allowed to stir for one hour. The reaction mixture was poured onto water and extracted with ethyl acetate (2x50 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 34 mg of the title compound (55 mg theoretical, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.4(br s, 1H), 7.6(br s,

1H), 7.2(m, 1H), 7.05(m, 1H), 7.0-6.9(m, 2H), 6.4(d, 1H, J = 7Hz), 3.3(m, 2H), 1.8(m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.19 (s, 3F), -121.68(s, 1F). Anal. ($C_{16}H_{10}N_2OF_4$) C, H, N.

Example 11

Compound **VIII**, wherein R=2-pyridylethynyl



Step F: Preparation of compound of formula **VII** (R=2-pyridylethynyl).

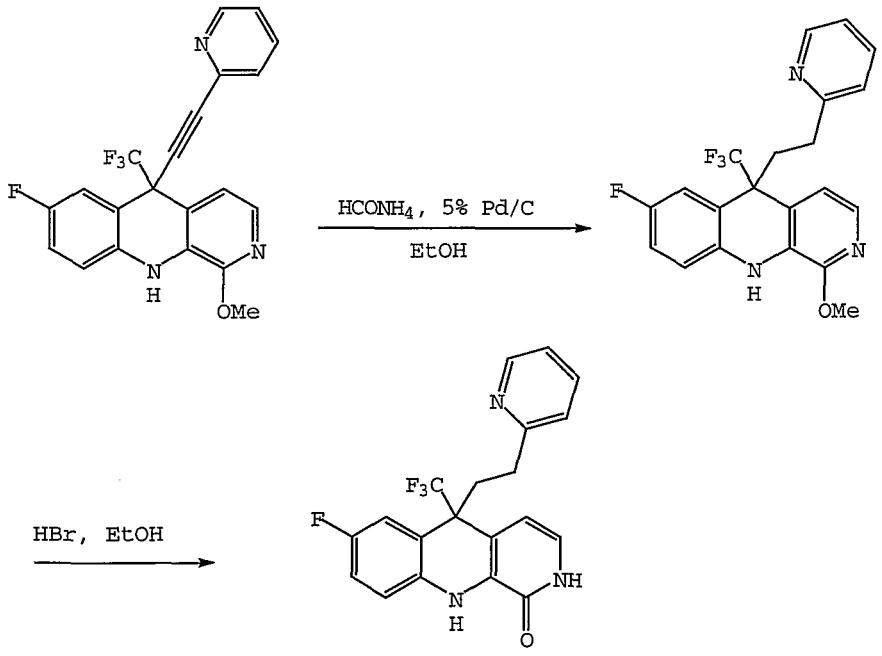
To a solution of 2-ethynylpyridine (157 µl, 1.52 mmol) in THF (1.5 mL) at -78°C was added a 1.6*M* solution of *n*BuLi in THF (0.85 mL, 1.36 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 15 minutes. Thereafter, compound **VI** (175 mg, 0.59 mmol) was added and the resulting reaction mixture was allowed to stir with warming to room temperature for 30 minutes. The reaction mixture was poured onto saturated NH_4Cl and thereafter partitioned between ethyl acetate and 0.1*N* HCl. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 39 mg of compound **VII** (R=2-pyridylethynyl)(136 mg theoretical, 29%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.65(m, 1H), 7.8-7.7(m, 2H), 7.65-7.55(m, 2H), 7.4-7.25(m, 2H), 7.1(m, 1H), 6.9(m, 1H), 6.85(br s, 1H), 4.08(s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.62(s, 3F), -121.98(s, 1F). Anal. ($C_{21}H_{13}N_3OF_4$) C, H, N.

Step G: Preparation of compound of formula **VIII** (R=2-pyridylethynyl).

To a solution of compound **VII** (R=2-pyridylethynyl)(26 mg, 0.065 mmol) in dichloromethane (2.5 mL) at room temperature was added TMSI (1 ml of a 1*M* solution in dichloromethane, 0.01 mmol) and the resulting reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was poured onto water and extracted with ethyl acetate (2x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, EtOAc eluant) provided 9 mg of the title compound (25 mg theoretical, 36%). ^1H NMR (300 MHz, acetone-d_6) δ 11.45(br s, 1H), 8.6 (m, 1H), 7.95(m, 1H), 7.75(m, 1H), 7.6-7.4(m, 3H), 7.25(m, 1H), 7.12(d, 1H, J = 7Hz), 6.67(d, 1H, J = 7Hz). ^{19}F NMR (282 MHz, acetone-d_6) δ -77.54(s, 3F), -123.67(s, 1F). Anal. ($C_{20}H_{11}N_3OF_4$) C, H, N.

Example 12

Compound **VIII**, wherein R=2-(2-pyridyl)ethyl



Step A: Preparation of compound **VII** (R=2-pyridylethynyl).

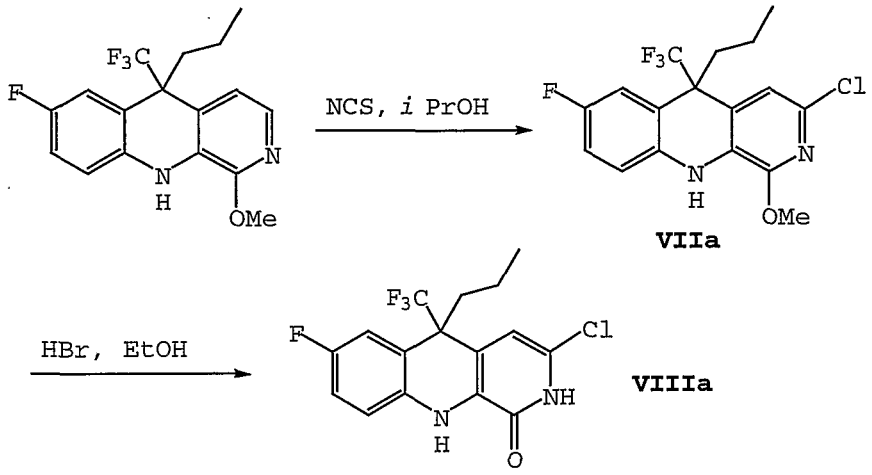
To a solution of **VII** (R=2-pyridylethynyl)(20 mg, 0.05 mmol) in ethanol (1 mL) at room temperature was added ammonium formate (20 mg) and 5% Pd/C (20 mg) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture was filtered through Celite and the filterate concentrated in vacuo. Chromatography (SiO_2, 40% EtOAc-hexanes eluant) provided 15 mg of compound **VII** (R=2-pyridylethyl)(20 mg theoretical, 75%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.5(m, 1H), 7.7(d, 1H, J = 6Hz), 7.5(m, 1H), 7.2(m, 1H), 7.15(m, 1H), 7.05-6.95(m, 3H), 6.8(m, 1H), 6.75(br s, 1H), 4.07(s, 3H), 2.8(m, 2H), 2.6(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.96(s, 3F), -122.34(s, 1F). High resolution mass spec: calculated for $C_{21}H_{18}N_3OF_4$ $(M+H)^+$: 404.1386, found 404.1385.

Step B: Preparation of compound **VIII**(R=(2-pyridyl)ethyl).

To a solution of **VII** (R=2-pyridylethyl)(15 mg, 0.037 mmol) in ethanol (1 mL) was added a 48% aqueous solution of HBr (1 mL) and the resulting reaction mixture was allowed to stir at reflux for 5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, EtOAc eluant) provided 5 mg of the title compound (15 mg theoretical, 36%). ^1H NMR (300 MHz, acetone-d_6) δ 10.9(br s, 1H), 8.5(m, 1H), 8.3 (br s, 1H), 7.6(m, 1H), 7.4(m, 2H), 7.2-7.05(m, 3H), 7.0(d, 1H, J = 7Hz), 6.4(d, 1H, J = 7Hz), 2.95(m, 2H), 2.6(m, 2H). ^{19}F NMR (282 MHz, acetone-d_6) δ -76.49(s, 3F), -124.17 (s, 1F). High resolution mass spec: calculated for $C_{20}H_{16}N_3OF_4$ $(M+H)^+$: 390.1221, found 390.1221.

Example 13

Compound **VIIIa**



Step A: Preparation of compound **VIIa**.

To a solution of compound **VII** (R=n-propyl)(75 mg, 0.22 mmol) in *i*PrOH (2 mL) at room temperature was added NCS (30 mg, 0.22 mmol) and the resulting reaction mixture was allowed to stir at reflux for 2 hours. The reaction mixture was poured onto water and extracted with ethyl acetate (2x50 mL). The combined ethyl acetate extracts were dried over anhydrous $NaSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 10% EtOAc-hexanes eluant) provided 48 mg of compound **VIIa** (82 mg theoretical, 59%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.15(m, 1H), 7.0(m, 1H), 6.95(m, 1H), 6.8(m, 1H), 6.6(br s, 1H), 2.3(m, 2H), 1.1(m, 2H), 0.95(m, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.05(s, 3F), -122.31 (s, 1F). High resolution mass spec: calculated for $C_{17}H_{16}ClN_3OF_4$ $(M+H)^+$: 375.0887, found 375.0883.

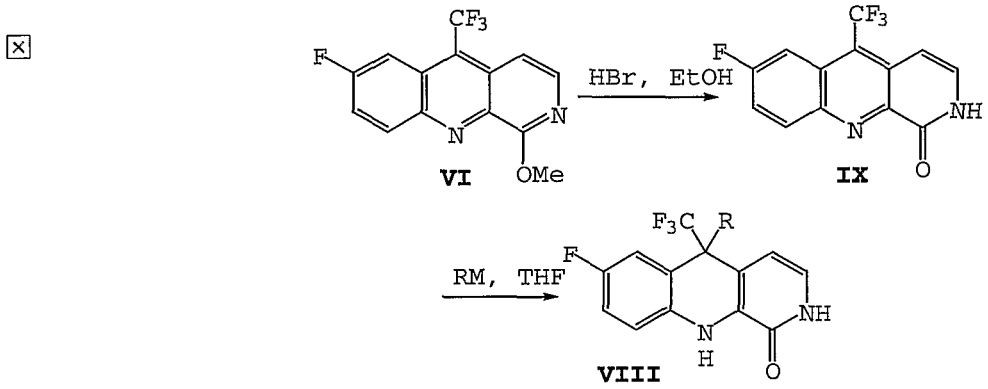
Step B: Preparation of compound of formula **VIIIa**.

To a solution of **VIIa** (48 mg, 0.13 mmol) in ethanol (1 mL) was added a 48% aqueous solution of HBr (1 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20%

acetone-hexanes eluant) provided 14 mg of the title compound (47 mg theoretical, 30%). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.4(br s, 1H), 7.4(m, 1H), 7.3(m, 1H), 7.1(m, 1H), 6.6(m, 1H), 2.4(m, 2H), 1.1(m, 1H), 0.95(m, 1H). ^{19}F NMR (282 MHz, acetone-d_6) δ -76.58(s, 3F), -124.11(s, 1F). Anal. ($C_{16}H_{13}N_2OClF_4$) C, H, N.

Example 14

Compound **VIII**, wherein R=3-propenyl



Step A: Preparation of compound **IX**.

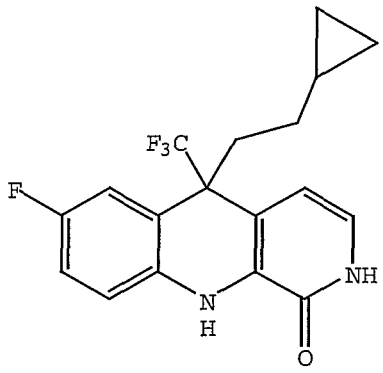
To a solution of compound **VI** (100 mg, 0.34 mmol) in ethanol (1 mL) at room temperature was added a 48% aqueous solution of HBr (1 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture was diluted with water and filtered and the solids were washed with water and dried *in vacuo* to give a yellow solid. Toluene was added to the solids and dried *in vacuo* to azeotrope traces of water to provide 89 mg of compound **IX** (96 mg theoretical, 93%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95(br s, 1H), 8.4(m, 1H), 7.95(m, 2H), 7.4(m, 1H), 6.8(m, 1H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -52.44(s, 3F), -105.16 (s, 1F). High resolution mass spec: calculated for $C_{13}H_7N_2OF_4$ $(M+H)^+$: 283.0495, found 283.0492.

Step B: Preparation of compound of formula **VIII** (R=3-propenyl).

To a solution of **IX** (170 mg, 0.60 mmol) in THF (3 mL) at -78°C was added a 1*M* solution of allyl magnesium bromide in ether (3.6 mL, 3.6 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 15 minutes. The reaction mixture was quenched with saturated NH_4Cl and poured onto water and extracted with ethyl acetate (2x50 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc-hexanes eluant) provided 37 mg of the title compound (195 mg theoretical, 19%). ^1H NMR (300 MHz, acetone-d_6) δ 12.4(br s, 1H), 7.6(br s, 1H), 7.1(m, 1H), 7.0-6.8(m, 3H), 6.4(d, 1H, J = 7Hz), 5.4(m, 1H), 5.0(m, 2H), 3.1(m, 2H). ^{19}F NMR (282 MHz, acetone-d_6) δ -75.83(s, 3F), -121.86(s, 1F). Anal. ($C_{16}H_{12}N_2OF_4$) C, H, N.

Example 15

Compound **VIII**, wherein R=2-cyclopropyl-1-ethyl



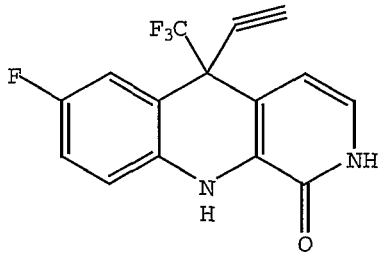
Step B: Preparation of compound of formula **VIII**(R=2-cyclopropyl-1-ethyl).

To a solution of 2-cyclopropylethyliodide (614 mg, 3.15 mmol) in hexanes (8 mL) at -78°C was added a 1.7*M* solution of *t*-BuLi in THF (3.7 mL, 6.3 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 10 minutes. Ether (8 mL) was added and the reaction mixture was allowed to

stir at room temperature for an hour. The reaction mixture was cooled back down to -78°C and THF (8 mL) was added followed by compound **IX** (178 mg, 0.63 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 30 minutes. The reaction mixture was poured onto saturated NH_4Cl and thereafter partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 45 mg of the title compound (222 g theoretical, 20%). ^1H NMR (300 MHz, $CDCl_3$) δ 12.55(br s, 1H), 7.6(br s, 1H), 7.2(m, 1H), 7.1-6.9(m, 3H), 6.45(d, 1H, J = 7Hz), 2.5(m, 2H), 1.1(m, 2H), 0.7(m, 1H), 0.5(m, 2H), 0.05(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.80(s, 3F), -122.05(s, 1F). Anal. ($C_{18}H_{16}N_2OF_4$) C, H, N.

Example 16

Compound **VIII**, wherein R=ethynyl



Step B: Preparation of compound of formula **VIII** (R=ethynyl).

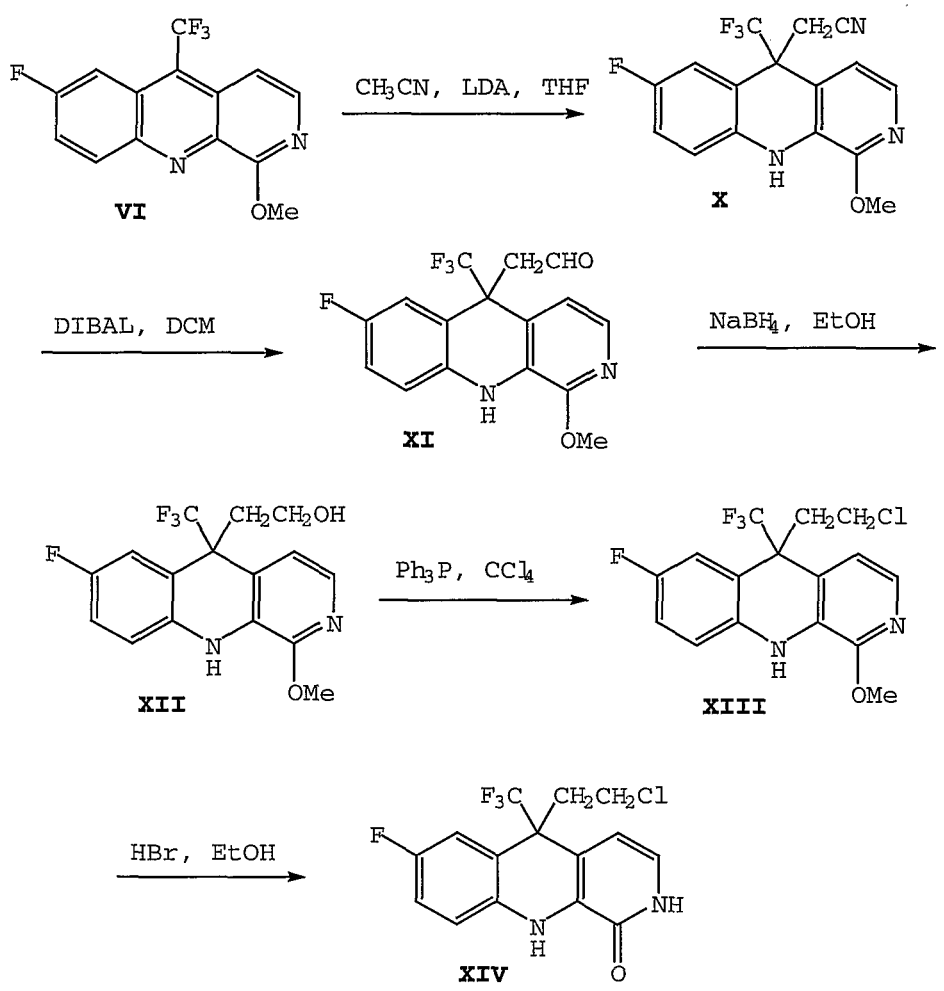
To a solution of trimethylsilylacetylene (432 µl, 3.06 mmol) in THF (5 mL) at 0°C was added a 1.6*M* solution of *n*-BuLi in THF (1.7 mL, 2.72 mmol) and the resulting reaction mixture was allowed to stir at 0°C for 30 minutes. Thereafter, compound **IX** (192 mg, 0.68 mmol) was added as a suspension in THF (2 mL) and the resulting reaction mixture was allowed to stir with warming to room temperature overnight. The reaction mixture was poured onto saturated NH_4Cl and thereafter partitioned between ethyl acetate and

water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, EtOAc eluant) provided 74 mg of the trimethylsilyl protected compound (258 mg theoretical, 29%). ^1H NMR (300 MHz, acetone-d_6) δ 11.2(br s, 1H), 8.8(br s, 1H), 7.45(m, 1H), 7.4(m, 1H), 7.1(m, 1H), 7.05(m, 1H), 6.55(m, 1H), 0.05(s, 9H). ^{19}F NMR (282 MHz, acetone-d_6) δ -77.59(s, 3F), -123.84(s, 1F). High resolution mass spec: calculated for $C_{18}H_{17}N_2OSiF_4$ $(M+H)^+$: 381.1046, found 381.1055.

To a solution of the trimethylsilyl protected compound (74 mg, 0.19 mmol) in methanol (1 mL) was added potassium carbonate (131 mg, 0.95 mmol) and the resulting reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was poured onto water and extracted with ethyl acetate (2x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc-hexanes eluant) provided 9 mg of the title compound (58 mg theoretical, 16%). ^1H NMR (300 MHz, acetone-d_6) δ 11.0(br s, 1H), 8.6(br s, 1H), 7.5(m, 1H), 7.2(m, 1H), 7.1(d, 1H, J = 7Hz), 6.6(d, 1H, J = 7Hz), 3.6(s, 1H). ^{19}F NMR (282 MHz, acetone-d_6) δ -77.98(s, 3F), -123.95 (s, 1F). High resolution mass spec: calculated for $C_{15}H_9N_2OF_4$ $(M+H)^+$: 309.065101, found 309.063882.

Example 17

Compound **XIV**, wherein R=2-chloroethyl



Step A: Preparation of compound **X**.

To a solution of acetonitrile (71 µl, 1.36 mmol) in THF (2 mL) at -78°C was added a 2*M* solution of LDA in THF (0.76 mL, 1.52 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 20 minutes. Thereafter, compound **VI** (100 mg, 0.34 mmol) was added and the resulting reaction mixture was allowed to stir at -78°C for 30 minutes. The reaction mixture was poured onto saturated NH_4Cl and thereafter partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc-hexanes eluant) provided 100 mg of compound **X** (115 mg theoretical, 87%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.8(d, 1H, J = 7Hz), 7.1(m, 2H), 6.9(m, 2H), 4.06(s, 3H), 3.5(m, 2H). ^{19}F

NMR (282 MHz, $CDCl_3$) δ -76.48(s, 3F), -121.2(s, 1F). Anal. ($C_{16}H_{11}N_3OF_4$) C, H, N.

Step B: Preparation of compound **XI**.

To a solution of compound **X** (100 mg, 0.3 mmol) in dichloromethane (1.5 mL) at -78°C was added a 1*M* solution of DIBAL in dichloromethane (0.45 mL, 0.45 mmol) and the resulting reaction mixture was allowed to stir at -78°C for 2 hours. The reaction mixture was poured onto 20% $KHSO_4$ and thereafter partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc-hexanes eluant) provided 43 mg of compound **XI** (102 mg theoretical, 42%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.5(s, 1H), 7.7(d, 1H, J = 7Hz), 7.1(m, 2H), 6.85(m, 2H), 4.07(s, 3H), 3,5(s, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.66(s, 3F), -121.57(s, 1F). High resolution mass spec: calculated for $C_{16}H_{13}N_2O_2F_4$ $(M+H)^+$: 341.0913, found 341.0888.

Step C: Preparation of compound **XII**.

To a solution of compound **XI** (300 mg, 0.88 mmol) in ethanol (5 mL) at room temperature was added sodium borohydride (100 mg, 2.64 mmol) and the resulting reaction mixture was allowed to stir at room temperature for 15 minutes. The reaction mixture was partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc-hexanes eluant) provided 257 mg of compound **XII** (301 mg theoretical, 85%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.7(d, 1H, J = 7Hz), 7.25(m, 1H), 7.0(m, 2H), 6.8(m, 1H), 6.7(br s, 1H), 4.06(s, 3H), 3.5(m, 2H), 2.7(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.51(s, 3F), -122.31(s,

1F). High resolution mass spec: calculated for $C_{16}H_{15}N_2O_2F_4$ $(M+H)^+$: 343.1070, found 343.1072.

Step D: Preparation of compound **XIII**.

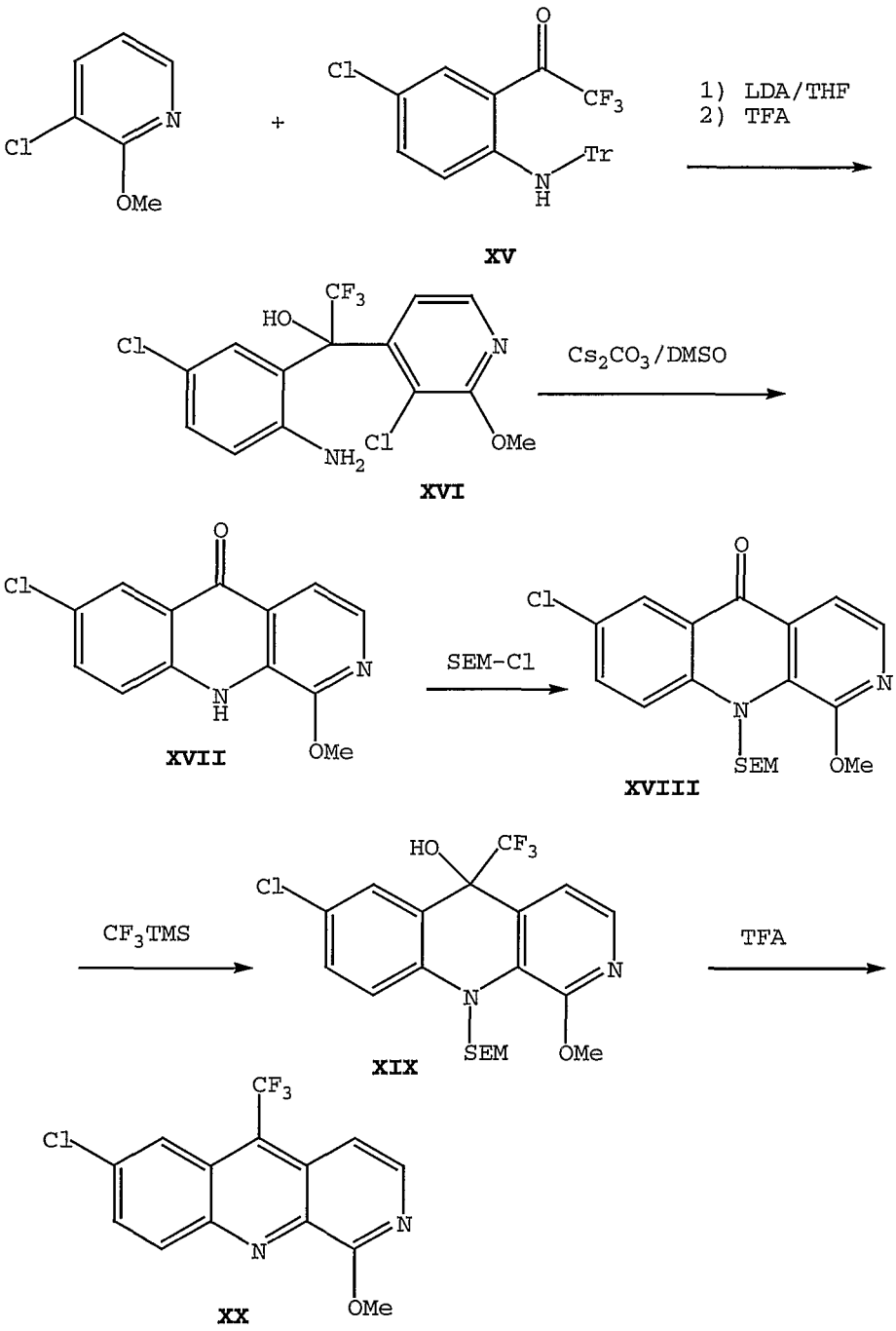
To a solution of compound **XII** (250 mg, 0.73 mmol) in acetonitrile (3 mL) at room temperature was added triphenyphosphine (289 mg, 1.10 mmol) followed by carbon tetrachloride (4 mL) and the resulting reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to provide 210 mg of compound **XIII** (263 mg theoretical, 80%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.75(d, 1H, J = 7Hz), 7.2(m, 1H), 7.1(m, 1H), 6.95(m, 1H), 6.8(m, 1H), 6.75(br s, 1H), 4.06(s, 3H), 3.25(m, 2H), 2.9(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.45(s, 3F), -121.76(s, 1F). High resolution mass spec: calculated for $C_{16}H_{14}N_2OF_4Cl$ $(M+H)^+$: 361.0731, found 361.0748.

Step E: Preparation of compound **XIV**.

To a solution of compound **XIII** (52 mg, 0.144 mmol) in ethanol (1 mL) at room temperature was added a 48% aqueous solution of HBr (1 mL) and the resulting reaction mixture was allowed to stir at reflux for 1.5 hours. The reaction mixture is poured onto saturated $NaHCO_3$ and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography (SiO_2, 50% acetone-hexanes eluant) provided 45 mg of compound **XIV** (50 mg theoretical, 90%). ^1H NMR (300 MHz, $CDCl_3$) δ 11.1(br s, 1H), 8.6(br s, 1H), 7.5-7.3(m, 2H), 7.1-7.0(m, 2H), 6.45(m, 1H), 3.4(m, 2H(, 2.95(m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.75(s, 3F), -123.74(s, 1F).

Examples 18-26 can be made according to the following procedures.

Example 18



Step A:

To a -78 ^{0}C solution of diisopropylamine (3.3 mL, 23.6 mmol) in THF (100 mL) was added a solution of 1.6 M BuLi (16.1 mL, 23.6 mmol) in hexane. After the reaction was

stirred for 0.5 h, a solution of 3-chloro-2-methoxypyridine (3.4 g, 23.6 mmol) in THF (2 mL) was added. After stirring for 20 min., ketone (**XV**) was added. The reaction was allowed to warm to -50 ^{0}C, quenched with saturated NH_4Cl, diluted with EtOAc, and washed with 0.5 N HCl (3x), saturated $NaHCO_3$, and saturated NaCl. The organic phase was dried over Na_2SO_4 and concentrated to an orange oil (17.5 g). The oil was triturated with CH_2Cl_2 (30 mL) to give a pale yellow solid (12.7 g, 97% yield) that was treated with TFA to give a detritylated product **XVI** (5.9 g, 77% yield).

Step B:

To a 120 ^{0}C suspension of Cs_2CO_3 (15 g) in DMSO (50 mL) was added a solution of **XVI** (5 g, 14.6 mmol) in DMSO (100 mL) dropwise over 1.5 h, then heated at that temperature for 4 h. The reaction was cooled to room temperature and EtOAc (300 mL), water (150 mL) and 1 N HCl (200 mL) were added. A yellow solid precipitated out and was filtered off and washed with water and then EtOAc. The compound was dried at 100 ^{0}C under high vacuum overnight to give **XVII** (2.83 g, 75% yield).

Step C:

To a 0^{0}C suspension of **XVII** (2.83 g, 10.9 mmol) and SEM-Cl (6 mL, 33.9 mmol) in DMF (100 mL) was added 60% NaH (1.33 g, 33.2 mmol) and the reaction was stirred for 4 days. The reaction was diluted with EtOAc, washed with water (3x) and brine, and evaporated to give an orange oil (6.85 g). Chromatography and crystallization gave **XVIII** as yellow crystals (3.72 g, 87% yield).

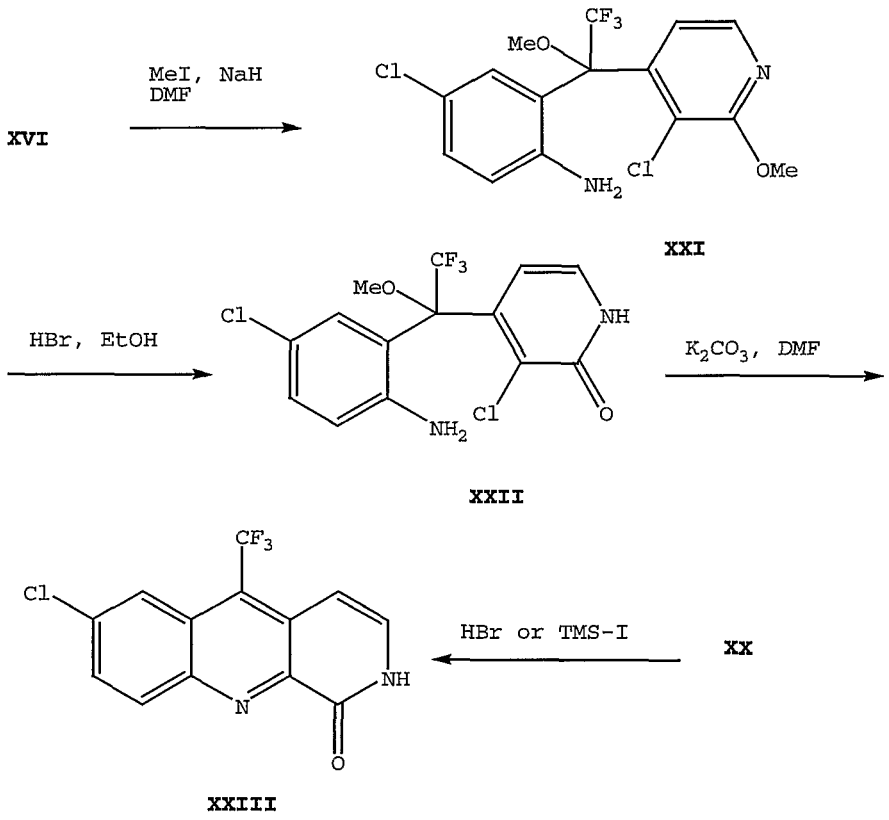
Step D:

To a 0^{0}C solution of **XVIII** (700 mg, 1.79 mmol) and CF_3TMS (0.35 mL, 2.37 mmol) in THF (7 mL) was added a solution of 1M TBAF in THF (0.2 mL, 0.2 mmol). After 10 min., additional TBAF (0.3 mL, 0.3 mmol) was added to

desilylate the silyl ether. After aqueous work-up, the crude oil was triturated with hexanes to give **XIX** as an off-white solid (518 mg, 63% yield).

Step E:

A solution of **XIX** (420 mg) in TFA was stirred for 1.5 h and concentrated to give an oil. The oil was partitioned between EtOAc and 1 N NaOH and washed with water and brine, and evaporated to give **XX** as a yellow solid (264 mg, 93% yield).



Alternative Method

Step A-2:

To a 0 ^{0}C solution of **XVI** (12 g, 32.7 mmol) and MeI (3.3 mL, 53.5 mmol) in DMF (120 mL) was added 60% NaH (1.44 g, 36 mmol) and stirred overnight. After aqueous work-up, chromatography and trituration gave **XXI** (6.22 g, 50% yield).

Step B-2:

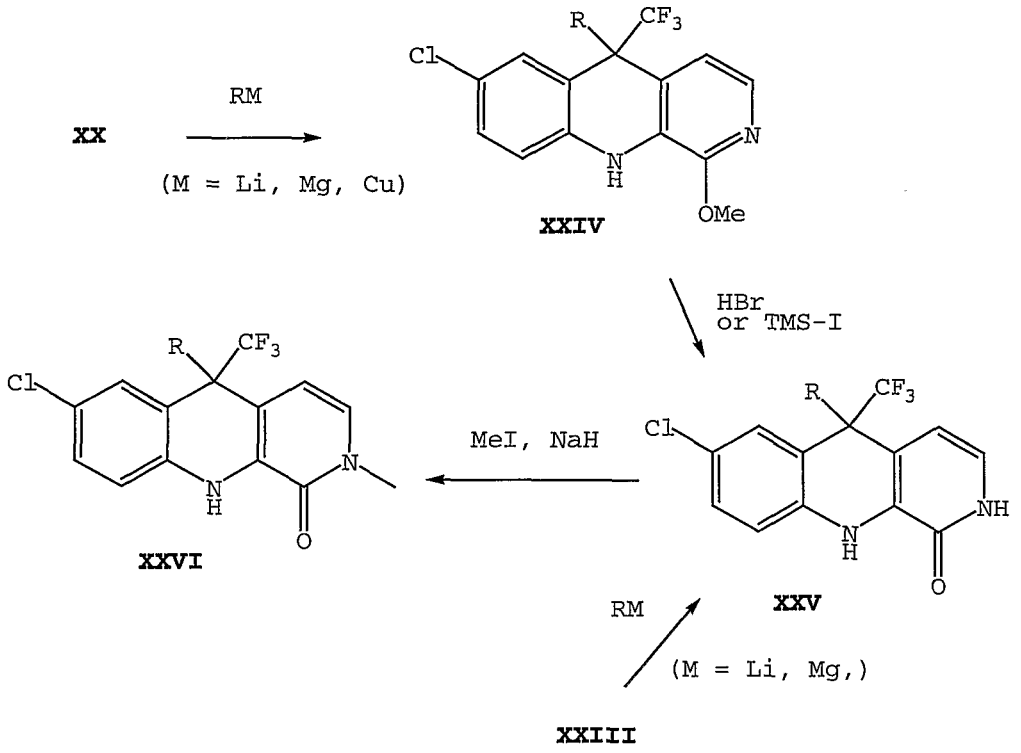
A solution of **XXI** (6.4 g, 16.8 mmol) in EtOH (20 mL) and a solution of 48% HBr (20 mL) was refluxed for 1.5 h. The reaction was diluted with EtOAc and neutralized, washed with brine, dried over Na_2SO_4 and concentrated to an orange thick oil (8 g). Trituration with ether and CH_2Cl_2 gave **XXII** as a white solid (5.86 g, 95% yield).

Step C-2:

A suspension of **XXII** (4.7 g) in DMF (95 mL) was refluxed for 1.5 h. EtOAc and water were added and the reaction was filtered and washed with water (2x) and EtOAc (2x). The wet product was dried at 80 ^{0}C under high vacuum overnight to give **XXIII** as a yellow solid (2.85 g, 76% yield).

Step D-2:

A mixture of **XX** (1.5 g) in 48% HBr (10 mL) and EtOH (10 mL) was refluxed for 2 h. The reaction was diluted with water and neutralized with NaOH. The resulting solid was filtered off and washed with saturated $NaHCO_3$ and water (2x), and dried at 100 ^{0}C under high vacuum overnight to give **XXIII** as a yellow solid (1.33 g, 93% yield).



Step F:

To a -78 ^{0}C solution of diisoproplylamine (1.08 mL, 7.68 mmol) in THF (10 mL) was added a solution of 1.6 M BuLi (4.921 mL, 7.78 mmol) in hexane. After the reaction was stirred for 15 min., 2-picoline (7.59 mL, 7.68 mmol) was added. After stirring for 20 min., **XX** (600 mg, 1.92 mmol) was added. The reaction was quenched with saturated NH_4Cl, then diluted with EtOAc, washed with 0.1 N HCl (4x), water and saturated NaCl. The organic phase was dried over Na_2SO_4 and concentrated to a dark orange glass (670 mg). Flash chromatography (50% EtOAc/hexanes) gave **XXIV** (R = 2-picolyl (2-pyridylmethyl)) (R = 2-picolyl (2-pyridylmethyl) as a thick pink oil (R = 2-picolyl, 600 mg, 70% yield).

Step G:

A solution of **XXIV** (R = 2-picolyl (2-pyridylmethyl)) , 1.53 g) in 48% HBr (7 mL) and EtOH (7 mL) was refluxed for 1.5 h. The reaction was diluted with EtOAc and THF and neutralized with 1 N NaOH, and washed with brine. The organic phase was dried over Na_2SO_4 and evaporated to give a

gray solid (1.32 g). The solid was triturated with boiling dichloroethane (10 mL) to give **XXV** (1.25 g).

Example 21

A solution of **XXIV** ((R = cyclopropyl acetylene, 56 mg), DIEA (15 uL) and a solution of 1 M TMS-I in methylene chloride (1 mL) in methylene chloride (5 mL) was stirred overnight. The reaction was diluted with EtOAc and washed with 1 N NaOH and brine. The organic phase was dried over Na_2SO_4 and evaporated to give an orange glass (64 mg). The glass was triturated with ether (2 mL) to give **XXV** (R = cyclopropyl acetylene) as off-white solid (7.5 mg).

Example 24

(XXV, single active enantiomer)

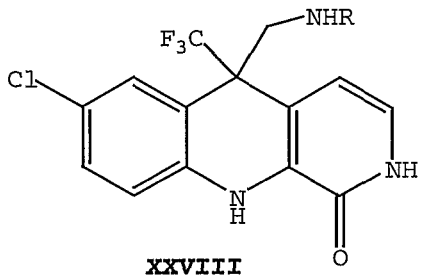
To a 0 ^{0}C solution of **XXV** (R = 2-picolyl (2-pyridylmethyl), 100 mg, 0.26 mmol) in DMF (2 mL) was added 60% NaH (11.2 mg, 0.28 mL). After stirred for 20 min., MeI (25 uL, 0.4 mmol) was added. After stirring for 10 min., the reaction was diluted with EtOAc and washed with water (2x) and brine. The organic phase was dried over Na_2SO_4 and evaporated to give a brown solid (127 mg). The solid was triturated with ether (2 mL) to give **XXVI** as a pale orange solid (81 mg, 84% yield).

Example 20

To a -78 ^{0}C solution of 85% cyclopropylethyl iodide (9.66 g, 41.5 mmol) in hexanes (75 mL) was added a solution of 1.7 M *t*-BuLi in pentane (49.3 mL, 83.8 mmol). After 5 min., ether (75 mL) was added and the reaction was warmed to room temperature for 1 h to destroy any excess of *t*-BuLi. The reaction was cooled back to -78 ^{0}C and THF (20 mL) was added. This -78 ^{0}C reaction mixture was added to a -78^{0}C suspension of **XXIII** (2.5 g, 8.38 mmol) in THF (100 mL) and TMEDA (10 mL). The reaction was quenched with saturated NH_4Cl, then diluted with EtOAc, washed with 1 N HCl, water

and saturated NaCl. The organic phase was dried over Na_2SO_4 and concentrated to an orange oil. Flash chromatography (25-50% EtOAc/hexanes) and trituration (dichloroethane and hexanes) gave **XXV** as a brown solid (R = cyclopropylethyl, 1.76 g, 58% yield).

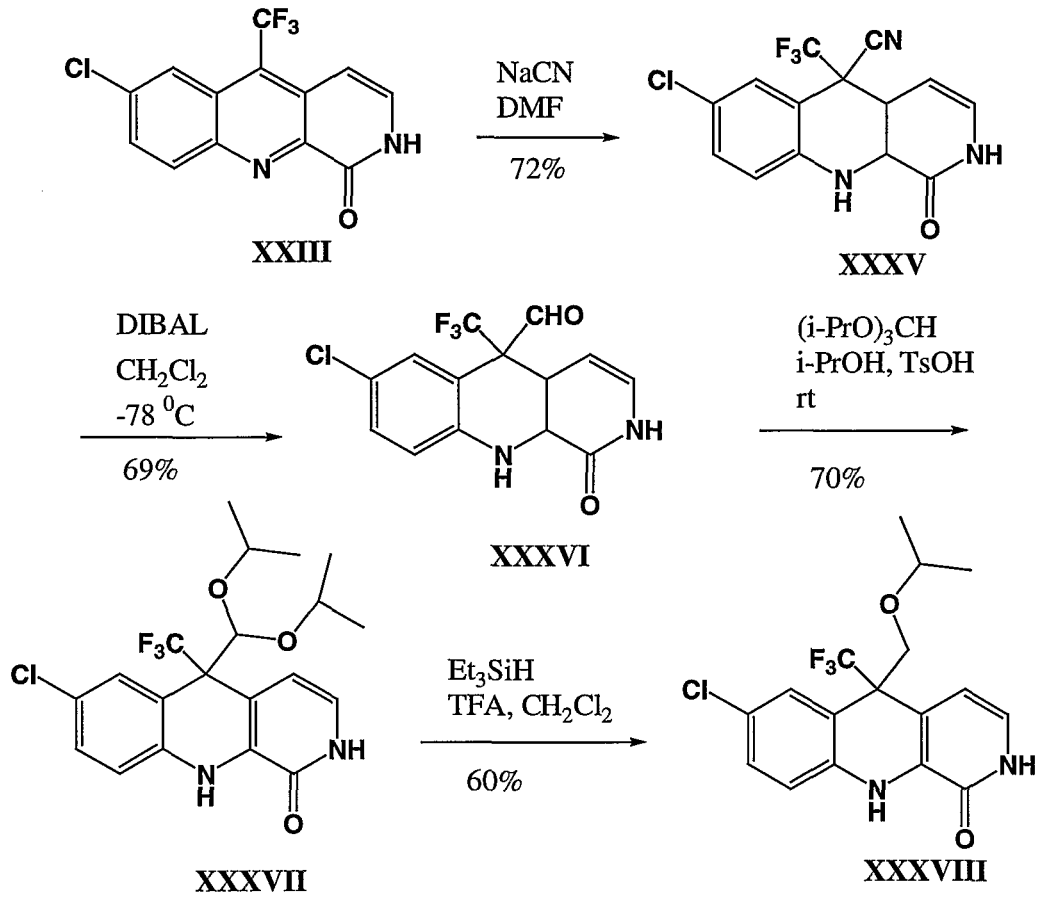
Example 22



XXVIII

The compound **XXVIII** (R=cyclopropylaminomethyl) was made by the method described in Example 30, below.

Example 28



Step A:

A suspension of **XXIII** (17.5 g) and NaCN (5.86 g) in DMF (450 mL) was stirred for 3 days. The reaction was diluted with EtOAc and washed with saturated $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4 and concentrated to a gray solid which triturated with methylene chloride (20 mL) to give a yellow solid **XXXV** (14.2 g, 72% yield). The compound **XXXV** was treated with DIBAL in methylene chloride at -78 ^{0}C to give a brown solid (14.2 g) after 3 N HCl/EtOAc workup. The crude solid was triturated with methylene chloride (20 mL) to give a yellow solid **XXXIV** (9.7 g, 69% yield).

Step B:

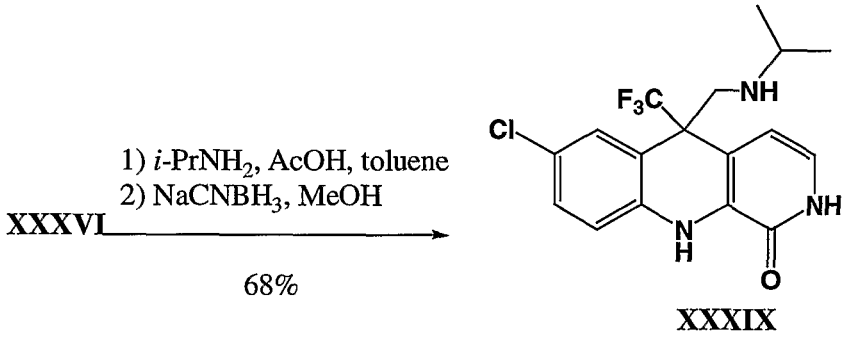
A suspension of **XXXIV** (5 g) and TsOH (4.6 g, 2 eq) in *i*-PrOH (100 mL) and $(i\text{-PrO})_3CH$ (40 mL) was stirred for 45

min. The reaction was diluted with EtOAc and washed with 1 N NaOH, water and brine. The organic phase was dried over Na_2SO_4 and concentrated. Flash chromatography (75% EtOAc/hexanes) and trituration (ether and hexanes) gave a pale yellow solid **XXXVII** (3.7 g, 70% yield).

Step C:

A solution of **XXXVII** (3.5 g) in Et_3SiH (70 mL), CH_2Cl_2 (35 mL) and TFA (70 mL) was stirred overnight and solvents were evaporated. The reaction was diluted with EtOAc and washed with 1 N NaOH, water and brine. The organic phase was dried over Na_2SO_4 and concentrated. Flash chromatography (75% EtOAc/hexanes) and trituration (ether and hexanes) gave a pale yellow solid **XXXVIII** (1.9 g, 60% yield).

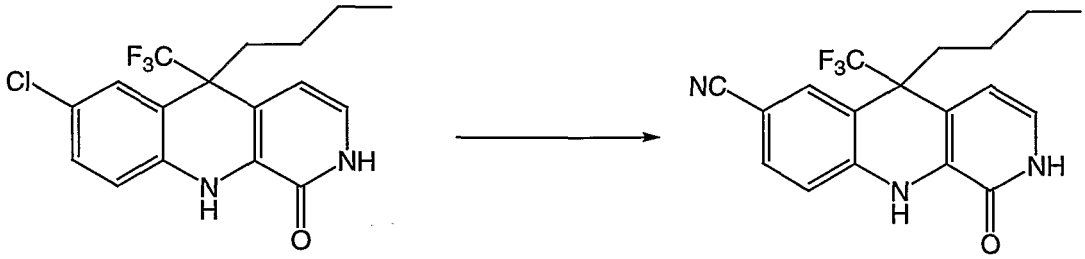
Example 30



XXXIX

A suspension of **XXXVI** (2.89 g), isopropylamine (4.5 mL) and acetic acid (9 mL) in toluene (440 mL) was stirred for 4 days. Then $NaCNBH_3$ (0.6 g) and MeOH (44 mL) were added to the reaction. After stirring for 2.5 h, The reaction was diluted with EtOAc and washed with saturated $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4 and concentrated to a yellow solid **XXXIX** (2.3 g, 68% yield).

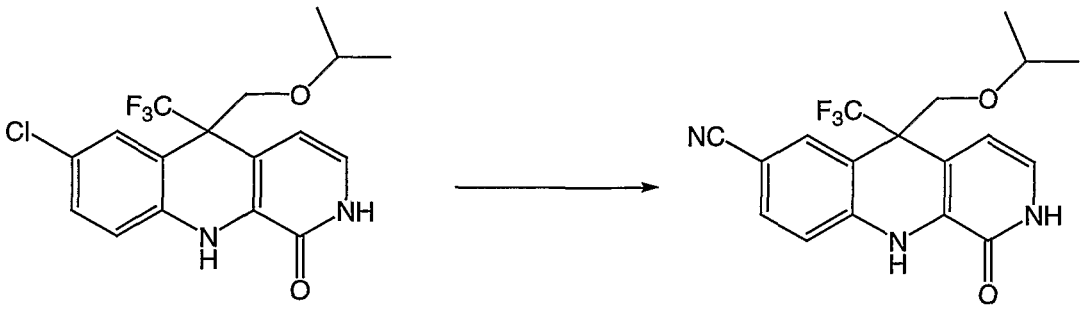
EXAMPLE 37



XL

The compound of Example 18 (2.13 grams) was dissolved in 150 ml of N,N-dimethylacetamide. 1,1'-bis(diphenylphosphino)ferrocene (1.33 g, 0.4 equivalents), zinc cyanide (1.40 g, 2.0 equivalents) and zinc powder (0.47 g 1.2 equivalents) were added. The mixture was degassed under high vacuum, and then 1.09 g (0.2 equivalents) of tris(dibenzylideneacetone)dipalladium(0) was added. The mixture was degassed once again, and heated to reflux for 18 hours. The black mixture was cooled and partitioned between ethyl acetate and 2N ammonium hydroxide. Both phases were filtered through Celite and separated. The organic phase was washed twice with water and dried over magnesium sulfate. Flash chromatography (silica gel, 50% EtOAc/hexane) yielded 1.44 g (69% yield) of compound **XL** as a brown solid M.S. 346.2 $(M-H)^-$.

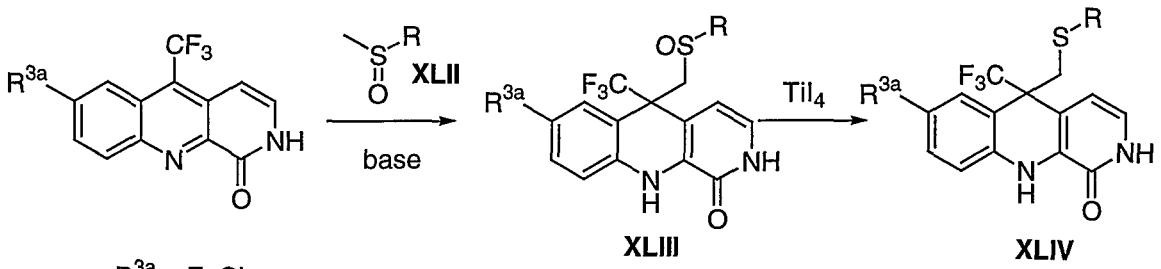
EXAMPLE 38



XXXVIII **XLI**

Pyridone **XXXVIII** (2.92 grams) was dissolved in 75 ml of N-methylpyrrolidinone. 1.92 g (2.0 equivalents) of zinc cyanide and 1.18 g (2.2 equivalents) of zinc powder were added. The mixture was degassed under high vacuum, and then 7.34 g (1.1 equivalents) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct was added. The mixture was degassed once again, and heated to 170°C 18 hours. The mixture was cooled and partitioned between ethyl acetate and 2N ammonium hydroxide. Both phases were filtered through Celite and separated. The organic phase was washed twice with water and dried over magnesium sulfate. Flash chromatography (silica gel, 50% EtOAc/hexane) yielded 1.76 g (59% yield) of compound **XLI** as a brown solid, M.S. 362.2 $(M-H)^-$.

The 4-alkylthiomethyl derivatives were synthesized using the synthetic Scheme shown below. Sulfoxide **XLII** was deprotonated with a strong base, such as lithium, sodium or potassium diisopropylamide or a similar amine anion in an inert solvent such as THF to give the corresponding deprotonated species. This was added to the pyridone core **XXIII,** to form a mixture of diastereomers **XLIII** at temperature ranges from -78 to 25 °C. The diastereomeric mixture or each individual diastereomer was deoxygenated by an appropriate reagent such as TiI_4 in an inert solvent such as acetonitrile by the process described by Shimizu et al. *Synlett.* **2000**, 1437, to give the corresponding sulfide.



R^{3a} = F, Cl

EXAMPLE 39

(Compound **XLIV** wherein R^{3a} is Cl, R is cyclopropyl)

Step A:

Cyclopropylmethyl sulfoxide: Cyclopropylbromide (8 mL, 0.1 mol) in ether (10 mL) was added dropwise into a suspension of Mg turnings (2.43 g, 0.1 mol) in ether (90 mL). After the addition was over the reaction was stirred at 25 °C for 3 hours and heated at reflux for 3 hours. Then it was cooled to 0 °C and $(CH_3S)_2$ (9 mL, 0.1 mol) was added dropwise and the mixture was stirred at 0 °C for 1 hour, at 25 °C for 20 hours and at reflux for 3 hours. After cooling it was quenched with water (5 mL) and 5% HCl (3 mL). The precipitated solids were filtered off and the filtrate was washed with water, brine, dried ($MgSO_4$), and distilled at atmospheric pressure. The fraction distilled at 100-110 °C consisted of a 1:1 mixture of cyclopropylmethylsulfide and methyl disulfide (4.4 g).

Step B:

Two grams of the above mixture (~22.2 mmol) in CH_2Cl_2 (50 mL) was cooled to -5 °C in a salt/ice bath and 4 g m-chloroperbenzoic, 70-75% acid was added in potions. The reaction was stirred at -5 °C for 2 hours and at 25 °C for 20 hours. Then it was quenched with satNaHCO$_3$, satNa$_2$S$_2$O$_5$, diluted with CH_2Cl_2 (50 mL) and washed with satNaHCO$_3$ (2x30 mL), brine, dried and stripped in vacuo. NMR analysis of the crude residue indicated that it consisted of the product, cyclopropyl methyl sulfoxide and ~10% of the corresponding sulfone. ^{1}H NMR($CDCl_3$) 2.66 (s, 3H), 2.14-2.19 (m, 1H), 0.8-1.22 (m, 4H).

Step C:

To a solution of diisopropylamine (0.22 mL, 1.64 mmol in THF (3 mL) at -78 °C (dry ice/acetone bath) a 1.6 solution of nBuLi in hexanes (0.84 mL, 1.36 mmol) was added and the mixture was warmed to 0 °C, stirred for 10 min and cooled

back to -78 °C. To the solution of LDA formed, cyclopropyl methyl sulfoxide (1.42 mg, 1.36 mmol) in THF (3 mL) was added and the reaction mixture was stirred at -78 °C for 30 min. Then the temperature was adjusted at -40 °C (acetonitrile/dry ice bath) and pyridone **XXIII** (100 mg, 0.34 mmol) was added as a solid. The reaction was stirred at -40 °C for 3 hours, quenched with 10% NH_4Cl and partitioned between EtOAc (100 mL) and brine (20 mL). The EtOAc extract was dried and stripped in vacuo. The residue was chromatographed on silica gel using EtOAc 1% methanol/EtOAc and 5% methanol/EtOAc to give the product. This was washed with ether to give the sulfoxide adduct **XLIII** as a mixture of diastereomers (47 mg).

EXAMPLE 39a

Step D:

The diastereomeric mixture of the sulfoxides from the previous reaction (43 mg, 0.11 mmol) was added into a mixture of TiI_4 (93 mg, 0.17 mmol) in acetonitrile (2 mL) at 0 °C. The reaction was stirred at 0 °C for 45 min and quenched with satNaHCO$_3$ (10 mL) and satNa$_2$S$_2$O$_5$ (5 mL). Then it was partitioned between EtOAc (100 mL) and water (20 mL), The EtOAc was washed with brine, dried (MgSO4), and stripped in vacuo. The crude product was purified by column chromatography using EtOAc and 2% methanol/EtOAc to give **XLIV** (26 mg). ^{1}H NMR($CDCl_3$): 10.7-10.8 (br s, 1H), 7.40 (br s, 1H), 7.25 (dd, 1 H, J = 2.2, 8.8 Hz), 6.89 (d, 1H, J = 7.3 Hz), 6.83 (d, 1H, J = 8.8 Hz), 6.32 (d, 1H, J = 7.3 Hz), 3.64 (d, 1H, J = 13.9 Hz), 3.55 (d, 1H, J = 13.9 Hz), 1.48-1-58 (m, 1H), 0.76-0.80 (m, 2H), 0.42-0.47 (m, 2H).

Examples 40 - 46 were prepared using the procedure described in Example 39.

EXAMPLE 40

Compound **XLIII** (**R^{3a}** is chloro and R is i-propyl)

The compound was prepared as described above. The compound was chromatographed on silica gel. The eluent used was a gradient of 90 % ethyl acetate/hexane to ethyl acetate to afford one diastereomer, brown solid, 59 mg, mp 238 °C (decomp). Yield 27 %. APCI-MS calcd. for $C_{17}H_{16}ClF_3N_2O_2S$ (404.057): $(M + H + CH_3CN)^+$ = 446.0, 100 %. ^1H NMR (DMSO): 11.8-11.9 (d, 1H); 9.3 (s, 1H); 7.5 (s, 1H); 7.33 (d, 1H, J = 8.8 Hz); 7.25 (d, 1H J = 7.0 Hz,); 6.92 (t, 1H); 6.33 (d, 1H, J = 7.0 Hz); 3.84 (d, 2H, J = 4.1 Hz); 2.95 (m, 1H); 1.20 (d, 3H, J = 7.0 Hz); 1.13 (d, 3H J = 6.9 Hz).

Chromatographed using the same conditions as in to afford the other diastereomer, yellow solid, 63 mg, 223 °C (decomp). Yield 28 %. APCI-MS calcd. For $C_{17}H_{16}ClF_3N_2O_2S$ (404.057): $(M + H + CH_3CN)^+$ = 446.0, 100 %. ^1H NMR (DMSO): 11.7 (d, 1H); 9.29 (s, 1H); 7.55 (s, 1H); 7.38 d, 1H, J = 8.8 Hz); 7.31 (d, 1H, J = 1.9 Hz); 6.8 (t, 1H); 6.3-6.4 (d, 1H); 3.6-4.0 (doublet of doublets, 2H); 2.9 (m, 1H); 1.18 (d, 3H, J = 6.6 Hz); 1.13 (d, 3H, J = 7 Hz).

Example 41

(Compound **XLIII** wherein R^{3a} is chloro and R is t-butyl)

The compound was chromatographed on silica gel. The eluent used was a gradient of 90 % ethyl acetate-hexane to 5% methanol/ethyl acetate to afford the diastereomer, which was washed with ether/hexanes to give a light yellow solid, 15 mg, 193 °C (decomp). Yield 13 %.

APCI-MS calcd. for $C_{18}H_{18}ClF_3N_2O_2S$ (418.073): $(M + H + CH_3CN)^+$ = 460.1, 100 %.

The compound was chromatographed on silica gel. The eluent used was a gradient of 90 % ethyl acetate-hexane to 5% methanol/ethyl acetate to afford the other diastereomer, which was recrystallized from ethyl acetate/methanol/hexanes to give a light brown solid, 9 mg. Yield 8 %.

APCI-MS calcd. for $C_{18}H_{18}ClF_3N_2O_2S$ (418.073): (M + H + $CH_3CN)^+$ = 460.1, 100 %.

EXAMPLE 42

(Compound **XLIV** wherein R^{3a} is chloro and R is methyl)

Synthesized in a similar manner as described earlier. The crude reaction product was washed with ether and had a purity of 95% by HPLC analysis (82% yield). ^1H NMR(dmso) 11.82 (brs, 1H), 9.25 (brs, 1H), 7.55 (brs, 1H), 7.34 (d, 1H, J = 8.7 Hz), 7.27 (dd, 1H, J = 2.2, 8.7 Hz), 6.91 (d, 1H, J = 6.9 Hz), 6.4 (d, 1H, J = 6.9 Hz), 3.82 (d, 1H, J = 13.5 Hz), 3.59 (d, 1H, J = 13.5 Hz), 2.00 (s, 3H).

EXAMPLE 43

(Compound **XLIV** wherein R^{3a} is chloro and R is ethyl)

Purified by silica gel chromatography (EtOAc eluent, 75% yield). ^1H NMR($CDCl_3$): 7.4 (brs, 1H), 7.35 (brs, 1H), 7.24 (dd, 1H, J = 2.2, 8.2 Hz), 6.92 (d, 1H), 6.83 (d, 1H, J = 8.2 Hz), 6.35 (d, 1H), 3.4-3.6 (d,d 2H), 2.48 (q, 2H), 1.20 (t, 3H).

EXAMPLE 44

(Compound **XLIV** wherein R^{3a} is chloro and R is i-propyl)

Pale yellow solid, 30 mg. mp = 220-221 °C. Yield 76 %. APCI-MS calcd. for $C_{17}H_{16}ClF_3N_2OS$ (388.062): (M + H + $CH_3CN)^+$ = 430.1, 88 %.

EXAMPLE 45

(Compound **XLIV** wherein R^{3a} is fluoro and R is i-propyl)

Orange solid, 14 mg. mp = 215-216 °C. Yield 40 %. APCI-MS calcd. for $C_{17}H_{16}F_4N_2OS$ (372.092): (M + H + CH_3CN)+ = 414.1, 100 %.

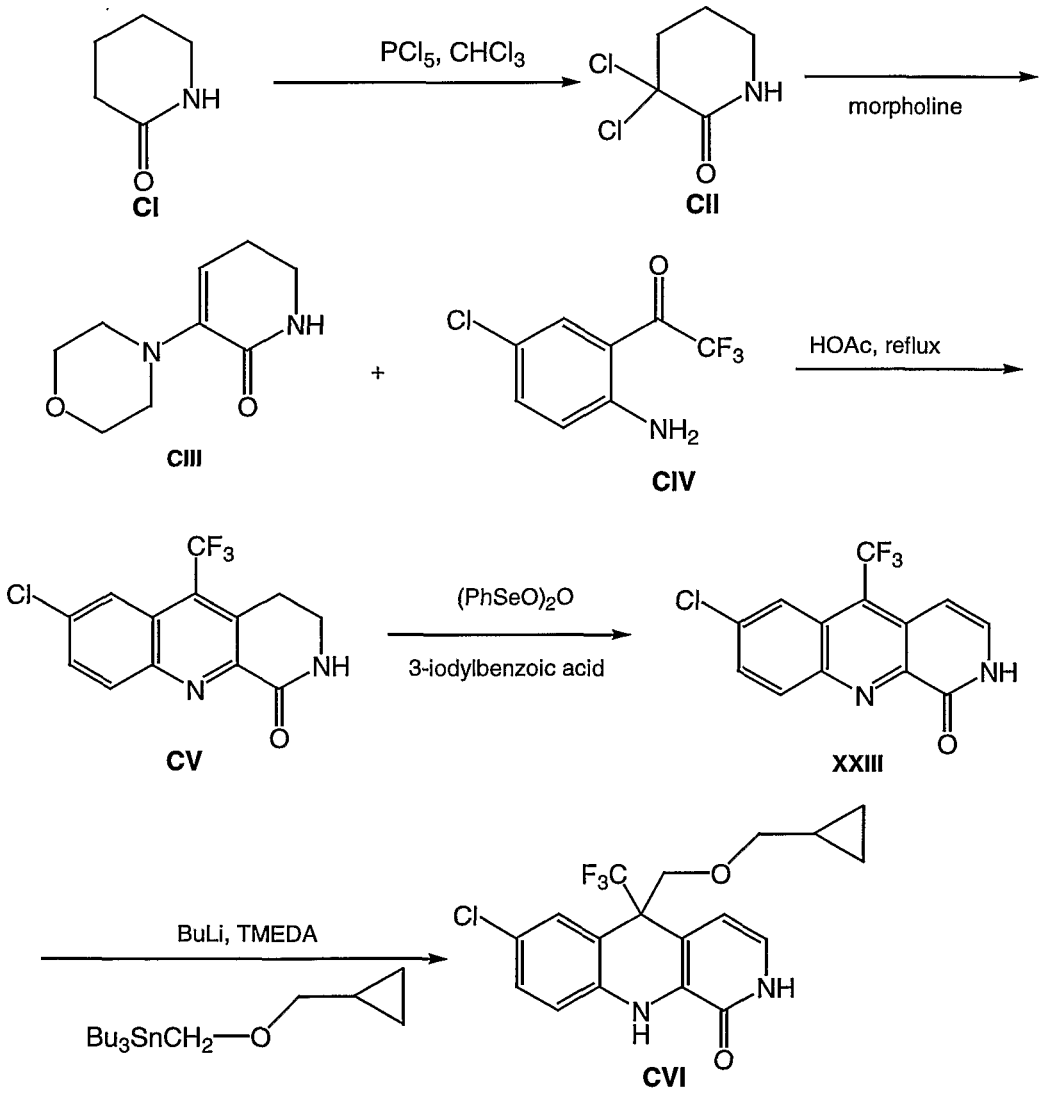
EXAMPLE 46

(Compound **XLIV** wherein R^{3a} is chloro and R is t-butyl)

White solid, 9 mg. mp = 247-249 °C. Yield 36 %. APCI-MS calcd. for $C_{18}H_{18}ClF_3OS$ (402.078): $(M + H + CH_3CN)^+$ = 444.1, 100 %.

Example 47

(Compound **CVI**)



Step A: Preparation of compound **CII**.

To a 50 °C solution of 20.8 g of phosphorous pentachloride in 150 mL of chloroform was added 2.97 g of 2-piperidone (**CI**) dropwise over 15 min. The reaction mixture was warmed to 75 °C and stirred at that temperature for 4.5 h. The cooled reaction mixture was slowly poured onto 150 mL of ice water with vigorous stirring keeping the temperature from 25-30 °C. After stirring an additional 15 min, the mixture was extracted with methylene chloride and the extracts were washed first with aqueous sodium bicarbonate then brine, dried over sodium sulfate, and evaporated to afford 4.5 g of **CII** as a pure solid.

Step B: Preparation of compound **CV**.

A mixture of 4.39 g of 3,3-dichloropiperidone (**CII**) and 13 ml of morpholine was heated at 128 °C for 2 h and then evaporated to dryness.
The crude morpholine enamine (**CIII**) thus obtained was combined with 6.43 g of **CIV** and 60 ml of acetic acid and was stirred for 6 h at reflux and overnight at room temperature. Evaporation of the solvent followed by trituration with water afforded a solid product which after recrystallization from ethyl acetate/hexane afforded 6.27 g of **CV**.

Step C: Preparation of compound **XXIII**.

A mixture of 500 mg of **CV**, 700 mg of 3-iodylbenzoic acid (prepared as described by Barton, **1982**, *J. Chem. Soc. Perkin Trans. I*, 1947-1952), 30 mg of benzeneseleninic acid (70%, from Aldrich Chemical Co.) and 35 mL of dry toluene was refluxed for 19 h. The mixture was evaporated to dryness, 80 mL of aqueous sodium bicarbonate was added, and the mixture was stirred vigorously for 30 min. The yellow solid was collected, washed with water and methanol to afford 390 mg of **XXIII** as bright yellow crystals.

Step D: Preparation of tributyl (cyclopropylmethoxymethyl)tin.

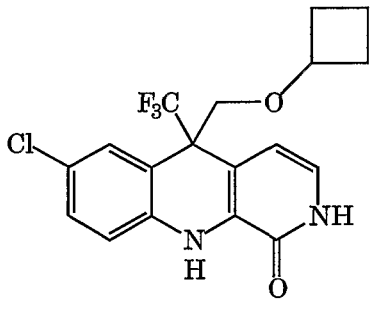
To a solution of 1.15 g of cyclopropyl carbinol in 30 mL of dry THF was added 312 mg of 98% sodium hydride. After stirring 1 h, 2.8 g of iodomethyl tributyltin (prepared as described by Seitz *et al*, **1983** *Synthetic Commun. 13*, 129) was added and the reaction mixture was stirred at room temperature for 24 h, and then poured onto water and extracted with hexanes. The extracts were washed with brine, dried and evaporated to a crude product that was purified by flash chromatography (hexanes then 30% ethyl acetate/hexanes eluents) to afford 1.03 g of tributyl (cyclopropylmethoxymethyl)tin as a colorless oil.

Step E: Preparation of compound **CVI**.

To a -78 °C solution of 565 mg of tributyl (cyclopropylmethoxymethyl)tin and 0.5 ml of TMEDA in 5 mL of anhydrous THF was added 0.53 ml of 2.5M butyllithium in hexane. After 5 min, 100 mg of **XXIII** was added in a single portion, and the stirred suspension was stirred at -50 °C for 45 min. The cold reaction mixture was quenched by the addition of aqueous ammonium chloride, and then extracted with ethyl acetate. The extracts were washed with brine, dried over sodium sulfate, and evaporated to an oily solid which was triturated with hexane to remove the tetraalkyltin byproduct. The crude solid was purified by preparative tlc (75% EtOAc/hexanes eluent) to give after crystallization (CH_2Cl_2/EtOAc/hexanes) 23 mg of **CVI** (mp 250 °C).

EXAMPLE 48

(compound CVII)



Step A: Preparation of tributyl (cyclobutyloxymethyl)tin.

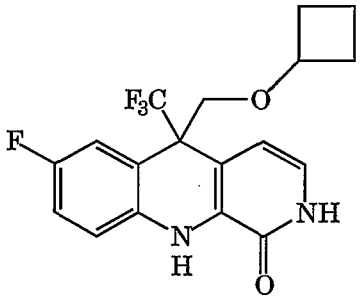
To a solution of 2.3 g of cyclobutanol in 60 mL of dry THF was added 624 mg of 98% sodium hydride. After stirring 2 h, 5.6 g of iodomethyl tributyltin (prepared as described by Seitz et al **1983** *Synthetic Comm. 13* 129) was added and the reaction mixture was stirred at room temperature for 48 h, and then poured onto water and extracted with hexanes. The extracts were washed with brine, dried and evaporated to a crude product that was purified by flash chromatography (hexanes then 67% ethyl acetate/hexanes eluents) to afford 1.64 g of tributyl (cyclobutyloxymethyl)tin as a colorless oil.

Step B: Preparation of compound **CVII**.

To a -78 °C solution of 565 mg of tributyl (cyclobutyloxymethyl)tin and 0.5 ml of TMEDA in 5 mL of anhydrous THF was added 0.625 ml of 1.6 M butyllithium in hexane. After 5 min, 75 mg of **XXIII** was added in a single portion, and the stirred suspension was stirred at -50 °C for 40 min. The cold reaction mixture was quenched by the addition of aqueous ammonium chloride, and then extracted with ethyl acetate. The extracts were washed with brine, dried over sodium sulfate, and evaporated to an oily solid which was triturated with hexane to remove the tetraalkyltin byproduct. The crude solid was purified preparative tlc (75% EtOAc/hexanes eluent) to give 11.3 mg of **CVII** (mp 245 °C).

EXAMPLE 49

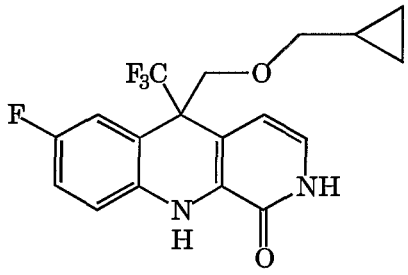
Compound **CVIII**



To a -78 °C solution of 565 mg of tributyl cyclobutyloxymethyltin and 0.5 ml of TMEDA in 5 mL of anhydrous THF was added 0.626 ml of 1.6 M butyllithium in hexane. After 5 min, 100 mg of **IX** was added in a single portion, and the stirred suspension was stirred at -50 °C for 40 min. The cold reaction mixture was quenched by the addition of aqueous ammonium chloride, and then extracted with ethyl acetate. The extracts were washed with brine, dried over sodium sulfate, and evaporated to an oily solid which was triturated with hexane to remove the tetraalkyltin byproduct. The crude solid was purified by preparative tlc (75% EtOAc/hexanes eluent) to give 12 mg of **CVIII** (mp 224 °C).

EXAMPLE 50

Compound **CIX**

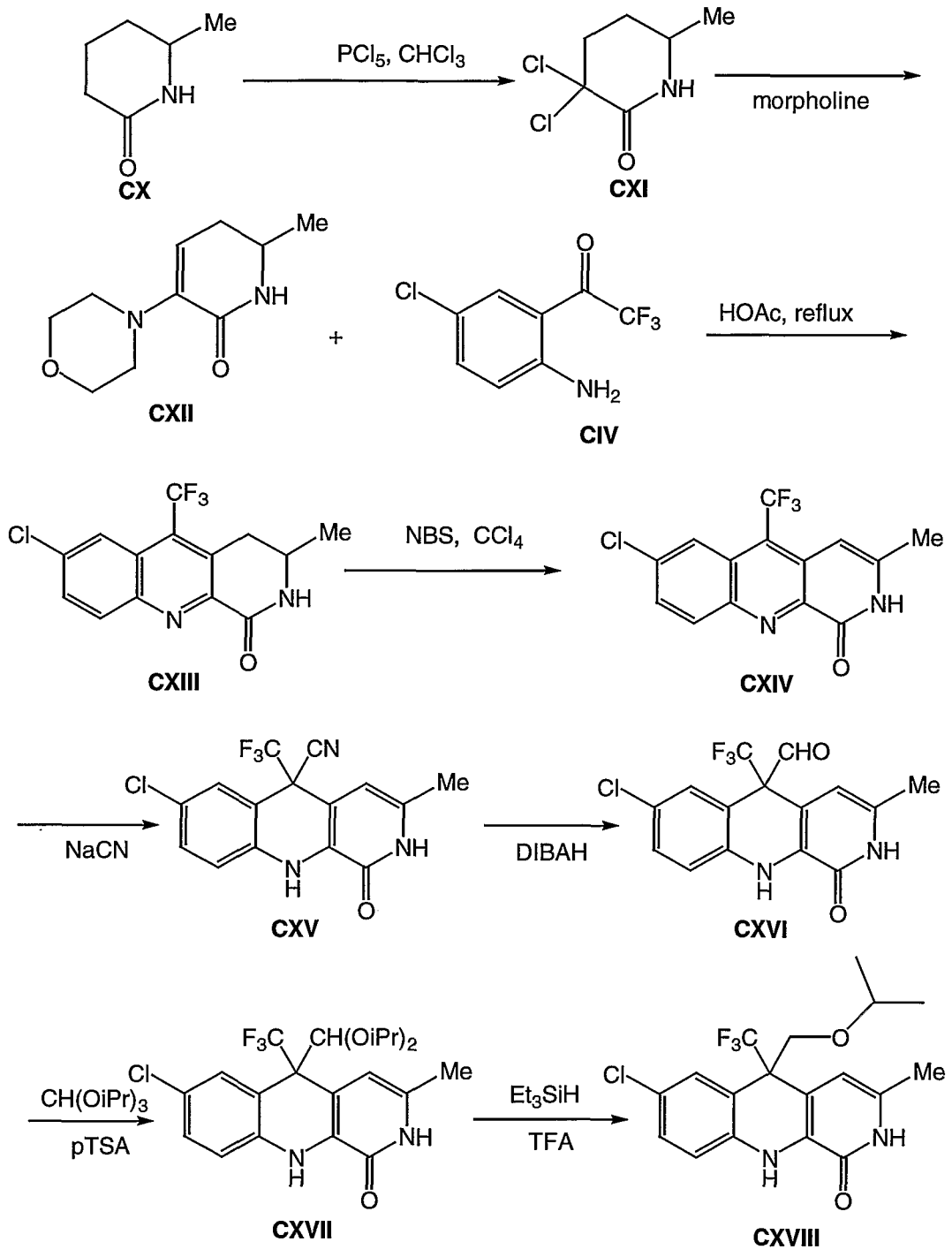


To a -78 °C solution of 800 mg of tributyl cyclopropylmethoxymethyltin and 0.7 ml of TMEDA in 7 mL of anhydrous THF was added 0.90 ml of 1.6 M butyllithium in hexane. After 5 min, 100 mg of **IX** was added in a single portion, and the stirred suspension was stirred at -50 °C for 40 min. The cold reaction mixture was quenched by the

addition of aqueous ammonium chloride, and then extracted with ethyl acetate. The extracts were washed with brine, dried over sodium sulfate, and evaporated to an oily solid which was triturated with hexane to remove the tetraalkyltin byproduct. The crude solid was purified by preparative tlc (75% EtOAc/hexanes eluent) to give 20 mg of **CIX** as a crystalline solid (mp 203-204 °C).

EXAMPLE 51

Compound **CXVIII**



Step A: Preparation of compound **CXI**.

To a 50 °C solution of 31.9 g of phosphorous pentachloride in 225 mL of chloroform was added 5.2 g of 6-methyl-2-piperidone (**CX**) portionwise over 15 min. The reaction mixture was warmed to 75 °C and stirred at that temperature for 4.5 h. and then at room temperature

overnight. The cooled reaction mixture was slowly poured onto 225 mL of ice water with vigorous stirring keeping the temperature from 25-30 °C. After stirring an additional 10 min, excess aqueous sodium bicarbonate was added and after 10 min, the mixture was extracted with methylene chloride and the extracts were washed with brine, dried over sodium sulfate, and evaporated to afford 6.7 g of **CXI** as a pure solid.

Step B: Preparation of compound **CXIII**.

A mixture of 1.56 g of 6-methyl-3,3-dichloropiperidone (**CXI**) and 4.5 ml of morpholine was heated at 128 °C for 2 h and then evaporated to dryness.

The crude morpholine enamine (**CXII**) thus obtained was combined with 2.14 g of **CIV** and 20 ml of acetic acid and was stirred for 3 h at reflux, and at room temperature overnight. Evaporation of the solvent followed by trituration with water afforded a solid product which after recrystallization from ethyl acetate/hexane afforded 1.86 g of **CXIII**.

Step C: Preparation of compound **CXIV**.

A mixture of 1.5 g of **CXIII**, 850 mg of N-bromosuccinimide, and 150 mg of Vazo52 in 250 ml of carbon tetrachloride was refluxed for 1 h and the solvent was removed on the rotary evaporator. Recrystallization of the crude product afforded 680 mg of **CXIV** as yellow crystals.

Step D: Preparation of compound **CXV**.

A mixture of 1.28 g of **CXIV**, 250 mg of sodium cyanide, and 25 mL of DMF was stirred at room temperature for 22 h. The reaction mixture was diluted with ethyl acetate, washed three times with water, dried over sodium sulfate and evaporated. Recrystallization from ether/hexane afforded 1.07 g of **CXV**.

Step E: Preparation of compound **CXVI**.

To a suspension of 500 mg of **CXV** in 50 ml of anhydrous methylene chloride at -78 °C was added dropwise 6.6 mL of 1M diisobutylaluminum hydride in toluene. After 2 h at -78 °C the cold reaction mixture was poured onto a mixture of 250 mL of 3N HCl and 250 ml of ethyl acetate which was stirred for 10 min. The organic layer was washed with aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated to 508 mg of **CXVI**.

Step F: Preparation of compound **CXVII**.

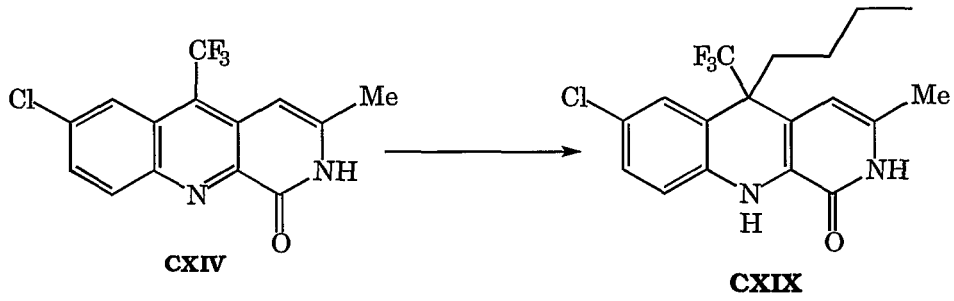
A mixture of 900 mg of **CXVI**, 180 mg of p-toluenesulfonic acid, 10 mL of triisopropyl orthoformate, and 10 mL of isopropanol. was stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate, washed 3X with 0.1N NaOH, water, then brine, dried over sodium sulfate and evaporated to a crude oil that was purified by flash chromatography (67% EtOAc/hexanes) to afford 600 mg of **CXVII**.

Step G: Preparation of compound **CXVIII**.

A mixture of 583 mg of **CXVII**, 6 mL of triethylsilane, 12 mL of trifluoroacetic acid, and 12 ml of dry methylene chloride was stirred overnight at room temperature and then evaporated to dryness. The crude product was dissolved in ethyl acetate, washed twice with aqueous sodium bicarbonate then brine, dried over sodium sulfate and evaporated to 570 mg of a solid. This was dissolved in a hot mixture of ethyl acetate and methylene chloride and the cooled solution deposited 140 mg of a crystalline byproduct. The mother liquor was subjected to flash chromatography on silica gel (eluted with 33%, 50%, and 67% ethylacetate/hexane) to afford 235 mg of **CXVIII** as colorless crystals (mp 234-235 °C).

EXAMPLE 52

Compound **CXIX**

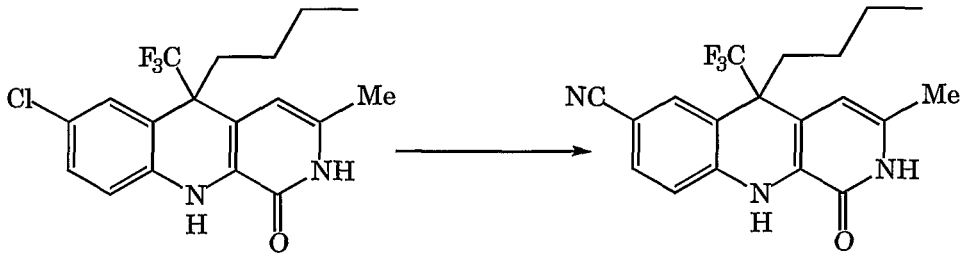


CXIV **CXIX**

To a -78 °C mixture of 107 mg of **CXIV** in 10 mL of dry THF and 1 mL of TMEDA was added dropwise 1.0 mL of 1.6 M butyllithium and the mixture was stirred 30 min at -78 °C. The cold reaction mixture was quenched by the addition of aqueous citric acid, and then extracted with ethyl acetate. The extracts were washed with brine, dried over sodium sulfate, and evaporated to an oil that was purified by flash chromatography (33% EtOAc/hexanes eluent) to give after recrystallization from ether/hexanes 60 mg of **CXIX** as a crystalline solid (mp 206-208 °C).

EXAMPLE 53

Compound **CXX**



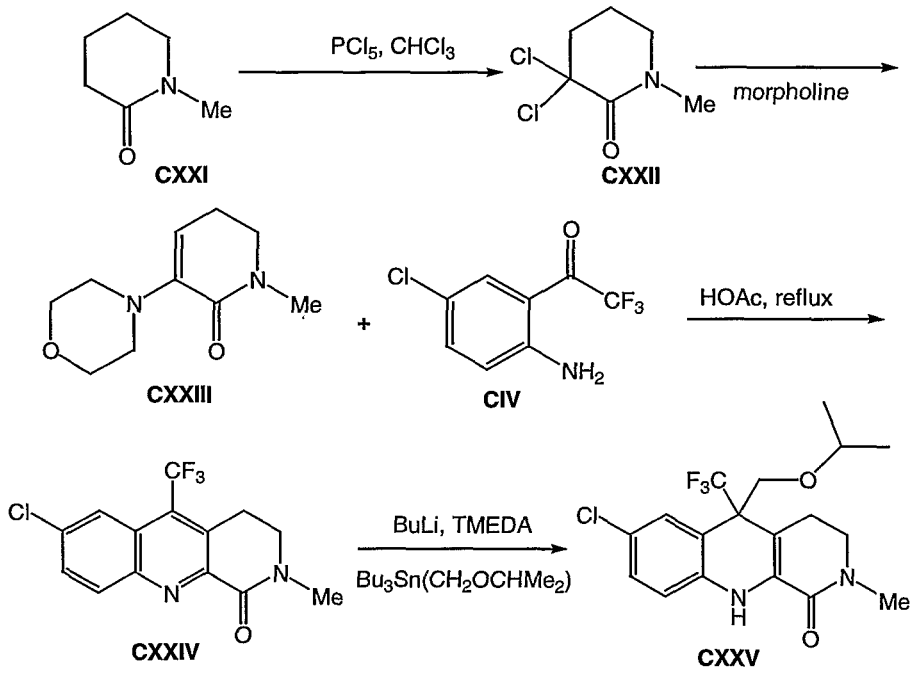
CXIX **CXX**

A degassed mixture of 41 mg of **CXIX**, 26 mg of zinc cyanide, 90 mg of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, 16 mg of zinc powder, and 1.5 mL of N-methylpyrrolidone was stirred under nitrogen for 25 h at 150 °C. The cooled mixture was diluted with ethyl acetate and filtered through a pad consisting of layers of sand, silica gel, and celite. The filtrate was

washed with 2N NaOH and brine, dried over sodium sulfate and evaporated. Flash chromatography (50% EtOAc/hexanes eluent) gave after recrystallization from ethyl acetate/hexanes 16 mg of **CXX** as a crystalline solid (mp 254-255 °C).

EXAMPLE 54

Compound **CXXV**



Step A: Preparation of compound **CXXII**.

To a 50 °C solution of 20.8 g of phosphorous pentachloride in 150 mL of chloroform was added 3.39 mL of 1-methyl-2-piperidone (**CXXI**) dropwise over 15 min. The reaction mixture was warmed to 75 °C and stirred at that temperature for 4.5 h. The cooled reaction mixture was slowly poured onto 150 mL of ice water with vigorous stirring keeping the temperature from 25-30 °C. After stirring an additional 15 min, the mixture was extracted with methylene chloride and the extracts were washed first with aqueous sodium bicarbonate then brine, dried over

sodium sulfate, and evaporated to afford 5.0 g of **CXXII** as a pure oil.

Step B: Preparation of compound **CXXIV**.

A mixture of 1.0 g of **CXXII** and 5 ml of morpholine was heated at 128 °C for 1.25 h and then evaporated to dryness. The residue was dissolved in methylene chloride, washed with water and aqueous citric acid, dried and evaporated to 0.5 g of **CXXIII** as an oil.

The crude morpholine enamine (**CXXIII**) thus obtained was combined with 500 mg of **CIV** and 9 ml of acetic acid and was stirred at reflux for 4.5 h. After evaporation of the solvent, the crude product was partitioned between methylene chloride and water and the organic layer was washed with aqueous sodium bicarbonate, dried, evaporated and purified by flash chromatography (10% MeOH/methylene chloride) to give 453 mg of **CXXIV** as a solid product.

Step C: Preparation of tributyl (isopropoxymethyl)tin

To a solution of 4.6 mL diisopropylamine in 40 mL of dry THF at -20 °C was added dropwise first 12.0 ml of 2.5 M butyllithium and then 8.1 ml of tributyltinhydride. After 10 min this solution was cooled to -78 °C, and 3.25 g of chloromethyl isopropyl ether (Molina *et al*, **1982** *Synthesis*, 944) was added dropwise. After 10 min the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 1.5 h. The mixture was poured onto water and extracted with hexanes and the extracts were dried over sodium sulfate and evaporated. The crude product was distilled (0.2 mm, 110-130 °C) to afford 7.8 g of tributyl (isopropoxymethyl)tin as a colorless liquid.

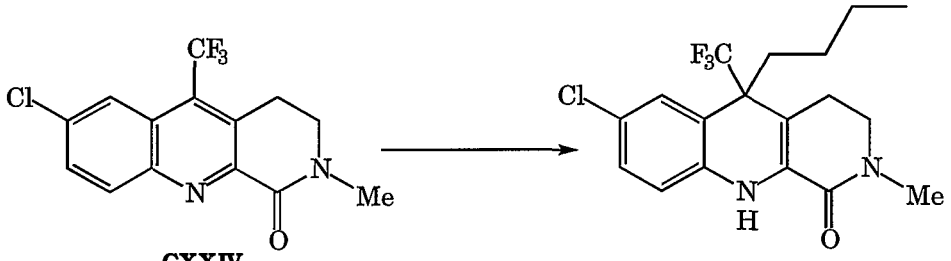
Step D: Preparation of compound **CXXV**.

To a -78 °C solution of 719 mg of tributyl (isopropoxymethyl)tin and 0.4 ml of TMEDA in 4 mL of anhydrous THF was added 0.53 ml of 2.5M butyllithium in

hexane. After 5 min, 100 mg of **XXIV** was added in a single portion, and the stirred suspension was allowed to stir at -78 °for 45 min. The cold reaction mixture was quenched by the addition of aqueous ammonium chloride, and then extracted with ethyl acetate. The extracts were washed with brine, dried over sodium sulfate, and evaporated to an oily solid. The crude solid was purified by flash chromatography (50% EtOAc/hexanes eluent) and then preparative tlc (50% EtOAc/hexanes eluent) to give 2 mg of **CXXV** [ms, $(m+H)^+$ = 389.0]

EXAMPLE 55

Compound **CXXVI**

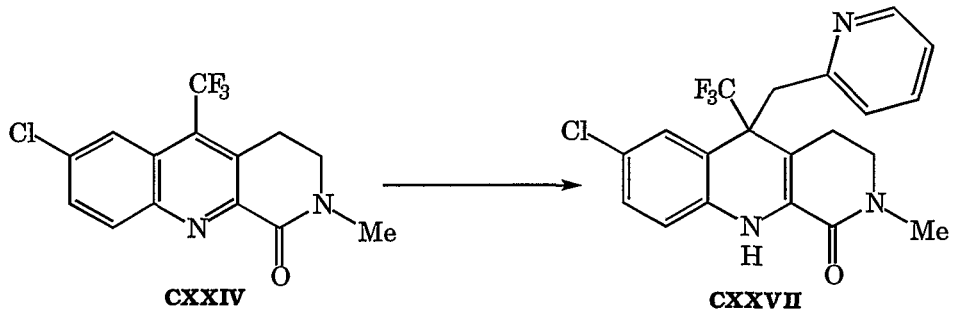


CXXIV **CXXVI**

To a -78 °C mixture of 225 mg of **CXXIV** in 20 mL of dry THF and 2 mL of TMEDA was added dropwise 1.22 mL of 2.5 M butyllithium and the mixture was stirred 30 min at -78 °C. The cold reaction mixture was quenched by the addition of aqueous ammonium chloride, and then extracted with ethyl acetate. The extracts were washed with 1N HCl, water, brine, dried over sodium sulfate, and evaporated to an oil that was purified by flash chromatography (10-20% EtOAc/hexanes eluent) and preparative tlc (50% EtOAc/hexanes eluent) to give 7 mg of **CXVII** as a crystalline solid (mp 221-223 °C).

EXAMPLE 56

Compound **CXXVII**

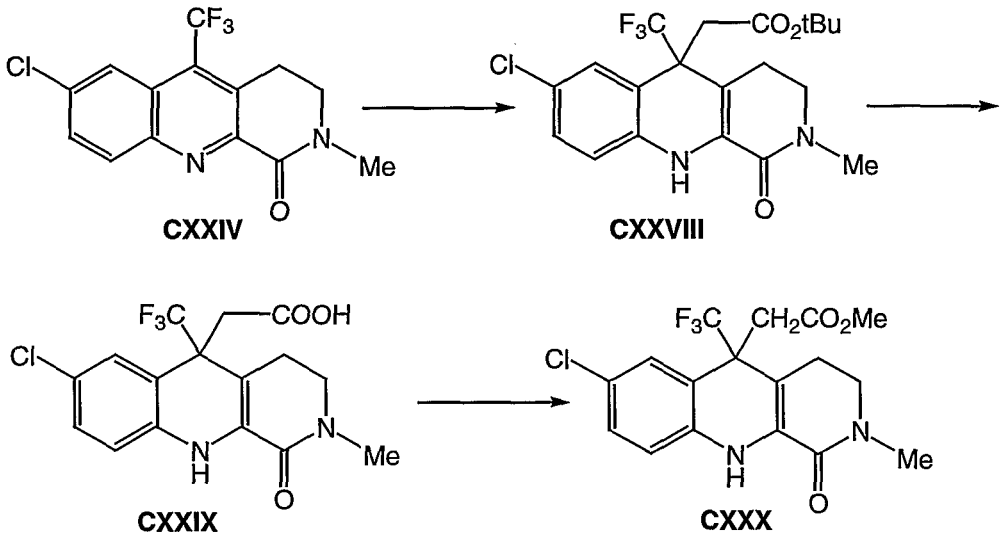


CXXIV **CXXVII**

To a -78 °C solution of 1.07 mL of diisopropylamine in 10 mL of dry THF was added dropwise 3.1 mL of 2.5 M butyllithium. After 15 min, 0.755 mL of 2-methylpyridine was added, andthe mixture was stirred 20 min at -78 °C. 600 mg of **CXXIV** was added, and after 30 min, the cold reaction mixture was quenched by the addition of aqueous ammonium chloride, and then extracted with ethyl acetate. The extracts were washed with 0.1N HCl, water, brine, dried over sodium sulfate, and evaporated to an oil that was purified by flash chromatography (50% EtOAc/hexanes then 5% MeOH/CH_2Cl_2 eluent) and preparative tlc (5% MeOH/CH_2Cl_2 eluent)) to give after recrystallization from methylene chloride/hexanes 60 mg of **CXXVII** as a crystalline solid (mp 192-193 °C).

EXAMPLE 57

Compound **CXXX**



Step A: Preparation of compound **CXXVIII**.

To a -78 °C solution of 0.45 mL ofdiisopropylamine in 10 mL of dry THF was added dropwise 0.90 mL of 1.6 M butyllithium. After 15 min, 0.45 mL of tert-butylacetate was added dropwise, and the mixture was stirred 30 min at -78 °C then allowed to warm to 0 °C. The reaction mixture was again cooled to -78 °C, 315 mg of **CXXIV** dissolved in 8 mL of THF was added dropwise, and it was stirred 30 min at -78 °C and 30 min at 0 °C. The cold reaction mixture was quenched by the addition of aqueous ammonium chloride, and then extracted with ethyl acetate. The extracts were washed with water and brine, dried over sodium sulfate, and evaporated to 400 mg of **CXXVIII** as a pure solid.

Step B: Preparation of **CXXIX**.

A mixture of 183 mg of **CXXVIII**, 12 ml of methylene chloride, and 4.0 mL of trifluoroacetic acid was stirred for 1 h at 50 °C. The cooled reaction mixture was poured onto water and extracted with methylene chloride. After drying

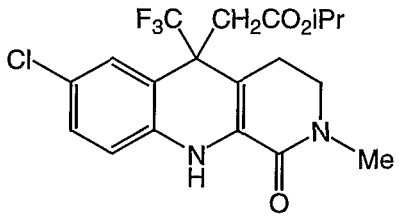
over sodium sulfate, the extracts were evaporated to give 183 mg of **CXXIX** as a pure solid.

Step C: Preparation of **CXXX**.

A solution of 30 mg of **CXXIX**, 0.100 mL of thionyl chloride, and 2.0 mL of methanol was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and evaporated to a crude product. This was purified by preparative tlc (50% EtOAc/hexanes eluent) to give after recrystallization from ether/hexanes 15 mg of **CXXX** as a crystalline solid (mp 200-201 °C).

Example 58

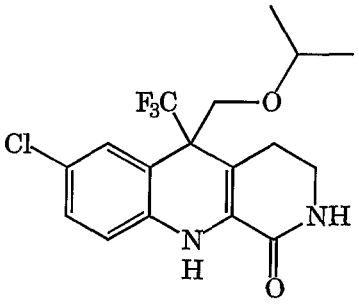
Compound **CXXXI**



A mixture of 50 mg of **CXXIX,** 5 mL of isopropanol and 20 drops of sulfuric acid was refluxed overnight. The reaction mixture was poured onto water and extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate, dried and evaporated to an oil. This was purified by flash chromatogeaphy (25% EtOAc/hexanes eluent) to give a solid that was recrystallized from ether/hexanes to give 24 mg of **CXXXI** as a crystalline solid (mp 153-154 °C).

Example 59

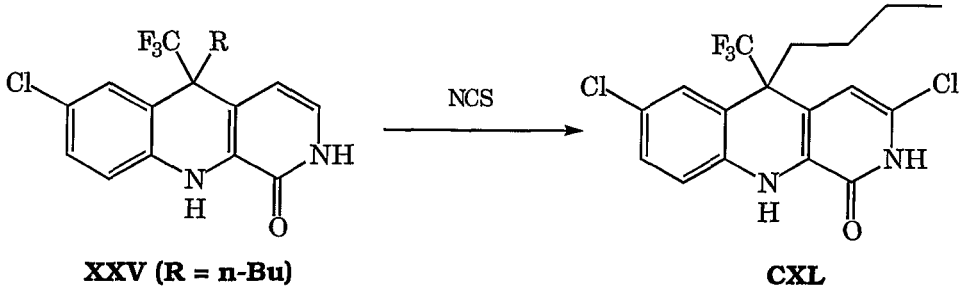
Compound **CXXXIX**



To a -78 °C solution of 719 mg of tributyl (isopropoxymethyl)tin and 0.4 ml of TMEDA in 4 mL of anhydrous THF was added 0.53 ml of 2.5M butyllithium in hexane. After 5 min, 100 mg of **CV** was added in a single portion, and the stirred suspension was allowed to warm to -20 °C over 35 min. The cold reaction mixture was quenched by the addition of aqueous ammonium chloride, and then extracted with ethyl acetate. The extracts were washed with brine, dried over sodium sulfate, and evaporated to an oily solid that was triturated with hexane to remove the tetraalkyltin byproduct. The crude solid was purified by flash chromatography (50% EtOAc/hexanes eluent) and then preparative tlc (67% EtOAc/hexanes eluent) to give after crystallization (ether/hexanes) 13 mg of **CXXXIX** (mp 163-164 °C)

Example 60

Compound **CXL**

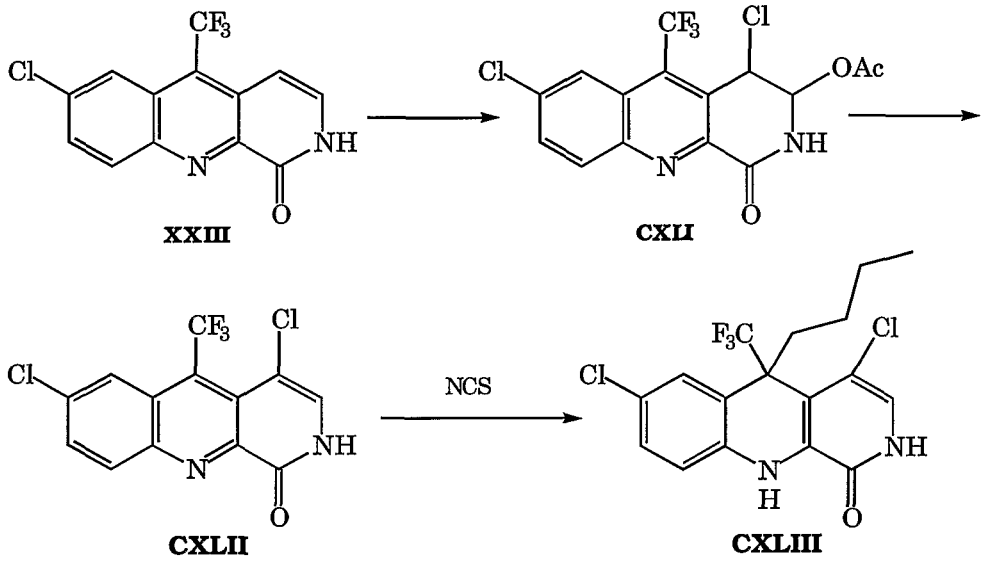


XXV (R = n-Bu) **CXL**

To a 0 °C solution of **XXV** (R = n-butyl) in 4 mL of dry acetonitrile was added 60 mg of N-chlorosuccinimide. After 30 min the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 1.5 h. The mixture was diluted with ethyl acetate, washed twice with water and once with brine, dried over sodium sulfate and evaporated to give after crystallization from ether/ hexanes 48 mg of **CXL** as pure crystals (mp 234-236 °C).

Example 61

Compound **CXLIII**



Step A: Preparation of **CXLII**.

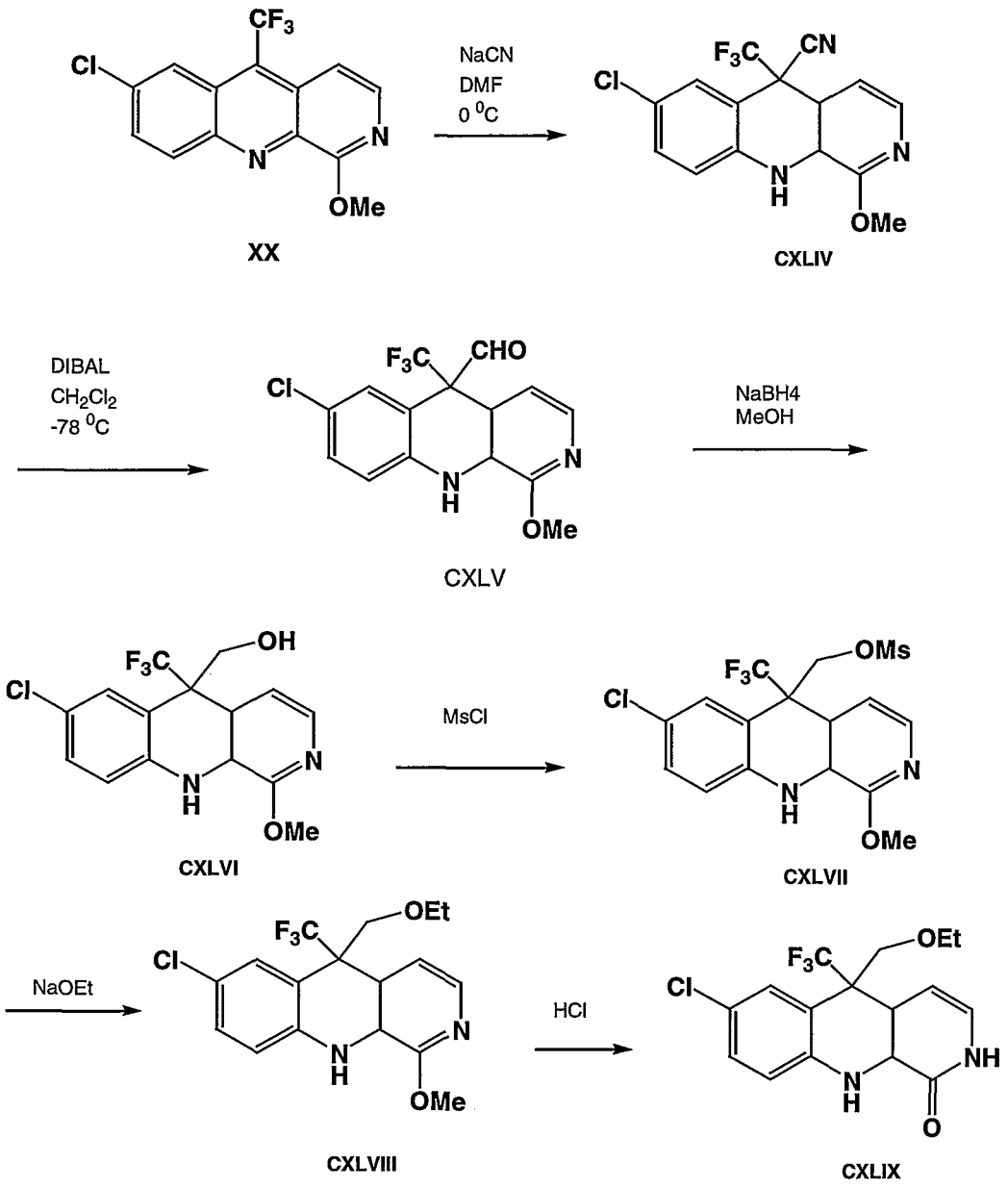
A mixture of 200 mg of **XXIII**, and 105 mg of N-chlorosuccinimide in 20 ml of acetic acid was refluxed for 1 h. The solvent was evaporated and the crude reaction product was dissolved in ethyl acetate and this solution was washed twice with water and once with brine, dried over sodium sulfate and evaporated to give the intermediate solid addition product **CXLI**. This material was heated neat at 130-140 °C for 3 h to give 125 mg of **CXLII** as bright yellow crystals.

Step B: Preparation of **CXLIII**.

To a -78 °C mixture of 100 mg of **CXLII** in 10 mL of dry THF and 1 mL of TMEDA was added dropwise 1.5 mL of 1.6 M butyllithium and the mixture was stirred 30 min at -78 °C. The cold reaction mixture was quenched by the addition of aqueous citric acid, and then extracted with ethyl acetate. The extracts were washed with water and brine, dried over sodium sulfate, and evaporated to crude product that was purified by flash chromatography (25-50% EtOAc/hexanes eluent) to give after crystallization from ether 11 mg of **CXLIII** as a crystalline solid (mp 252-255 °C).

EXAMPLE 62

CXLIX



Step A: preparation of **CXLIV**

To a 0 °C suspension of **XX** (700 mg, 1.7 mmol) in DMF (70 mL) was added NaCN (167 mg, 3.4 mmol). After stirring overnight, the reaction was diluted with EtOAc and washed with salturated $NaHCO_3$, water and brine. Concentration gave a brown solid (**CXLIV**, 800 mg).

Step B: preparation of **CXLV**

To -78 °C solution of **CXLIV** (800 mg) in dichloromethane (35 mL) was added a solution of 1 M DIBAL in dichloromethane (3.8 mL). The reaction was quenched with 3 N HCl and diluted

with EtOAc, washed with 3 N HCl (3x), saturated $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated to a pale orange solid (**CXLV**, 750 mg).

Step C: preparation of **CXLVI**

A suspension of **CXLV** (750 mg) and $NaBH_4$ (140 mg) in MeOH (7 mL) was stirred for 15 min. The reaction was diluted with EtOAc, washed with water (2x) and brine. The organic phase was dried over Na_2SO_4 and concentrated to a pale orange solid which was triturated with ether to give **CXLVI** (570 mg).

Step D: preparation of **CXLVII**

To a 0 ^{0}C solution of **CXLVI** (330 mg) and DIEA (0.95 mL) in DMF (4 mL) was added MsCl (0.21 mL). The reaction was diluted with EtOAc, washed with dilute HCl (2x), salturated $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated to an orange thick oil (**CXLVII**, 480 mg).

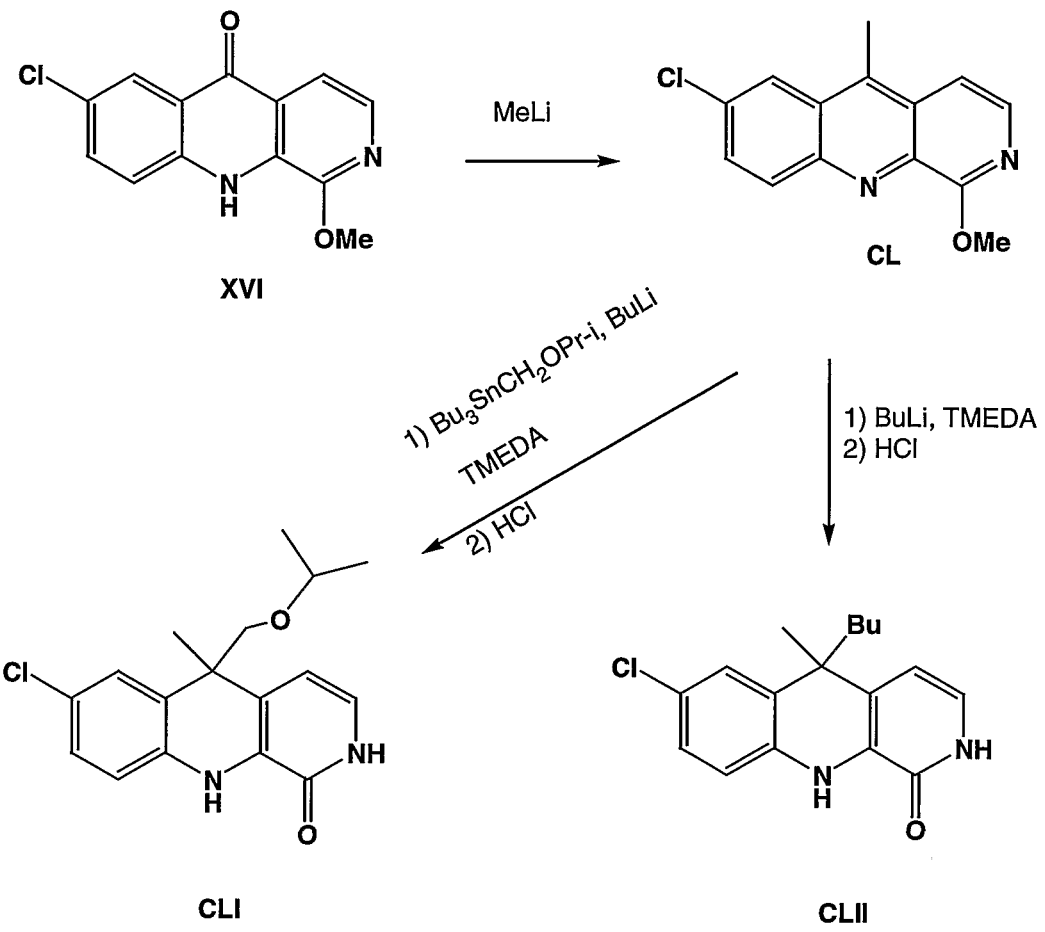
Step E: preparation of **CXLVIII**

A solution of **CXLVII** (415 mg) in EtOH (100 mL) and 21% NaOEt in EtOH (150 mL) was stirred for 3 days. The reaction was diluted with EtOAc, washed with water (2x) and brine. The organic phase was concentrated and chromatographied to give an orange oil (**CXLVIII**, 73 mg).

Step F: preparation of **CXLIX**

A solution of **CXLVIII** (70 mg) in EtOH (8 mL) and concentrated HCl (4 mL) was refluxed for 1 h. The reaction was diluted with EtOAc and neutralized with KOH, and washed with brine. The organic phase was dried over Na_2SO_4 and triturated with ether to give a brown solid (**CXLIX** 46 mg), M.P. 240-245°C.

EXAMPLE 61a



Step A:

To a 0 ^{0}C suspension of **XVI** (1.1 g, 4.2 mmol) in THF (10 mL) was added a solution of 1.4 M MeLi in ether (6.6 mL, 9.3 mmol). After stirred for 10 min., the reaction was quenched with sat. NH_4Cl. Partitioned between EtOAc and sat. NH_4Cl and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated to give 0.97 g of yellow solid (**CL**, 88% yield).

StepB:

To a -78 ^{0}C solution of **CL** (100 mg, 0.39 mmol) in THF (1 mL) and TMEDA (0.1 mL) was added a solution of 1.6 M BuLi in hexanes (0.73 mL, 1.16 mmol). The reaction was allowed to warm to 0 ^{0}C, then quenched with sat. NH_4Cl. Partitioned

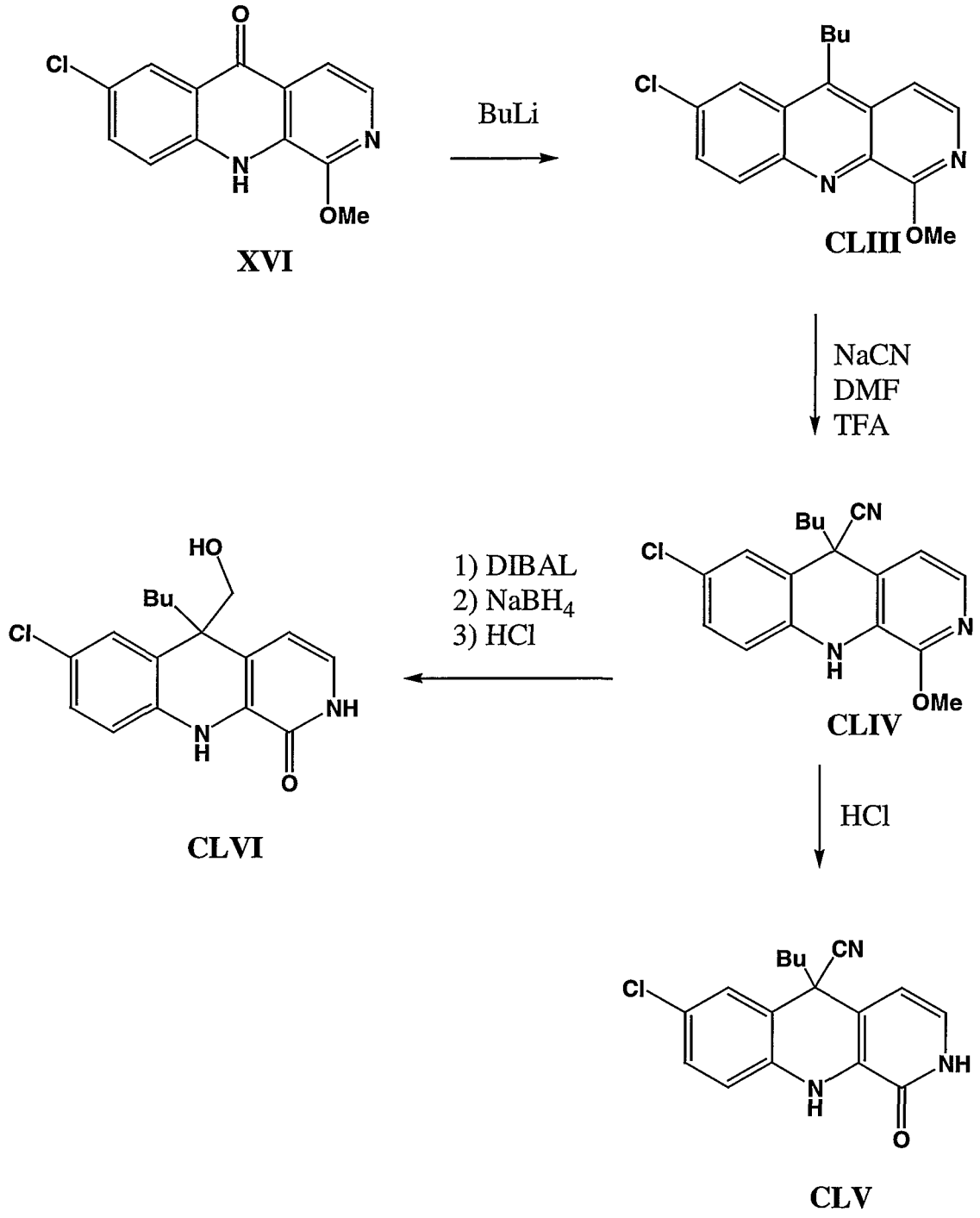
between EtOAc and sat. NH_4Cl and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated. Flash chromatography (15% EtOAc/hexanes) gave 41 mg of an orange oil.

Demethylation: The oil (41 mg) was refluxed in conc. HCl (1 Ml) and EtOH (3 ml) FOR 1 h. The reaction was diluted with EtOAc, washed with 10% NaOH, then water and brine. The organic phase was dried over Na_2SO_4 and concentrated. Crystallization from ether/hexanes gave 24 mg of brown solid (**CLII**).

EXAMPLE 62a

The compound **CLI** was prepared as described from **CLII.**

EXAMPLE 63



Step A:

CLIII was prepared as described in Compound **CL**.

Step B:

A suspension of **CLIII** (408 mg, 1.36 mmol) and NaCN (124 mg, 2.04 mmol) in DMF (4.5 mL) and TFA (0.11 mL,1.36

mmol) was stirred overnight. The reaction was diluted with EtOAc, washed with saturated $NaHCO_3$, then water and brine. The organic phase was dried over Na_2SO_4 and concentrated. Flash chromatography (25% EtOAc/hexanes) gave 390 mg of solid (**CLIV**, 88% yield).

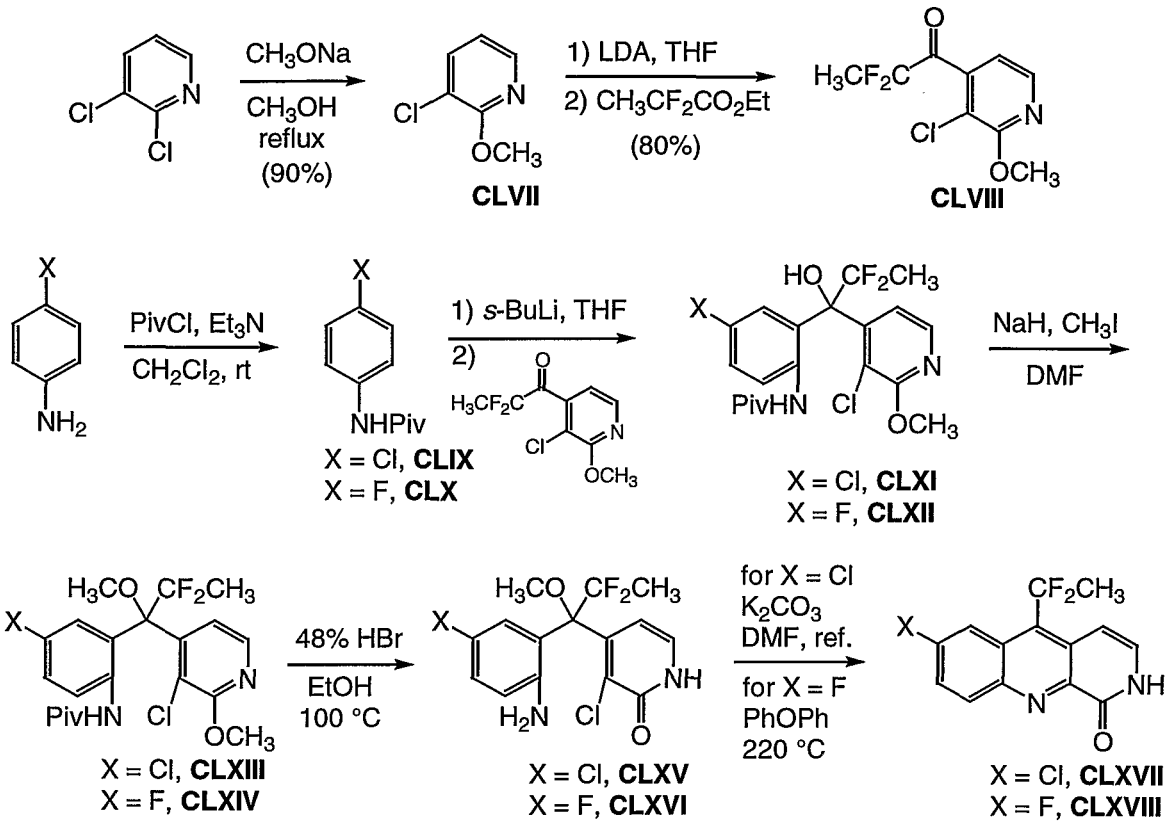
Step C:

CLIV was treated with HCl to give **CLV** as described in Compound **CLII.**

EXAMPLE 64

The compound **CLIV** (200 mg) was treated with DIBAL in methylene chloride at -78 ^{0}C to give an orange oil (187 mg, 93%) after 3 N HCl/EtOAc workup. The aldehyde was reduced to the alcohol with $NaBH_4$ in MeOH in nearly quantitative yield. The demethylation was as described in Compound **CLII** to give **CLVI.**

EXAMPLE 65



Step A:

2,3-Dichloropyridine (9.717 g, 65.00 mmol) was treated with 25wt% sodium methoxide in methanol (74.4 mL, 325.0 mmol). The resulting milky suspension was heated to reflux for 15 h 30 min. The reaction mixture was cooled to rt and quenched with H_2O (150 mL), extracted with EtOAc (2 X). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was distilled under *vacuo* (65 °C/8 mmHg) to give **CLVII** (8.354 g, 90% yield) as a colorless oil.

Step B:

To a stirred solution of **CLVII** (2.152 g, 15.0 mmol) in anhydrous THF (20 mL) at -78 °C was slowly added LDA (2M solution in THF, 7.50 mL, 15.0 mmol). After 1 hour at -78 °C, CH_3CF_2COOEt (1.30 mL, 10.0 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 2 h and then at 0

°C for one more hour. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 X). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (Hexane:Et_2O = 9:1) to give **CLVIII** (1.864 g, 79% yield).

Step C:

To a stirred solution of 4-chloroaniline (13.47 g, 104.5 mmol) in anhydrous CH_2Cl_2 (300ml) at 0 °C was added triethylamine (21.85 mL, 156.8 mmol) and pivaloyl chloride (15.60 mL, 125.4 mmol). The reaction mixture was stirred at rt for 1.5 h. The reaction was quenched with *1N* HCl (150 mL) and extracted with CH_2Cl_2 (2 X). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The off-white solid was suspended in hexanes (100 mL) and stirred at rt for 10 min. The product was filtered and dried under vacuum to give **CLIX** (21.687 g, 98% yield) as a white solid, m.p. 149 - 150 °C.

Step D:

To a stirred solution of 4-fluoroaniline (10.0 mL, 0.104 mol) in anhydrous CH_2Cl_2 (300ml) at 0 °C was added triethylamine (21.9 mL, 0.157 mmol) and pivaloyl chloride (15.6 mL, 0.125 mmol). After 3 h at rt, the reaction mixture was quenched with *1N* HCl (250 mL) and extracted with CH_2Cl_2 (3 X 200mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give white needle crystal. The crystal was rinsed with hexane and dried under vacuum to give **CLX** (19.4 g, 96% yield) as a white crystal.

Step E:

To a stirred solution of 4-Chloro-*N*-pivaloylaniline **CLIX** (3.36 g, 15.9 mmol) in anhydrous THF (60mL) -78 °C was added *sec*-BuLi (1.3 M in hexane, 25 mL, 31.8 mmol) dropwise. After 2 h at 0 °C, the reaction mixture was re-cooled to -78 °C and a solution of compound **CLVIII** (3.12 g, 13.24 mmol) in THF (20 mL) was added dropwise. The reaction mixture was warmed to -20 °C to -30 °C and stirred for 2.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography purification gave **CLXI** (4.14 g, 70% yield) as a white solid.

Step F:

To a stirred solution of 4-fluoro-*N*-pivaloylaniline **CLX** (730 mg, 3.74 mmol) in anhydrous THF (15mL) at -78 °C was added *sec*-BuLi (1.3M in Hexane, 5.75 mL, 7.48 mmol). After 1.5 h at 0 °C, the reaction mixture was re-cooled to -78 °C and a solution of compound **CLVIII** (734 mg, 3.10 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h and then stirred between -20 °C and -30 ° for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 X 60 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography purification gave **CLXII** (1.864 g, 67% yield) as a white solid.

Step G:

To a stirred solution of **CLXI** (4.134 g, 9.24 mmol) in anhydrous DMF (100mL) at 0 °C was added NaH (60% in mineral oil, 450 mg, 11.25 mmol) in 3 portions. The resulting suspension was stirred for 10min and MeI (750 µL, 11.8 mmol) was added. After 2 h at rt, another portion of NaH (25 mg, 0.625 mmol) and MeI (0.55 mmol) was added. After stirring for 45minutes at rt, the reaction was quenched with

saturated aqueous NH_4Cl and extracted with ethyl acetate (2 X). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a white solid. The solid was triturated with hexane, filtered to give **CLXIII** (4.156 g, 98% yield) as a white solid.

Step H:

To a stirred solution of **CLXII** (1.846 g, 4.3 mmol) in anhydrous DMF (25mL) at 0 °C was added NaH (60% in mineral oil, 225 mg, 5.57 mmol). The resulting suspension was stirred for 10 min and MeI (410 μL, 6.45 mmol) was added. The reaction mixture was stirred at 0°C for 2 h and then at rt for another 1.5 h. The reaction was quenched with water (50mL) and extracted with ethyl acetate (3 X 100mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (Hexane:EtOAc = 6:1) to give **CLXIV** (1.72 g, 99% yield) as a pale solid.

Step J:

To a stirred solution of **CLXIII** (4.156 g, 9 mmol) in ethanol (20 mL) was added HBr (48% aqueous solution, 40 mL 360 mmol). The reaction mixture was heated at 100 °C for 48 h. The mixture was cooled to 0 °C and neutralized carefully with concentrated NaOH (50%wt) and saturated aqueous Na_2CO_3 to pH 8-9, extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a light yellow solid. The solid was triturated with ether and filtered to give **CLXV** (3.2 g, 98% yield).

Step K:

To a stirred solution of **CLXIV**(445 mg, 1.0 mmol) in ethanol (6 mL) was added HBr (48% solution in H_2O, 3.4 mL, 30mmol). The reaction mixture was heated at 100 °C for 48 h. The mixture was cooled to 0 °C and neutralized carefully

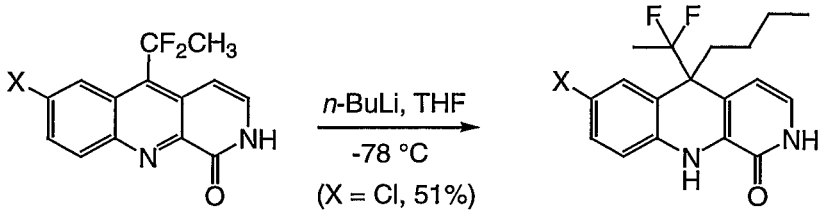
with concentrated NaOH (50%wt) and saturated aqueous Na_2CO_3 to pH 8-9, extracted with ethyl acetate (3 X). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a white solid. The solid was rinsed with ether and filter to give **CLXVI** (307 mg, 88% yield).

Step L:

To a stirred solution of **CLXV** (187 mg, 0.515 mmol) in dry DMF (25ml) was added K_2CO_3 (142 mg, 1.03 mmol). The reaction mixture was heated to reflux for 3 h. The reaction mixture was cooled to rt and quenched with H_2O (20 mL). The solid was filtered, washed with water and hexane, dried under vacuum to give **CLXVII** (150 mg, 99% yield) as a brown solid.

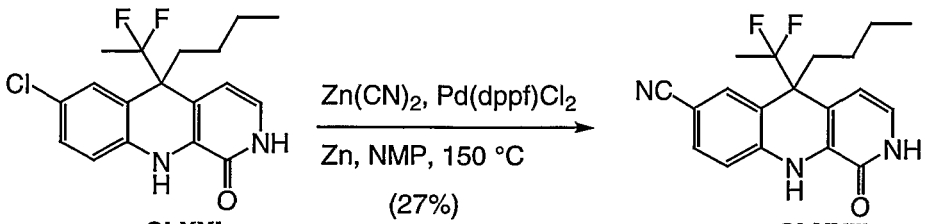
Step M:

A suspension of **CLXVI** (690 mg, 2 mmol) in diphenyl ether (5mL) was heated at 225°C for 1.5 h. The reaction mixture was cooled to rt and diluted with ether. The black solid precipitated and was filtered to give **CLXVIII** (527 mg, 95%) as the crude product.



CLXIX: X = Cl
CLXX: X = F

CLXXI: X = Cl
CLXXII: X = F



CLXXI **CLXXIII**

Step N:

To a stirred suspension of compound **CLXIX** (87 mg, 0.295 mmol) in anhydrous THF (5 mL) at -78 °C was slowly added *n*-BuLi (2.5 M in hexane, 1.18 mL, 2.95 mmol). The resulting brown solution was stirred at -78 °C for 3 h 30 min. The reaction was quenched with water (20 mL) and extracted with ethyl acetate (2 X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (EtOAc:Hexane = 3:2) to give **CLXXI** (53 mg, 51% yield) as a pale yellow solid, m.p. 120 - 122 °C, MS (ES): $(M+H)^+$ = 353.3, $(M-H)^-$ = 351.2.

EXAMPLE 66

Step O:

To a stirred suspension of compound **CLXX** (95 mg, crude) in anhydrous THF (6 mL) at -78 °C was slowly added *n*-BuLi (1.6 M in hexane, 1.5 mL, 2.4 mmol). The reaction mixture was stirred at -78 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 X 50mL). The combined ethyl acetate layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column (CH_2Cl_2:MeOH = 100:4) to give **CLXXII** (16 mg, 14% yield) as a white solid, m.p. 267 - 270 °C, MS (ES): $(M+H)^+$ = 337.3, $(M-H)^-$ = 335.3.

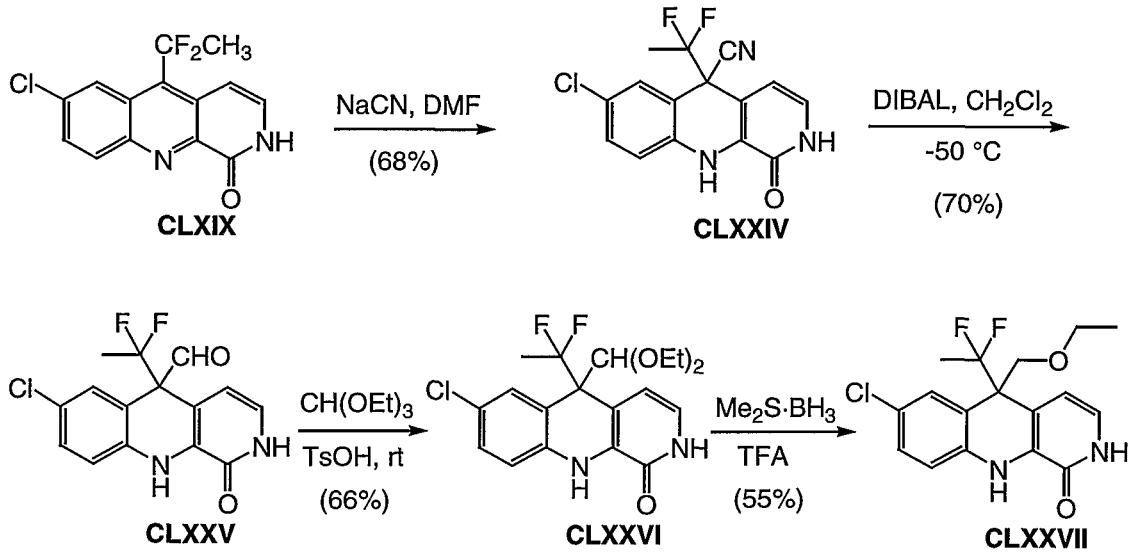
EXAMPLE 67

Step P:

A degassed mixture of **CLXXI** (105 mg, 0.298 mmol), $Zn(CN)_2$ (72 mg, 0.595 mmol), {Dichloro[1,1'-Bis(diphenylphosphino)ferrocene]Palladium(II) dichloromethane adduct} (98 mg, 0.12 mmol) and Zn powder (24 mg, 0.36 mmol) in 1-methyl-2-pyrrolidinone (3 mL) was heated at 150 °C for 48h. The reaction mixture was cooled to rt,

diluted with ethyl acetate, filtered through a pad of Celite and washed with ethyl acetate. The filtrate was washed with *2N* NH_4OH, brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (EtOAc:Hexane:AcCN = 7:20:3) to give **CLXXIII** (28 mg, 27% yield) as a light yellow solid. m.p. 132.2 - 134.7 °C, MS (ES): $(M+H)^+$ = 344.3, $(M-H)^-$ = 342.3.

EXAMPLE 68



Step A:

To a solution of compound **CLXIX** (694 mg, 2.355 mmol) in anhydrous DMF (15mL) was added NaCN (258 mg, 5.0 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2. 100mL of H_2O was added to the filtrate and the mixture was extracted with CH_2Cl_2 (3 X 150mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (CH_2Cl_2:MeOH = 100:4) to give **CLXXIV** (520 mg, 68% yield).

Step B:

To a stirred solution of **CLXXIV** (518 mg, 1.61 mmol) in anhydrous CH_2Cl_2 (20mL) at -78 °C was added slowly DIBAL (1 M in CH_2Cl_2, 2.0 mL, 2.0 mmol). After 3 h at -50 °C, another portion of 1 M (2.6 mL, 2.6 mmol) was added. The reaction mixture was stirred at at -50 °C for 2h. The reaction was quenched with 1 *N* HCl (20 mL) and extracted with ethyl acetate (3 X 150mL). The combined organic layers were washed by saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$, filtered and concentrated. The residue was crystallized in a small volume of ether to give **CLXXV** (364 mg, 70% yield) as a white crystal (70%).

Step C:

A solution of **CLXXV** (165 mg, 0.5 mmol), $CH(OEt)_3$ (5 mL, 29.5 mmol) and *p*-toluensulfonic acid monohydrate (245 mg, 1.29 mmol) was stirred at room temperature for 18h. The reaction mixture was neutralized by 1 *N* NaOH and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc:Hexane = 2:1) to give **CLXXVI** (131 mg, 66% yield).

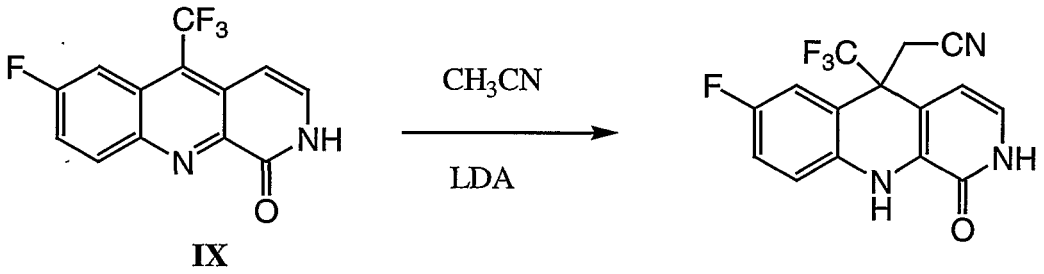
Step D:

To a stirred solution of compound **CLXXVI** (130 mg, 0.326 mmol) in TFA (2.5mL) /TFAA (0.08ml) at 0 °C was added $BH_3 \cdot Me_2S$ (10.0-10.2 M, 150 µL, 1.515 mmol) dropwise. After stirring at rt for 2 h, another portion of $BH_3 \cdot Me_2S$ (10.0-10.2M, 120 µL, 1.21 mmol) was added dropwise. After stirring at room temperature for another 2 h, the solvent TFA was removed *in vacuo*. The residue was neutralized with 1 *N* NaOH and extracted with ethyl acetate (3 X 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in 3mL of 4 N HCl in Dioxane and 3mL of MeOH. The mixture was stirred at room temperature for 2 h

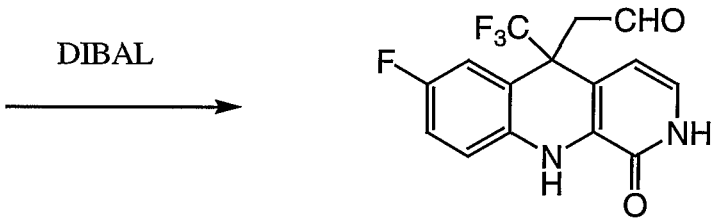
to hydrolyze the formed $B(OOCCF_3)_3$. The mixture was then concentrated and extracted with ethyl acetate (3 X 50mL). The combined organic layers were washed with 1 *N* NaOH, brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (CH_2Cl_2:MeOH = 100:4) to give **CLXXVII** (64 mg, 55% yield). m.p. 265 - 267 °C,. MS (ES): $(M+H)^+$ = 355.3, $(M-H)^-$ = 353.3.

Examples 101, 111, 112 and 113 were prepared using the procedure described in Example 4.

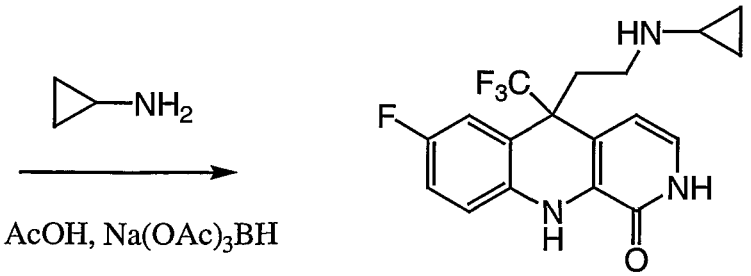
EXAMPLE 110



IX **CLXXVIII**



CLXXIX



CLXXX

Step A:

0.37 ml of anhydrous acetonitrile was dissolved in 10 ml of anhydrous THF, and cooled to -78°C. 4.0 ml of 2M lithium diisopropylamide in heptane/THF/ethylbenzene was added. The mixture was allowed to stir at -78°C for 20 minutes. Aromatic intermediate **IX** (500 mg) was added in one portion. The mixture was stirred an additional 1 hour at -78°C, and quenched with saturated aqueous ammonium chloride. Partitioning between EtOAc/water, drying over magnesium sulfate and concentration yielded a brown oil. Purification by flash chromatography (60% EtOAc/hexane, silica gel) gave 400 mg of **CLXXVIII** as a yellow solid. (70% yield)

Step B:

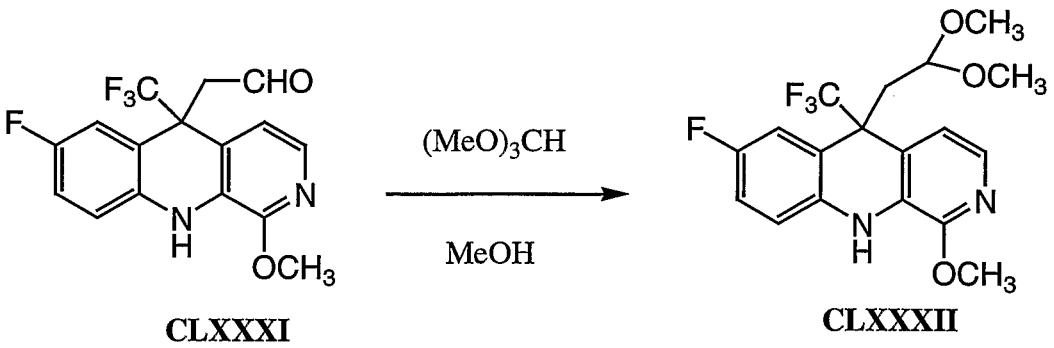
820 mg of nitrile **CLXXVIII** was dissolved in 6 ml of dichloromethane and cooled to -78°C. 7.3 ml (3 equivalents) of 1M diisobutylaluminum hydride in dichloromethane was added. The mixture was warmed to -30°C over 2 hours. The mixture was quenched with 3N HCl and extracted with EtOAc. Drying over sodium sulfate and concentration yielded a yellow oil which after flash chromatography (60% EtOAc/hexane, silica gel) gave aldehyde **CLXXIX**. (605 mg, 73% yield)

Step C:

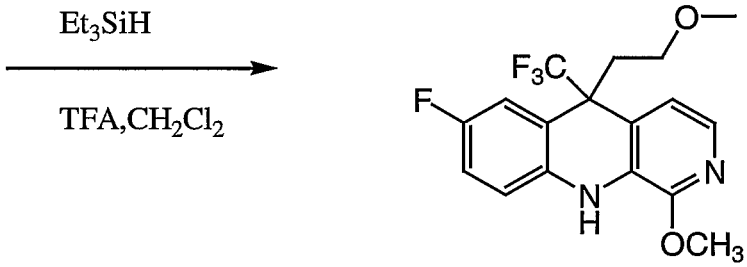
240 mg of aldehyde **CLXXIX**, 0.061 ml of cyclopropylamine (1.2 equivalents), 314 mg of sodium triacetoxyborohydride (2.0 equivalents) and 0.042 ml (1.0 equivalent) of acetic acid were combined in a flask and stirred 1 hour at 25°C. The mixture was partitioned between EtOAc/ saturated aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated. Flash chromatography (10% methanol/ dichloromethane, silica gel) gave 145 mg of **CLXXX** as a yellow solid. (53% yield)

Examples 104-106, 108-109 and 119-120 were prepared using the procedure described in example 110.

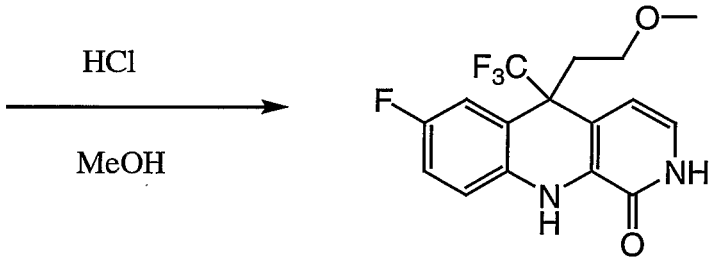
EXAMPLE 122



CLXXXI **CLXXXII**



CLXXXIII



CLXXXIIIa

Step A:

Aldehyde **CLXXXI** (83 mg), trimethyl orthoformate (1 ml), and p-toluenesulfonic acid hydrate (91 mg, 2 equivalents), were dissolved in 2 ml methanol and refluxed for 2 hours. The solution was cooled and concentrated to a yellow oil. Purification by flash chromatography (20% EtOAc/hexane, silica gel) yielded acetal **CLXXXII** as a clear oil, 87 mg. (93% yield)

Step B:

Compound **CLXXXII** was dissolved in 1 ml dichloromethane. I ml trifluoroacetic acid and 0.393 ml triethylsilane (10 equivalents) were added. The solution was stirred 1 hour at 25°C, then concentrated to a yellow oil. Purification by preparative TLC (20% EtOAc/hexane, silica gel) yielded compound **CLXXXIII** as a clear oil, 29 mg. (33% yield)

Step C:

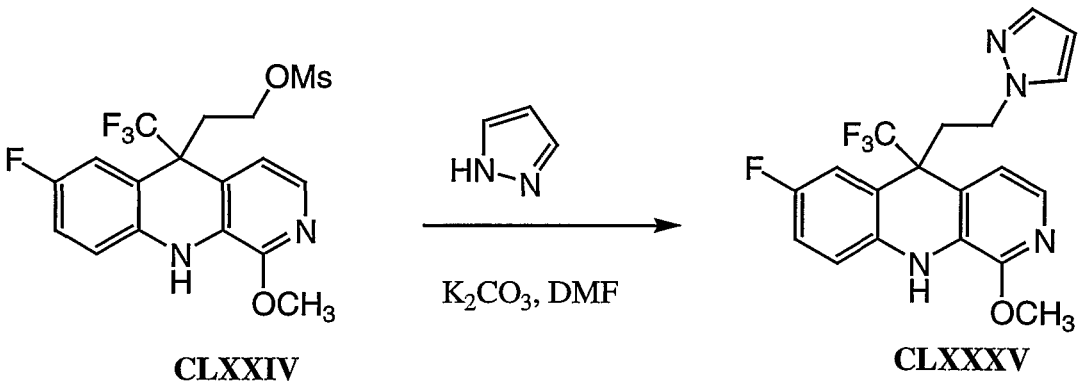
Compound **CLXXXIII** (29 mg) was dissolved in 2 ml methanol. 0.5 ml concentrated HCl was added. The solution was heated to reflux for 1 hr, then cooled. It was partitioned between EtOAc/ saturated aqueous sodium bicarbonate, washed once with water, dried over magnesium sulfate, and concentrated to a brown oil. Purification by preparative TLC (10% methanol/dichloromethane, silica gel) gave 12 mg of compound **CLXXXIIIa** as a brown solid. (43% yield)

Examples 107 and 118 were prepared using the procedure described in example 122.

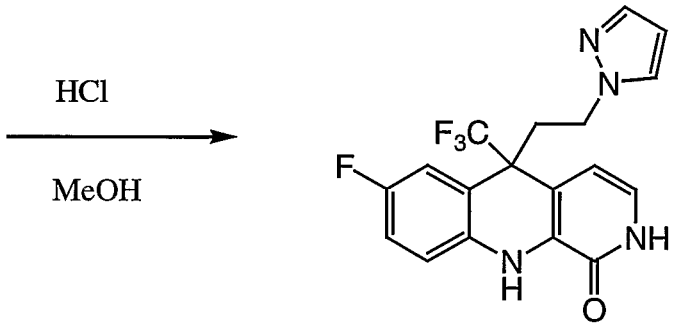
Examples 124, 126, 127-130, and 135 were prepared using the procedure described in example 30.

Example 123 was prepared using the procedure described in example 28.

EXAMPLE 115



CLXXIV CLXXXV



CLXXXVI

Step A:

Compound **CLXXXIV** (75 mg), potassium carbonate (249 mg, 10 equivalents), and pyrazole (122 mg, 10 equivalents) were dissolved in 1 ml anhydrous DMF and heated to 100°C 18 hours. The mixture was cooled and partitioned between EtOAc/water, washed once with water and dried over magnesium sulfate. Purification by preparative TLC (30% EtOAc/hexane, silica gel) gave compound **CLXXXV** as a yellow oil. (36 mg, 51% yield)

Step B:

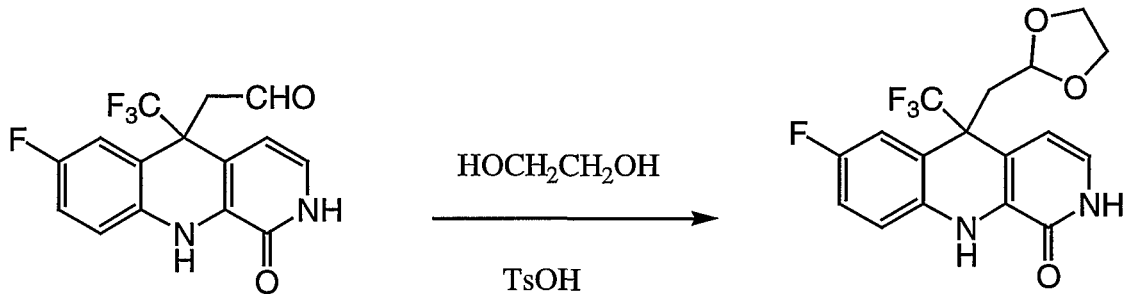
Compound **CLXXXV** (36 mg) was dissolved in 2 ml methanol. 1 ml concentrated HCl was added, and the solution was heated to reflux for 1 hr, then cooled. It was partitioned between EtOAc/ saturated aqueous sodium bicarbonate, washed once with water, dried over magnesium sulfate, and concentrated to a yellow oil. Purification by preparative TLC (5%

methanol/dichloromethane, silica gel) gave 23 mg of compound **CLXXXVI** as a white solid. (66% yield).

Examples 114 and 116 were prepared using the procedure described in example 115.

Examples 125, 131, 144 and 145 were prepared using the procedure described in example 28

EXAMPLE 146



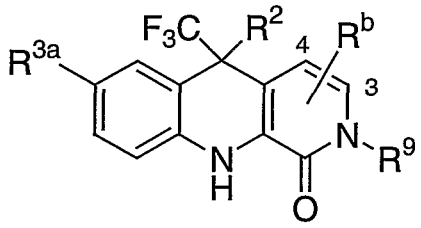
CLXXIX **CLXXXVII**

86 mg of aldehyde **CLXXIX**, 0.145 ml of ethylene glycol (10 equivalents), and 25 mg of p-toluenesulfonic acid hydrate (0.5 equivalents) were dissolved in 1.5 ml of benzene. The solution was heated to reflux 30 minutes, then cooled. It was partitioned between EtOAc/saturated aqueous sodium bicarbonate and washed once with water. The organic phase was reduced in volume on a rotary evaporator. The resulting white precipitate was filtered and washed with water and toluene to obtain pure compound **CLXXXVII** (70 mg, 73% yield).

Chiral HPLC separation was performed using chiral columns which gave the (*R*) and (*S*) enantiomers in >99% EE.

The following compounds have been made using the techniques described above.

Table 1*



(I)

Ex #	R^b	R^2	R^{3a}	R^9	Mass Spec	MP (°C)
1	H	(6-methylpyrid-2-yl)methyl	F	H		
2	H	Cyclopropylacetylenyl	F	H		
3	H	n-Propyl	F	H		
4	H	n-Butyl	F	H		
5	H	4-Fluorophenylmethyl	F	H		
6	H	2-Pyridylmethyl	F	H		
7	H	i-Propyl	F	H		
8	H	3-Pyridylmethyl	F	H		
9	H	4-Pyridylmethyl	F	H		
10	H	3-Propynyl	F	H		
11	H	2-Pyridylethynyl	F	H		
12	H	2-(2-Pyridyl)ethyl	F	H		
13	3-Cl	n-Propyl	F	H		
14	H	3-Propenyl	F	H		
15	H	2-Cyclopropylethyl	F	H		
16	H	Ethynyl	F	H		
17	H	2-Ethoxyethyl	F	H		
17a	H	2-chloroethyl	F	H		
18	H	n-Butyl	Cl	H		245-248
19	H	2-Pyridylmethyl	Cl	H		270-275
20	H	2-Cyclopropylethyl	Cl	H		220-222
21	H	Cyclopropylacetylenyl	Cl	H		247-250
22	H	N-	Cl	H		230-235

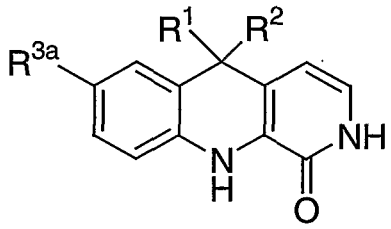
		Cyclopropylaminomethyl				
23	H	Hydroxymethyl	Cl	H		270-275
24	H	2-Pyridylmethyl	Cl	CH_3		166-168
25	H	2-Cyclopropylethyl	Cl	CH_3		150-152
27	H	n-Propoxymethyl	Cl	H		162-165
28	H	*i*-Propoxymethyl	Cl	H		185-190
29	H	Methoxyethyl	Cl	H		268-271
29a	H	diisopropoxymethyl	Cl	H		
30	H	*i*-Propylaminomethyl	Cl	H		235-240
31	H	N-Methyl-*i*-propylaminomethyl	Cl	H		105-110
32	H	Cyclopropylaminomethyl	Cl	H		242-245
33	H	*n*-Propylaminomethyl	Cl	H		243-245
34	H	Cyclobutylaminomethyl	Cl	H		250-254
35	H	*i*-Butylaminomethyl	Cl	H		210-215
36	H	*i*-Propoxymethyl	Cl	H		195-197
37	H	n-butyl	CN	H		
38	H	i-propoxymethyl	CN	H		
39	H	cyclopropylthiomethyl	Cl	H		
39a	H	cyclopropylsulfoxy methyl	Cl	H		
40	H	i-propylsulfoxymethyl	Cl	H		
41	H	t-butylsulfoxymethyl	Cl	H		
42	H	methylthiomethyl	Cl	H		
43	H	ethylthiomethyl	Cl	H		
44	H	i-propylthiomethyl	Cl	H		
45	H	i-propylthiomethyl	F	H		
46	H	t-butylthiomethyl	Cl	H		
47	H	cyclopropylmethoxy methyl	Cl	H		
48	H	cyclobutoxymethyl	Cl	H		
49	H	cyclobutoxymethyl	F	H		
50	H	cyclopropylmethoxy methyl	F	H		
51	3-CH_3	i-propoxymethyl	Cl	H		

52	3-CH_3	n-butyl	Cl	H		
53	3-CH_3	n-butyl	CN	H		
60	3-Cl	n-butyl	Cl	H		
61	4-Cl	n-butyl	Cl	H		
62	H	ethoxyethyl	Cl	H		240-245
100	H	allyl	F	H		
101	H	2-methyl-1-propenyl	F	H	337.1	
102	H	1-propynyl	F	H		
103	H	cyanomethyl	F	H		
104	H	2-(ethylamino)ethyl	F	H	356.4	
105	H	2-(dimethylamino)ethyl	F	H	356.4	
106	H	2-(methylamino)ethyl	F	H	340.3	
107	H	2-ethoxyethyl	F	H	355.3	
108	H	2-(i-propylamino)ethyl	F	H	370.4	
109	H	2-(diethylamino)ethyl	F	H	384.4	
110	H	2-(cyclopropylamino) ethyl	F	H	366.3	
111	H	pentyl	F	H	353.4	
112	H	i-butyl	F	H	339.4	
113	H	vinyl	F	H	309.3	
114	H	imidazolylethyl	F	H	379.4	
115	H	pyrazolylethyl	F	H	379.3	
116	H	1,2,4-triazolylethyl	F	H	378.3	
117	H	i-propylaminomethyl	F	H	356.4	
118	H	2-(i-propoxy)ethyl	F	H	369.3	
119	H	2-(methylethylamino) ethyl	F	H	370.4	
120	H	2-(i-propylmethylamino) ethyl	F	H	384.4	
121	H	2-(pyrrolidinyl)ethyl	F	H	382.4	
122	H	2-(methoxy)ethyl	F	H	341.3	

123	H	i-propoxymethyl	F	H	357.1	
124	H	3-pentanylaminomethyl	F	H	384.4	
125	H	dimethoxymethyl	F	H	357.3	
126	H	i-butylaminomethyl	F	H	370.4	
127	H	cyclopropylmethyl aminomethyl	F	H	368.3	
128	H	allylaminomethyl	F	H	354.3	
129	H	(R)-sec-butylaminomethyl	F	H	370.4	
130	H	(S)-sec-butylaminomethyl	F	H	370.3	
131	H	diethoxymethyl	F	H	387.3	
132	3-Cl	propyl	F	H		
133	H	butyl	F	Me	353.3	
134	H	2-(i-propoxy)ethyl	F	Me	383.3	
135	H	i-propylaminomethyl	F	Me	370.4	
136	H	i-propoxymethyl	F	Me	371.1	
137	H	2-ethoxyethyl	F	Me	371.1	
138	H	sec-butylaminomethyl	F	Me	384.4	
139	H	cyclopentylaminomethyl	F	H	382.1	
140	H	cyclobutylaminomethyl	F	H	368.3	
141	H	dimethylaminomethyl	F	H	342.3	
142	H	pyrrolidinylmethyl	F	H	368.3	
143	H	cyclopropylaminomethyl	F	H	354.3	
144	H	2-(dimethoxy)ethyl	F	H	371.2	
145	H	2-(diethoxy)ethyl	F	H	399.3	
146	H	2-(1,3-dioxolanyl)methyl	F	H	369.2	
147	H	2-(methoxy)ethyl	F	CH_3	357.1	

* Unless otherwise noted, stereochemistry is (+/-).

Table 1A*

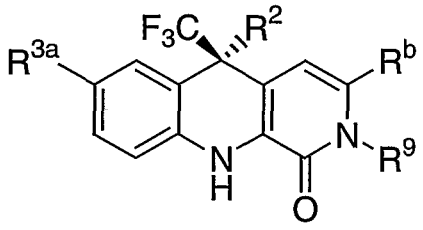


Ex #	R^{3a}	R^1	R^2	MP (°C)
61a	Cl	CH_3	butyl	177-179
62a	Cl	CH_3	i-propoxymethyl	
63	Cl	CN	butyl	182-185
64	Cl	CH_2OH	butyl	260-265
64a	Cl	CHF_2	butyl	198-200
64b	Cl	CHF_2	i-propoxymethyl	138-142
65	Cl	CF_2CH_3	n-butyl	
66	F	CF_2CH_3	n-Butyl	
67	CN	CF_2CH_3	n-butyl	
68	Cl	CF_2CH_3	ethoxymethyl	

* Unless otherwise noted, stereochemistry is (+/-).

The following compounds were prepared from the racemic mixtures using the procedure described above.

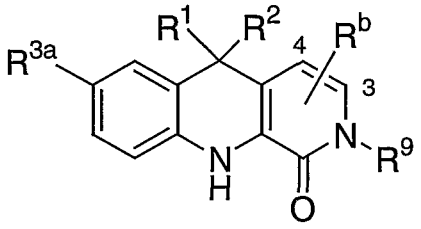
TABLE 1B



Ex #	R^{3a}	R^9	R^2	R^b	MP (°C)
200	F	H	2-pyridylmethyl	H	
201	F	H	butyl	H	
202	Cl	H	2-pyridylmethyl	H	
203	Cl	H	2-cyclopropylethyl	H	
204	F	H	2-(6-methyl)pyridylmethyl	H	
205	F	Me	butyl	H	
206	Cl	H	i-propoxymethyl	H	
207	Cl	H	i-propylaminomethyl	H	
208	Cl	H	cyclopropylaminomethyl	H	
209	Cl	Me	i-propoxymethyl	H	
210	F	H	i-propoxymethyl	H	
211	Cl	H	i-propylmethylaminomethyl	H	
212	Cl	H	2-methoxyethyl	H	
213	Cl	H	cyclobutoxymethyl	H	
214	Cl	H	ethoxymethyl	H	
215	CN	H	i-propoxymethyl	H	
216	Cl	H	i-propoxymethy	Me	

The following table contains representative examples of the present invention. Each entry in each table is intended to be paired with the formula at the start of the table. For example, in Table 2, the compound is intended to be paired with one of 1a-11a, one of 1b-4b, one of 1c-4c, one of 1d-5d and one of 1-60e.

TABLE 2



#	R^1
1a	CF_3
2a	CHF_2
3a	CH_3
4a	cyclopropyl
5a	CF_2CF_3
6a	methyl
7a	ethyl
8a	propyl
9a	butyl
10a	CN
11a	hydroxymethyl

#	R^{3a}
1b	H
2b	chloro
3b	fluoro
4b	CH_3

#	R^b
1c	3-chloro
2c	4-methyl

3c	4-chloro
4c	H

#	R^9
1d	H
2d	methyl
3d	ethyl
4d	propyl
5d	butyl

#	R^2
1e	(6-methylpyrid-2-yl)methyl
2e	Cyclopropylacetylenyl
3e	n-Propyl
4e	n-Butyl
5e	4-Fluorophenylmethyl
6e	2-Pyridylmethyl
7e	i-Propyl
8e	3-Pyridylmethyl
9e	4-Pyridylmethyl
10e	3-Propynyl
11e	2-Pyridylethynyl
12e	2-(2-Pyridyl)ethyl
13e	n-Propyl
14e	3-Propenyl
15e	2-Cyclopropylethyl
16e	Ethynyl
17e	2-Ethoxyethyl
18e	2-chloroethyl
19e	N-Cyclopropylaminomethyl
20e	Hydroxymethyl
21e	n-Propoxymethyl
22e	*i*-Propoxymethyl
23e	Methoxyethyl
24e	diisopropoxymethyl
25e	Propylaminomethyl
26e	N-Methyl-*i*-propylaminomethyl

27e	*n*-Propylaminomethyl
28e	Cyclobutylaminomethyl
29e	*i*-Butylaminomethyl
30e	cyclopropylthiomethyl
31e	i-propylsulfoxymethyl
32e	t-butylsulfoxymethyl
33e	methylthiomethyl
34e	ethylthiomethyl
35e	i-propylthiomethyl
36e	cyclopropylmethoxymethyl
37e	cyclobutoxymethyl
38e	cyanomethyl
39e	2-(ethylamino)ethyl
40e	2-(dimethylamino)ethyl
41e	2-(methylamino)ethyl
42e	2-(i-propylamino)ethyl
43e	2-(cyclopropylamino)ethyl
44e	pentyl
45e	vinyl
46e	imidazolylethyl
47e	pyrazolylethyl
48e	1,2,4-triazolylethyl
49e	2-(methylethylamino)ethyl
50e	2-(i-propylethylamino)ethyl
51e	2-(pyrrolidinyl)ethyl
52e	3-pentanylaminomethyl
53e	dimethoxymethyl
54e	i-butylaminomethyl
55e	cyclopropylmethyl aminomethyl
56e	allylaminomethyl
57e	(R)-sec-butylaminomethyl
58e	(S)-sec-butylaminomethyl
59e	1,3-dioxolanylmethyl
60e	1,3-dioxanylmethyl

UTILITY

The compounds of this invention possess reverse transcriptase inhibitory activity and HIV inhibitory efficacy. The compounds of formula (I) possess HIV reverse transcriptase inhibitory activity and are therefore useful as antiviral agents for the treatment of HIV infection and associated diseases. The compounds of formula (I) possess HIV reverse transcriptase inhibitory activity and are effective as inhibitors of HIV growth. The ability of the compounds of the present invention to inhibit viral growth or infectivity is demonstrated in standard assay of viral growth or infectivity, for example, using the assay described below.

The compounds of formula (I) of the present invention are also useful for the inhibition of HIV in an *ex vivo* sample containing HIV or expected to be exposed to HIV. Thus, the compounds of the present invention may be used to inhibit HIV present in a body fluid sample (for example, a serum or semen sample) that contains or is suspected to contain or be exposed to HIV.

The compounds provided by this invention are also useful as standard or reference compounds for use in tests or assays for determining the ability of an agent to inhibit viral replication and/or HIV reverse transcriptase, for example in a pharmaceutical research program. Thus, the compounds of the present invention may be used as a control or reference compound in such assays and as a quality control standard. The compounds of the present invention may be provided in a commercial kit or container for use as such standard or reference compound.

Since the compounds of the present invention exhibit specificity for HIV reverse transcriptase, the compounds of the present invention may also be useful as diagnostic reagents in diagnostic assays for the detection of HIV reverse transcriptase. Thus, inhibition of the reverse transcriptase activity in an assay (such as the assays described herein) by a compound of the present invention

would be indicative of the presence of HIV reverse transcriptase and HIV virus.

As used herein "μg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "μL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "μM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma" stands for the Sigma-Aldrich Corp. of St. Louis, MO.

Compounds tested in the assay described below are considered to be active if they exhibit a K_i of $\leq$10 μM. Preferred compounds of the present invention have K_i's of $\leq$1 μM. More preferred compounds of the present invention have K_i's of $\leq$0.1 μM. Even more preferred compounds of the present invention have K_i's of $\leq$0.01 μM. Still more preferred compounds of the present invention have K_i's of $\leq$0.001 μM.

Using the methodology described below, a number of compounds of the present invention were found to exhibit a K_i of $\leq$10 μM, thereby confirming the utility of the compounds of the present invention as effective HIV reverse transcriptase inhibitors.

HIV RNA Assay

DNA Plasmids and *in vitro* RNA transcripts:

Plasmid pDAB 72 containing both gag and pol sequences of BH10 (bp 113-1816) cloned into PTZ 19R was prepared according to Erickson-Viitanen et al. *AIDS Research and Human Retroviruses* **1989**, *5*, 577. The plasmid was linearized with Bam HI prior to the generation of *in vitro* RNA transcripts using the Riboprobe Gemini system II kit (Promega) with T7 RNA polymerase. Synthesized RNA was purified by treatment with RNase free DNAse (Promega), phenol-chloroform extraction, and ethanol precipitation. RNA transcripts were dissolved in water, and stored at -70°C. The concentration of RNA was determined from the A_{260}.

Probes:

Biotinylated capture probes were purified by HPLC after synthesis on an Applied Biosystems (Foster City, CA) DNA synthesizer by addition of biotin to the 5' terminal end of the oligonucleotide, using the biotin-phosphoramidite reagent of Cocuzza, *Tet. Lett.* **1989**, *30*, 6287. The gag biotinylated capture probe (5-biotin-CTAGCTCCCTGCTTGCCCATACTA 3') was complementary to nucleotides 889-912 of HXB2 and the pol biotinylated capture probe (5'-biotin -CCCTATCATTTTTGGTTTCCAT 3') was complementary to nucleotides 2374-2395 of HXB2. Alkaline phosphatase conjugated oligonucleotides used as reporter probes were prepared by Syngene (San Diego, CA.). The pol reporter probe (5' CTGTCTTACTTTGATAAAACCTC 3') was complementary to nucleotides 2403-2425 of HXB2. The gag reporter probe (5' CCCAGTATTTGTCTACAGCCTTCT 3') was complementary to nucleotides 950-973 of HXB2. All nucleotide positions are those of the GenBank Genetic Sequence Data Bank as accessed through the Genetics Computer Group Sequence Analysis Software Package (Devereau *Nucleic Acids Research* **1984**, *12*, 387). The reporter probes were prepared as 0.5 µM stocks in 2 x SSC (0.3 M NaCl, 0.03 M sodium citrate), 0.05 M Tris pH 8.8, 1 mg/mL BSA. The biotinylated capture probes were prepared as 100 µM stocks in water.

Streptavidin coated plates:

Streptavidin coated plates were obtained from DuPont Biotechnology Systems (Boston, MA).

Cells and virus stocks:

MT-2 and MT-4 cells were maintained in RPMI 1640 supplemented with 5% fetal calf serum (FCS) for MT-2 cells or 10% FCS for MT-4 cells, 2 mM L-glutamine and 50 µg/mL gentamycin, all from Gibco. HIV-1 RF was propagated in MT-4 cells in the same medium. Virus stocks were prepared approximately 10 days after acute infection of MT-4 cells

and stored as aliquots at -70°C. Infectious titers of HIV-1(RF) stocks were 1-3 x 10^7 PFU (plaque forming units)/mL as measured by plaque assay on MT-2 cells (see below). Each aliquot of virus stock used for infection was thawed only once.

For evaluation of antiviral efficacy, cells to be infected were subcultured one day prior to infection. On the day of infection, cells were resuspended at 5 x 10^5 cells/mL in RPMI 1640, 5% FCS for bulk infections or at 2 x 10^6/mL in Dulbecco's modified Eagles medium with 5% FCS for infection in microtiter plates. Virus was added and culture continued for 3 days at 37°C.

HIV RNA assay:

Cell lysates or purified RNA in 3 M or 5 M GED were mixed with 5 M GED and capture probe to a final guanidinium isothiocyanate concentration of 3 M and a final biotin oligonucleotide concentration of 30 nM. Hybridization was carried out in sealed U bottom 96 well tissue culture plates (Nunc or Costar) for 16-20 hours at 37°C. RNA hybridization reactions were diluted three-fold with deionized water to a final guanidinium isothiocyanate concentration of 1 M and aliquots (150 µL) were transferred to streptavidin coated microtiter plates wells. Binding of capture probe and capture probe-RNA hybrid to the immobilized streptavidin was allowed to proceed for 2 hours at room temperature, after which the plates were washed 6 times with DuPont ELISA plate wash buffer (phosphate buffered saline(PBS), 0.05% Tween 20) A second hybridization of reporter probe to the immobilized complex of capture probe and hybridized target RNA was carried out in the washed streptavidin coated well by addition of 120 µl of a hybridization cocktail containing 4 X SSC, 0.66% Triton X 100, 6.66% deionized formamide, 1 mg/mL BSA and 5 nM reporter probe. After hybridization for one hour at 37°C, the plate was again washed 6 times. Immobilized alkaline phosphatase activity was detected by addition of 100 µL of 0.2 mM 4-methylumbelliferyl phosphate

(MUBP, JBL Scientific) in buffer (2.5 M diethanolamine pH 8.9 (JBL Scientific), 10 mM $MgCl_2$, 5 mM zinc acetate dihydrate and 5 mM *N*-hydroxyethyl-ethylene-diamine-triacetic acid). The plates were incubated at 37°C. Fluorescence at 450 nM was measured using a microplate fluorometer (Dynateck) exciting at 365 nM.

Microplate based compound evaluation in HIV-1 infected MT-2 cells:

Compounds to be evaluated were dissolved in DMSO and diluted in culture medium to twice the highest concentration to be tested and a maximum DMSO concentration of 2%. Further three-fold serial dilutions of the compound in culture medium were performed directly in U bottom microtiter plates (Nunc). After compound dilution, MT-2 cells (50 µL) were added to a final concentration of 5×10^5 per mL (1×10^5 per well). Cells were incubated with compounds for 30 minutes at 37°C in a CO_2 incubator. For evaluation of antiviral potency, an appropriate dilution of HIV-1 (RF) virus stock (50 µL) was added to culture wells containing cells and dilutions of the test compounds. The final volume in each well was 200 µL. Eight wells per plate were left uninfected with 50 µL of medium added in place of virus, while eight wells were infected in the absence of any antiviral compound. For evaluation of compound toxicity, parallel plates were cultured without virus infection.

After 3 days of culture at 37°C in a humidified chamber inside a CO_2 incubator, all but 25 µL of medium/well was removed from the HIV infected plates. Thirty seven µL of 5 M GED containing biotinylated capture probe was added to the settled cells and remaining medium in each well to a final concentration of 3 M GED and 30 nM capture probe. Hybridization of the capture probe to HIV RNA in the cell lysate was carried out in the same microplate well used for virus culture by sealing the plate with a plate sealer (Costar), and incubating for 16-20 hrs in a 37°C incubator. Distilled water was then added to each well to dilute the

hybridization reaction three-fold and 150 µL of this diluted mixture was transferred to a streptavidin coated microtiter plate. HIV RNA was quantitated as described above. A standard curve, prepared by adding known amounts of pDAB 72 *in vitro* RNA transcript to wells containing lysed uninfected cells, was run on each microtiter plate in order to determine the amount of viral RNA made during the infection.

In order to standardize the virus inoculum used in the evaluation of compounds for antiviral activity, dilutions of virus were selected which resulted in an IC_{90} value (concentration of compound required to reduce the HIV RNA level by 90%) for dideoxycytidine (ddC) of 0.2 µg/mL. IC_{90} values of other antiviral compounds, both more and less potent than ddC, were reproducible using several stocks of HIV-1 (RF) when this procedure was followed. This concentration of virus corresponded to ~3 x 10^5 PFU (measured by plaque assay on MT-2 cells) per assay well and typically produced approximately 75% of the maximum viral RNA level achievable at any virus inoculum. For the HIV RNA assay, IC_{90} values were determined from the percent reduction of net signal (signal from infected cell samples minus signal from uninfected cell samples) in the RNA assay relative to the net signal from infected, untreated cells on the same culture plate (average of eight wells). Valid performance of individual infection and RNA assay tests was judged according to three criteria. It was required that the virus infection should result in an RNA assay signal equal to or greater than the signal generated from 2 ng of pDAB 72 *in vitro* RNA transcript. The IC_{90} for ddC, determined in each assay run, should be between 0.1 and 0.3 µg/mL. Finally, the plateau level of viral RNA produced by an effective reverse transcriptase inhibitor should be less than 10% of the level achieved in an uninhibited infection. A compound was considered active if its IC_{90} was found to be less than 20µM.

For antiviral potency tests, all manipulations in microtiter plates, following the initial addition of 2X

concentrated compound solution to a single row of wells, were performed using a Perkin Elmer/Cetus ProPette.

Protein Binding and Mutant Resistance

In order to characterize NNRTI compounds for their clinical efficacy potential the effect of plasma proteins on antiviral potency and measurements of antiviral potency against wild type and mutant variants of HIV that carry amino acid changes in the known binding site for NNRTIs were examined. The rationale for this testing strategy is two fold:

1. Many drugs are extensively bound to plasma proteins. Although the binding affinity for most drugs for the major components of human plasma, namely, human serum albumin (HSA) or alpha-1-acid glycoprotein (AAG), is low, these major components are present in high concentration in the blood. Only free or unbound drug is available to cross the infected cell membrane for interaction with the target site (i.e., HIV-1 reverse transcriptase, HIV-1 RT). Therefore, the effect of added HSA+AAG on the antiviral potency in tissue culture more closely reflects the potency of a given compound in the clinical setting. The concentration of compound required for 90% inhibition of virus replication as measured in a sensitive viral RNA-based detection method is designated the IC90. The fold increase in apparent IC90 for test compounds in the presence or added levels of HSA and AAG that reflect *in vivo* concentrations (45 mg/ml HSA, 1 mg/ml AAG) was then calculated. The lower the fold increase, the more compound will be available to interact with the target site.

2. The combination of the high rate of virus replication in the infected individual and the poor fidelity of the viral RT results in the production of a quasi-species or mixtures of HIV species in the infected individual. These species will include a majority wild type species, but also mutant variants of HIV and the proportion of a given mutant will reflect its relative fitness and replication

rate. Because mutant variants including mutants with changes in the amino acid sequence of the viral RT likely pre-exist in the infected individual's quasi-species, the overall potency observed in the clinical setting will reflect the ability of a drug to inhibit not only wild type HIV-1, but mutant variants as well. We thus have constructed, in a known genetic background, mutant variants of HIV-1 that carry amino acid substitutions at positions thought to be involved in NNRTI binding, and measured the ability of test compounds to inhibit replication of these mutant viruses. The concentration of compound required for 90% inhibition of virus replication as measured in a sensitive viral RNA-based detection method is designated the IC90. It is desirable to have a compound which has high activity against a variety of mutants.

Dosage and Formulation

The antiviral compounds of this invention can be administered as treatment for viral infections by any means that produces contact of the active agent with the agent's site of action, i.e., the viral reverse transcriptase, in the body of a mammal. 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 preferably are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. A daily dosage of active ingredient can be expected to be about 0.001 to about 1000 milligrams per

kilogram of body weight, with the preferred dose being about 0.1 to about 30 mg/kg.

Dosage forms of compositions suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders, or in liquid dosage forms, such as elixirs, syrups and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts, and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben and

chlorobutanol. Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences, supra*, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A capsule formulation of the present invention can be prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose, and 6 mg magnesium stearic.

Soft Gelatin Capsules

A soft gelatin capsule formulation of the present invention can be prepared as follows. A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules should then be washed and dried.

Tablets

A tablet formulation of the present invention can be prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch and 98.8 mg of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Suspension

An aqueous suspension formulation can be prepared for oral administration so that each 5 mL contain 25 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mg of vanillin.

Injectable

A parenteral formulation suitable for administration by injection can be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.

Combination Administration of Therapeutic Agents

The present invention provides a method for the treatment of HIV infection which comprises administering, in combination, to a host in need thereof a therapeutically effective amount of the following:

(a) a compound of formula (I); and

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors, in one or more sterile containers.

Each therapeutic agent component of this combination method (i.e., component (a) and (b) set forth above) can independently be administered in any separate dosage form, such as those described above, and can be administered in various ways, as described above. In the following description component (b) is to be understood to represent one or more agents as described previously. Each individual therapeutic agent comprising component (b) may also be independently be administered in any separate dosage form, such as those described above, and can be administered in various ways, as described above.

Components (a) and any one or more of the agents comprising component (b) of the combination method of the present invention may be formulated together, in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.) as a combination product. When component (a) and (b) are not formulated together in a single dosage unit, the component (a) may be administered at the same time as component (b) or in any order; for example component (a) of this invention may be administered first,

followed by administration of component (b), or they may be administered in the revserse order. If component (b) contains more that one agent, e.g., one RT inhibitor and one protease inhibitor, these agents may be administered together or in any order. When not administered at the same time, preferably the administration of component (a) and (b) occurs less than about one hour apart. Preferably, the route of administration of component (a) and (b) is oral. The terms oral agent, oral inhibitor, oral compound, or the like, as used herein, denote compounds which may be orally administered. Although it is preferable that component (a) and component (b) both be administered by the same route (that is, for example, both orally) or dosage form, if desired, they may each be administered by different routes or dosage forms (for example, one component of the combination method may be administered orally, and another component may be administered intravenously).

As is appreciated by a medical practitioner skilled in the art, the dosage of the combination therapy of the invention may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

The proper dosage of components (a) and (b) of the combination method of this invention will be readily ascertainable by a medical practitioner skilled in the art, based upon the present disclosure. By way of general guidance, typically a daily dosage may be about 100 milligrams to about 1.5 grams of each component. If component (b) represents more than one compound, then typically a daily dosage may be about 100 milligrams to about 1.5 grams of each agent of component (b). By way of general guidance, when the compounds of component (a) and component (b) are administered in combination, the dosage amount of each component may be reduced by about 70-80%

relative to the usual dosage of the component when it is administered alone as a single agent for the treatment of HIV infection, in view of the synergistic effect of the combination.

The combination products of this invention may be formulated such that, although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized. In order to minimize contact, for example, where the product is orally administered, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. Another embodiment of this invention where oral administration is desired provides for a combination product wherein one of the active ingredients is coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component. In each formulation wherein contact is prevented between components (a) and (b) via a coating or some other material, contact may also be prevented between the individual agents of component (b).

Dosage forms of the combination products of the present invention wherein one active ingredient is enteric coated can be in the form of tablets such that the enteric coated component and the other active ingredient are blended together and then compressed into a tablet or such that the enteric coated component is compressed into one tablet layer and the other active ingredient is compressed into an additional layer. Optionally, in order to further separate the two layers, one or more placebo layers may be present such that the placebo layer is between the layers of active ingredients. In addition, dosage forms of the present invention can be in the form of capsules wherein one active ingredient is compressed into a tablet or in the form of a plurality of microtablets, particles, granules or non-perils, which are then enteric coated. These enteric coated microtablets, particles, granules or non-perils are then placed into a capsule or compressed into a capsule along with a granulation of the other active ingredient.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time or concurrently by the same manner, will be readily apparent to those skilled in the art, based on the present disclosure.

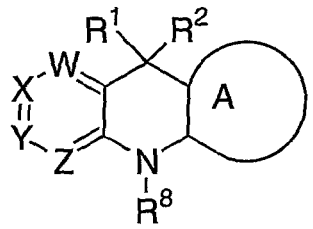
Pharmaceutical kits useful for the treatment of HIV infection, which comprise a therapeutically effective amount of a pharmaceutical composition comprising a compound of component (a) and one or more compounds of component (b), in one or more sterile containers, are also within the ambit of the present invention. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. Component (a) and component (b) may be in the same sterile container or in separate sterile containers. The sterile containers of materials may comprise separate containers, or one or more multi-part containers, as desired. Component (a) and

component (b) may be separate, or physically combined into a single dosage form or unit as described above. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

As will be appreciated by one of skill in the art, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

WHAT IS CLAIMED IS:

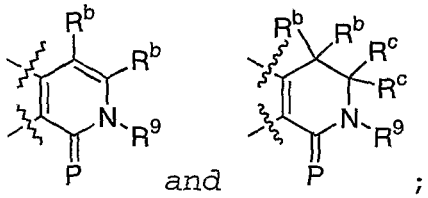
1. A compound of formula (I):



(I)

or a stereoisomeric form or mixture of stereoisomeric forms or a pharmaceutically acceptable salt form thereof, wherein:

A is a ring selected from:



;

P is O or S;

R^b, at each occurrence, is independently selected from H, F, Cl, Br, I, CN, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, C_{1-4} alkyl-O-, or C_{1-4} alkyl-NH-, NH_2;

R^c, at each occurrence, is independently selected from H, C_{1-4} alkyl, C_{1-4} alkenyl, and C_{1-4} alkynyl;

W is N or CR^3;

X is N or CR^{3a};

Y is N or CR^{3b};

Z is N or CR^{3c};

provided that if two of W, X, Y, and Z are N, then the remaining are other than N;

R^1 is selected from the group C_{1-4} alkyl substituted with 0-9 halogen, cyclopropyl, hydroxymethyl, and CN;

R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-6} alkyl substituted with 0-2 R^4, C_{2-6}haloalkyl, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, phenyl substituted with 0-2 R^{3d}, and 3-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3d};

R^3 is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, CF_3, F, Cl, Br, I, $-(CH_2)_tNR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-(CH_2)_tNHC(O)R^7$, $-(CH_2)_tNHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-S-C_{1-4}$alkyl, $-S(O)C_{1-4}$alkyl, $-S(O)_2C_{1-4}$alkyl, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

R^{3a} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, CF_3, F, Cl, Br, I, $-(CH_2)_tNR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-(CH_2)_tNHC(O)R^7$, $-(CH_2)_tNHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-S-C_{1-4}$alkyl, $-S(O)C_{1-4}$alkyl, $-S(O)_2C_{1-4}$alkyl, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^{3c} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3b} and R^{3c} together form $-OCH_2O-$;

R^{3d}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3e}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, CN, -OH, $-O-R^{11}$, OCF_3, $-O(CO)-R^{13}$, $-OS(O)_2C_{1-4}$alkyl, $-NR^{12}R^{12a}$, $-C(O)R^{13}$, $-NHC(O)R^{13}$, $-SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-NHSO_2R^{10}$, and $-SO_2NR^{12}R^{12a}$;

R^4 is selected from the group H, F, Cl, Br, I, C_{1-6} alkyl substituted with 0-2 R^{3e}, C_{3-10} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-10 membered heterocyclic system containing 1-3

heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H and C_{1-4} alkyl;

alternatively, R^5 and R^{5a}, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms;

R^6 is selected from the group H, OH, C_{1-4} alkyl, C_{1-4} alkoxy, and NR^5R^{5a};

R^7 is selected from the group H, C_{1-3} alkyl and C_{1-3} alkoxy;

R^8 is selected from the group H, (C_{1-6} alkyl)carbonyl, C_{1-6} alkoxy, (C_{1-4} alkoxy)carbonyl, C_{6-10} aryloxy, (C_{6-10} aryl)oxycarbonyl, (C_{6-10} aryl)methylcarbonyl, (C_{1-4} alkyl)carbonyloxy(C_{1-4} alkoxy)carbonyl, C_{6-10} arylcarbonyloxy(C_{1-4} alkoxy)carbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, phenyl(C_{1-4} alkoxy)carbonyl, and NR^5R^{5a}(C_{1-6} alkyl)carbonyl;

R^9 is selected from H, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, (C_{1-6} alkyl)carbonyl, C_{1-6} alkoxy, (C_{1-4} alkoxy)carbonyl, C_{6-10} aryloxy, (C_{6-10} aryl)oxycarbonyl, (C_{6-10} aryl)methylcarbonyl, (C_{1-4} alkyl)carbonyloxy(C_{1-4} alkoxy)carbonyl, C_{6-10} arylcarbonyloxy(C_{1-4} alkoxy)carbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, phenyl(C_{1-4} alkoxy)carbonyl, and NR^5R^{5a}(C_{1-6} alkyl)carbonyl;

R^{10} is selected from the group C_{1-4} alkyl and phenyl;

R^{11} is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyl substituted with C_{3-6}cycloalkyl substituted with 0-2 R^{3e}, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocycle substituted with 0-2 R^{3e};

R^{12} and R^{12a} are independently selected from H, C_{1-6} alkyl, C_{1-6} alkyl substituted with C_{3-6}cycloalkyl substituted with 0-2 R^{3e}, and C_{3-6} carbocycle substituted with 0-2 R^{3e};

alternatively, R^{12} and R^{12a} can join to form 4-7 membered heterocyclic ring;

R^{13} is selected from the group H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, $NR^{12}R^{12a}$, C_{3-6}carbocycle, and -O-C_{3-6}carbocycle; and

t is selected from 0 and 1.

2. A compound of Claim 1 or pharmaceutically acceptable salt forms thereof, wherein:

R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-5} alkyl substituted with 0-2 R^4, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, and phenyl substituted with 0-2 R^{3d}, and 3-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3d}, wherein the heterocyclic system is selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-oxazolyl, 2-thiazolyl, 4-isoxazolyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl;

R^3 and R^{3a}, at each occurrence, are independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, $NHC(O)NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} and R^{3c}, at each occurrence, are independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^4 is selected from the group H, Cl, F, C_{1-4} alkyl substituted with 0-2 R^{3e}, C_{3-6} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

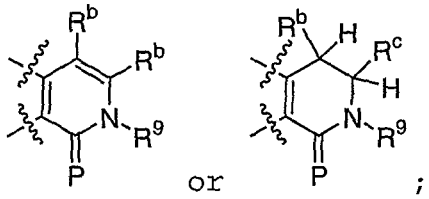
R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a}; and

R^7 is selected from the group CH_3, C_2H_5, $CH(CH_3)_2$, OCH_3, OC_2H_5, and $OCH(CH_3)_2$.

3. A compound of Claims 1-2, wherein:

P is O;

Ring A is:



;

R^b, at each occurrence, is selected from H, F, Cl, and Br, C_{1-4} alkyl, CN, C_{1-4} alkyl-NH-, NH_2;

R^c is selected from H and methyl;

W is CR^3;

X is CR^{3a};

Y is CR^{3b};

Z is CR^{3c};

R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-3} alkyl substituted with 0-2 R^4, C_{2-3} alkenyl substituted with 0-2 R^4, C_{2-3} alkynyl substituted with 0-1 R^4, and C_{3-6} cycloalkyl substituted with 0-2 R^{3d};

R^3, R^{3a}, R^{3b}, and R^{3c}, at each occurrence, are independently selected from the group H, C_{1-3} alkyl, OH, C_{1-3} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3e}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, $-NR^5R^{5a}$, $-C(O)R^6$, and $-SO_2NR^5R^{5a}$;

R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, CN, -OH, $-O-R^{11}$, , $-O(CO)-R^{13}$, $-SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, and $-NR^{12}R^{12a}$;

R^4 is selected from the group H, Cl, F, C_{1-4} alkyl substituted with 0-1 R^{3e}, C_{3-5} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-oxazolyl, 2-thiazolyl, 4-isoxazolyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl;

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5;

R^8 is H;

R^9 is H, methyl, ethyl, propyl, and i-propyl;

R^{11} is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, and C_{3-6} carbocycle substituted with 0-2 R^{3e} wherein the C_{3-6} carbocycle is selected from

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and phenyl; and

R^{12} and R^{12a} are independently selected from H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, and C_{3-6} carbocycle substituted with 0-2 R^{3e} wherein the C_{3-6} carbocycle is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and phenyl.

4. A compound of Claims 1-3, or a pharmaceutically acceptable salt form thereof, wherein:

R^2 is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-3} alkyl substituted with 1 R^4, C_{2-3} alkenyl substituted with 1 R^4, and C_{2-3} alkynyl substituted with 1 R^4;

R^3, R^{3a}, R^{3b}, and R^{3c}, at each occurrence, are independently selected from the group H, C_{1-3} alkyl, OH, C_{1-3} alkoxy, F, Cl, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3e}, at each occurrence, is independently selected from the group CH_3, -OH, OCH_3, OCF_3, F, Cl, and $-NR^5R^{5a}$;

R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, -OH, CN, $-O-R^{11}$, $-O(CO)-R^{13}$, and $-NR^{12}R^{12a}$, $-SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, and $-OS(O)_2$methyl;

R^4 is selected from the group H, Cl, F, CH_3, CH_2CH_3, cyclopropyl substituted with 0-1 R^{3e}, 1-methyl-

cyclopropyl substituted with 0-1 R^{3e}, cyclobutyl substituted with 0-1 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl;

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5; and

R^9 is selected from H and methyl.

5. A compound of Claims 1-4, or a pharmaceutically acceptable salt form thereof, wherein:

R^2 is selected from the group methyl substituted with 0-2 R^{3f}, methyl substituted with 0-2 R^4, ethyl substituted with 0-2 R^4, propyl substituted with 0-2 R^4, ethenyl substituted with 0-2 R^4, 1-propenyl substituted with 0-2 R^4, 2-propenyl substituted with 0-2 R^4, ethynyl substituted with 0-2 R^4, 1-propynyl substituted with 0-2 R^4, 2-propynyl substituted with 0-2 R^4, and cyclopropyl substituted with 0-1 R^{3d};

R^{3e}, at each occurrence, is independently selected from the group CH_3, -OH, OCH_3, OCF_3, F, Cl, and $-NR^5R^{5a}$;

R^4 is selected from the group H, Cl, F, CH_3, CH_2CH_3, cyclopropyl substituted with 0-1 R^{3e}, 1-methyl-cyclopropyl substituted with 0-1 R^{3e}, cyclobutyl substituted with 0-1 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl ;

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5;

R^8 is H.

6. A compound of claims 1-5, or a pharmaceutically acceptable salt form thereof, wherein:

R^1 is selected from methyl, ethyl, propyl, i-propyl, butyl, cyclopropyl, CF_3, CF_2CH_3, CN, and hydroxymethyl;

R^2 is selected from the group methyl substituted with 0-2 R^{3f}, methyl substituted with 0-2 R^4, ethyl substituted with 0-2 R^4, propyl substituted with 0-1 R^4, ethenyl substituted with 0-2 R^4, 1-propenyl substituted with 0-2 R^4, 2-propenyl substituted with 0-2 R^4, ethynyl substituted with 0-2 R^4, 1-propynyl substituted with 0-2 R^4;

R^3, R^{3b}, and R^{3c} are H;

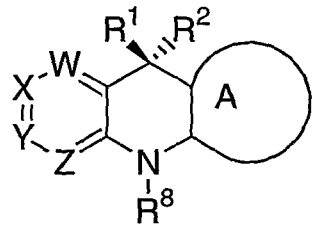
R^{3e} is CH_3;

R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, CN, -OH, -O-R^{11}, -SR^{11}, -S(O)R^{11}, -$S(O)_2R^{11}$, and -$NR^{12}R^{12a}$;

R^4 is selected from the group H, cyclopropyl substituted with 0-1 R^{3e}, and a 5-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic system is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-imidazolyl, pyrazolyl, triazolyl, 1,3-dioxolanyl, and 1,3-dioxanyl;

R^{12} and R^{12a} are independently selected from H, methyl, ethyl, propyl, and i-propyl, and C_{3-6} carbocycle substituted with 0-2 R^{3e} wherein the C_{3-6} carbocycle is selected from cyclopropyl.

7. A compound of Claims 1-6, or a pharmaceutically acceptable salt form thereof, wherein the compound is of formula (Ic):



(Ic).

8. A compound of Claim 1, or a pharmaceutically acceptable salt form thereof, wherein the compound of formula (I) is selected from:

7-fluoro-2-methyl-5-[(6-methyl-2-pyridinyl)methyl]-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

5-(2-cyclopropylethynyl)-7-fluoro-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-propyl-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

5-butyl-7-fluoro-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(4-fluorophenylmethyl) -5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(2-pyridylmethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(isopropyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(3-pyridylmethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(4-pyridylmethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(3-propynyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(2-pyridylethynyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(2-(2-pyridyl)ethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

3-chloro-7-fluoro-5-propyl-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(3-propenyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

5-(2-cyclopropylethyl)-7-fluoro-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(ethynyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

7-fluoro-5-(2-ethoxyethyl)-5-(trifluoromethyl)-5,10-dihydrobenzo[*b*]-1,7-naphthyridin-1(2*H*)-one;

5-Butyl-7-chloro-5-trifluoromethyl- 5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(2-pyridylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(2-cyclopropylethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-cyclopropylethynyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(N-cyclopropylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-hydroxymethyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-3-methyl-5-(2-pyridylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(2-cyclopropylethyl)-3-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(2-methoxyethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(N-methyl-N-*i*-propylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclopropylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(*n*-propylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclobutylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(*i*-butylaminomethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(*i*-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Cyano-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Cyano-5-(i-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclopropylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclopropanesulfinylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(t-butylsulfinylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(methylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(ethylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Fluoro-5-(i-propylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(t-butylsulfanylmethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclopropylmethoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(cyclobutoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(Cyclobutoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(Cyclopropylmethoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-3-methyl-5-(i-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-3-methyl-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Cyano-3-methyl-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-2-methyl-5-(i-propoxymethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

3,7-Dichloro-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

4,7-Dichloro-5-(n-butyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(ethoxyethyl)-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-methyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propoxymethyl)-5-methyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-cyano-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-(hydroxymethyl)-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-difluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(i-propoxymethyl)-5-difluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(n-Butyl)-5-(1,1-difluoroethyl)-7-Fluoro-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(n-butyl)-5-(1,1-difluoroethyl)-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Cyano-5-(n-butyl)-5-(1,1-difluoroethyl)-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

7-Chloro-5-(ethoxymethyl)-5-(1,1-difluoroethyl)-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(allyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-methyl-1-propenyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(1-propynyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyanomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(ethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(dimethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(methylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-ethoxyethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(i-propylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(diethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(cyclopropylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(pentyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-butyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(vinyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(imidazolylethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(pyrazolylethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(1,2,4-triazolylethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(methylethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(i-propylethylamino)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(pyrrolidinyl)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(methoxy)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(3-pentanylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(dimethoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-butylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyclopropylmethylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(allylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-((R)-sec-butylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-((S)-sec-butylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(diethoxymethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

3-chloro-5-(propyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(butyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(i-propoxy)ethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propylaminomethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(i-propoxymethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-ethoxyethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(sec-butylaminomethyl)-7-fluoro-2-methyl-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyclopentylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyclobutylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(dimethylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(pyrrolidinylmethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(cyclopropylaminomethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(dimethoxy)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(diethoxy)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one;

5-(2-(1,3-dioxolanyl)methyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one; and

5-(2-(methoxy)ethyl)-7-fluoro-5-trifluoromethyl-5,10-dihydrobenzo[b]-1,7-naphthyridin-1(2H)-one.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to one of Claims 1-8 or pharmaceutically acceptable salt form thereof.

10. A method for treating HIV infection which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound according to one of Claims 1-8 or pharmaceutically acceptable salt form thereof.

11. A method of treating HIV infection which comprises administering, in combination, to a host in need thereof a therapeutically effective amount of:

(a) a compound according to one of Claims 1-8; and,

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors, HIV protease inhibitors, fusion inhibitors, and CCR-5 inhibitors.

12. A method of Claim 11, wherein the reverse transcriptase inhibitor is selected from the group AZT, ddC, ddI, d4T, 3TC, delavirdine, efavirenz, nevirapine, Ro 18,893, trovirdine, MKC-442, HBY 097, HBY1293, GW867, ACT, UC-781, UC-782, RD4-2025, MEN 10979 AG1549 (S1153), TMC-120, TMC-125, Calanolide A, and PMPA, and the protease inhibitor is selected from the group saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, palinavir, BMS-232623, GS3333, KNI-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, VX-175, MK-944, and VX-478, the CCR-5 inhibitor is selected from TAK-779 (Takeda), SC-351125 (SCH-C, Schering) and SCH-D (Schering), and the fusion inhibitor is selected from T-20 and T1249.

13. A method of Claim 12, wherein the reverse transcriptase inhibitor is selected from the group AZT, efavirenz, and 3TC and the protease inhibitor is selected from the group saquinavir, ritonavir, nelfinavir, and indinavir.

14. A method of Claim 13, wherein the reverse transcriptase inhibitor is AZT.

15. A method of Claim 13, wherein the protease inhibitor is indinavir.

16. A pharmaceutical kit useful for the treatment of HIV infection, which comprises a therapeutically effective amount of:

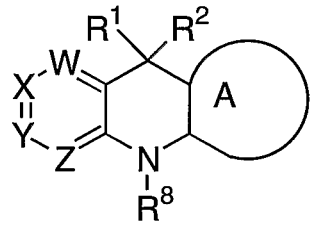
(a) a compound according to one of Claims 1-8; and,

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors, in one or more sterile containers.

17. A compound according to one of Claims 1-8 for use in therapy.

18. The use of a compound according to one of Claims 1-8 for the manufacture of a medicament for the treatment of HIV infection.

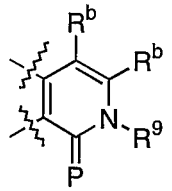
19. A compound of formula (I):



(I)

or a stereoisomeric form or mixture of stereoisomeric forms or a pharmaceutically acceptable salt form thereof, wherein:

A is a ring selected from:



P is O or S;

R^b is H, F, Cl, Br, I, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, C_{1-4} alkyl-O-, or C_{1-4} alkyl-NH-;

W is N or CR^3;

X is N or CR^{3a};

Y is N or CR^{3b};

Z is N or CR^{3c};

provided that if two of W, X, Y, and Z are N, then the remaining are other than N;

R^1 is selected from the group C_{1-3} alkyl substituted with 0-7 halogen and cyclopropyl;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCHR^{2a}R^{2b}$, $-OCH_2CHR^{2a}R^{2b}$, $-O(CH_2)_2CHR^{2a}R^{2b}$, $-OCHR^{2a}C(R^{2a})=C(R^{2b})_2$, $-OCHR^{2a}C(R^{2a})=C(R^{2b})_2$, $-OCHR^{2a}C\equiv C-R^{2b}$, $-SR^{2c}$, $-SCHR^{2a}R^{2b}$, $-SCH_2CHR^{2a}R^{2b}$, $-S(CH_2)_2CHR^{2a}R^{2b}$, $-SCHR^{2a}C(R^{2a})=C(R^{2b})_2$, $-SCHR^{2a}C(R^{2a})=(R^{2b})_2$, $-SCHR^{2a}C\equiv C-R^{2b}$, $-NR^{2a}R^{2c}$, $-NHCHR^{2a}R^{2b}$, $-NHCH_2CHR^{2a}R^{2b}$, $-NH(CH_2)_2CHR^{2a}R^{2b}$, $-NHCHR^{2a}C(R^{2a})=C(R^{2b})_2$, $-NHCHR^{2a}C(R^{2a})=(R^{2b})_2$, and $-NHCHR^{2a}C\equiv C-R^{2b}$;

R^{2a} is selected from the group H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $CH_2CH_2CH_3$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group methyl substituted with 0-3 R^{3f}, C_{1-6} alkyl substituted with 0-2 R^4, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, phenyl substituted with 0-2 R^{3d}, and 3-6 membered heterocyclic

system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3d};

alternatively, the group $-NR^{2a}R^{2c}$ represents a 4-7 membered cyclic amine, wherein 0-1 carbon atoms are replaced by O or NR^5;

R^3 is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

R^{3a} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^{3c} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3b} and R^{3c} together form $-OCH_2O-$;

R^{3d}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br,

I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3e}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3f}, at each occurrence, is independently selected from the group H, F, Cl, Br, I, C_{1-4} alkyl, -OH, $-O-R^{11}$, $-O-C_{3-10}$ carbocycle substituted with 0-2 R^{3e}, OCF_3, $-O(CO)-R^{13}$, $-OS(O)_2C_{1-4}$alkyl, $-NR^{12}R^{12a}$, $-C(O)R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2R^{10}$, and $-SO_2NR^{12}R^{12a}$;

R^4 is selected from the group H, F, Cl, Br, I, C_{1-6} alkyl substituted with 0-2 R^{3e}, C_{3-10} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-10 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H and C_{1-4} alkyl;

alternatively, R^5 and R^{5a}, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms;

R^6 is selected from the group H, OH, C_{1-4} alkyl, C_{1-4} alkoxy, and NR^5R^{5a};

R^7 is selected from the group H, C_{1-3} alkyl and C_{1-3} alkoxy;

R^8 is selected from the group H, (C_{1-6} alkyl)carbonyl, C_{1-6} alkoxy, (C_{1-4} alkoxy)carbonyl, C_{6-10} aryloxy, (C_{6-10} aryl)oxycarbonyl, (C_{6-10} aryl)methylcarbonyl, (C_{1-4} alkyl)carbonyloxy(C_{1-4} alkoxy)carbonyl, C_{6-10} arylcarbonyloxy(C_{1-4} alkoxy)carbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, phenyl(C_{1-4} alkoxy)carbonyl, and NR^5R^{5a}(C_{1-6} alkyl)carbonyl;

R^9 is selected from H, C_{1-4} alkyl, C_{1-4} alkenyl, and C_{1-4} alkynyl;

R^{10} is selected from the group C_{1-4} alkyl and phenyl;

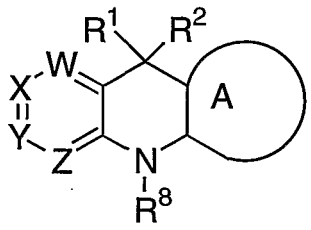
R^{11} is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyl substituted with C_{3-6}cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocycle substituted with 0-2 R^{3e};

R^{12} and R^{12a} are independently selected from H, C_{1-6} alkyl, and C_{3-6} carbocycle substituted with 0-2 R^{3e};

alternatively, R^{12} and R^{12a} can join to form 4-7 membered ring; and

R^{13} is selected from the group H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, $NR^{12}R^{12a}$, C_{3-6}carbocycle, and -O-C_{3-6}carbocycle.

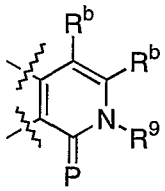
20. A compound of formula (I):



(I)

or a stereoisomeric form or mixture of stereoisomeric forms or a pharmaceutically acceptable salt form thereof, wherein:

A is a ring selected from:



P is O or S;

R^b is H, F, Cl, Br, I, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, C_{1-4} alkyl-O-, or C_{1-4} alkyl-NH-;

W is N or CR^3;

X is N or CR^{3a};

Y is N or CR^{3b};

Z is N or CR^{3c};

provided that if two of W, X, Y, and Z are N, then the remaining are other than N;

R^1 is selected from the group C_{1-3} alkyl substituted with 0-7 halogen and cyclopropyl;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCHR^{2a}R^{2b}$, $-OCH_2CHR^{2a}R^{2b}$, $-O(CH_2)_2CHR^{2a}R^{2b}$, $-OCHR^{2a}C(R^{2a})=C(R^{2b})_2$,

$-OCHR^{2a}C(R^{2a})=C(R^{2b})_2$, $-OCHR^{2a}C\equiv C-R^{2b}$, $-SR^{2c}$, $-SCHR^{2a}R^{2b}$, $-SCH_2CHR^{2a}R^{2b}$, $-S(CH_2)_2CHR^{2a}R^{2b}$, $-SCHR^{2a}C(R^{2a})=C(R^{2b})_2$, $-SCHR^{2a}C(R^{2a})=(R^{2b})_2$, $-SCHR^{2a}C\equiv C-R^{2b}$, $-NR^{2a}R^{2c}$, $-NHCHR^{2a}R^{2b}$, $-NHCH_2CHR^{2a}R^{2b}$, $-NH(CH_2)_2CHR^{2a}R^{2b}$, $-NHCHR^{2a}C(R^{2a})=C(R^{2b})_2$, $-NHCHR^{2a}C(R^{2a})=(R^{2b})_2$, and $-NHCHR^{2a}C\equiv C-R^{2b}$;

R^{2a} is selected from the group H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $CH_2CH_2CH_3$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group C_{1-6} alkyl substituted with 0-2 R^4, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, phenyl substituted with 0-2 R^{3d}, and 3-6 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3d};

alternatively, the group $-NR^{2a}R^{2c}$ represents a 4-7 membered cyclic amine, wherein 0-1 carbon atoms are replaced by O or NR^5;

R^3 is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

R^{3a} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, and a

5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^{3c} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3b} and R^{3c} together form $-OCH_2O-$;

R^{3d}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3e}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^4 is selected from the group H, R^{3d}F, Cl, Br, I, C_{1-6} alkyl substituted with 0-2 R^{3e}, C_{3-10} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-10 membered heterocyclic system containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H and C_{1-4} alkyl;

alternatively, R^5 and R^{5a}, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms;

R^6 is selected from the group H, OH, C_{1-4} alkyl, C_{1-4} alkoxy, and NR^5R^{5a};

R^7 is selected from the group H, C_{1-3} alkyl and C_{1-3} alkoxy;

R^8 is selected from the group H, (C_{1-6} alkyl)carbonyl, C_{1-6} alkoxy, (C_{1-4} alkoxy)carbonyl, C_{6-10} aryloxy, (C_{6-10} aryl)oxycarbonyl, (C_{6-10} aryl)methylcarbonyl, (C_{1-4} alkyl)carbonyloxy(C_{1-4} alkoxy)carbonyl, C_{6-10} arylcarbonyloxy(C_{1-4} alkoxy)carbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, phenyl(C_{1-4} alkoxy)carbonyl, and NR^5R^{5a}(C_{1-6} alkyl)carbonyl;

R^9 is selected from H, C_{1-4} alkyl, C_{1-4} alkenyl, and C_{1-4} alkynyl; and

R^{10} is selected from the group C_{1-4} alkyl and phenyl.