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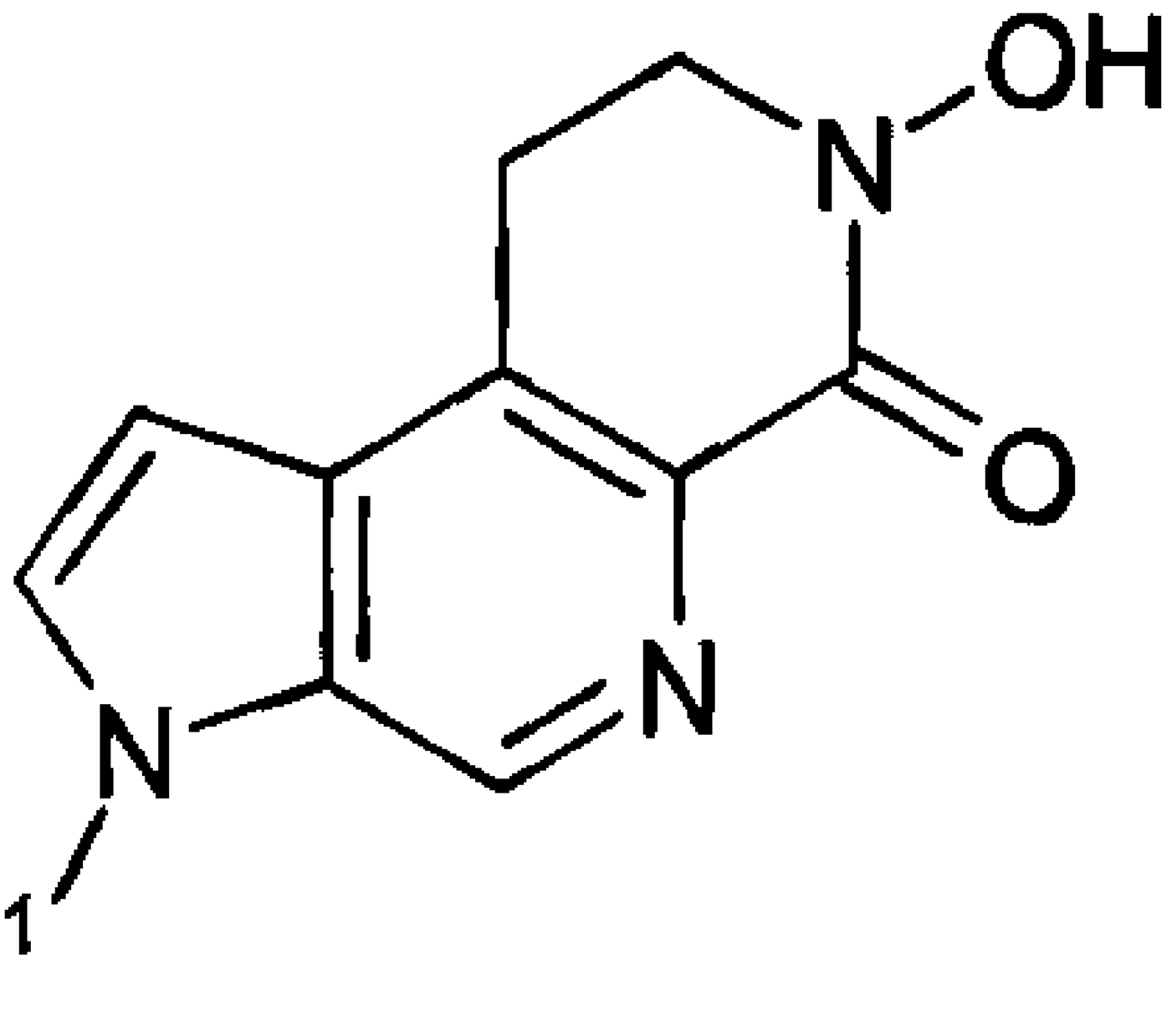
(54) Title: INHIBITORS OF THE HIV INTEGRASE ENZYME



(I)

(57) Abrégé/Abstract:
The present invention is directed to compounds of formula (I), and pharmaceutically acceptable salts and solvates thereof, their synthesis, and their use as modulators or inhibitors of the human immunodeficiency virus ("HIV") integrase enzyme.

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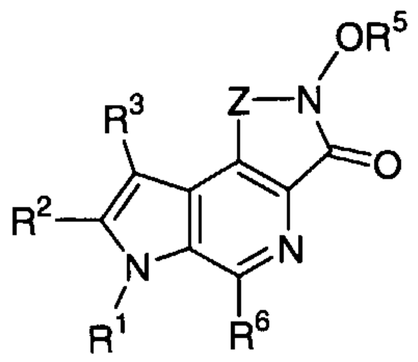
(54) Title: INHIBITORS OF THE HIV INTEGRASE ENZYME



(I)

(57) Abstract: The present invention is directed to compounds of formula (I), and pharmaceutically acceptable salts and solvates thereof, their synthesis, and their use as modulators or inhibitors of the human immunodeficiency virus ("HIV") integrase enzyme.

INHIBITORS OF THE HIV INTEGRASE ENZYME

Field

The present invention is directed to compounds, and pharmaceutically acceptable salts and solvates thereof, their synthesis, and their use as modulators or inhibitors of the human immunodeficiency virus ("HIV") integrase enzyme. The compounds of the present invention are useful for modulating (e.g. inhibiting) an enzyme activity of HIV integrase enzyme and for treating diseases or conditions mediated by HIV, such as for example, acquired immunodeficiency syndrome ("AIDS"), and AIDS related complex ("ARC").

Background

The retrovirus designated "human immunodeficiency virus" or "HIV" is the etiological agent of a complex disease that progressively destroys the immune system. The disease is known as acquired immune deficiency syndrome or AIDS. AIDS and other HIV-caused diseases are difficult to treat due to the ability of HIV to rapidly replicate, mutate and acquire resistance to drugs. In order to slow the proliferation of the virus after infection, treatment of AIDS and other HIV-caused diseases has focused on inhibiting HIV replication.

Since HIV is a retrovirus, and thus, encodes a positive-sense RNA strand, its mechanism of replication is based on the conversion of viral RNA to viral DNA, and subsequent insertion of the viral DNA into the host cell genome. HIV replication relies on three constitutive HIV encoded enzymes: reverse transcriptase (RT), protease and integrase.

Upon infection with HIV, the retroviral core particles bind to specific cellular receptors and gain entry into the host cell cytoplasm. Once inside the cytoplasm, viral RT catalyzes the reverse transcription of viral ssRNA to form viral RNA-DNA hybrids. The RNA strand from the hybrid is then partially degraded and a second DNA strand is synthesized resulting in viral dsDNA. Integrase, aided by viral and cellular proteins, then transports the viral dsDNA into the host cell nucleus as a component of the pre-integration complex (PIC). In addition, integrase provides the permanent insertion, i.e., integration, of the viral dsDNA to the host cell genome, which, in turn, provides viral access to the host cellular machinery for gene expression. Following integration, transcription and translation produce viral precursor proteins.

A key step in HIV replication, insertion of the viral dsDNA into the host cell genome, is believed to be mediated by integrase in at least three, and possibly, four, steps: (1) assembly of proviral DNA; (2) 3'-end processing causing assembly of the PIC; (3) 3'-end joining or DNA strand transfer, i.e., integration; and (4) gap filling, a repair function. *See, e.g.,* Goldgur, Y. et al., *PNAS 96(23):* 13040-13043 (Nov. 1999); Sayasith, K. et al., *Expert Opin. Ther. Targets 5(4):* 443-464 (2001); Young, S.D., *Curr. Opin. Drug Disc. & Devel. 4(4):* 402-410 (2001); Wai, J.S. et al., *J. Med. Chem. 43(26):* 4923-4926 (2000); Debyser, Z. *et al.*, *Assays for the Evaluation of HIV-1*

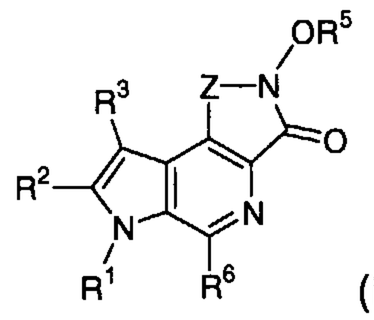
Integrase Inhibitors, from Methods in Molecular Biology *160:* 139-155, Schein, C.H. (ed.), Humana Press Inc., Totowa, N.J. (2001); and Hazuda, D. *et al.*, *Drug Design and Disc. 13:* 17-24 (1997).

Currently, AIDS and other HIV-caused disease are treated with an "HIV cocktail" containing multiple drugs including RT and protease inhibitors. However, numerous side effects and the rapid emergence of drug resistance limit the ability of the RT and protease inhibitors to safely and effectively treat AIDS and other HIV-caused diseases. In view of the shortcomings of RT and protease inhibitors, there is a need for another mechanism through which HIV replication can be inhibited. Integration, and thus integrase, a virally encoded enzyme with no mammalian counterpart, is a logical alternative. *See, e.g.,* Wai, J.S. et al., *J. Med. Chem. 43:*4923-4926 (2000); Grobler, J. et al., *PNAS 99:* 6661-6666 (2002); Pais, G.C.G. et al., *J. Med. Chem. 45:* 3184-3194 (2002); Young, S.D., *Curr. Opin. Drug Disc. & Devel. 4(4):* 402-410 (2001); Godwin, C.G. et al., *J. Med. Chem. 45:* 3184-3194 (2002); Young, S.D. et al., "L-870, 810: Discovery of a Potent HIV Integrase Inhibitor with Potential Clinical Utility," Poster presented at the XIV International AIDS Conference, Barcelona (July 7-12, 2002); and WO 02/070491.

It has been suggested that for an integrase inhibitor to function, it should inhibit the strand transfer integrase function. *See, e.g.,* Young, S.D., *Curr. Opin. Drug Disc. & Devel. 4(4):* 402-410 (2001). Thus, there is a need for HIV inhibitors, specifically, integrase inhibitors, and, more specifically, strand transfer inhibitors, to treat AIDS and other HIV-caused diseases. The inventive agents disclosed herein are novel, potent and selective HIV-integrase inhibitors, and, more specifically, strand transfer inhibitors, with high antiviral activity.

Summary

The present invention provides compounds of formula (I),



(I)

wherein:

R^1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl groups may be optionally substituted with at least one substituent independently selected from:

halo, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9

heteroaryl groups are optionally substituted with at least one substituent independently selected from halo, -C($R^{12a}R^{12b}R^{12c}$), –OH, and C_1-C_8 alkoxy;

R^2 is hydrogen or C_1-C_8 alkyl;

R^3 is hydrogen, C_1-C_8 alkyl, –(CR^7R^8)$_t$$NR^9R^{10}$, -$S(O)_zNR^9R^{10}$, -$C(O)NR^9R^{10}$, or C_1-C_8 heteroalkyl, wherein said C_1-C_8 heteroalkyl is optionally substituted with R^{11};

Z is -(CR^4R^4)$_n$-, -$C(R^4)$=$C(R^4)$-, -$C(R^4)$=$C(R^4)$-(CR^4R^4)$_n$-, -(CR^4R^4)$_n$-$C(R^4)$=$C(R^4)$-, or -(CR^4R^4)$_n$-$C(R^4)$=$C(R^4)$-(CR^4R^4)$_n$-;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

each R^7 and R^8, which may be the same or different, are independently selected from hydrogen and C_1-C_8 alkyl;

R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group; or

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

R^{11} is C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 cycloheteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which is optionally substituted with at least one substituent independently selected from C_1-C_8 alkyl, C_6-C_{14} aryl, C_2-C_9 heteroaryl, -CF_3, -COR^{12a}, -CO_2R^{12a}, and -OR^{12a};

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen, C_1-C_8 alkyl, and oxo; or

R^{12a} and R^{12b}, together with the nitrogen atom to which they are attached, may form a C_2-C_9 cycloheteroalkyl group;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, -(CR^7R^8)$_t$$OR^7$, -$C(O)R^{12a}$, -$S(O)_2R^7$, -($CR^7R^8$)$_z$$C(O)NR^{12a}R^{12b}$, -$NR^{12a}R^{12b}$, and -$CF_3$;

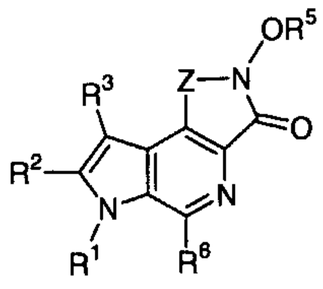
t is an integer from 1 to 3;

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; and

each z, which may be the same or different, is independently selected and is 0, 1, or 2; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $-(CH_2)-$, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

The present invention also provides compounds of formula (I),



(I)

wherein:

R^1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl groups may be optionally substituted with at least one substituent independently selected from:

halo, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl groups are optionally substituted with at least one substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, and C_1-C_8 alkoxy;

R^2 is hydrogen or C_1-C_8 alkyl;

R^3 is hydrogen, $-(CR^7R^8)_tNR^9R^{10}$ or C_1-C_8 heteroalkyl, wherein said C_1-C_8 heteroalkyl is optionally substituted with R^{11};

Z is $-(CR^4R^4)_n-$, $-C(R^4)=C(R^4)-$, $-C(R^4)=C(R^4)-(CR^4R^4)_n-$, $-(CR^4R^4)_n-C(R^4)=C(R^4)-$, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n-$;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

each R^7 and R^8, which may be the same or different, are independently selected from hydrogen and C_1-C_8 alkyl;

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group optionally substituted with at least one C_1-C_8 alkyl;

R^{11} is C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 cycloheteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which is optionally substituted with at least one substituent independently selected from C_1-C_8 alkyl, C_6-C_{14} aryl, C_2-C_9 heteroaryl, $-CF_3$, $-COR^{12a}$, $-CO_2R^{12a}$, and $-OR^{12a}$;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-NR^{12a}R^{12b}$, and $-CF_3$;

t is an integer from 1 to 3; and

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $–(CH_2)$-, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

In another aspect of the present invention are afforded compounds of formula (I), wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, and C_1-C_8 alkoxy;

R^2 is hydrogen;

R^3 is hydrogen, $–(CR^7R^8)_tNR^9R^{10}$ or C_1-C_8 heteroalkyl, wherein said C_1-C_8 heteroalkyl is optionally substituted with R^{11};

Z is $-(CR^4R^4)_n$-, $-C(R^4)=C(R^4)$-, $-C(R^4)=C(R^4)-(CR^4R^4)_n$-, $-(CR^4R^4)_n-C(R^4)=C(R^4)$-, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n$-;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

each R^7 and R^8, which may be the same or different, are independently selected from hydrogen and C_1-C_8 alkyl;

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group optionally substituted with at least one C_1-C_8 alkyl;

R^{11} is C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 cycloheteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which is optionally substituted with at least one substituent independently selected from C_1-C_8 alkyl, C_6-C_{14} aryl, C_2-C_9 heteroaryl, $-CF_3$, $-COR^{12a}$, $-CO_2R^{12a}$, and $-OR^{12a}$;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-NR^{12a}R^{12b}$, and $-CF_3$;

t is an integer from 1 to 3; and

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $-(CH_2)-$, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

In still a further aspect of the present invention are provided compounds of formula (I), wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one halo;

R^2 is hydrogen;

R^3 is hydrogen, $-(CR^7R^8)_tNR^9R^{10}$ or C_1-C_8 heteroalkyl, wherein said C_1-C_8 heteroalkyl is optionally substituted with R^{11};

Z is $-(CR^4R^4)_n-$, $-C(R^4)=C(R^4)-$, $-C(R^4)=C(R^4)-(CR^4R^4)_n-$, $-(CR^4R^4)_n-C(R^4)=C(R^4)-$, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n-$;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

each R^7 and R^8, which may be the same or different, are independently selected from hydrogen and C_1-C_8 alkyl;

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group optionally substituted with at least one C_1-C_8 alkyl;

R^{11} is C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 cycloheteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which is optionally substituted with at least one substituent independently selected from C_1-C_8 alkyl, C_6-C_{14} aryl, C_2-C_9 heteroaryl, $-CF_3$, $-COR^{12a}$, $-CO_2R^{12a}$, and $-OR^{12a}$;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-NR^{12a}R^{12b}$, and $-CF_3$;

t is an integer from 1 to 3; and

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $-(CH_2)-$, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

The present invention also affords compounds of formula (I), wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one halo;

R^2 is hydrogen;

R^3 is hydrogen;

Z is $-(CR^4R^4)_n-$, $-C(R^4)=C(R^4)-$, $-C(R^4)=C(R^4)-(CR^4R^4)_n-$, $-(CR^4R^4)_n-C(R^4)=C(R^4)-$, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n-$;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-NR^{12a}R^{12b}$, and $-CF_3$;

t is an integer from 1 to 3; and

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $-(CH_2)-$, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

Yet another aspect of the present invention are compounds of formula (I), wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one fluorine;

R^2 is hydrogen;

R^3 is hydrogen;

Z is $-(CR^4R^4)_n-$, $-C(R^4)=C(R^4)-$, $-C(R^4)=C(R^4)-(CR^4R^4)_n-$, $-(CR^4R^4)_n-C(R^4)=C(R^4)-$, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n-$;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-NR^{12a}R^{12b}$, and $-CF_3$;

t is an integer from 1 to 3; and

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $–(CH_2)$-, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

A still further aspect are compounds of formula (I), wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one halo;

R^2 is hydrogen;

R^3 is $–(CR^7R^8)_tNR^9R^{10}$;

Z is $-(CR^4R^4)_n$-, $-C(R^4)=C(R^4)$-, $-C(R^4)=C(R^4)-(CR^4R^4)_n$-, $-(CR^4R^4)_n-C(R^4)=C(R^4)$-, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n$-;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

each R^7 and R^8, which may be the same or different, are independently selected from hydrogen and C_1-C_8 alkyl;

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group optionally substituted with at least one C_1-C_8 alkyl;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-NR^{12a}R^{12b}$, and $-CF_3$;

t is an integer from 1 to 3; and

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $–(CH_2)$-, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

Also provided are compounds of formula (I), wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one fluorine;

R^2 is hydrogen;

R^3 is $–(CR^7R^8)_tNR^9R^{10}$;

Z is $-(CR^4R^4)_n$-, $-C(R^4)=C(R^4)$-, $-C(R^4)=C(R^4)-(CR^4R^4)_n$-, $-(CR^4R^4)_n-C(R^4)=C(R^4)$-, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n$-;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

each R^7 and R^8, which may be the same or different, are independently selected from hydrogen and C_1-C_8 alkyl;

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group optionally substituted with at least one C_1-C_8 alkyl;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-NR^{12a}R^{12b}$, and $-CF_3$;

t is an integer from 1 to 3; and

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $–(CH_2)$-, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

Also provided are compounds of formula (I), wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one halo;

R^2 is hydrogen;

R^3 is C_1-C_8 heteroalkyl optionally substituted with R^{11};

Z is $-(CR^4R^4)_n$-, $-C(R^4)=C(R^4)$-, $-C(R^4)=C(R^4)-(CR^4R^4)_n$-, $-(CR^4R^4)_n-C(R^4)=C(R^4)$-, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n$-;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

R^{11} is C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 cycloheteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which is optionally substituted with at least one substituent independently selected from C_1-C_8 alkyl, C_6-C_{14} aryl, C_2-C_9 heteroaryl, $-CF_3$, $-COR^{12a}$, $-CO_2R^{12a}$, and $-OR^{12a}$;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-NR^{12a}R^{12b}$, and $-CF_3$;

t is an integer from 1 to 3; and

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $-(CH_2)$-, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

Furthermore, compounds of formula (I) are provided, wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one fluorine;

R^2 is hydrogen;

R^3 is C_1-C_8 heteroalkyl optionally substituted with R^{11};

Z is $-(CR^4R^4)_n$-, $-C(R^4)=C(R^4)$-, $-C(R^4)=C(R^4)-(CR^4R^4)_n$-, $-(CR^4R^4)_n-C(R^4)=C(R^4)$-, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n$-;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

R^6 is hydrogen;

R^{11} is C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 cycloheteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which is optionally substituted with at least one substituent independently selected from C_1-C_8 alkyl, C_6-C_{14} aryl, C_2-C_9 heteroaryl, $-CF_3$, $-COR^{12a}$, $-CO_2R^{12a}$, and $-OR^{12a}$;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-NR^{12a}R^{12b}$, and $-CF_3$;

t is an integer from 1 to 3; and

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; or

pharmaceutically acceptable salts or solvates thereof, with the proviso that R^5 is not hydrogen when Z is $-(CH_2)$-, R^1 is 2,4-difluorobenzyl, and R^2, R^3, and R^6 are hydrogen.

In a still further aspect of the present invention are provided compounds of formula (I), wherein:

R^3 is $-(CR^7R^8)_tNR^9R^{10}$; and

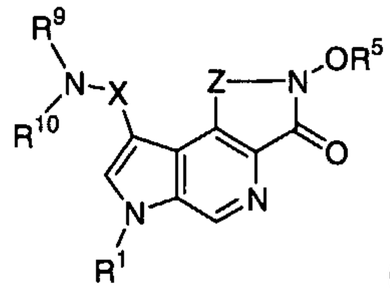
R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group;

Further provided are compounds of formula (I), wherein:

R^3 is $-(CR^7R^8)_tNR^9R^{10}$;

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group.

In yet a further aspect are afforded compounds of formula (II),



(II)

wherein:

R^1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl groups may be optionally substituted with at least one substituent independently selected from:

halo, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9

heteroaryl groups are optionally substituted with at least one substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, and C_1-C_8 alkoxy;

X is $–S(O)_2$-, $-CH_2$-, or –C(O)-;

Z is $-(CR^4R^4)_n$-, $-C(R^4)=C(R^4)$-, $-C(R^4)=C(R^4)-(CR^4R^4)_n$-, $-(CR^4R^4)_n-C(R^4)=C(R^4)$-, or $-(CR^4R^4)_n-C(R^4)=C(R^4)-(CR^4R^4)_n$-;

each R^4 is independently selected from hydrogen, halo, C_1-C_8 heteroalkyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, C_2-C_9 cycloheteroalkyl, and C_2-C_9 heteroaryl are optionally substituted with at least one R^{13};

R^5 is hydrogen, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, C_2-C_8 alkenyl, or C_1-C_8 alkyl, wherein said C_1-C_8 alkyl is optionally substituted with at least one C_3-C_8 cycloalkyl or C_6-C_{14} aryl group;

each R^7 and R^8, which may be the same or different, are independently selected from hydrogen and C_1-C_8 alkyl;

R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group; or

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen, C_1-C_8 alkyl, and oxo; or

R^{12a} and R^{12b}, together with the nitrogen atom to which they are attached, may form a C_2-C_9 cycloheteroalkyl group;

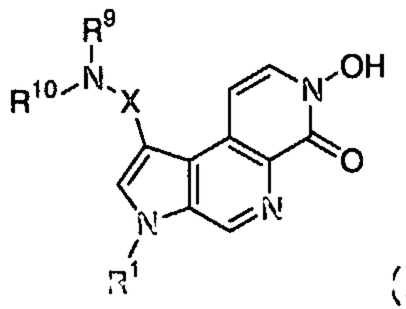
each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, and $-CF_3$;

each n, which may be the same or different, is independently selected and is an integer from 1 to 4; and

each z, which may be the same or different, is independently selected and is 0, 1, or 2; or

pharmaceutically acceptable salts or solvates thereof.

In still another aspect are provided compounds of formula (III),



(III)

wherein:

R^1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl groups may be optionally substituted with at least one substituent independently selected from:

halo, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl groups are optionally substituted with at least one substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, and C_1-C_8 alkoxy;

X is $–S(O)_2-$, $-CH_2-$, or –C(O)-;

each R^7 and R^8, which may be the same or different, are independently selected from hydrogen and C_1-C_8 alkyl;

R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group; or

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

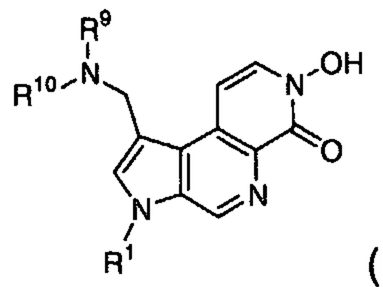
each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen, C_1-C_8 alkyl, and oxo; or

R^{12a} and R^{12b}, together with the nitrogen atom to which they are attached, may form a C_2-C_9 cycloheteroalkyl group;

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, and $-CF_3$; and

each z, which may be the same or different, is independently selected and is 0, 1, or 2; or pharmaceutically acceptable salts or solvates thereof.

Further provided herein are compounds of formula (IIIa):



(IIIa)

wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one substituent independently selected from halo, -C($R^{12a}R^{12b}R^{12c}$), –OH, and C_1-C_8 alkoxy;

R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group; or

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl; or

R^{12a} and R^{12b}, together with the nitrogen atom to which they are attached, may form a C_2-C_9 cycloheteroalkyl group; and

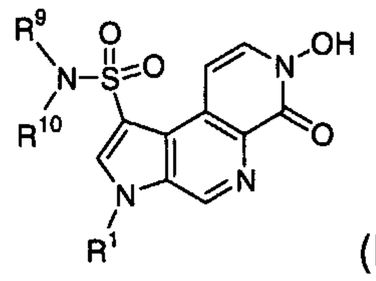
each R^{13} is independently selected from halo, C_1-C_8 alkyl, -$(CR^7R^8)_tOR^7$, -$C(O)R^{12a}$, -$S(O)_2R^7$, -$(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, -$NR^{12a}R^{12b}$, and -$CF_3$; or

pharmaceutically acceptable salts or solvates thereof.

Further provided are compounds of formula (IIIa), wherein R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group.

Also provided are compounds of formula (IIIa), wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group.

Further provided herein are compounds of formula (IIIb),



(IIIb)

wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one substituent independently selected from halo, -C($R^{12a}R^{12b}R^{12c}$), –OH, and C_1-C_8 alkoxy;

R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group; or

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl; or

R^{12a} and R^{12b}, together with the nitrogen atom to which they are attached, may form a C_2-C_9 cycloheteroalkyl group; and

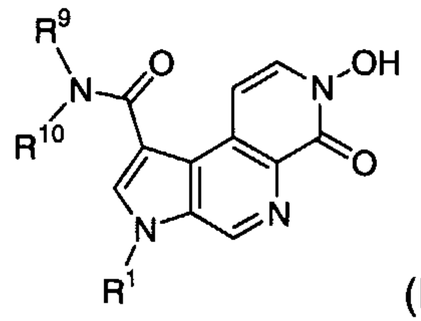
each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, and $-CF_3$; or

pharmaceutically acceptable salts or solvates thereof.

Further provided are compounds of formula (IIIb), wherein R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group.

Also provided are compounds of formula (IIIb), wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group.

In yet another aspect are provided compounds of formula (IIIc),



(IIIc)

wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, and C_1-C_8 alkoxy;

R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14}

aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group; or

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen and C_1-C_8 alkyl; or

R^{12a} and R^{12b}, together with the nitrogen atom to which they are attached, may form a C_2-C_9 cycloheteroalkyl group; and

each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, and $-CF_3$; or

pharmaceutically acceptable salts or solvates thereof.

Further provided are compounds of formula (IIIc), wherein R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_3-C_8 cycloalkyl, C_2-C_9 cycloheteroalkyl, and C_1-C_8 alkyl, wherein said C_1-C_8 alkyl may be optionally substituted by at least one C_2-C_9 cycloheteroalkyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be optionally substituted by at least one C_1-C_8 or halo group.

Also provided are compounds of formula (IIIc), wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group.

In yet another aspect are afforded any of the above compounds wherein Z is $-(CH_2)-$, $-(CH_2)_2-$, $-(CH_2)_3-$, or $-(CH=CH)-$.

Further provided are any of the above compounds wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group comprising 4 carbon atoms and a nitrogen atom; or wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group comprising 4 carbon atoms and 2 nitrogen atoms; or wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group comprising 4 carbon atoms, a nitrogen atom, and an oxygen atom, provided that said nitrogen atom and said oxygen atom are not bonded to each other; or wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group comprising 4 carbon atoms, a nitrogen atom, and a sulfur atom; or wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group comprising 4 carbon atoms, a nitrogen atom, and an oxidized sulfur atom; or wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group comprising three carbon atoms and three nitrogen atoms.

Also provided are compounds selected from 3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-

pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-7,8,9,10-tetrahydropyrrolo[3',2':4,5]pyrido[2,3-*c*]azepin-6(3*H*)-one; 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-L-prolinamide; 3-(4-fluorobenzyl)-7-hydroxy-1-[(3-oxopiperazin-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-methoxyethoxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-(3,4-dihydroisoquinolin-2(1H)-ylmethyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(pentyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-D-prolinamide; 3-(4-fluorobenzyl)-7-hydroxy-1-[(1-oxo-2,8-diazaspiro[4.5]dec-8-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[cyclohexyl(ethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(2-pyridin-2-ylethyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; (3R)-1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-N,N-dimethylpyrrolidine-3-carboxamide; 3-(4-fluorobenzyl)-7-hydroxy-1-({4-hydroxy-4-[(2-oxopyrrolidin-1-yl)methyl]piperidin-1-yl}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(5-oxo-1,4-diazepan-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]sulfonyl}-L-prolinamide; 3-(4-fluorobenzyl)-7-hydroxy-N-[2-(1H-indol-3-yl)ethyl]-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; 3-(4-fluorobenzyl)-7-hydroxy-1-[(3-oxopiperazin-1-yl)sulfonyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-N,N-dimethyl-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; 3-(4-fluorobenzyl)-7-hydroxy-6-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; N,3-bis(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylcarbonyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(4-acetylpiperazin-1-yl)carbonyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-6-oxo-N-(2-pyrazin-2-ylethyl)-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide; 3-(4-fluorobenzyl)-7-hydroxy-6-oxo-N-(pyridin-2-ylmethyl)-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide; 3-(4-fluorobenzyl)-7-hydroxy-6-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide; 1-[(4-ethylpiperazin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-

naphthyridin-6-one; 1-({[(2S)-2,3-dihydroxypropyl]oxy}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; tert-butyl 4-({[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methoxy}methyl)piperidine-1-carboxylate; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-pyridin-2-ylethoxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[2-(cyclohexyloxy)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[({[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}amino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-methoxyethoxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-yloxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(1R)-1-phenylethoxy]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-({[1-(hydroxymethyl)cyclopentyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(propylamino)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(3-methylbenzyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-({[(5-methylpyrazin-2-yl)methyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-({[4-(trifluoromethyl)benzyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(pyridin-2-ylmethyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-7,8,9,10-tetrahydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3H)-one; 8-butyl-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-8-methyl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one, 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-hydroxyethyl)(propyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[2-(hydroxymethyl)piperidin-1-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[[2-(diethylamino)ethyl](ethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[ethyl(4-methylbenzyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[4-(ethylsulfonyl)piperazin-1-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-hydroxypiperidin-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[benzyl(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(7R)-7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(3aR,7aR)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridin-5-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(morpholin-4-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[4-(2-morpholin-4-ylethyl)piperazin-1-yl]methyl}-3,7-dihydro-6H-

pyrrolo[2,3-c]-1,7-naphthyridin-6-one; and 3-(4-fluorobenzyl)-7-hydroxy-1-({methyl[(1-phenyl-1H-pyrazol-4-yl)methyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or pharmaceutically acceptable salts or solvates thereof.

In a further aspect are provided compounds selected from 3-(4-Fluorobenzyl)-7-hydroxy-3,7-dihydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one; 3-(4-Fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-methoxyethoxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-(3,4-dihydroisoquinolin-2(1H)-ylmethyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[({[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}amino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-methoxyethoxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(1R)-1-phenylethoxy]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-({[4-(trifluoromethyl)benzyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(pyridin-2-ylmethyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or pharmaceutically acceptable salts or solvates thereof.

Further provided are compounds selected from 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(pentyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-D-prolinamide; 1-{[cyclohexyl(ethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(2-pyridin-2-ylethyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-N,N-dimethyl-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylcarbonyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; tert-butyl 4-({[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methoxy}methyl)piperidine-1-carboxylate; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-pyridin-2-ylethoxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[2-(cyclohexyloxy)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-yloxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-({[1-(hydroxymethyl)cyclopentyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(propylamino)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(3-methylbenzyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; and 3-(4-fluorobenzyl)-7-hydroxy-1-({[(5-methylpyrazin-

2-yl)methyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or pharmaceutically acceptable salts or solvates thereof.

The present invention also provides pharmaceutical compositions, comprising a therapeutically effective amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or diluent.

Further provided are methods of inhibiting HIV replication in a mammal, comprising administering to said mammal an HIV replication-inhibiting amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof.

In still another aspect of the present invention are afforded methods of inhibiting HIV replication in a cell, comprising contacting said cell with an HIV replication-inhibiting amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof.

Further provided herein are methods of inhibiting HIV integrase enzyme activity, comprising contacting said integrase enzyme with an HIV integrase-inhibiting amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof.

Additionally, the present invention affords methods of treating acquired immune deficiency syndrome in a mammal, such as a human, comprising administering to said mammal a therapeutically effective amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof.

The present invention further provides methods of inhibiting HIV replication in a mammal, wherein said HIV is resistant to at least one HIV protease inhibitor, said method comprising administering to said mammal an HIV replication-inhibiting amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof.

Also herein are methods of inhibiting HIV replication in a mammal, wherein said HIV is resistant to at least one HIV reverse transcriptase inhibitor, said method comprising administering to said mammal an HIV replication-inhibiting amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof.

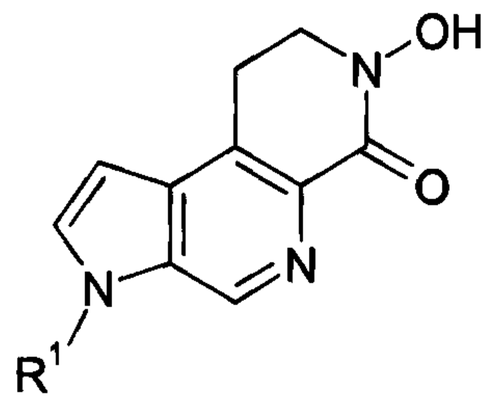
In yet another aspect are provided methods of inhibiting HIV replication in mammal, comprising administering to said mammal an HIV replication-inhibiting amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof, and an HIV replication-inhibiting amount of at least one other anti-HIV agent.

In still another aspect are methods of reducing HIV viral load in a mammal infected with HIV, such as a human, comprising administering to said mammal a therapeutically effective amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof.

Further are provided uses of at least one of any of the compounds herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of acquired immune deficiency syndrome (AIDS) or AIDS-related complex in an HIV-infected mammal.

It is to be understood that the compounds of the present invention do not include the compound of formula (I) wherein R^1 is 2,4-difluorobenzyl, R^2 is hydrogen, R^3 is hydrogen, Z is $-(CH_2)-$, and R^6 is hydrogen, which compound is named 6-(2,4-difluorobenzyl)-2-hydroxy-1,6-dihydrodipyrrolo[3,2-*d*:3',4'-*b*]pyridin-3(2*H*)-one.

In accordance with an aspect of the present invention, there is provided a compound of formula (I)



(I)

wherein:

R^1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl groups may be optionally substituted with at least one substituent independently selected from:

halo, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl groups are optionally substituted with at least one substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, and C_1-C_8 alkoxy;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen, C_1-C_8 alkyl, and oxo; or

R^{12a} and R^{12b}, together with the nitrogen atom to which they are attached, may form a C_2-C_9 cycloheteroalkyl group;

or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.

As used herein, the term "HIV" means Human Immunodeficiency Virus. The term "HIV integrase," as used herein, means the Human Immunodeficiency Virus integrase enzyme.

The term "C_1-C_8 alkyl", as used herein, means saturated monovalent hydrocarbon radicals having straight or branched moieties and containing from 1 to 8 carbon atoms. Examples

of such groups include, but are not limited to, methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl.

The term "C_1-C_8 heteroalkyl" refers to a straight- or branched-chain alkyl group having a total of from 2 to 12 atoms in the chain, including from 1 to 8 carbon atoms, and one or more atoms of which is a heteroatom selected from S, O, and N, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms. The S atoms in said chains may be optionally oxidized with one or two oxygen atoms, to afford sulfides and sulfones, respectively. Furthermore, the C_1-C_8 heteroalkyl groups in the compounds of the present invention can contain an oxo group at any carbon or heteroatom that will result in a stable compound. Exemplary C_1-C_8 heteroalkyl groups include, but are not limited to, alcohols, alkyl ethers, primary, secondary, and tertiary alkyl amines, amides, ketones, esters, sulfides, and sulfones.

The term "C_2-C_8 alkenyl", as used herein, means an alkyl moiety comprising 2 to 8 carbons having at least one carbon-carbon double bond. The carbon-carbon double bond in such a group may be anywhere along the 2 to 8 carbon chain that will result in a stable compound. Such groups include both the E and Z isomers of said alkenyl moiety. Examples of such groups include, but are not limited to, ethenyl, propenyl, butenyl, allyl, and pentenyl. The term "allyl," as used herein, means a $-CH_2CH=CH_2$ group. The term, "C(R)=C(R)," as used herein, represents a carbon-carbon double bond in which each carbon is substituted by an R group.

As used herein, the term "C_2-C_8 alkynyl" means an alkyl moiety comprising from 2 to 8 carbon atoms and having at least one carbon-carbon triple bond. The carbon-carbon triple bond in such a group may be anywhere along the 2 to 8 carbon chain that will result in a stable

compound. Examples of such groups include, but are not limited to, ethyne, propyne, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 1-hexyne, 2-hexyne, and 3-hexyne.

The term "C_3-C_8 cycloalkyl group" means a saturated, monocyclic, fused, spirocyclic, or polycyclic ring structure having a total of from 3 to 8 carbon ring atoms. Examples of such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptyl, and adamantyl.

The term "C_6-C_{14} aryl", as used herein, means a group derived from an aromatic hydrocarbon containing from 6 to 14 carbon atoms. Examples of such groups include, but are not limited to, phenyl or naphthyl. The terms "Ph" and "phenyl," as used herein, mean a $-C_6H_5$ group. The term "benzyl," as used herein, means a $-CH_2C_6H_5$ group.

The term "C_2-C_9 heteroaryl, " as used herein, means an aromatic heterocyclic group having a total of from 5 to 10 atoms in its ring, and containing from 2 to 9 carbon atoms and from one to four heteroatoms each independently selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O atoms or two adjacent S atoms. The heterocyclic groups include benzo-fused ring systems. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The C_2-C_9 heteroaryl groups may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached).

The term "C_2-C_9 cycloheteroalkyl," as used herein, means a non-aromatic, monocyclic, bicyclic, tricyclic, spirocyclic, or tetracyclic group having a total of from 4 to 10 atoms in its ring system, and containing from 2 to 9 carbon atoms and from one to four heteroatoms each independently selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O atoms or two adjacent S atoms. Furthermore, such C_2-C_9 cycloheteroalkyl groups may contain an oxo substituent at any available atom that will result in a stable compound. For example, such a group may contain an oxo atom at an available carbon or nitrogen atom. Such a group may contain more than one oxo substituent if chemically feasible. In addition, it is to be understood that when such a C_2-C_9 cycloheteroalkyl group contains a sulfur atom, said sulfur atom may be oxidized with one or two oxygen atoms to afford either a sulfoxide or sulfone. An example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Further examples of such C_2-C_9 cycloheteroalkyl groups include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl,

dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl quinolizinyl, 3-oxopiperazinyl, 4-methylpiperazinyl, 4-ethylpiperazinyl, and 1-oxo-2,8,diazaspiro[4.5]dec-8-yl.

The term "C_1-C_8 alkoxy", as used herein, means an O-alkyl group wherein said alkyl group contains from 1 to 8 carbon atoms and is straight, branched, or cyclic. Examples of such groups include, but are not limited to, methoxy, ethoxy, n-propyloxy, iso-propyloxy, n-butoxy, iso-butoxy, tert-butoxy, cyclopentyloxy, and cyclohexyloxy.

The terms “halogen” and “halo,” as used herein, mean fluorine, chlorine, bromine or iodine.

The term “substituted,” means that the specified group or moiety bears one or more substituents. The term “unsubstituted,” means that the specified group bears no substituents. The term “optionally substituted” means that the specified group is unsubstituted or substituted by one or more substituents. It is to be understood that in the compounds of the present invention when a group is said to be “unsubstituted,” or is “substituted” with fewer groups than would fill the valencies of all the atoms in the compound, the remaining valencies on such a group are filled by hydrogen. For example, if a C_6 aryl group, also called “phenyl” herein, is substituted with one additional substituent, one of ordinary skill in the art would understand that such a group has 4 open positions left on carbon atoms of the C_6 aryl ring (6 initial positions, minus one to which the remainder of the compound of the present invention is bonded, minus an additional substituent, to leave 4). In such cases, the remaining 4 carbon atoms are each bound to one hydrogen atom to fill their valencies. Similarly, if a C_6 aryl group in the present compounds is said to be “disubstituted,” one of ordinary skill in the art would understand it to mean that the C_6 aryl has 3 carbon atoms remaining that are unsubstituted. Those three unsubstituted carbon atoms are each bound to one hydrogen atom to fill their valencies.

The term "solvate," as used herein, means a pharmaceutically acceptable solvate form of a compound of the present invention that retains the biological effectiveness of such compound. Examples of solvates include, but are not limited to, compounds of the invention in combination with water, isopropanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof. It is specifically contemplated that in the present invention one solvent molecule can be associated with one molecule of the compounds of the present invention, such as a hydrate. Furthermore, it is specifically contemplated that in the present invention, more than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a dihydrate. Additionally, it is specifically

contemplated that in the present invention less than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a hemihydrate. Furthermore, solvates of the present invention are contemplated as solvates of compounds of the present invention that retain the biological effectiveness of the non-hydrate form of the compounds.

The term "pharmaceutically acceptable salt," as used herein, means a salt of a compound of the present invention that retains the biological effectiveness of the free acids and bases of the specified derivative and that is not biologically or otherwise undesirable.

The term "pharmaceutically acceptable formulation," as used herein, means a combination of a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, and a carrier, diluent, and/or excipients that are compatible with a compound of the present invention, and is not deleterious to the recipient thereof. Pharmaceutical formulations can be prepared by procedures known to those of ordinary skill in the art. For example, the compounds of the present invention can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as povidone, sodium starch glycolate, sodium carboxymethylcellulose, agar, calcium carbonate, and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate and solid polyethylene glycols. Final pharmaceutical forms may be pills, tablets, powders, lozenges, saches, cachets, or sterile packaged powders, and the like, depending on the type of excipient used. Additionally, it is specifically contemplated that pharmaceutically acceptable formulations of the present invention can contain more than one active ingredient. For example, such formulations may contain more than one compound according to the present invention. Alternatively, such formulations may contain one or more compounds of the present invention and one or more additional anti-HIV agents.

The term "inhibiting HIV replication" means inhibiting human immunodeficiency virus (HIV) replication in a cell. Such a cell may be present *in vitro*, or it may be present *in vivo*, such as in a mammal, such as a human. Such inhibition may be accomplished by administering a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, to the cell, such as in a mammal, in an HIV-inhibiting amount. The quantification of inhibition of HIV replication in a cell, such as in a mammal, can be measured using methods known to those of ordinary skill in the art. For example, an amount of a compound of the invention may be administered to a mammal, either alone or as part of a pharmaceutically acceptable formulation.

Blood samples may then be withdrawn from the mammal and the amount of HIV virus in the sample may be quantified using methods known to those of ordinary skill in the art. A reduction in the amount of HIV virus in the sample compared to the amount found in the blood before administration of a compound of the invention would represent inhibition of the replication of HIV virus in the mammal. The administration of a compound of the invention to the cell, such as in a mammal, may be in the form of single dose or a series of doses. In the case of more than one dose, the doses may be administered in one day or they may be administered over more than one day.

An "HIV-inhibiting agent" means a compound of the present invention or a pharmaceutically acceptable salt or solvate thereof.

The term "anti-HIV agent," as used herein, means a compound or combination of compounds capable of inhibiting the replication of HIV in a cell, such as a cell in a mammal. Such compounds may inhibit the replication of HIV through any mechanism known to those of ordinary skill in the art.

The terms "human immunodeficiency virus-inhibiting amount" and "HIV-inhibiting amount," as used herein, refer to the amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, required to inhibit replication of the human immunodeficiency virus (HIV) *in vivo*, such as in a mammal, or *in vitro*. The amount of such compounds required to cause such inhibition can be determined without undue experimentation using methods described herein and those known to those of ordinary skill in the art.

The term "inhibiting HIV integrase enzyme activity," as used herein, means decreasing the activity or functioning of the HIV integrase enzyme either *in vitro* or *in vivo*, such as in a mammal, such as a human, by contacting the enzyme with a compound of the present invention.

The term, "HIV integrase enzyme-inhibiting amount," as used herein, refers to the amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, required to decrease the activity of the HIV integrase enzyme either *in vivo*, such as in a mammal, or *in vitro*. Such inhibition may take place by the compound of the present invention binding directly to the HIV integrase enzyme. In addition, the activity of the HIV integrase enzyme may be decreased in the presence of a compound of the present invention when such direct binding between the enzyme and the compound does not take place. Furthermore, such inhibition may be competitive, non-competitive, or uncompetitive. Such inhibition may be determined using *in vitro* or *in vivo* systems, or a combination of both, using methods known to those of ordinary skill in the art.

The term "therapeutically effective amount," as used herein, means an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, that, when administered to a mammal in need of such treatment, is sufficient to effect treatment, as defined herein. Thus, a therapeutically effective amount of a compound of the present invention,

or a pharmaceutically acceptable salt or solvate thereof, is a quantity sufficient to modulate or inhibit the activity of the HIV integrase enzyme such that a disease condition that is mediated by activity of the HIV integrase enzyme is reduced or alleviated.

The terms "treat", "treating", and "treatment" refer to any treatment of an HIV integrase mediated disease or condition in a mammal, particularly a human, and include: (i) preventing the disease or condition from occurring in a subject which may be predisposed to the condition, such that the treatment constitutes prophylactic treatment for the pathologic condition; (ii) modulating or inhibiting the disease or condition, i.e., arresting its development; (iii) relieving the disease or condition, i.e., causing regression of the disease or condition; or (iv) relieving and/or alleviating the disease or condition or the symptoms resulting from the disease or condition, e.g., relieving an inflammatory response without addressing the underlying disease or condition.

The terms "resistant," "resistance," and "resistant HIV," as used herein, refer to HIV virus demonstrating a reduction in sensitivity to a particular drug. A mammal infected with HIV that is resistant to a particular anti-HIV agent or combination of agents usually manifests an increase in HIV viral load despite continued administration of the agent or agents. Resistance may be either genotypic, meaning that a mutation in the HIV genetic make-up has occurred, or phenotypic, meaning that resistance is discovered by successfully growing laboratory cultures of HIV virus in the presence of an anti-HIV agent or a combination of such agents.

The terms "protease inhibitor" and "HIV protease inhibitor," as used herein, refer to compounds or combinations of compounds that interfere with the proper functioning of the HIV protease enzyme that is responsible for cleaving long strands of viral protein into the separate proteins making up the viral core.

The terms "reverse transcriptase inhibitor" and "HIV reverse transcriptase inhibitor," as used herein, refer to compounds or combinations of compounds that interfere with the proper functioning of the HIV reverse transcriptase enzyme that is responsible for converting single-stranded HIV viral RNA into HIV viral DNA.

The terms "fusion inhibitor" and "HIV fusion inhibitor," as used herein, refer to compounds or combinations of compounds that bind to the gp41 envelope protein on the surface of CD4 cells and thereby block the structural changes necessary for the virus to fuse with the cell.

The terms "integrase inhibitor" and "HIV integrase inhibitor," as used herein, refer to a compound or combination of compounds that interfere with the proper functioning of the HIV integrase enzyme that is responsible for inserting the genes of HIV into the DNA of a host cell.

The term "CCR5 antagonist," as used herein, refer to compounds or combinations of compounds that block the infection of certain cell types by HIV through the perturbation of CCR5 co-receptor activity.

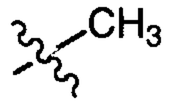
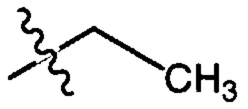
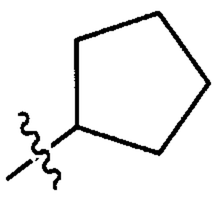
The terms "viral load" and "HIV viral load," as used herein, mean the amount of HIV in the circulating blood of a mammal, such as a human. The amount of HIV virus in the blood of

mammal can be determined by measuring the quantity of HIV RNA in the blood using methods known to those of ordinary skill in the art.

The term, "compound of the present invention" refers to any of the above-mentioned compounds, as well as those in the Examples that follow, and include those generically described or those described as species. The term also refers to pharmaceutically acceptable salts or solvates of these compounds.

Detailed Description

The compounds of the present invention are useful for modulating or inhibiting HIV integrase enzyme. More particularly, the compounds of the present invention are useful as modulators or inhibitors of HIV integrase activity, and thus are useful for the prevention and/or treatment of HIV mediated diseases or conditions (e.g., AIDS, and ARC), alone or in combination with other known antiviral agents.

In accordance with a convention used in the art, the symbol is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure. In accordance with another convention, in some structural formulae herein the carbon atoms and their bound hydrogen atoms are not explicitly depicted, e.g.,  represents a methyl group,  represents an ethyl group,  represents a cyclopentyl group, etc.

The compounds of the present invention may have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of the present invention may be depicted herein using a solid line (———), a solid wedge ( ), or a dotted wedge (). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of the invention may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of the invention and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present. Unless otherwise stated, all possible stereoisomers of the compounds of the present invention are meant to be included herein.

The term "stereoisomers" refers to compounds that have identical chemical constitution, but differ with regard to the arrangement of their atoms or groups in space. In particular, the term "enantiomers" refers to two stereoisomers of a compound that are non-superimposable mirror images of one another. The terms “racemic” or “racemic mixture,” as used herein, refer to a 1:1 mixture of enantiomers of a particular compound. The term "diastereomers", on the other hand, refers to the relationship between a pair of stereoisomers that comprise two or more asymmetric centers and are not mirror images of one another.

If a derivative used in the method of the invention is a base, a desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid; hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid; and the like, or with an organic acid, such as acetic acid; maleic acid; succinic acid; mandelic acid; fumaric acid; malonic acid; pyruvic acid; oxalic acid; glycolic acid; salicylic acid; pyranosidyl acid, such as glucuronic acid or galacturonic acid; alpha-hydroxy acid, such as citric acid or tartaric acid; amino acid, such as aspartic acid or glutamic acid; aromatic acid, such as benzoic acid or cinnamic acid; sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid; and the like.

If a derivative used in the method of the invention is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine; ammonia; primary, secondary, and tertiary amines; and cyclic amines, such as piperidine, morpholine, and piperazine; as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include, but are not limited to, compounds of the invention in combination with water, isopropanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof.

A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified derivative, containing pharmacologically acceptable anions, and is not biologically or otherwise undesirable. Examples of pharmaceutically acceptable salts include, but are not limited to, acetate, acrylate, benzenesulfonate, benzoate (such as chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, and methoxybenzoate), bicarbonate, bisulfate, bisulfite, bitartrate, borate, bromide, butyne-1,4-dioate, calcium edetate, camsylate, carbonate, chloride, caproate, caprylate, clavulanate, citrate, decanoate, dihydrochloride, dihydrogenphosphate, edetate, edislyate,

estolate, esylate, ethylsuccinate, formate, fumarate, gluceptate, gluconate, glutamate, glycollate, glycollylarsanilate, heptanoate, hexyne-1,6-dioate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, γ-hydroxybutyrate, iodide, isobutyrate, isothionate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, mesylate, metaphosphate, methane-sulfonate, methylsulfate, monohydrogenphosphate, mucate, napsylate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phenylacetates, phenylbutyrate, phenylpropionate, phthalate, phospate/diphosphate, polygalacturonate, propanesulfonate, propionate, propiolate, pyrophosphate, pyrosulfate, salicylate, stearate, subacetate, suberate, succinate, sulfate, sulfonate, sulfite, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention can be prepared by treating the base compound with a substantially equivalent amount of the selected mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding an appropriate mineral or organic acid to the solution.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of

reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

If the inventive compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

The compounds of the present invention may be formulated into pharmaceutical compositions as described below in any pharmaceutical form recognizable to the skilled artisan as being suitable. Pharmaceutical compositions of the invention comprise a therapeutically effective amount of at least one compound of the present invention and an inert, pharmaceutically acceptable carrier or diluent.

To treat or prevent diseases or conditions mediated by HIV, a pharmaceutical composition of the invention is administered in a suitable formulation prepared by combining a therapeutically effective amount (i.e., an HIV Integrase modulating, regulating, or inhibiting amount effective to achieve therapeutic efficacy) of at least one compound of the present invention (as an active ingredient) with one or more pharmaceutically suitable carriers, which may be selected, for example, from diluents, excipients and auxiliaries that facilitate processing of the active compounds into the final pharmaceutical preparations.

The pharmaceutical carriers employed may be either solid or liquid. Exemplary solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary liquid carriers are syrup, peanut oil, olive oil, water and the like.

Similarly, the inventive compositions may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate or the like. Further additives or excipients may be added to achieve the desired formulation properties. For example, a bioavailability enhancer, such as Labrasol, Gelucire or the like, or formulator, such as CMC (carboxy-methylcellulose), PG (propyleneglycol), or PEG (polyethyleneglycol), may be added. Gelucire®, a semi-solid vehicle that protects active ingredients from light, moisture and oxidation, may be added, e.g., when preparing a capsule formulation.

If a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form, or formed into a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension. If a semi-solid carrier is used, the preparation may be in the form of hard and soft gelatin capsule formulations. The inventive compositions are prepared in unit-dosage form appropriate for the mode of administration, e.g., parenteral or oral administration.

To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of a compound of the present invention may be dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3 M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents. Examples of suitable cosolvents include alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0-60% of the total volume. In an exemplary embodiment, a compound of Formula I is dissolved in DMSO and diluted with water. The composition may also be in the form of a solution of a salt form of the active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

Proper formulation is dependent upon the route of administration selected. For injection, the agents of the compounds of the present invention may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as crosslinked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active agents.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration intranasally or by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator and the like may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles

include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of the present invention may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD: 5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. The proportions of a co-solvent system may be suitably varied without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity due to the toxic nature of DMSO. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. These carriers and excipients may provide marked improvement in the bioavailability of poorly soluble drugs. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Furthermore, additives or excipients such as Gelucire®, Capryol®, Labrafil®, Labrasol®, Lauroglycol®, Plurol®, Peceol® Transcutol® and the like may be used. Further, the pharmaceutical composition may be incorporated into a skin patch for delivery of the drug directly onto the skin.

It will be appreciated that the actual dosages of the agents of this invention will vary according to the particular agent being used, the particular composition formulated, the mode of administration, and the particular site, host, and disease being treated. Those skilled in the art using conventional dosage-determination tests in view of the experimental data for a given compound may ascertain optimal dosages for a given set of conditions. For oral administration, an exemplary daily dose generally employed will be from about 0.001 to about 1000 mg/kg of body weight, with courses of treatment repeated at appropriate intervals.

Furthermore, the pharmaceutically acceptable formulations of the present invention may contain a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, in an amount of about 10 mg to about 2000 mg, or from about 10 mg to about 1500 mg, or from about 10 mg to about 1000 mg, or from about 10 mg to about 750 mg, or from about 10 mg to about 500 mg, or from about 25 mg to about 500 mg, or from about 50 to about 500 mg, or from about 100 mg to about 500mg.

Additionally, the pharmaceutically acceptable formulations of the present invention may contain a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, in an amount from about 0.5 w/w% to about 95 w/w%, or from about 1 w/w% to about 95 w/w%, or from about 1 w/w% to about 75 w/w%, or from about 5 w/w% to about 75 w/w%, or from about 10 w/w% to about 75 w/w%, or from about 10 w/w% to about 50 w/w%.

The compounds of the present invention, or a pharmaceutically acceptable salt or solvate thereof, may be administered to a mammal suffering from infection with HIV, such as a human, either alone or as part of a pharmaceutically acceptable formulation, once a day, twice a day, or three times a day.

Those of ordinary skill in the art will understand that with respect to the compounds of the present invention, the particular pharmaceutical formulation, the dosage, and the number of doses given per day to a mammal requiring such treatment, are all choices within the knowledge of one of ordinary skill in the art and can be determined without undue experimentation. For example, see "Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents," United States Department of Health and Human Services, available at http://www.aidsinfo.nih.gov/guidelines/ as of October 29, 2004.

The compounds of the present invention may be administered in combination with an additional agent or agents for the treatment of a mammal, such as a human, that is suffering from an infection with the HIV virus, AIDS, AIDS-related complex (ARC), or any other disease or condition which is related to infection with the HIV virus. The agents that may be used in combination with the compounds of the present invention include, but are not limited to, those useful as HIV protease inhibitors, HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, inhibitors of HIV integrase, CCR5 inhibitors, HIV fusion inhibitors, compounds useful as immunomodulators, compounds that inhibit the HIV virus by an unknown mechanism, compounds useful for the treatment of herpes viruses, compounds useful as anti-infectives, and others as described below.

Compounds useful as HIV protease inhibitors that may be used in combination with the compounds of the present invention include, but are not limited to, 141 W94 (amprenavir), CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir (invirase), lopinavir, TMC-126, atazanavir, palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, TMC-114, DPC-681, DPC-684, fosamprenavir calcium (Lexiva), benzenesulfonamide derivatives disclosed in WO 03053435, R-944, Ro-03-34649, VX-385, GS-224338, OPT-TL3, PL-100, SM-309515, AG-148, DG-35-VIII, DMP-850, GW-5950X, KNI-1039, L-756423, LB-71262, LP-130, RS-344, SE-063, UIC-94-003, Vb-19038, A-77003, BMS-182193, BMS-186318, SM-309515, JE-2147, GS-9005.

Compounds useful as inhibitors of the HIV reverse transcriptase enzyme that may be used in combination with the compounds of the present invention include, but are not limited to, abacavir, FTC, GS-840, lamivudine, adefovir dipivoxil, beta-fluoro-ddA, zalcitabine, didanosine, stavudine, zidovudine, tenofovir, amdoxovir, SPD-754, SPD-756, racivir, reverset (DPC-817), MIV-210 (FLG), beta-L-Fd4C (ACH-126443), MIV-310 (alovudine, FLT), dOTC, DAPD, entecavir, GS-7340, emtricitabine, alovudine,

Compounds useful as non-nucleoside inhibitors of the HIV reverse transcriptase enzyme that may be used in combination with the compounds of the present invention include, but are not limited to, efavirenz, HBY-097, nevirapine, TMC-120 (dapivirine), TMC-125, etravirine, delavirdine, DPC-083, DPC-961, TMC-120, capravirine, GW-678248, GW-695634, calanolide, and tricyclic pyrimidinone derivatives as disclosed in WO 03062238.

Compounds useful as CCR5 inhibitors that may be used in combination with the compounds of the present invention include, but are not limited to, TAK-779, SC-351125, SCH-D, UK-427857, PRO-140, and GW-873140 (Ono-4128, AK-602).

Compounds useful as inhibitors of HIV integrase enzyme that may be used in combination with the compounds of the present invention include, but are not limited to, GW-810781, 1,5-naphthyridine-3-carboxamide derivatives disclosed in WO 03062204, compounds

disclosed in WO 03047564, compounds disclosed in WO 03049690, 5-hydroxypyrimidine-4-carboxamide derivatives disclosed in WO 03035076, and L-000810810.

Fusion inhibitors for the treatment of HIV that may be used in combination with the compounds of the present invention include, but are not limited to enfuvirtide (T-20), T-1249, AMD-3100, and fused tricyclic compounds disclosed in JP 2003171381.

Other compounds that are useful inhibitors of HIV that may be used in combination with the compounds of the present invention include, but are not limited to, Soluble CD4, TNX-355, PRO-542, BMS-806, tenofovir disoproxil fumarate, and compounds disclosed in JP 2003119137.

Compounds useful in the treatment or management of infection from viruses other than HIV that may be used in combination with the compounds of the present invention include, but are not limited to, acyclovir, fomivirsen, penciclovir, HPMPC, oxetanocin G, AL-721, cidofovir, cytomegalovirus immune globin, cytovene, fomivganciclovir, famciclovir, foscarnet sodium, Isis 2922, KNI-272, valacyclovir, virazole ribavirin, valganciclovir, ME-609, PCL-016

Compounds that act as immunomodulators and may be used in combination with the compounds of the present invention include, but are not limited to, AD-439, AD-519, Alpha Interferon, AS-101, bropirimine, acemannan, CL246,738, EL10, FP-21399, gamma interferon, granulocyte macrophage colony stimulating factor, IL-2, immune globulin intravenous, IMREG-1, IMREG-2, imuthiol diethyl dithio carbamate, alpha-2 interferon, methionine-enkephalin, MTP-PE, granulocyte colony stimulating sactor, remune, rCD4, recombinant soluble human CD4, interferon alfa-2, SK&F106528, soluble T4 yhymopentin, tumor necrosis factor (TNF), tucaresol, recombinant human interferon beta, and interferon alfa n-3.

Anti-infectives that may be used in combination with the compounds of the present invention include, but are not limited to, atovaquone, azithromycin, clarithromycin, trimethoprim, trovafloxacin, pyrimethamine, daunorubicin, clindamycin with primaquine, fluconazole, pastill, ornidyl, eflornithine pentamidine, rifabutin, spiramycin, intraconazole-R51211, trimetrexate, daunorubicin, recombinant human erythropoietin, recombinant human growth hormone, megestrol acetate, testerone, and total enteral nutrition.

Antifungals that may be used in combination with the compounds of the present invention include, but are not limited to, anidulafungin, C31G, caspofungin, DB-289, fluconzaole, itraconazole, ketoconazole, micafungin, posaconazole, and voriconazole.

Other compounds that may be used in combination with the compounds of the present invention include, but are not limited to, acmannan, ansamycin, LM 427, AR177, BMS-232623, BMS-234475, CI-1012, curdlan sulfate, dextran sulfate, STOCRINE EL10, hypericin, lobucavir, novapren, peptide T octabpeptide sequence, trisodium phosphonoformate, probucol, and RBC-CD4.

In addition, the compounds of the present invention may be used in combination with anti-proliferative agents for the treatment of conditions such as Kaposi's sarcoma. Such agents

include, but are not limited to, inhibitors of metallo-matrix proteases, A-007, bevacizumab, BMS-275291, halofuginone, interleukin-12, rituximab, paclitaxel, porfimer sodium, rebimastat, and COL-3.

The particular choice of an additional agent or agents will depend on a number of factors that include, but are not limited to, the condition of the mammal being treated, the particular condition or conditions being treated, the identity of the compound or compounds of the present invention and the additional agent or agents, and the identity of any additional compounds that are being used to treat the mammal. The particular choice of the compound or compounds of the invention and the additional agent or agents is within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

The compounds of the present invention may be administered in combination with any of the above additional agents for the treatment of a mammal, such as a human, that is suffering from an infection with the HIV virus, AIDS, AIDS-related complex (ARC), or any other disease or condition which is related to infection with the HIV virus. Such a combination may be administered to a mammal such that a compound or compounds of the present invention are present in the same formulation as the additional agents described above. Alternatively, such a combination may be administered to a mammal suffering from infection with the HIV virus such that the compound or compounds of the present invention are present in a formulation that is separate from the formulation in which the additional agent is found. If the compound or compounds of the present invention are administered separately from the additional agent, such administration may take place concomitantly or sequentially with an appropriate period of time in between. The choice of whether to include the compound or compounds of the present invention in the same formulation as the additional agent or agents is within the knowledge of one of ordinary skill in the art.

Additionally, the compounds of the present invention may be administered to a mammal, such as a human, in combination with an additional agent that has the effect of increasing the exposure of the mammal to a compound of the invention. The term "exposure," as used herein, refers to the concentration of a compound of the invention in the plasma of a mammal as measured over a period of time. The exposure of a mammal to a particular compound can be measured by administering a compound of the invention to a mammal in an appropriate form, withdrawing plasma samples at predetermined times, and measuring the amount of a compound of the invention in the plasma using an appropriate analytical technique, such as liquid chromatography or liquid chromatography/mass spectroscopy. The amount of a compound of the invention present in the plasma at a certain time is determined and the concentration and time data from all the samples are plotted to afford a curve. The area under this curve is calculated and affords the exposure of the mammal to the compound. The terms "exposure," "area under

the curve," and "area under the concentration/time curve" are intended to have the same meaning and may be used interchangeably throughout.

Among the agents that may be used to increase the exposure of a mammal to a compound of the present invention are those that can as inhibitors of at least one isoform of the cytochrome P450 (CYP450) enzymes. The isoforms of CYP450 that may be beneficially inhibited include, but are not limited to, CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4. Suitable agents that may be used to inhibit CYP 3A4 include, but are not limited to, ritonavir and delavirdine.

Such a combination may be administered to a mammal such that a compound or compounds of the present invention are present in the same formulation as the additional agents described above. Alternatively, such a combination may be administered such that the compound or compounds of the present invention are present in a formulation that is separate from the formulation in which the additional agent is found. If the compound or compounds of the present invention are administered separately from the additional agent, such administration may take place concomitantly or sequentially with an appropriate period of time in between. The choice of whether to include the compound or compounds of the present invention in the same formulation as the additional agent or agents is within the knowledge of one of ordinary skill in the art.

Several different assay formats are available to measure integrase-mediated integration of viral DNA into target (or host) DNA and thus, identify compounds that modulate (e.g., inhibit) integrase activity. In general, for example, ligand-binding assays may be used to determine interaction with an enzyme of interest. When binding is of interest, a labeled enzyme may be used, wherein the label is a fluorescer, radioisotope, or the like, which registers a quantifiable change upon binding to the enzyme. Alternatively, the skilled artisan may employ an antibody for binding to the enzyme, wherein the antibody is labeled allowing for amplification of the signal. Thus, binding may be determined through direct measurement of ligand binding to an enzyme. In addition, binding may be determined by competitive displacement of a ligand bound to an enzyme, wherein the ligand is labeled with a detectable label. When inhibitory activity is of interest, an intact organism or cell may be studied, and the change in an organismic or cellular function in response to the binding of the inhibitory compound may be measured. Alternatively, cellular response can be determined microscopically by monitoring viral induced syncytium-formation (HIV-1 syncytium-formation assays), for example. Thus, there are various *in vitro* and *in vivo* assays useful for measuring HIV integrase inhibitory activity. *See, e.g.,* Lewin, S.R. *et al., Journal of Virology 73(7):* 6099-6103 (July 1999); Hansen, M.S. *et al., Nature Biotechnology 17(6):* 578-582 (June 1999); and Butler, S.L. et al., *Nature Medicine 7(5):* 631-634 (May 2001).

Exemplary specific assay formats used to measure integrase-mediated integration include, but are not limited to, ELISA, DELFIA® (PerkinElmer Life Sciences Inc. (Boston, MA))

and ORIGEN® (IGEN International, Inc. (Gaithersburg, MD)) technologies. In addition, gel-based integration (detecting integration by measuring product formation with SDS-PAGE) and scintillation proximity assay (SPA) disintegration assays that use a single unit of double stranded-DNA (ds-DNA) may be used to monitor integrase activity.

In one embodiment of the invention, the preferred assay is an integrase strand-transfer SPA (stINTSPA) which uses SPA to specifically measure the strand-transfer mechanism of integrase in a homogenous assay scalable for miniaturization to allow high-throughput screening. The assay focuses on strand transfer and not on DNA binding and/or 3' processing. This sensitive and reproducible assay is capable of distinguishing non-specific interactions from true enzymatic function by forming 3' processed viral DNA/integrase complexes before the addition of target DNA. Such a formation creates a bias toward compound modulators (e.g., inhibitors) of strand-transfer and not toward compounds that inhibit integrase 3' processing or prevent the association of integrase with viral DNA. This bias renders the assay more specific than known assays. In addition, the homogenous nature of the assay reduces the number of steps required to run the assay since the wash steps of a heterogenous assay are not required.

The integrase strand-transfer SPA format consists of 2 DNA components that model viral DNA and target DNA. The model viral DNA (also known as donor DNA) is biotinylated ds-DNA preprocessed at the 3' end to provide a CA nucleotide base overhang at the 5' end of the duplex. The target DNA (also known as host DNA) is a random nucleotide sequence of ds-DNA generally containing [^{3}H]-thymidine nucleotides on both strands, preferably, at the 3' ends, to enable detection of the integrase strand-transfer reaction that occurs on both strands of target ds-DNA.

Integrase (created recombinantly or synthetically and preferably, purified) is pre-complexed to the viral DNA bound to a surface, such as for example, streptavidin-coated SPA beads. Generally, the integrase is pre-complexed in a batch process by combining and incubating diluted viral DNA with integrase and then removing unbound integrase. The preferred molar ratio of viral DNA:integrase is about 1:about 5. The integrase/viral DNA incubation is optional, however, the incubation does provide for an increased specificity index with an integrase/viral DNA incubation time of about 15 to about 30 minutes at room temperature or at about 37°C. The preferred incubation is at about room temperature for about 15 minutes.

The reaction is initiated by adding target DNA, in the absence or presence of a potential integrase modulator compound, to the integrase/viral DNA beads (for example) and allowed to run for about 20 to about 50 minutes (depending on the type of assay container employed), at about room temperature or about 37°C, preferably, at about 37°C. The assay is terminated by adding stop buffer to the integrase reaction mixture. Components of the stop buffer, added sequentially or at one time, function to terminate enzymatic activity, dissociate integrase/DNA complexes, separate non-integrated DNA strands (denaturation agent), and, optionally, float the SPA beads to the surface of the reaction mixture to be closer in range to the detectors of, for

example, a plate-based scintillation counter, to measure the level of integrated viral DNA which is quantified as light emitted (radiolabeled signal) from the SPA beads. The inclusion of an additional component in the stop buffer, such as for example CsCl or functionally equivalent compound, is optionally, and preferably, used with a plate-based scintillation counter, for example, with detectors positioned above the assay wells, such as for example a TopCount® counter (PerkinElmer Life Sciences Inc. (Boston, MA)). CsCl would not be employed when PMT readings are taken from the bottom of the plate, such as for example when a MicroBeta® counter (PerkinElmer Life Sciences Inc. (Boston, MA)) is used.

The specificity of the reaction can be determined from the ratio of the signal generated from the target DNA reaction with the viral DNA/integrase compared to the signal generated from the di-deoxy viral DNA/integrase. High concentrations (e.g., $\geq$ 50 nM) of target DNA may increase the d/dd DNA ratio along with an increased concentration of integrase in the integrase/viral DNA sample.

The results can be used to evaluate the integrase modulatory, such as for example inhibitory, activity of test compounds. For example, the skilled artisan may employ a high-throughput screening method to test combinatorial compound libraries or synthetic compounds. The percent inhibition of the compound may be calculated using an equation such as for example (1-((CPM sample – CPM *min*)/(CPM *max* – CPM *min*)))*100. The *min* value is the assay signal in the presence of a known modulator, such as for example an inhibitor, at a concentration about 100-fold higher than the IC_{50} for that compound. The *min* signal approximates the true background for the assay. The *max* value is the assay signal obtained for the integrase-mediated activity in the absence of compound. In addition, the IC_{50} values of synthetic and purified combinatorial compounds may be determined whereby compounds are prepared at about 10 or 100-fold higher concentrations than desired for testing in assays, followed by dilution of the compounds to generate an 8-point titration curve with ½-log dilution intervals, for example. The compound sample is then transferred to an assay well, for example. Further dilutions, such as for example, a 10-fold dilution, are optional. The percentage inhibition for an inhibitory compound, for example, may then be determined as above with values applied to a nonlinear regression, sigmoidal dose response equation (variable slope) using GraphPad Prism curve fitting software (GraphPad Software, Inc., San Diego, CA) or functionally equivalent software.

The stINTSPA assay conditions are preferably optimized for ratios of integrase, viral DNA and target DNA to generate a large and specific assay signal. A specific assay signal is defined as a signal distinguishing true strand-transfer catalytic events from complex formation of integrase and DNA that does not yield product. In other integrase assays, a large non-specific component (background) often contributes to the total assay signal unless the buffer conditions are rigorously optimized and counter-tested using a modified viral DNA oligonucleotide. The non-

specific background is due to formation of integrase/viral DNA/target DNA complexes that are highly stable independent of a productive strand-transfer mechanism.

The preferred stINTSPA distinguishes complex formation from productive strand-transfer reactions by using a modified viral DNA oligonucleotide containing a di-deoxy nucleoside at the 3' end as a control. This modified control DNA can be incorporated into integrase/viral DNA/target DNA complexes, but cannot serve as a substrate for strand-transfer. Thus, a distinct window between productive and non-productive strand-transfer reactions can be observed. Further, reactions with di-deoxy viral DNA beads give an assay signal closely matched to the true background of the assay using the preferred optimization conditions of the assay. The true background of the assay is defined as a reaction with all assay components (viral DNA and [^{3}H]-target DNA) in the absence of integrase.

Assay buffers used in the integrase assay generally contain at least one reducing agent, such as for example 2-mercaptoethanol or DTT, wherein DTT as a fresh powder is preferred; at least one divalent cation, such as for example Mg^{++}, Mn^{++}, or Zn^{++}, preferably, Mg^{++}; at least one emulsifier/dispersing agent, such as for example octoxynol (also known as IGEPAL-CA or NP-40) or CHAPS; NaCl or functionally equivalent compound; DMSO or functionally equivalent compound; and at least one buffer, such as for example MOPS. Key buffer characteristics are the absence of PEG; inclusion of a high concentration of a detergent, such as for example about 1 to about 5 mM CHAPS and/or about 0.02 to about 0.15% IGEPAL-CA or functionally equivalent compound(s) at least capable of reducing non-specific sticking to the SPA beads and assay wells and, possibly, enhancing the specificity index; inclusion of a high concentration of DMSO (about 1 to about 12%); and inclusion of modest levels of NaCl ($\leq$ 50 mM) and $MgCl_2$ (about 3 to about 10 mM) or functionally equivalent compounds capable of reducing the dd-DNA background. The assay buffers may optionally contain a preservative, such as for example NaN_3, to reduce fungal and bacterial contaminants during storage.

The stop buffer preferably contains EDTA or functionally equivalent compound capable of terminating enzymatic activity, a denaturation agent comprising, for example, NaOH or guanidine hydrochloride, and, optionally, CsCl or functionally equivalent compound capable of assisting in floating the SPA beads to the top of the assay container for scintillation detection at the top of the reservoir and, possibly, minimizing compound interference. An example of an integrase strand-transfer SPA is set forth in Example 13.

Alternatively, the level of activity of the modulatory compounds may be determined in an antiviral assay, such as for example an assay that quantitatively measures the production of viral antigens (e.g., HIV-1 p24) or the activities of viral enzymes (e.g., HIV-1 reverse transcriptase) as indicators of virus replication, or that measures viral replication by monitoring the expression of an exogenous reporter gene introduced into the viral genome (HIV-1 reporter virus assays) (Chen, B.K. et al., *J. Virol. 68(2):* 654-660 (1994); Terwilliger, E.F. et al., *PNAS 86:*3857-3861

(1989)). A preferred method of measuring antiviral activity of a potential modulator compound employs an HIV-1 cell protection assay, wherein virus replication is measured indirectly by monitoring viral induced host-cell cytopathic effects using, for example, dye reduction methods as set forth in Example 14.

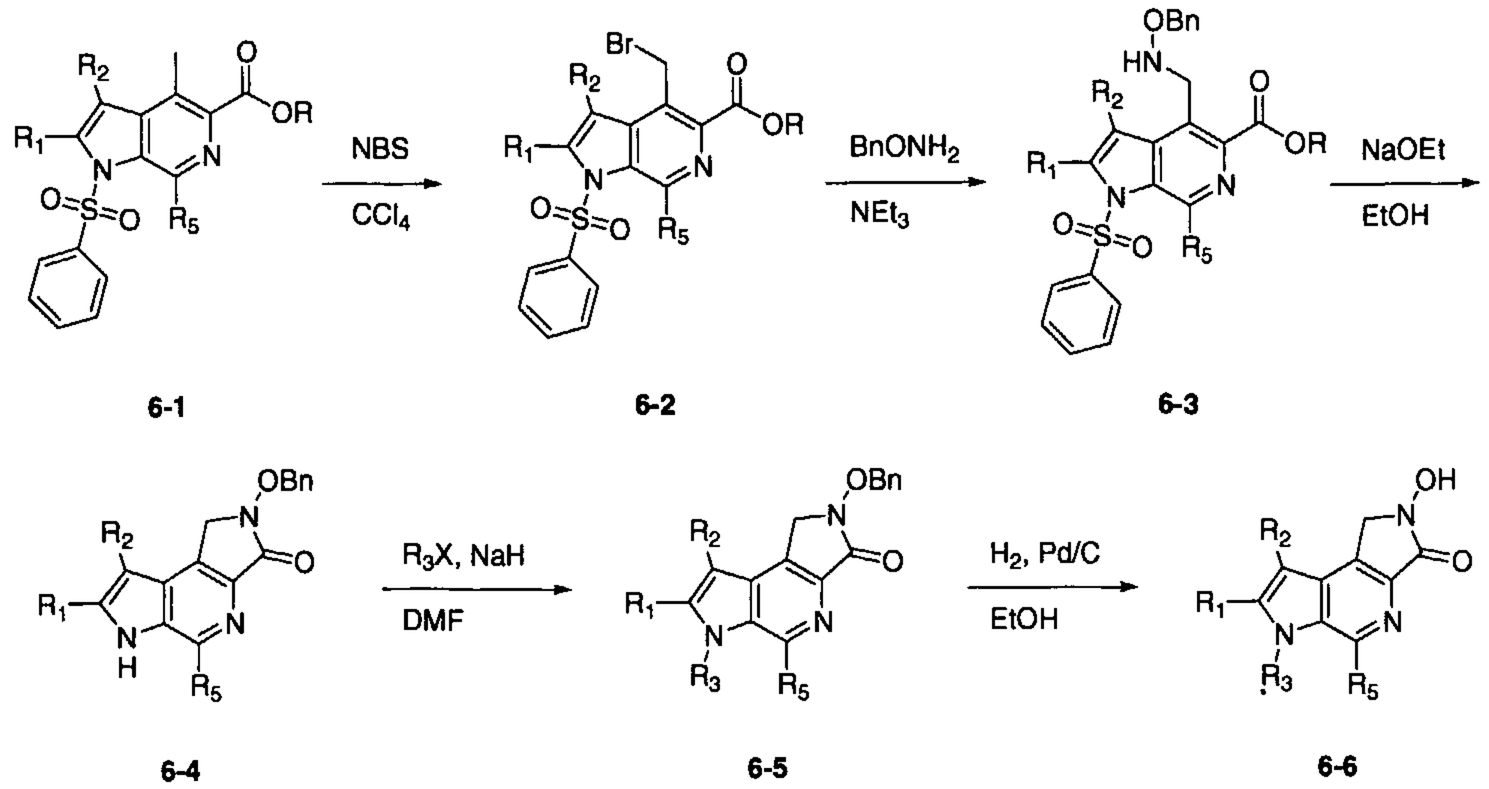
In one embodiment, the compounds of the present invention include those having an EC_{50} value against HIV integrase of at least 10^{-5} M (or at least 10 μM) when measured with an HIV cell protection assay. In another embodiment are compounds of the present invention with an EC_{50} value against HIV integrase of at least 1 μM when measured with an HIV cell protection assay. In yet another embodiment, the compounds of the present invention have an EC_{50} against HIV integrase of at least 0.1 μM when measured with an HIV cell protection assay.

The inventive agents may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available. The preparation of certain embodiments of the present invention is described in detail in the following examples, but those of ordinary skill in the art will recognize that the preparations described may be readily adapted to prepare other embodiments of the present invention. For example, the synthesis of non-exemplified compounds according to the invention may be performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having adaptability for preparing other compounds of the invention.

Methods of Preparation

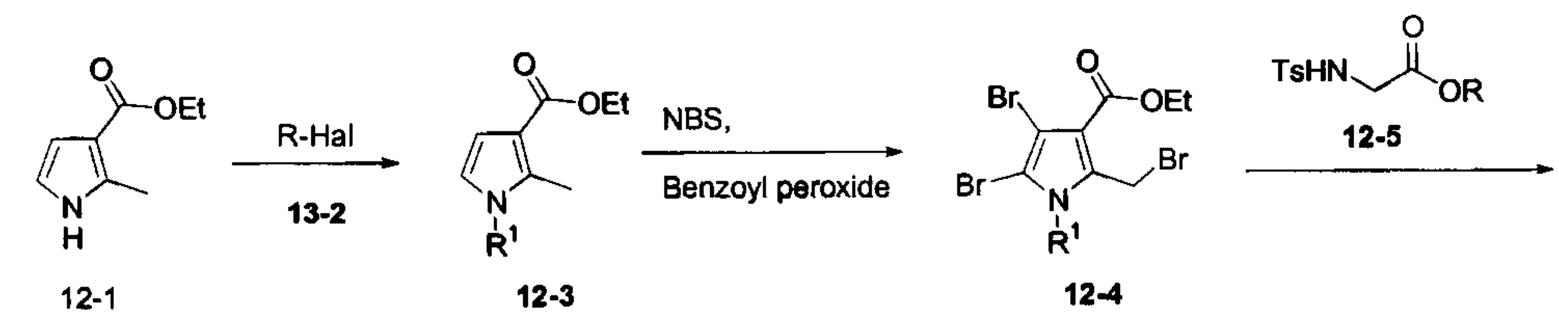
Scheme 1 depicts a method for formation of N-hydroxy lactam 6-5. Radical bromination of a methyl substituted indole 6-1 can be achieved by various reagents (Jerry March, Advanced Organic Chemistry, 5th edition, John Whiley & Sons, 2001, p. 911 – 914) the most common being N-bromosuccinimide (NBS). It will be apparent to those skilled in the arts that successful execution of this reaction can depend highly on the substitution pattern of the precursor 6-1. Reaction of an alkylhalide 6-2 (X. Doisy et al., *Bioorg. Med. Chem.* 1999, *7*, 921 – 932) with benzyl hydroxylamine in a presence of a base such as triethylamine can provide compound 6-3. Treatment with sodium ethoxide in ethanol can result in lactame formation and cleavage of the phenylsulfonyl protecting group. Alkylation of 6-4 with an alkylhalide in the presence of a base such as sodium hydride in DMF similar to the methods described in scheme 2 can provide N-benzyloxy lactame 6-5. The benzyl protecting group can be removed using various methods (T.W. Greene, Protective groups in Organic Chemistry, 3rd edition, John Wiley & Sons, 1999, p. 76 - 86) such palladium catalysed hydrogenation. As is obvious to those skilled in the art, different protecting groups instead of the benzyl group might be used to form the final product 6-6.

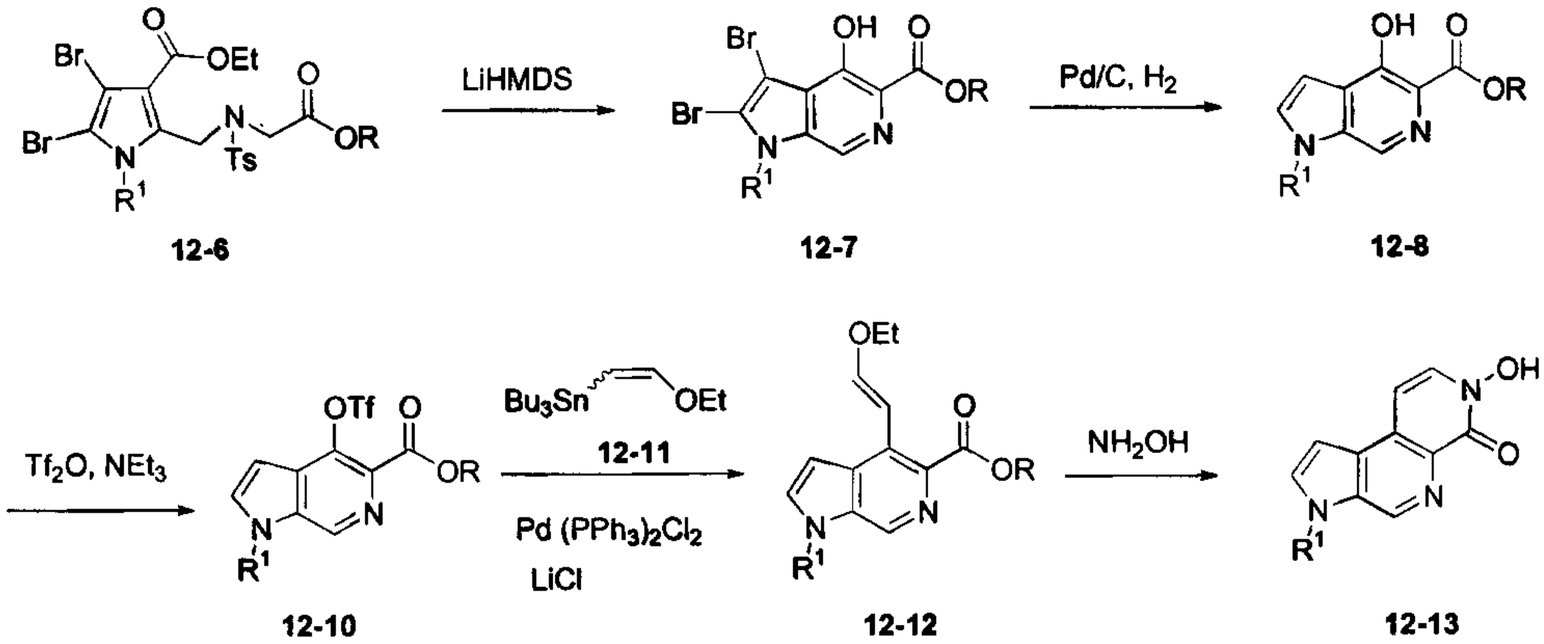
Scheme 1



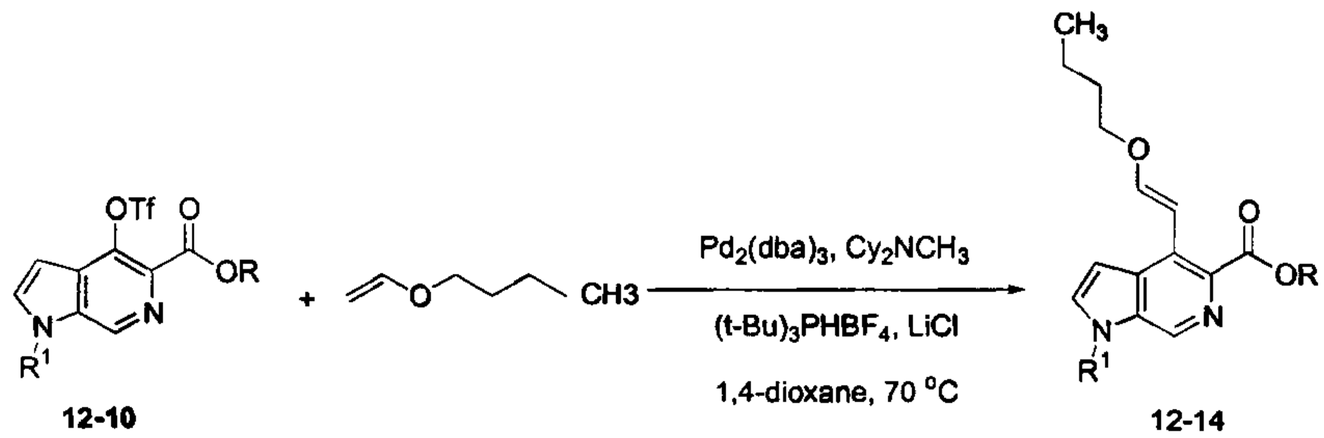
Scheme 2 depicts the synthesis of a 4-substituted azaindole 12-12. Ethyl 2-methyl-1H-pyrrole-3-carboxylate 12-1 (Wee, A.G.H.; Shu, A.Y.L.; Djerassi, C. *J. Org. Chem.* 1984, *49*, 3327-3336) can be treated with an organo halide in the presence of a base such as NaH to provide pyrrole 12-3. Bromination using a bromine source such as NBS followed by radical bromination after the addition of a radical initiator such as benzoyl peroxide can give compound 12-4 which can react with a tosyl glycine ester 12-5 (Ginzel K. D., Brungs, P.; Steckan, E. *Tetrahedron*, 1989, *45*, 1691-1701) to provide 12-6. Cyclization of 12-6 to 12-7 can be effected upon treatment with a base such as lithium hexamethyl disilazide. Catalytic hydrogenolysis (with e. g. Pd/C) can provide ester 12-8. Treatment of 12-8 with an organo halide and a base such as NaH can give 12-9. The hydroxy group in 12-8 can be converted to the triflate 12-10 using trifluoromethanesulfonic anhydride and a base such as triethyl amine. Triflate 12-10 can undergo palladium catalyzed couplings such as the Stille coupling with tributylstannylethene 12-11 in the presence of LiCl (J. K. Stille, *Angew. Chem.* 1986, *98*, 504; *Angew. Chem. Int. Ed. Engl.* 1986, *25*, 508; W. J. Scott, J. K. Stille, *J. Am. Chem. Soc.* 1986, *108*, 3033; C. Amatore, A. Jutand, and A. Suarez *J. Am. Chem. Soc.* 1993, *115*, 9531-9541) using a catalyst such $Pd(PPh_3)_2Cl_2$ (T. Sakamoto, C. Satoh, Y. Kondo, H. Yamanaka, *Chem. Pharm. Bull.* 1993, *41*, 81-86), to provide 12-12 which can be teated with hydroxylamine to form 12-13.

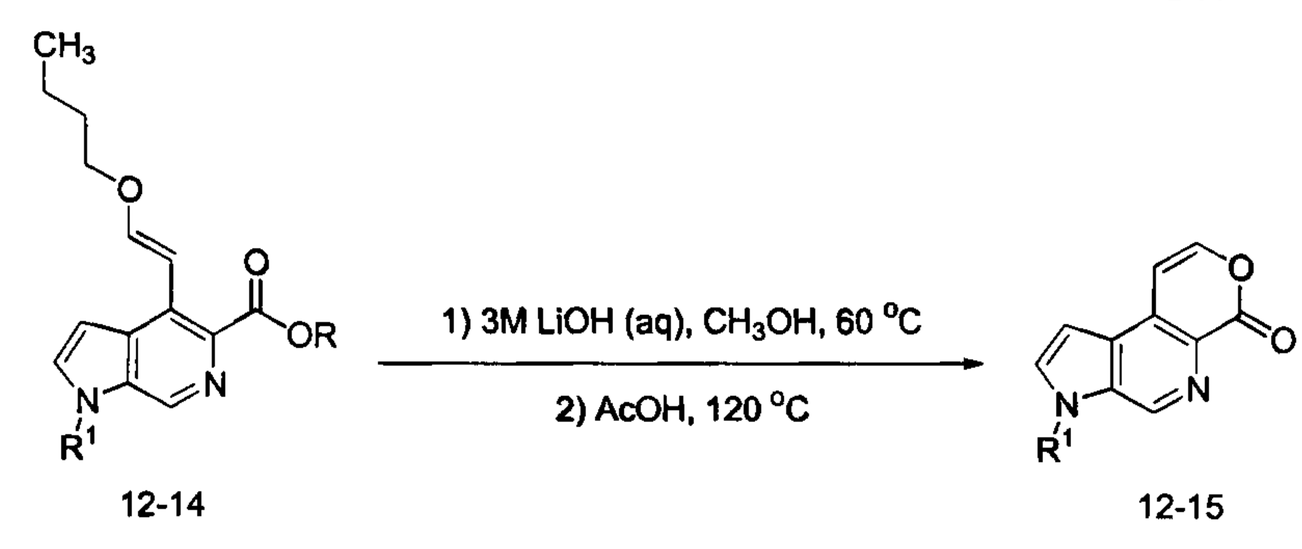
Scheme 2





Alternatively, compound 12-10 may be allowed to react with n-butyl vinyl ether in the presence of a palladium catalyst, a base, a phosphine, and lithium chloride, in a solvent at a temperature of about 70 °C, to provide compound 12-14. Compound 12-14 can then be allowed to react with a base, such as lithium hydroxide, and in the presence of a solvent, such as methanol, at about 60 °C, followed by reaction with acetic acid at a temperature of about 120 °C to provide compound 12-15.

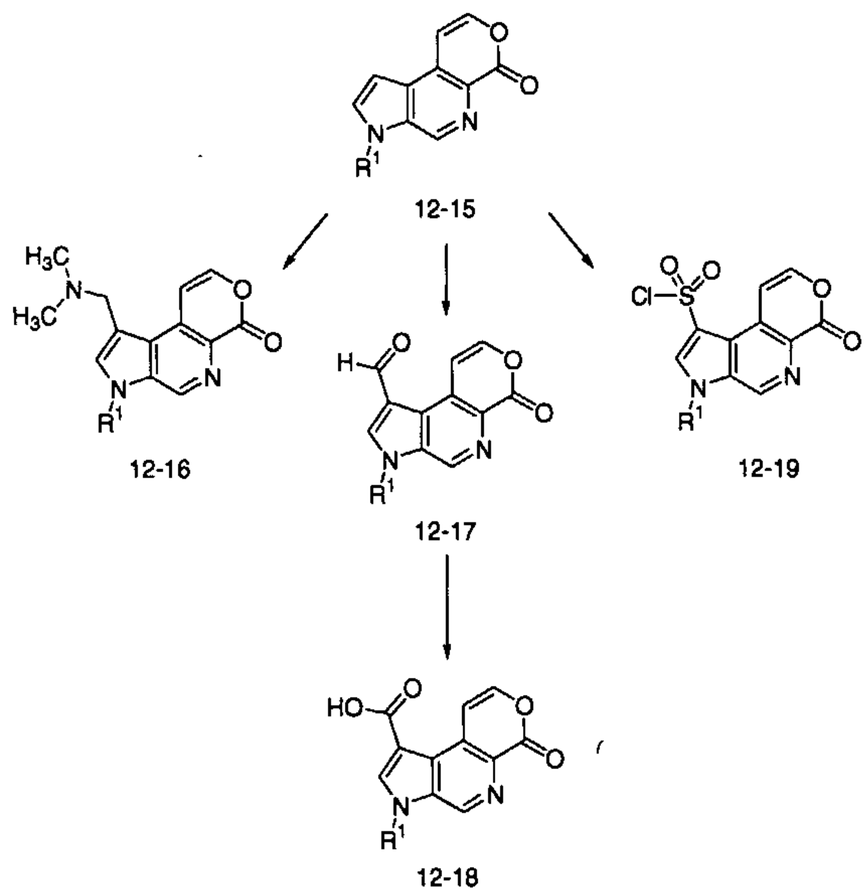




As shown in Scheme 2a below, compound 12-15 can be further functionalized at the 3-position to provide, for example, gramine derivatives (12-16), aldehyde derivatives (12-17), carboxylic acid derivatives (12-18), and sulfonyl chloride derivatives (12-19). Each of compounds

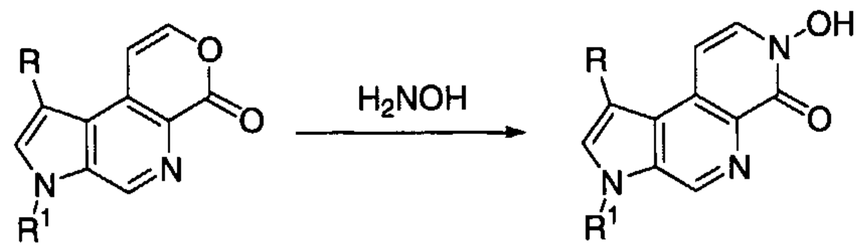
12-16, 12-17, 12-18, and 12-19 can then be further functionalized to provide additional intermediate compounds that can be further converted to compounds of formula (I).

Scheme 2a



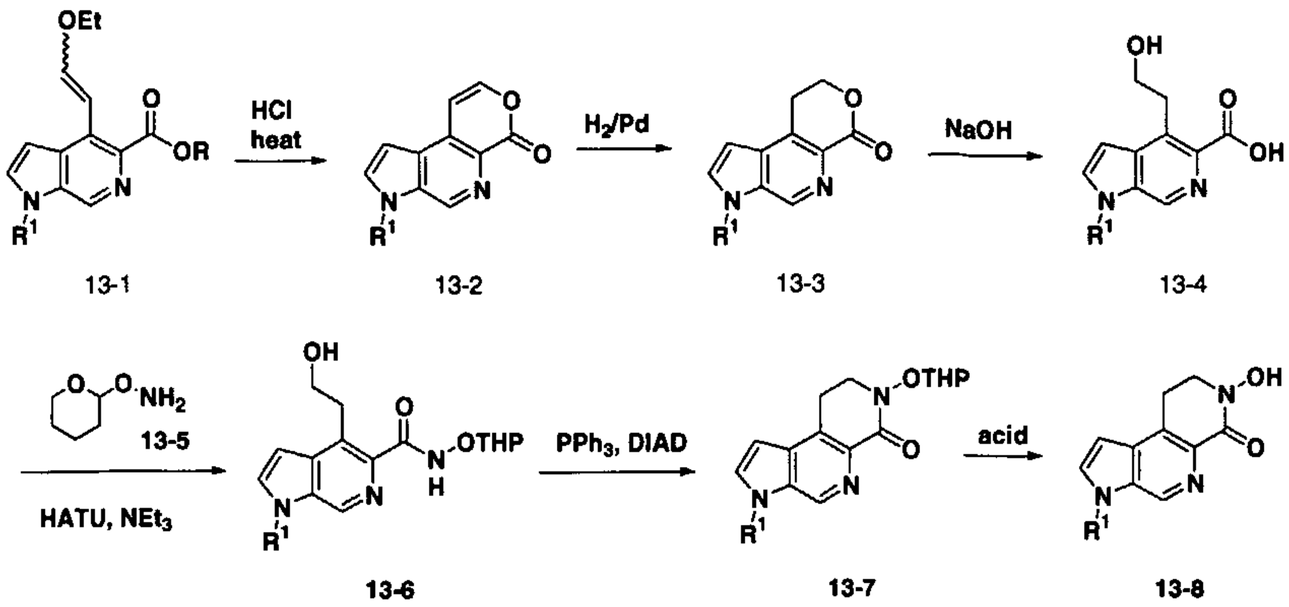
As shown in Scheme 2b, compound 12-15, or derivatives of 12-15 as shown in Scheme 2a, can then be allowed to react with hydroxylamine to afford compounds of formula (I).

Scheme 2b



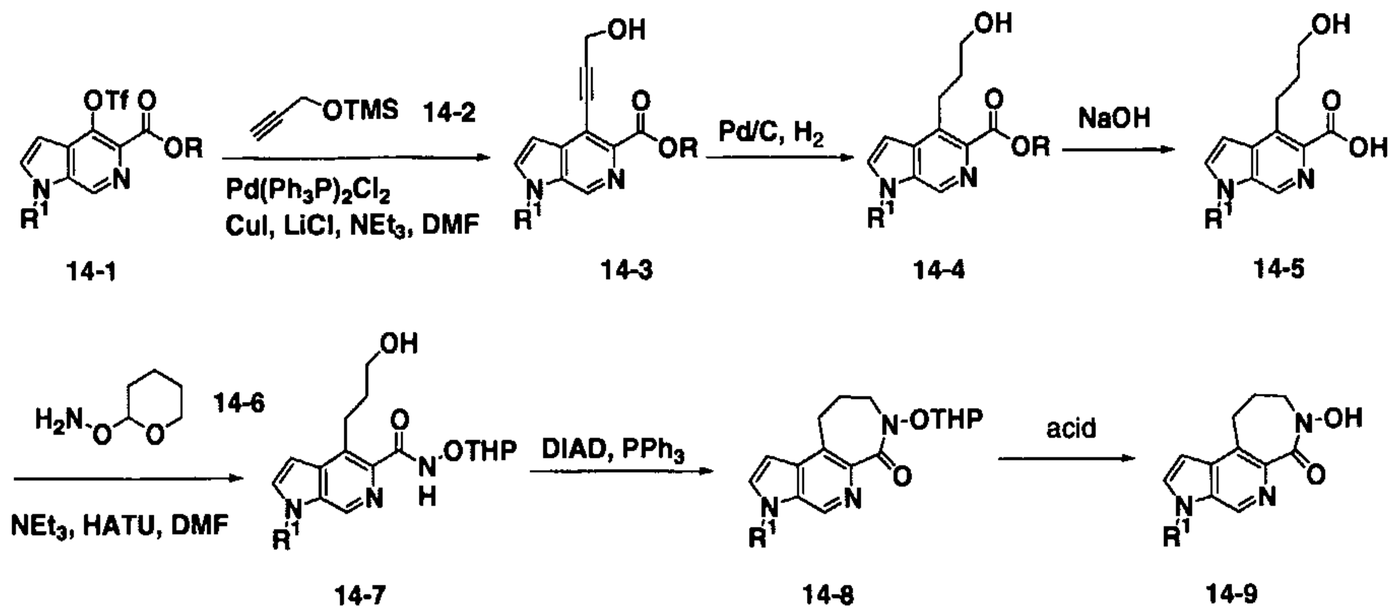
Scheme 3 depicts a route for preparation of a cyclic compound 13-7. Ester 13-1 can undergo cyclization to form pyranone 13 –4 as described by T. Sakamoto, Y. Kondo, A. Yasuhara, H. Yamanaka, *Tetrahedron* 1991, *47*, 1877–1886. Catalytic hydrogenation using a catalyst such as Pd/C can give lactone 13-3. Ring opening of the lactone with a base such as sodium hydroxide can give acid 13-5 which can be coupled with a suitable protected hydroxylamine (e. g. O-tetrahydropyranyl hydroxylamine 13-5) using a coupling reagent such as HATU to form 13-6. Mitsunobu reaction conditions (e. g. triphenylphosphine and diisopropyl azodicarboxylate) can effect cyclization of 13-6 to form 13-7 (for a review, see D. L. Hughes, *Org. Prep. Proced. Int.* 1996, *28*, 127-164). Removal of the tetrahydropyranyl group to provide 13-8 is expected to occur under acidic conditions.

Scheme 3



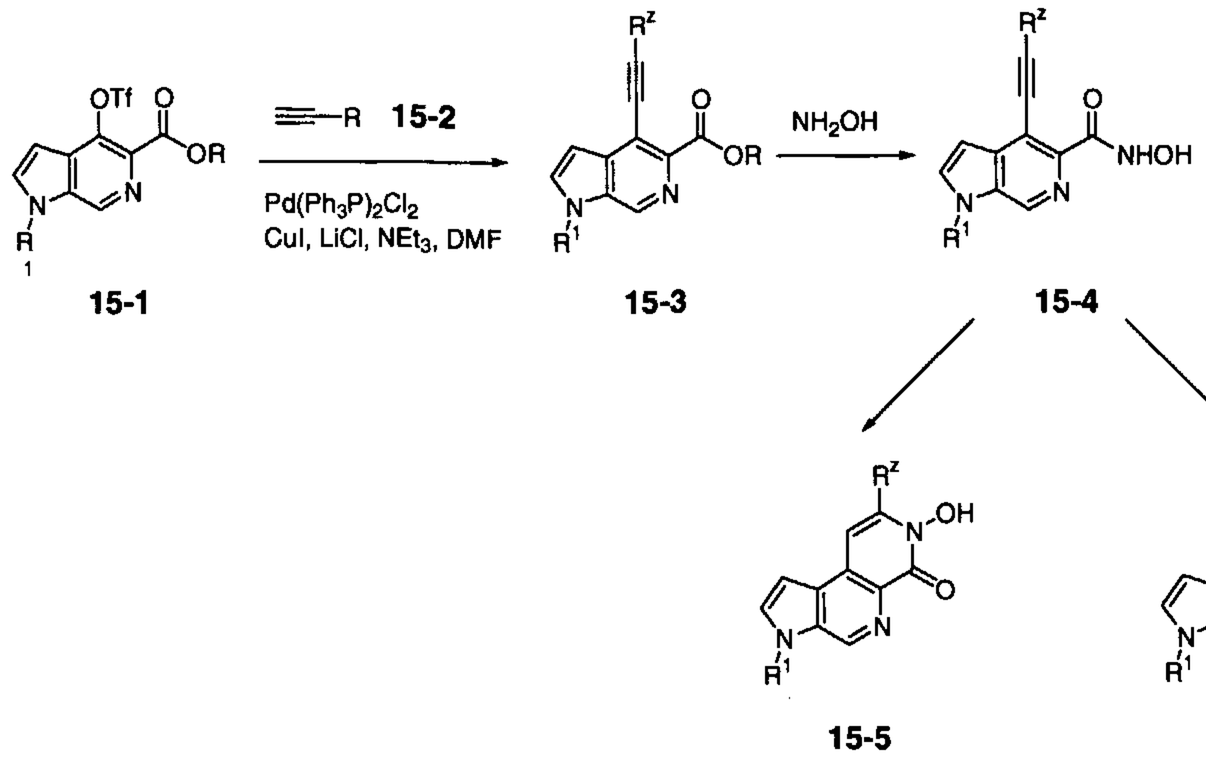
Compound 14-8 can be obtained according to Scheme 4. Palladium catalyzed reaction of triflate 14-1 with an alkyne such as 14-2 can give 14-3. Catalytic hydrogenation using a catalyst such as Pd/C can give the propanol 14-4. Saponification of the ester 14-4 with a base such as sodium hydroxide can give acid 14-5 which can be coupled with a suitable protected hydroxylamine (e. g. O-tetrahydropyranyl hydroxylamine 14-6) using a coupling reagent such as HATU to form 13-7. Mitsunobu reaction conditions (e. g. triphenylphosphine and diisopropyl azodicarboxylate) can effect cyclization of 14-7 to form 14-8 (for a review, see D. L. Hughes, *Org. Prep. Proced. Int.* 1996, *28*, 127-164). Removal of the tetrahydropyranyl group to provide 14-9 is expected to occur under acidic conditions.

Scheme 4



A general method for formation of compound 15-5 and 15-6 is shown in Scheme 5. Palladium catalyzed reaction of triflate 15-1 with an alkyne 15-2 can give ester 15-3. On treatment of the ester with hydroxylamine and a base such as sodium hydroxide using the conditions described by D. W. Knight, *Tetrahedron Lett.* 2002, *43*, 9187-9189 the formation of 15-5 and/or 15-6 is expected.

Scheme 5



Examples

The examples below are intended only to illustrate particular embodiments of the present invention and are not meant to limit the scope of the invention in any manner.

In the examples described below, unless otherwise indicated, all temperatures in the following description are in degrees Celsius (°C) and all parts and percentages are by weight, unless indicated otherwise.

Various starting materials and other reagents were purchased from commercial suppliers, such as Aldrich Chemical Company or Lancaster Synthesis Ltd., and used without further purification, unless otherwise indicated.

The reactions set forth below were performed under a positive pressure of nitrogen, argon or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents. Analytical thin-layer chromatography was performed on glass-backed silica gel 60°F 254 plates (Analtech (0.25 mm)) and eluted with the appropriate solvent ratios (v/v). The reactions were assayed by high-pressure liquid chromotagraphy (HPLC) or thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. The TLC plates were visualized by UV, phosphomolybdic acid stain, or iodine stain.

^{1}H-NMR spectra were recorded on a Bruker instrument operating at 300 MHz and ^{13}C-NMR spectra were recorded at 75 MHz. NMR spectra are obtained as DMSO-d_6 or $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or DMSO-d_6 ((2.50 ppm and 39.52 ppm)). Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in Hertz.

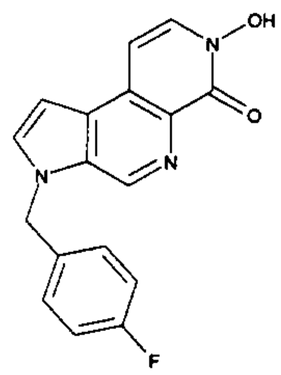
Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, as KBr pellets, or as $CDCl_3$ solutions, and when reported are in wave numbers (cm^{-1}). The mass spectra were obtained using LC/MS or APCI. All melting points are uncorrected.

All final products had greater than 95% purity (by HPLC at wavelengths of 220nm and 254nm).

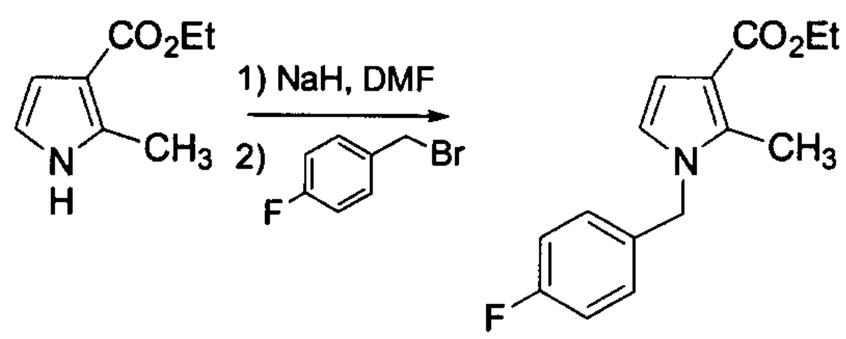
All elemental analyses for compounds herein, unless otherwise specified, provided values for C, H, and N analysis that were within 0.4% of the theoretical value, and are reported as "C, H, N."

In the following examples and preparations, "LDA" means lithium diisopropyl amide, "Et" means ethyl, "Ac" means acetyl, "Me" means methyl, "Ph" means phenyl, $(PhO)_2POCl$ means chlorodiphenylphosphate, "HCl" means hydrochloric acid, "EtOAc" means ethyl acetate, "Na_2CO_3" means sodium carbonate, "NaOH" means sodium hydroxide, "NaCl" means sodium chloride, "NEt_3" means triethylamine , "THF" means tetrahydrofuran, "DIC" means diisopropylcarbodiimide, "HOBt" means hydroxy benzotriazole, "H_2O" means water, "$NaHCO_3$" means sodium hydrogen carbonate, "K_2CO_3" means potassium carbonate, "MeOH" means methanol, "i-PrOAc" means isopropyl acetate, "$MgSO_4$" means magnesium sulfate, "DMSO" means dimethylsulfoxide, "AcCl" means acetyl chloride, "CH_2Cl_2" means methylene chloride, "MTBE" means methyl t-butyl ether, "DMF" means dimethyl formamide, "$SOCl_2$" means thionyl chloride, "H_3PO_4" means phosphoric acid, "CH_3SO_3H" means methanesulfonic acid, " Ac_2O" means acetic anhydride, "CH_3CN" means acetonitrile, and "KOH" means potassium hydroxide.

<u>Example 1</u>: 3-(4-Fluorobenzyl)-7-hydroxy-3,7-dihydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one



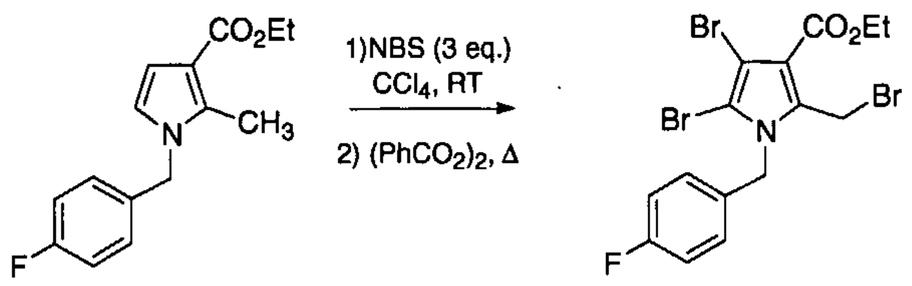
Step 1: Ethyl 1-(4-fluorobenzyl)-2-methyl-1H-pyrrole-3-carboxylate



To a solution of ethyl 2-methyl-1H-pyrrole-3-carboxylate (106.26g, 0.694mol) (prepared by the method of: Wee, A.G.H.; Shu, A.Y.L.; Djerassi, C. *J. Org. Chem.* 1984, *49*, 3327-3336) in anhydrous DMF (1.0L), under nitrogen, was added sodium hydride (60% in oil, 30.5g, 0.763mol, 1.1eq.) in 5 portions over 1 hour. When gas evolution ceased, 4-fluorobenzyl bromide (131.13g,

0.694mol) in anhydrous DMF (0.2L) was added *via* pressure equalized addition funnel over 45 minutes. The mixture was allowed to stir at room temperature for 16 hours after the addition was complete, then was poured into water (1.4L) in a 4L separatory funnel. The mixture was extracted with diethyl ether (5 x 1.0L) and the combined organic phases were washed with brine (3.0L) and dried (Na_2SO_4). Filtration, rinsing of the filter cake with diethyl ether (0.5L) and concentration *in vacuo* (approx. 20 Torr) gave the crude product and DMF. Residual DMF was removed on a cold finger trap rotary evaporator at full pump vacuum in a 40 °C water bath to give the crude benzylate pyrrole as an orange oil. The crude product was purified by chromatography on a column of silica gel (125mm OD, 1kg 230-400 mesh, packed with hexanes-EtOAc 95:5) eluted with hexanes:EtOAc (95:5, 2.0L) and hexanes:EtOAc (90:10, 8.0L) while collecting 500mL fractions, using the flash technique. Fractions 4-18 were combined to afford ethyl 1-(4-fluorobenzyl)-2-methyl-1H-pyrrole-3-carboxylate (172.3g, 95%) as a clear, pale yellow, viscous liquid. TLC (Merck, hexanes:EtOAc 85:15, UV-+, cerium molybdate-+): R_f = 0.26; LCMS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN – 5 minutes, APCI, + mode): RT- 3.711min, m/e = 262.1 (base), 263.2 (30); ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.33 (t, J = 7.06 Hz, 3H), 2.43 (s, 3H), 4.26 (q, J = 7.06 Hz, 2H), 5.00 (s, 2H), 6.52 (d, J = 3.20 Hz, 1H), 6.58 (d, J = 3.20 Hz, 1H), 6.92-7.04 (m, 4H).

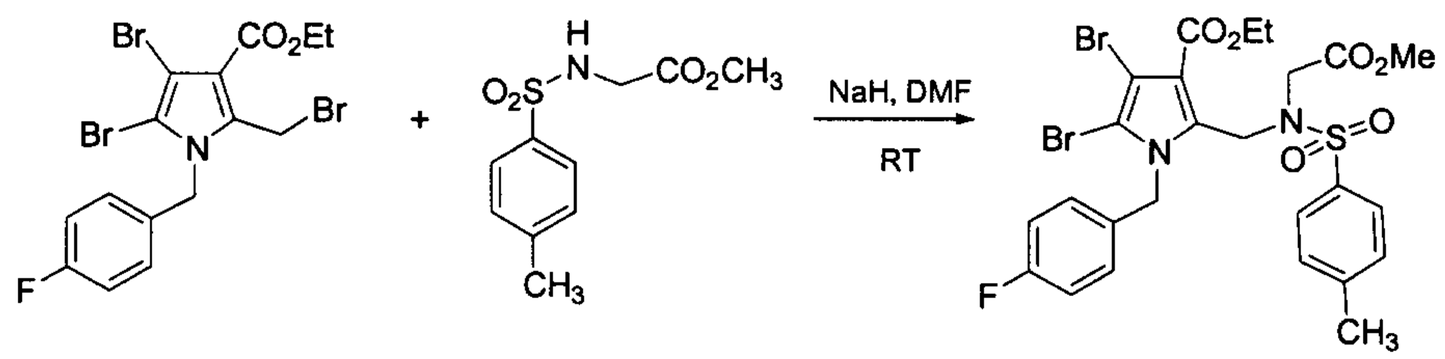
Step 2: Ethyl 4,5-dibromo-2-(bromomethyl)-1-(4-fluorobenzyl)-1H-pyrrole-3-carboxylate.



To NBS (267.5g, 1.503mol, 3 eq.) in anhydrous CCl_4 (0.5L) in a 3L, 3N round bottom flask, equipped with an internal temperature monitoring probe, addition funnel, and reflux condenser, was added ethyl 1-(4-fluorobenzyl)-2-methyl-1H-pyrrole-3-carboxylate (130.9g, 0.501mol) in anhydrous CCl_4 (0.5L) over 15 minutes. The internal temperature rose to 43°C during the addition and a transient red color developed, which faded upon completion of the addition. The mixture was allowed to stir for 15 minutes, then benzoyl peroxide (1.21g, 5mmol, 0.01 eq.) was added and the mixture was heated to an internal temperature of 77°C (reflux) and maintained at that temperature for 1.5 hours. At this time point LCMS (APCI) indicated complete reaction. The mixture was cooled to room temperature, the precipitated solid was removed by filtration, the filter cake was rinsed with CCl_4 (0.3L), and the combined filtrates were concentrated *in vacuo* to give the crude tribromide as a red-brown semi-solid. The crude material was treated with dichloromethane (50mL) and hexanes (250mL) to produce a tan solid and a red-brown liquid. The solid was isolated by filtration, was rinsed with dichloromethane:hexanes (10:90, 0.5L) and was dried *in vacuo* at room temperature to furnish 170.03g (69%) of ethyl 4,5-dibromo-2-

(bromomethyl)-1-(4-fluorobenzyl)-1H-pyrrole-3-carboxylate as a pale, tan solid. The filtrates were concentrated *in vacuo* to give a mother liquor that was purified by chromatography on a column of silica gel (70mm OD, 400g 230-400 mesh, hexanes:EtOAc 90:10, 250mL fractions) using the flash technique. Fractions 3-6 provided an additional 29.57g of ethyl 4,5-dibromo-2-(bromomethyl)-1-(4-fluorobenzyl)-1H-pyrrole-3-carboxylate as a pale, tan solid. Total: 199.6g (81%). TLC (Merck, hexanes:EtOAc 90:10, UV-+, cerium molybdate-+): R_f = 0.33; LCMS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN – 5 minutes, APCI, + mode): RT- 4.109 min, m/e = 416.0 (50), 417.9 (base), 419 (50), M-Br; ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.39 (t, J = 7.16 Hz, 3H), 4.35 (q, J = 7.16 Hz, 2H), 4.77 (s, 2H), 5.36 (s, 2H), 6.96-7.07 (m, 4H).

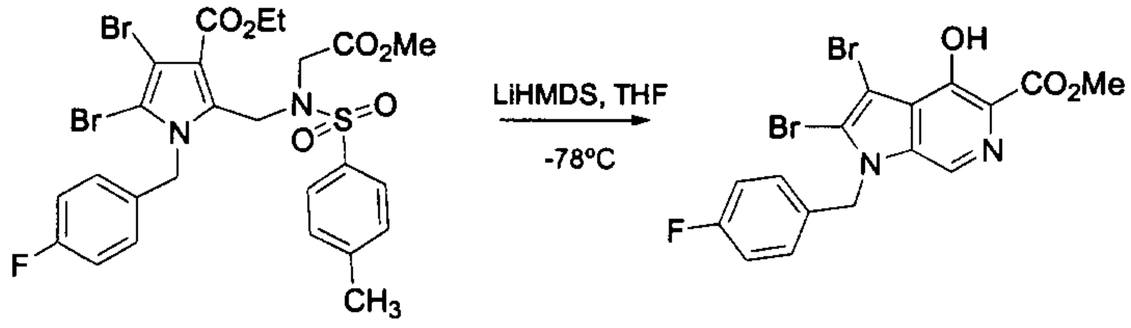
Step 3: Ethyl 4,5-dibromo-1-(4-fluorobenzyl)-2-({(2-methoxy-2-oxoethyl)[(4-methylphenyl)sulfonyl]amino}methyl)-1*H*-pyrrole-3-carboxylate



To a stirring solution of methyl *N*-[(4-methylphenyl)sulfonyl]glycinate (51.75g, 0.213mol, prepared by the method of: Ginzel, K.D.; Brungs, P.; Steckhan, E. *Tetrahedron* 1989, *45*, 1691-1701) in anhydrous DMF (0.5L) was added NaH (60% in oil, 8.59g, 0.215mol) in one portion. The mixture was allowed to stir for 30 minutes (warms and returns to room temperature) at which time a solution ethyl 4,5-dibromo-2-(bromomethyl)-1-(4-fluorobenzyl)-1H-pyrrole-3-carboxylate (105.92g, 0.213mol) in anhydrous DMF (0.5L) was added over 1 hour. The mixture was allowed to stir at room temperature for 16 hours, then the DMF was removed *in vacuo* (approx 2 Torr, 40°C water bath) and the oily residue was dissolved in dichloromethane (0.75L), the solution was washed with saturated aq. NH_4Cl (0.5L), brine (0.5L), and dried (Na_2SO_4). Filtration and concentration *in vacuo* provided the crude alkylated material as a viscous reddish oil. The crude material was heated in the presence of MeOH (0.75L) until the MeOH was boiling, then dichloromethane was added slowly until solution was achieved. The red solution was cooled to room temperature (see off-white crystals) and the crystallization was completed by cooling in a refrigerator (4°C) for 16 hours. The ivory solid was isolated by filtration, the solid was rinsed with diethyl ether:hexanes (0.5L, 10:90 v/v) and the solid was dried in a vacuum oven (approx. 20 Torr, 50°C) overnight to furnish ethyl 4,5-dibromo-1-(4-fluorobenzyl)-2-({(2-methoxy-2-oxoethyl)[(4-methylphenyl) sulfonyl]amino}methyl)-1*H*-pyrrole-3-carboxylate (108.2g, 77%) as a free flowing, fine, ivory solid. TLC (Merck, hexanes:EtOAc 75:25, UV-+, cerium molybdate-+ - purple): R_f = 0.38; LCMS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 H_2O (+0.1%

HOAc):CH_3CN – 5 minutes, ESI, + mode): RT- 4.436 min, m/e = 680.8 (55), 681.8 (18), 682.9 (base), 683.9 (30), 684.8 (62), 686.8 (10) – M+Na; ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.24 (t, J = 7.16 Hz, 3H), 2.14 (s, 3H), 3.49 (s, 3H), 3.89 (s, 2H), 4.19 (q, J = 7.16 Hz, 2H), 4.55 (s, 2H), 7.02 (d, J = 2.45 Hz, 2H), 7.04 (s, 2H), 7.28 (d, J = 8.19 Hz, 2H), 7.59 (d, J = 8.19 Hz, 2H)

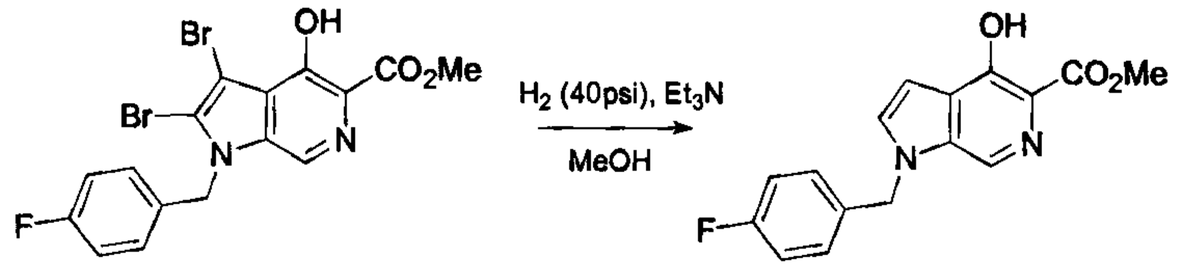
Step 4: Methyl 2,3-dibromo-1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



To solid LiHMDS (61.27g, 0.366mol), in a 3L, 3-neck round bottom flask equipped with a 0.5L pressure equalized addition funnel and an internal temperature probe, was added anhydrous THF (0.5L). The mixture was placed under nitrogen and immersed in a dry ice-*i*-PrOH bath. The solution was allowed to stir until the internal temperature reached -78°C (1.25h). To this stirring cold solution was added a solution of ethyl 4,5-dibromo-1-(4-fluorobenzyl)-2-({(2-methoxy-2-oxoethyl)[(4-methylphenyl) sulfonyl]amino}methyl)-1*H*-pyrrole-3-carboxylate (107.43g, 0.163mol) in anhydrous THF (0.5L) at such a rate that the internal temperature does not exceed -70°C (2 hours). During the course of the addition, a yellow color was first noticed giving way to an orange/yellow solution, which then produced a precipitate and an orange/yellow solution. The reaction was allowed to stir for 30 minutes after the addition was complete, at which point LCMS (sample taken at 15 minutes after addition) indicated the reaction was complete. The mixture was rapidly poured into a 6L separatory funnel, which had been charged with saturated aq. NH_4Cl (1.5L) and dichloromethane-methanol (95:5, 2L). The mixture was rapidly shaken to distribute the reaction mixture and quench the reaction. The organic phase was separated; the aq. layer was extracted with dichloromethane-methanol (95:5 v/v, 1L). The combined organic phases were filtered to remove a fine white precipitate and then dried (Na_2SO_4). Concentration *in vacuo* afforded the crude cyclized material as a yellow solid, which was triturated with EtOH (0.6L) and the resulting white solid was isolated by filtration, washed with anhydrous ethyl ether (50mL), and dried in a vacuum oven (approx. 20 Torr, 50°C, 16 hours) to give 40.51g (54.4%) of methyl 2,3-dibromo-1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate as a powdery white solid after drying in a vacuum oven . The filtrate was concentrated *in vacuo* and the residue was triturated with diethyl ether/hexanes (50:50 v/v, 0.25L) to give 10.69g (14.3%) of methyl 2,3-dibromo-1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate as a powdery white solid after drying in a vacuum oven (approx. 20 Torr, 50°C, 16 hours). The filtrate was again treated under the same conditions (0.1L, 50:50 v/v diethyl ether-hexanes) to give an additional 2.39g (3.2%) for a total yield of 53.59g (72%). TLC (Merck, CH_2Cl_2: EtOAc 50:50, UV-+, cerium

molybdate-+): R_f = 0.57; LCMS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN – 5 minutes, ESI, + mode): RT- 3.790 min, m/e = 456.9 (55), 458.8 (base), 459.9 (15)- M+, 480.9 – M+Na.; ^{1}H-NMR (300MHz, $CDCl_3$): δ = 4.03 (s, 3H), 5.48 (s, 2H), 6.96-7.04 (m, 2H), 7.05-7.12 (m, 2H), 8.28 (s, 1H), 11.60 (s, 1H).

Step 5: Methyl 1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



To a 2.5L Parr flask was added methyl 2,3-dibromo-1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (67.28g, 0.147mol), methanol (1.5L) and triethyl amine (32.70g, 0.323mol, 2.2 eq.). Into this mixture was bubbled nitrogen for 10 minutes, then 10% Pd/C (15.6g) was carefully added. The bottle was placed on a Parr apparatus; evacuated/purged with nitrogen (3x) and hydrogen was added to 40psi. Shaking was commenced and after 5 minutes the pressure had gone to zero and the bottle was re-pressurized to 40psi. This was repeated 2X at which point the pressure lowered to 35psi and remained. TLC and LCMS then indicated the reaction was complete (total time ca. 1 hour). The palladium was removed by filtration through a pad of Celite™, the filter cake was rinsed with dichloromethane (1.0L) and the combined filtrates were concentrated *in vacuo* to give the crude product plus amine salts. The mixture was taken into EtOAc (2L) and water (1.0L), the organic phase was separated, the aqueous layer was extracted with EtOAc (0.6L), and the combined organic phases were washed with brine (1.0L) and dried (Na_2SO_4). Filtration and concentration *in vacuo* gave a powdery white solid which was dried in a vacuum oven (approx. 20 Torr, 50°C, 16 hours) to afford 43.13g (98%) of methyl 1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate as a free flowing, powdery white solid. TLC (Merck, CH_2Cl_2:EtOAc 50:50, UV-+, cerium molybdate-+): R_f = 0.45 (fluorescent blue); LCMS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 v/v H_2O (+0.1% HOAc):CH_3CN – 5 minutes, APCI, + mode): RT- 3.217min, m/e = 301.1 (base, M+H); ^{1}H-NMR (300MHz, $CDCl_3$): δ = 4.02 (s, 3H), 5.36 (s, 2H), 6.83 (d, J = 3.10 Hz, 1H), 6.96-7.04 (m, 2H), 7.07-7.13 (m, 2H), 7.17 (d, J = 3.10 Hz, 1H), 8.31 (s, 1H), 11.40 (s, 1H).

Step 6: Methyl 1-(4-fluorobenzyl)-4-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate. To a stirred solution of the methyl 1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20.0 g, 66.7 mmol) and triethylamine (46.5 mL, 333 mmol) in dichloromethane (200 mL) at 0 °C was added trifluoromethanesulfonic anhydride (33.6 mL, 200 mmol) dropwisely and the reaction stirrred at 0 °C for 10 minutes. It was quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, concentrated, and purified by chromatography with ethyl acetate/hexanes (1/1) to provide the title compound as brown solid (25.28 g, 88% yield). ^{1}H NMR ($CDCl_3$): δ; 8.73 (s, 1H), 7.39 (d, 1H),

7.18 (t, 2H), 7.05 (t, 2H), 6.80 (d, 1H), 5.43 (s, 2H), 4.02 (s, 3H). LCMS (API-ES, $M+H^+$): 433.0. HPLC: 96% purity.

Step 7: Method 1: Methyl 4-[(*E*)-2-ethoxyvinyl]-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate. To a stirred solution of methyl 1-(4-fluorobenzyl)-4-[(trifluoroacetyl)oxy]-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (1.4g, 3.24mmol) and (E)-2-ethoxyvinyl tributyltin (E [prepared according to A. Leusik, H. A . Budding, J. W. Marsman, *J. Organomet. Chem.*, 1967, *9*, 285-294] (2.2 g, 6.48 mmol) in DMF (10 mL) under a nitrogen atmosphere were added triethylamine (0.48mL, 3.24 mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.24g, 0.32 mmol). The resulting mixture was heated to 140 ^{0}C for 2 hours. It was quenched with water, and extracted with ethyl acetate three times. The combined organic extracts were washed with water (2 x 30 mL), dried over sodium sulfate, concentrated in vacuo and purified by Biotage flash chromatography. Elution with hexane:ethyl acetate (1:1) provided the title compound as brown glue (0.40 g, 35% yield). ^{1}H NMR (MeOD) δ; 8.50 (s, 1H), 7.64 (d, 1H, J = 3.3 Hz), 7.22 (t, 2H, J = 6.8 Hz), 7.05 (t, 2H, J = 6.8 Hz), 6.89 (d, 1H, J = 3.3 Hz), 5.53 (s, 2H), 4.02 (q, 2H, J = 7.1 Hz), 1.37 (t, 3H, J= 7.1 Hz). LCMS (APCI, $M+H^+$): 355.2.

Method 2: Methyl 4-(2-ethoxyvinyl)-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate. To a solution of methyl 1-(4-fluorobenzyl)-4-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (2 g, 4.62 mmol) in DMF (27 mL) was added lithium chloride (0.59 mg, 13.88 mmol). Dry nitrogen was bubbled through the mixture for for 10 min, and then dichlorobis(triphenylphosphine)palladium(II) (0.16 g, 0.23 mmol) was added. The mixture was heated to 79°C, and a solution of ethoxyvinyl tributyltin (mixture of isomers: 1,2-E:1,2-Z:1,1 = 1:0: 0.97:0.18) [prepared according to A. Leusik, H. A . Budding, J. W. Marsman, *J. Organomet. Chem.*, 1967, *9*, 285-294] (1.82 g, 5.08 mmol) in DMF (23 mL). The resulting mixture was stirred for 9 h at 70 ^{o}C under nitrogen atmosphere. It was quenched with saturated sodium chloride and filtered to remove solid precipitate then concentrated. Purification by flash chromatography (Biotage) over silica gel (1:1 to 1:3, hexane/ethyl acetate) afforded the title product as brown glue (1.46 g, 89.2 % yield). LCMS (APCI, $M+H^+$): 355.2.

Step 8: 4-[(*E*)-2-Ethoxyvinyl]-1-(4-fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide. To methyl 4-[(*E*)-2-ethoxyvinyl]-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (0.1g, 0.28 mmol) in methanol (10 mL) were added hydroxylamine (1mL, 50% in water, 15.2mmol) and sodium hydroxide (63.8 mg, 1.59mmol). The mixture was stirred at room temperature for 2 h, and 4N hydrochloric acid (0.5mL, 1.9mmol) was added. The mixture was concentrated to provide 100 mg of the title compound that was used without further purification in the next step. ^{1}H NMR (DMSO-d_6) δ ppm 11.76 (d, 1H, J = 1.9 Hz), 8.88 (d, 1H, J = 1.9 Hz), 8.60 (s, 1H), 7.83 (d, 1H, J = 3.0 Hz), 7.31 (t, 2H, J = 8.9 Hz), 7.22 (d, 1H, J = 13.2 Hz), 7.05 (t, 2H, J =

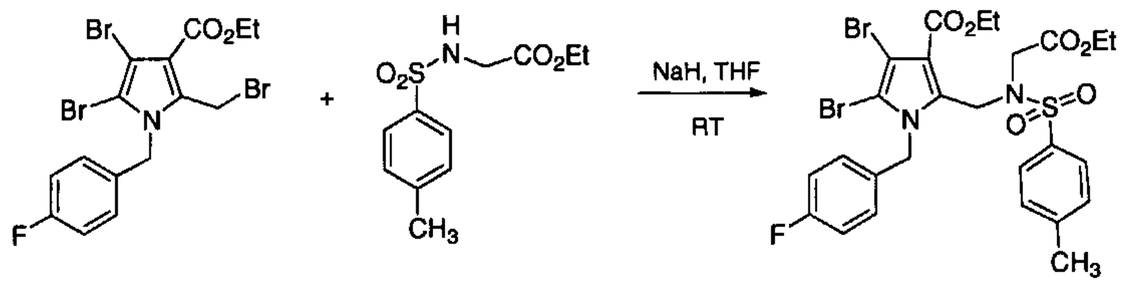
8.9 Hz), 6.82 (d, 1H, J = 3.0 Hz), 6.66 (d, 1H, J = 13.2 Hz), 5.54 (s, 2H), 3.96 (q, 2H, J = 7.0 Hz), 1.28 (t, 3H, J= 7.0 Hz). LCMS (APCI, $M+H^+$): 356.

Step 9: 3-(4-Fluorobenzyl)-7-hydroxy-3,7-dihydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one.

A solution of 4-[(*E*)-2-ethoxyvinyl]-1-(4-fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (100 mg, 0.28 mmol) in methanol (10mL) and hydrochloric acid (37w%, 1mL) was refluxed for 16 hours. It was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified by pre-HPLC to provide the title compound as white powder. ^1H NMR (DMSO-d_6) δ; 11.50 (s, 1H), 9.04 (s, 1H), 7.88 (d, 1H, J = 3.0 Hz), 7.84 (d, 1H, J = 7.5 Hz), 7.13-7.19 (m, 3H), 6.93 (d, 1H, J = 7.5 Hz), 5.65 (s, 2H). MS (APCI, $M+H^+$): 310.1. HRMS calcd for $C_{17}H_{13}N_3O_2F_1$ ($M+H^+$) 310.0992, found 310.0991. HPLC: 94.3% purity.

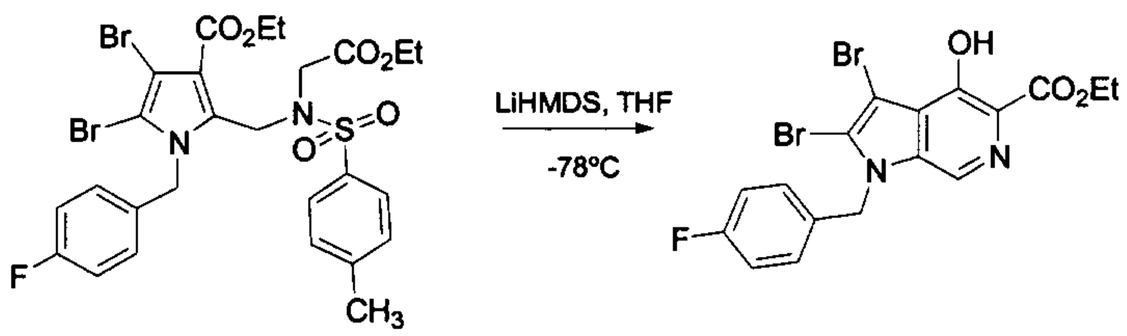
Alternative method for preparation of 4-[(*E*)-2-Ethoxyvinyl]-1-(4-fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide

Step 1: Ethyl 4,5-dibromo-1-(4-fluorobenzyl)-2-({(2-ethoxy-2-oxoethyl)[(4-methylphenyl) sulfonyl]amino}methyl)-1*H*-pyrrole-3-carboxylate



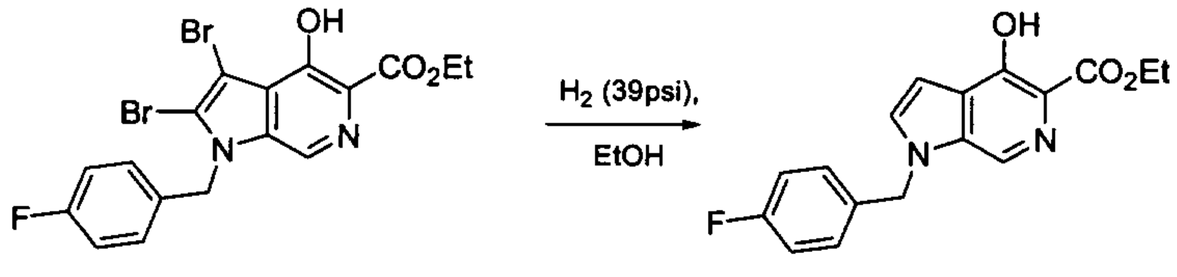
To a stirring solution of ethyl 4,5-dibromo-2-(bromomethyl)-1-(4-fluorobenzyl)-1H-pyrrole-3-carboxylate (104.0g, 0.209mol) and ethyl *N*-[(4-methylphenyl)sulfonyl]glycinate (53.7g, 0.209mol, prepared by the method of: Ginzel, K.D.; Brungs, P.; Steckhan, E. *Tetrahedron* 1989, *45*, 1691-1701) in anhydrous THF (1.5L) was added NaH (60% in mineral oil, 8.40g, 0.210mol) in several small portions. The mixture was allowed to stir at room temperature for 16 hours. It was quenched with aq. NH_4Cl solution, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated and the residue was purified by column chromatography with ethyl acetate/hexane (1:4, v:v) to provide the title compound as glue-like material (124g, 88% yield). ^1H NMR ($CDCl_3$) δ ppm 7.61 (d, J = 4.7 Hz, 2H), 7.30 (d, J = 5.7 Hz, 2 H), 7.04 (d, J = 5.6 Hz, 4 H), 5.60 (s, 2H), 4.55 (s, 2H), 4.20 (q, J = 7.1 Hz, 2 H), 3.94 (q, J = 7.2 Hz, 2 H), 3.89 (s, 2H), 2.42 (s, 2H), 1.25 (t, J = 7.2 Hz, 3 H), 1.14 (t, J = 7.1 Hz, 3 H).

Step 2: Ethyl 2,3-dibromo-1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



To a stirring solution of ethyl 4,5-dibromo-1-(4-fluorobenzyl)-2-({(2-ethoxy-2-oxoethyl)[(4-methylphenyl) sulfonyl]amino}methyl)-1*H*-pyrrole-3-carboxylate (124.2g, 184.3mol) in anhydrous THF (1.0L) was added LiHMDS (405 mL ,1.0M in THF, 0.405mol) at -78°C over 1 h. The mixture was quenched with aq. NH_4Cl, extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , and concentrated. The residue was purified by column chromatography with etyl acetate/hexane(1/1, v:v) to ethyl acetate/dichloromethane (9/1) to give the title product (52.0g 60% yield). ^{1}H NMR (DMSO-d6) δ ppm 11.50 (s, 1H), 8.63 (s, 1H), 7.16 (d, J = 7.2 Hz, 4H), 5.60 (s, 2H), 5.67 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H,), 1.33 (t, J= 7.2 Hz, 3H). LC/MS (API-ES, $M+H^+$): 473.0.

Step 3: Ethyl 1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



A suspension of ethyl 2,3-dibromo-1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (52.0g, 0.110mol) and 10% Pd/C (0.5g) in ethanol (2.0L) was shaken in a Parr shaker under hydrogen (39psi) for 23 h. The catalyst was removed by filtration. On concentration of the filtrate, the product precipitated out. It was collected by filtration and dried under vacuum to provide the title compound. (34 g, 98% yield) ^{1}H NMR (DMSO-d6) δ ppm 11.66 (s, 1H), 8.89 (s, 1H), 8.14 (d, J = 3.0 Hz, 1H) 7.37 (d, J = 5.7 Hz, 2H), 7.19 (d, J = 6.6 Hz, 2H), 7.11 (d, J = 3.0 Hz, 1H), 5.71 (s, 2H), 4.45 (q, J = 7.1 Hz, 2H), 1.37 (t, J= 7.2 Hz, 3H). LC/MS (API-ES, $M+H^+$): 315.1.

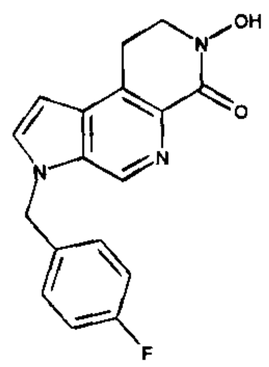
Step 4: Ethyl 1-(4-fluorobenzyl)-4-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate. To a stirred solution of the ethyl 1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20.0 g, 63.7 mmol) and triethylamine (44.4 mL, 318.5 mmol) in dichloromethane (150 mL) at 0 °C was added trifluoromethanesulfonic anhydride (32.0 mL, 190.1 mmol) dropwise and the reaction stirred for 1 h. It was quenched with water, extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, concentrated and purified by chromatography with ethyl acetate/hexane (1/1) to provide the title compound as brown solid (17.6 grams, 78% yield) . ^{1}H NMR (DMSO-d_6): δ; 8.10 (s, 1H), 8.08 (d, 1H), 7.41 (t, 2H), 7.18 (t, 2H), 6.74 (d, 1H), 5.64 (s, 2H), 4.34 (q, 2H), 1.31 (t, 3H). LC/MS (API-ES, $M+H^+$): 447.0.

Step 5: Ethyl 4-[(*E*)-2-ethoxyvinyl]-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate. To a stirred solution of ethyl 1-(4-fluorobenzyl)-4-{[(trifluoromethyl)sulfonyl]oxy}-

1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (10.0g, 22.4mmol) and ethoxyvinyl tributyltin [prepared according to A. Leusik, H. A . Budding, J. W. Marsman, *J. Organomet. Chem.*, 1967, *9*, 285-294] (9.7 g, 26.9 mmol, mixture of E -1,2: Z-1,2: 1:1, ratio = 1:0.3:0.1) in DMF (30 mL) under a nitrogen atmosphere were added triethylamine (3.2mL, 22.4 mmol) and dichlorobis(triphenylphosphine)palladium(II) (1.0g, 1.4 mmol). The resulting mixture was heated to 140 ^{0}C for 10 minutes. It was quenched with aq $NaHCO_3$ solution, and extracted with ethyl acetate. The organic layer was washed with brine (2 x), dried over sodium sulfate, concentrated in vacuo and purified by Biotage flash chromatography. Elution with hexane:ethyl acetate (3:2) provided the title compound as a brown glue (2.1 g) pure E-isomer together with 5.6 g of a mixture of E-1,2 and Z-1,2 and 1,1 isomers). ^{1}H NMR (DMSO-d6) δ; 8.69 (s, 1H), 7.85 (d, J = 3.3 Hz, 1H), 7.33 (t, J = 6.8 Hz, 2H), 7.13 - 7.20 (m, 3H), 6.86 (d, J = 3.3 Hz, 1 H), 6.43 (d, J = 13Hz, 1H), 5.55 (s, 2H), 4.27(q, J = 7.2 Hz, 2 H), 3.98 (q, J = 7.0 Hz, 2 H), 1.29 (t, J= 7.1 Hz, 6 H). LCMS (APCI, $M+H^{+}$): 369.1.

Step 6: 4-[(*E*)-2-ethoxyvinyl]-1-(4-fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide. To ethyl 4-[(*E*)-2-ethoxyvinyl]-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (0.2g, 0.54mmol) in methanol (5mL) were added hydroxylamine (1mL, 50% in water, 15.2mmol) and sodium hydroxide (0.0763g, 1.9mmol). The mixture was stirred at room temperature for 5h, neutralized with 4N aq. HCl solution (0.48mL, 1.9mmol), and extracted with ethyl acetate. The organic extract was concentrated and recrystallized from ethyl acetate/ethyl ether/hexane to give the title compound (0.12g, 62% yield). ^{1}H NMR (DMSO-d_6) δ; 11.76 (d, 1H, J = 1.9 Hz), 8.88(d, 1H, J = 1.9 Hz), 8.60 (s, 1H), 7.83 (d, 1H, J = 3.0 Hz), 7.31 (t, 2H, J = 8.9 Hz), 7.22 (d, 1H, J = 13.2 Hz), 7.05 (t, 2H, J = 8.9 Hz), 6.82 (d, 1H, J = 3.0 Hz), 6.66 (d, 1H, J = 13.2 Hz), 5.54 (s, 2H), 3.96 (q, 2H, J = 7.0 Hz), 1.28 (t, 3H, J= 7.0 Hz). LCMS (APCI, $M+H^{+}$): 356.1. Anal. ($C_{19}H_{18}FN_3O_3$) C, H, N. HPLC: 95% purity.

<u>Example 2</u>: 3-(4-Fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one



Step 1: 7-(4-Fluorobenzyl)pyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(7*H*)-one. Method 1: A solution of methyl 4-[2-ethoxyvinyl]-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (pure E, Z or E/Z mixture can be used) (0.17g, 0.48 mmol) in methanol (5 mL) and hydrochloric acid (37w%, 10 mL) was refluxed for 2 hours. The mixture was quenched with saturated aq. sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over sodium

sulfate, filtered, concentrated and purified by prep-HPLC to provide the title compound as white powder (20 mg, 14% yield). Method 2: A solution of ethyl 4-[2-ethoxyvinyl]-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (pure E, Z or E/Z mixture can be used) (1.1g, 2.98 mmol) in methanol (5 mL), water (5 mL) and hydrochloric acid (37w%, 5 mL) was refluxed for 16 hours. The mixture was was quenched with saturated aq. sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, concentrated and purified byBiotage chromatography to provide the title compound as white powder (0.3 g, 34% yield). ^{1}H NMR (MeOD) δ; 8.93 (s, 1H), 7.80 (d, J = 3.2 Hz, 1 H), 7.84 (d, J = 5.5 Hz, 1 H), 7.28 (d, 1H, J = 5.5 Hz, 1 H), 7.03 - 7.10 (m, 5H), 5.64 (s, 2H). MS (APCI, M+H$^+$): 295.1.

Step 2: 7-(4-Fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one. A solution of 7-(4-fluorobenzyl)pyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(7*H*)-one (0.30 g, 0.102mmol) and Pd/C (5% Pd, 50 mg) in methanol (100 mL) was shaken in a Parr shaker under hydrogen (20 psi) for 16 hours. The catalyst was filtered off, the filtrate was concentrated and dried in vacuum to provided the title compound as a solid (0.28 g, 4% yield). that was used without further purification in the next step^{1}H NMR (MeOD) δ; 8.77 (s, 1H), 7.76 (d, 1H, J = 3.0 Hz), 7.28 (d, 2H, J = 5.1 Hz), 7.07 (d, 2H, J = 5.1 Hz), 6.86 (d, 1H, J = 3.0 Hz), 4.66 (d, 2H, J = 6 Hz), 3.41 (d, 2H, J = 6 Hz). MS (APCI, M+H$^+$): 297.1.

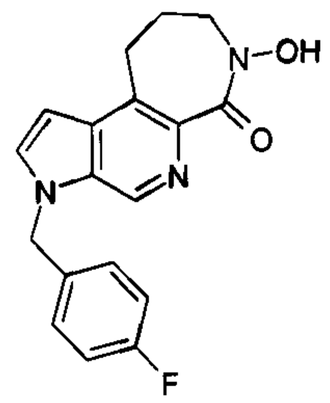
Step 3: 1-(4-Fluorobenzyl)-4-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic acid. To 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one (0.11 g, 0.37 mmol) in methanol (10 mL) was added sodium hydroxide (0.066 g, 1.65 mmol) in water (2.0 mL). The reaction was heated to 60°C for 3 hours. After cooling down, the reaction mixture was neutralized with 4N hydrochloric acid (0.42mL, 1.65 mmol). It was concentrated and dried in vacuo to provide the crude title compound as a white powder (0.11 g, 94%). ^{1}H NMR (DMSO-d_6) δ; 8.93 (d, 1H, J = 1.9 Hz), 8.06 (s, 1H), 7.36 (m, 2H), 7.16 (t, 2H, J = 6.6 Hz), 6.96 (s, 1H), 5.63 (s, 2H), 3.66 (t, 2H, J = 6.8 Hz), 3.44 (t, 2H, J= 6.8 Hz). LCMS (APCI, M+H$^+$): 315.1.

Step 4: 1-(4-Fluorobenzyl)-4-(2-hydroxyethyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide. To 1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic acid (0.11 g, 0.35 mmol) in DMF (10 mL) were added triethylamine (0.15 ml, 1.05 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine 2-(aminooxy)tetrahydro-2*H*-pyran (0.05 g, 0.43 mmol), and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU; 0.16 g, 0.42 mmol). The mixture was stirred for 16 hours at ambient temperature. It was quenched with water (30 mL), extracted with ethyl acetate (50 mL) and washed with brine (2 x 50mL). The organic extracts was dried over sodium sulfate, concentrated in vacuo and purified by Biotage chromatography using 5% methanol in dichloromethane as eluent to provide the title compound as a crude powder (0.16g) that was used without further purification in the next step. LCMS (APCI, M+H$^+$): 414.2.

Step 5: 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one. To a stirred solution of 1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (0.16g, 0.39mmol) and triphenylphosphine (0.12g, 0.46mmol) in THF (10mL), was added dropwise diisopropylazodicarboxylate (0.09 mL, 94 mg, 0.46 mmol) in THF (1mL) was added. The resulting mixture was stirred at room temperature for 1 hour, and the solvent was evaporated. Purification by Biotage chromatography provided 0.12 g of a crude material that was used without further purification in the next step. LCMS (APCI, $M+H^+$): 396.2.

Step 6: 3-(4-Fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one. A stirred solution of the 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one (0.12 g, 0.30mmol) in acetic acid (4 mL), THF (2mL) and water (1mL) was heated to 45°C for 16 h and 100°C for another 1 h. Concentratin and purification by pre-HPLC provided the title compound as white powder (0.023 g, 24% yield) . ^{1}H NMR (DMSO-d_6) δ; 9.87 (s, 1H), 8.84 (s, 1H), 7.85 (d, 1H, J = 3.0 Hz), 7.32-7.34 (m, 2H), 7.15 (d, 2H, J = 8.7 Hz), 6.72 (d, 1H, J = 3.0 Hz), 5.57 (s, 2H), 3.80 (d, 2H, J = 7.0 Hz), 3.30 (d, 2H, J = 7.0 Hz),. LCMS (APCI, $M+H^+$): 312.1. HRMS calcd for $C_{17}H_{15}N_3O_2F_1$ ($M+H^+$) 312.1148, found 312.1158. HPLC: 98.3% purity.

Example 3: 3-(4-Fluorobenzyl)-7-hydroxy-7,8,9,10-tetrahydropyrrolo[3',2':4,5]pyrido[2,3-*c*]azepin-6(3*H*)-one



Step 1: Ethyl 1-(4-Fluorobenzyl)-4-(3-hydroxyprop-1-yn-1-yl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate. To a solution of ethyl 1-(4-fluorobenzyl)-4-{[(trifluoromethyl)sulfonyl]oxy}-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (1.50g, 3.36mmol) in DMF (4 mL) was added propargyloxytrimethylsilane (0.73 g, 5.72 mmol), lithium chloride (0.214 g, 5.1mmol), copper iodide (0.028 g ml, 0.15 mmol), triethylamine (7ml, 50.4mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.052 g, 0.074 mmol). The resulting mixture was stirred for 20 min at 140 °C in a microwave reactor (Personal Chemistry). The solvent was evaporated and 10 mL ethyl acetate was added. After stirring for 10 min, the mixture was filtered through Celite™ and the filtrate was concentrated. Purification by flash chromatography (Biotage) over silica gel (1:3, hexane/ethyl acetate) afforded the title product as yellow oil (0.46 g, 46% yield). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 8.69 (s, 1 H) 7.36 (d, *J*=3.28 Hz, 1 H) 7.06 - 7.14 (m, 2 H) 6.98 - 7.06 (m, 2 H) 6.84 (d, *J*=2.53 Hz, 1 H) 5.40 (s, 2 H) 4.67 (s, 2 H) 4.48 (q, *J*=7.07 Hz, 2 H) 1.46 (t, *J*=7.20 Hz, 3 H). LC-MS (APCI, $M+H^+$): 353.1. HPLC: 96% purity.

Step 2: Ethyl 1-(4-fluorobenzyl)-4-(3-hydroxypropyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate. To a solution of ethyl 1-(4-fluorobenzyl)-4-(3-hydroxyprop-1-yn-1-yl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (0.46g, 1.31mmol) in MeOH (6 mL) was added palladium, (10 wt. % on activated carbon, 15 mg, 0.014 mmol). The resulting mixture was shaken in a Parr apparatus for 4 h at room temperature under H_2 at 60 psi. The mixture was filtered and concentrated to afford the title product as yellow oil (0.41 g, 88% yield). LC-MS (APCI, $M+H^+$): 357.2. HPLC: 96% purity.

Step 3: 1-(4-Fluorobenzyl)-4-(3-hydroxypropyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid. To a solution of ethyl 1-(4-fluorobenzyl)-4-(3-hydroxypropyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (0.41 g, 1.15 mmol) in MeOH (6 mL) was added a solution of sodium hydroxide (92mg, 2.30 mmol) in 1 mL of water. The resulting mixture was stirred for 5 h at 60 °C. The mixture was acidified to pH=6.5 by 1N HCl and concentrated to afford the title product as brown solid (358 mg, 95 % yield). LC-MS (APCI, $M+H^+$): 329.1. HPLC: 96% purity.

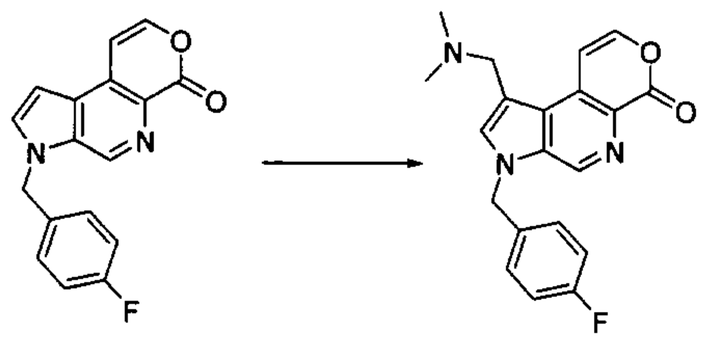
Step 4: 1-(4-Fluorobenzyl)-4-(3-hydroxypropyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-1*H*-pyrrolo[2,3-c]pyridine-5-carboxamide. To a solution of 1-(4-fluorobenzyl)-4-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-c]pyridine-5-carboxylic acid (358 mg, 1.1 mmol) in DMF (8 mL) was added triethylamine (333 mg, 3.3 mmol), HATU (627 mg, 1.65 mmol) and *O*-(tetrahydro-2*H*-pyran-2-yl)-hydroxylamine. The resulting mixture was stirred for 2.5 h at room temperature. The mixture was concentrated. Purification by flash chromatography (Biotage) over silica gel (100% ethyl acetate) afforded the title product as brown oil (149mg, 32% yield). LC-MS (APCI, $M+H^+$): 428.2. HPLC: 96% purity.

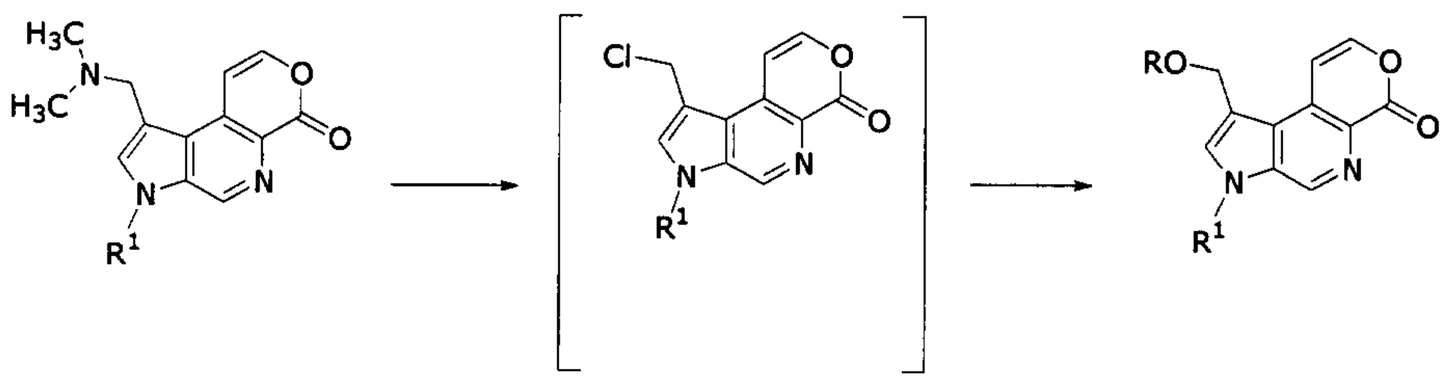
Step 5: 3-(4-Fluorobenzyl)-7-(tetrahydro-2*H*-pyran-2-yloxy)-7,8,9,10-tetrahydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3H)-one. To a solution of 1-(4-fluorobenzyl)-4-(3-hydroxypropyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-1*H*-pyrrolo[2,3-c]pyridine-5-carboxamide (149mg, 0.35 mmol) in THF (4 mL), was added PPh_3 (110 mg, 0.42mmol) and DIAD (85 mg, 0.42 mmol). The resulting mixture was stirred for 1 h at room temperature. The mixture was concentrated. Purification by flash chromatography (Biotage) over silica gel (100% ethyl acetate) afforded the title product as brown oil (18.5 mg, 13% yield). LC-MS (APCI, $M+H^+$): 410.1. HPLC: 96% purity.

Step 6: 3-(4-fluorobenzyl)-7-hydroxy-7,8,9,10-tetrahydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3*H*)-one. 3-(4-fluorobenzyl)-7-(tetrahydro-2*H*-pyran-2-yloxy)-7,8,9,10 tetrahydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3*H*)-one (18.53 mg, 0.045 mmol) was dissolved in acetic acid, THF and Water (3.5 ml, 5:1:1). The resulting mixture was stirred for 1 h at room temperature. The mixture was concentrated and purified by preparative HPLC to provide the title compound as a white powder (9.0 mg, 61% yield). 1H NMR (300 MHz, MeOH) □ ppm 8.57 (s, 1 H) 7.60 (d, *J*=3.20 Hz, 1 H) 7.11 - 7.20 (m, 2 H) 6.90 - 6.99 (m, 2 H) 6.72 (d, *J*=3.01 Hz, 1 H) 5.44 (s, 2 H) 3.51 (t, *J*=6.50 Hz, 2 H) 3.03 (t, *J*=7.16 Hz, 2 H) 2.14 - 2.25 (m, 2 H). LC-MS (APCI, $M+H^+$): 329.1. HPLC: 98% purity.

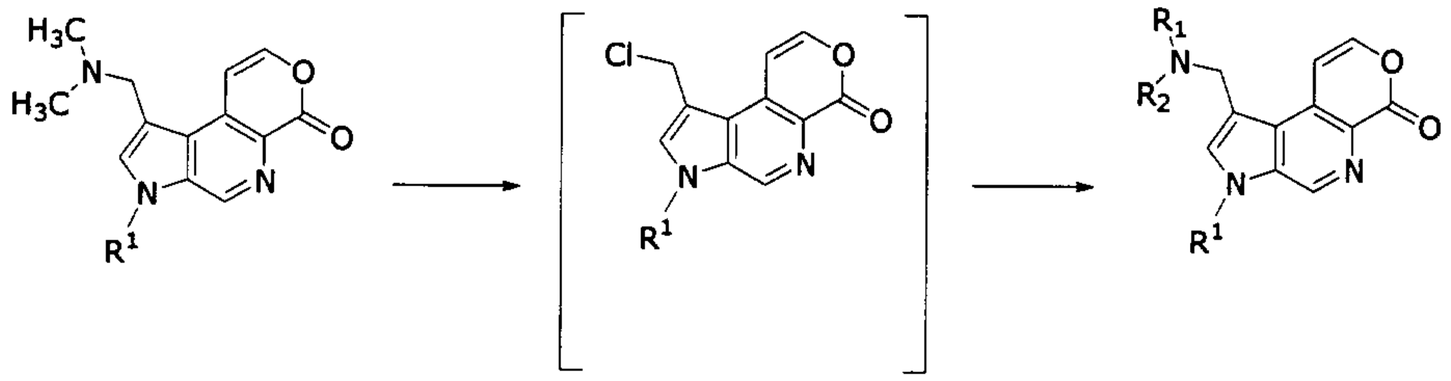
Examples 4-30:

Step 1: 9-[(dimethylamino)methyl]-7-(4-fluorobenzyl)pyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(7*H*)-one. To a solution of enol lactone (1.00 g, 3.401 mmol) stirred by an overhead stirrer in acetonitrile (25 mL) was added Eschenmoser's salt (0.64 g, 6.803 mmol) and the mixture was heated at reflux for 2 h. The solution was cooled to room temperature and the solid product was filtered. Saturated sodium bicarbonate was added to the filtrate and the mixture was extracted with dichloromethane (3x1000 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to give the product as a pure white solid (1.0 g, 84%). 1HNMR (DMSO-d6) δ, ppm: 9.10 (1H, s), 7.87 (1H, s), 7.68 (1H, d), 7.36 (1H, d), 7.34 (2H, m), 7.16 (2H, m), 5.62 (2H, s), 2.20 (6H, s). LCMS (ESI, M+1) 352.





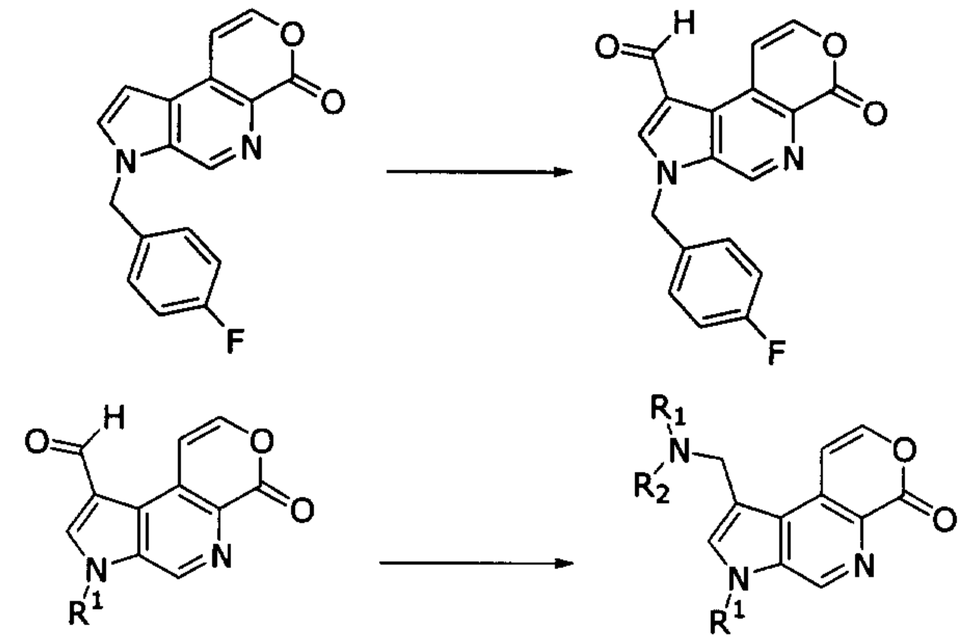
General Procedure A1: To a solution of the appropriate N,N-dimethylaminomethyl tricycle (1.0 eq, 0.197 M in dichloromethane) was added ethyl chloroformate (1.0 eq). The mixture was stirred for 1 h and then the appropriate alcohol (4.0 eq, 1 mM in anhydrous DMF) was added followed by diisopropyl ethylamine (5.0 eq). The mixture was placed under nitrogen and was warmed to 40 °C in an oil bath. After stirring for 48 h, the volatiles were removed *in vacuo* (ca. 2 torr) to give an oil. The crude material was diluted with ethyl acetate and washed with water and brine. The organic phase was separated, dried over sodium sulfate, and concentrated *in vacuo*. The residue was stirred in ether, filtered, and dried under vacuum to afford the desired product.



General Procedure A2: To a solution of the appropriate N,N-dimethylaminomethyl aromatic enol lactone (1.0 eq) in dichloromethane (6 mL/mmol enol lactone) were added diisopropylethylamine

(0.0 eq for free base, 1.0 eq for HI or HCl salt of N,N-dimethylaminomethyl aromatic enol lactone) and ethyl chloroformate (1.0 eq) at room temperature. After stirring at room temperature for ten minutes, DMF (4mL/mmol enol lactone), diisopropyl ethylamine (1.0 eq) and the amine (1.0 eq) were added to the reaction solution at room temperature. After stirring at room temperature for an additional hour, saturated aqueous sodium bicarbonate solution was added to the reaction mixture and it was extracted with dichloromethane (2X). The extracts were dried over sodium sulfate, the organic layer was concentrated under vacuum, and the product was optionally purified by reverse phase HPLC (acetonitrile:water, 0.1% acetic acid) to provide the desired compound.

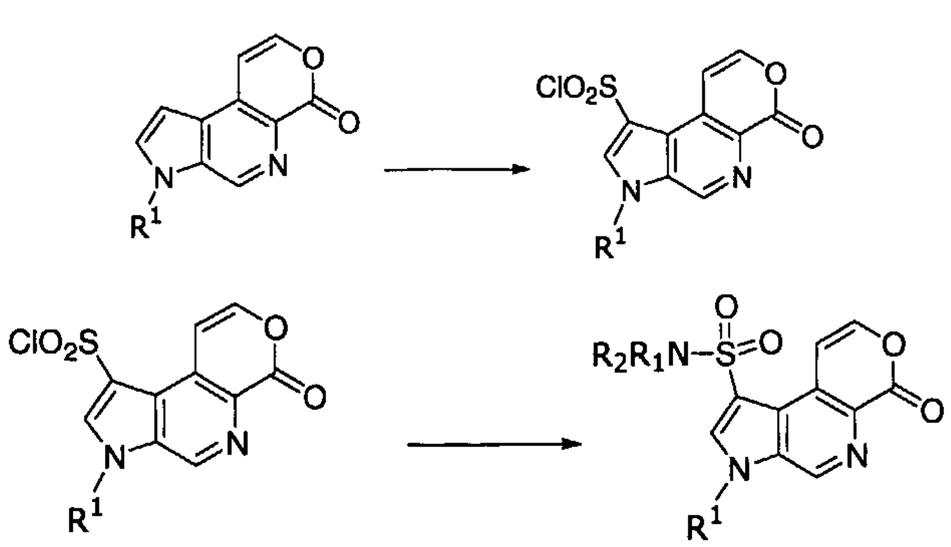
Step 2: 7-(4-fluorobenzyl)-4-oxo-4,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridine-9-carbaldehyde. To a solution of enol lactone (2.0 g, 6.803 mmol) in DMF (20 mL) was added Eschenmoser's salt (2.5 g, 13.605 mmol) and the mixture was heated in a microwave at 130 C for 2 h. More Eschenmoser's salt (2.5 g, 13.605 mmol) was added and the mixture was heated again in the microwave at 130 C for 2 h. The mixture was concentrated under reduced pressure and the resulting residue was suspended in acetone:water (1:1) and filtered to give a the aldehyde as a pure pale brown solid (1.41 g, 64%). 1NMR (DMSO-d6) δ 9.98 (1H, s), 9.26 (1H, s), 8.93 (1H, s), 8.12 (1H, d), 7.75 (1H, d), 7.47 (2H, m), 7.21 (1H, m), 5.77 (2H, s). LC/MS (ESI, M+1) 323.



General Procedure A3: To a solution of the appropriate aldehyde (1.0 eq) in dichloromethane (0.2 M) was added the appropriate amine (1.0 eq). After stirring at room temperature for 2 h, sodium triacetoxyborohydride (3.0 eq) was added. The mixture was allowed to stir at room temperature for an additional 18-24 h, after which time the solvent was removed under vacuum. The remaining residue was dissolved in DMSO and purified by reverse phase prep HPLC (acetonitrile:water, 0.1% acetic acid) to provide the desired compounds.

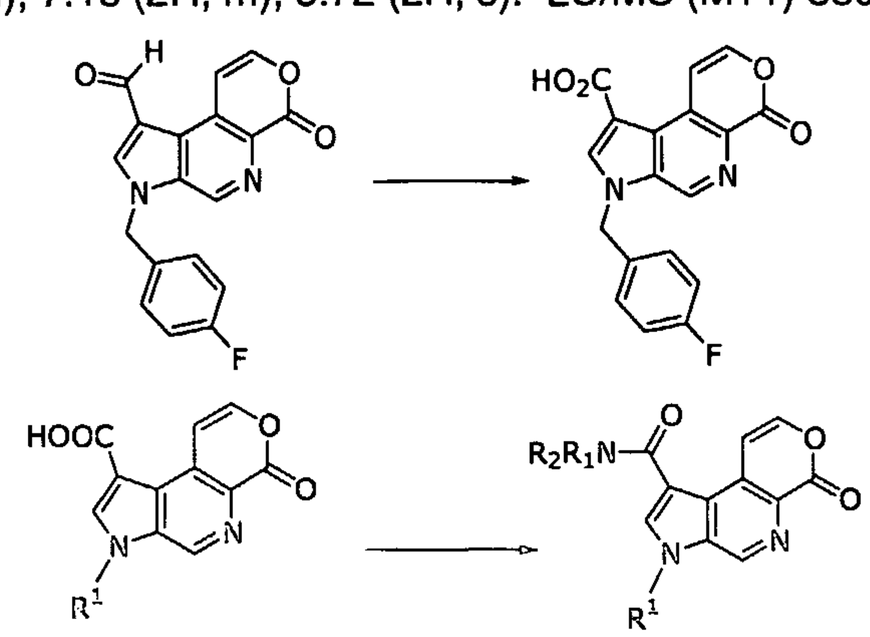
Step 3: 7-(4-fluorobenzyl)-4-oxo-4,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridine-9-sulfonyl chloride. To a solution of the 7-(4-fluorobenzyl)pyrano[3,4-b]pyrrolo[3,2-d]pyridin-4(7H)-one(1.0 eq) in chlorosulfonic acid (60 eq, 0.55 M) was added thionyl chloride(30 eq). The mixture was stirred for 2 hrs at room temperature and the reaction was judged to be complete by HPLC-MS

analysis. The mixture was added dropwise to ice water and the suspension was filtered to provide the sulfonyl chloride as a pure, white solid in 86% yield. 1HNMR (MeOH-d4) δ 9.31 (1H, s), 8.95 (1H, s), 7.79 (1H, d), 7.74 (1H, d), 7.47 (2H, m), 7.15 (2H, m), 5.80 (2H, s). LC/MS (ESI, M+1) 393..

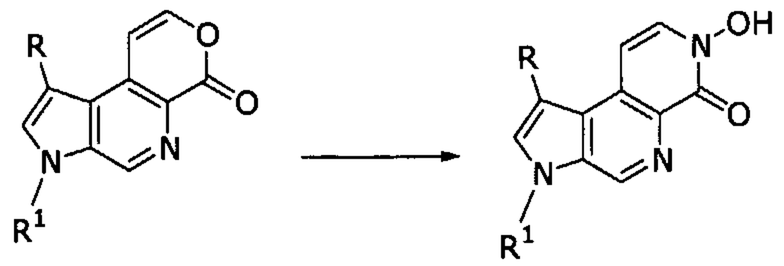


General Procedure A5: To a solution of the appropriate sulfonyl chloride (1.0 eq, 0.13 M in THF) and diisopropyl ethylamine (DIEA, 1.1 eq) was added the amine (1.0 eq). The mixture was stirred for 2 h at room temperature or until the reaction was judged to be complete by HPLC-MS analysis. The volatiles were removed under vacuum and the crude material was diluted with dichloromethane and washed with saturated sodium bicarbonate. The organic phase was separated, dried over sodium sulfate, and concentrated under vacuum. The crude material was purified by reverse phase HPLC (acetonitrile:water, 0.1% AcOH) to provide the desired compound.

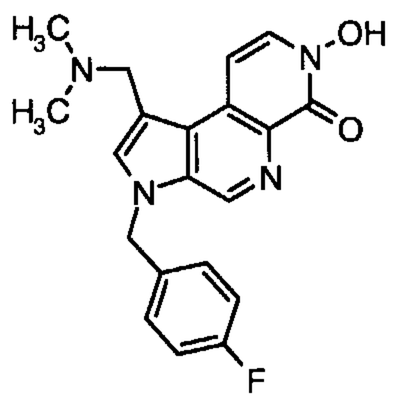
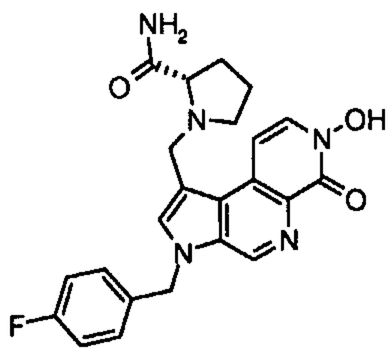
Step 4: 7-(4-fluorobenzyl)-4-oxo-4,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridine-9-carboxylic acid. To a stirring solution of the aldehyde (1.30 g, 4.034 mmol) in dioxane:water (3:1, 40 mL) was added sodium chlorite (0.547 g, 6.050 mmol) followed by sulfamic acid (2.23 g, 22.99 mmol). The solution was stirred for several hours until LC/MS showed the reaction to be complete. The dioxane was mostly removed under reduced pressure and the resulting suspension in water was filtered and the filtrate was washed with acetone to provide the acid as an off-white solid (1.20 g, 88%). 1HNMR (DMSO-d6) δ 9.20 (1H, s), 8.69 (1H, s), 8.38 (1H, d), 7.71 (1H, d), 7.44 (1H, m), 7.18 (2H, m), 5.72 (2H, s). LC/MS (M+1) 339.

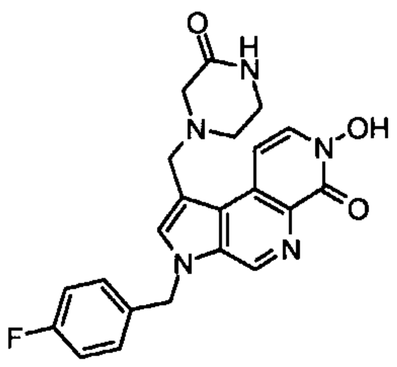
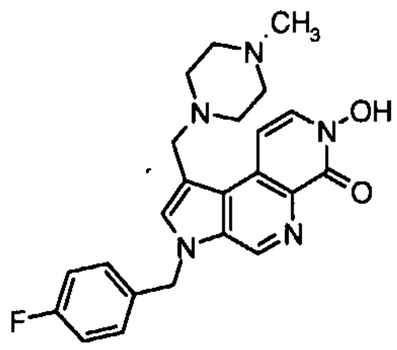
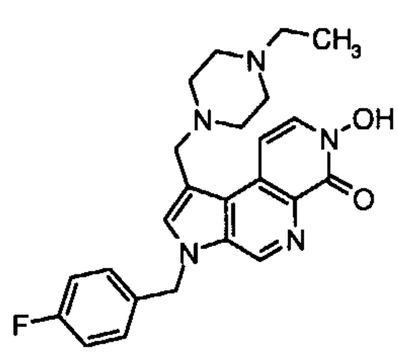
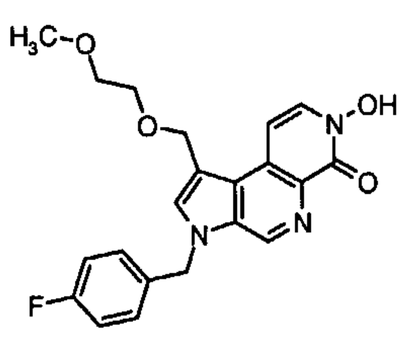
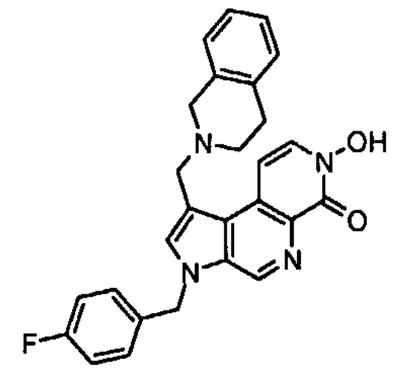


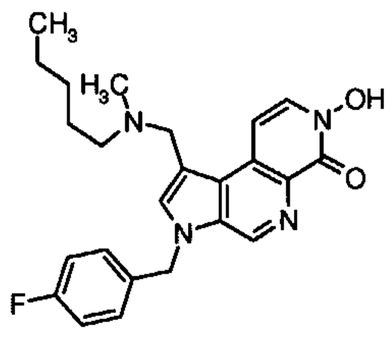
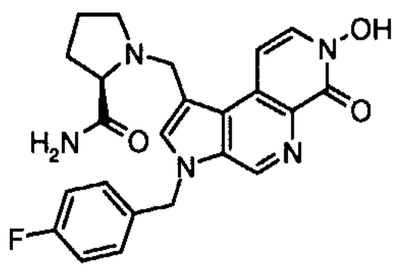
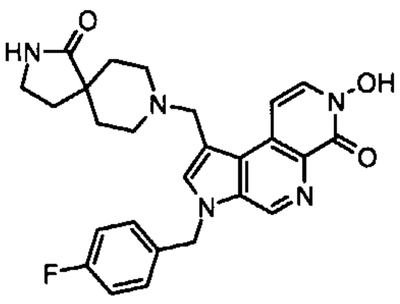
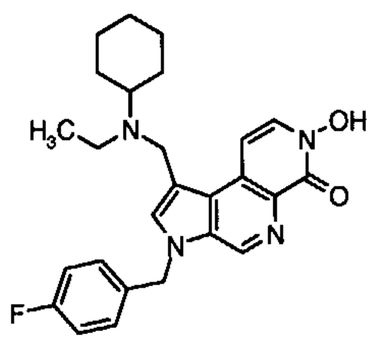
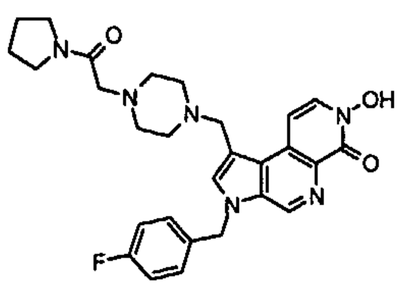
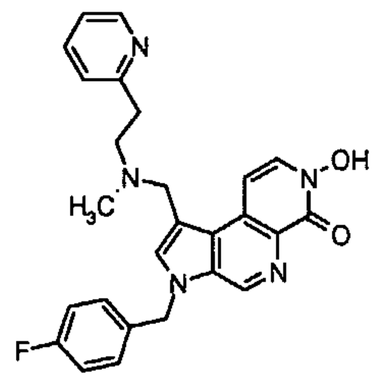
General Procedure A6: To a solution of the appropriate carboxylic acid (1.0 eq, 0.07 M in DMF) and 4-methylmorpholine (NMM, 3.2 eq) was added 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, 1.2 eq). The mixture was stirred at room temperature for 1h and the appropriate amine (2.0 eq) was added. The resulting mixture was allowed to stir at room temperature for several hours until the reaction was judged to be complete by HPLC-MS analysis. The volatiles were removed under vacuum and the crude material was diluted with ethyl acetate and washed with saturated sodium bicarbonate. The organic phase was separated, dried over sodium sulfate, and concentrated under vacuum. The crude material was purified by reverse phase HPLC (acetonitrile:water, 0.1% AcOH) to provide the desired compounds.

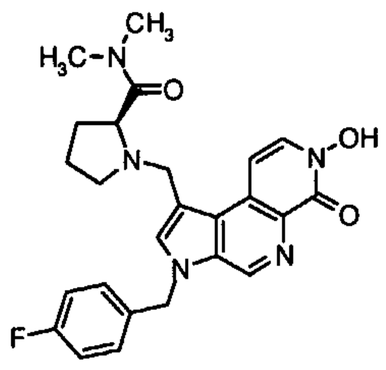
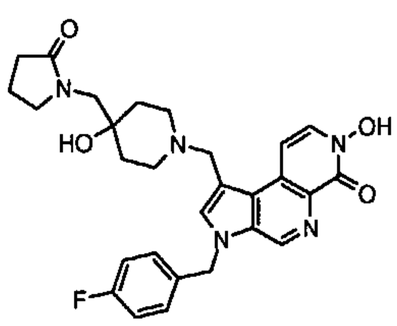
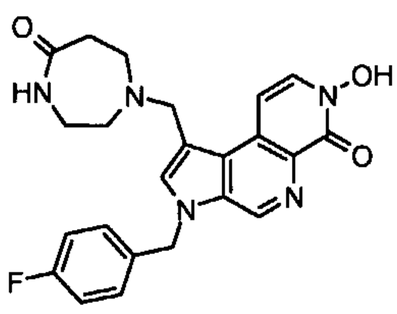
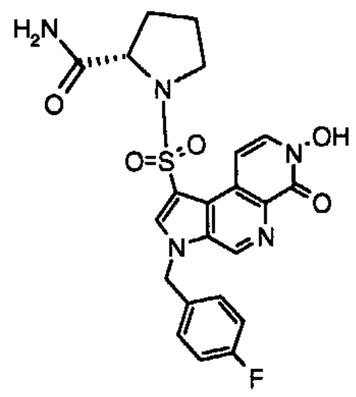
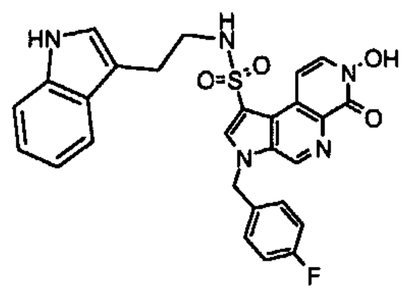


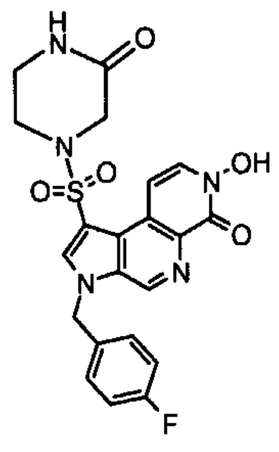
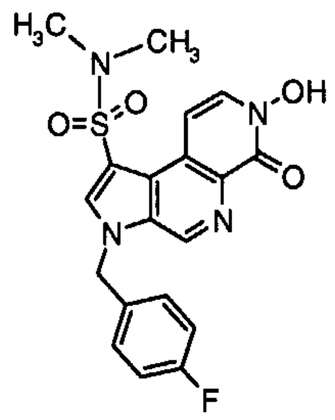
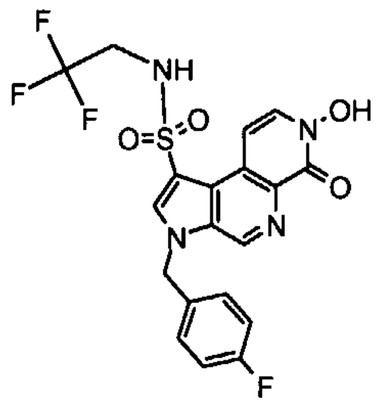
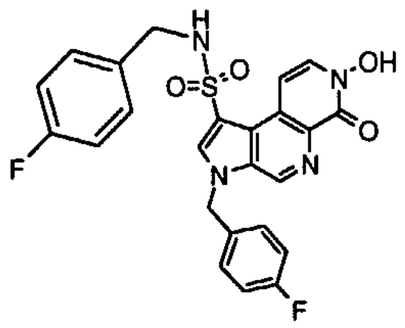
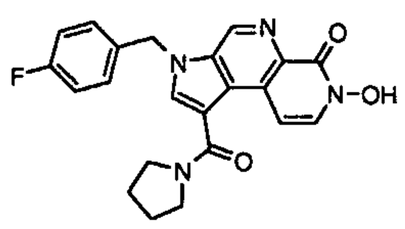
General Procedure B1: A solution of the enol lactone (1.0 eq) in ethanol (27 mL/mmol enol lactone) and hydroxylamine (50w% in water, 0.68 mL/ mmol enol lactone) was refluxed for 3 h or until the LC/MS showed complete conversion to the desired N-hydroxypyridone. The resulting solution was concentrated and purified by reverse phase HPLC (acetonitrile: water, 0.1% AcOH) to provide the desired compound.

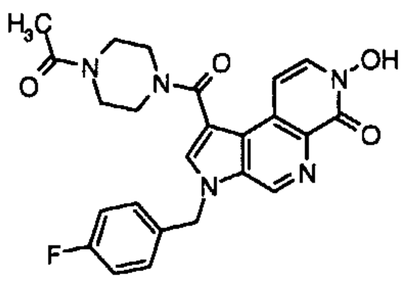
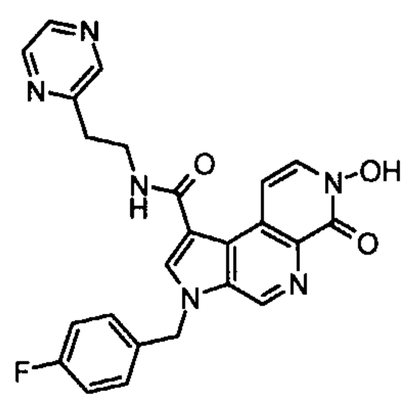
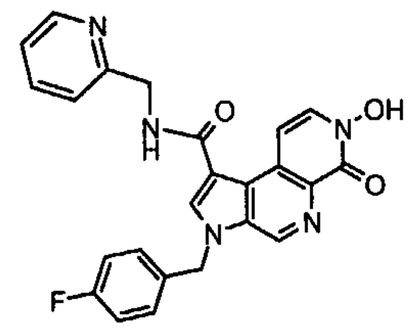
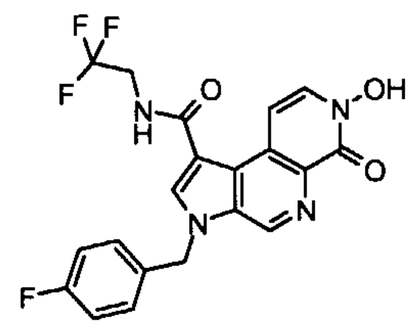
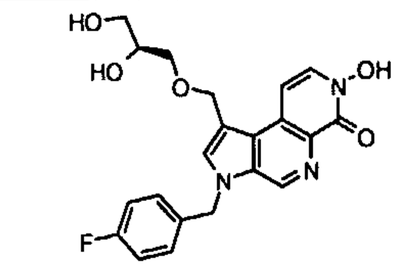
No.	Structure	Name	Proc.	^{1}H NMR
4		1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(DMSO-D6, 400 MHz) δ 9.01 (1H, s), 7.80 (1H, d), 7.77 (1H, s), 7.31 (2H, m), 7.17 (1H, d), 7.16 (2H, m), 5.61 (2H, s), 3.60 (2H, s), 2.19 (6H, s)
5		1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-L-prolinamide	A2, B1	(DMSO-d6, 400 MHz) δ 11.5 (1H, bs), 8.97 (1H, s), 7.84 (1H, s), 7.78 (1H, d), 7.26 (1H, d), 7.25 (2H, m), 7.13 (2H, m), 6.89 (1H, bs, NH), 6.77 (1H, bs, NH), 5.61 (2H, s), 3.95 (2H, s), 3.09 (2H, m), 2.10 (1H, m), 1.73 (4H, m)

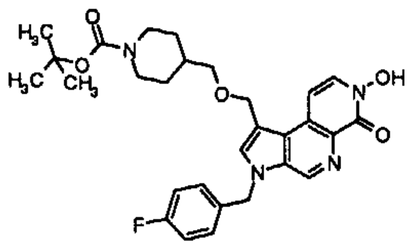
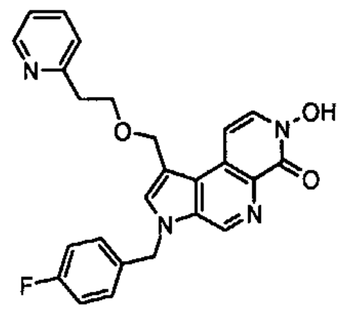
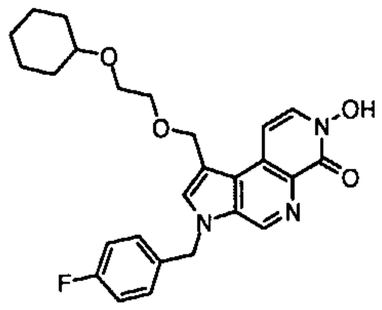
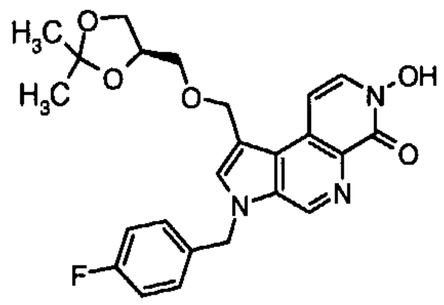
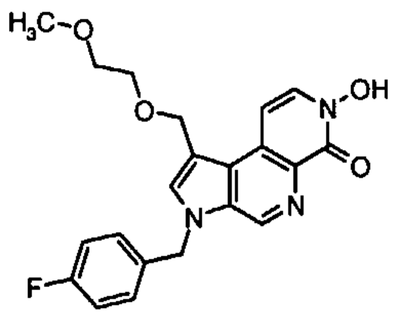
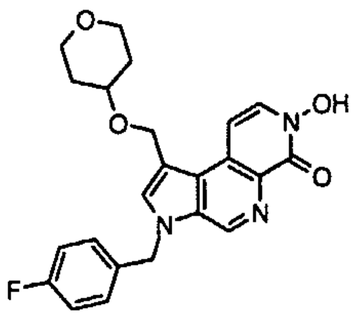
6		3-(4-fluorobenzyl)-7-hydroxy-1-[(3-oxopiperazin-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(DMSO-d6, 400 MHz) δ 9.03 (1H, s), 7.82 (1H, s), 7.80 (1H, s), 7.75 (1H, s), 7.34 (2H, m), 7.16 (2H, m), 5.62 (2H, s), 3.79 (2H, s), 3.12 (2H, m); 2.96 (2H, s), 2.63 (2H, m)
7		3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(MeOH-d4, 400 MHz) δ 8.93 (1H, s), 7.78 (1H, d), 7.68 (1H, s), 7.48 (2H, d), 7.26 (2H, m), 7.05 (2H, m), 5.59 (2H, s), 3.88 (2H, s), 2.50-3.00 (8H, m), 2.56 (3H, s)
8		1-[(4-ethylpiperazin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(MeOH-d4, 400 MHz) δ 8.94 (1H, s), 7.78 (1H, d), 7.70 (1H, s), 7.43 (2H, d), 7.27 (2H, m), 7.06 (2H, m), 5.60 (2H, s), 3.93 (2H, s), 3.75-2.50 (8H, m), 3.09 (2H, q), 1.29 (3H, t)
9		3-(4-fluorobenzyl)-7-hydroxy-1-[(2-methoxyethoxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A1, B1	(DMSO-D6, 300 MHz) d 9.10, (1H, s), 7.90 (1H, s), 7.88 (1H, d), 7.38 (2H, m), 7.22 (2H,t), 7.02 (1H, d), 5.66 (2H, s), 4.78 (2H, s), 3.66 (2H, m), 3.52 (2H, m), 3.38 (3H, s).
10		1-(3,4-dihydroisoquinolin-2(1H)-ylmethyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(DMSO-D6, 300 MHz) δ 11.44(1H, s), 9.03 (1H, s), 7.86(1H, s), 7.75 (1H, d), 7.35 (2H, m), 7.20 (3H, m), 7.08 (3H, m), 6.99(1H, m), 5.64 (2H, s), 3.90 (2H, s), 3.60 (2H, s), 2.79 (4H, m)

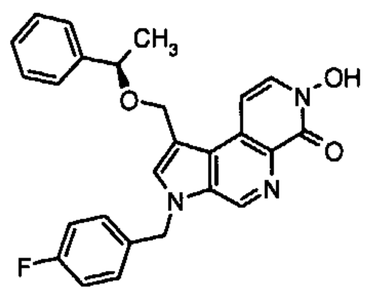
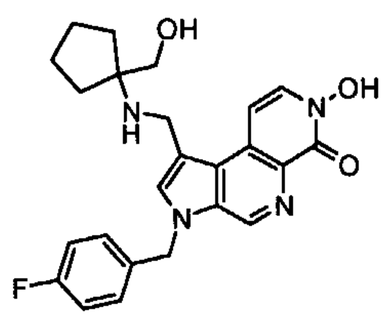
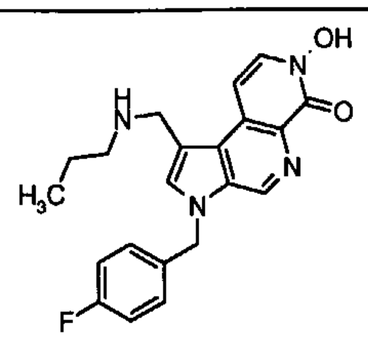
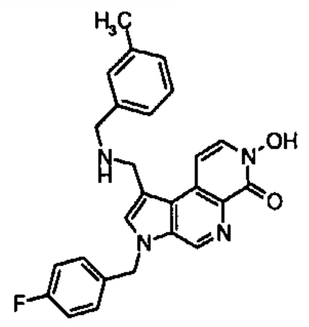
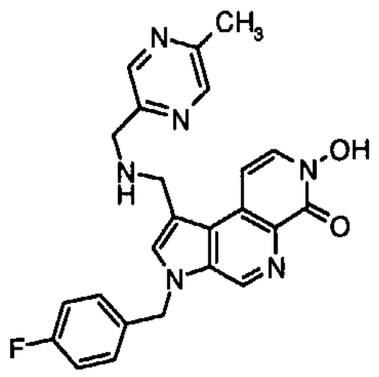
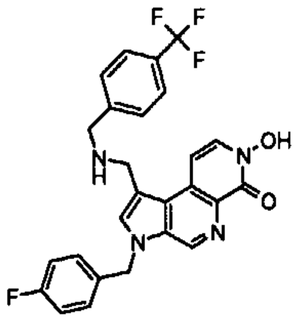
11		3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(pentyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(MeOD-D4, 300 MHz) δ 8.93 (1H, s), 7.75(2H, m), 7.40 (1H, d), 7.27 (2H, m), 7.06 (2H, t), 5.62 (2H, s), 4.17 (2H, s), 2.75 (2H, m), 2.49 (3H, m), 1.62 (1H,m), 1.26 (4H, m), 0.82 (3H, t)
12		1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-D-prolinamide	A2, B1	(DMSO-D6, 300 MHz) δ 11.46 (1H, s), 8.96 (1H, s), 7.83 (1H, s), 7.79 (1H, d), 7.25 (3H, m), 7.13 (2H, d), 6.88 (1H, s), 6.67 (1H, s), 5.60 (2H, s), 3.95 (2H, s), 3.07 (2H, m), 2.49 (1H, m), 2.15 (1H,m), 1.71 (3H, m)
13		3-(4-fluorobenzyl)-7-hydroxy-1-[(1-oxo-2,8-diazaspiro[4.5]dec-8-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(DMSO-D6, 300 MHz) δ 9.01 (1H, s), 7.82 (1H, d), 7.76 (1H, s), 7.51 (1H,s), 7.32 (2H, m), 7.26 (1H, d), 7.15 (2H, t), 5.61 (2H, s), 3.68 (2H, s), 3.13 (2H, t), 2.82 (2H, d), 2.03 (2H, d), 1.90 (2H, m), 1.63 (2H, t), 1.28 (2H, d)
14		1-{[cyclohexyl(ethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(DMSO-D6, 300 MHz) δ 11.44(1H, s), 9.02 (1H, s), 7.79 (2H, m), 7.44 (1H, d), 7.29 (2H, m), 7.14 (2H, t), 5.62 (2H, s), 3.90 (2H, s), 3.31 (1H, m), 2.53 (2H, q), 1.72 (3H, m), 1.52 (1H, m), 1.24 (2H,m), 1.04 (3H, m), 0.94 (4H, m)
15		3-(4-fluorobenzyl)-7-hydroxy-1-{[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(DMSO-D6, 300 MHz) δ 11.47 (1H, s), 9.01 (1H, s), 7.76 (2H, m), 7.75 (1H, d), 7.33 (2H, m), 7.15 (3H, m), 5.60 (2H, s), 3.90 (2H, s), 3.70 (2H, s), 3.43 (2H, t), 3.24 (2H, t), 3.03 (2H, s), 2.40 (4H, s), 1.82 (2H, m), 1.73 (2H, m)
16		3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(2-pyridin-2-ylethyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(DMSO-D6, 300 MHz) δ 11.41 (1H, s), 8.99 (1H, s), 8.33 (1H, d), 7.75 (1H, s), 7.65 (1H, d), 7.55 (1H, t), 7.30 (2H, t), 7.11 (5H, m), 5.60 (2H, s), 3.73 (2H, s), 2.89 (2H, m), 2.80 (2H, m), 2.25 (3H, s)

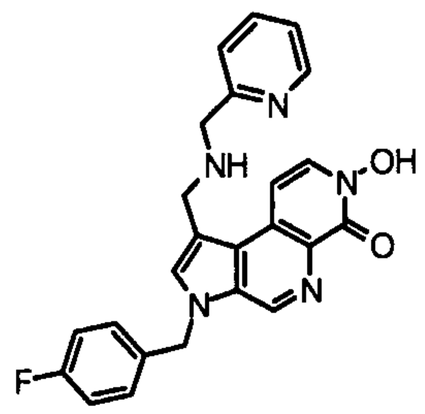
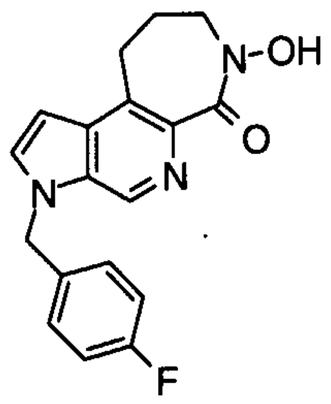
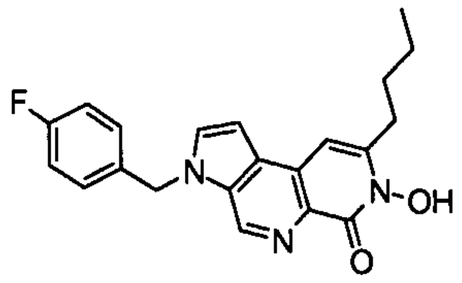
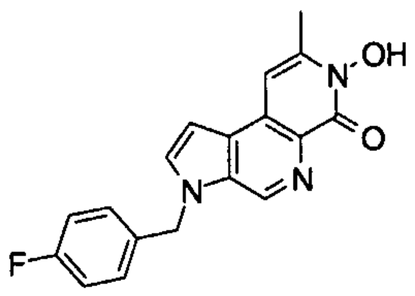
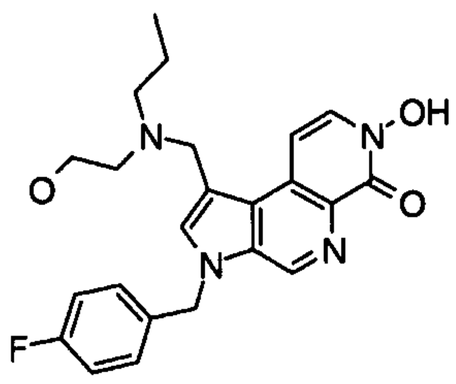
17		(3R)-1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-N,N-dimethylpyrrolidine-3-carboxamide	A2, B1	(DMSO-D6, 300 MHz) δ 11.46 (1H, s), 9.00 (1H, s), 7.68 (3H, m), 7.34 (2H, m), 7.16 (2H, t), 5.59 (2H, s), 4.08 (1H,d), 3.69 (1H, d), 3.45 (1H, m), 2.88 (2H, m), 2.82 (3H, s), 2.69 (3H, s), 2.10 (1H, m), 1.70 (3H, m)
18		3-(4-fluorobenzyl)-7-hydroxy-1-({4-hydroxy-4-[(2-oxopyrrolidin-1-yl)methyl]piperidin-1-yl}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(DMSO-D6, 300 MHz) δ 11.50 (1H, s), 9.00 (1H, s), 7.78 (2H, m), 7.33 (2H, m), 7.25 (1H, d), 7.16 (2H, t), 5.60 (2H, s), 4.39 (1H,s), 3.68 (2H, s), 3.48 (2H, t), 3.12 (2H, s), 2.50 (6H, m), 2.18 (2H, t), 1.87 (2H, m), 1.41 (4H, s)
19		3-(4-fluorobenzyl)-7-hydroxy-1-[(5-oxo-1,4-diazepan-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(DMSO-D6, 300 MHz) δ 11.46 (1H, s), 9.01 (1H, s), 7.78 (2H, m), 7.54 (1H, m), 7.32 (3H, m), 7.16 (2H, t), 5.61 (2H, s), 3.80 (2H, s), 3.09 (2H, m), 2.55 (4H, m), 2.41 (2H, m)
20		1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]sulfonyl}-L-prolinamide	A5, B1	(CD3OD, 400 MHz) d 8.97 (1H, s), 8.40 (1H, s), 7.90 (1H, d), 7.77 (1H, d), 7.26 (2H, m), 7.01 (2H, m), 5.60 (2H, s), 4.08 (1H, m), 3.52 (1H, m), 3.32 (1H, m), 1.85 (3H, m), 1.61 (1H, m)
21		3-(4-fluorobenzyl)-7-hydroxy-N-[2-(1H-indol-3-yl)ethyl]-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide	A5, B1	(CD3OD, 400 MHz) d 8.71 (1H, s), 7.96 (1H, s), 7.55 (1H, d), 7.35 (1H, d), 7.19 (2H, m), 6.98 (4H, m), 6.80 (1H, m), 6.56 (2H, m), 5.37 (2H, s), 3.27 (2H, m), 2.72 (2H, m)

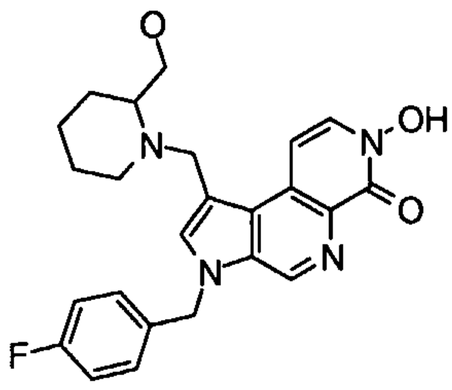
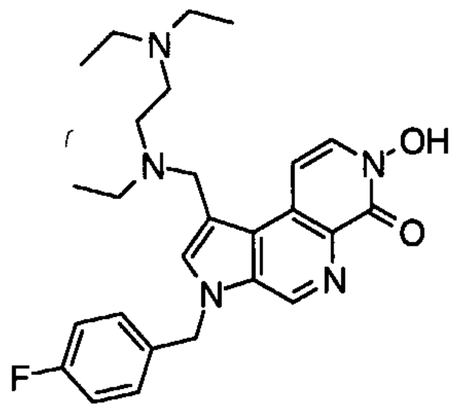
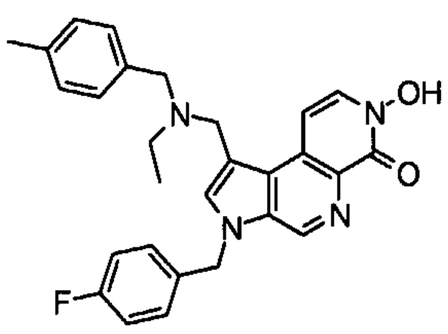
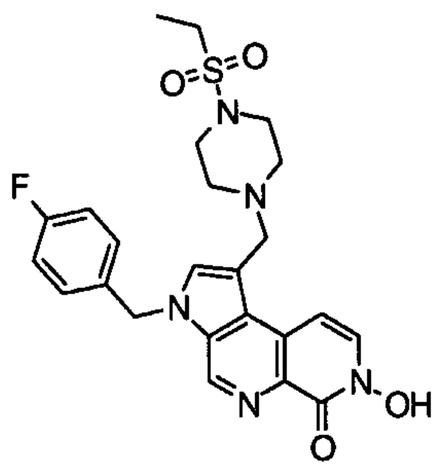
22		3-(4-fluorobenzyl)-7-hydroxy-1-[(3-oxopiperazin-1-yl)sulfonyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A5, B1	(DMSO-D6, 400 MHz) d 9.11 (1H, s), 8.64 (1H, s), 7.91 (1H, d), 7.45 (3H, m), 7.15 (2H, m), 5.72 (2H, s), 3.60 (2H, m), 3.34 (2H, m), 3.18 (2H, m)
23		3-(4-fluorobenzyl)-7-hydroxy-N,N-dimethyl-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide	A5, B1	(CD3OD, 400 MHz) d 8.99 (1H, s), 8.32 (1H, s), 7.80 (2H, m), 7.20 (2H, m), 7.05 (2H, m), 5.67 (2H, s), 2.69 (6H, s)
24		3-(4-fluorobenzyl)-7-hydroxy-6-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide	A5, B1	(CD3OD, 400 MHz) d 8.95 (1H, s), 8.28 (1H, s), 7.74 (1H, d), 7.66 (1H, d), 7.25 (2H, m), 7.02 (2H, m), 5.63 (2H, s), 3.65 (2H, m)
25		N,3-bis(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide	A5, B1	(CD3OD, 400 MHz) d 8.90 (1H, s), 8.15 (1H, s), 7.73 (1H, d), 7.69 (1H, d), 7.25 (2H, m), 7.05 (2H, m), 6.88 (2H, m), 6.53 (2H, m), 5.55 (2H, s), 4.07 (2H, s)
26		3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylcarbonyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A6, B1	(CD3OD, 400 MHz) d 8.92 (1H, s), 8.00 (1H, s), 7.69 (1H, d), 7.23 (2H, m), 7.14 (1H, d), 6.98 (2H, m), 5.60 (2H, s), 3.64 (2H, m), 3.44 (2H, m),1.95 (2H, m),1.85(2H, m)

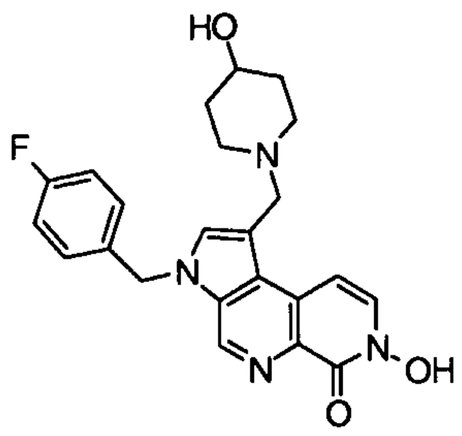
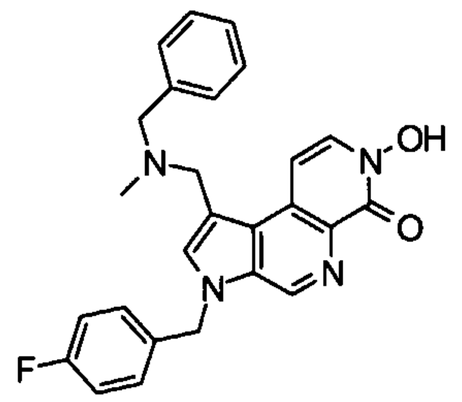
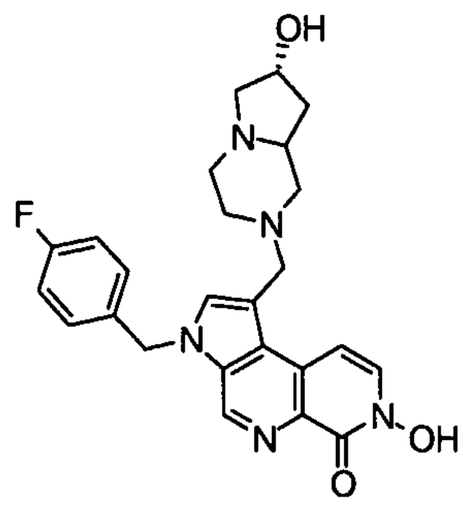
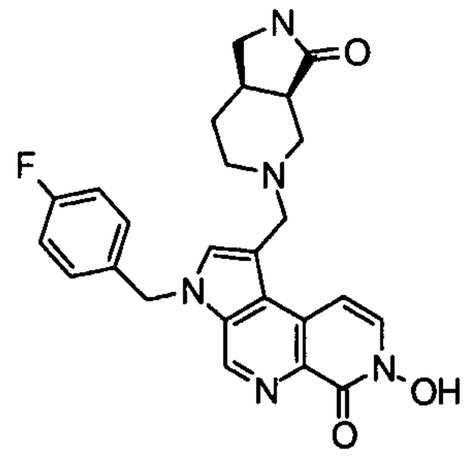
27		1-[(4-acetylpiperazin-1-yl)carbonyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A6, B1	(CD3OD, 400 MHz) d 8.94 (1H, s), 7.93 (1H, s), 7.71 (1H,d), 7.25 (2H, m), 6.98 (3H, m), 5.60 (2H, s), 3.70 (2H, m), 3.54 (4H, m), 2.05 (2H, s)
28		3-(4-fluorobenzyl)-7-hydroxy-6-oxo-N-(2-pyrazin-2-ylethyl)-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide	A6, B1	CD3OD, 400 MHz) d 8.90 (1H, s), 8.52 (1H, s), 8.48 (1H, d), 8.38 (1H, d), 7.96 (1H, s), 7.67 (2H, d), 7.23 (2H, m), 6.98 (2H, m), 5.60 (2H, s), 3.76 (2H, m), 3.11 (2H, m)
29		3-(4-fluorobenzyl)-7-hydroxy-6-oxo-N-(pyridin-2-ylmethyl)-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide	A6, B1	(CD3OD, 400 MHz) d 8.92 (1H, s), 8.54 (1H, s), 8.39 (1H, d), 8.12 (1H, s), 7.84 (2H, d), 7.65 (1H, d), 7.36 (1H, m), 7.24 (2H, m), 6.98 (2H, m), 5.60 (2H, s), 4.58 (2H, s)
30		3-(4-fluorobenzyl)-7-hydroxy-6-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide	A6, B1	(CD3OD, 400 MHz) d 8.92 (1H, s), 8.12 (1H, s), 7.88 (1H, d), 7.67 (1H, d), 7.24 (2H, m), 6.98 (2H, m), 5.60 (2H, s), 4.05 (2H, m)
31		1-({[(2S)-2,3-dihydroxypropyl]oxy}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A1, B1	(DMSO-D6, 300 MHz) δ 9.07, (1H, s), 7.92 (1H, s), 7.86 (1H, d), 7.36 (2H, m), 7.23 (2H, t), 7.07 (1H, d), 5.66 (2H, s), 4.82 (2H, s), 4.70 (1H, br), 4.52 (1H, br), 3.70-3.20 (4H, m).

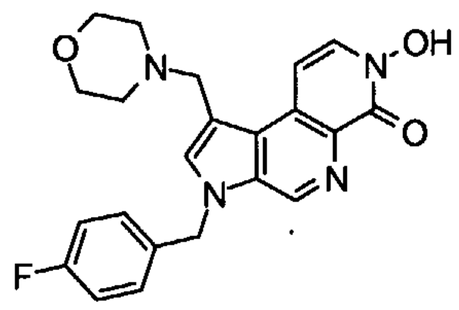
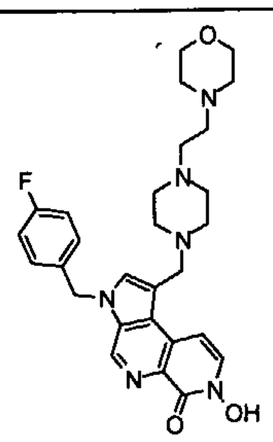
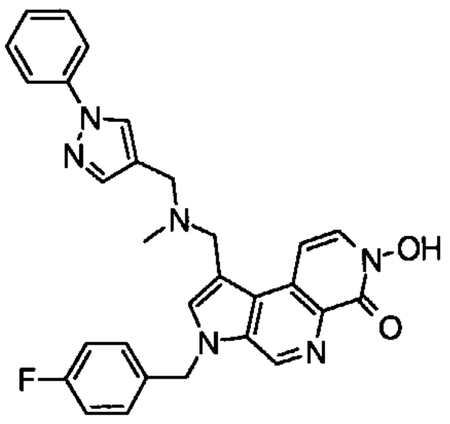
32		tert-butyl 4-({[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methoxy}methyl)piperidine-1-carboxylate	A1, B1	(DMSO-D6, 300 MHz) δ 9.08, (1H, s), 7.92 (2H, d), 7.36 (2H, t), 7.27 (2H, t), 6.96 (1H, d), 5.66 (2H, s), 4.77 (2H, s), 3.90 (2H, d), 3.36 (1H, m), 2.64 (3H, m), 1.60 (3H, m), 1.36 (9H, s), 1.02(2H, m)
33		3-(4-fluorobenzyl)-7-hydroxy-1-[(2-pyridin-2-ylethoxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A1, B1	(CD3OD, 300 MHz) δ 8.87 (1H, s), 8.16 (1H, d), 7.80-7.50 (2H, m), 7.44 (1H, d), 7.44-6.80 (7H, m), 5.63 (2H, s), 4.92 (2H, s), 3.88 (2H, m), 3.00 (2H, m).
34		1-{[2-(cyclohexyloxy)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A1, B1	(DMSO-D6, 300 MHz) δ 9.07, (1H, s), 7.92 (1H, s), 7.84 (1H, d), 7.37 (2H, m), 7.23 (2H, t), 7.08 (1H, d), 5.66 (2H, s), 4.83 (2H, s), 3.70-3.30 (4H, m), 3.23 (1H, m), 1.86-1.32 (5H, m), 1.30-1.00 (5H, m).
35		1-[({[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}amino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A1, B1	(DMSO-D6, 300 MHz) δ 9.10, (1H, s), 7.92 (1H, s), 7.87 (1H, d), 7.38 (2H, m), 7.22 (2H,t), 6.98 (1H, d), 5.66 (2H, s), 4.84 (2H, s), 4.22 (1H, m), 3.98 (1H,t), 3.56 (3H, t), 1.26 (6H, d).
36		3-(4-fluorobenzyl)-7-hydroxy-1-[(2-methoxyethoxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A1, B1	(DMSO-D6, 300 MHz) δ 9.10, (1H, s), 7.90 (1H, s), 7.88 (1H, d), 7.38 (2H, m), 7.22 (2H,t), 7.02 (1H, d), 5.66 (2H, s), 4.78 (2H, s), 3.66 (2H, m), 3.52 (2H, m), 3.38 (3H, s).
37		3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-yloxy)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A1, B1	(DMSO-D6, 300 MHz) δ 9.08, (1H, s), 7.90 (2H, m), 7.36 (2H, m), 7.23 (2H, m), 7.07 (1H, d), 5.68 (2H, s), 4.86 (2H, s), 3.86 (2H, m), 3.68 (1H, m), 3.38 (2H, m), 1.92 (2H, m,), 1.49 (2H, m).

38		3-(4-fluorobenzyl)-7-hydroxy-1-{[(1R)-1-phenylethoxy]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A1, B1	(DMSO-D6, 300 MHz) δ 9.07, (1H, s), 8.85 (1H, br) 7.83 (2H, m), 7.50-7.27 (7H, m), 7.20 (2H, t), 6.97 (1H, d) 5.66 (2H, s), 4.66 (3H, m),1.42 (3H, d).
39		3-(4-fluorobenzyl)-7-hydroxy-1-({[1-(hydroxymethyl)cyclopentyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A3, B1	(300 MHz, MeOH) d ppm 8.75 (s, 1 H) 7.65 - 7.78 (m, 2 H) 7.22 - 7.32 (m, 2 H) 7.19 (d, 1 H) 7.04 (t, 2 H) 5.52 (s, 2 H) 4.38 (s, 2 H) 3.77 (s, 2 H) 1.82 - 1.98 (m, 6 H) 1.72 (s, 2 H)
40		3-(4-fluorobenzyl)-7-hydroxy-1-[(propylamino)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A3, B1	(300 MHz, DMSO-D6) d ppm 9.02 (s, 1 H) 7.70 - 7.83 (m, 2 H) 7.33 (m, 2 H) 7.09 - 7.22 (m, 3 H) 5.60 (s, 2 H) 3.97 (m, 2 H) 1.44 (m, 2 H) 0.86 (t, 3 H)
41		3-(4-fluorobenzyl)-7-hydroxy-1-{[(3-methylbenzyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A3, B1	(300 MHz, MeOH) d ppm 8.78 (s, 1 H) 7.55 - 7.69 (m, 2 H) 7.23 (s, 4 H) 7.13 (s, 1 H) 7.02 (s, 3 H) 6.86 (s, 1 H) 5.53 (s, 2 H) 4.21 (s, 2 H) 3.99 (s, 2 H) 2.32 (s, 3 H)
42		3-(4-fluorobenzyl)-7-hydroxy-1-({[(5-methylpyrazin-2-yl)methyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A3, B1	(300 MHz, MeOH) d ppm 8.80 (s, 1 H) 8.42 - 8.50 (m, 1 H) 8.39 (s, 1 H) 7.78 (d, 1 H) 7.66 (s, 1 H) 7.18 - 7.33 (m, 3 H) 7.05 (t, 2 H) 5.57 (s, 2 H) 4.21 (s, 2 H) 4.03 (s, 2 H) 2.36 - 2.51 (s, 3 H)
43		3-(4-fluorobenzyl)-7-hydroxy-1-({[4-(trifluoromethyl)benzyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A3, B1	(300 MHz, MeOH) d ppm 8.89 (s, 1 H) 7.69 (m, 2 H) 7.59 (m , 4 H) 7.15 - 7.30 (m, 3 H) 6.95 - 7.09 (m, 2 H) 5.57 (s, 2 H) 4.17 (s, 2 H) 4.00 (s, 2 H)

44		3-(4-fluorobenzyl)-7-hydroxy-1-{[(pyridin-2-ylmethyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A3, B1	(CD3OD, 300 MHz) d 8.87 (1H, s), 8.16 (1H, d), 7.80-7.50 (2H, m), 7.44 (1H, d), 7.44-6.80 (7H, m), 5.63 (2H, s), 4.92 (2H, s), 3.88 (2H, m), 3.00 (2H, m).
45		3-(4-fluorobenzyl)-7-hydroxy-7,8,9,10-tetrahydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3H)-one		(300 MHz, MeOH) d ppm 8.65 (s, 1 H) 7.68 (d, 1 H) 7.19 - 7.29 (m, 2 H) 6.97 - 7.08 (m, 2 H) 6.81 (d, 1 H) 5.53 (s, 2 H) 3.60 (t, 2 H) 3.12 (t, 2 H) 2.22 - 2.35 (m, 2 H)
46		8-butyl-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one		(300 MHz, MeOH) d ppm 8.85 (s, 1 H) 7.69 (s, 1 H) 7.26 (dd, 2 H) 7.00 - 7.11 (m, 3 H) 6.90 (s, 1 H) 5.61 (s, 2 H) 2.87 - 2.97 (t, 2 H) 1.73 - 1.86 (m, 2 H) 1.42 - 1.57 (m, 2 H) 1.00 (t, 3 H)
47		3-(4-fluorobenzyl)-7-hydroxy-8-methyl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one		(400 MHz, MeOD) d ppm 8.85 (s, 1 H) 7.69 (d, 1 H) 7.26 (dd, 2 H) 7.02 - 7.09 (m, 3 H) 6.94 (s, 1 H) 5.61 (s, 2 H) 2.56 (s, 3 H)
48		3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-hydroxyethyl)(propyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one		(300 MHz, DMSO-D6) d ppm 9.03 (s, 1 H) 7.77 (d, 2 H) 7.30 (m, 3 H) 7.15 (m, 2 H) 5.63 (s, 2 H) 3.86 (m, 2 H) 3.46 (m, 2 H) 3.39 (s, 2 H) 1.43 (m, 2 H) 0.74 (m, 3 H)

49		3-(4-fluorobenzyl)-7-hydroxy-1-{[2-(hydroxymethyl)piperidin-1-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.02 (s, 1 H) 7.76 (d, 2 H) 7.47 (s, 1 H) 7.26 - 7.38 (m, 2 H) 7.16 (m, 2 H) 5.63 (s, 2 H) 4.55(m, 2H) 3.72 (s, 2 H) 3.59 (s, 2 H) 2.71 (m, 2H) 1.64 (m, 2 H) 1.33 (m, 2 H)
50		1-{[[2-(diethylamino)ethyl](ethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.06 (s, 1H) 7.74 - 7.86 (m, 2 H) 7.29 - 7.38 (m, 2 H) 7.16 (m, 3 H) 5.62 (s, 2 H) 3.86 (s, 2 H) 2.66 (d, *J*=6.78 Hz, 4 H) 2.54 - 2.60 (m, 8 H) 2.43 (m, 2 H) 1.08 (t, 3 H) 0.85 (t, 6 H)
51		1-{[ethyl(4-methylbenzyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.00 (s, 1H) 7.84 (s, 1 H) 7.72 (d, 1H) 7.31 (dd, 2 H) 7.24 (d, 1 H) 7.10 - 7.19 (m, 4 H) 7.03 - 7.10 (m, 2 H) 5.61 (s, 2 H) 3.81 (s, 2 H) 3.53 (s, 2 H) 3.38 (m, 2 H) 2.24 (s, 3 H) 0.99 (t, 3 H)
52		1-{[4-(ethylsulfonyl)piperazin-1-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.03 (s, 1 H) 7.75 - 7.85 (m, 2 H) 7.26 - 7.37 (m, 2 H) 7.11 - 7.25 (m, 3 H) 5.62 (s, 2 H) 3.79 (s, 2 H) 3.40 (m, 4H) 3.14 (m, 4 H) 3.01 (q, 2 H) 1.17 (t, 3 H)

53		3-(4-fluorobenzyl)-7-hydroxy-1-[(4-hydroxypiperidin-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.01 (s, 1 H) 7.70 - 7.84 (m, 2 H) 7.22 - 7.36 (m, 3 H) 7.16 (m, 2 H) 5.60 (s, 2 H) 3.66 (s, 2 H) 2.72 (m, 2 H) 2.08 (m, 2 H) 1.67 (m, 2 H) 1.36 (m, 2 H)
54		1-{[benzyl(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.01 (s, 1 H) 7.70 - 7.85 (m, 2 H) 7.26 - 7.35 (m, 6 H) 7.10 - 7.26 (m, 4 H) 5.61 (s, 2 H) 3.77 (s, 2 H) 3.55 (s, 2 H) 2.07 (s, 3 H)
55		3-(4-fluorobenzyl)-7-hydroxy-1-{[(7R)-7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.01 (s, 1H) 7.71 - 7.83 (m, 2 H) 7.23 - 7.36 (m, 3 H) 7.16 (t, 2 H) 5.60 (s, 2 H) 3.72 (s, 2 H) 3.18 - 3.27 (m, 2 H) 2.88 (m, 1 H) 2.78 (m, 2 H) 2.22 (m, 2 H) 2.11 (d, 2 H) 1.71 (m, 1H) 1.40 - 1.54 (m, 2 H)
56		3-(4-fluorobenzyl)-7-hydroxy-1-{[(3aR,7aR)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridin-5-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 8.96 (s, 1 H) 7.74 (s, 1 H) 7.54 (d, 1 H) 7.48 (s, 1 H) 7.23 - 7.38 (m, 3 H) 7.12 (t, 2 H) 5.55 (s, 2 H) 3.93 (m, 1H) 3.76 (d, 1 H) 3.46 (d, 1 H) 3.21 (s, 2 H) 2.61 - 2.70 (m, 1 H) 2.18 - 2.34 (m, 2 H) 1.81 (m, 1H) 1.48 - 1.62 (m, 1 H) 1.11 (m, 2 H)

57		3-(4-fluorobenzyl)-7-hydroxy-1-(morpholin-4-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.02 (s, 1 H) 7.71 - 7.84 (m, 2 H) 7.22 - 7.35 (m, 3 H) 7.16 (t, 2 H) 5.61 (s, 2 H) 3.72 (s, 2 H) 3.55 (m, 4 H) 2.43 (m, 4 H)
58		3-(4-fluorobenzyl)-7-hydroxy-1-{[4-(2-morpholin-4-ylethyl)piperazin-1-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.02 (s, 1H) 7.78 - 7.80 (m, 2 H) 7.30 - 7.35 (m, 2H) 7.10 - 7.25 (m, 3 H) 5.61 (s, 2H) 3.72 (s, 2 H) 3.55 (m, 16 H) 2.40 - 2.60 (m, 4 H)
59		3-(4-fluorobenzyl)-7-hydroxy-1-({methyl[(1-phenyl-1H-pyrazol-4-yl)methyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	A2, B1	(300 MHz, DMSO-D6) d ppm 9.01 (s, 1H) 8.42 (s, 1 H) 7.73 - 7.86 (m, 4 H) 7.69 (s, 1 H) 7.48 (t, 2 H) 7.24 - 7.35 (m, 3 H) 7.10 - 7.24 (m, 3 H) 5.62 (s, 2 H) 3.74 (s, 2 H) 3.58 (s, 2 H) 2.14 (s, 3 H)

Example 60: Integrase Strand-Transfer Scintillation Proximity Assay

Oligonucleotides: Oligonucleotide #1 -5'-(biotin)CCCCTTTTAGTCAGTGTGGAAAATCTCTAGCA-3' (SEQ ID NO: 1) and oligonucleotide #2 - 5'-ACTGCTAGAGATTTTCCACACTGACTAAAAG-3' (SEQ ID NO: 2), were synthesized by TriLink BioTechnologies, Inc. (San Diego, CA). The annealed product represents preprocessed viral ds-DNA derived from the LTR U5 sequence of the viral genome. A ds-DNA control to test for non-specific interactions was made using a 3' di-deoxy derivative of oligonucleotide #1 annealed to oligonucleotide #2. The CA overhang at the 5' end of the non-biotinylated strand of the ds-DNA was created artificially by using a complimentary DNA oligonucleotide shortened by 2 base pairs. This configuration eliminates the requisite 3' processing step of the integrase enzyme prior to the strand-transfer mechanism.

Host ds-DNA was prepared as an unlabeled and [^{3}H]-thymidine labeled product from annealed oligonucleotide #3 - 5-AAAAAATGACCAAGGGCTAATTCACT-3' (SEQ ID NO: 3), and oligonucleotide #4 - 5'-AAAAAAAGTGAATTAGCCCTTGGTCA-3' (SEQ ID NO: 4), both synthesized by TriLink BioTechnologies, Inc. (San Diego, CA). The annealed product had overhanging 3' ends of poly(dA). Host DNA was custom radiolabeled by PerkinElmer Life Sciences Inc. (Boston, MA) using an enzymatic method with a 12/1 ratio of [methyl-^{3}H]dTTP/cold ds-DNA to yield 5'-blunt end ds-DNA with a specific activity of > 900 Ci/mmol. The radiolabeled product was purified using a NENSORB cartridge and stored in stabilized aqueous solution (PerkinElmer). The final radiolabeled product had six [^{3}H]-thymidine nucleotides at both 5' ends of the host ds-DNA.

Reagents: Streptavidin-coated polyvinyltoluene (PVT) SPA beads were purchased from Amersham Biosciences (Piscataway, NJ). Cesium chloride was purchased from Shelton Scientific, Inc. (Shelton, CT). White, polystyrene, flat-bottom, non-binding surface, 96-well plates were purchased from Corning. All other buffer components were purchased from Sigma (St. Louis, MO) unless otherwise indicated.

Enzyme Construction: Full-length wild type HIV-1 integrase (SF1) sequence (amino acids 1-288) was constructed in a pET24a vector (Novagen, Madison, WI). The construct was confirmed through DNA sequencing.

Enzyme Purification: Full length wild-type HIV Integrase was expressed in E.coli BL21 (DE3) cells and induced with 1 mM isopropyl-1 thio-β-D-galactopyranoside (IPTG) when cells reached an optical density between 0.8-1.0 at 600 nm. Cells were lysed by microfluidation in 50 mM HEPES pH 7.0, 75 mM NaCl, 5 mM DTT, 1mM 4-(2-Aminoethyl)benzenesulfonylfluoride HCl (AEBSF). Lysate was then centrifuged 20 minutes at 11k rpm in GSA rotor in Sorvall RC-5B at 4°C. Supernant was discarded and pellet resuspended in 50 mM HEPES pH 7.0, 750 mM NaCl,

5 mM DTT, 1 mM AEBSF and homogenized in a 40 mL Dounce homogenizer for 20 minutes on ice. Homogenate was then centrifuged 20 minutes at 11k rpm in SS34 rotor in Sorvall RC-5B at 4°C. Supernant was discarded and pellet resuspended in 50 mM HEPES pH 7.0, 750 mM NaCl, 25 mM CHAPS, 5 mM DTT, 1 mM AEBSF. Preparation was then centrifuged 20 minutes at 11k rpm in SS34 rotor in Sorvall RC-5B at 4°C.

Supernant was then diluted 1:1 with 50 mM HEPES pH 7.0, 25 mM CHAPS, 1 mM DTT, 1 mM AEBSF and loaded onto a Q-Sepharose column pre-equilibrated with 50 mM HEPES, pH 7.0, 375 mM NaCl, 25 mM CHAPS, 1 mM DTT, 1 mM AEBSF. The flow through peak was collected and NaCl diluted to 0.1 M with 50 mM HEPES pH 7.0, 25 mM CHAPS, 1 mM DTT, 0.5 mM AEBSF and loaded onto a SP-Sepharose column pre-equilibrated with 50 mM HEPES pH 7.0, 100 mM NaCl, 25 mM CHAPS, 1 mM DTT, 0.5 mM AEBSF. After washing the column with the equilibration buffer, a 100 to 400 mM NaCl gradient was run. The eluted integrase was concentrated and run on a S-300 gel diffusion column using 50 mM HEPES pH 7.0, 500 mM NaCl, 25 mM CHAPS, 1 mM DTT, 0.5 mM AEBSF. The peak from this column was concentrated to 0.76 mg/mL and stored at –70°C and later used for strand transfer assays. All columns were run in a 4°C cold room.

Viral DNA Bead Preparation: Streptavidin-coated SPA beads were suspended to 20 mg/mL in 25 mM 3-morpholinopropanesulfonic acid (MOPS) (pH 7.2) and 1.0% NaN_3. Biotinylated viral DNA was bound to the hydrated SPA beads in a batch process by combining 25 pmoles of ds-DNA to 1 mg of suspended SPA beads (10 µL of 50 µM viral DNA to 1 mL of 20 mg/mL SPA beads). The mixture was incubated at 22°C for a minimum of 20 min. with occasional mixing followed by centrifugation at 2500 rpm for 10 min. However, the centrifugation speed and time may vary depending upon the particular centrifuge and conditions. The supernatant was removed and the beads suspended to 20 mg/mL in 25 mM MOPS (pH 7.2) and 1.0% NaN_3. The viral DNA beads were stable for several weeks when stored at 4°C. Di-deoxy viral DNA was prepared in an identical manner to yield control di-deoxy viral DNA beads.

Preparation of Integrase-DNA Complex: Assay buffer was made as a 10x stock of 250 mM MOPS (pH 7.2), 500 mM NaCl, 50 mM 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS), 0.5% (octylphenoxy)polyethoxyethanol (NP40) (IGEPAL-CA) and 0.05% NaN_3. Viral DNA beads were diluted to 2.67 mg/mL in 1x assay buffer plus 3 mM $MgCl_2$, 1% DMSO, and 10 mM fresh DTT. Integrase (IN) was pre-complexed to viral DNA beads in a batch process (IN/viral DNA/bead complex) by combining diluted viral DNA beads with integrase at a concentration of 385 nM followed by a minimum incubation time of 20 min. at 22°C with gentle agitation. The sample was kept at 22°C until transferred to the assay wells.

Preparation of Host DNA: Host DNA was prepared to 200 nM as a mixture of unlabeled and [^{3}H]T-labeled host DNA diluted in 1x assay buffer plus 8.5 mM $MgCl_2$ and 15 mM DTT.

Concentrations used were 4 nM [^{3}H]T-labeled host DNA and 196 nM unlabeled host DNA. This ratio generates a SPA signal of 2000 - 3000 CPM in the absence of modulators such as inhibitors.

Strand-transfer Scintillation Proximity Assay: The strand-transfer reaction was carried out in 96-well microtiter plates, with a final enzymatic reaction volume of 100 µL. Ten microliters of compounds or test reagents diluted in 10% DMSO were added to the assay wells followed by the addition of 65 µL of the IN/viral-DNA/bead complex and mixed on a plate shaker. Then 25 µL of host DNA was added to the assay wells and mixed on a plate shaker. The strand-transfer reaction was initiated by transferring the assay plates to 37°C dry block heaters. An incubation time of 50 min., which was shown to be within the linear range of the enzymatic reaction, was used. The final concentrations of integrase and host DNA in the assay wells were 246 nM and 50 nM, respectively.

The integrase strand-transfer reaction was terminated by adding 70 µL of stop buffer (150 mM EDTA, 90 mM NaOH, and 6 M CsCl) to the wells. Components of the stop buffer function to terminate enzymatic activity (EDTA), dissociate integrase/DNA complexes in addition to separating non-integrated DNA strands (NaOH), and float the SPA beads to the surface of the wells to be in closer range to the PMT detectors of the TopCount® plate-based scintillation counter (PerkinElmer Life Sciences Inc. (Boston, MA)). After the addition of stop buffer, the plates were mixed on a plate shaker, sealed with transparent tape, and allowed to incubate a minimum of 60 min. at 22°C. The assay signal was measured using a TopCount® plate-based scintillation counter with settings optimal for [^{3}H]-PVT SPA beads. The TopCount® program incorporated a quench standardization curve to normalize data for color absorption of the compounds. Data values for quench-corrected counts per minute (QCPM) were used to quantify integrase activity. Counting time was 2 min./well.

The di-deoxy viral DNA beads were used to optimize the integrase strand-transfer reaction. The di-deoxy termination of the viral ds-DNA sequence prevented productive integration of viral DNA into the host DNA by integrase. Thus, the assay signal in the presence of di-deoxy viral DNA was a measure of non-specific interactions. Assay parameters were optimized to where reactions with di-deoxy viral DNA beads gave an assay signal closely matched to the true background of the assay. The true background of the assay was defined as a reaction with all assay components (viral DNA and [^{3}H]-host DNA) in the absence of integrase.

Determination of Compound Activity: The percent inhibition of the compound was calculated using the equation (1-((QCPM sample – QCPM *min*)/(QCPM *max* – QCPM *min*)))*100. The *min* value is the assay signal in the presence of a known inhibitor at a concentration 100-fold higher than the IC_{50} for that compound. The *min* signal approximates the true background for the assay.

The *max* value is the assay signal obtained for the integrase-mediated activity in the absence of compound (i.e. with DMSO instead of compound in DMSO).

Compounds were prepared in 100% DMSO at 100-fold higher concentrations than desired for testing in assays (generally 5 mM), followed by dilution of the compounds in 100% DMSO to generate an 11-point titration curve with ½-log dilution intervals. The compound sample was further diluted 10-fold with water and transferred to the assay wells. The percentage inhibition for an inhibitory compound was determined as above with values applied to a nonlinear regression, sigmoidal dose response equation (variable slope) using GraphPad Prism curve fitting software (GraphPad Software, Inc., San Diego, CA). Concentration curves were assayed in duplicate and then repeated in an independent experiment.

Example 61: HIV-1 Cell Protection Assay

The antiviral activities of potential modulator compounds (test compounds) were determined in HIV-1 cell protection assays using the RF strain of HIV-1, CEM-SS cells, and the XTT dye reduction method (Weislow, O.S. *et al., J. Natl. Cancer Inst. 81:* 577-586 (1989)). Subject cells were infected with HIV-1 RF virus at an moi of 0.025 to 0.819 or mock infected with medium only and added at 2 x 10^4 cells per well into 96 well plates containing half-log dilutions of test compounds. Six days later, 50 µl of XTT solution (1 mg/ml XTT tetrazolium and 0.02 nM phenazine methosulfate) were added to the wells and the plates were reincubated for four hours. Viability, as determined by the amount of XTT formazan produced, was quantified spectrophotometrically by absorbance at 450 nm.

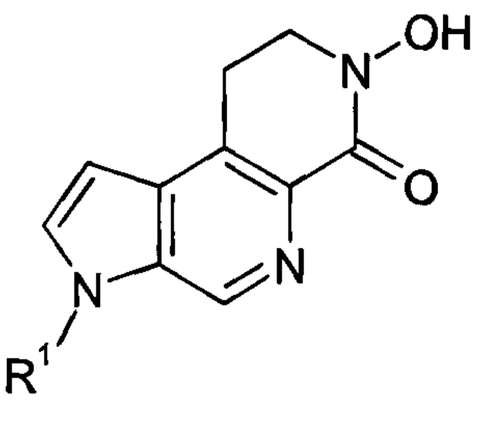
Data from CPE assays were expressed as the percent of formazan produced in compound-treated cells compared to formazan produced in wells of uninfected, compound-free cells. The fifty percent effective concentration (EC_{50}) was calculated as the concentration of compound that affected an increase in the percentage of formazan production in infected, compound-treated cells to 50% of that produced by uninfected, compound-free cells. The 50% cytotoxicity concentration (CC_{50}) was calculated as the concentration of compound that decreased the percentage of formazan produced in uninfected, compound-treated cells to 50% of that produced in uninfected, compound-free cells. The therapeutic index was calculated by dividing the cytotoxicity (CC_{50}) by the antiviral activity (EC_{50}).

Example 62: Antiviral data

Example	IC_{50} (nM)	EC_{50} (nM)	Example	IC_{50} (nM)	EC_{50} (nM)
1	20	0.4	31	9	
2	30	0.6	32	108	6
3	17	29	33	26	3
4	8	7	34	45	2
5	18	38	35	45	0.4
6	7	12	36	20	0.4
7	17	8	37	23	1
8	14	11	38	120	0.3
9	15	0.53	39	79	4
10	40	0.41	40	62	2
11	6	3	41	42	3
12	13	4	42	54	3
13	8	13	43	122	0.8
14	13	8	44	31	0.74
15	5	39	45	24	20
16	6	7	46	49	9.6
17	9	31	47	11	0.23
18	11	67	48	11	1.2
19	5	15	49	13	14
20	9	390	50	11.5	8.6
21	46	480	51	17.5	1.3
22	6	45	52	10.5	1.6
23	10	4	53	7	13
24	5	22	54	13.5	0.42
25	35	160	55	7	69
26	9	5	56	11.5	14
27	13	19	57	7	0.32
28	12	24	58	22	32
29	12	35	59	19	0.74
30	13	13			

We Claim:

1. A compound of formula (I)



(I)

wherein:

R^1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl, wherein said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_1-C_8 heteroalkyl groups may be optionally substituted with at least one substituent independently selected from:

halo, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl, wherein said C_1-C_8 alkyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, and C_2-C_9 heteroaryl groups are optionally substituted with at least one substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, and C_1-C_8 alkoxy;

each R^{12a}, R^{12b}, and R^{12c}, which may be the same or different, is independently selected from hydrogen, C_1-C_8 alkyl, and oxo; or

R^{12a} and R^{12b}, together with the nitrogen atom to which they are attached, may form a C_2-C_9 cycloheteroalkyl group;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, and C_1-C_8 alkoxy.

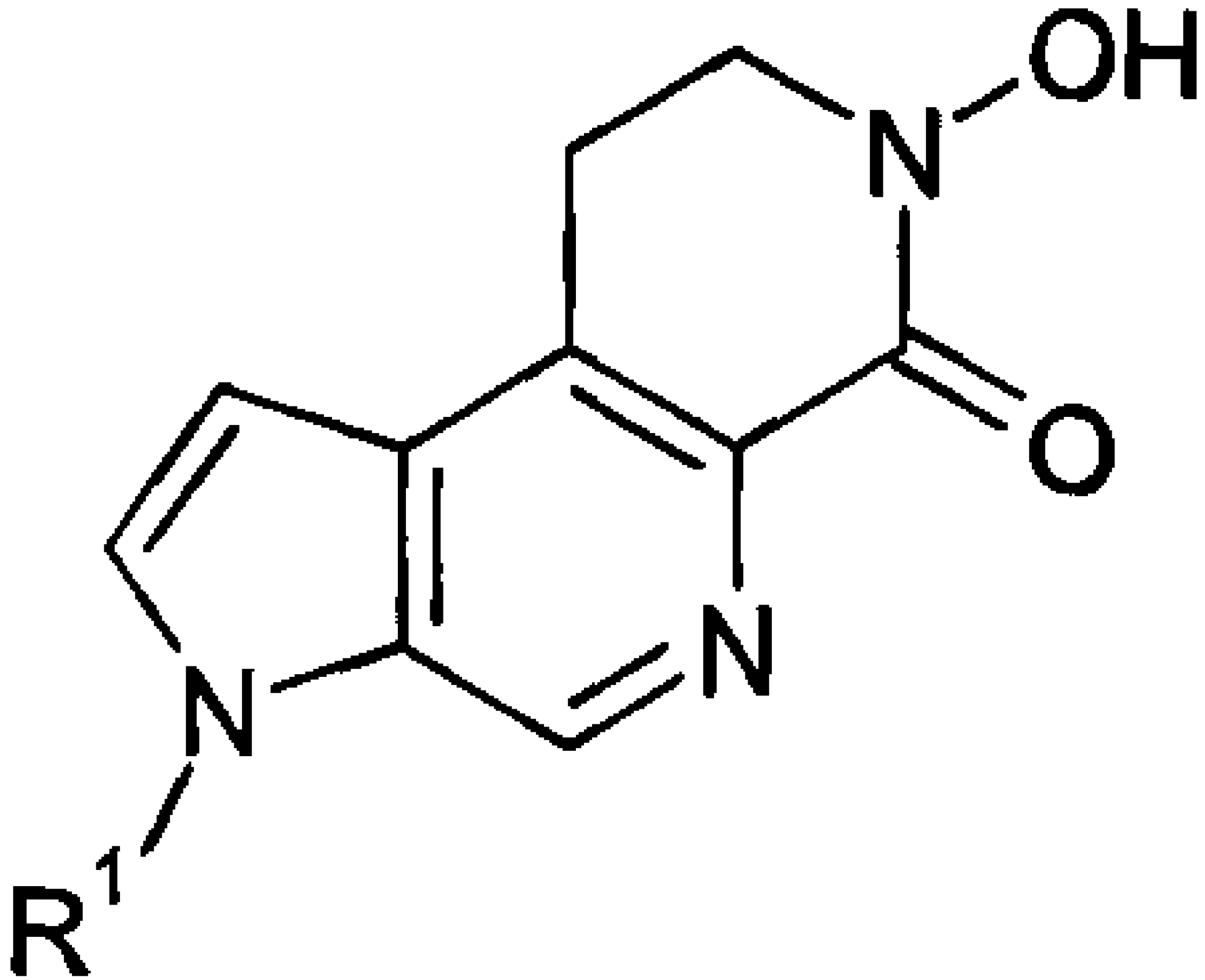
3. A compound according to claim 1, wherein R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl group is optionally substituted with at least one halo.

4. A compound according to claim 1, which is 3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate thereof.

5. A pharmaceutical composition, comprising at least one compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or diluent.

6. Use of a compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of acquired immune deficiency syndrome (AIDS) or AIDS-related complex in an HIV-infected mammal.

7. Use of a compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, for the treatment of acquired immune deficiency syndrome (AIDS) or AIDS-related complex in an HIV-infected mammal.



(I)