INHIBITORS OF THE HIV INTEGRASE ENZYME

This application claims priority to United States Patent Application No. 60/724,484, filed October 7, 2005, No. 60/730,701, filed October 26, 2005, No. 60/761,605, filed January 24, 2006, No. 60/823,954, filed August 30, 2006, and No. 60/826,379, filed September 20, 2006, all of which are hereby incorporated by reference.

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);

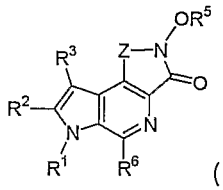
Wai, J.S., et al., *J. Med. Chem. 43(26):* 4923-4926 (2000); Debyser, Z. *et al.*, *Assays for the Evaluation of HIV-1 Integrase Inhibitors*, from Methods in Molecular Biology, *160:* 139-155, Schein, C.H. (ed.), Humana Press Inc., Totowa, N.J. (2001); and Hazuda, D., *et al.*, *Drug Design and Disc. 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); and 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). Finally, it was recently reported that compound L-000870810, an HIV integrase inhibitor, showed clinical efficacy in the treatment of HIV-infected patients (S. Little, et al., "Antiretroviral Effect of L-000870810, a Novel HIV-1 Integrase Inhibitor, in HIV-1 Infected Patients," 12th Conference on Retroviruses and Opportunistic Infections, Feb. 2005, Abstract 161).

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, halogen, -CN, C_1-C_8 alkyl, $-(CR^7R^8)_tNR^9R^{10}$, $-S(O)_zNR^9R^{10}$, $-C(O)NR^9R^{10}$, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, wherein said C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl groups are optionally substituted with at least one 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

R^{11} is halogen, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 heterocyclyl, 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 heterocyclyl 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 $-CF_3$;

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

a pharmaceutically acceptable salt or solvate 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.

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 heterocyclyl 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 heterocyclyl 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 heterocyclyl 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 heterocyclyl 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 heterocyclyl 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 heterocyclyl group comprising three carbon atoms and three nitrogen atoms.

Further provided herein 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 heterocyclyl group comprising 5 carbon atoms and a nitrogen atom.

Also provided herein are compounds of formula (I), wherein R^3 is halogen, -CN, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, wherein said C_6-C_{14} aryl or C_2-C_9 heteroaryl groups are optionally substituted with at least one R^{11}.

Further provided herein are compounds of formula (I), wherein R^3 is halogen.

Further provided herein are compounds of formula (I), wherein R^3 is is –CN.

Further provided herein are compounds of formula (I), wherein R^3 is C_6-C_{14} aryl or C_2-C_9 heteroaryl, wherein said C_6-C_{14} aryl or C_2-C_9 heteroaryl groups are optionally substituted with at least one R^{11}.

In another embodiment are provided compounds of formula (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 halogen, -CN, C_1-C_8 alkyl, $-(CR^7R^8)_tNR^9R^{10}$, $-S(O)_zNR^9R^{10}$, $-C(O)NR^9R^{10}$, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, wherein said C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl groups are optionally substituted with at least one 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

R^{11} is halogen, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 heterocyclyl, 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 heterocyclyl 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 $-CF_3$;

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

a pharmaceutically acceptable salt or solvate thereof.

In still another embodiment are provided compounds of formula (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, halogen, -CN, C_1-C_8 alkyl, $-(CR^7R^8)_tNR^9R^{10}$, $-S(O)_zNR^9R^{10}$, $-C(O)NR^9R^{10}$, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, wherein said C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl groups are optionally substituted with at least one R^{11};

Z is $-(CR^4R^4)_n-$, $-C(R^4)=C(R^4)-(CR^4R^4)_n-$, $-(CR^4R^4)_n-C(R^4)=C(R^4)-$, 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

R^{11} is halogen, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 heterocyclyl, 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 heterocyclyl 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 $-CF_3$;

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

a pharmaceutically acceptable salt or solvate thereof.

Further provided are compounds of formula (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, halogen, -CN, C_1-C_8 alkyl, $-(CR^7R^8)_tNR^9R^{10}$, $-S(O)_zNR^9R^{10}$, $-C(O)NR^9R^{10}$, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, wherein said C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl groups are optionally substituted with at least one R^{11};

Z is $-(CR^4R^4)_n-$;

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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl, 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 heterocyclyl or a C_2-C_9 heteroaryl group, each of which is optionally substituted with at least one R^{13} group;

R^{11} is halogen, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 heterocyclyl, 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 heterocyclyl 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 $-CF_3$;

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

a pharmaceutically acceptable salt or solvate thereof.

In a further embodiment are provided compounds of formula (I), wherein Z is $-(CR^4R^4)_n-$. Also provided herein are compounds of formula (I), wherein Z is $-(CH_2CH_2)-$.

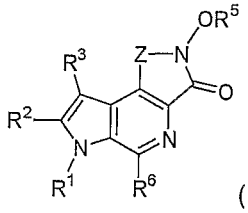
Also provided are compounds selected from: 8-butyl-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-({[(2S)-2-hydroxypropyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[ethyl(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-({[2-(dimethylamino)-1-methylethyl]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-(hydroxymethyl)piperidin-1-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(3-hydroxybutyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-[3-(4-

fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]-N,N-dimethylbenzamide; 3-(4-fluorobenzyl)-7-hydroxy-1-pyridin-2-yl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-7,8-dihydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3H)-one; 3-(4-fluorobenzyl)-7-hydroxy-N,N-dimethyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylsulfonyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylcarbonyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methoxypiperidin-1-yl)carbonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperidin-1-yl)sulfonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)carbonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; N,N-diethyl-3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-N-methyl-6-oxo-N-(tetrahydro-2H-pyran-4-yl)-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide; N-cyclopentyl-3-(4-fluorobenzyl)-7-hydroxy-N-methyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-methoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-({[(2S)-2,3-dihydroxypropyl]oxy}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one; 3-(4-fluorobenzyl)-7-hydroxy-N-(2-methoxyethyl)-N-methyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridine-1-sulfonamide; 3-(4-fluorobenzyl)-7-hydroxy-1-(morpholinosulfonyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-yloxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(2-ethoxyethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-L-prolinamide; 3-(4-fluorobenzyl)-7-hydroxy-1-({[(1R)-2-hydroxy-1-methylethyl]amino}methyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(morpholin-4-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-hydroxyethyl)(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-({[1-(4-bromophenyl)ethyl]amino}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(3,3-difluoropyrrolidin-1-yl)methyl]-3-

(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(piperidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(3,3-difluoropiperidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[tert-butyl(2-methoxyethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-N,N-dimethyl-L-prolinamide; 1-[(dimethylamino)methyl]-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-8-methyl-1-(morpholin-4-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-8-methyl-9-(morpholin-4-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-8-methyl-1-(pyrrolidin-1-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-8-methyl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(3,4-difluorobenzyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[4-(2-methoxyethyl)piperazin-1-yl]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(tetrahydro-2H-pyran-3-yl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(3-ethoxypropoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one hydrochloride; 1-chloro-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-1-{[(2-fluorobenzyl)oxy]methyl}-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one hydrochloride; 3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carbonitrile; 3-(4-fluorobenzyl)-7-hydroxy-1-[(pyridin-2-ylmethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(isobutoxymethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[2-(benzyloxy)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-isobutoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(2-butoxyethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-(butoxymethyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-bromo-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-pyridin-2-ylethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(4-oxopentyl)oxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-methylpyridin-3-yl)methoxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(cyclopropylmethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-

6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[2-(3-methoxyphenyl)ethoxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-phenoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-acetyl-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one - methane; 3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-ylamino)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[[(1-ethyl-1H-imidazol-2-yl)methyl](methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[ethyl(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(3R,4R)-3,4-difluoropyrrolidin-1-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(2,2,2-trifluoroethyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(3-pyridin-2-ylpropoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-propoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-isopropoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-methoxyethyl)(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(6-methylpyridin-2-yl)methoxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(cyclobutylmethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[2-(diisopropylamino)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(2,2-difluoroethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(2-butoxyethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment are provided 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 substituted with one or more substituent independently selected from:

halo, -CN, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$,

$-S(O)_2N(R^{12a}R^{12b})$, 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 may be substituted with one or more substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, C_1-C_8 alkoxy, and -CN;

R^2 is hydrogen or C_1-C_8 alkyl;

R^3 is C_1-C_8 alkyl, $-(CR^7R^8)_tNR^9R^{10}$, $-(CR^7R^8)_tOR^9$, $-S(O)_zNR^9R^{10}$, $-C(O)NR^9R^{10}$, $-C(O)R^9$, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, wherein said C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl groups may be substituted with one or more R^{11};

Z is $-(CR^4R^4)_n-$, $-C(R^4)=C(R^4)-(CR^4R^4)_n-$, $-(CR^4R^4)_n-C(R^4)=C(R^4)-$, 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 heterocyclyl, 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 heterocyclyl, and C_2-C_9 heteroaryl may be substituted with one or more 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 may be substituted with one or more 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, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 heterocyclyl or a C_2-C_9 heteroaryl group, each of which may be substituted with one or more R^{13};

R^{11} is halogen, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 heterocyclyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which may be substituted with one or more 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 heterocyclyl group;

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

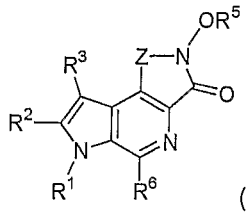
t is an integer from 1 to 3;

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

a pharmaceutically acceptable salt or solvate thereof.

Another embodiment 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 substituted with one or more substituent independently selected from:

halo, -CN, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, 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 may be substituted with one or more substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, C_1-C_8 alkoxy, and -CN;

R^2 is hydrogen or C_1-C_8 alkyl;

R^3 is C_1-C_8 alkyl, $-(CR^7R^8)_tNR^9R^{10}$, $-(CR^7R^8)_tOR^9$, $-S(O)_zNR^9R^{10}$, $-C(O)NR^9R^{10}$, $-C(O)R^9$, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, wherein said C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl groups may be substituted with one or more R^{11};

Z is $-(CR^4R^4)_n-$;

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 heterocyclyl, 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 heterocyclyl, and C_2-C_9 heteroaryl may be substituted with one or more 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 may be substituted with one or more 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, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 heterocyclyl or a C_2-C_9 heteroaryl group, each of which may be substituted with one or more R^{13} group;

R^{11} is halogen, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 heterocyclyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which may be substituted with one or more 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 heterocyclyl group;

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

t is an integer from 1 to 3;

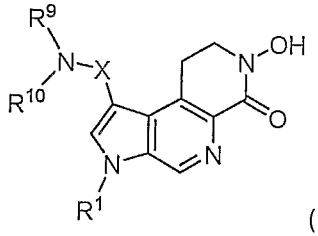
each n, which may be the same or different, is independently selected and is an integer from 1 to 4; and

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

a pharmaceutically acceptable salt or solvate thereof.

Further provided herein are any of the compounds of formula (I), wherein Z is $-(CH_2CH_2)-$, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment are provided 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 substituted with one or more substituent independently selected from:

halo, -CN, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, 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 may be substituted with one or more substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, C_1-C_8 alkoxy, and -CN;

X is $–S(O)_2$-, $-(CH_2)$-, $-(CH_2CH_2)$-, $-(CH_2CH_2CH_2)$-, or –C(O)-;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more 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, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

In still another embodiment are provided compounds of formula (II), 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 substituted with one or more substituent independently selected from halo and -CN;

X is $–S(O)_2$-, $-(CH_2)$-, $-(CH_2CH_2)$-, $-(CH_2CH_2CH_2)$-, or –C(O)-;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

Yet another embodiment provides compounds of formula (II), wherein:

R^1 is $-(CH_2)(C_6$-C_{14} aryl), wherein said C_6-C_{14} aryl group is substituted with one or more substituent independently selected from halo and -CN;

X is $-S(O)_2-$, $-(CH_2)-$, $-(CH_2CH_2)-$, $-(CH_2CH_2CH_2)-$, or $-C(O)-$;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

A further embodiment provides compounds of formula (II), wherein:

R^1 is 4-fluorobenzyl;

X is $-S(O)_2-$, $-(CH_2)-$, $-(CH_2CH_2)-$, $-(CH_2CH_2CH_2)-$, or $-C(O)-$;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

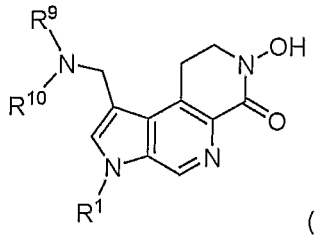
each z, which may be the same or different, is independently selected and is 0, 1, or 2; or

a pharmaceutically acceptable salt or solvate thereof.

In another embodiment are provided compounds of formula (II), wherein X is $-S(O)_2-$, or a pharmaceutically acceptable salt or solvate thereof. Also provided are compounds of formula (II), wherein X is $-(CH_2)-$, $-(CH_2CH_2)-$, or $-(CH_2CH_2CH_2)-$, or a pharmaceutically acceptable salt or solvate thereof. Further provided herein are compounds of formula (II), wherein X is $-(CH_2)-$, or a pharmaceutically acceptable salt thereof. Also provided are compounds of formula (II), wherein X is $-(CH_2CH_2)-$, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment are compounds of formula (II), wherein X is -(CH-

$_2CH_2CH_2$)-, or a pharmaceutically acceptable salt or solvate thereof. Also provided are compounds of formula (II), wherein X is –C(O)-, or a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides compounds of formula (III),



(III)

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 substituted with one or more substituent independently selected from halo and -CN;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, -$C(O)R^7$, -$C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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;

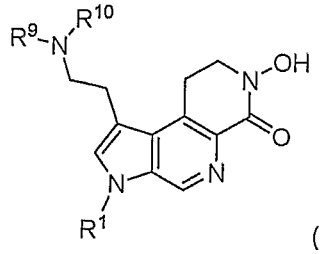
each R^{13} is independently selected from halo, C_1-C_8 alkyl, -$(CR^7R^8)_tOR^7$, -$C(O)R^{12a}$, -$S(O)_2R^7$, -$(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, -$NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and -CF_3;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides compounds of formula (IV),



(IV)

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 substituted with one or more substituent independently selected from halo and -CN;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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;

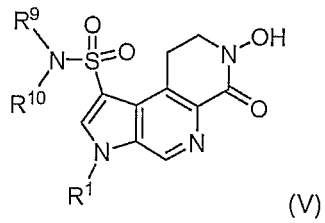
each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides compounds of formula (V),



(V)

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 substituted with one or more substituent independently selected from halo and -CN;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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;

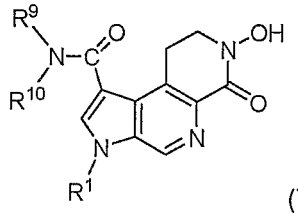
each R^{13} is independently selected from halo, C_1-C_8 alkyl, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides compounds of formula (VI),



(VI)

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 substituted with one or more substituent independently selected from halo and –CN;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14}

aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

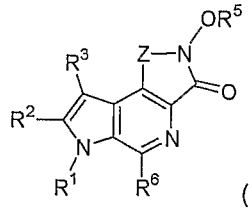
each z, which may be the same or different, is independently selected and is 0, 1, or 2; or

a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides any compounds of formula (I) to (VII), wherein R^1 is 4-fluorobenzyl, or a pharmaceutically acceptable salt or solvate thereof.

A further embodiment provides compounds of formula (I), wherein R^3 is halogen, -CN, C_6-C_{14} aryl or C_2-C_9 heteroaryl, wherein said C_6-C_{14} aryl or C_2-C_9 heteroaryl groups are optionally substituted with at least one R^{11}, or a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides compounds of formula (I)



(I)

wherein:

R^1 is C_1-C_8 alkyl substituted with C_2-C_9 heteroaryl, wherein said C_2-C_9 heteroaryl may be substituted with one or more substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, C_1-C_8 alkoxy, and -CN;

R^2 is hydrogen or C_1-C_8 alkyl;

R^3 is hydrogen;

Z is $–(CH_2CH_2)$-;

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 heterocyclyl, 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 heterocyclyl, and C_2-C_9 heteroaryl may be substituted with one or more 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 may be substituted with one or more 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, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 heterocyclyl or a C_2-C_9 heteroaryl group, each of which may be substituted with one or more R^{13};

R^{11} is halogen, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 heterocyclyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which may be substituted with one or more 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 heterocyclyl group;

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

t is an integer from 1 to 3;

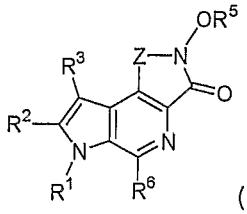
each n, which may be the same or different, is independently selected and is an integer from 1 to 4; and

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

a pharmaceutically acceptable salt or solvate thereof.

A further embodiment provides compounds of formula (I), wherein R^1 is $-(CH_2)$- substituted with pyridyl, wherein said pyridyl may be substituted with one or more substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, C_1-C_8 alkoxy, and –CN, or a pharmaceutically acceptable salt or solvate thereof.

In still another embodiment are provided compounds of formula (I)



(I)

wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl, wherein said C_6-C_{14} aryl is substituted with one or more –CN and is further optionally substituted with one or more 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$$NR^9R^{10}$, –($CR^7R^8$)$_t$$OR^9$, -S(O)$_z$$NR^9R^{10}$, -C(O)$NR^9R^{10}$, -C(O)$R^9$, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, wherein said C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl groups may be substituted with one or more R^{11};

Z is –(CH_2CH_2)-;

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 heterocyclyl, 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 heterocyclyl, and C_2-C_9 heteroaryl may be substituted with one or more 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 may be substituted with one or more 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, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, -C(O)R^7, -C(O)$_2$$R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 heterocyclyl or a C_2-C_9 heteroaryl group, each of which may be substituted with one or more R^{13} group;

R^{11} is halogen, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 heterocyclyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which may be substituted with one or more 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 heterocyclyl group;

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

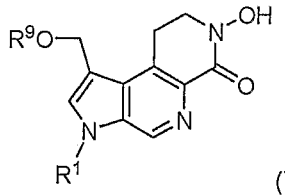
t is an integer from 1 to 3;

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

a pharmaceutically acceptable salt or solvate thereof. Still another embodiment provides these compounds of formula (I), wherein R^3 is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides compounds of formula (VII),



(VII)

wherein:

R^1 is C_1-C_8 alkyl substituted with C_6-C_{14} aryl or C_2-C_9 heteroaryl, wherein said C_6-C_{14} aryl and C_2-C_9 heteroaryl may be substituted with one or more substituent independently selected from halo and -CN;

R^7 is selected from hydrogen and C_1-C_8 alkyl;

R^9 is selected from hydrogen, C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl or halo group; or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment are provided compounds of formula (VII), 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 substituted with one or more substituent independently selected from halo and -CN; or a pharmaceutically acceptable salt or solvate thereof. A further embodiment provides compounds of formula (VII), wherein R^1 is 4-fluorobenzyl; or a pharmaceutically acceptable salt or solvate thereof. Another embodiment provides compounds of formula (VII), wherein R^1 is $-(CH_2)$-C_2-C_9 heteroaryl, wherein said C_2-C_9 heteroaryl may be substituted with one or more substituent independently selected from halo and –CN; or a pharmaceutically acceptable salt or solvate thereof. An additional embodiment provides compounds of formula (VII), wherein R^1 is $-(CH_2)$-pyridyl,

wherein said pyridyl may be substituted with one or more substituent independently selected from halo and –CN; or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment are provided any of compounds of formula (I) to (VII), wherein R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl or halo group, or a pharmaceutically acceptable salt or solvate thereof.

In still another embodiment are provided any of compounds of formula (I) to (VII), 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 may be substituted with one or more R^{13} group, or a pharmaceutically acceptable salt or solvate thereof.

A further embodiment provides any of compounds of formula (I) to (VII), wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group that may be substituted with one or more R^{13} group, or a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides a compound selected from 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-L-prolinamide; 3-(4-fluorobenzyl)-7-hydroxy-1-({[(1R)-2-hydroxy-1-methylethyl]amino}methyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(morpholin-4-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-hydroxyethyl)(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(3,3-difluoropyrrolidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(piperidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(3,3-difluoropiperidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[tert-butyl(2-methoxyethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-NN-dimethyl-L-prolinamide; 1-{[(2R,6S)-26-dimethylmorpholin-4-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(3,4-difluorobenzyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[4-(2-methoxyethyl)piperazin-1-yl]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-

hydroxy-1-{[methyl(tetrahydro-2H-pyran-3-yl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(cyclopropylmethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-ylamino)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-({[(1-ethyl-1H-imidazol-2-yl)methyl](methyl)amino}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[ethyl(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(3R,4R)-34-difluoropyrrolidin-1-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(2,2,2-trifluoroethyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-methoxyethyl)(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; and 1-{[(2,2-difluoroethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate thereof.

A further embodiment provides a compound selected from 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-L-prolinamide; 3-(4-fluorobenzyl)-7-hydroxy-1-(morpholin-4-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(3,3-difluoropyrrolidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(piperidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(3,3-difluoropiperidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-NN-dimethyl-L-prolinamide; 1-{[(2R,6S)-26-dimethylmorpholin-4-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[4-(2-methoxyethyl)piperazin-1-yl]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; and 1-{[(3R,4R)-34-difluoropyrrolidin-1-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate thereof.

Still another embodiment provides a compound selected from 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-({[(1R)-2-hydroxy-1-methylethyl]amino}methyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-hydroxyethyl)(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[tert-butyl(2-methoxyethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(3,4-difluorobenzyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-

c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(tetrahydro-2H-pyran-3-yl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[(cyclopropylmethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-ylamino)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-({[(1-ethyl-1H-imidazol-2-yl)methyl](methyl)amino}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[ethyl(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(2,2,2-trifluoroethyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-methoxyethyl)(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; and 1-{[(2,2-difluoroethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate thereof.

A further embodiment provides a compound selected from 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylcarbonyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methoxypiperidin-1-yl)carbonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)carbonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; N,N-diethyl-3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; and 3-(4-fluorobenzyl)-7-hydroxy-N-methyl-6-oxo-N-(tetrahydro-2H-pyran-4-yl)-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide; or a pharmaceutically acceptable salt or solvate thereof.

An additional embodiment provides a compound selected from 3-(4-fluorobenzyl)-7-hydroxy-N,N-dimethyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylsulfonyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperidin-1-yl)sulfonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; N-cyclopentyl-3-(4-fluorobenzyl)-7-hydroxy-N-methyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; 3-(4-fluorobenzyl)-7-hydroxy-N-(2-methoxyethyl)-N-methyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide; and 3-(4-fluorobenzyl)-7-hydroxy-1-(morpholin-4-ylsulfonyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides a compound selected from 3-(4-fluorobenzyl)-7-hydroxy-1-{3-[methyl(tetrahydro-2H-pyran-4-ylmethyl)amino]propyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{3-[methyl(pyridin-2-ylmethyl)amino]propyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-

fluorobenzyl)-7-hydroxy-1-(3-morpholin-4-ylpropyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; N-{3-[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]propyl}-N-methylacetamide; and 3-(4-fluorobenzyl)-7-hydroxy-1-[3-(4-methyl-3-oxopiperazin-1-yl)propyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate thereof.

A further embodiment provides a compound selected from 3-(4-fluorobenzyl)-7-hydroxy-1-(2-pyrrolidin-1-ylethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[2-(dimethylamino)ethyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{2-[methyl(tetrahydro-2H-pyran-4-yl)amino]ethyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(2-morpholin-4-ylethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[2-(tetrahydro-2H-pyran-4-ylamino)ethyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{2-[methyl(2,2,2-trifluoroethyl)amino]ethyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{2-[(cyclopropylmethyl)(methyl)amino]ethyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{2-[(2,2,2-trifluoroethyl)amino]ethyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{2-[(2,2-difluoroethyl)amino]ethyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{2-[(3,3,3-trifluoropropyl)amino]ethyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; and 3-(4-fluorobenzyl)-7-hydroxy-1-[2-(4-methyl-3-oxopiperazin-1-yl)ethyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate thereof.

Another embodiment provides a compound selected from 1-(azepan-1-ylmethyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(4-acetylpiperidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methoxypiperidin-1-yl)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; and 3-(4-fluorobenzyl)-7-hydroxy-1-{[isobutyl(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment is provided a compound selected from 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-methoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-({[(2R)-23-dihydroxypropyl]oxy}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-yloxy)methyl]-3,7,8,9-tetrahydro-6H-

pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(2-ethoxyethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(3-ethoxypropoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-1-{[(2-fluorobenzyl)oxy]methyl}-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(pyridin-2-ylmethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-(isobutoxymethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-{[2-(benzyloxy)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-isobutoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(2-butoxyethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-(butoxymethyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-pyridin-2-ylethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(4-oxopentyl)oxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-methylpyridin-3-yl)methoxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[2-(3-methoxyphenyl)ethoxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-phenoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(3-pyridin-2-ylpropoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-propoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-[(2-isopropoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 3-(4-fluorobenzyl)-7-hydroxy-1-{[(6-methylpyridin-2-yl)methoxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; 1-[(cyclobutylmethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; and 1-{[2-(diisopropylamino)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one; or a pharmaceutically acceptable salt or solvate 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.

Also provided herein are 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, at least one additional anti-HIV agent, 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.

Also provided herein are methods of treating HIV infection in an HIV-infected mammal, 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.

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.

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 heterocyclyl," 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 heterocyclyl 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 heterocyclyl 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 heterocyclyl 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," "HIV-inhibiting amount," and "HIV replication-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 terms "HIV integrase enzyme-inhibiting amount" and "HIV integrase-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.

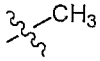
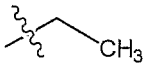
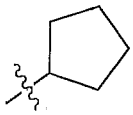
The term "CCR5 antagonist," as used herein, refer to compounds or combinations of compounds that block the infection of certain cell types by HIV through the perturbation of CCR5 co-receptor activity.

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 terms "compound of the present invention" or "any of the compounds herein" refers to any of the above-mentioned compounds, including any of the compounds of formula (I) to (VII), 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 bonds between atoms 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 and August 22, 2006.

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).

Other compounds useful as CCR5 inhibitors that may be used in combination with the compounds of the present invention include, but are not limited to, (N-{(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl}-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide), ethyl 1-*endo*-{8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine-5-carboxylate, and *N*-{(1*S*)-3-[3-*endo*-(5-Isobutyryl-2-methyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl}acetamide).

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 cytopathic effects, 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 37 °C 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., ≥ 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 3.

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 130.

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

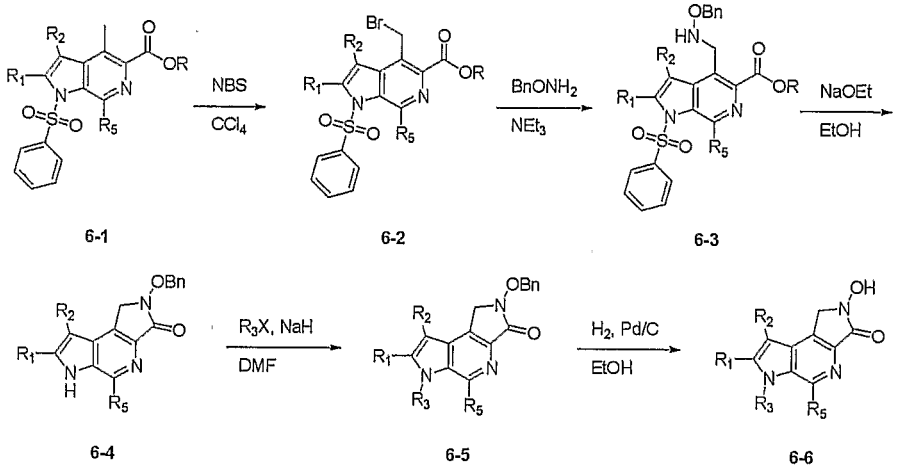
protection assay. In yet another embodiment, the compounds of the present invention have an EC_{50} against HIV integrase of at least 0.1 μM when measured with an HIV cell protection assay.

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

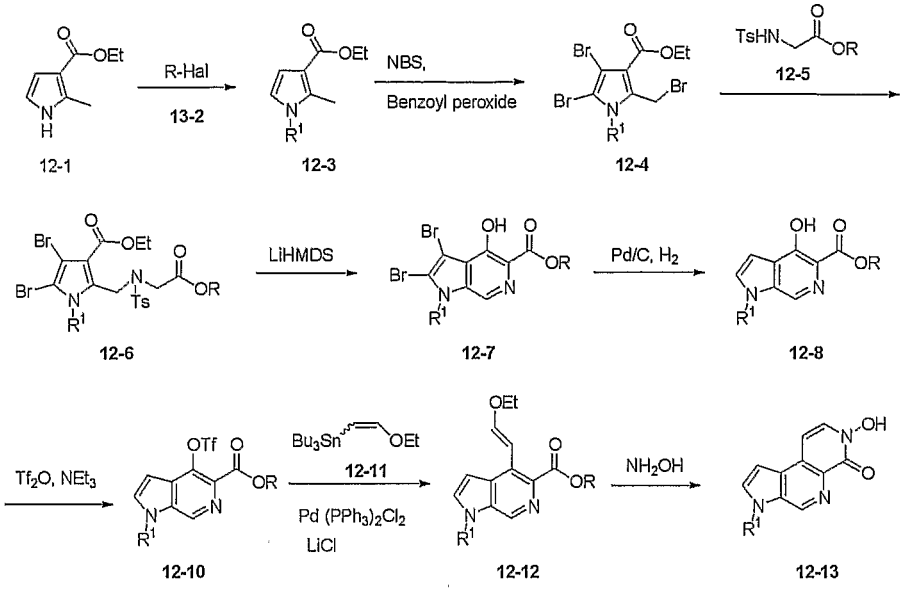
Scheme 1 depicts a method for formation of N-hydroxy lactam 6-5. Radical bromination of a methyl substituted indole 6-1 can be achieved by various reagents (Jerry March, Advanced Organic Chemistry, 5th edition, John Whiley & Sons, 2001, p. 911 – 914) the most common being N-bromosuccinimide (NBS). It 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

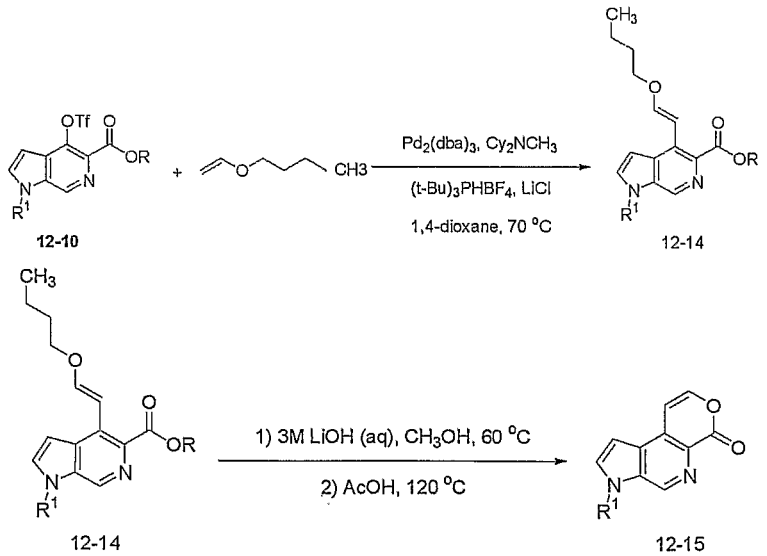


Scheme 2 depicts the synthesis of a 4-substituted azaindole 12-12. Ethyl 2-methyl-1H-pyrrole-3-carboxylate 12-1 (Wee, A.G.H.; Shu, A.Y.L.; Djerassi, C. *J., Org. Chem.,* 1984, *49*, 3327-3336) can be treated with an organo halide in the presence of a base such as NaH to provide pyrrole 12-3. Bromination 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

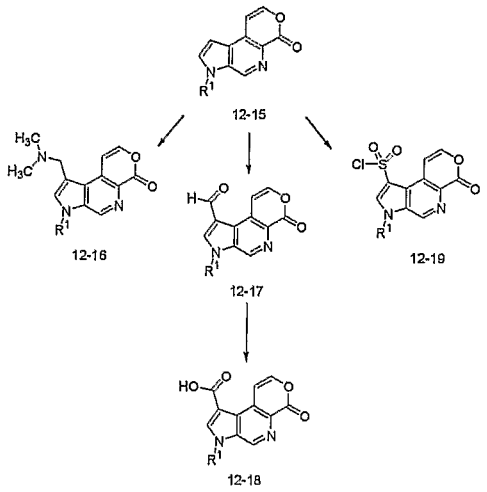


Alternatively, compound 12-10 may be allowed to react with n-butyl vinyl ether in the presence of a palladium catalyst, a base, a phosphine, and lithium chloride, in a solvent at a temperature of about 70 °C, to provide compound 12-14. Compound 12-14 can then be allowed to react with a base, such as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



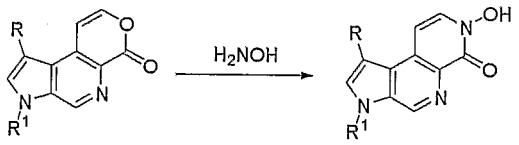
As shown in Scheme 2a below, compound 12-15 can be further functionalized at the 3-position to provide, for example, gramine derivatives (12-16), aldehyde derivatives (12-17), carboxylic acid derivatives (12-18), and sulfonyl chloride derivatives (12-19). Each of compounds 12-16, 12-17, 12-18, and 12-19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

Scheme 2a



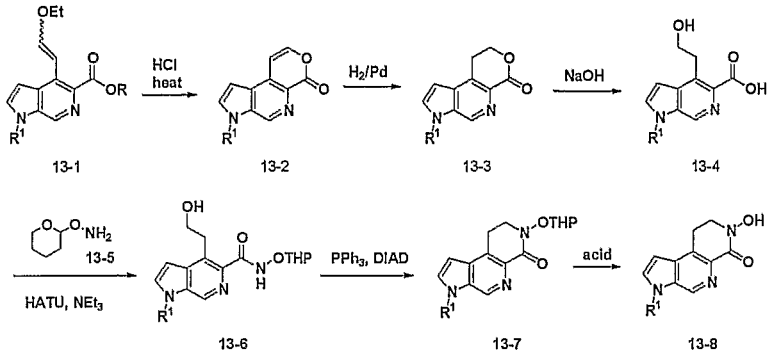
As shown in Scheme 2b, compound 12-15, or derivatives of 12-15 as shown in Scheme 2a, can then be allowed to react with hydroxylamine to afford compounds of formula (I).

Scheme 2b



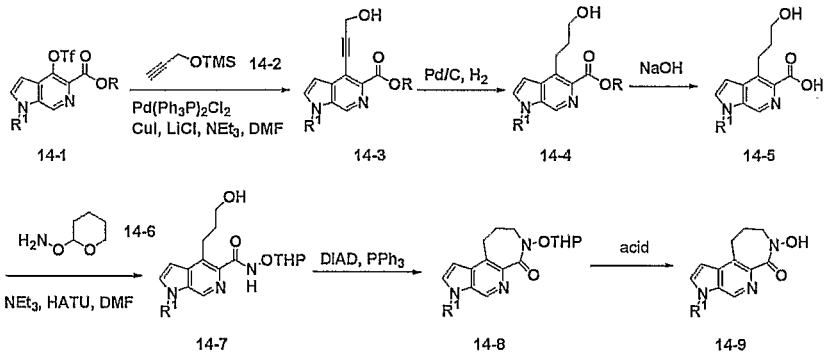
Scheme 3 depicts a route for preparation of a cyclic compound 13-7. Ester 13-1 can undergo cyclization to form pyranone 13 –4 as described by T. Sakamoto, Y. Kondo, A. Yasuhara, H. Yamanaka, *Tetrahedron* 1991, *47*, 1877–1886. Catalytic hydrogenation using a catalyst such as Pd/C can give lactone 13-3. 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



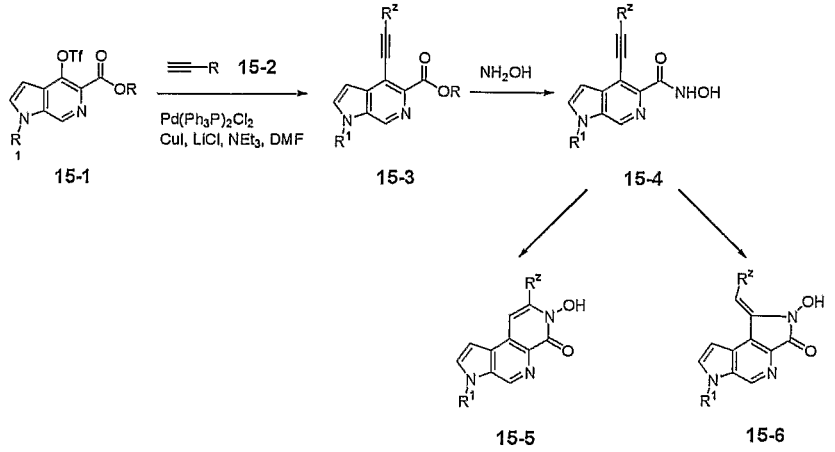
Compound 14-8 can be obtained according to Scheme 4. Palladium catalyzed reaction of triflate 14-1 with an alkyne such as 14-2 can give 14-3. Catalytic hydrogenation using a catalyst such as Pd/C can give the propanol 14-4. Saponification of the ester 14-4 with a base such as sodium hydroxide can give 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.

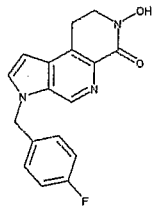
Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, as KBr pellets, or as $CDCl_3$ solutions, and when reported are in wave numbers (cm^{-1}). The mass spectra were obtained using LC/MS or APCI. All melting points are uncorrected.

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.

Example A: 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). ^1H 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.

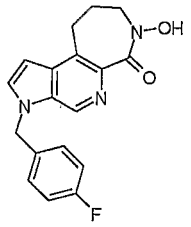
Step 3: 1-(4-Fluorobenzyl)-4-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic acid. To 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one (0.11 g, 0.37 mmol) in methanol (10 mL) was added sodium hydroxide (0.066 g, 1.65 mmol) in water (2.0 mL). The reaction was 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 B: 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.

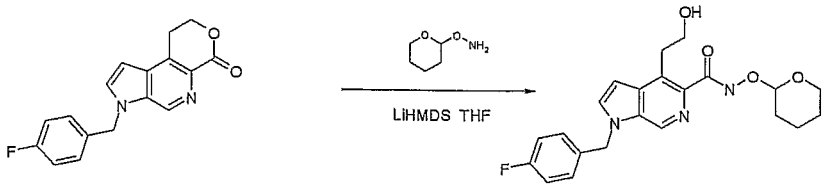
Step 3: 1-(4-Fluorobenzyl)-4-(3-hydroxypropyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid. To a solution of ethyl 1-(4-fluorobenzyl)-4-(3-hydroxypropyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (0.41 g, 1.15 mmol) in MeOH (6 mL) was added a solution of sodium hydroxide (92mg, 2.30 mmol) in 1 mL of water. 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.

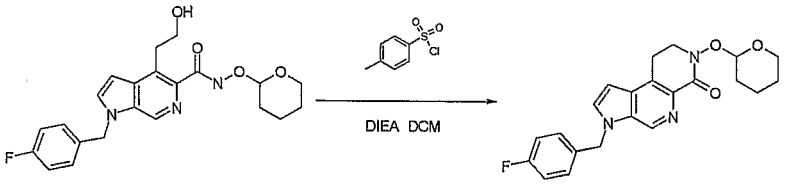
Step 6: 3-(4-fluorobenzyl)-7-hydroxy-7,8,9,10-tetrahydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3*H*)-one. 3-(4-fluorobenzyl)-7-(tetrahydro-2*H*-pyran-2-yloxy)-7,8,9,10 tetrahydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3*H*)-one (18.53 mg, 0.045 mmol) was dissolved in acetic acid, THF and Water (3.5 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) δ 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.

Example C: 1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide



7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one (3.50 g 11.81 mmol) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (2.77g 23.62 mmol. 2eq) was dried by evaporation from anhydrous THF (3X20ml) then dissolved in anhydrous THF (80 mL). To the resulting cloudy orange solution was added solid LiHMDS (3.95 g, 23.62 mmol, 2 eq) under N_2. The reaction mixture was heated reflux then cooled with stirring overnight. An additional portion of *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (1.3g) was added and the solution warmed to 40 ^{o}C for a further 5 hours. The volatiles were removed *in vacuo* (ca. 2 torr) to give an orange oil. The crude material was diluted with DCM:MeOH 95:5 (100 mL) and washed with saturated NH_4Cl: Brime 1:1 (80 mL) and brine (60 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo* to afford 12.8 g of a brown oil. The crude material was purified by chromatography on a silica column, eluted with a gradient of CH2Cl2 to CH2Cl2-MeOH 98:2 v/v. Fractions were combined to afford 3.81 g (78%) of the title compound as a colorless oil, The oil was taken up in DCM (100 mL) and washed with saturated $NaHCO_3$ (30 mL), 1M KOH (30 mL) and brine (60 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo* to afford a white solid which was slurred in ether (70 mL), filtered and washed with ether (20 mL) to give 1.81 g (38%) of the title compound. LC-MS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN – 3 minutes, APCI, + mode): RT- 1.150 min, m/e = 414.2 ($M+H^+$, base). ^1H NMR (300MHz, $CDCl_3$): δ 1.64 (m, 3H), 1.92 (m, 3H), 3.67 (m, 2H), 4.09 (m, 4H), 5.12 (s, 1H), 5.38 (s, 2H), 6.69 (d, 1H), 6.96-7.20 (m, 4H), 7.31 (d, 1H), 8.42(s, 1H), 10.46 (s, 1H).

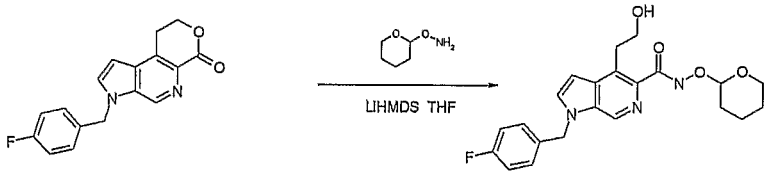
Example D: 3-(4-fluorobenzyl)-7-(tetrahydro-2*H*-pyran-2-yloxy)-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one



To 1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (460 mg 1.114 mmol) in DCM (30 mL) was added i-Pr_2NEt (0.58 mL 3.34 mmol, 3 eq.) followed by tosyl chloride (234 mg 1.225 mmol 1.1eq.) under N_2. The orange solution was stirred at room temperature overnight then for a further 3 hours at reflux. Extra tosyl chloride (240 mg) and i-Pr_2Net (0.6 mL) was added and the heating continued for a second night. The reaction was judged to be complete by HPLC-MS analysis and the reaction mixture washed with saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo* to afford 834 mg of a brown oil. The crude material was purified by chromatography on a silica column, eluted with a gradient of CH2Cl2 to CH2Cl2-MeOH 98:2 v/v. Fractions were combined to afford 234 mg (53%) of the title compound. LC-MS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN – 3 minutes, APCI, + mode):

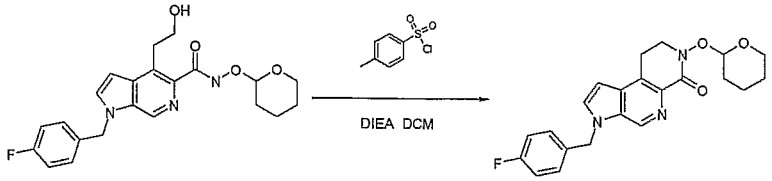
RT- 1.121min, m/e = 396.2 ($M+H^+$, base). ^1H NMR (300MHz, $CDCl_3$) δ 1.68 (m, 3H), 1.94 (m, 3H), 3.40 (m, 2H), 3.66 (m, 1H), 3.92-4.20 (m, 3H), 5.28 (s, 1H), 5.42 (s, 2H), 6.64 (d, 1H), 7.02 (m, 2H), 7.26 (m, 2H), 7.32 (d, 1H), 8.78 (s, 1H).

Example E: 1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide



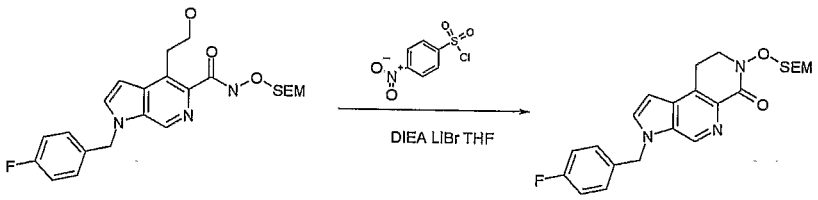
7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one (3.50g 11.812mmol) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (2.77g 23.62mmol 2eq) was dried by evaporation from anhydrous THF (3X20ml) then dissolves in anhydrous THF (80ml). To the resulting cloudy orange solution was added solid LiHMDS (3.95g 23.62mmol 2 eq) under N_2. The reaction mixture came to reflux then cooled with stirring overnight. More *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (1.3g) was added and the solution warmed to 40°C for a further 5 hours. The volatiles were removed *in vacuo* (ca. 2 torr) to give an orange oil. The crude material was diluted with DCM:MeOH 95:5 (100mL) and washed with saturated NH_4Cl: Brime 1:1 (80mL) and brine (60mL). The organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo* to afford 12.8g of a brown oil. The crude material was purified by chromatography on a silica column, eluted with a gradient of CH2Cl2 to CH2Cl2-MeOH 98:2 v/v. Fractions were combined to afford 3.81g (78%) of the title compound as a colorless oil, The oil was taken up in DCM (100ml) and washed with saturated $NaHCO_3$ (30ml), 1M KOH (30ml) and brine (60mL). The organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo* to afford a white solid which was slurred in ether (70ml), filtered and washed with ether (20ml) to give 1.81g (38%) of the title compound. LC-MS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN – 3 minutes, APCI, + mode): RT- 1.150min, m/e = 414.2 ($M+H^+$, base). ^1H-NMR (300MHz, $CDCl_3$): δ = 1.64 (m, 3H), 1.92 (m, 3H), 3.67 (m, 2H), 4.09 (m, 4H), 5.12 (s, 1H), 5.38 (s, 2H), 6.69 (d, 1H), 6.96-7.20 (m, 4H), 7.31 (d, 1H), 8.42(s, 1H), 10.46 (s, 1H).

Example F: 3-(4-fluorobenzyl)-7-(tetrahydro-2*H*-pyran-2-yloxy)-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one.



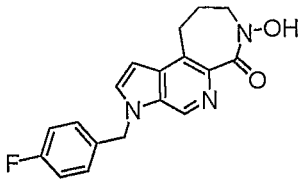
To 1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (460mg 1.114mmol) in DCM (30ml) was added i-Pr_2NEt (0.58ml 3.34mmol, 3 eq.) followed by tosyl chloride (234mg 1.225mmol 1.1eq.) under N_2. The orange solution was stirred at room temperature overnight then for a further 3 hours at reflux. Extra tosyl chloride (240mg) and i-Pr_2Net (0.6ml) was added and the heating continued for a second night. The reaction was judged to be complete by HPLC-MS analysis and the reaction mixture washed with saturated sodium bicarbonate (10mL) and brine (10mL). The organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo* to afford 834mg of a brown oil. The crude material was purified by chromatography on a silica column, eluted with a gradient of CH2Cl2 to CH2Cl2-MeOH 98:2 v/v. Fractions were combined to afford 234mg (53%) of the title compound. LC-MS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN – 3 minutes, APCI, + mode): RT- 1.121min, m/e = 396.2 ($M+H^+$, base). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.68 (m, 3H), 1.94 (m, 3H), 3.40 (m, 2H), 3.66 (m, 1H), 3.92-4.20 (m, 3H), 5.28 (s, 1H), 5.42 (s, 2H), 6.64 (d, 1H), 7.02 (m, 2H), 7.26 (m, 2H), 7.32 (d, 1H), 8.78 (s, 1H).

Example G: 3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one

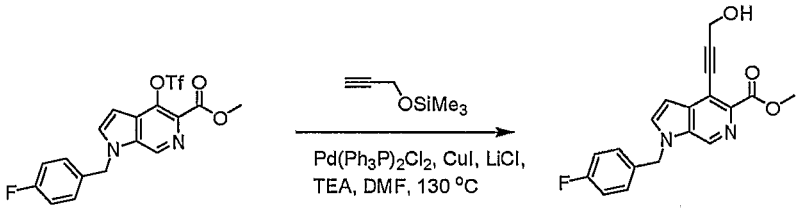


To 1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-*N*-{[2-(trimethylsilyl)ethoxy]methoxy}-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (4.57g 9.944mmol) in anhydrous THF (80 mL) was added LiBr (950 mg 10.934 mmol, 1.1 eq.) and the solution stirred for 30 minutes. Then i-Pr_2NEt (5.20 mL 29.831mmol, 3 eq.) was added followed by 4-nitrobenzenesulfonyl chloride (2.42 g 10.934 mmol 1.1 eq.). A white precipitate appeared and the orange solution was stirred at room temperature for a further 20 minutes. The reaction was judged to be complete by HPLC-MS analysis and the volatiles were removed *in vacuo* (ca. 2 torr) to give an orange oil. The crude material was diluted with EtOAc (100 mL) and washed with saturated sodium bicarbonate (2X80 mL) and brine (20 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo* to afford 5.2 g of a orange oil. The crude material was purified by chromatography on a Biotage 65i column, eluted with a gradient of CH2Cl2 to CH2Cl2-MeOH 95:5 v/v, over 5.0 L. Fractions were combined to afford 4.091 g (93%) of the title compound. LC-MS (Eclipse XDB-C8, 0.8mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN – 3 minutes, APCI, + mode): RT- 1.56 min, m/e = 442.2 ($M+H^+$, base). ^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.00 (s, 9H), 0.98 (t, 2H), 3.38 (m, 2H), 3.86 (t, 2H), 3.98 (t, 2H), 5.11 (s, 2H), 5.34 (s, 2H), 6.60 (s, 1H), 6.98 (m, 2H), 7.08 (m, 2H), 7.29 (s, 1H), 8.73 (s, 1H).

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

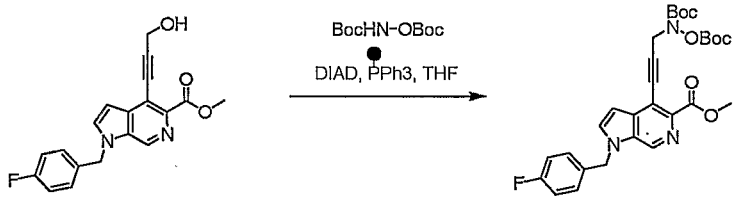


Step 1: methyl 1-(4-fluorobenzyl)-4-(3-hydroxyprop-1-yn-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



To a solution of methyl 1-(4-fluorobenzyl)-4-{[(trifluoromethyl)sulfonyl]oxy}-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (500 mg, 1.16 mmol) in anhydrous DMF (2 mL) was added propargyloxy-trimethylsilane (252 mg, 1.97 mmol) followed by lithium chloride (74 mg, 1.74 mmol), copper iodide (9.72 mg, 0.051 mmol), dichlorobis(triphenylphosphine) palladium (II) (18 mg, 0.026 mmol) and triethylamine (2.42 mL, 17.4 mmol). The mixture, filled with nitrogen, was placed in a Biotage microwave and heated to 130 °C. After stirring for 20 minutes, the reaction was judged to be complete by HPLC-MS analysis. The volatiles were removed via rotary evaporator to give a black solid residue. The crude material was diluted with ethyl acetate (30 mL) and filtered with celite, then washed with water. The extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The target product was further purified by prep HPLC to afford 298 mg (76.1% yield) as white solid. LC-MS (APCI, M+H+): 339.1. HPLC: > 95% purity. 1H NMR (300 MHz, DMSO-D6) δ ppm 8.90 (s, 1 H) 7.93 (d, 1 H) 7.30 - 7.38 (m, 2 H) 7.12 - 7.20 (m, 2 H) 6.73 (d, 1 H) 5.59 (s, 3 H) 4.41 (d, 2 H) 3.83 (s, 3 H).

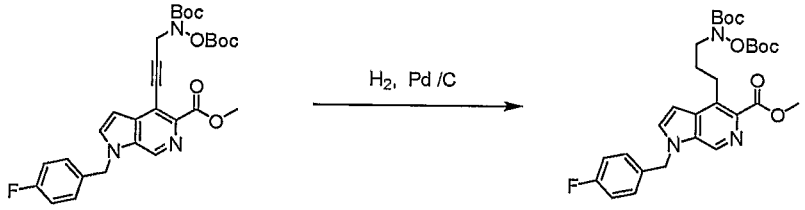
Step 2: methyl 4-(3-{(*tert*-butoxycarbonyl)[(*tert*-butoxycarbonyl)oxy]amino}prop-1-yn-1-yl)-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



To a solution of methyl 1-(4-fluorobenzyl)-4-(3-hydroxyprop-1-yn-1-yl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (70 mg, 0.207 mmol) in THF (5 mL) was added tert-butyl N-(tert-butoxycarbonyloxy)-carbamate (58 mg, 0.25 mmol), DIAD (80.2 uL, 0.414) and polymer bound triphenylphosphine (345 mg, 1.035 mmol). After stirring at room temperature for 6

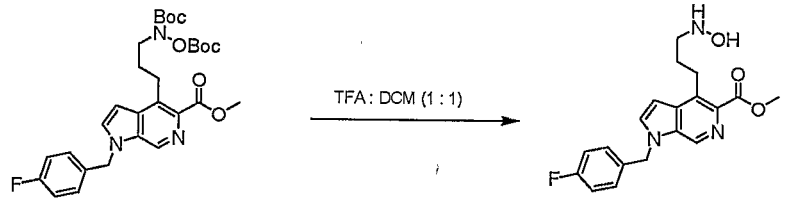
hours, the reaction was judged to be complete by HPLC-MS analysis. The polymer bound compound was removed by filtration. The volatiles were removed via rotary evaporator to give a brown solid residue that was purified by prep HPLC to give 46 mg (40.2% yield) of target product as a white powder. LC-MS (APCI, M+H+): 554.2 HPLC: > 95% purity. 1H NMR (300 MHz, MeOH) δ ppm 8.69 (s, 1 H) 7.74 (d, 1 H) 7.20 - 7.31 (m, 2 H) 6.99 - 7.11 (m, 2 H) 6.86 (m, 1H) 5.57 (s, 2 H) 4.73 (s, 2 H) 3.97 (s, 3 H) 1.51 (s, 9 H) 1.50 (s, 9 H)

Step 3: methyl 4-(3-{(*tert*-butoxycarbonyl)[(*tert*-butoxycarbonyl)oxy]amino}propyl)-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



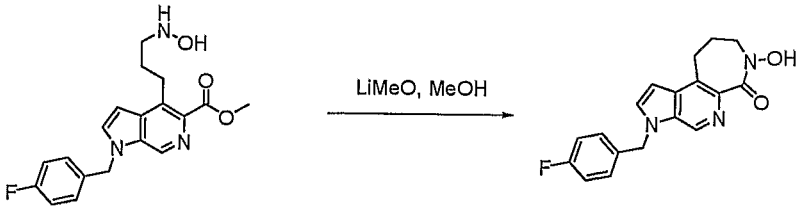
To a solution of methyl 4-(3-{(tert-butoxycarbonyl)[(tert-butoxycarbonyl)oxy]amino} prop-1-yn-1-yl)-1-(4-fluorobenzyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (40 mg, 0.072 mmol) in MeOH (2 mL) was added Pd / C (10 mg, 10 wt. %, support activated carbon). A hydrogen balloon was applied. After stirring at room temperature for 18 hours, the reaction was judged to be complete by HPLC-MS analysis. Pd / C was removed by filtration. The volatiles were removed via rotary evaporator to give a glue like desired product 38 mg (94 % yield). LC-MS (APCI, M+H+): 558.2 HPLC: > 90% purity. 1H NMR (300 MHz, MeOH) _ ppm 8.58 (s, 1 H) 7.66 (d, 1 H) 7.19 - 7.27 (m, 2 H) 6.99 - 7.08 (m, 2 H) 6.86 (d, 1H) 5.53 (s, 2H) 3.93 (s, 3 H) 3.66 (t, 2 H) 3.22 - 3.31 (m, 2 H) 1.88 - 2.01 (m, 2 H) 1.51 (s, 9 H) 1.44 (s, 9 H)

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



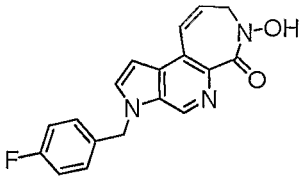
To a solution of methyl 4-(3-{(tert-butoxycarbonyl)[(tert-butoxycarbonyl)oxy]amino} propyl)-1-(4-fluorobenzyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (129 mg 0.231 mmol) in DCM (2 mL) was bubble by nitrogen for 10 minutes. TFA (2 mL) was added. The reaction mixture was stirred at room temperature for 2 hours. The reaction was judged to be complete by HPLC-MS analysis. The volatiles were removed via rotary evaporator to give a glue like desired product 80 mg (96.8 % yield). LC-MS (APCI, M+H+): 358.2 HPLC: > 90% purity. 1H NMR (300 MHz, DMSO-D6) δ ppm 8.78 (s, 1 H) 7.83 (d, 1 H) 7.23 - 7.37 (m, 2 H) 7.15 (t, 2 H) 6.83 (d, 1 H) 5.55 (s, 2 H) 3.82 (s, 3 H) 3.03 - 3.16 (m, 2 H) 2.87 - 3.02 (m, 2 H) 1.78 - 1.93 (m, 2 H)

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

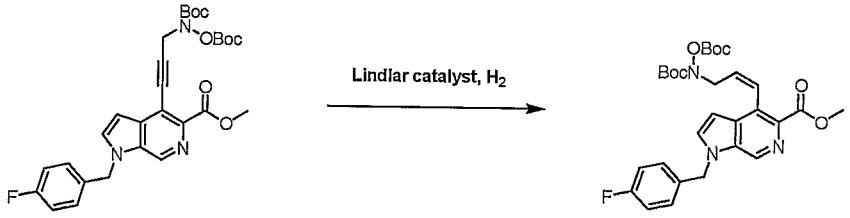


To a solution of methyl 1-(4-fluorobenzyl)-4-[3-(hydroxyamino)propyl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (80 mg, 0.22 mmol) in anhydrous MeOH (3 mL) was bubbled by nitrogen for 10 minutes. Then LiOMe (50 mg, 1.32 mmol) was added. After stirring at 60 °C for 48 hours, the reaction was judged to be complete by HPLC-MS analysis. The reaction was quenched with NH_4Cl solution and the mixture was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The target product was purified by prep HPLC to afford 42 mg (58 % yield) of 3-(4-fluorobenzyl)-7-hydroxy-7, 8,9,10-tetrahydropyrrolo [3',2':4,5]pyrido [2,3-c]azepin-6(3H)-one as white solid. LC-MS (APCI, M+H+): 326.2. HPLC: > 95% purity. 1H NMR (300 MHz, MeOH) δ 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).

Example I: 3-(4-fluorobenzyl)-7-hydroxy-7,8-dihydropyrrolo[3',2':4,5]pyrido[2,3-*c*]azepin-6(3*H*)-one



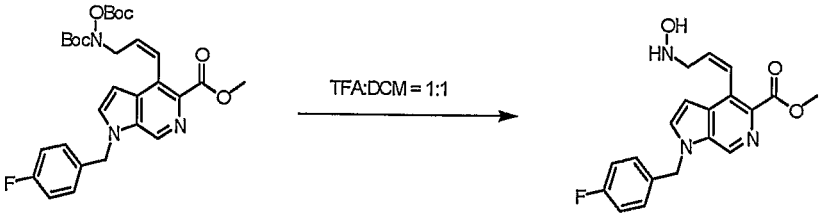
Step 1: methyl 4-((1*Z*)-3-{(*tert*-butoxycarbonyl)[(*tert*-butoxycarbonyl)oxy] amino}prop-1-en-1-yl)-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



To a solution of methyl 4-(3-{(tert-butoxycarbonyl)[(tert-butoxycarbonyl)oxy]amino} prop-1-yn-1-yl)-1-(4-fluorobenzyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (20 mg, 0.036 mmol) in toluene (2 mL) was added (10 mg, ~ 5% palladium on calcium carbonate; poisoned with lead). A hydrogen balloon was applied. After stirring at room temperature for 18 hours, the reaction was judged to be complete by HPLC-MS analysis. Lindlar's catalyst was removed

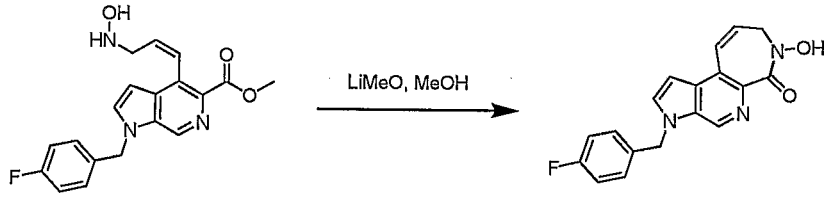
by filtration. The volatiles were removed via rotary evaporator to give a glue-like desired product 18.3 mg (91.0 % yield). LC-MS (APCI, M+H+): 556.2 HPLC: > 90% purity.

Step 2: methyl 1-(4-fluorobenzyl)-4-[(1*Z*)-3-(hydroxyamino)prop-1-en-1-yl]-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



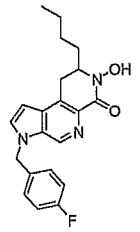
Through a solution of methyl 4-((1Z)-3-{(tert-butoxycarbonyl)[(tert-butoxycarbonyl)oxy] amino}prop-1-en-1-yl)-1-(4-fluorobenzyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (18.3 mg 0.033 mmol) in DCM (2 mL) was bubbled nitrogen for 10 minutes. TFA (2 mL) was added. The reaction mixture was stirred at room temperature for 1 hour. The reaction was judged to be complete by HPLC-MS analysis. The volatiles were removed via rotary evaporator. The target product was purified by prep HPLC to afford brown glue-like product 10.2 mg (87% yield). LC-MS (APCI, M+H+): 356.2 HPLC: > 90% purity. 1H NMR (300 MHz, MeOH) δ ppm 9.07 (s, 1 H) 8.19 (s, 1 H) 7.28 - 7.42 (m, 3 H) 7.02 - 7.15 (m, 2 H) 6.92 (d, 1 H) 6.16 – 6.24 (m, 1 H) 5.71 (s, 2 H) 4.02 (s, 3 H) 3.68 (d, 2 H).

Step 3: 3-(4-fluorobenzyl)-7-hydroxy-7,8-dihydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3H)-one



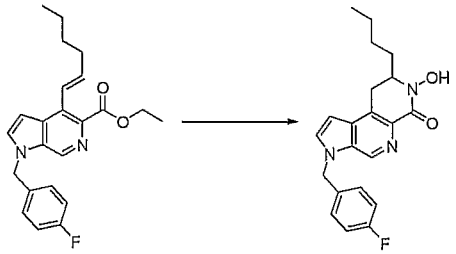
Through a solution of methyl 1-(4-fluorobenzyl)-4-[(1Z)-3-(hydroxyamino)prop-1-en-1-yl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (10.2 mg, 0.029 mmol) in anhydrous MeOH (2 mL) was bubbled nitrogen for 10 minutes. Then LiMeO (4.41 mg, 0.116 mmol) was added. After stirring at room temperature for 2 hours, the reaction was judged to be complete by HPLC-MS analysis. The reaction was quenched with NH_4Cl solution and the mixture was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The target product was purified by prep HPLC to afford 5.5 mg (59.3 % yield) of product as white solid. LC-MS (APCI, M+H+): 324.2. HPLC: > 95% purity. 1H NMR (300 MHz, MeOH) δ ppm 8.77 (s, 1 H) 7.72 (s, 1 H) 7.22 – 7.34 (m, 3 H) 6.97 - 7.11 (m, 2 H) 6.83 (d, 1 H) 6.67 (m, 1 H) 5.56 (s, 2 H) 4.11 (d, 2 H).

Example J: 8-butyl-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one.



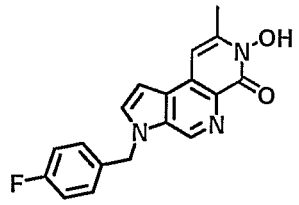
Step1: ethyl 1-(4-fluorobenzyl)-4-[(1*E*)-hex-1-en-1-yl]-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate: A solution of ethyl 1-(4-fluorobenzyl)-4-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (0.20 g, 0.46 mmol), 1-hexene (0.5 mL, 4.0 mmol), triethylamine (0.5 mL, 6.8 mmol) and palladium(II) acetate (0.1 g, 0.61 mmol) in DMF (5 mL) was heated in a Biotage Personal microwave at 100°C for 10 minutes and then at 150 °C for 5 minutes. It was quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, concentrated and purified by column chromatography using ethyl acetate/hexanes (8:2) to provide the title compound as solid (20 mg, 0.055 mmol). ^{1}H NMR (MeOD) δ; 8.63 (s, 1H), 7.85 (d, 1H, J = 3.0 Hz), 7.28-7.31 (m, 2H), 7.08-7.15 (m, 3H), 6.99 (d, 1H, J = 3.0 Hz), 6.33-6.43 (m, 1H), 5.61 (s, 2H), 3.96 (s, 3H), 2.34-2.41 (m, 2H), 1.43-1.62 (m, 4H), 0.99 (t, 3H, J= 7.1 Hz). MS (APCI, M+H$^+$): 367.2.

Step 2: 8-butyl-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one.

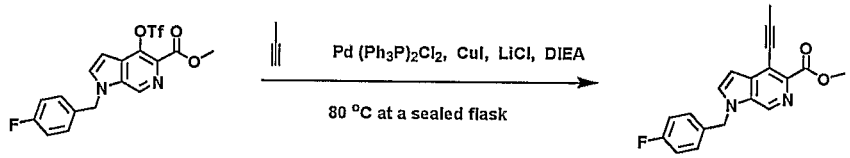


A solution of ethyl 1-(4-fluorobenzyl)-4-[(1*E*)-hex-1-en-1-yl]-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (0.009g, 0.031mmol) hydroxylamine (1.0 mL, 50% in water, 15.2 mmol) and sodium hydroxide (0.0485 g, 1.2 mmol) in methanol (8 mL) was stirred at room temperature for 2 hours. The reaction solution was concentrated to dryness and acetic acid (2.0 mL, 33.3 mmol) was added. It was run by microwave reaction at 150 °C for 10 minutes, concentrated and purified by prep-HPLC to provide the title compound as a solid (0.001 g, 5% yield). ^{1}H NMR (MeOD) δ; 8.69 (s, 1H), 7.70 (d, 1H, J = 3.0 Hz), 7.7.25-7.28 (m, 2H), 7.05 (d, 2H, J = 8.7 Hz), 6.85 (d, 1H, J = 3.0 Hz), 5.55 (s, 2H), 4.30 (m, 1H), 3.38-3.44 (m, 1H), 3.13-3.15 (m, 1H), 1.36-1.52 (m, 6H), 0.92 (t, 3H, J = 7.0 Hz),. LCMS (APCI, M+H$^+$): 368.2. HRMS calcd for $C_{21}H_{22}N_3O_2F_1$ (M+H$^+$) 368.1769, found 368.1756. HPLC: 100% purity.

Example K: 3-(4-fluorobenzyl)-7-hydroxy-8-methyl-3,7-dihydro-6*H*-pyrrolo[2,3-c]-1,7-naphthyridin-6-one



Step 1: methyl 1-(4-fluorobenzyl)-4-prop-1-yn-1-yl-1H-pyrrolo[2,3-c]pyridine-5-carboxylate

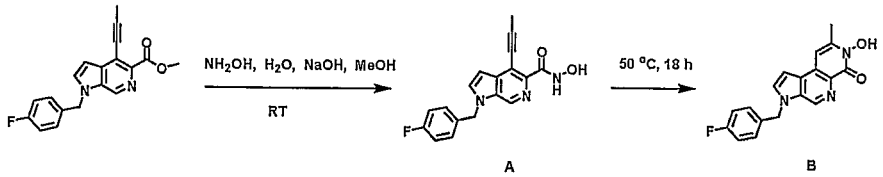


To a solution of methyl 1-(4-fluorobenzyl)-4-{[(trifluoromethyl)sulfonyl]oxy}-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (4 g, 9.25 mmol) in anhydrous DMF (20 ml) was added lithium chloride (1.18 g, 27.75 mmol), copper iodide (87.9 mg, 0.463 mmol), dichlorobis(triphenylphosphine) palladium (II) (649.35 mg, 0.925 mmol) and N,N-diisopropylethylamine (24.1 ml, 138.75 mmol). After the mixture was cooled down in a dry ice/acetone bath, excess propyne was added. The sealed flask with reaction mixture was placed in an oil bath and the bath was heated to 80 °C. After stirring for 24 hours (80 °C), the reaction was judged to be complete by HPLC-MS analysis. The volatiles were removed via rotary evaporator to give a black solid residue. The crude material was diluted with ethyl acetate (200 ml,) and filtered through celite, then extracted with water (3 x 200 ml). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude material was purified by chromatography on a column of silica gel to afford 2.06 mg (69 % yield) as yellow solid. LC-MS (APCI, M+H+): 323.2 HPLC: > 90% purity. 1H NMR (300 MHz, MeOD) δ ppm 8.60 (s, 1 H) 7.67 (d, J=3.01 Hz, 1 H) 7.20 - 7.27 (m, 2 H) 7.01 - 7.09 (m, 2 H) 6.77 - 6.82 (m, 1 H) 5.52 (s, 2 H) 3.93 (s, 3 H) 2.20 (s, 3 H)

Step 2:

A: 1-(4-fluorobenzyl)-*N*-hydroxy-4-prop-1-yn-1-yl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide

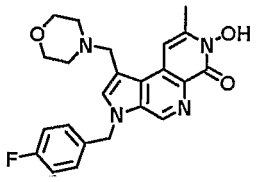
B: 3-(4-fluorobenzyl)-7-hydroxy-8-methyl-3,7-dihydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one



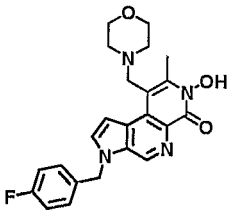
To a solution of methyl 1-(4-fluorobenzyl)-4-prop-1-yn-1-yl-1*H*-pyrrolo[2,3-c]pyridine-5-carboxylate carboxamide (274 mg, 0.85 mmol) in MeOH (5 ml) was added 0.85 mL of NH_2OH: H_2O = 1:1 and NaOH (170.2 mg, 4.25 mmol). After stirring for 2 hours at room

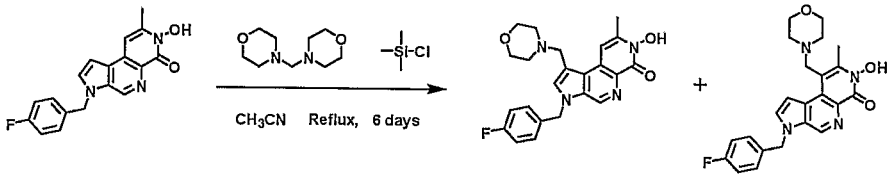
temperature, A was formed by analyzing HPLC-MS and NMR. Without any workup and purification, the same flask with reaction mixture was placed in an oil bath and the bath was warmed to 50 °C. After stirring for 18 hours (50 °C), the reaction was judged to be complete by HPLC-MS and NMR analysis. The volatiles were removed via rotary evaporator to give a brown solid residue that was purified by prep HPLC to give 112 mg (41 % yield) of target product as a light brown powder. A: LC-MS (APCI, M+H+): 324.1, HPLC: > 75% purity. 1H NMR (300 MHz, MeOD) μ ppm 8.59 (s, 1 H) 7.66 (d, 1 H) 7.24 (m, 2 H) 7.05 (m, 2 H) 6.77 (d, 1H) 5.53 (s, 2 H) 2.18 (s, 3 H). B: LC-MS (APCI, M+H+): 324.1, HPLC: > 95% purity. 1H NMR (300 MHz, MeOD) μ ppm 8.86 (s, 1 H) 7.70 (d, 1 H) 7.26 (m, 2 H) 7.06 (m, 3 H) 6.95 (d, 1H) 5.62 (s, 2 H) 2.57 (s, 3 H).

Example L: 3-(4-fluorobenzyl)-7-hydroxy-8-methyl-1-(morpholin-4-ylmethyl)-3,7-dihydro-6*H*-pyrrolo[2,3-c]-1,7-naphthyridin-6-one



Example M: 3-(4-fluorobenzyl)-7-hydroxy-8-methyl-9-(morpholin-4-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one



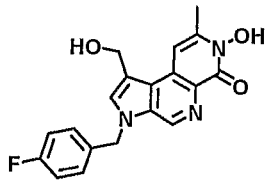


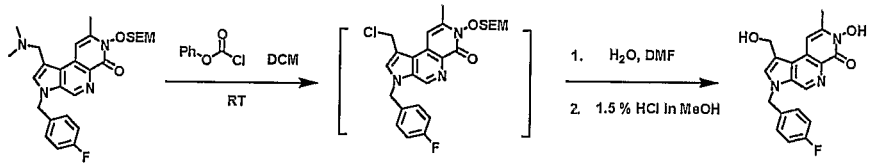
C D

To a solution of 3-(4-fluorobenzyl)-7-hydroxy-8-methyl-3,7-dihydro-6*H*-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (40 mg, 0.124 mmol) in anhydrous acetonitrile (3 mL) was added N,N'-dimorpholinomethane (138 mg, 0.47 mmol) and chlorotrimethylsilane (93.6 μL, 0.74 mmol). The mixture, under nitrogen, was placed in an oil bath and the bath was warmed to 90 °C. After stirring for 6 days (90 °C) the reaction was judged to be complete by HPLC-MS analysis. The volatiles were removed via rotary evaporator to give a brown solid residue that was purified by prep HPLC to give 7.8 mg (15 % yield) of C and 3 mg (6 % yield) of D as white

powder. C: LC-MS (APCI, M+H+): 423.2, HPLC: > 90% purity. 1H NMR (300 MHz, MeOD) δ ppm 8.84 (s, 1 H) 7.62 (s, 1 H) 7.46 (s, 1 H) 7.25 (m, 2 H) 7.05 (t, 2H) 5.57 (s, 2 H) 3.81 (s, 2 H) 3.68 (t, 4H) 2.56 (m, 7H). D: LC-MS (APCI, M+H+): 423.2, HPLC: > 90 % purity. 1H NMR (300 MHz, MeOD) μ ppm 8.92 (s, 1 H) 7.70 (s, 1 H) 7.28 (dd, 2 H) 7.20 (d, 1 H) 7.06 (t, 2H) 5.63 (s, 2 H) 3.95 (s, 2 H) 3.62 (t, 4H) 2.67 (s, 3H) 2.60 – 2.65 (m, 4H).

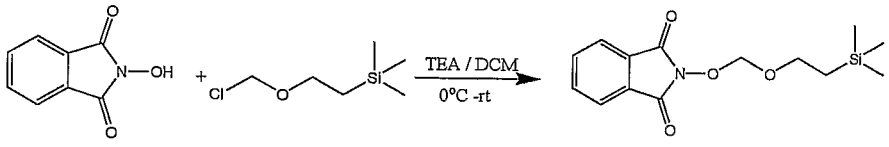
Example N: 3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-8-methyl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one





To a solution of 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-8-methyl-7-{[2-(trimethylsilyl)ethoxy]ethoxy}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (50 mg, 9.8 mmol) in anhydrous DCM (1.5 mL) was added phenyl chloroformate (12.3 uL, 9.8 mmol). The mixture, under nitrogen, was stirred at room temperature for 10 minutes. The reaction was judged to be complete by HPLC-MS analysis. Into the same pot, were added water (200 uL) and DMF (500 uL). After stirring for 2 hours at room temperature the reaction was complete and the volatiles were removed in vacuo to give a yellow solid. The residue was dissolved in 1.5% HCl in MeOH (2 mL) and stirred at room temperature for 18 hours. The reaction was judged to be complete by HPLC-MS analysis. The target product was purified by prep HPLC to afford 14.5 mg (42 % yield) of 3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-8-methyl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one as yellow solid. LC-MS (APCI, M+H+): 354.1. HPLC: > 95% purity. 1H NMR (300 MHz, MeOH) δ ppm 8.87 (s, 1 H), 7.67 (s, 1 H), 7.27 (m, 2 H), 7.19 (s, 1 H), 7.05 (t, 2 H), 5.59 (s, 2 H), 4.97 (s, 2 H), 2.57 (s, 3 H)

Example O: 2-((2-(trimethylsilyl)ethoxy)methoxy)isoindoline-1,3-dione 1

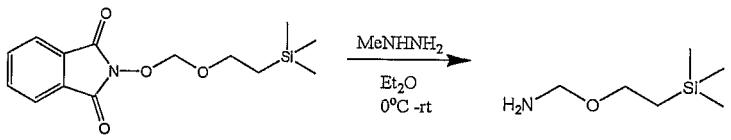


1

To a 2-Liter 3-neck round bottom flask, equipped with a stir bar, addition funnel (with a nitrogen line attached), and digital thermometer, under a static head of nitrogen, was added

N-hydroxyphthalimide (51.13 g, 0.313 mmol), SEM chloride (73.07 mL, 73.07 g, 0.438 mmol), and dichloromethane (700 mL). The flask was cooled to 0°C, then triethyl amine (60.96 mL, 44.32g, 0.438 mmol) was placed in the addition funnel and added drop wise to the suspension at such a rate that the internal temperature does not exceed 10°C. During the addition a transient red color is observed, remaining in the presence of an excess of amine base.) Once the addition was complete, the cooling bath was removed and the reaction was stirred at room temperature for 4 hours. The reaction was checked by adding an additional 1mL of triethyl amine, if any red color is observed, then the mixture was allowed to stir for an additional hour then repeat the test. Once the reaction was complete it was cast into dichloromethane (0.5 L), was washed with saturated aq. $NaHCO_3$ (750 mL), and brine (750 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in *vacuo*. The crude solid was recrystallized from hexanes overnight. The crystals were filtered, washed with cold hexanes, and dried to provide 2-((2-(trimethylsilyl)ethoxy)methoxy)isoindoline-1,3-dione 1, 85.4 g (93%). ^1H NMR (300 MHz, DMSO-D_6) δ 0.01 (s, 9 H), 0.84 - 0.95 (m, 2 H), 3.88 - 3.98 (m, 2 H), 5.11 (s, 2 H), 7.86 (s, 4 H).

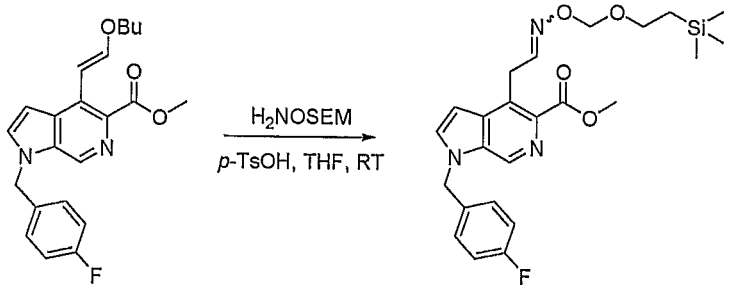
Example P: *O*-{[2-(trimethylsilyl)ethoxy]methyl}hydroxylamine 2



1 2

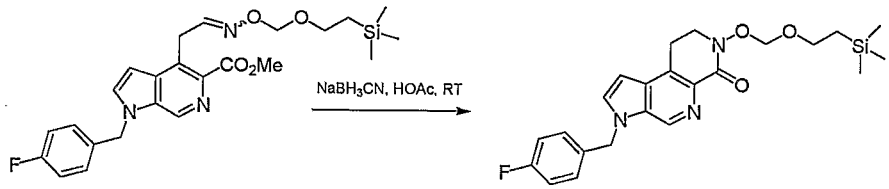
To a 2-liter three neck round bottom flask, equipped with an overhead stirrer, an addition funnel (w/N_2 line attached), and a digital thermometer, was added 2-((2-(trimethylsilyl)ethoxy)methoxy)isoindoline-1,3-dione 1 (77.69 g, 0.265 mmol) and Et_2O (700 mL). The mixture was cooled in an ice-salt bath (to ca. 0°C) and N-methyl hydrazine (20.9 mL, 18.29 g, 0.397 mmol) was added (with rapid stirring) at such a rate that the internal temperature did not exceed 5°C. When the addition was complete the bath was removed and the reaction was allowed to stir at room temperature for 4 hours. The white precipitate, which was formed during the reaction, was removed by filtration, rinsed with Et_2O (0.5 L), and the combined filtrates were concentrated in *vacuo* to furnish the crude product as a pale yellow oil. The crude oil was purified by distillation (55°C-58°C, mmHg) to give *O*-{[2-(trimethylsilyl)ethoxy]methyl}hydroxylamine 2 (39.4 g, 91%) as a clear colorless liquid. ^1H NMR (300 MHz, DMSO-D_6) δppm = 0.00 (s, 9 H) 0.83 - 0.91 (m, 2 H) 3.52 - 3.60 (m, 2 H) 4.60 (s, 2 H) 6.04 (s, 2 H).

Example Q: Methyl 1-(4-fluorobenzyl)-4-(2-((2-(trimethylsilyl)ethoxy)methoxyimino)ethyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate



To (E)-methyl 1-(4-fluorobenzyl)-4-(2-butoxyvinyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (10.00 g, 26.15 mmol) in anhydrous THF (250 mL) was added in order H_2NOSEM (4.91g , 30.07mmol, d = 0.81, 6.06 mL, 1.15eq.) and *p*-TsOH-H_2O (12.93g, 67.99mmol, 2.6eq.). HPLC-MS after 1 hour showed no reaction. HPLC-MS after 14.5 hours suggested 20% conversion to the target compound and a clean reaction. At 24hours, HPLC-MS suggested ca. 35% conversion; 38.5 hours, ca. 60% completion. Stirring was continued for an additional ca. 22 hours (60 hours total) at which time HPLC-MS suggested that the reaction was complete (RT = 1.76min, m/e = 472). The mixture was diluted with ether (0.25L) and was cast into CH_2Cl_2 (0.5L) and saturated aq. $NaHCO_3$ (0.75L). The organic phase was separated, the aq. layer was extracted with CH_2Cl_2 (0.5L) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to furnish the crude product as a tan oil. The crude material was triturated with ether, producing a fine, brown solid which was removed by filtration. Removal of the ether from the filtrate gave a beige oil. The crude product was purified by a short, flash column (50 mm OD, 100 g 230-400 mesh, packed DCM; eluted ether/DCM 10:90, 1.0 L; ether/DCM 17.5:82.5 1.0L; 50 mL fractions). Fractions 14-24 were combined to afford the desired product(s) as a clear, colorless, viscous oil 7.55g (71%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm -0.01 - 0.05 (m, 9 H), 0.92 - 1.05 (m, 2 H), 3.64 - 3.72 (m, 1 H), 3.73 - 3.80 (m, 1 H), 4.01 (d, *J*=3.20 Hz, 3 H), 4.26 (d, *J*=6.22 Hz, 1 H), 4.43 (d, *J*=5.09 Hz, 1 H), 5.11 (m, 1 H) 5.28 (m, 1 H) 5.42 (m, 2 H), 6.88 - 6.95 (m, 1 H) 7.04 (m, 2 H) 7.12 - 7.18 (m, 2 H) 7.34 (d, *J*=3.20 Hz, 1 H) 8.69 (d, *J*=3.96 Hz, 1 H)

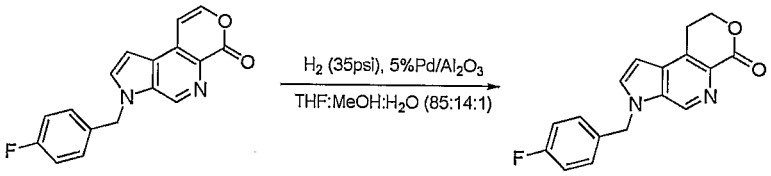
Example R: 3-(4-Fluorobenzyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one



To methyl 1-(4-fluorobenzyl)-4-(2-((2-(trimethylsilyl)ethoxy)methoxyimino)ethyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (7.48g, 15.86mmol) in glacial HOAc (125mL) was added sodium cyanoborohydride (2.10 g, 95%, 31.72 mmol, 2 eq.) in 2 portions (2 x 1.05 g), at the start of the reaction and after 1 hour. The reaction was monitored by HPLC and HPLC-MS

and appeared to be ca. 80-90% complete after 1 hour. After the addition of the second equivalent of $NaBH_3CN$, the mixture was allowed to stir for 1 additional hour at which time HPLC-MS suggested that the reaction was complete. The HOAc was then removed at full pump vacuum to give a clear, yellow viscous oil which was treated with 1.0 L of 95:5 ether/DCM and 0.8L of sat'd aq. $NaHCO_3$. The mixture was placed in a 2 L separatory funnel, shaken, and the organic phase was separated, the aq. phase was extracted with an additional 0.5 L of DCM and the combined organic phases were dried (Na_2SO_4). Filtration and concentration *in vacuo* gave the crude product as a pale yellow glass, which provided a white foam (7.4g) upon exposure to pump vacuum. The crude product was purified by Biotage (65, gradient 2% MeOH to 12% MeOH; 98% to 88% DCM over 12 column volumes, collection by UV, 240mL fractions). UV detection initiated collection at ca. 5% MeOH in DCM and collection continued until the gradient reached 6+% MeOH in DCM, a total of 2 fractions. Concentration *in vacuo* afforded 5.44 g (78%) of the target compound as a clear, colorless glass/foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 0.00 - 0.04 (m, 9 H), 0.92 - 1.03 (m, 2 H), 3.38 (t, *J*=6.88 Hz, 2 H), 3.80 - 3.90 (m, 2 H), 3.99 (t, *J*=6.88 Hz, 2 H), 5.11 (s, 2 H), 5.40 (s, 2 H), 6.62 (d, *J*=3.20 Hz, 1 H), 6.98 (t, *J*=8.67 Hz, 2 H), 7.06 - 7.13 (m, 2 H), 7.33 (d, *J*=3.20 Hz, 1 H), 8.78 (s, 1H).

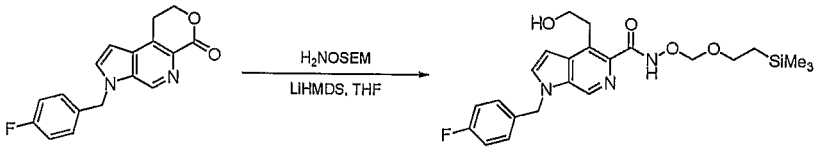
Example S: 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one



A solution / suspension of 7-(4-fluorobenzyl)pyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(7*H*)-one (17.90 g, 60.82mmol) in THF / MeOH / H_20 (1 L, 85:14:1) was sparged with nitrogen for 15 minutes in a 2L Parr hydrogenation bottle. To this solution, under N_2, was added 5% Pd/Al_2O_3 (1.79g, 10wt%) and the mixture was hydrogenated under 35psi of H_2 for 18 hours. HPLC and HPLC/MS indicated completion of the reaction, the mixture was sparged with nitrogen, filtered through a pad of celite (wet with CH_2Cl_2/MeOH 95:5), and the Parr bottle was rinsed with CH_2Cl_2/MeOH (750 mL, 95:5) and the combined filtrates were concentrated *in vacuo* to afford 19.08 g of crude product as a tan/pale yellow foam. Crude 1H NMR indicated a ca. 85:15 ratio of the desired saturated lactone / ring opened-over reduced material. The crude material was purified by Biotage chromatography in 3 portions (4 g, 65+M column gradient CH_2Cl_2/MeOH 99:1 to 95:5, 120 mL fractions), fractions 24-27 afforded 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one as a clear-colorless oil with was seeded with saturated lactone and recrystallized from ether/CH_2Cl_2 to furnish the target compound as white plates. The 4 g purification was repeated (65+M column gradient CH_2Cl_2/MeOH 99:1 to 95:5, 120 mL fractions), fractions 25-27 afforded the desired lactone as a clear-colorless oil with was seeded with saturated lactone and recrystallized from ether/CH_2Cl_2 to furnish the target compound as white plates. The remaining 11g of crude

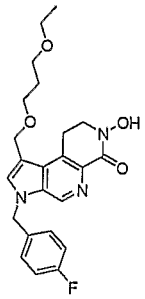
product was purified on the Biotage (65+M column gradient CH_2Cl_2/MeOH 99:1 to 95:5, 120mL fractions), fractions 25-28 gave the desired lactone as a clear-colorless oil with was seeded with saturated lactone and recrystallized from ether/CH_2Cl_2 to furnish the target compound as white plates. The combined material was recrystallized from ether/CH_2Cl_2 CH_2Cl_2 to afford 13.7 g (76%) of the desired saturated lactone as a white crystalline solid. From the combined mother liquors was isolated an additional 0.44g for a total of 14.14 g (78%) of 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one. 1H NMR (300 MHz, $CDCl_3$) δ ppm 3.33 (t, *J*=6.12 Hz, 2 H), 4.64 (t, *J*=6.12 Hz, 2 H), 5.45 (s, 2 H), 6.68 (d, *J*=3.01 Hz, 1 H), 6.98 - 7.06 (m, 2 H), 7.10 - 7.17 (m, 2 H), 7.39 (d, *J*=3.01 Hz, 1 H), 8.79 (s, 1 H).

Example T: 1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-N-((2-(trimethylsilyl)ethoxy)methoxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxamide

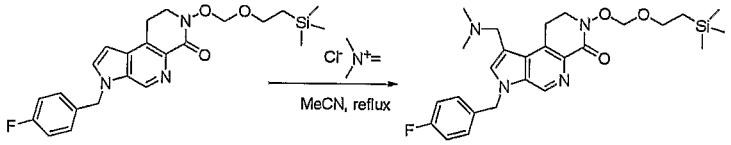


To a 250 mL 1N RB flask was added 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one (2.96g, 10.0mmol) and H_2NOSEM (3.56g, 20.0mmol). The mixture was placed under nitrogen, dissolved in anhydrous THF (100mL) and solid LiHMDS (3.35 g, 20.0mmol) was added in one portion. The mixture was allowed to stir at room temperature while being monitored by HPLC-MS. After 2 hours HPLC-MS suggested that the reaction was as complete as was reasonable, and consisted of ca. 60% ring opened, 30% SM, 10% hydrolysis product. At the 36 hour time point all starting material had been consumed (LCMS) and the mixture was judged to be composed of ca. 90:10 ring opened / eliminated material. The mixture was poured into ether (1.0L) and saturated aq. NH_4Cl (0.75 L). The organic phase was separated, washed with brine (0.1L), dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product as a pale, yellow oil. The crude material was purified *via* chromatography (Biotage® SP-1, 40M, 2% to 12% MeOH / DCM, 3 column volumes to waste followed by the collection of 25 mL fractions), and the combination and concentration *in vacuo* of fractions 27-42 provided 2.80 g (59%) of 1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-N-((2-(trimethylsilyl)ethoxy)methoxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxamide as a white crystalline solid. 1H NMR (300 MHz, $CDCl_3$) δ ppm 0.01 - 0.04 (9 H), 0.90 - 1.04 (m, 2 H), 3.53 - 3.65 (m, 2 H), 3.83 (dd, *J*=9.23, 7.72 Hz, 2 H), 4.05(t, *J*=5.93 Hz, 3 H), 5.02 (s, 2 H), 5.37 (s, 2 H), 6.69 (d, *J*=2.45 Hz, 1 H), 6.97 - 7.12 (m, 4 H), 7.30 (d, *J*=3.01 Hz, 1 H), 8.41 (s, 1 H), 10.44 (s, 1 H).

Example U: 3-(4-fluorobenzyl)-1-((3-ethoxypropoxy)methyl)-7-hydroxy-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one

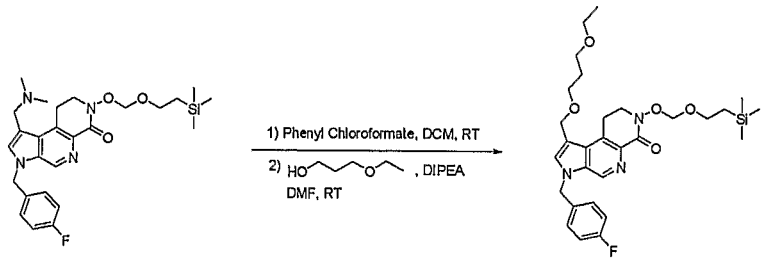


Step 1: 3-(4-fluorobenzyl)-1-((dimethylamino)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one



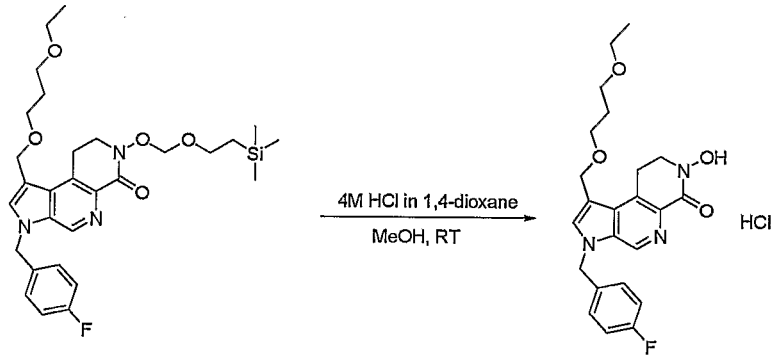
To 3-(4-fluorobenzyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (7.82 g, 17.71 mmol) in acetonitrile (0.3 L) was added *N,N*-dimethyliminium chloride (Fluka, 6.63 g, 70.84 mmol, 4 eq.). The mixture was allowed to stir under nitrogen, at RT for 21 hours at which point HPLC-MS suggested ca. 40-45% conversion to the desired dimethylaminomethyl compound. The flask was equipped with a reflux condenser and the mixture was immersed in a 90°C oil bath and warmed to reflux (under N_2) for 4 hours, HPLC-MS at this time point suggested complete reaction, hence reflux was discontinued. The cooled reaction mixture was concentrated *in vacuo* and the resulting semi-solid was partitioned between EtOAc/DCM (1 L, 95:5) and sat'd. aq. $NaHCO_3$ (0.75 L). The organic phase was separated, washed with brine (0.75L), and dried (Na_2SO_4). HPLC-MS analysis of the organic phase and the initial $NaHCO_3$ wash suggested that all target material was present in the initial organic phase. Concentration *in vacuo* then afforded the crude dimethylaminomethyl-substituted-SEM-blocked dihydro tricycle as a tan solid (7.732 g). The crude solid (1 peak by LC-MS was further purified by trituration with hot ether/hexanes (90:10) to give 3-(4-fluorobenzyl)-1-((dimethylamino)methyl)-7-((2-(trimethylsilyl) ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (6.82g) as fine ivory needles. The filtrate was passed through a small Biotage column (40M, 2-10% MeOH/DCM over 19 column volumes, 3 CV to waste, then collect 50mL fractions. Fraction 12 [9CV] provided an additional 0.72g of the target 3-(4-fluorobenzyl)-1-((dimethylamino)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one as a tan crystalline solid. Total purified yield 7.54 g (85%). 1H NMR (300 MHz, $CDCl_3$) δ ppm 0.03-0.07 (9 H), 0.98 - 1.07 (m, 2 H), 2.23 (s, 6 H), 3.51 (s, 2 H), 3.77 (t, *J*=6.03 Hz, 2 H), 3.85 - 4.00 (m, 4 H), 5.15 (d, *J*=2.07 Hz, 2 H), 5.35 (s, 2 H), 6.97 - 7.03 (m, 2 H), 7.03 - 7.17 (m, 3 H), 8.74 (s, 1 H).

Step 2: 3-(4-fluorobenzyl)-1-((3-ethoxypropoxy)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one



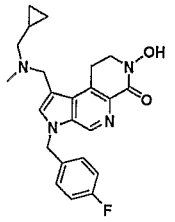
To an oven-dried 40mL vial with septum cap was added 3-(4-fluorobenzyl)-1-((dimethylamino)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (0.450 g, 0.902 mmol) followed by DCM (10 mL). Under a blanket of nitrogen, the mixture was stirred and to this was added phenyl chloroformate (0.143 g, 0.115mL, 0.902 mmol). This stirred for 1 hour at room temperature. To the stirring solution was added DIEPA (0.408 g, 0.55 mL, 3.158 mmol), 3-ethoxy-1-propanol (0.235 g, 0.26 mL, 2.256 mmol), and DMF (10 mL). The reaction stirred at 50° overnight. The reaction was quenched with MeOH (3 mL) and water (65 mL + 10 mL brine). The solution was extracted with DCM (3 x 70 mL). The organic phase was washed with saturated $NaHCO_3$ (30 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, concentrated in vacuo, and purified by flash chromatography on a biotage SP1 (method: TLC method 5% MeOH/DCM, column: 40+S). The pure fractions were combined and concentrated in vacuo yielding a clear colorless oil.

Step 3: 3-(4-fluorobenzyl)-1-((3-ethoxypropoxy)methyl)-7-hydroxy-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one

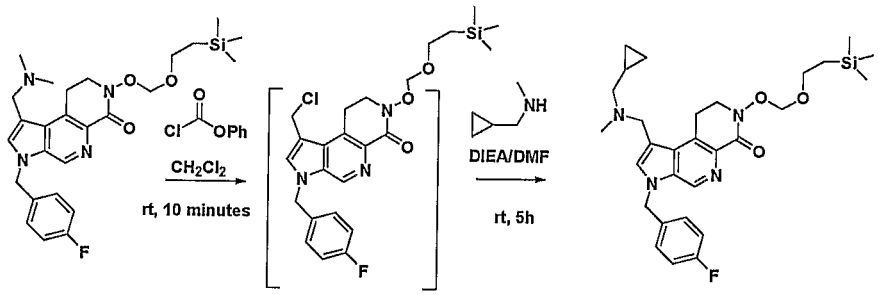


To a stirring solution of 3-(4-fluorobenzyl)-1-((3-ethoxypropoxy)methyl)-7-((2-(trimethylsilyl)ethoxy) methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (0.34g, 0.586mmol) in MeOH (30mL) was added 2M HCl in ether (10mL). The reaction stirred overnight at room temperature. The solvent was evaporated and the crude yellow solid was recrystalized from IPA (pale yellow needles).

Example V: 1-{[(cyclopropylmethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one.

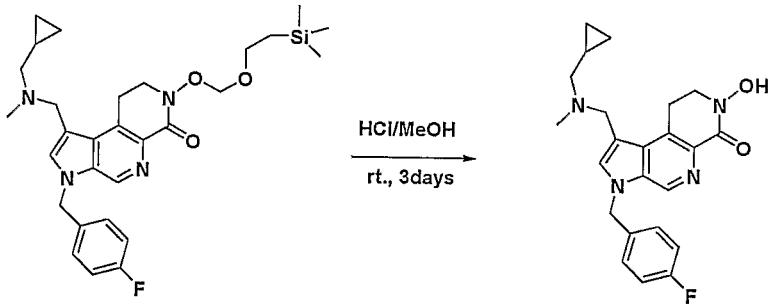


Step 1: 1-{[(cyclopropylmethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl) ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one.



To a solution of the 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one (0.50 g, 1.0 mmol) in dichloromethane (10 mL) was added phenylchloroformate (0.126 mL, 1.0mmol) at room temperature. After stirring at room temperature for ten minutes, the solution was added to the solution of (cyclopropylmethyl)methylamine hydrochloride (0.244 g, 2.0 mmol) and diisopropylethylamine (0.70 mL, 4.0 mmol) at room temperature. After stirring at room temperature for additional 5 hours, it was quenched with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane twice. After dried over sodium sulfate, the organic layer was concentrated and the residue was purified by reversed phase HPLC to provide a white powder (37% yield).

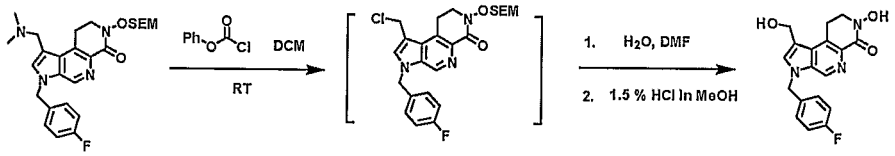
Step 2: 1-{[(cyclopropylmethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one.



A solution of 1-{[(cyclopropylmethyl)(methyl) amino]methyl}-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy] methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one (0.189g, 0.35mmol) in methanol (10mL) and HCl in methanol (9.42w% in methanol, 2 mL)

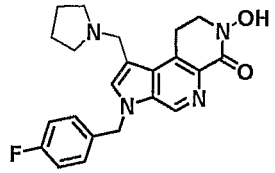
was stirred at room temperature for 3 days. It was concentrated, and the residue was purified by revered phase HPLC to provide the title compound as powder (35% yield).

Example W: 3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one

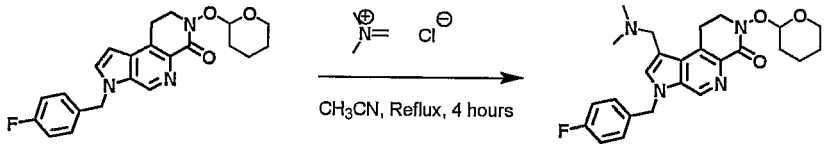


To a solution of 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (100 mg, 0.2 mmol) in anhydrous DCM (2 mL) was added phenyl chloroformate (25 µL, 0.2 mmol). The mixture, under nitrogen, was stirred at room temperature for 10 minutes. The reaction was judged to be complete by HPLC-MS analysis. Then 5 drops of water were added. After stirring for 20 minutes at room temperature the reaction was complete and the volatiles were removed in vacuo. The residue was dissolved in 1.5% HCl in MeOH (2 mL) and stirred at room temperature for 18 hours. The reaction was judged to be complete by HPLC-MS analysis. The target product was purified by prep HPLC to afford 34.8 mg (49 % yield) of 3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one as white solid. LC-MS (APCI, M+H+): 342.2. HPLC: > 95% purity. 1H NMR (300 MHz, MeOH) δ ppm 8.69 (s, 1 H), 7.65 (s, 1 H), 7.22 - 7.31 (m, 2 H), 7.04 (t, 2 H), 5.50 (s, 2 H), 4.60 (s, 2 H), 3.95 (t, 2 H), 3.70 (t, 2 H).

Example X: 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one



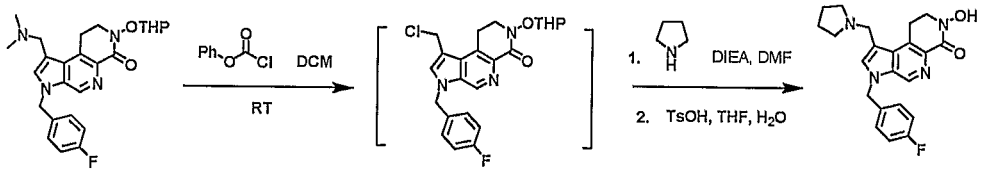
Step 1: 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one.



To a solution of 3-(4-fluorobenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (425 mg, 1.08 mmol) in anhydrous acetonitrile (70

mL) was added N,N-dimethylmethyleneiminium chloride (201.1 mg, 2.15 mmol). The mixture, under nitrogen, was refluxed for 4 hours. The reaction was judged to be complete by HPLC-MS analysis. The target product was purified by prep HPLC to afford 147 mg (30 % yield) of 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one as white solid. LC-MS (APCI, M+H+): 453.2. HPLC: > 95% purity.

Step 2: 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one



To a solution of 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (147 mg, 0.323 mmol) in anhydrous DCM (3 mL) was added phenyl chloroformate (41 µL, 0.323 mmol). The mixture, under nitrogen, was stirred at room temperature for 10 minutes. The reaction was judged to be complete by HPLC-MS analysis. At the same pot, the mixture of pyrrolidine (32.1 µL, 0.388 mmol), DIEA (169 µL, 0.969 mmol) and anhydrous DMF (1.5 mL) was added and stirred at room temperature for 2 hours. The reaction was judged to be complete by HPLC-MS analysis. The volatiles were removed in vacuo. The residue was dissolved in a solution of $TsOH \cdot H_2O$ (77.1 mg, 0.41 mmol) in THF (4mL) and Water (2 mL) and stirred at 50 °C for 4 hours. The reaction was judged to be complete by HPLC-MS analysis. The target product was purified by prep HPLC to afford 72 mg (56 % yield) of 3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one as white solid. LC-MS (APCI, M+H+): 395.2. HPLC: > 95% purity. 1H NMR (300 MHz, MeOH) δ ppm 8.60 (s, 1 H), 8.04 (s, 1 H), 7.19 - 7.30 (dd, 2 H), 7.00 (t, 2 H), 5.55 (s, 2 H), 4.67 (s, 2 H), 3.81 (s, 2 H), 3.44 (m, 6 H), 2.12 (m, 4 H).

Example Y: 3-(4-fluorobenzyl)-1-(2-hydroxyethyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one

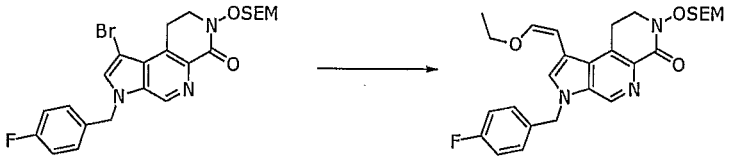
Step 1: 3-(4-fluorobenzyl)-1-bromo-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one



To a solution of 3-(4-fluorobenzyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (10.00 g, 22.65 mmol) in anhydrous DMF (110 mL) was added N-bromosuccinimide (4.43 g, 24.9 mmol) and the resulting mixture was stirred

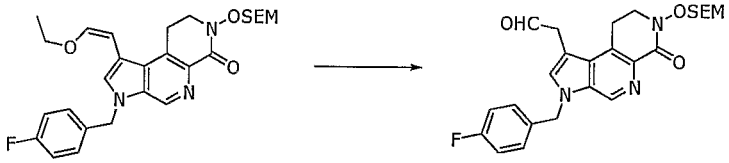
under nitrogen atmosphere at ambient temperature overnight. The reaction mixture was concentrated *in vacuo*, the resulting residue was dissolved in dichloromethane (250 mL), the organic layer was washed with 10% sodium carbonate solution (3x500 mL), brine (1x500 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give product as an off-white solid (11.5 g, 97% yield).

Step 2: (Z)-3-(4-fluorobenzyl)-1-(2-ethoxyvinyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one



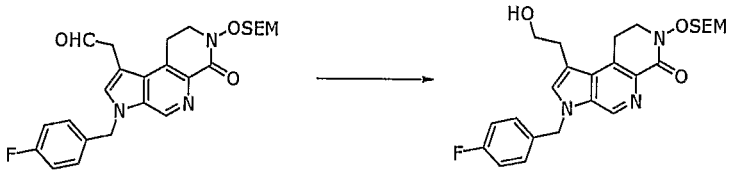
To an argon degassed solution of 3-(4-fluorobenzyl)-1-bromo-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (0.77 g, 1.48 mmol) in anhydrous DMF (8 mL) with stirring in a 50 mL Teflon capped and sealed tube was added (Z)-tributyl(2-ethoxyvinyl)stannane (0.901 mL, 0.961 g, 2.66 mmol), $PdCl_2(Ph_3P)_2$ (0.100 g, 0.15 mmol) and LiCl (0.316 g, 5.00 mmol) and reaction mixture was heated to 80 °C for 3h. The reaction mixture was then concentrated *in vacuo* and purified using Biotage 100% DCM to 10% MeOH/DCM. Final yield gave crude products as an amber oil (0.740 g).

Step 3: 2-(3-(4-fluorobenzyl)-6-oxo-7-((2-(trimethylsilyl)ethoxy)methoxy)-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-1-yl)acetaldehyde



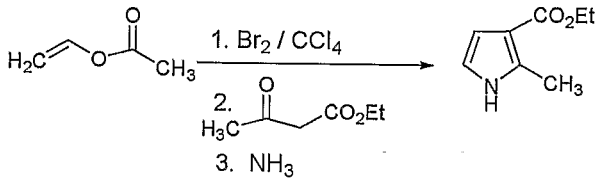
To a solution of (Z)-3-(4-fluorobenzyl)-1-(2-ethoxyvinyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (0.500 g, 0.98 mmol) in 1,4-dioxane (5 mL) was added pTSA-H_2O (0.206 g, 0.11 mmol) and reaction was stirred for 3 h at ambient temperature. The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in dichloromethane (30 mL), washed with saturated sodium bicarbonate solution (30 mL x 3), brine wash, dried organic layer over sodium sulfate, filtered, concentrated *in vacuo* to give crude product (0.335 g, 70% yield) that was used without further purification.

Step 4: 3-(4-fluorobenzyl)-1-(2-hydroxyethyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one



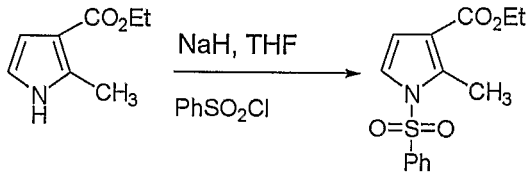
To a solution of 2-(3-(4-fluorobenzyl)-6-oxo-7-((2-(trimethylsilyl)ethoxy)methoxy)-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-1-yl)acetaldehyde (0.030 g, 0.06 mmol) in anhydrous methanol (0.3 mL) was prepared and cooled to 0°C in an ice bath and then sodium borohydride (1.2 mg, 0.03 mmol) was added and reaction was monitored by LCMS and complete within 1h. The reaction mixture was concentrated *in vacuo* and the remaining residue was dissolved in dichloromethane (5 mL), washed with saturated sodium bicarbonate solution (5 mL x 3), brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give crude product as a clear glass (20 mg, 66% yield).

Example Z: Ethyl 2-methyl-1H-pyrrole-3-carboxylate



Under nitrogen, vinyl acetate (172 g, 2 mol) was dissolved in dry carbon tetrachloride (100 mL) and bromine (102 mL) in dry carbon tetrachloride (100 mL) was added dropwise over 6 hours with vigorous stirring in an ice-water bath and reaction progress was monitored by a digital thermometer in order to keep the reaction temperature below 10 °C. The reaction mixture was stirred for additional 30 min thereafter and then the carbon tetrachloride was evaporated in vacuo. The crude α,β-dibromoethyl acetate was mixed with ethyl acetoacetate (260 g), and aqueous 10% ammonium hydroxide (2 L) was added dropwise. The addition was performed so that the reaction temperature was maintained below 10 °C. After the addition was complete, the reaction mixture was stirred for an additional 2 h and left to stand overnight at room temperature. The aqueous layer was decanted and the solids were dissolved into dichloromethane (700 mL). The dichloromethane layer was washed with water (500 mL x 2) and then dried. Most of the solvent (DCM) of the filtered solution was evaporated in vacuo at 50 °C until it became high concentration solution. This solution was cooled down at 3 °C in the refrigerator and the desired product, ethyl 2-methyl-1H-pyrrole-3-carboxylate, was recrystallized from dichloromethane twice to provide tan crystals (149 g, 49%).

Example AA: Ethyl 2-methyl-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate



To a stirred solution of ethyl 2-methyl-1H-pyrrole-3-carboxylate (40.0 g, 261.13 mM) in dry THF (1100 mL) at -78 °C (dry ice and acetone) under nitrogen was added Sodium hydride (15.66 g of a 60% dispersion in mineral oil, 392 mM), which is washed three times by hexanes to remove mineral oil. Sodium hydride was added in portions by a 20 mL syringe to a clear brownish solution. After sodium hydride addition, the reaction mixture was stirred for 30 min at -72 °C before being warmed to room temperature and stirred for an additional 20 min at room temperature before being cooled to -78 °C. Benzenesulfonyl chloride (35.2 mL, 274 mM) was added and the reaction mixture was allowed to warm to room temperature and stirred for 16 h before removal of the solvent in vacuo. To the residue was added saturated aqueous $NaHCO_3$, the mixture was extracted twice with ethyl acetate, the organic layers were combined, dried over Na2SO4, filtered and concentrated to leave low volume of EtOAc. The resulting solution was allowed to stand uncovered for about 48 hours to provide crystalline materials there were washed with cold hexane and dried in vacuo to provide 43.67 g of the title compound. The mother liquor was concentrated and cooled down to <4 °C in the refrigerator overnight to provide an additional crop of crystals there were washed with cold hexanes and dried in vacuo to provide an additional 22.96 g of the title compound.

Example AB: Ethyl 2-methyl-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate

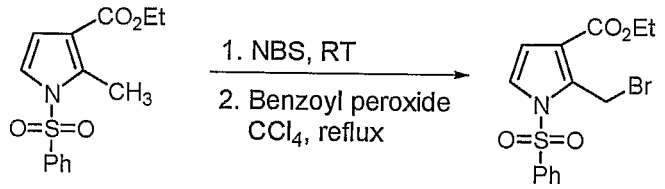
The title compound was prepared according to a method adapted from *Coll. Czech. Comm.* 1999, 499. To a solution of ethyl 2-methyl-1*H*-pyrrole-3-carboxylate (15.2 g, 99.3 mmol) and tetra-*n*-butylammonium bromide (3.2 g, 9.9 mmol., 0.1 equiv.) in toluene (500 mL) was added benzenesulfonyl chloride (26.4 g, 14.9 mmol., 1.5 equiv.) followed by a solution of sodium hydroxide (38 g, 0.95 mol., 10 equiv.) in water (50 mL). The mixture was vigorously stirred for 45 minutes. The reaction was monitored by TLC (20% ethyl acetate in hexanes. Upon completion, water (250 mL) was added to the reaction mixture, and the organic layer separated. The aqueous was extracted with a further portion of toluene (100 mL). The combined organics were dried over sodium sulfate, and the solvent removed to afford the product as a viscous oil that was purified by passing through a plug of silica gel, eluting with ethyl acetate/heptanes (initially 10% being increased to 15%). On removal of the volatiles *in vacuo*, the product crystallized from solution, and was collected by filtration washing with heptanes as a colorless solid (22.12 g, 76%). On standing, a second crop of product (2.75 g, 10%) was isolated.

Example AC: Ethyl 2-methyl-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate

To a solution of ethyl 2-methyl-1*H*-pyrrole-3-carboxylate (100 g, 0.65 mol) and tetra-*n*-butylammonium bromide (21 g, 65 mmol.) in toluene (3 L) cooled in an ice bath, was added

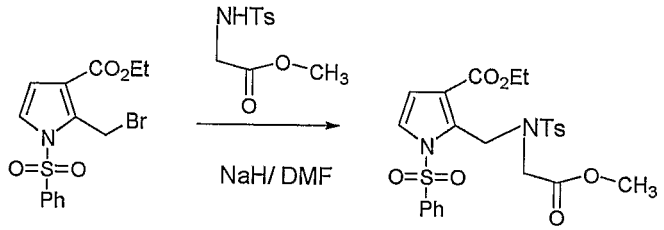
benzenesulfonyl chloride (173.5 g, 1 mol) followed by a solution of sodium hydroxide (250 g, 6.25 mol) in water (329 ml). The mixture was vigorously stirred for 45 minutes using an overhead stirrer. Upon completion, water (1L) was added to the reaction mixture, and the organic layer separated. The aqueous was extracted with a further portion of toluene (500 mL). The combined organics were dried over sodium sulfate, and the solvent removed to afford the product as a viscous oil that was purified by passing through a plug of silica gel eluting with ethyl acetate/heptane (initially 5% being increased to 15%). On removal of the volatiles *in vacuo*, the product crystallized from solution, and was collected by filtration washing with heptanes as a colorless solid (116 g, 61%). On standing, a second crop of product (17.9 g, 9%) was isolated.

Example AD: Ethyl 2-(bromomethyl)-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate



Ethyl 2-methyl-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate (30.0 g, 100 mmol) was dissolved in 400 mL carbon tetrachloride. N-bromosuccinimide (27.3 g, 153 mmol) and benzoyl peroxide (0.743 mg, 3.07 mmol) were added. The suspension was heated to reflux (oil bath, 100 °C) for 2 hours, after which time the reaction mixture was allowed to cool to room temperature and was filtered. The filtrate was concentrated via rotary evaporator and the resulting residue in was dissolved EtOAc and washed 2 times with saturated $NaHCO_3$ solution. The combined aqueous layers were extracted with an additional portion of EtOAc, the organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The resulting solid was precipitated from diethyl ether/hexanes solution using sonication and was then filtered and dried to provide the title compound (36.4 g, 96%).

Example AE: Ethyl 2-((N-(2-methoxy-2-oxoethyl)-4-methylphenylsulfonamido)methyl)-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate



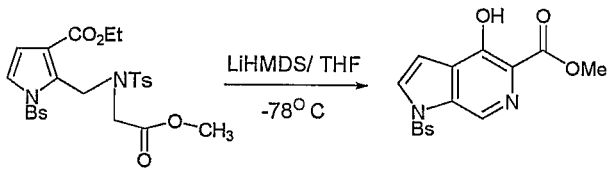
Ethyl 2-(bromomethyl)-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate (30.0 g, 80.6 mM) and tosyl-glycine (19.6 g, 80.6 mM) were dissolved in DMF (220 mL). Sodium hydride (6.45 g, 161 mM, 60% in mineral oil which was washed by hexanes 3 times) was added dropwise at -20 °C (Isopropanol and dry ice bath) by pipette. The reaction mixture was stirred for 2 hours at a temperature of from about -20 °C to about 0 °C. Saturated ammonium chloride was then

added to the reaction mixture and the mixture was extracted 2 times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered, concentrated. The concentrated mixture was allowed to stand uncovered at room temperature overnight to afford the title compound as crystals that were washed with cold hexanes and dried in vacuo overnight to afford 56 g of the title compound. The mother liquor was further purified by flash column (5% to 60% EtOAc/hexanes) to provide an additional 14.7 g of the title compound.

Example AF: Ethyl 2-((N-(2-methoxy-2-oxoethyl)-4-methylphenylsulfonamido)methyl)-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate

The title compound was prepared using a procedure adapted from *Bioorg. Med. Chem.* 2003, *11*, 1451. A solution of methyl *N*-[(4-methylphenyl)sulfonyl]glycinate (55.2 g, 0.23 mol), potassium carbonate (31.5 g, 0.23 mol) and potassium iodide (1.85 g, 0.011 mol) in acetone (600 mL) was stirred at 60 °C for 30 minutes. To this mixture was added ethyl 2-(bromomethyl)-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (75 g, 0.2 mol), and the reaction was stirred at 60 °C for 16 hours. The reaction was allowed to cool, filtered, and the solids washed with acetone (100 mL). The solvent was removed *in vacuo* and the resulting residue was dissolved in methylene chloride (500 mL). The organic layer was washed with water (3 x 250 mL) and dried over sodium sulfate. The solvents were removed *in vacuo* and ethyl acetate (150 ml) was added to the resulting residue. A seed crystal obtained from a previous reaction, the product of which had been purified by flash chromatography on silica gel (eluting with 20% to 50% ethyl acetate in heptanes) was added and the title compound was isolated as a colorless solid that was washed with diethyl ether and dried (70.3 g, 65%). A second crop of the title compound was isolated from the filtrate by allowing it to stand at room temperature.

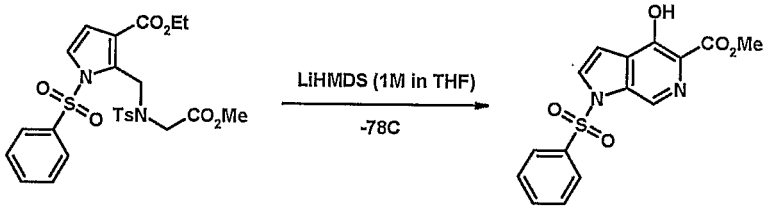
Example AG: Methyl 4-hydroxy-1-(phenylsulfonyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate



To a stirring solution of ethyl 2-((N-(2-methoxy-2-oxoethyl)-4-methylphenylsulfonamido)methyl)-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate (31.84 g, 59.56 mmol) in THF (400 mL) in a 1 L round-bottom flask was added LiHMDS (178 mL, 178 mmol, 1.0 M in THF) slowly by a graduated addition funnel at -78 °C (dry ice and acetone) over 2 h. The resulting mixture was allowed to stir at -78 °C for an additional 1 hour, after which time reaction was quenched by aqueous ammonium chloride (400 mL) was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate (2 x 600 mL), the combined organic layers were washed with water (2 x 400 mL), and the combined aqueous layers were extracted with additional ethyl acetate (2 x 400 mL). The resulting organic layers were combined, washed with saturated sodium chloride solution, dried over Na_2SO_4, filtered, and

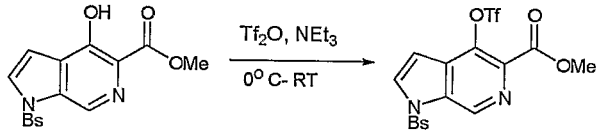
the solvents were removed by rotary evaporation until crystalline material was present. The remaining solution was then cooled to room temperature and left in refrigerator overnight to provide the title compound as crystalline material. Additional crops of crystals were obtained by allowing the filtrate to stand uncovered at room temperature. Additional materials were obtained by purification of the mother liquor by ISCO flash column.

Example AH: Methyl 4-hydroxy-1-(phenylsulfonyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate



A 500 mL, three necked flask was cooled to –78 °C using a dry ice/acetone bath. The flask was then charged with the substrate (16 g, 30 mmol) and anhydrous THF (200 mL). The resulting suspension was stirred, and a solution of LiHMDS (Aldrich, 1.0M in THF, 89mL, 89mmol) was added in a dropwise fashion via a dropping funnel over a period of 30 minutes. After stirring for 90 minutes at –78 °C, the reaction mixture was poured into saturated ammonium chloride solution (200 mL). The aqueous layer was extracted with ethyl acetate (3 x 250 ml), and the organics combined, and dried over sodium sulfate. After filtration, the volume of solvent was reduced *in vacuo* until a precipitate was present. The remaining mixture was then cooled for 30 minutes, and the resulting precipitate was filtered. The resulting solid was suspended in chloroform and the suspension was warmed, agitated for 10 minutes, and then filtered. The resulting solid was dried in vacuo to provide the title compound as a colorless solid (5 g, 50%).

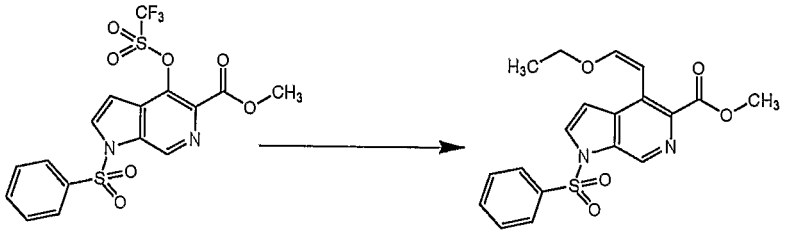
Example AI: Methyl 1-(phenylsulfonyl)-4-(trifluoromethylsulfonyloxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate



A solution of phenol (20.00 g, 60.02 mmol, 1.00 eq), triethylamine (42.00 mL, 300.0 mmol, 5.0 eq), and anhydrous dichloromethane (400 mL) was cooled to -5 °C in an ice/brine bath. To the mixture was added dropwise triflic anhydride (25.40 mL, 150.4 mmol, 2.50 eq) at a rate such that the internal temperature of the mixture was kept below 0 °C. After addition was complete the reaction mixture was stirred for an additional 30 minutes. Sodium bicarbonate solution (600 mL) was added and the mixture was extracted with dichloromethane (3 x 400 mL). The organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo to provide the crude products that was further purified by column chromatography (silica gel, 3:1 hexanes:EtOAc). LCMS (APCI, M+H) 465.2. ^{1}H NMR (300

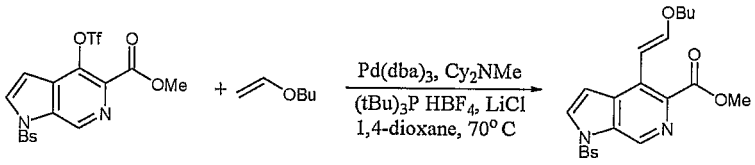
MHz, CHLOROFORM-D) δ 9.37 (d, *J*=0.75 Hz, 1 H) 7.94-8.01 (m, 2 H) 7.86 (d, *J*=3.58 Hz, 1 H) 7.63 - 7.74 (m, 1 H) 7.50-7.61 (m, 2 H) 6.89 (d, *J*=3.77 Hz, 1 H) 4.04 (s, 3 H).

Example AJ: Methyl 4-[(*Z*)-2-ethoxyvinyl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate



To a solution of the triflate (1.00 g, 2.15 mmol, 1.00 eq) in anhydrous 1,4-dioxane (20 mL, degassed with Argon balloon and needle) in a Teflon, capped, and sealed tube was added LiCl (228 mg, 5.38 mmol, 2.50 eq), ethoxyvinyl tri-t-butylstannane (1.09 mL, 3.23 mmol, 1.50 eq), and $PdCl_2(PPh_3)_2$ (0.151 g, 0.215 mmol, 0.10 eq). The resulting mixture was heated to 80 °C for 1 h and was then allowed to cool. Sodium bicarbonate solution was then added and the mixture was extracted with ethyl acetate to provide a mixture of colorless and black oils. The residues were dissolved in dichloromethane and purified by flash chromatography (silica gel, 2:1 hexanes:EtOAc to 1:1 hexanes:EtOAc) to provide the title compound as a colorless glass (0.630 g, 76% yield). LCMS (APCI, M+H) 387.2. 1H NMR (300 MHz, CHLOROFORM-D) δ 9.21 (s, 1 H), 7.89 - 7.99 (m, 2 H), 7.70 (d, *J*=3.58 Hz, 1 H), 7.54 - 7.63 (m, 1 H), 7.41 - 7.53 (m, 2 H), 6.78 (dd, *J*=3.58, 0.57 Hz, 1 H), 6.39 (d, *J*=6.97 Hz, 1 H), 5.93 (d, *J*=6.97 Hz, 1 H), 3.96 (s, 3 H), 3.91 (q, *J*=7.03 Hz, 2 H), 1.22 (t, *J*=7.06 Hz, 2 H).

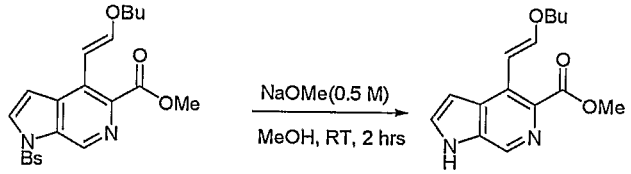
Example AK: (E)-methyl 4-(2-butoxyvinyl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate



To 3-neck, round-bottom flask equipped with a stir bar, a dry ice cold finger, 2 rubber septum, and under a blanket of N_2 was added methyl 1-(phenylsulfonyl)-4-(trifluoromethylsulfonyloxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (2.76 g, 5.95 mmol, 1 eq), $Pd_2(dba)_3$ (0.57 g,1.368 mmol, 0.03 eq), $(t\text{-}Bu)_3P{\bullet}HBF_4$ (0.4 g, 1.368 mmol, 0.03 eq), LiCl (1.53 g, 35.68 mmol, 3 eq), and anhydrous 1,4-dioxane (60 mL). With stirring, n-butyl vinyl ether (9.24 mL, 71.38 mmol, 12 eq) and dicyclohexylmethylamine (2.88 mL, 13.45 mmol, 2.26 eq) were added. The dry ice cold finger was filled with dry ice and IPA and the reaction was heated in an oil bath to an external temperature of 70 °C for 90 minutes and was then allowed to cool to room temperature. The mxiture was filtered through celite and the celite was washed with EtOAc until no color was observed coming from the filter. The solvents were evaporated under reduced pressure until a viscous oil was present and no 1,4-dioxane was present. The

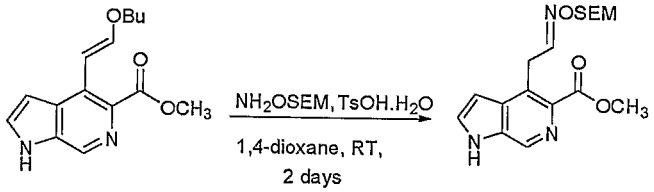
resulting oil was dissolved in a large portion of EtOAc (such as about 1.1 L of EtOAc for a 50 g reaction) with sonication. The resulting solution was stirred rapidly for 3 hours at which time a solid precipitated that was filtered and the resulting filtrate was concentrated to afford an oil. The oil was further purified by silica gel chromatography with ethyl acetate/hexane (1/1) to provide the title compound as solid (2.1 g, 85% yield).

Example AL: (E)-methyl 4-(2-butoxyvinyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate



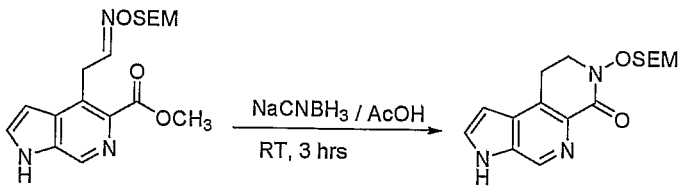
To a stirred solution of (E)-methyl 4-(2-butoxyvinyl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (1.86 g, 4.5 mmol) in MeOH was added sodium methoxide (9 mL, 4.5 mmol, 0.5 M in MeOH), the resulting solution was stirred at room temperature for about one hour. Reaction was checked by LC-MS and complete. Reaction was quenched with saturated NH_4Cl until solution was neutral. Combined organic layer was dried, concentrated and crude was purified by chromatography with 5% MeOH/DCM to provide the title compound as solid (1.03 g, 84% yield).

Example AM: 4-(2-((2-(trimethylsilyl)ethoxy)methoxyimino)ethyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate



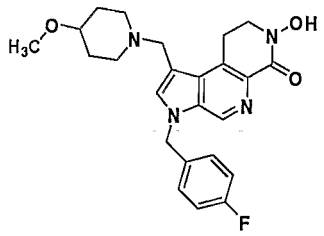
To (E)-methyl 4-(2-butoxyvinyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (1.03 g,3.76 mmol) in anhydrous 1,4-dioxane (35 mL) was added in order H_2NOSEM (1.7 mL, 8.76 mmol, d = 0.83, 2.30 eq.) and p-TsOH-H_2O (2.79 g, 14.66 mmol, 3.90 eq.). The reaction mixture was stirred at room temperature for 48 h. The mixture was cast into EtOAc (50 mL) and saturated aq. $NaHCO_3$ (50 mL). The organic phase was separated, the aq. layer was extracted with EtOAc (50 mL) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo to furnish the crude product (2.64 g, >100%) as a solid that was used in the next step w/o further purification.

Example AN: 7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one

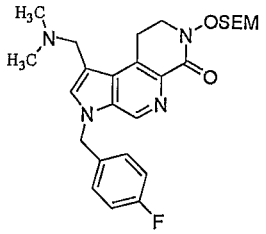


To methyl 4-(2-((2-(trimethylsilyl)ethoxy)methoxyimino)ethyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate(2.59 g, 7.13 mmol) in glacial acetic acid (25 mL) was added sodium cyanoborohydride (0.896 g, 14.26 mmol, 2 eq.) in 2 portions and the resulting reaction mixture was stirred at room temperature for 2 h. The acetic acid was removed and residue was dissolved in EtOAc and extracted with $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were dried and concentrated. The crude residue was treated with 1.0 L of 95:5 ether/DCM and 0.8 L of saturated aqueous $NaHCO_3$. The mixture was placed in a 2 L separatory funnel, shaken, and the organic phase was separated, the aq. phase was extracted with an additional 0.5L of DCM and the combined organic phases were dried (Na_2SO_4), filtered and the residue was dried in vacuo. The crude product was further purified by chromatography (100% EtOAc then 20% MeOH/DCM as eluant) to provide the title compound as a solid (0.95 g, 76% yield, two steps).

Example AO: 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methoxypiperidin-1-yl)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one

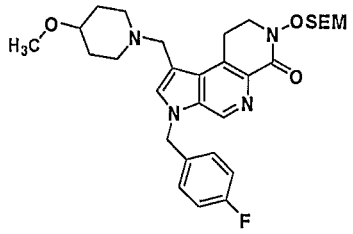


Step 1: 3-(4-fluorobenzyl)-1-((dimethylamino)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(*7H*)



A solution of 3-(4-fluorobenzyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (prepared in a manner similar that found in Example R; 15.4 g, 34.9 mmol) and N, N-dimethyleneiminium chloride (9.80 g, 105 mmol) in acetonitrile (100 mL) was heated to reflux temperature for 3 h. The resulting mixture was then concentrated under reduced pressure, treated with saturated aqueous sodium bicarbonate solution (400 mL), extracted with dichloromethane (3 X 400 mL), dried over sodium sulfate, concentrated and dried in vacuum to provide the title compound as a crude product (15.6 g) that was used without further purification. LCMS (APCI, $M+H^+$): 499.4

Step 2: 3-(4-fluorobenzyl)-1-((4-methoxypiperidin-1-yl)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one

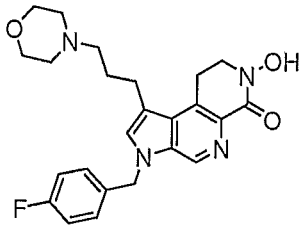


To a stirring solution of 3-(4-fluorobenzyl)-1-((dimethylamino)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(*7H*) (15.6 g, 31.3 mmol) in dichloromethane (80 mL) was added benzyl chloroformate (4.84 mL, 34.4 mmol) at 23 °C. After one half hour, 4-methyoxylpiperidine (5.0 g, 43 mmol) and diisopropylethylamine (15 mL, 86 mmol) were added and the resulting mixture was stirred for 1 h at 23 °C. The mixture was then treated with sodium bicarbonate aqueous solution (400 mL), extracted with dichloromethane (2 x 400 mL), dried over sodium sulfate, concentrated under reduced pressure, and purified by chromatography (MeOH in dichloromethane (0%-10%)) to provide 11.3 g of a yellow solid. The title compound was then isolated by dissolving the yellow solid in a mixture of dichloromethane and diethyl ether followed by the addition of hexanes to afford a white powder (5.8 g, 63%). LCMS (APCI, $M+H^+$): 569.4. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.03 (s, 9 H), 0.93 (t, J = 8.5 Hz, 2 H), 1.39 (m, 2 H), 1.77 (m, 2 H), 2.09 (m, 2H), 2.64 (m, 2H), 3.21 (m, 4 H), 3.55 (s, 2 H), 3.68 (t, J = 6.6 Hz, 2 H), 3.84 (m, 4 H), 5.00 (s, 2H), 5.52 (s, 2H), 7.16 (t, J = 7.0 Hz, 2H), 7.30 (m, 2 H), 7.69 (s, 1 H), 8.83 (s, 1H).

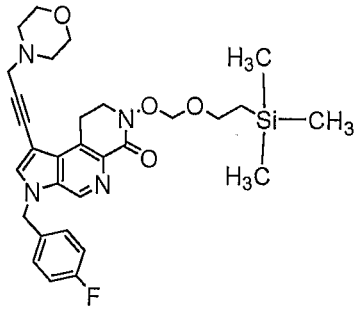
Step 3: 3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methoxypiperidin-1-yl)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one

To a solution of 3-(4-fluorobenzyl)-1-((4-methoxypiperidin-1-yl)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (5.8 g, 10.0 mmol) in MeOH (20 mL) was added hydrogen chloride solution (4M in dioxane, 15 mL, 60 mmol) at 23 °C . The resulting mixture was allowed to stir at 23 °C for about 16 h. The mixture was then concentrated under reduced pressure, treated with saturated aqueous sodium bicarbonate solution (200 mL), and extracted with DCM (2 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The title compound was then recrystallized using a mixture of MeOH, dichloromethane, and EtOAc. The resulting crystals were filtered and dried in vacuo to provide the title compound (3.66 g, 82%). LCMS (APCI, $M+H^+$): 439.2. ^{1}H NMR (300 MHz, DMSO- d_6) δ 1.23 - 1.45 (m, 2 H), 1.70 - 1.87 (m, 2 H), 2.02 - 2.19 (m, 2 H), 2.60 - 2.75 (m, 2 H), 3.10 - 3.25 (m, 4 H), 3.55 (s, 2 H), 3.65 (t, 2 H), 3.77 (t, 2 H), 5.51 (s, 2 H), 7.08 - 7.23 (m, 2 H), 7.25 - 7.37 (m, 2 H), 7.68 (s, 1 H), 8.79 (s, 1 H), 9.68 (s, 1H).

Example AP: 3-(4-fluorobenzyl)-7-hydroxy-1-(3-morpholin-4-ylpropyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one

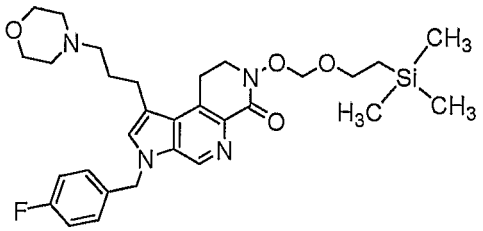


Step 1: 3-(4-fluorobenzyl)-1-(3-morpholin-4-ylprop-1-yn-1-yl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one



To anhydrous DMF (100 mL, sparged 5 minutes with nitrogen) was added, in order, 3-(4-fluorobenzyl)-1-iodo-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one (9.97 g, 17.6 mmol), 4-prop-2-yn-1-ylmorpholine (2.20 g, 17.6 mmol, 1 eq.), triethyl amine (9.8 mL, 70.3 mmol, 4 eq.), $PdCl_2(PPh_3)_2$ (617 mg, 0.879 mmol, 0.05 eq.) and CuI-SMe2 (335 mg, 1.76 mmol, 0.1 eq.). After stirring for about 24 hours at room temperature the DMF removed *in vacuo* (ca. 2 torr). The resulting dark oil was dissolve in ethyl acetate (200 mL) and was washed with water (2 X 150 mL) and brine (150 mL). The resulting ethyl acetate solution was stirred with Si-Thiol functionalized Silica gel (30 g) for about 10 hours and was then dried over sodium sulfate, filtered, and concentrated to give the crude product as a light yellow oil (10.7g). The crude material was purified by chromatography on a column of silica gel (750 g, 230-400 mesh, packed with CH_2Cl_2, eluted with CH_2Cl_2-MeOH 98:2 to 97:3 v/v, 4.0 L, 4.0 L, 200 mL fractions) using the flash technique. Fractions were combined to afford 7.708 g (78%) of 3-(4-fluorobenzyl)-1-(3-morpholin-4-ylprop-1-yn-1-yl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one as a light yellow solid. ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.05 (s, 8H), 1.02 (s, 2H), 2.58 (s, 1H), 2.64 (s, 4H), 3.54 (s, 2H), 3.77 (s, 7H) 3.88 (s, 2H), 3.99 (s, 2H), 5.15 (s, 2H), 5.36 (s, 2H), 7.04 (s, 2H), 7.14 (s, 2H), 7.43 (s, 1H), 8.77 (s, 1H).

Step 2: 3-(4-fluorobenzyl)-1-(3-morpholin-4-ylpropyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one



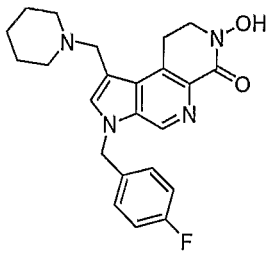
A solution of 3-(4-fluorobenzyl)-1-(3-morpholin-4-ylprop-1-yn-1-yl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one (7.708 g, 13.65 mmol) in methanol (200 mL) was sparged with nitrogen for 5 minutes, then 5% $Pd(OH)_2$ on carbon (0.908 g) was added and the mixture was placed under a balloon of hydrogen and allowed to stir for about 16 hours. The resulting mixture was then sparged with nitrogen for 5 minutes to remove hydrogen, filtered through a pad of celite, and the filter cake rinsed with methanol (200 mL). The combined filtrates were concentrated *in vacuo* to afford the crude product as a foam. The crude product was purified by chromatography on a column of silica gel (750 g, 230-400 mesh, packed with CH_2Cl_2, eluted with CH_2Cl_2-MeOH 97:3 to 90:10 v/v, 4.0 L, 9.0 L, 200 mL fractions) using the flash technique. Fractions were combined to afford 4.68 g (60%) of the title compound as a foam. ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.05 (s, 9H), 0.98-1.06 (m, 2H), 1.80 - 1.91 (m, 2H), 2.37-2.47 (m, 6H), 2.84-2.93 (m, 2H), 3.60 (t, *J*=6.69 Hz, 2H), 3.68-3.75 (m, 4H), 3.84-3.94 (m, 2H), 3.98 (t, *J*=6.78 Hz, 2H), 5.16 (s, 2H), 5.33 (s, 2H), 6.97 - 7.13 (m, 5H), 8.75 (s,1H).

Step 3: 3-(4-fluorobenzyl)-7-hydroxy-1-(3-morpholin-4-ylpropyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one

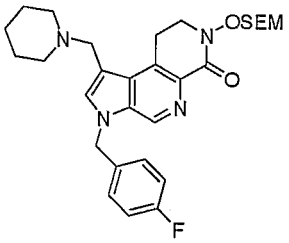
To a solution of 3-(4-fluorobenzyl)-1-(3-morpholin-4-ylpropyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one (4.68 g 8.23 mmol) in methanol (100 mL) under nitrogen was added 4M HCl in dioxane (20.6 mL, 82.3 mmol, 10 eq.). After stirring for about 48 hours at room temperature, the methanol was removed under vacuum and the resulting solid was azeotroped with ethanol (2 x 80 mL) to remove residual methanol. The resulting solid was then dissolved in hot ethanol (150 mL), the solution was allowed to cool to room temperature, resulting in the formation of a white solid appeared, after which time the mixture was cooled to ca. 4 °C for about 3 hours. The resulting solid was collected by filtration, washed with cold ethanol, and dried *in vacuo* to give the title product as a bis-HCl salt 3.596g (85%). The salt was neutralized with sodium bicarbonate solution and the free base extracted into dichloromethane (4 x 80 mL). The combined organic phases were washed with water (80 mL) and brine (80 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the title compound as a solid. The solid was azeotroped with tetrahydrofuran (2 x 80 mL) and diethyl ether (2 x 80 mL) to give afford a foam. The foam was stirred in diethyl ether (100 mL), filtered, washed with diethyl ether (500 mL), and dried under vacuum at 75 °C to afford the title compound as a powder (2.65 g, 72%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.86 (m, 2H), 2.38 - 2.52 (m, 6H), 2.88 (t, *J*=7.63 Hz, 2H),

3.60 (t,*J*=6.97 Hz, 2H), 3.72 (m, 4H), 3.99 (t, *J*=6.97 Hz, 2H), 5.34 (s, 2H), 6.97 - 7.13 (m, 5H), 8.72 (s, 1H).

Example AQ: 3-(4-fluorobenzyl)-7-hydroxy-1-(piperidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one



Step 1: Preparation of 3-(4-fluorobenzyl)-1-(piperidin-1-ylmethyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one.



To a stirring solution of 3-(4-fluorobenzyl)-1-((dimethylamino)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7*H*) (11.27 g, 22.60 mmol) in dichloromethane (80 mL) was added benzyl chloroformate (3.41 mL, 27.1 mmol) at 23 °C. After 30 minutes, piperidine (4.47 mL, 45.2 mmol) and diisopropylethylamine (20 mL, 110 mmol) were added and the resulting mixture was allowed to stir for for an additional 1 h at 23 °C. The resulting mixture was then treated with sodium bicarbonate aqueous solution (400 mL), extracted with dichloromethane (400 mLx2), dried over sodium sulfate, concentrated, and purified by column chromatograph using MeOH in in dichloromethane (0%-10%) as eluant to provide 5.8 g of a solid. The solid was dissolved in a mixture of dichloromethane/ethyl ether. The title compound was isolated by adding hexanes to the solution, followed by filtration and drying under vacuum to provide a white powder (4.0 g, 33%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.02 (s, 9 H), 0.82-1.02 (m, 2 H), 1.30-1.56 (m, 6 H), 2.22-2.43 (m, 4H), 3.52 (s, 2 H), 3.69 (t, *J* = 6.69 Hz, 2 H), 3.78-3.92 (m, 4 H), 5.00 (s, 2H), 5.52 (s, 2H), 7.09-7.22 (m, 2H), 7.26-7.37 (m, 2 H), 7.69 (s, 1 H), 8.83 (s, 1H).

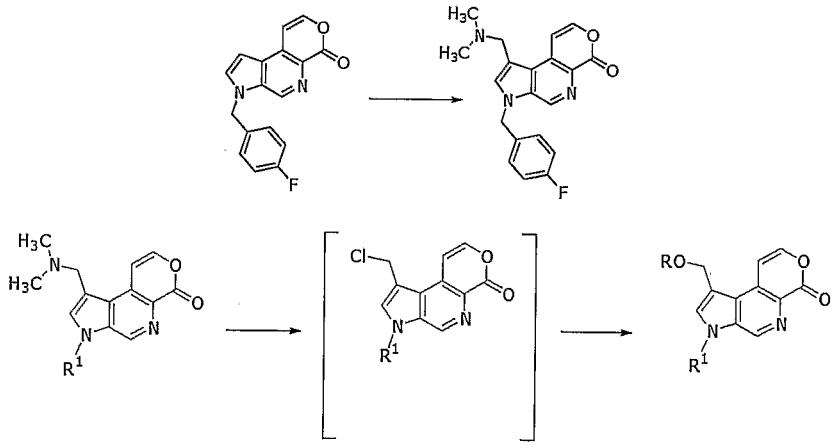
Step 2: Preparation of 3-(4-fluorobenzyl)-7-hydroxy-1-(piperidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one

To a stirring solution of 3-(4-fluorobenzyl)-1-(piperidin-1-ylmethyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (4.0 g, 7.4 mmol) in MeOH (20 mL) was added hydrogen chloride solution (4M in dioxane, 10 mL, 40 mmol) at 23 °C . The resulting mixture was allowed to stir at 23°C for 16 h, after which time it was concentrated under reduced pressure, treated with saturated aqueous sodium

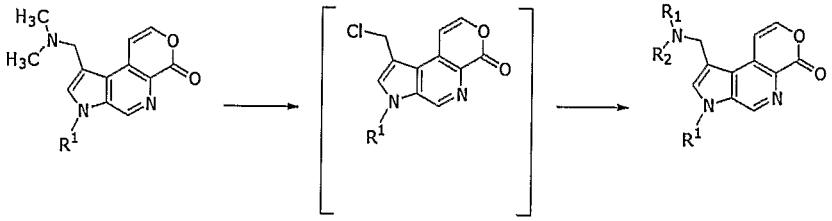
bicarbonate solution (200 mL), and extracted with DCM (200 mL x 2). The organic layers were combined, dried over sodium sulfate, filtered and concentrated. The title compound was obtained by concentration from a MeOH/dichloromethane/EtOAc mixture. It was filtered and dried in vacuum to provide a white solid (2.43 g, 80%). ^{1}H NMR (300 MHz, DMSO- d_6) δ 1.16-1.59 (m, 6 H), 2.22-2.24 (m, 4 H), 3.51 (s, 2 H), 3.66 (t, J = 6.31 Hz, 2 H), 3.76 (t, J = 6.31 Hz, 2 H), 5.50 (s, 2 H), 7.09 - 7.24 (m, 2 H), 7.26 - 7.41 (m, 2 H), 7.67 (s, 1 H), 8.79 (s, 1 H), 9.70 (s, 1H).

General Experimentals

Step 1: Preparation of 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%). ^{1}H NMR (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.

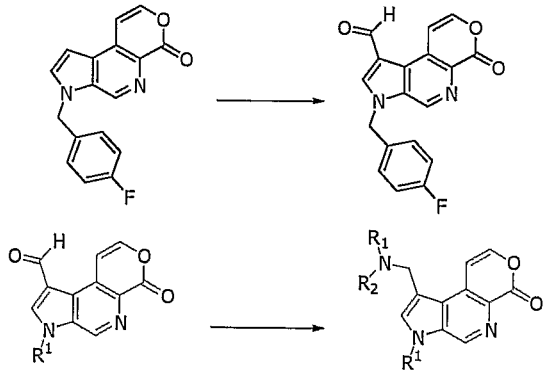


General Procedure A1: To a solution of the appropriate N,N-dimethylaminomethyl tricycle (1.0 eq, 0.197 M in dichloromethane) was added ethyl chloroformate (1.0 eq). The mixture was stirred for 1 h and then the appropriate alcohol (4.0 eq, 1 mM in anhydrous DMF) was added followed by diisopropyl ethylamine (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.

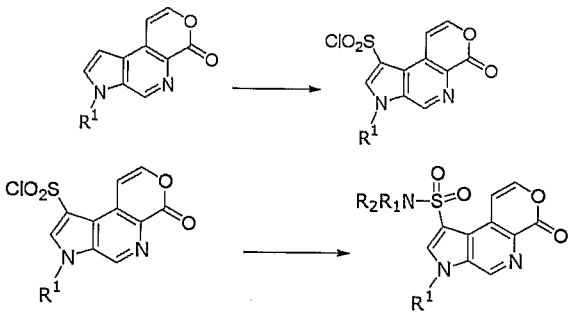
Step 2: Preparation of 7-(4-fluorobenzyl)-4-oxo-4,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridine-9-carbaldehyde. To a solution of enol lactone (2.0 g, 6.803 mmol) in DMF (20 mL) was added Eschenmoser's salt (2.5 g, 13.605 mmol) and the mixture was heated in a microwave at 130 °C for 2 h. More Eschenmoser's 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%). ^{1}H NMR (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

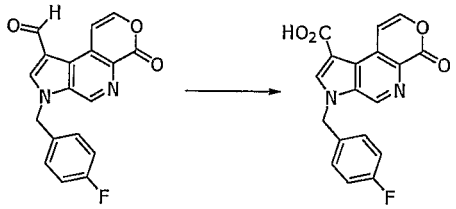
vacuum. The remaining residue was dissolved in DMSO and purified by reverse phase prep HPLC (acetonitrile:water, 0.1% acetic acid) to provide the desired compounds.

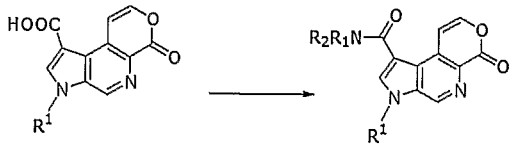
Step 3: Preparation of 7-(4-fluorobenzyl)-4-oxo-4,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridine-9-sulfonyl chloride. To a solution of the 7-(4-fluorobenzyl)pyrano[3,4-b]pyrrolo[3,2-d]pyridin-4(7H)-one(1.0 eq) in chlorosulfonic acid (60 eq, 0.55 M) was added thionyl chloride(30 eq). The mixture was 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. ^{1}HNMR (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: Preparation of 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%). ^{1}HNMR (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.



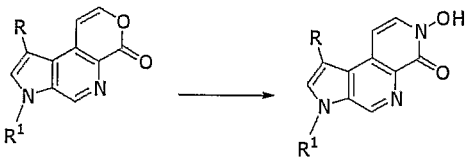


General Procedure A6: To a solution of the appropriate carboxylic acid (1.0 eq, 0.07 M in DMF) and 4-methylmorpholine (NMM, 3.2 eq) was added 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, 1.2 eq). The mixture was stirred at room temperature for 1h and the appropriate amine (2.0 eq) was added. The resulting 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 A7:

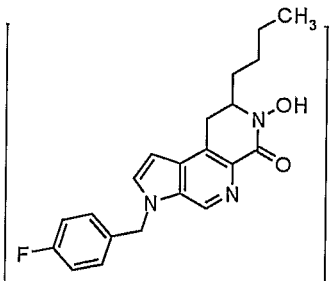
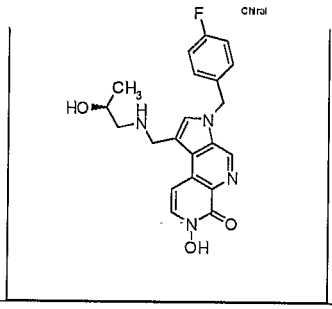
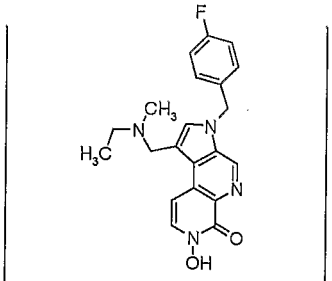
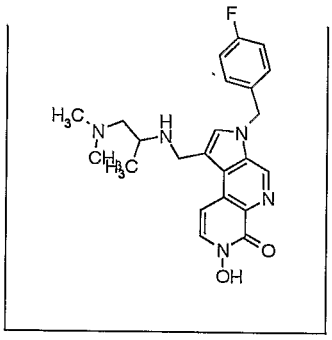


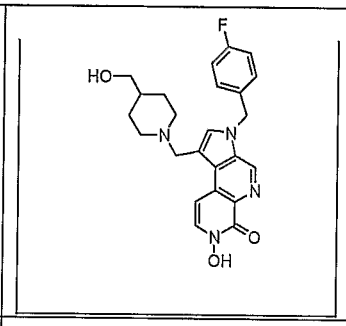
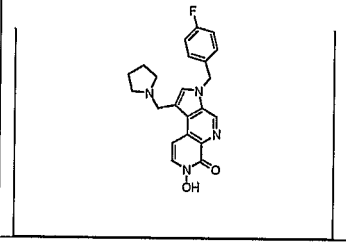
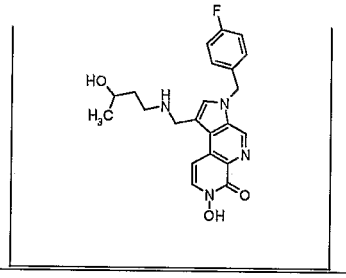
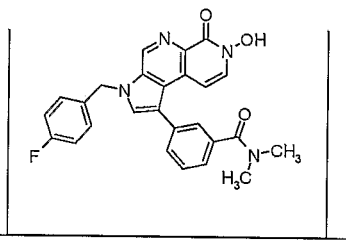
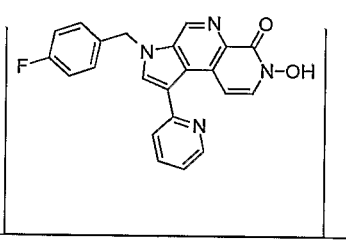
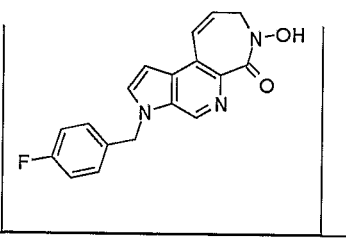
To a solution of the appropriate aldehyde in dichloromethane is added an appropriate primary or secondary amine (2 eq.) and glacial acetic acid (4 to 5 eq/eq. of aldehyde). The resulting mixture is allowed to stir at ambient temperature for about 1 hour. To the mixture is then added triacetoxyborohydride (about 4 eq/eq of aldehyde) and the resulting mixture is allowed to stir for an additional 1 to 24 hours. The resulting mixture is then diluted with dichloromethane, the organic layer is washed with saturated sodium bicarbonate solution (10 mL x 3), brine, and then dried with sodium sulfate, filtered, and concentrated *in vacuo* to give crude product.

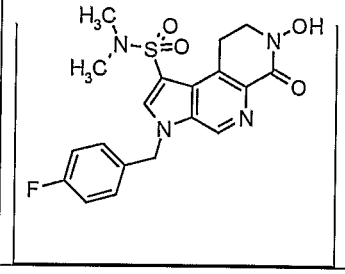
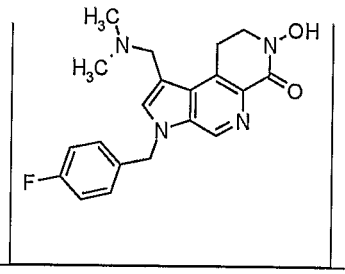
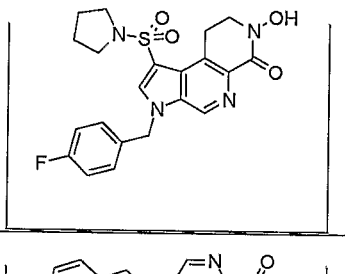
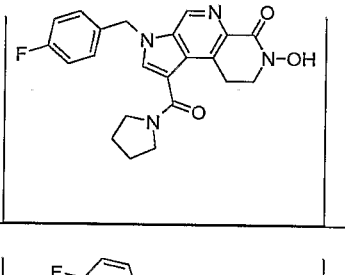
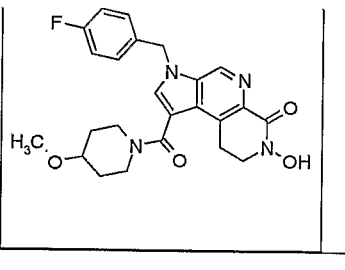
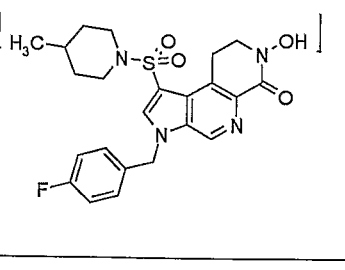


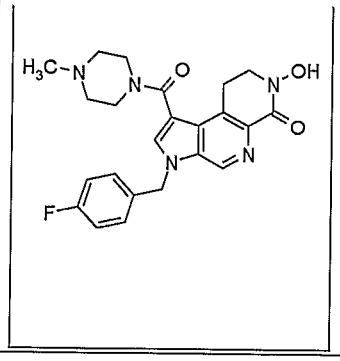
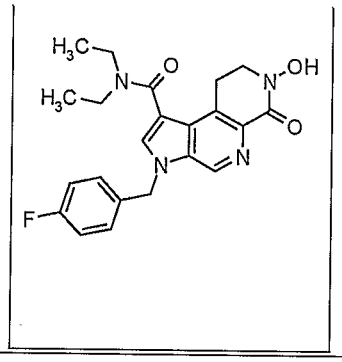
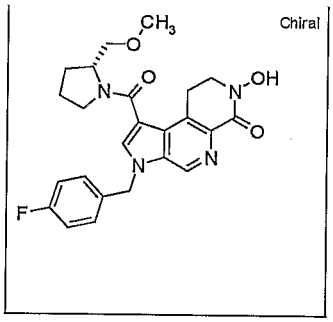
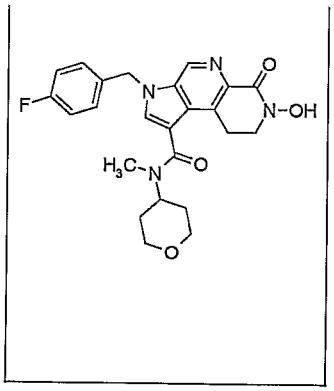
General Procedure B1: A solution of the enol lactone (1.0 eq) in ethanol (27 mL/mmol enol lactone) and hydroxylamine (50w% in water, 0.68 mL/ mmol enol lactone) was refluxed for 3 h or until the LC/MS showed complete conversion to the desired N-hydroxypyridone. The resulting solution was concentrated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

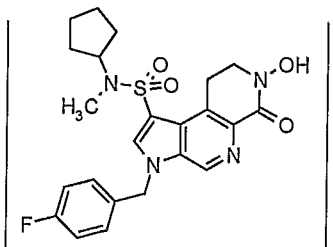
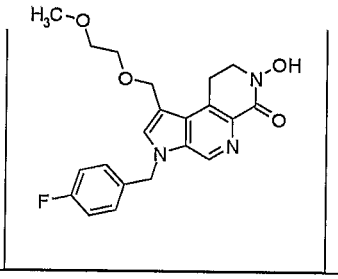
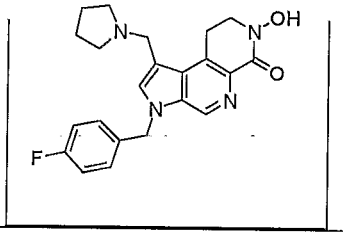
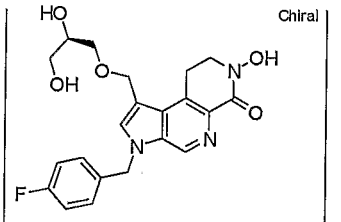
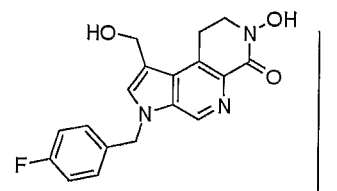
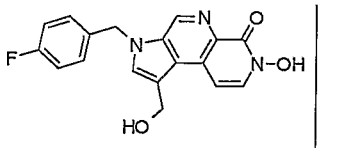
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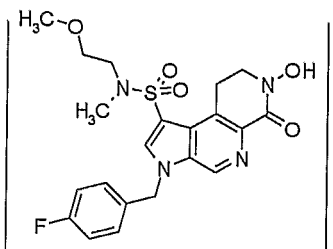
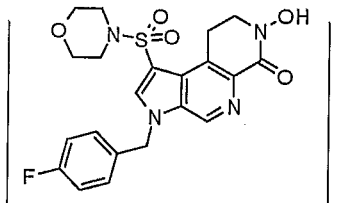
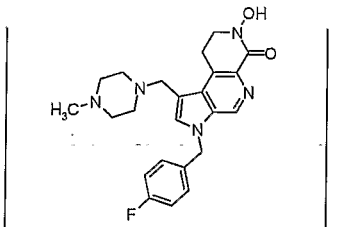
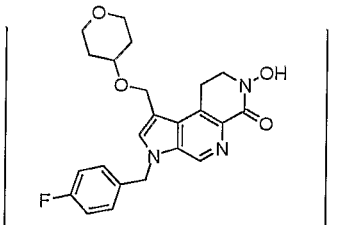
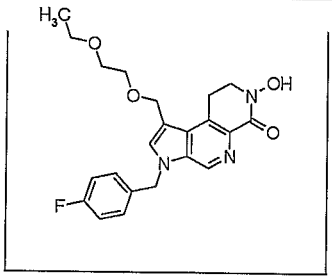
Example No.	STRUCTURE	NAME	^{1}H NMR
1		8-butyl-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (MeOD) δ: 8.69 (s, 1H), 7.70 (d, 1H, J = 3.0 Hz), 7.7.25-7.28 (m, 2H), 7.05 (d, 2H, J = 8.7 Hz), 6.85 (d, 1H, J = 3.0 Hz), 5.55 (s, 2H), 4.30 (m, 1H), 3.38-3.44 (m, 1H), 3.13-3.15 (m, 1H), 1.36-1.52 (m, 6H), 0.92 (t, 3H, J = 7.0 Hz)
2		3-(4-fluorobenzyl)-7-hydroxy-1-({[(2S)-2-hydroxypropyl]amino}methyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 9.02 (s, 1 H), 7.76 (m, 2 H), 7.33 (m, 2 H), 7.15 (m, 3 H), 5.60 (s, 2 H), 4.00 (s, 2 H), 3.73 (m, 1 H), 2.55 (m, 2 H), 1.02 (d, 3 H)
3		1-{[ethyl(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (CD_3OD, 400 MHz) d 8.83 (1H, s), 7.65 (2H, m), 7.33 (1H, d), 7.20 (2H, m), 6.99 (2H, t), 5.54 (2H, s), 3.98 (2H, s), 2.72 (2H, q), 2.33 (3H, s), 1.15 (3H, t)
4		1-({[2-(dimethylamino)-1-methylethyl]amino}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 9.04 (s, 1 H), 7.80 (t, 2 H), 7.34 (m, 2 H), 7.16 (m, 3 H), 5.61 (s, 2 H), 3.99 (m, 2 H), 2.42 (d, 2 H), 2.08 (s, 6 H), 1.05 (d, 3 H)

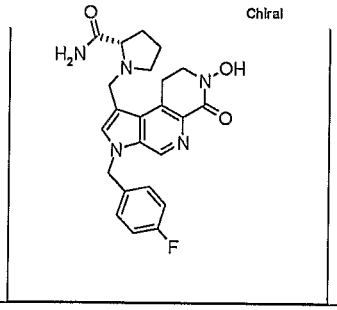
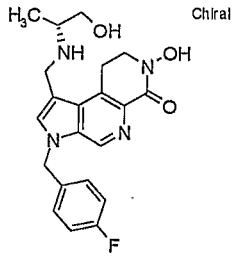
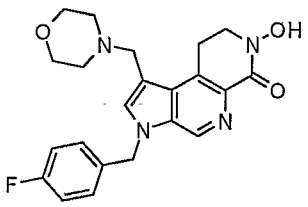
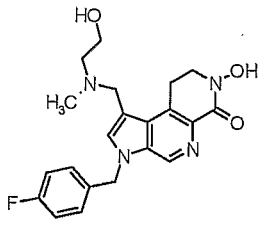
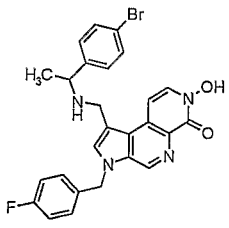
5		3-(4-fluorobenzyl)-7-hydroxy-1-{[4-(hydroxymethyl)piperidin-1-yl]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (DMSO-D6, 400 MHz) d 9.01 (1H, s), 7.79 (2H, m), 7.33 (2H, m), 7.27 (1H, d), 7.14 (2H, t), 5.61 (2H, s), 4.38 (1H, t), 3.67 (2H, s), 3.22 (2H, t), 2.89 (2H, m), 1.97 (2H, t) 1.61 (2H, m), 1.35 (1H, b), 1.09 (2H, m)
6		3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (CD_3OD, 400 MHz) d 8.77 (1H, s), 7.66 (2H, m), 7.20 (3H, m), 7.00 (2H, t), 5.54 (2H, s), 4.15 (2H, s), 3.28 (2H, m), 3.10 (2H, m), 2.83 (4H, b)
7		3-(4-fluorobenzyl)-7-hydroxy-1-{[(3-hydroxybutyl)amino]methyl}-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (DMSO-D6, 300 MHz) d 9.03 (1H, s), 7.80 (1H, d), 7.75 (1H, s), 7.35 (2H, m), 7.14-7.19 (3H, m), 5.61 (2H, s), 3.98 (2H, s), 3.67-3.93 (1H, m), 2.70 (2H, t), 1.47-1.54 (2H, m), 1.02 (3H, d)
8		3-[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7-dihydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]-N,N-dimethylbenzamide	1HNMR (CD3OD, 400 MHz) d 9.00 (1H, s), 7.77 (1H, s), 7.49 (4H, m), 7.37 (1H, m), 7.34 (2H, m), 7.08 (2H, t), 6.72 (1H, m), 5.67 (2H, s), 3.11 (3H, s), 3.06 (3H, s)
9		3-(4-fluorobenzyl)-7-hydroxy-1-pyridin-2-yl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1HNMR (CD3OD, 400 MHz) d 9.00 (1H, s), 8.69 (1H, s), 7.90 (2H, m), 7.73 (1H, m), 7.63 (1H, m), 7.42 (1H, m), 7.35 (2H, m), 7.20 (1H, m), 7.09 (2H, m), 5.71 (2H, s)
10		3-(4-fluorobenzyl)-7-hydroxy-7,8-dihydropyrrolo[3',2':4,5]pyrido[2,3-c]azepin-6(3H)-one	1H NMR (300 MHz, MeOH) d ppm 8.77 (s, 1 H) 7.72 (s, 1 H) 7.22 – 7.34 (m, 3 H) 6.97 - 7.11 (m, 2 H) 6.83 (d, 1 H) 6.67 (m, 1 H) 5.56 (s, 2 H) 4.11 (d, 2 H)

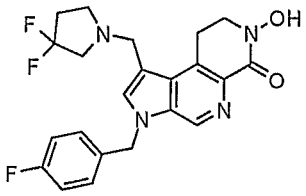
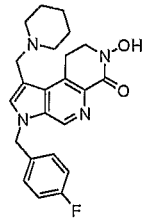
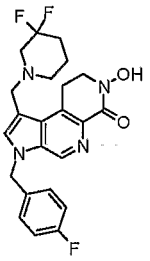
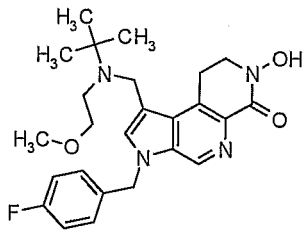
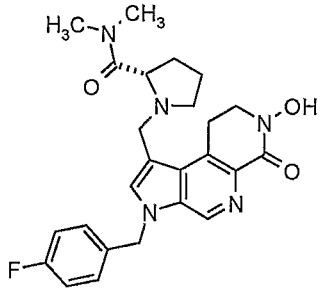
11		3-(4-fluorobenzyl)-7-hydroxy-N,N-dimethyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide	1HNMR (DMSO-D6, 300 MHz) d 9.01 (1H, s), 8.63 (1H, s), 7.47 (2H, dd), 7.21 (2H, t), 5.69 (2H, s), 3.82 (2H, t), 3.63 (2H, t), 2.75 (6H, s)
12		1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 8.97 (s, 1 H), 7.69 (s, 1 H), 7.29 (m, 2 H), 7.15 (t, 2 H), 5.51 (s, 2 H), 3.76 (t, 2 H), 3.62 (t, 2 H), 3.46 (s, 2 H), 2.15 (s, 6 H)
13		3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylsulfonyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1HNMR (DMSO-D6, 300 MHz) d 9.24 (1H, s), 8.84 (1H, s), 7.47 (4H, m), 7.24 (2H, t), 7.10 (2H, d), 5.78 (2H, s), 3.98 (2H, m), 3.75 (2H, m), 3.23 (4H, dd), 1.83 (4H, dd)
14		3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylcarbonyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1HNMR (CDCl3, 400 MHz) d 8.81 (1H, s), 7.43 (1H, s), 7.06 (2H, m), 7.03 (2H, m), 5.40 (2H, s), 3.97 (2H, m), 3.65 (2H, m), 3.56 (2H, m), 3.42 (2H, m), 1.95 (4H, m)
15		3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methoxypiperidin-1-yl)carbonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1HNMR (CDCl3, 400 MHz) d 8.90 (1H, s), 7.34 (1H, s), 7.16 (2H, m), 6.97 (2H, m), 5.40 (2H, s), 3.90 (4H, b), 3.47 (2H, m), 3.40 (2H, m), 3.34 (3H, s), 1.96 (1H, m), 1.81 (2H, m), 1.58 (2H, m)
16		3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperidin-1-yl)sulfonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1HNMR (DMSO-D6, 300 MHz) d 9.32 (1H, s), 8.90 (1H, s), 7.44 (5H, m), 7.25 (2H, t), 7.12 (2H, d), 5.79 (2H, d), 3.96 (2H, m), 2.62 (2H, m), 2.30 (4H, s), 1.40 (2H, d), 1.47 (1H, m), 1.16 (2H, m), 0.92 (3H, d)

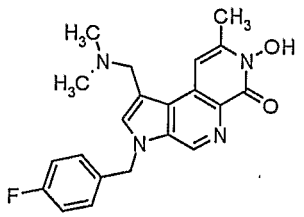
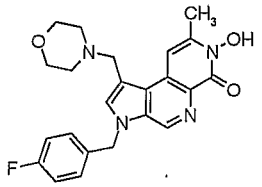
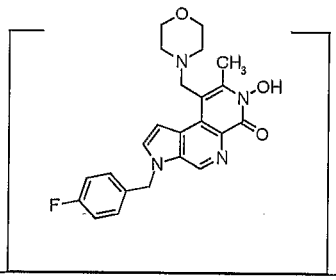
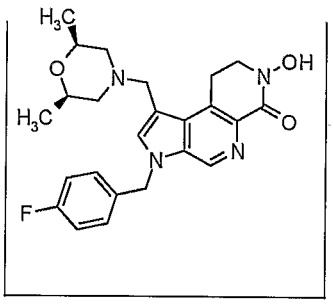
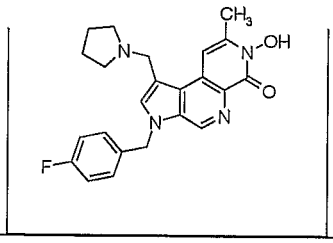
17		3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)carbonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (DMSO-D6, 300 MHz) d 10.36 (2H, s)(tosylate), 9.74 (1H, s), 9.27 (1H, s), 8.85 (1H, s), 7.47 (4H, d, J=8.10Hz)(tosylate), 7.41 (2H, dd), 7.21 (2H, t), 7.10 (4H, d, J=7.91Hz)(tosylate), 5.74 (2H, s), 4.06-4.46 (2H, m), 3.89 (2H, t), 3.24-3.60 (6H, m)
18		N,N-diethyl-3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide	^{1}HNMR (DMSO-D6, 300 MHz) d 9.96 (1H, s), 9.05 (1H, s), 8.19 (1H, s), 7.47 (0.72H, d, J=8.29Hz)(tosylate), 7.39 (2H, dd), 7.19 (2H, t), 7.11 (0.72H, d, J=7.91Hz)(tosylate), 5.64 (2H, s), 3.81 (2H, t), 3.25-3.51 (6H, m), 2.28 (1.1H, s)(tosylate), 1.10 (6H,
19		3-(4-fluorobenzyl)-7-hydroxy-1-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (DMSO-D6, 300 MHz) d 10.06 (1H, s), 9.09 (1H, s), 8.39 (1H, s), 7.47 (1.0H, d, J=8.10Hz)(tosylate), 7.40 (2H, dd), 7.19 (2H, dd), 7.10 (1.0H, d, J=8.29Hz)(tosylate), 5.66 (2H, s), 3.83 (2H, t), 3.20-3.63 (10H, m), 2.28 (1.5H, s)(tosylate), 1.72-2.08
20		3-(4-fluorobenzyl)-7-hydroxy-N-methyl-6-oxo-N-(tetrahydro-2H-pyran-4-yl)-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carboxamide	1HNMR (CD3OD, 400 MHz) d 8.86 (1H, s), 8.03 (1H, s), 7.62 (0.8H, d, 0.4eq tosylate salt), 7.15 (0.8H, d, 0.4eq tosylate salt), 7.27 (2H, m), 7.03 (2H, m), 5.58 (2H, s), 3.88 (2H, t), 3.32 (4H, m), 3.18 (2H, m), 2.95 (3H, s), 2.30 (1.2H, S, 0.4eq tosylate salt), 1.92 (3H, m), 1.63 (2H, m)

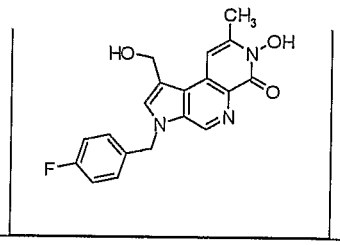
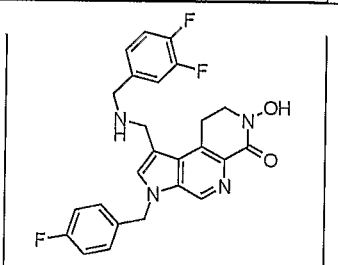
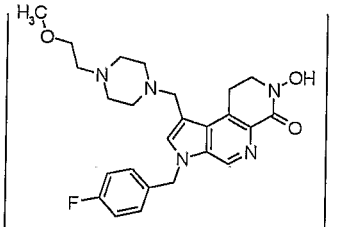
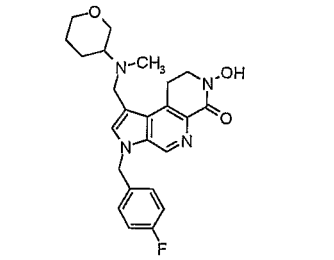
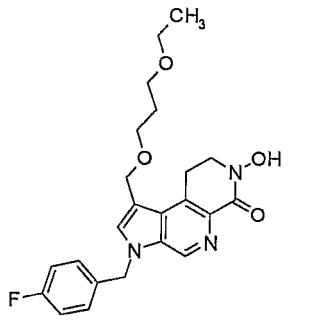
21		N-cyclopentyl-3-(4-fluorobenzyl)-7-hydroxy-N-methyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide	1HNMR (DMSO-D6, 300 MHz) d 10.1 (1H, s), 8.94 (1H, s), 8.53 (1H, s), 7.48 (dd, 2H), 5.67 (s, 2H), 4.35 (dd, 2H), 3.4 (dd, 2H), 2.75 (s, 4H), 1.5 (m, 10H)
22		3-(4-fluorobenzyl)-7-hydroxy-1-[(2-methoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (DMSO-D6, 400 MHz) d 10.17 (1H,s), 9.12 (1H, s), 8.16 (1H, s), 7.40 (2H, m), 7.22 (2H, t), 5.67 (2H, s), 4.72 (2H,s), 3.92 (2H, m), 3.65 (4H, m), 3.51(2H, m), 3.26 (3H, s)
23		3-(4-fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 8.60 (s, 1 H), 8.04 (s, 1 H), 7.19 - 7.30 (dd, 2 H), 7.00 (t, 2 H), 5.55 (s, 2 H), 4.67 (s, 2 H), 3.81 (s, 2 H), 3.44 (m, 6 H), 2.12 (m, 4 H)
24		1-({[(2S)-2,3-dihydroxypropyl]oxy}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (DMSO-D6, 400 MHz) d 9.16 (1H, s), 8.28 (1H, s), 7.36 (2H, m), 7.11 (2H, t), 5.69 (2H, s), 4.90 (2H, s), 4.06 (2H, m), 3.87 (2H, m), 3.78 (1H, m), 3.63 (1H, m), 3.54 (2H, m), 2.64 (1H, s).
25		3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 8.69 (s, 1 H), 7.65 (s, 1 H), 7.22 - 7.31 (m, 2 H), 7.04 (t, 2 H), 5.50 (s, 2 H), 4.60 (s, 2 H), 3.95 (t, 2 H), 3.70 (t, 2 H),
26		3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	^{1}HNMR (DMSO-D6, 400 MHz) d 11.50 (1H, b), 9.06 (1H, s), 7.81 (2H,t), 7.36 (2H, t), 7.17 (2H, t), 7.07 (1H, d), 5.61 (2H, s), 5.20 (1H, b), 4.79 (2H, s)

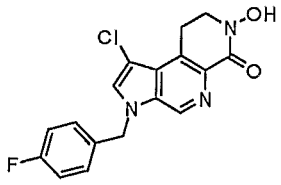
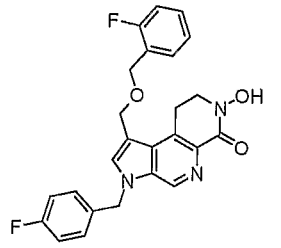
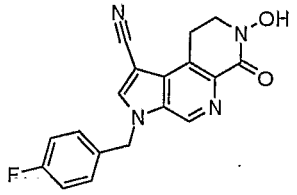
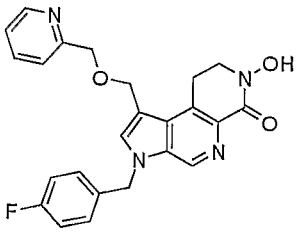
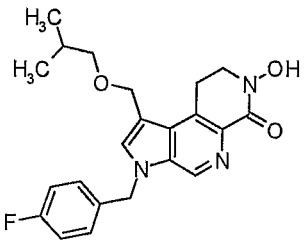
27		3-(4-fluorobenzyl)-7-hydroxy-N-(2-methoxyethyl)-N-methyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridine-1-sulfonamide	1HNMR (CDCl3-D6, 300 MHz) d 9.64 (1H, bs), 8.16 (1H, s), 7.50 (1H, d), 7.26 (2H, t), 6.94 (2H, t), 5.65 (2H, s), 3.94 (2H, bt), 3.69 (2H, bt), 3.47 (2H, bt), 3.36 (2H, bt), 3.19 (3H, s), 2.86 (3H, s)
28		3-(4-fluorobenzyl)-7-hydroxy-1-(morpholinosulfonyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	1HNMR (CDCl3-D6, 300 MHz) d 9.29 (1H, bs), 8.0 (1H, s), 7.26 (3H, bs), 7.04 (2H, bt), 5.51 (2H, bs), 4.11 (8H, bm), 3.68 (4H, bm)
29		3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methylpiperazin-1-yl)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (DMSO-D6, 300 MHz) d 9.68 (1H, s), 8.79 (1H, s), 7.70 (1H, s), 7.31 (2H, m), 7.16 (2H, m), 5.51 (2H, s), 3.76 (2H, t), 3.64 (2H), 3.56 (2H, s), 2.27-2.35 (8H, m), 2.13 (3H, s)
30		3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-yloxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (DMSO-D6, 400 MHz) d 9.91 (1H, s), 8.96 (1H, s), 7.95 (1H, s), 7.33 (2H, m), 7.14 (2H, m), 5.57 (2H, s), 4.70 (2H, s), 3.81 (4H, m), 3.57 (3H, m), 1.87 (2H, m), 1.42 (2H, m).
31		1-[(2-ethoxyethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (DMSO-D6, 400 MHz) d 8.82 (1H, s), 7.93 (1H, s), 7.22 (2H, m), 7.00 (2H, m), 5.52 (2H, s), 4.71 (2H, s), 3.93 (2H, m), 3.69 (2H, m), 3.60 (2H, m), 3.52 (2H, m), 3.41 (2H, q), 1.07 (3H, t).

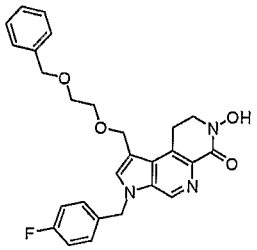
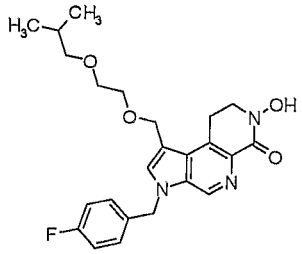
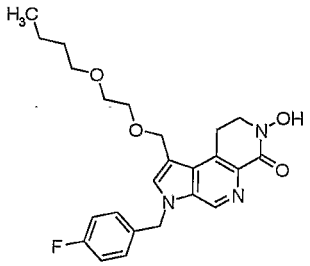
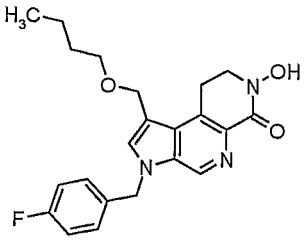
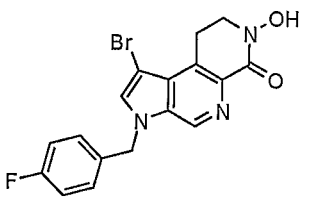
32		1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-L-prolinamide	^{1}HNMR (MeOD-D4, 300 MHz) d 8.60 (1H, s), 7.64 (1H, s), 7.20 (2H, m), 7.05 (2H, m), 5.49 (2H, s), 4.14 (1H, d), 3.95 (2H, t), 3.78-3.86 (3H, m), 3.19 (1H, m), 2.58 (1H, m), 2.25 (1H, m), 1.84-1.88 (4H, m)
33		3-(4-fluorobenzyl)-7-hydroxy-1-({[(1R)-2-hydroxy-1-methylethyl]amino}methyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD-D4, 300 MHz) d 8.72 (1H, s), 7.72 (1H, s), 7.26 (2H, m), 7.04 (2H, m), 5.52 (2H, s), 4.19 (1H, m), 3.95 (2H, t), 3.68 (3H, m), 3.49 (1H, m), 3.07(1H, m), 1.19 (3H, m)
34		3-(4-fluorobenzyl)-7-hydroxy-1-(morpholin-4-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 8.67 (s, 1 H), 7.61 (s, 1 H), 7.18 - 7.27 (m, 2 H), 7.04 (t, 2 H), 5.49 (s, 2 H), 3.93 (t, 2 H), 3.81 (t, 2 H), 3.70 (s, 2 H), 3.66 (m, 4 H), 2.49 (m, 4 H)
35		3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-hydroxyethyl)(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 8.69 (s, 1 H), 7.66 (s, 1 H), 7.14 - 7.28 (m, 2 H), 6.95 - 7.07 (m, 2 H), 5.50 (s, 2 H), 3.96 (m, 2 H), 3.91 (s, 2 H), 3.73 (m, 2 H), 3.66 (m, 2 H), 2.56 (s, 3 H), 2.43 (t, 2 H)
36		1-({[1-(4-bromophenyl)ethyl]amino}methyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 8.89 (s, 1 H), 7.80 (s, 1 H), 7.70 (d, 2 H), 7.57 (m, 3 H), 7.31 (m, 2 H), 7.06 (t, 2 H), 6.43 (d, 1 H), 5.59 (s, 2 H), 4.55 (s, 2 H), 4.36 (m, 1 H), 1.77 (d, 3 H)

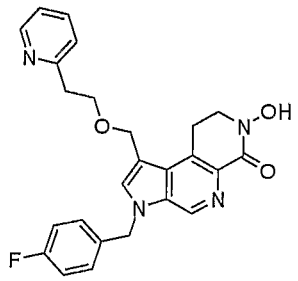
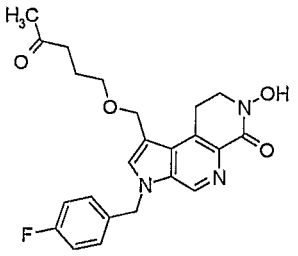
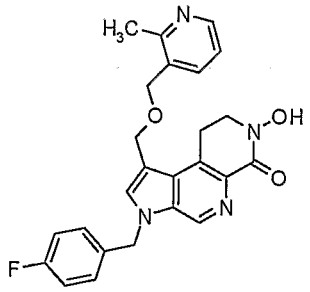
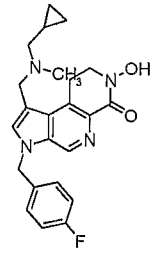
37		1-[(3,3-difluoropyrrolidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.78 (1H, s), 7.79 (1H, d), 7.27 (2H, m), 7.07 (2H, t), 5.55 (2H, s), 3.96 (2H, t), 3.86 (4H, m), 2.91 (2H, t), 2.76 (2H, t), 2.28 (2H,m)
38		3-(4-fluorobenzyl)-7-hydroxy-1-(piperidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.68 (1H, s), 7.82 (1H, d), 7.26 (2H, m), 7.05 (2H, t), 5.54 (2H, s), 4.25 (2H, s), 3.91 (2H, t), 3.65 (2H, t), 3.04 (4H, m), 1.77 (4H,m), 1.61 (2H, m)
39		1-[(3,3-difluoropiperidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.78 (1H, s), 7.74 (1H, d), 7.26 (2H, m), 7.05 (2H, t), 5.54 (2H, s), 3.90 (4H, m), 3.74 (2H, s), 2.66 (2H, m), 2.47 (2H, m), 1.89 (2H,m), 1.69 (2H, m)
40		1-{[tert-butyl(2-methoxyethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.82 (1H, s), 7.87 (1H, d), 7.31 (2H, m), 7.09 (2H, t), 5.58 (2H, s), 4.63 (2H, m), 3.98 (2H, t), 3.79 (2H, m), 2.96 (6H, m), 1.38 (9H, m)
41		1-{[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]methyl}-N,N-dimethyl-L-prolinamide	^{1}HNMR (MeOD, 300 MHz) d 8.97 (1H, s), 8.23 (1H, d), 7.36 (2H, m), 7.08 (2H, t), 5.56 (2H, s), 4.85 (1H, d), 4.73 (2H, t), 4.60 (1H, d), 4.04 (3H, m), 3.61 (2H, m), 3.40 (1H, m), 3.02 (3H, s), 2.92 (3H, s), 2.72 (1H, m), 2.26 (1H, m), 2.00 (2H, m)

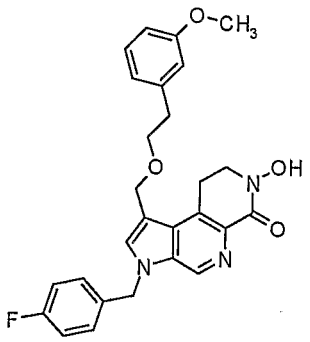
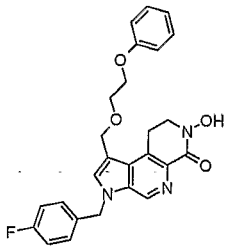
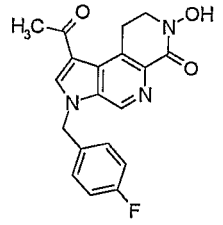
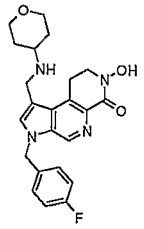
42		1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-8-methyl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 8.94 (s, 1 H) 7.73 (s, 1 H) 7.31 (m, 2 H) 7.16 (t, 2 H) 7.02 (s, 1 H) 5.59 (s, 2 H) 3.61 (s, 2 H) 2.42 (s, 3 H) 2.20 (s, 6 H)
43		3-(4-fluorobenzyl)-7-hydroxy-8-methyl-1-(morpholin-4-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOD) d ppm 8.84 (s, 1 H) 7.62 (s, 1 H) 7.46 (s, 1 H) 7.25 (m, 2 H) 7.05 (t, 2 H) 5.57 (s, 2 H) 3.81 (s, 2 H) 3.68 (m, 4 H) 2.56 (s, 7 H)
44		3-(4-fluorobenzyl)-7-hydroxy-8-methyl-9-(morpholin-4-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (400 MHz, MeOD) d ppm 8.92 (s, 1 H) 7.70 (s, 1 H) 7.28 (dd, 2 H) 7.20 (d, 1 H) 7.06 (t, 2 H) 5.63 (s, 2 H) 3.95 (s, 2 H) 3.62 (t, 4 H) 2.67 (s, 3 H) 2.60-2.65 (m, 4H)
45		1-{[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 8.67 (s, 1 H), 7.58 (s, 1 H), 7.23 (m, 2 H), 7.03 (t, 2 H), 5.49 (s, 2 H), 3.92 (m, 2 H), 3.79 (d, 2 H), 3.64 (s, 2 H), 3.61 (m, 2 H), 2.74 (d, 2 H), 1.73 (t, 2 H), 1.10 (s, 3 H), 1.08 (s, 3 H)
46		3-(4-fluorobenzyl)-7-hydroxy-8-methyl-1-(pyrrolidin-1-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 8.83 (s, 1 H), 7.76 (s, 1 H), 7.27 (m, 2 H), 7.06 (m, 3 H), 5.61 (s, 2 H), 4.38 (s, 2 H), 3.04 (m, 4 H), 2.47 (s, 3 H), 1.79 (m, 4 H)

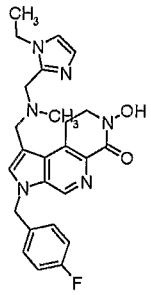
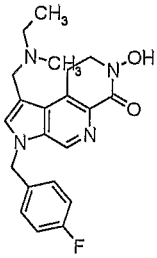
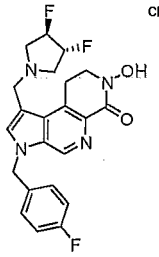
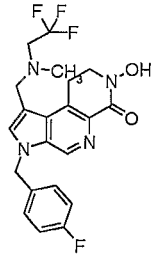
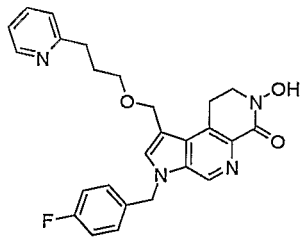
47		3-(4-fluorobenzyl)-7-hydroxy-1-(hydroxymethyl)-8-methyl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 8.87 (s, 1 H), 7.67 (s, 1 H), 7.27 (m, 2 H), 7.19 (s, 1 H), 7.05 (t, 2 H), 5.59 (s, 2 H), 4.97 (s, 2 H), 2.57 (s, 3 H)
48		1-{[(3,4-difluorobenzyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 9.13 (s, 1 H), 8.36 (s, 1 H), 7.52 (t, 1 H), 7.36 (m, 4 H), 7.10 (t, 2 H), 5.70 (s, 2 H), 4.66 (s, 2 H), 4.40 (s, 2 H), 4.03 (t, 2 H), 3.67 (t, 2 H)
49		3-(4-fluorobenzyl)-7-hydroxy-1-{[4-(2-methoxyethyl)piperazin-1-yl]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 8.67 (s, 1 H), 7.59 (s, 1 H), 7.23 (m, 2 H), 7.04 (t, 2 H), 5.49 (s, 2 H), 3.92 (t, 2 H), 3.79 (t, 2 H), 3.69 (s, 2 H), 3.54 (t, 2 H), 3.32 (t, 3 H) 3.30 (t, 2H), 2.66 (t, 4 H), 2.56 (t, 4 H)
50		3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(tetrahydro-2H-pyran-3-yl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, MeOH) d ppm 9.11 (s, 1 H), 8.35 (s, 1 H), 7.37 (m, 2 H), 7.12 (t, 2 H), 5.71 (s, 2 H), 4.06 (t, 2 H), 3.82 (m, 2H) 3.75 (t, 2 H), 3.61 (m, 2 H), 3.30 (t, 2H), 2.83 (s, 3 H), 2.27 (m, 1 H), 2.08 (m, 2 H), 1.77 (m, 2 H)
51		1-[(3-ethoxypropoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one hydrochloride	1H NMR (300 MHz, DMSO-D6) d ppm 1.06 (t, *J*=6.97 Hz, 3 H) 1.72 - 1.83 (m, *J*=6.36, 6.36, 6.36, 6.36 Hz, 2 H) 3.31 - 3.44 (m, *J*=6.78, 6.78, 6.78, 6.78 Hz, 4 H) 3.55 (t, *J*=6.41 Hz, 2 H) 3.68 (t, *J*=7.06 Hz, 2 H) 3.96 - 4.05 (m, 2 H) 4.72 (s, 2 H) 5.79 (s, 2 H)

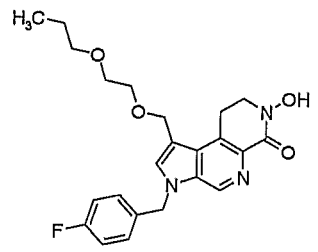
52		1-chloro-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1HNMR (DMSO-D6, 300 MHz) d 10.5 (1H, bs), 9.5 (1H, s), 8.7 (1H, s), 7.5 (2H, t), 7.2 (2H, t), 5.7 (2H, s), 4.0 (2H, t), 3.7(2H, t)
53		3-(4-fluorobenzyl)-1-{[(2-fluorobenzyl)oxy]methyl}-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one hydrochloride	1H NMR (300 MHz, DMSO-D6) d ppm 3.62 (t, J=6.88 Hz, 2 H) 3.92 (t, J=6.88 Hz, 2 H) 4.61 (s, 2 H) 4.80 (s, 2 H) 5.76 (s, 2 H) 7.13 - 7.25 (m, 4 H) 7.32 - 7.47 (m, 4 H) 8.49 (s, 1 H) 9.35 (s, 1 H) 10.56 (s, 1 H)
54		3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-carbonitrile	(300 MHz, DMSO-D6) d ppm 3.63 - 3.74 (m, 2 H) 3.88 - 4.01 (m, 2 H) 4.76 (s, 2 H) 4.91 (s, 2 H) 5.77 (s, 2 H) 7.20 (m, 2 H) 7.40 (m, 2 H) 7.55 (s, 1 H) 7.65 (s, 1 H) 8.06 (s, 1 H) 8.54 (s, 1 H) 8.65 (s, 1 H) 9.36 (s, 1 H)
55		3-(4-fluorobenzyl)-7-hydroxy-1-[(pyridin-2-ylmethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 3.63 - 3.74 (m, 2 H) 3.88 - 4.01 (m, 2 H) 4.76 (s, 2 H) 4.91 (s, 2 H) 5.77 (s, 2 H) 7.20 (m, 2 H) 7.40 (m, 2 H) 7.55 (s, 1 H) 7.65 (s, 1 H) 8.06 (s, 1 H) 8.54 (s, 1 H) 8.65 (s, 1 H) 9.36 (s, 1 H)
56		3-(4-fluorobenzyl)-7-hydroxy-1-(isobutoxymethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 0.87 (d, 6H), 1.84 (m, 1H), 3.26 (d, 2H), 3.67 (t, 2H), 3.98 (m, 2H), 4.74 (s, 2H), 5.76 (s, 2H), 7.24 (m, 2H), 7.42 (t, 2H), 8.44 (s, 1H), 9.36 (s, 1H), 10.57 (s, 1H).

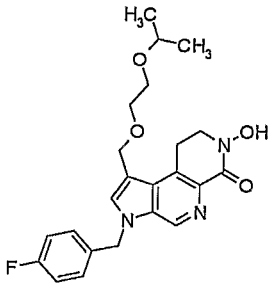
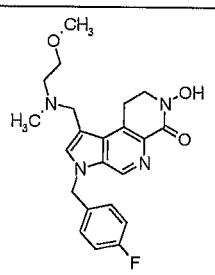
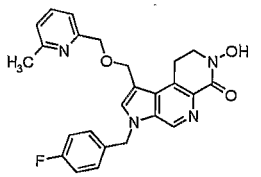
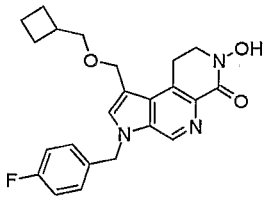
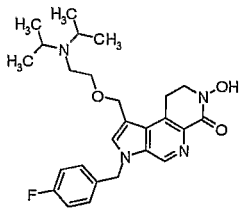
57		1-{[2-(benzyloxy)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 3.50-3.74 (m, 6H), 3.84 (m, 2H), 4.46 (s, 2H), 4.74 (s, 2H), 5.78 (s, 2H), 7.12-7.33 (m, 7H), 7.40 (m, 2H), 8.43 (s, 1H), 9.37 (s,1H), 10.54 (s, 1H).
58		3-(4-fluorobenzyl)-7-hydroxy-1-[(2-isobutoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 0.83 (d, 6H), 1.72 (m, 1H), 3.53 (m, 2H), 3.62 (m, 2H), 3.72 (t, 2H), 3.96 (t, 2H), 4.73 (s, 2H), 5.76 (s, 2H), 7.22 (m, 2H), 7.38 (m, 2H), 8.39 (s, 1H), 9.32 (s,1H), 10.48 (s,1H).
59		1-[(2-butoxyethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 0.83 (t, 3H), 1.21 (m, 2H), 1.38 (m,2H), 3.32 (m, 2H), 3.52 (m, 2H), 3.66 (m, 2H), 3.73 (m, 2H), 3.92 (m, 2H), 4.72 (s, 2H), 5.76 (s, 2H), 7.18 (m, 2H), 7.38 (m, 2H), 8.40 (s, 1H), 9.32 (s,1H), 10.52 (s,1H)..
60		1-(butoxymethyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 0.86 (m, 3H), 1.33 (m, 2H), 1.52 (m, 2H), 3.46 (m, 2H), 3.63 (m, 2H), 3.98 (m, 2H), 4.68 (s, 2H), 5.74 (s, 2H), 7.16 (m, 2H), 7.38 (m, 2H), 8.41 (s, 1H), 9.30 (s,1H), 10.48 (s,1H)..
61		1-bromo-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	

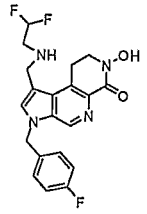
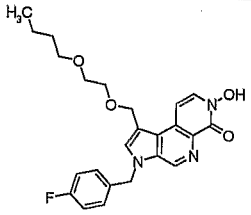
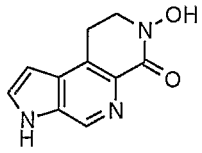
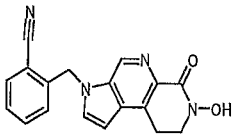
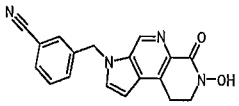
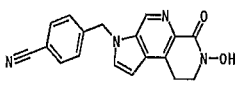
62		3-(4-fluorobenzyl)-7-hydroxy-1-[(2-pyridin-2-ylethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 3.22 (m, 2H), 3.42 (m, 2H), 3.84 (m, 2H), 3.92 (m,2H), 4.72 (s, 2H), 5.77 (s, 2H), 7.21 (m, 2H), 7.40 (m, 2H), 7.61 (t, 1H), 7.68 (d,1H), 8.16 (t, 1H), 8.48 (s, 1H), 8.62 (d, 1H), 9.36 (s, 1H), 10.62 (s, 1H).
63		3-(4-fluorobenzyl)-7-hydroxy-1-{[(4-oxopentyl)oxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 1.76 (q, 2H), 2.06 (s, 3H), 2.34 (t, 2H), 3.47 (m, 2H), 3.68 (t, 2H), 3.98 (m, 2H), 4.72 (s, 2H), 5.80 (s, 2H), 7.22 (m, 2H), 7.44 (m, 2H), 8.46 (s, 1H), 9.38 (s,1H), 10.64 (s,1H)..
64		3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-methylpyridin-3-yl)methoxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 2.62 (s, 3 H) 3.63 (t, *J*=7.06 Hz, 2 H) 3.94 (t, *J*=6.88 Hz, 2 H) 4.71 (s, 2 H) 4.89 (s, 2 H) 5.77 (s, 2 H) 7.15 - 7.25 (m, 2 H) 7.36 - 7.43 (m, 2 H) 7.72 (d, *J*=6.78 Hz, 1 H) 8.27 (d, *J*=7.91 Hz, 1 H) 8.51 (s, 1 H) 8.62 (d, *J*=4.71 Hz, 1 H) 9.37 (s, 1 H) 10.58 (s, 1 H)
65		1-{[(cyclopropylmethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.77 (1H, s), 7.80 (1H, d), 7.29 (2H, m), 7.07 (2H, t), 5.56 (2H, s), 4.21 (2H, m), 3.96 (2H, t), 3.74 (2H, m), 2.78 (2H, m), 2.59 (3H, S), 1.11 (1H, m), 0.70 (2H, m), 0.30 (2H, m)

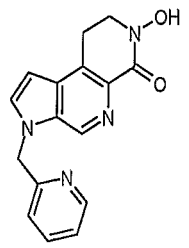
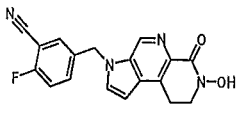
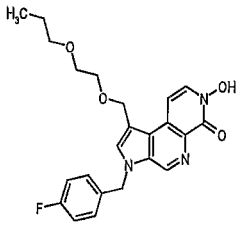
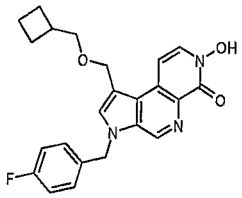
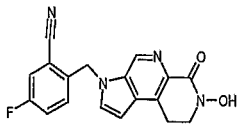
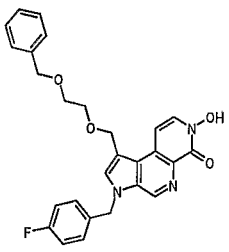
66		3-(4-fluorobenzyl)-7-hydroxy-1-{[2-(3-methoxyphenyl)ethoxy] methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 2.76 (t, J=6.31 Hz, 2 H) 3.38 (t, J=7.35 Hz, 2 H) 3.63 (s, 3 H) 3.69 (t, J=6.41 Hz, 2 H) 3.73 - 3.79 (m, 2 H) 4.67 (s, 2 H) 5.73 (s, 2 H) 6.64 (s, 1 H) 6.67 (ddd, J=6.26, 1.27, 1.13 Hz, 2 H) 7.05 (td, J=7.44, 1.32 Hz, 1 H) 7.20 (ddd, J=9.00, 6.73, 2.17 Hz, 2 H) 7.36 - 7.43 (m, 2 H) 8.39 (s, 1 H) 9.31 (s, 1 H) 10.51 (s, 1 H)
67		3-(4-fluorobenzyl)-7-hydroxy-1-[(2-phenoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 3.67 (t, J=6.97 Hz, 2 H) 3.79 - 3.89 (m, 4 H) 4.07 - 4.14 (m, 2 H) 4.78 (s, 2 H) 5.73 (s, 2 H) 6.84 - 6.93 (m, 3 H) 7.16 - 7.29 (m, 4 H) 7.35 - 7.42 (m, 2 H) 8.41 (s, 1 H) 9.30 (s, 1 H) 10.47 (s, 1 H)
68		1-acetyl-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one - methane (1:1)	^{1}HNMR (MeOD, 300 MHz) d 8.75 (1H, s), 8.60 (1H, d), 7.34 (2H, m), 7.09 (2H, t), 5.63 (2H, s), 3.91 (4H, m), 2.61 (3H,s)
69		3-(4-fluorobenzyl)-7-hydroxy-1-[(tetrahydro-2H-pyran-4-ylamino)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.74 (1H, s), 7.71 (1H, d), 7.27 (2H, m), 7.05 (2H, t), 5.53 (2H, s), 4.26 (3H, s), 3.96 (4H, m), 3.66 (2H, m), 3.45 (2H, m), 3.06 (1H, m), 2.05 2H, m), 1.57 (2H, m)

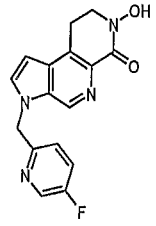
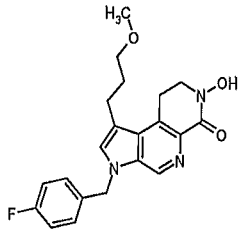
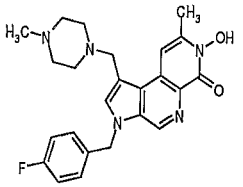
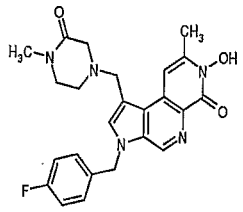
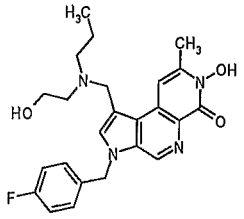
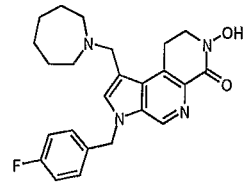
70		1-{[[(1-ethyl-1H-imidazol-2-yl)methyl](methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.75 (1H, s), 7.73 (1H, d), 7.31 (3H, m), 7.18 (1H, s), 7.07 (2H, t), 5.53 (2H, s), 3.92 (2H, t), 3.84 (4H, m), 3.75 (2H, s), 3.64(2H, t), 2.36 (3H, m), 1.03 (3H, t)
71		1-{[ethyl(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.70 (1H, s), 7.66 (1H, d), 7.25 (2H, m), 7.05 (2H, t), 5.52 (2H, s), 3.94 (2H, t), 3.83 (2H, s), 3.75 (2H, t), 2.65(2H, q), 2.30 (3H, s), 1.16 (3H, t)
72	 Chiral	1-{[(3R,4R)-3,4-difluoropyrrolidin-1-yl]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.69 (1H, s), 7.65 (1H, d), 7.23 (2H, m), 7.05 (2H, t), 5.51 (2H, s), 4.92-5.21 (2H, m), 3.86-3.90 (4H, m), 3.77 (2H, t), 2.97-3.08(2H, m), 2.68-2.80 (2H, m)
73		3-(4-fluorobenzyl)-7-hydroxy-1-{[methyl(2,2,2-trifluoroethyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.67 (1H, s), 7.61 (1H, d), 7.22 (2H, m), 7.04 (2H, t), 5.50 (2H, s), 3.76-3.92 (6H, m), 3.08 (2H, q), 2.45 (3H, s)
74		3-(4-fluorobenzyl)-7-hydroxy-1-[(3-pyridin-2-ylpropoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 1.94 (m, 2H), 2.76 (t, 2H), 3.48 (m, 2H), 3.54 (m, 2H), 3.81 (m, 2H), 4.62 (s, 2H), 5.54 (s, 2H), 7.17 (m, 4H), 7.32 (m, 2H), 7.60 (t, 1H), 7.83 (s, 1H), 8.44 (d, 1H), 8.88 (s, 1H), 9.77 (s, 1H).

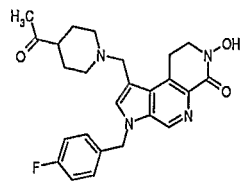
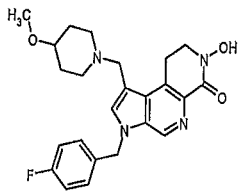
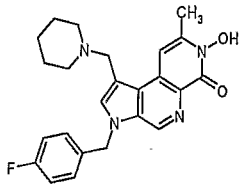
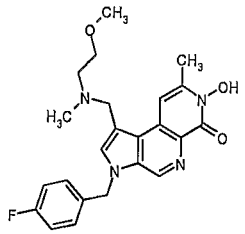
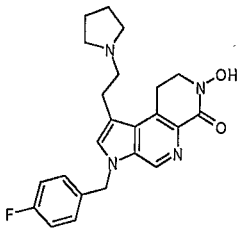
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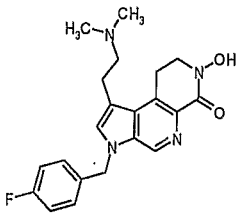
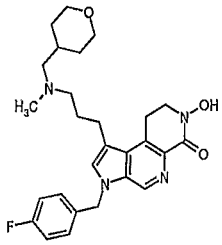
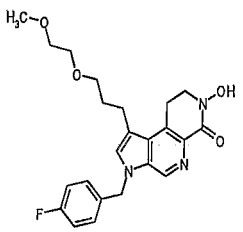
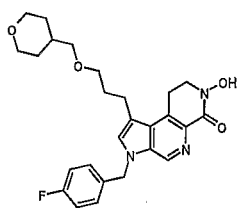
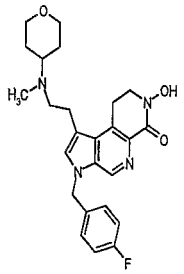
76		3-(4-fluorobenzyl)-7-hydroxy-1-[(2-isopropoxyethoxy)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	1H NMR (300 MHz, DMSO-D6) d ppm 1.02 (d, J=6.03 Hz, 6 H) 3.32 (s, 2 H) 3.44 - 3.57 (m, 6 H) 3.76 (t, J=6.78 Hz, 2 H) 4.62 (s, 2 H) 5.52 (s, 2 H) 7.11 - 7.22 (m, 2 H) 7.33 (dd, J=8.57, 5.56 Hz, 2 H) 7.81 (s, 1 H) 8.85 (s, 1 H) 9.74 (s, 1 H)
77		3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-methoxyethyl)(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	^{1}HNMR (MeOD, 300 MHz) d 8.72 (1H, s), 7.74 (1H, d), 7.27 (2H, m), 7.05 (2H, t), 5.53 (2H, s), 4.05 (2H, s), 3.94 (2H, t), 3.76 (2H, t), 3.61 (2H, t), 2.94(2H, m), 2.47 (3H, s)
78		3-(4-fluorobenzyl)-7-hydroxy-1-{[(6-methylpyridin-2-yl)methoxy]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) δ 2.63 (s, 3H), 3.70 (t, J=6.97 Hz, 2 H), 3.98 (t, J=7.06 Hz, 2 H), 4.80 (s, 2H) 4.93 (s, 2H), 5.80 (s, 2 H), 7.41 (t, 2 H), 7.43 (m, 2 H), 7.56 (s, 1 H), 8.06 (s, 1H), 8.56 (s, 1H), 9.40 (s, 1 H), 10.62 (br s, 1H).
79		1-[(cyclobutylmethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) δ 1.59-1.68 (m, 2 H), 1.73-1.84 (m, 2 H), 1.86 - 1.97 (m, 2 H), 3.39 (d, J=6.78 Hz, 2 H), 3.50 (t, J=6.78 Hz, 2 H), 3.77 (t, J=6.88 Hz, 2 H), 4.59 (s, 2 H) 5.52 (s, 2 H), 7.11 - 7.20 (m, 2 H), 7.33 (m, 2 H),7.81 (s, 1 H), 8.85 (s, 1 H), 9.74 (s, 1 H)
80		1-{[2-(diisopropylamino)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d ppm 0.87 (d, J=6.41 Hz, 12 H) 2.81 - 2.94 (m, 2 H) 3.28 - 3.40 (m, 3 H) 3.48-3.55 (m, 2 H) 3.72-3.82 (m, 2 H) 4.61 (s, 2 H) 5.52 (s, 2 H) 7.10-7.20 (m, 2 H) 7.27-7.33 (m, 2 H) 7.80 (s, 1 H) 8.85 (s, 1 H) 9.74 (s, 1 H)

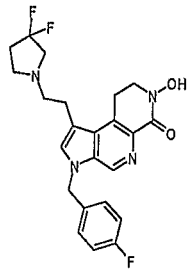
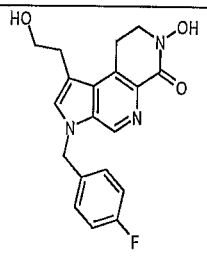
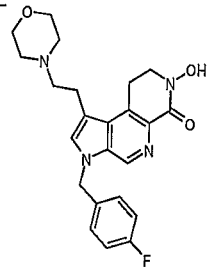
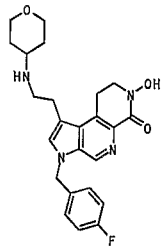
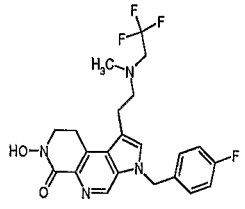
81		1-{[(2,2-difluoroethyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 8.70 (s, 1H), 7.74 (s, 1H), 7.26 - 7.29 (m, 2H), 7.06 (d, 2H, J = 8.6 Hz), 5.74-6.12 (m, 1H), 5.52 (s, 2H), 4.08 (s, 1H), 3.95 (t, 2H, J = 6.6 Hz), 3.76 (t, 2H, J = 6.8 Hz), 2.98 - 3.08 (m, 2H)
82		1-[(2-butoxyethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) δ 0.80 (t, J=7.35 Hz, 3 H), 1.15 - 1.27 (m, 2 H), 1.34 - 1.43 (m, 2 H) 3.32 (t, J=6.50 Hz, 2 H), 3.50 (m, 2 H), 3.63 (m, 2 H), 4.85 (s, 2 H), 5.81 (s, 2 H), 7.20 (t, J=8.67 Hz, 3 H), 7.41 (m, 2 H), 8.10 (d, J=7.54 Hz, 1 H), 8.42 (s, 1 H), 9.55 (s, 1 H), 12.37 (s, 1 H)
83		7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-d6) δ 13.18 (s, 1H), 10.54 (s, 1H), 8.96 (s, 1H), 8.36 (s, 1H), 7.17(s, 1H), 4.30 (t, 2H), 3.54 (t, 2H)
84		2-[(7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-3-yl)methyl]benzonitrile	(300 MHz, CD_3OD) δ 9.06 (b, 1H), 7.72 (d, 1H), 7.60 - 7.55 (m, 3H), 7.44 (m, 1H), 7.23 (m, 1H), 6.73 (s, 1H), 5.73 (s, 2H), 4.07 (t, 2H), 3.43 (m, 2H)
85		3-[(7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-3-yl)methyl]benzonitrile	(300 MHz, MeOD) δ 8.71 (s, 1H), 7.77 (s, 1H), 7.64 (m, 1H), 7.57 (s, 1H), 7.49 (m, 2H), 6.84 (d, 1H), 5.66 (s, 2H), 3.98 (t, 2H), 3.45 (t, 2H)
86		4-[(7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-3-yl)methyl]benzonitrile	(300 MHz, MeOD) δ 8.77 (s, 1H), 7.90 (d, 1H), 7.68 (d, 2H), 7.36 (d, 2H), 6.94 (d, 1H), 5.74 (s, 2H), 4.00 (t, 2H), 3.49 (t, 2H)

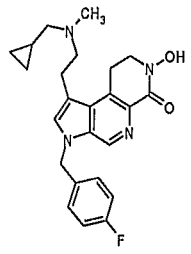
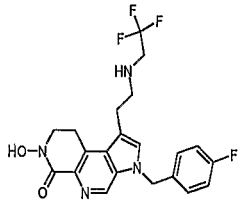
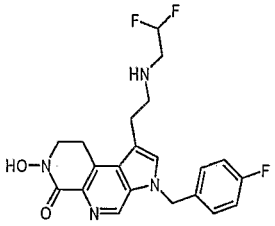
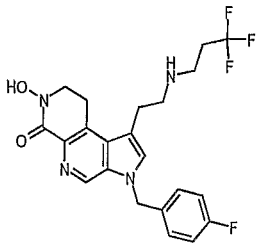
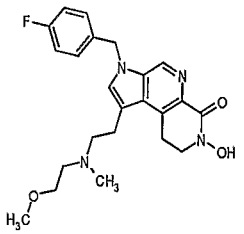
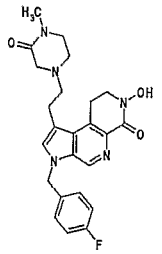
87		7-hydroxy-3-(pyridin-2-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 9.18 (s, 1H), 8.45 (d, 1H), 8.32 (d, 1H), 7.82 (t, 1H), 7.45 (d, 1H), 7.33 (m, 1H), 7.16 (d, 1H), 5.83 (s, 2H), 4.06 (t, 2H), 3.58 (t, 2H)
88		2-fluoro-5-[(7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-3-yl)methyl]benzonitrile	(300 MHz, MeOD) δ 8.70 (s, 1H), 7.74 (s, 1H), 7.60 (m, 1H), 7.50 (m, 1H), 7.30 (t, 1H), 6.82 (d, 1H), 5.61 (s, 2H), 3.97 (t, 2H), 3.43 (t, 2H)
89		3-(4-fluorobenzyl)-7-hydroxy-1-[(2-propoxyethoxy)methyl]-3,7-dihydro-6H-pyrrolo[23-c]-17-naphthyridin-6-one	(300 MHz, DMSO-D6) δ 0.78 (t, 3H), 1.43 (m, 2H), 3.29 (t, 2H), 3.51 (m, 2 H), 3.55 (m, 2H), 4.85 (s, 2H), 5.81 (s, 2H) 7.20 (t, 3H), 7.41 (t, 2H), 8.10 (d, 1H), 8.43 (s, 1H), 9.55 (s, 1H), 12.38 (brs, 1H).
90		1-[(cyclobutylmethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[23-c]-17-naphthyridin-6-one	(300 MHz, DMSO-D6) δ 1.65-1.73 (m, 2H), 1.74-1.79 (m, 1 H), 1.79-1.94 (m, 2H), 3.44 (d, J=6.78 Hz, 2H), 4.72 (s, 2H), 5.62 (s, 2H), 6.96-6.98 (d, 1H), 7.1 - 7.20 (m, 2H) 7.31-7.40 (m, 2 H), 7.81-7.88 (m, 2H), 9.06 (s, 1H), 11.25 (brs, 1H).
91		5-fluoro-2-[(7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-3-yl)methyl]benzonitrile	(300 MHz, MeOD) δ 9.19 (s, 1H), 8.20 (d, 1H), 7.67 (dd, 1H), 7.47 (m, 2H), 7.20 (d, 1H), 5.95 (s, 2H), 4.097 (t, 2H), 3.61 (t, 2H)
92		1-{[2-(benzyloxy)ethoxy]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d 3.63 (dt, J=17.61, 2.68 Hz, 4 H) 4.45 (s, 2 H) 4.78 (s, 2 H) 5.62 (s, 2 H) 7.01 (d, J=7.72 Hz, 1 H) 7.15 (t,J=8.85 Hz, 3 H) 7.22 - 7.30 (m, 5 H) 7.35 (d, J=8.48, 5.46 Hz, 3 H) 7.68 (d, J=7.72 Hz, 1 H) 7.86 (s, 1 H) 9.06 (s, 1H)

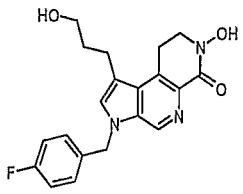
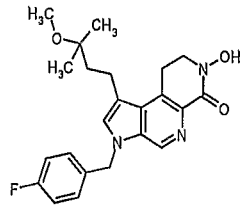
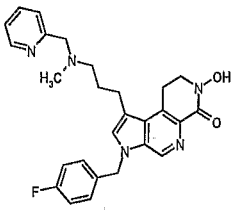
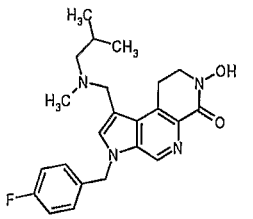
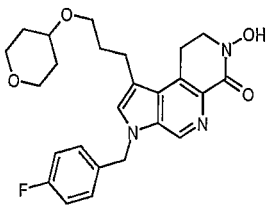
93		3-[(5-fluoropyridin-2-yl)methyl]-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 9.19 (s, 1H), 8.36 (d, 1H), 8.31 (d, 1H), 7.60 (m, 1H), 7.54 (m, 1H), 7.16 (d, 1H), 5.83 (s, 2H), 4.09 (t, 2H), 3.59 (t, 2H)
94		3-(4-fluorobenzyl)-7-hydroxy-1-(3-methoxypropyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d 1.82 - 1.94 (m, 2 H) 2.89 - 3.00 (m, 2 H) 3.23 (s, 3 H) 3.35-3.41 (m, 2 H) 3.62-3.69 (m, 2 H) 3.92-3.98 (m, 2 H) 5.72 (s, 2 H) 7.14 - 7.24 (m, 2 H) 7.33 - 7.41 (m, 2 H) 8.29 (s, 1 H) 9.27 (s, 1 H) 10.52 (s, 1 H)
95		3-(4-fluorobenzyl)-7-hydroxy-8-methyl-1-[(4-methylpiperazin-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOH) d 8.84 (s, 1 H), 7.62 (s, 1 H), 7.42 (s, 1 H), 7.25 (m, 2 H), 7.04 (m, 2 H), 5.56 (s, 2 H), 3.83 (s, 2 H), 2.55 (m, 11 H), 2.30 (s, 3 H)
96		3-(4-fluorobenzyl)-7-hydroxy-8-methyl-1-[(4-methyl-3-oxopiperazin-1-yl)methyl]-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOH) d 8.86 (s, 1 H), 7.67 (s, 1 H), 7.29 (s, 1 H), 7.27 (m, 2 H), 7.06 (m, 2 H), 5.58 (s, 2 H), 3.50 (s, 2 H), 3.37 (t, 2 H), 3.16 (s, 2 H), 2.92 (s, 3H), 2.85 (t, 2 H), 2.54 (s, 3H)
97		3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-hydroxyethyl)(propyl)amino]methyl}-8-methyl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOH) d 8.84 (s, 1 H), 7.67 (s, 1 H), 7.49 (s, 1 H), 7.24 (m, 2 H), 7.05 (m, 2 H), 5.58 (s, 2 H), 4.04 (s, 2 H), 3.62 (t, 2 H), 2.76 (t, 2 H), 2.56 (t, 2 H), 2.55 (s, 3 H), 1.53 (m, 2H), 0.82 (t, 3 H)
98		1-(azepan-1-ylmethyl)-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOH) d 9.03 (s, 1 H), 8.40 (s, 1 H), 7.38 (m, 2 H), 7.10 (t, 2 H), 5.70 (s, 2 H), 4.71 (s, 2 H), 4.05 (t, 2 H), 3.76 (t, 2 H), 3.56 (m, 2 H), 3.31 (m, 2 H), 1.97 (m, 4 H), 1.77 (m, 4 H)

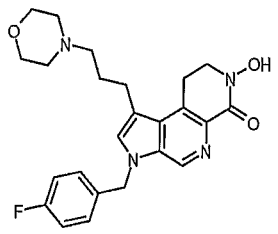
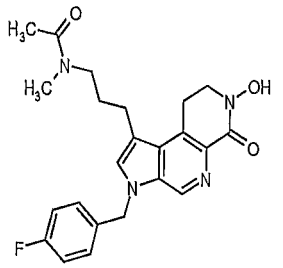
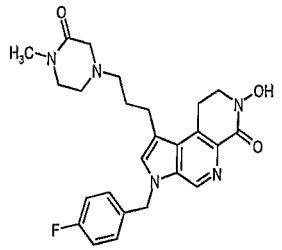
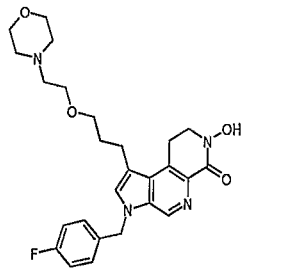
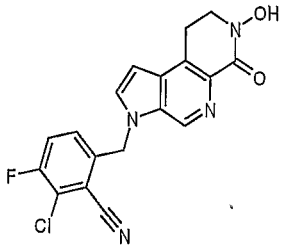
99		1-[(4-acetylpiperidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOH) d 8.66 (s, 1 H), 7.69 (s, 1 H), 7.23 (m, 2 H), 7.03 (t, 2 H), 5.50 (s, 2 H), 3.93 (s, 2 H), 3.91 (t, 2 H), 3.72 (t, 2 H), 3.14 (m, 2H), 2.53 (t, 1 H), 2.40 (t, 2H), 2.15 (s, 3 H), 1.90 (m, 2 H), 1.64 (m, 2 H)
100		3-(4-fluorobenzyl)-7-hydroxy-1-[(4-methoxypiperidin-1-yl)methyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-d_6) δ 1.23 - 1.45 (m, 2 H), 1.70 - 1.87 (m, 2 H), 2.02 - 2.19 (m, 2 H), 2.60 - 2.75 (m, 2 H), 3.10 - 3.25 (m, 4 H), 3.55 (s, 2 H), 3.65 (t, 2 H), 3.77 (t, 2 H), 5.51 (s, 2 H), 7.08 - 7.23 (m, 2 H), 7.25 - 7.37 (m, 2 H), 7.68 (s, 1 H), 8.79 (s, 1 H), 9.68 (s, 1H)
101		3-(4-fluorobenzyl)-7-hydroxy-8-methyl-1-(piperidin-1-ylmethyl)-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOH) d 8.83 (s, 1 H), 7.64 (s, 1 H), 7.40 (s, 1 H), 7.25 (m, 2 H), 7.04 (m, 2 H), 5.57 (s, 2 H), 3.93 (s, 2 H), 2.67 (m, 4 H), 2.54 (s, 3 H), 1.63 (m, 4H), 1.53 (m, 2H)
102		3-(4-fluorobenzyl)-7-hydroxy-1-{[(2-methoxyethyl)(methyl)amino]methyl}-8-methyl-3,7-dihydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOH) d 8.84 (s, 1 H), 7.63 (s, 1 H), 7.45 (s, 1 H), 7.25 (m, 2 H), 7.05 (m, 2 H), 5.58 (s, 2 H), 3.87 (s, 2 H), 3.57 (t, 2 H), 3.32 (s, 3 H), 2.74 (t, 2 H), 2.57 (s, 3 H), 2.27 (s, 3 H)
103		3-(4-fluorobenzyl)-7-hydroxy-1-(2-(pyrrolidin-1-yl)ethyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	(400 MHz, DMSO-D6) d ppm 10.50 (s, 1 H) 10.10 (s, 1 H) 9.01 (s, 1 H) 7.83 (s, 1 H) 7.34 (dd, J=7.45, 4.67 Hz, 2 H) 7.17 (t, J=8.72 Hz, 2 H) 5.58 (s, 2 H) 3.83 (t, J=6.57 Hz, 2 H) 3.66 - 3.76 (m, 2 H) 3.59 (t, 2 H) 3.45 - 3.53 (m, 2 H) 3.28 (d, J=7.07 Hz, 2 H) 3.11 (s, 2 H) 2.05 (s, 2 H), 1.93 (s, 2 H)

104		3-(4-fluorobenzyl)-1-(2-(dimethylamino)ethyl)-7-hydroxy-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	(300 MHz, CHLOROFORM-D) d 8.71 (s, 1 H) 7.15 (s, 1 H) 7.10 (dd, 2 H) 6.99 (t, J=8.57 Hz, 2 H) 5.34 (s, 2 H) 3.98 (t, J=6.97 Hz, 2 H) 3.68 (s, 1 H) 3.59 (t, J=6.88 Hz, 2 H) 3.04 (t, 2 H) 2.60 (t, 2 H) 2.34 (s, 6 H)
105		3-(4-fluorobenzyl)-7-hydroxy-1-{3-[methyl(tetrahydro-2H-pyran-4-ylmethyl)amino]propyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d 1.20 (m, 2 H), 1.61 (m, 1 H), 1.82 (s, 1 H) 2.13 (m, 2 H), 2.72 (d, J=4.52 Hz, 3 H), 2.95 (m, 4 H), 3.20 - 3.30 (m, 2 H), 3.25 (m, 2H), 3.67 - 3.76 (m, 3H), 3.78 (m, 2 H) 3.95 (t, J=6.69 Hz, 2H) 5.74 (s, 2H), 7.19 (t, J=8).
106		3-(4-fluorobenzyl)-7-hydroxy-1-[3-(2-methoxyethoxy)propyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d 1.87 (m, 2H), 2.93 (t, J=7.44 Hz, 2H), 3.23 (s, 3H), 3.38 - 3.50 (m, 6H), 3.57 - 3.69 (m, 2H), 3.85 - 3.97 (m, 2H) 5.70 (s, 2H), 7.18 (t, J=8.85 Hz, 2H), 7.36 (dd, J=8.38, 5.56 Hz, 2H), 8.20 (s, 1H), 9.22 (s, 1H), 10.43 (s)
107		methyl {3-[3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-1-yl]propoxy}acetate	(300 MHz, DMSO-D6) d 1.09 - 1.24 (m, 2H), 1.47 - 1.56 (m, 2H), 1.71 (m, 1H), 1.80 - 1.93 (m, 2H), 2.89 - 2.99 (m, 2H), 3.17 - 3.32 (m, 4H) 3.41 (t, J=6.03 Hz, 3 H) 3.66 (t, J=6.88 Hz, 2 H) 3.81 (dd, J=11.21, 2.92 Hz, 2H),3.95 (t, J=6.97 Hz, 2H)
108		3-(4-fluorobenzyl)-7-hydroxy-1-(2-(methyl(tetrahydro-2H-pyran-4-yl)amino)ethyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	(300 MHz, MeOH) d ppm 8.76 (s, 1 H) 7.61 (s, 1 H) 7.26 (t, 2 H) 7.06 (t, J=8.38 Hz, 2 H) 5.52 (s, 2 H) 4.04 (d, J=10.55 Hz, 2 H) 3.95 (t,J=6.50 Hz, 2 H) 3.61 (t, J=6.50 Hz, 2 H) 3.46 (t, J=11.21 Hz, 2 H) 3.32 - 3.37 (m, 2 H) 3.27 (s, 4 H) 1.94 (s, 2 H) 1.78 (d, J=9.23 Hz, 2 H)

109		3-(4-fluorobenzyl)-1-(2-(3,3-difluoropyrrolidin-1-yl)ethyl)-7-hydroxy-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	(300 MHz, MeOH) d ppm 8.69 (s, 1 H) 7.59 (s, 1 H) 7.18 - 7.37 (m, 2 H) 7.06 (t, J=8.29 Hz, 2 H) 5.51 (s, 2 H) 3.91 - 4.04 (m, 2 H) 3.58 - 3.70 (m, 2 H) 3.30 - 3.37 (m, 2 H) 3.10 - 3.19 (m, 2 H) 3.05 (t, J=13.28 Hz, 2 H) 2.78 - 2.95 (m, 2 H) 2.21 - 2.44 (m, 2 H)
110		3-(4-fluorobenzyl)-7-hydroxy-1-(2-hydroxyethyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	(300 MHz, MeOH) d 8.68 (s, 1 H) 7.56 (s, 1 H) 7.27 (dd, J=8.38, 5.37 Hz, 2 H) 7.07 (t, J=8.67 Hz, 2 H) 5.51 (s, 2 H) 3.97 (t, J=6.88 Hz, 2 H) 3.86 (t, J=6.88 Hz, 2 H) 3.67 (t, J=6.88 Hz, 2 H) 3.15 (t, J=6.88 Hz, 2 H)
111		3-(4-fluorobenzyl)-7-hydroxy-1-(2-morpholinoethyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	(300 MHz, MeOH) d 8.70 (s, 1 H) 7.58 (s, 1 H) 7.25 (dd, 2 H) 7.06 (t, J=8.38 Hz, 2 H) 5.50 (s, 2 H) 3.90 - 4.01 (m, 2 H) 3.79 (s, 4 H) 3.58 - 3.68 (m, 2 H) 3.09 - 3.23 (m, 2 H) 2.81 (s, 2 H) 2.64 - 2.76 (m, 4 H)
112		3-(4-fluorobenzyl)-7-hydroxy-1-(2-(tetrahydro-2H-pyran-4-ylamino)ethyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	(300 MHz, MeOH) d ppm 8.59 (s, 1 H) 7.39 (s, 1 H) 7.03 - 7.20 (m, 2 H) 6.82 - 7.02 (m, 2 H) 5.28 - 5.54 (m, 2 H) 3.73 - 3.97 (m, 4 H) 3.41 - 3.53 (m, 2 H) 3.02 - 3.41 (m, J=47.10 Hz, 8 H) 1.86 - 2.09 (m, 2 H) 1.64 (d, J=25.81 Hz, 2 H) 1.30 - 1.47 (m, 1 H)
113		3-(4-fluorobenzyl)-7-hydroxy-1-{2-[methyl(2,2,2-trifluoroethyl)amino]ethyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 8.69 (s, 1H), 7.57 (d, 1H), 7.24 - 7.26 (t, 2H), 7.05-7.09 (t, 2H), 5.51 (s, 2H), 4.59 (t, 2H), 3.96 - 3.98 (t, 2H), 3.68 - 3.70 (t, 2H), 3.22 (t, 2H), 3.13 (t, 2H), 2.55 (s, 1H)

114		1-{2-[(cyclopropylmethyl)(methyl)amino]ethyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 8.78 (s, 1H), 7.62 (d, 1H), 7.24 - 7.26 (t, 2H), 7.05-7.09 (t, 2H), 5.55 (s, 2H), 3.98 (t, 2H), 3.64 (t, 2H), 3.50 (t, 2H), 3.34 (t, 2H), 3.15 (t, 2H), 3.07 (s, 3H), 1.15-1.25 (b, 1H), 0.75 (t, 2H), 0.45 (t, 2H)
115		3-(4-fluorobenzyl)-7-hydroxy-1-{2-[(2,2,2-trifluoroethyl)amino]ethyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 8.69 (s, 1H), 7.57 (d, 1H), 7.24 - 7.26 (t, 2H), 7.05-7.09 (t, 2H), 5.51 (s, 2H), 3.96 - 3.98 (t, 2H), 3.68 - 3.70 (t, 2H), 3.32 (d, 2H), 3.26 (t, 2H), 3.10 (t, 2H)
116		1-{2-[(2,2-difluoroethyl)amino]ethyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 8.76 (s, 1H), 7.60 (d, 1H), 7.26 (t, 2H), 7.09 (t, 2H), 5.55 (s, 2H), 3.99 (t, 2H), 3.65 (t, 2H), 3.34 (m, 4H), 3.30 (m, 5H)
117		3-(4-fluorobenzyl)-7-hydroxy-1-{2-[(3,3,3-trifluoropropyl)amino]ethyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 8.75 (s, 1H), 7.48 (d, 1H), 7.24 - 7.26 (t, 2H), 7.05-7.09 (t, 2H), 5.51 (s, 2H), 3.96 - 3.98 (t, 2H), 3.60 - 3.62 (t, 2H), 3.32 (m, 2H), 3.24-3.30 (m, 4H), 255-2.65 (b, 2H)
118		3-(4-fluorobenzyl)-7-hydroxy-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 8.79 (s, 1H), 7.63 (d, 1H), 7.28 (t, 2H), 7.07 (t, 2H), 5.55 (s, 2H), 3.97 (t, 2H), 3.81 (t, 2H), 3.63 (t, 2H), 3.55 (d, 2H), 3.42 (s, 3H), 3.33 (m, 4H), 3.10 (s, 3H)
119		3-(4-fluorobenzyl)-7-hydroxy-1-[2-(4-methyl-3-oxopiperazin-1-yl)ethyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, MeOD) δ 8.71 (s, 1H), 7.59 (d, 1H), 7.26 (t, 2H), 7.08 (t, 2H), 5.52 (s, 2H), 4.59 (s, 2H), 3.99 (t, 2H), 3.68 (t, 2H), 3.39 (m, 2H), 3.25 (s, 2H), 3.15 (m, 2H), 2.99 (s, 3H), 2.75-2.87 (m, 2H)

120		3-(4-fluorobenzyl)-7-hydroxy-1-(3-hydroxypropyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(400 MHz, DMSO-D6) d 1.73 - 1.81 (m, 2H) 2.84 - 2.91 (m, 2H) 3.45 - 3.51 (m, 2H) 3.54 (t, J=6.82 Hz, 2H) 3.82 (t, J=6.82 Hz, 2H) 4.53 (s, 1H) 5.55 (s, 2H) 7.12 - 7.19 (m, 2H) 7.32 (dd, J=8.59, 5.56 Hz, 2H) 7.77 (s, 1H) 8.92 (s, 1H) 9.94 (s, 1H)
121		3-(4-fluorobenzyl)-7-hydroxy-1-(3-methoxy-3-methylbutyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d 1.18 (s, 6H), 1.74 - 1.86 (m, 2H), 2.83 - 2.95 (m, 2H), 3.11 (s, 3H), 3.68 (t, J=6.97 Hz, 2H), 3.96 (t, J=6.88Hz, 2H), 5.71 (s, 2 H) 7.18 (t, J=8.85 Hz, 2H), 7.33 - 7.44 (m, 2H), 8.31 (s, 1H), 9.26 (s, 1H), 10.51 (s, 1H)
122		3-(4-fluorobenzyl)-7-hydroxy-1-{3-[methyl(pyridin-2-ylmethyl)amino]propyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d 2.16 (s, 2H), 2.75 (s, 3H), 2.96 (s, 2H), 3.17 (s, 2H), 3.96 (t, J=6.88 Hz, 3H), 4.44 (s, 2H), 5.75 (s, 2H),7.19 (t, J=8.85 Hz, 2H), 7.33 - 7.47 (m, 3H), 7.69 (d, J=7.72 Hz, 1H), 7.88 (td, J=7.63, 1.70 Hz, 1H), 8.37 (s, 1H)
123		3-(4-fluorobenzyl)-7-hydroxy-1-{[isobutyl(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO) d 10.46 (s, 1 H), 9.38 (s, 1 H), 8.74 (s, 1 H), 7.40 - 7.45 (dd, 2 H), 7.20 (t, 2 H), 5.82 (s, 2 H), 4.71 (d, 1 H), 4.53 (d, 1 H), 3.97 (t, 2 H), 3.78 (t, 2 H), 2.99 (dd, 2 H), 2.73 (d, 3 H), 2.13 (m, 1 H), 0.96 (t, 6 H)
124		3-(4-fluorobenzyl)-7-hydroxy-1-(3-(tetrahydro-2H-pyran-4-yloxy)propyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one	(300 MHz, DMSO-D6) d ppm 1.29 - 1.42 (m, J=13.12, 9.36, 9.36, 4.14 Hz, 2H), 1.76 - 1.92 (m, 4 H), 2.96 (t, J=7.63 Hz, 2 H), 3.27 - 3.36(m, 3 H), 3.39 - 3.48 (m, 3 H), 3.68 (t, J=6.97 Hz, 2 H), 3.78 (dt, J=11.44, 4.17 Hz, 2 H), 3.95 (t, J=6.97 Hz, 2 H), 5.72 (s, 2 H), 7.18 (t, J=8.76 Hz, 2H), 7.37 (dd, J=8.48, 5.46 Hz, 2 H), 8.28 (s, 1 H), 9.28 (s, 1 H)

125		3-(4-fluorobenzyl)-7-hydroxy-1-(3-morpholin-4-ylpropyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d ppm 2.07 - 2.20 (m, 2H), 2.94 - 3.07 (m, 3H), 3.13 (m, 2H, 3.39 (d, J=11.49 Hz, 4H), 3.67 - 3.81 (m, 2H), 3.84- 3.98 (m, 5H), 5.74 (s, 2H), 7.15 - 7.23 (m, 2H), 7.34 - 7.41 (m, 2H), 8.38 (s, 1H), 9.30 (s, 1 H), 10.55 (s, 1H), 11.67 (s, 1H)
126		N-(3-(3-(4-fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-1-yl)propyl)-N-methylacetamide	(300 MHz, DMSO-D6) d ppm 1.06 (s, 1 H), 1.84 (d, J=7.16 Hz, 1 H), 1.90 - 1.97 (m, 3 H), 2.80 (s, 1 H), 2.83 - 2.97 (m, 4 H), 3.35 (td, J=7.35, 3.77 Hz, 3 H), 3.63 - 3.71 (m, 2 H), 3.96 (t, J=6.97 Hz, 2 H), 5.73 (s, 2 H), 7.14 - 7.23 (m, 2 H), 7.33 - 7.42 (m, 2 H), 8.35 (s, 1 H), 9.26 - 9.33 (m, 1 H)
127		3-(4-fluorobenzyl)-7-hydroxy-1-[3-(4-methyl-3-oxopiperazin-1-yl)propyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d 1.98 (m, 2H), 2.87 (s, 3H), 2.92 (m,2H), 3.46 (m, 2H), 3.65 (m, 4H), 3.93 (m, 3H), 5.70 (s, 2H), 7.19 (t,J=8.85 Hz, 2H), 7.35 (dd, J=8.57, 5.56 Hz, 2H), 8.21 (s, 1H), 9.23 (s, 1H), 10.44 (s, 1H)
128		3-(4-fluorobenzyl)-7-hydroxy-1-[3-(2-morpholin-4-ylethoxy)propyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one	(300 MHz, DMSO-D6) d 1.90 (m, 2H), 2.98 (t, 2H), 3.13 (m, 2H), 3.30 (m, 2H), 3.37 - 3.53 (m, 5H), 3.67 (t, J=6.97 Hz, 2H), 3.82 (m, 2H), 3.96 (m, 2H), 5.75 (s, 2H), 7.19 (t, J=8.85 Hz, 2H), 7.38 (dd, J=8.57, 5.56 Hz, 2H), 8.37 (s, 1H), 9.30 (s, 1H)
129		2-chloro-3-fluoro-6-[(7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridin-3-yl)methyl]benzonitrile	(300 MHz, MeOD) d 9.18 (s, 1 H) 8.21 (d, J=3.20 Hz, 1 H) 7.54 (t, J=8.67 Hz, 1 H) 7.23 (d, J=4.52 Hz, 1 H) 7.20 (d, J=3.77 Hz, 1H) 5.94 (s, 2 H) 4.05 (t, J=7.06 Hz, 2 H) 3.81 - 3.92 (m, 1 H) 3.58 (t, J=7.06 Hz, 2 H)

Example 130: 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 1-289) 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 131: 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 to affect about a 90% kill (for example, an moi in the range of from about 0.025 to about 0.819) or mock infected with medium only and added at 2×10^4 cells per well, with the addition of approximately 200 µL of medium, 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 20 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}).

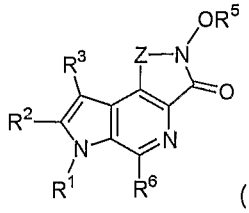
Antiviral data for Examples 1 to 129

Example No.	IC_{50} (nM)	EC_{50} (nM)	Example No.	IC_{50} (nM)	EC_{50} (nM)
1		460	33	21	13
2		60.9	34		
3		2.5	35	15	5
4		51	36	10	3
5		12	37	11.2	1.5
6		5.3	38	16.8	5.4
7			39	10.3	0.279
8	37	5	40	24.4	4.6
9	29	2	41	28.1	29
10	17	0.59	42	8.1	0.43
11	13	4	43	9.36	0.41
12	14.2	13	44	9.07	0.45
13	22	3	45	9.07	0.45
14	16	7	46	8.35	1.1
15	14	28	47	6	0.39
16	36	2	48	16.8	1
17	17	150	49	16.2	3.2
18	23.5	7	50	11.9	1.8
19	36	4.5	51	17	0.4
20	19	52	52	19	0.91
21	905	120	53	16	0.84
22	14	1.5	54	20	6.6
23	27	4	55	11	0.83
24	14	4	56	11	0.32
25	12	3	57	12	0.69
26	38	3	58	16	0.52
27	66	6	59	16	4.9
28	43	8	60	12	0.39
29	28	3	61	17	0.32
30	42	5	62	14	2
31	33	5	63	10	3

Example No.	IC_{50} (nM)	EC_{50} (nM)	Example No.	IC_{50} (nM)	EC_{50} (nM)
64	9	1	99	22	5
65	24	3	100	21	0.7
66	13	1	101	14	0.46
67	15	1	102	13	0.25
68	12	3	103	24	18
69	20	27	104	24	32
70	22	43	105	24	16
71	27	8	106	14	0.95
72	9	0.5	107	15	2
73	7	0.4	108	21	16
74	14	5	109	14	1
75	17	0.7	110	11	5
76	14	0.5	111	12	4
77	24	2	112	28	63
78	11	0.6	113	15	2
79	10	1	114	19	10
80	23	12	115	14	2
81	8	0.32	116		
82	10	0.37	117	17	6
83		14	118	20	13
84	125	32	119	12	70
85	558	460	120	13	9
86	108	27	121	14	0.4
87	89	35	122	26	5
88	9	0.45	123	44	1.6
89	10	1	124	14	0.85
90	59	14	125	13	2
91	1	2	126	14	6
92	3	10	127	14	40
93			128	21	5
94	12	0.25	129	78	15
95	14	0.45			
96	10	5			
97	17	0.69			
98	38	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 substituted with one or more substituent independently selected from:

halo, -CN, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, 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 may be substituted with one or more substituent independently selected from halo, $-C(R^{12a}R^{12b}R^{12c})$, –OH, C_1-C_8 alkoxy, and -CN;

R^2 is hydrogen or C_1-C_8 alkyl;

R^3 is C_1-C_8 alkyl, $-(CR^7R^8)_tOR^9$, $-(CR^7R^8)_tNR^9R^{10}$, $-(CR^7R^8)_tOR^9$, $-S(O)_zNR^9R^{10}$, $-C(O)NR^9R^{10}$, $-C(O)R^9$, C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, wherein said C_1-C_8 heteroalkyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl groups may be substituted with one or more R^{11};

Z is $-(CR^4R^4)_n-$;

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 heterocyclyl, 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 heterocyclyl, and C_2-C_9 heteroaryl may be substituted with one or more 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 may be substituted with one or more 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, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 heterocyclyl or a C_2-C_9 heteroaryl group, each of which may be substituted with one or more R^{13} group;

R^{11} is halogen, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_2-C_9 heterocyclyl, C_6-C_{14} aryl, or C_2-C_9 heteroaryl, each of which may be substituted with one or more 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 heterocyclyl group;

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

t is an integer from 1 to 3;

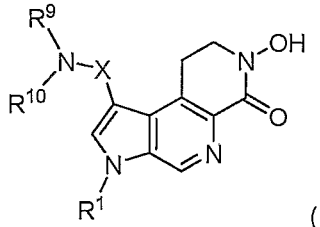
each n, which may be the same or different, is independently selected and is an integer from 1 to 4; and

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

a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein Z is $-(CH_2CH_2)-$, or a pharmaceutically acceptable salt or solvate thereof.

3. A compound 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 substituted with one or more substituent independently selected from:

halo, -CN, $-OR^{12a}$, $-N(R^{12a}R^{12b})$, $-C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)N(R^{12a}R^{12b})$, $-NR^{12a}C(O)R^{12a}$, $-NR^{12a}C(NR^{12a})N(R^{12a}R^{12b})$, $-SR^{12a}$, $-S(O)R^{12a}$, $-S(O)_2R^{12a}$, $-S(O)_2N(R^{12a}R^{12b})$, 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 may be substituted with one or more substituent

independently selected from halo, -C($R^{12a}R^{12b}R^{12c}$), –OH, C_1-C_8 alkoxy, and -CN;

X is –$S(O)_2$-, -(CH_2)-, -(CH_2CH_2)-, -($CH_2CH_2CH_2$)-, or –C(O)-;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, -C(O)R^7, -$C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more 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)$_t$OR^7, -C(O)R^{12a}, -$S(O)_2R^7$, -(CR^7R^8)$_z$C(O)N$R^{12a}R^{12b}$, -N$R^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and -CF_3;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

4. A compound according to claim 3, 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 substituted with one or more substituent independently selected from halo and -CN;

X is –$S(O)_2$-, -(CH_2)-, -(CH_2CH_2)-, -($CH_2CH_2CH_2$)-, or –C(O)-;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, -C(O)R^7, -$C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

5. A compound according to claim 4, wherein:

R^1 is $-(CH_2)(C_6$-C_{14} aryl), wherein said C_6-C_{14} aryl group is substituted with one or more substituent independently selected from halo and -CN;

X is $-S(O)_2-$, $-(CH_2)-$, $-(CH_2CH_2)-$, $-(CH_2CH_2CH_2)-$, or $-C(O)-$;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

6. A compound according to claim 5, wherein:

R^1 is 4-fluorobenzyl;

X is $-S(O)_2-$, $-(CH_2)-$, $-(CH_2CH_2)-$, $-(CH_2CH_2CH_2)-$, or $-C(O)-$;

each R^7 and R^8, which may be the same or different, is 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_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl 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 may be substituted with one or more R^{13} group;

each R^{12a} and R^{12b}, 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, $-(CR^7R^8)_tOR^7$, $-C(O)R^{12a}$, $-S(O)_2R^7$, $-(CR^7R^8)_zC(O)NR^{12a}R^{12b}$, $-NR^{12a}R^{12b}$, C_1-C_8 alkoxy, -OH, and $-CF_3$;

t is an integer from 1 to 3; and

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

a pharmaceutically acceptable salt or solvate thereof.

7. A compound according to any one of claims 1 to 6, wherein R^9 and R^{10}, which may be the same or different, are independently selected from hydrogen, C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, $-C(O)R^7$, $-C(O)_2R^7$, and C_1-C_8 alkyl, wherein said C_1-C_8 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_9 heterocyclyl, and C_1-C_8 alkyl may be substituted with one or more C_2-C_9 heterocyclyl, C_2-C_9 heteroaryl, halo, or C_6-C_{14} aryl group, and wherein said C_6-C_{14} aryl group may be substituted with one or more C_1-C_8 alkyl or halo group, or a pharmaceutically acceptable salt or solvate thereof.

8. A compound according to any one of claims 1 to 6, 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 may be substituted with one or more R^{13} group, or a pharmaceutically acceptable salt or solvate thereof.

9. A compound according to any one of claims 1 to 6, wherein R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a C_2-C_9 cycloheteroalkyl group that may be substituted with one or more R^{13} group, or a pharmaceutically acceptable salt or solvate thereof.

10. A pharmaceutical composition, comprising a therapeutically effective amount of at least one compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or diluent.

11. Use of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of an HIV-infected mammal.

12. Use of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of a mammal suffering from AIDS.