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(54) **THERAPEUTIC COMPOUNDS**

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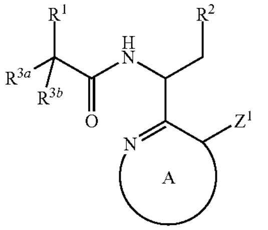
(57) **ABSTRACT**

Compounds of formula I:

I



or salts thereof are disclosed. Also disclosed are pharmaceutical compositions comprising a compound of formula I, processes for preparing compounds of formula I, intermediates useful for preparing compounds of formula I and therapeutic methods for treating a *Retroviridae* viral infection including an infection caused by the HIV virus.

THERAPEUTIC COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of and priority to U.S. Provisional Application Ser. No. 61/750,763, filed Jan. 9, 2013, the disclosure of which is hereby incorporated by reference in its entirety.

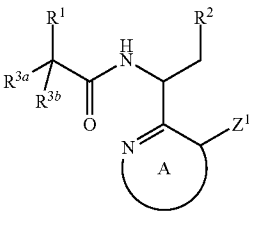
BACKGROUND

[0002] Positive-single stranded RNA viruses comprising the *Retroviridae* family include those of the subfamily *Orthoretrovirinae* and genera *Alpharetrovirus, Betaretrovirus, Gamaretrovirus, Deltaretrovirus, Epsilonretrovirus, Lentivirus*, and *Spumavirus* which cause many human and animal diseases. Among the *Lentivirus*, HIV-1 infection in humans leads to depletion of T helper cells and immune dysfunction, producing immunodeficiency and vulnerability to opportunistic infections. Treating HIV-1 infections with highly active antiretroviral therapies (HAART) has proven to be effective at reducing viral load and significantly delaying disease progression (Hammer, S. M., et al.; *JAMA* 2008, 300: 555-570). However, these treatments do lead to the emergence of HIV strains that are resistant to current therapies (Taiwo, B., *International Journal of Infectious Diseases* 2009, 13:552-559; Smith, R. J., et al., *Science* 2010, 327:697-701). Therefore, there is a pressing need to discover new antiretroviral agents that are active against emerging drug-resistant HIV variants.

SUMMARY

[0003] Provided herein are compounds and methods for the treatment of a viral infection.

[0004] One embodiment provides a compound of formula I



I

wherein:

[0005] A is a 6-membered heteroaryl with of one or two nitrogen atoms, wherein the 6-membered heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups;

[0006] R^1 is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups;

[0007] R^2 is phenyl, 5-membered heteroaryl, 6-membered heteroaryl or (C$_3$-C$_7$)carbocycle wherein any phenyl, 5-membered heteroaryl, 6-membered heteroaryl or (C$_3$-C$_7$)carbocycle of R^2 is optionally substituted with one or more (e.g., 1, 2 or 3) Z^5 groups;

[0008] each R^{3a} and R^{3b} is independently selected from H, halogen, (C$_1$-C$_3$)alkyl, and (C$_1$-C$_3$)haloalkyl, or R^{3a} is selected from H, (C$_1$-C$_3$)alkyl and (C$_1$-C$_3$)haloalkyl and R^{3b} is selected from —OH and —CN;

[0009] Z^1 is selected from aryl, heteroaryl, and heterocycle, wherein any aryl, heteroaryl and heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b};

[0010] each Z^{1a} is independently selected from (C$_3$-C$_7$) carbocycle, aryl, heteroaryl, heterocycle, halogen, —CN, —OR$_{n1}$, —OC(O)R$_{p1}$, —OC(O)NR$_{q1}$R$_{r1}$, —SR$_{n1}$, —S(O)R$_{p1}$, —S(O)$_2$OH, —S(O)$_2$R$_{p1}$, —S(O)$_2$NR$_{q1}$R$_{r1}$, —NR$_{q1}$R$_{r1}$, —NR$_{n1}$COR$_{p1}$, —NR$_{n1}$CO$_2$R$_{p1}$, —NR$_{n1}$CONR$_{q1}$R$_{r1}$, —NR$_{n1}$S(O)$_2$R$_{p1}$, —NR$_{n1}$S(O)$_2$OR$_{p1}$, —NR$_{n1}$S(O)$_2$NR$_{q1}$R$_{r1}$, NO$_2$, —C(O)R$_{n1}$, —C(O)OR$_{n1}$, —C(O)NR$_{q1}$R$_{r1}$ and —S(O)$_2$NR$_{n1}$COR$_{p1}$, wherein any (C$_3$-C$_7$)carbocycle, aryl, heteroaryl and heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

[0011] each Z^{1b} is independently selected from (C$_1$-C$_8$) alkyl, (C$_2$-C$_8$)alkenyl and (C$_2$-C$_8$)alkynyl, wherein any (C$_1$-C$_8$)alkyl, (C$_2$-C$_8$)alkenyl and (C$_2$-C$_8$)alkynyl of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

[0012] each Z^{1c} is independently selected from (C$_3$-C$_7$) carbocycle, aryl, heteroaryl, heterocycle, halogen, —CN, —OR$_{n2}$, —OC(O)R$_{p2}$, —OC(O)NR$_{q2}$R$_{r2}$, —SR$_{n2}$, —S(O)R$_{p2}$, —S(O)$_2$OH, —S(O)$_2$R$_{p2}$, —S(O)$_2$NR$_{q2}$R$_{r2}$, —NR$_{q2}$R$_{r2}$, —NR$_{n2}$COR$_{p2}$, —NR$_{n2}$CO$_2$R$_{p2}$, —NR$_{n2}$CONR$_{q2}$R$_{r2}$, —NR$_{n2}$S(O)$_2$R$_{p2}$, —NR$_{n2}$S(O)$_2$OR$_{p2}$, —NR$_{n2}$S(O$_2$NR$_{q2}$R$_{r2}$, NO$_2$, —C(O)R$_{n2}$, —C(O)OR$_{n2}$, —C(O)NR$_{q2}$R$_{r2}$, haloaryl, haloheteroaryl, haloheterocycle and (C$_1$-C$_8$)heteroalkyl;

[0013] each Z^{1d} is independently selected from (C$_1$-C$_8$) alkyl, (C$_2$-C$_8$)alkenyl, (C$_2$-C$_8$)alkynyl and (C$_1$-C$_8$)haloalkyl;

[0014] each R$_{n1}$ is independently selected from H, (C$_1$-C$_8$) alkyl, (C$_2$-C$_8$)alkenyl, (C$_2$-C$_8$)alkynyl, (C$_3$-C$_7$)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C$_3$-C$_7$)carbocycle, aryl, heteroaryl and heterocycle of R$_{n1}$ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C$_1$-C$_8$)alkyl, (C$_2$-C$_8$)alkenyl and (C$_2$-C$_8$)alkynyl of R$_{n1}$ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

[0015] each R$_{p1}$ is independently selected from (C$_1$-C$_8$) alkyl, (C$_2$-C$_8$)alkenyl, (C$_2$-C$_8$)alkynyl, (C$_3$-C$_7$)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C$_3$-C$_7$)carbocycle, aryl, heteroaryl and heterocycle of R$_{p1}$ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C$_1$-C$_8$)alkyl, (C$_2$-C$_8$)alkenyl and (C$_2$-C$_8$)alkynyl of R$_{p1}$ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

[0016] R$_{q1}$ and R$_{n1}$ are each independently selected from H, (C$_1$-C$_8$)alkyl, (C$_2$-C$_8$)alkenyl, (C$_2$-C$_8$)alkynyl, (C$_3$-C$_7$)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C$_3$-C$_7$)carbocycle, aryl, heteroaryl and heterocycle of R$_{q1}$ or R$_{n1}$ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C$_1$-C$_8$)alkyl, (C$_2$-C$_8$) alkenyl and (C$_2$-C$_8$)alkynyl of R$_{q1}$ or R$_{r1}$ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups, or R$_{q1}$ and R$_{r1}$ together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

[0017] each R$_{n2}$ is independently selected from H, (C$_1$-C$_8$) alkyl, (C$_2$-C$_8$)alkenyl, (C$_2$-C$_8$)alkynyl, (C$_3$-C$_7$)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_8)$haloalkyl and $(C_1\text{-}C_8)$heteroalkyl;

[0018] each R_{p2} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_8)$haloalkyl and $(C_1\text{-}C_8)$heteroalkyl;

[0019] R_{q2} and R_{r2} are each independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_8)$haloalkyl and $(C_1\text{-}C_8)$heteroalkyl, or R_{q2} and R_{r2} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

[0020] Z^2 is selected from —OR$_{s3}$—OC(O)R$_{p3}$, —OC(O)NR$_{q3}$R$_{r3}$, —SR$_{n3}$, —S(O)R$_{p3}$, —S(O)$_2$R$_{p3}$, —S(O)$_2$NR$_{q3}$R$_{r3}$, —NR$_{q3}$R$_{r3}$, —NR$_{n3}$COR$_{p3}$, —NR$_{n3}$CO$_2$R$_{p3}$, —NR$_{n3}$S(O)$_2$R$_{p3}$, —NR$_{n3}$S(O)$_2$OR$_{p3}$ and —NR$_{n3}$S(O)$_2$NR$_{q3}$R$_{r3}$;

[0021] each Z^{2a} is independently selected from $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl, heterocycle, halogen, —CN, —OR$_{n4}$, —OC(O)R$_{p4}$, —OC(O)NR$_{q4}$R$_{r4}$, —SR$_{n4}$, —S(O)R$_{p4}$, —S(O)$_2$OH, —S(O)$_2$R$_{p4}$, —S(O)$_2$NR$_{q4}$R$_{r4}$, —NR$_{q4}$R$_{r4}$, —NR$_{n4}$COR$_{p4}$, —NR$_{n4}$CO$_2$R$_{p4}$, —NR$_{n4}$CONR$_{q4}$R$_{r4}$, —NR$_{n4}$S(O)$_2$R$_{p4}$, —NR$_{n4}$S(O)$_2$OR$_{p4}$, —NR$_{n4}$S(O)$_2$NR$_{q4}$R$_{r4}$, NO$_2$, —C(O)R$_{n4}$, —C(O)OR$_{n4}$, —C(O)NR$_{q4}$R$_{r4}$, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of Z^{2a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

[0022] each Z^{2b} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$heteroalkyl and $(C_1\text{-}C_4)$haloalkyl;

[0023] each Z^{2c} is independently selected from halogen, —CN, —OR$_{n4}$, —OC(O)R$_{p4}$, —OC(O)NR$_{q4}$R$_{r4}$, —S(O)R$_{p4}$, —S(O)$_2$OH, —S(O)$_2$R$_{p4}$, (O)$_2$NR$_{q4}$R$_{r4}$, —NR$_{q4}$R$_{r4}$, —NR$_{n4}$COR$_{p4}$, —NR$_{n4}$CO$_2$R$_{p4}$, —NR$_{n4}$CONR$_{q4}$R$_{r4}$, —NR$_{n4}$S(O)$_2$R$_{p4}$, —NR$_{n4}$S(O)$_2$OR$_{p4}$, —NR$_{n4}$S(O)$_2$NR$_{q4}$R$_{r4}$, NO$_2$, —C(O)R$_{n4}$, —C(O)OR$_{n4}$, —C(O)NR$_{q4}$R$_{r4}$;

[0024] each R_{n3} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of R_{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl of R_{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups;

[0025] each R_{p3} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of R_{p3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{p3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups;

[0026] R_{q3} and R_{r3} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of R_{q3} or R_{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl and $(C_2\text{-}C_4)$alkenyl of R_{q3} or R_{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

[0027] each R_{s3} is independently selected from $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of R_{s3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl of R_{s3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R_{s3} is $(C_1\text{-}C_4)$alkyl substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups;

[0028] each R_{n4} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl;

[0029] each R_{p4} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $((C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl; and

[0030] R_{q4} and R_{r4} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl;

[0031] each Z^3 is independently selected from halogen, $(C_1\text{-}C_4)$alkyl, —OH, —CN, $(C_1\text{-}C_4)$heteroalkyl and $(C_1\text{-}C_4)$haloalkyl;

[0032] each Z^4 is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl, heterocycle, halogen, —CN, —OR$_{n5}$, —OC(O)R$_{p5}$, —OC(O)NR$_{q5}$R$_{r5}$, —SR$_{n5}$, —S(O)R$_{p5}$, —S(O)$_2$OH, (O)$_2$R$_{p5}$, —S(O)$_2$NR$_{q5}$R$_{r5}$, —NR$_{q5}$R$_{r5}$, —NR$_{q5}$COR$_{p5}$, —NR$_{n5}$CO$_2$R$_{p5}$, —NR$_{n5}$CONR$_{q5}$R$_{r5}$, —NR$_{n5}$S(O)$_2$R$_{p5}$, —NR$_{n5}$S(O)$_2$OR$_{p5}$, —NR$_{n5}$S(O)$_2$NR$_{q5}$R$_{r5}$, NO$_2$, —C(O)R$_{n5}$, —C(O)OR$_{n5}$, —C(O)NR$_{q5}$R$_{r5}$ and —B(OR$_{q5}$)(OR$_{r5}$) wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups;

[0033] each Z^{4a} is independently selected from $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl, heterocycle, halogen, —CN, —OR$_{n6}$, —OC(O)R$_{p6}$, —OC(O)NR$_{q6}$R$_{r6}$, —SR$_{n6}$, —S(O)R$_{p6}$, —S(O)$_2$OH, —S(O)$_2$R$_{p6}$, —S(O)$_2$NR$_{q6}$R$_{r6}$, —NR$_{q6}$R$_{r6}$, —NR$_{n6}$COR$_{p6}$, —NR$_{n6}$CO$_2$R$_{p6}$, —NR$_{n6}$CONR$_{q6}$R$_{r6}$, —NR$_{n6}$S(O)$_2$R$_{p6}$, —NR$_{n6}$S(O)$_2$OR$_{p6}$, —NR$_{n6}$S(O)$_2$NR$_{q6}$R$_{r6}$, NO$_2$, —C(O)R$_{n6}$, —C(O)OR$_{n6}$, and —C(O)NR$_{q6}$R$_{r6}$, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of Z^{4a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups;

[0034] each Z^{4b} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl, wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of Z^{4b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4c} groups;

[0035] each Z^{4c} is independently selected from $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl, heterocycle, halogen, —CN, —OR$_{n7}$, —OC(O)R$_{p7}$, —OC(O)NR$_{q7}$R$_{r7}$, —SR$_{n7}$, —S(O)R$_{p7}$, —S(O)$_2$OH, —S(O)$_2$R$_{p7}$, —S(O)$_2$NR$_{q7}$R$_{r7}$, —NR$_{q7}$R$_{r7}$, —NR$_{n7}$COR$_{p7}$, —NR$_{n7}$CO$_2$R$_{p7}$, —NR$_{n7}$CONR$_{q7}$R$_{r7}$, —NR$_{n7}$S(O)$_2$R$_{p7}$, —NR$_{n7}$S(O)$_2$OR$_{p7}$, —NR$_{n7}$S(O)$_2$ NR$_{q7}$R$_{r7}$, NO$_2$, —C(O)R$_{n7}$, —C(O)OR$_{n7}$, —C(O)NR$_{q7}$R$_{r7}$, haloaryl, haloheteroaryl, haloheterocycle and $(C_1\text{-}C_4)$heteroalkyl;

[0036] each Z^{4d} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, and $(C_1\text{-}C_4)$haloalkyl;

[0037] each R_{n5} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of R_{n5} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{n5} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups;

[0038] each R_{p5} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl, or heterocycle of R_{p5} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl of R_{p5} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups;

[0039] R_{q5} and R_{r5} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of R_{q5} or R_{r5} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{q5} or R_{r5} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups, or R_{q5} and R_{r5} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups;

[0040] each R_{n6} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of R_{n6} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{r6} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4c} groups;

[0041] each R_{p6} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of R_{p6} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{p6} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4c} groups;

[0042] R_{q6} and R_{r6} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and aryl, wherein any $(C_3\text{-}C_7)$carbocycle, aryl, heteroaryl and heterocycle of R_{q6} or R_{r6} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{q6} or R_{r6} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4c} groups, or R_{q6} and R_{r6} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups;

[0043] each R_{n7} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl;

[0044] each R_{p7} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl;

[0045] R_{q7} and R_{r7} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl, or R_{q7} and R_{r7} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

[0046] each Z^5 is independently selected from $(C_1\text{-}C_6)$alkyl, halogen, —CN, and $—OR_{n8}$, wherein any $(C_1\text{-}C_6)$alkyl of Z^5 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

[0047] each R_{n8} is independently selected from H, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$haloalkyl and $(C_3\text{-}C_7)$carbocycle; or a salt thereof.

[0048] One embodiment provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0049] One embodiment provides a method for treating a *Retroviridae* viral infection (e.g., an HIV viral infection) in a mammal (e.g., a human), comprising administering a compound of formula I, or a pharmaceutically acceptable salt thereof, to the mammal.

[0050] One embodiment provides a method for inhibiting the proliferation of the HIV virus, treating AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human), comprising administering a compound of formula I, or a pharmaceutically acceptable salt thereof, to the mammal.

[0051] One embodiment provides a method for treating an HIV infection in a mammal (e.g., a human), comprising administering a compound of formula I, or a pharmaceutically acceptable salt thereof, to the mammal.

[0052] One embodiment provides a method for treating an HIV infection in a mammal (e.g., a human), comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof.

[0053] One embodiment provides a compound of formula I, or a pharmaceutically acceptable salt thereof for use in medical therapy (e.g., for use in treating a *Retroviridae* viral infection (e.g., an HIV viral infection) or the proliferation of the HIV virus or AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human)).

[0054] One embodiment provides a compound of formula I, or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating a *Retroviridae* viral infection (e.g., an HIV viral infection) or the proliferation of the HIV virus or AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human).

[0055] One embodiment provides a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of the proliferation of a *Retroviridae* virus, an HIV virus or AIDS or for use in the therapeutic treatment of delaying the onset of AIDS or ARC symptoms.

[0056] One embodiment provides a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of a *Retroviridae* virus infection (e.g., an HIV virus infection).

[0057] One embodiment provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for a *Retroviridae* virus infection (e.g., an HIV virus infection) in a mammal (e.g., a human).

[0058] One embodiment provides processes and intermediates disclosed herein that are useful for preparing compounds of formula I or salts thereof.

[0059] Other embodiments, objects, features and advantages will be set forth in the detailed description of the embodiments that follows, and in part will be apparent from the description, or may be learned by practice, of the claimed invention. These objects and advantages will be realized and attained by the processes and compositions particularly pointed out in the written description and claims hereof. The foregoing Summary has been made with the understanding that it is to be considered as a brief and general synopsis of some of the embodiments disclosed herein, is provided solely for the benefit and convenience of the reader, and is not intended to limit in any manner the scope, or range of equivalents, to which the appended claims are lawfully entitled.

DETAILED DESCRIPTION

[0060] While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

DEFINITIONS

[0061] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0062] When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

[0063] "Alkyl" is a straight or branched saturated hydrocarbon. For example, an alkyl group can have 1 to 8 carbon atoms (i.e., (C_1-C_8)alkyl) or 1 to 6 carbon atoms (i.e., (C_1-C_6 alkyl) or 1 to 4 carbon atoms. Examples of suitable alkyl groups include, but are not limited to, methyl (Me, —CH_3), ethyl (Et, —CH_2CH_3), 1-propyl(n-Pr, n-propyl, —$CH_2CH_2CH_3$), 2-propyl(i-Pr, i-propyl, —$CH(CH_3)_2$), 1-butyl(n-Bu, n-butyl, —$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl(i-Bu, i-butyl, —$CH_2CH(CH_3)_2$), 2-butyl(s-Bu, s-butyl, —$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl t-butyl, —$C(CH_3)_3$), 1-pentyl (n-pentyl, —$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (—$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (—$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (—$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (—$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (—$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (—$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (—$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (—$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (—$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (—$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (—$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (—$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (—$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (—$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (—$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (—$CH(CH_3)C(CH_3)_3$, and octyl (—$(CH_2)_7CH_3$).

[0064] "Alkenyl" is a straight or branched hydrocarbon with at least one site of unsaturation, e.g., a carbon-carbon, sp^2 double bond. For example, an alkenyl group can have 2 to 8 carbon atoms (i.e., C_2-C_8 alkenyl), or 2 to 6 carbon atoms (i.e., C_2-C_6 alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl (—$CH{=}CH_2$), allyl (—$CH_2CH{=}CH_2$) and 5-hexenyl (—$CH_2CH_2CH_2CH_2CH{=}CH_2$)

[0065] "Alkynyl" is a straight or branched hydrocarbon with at least one site of unsaturation, i.e. a carbon-carbon, sp triple bond. For example, an alkynyl group can have 2 to 8 carbon atoms (i.e., C_2-C_8 alkynyl), or 2 to 6 carbon atoms (i.e., C_2-C_6 alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (—$C{\equiv}CH$), propargyl (—$CH_2C{\equiv}CH$), and the like.

[0066] The term "halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo.

[0067] The term "haloalkyl" as used herein refers to an alkyl as defined herein, wherein one or more hydrogen atoms are each replaced by a halo substituent. For example, a (C_1-C_6)haloalkyl is a (C_1-C_6)alkyl wherein one or more of the hydrogen atoms have been replaced by a halo substituent. Such a range includes one halo substituent on the alkyl group to complete halogenation of the alkyl group.

[0068] The term "heteroalkyl" as used herein refers to an alkyl as defined herein, wherein one or more of the carbon atoms of the alkyl are replaced by an O, S, or NR_q, (or if the carbon atom being replaced is a terminal carbon with an OH, SH or NR_{q2}) wherein each R_q is independently H or (C_1-C_6) alkyl.

[0069] The term "aryl" as used herein refers to a single all carbon aromatic ring or a multiple condensed all carbon ring system wherein at least one of the rings is aromatic. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Aryl includes a phenyl radical. Aryl also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) having about 9 to 20 carbon atoms in which at least one ring is aromatic and wherein the other rings may be aromatic or not aromatic (i.e., carbocycle). Such multiple condensed ring systems may be optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups on any carbocycle portion of the multiple condensed ring system. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the point of attachment of a multiple condensed ring system, as defined above, can be at any position of the ring system including an aromatic or a carbocycle portion of the ring. Typical aryl groups include, but are not limited to, phenyl, indenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracenyl, and the like.

[0070] "Arylalkyl" refers to an alkyl radical as defined herein in which one of the hydrogen atoms bonded to a carbon atom is replaced with an aryl radical as described herein (i.e., an aryl-alkyl-moiety). The alkyl group of the "arylalkyl" is typically 1 to 6 carbon atoms (i.e. aryl(C_1-C_6)alkyl). Arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 1-phenylpropan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl and the like.

[0071] The term “heteroaryl” as used herein refers to a single aromatic ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur; the term also includes multiple condensed ring systems that have at least one such aromatic ring, which multiple condensed ring systems are further described below. Thus, the term includes single aromatic rings of from about 1 to 6 carbon atoms and about 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the rings. The sulfur and nitrogen atoms may also be present in an oxidized form provided the ring is aromatic. Such rings include but are not limited to pyridyl, pyrimidinyl, oxazolyl or furyl. The term also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) wherein a heteroaryl group, as defined above, can be condensed with one or more rings selected from heteroaryls (to form for example a naphthyridinyl such as 1,8-naphthyridinyl), heterocycles, (to form for example a 1,2,3,4-tetrahydronaphthyridinyl such as 1,2,3,4-tetrahydro-1,8-naphthyridinyl), carbocycles (to form for example 5,6,7,8-tetrahydroquinolyl) and aryls (to form for example indazolyl) to form the multiple condensed ring system. Thus, a heteroaryl (a single aromatic ring or multiple condensed ring system) has about 1-20 carbon atoms and about 1-6 heteroatoms within the heteroaryl ring. Such multiple condensed ring systems may be optionally substituted with one or more (e.g., 1, 2, 3 or 4) oxo groups on the carbocycle or heterocycle portions of the condensed ring. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the individual rings of the multiple condensed ring system may be connected in any order relative to one another. It is also to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heteroaryl) can be at any position of the multiple condensed ring system including a heteroaryl, heterocycle, aryl or carbocycle portion of the multiple condensed ring system and at any suitable atom of the multiple condensed ring system including a carbon atom and heteroatom (e.g., a nitrogen). Exemplary heteroaryls include but are not limited to pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxalyl, quinazolyl, 5,6,7,8-tetrahydroisoquinolinyl benzofuranyl, benzimidazolyl, thianaphthenyl, pyrrolo[2,3-b]pyridinyl, quinazolinyl-4(3H)-one, triazolyl-4,5,6,7-tetrahydro-1H-indazole and 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole.

[0072] The term “heterocyclyl” or “heterocycle” as used herein refers to a single saturated or partially unsaturated ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur; the term also includes multiple condensed ring systems that have at least one such saturated or partially unsaturated ring, which multiple condensed ring systems are further described below. Thus, the term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6 or 7-membered rings) from about 1 to 6 carbon atoms and from about 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The ring may be substituted with one or more (e.g., 1, 2 or 3) oxo groups and the sulfur and nitrogen atoms may also be present in their oxidized forms. Such rings include but are not limited to azetidinyl, tetrahydrofuranyl or piperidinyl. The term “heterocycle” also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) wherein a single heterocycle ring (as defined above) can be condensed with one or more groups selected from heterocycles (to form for example a decahydronapthyridinyl), carbocycles (to form for example a decahydroquinolyl) and aryls to form the multiple condensed ring system. Thus, a heterocycle (a single saturated or single partially unsaturated ring or multiple condensed ring system) has about 2-20 carbon atoms and 1-6 heteroatoms within the heterocycle ring. Such multiple condensed ring systems may be optionally substituted with one or more (e.g., 1, 2, 3 or 4) oxo groups on the carbocycle or heterocycle portions of the multiple condensed ring. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the individual rings of the multiple condensed ring system may be connected in any order relative to one another. It is also to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heterocycle) can be at any position of the multiple condensed ring system including a heterocycle, aryl and carbocycle portion of the ring. It is also to be understood that the point of attachment for a heterocycle or heterocycle multiple condensed ring system can be at any suitable atom of the heterocycle or heterocycle multiple condensed ring system including a carbon atom and a heteroatom (e.g., a nitrogen). Exemplary heterocycles include, but are not limited to aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrofuranyl, dihydrooxazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,2,3,4-tetrahydroquinolyl, benzoxazinyl, dihydrooxazolyl, chromanyl, 1,2-dihydropyridinyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, spiro[cyclopropane-1,1'-isoindolinyl]-3'-one, isoindolinyl-1-one, 2-oxa-6-azaspiro[3.3]heptanyl, imidazolidin-2-one and pyrrolidin-2-one.

[0073] “Heteroarylalkyl” refers to an alkyl radical as defined herein in which one of the hydrogen atoms bonded to a carbon atom is replaced with a heteroaryl radical as described herein (i.e., a heteroaryl-alkyl-moiety). The alkyl group of the “heteroarylalkyl” is typically 1 to 6 carbon atoms (i.e. heteroaryl(C_1-C_6)alkyl). Heteroarylalkyl groups include, but are not limited to heteroaryl-CH_2—, heteroaryl-$CH(CH_3)$—, heteroaryl-CH_2CH_2—, 2-(heteroaryl)ethan-1-yl, and the like, wherein the “heteroaryl” portion includes any of the heteroaryl groups described above. One skilled in the art will also understand that the heteroaryl group can be attached to the alkyl portion of the heteroarylalkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. Examples of heteroarylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heteroaryls such as thiazolylmethyl, 2-thiazolylethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heteroaryls such pyridinylmethyl, pyridizylmethyl, pyrimidylmethyl, pyrazinylmethyl, etc.

[0074] “Heterocyclylalkyl” refers to an alkyl radical as defined herein in which one of the hydrogen atoms bonded to a carbon atom is replaced with a heterocyclyl radical as described herein (i.e., a heterocyclyl-alkyl-moiety). The alkyl group of the “heterocyclylalkyl” is typically 1 to 6 carbon atoms (i.e. heterocyclyl(C_1-C_6)alkyl). Typical heterocyclylalkyl groups include, but are not limited to heterocyclyl-CH_2—, heterocyclyl-$CH(CH_3)$—, heterocyclyl-CH_2CH_2—, 2-(heterocyclyl)ethan-1-yl, and the like, wherein the "heterocyclyl" portion includes any of the heterocyclyl groups described above. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl portion of the heterocyclyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. Examples of heterocyclylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such tetrahydrofuranylmethyl and pyrroldinylmethyl, etc., and 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, etc.

[0075] The term "carbocycle" or "carbocyclyl" refers to a single saturated (i.e., cycloalkyl) or a single partially unsaturated (e.g., cycloalkenyl, cycloalkadienyl, etc.) all carbon ring having 3 to 7 carbon atoms (i.e. (C_3-C_7)carbocycle). The term "carbocycle" or "carbocyclyl" also includes multiple condensed, saturated and partially unsaturated all carbon ring systems (e.g., ring systems comprising 2, 3 or 4 carbocyclic rings). Accordingly, carbocycle includes multicyclic carbocyles such as a bicyclic carbocycles (e.g., bicyclic carbocycles having about 6 to 12 carbon atoms such as bicyclo[3.1.0]hexane and bicyclo[2.1.1]hexane), and polycyclic carbocycles (e.g tricyclic and tetracyclic carbocycles with up to about 20 carbon atoms). The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. For example, multicyclic carbocyles can be connected to each other via a single carbon atom to form a spiro connection (e.g., spiropentane, spiro[4,5]decane, etc), via two adjacent carbon atoms to form a fused connection (e.g., carbocycles such as decahydronaphthalene, norsabinane, norcarane) or via two non-adjacent carbon atoms to form a bridged connection (e.g., norbornane, bicyclo[2.2.2]octane, etc). The "carbocycle" or "carbocyclyl" can also be optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl and 1-cyclohex-3-enyl.

[0076] "Carbocyclylalkyl" refers to an alkyl radical as defined herein in which one of the hydrogen atoms bonded to a carbon atom is replaced with a carbocyclyl radical as described herein (i.e., a carbocyclyl-alkyl-moiety). The alkyl group of the "carbocyclylalkyl" is typically 1 to 6 carbon atoms (i.e. carbocyclyl(C_1-C_6)alkyl). Typical carbocyclyl alkyl groups include, but are not limited to carbocyclyl-CH_2—, carbocyclyl-$CH(CH_3)$—, carbocyclyl-CH_2CH_2—, 2-(carbocyclyl)ethan-1-yl, and the like, wherein the "carbocyclyl" portion includes any of the carbocyclyl groups described above.

[0077] The term "haloaryl" as used herein refers to an aryl as defined herein, wherein one or more hydrogen atoms of the aryl are each replaced independently by a halo substituent. Such a range includes one halo substituent on the aryl group to complete halogenation of the aryl group.

[0078] The term "haloheteroaryl" as used herein refers to a heteroaryl as defined herein, wherein one or more hydrogen atoms of the heteroaryl are each replaced independently by a halo substituent. Such a range includes one halo substituent on the heteroaryl group to complete halogenation of the heteroaryl group.

[0079] The term "haloheterocycle" as used herein refers to a heterocycle as defined herein, wherein one or more hydrogen atoms of the heterocycle are each replaced independently by a halo substituent. Such a range includes one halo substituent on the heterocycle group to complete halogenation of the heterocycle group.

[0080] One skilled in the art will recognize that substituents and other moieties of the compounds of formula I should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of formula I which have such stability are contemplated as falling within the scope of the present invention.

[0081] The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity). The word "about" may also be represented symbolically by "~" in the context of a chemical measurement (e.g., ~50 mg or pH ~7).

[0082] The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Stereoisomers

[0083] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds* (1994) John Wiley & Sons, Inc., New York.

[0084] The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their minor image partner.

[0085] The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0086] "Diastereomer" refers to a stereoisomer with two or more centers or axes of chirality and whose molecules are not mirror images of one another. Diastereomers typically have different physical properties, e.g., melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0087] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable minor images of one another.

[0088] The compounds disclosed herein may have chiral centers, e.g., chiral carbon atoms. Such compounds thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds disclosed herein include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures can be separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. The desired optical isomer can also be synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

[0089] It is to be understood that for compounds disclosed herein when a bond is drawn in a non-stereochemical manner (e.g., flat) the atom to which the bond is attached includes all stereochemical possibilities. It is also to be understood that when a bond is drawn in a stereochemical manner (e.g., bold, bold-wedge, dashed or dashed-wedge) the atom to which the stereochemical bond is attached has the stereochemistry as shown unless otherwise noted. Accordingly, in one embodiment, a compound disclosed herein is greater than 50% a single enantiomer. In another embodiment, a compound disclosed herein is at least 80% a single enantiomer. In another embodiment, a compound disclosed herein is at least 90% a single enantiomer. In another embodiment, a compound disclosed herein is at least 98% a single enantiomer. In another embodiment, a compound disclosed herein is at least 99% a single enantiomer. In another embodiment, a compound disclosed herein is greater than 50% a single diastereomer. In another embodiment, a compound disclosed herein is at least 80% a single diastereomer. In another embodiment, a compound disclosed herein is at least 90% a single diastereomer. In another embodiment, a compound disclosed herein is at least 98% a single diastereomer. In another embodiment, a compound disclosed herein is at least 99% a single diastereomer.

Tautomers

[0090] The compounds disclosed herein can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Protecting Groups

[0091] "Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See e.g., *Protective Groups in Organic Chemistry*, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g., making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Salts and Hydrates

[0092] Examples of pharmaceutically acceptable salts of the compounds disclosed herein include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1-C_4 alkyl). Pharmaceutically acceptable salts of a nitrogen atom or an amino group include for example salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, hydrobromic, sulfuric, phosphoric and sulfamic acids. Pharmaceutically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein each X is independently selected from H or a C_1-C_4 alkyl group).

[0093] For therapeutic use, salts of active ingredients of the compounds disclosed herein will typically be pharmaceutically acceptable, i.e., they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a compound of formula I or another compound disclosed herein. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

[0094] Metal salts typically are prepared by reacting the metal hydroxide with a compound disclosed herein. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

[0095] In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, such as amines. Finally, it is to be understood that the compositions herein comprise compounds disclosed herein in their unionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

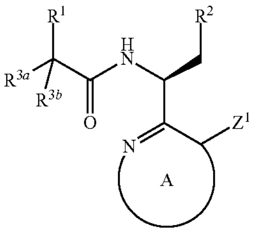
Isotopes

[0096] It is understood by one skilled in the art that this invention also includes any compound claimed that may be enriched at any or all atoms above naturally occurring isotopic ratios with one or more isotopes such as, but not limited to, deuterium (^2H or D). As a non-limiting example, a $—CH_3$ group may be substituted with $—CD_3$.

[0097] Specific values listed below for radicals, substituents, and ranges in the embodiments of the invention are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

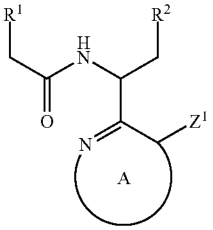
Compounds of Formula I.

[0098] A specific group of compounds of formula I are compounds of formula Ia.


Ia

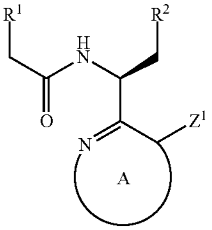
or a salt thereof.

[0099] Another specific group of compounds of formula I are compounds of formula Ib.


Ib

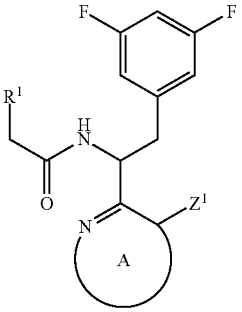
or a salt thereof.

[0100] Another specific group of compounds of formula I are compounds of formula Ic.


Ic

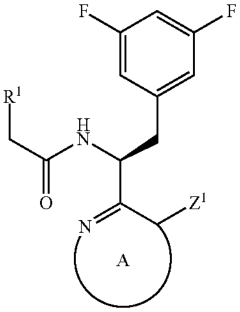
or a salt thereof.

[0101] Another specific group of compounds of formula I are compounds of formula Id.


Id

or a salt thereof.

[0102] Another specific group of compounds of formula I are compounds of formula Ie.


Ie

or a salt thereof.

[0103] Specific values listed below are values for compounds of formula I as well as all related formulas (e.g., formulas 1a, 1b, 1c, 1d, 1e).

[0104] A specific value for R^{3a} and R^{3b} is H.

[0105] A specific value for R^2 is phenyl or a 5-membered heteroaryl, wherein any phenyl or 5-membered heteroaryl of R^2 is optionally substituted with one or more Z^5 groups.

[0106] A specific value for R^2 is phenyl optionally substituted with one or more Z^5 groups.

[0107] A specific value for Z^5 is halo.

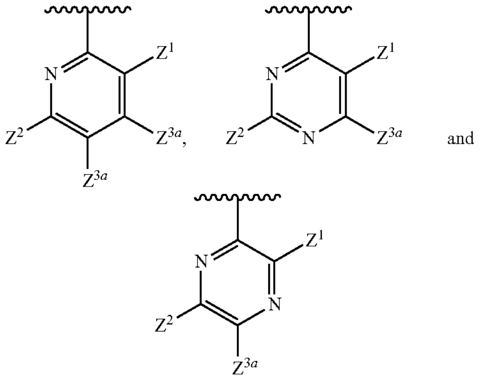
[0108] A specific value for Z^5 is fluoro.

[0109] A specific value for R^2 is 3,5-difluorophenyl.

[0110] A specific value for A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups.

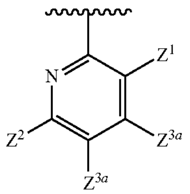
[0111] A specific value for A is pyridinyl or pyrimidinyl, wherein any pyridinyl or pyrimidinyl of A is substituted with one Z^1 group, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups.

[0112] A specific value for A is selected from:



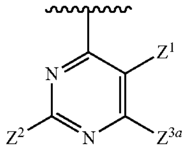
wherein each Z^{3a} is independently selected from H and Z^3.

[0113] A specific value for A is:



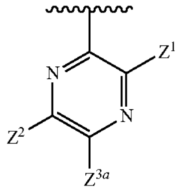
wherein each Z^{3a} is independently selected from H and Z^3.

[0114] A specific value for A is:



wherein each Z^{3a} is independently selected from H and Z^3.

[0115] A specific value for A is:



wherein each Z^{3a} is independently selected from H and Z^3.

[0116] A specific value for Z^{3a} is H.

[0117] A specific value for Z^1 is selected from phenyl, monocyclic-heteroaryl and bicyclic-heterocycle, wherein any phenyl, monocyclic-heteroaryl, and bicyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0118] A specific value for Z^1 is selected from phenyl, monocyclic-heteroaryl and bicyclic-heterocycle, wherein the monocyclic-heteroaryl and bicyclic-heterocycle have 2-12 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any phenyl, monocyclic-heteroaryl and bicyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0119] A specific value for Z^1 is selected from phenyl, monocyclic-heteroaryl and bicyclic-heterocycle, wherein the monocyclic-heteroaryl and bicyclic-heterocycle have 4-8 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any phenyl, monocyclic-heteroaryl and bicyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0120] A specific value for Z^1 is selected from phenyl, monocyclic-heteroaryl and bicyclic-heteroheterocycle, wherein the monocyclic-heteroaryl and bicyclic-heterocycle have 1-12 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any phenyl, monocyclic-heteroaryl and bicyclic-heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0121] A specific value for Z^1 is selected from phenyl, isoindolinyl-1-one and pyridinyl, wherein any phenyl, isoindolinyl-1-one and pyridinyl of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0122] A specific value for Z^1 is phenyl, wherein the phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups.

[0123] A specific value for Z^{1a} is independently selected from halogen, $—OR_{n1}$, $—S(O)_2NR_{q1}R_{r1}$, and $—C(O)NR_{q1}R_{r1}$, and each Z^{1b} is $(C_1\text{-}C_8)$alkyl, wherein any $(C_1\text{-}C_8)$alkyl of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups.

[0124] A specific value for Z^{1c} is $—OR_2$.

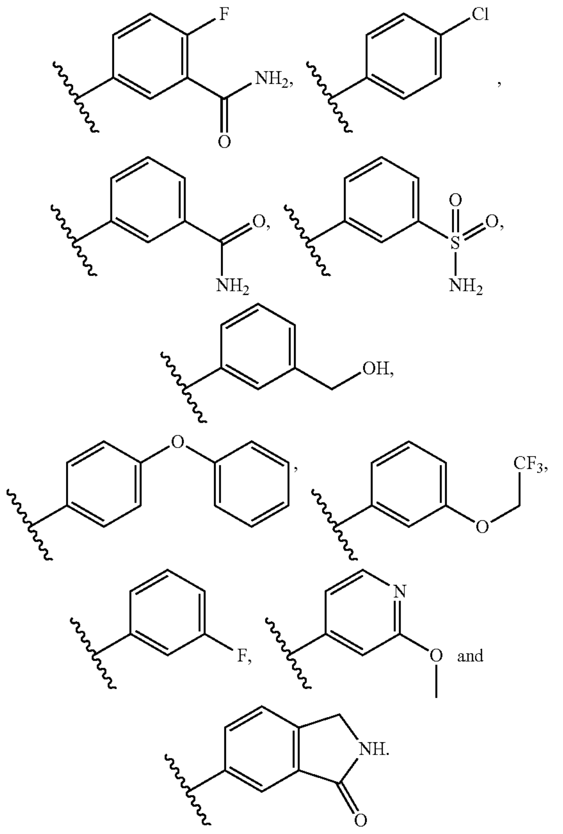
[0125] A specific group of compounds of formula I are compounds wherein R_{q1} and R_{r1} are each H, R_{n1} is phenyl or $(C_1\text{-}C_8)$alkyl wherein any $(C_1\text{-}C_8)$alkyl of R_{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen, and R_{n2} is H.

[0126] A specific value for each R_{q1} and R_{r1} is H.

[0127] A specific value for R_{n1} is phenyl or $(C_1\text{-}C_8)$alkyl wherein any $(C_1\text{-}C_8)$alkyl of R_{n1} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) halogen.

[0128] A specific value for R_{n2} is H.

[0129] A specific value for Z^1 is selected from:



[0130] A specific value for Z^2 is selected from $—OC(O)R_{p3}$ and $—NR_{q3}R_{r3}$.

[0131] A specific value for Z^2 is $—OC(O)R_{p3}$.

[0132] A specific value for R_{p3} is $(C_1\text{-}C_4)$alkyl, wherein any $(C_1\text{-}C_4)$alkyl, is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups.

[0133] A specific value for R_{p3} is $(C_1\text{-}C_4)$alkyl.

[0134] A specific value for Z^2 is —$NR_{q3}R_{r3}$.

[0135] A specific group of compounds of formula I are compounds wherein R_{q3} and R_{r3} are each independently selected from H, $(C_1\text{-}C_4)$alkyl and heterocycle, wherein any heterocycle of R_{q3} or R_{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl of R_{q3} or R_{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups.

[0136] A specific group of compounds of formula I are compounds wherein R_{q3} and R_{r3} are each independently selected from H, $(C_1\text{-}C_4)$alkyl and monocyclic heterocycle, wherein any monocyclic heterocycle of R_{q3} or R_{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl of R_{q3} or R_{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a monocyclic heterocycle, bicyclic heterocycle or monocyclic heteroaryl, wherein the monocyclic heterocycle, bicyclic heterocycle or monocyclic heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups.

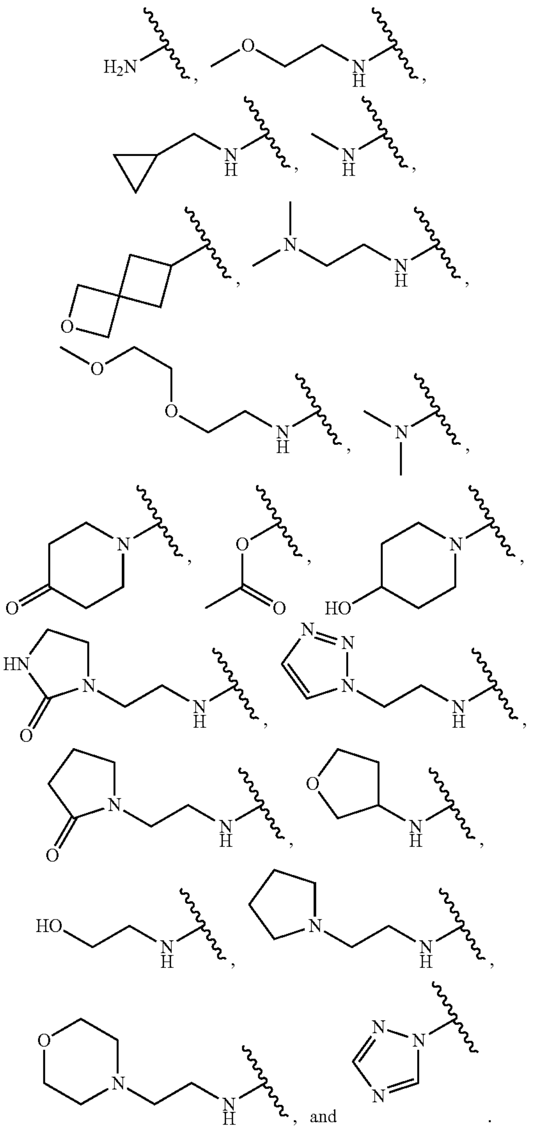
[0137] A specific group of compounds of formula I are compounds wherein R_{q3} and R_{r3} are each independently selected from H, $(C_1\text{-}C_4)$alkyl and monocyclic heterocycle, wherein the monocyclic heterocycle has 1-5 carbon atoms and 1-4 heteroatoms in the ring system, wherein any monocyclic heterocycle of R_{q3} or R_{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl of R_{q3} or R_{r43} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a monocyclic heterocycle, bicyclic heterocycle or monocyclic heteroaryl, wherein the monocyclic-heteroaryl, bicyclic-heteroaryl and bicyclic-heterocycle have 1-8 carbon atoms and 1-4 heteroatoms in the ring system and wherein the monocyclic heterocycle, bicyclic heterocycle or monocyclic heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups.

[0138] A specific value for each Z^{2a} is independently selected from $(C_3\text{-}C_7)$carbocycle, monocyclic heteroaryl, monocyclic heterocycle, —OR_{n4}, and —$NR_{q4}R_{r4}$, wherein any $(C_3\text{-}C_7)$carbocycle, heteroaryl and heterocycle of Z^{2a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups.

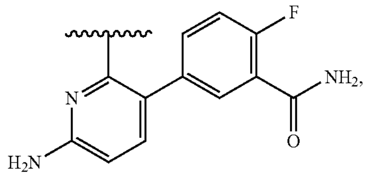
[0139] A specific group of compounds of formula I are compounds wherein each Z^{ea} is independently selected from $(C_3\text{-}C_7)$carbocycle, monocyclic heteroaryl, monocyclic heterocycle, —OR_{n4}, and —$NR_{q4}R_{r4}$, wherein the monocyclic heteroaryl and monocyclic heterocycle have 1-5 carbon atoms and 1-4 heteroatoms in the ring system, wherein any $(C_3\text{-}C_7)$carbocycle, heteroaryl and heterocycle of Z^{2a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein each Z^2c is —OR_{n4}.

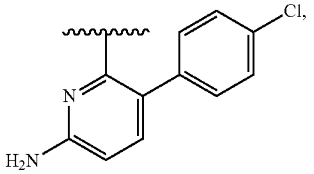
[0140] A specific group of compounds of formula I are compounds wherein each R_{r4} is independently selected from H, $(C_1\text{-}C_4)$alkyl, and $(C_1\text{-}C_4)$heteroalkyl, and wherein R_{q4} and R_{r4} are each $(C_1\text{-}C_4)$alkyl.

[0141] A specific value for Z^2 is selected from:



[0142] A specific value for A is selected from:





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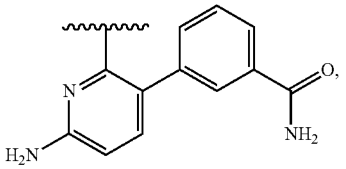

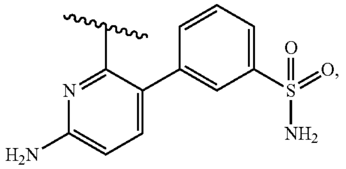

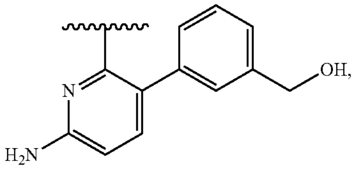

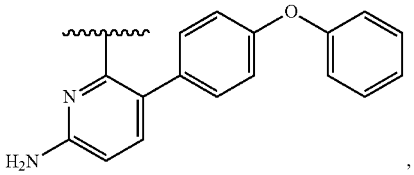

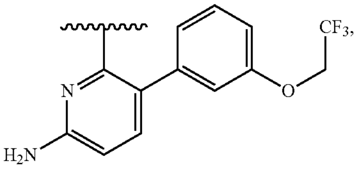

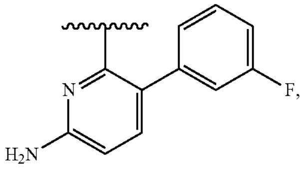

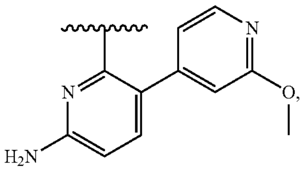

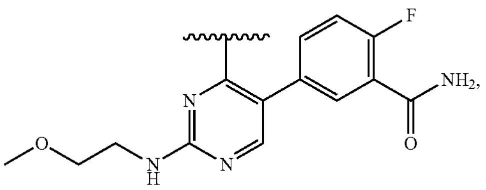

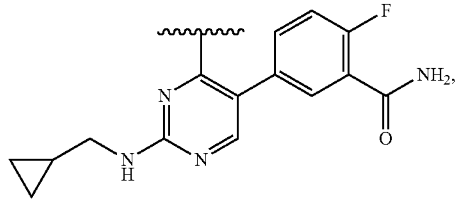

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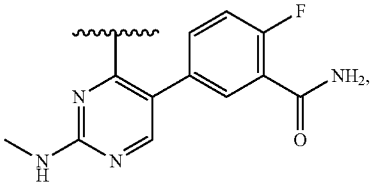

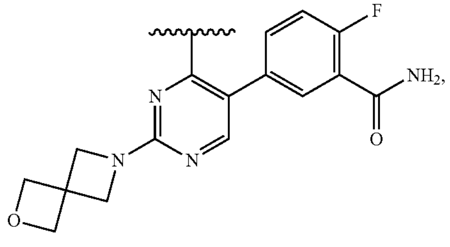

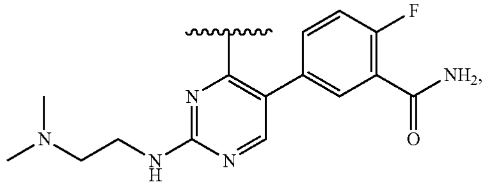

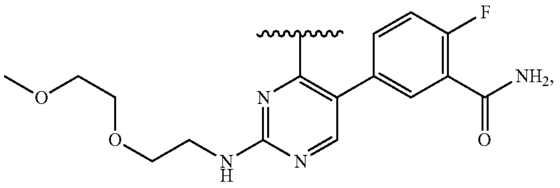

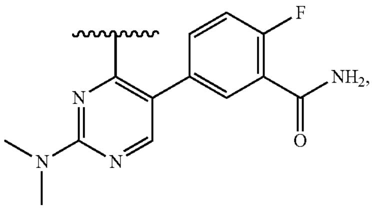

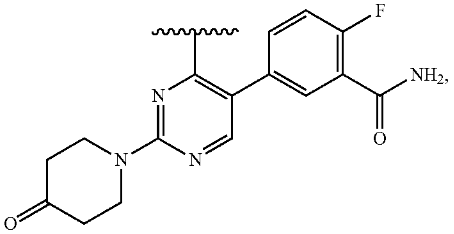

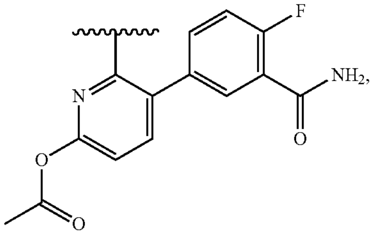

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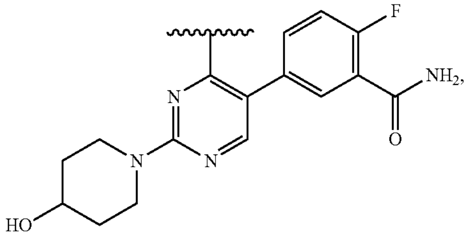

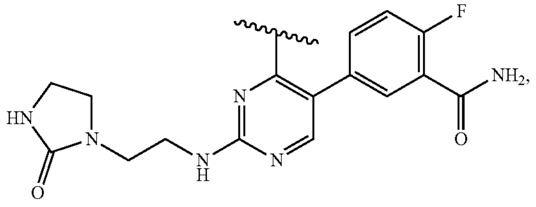

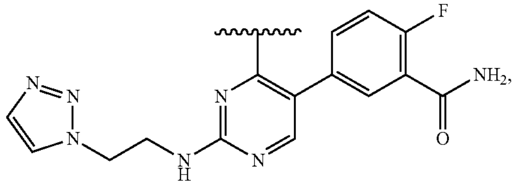

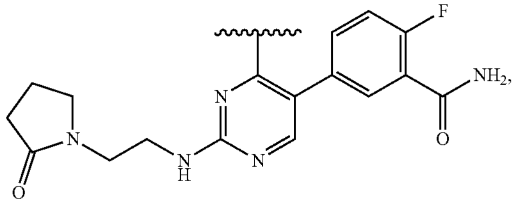

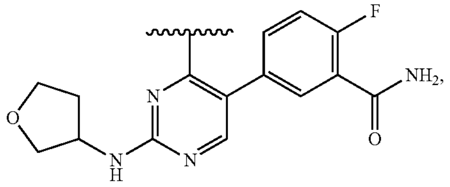

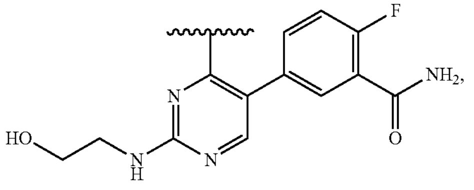

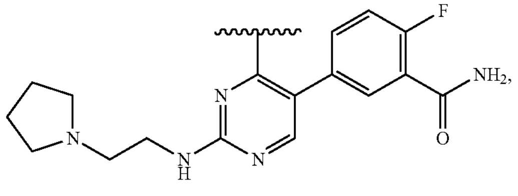

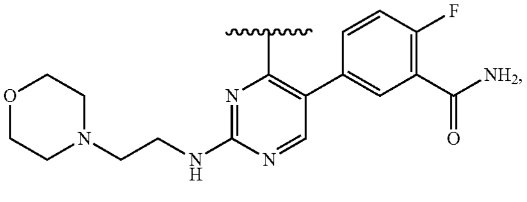

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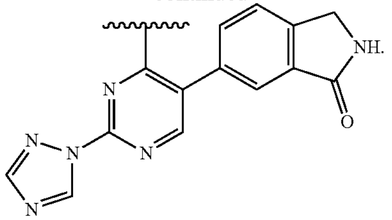


[0143] A specific value for R^1 is a heteroaryl, wherein any heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0144] A specific value for R^1 is a bicyclic-heteroaryl, wherein any bicyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0145] A specific value for R^1 is a bicyclic-heteroaryl or tricyclic-heteroaryl, wherein any bicyclic-heteroaryl or tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0146] A specific value for R^1 is a bicyclic-heteroaryl, wherein the bicyclic-heteroaryl of R^1 contains at least one partially unsaturated ring, and wherein any bicyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0147] A specific value for R^1 is a bicyclic-heteroaryl or tricyclic-heteroaryl, wherein the bicyclic-heteroaryl or tricyclic-heteroaryl of R^1 contains at least one partially unsaturated ring, and wherein any bicyclic-heteroaryl or tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0148] A specific value for R^1 is a bicyclic-heteroaryl, wherein the bicyclic-heteroaryl has 4-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any bicyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0149] A specific value for R^1 is a bicyclic-heteroaryl or tricyclic-heteroaryl, wherein the bicyclic-heteroaryl or tricyclic-heteroaryl has 4-9 carbon atoms and 1-5 heteroatoms in the ring system, and wherein any bicyclic-heteroaryl or tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0150] A specific value for R^1 is a bicyclic-heteroaryl, wherein the bicyclic-heteroaryl has 6-9 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any bicyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0151] A specific value for R^1 is a bicyclic-heteroaryl or tricyclic-heteroaryl, wherein the bicyclic-heteroaryl or tricyclic-heteroaryl has 6-9 carbon atoms and 1-3 heteroatoms in the ring system, and wherein any bicyclic-heteroaryl or tricyclic-heteroaryl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0152] A specific value for R^1 is selected from indolyl and 4,5,6,7-tetrahydro-indazolyl, wherein any indolyl and 4,5,6,7-tetrahydro-indazolyl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0153] A specific value for R^1 is selected from indolyl, 4,5,6,7-tetrahydro-indazolyl, 3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole and 1,4,5,5a,6,6a-hexahydrocyclopropa[g]indazole, wherein any indolyl, 4,5,6,7-tetrahydro-indazolyl, 3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole and 1,4,5,5a,6,6ahexahydrocyclopropa[g]indazole of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0154] A specific value for R^1 is selected from indol-3-yl and 4,5,6,7-tetrahydro-1H-indazol-1-yl, wherein any indol-3-yl and 4,5,6,7-tetrahydro-1H-indazol-1-yl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

[0155] A specific value for R^1 is selected from indol-3-yl, 4,5,6,7-tetrahydro-1H-indazol-1-yl, 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 1,4,5,5a,6,6a-hexahydrocyclopropa[g]indazol-1-yl, wherein any indol-3-yl, 4,5,6,7-tetrahydro-1H-indazol-1-yl, 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl and 1,4,5,5a,6,6a-hexahydrocyclopropa[g]indazol-1-yl of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups.

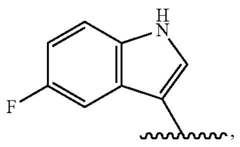
[0156] A specific value for each Z^4 is independently selected from $(C_1\text{-}C_6)$alkyl and halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen.

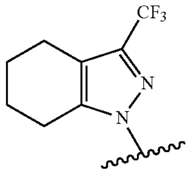
[0157] A specific value for each Z^4 is independently selected from $(C_1\text{-}C_6)$alkyl, —CN and halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen.

[0158] A specific value for each Z^4 is independently selected from fluoro, trifluoromethyl and difluoromethyl.

[0159] A specific value for each Z^4 is independently selected from fluoro, trifluoromethyl, —CN and difluoromethyl.

[0160] A specific value for R^1 is selected from:





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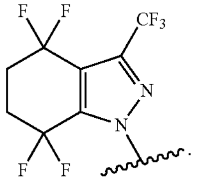
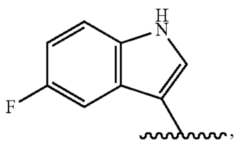
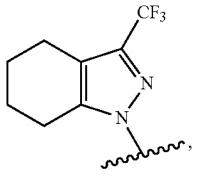


[0161] A specific value for R^1 is selected from:





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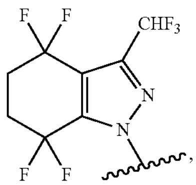

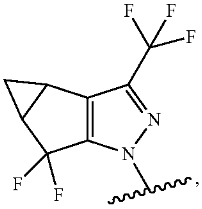

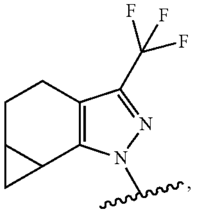

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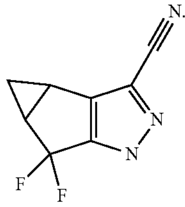
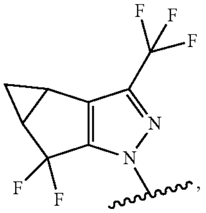
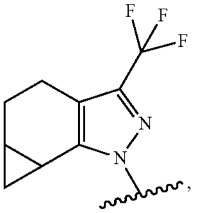


[0162] A specific value for R^1 is selected from:





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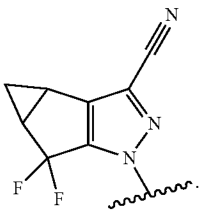
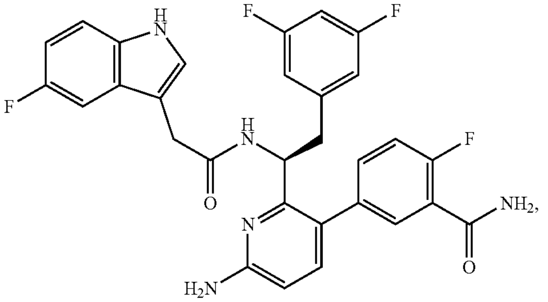


[0163] In one embodiment the compound of formula I is selected from:



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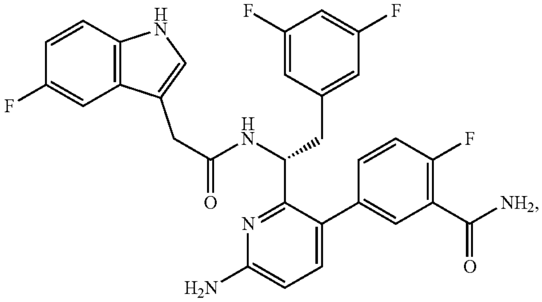

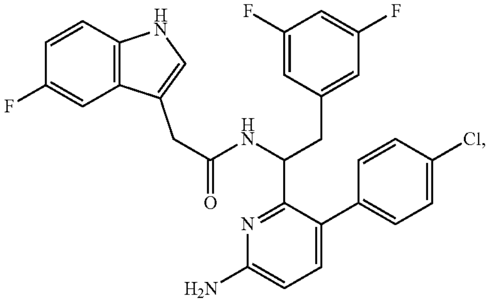

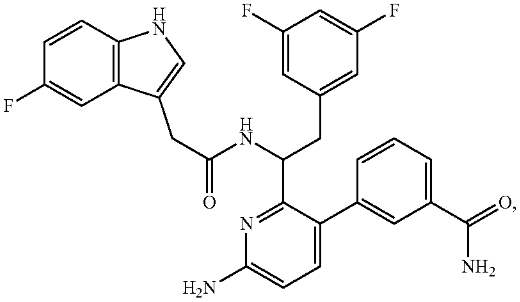

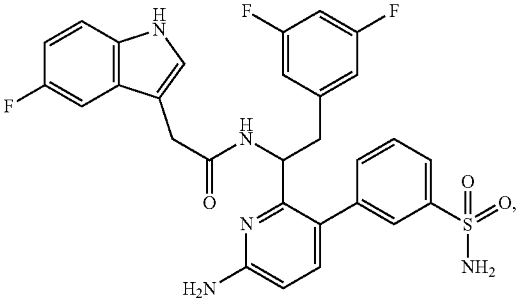

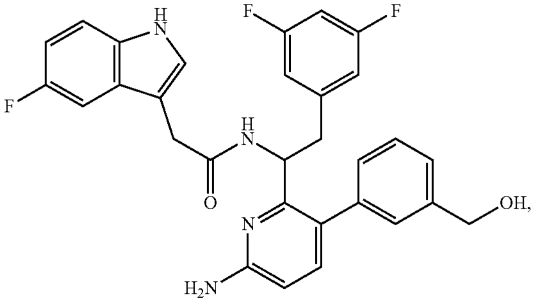

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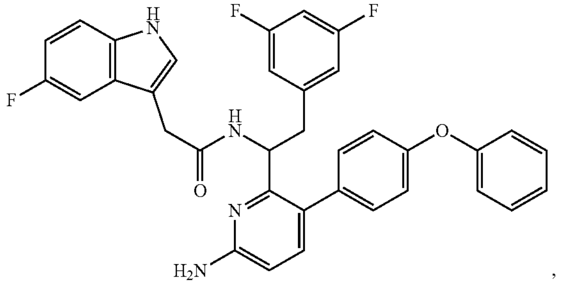

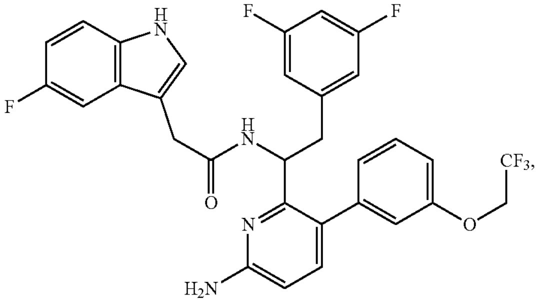

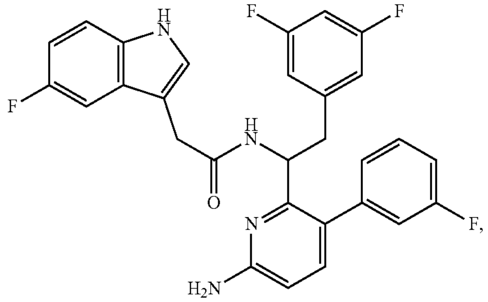

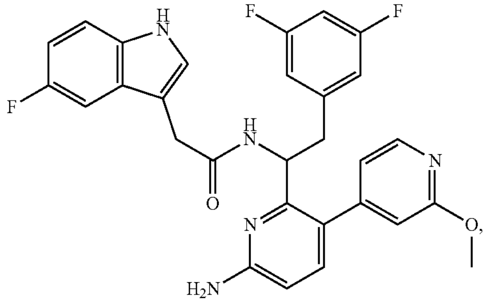

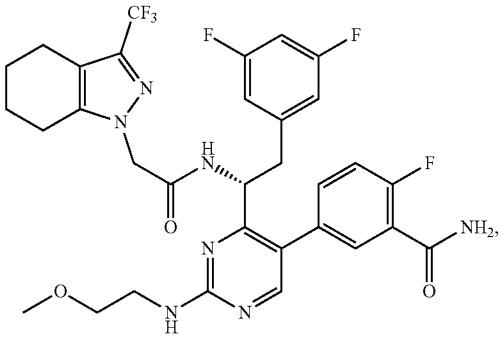

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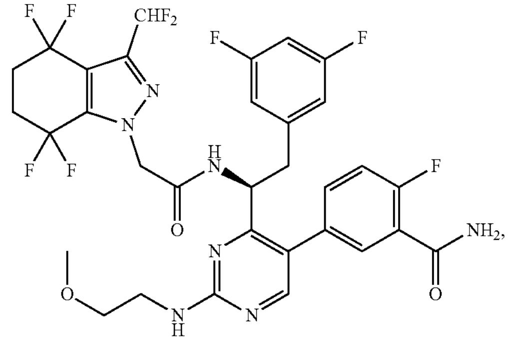

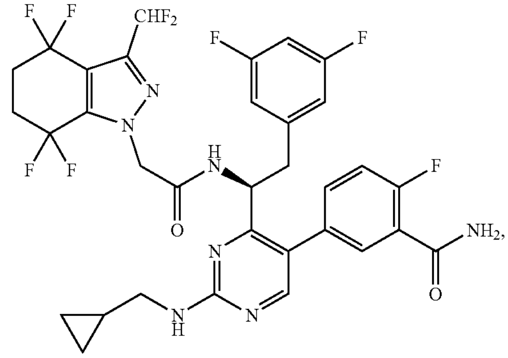

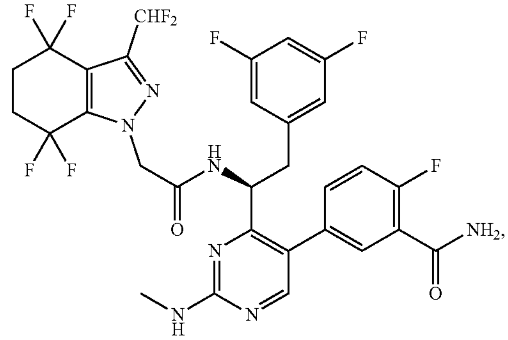

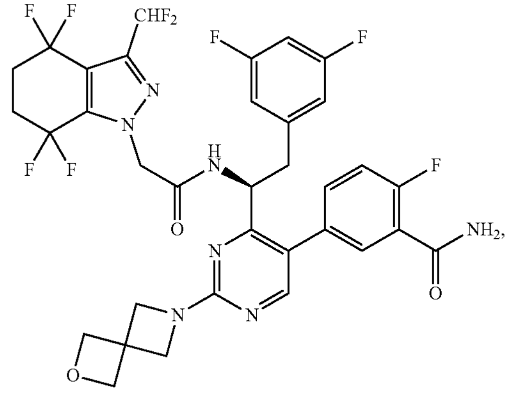

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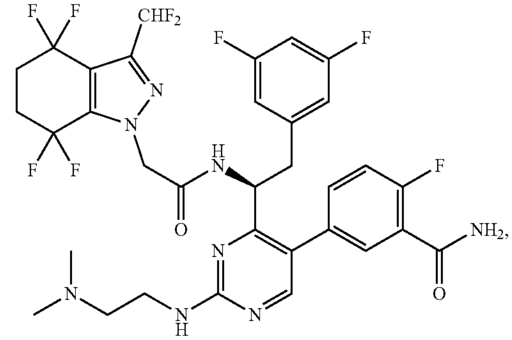

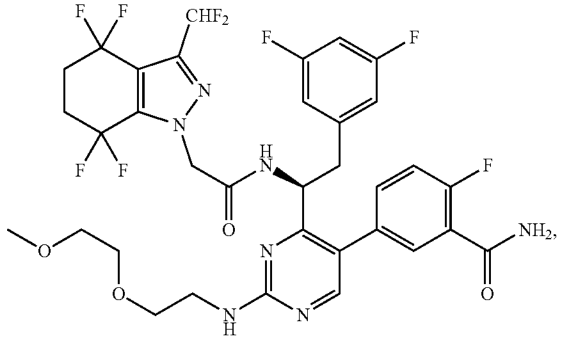

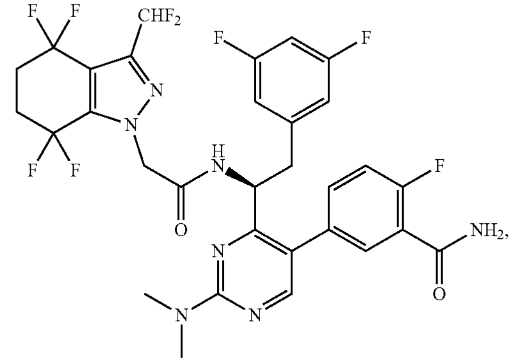

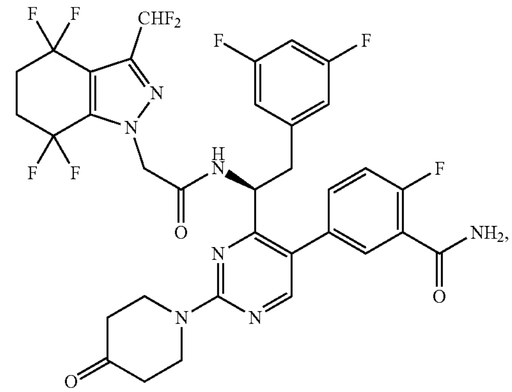

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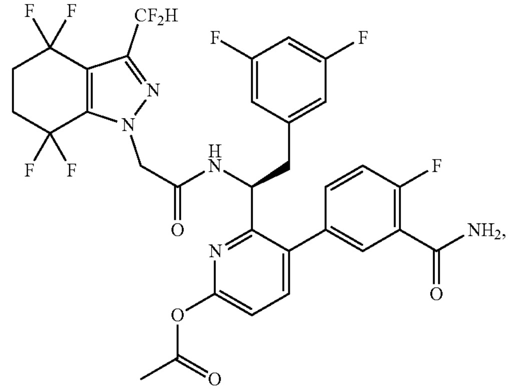

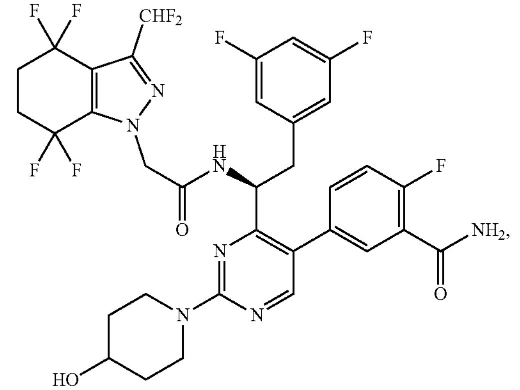

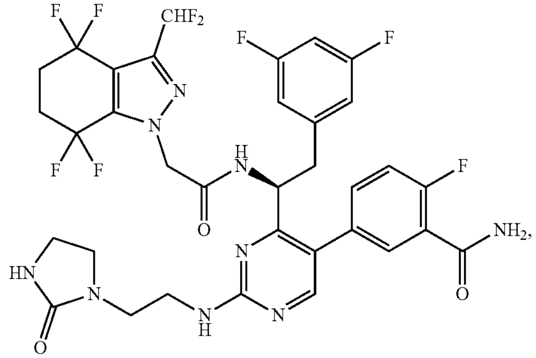

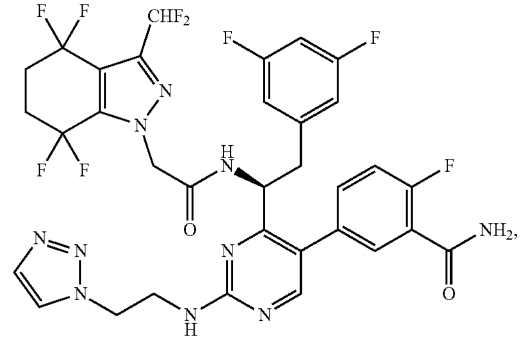

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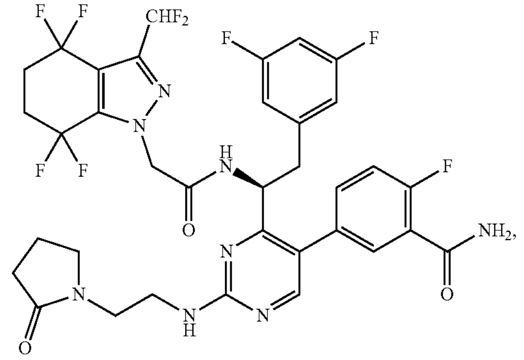

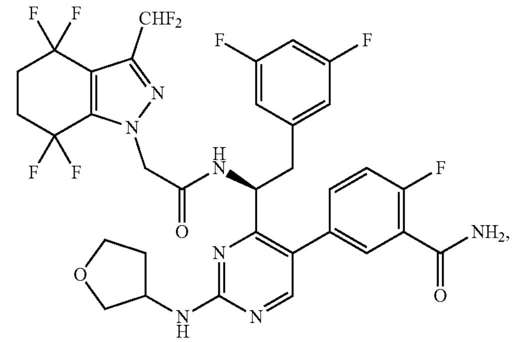

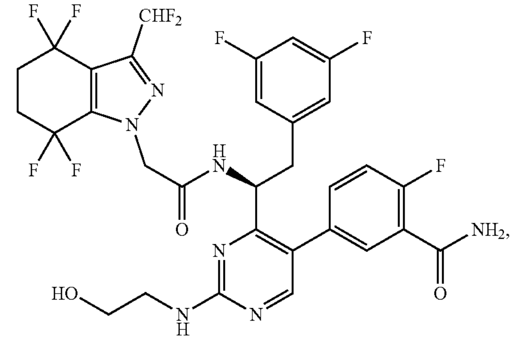

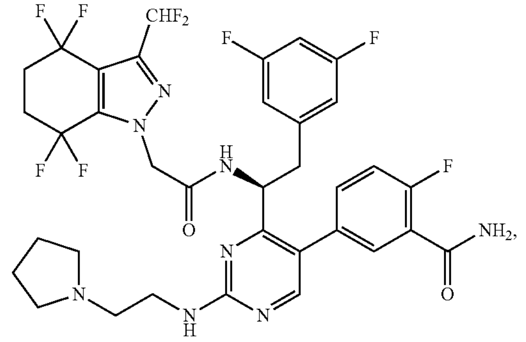

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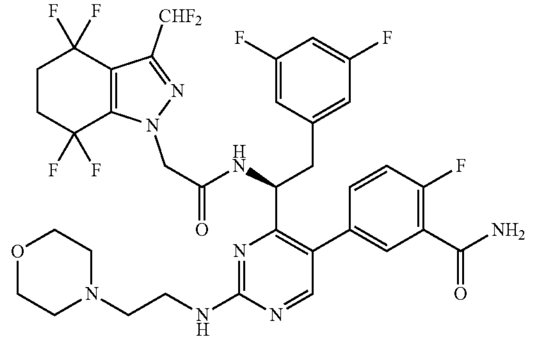

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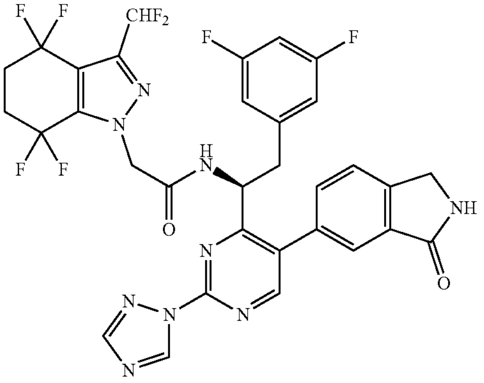
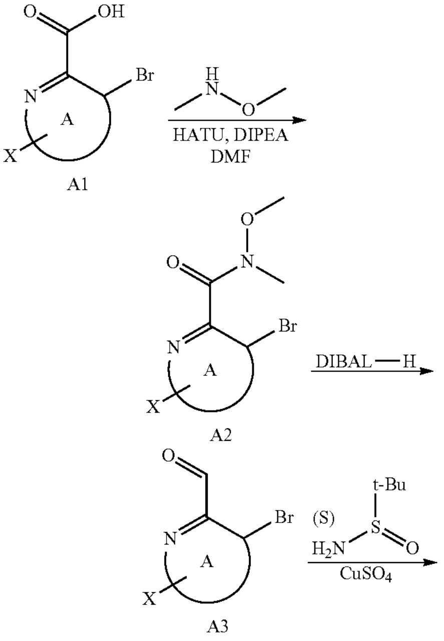


and salts thereof.

General Synthetic Procedures

[0164] The following scheme describes methods that are useful for preparing compounds of formula I.

Scheme 1



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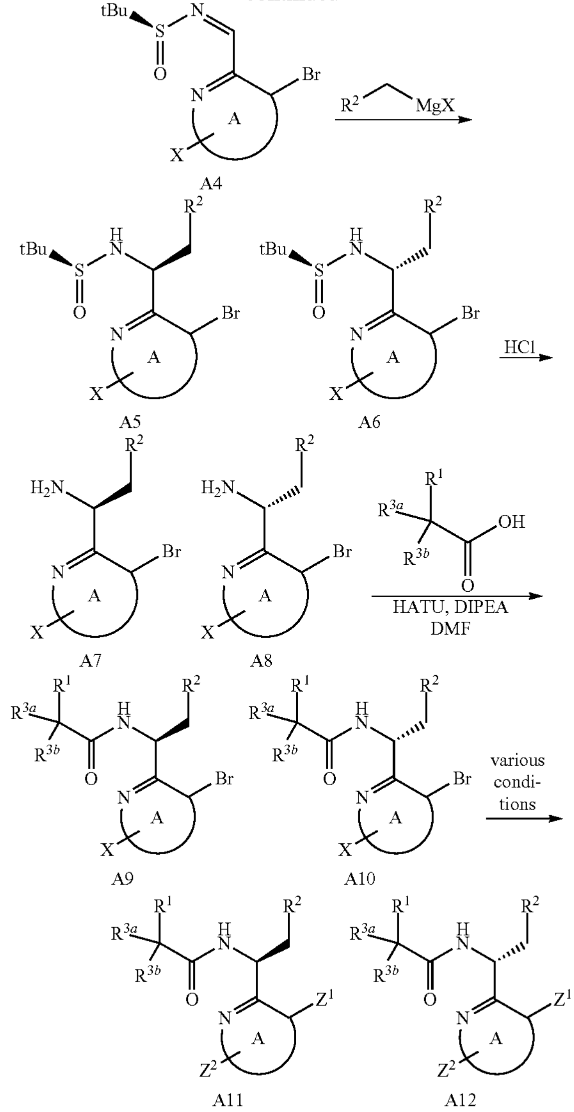


[0165] Scheme 1 describes a general stereoselective route which can be used to prepare compounds of formula I. Heteroaryl acids of formula A1 (where X represents diversifiable chemical group such as NH_2, SH, or halogen that may be suitably protected) can be converted to the corresponding aldehydes then condensed with a chiral auxiliary to provide a stereoselective addition of a nucleophilic reagent. Depicted in Scheme 1 is the conversion of a heteroaryl acid A1 containing two diversifiable functional groups to the corresponding aldehyde. This is followed by the condensation of the aldehyde A3 with (S) tert-butane sulfonamide and the addition of a Grignard reagent to provide a mixture of A5 and A6 enriched in A5. This mixture may be separated by column chromatography on silica gel to provide pure diastereomers. Removal of the auxiliary provides amines A7 and A8 which can be coupled to a variety of carboxylic acids to provide heteroaryl compounds of formula A9 and A10. Diversification of A9 and A10 may be accomplished by a variety of methods including alkylation, acylation, cyanation, nucleophilic aromatic displacement, and metal catalyzed cross coupling reactions such as Suzuki couplings, Buchwald-Hartwig type couplings, and Sonogashira couplings.

Combination Therapy

[0166] In one embodiment, the invention provides a method for treating an HIV infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0167] In one embodiment, the invention provides pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier. For example, the therapeutic agent used in combination with the compound disclosed herein can be any anti-HIV agent.

[0168] One embodiment provides pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drug for treating HIV, and combinations thereof, and a pharmaceutically acceptable carrier.

[0169] One embodiment provides pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent selected from the group consisting of:

[0170] (1) HIV protease inhibiting compounds selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

[0171] (2) HIV non-nucleoside inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MW-150, and TMC-120, rilpivirene, BILR 355 BS, VRX 840773, UK-453061, RDEA806 and KM023;

[0172] (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003);

[0173] (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix);

[0174] (5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810, raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, GS-5696, elvitegravir and dolutegravir;

[0175] (6) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, FB006M, and TRI-1144;

[0176] (7) the CXCR4 inhibitor AMD-070;

[0177] (8) the entry inhibitor SP01A;

[0178] (9) the gp120 inhibitor BMS-488043;

[0179] (10) the G6PD and NADH-oxidase inhibitor immunitin;

[0180] (11) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5 mAb004;

[0181] (12) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040).

[0182] In some embodiments, one or more of the compounds disclosed herein are combined with one or more other active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0183] In some embodiments, one or more of the compounds disclosed herein are co-administered with one or more other active therapeutic agents. Co-administration of a compound disclosed herein with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more other active therapeutic agents, such that therapeutically effective amounts of disclosed herein and one or more other active therapeutic agents are both present in the body of the patient.

[0184] In yet another embodiment, the present application provides a method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents such as those disclosed above.

Pharmaceutical Formulations

[0185] The compounds disclosed herein are formulated with conventional carriers (e.g., inactive ingredient or excipient material) which will be selected in accord with ordinary practice. Tablets will contain excipients including glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the *Handbook of Pharmaceutical Excipients* (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. One embodiment provides the formulation as a solid dosage form including a solid oral dosage form. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

[0186] While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations (compositions). The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

[0187] The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, Pa.). Such methods include the step of bringing into association the active ingredient with inactive ingredients (e.g., a carrier, pharmaceutical excipients, etc.) which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0188] Formulations of the present invention suitable for oral administration may be presented as discrete units including but not limited to capsules, cachets or tablets each containing a predetermined amount of the active ingredient.

[0189] Pharmaceutical formulations according to the present invention comprise one or more compounds disclosed herein together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0190] The amount of active ingredient that is combined with the inactive ingredients to produce a dosage form will vary depending upon the host treated and the particular mode of administration. For example, in some embodiments, a dosage form for oral administration to humans contains approximately 1 to 1000 mg of active material formulated with an appropriate and convenient amount of carrier material (e.g., inactive ingredient or excipient material). In certain embodiments, the carrier material varies from about 5 to about 95% of the total compositions (weight:weight).

[0191] It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0192] The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier.

[0193] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

[0194] Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

Routes of Administration

[0195] One or more compounds disclosed herein (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds disclosed herein is that they are orally bioavailable and can be dosed orally.

[0196] The antiviral properties of a compound of the invention may be determined using Test A described below.

Test A: Antiviral Assay in MT4 Cells

[0197] For the antiviral assay, 40 μL of 1× test concentration of 3-fold serially diluted compound in culture medium with 10% FBS was added to each well of a 384-well plate (10 concentrations) in quadruplicate. MT-4 cells were next mixed with HIV-IIIb at an m.o.i of 0.003 for 1 hour, after which time 35 μL of virus/cell mixture (2000 cells) was immediately added to each well containing 40 μL of diluted compound. The plates were then incubated at 37° C. for 5 days. After 5 days of incubation, 25 μl of 2× concentrated CellTiter-Glo™ Reagent (catalog #G7571, Promega Biosciences, Inc., Madison, Wis.) was added to each well containing MT-4 cells. Cell lysis was carried out by incubating at room temperature for 10 min and then chemiluminescence was read. EC50 values were defined as the compound concentration that caused a 50% decrease in luminescence signal, a measure of HIV-1 replication. Percent inhibition of virus-induced cell killing calculated from the dose response curve at 3 μM drug concentration is shown in the table below.

Test B: Cytotoxicity Assay

[0198] Compound cytotoxicity and the corresponding CC50 values was determined using the same protocol as described in the antiviral assay (Test A) except that uninfected cells were used.

[0199] Compounds of the present invention demonstrate antiviral activity (Test A) as depicted in the table below. Shown below are the corresponding values for CC50 and percent inhibition of virus-induced cell killing in the presence of 3 μM drug concentration.

Compound	% inhibition at 3 μM	CC50 (nM)
1H	98	22082
2	0	25239
3	87	9337
4	94	13074
5	87	28652
6	59	14439
7	37	11466
8	50	11677
9	41	17525
10	38	23835
11J	0	16271
12E	86	18198
13B	42	7722
14B	89	28633
15B	70	36296
16B	41	15417
17B	83	48760
18B	16	38913
19C	26	>51513
20B	1	>53192
21	41	22526
22B	93	34113
23F	77	32713
24	79	37217
25	69	37675
26	86	19885
27	n.d.	3500
28	81	14089
29D	101	39974

(n.d.—not determined)

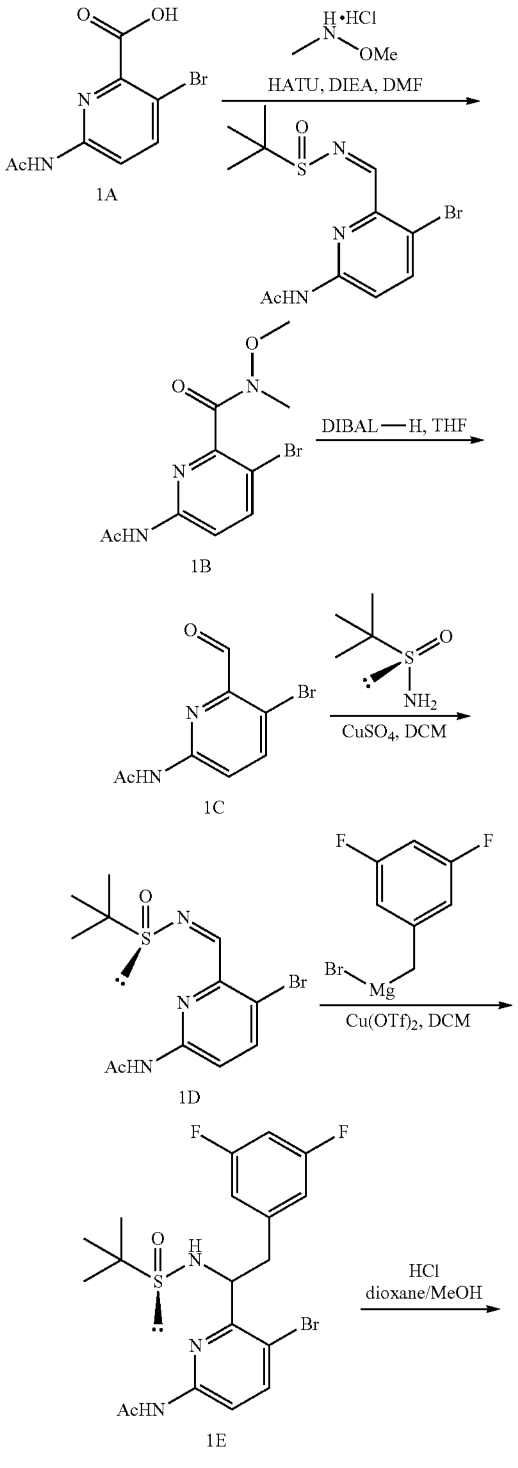
[0200] In one embodiment, the compounds demonstrate >10% inhibition at 3 μM. In one embodiment, the compounds demonstrate >30% inhibition at 3 μM. In one embodiment, the compounds demonstrate >50% inhibition at 3 μM. In one embodiment, the compounds demonstrate >70% inhibition at 3 μM. It is to be understood that the compounds disclosed herein can be grouped according to their % inhibition as described above.

[0201] The specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present invention.

[0202] The Examples provided herein describe the synthesis of compounds disclosed herein as well as intermediates used to prepare the compounds. It is to be understood that individual steps described herein may be combined. It is also to be understood that separate batches of a compound may be combined and then carried forth in the next synthetic step.

Example 1 and 2

[0203]



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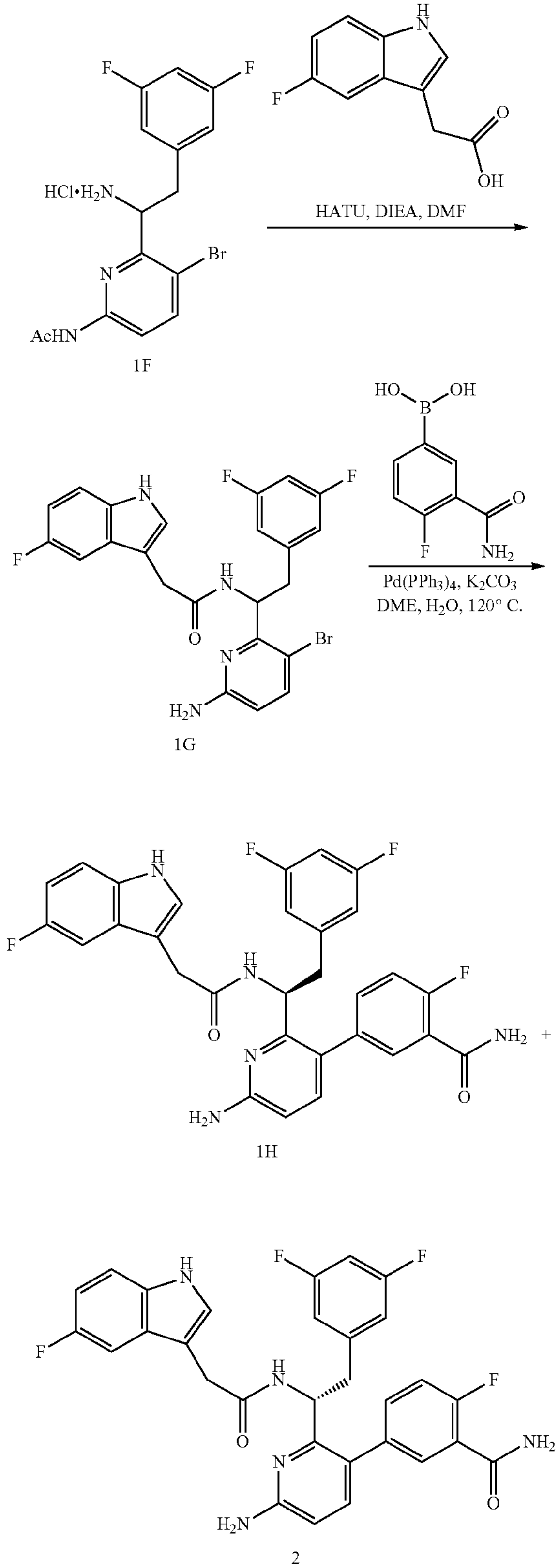


Synthesis of 6-acetamido-3-bromo-N-methoxy-N-methylpicolinamide (1B)

[0204] HATU (4.56 g, 12.0 mmol) was added to a solution of 6-acetamido-3-bromopicolinic acid (2.6 g, 10.0 mmol) and DIPEA (5.2 ml, 30 mmol) in DCM (10 ml). After 10 minutes, N,O-dimethylhydroxylamine hydrochloride (1.5 g, 15.0 mmol) was added to the reaction. The reaction was stirred at room temperature for 5 min. The reaction mixture was partitioned between EtOAc and saturated NH_4Cl solution. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was used in the next step without further purification. MS (m/z) 302.1 $[M+H]^+$. ^1H NMR (400 MHz, cd3cl) δ 8.14 (s, 1H), 8.13 (d, J=8.4 Hz, 1H), 7.85 (d, J=8.4 Hz, 1H), 3.56 (s, 3H), 3.37 (s, 3H), 2.20 (s, 3H).

Synthesis of N-(5-bromo-6-formylpyridin-2-yl)acetamide (1C)

[0205] To the crude material from last step (1B, 2.6 g, 8.6 mmol) in THF (30 mL) was added DIBAL-H (13 mmol, 1.5 equiv) dropwise at −70° C. The reaction was stirred for 1 h and was then quenched with NH_4Cl solution. The reaction mixture was partitioned between EtOAc and saturated NH_4Cl solution. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was used in the next step without further purification. MS (m/z) 244.1 $[M+H]^+$.

Synthesis of (S)—N-(5-bromo-6-(((tert-butylsulfinyl)imino)methyl)pyridin-2-yl)acetamide (1D)

[0206] Copper(II) sulfate (anhydrous 2.8 g, 17.2 mmol) was added to a solution of N-(5-bromo-6-formylpyridin-2-yl)acetamide (crude material, assume 8.6 mmol) and (S)-2-methylpropane-2-sulfinamide (1.2 g, 9.4 mmol) in DCM (30 ml). The suspension was stirred overnight at room temperature. The reaction was filtered and washed with DCM (3×20 ml). The filtrate was concentrated. The crude product was purified by flash column (30% EtOAc/Hexanes). MS (m/z) 346.1 $[M+H]^+$.

Synthesis of (S)—N-(5-bromo-6-(2-(3,5-difluorophenyl)-1-(1,1-dimethylethylsulfinamido)ethyl)pyridin-2-yl)acetamide (1E)

[0207] (3,5-Difluorobenzyl)magnesium bromide (0.25 M in ether, 10 ml, 2.5 mmol) was added dropwise to a solution of (S)—N-(5-bromo-6-(((tert-butylsulfinyl)imino)methyl)pyridin-2-yl)acetamide (1D, 0.47 g, 1.36 mmol) in DCM (5 ml) at −78° C. The reaction was stirred for 3 h at −78° C. Ammonium chloride (aq, 10 mL) was added to the reaction and the mixture was allowed to warm to r.t. The mixture was extracted with EtOAc (2×30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product contained a mixture of diastereomers which were used in the next step without further purification. MS (m/z) 474.1 $[M+H]^+$.

Synthesis of N-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-bromopyridin-2-yl)acetamide hydrochloride (1F)

[0208] (S)—N-(5-Bromo-6-(2-(3,5-difluorophenyl)-1-(1,1-dimethylethylsulfinamido)ethyl)pyridin-2-yl)acetamide

(1E, crude material from last step) was treated with a mixture of 2 ml of 1.25 M HCl in MeOH/1 ml of 4 M HCl in dioxane for 1 hour. The solvent was removed in vacuo. The crude material was used without further purification. MS (m/z) 369.9 $[M+H]^+$.

Synthesis of N-(1-(6-amino-3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (1G)

[0209] HATU (741 mg, 1.95 mmol) was added to a solution of 2-(5-fluoro-1H-indol-3-yl)acetic acid (251 mg, 1.3 mmol) and DIPEA (1.2 mL, 6.5 mmol) in DMF (5 mL). After 10 minutes, N-(6-(1-amino-2-(3,5-difluorophenyl)ethyl)-5-bromopyridin-2-yl)acetamide hydrochloride (1F, 480 mg, 1.3 mmol) in 2 mL of DMF was added. The reaction was stirred for 1 h at room temperature. The DMF solution was filtered and purified by RP HPLC using a C18 column and a gradient of 20% B to 85% B over 25 minutes (A=0.1% TFA/H_2O, B=0.1% TFA/acetonitrile) to provide the desired product (acetyl group was removed during reverse phase purification). ^1H NMR (400 MHz, $cdcl_3$) δ 8.14 (s, 1H), 7.71 (d, J=9.2 Hz, 1H), 7.52 (d, J=8.6 Hz, 1H), 7.26 (m, 3H), 7.16 (s, 1H), 6.89 (t, J=8.6 Hz, 2H), 6.64-6.46 (m, 4H), 5.62 (d, J=8.1 Hz, 1H), 3.59 (s, 2H), 3.01-2.90 (m, 2H). MS (m/z) 502.5 $[M+H]^+$.

Synthesis of (S)-5-(6-amino-2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (1H) and (R)-5-(6-amino-2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (2)

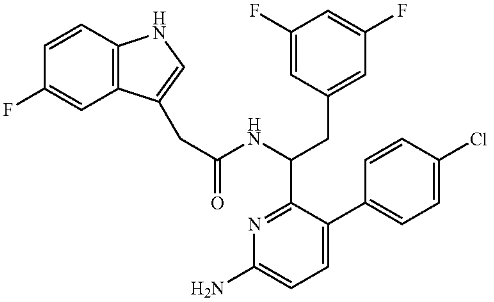
[0210] A suspension of N-(1-(6-amino-3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (1G, 30 mg, 0.06 mmol), potassium carbonate (0.06 mL, 2M in water), (3-carbamoyl-4-fluorophenyl)boronic acid (13 mg, 0.072 mmol) and tetrakis(triphenylphosphine) palladium (1.0 mg, 0.0009 mmol) in DME (1.0 mL) was degassed for 30 minutes. The mixture was submitted to microwave heating at 120° C. for 30 min. The reaction was cooled and filtered through celite. The filtrate was extracted with EtOAc (2×10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by reverse phase HPLC to give a mixture of enantiomers. MS (m/z) 562.4 $[M+H]^+$. ^1H NMR (400 MHz, $cdcl_3$) δ 8.08 (s, 1H), 7.71 (d, J=7.9 Hz, 2H), 7.62 (s, 1H), 7.45 (d, J=9.2 Hz, 1H), 7.28-7.15 (m, 3H), 7.10 (s, 1H), 6.91 (s, 1H), 6.82 (t, J=8.4 Hz, 2H), 6.58 (d, J=9.0 Hz, 1H), 6.52-6.40 (m, 2H), 6.22-6.05 (m, 3H), 5.16 (d, J=8.1 Hz, 1H), 3.52 (s, 2H), 3.01-2.87 (m, 1H), 2.83-2.78 (m, 1H).

[0211] The mixture of enantiomers were separated by chiral chromatography (Chiralcel AZ-H, Heptane:IPA 70:30) to gave (S)-5-(6-amino-2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (1H, slow eluting peak) and (R)-5-(6-amino-2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (2, fast eluting peak).

Example 3

[0212]

3



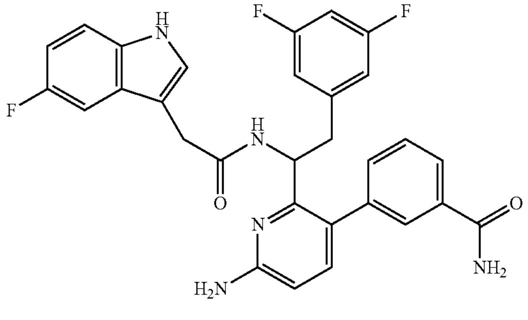
Synthesis of N-(1-(6-amino-3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (3)

[0213] The title compound was prepared according to the method presented for the synthesis of compound 1H of Example 1 utilizing 1G and 4-chlorophenyl boronic acid. ^1H NMR (400 MHz, $cdcl_3$) δ 8.17 (s, 1H), 7.63 (d, J=8.1 Hz, 1H), 7.52 (d, J=9.0 Hz, 1H), 7.45 (d, J=8.5 Hz, 2H), 7.31-7.23 (m, 6H), 7.19 (s, 1H), 6.89 (t, J=10.0 Hz, 2H), 6.65 (d, J=8.9 Hz, 1H), 6.52 (t, J=8.9 Hz, 1H), 6.26 (d, J=5.9 Hz, 2H), 5.27 (dd, J=16.5, 8.2 Hz, 1H), 3.61 (s, 2H), 3.00 (dd, J=13.6, 9.3 Hz, 1H), 2.85 (dd, J=13.7, 7.5 Hz, 1H). MS (m/z) 535.4 $[M+H]^+$.

Example 4

[0214]

4



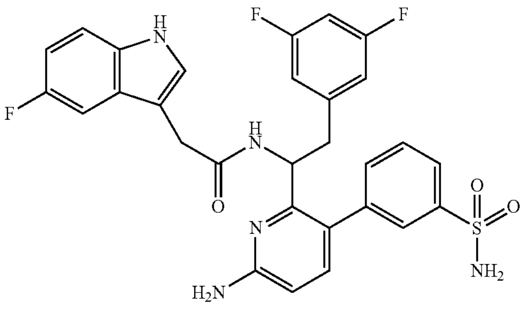
Synthesis of 3-(6-amino-2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (4)

[0215] The title compound was prepared according to the method presented for the synthesis of compound 1H of Example 1 utilizing 1G and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide. ^1H NMR (400 MHz, $cdcl_3$) δ 8.06-7.95 (m, 4H), 7.50-7.38 (m, 2H), 7.26-7.20 (m, 1H), 7.13 (m, 1H), 6.89-6.81 (m, 3H), 6.60 (d, J=8.9 Hz, 1H), 6.50-6.39 (m, 2H), 6.07 (d, J=5.8 Hz, 2H), 5.43 (d, J=8.8 Hz, 1H), 3.59 (s, 2H), 2.88 (dd, J=13.6, 9.3 Hz, 1H), 2.76 (dd, J=13.7, 7.5 Hz, 1H). MS (m/z) 535.4 $[M+H]^+$.

Example 5

[0216]

5



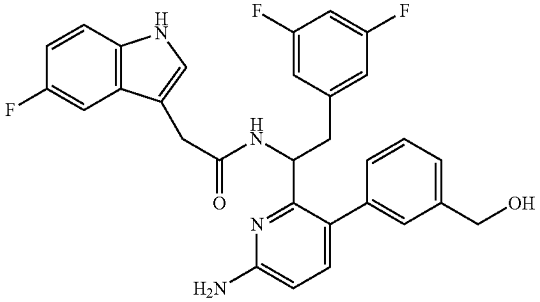
Synthesis of N-(1-(6-amino-3-(3-sulfamoylphenyl) pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (5)

[0217] The title compound was prepared according to the method presented for the synthesis of compound 1H of Example 1 utilizing 1G and (3-sulfamoylphenyl)boronic acid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.15 (s, 1H), 8.03 (d, J=7.7 Hz, 1H), 7.96 (s, 2H), 7.91 (m, 1H), 7.57 (m, 3H), 7.24 (m, 1H), 6.92 (d, J=9.3 Hz, 2H), 6.70 (d, J=8.7 Hz, 1H), 6.54 (s, 1H), 6.20 (d, J=5.7 Hz, 2H), 5.54 (s, 2H), 5.33 (d, J=9.0 Hz, 1H), 3.63 (s, 2H), 2.99-2.85 (m, 2H). MS (m/z) 580.0 [M+H]$^+$.

Example 6

[0218]

6



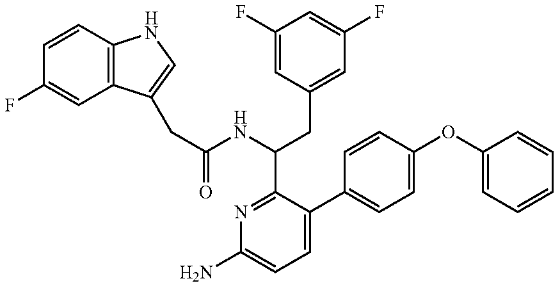
Synthesis of N-(1-(6-amino-3-(3-(hydroxymethyl) phenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (6)

[0219] The title compound was prepared according to the method presented for the synthesis of compound 1H of Example 1 utilizing 1G and (3-(hydroxymethyl)phenyl)boronic acid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.09 (s, 1H), 7.65 (d, J=8.9 Hz, 1H), 7.52 (d, J=9.1 Hz, 1H), 7.42-7.38 (m, 2H), 7.38-7.16 (m, 1H), 7.11 (s, 1H), 7.02 (s, 1H), 6.81 (d, J=9.5 Hz, 2H), 6.58 (d, J=8.8 Hz, 1H), 6.43 (s, 1H), 6.17 (m, 2H), 5.35-5.24 (m, 1H), 4.71 (s, 2H), 3.53 (s, 2H), 2.96-2.84 (m, 1H), 2.81 (d, J=7.1 Hz, 1H). MS (m/z) 531.2 [M+H]$^+$.

Example 7

[0220]

7



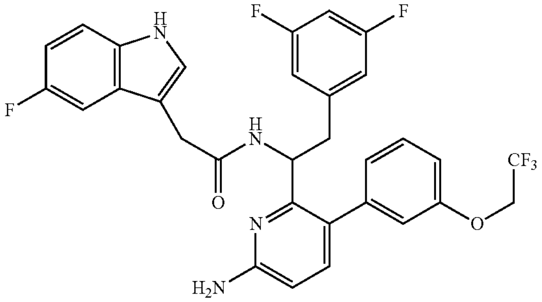
Synthesis of N-(1-(6-amino-3-(4-phenoxyphenyl) pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (7)

[0221] The title compound was prepared according to the method presented for the synthesis of compound 1H of Example 1 utilizing 1G and (4-phenoxyphenyl)boronic acid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.03 (s, 1H), 7.65 (d, J=7.8 Hz, 1H), 7.49 (d, J=9.0 Hz, 1H), 7.32 (t, J=7.8 Hz, 2H), 7.29-7.18 (m, 1H), 7.10 (m, 2H), 7.01 (m, 5H), 6.82 (t, J=9.1 Hz, 4H), 6.56 (d, J=8.9 Hz, 1H), 6.43 (s, 1H), 6.19 (d, J=6.4 Hz, 2H), 5.30 (d, J=8.0 Hz, 1H), 3.52 (s, 2H), 2.97-2.85 (m, 1H), 2.75 (dd, J=14.0, 6.9 Hz, 1H). MS (m/z) 592.8 [M+H]$^+$.

Example 8

[0222]

8



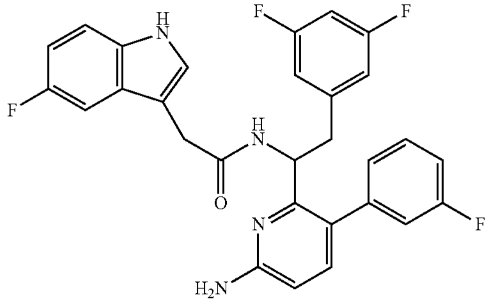
Synthesis of N-(1-(6-amino-3-(3-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-yl)-2-(3,5-difluorophenyl) ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (8)

[0223] The title compound was prepared according to the method presented for the synthesis of compound 1H of Example 1 utilizing 1G and (3-(2,2,2-trifluoroethyl)phenyl) boronic acid. ^{1}H NMR (400 MHz, dmso) δ 10.96 (s, 1H), 7.61-7.55 (m, 3H), 7.30 (dd, J=8.7, 4.6 Hz, 2H), 7.26-7.11 (m, 2H), 7.11-6.95 (m, 4H), 6.87 (t, J=9.4 Hz, 1H), 6.47 (m, 2H), 5.02 (d, J=6.6 Hz, 1H), 4.79-4.61 (m, 2H), 2.91 (m, 2H). MS (m/z) 599.2 $[M+H]^+$.

Example 9

[0224]

9



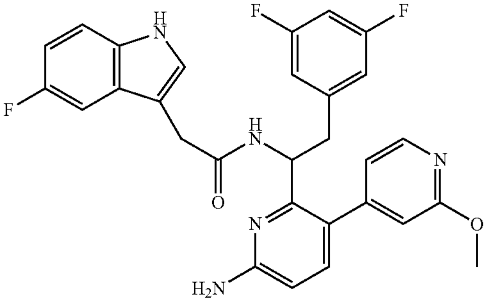
Synthesis of N-(1-(6-amino-3-(3-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (9)

[0225] The title compound was prepared according to the method presented for the synthesis of compound 1H of Example 1 utilizing 1G and (3-fluorophenyl)boronic acid. ^1H NMR (400 MHz, dmso) δ 10.95 (s, 1H), 8.42 (s, 1H), 7.63-7.32 (m, 3H), 7.32-7.26 (m, 2H), 7.17 (dd, J=22.4, 9.7 Hz, 3H), 6.98-6.81 (m, 4H), 6.47 (d, J=6.7 Hz, 2H), 5.03 (d, J=6.8 Hz, 1H), 2.98-2.82 (m, 2H). MS (m/z) 519.4 $[M+H]^+$.

Example 10

[0226]

10

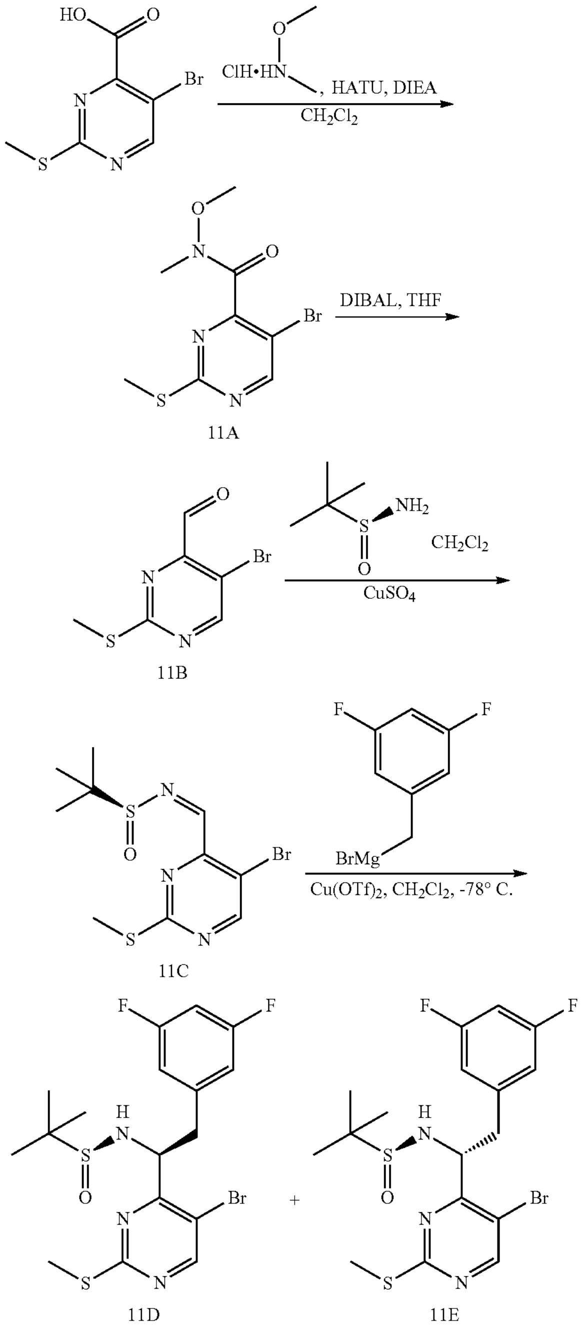


Synthesis of N-(1-(6-amino-2'-methoxy-[3,4'-bipyridin]-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (10)

[0227] The title compound was prepared according to the method presented for the synthesis of compound 1H of Example 1 utilizing 1G and (2-methoxypyridin-4-yl)boronic acid. ^1H NMR (400 MHz, dmso) δ 10.89 (s, 1H), 7.96 (d, J=5.2 Hz, 1H), 7.25 (dd, J=8.9, 4.3 Hz, 2H), 7.14-7.10 (m, 3H), 6.88-6.80 (m, 3H), 6.67 (d, J=5.2 Hz, 1H), 6.45-6.38 (m, 5H), 5.00 (d, J=7.3 Hz, 1H), 3.75 (s, 2H), 2.89 (m, 2H). MS (m/z) 532.4 $[M+H]^+$.

Example 11

[0228]



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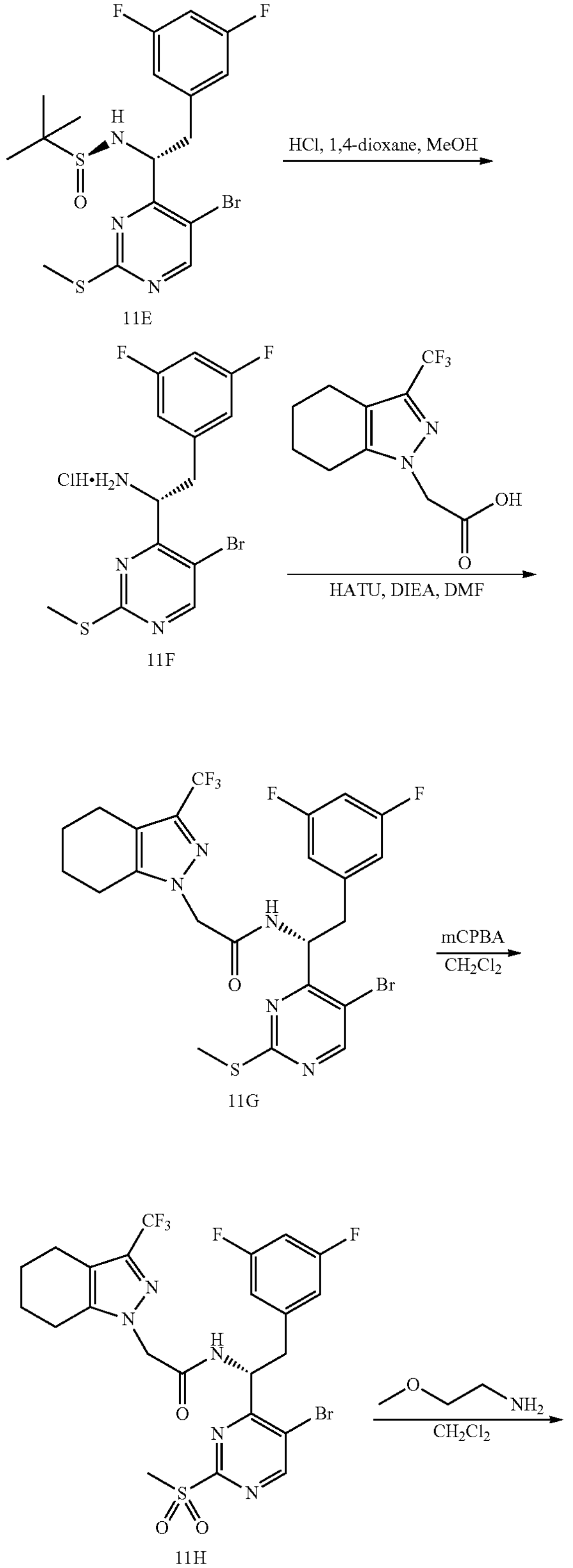

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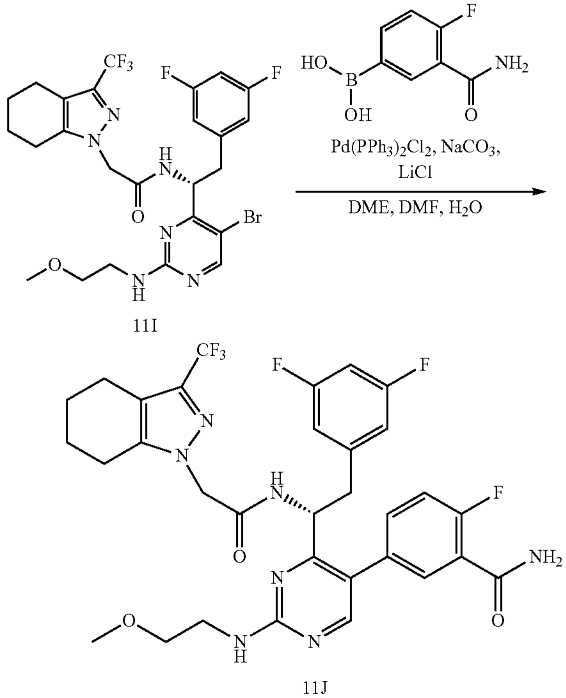


Synthesis of 5-bromo-N-methoxy-N-methyl-2-(methylthio)pyrimidine-4-carboxamide (11A)

[0229] The title compound (11A) was prepared according to the method presented for the synthesis of compound IB of Example 1 utilizing 5-bromo-2-(methylthio)pyrimidine-4-carboxylic acid. MS (m/z) 292.16 [M+H]$^+$.

Synthesis of 5-bromo-2-(methylthio)pyrimidine-4-carbaldehyde (11B)

[0230] A solution of 5-bromo-N-methoxy-N-methyl-2-(methylthio)pyrimidine-4-carboxamide (11A, 8.2 g, 28 mmol) in THF (120 mL) was added dropwise to a suspension of lithium aluminum hydride (1.06 G, 28 mmol) and THF (120 mL) at −78° C. The mixture was stirred for 10 minutes after addition finish. H_2O (1.06 mL), 15% aqueous NaOH solution (1.06 mL) and H_2O (3.18 mL) were successively added to the mixture at 0° C. very slowly. The resulting precipitate was filtered and washed with THF. The filtrate was concentrated in vacuo to afford crude of the title compound. MS (m/z): 233.14, [M+H]$^+$.

Synthesis of (S)—N-((5-bromo-2-(methylthio)pyrimidin-4-yl)methylene)-2-methylpropane-2-sulfinamide (11C)

[0231] The title compound (11C) was prepared according to the method presented for the synthesis of compound ID of Example 1 utilizing 11B. MS (m/z) 337.7 [M+H]$^+$.

Synthesis of (S)—N—((R)-1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (11E)

[0232] To a solution of (S)—N-((5-bromo-2-(methylthio)pyrimidin-4-yl)methylene)-2-methylpropane-2-sulfinamide

(11C, 2.97 g. 8.8 mmol) in THF (18 mL) cooled to −78° C. was drop wise added 3,5-Difluorobenzylmagnesium bromide (53 mL, 0.25 M in Ether, 13.3 mmol). After stirring at −78° C. for 10 min, NH_4Cl (sat. aq.) (10 ml) was added to the reaction and warmed up to ambient temperature. Extracted with EtOAc and the organic layer was dried with Na_2SO_4(s). The solvent was removed and the residue was purified by flash column to yield the title compound (11E) and (S)—N—((S)-1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (11D). MS (m/z) 465.87 [M+H]+

Synthesis of (R)-1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride (11F)

[0233] The title compound (11F) was prepared according to the method presented for the synthesis of compound IF of Example 1 utilizing 11E. MS (m/z) 361.66 $[M+H]^+$.

Synthesis of ((R)—N-(1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (11G)

[0234] 2-(3-(Trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (124 mg, 0.5 mmol) and 11F (200 mg, 0.5 mmol) were dissolved in 3 mL of DMF and cooled down to 0° C. To it were added N,N-diisopropylethylamine (435 μL, 2.5 mmol) and HATU (228 mg, 0.6 mmol). The reaction mixture was stirred at 0° C. for 5 minutes, and then partitioned between EtOAc and 5% LiCl aqueous solution. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in methylene chloride and to it added hexanes. The precipitate was collected by vacuum filtration and dried under high vacuum overnight to afford the title compound 11G. MS (m/z) 592.25 $[M+H]^+$.

Synthesis of (R)—N-(1-(5-bromo-2-(methylsulfonyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (11H)

[0235] Compound 11G (198 mg, 0.33 mmol) was charged in dichloromethane (2 ml) at 0° C. MCPBA (185 mg, 0.8 mmol, content 77 percent; 2.5 eq.) was added a little at a time. The mixture was slowly warmed to room temperature and stirred for 4 h and then water was added. The reaction mixture was partitioned between dichloromethane and saturated $NaHCO_3$ aqueous solution. The organic layer was separated and concentrated to afford the title product. MS (m/z) 622.98 $[M+H]^+$.

Synthesis of (R)—N-(1-(5-bromo-2-((2-methoxyethyl)amino)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (11I)

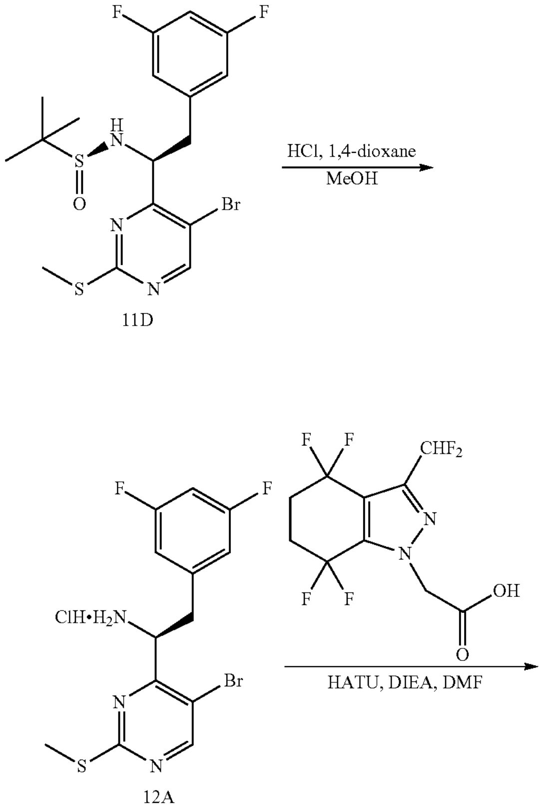
[0236] 2-Methoxyethylamine (0.086 ml, 1 mmol) was added at room temperature to a solution of compound 11H (62 mg, 0.1 mmol) in dichloromethane (5 mL). Stirring was continued at 45° C. for overnight. The solvent was evaporated and the crude product was purified by silica gel chromatography using an ethyl acetate/hexanes eluent to yield the title compound. MS (m/z) 618.00 $[M+H]^+$.

Synthesis of (R)-5-(4-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)-2-((2-methoxyethyl)amino)pyrimidin-5-yl)-2-fluorobenzamide (11J)

[0237] In a microwave tube were charged with compound 11I (29 mg, 0.1 mmol), (3-carbamoyl-4-fluorophenyl)boronic acid (27 mg, 0.15 mmol), LiCl (13 mg, 0.3 mmol), Na_2CO_3 (17 mg, 0.2 mmol), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol). To the mixture was added 2 mL of DME/DMF/H_2O (4/1/1). The mixture was heated up to 150° C. for 30 min in a Microwave Synthesizer. After cooled down and filtered through a syringe filter, purified on reverse phase HPLC eluting with acetonitrile and water (with 0.1% TFA) to afford the title product. ^1H NMR (400 MHz, cd_3od) δ 8.61 (d, J=8.0 Hz, 1H), 8.07 (s, 1H), 7.48 (dd, J=6.9, 2.3 Hz, 1H), 7.40-7.33 (m, 1H), 7.22 (dd, J=10.7, 8.5 Hz, 1H), 6.70 (t, J=9.2 Hz, 1H), 6.45 (d, J=6.2 Hz, 2H), 5.24 (q, J=7.5 Hz, 1H), 4.76 (s, 2H), 3.85-3.56 (m, 4H), 3.41 (s, 3H), 3.01 (ddd, J=29.2, 13.3, 7.4 Hz, 2H), 2.63-2.34 (m, 4H), 1.88-1.60 (m, 4H). MS (m/z) 676.46 $[M+H]^+$.

Example 12

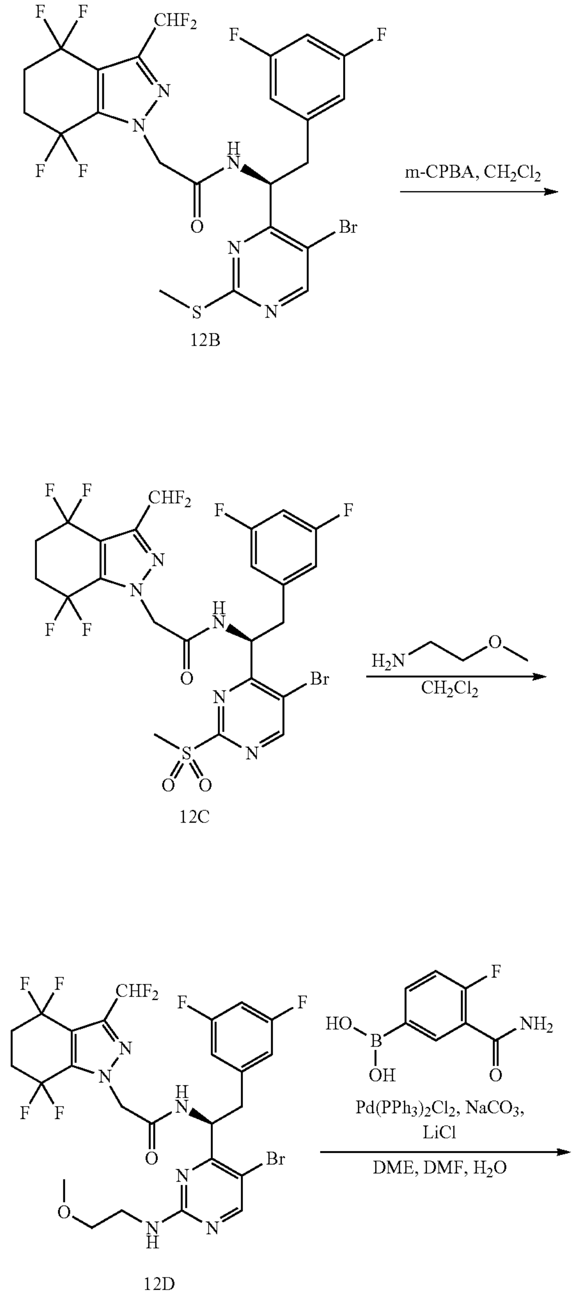
[0238]



11D

12A

-continued



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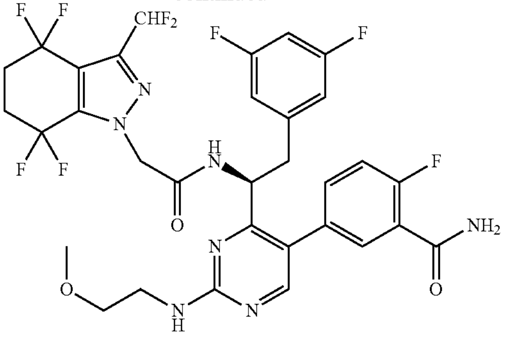


12E

Synthesis of (S)-1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride (12A)

[0239] The title compound (12A) was prepared according to the method presented for the synthesis of compound IF of Example 1 utilizing 11D. MS (m/z) 362.13 $[M+H]^+$.

Synthesis of (S)—N-(1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (12B)

[0240] The title compound (12B) was prepared according to the method presented for the synthesis of compound 11G of Example 11 utilizing 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid and 12A. MS (m/z) 644.22 $[M+H]^+$.

Synthesis of (S)—N-(1-(5-bromo-2-(methylsulfonyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (12C)

[0241] The title compound (12C) was prepared according to the method presented for the synthesis of compound 11H of Example 11 utilizing 12B. MS (m/z) 677.97 $[M+H]^+$.

Synthesis of (S)—N-(1-(5-bromo-2-((2-methoxyethyl)amino)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (12D)

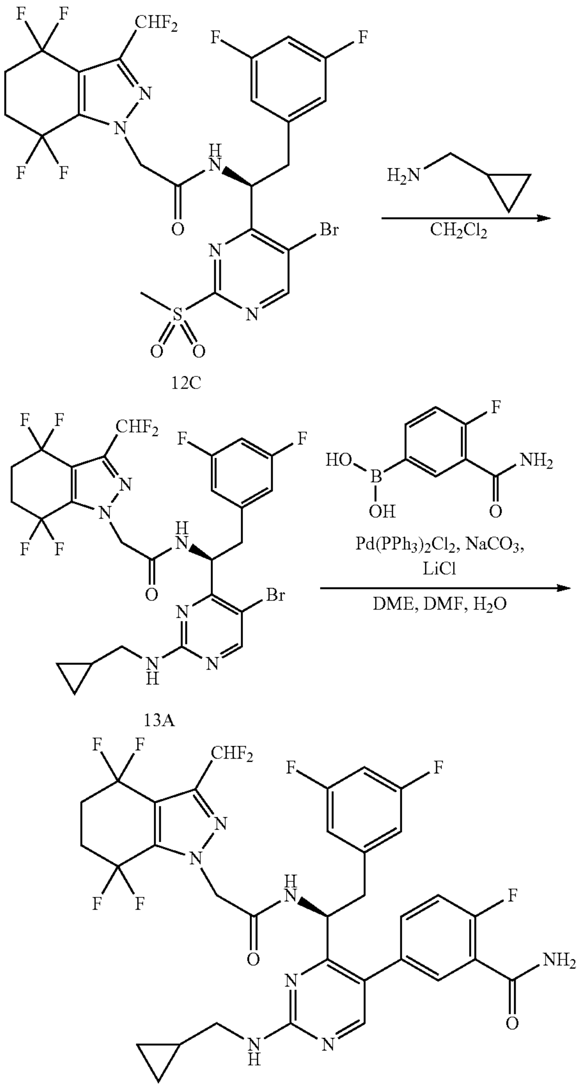
[0242] The title compound (12D) was prepared according to the method presented for the synthesis of compound 11I of Example 11 utilizing 12C. MS (m/z) 671.34 $[M+H]^+$.

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-((2-methoxyethyl)amino)pyrimidin-5-yl)-2-fluorobenzamide (12E)

[0243] The title compound (12E) was prepared according to the method presented for the synthesis of compound 11J of Example 11 utilizing 12D. ^1H NMR (400 MHz, cd_3od) δ 8.80 (d, J=8.0 Hz, 1H), 8.05 (s, 1H), 7.47-7.29 (m, 2H), 7.21 (dd, J=10.7, 8.6 Hz, 1H), 6.97-6.61 (m, 2H), 6.44 (d, J=6.1 Hz, 2H), 5.22 (dd, J=14.9, 7.7 Hz, 1H), 5.05 (s, 2H), 3.89-3.51 (m, 4H), 3.41 (s, 3H), 3.02 (ddd, J=20.2, 13.2, 7.5 Hz, 2H), 2.66-2.28 (m, 4H). MS (m/z) 730.24 $[M+H]^+$.

Example 13

[0244]



13B

Synthesis of (S)—N-(1-(5-bromo-2-((cyclopropylmethyl)amino)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (13A)

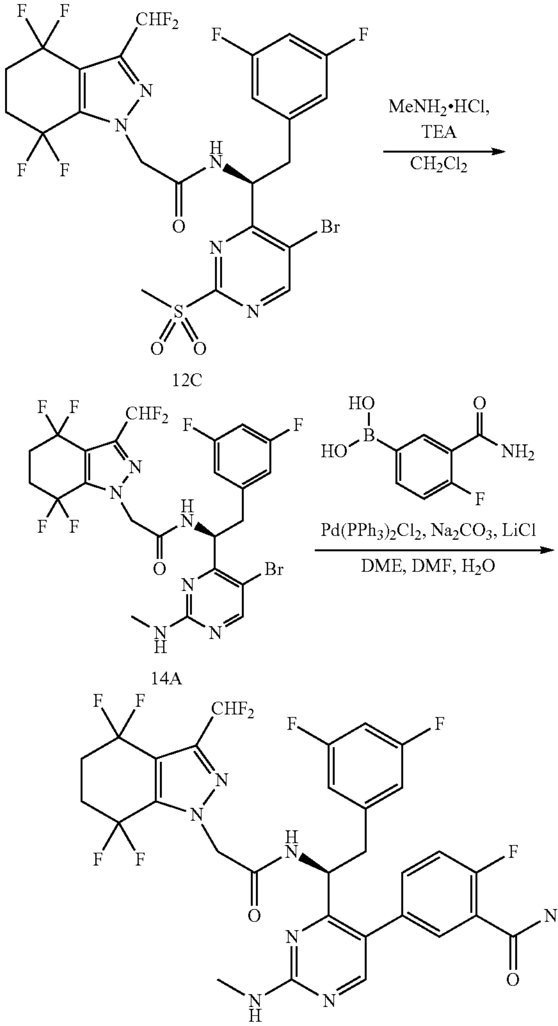
[0245] The title compound (13A) was prepared according to the method presented for the synthesis of compound 11I of Example 11 utilizing cyclopropylmethanamine and 12C. MS (m/z) 668.95 [M+H]$^+$.

Synthesis of (S)-5-(2-((cyclopropylmethyl)amino)-4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyrimidin-5-yl)-2-fluorobenzamide (13B)

[0246] The title compound (13B) was prepared according to the method presented for the synthesis of compound 11J of Example 11 utilizing 13A. ^{1}H NMR (400 MHz, cd$_3$od) δ 8.50 (d, J=7.7 Hz, 1H), 7.73 (s, 1H), 7.24-7.02 (m, 2H), 6.90 (dd, J=10.7, 8.6 Hz, 1H), 6.65-6.24 (m, 2H), 6.13 (d, J=6.1 Hz, 2H), 4.91 (m, 1H), 4.83-4.62 (m, 2H), 3.09 (m, 2H), 2.71 (ddd, J=20.2, 13.3, 7.4 Hz, 2H), 2.37-2.06 (m, 4H), 0.88 (m, 1H), 0.47-0.16 (m, 2H), 0.02 (q, J=5.1 Hz, 2H). MS (m/z) 726.30 [M+H]$^+$.

Example 14

[0247]



14B

Synthesis of (S)—N-(1-(5-bromo-2-(methylamino)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (14A)

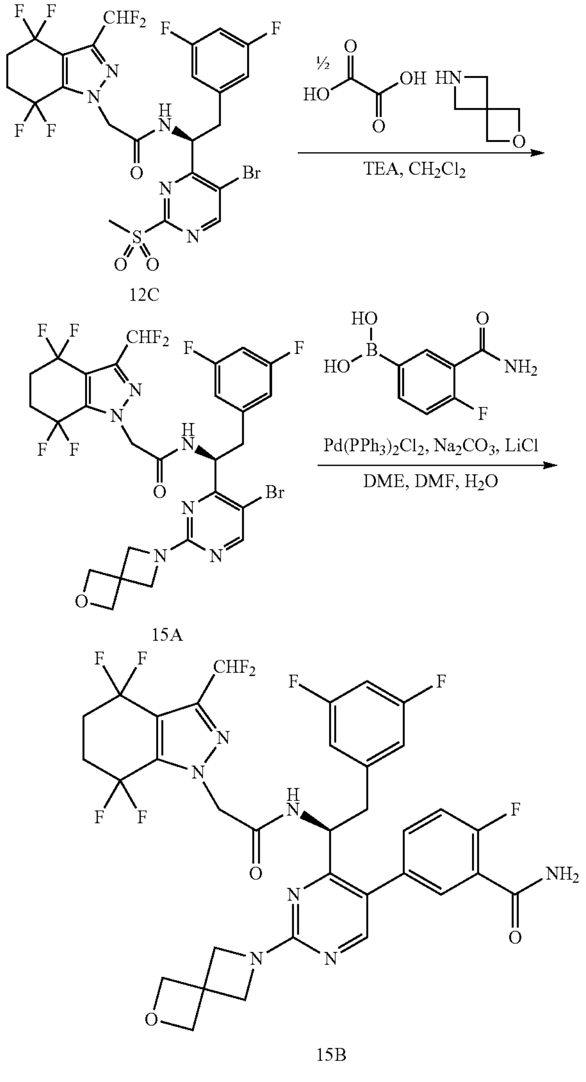
[0248] To the mixture of compound 12C (68 mg, 0.1 mmol) and Methylamine hydrochloride (34 mg, 0.5 mmol) in dichloromethane (5 ml) was added triethylamine (697 μL, 0.5 mmol). The reaction mixture was stirring at ambient temperature for 2 hours. The solvent was evaporated and the crude product was purified on reverse phase HPLC eluting with acetonitrile and water (with 0.1% TFA) to afford the title product. MS (m/z) 627.24 [M+H]$^+$.

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(methylamino)pyrimidin-5-yl)-2-fluorobenzamide (14B)

[0249] The title compound (14B) was prepared according to the method presented for the synthesis of compound 11J of Example 11 utilizing 14A. ^{1}H NMR (400 MHz, cd$_3$od) δ 8.82 (d, J=7.9 Hz, 1H), 8.06 (s, 1H), 7.44 (m 7.37 (m, 1H), 7.23 (dd, J=10.7, 8.5 Hz, 1H), 6.73 (m, 2H), 6.46 (d, J=6.2 Hz, 2H), 5.23 (q, J=7.5 Hz, 1H), 5.04 (s, 2H), 3.17-2.89 (m, 5H), 2.65-2.29 (m, 4H). MS (m/z) 686.26 [M+H]$^+$.

Example 15

[0250]



12C

15A

15B

Synthesis of (S)—N-(1-(5-bromo-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (15A):^{15A}

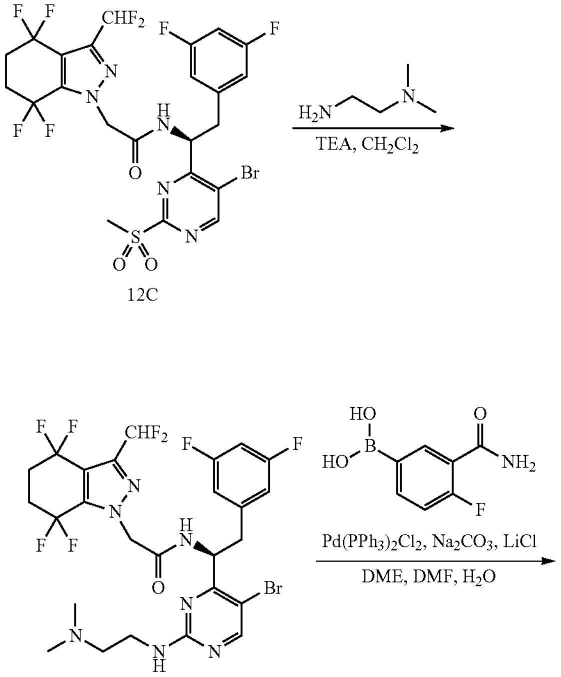
[0251] The title compound (15A) was prepared according to the method presented for the synthesis of compound 14A of Example 14 utilizing 12C and 2-Oxa-6-azaspiro[3.3]heptane hemioxalate. MS (m/z) 695.04 [M+H]$^+$.

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidin-5-yl)-2-fluorobenzamide (15B)

[0252] The title compound (15B) was prepared according to the method presented for the synthesis of compound 11J of Example 11 utilizing 15A. ^{1}H NMR (400 MHz, cd$_3$od) δ 8.69 (d, J=8.0 Hz, 1H), 8.09 (s, 1H), 7.45-7.31 (m, 2H), 7.21 (dd, J=10.7, 8.6 Hz, 1H), 7.03-6.63 (m, 2H), 6.42 (d, J=6.1 Hz, 2H), 5.23 (dd, J=15.1, 7.6 Hz, 1H), 5.05 (s, 2H), 4.88 (s, 4H), 4.39 (q, J=9.9 Hz, 4H), 3.00 (m, 2H), 2.50 (m, 4H). MS (m/z) 754.24 [M+H]$^+$.

Example 16

[0253]



12C

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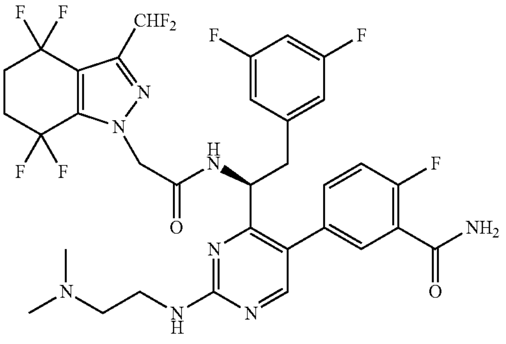


16B

Synthesis of (S)—N-(1-(5-bromo-2-((2-(dimethylamino)ethyl)amino)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl) acetamide (16A)

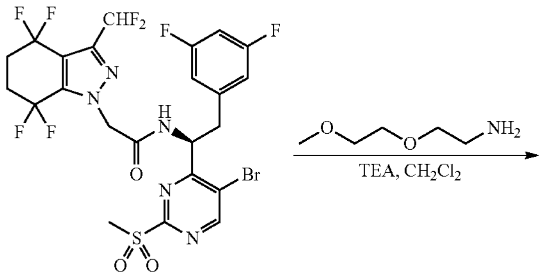
[0254] The title compound (16A) was prepared according to the method presented for the synthesis of compound 14A of Example 14 utilizing 12C and N,N-dimethylethane-1,2-diamine. MS (m/z) 686.00 [M+H]$^+$.

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl) acetamido)-2-(3,5-difluorophenyl)ethyl)-2-((2-(dimethylamino)ethyl)amino)pyrimidin-5-yl)-2-fluorobenzamide (16B)

[0255] The title compound (16B) was prepared according to the method presented for the synthesis of compound 11J of Example 11 utilizing 16A. ^{1}H NMR (400 MHz, cd3od) δ 8.75 (d, J=7.4 Hz, 1H), 8.13 (s, 1H), 7.38 (m, 2H), 7.21 (dd, J=10.8, 8.4 Hz, 1H), 6.98-6.63 (m, 2H), 6.42 (m, 2H), 5.23 (d, J=7.6 Hz, 1H), 5.02 (q, J=16.8 Hz, 2H), 3.88 (m, 2H), 3.45 (t, J=5.5 Hz, 2H), 3.15-2.93 (m, 8H), 2.52 (m, 4H). MS (m/z) 743.60 [M+H]$^+$.

Example 17

[0256]



12C

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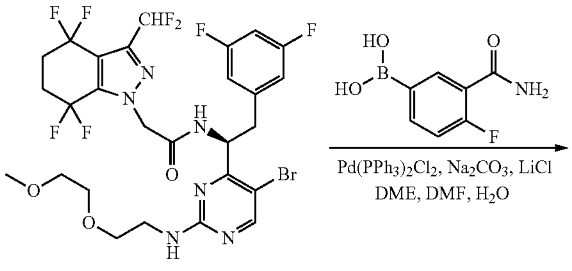
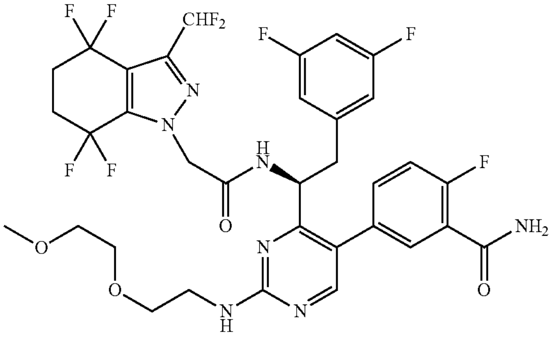


17A



17B

Synthesis of (S)—N-(1-(5-bromo-2-((2-(2-methoxyethoxy)ethyl)amino)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl) acetamide (17A)

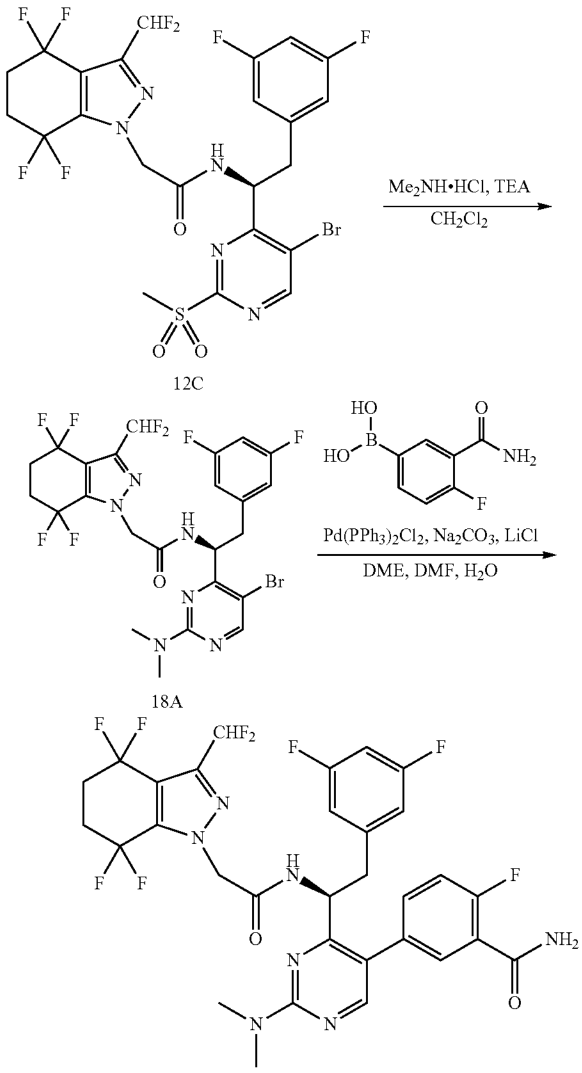
[0257] The title compound (17A) was prepared according to the method presented for the synthesis of compound 14A of Example 14 utilizing 12C and 2-(2-methoxyethoxy)ethanamine. MS (m/z) 716.15 [M+H]$^+$.

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl) acetamido)-2-(3,5-difluorophenyl)ethyl)-2-((2-(2-methoxyethoxy)ethyl)amino)pyrimidin-5-yl)-2-fluorobenzamide (17B)

[0258] The title compound (17B) was prepared according to the method presented for the synthesis of compound 11J of Example 11 utilizing 17A. ^{1}H NMR (400 MHz, cd3od) δ 8.82 (d, J=8.2 Hz, 1H), 8.06 (s, 1H), 7.52-7.31 (m, 2H), 7.21 (dd, J=10.7, 8.5 Hz, 1H), 7.01-6.56 (m, 2H), 6.44 (d, J=6.0 Hz, 2H), 5.23 (t, J=6.7 Hz, 1H), 5.05 (s, 2H), 3.84-3.63 (m, 6H), 3.57 (m, 2H), 3.37 (s, 3H), 3.17-2.90 (m, 2H), 2.65-2.39 (m, 4H). MS (m/z) 774.58 [M+H]$^+$.

Example 18

[0259]



12C

18A

18B

Synthesis of (S)—N-(1-(5-bromo-2-(dimethylamino)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (18A)

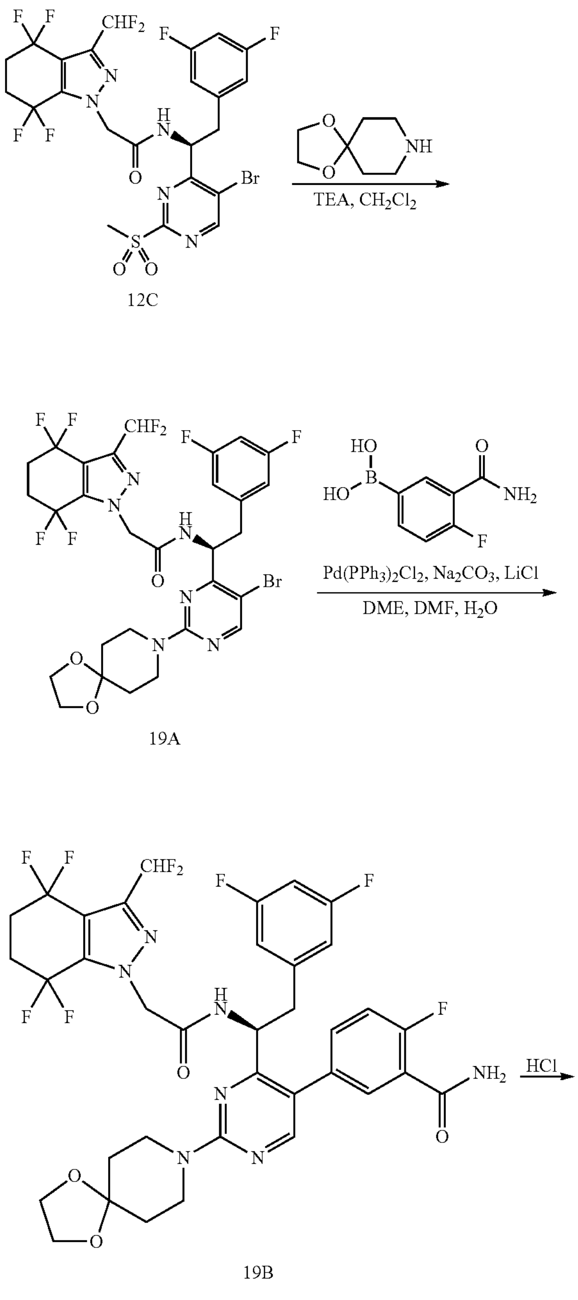
[0260] The title compound (18A) was prepared according to the method presented for the synthesis of compound 14A of Example 14 utilizing 12C and dimethylamine hydrochloride. MS (m/z) 643.09 [M+H]$^+$.

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(dimethylamino)pyrimidin-5-yl)-2-fluorobenzamide (18B)

[0261] The title compound (18B) was prepared according to the method presented for the synthesis of compound 11J of Example 11 utilizing 18A. ^{1}H NMR (400 MHz, cd$_3$od) δ 8.72 (d, J=7.8 Hz, 1H), 8.08 (s, 1H), 7.51-7.29 (m, 2H), 7.21 (dd, J=10.7, 8.5 Hz, 1H), 7.03-6.55 (m, 2H), 6.43 (d, J=6.2 Hz, 2H), 5.25 (dd, J=14.1, 6.5 Hz, 1H), 5.12-4.97 (m, 2H), 3.28 (s, 6H), 3.03 (m, 2H), 2.66-2.31 (m, 4H). MS (m/z) 700.56 [M+H]$^+$.

Example 19

[0262]

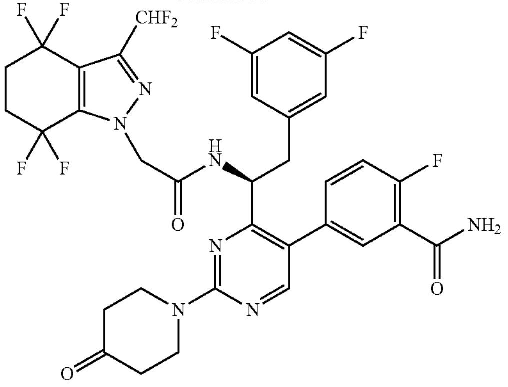


12C

19A

19B

-continued



19C

Synthesis of (S)—N-(1-(5-bromo-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl) acetamide (19A)

[0263] The title compound (19A) was prepared according to the method presented for the synthesis of compound 14A of Example 14 utilizing 12C and 1,4-dioxa-8-azaspiro[4.5]decane. MS (m/z) 740.04 $[M+H]^+$.

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl) acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pyrimidin-5-yl)-2-fluorobenzamide (19B)

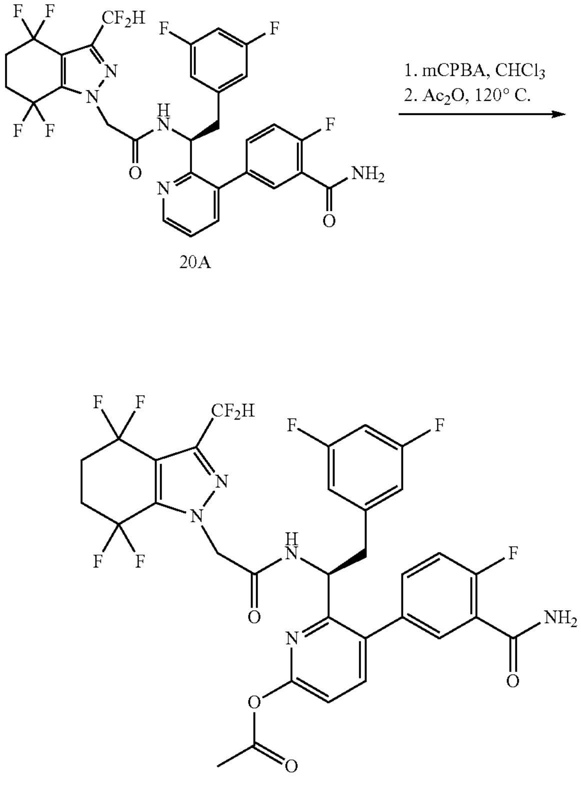
[0264] The title compound (19B) was prepared according to the method presented for the synthesis of compound 11J of Example 11 utilizing 19A. MS (m/z) 798.63 $[M+H]^+$.

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl) acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(4-oxopiperidin-1-yl)pyrimidin-5-yl)-2-fluorobenzamide (19C)

[0265] Compound 19B (40 mg, 0.05 mmol) was dissolved in 2 mL of THF and to it was added 1 mL of 6N HCl. The mixtures was stirred at ambient temperature for 16 hours and then extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford the title compound. ^{1}H NMR (400 MHz, cdcl3) δ 8.21 (s, 1H), 7.71 (d, J=5.0 Hz, 1H), 7.46 (s, 1H), 7.33 (m, 1H), 7.30-7.18 (m, 1H), 7.11 (d, J=11.0 Hz, 1H), 6.98 (m, 1H), 6.78 (t, J=53.6 Hz, 1H), 6.58 (m, 1H), 6.20 (d, J=6.2 Hz, 2H), 5.37 (d, J=7.4 Hz, 1H), 5.11-4.89 (m, 2H), 4.22-3.98 (m, 4H), 2.83 (m, 2H), 2.54 (m, 8H). MS (m/z) 754.11 $[M+H]^+$.

Example 20

[0266]



20A

20B

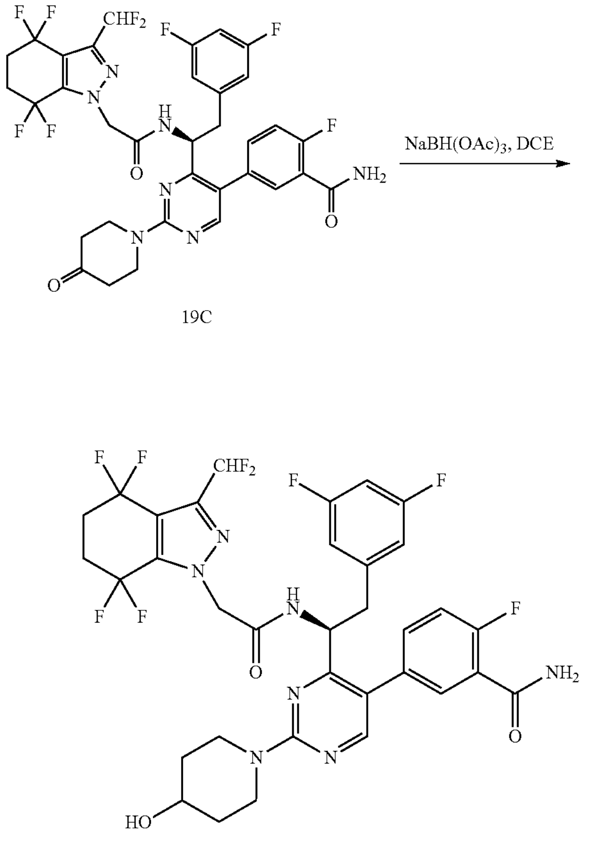
Synthesis of (S)-5-(3-carbamoyl-4-fluorophenyl)-6-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl acetate (20B)

[0267] To a solution of (S)-5-(2-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (50 mg, 0.076 mmol) in chloroform (1 mL) was added mCPBA (27.6 mg, 0.16 mmol). The reaction was heated at 60° C. for 30 min. After cooled to room temperature, the reaction mixture was partitioned between chloroform and saturated $NaHCO_3$ solution. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was used in the next step without further purification. MS (m/z) 672.4 $[M+14]^+$.

[0268] The crude material from last step was dissolved in acetic anhydride (2 mL) and heated over night in a seal tube. The crude product was purified by reverse phase HPLC to give (S)-5-(3-carbamoyl-4-fluorophenyl)-6-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-2-yl acetate. MS (m/z) 714.13 $[M+H]^+$.

Example 21

[0269]



19C

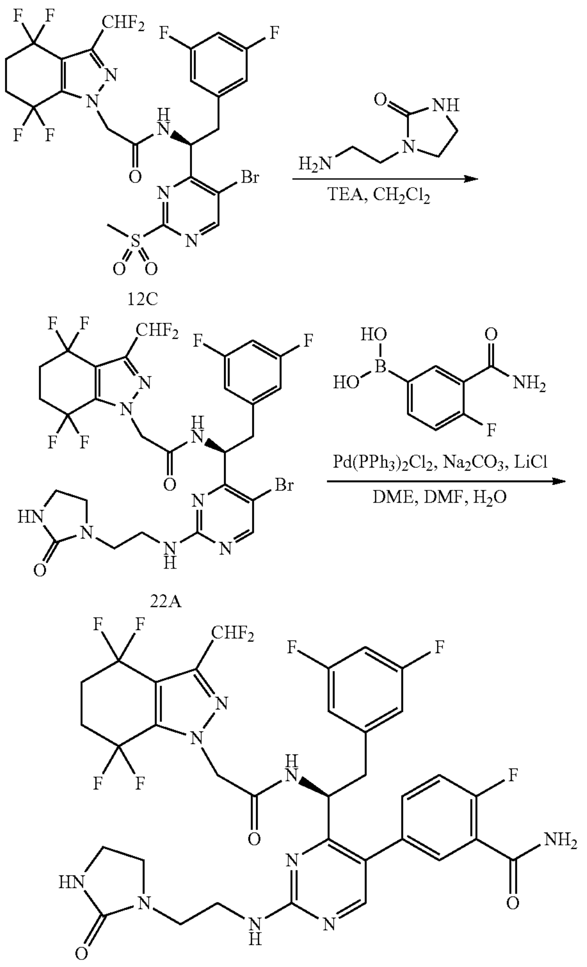
21

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-(4-hydroxypiperidin-1-yl)pyrimidin-5-yl)-2-fluorobenzamide (21A)

[0270] To a solution of compound 19C (18 mg, 0.023 mmol) in 1,2-dichloroethane (0.5 ml), was added acetic acid (13 µL, 0.23 mmol) and sodium triacetoxyborohydride (9.7 mg, 0.046 mmol) at room temperature. After being stirred for 3 hours, the mixture was treated with EtOAc (10 mL) and water (3 mL). The organic layer was washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified on reverse phase HPLC eluting with acetonitrile and water (with 0.1% TFA) to afford the title product. ^{1}H NMR (400 MHz, cd$_3$od) δ 8.71 (d, J=8.5 Hz, 1H), 8.09 (s, 1H), 7.41 (dd, J=7.0, 2.3 Hz, 1H), 7.33 (m, 1H), 7.20 (dd, J=10.8, 8.5 Hz, 1H), 6.97-6.61 (m, 3H), 6.42 (d, J=6.2 Hz, 2H), 5.24 (t, J=7.2 Hz, 1H), 5.13-4.96 (m, 2H), 4.51 (m, 2H), 4.01-3.83 (m, 1H), 3.42 (m, 2H), 3.14-2.82 (m, 2H), 2.50 (m, 4H), 2.08-1.84 (m, 2H), 1.68-1.37 (m, 2H); MS (m/z) 756.22 [M+H]$^+$.

Example 22

[0271]



12C

22A

22B

Synthesis of (S)—N-(1-(5-bromo-2-((2-(2-oxoimidazolidin-1-yl)ethyl)amino)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (22A)

[0272] The title compound (22A) was prepared according to the method presented for the synthesis of compound 14A of Example 14 utilizing 12C and 1-(2-aminoethyl)imidazolidin-2-one. MS (m/z) 725.15 [M+H]$^+$.

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-((2-(2-oxoimidazolidin-1-yl)ethyl)amino)pyrimidin-5-yl)-2-fluorobenzamide (22B)

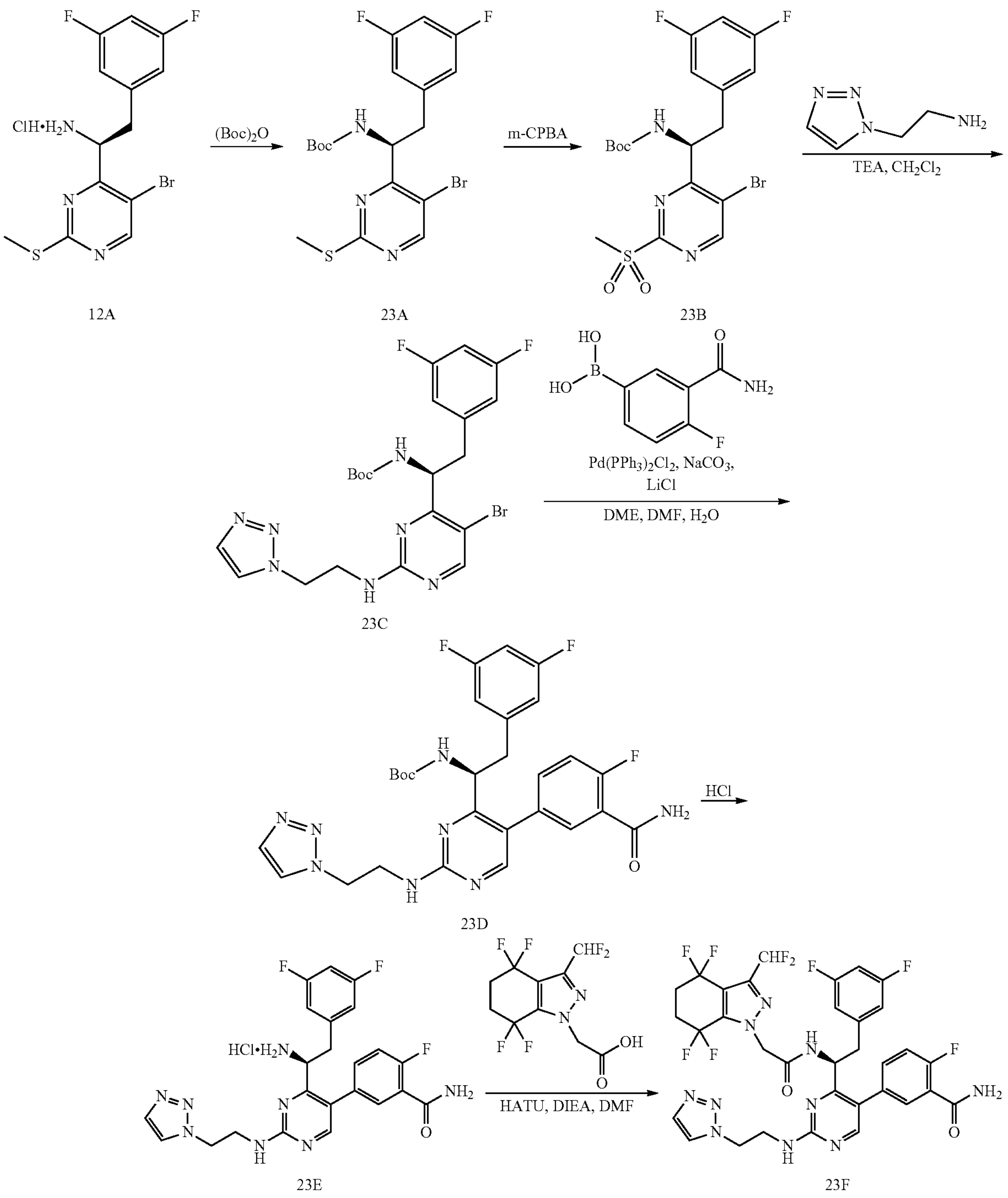
[0273] The title compound (22B) was prepared according to the method presented for the synthesis of compound 11J of Example 11 utilizing 22A. ^{1}H NMR (400 MHz, cd3od) δ 8.88 (m, 1H), 8.07 (s, 1H), 7.47-7.29 (m, 2H), 7.27-7.14 (m, 1H), 6.96-6.59 (m, 2H), 6.45 (d, J=6.4 Hz, 2H), 5.26 (m, 1H), 5.09 (s, 2H), 3.82-3.49 (m, 6H), 3.40 (m, 2H), 3.15-2.95 (m, 2H), 2.51 (m, 4H). MS (m/z) 784.22 $[M+H]^+$.

Example 23

[0274]

Synthesis of (S)-tert-butyl (1-(5-bromo-2-(methylthio)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl) carbamate (23A)

[0275] To the compound 12A (310 mg, 0.78 mmol) in dichloromethane (3 mL) was added triethylamine (0.22 mL, 1.56 mmol) and di-tert-butyldicarbonate (170 mg, 0.78



mmol). The mixture was stirred for one hour at ambient temperature then concentrated in vacuo.

[0276] The residue was purified by silica gel chromatography using an ethyl acetate/hexanes eluent to yield the title compound. MS (m/z) 459.86 [M+H]+.

Synthesis of (S)-tert-butyl (1-(5-bromo-2-(methylsulfonyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (23B)

[0277] The title compound (23B) was prepared according to the method presented for the synthesis of compound 11H of Example 11 utilizing 23A. MS (m/z) 394.03 [M+H-Boc]+.

Synthesis of (S)-tert-butyl (1-(2-((2-(1H-1,2,3-triazol-1-yl)ethyl)amino)-5-bromopyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (23C)

[0278] The title compound (23C) was prepared according to the method presented for the synthesis of compound 14A of Example 14 utilizing 23B and 2-(1H-1,2,3-triazol-1-yl)ethanamine. MS (m/z) 545.97 [M+Na]+.

Synthesis of (S)-tert-butyl (1-(2-((2-(1H-1,2,3-triazol-1-yl)ethyl)amino)-5-(3-carbamoyl-4-fluorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (23D)

[0279] In a microwave tube were charged with compound 23C (52 mg, 0.1 mmol), (3-carbamoyl-4-fluorophenyl)boronic acid (27 mg, 0.15 mmol), K_2CO_3 (41 mg, 0.3 mmol), Pd(dppf)Cl_2 (5 mg). To the mixture was added 2 mL of Toluene/2-propanol/H_2O (3/1/1). The mixture was heated up to 120° C. for 20 min in a Microwave Synthesizer. The mixture was partitioned between ethyl acetate and water. The organic layer was separated and concentrated to afford crude product used for next step without further purification. MS (m/z) 582.73 [M+H]+.

Synthesis of (S)-5-(2-((2-(1H-1,2,3-triazol-1-yl)ethyl)amino)-4-(1-amino-2-(3,5-difluorophenyl)ethyl)pyrimidin-5-yl)-2-fluorobenzamide hydrochloride (23E)

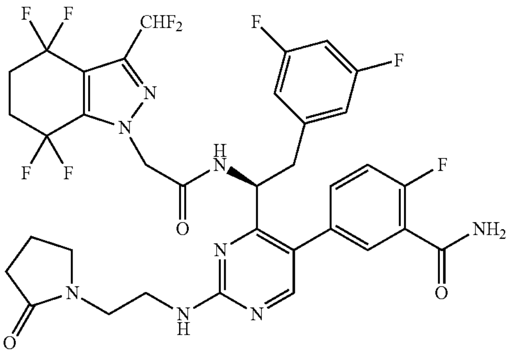
[0280] Compound 23D was dissolved in 2 mL of 4N HCl in dioxane and stirred at ambient temperature for overnight. The solvent was removed to afford the title product. (m/z) 483.08 [M+H]+.

Synthesis of (S)-5-(2-((2-(1H-1,2,3-triazol-1-yl)ethyl)amino)-4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyrimidin-5-yl)-2-fluorobenzamide (23F)

[0281] The title compound (23F) was prepared according to the method presented for the synthesis of compound 11G of Example 11 utilizing 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid and 23E. ^1H NMR (400 MHz, cd3od) δ 8.71 (d, J=7.6 Hz, 1H), 8.06 (s, 1H), 7.99 (s, 1H), 7.74 (s, 1H), 7.43-7.25 (m, 2H), 7.20 (dd, J=10.8, 8.5 Hz, 1H), 6.97-6.58 (m, 2H), 6.42 (d, J=6.2 Hz, 2H), 5.32-5.18 (m, 2H), 5.09 (s, 2H), 4.73 (m, 2H), 4.01 (m, 2H), 3.01 (m, 2H), 2.66-2.34 (m, 4H). MS (m/z) 767.06 [M+H]+.

Example 24

[0282]



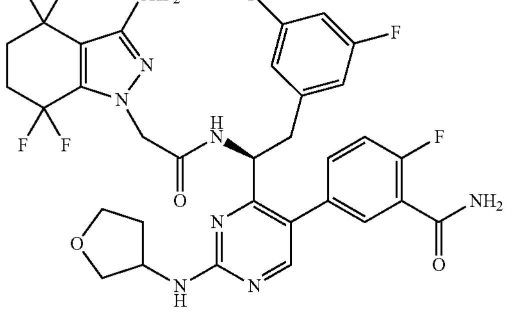
24

Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-((2-(2-oxopyrrolidin-1-yl)ethyl)amino)pyrimidin-5-yl)-2-fluorobenzamide (24)

[0283] The title compound (24) was prepared according to the method presented for the synthesis of compound 23F of Example 23 Starting with 1-(2-aminoethyl)pyrrolidin-2-one and 23B. MS (m/z) ^1H NMR (400 MHz, cd_3od) δ 8.84 (m, 1H), 8.07 (s, 1H), 7.50-7.27 (m, 2H), 7.24-7.11 (m, 1H), 6.97-6.61 (m, 2H), 6.45 (d, J=6.2 Hz, 2H), 5.27 (m, 1H), 5.10 (s, 2H), 3.57 (m, 6H), 3.18-2.87 (m, 2H), 2.51 (m, 4H), 2.41-2.28 (m, 2H), 2.12-1.89 (m, 2H). 783.12 [M+H]+.

Example 25

[0284]



25

Synthesis of 5-(4-((S)-1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-((tetrahydrofuran-3-yl)amino)pyrimidin-5-yl)-2-fluorobenzamide (25)

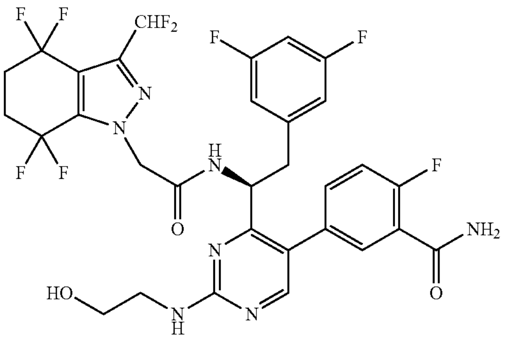
[0285] The title compound (25) was prepared according to the method presented for the synthesis of compound 23F of

Example 23 Starting with tetrahydrofuran-3-amine and 23B. ^{1}H NMR (400 MHz, cd_3od) δ 8.71 (d, J=7.6 Hz, 1H), 8.06 (s, 1H), 7.43-7.26 (m, 2H), 7.24-7.14 (m, 1H), 6.95-6.63 (m, 2H), 6.42 (d, J=5.9 Hz, 2H), 5.22 (m, 1H), 5.04 (s, 2H), 4.66 (m, 1H), 4.01 (m, 2H), 3.93-3.84 (m, 1H), 3.76 (m, 1H), 3.02 (m, 2H), 2.51 (m, 4H), 2.37 (m, 1H), 1.99 (m, 1H). MS (m/z) 742.15 [M+H]$^+$.

Example 26

[0286]

26



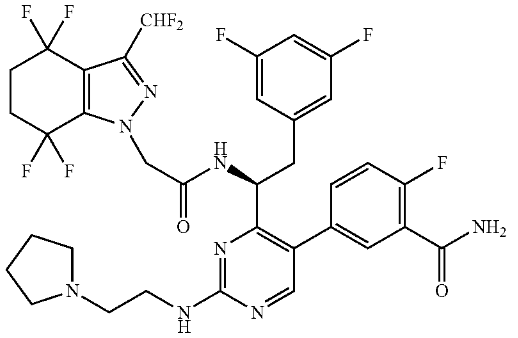
Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-((2-hydroxyethyl)amino)pyrimidin-5-yl)-2-fluorobenzamide (26)

[0287] The title compound (26) was prepared according to the method presented for the synthesis of compound 14B of Example 14 starting with 2-aminoethanol and 12C. ^{1}H NMR (400 MHz, cd_3od) δ 8.83 (d, J=7.7 Hz, 1H), 8.06 (s, 2H), 7.49-7.32 (m, 2H), 7.21 (dd, J=10.7, 8.5 Hz, 1H), 7.02-6.58 (m, 2H), 6.45 (d, J=6.1 Hz, 2H), 5.22 (m, 1H), 5.05 (s, 2H), 3.86-3.58 (m, 4H), 3.18-2.85 (m, 2H), 2.66-2.23 (m, 4H). MS (m/z) 716.23 [M+H]$^+$.

Example 27

[0288]

27



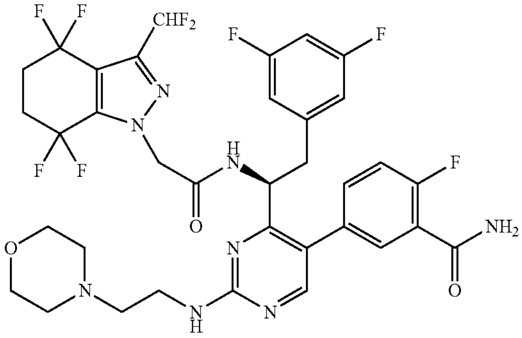
Synthesis of ((S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-((2-(pyrrolidin-1-yl)ethyl)amino)pyrimidin-5-yl)-2-fluorobenzamide (27)

[0289] The title compound (27) was prepared according to the method presented for the synthesis of compound 23F of Example 23 starting with 2-(pyrrolidin-1-yl)ethanamine and 23B. ^{1}H NMR (400 MHz, cd_3od) δ 8.67 (d, J=7.8 Hz, 1H), 8.05 (s, 1H), 7.41-7.23 (m, 2H), 7.13 (dd, J=10.7, 8.5 Hz, 1H), 6.95-6.48 (m, 2H), 6.35 (d, J=6.2 Hz, 2H), 5.15 (m, 1H), 4.95 (q, J=16.7 Hz, 2H), 3.74 (m, 4H), 3.43 (m, 2H), 3.11 (m, 2H), 3.00-2.88 (m, 2H), 2.70-2.28 (m, 4H), 2.13-1.89 (m, 4H). MS (m/z) 769.29 [M+H]$^+$.

Example 28

[0290]

28

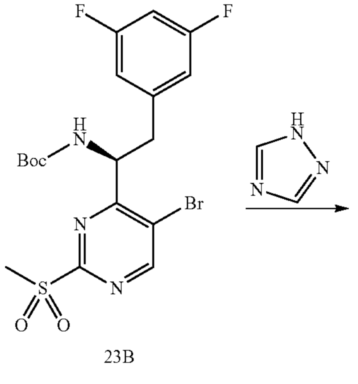


Synthesis of (S)-5-(4-(1-(2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-2-((2-morpholinoethyl)amino)pyrimidin-5-yl)-2-fluorobenzamide (28)

[0291] The title compound (28) was prepared according to the method presented for the synthesis of compound 23F of Example 23 starting with 2-morpholinoethanamine and 23B. ^{1}H NMR (400 MHz, cd_3od) δ 8.76 (d, J=7.8 Hz, 1H), 8.14 (s, 1H), 7.46-7.32 (m, 2H), 7.22 (dd, J=10.7, 8.5 Hz, 1H), 7.00-6.59 (m, 2H), 6.43 (d, J=6.2 Hz, 2H), 5.23 (m, 1H), 5.02 (q, J=16.6 Hz, 2H), 3.97 (m, 6H), 3.70-3.39 (m, 6H), 3.10-2.93 (m, 2H), 2.66-2.38 (m, 4H). MS (m/z) 785.29 [M+H]$^+$.

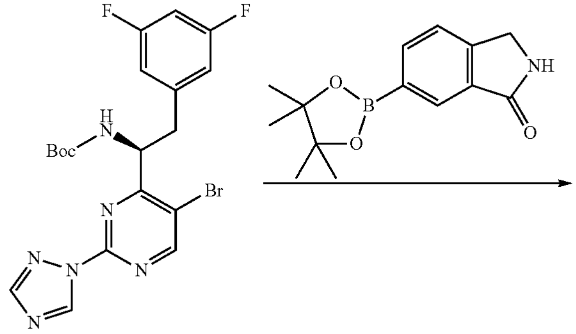
Example 29

[0292]

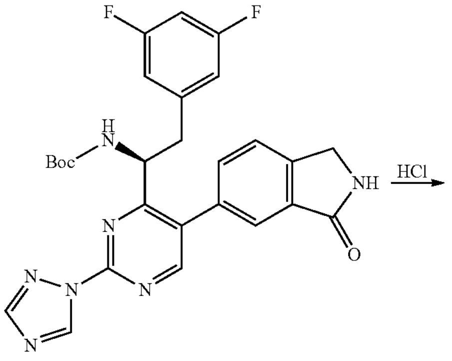


23B

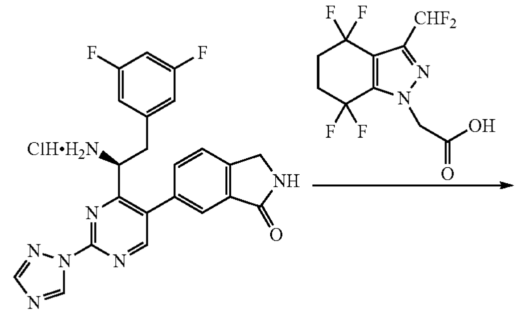
-continued



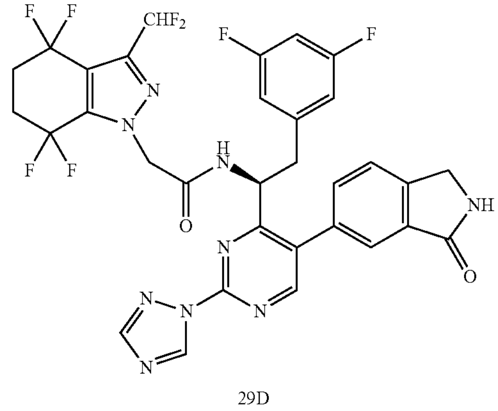
29A



29B



29C



29D

Synthesis of (S)-tert-butyl (1-(5-bromo-2-(1H-1,2,4-triazol-1-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl) ethyl)carbamate (29A)

[0293] In a microwave tube were charged with compound 23B (100 mg, 0.2 mmol), 1H-1,2,4-triazole2 (42 mg, 0.6 mmol), triethylamine (84 μL, 0.6 mmol) and DMF (0.6 mL, The mixture was heated up to 120° C. for 15 min in a Microwave Synthesizer. After cooled down, it was partitioned between ethyl acetate and 5% of LiCl aqueous solution. The organic layer was separated and concentrated. The residue was purified on silica gel chromatography eluting with ethyl acetate and hexanes to afford the title compound. MS (m/z) 481.21 $[M+H]^+$.

Synthesis of (S)-tert-butyl (2-(3,5-difluorophenyl)-1-(5-(3-oxoisoindolin-5-yl)-2-(1H-1,2,4-triazol-1-yl) pyrimidin-4-yl)ethyl)carbamate (29B)

[0294] In a microwave tube was charged with 29B (50 mg, 0.1 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) isoindolin-1-one (39 mg, 0.15 mmol), LiCl (13 mg, 0.3 mmol), Na_2CO_3 (25 mg, 0.3 mmol) and 3 mg of $Pd(PPh_3)_2Cl_2$ To the mixture was added 0.7 mL of 1,4-dioxane, 0.2 mL of methanol and 0.2 mL of H_2O. The mixture was heated up to 160° C. for 20 min in a Microwave Synthesizer. After cooled down, it was partitioned between ethyl acetate and water. The organic layer was separated and concentrated. The residue was purified on silica gel chromatography eluting with ethyl acetate and hexanes to afford the title compound. MS (m/z) 533.78 $[M+H]^+$.

Synthesis of (S)-6-(4-(1-amino-2-(3,5-difluorophenyl)ethyl)-2-(1H-1,2,4-triazol-1-yl)pyrimidin-5-yl) isoindolin-1-one hydrochloride (29C)

[0295] The title compound (29C) was prepared according to the method presented for the synthesis of compound 23E of Example 23 utilizing 29B. MS (m/z) 434.11$[M+H]^+$

Synthesis of (S)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(5-(3-oxoisoindolin-5-yl)-2-(1H-1,2,4-triazol-1-yl)pyrimidin-4-yl)ethyl) acetamide (29D)

[0296] The title compound (29D) was prepared according to the method presented for the synthesis of compound 11G of Example 11 utilizing 29C. ^1H NMR (400 MHz, cd_3od) δ 9.59 (s, 1H), 9.19 (d, J=8.4 Hz, 1H), 8.71 (s, 1H), 8.39 (s, 1H), 7.66 (q, J=7.9 Hz, 2H), 7.46 (s, 1H), 6.93-6.54 (m, 2H), 6.38 (d, J=6.2 Hz, 2H), 5.55 (q, J=7.6 Hz, 1H), 5.09 (s, 2H), 4.52 (s, 2H), 3.20-2.91 (m, 2H), 2.47 (m, 4H). MS (m/z) 718.08 $[M+H]^+$

Example 30

[0297] The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
Compound X =	100.0
Lactose	77.5

-continued

(i) Tablet 1	mg/tablet
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
Compound X =	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
Compound X =	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection 1 (1 mg/ml)	mg/ml
Compound X = (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
1.0N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
Compound X = (free acid form)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
1.0N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(vi) Aerosol	mg/can
Compound X =	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

[0298] The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

[0299] All references, including publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

[0300] The use of the terms "a" and "an" and "the" and similar references in the context of this disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., such as, preferred, preferably) provided herein, is intended merely to further illustrate the content of the disclosure and does not pose a limitation on the scope of the claims. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the present disclosure.

[0301] Alternative embodiments of the claimed disclosure are described herein, including the best mode known to the inventors for practicing the claimed invention. Of these, variations of the disclosed embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing disclosure. The inventors expect skilled artisans to employ such variations as appropriate (e.g., altering or combining features or embodiments), and the inventors intend for the invention to be practiced otherwise than as specifically described herein.

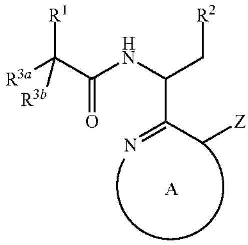
[0302] Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0303] The use of individual numerical values is stated as approximations as though the values were preceded by the word "about" or "approximately." Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about" or "approximately." In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms "about" and "approximately" when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the disclosed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered include the criticality of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to limit how the use of the words "about" or "approximately" will serve to broaden a particular numerical value or range. Thus, as a general matter, "about" or "approximately" broaden the numerical value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term "about" or "approximately." Thus, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.

[0304] It is to be understood that any ranges, ratios and ranges of ratios that can be formed by, or derived from, any of the data disclosed herein represent further embodiments of the present disclosure and are included as part of the disclosure as though they were explicitly set forth. This includes ranges that can be formed that do or do not include a finite upper and/or lower boundary. Accordingly, a person of ordinary skill in the art most closely related to a particular range, ratio or range of ratios will appreciate that such values are unambiguously derivable from the data presented herein.

1: A compound of formula I:

I



wherein:

A is a 6-membered heteroaryl with of one or two nitrogen atoms, wherein the 6-membered heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups;

R^1 is heteroaryl, wherein the heteroaryl of R^1 is a bicyclic-heteroaryl or tricyclic-heteroaryl, wherein the bicyclic-heteroaryl or tricyclic-heteroaryl has 4-9 carbon atoms and 1-5 heteroatoms and wherein the heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups;

R^2 is phenyl, 5-membered heteroaryl, 6-membered heteroaryl or $(C_3\text{-}C_7)$carbocycle wherein any phenyl, 5-membered heteroaryl, 6-membered heteroaryl or $(C_3\text{-}C_7)$carbocycle of R^2 is optionally substituted with 1, 2, or 3 Z^5 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, $(C_1\text{-}C_3)$alkyl, and $(C_1\text{-}C_3)$haloalkyl, or R^{3a} is selected from H, $(C_1\text{-}C_3)$alkyl and $(C_1\text{-}C_3)$haloalkyl and R^{3b} is selected from —OH and —CN;

Z^1 is phenyl, monocyclic-heteroaryl or bicyclic-heterocycle, wherein the monocyclic-heteroaryl or bicyclic-heterocycle has 2-12 carbon atoms and 1-5 heteroatoms and, wherein any phenyl, monocyclic-heteroaryl or bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b};

each Z^{1a} is independently selected from $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20}$ aryl, heteroaryl, heterocycle, halogen, —CN, OR_{n1}, —$OC(O)R_{p1}$, —$OC(O)NR_{q1}R_{r1}$, —SR_{n1}, —$S(O)R_{p1}$, —$S(O)_2OH$, —$S(O)_2R_{p1}$, —$S(O)_2NR_{q1}R_{r1}$, —$NR_{q1}R_{r1}$, —$NR_{n1}COR_{p1}$, —$NR_{n1}CO_2R_{p1}$, —$NR_{n1}CONR_{q1}R_{r1}$, —$NR_{n1}S(O)_2R_{p1}$, —$NR_{n1}S(O)_2OR_{p1}$, —$NR_{n1}S(O)_2NR_{q1}R_{r1}$, NO_2, —$C(O)R_{n1}$, —$C(O)OR_{n1}$, —$C(O)NR_{q1}R_{r1}$ and —$S(O)_2NR_{n1}COR_{p1}$, wherein any heteroaryl of Z^{1a} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of Z^{1a} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4, or 5 Z^{1c} or Z^{1d} groups;

each Z^{1b} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl, wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of Z^{1b} is optionally substituted with 1, 2, 3, 4, or 5 Z^{1c} groups;

each Z^{1c} is independently selected from $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl, heterocycle, halogen, —CN, OR_{n2}, —$OC(O)R_{p2}$, —$OC(O)NR_{q2}R_{r2}$, —SR_{n2}, —$S(O)R_{p2}$, —$S(O)_2OH$, —$S(O)_2R_{p2}$, —$S(O)_2NR_{q2}R_{r2}$, —$NR_{q2}R_{r2}$, —$NR_{n2}COR_{p2}$, —$NR_{n2}CO_2R_{p2}$, —$NR_{n2}CONR_{q2}R_{r2}$, —$NR_{n2}S(O)_2R_{p2}$, —$NR_{n2}S(O)_2OR_{p2}$, —$NR_{n2}S(O_2NR_{q2}R_{r2}$, NO_2, —$C(O)R_{n2}$, —$C(O)OR_{n2}$, —$C(O)NR_{q2}R_{r2}$, $(C_6\text{-}C_{20})$haloaryl, haloheteroaryl, haloheterocycle and $(C_1\text{-}C_8)$heteroalkyl, wherein any heteroaryl or haloheteroaryl of Z^{1c} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle or haloheterocycle of Z^{1c} has 2-20 carbon atoms and 1-6 heteroatoms;

each Z^{1d} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl and $(C_1\text{-}C_8)$haloalkyl;

each R_{n1} is independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{n1} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{n1} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{n1} is optionally substituted with 1, 2, 3, 4, or 5 Z^{1c} or Z^{1d} groups, and wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of R_{n1} is optionally substituted with 1, 2, 3, 4, or 5 Z^{1c} groups;

each R_{p1} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{p1} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{p1} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{p1} is optionally substituted with 1, 2, 3, 4, or 5 Z^{1c} or Z^{1d} groups, and wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of R_{p1} is optionally substituted with 1, 2, 3, 4, or 5 Z^{1c} groups;

R_{q1} and R_d are each independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{g1} and R_{r1} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{q1} and R_{r1} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{q1} or R_{r1} is optionally substituted with 1, 2, 3, 4, or 5 Z^{1c} or Z^{1d} groups, and wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of R_{q1} or R_{r1} is optionally substituted with 1, 2, 3, 4, or 5 Z^{1c} groups, or R_{q1} and R_{r1} together with the nitrogen to which they are attached form a 5, 6 or

7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4, or 5 Z^{1c} or Z^{1d} groups;

each R_{n2} is independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, $(C_6\text{-}C_{20})$aryl, $(C_6\text{-}C_{20})$haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_8)$haloalkyl and $(C_1\text{-}C_8)$heteroalkyl, wherein any heteroaryl or haloheteroaryl of R_{n2} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle or haloheterocycle of R_{n2} has 2-20 carbon atoms and 1-6 heteroatoms;

each R_{p2} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, $(C_6\text{-}C_{20})$aryl, $(C_6\text{-}C_{20})$haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_8)$haloalkyl and $(C_1\text{-}C_8)$heteroalkyl, wherein any heteroaryl or haloheteroaryl of R_{p2} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle or haloheterocycle of R_{p2} has 2-20 carbon atoms and 1-6 heteroatoms;

R_{q2} and R_{r2} are each independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, $(C_6\text{-}C_{20})$aryl, $(C_6\text{-}C_{20})$haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_8)$haloalkyl and $(C_1\text{-}C_8)$heteroalkyl, or R_{q2} and R_{r2} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein any heteroaryl or haloheteroaryl of R_{q2} and R_{r2} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle or haloheterocycle of R_{q2} and R_{r2} has 2-20 carbon atoms and 1-6 heteroatoms;

Z^2 is selected from —OR_{s3}—$OC(O)R_{p3}$, —$OC(O)NR_{q3}R_{r3}$, —SR_{n3}, —$S(O)R_{p3}$, —$S(O)_2R_{p3}$, —$S(O)_2NR_{q3}R_{r3}$, —$NR_{q3}R_{r3}$, —$NR_{n3}COR_{p3}$, —$NR_{n3}CO_2R_{p3}$, —$NR_{n3}S(O)_2R_{p3}$, —$NR_{n3}S(O)_2OR_{p3}$ and —$NR_{n3}S(O)_2NR_{q3}R_{r3}$;

each Z^{2a} is independently selected from $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl, heterocycle, halogen, —CN, —OR_{n4}, —$OC(O)R_{p4}$, —$OC(O)NR_{q4}R_{r4}$, —SR_{n4}, —$S(O)R_{p4}$, —$S(O)_2OH$, —$S(O)_2R_{p4}$, —$S(O)_2NR_{q4}R_{r4}$, —$NR_{q4}R_{r4}$, —$NR_{n4}COR_{p4}$, —$NR_{n4}CO_2R_{p4}$, —$NR_{n4}CONR_{q4}R_{r4}$, —$NR_{n4}S(O)_2R_{p4}$, —$NR_{n4}S(O)_2OR_{p4}$, —$NR_{n4}S(O)_2NR_{q4}R_{r4}$, NO_2, —$C(O)R_{n4}$, —$C(O)OR_{n4}$, —$C(O)NR_{q4}R_{r4}$, wherein any heteroaryl of Z^{2a} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of Z^{2a} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of Z^{2a} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups;

each Z^{2b} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$heteroalkyl and $(C_1\text{-}C_4)$haloalkyl;

each Z^{2c} is independently selected from halogen, —CN, —OR_{n4}, —$OC(O)R_{p4}$, —$OC(O)NR_{q4}R_{r4}$, —SR_{n4}, —$S(O)R_{p4}$, —$S(O)_2OH$, —$S(O)_2R_{p4}$, —$S(O)_2NR_{q4}R_{r4}$, —$NR_{q4}R_{r4}$, —$NR_{n4}COR_{p4}$, —$NR_{n4}CO_2R_{p4}$, —$NR_{n4}CONR_{q4}R_{r4}$, —$NR_{n4}S(O)_2R_{p4}$, —$NR_{n4}S(O)_2OR_{p4}$, —$NR_{n4}S(O)_2NR_{q4}R_{r4}$, NO_2, —$C(O)R_{n4}$, —$C(O)OR_{n4}$, —$C(O)NR_{q4}R_{r4}$;

each R_{n3} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{n3} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{n3} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{n3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl of R_{n3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2a} groups;

each R_{p3} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{p3} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{p3} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{p3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{p3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2a} groups;

R_{q3} and R_{r3} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{q3} or R_{r3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl and $(C_2\text{-}C_4)$alkenyl of R_{q3} or R_{r3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2a} groups, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups, wherein any heteroaryl of R_{q3} and R_{r3} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{q3} and R_{r3} has 2-20 carbon atoms and 1-6 heteroatoms;

each R_{s3} is independently selected from $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{s3} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{s3} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{s3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl of R_{s3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2a} groups, or R_{s3} is $(C_1\text{-}C_4)$alkyl substituted with 1, 2, 3, 4, or 5 Z^{2a} groups;

each R_{n4} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl;

each R_{p4} is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl;

R_{q4} and R_{r4} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl;

each Z^3 is independently selected from halogen, $(C_1\text{-}C_4)$alkyl, —OH, —CN, $(C_1\text{-}C_4)$heteroalkyl and $(C_1\text{-}C_4)$haloalkyl;

each Z^4 is independently selected from $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl, heterocycle, halogen, —CN, —OR_{n5}, —$OC(O)R_{p5}$, —$OC(O)NR_{q5}R_{r5}$, —SR_{n5}, —$S(O)R_{p5}$, —$S(O)_2OH$, $(O)_2R_{p5}$, —$S(O)_2NR_{q5}R_{r5}$, —$NR_{q5}R_{r5}$, —$NR_{n5}COR_{p5}$, —$NR_{n5}CO_2R_{p5}$, —$NR_{n5}CONR_{q5}R_{r5}$, —$NR_{n5}S(O)_2R_{p5}$, —$NR_{n5}S(O)_2OR_{p5}$, —$NR_{n5}S(O)_2NR_{q5}R_{r5}$, NO_2, —$C(O)R_{n5}$, —$C(O)OR_{n5}$—$C(O)NR_{q5}R_{r5}$ and —$B(OR_{q5})(OR_{r5})$, wherein any heteroaryl of Z^4 has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of Z^4 has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of Z^4 is optionally substituted with 1, 2, 3, 4, or 5 Z^{4a} or Z^{4b} groups, and wherein any $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl and $(C_2\text{-}C_8)$alkynyl of Z^4 is optionally substituted with one or more 1, 2, 3, 4, or 5 Z^{4a} groups;

each Z^{4a} is independently selected from $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl, heterocycle, halogen, —CN, —OR_{n6}, —$OC(O)R_{p6}$, —$OC(O)NR_{q6}R_{r6}$, —SR_{n6}, —$S(O)R_{p6}$, —$S(O)_2OH$, —$S(O)_2R_{p6}$, —$S(O)_2NR_{q6}R_{r6}$, —$NR_{q6}R_{r6}$, —$NR_{n6}COR_{p6}$, —$NR_{n6}CO_2R_{p6}$, —$NR_{n6}CONR_{q6}R_{r6}$, —$NR_{n6}S(O)_2R_{p6}$, —$NR_{n6}S(O)_2OR_{p6}$, —$NR_{n6}S(O)_2NR_{q6}R_{r6}$, NO_2, —$C(O)R_{n6}$, —$C(O)OR_{n6}$, and —$C(O)NR_{q6}R_{r6}$ wherein any heteroaryl of Z^{4a} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of Z^{4a} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of Z^{4a} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4c} or Z^{4d} groups;

each Z^{4b} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl, wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of Z^{4b} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4c} groups;

each Z^{4c} is independently selected from $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl, heterocycle, halogen, —CN, —OR_{n7}, —$OC(O)R_{p7}$, —$OC(O)NR_{q7}R_{r7}$, —SR_{n7}, —$S(O)R_{p7}$, —$S(O)_2OH$, —$S(O)_2R_{p7}$, —$S(O)_2NR_{q7}R_{r7}$, —$NR_{q7}R_{r7}$, —$NR_{n7}COR_{p7}$, —$NR_{n7}CO_2R_{p7}$, —$NR_{n7}CONR_{q7}R_{r7}$, —$NR_{n7}S(O)_2R_{p7}$, —$NR_{n7}S(O)_2OR_{p7}$, —$NR_{n7}S(O)_2NR_{q7}R_{r7}$, NO_2, —$C(O)R_{n7}$, —$C(O)OR_{n7}$, —$C(O)NR_{q7}R_{r7}$, $(C_6\text{-}C_{20})$haloaryl, haloheteroaryl, haloheterocycle and $(C_1\text{-}C_4)$heteroalkyl, wherein any heteroaryl or haloheteroaryl of Z^{4c} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle or haloheterocycle of Z^{4c} has 2-20 carbon atoms and 1-6 heteroatoms;

each Z^{4d} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, and $(C_1\text{-}C_4)$haloalkyl;

each R_{n5} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{n5} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4a} or Z^{4b} groups, wherein any heteroaryl of R_{n5} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{n5} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{n5} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4a} groups;

each R_{p5} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{p5} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{p5} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl, or heterocycle of R_{p5} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4a} or Z^{4b} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl of R_{p5} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4a} groups;

R_{q5} and R_{r5} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{q5} or R_{r5} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4a} or Z^{4b} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{q5} or R_{r5} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4a} groups, or R_{q5} and R_{r5} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4, or 5 Z^{4a} or Z^{4b} groups, wherein any heteroaryl of R_{q5} and R_{r5} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{q5} and R_{r5} has 2-20 carbon atoms and 1-6 heteroatoms;

each R_{n6} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{n6} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{n6} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{n6} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4c} or Z^{4d} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{n6} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4c} groups;

each R_{p6} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{p6} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{p6} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{p6} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4c} or Z^{4d} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{p6} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4c} groups;

R_{q6} and R_{r6} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl and $(C_6\text{-}C_{20})$aryl, wherein any heteroaryl of R_{q6} and R_{r6} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{q6} and R_{r6} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any $(C_3\text{-}C_7)$carbocycle, $(C_6\text{-}C_{20})$aryl, heteroaryl and heterocycle of R_{q6} or R_{r6} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4c} or Z^{4d} groups, and wherein any $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl of R_{q6} or R_{r6} is optionally substituted with 1, 2, 3, 4, or 5 Z^{4c} groups, or R_{q6} and R_{r6} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4, or 5 Z^{4c} or Z^{4d} groups;

each R_{n7} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, $(C_6\text{-}C_{20})$aryl, $(C_6\text{-}C_{20})$haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl, wherein any heteroaryl or haloheteroaryl of R_{n7} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle or haloheterocycle of R_{n7} has 2-20 carbon atoms and 1-6 heteroatoms;

each R_{p7} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, $(C_6\text{-}C_{20})$aryl, $(C_6\text{-}C_{20})$haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_4)$haloalkyl and $(C_1\text{-}C_4)$heteroalkyl, wherein any heteroaryl or haloheteroaryl of R_{p7} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle or haloheterocycle of R_{p7} has 2-20 carbon atoms and 1-6 heteroatoms;

R_{q7} and R_{r7} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, heteroaryl, $(C_6\text{-}C_{20})$aryl, $(C_6\text{-}C_{20})$ haloaryl, haloheteroaryl, haloheterocycle, $(C_1\text{-}C_4)$ haloalkyl and $(C_1\text{-}C_4)$heteroalkyl, or R_{q7} and R_{r7} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein any heteroaryl or haloheteroaryl of R_{q7} and R_{r7} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle or haloheterocycle of R_{q7} and R_{r7} has 2-20 carbon atoms and 1-6 heteroatoms;

each Z^5 is independently selected from $(C_1\text{-}C_6)$alkyl, halogen, —CN, and —OR_8, wherein any $(C_1\text{-}C_6)$alkyl of Z^5 is optionally substituted with 1, 2, 3, 4, or 5 halogen; and

each R_{n8} is independently selected from H, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$haloalkyl and $(C_3\text{-}C_7)$carbocycle;

or a salt thereof.

2: The compound of claim **1**, or a salt thereof, wherein R^{3a} and R^{3b} are each H.

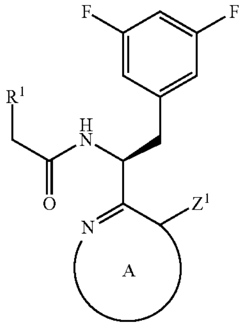
3-6. (canceled)

7: The compound of claim **1**, or a salt thereof, wherein R^2 is 3,5-difluorophenyl.

8. (canceled)

9: The compound of claim **1** which is a compound of formula Ie:

Ie

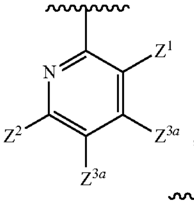


or a salt thereof.

10: The compound of claim **1**, or a salt thereof, wherein A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl of A is substituted with one Z^1 group, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups.

11: The compound of claim **1**, or a salt thereof, wherein A is pyridinyl or pyrimidinyl, wherein any pyridinyl or pyrimidinyl of A is substituted with one Z^1 group, one Z^2 group, and optionally substituted with 1 or 2 Z^3 groups.

12: The compound of claim **1**, or a salt thereof, wherein A is selected from:



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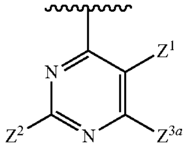

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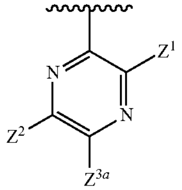


wherein each Z^{3a} is independently selected from H and Z^3.

13-16. (canceled)

17: The compound of claim **1**, or a salt thereof, wherein Z^1 is selected from phenyl, monocyclic-heteroaryl and bicyclic-heterocycle, wherein any phenyl, monocyclic-heteroaryl, and bicyclic-heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^{1a} or Z^{1b} groups.

18-25. (canceled)

26: The compound of claim **1**, or a salt thereof, wherein Z^2 is selected from —$OC(O)R_{p3}$ and —$NR_{q3}R_{r3}$.

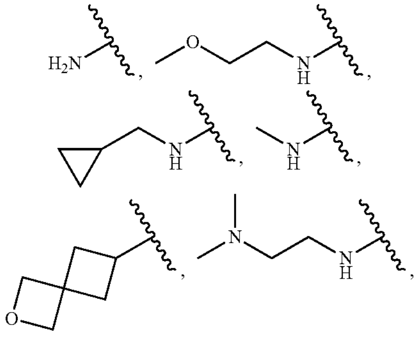
27-29. (canceled)

30: The compound of claim **1**, or a salt thereof, wherein Z^2 is —$NR_{q3}R_{r3}$.

31: The compound of claim **1**, or a salt thereof, wherein R_{q3} and R_{r3} are each independently selected from H, $(C_1\text{-}C_4)$alkyl and heterocycle, wherein any heterocycle of R_{q3} and R_{r3} has 2-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of R_{q3} or R_{r3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups, and wherein any $(C_1\text{-}C_4)$alkyl of R_{q3} or R_{r3} is optionally substituted with 1, 2, 3, 4, or 5 Z^{2a} groups, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with 1, 2, 3, 4, or 5 Z^{2b} or Z^{2c} groups, wherein any heteroaryl of Z^{2b} or Z^{2c} has 1-20 carbon atoms and 1-6 heteroatoms and wherein any heterocycle of Z^{2b} or Z^{2c} has 2-20 carbon atoms and 1-6 heteroatoms.

32-36. (canceled)

37: The compound of claim **1**, or a salt thereof, wherein Z^2 is selected from:



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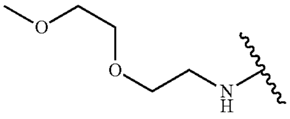
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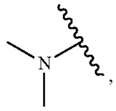
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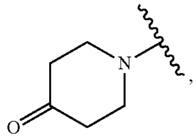
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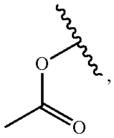
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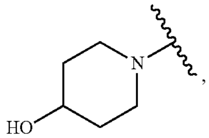
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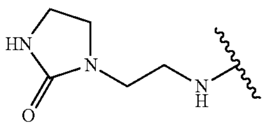
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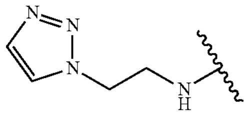
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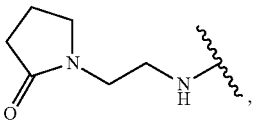
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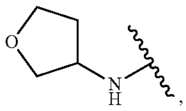
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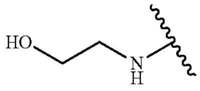
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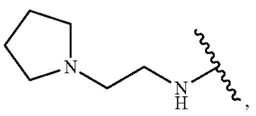
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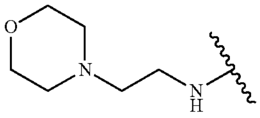
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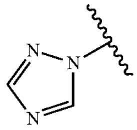
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38-39. (canceled)

40: The compound of claim **1**, or a salt thereof, wherein R^1 is a bicyclic-heteroaryl or tricyclic-heteroaryl, wherein any bicyclic-heteroaryl or tricyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups.

41. (canceled)

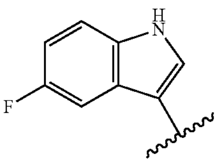
42: The compound of claim **1**, or a salt thereof, wherein R^1 is a bicyclic-heteroaryl, wherein the bicyclic-heteroaryl of R^1 contains at least one partially unsaturated ring, and wherein any bicyclic-heteroaryl of R^1 is optionally substituted with 1, 2, 3, 4, or 5 Z^4 groups.

43-47. (canceled)

48: The compound of claim **1**, or a salt thereof, wherein each Z^4 is independently selected from $(C_1\text{-}C_6)$alkyl and halogen, wherein any $(C_1\text{-}C_6)$alkyl of Z^3 is optionally substituted with 1, 2, 3, 4, or 5 halogen.

49. (canceled)

50: The compound of claim **1**, or a salt thereof, wherein R^1 is selected from: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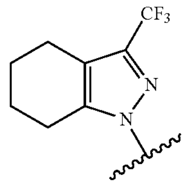
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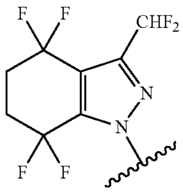
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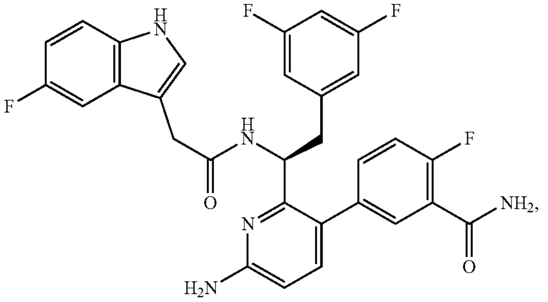
51: The compound of claim **1** selected from: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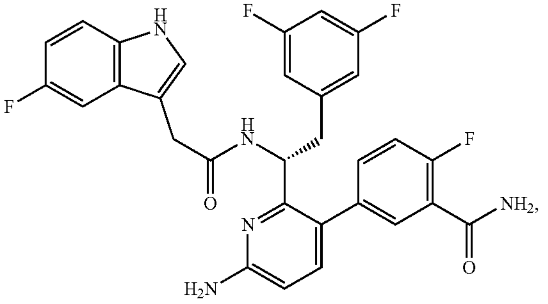
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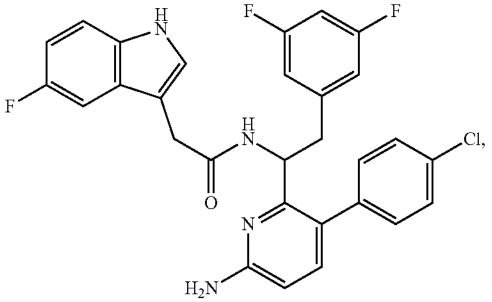
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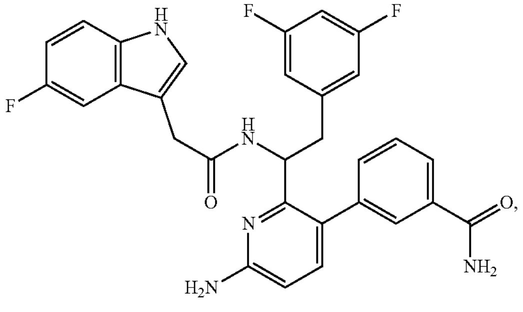
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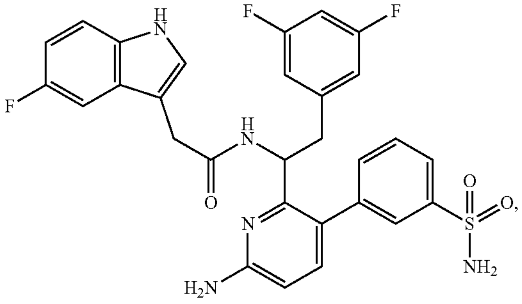

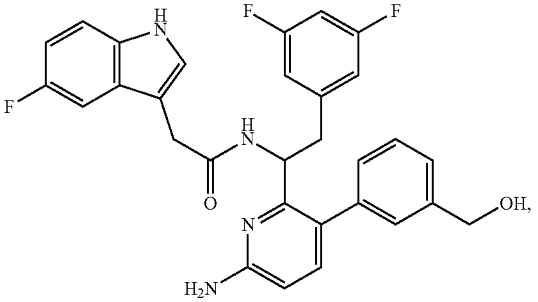

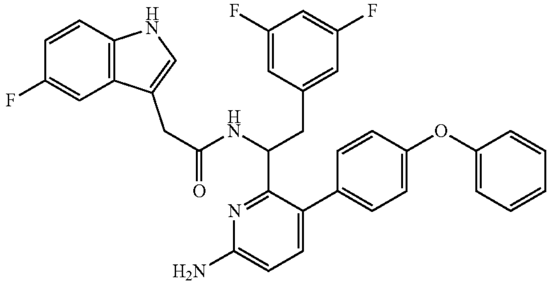

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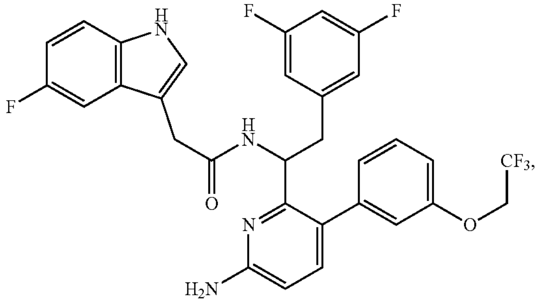

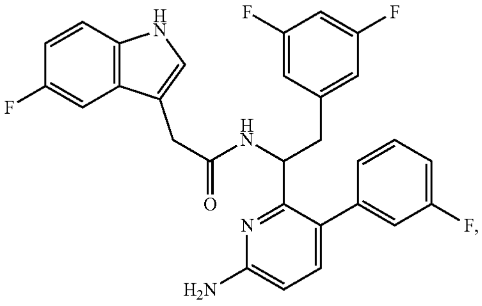

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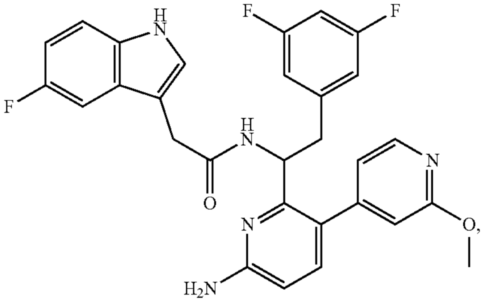

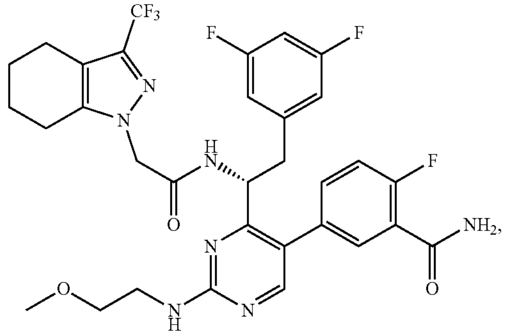

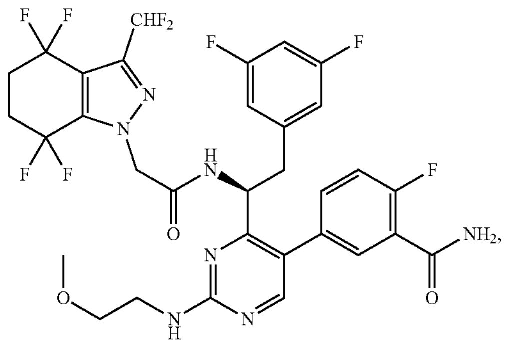

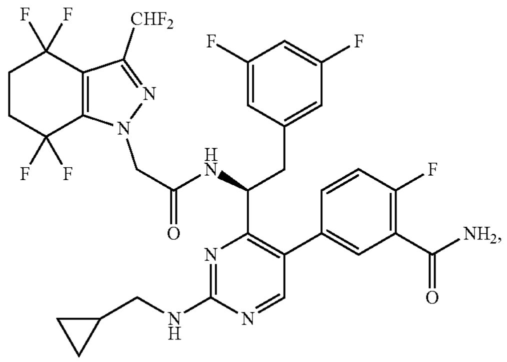

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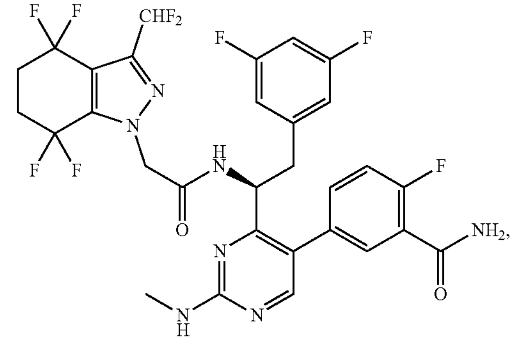

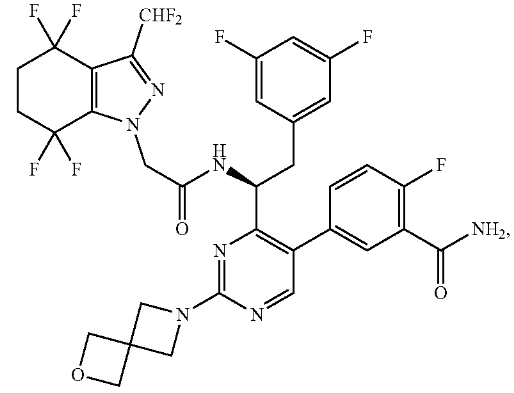

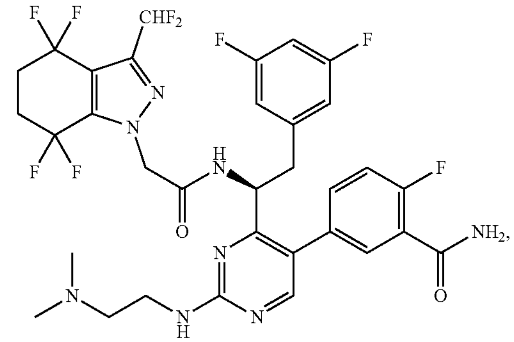

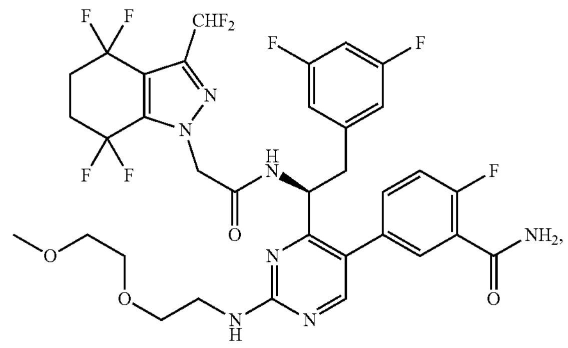

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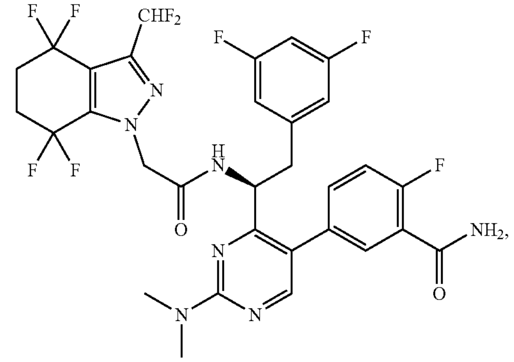

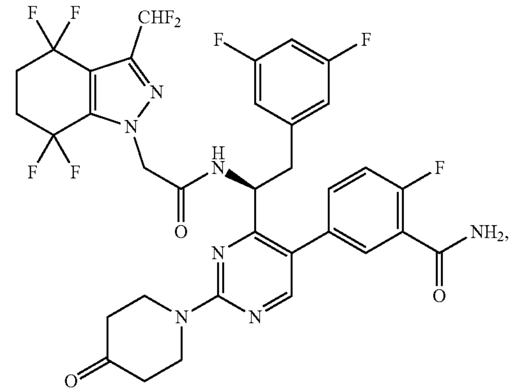

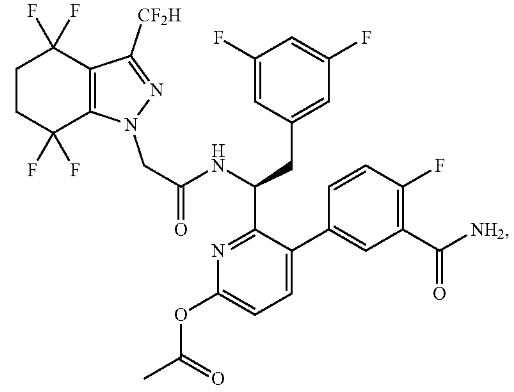

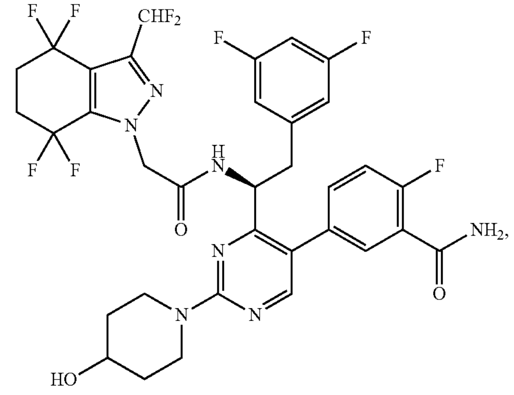

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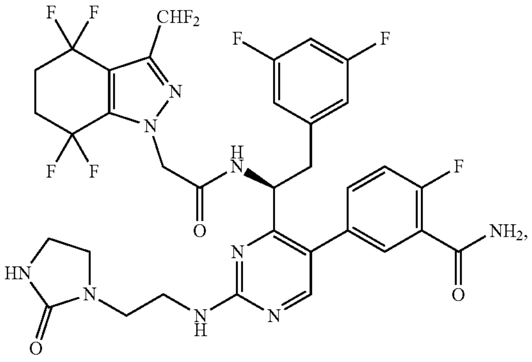

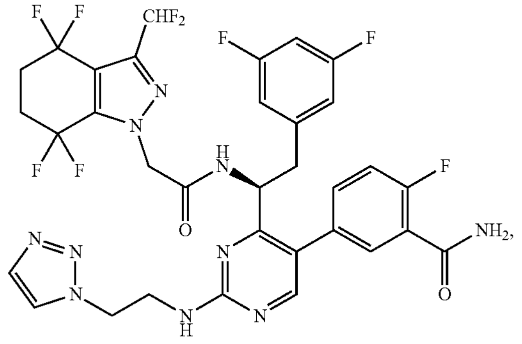

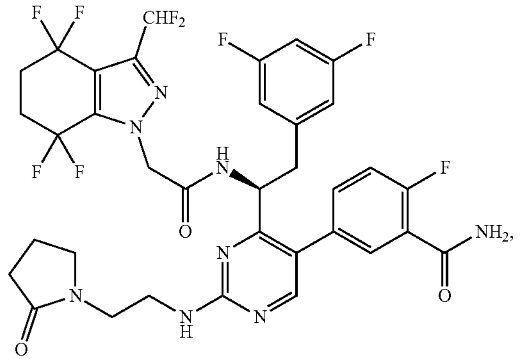

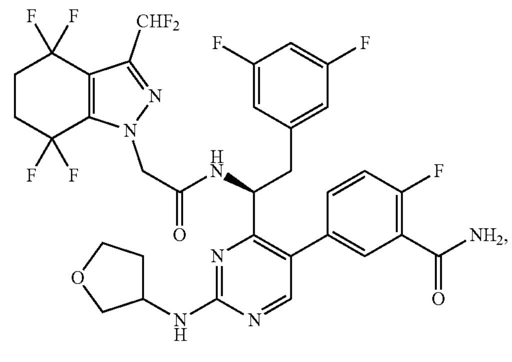

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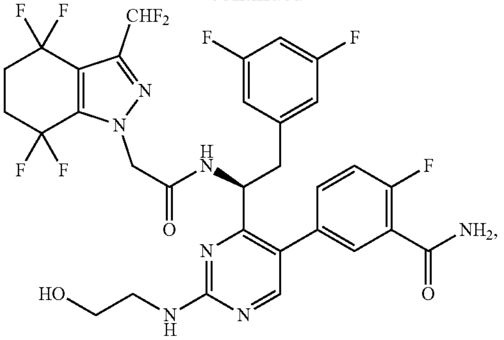

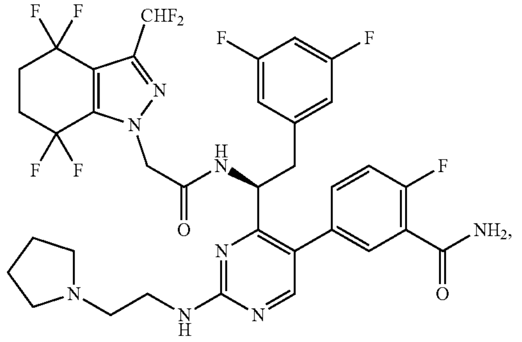

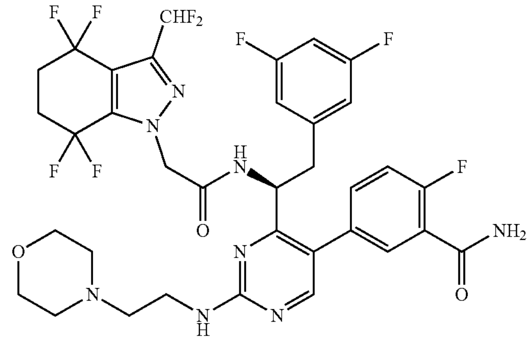

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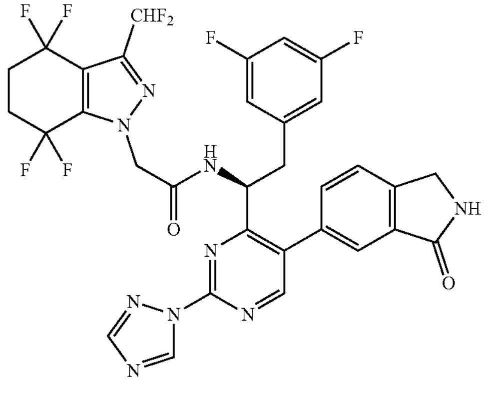

and salts thereof.

52: A pharmaceutical composition comprising a compound of claim **1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

53: A method for treating an HIV infection in a mammal comprising administering a therapeutically effective amount of a compound of claim **1**, or a pharmaceutically acceptable salt thereof, to the mammal.

54. (canceled)

55: A method for treating an HIV infection in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of claim **1**, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof.

56-**59**. (canceled)

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